IRBESARTAN DISSOLUTION ENHANCEMENT USING PEG-BASED SOLID DISPERSIONS: THE EFFECT OF PEG MOLECULAR WEIGHTS

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Abstract

The aim of the present study was to enhance the dissolution of irbesartan (IBS, a poorly soluble drug, using solid dispersion (SD) with different molecular weights of polyethylene glycol (PEG)). Irbesartan loaded SDs and PMs (physical mixtures) were prepared with different drug: carrier ratios using PEG 6000, 10000 and 20000. Dissolution behaviour, physical state of formulations as well as solubility were studied on the formulations. Based on the results, the dissolution rate was remarkably increased in all formulations compared to the intact IBS. However, the dissolution improvement in SDs was more than related PMs. The PEG molecular weight was an effective factor on the results. The highest dissolution efficiency (DE$_{60}$ = 95.47%) was obtained for IBS:PEG 10000 ratio of 1:5. Saturation solubility of IBS was also increased significantly due to the presence of hydrophilic carrier as well as reduced drug particle size. The negative values of Gibbs free energy revealed the spontaneous process of drug solubilisation in aqueous polymer environment. The results confirmed no polymorphic changes during sample preparation.

Keywords: irbesartan, solid dispersion (SD), PEG, dissolution, physical mixture (PM)

Introduction

Irbesartan (IBS), a specific competitive blocker of the angiotensin II receptor, is orally used for the treatment of hypertension as well as renal disease in hypertensive diabetic patients [1]. It also decreases the risk of the end stage renal disease [2]. IBS is classified as a Biopharmaceutics Classification System (BCS) class-II compound, a lipophilic and highly membrane permeable drug, with negligible water solubility [3, 4]. The low aqueous solubility and slow dissolution rate of IBS leads to low bioavailability [5]. It seems that, improving IBS dissolution rate could be an approach to improve its bioavailability [6].

There are many strategies to improve the dissolution rate of poorly water-soluble drugs [7, 8]. Changing the physical properties (particle size reduction) increases the surface area and consequently improves the drug dissolution. However, lower particle size can lead to poor mechanical properties. Chemical changes in the drug structure such as adding polar or ionisable groups as well as salt formation are other methods. Although salt formation is commonly used, it can be a choice only for acidic or basic compounds and it could not be performed on neutral drugs [9]. Modification of crystalline behaviour in order to obtain desirable solubility could be a suitable method, although, meta-stable polymorphs usually transform to the stable form during storage [8].

Solid dispersion (SD) which is defined as “dispersion of drug molecules in an inert carrier in the solid state” could be considered as an effective method of dissolution rate enhancement [10]. Food and Drug Administration (FDA) recommends solid dispersion as the first choice of solution for solubility problems [11].

Various possible mechanisms could be considered to explain the dissolution rate enhancement of drugs from SDs. Particle size reduction, formation of eutectic
mixture as well as solid solution, wetting improvement due to the presence of high concentration of water soluble carrier on the surface of SD and decreased agglomeration are some explanations for increasing the dissolution and the solubility of slightly soluble drugs from these systems [12, 13].

Solid dispersion is an economic and feasible method [14], in which carrier selection and the method of preparation have important roles in the final properties. Different methods including spray-drying, solvent evaporation and hot-melt extrusion, and various materials such as hydrophilic polymers and surfactants are used to prepare SDs [15, 16]. Polyethylene glycol (PEG) is regarded as an efficient pharmaceutical excipient which interacts with many water insoluble drugs or their lipophilic moieties via dynamic complex formation, thereby overcoming undesirable physicochemical properties including poor dissolution rate, low aqueous solubility and limited drug stability [17, 18]. It was confirmed that as a hydrophilic carrier, PEG molecular weight has an apparent influence on the drug dissolution rate from SDs [19-21].

Only a few investigations were performed regarding IBS dissolution rate enhancement using solid dispersion. The effect of high molecular weight polymers such as hydroxypropyl methylcellulose and polyvinyl pyrrolidone on IBS solid dispersion properties was previously studied [3, 6, 22, 23]. It was also reported that hydroxypropyl-β-cyclodextrin and its derivative enhanced dissolution rate of IBS by complex formation [4, 24]. PEG 6000-containing formulations were also used to prepare fast dissolving tablet in another investigation [25]. After a vigorous consultation of the scientific data, no study has been carried out regarding the effect of PEG with different molecular weights on IBS solid dispersions.

The aim of the present study was to evaluate and to improve the IBS physical properties and the dissolution rate by preparing solid dispersions using different molecular weights of PEG and compare their effect on IBS dissolution profile.

\[
\text{Dissolution Efficiency (DE\%)} = \left( \frac{\int_0^{t_f} y(y_0t) \, dt}{y_0 t_f} \right) \times 100\% ,
\]

Mean dissolution time (MDT) was calculated arithmetically by the following equation [27]:

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

where \(j\) is the dissolution sample, \(n\) is the number of dissolution sample time, \(t_j\) is the time at the midpoint between times \(t_j\) and \(t_{j+1}\) (calculated by \([t + (t-1)/2]\)\)

Materials and Methods

**Materials.** IBS and PEGs were purchased from Zhejiang Tianyu Pharmaceutical Co. (China) and Fluka (Germany), respectively. All other solvents and chemicals were of pharmaceutical grades.

**Preparation of solid dispersions.** SDs of IBS: PEGs with different weight ratios of 1:1, 1:3 and 1:5 were prepared by solvent evaporation method. Sufficient amount of IBS and PEG were dissolved in 20 mL ethanol for 30 min, stirred at 300 rpm. The mixture was kept in oven for 48 h at 40°C in order to obtain a dry cake. After milling, the resulting mixtures were sieved and particles between 80 to 200 mesh sizes were isolated for the experiments. The mixtures were stored in a screw-cap vial at room temperature until use. Different PEG grades (6000, 10000 and 20000) were used for SDs preparation.

**Preparation of physical mixtures.** Physical mixtures (PM) of IBS with different above mentioned grades of PEG were prepared by homogeneous mixing of individual components that had previously been sieved through no. 80 - 200 sieves to reach weight ratios of 1:1, 1:3 and 1:5 of IBS:PEG.

**In vitro dissolution tests.** Dissolution rate of all samples was studied using USP type I (basket) dissolution test apparatus (Erweka DT6R, Germany) in 500 mL 0.1 N hydrochloric acid at 37 ± 0.5°C at a rotation speed of 50 rpm. Five millilitres of the medium was withdrawn at predetermined time intervals and replaced with the same amount of fresh dissolution medium after each sampling. The sample solutions were analysed for drug content at 244 nm by a UV spectrophotometer (Shimadzu UV1201, Japan).

**Dissolution data analysis.** The amount of dissolved IBS during the first 10 min of dissolution test was considered as \(Q_{t=0}\) and used to compare the formulations. In addition, dissolution efficiency which is the area under the dissolution curve from 0 to 30 min (DE\%\(_{30}\)) and 0 to 60 min (DE\%\(_{60}\)) was calculated based on the below formula, where \(y\) is the amount of drug dissolved in time of \(t\), numerator shows area under the dissolution curve till time \(t\) and denominator shows area until time \(t\) [18, 26].

\[
\text{Relative dissolution (RD) was calculated by following equation in which numerator and denominator demonstrate the amount of the dissolved drug in the t time (10 min) from the prepared formulations and pure sample, respectively [28].}
\]

\[
\text{RD\%_}{t} = \frac{Q_{t(formulation)}}{Q_{t(Pure\ drug)}}
\]
**X-ray powder diffraction (XRD).** To evaluate the crystalline properties of the prepared samples, XRD patterns were recorded using Phillips Analytical X’Pert diffractometer (The Netherlands) using CuKα radiation generated at 30 mA and 40 kV with the scan rate of 1°/min. Samples were analysed between 20 angles of over 2 - 40.

**Differential scanning calorimetry (DSC).** The DSC measurements were performed on a Shimadzu DSC-60 (Japan) differential scanning calorimeter. After calibrating the apparatus by indium standard, accurately weighed samples (3 - 5 mg) were placed in sealed aluminium pans and heated up to 200°C with the rate of 10°C/min.

**Infrared spectroscopy (IR).** About 2 mg of selected samples was triturated with about 70 mg of potassium bromide and compressed into a 12 mm disc at 10 ton pressure. IR adsorption spectra were recorded over a range of 200 - 4000 cm⁻¹ using Perkin-Elmer 843 (UK) spectrophotometer.

**Scanning electron microscopy (SEM).** In order to evaluate the external morphology and shape of the particles, the intact drug and selected samples were coated with gold layer and analysed using scanning electron microscope (Philips XL30, The Netherlands).

**Saturation solubility.** In order to study the effect of hydrophilic carrier on the drug solubility, saturation solubility tests were performed in distilled water. Excess amounts of pure drug, selected PM and SD were added to 10 mL water in glass vials which were subsequently tightly closed and stirred for 48 h at ambient temperature. After centrifuging the samples for two 15 min periods at 12000 rpm, appropriate aliquots were withdrawn, filtered, diluted and analysed spectrophotometrically at 244 nm. The mean results of triplicate measurements were reported for each sample.

**Phase solubility.** Excess amount of IBS was added to 10 mL of aqueous solutions containing different concentrations (2.5, 5, 7.5 and 10% w/v) of PEG. The samples were then kept under stirring at 300 rpm for 48 h, at ambient temperature before being centrifuged in two 15 min periods at 12000 rpm, filtered and assayed spectrophotometrically at 244 nm. Each test was performed in triplicate.

The data obtained from phase solubility studies were used to calculate the Gibbs free energy of transfer of IBS as follows [29]:

\[ \Delta G_{tr}^0 = -2.303RT \log S_0/S_1 \]

\( S_0/S_1 \) is defined as the ratio of the molar solubility of IBS in aqueous PEG to pure water.

**Statistical analysis.** Statistical analysis of the dissolution parameters was carried out using the two-way analysis of variance (ANOVA). Significance was tested at the 0.05 level of probability.

**Results and Discussion**

The dissolution profiles obtained for untreated IBS, PMs and SDs prepared with drug: carrier ratios of 1:1, 1:3 and 1:5 using various molecular weights of PEG are shown in Figures 1.

Based on Figure 1, dissolution of SDs and PMs made by IBS:PEG 6000 with all ratios was obviously higher than that of the intact drug (p < 0.01). According to Table I, during the first 10 min of dissolution study, more than 78% of IBS was dissolved from SDs prepared using various concentrations of PEG 6000, which was significantly enhanced compared to the untreated IBS (p < 0.001). This is a better achievement in comparison with a previous study in which the same amount of drug from IBS:PEG 6000 solid dispersion (1:1) was dissolved during 60 min [30]. \( \text{DE}_{50} \) was reported 64.8 and 70.2 % for the ratios of 1:1 and 1:2, respectively, while in the present study, it was obtained about 80 % for the sample with drug: carrier ratio of 1:1 (Table I).

All SDs containing PEG 6000 dissolved faster compared to PMs (p < 0.05), confirming the positive effect of solid dispersions in dissolution enhancement. Although, no significant difference was observed between \( \text{DE}_{30} \) and \( \text{DE}_{50} \) for these formulations, but the values of \( Q_{10} \) and MDT were improved obviously for the ratio of 1:5 compared to the ratios of 1:3 and 1:1 (Table I). Based on the results, relative dissolution (RD) of the above mentioned formulations was in the range of 1.65 - 1.81 and 1.36 - 1.6 for SDs and PMs, respectively.

Using PEG 10000 in the preparation of IBS solid dispersions generated in formulations with desirable dissolution behaviour. Figure 1 show that more than 95% of drug was dissolved in the first 10 min of dissolution test from SD10000-5, which is more than 4 times higher than the intact drug. Comparing the dissolution data (Table I) reveals that \( Q_{10} \), \( \text{DE}_{30} \) and \( \text{DE}_{50} \) of this formulation were significantly higher than the related PM (p < 0.01). MDT values for all these samples were significantly lower than the related PMs as well as all other formulations with the same drug: carrier ratios (p < 0.01). The best results obtained for the ratio of 1:5 with \( \text{DE}_{50} = 95.47 \pm 0.85 \% \), \( \text{MDT} = 2.67 \pm 0.71 \text{ min} \) and \( \text{RD} = 2.04 \pm 0.02 \). It seems that increasing the molecular weight of PEG had an obvious positive influence on the dissolution behaviour of SDs.
Figure 1.
A: Dissolution profiles of IBS, PMs and SDs prepared by PEG 6000 in different ratios (n = 3); B: Dissolution profiles of IBS, PMs and SDs prepared by PEG 10000 in different ratios (n = 3); C: Dissolution profiles of IBS, PMs and SDs prepared by PEG 20000 in different ratios (n = 3)

Table I
Composition of samples and the dissolution parameters (mean ± SD, n = 3)

<table>
<thead>
<tr>
<th>Sample</th>
<th>IBS:PEG ratio</th>
<th>Q10 (%)</th>
<th>DE30 (%)</th>
<th>DE60 (%)</th>
<th>MDT (min)</th>
<th>RD10 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBSa</td>
<td>1:0</td>
<td>22.27 ± 2.36</td>
<td>34.42 ± 1.65</td>
<td>43.16 ± 0.66</td>
<td>12.41 ± 1.13</td>
<td>1</td>
</tr>
<tr>
<td>SD6000_1</td>
<td>1:1</td>
<td>78.37 ± 1.38</td>
<td>79.60 ± 0.22</td>
<td>90.20 ± 0.43</td>
<td>7.09 ± 0.21</td>
<td>1.65 ± 0.02</td>
</tr>
<tr>
<td>SD6000_3</td>
<td>1:3</td>
<td>80.98 ± 1.20</td>
<td>80.10 ± 1.76</td>
<td>90.06 ± 1.65</td>
<td>6.01 ± 0.13</td>
<td>1.71 ± 0.02</td>
</tr>
<tr>
<td>SD6000_5</td>
<td>1:5</td>
<td>86.89 ± 3.07</td>
<td>83.96 ± 2.87</td>
<td>92.71 ± 1.97</td>
<td>5.39 ± 0.51</td>
<td>1.81 ± 0.06</td>
</tr>
<tr>
<td>PM6000_1</td>
<td>1:1</td>
<td>64.48 ± 2.61</td>
<td>63.87 ± 1.56</td>
<td>72.25 ± 3.65</td>
<td>7.01 ± 1.40</td>
<td>1.36 ± 0.05</td>
</tr>
<tr>
<td>PM6000_3</td>
<td>1:3</td>
<td>70.97 ± 1.96</td>
<td>73.26 ± 1.45</td>
<td>82.34 ± 1.79</td>
<td>5.98 ± 0.25</td>
<td>1.49 ± 0.03</td>
</tr>
<tr>
<td>PM6000_5</td>
<td>1:5</td>
<td>75.91 ± 3.21</td>
<td>75.25 ± 0.46</td>
<td>87.01 ± 0.45</td>
<td>8.70 ± 2.17</td>
<td>1.60 ± 0.06</td>
</tr>
<tr>
<td>SD10000_1</td>
<td>1:1</td>
<td>78.56 ± 4.30</td>
<td>79.73 ± 3.30</td>
<td>88.53 ± 2.12</td>
<td>5.85 ± 1.20</td>
<td>1.66 ± 0.09</td>
</tr>
<tr>
<td>SD10000_3</td>
<td>1:3</td>
<td>90.28 ± 2.48</td>
<td>84.54 ± 1.36</td>
<td>91.59 ± 2.56</td>
<td>4.39 ± 0.76</td>
<td>1.90 ± 0.05</td>
</tr>
<tr>
<td>SD10000_5</td>
<td>1:5</td>
<td>96.51 ± 1.21</td>
<td>90.34 ± 0.66</td>
<td>95.47 ± 0.85</td>
<td>2.67 ± 0.71</td>
<td>2.04 ± 0.02</td>
</tr>
<tr>
<td>PM10000_1</td>
<td>1:1</td>
<td>69.63 ± 2.94</td>
<td>71.01 ± 1.42</td>
<td>83.74 ± 1.12</td>
<td>8.55 ± 0.30</td>
<td>1.47 ± 0.06</td>
</tr>
<tr>
<td>PM10000_3</td>
<td>1:3</td>
<td>84.41 ± 1.81</td>
<td>80.27 ± 1.10</td>
<td>89.61 ± 0.99</td>
<td>6.07 ± 0.42</td>
<td>1.78 ± 0.02</td>
</tr>
<tr>
<td>PM10000_5</td>
<td>1:5</td>
<td>84.53 ± 1.39</td>
<td>82.57 ± 2.17</td>
<td>90.42 ± 1.01</td>
<td>4.86 ± 0.91</td>
<td>1.78 ± 0.03</td>
</tr>
<tr>
<td>SD20000_1</td>
<td>1:1</td>
<td>58.05 ± 2.14</td>
<td>63.17 ± 0.37</td>
<td>76.78 ± 0.99</td>
<td>11.15 ± 0.25</td>
<td>1.23 ± 0.04</td>
</tr>
<tr>
<td>SD20000_3</td>
<td>1:3</td>
<td>79.66 ± 5.65</td>
<td>75.90 ± 3.46</td>
<td>86.92 ± 3.23</td>
<td>5.71 ± 2.18</td>
<td>1.58 ± 0.12</td>
</tr>
<tr>
<td>SD20000_5</td>
<td>1:5</td>
<td>75.19 ± 3.85</td>
<td>77.20 ± 1.23</td>
<td>86.34 ± 1.86</td>
<td>5.48 ± 1.24</td>
<td>1.59 ± 0.08</td>
</tr>
<tr>
<td>PM20000_1</td>
<td>1:1</td>
<td>42.82 ± 4.27</td>
<td>46.84 ± 3.41</td>
<td>58.54 ± 1.81</td>
<td>11.99 ± 1.39</td>
<td>0.90 ± 0.09</td>
</tr>
<tr>
<td>PM20000_3</td>
<td>1:3</td>
<td>57.99 ± 2.09</td>
<td>60.07 ± 2.82</td>
<td>69.80 ± 2.44</td>
<td>7.40 ± 1.02</td>
<td>1.22 ± 0.04</td>
</tr>
<tr>
<td>PM20000_5</td>
<td>1:5</td>
<td>60.98 ± 3.01</td>
<td>61.43 ± 1.51</td>
<td>72.38 ± 0.96</td>
<td>8.23 ± 0.81</td>
<td>1.29 ± 0.06</td>
</tr>
</tbody>
</table>

a IBS – Irbesartan; b SD – Solid dispersion; c PEG – grade; d PM – Physical mixture
Dissolution profile of samples prepared in the presence of PEG 20000 (Figure 1) shows that even the drug dissolution was improved significantly for SDs compared to the related PMs as well as intact IBS (p < 0.05 and 0.01), but was not as good as samples made by other carriers. In fact, further, increasing the carrier molecular weight did not lead to improved dissolution characteristics. This was in agreement with the results obtained in a previous study in which the formation of highly viscous solution around the particles due to the presence of PEG 20000 was considered as a cause of slowing down the dissolution rate [18]. It should be noted that increasing the concentration of PEG 20000 was not as effective as other carriers, which confirms the above mentioned reason.

Reviewing dissolution data of samples with the same ratios of IBS: PEG using different grades of polymer revealed that the formulations prepared by PEG 10000 had better dissolution behaviour. This could be attributed to the desirable hydrophilicity and viscosity of this carrier compared to lower and higher molecular weight PEGs. In all samples with drug: polymer ratio of 1:5, SD10000_5 had a significantly higher DE and lower MDT values compared to the other ratios. In fact, in addition to the type of the carrier and its molecular weight, the provided ratio has a significant impact on improving the dissolution of poorly soluble drugs.

X-ray powder diffraction (XRD)
The XRD spectra of IBS, PEG 10000 and selected SD (SD10000_5) as well as the corresponding PM (PM10000_5) are depicted in Figure 2. The diffraction spectrum of pure IBS indicated its crystalline nature (form A) as demonstrated by numerous peaks observed at 2θ of 4.7, 12.5, 13.3, 17.1, 19.4, 21.2, 22.6, 23.2 and 27.3 [31]. Crystalline properties of PEG were also confirmed by two peaks with the highest intensity at 2θ of 19.3 and 23.4 [32]. The XRD peaks of the intact IBS could be observed in SD and PM samples which confirmed the crystalline properties of drug in these formulations. In other words, no polymorphic changes and amorphization occurred during sample preparation method. Based on these findings, IBS dissolution rate improvement could be attributed to the other factors, such as improved wettability, rather than crystalline changes.

Differential scanning calorimetry (DSC)
The DSC thermograms of the selected samples including SD10000_5, PM10000_5, as well as PEG 10000 and the intact drug are illustrated in Figure 3.

Endothermic peaks with the onset temperatures of 182.57 and 58.95°C were exhibited for the intact IBS and PEG, respectively, corresponding to the melting point of each component [33]. Based on the thermograms, characteristic peak of IBS was disappeared in both solid dispersion and physical mixture and only one endothermic peak was detected, that corresponds to PEG. Disappearance of IBS melting endotherm could be attributed to either changing drug crystalline form to amorphous state or because of dissolving IBS particles in the melted PEG during DSC analysis. The first possibility is rejected because XRD spectra already confirmed the crystalline structure of drug in both solid dispersion and physical mixture.

Infrared spectroscopy (IR)
Any possible interaction between the drug and the carrier could be detected using IR spectroscopy. Figure 4 shows the IR spectra of IBS, PEG 10000,
SD and corresponding PM. The main signals of PEG appeared at 2903 cm\(^{-1}\) (C-H stretching vibration), 1108 cm\(^{-1}\) (C-O stretching vibration) and 3354 cm\(^{-1}\) (H-O stretching vibration). In addition, the spectrum of the intact drug presented characteristic peaks at 1728 cm\(^{-1}\) (C=O stretching vibration), 2934 cm\(^{-1}\) and 2960 cm\(^{-1}\) (N-H stretching vibration) and 1610 cm\(^{-1}\) (C-N stretching vibration) [3]. Since the main signals of IBS and PEG appeared in both SD and PM samples, no well-defined intermolecular interaction seems to be occurred between the two components.

**Scanning electron microscopy (SEM)**

The SEM micrographs of the intact IBS, IBS-containing solid dispersion and physical mixture with PEG 10000 (1:5) are presented in Figure 5. The intact drug appeared as different size needle shape crystals with smooth surfaces and partially agglomerated (Figure 5: A and B). The drug particles could be observed clearly in physical mixture which seems as a combination of IBS and the carrier (Figure 5: C and D). Although, in the case of related solid dispersion it is not possible to identify pure components (Figure 5: E and F). It seems that drug particles were uniformly distributed in and surrounded by the polymer matrix after solvent evaporation method which indicates a reduction in drug particle size and alteration of its surface properties.

**Saturation solubility**

The dissolution rate of poorly soluble drugs could be improved by increasing the solubility. The saturation solubility of intact IBS, SD10000_5 and related physical mixture were measured in water. Based on the results, the solubility of SD10000_5 (42.38 ± 1.46 µg/mL) and PM10000_5 (35.4 ± 1.15 µg/mL) were significantly higher (p < 0.05) compared to IBS (31.70 ± 1.46 µg/mL). The increased solubility for PM was less than SD with similar drug: carrier ratio, indicating that other factors (such as reduced particle size) along with the presence of hydrophilic polymer in the formulations must be considered as the reasons for these findings.

**Phase solubility**

The phase solubility diagram of IBS in aqueous medium containing various concentrations of PEG 10000 is shown in Figure 6.
It is demonstrated that the increase in drug solubility was linear with respect to weight fraction of the carrier. In fact, the presence of PEG in various percentages ranging from 0 to 10% enhanced IBS solubility from 31.7 to 65.7 µg/mL, respectively (p < 0.001), which could be explained by increased wettability. These findings are in accordance with previous studies reported in the literature [23]. Therefore, the drug solubilisation by PEG is probably one of the mechanisms for IBS dissolution enhancement.

The indication of process transfer of IBS from pure water to different concentrations of PEG 10000 aqueous solution may be obtained from the values of Gibbs free energy change [29]. Referring to Table II, the values of Gibbs free energy of transfer were all negative, indicating the spontaneous nature of drug solubilisation. In addition, increasing PEG concentration, resulted in lower spontaneous Gibbs free energy, demonstrating that reaction (solubilisation) was more favourable as PEG percentage increased.

<table>
<thead>
<tr>
<th>PEG Concentration (% w/v)</th>
<th>IBS Solubility (µg/mL)</th>
<th>∆G (KJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>31.7 ± 1.46</td>
<td>0</td>
</tr>
<tr>
<td>2.5</td>
<td>38.11 ± 2.72</td>
<td>-0.55</td>
</tr>
<tr>
<td>5</td>
<td>43.97 ± 2.47</td>
<td>-0.93</td>
</tr>
<tr>
<td>7.5</td>
<td>57.06 ± 2.46</td>
<td>-1.55</td>
</tr>
<tr>
<td>10</td>
<td>65.71 ± 2.61</td>
<td>-1.90</td>
</tr>
</tbody>
</table>

Table II: The effect of PEG concentration and Gibbs free energy on IBS solubility

Conclusions
Irbesartan dissolution rate was obviously improved in the form of SD using different PEG grades as hydrophilic carriers. The noticeable effect of carrier molecular weight on the drug dissolution in these systems was also verified. Formulations prepared in the presence of PEG 10000 showed better results, probably due to its desirable hydrophilicity and viscosity. Improved wettability, solubilisation of drug by the carrier, alteration of the surface properties of particles as well as drug particle size reduction could be responsible for the improved dissolution and solubility of IBS from these systems.

Conflict of interest
The authors declare that they have no conflict of interests.

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References
13. Kumar P., Mohan C., Shankar M.K.U., Gula M., Physiochemical characterization and release rate studies of solid dispersions of ketoconazole with