Sorbitol based proniosomes to improve the permeability and stability of an oral cephalosporin

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Abstract

In the present study, dry free-flowing proniosomes containing Cefuroxime axetil has been prepared with sorbitol. Span 40, 60 and 80 have been used in different molar ratios with cholesterol and stearylamine. Proniosomes are characterized by SEM, flowability, entrapment efficiency, release study and ex-vivo permeation study. Stability study of proniosomes has been determined at room-temperature. The vesicle size is found to be less than 5µm. Decreased angle of repose indicates the coating of niosomes with sorbitol carrier. Entrapment efficiency of Span 60 is found to be maximum. Both proniosomes and niosomes indicate the similar controlled release profile. Permeation study of cefuroxime axetil, follows the order of Span 60 with bile salt > Span 60 only > Span 40. Upon ageing, proniosomes indicate no change in its physical property and the entrapment efficiency is found to be more than 90%, indicating no leakage or degradation of drug from proniosomes whereas niosomes indicate slight sedimentation and aggregation of particles. These factors indicate the commercial viability and easy scale up of proniosomes.

Keywords: Sorbitol Based Proniosomes Permeability Oral Cephalosporin

Introduction

New generation dosage form mainly comprises of colloidal drug carrier system. The carrier serves to protect the drug from premature degradation, inactivation and protects the host from unwanted immunological or pharmacological effects [1]. Colloidal drug delivery system consists of nanoparticles, microparticles, microspheres, microemulsion, magnetic microspheres, resealed erythrocytes, liposomes and niosomes etc.[2] Encapsulation of a drug in vesicular structures can be predicted to prolong the existence of the drug in systemic circulation and perhaps reduce the toxicity if selective uptake can be achieved. Vesicular systems are of considerable interest because they can be used as membrane models, in chemical reactivity or in drug delivery and targeting [3]. Liposomes are simple microscopic vesicles where an aqueous space is enclosed by lipid bilayers [4]. Because of their entrapping ability, liposomes are being considered as drug delivery structures or vesicles. But liposomes possess certain disadvantages associated with degradation by hydrolysis or oxidation and sedimentation, leaching of drugs, aggregation or fusion of liposomes during storage. Some problems associated with clinical applications of liposomes are the difficulties experienced in sterilization and large scale production. Moreover, it is difficult to obtain large quantities of sterile products with defined and reproducible properties that display adequate chemical and physical stability. The cost and purity of phospholipids is another limiting factor. They are suitable for parental administration but oral administration is not possible because of the inability of liposomes to survive the action of bile salts and phospholipids. Tedious conditions dealt in handling liposomes under cryogenic atmosphere also prompted the use of non-ionic surfactant vesicles or niosomes as an alternative to liposomes.

Since niosomes also suffer from the physical instability of aqueous niosomal dispersions like aggregation, fusion or leakage, the proniosomes have come into existence. They do not suffer from physical instabilities as well as their encapsulation efficiency is very high. They are capable of incorporating lipophilic, hydrophilic and amphiphilic drugs. The particle size distribution can be easily controlled. A vacuum or nitrogen atmosphere is not required for stability maintenance. All these characteristics point to the commercial viability of the proniosomes [3].

Dry granular type of proniosomes involves coating of water soluble carrier such as sorbitol or maltodextrin with surfactant. The result of coating process is a dry formulation in which each water soluble particle is covered with thin film of surfactant. The proniosomes are reconstituted by addition of aqueous phase at a temperature greater than than temperature and brief agitation. The desirable characteristics of the carrier material include good water
solubility (for ease of hydration), poor solubility in chloroform or in methanol (for ease of processing) and suitability for intravenous use. The sorbitol is reported to have offered the best compromise of desirable characteristics and has been selected for the present study. Though maltodextrin is also used as a water soluble carrier, it shows advantages only in preparation of the dry formulation but no significant change in the entrapment efficiency or drug release is reported through formulation of maltodextrin based proniosomes. Therefore sorbitol has been selected as the carrier for dry granular proniosomes.

Among the cephalosporins, cefuroxime axetil belongs to second-generation antibiotic, having the broad spectrum of activity and is active against β-lactamase producing strains. It is an ester produg of cefuroxime. Its activity depends upon in-vivo hydrolysis and release of cefuroxime [5]. Cefuroxime is rendered more lipophilic by esterification of the C4 carboxyl group of the molecule by the racemic 1-acetoxyethyl bromides, thus enhancing oral absorption. Cefuroxime axetil is an orally active drug though its absorption is incomplete. Its bioavailability is only 25%. It is the axetil form of cefuroxime that is absorbed but when it is hydrolysed to cefuroxime, its permeation is low [6]. So encapsulation of a drug in vesicular structures can be predicted to prolong the existence of the drug in systemic circulation and perhaps increase the

Preparation of dry granular proniosomes

1 gm of sorbitol was taken in a round bottom flask. It was attached to the rotary evaporator. Surfactant mixture was prepared in different ratios, along with cholesterol and stearylamine. 5 mg of the drug was introduced in the surfactant mixture. The surfactant solution was introduced into the round bottom flask on the rotary evaporator. During the spraying period, the rate of application was controlled so that the powder bed of the sorbitol did not become over wet. The rotating flask was then lowered into a water bath at 65-70°C. The flasks were rotated in the water bath under vacuum for 15-20 min or until sorbitol appeared to be dry. Another aliquot of surfactant solution was introduced. This process was repeated until all of the surfactant solution had been applied. After addition of final aliquot, evaporation was continued until the powder was completely dry. The material was further dried in desiccators under vacuum at room temperature overnight. The dry preparation was referred to as proniosomes [3].

Proniosomes dry powder was then hydrated with 5 ml of phosphate buffer pH 7.4 and vortex mixing was performed for 2 min, to convert this into niosomes.

Characterization of dry granular proniosomes

The proniosomes prepared were characterized for particle size, surface morphology and polydispersity index by SEM and TEM, angle of repose for their flowability by funnel method, entrapment efficiency by dialysis, centrifugation and size exclusion chromatography, in-vitro drug release by dialysis and ex-vivo permeation study by everted sac-method. The stability study for proniosomes and niosomes were performed at room temperature.

Morphological Characterization

Morphological Studies (SEM)
The surface morphology of dry granular proniosomes powder and hydrated proniosomes were examined by phase contrast microscopy (Manconi et. al) [7]. The sample of proniosomes and niosomal dispersion was taken in separate glass slide, covered with coverslip and then analyzed under optical microscope attached with camera (Nikon Eclipse E200) and photographs were recorded. The vesicular formulations were also observed under cross polarizer to study bilayer structures.

Transmission electron microscopy (TEM)
The morphology of derived niosomal dispersion was determined using transmission electron microscopy (TEM) (Philips- FEI Techai-12, Netherlands). A drop of niosome dispersion was cleaned with isotonic Phosphate buffer (IPB) pH 7.4 and applied to the carbon coated 300 mesh copper grid and left for 1min. Some niosomes were allowed to adhere to the carbon substrate. The remaining dispersion was removed by absorbing the drop with the comer of a piece of filter paper. After rinsing the grid twice (with deionised water for 3-5secs), a drop of 1 % uranyl acetate was applied for 10 sec. the remaining solution was removed by absorbing the liquid with the tip of a piece of filter paper and sample was air dried. The sample was examined in a TEM [5].

Entrapment efficiency

The entrapment efficiency of the niosomes was determined by dialysis, centrifugation and size-exclusion chromatography.

Dialysis

The unentrapped (free) cefuroxime axetil was removed from the niosomal dispersion by placing in a dialysis tube and exhaustively dialyzed against 300ml of phosphate buffer with 2 % methanol. The niosomes were lysed with 0.1 % v/v Triton X-100 and filtered with 0.2 µm membrane filter. The drug content estimated by HPLC and Entrapment efficiency was calculated as:

Entrapment efficiency= \[ \frac{\text{Total drug loaded}}{\text{free drug}} \times 100 \]
Entreapment efficiency is used as a parameter in selecting the type of spans, surfactant mixture ratio and amount of drug encapsulated in proniosomes.

Centrifugation
In this method, hydrated proniosomes were centrifugated at 14000 rpm for 5 minutes and the supernatant were analyzed for free drug content. Entrapment efficiency was calculated using the above formula.

Size-exclusion Chromatography
In this method chromatographic column was packed using Sephadex 15. Then hydrated proniosomes were poured from the top. The clear and turbid eluate was collected separately. The clear portion was analyzed for free drug content, by HPLC method. Alternatively the Triton X could be added to turbid portions and the drug present inside the vesicle could be determined.

Measurement of angle of repose
The angle of repose of dry granular proniosomes powder was measured by the funnel method. The sorbitol powder and proniosomes were poured through a funnel that was fixed at a certain height. The powder flowed down from the funnel to form a cone on the surface, and the angle of repose was calculated by measuring the height of the cone (H) and radius of the base (R) by the formula:

\[ \theta = \tan^{-1} \left( \frac{H}{R} \right) \]

In-vitro release rate
In vitro release rate of proniosomes, derived niosome dispersion was carried out and the drug in 30% PEG was used as a control. Initially the treatment of dialysis tube was done by washing in running water for 3-4 hours to remove glycerin. The sulphur compounds were removed by treating it with 0.3 % w/v solution of sodium sulphide. Then it was washed in boiling water at 70°C for 0.5 hours, followed by acidification with 0.3 % v/v solution of sulphuric acid. Finally the membrane was rinsed with water and stored in phosphate buffer pH 7.4. Then 2ml of niosomal dispersion was placed inside the pretreated dialysis tube, tied at both the ends. It was then transferred to a beaker containing 20ml of phosphate buffer with 50% methanol. The assembly was stirred on a magnetic stirrer at 37°C. 1ml samples were withdrawn at fixed intervals and replaced with equal volume of fresh media. The samples withdrawn were analyzed for drug by HPLC.

Ex-vivo permeation study
In-vitro absorption study of proniosomes formulation was done by everted sac method [7]. The small intestine of the rat was taken; it was washed with phosphate buffer pH 7.4, 6-7 times. Then the intestine was everted using the modified glass rod. It was then cut into 4-6cm pieces. One end of the intestine pieces was tied with thread, then 1ml of buffer was introduced in the intestine, and the other end was also tied. The intestine pouch was put in a test tube containing hydrated proniosomal dispersion. At different time intervals, the sample inside pouch was collected and analyzed for drug concentration. The pouch was again filled with fresh buffer medium, collected and analyzed.

Stability studies
The proniosomes as well as niosomes of the same composition were kept at room-temperature as well as at 4°C. Upon two months of storage, the physical examination was done and also the entrapment efficiency was determined.

HPLC method

HPLC method used for determination of drug content has been discussed by Zajac et al [8] with a flow rate of 1ml/min and RP C-18 (Merck) column.

Result and discussion
Though niosomes function as sustained release systems showing reduced toxicity, eliminating problems of drug insolubility, irritancy and poor bioavailability, but they also show physical instability. During storage, the vesicles have natural tendency to undergo fusion and aggregation as well as chemical hydrolysis. To overcome these problems, proniosomes has been prepared by coating the surfactant mixture containing cefuroxime axetil over porous sorbitol to get free flowing particles, which on hydration transforms readily into opalescent vesicular dispersion or niosomes. Proniosomes are characterized for various parameters and contrasting features have been compared with conventional niosomes. The formulation composition of proniosomes is shown in Table 1. The optimum composition has been chosen on the basis of entrapment efficiency. Upon hydration with water (preheated at 70°C) multilamellar vesicles (MLV) are formed with size ranging from 0.5-5µm. The photomicrographs of dry granular proniosomes powder and niosomal dispersion under SEM are shown in Fig 1 & 2 respectively. Scanning electron microscopy of uncoated sorbitol particles and dry proniosomes powder depicts a slight difference in the appearance of the surface of the two formulations. The sorbitol powder reveals some of the fine crystalline structures on the surface whereas the proniosomes powder appears to be smoother and to have fewer fine structures such as sharp edges. When the hydrated proniosomes are observed under SEM using cross polarizer, maltese cross was detected, indicating the formation bilayers as shown in Fig 3.
Upon hydration, it is converted to niosomes of average size between the range 200nm to 2.5µm. Transmission electron microphotograph has been shown in Fig 4. The vesicles seem to be like a spherical reservoir and devoid of any surface artifacts. The polydispersity index is very low indicating uniform dispersion. Entrapment efficiency is determined using dialysis, centrifugation and size exclusion chromatography. In all the cases, similar results have been found, so we restricted the use of dialysis method only. Maximum entrapment efficiency of 91.03±2 has been found in case of formulation 1b (i.e. span 60: cholesterol: stearylamine:: 67:30:3). Maximum entrapment in case of Span 40 and Span 60 could be attributed due to their structure, orientation and packing behavior [9], as both of them have same head group and different alkyl chain. Among the surfactants used, only Span 80 in formulation 1c has an unsaturated alkyl chain. The introduction of double bonds makes the chain bend. This means that adjacent molecule cannot be tight when they form the niosomes. This causes the membranes to be more permeable and therefore the yield of vesicle formation is appreciable which possibly explains the lowest entrapment efficiency. Span 60 has the longest saturated alkyl chain and shows the highest entrapment. Therefore the alkyl chain is the crucial factor for the permeability of long chain products. Moreover the Span 60 and span 40 are solid at room temperature and exhibit the higher phase transition temperature (Tc) that reflects the effect of phase transition temperature on the entrapment efficiency. Therefore Span 40 and Span 60 have been selected for further studies. As for vesicle size, increasing the hydrophobicity of the surfactant monomer leads to small vesicles. The order of increasing the vesicle diameter with various spans is as follows: Span 80 (formulation 1c) < Span 60 (formulation 1b) < Span 40 (formulation 1a).

This is because surface free energy decreases with the increasing hydrophobicity i.e. Span 80 < Span 60 < Span 40 [9].

Maximum entrapment of drug (91.03±2) when Span 40: cholesterol: stearylamine were used in the ratio of 67:30:3 (formulation 2d) and the formulation 2a showed minimum entrapment of 80.26±2 when ratio was 30:67:3. Above 70% concentration of nonionic surfactants in formulation led to a decrease in texture, shape and formation of vesicles. The concentration of stearylamine was kept constant. The amount of stearylamine was taken in accordance with the permissible concentration as reported in literature. The increase in entrapment efficiency in 2d formulation with 30 mM cholesterol could be explained by the fact that cholesterol was intercalated into the bilayers, thereby preventing the leakage of the drug through the bilayers [15] but a decline in the entrapment efficiency from 2c to 2a beyond a certain cholesterol level (55.0: 42.0: 3.0) could be attributed to the reason that when cholesterol is increased beyond the saturation limit, all the available spaces between the bilayers are filled up with the hydroxy moiety of cholesterol. It resulted in an increase in the rigidity of the vesicles [19]. Further addition of cholesterol would tend to destabilize the vesicle, leading to possible decrease of drug entrapment [31]. From Table 1, the entrapment efficiency remained high on increasing the amount of drug from 1 to 4mg which is attributed to higher log P value of the drug. The higher lipophilicity would facilitate interaction with surfactants and lipidic ingredients [9]. But for experimental purpose 1gm of drug was taken for further study.

The flowability of proniosomes powder was compared with uncoated sorbitol powder (Table 2).

The results revealed that the angle of repose of the proniosomes was smaller than that of sorbitol powder. As the angle of repose indicated the surface irregularity and roughness, the lower angle of repose of proniosomes confirmed that the surfactant coating of sorbitol powder had been achieved, resulting in the smoothening of surface. If the sorbitol powder was added to the proniosomes, the angle of repose was found increasingly approaching towards angle of repose of pure sorbitol powder.

In vitro release rate of cefuroxime axetil from proniosomes was determined and compared with niosomes and drug in 30% Propylene glycol as shown in Fig 5 & 6. In conducting the experiment continuously almost 75% of drug was released within 5 hours in case of propylene glycol, while in case of niosomes and proniosomes, a clear sustained release profile was achieved releasing about 30% in 6 hours (Table 3).

In case of our formulations the drug release was evident even after 20 hours, 65% in case of proniosomes and 44% in case of niosomes, showing better performance of formulation. It has been documented that in dissolved condition and in the acidic environment of the stomach, the hydrolysis of the Cefuroxime axetil occurs, and it gets converted into the Cefuroxime and the absorption of the Cefuroxime as such is negligible. It is the axetil form of the Cefuroxime that is absorbed. So, the drug in Propylene glycol can overcome the problem of insolubility but not the permeability. But when the drug is entrapped in the vesicles, it can easily cross the membrane, protect the drug from acid environment and additional mechanism apart from phagocytic uptake which occurs thereby enhancing the drug absorption.

In-vitro absorption (ex-vivo permeation) study using everted sac method has been shown in Fig 7 & 8. The formulation containing bile salt with Span 60 showed maximum absorption followed by formulation with Span 60 only then did various formulations of Span 40 come in (Table 4), thereby proving again that performance of drug depends on the entrapment efficiency.

Upon storage of proniosomes and niosomes of same composition (1b) for two months, the visual examination revealed the sedimentation of niosomal dispersion whereas proniosomes appeared to be amorphous powder. When they were observed under SEM, marked aggregation was detected in case of niosomes and the mean particle size increased to 10 folds. But for proniosomes (just hydrated), a uniform dispersion was observed and aggregation was absent. When entrapment efficiency was determined for hydrated proniosomes (just prior to experiment) and niosomes that was already stored, a decrease in entrapment efficiency was observed, which was due to some leakage or drug degradation.
Table 1: Composition of various Proniosomal formulations

<table>
<thead>
<tr>
<th>FORMULATION CODE</th>
<th>SORBITOL (mg)</th>
<th>CEFUROXIME AXETIL (mg)</th>
<th>SPAN 40</th>
<th>SPAN 60</th>
<th>SPAN 80</th>
<th>CHOLESTEROL</th>
<th>STEARYLAMINE</th>
<th>ENTRAPMENT EFFICIENCY</th>
<th>SIZE (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>5</td>
<td>1</td>
<td>67</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>3</td>
<td>91.03±4</td>
<td>5</td>
</tr>
<tr>
<td>1b</td>
<td>5</td>
<td>1</td>
<td>67</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>3</td>
<td>97.0±3</td>
<td>1-2</td>
</tr>
<tr>
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<td>1</td>
<td>-</td>
<td>67</td>
<td>-</td>
<td>30</td>
<td>3</td>
<td>ind</td>
<td>0.8-2</td>
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<td>2a</td>
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<td>30</td>
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<td>-</td>
<td>67</td>
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<td>80.26±2</td>
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<tr>
<td>2b</td>
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<td>1</td>
<td>47</td>
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<td>-</td>
<td>50</td>
<td>3</td>
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<tr>
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<td>55</td>
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<td>-</td>
<td>42</td>
<td>3</td>
<td>83.74±4</td>
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<td>-</td>
<td>-</td>
<td>30</td>
<td>3</td>
<td>91.0±2</td>
<td>-</td>
</tr>
<tr>
<td>3a</td>
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<td>1</td>
<td>67</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>3</td>
<td>91.0±3</td>
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<td>3b</td>
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<td>67</td>
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<td>88.54±3</td>
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<td>-</td>
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<td>3</td>
<td>89.46±3</td>
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<tr>
<td>3d</td>
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<td>4</td>
<td>67</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>3</td>
<td>92.78±2</td>
<td>-</td>
</tr>
</tbody>
</table>

- All the ratios are in millimole

Table 2: Measurement of angle of repose of sorbitol powder and dry granular proniosomes

<table>
<thead>
<tr>
<th>S. NO.</th>
<th>TYPE OF PREPARATION</th>
<th>HEIGHT (H) ± S.D. (N=3) IN CM</th>
<th>RADIUS (R) ± S.D. (N=3) IN CM</th>
<th>TAN Θ = H/R</th>
<th>ANGLE OF REPOSE (Θ) = TAN⁻¹ (H/R) ± S.D. (N=3)</th>
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<tbody>
<tr>
<td>1</td>
<td>Sorbitol powder</td>
<td>1.8</td>
<td>3</td>
<td>0.6</td>
<td>30.96±2.1</td>
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<tr>
<td>2</td>
<td>Proniosomes powder</td>
<td>1.5</td>
<td>3</td>
<td>0.5</td>
<td>26.56±2.1</td>
</tr>
<tr>
<td>3</td>
<td>Proniosomes (with double quantity of Sorbitol)</td>
<td>1.3</td>
<td>5</td>
<td>0.52</td>
<td>27.47±1.6</td>
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</table>

Table 3: The comparative release profile of conventional niosomes and dry granular proniosomes and Drug in 30% PG.

<table>
<thead>
<tr>
<th>Time (Hrs)</th>
<th>% drug release</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>proniosomes Niosome Drug in 30% PG</td>
</tr>
<tr>
<td>0.5</td>
<td>36.33±3.12 21.64±2.13 47.24±1.34</td>
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<tr>
<td>1</td>
<td>25.10±2.24 35.44±2.13 70.45±2.31</td>
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<tr>
<td>1.5</td>
<td>26.87±1.45 35.82±2.31 74.11±1.42</td>
</tr>
<tr>
<td>2</td>
<td>27.28±3.24 37.95±3.24 77.04±2.31</td>
</tr>
<tr>
<td>2.5</td>
<td>31.74±2.31 37.07±1.32 77.46±2.31</td>
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<tr>
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<td>31.03±2.56 35.37±2.13 71.73±1.34</td>
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<td>4</td>
<td>30.40±1.56 32.65±2.31 75.15±2.43</td>
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<tr>
<td>4.5</td>
<td>31.96±3.24 31.56±2.31 -</td>
</tr>
<tr>
<td>5</td>
<td>30.91±2.34 32.56±2.31 -</td>
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<tr>
<td>5.5</td>
<td>29.86±1.56 32.77±3.23 -</td>
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<tr>
<td>6</td>
<td>27.54±3.21 34.16±4.32 -</td>
</tr>
<tr>
<td>20</td>
<td>63.51±2.14 43.03±2.31 -</td>
</tr>
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Table 4: In-vitro absorption study of various proniosomal formulations by everted sac method.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>2a</th>
<th>2b</th>
<th>2c</th>
<th>2d</th>
<th>2e</th>
<th>2f</th>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>1.86</td>
<td>2.17</td>
<td>2.04</td>
</tr>
<tr>
<td>0.5</td>
<td>3.76</td>
<td>3.89</td>
<td>4.25</td>
<td>4.08</td>
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<tr>
<td>1</td>
<td>6.36</td>
<td>5.17</td>
<td>6.43</td>
<td>5.45</td>
<td>8.38</td>
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<td>1.5</td>
<td>7.92</td>
<td>6.37</td>
<td>8.69</td>
<td>7</td>
<td>10.04</td>
<td>10.42</td>
</tr>
</tbody>
</table>

2e formulation composition same as 2d but have Span 60 instead of Span 40.

2f formulation composition same as 2e with 10 mM bile salts.

Figure 1: Surface morphology of dry granular proniosomes

Figure 2: Hydrated proniosomes evident by SEM

Figure 3: Hydrated proniosomes using cross polarizer

Figure 4: TEM photomicrograph of Hydrated proniosomes
Figure 5: Release Profile of Proniosomes, Niosomes and drug in 30% PG in 6 hours

Figure 6: Release Profile of Proniosomes, Niosomes and drug in 30% PG in 20 hours
Figure 7: In-vitro absorption study of different formulations

Figure 8: Permeation flux of different formulations
Conclusions
An attempt has been made to prepare dry granular proniosomes which has been anticipated to provide improved stability as compared to conventional vesicular delivery systems in terms of aggregation, leakage etc. The proposed formulation based on present study is expected to have industrial scalability. This may also provide the high absorption inside the lumen and the same may be expected even in blood circulation. However, it will require a detailed study in terms of in-vivo behavior.

Conflict of Interests: The author declare no conflict of interests

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References


