Original Article

DESIGN AND EVALUATION OF FAST DISPERSIBLE ACECLOFENAC TABLETS

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Abstract

Oral route of administration have wide acceptance up to 50-60% to total drug forms. Fast disintegrating drug delivery system has number of advantage such as faster onset of action, attractive elegance, ease of administration, manufacturing, storage and transport. In this study, an attempt has been made to formulate fast disintegrating tablets of Aceclofenac, an analgesic and anti-inflammatory drug in view of enhancing bioavailability in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondilytis. The tablets were formulated by preparing an inclusion complex with Beta Cyclodextrin and molecular dispersion with Polyethylene glycol 6000. The precompression parameters were characterized for flow properties and prepared formulations were evaluated for physico-chemical parameters, *in vivo*, bioequivalence and pharmacokinetic studies. All four formulations possessed good disintegration properties with total disintegration time of 60 to 240 seconds. The effects of different polymers Beta Cyclodextrin, Polyethylene glycol 6000 and process variables on drug release profile and disintegration property were evaluated and results revealed the better drug release with 2.5% of Polyethylene glycol 6000. Hence, it is evident from this study that fast dispersible tablets could be a promising delivery system for Aceclofenac delivery with good mouth feel and improved drug availability with better patient compliance.

Keywords: Aceclofenac, Polymers, Inclusion Complex, Molecular Dispersion.

Introduction

Aceclofenac,(2-[2-[2-(2,6-dichlorophenyl) aminophenyl] acetyl] oxyacetic acid); a non steroidal anti-inflammatory drug (NSAID) is used for posttraumatic pain and rheumatoid arthritis[1] and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, resulted in a greater compliance with treatment[2]. Aceclofenac is practically insoluble in water. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. This is influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

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Out of all the orally administered dosage forms, tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of change of various physiological functions associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy. The paediatrics and geriatrics patients are of particular concern. To overcome this, dispersible tablets and fast-disintegrating tablets have been developed. Most commonly used methods to prepare these tablets include; Freeze drying / Lyophilization, Tablet molding and Direct-compression methods.[3-9]

Materials and methods

Aceclofenac (Aeon Therapeutics. Chennai, India), Beta-Cyclodextrin LR (S.D. Fine Chem Ltd., Mumbai), Polyethylene glycol (S.D. Fine Chem Ltd., Mumbai) were obtained. Other materials and solvents used were of analytical grade.

Preparation of tablets

Granulation with Beta-cyclodextrin[10]

Inclusion complexes were prepared by adding aceclofenac solution to aqueous solution of beta cyclodextrin. The above suspension was agitated for 1 hour at 50°C and filtered. Then water was removed by evaporation and the complex dried. The dried complex was then passed through sieve no 60. This complex was mixed with other excipients and granulated using starch paste.

Granulation with Polyethylene glycol 6000

Molecular dispersions were prepared by adding aceclofenac to molten polyethylene glycol 6000. The above mixed solidified mass was then passed through sieve no. 60. The dispersion was granulated with starch paste along with other excipients.

The granules were dried mixed with lubricants and punched using cadmach tableting machine with 7mm concave punch set to a hardness around 4kg/cm^2. The various formulations obtained are tabulated (Table 1).

Table 1: Formula used in the preparation of dispersible tablets

Ingredients (%)	F I	F II	F III	F IV
Aceclofenac	20	20	20	20
Micro crystalline cellulose	10	10	10	10
Lactose q.s	100	100	100	100
Starch (soluble)	10	10	10	10
Mannitol	13	13	13	13
Starch paste	5	5	5	5
Beta-cyclodextrin (Drug:Bcd molar ratio)	40 (1:1)	24.6 (2:1)	-	-
Polyethylene glycol 6000	-	-	5	2.5
Magnesium stearate	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5
Colloidal silicon dioxide	0.5	0.5	0.5	0.5

Evaluation of dispersible tablets

Tablets were evaluated for weight variation, hardness, friability, thickness, disintegration time, wetting time, stability and *in vivo* bioavailability (Table 2).[11] Twenty tablets were weighed and individual weight was compared with the average weight to access weight variation of tablets. Hardness and Friability were tested using Pfizer hardness tester and Roche friabilator respectively. Thickness of tablet was determined using dial calliper. Disintegration time was observed with USP tablet disintegration test apparatus (ED2L, Electrolab, India) using 900ml of distilled water without disk at room temperature (Table 3). To measure wetting time of tablets a piece of tissue paper was folded twice and placed in a small petri dish containing sufficient water. A tablet was kept on the paper and time for complete wetting of tablet was measured[12].

Table 2

Physicochemical Parameters for Formulations

Formulation	Hardness (Kg/cm^3)	Friability (%)	Thickness (mm)	Drug content (%)	Disintegration time (sec)
F I	4.96 ± 0.56	0.68 ± 0.13	6.61 ± 0.04	97.68 ± 2.36	242 ± 2.14
F II	4.86 ± 0.49	0.39 ± 0.05	6.06 ± 0.04	97.30 ± 2.64	60 ± 2.12
F III	4.60 ± 0.49	0.08 ± 0.04	5.53 ± 0.05	98.26 ± 2.45	180 ± 1.38
F IV	4.53 ± 0.58	0.22 ± 0.17	5.53 ± 0.05	96.14 ± 2.12	124 ± 2.01

Table 3: Disintegration time of Formulations F I – FVIII

Formulation	DT (secs)
F I	242
F II	60
F III	180
F IV	124

DT = Disintegration time

Drug Content

Twenty tablets of each formulation were weighed and powdered. The powder equivalent to 50mg of Aceclofenac was dissolved in 100ml of pH 7.4 phosphate buffer. 2mL of the solution was diluted to 100 mL with the buffer solution and the absorbance was measured spectrometrically at 274nm[12].

Dissolution Study

In vitro release of Aceclofenac from formulated tablets was monitored using 900mL of simulated intestinal fluid (USP phosphate buffer solution, pH 7.4) at 37±0.5°C and 50rpm using programmable dissolution tester (paddle type, TDT-08L, Electro Lab, India). Aliquots were withdrawn at ten minute interval and were replenished immediately with the same volume of

buffer medium. After suitable dilution the aliquots were assayed spectrometrically at 274nm (Table 4).

Table 4: In-vitro dissolution profile of Formulation FI - FIV

ST	Percentage drug released			
(min)	FI	FII	FIII	FIV
10	27.62	45.56	51.80	75.97
20	41.53	57.65	63.14	83.80
30	61.26	63.64	73.74	89.04
40	67.89	76.75	82.06	91.13
50	80.08	86.71	88.56	93.51
60	88.65	92.59	92.78	94.95

ST = Sampling time

***In vivo* Bioequivalence Study**

Formulated Aceclofenac tablets and marketed formulation were evaluated for their bioavailability using male rabbits (New Zealand strain) of 1.5kg. Animals were housed individually under standard conditions and were fasted overnight and allowed to free access of water. Six rabbits were divided into two groups each. Formulations were administered to rabbits by gastric intubation method and 2 mL of blood samples were withdrawn from marginal ear vein of rabbits at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 9 hours. The plasma obtained after centrifugation was estimated for its Aceclofenac concentration by high performance liquid chromatography HPLC using C_{18}ODS column.

Stability Studies

The stability of selected formulation was tested according to ICHG - International Conference on Harmonization Guidelines. The formulations were stored in accelerated test conditions (40°C ± 2°C, 75 ± 5% RH) in a stability chamber and the sample tablets were analyzed at 0, 15 and 30th day for physical characters and assay was performed followed by disintegration and dissolution test (Table 5).

Statistical Analysis

Each tablet formulation was reared in duplicate and each analysis was duplicated. Each formulation variables on disintegration time and release parameters were tested for significance by using analysis of variance (ANOVA). Difference was considered significant when $P<0.05$.

Results and discussion

The flow properties of the powder blend influences the uniformity of weight of tablet and drug content, the flow of the powder mixture was analyzed before compression into tablets. The bulk density of the blend, angle of repose, Carr's index and compressibility index was ≤ 0.664 g/mL, ≤ 29°C and ≤ 14% respectively and also the values indicated that the powder blend had good flow ability. The tablets produced were of uniform weight with acceptable weight variation of ≤ 4.27%. Hardness of 4.53 – 4.96 and friability loss of 0.08 – 0.68 indicated that tablets had a good mechanical resistance. Drug content was found to be higher than 96.14% and uniform coefficient of variation was 0.46 – 2.12% in all formulations. The most important parameter that needs to be optimized in the development of fast dispersible tablets is the disintegration time. In the present study, formulation II showed the least disintegration time of 60secs complying with the official requirements of < 3 mins for fast dispersible tablets (Table 3) depicts the change in disintegration time with respect to the concentration of beta-cyclodextrin added in the formulation. It was observed that the disintegration time of the tablets decreased from 242secs to 60secs with increase in level of drug:beta-cyclodextrin ratio. In case of tablets containing Polyethylene glycol 6000, decrease in disintegration time from 180 sec to 124 sec with decrement in its concentration was observed. Eventually the slow disintegration of the complex may be due to inclusion complex formed between aceclofenac and beta-cyclodextrin. Formulation I and III failed the uniformity of dispersion test this may be due to the presence of inclusion complex in the former formulation and the higher concentration of polyethylene glycol. Thus the present results suggest that the disintegration time may be decreased by using beta-cyclodextrin inclusion complex. The *in vitro* release profile also concluded that formulation IV showed a greater percentage of drug release among the four formulations (Fig 1). The *in-vivo* pharmacokinetic for formulation FIV was compared with the marketed formulation (Table 6). The C_{max} for FIV was found to be 174.39µg/mL, which is comparatively more than the C_{max} of the marketed sample (167.08µg/mL) and the T_{max} was 4 hr for both the test and marketed formulation.

Table 5: Stability study data of FIV

No. of days	Temp °C	RH %	Hardness (Kg/cm³)	Thickness (mm)	Drug Content (%)	Disintegration time (sec)	% Released at the end of 60min
0	40	75	4.56	5.43	96.13	125	93.41
15	40	75	4.53	5.46	96.61	125	94.51
30	40	75	4.56	5.43	96.28	130	94.59

F I= Formulation I

Table 6: *In vivo* pharmacokinetics of FIV and marketed tablet

Parameters	Test formulation (FIV)	Marketed formulation
c_{max} (µg/mL)	174.39	167.08
t_{max} (hr)	4	4
AUC (µg-hr/mL)	292.60	247.30
AUMC (µg-r*hr/mL)	511.90	324.00

F=Formulation

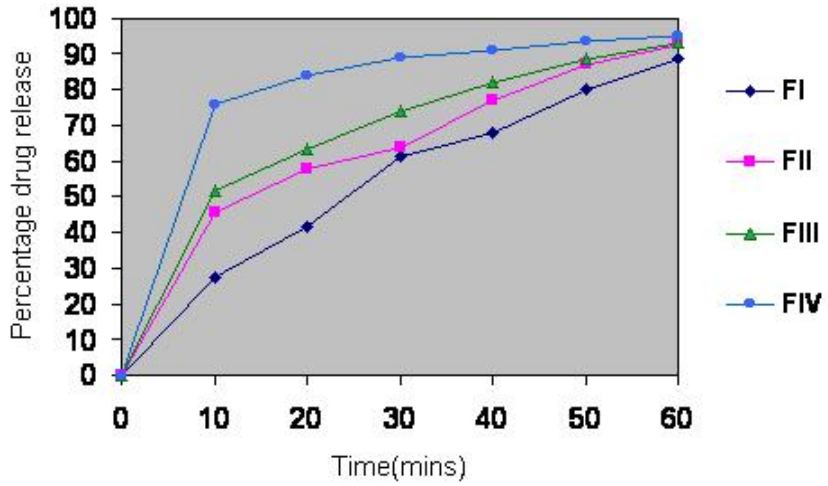

Fig 1: Cumulative % drug release of Formulation FI, FII, FIII, FIV

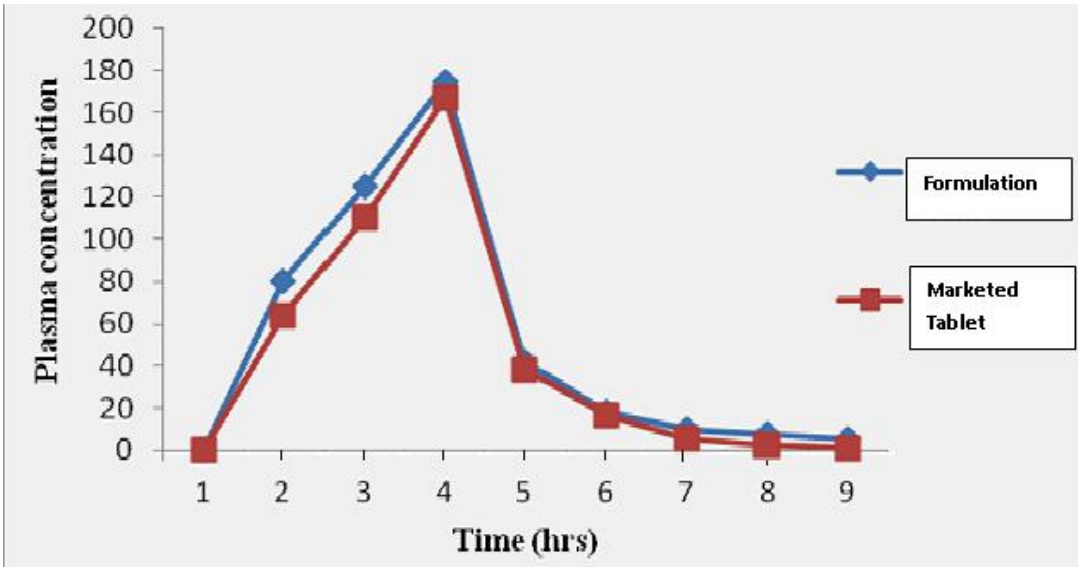

Fig 2: Showing comparative in-vivo drug release from prepared formulation of dispersible tablets of Aceclofenac and marketed tablet of Aceclofenac

Other parameters like AUC and AUMC were 292.6 and 511.9 respectively, comparatively higher than the market sample's value of 247.3 and 324.0 (Fig 2). The stability studies were conducted for FIV and there was no significant difference in thickness, hardness, disintegration time, drug content and dissolution profile.

Conclusion

Thus, dispersible tablets consisting of polymers Beta-Cyclodextrin and Polyethylene Glycol 6000 could be prepared by wet granulation method. The dispersible tablets exhibited good physicochemical properties. From the results formulation F-IV was found to be better than other three formulations. The results also proved that formulation F1V was better than the marketed sample in terms of disintegration, drug release and in-vivo studies. The Aceclofenac dispersible tablets are suitable for immediate release tablets.

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