

Improved Dissolution Rate of Piroxicam by Fusion Solid Dispersion Technique

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Abstract

Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique presents a challenge to the formulation scientists. In the present work solid dispersed drug was prepared by Fusion technique as a novel system for enhancing the delivery of piroxicam, a non-steroidal anti-inflammatory drug. This solid dispersed drug was prepared from polyvinyl pyrrolidone (PVP) (pharmaceutical grade), a biodegradable polymer, to obtain a solution with drug: polymer ratio of 1:5. The release rate of the piroxicam solid dispersed drug was studied in simulated gastric fluid. Fourier transform infrared (FTIR) and scanning electron microscopy (SEM) are used to evaluate the chemical and physical nature. The results showed that the release rates were twice increased in comparison with the pure drug. However, the blend of drug and polymer could be varied to optimize the release rates depending upon the need and formulation.

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INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, the major problem associated with poorly-water soluble drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration (Sekiguchi, and Obi, 1961; Leunner, and Dressman, 2000). A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption (Goldberg *et al.*, 1966). Therefore, pharmaceutical researchers' focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs (Amidon *et al.*, 1995).

Piroxicam is a member of the oxycam group of non-steroidal anti-inflammatory drugs (NSAIDs). The chemical name for piroxicam is 4-hydroxyl-2-methyl-N-2-pyridinyl-2 H-1, 2- benzothiazine-3-carboxamide 1,1-dioxide. It is indicated for acute or long-term use in the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis (Physicians' Desk reference, 56th ed, 2002). According to the Biopharmaceutic Drug Classification System (BCS) (Amidon *et al.*, 1995) piroxicam is a class 2 drug, characterized by low solubility-high permeability. Drug dissolution in vivo is the rate-controlling step in drug absorption. Several techniques have been used to improve the oral bioavailability of piroxicam by accelerating its dissolution rate. These mainly include the solid dispersion techniques based on cyclodextrin

inclusion complexes (Reddy and udupa 1993; Cavallari *et al.*, 2002), polyvinyl pyrrolidone (Tantishaiyakul *et al.*, 1999), polyethylene glycols 4000 and 6000 (Bhattacharyya *et al.*, 1993; Fernandez *et al.*, 1992).

Solid dispersions technique have tremendous potential for improving drug solubility due to the following factors (Leuner and Dressman, 2000; Damian *et al.*, 2000; Govindasamy *et al.*, 2013): a reduction of drug's particle size to nearly a molecular level, a solubilising or a cosolvent effect on the drug by the water soluble carrier, better wettability and dispersibility of the drug by the carrier material, and the formation of amorphous forms of drug and carriers. Polymerization of vinyl pyrrolidone leads to polyvinyl pyrrolidone (PVP) of molecular weights ranging from 2500 to 3,000,000. These can be classified according to the K value (Walking 1994). Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid (Aso *et al.*, 2009). The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer and viscosity lowers with increasing chain length.

PVP as excipients has been studied extensively for increasing solubility and enhancing intestinal permeability and oral bioavailability of poorly water soluble drugs (Damian *et al.*, 2000; Itoh *et al.*, 2002). The present study was designed to improve the dissolution rate of piroxicam at the physiological pH's through its increased solubility by preparing semi-solid dispersions of the drug with polyvinyl pyrrolidone (PVP). The effect of PVP as excipients on the solubility and dissolution rate of piroxicam was evaluated. FTIR analysis between drug and polymer was performed to investigate possible interactions between drug and excipients.

MATERIALS AND METHODS

Materials

Piroxicam ($\geq 98.0\%$), Polyvinyl Pyrrolidone (PVP) (Mw=13, 00,000) and Dialysis tubing cellulose membrane have been purchased from Sigma-Aldrich, Bangalore, India. Ethanol, Monobasic sodium phosphate (NaH_2PO_4) and dibasic sodium phosphate (Na_2HPO_4) were purchased from Emplura[®], Merck Specialities Private Limited, Bangalore, India.

Preparation of Piroxicam Based Solid Dispersed Drug

Piroxicam based solid dispersed drug was prepared by Fusion/ Melt technique (Sekiguchi, and Obi, 1961). 150 mg Piroxicam drug was dissolved in 10 ml of 0.75% of PVP polymer containing heated ethanol by continuous stirring, giving the drug and polymer concentration ratio of 1: 5 (Piroxicam : PVP). After complete dissolving of Piroxicam drug, drug polymer solution was transferred to the mortar and allowed it to cool under room temperature. After complete cooling and solidification of drug polymer solution in mortar it was finely churned to powder by using passel giving Piroxicam based PVP solid dispersed drug.

Characterization of Solid Dispersed Drug

SEM Analysis

The external surface morphology and diameter of Piroxicam based PVP solid dispersed drug were studied by SEM. The solid dispersed drug was observed under a scanning electron microscope (FEI Quanta 200, Indian Institute of Science, Bangalore). They were mounted directly on to the SEM sample stub using double-sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (10^{-4} mm of Hg).

FTIR Analysis

The procedure involving sample preparation and spectral recordings was carried out by previously described method (Stuart *et al.*, 2004). IR spectra of Piroxicam, PVP and PVP solid dispersed drug were recorded using FTIR Nicolet 6700 (Thermo Fisher Scientific, Madison, WI, USA) operated by Omnic software 8.1. In particular, for oral thin films measurement the spectra were obtained by attenuated total reflectance (ATR) method using smart orbit diamond ATR. Briefly, the formulations were placed individually on the sample plate of the smart orbit and screwed lightly to record IR spectra in ATR mode.

In vitro Dissolution Studies

Construction of Calibration Curve

Piroxicam can be estimated spectrophotometrically at λ_{max} 330 nm. 100 mg of piroxicam was dissolved in 0.1 N methanolic HCl to obtain a solution with the piroxicam concentration of $100 \mu\text{g ml}^{-1}$. Serial dilutions containing 2, 4, 6, 8, 10 $\mu\text{g ml}^{-1}$ of piroxicam were prepared with the

same solvent. Absorbance of each solution was measured at 333 nm. A plot of concentrations of drug versus absorbance was plotted (Figure 1).

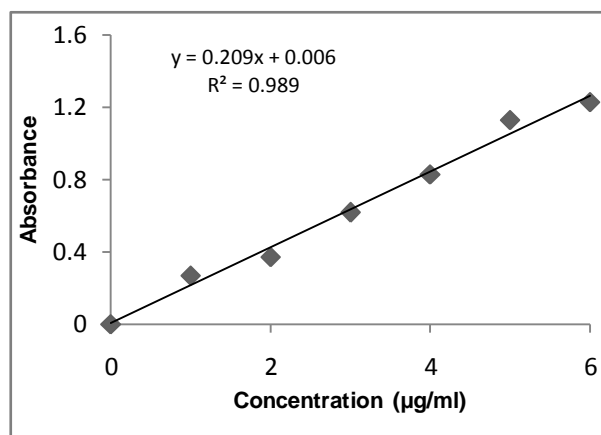


Figure 1: Calibration curve for the estimation of piroxicam in 0.1N methanolic HCl at 333nm.

Estimation of Piroxicam Concentration

Piroxicam based PVP solid dispersed drug equivalent to 20 mg of piroxicam were weighed and dissolved in 0.1 N methanolic HCl and the absorbance was measured at 333 nm.

In vitro Release Behavior of Piroxicam

The *in vitro* dissolution studies were done to compare the rate of dissolution of these prepared Piroxicam based PVP solid dispersed drug with that of the pure drug. The test was performed in the United States Pharmacopeia Convention USP paddle apparatus using 900 ml of 0.1 N HCl (pH 1.2) at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. Aliquots of 5 ml were withdrawn at various time intervals of 5, 10, 20, 30 and 60 min and analyzed by UV spectrophotometer (Evolution 300; Thermo Fisher Scientific, Madison, WI, USA) at 333 nm.

RESULTS AND DISCUSSION

Physico-Chemical Characterization

SEM Analysis

The solid dispersed drug was observed under a scanning electron microscope (FEI Quanta 200, Indian Institute of Science, Bangalore). Solid dispersed drug obtained was with average diameter of about 3600 nm (Image J software, provided by National Institutes of Health, USA). Piroxicam solid dispersed drug was detected by electron microscopy, indicating uniform distribution of drug and polymer solution (Figure-2a & 2b). The Piroxicam-PVP loaded solid dispersed drug diameter is large and can be decreased by further optimizing the parameters used for the fusion/melt process.

FTIR Analysis

IR spectra of piroxicam and Polyvinyl pyrrolidone were shows the prominent peaks for functional group like N-H, C-H (aliphatic and aromatic), C=O, C-O, C-N, C-F and S=O. When comparing the solid dispersed piroxicam with Polyvinyl pyrrolidone, have found no interaction of piroxicam with Polyvinyl pyrrolidone, which are confirmed with the prominent peaks of functional groups and does not show any additional peaks for other functional groups (Figure 3 and Table 1).

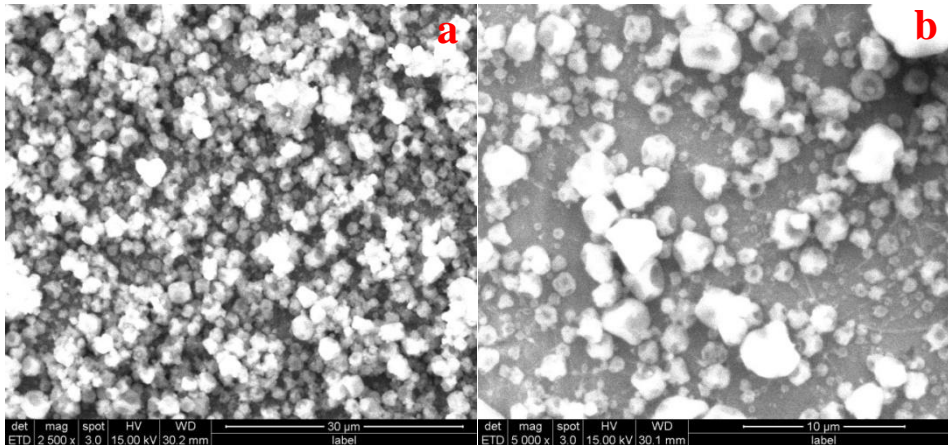


Figure 2: SEM images of Piroxicam-PVP solid dispersed drug a) Lower magnification b) Higher magnification.

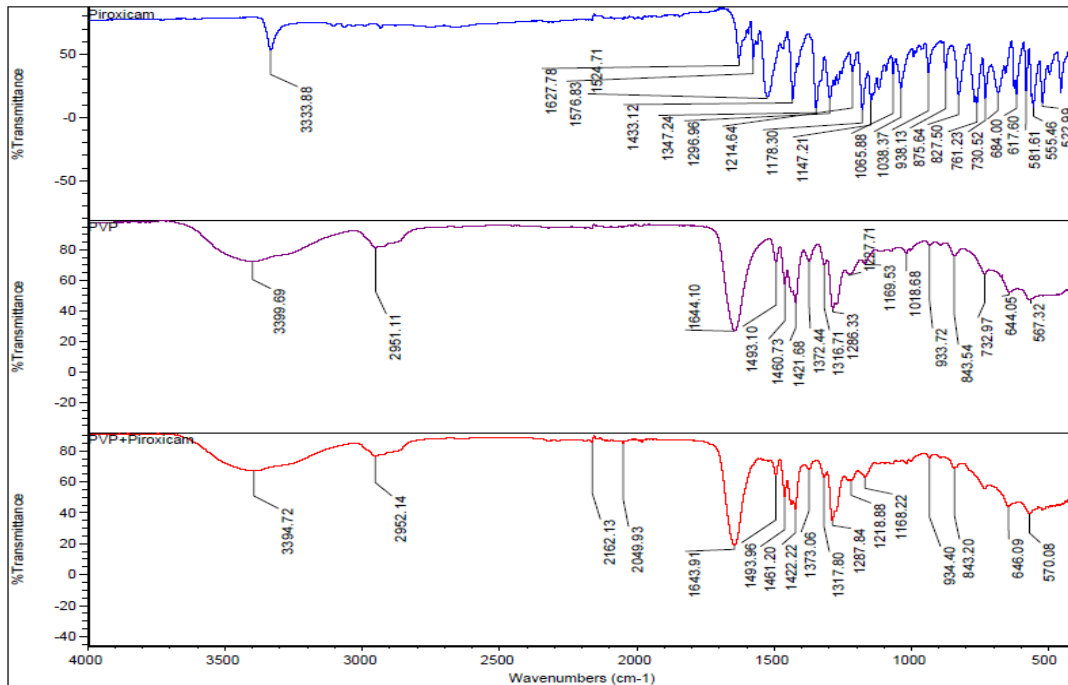


Figure 3: FTIR spectra of Piroxicam, PVP and Piroxicam solid dispersion with PVP.

Table 1: FTIR assignments of free and entrapped Piroxicam in PVP.

Fundamental Vibrations	Wave number (cm ⁻¹)	
	Piroxicam	Piroxicam: PVP solid dispersed drug
N-H (stretch)	3333.88	3394.72
C-H(stretch)	3010.2	2952.14
C=O	1627.78	1643.91
C-O	1214.64	1287.84
C=C	1433.12	1461.20
C-N	1347.24	1373.06
S=O	1038.37	1050.02
C-F		1422.22

In vitro Dissolution Studies

The rate of piroxicam released from Piroxicam based PVP solid dispersed drug was studied at pH 1.2 and at temperature of 37±0.5°C. The rate of release of piroxicam from solid drug is governed by temperature, nature of the used polymer and pH of the used simulated fluid. The solid dispersion technique is newly utilized in the field of drug delivery. It provides a unique and simple technique for improving drug delivery. The advantages of this technique are that it could be applied for a wide range of pharmaceutical compounds depending upon their nature. It could be applied for a mixture of drugs at the same time;

besides, polymer blends could be used as solid dispersed drug at the same time. Also, it is possible to mix different polymeric drug molecules as layers which will help in layer-by-layer assembly to enhance the dissolution rate. The release rate of piroxicam based PVP solid dispersed drug showed a relatively higher rate than that of pure drug (Table 2 and Figure 4). After 60 min of dissolution time there is a marked increase in dissolution rate from 71.47 ± 0.81 to 94.32 ± 0.59 which clearly indicates that around 91% of the drug concentration is available with solid dispersed drug and only 63% for pure drug.

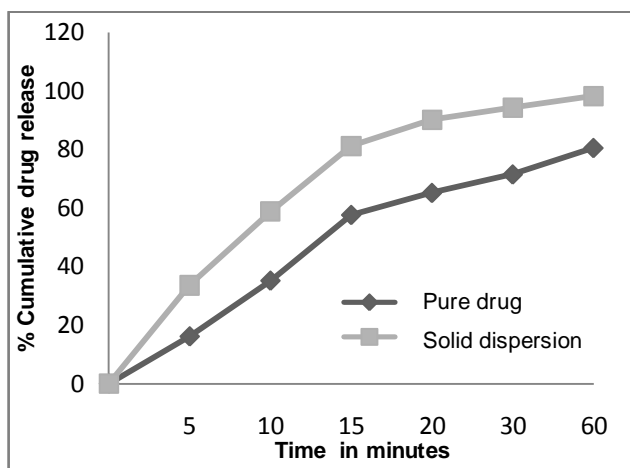


Figure 4: Comparative dissolution profile of Solid dispersed Drug and pure drug in 0.1N HCl.

Table 2: Comparative dissolution profile of Solid dispersed Drug and pure drug at pH 1.2.

Time (min)	Cumulative % of drug dissolved	
	Piroxicam pure drug	Piroxicam: PVP (1:5) solid dispersed drug
5	16.12 ± 0.33	33.58 ± 0.46
10	35.17 ± 0.72	58.81 ± 0.72
20	57.63 ± 0.87	81.15 ± 0.53
30	65.16 ± 0.53	90.22 ± 0.92
60	71.47 ± 0.81	94.32 ± 0.59

CONCLUSION

In the present study PVP was employed in the preparation of solid dispersed drug, as it acts as a hydrophilic carrier, thereby enhancing the dissolution rate of the drug. The release rate of Piroxicam-PVP solid dispersed drug dissolution was twice increased as compared with the pure drug. SEM analysis indicated the average diameter of PVP solid dispersed drug (3600 nm). FTIR spectra indicated the absence of drug-polymer interactions. A new drug delivery system for piroxicam, a non-steroidal anti-inflammatory drug (NSAID), was developed. These systems were based on fusion method/melt method of piroxicam with a suitable polymer. PVP polymer is biodegradable and biocompatible. Further research will be focused on optimization of parameters like pH, temperature and drug: polymer ratio etc to control the release and structure of these drug polymer solid dispersed drugs.

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