RESEARCH ARTICLE

Crystal modification of Irbesartan in presence of additive

P.A. Pangarkar*, R. R. Thenge, N.M. Mahajan, V.S. Adhao, P.V. Ajmire

Department of Pharmaceutics, IBSS College of Pharmacy, Malkapur-443101, Maharashtra, India.

J. Adv. Pharm. Edu. & Res.

ABSTRACT

Irbesartan is a non peptide specific competitive antagonist of the angiotensin II receptor used orally for treatment of hypertension. Irbesartan exhibits low bioavailability related to its poor water solubility. The present research carried out for crystal modification irbesartan in the presence of different additives, to improve the solubility and dissolution rate. The additives used for the crystal modification were PVP K30, PEG 4000, HPMC and Tween 80. The modified crystals were characterized by Scanning electron microscopy, FT-IR spectroscopy, differential scanning calorimetry and X-ray diffraction. The comparative solubility and dissolution rate of modified crystals and the untreated irbesartan were studied. The SEM results different morphology (size and shape) in the presence of additives. FT-IR spectra of untreated irbesartan when compared with the various crystals obtained in the presence of additives showed no significant change in their characteristic peaks. Also DSC spectra showed slight change in the melting endotherm of modified crystals and the XRD spectra revealed slight change in diffraction pattern. The FT-IR, DSC and XRD indicate crystal modification in the presence of additives. The modified crystals obtained in the presence of PEG 4000 showed maximum solubility and dissolution rate compared to other modified crystals and untreated irbesartan.

Keywords: Crystal modification, Irbesartan, FT-IR, DSC, Solubility, dissolution rate.

INTRODUCTION

Polymorphism is the ability of the drug exist in different crystalline forms, one of the most important physical factors, which affect the bioavailability and therapeutic efficacy of drug, is the existence of active ingredients in various crystal forms having different internal structure and physical properties.[1-2] Possible reasons are a change of the relative growth rates of the different crystal faces caused by solvent and impurity interaction. [3-5] Crystallization of API by various methods using different solvents and in the presence of additive can affect the different physicochemical properties, namely crystal shape, crystal size, melting point, solubility pattern, dissolution characteristics. [6-7]

Impurity molecules generally absorbed on all the crystal faces, totally inhibiting crystallization, or on selective faces, leading to alter morphology. Crystallization in the presence of additives has considerable effect on shape of carbamazepine crystals. [8] It has long been recognized that the presence of trace amounts of impurities can have substantial effects on the kinetics of crystal nucleation, growth morphology and dissolution. [9-10] the adsorbed molecule may become incorporated in the crystal surface, thereby introducing lattice strains that influence the apparent solubility of crystal habit modification. This leads to inhibition of active site necessary for crystal growth. Currently, there is considerable interest in modifying the properties of drug using different crystallization techniques or additives in order to improve the compaction behaviour of the crystals. Irbesartan is a non peptide specific competitive antagonist of the angiotensin II receptor (AT1 subtype) used orally for treatment of hypertension. Irbesartan is water-insoluble, lipophilic and highly permeable according to Biopharmaceutical Classification System. The drug exhibits low bioavailability related to its poor water solubility. Thus present study reveals to modify the crystals of irbesartan in the presence of additives to improve

Address for correspondence

P. A. Pangarkar
Department of Pharmaceutics
IBSS College of Pharmacy,
Malkapur-443101,
Maharashtra, India.
E-mail: raju.thenge11@gmail.com

Access this article online
www.japer.in

solubility, dissolution rate and compaction characteristics.

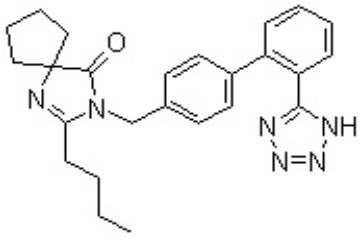


Fig.1. Irbesartan

MATERIALS AND METHODS

Irbesartan obtained as a gift sample from Aurobindo Pharmaceutical, Hyderabad, India.

PVP K-30, PEG 4000, HPMC, and Tween 80 were purchased from SD Fine Chem. Mumbai. All the solvents used for recrystallization purchased from Qualigens, Mumbai and of analytical grade. Modification of Irbesartan crystals in the presence of additives Irbesartan (2 gm) was dissolved in 25 ml of ethanol at 65^{0}C on water bath containing additives such as polyvinyl-pyrollidone (PVP-K30), polyethylene glycol (PEG-4000), hydroxypropyl methyl cellulose (HPMC) and Tween 80 with the concentration of 1% W/V. The solution was then filtered through Whatmann filter paper and the filtrate was kept at room temperature for 24 hours to afford well defined crystals of irbesartan. Then the crystals were spread on a Petri plates and dried overnight in a vacuum desiccators for 2 days. The modified crystals were stored in well closed container for further studies.

Scanning electron microscopy

The surface morphology of untreated irbesaran and modified crystals were characterized by scanning electron microscope (Jeol Instruments, Japan). Samples were mounted on a metal stub with an adhesive and coated with gold ions for 5-6 minutes under vacuum. The photomicrographs of samples were taken at 10kV and various magnifications.

Infrared spectroscopy

The modified crystals and untreated irbesartan were scanned and recorded in the range of 4000-400 cm^{-1} by using Infrared spectrophotometer, (Bruker, Alfa-T, Germany). The crystal samples were triturated with dried potassium bromide (KBr) using mortar and pestle. The mixture after grinding into fine powder was kept uniformly in suitable die and compressed into a pellet form by using hydraulic press. The resultant pellet was mounted in a suitable holder in the IR spectrophotometer.

Differential scanning calorimetry

After calibration, thermograms were obtained by DSC (DSC 821e, Mettler Toledo, Switzerland) heating all the samples (5 mg) of untreated irbesartan and modified crystals at a constant heating rate of 10^{0}C/min with chart speed of 40 ml/min under an atmosphere of nitrogen. The exact peak temperatures, melting point and heat of fusion were automatically calculated. The temperature range for the scan was 30^{0}C to 300^{0}C for all the samples.

X-ray diffraction spectroscopy

X-ray diffraction pattern of untreated Irbesartan and modified crystals were obtained using the X-ray diffractometer (Bruker, D8 Advance, Germany) at 40 kV, 30 mA and a scanning rate of 0.02^0 /min at the diffraction angle 2 θ over the range of 10- 80 using Cu (as anode) radiation of wavelength 1.5406 Å.

Solubility studies

The solubility of untreated Irbesartan and modified crystals were determined by adding excess solid (150 mg) to 100 ml media (distilled water) taken in a well stopper flask. The samples were stirred for 8 hours with the help of a magnetic stirrer with hot plate at 100 rpm at 37.5^{0}C. The temperature was controlled using a water bath. After 8 hours of stirring, an aliquot of the samples were withdrawn, filtered through Whatmann filter paper, suitably diluted and absorbance was measured spectrophotometrically using UV visible spectrophotometer (Shimazdu, SL-1800, Japan.) at 244 nm.

Dissolution studies

The dissolution studies of untreated irbesartan and modified crystals were carried out using USP dissolution type-2 apparatus, (Paddle type) (Electrolab, TDT-081, India.). after introducing of an

appropriate amount of sample, paddle was rotated at the speed of 75 rpm and the dissolution medium (900 ml) 0.1 *N* HCL was maintained at temperature 37 ± 0.5^{0}C. After specific time intervals, an aliquot (5 ml) was withdrawn and replaced with fresh and equal quantity of dissolution medium. The samples were suitably diluted and absorbance was measured at 244 nm using U.V. spectrophotometer (Shimazdu, SL-1800, Japan.).

Preparation of compacts

All the crystal samples were ground using mortar and pestle to achieve a similar particle size distribution for each batch. Compact were prepared directly from the ground crystals using 10 mm flat-faced punches on a hydraulic press (Chamunda, Pilot Press-II, India). The material for each tablet was weighed (150 mg), introduced into the die and compacted at various compression pressures, 0.5, 1, and 1.5 tons. The compaction surfaces were lubricated with 2% w/w magnesium Stearate before compaction.

Crushing strength of compact

Crushing strengths were determined from the force required to fracture the compacts by diametric compression using tablet hardness tester (Pfizer type). The crushing strength of various crystal samples was noted.

RESULT AND DISCUSSION

Scanning electron microscopy

The crystal morphology of untreated irbesartan and modified crystals obtained in presence of additives were studies by scanning electron microscopy. The SEM showed that the untreated irbesartan has smaller and irregular size and shape of crystals shown in Fig.2 (a). After crystallization of commercial sample from ethanol and in the presence of additives showed difference in the crystal morphology. The recrystallized irbesartan from ethanol showed the needle shaped crystals Fig.2 (b). This is due to the effect of solvent on the crystal habit of the irbesartan. The crystals obtained in the presence of additives had also changed the size and shape (crystal habit). The crystals obtained in the presence of PVP K30 have thin rod shaped crystals Fig.2 (c) where as the crystals obtained from HPMC showed equant shape crystal Fig.2 (e). The crystals in presence of PEG 4000 and Tween 80 and showed thin pole shaped crystals Fig.2 (d) and (f). SEM results conclude that the crystals obtained in the presence of additives showed the morphological changes and confirms the variation in the crystal habit, which indicate the influence of additives on crystallization of irbesartan. The changes in morphology of irbesartan crystals could be due to variations in face dimensions or the appearance or disappearance of some faces. Under certain conditions of crystallization, one set of crystal faces may be induced to grow faster than others, or the growth of another set of faces may be retarded.

Infrared spectroscopy

All the crystals including untreated irbesartan, recrystallized from ethanol and crystals grown in presence of additives prepared by solvent evaporation showed characteristic peaks in Fig.3.(a-h) Characteristic peaks of Irbesartan appeared at 3436.51 cm^{-1} (N-H stretching), 2959.70 cm^{-1} (C-H stretching), 1732.65 cm-1 (C=O stretching), 1408.96 cm-1 (C=C stretching) and 1616.01 cm^{-1} (N-H bending). FT-IR spectra of untreated irbesartan when compared with the modified crystals obtained in the presence of additives shows slight or no significant changes in their characteristic peaks indicates no polymorphic modifications (structural modification). The characteristic peaks of untreated irbesartan and modified crystals were shown in Table.1.

Differential scanning calorimetry

The thermal behaviour of untreated irbesartan and crystals in the presence of additives are shown in Fig.4.(a-h). The DSC thermo gram of all the modified crystals showed slight variation in their endothermic peaks compare to untreated irbesartan. The DSC curve showed that untreated irbesartan appeared on sharp endothermic peak at about 189.89^{0}C corresponding to its melting point followed by decomposition exotherm 220.63^{0}C. However the crystals obtained in the

presence of PVP K30, PEG 4000 showed the shift of endothermic peak towards lower temperature at 189.21^{0}C, and 188.56^{0}C respectively. Shift of endothermic peak towards lower temperature indicates the decrease in the melting point of drug in crystals. This decreased melting point accounts for increased solubility of drug, where as the irbesartan recrystallized from ethanol, crystals obtained in presence of HPMC and Tween 80 showed shift of endothermic peak towards upper temperature at 190.07^{0}C, 192.02^{0}C, 190.61^{0}C and respectively, indicating increase in melting point of drug in crystals. This melting point accounts for the decrease in the solubility of drug. Also the DSC data showed that there was slight modification in the crystal of irbesartan due to the presence or absence of additives.

Powder X-ray diffraction

The XRD spectra of modified crystals were studied by X-ray diffractometer. In the XRD spectra the sharp peaks at diffraction angle (2θ) 7.20, 7.12, 7.16, 7.07, 7.11, 7.14 were obtained in untreated irbesartan, methanol, PVP-K30, PEG-4000, HPMC, Tween 80 respectively. The X-ray diffraction pattern of untreated irbesartan has more number of peaks when compared to modified crystals in the presence of additives shown in Fig.5. The XRD spectra obtained from ethanol and PEG-4000 were similar and no significant difference occurred. The spectra obtained from PVP-K30, HPMC and Tween showed difference in d-spacing values and intensity of peaks. The XRD spectra of untreated irbesartan and recrystallized from alcohol in the absence or presence of various additives exhibited essentially similar diffraction patterns (2θ values), suggesting that particles crystallized in the presence of additives did not undergo structural modification. However, the differences in the relative intensities of their peaks may be attributed to differences in the habit of crystals, which may be attributed to the different solubility of the drug in the crystallization media.

Solubility studies

The solubility study showed that the untreated irbesartan was the least soluble (3.402 µg/ml) and the crystals obtained in presence hydrophilic polymer showed the improvement in the solubility. Increased in the solubility of crystals obtained in the presence of polymer are due the increased in the wettabiliy of crystals in the presence of polymer. Crystals obtained in presence of PVP was the most soluble (12.09 µg/ml) with 3.55-fold increase in solubility. The order of increasing solubility is PEG-4000 > PVP K-30 > Tween 80 > HPMC > recrystallized from ethanol > untreated irbesartan.

Dissolution studies

The dissolution profile of untreated irbesartan and modified crystals were shown in Figure.6. All the crystals obtained in the presence of additives showed better dissolution rate than untreated irbesartan. Crystals obtained in the presence of PEG-4000 show highest dissolution rate in 60 min. than crystals obtained in the presence of PVP K-30, Tween 80, HPMC and ethanol. Increased in the dissolution rate of modified crystals in the presence of various additives are due to the adsorption of hydrophilic polymer on the surface of crystals. These may increase the wetting properties of crystals in the presence of polymers.

Compressional studies

Compression of untreated irbesartan crystals at all compaction pressures produced weak compacts with low crushing strength and high tendency to cap. Recrystallized irbesartan crystals without presence of additives and irbesartan crystals grown in presence of Tween 80 showed much weaker compacts with low crushing strengths than untreated irbesartan. Crystals which were obtained in presence HPMC showed the highest improvement in compaction property as the compacts formed had showed the highest crushing strength. Again, the crystals grown in presence of PVP K30, PEG 4000 also showed the improvement in the Compressional properties as the force required to break these compacts of crystals was much higher than required for the pure untreated irbesartan. Thus

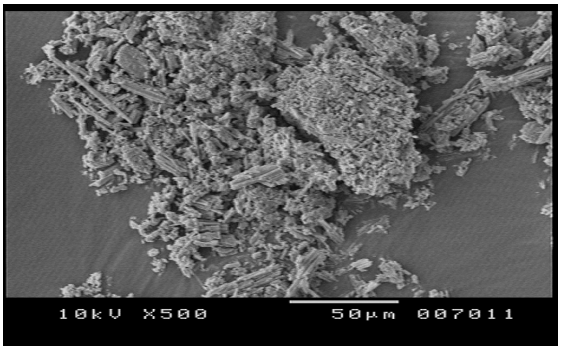
the growth of crystals in the presence of polymer improved the compression properties.

CONCLUSION

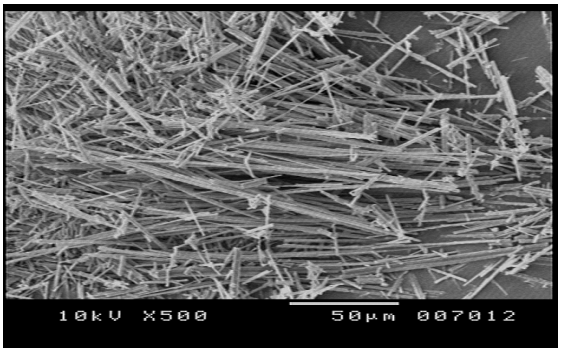
Crystal modification of irbesartan was carried out in the presence of additives. The modified crystals showed the significant change in size and shape. Solubility and dissolution rate of modified crystals were markedly increased compared to untreated irbesartan. The FT-IR, DSC and XRD data supports the change in the crystal habit of irbesartan with improved dissolution rate and compaction properties.

ACKNOWLEDGEMENT

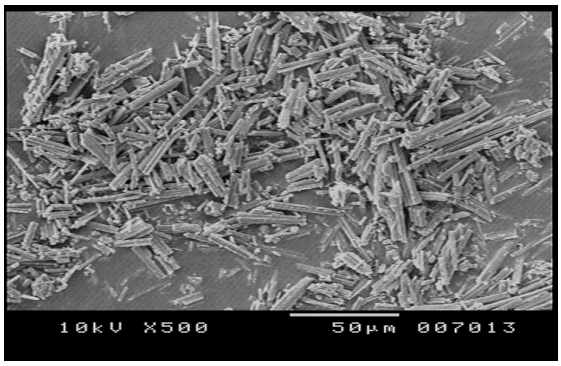
The Author are thankful to the Management and Principal, IBSS College of Pharmacy, Malkapur for providing necessary facilities to carried out this work. Authors also thankful to Diya Labs, Mumbai and AISSMS college of Pharmacy, Pune for providing SEM, FTIR, XRD and DSC facilities repectively.



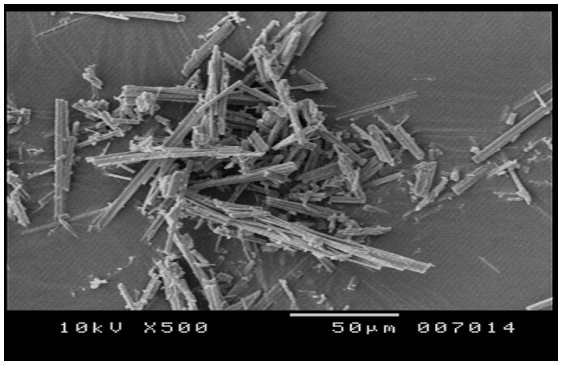
(a)



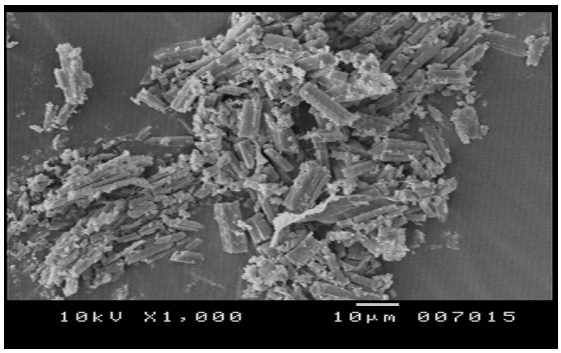
(b)



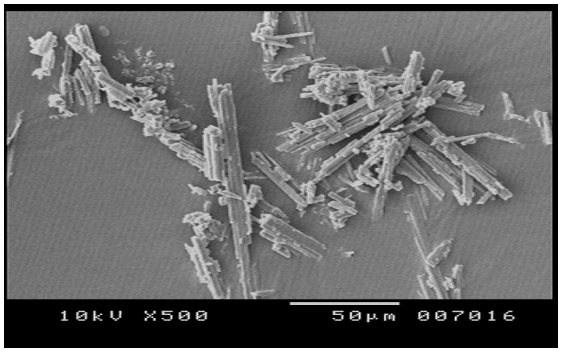
(c)



(d)



(e)



(f)

Fig.2. SEM of (a) untreated irbesartan (b) recrystallised from ethanol, (c) PVP-K30, (d) PEG-4000, (e) HPMC and (f) Tween

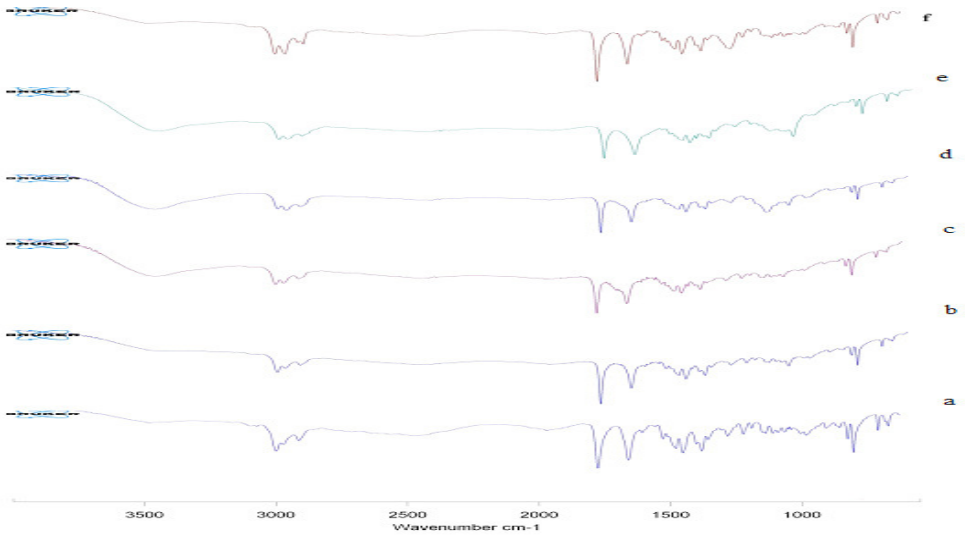


Fig.3. FT-IR spectra of : (a) untreated irbesartan, (b) recrystallised in ethanol, (c) PVP-K30, (d) PEG-4000, (e) HPMC and (f) Tween80.

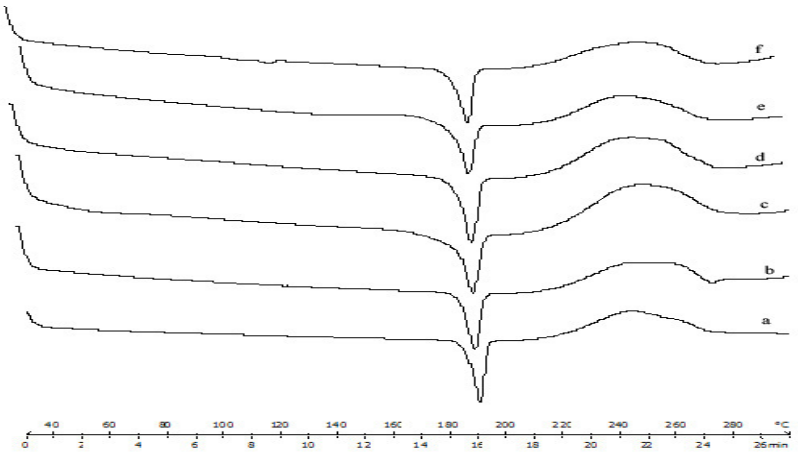


Fig.4. DSC thermogram: (a) untreated irbesartan, (b) recrystallised in ethanol, (c) PVP-K30, (d) PEG 4000, (e) HPMC (f) Tween 80.

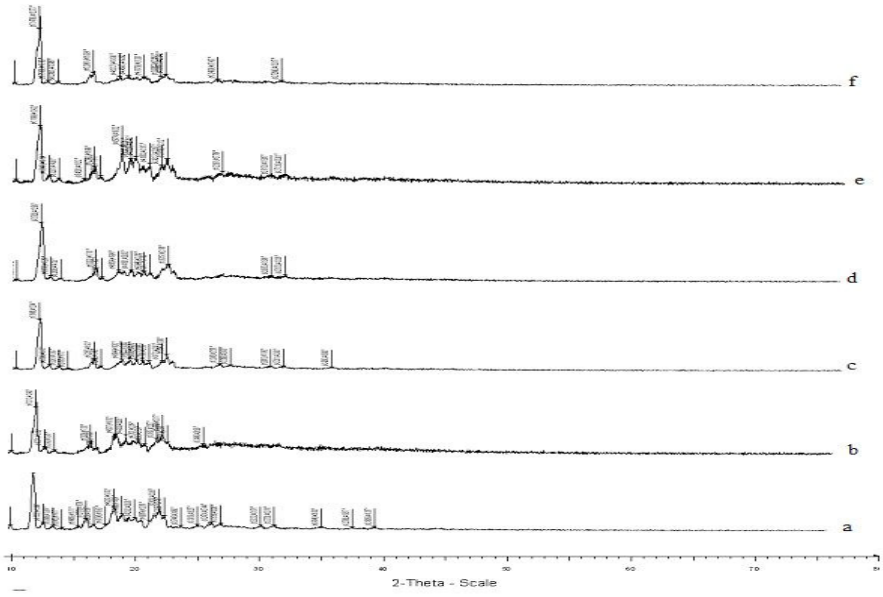


Fig.5. X-ray diffractrogram of: (a) untreated irbesartan (b) recrystallised in ethanol, (c) PVP-K30, (d) PEG 4000, (e) HPMC and (f) Tween80.

Table 1: Melting point, DSC and FT-IR data of modified crystals in the presence of additives

Crystal forms	M.P (°C)	DSC data			Characteristic peaks of IR			
		Onset temp. (C)	Peak fusion point (°C)	Heat of fusion (J/g)	N-H Stretch (cm^{-1})	C=H Stretch (cm^{-1})	C=O Stretch (cm^{-1})	C=C Stretch (cm^{-1})
Untreated irbesartan	187-189	186.32	189.89	73.43	3436.51	2959.70	1732.65	1408.96
recrystallized from ethanol	189-191	184.56	190.07	22.99	3436.51	2958.12	1732.61	1409.00
PVP K-30	187-189	183.88	189.21	27.09	3430.43	2959.95	1732.95	1408.81
PEG-4000	186-188	183.43	188.56	24.84	3423.28	2926.00	1732.95	1409.36
HPMC	188-190	186.20	190.61	27.00	3422.68	2946.22	1732.76	1409.03
Tween 80	191-193	186.45	192.02	27.64	3430.27	2959.18	1732.82	1409.01

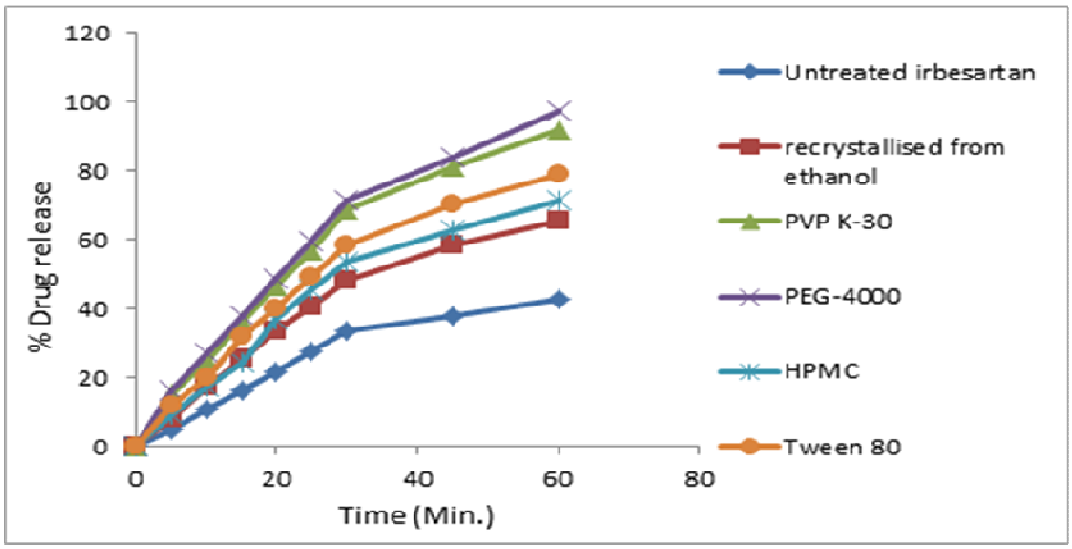


Fig. 6: Dissolution rate profile of untreated irbesartan and modified crystals in the presence of additives.

REFERENCES

1. Kapoor A, Majumdar D. K, Yadav M.R. Crystal forms of nimesulide-asulfonanilide (non-steroidal anti inflammatory drug). Indian J. Chem. 1988;37B: 572-575.
2. Shekunov B. Yu, Grant D.J.W Latham, R.J, Sherwood J.N. In situ optical interferometric studies of the growth and dissolution behaviour of paracetamol (acetaminophen) crystals. 3. Influence of growth in the presence of p-acetoxyacetanilide. J. Phys. Chem., 1997; B101: 9107–9112.
3. Finnie S, Ristic R.I, Sherwood J.N, Zikic A.M. Characterisation of growth behaviour of small paracetamol crystals grown from pure solutions. Chem. Eng. Res. Design (Trans. IChemE), 1996; A 74: 835–838.
4. Prasad K. V. R, Ristic R. I, Sheen, D. B, Sherwood J. N. Crystallization of paracetamol from solution in the presence and absence of impurity. Int. J. Pharm. 2001;215: 29-24
5. Adhiyaman. R., Bsau. SK., Crystal modification of dipyridamole using different solvents and crystallization conditions. Int. J Pharm. 2006; 14: 321(1-2):27-34.
6. Nokhodchi A, Bolourtchian N, Dinarvand D. Crystal modification of phenytoin using different solvent and crystallization condition. Int J Pharm. 2003; 250: 85-97.
7. Nokhodchi A, Bolourtchian N, Dinarvand D. Dissolution and mechanical behaviour of recrystallized carbamazepine from alcohol solution in the presence of additives. J Cryst Growth. 2005; 250: 85-97
8. Klug, D.L, The influence of impurities and solvents on crystallisation. In: Myerson, A. (Ed.), Handbook of

Industrial Crystallization. Butterworth-Heinemann, Boston, 1993. pp. 65–87.

9. Weissbuch, I, Leiserowitz, L, Lahav M. Tailor-made additives and impurities. In: Mersmann, A. (Ed.), Crystallization Technology Handbook. Marcel Dekker, New York, 1995. pp. 401–457.
10. Fachaux J.M, Guyot-Hermann A.M, Guyot J.C, Conflant P, Drache M, Veesler S, Boistelle R. Pure paracetamol for direct compression. Part II. Study of the physicochemical and mechanical properties of sintered-like crystals of paracetamol., Powder Technol. 1995; 82b: 129–133.
11. Femi-Oyewo M.N, Spring M.S. Studies on paracetamol crystals produced by growth in aqueous solutions. Int. J. Pharm. 1994; 112: 17–28.
12. Friedrich H, Fussnegger B, Kolter K, Bodmeier R. Dissolution rate improvement of poorly water-soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers. Eur. J. Pharm. Biopharm. 2006; 62: 171–177.
13. Grzesiak A.L, Lang M.D, Kim K, Matzger A.J, Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J. Pharm Sci. 2003; 92: 2260–2271.
14. Sekizaki H, Danjo K, Eguchi H, Yonezawa Y, Sunada H, Otsuka A. Solidstate interaction of ibuprofen with polyvinylpyrrolidone. Chem. Pharm. Bull. 1995; 43: 988–993.

How to cite this article: P.A. Pangarkar*, R. R. Thenge, N.M. Mahajan, V.S. Adhao, P.V. Ajmire; Crystal modification of Irbesartan in presence of additive; J. Adv. Pharm. Edu. & Res. 2014: 4(1): 106-113.

Source of Support: Nil, **Conflict of Interest:** Nil