



Solubility Enhancement of Diclofenac Using Solid Dispersions

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Abstract

Background: The phenomenon which gives rise to a homogenous system, formed by the dissolution of solute in a solvent is known as solubility. Low solubility is the limiting factor in formulation development. Diclofenac being BCS class II drug have low aqueous solubility of 0.00401mg/ml. Amongst various solubility enhancement techniques, solid dispersion is the easiest one.

Objective: Present work is primarily focused on the development of solid dispersions of diclofenac through solvent evaporation technique utilizing Eudragit E100 as a carrier.

Methods: Solid dispersion consists of at least one active pharmaceutical ingredient as a carrier in solid state. Various methods for preparing solid dispersions includes melt extrusion, fusion lyophilization, spray drying, solvent evaporation, and super critical fluid (SCF) technology. Solvent evaporation technique is used among various solid dispersion methods.

Conclusion: The enhanced solubility found to be 0.485mg/ml. The dissolution was performed using USP Type II apparatus was %CDR of pure drug and its solid dispersion in 8 hr were found out to be 45.14926% and 98.04758% respectively. Henceforth, solid dispersion technique results marked solubility enhancement of diclofenac sodium.

Keywords: Solid dispersion; Diclofenac; Eudragit E100; Solvent evaporation; Solubility; Dissolution; Bioavailability

Introduction

Solubility is a critical parameter for achieving desired concentration in a systemic circulation by the homogenous dissolution of the solute in a suitable solvent for attaining required pharmacological response [1]. The major issue with the development of drug formulation is the low solubility of the drug. Only 50%-60% of new chemical entities (NCEs) develop in industry are soluble in water rest are partially insoluble in water. The enhancement of solubility and bioavailability of low aqueous soluble drug is one of the most challenging aspects for drug development [2].

Diclofenac belongs to phenylacetic acid class and is a nonsteroidal anti-inflammatory drug (NSAIDs) having

analgesic, anti-inflammatory and antipyretic actions. It was introduced in 1973 and belong to BCS class II with high permeability and low solubility. Various formulation consisting of diclofenac has been developed for increasing patient adherence and efficacy. Controlled release formulation of diclofenac sodium was developed with a goal of improvement in the safety profile, patient adherence and one daily dosage regimen in chronic pain patients [3]. It is sparingly soluble in water, acetic acid and glacial acetic acid; partially insoluble in chloroform, toluene and ether; soluble in ethanol and freely soluble in methanol [4].

Formulating a poorly water-soluble drug for oral route is always a challenge for scientists. There are many techniques such as particle size reduction (micronization and nanonization) modification of crystal habit can be done by manipulating crystalline state of the drug, drug dispersion can be made by formulating a eutectic mixture, using complexing agents complexation can be done, solid solution or solid dispersion, self-emulsifying drug delivery system and surfactants are used for the solubilization for formation of nano/micro-emulsion [5].

Formulating surface solid dispersion helps in reduction of agglomeration of the drug due to increase in surface area which further increases dissolution rate [6]. This technique can be achieved through incorporation of drug into a hydrophilic carrier system and further the subsequent deposition of the drug solution onto the adsorbent materials [7-10].

The aim of our work is to determine the extent of solubility enhancement in individual carrier in different proportion and to formulate a solid dispersion of diclofenac sodium.

Materials and Method

Materials

Drug diclofenac was received as a gift sample from Yarrow Chem, Pharmaceutical Lab, Mumbai, Maharashtra; Eudragit E-100, Sodium hydroxide and Anhydrous potassium dihydrogen orthophosphate were procured from Loba Chemie, Mumbai, Yarrow Chem, Mumbai and Central drug house, New Delhi respectively. Solvents like methanol and hydrochloric acid were supplied by Renkem, New Delhi.

Methodology

Solubility study of Diclofenac in water

Diclofenac solubility was measured in water by UV visible spectrophotometric method. Excess amount of Diclofenac was added in beaker containing fixed volume of water and is placed in magnetic stirrer for 24hrs. After 24hrs the solution was filtered, dilution of filtrate was done using water and was analysed by spectrophotometer at 276 nm [11-16].

Preparation of Solid Dispersion

Solvent evaporation method was employed for solid dispersion of diclofenac sodium. Weighed amount of diclofenac sodium and Eudragit E-100 in various drug-to-polymer ratio ($S_1 = 1:1$, $S_2 = 1:2$, $S_3 = 1:3$) were dissolved in sufficient amount of methanol. The solution was stirred manually on water bath and solvent was evaporated. Residues were dried in a desiccator up

to 24 hours. The obtained product was triturated in mortar and pestle after which it was passed through sieve number 80 and stored in a closed [17-21].

Evaluation of prepared solid dispersion

Percentage yield

For determining the efficiency of the method used the percentage yield of solid dispersion was calculated. For calculating the percentage yield, total weight of the solid dispersion is determined, and yield is calculated by the following formula [22].

$$\begin{aligned} \text{Percentage yield} \\ &= \frac{\text{Initial weight of the drug and carrier}}{\text{Weight of the solid dispersion}} \times 100 \end{aligned}$$

Determination of drug content

For determination of drug content of the solid dispersion triplicate manner was employed. From each batch 10mg of solid dispersion were taken and separately placed in 100ml of volumetric flask and dissolved in water and volume was made up to 100ml. The absorbance was noted using UV spectrophotometry at 276 nm [17].

Solubility studies

Aqueous solubility of solid dispersion was measured using UV visible spectrophotometer in triplicate manner. Excess amount of the prepared solid dispersion was introduced in the beaker containing fixed volume of water and is placed in magnetic stirrer at 300 ± 5 rpm for 24 hours. After 24 hours the solution was filtered, diluted and then analysed spectrophotometrically at 276 nm [17,23,24].

In-vitro drug release

Preparation of 0.1N HCL

8.3 ml of concentrated HCl was taken and dissolved in 1000 ml of water [25].

Preparation of pH 7.4 phosphate buffer

1.36 g of potassium dihydrogen orthophosphate anhydrous and 0.4 g of NaOH was dissolved in 50ml water in different volumetric flask. Then, 50ml of potassium dihydrogen orthophosphate anhydrous solution was added into 39 ml of NaOH solution in a volumetric flask and volume was made up to 1000 ml [25].

Dissolution

The dissolution study of solid dispersion was performed using USP II dissolution test apparatus. Conditions were kept constant for all dissolution studies having the volume of media 900 ml with a stirring speed of 50 rpm and the temperature of the medium was maintained at

37 ± 0.5°C. For evaluating the drug release 0.1N HCl was employed. Later release studies were carried out in phosphate buffer solution of pH 7.4. 5 ml of sample was withdrawn and transferred into 5 ml fresh media after an interval of 30 minutes. Diclofenac concentration was determined by UV spectrophotometer at a wavelength 276 nm. The percent cumulative drug release at different time intervals was further calculated [17,26-30].

Kinetics modelling of drug release

For evaluating the mechanism of drug release from the solid dispersion the dissolution data was fitted in kinetic models. The release kinetics were analysed *via* linear regression analysis using mathematical models of zero-order kinetics, Higuchi diffusion model and Korsmeyer Peppas kinetic model [31,32].

Result and Discussion

Solubility of diclofenac in water

The water-solubility of diclofenac was found to be 0.00401 mg/ml whereas the reported solubility of Diclofenac is 0.00482 mg/ml.

Evaluation of solid dispersion

Percentage yield

Percentage yield was checked expressed on the basis of dry weight of drug and the carrier. It was noted that the yield of solid dispersion ranged between 57.9-61.1% (Table 1) [30,33].

Table 1: Percentage yield.

S. No.	Formulation	Percentage yield Mean ± SD (n=3)
1.	S ₁ (1:1)	61.1 ± 1.314
2.	S ₂ (1:2)	59.8 ± 1.758
3.	S ₃ (1:3)	57.9 ± 2.164

Determination of drug content

The drug content of the formulated solid dispersion was observed ranging between 26.6-87.92% as shown in the Table 2 [34].

Table 2: Percentage drug content.

S. No	Formulation	% Drug content Mean ± SD (n=3)
1.	S ₁ (1:1)	87.92 ± 5.269
2.	S ₂ (1:2)	64.56 ± 7.953
3.	S ₃ (1:3)	26.6 ± 12.418

Determination of solubility of solid dispersion

The results of the solubility test on S₁, S₂ and S₃ observed in distilled water were 0.485, 0.2186, 0.1748 respectively as shown in table 3. It was noted that the solubility of the prepared solid dispersion decreased as the ratio of carrier increases [35-37].

Table 3: Solubility of solid dispersion.

S. No	Formulation	Solubility(mg/ml) Mean ± SD (n=3)
1.	S ₁ (1:1)	0.485 ± 0.137
2.	S ₂ (1:2)	0.2186 ± 0.291
3.	S ₃ (1:3)	0.1748 ± 0.174

In-vitro drug release profile

The release of drug from solid dispersion (S₁) and its pure form was studied and it was noted that the drug release from solid dispersion was swift as contrast to its pure form because of the enhanced solubility in solid dispersion which enhances the dissolution rate. The drug releases from solid dispersion and its pure form is almost same in acidic media but drug releases in phosphate buffer was faster than its pure form. More than 90% of drug releases in phosphate buffer pH 7.4 as shown in Figure 1.

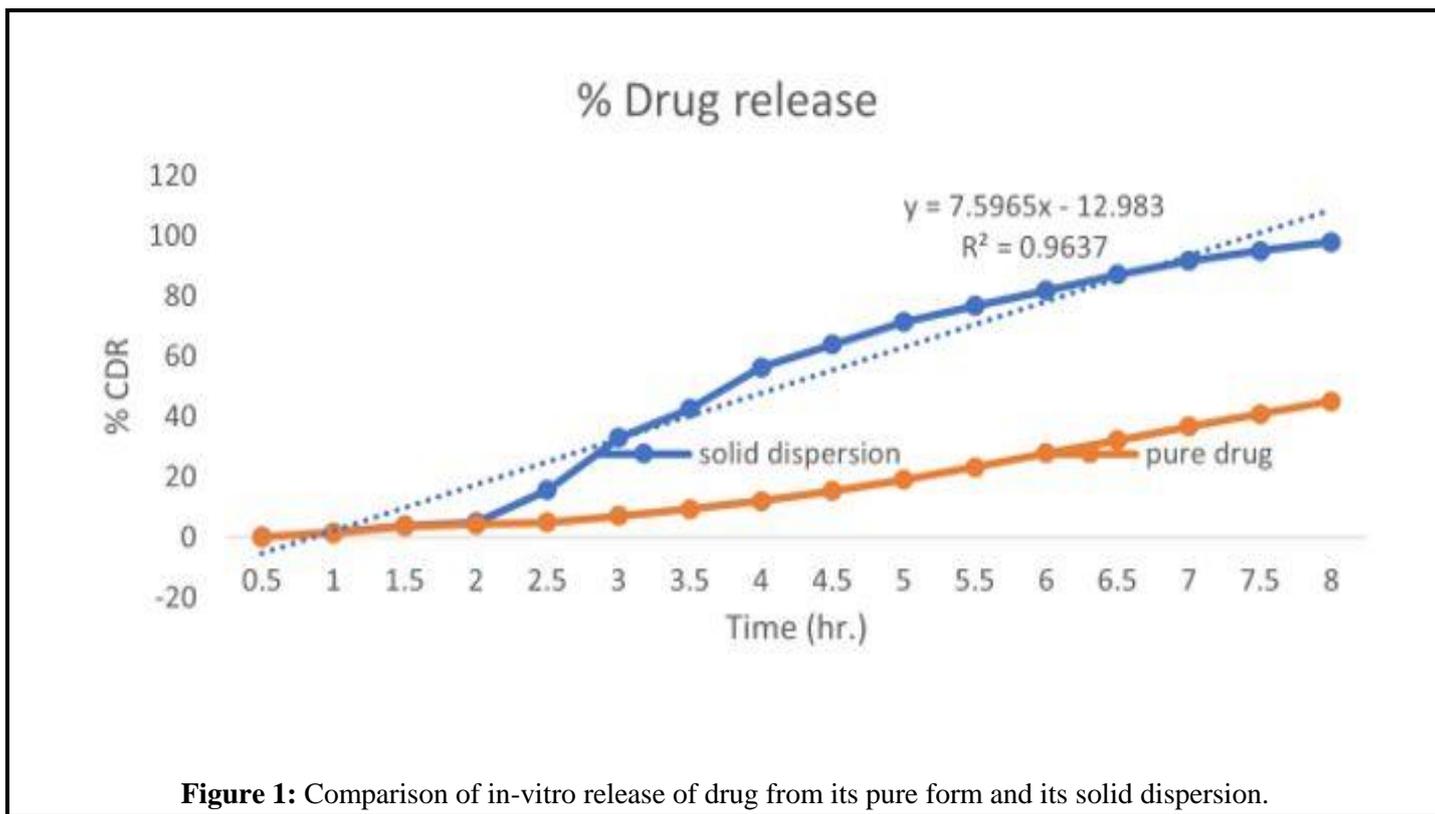


Figure 1: Comparison of in-vitro release of drug from its pure form and its solid dispersion.

Drug release kinetics from solid dispersion

For interpreting the release kinetics and mechanism of the drug release from SD mathematical model for drug

release were used and it was found that the release was zero-order as shown in Figure 2.

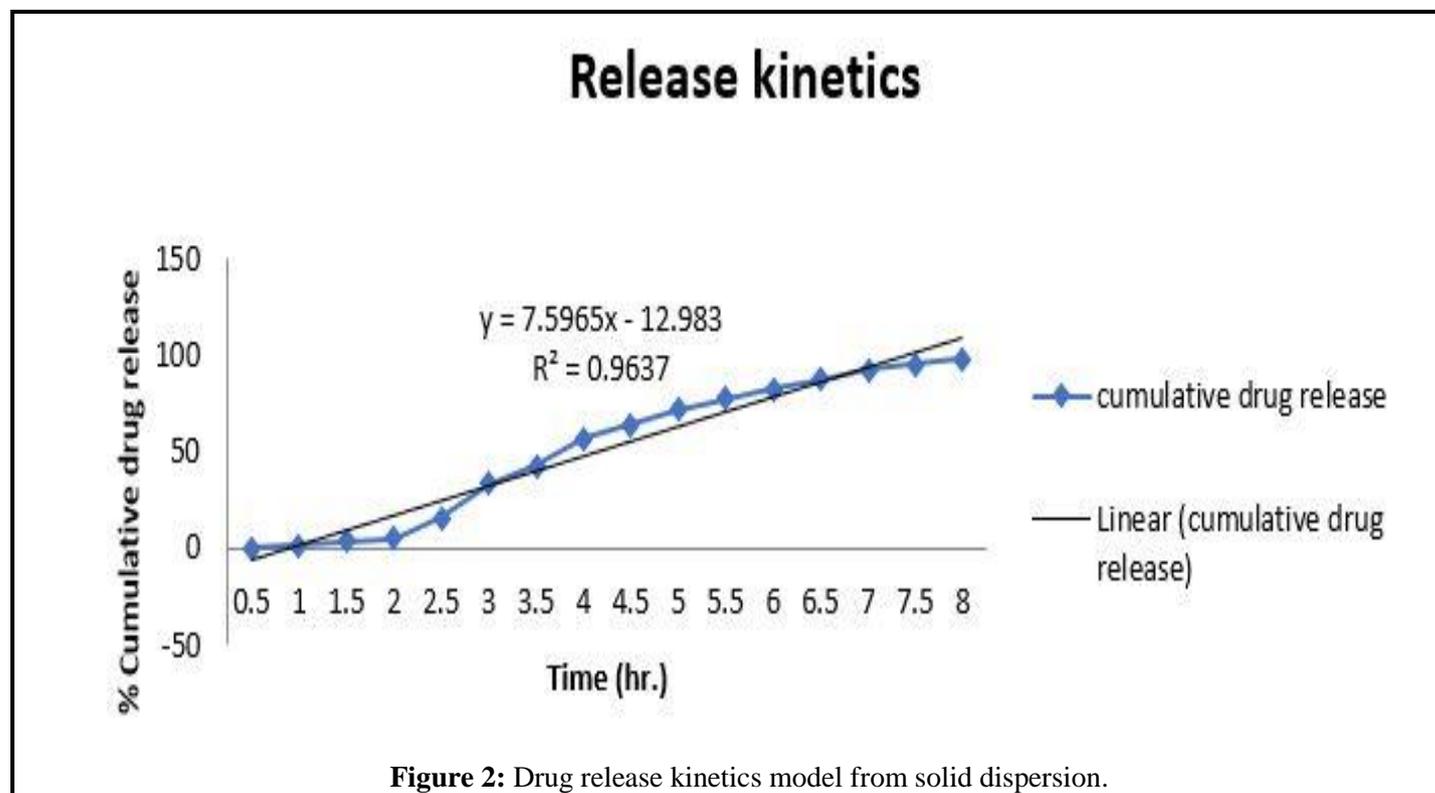


Figure 2: Drug release kinetics model from solid dispersion.

Conclusion

Diclofenac was chosen as a drug for its solubility enhancement. Diclofenac is a BCS class II drug having low aqueous solubility. The observed solubility of diclofenac in water is 0.00401mg/ml and reported was 0.00482 mg/ml at 276 nm. For enhancing the solubility of drug solid dispersions were made using eudragit-E100 (carrier) in various ratio (1:1, 1:2, 1:3). Prepared solid dispersions were evaluated for various parameters. Solid dispersions with drug: carrier 1:1 (S₁) was found to have maximum percentage yield 61.1% drug content 87.92% and solubility (0.485 mg/ml), The in-vitro drug release of selected formulation and pure drug was done for 8 hours in various pH using USP II dissolution test apparatus and results showed that the solid dispersions have higher percentage drug release than pure drug.

Conflict of Interest

The authors have no conflict of interest, financial or otherwise.

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