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Pharmacokinetic Studies of A Poorly Soluble BCS Class II Non-Steroidal Anti-Inflammatory Drug in Oral Formulations

D.Chandra Sekhar Naik*[1], A.Bharathi2'
Research scholar, Krishna University, Machilipatnam[1],
KVSR Siddhartha College of Pharmaceutical Sciences[2], A.P, India.

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ABSTRACT: The current examination reports the different pharmacokinetic studies of Aceclofenac quick dissolving tablets utilizing with Ocimum gratissimum adhesive an original super disintegrate. The tablets were arranged utilizing unadulterated medication alongside regular super disintegrate by the immediate direct compression technique and its contrast and advertised detailing. The outcomes were contrasted and those of the streamlined equation, promoted brand and unadulterated medication. The P-values showed that mean plasma fixations were altogether unique among each of the three definitions managed (P<0.05, P<0.01). The optimized (F2) showed altogether higher plasma levels when contrasted with the unadulterated medication and stamped brand (P<0.01). The Cmax ,Tmax and AUC of Aceclofenac enhanced recipe (F2) were fundamentally higher (P<0.05) contrasted with the unadulterated medication and advertised definition. Moreover, the first-request generally speaking rate of elimination (Ke) of Aceclofenac enhanced formula (F2) was likewise essentially higher (P<0.05) contrasted with the unadulterated medication and its promoted plan. These outcomes recommended that tablets arranged by Aceclofenac quick dissolving tablets utilizing with Ocimum gratissimum adhesive an original super break down would give a more fast beginning of pharmacological impacts in contrast with the showcased definition and unadulterated medication.

Keywords: mucilage, immediate release tablets, Bioavailability, In vivo studies, Pharmacokinetic parameters

I.INTRODUCTION

Aceclofenac (AC), a phenyl acidic corrosive subsidiary, ({[2-(2,6-dichloroanilino)phenyl]acetyl}oxy) aceticacid, is a non-steroidal medication (NSAID) showed for the suggestive treatment of torment and irritation with a decreased incidental effect profile, particularly gastrointestinal occasions that are habitually knowledgeable about NSAID therapy[1] .AC gives off an impression of being especially very much endured among the NSAIDs, with a lower occurrence of gastrointestinal harming results. This proper decency profile results in a decreased withdrawal rate and consequently, additional consistence with treatment. AC is a BCS class II medication (low dissolvability, unreasonable penetrability) with a determined log segment coefficient worth of (log P) =2.170; its poor watery solvency and wet capacity give ascend to issues in drug definitions for oral conveyance which may furthermore prompt variable bioavailability. to conquer those downsides, developing the fluid dissolvability of AC is a significant objective [2].

The detailing and in vitro assessment of the aceclofenac with Ocimum gratissimum adhesive an original super break down and its tablet definition have been distributed before and depicted here momentarily [3,4]. The primary goal of this work was to lay out the capability of quick dissolving tablets as a bioavailability improvement strategy for ineffectively water-solvent medications. In this specific situation, different pharmacokinetic boundaries of the pre-arranged tablet detailing were contrasted and that of the promoted brand and unadulterated medication.

II.MATERIALS AND METHODS

Materials

Aceclofenac pure drug obtained from yarrow chemicals Mumbai. Mannitol, Sodium starch glycolate, Croscarmellose sodium was obtained from Yarrow chem. products, Mumbai. Microcrystalline cellulose was bought from Qualigens fine chemicals, Mumbai. Talc and magnesium stearate was obtained from Molychem, Mumbai.

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Preparation of Aceclofenac fast dissolving tablets

The tablets were ready by direct pressure technique utilizing 2^3factorial plan in which 3 free factors {superdisintegrants i.e.,Ocimum gratissimum (A), sodium starch glycolate(B), Croscarmellose Sodium (C)} and 2 ward variable (water retention and percent of medication dissoved in 5 min) were chosen. The piece of plan given in table no 1 For Ocimum gratissimum (A), the lower level i.e., 0 % fixation and upper level for example 5% focus. For sodium starch glycolate (B) and Croscarmellose Sodium (C), the lower level is zero focus and more elevated level i.e., 5% fixation. For consistency in molecule size, every fixing was gone through # 100 lattice measured screen prior to blending. Ocimum gratissimum, sodium starch glycolate, Croscarmellose Sodium, mannitol and microcrystalline cellulose were precisely gauged and blended utilizing mortar and pestle, and the additional to aceclofenac. At long last, powder and magnesium stearate were added to the powder blend [5].

Table1: Formulae of aceclofenac fast dissolving tablets employing Ocimum gratissimum mucilage.

Ingredients (mg/tablet)	pure	F2
Aceclofenac	100	100
Ocimum gratissumum	----	25
Sodium starch Glycolate	----	---
Croscarmellose Sodium	----	---
Mannitol	130	105
MCC	250	250
Talc	10	10
Magnesium Stearate	10	10
Total	**500**	**500**

Evaluation of Tablets: Both the breadth and thickness of the tablets have been concluded in millimeters utilizing the normal of three estimations, for each situation with the utilization of Vernier calipers. Hardness is estimated using the Monsanto hardness analyzer regarding kg/square cm. The typical hardness of ten tablets was taken to concentrate on the reproducibility. Ten medications from each group were presented to the friability test mechanical assembly for 100 revolutions, and the rate misfortune in weight was estimated against the underlying weight. Additionally, 20 tablets have been settled on at arbitrary from each figured out group to really look at the consistency of weight and the use of electronic dependability. The typical weight and most extreme rate deviation (positive and negative) not entirely set in stone. The breaking down test is completed utilizing the deterioration test contraption USP and refined water as the crumbling medium. One tablet was brought into each cylinder, and a circle was conveyed to each cylinder. The get together was changed into suspension in the measuring utencil containing 900 ml of refined water. The ideal opportunity for the crumbling of every one of the six tablets is referenced. For the examiner, 20 tablets were settled on at arbitrary from each group of figured out tablets and powdered. Ten mg of powder from each tablet cluster becomes weakened to 10 ml utilizing methanol and the following arrangement is shaken briefly with the utilization of a vortex blender. Every one of the examples were sifted utilizing Which man No.1 channel paper. From this, 0.5 ml of arrangement was removed and weakened to 10 ml with methanol. The groupings of AC in the filtrates have been chosen spectrophotometrically at 275 nm with respect to a reasonably built alignment bend of AC in methanol.

In–vitro dissolution studies

The in vitro Dissolution rate investigation of Aceclofenac quick dissolving tablets were performed utilizing 8 phase disintegration test contraption (lab india) fitted with paddles (50 rpm) at 37±0.5 °C, utilizing pH 7.2 phosphate support (900 ml) as a Dissolution media. At the foreordained time spans, 5 ml tests were removed, separated through a 0.45µ layer channel, weakened and measured at 276 nm utilizing a Scientific technol Ocimum gratissimum Eli co SL 218 UV/Noticeable Twofold bar spectrophotometer. Aggregate rate discharge was determined utilizing standard absorbance from the adjustment bend. All the disintegration tests were led in three-fold (n = 3) [6].

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Pharmacokinetic Studies of Optimized Fast Dissolving Tablets (Aceclofenac):

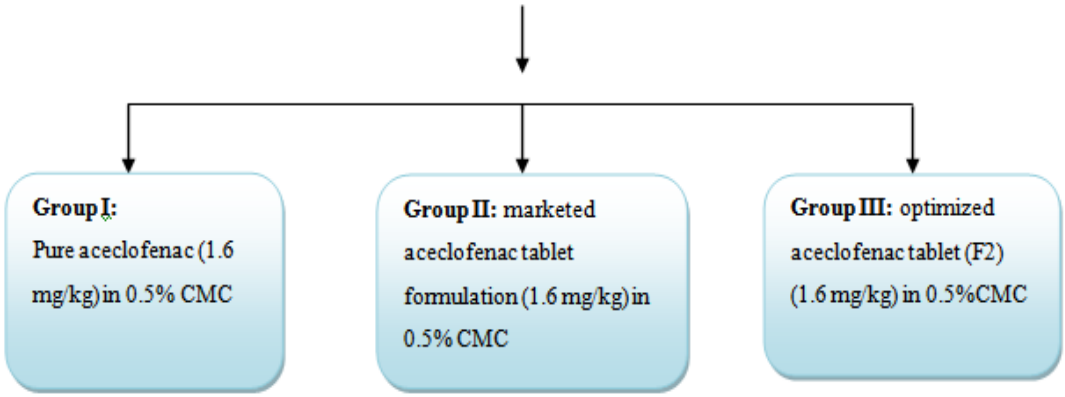
The study was carried as a crossover randomized block design in male wister rats by employing pure drug (aceclofenac), marketed tablet and optimized fast dissolving tablets of aceclofenac (F2) formulated by employing OG as a novel superdisintegrant.

Housing of Animals

Male Wistar rodents (three rodents in a single enclosure) were put in a spotless room with controlled temperature for example 20-25°C and gave free admittance to food (Lipton feed, Mumbai, India) and water. These rodents were presented to 12hr light and dim cycles in a day [7].

Pharmacokinetic Studies

The overnight-fasted rats were divided into three groups (n=3) and treated as follows:



Blood tests were gathered from parallel tail vein at indicated time spans (for example at 0 (pre-portion), 0.5, 1, 2, 3, 4, 5, 6, 7 and 8hr after organization) Blood tests were gathered in miniature axis tubes containing 6mg of EDTA (Against Coagulant) centrifuged at 5000 RPM for 25minutes to isolate plasma and Plasma tests were put away at - 20°C until examination.

Chromatographic Conditions

A delicate superior presentation high-performance liquid chromatographic (HPLC) technique was utilized to dissect aceclofenac in plasma. The HPLC framework (Shimadzu Programming (Class VP 6.12version) with two siphons (LC-10AT VP), a variable frequency programmable UV/VIS indicator (SPD-10A VP), a framework regulator (SCL-10A VP), and a RP C-18 section (Hypersil BDS C18; 250 cm × 4.6 mm; 5 µ) was utilized. The portable stage was Acetonitrile: Phosphate cradle (40:60) utilized as a versatile stage Stream pace of 1.0 ml/min the location frequency was 275 nm.

Preparation of stock solution for aceclofenac: [8]

A standard solution of Aceclofenac was prepared by dissolving 8 mg of Aceclofenac in 25ml of HPLC grade methanol so that the final concentration was 320000ng/ml. Further dilute 2 ml of above solution to 10ml flask (64000ng/ml).

Preparation of dilutions:

From stock solution (6400ng/ml), 0.1 ml of solution was taken and diluted to10ml (640ng/ml). To this 640ng/ml solution, a series of dilutions were made to prepare working standard solutions containing concentrations as 8 to 320 ng/ml of Aceclofenac and the consequences of focus versus top region given in the accompanying Table 2 diagram in 1.

Pharmacokinetic and Statistical Analysis [8]

The pharmacokinetic parameters not set in stone or determined by the standard compartmental model of free examination. Both the maximum plasma concentration (C) and time to peak plasma concentration (t) were gotten straightforwardly from the information. The end half-life (t) was determined as 0.693/K where K is the evident disposal rate consistent. K was thusly determined as the incline of the straight relapse line of regular log-changed plasma focuses. The last five to six quantifiable levels were utilized to decide K The retention rate steady (K) and slack time were

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determined utilizing strategy for residuals, while ingestion half-life (t) was acquired as 0.693/K .The region under the plasma fixation time bend (AUC) was determined from the deliberate levels, from time zero to the last quantifiable level, by the direct trapezoidal rule. AUC was determined by the accompanying formula:

AUC = AUC + C*/K

Where C* is the last quantifiable plasma level

The area under the first moment curve (AUMC) was gotten from a plot of the result of plasma drug focus and time versus time t from zero to endlessness utilizing the trapezoidal rule. Mean resident time (MRT) is characterized as the normal measure of time spent by the medication in the body prior to being disposed of, and was acquired as the AUMC/AUC. Parametric measurable assessment of the information was performed by Understudy's t-test and one-way difference examination followed by Tukey different correlations utilizing Chart Cushion in Detail 8.0 for Windows and values are indicated in tables no 3,4 & graph 1&2.

III.RESULTS AND DISCUSSIONS

All tablet definitions were seen as acceptable as for actual boundaries and urge dial guidelines. In addition, the medication discharge (rate drug delivered at 10 min) values for unadulterated Aceclofenac drug, advanced quick dissolving tablet details F2, and showcased values were viewed as 9.41, 99.82, and 84.69, separately.

Table 2: Plasma Samples Concentration vs Peak Area for Aceclofenac

S. No	Concentration (ng/ml)	Peak Area (on AU min)
1	8	2548
2	16	5115
3	40	12578
4	80	25115
5	120	37895
6	160	51154
7	200	63987
8	240	76985
9	320	102874

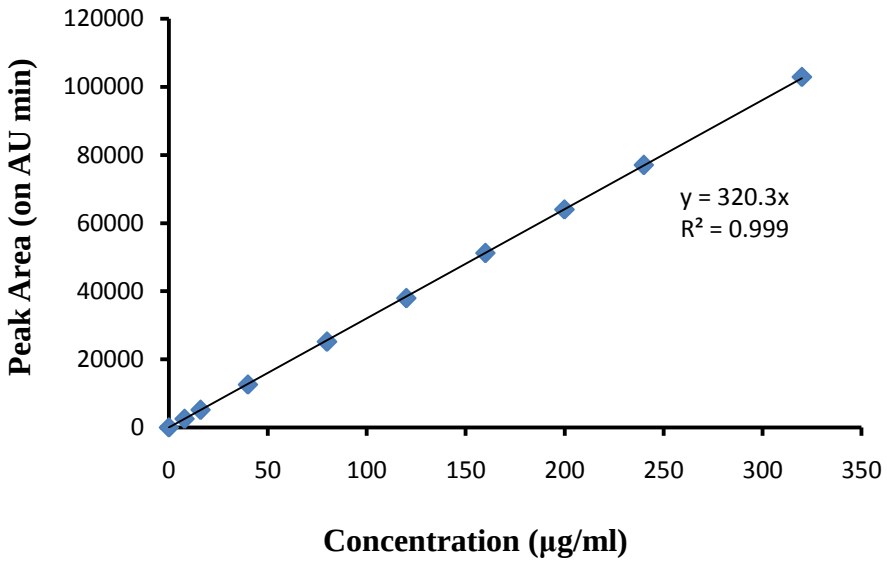

Figure 1: Calibration Curve for Concentration vs Peak area of Aceclofenac

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Table 3: Plasma Concentration of Aceclofenac Following the Oral Administration of Aceclofenac (A), Optimized Aceclofenac Formulation F2 (B) and market formulation (C) in Rats

Time(hr)	Plasma Concentration of Aceclofenac (ng/ml) (x ± s.d)		
	Pure Drug	Optimized formula	Marketed formula
0.5	0.878	82.151	74.049
1	3.320	158.254	152.183
2	6.949	131.484	123.510
3	11.081	100.725	96.577
4	32.981	80.004	73.321
5	21.112	61.383	55.616
6	19.384	38.814	32.919
7	16.555	20.462	17.020

A: Aceclofenac; B: Optimized aceclofenac tablet formulation (F2); C: Marketed formula

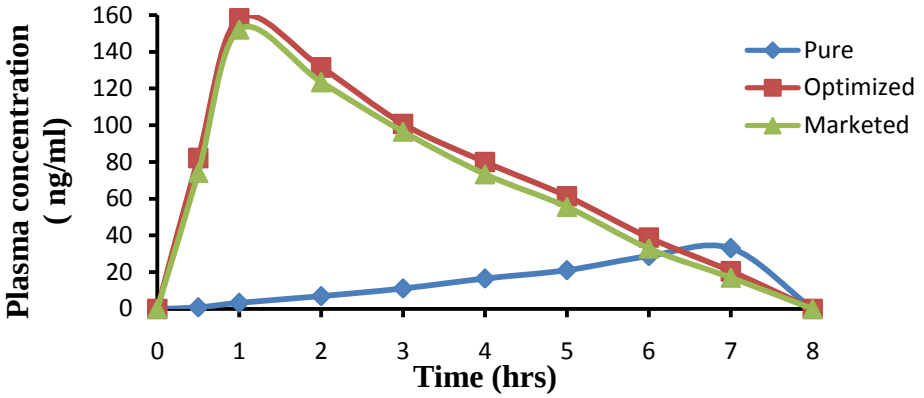

Figure 2: Time vs Plasma Concentration profiles of Aceclofenac Following the Oral Administration of Ibuprofen (A), its Optimized Aceclofenac Tablet Formulation F2 (B) and Marketed formulation (C) in Rats

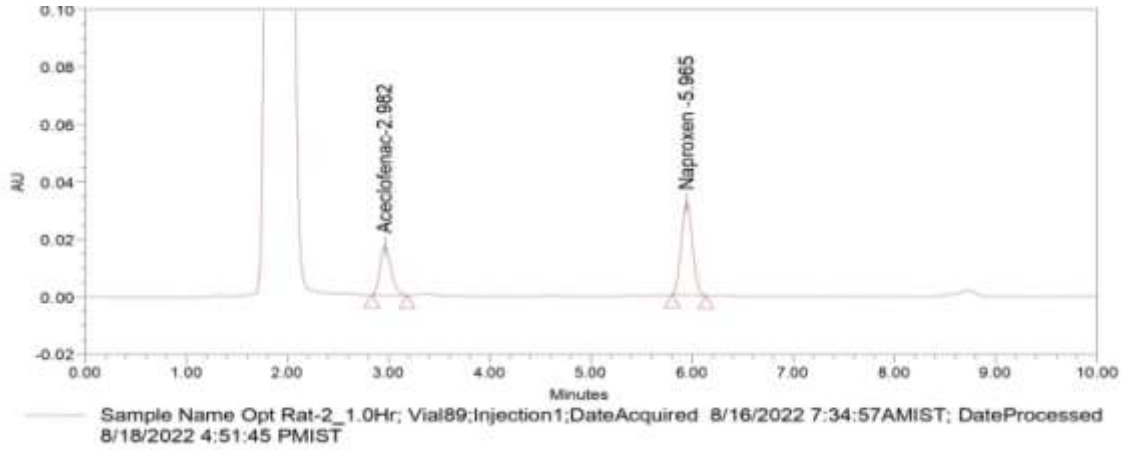

Figure no: 2 HPLC chromatogram of Aceclofenac optimized formula (F2) compared with internal standard sample

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Table: 4 Summary on Pharmacokinetic Parameters of aceclofenac pure drug and optimized aceclofenac fast dissolving tablet formulation F2 and Marketed formula

Pharmacokinetic Parameter	Pure Aceclofenac	Optimized Formulation (F2)	Marketed tablet
C_{max} (ng/ml)	32.98	158.25	152.18
T_{max} (h)	4.0	1.0	1.0
AUC $_{0\text{-}7h}$ (ng.h/ml)	102.71	582.41	584.73
AUC $_{0\text{-}\infty}$ (ng.h/ml)	241.01	640.03	586.01
K_a (h^{-1})	0.36	2.23	2.37
K_{el} (h^{-1})	0.12	0.36	0.38
MRT (h)	3.97	2.47	2.43

The mean residence time (MRT) of Aceclofenac pure drug was found to be 3.97(hr^{-1}) whereas Optimized Aceclofenac fast dissolving tablet formulation F2 employing Ocimum gratissimum mucilage& Marketed formulation was found to be 2.47& 2.43(hr^{-1}) which means optimized Aceclofenac fast dissolving tablet formulation F2 and marketed formulation showed a decrease in mean residence time. Plasma concentrations (Cmax) & absorption rate constant (Ka) of Optimized Aceclofenac fast dissolving tablet formulation F2 and marketed formulations was found to be greater than that of plasma concentrations of Aceclofenac pure drug i.e. Cmax is 158.25& 152.18 ng/ml & Ka is 2.23 & 2.37 (h^{-1}) for optimized Aceclofenac fast dissolving tablet formulation F2 whereas Cmax is 32.98 ng/ml &Ka is 0.36(h^{-1}) for Aceclofenac pure drug. The results indicated Ocimum gratissimum mucilage (novel superdisintegrant) aids in an increase in plasma concentration and absorption rate constant of Aceclofenac. Optimized Aceclofenac fast dissolving tablet formulation F2 and marketed formulation biological half-life is one hour whereas aceclofenac pure drug biological half-life is four hours. Optimized aceclofenac fast dissolving tablet formulation (F2) resulted in faster elimination rate (0.36& 0.38 h^{-1}) compared to the pure drug (0.12h^{-1}).

Optimised rapid dissolving tablet formulations (aceclofenac) using Ocimum gratissimum as superdisintegrant achieved peak plasma concentration in a short time with enhanced absorption and relative bioavailability of the drug, according to pharmacokinetic tests.

IV.CONCLUSION

The prompt release In comparison to the tablet containing the pure drug and its marketed version, the aceclofenac tablet formulation using natural super disintegrate produced a shorter t_{max} and a higher C_{max} as well as a significantly higher degree of absorption. The produced tablets had a better bioavailability of the drug than the commercial formulation, according to the pharmacokinetic analysis, which was supported by lower t_{max} values and higher AUC and C_{max} values. The potential outcomes from these studies suggested that the optimised fast dissolving tablets (F2) represent an important strategy for developing a better oral dosage form than what is currently available on the commercial market, and if scaled-up, may be promising for the formulation development of other poorly water-soluble drugs.

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