Discriminating power of dissolution medium in comparative study of solid dispersion tablets of Biopharmaceutics Classification System class 2 drug

Ushasi Das, Gopa Roy Biswas and Sutapa Biswas Majee*

Division of Pharmaceutics, NSHM College of Pharmaceutical Technology NSHM Knowledge Campus, Kolkata-Group of Institutions, 124 B.L. Saha Road, Kolkata 700053, India.

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In vitro dissolution testing should discriminate between the impact of excipients on release profile of Biopharmaceutics Classification System class 2 drugs. Among the four batches of carvedilol solid dispersion tablets, SDT-2-L containing 30% w/w mannitol and 2.5% w/w L-hydroxypropyl cellulose LH-11 exhibited least mean dissolution time in gastric buffer (pH = 1.2) and phosphate buffer (pH = 6.8). However, inter-batch differences in release parameters from phosphate buffer were usually higher and also statistically significant at p < 0.05. Drug release from an individual formulation exhibited different kinetics in two media. Therefore, improper selection of dissolution medium may fail to discriminate between product performances.

Key words: Solid dispersion tablet, dissolution efficiency, mean dissolution time.

INTRODUCTION

For drugs belonging to Biopharmaceutics Classification System (BCS) Class 2, strong correlation exists between in vitro dissolution and in vivo absorption. Dissolution procedure should be able to detect, discriminate and predict the effect of minor changes in product composition on the in vivo performance. The discriminatory power of the dissolution medium is affected by its pH, speed of agitation, presence of surfactants in the medium etc. Selection of the most appropriate dissolution condition depends on the discriminatory ability, accuracy, reproducibility, robustness and level of correlation with in vivo performance. Products possessing different pharmaceutical attributes (for example, formulation variables or process variables) can be appropriately differentiated with the help of discriminatory dissolution profiles (Qureshi, 2006; Bajerski et al., 2010; Hurtado et al., 2012; Lagace et al., 2004).

Carvedilol, an anti-hypertensive drug and a member of BCS Class 2 suffers from low bioavailability following oral administration due to its poor aqueous solubility (Shete et al., 2012). Solubility improvement can be achieved by fabrication of tablets from polyethylene glycol 6000 (PEG 6000)-hydroxypropylmethyl cellulose (HPMC)-Tween 80(T-80) based solid dispersion of carvedilol using...
various excipients in definite proportions by direct compression (Dannenfelser et al., 2004). The objective of the present study was to compare the dissolution profiles of the various batches of carvedilol solid dispersion tablets and to identify the discriminatory power of the dissolution medium based on pH, in assessment of the effect of excipients like mannitol and L-hydroxypropyl cellulose LH-11 (L-HPC LH11) on dissolution process related parameters. For treatment and analysis of data, both model-dependent and model-independent approaches were adopted and parameters like dissolution efficiency, mean dissolution time, Qxmins and Ty% were determined.

METHODOLOGY

Formulation of carvedilol solid dispersion tablets

The quaternary solid dispersion (Carvedilol: Polyethylene glycol 6000: HPMC: T-80= 1:8.675:0.075:0.25) was processed by melting-solvent evaporation technique. The ratios are expressed as weight/weight. Enhancement in solubility and improvement in dissolution characteristics of the solid dispersion (SD) compared to pure drug was investigated in water and the probable mechanism was also studied with the help of X-ray diffraction, differential scanning calorimetry and scanning electron microscopy. Four batches of carvedilol tablets were fabricated from quaternary solid dispersion by direct-compression technique using Avicel PH102, dicalcium phosphate dihydrate, mannitol, magnesium stearate as excipients. The batches differed in the percentages of mannitol and L-HPC LH-11 and were represented as SDT-1 [Mannitol: 19.75% w/w], SDT-1-L [Mannitol: 19.75% w/w; L-HPC: 2.5% w/w], SDT-2 [Mannitol: 30% w/w] and SDT-2-L [Mannitol: 30% w/w; L-HPC: 2.5% w/w]. Carvedilol and HPMC were obtained as gift samples from Zydus Cadilla, Mumbai, India and Colorcon, respectively. L-HPC LH-11 was generously provided by Mylan Laboratories, Hyderabad. All the reagents and chemicals used were procured from Merck, India. Prior to compression, drug-excipient compatibility study was carried out. Powder flow behavior was characterized by angle of repose, compressibility index and Hausner ratio. Excipients were dried and sieved through mesh no. 60. Solid dispersion tablet batches were prepared by mixing the various ingredients and finally compressed in 10-station Minipress single punch tablet machine (Karnavati Engg. Pvt. Ltd., India) to produce round, flat-faced tablets, each designed to weigh around 180 mg ± 5% and contain 12.5 mg of carvedilol. The tablet shape, size, thickness and hardness were held constant for all the batches.

Evaluation of carvedilol solid dispersion tablets

Determination of wetting time

A twice-folded tissue paper (10.75 mm × 12 mm) was placed in two separate 6.5 cm diameter culture dishes containing definite volume of gastric buffer (pH = 1.2) and simulated saliva (phosphate buffer, pH = 6.8). Two drops of water soluble dye eosin was added to both the media and observations carried out at 37°C. Two tablets were carefully placed on the surface of tissue paper in the two dishes and the time required for the two buffers to reach the upper surface of the tablet was noted as the wetting time. The experiments were repeated thrice in both cases.

Determination of in vitro disintegration time

Disintegration time for the tablets was determined using digital US Pharmacopeial (USP) disintegration test apparatus (Veego India Pvt. Ltd., India) with 900 ml of gastric buffer (pH = 1.2) and simulated saliva (phosphate buffer, pH = 6.8) as the disintegrating medium. Temperature was maintained at 37°C.

In vitro dissolution study

In vitro drug dissolution of all tablet batches was carried out using USP-type II dissolution apparatus (paddle type) (8-station dissolution test apparatus, LABINDIA Model No. DS-8000). The dissolution medium [900 ml gastric buffer (pH = 1.2) or phosphate buffer (pH = 6.8)] was placed into the dissolution vessel maintained at 37 ± 0.5°C and 50 rpm and dissolution studies were carried out for 180 and 300 mins, respectively. Aliquot of 10 ml was withdrawn, replenished with fresh medium, filtered and analysed spectrophotometrically at 240 nm in both cases. The absorbance values were transformed to concentration using calibration curves in corresponding medium obtained experimentally (r2 = 0.9878 and 0.996, respectively). All tests were done in triplicate.

Comparison of in vitro dissolution data

For comparison of dissolution profiles, model-independent approaches based on the ratio of area under the dissolution curve (dissolution efficiency) or mean dissolution time were adopted. The differences between the drug release data of the tablet batches were compared using Tukey test. The significance level (α = 0.05) was based on the 95% probability value (p < 0.05). The dissolution Efficiency (DE %) was used to evaluate the dissolution performance of the batches in comparison to the marketed formulation. DE was calculated as follows (Costa et al., 2001).

\[
(\% \text{DE}) = \frac{\int_0^t Y \, dt}{Y_{100} \times 100}
\]

Where y is the percentage of drug dissolved at time t. DE was determined for the entire time period of release study for each batch. The mean in vitro drug release data (n = 3) from 0 to 85% release were fitted to different kinetic models (first order, Higuchi and Hixon- Crowell). The value of the coefficient of determination (R²) was selected as the criterion to identify the best-fit model of drug release from the tablets. The mean dissolution time (MDT) for each batch has been determined with the help of the following equation (Costa et al., 2001).

\[
\text{Mean Dissolution Time (MDT)} = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}
\]

Where j is the sample number, n is the number of dissolution sampling points, \( t_j \) is the time at midpoint between \( t_j \) and \( t_{j-1} \) [calculated as \( (t_j+t_{j-1})/2 \)], and \( \Delta M_j \) is the additional percentage of drug released in the time interval between \( t_{j-1} \) and \( t_j \). Other release parameters used to characterize and compare dissolution profiles.
Table 1. Data for determination of wetting time, disintegration time and drug release studies in phosphate buffer (pH 6.8) at 37°C (Values in the parentheses indicate mean ± standard deviation; n=3).

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Disintegration data in phosphate buffer (pH = 6.8)</th>
<th>Drug release data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wetting time (0 min: 0.0 s)</td>
<td>Disintegration time (0 min: 0.0 s)</td>
</tr>
<tr>
<td>SDT-1</td>
<td>01:48.42±0.960</td>
<td>0.038±0.010</td>
</tr>
<tr>
<td>SDT-1-L</td>
<td>00:58.98±0.080</td>
<td>0.088±0.007</td>
</tr>
<tr>
<td>SDT-2</td>
<td>00:09.01±0.140</td>
<td>0.049±0.005</td>
</tr>
<tr>
<td>SDT-2-L</td>
<td>00:06.05±0.110</td>
<td>0.102±0.004</td>
</tr>
</tbody>
</table>

for tablet batches include cumulative percent released at x mins [Q_{x mins}(%)] and time taken for a fixed percentage of drug to be released [T_{y%} (mins)]. The results obtained in two buffers are displayed in Tables 1.

RESULTS

Presence of mannitol in higher percentage (30% w/w) and simultaneous addition of 2.5% w/w L-HPC LH-11 in SDT-2-L promotes minimum wetting time and fastest disintegration in 7 mins 29.44 ± 14.91 s in phosphate buffer (pH = 6.8) (Table 1). Similar pattern in wetting time and disintegration time was also observed with the study in gastric buffer (pH = 1.2) (Table 1). It is to be noted that wetting and disintegration occurred comparatively faster in acidic pH. Positive influence of L-HPC LH-11 as well as synergistic effect of optimum percentages of mannitol and L-HPC on wetting and disintegration is clearly evident from the data. Compared to the batches containing both mannitol and L-HPC LH-11 (that is, SDT-1-L and SDT-2-L), the batches containing mannitol only (that is, SDT-1 and SDT-2) were found to perform poorly with respect to the aforementioned parameters in both the buffers. Lower percentage of mannitol along with absence of L-HPC in the batch SDT-1 resulted in slow wetting and disintegration in the buffers tested. However, increasing the percentage of mannitol to 30% in the batch SDT-2 improved the wetting and disintegration profile.

Analysis of dissolution profiles in two media with respect to Q_{45 mins}, T_{75%} and mean dissolution time (MDT) showed that the differences observed among the batches were higher in phosphate buffer (Costa et al., 2001). There was 5-fold difference in MDT and 7-fold difference in T_{75%} between SDT-2-L and SDT-1 in phosphate buffer. However, the difference in both of the aforementioned parameters between the same pair of formulations was 3-fold, respectively in gastric buffer (pH = 1.2) (Figures 1 and 2). Comparison of the drug release data for all the four batches in the buffers studied revealed that with SDT-2-L, MDT was least, Q_{45 mins} was highest and T_{75%} could be achieved fastest and just the reverse was observed with SDT-1. SDT-1 was found to possess exceptionally high MDT of 139.26 min in phosphate buffer. This indicated that comparative disintegration time between the formulations may not always predict comparable dissolution profiles. It can be concluded that presence of mannitol and L-HPC LH-11 in the batch SDT-2-L in optimum percentage promoted not only rapid wetting and disintegration but also comparatively faster and complete dissolution in contrast to other batches. Therefore, SDT-2-L can be considered as the best among the studied batches.

Tukey test procedure on data sets from phosphate buffer revealed that differences in release profiles among the four formulation batches were statistically significant at p < 0.05. But the differences between the means of cumulative release data in gastric buffer were statistically insignificant. All the formulations, except SDT-1, were found to possess similar values of dissolution efficiency (DE) in both the media, with slightly higher magnitudes in phosphate buffer. SDT-1 possessed less than 40% DE in gastric buffer, indicating incomplete and very poor drug release. Since SDT-1 was found to have least DE (%) in both the buffers, it can be concluded that inclusion of 19.75% w/w mannitol in the formulation failed to produce fast disintegration and dissolution. Summing up and comparing the results in both the media showed that mannitol percentage as well as presence of L-HPC in the formulations played a crucial role in dispersion tablets and can be successfully used to improve solubility-limited
In gastric buffer, all the tablet batches exhibited Higuchi kinetics. This indicates that drug release occurred from constant area planar surface and tablet is granular in nature, which is overruled by the direct compression method of manufacture used in the study as well as the rupture of tablets into smaller free particles during dissolution. The batches SDT-1, SDT-2 and SDT-1-L obeyed first-order kinetics in phosphate buffer whereas the best formulation, SDT-2-L followed Hixon-Crowell kinetics assuming dissolution-limited drug release rate, as is expected from a tablet of BCS Class 2 drug. Based
on the *in vitro* drug release data of the four batches in the two buffers, the order of the formulations may be represented as SDT-2-L > SDT-1-L > SDT-2 > SDT-1. But the magnitude of difference among the parameters differs greatly. Therefore, dissolution medium is found to affect the rate, kinetics and performance efficiency of dissolution process of carvedilol tablets. Unless a proper dissolution medium is selected, it is not possible to explain and characterize the influence of varying percentages of excipients on the performance of the various batches of solid dosage forms. Moreover, improper selection of dissolution medium may also misinterpret drug release kinetics from the formulations.

**DISCUSSION**

Mannitol is used in tablet manufacture to improve mouth-feel properties and promote swelling-induced faster disintegration and/or dissolution whose action is further accentuated by addition of low percentage of hydrophilic low-substituted cellulose ether, like L-hydroxypropylcelluloses (L-HPC). Synergistic effect of increasing percentage of mannitol and constant level of L-HPC on wetting time and oral disintegration time is observed progressively in the four tablet batches. Similar pattern was followed during *in vitro* release study from the tablets in phosphate buffer. However, gastric buffer as the dissolution medium failed to discriminate between the effects of the excipients on the *in vitro* performance of the tablet batches studied. Therefore, characterization and proper gradation of different tablet formulations of a BCS Class 2 drug essentially depends on the selection of a dissolution medium possessing high discriminatory power.

**REFERENCES**


