PREPARATION AND CHARACTERIZATION OF SOLID SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM BY ADSORBENT TECHNIQUE TO IMPROVE DISSOLUTION PROFILE OF POORLY AQUEOUS SOLUBLE DRUG RAMIPRIL

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ABSTRACT

The main purpose of this work is to prepare solid self-microemulsifying drug delivery system (S-SMEDDS) to improve drug dissolution profile of poorly aqueous soluble drug. Optimized formulation of SMEDDS consists of Ramipril (RAM) (10 mg), Tween 80 (160mg), Cremophor EL (640mg) and Capmul MCM (CAP) as oil (200mg). SMEDDS was adsorbed at various SMEDDS: adsorbent ratio i.e. 3:1, 1:1, 1:3 on the solid carrier Aerosil 200. Powder flow properties and drug content were evaluated of the resulting formulations. The S-SMEDDS which showed maximum drug content in formulation & good flow properties were further evaluated & characterized for globule size, reconstitution properties, DSC, SEM & in-vitro dissolution profile. Converting liquid SMEDDS formulation to solid SMEDDS formulation is easy by adsorption on solid carrier technique. Formulation to Aerosil 200 ratio of 1:1 showed passable flow properties and high drug content. Also the reconstitution properties of the S-SMEDDS were not much altered. DSC study revealed that the drug was in solubilised form. SEM photographs showed that the formed particle were smooth and not much aggregation. Dissolution profile for Ramipril from S-SMEDDS was significantly higher than the conventional capsule. After three month stability study S-SMEDDS did not show any drug precipitation as well as phase separation. Our studies suggest that solid SMEDDS could be used as an effective oral solid dosage form to improve the dissolution profile of poorly aqueous soluble drug.

Keywords: S-SMEDDS, Ramipril, % Transmittance, DSC, SEM

INTRODUCTION

Self-emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or one or more hydrophilic solvents and co-solvents/surfactants1,2,3. Upon mild agitation followed by dilution in aqueous media, these systems can form fine oil-in-water (o/w) emulsions or microemulsions (SEDDS). Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification4. SEDDS produce emulsification with a droplet size between 100-300nm. While SMEDDS form transparent microemulsions with a droplet size of less than 50nm. Thus for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and the extent of absorption. However, self-emulsifying formulations are normally prepared as liquids that produce some disadvantages, for example, high production costs, low stability and portability and few choices of dosage forms. Irreversible drugs/excipients precipitation may also be problematic. More importantly, the large quantity of surfactants in the formulations can induce gastrointestinal (GI) irritation. To address these problems, Solid-SEDDS (S-SEDDS) have been investigated, as alternative approaches. Such systems require the solidification of liquid self-emulsifying ingredients into powders to create various solid dosage forms as SEDDS tablets and SEDDS pellets. Thus, S-SEDDS combine the advantages of SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance). Few techniques have been investigated to transform such liquid formulations into solid ones. Techniques reported are sprays drying5, melt granulation6,7, extrusion/spheronization8, rotary evaporator9, freeze drying10 and adsorption to solid carriers. Selecting the technique for solidification depends on many factors like, the viscosity, moisture content, and residual solvent content of the formulation. The flow properties of the produced solid SEDDS is important with regards to...
further process of conversion into dosage form like tablet, or capsule. Stability of the drug during various processes of solidification is an important issue and should be address thoroughly as most of the process may put stress condition on the drug. In our previous study we have optimised a liquid SMEDDS formulation for Ramipril which consist of Ramipril (RAM) (10 mg), Tween 80 (160mg), Cremophor EL (640mg) and Capmul MCM (CAP) as oil (200mg). The developed formulation proved to increases the dissolution of Ramipril as compared to marketed formulation. Thus the aim of the present study was to convert this liquid SMEDDS formulation into free flowing powder by a simple technique i.e. adsorption to solid carriers.

MATERIALS AND METHODS
Ramipril (RAM) was received as a gift sample from Sharya life sciences limited, (Aurangabad, India). Polyoxyethylene (20) sorbitan mono oleic acid (Twee 80), Potassium dihydrogen orthophosphate were purchased from S.D. Fine Chemicals (Mumbai, India). Cremophor EL was a generous gift form BASF Chemical (Germany), Capmul MCM (CAP) was a procured from Abitec corporation (USA). Aerosil 200 was gift sample from Elkay Chemical Pvt. Ltd. Pune. All other Chemicals were reagent grade.

EXPERIMENTAL
Preparation of self-microemulsifying formulation loaded with Ramipril
In all the formulations, the level of RAM was kept constant (i.e. 10mg). Accurately weighed RAM was placed in a glass vial; surfactants Tween 80 (160mg), Cremophor EL (640mg) and oil Capmul MCM (CAP) (200mg) were added to the vial and mixed on a cyclomixer (Remi, Mumbai) to aid mixing. Further the formulations were warmed on a water bath at 40°C to help in solubilization. The formulations were observed for isotropicity and were stored at room temperature until further use.

Preparation of solid self-microemulsifying formulation loaded with Ramipril
For the preparation of solid SMEDDS, the selected liquid SMEDDS (Ramipril content 10mg) formulation was mixed with solid carriers, Aerosil 200 at various SMEDDS to carrier ratios (3:1, 1:1 and 1:3 %w/w). Briefly, the SMEDDS was added drop wise over the solid adsorbent contained in a broad porcelain dish. After each addition, the mixture was homogenized using glass rod to ensure uniform distribution of the formulation. The resultant damp mass was passed through sieve no.120 dried at ambient temperature and stored until further use.

CHARACTERIZATION OF THE SOLID SEDDS
Powder flow properties
Angle of repose
The angle of repose for the each formulation was determined by the funnel method. The fixed amount of S- SMEDDS was allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the blend from the funnel mouth forms a pile at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the powder cone was measured. Angle of repose was then calculated with the use of the following formula: \[ \tan \theta = \frac{h}{r} \]
Where, 
\( \theta \) = angle of repos
\( h \) = height of the pile
\( r \) = average radius of the powder cone

Bulk density
Bulk density of the S- SMEDDS was determined by pouring gently 10 gm of powder through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated as follows:

\[ \text{Bulk Density (g/ml)} = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the sample}} \]

Tapped density
10 grams of sample was poured gently through a glass funnel into a 50ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated as follows:

\[ \text{Tapped Density (g/ml)} = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the sample}} \]

Carr’s compressibility index (CI)
The compressibility index of the powder blend was determined using Carr’s compressibility index:

\[ CI = \left( \frac{TBD - LBD}{TBD} \right) \times 100 \]
Where, TBD- tapped Bulk Density
LBD- loose Bulk Density

Hausner ratio
Hausner ratio was determined for characterization of flow of powder blend. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. Formula used was as follows:
**Hausner Ratio**

\[
\text{Hausner Ratio} = \frac{\text{Tapped Bulk Density}}{\text{Loose Bulk Density}}
\]

**Assay**

The quantity equivalent to 10 mg of Ramipril was dissolved in 100 ml methanol. The solution was filtered and the absorbance for drug content was measured spectrophotometrically at 210nm.

**RECONSTITUTION PROPERTIES**

%Transmittance

%Transmittance measurement of the dispersion was made to denote the reconstitution property of the formed S-SMEDDS. The S-SMEDDS (750 mg which is equivalent to 5mg of Ramipril) was accurately weighted and diluted with double distilled water to 100 ml in a 500 ml volumetric flask. To facilitate emulsification the flask was inverted once to yield a fine emulsion. The resultant dispersion kept it for 1hr to settle the solid content. The resulting emulsion were observed visually for the relative turbidity and their % transmittance were measured at 530nm by UV-160A double beam spectrophotometer (Jasco530 Japan) using double distilled water as blank.

**Globule size**

The globule size of the microemulsion formed after dispersion of S-SMEDDS was determined by photon correlation spectroscopy (PCS; Beckman N4 plus submicron particle size analyzer, Wipro, India). Formulation were diluted with double distilled water to ensure that the light scattering intensity (between 6e+004 and 1e+006), was within the instrument’s sensitivity range. Double distilled water was filter through 0.45m membrane filters (Pall Life sciences, Mumbai) prior to particle size determination.

**Differential scanning calorimetry analysis**

The physical state of RAM in solid SMEDDS was characterized by the differential scanning calorimetry (Mettler Toledo, Melbourne Australia). The samples (about 3.00 mg) were placed in standard aluminum pans, and dry nitrogen was used as effluent gas. All samples were scanned at a temperature amp speed of 10 °C/min and the heat flow from 0 to 180°C.

**Scanning electron microscopy (SEM)**

The surface morphology of S-SMEDDS was determined using analytical scanning electron microscope (JSM-6360A, JEOL, Tokyo, Japan). The samples were lightly sprinkled on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Afterwards, the stub containing the coated samples was placed in the scanning electron microscope chamber.

**In vitro release**

The quantitative in vitro release test was performed in 500 mL (0.1N HCl pH 1.3) maintained at 37 ± 0.5°C using USP type II (Scientific) dissolution apparatus. The paddles were rotated at 50 rpm. The S-SMEDDS formulations were filled into HPMC capsules “size 0” (Flofit™, Associate capsule, Pune) and were used for release studies. Five mL aliquots were collected periodically (5, 10, 20, 30, 45, 60, min) and replaced with fresh dissolution medium. Aliquots, after filtration through 0.45mm membrane filters, were analyzed by in house developed and validated HPTLC method.

**Stability study**

The formulations were subjected to stability study for a period of three months at room temperature and refrigeration conditions. After three months of storage the microemulsion were subjected to test for physical stability, drug content.

1) Physical stability: after three months the microemulsion were visualized for any precipitation of the drug, creaming, phase separation or flocculation.

2) Drug content

**RESULT & DISCUSSION**

**Preparation of solid SMEDDS of Ramipril**

The S-SMEDDS wear prepared by the solid adsorption technique by varying the adsorbent: SMEDDS ratio. It was observed as the weight of the liquid SMEDDS increased in the ratio, it took longer time in drying. This might me because the moisture content was high and ambient temperature was not sufficient for drying the formed damp mass. Thus these samples were dried in oven at a temperature of 40°C for 3 hr. These formulations were evaluated for flow properties and drug content.

**Characterization of S-SMEDDS**

Solid SMEDDS were prepared and evaluated for powder flow properties and drug content. The results are indicated in the Table 2 and 3. When the ratio of formulation: adsorbent was high (3:1) the mixture tends to be sticky and thus had poor flow properties. Also when the ratio was low (1:3) there was no uniform distribution and the volume produced was more than to be packed in “size 0” capsule. Formulation to adsorbent ratio of 1:1 showed passable flow properties and high drug content. Such result can be solely attributed the capacity adsorbent to absorb liquid and the property of the liquid formulation to get adsorbed. Aerosil 200 is micro-porous inert material and showed a limiting capacity to absorb the liquid formulation.

**%Transmittance & globule size determination**

Formulation N2 was selected was further evaluated for...
reconstitution property and were indicated by the % Transmittance & globule size determination. Solid SMEDDS are anticipated to disperse into a microemulsion having higher value for % T (formation of bluish or clear dispersion) and small globule size. The result is shown in Table 4. It is clear that even after conversion of the liquid SMEDDS into solid one there no signification alteration into the reconstitution property of the solid SMEDDS.

**DSC analysis solid SMEDDS**

The DSC thermogram of pure drug, adsorbent, and solid SMEDDS formulation are shown in Fig.1 Pure drug substance showed sharp endothermic peaks at 107°C indicating that the drug is highly crystalline. The absence of drug peaks in the solid SMEDDS formulation indicates change in the melting behavior of drug and inhibition of crystallization thus it can be confirmed that the drug has got solubilised into the excipients of the SMEDDS.

**SEM analysis**

The SEM images of solid SMEDDS and Aerosil 200 are shown in Fig. 2a &2b. The SEM images of solid SMEDDS show well-separated particles with no agglomeration. Also the rough surface of Aerosil 200 has got converted in to the smooth surface in solid SMEDDS, the possible reasons for this may be the absorption of liquid SMEDDS in to the solid carrier aerosil.

**In-vitro dissolution studies**

The drug dissolution from solid SMEDDS in capsules was compared to liquid SMEDDS and marketed formulation. Significantly higher release was observed than the marketed product but was less than the liquid formulation (Fig.5). This may be because of the longer emulsification time needed than the liquid formulation to release the drug. Also after dispersion of Solid SMEDDS there but be a formation of viscous layer of Aerosil around the drug to get release into the bulk. Thus such retardation might help in direct contact of the surfactant with GIT membrane lowering the GIT irritation and also drug is presented into solubilised form for absorption.

**Stability study**

Drug precipitation as well as phase separation in the batch N2 was not observed after until the period of two months, percent drug content of formulation & % T values wears 96.5±0.75, 96.0±1.3 respectively. Thus it can be concluded the formulation are stable.

**CONCLUSION**

The solid SEDDS of Ramipril was prepared by solid adsorbent technique, using water-insoluble adsorbent Aerosil 200. The solid SMEDDS consisted of separated particles with having smooth appearance and preserved the self-emulsification properties of the liquid SMEDDS. The optimized solid SMEDDS shown passable powder flow properties and high drug content DSC study suggested that Ramipril in the solid SMEDDS may be in the molecular dispersion state. In vitro dissolution test showed that the solid SMEDDS high drug release as compare to the marketed capsule. Thus, solid self-emulsifying system may provide a useful oral solid dosage form for poorly aqueous drug Ramipril.

**REFERENCES**

Table 1: Flow properties of S-SMEDDS

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Bulk density gm/ml</th>
<th>Tapped density</th>
<th>Compressibility index (%)</th>
<th>Hausner ratio</th>
<th>Angle of repose (degrees)</th>
<th>Flow character</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 (3:1)</td>
<td>0.2631</td>
<td>0.4545</td>
<td>72.74</td>
<td>1.727</td>
<td>-</td>
<td>Very poor</td>
</tr>
<tr>
<td>N2 (1:1)</td>
<td>0.2564</td>
<td>0.3225</td>
<td>29.99</td>
<td>1.25</td>
<td>33.10</td>
<td>passable</td>
</tr>
<tr>
<td>N3 (1:3)</td>
<td>0.3448</td>
<td>0.4166</td>
<td>20.82</td>
<td>1.20</td>
<td>26.012</td>
<td>passable</td>
</tr>
</tbody>
</table>

Table 2: Drug content of S-SMEDDS formulations:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Adsorbent</th>
<th>Ratio of Formulation : adsorbent</th>
<th>Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Aerosil</td>
<td>3:1</td>
<td>79.46</td>
</tr>
<tr>
<td>N2</td>
<td>Aerosil</td>
<td>1:1</td>
<td>96.06</td>
</tr>
<tr>
<td>N3</td>
<td>Aerosil</td>
<td>1:3</td>
<td>93.33</td>
</tr>
</tbody>
</table>

Table 3: %T & globule size of liquid and solid SMEDDS

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Globule size</th>
<th>% T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid SMEDDS</td>
<td>13.2±0.1</td>
<td>99.34±2.89</td>
</tr>
<tr>
<td>Solid SMEDDS (N2)</td>
<td>15.6±0.05</td>
<td>95.28±1.22</td>
</tr>
</tbody>
</table>

Data: mean±S.D (n=3)

Table 4: Stability study data

<table>
<thead>
<tr>
<th>TEST</th>
<th>S-SMEDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Assay</td>
<td>96.3±0.75</td>
</tr>
<tr>
<td>% Transmittance (530 nm)</td>
<td>96.0±1.3</td>
</tr>
</tbody>
</table>

Data: mean±S.D (n=6)

Figure 1. DSC therogram of Ramipril (pure), Aerosil 200 & S-SMEDDS
Figure 3. Dissolution profile of S-SMEDDS Liquid SMEDDS and Marketed formulation.

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