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Provesicular drug delivery systems: An overview and appraisal

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ABSTRACT

Drug delivery systems using colloidal particulate carriers such as liposomes and niosomes have distinct advantages over conventional dosage forms. This class of drug carrier systems will likely play an increasingly important role in drug delivery. However, there remain significant problems like instability in the general application of liposomes and niosomes for drug delivery. Provesicular concept has evolved to resolve the stability issues pertaining to the conventional vesicular systems i.e. liposomes and niosomes. Provesicular systems are composed of water soluble porous powder as a carrier upon which one may load phospholipids/nonionic surfactants and drugs dissolved in organic solvent. The resultant dry free-flowing granular product could be hydrated immediately before use and can avoid many of the problems associated with aqueous vesicular dispersions. The new emerging concept has demonstrated the potential of proliposomes/proniosomes in improving the oral bioavailability and permeation of drugs across the stratum corneum. Based on the investigations it is clear that provesicular systems appear to be an alternate drug carrier for various routes of drug administration.

Key words: Provesicular systems, drug delivery, liposomes, niosomes, transdermal.

INTRODUCTION

The main aim of novel drug delivery systems is to provide some control of drug release in the body, which is either of temporal or spatial nature, or both. It attempts to either sustain drug action at a predetermined rate, or maintains a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. It also localizes drug action by spatial placement of control release systems adjacent to, or in the diseased tissue or organ; or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type.

At present, no available drug delivery system behaves ideally for achieving all the lofty goals, but many attempts have been made to achieve them through novel approaches in drug delivery. 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 expected to prolong the duration of the

drug in systemic circulation, and reduce the toxicity by selective uptake. Consequently a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes, and pharmacosomes and pro-vesicular systems like proliposomes and proniosomes have been developed.

Vesicular systems like liposomes [1] or niosomes [2] have specific advantages while avoiding demerits associated with conventional dosage forms because these particles can act as drug reservoirs. These carriers play an increasingly important role in drug delivery because by slowing drug release rate, it is possible to reduce the toxicity of drug. Liposomes are unilamellar or multilamellar spheroid structures composed of lipid molecules, often phospholipids, assembled into bilayers. 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 [3-5] for drug targeting [6] for controlled release [7] or for increasing solubility [8]. But the main disadvantage with aqueous dispersions of liposomes is that they often have tendency to aggregate or fuse and may be susceptible to hydrolysis and/or oxidation. Therefore proliposomes offer an elegant alternative to conventional liposomal formulations. Here, lipid and drug are coated onto a soluble carrier to form a free-flowing granular material which, on hydration, forms an isotonic liposomal suspension. Problems with the physical stability of aqueous suspensions of liposomes have been addressed by Payne *et al.*, who introduced proliposomes [8,9].

Proliposomes are composed of water soluble porous powder as a carrier upon which one may load phospholipids and drugs dissolved in organic solvent. Proliposomes can be stored sterilized in a dry state and dispersed/dissolved to form an isotonic multilamellar liposomal suspension by addition of water as needed. Even though proliposome formulations are an improvement over conventional liposome dispersions in terms of the physical stability of the preparation, a vacuum or nitrogen atmosphere is still recommended during preparation and storage to prevent the oxidation of phospholipids [8,10]. To avoid technical difficulties associated with this requirement, alternatives to phospholipids should be of great interest.

Another vesicular system often studied are niosomes. They are non-ionic surfactant based multilamellar or unilamellar vesicles in which an aqueous solution of solute is entirely enclosed by a membrane resulted from the organization of surfactant macro-molecules as bilayers. The nonionic surfactants for this use are usually single-alkyl chain surfactant and: or sorbitan esters. They are biodegradable, biocompatible and non immunogenic in nature and exhibit flexibility in their structural characterization [11]. They are capable of entrapping solutes, are quite stable, and require no special conditions, such as low temperature or inert atmosphere for production or storage.

Niosomes are now widely studied as an alternative to liposome because they alleviate the disadvantages associated with liposome such as chemical instability, variable purity of phospholipids, high cost [11] and low toxicity due to non ionic nature [12]. Even though niosomes as drug carriers have shown advantages such as being cheap and chemically stable, they have some problems related to physical stability such as fusion, aggregation, sedimentation and leakage on storage. The proniosome approach minimizes these problems as it is a dry and free flowing product which is more stable during sterilization and storage. Ease of transfer, distribution, measuring and storage make it a versatile delivery system.

Proniosomes are water-soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media. The resulting niosomes are very similar to conventional niosomes and more uniform in

size [13,14]. The additional convenience of the transportation, distribution, storage, and dosing would make 'dry niosomes' a promising industrial product.

Strategies for the preparation of provesicles

In the preparation of proniosomes non-ionic surfactants, coating carriers and membrane stabilizers are commonly used. The non-ionic surfactants used are Span (20, 40, 60, 80, 85), Tween (20, 60, 80). The coating carriers used are sucrose stearate, sorbitol, maltodextrin (Maltrin M500, M700), glucose monohydrate, lactose monohydrate, spray dried lactose and membrane stabilizers like cholesterol and lecithin are also used [12,14-18,20].

Slurry method

This method involves formation of slurry by addition of the carrier and the entire surfactant solution in a round bottomed flask. This is fitted to a rotary flash evaporator and vacuum was applied to form a dry and free flowing powder. Then the flask was removed and kept under vacuum over night. The obtained powder was collected in a sealed container and kept at 4°C. The time required for proniosome production is independent of the ratio of surfactant solution to carrier material and appears to be sealable [16,17,19,21].

Slow spray-coating method

In this method, the surfactant is added to an organic solvent and sprayed onto carrier. Then the solvent is evaporated. This process is repeated until the desired surfactant loading is achieved, because the carrier is soluble in the organic solvent. As the carrier dissolved, hydration of this coating allows the formation of multilamellar vesicles [22,23]. These niosomes have uniform size distribution and similar to those produced by conventional methods. The main advantage of this method is to provide a means to formulate hydrophobic drugs in a lipid suspension with out problem with instability of the suspension or susceptibility of active ingredient to hydrolysis [24]. The disadvantage is that, this method is tedious since the sorbitol carrier for formulating proniosomes is soluble in the solvent used for the deposition of the surfactant. Sorbitol also interferes with encapsulation of certain drugs.

Co-acervation phase separation method

In this method, surfactant, lipid and drug are taken in a wide mouthed glass vial and small amount of alcohol is added to it. All the ingredients are mixed well and warmed over water bath at 60-70°C for 5min until the surfactant mixture is dissolved completely. Then the aqueous phase is added to the above vial and warmed still a clear solution is formed which is then converted into proniosome gel on cooling [12,20].

Preparation of niosomes from proniosomes by hydration [16]

Prepared proniosome powder is weighed and filled in screw cap vials. Water or saline at 80°C is added and the vials capped. The vials are attached to a vortex mixer and agitated for 2 minutes to get niosomal suspension [Fig. 1].

Factors affecting the formulation of provesicles

Various processing and formulation variables affect the provesicle characteristics. They include surfactant chain length, cholesterol content, drug concentration, total lipid concentration, charge of lipids, pH of the dispersion medium and type of alcohol used in the preparation.

1. Surfactant chain length

Spans are commonly used in the preparation of provesicles. All span types have the same head group and different alkyl chain. Increasing the alkyl chain length is leading to higher entrapment

efficiency [25]. The entrapment efficiency followed the trend Span60 (C18)>Span40 (C16)>Span20 (C12)>Span80 (C18). Span 60 and Span 80 have the same head groups but Span 80 has an unsaturated alkyl chain. De Giere demonstrated that the introduction of double bonds into the paraffin chains causes a marked enhancement of the permeability of liposomes, possibly explaining the lower entrapment efficiency of the Span80 formulation [26].

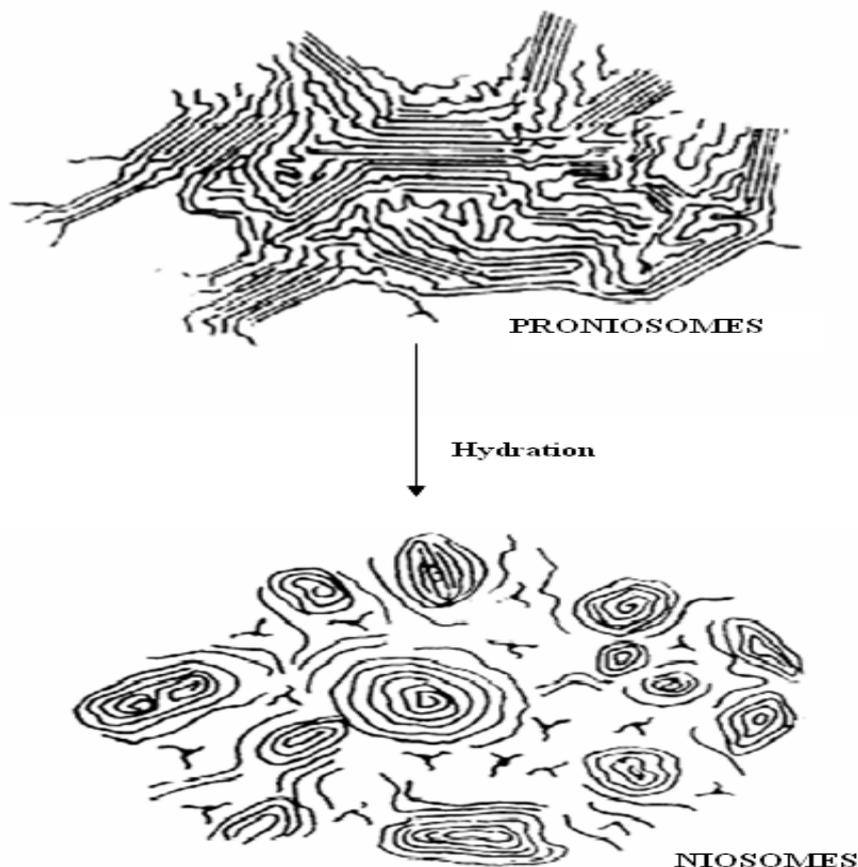


Fig. 1 Schematic illustration of niosome formation

2. Cholesterol content

Cholesterol increases or decreases the percentage encapsulation efficiency depending on either the type of the surfactant or its concentration within the formulae.

3. pH of the hydration medium

The percentage encapsulation efficiency of niosomes prepared by hydration of proniosomal gels of Span 60/cholesterol (9:1) was found to be greatly affected by the pH of the hydrating medium. For example, the fraction of flurbiprofen encapsulated was increased to about 1.5 times as the pH decreased from pH 8 to 5.5. The increase in the percentage encapsulation efficiency of flurbiprofen by decreasing the pH could be attributed to the presence of the ionizable carboxylic group in its chemical structure. Decreasing the pH could increase the proportions of the unionized species of flurbiprofen, which have higher partitioning to the bilayer lipid phase compared to the ionized species [27].

4. Total lipid concentration

The percentage encapsulation efficiency of flurbiprofen was increased as the lipid concentration was increased from 25 to 200mol/ml, respectively. The increase in percentage encapsulation efficiency of flurbiprofen as a function of total lipid concentration was linear. On the other hand,

the amount of flurbiprofen entrapped was decreased on increasing the lipid concentration from 25 to 200mol/ml, respectively. This leads to the fact that the fraction of lipid taking part in encapsulation decreases as the concentration of lipid increases [28].

5. Drug concentration

Increasing flurbiprofen concentration from 25 to 75mg/mmol lipids in the Proniosomes prepared from Span 60/cholesterol (9:1) showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mol total lipids upon hydration and formation of niosomes.

6. Charge of the lipids

Incorporation of either dicetyl phosphate (DCP) which induces negative charge or stearylamine (SA) which induces positive charge decreased the percentage encapsulation efficiency of flurbiprofen into niosomal vesicles.

Characterization of provesicles

Provesicles are characterized for vesicle size and size distribution, surface morphological characteristics, angle of repose, sieve fractionation, aerodynamic behavior, spontaneity are listed in table 1.

Table 1. Shows methods for the characterization of provesicles

Parameter	Method/ instrument
Particle size & size distribution	Lazer diffraction particle size analyzer, Photon correlation spectroscopy(PCS) [17,24]
Vesicle size	Lazer diffraction particle size analyzer [17,24]
Shape & surface morphology	Scanning electron microscopy(SEM) [15] Transmission electron microscopy(TEM) [18] Optical microscopy [20]
Angle of repose	Funnel method [29]
Sieve fractionation	Fritsch analysette sieve shaker
Aerodynamic behavior	Twin-Stage impinger [18]
Spontaneity(Rate of hydration)	Neubaur's chamber [12]
Separation of untrapped drug	Centrifugation [14,24] Cellophane dialysis tubing [12,17]
Determination of entrapment efficiency	Vesicle lysis using alcohol and propylene glycol [12] Dialysis method [18]
<i>In vitro</i> drug release studies	Franz diffusion cells [14] Keshary-chein diffusion cell [12] Cellophane dialyzing membrane [15] USP dissolution apparatus-I [20] Spectarpor molecular porous membrane tubing [18] <i>In vitro</i> skin permeation studies [12,14]

Separation of free (untrapped) drug

The untrapped drug can be separated from entrapped drug using techniques like centrifugation [12,15,16,18,20,24] and by using cellophane dialysis tubing D-9777 and dialyzing exhaustively against 400mL saline at 4°C for 24 hours [12,17].

Determination of entrapment efficiency (measurement of partitioning)

The vesicles obtained after removal of drug by centrifugation were collected and resuspended in 0.9% saline and lysed using 1:1 ratio of absolute alcohol: propylene glycol mixture [12]. The vesicles obtained after removal of untrapped drug by dialysis is then resuspended in 30% v/v

of PEG-200 and 1ml of 0.1% v/v Triton X-100 solution was added to solubilize vesicles [18]. The resulting clear solution is then filtered and analysed for drug content. The percentage of drug entrapped is calculated using the following formula [18,25].

$$EE \% = ED / TD \times 100$$

Where EE% is the entrapment efficiency percent, ED is the entrapped drug concentration and TD is the theoretical drug concentration.

***In vitro* drug release from provesicles**

Wide variety of techniques are used to determine the invitro drug release and skin permeation studies like Franz diffusion cell [14], Keshary-Chien diffusion cell [12], Cellophane dialyzing membrane [15, 20], USP Dissolution apparatus Type I [15], Spectrapor© molecular porous membrane tubing [18]. *In vitro* skin permeation studies have been carried out using dorsal skin of albino rabbit [15], female albino rat (Sprague-Dawley strain), flank skin [12] and wistar rat skin (7-9 weeks old) [14]. Drug release from these vesicles can follow any one or more of the following mechanisms; desorption from surface of vesicles or diffusion of drug from bilayered membrane or a combined desorption and diffusion mechanism.

Stability of provesicles

Stability studies were carried out by storing the prepared provesicles at various temperature conditions like refrigeration temperature (2-8°C), room temperature (25±0.5°C) and elevated temperature (45±0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter were periodically monitored [12,18,20]. ICH guidelines suggests stability studies for the dry provesicular powders meant for reconstitution should be studied for accelerated stability at 40°C/75% relative humidity as per international climatic zones and climatic conditions (WHO, 1996). For long term stability studies the temperature is 25°C/60% RH for the countries in zone I & II and for the countries in zone III & IV the temperature is 30°C/65% RH. Product should be evaluated for appearance, color, assay, pH, preservative content, particulate matter, sterility and pyrogenicity.

Applications

Liposomal microcapsulation of enzymes by proliposome method with Chitosan-Coating was studied [30]. Liposomal microcapsules containing enzymes were prepared by proliposome method to improve the stability of enzymes under acidic conditions.

A proliposomal gel encapsulating chloramphenicol was developed for the local treatment of bacterial vaginosis, capable to efficiently deliver entrapped drug during an extended period of time [31].

Oral formulation of peptide drug was developed as proliposomal product [32]. The oral formulation remarkably enhances bioavailability and stability of the peptide drug.

Zhang et al prepared the proliposome tablets [PTs] containing nimodipine and the release behavior of drug from proliposome tablet was studied [30]. Lin *et al.*, 2004 have evaluated the preparation of Podophyllotoxin-dipalmitoylphosphatidylcholine proliposome for improving stability of Podophyllotoxin dipalmitoylphosphatidylcholine liposome [34].

Turanek *et al.*, evaluated a stirred thermostated cell and link-up with a liquid delivery system for the rapid production of multilamellar liposomes by the proliposome-liposome method [35].

The vitamin A proliposomes were prepared for enhancing the stability of vitamin A [36]. Freeze-drying method was used to prepare vitamin A proliposomes.

Chakraborty and Naik, 2003 have evaluated the therapeutic and hemolytic effects of liposomal preparation derived from proliposome entrapping inclusion complex of amphotericin B [AmB] with the chemically modified β -cyclodextrin (β -CD) [37].

Enteric-coated proliposomal formulations for poorly water soluble drugs were developed [38]. A composition comprised of halofantrine and distearoyl phosphatidyl choline powder and this was coated with cellulose acetate phthalate.

Brocks *et al.*, evaluated the ability of a coated, encapsulated proliposomal formulation to increase the oral bioavailability of $[\pm]$ halofantrine [HLF] enantiomers, a drug with low and erratic oral bioavailability [39].

Proliposomes containing nimodipine were prepared by a novel method, and its quality and brain pharmacokinetics in the rats were evaluated. The encapsulation efficiency reached more than 95% and proliposome had the good stability.

Liposomal gels containing different drug: lipid ratios were prepared by proliposome approach and studied for skin permeation and skin deposition of ketoconazole [40]. Higher ketoconazole deposition in skin with more lipid content of liposomal gel compared to marketed conventional non-liposomal cream implies better efficacy for deeply seated topical fungal infection.

The oral delivery system of peptide using the proliposome and the enteric preparation remarkably increases stability and bioavailability of a peptidyl drug. Proliposomes containing Salmon calcitonin were prepared [41].

Solid proliposome of anti-hepatitisB immune RNA [iRNA] was prepared and the biological activity of anti-hepatitisB immune RNA wrapped in liposome against enzymolysis by RNase was determined by leukocyte adherence inhibition test *in vitro* and *in vivo* in mice [42]. The results indicated that anti-hepatitisB immune RNA wrapped in liposome could obviously inhibit the adherence of leukocyte in mice. These results suggested that anti-hepatitisB immune RNA wrapped in liposome might be a promising oral preparation.

Wang *et al.*, reported the preparation and application of acid sensitive proliposome in biotechnological encapsulation. The proliposome is useful as biological molecular carrier for gene therapy [43]. Wang has patented the pro-liposome product [liposome precursor] composed of soybean phospholipids/cholesterol or its derivatives [44]. The molecular ratio of soybean phospholipids to cholesterol is 7:3.

The feasibility of proliposomes as a sustained transdermal dosage form was examined by Hwang *et al.*, [45]. Proliposomes containing varying amount of nicotine were prepared by a standard method using sorbitol and lecithin. Thus, sustained transdermal delivery of nicotine is feasible using proliposomal formulations if the formulations are topically applied under occlusive conditions.

Deo *et al.*, developed a liquid crystalline proliposomal gel of ketoprofen for sustained ophthalmic drug delivery [46]. Mesophasic, a proliposome system for levonorgestrel was

developed and evaluated both *in vitro* and *in vivo* [47]. This system was superior to the PEG-based ointment system which was employed as the control formulation.

The manufacture and evaluation of proliposomes containing 5-FU: a dry free-flowing granular product which, on addition of water, disperses to form a liposomal suspension suitable for administration either *i.v.* or by other routes was studied [48]. Liposomal 5-FU accumulates preferentially in liver, spleen, lungs, and some solid tumors; antitumor activity was enhanced. Free flowing proliposomes containing propranolol hydrochloride [pH] were evaluated for their potential as a nasal drug delivery system of propranolol to sustain the plasma concentration of the drug [49].

Proliposomes of ibuprofen were successfully prepared using effervescent granules as solid carriers of dried phospholipids along with other lipids [soybean lecithin, stearylamine, and cholesterol] [50].

Varshosaz *et al.*, developed a proniosomal gel for transdermal drug delivery of chlorpheniramine maleate [CPM] based on Span 40 and extensively characterized *in vitro* [51].

Permeation of a potent nonsteroidal anti-inflammatory, ketorolac, across excised rabbit skin from various proniosome gel formulations was investigated [15] using Franz diffusion cells. Each of the prepared proniosomes significantly improved drug permeation and reduced the lag time.

Kumhar *et al.*, evaluated the transdermal drug delivery of ethinylestradiol and levonorgestrel for contraception and hormone replacement therapy from the proniosomal gel formulations prepared by coacervation phase separation technique [52].

The skin permeation of estradiol from various proniosome gel formulations across excised rat skin was investigated *in vitro* [14]. Proniosomes with Span 40 and Span 60 increased the permeation of estradiol across skin. The data is in well correlation with the reports cited [53].

Table 2: Provesicular systems studied for transdermal applications

Drug	Pro-vesicle type	Evaluation	Composition/permeation enhancer used
Flurbiprofen	Proniosomes (gel)	<i>In vitro</i> studies [12,54]	Span (20,40,60,80), absolute ethanol
Fruzemide	Proniosomes (gel, patch)	Ex vivo (rat and human skin)[14,20] <i>In vivo</i> (male albino rats) [55]	Span 40
Levonorgestrel	Proniosomes (gel, patch)	<i>In vitro</i> permeation studies <i>In vivo</i> (female albino rats)	Span 40, alcohol
Estradiol	Proniosomes (gel)	<i>In vitro</i> skin permeation studies [17]	Span (40,60,85) Tween (20,40) Cholesterol, lecithin
Ketorolac	Proniosomes (gel)	<i>In vitro</i> skin permeation study (albino rat skin)	Span 60, ethanol
Chlorpheniramine maleate	Proniosomes	<i>In vitro</i> skin permeation studies[12,56]	Span 40, alcohol
Nicotine	Proliposomes	<i>In vitro</i> skin permeation studies [15]	Span 60
Losartan potassium	Proniosomes (gel)	<i>In vitro</i> skin permeation studies [58] <i>In vivo</i> pharmacokinetics	Span (20,40,60,80) Tween (20,40,80)
Captopril	Proniosomes (gel)	<i>In vitro</i> skin permeation studies [20]	Surfactants

A proniosome base transdermal drug delivery system of levonorgestrel was developed and extensively characterized both *in vitro* and *in vivo* [12]. The proniosomal structure was liquid crystal-compact niosomes hybrid which could be converted into niosomes upon hydration.

Table 3: Provesicular systems studied for improving oral bioavailability

Drug	Pro-vesicle type	Evaluation	Composition/permeation enhancer used
Indomethacin	Proniosomes	<i>In vitro</i> dialysis <i>In vivo</i> studies (male wistar rats) [59]	Span 60
Cromolyn	Proliposomes (beads)	<i>In vitro</i> studies Caco-2 cell study [60] Everted intestinal sac study (rat)	Cromolyn, PVP, isopropyl alcohol
Exemestane	Proliposomes	Caco-2 cell study [61] <i>In vitro</i> studies Ex vivo studies (rats)	Dimyristoyl Phosphatidyl glycerol
Halofantrine	Proliposomes	Ex vivo studies (rats)	Span 60

Table 4: Provesicular systems studied for intravenous administration

Drug	Pro-vesicle type	Evaluation	Composition/permeation enhancer used
Adriamycin and adriamycinol	Neutral proliposomes	<i>In vivo</i> studies (male wistar rats)[62]	Egg lecithin

Table 5: Provesicular systems studied for nasal delivery

Drug	Pro-vesicle type	Evaluation	Composition/permeation enhancer used
Nicotine	Proliposomes	<i>In vivo</i> studies (male wistar rats)	Egg lecithin.sorbitol
Isoniazide & pyrazinamide	Proliposomes (Dry powder aerosol)	<i>In vitro</i> studies (anderson cascade impactor) [63]	Phosphatidylcholine
Propranolol	Proliposomes	<i>In vitro</i> studies, <i>in vivo</i> studies(rats) [64]	Sorbitol, lecithin

Table 6: Provesicular systems studied for enhancing dissolution

Drug	Pro-vesicle type	Evaluation	Composition/permeation enhancer used
Aceclofenac	Proniosomes	<i>In vitro</i> studies [65]	Span 60
Teniposide	Proliposomes	Solubility studies [66]	Bile salts, phospholipid,
Piroxicam	Proniosomes	<i>In vitro</i> studies	Span 60
Fenofibrate	Proliposomes	Dissolution enhancement	Several phospholipids

CONCLUSION

Provesicular systems are promising drug carriers for the future with greater physical and chemical stability and potentially scalable for commercial viability. The delivery system holds promise for the effective drug delivery for amphiphilic drugs. Provesicular systems had attracted researchers as an alternate strategy for transdermal delivery of drugs because of the non-toxicity and penetration effect of lecithin/surfactants. Provesicular systems have been exploited in oral drug delivery in the form of tablets, beads or capsules and have shown improved dissolution and absorption characteristics. Based on the investigations provesicular systems appear to be an alternate drug carrier for various routes of drug administration.

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