Formulation and Evaluation of Carvedilol Liquisolid Tablets

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ABSTRACT

The present study is an attempt to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs, such as Carvedilol. A novel “Powder Solution Technology” involves absorption and adsorption efficiency, which makes use of liquid medications, admixed with suitable carriers, coating materials and formulated into a free flowing, dry looking, non adherent and compressible powder forms. Based upon a new mathematical model expression, improved flow characteristics and hardness of the formulation have been achieved by changing the proportion of Avicel® PH 200 and Aerosil® PH 200 from 20:1 ratio to 5:1. Higher dissolution rates (90-99.9%) were observed in all liquisolid formulations, when compared with a conventional marketed product (CARCA® 12.5 mg) within twenty minutes. The crystalline state of drug is changed to amorphous state due to liquisolid formation and is confirmed by both differential scanning calorimetry and X-ray diffraction results. This transition occurs because the drug is in solution form. The amorphous form exhibited increased wetting properties because of subsequent increased surface area of the particle size. Aging studies indicate, there is no significant effect on dissolution rate, hardness of the formulation of fresh and stored tablets at 40 ±2 c/ 75±5% relative humidity for 3 months.

KEYWORDS: Carvedilol, liquisolid tablets, dissolution rate, solubility.
INTRODUCTION

One of the major concerns of present Pharmaceutical research is how to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs. During the past few years many techniques have been developed such as drug micronization, solid dispersions, co-precipitation, lyophilization, micro – encapsulation, use of pro-drug, drug derivatization processes and inclusion of drug solutions into soft gelatin capsules (1).

Micronization is the most common method used to increase the surface area of a drug, but this becomes less effective, when the drug is formulated as tablets or capsules (2-4). In case of soft gelatin capsules, Ebert’s (5) review stated that these products demonstrated most efficient bioavailability since the drug was already in solution form. The formulation of soft gelatin capsules is expensive and requires sophisticated technology; better approaches are still available to prepare the liquid oily medications and drug solutions of water insoluble solid drugs.

A novel “Powder Solution Technology” makes use of liquid medications admixed with suitable carriers, coating materials and formulated into a moderately flowing, dry looking, non adherent and compressible powder forms with increased drug dissolution rates was employed in this study. Liquisolid compacts are formulated using non volatile oils as vehicles to produce liquid medications such as oily liquid drugs, solutions or suspensions of water insoluble solid drugs (6). The quantities of various excipients required for powder solution formulations are determined in accordance with a new mathematical model expression (7). The absorbate molecules diffuse inside the absorbent and are eventually captured by the powder particles within their bulk, and thus absorption of the liquid occurs. Adsorption is the phenomenon in which liquid is not truly absorbed and instead of being dispersed throughout the interior of the solid, the molecules only cling to its available surface, internal and external. Depending on the sorbent properties, both of these processes can occur simultaneously, thus referred to as sorption. Initially the liquid is absorbed into the interior of the particles and captured by its internal structure after saturation of this process then adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occurs (8).

Shewale et al (9) examined the effect of pH and concentration of hydroxypropyl-β-cyclodextrin on the solubility of Carvedilol and observed that hydroxypropyl-β-cyclodextrin inclusion resulted in increased solubility of Carvedilol at different pHs. Poor aqueous solubility has always been a very challenging obstacle. The present research was aimed at improving the solubility of poorly water soluble drugs such as Carvedilol by using liquisolid technique (6, 10-25). Carvedilol is a non-cardio selective beta-blocker and also has vasodilating properties attributed mainly to its blocking activity at α₁ receptors. It is used in the management of hypertension. It is well absorbed from the gastrointestinal tract, but is subject to considerable first pass metabolism in the liver (25).
MATERIALS AND METHODS
Carvedilol was obtained as gift sample from Vilin Biomed (Roorke, India). Microcrystalline cellulose 200 (Avicel® PH 200) and colloidal silicon dioxide (Aerosil® PH 200) were received as gift samples from Cadilla Pharmaceuticals (Ahmedabad, India). Crospovidone was also obtained as a gift sample from Alred (Roorke, India) and Poly Ethylene Glycol 400 (PEG 400) was procured from S.d. fine chem. Ltd. (Mumbai, India).

Calculation of the load factor (L_f)
In the present study, Polyethylene glycol 400 (PEG 400) was used as a non-volatile solvent. Avicel® PH 200 and Aerosil® PH 200 were used as carrier and coating materials respectively. To calculate the loading factor, 30 g of Avicel® PH 200 and Aerosil® PH 200 in 2:1 (w/w) ratio were added to the PEG 400 and blended for 10 min (16). Using a flow meter higher than 10cm³/s was considered as an acceptable flow rate and the step was repeated to achieve optimum flow property. According to new mathematical model expression of liquisolid systems, liquid load factor is the ratio of the weight of liquid medication (W) and the weight of the carrier system (Q).

\[ L_f = \frac{W}{Q} \]  

Depending on the carrier and coating material ratio (R) acceptable and compressible properties were obtained. Different carrier (Q) and coating material (q) ratios ranging from 5, 10, 15, 20 were taken (12).

Load Factor preparation of liquisolid tablets.
Specific quantities of previously weighed solid drug were mixed with PEG 400 and constantly stirred until a homogeneous liquid medications were obtained for 10%, 20% and 30% respectively. According to a new mathematical model expression (16) calculated amounts of carrier (Avicel® PH 200) (Q) was added to the liquid medication and blended for 10 minutes. The resulting mixture was blended with the calculated amounts of coating material (Aerosil® PH 200) (q). Crospovidone (5%) were added as a super disintegrant to the mixture of carrier and coating materials and blended thoroughly. The prepared liquisolid systems were compressed into tablets by using 16 station rotary compression machine (Cadmach, Ahmedabad).
Table 1:
Key formulation characteristics of prepared formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Carvedilol conc. in PEG 400 (mg)</th>
<th>Avicel® PH 200 (mg)</th>
<th>Aerosil® PH 200 (mg)</th>
<th>Unit dose weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>10%</td>
<td>5</td>
<td>0.400</td>
<td>0.80</td>
</tr>
<tr>
<td>F2</td>
<td>10</td>
<td></td>
<td>0.400</td>
<td>0.40</td>
</tr>
<tr>
<td>F3</td>
<td>15</td>
<td></td>
<td>0.400</td>
<td>0.26</td>
</tr>
<tr>
<td>F4</td>
<td>20</td>
<td></td>
<td>0.400</td>
<td>0.20</td>
</tr>
<tr>
<td>F5</td>
<td>20%</td>
<td>5</td>
<td>0.200</td>
<td>0.40</td>
</tr>
<tr>
<td>F6</td>
<td>10</td>
<td></td>
<td>0.200</td>
<td>0.20</td>
</tr>
<tr>
<td>F7</td>
<td>15</td>
<td></td>
<td>0.200</td>
<td>0.13</td>
</tr>
<tr>
<td>F8</td>
<td>20</td>
<td></td>
<td>0.200</td>
<td>0.10</td>
</tr>
<tr>
<td>F9</td>
<td>30%</td>
<td>5</td>
<td>0.200</td>
<td>0.40</td>
</tr>
<tr>
<td>F10</td>
<td>10</td>
<td></td>
<td>0.200</td>
<td>0.20</td>
</tr>
<tr>
<td>F11</td>
<td>15</td>
<td></td>
<td>0.200</td>
<td>0.13</td>
</tr>
<tr>
<td>F12</td>
<td>20</td>
<td></td>
<td>0.200</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*R* = carrier and coating material ratio, *L* = loading factor, formulations contain 5% crospovidone.

Pre compression studies of the liquisolid powder systems
Pre-compression studies may play a key role in dose variations, to get a uniform filling of tablet dies and acceptable flow properties are required for the proposed liquisolid powder systems. Angle of repose, Carr’s Index and Hausner’s Ratio were calculated (26-31). The fixed height cone method was used to determine the angle of repose in triplicate and the average value was calculated for each powder:

\[ \theta = \frac{H}{R} \]  

(2)

Hausner’s Ratio was determined by following equation:

\[ \text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \]  

(3)

Carr’s Index =

\[ \frac{(\text{tapped density} – \text{bulk density}) \times 100}{\text{tapped density}} \]

Differential scanning calorimetry (DSC) studies
The possible physical and chemical interaction between the drug and excipient was determined by using Differential scanning calorimetry.
(DSC Q100 V9.7). Approximately 2-3 mg of Carvedilol drug, Avicel® PH 200, Aerosil® PH 200 and crushed Carvedilol liquidolid tablet powder were sealed individually in a 40-µl aluminum pans at a constant heating rate of 5°C/min under nitrogen atmosphere. The probes tests were done at temperature versus heat flow heating range from 5°C - 150°C.

**X-Ray Powder diffraction (XRD) studies**

X-ray powder diffraction studies were conducted for characterization of the different polymorphic forms of solvated and unsolvated forms of the compounds. These samples were then exposed to Cu-Kα radiation at a scan rate of 2°/ min over the 20 range of 3°-40°.

**In Vitro Dissolution studies**

The in vitro drug release studies were performed with Unites States Pharmacopeia type II paddle apparatus using 900 mL of 0.1 N HCl with paddle rotation of 50 rpm at 37°C ± 0.5°C. The samples were withdrawn at specific time intervals and replaced by the fresh medium. Obtained samples were filtered on a 0.45µm filter paper and analyzed at 284 nm by using on a UV visible spectrophotometer (UV-2202, systronics, India).

**RESULTS**

Angle of repose, Carr’s index and Hausner’s ratio were performed for all the Carvedilol liquidolid formulation and presented in Table 3. Among those F1, F5 and F9 exhibited better flow properties (θ=33.9, 33.5, 33.5; Carr’s Index =14.2, 12.5, 11.5; Hausner’s ratio=1.16, 1.14, 1.15 respectively) when compared to other formulations. All the liquidolid tablets had acceptable friability and percentage loss in weight not more than 1%. All the liquidolid tablets exhibited acceptable durability and resisted abrasion during handling. The liquidolid formulations were compressed at a compression force such that they could pass the friability and hardness tests, while at same time maintaining the required disintegration time and dissolution profiles. Disintegration studies were performed for the liquidolid formulations and all the exhibited disintegration time of less than 5min. All the formulations should meet the required United States Pharmacopeia specifications.
Table 2:
Loading Factor for Carvedilol Liquisol tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Carvedilol conc. in PEG 400</th>
<th>R*</th>
<th>*L_f=W/Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>10%</td>
<td>5</td>
<td>0.312</td>
</tr>
<tr>
<td>F2</td>
<td>10%</td>
<td>10</td>
<td>0.312</td>
</tr>
<tr>
<td>F3</td>
<td>15%</td>
<td>15</td>
<td>0.312</td>
</tr>
<tr>
<td>F4</td>
<td>20%</td>
<td>20</td>
<td>0.312</td>
</tr>
<tr>
<td>F5</td>
<td>20%</td>
<td>5</td>
<td>0.312</td>
</tr>
<tr>
<td>F6</td>
<td>10%</td>
<td>10</td>
<td>0.312</td>
</tr>
<tr>
<td>F7</td>
<td>15%</td>
<td>15</td>
<td>0.312</td>
</tr>
<tr>
<td>F8</td>
<td>20%</td>
<td>20</td>
<td>0.312</td>
</tr>
<tr>
<td>F9</td>
<td>30%</td>
<td>5</td>
<td>0.208</td>
</tr>
<tr>
<td>F10</td>
<td>30%</td>
<td>10</td>
<td>0.208</td>
</tr>
<tr>
<td>F11</td>
<td>15%</td>
<td>15</td>
<td>0.208</td>
</tr>
<tr>
<td>F12</td>
<td>20%</td>
<td>20</td>
<td>0.208</td>
</tr>
</tbody>
</table>

Loading factor was calculated according to the mentioned equation no.1 in that liquid medication (W) is 120 for F1 to F4 Formulations, 60 for F5 to F8 formulations and 42.5 for F9 to F12. Carrier material (Q) is mentioned above Table 1.
Table 3:
Micromeritic parameters and evaluation studies of Carvedilol liquisolid tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose(θ)</th>
<th>Carr's index (%)</th>
<th>Hardness Test (kg/cm²)</th>
<th>Friability test (%)</th>
<th>Disintegration time( min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>35.53±0.60</td>
<td>14.20±0.36</td>
<td>5.8±0.20</td>
<td>0.26</td>
<td>3.10±0.40</td>
</tr>
<tr>
<td>F2</td>
<td>37.90±0.75</td>
<td>19.98±0.34</td>
<td>5.9±0.30</td>
<td>0.48</td>
<td>3.40±0.20</td>
</tr>
<tr>
<td>F3</td>
<td>38.20±0.40</td>
<td>23.20±0.80</td>
<td>5.5±0.20</td>
<td>0.52</td>
<td>2.40±0.30</td>
</tr>
<tr>
<td>F4</td>
<td>39.50±0.50</td>
<td>22.50±0.50</td>
<td>5.1±0.30</td>
<td>0.61</td>
<td>2.50±0.35</td>
</tr>
<tr>
<td>F5</td>
<td>33.90±0.20</td>
<td>12.50±1.20</td>
<td>3.9±0.20</td>
<td>0.21</td>
<td>1.50±0.20</td>
</tr>
<tr>
<td>F6</td>
<td>34.70±0.35</td>
<td>13.30±0.90</td>
<td>3.8±0.20</td>
<td>0.36</td>
<td>1.40±0.30</td>
</tr>
<tr>
<td>F7</td>
<td>36.20±0.42</td>
<td>17.20±0.50</td>
<td>3.8±0.30</td>
<td>0.49</td>
<td>1.35±0.20</td>
</tr>
<tr>
<td>F8</td>
<td>36.40±0.40</td>
<td>17.20±1.50</td>
<td>3.7±0.30</td>
<td>0.51</td>
<td>1.30±0.20</td>
</tr>
<tr>
<td>F9</td>
<td>33.50±0.15</td>
<td>11.50±1.90</td>
<td>4.1±0.40</td>
<td>0.23</td>
<td>3.40±0.35</td>
</tr>
<tr>
<td>F10</td>
<td>34.90±0.20</td>
<td>17.50±1.20</td>
<td>4.5±0.30</td>
<td>0.34</td>
<td>4.50±0.40</td>
</tr>
<tr>
<td>F11</td>
<td>34.80±0.40</td>
<td>15.40±0.80</td>
<td>4.9±0.20</td>
<td>0.41</td>
<td>4.10±0.20</td>
</tr>
<tr>
<td>F12</td>
<td>35.40±0.30</td>
<td>16.90±0.50</td>
<td>4.8±0.20</td>
<td>0.49</td>
<td>4.00±0.20</td>
</tr>
</tbody>
</table>

F1-F4 formulations containing 10% and F5-F8 formulations containing 20% drug solution, (Fig.1, Fig.2) exhibited similar drug release profiles within 20 minutes with very small variations but these release profiles were found to be higher for the F1, F2, F3, F4 formulations, probably due to the higher amount of PEG 400, which might have contributed to the increase in the saturation solubility of the drug at the microenvironment. At this microenvironment, it may be possible that the infinite amounts of PEG 400 diffusing with the drug molecules out of a single liquisolid particle and excessive amount of Avicel ® PH 200 may be responsible for its disintegration property (10).
**Figure 1:**
Dissolution profiles of 10% drug solution of Carvedilol liquisolid tablets mean

![Graph](image1)

*Mean ±S.D (n=6)*

**Figure 2:**
Dissolution profiles of 20% drug solution of Carvedilol liquisolid tablets mean

![Graph](image2)

*Mean ±S.D (n=6)*
F1 and F5 formulations also showed the higher dissolution profiles (98.4%, 98.35%) when compared to the rest of the three formulations in 10% (F2=94.6%, F3=93.4%, F4=92.3%) and 20% (F6=95.3%, F7=93.3%, F8=90.14%). This is due to the higher amount of Aerosil \textsuperscript{®} PH 200 which aids in adsorbing excessive amount of liquid in the physical mixture.

**Figure 3:**
**Dissolution profiles of 30% drug solution of Carvedilol liquisolid tablets**

![Dissolution profiles of 30% drug solution of Carvedilol liquisolid tablets](image)

Formulations F9, F10, F11 and F12 containing 30% drug solution in Fig. 3 had the lowest drug release profiles (F9=92.3%, F10=89.4%, F11=87.3%, F12=85.1%) when compared to 10% and 20%, because of low amount of PEG 400. In these formulations the drug is dispersed in the solvent, forming a drug suspension with no further change in drug state. Fig. 4 depicts Carvedilol liquisolid tablets compared with Carvedilol conventional CARCA \textsuperscript{®} 12.5 mg marketed product (71.11%), F1 and F5 formulations attained maximum result within 20 minutes and showed the highest dissolution pattern in both rate and extent of drug release.
Figure 4:
Comparison dissolution rate profiles between Carvedilol liquisolid tablets (F5) and conventional tablets CARCA ® tablets.

![Dissolution Rate Profiles](image)

Mean ± S.D (n=6)

DSC thermograms of pure Carvedilol and other excipients in Fig. 5 indicate qualitative information about the physical mixture. Pure Carvedilol in Fig. 5d shows a sharp characteristic endothermic peak at 115.85°C, is in agreeing with its melting temperature (Tm) and denoting that Carvedilol is in crystalline state. Thermograms of Avicel ® PH 200 in Fig. 5c shows two broad endothermic peaks at 43.2°C and 118°C that might explain the volatilization of absorbed water followed by melting decomposition. Fig. 5b confirmed coating material Aerosil ® PH 200 was almost in an amorphous state and did not show any sharp peaks. The thermal behaviors of the liquisolid physical mixture, shown in Fig. 5a with the disappearance of both characteristic peaks of Carvedilol, correspond with formulation of the drug solution in the liquisolid physical mixture. This can be attributed to the fact that the drug is in a dissolved molecular state. The formation of a new broad endothermic peak at 98.4°C may be due to the melting and decomposition of the whole liquisolid system. Such disappearance of the drug peaks upon the formulation of the liquisolid system is indicative of complete formation of an amorphous solid solution.
Figure 5:
DSC thermograms of (a) liquisolid system (b) Aerosil® PH 200 (c) Avicel® PH 200 (d) pure Carvedilol

XRD is a technique of choice to identify different polymorphic forms of a compound and also used to identify the solvated and unsolvated forms of a compound. X-ray diffraction studies of pure Carvedilol in Fig. 6a demonstrated a sharp, distinct peak notably at diffraction angles of 5.7°, 12.9°, 14.8°, 17.4°, 18.4° and 24.2° confirming that it is in the crystalline state. The X-ray diffraction of the liquisolid powder in Fig. 6b indicating the absence of Carvedilol constructive peak points out that Carvedilol has almost entirely converted from crystalline to the amorphous state. This transition is due to Carvedilol solubilization in the liquid vehicle that was absorbed into the carrier such as Avicel® PH 200 and adsorbed on to the coating material such as Aerosil® PH 200. Fig. 6d shows Carvedilol characteristic peaks were observed in the physical mixture implying that its crystalline structures remained unchanged during the physical mixing. These results confirm that improvement in dissolution rates as well as apparent solubility was obtained because of the solubilization of Carvedilol.
CONCLUSION:
Powder solution technology is one of the promising approaches to increase dissolution rate and is confirmed by the experimental results. Rationale of the present study suggesting that the use of Avicel® PH 200 can provide good flow properties and hardness. DSC and XRD results demonstrated Carvedilol had almost entirely converted from crystalline to amorphous state. All Carvedilol liquisolid tablets showed highest dissolution rate when compared with conventional marketed product CARCA®12.5 mg tablets. This was due to increase in wetting properties and surface area of drug available for dissolution media and thus the Carvedilol liquisolid tablets were stable. Aging studies had no effect on hardness or dissolution profile.
REFERENCE


