IMPROVEMENT OF SOLUBILITY AND DISSOLUTION RATE OF MEFENAMIC ACID BY SOLID DISPERSIONS IN PEG4000

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ABSTRACT
The aim of this study was to prepare and characterize solid dispersions of water insoluble non-steroidal anti-inflammatory drug, mefenamic acid (MA), with polyethylene glycol 4000 (PEG4000) for enhancing the dissolution rate of the drug. The solid dispersions (SDs) were prepared by hot melting method at 1:1, 1:2 and 1:4 drug to polymer ratios. Scanning electron microscopy (SEM), X-ray powder diffractometry (XRD) and differential scanning calorimeter (DSC) were used to examine the physical state of the drug. Furthermore, the solubility and the dissolution rate of the drug in its different systems were explored. The data from the XRD showed that the drug was disappeared in case of higher ratio of IND–PEG4000. DSC thermograms showed the significant change in melting peak of the IND when prepared as SDs suggesting the change in crystallinity of MA. The highest ratio of the polymer (1:4) enhanced the drug solubility about 4-folds in case of SDs of MA–PEG 4000. An increased dissolution rate of MA at pH 7.4 was observed when the drug was dispersed in these carriers in form of physical mixtures (PMs) or SDs. IND released faster from the SDs than from the pure crystalline drug or the PMs. The dissolution rate of MA from its PMs or SDs increased with an increasing amount of polymer.

KEYWORDS: Mefenamic acid, solid dispersion, dissolution, solubility.

INTRODUCTION
Mefenamic acid is a potent prostaglandin synthetase inhibitor that is used widely as a non-steroidal anti-inflammatory and analgesic–antipyretic drug. It is used in mild to moderate pain including headache, dental pain, postoperative and postpartum pain, dysmenorrheal, osteoarthritis. Since its introduction, there have been numerous manuscripts published that discuss various aspects of the compound including important structural and physical properties. It has been suggested that solubility is a key factor in determining bioavailability. Likewise, crystallographic measurements of fenamates, including mefenamic acid, and their complexes have shown that they share a common and invariant feature. Most of the NSAIDs belong to class II category under Biopharmaceutical classification system (BCS) i.e., they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. Rate of absorption and / or extent of bioavailability for such insoluble hydrophobic drug are controlled by rate of dissolution in gastro-intestinal fluids. However, its oral bioavailability is very low, probably due to poor solubility in water and insufficient dissolution rate. 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, surfactant, hydrotropism and cosolvents; preparing co precipitate, liquid solid compacts, fast releasing microparticle, interactive mixtures, solid dispersion, compressing with buffers or complexation with cyclodextrins. 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 drugs9 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 hydrophilicity. These are available with a range of properties depending on their hydrophilic–lipophilic balance (HLB) and melting point range (33– 65 °C). They have a wide variety of...
applications in pharmaceutical formulations as the preparation of fast release and sustained release formulations.\textsuperscript{13,14} The purpose of the current study is to characterize the solid-state properties of the solid dispersion system of mefenamic acid in 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**
Mefenamic acid 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 (SDs) at various weight ratios were prepared by melting method. MA was added to the molten base comprising PEG4000. The blend was heated 100°C above the melting point of each carrier for 5 min with continuous stirring. The systems were placed in a freezer at -20°C for 24 h. The mass was crushed, ground gently with a mortar and pestle and passed through 500 µm sieve. The samples were kept in desiccators until the next experiments.

**Preparation of physical mixture**
Physical mixtures (PMs) of MA with PEG4000, at 1:1, 1:2 and 1:4 weight ratio of MA: drug, were prepared by blending them by triturating for 10 min followed by sieving (500 µm).

**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 mefenamic acid.

SD particles\textsuperscript{2} (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 285 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 Shimasuzu, 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 MDP diffractometer, 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 (20).

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

**Solubility studies**
The solubility of mefenamic acid SD 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 285 nm.

**Dissolution studies of microparticle**
The dissolution of mefenamic acid 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 285 nm.

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

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

X-Ray diffraction was used to analyze potential changes in the inner structure of mefenamic acid crystal 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 mefenamic acid, PM, and FDT are shown in Fig. 3. The result showed that mefenamic acid crystals could be seen in the PM while the micrograph of FDT shows a matrix in which no crystals of mefenamic acid could be seen.

Solubility of mefenamic acid 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 mefenamic acid 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 mefenamic acid versus time in minute.

**DISCUSSION**

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 mefenamic acid was found to be in the range of 79-91 %. 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 mefenamic acid formulation was found to be in the range of 79-98 \( \pm \) 0.013.

In DSC curve, pure mefenamic acid had a sharp endothermic peak at 233°C that corresponded to the melting point of mefenamic acid. The thermogram of the PM showed the endothermic peak of mefenamic acid, although broader, spitted, and slightly shifted to the left, indicating that the crystalline state is maintained but decreased in the PM and shown sharp 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 mefenamic acid was molecularly or amorphously dispersed in the solid dispersion (SD).

In XRD study, the characteristic peak of the mefenamic acid appeared in the 2\( \theta \) range of 10–30\(^{\circ}\) indicating that the unprocessed mefenamic acid 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 mefenamic acid 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 mefenamic acid 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 mefenamic acid 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 mefenamic acid drug in SD, that indicates the super-saturation obtained from the SD. Increase in solubility of mefenamic acid 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 mefenamic acid 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 mefenamic acid was slow compared with physical mixtures and SD. mefenamic acid in the SD was dispersed and almost completely dissolved (94.57%) in 30 min. Initial dissolution rate of mefenamic acid in the SD increased markedly about twenty three fold compared to pure mefenamic acid in 30 min. The dissolution rate was also higher and faster in SD than in PM. The percentage of mefenamic acid dissolved from its PM for 60 min (64.32%) increased approximately four fold compared to mefenamic acid 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–PEG4000 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.

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