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Original research paper

Improved dissolution of a poorly water soluble drug in solid dispersions with polymeric and non-polymeric hydrophilic additives

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Irbesartan (IBS) is a hydrophobic drug with poor aqueous solubility and dissolution rate. Solid dispersions (SDs) of IBS were prepared with both small molecules (tartaric acid and mannitol) and polymeric additives (polyvinylpyrrolidone, PVP, and hydroxypropyl methylcellulose, HPMC). A 9.5 and 7 folds enhancement in solubility over the crystalline form (14.6 μg mL^{-1}) was observed for tartaric acid (138 μg mL^{-1}) and PVP (103 μg mL^{-1}), respectively. Powder X-ray diffraction confirmed that IBS existed in the glassy state in all cases, even with excipients having low glass transition temperature. Thermal methods (differential scanning calorimetry and hot stage microscopy) were used to evaluate the miscibility of the drug and additives. These techniques suggested that tartaric acid led to generation of »amorphous solutions« in contrast to »amorphous suspensions« in other three cases. The *in vitro* dissolution of IBS depended on the additive load and increased with increasing concentration in the case of tartaric acid, an acidifying excipient. The results indicate the suitability of even small molecules for providing solubility benefits, which can be attributed to the good glass forming ability and reasonable ability of IBS to remain in the glassy state.

Keywords: irbesartan, solid dispersion, amorphous form, solubility, dissolution rate

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Aqueous solubility of a drug can be a critical limitation to its oral absorption. Lipophilic molecules, especially those belonging to the biopharmaceutics classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability (1). Many solubilization techniques have been described that either change the nature of the solvent environment (co-

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-solvent systems, emulsions, micellization) or the chemical identity of the dissolved solute (salt formation, complexation, pro-drugs) (2).

Alteration of the solid state at the particle or molecular level involves a physical change in the drug and is an attractive option for improving drug solubility (3).

Particle size reduction by micronization or nanonization can enhance the dissolution rate; however, the apparent solubility remains unaltered. At the molecular level, polymorphs offer a limited solubility advantage because of a small difference in free energy (4). In contrast, amorphous systems with excess thermodynamic properties and lower energetic barrier can offer significant solubility benefits (4). This solubility benefit can be further enhanced by preparing solid dispersions (SDs). SDs contribute by slowing devitrification, enhancing wettability and modulating the properties of the solvent (5).

The aim of the present study was to examine the solubility and dissolution properties of SDs of irbesartan (IBS), prepared with small molecules such as tartaric acid and mannitol and polymeric additives like polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC). IBS, 2-butyl-3-[[29-(1*H*-tetrazol-5-yl) [1,19-biphenyl]-4-yl] methyl]1,3-diazaspiro[4,4] non-1-en-4-one (Fig. 1), is a potent long acting non-peptide AII receptor antagonist used in the treatment of hypertension (6). IBS was chosen as a model candidate because of its low dissolution rate and solubility-limited bioavailability (7). We have previously reported that the amorphous form of IBS improves solubility over the crystalline form (7).

EXPERIMENTAL

Materials

IBS (purity > 99%) was gift of Dr Reddy's Labs (India). All high-performance liquid chromatography (HPLC) solvents were of HPLF grade and procured from Merck (Germany), tartaric acid (DL) was obtained from s.d. Fine-chem Ltd. (India), mannitol from Qualigens (India), poly(vinylpyrrolidone) (PVP) K30 was obtained from ISP Technologies (USA), and hydoxypropyl methylcellulose (HPMC) K100LV was obtained from Colorcon Asia Pvt. Ltd. (India). All other chemicals were of analytical grade. The materials were used as received without any further purification.

Preparation of amorphous IBS by quench cooling

Amorphous IBS was prepared by melting the drug in a stainless steel beaker at 200 °C and subsequent quench cooling of the melt over crushed ice. The quench-cooled product was ground, sieved (BSS No. 60, mesh size 250 μm) and found to be amorphous by powder X-ray diffraction (PXRD) immediately after preparation. HPLC analysis (method described below) confirmed that no degradation had occurred during the procedure.

Generation of solid dispersions of IBS

As discussed in previous section, quench cooling was used for preparation of SDs of IBS. Temperature was controlled in dependence on the melting temperature of the

drug/excipients. Physical mixtures of the drug and additives were prepared by geometric mixing, by triturating using the mortar and pestle. The quench-cooled product was ground, sieved (BSS No. 60 mesh size, 250 μm) and used immediately after preparation. Initially, 20% (*m*/*m*) of the excipient (tartaric acid, mannitol, PVP and HPMC) was used. The effect of the concentration of tartaric acid and PVP (selected excipients) was also studied.

Powder X-ray diffraction (PXRD)

PXRD patterns of freshly prepared powdered samples (under controlled temperature and humidity conditions) were recorded at room temperature on Bruker's D8 Ad-

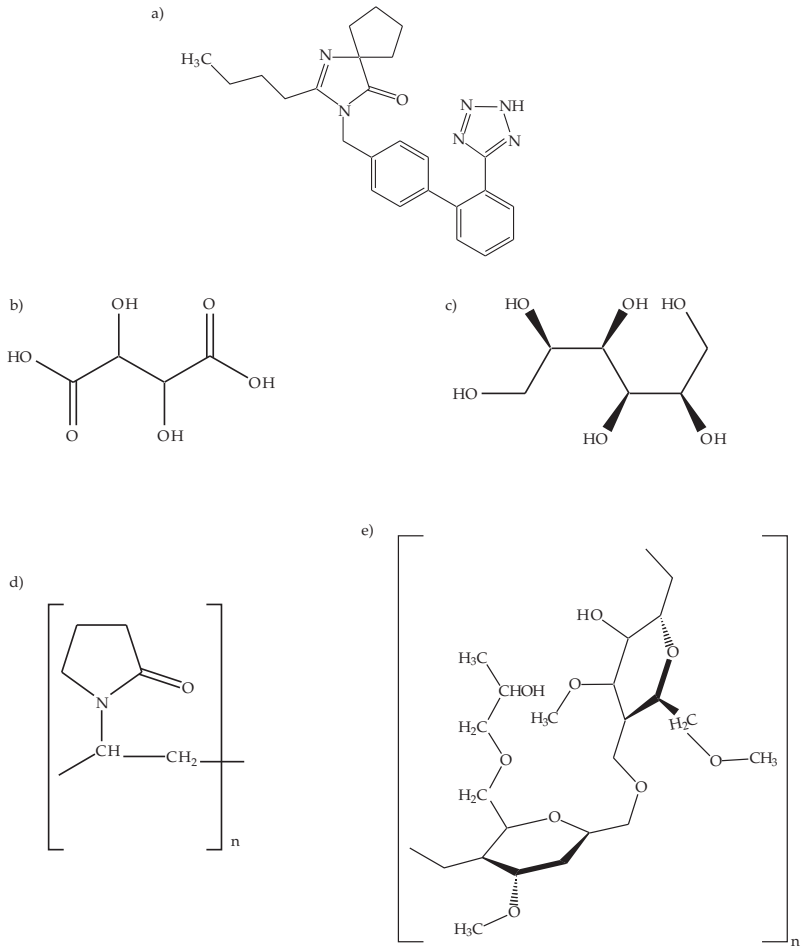


Fig. 1. Chemical structure of IBS and additives: a) IBS, b) tartaric acid, c) mannitol, d) PVP, e) HPMC.

vance diffractometer (Germany) with CuKα radiation (1.54 Å), at 40 kV, 40 mA, passing through a nickel filter with a divergence slit (0.5°), antiscattering slit (0.5°), and receiving slit (1 mm). The diffractometer was equipped with a 2θ compensating slit and was calibrated for accuracy of peak positions with a silicon pellet. Samples were mounted either on a 25-mm holder made of polymethyl methacrylate (PMMA) or a zero background small sample holder, depending on sample size, and were subjected to X-ray powder diffraction analysis in continuous mode with a step size of 0.01° and step time of 1 second over an angular range of 3 to 40° 2θ. Sample holders were rotated in a plane parallel to their surface at 30 rpm during the measurements. Obtained diffractograms were analyzed with DIFFRAC^{plus} EVA (ver. 9.0) diffraction software.

Differential scanning calorimetry (DSC)

Thermal transitions were determined using a Mettler Toledo 821e DSC (Mettler Toledo, Switzerland) operating with version 5.1 of Star^{e} software using (4–6 mg) samples in aluminium pans with pierced lids at heating rates of 20 °C min^{-1} under nitrogen purge at 80 mL min^{-1}. The instrument was calibrated for temperature and heat flow using high purity indium and zinc standards.

Hot stage microscopy (HSM)

Thermal transitions were visually observed under a Leica DMLP polarized microscope (Leica Microsystems, Germany) equipped with Leica LMW hot stage. Photomicrographs were acquired using a Leica DC 300 camera and analyzed using Leica IM 50 (version 1.20) software.

High performance liquid chromatography

The HPLC method for solubility and dissolution rate studies has been described previously (6). All solubility and dissolution samples were analyzed on an HPLC system (Shimadzu, Japan) using Lichrospher® 100 RP-18e (5 μm) (Merck, Germany) analytical column under isocratic conditions at a flow rate of 0.7 mL min^{-1} at 25 °C. Injection volume 10 μL and effluent were monitored at 275 nm. The mobile phase was 10 mmol L^{-1} potassium dihydrogen orthophosphate/methanol/acetonitrile (15:75:10) (pH 2.5).

In vitro *dissolution studies*

Dissolution experiments of crystalline, amorphous and SD samples were carried out in triplicate with a United States Pharmacopeia Apparatus I (basket-type) (TDT-08L, Electrolab, India), employing 900 mL of deionized water and 0.1 mol L^{-1} HCl, at a temperature of 37 ± 0.5 °C, at rotational speed of 100 rpm. Sample mass maintaining the sink conditions (*i.e.*, three times the solubility) was filled into hard gelatin capsule shells. At predetermined intervals (5, 15, 30, 60, 90, 120, 240, 360 and 480 min), samples were withdrawn (with replacement of equal volume of an pre-warmed medium into the vessel), filtered, appropriately diluted and analyzed for drug concentration using HPLC. It was first confirmed that the method was specific for the analysis of IBS and additives did not interfere with the drug. *In vitro* dissolution studies of SDs were also performed using

different concentrations of excipients, tartaric acid and PVP [10, 20, 40, 50, 60 and 80% (*m*/*m*)].

The effects of rotational speed (25, 50 and 100 rpm), sample fill mass in the capsule and degassing of media on the dissolution rate were also studied.

Solubility studies

The dynamic solubility of crystalline, amorphous and various SDs of IBS was determined by adding excess solid (150 mg) to 100 mL deionized water placed in stoppered conical flasks, pre-equilibrated to 37 ± 0.5 °C. The flasks were mechanically shaken in a shaking water bath (SW 23, Julabo Labortechnik GmbH, Germany) at 100 rpm. At pre--determined intervals, an aliquot was withdrawn, filtered through a 0.45-μm syringe filter, diluted and analyzed by HPLC. Simultaneously, the solid phase was analyzed by PXRD.

Solubility studies of the physical mixture (prepared by geometric mixing) of drug--excipient and in solution of 20% (*m*/*m*) excipient in water were performed.

RESULTS AND DISCUSSION

IBS is a non-polar compound with a partition coefficient (octanol/water) of 10.1 at pH 7.4, and low aqueous solubility (< 0.1 mg mL^{-1} in water at 25 °C). The crystalline form A crystallizes with 2 hydrophobic channels containing aliphatic chains, leading to weak solubility and strong aggregation in water. Previous work by the authors (6) illustrated a 2.5 fold higher »apparent« solubility of amorphous IBS over its crystalline phase. Lower heat of solution (ΔH_s) for amorphous IBS (–12.6 kJ mol^{-1}) in comparison to crystalline form (–37.6 kJ mol^{-1}), absence or reduced crystal packing energy and higher Gibb's free energy (ΔG) indicated the ease and spontaneity of IBS molecules to leave the disordered amorphous system and be molecularly dispersed in the solvent (8).

Conventionally, this enhanced solubility of the amorphous system would translate into an increased dissolution rate. However, dissolution rate of amorphous IBS was lower than the dissolution rate of the crystalline form of IBS, in water and in 0.1 mol L^{-1} HCl (Fig. 2a). Visual observation revealed that the amorphous material had formed a hard plug that prevented penetration of water to deeper layers (Fig. 2b). This was confirmed by the cross sectional view of the plug, wherein the outer surface was wet, and the inner portion was found to be comparatively dry. The residual material at the end of the eight hours long dissolution experiment was characterized by PXRD and polarized light microscopy. The outer sample surface of IBS indicated partial crystallization as it was evident from the appearance of sharp diffraction peaks. The sample core essentially retained the amorphous nature (Fig. 2c). Similar observations have been made previously with drugs like ritonavir and carvedilol wherein amorphous forms exhibited incomplete release in comparison with the crystalline form; however, generation of SD improved the dissolution rate (10,11). Higher apparent solubility of amorphous IBS at all pH values and a higher intrinsic dissolution rate (6) suggested that IBS could be a good candidate for dissolution rate improvement through SD formation.

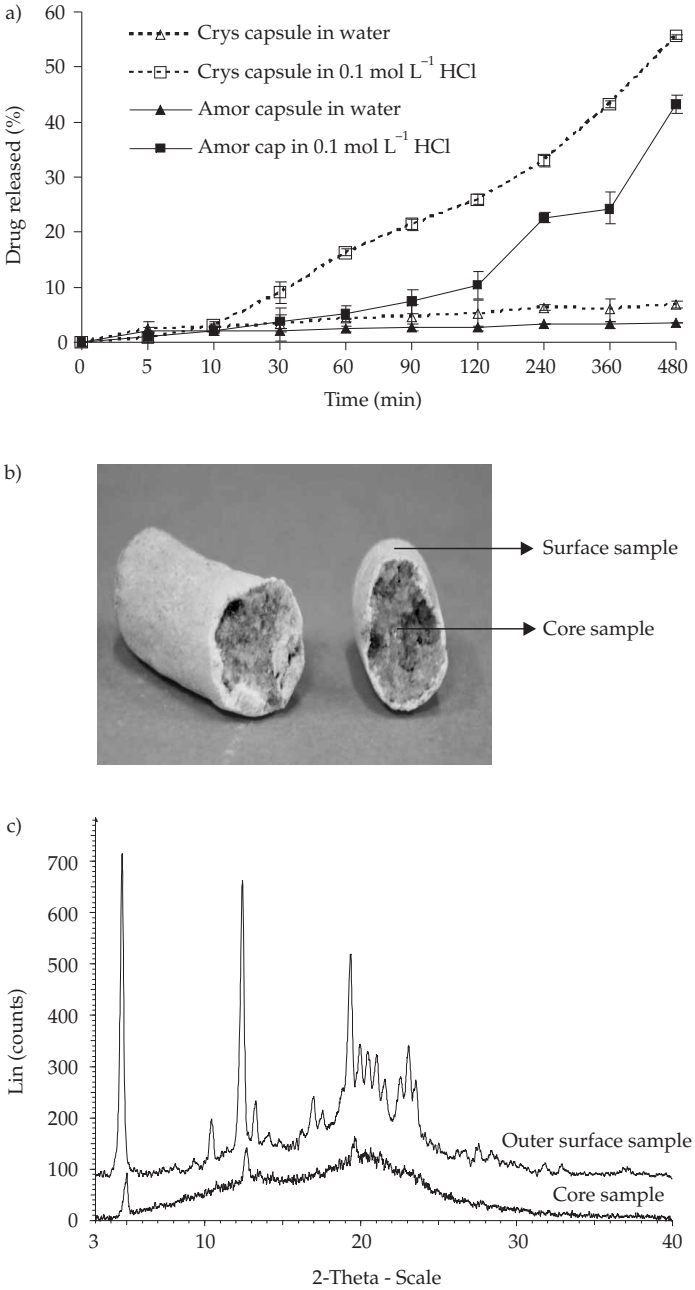


Fig. 2. *In vitro* dissolution-time profile of amorphous IBS: a) concentration time profile of crystalline and amorphous IBS, b) plug formed in amorphous IBS in dissolution media, c) PXRD pattern of residual dissolution samples.

Amorphous materials have the ability to form molecular level single-phase dispersions with pharmaceutical excipients. These »amorphous alloys« permit creation of custom pharmaceuticals with unique properties by selection of appropriate interacting excipients (12). Numerous reports have cited dissolution rate improvement of poorly soluble drugs through production of SDs using various hydrophilic carriers, such as polyvinylpyrrolidone, hydroxypropyl methylcellulose, sugars, and mannitol (13–16). Dispersions of IBS were formed using two non-polymeric excipients, tartaric acid and mannitol, and two polymeric excipients, PVP and HPMC.

Fig. 3a exhibits the needle-shaped crystals of the drug. Amorphous material on the other hand exhibits irregularly shaped birefringent particles. SDs of IBS were formed using quench cooling, which led to generation of a non-birefringent glassy material observed under polarized light (Fig. 3b). All freshly prepared dispersions, except the one with mannitol, exhibited a halo pattern in PXRD, thus confirming their amorphous nature. Comparison of PXRD patterns of IBS-mannitol dispersions revealed that the peaks matched that of mannitol and peaks corresponding to IBS were absent (Fig. 3c). Hence, it can be inferred that IBS was present in the amorphous state in the dispersion and mannitol was in the crystalline state. Similar behavior has been reported for mannitol with other drug substances in earlier studies (14, 17).

DSC analysis of crystalline IBS showed a single sharp fusion endotherm in the temperature range of 183–190 (± 0.5) °C (ΔH_f = 107 ± 2 J g^{-1}) at a heating rate of 20 °C min^{-1}. Quench-cooled IBS exhibited a glass transition event at 71.7 ± 1.0 °C (onset T_g) and no other exothermic peak of crystallization or endothermic peak of melting was observed. Even when heated at a slow rate of 1 °C min^{-1}, amorphous IBS did not crystallize spontaneously, thus suggesting lack of crystallization tendency of amorphous IBS. IBS exhibited a T_g/T_m of 0.75 and is expected to be a relatively good glass former (10).

The nature of SD was also studied using HSM and DSC by performing studies on both physical mixtures and SDs. In DSC, changes in the melting endotherm of the drug and single T_g at a temperature between T_g values of both components is evidence for formation of a miscible system (18). SDs can thus be classified as an »amorphous solution« (with single T_g), »amorphous suspension« (two T_gs) or crystalline suspension (T_g and melting event).

Unlike mannitol, tartaric acid exhibited complete miscibility with molten IBS. However, these events cannot be resolved with DSC as the melt endotherms may be a mixture of the heat of fusion and heat of solution (Fig. 3d). HSM clearly allowed visualization of the events, melting and dissolution of one component in the melt of the other (Fig. 3e). On a hot stage microscope, tartaric acid melted in the range of 180–207 °C. In the presence of IBS, a single event of melting of both components was observed at 170–180 °C, resulting in a clear melt. This indicated miscibility of the two components. In DSC, quench cooled IBS-tartaric acid dispersions showed a single T_g at 79 °C (T_g^{onset}), thus proving formation of an »amorphous solid solution«. However, the glass transition event of this phase was observed at a temperature higher than the temperature expected based on the composition (Table I). Such an increase in T_g has been observed previously as a result of ionic and heteromolecular interactions (14, 19, 20). Theoretical T_g of the drug-additive mix (Table I) was calculated using the Gordon-Taylor/Kelley-Bueche equation (21):

$$T_{gmix} = \frac{wT_{g1} + Kw_2T_{g2}}{w_1 + Kw_2} \quad (1)$$

where subscripts represent the two components (drug and additive), w represents their mass fractions, and K is the ratio of their free volumes given by Eq. *(2)*, where ρ is the density of the two materials (obtained from literature):

$$K = \frac{(\rho_1 T_{g1})}{(\rho_2 T_{g2})} \quad (2)$$

With mannitol, molten additive gave rise to an immiscible liquid phase within the molten drug (Figs. 3f,g). This immiscibility was observed in HSM as droplets of mannitol within the melt of IBS. In addition, mannitol recrystallizes quickly on a hot stage microscope upon melt cooling (Fig. 3h), thus giving sharp peaks in PXRD. Pure mannitol exhibited a sharp melting endotherm in the temperature range of 164–176 °C. Two T_gs, at 59 and 71 °C (Fig. 3i) in the case of quench cooled IBS-mannitol dispersions suggested the formation of an »amorphous suspension«. With time, when stored under room temperature and humidity, this dispersion can be categorized as a »crystalline suspension« containing amorphous drug and crystalline mannitol. Similar behavior of D-mannitol has been observed by other authors with drugs such as sulphonamides, tolbutamide, isopropylantipyrin and oxazepam (17).

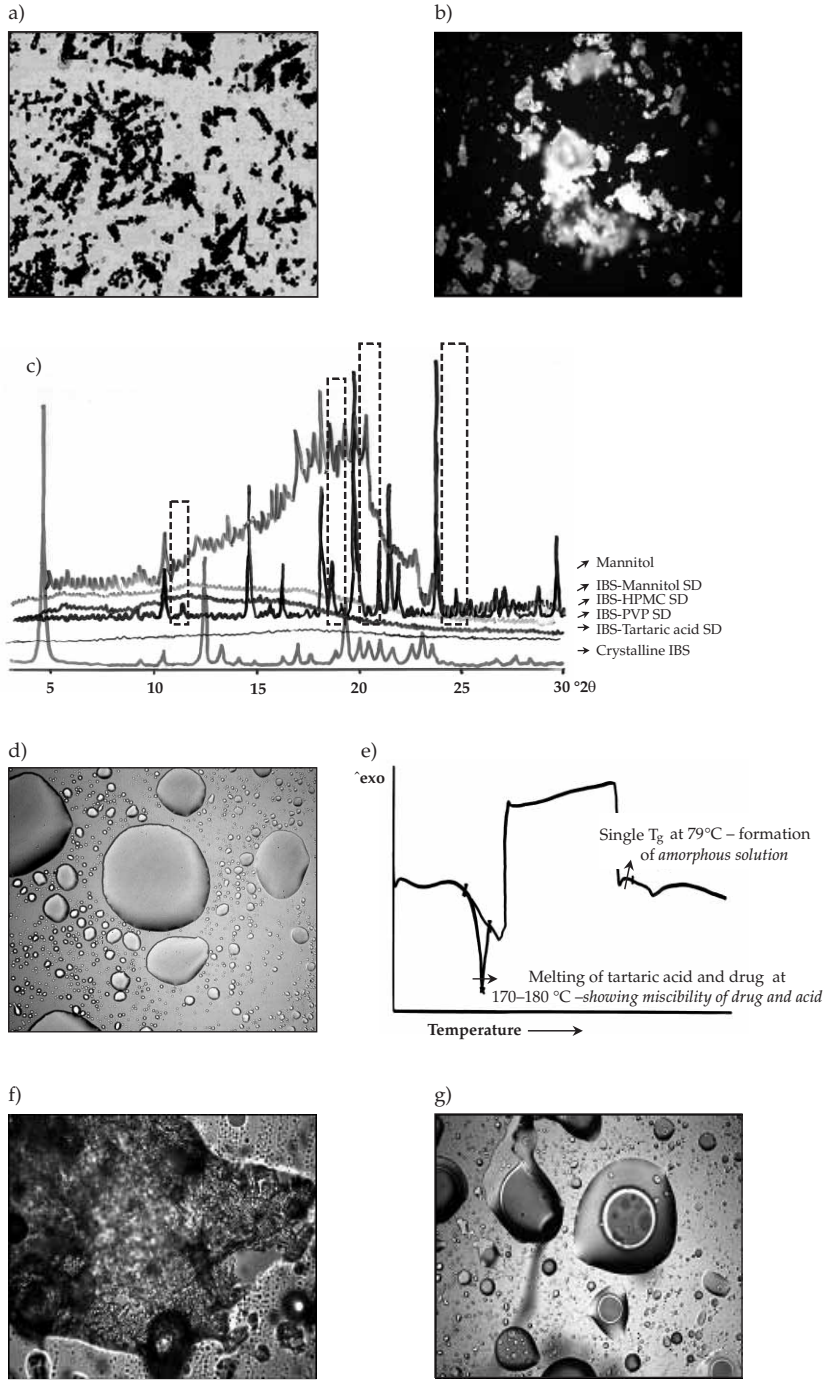
Polymeric excipients PVP and HPMC did not mix with the drug melt in their molten state. In DSC, no melting endotherms were observed with pure PVP and HPMC due to their amorphous nature. Immiscibility was observed on both HSM and DSC. Droplets of softened PVP were observed in the melt of the drug (Fig. 3j), while solid particles of HPMC were entrapped in the melt droplets of the drug (Fig. 3k). HPMC remained as a solid until a temperature of 230 °C. In quench cooled dispersions T_gs were observed at about 81 °C for IBS and near 167 °C for the excipients (Fig. 3l). High viscosity of polymers has been reported previously to limit the miscibility of drugs with polymers (22). These dispersions can be also classified as »amorphous suspensions« containing two, partial or complete, amorphous phases (23).

IBS, a hydrophobic molecule, achieves an equilibrium aqueous solubility of 14.6 μg mL^{-1} in about 480 min. The crystalline material adhered to the walls of the flask and

Table I. T_g *of additives and theoretical* T_g *of SDs*

Additive	T_g (°C)	Theoretical T_{gmix} of SD (°C)	Peak concentration (μg mL^{-1})
Tartaric acid	18	63	138
Mannitol	11	60	55
PVP	168	87	103
HPMC	150–180	87[a]	81

[a] Average T_g taken


a)
b)
c)
Mannitol
IBS-Mannitol SD
IBS-HPMC SD
IBS-PVP SD
IBS-Tartaric acid SD
Crystalline IBS
5
10
15
20
25
30 °2θ
d)
e)
ˆexo
Single T_g at 79°C – formation
of *amorphous solution*
Melting of tartaric acid and drug at
170–180 °C –*showing miscibility of drug and acid*
Temperature
f)
g)

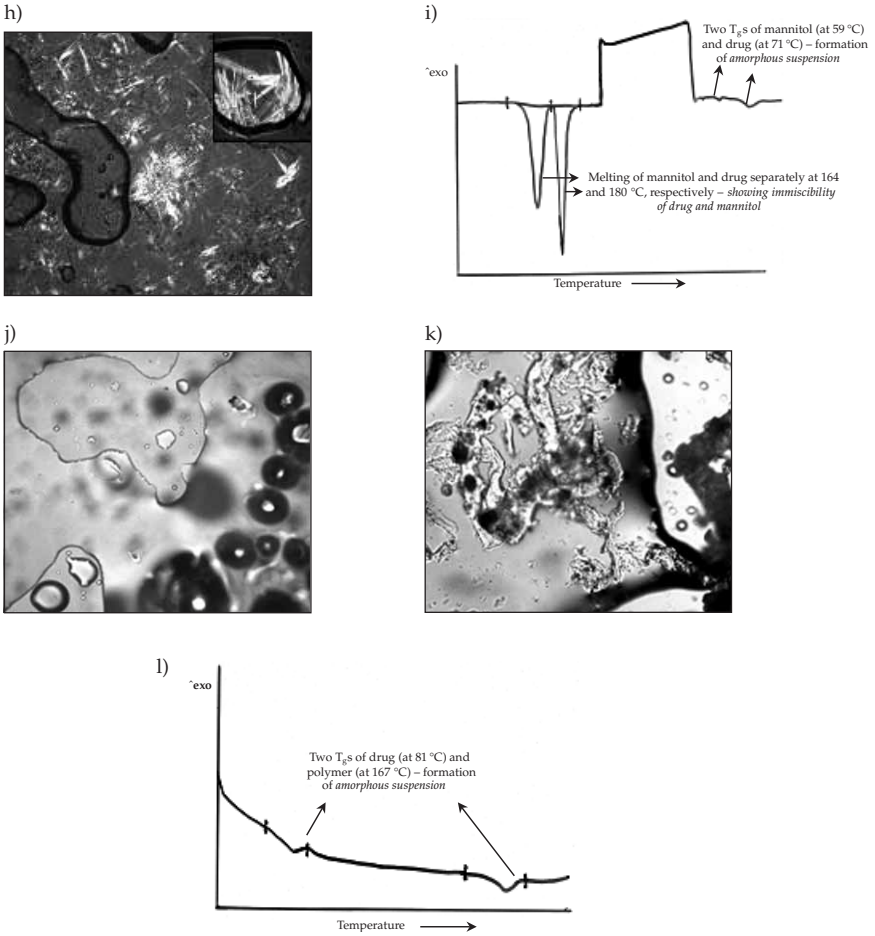


Fig. 3. Thermal and PXRD characterization of crystalline, quench cooled SD and IBS-additive (20%, *m*/*m*) physical mixture: a) crystalline IBS under HSM, 100x, RT, b) SD prepared using quench cooling under HSM, 100x, RT, c) PXRD of SD and mannitol (dashed boxes highlight the peaks of mannitol in IBS-mannitol SD), d) IBS-tartaric acid physical mixture under HSM, 200x, 200 °C, e) DSC curve of IBS-tartaric acid physical mixture and SD, f) IBS-mannitol under HSM, 200x 190 °C, g) IBS-mannitol under HSM, 200x, 200 °C, h) IBS-mannitol cooled after melting under HSM, 200x, 185 °C (inset shows a magnified view at 630x), i) DSC curve of IBS-mannitol physical mixture and SD, j) IBS-PVP under HSM, 200x, 203 °C, k) IBS-HPMC under HSM, 200x, 223 °C, l) DSC curve of IBS-PVP SD.

floated on the surface of medium. Glassy IBS, on the other hand, sank in water in about 10 min and exhibited enhanced peak solubility of 36.4 μg mL^{-1}. This initial solubility peak value started to drop after 60 min, became equivalent to the crystalline form in 120 min and in 480 min reduced to 10 μg mL^{-1} (73% drop from peak), which is even less

than the pure crystalline form, due to formation of the lower solubility polymorph-form B (6). SDs prepared using both types of excipients showed significant enhancement in solubility over the crystalline and amorphous forms (Fig. 4). As observed from Fig. 4, maximum enhancement in solubility was achieved using tartaric acid (solubility peak 138 μg mL^{-1} in 90 min). Mannitol exhibited the least improvement in solubility peak (55 μg mL^{-1} in 30 min), but was still higher than amorphous or crystalline IBS. In case of polymeric excipients, PVP (solubility peak 103 μg mL^{-1} in 240 min) exhibited higher solubility than HPMC (solubility peak 81 μg mL^{-1} in 60 min). Even at a concentration of 20% (*m*/*m*), a marked solubility advantage was observed with tartaric acid and PVP. Another interesting observation relating to polymeric excipients was the duration of solubility peak. The drop in solubility values after attaining »metastable« solubility was less in polymeric dispersions compared to dispersions of non-polymeric molecules. Polymeric excipients exhibited a negligible drop from the solubility peak values (PVP 1.2; HPMC 1.1 folds) in contrast to the 8.2 fold drop from the solubility peak value in 480 min in pure amorphous IBS.

Excipients in SDs can affect solubility primarily by two mechanisms: (*i*) capacity to stabilize amorphous drug against water-induced crystallization, or (*ii*) specific contribution towards the solubilization process.

Water, which is a strong plasticizer, leads to reduction in T_g of the system causing devitrification. Polymeric materials have been reported to have higher T_g values (PVP 168 °C, HPMC 168 °C) and would therefore act as better stabilizers compared to small molecules that have lower T_g values (17). The high T_g values of polymers PVP and HPMC may thus induce an anti-plasticization effect along with improved wettability due their hydrophilic nature. Polymers may help in maintaining supersaturation by coating and passivating small embryos to arrest growth by preventing condensation of drug molecules onto the surface embryos (24). This may be the probable reason for lower drop in solubility from the peak value in case of dispersions prepared using polymers. Both PVP and

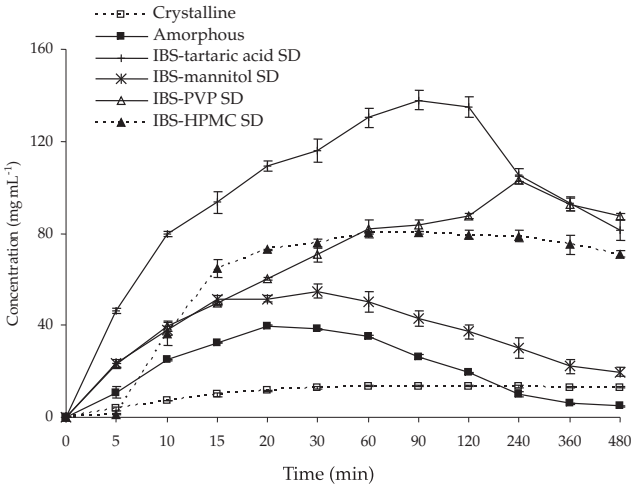


Fig. 4. Concentration-time profiles of crystalline, amorphous and SDs of IBS [using 20% (*m*/*m*) of the excipient]. SD bars for *n* = 3.

HPMC showed almost similar solubility profiles. Moreover, being hydrophilic in nature the polymers would not act as rate controlling parameters for dissolution.

Small molecules with low T_g values are not expected to stabilize the amorphous system against water-induced recrystallization. Tartaric acid was found to decrease the pH of the solution [pH of water after addition of 20% (*m*/*m*) tartaric acid was 2.27, *i.e.* a drop of about 6.7 units] and as IBS exhibited improved solubility at lower pH values (6), solubilization would be aided by this drop in pH. As reported earlier, at low pH values IBS exhibited high solubility and after attaining the peak, a plateau was achieved with no drop in solubility. A similar case was that of tartaric acid and only a 1.7 fold drop in solubility was observed. In contrast, no change in pH was observed with the other excipient-mannitol. Sugars and highly soluble polyolic materials act as »water structure formers«. These substances have been reported to strengthen the intermolecular hydrogen bonding in water, making it more hydrophobic, and thus favor the dissolution of a poorly hydrosoluble drug (25).

Two additives, namely tartaric acid and PVP, were selected as representatives of small molecules and polymers, respectively. The additive concentration was found to play a significant role in the solubility of dispersions, especially for tartaric acid. In case of tartaric acid SDs, it was observed that the concentration of tartaric acid controlled both the time taken to reach the peak and the peak solubility values (Fig. 5a). Peak solubility and time taken to achieve this peak was found to increase with the increasing concentration of tartaric acid. In addition, pH values were dependent on concentration of tartaric acid, with the highest of 2.33 with 10% and a minimum of 1.96 with 80% (*m*/*m*) of tartaric acid. This dependence of performance on the content of additive in tartaric acid dispersions may be due to the pH shift caused by the acid. A marginal change in pH may be sufficient to influence the solubility of IBS owing to its strong pH dependent solubility, as observed in the previous report (6). On the other hand, in the case of PVP, differences in solubility were observed at 20% (*m*/*m*) (105 μg mL^{-1} in 240 min) and 80% (*m*/*m*) (169 μg mL^{-1} in 360 min). Solubility values in PVP at different concentrations remained within a close range, with a sudden rise seen at 80% (*m*/*m*).

PXRD of dispersions was performed and it was observed that IBS was amorphous at all concentrations. Halo pattern was observed in all SDs; however, in dispersions containing more than 40% (*m*/*m*) tartaric acid, few diffraction peaks of low intensity were observed. The peaks increased both in number and intensity with the increase in concentration. IBS was present in amorphous form at all concentrations since no peaks of IBS were observed in PXRD.

The PXRD and HSM studies suggested that tartaric acid was miscible with IBS at all concentrations, but at high concentrations, tartaric acid crystallized on cooling. However, being a relatively stable molecule in the glassy state, IBS does not crystallize out even with a low T_g (18 °C) substance like tartaric acid. Also, the absence of endothermic peak in DSC corresponding to IBS melting indicated that the drug was dispersed amorphously. In the case of PVP, a halo pattern was observed in all cases. However, on the hot stage microscope, at concentration higher than 20% (*m*/*m*), PVP did not melt and remained as solid particles dispersed in the drug melt.

The relative contribution of additives, present either in solid phase (in drug-additive mixtures, PM) or in solution (in pre-dissolved state in water, phase solubility), was ascertained by studying the solubilities of the physical mixtures and by dissolving the

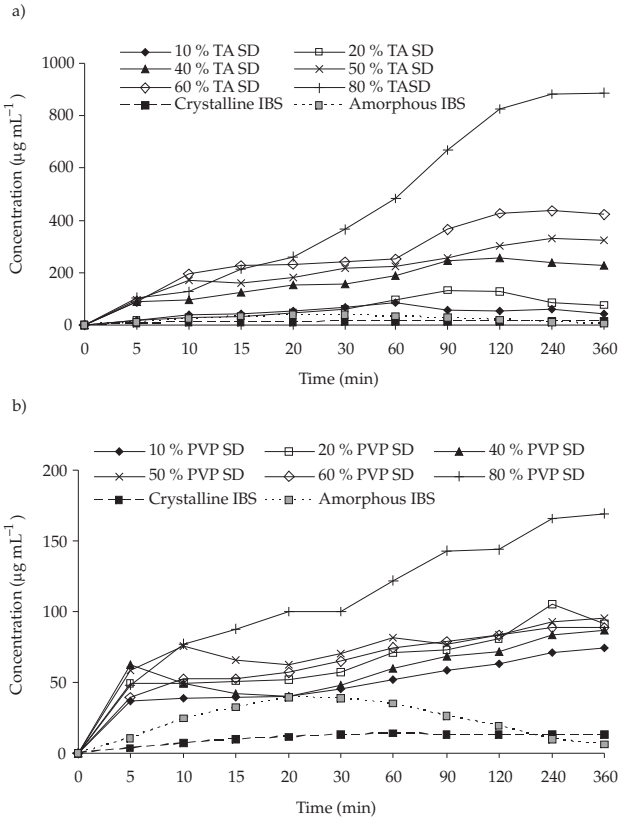


Fig. 5. Solubility profiles of SDs with different concentrations of additive: a) IBS--tartaric acid, b) IBS-PVP SD (SD bars for n = 3).

additive in water. Fig. 6 shows the solubility values of the physical mixture and in pre--dissolved solutions of tartaric acid and PVP at a concentration of 20% (m/m). Both additives led to a significant increase in solubility of both crystalline and amorphous IBS. In the case of tartaric acid, the »acidifying« excipient, physical solubility and phase solubility values followed the order: amorphous phase solubility > amorphous PM > SD > crystalline phase solubility > crystalline PM indicating that the amorphous state of the drug has some role to play in interaction of ionic groups of the excipient. This also confirmed the acidifying nature of tartaric acid and suggested that its role as an acidifier is less pronounced when present in molecularly dispersed state with the drug in SD. The solubility values were considerably low in crystalline PM and crystalline phase solubility. The drop in solubility peak was faster in amorphous phase solubility (30 min) compared to SD and amorphous PM (90 min). The trend was quite different with the polymeric excipient PVP. Highest solubility was observed in SD and the lowest with crystalline PM. Amorphous phase solubility, crystalline phase solubility and amorphous PM exhibited almost similar values. This further confirmed the stabilization role (ability to keep the drug in amorphous form) played by high T_g excipients in their solid state.

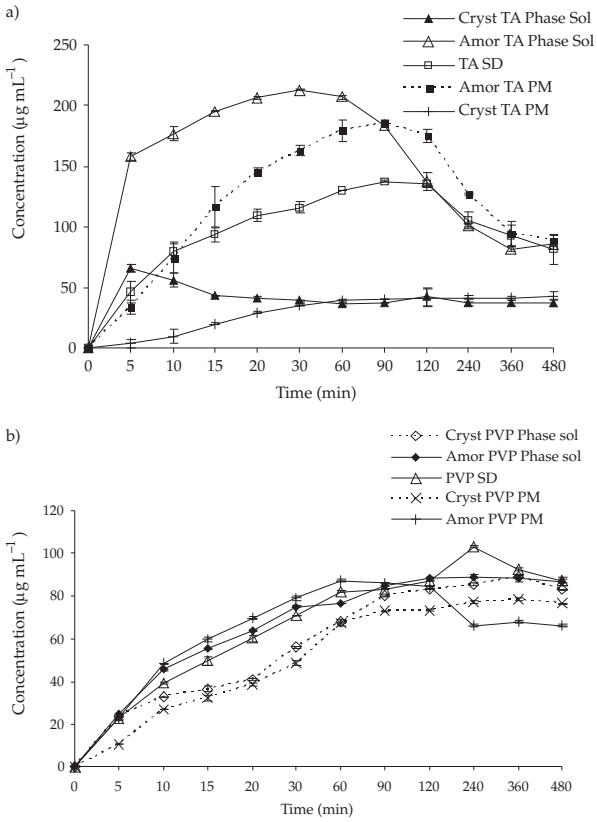


Fig. 6. Phase solubility and physical mixture solubility of IBS with: a) tartaric acid and b) PVP (SD bars for n = 3).

Dissolution studies at different concentrations of solid dispersions were carried out in 0.1 mol L^{-1} HCl. The trend was similar to solubility studies and the percentage released increased with increasing concentration of tartaric acid (Fig. 7). The percentage released was more than that of tartaric acid amorphous form (24% released in 360 min) even at the concentration of 10% (m/m) (31% released in 360 min). The highest percentage release was observed at 80% (m/m) (85% in 360 min) and more than 75% release was seen within 15 min. The release of IBS was faster in the initial phases of dissolution at high concentrations of tartaric acid (60 and 80%, m/m). In the case of PVP, 10 and 20% concentrations exhibited maximum release of 59 and 71%, respectively, in 360 min (Fig. 7). Unlike tartaric acid, also in PVP a gradual increase was seen over the entire period of dissolution at all concentrations. No devitrification to crystalline form was observed in either case during the dissolution studies. The problem of plug formation seen in the case of pure amorphous form was not observed at concentrations higher than 40% (m/m) of the excipient.

A number of mechanisms have been proposed for the increase in the dissolution rate by SDs (5). These include reduction in size of the crystallite, solubilization effect of the carrier, absence of aggregation of crystallites, improved wettability and dispersibility

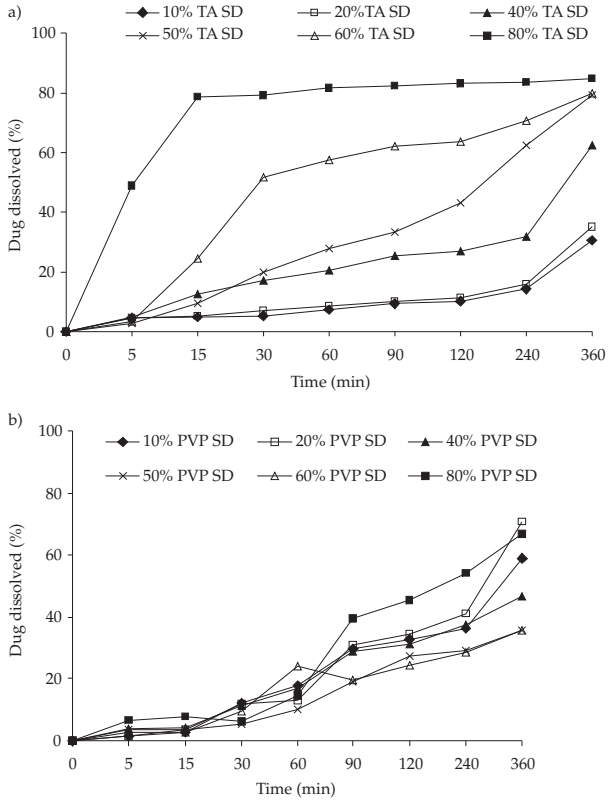


Fig. 7. *In vitro* dissolution studies of SDs containing different concentrations of additives: a) tartaric acid and b) PVP (SD bars for $n = 3$).

of the drug from dispersion, drug dissolution in hydrophilic carrier, drug conversion to amorphous state, and combination of the mentioned factors. The dissolution process can be described by two distinct processes – the rate of the interfacial/solid-solvent reaction leading to solubilization of the molecule and the rate of diffusion/transport of the solvated molecule to the bulk of dissolution medium. The initial rise at higher concentrations of tartaric acid and in PVP can be due to the decrease in interfacial tension between the hydrophobic drug and the medium owing to the hydrophilic additive and local solubility effect during early stages in the drug microenvironment.

CONCLUSIONS

SDs provide a practical means of further enhancing the solubility benefit achieved using amorphous systems. IBS served as a model candidate for formation of solid solutions or dispersions of amorphous IBS into a fast dissolving matrix. The »amorphous alloys« generated using small molecules like tartaric acid and mannitol or high molecular mass polymers like PVP and HPMC led to a significant enhancement of solubility over

the crystalline form. In case of molecules that are relatively stable in their amorphous state, it was anticipated that small molecules like acids and sugars could also be used for generation of dispersions. Tartaric acid, by virtue of its pH altering capacity and mannitol by its water structure forming ability led to a significant improvement in solubility over crystalline IBS. High T_g polymers like PVP and HPMC, apart from their antiplasticization effect, increase the wettability and hydrophilicity of the system and maintain the molecules in the disordered state for a longer period.

Significant opportunities lie in the field of amorphous pharmaceuticals. Through an understanding of the relationship between the glassy behavior and product performance and a thorough insight into the thermodynamic and kinetic properties, it is possible to commercially utilize these molecularly disordered systems in pharmaceuticals.

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S A Ž E T A K

Poboljšana topljivost teško topljivog lijeka u čvrstim disperzijama s polimernim i nepolimernim hidrofilnim dodacima

GARIMA CHAWLA i ARVIND K. BANSAL

Irbesartan (IBS) je hidrofobni lijek teško topljiv u vodi koji se slabo oslobađa iz ljekovitih pripravaka. U radu je opisana priprava čvrstih disperzija (SDs) IBS-a pomoću aditiva male relativne molekulske mase (vinska kiselina i manitol) i polimera (polivinilpirolidona, PVP, i hidroksipropil metilceluloze, HPMC). Koristeći vinsku kiselinu i PVP

topljivost je povećana 9,5 puta (138 μg mL^{-1}), odnosno 7 puta (103 μg mL^{-1}) u odnosu na kristaliničnu formu (14,6 μg mL^{-1}). Difrakcijom X-zrakama praškastog uzorka potvrđeno je da je IBS uvijek u staklastom stanju, pa i s pomoćnim tvarima koje pri niskim temperaturama prelaze u staklasto stanje. Termičke metode (diferencijalna pretražna kalorimetrija i mikroskopija s vrućom pločom) korištene su za procjenu sposobnosti miješanja lijeka s aditivima. Rezultati ukazuju da vinska kiselina stvara amorfnu otopinu, a ostale tvari amorfne suspenzije. Oslobađanje IBS-a *in vitro* ovisi o količini aditiva i raste s povećanjem koncentracije vinske kiseline, (kisele pomoćne tvari). Poboljšanje topljivosti dodatkom malih molekula može se pripisati sposobnosti prelaska IBS-a u staklasto stanje i sposobnosti zadražavanja u tom stanju.

Ključne riječi: irbesartan, čvrsta disperzija, amorfno stanje, topljivost, oslobađanje

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