UNIVERSIDADE DE SÃO PAULO

FACULDADE DE CIÊNCIAS FARMACÊUTICAS DE RIBEIRÃO PRETO

Entrapment of *Rosmarinus officinalis* polyphenols in redispersible lipid-based systems

Encapsulação de polifenóis de *Rosmarinus officinalis* em sistemas lipídicos redispersíveis

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Ribeirão Preto

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Doctoral thesis presented to the Graduate Program in Pharmaceutical Sciences of School of Pharmaceutical Sciences of Ribeirão Preto/USP for the degree of Doctor of Sciences.

Concentration Area: Medicaments and Cosmetics.

Supervisor: Prof. Dr. Wanderley Pereira Oliveira
Co-supervisor: Dr. Claudia Regina F. Souza

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Victor Oloruntoba Bankole

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“A horse is prepared for the day of battle,
but victory comes from the Lord”
Proverbs 21:31 (HCSB)

RESUMO

BANKOLE, V.O. **Encapsulação de polifenóis de *Rosmarinus officinalis* em sistemas lipídicos redispersíveis.** 2020. 179 p. Tese de Doutorado. Faculdade de Ciências Farmacêuticas de Ribeirão Preto - Universidade de São Paulo, Ribeirão Preto, 2020.

Rosmarinus officinalis L. (alecrim) compreende compostos polifenólicos, principalmente ácidos fenólicos e diterpenos que possuem excelentes propriedades antioxidantes e antimicrobianas. No entanto, obter o máximo de benefícios desse material é limitado por várias desvantagens; incluindo baixa solubilidade em água, biodisponibilidade e estabilidade, entre outros problemas. O encapsulamento de extratos vegetais em diferentes materiais é uma maneira confiável de melhorar suas propriedades físico-químicas e contornar os desafios. O encapsulamento em prolipossomas é particularmente interessante, tendo outras vantagens de incorporar múltiplos componentes de polaridade variável com estabilidade relativamente maior em comparação com formulações líquidas. Portanto, este estudo tem como objetivo preparar prolipossomas de polifenóis de alecrim com o desejo de encapsular compostos bioativos de polaridade variável e melhorar o escopo de sua aplicabilidade. Os polifenóis das folhas secas e moídas de alecrim foram extraídos por maceração dinâmica, filtrados, concentrados e liofilizados. Após estudos preliminares, as composições lipossômicas (usando fosfatidilcolina hidrogenada de soja e colesterol) encapsulando polifenóis de alecrim (ácidos cafeico, rosmarínico e carnósico e carnosol como marcadores) foram preparadas pelo método de substituição de solvente. As composições foram secas em um *spray dryer* em escala de laboratório a uma vazão de 4,0 g/min e temperatura de 100 °C, usando a lactose como adjuvante de secagem. As formulações de prolipossomas foram otimizadas por planejamento experimental, utilizando o Planejamento Composto Central, e validadas pela correlação de valores experimentais de atributos críticos de qualidade com valores preditos. Prolipossomas secas por *spray drying* (SDP) foram caracterizados pelo teor de umidade, atividade da água, retenção e conteúdo total dos polifenóis marcadores, densidade e propriedades de fluxo, cristalinidade, morfologia, espectroscopia no infravermelho, e redispersibilidade – incluindo tamanho da vesícula e potencial zeta após a hidratação. O desempenho de secagem foi caracterizado pela determinação da recuperação do pó. O SDP otimidado e o extrato liofilizado (LE) foram avaliados quanto às propriedades antioxidantes (método $DPPH^{\bullet}$) e antimicrobiano (antibacteriano e antifúngico). Um estudo de estabilidade foi realizado para avaliar o efeito da umidade e temperatura relativa no SDP e LE. As amostras de armazenamento foram analisadas de forma semelhante quanto a alterações nas propriedades físico-químicas. Os resultados das execuções experimentais mostraram que o SDP exibiu retenção de polifenóis, variando de 62,0 – 100,0% p/p; sendo dependente das variáveis de composição e lipofilicidade dos polifenois. A recuperação do SDP variou de 20,1 a 45,8 %, com teor de umidade e atividade da água entre 1,7 ± 0,14 - 2,5 ± 0,23% p/p e 0,30 ± 0,004 - 0,47 ± 0,003, respectivamente. As variáveis de composição influenciaram as propriedades do prolipossomas, com combinações ótimas de 4,26% p/p, 4,48% p/p e 7,55% p/p para a concentração de lipídeos, concentração de LE e a razão de adjuvante de secagem:(lipídio+extrato), respectivamente, em base úmida. Os resultados mostraram concordância entre os valores preditos e experimentais, exceto a retenção de carnosol, que foi 22 % menor. O SDP ideal apresentou alta atividade antioxidante com IC_{50} de 9,2 ± 0,2 µg/mL, superior aos resultados obtidos para LE (10,8 µg/mL) e hidroxitolueno butilado (BHT), um antioxidante sintético (12,5 µg/mL). MIC e MFC contra *Candida albicans* (ATCC1023) foram 312,5 µg/mL e 1.250 µg/mL, respectivamente, abaixo de valores obtidos para várias cepas de bactérias também avaliadas. A estabilidade do produto sofreu maior influência da umidade de armazenagem (em relação à temperatura), indicando a necessidade de armazenamento em embalagem impermeável. O SDP é mostrado como um excelente método para encapsular polifenóis hidrofílicos e lipofílicos de alecrim, gerando um produto inovador com propriedades físico-químicas e biológicas aprimoradas.

Palavras chave: Polifenois de alecrim, *Spray drying*, Prolipossomas, Atividade antioxidante, Atividade antimicrobiana, Estudos de estabilidade.

ABSTRACT

BANKOLE, V.O. **Entrapment of *Rosmarinus officinalis* polyphenols in redispersible lipid-based systems.** 2020. 179 p. Thesis (Doctoral). School of Pharmaceutical Sciences of Ribeirão Preto - Universidade of São Paulo, Ribeirão Preto, 2020.

Rosmarinus officinalis L. (rosemary) comprise polyphenolic compounds, principally phenolic acids and diterpenes which possess excellent antioxidant and antimicrobial properties. However, deriving maximum benefits from this material is limited by several drawbacks; including low solubility, bioavailability, and stability among others issues. Encapsulation of plant extracts in different materials is a credible way to improve their physicochemical properties and circumvent these challenges. Encapsulation in proliposomes is particularly interesting, having further advantages of incorporating multiple components of varying polarity with relatively higher stability compared to liquid formulations. Hence, this study aims at preparing proliposomes of rosemary polyphenols with a view to encapsulating bioactive compounds of varying polarity, thus enhancing the scope of their applicability. Polyphenol-rich extract from dried and milled rosemary leaves was obtained by dynamic maceration, filtered, concentrated and freeze-dried. Following preliminary studies, liposomal compositions (using hydrogenated soyphosphatidylcholine and cholesterol) encapsulating rosemary polyphenols (caffeic, rosmarinic and carnosic acids, and carnosol as markers) were prepared by a modified solvent replacement method. The compositions were dried in a lab-scale spray dryer at flow rate of 4.0 g/min and temperature of 100 °C, using lactose as the drying aid to obtain proliposomes. The proliposome formulations were optimized by experimental design, using the Central Composite Design, and validated by correlating experimental values of critical quality attributes with the predicted. Spray dried proliposomes (SDP) were characterized by moisture content, water activity, retention and total content of marker polyphenols, density and flow properties, crystallinity, morphology, infrared spectroscopy, and redispersibility – including vesicle size and zeta potential on hydration. The spray drying performance was characterized by determination of the powder recovery. The optimal SDP and lyophilized extract (LE) were evaluated for antioxidant ($DPPH^{\bullet}$ method) and antimicrobial (antibacterial and antifungal) properties. Stability study was carried out to evaluate the effect of relative humidity and temperature on SDP and LE. Storage samples were similarly analysed for changes in physicochemical properties. Results of experimental runs showed that SDP exhibited polyphenol retention, ranging from 62.0 – 100.0% w/w; showing dependence on composition variables and polyphenol lipophilicity. SDP recovery ranged from 20.1 to 45.8 %, with moisture content and water activity of 1.7±0.14 – 2.5±0.23 %w/w and 0.30±0.004 – 0.47±0.003, respectively. Composition variables influenced proliposome properties with optimal combinations being 4.26% w/w, 4.48% w/w, and 7.55% w/w for lipid concentration, LE concentration, and drying aid:(lipid+extract) ratio, respectively on wet basis. Results showed concurrence between predicted and experimental values except carnosol retention, being 22 % lower. Optimal SDP showed high antioxidant activity with IC_{50} of 9.2±0.2 µg/mL, superior to results obtained for LE (10.8 µg/mL) and Butylated Hydroxytoluene, a synthetic antioxidant (12.5 µg/mL). MIC and MFC against *Candida albicans* (ATCC1023) were 312.5 µg/mL and 1,250 µg/mL, respectively; lower than values obtained for bacteria strains used. The product stability was more affected by storage humidity (compared to temperature), indicating need for waterproof packaging. SDP is shown as a veritable tool to encapsulate hydrophilic and lipophilic rosemary polyphenols generating a product with improved physicochemical and biological properties.

Keywords: Rosemary polyphenols, Spray drying, Proliposomes, Antioxidant activity, Antimicrobial activity, Stability studies.

LIST OF ABBREVIATIONS AND ACRONYMS

ABS	Absorbance
ANOVA	Analysis of Variance
ANVISA	Agencia Nacional de Vigilancia Sanitaria (National Sanitary Surveillance Agency)
AS	Analytical Standard
AST	Accelerated Stability Testing
ATCC	American Type Culture Collection
A_w	Water Activity
BHA	Butylated Hydroxy Anisole
BHT	Butylated Hydroxy Toluene
CAF	Caffeic Acid
CAR	Carnosol
CCD	Central Composite Design
CH	Cholesterol
CIE	Comission Internacionale l'Eclairage
CLSI	Clinical and Laboratory Standards Institute
CMC	Carboxymethylcellulose
CNA	Carnosic Acid
C_s	Solid Content
CVA	Carvacrol
DLS	Dynamic Light Scattering
DoE	Design of Experiments
$DPPH^{\bullet}$	1,1-Diphenyl-2-picrylhydrazyl free radica
EO	Essential Oil
EU	European Union
FD	Factor of Dilution
FTIR	Fourier Transform Infrared
GAE	Gallic Acid Equivalent
GRAS	Generally Regarded as Safe
HPLC-DAD	High Performance Liquid Chromatography-Diode Array Detector
HPMC	Hydroxypropyl Methylcellulose
HSDP	Hydrated Spray Dried Proliposome

HSDP	Hydrated Spray Dried Proliposomes
HSPC	Hydrogenated Soy Phosphatidyl Choline
IC_{50}	50 % Inhibition Concentration
I_{Carr}	Carr's Index
$I_{Hausner}$	Hausner's Factor
KF	Karl Fischer
LA	Lactose
L_D	Loss on Drying
LE	Lyophilized Extract
LLF	Liquid Liposomal Formulation
MBC	Minimum Bactericidal Concentration
MFC	Minimum Fungicidal Concentration
MIC	Minimum Inhibitory Concentration
NLC	Nanostructured Lipid Carriers
PDI	Polydispersibility Índex
PG	Propyl Gallate
PL	Phospholipid
PVP	Polyvinylpyrrolidone
QbD	Quality by Design
QE	Quercetin Equivalent
R_{EC}	Powder Recuperation
RH	Relative Humidity
ROA	Rosmarinic Acid
RSD	Relative Standard Deviation
RSM	Response Surface Methodology
SAS	Supercritical Anti-solvent
SD	Spray Drying
SDP	Spray Dried Proliposomes
SEM	Scanning Electron Microscopy
SLN	Solid Lipid Nanoparticles
T_E	Total Extractive Content
T_F	Total Flavonoid
Tg	Glass Transition Temperature
Tgi	Inlet Drying Gas Temperature

T_p	Total Polyphenol
US/USA	United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet
Ws/Wmax	Feed Rate to Maximum Capacity Ratio
X_P	Moisture Content
XRD	X-Ray Diffraction
ZP	Zeta Potential
ρ_a	Apparent Density
ρ_c	Compaction Density

1. Introduction

1 INTRODUCTION

Antioxidants are substances that, when present in low concentrations compared to that of an oxidisable substrate, significantly delay and/or inhibit the oxidation of that substrate or removes oxidative damage to a target molecule (YADAV et al, 2016; DAUQAN; ABDULLAH; SANI, 2011). They are capable of preventing the damaging effects of free radicals both in the human body and in various synthetic materials (IONITA et al., 2015). As such, they are suggested to play the physiological role of preserving the integrity of cellular components which may be compromised as a consequence of chemical reactions involving free radicals (BREWER, 2011; NIMSE; PAL, 2015).

A substantial body of evidence has been gathered to support claims that free radicals are involved in key roles during fundamental cellular reactions, suggesting that oxidative stress might be important in the pathophysiology of common diseases including atherosclerosis, chronic renal failure, and diabetes mellitus (DEVASAGAYAM et al., 2004; PERCIVAL, 1998). Antioxidants have also been found very useful in the food industry to prevent lipid peroxidation, the mechanism by which lipid components of nutrients become rancid (NEDOVIC et al., 2011). The general mechanism of an antioxidant action involves two stages: (i) the radical trapping stage and (ii) the radical termination stage (ANTOLOVICH et al., 2002; MASUDA et al., 2001; THATOI; PATRA; DAS, 2014).

With respect to how they are derived, antioxidants can be classified as either endogenous or exogenous. The former refers to those that are produced in the body (living tissues) as a component of innate defense mechanism; being largely composed of enzymes. The latter, however, refers to those that are incorporated from the external environment; they can either be synthetically derived or naturally sourced (YADAV et al., 2016). Although synthetic antioxidant compounds enjoyed patronage in the recent past, there is currently increasing interest in the use of natural antioxidants, such as tocopherols, flavonoids and plant polyphenols as additives in foods and pharmaceutical systems (FRUTOS; HERNÁNDEZ-HERRERO, 2005; HERNÁNDEZ et al., 2009; KAMKAR et al., 2014; WILLIAMS; SPENCER; RICE-EVANS, 2004).

Like other naturally sourced antioxidants, extracts of some aromatic plants have been favourably applied as functional materials in these systems due to their biocompatibility, multifunctionality, relative affordability and/or availability (CHEN et al., 2011; CHRISTAKI et al., 2012; OZSOY ET AL., 2017; SHAIKH et al., 2014), as well as avoidance of toxicity problems associated with the use of synthetic antioxidants, such as butylated hydroxy anisole

(BHA), butylated hydroxy toluene (BHT) and propyl gallate (PG) which are now known to form hazardous quinones (AMAROWICZ; NACZK; SHAHIDI, 2000; IONITA et al., 2015; KAMKAR et al., 2014). The market for antioxidants of vegetable origin is expected to experience a huge growth just as demands for natural products are generally on the increase (LACATUSU et al., 2010a). This preference may be sustained following evidence that antioxidant effects of natural extracts are often more effective than many other individual antioxidants (RUKTANONCHAI et al., 2009).

Research into polyphenols, a class of antioxidants of natural origin, started more recently than others (SCALBERT et al., 2005) but has garnered much momentum over the years (CORTÉS-ROJAS; SOUZA; OLIVEIRA, 2016; SECOLIN; SOUZA; OLIVEIRA, 2017). Currently, plant polyphenols have received high attention of the pharmaceutical, nutraceutical, cosmetic, and food sectors mainly due to their attributed biological activities (HABTEMARIAM, 2016a). They have indeed proven to be very worthy antioxidants with evidence of protection of cell constituents against oxidative damage, therefore, limiting the risk of various degenerative diseases associated to oxidative stress such as cancers, cardiovascular diseases, neurodegenerative diseases, diabetes, age-related skin damage, and osteoporosis (ARTS; HOLLMAN, 2005; SCALBERT et al., 2005; VITA, 2005).

One of such plants whose extract has been studied and found to be rich in polyphenols is *Rosmarinus officinalis* L. (Lamiaceae) commonly called rosemary or romero. The rosemary is a polyphenol-rich herb, supporting its use as preservative and antioxidant in cosmetics, foods and other multi-component systems, as well as herbal remedy in protection from and management of various diseases.

Native to the Mediterranean, rosemary is cultivated in many parts of the world as a valuable household spice for flavoring and preserving foods, and as herbal drug in folk medicine (MORENO et al., 2012; SÁNCHEZ-CAMARGO; HERRERO, 2017). While folkloric uses include as antispasmodic and hair growth stimulant, the plant has been scientifically evaluated for a wide range of activities such as neurologic, anti-inflammatory, antidiabetic, hepatoprotective, antitumerogenic, antimicrobial (including antiviral) and antioxidant activity, as well as its potential to relax the smooth muscles of the trachea and intestine (HASSANI; SHIRANI; HOSSEINZADEH, 2016). Its biological activities are linked to high concentrations of phenolic compounds in three main classes, among others: phenolic diterpenes – e.g. carnosic acid, carnosol, rosmanol, epirosmanol, and methyl carnosate; flavonoids – e.g. cirsimaritin, genkwanin; and phenolic acids – e.g. rosmarinic and caffeic acids (ANDRADE et al., 2018; GENENA et al., 2008; LAURA; GARZON; VICENTE, 2010;

MORENO et al., 2006; SOUZA et al., 2008; ZHANG et al., 2012). Specifically, its high antioxidant activity is attributable to carnosic, caffeic, and rosmarinic acids; carnosol; and the flavonoids (LUIS; JOHNSON, 2005; TAVASSOLI; DJOMEH, 2011; THORSEN; HILDEBRANDT, 2003). In fact, it is suggested that rosemary has enjoyed the greatest level of attention among herbs and spices as source of antioxidants (ERKAN; AYRANCI; AYRANCI, 2008; HASSANI et al., 2016; MORENO et al., 2012). Indeed, the rosemary extracts are commercially available for use as a natural antioxidant for foods, being considered safe and effective (NIETO; ROS; CASTILLO, 2018).

It is known that the extraction procedure (e.g. extraction method, duration, temperature, solvent type, and so on) has significant influence on the composition of a plant extract and, consequently, its antioxidant – and other biological – activity (DELFANIAN et al., 2015; DO et al., 2014; PIETRZAK; NOWAK; OLECH, 2014; TIR; DUTTA; BADJAH-HADJ-AHMED, 2012). Biological activity may further be influenced by loading plant extracts in different materials, causing a reduction or an outright prevention of degradation of the active principles as well as controling their availability in biological systems (IONITA et al., 2015; VISENTIN et al., 2012a). This observation is particularly true for polyphenols whose high scavenging properties towards radical oxygen species make them susceptible to degradation reactions during storage due to several factors such as heat, humidity exposure and processing conditions, thereby impairing their long-term stability (DENG et al., 2018; GAFNER; BERGERON, 2005; VOLF et al., 2013; ZHANG et al., 2012).

Similar to other bioactive substances, encapsulation of plant extracts in different materials is a credible way to improve their physicochemical properties and to slow down the degradation rates of their main active constituents. The improvement of bioavailability of the bioactive compounds in biological systems has also been reported (IONITA et al., 2015; VISENTIN et al., 2012a). In the literature, polyphenols of rosemary and other plants have been encapsulated in solid lipid nanoparticles and similar systems (CAMPOS et al., 2017; GUPTA; SHARMA, 2006; SECOLIN et al., 2017; SECOLIN, 2014), mostly with primary focus on encapsulation of carnosic acid rather than various compounds (VISENTIN et al., 2012). Because food and pharmaceutical systems are often complex in nature, ensuring incorporation of multiple bioactive compounds for their synergistic activity is essential to optimal protection and activity. However, these previously developed systems have the limitation of failure to accommodate compounds of varying polarity; a situation which might impair product activity and stability, among other considerations.

Proliposome is an innovative approach to retain these compounds of varying lipo/hydrophilicity in the same formulation system. Proliposomes are dry, free-flowing powders usually developed from phospholipids together with cholesterol and other excipients, compositions that can immediately form liposome suspension through simple redispersion of these systems in aqueous medium (GANGISHETTY; EEDARA; BANDARI, 2015; XU et al., 2009). Their solid properties confer an improvement on the otherwise challenging physical stability of liposomes without influencing their intrinsic characteristics (KARN et al., 2014; NEKKANTI et al., 2016).

An attempt to encapsulate plant polyphenols in this type of structure is an attractive exercise following from many considerations. Firstly, encapsulation is a promising approach towards protecting polyphenols as well as improving their physicochemical properties and their functionality (KUMARI et al., 2014; MUNEER et al., 2017). Secondly, compounds of varying polarity can be retained in the liposomal system. While the hydrophilic core provides suitable ambient and protection for more polar compounds, the hydrocarbon complex in the liposomal wall can be explored to accommodate polyphenol compounds that exhibit lipophilicity (MUNEER et al., 2017). Moreover, polyphenols often present a poor bioavailability mainly due to low water solubility (BELŠČAK-CVITANOVIĆ et al., 2018; PICCOLELLA; PACIFICO, 2017). Lastly, many of these molecules possess a very astringent and bitter taste, which might limit their use in food or in oral medications (FANG; BHANDARI, 2010; KALOGEROPOULOS et al., 2010; MUNIN; EDWARDS-LEVY, 2011; NEDOVIC et al., 2011). The proliposome encapsulation approach had been employed in the formulation of different compounds of natural origin (CHU et al., 2011; HAO et al., 2015; JAISWAL, 2013; SILVA et al., 2017; WANG et al., 2015; ZHENG et al., 2015).

To this end, spray drying has been widely used both on bench-top scale and industrially, because in addition to producing stable systems in the form of powders; reducing the risks of microbial contamination; and transport and storage costs, it is a robust method that allows the optimization of particle characteristics, which can be used in thermo-sensitive products, in addition to having low operating costs (OLIVEIRA; FREITAS; FREIRE, 2009; INGVARSSON et al., 2011; INGVARSSON et al., 2013). It is therefore, considered suitable for the preparation of proliposomes encapsulating rosemary polyphenols.

Nevertheless, the production of proliposomes by spray drying is a multivariate process. The physicochemical properties of product are affected by composition variables and spray drying operating conditions (PATIL-GADHE; POKHARKAR, 2014). Understanding the effects of these multiple input variables on product properties is an important step towards

consistently engineering a product with preset requirements (LIONBERGER et al., 2008; TELFORD, 2007; VERMA et al., 2009). Rather than assessing the effect of each input variable on desirable outcomes per time, the Design of Experiment (DoE) is an efficient methodology usually adopted to simultaneously determine the effects of multiple variables on product properties. (CZITROM, 1999; JAIN et al., 2015; KASINATHAN; VOLETY; JOSYULA, 2014). This way, products with optimal physicochemical and biological properties can be prepared in a rapid, cost effective and reproducible manner (BAN et al., 2017; KURHAJEC et al, 2017).

This work presents a systematic study that aimed to stabilize and improve the functionality of rosemary polyphenols by employing the spray drying method to develop an optimal proliposome product. This is with a view to preparing an innovative product which simultaneously retain polyphenols of varying polarity contained in the rosemary extract. Antioxidant and antimicrobial properties were evaluated to highlight the potential for application of developed proliposome in food, pharmaceutical, nutraceutical and cosmetic products.

6. Conclusions

6 CONCLUSIONS

In this study, a review of the literature was carried out to establish the level of research and options available and already used in encapsulating polyphenols contained in the extract of rosemary towards improving their stability and functionality. Materials and methods were carefully selected to meet the objectives of the work; bearing in mind compatibility and relative toxicity of ingredients, simplicity and reproducibility of methods, as well as product affordability.

6.1 Preliminary studies

Proliposome was considered in this study for effective encapsulation of different polyphenols of rosemary. Following initial tests of various solvents, ethanol was found appropriate for both polyphenol extraction and preparation of liposomal composition, being volatile and providing solubility for the lipids and polyphenol components. From an array of drying carriers that have been explored in related studies by our group and others, lactose was selected from the point of view of efficiency and cost. Spray drying was carried out at conditions used in previous studies by our group, bearing in mind the transition temperature of lipids used in this study. The performance of the process was adequate and the results confirmed that lactose has potential for use as a drying aid for lipid carriers.

6.2 Formulation preparation and optimization

The possibilities of changes in product properties resulting from variations in input factors underscore the importance of Quality by Design strategy for preparing products with predetermined properties and fit for intended use. This is achievable by Design of Experiments, a systematic approach to determine the relationship between factors involved in a process and the effects of those factors on process output. The Central Composite Design was demonstrated as an efficient approach in which the effects of changes in composition variables were assessed within a workable number of experiments to arrive at the targeted product quality.

The optimization of the processing variables using multi-response analysis was successfully validated. The experimental responses determined at optimum processing condition exhibited good agreement with estimated values. It was shown that relative concentration and retention of each rosemary polyphenol in spray dried proliposomes was a function of its own polarity and composition variables. Whereas retention of rosmarinic acid is

largely dependent on concentration of the extract, values for carnosol and carnosic acid were shown to be influenced by lipid, extract and drying aid concentrations. Water activity was shown to depend on the drying aid (lactose) concentration while moisture content was only slightly influenced by both lipid and extract concentrations. Although spray dried proliposome products obtained did not show excellent flow and compressibility properties, these parameters could be improved by inclusion of certain other excipients with acceptable characteristics.

6.3 Potential biological activities

Lyophilized extract of rosemary showed good antimicrobial activity against yeast, and both Gram-positive and Gram-negative organisms. It was therefore, considered suitable for application as therapeutic pharmaceutical agent or as preservatives in various industries. The antimicrobial activity demonstrated is in addition to the antioxidant activity established by the DPPH free radical sequestering method.

These potentials of biological activity could be enhanced by preparing the extract in systems that aid their biaoctivity and stability such as proliposome-liposome systems. The optimized SDP loaded with the rosemary polyphenols showed an enhancement of the antioxidant activity and improved efficacy against the test microorganisms when compared to pure lyophilized extract. In this manner, lower concentrations could be applied to achieve the desired activity due to higher potency of the polyphenols encapsulated in the proliposome system; possibly by enhancing solubility of bioactive compounds as well as improving their ability to penetrate cellular barriers.

6.4 Stability studies

Stability studies carried out for pure lyophilized extract and proliposome product revealed not only changes in visual and pharmacotechnical properties, but also degradation of polyphenol components; the extent of which was shown to be dependent on the storage condition. This degradation adversely affected the antioxidant activity of the test materials, reducing the potency by up to 50 %. Although storage temperature adversely affected evaluated product properties, relative humidity was shown as the more critical factor responsible for changes observed in both the extract and proliposome. Although encapsulation of proliposomes offered protection and higher stability for the polyphenol, this gain might be limited by the environmental condition to which the product is exposed. While degradation of polyphenols is slower in proliposomes compared to unencapsulated extract

stored at similar conditions, significant polyphenol degradation was observed for both ordinary extract and proliposome product exposed to unfavourable environmental conditions.

The First-order kinetics best fitted the degradation of both carnosol and carnosic acid. Based on these components, the shelf life of the proliposome product was determined as 12 days at 45 ^{o}C/63.5 % relative humidity, 90 days at 25 ^{o}C/32.4 % relative humidity, and 180 days when stored in a sealed packaging material inside a refrigerator at 8 ^{o}C. Hence, it is important to ensure a storage condition adequate enough to preserve the encapsulated polyphenol and prolong product shelf life.

6.5 General conclusions

In this study, proliposome was shown as a viable system for encapsulation of rosemary polyphenols through a systematic study of the relationships between composition variables and their effects on desirable responses, guided by experimental design. The proliposome powder obtained presented adequate retention and concentration of bioactive polyphenols, and other physicochemical properties following spray drying of liposomal composition. The product displayed ready redispersibility in aqueous medium to form liposomes with acceptable properties including particle size, and improved stability. It is projected that these advantages over ordinary lyophilized extract adequately justify the costs incurred with respect to materials and process of proliposome production. The increased efficacy achieved will mean lower quantities of bioactive required for desired effects, while the enhanced efficiency of redispersion compensates for the cost of intense mixing and solubilization operations.

Results obtained in this work furnish strong evidences that the proliposome product, having improved physicochemical properties and superior bioactivity, might be applicable as a natural antioxidant or as a phytopharmaceutical agent in treatment and prevention of several acute/chronic diseases in humans, either singly or as a component of a pharmaceutical dosage form. It might also be used as natural preservative in several categories of products such as foods, nutraceuticals, cosmetics and skin care preparations where microorganisms remain a source of contamination and degradation. However, storage condition is very critical to maintenance of these activities. It is important that the proliposome product is stored in an environment of low relative humidity and low temperature. This ensures prevention of degradation of the polyphenol compounds while maintaining the physicochemical and organoleptic properties.

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