

Preparation, Characterization and Dissolution of Solid Dispersion of Diclofenac Sodium Using Eudragit E-100

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ABSTRACT

Solid dispersions (SDs) traditionally have been used as effective methods to improve the dissolution properties and bioavailability of poorly water-soluble drugs. Diclofenac Sodium, a non steroidal anti-inflammatory drug with analgesic and anti-inflammatory property was selected as the model drug. The poor aqueous solubility of the drug results in variable dissolution rate and hence poor bioavailability. The aim of the present study was to improve the solubility and dissolution rate of a poorly water-soluble drug, diclofenac sodium, by SD technique as using Eudragit E100. SD was prepared by solvent evaporation technique. The SD was characterized for particle size, particle size distribution and solubility studies. Solid state characterizations i.e., Differential Scanning Calorimetry and Scanning Electron Microscopy were also carried out for the best formulation. It was concluded that the SD prepared by solvent evaporation technique using Eudragit E100 enhanced solubility and dissolution and hence better patient compliance and effective therapy.

INTRODUCTION

Solid Dispersions (SDs) are resulted by dispersion of drug in biologically inert matrix. They can be used to increase the solubility of a drug with low aqueous solubility, thereby improving its oral bioavailability. Higher drug dissolution rates from a SD can be facilitated by optimizing the wetting characteristics of the compound surface, as well as increasing the interfacial area available for drug dissolution. Although the latter can be easily accomplished by, for example, decreasing the particle size of the drug powder but micronized powders may result in further complications as they occasionally tend to agglomerate. A more preferable solution would be to introduce the drug in the form of a molecular dispersion. The formulation of poorly soluble compounds for oral delivery now presents one of the greatest and most frequent challenges to formulation scientists in the pharmaceutical industry (Singh G *et al.*, 2011; Leuner C, 2000; Nighalb, 2012). The therapeutic efficacy of a drug product intended to be administered by the oral route depends first of all on its absorption by the gastro-intestinal tract. The relationship between dissolution rate and absorption is particularly distinct

when considering drugs of low aqueous solubility. Poorly soluble drugs have shown to possess unpredictable absorption pattern and are slowly absorbed as compared with drugs with higher solubility. Several methods have been employed to improve the solubility of poorly water soluble drugs (Singh *et al.*, 2012).

The mechanisms of enhancement of dissolution rate of SDs have been proposed by several investigators. A molecular dispersion of the drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which results in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process, and there is an improvement in drug solubility and wettability due to surrounding hydrophilic carriers (Amte *et al.*, 2012; Almeida *et al.*, 2012; Singh *et al.*, 2012). The method of preparation and type of the carrier used are important influences on the properties of SD. The method used to prepare the SDs include the melting or fusion method, solvent evaporation method, kneading method, spray-dried method and supercritical fluid process (Otuska *et al.*, 1993; Singh *et al.*, 2012). Among the carriers used in the formulation of SDs, polyethylene glycol and polyvinylpyrrolidone are the most commonly used. Both polymers show excellent water solubility (Chowdary *et al.*, 2013; Kavitha *et al.*, 2013; Kadir *et al.*, 2012). The purpose of the present work was to improve the aqueous solubility and dissolution rate of diclofenac sodium by preparing the SD with Eudragit E-100.

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MATERIALS AND METHODS

Diclofenac sodium was received as gift sample from Micro labs, Bangalore, India. Eudragit E-100 was obtained from Evonik Degussa India Pvt. Ltd, Mumbai. All other chemicals and solvents used were of analytical grade.

Determination of solubility of diclofenac sodium in water

Solubility studies were performed by placing single dose of the drug in 25 ml of screw- capped bottles containing 20 ml of water and placed in a water bath shaker. The bottle was capped tightly, thermostated at 37 ± 0.2 °C and was shaken at 40 rpm. After 24 h, 2 ml of the solution were filtered (pore size 0.45 μm), suitably diluted and assayed for diclofenac sodium spectrophotometrically at 278nm (Model UV-1700, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan).

Preparation of SDs (Solvent evaporation method)

Weighed amount of diclofenac sodium, Eudragit E-100 in drug-to-polymer ratio (1:2) was dissolved in 15ml of methanol. The solution was stirred at room temperature for 10 mins, and the solvent was then evaporated at room temperature. Solid residue was dried in a desiccator for 24 hrs. The product thus obtained was ground in a mortar and passed through a sieve # 85 and stored in amber coloured screw capped bottles.

Evaluation of SDs

Determination of drug content

The drug content of the SDs was determined in triplicate. SDs equivalent to one dose (20 mg) of drug was taken and dissolved in 100 ml of 0.1M NaOH. The samples were filtered, suitably diluted and assayed spectrophotometrically at 278 nm (Model UV-1700, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan). The polymers did not interfere with the drug extraction and determination at the specified wavelength.

Determination of solubility of SDs

Solubility studies were performed by placing the SD equivalent to one dose of the drug (20 mg) in 25 ml of water in different screw-capped solubility bottles and placed in water bath shaker. The bottles were capped tightly, thermostated at 37 ± 0.2 °C. After specific time interval the samples were withdrawn filtered through membrane filters (whatman filter paper pore size 0.45 μm) and assayed spectrophotometrically at 278nm.

Particle size analysis

Particle size of SDs was determined by microscopic method (optical microscope) with glycerine as dispersion medium for sample. In optical microscopy method particle size of SDs was determined by using 10 X objective lens. A clean glass slide was taken and small drop of glycerine was added and spread over the slide. Small quantities of SDs particles were then place over the slide and size of about 100 particles was determined.

In-vitro drug release profile

The dissolution studies were carried out in (TDT -06PL, Electrolab, Mumbai, India) Dissolution apparatus USP Type 2. The Temperature and paddle speed were maintained at 37.0 ± 0.5 °C at 75 rpm for 2 hrs. The dissolution medium consisted of 500 ml of pH (1.2) simulated gastric medium. At predetermined time, 5 ml samples were withdrawn filtered through 0.45 μm Whatman filter paper, diluted suitably and analyzed spectrophotometrically at 278 nm (Model UV- 1700, UV- Visible spectrophotometer, Shimadzu, Kyoto, Japan). An equal volume of fresh dissolution medium maintained at the same temperature was added to maintain the sink conditions. The polymers did not interfere with the UV analysis of the drug. The mean of three determinations was calculated.

Kinetic modeling of drug release

To find out the mechanism of drug release from SD, the dissolution data of SD was treated with kinetics release equation. Higuchi's square root at time: $Q = KH t^{1/2}$. Where Q is the amount of drug released at time t, KH is Higuchi's square root of time kinetics drug release constant. Prepared SD was subjected for DSC and SEM analysis.

Differential scanning calorimeter (DSC)

DSC analysis was performed using Shimadzu-Thermal Analyzer DT 40 (Kyoto, Japan) on 2- to 8-mg samples (Sartorius BP 210 S electronic microbalance, Goettingen, Germany). Samples were heated in an open aluminum pans at a rate of 10oC per min-1 in a 30 to 300 °C temperature range under a nitrogen flow of 40 mL/min.

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to visualise the surface morphology. SDs were coated with platinum sputter coater 208 HR (Cressington Sci-entific Instruments Ltd., Watford, UK) to assure conductivity. Photomicrographs were taken with a scanning electron microscope (Jeol JSM 5600 LV, Jeol, Tokyo, Japan).

Accelerated stability studies

Stability studies were carried out for SD formulation as per ICH guidelines for six months under the storage conditions of 40 ± 2 oC/ 75 % \pm 5% RH and various physicochemical parameter (appearance, percentage drug content and release profile) were monitored periodically for six months.

RESULTS AND DISCUSSION

The present investigation was aimed to prepare SDs of diclofenac sodium by solvent evaporation method using Eudragit E-100. Eudragit E-100 has a lower content of quaternary ammonium groups and is considered as more permeable to water. Methanol was employed as a common solvent to dissolve the polymers as well as drug.

The preliminary trials conducted revealed that SDs with low polymer ratio resulted in poor drug release whereas those prepared with high polymer ratio exhibited quicker drug release.

Solubility of diclofenac sodium, physical mixture and SD in water

The solubility of diclofenac sodium and SDs were carried out in water. It showed that the solubility of diclofenac sodium is 0.014 mg/ml and 0.823 mg/ml from the SDs formulation.

Drug content and particle size

The content of the drug in the SDs formulation was $99.74 \pm 0.142\%$, and within limit 98.43% . The Particle size of SDs was determined and showed uniformity in particle size. The particle size of SD was $115\mu\text{m}$.

Dissolution studies

Release of diclofenac sodium from SD formulations in acidic medium showed that the release rates of diclofenac sodium from SDs were faster as compared with pure drug as well as from marketed formulation as shown in (Fig. 1). The significant drug particle size reduction achieved in S.D contributes to this improved dissolution rate. This phenomenon could be attributed to the high permeability characteristic of Eudragit E-100 in water. About 60% of diclofenac sodium was released at pH 1.2 for 2 hrs as compared to pure drug and marketed formulation, probably due to the favourable solubility of the drug in the gastric juice.

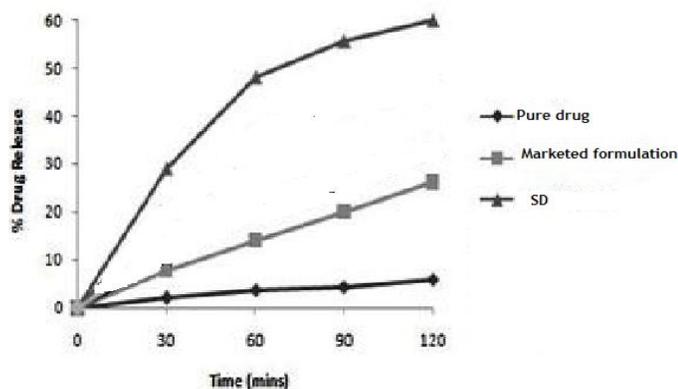


Fig. 1: Comparative dissolution profile between Pure Drug, Marketed and SD Formulation.

Kinetic treatment of Dissolution Data

To interpret the release kinetics and mechanism of drug release from SD. The best fit with higher correlation ($r^2 > 0.98$) was found with the Higuchi's equation. SD formulations follows Higuchi model with R^2 values 0.9983.

Differential scanning calorimetry (DSC)

DSC thermogram of pure drug, Eudragit E-100, SD formulation is presented in (Fig. 2) compared with pure drug. DSC results showed that diclofenac sodium melted at 230°C ; however, the acrylic resin Eudragit E-100 does not present any thermal transition, as the melting point did not shift significantly.

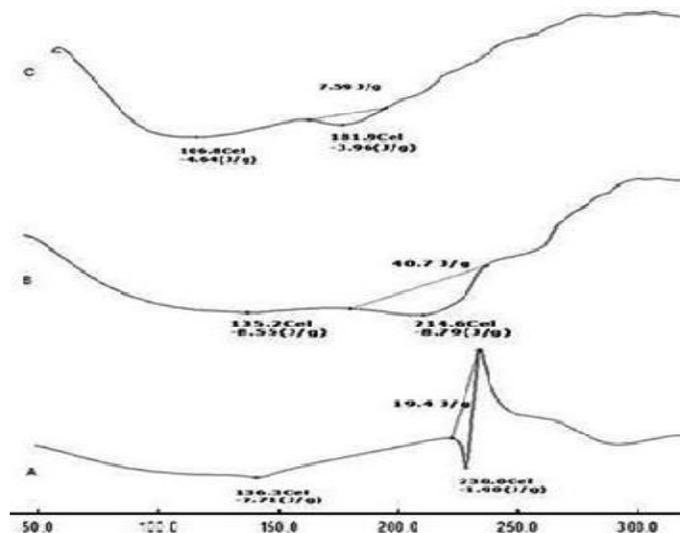


Fig. 2: DSC Curves of A) Pure Drug, B) Eudragit E-100 and C) Sd Formulation.

Scanning electron microscopy (SEM)

SEM of pure drug, Eudragit E-100 and SD formulation confirmed the crystalline character of diclofenac sodium and the amorphous character of the carrier Eudragit E-100 (Fig. 3). Electronic microscopy micrographs showed that the diclofenac sodium crystalline habit changed to a new phase. At the lower concentration of Eudragit E-100, diclofenac sodium needle crystals were still observed, however, at higher Eudragit E-100 concentration the diclofenac sodium needle crystals were not present.



Fig. 3: Scanning electronic micrograph of a) pure drug, b) Eudragit E-100 and c) SDS formulation.

CONCLUSIONS

It is concluded that stable SDs of diclofenac sodium can be obtained by solvent evaporation technique with Eudragit E-100 as the carrier. The S.D exhibits better dissolution profile than the marketed formulations.

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