Solubility, Dissolution Rate and Bioavailability Enhancement of Irbesartan by Solid Dispersion Technique

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The objective of present work was to enhance the solubility and bioavailability of poorly aqueous soluble drug Irbesartan (IBS). The solid dispersions were prepared by spray drying method using low viscosity grade HPMC E5LV. Prepared solid dispersions were characterized by dissolution study, fourier transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and X-ray diffraction studies (XRD). Results of the SEM, DSC and XRD study showed the conversion of crystalline form of IBS to amorphous form. The dissolution rate was remarkably increased in case of solid dispersion compared to pure IBS. Solubility and stability of solid dispersion was increased due to surfactant and wetting property, slowing devitrification and having anti-plasticization effect of HPMC E5LV. *In vivo* studies were performed in healthy rabbits (New Zealand grey) and compared with plain IBS. Solid dispersions showed increase in relative bioavailability than the plain IBS suspension. In conclusion, the prepared solid dispersions showed remarkable increase in solubility, dissolution rate and hence bioavailabilty of poorly water soluble drug Irbesartan.

Key words Irbesartan; solubility enhancement; solid dispersion; bioavailability; devitrification

Most of the new chemical entity suffers from low bioavailability due to their low aqueous solubility and dissolution. Many approaches have been used like micronization, solubilization, complexation with polymer, salt formation, use of prodrug, addition of surfactant, solid dispersions, *etc.* But all these methods suffer from limitations like size reduction by micronization, form surface charges which show poor flow property.[1] Amorphous system exhibits significant solubility benefits, due to excess thermodynamic properties and lower energetic barrier than its crystalline form.[2] The major reason for limited solubility benefit from amorphous system is their devitrification, on exposure to primary aqueous dissolution medium. This limited solubility can be overcome by further increases in solubility by preparing solid dispersions (SD) with polymer having high glass transition temperature (Tg) value like hydroxypropyl methylcellulose (HPMC), polyvinyl pyrrolidone (PVP).[3] SD increases the solubility by slowing devitrification, and increased wettability due to hydrophilic nature.[4] Solid dispersion is useful method to disperse drugs in the molecular state in a carrier matrix.[5,6] Various methods have been reported for preparation of solid dispersion like physical mixture, kneading method, spray drying, solvent wetting, and modified solvent evaporation method.[7] Most of these methods are amenable only to research laboratory set up, with the exception of spray drying, which can be scaled-up industrially.[8] Solid dispersions by spray drying technique has been reported for wide variety of poorly aqueous soluble drug like glibenclamide,[9] curcumin,[10] albendazole,[11] tolbutamide,[12] loperamide.[13]

Irbesartan (IBS), 2-butyl-3-[[2-(1*H*-tetrazole-5-yl)(1,1-biphenyl)-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-en-4-one antagonizes angiotensin II by blocking AT_1 receptors is indicated for treatment of hypertension.[14] It belongs to class II drug according to biopharmaceutical classification system (BCS) *i.e.* low solubility and high permeability. According to BCS drug substance is considered to be highly soluble when highest dose of drug dissolve in less than 250 ml of water. It is considered to be highly permeable when the extent of absorption in human is more than 90% of an administered dose. Although it has excellent oral bioavailability (60—80%), but theoretically IBS exhibits solubility limited bioavailability and it would be advantageous to increase the solubility of such molecule.[15] Solubility of IBS was found to be increased after complexation with polymer like β-cyclodextrin.[16]

In this study solid dispersions of IBS were prepared by spray drying technique using low viscosity grade of HPMC E5 LV having the high Tg value in order to enhance its solubility, dissolution rate and bioavailability. Spray drying technique has advantages like generation of amorphous system and formation of solid dispersions simultaneously. The physical properties of the prepared solid dispersions were characterized by differential scanning calorimetry (DSC), scanning electron microscopy (SEM), powder X-ray diffractometry (PXRD), Fourier transform infrared spectroscopy (FT-IR) and solubility studies. Solubility and dissolution rate of solid dispersions were compared with IBS, and *in vivo* study was performed in rabbits (New Zealand grey).The objective of present investigation was to study the oral bioavailability of IBS from its pure form and from solid dispersions prepared by spray drying method. The oral bioavailability of IBS in suspension was also estimated to determine the relative bioavailability of the solid dispersions.

Experimental

Materials Irbesartan (IBS) was obtained as a gift sample from Zydus Cadila Healthcare Ltd., Mumbai, India. Hydroxypropyl methylcellulose (HPMC E5 LV) was gifted by Dow Chemical Co., Midland and Methyl paraben from S.D. Fine Chemicals, Mumbai, India. Ethanol, Acetonitrile and all other reagents used were of analytical grade.

Methods. Ratio Optimization by Solubility Method The physical mixture of IBS and HPMC E5 (PM) was prepared by simple mixing method using mortar and pestle in different ratios such as 1 : 1 to 1 : 5 w/w. Ratio optimization was done by solubility determination method.

Preparation of Solid Dispersions by Spray Drying The solid dispersions of irbesartan (ISSD) were prepared by evaporation of hydro alcoholic

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solution of IBS and HPMC E5 LV in optimized ratio (1 : 5 w/w) using spray dryer (LU- 222, Labultima, India). The solution was prepared by dissolving 1 g of IBS in 50 ml of ethanol and 5 g of HPMC E5 LV in 100 ml of distilled water and mixing both solutions, which produce clear solution. The solvent was evaporated at inlet 130 °C and outlet 90 °C, feed pump speed 10 ml per minute and aspiration speed 35%.

Characterization of Solid Dispersions. Solubility Study The solubility of pure IBS, PM and ISSD were determined in pH 1.2 buffer. The solubility were determined by taking IBS in an excess amount 30 mg and the mixture equivalent to 30 mg of IBS in 10 ml of pH 1.2 buffer, in teflon facing screw capped vials. The vials were kept at equilibrium for period of 24 h on orbital shaking incubator (CIS-24, Remi instrument, Mumbai, India) at 37±0.5 °C and 100 rpm. The content of vials were filtered through 0.2 μm membrane filter and analyzed using UV spectrophotometer (1700, Shimadzu, Japan) at 244 nm.[17)]

Differential Scanning Calorimetry (DSC) The DSC profiles of IBS, PM, ISSD were obtained by using differential scanning calorimeter (DSC 60, Shimadzu, Japan) at a heating rate of 10 °C/min from 30 to 300 °C in nitrogen atmosphere.

Powder X-Ray Diffraction (PXRD) Powder XRD patterns of IBS, PM, ISSD were recorded using diffractometer (Brucker Axs, 08 Advance, Germany) and Cu$K\alpha$ radiation. Diffractometer was run at a scanning speed of 2°/min and a chart speed of 2°/2 cm per 2θ.

Scanning Electron Microscopy (SEM) The SEM photograph of IBS and solid dispersions prepared by spray drying method (ISSD) were obtained using scanning electron microscope (JSM 6390, JEOl, Japan) with 10-kV accelerating voltage.

Fourier Transform Infrared Spectroscopy (FT-IR) FT-IR spectra of IBS, PM and ISSD were recorded using FT-IR instrument (8400S, Shimadzu, Japan) using KBr disk method (20 mg sample in 200 mg KBr). The instrument was operated under dry air purge and scanning range was of 4000—400 cm^{-1} and resolution was 1 cm^{-1}. Structural changes and the lack of a crystal structure can lead to changes in bonding between functional groups that can be detected by FT-IR.

***In Vitro* Drug Release Study** Dissolution test of pure IBS and ISSD were performed using USP dissolution test apparatus II (paddle type) at 100 rpm and 37±0.5 °C containing 0.1 N HCl (pH 1.2) as a dissolution medium. Test samples (5 ml) were withdrawn at particular time interval (5, 10, 15, 30, 45, 60, 75, 90, 105, 120 min) and replaced with fresh dissolution media maintained at 37±0.5 °C. Test samples were filtered (membrane filter, 0.45 μm), suitably diluted and assayed spectrophotometrically at 244 nm. Each dissolution test was repeated 3 times.[18)]

***In Vivo* Evaluation of Solid Dispersions** The study protocol for *in vivo* was approved by the Institutional Animal Ethics Committee (IAEC) of R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur and is in accordance with guidance of Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India.

The bioavailability of ISSD was determined in comparison with pure IBS in healthy rabbits (New Zealand grey) of average weight 2.1±0.01 kg. The rabbits were divided into 2 groups of 6 animals each (n=6). One group received pure IBS suspension whereas the other group received formulation containing solubility enhanced irbesartan of same dose. The solubility of IBS is very less in water and it floats on water so it is difficult to prepare the solution in water.[15)] Hence the dose equivalent to 200 mg (one tenth of LD_{50}) of pure drug and ISSD suspension in the 0.01 N hydrochloric acid and administered orally with help of syringe. Blood samples were collected from marginal ear vein at intervals of 0 (before drug administration), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 5 h after administration of the drug. Blood was transferred into tube containing dilute heparin and centrifuge at 5000 rpm for 25 min. The plasma was separated and stored at −20 °C until analysis. During the entire study, the rabbits had free access to water only.[19)] Rabbits remained conscious during whole study.

Sample Processing The plasma (0.5 ml) was transferred into test tube and 10 μl of internal standard (methyleparaben) working solution (20 ng/μl) was spiked. Solution was vortexed and acidified with 150 μl of 1 M orthophosphoric acid. Then 3 ml of extraction solvent diethyl ether : dichloromethane (7 : 3, v/v) was added. The sample was vortexed for 5 min using Vibrax Vortexer and centrifuged for 10 min at 2000 rpm. The organic layer was transferred to vials and evaporated at 70 °C to remain residue. The sample was reconstituted using mobile phase at the time of analysis.[20)]

The drug concentration in plasma was analyzed by a high-performance liquid chromatography (HPLC) method using Rheodine type manual injector. The HPLC system (Agilent 1200 Series) consisted of column (Eclipsed XDB 5 μm, 4.6 mm×150 mm, Singapore), Ezchrome Elite Software, quaternary pump, Model G1354 A and Ultraviolet variable wavelength Diode Array detector, Model G1315D. The detection wavelength was 244 nm. The mobile phase consisted of 0.01 M potassium dihydrogen phosphate buffer (containing 0.07% triehylamine, pH was adjusted with orthophosphoric acid to pH 3.0) and acetonitrile (66 : 34, v/v) at a flow rate of 1 ml/min.

Data Analysis Data were generated assuming first-order absorption. The maximum plasma concentration (C_{max}) and time of its occurrence (T_{max}) were directly computed from the plasma concentration *vs.* time plot. The C_{max}, T_{max}, AUC_{0-5}, *MRT* was calculated using Kinetica5 (Thermo Fisher Scientific Demo version) software. Relative bioavailability was calculated with reference to oral suspension of pure IBS.

Statistical Evaluation All results are expressed as mean values±S.D. Differences between two related parameters were considered statistically significant for p-values of or less than 0.05. Drug to polymer ratio optimization, solubility determination and dissolution efficiency results were analyzed by applying unpaired student 't' test.

Results and Discussion

Solubility Study Results for ratio optimization of drug to polymer are summarized in Table 1. Solubility data for IBS, PM and ISSD are given in Table 2. Solubility data showed that HPMC E5 enhanced the solubility of IBS using spray drying method of solid dispersions. Drug : polymer in ratio 1 : 5 significantly enhances the solubility of IBS ($p<0.001$). The optimization of drug : polymer ratio was done by solubility determination in pH 1.2 buffer. Drug : polymer in ratio 1 : 5 significantly enhance the solubility ($p<0.001$). The enhancement of solubility and dissolution of IBS from drug : polymer system can be attributed to a number of factors namely, decrease in crystallinity, surfactant and wetting property, slowing devitrification and anti-plasticization effect of polymer.

Differential Scanning Calorimetry (DSC) The DSC profiles of IBS, PM and ISSD prepared by spray drying method are depicted in Fig. 1. DSC analysis of crystalline IBS showed a single sharp fusion endotherm at 184.39 °C. It is revealed from DSC thermogram of PM, ISSD there is decrease in sharpness and intensity of characteristic endothermic peak of drug which could be attributed to the conversion of most of the crystalline form of the drug to the amorphous form.

Powder X-Ray Diffraction (PXRD) XRD patterns of

Table 1. Drug to Polymer Ratio Optimization

Drug : polymer ratios	Solubility (mg/ml)[a)]
1 : 1	1.19±0.13
1 : 2	2.32±0.25
1 : 3	4.13±0.64
1 : 4	5.79±0.42
1 : 5	7.88±0.07

All results were calculated as mean±3 S.D., *a*) Value indicate $p<0.001$.

Table 2. Solubility Study of IBS, Physical Mixture, and Solid Dispersions Prepared by Spray Drying Method

Sample	Solubility (mg/ml)[a)]
IBS	0.94±0.04
PM	7.88±0.07
ISSD	14.93±0.03

All results were calculated as mean±3 S.D., *a*) Value indicate $p<0.001$. IBS Irbesartan, PM physical mixture of drug and polymer, ISSD solid dispersions.

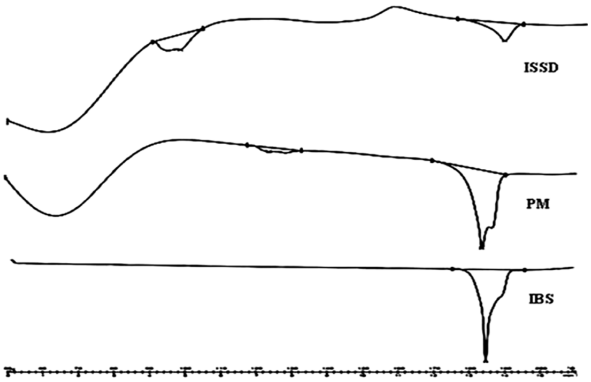

Fig. 1. DSC Profiles of IBS, Physical Mixture of HPMC and Drug (PM), ISSD Solid Dispersions by Spray Drying Method

IBS: Irbesartan, PM: physical mixture of drug and polymer, ISSD: IBS solid dispersions prepared by spray drying method.

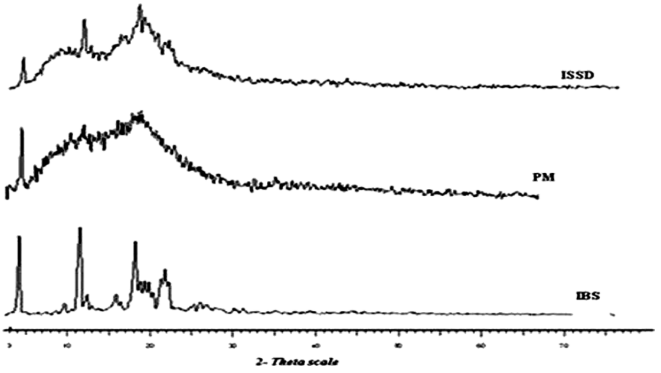

Fig. 2. Powder X-Ray Diffraction Patterns of IBS, Physical Mixture of HPMC and Drug (PM), ISSD Solid Dispersions by Spray Drying Method

IBS: Irbesartan, PM: physical mixture of drug and polymer, ISSD: IBS solid dispersions prepared by spray drying method.

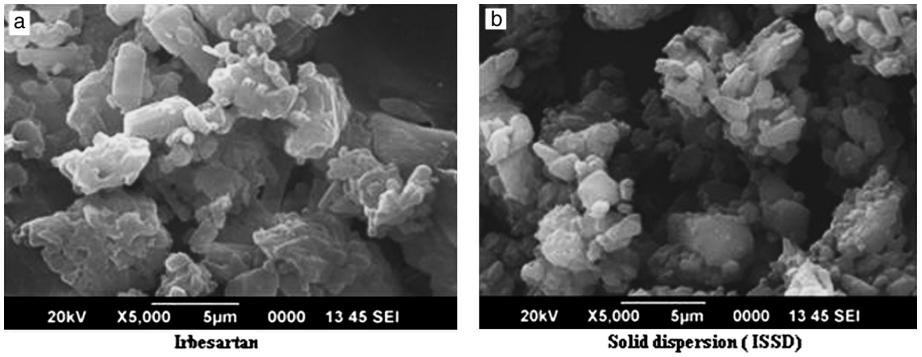

Fig. 3. SEM Photograph of Irbesartan (a) and Solid Dispersions (ISSD) (b)

ISSD: IBS solid dispersions by spray drying method.

pure IBS, HPMC E5, PM and ISSD are depicted in Fig. 2. The characteristic peaks appeared in the XRD of IBS at diffraction angles (2θ) 4.83°, 12.54°, 10.57°, 13.42°, 17.05°, 19.51°, 21.22°, 23.26°, and 27.77° showing a typical crystalline pattern. However, all major characteristic crystalline peaks appeared in the diffractogram of PM as well as ISSD but of low intensity suggesting decrease in crystallinity of IBS. XRD of IBS showed sharp and intense characteristic peaks at different angles suggesting crystalline nature of IBS. However, decrease in intensity of characteristic peaks of IBS in case of ISSD indicated conversion of some of crystalline IBS to amorphous form. The XRD result of PM and ISSD suggest more amorphous nature of IBS in case of ISSD than in PM. Thus, results of XRD support the findings of the DSC study.

Scanning Electron Microscopy (SEM) The SEM image of IBS and ISSD are shown in Fig. 3. IBS particles appeared as longer, platy shape with smooth surface which were very specific in their morphology, whereas SEM image of ISSD showed irregular and discrete particles. SEM images showed that the crystalline IBS is converted to its amorphous form which is further confirmed by DSC and XRD study.

FT-IR Spectroscopic Study FT-IR spectra of IBS, HPMC E5, PM, ISSD are depicted in Fig. 4. The characteristic absorption peaks of IBS was found at 3055 cm^{-1} and 3032 cm^{-1} (N–H stretch), 1731 cm^{-1} (C=O stretch), 1622 cm^{-1} (C–N stretch). The FT-IR study indicated that the

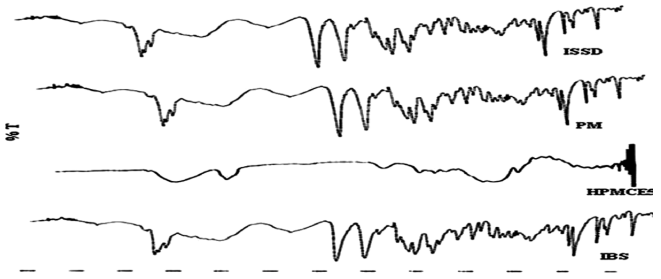

Fig. 4. FT-IR Spectra of IBS, HPMC E5, Physical Mixture (PM), IBS Solid Dispersions by Spray Drying Method (ISSD)

IBS: Irbesartan, PM: physical mixture of drug and polymer, ISSD: IBS solid dispersions prepared by spray drying method.

characteristic peaks of IBS which were also present in the PM as well as in ISSD. It showed that there is no interaction between drug and excipients which was further confirmed by DSC analysis.

***In Vitro* Drug Release Study** *In vitro* dissolution profiles of IBS and ISSD are represented in Fig. 5. Table 3, summarize dissolution efficiency data (DE_{30} and DE_{60}) which showed significant enhancement ($p<0.001$) of dissolution rate of IBS from ISSD than pure IBS. Results of dissolution study indicated that the dissolution rate of IBS was improved from solid dispersions with HPMC E5 LV by spray drying method. It was reported that amorphous IBS is prone to devitrification in dissolution media.[3] However, the phenome-

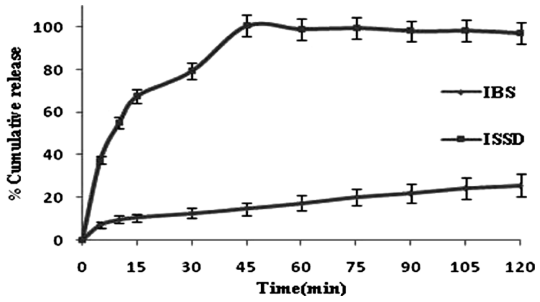

Fig. 5. Dissolution Profile of IBS, and ISSD in 1.2 Buffer

ISSD IBS solid dispersions by spray drying method. All the result were calculated as mean±3 S.D. IBS: Irbesartan, ISSD: IBS solid dispersions prepared by spray drying method.

Table 3. Dissolution Efficiency (DE) of IBS and Solid Dispersions Prepared by Spray Drying Method

Product	DE_{30} [a)]	DE_{60} [a)]
IBS	9.33±0.92	12.01±0.76
ISSD	57.99±1.60	76.24±2.19

All results were calculated as mean±3 S.D., *a*) Value indicate $p<0.001$. IBS: Irbesartan, ISSD: IBS solid dispersions by spray drying method.

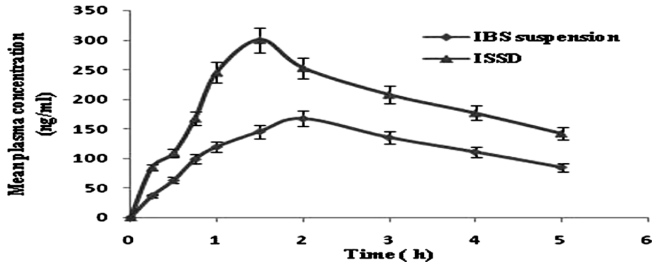

Fig. 6. Mean Plasma Concentration–Time Profile of IBS after Oral Administration of IBS Suspension, ISSD Solid Dispersions at a Dose 200 mg to Rabbits Showing Significant Enhancement in C_{max} and *AUC* ($p<0.001$)

Each data point represents the mean±standard deviation. IBS: Irbesartan, ISSD: IBS solid dispersions prepared by spray drying method.

non of devitrification can be slowed down by formulating it as solid dispersions.

***In Vivo* Evaluation of Solid Dispersions** *In vivo* study was carried out to evaluate the pharmacokinetic parameters of IBS from IBS suspension and ISSD, which were administered orally to rabbits. Figure 6 shows the plasma drug concentration as a function of time after oral administration. The pharmacokinetic parameters of IBS such as C_{max}, T_{max}, and AUC_{0-5} are showed in Fig. 6. The time occurrence for peak plasma concentration (T_{max}) of IBS suspension was obtained at 2 h and that of solid dispersions is 1.5 h, as shown in Fig. 6. Peak plasma concentration (C_{max}) values of IBS suspension and ISSD were found to be 167.10±5.37 and 300.49±7.38 ng/ml respectively after oral administration. The relative bioavailability of IBS from solid dispersions was found to be 176.13±2.03%. These results are in congruence with the previous reported results[19] where authors concluded that oral bioavailability of nimodipine was increased from its co-grinding mixture with modified gum karaya (MGK) due to increase in solubility as compared to nimodipine solution.

Stability Studies Stability studies of the formulated solid dispersion were carried out as per ICH guidelines. Various parameters such as drug content and *in vitro* release were determined during study. There was no colour chang observed after stability study. The *in vitro* drug release profile of SD after 45 min is shown in Table 4. From the results of stability studies it was found that, solid dispersion was stable at 40 °C/75% RH.

Table 4. Physicochemical Evaluation of Solid Dispersion (ISSD) after Stability Studies

Time (d)	Drug content (%)	*In vitro* drug release (%)
0	92.54±0.14	98.21±0.12
30	93.82±0.43	99.24±0.35
60	92.78±0.21	97.99±0.11
90	91.99±0.17	96.72±0.34

Conclusion

In conclusion, solid dispersions of IBS with HPMC E5 LV by spray drying method which can be scaled-up industrially is promising approach for enhancing solubility and dissolution rate which increases oral bioavailability of poorly water soluble IBS. The mechanism involved in the solubility and dissolution rate enhancement of IBS from ISSD may be attributed to surfactant and wetting property, slowing devitrification and anti-plasticization effect of HPMC E5 due to high Tg value.

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References

1) Feeley J., York P., Sumbly B., Dicks H., *Int. J. Pharm.*, **172**, 89—96 (1998).
2) Pudipeddi M., Serajuddin A. T. M., *J. Pharm. Sci.*, **94**, 929—939 (2005).
3) Chawla G., Bansal A. K., *Acta Pharm.*, **58**, 257—274 (2008).
4) Craig D. Q. M., *Int. J. Pharm.*, **231**, 131—144 (2002).
5) Serajuddin A. T. M., *J. Pharm. Sci.*, **88**, 1058—1999 (1999).
6) Chiou W. L., *J. Pharm. Sci.*, **60**, 1281—1302 (1971).
7) Patel M., Tekade A., Gattani S., Surana S., *AAPS PharmSciTech*, **9**, 1262—1269 (2008).
8) Gupta P., Bansal A. K., *Pharm. Dev. Tech.*, **10**, 73—281 (2005).
9) Chauhan B., Shimpi S., Paradkar A., *Eur. J. Pharm. Sci.*, **26**, 219—230 (2005).
10) Paradkar A., Ambike A., Jadhav B., Mahadik K., *Int. J. Pharm.*, **271**, 281—289 (2004).
11) Alanazi F., Badry M., Ahmed M., Ibrahim A., *Sci. Pharm.*, **75**, 63—79 (2007).
12) Takeuchi H., Nagira S., Yamamoto S., Kawashima Y., *Powder Technology*, **141**, 187—195 (2004).
13) Weuts I., Kempen D., Verreck G., Decorte A., Heymans K., Peeters J., Brewster M., *Eur. J. Pharm. Biopharm.*, **59**, 119—126 (2005).
14) Pouleur H. G., *Am. J. Hypertens.*, **10**, 318—324 (1997).
15) Chawla G., Bansal A. K., *Eur. J. Pharm. Sci.*, **32**, 45—57 (2007).
16) Hirlekar R., Kadam V., *AAPS PharmSciTech*, **10**, 276—281 (2007).
17) Pandya P., Gattani S., Jain P., Khirwal L., Surana S., *AAPS PharmSciTech*, **9**, 1247—1252 (2008).
18) Mohammad B. J., Valizadeh H., Dastmalchi S., *Int. J. Pharm. Res.*, **6**, 159—165 (2007).
19) Murali Mohan Babu G. V., Kumar N. R., Sankar K. H., *AAPS PharmSciTech*, **3**, 1—9 (2002).
20) Shakya A. K., Al-hiari Y. M., Alhamami O. M., *J. Chromatogr.*, **848**, 245—250 (2007).