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Solubility enhancement of a poorly aqueous soluble drug ketoprofen using solid dispersion technique

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ABSTRACT

Ketoprofen has low solubility in water and it is having dissolution problems. The objective of the present research is to enhance the aqueous solubility of the poorly water soluble drug (Ketoprofen) by formulation of solid dispersion systems with the use of Gelucire 44/14 and PVP K30 as a polymer in the formulation. The formulation of solid dispersion by solvent evaporation method is introduced to reduce the drug particle size and hence increase the dissolution rate. These dispersions were characterized with the help of DSC and X-ray diffraction studies. Dissolution of solid dispersions of ketoprofen in phosphate buffer (pH 7.4) was studied using USP dissolution test apparatus II. The results reveal that the solid dispersions of ketoprofen showed an improvement in the rate and extent of drug dissolution.

Key words: Solid dispersion, Gelucire 44/14, PVP K30, Solvent evaporation method, X-ray diffractions studies, DSC.

INTRODUCTION

Ketoprofen exhibits short half-life, poor compressibility, caking tendency, gastrointestinal irritation & ulcerogenic effect [1]. Ketoprofen is a nonsteroidal anti inflammatory drug (NSAID) with analgesic and antipyretic properties. Ketoprofen has pharmacologic actions similar to those of other prototypical NSAIDs that are thought to be associated with the inhibition of prostaglandin synthesis [2]. Ketoprofen is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and to alleviate moderate pain. Ketoprofen available in various dosage forms like ketoconazole, ketolac. Dosing frequency is 50-100 mg twice a day. Its half life is 0.5 to 2 hrs. Ketoprofen is poorly aqueous soluble i.e. 0.5µg/ml. Problem associated with ketoprofen is that it is poorly soluble in water which leads to poor dissolution rate and subsequent decrease in its gastrointestinal absorption [3].

Hence, to increase dissolution rate of a drug, solubility of drug must be increases. Solubility of drug can be increased by various techniques out of which in this study we use solid dispersion technique because it is economic, easy to use, safe and non-toxic method [4]. The proposed solubilizers (Gelucire 44/14 and PVP K30) are known to be safe hence; toxicity/safety related issues may not raise concern, suggesting the adoptability for large scale manufacturing i.e. industrial feasibility. The proposed techniques would be economical, convenient, and safe. Thus, the study opens the chances of preparing such solid dispersion formulation of poorly water-soluble drugs. If chemical stability of the drug remains unaffected, it opens a new era of more stable economic and safe products in the market [5].

The solid dispersion approach has been widely applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly water soluble drugs [9]. Sekiguchi and Obi introduced the concept of solid dispersion. Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve enhanced dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs from ointment and suppository bases. By increasing the dissolution rate in the GI tract, the absorption rate is increased. This commonly occurs for drugs with poor water solubility. The solubility characteristics of the drugs may also be altered by reduction of particle size, formation of eutectic mixtures, molecular dispersion, amorphous dispersion, metastable polymorph dispersion and increased wettability [2].

MATERIALS AND METHODS

Ketoprofen was received as a gift sample from Ranbaxy Lab Ltd (Dewas). Polyoxylglycerides (Gelucire 44/14) was procured from Gattefosse Pvt. Ltd. (Mumbai). Poly vinyl pyrrolidine (K30) was acquired from Central Drug House (CDH) (Mumbai). All other solvents and reagents (like Ethanol, Acetone, Methanol, Carbon Tetra Chloride, NaOH, NaCl, Na_2HPO_4, and KH_2PO_4 etc.) were of analytical grade and procured from MERCK (Mumbai) and SDFCL (Mumbai).

Preparation of Solid Dispersions:

An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier should be sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Ketoprofen and carrier like PVP K30 and Gelucire 44/14 in a ratio of 1:1, 1:2, 1:3, 1:4 Respectively were dissolved in minimum volume of organic solvent (Methanol) and solvent was evaporated on hot plate by placing it on hot plate. The resultant solid dispersion was kept in refrigerator for about 5 min and solidified. The hardened mixtures were then powdered in mortar, sieved through an 80-mesh screen and stored in desiccators at room temperature until further use [7].

Powder X-ray Diffraction Studies:

DSC analyses were performed with a Mettler TA 4000 apparatus equipped with a DSC 25 cell. Weighed samples (5-10mg, Mettler M3 microbalance) were scanned in pierced aluminum pans under static air at a scan rate of 10ºC min^{-1} over a 30-200ºC temperature range. The instrument is calibrated for temperature and heat flow using Indium as a standard. Graphs are shown in fig. 1 & fig. 2 [1].

Differential Scanning Calorimetry:
X-ray powder diffractograms were obtained with a bruker D8 (Θ/Θ Geometry) differactometer using a Cu Kα radiation and a graphite monochromator. The samples were analyzed at ambient temperature over the 10-38 2Θ range at a scan rate of $0.03s^{-1}$. Graphs are shown in fig. 3 & fig. 4 [6].

Dissolution Rate Studies:
Dissolution rate of Ketoprofen from its Physical Mixture was significantly higher than for the pure drug. Dry mixing brings the drug in close contact with the hydrophilic polymer and the increased dissolution rate can thus be explained as being due to increased wettability and dispersibility of Ketoprofen. During dissolution experiment it was noticed that Physical Mixtures immediately sinks to bottom of the dissolution vessels as Solid Dispersions do, where as the pure ketoprofen floats for a long period on the surface of dissolution medium [6].

Dissolution studies were performed using USP type II apparatus. Samples of pure ketoprofen, Physical Mixtures (PM) and Solid Dispersions (SDs) equivalent to 50 mg of ketoprofen were added to the dissolution medium 900 ml of phosphate buffer saline pH 7.4 (PBS 7.4) at a temp. 37°C, the rpm was set at 75. In all experiments, samples was withdrawn at 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180 min and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were analyzed by U.V. spectrophotometer at 258 nm. Readings were taken in triplicate. Cumulative percentages of the drug dissolved from the formulations were calculated using calibration equation. Results are reported in fig. 5 and fig. 6 [8].

RESULTS AND DISCUSSION

X-ray diffractions patterns of ketoprofen, Gelucire 44/14, PVP K30 are reported in fig. 1 & fig. 2. The ketoprofen spectrum shows several sharp diffractions peaks typical of its crystalline state, whereas formulations of ketoprofen shows peaks in broad region or diffuse peaks, it shows amorphous nature of formulation.

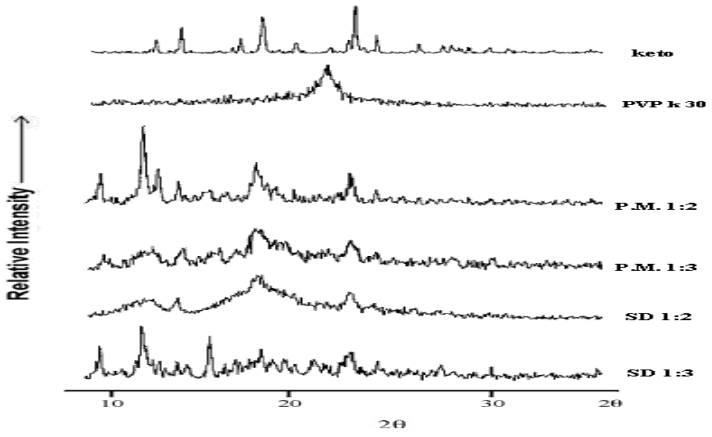

Fig. 1: XRD spectra of ketoprofen PVP K30 and their binary mixtures

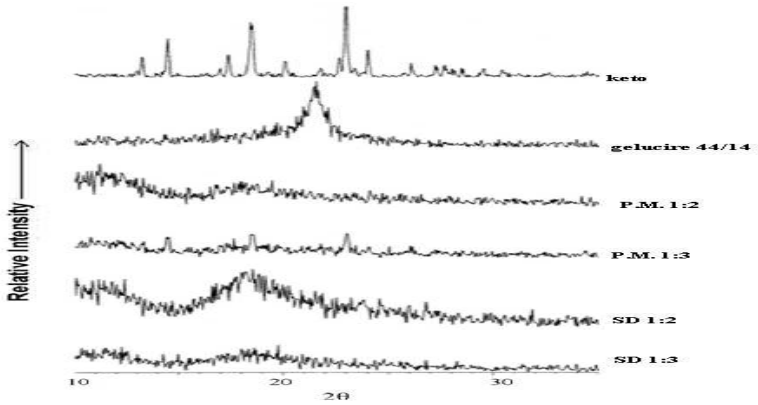

Fig. 2: XRD spectra of ketoprofen, gelucire 44/14 and various binary systems

DSC of pure Ketoprofen exhibited a sharp endothermic peak at 96.5°C inductive of its crystalline anhydrous state, corresponding to its melting point. In DSC thermograms of formulations (selected for characterization studies), there is suppression of the melting peak which indicate that the drug is in amorphous rather than in crystalline form.

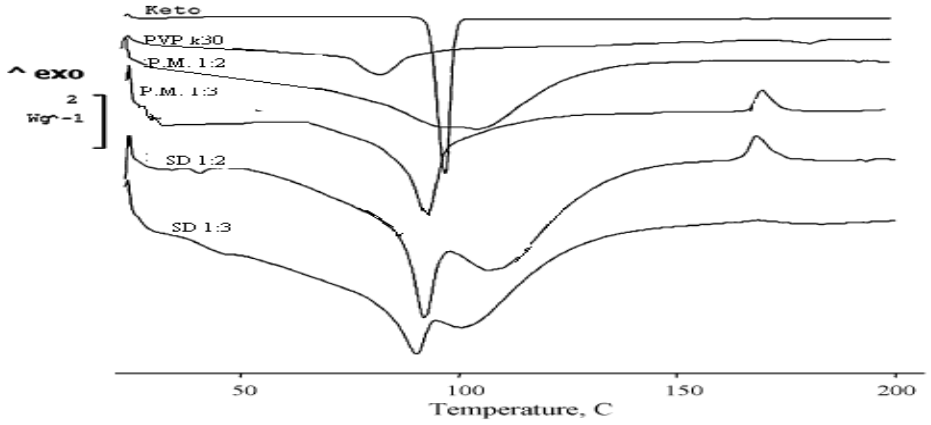

Fig. 3: DSC curves of ketoprofen, PVP K30, their physical mixtures and solid dispersions of different ratios.

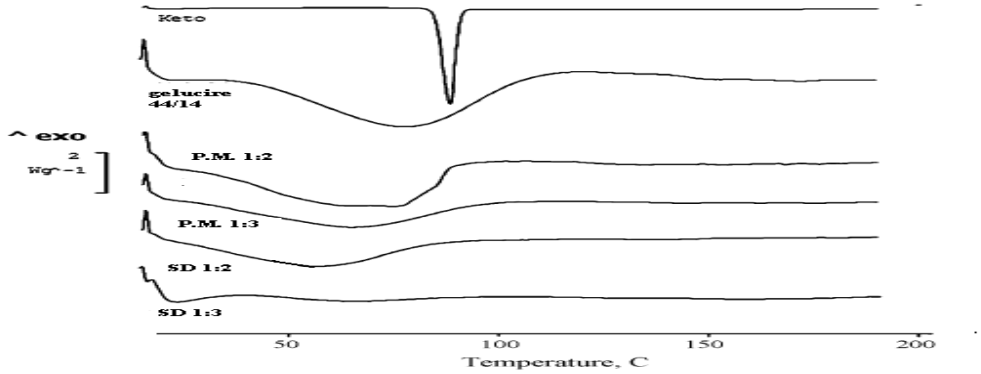

Fig. 4: DSC curves of ketoprofen, Gelucire 44/14, their physical mixtures and solid dispersions of different ratios.

Dissolution profiles of pure ketoprofen, Solid Dispersion in dissolution medium are shown in (**Fig.: 5 and 6)** Solid Dispersion of ketoprofen showed a significant increase in the dissolution rate as compared with pure Ketoprofen. The amount dissolved in 3 hours (i.e. 180 min) were 87±1.56% for SD with PVP K30 (1:2), 90±1.34% for SD with PVP K30 (1:3), 92.5±0.97% for SD of Gelucire 44/14 (1:2), 96.5±1.34% for SD of Gelucire 44/14 (1:3), where as it was only 42.5±1.77% for crystalline ketoprofen**.** All solid dispersion samples showed improved dissolution of ketoprofen over pure ketoprofen.

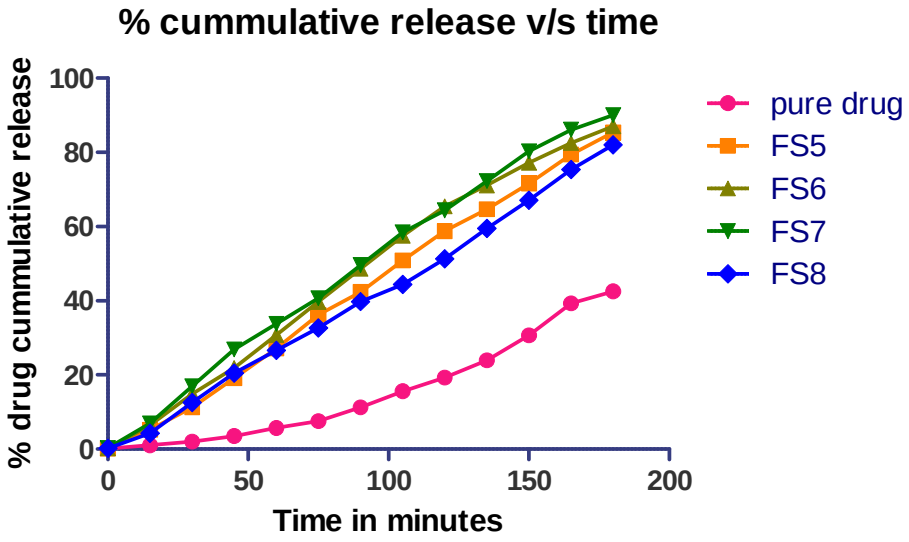

Fig. 5: Effect of drug: Polymer ratios on the dissolution of ketoprofen from ketoprofen: PVP K30 Solid Dispersion

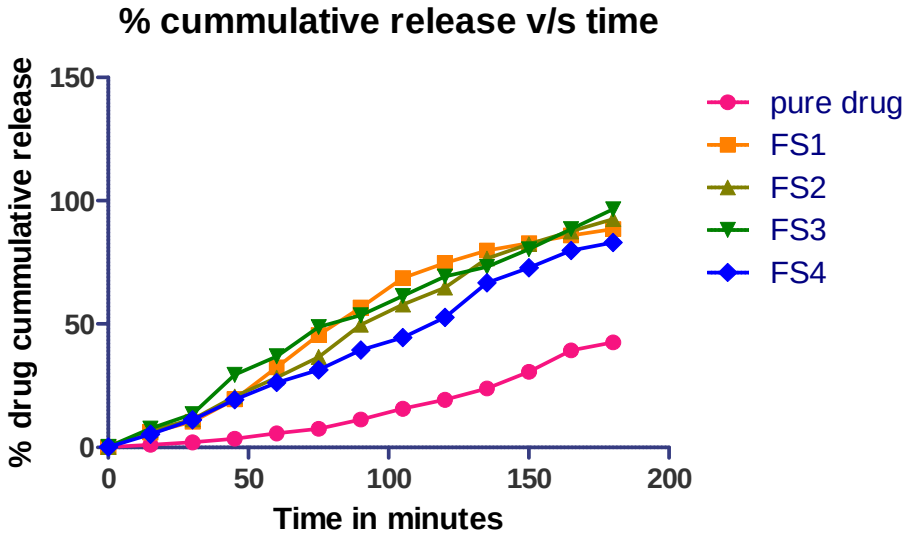

Fig. 6: Effect of drug: Polymer ratios on the dissolution of ketoprofen from ketoprofen: Gelucire 44/14 Solid Dispersion

The solid dispersion of ketoprofen with Gelucire 44/14 and PVP K30 gave increased dissolution rates than the corresponding physical mixtures and pure drug. The slight increase in dissolution

of drug when it is physically mixed with Gelucire 44/14 and PVP K30 is probably due to wettability improvement and local solubilization effect of the carrier at diffusion layer. In addition to these factors, enhancement of dissolution of drug from Gelucire 44/14 and PVP K30 solid dispersions could be attributed to the amorphous state of the drug in solid dispersions, absence of aggregation and reduction in particle size. It is observed that Gelucire 44/14 and PVP K30 solid dispersions showed increase in dissolution rate in comparison with that of pure drug at 1:2 & 1:3 drug:carrier ratios respectively.

The dissolution rate of ketoprofen was strongly dependent on the relative concentration of the drug to Gelucire 44/14/PVP K30 ratio. The dissolution rate of ketoprofen increased with increase in concentration of carrier but formulation FS2, FS3, FS6 & FS7 (selected for characterization studies) showed maximum dissolution rate compared to other formulations. The further increase in amount of Gelucire 44/14 and PVP K30 in solid dispersions decreased the dissolution rate. The decrease in dissolution rate of solid dispersions containing higher polymer proportions might be due to dissolution formation a concentric layer of solution around the drug particles to the bulk of the dissolution.

CONCLUSION

The present study has shown that it is possible to increase the dissolution rate of poorly water soluble drug ketoprofen, by preparing a solid dispersion with water soluble carriers i.e. Gelucire 44/14 and PVP K30. The solid dispersions show faster dissolution characteristics as compared to pure ketoprofen. This might be due to solubilising effect of carriers or crystallization of the drug or entrapping of the drug in molecular state by the carrier.

The prepared solid dispersion formulations of ketoprofen were found to be quite stable. The proposed solubilizers are known to be safe hence; toxicities/safety related issues may not raise concern, suggesting the adoptability for large scale manufacturing i.e. industrial feasibility. The proposed techniques would be economical, convenient, and safe. Thus, the study opens the chances of preparing such solid dispersion formulation of poorly water-soluble drugs. If chemical stability of the drug remains unaffected, it opens a new era of more stable economic and safe products in the market.

It can be concluded that with the carefully designed experimental technique, solubility of poorly water-soluble drugs can be improved by using “SOLID DISPERSION TECHNIQUE.’’ It would not be surprising that many types of solid dispersion of poorly water-soluble drugs based on these phenomena would enter into the market.

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