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Proniosomes: An Emerging Vesicular System in Drug Delivery and Cosmetics

¹Rishu Kakar, ^{*1}Rekha Rao, ¹Anju Goswami, ²Sanju Nanda, ³Kamal Saroha

¹M.M. College of Pharmacy, M.M. University, Mullana, Ambala 133001, India

²Department of Pharmaceutical Sciences, M. D. University, Rohtak124-001, India

³Department of Pharmaceutical Sciences, K.University, Kurukshetra.

ABSTRACT

A number of novel drug delivery systems have emerged encompassing various routes of administration to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one such system, which can be predicted to prolong the existence of the drug in systemic circulation and reduce the toxicity, if selective uptake can be achieved. Consequently, a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes, ethosomes and proniosomes were developed. Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form a niosomal dispersion immediately before use on brief agitation in hot aqueous media. This review presents an overview about proniosomes reporting the preparation methods, characterization techniques and the studies of penetration and transport of various drugs through skin.

Key words: Proniosomes, Niosomes, Transdermal drug delivery, Cosmetics.

INTRODUCTION

One of the major advances in vesicle research was the finding that some modified vesicles possessed properties that allowed them to successfully deliver drugs in deeper layers of skin. Transdermal drug delivery offers an attractive alternative to conventional oral and injection therapies as a means of achieving constant therapeutic levels of drugs. [1] Percutaneous administration by-passes the hepatic first pass effect and provides better compliance. However, the barrier properties of the stratum corneum, the outermost layer of skin, prevent the percutaneous absorption of many drugs. [2] To overcome the stratum corneum barrier, various

permeation enhancement techniques have been investigated, including use of chemical enhancers, iontophoresis, electroporation and sonophoresis. [3-6]

Vesicular systems have been widely studied as vehicles for dermal and transdermal drug delivery. Their benefits in enhancing drug permeation have been well established. [7] Liposomes also have been the potential of overcoming the skin barrier, as these are bilayered lipid vesicles, consisting primarily of phospholipids and cholesterol.[8] Drug encapsulated in lipid vesicles prepared from phospholipids and nonionic surfactant is known to be transported into and across the skin. Because of their ability to carry a variety of drugs, liposomes have been extensively investigated for their potential application in pharmaceuticals; such as drug delivery for drug targeting; for controlled release or for increasing solubility.[9-12] Amongst the liposomes, transferosomes, ethosomes and niosomes have been reported to offer enhanced permeability through stratum corneum barriers.

In recent years, non ionic surfactant vesicles known as niosomes received great attention as an alternative potential drugs delivery system to conventional liposomes. [13] Niosomes or non ionic surfactant vesicles are microscopic lamellar structure formed on admixture of non ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media.[14] Stability is a prime concern in the development of any formulation. Niosomes have shown advantages as drug carriers, such as being cheap and chemically stable alternative to liposomes, but they are associated with problems related to physical stability, such as fusion, aggregation, sedimentation and leakage on storage. [15-17] The proniosome approach minimizes these problems by using dry, free flowing product, which is more stable during sterilization and storage. Ease of transfer, distribution, dosing and storage make proniosomes a versatile delivery system.[18-19] Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form a niosomal dispersion immediately before use on brief agitation in hot aqueous media.

MATERIALS AND METHODS

Preparation and Characterization

Proniosomes are product of nonionic surfactants easily prepared by dissolving the surfactant in a minimal amount of an acceptable solvent and least amount of water. Typically, proniosomes may contain various nonionic surfactants like span 20, 40, 60, 80 and 85, tween 20, 40, 80; lecithin, alcohol (ethanol, methanol, isopropyl alcohol) and chloroform. Chemical structure of surfactants influences drug entrapment efficiency. Increasing the alkyl chain length is leading to higher entrapment efficiency.[20] It had also been reported that spans having highest phase transition temperature provides highest entrapment for the drug and vice- versa.[21] Drug can be entrapped into proniosomes composed of tweens, however the encapsulation efficiency was relatively low as compared to those composed of spans.[22] Most of surfactants used to make nonionic surfactant vesicles have a low aqueous solubility. However, freely soluble nonionic surfactants such as tween can form the micelles on hydration in presence of cholesterol.[23] Cholesterol concentration into proniosomal formulations could effect vesicle stability and permeability.[24-25] In addition, nonionic surfactant and cholesterol can be combined with lecithin in these preparations. Formulations containing lecithin increase the entrapment efficiency of drugs compared to formulation containing cholesterol only.[26] However, the incorporation of lecithin

into formulation requires special treatment during preparation and storage, which makes the product less stable and highly expensive.[24] As stated earlier, proniosomes require minimal amount of acceptable solvent like ethanol, methanol, isopropyl alcohol and chloroform for dissolving surfactants. Various examples of different component of proniosomes are enlisted in Table I along with their use.

Table I: Commonly used materials for proniosomes preparation

S. No.	Class	Examples	Use	Ref(s)
1.	Surfactants	Span 20, 40, 60, 80, 85, Tween 20, 40, 80	To increase drug flux rate across the skin.	27
2.	Cholesterol	Cholesterol	To prevent leakage of drug formulation.	28,29
3.	Lecithin	Lecithin	Penetration enhancer.	30
4.	Maltodextrin	Maltodextrin	Provides flexibility in surfactant and other component ratio.	31
5.	Sorbitol	Sorbitol	Alters the drug distribution.	18

Methods for preparing proniosomes

Proniosomal formulations may be prepared by coacervation phase separation method, slurry method and slow spray coating method.

Slurry method

Proniosomes can be prepared from a stock solution of surfactants and cholesterol in suitable solvent. The required volume of surfactant and cholesterol stock solution per gram of carrier and drug should be dissolved in the solvent in 100 ml round bottom flask containing the carrier (maltodextrin or lecithin). Additional chloroform can be added to form the slurry in case of lower surfactant loading. The flask has to be attached to a rotary flash evaporator to evaporate solvent at 50- 60 rpm at a temperature of $45\pm 2^{\circ}\text{C}$ and a reduced pressure of 600mm Hg until the mass in the flask had become a dry, free flowing product. Finally, the formulation should be stored in tightly closed container under refrigeration in light.[19,32]

Coacervation phase separation method

Accurately weighed or required amount of surfactant, carrier (lecithin), cholesterol and drug can be taken in a clean and dry wide mouthed glass vial (5 ml) and solvent should be added to it. All these ingredients has to be heated and after heating all the ingredients should be mixed with glass rod. To prevent the loss of solvent, the open end of the glass vial can be covered with a lid. It has to be warmed over water bath at $60-70^{\circ}\text{C}$ for 5 minutes until the surfactant dissolved completely. The mixture should be allowed to cool down at room temperature till the dispersion get converted to a proniosomal gel.[15,33].

Slow spray coating method

A 100 ml round bottom flask containing desired amount of carrier can be attached to rotary flash evaporator. A mixture of surfactants and cholesterol should be prepared and introduced into round bottom flask on rotary evaporator by sequential spraying of aliquots onto carrier's surface. The evaporator has to be evacuated and rotating flask can be rotated in water bath under vacuum at 65-70°C for 15 – 20 min. This process has to be repeated until all of the surfactant solution had been applied. The evaporation should be continued until the powder becomes completely dry.[18]

Characterization methods of proniosomal formulations

Various methods for characterization of proniosomes are shown in Table II.

Table II: Methods of Characterization of Proniosomes

S. No.	Parameter(s)	Method(s)	Ref (s)
1.	Vesicle size analysis	Scanning electron microscopy, transmission electron microscopy, laser diffraction method	18,18,32
2.	Entrapment efficiency	Diode array spectrophotometer, centrifugation method, dialysis method	18,31,38
3.	<i>In- vitro</i> permeation study	Franz diffusion cell, Flow through diffusion cell, Keshary chien diffusion cell.	31,26,15
4..	<i>In- vitro</i> release study	Dialysis bag method	37
5.	Zeta potential determination	Zeta potential probe model	37

Vesicle morphology

Vesicle morphology involves the measurement of size and shape of proniosomal vesicles. Size of proniosomal vesicles can be measured by dynamic light scattering method in two conditions; without agitation and with agitation. Hydration without agitation results in largest vesicle size.[34] Scanning electron microscopy(SEM) can also be used for the measurement of vesicle size and shape.[35]

Determination of vesicle size is important for the topical application of vesicles. Size of captopril vesicles was found reduced after agitation of dispersion as energy applied in agitation resulted in the breakage of the larger vesicles to smaller vesicles. The size range of captopril vesicles was found 11.38– 25.06 micrometer (without agitation) and 4.14 – 8.36 (with agitation). Hence, it can be concluded that increasing hydrophobicity of the surfactant monomer leads to a smaller size vesicles, since surface energy decreases with increasing the hydrophobicity.[36]

The size distribution of niosomes with tweens was significantly lower than that with span surfactants. The vesicle size analysis of indomethacin niosomes showed that vesicles were

discrete and separate with no aggregation or agglomeration. The diameter of indomethacin niosomes was found to be in the range of 10 – 15 micrometer.[37]

Haloperidol proniosomes with lower HLB values seemed to be mostly spherical and discrete with sharp boundaries having smooth and rigid surfaces. The main difference between deformable and rigid vesicles was found due to fluidity of the lipid bilayer of the deformable vesicles.[26]

Encapsulation efficiency

Different methods can be used to evaluate the loading capacity of proniosomal systems such as dialysis method, freeze thawing or centrifugation method.[38-39] In dialysis method, amount of entrapped drug can be obtained by subtracting the amount of untrapped drug from total drug incorporated.

$$\text{Entrapment efficiency} = \text{Amount of drug entrapped} / \text{total amount of drug} \times 100$$

In centrifugation method, centrifugation should be used at 1400 rpm for 40 minutes at 4⁰C and entrapment efficiency can be calculated as above.[24] The another method that can be used for evaluating the entrapment efficiency is sonication, using sonicator and the resulting solution can be assayed by high performance liquid chromatography.

The encapsulation efficiency of proniosomal gels using span 40, 60 and 85 was found to exhibit a very high value. The encapsulation efficiency studies from literature search revealed that the entrapment efficiency of proniosomes composed of tweens was relatively low as compared to spans. The cholesterol content was also found to affect the encapsulation efficiency of drug. As the cholesterol content of the formulation decreased, the encapsulation of drug also decreased.[22] Higher entrapment efficiency of vesicles of span 60 was predictable because of its higher alkyl chain length.[35] Dicetyl phosphate also have an effect on drug entrapment efficiency. At lower concentration of dicetyl phosphate, the entrapment efficiency becomes slightly lower but the ratio of span 60 to cholesterol still has little effect. The entrapment efficiency of drug was found to depend on the drug characteristics like lipophilic drugs have high entrapment efficiency than hydrophilic drugs.[18]

Release rate profiles of drugs

One of the most important features of proniosomal formulations is their sustained release characteristic. Indomethacin proniosome formulations showed a prolonged release rate profile of the indomethacin. *In-vitro* release profile of proniosomal formulations of this drugs was reported by dialysis bag method which was analysed for drug content using Ultra violet spectrophotometer.[37]

The study of release rate of ibuprofen showed that the release of drug from niosomes in gastric fluid was much slower as compared to its solution. Overall, gastric fluid release profiles of ibuprofen from niosome dispersions prepared from proniosomes or by conventional method showed little difference.[18]

In-vitro release profile can be performed using Franz diffusion cell. The release rate of captopril showed a controlled release from 10 - 24 hrs. Thus, formulation exhibited zero order release over this period. The amount of drug retained within the vesicles under defined conditions ultimately govern the shelf- life of the drug. Percent drug retained at 45⁰C might have decreased due to melting of surfactant and lipid present in formulation.[36]

It had been reported that estradiol release from niosomes and permeation of estradiol across skin occurred very rapidly. The release rate of estradiol across membrane from S85 formulation was found slow in comparison.[22]

Stability Studies

Physical stability studies of aceclofenac proniosomes investigated the degradation of drug during storage. Best three formulations composed of surfactants and cholesterol were sealed in glass vial and kept at temperature of 2 – 8⁰C for 3 months. Samples from each batch were withdrawn after the definite time interval, converted into niosomes and the residual amount of the drug in vesicle determined. Stability data of three formulations was analysed by paired t- test. It can be concluded that the proniosomes were stable under refrigeration conditions with least leakage.[35]

Solanki *et al* analysed piroxicam proniosomes for drug leakage from vesicles, colour change and surface characteristics. The percentage drug retained was determined from ratio of the entrapment to the initial entrapment of drug.[32]

Stability studies of indomethacin niosomes were performed by storing at 4⁰, 25⁰, and 37⁰ C for 3 months. It was reported that drug leakage from vesicles was least at 4⁰ followed by 25⁰ and 37⁰ C.[37]

The stability studies of captopril proniosomes showed that percent drug retained at 45⁰ C might have decreased due to the melting of the spans (m.p. 48) and lecithin present in the formulation. Therefore, It can be concluded from the above mentioned studies that proniosomal gel formulation can be stored at refrigeration or room temperature.[36]

***In-Vitro* permeation study**

The rate of permeation of drugs from proniosomal formulations can be determined by using Franz diffusion cell, Keshary Chien diffusion cell and drug content can be estimated by suitable analytical method. The interaction between skin and proniosomes may be an important contribution to the improvement of transdermal drug delivery. One of the possible mechanisms for niosomal permeability enhancement is structural modification of stratum corneum. Both phospholipids and nonionic surfactants used in proniosomes act as penetration enhancers, leading to increase the permeation of many drugs.[30]

The permeation of haloperidol from proniosomal formulations was determined by Flow through diffusion cell. Direct contact and adherence of vesicles with skin surface is important for the drug to penetrate and partition between the stratum corneum and formulation.[26]

Zeta potential determination

Zeta potential can be analysed to measure the stability of niosomes by studying its colloidal property. The zeta potential of indomethacin proniosomes was measured by a zeta potential probe. Zeta potential analysis is a measure of net charge of niosomes. The higher charge on the surface of vesicles produce repulsive force between the vesicles which made them stable, devoid of agglomeration and faster settling, providing an evenly distributed suspension.[37]

Proposed mechanism of skin permeation of proniosomes

The experimental results of ketorolac proniosomes suggested that either fusion of the vesicles with the intercellular lipid of the stratum corneum and direct transfer of drug from vesicles to the skin and/or nonionic surfactants may contribute to drug permeation enhancement in proniosomal formulations. Several mechanisms can be used to explain the ability of niosome to modulate drug transfer across the skin including[7,15,23,40]

1. Adsorption and fusion of niosomes on to the surface of skin leading to a high thermodynamic activity gradient of drug at the interface, which is the driving force for permeation of lipophilic drugs.
2. The effects of vesicles as the permeation enhancers reduce the barrier properties of stratum corneum.
3. The lipid bilayers of niosomes act on rate limiting membrane barrier for drugs, stratum corneum in transdermal delivery.

Different studies related to application of proniosomes as a carrier system

Proniosomes as a carrier of various drug molecules has been cited in Table III.

Table III: Applications of proniosomes as a drug carrier

S. No.	Drug	Hydrophilic or Lipophilic	Category	Result(s)	Ref.
1.	Ibuprofen	Lipophilic	NSAIDS	Proniosomes derived niosomes are superior in their ability to release the drug at a constant rate.	18
2.	Aceclofenac	Lipophilic	NSAIDS	The polynomial equation and contour plots developed by using central composite design allowed to prepare Proniosomes with optimum characteristic.	35
3.	Haloperidol	Hydrophilic	Antipsychotic effect	The formulation with single surfactant increased the permeation of drug more than those with mixture of surfactants.	26
4.	Piroxicam	Lipophilic	NSAIDS	Span 60 based lecithin vesicle showed significant decrease in paw swelling. There is a increased drug delivery from lipid vesicles.	41

5.	Indomethacin	Lipophilic	NSAIDS	The release rate of the drug from the vesicle was in the controlled manner.	37
6.	Alprenolol hydrochloride	Lipophilic	Antihypertensive	The use of the maltodextrin in Proniosomes helps in enhancement of drug release.	19
7.	Captopril	Hydrophilic	Antihypertensive	Prolonged release of captopril	36
8.	Griseofulvin	Lipophilic	Antifungal	Enhanced absorption of the drug	42
9.	Flurbiprofen	Lipophilic	NSAIDS	The drug release rate from cholesterol free proniosomes was found to be high.	24
10.	Estradiol	Lipophilic	For symptomatic treatment of the usual symptoms associated with menopause	The non ionic surfactant in Proniosomal formulation helps in enhancement of drug permeation through the skin.	22
11.	Ketorolac	Lipophilic	NSAIDS	The drug entrapment was high within the lipid bilayers of vesicles.	30
12.	Losartan potassium	Hydrophilic	Antihypertension	Enhanced bioavailability & skin permeation of drug	43
13.	Levonorgestrel	Lipophilic	Anticonceptives	The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraception.	15
14.	Celecoxib	Lipophilic	Cyclooxygenase - inhibitor	Enhanced bioavailability of celecoxib	44
15.	Cromolyn Sodium	Hydrophilic	Antiasthmatic and antiallergic	High nebulisation efficiency percentage and good physical stability were observed.	45
16.	Chlorpheniramine maleate	Hydrophilic	Antihistamine	Span 40 proniosomes showed optimum stability, loading efficiency and particle size and release kinetics suitable for transdermal delivery of drug.	46

Ibuprofen proniosomes were prepared and studied by Hu & Rhodes. Cholesterol, diacetyl phosphate, span 60, sorbital were used along with chloroform as a solvent for preparation of

proniosomes. These were hydrated with warm distilled water and vortex mixed for 2 minutes to give rise to niosome dispersions. It was indicated that proniosomes are very promising drug carriers. Also it was reported that ibuprofen proniosomes are dry powders which may be processed further to make beads, tablets or capsules.[18]

Solanki *et al* prepared characterized and optimized the aceclofenac proniosomes using central composite design. Three independent variables selected were molar ratio of drug to lipid, surfactant loading and volume of hydration. Proniosomes were prepared by slurry method using maltodextrin as a carrier. It was found proniosomes stored at refrigerator and room temperature were stable.[32]

Azarbayjani *et al* studied proniosomal formulations with nonionic surfactants using haloperidol as model drug. Haloperidol proniosomes were prepared using different spans and tweens along with cholesterol, sodium phosphate monobasic monohydrate and lecithin. Single surfactant increased the permeation of haloperidol than mixture of surfactants. Interfacial tension and surfactant hydrophobicity appeared to be useful for elucidating mechanism of skin permeation and for comparing drug fluxes from different proniosomal formulations.[26]

Chandra & sharma formulated piroxicam proniosomes using spans, cholesterol, lecithin and isopropylalcohol. It was suggested that proniosome vesicles transfer drug from vesicles to the skin and penetration enhancement may be due to surfactants.[41]

Indomethacin is considered to be first line drug in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The short biological half-life and dosing frequency more than once a day required to make it ideal candidate for sustained release formulations. Indomethacin proniosomes were prepared by Tamizharasi *et al* using cholesterol, span 60, methanol and maltodextrin as a carrier. It was concluded that maltodextrin based proniosomes could be promising for indomethacin delivery with improved bioavailability and prolonged drug release profile.[37]

Blazek-welsh and Rhodes reported a novel method for rapid preparation of proniosomes with a wide range of surfactants. They developed a slurry method to produce proniosomes using maltodextrin as the carrier. The proniosomes were prepared for alprenolol hydrochloride using span 60, dicetyl phosphate and cholesterol using chloroform as a solvent. Although maltodextrin is a polysaccharide, it has minimal solubility in organic solvents tested here. Thus, it was possible to coat the maltodextrin particles by simply adding surfactant in organic solvent. For drugs where maltodextrin is found to affect encapsulation efficiency, the maltodextrin can be minimized for producing proniosomes with greater surface loading.[19]

The potential of proniosomes as a transdermal drug delivery system for captopril was investigated by Gupta *et al*. The drug was encapsulated in various formulations of proniosomal gel composed of different ratios of sorbitan fatty acid esters, cholesterol, and lecithin by coacervation phase separation method. The formulated system were characterized *in-vitro* for drug entrapment, drug release profiles and vesicular stability at different storage conditions. It is evident from the study that proniosomes are promising for prolonged delivery of captopril and

have reasonably good stability characteristics. Moreover, the use of transdermal drug delivery system can reduce the side effects associated with captopril.[36]

Gupta *et al* formulated and evaluated the performance of vesicular drug carrier system of proniosomal gel for transdermal delivery of antifungal agent, griseofulvin. Proniosomal gels of griseofulvin were prepared and characterized for vesicle shape, size, entrapment efficiency and drug permeation. A 131.5 fold increase in transdermal flux of griseofulvin was found as compared to plain drug solution and hence it was suggested that proniosomal gel formulation provide a better *in-vitro* skin delivery of griseofulvin.[42]

Proniosomal gel of flurbiprofen was developed by Mokhtar *et al* based on different spans without and with cholesterol. This study suggested the potential of proniosomes as stable precursor for immediate preparation of niosome carrier systems. The entrapment efficiency of flurbiprofen into niosomes prepared from proniosomes was function of formulation processing variables like method of drug separation, cholesterol content, total lipid concentration, pH of hydration medium and drug concentration. Also, it was reported that niosomal formulations containing 10% cholesterol were found most stable among all the prepared formulations.[24]

Fang *et al* studied skin permeation of estradiol from various proniosomal gel formulations across excised rat skin. Proniosomes prepared using spans and tweens as surfactants, lecithin and cholesterol. Estradiol was entrapped within lipid bilayers of proniosomes with very high efficiency. Permeation enhancement of estradiol from proniosomes (diluted proniosome formulation) was not observed. This indicated that only proniosomes gel not niosome suspension appears to efficiently deliver estradiol by transdermal route in this study. It was reported that proniosome may become a useful dosage form for estradiol, specifically due to their simple, scaling of production procedure and ability to modulate drug transfer across the skin.[22]

Permeation of potent non steroidal anti inflammatory drug, ketorolac across excised rabbit skin from various proniosome gel formulation was investigated using Franz diffusion cells by Alsarra *et al*. Proniosomes were prepared using spans, tweens, lecithin and cholesterol with ethanol as a solvent. Each of prepared proniosomes significantly improved drug permeation and the reduced the lag time ($p < 0.05$). A change in the cholesterol content did not affect the entrapment efficiency of proniosomes and reduction in the lecithin content did not significantly decrease the flux ($p > 0.05$). Each of prepared niosomal formulations achieved approximately 99% drug encapsulation. Hence, it was concluded that proniosomes may be a promising carrier for ketorolac.[30]

Thakur *et al* investigated the feasibility of proniosomes as transdermal drug delivery system for losartan potassium. Different preparations of proniosomes were fabricated using different nonionic surfactants, such as Span 20, Span 40, Span 60, Span 80, Tween 20, Tween 40, and Tween 80. The best *in-vitro* skin permeation profile was obtained with proniosomal formulation prepared using span 40 in 24 h.[43]

A proniosome based transdermal drug delivery system of levonorgestrel (LN) was developed and extensively characterized both *in-vitro* and *in-vivo* by Vora *et al*. The system was evaluated *in-vitro* for drug loading, rate of hydration (spontaneity), vesicle size, polydispersity, entrapment efficiency and drug diffusion across rat skin. The effect of composition of formulation, amount

of drug, type of Spans, alcohols and sonication time on transdermal permeation profile was observed. The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraception.[15]

Nasr prepared celecoxib proniosomes and evaluate the influence of proniosomal formulation on the oral bioavailability of the drug in human volunteers. Proniosomes were prepared by sequential spraying method, which consisted of cholesterol, span 60, and dicetyl phosphate in a molar ratio of 1:1: 0.1, respectively. The average entrapment percent of celecoxib proniosome-derived niosomes was about 95%. The prepared proniosomes showed marked enhancement in the dissolution of celecoxib as compared to pure drug powder. The obtained results showed that the proniosomal formulation significantly improved the extent of celecoxib absorption than conventional capsule. It was established that the proniosomal oral delivery system of celecoxib showed improved bioavailability.[44]

Elbray *et al* developed a novel approach for the preparation of controlled release proniosome-derived niosomes, using sucrose stearates as non-ionic biocompatible surfactants for the nebulisable delivery of cromolyn sodium. Conventional niosomes were prepared by a reverse phase evaporation method followed by the preparation of proniosomes by spraying the optimized surfactant-lipid mixture of sucrose stearate, cholesterol and stearylamine in 7:3:0.3 molar ratio onto the surface of spray dried lactose powder. All vesicles were evaluated for their particle size, morphological characteristics, entrapment efficiency, *in-vitro* drug release, nebulisation efficiency and physical stability at 2-8 °C. High nebulisation efficiency percentage and good physical stability were achieved. The results offered an alternative approach to minimize the problems associated with conventional niosomes like degradation, sedimentation, aggregation and fusion.[45]

A proniosomal gel for transdermal drug delivery of chlorpheniramine maleate (CPM) was developed by Varshosaz *et al* based on Span 40 and extensively characterized *in-vitro*. The system was evaluated for the effect of composition of formulation, type of surfactants and alcohols on the drug loading, rate of hydration, vesicle size, polydispersity, entrapment efficiency, and drug release across cellulose nitrate dialysis membrane. The stability studies were performed at 4 degrees C and at room temperature. The results showed that lecithin produced more stable and larger vesicles with higher loading efficiency but lower dissolution efficiency than cholesterol (chol) and dicethyl phosphate (DCP). The type of alcohol had no significant effect on the stability of vesicles, but ethanol produced larger vesicles (approximately equal to 44 micron) and entrapped a greater amount of drug. The proniosomes that contained Span 40/lecithin/cholesterol prepared by ethanol showed optimum stability, loading efficiency, and particle size and release kinetic suitable for transdermal delivery of CPM.[46]

Cosmetics and cosmeceuticals

In general, cosmetic formulations have usually aesthetic and personal hygiene functions. In the majority of the cases, cosmetics are concerned with the biological variations of normal skin.[47] Nowadays consumers are replacing cosmetics frequently with cosmeceuticals. Skin care medicines which combine cosmetics and medicines. Many times consumer claims that their cosmetics are not effective; this is true because the availability of the cosmetic agent is must at the site of action. The skin is a complex organ and allows entry of only selective components. So

the formulation of a cosmetic/cosmeceuticals is very important in terms of delivering the active agent at the site of action. The new drug delivery systems are required to deliver the actives into the skin. Applying a cosmetic/cosmeceuticals in a certain way may change its activity. For example, increased time of application usually leads to higher activity. Proniosome gels can be used as-an effective delivery systems for cosmetics and cosmeceuticals due to their unique properties.[48]

CONCLUSION

Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form a niosomal dispersion immediately before use on brief agitation in hot aqueous media. These systems have been found to be more stable during sterilization and storage than niosomes. Proniosomes have been tested to encapsulate lipophilic as well as hydrophilic drug molecules. The use of proniosomal carriers results in delivery of high concentrations of active agent(s) to/through skin, regulated by system composition and their physical characteristics. Hence, enhanced delivery of bioactive molecules through skin by means of proniosomal carrier opens new challenges and opportunities for the development of novel improved therapies.

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