INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Research Article

IMPROVEMENT OF SOLUBILITY AND DISSOLUTION RATE OF PIROXICAM BY SOLID DISPERSIONS IN PEG4000

Kulkarni Parthasarathi Keshavarao*, Dixit Mudit, Panner Selvam, Achin Jain
Department of Pharmaceutics, J.S.S College of Pharmacy, J.S.S. University, S.S Nagar, Mysore-570015, India

Article Received on: 14/01/12 Revised on: 29/03/12 Approved for publication: 10/04/12

*Parthasarathi K Kulkarni, Department of Pharmaceutics, J.S.S College of Pharmacy, J.S.S University, S.S Nagar, Mysore-570015, India.
Email: pkkulk@lycos.com

ABSTRACT
The aim of the present study was to enhance the dissolution rate of piroxicam (PX) using its solid dispersions (SDs) with polyethylene glycol (PEG) 6000. The phase solubility behavior of piroxicam in presence of various concentrations of PEG 6000 in distilled water was obtained at 37 °C. The solubility of PX increased with increasing amount of PEG 6000 in water and demonstrating that the reaction conditions became more favorable as the concentration of PEG 6000 increased. The SDs of PX with PEG 6000 were prepared using 1:1, 1:2,1:3,1:4 and1:5 (PX/PEG 6000) ratio by Hot-melt method and solvent evaporation method. Evaluation of the properties of the SDs was performed by using dissolution, Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC). The SDs of PX with PEG 6000 exhibited enhanced dissolution rate of PX and the rate increased with increasing concentration of PEG 6000 in SDs. Mean dissolution time (MDT) of PX decreased significantly after preparation of SDs and physical mixture with PEG6000. The FTIR spectroscopic studies revealed that there is no chemical interaction and drug was stable. The DSC studies indicated the microcrystalline or amorphous state of PX in SDs with PEG 6000.
Key words: piroxicam, solid dispersion, dissolution, solubility.

INTRODUCTION

Piroxicam (PX) is a non-steroidal anti-inflammatory drug with low solubility and high permeability classified in class II of the Biopharmaceutical Drug Classification System[1]. It is used as analgesic and in acute or long-term treatment of osteoarthritis, rheumatoid arthritis and in a variety of other acute and chronic musculoskeletal disorders, such as dysmenorrheal[2]. After oral administration, PX is completely but slowly and gradually absorbed through the gastrointestinal tract and it reaches the maximum haematic concentrations after 2–4h[3]. Since the drug is slightly soluble in biological fluids, PX dissolution rate turns out to be the absorption rate-limiting step and consequently it critically affects its analgesic effect onset. As a consequence, many strategies have been proposed with the aim of improving PX dissolution rate and to obtain formulations with fast analgesic effect onset, particularly useful in the treatment of dysmenorrhea, migraine, renal colic and postoperative pain[4-6].

Over the years, a variety of solubilization techniques have been studied to improve the dissolution rate of this widely used anti rheumatic agent, to obtain more rapid and complete absorption such as; using adsorbants[9], surfactant, hydrotropism and cosolvents[8], preparing co precipitate, liquid solid compacts, fast releasing microparticle, interactive mixtures[6], solid dispersion[7], compressing with buffers or complexation with cyclodextrins[10].

Solid dispersion technique was selected as it was utilized in a limited number of researches to increase the solubility of indomethacin. Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent, or solvent-fusion methods. It has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs[11] solid dispersions, the particle size of the drugs was reduced, the wettability and the dispensability were enhanced; therefore, drug dissolution was improved markedly.

PEG is among the several carriers which have been employed in preparing solid dispersions PEG polymers are widely used for their low melting point, low toxicity, wide drug compatibility and hydropholicity[12]. These are available with a range of properties depending on their hydrophilic– lipophilic balance (HLB) and melting point range (33– 65 ^{0}C) [13, 14]. They have a wide variety of applications in pharmaceutical formulations as the preparation of fast release and sustained release formulations[15, 16].

The purpose of the current study is to characterize the solid-state properties of the solid dispersion system of Piroxicam PEG4000 prepared at different ratios. The methods of characterization were achieved through using different tools as scanning electron microscopy (SEM), differential scanning calorimeter (DSC), powder X-ray diffractometry (XRD). Moreover, solubility and dissolution rate study were performed to qualify the solid dispersion comparing with the drug alone or as physical mixture (PM).

MATERIALS AND METHODS

Materials

Piroxicam was obtained as a gift sample from Micro labs, Bangalore, India. All chemicals and buffers used were of analytical grade.

Preparation of solid dispersion (SD)

Solid dispersions are prepared by using various ratios of PX and poly ethylene glycol 6000. The methods used for the preparation of solid dispersions are hot melt method and solvent evaporation method (Table 1).

Evaluation of solid dispersion

Determination of percentage yield and drug content

The percentage yield of each SD formulation was determined according to the total recoverable final weight of SD particles and the total original weight of Piroxicam.

SD particals[7] (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and

methanol was added to produce 100 ml. After suitable dilution, samples were measured at 332 nm. Drug content was determined from standard plot.

Differential scanning calorimeter (DSC)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray analysis (XRD)

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometar, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV. The process parameters used were set as scan step size of 0.0170 (2θ).

Scanning electron microscopy (SEM)

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm nature and Surface topography of the SD.

Solubility studies

The solubility of Piroxicam particles in water was determined by taking excess quantity of SD particles in 50 ml to screw-capped glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and drug concentration was determined at 332 nm.

Dissolution studies of microparticle

The dissolution of Piroxicam pure sample, SD particles (prepared by spray drying and spray chilling) and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml pH 7.4 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 332 nm.

RESULTS

The percentage yield of SD particles of different ratios of PEG4000 and Piroxicam was found to be in the range of 79-91 %. Drug content for the SD particles of different ratio of PEG4000 and Piroxicam formulation was found to be in the range of 79-98 %±0.013.

DSC curves obtained for pure Piroxicam and SD shown in Fig. 1. DSC studied carried out to evaluate the crystalline properties of Piroxicam in SD and pure drug,

X-Ray diffraction was used to analyze potential changes in the inner structure of Piroxicam SD during the formulation of SD. The extent of such changes depends on the chemical nature and physical hardness of the active ingredient. The powder X-ray diffraction patterns of the pure drug, physical mixture and SD showed in Fig. 2. The results of DSC were further conformed by X-ray diffraction studies (Fig 2).

SEM micrographs of Pure Piroxicam, PM, and FDT are shown in Fig. 3. The result showed that Piroxicam SD could be seen in the PM while the micrograph of FDT shows a matrix in which no SD of Piroxicam could be seen.

Solubility of Piroxicam increased from SD (0.75 mg/ml), nearly four and half times higher when compared to the solubility of the pure drug (0.19 mg/ml).

The dissolution curves of Piroxicam in 7.4 Phosphate buffer shown in Fig. 4. The dissolution rate profiles were plotted as the % release from the SD, physical mixture and pure Piroxicam versus time in minute.

DISCUSIONS

The solid dispersions formulations were collected and were found to be free-flowing and white in color. The percentage yield of SD particles of different ratios of PEG4000 and Piroxicam was found to be in the range of 83-94 %. This small yield could be increased by addition of solid substance or in large scale production. Drug content for the SD particles of different ratio of PEG4000 and Piroxicam formulation was found to be in the range of 92-99 %±0.013.

In DSC curve, pure Piroxicam had ash PX endothermic peak at 233°C that corresponded to the melting point of Piroxicam. The thermogram of the PM showed the endothermic peak of Piroxicam, although broader, spitted, and slightly shifted to the left, indicating that the crystalline state is maintained but decreased in the PM and shown PX endothermic peak at 231°C. However, the melting endotherm was absent on the DSC thermogram of the SD, suggesting absence of crystallinity and presence of amorphous state of the drug. This could be because of Piroxicam was molecularly or amorphously dispersed in the solid dispersion (SD).

In XRD study, the characteristic peak of the Piroxicam appeared in the 2θ range of $10–30^{0,}$ indicating that the unprocessed Piroxicam was a crystalline material. The pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity. The X-ray diffraction study of the PM of drug and excipients showed the peak corresponding to the crystalline drug molecules present in the mixture, although their intensity was lower due to the high excipients-drug ratio employed. The diffraction pattern of the SD of drug showed absence, broadening and reduction of major Piroxicam diffraction peaks indicating that mostly an amorphous from (disordered state) existed in the SD. These results could explain the observed enhancement of solubility and rapid dissolution of Piroxicam in SD.

The SEM micrograph of SD suggests that the particles of drug might have been reduced during dissolution in the PEG 4000 dispersion.

The solubility of Piroxicam increase from SD (1:4) (0.75 mg/ml), nearly four times higher when compared to the solubility of the pure drug (0.19 mg/ml), suggesting the presence of high amount of amorphous form of the Piroxicam drug in SD, that indicates the super-saturation obtained from the SD. Increase in solubility of Piroxicam from the PM (0.29 mg/ml), almost one and half times higher than the pure drug. This could be due to the solubilizing effect of carrier materials used in the formulation such as PEG 4000. The higher solubility of Piroxicam from SD may be due to the increased in surface area, wetability and solubilizing effect of PEG 4000 used in the formulations.

The rate of dissolution of pure Piroxicam was slow Compared with physical mixtures and SD. Piroxicam in the SD was dispersed and almost completely dissolved (94.57%) in 30 min. initial dissolution rate of Piroxicam in the SD increased markedly about twenty three fold compared to pure Piroxicam in 30 min. The dissolution rate was also

higher and faster in SD than in PM. The percentage of Piroxicam dissolved from its PM for 60 min (64.32%) increased approximately four fold compared to Piroxicam pure alone (18.43%).

CONCLUSION

The study has demonstrated that dispersions of MA into water-soluble carriers like PEG4000 changed the crystallinity of MA according to type and amount of the polymer. The formation of MA–PEG-4000 solid dispersion destroyed almost completely the crystallinity of the drug and represents a suitable modification for improving its availability. However, it decreased the crystallinity of MA. Many factors contributed to faster release rate such as decrease in particle size, decrease in agglomeration of particles, increase wetability and decrease in crystallinity of the drug.

ACKNOWLEDGMENT

The authors are thankful to Micro Labs, Bangalore, India for the gift samples of Piroxicam and Principal, J.S.S.College of Pharmacy, Mysore for providing facilities to carry out this work.

REFERENCES

1. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basic for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vitro bioavailability. Pharm. Res., 1995; 12: 413–420.
2. Gennaro AR. Remington's Pharmaceutical Sciences. XVIII. Mack Publishing Company, Easton, PA, p. 1116, 1990.
3. Tagliati CA, Kimura E, Nothenberg MS, Santos JC, Oga S. Pharmacokinetic profile and adverse gastric effect of zinc-piroxicam in rats. Gen. Pharmacol. 1999; 33: 67–71.
4. Prabhu S, Ortega M, Ma C. Novel lipid-based formulations enhancing the in vitro dissolution and permeability characteristics of a poorly water-soluble model drug, piroxicam. Int. J. Pharm. 2005; 301: 209–216.
5. Karatas A, Yuksel N, Baykara T. Improved solubility and dissolution rate of piroxicam using gelucire 44/14 and labrasol. Il Farmaco 2005; 60: 777–782.
6. Yuksel N, Karatas A, Ozkan Y, Savaser A, Ozkan SA, Baykara T. Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: in vitro and in vivo evaluation. Eur. J. Pharm. Biopharm. 2003; 56: 453–459.
7. Bogdanova S, Bontcheva E, Avramova N. Phase characterization of indomethacin in adsorbates onto hydroxyl-ethylcellulose. Drug Dev. Ind. Pharm 2007; 33: 900–906.
8. Cavallari C, Rodriguez L, Albertini B, Passe-rini, Fini A. Thermal and fractal analysis of diclofenac/Gelucire 50/13 microparticles obtained by ultra-sound-assisted atomization. J. Pharm. Sci 2005; 94: 1124–1134.
9. Cavallari C, Luppi B, Di P, Rodriguez AM. Enhanced release of indomethacin from PVP/stearic acid microcapsules prepared coupling Co-freeze-drying and ultrasound assisted spray-congealing process. Pharm. Res 2007; 24: 521–529.
10. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci 1997; 60: 1281–1302.
11. Craig DQM, The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm 2002; 231: 131–144.
12. Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. In vivo evaluation of rapid release and sustained release gelucire capsule formulation. Int. J. Pharm 1990; 65: 85–100.
13. Douroumis D, Bouropoulos N, Fahr A. Physicochemical characterization of solid dispersions of three antiepileptic drugs prepared by solvent evaporation method. J. Pharm. Pharmacol 2007; 59: 645–653.
14. El-Badry M, Fathy M. Properties of solid dispersions of piroxicam in pluronic F-98. J. Drug Del. Sci. Technol 2005; 14: 199–205.
15. El-Badry M, Fathy M. Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polvvinylpyrrilidone k-30. Drug Dev. Ind. Pharm 2006; 32: 141–150.
16. Etman MA, Nada AH. Hydrotropic and co solvent solubilisation of indomethacin. Acta Pharm 1999; 49: 291–298.

Formulation chart

Formulation code	PX:PEG(SE)	PX:PEG(HM)
F1	PX (pure)	PX (pure)
F2	1:1	1:1
F3	1:2	1:2
F4	1:3	1:3
F5	1:4	1:4
F6	1:5	1:5

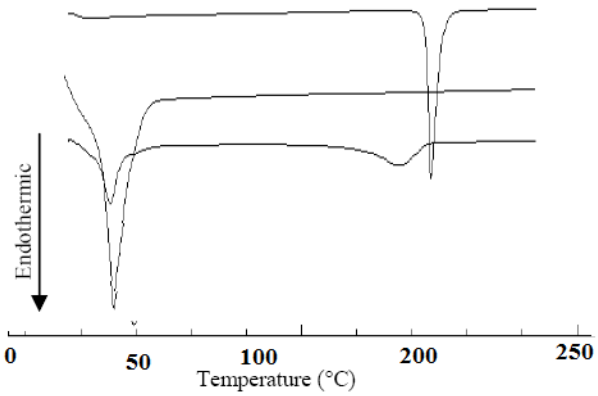

Figure 1 DSC spectrum of Piroxicam samples

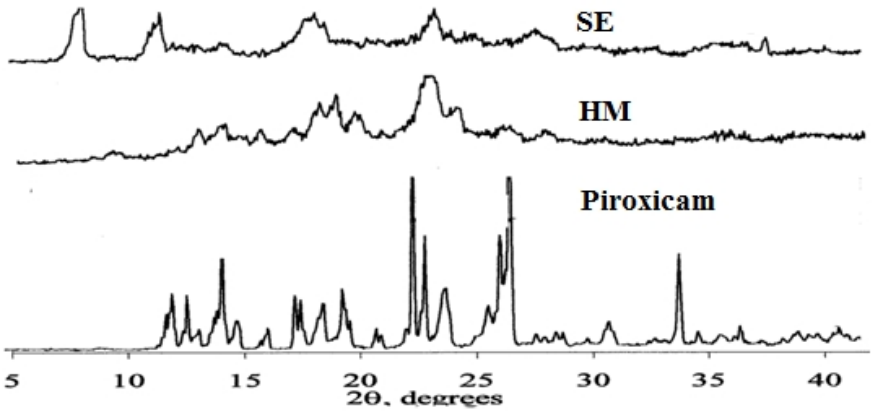

Figure 2 X-ray powder diffractions of Piroxicam samples

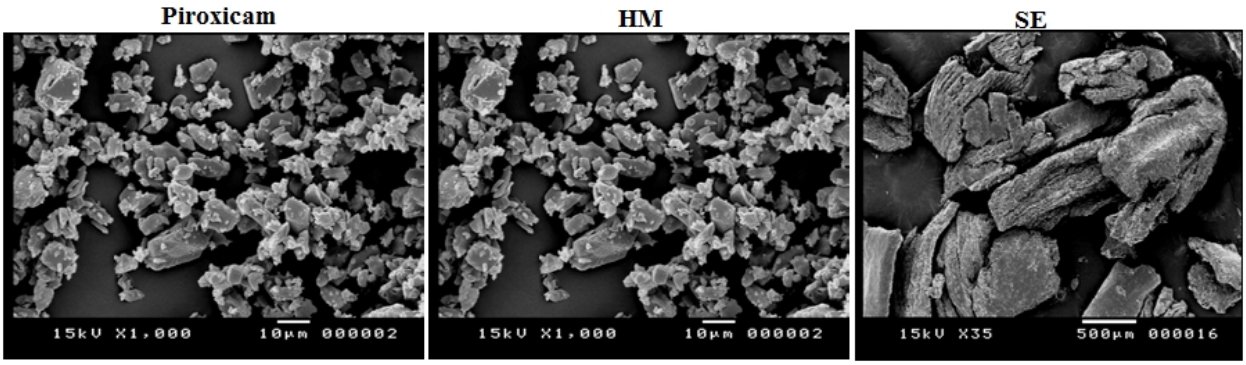

Figure 3 Scanning electron micrographs of Piroxicam samples

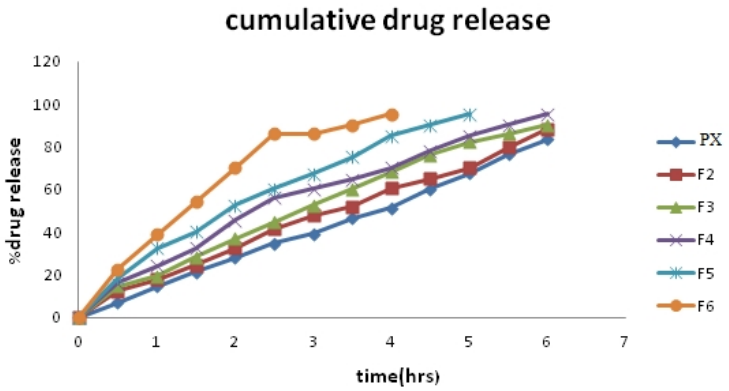

Figure 4 Comparison of dissolution profile of PX, solid dispersions (SD) prepared with different polymer ratio. Each data represents the mean ± SD of three experiments

Source of support: Nil, Conflict of interest: None Declared