Formulation and Characterization of Solid Self-Microemulsifying Cefuroxime Axetil Products

Satish Puttachari¹*, Navanath V. Kalyane², Sarbani Duttagupta³ and Koushik Yetukuri⁴

¹Department of Pharmaceutics, Jawaharlal Nehru Technological University, Hyderabad 5000385, India. ²Department of Pharmacchemistry, B.L.D.E.A’s College of Pharmacy, Bijapur 586103, India. ³Department of Pharmaceutics, Jadavpur University, Kolkata 700032, India. ⁴Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bengaluru, India.

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ABSTRACT

The Cefuroxime axetil has been used in treatment of wide range of infections but exhibits poor and variable bioavailability thus it is difficult to establish optimal oral dosage schedule. The purpose of this work was to prepare stable solid self-microemulsifying drug delivery system (SMEDDS) of cefuroxime to improve the solubility and dissolution. The saturation solubility of drug in oils, solvents, surfactants and co-surfactants were determined and ternary phase diagram was drawn. Based on the results SMEDDS were prepared and characterized for self-emulsification properties and in-vitro dissolution. One of the best SMEDDS formulations was converted to S-SMEDDS by adsorption technique using maltodextrin as adsorbent. SEM of the S-SMEDDS revealed that particles were well separated and were free flowing, characterization by DSC, XRD revealed no interaction between drug and excipients. In-vitro dissolution was rapid and complete and no marked changes in physical and emulsification property were observed on stability.

KEYWORDS: Self-emulsification; Adsorption technique; Scanning electron microscope.

Introduction

Cefuroxime (C) is a second generation cephalosporin used against different kinds of bacterial infections. The prodrug, 1-acetyloxyethyl (axetil) ester of C known as Cefuroxime axetil (CA) has been used in oral dosage forms. CA is an acid stable lipophilic oral prodrug hydrolyzed to C by intestinal or plasma enzymes. It is reported to have bioavailability of 35 to 50%, maximum drug concentration occurs at 1 to 4 hours and elimination half-life is 1 to 2 hours (Ruiz-Carretero et al., 2004; Ravindra et al., 2009; Anna Szlagowska et al., 2010). It is difficult to establish optimal oral dosage schedule due to its poor and variable bioavailability.

Very limited work has been published on increasing the solubility and dissolution of CA. The approaches reported for increasing the dissolution are preparation of solid dispersion using urea as carrier (Arora SC et al., 2010) and preparation of gastro retentive mucoadhesive tablets for controlled release (Gudigennavar et al., 2013).

Self-microemulsifying drug delivery systems (SMEDDS) are the preferred method for enhancing solubility and bioavailability of poorly bio available drugs. But these formulations are having low stability, shows irreversible drugs/excipients precipitation, interaction of the content with capsule shell, capsule leaking and on storage dissolved drug or excipient reprecipitate leads to slow release or partial release of drug (Bo Tang et al., 2008).

To address these problems, S-SMEDDS have been investigated as alternative technique. Such system involves conversion of SMEDDS into powder; these can be further compressed into tablets or filled in to capsules. The S-SMEDDS are self emulsifiable, exhibits higher solubility, bioavailability and stability (Karanakar Reddy et al., 2011; Karunakar Reddy et al., 2010). Different methods have been used for manufacture of S-SMEDDS, they are adsorptions on to solid carriers, spray drying, melt extrusion etc. Among these methods, adsorption process is preferred as it involves mixing of liquid formulation with carriers in a blender to convert in to powder. The powder can be filled into capsules or mixed with suitable excipients and compressed into tablets (Puttachari et al., 2013; Katteboina et al., 2009; Katteboina et al., 2008; Koushik et al., 2013). The objective of this study was to prepare stable solid form of Cefuroxime with self-emulsifying properties to overcome the poor bioavailability.

Materials and Methods

CA was received from Indoco Remedies, Mumbai. Labrasol and Gelucire were received from Gattefosse and PEG 400 (Lutrol E-400) from Signet. Hard gelatin capsules were received from Associated Capsules, Mumbai, India and all other reagents were purchased from SD fine chemicals. All the excipients and reagents...
were used as received. Double distilled water was prepared freshly and used whenever required.

**Preparation of SMEDDS**

Saturation solubility of Cefuroxime was determined with number of surfactants, co surfactants, oils and solvents. Based on the results, Labrasol was selected as surfactant, Gelucire as co surfactant and LutrolE-400 as solvent. Tertiary phase diagram was prepared as shown in fig 1 for finding the self-emulsification area. Based on these findings prototype SMEDDS were prepared, the composition is given in Table 1. The formulations were evaluated for self-emulsification properties and *in-vitro* dissolution. (Puttachari et al., 2013). In this work optimized SMEDDS formula was converted into solid SMEDDS and characterized for solid state properties and self-emulsification properties.

**Preparation of Solid SMEDDS**

The SMEDDS was added part by part to maltodextrin, mixed well, blended in a blender and filled in to capsules (Ajay Kumar et al., 2010; Nekkanti et al., 2010). Formula composition of S-SMEDDS is mentioned in Table 2.

<p>| TABLE 2 Formula composition of prototype SMEDDS formulations. |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Labrasol E 44/14 (ml)</th>
<th>Lutrol E 44/14 (ml)</th>
<th>Gelucire 44/14 (ml)</th>
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<tr>
<td>F1</td>
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<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>F2</td>
<td>0.52</td>
<td>0.24</td>
<td>0.24</td>
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<tr>
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<td>0.6</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>F4</td>
<td>0.54</td>
<td>0.23</td>
<td>0.23</td>
</tr>
<tr>
<td>F5</td>
<td>0.64</td>
<td>0.28</td>
<td>0.08</td>
</tr>
<tr>
<td>F6</td>
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<td>0.5</td>
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<tr>
<td>F7</td>
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</tr>
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</tr>
<tr>
<td>F10</td>
<td>0.64</td>
<td>0.08</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Solid State Characterization of Solid-SMEDDS**

**Differential Scanning Calorimeter (DSC):** The thermal properties of Cefuroxime axetil and S-SMEDDS formulation was assessed by DSC. (DSC Q200 v24.2 build 107, TA Instruments, USA). About 3.0 mg of sample was placed on standard aluminum pans and dry nitrogen was used as effluent gas. The sample was scanned with temperature ramp speed of 50°C/min at the heat flow of 80-150°C/min.

**X-ray powder diffraction (XRPD):** XRPD measurements were performed with X’Pert PRO diffractometer (PAN analytical, Netherlands) at room temperature using monochromatic CuKa-radiation (k = 1.5406 A) at 30 mA and at 40 kV over a range of 2θ angles from 10° to 50° with an angular increment of 0.02° per second. (Shanmugam et al., 2011; Balakrishnan et al., 2009; Wonkyung Cho et al., 2013).

**Morphological analysis of Solid-SMEDDS:** Morphological analysis of S-SMEDDS was performed using S-4100 scanning electron microscope (Hitachi, Japan). The sample was placed on brass stub using double-sided adhesive tape and made electrically conductive by coating in vacuum (6 Pa) with platinum (6 nm/min) using Hitachi Ion Sputter (E-1030) for 240s at 15 mA. The SEM images were analyzed with an image analysis system (Image InsideVer 2.32) (Srinivasan et al., 2011; Balakrishnan et al., 2009; Wonkyung Cho et al., 2013).

**Self-emulsification time:** Self-emulsification time of formulation was determined using USP II dissolution apparatus. Approximately 1 gm of S-SMEDDS was added to 500 ml of purified water at 37°C, gentle agitation was provided by dissolution paddle rotating at 50 rpm/min. Time taken for formation of clear solution was noted as self-emulsification time, target time was fixed at 1 minute (Bhagwat et al., 2012).

**Droplet size of emulsions:** Droplet size of emulsion on addition of S-SMEDDS to water was determined by Zeta Nano S90 (Malver Instruments, UK) dynamic light scattering particle size analyzer. The measurement was done at wavelength of 635 nm at a scattering angle at 90° at 25°C, (k = 1.5406 A) at 30 mA and at 40 kV over a range of 2θ angles from 100 to 500 with an angular increment of 0.020 per second.

**In-vitro dissolution:** In-vitro dissolution study of SMEDDS, S-SMEDDS and marketed tablet product was performed as per pharmacopoeia method. Based on drug content, calculated quantity of SMEDDS and Solid SMEDDS containing 125 mg of C was filled into separate gelatin capsules. The USP dissolution apparatus-II (make: Lab India, Mumbai) was used for dissolution study. Dissolution medium of 900 ml of 0.07N HCl at 37 ± 0.5°C and speed of the paddle at 100 rpm was used. At predetermined time intervals of 5, 10, 15, 30, 45 and 60 min an aliquot (3 ml) of the sample was collected, filtered and analyzed for CA content by measuring absorbance at 282 nm using UV spectroscopy (The United States of Pharmacopoeia 2011), (make: Shimadzu corporation, Japan. Model: 1700). An equivalent volume (3 ml) of fresh dissolution medium was added at each sampling time to compensate for the sampled volume.

**Stability:** The S-SMEDDS formulation was filled in to capsules and subjected to stability study 40°C, 25°C, 2-8°C (refrigerator). The samples were withdrawn at 1, 2 & 3M and checked for appearance, self-emulsification properties and *in-vitro* dissolution.

**Results and Discussions**

**Preparation of SMEDDS**

Based on saturation solubility results, Labrasol was selected as surfactant, Gelucire as co surfactant & Lutrol E 400 as solvent. The ternary phase diagram was drawn as shown in Fig. 1. The emulsification area is denoted by closely drawn rectangles and non-emulsification area by...
broadly drawn vertical and horizontal lines. The prepared formulations were clear and moderately viscous. All the prototype formulations produced clear solution on addition to water.

**Self-emulsification time:** All the prototype formulations formed clear solution within a minute on addition to water.

**In-vitrodissolution:** In-vitro dissolution of all the prototype formulations was rapid and complete. No marked difference in dissolution profile was observed between the formulations. At 15 minutes of dissolution, nearly 100% of drug was released.

The drug loading capacity of formulation coded with No. F-10 was 152 mg/ml and was highest as compared to other formulations. Based on this property, F-10 formulation was selected for further characterization and converting in to S-SMEDDS.

**Evaluation of S-SMEDDS**

**Differential scanning calorimetry:** The DSC thermogram of Cefuroxime and S-SMEDDS are shown in Fig. 2 & 3. The thermogram of cefuroxime exhibited sharp endothermic max peak at 85.92 °C, with a glass transition point at 244 °C whereas the S-SMEDDS formulation showed broader endothermic peak with max at 81.99 °C with a glass transition point at 211.93 °C.

**X-ray diffraction study:** The X-ray diffraction of Cefuroxime and S-SMEDDS are shown in Fig. 4 & 5. No significant differences were observed between S-SMEDDS and Cefuroxime with respect to peak intensities.

**Scanning electron microscopy:** The SEM pictures of Cefuroxime (B) and S-SMEDDS (D) are shown in Fig 6 and 7 respectively. The Cefuroxime appeared as spherical particles with uniform and even surface. The S-SMEDDS particles are discrete and spherical in shape with a rough outer surface.

**Self-emulsification time:** The self-emulsification time of S-SMEDDS was well within 1 minute.

**Droplet size of emulsions:** The graphical representation of globule size of S-SMEDDS on addition to water was shown in Fig. 8. The average droplet size range of self-emulsified system was 74.03 nm. The result indicates that S-SMEDDS produced nano emulsion.

**In-vitro dissolution:** At 60 min, percentage drug release from S-SMEDDS, SMEDDS, and marketed products are 99.13%, 99.15% and 72.48% respectively. The S-SMEDDS and SMEDDS showed comparable drug release whereas release from marketed product was slow and incomplete.

**Stability:** No major change in the appearance, self-emulsification properties and in-vitro dissolution was observed up to 3 months stability as compared to initial.
**Fig. 3.** DSC of S-SMEDDS.

**Fig. 4.** XRD of Cefuroxime Axetil.
Fig. 5. XRD of S-SMEDDS.

Fig. 6. SEM of Cefuroxime Axetil.
Conclusions

The S-SMEDDS of cefuroxime was prepared by adsorption technique using 1:1 of maltodextrin as inert carrier. The SEM study revealed that the S-SMEDDS consisted of well-separated particles with smooth surface. The DSC and X-ray diffraction analysis indicates that Cefuroxime does not interacted with adsorbent or other excipients. Self-emulsification study showed that S-SMEDDS exhibited self-emulsification properties. The in-vitro dissolution of SMEDDS and S-SMEDDS were rapid and complete whereas the dissolution of marketed product was slow and incomplete. The increase in dissolution of SMEDDS and S-SMEDDS were due to its quick dispersibility and emulsifying properties. Good thermal stability of S-SMEDDS was observed as compared to SMEDDS. The S-SMEDDS system could be a novel approach for increasing the solubility of hydrophobic drugs thereby absorption and bioavailability could be improved. These formulations are easier to manufacture does not give much formulation challenges and improves the patient compliance.
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References


Address correspondence to: Satish Puttachari, B.L.D.E’s College of Pharmacy, Bijapur 586103, India.

Mob: +91-9819350531; E-mail: satishputtachari@gmail.com