Formulation and Evaluation of Proniosomes of Felodipine

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Abstract

Novel drug delivery systems have emerged embracing various routes of administration, oral drug delivery is the most common and preferred method of drug administration. A lipid based drug delivery has become an emerging strategy for improved oral delivery of poorly soluble drugs. Drug encapsulation in the vesicles is one such system which helps to prolong drug duration in systemic circulation and decreases the toxicity by selective uptake. Based on this technique, a number of vesicular drug delivery systems such as liposomes, niosomes and provesicular systems like proliposomes and proniosomes have been developed. The aim of the present investigation was to develop felodipine proniosomes to enhance the solubility. Felodipine loaded proniosomes were prepared by varying ratios of span 60 and cholesterol by solvent evaporation method. Proniosomes were characterized for vesicle size, micromeritics, entrapment efficiency and dissolution behavior. Solid state behavior was evaluated by Differential scanning calorimetry (DSC), Scanning electron microscopy (SEM) and Fourier transform infrared (FTIR) studies. The formulated proniosomes showed improved dissolution characteristics which were assessed from dissolution rate data. The transformation of crystalline form of the drug to amorphous and/or molecular state was represented by solid state characterization. FTIR studies showed that absence of interaction between drug and other formulation excipients.

Keywords: Felodipine; Neusilin; Cholesterol

Introduction

Novel drug delivery systems have emerged embracing various routes of administration, to attain targeted and controlled drug delivery. Drug encapsulation in the vesicles is one such system which helps to prolong drug duration in systemic circulation and decreases the toxicity by selective uptake. Based on this technique, a number of vesicular drug delivery systems such as liposomes, niosomes and provesicular systems like proliposomes and proniosomes have been developed [1].

Though the oral route drug administration is advantageous it is continuously looking into newer avenues due to realization of the factors like poor drug solubility and/or absorption, rapid metabolism, high fluctuation in the drug plasma and variability due to food effect which are playing major role in disappointing in vivo results leading to failure of the conventional delivery system [2]. Recently, it has been estimated that from 40-70% of all new chemical entities (NCE) entering drug development programs possess insufficient aqueous solubility to allow consistent gastrointestinal absorption of a magnitude sufficient to ensure therapeutic efficacy [3].

The role of the drug delivery is not only limited to a drug package just meant for convenience and administration but to bring a required change in therapeutic efficacy and safety by carrying the drug molecules to the desired site in the most convenient manner. The oral administration of drugs often lead to degradation due to highly acidic gastric environment, enzymes of the mucosa or liver, they enter the systemic circulation. Beside many highly polar drugs, macro molecular drugs may not be absorbed because of their insufficient solubility, lipophilicity and large molecular weight [4].

The oral bioavailability of poorly water soluble, lipophilic drugs can be enhanced when co-administered with rich in fat [5,6]. Based on this concept colloidal lipid carrier systems have been developed as a means to improve drug solubilization and permeation across the gastrointestinal barrier [7,8].

Felodipine belongs to dihydropyridine derivative, used as antihypertensive and anti angina by blocking calcium channels. Felodipine belongs to BCS class II which is poorly water soluble, lipophilic character of felodipine limits its absorption. Due to high extensive first pass metabolism results in low bioavailability of 15% [9,10].

The use of the both conventional and new drug delivery systems (DDS) allows facing the major issues in drug release:

1. Unfavorable pharmacokinetics and biodistribution which lead to unwanted side effects (e.g. chemotherapy).
2. Early drug degradation in the bloodstream by reticuloendothelial system (RES),
3. Inefficient uptake at target sites that leads to low drug efficacy.

Due to the rapid growth in nanotechnology, it can be asserted that the study of drug delivery and disease treatment has been revolutionized. By molding nanomaterials into vesicles, numerous nanocarriers have been developed to securely deliver drugs and various other therapeutic agents specifically into target sites. Many of the conventional nano DDS (e.g. liposomes, micelles and polymer based nano devices) have reached the late stages of development and some of them were approved.

A successful nanocarrier should ideally meet the following requirements:

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1. Formulation with biocompatible/biodegradable/bioexcretable materials,
2. High drug and cargo loading capacity,
3. Site specific delivery mechanism to avoid normal cells and tissues,
4. Zero or negligible premature drug release,
5. Controlled release mechanism to provide an effective dose to the target site.

There are a very limited number of nanocarriers which can achieve such prerequisites [11].

Among the several colloidal lipid carrier systems liposomes or niosomes (vesicular approach) have specific advantages over 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, to reduce the toxicity of drug.

Vesicles are colloidal particles in which a concentric bilayer made up of amphiphilic molecules surrounds an aqueous compartment. They are a useful vehicle for drug delivery of both hydrophobic drugs, which associate with the lipid bilayer and hydrophilic drugs, which are encapsulated in the interior aqueous compartment [12].

Materials and Methods

Materials

Felodipine is gift sample from Dr. Reddy’s laboratories, Hyderabad, India. Neusilin gift sample from Fuji Chemical Industry, Japan. Cholesterol gift sample from FINAR Reagents span 60 purchased from Merck, Germany. And chloroform purchased from Qualikems Fine Chem. Pvt. Ltd.

Methods

Construction of calibration curve of felodipine in ethanol by UV spectrophotometry: Accurately weighed quantity of felodipine (100 mg) was taken into volumetric flask (100 ml) and dissolved in small amount of ethanol and then volume was made up to 100 ml with ethanol to prepare main stock (1 mg/ml or 1000 µg/ml) solution. From main stock 10 ml solution was withdrawn and diluted to 100 ml with ethanol in a 100 ml volumetric flask to get 100 µg/ml concentration of felodipine. 10 µg/ml concentration of felodipine was obtained by diluting 10 ml of 100 µg/ml to 100 ml with pH 6.8 phosphate buffer. Aliquots of respective stock solutions (10 and 100 µg/ml) were taken and serial dilutions were made to get the final desired concentrations (10, 20, 30, 40 and 50 µg/ml). The absorbance of these samples was measured Spectrophotometrically at 364 nm using UV-Visible spectrophotometer. The standard graph was plotted and the straight line equation obtained from regression analysis was used to calculate the concentration of felodipine in unknown samples.

Preparation method

Preparation of proniosomal powders: Proniosome powders were prepared by using slurry method reported elsewhere. The composition of different proniosomal formulations is represented in Table 1. In brief, equally weighed amounts of lipid mixture (250 µM) comprising of span 60 and cholesterol at various molar ratios (2.5:1, 1.5:1, 1:1, 1:1.5, 1:2.5 respectively) and drug (10 mg) were dissolved in 20 ml of solvent mixture containing chloroform and ethanol (2:1). The resultant solution was transferred into a 250 ml round bottomed flask and neusilin (250 mg) (1 g of carrier per 1 mL of lipid mixture) was added to form slurry. The slurry was attached to a rotary flash evaporator (Laborota 4000, Heidolph, Germany) and the organic solvent was evaporated under reduced pressure at a temperature of 45 ± 2°C. After ensuring the complete removal of solvent, the resultant powders were further dried overnight in a vacuum oven at room temperature so as to obtain dry, free-flowing product. The dried product was passed through #60 sieve to obtain fine flowing powder and stored in a tightly closed container at 4°C for further evaluation [13,14] (Table 1).

Total 250 µM lipid mixture was used in all the preparations. 1 g of carrier per 1 µM of lipid mixture. Each formulation contains 10 mg of felodipine and total weight of powder 300 mg.

Formation of niosomes from proniosomes powders: The optical microscope was used to demonstrate the formation of the noisome upon hydration of proniosome powders. The proniosome powder was sprinkled on a cavity glass slide and few micro litre of distilled water was added drop wise along the side of the cover slip. The transformation of vesicles on the surface of solid particle due to hydration was monitored and recorded using optical microscope (Coslabs micro, India) [15,16].

Characterization of proniosomes

Micromeritic properties of proniosome powders: The content uniformity of the powder formulations can be dictated by the flow
Drug*100 powder formulations were taken in 50 ml of pH 6.8 phosphate buffer. Felodipine in the resulting niosomes was determined by the proniosomal method. Each sample was diluted to a suitable concentration with phosphate buffer pH 6.8. Size analysis was performed at 25°C with an angle of detection of 90°. Size, polydispersity index of niosomes and their mean zeta potential values (± SD) were obtained from the instrument [26-28].

In vitro dissolution study: In vitro dissolution study of control (pure drug) and proniosomal powder formulation was performed using USP type II (paddle) apparatus (Electrolab, TDL8, Mumbai, India) in pH 6.8 phosphate buffer. The temperature of the dissolution medium (900 ml) was maintained at 37 ± 0.5 °C with paddle speed set at 50 rpm throughout the experiment. At predetermined time intervals (2, 4, 6, 8, 10, 12 min) an aliquot of 5 ml was withdrawn and replenished with fresh dissolution medium to maintain constant volume. The samples were analyzed by UV spectrophotometer [29].

Table 2: Limitation values of angle of repose, Hausner's ratio and Carr's index.

<table>
<thead>
<tr>
<th>Flow properties</th>
<th>Angle of repose</th>
<th>Hausner's ratio</th>
<th>Carr's index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>25-30</td>
<td>1.00-1.11</td>
<td>≤ 10</td>
</tr>
<tr>
<td>Good</td>
<td>31-35</td>
<td>1.12-1.18</td>
<td>11-15</td>
</tr>
<tr>
<td>Fair</td>
<td>36-40</td>
<td>1.19-1.25</td>
<td>16-20</td>
</tr>
<tr>
<td>Passable</td>
<td>41-45</td>
<td>1.26-1.34</td>
<td>21-25</td>
</tr>
<tr>
<td>Poor</td>
<td>46-55</td>
<td>1.35-1.45</td>
<td>26-31</td>
</tr>
<tr>
<td>Very poor</td>
<td>56-65</td>
<td>1.46-1.59</td>
<td>32-37</td>
</tr>
<tr>
<td>Very very poor</td>
<td>&gt;66</td>
<td>≥ 1.60</td>
<td>≥ 38</td>
</tr>
</tbody>
</table>

Solid state characterization

Fourier transforms infrared spectroscopy (FTIR): Platinum ATR method [30-32]: FTIR analysis was executed to assess any possible interactions that might have occurred between felodipine and other excipients during the formulation. Solids are generally best analyzed on the single reflection ATR accessories; The infrared spectra of felodipine, span 60, neusilin and optimized proniosome powder formulation (F3) were recorded using Bruker Alpha E, FTIR spectrometer (Bruker Alpha E, Opus-7.0.122) equipped with a ATR (Avttenuated Total Reflectance). The spectra were scanned at room temperature in transmission mode over the wave number range of 400-650 cm⁻¹.

Differential scanning calorimetry (DSC): DSC studies were performed to know the physical state of the drug in the proniosomal formulations. The DSC measurements were performed on a differential scanning calorimeter (Shimadzu, Thermal Analyzer DSC 60). The peak transition temperature (Tm) and heat of fusion (enthalpy) (Hf) were determined and used in the analysis. Indium (Tm=159.2°C; Hf=28.8 J/g) was used as a standard for routine calibration. An empty aluminium pan was used as reference and nitrogen (purity>99.99%) was used as the purge gas. Samples of 2.4-2.8 mg were weighed and placed in open aluminium pans and scanned at a speed of 10°C/min, over the temperature range from 30 to 350°C [33-36].

Scanning electron microscopy (SEM): The surface morphology of felodipine, neusilin and felodipine proniosomal formulation (F3) were examined by means of ZEISS 18 scanning electron microscope. The powders were previously fixed on a brass stub using double-sided adhesive tape and when were made electrically conductive by coating, in a vacuum. The pictures were taken at an excitation voltage of 10-15 Kv and different magnifications [37,38].

Results and Discussion

Calibration curve of felodipine in ethanol

Calibration curve of felodipine was plotted in ethanol at λ_max of 362 nm. Graph obtained was shown that good correlation established with R² value of 0.997 and straight line equation was y=0.019x-0.018 (Table 3 and Figure 1).

Calibration curve of felodipine in pH 6.8 phosphate buffer

Calibration curve of felodipine was plotted in pH 6.8 phosphate buffer at λ_max 364 nm, and the straight line equation obtained was y=0.024x+0.011 (Table 4 and Figure 2).
Preparation and characterization of proniosomal powders

Preparation of proniosomal powders: Provesicular systems of felodipine were successfully prepared using earlier reported slurry method [22]. Provesicular systems offer a simple and stable way of administering the vesicles liposomes and niosomes; possess dosing accuracy and flexibility in handling of solid dosage forms. Further a suitable inert carrier (neusilin) may increases flow ability of formulation. Combination of chloroform and ethanol was selected as solvent system because of greater solubility of drug and lipids in this mixture and also ethanol was less toxic over methanol. There is no need of vacuum assisted drying for complete removal of solvent from formulation with ethanol. The different span types have the same polar head group with varied alkyl chain and highest entrapment could be observed with an increase in phase transition temperature of span. The phase transition temperatures for span 20, 40 and 60 are 16, 42 and 52°C, respectively and span 80 having the lowest phase transition temperature at -12°C. Due to the high phase transition temperature (52°C) [39], span 60 was used in our study to facilitate stable vesicle formation and to improve the oral delivery of felodipine from proniosomes. Cholesterol itself does not form bilayers, but it can be added to the lipid phase to improve the stability of the vesicles as it has modulatory effect on the membrane bilayers. Cholesterol was added due to its ability to enhance the encapsulation of hydrophilic drugs. The stability and entrapment efficiency of the formed vesicles is of great importance in vesicular systems which depend on the concentration of lipid and cholesterol used in formulation. Any alteration in the composition of lipid and cholesterol results in the deformation of vesicle leads to leakage of drug before diffusion and fusion of vesicle with gastrointestinal epithelium. Hence in this investigation effect of cholesterol was investigated by varying the ratio of Span 60 to cholesterol (Total lipid mixture of 250 µM) [40-42] (Figure 3).

Formation of niosomes from proniosomal powder: Formation of niosomes from proniosomal powder was shown in Figure 4. Formation or morphological evaluation of niosomes from proniosomes was observed in three stages, stage 1-“bubbling off” tubular structures on surface of carrier due to dispersion of lipid surface of proniosomes upon hydration [43], stage 2-formation of niosomal aggregates upon detachment of tubular structures from the core of proniosomes due to dissolution of lipid as well as neusilin in aqueous media and stage-3 formation of niosomal dispersion upon gentle agitation in Figure 4.

Micromeritics: Flow property of the powders is of greater importance in handling and processing of solid dosage forms. Optimal amount of solid carrier to coat the lipid mixture plays a major role in maintenance of flow property of powders. Based on reports in our laboratory 1 g of carrier for 1 µM of total lipid was considered for all the formulations (Tables 5 and 6).

Flow property results were listed in Table 6. Angle of repose values of less than 40 and Carr’s index and Hausner’s ratio values of less than 31 and 1.45, respectively. The present results indicate for angle of repose good to fair flow behavior and for Carr’s index, Hausner’s ration results poor to passable due to higher proportion of lipid in their molar lipid ratio. The probable reason for this may be increase in the concentration of lipid increases.

Physico-chemical evaluation of proniosomal powder: Vesicle size and zeta potential are of great importance in case of vesicular systems. Concentration of cholesterol might have influence on the size and

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.147</td>
</tr>
<tr>
<td>20</td>
<td>0.369</td>
</tr>
<tr>
<td>30</td>
<td>0.581</td>
</tr>
<tr>
<td>40</td>
<td>0.751</td>
</tr>
<tr>
<td>50</td>
<td>0.957</td>
</tr>
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</table>

Table 3: Calibration curve of felodipine in ethanol.

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.246</td>
</tr>
<tr>
<td>20</td>
<td>0.543</td>
</tr>
<tr>
<td>30</td>
<td>0.776</td>
</tr>
<tr>
<td>40</td>
<td>0.952</td>
</tr>
</tbody>
</table>

Table 4: Calibration curve of felodipine in pH 6.8 phosphate buffer.

![Figure 1: Calibration curve of felodipine in ethanol.](standard graph in ethanol)

![Figure 2: Calibration curve of felodipine in pH 6.8 phosphate buffer.](standard graph in pH 6.8 phosphate buffer)
surface charge of vesicles. In this investigation we could notice that F3 formulation with equimolar ratio of lipid and cholesterol had small size and greater zeta potential. Zeta potential of proniosomal formulation (F3) was -34.1 mV and poly dispersity index was found to be -0.8 and good results were obtained. The mean size of vesicles was in the range of 6 to 14 µm, it can also be noted that increasing cholesterol content subsequently decreased mean vesicle size and this may be due to the increase in the hydrophobicity of bilayers which limits the water intake to the vesicles core.

As the concentration of cholesterol increased, the entrapment efficiency has been increased (F1 to F3). This could be well explained based on the fact that, upon addition of cholesterol the bilayer hydrophobicity as well as stability is greatly improved with reduced permeability of the bilayer, thus leading to the effective intercalation of hydrophobic drug within the hydrophobic core of the bilayer with an enhanced drug payload. However we could not extrapolate the findings with high cholesterol content and in contrary the entrapment values declined with increase in cholesterol content in the formulation (F4 and F5). The higher amounts of cholesterol may compete with the drug for the packing space available in the bilayer during the noisome formation and also perturb the linear regular structure of bilayer resulting in limited accommodation of drug molecules [44,45] (Table 7).

**In vitro dissolution study:** Solid dissolution is a complex process influenced by solubility, particle size, surface area, crystal habit and wettability, etc. (Figure 5). illustrates the dissolution profiles of felodipine and felodipine proniosomal formulations in pH 6.8 phosphate buffer. Pure felodipine showed poor dissolution behavior, whereas proniosomal formulations showed enhanced dissolution of drug. The attributing reason for poor dissolution of felodipine may be poor solubility, hydrophobic nature and poor wettability which were evident from particle aggregation and floating behavior of drug during dissolution. The percent drug release was found to be greater for all the formulations compared to pure drug. The percentage drug released with the increase in HLB since hydrophilic surfactants have higher solubilizing power on hydrophobic solutes in aqueous medium compared to hydrophobic surfactants.

Among the different proniosomal formulations F3 showed 99.32% drug release at the end of 10 min of dissolution. Consequently dissolution

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Angle of repose (°)</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>31.9 ± 2.09</td>
<td>Good</td>
</tr>
<tr>
<td>F2</td>
<td>35.86 ± 4.30</td>
<td>Good</td>
</tr>
<tr>
<td>F3</td>
<td>36.78 ± 2.59</td>
<td>Fair</td>
</tr>
<tr>
<td>F4</td>
<td>36.92 ± 2.74</td>
<td>Fair</td>
</tr>
<tr>
<td>F5</td>
<td>39.80 ± 2.90</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Table 5: Micromeritic properties of varying compositions of proniosomal powders.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Carr's compressibility index</th>
<th>Hausner's ratio</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>26.67 ± 2.98</td>
<td>1.36 ± 0.05</td>
<td>Poor</td>
</tr>
<tr>
<td>F2</td>
<td>26.31 ± 0.80</td>
<td>1.35 ± 0.01</td>
<td>Poor</td>
</tr>
<tr>
<td>F3</td>
<td>24.81 ± 2.03</td>
<td>1.33 ± 0.03</td>
<td>Passable</td>
</tr>
<tr>
<td>F4</td>
<td>30.22 ± 2.11</td>
<td>1.43 ± 0.04</td>
<td>Poor</td>
</tr>
<tr>
<td>F5</td>
<td>29.27 ± 3.13</td>
<td>1.42 ± 0.06</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Table 6: Flow properties of varying compositions of proniosomal powders.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Size (µm)</th>
<th>Entrapment efficiency (%)</th>
<th>No. of vesicles per mm³ x 10³</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>13.8</td>
<td>68.50</td>
<td>3.02</td>
</tr>
<tr>
<td>F2</td>
<td>10.2</td>
<td>70.12</td>
<td>3.13</td>
</tr>
<tr>
<td>F3</td>
<td>6.2</td>
<td>72.35</td>
<td>3.15</td>
</tr>
<tr>
<td>F4</td>
<td>11.6</td>
<td>69.23</td>
<td>2.98</td>
</tr>
<tr>
<td>F5</td>
<td>14.5</td>
<td>65.56</td>
<td>2.87</td>
</tr>
</tbody>
</table>

Table 7: Physico chemical parameters of felodipine loaded proniosomal powders.
efficiency (DE) was also higher for F3 (89 ± 6.497) formulation than all other formulations and pure drug (8.3 ± 0.971). Enhanced dissolution rate for proniosomal formulations than pure drug was revealed from the dissolution parameters such as mean dissolution rate (12.95) and initial dissolution rate (36.41) and time taken to 70% of drug release from formulation (T_{70%}) less than 2 min for F3 formulation (Table 8) when compared with all other formulations. Hence F3 formulation containing equimolar ratio of span 60 and cholesterol was selected for further studies (Tables 8 and 9 and Figure 5).

Fourier transform infra red spectroscopic studies (FTIR): FTIR studies were performed to know the chemical interactions between drug and excipients. Figure 6 represents the IR spectra of neusilin, pure felodipine, felodipine loaded proniosomal formulation (F3) and span 60. Two characteristic, well defined peaks were observed for pure felodipine at 2944.05 cm^{-1} (C-H stretching), 1688.89 cm^{-1} (C=O stretching). Both peaks appeared at 2924.11 cm^{-1} (C-H stretching) and 1632.94 cm^{-1} (C=O stretching) in the felodipine loaded proniosomal formulation (F3) indicate that the drug and all the excipients were compatible (Figure 6).

Differential scanning calorimetry (DSC): DSC studies were performed for pure felodipine, Neusilin and felodipine proniosomal powder (F3) to know the thermal behavior and physical state of the drug (crystalline/amorphous) in the formulation through characteristics melting points. As shown in Figure 7 endothermic peak at 146.3ºC for pure felodipine indicates crystallinity of drug. Neusilin used as inert carrier got characteristic peak at 225.01ºC. Endotherm of proniosomal formulation clearly indicates the transformation of crystalline form of pure felodipine to amorphous state (Figure 7).

Scanning electron microscopy (SEM): Figure 8 shows SEM images of pure felodipine, neusilin, felodipine loaded proniosomal formulation (F3). Figure 8A shows that the pure felodipine consists of crystalline nature. Figure 8B indicates microporous nature of neusilin which

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**Table 8:** Dissolution data of pure drug and different proniosomal formulations, each data expressed as mean ± SD; n=3

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Pure drug</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3.31 ± 2.5</td>
<td>58.63 ± 4.3</td>
<td>60.61 ± 1.7</td>
<td>72.62 ± 8.5</td>
<td>66.38 ± 4.8</td>
<td>63.34 ± 7.7</td>
</tr>
<tr>
<td>4</td>
<td>3.7 ± 1.2</td>
<td>76.26 ± 1.6</td>
<td>77.82 ± 2.1</td>
<td>81.45 ± 7.1</td>
<td>73.37 ± 8.8</td>
<td>72.22 ± 5.9</td>
</tr>
<tr>
<td>6</td>
<td>3.72 ± 1.35</td>
<td>73.28 ± 3.5</td>
<td>73.87 ± 2.5</td>
<td>85.87 ± 7.4</td>
<td>81.72 ± 10</td>
<td>73.85 ± 6.4</td>
</tr>
<tr>
<td>8</td>
<td>4.85 ± 2.01</td>
<td>70.66 ± 5.0</td>
<td>71.81 ± 2.2</td>
<td>88.15 ± 5.3</td>
<td>80.75 ± 10</td>
<td>76.32 ± 7.3</td>
</tr>
<tr>
<td>10</td>
<td>3.77 ± 1.2</td>
<td>67.45 ± 7.8</td>
<td>66.72 ± 4.9</td>
<td>99.32 ± 5.5</td>
<td>90.8 ± 14.0</td>
<td>85.93 ± 2.2</td>
</tr>
</tbody>
</table>

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**Table 9:** Dissolution parameters of felodipine from proniosomal powder formulations

<table>
<thead>
<tr>
<th>Formulations</th>
<th>DE (%)</th>
<th>MDR</th>
<th>IDR</th>
<th>T_{70%}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure drug</td>
<td>8.3 ± 0.971</td>
<td>0.58</td>
<td>0.16</td>
<td>------</td>
</tr>
<tr>
<td>F1</td>
<td>84.09 ± 3.99</td>
<td>10.43</td>
<td>3.10 min</td>
<td>2.58</td>
</tr>
<tr>
<td>F2</td>
<td>88.37 ± 1.77</td>
<td>10.729</td>
<td>3.00 min</td>
<td>&lt;2 min</td>
</tr>
<tr>
<td>F3</td>
<td>89.6 ± 6.497</td>
<td>12.95</td>
<td>36.41</td>
<td>&lt;2 min</td>
</tr>
<tr>
<td>F4</td>
<td>84.9 ± 4.577</td>
<td>11.89</td>
<td>33.19</td>
<td>3.50 min</td>
</tr>
<tr>
<td>F5</td>
<td>82.97 ± 2.319</td>
<td>11.31</td>
<td>31.67</td>
<td>3.55 min</td>
</tr>
</tbody>
</table>

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*average of three determinations ± SD; MDR- Mean dissolution rate, IDR- Initial dissolution rate, T_{70%}- Time taken for 70% drug release

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Figure 6: Fourier transform IR spectra of A) Neusilin B) Felodipine C) Felodipine proniosomal formulation (F3) D) Span 60.
enables higher surface area for coating the lipid mixture containing drug. Disappearance of crystals of pure felodipine in the formulation and transformation of characteristic crystalline nature to amorphous or molecular state was evident from the Figure 8C.

**Summary**

- Neusilin was selected as suitable solid carrier for formulation of proniosomal felodipine.
• Felodipine loaded proniosomal powders of varying ratios have been prepared successfully by solvent evaporation method.

• Felodipine loaded proniosomal powders upon hydration resulted niosomal tubular structures.

• Micromeritic evaluation showed good to fair flow properties for F1 to F5.

• Vesicle size of all the formulations found to be within the range of 6 to 14 µm. zeta potential of felodipine loaded proniosomal formulation (F3) was found to be -34.01 mV.

• The entrapment efficiency of all the formulations was found to be between 68% and 72%.

• The formulation containing equimolar ratio of span 60 and cholesterol (F3) showed smaller vesicle size, high zeta potential and entrapment efficiency when compared to other proniosomal formulations.

• The felodipine loaded proniosomal formulation (F3) improved the dissolution of felodipine compared to other formulations. This indicates that enhanced dissolution was also evident from the adsorption of lipid coat on to the solid carrier which increases effective surface area and also due to a possible change in the physical state of the drug from crystalline to amorphous.

• Enhanced dissolution of drug from formulation assessed from parameters such as MDR, IDR and T_{50} were higher for F3 formulation.

• Solid state characterization revealed transformation of crystalline form of drug to amorphous or molecular state.

Conclusion

Felodipine loaded proniosomal formulations were successfully prepared using varying ratios of span 60 and cholesterol by solvent evaporation method. The proniosomal formulation F3 containing equimolar ratio of span 60 and cholesterol was selected as optimized formulation based on the physico-chemical evaluation and in vitro dissolution parameters, percent drug release was found to be higher for formulation than pure drug.

References


