Formulation and characterization of self emulsifying pellets of carvedilol

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The purpose of present study was aimed at developing self emulsifying drug delivery system in liquid and then in pellet form that would result in improved solubility, dissolution and permeability of the poorly water soluble drug carvedilol. Pellets were prepared using extrusion-spheronization technique incorporating liquid SEDDS (carvedilol, capmul MCM EP, cremophore EL, tween 20, propylene glycol), adsorbents (and crospovidone), microcrystalline cellulose and binder (povidone K-30). Ternary phase diagram was constructed to identify different oil-surfactant-cosurfactant mixtures according to the proportion of each point in it. The optimal CAR-SEDDS pellets showed a quicker redispersion with a droplet size of the reconstituted microemulsion being 160.47 nm, which was almost unchanged after solidification. SEM analysis confirmed good spherical appearance of solid pellets; DSC and XRD analysis confirmed that there was no crystalline carvedilol in the pellets. Pellets were then capable of transferring lipophilic compounds into the aqueous phase and significantly enhancing its release with respect to pure drug.


INTRODUCTION

In recent years, an increasing number of new chemical entities and many already existing drugs show low aqueous solubility, which are prone to poor oral absorption, high intra-inter-subject variability and lack of dose availability. Thus, to increase solubility of drugs which are mainly BCS II type, various solubilization techniques or formulation strategies have been developed like the use of cyclodextrins, nanoparticles, solid dispersions, permeation enhancers, liposomes, etc. (Wang et al., 2010).

Self-emulsifying drug delivery system (SEDDS) is among the methods used to improve the oral bioavailability of poorly soluble drugs by presenting and maintaining the drug in a dissolved state, in small droplets of oil, all over its transit through the gastrointestinal tract (GIT). SEDDS are composed of a mixture of oil, surfactant and cosurfactant

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that are capable of forming oil-in-water emulsions upon gentle agitation provided by the GIT motion (Abdalla, Klein, Mader, 2008).

However, SEDDS are present in the liquid state, which can be packed in hard or soft gelatin capsule directly but suffer from the drawbacks related to stability and compatibility. Incorporation of liquid SEDDS into solid dosage form is therefore compatible and desirable where spray drying, self emulsifying granules, tablet or pellets can be a preferred and viable option (Iosio et al., 2008).

Pellets have many advantages, over conventional solid dosage forms viz; flexibility in designing and developing the dosage form and improving the safety and efficacy. Because the pellets disperse freely in the gastrointestinal tract, drug absorption is maximized with a subsequent reduction in peak plasma fluctuations and hence minimizing potential side effects without lowering drug bioavailability. The pellets also reduce variations in gastric emptying rates and overall transit time and therefore a reduction of intra and inter-subject variability of plasma profiles is achieved. In addition, pellets reduce the problem of high local concentration of drugs and thus avoiding irritation that may be caused by certain active constituents.

The most widely used techniques for pellet production in the pharmaceutical industry are extrusion/spheronization (ES), solution/suspension layering, and powder layering. The process of ES has become the method of choice in the preparation of pellet-based dosage forms since it offers many advantages over the other methods, including the spherical shape with a narrow size distribution, good flow properties, low friability, uniform packing characteristics and reproducible scalability (Abdalla, Mader, 2007).

Carvedilol is a non-selective beta-blocker indicated in the treatment of mild to moderate congestive heart failure (CHF). It blocks beta-1 and beta-2 adrenergic receptors as well as the alpha-1 adrenergic receptors and is classified according to the Biopharmaceutical Classification System as a drug with low solubility and is presented as an immediate-release dosage form in the WHO essential drug list. Carvedilol is available in the market in 3.125, 6.25, 12.5, and 25mg tablets. Its serum concentration is not only affected by its low solubility but also by P-glycoprotein (P-gp) activity and first pass metabolism (http://www.drugbank.ca/drugs/DB01136).

In this study, we developed a novel CAR-loaded SEDDS pellets using extrusion-spheronization technique. An efficient CAR-SEDDS formulation was evaluated by solubility study, self-emulsifying grading test, phase diagrams, and redispersibility study. Finally, the optimum pellets were characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and reconstitution test (Hua et al., 2012).

**MATERIAL AND METHODS**

**Material**

Carvedilol was kindly gifted by Medley Pharmaceuticals Ltd. Capmul MCM EP, capmul PG12, captex 500, captex 300 were gifted by Abitec Corp., USA. Capryol 90, labrafil M 2125 CS, labrafil M 2130 CS, labrafac CC, labrasol, lauroglycol FCC, transcutol P were supplied by Gattefosse, France. Oleic acid, tween 80, tween 20, span 20, span 80, propylene glycol, PEG 400, PEG 200 were purchased from Loba Chemie Pvt. Ltd., Mumbai. Cremophore EL, cremophore RH 40 were obtained from Signet Chemicals, Mumbai. Polaxamer 407, solutol HS 15 was supplied by BASF. MCC PH 101 was obtained from RanQ Pharmaceuticals Nashik. Crospovidone, povidone K-30 and were obtained from and used in R & D Medley Pharmaceuticals Ltd., Mumbai.

**Solubility of carvedilol**

The solubility of carvedilol in various oils, surfactants and co surfactants was determined by using the shake flask method. An excess amount (50 mg) of carvedilol was added to each vial containing 1ml of the selected vehicle i.e. oil, surfactant or cosurfactant. Oils used were capmul MCM C8, capryol 90, labrafil M 2125, labrafil M 2130, captex 500, captex 300, oleic acid, capmul PG 12, capmul MCM EP. Surfactants was selected from labrafac, cremophore EL, cremophore RH 40, labrasol, tween 20, tween 80, solutol HS 15, polaxamer 407; while propylene glycol, PEG 400, transcutol P, span 20, PEG 200, lauroglycol FCC, span 80 were used as cosurfactants. After sealing of each vial proper mixing of carvedilol with the vehicles was done in order to facilitate solubilization. Mixtures were shaken for 48 h in a mechanical shaker maintained at room temperature. After 48h each vial was centrifuged at 5,000 rpm for 10min.

Undissolved carvedilol was removed by filtering through 0.44 µ Whatman filter paper. Aliquots of filtrate were diluted with methanol, and the concentration of dissolved carvedilol was quantified by U.V. Spectrophotometer at 285 nm (Hua et al., 2012).

**Selection of surfactant and cosurfactant**

The self - emulsification ability of surfactants was assessed to select the best surfactant from a large pool of surfactants. Selected oil and different surfactants were...
mixed in 1:3 (v/v) and vortexed to form a homogenous mixture (Borhade, Nair, Hedge, 2008). The ratio of oil to surfactant was decided on the basis of the requirements stated by Pouton for spontaneously emulsifying systems and represents a Type III system. Oil-surfactant mixture, 1 mL dispersed in 100 mL of double distilled water in a glass beaker was mixed with gentle stirring. Visual test was used to assess self-emulsification of surfactants in terms of dispersibility, ease of emulsification and final appearance using a grading system as mentioned below. Various cosurfactants were screened by mixing them with the selected surfactants in 1:2 v/v ratio. An oily phase was added to each of this (S+Co-S) mixture in 1:3 (v/v) and vortexed gently to form a homogenous mixture. They were evaluated using a visual test as explained below. The emulsions were allowed to stand for 2 h and their transmittance was measured at 638.2 nm by UV-1800 double beam spectrophotometer (Shimadzu, Japan) using double distilled water as blank (Date, Nagarsenker, 2007).

**Self emulsifying grading test**

The selected oil, surfactants, and cosurfactants were homogenized at different ratios (4:4:2, 3:4:3, 2:4:4 etc. v/v/v) in eppendrof tubes by vortexing for 5 min. Then 1 mL of the mixture that has a transparent appearance was added to 100 mL water with magnetic stirring (50 rpm) to determine the emulsion forming process and final appearance, which has been divided into four grades using a visual grading system.

Grade A: Rapid forming micro emulsion, which is clear or slightly bluish in appearance, self-emulsification time-less than 1 min.

Grade B: Rapid forming, slightly less clear emulsion, which has a bluish white appearance, self-emulsification time-less than 2 min.

Grade C: Bright white emulsion (similar to milk in appearance), self-emulsification time-less than 2 min.

Grade D: Dull, grayish white emulsion with a slightly oily appearance that is slow to emulsify, self-emulsification time-more than 2 min.

**Construction of ternary phase diagram**

Ternary diagrams of surfactant, cosurfactant and oil were plotted using ProSim software; each of them, representing an apex of the triangle. Ternary mixtures with varying compositions of oil, surfactant, and cosurfactant were prepared. For any mixture, the total of surfactant, cosurfactant and oil concentrations always added to 100%. The large numbers of such mixtures with varying surfactant, cosurfactant and oil concentrations were prepared in this investigation as mentioned in Table I and Table II. The percentage of surfactant, cosurfactant and oil used herein was decided based on the requirements stated by Pouton for the spontaneously emulsifying systems. Compositions were evaluated for SEDDS formation by diluting 100µl of each of the mixtures to 10ml double distilled water. The globule size of the resulting dispersion was determined by Nanophox (NX0088). Dispersions, having globule size 250nm or below were considered desirable. The area of SEDDS formation was identified in the ternary system based on the desired globule size (Date, Nagarsenker, 2007).

**Formulation optimization of SEDDS**

SEDDS were optimized for following parameters:

- Drug loading
- Amount of oily phase
- Droplet size

Different batches of SEDDS were prepared as shown in Table I and Table II. Oil, surfactant and cosurfactant were accurately measured and mixed using stirrer followed by vortex mixing until a solution (CAR-SEDDS) was obtained (Setthacheewakul et al., 2010).

**Development of CAR-SEDDS pellets**

**Preparation of CAR-SEDDS pellets**

SEDDS 20ml containing carvedilol 5% was adsorbed on (specific surface area 110 m²/g). This was

<table>
<thead>
<tr>
<th>TABLE I - Different batches of SEDDS (primary batches)</th>
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<tbody>
<tr>
<td>Ingredients (µL)</td>
</tr>
<tr>
<td>Capmul MCM EP</td>
</tr>
<tr>
<td>Cremophore EL</td>
</tr>
<tr>
<td>Tween 20</td>
</tr>
<tr>
<td>S/CoS ratio</td>
</tr>
<tr>
<td>Propylene glycol</td>
</tr>
</tbody>
</table>
further passed through mesh size 30 (595 microns) and mixed with microcrystalline cellulose PH 101, crospovidone, povidone K-30 in planetary mixture for 10 min. Sufficient quantity of water was added to form a wet mass. This wet mass was then extruded through the extruder (Umang Pharmatech Pvt. Ltd. Mumbai, India) at 10 rpm which was then spheronised on spheroniser at 500 rpm for 2-5 min. Pellets were dried in hot air oven at 60 °C for 40 min. Dried pellets were passed through mesh size 16 (1190 microns) to get uniform sized pellets. Pellets were filled into size 0 hard gelatin capsules (Iosio et al., 2011).

Characterization of CAR-SEDDS and CAR-SEDDS pellets

Scanning electron microscopy (SEM)
The outer macroscopic structure of the pellets was examined by scanning electron microscopy (JEOL JSM-6360 A). Prior to microscopy, samples were coated with carbon by sputtering for 2 min by autofine coater (JEOL JFC-1600). The samples were scanned at a voltage of 10 kV (Zhang et al., 2012).

Differential scanning calorimetry (DSC)
The physical state of carvedilol in solid SEDDS was characterized by the differential scanning calorimetry analysis by DSC-SIO6300, Japan. The sample (about 2.5 mg) was placed on standard aluminum pans, and dry nitrogen was used as effluent gas. The sample was scanned at a scanning rate of 10°C/min between 40-260 °C and 40 ml/min nitrogen flow (Prabagar et al., 2009).

X-ray powder diffraction (XRPD)
To verify the physical state of carvedilol in solid SEDDS, X-ray powder scattering measurement were carried out with an X-ray diffractometer (Bruker AXS, DH Advanced, Germany) at room temperature using monochromatic CuKα-radiation (k = 1.5406 Å) at 30 mA and at 40 kV over a range of 2θ angles from 0 ° to 40 ° with an angular increment of 0.02 °/per s (Yi et al., 2008).

**Reconstitution study**
Solid SEDDS 100 mg prepared as described above were dispersed in 10 mL distilled water, by vortex mixing (30 s), and then incubated for 30 min at 25 °C (Borhade, Nair, Hedge, 2008). The particle size of reconstituted solid SEDDS emulsion was determined by Nanophox (NX0088) (Yi et al., 2008).

**In vitro dissolution Test**
The quantitative in vitro release test was performed in 500 mL of 0.1 N HCl using USP XXIV dissolution apparatus 1. The basket was rotated at 50 rpm. The liquid and solid SEDDS formulations (pellets in hard gelatin capsules) were analysed to dissolution studies. Results were compared with those of plain drug and marketed formulation. During the release studies, 5 mL sample of the medium was taken out and subjected to drug analysis using UV spectrophotometrically at 285 nm. The removed volume was replaced each time with 5ml of fresh medium. Similarly, dissolution studies were also done in pH 4.6 acetate buffer and pH 6.8 phosphate buffer to study the effect of pH on carvedilol release.

**Permeability studies**
The methods employed were modified with respect to the experimental procedures described in the literature. To check the intraduodenal permeability, the duodenal part of the small intestine of the chick was isolated and taken for in vitro diffusion study. Then this tissue was thoroughly washed with Ringer’s solution to remove the mucous and lumen contents. The liquid SEDDS sample was diluted with 1 mL of distilled water while for the tablet and pellet sample a suspension was made in distilled water. The resultant sample (6.25 mg/mL) was injected into the lumen of the duodenum using a syringe, and two ends of intestine were tightly closed. Then the tissue was placed in a chamber of organ bath with continuous aeration. The receiver compartment was filled with 30 ml of phosphate-buffer (pH 6.8). The absorbance was measured using a UV-VIS spectrophotometer at a wavelength of 285 nm.

### TABLE II - Different batches of SEDDS (final batches)

<table>
<thead>
<tr>
<th>Ingredients (µL)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capmul MCM EP</td>
<td>350</td>
<td>400</td>
<td>450</td>
<td>350</td>
<td>400</td>
<td>450</td>
</tr>
<tr>
<td>Cremophore EL</td>
<td>433</td>
<td>400</td>
<td>367</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Tween 20</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>433</td>
<td>400</td>
<td>367</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>217</td>
<td>200</td>
<td>183</td>
<td>217</td>
<td>200</td>
<td>183</td>
</tr>
<tr>
<td>Droplet Size (nm)</td>
<td>136.22±1.32</td>
<td>142.89±1.17</td>
<td>246.29±1.38</td>
<td>213.63±1.27</td>
<td>244.95±1.24</td>
<td>291.83±1.15</td>
</tr>
</tbody>
</table>
The percent diffusion of the drug was calculated against time and plotted on a graph (Ghosh et al., 2006).

RESULTS AND DISCUSSION

Solubility of carvedilol

Among the various oils higher solubility of carvedilol was found in capmul MCM EP, so it was selected as the oil phase. Data suggested that drug has more solubility in MCT rather than LCT because medium chain triglycerides (MCT) possess higher ester content per gram than long chain triglycerides (LCT), so drug has higher solubility in MCT than LCT Among the various surfactants, solubility of carvedilol was found highest in labrasol, cremophore EL and tween 20 while among the cosurfactants higher solubility was found in transcutol P, propylene glycol, polyethylene glycol 200. According to self emulsification ability and % transmittance study cremophore EL and tween 20 were selected as surfactants and propylene glycol was selected as cosurfactant for further study. Solubility of carvedilol in various vehicles (oil, surfactant, cosurfactant) is shown in Figure 1.

Self-emulsifying grading test

It was seen that as the oil component increases in the formulation beyond a certain limit there was generation of non-clear dispersion. Among the X1-X4 and Y1-Y4 the X3, X4, Y3, Y4 show grade B while X1, X2, Y1, Y2 exhibited grade A type emulsion. Formulation F1-F6 shows grade B type of emulsion.

Ternary phase diagrams

Ternary phase diagrams of oil (capmul MCM EP), Surfactants (cremophor EL, tween 20) and cosurfactant (Propylene glycol) were constructed (Figure 2). The largest microemulsion region was observed when cremophore EL was used as surfactant. The coloured region indicates better self-emulsification region. Self-emulsion formation area was increased with an increase in surfactant concentration.

Formulation optimization of SEDDS

Based on the ternary phase diagram, eight different preliminary batches of SEDDS were formulated using capmul MCM as oil, cremophore EL and tween 20 as a surfactant and propylene glycol as cosurfactant (Table I). For further characterization through particle size analysis formulation, which contained cremophore EL as a surfactant showed lower particle size than other formulations. Different batches F1-F6 (Table II) were prepared using capmul MCM EP, cremophore EL, tween 20 and propylene glycol.

Though the batch containing 10% oil had the least particle size the required amount of carvedilol could not be solubilized into it. The same was the case with SEDDS containing 20 or 30% oil. Beyond 40% the globule size
was get increased which was not acceptable. So, according to % of oil content, drug loading and droplet size analysis formulation F2 and F5 were taken for further study.

Development of CAR-SEDDS pellets

Preparation of CAR-SEDDS pellets

Solid SEDDS were successfully prepared using colloidal silicon dioxide and microcrystalline cellulose PH 101 as a solid carrier, crospovidone as a disintegrant and povidone K-30 as a binder. Solid pellets were prepared using an extrusion-spheronization technique and then filled into 0 size gelatin capsule.

Characterization of CAR-SEDDS pellets

Scanning electron microscopy (SEM)

Pellet surfaces and cross-sections were studied using scanning electron microscope. As shown in Figure 3 SEM micrographs of carvedilol-SEDDS pellets reveal that the pellets had a spherical shape. Carvedilol-SEDDS appear to be entrapped in the matrices. The images show that the surface of the pellets is full of pinholes, which probably allow the ingress of the aqueous phase into the matrix, and allow diffusion of the entrapped carvedilol from SEDDS out of the surface and the core of the matrix. Due to this, the liquid carvedilol-SEDDS is released through the mini-channels and then forms oil-in-water microemulsion thus making carvedilol ready for absorption as an oily droplet solution.

X-ray powder diffraction (XRPD)

From X-ray powder diffractograms shown in Figure 5, the internal physical state of carvedilol in the solid SEDDS was further verified. No obvious peaks representing crystals of carvedilol were seen for the solid SEDDS, indicating that the drug is present in the molecularly dissolved state in solid SEDDS (Dixit, Nagarsenker, 2008).

Reconstitution properties of CAR-SEDDS pellets

The average droplet size of emulsion from both liquid and solid SEDDS was less than 250 nm. The droplet size of the emulsion from the solid SEDDS was no significantly different from the droplet size of the liquid SEDDS. From these results, incorporating the liquid SEDDS in colloidal silicon dioxide and MCC PH 101 by extrusion and spheronization did not have a remarkable effect on droplet size. The solid SEDDS preserved the self-emulsification performance of the liquid SEDDS. Droplet size of liquid SEDDS is 142.89 nm and that of solid SEDDS is 160.47 nm.

The mean droplet size of the diluted SEDDS preconcentrates was low, and all were found to be in the
Formulation and characterization of self emulsifying pellets of carvedilol

Droplets size results of SEDDS formulation are reported in Table III. In all eight formulations, which were tested, the droplet size increased upon decreasing amount of S-Co-S mix. SEDDS shows good uniformity in the droplet size distribution even after diluted with water.

**In vitro dissolution Test**

As shown in Figure 6, the release performance of CAR from solid and liquid SEDDS was significantly improved compared to conventional tablets and plain drug. From the *in vitro* dissolution studies, it was observed that, plain drug showed very less release (46%) after 60 min, 6.25 mg immediate release tablet showed only 68% release after 60 min, whereas, liquid SEDDS showed a rapid release of 75% (F2) and 65% (F5) in 0.1 N HCl in just 10 min and 86% (F2) and 80% (F5) in 20 min. Solid SEDDS showed a release of 90% (F2) and 80% (F5) within 30 min only.

**Permeability studies**

*In vitro* intestinal permeability data are shown in Figure 8. The drug diffused at a faster rate from the SEDDS than from the tablet dosage form. The total percentage diffusion was much higher for the SEDDS than for the tablet dosage form. After 1 hour of diffusion, 97.8% of the drug was diffused from the liquid SEDDS, as compared to 91% from the CAR-SEDDS pellets and 32% from marketed tablet.

**Table III - Droplet size of SEDDS**

<table>
<thead>
<tr>
<th>Batch</th>
<th>X1</th>
<th>X2</th>
<th>X3</th>
<th>X4</th>
<th>Y1</th>
<th>Y2</th>
<th>Y3</th>
<th>Y4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23.41±0.64</td>
<td>33.41±0.55</td>
<td>130.89±0.68</td>
<td>144.84±1.27</td>
<td>37.62±0.58</td>
<td>69.25±0.67</td>
<td>196.33±0.64</td>
<td>249.58±1.38</td>
</tr>
</tbody>
</table>

**Figure 6 - In vitro** Dissolution release study of marketed drug, plain drug and CAR-SEDDS pellet formulations F2 & F5 in 0.1 N HCl, where, L F2-SEDDS F2, L F5-SEDDS F5, S F2-solid SEDDS F2, S F5-solid SEDDS F5, MR-market product, Plain-plain drug tablet.

Figure 7 illustrates that, % drug release from CAR SEDDS pellets was 100% and surprisingly same at different pH conditions viz; 0.1 N HCl, pH 4.6 and pH 6.8 buffer while plain drug does not show it. This indicates that SEDDS has rendered the release of carvedilol independent of the pH which is not so with the plain drug nor with the marketed product.

Carvedilol as such is reported to have pH dependant solubility, maximum solubility being in the acidic pH. One of the objectives of the present study was also to nullify the effect of pH on the release of carvedilol so as to achieve uniform drug release through GIT. So, the release of carvedilol, the prepared CAR-SEDDS and the marketed product was seen in different pH conditions, which mimic the in-vivo conditions.

**Figure 7 - Effect of pH on carvedilol release.**

**Figure 8 - In vitro** intestinal permeability of liquid SEDDS, pellets and marketed formulation.
CONCLUSION

Carvedilol has only 25-35% absolute bioavailability due to high first pass metabolism and insolubility in water. The present research work was directed towards the development of SEDDS which were incorporated into pellets, which would increase solubility and permeability of carvedilol.

Type of oil, surfactant and cosurfactant concentration play a vital role in SEDDS formation. Based on the solubility studies capmul MCM EP was selected as oil phase, cremophore EL, tween 20 was selected as the surfactant and propylene glycol was selected as cosurfactant based on its emulsification properties and the resulting droplet size.

Fastest reconstitution and smallest particle size was achieved with formulation F2, in which the liquid SEDDS had a droplet size of 142.89 nm and solid SEDDS had a droplet size of 160.47 nm.

Conclusively, a SEDDS consisting of capmul MCM EP (40% v/v) emulsified with cremophore EL (40% v/v) and propylene glycol (20% v/v) was successfully developed with an increased dissolution rate, increased solubility and ultimately, increased permeability of a poorly water soluble drug, carvedilol. The liquid CAR SEDDS were converted into solid pellets by using the extrusion spheronization technique. The SEM characterization of SEDDS pellets revealed spherical shape of pellets. The developed formulation exhibited significantly higher dissolution property compared to 6.25 mg immediate release marketed tablet.

Thus, the SEDDS pellets could be an effective formulation strategy for other oil-soluble drugs with low oral absorption.

LIST OF ABBREVIATIONS

CAR: Carvedilol
SEDDS: Self emulsifying drug delivery system
SEM: Scanning electron microscopy
XRD: X-ray diffraction
ES: Extrusion-spheronization
DSC: Differential scanning calorimetry
rpm: Revolutions per minute
nm: Nanometer
GIT: Gastro intestinal tract

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