UNIVERSIDADE DE SÃO PAULO
INSTITUTO DE FÍSICA DE SÃO CARLOS

PAULO DE SOUSA CARVALHO JÚNIOR

**Pharmaceutical salts of the antidepressants Paroxetine and Fluoxetine,
selective serotonin reuptake inhibitors: crystal engineering, solid-state
characterization and thermodynamic aspects**

São Carlos
2016

PAULO DE SOUSA CARVALHO JÚNIOR

**Pharmaceutical salts of the antidepressants Paroxetine and Fluoxetine,
selective serotonin reuptake inhibitors: crystal engineering, solid-state
characterization and thermodynamic aspects**

Thesis presented to the Graduate Program in
Physics at the Instituto de Física de São
Carlos, Universidade de São Paulo to obtain
the degree of Doctor of Science.

Concentration area: Applied Physics
Option: Biomolecular Physics

Advisor:
Prof. Dr. Javier Alcides Ellena

Corrected Version
(Original version available on the Program Unit)

São Carlos
2016

AUTHORIZE THE REPRODUCTION AND DISSEMINATION OF TOTAL OR PARTIAL COPIES OF THIS THESIS, BY CONVENCIONAL OR ELECTRONIC MEDIA FOR STUDY OR RESEARCH PURPOSE, SINCE IT IS REFERENCED.

Cataloguing data reviewed by the Library and Information Service
of the IFSC, with information provided by the author

Carvalho Júnior, Paulo de Sousa
Pharmaceutical salts of the antidepressants
Paroxetine and Fluoxetine, selective serotonin
reuptake inhibitors: crystal engineering, solid-
state characterization and thermodynamic aspects /
Paulo de Sousa Carvalho Júnior; advisor Javier
Alcides Ellena - reviewed version -- São Carlos 2016.
157 p.

Thesis (Doctorate - Graduate Program in Basic
Physics) -- Instituto de Física de São Carlos,
Universidade de São Paulo - Brasil , 2016.

1. Crystal engineering. 2. Solid-state. 3.
Selective serotonin reuptake inhibitor
antidepressants. I. Ellena, Javier Alcides, advisor.
II. Title.

To my Family and friends.

ACKNOWLEDGEMENTS

To God for the support and care during the period.

To my family, Paulo de Sousa Carvalho and Eloina Mota de Carvalho, for providing more love and support than I can repay with this thesis. Also, for inspiring me along my life.

To my brother and his family (Ana and Isabela) for the same reasons.

To Prof. Dr. Javier Ellena, my supervisor. The person who I have admiration and gratitude for the friendship, encouragement, patience, and competent guidance.

To Prof. Dra Judith A. K. Howard and Dr Dmitry S. Yufit, for examples of competent scientists and professors. During my stay in Durham, they gave me valuable opportunities that have enriched my understanding of chemistry as well as the context in which scientific research is performed at University. Humility and patience to teach and collaboration will always be remembered by me. For the same reasons, I would like to thanks Durham University for providing me an exceptional experience.

To the University of São Paulo, represented by the Graduate Program in Physics, by the institutional support. Also to the university staffs, especially at the Institute of Physics of São Carlos.

To my PhD's colleagues and friends, Juan Carlos, Cecilia Carolina, Cristiane, Marcelo, Karina, Luan, Matheus, and others students belonging to the Crystallography Group of Small Molecules, by collaboration, trust and good laughs, beyond good coffee times.

To the friends that I made during the development of the PhD, who gave me and shared their good mood and experiences (such as Valter H. C. Silva, Nayara Dantas, Clayton Rodrigues, Francisco Neto, Silvia Mara, Juan Carlos, Marcelo Andrade, Rivaldo Varandas, Alysson Martins, Tiago Rodrigues, Richard D'vries, Jussara Carneiro, Franciele Marcos, Luan Diniz, and Matheus Souza).

To Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for financial support.

(...)
Oh simple thing where have you gone
I'm getting old and I need something to rely on
(Somewhere Only We Know -Keane)

ABSTRACT

CARVALHO JUNIOR, P. S. **Pharmaceutical salts of the antidepressants Paroxetine and Fluoxetine, selective serotonin reuptake inhibitors:** crystal engineering, solid-state characterization and thermodynamic aspects. 2016. 157 p. Tese (Doutorado em Ciências), Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, 2016.

The development of new solid forms of active pharmaceutical ingredients (API) is relevant both from fundamental as well as industrial perspectives. To this end, Crystal Engineering plays an ever-increasing important role in pharmaceutical sciences. Among the crystal engineering strategy, salt formation is the most important and implemented approach. The salt forms of API could be used to modulate and tuned the solubility and stability of API to provide optimal practical uses. Herein, we report pharmaceutical salts of two Selective Serotonin Reuptake Inhibitor antidepressants used in the treatment of depression and anxiety disorders, Paroxetine (PRX) and Fluoxetine (FLX). For this purpose, salt formers, supramolecular synthesis and crystallization protocols have been driven by the systematization of structural and supramolecular data of molecules and analogues from the *Cambridge Structural Database*. Paroxetine bromide hemihydrate ((PRXBr) $0.5\text{H}_2\text{O}$), Paroxetine Nitrate hydrate (PRXNO $_3\text{H}_2\text{O}$) and two polymorphs of Fluoxetine Nitrate (FLXNO $_3$) have obtained. All were characterized by a combination of techniques including Single Crystal X-ray Diffraction, Differential Scanning Calorimetry (DSC), Thermogravimetry analysis (TGA), Hot Stage Microscopy, Fourier transform infrared spectroscopy (IR) and solubility measurements. Since the hydration/dehydration process in APIs induces phase transitions that compromise its efficiency, the structural characterization of (PRXBr) $0.5\text{H}_2\text{O}$ help to understand its reversible dehydration process. Also, this study has implication in the understating of dehydration of isostructural PRX hydrochloride salt. Additionally, the (PRXNO $_3$) H_2O have shown the conformational flexibility and supramolecular diversity of PRX. On the other hand, the chirality of FLX is related to two nitrate salt polymorphs. A racemate and a non-centrosymmetric structure with independent enantiomers in the asymmetric unit were obtained for FLXNO $_3$. Their packing have shown the existence of different racemic motifs, resulting in different enantiomer orientations. The rare occurrence of racemic systems in non-centrosymmetric space groups becomes this event a noteworthy case. By their physicochemical properties, the polymorphs were monotropically related. The scientific contributions of this thesis show the diversity of the solid forms and define candidates to new antidepressants APIs solid formulations.

Keywords: Crystal engineering. Solid-state. Selective serotonin reuptake inhibitor antidepressants.

RESUMO

CARVALHO JUNIOR, P. S. **Sais farmacêuticos dos antidepressivos Paroxetina e Fluoxetina, inibidores seletivos de recaptação de serotonina:** engenharia de cristais, caracterização de estado sólidos e aspectos termodinâmicos. 2016. 157 p. Tese (Doutorado em Ciências), Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, 2016.

O desenvolvimento de novas formas sólidas de ingredientes farmacêuticos ativos (API) é relevante tanto numa perspectiva fundamental como industrial. Para tal, a Engenharia de cristais tem desempenhado um papel importante nas ciências farmacêuticas. Dentre as estratégias, a formação de sais é a abordagem mais importante e implementada. Os sais de APIs são capazes de modular e ajustar a solubilidade e a estabilidade, a fim de proporcionar uso prático. Nesta tese, são reportados sais de dois fármacos Inibidores Seletivos de Recaptação de Serotonina, consolidados no tratamento da depressão e distúrbios de ansiedade, a Paroxetina (PRX) e a Fluoxetina (FLX). Brometo de Paroxetina hemiidratado ((PRXBr) $0.5\text{H}_2\text{O}$), Nitrato de Paroxetina hidratado (PRXNO $_3\text{H}_2\text{O}$) e polimorfos de Nitrato de Fluoxetina (FLXNO $_3$), síntese e protocolos de cristalização foram cuidadosamente delineados, com base na sistematização de dados estruturais e supramoleculares das moléculas e seus análogos, depositados no *Cambridge Structural Database*. Todos os sais foram caracterizados por Difração de Raios-X por Monocristal, Calorimetria Explanatória Diferencial (DSC), Análise termogravimétrica (TGA), Termomicroscopia, Espectroscopia vibracional na região do infravermelho (IR) e solubilidade. Considerando que a hidratação/desidratação induz mudanças de fases que comprometem a eficiência do API, a caracterização do (PRXBr) $0.5\text{H}_2\text{O}$ auxiliou no entendimento do processo de desidratação reversível que ocorre para esse fármaco. Estas mudanças de fase resultam também em implicações sobre a compreensão do processo de desidratação do sal isoestrutural de cloreto de PRX hemiidratado. Além disso, por meio da elucidação estrutural do (PRXNO $_3$) H_2O , foi possível analisar a diversidade conformacional e supramolecular da PRX. Quanto à FLX, verificou-se que sua quiralidade está relacionada com seu polimorfismo. Um racemato e uma estrutura não centrossimétrica com dois enantiômeros independentes na unidade assimétrica foram obtidos para o FLXNO $_3$. A comparação destas estruturas permitiu mostrar a existência de arranjos supramoleculares racêmicos, constituídos por diferentes orientações de enantiômeros. A rara ocorrência de sistemas racêmicos em grupos espaciais não-centrossimétricos tornou este evento um caso notável. A partir das propriedades físico-químicas, os polimorfos puderam ser monotropicamente relacionados. Os resultados desta tese trazem importantes contribuições científicas para diversidade de formas sólidas e também define novas formulações sólidas para utilização como antidepressivos.

Palavras-chave: Engenharia de cristais. Estado sólido. Inibidores seletivos de recaptação de serotonina.

LIST OF FIGURES

Figure 1 -	Schematic illustration of SSRIs mechanism: (1) Tryptophan enters the cellular system; (2) Conversion of tryptophan into 5-hydroxytryptophan (5-HTP); (3) 5-HTP is converted to 5-HT; (4) 5-HT passes through the membrane into the synaptic cleft; (5) 5-HT stimulates its receptor; (6) 5-HT binds to its reuptaker. (7) Inhibition of the Receptor agent of the 5-HT by a SSRI, resulting in the increasing of 5-HT in the synaptic cleft.....	22
Figure 2 -	Molecular structure of the Paroxetine cation.....	23
Figure 3 -	Crystal structure of (a) (PRX.HCl)0.5H ₂ O (Form I), (b) PRX HCl acetone solvate, and (c) (PRX.HCl)H ₂ O (Form II), all viewed along the crystallographic <i>b</i> -axis	24
Figure 4 -	Molecular structure of Fluoxetine cation	25
Figure 5 -	Reported solid forms of FLX, and their respective crystalline packing.....	26
Figure 6 -	(a) Obtaining different solid forms of APIs. (b) Classification for different solid forms of APIs.....	28
Figure 7 -	(a) The occurrence of pharmaceutical salts of N-based compounds with acceptable GRAS anions. (b) The most frequent (H ₂ O) _n clusters observed in organic molecular crystals of the CSD.....	34
Figure 8 -	The occurrence (%) of pharmaceutically acceptable anions in organic salts on the (a) CSD and (b) Orange Book Database (OBD) as found for Haynes ¹⁵¹ and Saal's ¹⁵⁰ , respectively	36
Figure 9 -	Steps of designing of new solid forms of API- emphasis on obtaining salts	39
Figure 10 -	Synopsis of the main crystallization experiments performed for PRX and FLX. The figures the morphology of the resulting crystals from the experimental procedure and 'x' indicated that no solid forms were obtained	43

LIST OF ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient
CAHB	charge assisted Hydrogen bonds
CSD	Cambridge Structural Database
DSC	Differential Scanning Calorimetry
FDA	Food and Drug Administration
FLX	Fluoxetine
GRAS	Generally Regarded As safe
HB	Hydrogen Bond
HBr	Hydrobromic acid
HNO ₃	Nitric acid
5-HT	5-hydroxytryptamine
IMAOs	Monoaminoxidase Inhibitor
IR	Infrared Spectroscopy
PRX	Paroxetine
SCXRD	Single Crystal X-Ray Diffraction
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
SSNRI	Selective Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitors
TGA	Termogravimetry analysis
WHO	World Health Organization

CONTENTS

1	INTRODUCTION	19
1.1	Depression and Selective Serotonin Reuptake Inhibitors	20
1.2	Paroxetine	23
1.3	Fluoxetine	25
1.4	Pharmaceutical Solid forms	26
1.5	Polymorphism of Pharmaceutical compounds	29
1.6	Pharmaceutical hydrates	31
1.7	Pharmaceutical salts	34
1.8	Crystal Engineering and Supramolecular Chemistry	37
1.9	Goals	39
2	MATERIALS AND METHODS	41
2.1	Supramolecular synthesis and selection of salt formers	41
2.2	Crystallization screening	42
2.3	Solid State Characterization	43
3	PAPERS	45
4	CONCLUSIONS	81
	REFERENCES	83
	APPENDIX A - Supporting Information of the paper 'Reversible Solid-State Hydration/Dehydration of Paroxetine Hydrobromide Hemihydrate: Structural and Thermochemical Studies'	93
	APPENDIX B - Supporting Information of the paper ' X-Ray Diffraction, Spectroscopy and Thermochemical Characterization of the Pharmaceutical Paroxetine Nitrate Salt'	121
	APPENDIX C - Supporting Information of the paper 'Rare case of racemic Fluoxetine Nitrate polymorphs: Phase Behavior and Relative Stability'	135

1 INTRODUCTION

Depression is a common¹⁻⁵, costly (US\$1 trillion/year of the global economy)⁶⁻⁹, and recurrent mental disorder among adults.¹⁰⁻¹¹ The term '*depression*' has been attributed to different contexts, such as symptom, syndrome, and disease.¹² As a pathological case, it is associated with considerable morbidity¹³⁻¹⁴ and mortality^{7,11,15}, being, according to the World Health Organization (WHO), the fourth leading cause of disability worldwide.^{10,16-17} Projections are that, until 2020, it will be the second one^{15,18-19}, followed by cancer and heart diseases, mainly due its difficult diagnosis and its highly complexity, social impact, and pronounced prevalence. In this way, depression is a challenge for public health and requires a wide contribution of the society, as a whole.⁸

The psychopharmacological treatment for depression is mainly conducted through the use of antidepressants, in particular, Selective Serotonin Reuptake Inhibitors (SSRI).²⁰ Since 80's, when discovered, these compounds have been established as the major intervention for the treatment of this disease, not only due their therapeutic effects, but especially due their reduced side effects. However, although SSRI's constitute a class of widely prescribed and marketed drugs worldwide²¹, as pharmaceutical products they are still being widely investigated from structural and biological viewpoints²²⁻³¹, once the effectiveness/performance and manufacturability of these drugs are solid-state dependent.

In Pharmaceutical Sciences, the development of new solid forms directly impacts on the generation of improved active pharmaceutical ingredients (APIs), since each new crystalline form of a drug can be expected to exhibit new physicochemical properties, arising from its particular solid structure. In the view that the SSRI's are of significant importance to treat depression, and also in order to provide and support the development of novel solid forms of some of these APIs, this thesis focused on the solid-state characterization of multicomponent crystals and possible polymorphs of SSRI antidepressants. Specifically, this study aimed the design and supramolecular synthesis of multicomponent crystals of Paroxetine (PRX) and Fluoxetine (FLX) by the use of crystal engineering strategies. For this purpose, salts of PRX and FLX were rationalized using as structural motifs of crystals, (1) statically analysis of supramolecular synthons, (2) reactivity of each API, and (3) charge assisted Hydrogen bonds (CAHB) schemes.

For the salt formation approach, the following characteristics were established for selection of salt coformers: anion charge, acidity of the coformers (pK_a), reactivity with the APIs, possibility of formation of isostructural arrangements, solution stability, and acceptance

as a *Generally Recognized as Safe* (GRAS) specie. For this purpose, in the crystallization screening, the hydrobromic (HBr) and nitric (HNO₃) acids were utilized. The crystallizations were carried out under different conditions (solvent, temperature, evaporation rate, pH, *etc.*). By considering that they were supramolecularly designed, the solid-state characterization of each crystalline salt was performed using the Single Crystal X-ray diffraction technique, in combination with Infrared spectroscopy, Differential Scanning Calorimetry (DSC), Thermogravimetry (TGA), Polarized Hot-stage Microscopy, and solubility measurements.

1.1 Depression and Selective Serotonin Reuptake Inhibitors

Along the history, mood disorders were initially related to melancholy and the Latin word “*deprimere*” (meaning press down) was used to designate such cases. After over two millennia and many meanings, the term “*depression*” was consolidated as a disease only in the twentieth century, with the development of psychiatry, pharmacology, pathology, neurology, and genetics. As disease, depression was characterized by the recurrence and durability of specific symptoms associated to mood, appetite, sleep issues, irritability, among others.^{12,32} In this sense, two main approaches have been applied in the treatment of depression: classical drug therapy and psychotherapy sessions, or combination of both.^{7,33} Nevertheless, antidepressant drugs remain the basis for treating the disease, in most cases.⁸

Historically, the development of antidepressant drugs (Table 1) has been performed over several stages, wherein the first, *i.e. first-generation antidepressants*, were accidentally discovered.³⁴⁻³⁶ Monoamine oxidase Inhibitor (IMAOs) and Tricyclic drugs are the main representative compounds of this class. Subsequently, from the research and identification of neurochemical properties associated with first-generation antidepressants, the variation of chemical structure of compounds led to the development of new compounds with fewer side effects and improved tolerability.³⁴ The Selective Serotonin Reuptake Inhibitors (SSRIs) were the result of this research and constitute the *second-generation antidepressants*.^{9,37} These drugs have high safety and a reduced propensity to cause side effects when compared with tricyclic antidepressants.³⁸⁻³⁹ *Third-generation of antidepressants*, represented by Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are still under development, but they are clinically more effective than SSRIs.³⁷

Table 1 - Classification of antidepressant compounds.

Antidepressant drug	Class	Representative compounds
First-generation Class	Tricyclic Antidepressants	Amitriptyline (1961), Imipramine (1959), Trimipramine (1982), Lofepramine (1983)
	Monoamine Oxidase Inhibitors	Moclobemide, Phenelzine
Second-generation Class	Other second- generation antidepressants	Bupropion (1985), Mirtazapine (1996), Nefazodone (1994)
	Selective Serotonin Reuptake Inhibitors	Fluoxetine (1987), Sertraline(1991), Paroxetine (1992), Citalopram (1999), Fluvoxamine (2000),Escitalopam(2002).
Third-generation Class	Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine(1993), Reboxetine(1997) and Duloxetine (2004), Desvenlafaxine (2008),

Source: Adapted from GARTLEHNER et al.⁹; LÓPEZ-MUÑOZ et al.³⁵

At cerebral level, physiological responses to humor and thought are related to communication of neurotransmitters, thus, depression (despite the lack of cause and origin) is related to disorder of these endogen agents in the synaptic cleft. This process, together with the general mechanism of antidepressant action is illustrated in Figure 1. In the diagram, communication between two nerve cells (pre- and post-synaptic) is made by neurotransmitters which are transported between cells by enzymatic agents. Although not yet completely understood, the general mechanism of action of antidepressants focuses on the inhibition of these enzymes, acting on the release, reuptake, and absorption of the neurotransmitters.

Figure 1 - Schematic illustration of SSRIs mechanism: (1) Tryptophan enters the cellular system; (2) Conversion of tryptophan into 5-hydroxytryptophan (5-HTP); (3) 5-HTP is converted to 5-HT; (4) 5-HT passes through the membrane into the synaptic cleft; (5) 5-HT stimulates its receptor; (6) 5-HT binds to its reuptake. (7) Inhibition of the Receptor agent of the 5-HT by a SSRI, resulting in the increasing of 5-HT in the synaptic cleft.

Source: Adapted from CRYAN³⁷

As focus of this thesis, the SSRIs act on several targets in the serotonergic system modulating the reuptake of the endogenous ligand 5-hydroxytryptamine (5-HT) or serotonin in the central nervous system.^{20,40} These antidepressants began to be marketed worldwide in the late 1980s with the introduction of Fluoxetine, followed by Sertraline, Paroxetine, Fluvoxamine, Citalopram and Escitalopram.⁹ Due to their safety and convenient administration to the patient (once-a-day dose), the SSRIs became widely market and have significantly changed the understanding and nature of depression over the last 30 years. Despite the widespread prescription, the use and application of SSRIs has been widely analyzed, criticized and investigated.^{8,41–42} This implied in drastic changes in the prescription of SSRIs in the last 20 years that contributes to the progressive increase of the total costs of these drugs^{8,41,43}. Furthermore, several studies have indicated secondary effects related to treatment with SSRIs⁴⁴ as well as their advantages over other treatments such as the ratio of SSRI ability to modulate inflammatory processes^{8,41}, among others.^{29–30,45} This diversity of studies put the SSRI in evidence in the structural context, especially in the development of new crystalline solid forms. Paroxetine and Fluoxetine are SSRI that have been highlighted in

this structural perspective and are the antidepressants whose research was focused in this work. Both antidepressant drugs are better depicted in the following sections.

1.2 Paroxetine

Paroxetine (PRX), (3*S*,4*R*)-3-[(2*H*-1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, was initially synthesized as a part of the scope of a U.S. patent issued in 1977⁴⁶ and was pharmaceutically marketed as a hemihydrate hydrochloride salt (PRX.HCl)0.5H₂O since 80's. Structurally, the PRX molecule is composed by three important domains: a piperidine, a fluorobenzene and a benzodioxole groups. The molecular structure of the paroxetine cation (C₁₉H₂₁FNO₃) is given in Figure 2 and these domains are highlighted. Therapeutically, PRX is used in the treatment of diverse cases of depression, general anxiety and mental disorders.^{39,47} It is the compound with the highest affinity for 5-HT receptors, turning it more selective and 23 times most potent than the others SSRIs.^{22,39,47} Due this, PRX was one of the top 200 prescriptions in 2010, according to a research released by Prohotsky and Zhao.⁴⁸

Figure 2 - Molecular structure of the Paroxetine cation.

Source: By the author

Historically, several patents have established three systems of classification for the Paroxetine hydrochloride salt, PRX HCl. The first patent for this compound, granted to Barnes *et al.*⁴⁹, described the preparation of the PRX HCl hemihydrate and an correspondent anhydrous form. In 1987, Buxton *et al.*⁵⁰ further investigated these forms and named the hemihydrate as Form I and the anhydrous one as Form II. The Form I is described as a stable solid form with a melting point (*m.p*) of 143 °C. This form is the currently available for pharmaceutical formulations. On the other hand, the Form II is described as a hygroscopic

anhydrate, with a *m.p* of 118 °C. Subsequently, Ward *et al.*⁵¹ described a patent in which the preparation of the three forms of anhydrous PRX, designed: A (*m.p* 123-125 °C), B (*m.p* 137 °C) and C (*m.p* 161 °C). The variety of classification leads to an issue of nomenclature, and hence the confusion in the identification of PRX HCl phases.

Until now, six crystalline solid forms for PRX (including redeterminations), are deposited in the Cambridge Structural Database (CSD).⁵² The CSD consists in a world repository of small-molecule organic and metal-organic crystalline structures. Interestingly, all of PRX structures found in CSD belong to the Monoclinic $P2_1$ space group. The comparison between these structures have probed the conformational multiplicity of PRX and the relevance of $-\text{NH}_2^+-$ group to form hydrogen bonds stabilizing their crystal structures. The first crystalline structures of PRX, hemihydrate hydrochloride salt (PRX.HCl)0.5H₂O (Form I) and PRX HCl acetone solvate, were concomitantly reported in 1999, by Ibers⁵³ and Yokota and co-authors.⁵⁴ (PRX.HCl)0.5H₂O (Form I) exhibited unit cell parameters of $a = 12.8953(17)\text{\AA}$, $b = 10.0927(11)\text{\AA}$, $c = 14.413(2)\text{\AA}$, and $\beta = 106.638^\circ$ ⁵³, while the parameters for the solvated salt were of $a = 11.4532(5)\text{\AA}$, $b = 5.7545(2)\text{\AA}$, $c = 16.2992(7)\text{\AA}$, and $\beta = 90.510(2)^\circ$. In 2003, (PRX.HCl)H₂O (Form II) crystalline structure was solved (unit cell parameters $a = 11.400(2)\text{\AA}$, $b = 5.9747(12)\text{\AA}$, $c = 13.898(3)\text{\AA}$ and $\beta = 100.62(3)^\circ$ ⁵⁵) and proved to be thermodynamically less stable than (PRX.HCl)0.5H₂O (Form I).^{26,50} Figure 3 depicts the crystalline packing of (PRX.HCl)0.5H₂O (Form I), PRX HCl acetone solvate, and (PRX.HCl)H₂O (Form II), evidencing the anions and the solvent molecules.

Figure 3 - Crystal structure of (a) (PRX.HCl)0.5H₂O (Form I), (b) PRX HCl acetone solvate, and (c) (PRX.HCl)H₂O (Form II), all viewed along the crystallographic *b*-axis.

Source: By the author

Indeed, the inclusion of solvent molecules is commonly observed for PRX. However, far beyond the nomenclature problems, understand the dehydration behavior of the hemihydrate form, and their phase transitions, became an important issue. Pina and co-authors²⁶ have showed the conversion of Form II into Form I using thermal analysis, powder X-ray diffraction, infrared spectroscopy and molecular modeling. Recently, the amorphous

form of Paroxetine HCl hemihydrate and hydrate forms have been identified and characterized by the same research group.⁵⁶ This investigation showed that the dehydration of these distinct forms leads to the same anhydrous form of PRX HCl, but the mechanism and features of this dehydration phenomenon remains unclear.

1.3 Fluoxetine

Fluoxetine (FLX), *N*-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine, the first SSRI to be discovered, is a beta-blocker second generation antidepressant drug that shows good efficacy and very low toxicity when compared with other antidepressants.^{39,57} This pharmaceutical compound is also prescribed in the treatment of obsessive-compulsive disorder, nervous bulimia, panic, and premenstrual dysphoric disorders.^{39,58} FLX is still one of the best-selling drugs in the USA, since the introduction of antidepressant drugs in the market about three years ago.^{48,58–59} Currently, FLX is the only antidepressant approved for pediatric populations use, both in the USA and Europe.^{57–59} Structurally, FLX constitutes a secondary amine derivative (Figure 4) showing a considerable ionization ability [$pK_a = 10.1$].^{60–61} The substitution at the *para* position on the aromatic ring, by a CF_3 group, is decisive in its potency for blocking the reuptake of 5-HT.⁶² Also, the FLX chirality is an important property toward regulating its effectiveness.⁶³ This drug is marketed as a racemic chloride salt, FLX HCl, in which both enantiomers have similar effects regarding the inhibition of 5-HT reuptake. However, the *S*-FLX has a longer duration of action than *R*-FLX due to the higher potency of its metabolite.^{64–66}

Figure 4 - Molecular structure of Fluoxetine cation.

Source: By the author

Although there are only four crystalline forms reported for FLX, analysis of these structures point out to its potential to crystallize in novel solid forms. The oldest reported FLX crystalline structure dated from 1988 and refers to its hydrochloride salt (FLX HCl)

racemate, which is utilized in the pharmaceutical product, and crystallizes in the orthorhombic *Pcab* space group with unit cell parameters of $a = 10.457(2)$ Å, $b = 10.387(2)$ Å, and $c = 32.345(6)$ Å. Its crystal packing shows hydrogen bonds linking the chloride anions and the protonated aliphatic $-\text{NH}_2^+$ group (Figure 5). In 2004, Childs and co-authors²⁸ have obtained co-crystals of FLX HCl with benzoic (FLXCl·Benz), succinic (FLXCL·suc), and fumaric acids (FLXCL·Fum). In these compounds, the chloride anion is H-bonded to the secondary $-\text{NH}_2^+$ group ($\text{N}^+-\text{H}\cdots\text{Cl}^-$) and to carboxylic groups of the organic acid via acid-chloride interactions.²⁸ Thus, the FLX^+Cl^- ionic pair is combined with the organic acid, resulting in its inclusion into the lattice. Figure 5 show the recurrence of this motif in all FLX HCl co-crystals. These co-crystals demonstrated optimized solubility when compared with the one exhibited by the parent salt molecule. Noteworthy, FLX was one of first drugs to have a reported “salt-co-crystals”.⁶⁷ This term will be better presented and discussed in the following section.

Figure 5 - Reported solid forms of FLX, and their respective crystalline packing.

Source: By the author

1.4 Pharmaceutical Solid forms

Usually, about 80% of the APIs are delivered in an appropriate solid-phase dosage to the patients. Solid-state is preferred due its evident advantages in terms of stability, longer storage, convenience of intake, manufacturability, and low degradability, when compared to solution dosages.⁶⁸⁻⁷¹ Nevertheless, this does not imply that the APIs' solid-state does not present its own challenges, given that different solid forms may exhibit undesirable physicochemical properties that affects the performance, quality, and safety of the

pharmaceutical product.⁷²⁻⁷³ Among them, solubility, stability (chemical and thermodynamic), and bioavailability are the main three pharmaceutically relevant physicochemical properties that should be modulated and fine-tuned in order to provide optimal solid forms for practical use.⁷⁴ Although only molecules in solution are able to permeate the biological wall, by passive diffusion or by conducting biological carriers⁷⁵, to exert therapeutic effects, the rate in which these molecules become available in the systemic system is intrinsically related with the solid arrangement of the API in the crystal lattice.^{72,76-77}

APIs can exist in different crystalline forms^{72,76-78} and, then, have been subjected to various complications arising from polymorphism, multicomponent crystals, and amorphous phases, etc. One of the straightforward ways to considerably improve the physicochemical and biological properties of an API without modifying its pharmacophore structure is to develop novel solid forms, such as multicomponent crystals. In recent decades, crystalline multicomponent phases have been gaining increased attention, not only in scientific discussions worldwide, but also by industries, once it provides a very interesting alternative methodology to improve different physical-chemical properties (*e.g.*, melting point, color, stability, manufacturability, hygroscopic, toxicity, solubility, dissolution, bioavailability) of the APIs.^{72-73,77,79-81} On the other hand, the classification and designation of these multicomponent solid forms is still being discussed.^{67,79,82} Figure 6(a) shows a possible systematization of them with emphasis in the pharmaceuticals modifications. In this diagram, it is assumed that the API contains one or more ionisable functional groups and it is implied that all of these forms can exhibit polymorphism. Hydrates and solvates, for example, are the most common form in crystallization screens⁸³ and it occurs when the solvent molecules from crystallization medium are included in the lattice.⁸⁴⁻⁸⁶ Similarly, aggregation of neutral compounds with the active ingredient via supramolecular synthons⁸⁷ originate co-crystals.^{72,79} On the other hand, the ionization of species as a result of the association in the solid results in the formation of salts.^{72,88} As described by Grothe and co-authors⁸², the crystalline multicomponent forms can be classified into co-crystals, salts, solvates and sub-classes formed by their combinations (Figure 6b). As focus of this thesis, the following sections will depict in details the definition of polymorphs, pharmaceutical hydrates, and pharmaceutical salts.

Figure 6 - (a) Obtaining different solid forms of APIs. (b) Classification for different solid forms of APIs.

Source: (a) Adapted from CHERUKUVADA et al.⁸⁹; (b) Adapted from GROTHE et al.⁸².

Regardless of the solid form, the North American federal agency Food and Drug Administration (FDA), responsible for protecting and promoting public health, requires the full characterization not only of the API, but also of its different solid forms. This control has to be carefully performed as an attempt to prevent structural changes that may hinder manufacturability of the final pharmaceutical product.^{76-77,90} Then, this is a crucial stage in the development of new solid forms in order to prevent the appearance of unexpected phases after the approval of a drug.⁸¹

Also, the impact on the economy is another aspect to be carefully considered due the diversity of solid forms of API, once the appearance of new solid forms may provide reduced costs to the development of the pharmaceutical product, consequently causing the cheapening of the product and thus stimulating competition among industries.⁷² Another important aspect of the development of new solid forms extends to the domain of the intellectual property field. Since API's modified forms may have different properties, they can be considered as a technological innovation. Thus, patent protection applications may be performed, ensuring to the inventor exclusive rights over the new generic solid form.⁹¹⁻⁹⁴ In this field, polymorphism of APIs is focus of intense discussion, in a fashion that the pharmaceutical relevance of polymorphism has got particular attention.⁹²⁻⁹³

In the last decades, the research on new APIs for drug have been recognized as important for the attainment of technological innovations, despite the increasing requirements and regulatory requirements by governmental agencies.^{77, 88, 92} Also, it impact the discovery and development of new drugs. This process involves a screening a large number of candidate compounds produced over many years. These protocols require the selection and optimization of a suitable solid form of candidate for the pharmaceutical formulation and, are, generally,

carried out in years of research. Selection of an adequate solid form influences the candidate's pharmacokinetics, especially the absorption and bioavailability, thereby modifying or modulating their pharmacodynamics and toxicity. This is the reason why regulatory agencies have begun to treat new salts of registered APIs as new chemical entities, requiring, in essence, an evaluation of these pharmaceutical salts.

1.5 Polymorphism of Pharmaceutical compounds

In molecular crystals, the organic compounds are held together by multiples chemical interactions^{72,87,95–96}, thus, a large number of free-energy states are possible to exist. Polymorphism is the ability of a molecule to crystallize in more than one crystal arrangement.^{76–77,80} Thus, polymorphs are crystalline phases that have identical chemical composition but different crystal structures.^{76–77, 97} Usually, APIs present a diversity of functional groups on their structures and, as a result, many of them can be polymorphs.

Although the phenomenon is still a challenge in terms of prediction and obtaining^{80,98}, a variation in crystal structure and, hence the occurrence of polymorphs, have been related to several structural and conformational features of molecules, providing diversity of molecular packing. In parts, the packing of molecules is defined by the molecular structure itself and also by the possibility to form different stable supramolecular assemblies. Therefore, as defined in the context of the Gibbs' Phase Rule, the polymorphs will present different lattice energies, by at most a few kJ mol^{-1} .^{99–102}

It follows from this definition that a pair of multicomponent crystals with identical composition but different crystal structures can be correctly classified as polymorphs. In the pharmaceutical context, it is estimated that 50% of the multicomponent drugs exhibit polymorphism^{76,78} and the propensity for polymorphism in multicomponent crystal remains a subject of interest and debate. An even more recent CSD analysis allowed to conclude that co-crystals were found to be just as likely of being polymorphic as single component systems^{101,103}, although they might be less recurrent with respect to polymorphism, such as solvates/hydrates, when compared with their parent components.

Considering the chemical stability and safety principles (*e.g.*, behaviour to processing and formulation), unexpected polymorphic transformations of API are undesirable during manufacturing or administration, since this can affect biological availability of the API or its therapeutic effectiveness. A classical case is known for the anti-HIV drug Ritonavir. In the 90's, this drug withdrew due the unexpected appearance of a new crystal form in its

manufacture, that had different dissolution and absorption characteristics from the standard product. These two phases were distinguished and, posteriorly, were identified as polymorphs.⁷⁷ In this case, maybe many billions of dollars could be saved if, for example, instead of driving efforts to recover the original polymorph, scientists tried to regain the original drug by formulating it as a salt, which does not exhibit polymorphs during manufacture.⁷⁶⁻⁷⁷

With a view to understand and control the nature of polymorphs, it is crucial the establishment of their relative thermodynamic stability¹⁰⁴⁻¹⁰⁶ and the analysis of the kinetic factors' influence for the phase stability and the formation of each or concomitant phases. This because although the steps of nucleation and growth kinetics are decisive in crystallization¹⁰⁷⁻¹⁰⁸, often, it is possible that kinetic factors override thermodynamic considerations^{106,109}, resulting in some case in the appearance of concomitant polymorphs.¹¹⁰ Since the nucleation and growth of an individual form is sensitive to a series of factors¹⁰⁷, often the outcome of crystallization of determined polymorph is featured by fastest growing form (kinetic form) and not by the thermodynamically more stable. Besides these factors, the occurrence of a given polymorph have been related to a number of factors that guide its diversity of cases such as (a) conformational flexibility of the molecule ("conformational polymorphism"¹¹¹⁻¹¹³), (b) packaging diversity (*e.g* due to the presence of different Z' ¹¹⁴⁻¹¹⁶), and (c) racemic units (only chiral systems; "*racemic polymorphism*"). The *conformational polymorphism* denotes the case where distinct molecular conformations result in various crystal forms.¹¹³ Otherwise, in the case of chiral compounds, *racemic polymorphism* denotes the of occurrence of different racemic systems, by the possibility different racemic packing.¹¹⁷

With respect to the evaluation of the thermodynamic stability of polymorphs, several techniques have been applied for this purpose¹⁰⁵, being divided into direct and indirect. Direct measurements involve the observation of phase transformation due to the storage at various temperatures of slurry conversion/solution-mediated transformation.^{68-70,76,118} Indirect measurements can be mainly performed by using solubility or thermal analysis experiments.¹¹⁹⁻¹²¹ Beyond the recognition of the most stable polymorph, the relationship between the different phases of a system is the most important information to pharmaceutical sciences. For that, the application of the established stability rules, such as the heat-of-transition rule, the heat-of-fusion rule, density rule, and/or infrared rule are useful.^{72,92,104,122}

Finally, one last valuable approach concerning polymorphs is the construction and use of the Energy/Temperature (E/T) and Pressure/Temperature(P/T) diagrams, derived from the

Gibbs' fundamental equation ($\Delta G = \Delta H - T\Delta S$).¹⁰⁵ For this purpose, a wide characterization of both phases is necessary (*m.p.*, melting enthalpy, Variable-temperature X-ray diffraction, infrared spectroscopy, etc.).^{105,123} By definition, enantiotropic polymorphs suffer phase transitions as a function of the temperature, while in the monotropic polymorphs only one polymorphic form is stable over the entire temperature range up to the melt. Various empirical rules have also been applied in the assignment of relative stability, including density, heat of fusion and infrared rules¹²³. In enantiotropic systems, the higher melting structure has the higher melting enthalpy and in monotropic systems it is observed the opposite situation. It means that enantiotropic systems can exhibit interconversion of phases at temperatures below the melting of the polymorphs. This transition temperature represents a point at which the difference in the free energy between the two forms is zero. On the other hand, in the monotropic systems, the transition temperature is virtual and “occurs” after the melting of the phases.

McCrone stated that the polymorphic diversity of a molecule (number of polymorphs identified) is directly proportional to the time and the efforts spent in researching them.¹²⁴ In this context, the search for polymorphs has been assigned in many approaches, including transitions mediated by the solvent, recrystallization induced by temperature and pressure (Solvothermal synthesis), mechanochemical experiments, among others. Often, polymorphs can be also serendipitously obtained.^{72,80,122} However, as well as for others solid forms of a drug, a paradigm still remains: although the variation in physicochemical properties between the polymorphs is well recognized, no one knows how different these physicochemical properties would be modified a priori. Thus, it is ideal to try to obtain as many as possible polymorphs, in order to provide important information of how to influence the crystallization of one polymorph over another one.

1.6 Pharmaceutical hydrates

Pharmaceutical hydrates consist in molecular systems that have, stoichiometrically or not, water molecules incorporated into their crystal lattice.^{84–85,122,125} To the market, these multicomponent forms have their value, when considering that about 33.3% of the APIs are delivered as hydrates^{69,85–86,126} The formation and structure of solid-state hydrates, even when composing mixed forms with salts and co-crystals, continues to be an important topic in Pharmaceutical Sciences and Industry.^{76,127–131} From a structural viewpoint, the water molecule fulfils four main roles in the structure of solids¹²⁷: (i) it acts as an acceptor and/or a

donor agent in hydrogen bonding schemes, (ii) it fills void spaces, (iii) it completes coordination around metal ions, and (iv) it acts as a bridge among polar and non-polar regions in the crystal.

Given the stabilizing function of the water molecule, typically, the formation of hydrates consists of a fragile thermodynamic equilibrium (enthalpy *vs.* entropy) in which there is a net increase in favorable intermolecular interactions, hence improving the packing efficiency within the three-dimensional framework.^{84–85,128} The presence of water molecules can alter the free energy of a crystal structure and, consequently, can result in the occurrence of different physicochemical properties from those of the corresponding anhydrous phase.^{84–85,128} Also, physicochemical, processing, mechanical and compression behaviour may also be modified. For example, in stoichiometric hydrates, where the water molecules have a crucial role in the maintenance of the crystal lattice, the removal of these water molecules will lead to a total collapse of the structure that, subsequently, can either stay as an amorphous phase or can re-crystallize as a new crystal form with a reduced water content, thus undergoing a phase transition. In non-stoichiometric hydrates, on the other hand, the dehydration of is not accompanied by phase transitions neither amorphization. It is usually related with crystalline structures in which the host molecules are arranged in a fashion of constituting channels, through which the water molecules may easily diffuse, without interfering in the maintenance of the crystal lattice.^{84,132}

In this context, the importance of having a broad spectrum of characterized hydrates is the fact that hydrated APIs can be dehydrated during the manufacturing process generating additional phases, such as anhydrous, amorphous, or even polymorphs.⁹⁰ Particularly, in the drying and storage steps, a considerable proportion of water can often be removed, disturbing the crystal network. When, luckily, it is a reversible process, the dehydrated crystals can subsequently rehydrate resulting in the initial crystal form. If not, an entire batch of the pharmaceutical product can be lost and the desired properties never found again. The literature reports many issues regarding these dehydration/hydration processes. One of the most noteworthy cases was reported to the antidepressant drug PRX HCl. The control of the anhydrous/hydrate forms and the lack of a reversible dehydration process generated the historical and classic case of patenting disputes between important pharmaceutical corporations. The patent of the hemihydrate form of this antidepressant (Paxil®) was originally owned by GlaxoSmithKline Beecham Corporation and was ended in the late 90's. In an attempt to early access the generic drug, in 1998, the Apotex Corporation submitted a new application for an abbreviated generic drug, the anhydrous Paxil, based on the anhydrate

form of PRX hemihydrate. This patent filed the certification that its proposed product would not infringe the original patent of the PRX hemihydrate product. However, GSK claimed that Apotex's anhydrate version naturally converts into the hemihydrate version, making it likely that there would be some hemihydrate in Apotex's product, therefore infringing the patent.^{76–77,133} After years of dispute, the anhydrous/hydrate conversion for the antidepressant still remains under investigation on various aspects.^{26–27,56}

Given the complexity of the dehydration events, the control of the hydrate/anhydrous conversion can generate many scientific challenges as those related to polymorphic transitions. Therefore, in order to produce only a given desired form, it is very important within the pharmaceutical industry to characterize and to understand the diversity of solid forms that can be accessed by a given molecule, in a fashion of establishing reliable and reproducibly for each solid form.^{72,83} As part of this, one final consideration concerning hydrates is related to the tendency for salts and/or co-crystals to crystallize as hydrates.^{85–86,125,134–135} About 1/3 of API are capable of forming crystalline hydrates.^{126,136} As for the other topics, there are many researches focused in correlating the structural features salts/co-crystals with hydrate formation. For example, Haynes and co-authors¹³⁰ have studied the hydration behaviour of salts formed by the association of the NH^+ cation from a pyridine or an amine (1° , 2° and 3° substitution at nitrogen) with the following pharmaceutically acceptable anions: halides, carboxylates and carbonates ($\text{CO}_2^-/\text{CO}_3^{2-}$), sulfates and sulfonates ($\text{SO}_4^{2-}/\text{RSO}_3^-$), phosphates ($\text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}/\text{PO}_4^{3-}$), nitrates (NO_3^-), and thiocyanate (SCN^-). In addition, there are also important researches focused toward investigating the formation of water motifs and $(\text{H}_2\text{O})_n$ clusters.^{137–141} For example, Infantes¹⁴² has systematized the different patterns of water clusters from structures deposited in the CSD. By considering these two examples, it is possible to observe, in Figure 7, the main conclusions and implications resulting of these researches. The plot (a) of Figure 7 was constructed by considering the percentage of hydration as a function of the involved cation group, and allow to conclude that (i) the amount of hydrates derived from halide salts is significant in all the anions ($> 13\%$), (ii) having a maximum when involving the pyridinium group (34.8%) (iii) except for pyridinium, sulfate and phosphate salts have a greater number of hydrates in all cases. The plot (b) of Figure shows the main patterns of water clusters surveyed within the CSD. The most predominant patterns are found for discrete clusters as 4-membered water rings, and in chains with a repeat unit of 4 waters.

Figure 7 - (a) The occurrence of pharmaceutical salts of N-based compounds with acceptable GRAS anions. (b) The most frequent (H₂O)_n clusters observed in organic molecular crystals of the CSD.
Source: (a) Adapted from HAYNES et al.¹³⁰; (b) Adapted from INFANTES et al.¹⁴².

1.7 Pharmaceutical salts

The term '*Pharmaceutical salt*' refers to an ionisable API molecule associated with counter-ions by a charge assisted hydrogen bond (CAHB) to form a neutral complex. These salts are often a good alternative when the neutral form of the API is not optimal for dissolution and/or body absorption. Because the properties of salts can be modified by switching the counter-ion, the design of different pharmaceutical salts can be a streamlined process supported by the crystal engineering of CAHB. The salification of an API with different counter-ions find applications in diverse steps of drug formulation^{72-73,88,143-145}, such as a purification technique, for the removal of impurities, racemic resolution, diastereomeric salt formation, and fractional crystallization, beyond being a standard operation performed during drug development. Converting a neutral API into a salt can result in significant gains to the pharmacokinetic profile of a drug, such as increased chemical stability and absorption, more feasible manufacturability and administration.¹⁴⁶ Therefore, salification emerges as an improver for undesirable properties, in a fashion that the discovery/development of the optimum salt form highlights its importance for quality, safety, development, and performance of its respective API.

The versatility of the salt formation process has encouraged a rapid increase in the amount of APIs produced in the form of a salt, so until the present it is estimated that almost 50% of all drug molecules utilized in drug therapy are administered as salts.⁷² The properties of the counter-ions can significantly affect the pharmaceutical properties of the API and can greatly benefit chemists and formulators in the various facets of drug discovery and

development.^{72,88,123} The FDA recognizes about 120 species, among acid and bases, in a fashion that the choice of the salt former is limited by safety considerations, as dictated by the Generally Regarded As Safe (GRAS) list of substances. Pharmaceutical companies previously selected salts at various stages in drug development^{88,123,146–147}, however, companies now tend to move the salt-selection process to the research phase to make the process more foolproof. Ideally, the salt form should be chosen before the long-term toxicology studies (*i.e.*, at the beginning of Phase I clinical trials).^{123,147}

In 2007, the Saal's groups¹⁴⁸ have reported the distribution of pharmaceutically acceptable counterions for the period of 2002-2006, in the Orange Book Database (OBD)¹⁴⁸, which includes only pharmaceutically acceptable species. These results are presented in Figure 8 together with a corresponding CSD analysis performed by Haynes in 2005.¹⁴⁹ In both surveys, the hydrochloride is the most prevalent ion, accounting for 38% of the FDA approved pharmaceutical salts and 54% of the organic salts in the CSD. However, despite its prevalence, researches also show that this ion has been replaced by different counterions, such as for the bromide one, listed as the second most frequent occurring anion, accounting 26% of the pharmaceutical salts present in the OBD, and 7% of organic salts in the CSD. Also, organic anions (including acetate, tartrate, oxalate, citrate, formate, maleate, succinate, malate and fumarate ones) totaling 29% of the pharmaceutical salts approved by the FDA (corresponding to 9% in Haynes survey). Similarly, sulfonate species also exhibit a significant percentage of pharmaceutical salts (~17%). Such behavior is a result of the intensification of the research concerning the optimization of APIs, and highlights the importance of selecting an appropriate dosage form for a drug compound.

Figure 8 - The occurrence (%) of pharmaceutically acceptable anions in organic salts on the (a) CSD and (b) Orange Book Database (OBD) as found for HAYNES¹⁴⁹ and SAAL'S¹⁴⁸, respectively.
Source: (a) Adapted from HAYNES et al.¹⁴⁹; (b) Adapted from SAAL'S et al.¹⁴⁸

In the supramolecular synthesis process of multicomponent crystals, particularly to prediction whether a co-crystal or salt can be formed, the ionisation state of API is established by its pK_a value. Although this parameter indicates a solid/aqueous equilibrium condition, the formation of salts in the solid state is reliably found when the difference between the pK_a of the salt formers is high enough. This approach is named the pK_a rule and it is defined by $\Delta pK_a = pK_a(\text{conjugate acid of the base}) - pK_a(\text{acid})$. Beyond just cocrystals and salts, the multicomponent forms of API include also mixed crystal forms such as the salts-cocrystals. One of the first cases was reported for Fluoxetine in which the Fluoxetine hydrochloride was cocrystallized with carboxylic acids like benzoic, succinic and fumaric acids.²⁸ These forms show not only improved stability but also a significant improvement in the solubility and dissolution profiles.

A final, but crucial topic concerning pharmaceutical salts is their versatility, which can support the increase in generic drug production.

Since different salts of a given API can be similar in performance, they can, and indeed they have been, marketed in more than one salt form as therapeutically equivalent drug products. This approach fits well in the field of intellectual property since different salts have different properties, they can be considered as scientific innovation and possess utility, therefore, it can be patented. Pharmaceutical salts can be patented when combined as part of a proprietary drug product. A new salt form may alter the way a drug is delivery or even it dosage form.

To exemplify how pharmaceutical salts is challenging the patents of the originator, Olazepine, an atypical antipsychotic and Diclofenac, an antiinflammatory, are good cases. Diclofenac sodium salt was originally marketed orally as the brand Voltaren. However, other salts, like diclofenac epolamine, exhibiting good skin penetration, were also developed and patented. Today Diclofenac transdermal is one of the new diclofenac salt forms approved and marketed in the US. Omeprazole was originally developed in a capsule dosage form, but was later formulated into a tablet after it was combined with a magnesium salt. A new patent timeline would be issued with the new molecular entity.

In spite of the numerous advantages associated with salt forms, developing them is not always feasible. The preparation of a stable salt may not be possible for some drugs, and, although predictable, its synthesis is not obvious. However, this setback is not so negative since non-obviousness is one of the three main criteria concerning patent issues followed by utility and novelty. It is, therefore, important to understand the essential principle that salts formed either by the sharing of electrons or ionic association between the neutralization agents (counter-ion and ionizable API).

1.8 Crystal Engineering and Supramolecular Chemistry

The screening of different crystal forms for a given API has become an integral part of the pharmaceutical sciences guided by the crystal engineering.

Because different crystalline forms of an API can differ in their physical properties, it is imperative to find out an optimal phase for the targeted application.^{101,150} For this reason, the understanding of the diversity of solid forms that can be accessed by a given molecule and the preparation routes that can produce each solid form in a reliably and reproducibly way, are of estimated scientific interest.⁹⁶

As defined by Gautam Desiraju¹⁰⁹, a pioneer in the supramolecular chemistry field, crystal engineering is “*the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties*”. This concept states that the properties of the compound depend on the structural arrangement of its molecules in the crystal, so modifying its crystal structure by the control over its intermolecular interactions allows to rationalize the design of new crystals exhibiting specific features. This opened the doors to the design and develops of tailor made materials. Noteworthy, the crystal packing of a molecule represents a delicate equilibrium between conformation and chemical interactions, as well as its

thermodynamic behavior comprises tendencies toward low energy and high entropy ($\Delta G = \Delta H - T\Delta S$).

Chemical interactions, *i.e.* hydrogen bondings, van der Waals forces, hydrophobic forces, electrostatic forces, and π - π interactions, are the fundamental principles of molecular recognition and auto-assembly of molecules in crystals.^{96,151-153} The potential of crystal engineering and materials science applied to optimize the performance of drugs occurred in the first part of the 21st century, as part of an emerging interest into the co-crystallization of pharmaceutical compounds, by the Pharmaceutical Industry and the Academy, followed by polymorphs, hydrates, salts and amorphous materials screenings. Particularly for the synthesis of salts and co-crystals, a considerable effort has been directed towards understanding the relationship between the intermolecular interactions and the classes of compounds, leading to new approaches for engineering crystals. Among these, a valuable approach to design new solid modifications of an API is to identify the association between complementary chemical entities in terms of their structural motifs, leading to the formation of "*synthons*".^{73,91,129,154} Figure 9 summarizes the steps usually adopted in the search for these synthons, particularly for the synthesis of salts and co-crystals: (1) identify in the API molecule the main functional groups, (2) draw these functional groups separately, (3) insert these functional groups in systematic searches in the CSD in an attempt to select the most probable coformers, (4) validate which coformers are indeed capable of interacting with the API molecule, and (5) perform crystallization screenings by utilizing as many as possible crystallization.^{146,155} Although this has been being a very successful approach in the present, a major challenge in this field still lies in understand the parameters that control the self-assembly of molecules, which act as molecular building blocks for synthetically designed new materials.

Figure 9 - Steps of designing of new solid forms of API- emphasis on obtaining salts

Source: By the author.

1.9 Goals

This thesis focuses on the supramolecular synthesis and characterization of new solid forms of antidepressant APIs. Due to clinical relevance and unfavorable pharmaceutical properties, such as solubility and stability, Paroxetine and Fluoxetine antidepressants from Selective Reuptake Inhibitors Serotonin (SSRI) class were chosen for screening of new solid forms. The lack of studies of new solid forms also motivated the selection of these compounds.

The thesis goals are: (a) to develop new solid forms for Paroxetine and Fluoxetine by supramolecular synthesis based on engineering techniques of molecular crystals; (b) to characterize and elucidate new solid forms and polymorphs using, primarily, the X-ray crystallography and also applying complementary techniques; (c) to recognize chemical, conformational and supramolecular aspects of the new solid forms; (d) to establish relation between physical properties, such as solubility and thermal behavior, and crystal structure for these new solid forms.

2 MATERIALS AND METHODS

2.1 Supramolecular synthesis and selection of salt formers

Structurally, PRX and FLX present secondary amine groups, $-\text{NH}_2^+$, on their structure. This feature gives to these compounds a high basic character (PRX, $\text{pK}_a = 9.8$ and FLX, $\text{pK}_a = 10.8$). For both compounds, the $-\text{NH}_2^+$ is the only group capable of forming hydrogen bonds (HB). Thus, the design of new solid forms of PRX and FLX was designed to involve mainly the formation of salts via CAHBs with the $-\text{NH}_2^+$ group. For this purpose, the search and statistical analysis of the of possible synthons and salt formers were performed on the CSD.⁵² The search for structures having secondary cyclic e aliphatic amine analogue structures and CAHB associated to protonation of them were performed. Also, the packing feature provided by such CAHBs were also evaluated.

The results of these searches were in agreement with the Haynes and co-authors¹³⁰ observations (see section 1.7). Based on this starting search, it could be noted that the association of the secondary N-based organic salts in the CSD with the bromide, nitrate and sulphate are the most occurring pharmaceutically acceptable anions. In a supramolecular view point, the $\text{N}-\text{H}\cdots\text{X}$ ($\text{X} = \text{Br}^-$ and NO_3^-) tend to generate one-dimensional chains similar to those provided by the hydrochloride salts of PRX and FLX. Additionally, the tendency of hydrate formation for N-based compounds was also considered. For the antidepressants of this study, the inclusion of water molecules was rationalized as a way to balance the deficiency of H-bond donor groups. Furthermore, the conformational multiplicity was another parameter considered to design the salts. Both, PRX and FLX are flexible molecules and this aspect is able to provide different crystal arrangements and packings. Particularly, the chirality of FLX was also considered as a valuable variant capable of generating a wide diversity of new solid forms. Thus, from these analysis, and by considering complementary features such as charge, ionic sizes, and occurrence of the anions as salt formers, the HBr and HNO_3 acids were chosen for synthesizing new salts of PRX and FLX. Taking into account the solubility of the APIs, the crystallization protocols were performed utilizing mixture of solvents containing water: acetone, methanol, ethanol (98% and 70%), isopropyl alcohol and dichloromethane. Several crystallization screenings were performed in an attempt to obtain the best crystallization conditions, also considering the influence of the methodologies for polymorph, anhydrate and hydrate formation. Due to the pharmaceutical relevance, only solvents of class 3 from list of solvents included in the q3c guidance were used in the crystallization trials.

2.2 Crystallization screening

Before synthesizing the new salts of PRX and FLX, it was necessary to produce deprotonated forms, *i.e.* free bases, of these compounds from their respective commercialized chloride salts, (PRXCl) $\cdot$ 0.5H₂O and FLX HCl. This proceeding consisted in reacting the chloride salts of each API with an excess of sodium hydroxide. By solubility difference, the free bases of these APIs precipitate and then can be extracted in ethyl ether.

Once extracted the free bases, the crystallization proceedings with the HBr and HNO₃ acids could be initiated. For this, the free bases were initially dissolved in a mixture of water/ethanol, by considering their tendency to form hydrates and in order to favor the reaction. For both APIs, the addition of the acids promoted the immediate and complete solubilization of the free bases. After solubilization, all the systems were kept at rest. It is worth mentioning that all the crystallization experiments were conducted in the same way, utilizing 5, 10, and 20 mL flasks, but variations in temperature storage and evaporation rate were applied. Three different temperatures were chosen (-2, 10 e 25 °C) and three sealing methods were adopted (closed with Parafilm®, semi-closed – performing roles in the Parafilm®, and opened). For synthesis performed with the HBr acid, crystal growth was only observed for the PRX antidepressant, being the optimal condition for this crystal growth obtained at 25° C using ethanol/water in a 50:50 ratio. For synthesis performed with the HNO₃ acid, both antidepressants presented crystal growth. For PRX, the best crystal growth condition was observed at -2°C using ethanol/water in a 20:80 ratio. On the other hand, depending of the temperature, polymorphs were obtained for FLX nitrate, exhibiting different morphologies (Figure 10). Unfortunately, experiments with HBr and FLX did not result in any novel solid forms, even after changing the solvent and the stoichiometric ratio of the precursors.

Figure 10 - Synopsis of the main crystallization experiments performed for PRX and FLX. The figures show the morphology of the resulting crystals from the experimental procedure and 'x' indicated when no solid forms were obtained.

Source: By the author

2.3 Solid State Characterization

After obtaining crystals of the rationally designed salts for PRX and FLX, a complete solid-state characterization was performed, based on the following techniques and methodologies:

- (1) **Thermal Polarized Microscopy.** For the characterization of the new solid forms, the following methods can be utilized: polarized light optical microscopy, thermal polarized light microscopy, and scanning electron microscopy. These techniques enable the visualization, among others things, of the crystal habit and the screening of new polymorphs. Also, the hot/cold stage allows visualizing the behavior of the crystal in function of the temperature.
- (2) **Single Crystal X-ray Diffraction.** This technique provides the three-dimensional structure of crystalline forms. As this thesis deal with the supramolecular synthesis of new solid forms of APIs, single crystal X-ray diffraction allow the interpretation and analysis of the structural data, in particular, the intermolecular interactions holding the new crystalline arrangements. In addition, this technique allows identifying and differentiating polymorphs. Although most of the data collection were performed in the Physics Institute of São Carlos (IFSC/USP), specific data collections were performed in collaboration with the Department of Chemistry of the Durham University. These data collections were performed in an attempt to verify the

occurrence of phase transitions as well as other structural changes associated with temperature variations. Data collection at 120K and 298K were adopted as patterns. Nevertheless, the absence of structural alterations among these temperatures leads us to choose the low temperature structural data to be used for the structural analysis of the new salts. In particular, for the PRX HBr salt, this technique proves the occurrence of a reversible hydration/dehydration process.

- (3) **Thermal analysis.** Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) are thermal techniques applied to distinguish polymorphs, and are based on the principle of those phase transitions that the crystal undergoes with heating. The DSC measures the energy absorbed/released by the sample when it is heated, cooled or held at constant temperature. The DSC and TGA curves indicate the thermal behavior of the polymorphic phases and thus constitute a parameter to distinguish them. Additional information such as phase transitions, relative stability, melting point, desolvation, crystallization and glass transition are also obtained and are important for polymorphic characterization. The results obtained from these two techniques can be directly compared with those obtained by using the thermal polarized light microscopy technique
- (4) **Solubility measurements.** These measurements are capable of providing parameters to guide the sequence of stabilities concerning identical phases, dehydration, and polymorphs. The applied proceedings in this thesis was performed by the flask saturation method¹⁵⁶, which consist in promoting the supersaturation of a solution in thermodynamic equilibrium. The solubility experiments were all performed via UV spectroscopy.
- (5) **Infrared Spectroscopy.** The Infrared spectroscopy (IR) results in specific and characteristic spectra highly dependent of the structural features of the various solid forms. In the solid state, this spectroscopic technique allows to characterize polymorphs of APIs, beyond being able of characterizing solvates and isomorphic dessolvates. In addition, information related to structural and conformational features of the solids can also be identified.

3 PAPERS

The discovery and characterization of new solid forms has a significant impact in materials and pharmaceutical sciences. Pharmaceutical salts, for example, are multicomponent solid forms of high demand and importance among drugs (*c.a* 50% of marketed drugs). The salt formation is often used to preparation of new pharmaceutical solids to overcome drug delivery problems, such as stability, solubility, polymorphism, among others. In this context, this thesis investigates the application of crystal engineering to supramolecular synthesis of pharmaceutical salts of antidepressants Paroxetine and Fluoxetine. These APIs have low solubility and stability. To this end, a screening for multicomponent solid forms of these compounds using inorganic acids lead to obtaining four novel pharmaceutical salts: Paroxetine HBr Hemihydrate, Paroxetine Nitrate hydrate and Fluoxetine Nitrate polymorphs ($Pca2_1$ and $P2_1/c$). All new crystal structures were solved using single-crystal x-ray diffraction technique. The crystal structure analysis accompanied by thermochemical and solubility study allowed us to study three cases that compose this thesis, *i.e.*, a reversible case of dehydration to Paroxetine HBr hemihydrate, the crystalline structure of Paroxetine Nitrate hydrate and the polymorphism of Fluoxetine Nitrate. A total of three papers are presented here, as part of the results obtained for the antidepressants PRX and FLX.

In the first paper, the crystalline structures of $PRXBrH_2O$ and its respective dehydrate are depicted. This salt is isostructural to the commercialized form of this API, the $PRXCl0.5H_2O$. The reversible hydration/dehydration solid phase transitions for the bromide salt was explored and correlated to the structural features of the anhydrate form. This analysis provides information concerning controversial case of the non-reversible dehydration process of the chloride salt form which is even today subject of discussions.

In the second paper, the crystalline structure of the HNO_3 PRX is depicted as a solid form exhibiting a different conformation of the PRX molecule, in a C-centered crystalline lattice. Supramolecular features are explored and related with the physicochemical properties, such as melting point and solubility. In comparison with the marketed chloride salt form, this new form showed to be less stable and soluble.

Finally, the third paper depicts a very rare case of racemic polymorphs occurring for the HNO_3 FLX salt: a racemate ($P2_1/n$, $Z=4$, $Z'=1$) and a non-centrosymmetric structure with both independent enantiomers in the asymmetric unit ($Pca2_1$, $Z=4$, $Z'=2$). This phenomenon is discussed in terms of the ability of the FLX enantiomers to pack involving different racemic

supramolecular motifs. This study allowed to face this phenomenon as rare, by considering the low incidence in literature reports concerning racemic systems in non-centrosymmetric space groups. The relative stability of these polymorphs could be established through a combination of techniques, to know DSC, TGA, Hot stage Microscopy (HSM), and solubility measurements.

PAPER 1:

CARVALHO JR, P.S.; DE MELO, C.C.; AYALA, A. P.; DA SILVA, C. C. P.; ELLENA, J.
Reversible Solid-State Hydration/Dehydration of Paroxetine Bromide Hemihydrate: Structural and Thermochemical Studies, *Crystal Growth & Design*, 2016, 10 (6), pp 2734–2745

Reversible Solid-State Hydration/Dehydration of Paroxetine HBr Hemihydrate: Structural and Thermochemical Studies

Paulo S. Carvalho, Jr.,[†] Cristiane C. de Melo,^{†,‡} Alejandro P. Ayala,[‡] Cecilia C. P. da Silva,[†] and Javier Ellena^{*,†}

[†]Instituto de Física de São Carlos, Universidade de São Paulo, CP 369, 13560-970 São Carlos, SP, Brazil

[‡]Departamento de Física, Universidade Federal do Ceará, CP 6030, Fortaleza, Ceará 60455-970, Brazil

S Supporting Information

ABSTRACT: For active pharmaceutical ingredients (API) in the solid state, the occurrence of hydration/dehydration phase transitions may have implications upon the efficiency of the pharmaceutical product, once they are often accompanied by changes of physicochemical properties. Thus, it is important for pharmaceutical research and development to investigate these mechanisms based on the crystal structures of the API. In this work, beyond the structural characterization of a new salt of the antidepressant drug Paroxetine [an HBr hemihydrate, (PRX⁺Br⁻)·0.5H₂O], by single crystal X-ray diffraction (SXRD), thermal analysis (DSC/TGA), and hot stage microscopy (HSM), we were able to perform a complete investigation toward the reversible hydration/dehydration solid phase transitions occurring for this salt. In addition, solubility measurements for the anhydrous and hemihydrate solid forms of the new salt are compared with those of its isostructural hydrochloride hemihydrate salt, (PRX⁺Cl⁻)·0.5H₂O, for which hydration/dehydration processes are still not completely understood due to structure instability after dehydration.

1. INTRODUCTION

Hydrates constitute the most physically stable form of an active pharmaceutical ingredient (API) under conditions of relative humidity (RH).^{1–4} In the pharmaceutical context, it has been estimated that about one-third of API's are able to form hydrated structures⁵ wherein the water is incorporated, stoichiometrically or nonstoichiometrically, in the crystal lattice. An important aspect of these compounds is the possibility of hydrate/dehydrate transformations induced by environmental changes. During manufacturing and storage steps, the drug product is exposed to a range of temperatures and water vapor pressures where the interaction between API and the water makes this ordinary phase transition possible.^{2–4,6–9} Therefore, for practical and regulatory reasons, the search for the dehydrated phase(s) and the dehydration pathway are crucial to the development of a pharmaceutical product.^{3,8,10–12}

Dehydration is a complex phenomenon that can involve the formation of multiples solid forms. The removal of water from the hydrated lattice may result in three possible scenarios: (a) an anhydrous solid form, generated by collapse of lattice; (b) an isomorphic/isostructural dehydrate, generated by the retention of the molecular packing of the parent hydrate; or (c) the complete alteration of lattice packing. Despite the systematic contributions to the mechanisms of solid state dehydrations, the topic remains a challenge, mainly due to the nonobvious relationship between hydrate/anhydrous lattices and the reversibility of the process. Also relevant, the lack of theses information can cause serious intellectual property (IP) issues

in the end-use of a compound, as illustrated by a number of striking examples, such as the Paroxetine HCl case.^{13,14}

Paroxetine (PRX) (Scheme 1) is an important antidepressant agent, widely used in the treatment of depression, panic, and obsessive-compulsive disorders, posttraumatic stress, and general anxiety.^{15–23} Paroxetine HCl, the clinically utilized form of this API, can exist as a nonstoichiometric hydrate

Scheme 1. Chemical Structure of Charged Paroxetine (PRX⁺) with the Numbering of Non-Hydrogen Atoms^a

^aThe numerical atoms denomination for the two distinct conformers differ by adding the indices (').

Received: November 25, 2015

Revised: January 22, 2016

Published: January 28, 2016

(Form II), or as a hemihydrate (Form I, $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$). In the last decades, efforts to protect PRX's patent from generic competition led to a big IP issue.^{13,14,24,25} The production of the anhydrate from the $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ phase without the unknown conversion of anhydrous into hemihydrate was the core of patent litigations. The dehydration/rehydration process is complex, and even with concentrated efforts, it was difficult to control the presence of hemihydrate in the anhydrous product. Recent studies²⁶ have identified different anhydrous phases from the dehydration of Paroxetine HCl. Upon heating, Forms I and II give rise, respectively, to an anhydrous¹⁴ and an isomorphous dehydrate.²⁶ The reversibility of each dehydration process was observed at low relative humidity conditions.²⁶

In this study, with the aim of extending the solid state knowledge about PRX, we have rationalized the stability of Paroxetine HBr hemihydrate, $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$, with respect to its hydration/dehydration phenomenon. From a more fundamental point of view, the comparison between the isostructural $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ and $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ salts have provided important features about relative stability among those phases. Finally, insights concerning the mechanism of the hydration/dehydration processes occurring for PRX could be completely provided for the first time, at the best of our knowledge, by combining structural information, molecular packing analysis, and direct observations of crystalline properties based on Differential Scanning Calorimetric (DSC), Thermogravimetric analysis (TGA), Hot-Stage Microscopy (HSM) and Variable temperature Single-Crystal X-ray diffraction (VT-SC-XRD) experiments. It is worth mentioning that this complete description was still not reported for the parent $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ salt, due its crystalline instability after dehydration, thus hindering the complete understanding of its spontaneous dehydration/rehydration mechanism.

2. EXPERIMENTAL DETAILS

Paroxetine HCl was obtained from commercial sources and used without any further purification. The sample consisted of Form I (Hemihydrate), as determined by powder X-ray diffraction (PXRD) pattern^{27,28} and DSC analysis.^{14,29} Organic solvents (analytical or spectroscopic grade) were also purchased from commercial sources and used as received.

2.1. Supramolecular Synthesis of Paroxetine HBr. In order to be able of synthesizing the proposed new salt, the first step was the achievement of PRX free base. For this, $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ (Form I) was used as the starting material, being dissolved in water, treated with excess of sodium hydroxide, and followed by gradual addition of ethyl ether. The mixture was then stirred until two phases became clear. The organic phase was separated from the water fraction and the ethyl ether phase was dried over Na_2SO_4 . After removal of hydrated Na_2SO_4 by filtration, the evaporation of ethyl ether resulted in the oily free base of PRX. In sequence, 15 mg (0.045 mmol) of PRX free base was dissolved in 2 mL of ethanol 95%. After dissolution, 150 μL of HBr (1 $\text{mol} \cdot \text{L}^{-1}$) were added to the system. The mixture was left to stand at -2°C to allow for slow evaporation of the solvent. Colorless crystals appeared within a few days.

2.2. Single Crystal Determination Measurements. The crystallographic data for the $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ were collected on a Bruker Super-Duo APEX II CCD diffractometer³⁰ using MoK α radiation (0.71073 Å). X-ray diffraction data collection for the PRX^+Br^- dehydrate was performed on an Enraf-Nonius Kappa-CCD diffractometer (95 mm CCD camera on κ -goniostat) using graphite-monochromated MoK α radiation (0.71073 Å) and an Oxford Cryo Systems CryoStream 700Plus to control the temperature. Using the Olex2³¹ software, the structures were solved by direct methods and the models obtained were refined by full-matrix least-squares on F^2 (SHELXTL-97³²). All the hydrogen atoms were placed in calculated

positions and refined with fixed individual displacement parameters [$U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}$ or $1.5U_{\text{eq}}$] according to the riding model (C–H bond lengths of 0.97 Å and 0.96 Å, for methylene and methyl groups, respectively). Molecular representations, tables and pictures were generated by Olex2,³¹ MERCURY 3.2³³ and Crystal Explorer v2.1³⁴ programs.

The CIFs files of the $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ collected at -173°C , dehydrated at 87°C and rehydrated at 25°C were deposited in the Cambridge Structural Data Base³⁵ under the codes CCDC 1436946, CCDC 1436947, CCDC 1436953, respectively. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk.

2.3. Thermal Analysis. Thermogravimetric analyses were carried out on a Shimadzu TGA-60 thermobalance. Approximately 3.5 mg of sample were placed on an alumina pan and heated from room temperature up to 200°C , at $10^\circ\text{C} \cdot \text{min}^{-1}$, under nitrogen flow (50 $\text{mL} \cdot \text{min}^{-1}$). Differential Scanning Calorimetric measurements were performed on a Shimadzu DSC-60 instrument. Samples (3.5 ± 0.5 mg) were aluminum pans and heated from room temperature up to 296°C , at $10^\circ\text{C} \cdot \text{min}^{-1}$, under nitrogen flow (50 $\text{mL} \cdot \text{min}^{-1}$). All data were processed using the Shimadzu TA-60 thermal data analysis software.

2.4. Hot-Stage Polarized Optical Microscopy. Microscopy was performed on a Leica DM2500P microscope connected to the Linkam T95-PE hot-stage equipment. Data were visualized with the Linksys 32 software for hot stage control. $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ crystals were placed on a 13 mm glass coverslip, placed on a 22 mm diameter pure silver heating block inside of the stage. The sample was heated at a ramp rate of $10^\circ\text{C} \cdot \text{min}^{-1}$ up to a final temperature of 200°C and interrupted after the melting of material.

2.5. Fourier Transform Infrared Spectroscopy (FTIR). FTIR spectra were recorded on a PerkinElmer Paragon 1000 spectrometer using KBr disks. Each spectrum was an average of 64 scans from 4000 to 400 cm^{-1} at 2 cm^{-1} of resolution. The spectrum of a blank KBr disk was used for the background correction.

2.6. DFT Calculations. Considering the presence of two conformer of PRX^+ (A and B) in the asymmetric unit of $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$, the electronic structure of A and B conformers of $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ asymmetric unit was investigated within Density Functional Theory (DFT).^{36,37} Starting from the X-ray structure the hydrogen position optimization was carried out using the 6-311++g(d,p) basis set and, M062X functional.³⁸ This functional was chosen due to its well-established performance for both hydrogen bonds and dispersion interactions. The zero-point vibrational energy (ZPVE) contributions ($E(\text{A})_{\text{ZPVE}}$ and $E(\text{B})_{\text{ZPVE}}$) were not neglected and energy difference (ΔE) between the conformers was calculated according to equation: $\Delta E = [E(\text{A}) + E(\text{A})_{\text{ZPVE}}] - [E(\text{B}) + E(\text{B})_{\text{ZPVE}}]$ where ($E + E_{\text{ZPVE}}$) represent the sum of electronic and zero-point Energies. All calculations were performed using Gaussian 09³⁹ suite program.

2.7. Solubility. Aqueous solubility was measured in distilled-deionized water by the flask saturation method.⁴⁰ The saturated solution of $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ and $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ was prepared stirring a predetermined excess quantity (30 mg) of drugs in 400 μL of water for 24 h allowing to reach the thermodynamic equilibrium at 20 and 37°C . After 4 h of sedimentation, the solution was filtered through a 0.45 mm filter (Millipore). The concentration of supernatant was measured by UV spectroscopy. Samples were then diluted 100-fold in water before analysis. The specific absorptivity was determined in distilled water, at the selected wavelength of $\lambda_{\text{max}} = 293 \text{ nm}$ and the standard solutions used to generate the calibration curve were prepared using $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$. The concentration of the compound in the filtrate was quantified by interpolating of spectroscopic measurements from the diluted solutions in a calibration curve whose concentrations ranged from 0.005 to $0.2 \text{ mg} \cdot \text{mL}^{-1}$. The solubility of PRXBr was determined in 2-propanol at 20°C follow similar procedure.

Table 1. Crystal Data and Structure Refinement of (PRX⁺Br[−])·H₂O and (PRX⁺Br[−])

	(PRX ⁺ Br [−])·0.5H ₂ O	PRX ⁺ Br [−]
Empirical formula	C ₃₈ H ₄₄ Br ₂ F ₂ N ₂ O ₇	C ₁₉ H ₂₁ BrFNO ₃
Formula weight	838.57	410.28
Temperature/K	100(2)	360(2)
Crystal system	Monoclinic	Monoclinic
Space group	P2 ₁	P2 ₁
a/Å	12.9368(4)	12.9190(19)
b/Å	10.3393(4)	10.4970(10)
c/Å	14.3259(4)	14.5580(3)
β/°	107.464(2)	109.871(7)
Volume/Å ³	1827.87(11)	1856.7(5)
Z, Z'	4, 2	4, 2
ρ _{calc} (g/cm ³)	1.524	1.468
μ/mm ^{−1}	2.280	2.241
F(000)	860.0	840.0
Crystal size/mm ³	0.083 × 0.05 × 0.044	0.083 × 0.277 × 0.543
Radiation	Mo Kα (λ = 0.71073)	Mo Kα (λ = 0.71073)
2θ range for data collection/°	3.724 to 51.628	5.96 to 49.86
Index ranges	−15 ≤ h ≤ 15, −12 ≤ k ≤ 12, −17 ≤ l ≤ 17	−15 ≤ h ≤ 15, −12 ≤ k ≤ 11, −17 ≤ l ≤ 17
Reflections collected	30984	14094
Independent reflections	6893 [R _{int} = 0.0632, R _{sigma} = 0.0712]	6222 [R _{int} = 0.094, R _{sigma} = 0.05]
Data/restraints/parameters	6893/1/472	6222/1/461
Goodness-of-fit on F ²	1.027	1.012
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0370, wR ₂ = 0.0715	R ₁ = 0.0597, wR ₂ = 0.1498
Final R indexes [all data]	R ₁ = 0.0477, wR ₂ = 0.0747	R ₁ = 0.0903, wR ₂ = 0.1723
Largest diff. peak/hole/(e Å ^{−3})	0.35/−0.41	0.28/−0.44
Flack parameter	0.008(5)	−0.0071(2)

Figure 1. (a) Asymmetric unit of (PRX⁺Br[−])·0.5H₂O. The ellipsoids were drawn at 30% of probability, the disorder occurring in the molecules H₂O and Br1 was omitted for clarity, and dashed red lines refer to the N⁺–H···Br[−] and N⁺–H···O_w charge assisted H-bonds. (b) Overlap diagram of A-PRX⁺ (green) and B-PRX⁺ (yellow) conformers at their solid-state geometries, as determined by the diffraction experiment at T = −173 °C. The hydrogen atoms were hidden for clarity. The main conformational discrepancies are related with the C6–O4–C7–C8 torsion angle. (c) Asymmetric unit of (PRX⁺Br[−]). The ellipsoids were drawn at 30% of probability, the disorder occurring in the Br1 anion was omitted for clarity, and dashed red lines refer to the N⁺–H···Br[−] charge assisted H-bonds.

3. RESULTS AND DISCUSSION

3.1. Structural Description. A detailed description of the (PRX⁺Br[−])·0.5H₂O and (PRX⁺Br[−]) structures is depicted below. Table 1 exhibits the crystallographic data for the structures. The main intermolecular interactions for each salt are listed in Table S1 (Supporting Information). In Figure 1, a view of the asymmetric unit of each salt is shown.

Paroxetine HBr Hemihydrate Salt. The (PRX⁺Br[−])·0.5H₂O was successfully prepared by considering the similarity between the bromide and chloride anions. The salt was obtained by the simple acid–base reaction between the PRX free base and the HBr acid. The (PRX⁺Br[−])·0.5H₂O crystallizes in the monoclinic Sohncke space group P2₁ with two protonated PRX⁺ molecules (A and B), two Br[−] anions, and one crystallization

water molecule in the asymmetric unit, exhibiting Z' = 2 (Figure 1a). The A and B molecules constitute different conformations of PRX⁺. Therefore, two nonequivalent PRX⁺Br[−] ionic pairs are present in the crystal structure, with one of the Br[−] anions and the water molecule disordered. The PRX⁺ molecular skeleton is dominated by σ-bonds. Then, this compound has a significant conformational flexibility that leads to conformational differences between conformers A and B. Figure 1b shows the main differences between the PRX⁺ conformers, which were superimposed through their piperidinium moieties. The conformers differ by the orientation of the C6–O1–C7–C8 torsion angle [A: −147.4(4)° and B: −40.8(7)°, respectively]. Moreover, the five-membered 1,3-dioxolane rings (ring C) adopt different envelope conforma-

tions with puckering coordinates⁴¹ $Q(2)A = 0.4196$, $\phi(2)A = -46.90^\circ$ for the A backbone and $Q(2)B = 0.5103$, $\phi(2)B = -44.91^\circ$ for the B one. Nevertheless, both conformers are very close in terms of energy, with the B being more stable than the A conformation by just $2.41 \text{ kcal}\cdot\text{mol}^{-1}$ at the M062X/6-311++g(d,p) theory level.

PRX⁺ lacks strong H-Bond donor functions, in a fashion that just two possible N⁺–H hydrogen bond donors are available, belonging to the NH₂⁺ group (Scheme 1), and is involved in charge assisted H-bonds (CAHB) of the types N⁺–H $\cdots$ Br[−] and N⁺–H $\cdots$ O (Figure 1a). As could be observed, in the crystal packing of (PRX⁺Br[−])·0.5H₂O the water molecules play a key role in the formation of the main motifs between the PRX⁺ conformers and the Br[−] anions, acting as ionic pair connectors. Along the [010] direction, a one-dimensional supramolecular C_s⁵(10) motif (highlighted in Figure 2) is formed between the

Figure 2. Perspective view of the PRX⁺ framework along the *b*-axis showing the channels along the structure (highlighted in yellow circles), where the H₂O molecules and the Br[−] anions are hosted. Symmetry independent molecules of A host (blue) and B conformer guest (red) arrays in the crystal. Two distinct hydrogen bonded networks in the crystal structure of (PRX⁺Br[−])·0.5H₂O.

Ow1 and both independent ionic pairs. In the same direction, symmetric C_s⁵(10) motifs merge into each other forming a R₆⁶(12) motif, leading to a complex infinite 2D-layer of molecules. This arrangement orientation of the conformers such as the drug framework can be understood as a host–guest complex, where “host” and “guest” molecules refer to PRX⁺ conformers A and B, respectively (Figure 2). In this way, the host molecules are H-bonded to Br[−] and water molecules, forming zigzag chains (red in Figure 2), while the guest molecules are H-bonded only to Br[−], resulting in a square suprastructure (blue in Figure 2). The guest–host contacts are made by nonclassical C8–H8 $\cdots\pi$, C1–H1B $\cdots$ O2', and C13–H13B $\cdots\pi$ intermolecular interactions (see Table 1S in the Supporting Information). In addition, the water molecules and Br[−] anions are located in circular channels running along the *b*-axis (highlighted in yellow in Figure 2).

Paroxetine HBr. The anhydrous PRX⁺Br[−] crystalline phase (Figure 1c) was identified at 87 °C and is an isomorphic dehydrate (monoclinic Sohncke space group *P*2₁, *Z'* = 2) of its parent hydrated form, (PRX⁺Br[−])·0.5H₂O. In this way, similar volume and unit cell parameters are observed between both salts, being the differences smaller than 1.55% (Table 1). Also interesting is that even after dehydration no significant conformational changes on the PRX⁺ molecules are observed.

From a structural point of view, however, the dehydration requires a significant rearrangement of the main hydrogen bonds (see Figure S1 in the Supporting Information), in a fashion that the two strong N–H $\cdots$ O_w and O_w–H $\cdots$ Br hydrogen bonds observed in the (PRX⁺Br[−])·0.5H₂O are replaced by NH₂⁺ $\cdots$ Br[−] hydrogen bonds in the anhydrous phase (Figure 1c). Nevertheless, it is worth noting that the radius of the circular channels, now composed only by Br[−] anions, remains unchanged.

3.2. Solid State Dehydration/Hydration Processes for Paroxetine HBr Hemihydrate. As depicted earlier, the dehydrated form of (PRX⁺Br[−])·0.5H₂O is obtained at 87 °C. In this way, DSC, TGA and HSM measurements were carefully carried out aiming to understand the thermal behavior of (PRX⁺Br[−])·H₂O during these dehydration/hydration processes. The curve of the first heating DSC cycle (Figure 3a)

Figure 3. Heat–cool–reheat DSC curves (lines (a), (b), and (c), respectively), TGA (dashed gray line), and HSM for (PRX⁺Br[−])·0.5H₂O, showing the crystal formation of the isomorphic dehydrate.

presents an endothermic peak in the temperature range of 50–80 °C and can be assigned as the dehydration process, once the TGA curve (Figure 3a) is accompanied by a small mass decrease in this same region, which agrees quite well with the release of water molecules from the crystal structure. Since the DSC cell is a closed system under nitrogen purge gas, no equivalent peak is observed during the cooling process (Figure 3b). However, a second endothermic peak is observed at 155 °C during the reheating process of the same sample (Figure 3c). This peak can be assigned as the melting of the resultant dehydrated material. In addition, it can be observed in the HSM experiment (right side of Figure 3) that at 158 °C the crystal starts to melt, changing its morphology, and that above 165 °C it has completely melted into a liquid droplet. Notoriously, the complete dehydration of (PRX⁺Br[−])·H₂O is not associated with any amorphization of the sample, neither change of habit or color before fusion. Also, according to the TGA data, after water loss the next event occurs only between 232 and 300 °C and is related with the thermal decomposition of the sample.

Based on the thermal analysis, a VT–SC–XRD experiment have been performed for (PRX⁺Br[−])·H₂O, in a fashion that the dehydrated crystalline phase, identified at 87 °C, can be measured and the structure solved. Knowing that the porous channels present in the structure of PRX⁺Br[−] (see section 3.1) can be readily accessible by water molecules, the consequent rehydration can be possible. In this way, if true, the reincorporation of water molecules in the solid state should give back the hydrated crystalline state, (PRX⁺Br[−])·0.5H₂O.

Figure 4. Crystal structure of (a) $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ and (b) $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ hemihydrates with the water-containing channels highlighted in blue.

Thus, to state the reversibility of the dehydration of $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ in the solid-state, the following protocol was adopted: (a) original crystalline samples were subjected to oven at 90 °C for 4 h to get complete dehydration; (b) X-ray diffraction experiments of the dehydrated single crystals were performed to ensure complete dehydration at 87 °C; (c) the dehydrated crystalline samples were exposed to humid atmosphere for 2 h; (d) the samples were measured by SXRD at 25 °C and DSC in order to confirm rehydration.

3.3. Comparison and Phases Relationship between $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ and $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ Structures. Apart from similarity between chloride and bromide anions, it is interesting to note that the $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ and $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ ^{27,28} salts are isostructural (see Hirshfeld discussion in the [Supporting Information](#)). In the Mercury 3.6,³³ a 20 PRX⁺ molecules overlay (see Figure S2 in the [Supporting Information](#)) confirmed a high packing similarity between these crystal structures, having 20 out of 20 PRX⁺ cations in common (RMSD = 0.204279 Å, 20% geometry tolerance and ignoring the smallest molecular component). This similarity suggests that the resultant motif formed by interactions of the type $\text{N}^+-\text{H}\cdots\text{X}$ ($\text{X} = \text{Cl}, \text{Br}$) is robust enough to mask the disturbances caused by electronegativity change, when Cl^- is replaced by Br^- .^{42,43} In fact, a search of the Cambridge Structural Database³⁵ (Version 5.36 + updates), have shown that this is a very common supramolecular motif, not only occurring for Cl^- or Br^- anions, but also for others pairs of $\text{N}^+-\text{H}\cdots\text{X}$ CAHB involving protonated amide $\cdots$ halide ($\text{X} = \text{F}^-, \text{Cl}^-, \text{Br}^-, \text{I}^-$): a total of 4002 hits with 58.7% of them exhibiting chain motif, such as observed in the isostructural salts.

Differently from the $(\text{PRX}^+\text{Br}^-) \cdot \text{H}_2\text{O}$, no evident dehydration peak is observed in the DSC curve of $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ (see Figure S3 in the [Supporting Information](#)). The water loss in the HBr Form is detected in a large range of temperatures.^{14,26,29} Despite the isostructurality, the thermal behavior differences between both salts suggest a dissimilar dehydration mechanism resulting in similar isomorphous hydrates. However, dehydrated lattices from bromide and chloride hydrates differ in stability. The $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ salt have the lowest melting point, whereas the $(\text{PRX}^+\text{Br}^-) \cdot \text{H}_2\text{O}$ have the highest melting point. This observation agrees with the assumption that the CAHB $\text{N}^+-\text{H}\cdots\text{Y}$ ($\text{Y} = \text{Br}^-$ or Cl^-) in the dehydrated lattice in both hemihydrates is stronger in the $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ than in $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$. In addition, the HCl salt degrades at a higher temperature relative to the HBr Form. This difference can result from the high reactivity of the bromide anion in the melting medium. Then, the

$(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ is more thermally stable than $(\text{PRX}^+\text{Br}^-) \cdot \text{H}_2\text{O}$.

As shown by Pina and coauthors,^{14,26} the complex dehydration of the $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ occurs in a completely dry environment, $\text{RH} \sim 1\%$, at high temperatures, $\sim 75\text{--}100$ °C. The resultant dehydrated phase is unstable and shows high affinity for water, which results in the fast spontaneous rehydration. For this reason, the detection of the event is not clearly evident, such as observed for the $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$. This supports the idea that changing the chloride by bromide results in slight structural differences that turn the dehydrate state more stable in the $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ than in the $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$. Although no crystal structure has been elucidated from the dehydration of $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ until now, similar conclusions can be inferred to this compound, by considering the packing similarity between both salts. Notwithstanding, the different rehydration mechanism for the PRX^+Br^- and PRX^+Cl^- dehydrates should be related to their respective structural features. After dehydration, it is impossible to fully satisfy the acceptor capacity of bromide ions (see Figure S1 in the [Supporting Information](#)). The replacement of water interactions by the Br^- in the PRX^+Br^- lattice induces steric strains resulting in a chemically unstable isomorphous system. Indeed, the channel structure is a fundamental feature to dehydration/rehydration behavior of both chloride and bromide salts. The channel structure of dehydrates allows the reincorporation of water without large structural rearrangement. However, the difference in the topology of the channels where the rehydration is preceded has a great impact in their phenomena kinetics. Because the bromide has the higher ionic radius than chloride, the channels in $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ are twice as larger as in the $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$. In addition, as shown in [Figure 4](#), the spatial topography of channels in the HCl Form differ from the HBr by the presence of curvatures near $y = 1/2$ and $y = 1$. On one hand, the linear and more voluminous geometry of the channels in the $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ facilitates the outflow of water in the dehydration, and in the other hand it also contributes to reducing the destabilizing effects in dehydrate structure when compared to the $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$. As a result, while the rehydration of chloride occurs at ~ 1 h, 75 °C at $\text{RH} < 1\%$,²⁶ the rehydration of bromide was only observed at 2 h, 25 °C at $\text{RH} \sim 75\%$ (see [Figure S4](#) in the [Supporting Information](#)).

3.4. Fourier Transform Infrared Spectroscopy. The structural similarities between $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$, $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ can also be inferred from their infrared spectra. The FTIR spectrum of $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ (Form I) is shown in [Figure 5](#). The FTIR spectrum of Form II (the dehydrated HBr

Figure 5. FTIR spectrum of the isostructural salts $(\text{PRXBr})\cdot 0.5\text{H}_2\text{O}$ and $(\text{PRXCl})\cdot 0.5\text{H}_2\text{O}$, showing the stretching bands of the NH_2^+ group.

Form) was identical to Form I, and is thus omitted. In an attempt to establish a comparison, the FTIR spectrum of $(\text{PRX}^+\text{Cl}^-)\cdot 0.5\text{H}_2\text{O}$ is also shown in Figure 5. The similarity in the molecular packing of these two isostructural salts is reflected on the similarity of their FTIR spectrum. For both salts, the main spectral features of the protonated PRX^+ molecule, such as the N–H stretching modes, could be easily identified. In fact, the amine group is used as fingerprint due its participation in strong hydrogen bonds. Primary amines are known to give rise to two NH stretching bands in the region of $3500\text{--}3300\text{ cm}^{-1}$, and another band between 1650 and 1560 cm^{-1} due to the NH deformation mode. Stretching modes for the NH_2^+ group are seen at 3416 and 3356 cm^{-1} for $(\text{PRXBr})\cdot 0.5\text{H}_2\text{O}$ and at 3401 and 3336 cm^{-1} for $(\text{PRXCl})\cdot 0.5\text{H}_2\text{O}$. Since the amine groups are particularly involved in hydrogen bonds with the counterion in both salts this considerable shift to higher frequencies in $(\text{PRXBr})\cdot 0.5\text{H}_2\text{O}$ is attributed to the decreasing electronegativity difference between Cl^- and Br^- .

3.5. Solubility of $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$, $(\text{PRX}^+\text{Cl}^-)\cdot 0.5\text{H}_2\text{O}$, and PRX^+Br^- . Solubility, by definition, is the measure of the maximum amount of solute dissolved in a given volume of solvent at a specified temperature.^{44–46} This property is typically related to the melting point, the enthalpy of fusion, and supramolecular features together with the crystal lattice energy. This correlation is not a simple exercise and there are no reliable general rules, especially for salts.⁴⁵ The water solubility of $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$ at 20 and $37\text{ }^\circ\text{C}$ has been determined from a saturated aqueous solution. Due to spontaneous rehydration, the solubility of the PRX^+Br^- dehydrate has been determined only in 2-propanol.

The aqueous solubility of the $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$ increases with temperature. At $20\text{ }^\circ\text{C}$, the $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$ solubility is 2.66 ± 0.015 and increases to $3.10 \pm 0.018\text{ mg}\cdot\text{mL}^{-1}$ when the temperature reach $37\text{ }^\circ\text{C}$. This small difference ($\sim 0.44\text{ mg}\cdot\text{mL}^{-1}$) indicates the high stability of this solid form when compared with its isostructural $(\text{PRX}^+\text{Cl}^-)\cdot 0.5\text{H}_2\text{O}$ salt ($S = 6.890 \pm 0.2\text{ mg/mL}$ at $20\text{ }^\circ\text{C}$). The $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$ is more soluble in 2-propanol, with the values differing ($S = 8.61 \pm 0.01$ at $20\text{ }^\circ\text{C}$), from those estimated in water. As expected, due to the instability generated by the water removal, the PRX^+Br^- dehydrate displays a higher solubility in this organic solvent ($S = 15.62 \pm 0.01\text{ mg}\cdot\text{mL}^{-1}$). The value is significantly higher than its hydrate parent in the same solvent, and the solubility difference between the hydrated and anhydrous forms is approximately twice. In this view, the stability order of the

forms was estimated. The $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$ is thermodynamically more stable than its PRX^+Br^- dehydrate and, hence, less soluble. This thermodynamic relationship is consistent with those obtained by DSC.

4. CONCLUSIONS

The structural and thermal investigation of Paroxetine HBr has been performed. The determination of the crystal structure of the anhydrous and hydrate paroxetine HBr shows that the hydrate is isostructural to the $(\text{PRX}^+\text{Cl}^-)\cdot \text{H}_2\text{O}$. Despite the packing similarity, both forms have different thermal properties, mainly involving the desolvation process. The $(\text{PRX}^+\text{Cl}^-)\cdot \text{H}_2\text{O}$ hemihydrate does not present a structural desolvation process while the $(\text{PRX}^+\text{Br}^-)\cdot \text{H}_2\text{O}$ loses water molecules above $87\text{ }^\circ\text{C}$ and still remains crystalline. The phenomenon is endothermic and is associated with the supramolecular arrangement of the water in the cavity and the organization of the channel. A cooperative desolvation mechanism has been proposed, since structural information is maintained after the water loss. No significant changes are observed in the molecular conformation and the relative position of the paroxetine molecules during the dehydration process, which results in an isomorphic dehydrate solid form. The anhydrous structure exhibits an increased solubility, indicating the relative stability among both forms. This work also suggests that the spontaneous rehydration process of $(\text{PRX}^+\text{Br}^-)$ is related to the following features: (i) higher conformational similarity between PRX^+ molecules in anhydrous and hydrated forms; (ii) the relative stability of both forms; (iii) the presence of channels in the structure in which the molecule of water is accommodated; (vi) the restoration of strong $\text{OH}\cdots\text{Br}$ hydrogen bonds broken during the desolvation process; (vii) the more stable and cohesive structure generated after the rehydration.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.5b01672.

Crystal data and structure refinement, fractional atomic coordinates and equivalent isotropic displacement parameters, anisotropic displacement parameters, bond lengths and angles, torsion angles, hydrogen atom coordinates and isotropic displacement parameters, and atomic occupancy for $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$ and PRX^+Br^- , and Hirshfeld surface and fingerprint plots, plus additional complementary tables and figures (PDF)

Accession Codes

CCDC 1436946, 1436947, and 1436953 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail address: javiere@ifsc.usp.br.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to acknowledge Brazilian funding agencies FAPESP (P.S.C.-Jr. grant 12/05616-7), CAPES, and CNPq for financial support.

■ REFERENCES

- (1) Infantes, L.; Fabian, L.; Motherwell, W. D. S. *CrystEngComm* **2007**, *9*, 65.
- (2) Aakeroy, C. B.; Forbes, S.; Desper, J. *CrystEngComm* **2012**, *14*, 2435.
- (3) Khankari, R. K.; Grant, D. J. W. *Thermochim. Acta* **1995**, *248*, 61.
- (4) Giron, D.; Goldbronn, C.; Mutz, M.; Pfeffer, S.; Piechon, P.; Schwab, P. J. *Therm. Anal. Calorim.* **2002**, *68*, 453.
- (5) Griesser, U. J. In *Polymorphism*; Wiley-VCH Verlag GmbH & Co. KGaA: 2006; p 211.
- (6) Bauer, J.; Spanton, S.; Henry, R.; Quick, J.; Dziki, W.; Porter, W.; Morris, J. *Pharm. Res.* **2001**, *18*, 859.
- (7) Brittain, H. G. J. *Pharm. Sci.* **2008**, *97*, 3611.
- (8) Kobayashi, K.; Kimura, S.; Togawa, E.; Wada, M.; Kuga, S. *Carbohydr. Polym.* **2010**, *80*, 491.
- (9) Koradia, V.; Fontelongo de Lemos, A. F.; Alleso, M.; Lopez de Diego, H.; Ringkjøbing-Ellema, M.; Müllertz, A.; Rantanen, J. J. *Pharm. Sci.* **2011**, *100*, 2896.
- (10) Malaj, L.; Censi, R.; Gashi, Z.; Di Martino, P. *Int. J. Pharm.* **2010**, *390*, 142.
- (11) Zhang, G. G. Z.; Law, D.; Schmitt, E. A.; Qiu, Y. *Adv. Drug Delivery Rev.* **2004**, *56*, 371.
- (12) Tian, F.; Qu, H.; Zimmermann, A.; Munk, T.; Jørgensen, A. C.; Rantanen, J. J. *Pharm. Pharmacol.* **2010**, *62*, 1534.
- (13) Bernstein, J. In *Polymorphism*; Wiley-VCH Verlag GmbH & Co. KGaA: 2006; p 365.
- (14) Pina, M. F.; Pinto, J. F.; Sousa, J. J.; Fábán, L.; Zhao, M.; Craig, D. Q. M. *Mol. Pharmaceutics* **2012**, *9*, 3515.
- (15) Stein, D. J.; Versiani, M.; Hair, T.; Kumar, R. *Arch. Gen. Psychiatry* **2002**, *59*, 1111.
- (16) Bourin, M.; Chue, P.; Guillon, Y. *CNS Drug Rev.* **2001**, *7*, 25.
- (17) Thal, D. M.; Homan, K. T.; Chen, J.; Wu, E. K.; Hinkle, P. M.; Huang, Z. M.; Chuprun, J. K.; Song, J.; Gao, E.; Cheung, J. Y.; Sklar, L. A.; Koch, W. J.; Tesmer, J. J. G. *ACS Chem. Biol.* **2012**, *7*, 1830.
- (18) Hiemke, C.; Härtter, S. *Pharmacol. Ther.* **2000**, *85*, 11.
- (19) Tanrikut, C.; Feldman, A. S.; Altemus, M.; Paduch, D. A.; Schlegel, P. N. *Fertil. Steril.* **2010**, *94*, 1021.
- (20) Bowen, P. D. *Geriatric Nursing* **2009**, *30*, 85.
- (21) Goudie, A. J.; Dubicki, W.; Leathley, M. J. *Pharm. Pharmacol.* **1988**, *40*, 192.
- (22) Keller, M. B. Paroxetine treatment of major depressive disorder. *Psychopharmacol. Bull.* **2003**, *37* (Suppl 1), 42.
- (23) Saxena, S.; Brody, A. L.; Ho, M. L.; et al. *Arch. Gen. Psychiatry* **2002**, *59*, 250.
- (24) Bernstein, J. *Polymorphism in Molecular Crystals*; Clarendon Press: 2002.
- (25) Hilfiker, R. *Polymorphism: In the Pharmaceutical Industry*; Wiley: 2006.
- (26) Pina, M. F.; Zhao, M.; Pinto, J. F.; Sousa, J. J.; Frampton, C. S.; Diaz, V.; Suleiman, O.; Fábán, L.; Craig, D. Q. M. *Cryst. Growth Des.* **2014**, *14*, 3774.
- (27) Ibers, J. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1999**, *55*, 432.
- (28) Yokota, M.; Hidehiro, Uekusa; Yuji, Ohashi *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1731.
- (29) Bruni, G.; Sartor, F.; Berbenni, V.; Milanese, C.; Maietta, M.; Franchi, D.; Marini, A. J. *Therm. Anal. Calorim.* **2012**, *108*, 381.
- (30) APEX2; Madison, Wisconsin, USA, 2009.
- (31) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339.
- (32) Sheldrick, G. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112.
- (33) Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Crystallogr.* **2006**, *39*, 453.
- (34) Wolff, S.; Grimwood, D.; McKinnon, J.; Jayatilaka, D.; Spackman, M. *Crystal Explore 2.1*. University of Western Australia, Perth, 2007.
- (35) Allen, F. *Acta Crystallogr., Sect. B: Struct. Sci.* **2002**, *58*, 380.
- (36) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864.
- (37) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133.
- (38) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
- (39) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian*; Wallingford, CT, 2009.
- (40) Eirkson, C. H. M.; Osbourne, C. M.; Sayre, P. G.; Zeeman, M. In *Environmental assessment technical assistance handbook*; U.S.F.D.A.: Washington, DC, 1987; Vol. 31, p 1.
- (41) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354.
- (42) Kalman, A.; Argay, G.; Scharfenberg-Pfeiffer, D.; Hohne, E.; Ribar, B. *Acta Crystallogr., Sect. B: Struct. Sci.* **1991**, *47*, 68.
- (43) Haynes, D. A.; Jones, W.; Motherwell, W. D. S. *J. Pharm. Sci.* **2005**, *94*, 2111.
- (44) Bhattachar, S. N.; Deschenes, L. A.; Wesley, J. A. *Drug Discovery Today* **2006**, *11*, 1012.
- (45) Black, S. N.; Collier, E. A.; Davey, R. J.; Roberts, R. J. *J. Pharm. Sci.* **2007**, *96*, 1053.
- (46) Cassens, J.; Prudic, A.; Ruether, F.; Sadowski, G. *Ind. Eng. Chem. Res.* **2013**, *52*, 2721.

PAPER 2:

CARVALHO JR, P.S.; DE MELO, C.C.; AYALA, A. P.; ELLENA, J. **X-Ray Diffraction, Spectroscopy And Thermochemical Characterization Of The Pharmaceutical Paroxetine Nitrate Salt.** Journal of Molecular Structure, 1118,15,2016, pp 288–292.

X-Ray diffraction, spectroscopy and thermochemical characterization of the pharmaceutical paroxetine nitrate salt

Paulo S. Carvalho Jr.^a, Cristiane C. de Melo^{a,b}, Alejandro P. Ayala^b, Javier Ellena^{a,*}

^a Instituto de Física de São Carlos, Universidade de São Paulo, CP 369, 13560-970, São Carlos, SP, Brazil

^b Departamento de Física, Universidade Federal do Ceará, CP 6030, Fortaleza, Ceará 60455–970, Brazil

ARTICLE INFO

Article history:

Received 4 March 2016

Received in revised form

5 April 2016

Accepted 6 April 2016

Available online 14 April 2016

Keywords:

Antidepressant

Paroxetine nitrate

Solid state

DSC/TGA

Infrared spectra

ABSTRACT

A comprehensive solid state study of Paroxetine nitrate hydrate, $(\text{PRX}^+ \cdot \text{NO}_3^-) \cdot \text{H}_2\text{O}$, is reported. This salt was characterized by a combination of methods, including Single crystal X-ray diffraction, Thermal analysis, Fourier transform infrared spectroscopy (FTIR) and Solubility measurements. $(\text{PRX}^+ \cdot \text{NO}_3^-) \cdot \text{H}_2\text{O}$ crystallizes in the monoclinic C2 space group ($Z' = 1$) and its packing was analyzed in details, showing that the main supramolecular motif consists in a $C_2^2(4)$ chain formed by charge-assisted $\text{N}^+ \cdots \text{H} \cdots \text{O}^-$ hydrogen bonds. The salt formation and conformation features were also accurately established via FTIR spectra. In comparison with the pharmaceutical approved $(\text{PRX}^+ \cdot \text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$, $(\text{PRX}^+ \cdot \text{NO}_3^-) \cdot \text{H}_2\text{O}$ showed a decrease of 24 °C in the drug melting peak and a slight reduction in its water solubility value.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Paroxetine (PRX), [(3S-trans)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidine (Scheme 1), is the most potent inhibitor of the neuronal reuptake of serotonin (5-hydroxytryptamine, 5-HT) [1] and is clinically approved for the treatment of major depression, obsessive compulsive disorder, generalized anxiety and social phobia [1–7]. Furthermore, PRX is well tolerated and effective in the depression/anxiety treatment of young and elders [2], being one of the most widely prescription drugs in the world [8]. PRX has been pharmaceutically administered as a hydrochloride salt. Two polymorphic forms are recognized for this salt: a stoichiometric hydrate, $(\text{PRX}^+ \cdot \text{Cl}^-) \cdot \text{H}_2\text{O}$, and a hemihydrate form, $(\text{PRX}^+ \cdot \text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$; in which the latter is the thermodynamically most stable. Additionally, anhydrate [9] and solvate salts containing propan-2-ol (isopropyl alcohol) [10] have been reported. Recently, Paroxetine bromide hemihydrate, $(\text{PRX}^+ \cdot \text{Br}^-) \cdot 0.5\text{H}_2\text{O}$ and its corresponding dehydrate phase have been reported for us, as a part of our studies on designing of better antidepressant solid forms [11]. Beyond these structures, novel PRX salts with improved solubility and stability are still requested to

provide a better manufacturing and pharmaceutical performance of this drug.

Salt selection is a common strategy applied to improve pharmaceutical properties of ionic APIs. In general, the salt confers valuable attributes such as the increasing of chemical stability, aqueous solubility and bioavailability [12–15]. For this purpose, there are a wide variety of salt formers included into the GRAS list with different chemical properties (pK_a , molecular weight, solubility) that can be combined with PRX to achieve a salt. Within this context, we have been rationally prepared the paroxetine nitrate hydrate salt, $(\text{PRX}^+ \cdot \text{NO}_3^-) \cdot \text{H}_2\text{O}$, following a supramolecular approach based on the establishment of charge-assisted hydrogen bonds (CAHBs). Structural correlations between $(\text{PRX}^+ \cdot \text{NO}_3^-) \cdot \text{H}_2\text{O}$, $(\text{PRX}^+ \cdot \text{Cl}^-) \cdot \text{H}_2\text{O}$ and $(\text{PRX}^+ \cdot \text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ salts were also accurately established. Furthermore, thermal behavior, spectroscopy properties and solubility measurements were performed for supporting the crystallographic results.

2. Experimental details

2.1. Preparation of paroxetine nitrate salt

Paroxetine chloride hemihydrate, $(\text{PRX}^+ \cdot \text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$, was used as a precursor for the synthesis of the nitrate salt. Chemicals and solvents, such as sodium hydroxide, sodium sulfate anhydrous,

* Corresponding author.

E-mail address: javiere@ifsc.usp.br (J. Ellena).

Scheme 1. Structure of Paroxetine cation (PRX^+). The $\text{N1}-\text{C1} \rightarrow \text{C5}$, $\text{C7} \rightarrow \text{C12}$, $\text{C14} \rightarrow \text{C19}$ and $\text{C10}-\text{C11}-\text{O5}-\text{C13}-\text{O6}$ are designed A, B, C and D rings, respectively.

nitric acid, ethanol 95%, ethyl ether were of reagent grade quality and used without further purification. Paroxetine free base was obtained after deprotonation of $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$, following a protocol previously reported for us [11]. $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$ was prepared through the reaction of PRX free base and HNO_3 acid. Single crystals were grown from an ethanol solution 95%(v/v).

2.2. Single-crystal X-ray diffraction (SCXRD)

X-ray data of $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$ were acquired at 120 K (Cryo-stream, Oxford Cryosystems) on a Bruker D8 VENTURE diffractometer with PHOTON 100 CMOS detector system, using $\text{Cu K}\alpha$ radiation. The data were integrated and processed via SAINT [16] and SADABS [17] softwares. The structure was determined using the Olex2 [18] program as a graphical interface together with the SHELXS and SHELXL programs [19], in order to solve and refine the structure, respectively. Hydrogen atoms were placed in geometric positions and refined with fixed individual displacement parameters [$U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}$ or $1.5U_{\text{eq}}$] according to the riding model (C–H bond lengths of 0.97 Å and 0.96 Å, for methylene and methyl groups, respectively). Molecular representations, tables and pictures were generated by Olex2 [18] and MERCURY 3.2 [20] programs. The crystallographic data were deposited at the Cambridge Crystallographic Data Center under the numbers CCDC 1456602. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk.

2.3. Vibrational spectroscopies

Middle infrared spectrum ($4000\text{--}400\text{ cm}^{-1}$) was recorded for $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$ and $(\text{PRX}^+\text{Cl}^-) \cdot \text{H}_2\text{O}$ salts as KBr pellets on a Shimadzu IR Prestige FTIR Spectrometer. The spectra were acquired under 64 scans of accumulation and at 4 cm^{-1} of resolution.

2.4. Thermal analysis

Differential Scanning Calorimetric measurements (DSC) were carried out on a Shimadzu DSC-60 instrument. Samples ($2.5 \pm 0.5\text{ mg}$) were sealed in a crimped aluminum pan and heated under a flow of 5% $\text{O}_2\text{--N}_2$ from 25 to $300\text{ }^\circ\text{C}$ at a heating rate of $10\text{ }^\circ\text{C}/\text{min}$. Thermogravimetric analyses (TGA) were performed on a Shimadzu TGA-60 thermobalance. Approximately 2.5 mg of sample

were placed on an alumina pan and heated under a flow of 5% $\text{O}_2\text{--N}_2$ from 25 to $300\text{ }^\circ\text{C}$ at a heating rate of $10\text{ }^\circ\text{C}/\text{min}$. All data were processed using the Shimadzu TA-60 thermal data analysis software.

2.5. Hot-stage microscopy (HSM)

Hot-stage (HS) microscopy was performed using a Linkam T95-PE device coupled to an optical microscope Leica DM2500 P. The $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$ crystal was heated at a constant rate of $10\text{ }^\circ\text{C}/\text{min}$ from $25\text{ }^\circ\text{C}$ to $150\text{ }^\circ\text{C}$, with this process being stopped after the melting of the compound. Images were recorded by a CCD camera attached to the microscope in time intervals of 10 s via the software Linksys 32.

2.6. Solubility

Aqueous solubility of $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$ was determined by the classical saturation shake-flask method at $20\text{ }^\circ\text{C}$ in deionized water [21]. A saturated solution of $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$ was obtained stirring an excess amount of $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$ salt (30 mg) in 600 μL of water for 48 h. After this time, an aliquot of the saturated solution was removed, filtered through a 0.45 mm filter (Millipore), diluted 100-fold in water and its concentration measured by UV spectroscopy at $\lambda_{\text{max}} = 293\text{ nm}$. The standard solutions used to generate the calibration curve were prepared using $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ salt. The concentration of PRX^+ in the saturated aliquots was quantified by interpolating of spectroscopic measurements in a calibration curve whose concentrations ranged from 0.005 to 0.2 mg mL^{-1} . This experiment was run in triplicate.

3. Results and discussion

3.1. Crystal structure of paroxetine nitrate hydrate

Considering the strong tendency of PRX to form salts ($\text{pK}_a = 9.9$ of piperidine N), and the dominance of CAHBs in the crystal packing of chloride and bromide PRX forms [10,11,22], a stoichiometric paroxetine nitrate hydrate salt was prepared, $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$. This salt crystallizes in the monoclinic Sohncke space group C2 in a needle-shaped morphology. The C-centered unit cell shows a very long a axis compared to b and c -axis. Details of the structure determination and the refinement parameters are presented in Table 1. The asymmetric unit encloses a protonated PRX^+ molecule, a NO_3^- anion and a H_2O molecule. The water molecule lies on the crystallographic 2-fold axis and had its H atoms refined with 0.5 of occupancy. A view of crystallographic asymmetric unit is shown in Fig. 1.

PRX^+ is a six-membered piperidinium ring in the usual chair conformation (puckering parameters [23]: $q_2 = 0.0284(3)$, $q_3 = -0.5705(3)$, $Q_T = 0.5713(3)$, $\varphi_2 = -52.69(5.10)$ and $\theta_2 = 177.15(3)^\circ$) with the ethoxyl-benzodioxole and fluorophenyl substituents in the equatorial position. The geometric parameters of PRX^+ are listed in Table S1. Due to protonation, the sp^3 hybridized N1 atom bears a positive charge and assumes a tetrahedral configuration. In the present structure, the ethoxyl bridge between the piperidine ring and benzodioxole group (C + D ring) has an antiperiplanar conformation with C5-C6-O4-C7 of $172.2(3)^\circ$ (Table S1, support information). As reported previously, the conformational flexibility of PRX^+ is related to the rotation freedom about C6-O4 bond. Additionally, the C6-O4-C7-C12 torsion angle that defines the orientation of benzodioxole groups with respect to C5-C6-O4 mean plane assumes the value of $-169.2(3)^\circ$. Although the conformation of PRX^+ in $(\text{PRX}^+\text{NO}_3^-) \cdot \text{H}_2\text{O}$ salt differs from those reported in $(\text{PRX}^+\text{Cl}^-) \cdot 0.5\text{H}_2\text{O}$ [10,22] and $(\text{PRX}^+\text{Br}^-) \cdot 0.5\text{H}_2\text{O}$

Table 1Crystal data and structure refinement of (PRX⁺NO₃⁻)H₂O.

Structure	(PRX ⁺ NO ₃ ⁻)H ₂ O
Empirical formula	C ₁₉ H _{21.5} FN ₂ O _{6.5}
Formula weight	400.88
Temperature/K	150.0(2)
Crystal system	Monoclinic
Space group	C2
a/Å	39.7779(13)
b/Å	5.8787(2)
c/Å	7.9925(3)
β/°	97.022(2)
Volume/Å ³	1854.97(11)
Z, Z'	4, 1
ρ _{calc} g/cm ³	1.435
μ/mm ⁻¹	0.979
F(000)	842.0
Crystal size/mm ³	0.562 × 0.122 × 0.06
Radiation	CuKα (λ = 1.54178)
2θ range for data collection/°	4.476 to 140.402
Index ranges	−48 ≤ h ≤ 47 −7 ≤ k ≤ 7 −9 ≤ l ≤ 9
Reflections collected	7890
Independent reflections	3312 [R _{int} = 0.0624, R _{sigma} = 0.0670]
Data/restraints/parameters	3312/1/259
Goodness-of-fit on F ²	1.049
Final R indexes [I ≥ 2σ(I)]	R ₁ = 0.0413, wR ₂ = 0.0830
Final R indexes [all data]	R ₁ = 0.0567, wR ₂ = 0.0892
Largest diff. peak/hole/e Å ⁻³	0.17/−0.26
Flack parameter	−0.16(17)

Fig. 1. Crystallographic asymmetric unit view of (PRX⁺NO₃⁻)H₂O. The hydrogen atoms are label following the nomenclature of heavy atoms to which they are bonded.

hemihydrates [11], it is similar to the one found in (PRX⁺Cl⁻)H₂O (Fig. 2). Interestingly, only in the nitrate salt, the C13 atom is coplanar with the 1,3-dioxolane ring (D ring).

PRX nitrate is formed via the N1⁺–H1A···O1⁻ CAHB (see Table S2 for H-bond geometry, Supporting Information). The PRX⁺ NO₃⁻ ionic pairs are connect to each other by N1⁺–H1B···O3⁻ CAHB into an one-dimensional supramolecular C₂²(4) chain along the [010] direction. The ionic pairs are also stabilized by C18–H18···O5 interactions. Parallel layers of PRX⁺NO₃⁻ intercalated by H₂O channels (Fig. 3) characterize the 2-D assembly. The water molecules, in turn, stabilize the NO₃⁻ anions via the O1w–H1'···O2 hydrogen bonds, by reducing the electronic repulsion between the anions. Furthermore, two C–H···π interactions contribute to the overall supramolecular arrangement: C12–H12···C-ring and C13–H13B···B-ring. The directionality of C13–H13B···π is the feature that seems to corroborate with the planarity of the D ring. Also, the PRX⁺ molecule exhibits an intramolecular C19–H19···O4 interaction

Fig. 2. The superposed of PRX⁺ molecule from different solid forms. The red molecule is from (PRX⁺NO₃⁻)H₂O, the yellow one from (PRX⁺Cl⁻)H₂O [24] and black ones are from the isostructural (PRX⁺Cl⁻)0.5H₂O [10] and (PRX⁺Br⁻)0.5H₂O [11] hemihydrates.

(*d*_{C...O} = 3.285(4) Å), which can explain the slight conformational differences between (PRX⁺NO₃⁻)H₂O and (PRX⁺Cl⁻)H₂O [24].

3.2. Vibrational spectra and assignments.

The analysis of the vibrational modes confirmed the conformational and supramolecular features observed in the crystallographic study. For a better understanding of the FTIR spectrum of (PRX⁺NO₃⁻)H₂O, the FTIR spectrum of (PRX⁺Cl⁻)0.5H₂O is also included in Fig. 4. Analysis and band assignments were made as previously described [11,25,26].

As expected, both spectra are affected by the protonation of the secondary amine. For the nitrate salt, the band at 1345 cm⁻¹, associated to the piperidine C–N stretching mode, appears red-shifted to 1324 cm⁻¹. Another significant shift observed in the spectra of this salt, refers to the band at 803 cm⁻¹. This band arises from the coupling of phenyl-ring breathing and N–H bendings and undergoes a blue-shifted of 13 cm⁻¹ (816 cm⁻¹).

Fig. 3. Crystal packing view along the *b* and *c* axis. The blue selection indicate the water channels which the H₂O molecules are link two adjacent nitrate ions by O–H···O hydrogen bond.

Fig. 4. FTIR spectrum of $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ and $(\text{PRX}^+\text{Cl}^-)0.5\text{H}_2\text{O}$.

Unfortunately, the N-H stretching vibrations, arising from protonation of the secondary amine, only can be seen in the PRX chloride spectrum (3401 and 3336 cm^{-1}). A broad band corresponding to the water O-H stretching overlaps these two bands in PRX nitrate. Additionally, the nitrate salt also shows the presence of

new bands associated to the vibrational modes of the nitrate anion. The bands at 1324 and 1386 cm^{-1} , only presented in PRX nitrate, has been assigned to the stretching mode of the N=O bonds, once PRX chloride has no absorption bands in this region.

3.3. Thermal analysis

The thermal behavior of $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ was analyzed by DSC, TGA and HS microscopy. The DSC and TGA results are presented in Fig. 5. For comparative purposes, the DSC curve of $(\text{PRX}^+\text{Cl}^-)0.5\text{H}_2\text{O}$ was also included in the plot. The DSC curve of PRX nitrate is characterized by an endothermic peak at 109.0 $^{\circ}\text{C}$, attributed to the melting event. Also no dehydration event is observed for $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ until its melting, which can be seen as an advantage, since the stability of the drug is a basic requirement for their pharmaceutical development and manufacturability. The thermal decomposition appears in the DSC curve as an exothermic peak at $\sim 169^{\circ}\text{C}$ and as expected, it is followed by an abrupt weight loss in the TGA curve. All thermal events assigned in the DSC curve were further confirmed by HS microscopy (Fig. 6). No habit or color change is observed for the nitrate salt between 25 and 80 $^{\circ}\text{C}$. At 110 $^{\circ}\text{C}$, the crystal starts to melt changing its morphology and above 112 $^{\circ}\text{C}$, it has completely melting into a liquid droplet.

The melting temperature of PRX nitrate is about 24 $^{\circ}\text{C}$ less than the one found for $(\text{PRX}^+\text{Cl}^-)0.5\text{H}_2\text{O}$ (Fig. 5). When compared with the $(\text{PRX}^+\text{Cl}^-)\text{H}_2\text{O}$, in which the reported melting point is 117 $^{\circ}\text{C}$ [27–29], it shows a decrease of 15 $^{\circ}\text{C}$. The melting point differences reinforces, among others supramolecular aspects, the differences in the nature of the CAHBs and consequently, in the lattice energy of these salts.

Fig. 5. DSC (line filled) and TGA (dash line) thermograms of $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ and $(\text{PRX}^+\text{Cl}^-)0.5\text{H}_2\text{O}$.

3.4. Solubility measurements

Equilibrium solubility is a thermodynamic parameter that shows the maximum amount of the solute dissolved in a given solvent at a specific temperature. From a pharmaceutical perspective, it constitutes an important parameter to the bioavailability of a drug. The water solubility of $(\text{PRX}^+\text{Cl}^-)0.5\text{H}_2\text{O}$ and $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ was measured at 20 $^{\circ}\text{C}$ in deionized water. Despite our efforts, $(\text{PRX}^+\text{Cl}^-)\text{H}_2\text{O}$ is a form difficult to obtain, and thus only the solubility of $(\text{PRX}^+\text{Cl}^-)0.5\text{H}_2\text{O}$ hemihydrate, which is the formulation pharmaceutically approved, was determined. The solubility results for $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ and $(\text{PRX}^+\text{Cl}^-)0.5\text{H}_2\text{O}$ are 4.01 mg mL^{-1} and 6.89 mg mL^{-1} , respectively, showing a decrease in the solubility of the nitrate salt in comparison with the chlorine one. In fact, the relative structural stability of these salts appears to be reflected in their solubility differences. Although the relationship between solubility and crystal structure is not so simple, it is well accepted that this process is associated with the ability of the salt to alter both the crystal lattice energy and the degree of solvation.

Fig. 6. Photomicrographs of the $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ under heat rate of 10 $^{\circ}\text{C}/\text{min}$.

Following this assumption, since a larger molecular ion, like nitrate, is generally not as easy to solvate as a small one, it is plausible that $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ is less water soluble than $(\text{PRX}^+\text{Cl}^-)0.5\text{H}_2\text{O}$.

4. Conclusions

In summary, the crystal structure of Paroxetine nitrate hydrate salt, $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$, has been determined and its solid state characterization was performed using thermal analysis (DSC/TGA and HS Microscopy), FTIR spectroscopy and solubility measurements. Conformational similarity is observed between $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ and $(\text{PRX}^+\text{Cl}^-)\text{H}_2\text{O}$ forms. The packing of PRX nitrate is essentially characterized by formation of ionic layers of PRX^+ molecules connected to NO_3^- anions. In the crystal packing, these layers are intercalated by water channels. The presence of H_2O channels plays an important role in the supramolecular assembly of $\text{PRX}^+\text{NO}_3^-$ ionic pairs, by reducing the electronic repulsion between the anions. The packing of $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ is also stabilized by C–H $\cdots$ O and C–H $\cdots\pi$ interactions. From a pharmaceutical perspective, this salt shows desirable properties for processing, storage and drug performance. There is no occurrence of any dehydration event and the structure is thermally stable between 25 and 100 °C. The present study shows that a better comprehension of the supramolecular features of PRX salts can be crucial for a successful development of a highly safe and efficient drug.

Acknowledgments

The authors would like to acknowledge Brazilian funding agencies FAPESP (P.S.C.-Jr. grant 12/05616-7), CAPES (C.C. M) and CNPq for financial support. Also, the authors would like to thanks Dr. Judith A. K. Howard Department of Chemistry, Durham University, UK for access to their X-ray facilities.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.molstruc.2016.04.014>.

References

- [1] C. Hiemke, S. Härtter, Pharmacokinetics of selective serotonin reuptake inhibitors, *Pharmacol. Ther.* 85 (2000) 11–28.
- [2] M. Bourin, P. Chue, Y. Guillon, Paroxetine: A Review, *CNS Drug Rev.* 7 (2001) 25–47.
- [3] A.J. Goudie, W. Dubicki, M. Leathley, Paroxetine, a Selective 5-Hydroxytryptamine Uptake Inhibitor with Antidepressant Properties, Lacks Amphetamine-like Stimulus Properties in an Operant Drug Discrimination Bioassay in Rodents, *J. Pharm. Pharmacol.* 40 (1988) 192–196.
- [4] M.B. Keller, Paroxetine Treatment of Major Depressive Disorder, 2003.
- [5] M. Vaswani, F.K. Linda, S. Ramesh, Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review, *Prog. Neuro Psychopharmacol. Biol. Psychiatry* 27 (2003) 85–102.
- [6] P. Blier, M. El Mansari, Serotonin and beyond: therapeutics for major depression, *Philos. Trans. R. Soc. B Biol. Sci.* 368 (2013).
- [7] P.D. Bowen, Use of Selective Serotonin Reuptake Inhibitors in the Treatment of Depression in Older Adults: Identifying and Managing Potential Risk for Hyponatremia, *Geriatr. Nurs.* 30 (2009) 85–89.
- [8] D.L. Prohotsky, F. Zhao, A survey of top 200 drugs—inconsistent practice of drug strength expression for drugs containing salt forms, *J. Pharm. Sci.* 101 (2012) 1–6.
- [9] M.F. Pina, M. Zhao, J.F. Pinto, J.J. Sousa, C.S. Frampton, V. Diaz, O. Suleiman, L. Fábán, D.Q.M. Craig, An Investigation into the Dehydration Behavior of Paroxetine HCl Form I Using a Combination of Thermal and Diffraction Methods: The Identification and Characterization of a New Anhydrous Form, *Cryst. Growth & Des.* 14 (8) (2014) 3774–3782, <http://dx.doi.org/10.1021/cg500150r>.
- [10] M. Yokota, Uekusa, Hidehiro, Ohashi, Yuji structure analyses of two crystal forms of paroxetine hydrochloride, *Bull. Chem. Soc. Jpn.* 72 (1999) 1731–1736.
- [11] P.S. Carvalho, C.C. de Melo, A.P. Ayala, C.C.P. da Silva, J. Ellena, Reversible Solid-State Hydration/Dehydration of Paroxetine HBr Hemihydrate: Structural and Thermochemical Studies, *Cryst. Growth & Des.* 16 (2016) 1543–1549.
- [12] S.M. Berge, L.D. Bighley, D.C. Monkhouse, Pharmaceutical salts, *J. Pharm. Sci.* 66 (1977) 1–19.
- [13] D.P. Elder, R. Holm, H.L.d. Diego, Use of pharmaceutical salts and cocrystals to address the issue of poor solubility, *Int. J. Pharm.* 453 (2013) 88–100.
- [14] P.H. Stahl, C.G. Wermuth, I.U.o. Pure, A, Chemistry, *Pharmaceutical Salts: Properties, Selection, and Use*, Wiley, 2002.
- [15] J. Wouters, L. Quere, D.E. Thurston, *Pharmaceutical Salts and Co-crystals*, Royal Society of Chemistry, 2011.
- [16] Bruker, Saint, Bruker AXS Inc., Madison, Wisconsin, USA.
- [17] Bruker, Sadabs, Bruker AXS Inc., Madison, Wisconsin, USA., 2001.
- [18] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program, *J. Appl. Crystallogr.* 42 (2009) 339–341.
- [19] G. Sheldrick, A short history of SHELX, *Acta Crystallogr. Sect. A* 64 (2008) 112–122.
- [20] C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J. van de Streek, Mercury: visualization and analysis of crystal structures, *J. Appl. Crystallogr.* 39 (2006) 453–457.
- [21] M. Harrass, C. Eirkson, C.M. Osbourne, P.G. Sayre, M. Zeeman, Water solubility, in: U.S.F.a.D. Administration (Ed.), *Environmental Assessment Technical Assistance Handbook*, 1987, pp. 1–11. Washington DC.
- [22] J. Ibers, Paroxetine hydrochloride hemihydrate, *Acta Crystallogr. Sect. C* 55 (1999) 432–434.
- [23] D. Cremer, J.A. Pople, General definition of ring puckering coordinates, *J. Am. Chem. Soc.* 97 (1975) 1354–1358.
- [24] J.A.K. Howard, P. Pattison, O. Chetina, Private Communication to the Cambridge Crystallographic Data Centre, 2003.
- [25] I.B. Cozar, L. Szabó, D. Mare, N. Leopold, L. David, V. Chiş, IR, Raman, SERS and DFT study of paroxetine, *J. Mol. Struct.* 993 (2011) 243–248.
- [26] F.A. Miller, C.H. Wilkins, *Infrared Spectra and Characteristic Frequencies of Inorganic Ions*, Anal. Chem. 24 (1952) 1253–1294.
- [27] M.F. Pina, J.F. Pinto, J.J. Sousa, L. Fábán, M. Zhao, D.Q.M. Craig, Identification and Characterization of Stoichiometric and Nonstoichiometric Hydrate Forms of Paroxetine HCl: Reversible Changes in Crystal Dimensions as a Function of Water Absorption, *Mol. Pharm.* 9 (2012) 3515–3525.
- [28] G.V. Buxton, C.L. Greenstock, W.P. Helman, A.B. Ross, W. Tsang, Critical Review of rate constants for reactions of hydrated electrons, *Chemical Kinetic Data Base for Combustion Chemistry. Part 3: Propane*, *J. Phys. Chem. Ref. Data* 17 (1988), 513–513.
- [29] N. Ward, V.W. Jacewicz, Paroxetine hydrochloride form A or C, Google Pat. (2000).

PAPER 3:

CARVALHO JR, P. S.; ELLENA, J.; YUFIT, D. S.; HOWARD, J. A. K. **Rare case of polymorphism in a racemic Fluoxetine Nitrate salt: Phase Behavior and Relative Stability.** *Crystal Growth & Design*, 2016, 160 (7), pp 3875–3883

Correction to Rare Case of Polymorphism in a Racemic Fluoxetine Nitrate Salt: Phase Behavior and Relative Stability

Paulo S. Carvalho, Jr., Javier Ellena,* Dmitry S. Yufit, and Judith A. K. Howard

Cryst. Growth Des. **2016**, *16*(7), 3875–3883. DOI:10.1021/acs.cgd.6b00442. Publication Date (Web): May 12, 2016

In the aforementioned paper, the fluoxetine nitrate crystallized in the space group $Pca2_1$ and was described as a *kryptoracemate*. However, since this is a polar space group and not a Sohncke one,^{1,2} this classification is not applicable, as has been kindly pointed out by Prof. Dr. Ivan Bernal. We are grateful to Prof. Bernal for his careful reading of our manuscript. Although this new definition does not alter our discussion of the polymorphism discovered, we suggest that in the paper where it is written “kryptoracemate”, this should be understood as a “non-centrosymmetric structure composed of two independent enantiomers in the asymmetric unit”, which is also a rare occurrence. Thus, we emphasize that despite the misnomer, the paper does not fail to describe a rare case of polymorphism.

■ REFERENCES

- (1) Bernal, I.; Cai, J.; Massoud, S. S.; Watkins, S. F.; Fronczek, F. R. the Phenomenon of Kryptoracemic Crystallization. Part 1. Counterion Control of Crystallization Pathway Selection. Part 4. the Crystallization Behavior of $(\pm)$ -[Co(tren)(NO₂)₂]Br(I), $(\pm)$ -[Co(tren)(NO₂)₂]2Br(ClO₄)·H₂O(II), (+)/(-)-[Co(tren)(NO₂)₂]ClO₄(III) and Attempts to Solve the Structure of $(\pm)$ -[Co(tren)(NO₂)₂]-NO₃(IV). *J. Coord. Chem.* **1996**, *38* (1–2), 165–181.
- (2) Bernal, I.; Watkins, S. A list of organometallic kryptoracemates. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71* (3), 216–221.

Published: October 4, 2016

Rare Case of Polymorphism in a Racemic Fluoxetine Nitrate Salt: Phase Behavior and Relative Stability

Paulo S. Carvalho, Jr.,[†] Javier Ellena,^{*,†} Dmitry S. Yufit,[‡] and Judith A. K. Howard[‡]

[†]Instituto de Física de São Carlos, Universidade de São Paulo, CP 369, 13560-970 São Carlos, São Paulo, Brazil

[‡]Department of Chemistry, Durham University, South Road, Durham, U.K. DH1 3LE

S Supporting Information

ABSTRACT: Polymorphism in racemic pharmaceutical compounds is relatively unexplored. However, this phenomenon may provide an additional tool to crystal engineering, opening the doors to rational design of chiral resolution, chiral enrichment, and chiral purification of pharmaceutical compounds. In this work we report two racemic polymorphs occurring for the nitrate salt of the antidepressant drug fluoxetine (FLX): a racemate ($P2_1/n$, $Z = 4$, $Z' = 1$) and a kryptoracemate ($Pca2_1$, $Z = 4$, $Z' = 2$). The relative stability of these polymorphs was established through a combination of techniques, namely, differential scanning calorimetric (DSC), thermogravimetric analysis (TGA), hot stage microscopy (HSM), and solubility measurements. Though the two polymorphs share some structural features, the $N^+-H\cdots O^-$ hydrogen bonds have created dissimilar racemic motifs in their packing, resulting in different enantiomer orientations. The racemate is more stable over the temperature ranges we studied and is monotropically related to kryptoracemate. In our experiments, the obtaining of non-centrosymmetric lattice of racemic fluoxetine nitrate was shown to be dependent on kinetic factors. The thermodynamic relationships between both polymorphs were further confirmed by measuring their water solubility at 20 and 37 °C.

1. INTRODUCTION

Polymorphism is an important topic in crystal engineering, materials, and pharmaceutical sciences.^{1–3} Polymorph occurrence has been associated, among other phenomena, with conformational and/or molecular packing diversity.^{1,2,4–6} In racemic systems, on the other hand, the presence of two molecular components of opposite absolute configuration (enantiomers)⁷ in the crystallization medium is an additional cause of the formation of polymorphs.^{3,6,8} Although chiral molecules are less likely to exhibit polymorphism than achiral ones,⁶ the different arrangement of enantiomers and the possibility of generation of different racemic motifs can give rise to a special kind of “racemic polymorphism” in a racemic system.⁸ Depending on the crystallization conditions, racemate, *kryptoracemates* (also denoted as false conglomerate chiral), or a physical mixture of enantiomers crystals (i.e., conglomerates) can be obtained.^{9–11} When a racemate is aggregated, a racemic equimolar arrangement of enantiomers is formed in which the enantiomers are related to one another by a crystallographic inversion or glide operation.^{8,9,11,12} Alternatively, the spontaneous resolution of a racemic mixture can produce chiral *kryptoracemates* that are a racemic mixture of enantiomers adopting a chiral packing arrangement in one of the 65 Sohnke space groups.^{9,13}

In general, the crystallization of racemic systems results in racemates,^{8,12,14} whereas the *kryptoracemates* formation is more rare event.⁸ In a survey of the Cambridge Structural Database

(CSD),¹³ only 181 *kryptoracemates* structures have been identified showing that they represent only 0.1% of structures deposited in CSD.¹³ This fact agrees with the rarity of reports involving racemate and *kryptoracemates* as polymorphs in the literature.^{10,11,13,15–29} In these research articles, chirality and symmetry have been attributed to different structural features of these compounds. While the chiral space group of racemates generates only one enantiomer in the asymmetric unit (ASU), the *kryptoracemates* show $Z' > 1$, and in most of them¹³ (about 60%) they exhibit a pseudosymmetric relationship between the enantiomers.^{10,11,13} In addition, the self-assembly of chiral molecules in racemic chains motifs and their supramolecular chirality are the main structural differences between these polymorphs.^{21,22,28} The formation of such polymorphs of racemic systems is well recognized, but they remain relatively unexplored. Thus, “racemic polymorphism” potentially provides an additional tool to crystal engineering and opens the door to rational design of chiral resolution, chiral enrichment, and chiral purification of pharmaceutical compounds.

Fluoxetine (FLX), *N*-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine (Scheme 1), is a selective serotonin reuptake inhibitor (SSRI), which is used in treating a variety of depression cases and other mood disorders.^{30–32} This

Received: March 18, 2016

Revised: April 27, 2016

Published: May 12, 2016

Scheme 1. Chemical Structure of Fluoxetine Cation (FLX⁺)^a

^aThe C1 → C6 ring is designed A and the C11 → C16 ring as B.

antidepressant drug is administered orally and marketed as a racemic mixture of the chloride salt. Novel racemate crystalline forms of FLX have been discovered in recent decades, and interesting properties have been related to them.^{33,34} The FLX cocrystals containing benzoic, fumaric, and succinic acids have greater solubility than fluoxetine hydrochloride.³³ Until now, only racemate crystal structures have been reported for FLX molecule. Herein, we report the rare case of crystal structures of “racemic polymorphs” of fluoxetine nitrate (FLX⁺NO₃[−]): a racemate, FLXNO3-I (monoclinic, $P2_1/n$, $Z = 4$, $Z' = 1$), and a *kryptoracemate* FLXNO3-II (orthorhombic, $Pca2_1$, $Z = 4$, $Z' = 2$) salts, as well as the thermodynamic basis of the stereoselective interactions in FLX⁺NO₃[−] systems and their effects on thermal profile and solubility properties.

2. EXPERIMENTAL DETAILS

Commercially available fluoxetine hydrochloride, FLXCl, (TCI Chem, UK) and all other compounds were used without further purification. Ethanol and methanol solvents (St. Louis, MO) were of analytical or chromatographic grade and purchased from local suppliers. FLXCl was used for synthesis of nitrate polymorphs salts. FLXCl was dissolved in water, and excess amounts of sodium hydroxide were added followed

by gradual addition of ethyl ether. The biphasic system was stirred until both phases became clear. The ethyl ether phase was separated out from the water one and dried with Na₂SO₄, and its evaporation results in an oil phase corresponding to fluoxetine free bases. The compound obtained was used without further purification. The fluoxetine nitrate polymorphs were prepared by protonation of free base by nitrate acid 1 mol·L^{−1}. The formation of the FLXNO3-I form was observed in ethanol 95% by slow evaporation at −5 °C, while the FLXNO3-II was obtained by slow evaporation in methanol solution of racemic fluoxetine nitrate system at room temperature (20 °C).

2.1. Single Crystal Structure Determination. The X-ray diffraction data for the FLXNO3-I and FLXNO3-II polymorphs were collected at 120 K (Cryostream, Oxford Cryosystems) on a Bruker D8 VENTURE diffractometer with PHOTON 100 CMOS detector system equipped with a Cu INCOATEC μ S microfocus source ($\lambda = 1.54178$ Å). The data were integrated via SAINT.³⁵ Lorentz and polarization effect and multiscan absorption corrections were applied with SADABS.³⁶ Using Olex2,³⁷ the structures were solved by direct methods, and the models obtained were refined by full-matrix least-squares on F^2 (SHELXTL-97³⁸). All the hydrogen atoms were placed in calculated positions and refined with fixed individual displacement parameters [$U_{iso}(H) = 1.2U_{eq}$ or $1.5U_{eq}$] according to the riding model (C–H bond lengths of 0.97 Å and 0.96 Å, for methylene and methyl groups, respectively). Molecular representations, tables, and pictures were generated by Olex2,³⁷ MERCURY 3.2,³⁹ and Crystal Explorer v2.1⁴⁰ programs.

CIF files of the FLXNO3-I and FLXNO3-II were deposited in the Cambridge Structural Data Base⁴¹ under the codes CCDC 1469288 and CCDC 1469294. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk.

2.2. Thermal Analysis. Differential scanning calorimetric measurements were performed on a PerkinElmer Pyris instrument with a constant sample weight (2.5 ± 0.5 mg), scanning rate of 10 °C·min^{−1}, under dry N₂ as the purge gas, and a pierced lid in the sample pan to ease any pressure build-up. Thermogravimetric analyses were carried out on PerkinElmer Pyris thermobalance. Approximately 2.5 mg of

Table 1. Crystal Data, Data Collection, and Structure Refinement Parameters of FLXNO3-I and FLXNO3-II Polymorphs

structure	FLXNO3-I	FLXNO3-II
empirical formula	C ₁₇ H ₁₉ F ₃ N ₂ O ₄	C ₁₇ H ₁₉ F ₃ N ₂ O ₄
formula weight	372.34	372.34
temperature/K	120(2)	120(2)
crystal system	monoclinic	orthorhombic
space group	$P2_1/n$	$Pca2_1$
<i>a</i> /Å	6.5389(3)	21.1740(5)
<i>b</i> /Å	24.7851(12)	6.8422(2)
<i>c</i> /Å	11.2707(6)	24.9331(6)
β /°	105.3610(16)	90
cell volume/Å ³	1761.36(15)	3612.23(16)
<i>Z</i> , <i>Z'</i>	4, 1	4, 2
ρ_{calc} /g/cm ³	1.404	1.369
μ /mm ^{−1}	1.044	1.018
<i>F</i> (000)	776.0	1552.0
crystal size/mm ³	0.344 × 0.147 × 0.133	0.851 × 0.123 × 0.054
radiation	CuK α ($\lambda = 1.54178$)	CuK α ($\lambda = 1.54178$)
2 θ range for data collection/°	7.132–149.932	7.09–136.974
index ranges	−8 ≤ <i>h</i> ≤ 8, −31 ≤ <i>k</i> ≤ 29, −14 ≤ <i>l</i> ≤ 13	−25 ≤ <i>h</i> ≤ 25, −6 ≤ <i>k</i> ≤ 8, −29 ≤ <i>l</i> ≤ 28
reflections collected	26294	20623
independent reflections	3600 [$R_{\text{int}} = 0.0415$, $R_{\text{sigma}} = 0.0236$]	6022 [$R_{\text{int}} = 0.0813$, $R_{\text{sigma}} = 0.0732$]
data/restraints/parameters	3600/54/266	6022/149/480
goodness-of-fit on F^2	1.050	1.057
final <i>R</i> indexes [$I > 2\sigma(I)$]	$R_1 = 0.0389$, $wR_2 = 0.0948$	$R_1 = 0.0688$, $wR_2 = 0.1636$
final <i>R</i> indexes [all data]	$R_1 = 0.0466$, $wR_2 = 0.1004$	$R_1 = 0.0854$, $wR_2 = 0.1755$
largest diff. peak/hole/e·Å ^{−3}	0.26/−0.27	0.67/−0.56
Flack parameter		0.38(15)

samples were placed on an aluminum pan and heated under N_2 flow from 25 to 350 °C at a heating rate of 10 °C/min.

2.3. Hot-Stage Polarized Optical Microscopy. Microscopy was performed on a Leica DM2500P microscope connected to a Linkam T95-PE hot-stage equipment under air atmosphere. Data were visualized with a Linksys 32 software for hot-stage control. Crystals of FLXNO3-I and FLXNO3-II were placed on a 13 mm glass coverslip within a 22 mm diameter pure silver heating block inside of the stage. The samples were heated at a ramp rate of 10 °C·min⁻¹ up to a final temperature of 200 °C but discontinued on melting of all material.

2.4. Solubility Measurements. Aqueous solubility of both polymorphs was measured in distilled–deionized water by the flask saturation method.⁴² The saturated solutions of FLXNO3-I and FLXNO3-II were prepared stirring a predetermined excess quantity (30 mg) of drugs in 700 μ L of water for 24 h allowing them to reach the thermodynamic equilibrium at 20 and 37 °C respectively. The identity of solid phase(s) in equilibrium with saturated solution was monitored by DSC analysis. After 4 h of sedimentation, the solution was filtered through a 0.45 mm filter (Millipore). The concentration of supernatant was measured by UV spectroscopy. Samples were then diluted 100-fold in water before analysis. The specific absorptivity was determined in distilled water, at the selected wavelength of $\lambda = 274$ nm, and the standard solutions used to generate the calibration curve were prepared using FLXCl. The concentration of the compound in the filtrate was quantified by interpolating the spectroscopic measurements from the diluted solutions in a calibration curve whose concentrations ranged from 0.005 to 0.2 mg·mL⁻¹.

3. RESULTS AND DISCUSSION

3.1. Structural Description. Depending on the crystallization conditions, a racemic fluoxetine nitrate system (section 2) leads to formation of two different polymorphs, namely, FLXNO3-I and FLXNO3-II. The FLXNO3-I crystallizes in the monoclinic centrosymmetric space group $P2_1/n$ ($Z' = 1$) as a *racemate*, while the FLXNO3-II crystallizes in the orthorhombic non-centrosymmetric space group $Pca2_1$ ($Z' = 2$) (Table 1) as a *kryptoracemate*.^{9,12,43} In contrast to FLXNO3-I, where $Z' = 1$ (Figure 1a), the asymmetric unit of FLXNO3-II comprises two oppositely handed FLX⁺ enantiomeric cations (*R* and *S* cations) and two NO₃⁻ anions (A and B) (Figure 1b). The cell volume of FLXNO3-II is about 2 times larger than that of FLXNO3-I, and a significant difference is observed to polymorphs densities: 1.405 and 1.369 g·cm⁻³ for FLXNO3-I and FLXNO3-II, respectively. It indicates that their crystal packing differs significantly.

In the FLXNO3-II structure, the *R* and *S* enantiomers exhibit equivalent conformations (*but not identical- similarity by inversion*). These configurations show close correspondence with that found in FLXNO3-I. This can be rationalized from the superposition of non-hydrogen atoms of FLX⁺ of different solid forms (Figure 2). In the figure, the aromatic groups (A and B rings) of FLX⁺ molecules are similar, while the amine moieties show different orientations. In both polymorphs, the FLX⁺ presents a protonated secondary amine, $-NH_2^+$, synclinally oriented to C7 atom [$N1-C9-C8-C7$: $-74.96(14)^\circ$ for FLXNO3-I; $70.9(5)^\circ$ and $73.7(5)^\circ$ for *R* and *S* molecules in FLXNO3-II respectively]. In addition, the C10 atom from the amine domain is antiperiplanar orientated with respect to the C8 atom [$C10-N1-C9-C8$: $-174.59(11)^\circ$ for FLXNO3-I; $171.1(5)^\circ$ and $-173.4(5)^\circ$ for *R* and *S* molecules in FLXNO3-II respectively]. As a consequence, the $C10-N1-C9-C8$ fragment is in a plane that is almost perpendicular to the B ring ($C11 \rightarrow C16$) [$83.9(2)^\circ$ for FLXNO3-I; $97.8(3)^\circ$ and $89.4(6)^\circ$ for *R* and *S* in the FLXNO3-II respectively]. Only in the FLXCl form³⁴ the

Figure 1. ASU of FLXNO3-I (a) and FLXNO3-II (b) at $T = 120(2)$ K. Thermal ellipsoids are drawn at the 30% probability level and intermolecular $N^+-H \cdots O^-$ hydrogen bonds are highlighted as red dotted lines. The $-CF_3$ fragments in the FLX⁺ in FLXNO3-I and the *R* enantiomer in FLXNO3-II is disordered into two positions with occupational factors of 45:55 and 25:75, respectively. The less occupancy conformations are omitted for clarity. In the FLXNO3-II, the *R* and *S* enantiomers exhibit statistically similar geometrical parameters and are related by a noncrystallographic inversion center at $[0.37695(2), 0.24660(2), 0.19825(2)]$. The atom labels to the *R* cation differ from the *S* one by the (') symbol.

amine fragment adopts anti-periplanar orientation for N1 and C7 atoms [$N1-C9-C8-C7$: $-180.0(4)^\circ$] and synclinal relation to C10 and C8 atoms. The orientation of $-NH_2^+$ fragment of FLX⁺ may be affected by its involvement into the formation of strong hydrogen bonds to anion. The FLX⁺ conformations from both polymorphs are also comparable with those found in FLX salt cocrystals.³³ Selected torsion angles characterizing conformations of FLX⁺ in FLXNO3-I and FLXNO3-II are summarized in Table 2.

The molecular packing arrangements of FLXNO3-I and FLXNO3-II are presented in the Figure 3 and Figure 4, respectively. The $N^+-H \cdots O^-$ charge assisted hydrogen bond (CAHB) in FLXNO3-I binds the isomers, *R* and *S*, to each other to form an infinite $C_4^4(8)$ racemic chains along the $[100]$ direction. Along these chains, an alternating arrangement of FLX⁺ enantiomers and NO₃⁻ anions is formed, such that the $S \cdots NO_3^- \cdots R \cdots$ moiety is established. This arrangement is influenced by the presence of the $C1-H1 \cdots O1$ interaction

Figure 2. Overlaid conformations of FLX molecules in FLXNO3-I (green), FLXNO3-II (R: light yellow; inverted S: dark yellow), salt cocrystal of fluoxetine hydrochloride with benzoic (FLXCl-Benz), succinic (FLXCL-suc), and fumaric (FLXCL-Fum) acids (all in black) and FLXCl forms (gray). Hydrogen atoms have been omitted for clarity.

Table 2. Selected Torsion Angles in Polymorphs of Fluoxetine Nitrate

	FLXNO3-I	FLXNO3-II	
		R	S
C10–N1–C9–C8	−174.59(11)	171.1(5)	−173.4(5)
N1–C9–C8–C7	−74.96(14)	70.9(5)	−73.7(5)
C8–C7–C6–C1	83.5(5)	83.5(5)	−85.6(6)
C7–O4–C11–C16	175.32(11)	−176.2(5)	179.7(5)
O4–C7–C8–C9	−77.19(13)	71.4(5)	−76.5(5)

$[d_{C1\cdots O1} = 3.441(2) \text{ \AA}]$, Table 3] which constrains the NO_3^- anion in an almost perpendicular position to the C8–C9–N1–C10 portions of both adjacent isomers. In the FLXNO3-I packing, the $R\cdots S$ assemblies are also linked by the C10–

H10B $\cdots\pi$ interactions which involve the amino-methyl groups and B ring of adjacent molecules. This connection is not observed in the FLXCl structure and may be responsible for the conformational difference of FLX $^+$ molecules in the chloride and nitrate forms (Figure 2). The racemic $C_4^4(8)$ chains are held additionally together by C3–H3 $\cdots\pi$ interactions resulting in the formation of homochiral chains along the [100] and [001] directions as shown in Figure 3.

The FLX $^+$ isomers (R and S) and NO_3^- anions linked by $\text{N}^+ \cdots \text{H} \cdots \text{O}^-$ hydrogen bonds in FLXNO3-II form a $C_8^8(12)$ chain parallel to the a -axis (Figure 4). Along this chain, the $(\text{NO}_3^-)_A$ anion links the R to S isomers, while the $(\text{NO}_3^-)_B$ anion connects enantiomers so that the racemic chain has the following sequence: $S \cdots (\text{NO}_3^-)_A \cdots R \cdots (\text{NO}_3^-)_B \cdots R \cdots (\text{NO}_3^-)_A \cdots S \cdots$ (Figure 4). Similarly to FLXNO3-I, the $C_8^8(12)$ racemic arrangement provides the connection between the B ring and the terminal C10 atom by weak C10–H10E $\cdots\pi$ and C10'–H10B $\cdots\pi$ interactions [$d_{C10\cdots\pi} = 3.733(8) \text{ \AA}$; $d_{C10'\cdots\pi} = 3.553(7) \text{ \AA}$] resulting in the $R\cdots S$ and $S\cdots R$ assemblies, respectively. In the FLXNO3-II crystal structure, adjacent racemic $C_8^8(12)$ chains along the [001] direction are connected by C3–H3 $\cdots\pi$ and C3'–H3' $\cdots\pi$ contacts [$d_{C3\cdots\pi} = 3.796(8) \text{ \AA}$; $d_{C3'\cdots\pi} = 3.766(8) \text{ \AA}$] resulting, as in FLXNO3-I, in the homochiral chains along the [010] and [001] directions (Figure 4). The data on the geometry of hydrogen bonds at 120 K are summarized in Table 3.

The comparison of polymorphs structures suggests that $\text{N}^+ \cdots \text{H} \cdots \text{O}^-$ hydrogen bonds in the FLXNO3-I are slightly shorter than in the FLXNO3-II polymorph (Table 3). The $\text{N} \cdots \text{O}$ distances in the $C_4^4(8)$ motif of FLXNO3-I differ slightly from those found in the $C_8^8(12)$ motif of FLXNO3-II [$\langle \text{N} \cdots \text{O} \rangle_{\text{FLXNO3-I}}: 2.8465(2) \text{ \AA}$ and $\langle \text{N} \cdots \text{O} \rangle_{\text{FLXNO3-II}}: 2.880(2) \text{ \AA}$]. The possibility of formation of different racemic assemblies via $\text{N}^+ \cdots \text{H} \cdots \text{O}^-$ hydrogen bonds agrees with the assumption that this process is strongly enthalpy dependent. This aspect became clearly evident during the crystallization. While the prismatic crystals of FLXNO3-I were slowly grown from the ethanolic solution of FLXNO3 at -5°C , the platelet-shaped crystals of

Figure 3. Molecular packing for FLXNO3-I. The $S \cdots \text{NO}_3^- \cdots R \cdots$ assembly provided by racemic $C_4^4(12)$ motif. The R and S enantiomers are presented in blue and red, respectively. The $\text{N}^+ \cdots \text{H} \cdots \text{O}^-$ bonds are presented in a red dotted line, while the C1–H1 $\cdots$ O1 interactions are a green dotted line.

Figure 4. Molecular packing for FLXNO3-II. The racemic $C_8^8(12)$ motif aggregates the FLX⁺ enantiomers as $S \cdots (NO_3^-)_A \cdots R \cdots (NO_3^-)_B \cdots R \cdots (NO_3^-)_A \cdots S \cdots$. The R and S enantiomers are presented in blue and red, respectively. The $N^+ \cdots H \cdots O^-$ H-bonds are presented in red dotted lines.

Table 3. Hydrogen-Bond Geometry for Two Polymorphs of Fluoxetine Nitrate at 120 K^a

	D–H...A	<i>d</i> (D...A) (Å)	<i>d</i> (H...A) (Å)	∠D–H...A (deg)	symmetry codes
FLXNO3-I	N1–H1A...O1	2.8800(16)	1.9773(11)	171.23(7)	<i>x</i> , <i>y</i> , <i>z</i>
	N1–H1B...O2	2.8129(16)	1.9344(11)	161.71(8)	<i>x</i> , <i>y</i> , <i>z</i>
	C1–H1...O3	3.440(2)	2.574(2)	155.04(11)	<i>x</i> – 1/2, – <i>y</i> + 1/2 + 1, + <i>z</i> – 1/2
	C7–H7...O1	3.347(2)	2.381(1)	168.51(1)	<i>x</i> , <i>y</i> , <i>z</i>
	C10–H10C...O1	3.275(2)	2.557(1)	131.72(2)	<i>x</i> – 1, + <i>y</i> , + <i>z</i>
	C3–H3...Cg1	3.763(2)	2.983(1)	142.42(2)	– <i>x</i> , – <i>y</i> , 2 – <i>z</i>
	C10–H10B...Cg1	3.725(2)	2.787(2)	166.09(2)	1/2 + <i>x</i> , 1/2 – <i>y</i> , 1/2 + <i>z</i>
FLXNO3-II	N1–H1B...O1	2.922(7)	2.052(5)	159.6(3)	– <i>x</i> + 1, – <i>y</i> + 1, + <i>z</i> + 1/2
	N1–H1A...O2'	2.836(6)	1.939(4)	168.6(4)	– <i>x</i> + 1, – <i>y</i> + 2, + <i>z</i> + 1/2
	N1'–H1'B...O1'	2.954(7)	2.071(5)	163.3(3)	<i>x</i> , <i>y</i> , <i>z</i>
	N1'–H1'B...O2	2.810(6)	1.905(4)	172.7(4)	– <i>x</i> + 1, – <i>y</i> + 1, + <i>z</i> + 1/2
	C7–H7...O1	3.341(8)	2.349(6)	171.7(4)	– <i>x</i> + 1, – <i>y</i> + 1, + <i>z</i> + 1/2
	C7'–H7'...O1'	3.367(7)	2.395(5)	171.62(3)	<i>x</i> , <i>y</i> , <i>z</i>
	C10–H10E...Cg1	3.554(5)	2.982(2)	119.51(2)	–1/2 + <i>x</i> , 1 – <i>y</i> , <i>z</i>
	C10'–H10D...Cg'1	3.711(7)	2.856(2)	148.73(4)	<i>x</i> , <i>y</i> , <i>z</i>
	C3–H3...Cg'1	3.759(7)	2.989(2)	141.08(4)	<i>x</i> , 1 + <i>y</i> , <i>z</i>

^aCg1: C11 → C16 and Cg'1: C11' → C16' *When available, estimated standard deviations are reported in parentheses.

FLXNO3-II (Figure 7; Figure S2, Supporting Information) were obtained at 20 °C (see Experimental Section). A mix of polymorphs is obtained by evaporation of an ethanol solution at room temperature (Figure S2, Supporting Information). The concomitant growth of both polymorphs in the same crystallization medium occurs due to an interplay of kinetic and thermodynamic factors, with the dominance of the kinetic ones.⁴⁴ On the other hand, the recrystallization of any form using more volatile solvents than ethanol provides only the formation of FLXNO3-II crystals.

It is noteworthy that the polymorphism of fluoxetine nitrate involves however some structural similarities between polymorphs. This is, first, noted from the respective unit cell parameters (see Table 1). The FLXNO3-I *a* and *b* axis are similar to the *b* and *c* axis of FLXNO3-II, respectively. In spite of the differences in the $C_4^4(8)$ and $C_8^8(12)$ racemic chains from FLXNO3-I and FLXNO3-II, homochiral chains in both polymorphs show a similar separation between enantiomers

(~6.5 Å). Similarly, the engagement (coupling) of adjacent chain motifs in each polymorph arranges symmetrically equivalent FLX⁺ molecules spaced at ~24.7 Å, but in different directions (Figure S3, Supporting Information). However, the $C_4^4(8)$ and $C_8^8(12)$ racemic motifs differ in the R...S distances along the chain (FLXNO3-I: ~9.085(2) Å; FLXNO3-II: ~8.811(2) Å). This observation is in agreement with the assumption that the occurrence of these racemic polymorphs is related to the different processes of chiral molecular recognition, provided by CAHB, and resulting in the formation of different stable motifs.

3.2. Hirshfeld Surface Fingerprint Plots. The fingerprint plot for the FLX⁺ cation in FLXNO3-I is depicted in Figure 5a, while those for the FLX⁺ cations in FLXNO3-II are depicted in Figure 5b,c. The Hirshfeld surface analysis is a powerful tool for exploring and comparing packing modes and intermolecular interactions in polymorphs.^{45–47} By definition, this surface encloses the volume of space surrounding a molecule in a

Figure 5. Hirshfeld surface fingerprint plots of the nearest internal distance (d_i) versus the nearest external distance (d_e) for the FLX⁺ cation from (a) FLXNO3-I and (b) FLXNO3-II at $T = 120$ K. The colors represent the frequency of number of points that share the same (d_i , d_e) coordinate (light blue: many; dark blue: few). Close contacts are labeled as follows: N...H (1), H...H (2), C...H (3), and F...H (4).

crystal where the electron density of the promolecule exceeds that due to any other molecules.^{45,47,48} The 2-D fingerprint plot is a map that exhibits the number of combinations of d_i (i.e., distance from the surface to the nearest atom interior to the surface) and d_e (i.e., distance from the surface to the nearest atom exterior to the surface) values on the Hirshfeld surfaces. Thus, these plots summarize the topological contribution of intermolecular interactions in the nearest environment of molecule.

From Figure 5, it is remarkable that: (i) Similar prominent sharp spikes at $d_e + d_i \approx 1.8$ – 1.9 Å, indicated by (1) is present in the diagrams and are assigned to N⁺–H...O[−] H-bonds. The 2-D fingerprint plots for the cations are reasonably different from that normally found in molecular crystals, in this case, due to the unidirectionality of the CAHB donation to the NO₃[−] anion. (ii) With exception of those (d_e , d_i) associated with the CAHBs, the FLXNO3-I plot is almost symmetrical with respect to main diagonal which indicates that all intermolecular contacts are set up between the same pairs of donor and acceptor molecules. On the other hand, the asymmetry of the plot of both enantiomer in the FLXNO3-II results from the presence of more than one cation in the ASU ($Z' = 2$). (iii) A characteristic hump at $d_i = d_e = 1.2$ Å (denoted by (2)) is more frequent in the diagrams of FLXNO3-II than in FLXNO3-I. (iv) A narrow light blue along the diagonal, $d_i + d_e \approx 2.2$ Å, is considerable in the FLXNO3-I plot, but not in that of the FLXNO3-II. This feature is attributed to unusually close H...H intermolecular contacts such as those observed between the phenyl groups in FLXNO3-I (the R and S enantiomers show the H5...H5' distanced from $\sim 2.19(2)$ Å) and in FLXNO3-II (H1...H5 distance is $\sim 2.26(2)$ Å) (Figure S4, Supporting Information). In the crystal structure of both polymorphs, racemic chains form an antiparallel arrangement orientating the aromatic groups in hydrophobic regions. In addition, these plot differences also reveal that the FLX⁺ cation in FLXNO3-I experiences a slightly more crowded environment those in FLXNO3-II.^{22,45,47} (v) As expected, the densest FLXNO3-I has the more compact fingerprint plot.⁴⁹ (vi) In the FLXNO3-II diagrams, it is possible to identify complementary regions where one molecule acts as a donor and the other one as an acceptor. The small “wings” at 1.6 Å $< (d_e + d_i) < 2.6$ Å, designated as (3) in Figure 5b,c correspond to the C3–H3... π

and C10–H10B... π interactions, in which molecule R acts as a donor and molecule S as an acceptor. (vii) Because of the CF₃ disordered group, a small spike at $d_e + d_i \approx 2.5$ Å, designated as (4) and corresponding to the C–H...F interactions observed along the homochiral chains, is only evident in the plot of S but not in the R enantiomer.

3.3. Phase Relationships. Since the structural differences between FLXNO3-I and FLXNO3-II polymorphs were identified, understanding the relative stability of both phases is important once it allows selecting which form will be produced via the crystallization process. The thermal profiles of polymorphs were performed using DSC/TGA and HSM microscopy in the temperature range of 25–300 °C. The results are presented in the Figure 6, and summary data are shown in Table 4. The DSC curve for FLXNO3-I (Figure 6a) shows three thermal events with temperatures centered at 119.88 ± 0.02 °C, 253.45 ± 0.02 °C, and 282.51 ± 0.02 °C. The first endothermic event, $\Delta H = +57.76$ J·g^{−1}, corresponds to the melting of sample (confirmed by TGA curve), while the other events are associated with thermal decomposition process. No significant weight loss is observed until 253 °C. After this temperature, a single weight loss step is observed in the TGA curve. On the other hand, the FLXNO3-II shows a single endothermic peak at 116.75 ± 0.01 °C, $\Delta H = +34.97$ J·g^{−1}, corresponding to a melting event and an exothermic one centered at 186.78 ± 0.01 °C. The exothermic event is associated with the decomposition of the sample and a two-step weight loss is observed in the TGA curve above ~ 198 °C. Although HSM and DSC/TG experiments were recorded under different atmospheres, it is worth mentioning that all the temperature analyses are in good agreement to each other. From Figure 7, it can be seen that at 120 °C the crystal of FLXNO3-I starts to melt and changes its morphology and that above 122 °C it has completely melted into a liquid droplet. Meanwhile, the FLXNO3-II starts to melt at 112 °C, and it is that completely melted above 116 °C. The polymorphs show no change of habit or color before their respective fusions. The FLXNO3-I and FLXNO3-II have close melting temperatures, but the melting enthalpy of FLXNO3-I is 1.65 times greater than the respective enthalpy observed in FLXNO3-II (Table 4). The packing differences between FLXNO3-I and FLXNO3-II result in different mechanisms by which heat is dissipated by

Figure 6. DSC/TGA curves recorded with (a) FLXNO3-I and (b) FLXNO3-II.

the molecules in each polymorphic lattice; i.e., the higher melting point of FLXNO3-I is the result of a close packing formed by stronger intermolecular interactions. The conformational, supramolecular, and packing efficiency similarities (FLXNO3-I: 68.1% and FLXNO3-II: 65.4%) may explain their similar properties and conformation (section 3, Figure S2, Supporting Information). Furthermore, there is no difference in the structures of each polymorphs collected at 120 and 298 K, respectively (Table S1, Supporting Information).

Considering the results from the methods discussed above, we observe that (i) the higher melting point of FLXNO3-I (Table 4) indicates that it is more stable than FLXNO3-II near the melting region. (ii) No phase transition is observed in both forms in the range between 120 K and their respective melting points. (iii) The lower heat of fusion of the lower melting FLXNO3-II ($34.97 \text{ J}\cdot\text{g}^{-1}$ in FLXNO3-II vs $57.76 \text{ J}\cdot\text{g}^{-1}$ in FLXNO3-I) indicates that the crystal forms are monotropically related (Heat of Fusion Rule).^{1,2,50} It means that FLXNO3-II

and FLXNO3-I are thermodynamically stable in the entire temperature range between 120 K and the melting point.^{21,51,52} The polymorphs show very different racemic packing motifs (Figures 3 and 4), so that the possible transitions between must necessarily involve a reconstructive process. The FLXNO3-I (higher melting) is indeed less stable (less soluble) near ambient temperature. On the basis of these observations, the schematic energy–temperature diagram of fluoxetine nitrate polymorphs was constructed (Figure S4, Supporting Information). Since both polymorphs are stable, the coexistence (coformation) of phases at wide range of temperatures can be explained straightforwardly by kinetic models. These results correlate well with the relative solubility of the racemic polymorphs.

3.4. Solubility. The relative stability of FLXNO3-I and FLXNO3-II racemic polymorphs was also determined from their aqueous solubility. Since the dissolution process involves the breakdown of crystal lattice to separate the crystal components into soluble species, the solubility can be applied as a measurement of stability between polymorphs.^{53–55} The water solubility of FLXNO3-I and FLXNO3-II were determined at 20 and 37 °C, and the results are shown in the Table 4. The solubility, for both polymorphs, increases with temperature, and both phases show significant differences at both temperatures (Table 4). Over the temperature ranges studied, the FLXNO3-I is thermodynamically more stable than FLXNO3-II and hence is less soluble. Thus, these thermodynamic relationships of the two polymorphs obtained by the solubility measurements are consistent with those obtained by DSC, $m.p(\text{FLXNO3-I}) > m.p(\text{FLXNO3-II})$. The standard molar Gibbs free energy of transfer from the solid phase to the soluble medium (ΔG_T) for FLXNO3-I and FLXNO3-II were estimated at 300 K^{1,2,56,57} using the aqueous solubility data (Table 4). The difference between the ΔG_T of FLXNO3-I and FLXNO3-II is about 1.50 kJ mol^{-1} and reflects not only differences in polymorphs energies but also shows that the solubility process of FLXNO3-II is thermodynamically more favorable.

4. CONCLUSIONS

Herein, we have synthesized and investigated the crystal structures of two polymorphs of racemic fluoxetine nitrate. From a racemic system, a racemate, FLXNO3-I, and a kryptoracemate, FLXNO3-II, were obtained via different crystallization conditions and then were analyzed using several methods. Since the occurrence of kryptoracemates is rare, this case of polymorphism is unusual. The analysis of the structures revealed the presence of different racemic chain motifs formed by $\text{N}^+ - \text{H} \cdots \text{O}^-$ interactions generating different orientations of the FLX enantiomers in the packing diagrams of FLXNO3-I

Table 4. Thermal Properties and Solubility of FLXNO3-I and FLXNO3-II

	FLXNO3-I	FLXNO3-II
density ^a , $\text{g}\cdot\text{cm}^{-3}$	1.405	1.369
melting point ^b , °C	119.88	116.75
enthalpy of fusion ^c , $\text{J}\cdot\text{g}^{-1}$	57.76	34.97
water solubility at 20 °C, $\text{mg}\cdot\text{mL}^{-1}$	3.287 ± 0.004	4.439 ± 0.0044
water solubility at 37 °C, $\text{mg}\cdot\text{mL}^{-1}$	5.444 ± 0.017	7.363 ± 0.060
ΔG_T at 300 K, kJ mol^{-1}	21.599	20.098

^aCalculated from crystallographic data. ^bMaximum temperature of melting peak from DSC curves. ^cThe heats of fusion measured by integration of melting endotherm in the total heat flow.

Figure 7. Hot sStage micrographs of FLXNO3-I and FLXNO3-II during the heating process at 10 °C/min.

and FLXNO3-II. Although the crystal packing is different in the two polymorphs, their densities do not differ greatly, i.e., 1.405 and 1.369 g·cm⁻³ for FLXNO3-I and FLXNO3-II, respectively. While the centrosymmetric arrangement of FLXNO3-I (*P*₂₁/*n*) results in a denser and more stable structure, the crystallization of kryptoracemate lattice of FLXNO3-II (*Pca*2₁) is related to the dominance of the kinetic factors. In the crystallization experiments, the fast evaporation condition favored the formation of FLXNO3-II. Solid-state characterization showed that the difference in melting points of the two polymorphs is small, but the difference in the melting heat of fusion is substantial. The FLXNO3-I is thermodynamically more stable than FLXNO3-II. Solubility measurements performed for both polymorphs at 20 and 37 °C also confirmed their thermodynamic relationships. On the basis of the heat-of-fusion rule,^{1,2,50} it was concluded that the polymorphs are monotropically related. These findings introduce insights and properties of these new compounds that may find suitable applications for pharmaceutical formulations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.6b00442.

Refinement details, tables of X-ray crystallographic data, bond lengths (Å) and angles (deg), data and figures related to supramolecular arrangement, H···H contacts, and qualitative *E*–*T* plot for the two polymorphs of fluoxetine nitrate salts (FLXNO3-I and FLXNO3-II) (PDF)

Accession Codes

CCDC 1469288, 1469294, 1469371, 1469373, 1469431, and 1469448 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: javiere@ifsc.usp.br.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

P.S.C. and J.E. would like to acknowledge Brazilian funding agencies FAPESP (Grant Nos. 12/05616-7 and 2014/12429-4), CAPES, and CNPq for financial support. Also, the authors

would like to thank the University of Durham for access to their X-ray facilities.

■ REFERENCES

- (1) Bernstein, J. *Polymorphism in Molecular Crystals*; Clarendon Press: Gloucestershire, U.K., 2002.
- (2) Hilfiker, R. *Polymorphism: In the Pharmaceutical Industry*; Wiley: New York, 2006.
- (3) Reddy, I. K.; Mehvar, R. *Chirality in Drug Design and Development*; Taylor & Francis: Oxfordshire, U.K., 2004.
- (4) Bernstein, J. Polymorphism – A Perspective. *Cryst. Growth Des.* **2011**, *11* (3), 632–650.
- (5) Lee, A. Y.; Erdemir, D.; Myerson, A. S. Crystal Polymorphism in Chemical Process Development. *Annu. Rev. Chem. Biomol. Eng.* **2011**, *2* (1), 259–280.
- (6) Cruz-Cabeza, A. J.; Reutzel-Edens, S. M.; Bernstein, J. Facts and fictions about polymorphism. *Chem. Soc. Rev.* **2015**, *44* (23), 8619–8635.
- (7) Chong-Hui, G.; David, J. W. G. Effects of Crystal Structure and Physical Properties on the Release of Chiral Drugs. In *Chirality in Drug Design and Development*; CRC Press: Boca Raton, FL, 2004.
- (8) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Krieger Pub. Co.: Malabar, FL, 1994.
- (9) Bishop, R.; Scudder, M. L. Multiple Molecules in the Asymmetric Unit (*Z'* > 1) and the Formation of False Conglomerate Crystal Structures†. *Cryst. Growth Des.* **2009**, *9* (6), 2890–2894.
- (10) Gubaidullin, A. T.; Samigullina, A. I.; Bredikhina, Z. A.; Bredikhin, A. A. Crystal structure of chiral ortho-alkyl phenyl ethers of glycerol: true racemic compound, normal, false and anomalous conglomerates within the single five-membered family. *CrystEngComm* **2014**, *16* (29), 6716–6729.
- (11) Steed, K. M.; Steed, J. W. Packing Problems: High *Z'* Crystal Structures and Their Relationship to Cocrystals, Inclusion Compounds, and Polymorphism. *Chem. Rev.* **2015**, *115* (8), 2895–2933.
- (12) Srisanga, S.; ter Horst, J. H. Racemic Compound, Conglomerate, or Solid Solution: Phase Diagram Screening of Chiral Compounds. *Cryst. Growth Des.* **2010**, *10* (4), 1808–1812.
- (13) Fabian, L.; Brock, C. P. A list of organic kryptoracemates. *Acta Crystallogr., Sect. B: Struct. Sci.* **2010**, *66* (1), 94–103.
- (14) Stahly, G. P. Diversity in Single- and Multiple-Component Crystals. The Search for and Prevalence of Polymorphs and Cocrystals. *Cryst. Growth Des.* **2007**, *7* (6), 1007–1026.
- (15) Laubenstein, R.; Serb, M. D.; Englert, U.; Raabe, G.; Braun, T.; Braun, B. Is it all in the hinge? A kryptoracemate and three of its alternative racemic polymorphs of an aminonitrile. *Chem. Commun.* **2016**, *52* (6), 1214–1217.
- (16) He, Q.; Rohani, S.; Zhu, J.; Gomaa, H. Sertraline Racemate and Enantiomer: Solid-State Characterization, Binary Phase Diagram, and Crystal Structures. *Cryst. Growth Des.* **2010**, *10* (4), 1633–1645.
- (17) Bredikhin, A. A.; Zakharychev, D. V.; Gubaidullin, A. T.; Fayzullin, R. R.; Pashagin, A. V.; Bredikhina, Z. A. Crystallization Features of the Chiral Drug Timolol Precursor: The Rare Case of Conglomerate with Partial Solid Solutions. *Cryst. Growth Des.* **2014**, *14* (4), 1676–1683.

- (18) Burger, A.; Rollinger, J. M.; Brüggeller, P. Binary system of (R)- and (S)-nitrendipine—polymorphism and structure. *J. Pharm. Sci.* **1997**, *86* (6), 674–679.
- (19) Sunatsuki, Y.; Fujita, K.; Maruyama, H.; Suzuki, T.; Ishida, H.; Kojima, M.; Glaser, R. Chiral Crystal Structure of a P212121 Kryptoracemate Iron(II) Complex with an Unsymmetric Azine Ligand and the Observation of Chiral Single Crystal Circular Dichroism. *Cryst. Growth Des.* **2014**, *14* (8), 3692–3695.
- (20) Brandel, C.; Amharar, Y.; Rollinger, J. M.; Griesser, U. J.; Cartigny, Y.; Petit, S.; Coquerel, G. Impact of Molecular Flexibility on Double Polymorphism, Solid Solutions and Chiral Discrimination during Crystallization of Diprophylline Enantiomers. *Mol. Pharmaceutics* **2013**, *10* (10), 3850–3861.
- (21) Reutzel-Edens, S. M.; Russell, V. A.; Yu, L. Molecular basis for the stability relationships between homochiral and racemic crystals of tazofelone: a spectroscopic, crystallographic, and thermodynamic investigation. *Journal of the Chemical Society, Perkin Transactions 2* **2000**, No. 5, 913–924.
- (22) Lo Presti, L.; Sist, M.; Loconte, L.; Pinto, A.; Tamborini, L.; Gatti, C. Rationalizing the Lacking of Inversion Symmetry in a Noncentrosymmetric Polar Racemate: An Experimental and Theoretical Study. *Cryst. Growth Des.* **2014**, *14* (11), 5822–5833.
- (23) Ichikawa, A.; Ono, H.; Echigo, T.; Mikata, Y. Crystal structures and chiral recognition of the diastereomeric salts prepared from 2-methoxy-2-(1-naphthyl)propanoic acid. *CrystEngComm* **2011**, *13* (14), 4536–4548.
- (24) Isakov, A. L.; Kotelnikova, E. N.; Kryuchkova, L. Y.; Lorenz, H. Effect of crystallization conditions on polymorphic diversity of malic acid RS — Racemate. *Trans. Tianjin Univ.* **2013**, *19* (2), 86–91.
- (25) Kaemmerer, H.; Lorenz, H.; Black, S. N.; Seidel-Morgenstern, A. Study of System Thermodynamics and the Feasibility of Chiral Resolution of the Polymorphic System of Malic Acid Enantiomers and Its Partial Solid Solutions. *Cryst. Growth Des.* **2009**, *9* (4), 1851–1862.
- (26) Chaimbault, C.; Bosc, J. J.; Leger, J. M.; Negrier, P.; Capelle, F.; Jarry, C. Physicochemical and crystallographic evidence for polymorphism of the racemic ethyl (2-chloromethyl-2,3-dihydro-5H-oxazolo [3,2-a]pyrimidin-5-one)-6-carboxylate. *J. Pharm. Sci.* **2000**, *89* (11), 1496–1504.
- (27) Rollinger, J. M.; Burger, A. Polymorphism of racemic felodipine and the unusual series of solid solutions in the binary system of its enantiomers. *J. Pharm. Sci.* **2001**, *90* (7), 949–959.
- (28) Bao, R.-Y.; Yang, W.; Liu, Z.-Y.; Xie, B.-H.; Yang, M.-B. Polymorphism of a high-molecular-weight racemic poly(l-lactide)/poly(d-lactide) blend: effect of melt blending with poly(methyl methacrylate). *RSC Adv.* **2015**, *5* (25), 19058–19066.
- (29) Gautier, R.; Norquist, A. J.; Poepelmeier, K. R. From Racemic Units to Polar Materials. *Cryst. Growth Des.* **2012**, *12* (12), 6267–6271.
- (30) Hiemke, C.; Härtter, S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol. Ther.* **2000**, *85* (1), 11–28.
- (31) Wong, D. T.; Horng, J. S.; Bymaster, F. P.; Hauser, K. L.; Molloy, B. B. A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-Trifluoromethylphenoxy)-n-methyl-3-phenylpropylamine. *Life Sci.* **1974**, *15* (3), 471–479.
- (32) Walker, F. R. A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: Do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? *Neuropharmacology* **2013**, *67* (0), 304–317.
- (33) Childs, S. L.; Chyall, L. J.; Dunlap, J. T.; Smolenskaya, V. N.; Stahly, B. C.; Stahly, G. P. Crystal Engineering Approach To Forming Cocrystals of Amine Hydrochlorides with Organic Acids. Molecular Complexes of Fluoxetine Hydrochloride with Benzoic, Succinic, and Fumaric Acids. *J. Am. Chem. Soc.* **2004**, *126* (41), 13335–13342.
- (34) Robertson, D. W.; Jones, N. D.; Swartzendruber, J. K.; Yang, K. S.; Wong, D. T. Molecular structure of fluoxetine hydrochloride, a highly selective serotonin-uptake inhibitor. *J. Med. Chem.* **1988**, *31* (1), 185–189.
- (35) SAINT; Bruker: Madison, Wisconsin, USA.
- (36) SADABS; Bruker: Madison, Wisconsin, USA, 2001.
- (37) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009**, *42* (2), 339–341.
- (38) Sheldrick, G. A short history of SHELX. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64* (1), 112–122.
- (39) Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. Mercury: visualization and analysis of crystal structures. *J. Appl. Crystallogr.* **2006**, *39* (3), 453–457.
- (40) Wolff, S.; Grimwood, D.; McKinnon, J.; Jayatilaka, D.; Spackman, M. *CrystalExplorer 2.1*; University of Western Australia, Perth, 2007.
- (41) Allen, F. The Cambridge Structural Database: a quarter of a million crystal structures and rising. *Acta Crystallogr., Sect. B: Struct. Sci.* **2002**, *58* (3 Part 1), 380–388.
- (42) Erikson, C. H. M.; Osbourne, C. M.; Sayre, P. G.; Zeeman, M. In *Environmental Assessment Technical Assistance Handbook*; U.S. Food and Drug Administration: Washington, D.C., 1987; Vol. 31, pp 1–11.
- (43) Steinberg, A.; Ergaz, I.; Toscano, R. n. A.; Glaser, R. Crystallization of a Racemate Affords a P21 Chiral Crystal Structure: Asymmetric Unit of Two Opposite Handed Molecules Simulates Achiral P21/n Packing via Pseudosymmetry. *Cryst. Growth Des.* **2011**, *11* (4), 1262–1270.
- (44) Bernstein, J.; Davey, R. J.; Henck, J.-O. Concomitant Polymorphs. *Angew. Chem., Int. Ed.* **1999**, *38* (23), 3440–3461.
- (45) Spackman, M. A.; Jayatilaka, D. Hirshfeld surface analysis. *CrystEngComm* **2009**, *11* (1), 19–32.
- (46) Mark, A. S. *Phys. Scr.* **2013**, *87* (4), 048103.
- (47) McKinnon, J. J.; Spackman, M. A.; Mitchell, A. S. Novel tools for visualizing and exploring intermolecular interactions in molecular crystals. *Acta Crystallogr., Sect. B: Struct. Sci.* **2004**, *60* (6), 627–668.
- (48) Bernardes, C. E. S.; Lopes, M. L. S. M.; Ascenso, J. R.; da Piedade, M. E. M. From Molecules to Crystals: The Solvent Plays an Active Role Throughout the Nucleation Pathway of Molecular Organic Crystals. *Cryst. Growth Des.* **2014**, *14* (11), 5436–5441.
- (49) Durka, K.; Hoser, A. A.; Kaminski, R.; Lulinski, S.; Serwatowski, J.; Kozminski, W.; Wozniak, K. Polymorphism of a Model Arylboronic Azaster: Combined Experimental and Computational Studies. *Cryst. Growth Des.* **2011**, *11* (5), 1835–1845.
- (50) Burger, A.; Ramberger, R. On the polymorphism of pharmaceuticals and other molecular crystals. *Microchimica Acta* **1979**, *72* (3), 273–316.
- (51) Yu, L. Inferring thermodynamic stability relationship of polymorphs from melting data. *J. Pharm. Sci.* **1995**, *84* (8), 966–974.
- (52) Park, Y.; Lee, J.; Lee, S. H.; Choi, H. G.; Mao, C.; Kang, S. K.; Choi, S.-E.; Lee, E. H. Crystal Structures of Tetramorphic Forms of Donepezil and Energy/Temperature Phase Diagram via Direct Heat Capacity Measurements. *Cryst. Growth Des.* **2013**, *13* (12), 5450–5458.
- (53) Bhattachar, S. N.; Deschenes, L. A.; Wesley, J. A. Solubility: it's not just for physical chemists. *Drug Discovery Today* **2006**, *11* (21–22), 1012–1018.
- (54) Black, S. N.; Collier, E. A.; Davey, R. J.; Roberts, R. J. Structure, solubility, screening, and synthesis of molecular salts. *J. Pharm. Sci.* **2007**, *96* (5), 1053–1068.
- (55) Cassens, J.; Prudic, A.; Ruether, F.; Sadowski, G. Solubility of Pharmaceuticals and Their Salts As a Function of pH. *Ind. Eng. Chem. Res.* **2013**, *52* (7), 2721–2731.
- (56) Noubigh, A.; Abderrabba, M.; Provost, E. Temperature and salt addition effects on the solubility behaviour of some phenolic compounds in water. *J. Chem. Thermodyn.* **2007**, *39* (2), 297–303.
- (57) Lohani, S.; Grant, D. J. W. Thermodynamics of Polymorphs. In *Polymorphism*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006; pp 21–42.

4 CONCLUSIONS

The solid state crystal engineering principles were used in this work to perform the supramolecular synthesis of novel multicomponent solid forms of the SSRI antidepressants Paroxetine and Fluoxetine. Specifically, the crystal structures of the Paroxetine Bromide Hemihydrate ((PRXBr) $0.5\text{H}_2\text{O}$) and its dehydrate (PRXBr) forms have been determined. Its study and comparison allow as understanding a reversible hydration/dehydration process in this solid form as a function of temperature as well as correlating that with their crystal packings. This information were used lately to enlighten the non-reversible dehydration process found in the isostructural salts (PRXCl) $0.5\text{H}_2\text{O}$ which have been for long time a highly scientific and legally debated issue due to its commercial importance. Despite the similarity in their crystal packings, the bromide and chloride salts show different thermal properties and dehydration processes. The differences in the process are related to the supramolecular arrangement of the water molecules in the cavity as well as the tridimensional form of the channels in which they are allocated. Furthermore, Paroxetine Nitrate Hydrate ((PRXNO₃) H_2O) was elucidated and its thermal properties correlated with its solubility. This salt is less stable and soluble than the commercial form, (PRXCl) $0.5\text{H}_2\text{O}$. The solid state physico-chemical study of the Fluoxetine Nitrate show the presence of a rare case of racemic polymorphs related to the ability of FLX to crystallize as a non-centrosymmetric structure with independent enantiomers in the asymmetric unit ($Pca2_1$, $Z' = 2$) or a racemate ($P2_1/c$). The existence of a racemate and a non-centrosymmetric structure for the racemic arrangement of Fluoxetine Nitrate is a critical case of polymorphism and represents a valuable contribution to the context of the polymorphism research and the discovery of polymorphic systems having $Z' > 1$.

In the pharmaceutical scenario, the present study open opportunities for the repositioning of multicomponent salts of Paroxetine and Fluoxetine as antidepressant drugs, with improved physico-chemical properties. Also, the results add to the diversity of solid forms of antidepressants and expand the scope of supramolecular solid forms for different applications. This fact contributes to the manufacturability of these ingredients opening new route to the development of new low cost generic drugs.

Given the potential of new solid multicomponent formulations of APIs in the generation of functional materials with improved physicochemical properties, the future perspectives of this work involve the synthesis and characterization of new Sertraline and Fluoxetine salts. In addition to the structures presented in this thesis, others Sertraline and

Fluoxetine salts were obtained during the PhD activities. In particular, sertraline salts were obtained during completion of academic collaboration internship at the Chemistry Department of the Durham University. The analysis of these new solid forms is still in progress.

REFERENCES

- 1 GOMEZ, R. Depression anxiety stress scales: factor structure and differential item functioning across women and men. **Personality and Individual Differences**, v. 54, n. 6, p. 687-691, 2013.
- 2 KELLER, M. B.; GELENBERG, A. J.; HIRSCHFELD, R. M.; RUSH, A. J.; THASE, M. E.; KOCSIS, J. H.; MARKOWITZ, J. C.; FAWCETT, J. A.; KORAN, L. M.; KLEIN, D. N.; RUSSEL, J. M.; KORNSTEIN, S. G.; MCCULLOUGH, J. P.; DAVIS, S. M.; HARRISON, W. The treatment of chronic depression, part 2: a doubleblind, randomized trial of sertraline and imipramine. **Journal of Clinical Psychiatry**, v. 59, n. 11, p. 598-607, 1998.
- 3 SOUCY CHARTIER, I.; PROVENCHER, M. D. Behavioural activation for depression: efficacy, effectiveness and dissemination. **Journal of Affective Disorders**, v. 145, n. 3, p. 292-299, 2013.
- 4 KESSLER, R. C.; MCGONAGLE, K. A.; ZHAO, S.; NELSON, C. B.; HUGHES, M.; ESHLEMAN, S.; WITTCHEN, H.U.; KENDLER, K.S. Lifetime and 12-month prevalence of dsm-iii-r psychiatric disorders in the united states: results from the national comorbidity survey. **Archives of General Psychiatry**, v. 51, n. 1, p. 8-19, 1994.
- 5 BOCK, J. O.; BRETTSCHEIDER, C.; WEYERER, S.; WERLE, J.; WAGNER, M.; MAIER, W.; SCHERER, M.; KADUSZKIEWICZ, H.; WIESE, B.; MOOR, L.; STEIN, J.; RIEDEL-HELLER, S. G.; KÖNIG, H.H. Excess health care costs of late-life depression – results of the AgeMooDe study. **Journal of Affective Disorders**, v. 199, n.15, p. 139-147, 2016.
- 6 WORLD HEALTH ORGANIZATION. WHO. **Investing in treatment for depression and anxiety leads to fourfold return.** Available from: <<http://www.who.int/mediacentre/news/releases/2016/depression-anxiety-treatment/en/>, 2016> Accessible at: July 26, 2016.
- 7 KESSLER, R. C. The costs of depression. **Psychiatric Clinics of North America**, v. 35, n. 1, p. 1-14, 2012.
- 8 PAN, Y.-J.; KNAPP, M.; MCCRONE, P. Cost-effectiveness comparisons between antidepressant treatments in depression: evidence from database analyses and prospective studies. **Journal of Affective Disorders**, v. 139, n. 2, p. 113-125, 2012.
- 9 GARTLEHNER, G.; HANSEN, R. A.; REICHENPFADER, U.; KAMINSKI, A.; KIEN, C.; STROBELBERGER, M.; VAN NOORD, M.; THIEDA, P.; THALER, K.; GAYNES, B. **Drug class review:** second-generation antidepressants: final update 5 report. Available from: < <http://www.ncbi.nlm.nih.gov.ez67.periodicos.capes.gov.br/books/NBK54355/>>. Accessible at: July 26, 2016.
- 10 FERRARI, A. J.; CHARLSON, F. J.; NORMAN, R. E.; PATTEN, S. B.; FREEDMAN, G.; MURRAY, C. J. L.; VOS, T.; WHITEFORD, H. A. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. **PLoS Medicine**, v. 10, n. 11, p. e1001547, 2013.

11 RICHARDS, D. Prevalence and clinical course of depression: a review. **Clinical Psychology Review**, v. 31, n. 7, p. 1117-1125, 2011.

12 DEL PORTO, J. A. Conceito e diagnóstico. **Revista Brasileira de Psiquiatria**, v. 21, n. 21, p. 06-11, 1999.

13 BROADHEAD, W.; BLAZER, D. G.; GEORGE, L. K.; TSE, C. Depression, disability days, and days lost from work in a prospective epidemiologic survey. **Journal of American Medical Association**, v. 264, n. 19, p. 2524-2528, 1990.

14 ÜSTÜN, T. B.; REHM, J.; CHATTERJI, S.; SAXENA, S.; TROTTER, R.; ROOM, R.; BICKENBACH, J. Multiple-informant ranking of the disabling effects of different health conditions in 14 countries. **The Lancet**, v. 354, n. 9173, p. 111-115, 1999.

15 MATHERS, C. D.; LONCAR, D. Projections of global mortality and burden of disease from 2002 to 2030. **PLoS Medicine**, v. 3, n. 11, p. e442, 2006.

16 MURRAY, C. J. L.; LOPEZ, A. D. Evidence-based health policy-lessons from the global burden of disease study. **Science**, v. 274, n. 5288, p. 740-743, 1996.

17 WORLD HEALTH ORGANIZATION. WHO. **Mental Health**: depression. Available from <http://www.who.int/mental_health/management/depression/definition/en/S> Accessible at: July 26, 2016.

18 LOPEZ, A. D.; MURRAY, C. C. J. L. The global burden of disease, 1990-2020. **Nature Medicine**, v. 4, n. 11, p. 1241-1243, 1998.

19 MURRAY, C. J. L.; LOPEZ, A. D. **The global burden of disease**: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Available from: <http://webcache.googleusercontent.com/search?q=cache:L6mMPdpgft8J:apps.who.int/iris/bits/tstream/10665/41864/1/0965546608_eng.pdf+&cd=1&hl=pt-BR&ct=clnk&gl=br>. Accessible at: July 26, 2016.

20 BLIER, P.; EL MANSARI, M. Serotonin and beyond: therapeutics for major depression. **Philosophical Transactions of the Royal Society B: biological sciences**, v. 368, n. 1615, 2013.

21 PROHOTSKY, D. L.; ZHAO, F. A survey of top 200 drugs—inconsistent practice of drug strength expression for drugs containing salt forms. **Journal of Pharmaceutical Sciences**, v. 101, n. 1, p. 1-6, 2012.

22 BEGG, E. J.; DUFFULL, S. B.; SAUNDERS, D. A.; BUTTIMORE, R. C.; ILETT, K. F.; HACKETT, L. P.; YAPP, P.; WILSON, D. A. Paroxetine in human milk. **British Journal of Clinical Pharmacology**, v. 48, n. 2, p. 142-147, 1999.

23 BRUNI, G.; SARTOR, F.; BERBENNI, V.; MILANESE, C.; MAIETTA, M.; FRANCHI, D.; MARINI, A. Compatibility of paroxetine hydrochloride and GW597599B. **Journal of Thermal Analysis & Calorimetry**, v. 108, n. 1, p. 381-388, 2012.

- 24 COZAR, I. B.; SZABÓ, L.; MARE, D.; LEOPOLD, N.; DAVID, L.; CHIȘ, V. IR, Raman, SERS and DFT study of paroxetine. **Journal of Molecular Structure**, v. 993, n. 1–3, p. 243-248, 2011.
- 25 KITAICHI, Y.; INOUE, T.; NAKAGAWA, S.; BOKU, S.; KAKUTA, A.; IZUMI, T.; KOYAMA, T. Sertraline increases extracellular levels not only of serotonin, but also of dopamine in the nucleus accumbens and striatum of rats. **European Journal of Pharmacology**, v. 647, n. 1–3, p. 90-96, 2010.
- 26 PINA, M. F.; PINTO, J. F.; SOUSA, J. J.; FÁBIÁN, L.; ZHAO, M.; CRAIG, D. Q. M. Identification and characterization of stoichiometric and nonstoichiometric hydrate forms of paroxetine HCl: reversible changes in crystal dimensions as a function of water absorption. **Molecular Pharmaceutics**, v. 9, n. 12, p. 3515-3525, 2012.
- 27 YOSHIMURA, R.; KISHI, T.; HORI, H.; IKENOUCI-SUGITA, A.; KATSUKI, A.; UMENE-NAKANO, W.; IWATA, N.; NAKAMURA, J. Comparison of the efficacy between paroxetine and sertraline augmented with aripiprazole in patients with refractory major depressive disorder. **Progress in Neuro-Psychopharmacology and Biological Psychiatry**, v. 39, n. 2, p. 355-357, 2012.
- 28 CHILDS, S. L.; CHYALL, L. J.; DUNLAP, J. T.; SMOLENSKAYA, V. N.; STAHLY, B. C.; STAHLY, G. P. Crystal engineering approach to forming cocrystals of amine hydrochlorides with organic acids. Molecular complexes of fluoxetine hydrochloride with benzoic, succinic, and fumaric acids. **Journal of the American Chemical Society**, v. 126, n. 41, p. 13335-13342, 2004.
- 29 DJORDJEVIC, J.; DJORDJEVIC, A.; ADZIC, M.; ELAKOVIĆ, I.; MATIĆ, G.; RADOJCIC, M. B. Fluoxetine affects antioxidant system and promotes apoptotic signaling in wistar rat liver. **European Journal of Pharmacology**, v. 659, n. 1, p. 61-66, 2011.
- 30 FRICK, L. R.; RAPANELLI, M. Antidepressants: influence on cancer and immunity? **Life Sciences**, v. 92, n. 10, p. 525-532, 2013.
- 31 LI, Q.; SULLIVAN, N. R.; MCALLISTER, C. E.; VAN DE KAR, L. D.; MUMA, N. A. Estradiol accelerates the effects of fluoxetine on serotonin 1A receptor signaling. **Psychoneuroendocrinology**, v. 38, n. 7, p. 1145-1157, 2013.
- 32 PAYKEL, E. S. Basic concepts of depression. **Dialogues in Clinical Neuroscience**, v. 10, n. 3, p. 279-289, 2008.
- 33 WORLD HEALTH ORGANIZATION. WHO. **Depression**. Available from: <<http://www.who.int/mediacentre/factsheets/fs369/en/>> Accessible at: July 26, 2016.
- 34 RAMACHANDRAI, C. T.; SUBRAMANYAM, N.; BAR, K. J.; BAKER, G.; YERAGANI, V. K. Antidepressants: From MAOIs to SSRIs and more. **Indian Journal of Psychiatry**, v. 53, n. 2, p. 180-182, 2011.
- 35 LÓPEZ-MUÑOZ, F.; ÁLAMO, C.; JUCKEL, G.; ASSION, H.-J. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part I: monoamine oxidase inhibitors. **Journal of Clinical Psychopharmacology**, v. 27, n. 6, p. 555-559, 2007.

- 36 FANGMANN, P.; ASSION, H.-J.; JUCKEL, G.; GONZÁLEZ, C. Á.; LÓPEZ-MUÑOZ, F. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part II: tricyclics and tetracyclics. **Journal of Clinical Psychopharmacology**, v. 28, n. 1, p. 1-4, 2008.
- 37 CRYAN, J. F.; LEONARD, B. E. **Depression: from psychopathology to pharmacotherapy**: Basel, Switzerland: S. Karger AG, 2010.
- 38 BOWEN, P. D. Use of selective serotonin reuptake inhibitors in the treatment of depression in older adults: identifying and managing potential risk for hyponatremia. **Geriatric Nursing**, v. 30, n. 2, p. 85-89, 2009.
- 39 HIEMKE, C.; HÄRTTER, S. Pharmacokinetics of selective serotonin reuptake inhibitors. **Pharmacology & Therapeutics**, v. 85, n. 1, p. 11-28, 2000.
- 40 SCAHILL, L.; HAMRIN, V.; PACHLER, M. E. The use of selective serotonin reuptake inhibitors in children and adolescents with major depression. **Journal of Child and Adolescent Psychiatric Nursing**, v. 18, n. 2, p. 86-89, 2005.
- 41 WALKER, F. R. A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? **Neuropharmacology**, v. 67, n. 1, p. 304-317, 2013.
- 42 BUTLER, S. G.; MEEGAN, M. J. Recent developments in the design of anti-depressive therapies: targeting the serotonin transporter. **Current Medicinal Chemistry**, v. 15, n. 17, p. 1737-1761, 2008.
- 43 BARBUI, C.; CAMPOMORI, A.; MEZZALANA, L.; LOPATRIELLO, S.; DA CAS, R.; GARATTINI, S. Psychotropic drug use in Italy, 1984-99: the impact of a change in reimbursement status. **International Clinical Psychopharmacology**, v. 16, n. 4, p. 227-233, 2001.
- 44 TANRIKUT, C.; FELDMAN, A. S.; ALTEMUS, M.; PADUCH, D. A.; SCHLEGEL, P. N. Adverse effect of paroxetine on sperm. **Fertility and Sterility**, v. 94, n. 3, p. 1021-1026, 2010.
- 45 ZIMPEL, R. R.; FLECK, M. P. Depression as a major impact on the quality of life of HIV-positive brazilians. **Psychology, Health & Medicine**, v. 19, n. 1, p. 47-58, 2013.
- 46 A/S FERROSAN. Jorgen Anders Christensen and Richard Felt Squires. **4-Phenylpiperidine compounds**. US4007196 A, 23 July 1975, 08 Feb. 1977.
- 47 BOURIN, M.; CHUE, P.; GUILLON, Y. Paroxetine: a review. **CNS Drug Reviews**, v. 7, n. 1, p. 25-47, 2001.
- 48 VERISPAN. **Top 200 generic drugs by units in 2010**. Drug Topics. 2014. Available from: <http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/252011/727243/article.pdf>. Accessible at: July 2016
- 49 BEECHAM GROUP P.L.C. Roger D. Barnes, Marian W. Wood-Kaczmar, Alan D. Curzons, Ian R. Lynch, John E. Richardson and Philip C. Buxton. **Anti-depressant**

crystalline paroxetine hydrochloride hemihydrate. US4721723 A, 23 Oct.1986, 26 Jan.1988.

50 BUXTON, P. C.; LYNCH, I. R.; ROE, J. M. Solid-state forms of paroxetine hydrochloride. **International Journal of Pharmaceutics**, v. 42, n. 1–3, p. 135-143, 1988.

51 SMITHKLINE BEECHAM CORPORATION. Neal Ward and Victor Witold Jacewicz. **Paroxetine hydrochloride form A or C.** US6133289 A, 02 Sept.1997, 17 Oct.2000.

52 ALLEN, F. The Cambridge Structural Database: a quarter of a million crystal structures and rising. **Acta Crystallographica Section B**, v. 58, n. 3 Part 1, p. 380-388, 2002.

53 IBERS, J. Paroxetine hydrochloride hemihydrate. **Acta Crystallographica Section C**, v. 55, n. 3, p. 432-434, 1999.

54 YOKOTA, M.; UEKUSA, H.; OHASHI, Y. Structure analyses of two crystal forms of paroxetine hydrochloride. **Bulletin of the Chemical Society of Japan**, v. 72, n.8, p. 1731-1736, 1999.

55 HOWARD, J. A. K. P., P.; CHETINA, O. **Private communication to the Cambridge Crystallographic Data Centre.** EHOXEE. 2003. Available from: < www.ccdc.cam.ac.uk >. Accessible at: 25 jul. 2016..

56 PINA, M. F.; ZHAO, M.; PINTO, J. F.; SOUSA, J. J.; FRAMPTON, C. S.; DIAZ, V.; SULEIMAN, O.; FÁBIÁN, L.; CRAIG, D. Q. M. An investigation into the dehydration behavior of paroxetine HCl Form I using a combination of thermal and diffraction methods: the identification and characterization of a new anhydrous form. **Crystal Growth & Design**, v.14, n.8, 2014.

57 WENTHUR, C. J.; BENNETT, M. R.; LINDSLEY, C. W. Classics in chemical neuroscience: fluoxetine (Prozac). **ACS Chemical Neuroscience**, v. 5, n. 1, p. 14-23, 2014.

58 WONG, D. T.; HORNG, J. S.; BYMASTER, F. P.; HAUSER, K. L.; MOLLOY, B. B. A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-n-methyl-3-phenylpropylamine. **Life Sciences**, v. 15, n. 3, p. 471-479, 1974.

59 USALA, T.; CLAVENNA, A.; ZUDDAS, A.; BONATI, M. Randomised controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: a systematic review and meta-analysis. **European Neuropsychopharmacology**, v. 18, n. 1, p. 62-73, 2008.

60 NAKAMURA, Y.; YAMAMOTO, H.; SEKIZAWA, J.; KONDO, T.; HIRAI, N.; TATARAZAKO, N. The effects of pH on fluoxetine in Japanese medaka (*Oryzias latipes*): acute toxicity in fish larvae and bioaccumulation in juvenile fish. **Chemosphere**, v. 70, n. 5, p. 865-873, 2008.

61 GARRIDO, E. M.; GARRIDO, J.; CALHEIROS, R.; MARQUES, M. P. M.; BORGES, F. Fluoxetine and norfluoxetine revisited: new insights into the electrochemical and spectroscopic Properties. **The Journal of Physical Chemistry A**, v. 113, n. 36, p. 9934-9944, 2009.

62 BRUNTON, L. L.; CHABNER, B. A.; KNOLLMANN, B. C. **As bases farmacológicas da terapêutica de Goodman & Gilman**. 12.ed. Porto Alegre: McGraw Hill Brasil, 2012.

63 EL-DAWY, M. A.; MABROUK, M. M.; EL-BARBARY, F. A. Liquid chromatographic determination of fluoxetine. **Journal of Pharmaceutical and Biomedical Analysis**, v. 30, n. 3, p. 561-571, 2002.

64 BAUMANN, P.; ZULLINO, D. F.; EAP, C. B. Enantiomers' potential in psychopharmacology—a critical analysis with special emphasis on the antidepressant escitalopram. **European Neuropsychopharmacology**, v. 12, n. 5, p. 433-444, 2002.

65 KASPRZYK-HORDERN, B. Pharmacologically active compounds in the environment and their chirality. **Chemical Society Reviews**, v. 39, n. 11, p. 4466-4503, 2010.

66 WONG, D. T.; BYMASTER, F. P.; REID, L. R.; MAYLE, D. A.; KRUSHINSKI, J. H.; ROBERTSON, D. W. Norfluoxetine enantiomers as inhibitors of serotonin uptake in rat brain. **Neuropsychopharmacology**, v. 8, n. 4, p. 337-344, 1993.

67 AITIPAMULA, S.; BANERJEE, R.; BANSAL, A. K.; BIRADHA, K.; CHENEY, M. L.; CHOUDHURY, A. R.; DESIRAJU, G. R.; DIKUNDWAR, A. G.; DUBEY, R.; DUGGIRALA, N.; GHOGALE, P. P.; GHOSH, S.; GOSWAMI, P. K.; GOUD, N. R.; JETTI, R. R. K. R.; KARPINSKI, P.; KAUSHIK, P.; KUMAR, D.; KUMAR, V.; MOULTON, B.; MUKHERJEE, A.; MUKHERJEE, G.; MYERSON, A. S.; PURI, V.; RAMANAN, A.; RAJAMANNAR, T.; REDDY, C. M.; RODRIGUEZ-HORNEDO, N.; ROGERS, R. D.; ROW, T. N. G.; SANPHUI, P.; SHAN, N.; SHETE, G.; SINGH, A.; SUN, C. C.; SWIFT, J. A.; THAIMATTAM, R.; THAKUR, T. S.; KUMAR THAPER, R.; THOMAS, S. P.; TOTHADI, S.; VANGALA, V. R.; VARIANKAVAL, N.; VISHWESHWAR, P.; WEYNA, D. R.; ZAWOROTKO, M. J. Polymorphs, salts, and cocrystals: what's in a name? **Crystal Growth & Design**, v. 12, n. 5, p. 2147-2152, 2012.

68 BRITTAİN, H. G. **Polymorphism in pharmaceutical solids**. 2nd ed. New York: Informa Healthcare USA, 2009.

69 MORISSETTE, S. L.; ALMARSSON, Ö.; PETERSON, M. L.; REMENAR, J. F.; READ, M. J.; LEMMO, A. V.; ELLIS, S.; CIMA, M. J.; GARDNER, C. R. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. **Advanced Drug Delivery Reviews**, v. 56, n. 3, p. 275-300, 2004.

70 BYRN, S. R.; PFEIFFER, R. R.; STOWELL, J. G. **Solid-state chemistry of drugs**. Michigan: SSCI, Inc., 1999.

71 VIPPAGUNTA, S. R.; BRITTAİN, H. G.; GRANT, D. J. W. Crystalline solids. **Advanced Drug Delivery Reviews**, v. 48, n. 1, p. 3-26, 2001.

72 WOUTERS, J.; QUERE, L.; THURSTON, D. E. **Pharmaceutical salts and co-crystals**. London: Royal Society of Chemistry, 2011.

73 HILFIKER, R.; BLATTER, F.; RAUMER, M. V. Relevance of solid-state properties for pharmaceutical products. In: HILFIKER, R. (Ed.). **Polymorphism: in the pharmaceutical industry**. Weinheim: Wiley-VCH Verlag GmbH, 2006. p. 1-19.

- 74 BLAGDEN, N.; DE MATAS, M.; GAVAN, P. T.; YORK, P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. **Advanced Drug Delivery Reviews**, v. 59, n. 7, p. 617-630, 2007.
- 75 PEZZINI, B.R.; SILVA, M. A. S.; FERRAZ, H. G. Formas farmacêuticas sólidas orais de liberação prolongada: sistemas monolíticos e multiparticulados. **Revista Brasileira de Ciências Farmacêuticas**, v. 43, n. 4, p. 441-502, 2007.
- 76 HILFIKER, R. **Polymorphism**: in the pharmaceutical industry. Berlin: Wiley-VCH, 2006.
- 77 BERNSTEIN, J. **Polymorphism in molecular crystals**. New York: Oxford University Press, 2002.
- 78 STAHLY, G. P. Diversity in single- and multiple-component crystals. the Search for and prevalence of polymorphs and cocrystals. **Crystal Growth & Design**, v. 7, n. 6, p. 1007-1026, 2007.
- 79 AAKERÖY, C. B.; FASULO, M. E.; DESPER, J. Cocrystal or salt: does it really matter? **Molecular Pharmaceutics**, v. 4, n. 3, p. 317-322, 2007.
- 80 BERNSTEIN, J. Polymorphism – a perspective. **Crystal Growth & Design**, v. 11, n. 3, p. 632-650, 2011.
- 81 HILFIKER, R.; DE PAUL, S. M.; SZELAGIEWICZ, M. Approaches to polymorphism screening. In: HILFIKER, R. (Ed.). **Polymorphism**. Weinheim: Wiley-VCH Verlag GmbH, 2006. p. 287-308.
- 82 GROTHE, E.; MEEKES, H.; VLIEG, E.; TER HORST, J. H.; DE GELDER, R. Solvates, salts, and cocrystals: a proposal for a feasible classification system. **Crystal Growth & Design**, v.16, n.6, 2016.
- 83 BECHTLOFF, B.; NORDHOFF, S.; ULRICH, J. Pseudopolymorphs in industrial use. **Crystal Research and Technology**, v. 36, n. 12, p. 1315-1328, 2001.
- 84 KHANKARI, R. K.; GRANT, D. J. W. Pharmaceutical hydrates. **Thermochimica Acta**, v. 248, p. 61-79, 1995.
- 85 GIRON, D.; GOLDBRONN, C.; MUTZ, M.; PFEFFER, S.; PIECHON, P.; SCHWAB, P. Solid state characterizations of pharmaceutical hydrates. **Journal of Thermal Analysis and Calorimetry**, v. 68, n. 2, p. 453-465, 2002.
- 86 INFANTES, L.; FABIAN, L.; MOTHERWELL, W. D. S. Organic crystal hydrates: what are the important factors for formation. **CrystEngComm**, v. 9, n. 1, p. 65-71, 2007.
- 87 DESIRAJU, G. R. Supramolecular synthons in crystal engineering— a new organic synthesis. **Angewandte Chemie International Edition in English**, v. 34, n. 21, p. 2311-2327, 1995.
- 88 STAHL, P. H.; WERMUTH, C. G. (Ed.) **Handbook of pharmaceutical salts**: properties, selection, and use. Berlin: Wiley-VCH, 2002.

- 89 CHERUKUVADA, S.; GURU ROW, T. N. Comprehending the formation of eutectics and cocrystals in terms of design and their structural interrelationships. **Crystal Growth & Design**, v. 14, n. 8, p. 4187-4198, 2014.
- 90 ZHANG, G. G. Z.; LAW, D.; SCHMITT, E. A.; QIU, Y. Phase transformation considerations during process development and manufacture of solid oral dosage forms. **Advanced Drug Delivery Reviews**, v. 56, n. 3, p. 371-390, 2004
- 91 TRASK, A. V. An overview of pharmaceutical cocrystals as intellectual property. **Molecular Pharmaceutics**, v. 4, n. 3, p. 301-309, 2007.
- 92 BERNSTEIN, J. Polymorphism and patents from a chemist's point of view. In: HILFIKER, R. (Ed.). **Polymorphism: in the pharmaceutical industry**. Weinheim: Wiley-VCH Verlag GmbH, 2006. p. 365-384.
- 93 GELLIE, B.; JOHNSON, C.; WEISBROD, T. Patenting of inventions relating to polymorphs. In: STOREY, R. A.; YMEN, I. (Ed.). **Solid state characterization of pharmaceuticals**. New York: John Wiley & Sons, 2011. p. 451-471.
- 94 SCHLEIFER, K. Challenges in agrochemicals design. **Journal of Cheminformatics**, v. 5, n. Suppl 1, p. O17, 2013.
- 95 HOLLINGSWORTH, M. D. Crystal engineering: from structure to function. **Science**, v. 295, n. 5564, p. 2410-2413, 2002.
- 96 DESIRAJU, G. R. Crystal engineering: from molecule to crystal. **Journal of the American Chemical Society**, v. 135, n. 27, p. 9952-9967, 2013.
- 97 REDDY, I. K.; MEHVAR, R. (Ed.) **Chirality in drug design and development**. New York: Marcel Dekker, 2004.
- 98 CHAWLA, G., BANSAL, K. A. Challenges in polymorphism of pharmaceuticals. **CRIPS**, v. 4, n. 1, p. 9-12, 2004.
- 99 GAVEZZOTTI, A.; FILIPPINI, G. Polymorphic forms of organic crystals at room conditions: thermodynamic and structural implications. **Journal of the American Chemical Society**, v. 117, n. 49, p. 12299-12305, 1995.
- 100 CHAN, H. C. S.; KENDRICK, J.; LEUSEN, F. J. J. Molecule VI, a benchmark crystal-structure-prediction sulfonimide: are its polymorphs predictable? **Angewandte Chemie International Edition**, v. 50, n. 13, p. 2979-2981, 2011.
- 101 CRUZ-CABEZA, A. J.; REUTZEL-EDENS, S. M.; BERNSTEIN, J. Facts and fictions about polymorphism. **Chemical Society Reviews**, v. 44, n. 23, p. 8619-8635, 2015.
- 102 CHAN, H. C. S.; KENDRICK, J.; NEUMANN, M. A.; LEUSEN, F. J. J. Towards ab initio screening of co-crystal formation through lattice energy calculations and crystal structure prediction of nicotinamide, isonicotinamide, picolinamide and paracetamol multi-component crystals. **CrystEngComm**, v. 15, n. 19, p. 3799-3807, 2013.

- 103 AITIPAMULA, S.; CHOW, P. S.; TAN, R. B. H. Polymorphism in cocrystals: a review and assessment of its significance. **CrystEngComm**, v. 16, n. 17, p. 3451-3465, 2014.
- 104 A. BURGER; R. RAMBERGER, M. On the polymorphism of pharmaceuticals and other molecular crystals. II. **Microchimica Acta**, v.12, n3, p. 273–316, 1979.
- 105 PARK, Y.; LEE, J.; LEE, S. H.; CHOI, H. G.; MAO, C.; KANG, S. K.; CHOI, S.-E.; LEE, E. H. Crystal structures of tetramorphic forms of donepezil and energy/temperature phase diagram via direct heat capacity measurements. **Crystal Growth & Design**, v. 13, n. 12, p. 5450-5458, 2013.
- 106 BRANDEL, C.; AMHARAR, Y.; ROLLINGER, J. M.; GRIESSER, U. J.; CARTIGNY, Y.; PETIT, S.; COQUEREL, G. Impact of molecular flexibility on double polymorphism, solid solutions and chiral discrimination during crystallization of diprophylline enantiomers. **Molecular Pharmaceutics**, v. 10, n. 10, p. 3850-3861, 2013.
- 107 MULLIN, J. W. (Ed.). **Crystallization**. 4th ed. Oxford: Butterworth-Heinemann, 2001.
- 108 CHEN, J.; SARMA, B.; EVANS, J. M. B.; MYERSON, A. S. Pharmaceutical crystallization. **Crystal Growth & Design**, v. 11, n. 4, p. 887-895, 2011.
- 109 DESIRAJU, G. R. **Crystal engineering: the desing of organic solid**. Amsterdam: Elsevier, 1989.
- 110 BERNSTEIN, J.; DAVEY, R. J.; HENCK, J.-O. Concomitant polymorphs. **Angewandte Chemie International Edition**, v. 38, n. 23, p. 3440-3461, 1999.
- 111 NANGIA, A. Conformational polymorphs, multiple Z' crystal structures and phase transformations. **Journal of the Indian Institute of Science**, v. 87, n. 2, p. 133-147, 2007.
- 112 BERNSTEIN, J.; HAGLER, A. T. Conformational polymorphism. the influence of crystal structure on molecular conformation. **Journal of the American Chemical Society**, v. 100, n. 3, p. 673-681, 1978.
- 113 CRUZ-CABEZA, A. J.; BERNSTEIN, J. Conformational polymorphism. **Chemical Reviews**, v. 114, n. 4, p. 2170-2191, 2014.
- 114 BERNSTEIN, J.; DUNITZ, J. D.; GAVEZZOTTI, A. Polymorphic perversity: crystal structures with many symmetry-independent molecules in the unit cell. **Crystal Growth & Design**, v. 8, n. 6, p. 2011-2018, 2008.
- 115 STEED, K. M.; STEED, J. W. Packing problems: high Z' crystal structures and their relationship to cocrystals, inclusion compounds, and polymorphism. **Chemical Reviews**, v. 115, n. 8, p. 2895-2933, 2015.
- 116 BISHOP, R.; SCUDDER, M. L. Multiple molecules in the asymmetric unit ($Z' > 1$) and the formation of false conglomerate crystal structures. **Crystal Growth & Design**, v. 9, n. 6, p. 2890-2894, 2009.

117 ROLLINGER, J. M.; BURGER, A. Polymorphism of racemic felodipine and the unusual series of solid solutions in the binary system of its enantiomers. **Journal of Pharmaceutical Sciences**, v. 90, n. 7, p. 949-959, 2001.

118 LEE, A. Y.; ERDEMIR, D.; MYERSON, A. S. Crystal polymorphism in chemical process development. **Annual Review of Chemical and Biomolecular Engineering**, v. 2, n. 1, p. 259-280, 2011.

119 YU, L. Inferring thermodynamic stability relationship of polymorphs from melting data. **Journal of Pharmaceutical Sciences**, v. 84, n. 8, p. 966-974, 1995.

120 YU, L.; STEPHENSON, G. A.; MITCHELL, C. A.; BUNNELL, C. A.; SNOREK, S. V.; BOWYER, J. J.; BORCHARDT, T. B.; STOWELL, J. G.; BYRN, S. R. Thermochemistry and conformational polymorphism of a hexamorphic crystal system. **Journal of the American Chemical Society**, v. 122, n. 4, p. 585-591, 2000.

121 DONG, Z.; MUNSON, E. J.; SCHROEDER, S. A.; PRAKASH, I.; GRANT, D. J. W. Neotame anhydrate polymorphs II: quantitation and relative physical stability. **Pharmaceutical Research**, v. 19, n. 9, p. 1259-1264, 2002.

122 BRITTAIN, H. G. Polymorphism and solvatomorphism 2006. **Journal of Pharmaceutical Sciences**, v. 97, n. 9, p. 3611-3636, 2008.

123 SAAL, C.; BECKER, A. Pharmaceutical salts: a summary on doses of salt formers from the Orange Book. **European Journal of Pharmaceutical Sciences**, v. 49, n. 4, p. 614-623, 2013.

124 MCCRONE, W. C. Polymorphism. In: FOX, D.; LABES, M. M.; WEISSBERGER, A. **Physics & chemistry of the organic solid state**. New York: Interscience, 1965. p. 725-767.

125 RAIJADA, D.; BOND, A.; LARSEN, F.; CORNETT, C.; QU, H.; RANTANEN, J. Exploring the solid-form landscape of pharmaceutical hydrates: transformation pathways of the sodium naproxen anhydrate-hydrate system. **Pharmaceutical Research**, v. 30, n. 1, p. 280-289, 2013.

126 GILLON, A. L.; FEEDER, N.; DAVEY, R. J.; STOREY, R. Hydration in molecular crystals: a Cambridge Structural Database analysis. **Crystal Growth & Design**, v. 3, n. 5, p. 663-673, 2003.

127 SANSAM, B. C. R.; ANDERSON, K. M.; STEED, J. W. A simple strategy for crystal engineering water clusters. **Crystal Growth & Design**, v. 7, n. 12, p. 2649-2653, 2007.

128 AAKERROY, C. B.; FORBES, S.; DESPER, J. The effect of water molecules in stabilizing co-crystals of active pharmaceutical ingredients. **CrystEngComm**, v. 14, n. 7, p. 2435-2443, 2012.

129 ABRAMOV, Y. A. Virtual hydrate screening and coformer selection for improved relative humidity stability. **CrystEngComm**, v. 17, 2015.

130 HAYNES, D. A.; JONES, W.; SAMUEL MOTHERWELL, W. D. Hydrate formation in NH^+ -containing salts of pharmaceutically acceptable anions: A CSD survey. **CrystEngComm**, v. 7, n. 55, p. 342-345, 2005.

- 131 TIAN, F.; QU, H.; ZIMMERMANN, A.; MUNK, T.; JØRGENSEN, A. C.; RANTANEN, J. Factors affecting crystallization of hydrates. **Journal of Pharmacy and Pharmacology**, v. 62, n. 11, p. 1534-1546, 2010.
- 132 GRIESSER, U. J. The importance of solvates. In: HILFIKER, R. (Ed.). **Polymorphism: in the pharmaceutical industry**. Weinheim: Wiley-VCH Verlag GmbH, 2006. p. 211-233.
- 133 APOTEX wins latest round in generic Paxil litigation. **Nature Reviews Drug Discovery**, v.3, n.6, p.468, 2004.
- 134 FETH, M. P.; NAGEL, N.; BAUMGARTNER, B.; BRÖCKELMANN, M.; RIGAL, D.; OTTO, B.; SPITZENBERG, M.; SCHULZ, M.; BECKER, B.; FISCHER, F.; PETZOLDT, C. Challenges in the development of hydrate phases as active pharmaceutical ingredients – an example. **European Journal of Pharmaceutical Sciences**, v. 42, n. 1–2, p. 116-129, 2011.
- 135 RUSCICA, R.; BIANCHI, M.; QUINTERO, M.; MARTINEZ, A.; VEGA, D. R. Solid-state forms of zoledronic acid: polymorphism in hydrates. **Journal of Pharmaceutical Sciences**, v. 99, n. 12, p. 4962-4972, 2010.
- 136 BREIMER, D. D.; PHARMACEUTIQUE, F. I. Towards better safety of drugs and pharmaceutical products. In: INTERNATIONAL CONGRESS OF PHARMACEUTICAL SCIENCES of F.I.P., 39th, 1979, Brighton, U.K. **Proceedings ...** New York: Elsevier/North-Holland Biomedical Press, 1980.
- 137 AGHABOZORG, H.; ESHTIAGH-HOSSEINI, H.; SALIMI, A. R.; MIRZAEI, M. A brief review on formation of (H₂O)_n clusters in supramolecular proton transfer compounds and their complexes. **Journal of the Iranian Chemical Society**, v. 7, n. 2, p. 289-300, 2010.
- 138 CHEN, W.-J.; LONG, L.-S.; HUANG, R.-B.; ZHENG, L.-S. A dihalide–decahydrate cluster of [X₂(H₂O)₁₀]²⁻ in a supramolecular architecture of {[Na₂(H₂O)₆(H₂O@TMEQ[6])]}·2(C₆H₅NO₃)}X₂(H₂O)₁₀ (TMEQ[6] = α,α',δ,δ'-tetramethylcucurbit[6]uril; X = Cl, Br). **Crystal Growth & Design**, v. 13, n. 6, p. 2507-2513, 2013.
- 139 LUO, G. G.; XIONG, H. B.; SUN, D.; WU, D. L.; HUANG, R. B.; DAI, J. C. A Discrete spirocyclic (H₂O)₉ cluster and 1D novel water chain with tetrameric and octameric clusters in cationic hosts. **Crystal Growth & Design**, v. 11, n. 5, p. 1948-1956, 2011.
- 140 INFANTES, L.; CHISHOLM, J.; MOTHERWELL, S. Extended motifs from water and chemical functional groups in organic molecular crystals. **CrystEngComm**, v. 5, n. 85, p. 480-486, 2003.
- 141 SAEED, M. A.; WONG, B. M.; FRONCZEK, F. R.; VENKATRAMAN, R.; HOSSAIN, M. A. Formation of an amine-water cyclic pentamer: a new type of water cluster in a polyazacryptand. **Crystal Growth & Design**, v. 10, n. 4, p. 1486-1488, 2010.
- 142 INFANTES, L.; MOTHERWELL, S. Water clusters in organic molecular crystals. **CrystEngComm**, v. 4, n. 75, p. 454-461, 2002.
- 143 BERGE, S. M.; BIGHLEY, L. D.; MONKHOUSE, D. C. Pharmaceutical salts. **Journal of Pharmaceutical Sciences**, v. 66, n. 1, p. 1-19, 1977.

- 144 ELDER, D. P.; HOLM, R.; DIEGO, H. L. D. Use of pharmaceutical salts and cocrystals to address the issue of poor solubility. **International Journal of Pharmaceutics**, v. 453, n. 1, p. 88-100, 2013.
- 145 BLACK, S. N.; COLLIER, E. A.; DAVEY, R. J.; ROBERTS, R. J. Structure, solubility, screening, and synthesis of molecular salts. **Journal of Pharmaceutical Sciences**, v. 96, n. 5, p. 1053-1068, 2007.
- 146 STAHL, P. H.; WERMUTH, C. G. **Handbook of pharmaceutical salts properties, selection, and use**. 2nd ed. New York: Wiley, 2008.
- 147 KUMAR, L.; AMIN, A.; BANSAL, A. K. Salt selection in drug development. **Pharmaceutical Technology**, v.32, n.3, 2008.
- 148 PAULEKUHN, G. S.; DRESSMAN, J. B.; SAAL, C. Trends in active pharmaceutical ingredient salt selection based on analysis of the Orange Book Database. **Journal of Medicinal Chemistry**, v. 50, n. 26, p. 6665-6672, 2007.
- 149 HAYNES, D. A.; JONES, W.; MOTHERWELL, W. D. S. Occurrence of pharmaceutically acceptable anions and cations in the Cambridge Structural Database. **Journal of Pharmaceutical Sciences**, v. 94, n. 10, p. 2111-2120, 2005.
- 150 DUGGIRALA, N. K.; PERRY, M. L.; ALMARSSON, O.; ZAWOROTKO, M. J. Pharmaceutical cocrystals: along the path to improved medicines. **Chemical Communications**, v. 52, n. 4, p. 640-655, 2016.
- 151 DESIRAJU, G. R. Crystal engineering: a brief overview. **Journal of Chemical Sciences**, v. 122, n. 5, p. 667-675, 2010.
- 152 DESIRAJU, G. R. Crystal engineering: a holistic view. **Angewandte Chemie International Edition**, v. 46, n. 44, p. 8342-8356, 2007.
- 153 BOSCH, E. Role of sp-C-H...N hydrogen bonding in crystal eEngineering. **Crystal Growth & Design**, v. 10, n. 8, p. 3808-3813, 2010.
- 154 BRITTAIN, H. G. Cocrystal systems of pharmaceutical interest: 2010. **Crystal Growth & Design**, v. 12, n. 2, p. 1046-1054, 2012.
- 155 ALMARSSON, Ö. Z., M. J. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? **Chemical Communication**, v.7, n.17, p. 1889-1896, 2004.
- 156 EIRKSON C, H. M.; OSBOURNE, C.M.; SAYRE, P. G.; ZEEMAN, M. Water solubility. In: ENVIRONMENTAL assessment technical assistance handbook. Washington DC: National Technical Information Service,1987.p. 1-11.

APPENDIX A - Supporting Information of the paper 'Reversible Solid-State Hydration/Dehydration of Paroxetine Hydrobromide Hemihydrate: Structural and Thermochemical Studies'

SUPPORTING INFORMATION

Reversible Solid-State Hydration/Dehydration of Paroxetine Hydrobromide Hemihydrate: Structural and Thermochemical Studies

Paulo S. Carvalho-Jr.^a, Cristiane Cabral^{a,b}, Alejandro Ayala^b, Cecilia C. P. da Silva^a, Javier Ellena^{a*}

^a Instituto de Física de São Carlos, Universidade de São Paulo, CP 369, 13560-970 - São Carlos, SP, Brazil; ^b Departamento de Física, Universidade Federal do Ceará, CP 6030, Fortaleza, Ceará 60455-970, Brazil; * e-mail address: javiere@ifsc.usp.br

PAROXETINE HBr HEMIHYDRATE

Table 1A. Crystal data and structure refinement for (PRX⁺Br⁻)0.5H₂O.

Empirical formula	C ₃₈ H ₄₄ Br ₂ F ₂ N ₂ O ₇
Formula weight	838.57
Temperature/K	100(2)
Crystal system	Monoclinic
Space group	P2 ₁
<i>a</i> /Å	12.9368(4)
<i>b</i> /Å	10.3393(4)
<i>c</i> /Å	14.3259(4)
β /°	107.464(2)
Volume/Å ³	1827.87(11)
<i>Z</i> , <i>Z'</i>	4, 2
ρ_{calc} g/cm ³	1.524
μ /mm ⁻¹	2.280
<i>F</i> (000)	860.0
Crystal size/mm ³	0.083 × 0.05 × 0.044
Radiation	MoK α (λ = 0.71073)
2 θ range for data collection/°	3.724 to 51.628
Index ranges	-15 ≤ <i>h</i> ≤ 15, -12 ≤ <i>k</i> ≤ 12, -17 ≤ <i>l</i> ≤ 17
Reflections collected	30984
Independent reflections	6893 [<i>R</i> _{int} = 0.0632, <i>R</i> _{sigma} = 0.0712]
Data/restraints/parameters	6893/1/472
Goodness-of-fit on <i>F</i> ²	1.027
Final <i>R</i> indexes [<i>I</i> > 2 σ (<i>I</i>)]	<i>R</i> ₁ = 0.0370, <i>wR</i> ₂ = 0.0715
Final <i>R</i> indexes [all data]	<i>R</i> ₁ = 0.0477, <i>wR</i> ₂ = 0.0747
Largest diff. peak/hole / e Å ⁻³	0.35/-0.41
Flack parameter	0.008(5)

Table 2A. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for $(\text{PRX}^+\text{Br}^-)0.5\text{H}_2\text{O}$. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
Br1'	3817.2(4)	2810.3(5)	5691.0(3)	20.93(13)
Br1A	480.5(9)	8852.9(8)	5854.9(7)	32.7(3)
O1	5511(3)	3678(3)	3060(2)	24.2(8)
O1'	6197(3)	6004(3)	505(3)	25.8(9)
O2	2212(3)	6075(4)	292(3)	29.5(10)
C19	8102(4)	5067(5)	6041(4)	23.5(13)
F1'	10572(3)	3997(3)	-873(2)	33.5(8)
O3	3003(3)	7227(3)	1712(3)	31.0(9)
N1'	7983(4)	6480(4)	3461(3)	27.1(11)
F1	7970(3)	8096(3)	7255(2)	35.4(8)
O2'	2563(3)	5498(4)	-2630(3)	32.4(9)
N1	7191(4)	679(4)	4766(3)	23.2(10)
C4'	8456(4)	6349(5)	1600(4)	20.1(12)
C7	4642(4)	4275(5)	2395(4)	17.9(11)
O3'	2598(3)	7080(3)	-1491(3)	26.2(9)
C10	2985(4)	5318(6)	938(4)	23.6(13)
C3'	9251(4)	6915(5)	2528(4)	20.9(12)
C11	3461(4)	5997(5)	1782(4)	21.1(12)
C14	7197(4)	4427(5)	6140(3)	17.5(11)
C6	5677(4)	3880(5)	4091(3)	18.9(11)
C12'	4422(4)	6567(5)	-391(4)	20.4(12)
C10'	3536(5)	5434(5)	-1887(4)	22.3(12)
C11'	3551(4)	6380(5)	-1192(4)	22.4(12)
C6'	6800(4)	4899(5)	976(4)	25.8(13)
C8'	5313(5)	4833(5)	-996(4)	27.3(13)
C8	4186(4)	3596(5)	1544(4)	21.5(12)
C16	6823(4)	6292(5)	7011(4)	25.8(13)
C12	4297(4)	5522(5)	2538(4)	22.3(12)
C9	3338(4)	4120(5)	783(4)	25.3(12)
C5'	7678(4)	5387(5)	1868(4)	20.7(12)
C9'	4401(5)	4642(5)	-1808(4)	28.0(13)
C15'	9837(4)	4792(5)	1294(4)	21.5(12)
C14'	9026(4)	5721(5)	937(4)	17.8(12)
C5	6600(4)	2978(5)	4619(3)	17.6(11)
C15	6568(4)	5053(5)	6628(4)	22.6(12)
C3	7813(4)	2104(5)	6193(4)	22.9(12)
C1'	7154(4)	5969(5)	2586(4)	25.4(13)
C2	7525(5)	735(5)	5854(4)	24.3(13)
C18'	9251(4)	5430(5)	-671(4)	24.9(13)
C17	7721(5)	6870(5)	6888(4)	24.3(13)
C17'	10059(4)	4564(5)	-275(4)	24.4(12)

continue

C13'	1890(5)	6285(5)	-2217(4)	31.0(14)
C16'	10357(4)	4213(5)	694(4)	25.5(13)
C19'	8741(4)	6003(5)	-49(4)	25.0(13)
C7'	5310(4)	5747(5)	-300(4)	21.9(13)
C4	6901(4)	3058(5)	5733(3)	18.0(12)
C13	2054(4)	7137(5)	865(4)	33.4(14)
C18	8371(4)	6309(5)	6424(4)	23.1(12)
C1	6284(4)	1582(5)	4295(4)	22.4(13)
C2'	8680(4)	7488(5)	3212(4)	28.5(14)
OW1A	851(12)	5921(8)	5589(11)	75(3)
Br1B	-32(2)	9377(2)	5474.1(19)	39.3(6)
OW2B	810(30)	6530(20)	5500(30)	75(3)

conclusion

Table 3A. Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for $(\text{PRX}^+\text{Br}^-)0.5\text{H}_2\text{O}$. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
Br1'	25.7(3)	15.9(2)	23.6(3)	1.7(2)	11.1(2)	-2.8(3)
Br1A	38.0(6)	32.6(6)	24.8(5)	0.3(4)	5.5(4)	-16.1(5)
O1	29(2)	26(2)	21(2)	1.8(16)	12.0(17)	10.9(17)
O1'	28(2)	17.7(19)	32(2)	2.4(17)	9.2(19)	5.0(17)
O2	28(2)	38(2)	24(2)	7.8(19)	9.9(19)	3.5(19)
C19	28(3)	21(3)	25(3)	-1(2)	13(3)	-1(2)
F1'	44(2)	32.4(18)	32.2(19)	-3.0(15)	24.0(16)	8.1(16)
O3	31(2)	18.8(19)	41(2)	3.2(17)	7(2)	10.0(17)
N1'	34(3)	26(3)	28(3)	6(2)	19(2)	11(2)
F1	53(2)	16.9(19)	33.3(18)	-9.7(14)	8.0(16)	-5.9(15)
O2'	36(3)	27(2)	32(2)	-1.6(18)	8(2)	-1.5(19)
N1	30(3)	12(2)	28(3)	-1.9(19)	9(2)	2.0(19)
C4'	21(3)	17(3)	23(3)	5(2)	8(2)	2(2)
C7	20(3)	16(3)	21(3)	-1(2)	12(2)	0(2)
O3'	27(2)	21(2)	31(2)	2.0(17)	9.0(18)	1.3(17)
C10	19(3)	33(3)	22(3)	7(3)	11(2)	-1(3)
C3'	24(3)	19(3)	23(3)	0(2)	11(2)	-1(2)
C11	24(3)	13(3)	29(3)	5(2)	12(3)	0(2)
C14	21(3)	17(3)	15(3)	2(2)	7(2)	-3(2)
C6	23(3)	13(3)	22(3)	0(2)	8(2)	2(2)
C12'	27(3)	12(3)	24(3)	-1(2)	10(3)	-4(2)
C10'	34(4)	16(3)	18(3)	4(2)	10(3)	1(3)
C11'	30(3)	13(3)	32(3)	7(2)	20(3)	5(2)
C6'	27(3)	18(3)	35(3)	2(3)	14(3)	2(2)
C8'	34(3)	19(3)	34(3)	6(3)	18(3)	5(3)
C8	27(3)	14(3)	30(3)	0(2)	19(3)	-3(2)
C16	34(3)	21(3)	25(3)	-5(2)	12(3)	5(3)
C12	27(3)	19(3)	23(3)	-4(2)	10(3)	-5(2)

continue

C9	28(3)	28(3)	22(3)	-4(2)	10(3)	-8(3)
C5'	22(3)	19(3)	26(3)	2(2)	15(3)	4(2)
C9'	42(4)	18(3)	27(3)	-1(3)	16(3)	-4(3)
C15'	25(3)	20(3)	22(3)	5(2)	10(2)	3(2)
C14'	17(3)	19(3)	20(3)	3(2)	9(2)	-1(2)
C5	17(2)	13(3)	23(3)	-2(2)	7(2)	-2(2)
C15	25(3)	19(3)	27(3)	1(2)	12(3)	0(2)
C3	33(3)	17(3)	20(3)	-1(2)	9(3)	2(2)
C1'	23(3)	25(3)	30(3)	2(3)	12(3)	2(2)
C2	31(4)	18(3)	24(3)	8(2)	9(3)	5(3)
C18'	31(3)	24(3)	23(3)	2(2)	13(3)	-2(3)
C17	40(3)	11(3)	19(3)	-1(2)	4(3)	-4(3)
C17'	29(3)	20(3)	30(3)	-4(2)	18(3)	-2(3)
C13'	32(3)	26(3)	34(4)	0(3)	9(3)	1(3)
C16'	25(3)	21(3)	31(3)	1(2)	10(3)	5(2)
C19'	25(3)	21(3)	30(3)	6(2)	10(3)	3(2)
C7'	23(3)	18(3)	27(3)	6(2)	11(3)	-3(2)
C4	23(3)	15(3)	21(3)	0(2)	14(2)	3(2)
C13	32(4)	29(3)	39(4)	15(3)	11(3)	5(3)
C18	26(3)	22(3)	21(3)	5(2)	6(3)	-7(2)
C1	23(3)	21(3)	26(3)	0(2)	11(3)	4(2)
C2'	34(3)	26(3)	29(3)	-1(2)	14(3)	6(2)
OW1A	73(4)	73(9)	79(5)	-14(8)	22(4)	-4(8)
Br1B	45.1(16)	42.0(16)	41.6(16)	-25.9(12)	29.2(13)	-23.5(12)
OW2B	73(4)	73(9)	79(5)	-14(8)	22(4)	-4(8)

conclusion

Table 4A. Bond Lengths for (PRX⁺Br⁻)0.5H₂O.

Atom-Atom	Length/Å	Atom-Atom	Length/Å
O1-C7	1.383(6)	C3'-C2'	1.515(6)
O1-C6	1.443(6)	C11-C12	1.372(7)
O1'-C6'	1.433(6)	C14-C15	1.383(7)
O1'-C7'	1.386(6)	C14-C4	1.534(7)
O2-C10	1.384(6)	C6-C5	1.525(7)
O2-C13	1.422(7)	C12-C11'	1.360(7)
C19-C14	1.389(7)	C12'-C7'	1.401(7)
C19-C18	1.398(7)	C10'-C11'	1.392(7)
F1'-C17'	1.364(5)	C10'-C9'	1.363(7)
O3-C11	1.393(6)	C6'-C5'	1.518(7)
O3-C13	1.447(6)	C8'-C9'	1.399(8)
N1'-C1'	1.481(7)	C8'-C7'	1.375(7)
N1'-C2'	1.490(6)	C8-C9	1.402(7)
F1-C17	1.373(6)	C16-C15	1.394(7)
O2'-C10'	1.385(6)	C16-C17	1.364(7)
O2'-C13'	1.442(6)	C5'-C1'	1.516(7)

continue

N1-C2	1.488(6)	C15'-C14'	1.401(7)
N1-C1	1.493(6)	C15'-C16'	1.377(7)
C4'-C3'	1.531(7)	C14'-C19'	1.379(7)
C4'-C5'	1.544(7)	C5-C4	1.528(6)
C4'-C14'	1.513(7)	C5-C1	1.534(7)
C7-C8	1.376(7)	C3-C2	1.506(7)
C7-C12	1.399(7)	C3-C4	1.528(7)
O3'-C11'	1.382(6)	C18'-C17'	1.364(7)
O3'-C13'	1.423(6)	C18'-C19'	1.392(7)
C10-C11	1.374(7)	C17-C18	1.349(7)
C10-C9	1.361(7)	C17'-C16'	1.374(7)

conclusion

Table 5A. Bond Angles (°) for (PRX⁺Br⁻)0.5H₂O.

Atom-Atom-Atom	Angle/°	Atom-Atom-Atom	Angle/°
C7-O1-C6	118.7(4)	C11-C12-C7	115.2(5)
C7'-O1'-C6'	115.9(4)	C10-C9-C8	116.6(5)
C10-O2-C13	104.5(4)	C6'-C5'-C4'	112.6(4)
C14-C19-C18	121.1(5)	C1'-C5'-C4'	111.8(4)
C11-O3-C13	103.7(4)	C1'-C5'-C6'	109.2(4)
C1'-N1'-C2'	112.5(4)	C10'-C9'-C8'	116.8(5)
C10'-O2'-C13'	103.5(4)	C16'-C15'-C14'	121.5(5)
C2-N1-C1	113.0(4)	C15'-C14'-C4'	121.1(4)
C3'-C4'-C5'	110.4(4)	C19'-C14'-C4'	121.4(5)
C14'-C4'-C3'	112.5(4)	C19'-C14'-C15'	117.4(5)
C14'-C4'-C5'	110.9(4)	C6-C5-C4	113.6(4)
O1-C7-C12	122.7(5)	C6-C5-C1	109.1(4)
C8-C7-O1	115.2(4)	C4-C5-C1	109.1(4)
C8-C7-C12	122.0(5)	C14-C15-C16	121.6(5)
C11'-O3'-C13'	104.0(4)	C2-C3-C4	112.5(4)
C11-C10-O2	110.0(5)	N1'-C1'-C5'	111.0(4)
C9-C10-O2	128.1(5)	N1-C2-C3	109.9(4)
C9-C10-C11	121.7(5)	C17'-C18'-C19'	117.7(5)
C2'-C3'-C4'	112.3(4)	C16-C17-F1	117.8(5)
C10-C11-O3	109.6(5)	C18-C17-F1	118.4(5)
C12-C11-O3	127.0(5)	C18-C17-C16	123.8(5)
C12-C11-C10	123.4(5)	F1'-C17'-C16'	118.7(5)
C19-C14-C4	121.5(4)	C18'-C17'-F1'	118.5(5)
C15-C14-C19	118.0(5)	C18'-C17'-C16'	122.8(5)
C15-C14-C4	120.4(4)	O3'-C13'-O2'	106.9(4)
O1-C6-C5	105.8(4)	C17'-C16'-C15'	118.3(5)
C11'-C12'-C7'	116.2(5)	C14'-C19'-C18'	122.3(5)
O2'-C10'-C11'	109.3(5)	O1'-C7'-C12'	114.3(4)
C9'-C10'-O2'	128.8(5)	C8'-C7'-O1'	123.6(5)

continue

C9'-C10'-C11'	121.9(5)	C8'-C7'-C12'	121.9(5)
O3'-C11'-C10'	109.1(5)	C5'-C4'-C14	113.8(4)
C12'-C11'-O3'	128.6(5)	C5'-C4'-C3	109.7(4)
C12'-C11'-C10'	122.2(5)	C3'-C4'-C14	111.1(4)
O1'-C6'-C5'	107.2(4)	O2'-C13'-O3	107.5(4)
C7'-C8'-C9'	121.0(5)	C17'-C18'-C19	118.0(5)
C7'-C8'-C9	121.2(5)	N1'-C1'-C5	110.5(4)
C17'-C16'-C15	117.5(5)	N1'-C2'-C3'	109.2(4)

conclusion

Table 6A. Torsion angles (°) for (PRX⁺Br⁻)0.5H₂O.

A-B-C-D	Angle/°	A-B-C-D	Angle/°
O1-C7-C8-C9	-176.4(4)	C9-C10-C11-C12	-1.8(8)
O1-C7-C12-C11	176.5(4)	C5'-C4'-C3'-C2'	-52.9(6)
O1-C6-C5-C4	179.8(4)	C5'-C4'-C14'-C15'	-72.2(6)
O1-C6-C5-C1	-58.2(5)	C5'-C4'-C14'-C19'	105.3(5)
O1'-C6'-C5'-C4'	-60.1(5)	C9'-C10'-C11'-O3'	176.5(4)
O1'-C6'-C5'-C1'	64.7(5)	C9'-C10'-C11'-C12'	-0.4(8)
O2-C10-C11-O3	0.3(6)	C9'-C8'-C7'-O1'	-178.2(5)
O2-C10-C11-C12	-176.6(5)	C9'-C8'-C7'-C12'	-3.2(8)
O2-C10-C9-C8	176.0(5)	C15'-C14'-C19'-C18'	-2.0(8)
C19-C14-C15-C16	0.3(8)	C14'-C4'-C3'-C2'	-177.4(4)
C19-C14-C4-C5	-64.7(6)	C14'-C4'-C5'-C6'	-60.4(6)
C19-C14-C4-C3	59.6(6)	C14'-C4'-C5'-C1'	176.2(4)
F1'-C17'-C16'-C15'	179.8(4)	C14'-C15'-C16'-C17'	-0.3(8)
O3-C11-C12-C7	-176.4(5)	C15-C14-C4-C5	116.0(5)
F1-C17-C18-C19	-179.2(4)	C15-C14-C4-C3	-119.6(5)
O2'-C10'-C11'-O3'	-1.3(5)	C15-C16-C17-F1	179.4(4)
O2'-C10'-C11'-C12'	-178.1(4)	C15-C16-C17-C18	-0.3(8)
O2'-C10'-C9'-C8'	176.7(5)	C1'-N1'-C2'-C3'	-59.4(5)
C4'-C3'-C2'-N1'	56.5(6)	C2-N1-C1-C5	58.0(5)
C4'-C5'-C1'-N1'	-53.8(6)	C2-C3-C4-C14	176.7(4)
C4'-C14'-C19'-C18'	-179.6(5)	C2-C3-C4-C5	-56.6(6)
C7-O1-C6-C5	173.4(4)	C18'-C17'-C16'-C15'	-1.9(8)
C7-C8-C9-C10	-0.9(7)	C17'-C16'-C15'-C14	-0.1(8)
C10-O2-C13-O3	21.1(5)	C17'-C18'-C19'-C14'	0.0(8)
C10-C11-C12-C7	-0.1(7)	C13'-O2'-C10'-C11'	-14.9(5)
C3'-C4'-C5'-C6'	174.3(4)	C13'-O2'-C10'-C9'	167.6(5)
C3'-C4'-C5'-C1'	50.9(6)	C13'-O3'-C11'-C12'	-166.3(5)
C3'-C4'-C14'-C15'	52.0(6)	C13'-O3'-C11'-C10'	17.1(5)
C3'-C4'-C14'-C19'	-130.5(5)	C16'-C15'-C14'-C4'	179.8(5)
C11-O3-C13-O2	-20.8(5)	C16'-C15'-C14'-C19'	2.2(7)
C11-C10-C9-C8	2.3(7)	C19'-C18'-C17'-F1'	-179.7(5)
C14-C19-C18-C17	-0.4(8)	C19'-C18'-C17'-C16'	2.1(8)
C6-O1-C7-C8	-147.4(4)	C7'-O1'-C6'-C5'	-176.3(4)

continue

C6-O1-C7-C12	37.3(6)	C7'-C12'-C11'-O3'	-176.5(4)
C6-C5-C4-C14	-56.1(5)	C7'-C12'-C11'-C10'	-0.3(7)
C6-C5-C4-C3	178.8(4)	C7'-C8'-C9'-C10'	2.3(7)
C6-C5-C1-N1	177.5(4)	C4-C14-C15-C16	179.5(5)
C10'-O2'-C13'-O3'	25.5(5)	C4-C5-C1-N1	-57.8(5)
C11'-O3'-C13'-O2'	-26.3(5)	C4-C3-C2-N1	54.8(6)
C11'-C12'-C7'-O1'	177.5(4)	C13-O2-C10-C11	-13.4(5)
C11'-C12'-C7'-C8'	2.0(7)	C13-O2-C10-C9	172.3(5)
C11'-C10'-C9'-C8'	-0.6(7)	C13-O3-C11-C10	12.6(5)
C6'-O1'-C7'-C12'	143.8(4)	C13-O3-C11-C12	-170.6(5)
C6'-O1'-C7'-C8'	-40.8(7)	C18-C19-C14-C15	0.0(8)
C6'-C5'-C1'-N1'	-179.0(4)	C18-C19-C14-C4	-179.3(5)
C8-C7-C12-C11	1.5(7)	C1-N1-C2-C3-	-55.5(6)
C16-C17-C18-C19	0.5(8)	C1-C5-C4-C14	-178.1(4)
C12-C7-C8-C9	-1.0(7)	C1-C5-C4-C3	56.8(5)
C9-C10-C11-O3	175.1(4)	C2'-N1'-C1'-C5'	58.7(5)

conclusion

Table 7A. Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for $(\text{PRX}^+\text{Br}^-)0.5\text{H}_2\text{O}$.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
H19	8537	4664	5715	28
H1'A	8399	5831	3769	33
H1'B	7654	6816	3869	33
H1A	6987	-125	4574	28
H1B	7758	872	4562	28
H4'	8019	7064	1237	24
H3'A	9740	6239	2868	25
H3'B	9682	7581	2345	25
H6A	5024	3672	4260	23
H6B	5870	4773	4267	23
H12'	4429	7203	69	24
H6'A	7122	4459	534	31
H6'B	6329	4297	1172	31
H8'	5930	4334	-927	33
H8	4445	2774	1472	26
H16	6397	6710	7338	31
H12	4612	5994	3105	27
H9	3033	3672	203	30
H5'	8106	4639	2186	25
H9'	4386	4006	-2270	34
H15'	10028	4561	1951	26
H5	7240	3208	4423	21
H15	5960	4637	6704	27
H3A	8458	2361	6028	27

continue

H3B	7980	2138	6900	27
H1'C	6672	6664	2270	31
H1'D	6726	5315	2785	31
H2A	8145	176	6122	29
H2B	6937	432	6087	29
H18'	9049	5631	-1335	30
H13C	1407	6816	-2721	37
H13D	1457	5744	-1927	37
H16'	10897	3600	940	31
H19'	8189	6597	-306	30
H4	6265	2784	5920	22
H13A	1412	7000	1069	40
H13B	1962	7930	488	40
H18	8980	6735	6361	28
H1C	5645	1339	4476	27
H1D	6110	1520	3589	27
H2'A	9210	7795	3804	34
H2'B	8238	8217	2900	34
HW1A	410	6475	5723	113
HW1B	480	5342	5184	113
HW2A	507	7136	5752	113
HW2B	325	5946	5233	113

conclusion

Table 8A. Atomic Occupancy for (PRX⁺Br⁻)0.5H₂O.

Atom	<i>Occupancy</i>	Atom	<i>Occupancy</i>	Atom	<i>Occupancy</i>
Br1A	0.7	OW1A	0.7	HW1A	0.7
HW1B	0.7	Br1B	0.3	OW2B	0.3
HW2A	0.3	HW2B	0.3		

PAROXETINE HBr

Table 1B. Crystal data and structure refinement for PRX⁺Br⁻.

Empirical formula	C ₁₉ H ₂₁ BrFNO ₃
Formula weight	410.28
Temperature/K	360(2)
Crystal system	Monoclinic
Space group	P2 ₁
<i>a</i> /Å	12.9190(19)
<i>b</i> /Å	10.4970(10)
<i>c</i> /Å	14.5580(3)
β /°	109.871(7)
Volume/Å ³	1856.7(5)
<i>Z</i> , <i>Z'</i>	4, 2
ρ_{calc} g/cm ³	1.468
μ /mm ⁻¹	2.241
<i>F</i> (000)	840.0
Crystal size/mm ³	0.083 × 0.277 × 0.543
Radiation	MoK α (λ = 0.71073)
2 θ range for data collection/°	5.96 to 49.86
Index ranges	-15 ≤ <i>h</i> ≤ 15, -12 ≤ <i>k</i> ≤ 11, -17 ≤ <i>l</i> ≤ 17
Reflections collected	14094
Independent reflections	6222 [<i>R</i> _{int} = 0.094, <i>R</i> _{sigma} = 0.05]
Data/restraints/parameters	6222/1/461
Goodness-of-fit on <i>F</i> ²	1.012
Final <i>R</i> indexes [<i>I</i> > 2 σ (<i>I</i>)]	<i>R</i> 1 = 0.0597, <i>wR</i> 2 = 0.1498
Final <i>R</i> indexes [all data]	<i>R</i> 1 = 0.0903, <i>wR</i> 2 = 0.1723
Largest diff. peak/hole / e Å ⁻³	0.28/-0.44
Flack parameter	-0.0071(2)

Table 2B. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for PRX^+Br^- . U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
Br1	6190.2(6)	9126.5(6)	4286.0(5)	87.7(3)
Br2	9836(7)	5522(8)	4390(7)	125(2)
C4	6957(5)	4322(6)	5790(5)	77.9(17)
C4'	8353(5)	7648(6)	1550(5)	74.8(16)
C5	6646(5)	4182(7)	4657(5)	76.8(15)
O4'	6029(4)	7258(4)	500(4)	90.1(14)
O5'	2427(4)	8433(6)	-1652(4)	104.5(16)
O4	5501(4)	4833(5)	3070(4)	92.4(13)
C5'	7616(5)	6710(6)	1851(5)	73.6(16)
C14	7239(6)	5668(7)	6155(5)	78.5(17)
Fl1'	10478(5)	5297(6)	-801(4)	128.4(18)
C7	4628(6)	5488(7)	2392(5)	78.6(17)
N1	7265(5)	1911(6)	4887(5)	95.6(18)
C19'	8635(6)	7320(7)	-64(6)	85.5(19)
C9	3465(6)	7216(7)	1773(7)	91(2)
O6'	2380(5)	6919(6)	-2835(5)	116.1(19)
C10	2977(6)	6601(8)	911(6)	86.4(19)
N1'	8025(5)	7834(7)	3447(4)	92.5(18)
C15'	9751(6)	6107(7)	1307(5)	83.8(18)
O5	2194(5)	7396(7)	275(5)	116.4(19)
C7'	5146(6)	7032(6)	-337(5)	79.6(18)
C8	4309(6)	6705(7)	2559(6)	85.5(19)
C3	7910(7)	3393(7)	6279(6)	92(2)
C14'	8926(5)	7020(6)	926(5)	74.2(16)
C1	6336(6)	2785(7)	4368(6)	90(2)
O6	3033(6)	8435(6)	1747(5)	123(2)
C12'	4251(6)	7867(7)	-483(6)	83.1(18)
C11	3297(7)	5439(9)	748(6)	96(2)
C3'	9197(6)	8266(7)	2480(5)	83.9(18)
C19	6621(6)	6265(7)	6639(6)	89(2)
C6'	6702(6)	6208(7)	977(5)	80.8(18)
C2	7613(8)	2042(8)	5986(7)	99(2)
C6	5706(6)	5047(7)	4098(5)	81.4(18)
C11'	3370(6)	7715(7)	-1340(6)	84.0(18)
C12	4137(6)	4844(7)	1516(5)	86.3(19)
C10'	3363(7)	6801(7)	-2023(6)	89(2)
C15	8116(7)	6323(7)	6032(6)	92(2)
C17'	9968(7)	5866(8)	-235(6)	92(2)
C9'	4220(7)	6008(8)	-1912(6)	96(2)
C16'	10250(6)	5518(8)	729(6)	95(2)
C18'	9158(8)	6734(8)	-647(6)	97(2)
C1'	7145(6)	7272(8)	2582(6)	86.5(19)

continue

C2'	8645(7)	8842(7)	3145(6)	95(2)
C8'	5137(6)	6126(7)	-1034(6)	86.2(19)
F1	7983(6)	9329(5)	7188(5)	144(2)
C17	7747(9)	8097(8)	6844(6)	104(3)
C13	2112(8)	8472(11)	866(9)	124(3)
C18	6873(8)	7498(8)	7000(6)	105(2)
C16	8382(8)	7543(9)	6390(7)	105(3)
C13'	1703(8)	7768(11)	-2508(9)	123(3)
Br2'	10016(8)	5822(10)	4547(8)	124(3)

conclusion

Table 3B. Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for PRX^+Br^- . The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	88.1(5)	88.0(4)	90.3(5)	-5.1(4)	34.5(4)	5.1(4)
Br2	145(5)	140(3)	96.8(19)	25.9(19)	49(3)	61(3)
C4	75(4)	75(4)	85(4)	4(3)	29(3)	3(3)
C4'	78(4)	74(4)	75(4)	2(3)	29(3)	1(3)
C5	76(4)	75(3)	82(4)	-7(4)	29(3)	7(4)
O4'	84(3)	79(3)	91(3)	-5(2)	9(3)	12(2)
O5'	77(3)	109(4)	113(4)	2(3)	13(3)	11(3)
O4	98(3)	99(3)	78(3)	4(3)	28(3)	22(3)
C5'	67(4)	76(4)	79(4)	4(3)	27(3)	-2(3)
C14	80(4)	76(4)	77(4)	-3(3)	22(3)	5(3)
F1'	141(4)	145(4)	122(4)	-25(3)	74(3)	15(3)
C7	76(4)	84(4)	78(4)	7(4)	29(3)	6(4)
N1	92(4)	86(4)	108(5)	-6(3)	33(4)	6(3)
C19'	84(4)	93(5)	77(5)	7(4)	24(4)	7(4)
C9	79(5)	88(5)	109(6)	5(4)	36(5)	2(4)
O6'	104(4)	116(4)	102(4)	-2(3)	1(4)	-11(4)
C10	72(4)	107(5)	79(5)	14(4)	25(4)	4(4)
N1'	92(4)	110(4)	79(4)	-3(3)	34(3)	23(4)
C15'	77(4)	97(5)	75(4)	11(4)	23(3)	12(4)
O5	92(4)	150(6)	102(4)	22(4)	25(3)	16(4)
C7'	82(4)	74(4)	77(4)	2(3)	18(4)	-11(3)
C8	80(4)	83(4)	89(5)	-6(4)	22(4)	7(4)
C3	93(5)	94(5)	82(5)	5(4)	22(4)	17(4)
C14'	71(4)	76(4)	77(4)	3(3)	27(3)	1(3)
C1	91(5)	77(4)	95(5)	-6(4)	24(4)	6(4)
O6	117(4)	100(4)	142(6)	1(4)	32(4)	37(4)
C12'	81(4)	78(4)	93(5)	1(4)	35(4)	-1(4)
C11	102(5)	106(6)	77(5)	-8(4)	26(4)	-4(5)
C3'	76(4)	87(4)	85(5)	-2(3)	23(4)	-2(3)
C19	88(5)	92(5)	92(5)	-10(4)	36(4)	2(4)
C6'	81(4)	75(4)	86(5)	0(3)	28(4)	-1(3)

continue

C2	97(6)	90(5)	103(6)	14(4)	27(5)	19(4)
C6	83(4)	75(4)	85(5)	5(3)	27(4)	9(3)
C11'	76(4)	84(4)	86(5)	3(4)	20(4)	-3(4)
C12	93(5)	85(4)	85(5)	-8(4)	36(4)	-6(4)
C10'	89(5)	83(4)	81(5)	2(4)	11(4)	-8(4)
C15	87(5)	88(5)	102(6)	0(4)	34(4)	-10(4)
C17'	91(5)	97(5)	97(5)	-16(4)	44(4)	-2(4)
C9'	99(5)	93(5)	89(5)	-10(4)	21(4)	3(5)
C16'	89(5)	100(5)	101(6)	4(4)	36(4)	24(4)
C18'	121(6)	100(5)	77(5)	-3(4)	44(5)	-1(5)
C1'	80(4)	99(5)	83(5)	-3(4)	31(4)	5(4)
C2'	105(5)	85(5)	94(5)	-16(4)	34(4)	-2(4)
C8'	86(5)	82(4)	85(5)	-2(4)	21(4)	14(4)
F1	187(5)	87(3)	135(4)	-20(3)	22(4)	-21(3)
C17	129(7)	76(4)	83(5)	-2(4)	6(5)	-4(5)
C13	105(7)	124(7)	145(9)	34(7)	43(7)	19(6)
C18	119(7)	101(6)	91(6)	-19(4)	29(5)	13(5)
C16	104(6)	101(6)	106(6)	10(5)	28(5)	-19(5)
C13'	96(6)	127(7)	131(8)	1(6)	20(6)	-1(6)
Br2'	90.0(18)	170(6)	122(5)	65(4)	50(3)	32(3)

conclusion

Table 4B. Bond Lengths for PRX⁺Br⁻.

Atom-Atom	Length/Å	Atom-Atom	Length/Å
C4-C14	1.510(10)	C9-O6	1.392(10)
C4-C3	1.542(10)	O6'-C10'	1.416(9)
C4-C5	1.566(9)	O6'-C13'	1.439(12)
C4'-C14'	1.505(9)	C10-C11	1.335(12)
C4'-C5'	1.533(9)	C10-O5	1.393(10)
C4'-C3'	1.562(10)	N1'-C2'	1.480(10)
C5-C6	1.513(10)	N1'-C1'	1.500(10)
C5-C1	1.540(11)	C15'-C16'	1.370(10)
O4'-C7'	1.378(9)	C15'-C14'	1.400(10)
O4'-C6'	1.429(8)	O5-C13	1.446(13)
O5'-C11'	1.372(9)	C7'-C8'	1.387(10)
O5'-C13'	1.457(11)	C7'-C12'	1.409(10)
O4-C7	1.401(8)	C3-C2	1.493(12)
O4-C6	1.446(9)	O6-C13	1.423(12)
C5'-C6'	1.507(10)	C12'-C11'	1.382(10)
C5'-C1'	1.514(10)	C11-C12	1.412(11)
C14-C19	1.381(10)	C3'-C2'	1.511(10)
C14-C15	1.388(10)	C19-C18	1.393(11)
F1'-C17'	1.355(9)	C11'-C10'	1.380(11)
C7-C8	1.388(10)	C10'-C9'	1.351(11)
C7-C12	1.392(10)	C15-C16	1.382(13)

continue

N1-C1	1.496(10)	C17'-C18'	1.364(12)
N1-C2	1.513(11)	C17'-C16'	1.374(11)
C19'-C18'	1.394(11)	C9'-C8'	1.422(11)
C19'-C14'	1.396(10)	F1-C17	1.383(10)
C9-C10	1.361(12)	C17-C16	1.348(13)
C9-C8	1.391(11)	C17-C18	1.377(13)

conclusion

Table 5B. Bond Angles for PRX⁺Br⁻.

Atom-Atom-Atom	Angle/°	Atom-Atom-Atom	Angle/°
C14-C4-C3	111.8(6)	C2-C3-C4	112.4(7)
C14-C4-C5	113.8(6)	C19'-C14'-C15'	117.7(6)
C3-C4-C5	107.8(6)	C19'-C14'-C4'	120.6(6)
C14'-C4'-C5'	111.8(5)	C15'-C14'-C4'	121.7(6)
C14'-C4'-C3'	111.3(5)	N1-C1-C5	110.8(6)
C5'-C4'-C3'	109.7(5)	C9-O6-C13	104.8(8)
C6-C5-C1	109.7(6)	C11'-C12'-C7'	116.4(7)
C6-C5-C4	112.5(5)	C10-C11-C12	117.7(7)
C1-C5-C4	109.1(6)	C2'-C3'-C4'	112.3(6)
C7'-O4'-C6'	118.7(5)	C14-C19-C18	120.8(8)
C11'-O5'-C13'	105.1(6)	O4'-C6'-C5'	108.3(5)
C7-O4-C6	118.2(5)	C3-C2-N1	110.1(7)
C6'-C5'-C1'	110.1(6)	O4-C6-C5	107.1(5)
C6'-C5'-C4'	111.5(6)	O5'-C11'-C10'	110.8(7)
C1'-C5'-C4'	112.8(6)	O5'-C11'-C12'	126.9(7)
C19-C14-C15	118.7(7)	C10'-C11'-C12'	122.2(7)
C19-C14-C4	119.5(6)	C7-C12-C11	120.0(7)
C15-C14-C4	121.8(6)	C9'-C10'-C11'	122.5(7)
C8-C7-C12	122.5(7)	C9'-C10'-O6'	128.3(8)
C8-C7-O4	123.0(7)	C11'-C10'-O6'	109.0(7)
C12-C7-O4	114.5(6)	C16-C15-C14	121.3(8)
C1-N1-C2	112.2(6)	F1'-C17'-C18'	119.1(8)
C18'-C19'-C14'	120.8(7)	F1'-C17'-C16'	119.2(8)
C10-C9-C8	124.3(7)	C18'-C17'-C16'	121.6(7)
C10-C9-O6	110.8(7)	C10'-C9'-C8'	116.9(7)
C8-C9-O6	124.9(8)	C15'-C16'-C17'	119.4(7)
C10'-O6'-C13'	104.6(7)	C17'-C18'-C19'	119.1(8)
C11-C10-C9	121.5(8)	N1'-C1'-C5'	111.8(6)
C11-C10-O5	128.9(8)	N1'-C2'-C3'	109.0(6)
C9-C10-O5	109.4(7)	C7'-C8'-C9'	120.9(7)
C2'-N1'-C1'	111.3(6)	C16-C17-C18	123.6(8)
C16'-C15'-C14'	121.3(7)	C16-C17-F1	119.0(10)
C10-O5-C13	104.9(7)	C18-C17-F1	117.4(9)
O4'-C7'-C8'	124.3(6)	O6-C13-O5	107.9(7)

continue

O4'-C7'-C12'	114.6(6)	C17-C18-C19	117.5(8)
C8'-C7'-C12'	120.9(7)	C17-C16-C15	118.0(8)
C7-C8-C9	114.0(7)	O6'-C13'-O5'	107.1(7)

conclusion

Table 6B. Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for PRX^+Br^- .

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
H4	6321	4050	5963	93
H4'	7883	8327	1164	90
H5	7292	4401	4481	92
H5'	8075	5982	2166	88
H2	7844	2084	4697	115
H1	7058	1101	4719	115
H19'	8086	7918	-338	103
H1'	7716	8165	3862	111
H2'	8493	7215	3763	111
H15'	9964	5895	1966	101
H8	4630	7140	3143	103
H3A	8543	3631	6102	110
H3B	8117	3465	6983	110
H1A	5691	2557	4530	108
H1B	6154	2690	3668	108
H12'	4252	8488	-27	100
H11	2978	5035	149	115
H3A'	9718	7623	2837	101
H3B'	9604	8925	2282	101
H19	6030	5838	6725	107
H6A'	7007	5791	531	97
H6B'	6266	5592	1183	97
H2A	7016	1776	6204	119
H2B	8241	1496	6294	119
H6A	5054	4849	4258	98
H6B	5901	5930	4264	98
H12	4362	4022	1437	104
H15	8533	5933	5701	110
H9'	4212	5412	-2388	116
H16'	10775	4888	986	114
H18'	8956	6932	-1307	116
H1A'	6617	7929	2266	104
H1B'	6760	6612	2804	104
H2A'	9194	9207	3716	114
H2B'	8147	9515	2806	114
H8'	5739	5587	-925	103
H13A	2112	9261	519	149

continue

H13B	1433	8425	1011	149
H18	6466	7901	7333	126
H16	8982	7970	6321	127
H13C	1149	7291	-2341	147
H13D	1334	8373	-3018	147

conclusion

Table 7B Atomic Occupancy for PRX^+Br^- .

Atom	<i>Occupancy</i>	Atom	<i>Occupancy</i>
Br2	0.54	Br2'	0.46

DISCUSSION: Hirshfeld Surface and Fingerprint Plots

The detailed similarities between the packing of $(\text{PRX}^+\text{Cl}^-)\cdot 0.5\text{H}_2\text{O}$, $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$ and PRXBr have been performed through the analysis of 2D fingerprint plots derived from Hirshfeld surface (Figures D1 and D2)^{45,46}. Since the Hirshfeld surface is a molecular volume occupied by a molecule in a crystal derived from the partitioning of crystal electron density, the fingerprint plots summarizes information about the all intermolecular interactions^{41,42}. These are important tools to explore packing differences of a molecule in different crystal environment.

Figure D1. Fingerprint plots of PRX^+ conformers and Br^- anion in the $(\text{PRX}^+\text{Br}^-)\cdot 0.5\text{H}_2\text{O}$ and the PRX^+Br^- dehydrate.

Figure D2. Fingerprint plots of PRX⁺ conformers for (PRX⁺Cl⁻)0.5H₂O. The plot similarity between (PRX⁺Cl⁻)0.5H₂O and (PRX⁺Br⁻).H₂O show the isostructurality of the salts.

From Figures D1 and D2, the following analogies and differences between the PRX⁺ conformers (A and B) in the (PRX⁺Br⁻)0.5H₂O and (PRX⁺Cl⁻)0.5H₂O forms are noted: (i) the

notoriously aspect of these fingerprint plots is their similarity indicating analogous intermolecular interactions for the A and B conformers in the HCl and HBr crystal structures; (ii) in Figure D1, the long and sharp lateral spikes with maximum at $d_i + d_e \approx 2.2\text{--}2.3 \text{ \AA}$ are assigned to $\text{NH}^+\cdots\text{Br}^-$ hydrogen bond between the PRX^+ and the inorganic anions. Only the A conformer shows an additional sharp spike with maximum at $d_i + d_e \approx 1.8 \text{ \AA}$, due to the water molecules in the crystal structure. The asymmetry of plots of conformers are related to the cell with $Z' > 1$; (iii) in the $(\text{PRX}^+\text{Br}^-)0.5\text{H}_2\text{O}$ plots, a narrow light blue spike along the main diagonal $\sim d_i + d_e \approx 2.2 \text{ \AA}$ is appreciable in the plot of the conformer A, but not in that of the conformer B. This feature refers to $\text{H}\cdots\text{H}$ contacts and reveals that the A conformer experiences a slightly more crowded environment than B one; (iv) the couple of lateral ‘wings’ at $1.6\text{ \AA} < (d_e + d_i) < 2.6 \text{ \AA}$ are evident in the plots and are identified as a result of $\text{C}\text{--}\text{H}\cdots\pi$ interactions.

Concerning the PRX^+Br^- dehydrated structure, the Hirshfeld plot indicates particular differences with respect its $(\text{PRXBr})0.5\text{H}_2\text{O}$ hydrate one. The dehydration generate an isomorphous structure, then, their plot are very similar since the drug framework was not broken after the process. However, the peak corresponding to $\text{N}^+\text{--}\text{H}\cdots\text{O}$ in the plots of conformer A is absence since this interaction was replaced by the $\text{N}^+\text{--}\text{H}\cdots\text{Br}^-$ in the dehydrated structure. As results of dehydration, the arrangement of PRX^+ molecules remains unchanged, while the supramolecular arrangement of Br significantly change. The comparison of Hirshfeld plot to Br1^- anions in $(\text{PRXBr})0.5\text{H}_2\text{O}$ and PRXBr dehydrate forms show the presence of a number of longer contacts (notice the points at high d_i and d_e values in Figure D1), in the dehydrated forms indicating less efficient packing. The plots to Br1 does not show significant difference

Figure D2).

COMPLEMENTARY TABLES AND FIGURES

Table S1. Hydrogen-bonds geometry and contact geometry ($\text{\AA}$, $^\circ$) for $(\text{PRX}^+\text{Br}^-)\cdot\text{H}_2\text{O}$ and PRX^+Br^- .

$(\text{PRX}^+\text{Br}^-)\cdot\text{H}_2\text{O}^*$			
Interaction	H...A	D...A	D-H...A
C1'-H1'D...O1	2.42022(6)	3.38433(8)	172.5320(3)
OW1A-HW1A...Br1A	2.46558(10)	3.11025(11)	131.4137(14)
N1'-H1'A...Br1A ⁽¹⁾	2.47066(7)	3.33448(9)	163.7696(6)
N1-H1B...Br1 ⁽¹⁾	2.35491(8)	3.22667(11)	166.3693(5)
N1-H1B...OW1A ⁽¹⁾	1.87678(6)	2.74105(8)	163.2549(6)
N1'-H1'B...Br1' ⁽²⁾	2.40764(6)	3.23851(7)	155.4803(8)
C12-H12...Br1 ⁽²⁾	2.92057(7)	3.77801(9)	153.9112(8)
C8'-H8'...O3 ⁽³⁾	2.97499(7)	3.79449(9)	147.8071(10)
C2'-H2'B...O2 ⁽¹¹⁾	2.55808(9)	3.48683(11)	160.3377(6)
OW1A-HW1B...Br1A ⁽¹²⁾	2.24111(6)	3.11095(8)	179.73226(9)
C8-H8...Cg1' ^{1-X,-1/2+Y,-Z}	2.82203(8)	3.73344(10)	150.9402(19)
C13-H13B...Cg2' ^{1-x,1/2+y,-z}	3.03393	3.73809(10)	131.7047(14)
PRX^+Br^-			
N1'-H1'A...Br1 ⁽⁰⁾	2.481(6)	3.305(6)	154.18(14)
N1'-H1'B...Br2 ⁽⁰⁾	2.444(8)	3.326(9)	171.0(2)
N1-H1B...Br1 ⁽⁷⁾	2.349(6)	3.227(6)	168.98(15)
N1-H1A...Br1 ⁽⁸⁾	2.929(11)	3.516(10)	124.98(18)
C8-H8...Br1 ⁽⁰⁾	2.983(8)	3.813(8)	149.37(14)
C1'-H1'...O1 ⁽⁰⁾	2.591(9)	3.550(9)	169.6(2)
C2'-H2'1...Br2 ⁽⁹⁾	2.991(11)	3.639(11)	125.3(2)
C2'-H2'...O2 ⁽¹⁰⁾	2.619(9)	3.462(9)	145.6(2)
C8-H8...Cg1'	2.940(8)	3.574(8)	151.26(17)
C13-H13B...Cg2'	3.013(10)	3.788(10)	136.37(2)

C7'→C12' = Cg1; C14'→C19' = Cg2' Symmetry codes: (0) x, y, z; (1) -x+1,+y-1/2,-z+1; (2) -x+1,+y+1/2,-z+1; (3)-x+1,+y-1/2,-z; (11)-x+1,+y+1/2,-z; (12) -x,+y-1/2,-z+1

* Only high occupancy part was considered in this analysis.

Figure S1. Hydrogen bond around the independent Br anions (a) and (b) in (PRXBr)0.5H₂O at 100K and 360K.

Figure S2. Packing overlay for pair (a) (PRX+Br⁻)·0.5H₂O (light color)/(PRX+Cl⁻)·0.5H₂O²⁷ (dark color); (b) (PRX+Br⁻)·0.5H₂O (light color)/(PRX+Cl⁻)·0.5H₂O²⁸ (dark color) and (c) (PRX+Br⁻)·0.5H₂O (light color)/PRX+Br⁻ (dark color).

Figure S3. Standard DSC analyses (10 °C/min) for (a) Paroxetine HCl form I (Hemihydrate), (b) Paroxetine HCl form II and (c) (PRXBr)0.5H₂O. The results of chloride forms shown good agreement with reported values from Bruni *et al.* (2012)²⁹ (mp 121.8°C) for Form I, Buxton *et al.* (mp 118.3° C)⁴¹ for Form II, Ward *et al.* (mp 123–125 °C)⁴² Form A. TGA curve of (PRXBr)0.5H₂O, showing the weight loss (---) curves relative to release of water under heating.

Figure S4. Standard DSC runs to (PRX+Br-)0.5H₂O at 20 min and 2h after Dehydration (T = 0).

APPENDIX B - Supporting Information of the paper ' X-Ray Diffraction, Spectroscopy and Thermochemical Characterization of the Pharmaceutical Paroxetine Nitrate Salt'

SUPPORTING INFORMATION

X-Ray Diffraction, Spectroscopy and Thermochemical Characterization of the Pharmaceutical Paroxetine Nitrate Salt.

Paulo S. Carvalho Jr.^a, Cristiane Cabral de Melo^{a,b}, Alejandro P. Ayala^b, Javier Ellena^{a*},

^a Instituto de Física de São Carlos, Universidade de São Paulo, CP 369, 13560-970 - São Carlos, SP, Brazil; ^bDepartamento de Física, Universidade Federal do Ceará, CP 6030, Fortaleza, Ceará 60455-970, Brazil; * e-mail address : javiere@ifsc.usp.br

PAROXETINE NITRATE HYDRATE

Table 1A: Crystal data and structure refinement for (PRX⁺NO₃⁻)H₂O

Structure	(PRX ⁺ NO ₃ ⁻)H ₂ O
Empirical formula	C ₁₉ H _{21.5} FN ₂ O _{6.5}
Formula weight	400.88
Temperature/K	150(2)
Crystal system	Monoclinic
Space group	C2
a/Å	39.7779(13)
b/Å	5.8787(2)
c/Å	7.9925(3)
β/°	97.022(2)
Volume/Å ³	1854.97(11)
Z, Z'	4, 1
ρ _{calc} g/cm ³	1.435
μ/mm ⁻¹	0.979
F(000)	842.0
Crystal size/mm ³	0.562 × 0.122 × 0.06
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	4.476 to 140.402
	-48 ≤ h ≤ 47
Index ranges	-7 ≤ k ≤ 7
	-9 ≤ l ≤ 9
Reflections collected	7890
Independent reflections	3312 [R _{int} = 0.0624, R _{sigma} = 0.0670]
Data/restraints/parameters	3312/1/259
Goodness-of-fit on F ²	1.049
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0413, wR ₂ = 0.0830
Final R indexes [all data]	R ₁ = 0.0567, wR ₂ = 0.0892
Largest diff. peak/hole / e Å ⁻³	0.17/-0.26
Flack parameter	-0.16(17)

Table 2A. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij} tensor

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
F1	3514.7(6)	6967(4)	8146(3)	43.3(7)
O3	4693.0(7)	7435(4)	8266(3)	33.6(7)
O4	3484.2(6)	-821(4)	2038(3)	24.7(6)
O6	2644.6(6)	-5802(4)	3866(3)	33.5(7)
O1	4491.1(7)	5128(4)	10001(3)	32.7(6)
N1	4476.5(7)	410(5)	707(4)	27.7(7)
N2	4649.0(7)	5442(5)	8741(4)	24.9(7)
O5	2194.7(6)	-3725(5)	2545(3)	31.5(6)
C12	3094.3(8)	-3362(6)	2982(4)	23.6(8)
C6	3555.6(9)	1388(6)	1416(5)	23.5(8)
C19	3657.1(8)	2155(6)	5516(5)	25.3(8)
C9	2544.1(9)	-723(6)	1459(5)	27.1(8)
C5	3938.5(8)	1727(6)	1697(4)	21.6(8)
C15	4078.2(9)	4978(6)	5239(5)	24.2(8)
C11	2763.8(9)	-3951(6)	3066(5)	23.6(8)
C4	4092.9(8)	1306(6)	3546(4)	21.9(8)
O2	4756.0(7)	3799(4)	7991(4)	35.5(7)
C18	3513.5(9)	3522(6)	6643(5)	29.6(9)
C7	3148.1(8)	-1357(6)	2095(4)	21.9(8)
C16	3938.8(9)	6364(6)	6376(4)	26.9(8)
C10	2497.4(8)	-2675(6)	2303(5)	24.4(8)
C3	4480.8(9)	1484(7)	3683(5)	28.8(9)
C13	2283.9(10)	-5490(6)	3724(5)	33.6(9)
C8	2881.5(9)	-52(6)	1354(5)	25.8(8)
C2	4626.3(9)	-110(6)	2470(5)	28.7(9)
C14	3941.9(8)	2852(6)	4779(5)	21.3(8)
C17	3658(1)	5611(6)	7038(5)	28.7(9)
C1	4101.3(9)	188(6)	484(5)	27.1(8)
Ow1	5000	6420(8)	5000	54.0(12)

Table 3A. Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^2U_{11}+2hka^2b^2U_{12}+\dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	42.0(13)	49.8(15)	40.8(15)	-20.0(12)	15.6(11)	4.6(12)
O3	43.6(16)	21.7(14)	39.1(18)	-0.4(12)	19.5(13)	-8.6(12)
O4	24.7(13)	20.5(12)	29.1(15)	0.3(11)	4.3(11)	0.4(10)
O6	31.4(15)	32.0(14)	39.0(17)	13.0(13)	12.2(12)	0.6(12)
O1	44.7(16)	25.6(13)	31.3(16)	2.4(11)	18.8(13)	-2.7(13)
N1	32.5(17)	20.7(14)	33.2(19)	-1.2(14)	17.4(14)	-1.1(14)
N2	24.5(16)	24.5(16)	26.1(19)	-3.9(13)	4.7(13)	-1.5(13)
O5	26.9(14)	42.7(15)	26.3(16)	5.1(12)	8.8(11)	-2.7(12)
C12	25.5(18)	21.8(16)	24(2)	-3.3(15)	6.0(15)	5.6(15)
C6	29.7(19)	19.7(16)	21(2)	1.8(15)	3.9(15)	3.8(16)
C19	24.6(18)	26.3(19)	25(2)	-0.3(16)	4.4(15)	-2.3(16)
C9	27.4(19)	30.9(19)	23(2)	0.4(17)	2.5(15)	4.1(17)
C5	28.0(18)	15.7(16)	22(2)	1.2(14)	6.2(15)	1.0(14)
C15	22.3(18)	25.0(17)	26(2)	0.6(15)	5.3(15)	0.4(15)
C11	31(2)	19.0(17)	21(2)	-3.1(14)	4.9(15)	3.1(14)
C4	24.0(18)	18.3(15)	24(2)	-1.0(15)	5.8(15)	2.6(15)
O2	42.2(16)	27.8(14)	38.5(18)	-8.4(13)	13.3(13)	4.6(12)
C18	26(2)	40(2)	24(2)	1.9(18)	8.0(16)	1.7(17)
C7	22.1(19)	21.2(17)	23(2)	-5.4(15)	5.9(15)	2.3(14)
C16	33(2)	22.2(17)	26(2)	-3.9(16)	3.9(16)	1.0(16)
C10	23.6(18)	29.6(18)	21(2)	-4.7(16)	6.8(15)	-1.1(16)
C3	24.8(19)	31.4(18)	31(2)	-4.9(17)	5.3(16)	4.8(17)
C13	35(2)	31(2)	37(3)	4.0(17)	11.7(18)	-1.2(18)
C8	28.3(19)	26.8(18)	22(2)	3.5(15)	2.3(15)	1.0(16)
C2	26.1(19)	23.1(18)	38(2)	-1.7(16)	9.4(16)	3.5(15)
C14	22.6(19)	21.8(17)	20(2)	0.1(14)	3.5(15)	3.9(15)
C17	33(2)	31.7(19)	22(2)	-5.6(17)	6.5(16)	9.2(17)
C1	32(2)	25.3(17)	26(2)	-2.1(16)	9.3(16)	1.1(17)
Ow1	72(3)	51(3)	40(3)	0	12(2)	0

Table 4A. Bond Lengths for PRXNO3

Bond	Length/Å	Bond	Length/Å
F1–C17	1.366(4)	C19–C18	1.382(5)
O3–N2	1.251(4)	C19–C14	1.401(5)
O4–C6	1.431(4)	C9–C10	1.355(5)
O4–C7	1.380(4)	C9–C8	1.411(5)
O6–C11	1.375(4)	C5–C4	1.549(5)
O6–C13	1.437(5)	C5–C1	1.527(5)
O1–N2	1.264(4)	C15–C16	1.385(5)
N1–C2	1.493(5)	C15–C14	1.394(5)
N1–C1	1.487(4)	C11–C10	1.379(5)
N2–O2	1.239(4)	C4–C3	1.537(5)
O5–C10	1.388(4)	C4–C14	1.517(5)
O5–C13	1.418(5)	C18–C17	1.376(5)
C12–C11	1.369(5)	C7–C8	1.382(5)
C12–C7	1.405(5)	C16–C17	1.367(5)
C6–C5	1.525(5)	C3–C2	1.514(5)

Table 5A. Bond Angles for (PRX⁺NO₃[−])H₂O.

Bond Angle	Angle/°	Bond Angle	Angle/°
C7–O4–C6	116.9(3)	C14–C4–C3	112.7(3)
C11–O6–C13	105.1(3)	C17–C18–C19	118.3(3)
C1–N1–C2	112.0(3)	O4–C7–C12	114.6(3)
O3–N2–O1	118.7(3)	O4–C7–C8	123.7(3)
O2–N2–O3	120.9(3)	C8–C7–C12	121.7(3)
O2–N2–O1	120.4(3)	C17–C16–C15	118.4(3)
C10–O5–C13	105.5(3)	C9–C10–O5	128.3(3)
C11–C12–C7	116.3(3)	C9–C10–C11	122.4(3)
O4–C6–C5	107.7(3)	C11–C10–O5	109.2(3)
C18–C19–C14	121.6(3)	C2–C3–C4	111.8(3)
C10–C9–C8	117.1(3)	O5–C13–O6	108.2(3)
C6–C5–C4	113.0(3)	C7–C8–C9	120.3(3)
C6–C5–C1	108.8(3)	N1–C2–C3	109.7(3)
C1–C5–C4	111.2(3)	C19–C14–C4	120.2(3)
C16–C15–C14	121.7(3)	C15–C14–C19	117.4(3)
O6–C11–C10	110.3(3)	C15–C14–C4	122.4(3)
C12–C11–O6	127.7(3)	F1–C17–C18	118.3(3)
C12–C11–C10	122.1(3)	F1–C17–C16	119.2(3)
C3–C4–C5	109.5(3)	C16–C17–C18	122.5(3)
C14–C4–C5	112.5(3)	N1–C1–C5	111.7(3)

Table 6A. Torsion Angles for (PRX⁺NO₃⁻)H₂O.

Torsion Angle	Angle/°	Torsion Angle	Angle/°
O4-C6-C5-C4	-53.4(4)	C18-C19-C14-C15	0.6(5)
O4-C6-C5-C1	70.7(3)	C18-C19-C14-C4	-180.0(3)
O4-C7-C8-C9	179.6(3)	C7-O4-C6-C5	172.2(3)
O6-C11-C10-O5	-2.0(4)	C7-C12-C11-O6	-179.3(3)
O6-C11-C10-C9	178.4(3)	C7-C12-C11-C10	1.0(5)
C12-C11-C10-O5	177.7(3)	C16-C15-C14-C19	-0.1(5)
C12-C11-C10-C9	-1.9(6)	C16-C15-C14-C4	-179.6(3)
C12-C7-C8-C9	-0.6(5)	C10-O5-C13-O6	-13.3(4)
C6-O4-C7-C12	-169.3(3)	C10-C9-C8-C7	-0.2(5)
C6-O4-C7-C8	10.5(5)	C3-C4-C14-C19	-144.9(3)
C6-C5-C4-C3	175.2(3)	C3-C4-C14-C15	34.5(5)
C6-C5-C4-C14	-58.6(4)	C13-O6-C11-C12	174.0(4)
C6-C5-C1-N1	-179.2(3)	C13-O6-C11-C10	-6.2(4)
C19-C18-C17-F1	179.6(3)	C13-O5-C10-C9	-170.9(4)
C19-C18-C17-C16	-0.8(6)	C13-O5-C10-C11	9.5(4)
C5-C4-C3-C2	-55.3(4)	C8-C9-C10-O5	-178.1(3)
C5-C4-C14-C19	90.6(4)	C8-C9-C10-C11	1.4(5)
C5-C4-C14-C15	-90.0(4)	C2-N1-C1-C5	57.4(4)
C15-C16-C17-F1	-179.2(3)	C14-C19-C18-C17	-0.1(5)
C15-C16-C17-C18	1.2(6)	C14-C15-C16-C17	-0.7(6)
C11-O6-C13-O5	12.1(4)	C14-C4-C3-C2	178.7(3)
C11-C12-C7-O4	180.0(3)	C1-N1-C2-C3	-58.8(4)
C11-C12-C7-C8	0.2(5)	C1-C5-C4-C3	52.4(4)
C4-C5-C1-N1	-54.0(4)	C1-C5-C4-C14	178.6(3)
C4-C3-C2-N1	58.2(4)		

Table 7A. Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for (PRX⁺NO₃⁻)H₂O

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
H1A	4534	1853	441	33
H1B	4565	-557	-14	33
H12	3277	-4259	3494	28
H6A	3442	2571	2026	28
H6B	3472	1502	201	28
H19	3560	707	5234	30
H9	2358	155	960	33
H5	3987	3340	1408	26
H15	4272	5491	4760	29
H4	4037	-294	3834	26
H18	3320	3032	7132	35
H16	4036	7802	6687	32
H3A	4545	3067	3441	35

continue

H3B	4579	1116	4849	35
H13A	2167	-6917	3338	40
H13B	2215	-5079	4835	40
H8	2926	1303	772	31
H2A	4875	70	2573	34
H2B	4575	-1704	2748	34
H1C	4039	-1412	679	32
H1D	4012	589	-690	32
H1'	4963	5318	5968	81

conclusion

CHECK CIF INFORMATION

Datablock: (PRX⁺NO₃⁻)H₂O- **CCDC 1456602**

Bond precision: C-C = 0.0050 Å Wavelength=1.54178 Cell: a=39.7779(13) b=5.8787(2)
c=7.9925(3) alpha=90 beta=97.022(2) gamma=90
Temperature: 150 K

Alert level C

PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds 0.005 Å.
PLAT911_ALERT_3_C Missing # FCF Refl Between THmin & STh/L= 0.600 22 Report
PLAT915_ALERT_3_C No Flack x Check Done: Low Friedel Pair Coverage 87 %

Alert level G

PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms 3 Report
PLAT042_ALERT_1_G Calc. and Reported MoietyFormula Strings Differ Please Check
PLAT045_ALERT_1_G Calculated and Reported Z Differ by a Factor ... 0.50 Check
PLAT128_ALERT_4_G Alternate Setting for Input Space Group C2 I2 Note
PLAT300_ALERT_4_G Atom Site Occupancy of *H0AA is Constrained at 0.5 Check
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels 3 Note
PLAT791_ALERT_4_G The Model has Chirality at C4 (Chiral SPGR) R Verify
PLAT791_ALERT_4_G The Model has Chirality at C5 (Chiral SPGR) S Verify
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600 6 Note
PLAT913_ALERT_3_G Missing # of Very Strong Reflections in FCF 1 Note
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density 1 Note

0 **ALERT level A** = Most likely a serious problem - resolve or explain

0 **ALERT level B** = A potentially serious problem, consider carefully

3 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight

11 **ALERT level G** = General information/check it is not something unexpected

COMPLEMENTARY TABLES AND FIGURES

Table S1. Selected bond lengths (Å), bond angles (°) and dihedral angles (°) for (PRX⁺NO₃⁻)H₂O.

F1–C17	1.366(4)		
O3–N2	1.251(4)	O4–C6–C5–C4	-53.4(4)
O4–C6	1.431(4)	O4–C6–C5–C1	70.7(3)
O4–C7	1.380(4)	O6–C11–C10–O5	-2.0(4)
O1–N2	1.264(4)	O6–C11–C10–C9	178.4(3)
N1–C2	1.493(5)	C12–C7–C8–C9	-0.6(5)
N1–C1	1.487(4)	C6–O4–C7–C12	-169.3(3)
N2–O2	1.239(4)	C6–C5–C1–N1	-179.2(3)
C7–O4–C6	116.9(3)	C4–C5–C1–N1	-54.0(4)
C1–N1–C2	112.0(3)	C4–C3–C2–N1	58.2(4)
C10–O5–C13	105.5(3)	C5–C6–O4–C7	172.2(3)
C6–C5–C4	113.0(3)	C13–O6–C11–C12	174.0(4)
C1–C5–C4	111.2(3)	C13–O6–C11–C10	-6.2(4)
O4–C7–C12	114.6(3)	C13–O5–C10–C9	-170.9(4)
O4–C7–C8	123.7(3)	C13–O5–C10–C11	9.5(4)
N1–C2–C3	109.7(3)	C2–N1–C1–C5	57.4(4)
N1–C1–C5	111.7(3)	C1–N1–C2–C3	-58.8(4)

Table S2. Hydrogen-bonds geometry ($\text{\AA}$, $^\circ$) for $(\text{PRX}^+\cdot\text{NO}_3^-)\cdot\text{H}_2\text{O}$

D–H...A	$d(\text{D}\cdots\text{A})$ ($\text{\AA}$)	$d(\text{H}\cdots\text{A})$ ($\text{\AA}$)	$\angle\text{D–H}\cdots\text{A}$ ($^\circ$)	symmetry codes
N1–H1A...O1	2.832(3)	1.970(2)	159.93(15)	x,+y,+z-1
N1–H1B...O3	2.831(3)	1.937(2)	172.08(15)	x,+y-1,+z-1
C19–H19...O4	3.285(4)	2.698(2)	121.74(2)	X, y, z
C15–H15...OW1	3.789(3)	2.947(1)	151.26(2)	X, y, z
C5–H5...O1	3.376(3)	2.649(2)	131.24(15)	x,+y,+z-1
C18–H18...O5	3.250(4)	2.356(2)	161.17(2)	-x+1/2,+y+1/2,-z+1
C8–H8...O5	3.191(3)	2.645(2)	118.13(2)	-x+1/2,+y+1/2,-z
O1w–H1...O2	3.0987(4)	2.101(3)	161.38(16)	-x+1,+y,-z+1
C12–H12...Cg1	3.709(4)	2.806(2)	159.18(2)	x,-1+y, z
C13–H13A...Cg2	3.446(4)	2.643(15)	138.34(2)	1/2-x, -1/2+y, -z

Cg1: ring C Cg2: ring B

Figure S1. View of asymmetric unit of $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$ showing atoms labels including H atoms.

Figure S2. packing view of $(\text{PRX}^+\text{NO}_3^-)\text{H}_2\text{O}$

APPENDIX C - Supporting Information of the paper 'Rare case of racemic Fluoxetine Nitrate polymorphs: Phase Behavior and Relative Stability'

SUPPORTING INFORMATION

Rare case of racemic Fluoxetine Nitrate polymorphs: Phase Behavior and Relative Stability.

Paulo S. Carvalho-Jr^a, Javier Ellena^{a*}, Dimitri Yufit^b, Judith A. K. Howard^b

^a Instituto de Física de São Carlos, Universidade de São Paulo, CP 369, 13560-970 - São Carlos, SP, Brazil; ^b Department of Chemistry, Durham University, South Rd, Durham, UK DH1 3LE. * e-mail address: javiere@ifsc.usp.br

FLUOXETINE NITRATE- RACEMATE

Table 1A. Crystal data and structure refinement for the Fluoxetine Nitrate-Racemate (FLXNO3-I).

Empirical formula	C ₁₇ H ₁₉ F ₃ N ₂ O ₄
Formula weight	372.34
Temperature/K	120(2)
Crystal system	Monoclinic
Space group	P2 ₁ /n
a/Å	6.5389(3)
b/Å	24.7851(12)
c/Å	11.2707(6)
β/°	105.3610(16)
Cell volume/Å ³	1761.36(15)
Z, Z'	4, 1
ρ _{calc} /cm ³	1.404
μ/mm ⁻¹	1.044
F(000)	776.0
Crystal size/mm ³	0.344 × 0.147 × 0.133
Radiation	CuKα (λ = 1.54178)
2θ range for data collection/°	7.132 to 149.932
	-8 ≤ h ≤ 8
Index ranges	-31 ≤ k ≤ 29
	-14 ≤ l ≤ 13
Reflections collected	26294
Independent reflections	3600 [R _{int} = 0.0415, R _{sigma} = 0.0236]
Data/restraints/parameters	3600/54/266
Goodness-of-fit on F ²	1.050
Final R indexes [I > 2σ (I)]	R1 = 0.0389, wR2 = 0.0948
Final R indexes [all data]	R1 = 0.0466, wR2 = 0.1004
Largest diff. peak/hole / e Å ⁻³	0.26/-0.27

Table 2A. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for FLXNO3-I. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{II} tensor.

Atom	x	y	z	U_{eq}
O4	5550.0(15)	8961.1(4)	1101.7(9)	24.0(2)
O1	7807.0(18)	7478.0(5)	238.4(10)	32.8(3)
N2	8145(2)	7432.7(5)	1387.2(12)	27.5(3)
N1	3264.5(19)	7585.9(5)	-586.7(11)	23.4(3)
O2	6581.7(18)	7457.1(5)	1845(1)	39.2(3)
O3	9962.6(17)	7380.0(5)	2064.9(10)	35.8(3)
C7	5615(2)	8707.6(5)	-39.7(12)	20.8(3)
C16	7216(2)	9271.0(6)	3074.8(12)	21.9(3)
C15	8944(2)	9307.3(5)	4087.8(12)	22.0(3)
C13	11008(2)	8778.2(6)	3038.5(13)	24.5(3)
C6	6687(2)	9057.4(6)	-798.0(12)	21.2(3)
C11	7369(2)	8984.0(5)	2037.4(12)	20.6(3)
C12	9282(2)	8742.3(6)	2013.4(13)	24.3(3)
C2	8285(2)	9120.2(7)	-2494.8(14)	31.5(3)
C14	10854(2)	9057.8(5)	4075.1(12)	21.2(3)
C5	7025(2)	9606.3(6)	-581.8(14)	28.9(3)
C1	7323(2)	8816.5(6)	-1762.9(13)	25.6(3)
C9	2427(2)	8094.7(6)	-187.5(13)	23.3(3)
C8	3306(2)	8586.2(6)	-699.2(13)	23.8(3)
C3	8616(3)	9669.1(7)	-2273.7(15)	35.4(4)
C4	7981(3)	9910.3(7)	-1325.8(16)	36.1(4)
C10	2321(3)	7090.2(6)	-219.6(16)	32.7(4)
C17	12688(14)	9067(4)	5207(8)	25.4(8)
F3	14447(8)	8889(2)	5016(5)	49.4(13)
F1	12355(3)	8753.2(11)	6094.6(18)	46.7(5)
F2	13014(5)	9556.6(9)	5672(3)	65.5(9)
F2A	12290(4)	9162(2)	6220(2)	63.3(9)
F3A	13788(5)	9599.2(12)	5088(3)	49.6(7)
F1A	14213(10)	8769(2)	5207(6)	75(2)
C3A	12733(17)	9139(4)	5133(10)	25.4(8)

Table 3A Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for FLXNO3-I. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O4	18.8(5)	31.1(5)	21.0(5)	-2.0(4)	3.5(4)	1.5(4)
O1	34.4(6)	40.6(6)	24.9(5)	5.4(5)	10.8(4)	10.0(5)
N2	29.6(7)	25.8(6)	26.8(6)	3.4(5)	7.2(5)	5.7(5)
N1	22.5(6)	25.6(6)	24.1(6)	-2.1(5)	9.8(5)	-0.9(5)

continue

O2	30.4(6)	62.3(8)	27.0(6)	6.5(5)	11.3(5)	5.4(5)
O3	28.5(6)	41.1(6)	34.4(6)	4.6(5)	2.6(5)	8.9(5)
C7	20.5(7)	21.0(6)	19.5(6)	-0.3(5)	2.7(5)	0.1(5)
C16	21.7(7)	21.7(7)	23.7(7)	2.6(5)	8.5(5)	2.3(5)
C15	27.4(7)	19.7(6)	19.9(6)	0.7(5)	8.1(5)	0.3(5)
C13	21.1(7)	27.5(7)	24.6(7)	0.2(6)	5.6(5)	3.6(5)
C6	16.3(6)	23.3(7)	21.3(6)	2.7(5)	0.1(5)	-0.5(5)
C11	19.7(6)	21.5(6)	20.0(6)	2.6(5)	4.4(5)	-1.1(5)
C12	23.0(7)	27.4(7)	22.7(7)	-3.7(6)	6.4(5)	1.8(5)
C2	26.3(7)	44.4(9)	23.6(7)	3.6(6)	5.9(6)	-2.9(6)
C14	23.3(7)	19.7(6)	20.0(6)	3.5(5)	4.5(5)	-0.8(5)
C5	28.1(7)	24.7(7)	31.9(8)	0.8(6)	4.6(6)	-0.4(6)
C1	23.7(7)	27.8(7)	23.7(7)	0.5(6)	3.1(5)	-2.2(5)
C9	20.7(7)	24.8(7)	25.6(7)	-1.9(5)	8.2(5)	0.2(5)
C8	20.0(7)	25.2(7)	24.0(7)	1.6(5)	1.6(5)	-1.0(5)
C3	28.5(8)	42.0(9)	33.0(8)	15.1(7)	3.2(6)	-8.6(7)
C4	36.2(9)	24.8(8)	42.9(9)	8.5(7)	2.7(7)	-6.0(6)
C10	33.6(8)	23.8(7)	45.4(9)	-1.0(7)	18.5(7)	-2.6(6)
C17	28.4(8)	25(2)	21.3(10)	1.0(12)	4.3(7)	3.0(11)
F3	18.3(12)	101(4)	28.1(12)	-11.3(17)	4.9(10)	7.7(17)
F1	42.4(11)	70.1(15)	23.4(9)	15.6(10)	1.3(8)	-4.2(11)
F2	68.0(18)	28.9(11)	68.5(19)	-23.1(13)	-36.4(14)	15.0(12)
F2A	34.7(14)	136(3)	17.3(11)	-0.1(17)	4.7(9)	-9.0(18)
F3A	45.3(16)	45.6(15)	44.7(16)	2.8(13)	-11.1(12)	-17.7(12)
F1A	65(4)	43(2)	82(4)	-38(2)	-44(3)	40(2)
C3A	28.4(8)	25(2)	21.3(10)	1.0(12)	4.3(7)	3.0(11)

conclusion

Table 4A. Bond Lengths (Å) for FLXNO3-I.

Bond	Length/Å	Bond	Length/Å
O4–C7	1.4422(16)	C6–C1	1.397(2)
O4–C11	1.3659(16)	C11–C12	1.3934(19)
O1–N2	1.2595(16)	C2–C1	1.385(2)
N2–O2	1.2629(17)	C2–C3	1.390(2)
N2–O3	1.2376(17)	C14–C17	1.502(8)
N1–C9	1.4911(17)	C14–C3A	1.482(10)
N1–C10	1.4821(18)	C5–C4	1.393(2)
C7–C6	1.5135(19)	C9–C8	1.5240(19)
C7–C8	1.5255(18)	C3–C4	1.381(3)
C16–C15	1.380(2)	C17–F3	1.301(9)
C16–C11	1.3946(19)	C17–F1	1.330(9)
C15–C14	1.397(2)	C17–F2	1.318(9)
C13–C12	1.388(2)	F2A–C3A	1.332(11)
C13–C14	1.385(2)	F3A–C3A	1.341(11)
C6–C5	1.389(2)	F1A–C3A	1.320(11)

Table 5A. Bond Angles (°) for FLXNO3-I.

Bond angle	Angle/°	Bond angle	Angle/°
C11–O4–C7	118.78(10)	C13–C14–C17	120.2(4)
O1–N2–O2	118.37(12)	C13–C14–C3A	121.1(5)
O3–N2–O1	121.49(13)	C3A–C14–C17	7.8(8)
O3–N2–O2	120.12(13)	C6–C5–C4	120.01(15)
C10–N1–C9	113.79(11)	C2–C1–C6	120.48(14)
O4–C7–C6	112.43(11)	N1–C9–C8	110.86(11)
O4–C7–C8	105.16(11)	C9–C8–C7	113.40(11)
C6–C7–C8	112.60(11)	C4–C3–C2	119.87(15)
C15–C16–C11	120.13(13)	C3–C4–C5	120.45(15)
C16–C15–C14	120.06(13)	F3–C17–C14	113.4(7)
C14–C13–C12	120.63(13)	F3–C17–F1	104.8(6)
C5–C6–C7	122.53(13)	F3–C17–F2	108.7(7)
C5–C6–C1	119.25(13)	F1–C17–C14	112.2(6)
C1–C6–C7	118.21(12)	F2–C17–C14	111.1(6)
O4–C11–C16	115.30(12)	F2–C17–F1	106.3(6)
O4–C11–C12	124.72(12)	F2A–C3A–C14	114.2(8)
C12–C11–C16	119.98(13)	F2A–C3A–F3A	103.8(7)
C13–C12–C11	119.51(13)	F3A–C3A–C14	114.2(7)
C1–C2–C3	119.94(15)	F1A–C3A–C14	113.2(8)
C15–C14–C17	120.0(4)	F1A–C3A–F2A	107.8(8)
C15–C14–C3A	119.0(4)	F1A–C3A–F3A	102.6(8)
C13–C14–C15	119.68(13)		

Table 6A Torsion Angles (°) for FLXNO3-I.

Torsion angle	Angle/°	Torsion Angle	Angle/°
O4–C7–C6–C5	-16.49(18)	C13–C14–C3A–F3A	92.1(8)
O4–C7–C6–C1	164.57(11)	C13–C14–C3A–F1A	-24.8(10)
O4–C7–C8–C9	-77.19(14)	C6–C7–C8–C9	160.06(12)
O4–C11–C12–C13	-177.86(13)	C6–C5–C4–C3	-0.6(2)
N1–C9–C8–C7	-74.95(15)	C11–O4–C7–C6	-74.95(14)
C7–O4–C11–C16	175.31(11)	C11–O4–C7–C8	162.18(11)
C7–O4–C11–C12	-5.20(19)	C11–C16–C15–C14	0.2(2)
C7–C6–C5–C4	-178.68(13)	C12–C13–C14–C15	-0.2(2)
C7–C6–C1–C2	179.15(13)	C12–C13–C14–C17	176.3(4)
C16–C15–C14–C13	0.5(2)	C12–C13–C14–C3A	-174.7(5)
C16–C15–C14–C17	-176.0(4)	C2–C3–C4–C5	0.5(2)
C16–C15–C14–C3A	175.2(5)	C14–C13–C12–C11	-0.9(2)
C16–C11–C12–C13	1.6(2)	C5–C6–C1–C2	0.2(2)
C15–C16–C11–O4	178.25(12)	C1–C6–C5–C4	0.2(2)

continue

C15	C16	C11	C12	-1.3(2)	C1–C2–C3–C4	-0.1(2)
C15	C14	C17	F3	-170.7(4)	C8–C7–C6–C5	102.09(15)
C15	C14	C17	F1	70.8(7)	C8–C7–C6–C1	-76.85(15)
C15	C14	C17	F2	-47.9(7)	C3–C2–C1–C6	-0.2(2)
C15	C14	C3A	F2A	36.8(10)	C10–N1–C9–C8	-174.59(12)
C15	C14	C3A	F3A	-82.5(8)	C17–C14–C3A–F2A	-63(5)
C15	C14	C3A	F1A	160.6(6)	C17–C14–C3A–F3A	178(6)
C13	C14	C17	F3	12.8(8)	C17–C14–C3A–F1A	61(5)
C13	C14	C17	F1	-105.7(6)	C3A–C14–C17–F3	-86(6)
C13	C14	C17	F2	135.6(5)	C3A–C14–C17–F1	156(6)
C13	C14	C3A	F2A	-148.7(6)	C3A–C14–C17–F2	37(5)

conclusion

Table 7A. Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for FLXNO3-I.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
H1A	3016	7590	-1411	28
H1B	4679	7575	-263	28
H7	6391	8366	145	25
H16	5947	9438	3084	26
H15	8837	9498	4779	26
H13	12281	8613	3029	29
H12	9400	8558	1316	29
H2	8710	8957	-3134	38
H5	6613	9771	60	35
H1	7098	8449	-1915	31
H9A	2819	8112	704	28
H9B	891	8096	-473	28
H8A	2447	8898	-633	29
H8B	3190	8527	-1565	29
H3	9265	9874	-2763	43
H4	8192	10278	-1183	43
H10A	813	7095	-571	49
H10B	2621	7076	661	49
H10C	2917	6779	-511	49

Table 8A. Atomic Occupancy for FLXNO3-I.

Atom	Occupancy	Atom	Occupancy	Atom	Occupancy
C17	0.55	F3	0.55	F1	0.55
F2	0.55	F2A	0.45	F3A	0.45
F1A	0.45	C3A	0.45		

FLUOXETINE NITRATE- KRYPTORACEMATE**Table 1B.** Crystal data and structure refinement for the Fluoxetine Nitrate- kryptoracemate (FLXNO3-II)

Empirical formula	C ₁₇ H ₁₉ F ₃ N ₂ O ₄
Formula weight	372.34
Temperature/K	120(2)
Crystal system	Orthorhombic
Space group	Pca2 ₁
a/Å	21.1740(5)
b/Å	6.8422(2)
c/Å	24.9331(6)
Cell volume/Å ³	3612.23(16)
Z, Z'	8, 2
$\rho_{\text{calc}}/\text{cm}^3$	1.369
μ/mm^{-1}	1.018
F(000)	1552.0
Crystal size/mm ³	0.851 × 0.123 × 0.054
Radiation	CuK α (λ = 1.54178)
2 θ range for data collection/°	7.09 to 136.974
	-25 ≤ h ≤ 25
Index ranges	-6 ≤ k ≤ 8
	-29 ≤ l ≤ 28
Reflections collected	20623
Independent reflections	6022 [R _{int} = 0.0813, R _{sigma} = 0.0732]
Data/restraints/parameters	6022/149/480
Goodness-of-fit on F ²	1.057
Final R indexes [I > 2 σ (I)]	R1 = 0.0688, wR2 = 0.1636
Final R indexes [all data]	R1 = 0.0854, wR2 = 0.1755
Largest diff. peak/hole / e Å ⁻³	0.67/-0.56
Flack parameter	0.38(15)

Table 2B. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for FLXNO3-II FLX. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
O4*	4396.1(13)	2952(4)	4607.2(12)	28.5(7)
O4	3188.5(12)	12204(4)	6689.0(12)	27.8(7)
O1*	3906.2(14)	5773(5)	3162.2(13)	37.1(7)
O2	7271.9(14)	-2007(5)	3118.3(14)	37.5(7)
O2*	4814.7(14)	7221(4)	3096.9(13)	35.8(7)
N2*	4492.9(16)	5695(5)	3088.5(15)	28.7(8)
N2	7048.0(17)	-352(6)	3240.2(16)	34.6(9)
O3*	4754.7(15)	4099(5)	3021.7(16)	44.0(8)
C11	2723.1(18)	10828(7)	6671.2(17)	25.9(9)
C7	3779.8(17)	11712(6)	6949.8(17)	25.6(9)
C6*	3406.9(17)	4839(6)	4699.4(18)	23.1(9)
N1*	3584.8(16)	1581(5)	3227.3(14)	28.7(8)
C5*	2983(2)	6044(7)	4448(2)	32.5(10)
C6	4174.3(18)	10305(7)	6620.8(18)	27.1(9)
C11*	4864.8(18)	4303(6)	4637.6(17)	26.0(9)
C13	1688(2)	10107(7)	6339.9(19)	30(1)
O3	7403.4(16)	977(5)	3381.7(16)	45.4(9)
C1*	3455(2)	4858(7)	5258(2)	34.6(11)
C7*	3813.2(17)	3487(6)	4349.5(16)	22.8(8)
C9	3815.2(19)	14959(6)	7457.8(17)	26.1(9)
C15*	5919(2)	4885(7)	4954.9(19)	31.4(10)
C12	2190(2)	11378(7)	6384.7(17)	31.9(10)
C13*	5357.8(19)	7414(7)	4487.6(17)	29.5(9)
C12*	4840.6(19)	6185(6)	4437.7(18)	27.8(9)
C14	1711.3(19)	8297(8)	6577.6(19)	34.9(11)
N1	3927.0(16)	14157(5)	8004.5(14)	28.6(8)
C8	4111(2)	13682(6)	7033.3(18)	28.9(9)
C16*	5407(2)	3641(6)	4896.6(18)	30.3(10)
O1	6465.5(15)	-124(5)	3201.1(17)	46.1(9)
C9*	3768.3(19)	547(6)	3733.6(18)	26.4(9)
C3*	2638(3)	7286(8)	5293(2)	48.6(14)
C5	4102(2)	10107(8)	6069(2)	36.3(11)
C1	4634.1(19)	9215(6)	6872.8(19)	31(1)
C14*	5894.9(19)	6763(7)	4749.4(17)	28.5(9)
C16	2753.3(19)	9001(7)	6907(2)	32.9(10)
C15	2244(2)	7719(7)	6856(2)	36.0(11)
C10	3728(2)	15535(8)	8434(2)	42.2(12)
C2	5010(2)	7948(7)	6587(2)	38.5(11)
C3	4935(2)	7751(8)	6037(2)	44.5(13)
C8*	3485.7(19)	1586(6)	4217.5(17)	26.8(9)
C10*	3779(2)	544(8)	2737.0(19)	35.6(11)

continue

C2*	3060(2)	6059(9)	5547(2)	45.3(13)
C4*	2602(2)	7267(7)	4740(2)	41.4(12)
C4	4477(3)	8844(9)	5783(2)	47.5(13)
F0AA	6790.1(17)	8143(7)	4346.0(14)	84.7(14)
F2	6315.2(14)	9816(5)	4971(2)	79.5(14)
F1AA	806(2)	6925(9)	6964.1(17)	66.7(15)
F2AA	6887.7(15)	7416(6)	5151.6(16)	68(1)
F5	1320(2)	5229(6)	6313(3)	73.1(17)
C17	1167(2)	6935(8)	6530(2)	44.0(13)
F7	730(2)	7561(7)	6149(2)	62.6(12)
C17*	6459(2)	8069(8)	4794(2)	38.0(11)
F1	1286(6)	5090(20)	6897(6)	62.6(12)
F3	698(8)	7260(30)	6723(5)	66.7(15)
F4	1089(6)	6020(20)	6157(9)	73.1(17)

conclusion

Table 3B. Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for FLXNO3-II. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O4*	23.4(15)	27.0(15)	35.1(16)	-2.0(13)	-6.7(12)	2.5(12)
O4	17.1(13)	25.8(16)	40.7(17)	3.8(13)	-6.4(12)	-1.9(12)
O1*	28.1(15)	46.3(19)	37.0(17)	7.0(16)	4.9(14)	-3.9(14)
O2	29.1(15)	33.5(17)	50.1(19)	-8.9(16)	-1.9(15)	-0.9(13)
O2*	33.1(16)	32.9(17)	41.4(18)	0.4(15)	3.2(14)	-4.9(14)
N2*	25.4(17)	31(2)	29.4(19)	-0.9(16)	2.9(15)	1.3(16)
N2	25.6(19)	43(2)	36(2)	-10.8(18)	-4.1(16)	-5.7(17)
O3*	34.3(17)	32.1(18)	65(2)	-3.4(17)	1.1(17)	3.6(15)
C11	16.7(19)	29(2)	32(2)	-5.7(19)	1.1(16)	-1.6(16)
C7	15.6(19)	28(2)	33(2)	2.7(19)	-2.3(16)	-1.3(16)
C6*	12.8(17)	25(2)	31(2)	-7.1(17)	4.2(16)	-5.4(15)
N1*	26.3(17)	27.0(18)	32.7(19)	-5.5(16)	-2.1(14)	1.3(14)
C5*	27(2)	31(2)	39(2)	3(2)	8.5(18)	4.8(19)
C6	16.1(19)	32(2)	33(2)	1.1(19)	3.0(17)	-6.1(17)
C11*	16.5(19)	28(2)	33(2)	-2.2(19)	1.1(16)	1.2(16)
C13	23(2)	39(3)	28(2)	-15(2)	-1.3(16)	1.7(18)
O3	31.3(17)	37.7(18)	67(2)	-14.6(18)	-14.1(16)	0.0(15)
C1*	33(2)	41(3)	31(2)	-7(2)	-2.6(19)	1(2)
C7*	16.5(18)	26(2)	25(2)	-4.6(17)	0.3(15)	-0.3(16)
C9	24(2)	23(2)	32(2)	6.1(17)	-6.4(17)	-1.8(17)
C15*	20(2)	45(3)	29(2)	-3(2)	-5.2(17)	8.0(19)
C12	24(2)	41(3)	31(2)	-6(2)	1.0(17)	7.1(19)
C13*	24(2)	33(2)	32(2)	-3.7(19)	4.8(17)	1.5(18)
C12*	15.8(19)	31(2)	37(2)	-5.5(19)	-3.5(16)	1.2(17)
C14	16(2)	49(3)	39(2)	-24(2)	9.6(18)	-4.8(19)

continue

N1	23.3(17)	29.6(19)	32.8(19)	4.1(15)	-0.4(14)	-0.3(15)
C8	23(2)	31(2)	33(2)	5.3(19)	-2.4(17)	-3.8(17)
C16*	30(2)	26(2)	35(2)	-1.0(19)	-0.4(18)	7.2(18)
O1	22.5(15)	54(2)	62(2)	-22.1(19)	-7.7(15)	2.9(14)
C9*	19.7(19)	25(2)	35(2)	-2.1(19)	-0.3(17)	2.4(17)
C3*	40(3)	43(3)	63(4)	-23(3)	21(3)	-7(2)
C5	26(2)	48(3)	35(3)	2(2)	-2.1(19)	-2(2)
C1	22(2)	31(2)	40(3)	3(2)	2.6(18)	-6.2(18)
C14*	22(2)	34(2)	29(2)	-14.0(19)	3.2(16)	-0.2(18)
C16	15.1(19)	35(3)	49(3)	1(2)	1.2(18)	0.1(17)
C15	28(2)	31(3)	50(3)	-5(2)	7(2)	-3.0(19)
C10	39(3)	45(3)	42(3)	-2(2)	5(2)	4(2)
C2	19(2)	31(3)	66(3)	1(2)	5(2)	-4.1(19)
C3	32(3)	39(3)	62(4)	-14(3)	19(2)	-5(2)
C8*	20(2)	29(2)	32(2)	-3.3(18)	-0.7(17)	0.3(17)
C10*	36(3)	41(3)	30(2)	-8(2)	0.3(19)	3(2)
C2*	41(3)	59(4)	35(3)	-14(2)	12(2)	-8(3)
C4*	35(3)	29(3)	60(3)	6(2)	15(2)	8(2)
C4	47(3)	56(4)	40(3)	-12(3)	9(2)	-6(3)
F0AA	58(2)	145(4)	51(2)	-9(2)	13.4(17)	-62(2)
F2	28.5(16)	41.8(18)	168(4)	-26(2)	-4(2)	-7.1(14)
F1AA	54(3)	124(4)	22(2)	-14(3)	13(2)	-52(3)
F2AA	42.9(18)	83(3)	78(3)	-6.4(19)	-24.5(17)	-12.5(17)
F5	25(2)	31(3)	163(5)	-37(3)	6(3)	3.5(17)
C17	25(2)	58(3)	49(3)	-30(3)	11(2)	-13(2)
F7	42(2)	72(3)	74(3)	-2(2)	-32(2)	-26(2)
C17*	22(2)	49(3)	42(3)	-8(2)	4(2)	-5(2)
F1	42(2)	72(3)	74(3)	-2(2)	-32(2)	-26(2)
F3	54(3)	124(4)	22(2)	-14(3)	13(2)	-52(3)
F4	25(2)	31(3)	163(5)	-37(3)	6(3)	3.5(17)

conclusion

Table 4B. Bond Lengths (Å) for FLXNO3-II

Bond	Length/Å	Bond	Length/Å
O4*–C11*	1.358(5)	C9–N1	1.488(5)
O4*–C7*	1.439(5)	C9–C8	1.509(6)
O4–C11	1.363(5)	C15*–C16*	1.387(6)
O4–C7	1.450(5)	C15*–C14*	1.385(7)
O1*–N2*	1.257(4)	C13*–C12*	1.386(6)
O2–N2	1.265(5)	C13*–C14*	1.385(6)
O2*–N2*	1.247(5)	C14–C15	1.382(7)
N2*–O3*	1.236(5)	C14–C17	1.487(6)
N2–O3	1.232(5)	N1–C10	1.488(6)
N2–O1	1.247(5)	C9*–C8*	1.523(6)
C11–C12	1.388(6)	C3*–C2*	1.381(8)

continue

C11–C16	1.383(7)	C3*–C4*	1.382(8)
C7–C6	1.516(6)	C5–C4	1.373(7)
C7–C8	1.534(6)	C1–C2	1.376(7)
C6*–C5*	1.371(6)	C14*–C17*	1.496(6)
C6*–C1*	1.397(6)	C16–C15	1.396(6)
C6*–C7*	1.535(5)	C2–C3	1.388(8)
N1*–C9*	1.498(6)	C3–C4	1.380(8)
N1*–C10*	1.472(6)	F0AA–C17*	1.320(6)
C5*–C4*	1.371(7)	F2–C17*	1.310(6)
C6–C5	1.391(7)	F1AA–C17	1.326(7)
C6–C1	1.378(6)	F2AA–C17*	1.348(6)
C11*–C12*	1.382(6)	F5–C17	1.326(7)
C11*–C16*	1.392(6)	C17–F7	1.393(7)
C13–C12	1.378(7)	C17–F1	1.580(16)
C13–C14	1.374(7)	C17–F3	1.127(18)
C1*–C2*	1.375(7)	C17–F4	1.133(19)
C7*–C8*	1.510(6)		

conclusion

Table 5B. Bond Angles (°) for FLXNO3-II.

Angle	Angle/°	Angle	Angle/°
C11*–O4*–C7*	118.6(3)	C2*–C3*–C4*	119.2(5)
C11–O4–C7	118.6(3)	C4–C5–C6	120.7(5)
O2*–N2*–O1*	120.1(4)	C2–C1–C6	120.9(5)
O3*–N2*–O1*	120.1(4)	C15*–C14*–C17*	119.8(4)
O3*–N2*–O2*	119.8(3)	C13*–C14*–C15*	120.2(4)
O3–N2–O2	120.0(4)	C13*–C14*–C17*	119.9(4)
O3–N2–O1	122.3(4)	C11–C16–C15	119.6(4)
O1–N2–O2	117.7(4)	C14–C15–C16	119.8(5)
O4–C11–C12	114.7(4)	C1–C2–C3	120.4(5)
O4–C11–C16	125.2(4)	C4–C3–C2	118.8(5)
C16–C11–C12	120.1(4)	C7*–C8*–C9*	113.2(3)
O4–C7–C6	112.4(3)	C1*–C2*–C3*	121.2(5)
O4–C7–C8	104.6(3)	C5*–C4*–C3*	120.2(5)
C6–C7–C8	112.3(3)	C5–C4–C3	120.7(5)
C5*–C6*–C1*	119.9(4)	F1AA–C17–C14	112.6(4)
C5*–C6*–C7*	118.0(4)	F1AA–C17–F7	100.0(4)
C1*–C6*–C7*	122.1(4)	F1AA–C17–F1	67.3(7)
C10*–N1*–C9*	113.6(3)	F5–C17–C14	113.3(4)
C6*–C5*–C4*	120.7(5)	F5–C17–F1AA	118.0(6)
C5–C6–C7	122.4(4)	F5–C17–F7	99.0(5)
C1–C6–C7	119.1(4)	F5–C17–F1	59.6(7)
C1–C6–C5	118.4(4)	F7–C17–C14	112.1(5)
O4*–C11*–C12*	125.9(4)	F7–C17–F1	138.2(6)
O4*–C11*–C16*	114.0(4)	F1–C17–C14	109.4(5)

continue

C12*-C11*-C16*	120.1(4)	F3-C17-C14	121.6(10)
C14-C13-C12	120.4(4)	F3-C17-F1AA	31.1(8)
C2*-C1*-C6*	118.9(5)	F3-C17-F5	124.4(11)
O4*-C7*-C6*	112.3(3)	F3-C17-F7	69.1(9)
O4*-C7*-C8*	105.8(3)	F3-C17-F1	93.0(12)
C8*-C7*-C6*	112.7(3)	F4-C17-C14	121.7(9)
N1-C9-C8	111.3(3)	F4-C17-F1AA	125.7(9)
C14*-C15*-C16*	120.2(4)	F4-C17-F5	38.2(9)
C13-C12-C11	119.9(5)	F4-C17-F7	61.0(9)
C14*-C13*-C12*	119.8(4)	F4-C17-F1	93.2(12)
C11*-C12*-C13*	120.2(4)	F4-C17-F3	109.4(11)
C13-C14-C15	120.3(4)	F0AA-C17*-C14*	112.6(4)
C13-C14-C17	120.2(4)	F0AA-C17*-F2AA	102.4(4)
C15-C14-C17	119.6(5)	F2-C17*-C14*	112.6(4)
C9-N1-C10	112.4(4)	F2-C17*-F0AA	112.0(5)
C9-C8-C7	114.5(4)	F2-C17*-F2AA	103.7(4)
C15*-C16*-C11*	119.6(4)	F2AA-C17*-C14*	112.9(4)
N1*-C9*-C8*	110.2(3)		

conclusion

Table 6B. Torsion Angles (°) for FLXNO3-II .

Torsion Angle	Angle/°	Torsion Angle	Angle/°
O4*-C11*-C12*-C13*	-178.9(4)	C7*-C6*-C5*-C4*	179.2(4)
O4*-C11*-C16*-C15*	-179.8(4)	C7*-C6*-C1*-C2*	-177.8(4)
O4*-C7*-C8*-C9*	-76.3(4)	C15*-C14*-C17*-F0AA	99.9(6)
O4-C11-C12-C13	-179.9(4)	C15*-C14*-C17*-F2	-132.3(5)
O4-C11-C16-C15	-179.6(4)	C15*-C14*-C17*-F2AA	-15.4(6)
O4-C7-C6-C5	22.7(6)	C12-C11-C16-C15	-0.2(7)
O4-C7-C6-C1	-159.1(4)	C12-C13-C14-C15	-1.2(7)
O4-C7-C8-C9	71.3(4)	C12-C13-C14-C17	179.8(4)
C11-O4-C7-C6	72.8(5)	C13*-C14*-C17*-F0AA	-78.0(6)
C11-O4-C7-C8	-165.1(3)	C13*-C14*-C17*-F2	49.7(6)
C11-C16-C15-C14	-1.0(7)	C13*-C14*-C17*-F2AA	166.7(4)
C7-O4-C11-C12	-176.0(4)	C12*-C11*-C16*-C15*	0.4(7)
C7-O4-C11-C16	3.4(6)	C12*-C13*-C14*-C15*	0.8(6)
C7-C6-C5-C4	178.7(4)	C12*-C13*-C14*-C17*	178.7(4)
C7-C6-C1-C2	-178.7(4)	C14-C13-C12-C11	0.0(6)
C6*-C5*-C4*-C3*	-0.6(8)	N1-C9-C8-C7	70.9(5)
C6*-C1*-C2*-C3*	-2.3(8)	C8-C7-C6-C5	-94.9(5)
C6*-C7*-C8*-C9*	160.6(4)	C8-C7-C6-C1	83.3(5)
N1*-C9*-C8*-C7*	-73.8(4)	C8-C9-N1-C10	171.1(4)
C5*-C6*-C1*-C2*	1.6(7)	C16*-C11*-C12*-C13*	0.9(6)
C5*-C6*-C7*-O4*	155.1(4)	C16*-C15*-C14*-C13*	0.4(7)
C5*-C6*-C7*-C8*	-85.5(5)	C16*-C15*-C14*-C17*	-177.5(4)
C6-C7-C8-C9	-166.6(4)	C5-C6-C1-C2-	-0.4(6)
C6-C5-C4-C3	-0.2(8)	C1-C6-C5-C4	0.4(7)
C6-C1-C2-C3	0.3(7)	C1-C2-C3-C4	-0.1(7)

continue

C11*–O4*–C7*–C6*	-74.7(4)	C14*–C15*–C16*–C11*	-1.0(7)
C11*–O4*–C7*–C8*	162.0(3)	C14*–C13*–C12*–C11*	-1.4(6)
C13–C14–C15–C16	1.6(7)	C16–C11–C12–C13	0.6(6)
C13–C14–C17–F1AA	-100.3(6)	C15–C14–C17–F1AA	80.6(6)
C13–C14–C17–F5	122.6(6)	C15–C14–C17–F5	-56.5(7)
C13–C14–C17–F7	11.6(6)	C15–C14–C17–F7	-167.5(5)
C13–C14–C17–F1	-173.1(7)	C15–C14–C17–F1	7.9(8)
C13–C14–C17–F3	-66.8(13)	C15–C14–C17–F3	114.2(12)
C13–C14–C17–F4	80.2(13)	C15–C14–C17–F4	-98.8(13)
C1*–C6*–C5*–C4*	-0.2(7)	C2–C3–C4–C5	0.0(8)
C1*–C6*–C7*–O4*	-25.5(6)	C10*–N1*–C9*–C8*	-173.5(4)
C1*–C6*–C7*–C8*	93.9(5)	C2*–C3*–C4*–C5*	0.0(8)
C7*–O4*–C11*–C12*	-0.5(6)	C4*–C3*–C2*–C1*	1.5(8)
C7*–O4*–C11*–C16*	179.7(4)	C17–C14–C15–C16	-179.3(4)
conclusion			

Table 7B. Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for FLXNO3-II

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
H7	3690	11125	7300	31
H1*A	3163	1735	3223	34
H1*B	3760	2779	3227	34
H5*	2953	6031	4076	39
H13	1331	10477	6148	36
H1*	3748	4070	5432	42
H7*	3912	4165	4014	27
H9A	3992	16264	7435	31
H9B	3364	15053	7394	31
H15*	6280	4456	5132	38
H12	2172	12602	6223	38
H13*	5344	8670	4346	35
H12*	4476	6629	4269	33
H1A	4341	13889	8043	34
H1B	3712	13030	8041	34
H8A	4548	13440	7130	35
H8B	4111	14388	6696	35
H16*	5425	2372	5030	36
H9*A	4225	521	3765	32
H9*B	3618	-792	3722	32
H3*	2380	8115	5492	58
H5	3796	10837	5892	44
H1	4691	9337	7241	37
H16	3111	8629	7099	39
H15	2263	6481	7009	43
H10A	3961	16733	8401	63
H10B	3811	14962	8779	63

continue

H10C	3285	15801	8401	63
H2	5317	7220	6764	46
H3	5189	6896	5843	53
H8*A	3043	1846	4148	32
H8*B	3510	726	4526	32
H10D	3641	1266	2428	53
H10E	3592	-734	2733	53
H10F	4231	425	2730	53
H2*	3079	6046	5919	54
H4*	2318	8087	4564	50
H4	4421	8725	5415	57

conclusion

Table 8B.. Atomic Occupancy for FLXNO3-II

Atom	<i>Occupancy</i>	Atom	<i>Occupancy</i>	Atom	<i>Occupancy</i>
F1AA	0.75	F5	0.75	F7	0.75
F1	0.25	F3	0.25	F4	0.25

DISCUSSION: Refinement details and data collection at 100 and 298K

The occurrence of kryptoracemate FLXNO3-II, which a racemic mixture of FLX⁺ enantiomers crystallizes in a non-centrosymmetric space group, motives us to collect the structures of present study using Cu radiation (Table 1). In the structure determination of FLXNO3-I and FLXNO3-II, several restraint were applied to disorder refinement of CF₃ fragment. Additionally, the command 'RIGU' were applied in the to the atoms of aromatic groups. Thus, 54 restrains were observed in the models. of FLXNO3-I.

In order to investigate a possible phase transition between polymorphs¹ and also to determine the stability of them^{1b, c, 2}, the crystal structure of FLXNO3-I and FLXNO3-II were collected at 100 and 298K. The crystallographic data for the FLXNO3-II were collected at 100K on a Bruker Super-Duo APEX II CCD diffractometer³ using MoK α radiation (0.71073 Å). X-ray diffraction data collection for the FLXNO3-II was performed at 100K on an Enraf-Nonius Kappa-CCD diffractometer (95 mm CCD camera on κ -goniostat) using graphite-monochromated MoK α radiation (0.71073 Å) and an *Oxford Cryo Systems CryoStream 700Plus* to control the temperature. Furthermore, the FLXNO3-I and FLXNO3-II crystals were collected at 298K on an Enraf-Nonius Kappa-CCD diffractometer (95 mm CCD camera on κ -goniostat) using graphite-monochromated MoK α radiation (0.71073 Å).

Using the Olex2⁴ software, the structures were solved by direct methods and the models obtained were refined by full-matrix least squares on F² (SHELXTL-97⁵). All the hydrogen atoms were placed in calculated positions and refined with fixed individual displacement parameters [$U_{iso}(H) = 1.2U_{eq}$ or $1.5U_{eq}$] according to the riding model (C–H bond lengths of 0.97 Å and 0.96 Å, for methylene and methyl groups, respectively).

The CIFs files of the FLXNO3-I and FLXNO3-II (collected with Mo radiation at 100 and 298K) were deposited in the Cambridge Structural Data Base⁶ under the codes CCDC 1469371 (FLXNO3-I, 100K), CCDC 1469431 (FLXNO3-I, 298K), CCDC 1469373 (FLXNO3-II, 100K) and CCDC 1469448 (FLXNO3-II, 298K). Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk.

As shown in Table S1, no significant change is observed for cell parameters of polymorphs collected at 100 and 298K. As expected, thermal expansion are responsible for slight differences. After refinement, the structures of each polymorphs collected at 120K and 298K, respectively, were correspondents.

COMPLEMENTARY FIGURES AND TABLES

Figure S 1. In the unit cell of FLXO3-II, the $(\text{NO}_3^-)_A$ and $(\text{NO}_3^-)_B$ anions are alternately arranged along the $[100]$ direction, such that, the independent NO_3^- anions are offset by $17.4(3)^\circ$. In this figure the red plane is define to $(\text{NO}_3^-)_A$ while the blue one is define by $(\text{NO}_3^-)_B$.

Figure S 2: Outcome of crystallization of Fluoxetine Nitrate (FLXNO₃) at different conditions.

(a)

(b)

(c)

Figure S 3: Systematic comparison of crystal packing of FLXNO3-I and FLXNO3-II.

The FLXNO3-I and FLXNO3-II occur due to formation of different racemic motifs by $N^+-H \cdots O^-$ Hydrogen Bond. The R -FLX⁺ and S -FLX⁺ enantiomers are, respectively, blue and red colored in the Figure. The antiparallel arrangement of racemic motif forms a plane in both polymorphs structures, such as, equivalent molecules are space $\sim 24.7 \text{ \AA}$. Homochiral chains of FLX⁺ enantiomers are also observed with the enantiomers spaced $\sim 6.5 \text{ \AA}$. These chains are orientated along [100] direction in FLXNO3-I and along [100] in the FLXNO3-II.

Figure S 4: Qualitative E - T plot (not on scale) for Fluoxetine Nitrate, showing the relationship between FLXNO3-I and FLXNO3-II.

Table S 1: Crystal Data, Data Collection, and Structure Refinement Parameters of Fluoxetine Nitrate polymorphs at 100 and 298K.

Structure	FLXNO3-I		FLXNO3-II	
Empirical formula	C ₁₇ H ₁₉ F ₃ N ₂ O ₄	C ₁₇ H ₁₉ F ₃ N ₂ O ₄	C ₃₄ H ₃₈ N ₄ O ₈ F ₆	C ₁₇ H ₁₉ F ₃ N ₂ O ₄
Temperature/K	100(2)	298(2)	100(2)	298(5)
Formula weight	372.34	372.44	744.68	372.34
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic
Space group	P2 ₁ /c	P2 ₁ /c	Pca2 ₁	Pca2 ₁
a/Å	6.53400(10)	6.6410(2)	21.1480(12)	21.3390(2)
b/Å	24.7430(5)	25.3100(12)	6.8544(5)	6.9100(5)
c/Å	11.4310(3)	11.4710(6)	24.8971(17)	25.3750(9)
α/°	90	90	90	90
β/°	108.1730(10)	108.343(3)	90	90
γ/°	90	90	90	90
Cell volume/Å ³	1755.88(6)	1830.12(14)	3609.0(4)	3741.6(3)
Z	4	4	8	8
ρ _{calc} /g/cm ³	1.408	1.352	1.371	1.322
μ/mm ⁻¹	0.121	0.116	0.118	0.114
F(000)	776.0	776.0	1552.0	1552.0
Crystal size/mm ³	0.401 × 0.364 × 0.242	0.53 × 0.306 × 0.26	0.77 × 0.102 × 0.056	0.851 × 0.123 × 0.054
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
Diffractometer	Kappa	Kappa	APEX	Kappa
2θ range for data collection/°	6.202 to 50.708	6.11 to 52.806	3.852 to 52.734	5.896 to 39.954
Index ranges	-7 ≤ h ≤ 7, -29 ≤ k ≤ 29, -13 ≤ l ≤ 13	-8 ≤ h ≤ 8, -31 ≤ k ≤ 31, -14 ≤ l ≤ 14	-24 ≤ h ≤ 26, -5 ≤ k ≤ 8, -27 ≤ l ≤ 31	-20 ≤ h ≤ 20, -6 ≤ k ≤ 6, -24 ≤ l ≤ 24
Reflections collected	6299	7292	14601	34503
Independent reflections	3202 [R _{int} = 0.0287, R _{sigma} = 0.0380]	3697 [R _{int} = 0.0165, R _{sigma} = 0.0250]	6178 [R _{int} = 0.0553, R _{sigma} = 0.0686]	3484 [R _{int} = 0.1175, R _{sigma} = 0.0471]
Data/restraints/parameters	3202/0/263	3697/0/270	6178/1/480	3484/199/525
Goodness-of-fit on F ²	1.092	1.065	1.051	1.085
Final R indexes [I>2σ (I)]	R1 = 0.0443, wR2 = 0.1153	R1 = 0.0511, wR2 = 0.1406	R1 = 0.0703, wR2 = 0.1762	R1 = 0.0499, wR2 = 0.1053
Final R indexes [all data]	R1 = 0.0680, wR2 = 0.1358	R1 = 0.0707, wR2 = 0.1603	R1 = 0.0959, wR2 = 0.1973	R1 = 0.0816, wR2 = 0.1219
Largest diff. peak/hole Å ⁻³	0.39/-0.35	0.23/-0.24	0.65/-0.34	0.15/-0.12
Flack parameter	-	-	-0.3(8)	0.1(8)
Hooft parameter	-	-	-0.5(7)	-0.1(4)

REFERENCES

- (a) Bernstein, J.; Davey, R. J.; Henck, J.-O., Concomitant Polymorphs. *Angewandte Chemie International Edition* **1999**, 38 (23), 3440-3461; (b) Wouters, J.; Quere, L.; Thurston, D.

- E., *Pharmaceutical Salts and Co-crystals*. Royal Society of Chemistry: 2011; (c) Hilfiker, R., *Polymorphism: In the Pharmaceutical Industry*. Wiley: 2006.
2. Clarke, H. D.; Arora, K. K.; Wojtas, Ł.; Zaworotko, M. J., Polymorphism in Multiple Component Crystals: Forms III and IV of Gallic Acid Monohydrate. *Crystal Growth & Design* **2011**, *11* (4), 964-966.
 3. APEX2 APEX2, Madison, Wisconsin, USA, 2009.
 4. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H., OLEX2: a complete structure solution, refinement and analysis program. *Journal of Applied Crystallography* **2009**, *42* (2), 339-341.
 5. Sheldrick, G., A short history of SHELX. *Acta Crystallographica Section A* **2008**, *64* (1), 112-122.
 6. Allen, F., The Cambridge Structural Database: a quarter of a million crystal structures and rising. *Acta Crystallographica Section B* **2002**, *58* (3 Part 1), 380-388.