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REVIEW ARTICLE

PHARMACEUTICS

ENHANCEMENT OF DISSOLUTION RATE STUDIES ON SOLID DISPERSION OF ACECLOFENAC

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ABSTRACT

Aceclofenac is a Non- Steroidal Anti Inflammatory drug indicated for the relief of pain and inflammation, associated with rheumatoid arthritis, osteo arthritis, ankylosing, spondylitis. The percentage of dissolution rate of drug released from pure Aceclofenac was obtained 26.48% in 180min. The aim of the study was to enhance the dissolution rate on solid dispersion of Aceclofenac by using PEG6000 as carrier in three different ratios such as ACF:PEG6000-1:1, 1:2 and 1:4 by fusion method or melting method. The percentage of drug release of Aceclofenac from solid dispersions ACF:PEG6000-1:1,1:2 and 1:4 was 59.65%,84.75%,98.34% respectively in 180min. Aceclofenac from solid dispersions due to enhancing effect of PEG6000.

KEYWORDS

Aceclofenac, Solid – dispersion, solubility enhancement

INTRODUCTION

Solid – dispersion technology can be used to improve the invitro and invivo dissolution properties of slightly water soluble drugs and to control the dissolution rate of fully water soluble drugs. Solid dispersion systems have been considered over the last 20 years as a means of increasing the solubility dissolution and absorption of poorly water soluble drugs. The effect of the particle size of the drug on their dissolution rates and biological availability was reviewed comprehensively by Fincher. For

drugs whose GI absorption is rate limited by dissolution reduction of the particle size generally increases the rate of absorption and or total bioavailability. This commonly occurs for drugs with poor water solubility. For example the therapeutic dose of Griseofulvin was reduced to 50% by micronization and is also produced a more constant and reliable blood level. The commercial dose of Spironolactone was also decreased to half by just a slight reduction to particle size. Such enhancement of drug absorption could further be increased several fold if a micronized product was used.

Reduction of particle size can be easily and directly accomplished by the first four methods and the resultant fine particles may not produce the expected faster dissolution and absorption. This primarily text is possible when aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger vanderwaals attraction between nonpolar molecules. Another inherent disadvantage of these pure fine powders of poorly soluble drugs is their poor wettability in water. The significance of the solid dispersion technique was strengthened by the demonstration of Chiou and Riegelman of the fast and almost complete absorption of the insoluble Griseofulvin in man and dogs while the commercial micronized Griseofulvin was incompletely absorbed (30 – 60 %). They used polyethylene glycol6000 as a dispersion carrier. The main advantages of using water soluble polymers as carriers are their no toxicity and general applicability to most drugs.

The significance of the solid dispersion technique was strengthened by the demonstration of Chiou and Riegelman of the fast and almost complete absorption of the insoluble Griseofulvin in man and dogs while the commercial micronized Griseofulvin was incompletely absorbed (30 – 60 %). They used polyethylene glycol 6000 as a dispersion carrier. The main advantages of using water – soluble polymers as carriers are their no toxicity and general applicability to most drugs.

Methods employed to improve dissolution rate of drugs

1. solubility enhancement:

a. Buffering the pH of the diffusion layer. Eg. Buffered aspirin tablets.
b. Use of salts of weak acids and weak bases. Eg. Sodium and potassium salts of penicillin.
c. Use of solvates and hydrates. Eg. Ampicillin trihydrate.
d. Use of selected polymeric forms. Eg. Digoxin – hydroquinone
e. Prodrug approach Eg. 2, 2-disodium phosphate ester of methasone.

2. increasing the surface area:

a. Micronization or particle size reduction.
b. Use of surfactants (to increase surface area by proper wetting).

c. Solid dispersions using highly water soluble carriers.

methods of preparation of solid dispersion

methods of preparation: basically there are three methods

1. Melting method.
2. Solvent method.
3. Melting-Solvent method.

1. Melting method.

Sekiguchi and obi first proposed the melting or fusion method, to prepare fast release solid dispersion dosage forms. In this method, the physical mixture of drug and water-soluble carrier is heated directly until it is melted. The melted mixture is then cooled and solidified in an ice bath under vigorous stirring. The final mass is crushed, pulverized and sieved. The dispersion can also be cooled through the process of spray congealing using spray-drying equipment. The melted material is sprayed onto cold metal surfaces, which forms pellets of the dispersion. This does not require grinding and therefore no alteration of the crystal modification of the drug occurs. In addition, this dispersion can be cooled at a controlled rate. Fusion system can also be done by a slight modification. Here the homogenous melt was poured in the form of a thin layer onto a ferrite plate or stainless steel plate and cooled by flowing air or water onto the opposite side of the plate. The solidified masses were stored in the desiccators at ambient temperature.

2. Solvent evaporation method.

This method involves dissolving the drug and carrier in a suitable organic solvent, followed by evaporation of the solvent to form solid dispersion. The mass was then stored in a desiccators, pulverized and sieved.

Solvent removal is accomplished by various means. The most common approach is the application of reduced pressure at a fixed temperature to evaporate the organic solvent. Temperatures of 125°C for 25 minutes. 115°C for one hour, -5°C and reduced pressure followed by drying for 12 hours in vacuum has been used. Spray drying is another approach by which solvent removal can be accomplished and it is probably the fastest way of removing solvent. The freeze-drying technique is also employed to prepare solid dispersions by removal of aqueous solutions.

3. ***Melting-solvent method:***

The drug is first dissolved in a suitable liquid solvent and solution is then incorporated directly into a melt of PEG obtained below 70 °C without removing the liquid solvent. It was shown that 5 – 10 % w/w of liquid-components would be incorporated into PEG 6000 without significant loss of its solid property.

MATERIALS AND METHODS

Materials

1. Drug – Aceclofenac.
2. Polyethylene glycol 6000.
3. Methanol.
4. Potassium dihydrogen phosphate.
5. Sodium hydroxide.
6. Distilled water.

Instruments

1. Electronic single pan balance.
2. Water bath.
3. Desiccators.
4. Digital tablet dissolution test apparatus – LAB INDIA DISSO 2000
5. UV spectrophotometer – shimadzu – UV - 1700.
6. pH – meter.

Preparation of reagents

preparation of phosphate buffer solution - ph 7.4 [37]

13.61 grams of potassium dihydrogen phosphate and 3.128 grams of sodium

hydroxide were dissolved in 2 liters of distilled water.

Preparation of aceclofenac solid dispersion by fusion method.

Aceclofenac with polyethylene glycol 6000 (PEG-6000) solid dispersions in different proportions 1:1 (1g of drug: 1 g of polymer) 1:2 (1g of drug: 2 g of polymer) and 1:4 (1g of drug: 4 g of polymer) were prepared by fusion method.

Weighed quantities of aceclofenac and PEG 6000 in three different proportions were mixed respectively in a clean, dried china dish. The china dish was placed on a water bath and heated.

The drug carrier mixture was melted by increasing the temperature with constant stirring. The stirring was continued until a homogenous mass was resulted. Then the melt was poured on a clean, dried tile and cooled in room temperature. The resulting solidified mass dried in desiccators. The dried material was pulverized and passed through sieve.no.80. The product was stored in an tight container and kept in desiccators for further studies

Preparation of standard curve.

An accurately weighed quantity of 100 mg of Aceclofenac was transferred to clean and dried 100 ml standard flasks. It is dissolved in small quantity of methanol and made up to 100 ml with the same.

From this primary stock solution, 10 ml was pipette out, transferred into a separate standard flask and diluted to 100 ml with phosphate buffer pH – 7.4.

From this secondary stock solution, 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml, 9ml, and 10ml were pipette out and diluted to 100ml with phosphate buffer pH 7.4 to give a concentration of 1,2,3,4,5,6,7,8,9, and 10 µ/ml. the absorbance of the resulting solutions were measured at 275nm using the buffer solution as blank by UV-spectrophotometer.

A calibration curve was drawn by plotting absorbance and concentration of drug. This standard curve was used to estimate the concentration of the drug released from the solid dispersion formulations of aceclofenac.

STANDARD CURVE
Table

S.No	Concentration (µg/ml)	Absorbance (275 nm)
1	1	0.025
2	2	0.051
3	3	0.074
4	4	0.100
5	5	0.126
6	6	0.150
7	7	0.177
8	8	0.202
9	9	0.228
10	10	0.252

RESULTS AND DISCUSSION

Aceclofenac is a potent non steroidal anti-inflammatory drug but poorly water soluble in nature. So, an opportunity was taken to enhance its aqueous solubility and thereby bioavailability by preparing it as solid dispersion.

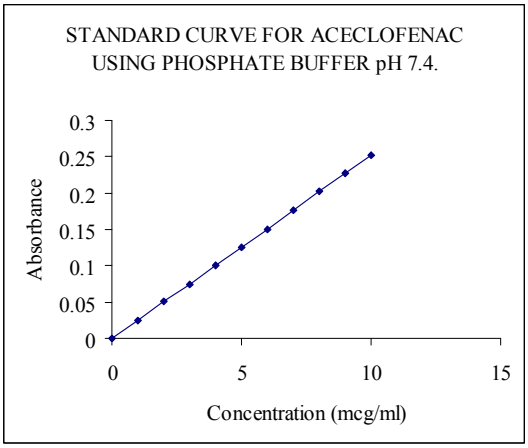
Preparation of solid dispersion

Solid dispersion of aceclofenac with polyethylene glycol 6000 was prepared in 3 different ratios (ACF: PEG 6000 – 1:1, ACF: PEG 6000 – 1:2, and ACF: PEG 6000 – 1:4) by fusion method. The formulations were found to be fine, free flowing and easy to prepare.

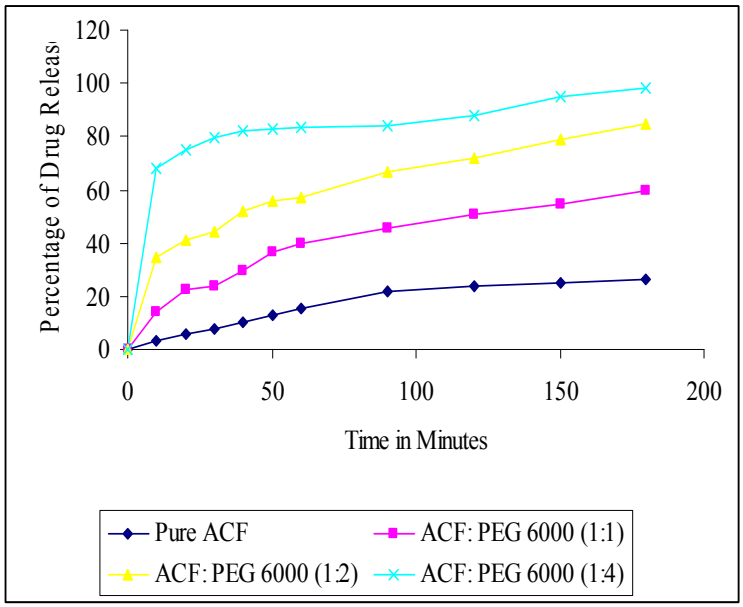
Standard curve

The standard curve relating the absorbance and concentration of aceclofenac (Table No-2, Figure No-1) was used to estimate the concentration of aceclofenac released from the solid dispersion formulations and from the marketed samples of aceclofenac.

Standard curve of aceclofenac



COMPARITIVE ASSESSMENT OF THE DISSOLUTION RATE PATTERN OF ACECLOFENAC PURE DRUG AND FORMULATIONS



COMPARITIVE ASSESSMENT OF THE DISSOLUTION RATE PATTERN OF ACECLOFENAC PURE DRUG AND FORMULATIONS ACF: PEG 6000 (1:1), ACF: PEG 6000 (1:2) & ACF: PEG 6000

S.No	Time in mins	Percentage of Drug Release (%)			
		Pure drug	Formulations (Drug : Polymer)		
			1:1	1:2	1:4
1	10	3.50	14.17	34.71	68.33
2	20	5.46	22.20	40.86	75.22
3	30	7.60	23.67	44.43	79.83
4	40	10.45	29.70	52.12	81.97
5	50	12.94	36.80	56.05	82.91
6	60	15.26	39.87	57.13	83.13
7	90	21.67	45.27	66.94	84.10
8	120	23.99	50.75	71.59	87.78
9	150	24.88	54.43	79.10	94.77
10	180	26.48	59.65	84.75	98.34

CONCLUSION

- Solid dispersion of aceclofenac was prepared by fusion method using carrier polyethylene glycol 6000 in 3 different ratios (ACF: PEG 6000 – 1:1, ACF: PEG 6000 – 1:2, and ACF: PEG 6000 – 1:4) (drug : polymer ratio)
- The formulations are fine, free flowing and easy to prepare.
- Drug content estimation revealed that the percentage of aceclofenac in all the solid dispersion formulations was between 98% to 100%. The shows that aceclofenac was uniformly dispersed in all the formulations and there was no wastage during the preparation.
- The dissolution studies showed that the carrier PEG 6000 used in the formulation enhanced the invitro dissolution of aceclofenac from the solid dispersion formulation than that of the pure drug and formulations.
- Out of the three formulations prepared, the formulation ACF: PEG 6000 – 1:4 showed better release of aceclofenac than the formulation of ACF: PEG 6000 – 1:2, and ACF: PEG 6000 – 1:1. It indicates that an increase in the polymer concentration may increase the dissolution rate.

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