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Dissolution rate enhancement of aceclofenac by solid dispersion technique

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ABSTRACT

The aim of this study was to prepare and characterize solid dispersions of aceclofenac, employing a mixed excipient system composed of lactose, corn starch as a carrier and to study the effect of a mixed excipient system on rate of dissolution of drug. The solid dispersions were prepared by physical mixture method and solvent wetting method using 1:1 ratios of drug to mixed exciepient system. The formulations were evaluated for % practical yield, drug content, bulk density, tapped density, Hausner's ratio, Carr's index, angle of repose and in vitro drug release. In this study it was concluded that there was considerable increase in in vitro drug release for solid dispersion as compared to the pure drug taken alone. Based on the drug release pattern, the solvent wetting method showed more in vitro drug release as compared to physical mixture method. It was observed that the dissolution rate of drug from solid dispersions increases with the increase in lactose amount in comparison to corn starch with the optimum ratio of (1.0) lactose:(0.5) corn starch showing the best result.

Key words: *Dissolution, bioavailability, solid dispersion, physical mixture, solvent wetting, aceclofenac.*

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INTRODUCTION

Oral drug delivery is the easiest and simplest way of administering solid dosage form. Oral bioavailability of a drug depends on its solubility and/or dissolution rate. If these drugs are not completely released in the gastrointestinal tract, they will have a low bioavailability [1-4]. Drug release is a critical and rate limiting step for oral drug bioavailability, particularly for drugs possessing low gastrointestinal solubility and high permeability. Thus, attempts to increase the rate of dissolution of drugs having limited water-solubility are frequently required [5]. Enhancement in the dissolution rate of such drugs is one of the most important concerning aspects of the pharmaceutical industries [6-8]. Various techniques are available to improve this characteristic such as solid dispersions, micronization, salt formation of drug and addition of surfactants. Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) and is poorly water-soluble. It is widely used to treat swelling and pain in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Solid dispersion technique is used to enhance the dissolution of a poorly water-soluble drug. Solid dispersions are one of the most successful techniques to improve dissolution rate of poorly water-soluble drugs [7, 9, 10]. Solid dispersions are molecular mixtures of poorly aqueous soluble solid drug with an inert hydrophilic carrier. Drug release profile from such mixtures is driven by the carrier properties [11]. Various hydrophilic carriers employed in preparation of solid dispersions include polyethylene glycols, carbohydrates (lactose), poloxamers, polyvinyl pyrollidone K-25, polyols (such as sorbitol and mannitol), organic acid (citric acid) and hydrotopes (urea) [12-15]. Among these, lactose is the most widely used in pharmaceutical industries because of its inertness and cost. There are

 ISSN 2231 – 4423

various methods for preparing solid dispersion which includes solvent wetting method, physical mixture, solvent evaporation method, melting method, solvent wetting method, fusion method, kneading method and super critical fluid method, etc [16- 19].

MATERIALS AND METHODS

Materials

Aceclofenac was of pharmaceutical grade sample, gifted from Cipla Ltd, Mumbai, India. Lactose and corn starch were purchased from SD Fine Chemicals Ltd, Mumbai, India. All solvents were of analytical grade and were used without further purification.

Methods

Preparation of solid dispersions

a) Preparation by physical mixture method

The ratio of drug: mixed excipient system was kept constant (1:1 w/w) in all formulations. Physical mixtures of aceclofenac with mixed excipient system including lactose and corn starch were prepared by mixing accurately the weighed amount of drug and carrier with the help of a spatula in a glass mortar.

b) Preparation by solvent wetting method

The required amount of aceclofenac was dissolved in an appropriate amount of isopropyl alcohol. This solution was dropped onto mixed excipient system placed in mortar and was constantly stirred. Finally the solvent was removed by evaporation at room temperature. The powder so obtained was ground in a mortar and stored in desiccators.

Various ratios of lactose and corn starch used for preparation of solid dispersion

Physical mixture method

1:0.5 ratio of lactose and corn starch (F1)
0.5:1 ratio of lactose and corn starch (F2)
1:1 ratio of lactose and corn starch (F3)

Solvent wetting method

1:0.5 ratio of lactose and corn starch (F4)
0.5:1 ratio of lactose and corn starch (F5)
1:1 ratio of lactose and corn starch (F6)

EVALUATION PARAMETERS

Determination of % practical yield

Determination of practical yield is useful to determine the efficiency of a preparation technique. The practical yield is calculated by using following equation:

$$\% \text{ Practical yield } (\%) = \frac{(\text{Weight of prepared solid dispersions} \times 100)}{\text{Theoretical weight}}$$

Estimation of drug content

Dissolve solid dispersions (equivalent to 100 mg of drug) in 100 ml of methanol. The solution was filtered, diluted suitably and analyzed at 275 nm by employing UV spectrophotometer. The drug content is calculated by following formula:

$$\text{Percent drug content} = \frac{(\text{Aceclofenac amount in weighed quantity of solid dispersions} \times 100)}{\text{Theoretical amount of drug in solid dispersion}}$$

PHYSICAL CHARACTERIZATION OF SOLID DISPERSIONS

Micromeritic study

Determination of apparent bulk density:

The powder blend was weighed first and then placed in a graduated cylinder and measure the volume of it. This gives the relationship to find out the apparent bulk density (g/ml).

$$\text{Apparent bulk density} = \frac{\text{Weight of powder blend}}{\text{Volume of powder blend}}$$

Determination of tapped density:

Tapped density was measured for each batch using Tap Density Tester (USP) (Electro lab Etd-1020). The pre-weighed amount of powder blend was placed in a graduated cylinder and tapped for fixed number of taps (around 100) on mechanical tapping apparatus.

 ISSN 2231 – 4423

From this the tapped volume was noted. Finally the tapped density was computed using the formula:

$$\text{Tapped density} = \frac{\text{Weight of powder blend}}{\text{Tapped volume of powder blend}}$$

Determination of Carr's index: It was used to determine the % compressibility of powder blends. It was calculated by using the value of tapped density and bulk density.

$$\text{Carr's index} = \frac{\text{(Tapped density - Apparent bulk density)}}{\text{Tapped density}}$$

Determination of angle of repose: It was determined by using funnel method. A funnel with its tip at a given height (H), above a piece of graph paper was fixed on a plane surface. Powder blend was poured through the funnel such that the apex of the conical pile touched the tip of the funnel. The angle of repose (θ) was then calculated as follows:

$$\tan \theta = \frac{H}{R}$$

where, R is the radius of the conical pile.

Dissolution studies

In vitro release profiles for each batch was performed using USP dissolution apparatus (Electro lab TDL-8L, Mumbai, India). Pure drug and solid dispersions of drug (prepared by both the techniques) were kept in the baskets of dissolution apparatus. The dissolution testing was carried out at a temperature 37 ± 0.5° C and a sterring rate of 50 rpm in 900 ml of 1.2 pH of HCl solution. Aliquot of 5 ml were withdrawn every ten minutes upto 90 minutes. The same amount of withdrawn volume was replaced with the dissolution medium in order to maintain the sink condition. Aceclofenac concentration was determined spectrophotometrically at 275 nm.

RESULTS AND DISCUSSION

Solid dispersions of aceclofenac were prepared with mixed excipient system using physical mixture method as well as solvent wetting method. Drug content in all prepared batches was determined, which were fairly within the limits. Percentage yield and percent drug content of all formulations formed were determined. It was found that percent drug content and percent practical yield were found to be 99.00% and 99.64% respectively in case of F4 formulation and 99.01% and 99.22% in case of F1 formulation. The data illustrates the fact that, formulation, F4 and F1 releases more drugs in comparison to other formulations during same time interval. The result studies of various parameters are shown in table 1. Findings of study reveal the fact that granules prepared by both method posses better flow behaviour. Granules were having bulk density and tapped density within good range; hence their compression is easily done. This factor is thus of greatest importance while studying the physical parameters. The dissolution behaviour showed that formulations prepared by solvent wetting method has better release characteristics as compared to the formulations prepared by physical mixture method. Aceclofenac and (1.0) lactose:(0.5) corn starch solid dispersion (F4) prepared by solvent wetting method showed the greatest drug release profile than all other formulations. The release data is shown in following fig 1. Thus the experiment showed that lactose and solvent wetting method can be used to improve the dissolution characteristics of poorly water-soluble drug in pharmaceutical formulations.

CONCLUSION

The major problem of aceclofenac is its very poor solubility in biological fluids. From the present study it can be easily demonstrated that lactose has immense potential to improve dissolution characters of any less soluble or poorly water-soluble drug. The results revealed that it is possible to enhance the dissolution rate of aceclofenac by increasing the surface area of the drug by solid dispersion method. Formulation prepared by solvent wetting method using aceclofenac and (1.0) lactose:(0.5) corn starch

 ISSN 2231 – 4423

of ratio 1:1 (F4) yielded best results in terms of dissolution rate. This work also illustrates the fact that lactose has more characteristic to form solid dispersions with the drug molecules, thereby increasing the dissolution rate of drug and decreasing the time of release of drug from the formulated mixture.

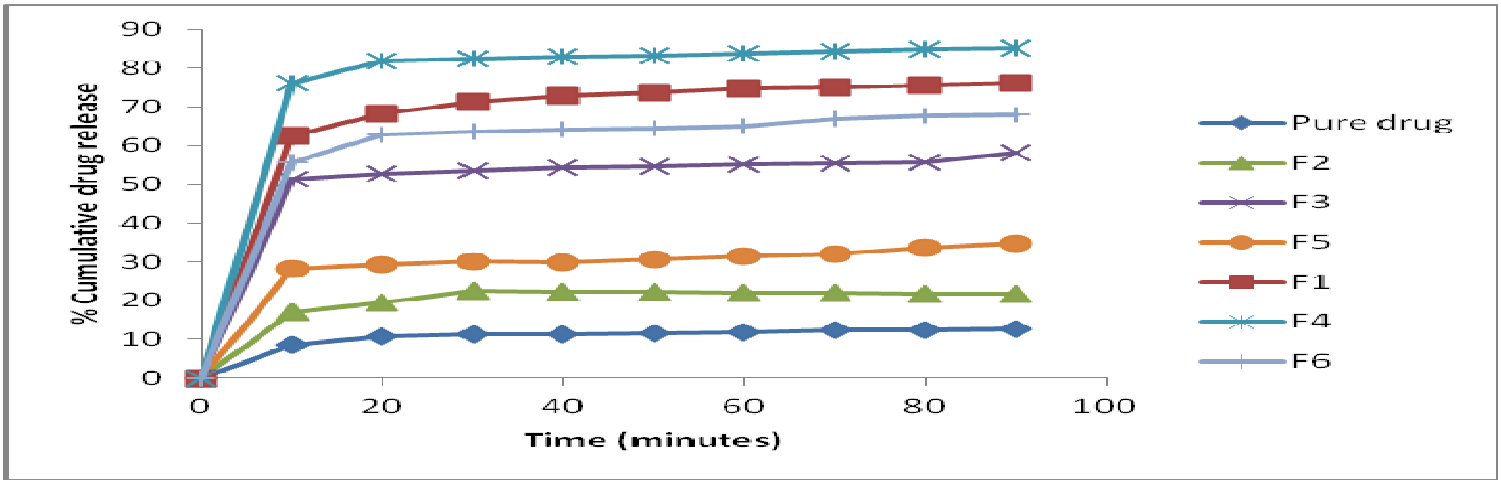

Fig 1: *In-vitro* drug release profile of aceclofenac in HCl solution (pH 1.2) from solid dispersion

Table 1: Evaluation parameters for solid dispersions

Evaluation parameters	F1	F2	F3	F4	F5	F6
% practical yield	99.22	99.61	99.70	99.64	99.35	99.67
Bulk density (gm/cm)	0.75	0.73	0.75	0.73	0.70	0.69
Tapped density (gm/cm)	0.81	0.80	0.82	0.82	0.77	0.77
Carr's index (%)	7.40	8.75	8.53	10.97	9.09	10.38
Hausner' ratio	1.08	1.09	1.09	1.03	1.05	1.11
Drug content (%)	99.01	99.11	98.43	99.00	99.21	99.03
Angle of repose (Degree)	24.07	23.22	22.76	15.32	12.05	11.89

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