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Enhancement of Dissolution Rate of Glimepiride using Solid Dispersions with Polyvinylpyrrolidone K 90

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Abstract

The aim of the present study was to enhance the dissolution rate of glimepiride using its solid dispersions (SDs) with polyvinylpyrrolidone K 90. The phase solubility behavior of glimepiride in presence of various concentrations of polyvinylpyrrolidone K 90 in phosphate buffer pH 7.4 was obtained at 37°C. The solubility of glimepiride increased with increase in amount of polyvinylpyrrolidone K 90 in buffer pH 7.4. Gibbs free energy (ΔG^{o}_{tr}) values were all negative. The solid dispersions of glimepiride with polyvinylpyrrolidone K 90 were prepared at 1:1, 1:3 and 1:5 (glimepiride: PVPK 90) ratio by kneading method. Evaluation of the properties of the solid dispersions was performed by using dissolution, Fourier-transform infrared (FTIR) spectroscopy and X-ray diffraction (XRD) studies. The solid dispersions of glimepiride with polyvinylpyrrolidone K 90 exhibited enhanced dissolution rate of glimepiride. The mean dissolution time (MDT) of glimepiride decreases significantly in solid dispersions. The Fourier-transform infrared spectroscopic studies showed formation of intermolecular hydrogen bonding between glimepiride and polyvinylpyrrolidone K 90. The X-ray diffraction studies indicated the partially amorphous state of glimepiride in SD of glimepiride with polyvinylpyrrolidone K 90.

Keywords: Glimepiride, polyvinylpyrrolidone K 90, solubility, dissolution rate

INTRODUCTION

Glimepiride, 1-(p-(2-(3-ethyle-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl) phenyl) sulfonyl)-3-(trans-4-methylcyclohexyl) urea is a third generation of hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM) [1, 2]. Prior reports reveal that the drug shows more potential benefits over currently available sulfonylureas such as lower dose, rapid onset of action, longer duration of action and lower insulin C-peptide level [3, 4]. Glimepiride is a white crystalline powder, relatively insoluble in water (pKa=6.2). Glimepiride exhibits slow GI absorption rate and inter individual variations in its bioavailability due to its poor water solubility [1, 5, 6]. From an economic point of view, low bioavilability of drug leads to wastage of more amount of drug after oral administration, in case of costly drug increases cost of formulation. The approach solid dispersion has been used to increase water solubility and dissolution rate of poorly water soluble drug and to solve bioavalability problems. Ammar et al., reported that the bioavailability and stability of glimepiride can be enhanced in its complex form with β-cyclodextrin [7, 8]. However, there is no report on the preparation and evaluation of glimepiride solid dispersion with polyvinylpyrrolidone K 90.

In our previous study, the potentiality of improvement of solubility and dissolution rate of the gliclazide by preparing SDs with PEG 6000, PEG 8000 and polyvinylpyrrolidone K 90 was found[9-11]. The authors investigated the physicochemical characteristics and dissolution behaviors of glimepiride in physical mixtures as well as solid dispersions with polyethylene glycol 20, 000 in a previous study[12].

The primary objective of the present study is to enhance dissolution rate of glimepiride using solid dispersion with polyvinylpyrrolidone K90. The possible interactions

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between glimepiride and PVP K 90 in both solid state and liquid states were investigated. Interaction in the solid state was investigated by Fourier-transform infrared (FT-IR) spectroscopy and X-ray diffraction analysis (XRD). Interaction in solution was studied by phase solubility analysis and dissolution experiments.

MATERIALS AND METHODS

Materials

A gift sample of glimepiride was received from Aristo Pharmaceuticals Ltd., (Mumbai, India). PVP K 90 was received from Clariant (Germany).

Methods

Preparation of SDs

The SDs of glimepiride with PVP K 90 containing three different weight ratios (1:1, 1:3, 1:5) (glimepiride: PVP K 90) and denoted as SD1/1, SD1/3 and SD 1/5 respectively, were prepared by kneading method. In kneading method, a required amount of PVP K 90 was taken in a glass mortar along with 10% lactose. A required amount of glimepiride was added to mortar and kneaded thoroughly with a glass rod by using ethanol. The mixture was kept for drying in a desiccator. The hardened mixture was powdered in a mortar, sieved through a 100-mesh screen, and stored in screw-cap vial at room temperature until further use.

Physical mixtures of glimepiride with PVPK 90 containing three different weight ratios (1:1, 1:3, 1:5) and denoted as PM 1/1, PM 1/3 PM 1/5 were prepared separately. Glimepiride and PVPK 90 were accurately weighed, pulverized and mixed thoroughly by light trituration for 5 min in a mortar. The mixture was passed through a sieve no. 100.

Phase Solubility Studies

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors[13]. The effect of concentrations of PVPK 90 on the equilibration solubility of glimepiride in phosphate buffer pH 7.4 at room temperature was carried out by adding an excess of drug (50 mg) into a screw-capped glass vial containing 10 mL of phosphate buffer pH 7.4 and various amounts of the carrier (2-10% w/v). The samples were placed on a rotary shaker and agitated at room temperature for 48 hr. An aliquot of each solution was withdrawn and filtered through a 0.45 μm pore size Millipore membrane filter fitted with syringe holder. The assay of glimepiride was determined spectrophotometrically at 226 nm, a wave length at which PVPK 90 does not interfere.

The Gibbs free energy of transfer (ΔG_{tr}^{o}) of glimepiride from pure water to the aqueous solutions of carrier was calculated as

$$\Delta Gtr = -2.303RT Log \frac{So}{Ss} \qquad (1)$$

Where $\frac{So}{Ss}$ is the ratio of molar solubility of glimepiride in aqueous solution of PVP K 90 to that of the same medium without PVP K 90[14].

Dissolution Studies

Dissolution studies of glimepiride in powder form, SDs, and PMs were performed by using the U. S. Pharmacopoeia (USP) model digital tablet dissolution test apparatus-2 (Veego Scientific Co.) at the paddle rotation speed of 50 rpm in 900 mL of phosphate buffer pH 7.4. The SDs or PMs equivalent to 10 mg of glimepiride was weighed using a digital balance (Ohaus Corp) and added into the dissolution medium. At the specified times (every 10 min for 1 hr), 10 mL samples were withdrawn by using syringe filter (0.45μm) (Sepyrane, Mumbai) and then assayed for glimepiride content by measuring the absorbance at 226 nm using the UV-Visible spectrophotometer (Shimadzu 1601PC, Japan). Fresh medium (10 mL), which was prewarmed at 37°C, was replaced into the dissolution medium after each sampling to maintain its constant volume throughout the test. Dissolution studies were performed in triplicate (n=3), and calculated mean values of cumulative drug release were used while plotting the release curves.

Fourier-Transform Infrared Spectroscopy

Fourier-transform infrared (FT-IR) spectra were obtained by using an FT-IR spectrometer-430 (Jasco, Japan). The samples (glimepiride or SDs or PMs) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4600 to 300 cm^{-1}.

X-Ray Diffraction

The X-Ray powder diffraction patterns were obtained at room temperature using a PW1710 X-ray diffractometer (Philips, Holland) with Cu as anode material and graphite

monochromatic, operated at a voltage of 35 kV, current 20 mA. The samples were analyzed in the 2θ angle range of 5˚–70˚and the process parameters were set as: scan step size of 0.02˚ (2θ), scan step time of 0.5s.

RESULTS AND DISCUSSION

Solubility Studies

Phase solubility experiments showed that the concentration of glimepiride in buffer pH 7.4 is notably affected by the presence of PVP K 90. The phase-solubility diagram investigated in buffer pH 7.4 was linear up to concentration 8% range of PVP K 90 concentrations and correspond to A_N -type profiles (Figure 1). These results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and poorly water soluble drugs[15]. At 8% (w/v) concentration of PVPK 90, the solubility of glimepiride increased by 4.04 fold. An indication of the process of transfer of glimepiride from pure water to the aqueous solution of PVPK 90 may be obtained from the values of Gibbs free energy change. The values of Gibbs free energy associated with the aqueous solubility of glimepiride in presence of PVPK 90. ΔG_{tr}° values were all negative for PVPK 90 at various concentrations indicating the spontaneous nature of the drug solubilization. The values decreased by increasing PVPK 90 concentration, demonstrating that the solubilization more favorable as concentration of PVPK 90 increased.

Dissolution Studies

The results of the dissolution studies for individual samples (glimepiride alone, PMs and SDs) over the period of 1 hour are shown in Figure 2 and reported values are the mean of three determinations (CV<10%). Q_{10}, Q_{20} and Q_{30} values (percent drug dissolved in 30 minutes) are reported in Table 1. Onset of dissolution of pure glimepiride is very low about 36.08 % of drug being dissolved in 60 min. SDs of glimepiride with PVPK 90 considerably enhanced dissolution rates within 30 minute compared to pure glimepiride and PMs.

Percentage dissolution efficiencies (%DE) values were computed, for comparative analysis all the formulations. The % DE values in the initial time period of dissolution study i.e. $\%DE_{10min}$ provide comparative information for very fast releasing formulations, where as, $\%DE_{30min}$ provide relative information about both fast and slow releasing formulations. The value of $\%\ DE_{30min}$ for the pure drug was increased to 33.80 % in PM (1:5) and up to 49.29% in SD (1:5). The change of DE_{30min} of drug in its PMs and SDs is statistically significant ($p<0.05$).

In order to understand the extent of glimepiride dissolution rate enhancement from its SDs and PMs, the obtained dissolution data of pure glimepiride, SDs, and PMs were fit in Eq. 2 [16].

$$MDT = \frac{\sum_{i=1}^{n} TmidAM}{\sum_{i=1}^{n} AM} \quad (2)$$

Here, i is dissolution sample number, n is number of dissolution sample times, T mid is time at the mid point between times Ti and T_{i-1}, and ΔM is the amount of glimepiride dissolved (µg) between times Ti and T_{i-1}. In order to calculate the mean dissolution time (MDT) of pure glimepiride, SDs, and PMs, the mean (n=3) of cumulative drug release (µg) was used. The obtained values of MDT for pure glimepiride, SDs, and PMs are presented in Table 2. The MDT of glimepiride is 13.35 min, then it decreased to a greater extent 7.17 min after preparing its SDs with PVPK 90 at 1:5 (glimepiride: PVPK 90) ratio.

The results of the dissolution study indicate an improvement of dissolution rate of glimepiride in solid dispersion. The rate of dissolution increases as concentration of PVPK 90 increases in SDs. The improvement of dissolution rate is possibly caused by several factors. Such factors are: a) the strong hydrophilic character of PVPK 90, which improves the water penetration and the wettability of the hydrophobic glimepiride, b) the optimal dispersion of glimepiride to PVPK 90, c) the absence of crystals (amorphous dispersions) corresponds to lower energy required for dissolution and d) the inter molecular hydrogen bonds and the molecular dispersion of glimepiride on PVP leads to partial miscibility, improving the hydrophilic characteristics of the drug substance via interactions within the polymer [17]. The improvement of dissolution rate of glimepiride in PMs is due to increased wettability of the drug powder [18].

Fourier-Transform Infrared Spectroscopy

The IR spectra of SD and PM were compared with the

standard spectrum of glimepiride (Figure 3). IR spectrum of glimepiride is characterized by the absorption of carbonyl (C=O) sulphonyl urea group at 1708 and 1674 cm^{-1}. Also the NH group which is located at 3369 cm^{-1} and 3288 cm^{-1} from the IR spectrum of glimepiride shifted to 3372 cm^{-1} and 3295 cm^{-1} in SD. The sulphonyl group bands are located at 1345 cm^{-1} and 1153 cm^{-1} in pure glimepiride. In SD, the asymmetrically vibration peak of S=0 band was shifted from 1345 cm^{-1} to 1338 cm^{-1} with decreased frequencies. In SD, the symmetrically stretching vibration band of S=0 was shifted from 1153 cm^{-1} to 1150 cm^{-1} with decreased frequencies. The spectrum of PVP K 90 exhibited important bands at 2953 cm^{-1} (C–H stretch) and 1652 cm^{-1} (C=O).

The shift in the peaks associated with C=O, S=O and NH group of glimepiride indicates some sort of solid state interactions between the drug and the polymer in SD and PM. The interactions are due to intermolecular hydrogen bonding between drug and polymer. Intermolecular hydrogen bond expected to occur between the hydrogen atom of the NH group of glimepiride and one of the lone pairs electron of C=O group of polymer or/ and C=O group of glimepiride and one of the hydrogen atom of PVPK 90 [19]. The FTIR data suggests formation of intermolecular hydrogen bonding between glimepiride and PVPK 90.

X-Ray Diffractions (XRD)

The diffraction spectrum of pure glimepiride showed that the drug was of crystalline nature as demonstrated by numerous peaks. Numerous diffraction peaks of glimepiride were observed at 2θ of 13.41, 14.62, 16.67, 18.13, 19.18 21.03, 21.11, 22.95 and 26.33 (finger print region) etc (Figure 4) indicating crystalline glimepiride. Pure PVPK 90 showed absence of peak. All principal peaks from glimepiride were present in their respective PM and SD with decreased intensity, which suggested that some portion of drug was converted into amorphous form. The X-ray diffraction findings also suggested that some portion of drug still existed in the same crystal structures of pure drug and/or formation of microcrystals but the relative reduction of diffraction intensity of drug in SD at these angles suggests that the drug partially converted into amorphous form [20].

CONCLUSIONS

The solubility and dissolution rate of glimepiride can be enhanced by the use of SDs of glimepiride with PVPK 90. The solubilization effect of PVPK 90, reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of glimepiride from its SDs and PMs.

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	Concentration of PVP K90 (% w/v)	Concentration of glimepiride(mg/ml) at 37 °C	ΔG_{tr}^{0}(J/Mol)
1.	0	0.12	0
2.	2	0.14	-397.37
3.	4	0.19	-1190.36
4.	6	0.24	-1792.60
5.	8	0.27	-2095.11
6.	10	0.25	-1895.4

Table 1. Effect of PVP K-90 concentration and Gibbs free energy on solubility glimepiride

Formulations	Dissolution parameters				
	Q_{10min}	Q_{20min}	Q_{30min}	$\%DE_{30min}$	MDT(min)
Glimepiride	5.34	8.60	12.12	6.61	13.35
PM 1/ 1	7.58	11.59	13.89	8.71	11.20
PM 1 / 3	8.57	11.85	28.29	11.42	7.69
PM 1 / 5	28.9	44.6	55.8	33.80	8.51
SD 1 / 1	8.8	14.0	19.8	10.89	8.68
SD 1 / 3	18.8	28.3	30.8	20.81	8.37
SD 1/ 5	50.5	64.6	65.4	49.26	7.17

Table 2: In-vitro dissolution profile of glimepiride, physical mixture of glimepiride and solid dispersion of glimepiride in pH 7.4 buffer

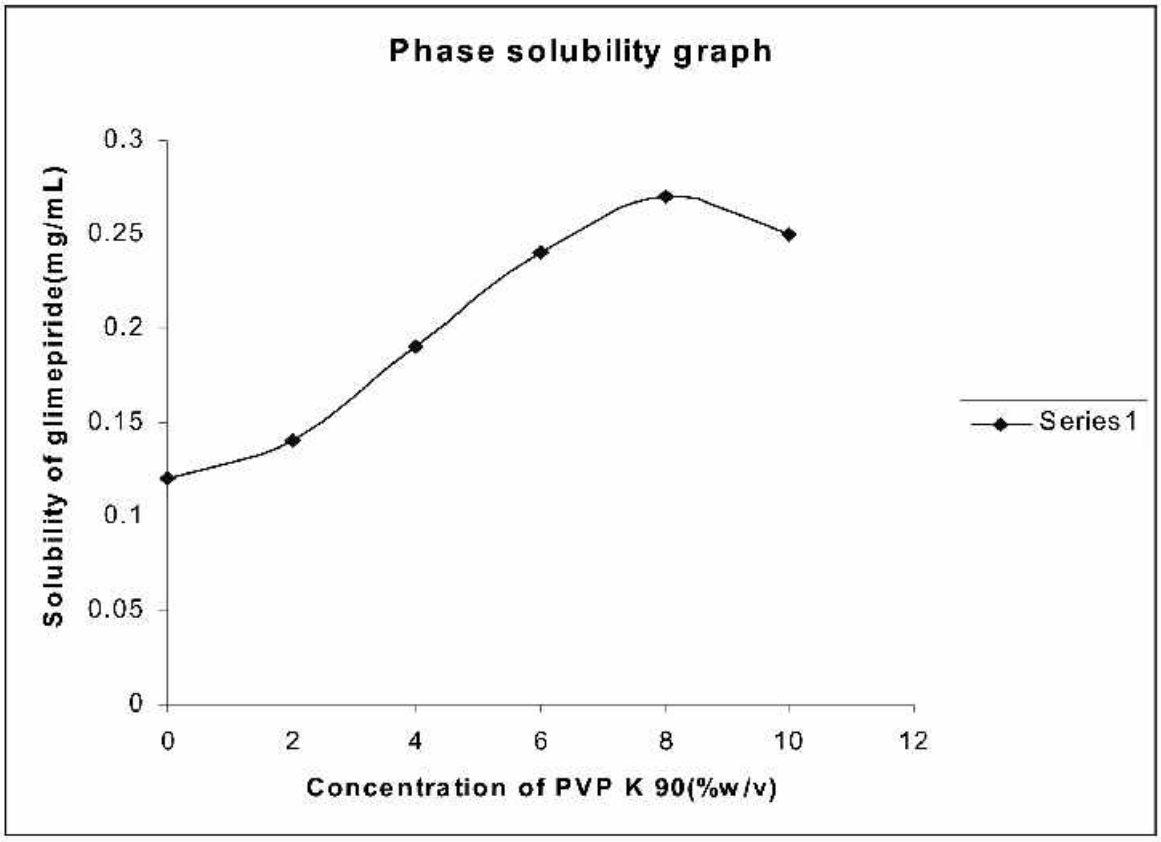

Fig. 1: Phase solubility graph of glimepiride in pH 7.4 buffer

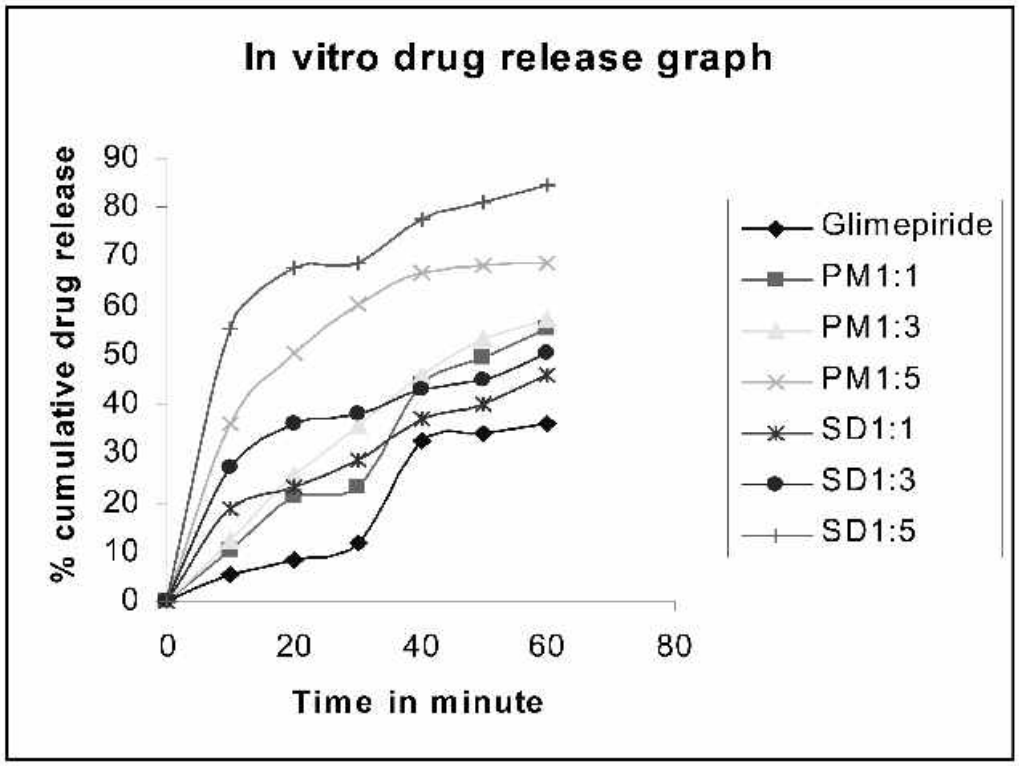

Fig. 2 : In-vitro dissolution profiles of glimepiride, physical mixtures and solid dispersion of glimepiride with PVP K 90 in pH 7.4 buffers

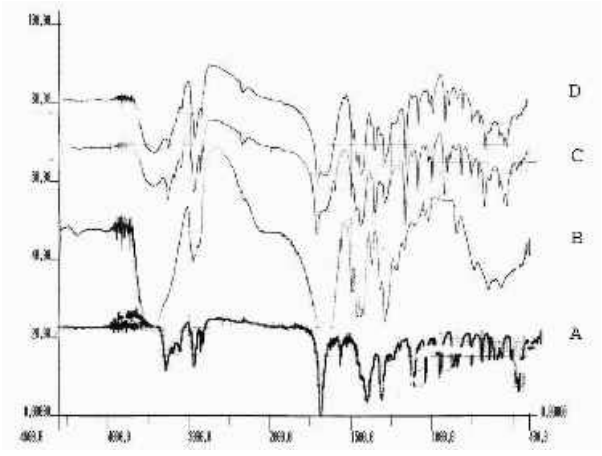

Fig. 3 : FTIR Spectrograms of pure glimepiride (A), Pure PVP K 90(B), glimepiride -PVP K 90 PM (C), glimepiride -PVP K 90 SD (D).

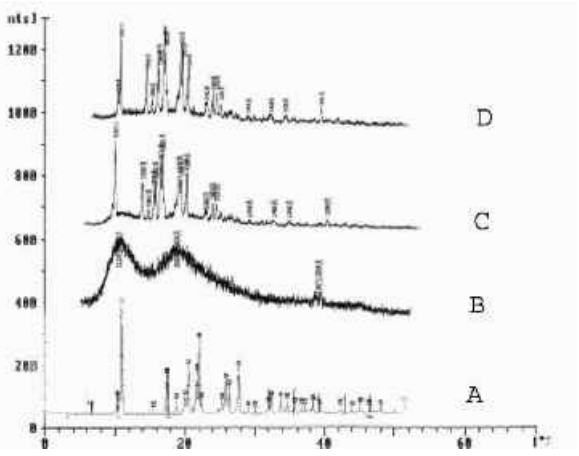

Fig. 4: X-Ray Diffractograms of pure glimepiride (A), Pure PVP K 90(B), glimepiride -PVP K 90 PM(C), glimepiride -PVP K 90 SD (D).

REFERENCES

1. Massimo MB. Glimepiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience. Clin Ther 2003; 25: 799–816.
2. Kouichi I, Masaki W, Youhei N, Takahiro S, Nobuki T, Masahiko T, et al.,. Efficacy of glimepiride in Japanese type 2 diabetic subjects. Diab Res Clin Pract. 2005; 68: 250-7.
3. Geinsen K. Special pharmacology of the new sulfonylurea glimepiride. Drug Res. 1988; 38: 1120–1130.
4. Muller G, Wied S, Wetekam E, Crecelius A, Unkelbach A. Stimulation of glucose utilization in 3P3 adipocytes and rat diaphragm in vitro by the sulfonylureas glimepiride and glibenclamide is correlated with modulations of the cAMP regulatory cascade. Biochem Pharmacol. 1994; 48: 985–996.
5. Frick A, Moller H, Wirbitzki E. Biopharmaceutical characterization of oral immediate release drug products. In vitro/in vivo comparison of phenoxymethylpenicillin potassium, glimepiride and levofloxacin. Eur J Pharm Biopharm. 1998; 46: 305–11.
6. Thummel KE. Preface. Adv Drug Del Rev. 1997; 27: 97–8.
7. Ammar HO, Salama HA, Ghorab M, Mahmoud AA. Formulation and biological evaluation of glimepiride–cyclodextrin–polymer systems. Int J Pharm. 2006; 309: 129–38.
8. Ammar HO, Salama HA, Ghorab M, Mahmoud AA. Implication of inclusion complexation of glimepiride in cyclodextrin–polymer systems on its dissolution, stability and therapeutic efficacy. Int J Pharm. 2006; 320: 53–7.
9. Biswal S, Sahoo J, Murthy PN, Giradkar PR, Avari JG. Enhancement of dissolution rate of gliclazide using solid dispersions with polyethylene glycol 6000. AAPS Pharma SciTech. 2008; 9(2): 563-70.
10. Biswal S, Sahoo J, Murthy P N. Characterisation of gliclazide-PEG 8000 solid dispersions. Tropical Journal of Pharmaceutical Research. In press 2009.
11. Biswal S, Sahoo J, Murthy PN. Physicochemical properties of solid dispersions of gliclazide in polyvinylpyrollidone K-90. AAPS Pharm SciTech.2009;10(2):329-34.
12. Baliar Singh OP, Biswal S, Sahoo J, Murthy PN. Physicochemical properties of glimepiride in solid dispersions with polyethylene glycol 20,000. Int J Pharm Sc and Nanotech. 8(5):417-424.
13. Higuchi T, Connors K. Phase solubility techniques. Adv Ana Chem and Instrument. 1965; 4:17–123.
14. Chengsheng L, Kashappa GHD, Chenguang L. Enhancement of dissolution rate of valdecoxib using solid dispersions with polyethylene glycol 4000. Drug Dev Ind Pharm. 2005; 31:1–10.
15. Mura P, Manderioli A, Bramanti G, Ceccarelli L. Properties of solid dispersions of naproxen in various polyethylene glycols. Drug Dev Ind Pharm. 1996; 22 (9&10): 909-16.
16. Barzegar-Jalali M, Maleki N, Garjani A, et al. Enhancement of dissolution rate and anti-inflammatory effects of piroxicam using solvent deposition technique. Drug Devl Ind Pharm. 2002; 28 (6): 681– 6.
17. Karavas E, Ktistis G, Xenakis A, Georgarakis E. Miscibility behavior and formation mechanism of stabilized felodipine-polyvinylpyrrolidone amorphous solid dispersions. Drug Dev Ind Pharm. 2005; 31(4): 473–89.
18. Ford J L. The current status of solid dispersions. Pharm Acta Helv. 1986; 61: 69-88.
19. Van den MG, Augustijns P, Blaton N, Kinget R. Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. Int J Pharm. 1998; 164:67-80.
20. Valizadeh H, Nokhodchi A, et al. Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, Lactose, Sorbitol, Dextrin, and Eudragit E100. Drug Dev