Formulation of Irbesartan by Microcrystal Technology for Enhancing the Solubility and Dissolution Properties

Stuti A. Jain* and Nalini S. Kurup

Department of Pharmaceutics, Prin. K. M. Kundnani College of Pharmacy, Cuffe Parade, Colaba, Mumbai 400005, India.

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ABSTRACT

The aim of this study was to develop the formulation of irbesartan by microcrystal technology to enhance the solubility and dissolution property of the drug. The area of interest in the study carried out is Class II drugs cited in the Biopharmaceutical Classification System. Microcrystal technology is a new carrier-free colloidal drug delivery system with reduced drug particle size and is considered a viable strategy in drug delivery to develop formulations of poorly soluble drugs. In the present study, an attempt was made to enhance the solubility of the drug irbesartan compared to its pure form by microcrystal technology. Drug microcrystals were prepared by the anti-solvent precipitation process. The specified amount of drug was dissolved in methanol and PVP K30 was dissolved in water. The two phases were mixed instantaneously, wherein the drug solution was kept on continuous stirring and the aqueous phase was added to this continuous phase. The particle size of the drug was not reduced, but enhancement in solubility and dissolution properties of the drug were still observed. This could be due to the wettability property of PVP K30. The FT-IR spectra and DSC thermograms confirmed no interference of drug and the stabilizer. XRD studies confirmed the formation of crystals of the drug irbesartan. Thus, it could be concluded that microcrystal technology is a promising approach for solubility enhancement of irbesartan.

KEYWORDS: Poor solubility; Irbesartan; PVP K30; microcrystals; solubility enhancement.

Introduction

More than 40% of active substances during formulation development by the pharmaceutical industry are poorly water soluble (Martinez et al., 2002). Poor water solubility is associated with poor dissolution characteristics. Dissolution rate in the gastrointestinal tract is the rate limiting factor for the absorption of these drugs, and so they suffer from poor oral bioavailability (Amidon et al., 1995). For BCS class II-drugs, the dissolution rate is the limiting factor for the drug absorption rate (Lobenberg et al., 2000). An enhancement in the dissolution rate of these drugs can increase the blood-levels to a clinically suitable level. The increasing frequency of poorly soluble new chemical entities exhibiting therapeutic activity is a major concern to the pharmaceutical industry. Such drugs are difficult to process or administer to patients due to poor dissolution. This is the major hurdle that prevents the commercialization of poorly water soluble drugs (Bindu et al., 2010).

Irbesartan is a non-peptide, angiotensin II receptor antagonist with high specificity for the AT1 subtype used in the treatment of hypertension. The drug is lipophilic and practically insoluble in water. The oral route is the easiest and most convenient way of non-invasive administration. However, oral drug delivery may hamper drug molecules that exhibit a poor aqueous solubility (Patel et al., 2011). The main objective of the project was to develop an oral dosage form which can provide immediate release of orally administered Irbesartan so that the immediate dissolution of irbesartan in the aqueous contents of the stomach is achieved, complementing its increase in solubility as well as permeability, prompting fast onset of action and maximum drug release within few minutes.

Materials and Methods

Chemicals and Drugs

Irbesartan (IBS) [1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyI-3-[(2’-1H-tetrazol-5-yl)1-[1,1’-biphenyl]-4-y] methyl] -2-Butyl-3-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one] was provided as a gift sample by Cadila Healthcare Ltd., Vadodara. PVP K 30 was provided as a gift sample by SD Fine Chem Ltd, Mumbai. Methanol and hydrochloric acid used were of Merck grade. Double distilled water was used throughout the study.

Phase-solubility Analysis

Phase-solubility measurements were carried out according to the method of Higuchi and Connors (Higuchi
The resulting mixture was equilibrated by placing the flasks on the rotary shaker at room temperature for 48 hrs at 150 rpm. To minimize photochemical degradation, flasks were covered with aluminum foil. Then, suspensions were filtered through Whatman filter paper (grade 1, 110 mm diameter) to remove undissolved solids. An aliquot from each vial was adequately diluted and spectrophotometrically analyzed for Irbesartan at 244 nm. Shaking was continued until three consecutive experiments yielded similar results.

**Preparation of Microcrystals**

**Optimization of solvent change precipitation procedure:**

The solvent change precipitation procedure was carried out by mixing two liquids instantaneously in the presence of a stabilizing agent. The organic (solvent) phase was a methanolic solution of irbesartan (1g/40ml). Here, PVP K 30 was selected as the stabilizing agent present in the aqueous phase (Keraliya et al., 2010). Firstly, the organic solution of the drug was prepared by dissolving 150 mg of the drug in 15 ml of methanol and kept on a magnetic stirrer at 400 rpm. The aqueous (non-solvent) phase as specified for the mentioned ratios was then poured instantaneously to the methanolic drug solution of Irbesartan kept under stirring using a magnetic stirrer. This leads to supersaturation of the drug, subsequent nucleation, and crystal formation. The entire process was carried out at room temperature conditions. The solution mixture was stirred for 1 hour. The crystals were collected on Whatman filter paper (grade 1, 110mm diameter) followed by 3 washings with cold water to remove non-adsorbed excipients if any. The crystals so obtained were dried in an oven at 50°C for 2 hours. In the experiment four different solvent ratios (1:2, 1:4, 1:8, 1:16) of solvent to anti-solvent were tried for selection of most appropriate ratio to get crystals of smallest size and with maximum yield. Here the concentration of stabilizing agent was selected as 0.5% and was kept constant for all the four batches to avoid stabilizing agent concentration as a limiting factor. Then a second experiment was conducted using the selected solvent ratio and six different concentrations of the stabilizing agent (0.01, 0.02, 0.05, 0.1, 0.2, 0.5%) in order to estimate the minimum concentration of PVP (stabilizer) required to obtain the smallest stable drug particle size with maximum yield (Marcilio et al., 2008).

**Characterization of Crystals**

**Solubility study**

An excess amount of Irbesartan (pure drug) and microcrystals equivalent to 15mg of drug were weighed and added to stoppered conical flasks containing 10ml of distilled water and subjected to shaking on a rotary shaker for 48 h at 37°C. The flasks were then equilibrated for 2 days, and aliquots filtered and analyzed using UV-Vis spectrophotometer at 244 nm for drug content after appropriate dilution with distilled water and compared with pure drug solubility (Mahapatra, 2011).

**Drug content estimation**

The percent drug content of microcrystals was estimated by dissolving 150 mg quantities of microcrystals in methanol, mixing thoroughly by shaking, and the making up volume to the mark with the solvent (0.1 N HCl). The solution was filtered and the filtrate was diluted suitably with 0.1 N HCl pH 1.2 and analyzed at 244 nm using UV-Vis spectrophotometer (Aruna et al., 2011).

**Particle size analysis**

Particle size determination for drug and the microcrystal formulation batches M1-M9 was determined by using a particle size analyzer (Mastersizer, 2000). Particle size was reported as a mean for the microcrystal batches. Prior to the measurement, the samples were diluted appropriately with water to a suitable scattering intensity and re-dispersed by shaking before measurement.

**Fourier transform infrared spectroscopy (FTIR)**

FTIR Spectroscopy was performed on each of the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample. FT-IR spectra were recorded using an FT-IR spectrophotometer (Shimadzu) and examined in the transmission mode. The samples (Irbesartan and its microcrystals) were ground to a fine powder using agate mortar & pestle and transparent discs formed using a pellet press and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:10 (Sample: KBr) ratio, respectively. The discs were placed in FTIR spectrophotometer apparatus and spectra were recorded. Forty scans were obtained at a resolution of 4 cm⁻¹, from 4000 to 400 cm⁻¹.

**Differential scanning calorimetry (DSC)**

A differential scanning calorimeter (Perkin-Elmer) was used. The equipment was calibrated using indium and zinc. Samples were heated at 10 °C/min in aluminium pans under nitrogen atmosphere. The onsets of the melting points and enthalpies of fusion were calculated by the software (STAR SW® 9.20). DSC graphs for drug, physical mixture of drug with PVP K30, and drug microcrystals were recorded. DSC was used to confirm the formation of the final selected formulation of microcrystals of Irbesartan. The melting point, peak maxima, and the presence and absence of endotherm peaks were observed in the DSC graphs.

**Scanning electron microscopy**

Scanning electron micrographs of Irbesartan, Irbesartan microcrystals without PVP K30, Irbesartan microcrystals optimized batch 1:2, 0.1% PVP K30, and Irbesartan microcrystals batch 1:2, 0.5% PVP K30 were...
taken using scanning electron microscope. Samples were fixed on an aluminum stub with conductive double-sided tape and coated with gold by a sputter coater (50 Pa) at 50mA for 50 sec.

**Powder X-ray diffraction**

Samples were evaluated using an Xpert Diffractometer to assess the solid state of Irbesartan, excipient, and microcrystals. The samples were radiated using a Cu target tube and exposed to all lines. The scanning angle ranged from 2’ to 40’ of 2θ, steps were 0.02’ of 2θ, and the counting time was 0.6 s per step. The current used was 40mA and the voltage 40 kV (Chawla and Bansal, 2007).

**Flow property study**

The bulk density and tapped density of pure drug and microcrystal batch M5 and M6 were determined. The Carr’s index and Hausner’s ratio were calculated from the bulk and tapped density. The angle of repose was calculated by the fixed funnel method.

**Wettability study**

Drug powder and selected microcrystal formulations M5 and M6 were placed in a sintered glass funnel with 33 mm internal diameter. The funnel was plunged into a beaker containing water such that the surface of water in the beaker was at the same level as the powder in the funnel. Methylene blue powder (10 mg) was layered uniformly on the surface of the drug and formulations in the funnel. The time required for wetting of methylene blue powder was measured. The mean of three observations was used for drawing the conclusions.

**In vitro dissolution study**

Microcrystals were filled in capsules and the dissolution tests for Irbesartan (pure drug), the marketed formulation, and all microcrystal batches were performed.

The dissolution testing was performed using USP Type II apparatus (paddle).

The dissolution medium used was 0.1 N HCl pH 1.2 (900 ml) and was set at a speed of 50 rpm at 37±0.5 °C. 5ml of the sample was withdrawn at specific time intervals and replaced with fresh dissolution medium at suitable time intervals up to 120 minutes. The sample solution was diluted with the dissolution medium and analyzed by UV-Vis spectrophotometer at 244 nm. The batch that gave the maximum drug release was selected as the final formulation (Patel et al., 2011).

**Results and Discussions**

**Phase Solubility Study**

Phase solubility study was performed according to the method reported by Higuchi and Connors. The phase solubility diagram showed a linear increase in drug solubility with an increase in the concentration of the stabilizer. Hydrophilic carriers mainly interact with drug molecules by electrostatic bonds, even though other forces like such as Vander Waals forces and hydrogen bonds may also play a role in the drug-carrier interaction. Drug solubility increased linearly with increasing concentration of PVP K30, indicating an A1-type phase solubility diagram.

**Optimization of Solvent Change**

**Precipitation Procedure**

Table 1 represents the particle size of pure drug and all microcrystal batches formulated using different concentrations of PVP K30. The minimum concentration of the stabilizer PVP K30 required for obtaining maximum yield of the drug and a stable particle size was observed to be 0.1%. The selection of the solvent: antisolvent ratio was based on the crystal yield of microcrystals at various ratios and different stabilizer concentrations. The batch 1:2 gave maximum yield of the drug so this batch was optimized for the different concentrations of PVP K30. The batches 1:4, 1:8 and 1:16 would have been insufficient to produce high crystal yield, which may be due to the high aqueous phase volume that could have solubilized a fraction of Irbesartan. The batch 1:2 would have entailed efficient polarity change to bring out maximum crystallization of the drug. It was also observed that as the stabilizer concentration decreased, a reduction in particle size was observed and a fluffy powder was obtained.

**TABLE 1**

<table>
<thead>
<tr>
<th>% Carrier (w/w)</th>
<th>Amount of drug solubilized (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.0958</td>
</tr>
<tr>
<td>0.02</td>
<td>0.1097</td>
</tr>
<tr>
<td>0.05</td>
<td>0.1145</td>
</tr>
<tr>
<td>0.1</td>
<td>0.1223</td>
</tr>
<tr>
<td>0.2</td>
<td>0.1357</td>
</tr>
<tr>
<td>0.5</td>
<td>0.1758</td>
</tr>
</tbody>
</table>

**Solubility Study**

The saturation solubility of the microcrystals showed an increase in the solubility of the drug in the formulation. Thus, micronization of the drug leads to an increase in the solubility of the drug. Therefore, it can theoretically be stated that an increase in the saturation solubility of the Irbesartan microcrystal formulation may also lead to bioavailability enhancement. The batch M6 showed a saturation solubility of 7.24 and that of pure drug was 0.0864mg/ml. Thus, there was found to be an 84-fold enhancement in solubility of the drug in the form of microcrystals.

**Particle size Analysis**

The batch M6 showed particle size of 31.930 µm with 90% of particles in this range, whereas the particle size of pure drug was reported to be 19.554 µm. The microcrystals prepared using PVP K30 as a stabilizing agent showed greater particle size than the drug, still higher aqueous solubility, and high in vitro dissolution.
confirmed that the drug remained in the crystalline state. The batch M6 showed the least particle size of all the batches prepared as well as maximum crystal yield and showed maximum drug release compared to all other batches. This could be due to the increase in the wettability of the drug by the stabilizing agent.

Fourier Transform Infrared Spectroscopy (FTIR)

All the characteristic peaks representing respective functional groups for Irbesartan are present in the spectrum of the formulation. No additional peak was found in the above spectrum which indicates that there is absence of any incompatibility between Irbesartan and PVP K30.

Differential Scanning Calorimetry (DSC)

DSC is a highly useful means of detecting drug-excipient interactions. Thermal behavior of Irbesartan, PVP K30 and the physical mixture of IBS and PVP K 30 were studied using DSC. DSC thermogram of Irbesartan showed an endotherm at 186.70°C (Fig. 14). Broad peak was observed for PVP K30 at 95.69 °C (Fig. 15) respectively. The thermogram of the physical mixture of PVP K30 and Irbesartan (Fig. 16) almost the overlapped each individual component, except for some slight differences, and showed the peak of PVP K30 at 95.81°C, and integrated peak of Irbesartan at 184.75°C. The area under the curve for the Irbesartan thermogram in physical mixtures (Fig. 14 and Fig. 16) was less compared to that of Irbesartan alone. This may be due to the melting of the stabilizer and its interaction with Irbesartan. The DSC thermogram of Irbesartan microcrystals (Fig. 17) reveals the characteristic presence of the melting peak of Irbesartan at 178°C that confirmed that the drug remained in the crystalline state. Besides this, no additional peaks to demonstrate significant changes in the melting characteristics of Irbesartan in the formulation were found. It can also be concluded that the melting curve of Irbesartan was not influenced by the stabilizer or by the formulation technique.

Scanning Electron Microscopy

Scanning electron micrographs of Pure IBS drug powder showed irregular rectangular platy shaped crystals, while crystals without PVP appeared as elongated irregular platy shaped crystals. The batch prepared using 0.1% PVP were seen as thin needle like and 0.5% PVP microcrystals as thin rods.

Powder X-ray Diffraction

As seen in Fig. 19, irbesartan has a characteristic X-ray diffraction pattern in the fingerprint region as compared to PVP which shows broad reflectance. PVP being amorphous meant it did not show any sharp peaks. The powder X-ray diffraction patterns of irbesartan and formulations with 0.5% PVP and 0.1% PVP showed characteristic high intensity diffraction peaks, which are the characteristic features of a crystalline compound. This indicates that the formulation technique did not influence the crystallinity or polymorphic transition of the drug and the stabilizers did not influence the crystallinity of Irbesartan microcrystals.

Flow Property Study

The Bulk density, Tapped density, Angle of repose, % Carr’s index, and Hausner’s ratio for pure drug and Irbesartan microcrystals prepared with PVP K30 are reported in table 4. Pure drug powder exhibited poor flowability and compressibility, as indicated by high values of Carr’s index (29.49 ± 2.22%), Hausner’s ratio (1.42 ± 0.004) and angle of repose (37.700 ± 1.1). This could be due to the irregular rod shape, which put hurdles in the uniform flow of powder from the funnel.

Wetting Time

The wetting time of pure drug and Irbesartan microcrystals prepared with PVP K30 is reported in table 4. The wetting time of pure drug was observed to be 89 seconds, which indicated poor wettability of the drug. The wetting time of microcrystals batch M6 was observed to be 70 seconds, which was less than that of pure drug. This may be due to the increased wetting action of the hydrophilic stabilizer PVP K30 used in the formulation.

In vitro Dissolution Study

The in vitro dissolution data showed that 66-89% of the drug was dissolved in 90 minutes, and there was increase in the dissolution of drug in formulations compared to the pure form. The batch 1:2 accounted for maximum yield of the drug microcrystals and in turn resulted as the batch that gave a % cumulative release (%CR) of 89.08% as compared to the pure drug which gave 40.436% release. Formation of partially amorphous irbesartan during crystallization as seen from X-ray diffraction spectra could also be a minor factor involved in dissolution enhancement.

The formulation strategy for preparing microcrystals led to solubility enhancement of irbesartan. The successfully formulated microcrystals led to a better solubility profile of the drug in its microcrystal form when compared to its pure form. The saturation solubility of Irbesartan microcrystals showed an 84-fold enhancement over pure drug. The XRD and DSC pattern of the drug and formulation confirmed that the crystalline nature of the drug remained unchanged in the formulation as well. The enhanced dissolution profile of drug microcrystals attributed to the increased wettability of the drug in the formulation and formation of a hydrophilic surface. In conclusion, it can be stated that microcrystal technology is a promising strategy to increase the solubility and dissolution rate of poorly soluble drugs.
Phase solubility analysis

![Phase solubility diagram of microcrystals.](image)

**Fig. 1.** Phase solubility diagram of microcrystals.

**TABLE 2**
Crystal yield, mean particle size and drug content of microcrystal batches M1-M9.

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Formulation</th>
<th>PVP conc. (%)</th>
<th>Code</th>
<th>Crystal yield (mg)</th>
<th>Mean particle size (µm)</th>
<th>Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IBS</td>
<td>-</td>
<td>-</td>
<td>150</td>
<td>19.554</td>
<td>98.93±0.76</td>
</tr>
<tr>
<td>2</td>
<td>1:2</td>
<td>0.5</td>
<td>M1</td>
<td>130.1</td>
<td>50.350</td>
<td>90.89±0.36</td>
</tr>
<tr>
<td>3</td>
<td>1:4</td>
<td>0.5</td>
<td>M2</td>
<td>123.5</td>
<td>54.430</td>
<td>86.44±0.78</td>
</tr>
<tr>
<td>4</td>
<td>1:8</td>
<td>0.5</td>
<td>M3</td>
<td>115.8</td>
<td>58.420</td>
<td>77.39±0.62</td>
</tr>
<tr>
<td>5</td>
<td>1:16</td>
<td>0.5</td>
<td>M4</td>
<td>99.4</td>
<td>57.793</td>
<td>66.26±0.56</td>
</tr>
<tr>
<td>6</td>
<td>1:2</td>
<td>0.2</td>
<td>M5</td>
<td>111.5</td>
<td>47.253</td>
<td>90.28±0.55</td>
</tr>
<tr>
<td>7</td>
<td>1:2</td>
<td>0.1</td>
<td>M6</td>
<td>123.8</td>
<td>31.930</td>
<td>92.88±0.78</td>
</tr>
<tr>
<td>8</td>
<td>1:2</td>
<td>0.05</td>
<td>M7</td>
<td>135.4</td>
<td>37.479</td>
<td>85.78±0.24</td>
</tr>
<tr>
<td>9</td>
<td>1:2</td>
<td>0.02</td>
<td>M8</td>
<td>138.3</td>
<td>44.253</td>
<td>82.44±0.44</td>
</tr>
<tr>
<td>10</td>
<td>1:2</td>
<td>0.01</td>
<td>M9</td>
<td>133.7</td>
<td>55.563</td>
<td>76.89±0.90</td>
</tr>
</tbody>
</table>

Particle size data

![Particle size data of irbesartan.](image)

**Fig. 2** Particle size data of irbesartan.
Fig. 3 Batch M1.

Fig. 4 Batch M2.

Fig. 5 Batch M3.
Fig. 6 Batch M4

Fig. 7 Batch M5.

Fig. 8 Batch M6.
Fig. 9 Batch M7.

Fig. 10 Batch M8.

Fig. 11 Batch M9.
**Fig. 12.** IR spectra of Irbesartan.

**Fig. 13.** IR spectra of microcrystals batch 1:2; 0.1% PVP.

**Table 3**
Comparison of IR spectra of pure drug and formulation.

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Bond</th>
<th>Frequency range cm⁻¹</th>
<th>Pure drug IR bonds cm⁻¹</th>
<th>Formulation, IR bonds cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-H Stretch</td>
<td>3600-3300</td>
<td>3446.79</td>
<td>3439.08</td>
</tr>
<tr>
<td>2</td>
<td>Aromatic C-H Stretch</td>
<td>3150-3000</td>
<td>3053.32</td>
<td>3053.32</td>
</tr>
<tr>
<td>3</td>
<td>Aliphatic C-H Stretch</td>
<td>3000-2850</td>
<td>2960.73 and 2873.94</td>
<td>2953.02 and 2872.01</td>
</tr>
<tr>
<td>4</td>
<td>C=O Stretch</td>
<td>1750-1730</td>
<td>1732.08</td>
<td>1732.08</td>
</tr>
<tr>
<td>5</td>
<td>C-N Stretch</td>
<td>1700-1615</td>
<td>1616.35</td>
<td>1614.42</td>
</tr>
<tr>
<td>6</td>
<td>Aromatic C=C Bend and Stretch</td>
<td>1600-1400</td>
<td>1435.04 and 1409.96</td>
<td>1433.11 and 1415.75</td>
</tr>
</tbody>
</table>

**Fig. 14** DSC of irbesartan.
Fig. 15 DSC of PVP K30.

Fig. 16 DSC thermogram of physical mixture.

Fig. 17 DSC thermogram of irbesartan microcrystals.
Fig. 18. Photographs of (a) pure drug, (b) microcrystals without PVP, (c) microcrystals with 0.1% PVP, and (d) microcrystals with 0.5% PVP.

Fig. 19. X-Ray powder diffraction pattern of irbesartan, PVP K30, microcrystals with 0.1% PVP K30 and microcrystals with 0.5% PVP K30.

TABLE 4
Flow property and wettability study of drug and formulation.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Bulk density</th>
<th>Tapped density</th>
<th>Carr’s index</th>
<th>Hausner's ratio</th>
<th>Angle of repose</th>
<th>Wetting time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure drug</td>
<td>41.25°</td>
<td>2.8</td>
<td>1.9</td>
<td>0.678</td>
<td>47.368</td>
<td>89</td>
</tr>
<tr>
<td>M6</td>
<td>28.09°</td>
<td>2.5</td>
<td>1.8</td>
<td>0.576</td>
<td>38.888</td>
<td>70</td>
</tr>
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</table>

TABLE 5
Dissolution profile of batches M1-M4.

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Pure drug</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>11.708±0.59</td>
<td>4.8399±0.45</td>
<td>5.466±0.65</td>
<td>20.088±0.37</td>
<td>19.02±0.55</td>
</tr>
<tr>
<td>10</td>
<td>23.246±0.43</td>
<td>9.05±0.73</td>
<td>34.25±0.52</td>
<td>40.16±0.67</td>
<td>40.16±0.67</td>
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<tr>
<td>15</td>
<td>42.705±0.28</td>
<td>58.56±0.64</td>
<td>60.24±0.49</td>
<td>52.08±0.42</td>
<td>52.08±0.42</td>
</tr>
</tbody>
</table>

*Values expressed as Mean±S.D.

TABLE 6
Dissolution profile of batches M5-M9.

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>M5</th>
<th>M6</th>
<th>M7</th>
<th>M8</th>
<th>M9</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>14.965±0.82</td>
<td>8.1942±0.73</td>
<td>7.868±0.53</td>
<td>1.268±0.63</td>
<td>14.19±0.57</td>
</tr>
<tr>
<td>10</td>
<td>23.554±0.43</td>
<td>22.66±0.29</td>
<td>23.79±0.35</td>
<td>24.63±0.25</td>
<td>24.63±0.25</td>
</tr>
<tr>
<td>15</td>
<td>38.725±0.74</td>
<td>38.67±0.74</td>
<td>37.16±0.84</td>
<td>49.30±0.44</td>
<td>49.30±0.44</td>
</tr>
<tr>
<td>20</td>
<td>61.36±0.55</td>
<td>54.46±0.34</td>
<td>54.46±0.34</td>
<td>45.97±0.33</td>
<td>45.97±0.33</td>
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<tr>
<td>30</td>
<td>76.017±0.36</td>
<td>73.69±0.58</td>
<td>84.76±0.67</td>
<td>62.45±0.30</td>
<td>62.45±0.30</td>
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<tr>
<td>60</td>
<td>84.78±0.35</td>
<td>83.36±0.64</td>
<td>77.24±0.65</td>
<td>73.26±0.83</td>
<td>73.26±0.83</td>
</tr>
<tr>
<td>90</td>
<td>88.47±0.46</td>
<td>85.93±0.34</td>
<td>85.93±0.34</td>
<td>74.02±0.45</td>
<td>74.02±0.45</td>
</tr>
<tr>
<td>120</td>
<td>88.08±0.75</td>
<td>86.85±0.34</td>
<td>86.85±0.34</td>
<td>74.07±0.26</td>
<td>74.07±0.26</td>
</tr>
</tbody>
</table>

*Values expressed as Mean±S.D.
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**References**


Address correspondence to: Stuti A. Jain, A/703, Ramdev Park, Chandavarkar Road, Borivali (West), Mumbai-400092. Mob: 9819335532 E-mail: stuti.j19@gmail.com