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Short Communication

Improvement of physicochemical characteristics and dissolution profile of poorly water soluble drug: ketoprofen by solid dispersion technique

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ABSTRACT

Ketoprofen solid dispersion was prepared by the solvent fusion method using polyvinylpyrrolidone (PVP) as carrier to improve physicochemical characteristics and dissolution profile of ketoprofen. The prepared solid dispersions were evaluated for the flowability, solubility and dissolution behaviour. Flowability studies of powders showed that solid dispersion technique improve flow properties compared with the physical mixtures. Solid dispersion technique found to be effective in increasing the aqueous solubility of ketoprofen. The dissolution of ketoprofen and polymers (PVP) were investigated by UV spectroscopy in phosphate buffer (pH 6.8) using a standard USP II dissolution apparatus. In vitro dissolution studies showed that in the dispersion system containing ketoprofen:PVP in the ratio of 1:1.5 gives faster dissolution rate of ketoprofen than the physical mixtures. Finally, solid dispersion of ketoprofen:PVP prepared in 1:1.5 ratio showed excellent physicochemical characteristics and was optimised.

Keywords: solid dispersion, PVP, UV spectroscopy, phosphate buffer, ketoprofen.

INTRODUCTION

When a drug is administered orally in a solid dosage form such as tablet or capsule, it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. Therefore the bioavailability of many poorly water soluble drugs is limited by their dissolution rates (Habib MJ, 2001). Increase in dissolution of poorly soluble drugs by solid dispersion techniques presents a challenge to the formulation scientist (Khan GM and Jiabi Z, 1998; Dehghan MHG and Jafar M, 2006; Abu TMS, 1999). The poor dissolution characteristics of relatively insoluble drugs have been and still remain a problem to the pharmaceutical industry because the dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form (Ghebremeskel AN et al, 2007).

Ketoprofen is an anti-rheumatic drug with well-known anti-inflammatory, antipyretic and analgesic properties (Charles MH et al, 2003) as well as mild to moderate pain and dysmenorrhoea (Kim JH & Choi HK, 2002). Also it is an inhibitor of prostaglandin synthetase (Yalcin T et al, 1999). However, it is not freely soluble in water and causes systemic disturbances in gastrointestinal tract (Jachowicz R et al, 2000).

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Solid dispersion technique can be used to improve dissolution of poorly water-soluble drugs, ketoprofen. Polymer such as PVP (Ohara T et al, 2005) was used as a carrier in this system. In the present work the physicochemical characteristics of active pharmaceutical substances and excipients including flow rate and solubility. Thus ketoprofen solid dispersion was prepared by solvent fusion method using PVP as a carrier to improve physicochemical characteristics and dissolution profile of ketoprofen.

MATERIALS AND METHODS

Ketoprofen (Cipla Ltd.), PVP (Loba chem. India.) All other reagents were of analytical grade from local market. Assay of ketoprofen was performed by dissolving 0.200 g in 25 ml of ethanol (96%). In to this 25 ml of water was added. Titration was carried out with 0.1 M sodium hydroxide. End point was determined potentiometrically (British pharmacopoeia, 2007). Physical mixture of ketoprofen and polymer (PVP) in powder form were mixed and passed through sieve mesh no. 35. Solid dispersion of ketoprofen and PVP were prepared by solvent fusion method. The required amount of ketoprofen was dissolved in methanol. PVP was melted and added to the ketoprofen solution and mixed thoroughly (Cabbagh MA et al, 1999). The obtained mixtures were kept at 50-60 ^{0}C for 72 h and then the solutions were cooled at the room temperature to form solid. The prepared solid dispersions were milled to pass through sieve mesh no. 35. The physical mixtures and solid dispersions were prepared in the ratios of 1:1, 1:1.5, 1:2 and 1:5.

A modification method of solubility determination was used to determine the solubility of different ketoprofen solid dispersions (Cabbagh MA & Taghipour B, 2007; Habib MJ et al, 2001). Weighed amounts of ketoprofen (pure drug), solid dispersions and physical mixture each sample equivalent to 0.5 g of ketoprofen were separately introduced into 15 ml stoppered conical flasks containing 5 ml of phosphate buffer solution (pH 6.8). The sealed flask were agitated on a rotary shaker for 72 h at 37^0C and equilibrated for 2 h. The supernatant solution was filtered through 0.45 µm membrane filter, and the filtrate was suitably diluted and analyzed on a UV spectrophotometer at 254 nm. Determinations were carried out in triplicate.

All prepared powders (physical mixtures and solid dispersions) were mixed with 1% magnesium stearate as lubricant. Flow properties of powders are important parameters in mixing and passing through hoper, especially during tableting and capsule filling (Aiache JM & beyssac E, 2002). Therefore, for investigating prepared physical mixture and solid dispersions, their flow property, angle of repose and compressibility's were determined and compared. Flowability measurement or powders were conducted by Erweka apparatus model GT. The outlet funnel and nozzle of 15 mm were used in all tests. The time required to empty the complete sample from the hoper was measured. The measured value was normalized to 100 g and was corresponding to the flowability. The test was repeated three times and the mean data was used as flowability value. The volume flow rates were measured as the same, using 100 ml of the powder (Erweka Instruction Manual, 2001). Determinations of angles of repose are relatively simple practical techniques for measuring resistance to particle volume. It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. Such measurements give at least a qualitative assessment of the internal cohesive and frictional effects under low levels of external loading, as might apply in powder mixing, or in tablet die or capsule shell filling operations (Marshall K, 1986). The angle of repose (θ) was determined with same funnel as the flow determination (15 mm nozzle) using the equation 1:

$$\text{Tan } \theta = 2\ h / D \qquad \text{Equation 1}$$

Where D is the diameter of a conical bed of the powder and h is the bed height.

Approximately 15 g of powder was poured through a stainless steel funnel from a height of 6 centimeters onto a level bench top. The angle that the side of the conical heap made with the horizontal plane was recorded as the angle of repose. Lower angle of repose values represented better flow (Crowder TM & Hickey AJ, 2000).

Approximately 100 ml of powder (V_b) was gently poured into a tarred graduated cylinder and the initial volume (bulk density d_b) and weight of the material (M) was recorded. The graduated cylinder was placed on a tap density tester and the final volume was recorded after 200 taps (V_t). The data obtained were used to calculate bulk density and tap density of the powders which were used to determine the percent compressibility index (I). Lower compressibility values represent better flow. Percent compressibility index was determined using the equation 2:

$$I = 100 \times (\text{Tap density} - \text{Bulk density}) / \text{Tap density} \qquad \text{Equation 2}$$

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using Jassco, model no.250. Samples were prepared in KBr disks in a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1}. X-ray powder diffraction pattern were recorded on an X-ray powder diffraction system (X-philips analytical XRD) using copper target, a voltage of 40 Kv and a current of 30 mA. The scanning range was done over 2θ range of 5^0 to 60^0.

Dissolution study was carried out by dissolution apparatus (VEEGO type DA-6D paddle method) dissolution studies was used at a rotation speed of 100 rpm in 900 ml phosphate buffer (pH 6.8 with 0.2 M) maintained at 37°C. Sample of 5 ml ware taken at 15 min. intervals. The concentration of ketoprofen was determined using UV spectroscopy at 254 nm. Dissolution studies were carried out in duplicate for each batch.

RESULT AND DISCUSSION

Assay of ketoprofen powder used in this study was in the range of 99.02 to 100.1% purity. The maximum absorption of ketoprofen was obtained at 254 nm. From result of saturated solubility study shown in Table 1 it was observed that all solid dispersions shows more saturated solubility than their respective physical mixtures. Physical mixture and solid dispersions produces a mass with a high viscosity which makes it difficult to flow.

Table 1: Saturated Solubility of Physical Mixtures and Solid Dispersions

Ratio	Physical mixtures	Solid dispersion
1:1	4.03±0.34	5.02±0.7
1:1.5	4.13±1.58	5.34±2.5
1:2	4.41±0.62	5.76±3.9
1:5	4.80±1.56	4.34±09

Determination of angle of repose and compressibility studies are shown in the Table 2 in which it is seen that preparation of solid dispersion in the ratios of 1:1.5 and 1:2 of ketoprofen:PVP promotes physicochemical properties compared with physical mixture. The IR studies showed no change in the spectral characteristics of in solid dispersion from (fig. 1). It suggests that there was no chemical interaction between the polymer and ketoprofen. The distinct, high, intense peaks were ob-

served in the X-ray diffraction of the pure ketoprofen (fig. 2). These suggest that the drug is crystalline in nature. However, the X-ray diffraction of PVP and solid dispersion did not show any intense peak that is characteristic of the crystal structure. It reflects that the drug was essentially in amorphous form in the solid dispersion. The PVP may be inhibiting the crystallization and changing the ketoprofen into amorphous form during preparation of solid dispersion. The amorphous form has highest energy of a pure compound and therefore, produces faster dissolution rate.

Table 2: Angle of Repose and Compressibility Determination from Physical Mixture and Solid Dispersions Containing Ketoprofen

Ratio	Physical mixture		Solid dispersion	
	(θ)	(I) (%)	(θ)	(I) (%)
1:1	20.82±1.57	12	18.78±0.2	10
1:1.5	22.67±0.21	10	17.10±0.7	10
1:2	24.87±1.89	10	19.17±1.7	16
1:5	17.26±0.36	13	26.09±0.3	18

The dissolution profile of physical mixture and solid dispersion is shown in Table no. 3 and in fig. 3&4. It is evident that the solid dispersion technique improved the dissolution rate of the drug to a great extent. The result indicates that ketoprofen:PVP in 1:1.5 shows 89.24% drug dissolution in 120 min which was the highest dissolution rate followed by 1:1 shows 83.16%.

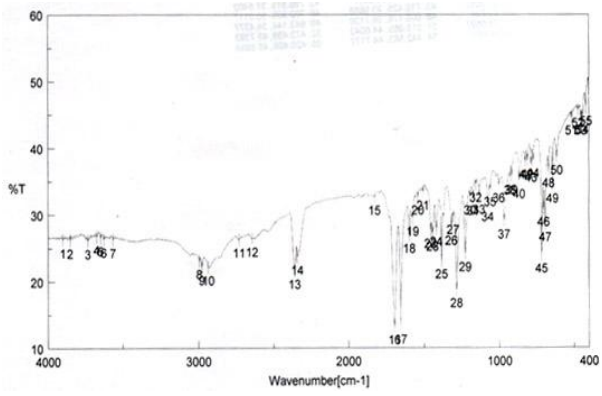

Figure 1: IR spectra of ketoprofen

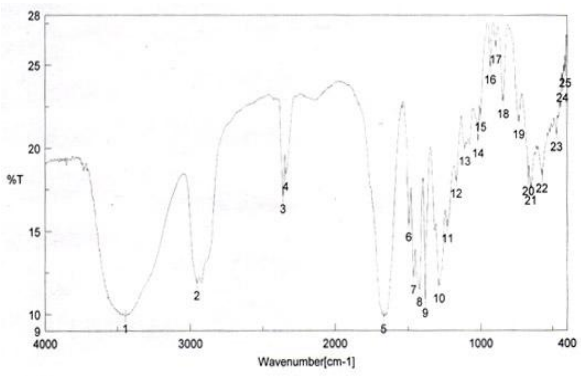

Figure 2: IR spectra of PVP

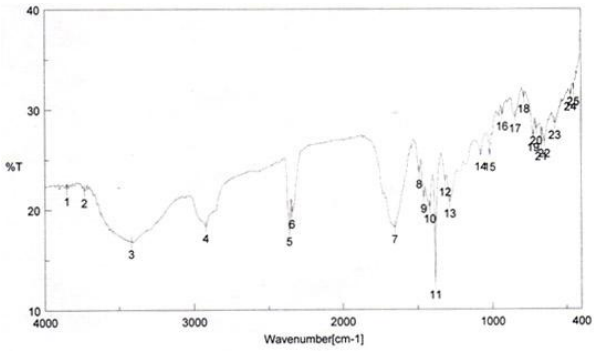

Figure 3: IR spectra of ketoprofen and PVP

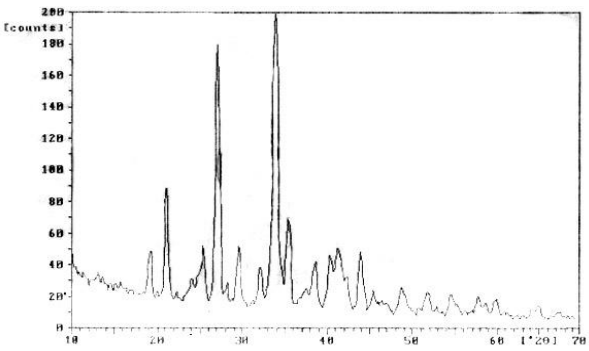

Figure 4: XRD spectra of ketoprofen

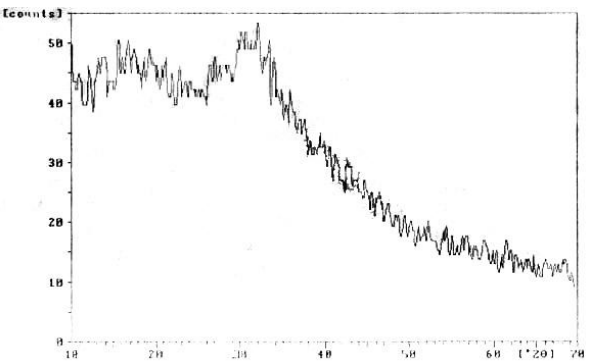

Figure 5: XRD spectra of ketoprofen and PVP

CONCLUSION

Ketoprofen solid dispersion was prepared using PVP as a carrier to improve physicochemical characteristics and dissolution profile of ketoprofen. Solid dispersion technique found to be effective in increasing the aqueous solubility of ketoprofen. *In vitro* dissolution studies showed that in the dispersion system containing PVP as a carrier gave faster dissolution rate than physical mixtures.

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