ORIGINAL ARTICLE

Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan

Chella Naveena, Nalini Shastri, Rama Rao Tadikonda

National Institute of Pharmaceutical Education and Research, Hyderabad 500037, India
Blue Birds College of Pharmacy, Hanamkonda 506001, India
Department of Pharmacy, Acharya Nagarjuna University, Guntur 522510, India

Received 8 March 2012; revised 29 March 2012; accepted 18 May 2012

KEY WORDS
Liquisolid compact; Valsartan; Dissolution; Poorly soluble drug

Abstract The aim of this study was to improve the dissolution rate of the poorly soluble drug valsartan by delivering the drug as a liquisolid compact. Liquisolid compacts were prepared using propylene glycol as solvent, Avicel PH102 as carrier, and Aerosil 200 as the coating material. The crystallinity of the newly formulated drug and the interaction between excipients was examined by X-ray powder diffraction and Fourier-transform infrared spectroscopy, respectively. The dissolution studies for the liquisolid formulation and the marketed product were carried out at different pH values. The results showed no change in the crystallinity of the drug and no interaction between excipients. The dissolution efficiency of valsartan at 15 min was increased from 4.02% for plain drug and 13.58% for marketed product to 29.47% for the liquisolid formulation. The increase in the dissolution rate was also found to be significant compared to the marketed product at lower pH values, simulating the gastric environment where valsartan is largely absorbed. The liquisolid technique appears to be a promising approach for improving the dissolution of poorly soluble drugs like valsartan.

© 2012 Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association. Production and hosting by Elsevier B.V. All rights reserved.
1. Introduction

The oral route is the most preferred means of drug administration due to the ease, high patient compliance, and low cost of production. The drug must be presented in solution form for absorption through gastrointestinal tract (GIT) when given orally. In the case of poorly soluble drugs, dissolution is the rate-limiting step in absorption process. Generally, compounds with aqueous solubility lower than 100 μg/mL show dissolution-limited absorption and erratic and/or incomplete absorption from the gastrointestinal tract of animals and humans. Advancements in the fields of biotechnology and drug discovery have led to the discovery of increasingly large number of active molecules. However, 40% of all newly developed drugs are poorly soluble or insoluble in water, leading to ineffective absorption and therapeutic failure.

Various techniques are reported to improve the dissolution of poorly soluble drugs, including solid dispersions, crystal engineering, ball milling, self-emulsifying drug delivery systems and the use of mesoporous silica carriers. Recently, the liquisolid technique has shown promise for improved dissolution.

The concept of liquisolid tablets was developed from powdered solution technology that can be used to formulate liquid medication. A liquisolid system is defined as dry, non-adherent, free-flowing and compressible solid using carrier and coat materials. In this technique, the drug is dissolved in a non-volatile liquid and converted to dry, free-flowing and compressible solid using carrier and coat materials. Since non-volatile solvents are used to prepare the drug solution/suspension, the liquid is not evaporated and the drug is carried in a liquid system and is dispersed throughout the final product. A mathematical model by Spireas and Bolton was used to calculate the required quantities of carrier and coating material to be added to produce acceptable flow and compressibility. The liquisolid technique has shown promising results for the drugs like carbamazepine, atorvastatin calcium, and fenofibrate. Valsartan is an antihypertensive agent which selectively inhibits the type 1 angiotensin II receptor. Valsartan is poorly soluble and the aqueous solubility was reported to be less than 1 mg/mL. The drug is rapidly absorbed following oral administration with a bioavailability of about 23%. Valsartan is weakly acidic so it is poorly soluble in the acidic environment where its absorption window exists. It is necessary to improve the dissolution rate in stomach so as to improve the bioavailability of the drug. Various techniques, such as orodispersible tablet, self-emulsifying drug delivery system and solid dispersions, were reported previously. The present study was aimed to improve the dissolution of valsartan using liquisolid compaction technique.

2. Materials and methods

2.1. Materials

Valsartan was kindly gifted by Aurobindo Pharmaceuticals (Hyderabad, India). Aerosil 200 and Avicel PH102 were gift samples from AVL Pharmaceuticals (Hyderabad, India) and Signet Chemicals Corporation (Mumbai, India). Croscarmellose sodium, tween 20, tween 80, polyethylene glycol (PEG200, PEG400 and PEG600), propylene glycol (PG), sodium hydroxide, potassium dihydrogen orthophosphate were purchased from Sd Fine-Chem Ltd. (Mumbai, India). Lactose and dicalcium phosphate (DCP) were purchased from Nehal traders (Hyderabad, India). All other chemicals, reagents and solutions used were of analytical grade. Marketed product Valzaar 40 mg (Torrent Pharmaceutical Ltd., Ahmadabad) was procured from local pharmacy.

2.2. Solubility studies

To select the best non-volatile solvent to dissolve valsartan, solubility studies of valsartan were carried out in six different non-volatile solvents, i.e., PEG200, PEG400, PEG600, tween 20, tween 80 and propylene glycol. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the incubator shaker (JEIOITECH, Korea) for 48 h at 25±1 °C. After shaking, the solutions were filtered through a 0.45 μm Millipore filter, diluted with distilled water and analyzed by UV-spectrophotometer (JASCO V-650, Japan) at a wavelength of 250 nm against blank (blank sample contained the same concentration of specific solvent without drug). Six determinations were carried out for each sample and the mean values along with standard deviations were reported.

2.3. Binding capacity of adsorbents for the solvents

Binding capacity is defined as the capacity of powder excipients to hold liquid without change in their flow properties. It was determined by the following simple method. A constant weight of 5 g of different powder excipients (Avicel PH102, lactose and dicalcium phosphate) were put into a mortar and propylene glycol was added in increments of 0.01 mL. The mixture was triturated after each addition to help distribution of the liquid throughout the powder particles. Addition of liquid was continued until lumps appeared in the powder mixture.

2.4. Calculation of load factor

In a liquisolid system, the amount of liquid retained by the carrier and coating materials depends on the excipient ratio (R) while maintaining acceptable flow and compression properties. The excipient ratio R (R=Q/q) of a powder is defined as the ratio between the weights of carrier (Q) and coating materials (q) present in the formulation. Preparation of a liquisolid system with an acceptable flow rate and compressibility is possible when a maximum amount of retained liquid of the carrier material is not exceeded. This characteristic amount of liquid is termed as liquid load factor (Lq). The liquid load factor (Lq) is defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system (i.e., Lq=W/Q). To calculate the loading factor, propylene glycol (liquid medication without drug) was added to 10 g carrier material and blended for 1 min. The above procedure was repeated until a powder with acceptable flow rate was obtained.
2.5. Flow properties of liquisolid powders

Fixed funnel and the free-standing cone method were employed to measure the angle of repose. A funnel was secured with its tip at a given height (H) above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The mean radius (r) of the base of the conical pile was determined and the tangent of angle of repose was given by \( \tan \alpha = \frac{H}{r} \), where \( \alpha \) is the angle of repose.

2.6. X-ray powder diffraction (XRD)

XRD patterns were studied using Philips PW 3710 X-ray diffractometer. Samples were exposed to 1.540 Å Cu radiation wavelength and analyzed over the 2\( \theta \) range of 2–80°. XRD patterns were determined for valsartan, formulation without drug (blank formulation) and liquisolid system with drug. From the literature, it was evident that Aerosil 200 was a non-gritty amorphous powder, and from the blank formulation, Avicel PH102 spectra can be evaluated.

2.7. Preparation of conventional tablet and liquisolid compacts

The liquisolid compacts were prepared according to the method described by Spireas and Bolton. Valsartan was dissolved in propylene glycol which is used as a liquid vehicle to prepare the drug solution. The mixture of carrier-coating materials (Avicel PH102, lactose or DCP as the carrier powder and Aerosol 200 as the coating material) was added to the liquid medication and blended in a porcelain mortar avoiding excessive trituration and particle size reduction. The mixing was done in three stages: first, the system was mixed slowly to allow uniform distribution of liquid medication; second, the mixture was spread as a uniform layer on the surface of the mortar and left standing for a few minutes; finally, 10% of disintegrant (croscarmellose sodium) was added to the powder and mixed thoroughly. The final mixture was compressed into tablets.

2.8. Evaluation of liquisolid tablets

The prepared liquisolid tablets were evaluated for hardness, friability and disintegration time. Hardness was determined by the Pfizer hardness tester and friability by a digital tablet friability tester. The disintegration time was measured using a USP disintegration tester (Electrolab). All the studies were done in triplicate.

2.9. Dissolution studies

Dissolution studies were performed for liquisolid compacts, plain drug and marketed product (Valzaar-40 mg). The USP paddle method was used for all in vitro dissolution studies. The dissolution was carried out at different pH values using different media, i.e., 0.1 M HCl (pH 1.2), 0.001 M HCl (pH 3.0), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8). The stirring rate was 50 ± 1 rpm. The amount of valsartan was 40 mg in all formulations. The dosage forms were placed in 1 L dissolution medium and maintained at 37 ± 0.5 °C. At appropriate intervals (5, 10, 15, 20, 25, 30 and 45 min), 5 mL of samples were taken and filtered through a 0.45 μm filter. The samples were analyzed at 250 nm by UV–visible spectroscopy. The mean value of six determinations was used to calculate the drug release from each formulation. For the comparison of dissolution data in different media for each formulation, percentages of drug dissolved at 10 min (\( Q_{10\text{ min}} \)), 30 min (\( Q_{30\text{ min}} \)), mean dissolution time (MDT) and dissolution efficiency (DE) at 15 min were calculated.

2.10. FTIR spectroscopy

FTIR spectra of drug, Avicel PH102, Aerosil, liquisolid placebo and liquisolid tablet were obtained. About 5 mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12,000 psi for 3 min. The resultant disk was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 4000 cm\(^{-1}\) to 625 cm\(^{-1}\) in a scan time of 12 min. The resultant spectra were compared for any spectral changes.

3. Results and discussion

Valsartan is given as an immediate release tablet and has an absorption window in the upper gastrointestinal tract. Hence, the objective of this work was to improve the dissolution of valsartan at pH values that simulate gastric conditions so as to improve gastric absorption.

3.1. Vehicle selection

The solubility of valsartan was determined in a number of solvents and is presented in Table 1. Drug solubility in a non-volatile vehicle is the most important aspect in liquisolid systems. The solubility of the drug contributes to molecular dispersion in a non-volatile solvent which will improve the dissolution rate. Based on the solubility data, PG was selected as the vehicle for valsartan.

3.2. Liquisolid compacts

Spireas et al. suggested that particles with high absorption properties due to a porous surface should be used as the carrier material, such as cellulose, starch and lactose.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tween 20</td>
<td>69.73 ± 2.38</td>
</tr>
<tr>
<td>Tween 80</td>
<td>76.57 ± 2.67</td>
</tr>
<tr>
<td>PEG 200</td>
<td>65.41 ± 1.23</td>
</tr>
<tr>
<td>PEG 400</td>
<td>69.57 ± 1.98</td>
</tr>
<tr>
<td>PEG 600</td>
<td>83.91 ± 2.89</td>
</tr>
<tr>
<td>PG</td>
<td>109.23 ± 3.21</td>
</tr>
</tbody>
</table>

PEG, polyethylene glycol; PG, propylene glycol.
Increasing the moisture content of carrier materials may result in decreased powder flowability. The coating material is required to cover the surface, and further, maintain the powder flowability. Accordingly, the coating material should be a very fine and highly adsorptive silica powder. From the preliminary binding capacity experiments conducted with different excipients, Avicel PH102 was selected as carrier and Aerosil 200 as the coat material.Valsartan liquisolid tablets (F1–F12) were prepared with different excipient ratios (R) using PG as vehicle (Table 2). The appropriate amounts of the carrier and coating material were derived from their liquid load factors. The $L_f$ was greater than 0.25 for formulations F1–F8 and F12 (Table 2), showing poor flowability and compressibility.

The angle of repose is a result of internal frictional forces of the particles. The angle of repose will be high if the particles are cohesive. Angles of repose $\leq 30^\circ$ indicate free flow while angles $\geq 40^\circ$ indicate poor flow. Powder formulations with angles of repose greater than $40^\circ$ were not acceptable (formulations F1–F8 and F12). Formulations F9, F10 and F11 showed 28°, 35° and 32°, respectively. Formulation F9 showed good flowability but required a higher amount of carrier material which increased

**Table 2** Formulations of liquisolid compacts (LSC).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug conc. in PG (% w/w)</th>
<th>R</th>
<th>$L_f$</th>
<th>Avicel PH102</th>
<th>Aerosil 200</th>
<th>Formulation weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>15</td>
<td>5</td>
<td>0.665</td>
<td>400</td>
<td>80</td>
<td>580</td>
</tr>
<tr>
<td>F2</td>
<td>10</td>
<td>10</td>
<td>0.532</td>
<td>500</td>
<td>50</td>
<td>650</td>
</tr>
<tr>
<td>F3</td>
<td>20</td>
<td>10</td>
<td>0.443</td>
<td>600</td>
<td>30</td>
<td>750</td>
</tr>
<tr>
<td>F4</td>
<td>20</td>
<td>5</td>
<td>0.666</td>
<td>300</td>
<td>60</td>
<td>460</td>
</tr>
<tr>
<td>F5</td>
<td>10</td>
<td>10</td>
<td>0.5</td>
<td>400</td>
<td>40</td>
<td>530</td>
</tr>
<tr>
<td>F6</td>
<td>20</td>
<td>10</td>
<td>0.4</td>
<td>500</td>
<td>25</td>
<td>620</td>
</tr>
<tr>
<td>F7</td>
<td>40</td>
<td>5</td>
<td>0.333</td>
<td>300</td>
<td>60</td>
<td>450</td>
</tr>
<tr>
<td>F8</td>
<td>10</td>
<td>10</td>
<td>0.25</td>
<td>400</td>
<td>40</td>
<td>530</td>
</tr>
<tr>
<td>F9</td>
<td>20</td>
<td>10</td>
<td>0.20</td>
<td>500</td>
<td>25</td>
<td>610</td>
</tr>
<tr>
<td>F10</td>
<td>60</td>
<td>5</td>
<td>0.22</td>
<td>300</td>
<td>60</td>
<td>440</td>
</tr>
<tr>
<td>F11</td>
<td></td>
<td>10</td>
<td>0.24</td>
<td>275</td>
<td>27.5</td>
<td>370</td>
</tr>
<tr>
<td>F12</td>
<td></td>
<td>20</td>
<td>0.264</td>
<td>250</td>
<td>12.5</td>
<td>340</td>
</tr>
</tbody>
</table>

*aExcipient ratio, $R=Q/q$. $Q$, weight of carrier; $q$, weight of coating material.

*bLiquid load factor, $L_f=W/Q$. $W$, weight of liquid medication.

*c$Q=W/L_f$.

*d$q=Q/R$.

**Figure 1** FTIR spectra of pure drug and different excipients. (a) Aerosil 200, (b) Avicel PH102, (c) valsartan, (d) physical mixture and (e) LSC formulation (F11).
the tablet size to 610 mg. Hence formulation F10 and F11 were selected for compression.

The tablets should have sufficient hardness to resist the breakage during handling, and at the same time, it should disintegrate after swallowing. Formulation F11 showed good compressibility with an acceptable hardness (3–4 kg). Some liquid was squeezed out from formulation F10 at the same hardness. This could be attributed to a lesser quantity of coat material in F10, which is not sufficient to adsorb liquid on its surface and maintain sufficient flowability and compressibility. Based on this study, F11 was selected for further evaluation. Formulation F11 shows satisfactory flowability (angle of repose 32°), hardness (3.5 kg) and disintegration time (2 min) at a total tablet weight of 370 mg.

3.3. FTIR and XRD

Samples of valsartan, Aerosol 200, Avicel PH102, as physical mixtures and liquid solid formulations were subjected to FTIR spectroscopic analysis and their spectra are shown in Fig. 1. Fig. 2 shows XRD diffraction spectra of valsartan, formulation without drug and final liquisolid formulation F11.

The IR spectrum of valsartan (Fig. 1c) exhibits characteristic peaks at 3300 cm⁻¹ (N–H functional group), 2963 cm⁻¹ (C–H group stretching vibration), 1734 cm⁻¹ (carboxyl carbonyl), 1603 cm⁻¹ (amide carbonyl group). The peak at 1458 cm⁻¹ indicates the presence of C=C aromatic group. Appearance of these peaks in the physical mixture and
From the results shown in Fig. 2, it is evident that the peaks in the dissolution profiles. The percentage of drug dissolved at 4.5 and 6.8 to differentiate the media and to compare So dissolution was carried out at different pH values (1.2, 3.0, marketed formulation in 30 min in phosphate buffer (pH 90% of the drug was released from both liquisolid and 0.1 M HCl and 0.001 M HCl, respectively.

formulation, which contributes to increased wetting properties, probably due to the drug presenting in a solubilised state in the marketed product. DE values also increased with an increase fold compared to plain drug and doubled when compared with

the physical mixture and final formulation were characteristic of Avicel PH102. It can be concluded that the increase in dissolution was not due to a change in crystallinity, but rather to increased wetting.

3.4. Dissolution improvement

Dissolution studies for the liquisolid formulation (F11) and marketed product (valzar 40 mg) were conducted in different media as noted in Section 2.9, and the percent drug release at different time intervals is shown in Fig. 3. MDT, \( Q_{10\text{ min}} \) \( Q_{30\text{ min}} \) and DE of the liquisolid formulation and marketed product were calculated in different media and reported in Table 3. DE at 15 min for the plain drug was found to be 4.02% and 7.52% in 0.1 M HCl and 0.001 M HCl, respectively.

From the dissolution data it was observed that more than 90% of the drug was released from both liquisolid and marketed formulation in 30 min in phosphate buffer (pH 6.8) and in 60 min in acetate buffer (pH 4.5, data not shown). So dissolution was carried out at different pH values (1.2, 3.0, 4.5 and 6.8) to differentiate the media and to compare the dissolution profiles. The percentage of drug dissolved at 10 and 30 min \( Q_{10\text{ min}} \) \( Q_{30\text{ min}} \) of LSC formulation (F11) was greater than that of marketed product in all dissolution media. The dissolution rate was significantly increased \( (P<0.05) \) at lower pH (pH 1.2 and 3.0) and no significant difference was found at higher pH (pH 4.5 and 6.8) due to the high solubility of the drug at higher pH. This result was also supported by further analysis of dissolution data using MDT and DE at 15 min. The DE of valsartan was increased seven-fold compared to plain drug and doubled when compared with marketed product. DE values also increased with an increase in pH due to the high solubility of the drug at higher pH values. MDT values of the test product were low at all pH, indicating faster dissolution than marketed dosage form.

The increased dissolution of the liquisolid formulation is probably due to the drug presenting in a solubilised state in the formulation, which contributes to increased wetting properties, thereby enhancing the dissolution rate. Similarly, the drug will be presented in a state of molecular dispersion as the formulation disintegrates in dissolution media. This will increase the effective surface area of the particles available for dissolution.

4. Conclusions

The liquisolid technique was found to be a promising approach for improving the dissolution of a poorly soluble drug like valsartan. The dissolution of valsartan was significantly increased in liquisolid formulation compared to the marketed product. XRD and IR spectra indicate that there was no change in the crystalline state of the drug and no interactions between the drug and excipients. The increased dissolution rate may be due to increased wetting and increased surface area of the particles.

Acknowledgment

The authors would like to thank Project Director, NIPER - Hyderabad Dr. K. Ravi Kumar IICT, Hyderabad and Dr. VGM Naidu, NIPER-Hyderabad, for providing facilities used in the research.

References


