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Research Article

SOLID DISPERSION-A COMPARATIVE STUDY ON THE DISSOLUTION RATE OF ACECLOFENAC

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ABSTRACT

Aceclofenac, an analgesic and anti- inflammatory agent used in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results in poor bioavailability after oral administration.

Objective: The objective of the present study was to prepare solid dispersions of aceclofenac using PEG-6000, mannitol and β- cyclodextrine to increase its aqueous solubility.

Methodology: Aceclofenac solid dispersions were prepared in 1:1, 1:2, 1:3, 1:4 w/w ratios of the drug to polymer, using physical mixture and solvent evaporation methods. Prepared aceclofenac solid dispersions were evaluated for particle size, % practical yield, % drug content, and *in-vitro* dissolution studies.

Results: The highest dissolution was exhibited by solid dispersions containing 1:4w/w ratio of drug: PEG-6000, prepared by solvent evaporation method. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier, and due to reduction in drug crystallinity.

Keywords: Aceclofenac, Solid dispersions, Solubility, In-vitro dissolution, Stability.

INTRODUCTION

Drug solubility enhancement is one of the most important challenges in the field of pharmaceutics. Nearly 40% of all new pharmacologically potent molecules show poor aqueous solubility, leading to their low effective concentration in biofluids and therefore poor bioavailability. [1]

Many methods are available to improve dissolution rate, solubility characteristics, including salt

formation, micronization, and addition of solvent or surface active agents. Solid dispersions is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The concept of solid dispersions was introduced in 1961 by Sekiguchi and Obi,[2] in which the drug is dispersed in inert water - soluble carrier at solid state. In 1965, Tachibana and Nakamura described a new approach utilizing water- soluble polymers for the preparation of aqueous dispersions of β- carotene. [3] Mayersohn and Gibaldi applied the same approach to improve the solubility and dissolution characteristics of griseofulvin. [4]

The dispersion method allows the preparation of physically modified forms of the drug that are much more rapidly soluble in water than the pure compound. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone (PVP) and poly ethylene glycols are used as carriers for Solid dispersions. [5-8]

Aceclofenac (BCS Class IIdrug) comes under Non Steroidal Anti-Inflammatory Drugs and widely used as an analgesic. It is chemically designated as 2-[[2-[2-[(2, 6-dichlorophenyl) amino] phenyl]acetyl] oxy] acetic acid.

Solid dispersions of aceclofenac were formulated to overcome problems like gastric irritation and other side effects that are frequently experienced with NSAID drug therapy. Aceclofenac is practically insoluble in water leading to poor dissolution and variable bioavailability upon oral administration. [9-12]

The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Aceclofenac by preparing SDs with various water-soluble polymers such as PEG-6000, mannitol, β-cyclodextrin.

MATERIALS AND METHODS

Aceclofenac was obtained as gift sample from Ipca laboratories, Mumbai, India, PEG-6000,Mannitol and β- cyclodextrine were of IP grade. All other chemicals were of analytical grade.

Preparation of solid dispersions

Solid dispersions of aceclofenac were prepared with carriers (PEG-6000, mannitol and β- cyclodextrine) in1:1, 1:2, 1:3 and 1:4 weight ratios by physical mixtures and solvent evaporation methods.

a) Preparation of physical mixture

The physical mixture of aceclofenac were prepared with carriers (PEG-6000 or mannitol or β- cyclodextrine) by mixing pulverized powders of drugs and various carriers with the help of a spatula.[13]

b) Preparation by Solvent evaporation method

A weighed quantity of carriers (PEG-6000 or mannitol or β-cyclodextrine) and aceclofenac was dissolved in ethanol and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a 250µm sieve before packing in an airtight container. [14]

Characterization

Particle size analysis

The prepared formulations were evaluated for particle size distribution and average diameter by optical microcopy. Small quantity of the formulation was dispersed using liquid paraffin and spread into a thin film on a microscopic slide. Particles were observed under high power (45X) and the size of randomly selected 100 particles from different locations were measured and average size of the particles was calculated.[15]

% Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation. [16]

$$PY\ (\%) = \frac{\text{Practical Mass (solid dispersion)}}{\text{Theoritical Mass (Drug + Carrier)}} \times 100$$

Drug content

Solid dispersions equivalent to 10 mg of Aceclofenac were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 275 nm by UV spectrophotometer. [17] The Actual Drug Content was calculated using the following equation.

$$\%\ \text{Drug content} = \frac{M_{act}}{M_{ss}} \times 100$$

M_{act} = actual amount of drug in solid dispersion.
M_{ss} = theoretical amount of drug in solid dispersion.

Table 1: Formulation Plan of Aceclofenac Solid Dispersions

S. No.	Method	Formulation	Composition Drug: Polymer
1	Physical mixture	P-1	Aceclofenac + PEG-6000 1:1
2		P-2	Aceclofenac + PEG-6000 1:2
3		P-3	Aceclofenac + PEG-6000 1:3
4		P-4	Aceclofenac + PEG-6000 1:4
5		M-1	Aceclofenac + Mannitol 1:1
6		M-2	Aceclofenac + Mannitol 1:2
7		M-3	Aceclofenac + Mannitol 1:3
8		M-4	Aceclofenac + Mannitol 1:4
9		B-1	Aceclofenac+Beta- cyclodextrine 1:1
10		B-2	Aceclofenac+Beta-cyclodextrine 1:2
11		B-3	Aceclofenac+Beta-cyclodextrine 1:3
12		B-4	Aceclofenac+Beta-cyclodextrine 1:4
13		PS-1	Aceclofenac + PEG-6000 1:1
14	Solvent	PS-2	Aceclofenac + PEG-6000 1:2
15	evaporation	PS-3	Aceclofenac + PEG-6000 1:3
16	method	PS-4	Aceclofenac + PEG-6000 1:4
17		MS-1	Aceclofenac + Mannitol 1:1
18		MS-2	Aceclofenac + Mannitol 1:2
19		MS-3	Aceclofenac + Mannitol 1:3
20		MS-4	Aceclofenac + Mannitol 1:4
21		BS-1	AceclofenacBeta- cyclodextrine 1:1
22		BS-2	Aceclofenac+Beta-cyclodextrine 1:2
23		BS-3	Aceclofenac+Beta-cyclodextrine 1:3
24		BS-4	Aceclofenac+Beta-cyclodextrine 1:4

Table 2: Characterization of prepared solid dispersions:

Method	Carrier	Drug:Carrier	Drug content %yield Avg particle (µg/ml) Size(µm)
Physical mixture	PEG-6000	1:1	90.54 94.25 62
	PEG-6000	1:4	93.24 95.52 58
	Mannitol	1:1	82.37 96.25 73
	Mannitol	1:4	84.35 94.26 65
	β- cyclodextrine	1:1	89.36 95.79 70
	β- cyclodextrine	1:4	91.75 95.42 74
Solvent evaporation method	PEG-6000	1:1	99.57 96.24 59
	PEG-6000	1:4	96.12 98.53 54
	Mannitol	1:1	84.65 96.36 60
	Mannitol	1:4	86.86 95.41 62
	β- cyclodextrine	1:1	92.58 97.22 65
	β- cyclodextrine	1:4	94.46 96.53 70

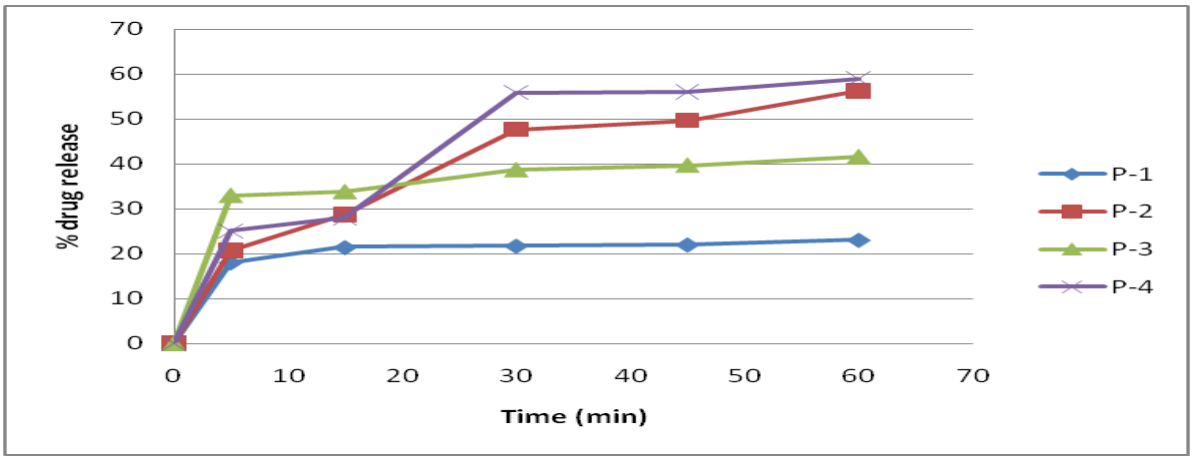

Fig. 1: it shows Dissolution Profile of Accecloenac with PEG-6000 Physical mixture

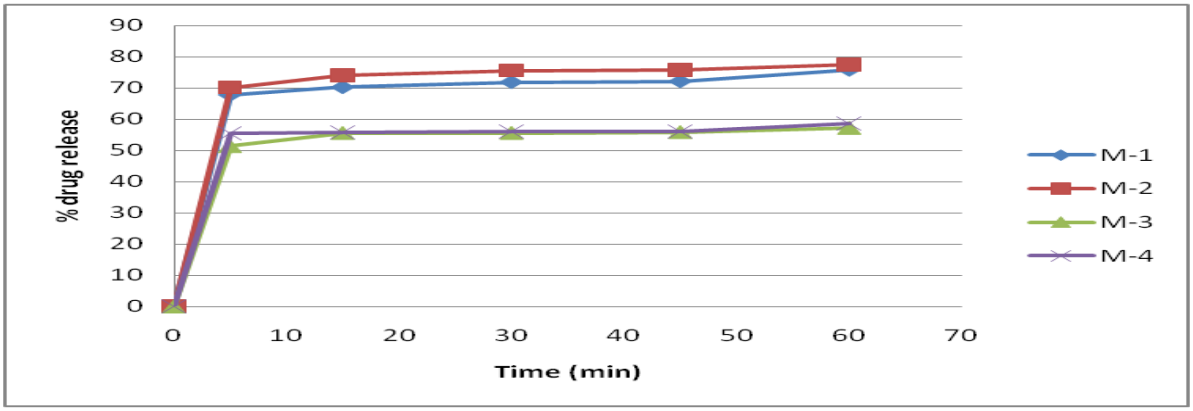

Fig. 2: It shows Dissolution Profile of Aceclofenac with Mannitol Physical mixture

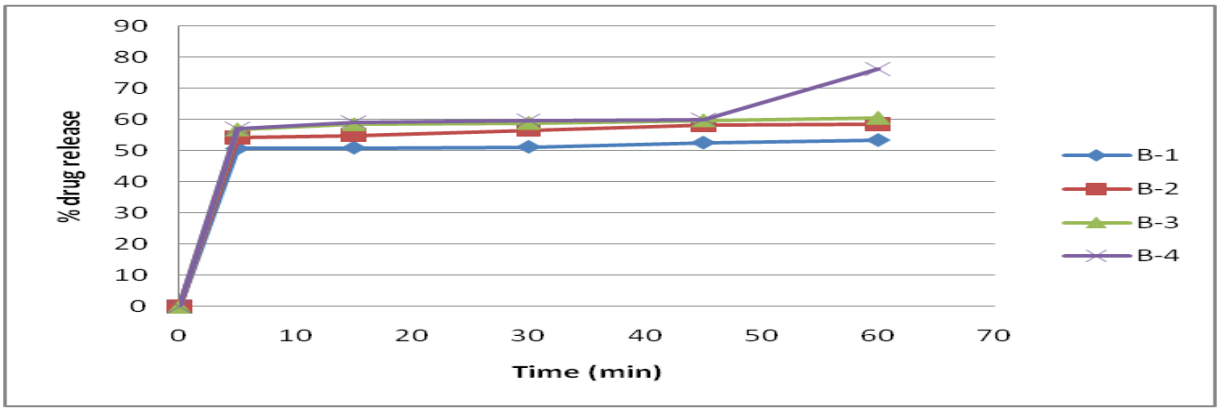

Fig. 3: it shows Dissolution Profile of Accecloenac with β-cyclodextrine Physical mixture

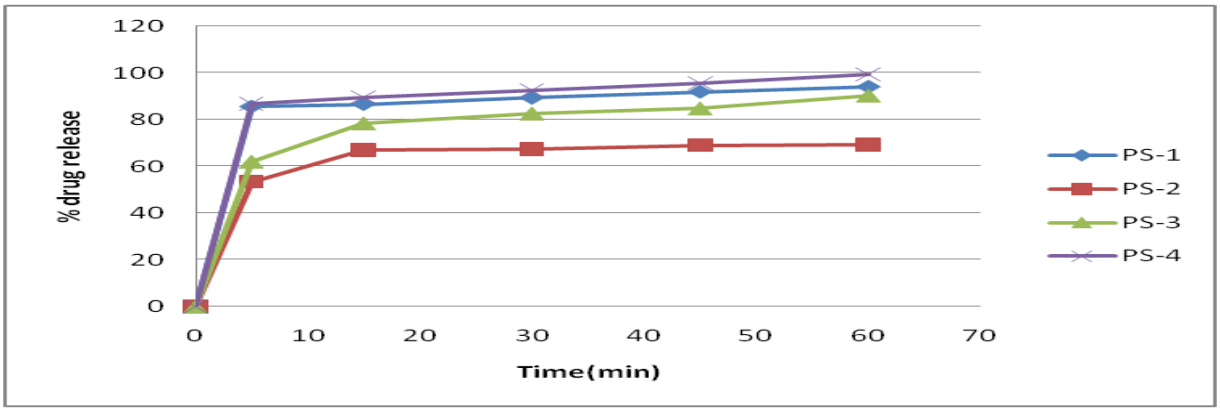

Fig. 4: It shows Dissolution Profile of Aceclofenac solid dispersion with PEG-6000 by solvent Evaporation.

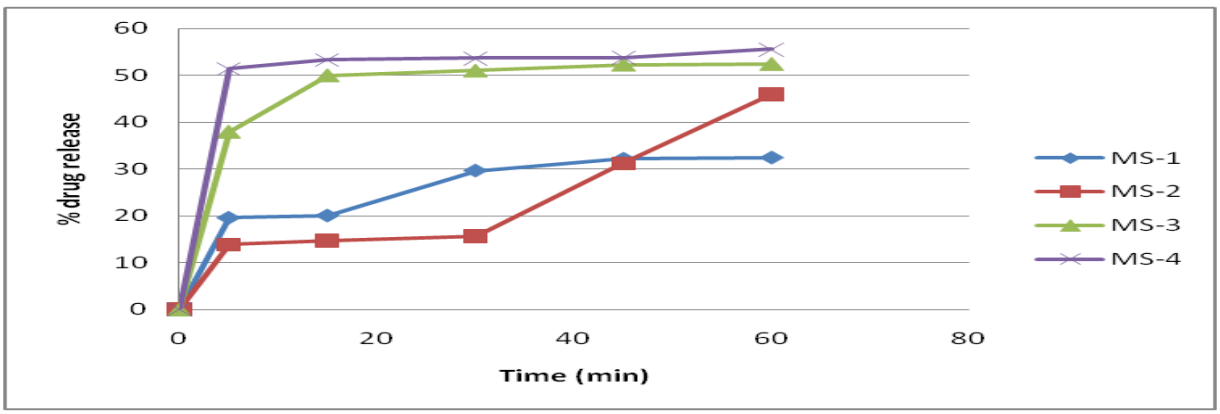

Fig. 5: It shows Dissolution profile of Aceclofenac solid Dispersions with Mannitol by Solvent Evaporation.

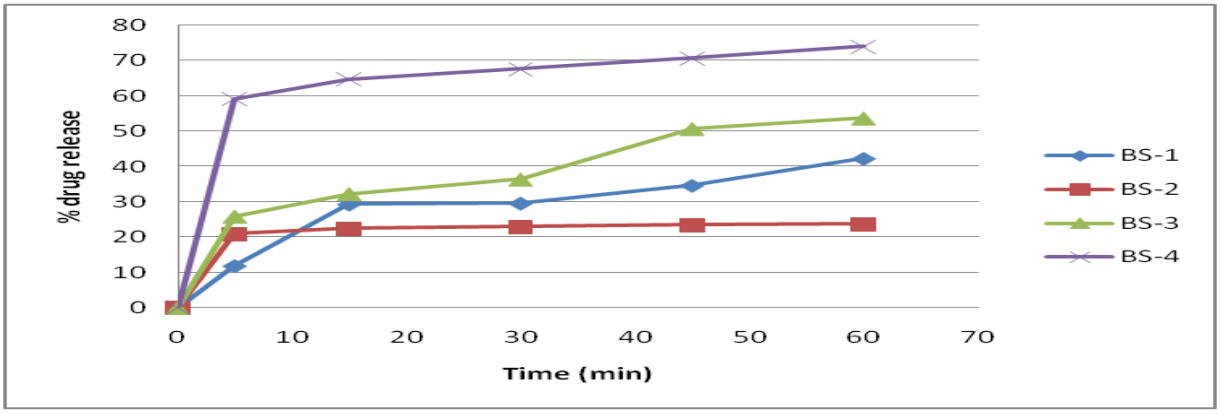

Fig. 6: It shows Dissolution profile of Aceclofenac solid dispersions with B-cyclodextrin by solvent evaporation.

In Vitro Release Studies

In vitro release studies were carried out using basket type USP XXII dissolution test apparatus.[18]Release studies were carried separately for physical mixtures and Solid dispersions for 1hr in 900 ml of phosphate buffer, pH 6.8, with a stirring speed of 50 rpm at a temperature of 37±0.5 °C. 5 ml aliquots ofdissolution medium were withdrawn at an interval of 5,15,30,45 and 60 minutes for one-hour study. Absorbance of the suitably diluted solutions was measured at 275 nm using Shimadzu-1700 UV- visible spectrophotometer. The drug content was calculated using regression equation.The dissolution experiments were conducted in triplicate.[19,20] The results were depicted in the figures.

In situ rat gut technique

Comparison of extent of intestinal absorption of drug from a selected solid dispersion, which gave good in vitro release performance and pure drug, was performed using in situ rat gut technique. It was carried out by introducing a suspension of selected solid dispersion containing 100mg of drug and 100mg of pure drug in 10ml of sodium CMC into the rat intestine. Samples of 0.1ml were withdrawn at pre-determined intervals up to 8 hours [25]. The collected samples were analyzed spectrophotometrically at 275nm. The studies were performed in three trials and mean values were taken. The results obtained for pure drug and the solid dispersion were compared.

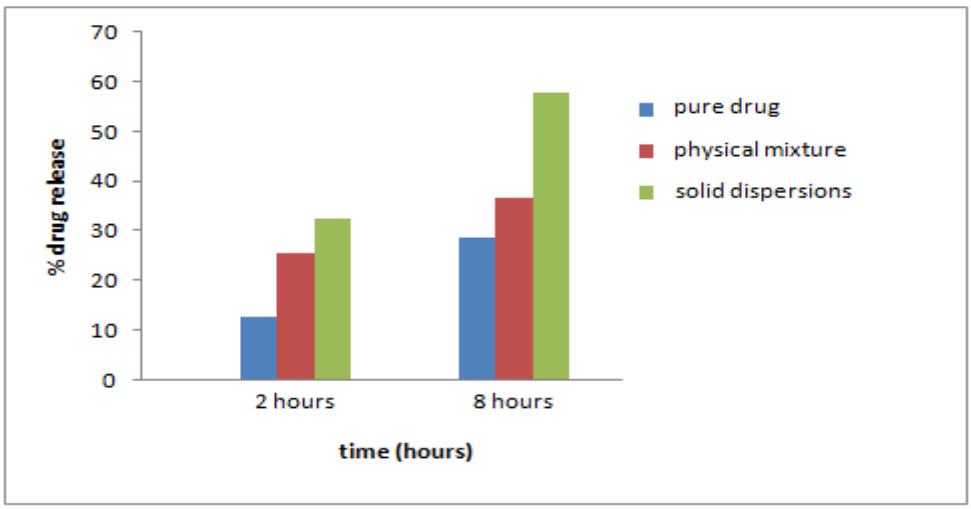

Fig. 7: It shows Dissolution Profile of Solid Dispersions in Simulated Intestinal fluid at 8 hours

RESULTS AND DISCUSSION

Aceclofenac solid dispersions was prepared by using carriers like PEG-6000, mannitol, β- cyclodextrine. In the present work, 24formulations were prepared and their complete composition is shown in Table 1. All the solid dispersions prepared were found to be fine and free flowing powders. The results of % practical yield studies are shown in Table -2. Percent practical yield for all formulations of solid dispersions found to be 94.02-98.53%. Maximum yield was found to be 98.53 % in (PS-4). Actual drug content of all formulations are shown in Table -2.The drug content of the prepared solid dispersions was found to be in the range of 82.37- 99.57 %. Maximum % drug content was found in the formulation PS-1. The particle size of solid dispersions with PEG-6000, mannitol and β- cyclodextrine ranged from 10-100µm and the average diameter was found out to be in the range of 50 to 80µm.

Dissolution profile

The in vitro release studies of different batches of solid dispersions are shown in Table 3,4,5,6,7 and 8.the physical mixtures and solid dispersions with all drug: carrier ratios exhibited faster dissolution rates than that of pure aceclofenac at all time points. The dissolution rate of solid dispersions was faster as compared to their

corresponding physical mixtures at all the time intervals. With the increase in the proportion of carrier, rate of dissolution of solid dispersions also increases. The solid dispersions with 1:4(PS-4) drug carrier ratio exhibited higher dissolution rate than others with lower carrier content (1:1, 1:2 and 1:3). The order of dissolution shown by the solid dispersions was found to be 1:4 > 1:3 > 1:2 > 1:1.

Formulations containing PEG-6000 showed maximum dissolution rate in comparison to formulation containing mannitol and β-cyclodextrine which is in agreement with previous study on griseofulvin with PEG-6000 as carrier. [5] The present study revealed that 1:4 ratio of aceclofenac-PEG-6000 showed maximum drug release. Among all the solid dispersions, Aceclofenac-PEG-6000 (PS-4) showed the maximum dissolution in phosphate buffer pH 6.8 (99.35%). Due to the hydrophilic nature, PEG-6000 enhances the wetting of hydrophobic drugs in solid dispersions. Since, wetting is prerequisite for dissolution, this effect contributed to the faster drug release as reported by Simonelliet al. [21] and Leuner and Dressman. [7]

Another mechanism for this preferential enhancement of dissolution rate from solid dispersions may be due to the formation of a eutectic mixture, or a solid solution. Such a solid solution cannot result from just physically mixing the two components and hence, physical mixture fails to increase the dissolution rate. [22]Enhancement of dissolution rate from solid dispersions can also be attributed to the amorphization of drug and the particle size reduction. The particle size reduction results in increased surface area available and thus, acceleration of dissolution. [23] In solid dispersions, the presence of the water soluble carrier results in improvement of wetting characteristics of poorly soluble drug like aceclofenac. [24]Studies on Insitu rat-gut technique revealed that the extent of intestinal absorption was more in solid dispersions with PEG-6000 (57.7%) as carrier in comparison to the pure drug (28.5%) and physical mixture (36.4%).

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