A Modified Solvent Method for Preparation of Solid Dispersions

Sanjay J. Kshirsagar*, Anand Ubhe, Jasmine Malshe, Vidula Sengaokar

A.I.S.S.M.S. College of Pharmacy, Pune - 411001, Maharashtra, India

Abstract

The first aim of the present investigation was to prepare solid dispersions to improve the dissolution properties of oxcarbazepine and quetiapine using PEG 6000 as a carrier with the help of two methods of preparations viz. spray drying and modified solvent method, and to compare the two methods. The second objective was to apply the modified solvent method for preparation of sustained release solid dispersions of domperidone with Eudragit RLPO as a carrier. The solid dispersions of oxcarbazepine and quetiapine were prepared using spray drying and a modified solvent evaporation method. The modified method was then used to prepare solid dispersion of domperidone. All the preparations were evaluated for solubility and dissolution. The characterization was done using FTIR, PXRD and DSC. The solubility and dissolution rates increased significantly for oxcarbazepine and quetiapine in the solid dispersion with PEG 6000. The release of domperidone was decreased in the solid dispersion with Eudragit RLPO. The solubility and dissolution rates of oxcarbazepine and quetiapine were increased significantly in the solid dispersions prepared by both spray drying and modified solvent method. There was no significant difference in the release profiles of solid dispersion prepared by the two methods. The modified solvent method was effectively used for preparing sustained release solid dispersion of domperidone.

Keywords: Domperidone; Oxcarbazepine; Quetiapine; Solid dispersions; Solvent; Spray drying.

Received: January 15, 2011; Accepted: September 10, 2011.

1. Introduction

The use of poorly water-soluble drugs has a number of drawbacks, such as higher dose, higher administration frequency and the resultant occurrence of side effects. Furthermore, as the rate limiting step in the absorption process for poorly water-soluble drugs is the dissolution rate of such drugs in the gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall. It is important to improve the oral bioavailability of these drugs by improving their dissolution rate and solubility. Various techniques used for the improvement of the dissolution rate of poorly water-soluble drugs include micronization, formation of inclusion complexes with cyclodextrin, formation of amorphous drug and the formation of solid
dispersions (SDs) with hydrophilic carriers. The preparation of SDs, by which a drug is dispersed in a carrier to make it amorphous, is one of the most commonly employed pharmaceutical approaches to enhance bioavailability of poorly water-soluble drugs. Some of these carriers are PEGs, Gelucires, Poloxamers, PVP, Sugar or Urea [1-3]. PEG polymers are used widely because of their low melting point, low toxicity, wide drug compatibility and hydrophilicity. SDs have also been used for sustaining the release of drugs [4, 5]. Various pharmaceutical approaches for preparation of SDs including co-precipitation, lyophilization, spray drying, solvent evaporation, fusion and powder mixing methods, have been reported.

Oxcarbazepine (C\textsubscript{15}H\textsubscript{13}N\textsubscript{2}O\textsubscript{2}) is chemically known as 10,11-dihydro-10-oxo-5H-dibenz-[b,f]azepine-5-carboxamide and is used as an antiepileptic agent. Oxcarbazepine is a poorly water-soluble drug according to the BCS system (class II), and its dissolution is rate-limiting step for its absorption. Quetiapine ([C\textsubscript{21}H\textsubscript{25}N\textsubscript{3}O\textsubscript{2}S] 2-(2-(4-dibenzo[b,f][1,4]thiazepine-11-yl-1-piperazinyl) ethoxy)ethanol), is a dopamine antagonist and is used as an antipsychotic. Domperidone ([C\textsubscript{22}H\textsubscript{24}ClN\textsubscript{5}O\textsubscript{2}] (D), 5-chloro-1-{1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4-piperidyl} benzimidazolin-2-one) is also a dopamine antagonist used as an antiemetic and for the treatment of nausea. It is a weak base (pKa=7.89) poorly soluble in water.

The objective of the present study was to evaluate the feasibility of the modified solvent method by comparing with the conventional method i.e. spray drying, for preparation of SDs. SDs of oxcarbazepine and quetiapine were prepared using modified solvent method and compared with the SDs prepared by spray drying. The modified solvent method was then applied to prepare the sustained release SDs of domperidone with Eudragit RLPO. Attempts have been made to prepare sustained release co-evaporates of domperidone with other carriers [4].

All of the formulations were subjected to evaluation by solubility and dissolution studies. Characterization of the prepared solid

![Figure 1](image-url). Saturation solubility values.
Preparation of solid dispersions was done using Powder X-ray diffraction (PXRD), Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC).

2. Materials and methods

2.1. Materials

Oxcarbazepine, quetiapine and domperidone were kindly supplied by Ranbaxy Laboratories Limited, India, Lupin Research Park, India and Dr. Reddy’s Laboratories Ltd, India, respectively. Eudragit RLPO was obtained as a gift sample from Degussa India Pvt. Ltd.. PEG 6000 was purchased from Otto Kemi, Mumbai. All other reagents and chemicals used were of analytical grade.

2.2. Preparation of Physical mixture

Previously sieved (60 # mesh screen) quetiapine, oxcarbazepine and PEG 6000 were accurately weighed and mixed in the ratio of 1:5 w/w of drug to carrier. Pre-sieved (60 # mesh screen) domperidone and Eudragit RLPO were weighed accurately and mixed in the ratio 1:2 w/w of drug to carrier. Physical mixtures were obtained by mixing the components using spatula in a mortar for 3 min.

2.3. Preparation of solid dispersions

2.3.1. Spray drying

Solid dispersions of oxcarbazepine and quetiapine with PEG 6000 were prepared in

Table 1. Drug content values.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug to carrier ratio</th>
<th>Drug content (% W/W) for SDs prepared by</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Spray drying</td>
</tr>
<tr>
<td>1.</td>
<td>1:5 Oxc : PEG 6000</td>
<td>98.59±0.30</td>
</tr>
<tr>
<td>2.</td>
<td>1:5 Quet : PEG 6000</td>
<td>99.19±0.26</td>
</tr>
<tr>
<td>3.</td>
<td>1:2 Dom : Eudragit RLPO</td>
<td>-</td>
</tr>
</tbody>
</table>

289

Figure 2. FTIR spectra of oxcarbazepine preparations.

Figure 3. FTIR spectra of quetiapine preparations.
For each drug the components were weighed in the specified ratio such that the total weight was 5 g. Then for both drugs the components were dissolved in methanol (AR grade) to get the drug-carrier solutions. The resultant solutions were spray dried using Spray Dryer (LU-222 Labultima, India). The inlet temperature and outlet temperature were set at 55 °C and 40 °C, respectively, while the feed pump speed was kept at 8 ml/min. The aspiration speed was adjusted from 40 to 50 to maintain the vacuum at 100 mm of water column. The spray dried products were stored in desiccator for 48 h and then in air tight containers until evaluation.

2.3.2. Modified solvent method

Drug carrier solutions of oxcarbazepine and quetiapine were prepared in a similar manner as stated in the spray drying method. For preparation of solid dispersions of domperidone, the two components domperidone and Eudragit RLPO were

![Figure 4. FTIR spectra of domperidone preparations.](image)

![Figure 5. X-ray diffraction spectra for oxcarbazepine preparations.](image)

**Table 2.** Dissolution parameters for oxcarbazepine and quetiapine preparations.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Sample &amp; preparation method</th>
<th>Drug to carrier ratio</th>
<th>Dissolution parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q(t)_{15min} (%)</td>
</tr>
<tr>
<td>1. Pure drugs</td>
<td>Oxcarbazepine</td>
<td>10.8</td>
<td>27.8</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>20</td>
<td>67.5</td>
</tr>
<tr>
<td>2. Physical mixtures</td>
<td>Oxcarbazepine:PEG 6000 (1:5)</td>
<td>12</td>
<td>33.9</td>
</tr>
<tr>
<td></td>
<td>Quetiapine:PEG 6000 (1:5)</td>
<td>20</td>
<td>69.9</td>
</tr>
<tr>
<td>3. Solid dispersions prepared by Spray drying</td>
<td>Oxcarbazepine:PEG 6000 (1:5)</td>
<td>19.5</td>
<td>58.4</td>
</tr>
<tr>
<td>4. Solid dispersions prepared by modified solvent method</td>
<td>Quetiapine:PEG 6000 (1:5)</td>
<td>36.3</td>
<td>98.7</td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine:PEG 6000 (1:5)</td>
<td>18.8</td>
<td>60.0</td>
</tr>
<tr>
<td></td>
<td>Quetiapine : PEG 6000 (1:5)</td>
<td>35.3</td>
<td>98.6</td>
</tr>
</tbody>
</table>
Preparation of solid dispersions

weighed accurately in the ratio of 1:2 w/w, respectively, and then dissolved in methanol (AR grade). These solutions were then subjected to distillation using laboratory scale distillation assembly. During the process the temperature was maintained at 65 °C using heating mantle. The solid dispersions were obtained in the round bottom flask and pure methanol was recovered as a by-product. The solid dispersions were passed through sieve (60 # mesh screen), stored in desiccator for 48 h and then in air tight containers until evaluation.

2.4. Evaluation of solid dispersions

2.4.1. Drug Content

Solid dispersions of oxcarbazepine, quetiapine and domperidone equivalent to 50 mg were weighed accurately and dissolved in a suitable quantity of acetonitrile for oxcarbazepine and in methanol for quetiapine and domperidone. The stock solutions were diluted suitably in distilled water. The drug content was analyzed by UV spectrophotometer (Jasco V-550, Japan) at 256, 250 and 284 nm for oxcarbazepine, quetiapine and domperidone respectively. Each sample was analyzed in triplicate.

2.4.2. Solubility studies

Pure drugs oxcarbazepine, quetiapine, domperidone; their physical mixtures and solid dispersions (excess quantity of all) were placed separately in glass stoppered flasks containing 10 ml distilled water. The samples were placed in orbital shaker (CIS-24 Remi, India), at 25 °C and 100 rpm, until equilibrium was achieved (48 h). The aliquots were filtered through Whatmann filter paper no. 41. The filtered samples of oxcarbazepine, quetiapine and domperidone were diluted suitably in distilled water and assayed spectrophotometrically at 256, 250 and 284 nm, respectively [6].

2.4.3. Dissolution studies

Dissolution studies were carried out using USP XXIII paddle apparatus to estimate the in vitro drug release. Samples equivalent to 150 mg of oxcarbazepine, 50 mg of quetiapine and 30 mg of domperidone were added to 900 ml of distilled water at 37.0±0.5 °C and stirred at 75 rpm. An aliquot of 5 ml was withdrawn at different time intervals and filtered through Whatmann filter paper no. 41.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Sample</th>
<th>Dissolution parameters</th>
<th>Dissolution parameters</th>
<th>Dissolution parameters</th>
<th>Dissolution parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$Q(t)_{30min}$ (%)</td>
<td>$Q(t)_{120min}$ (%)</td>
<td>$t_{90%}$ (min)</td>
<td>$k$</td>
</tr>
<tr>
<td>1.</td>
<td>Domperidone pure</td>
<td>23.4</td>
<td>76.9</td>
<td>148.7</td>
<td>1.4281</td>
</tr>
<tr>
<td>2.</td>
<td>PM domperidone: Eudragit RLPO (1:2)</td>
<td>23.1</td>
<td>73.9</td>
<td>153.3</td>
<td>1.5525</td>
</tr>
<tr>
<td>3.</td>
<td>SD domperidone: Eudragit RLPO (1:2)</td>
<td>4.8</td>
<td>16.4</td>
<td>562.3</td>
<td>0.0864</td>
</tr>
</tbody>
</table>

Table 3. Dissolution parameters for domperidone preparations.

![X-ray diffraction spectra for quetiapine preparations.](image)
An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples of oxcarbazepine, quetiapine and domperidone were assayed spectrophotometrically at 256, 250 and 284 nm, respectively [7].

2.5. Data analysis

The values of percent drug dissolved \( Q(t)_{15\text{min}} \), \( Q(t)_{30\text{min}} \), \( Q(t)_{120\text{min}} \) were calculated for oxcarbazepine, quetiapine and domperidone preparations [8]. For domperidone preparations, \( t_{90\%} \) was estimated. The dissolution data for domperidone was subjected to model fitting analysis using PCP Disso software (version 3.0).

Dissolution data of oxcarbazepine and quetiapine was also subjected to model-independent analyses (pair-wise approach) in order to determine the release profiles similarity for solid dispersions prepared by the modified solvent method and spray drying. The pair-wise procedures include the Rescigno indices (\( \xi_1, \xi_2 \)) [9], the difference \( (f_1) \) and similarity \( (f_2) \) factors [10]. Because of its simple calculation and increasing importance [11, 12] the dissolution profiles were compared by computing the similarity factor \( (f_2) \) (Eq. 1):

\[
f_2 = 50 \times \log \left\{ 1 + \left( \frac{\xi_2}{\xi_1} \right) \sum_{i=1}^{n} \left[ \frac{R_i - T_i}{R_i} \right]^2 \right\}^{0.5} \times 100
\]

Where \( n \) is the number of experimental points in the in vitro dissolution assay, \( R_i \) and \( T_i \) are the mean percentages of dissolved drug from the reference and test formulations, respectively, at each time point “t”.

In this study, solid dispersions prepared by spray drying were considered as reference formulations while those prepared by the modified solvent method as test formulations.

The Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) [13] recommend the use of \( f_2 \) and consider that two dissolution profiles are similar if \( f_2 \) is between 50 and 100, i.e. the two profiles show differences lower than 10% [14]. All these parameters were calculated using PCP Disso software (version 3.0).

2.6. Characterization

2.6.1. Fourier transform infra-red spectroscopy (FTIR)

The IR spectra of pure drugs, physical mixtures and solid dispersions were recorded using FTIR spectrophotometer (450 plus, Jasco Japan) with diffuse reflectance principle. Sample preparation involved, mixing the sample with KBr, triturating in glass mortar and finally placing in the sample holder. The spectra were recorded over a frequency range 4000 cm\(^{-1}\) to 400 cm\(^{-1}\).

![Figure 7. X-ray diffraction spectra for domperidone preparations.](image)

Table 4. Similarity factor \((f_2)\) values.

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>Similarity factor ((f_2)) values for oxcarbazepine preparations</th>
<th>Similarity factor ((f_2)) values for quetiapine preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>97.30</td>
<td>95.20</td>
</tr>
<tr>
<td>30</td>
<td>91.95</td>
<td>86.78</td>
</tr>
<tr>
<td>45</td>
<td>90.08</td>
<td>84.93</td>
</tr>
<tr>
<td>60</td>
<td>87.04</td>
<td>86.07</td>
</tr>
<tr>
<td>90</td>
<td>84.83</td>
<td>86.64</td>
</tr>
<tr>
<td>120</td>
<td>84.93</td>
<td>87.60</td>
</tr>
<tr>
<td>Average</td>
<td>89.35</td>
<td>87.87</td>
</tr>
</tbody>
</table>
2.6.2. Differential scanning calorimetry (DSC)

The DSC thermograms of pure drugs, physical mixtures and solid dispersions were recorded using Differential scanning calorimeter (DSC 823e, Mettler Toledo, Japan). Approximately 2 to 5 mg of each sample was heated in a pierced aluminum pan from 30 °C to 300 °C at a heating rate of 10 °C/min. and under a stream of nitrogen, at the flow rate of 50 ml/min. Thermal data analysis of the DSC thermograms was done using STAR® software (version 5.21).

2.6.3. Powder X-ray Diffraction Analysis (PXRD)

Powder X-ray diffraction patterns of drugs, physical mixtures and solid dispersions were recorded using a powder X-ray diffractometer (PW 1729 X-ray Generator, Philips Netherlands) under the following conditions:
- Scanning range 5° to 50°
- X-Ray Target - Copper
- Filter - Nickel
- Cu wavelength - 1.542

3. Results and discussion

The drug content values of the prepared solid dispersion systems were found in the range of 98.59±0.30 to 99.72±0.41% (w/w) (Table 1). The drug content values were found to be uniform in all solid dispersions.

Figure 1 represents graphical representation of the saturation solubility of oxcarbazepine, quetiapine and domperidone in the physical mixtures and solid dispersion systems. In case of oxcarbazepine and quetiapine the saturation solubility increased for both solid dispersions as well as physical mixtures with PEG 6000. Similar findings were reported by Verheyen et al. [15]. The magnitude of increase in the solubility for oxcarbazepine was approximately 4 times in solid dispersions prepared by the modified solvent method and the spray drying while the magnitude of increase in the solubility in the physical mixture of the same was lesser i.e. approximately 2 times compared to the solubility of pure oxcarbazepine. For quetiapine the increase in solubility of the solid dispersions was approximately 2 times while of physical mixture it was approximately 1.5 times that of pure quetiapine. The increase in solubility of physical mixtures as well as the solid dispersions of both oxcarbazepine and quetiapine indicated the solvent properties of PEG 6000 for both the drugs. However, the higher magnitude of increase in the solubility

![Figure 8. DSC thermograms of oxcarbazepine preparations.](image1)

![Figure 9. DSC thermograms of quetiapine preparations.](image2)

293
of both the drugs in the solid dispersions prepared by the two methods suggested crystal changes or amorphization of the drug molecules in the solid dispersions with PEG 6000. The magnitude of increase in the solubility for both the drugs was similar in the solid dispersions prepared by the modified solvent method and the spray drying.

In case of domperidone the solubility decreased by as much as 2.5 times in the solid dispersion with Eudragit RLPO. The decrease in the solubility in the physical mixture was not significant. However, the significant decrease in the solubility of domperidone in the solid dispersion with Eudragit RLPO was due to the water insolubility of Eudragit RLPO and embodiment of the drug molecules in its matrix [16, 17].

In the solid state characterization by FTIR, PXRD and DSC the physical mixtures were considered as reference. Figures 2, 3 and 4 represent the FTIR spectra of oxcarbazepine, quetiapine and domperidone preparations, respectively.

For oxcarbazepine (Figure 2) the characteristic amide I and amide II bands at around 1600 cm\(^{-1}\) to 1700 cm\(^{-1}\) were still visible in the physical mixture as well as in the solid dispersion, suggesting that there was no chemical interaction between oxcarbazepine and PEG 6000 in both physical mixture as well as solid dispersions. Also, the N-H stretch at around 3200 cm\(^{-1}\) could be seen in both physical mixture and solid dispersions. This indicated that there was no chemical interaction between oxcarbazepine and PEG 6000 in both physical mixture as well as solid dispersions. Similar findings were seen with domperidone preparations (Figure 4) where the characteristic C=O at around 1700 cm\(^{-1}\) stretch is visible in both physical mixture and solid dispersion. This also suggested that there was no chemical interaction between domperidone and Eudragit RLPO in both physical mixture and the solid dispersion. In case of quetiapine (Figure 2), although the characteristic bands for C-O bond between 1050 cm\(^{-1}\) - 1400 cm\(^{-1}\) can be seen in the physical mixture, the bands were broadened and altered in the solid dispersions. Also, strong band at around 3600 cm\(^{-1}\) corresponding to O-H stretch was present in physical mixture but disappeared in the solid dispersions. These modifications in the IR spectra of solid dispersions suggested intermolecular hydrogen bonding between quetiapine and PEG 6000 in the solid dispersions prepared by both the methods. For both oxcarbazepine and quetiapine the FTIR spectra of solid dispersion prepared by modified solvent method were similar to the FTIR spectra of solid dispersion prepared by spray drying.

The X-ray diffraction spectra of oxcarbazepine and quetiapine show numerous distinct lines indicating that they are present in highly crystalline state (Figures 5, and 6).
The diffraction spectra of domperidone and PEG 6000 show few distinctive lines indicating lower degree of crystallinity (Figures 6, and 7). The diffraction spectrum of Eudragit RLPO (Figure 7) shows lack of any definite lines typical of amorphous materials. The characteristic lines for the pure drugs were maintained in the respective physical mixtures of all the three drugs. But, these characteristic peaks were suppressed in the respective solid dispersions. This suggested possible crystal changes or amorphization of the drug molecules in their solid dispersions. The suppression of the characteristic drug peaks of oxcarbazepine and quetiapine was similar for solid dispersions prepared by the modified solvent method and the spray drying.

The DSC thermograms of oxcarbazepine, quetiapine and domperidone preparations are shown in Figures 8, 9 and 10, respectively. The DSC runs of pure components showed sharp endothermic peaks at 230 °C, 178 °C, 250 °C and 62 °C for oxcarbazepine, quetiapine, domperidone and PEG 6000, respectively, corresponding to their melting points. The peaks for melting of pure drugs were completely suppressed in physical mixtures and solid dispersions of oxcarbazepine as well as quetiapine (Figures 8, and 9). This was thought to be due to the dissolution of the drug molecules in the melted PEG 6000 before reaching its own melting point, a phenomenon already observed with other drugs [18, 19]. However, the thermograms of the physical mixtures were differing from that of solid dispersions in case of both oxcarbazepine and quetiapine. The thermograms of solid dispersions prepared by the modified solvent method were similar to that of the thermograms of solid dispersions prepared by spray drying in case of both the drugs. For domperidone preparations the drug melting peak at 250 °C was maintained in the physical mixture but was completely suppressed in the solid dispersion indicating the possible solid solution of drug in polymer.

Figures 11 and 12 show the dissolution profiles of oxcarbazepine and quetiapine preparations, respectively. The dissolution profiles of pure drugs and the respective physical mixtures were found to be similar; while for the solid dispersions, a significant improvement in the dissolution rate was seen for both oxcarbazepine and quetiapine. This again suggested crystal changes or amorphization of the drug molecules in the solid dispersions. For both the drugs the Q(t)_{15min} and Q(t)_{120min} values (Table 2) were almost doubled for solid dispersions prepared by both the methods. As both spray drying and the modified solvent method are types of common solvent method, for comparing the two methods the similarity factor ($f_2$) values were calculated. The $f_2$ values (Table 4), at all the time intervals were greater than 65, hence the dissolution profiles of the solid dispersions...
prepared by the two methods can be considered to be more than 95% similar [14].

The dissolution profile of domperidone (Figure 13) was also significantly influenced in the solid dispersion with Eudragit RLPO. A significant decrease in the dissolution rate of domperidone was seen in the solid dispersion; however, the dissolution profile of the physical mixture was similar to that of the pure drug. This indicated that the drug molecules were dispersed in the water insoluble matrix of Eudragit RLPO. The values of $Q(t)_{30\text{min}}$ and $Q(t)_{120\text{min}}$ (Table 3) were reduced by almost five to six times. The value of $t_{90\%}$ increased from 148 to 562 min. The release kinetics for the domperidone preparations followed zero order with ‘n’ value around 1 (Table 3).

4. Conclusion

The solid dispersions prepared with PEG 6000 as carrier improved the dissolution properties of oxcarbazepine as well as quetiapine. The mechanism of improvement in the dissolution properties, on the basis of characterizations was predicted to be the changes in the crystal form or amorphization of the drug molecules in the solid dispersions. The extent of improvement in the dissolution properties of the two drugs was similar with the solid dispersions prepared by spray drying as well and the modified solvent method, which was corroborated by the similarity factor evaluation. A significant decrease in the dissolution rate of domperidone in the solid dispersion with Eudragit RLPO implied successful application of the modified solvent method for preparation of sustained release solid dispersions. Thus, the modified solvent method was found to be suitable for preparation of solid dispersions to improve the dissolution properties as well as to sustain the drug release with the added advantage of simple assembly and solvent recovery.

References

B. transdermal dosage forms: Section 1 (Quality) 1999; CPMP/QWP/604/96.


