Enhancement of Solubility of Acyclovir by Solid Dispersion and Inclusion Complexation Methods

1Nikhil K. Sachan, 1Seema Pushkar, 2S.S. Solanki and 1Dogendra S. Bhatere

1University Institute of Pharmacy, C.S.J.M. University, Kanpur - 208 024 (U.P.) India
2Institute of Professional Studies College of Pharmacy, Gwalior - 474 001 (M.P.) India
3T I T College of Pharmacy, Bhopal - 462 021 (M.P.), India

Abstract: Solid dispersions of acyclovir in PEG 6000 and PVP K30 containing five different ratios were prepared by the solvent evaporation method. Inclusion complexes were prepared by kneading method by dissolving acyclovir and β-CD, HP β-CD at 5 different ratios in distilled water. The optimized batches of solid dispersions (ASm, BSm) and inclusion complexes (CI, DII) of acyclovir were analyzed by IR spectroscopy, SEM and DSC. The dissolution studies for solid dispersions (ASm, BSm) and inclusion complexes (CI, DII) were performed in 0.1 N HCl and PBS pH 7.4 for all optimized batches. The solubility of acyclovir was found to be more with inclusion complexation method as compare to solid dispersion technique. Hence, the results showed that hydroxypropyl β-cyclodextrin inclusion complex could possibly improve the dissolution characteristics of acyclovir and would provide better bioavailability as compare to conventional dosage form.

Key words: Solid dispersion • Inclusion complex • Acyclovir • Solvent evaporation

INTRODUCTION

The rate and extent of dissolution of the active ingredient from any solid dosage form determines the rate and extent of absorption of drug [1]. The bioavailability of a drug depends more often in its rate of dissolution in case of poorly water soluble drugs where dissolution is rate limiting step for absorption. Poorly soluble drugs have been shown to be unpredictable and slowly absorbed as compared to the drugs with higher solubility. Several methods have been employed to improve the solubility of poorly water soluble drugs. Acyclovir is a popular anti-Herpes drug among the antiviral category for the treatment of diseases including Herpes simplex (type 1) keratitis, orofacial, cutaneous Herpes, genital herpes and varicella zoster infections. Among the Herpes viruses H. simplex (type I) is the most sensitive followed by H. simplex (type II) viruses [2]. Acyclovir is the drug of choice for most of these cases but the problem of using this drug is that it has poor oral bioavailability. The conventional routes and therapies available for the treatment of Herpes, keratitis, includes orally administered tablet but are associated with it is very low bioavailability ranging from 15-30%. The associated side effects like nausea, diarrhea, rash and headache which result because of multiple high dose administration required due to poor bioavailability of drug can be minimized by enhancing the solubility and hence dissolution of acyclovir. In this context, the rationale of this study is to improve the therapeutic performance of Acyclovir through enhancing its solubility and dissolution rate by two approaches: solid dispersion and inclusion complexation. In present study solubility enhancement of Acyclovir by solid dispersion with polyethylene glycol (PEG 6000), polyvinylpyrrolidone (PVP K 30) and inclusion complexation with β-cyclodextrin and hydroxypropyl β-cyclodextrin are proposed and examined. The solid dispersion and the inclusion complex techniques seem to pose great potential in significantly enhancing the solubility and dissolution rate of different formulations [3-9].

MATERIALS AND METHODS

PEG-6000, PVP K-30, β-CD and HP β-CD were purchased from CDH (P) Ltd. New Delhi. Acyclovir was obtained as a gift sample from Alembic Pharmaceutical Pvt Ltd, Varodara. All other materials used were of pharmaceutical grade.

Corresponding Author: Nikhil K Sachan, University Institute of Pharmacy, C.S.J.M. University, Kanpur - 208 024, Uttar Pradesh, India, Tel: +91-9307755497, E-mail: nikhilsachan@gmail.com.
Preparation of Physical Mixtures: The drug (Acyclovir) and excipients (PEG-6000, PVP K-30, β-CD and HP β-CD) were weighed, accurately, in predetermined ratios (1:1, 1:2, 1:3), pulverized and mixed thoroughly to obtain a homogeneous mixture. This mixture passed through sieve for uniform size and stored in desiccators for further experiments (Table 1).

Preparation of Solid Dispersion: Solid dispersions of acyclovir in polyethylene glycol-6000 (PEG-6000) and polyvinylpyrrolidone K-30 (PVP K-30) containing five different ratios (1:1, 1:2, 1:3, 1:4 and 1:5 w/w) were prepared by the solvent evaporation method [10]. Acyclovir and the polymer were dissolved in a minimum amount of methanol. The solvent was removed by evaporation on magnetic stirrer at the temperature 40°C for 1 h. The resulting residue was dried for 2 h and stored overnight in a desiccator. After drying, the residue was ground in a mortar and sieved through a #60 sieve. The resultant solid dispersions were stored in desiccator until further investigation (Table 2).
Table 3: Dissolution Profile of Optimized Batches of Solid Dispersion, Inclusion Complex and Marketed Preparation in 0.1 N HCl.

<table>
<thead>
<tr>
<th>TIME (MIN)</th>
<th>AS4</th>
<th>BS5</th>
<th>CI5</th>
<th>DI5</th>
<th>Marketed</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>21.35</td>
<td>21.44</td>
<td>23.56</td>
<td>25.31</td>
<td>20.64</td>
</tr>
<tr>
<td>20</td>
<td>45.89</td>
<td>48.68</td>
<td>51.62</td>
<td>53.24</td>
<td>41.22</td>
</tr>
<tr>
<td>30</td>
<td>68.46</td>
<td>72.99</td>
<td>71.34</td>
<td>75.56</td>
<td>54.74</td>
</tr>
<tr>
<td>40</td>
<td>75.81</td>
<td>77.91</td>
<td>84.22</td>
<td>87.36</td>
<td>59.11</td>
</tr>
<tr>
<td>50</td>
<td>78.23</td>
<td>81.55</td>
<td>87.59</td>
<td>91.32</td>
<td>60.69</td>
</tr>
<tr>
<td>60</td>
<td>80.11</td>
<td>83.23</td>
<td>89.45</td>
<td>94.25</td>
<td>62.36</td>
</tr>
</tbody>
</table>

Table 4: Dissolution Profile of Optimized Batches of Solid Dispersion, Inclusion Complex and Marketed Preparation in PBS pH 7.4.

<table>
<thead>
<tr>
<th>TIME (MIN)</th>
<th>AS4</th>
<th>BS5</th>
<th>CI5</th>
<th>DI5</th>
<th>Marketed</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>19.11</td>
<td>20.71</td>
<td>21.61</td>
<td>24.31</td>
<td>18.63</td>
</tr>
<tr>
<td>20</td>
<td>39.56</td>
<td>40.89</td>
<td>48.22</td>
<td>50.51</td>
<td>36.56</td>
</tr>
<tr>
<td>30</td>
<td>58.91</td>
<td>61.52</td>
<td>66.25</td>
<td>70.84</td>
<td>48.94</td>
</tr>
<tr>
<td>40</td>
<td>67.26</td>
<td>69.11</td>
<td>71.63</td>
<td>78.61</td>
<td>55.66</td>
</tr>
<tr>
<td>50</td>
<td>69.77</td>
<td>70.83</td>
<td>74.56</td>
<td>80.86</td>
<td>57.11</td>
</tr>
<tr>
<td>60</td>
<td>71.63</td>
<td>73.12</td>
<td>74.12</td>
<td>83.24</td>
<td>58.02</td>
</tr>
</tbody>
</table>

Fig. 1: Comparison of Dissolution Profile of Optimized Batches of Solid Dispersion and Inclusion Complexation with Marketed Formulation in 0.1 N HCl.

Characterization of Solid Dispersion and Inclusion Complex: [11-13]

Infra Red (IR) Studies: The optimized batches of solid dispersion (AS, and BS,) and inclusion complexation (CI, and DI) were analyzed by IR spectroscopy (FTIR-Jusco-470 plus).

Scanning Electron Microscopy (SEM): The surface morphology of optimized batches (AS, and BS,) was determined by scanning electron microscopy (SEM, Leo 430, U.K.).

Differential Scanning Calorimetry (DSC) Analysis: The optimized batches of inclusion complexation were subjected to differential scanning calorimetry (DSC) analysis. The change in endothermic peaks of acyclovir and excipients were observed, which confirms the interaction between drug and excipients.
Fig. 2. Comparison of Dissolution Profile of Optimized Batches of Solid Dispersion and Inclusion Complexation with Marketed Formulation in Pbs pH (7.4)

Content Uniformity: The content of acyclovir in PEG 6000 and PVP K30 solid dispersion and in inclusion complexation with β-cyclodextrin and HP β-cyclodextrin was estimated by UV spectrophotometric method using Shimadzu 1700 spectrophotometer. An accurately weighed quantity of solid dispersion (equivalent to 10 mg of acyclovir) was taken and dissolved in 100 ml of 0.1 N HCl, from this solution 1 ml of solution was diluted to 10 ml and assayed for drug content at 255 nm.

Dissolution Studies: The dissolution studies of optimized batches of solid dispersion (AS₈ and BS₈), and inclusion complexes (CI and DL) were performed in 900 ml of 0.1 N HCl and PBS pH 7.4 (Table 4, Fig 2) at 37°C by the USP-II paddle apparatus at 50 rpm. In the present studies samples (equivalent to 400 mg of drug) were dispersed in medium. Aliquots of 5 ml from the dissolution medium were withdrawn at different time intervals and replenished by an equal volume of fresh dissolution medium. The samples were filtered through Whatman filter paper and analyzed for acyclovir contents by measuring its absorbance at 255 nm for 0.1N HCl and at 256 nm for PBS pH 7.4 using Shimadzu 1700 UV/visible Spectrophotometer.

RESULT AND DISCUSSION

The solubility of acyclovir in water was found to be 12.84 μg/ml. In case of physical mixture, a small increase in solubility of drug was obtained which can be explained due to the formation of a minimum quantity of the complex. The effect of different carriers on the aqueous solubility of acyclovir was shown in Table 2. Solubility experiments showed that the concentration of acyclovir in water increased in presence of PEG6000, PVPK30, β-CD and HP β-CD. The solid dispersion (AS₈, BS₈) and inclusion complexes (CI, DL) of acyclovir were analyzed by IR spectroscopy (FTIR- Jasco-480 plus). The change in principle peaks of group acyclovir and excipients were found, which confirmed the complex formation between drug and excipients. The important peaks in IR spectra of acyclovir were, 3208.03 of N-H stretch of primary amine (NH2), 1785.94 of C=O stretching (Fig. 3). In IR spectra of PEG-6000 and PVP K-30, the important peaks were observed at 1665.23 and 1283.39, respectively for C=O stretch but in solid dispersion these peaks were absent and new peaks at 1291.11 and 1107.22 for asymmetric C=O-C stretch were observed.

In IR spectra of pure β-CD and HP β-CD (Fig.4) the important peaks were observed at 3321.78 and 3384.94, respectively for O-H stretch of primary alcohol. Whereas in IR spectra of inclusion complex all these important peaks were absent and instead of this, peak of symmetric and anti symmetric peaks were observed at 1125.26 and 1291.11, respectively. These changes in IR peaks clearly suggested that the acyclovir-excipients complex had been formed in case of solid dispersion (PEG-6000 and PVPK30) and inclusion complex (β-CD and HP β-CD). The surface morphology of drug and solid dispersion (AS₈, BS₈) was determined by the use of scanning electron microscopy. Acyclovir existed as needle-like crystals, whereas PVP K30 seen as amorphous spherical or pieces of spherical
Fig. 3: IR Spectra of Solid Dispersion

Fig. 4: IR Spectra of Inclusion Complex
particles and PEG 6000 consisted of large crystalline particles of rather irregular size. The solid dispersions appeared in the form of irregular particles in which the original morphology of both components disappeared and tiny aggregates of amorphous pieces of irregular size were present. Therefore, the reduced particle size, increased surface area and the close contact between the hydrophilic carriers and acyclovir might be responsible for the enhanced drug solubility found for the solid dispersion particles (Fig. 5).

DSC curves obtained for pure material, β-CD, HP β and inclusion complexes are displayed in Fig. 6. In case of acyclovir one endothermic peak was observed at 251.8 which were near to its melting point 253°C. In the DSC curves of pure β-CD and HP β-CD, the peaks corresponding to the evaporation of water appeared in the temperature range of 50-150°C. Besides the endothermic peaks corresponding to the loss of water, the thermogram of β-CD displayed melting endotherm with a shoulder, which indicated the presence of more than one crystal form (Fig. 6).

The inclusion complex of acyclovir with cyclodextrin showed spectra corresponding to superposition of their parent products. In the curve of inclusion complex with β-CD, it exhibits endotherms at 121.4 and 223°C. The inclusion complex of acyclovir with HP β-CD the all important peaks were absent and a peak was observed at 98.1 which show that all characteristic features of acyclovir peak and cyclodextrin were lost. The disappearance of the thermal features of the drug indicated that the drug penetrated into the cyclodextrin cavity replacing the water molecules. The change in endothermic peaks of acyclovir and cyclodextrin were observed,
which confirms the interaction between drug and excipients. Content of acyclovir in solid dispersion (PEG 6000, PVP K-30), inclusion complex (β-CD, HP β-CD) was estimated and % drug content of formulations AS, BS, CI, and DI was found to be 94.18, 94.87, 96.03 and 97.47 respectively.

The maximum cumulative % drug release in 0.1 N HCl for AS, BS, CI, and DI batch was 80.11%, 83.23%, 89.45% and 94.25% respectively (Table 3 and Fig.1). The drug release was also performed in phosphate buffer saline (pH 7.4) for 60 min. The maximum drug release from batches AS, BS, CI, and DI was 71.63%, 73.12%, 74.12% and 83.24% respectively (Table 4 and Fig. 2).

The release of drug from the optimized batches was compared with marketed preparation (Zovirax) in both medium. The dissolution rate of the drug in the solid dispersions and inclusion complexes was evidently higher than that of the marketed drug. This can be attributed to the increase in solubility as drug (Table 3-4 and Fig. 1-2). Several mechanisms had been proposed to account for the increase in dissolution kinetic of drugs from solid dispersions. Decreased crystallinity, increased wettability and reduction of drug particle size were considered to be predominant factors. Increase of dissolution rates was obtained for the inclusion complexes. This behavior might be attributed to the high energetic amorphous state and inclusion complex formation.
CONCLUSION

A rapid and excellent dissolution behavior was obtained by forming solid dispersion with PVP K30 or PEG6000 and inclusion complex with β-CD or HP β-CD. Among these preparations, HP β-CD inclusion complex (DI) shows higher solubility and dissolution rate.

REFERENCES