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Development, Optimization and Evaluation of Tablet containing Aceclofenac as a NSAIDs by using Piperine as a Bioavailability Enhancer / Facilitator

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The nonsteroidal anti-inflammatory medicine (NSAID) aceclofenac has a low absorption rate, which limits its bioavailability. By employing piperine as a bioavailability enhancer, this study attempted to design, optimize, and assess Aceclofenac tablets. Tablets containing different amounts of piperine (0.5-2%) were made using a solvent evaporation technique. When comparing the dissolution rate and bioavailability of the optimized formulation (F3) with 1% piperine to the conventional formulation, the former shown improvements. Superior analgesic and anti-inflammatory properties were shown in both in vitro and in vivo tests. With respect to the standard formulation, the bioavailability of the improved tablets increased by a factor of 2.5. With piperine's potential to increase Aceclofenac's bioavailability and improve therapeutic efficacy, this study provides evidence for its use.
Keywords:*nonsteroidal anti-inflammatory medicine, aceclofenac, Superior analgesic*

Abstract:

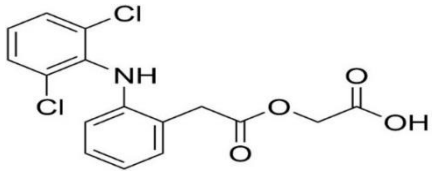
Introduction of Aceclofenac:

Non-steroidal anti-inflammatory drugs (NSAIDs) like aceclofenac (AC) have both analgesic and anti-inflammatory qualities. It functions by preventing prostaglandins, the molecules that cause inflammation and discomfort, from being produced. One form of NSAID that can be used to lessen pain and inflammation related to a number of illnesses, including rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, is the Aceclofenac pill.

Chemistry of Aceclofenac:

Formula : $C_{16}H_{13}Cl_2NO_4$,
Molar mass : 354.18 g·mol^{-}
IUPAC name : 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid.

FIG : Chemical Structure of Aceclofenac.



Mechanism of Action:

Aceclofenac suppresses COX-2, which lowers the production of many inflammatory mediators from the arachidonic acid (AA) pathway, including TNF, IL-1β, and prostaglandin E2 (PGE2). The suppression of IL-6 is thought to be mediated by diclofenac, which is produced from aceclofenac. Inflammatory cytokines' inhibited activity lowers the production of reactive oxygen species. Aceclofenac has been shown to decrease the production of nitrous oxide in human articular chondrocytes. Furthermore, aceclofenac suppresses lymphocytes' synthesis of the cell adhesion protein L-selectin (CD62L), which stops neutrophils from sticking to endothelium. Aceclofenac is hypothesized to increase the synthesis of glycosaminoglycan in human osteoarthritic cartilage, potentially through the suppression of IL-1 production and action. By preventing chrondrocytes from releasing proteoglycan and by blocking IL-1-mediated promatrix metalloproteinase-1 and metalloproteinase-3 production, 4'-hydroxyaceclofenac has chrondroprotective properties.

Introduction of Piperine:

Black pepper (Piper nigrum) contains piperine, commonly referred to as piperidine, a naturally occurring alkaloid. Its many biological actions have been demonstrated, encompassing: -Improving Bioavailability, Adjustment of Immune System, Effects that are antioxidant and anti-inflammatory, Properties that are antiviral and antibacterial, Possible advantages for cognition.

Chemistry and Properties of Piperine:

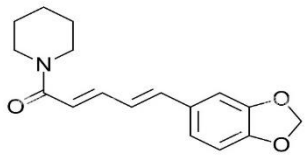


FIG : Chemical Structure of Aceclofenac.

Chemical formula	$C_{17}H_{19}NO_3$	
Molar Maas	285.343 $g.mol^{-1}$	
Density	1.193g/cm^3	
Melting Point	128^{o}c to 130 ^{o}c (266 ^{o}F; 403 k)	
Boiling Point	Decomposes	
Solubility		
In Water	In Ethanol	In Chloroform
40 mg / l	Soluble	1g/1.7 ml

Mechanism of action:

There are several theories as to how piperine's bioenhancer action works, such as DNA receptor binding, altered cell signal transmission, and drug efflux pump inhibition. It generally inhibits the enzymes involved in drug metabolism, promotes absorption through the activation of gut amino acid transporters, blocks the cell pump that removes drugs from cells, and prevents the intestinal formation of glucuronic acid. It could speed up a medication's absorption in the gastrointestinal tract (GIT) or block the enzymes in the liver that are involved in drug metabolism, particularly when the drug travels via the liver after being absorbed from the GIT. Rats' hepatic arylhydrocarbon hydroxylase and UDP-

glucuronyltransferase activity were significantly reduced by oral piperine treatment. Another research shows that piperine inhibits transferase activity and lowers the endogenous UDP-glucuronic acid concentration to alter the rate of glucuronidation. Cytochrome P450 3A4 (CYP3A4) and human P-glycoprotein are inhibited by piperine. Both proteins play a significant role in the first-pass clearance of several medications. Piperine inhibits or induces metabolizing enzymes such as CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4, and others. Bioenhancers will thus have an impact on the majority of medications that these enzymes metabolize. Other processes that have been proposed include enhancing the reactivity of target receptors to pharmaceuticals, serving as receptors for drug molecules, vasodilating the GIT vasculature to improve drug absorption, and modifying the dynamics of cell membranes to increase drug transport across cell membranes.

Uses of Piperine:
Ache Comfort, Strain Management, Bioactivity (Bioavailability), Breathing, Therapy for Stomach Ulcers, Botanical (Herbal) Medicine, Joint Health, Anti-inflammatory.

COMPATIBILITY STUDY OF ACECLOFENAC WITH PIPERINE:

The details or information mentioned below have been used in the current research work.
Analyzing the stability and any interactions between piperine and aceclofenac together would be the goal of a compatibility study. Some potential areas of inquiry are as follows:-

- Examine the mixture's look, color, and texture to determine its physical compatibility.
- Chemical compatibility: Utilizing methods such as HPLC, FTIR, and DSC, assess the stability of Aceclofenac and piperine.
- Aceclofenac release from the combination should be measured in an in vitro release study utilizing a dissolving device.
- Study of stability: Keep the combination in various temperatures, humidity levels, and light levels and assess its stability over time.
- Study of probable interactions: Apply methods such as FTIR, NMR, and molecular modeling to examine possible interactions between Aceclofenac and piperine.

The study's overall findings indicate that piperine and aceclofenac are compatible and that their combination has no effect on the drug's stability or release. This lends credence to the possible creation of a formulation with piperine and aceclofenac combined for improved therapeutic effects.

MATERIAL AND METHODS:

Table :Chemicals used in present research work

S.No	Chemical used	Manufacturer
01	Aceclofenac	Guinness Remedies
02	Piperine	Guinness Remedies
03	Sodium chloride	Merck
04	HCL	Qualigens

05	Methanol	Fisher
06	Dichloromethane	Merck
07	Lactose Mono Hydrate	Sigma-Aldrich
08	Micro crystalline cellulose	Fisher
09	Sodium starch glycolate	Sigma-Aldrich
10	Magnesium Stearate	Rankem
11	Talc	Merck

Table :Instruments used in present research work

S.No.	Instrument Name	Make
01	pH meter	Toschon industries
02	Magnetic Stirrer	-
03	Dissolution apparatus	Veego
04	Balance	Dhona
05	Tablet Hardness Tester	-
06	UV Spectrophotometer 1800	Shimadzu
07	Disintegration apparatus	DBK

Table :Formula for current research work formulation:

S.No	Ingredients (API / Excipients)	Quantity
01	Aceclofenac	100mg
02	Piperine	25 mg
03	Lactose Mono Hydrate	150mg
04	Micro crystalline cellulose	50mg
05	Sodium starch glycolate	20mg
06	Magnesium Stearate	5mg
07	Talc	5mg

Method of Preparation :

This is how to make aceclofenac tablets with piperine using the **wet granulation process**. Step involves –

- Weighing &Milling :Weighed the magnesium stearate, sodium starch glycolate, lactose monohydrate, piperine, and aceclofenac as per specific quantity which is given into the Table no. 3.3.Used a grinder, grind each ingredient individually to a consistent or uniformed size.

- Mixing :Combined piperine with aceclofenac in a mixing vessel in a predetermined order (AC first, Piperine second). Mixed well after adding lactose monohydrate. Then added MCC and again mixed well until fully combined.
- Granulation :To make a paste, combine AC and piperine with water as a solvent and starch as a binder and to create a wet granulate, run the mixture through a granulator.
- Drying :Dried the wet granulate at 50–600C in an oven until the moisture level is less than 5%.
- Grinding and Sizing :To get a consistent size, grinded the dry granulate in a grinder and to get a homogenous powder, strain the ground granules through a 20 mesh screen.
- Lubrication : In a certain sequence, combine the powder with magnesium stearate. (sequence is powder first then magnesium stearate second).
- Compression : Using a tablet press, compact or compress the lubricated powder into tablets.

Evaluation Parameters:

- **Organoleptic Properties-** The colour of tablet formulation produced off-white colour, oblong and slightly bitter in taste tablet produced.

- **Solubility-** Soluble in Gastric Fluid.

- **Physicochemical Tests:**

RESULT AND DISCUSSION :

In-Vitro Dissolution data of formulation drug-

Table: Dissolution data on different formulation.

Time	F1	F2	F3
7 min	0.111	0.120	0.115
15 min	0.175	0.177	0.173
30 min	0.208	0.214	0.211
45 min	0.299	0.297	0.302

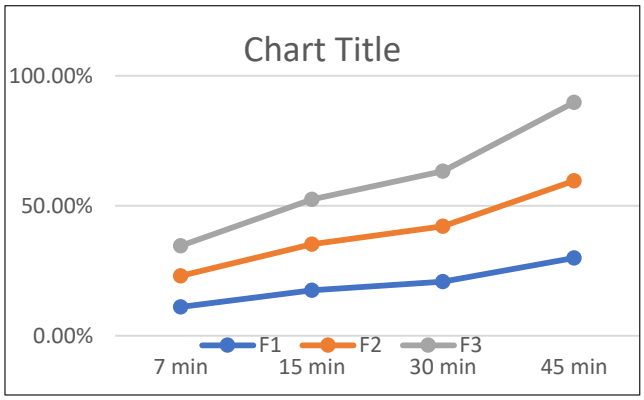


Fig. Graph between Time v/s percentage drug release

Table: Standard Market Tablet formulation of Aceclofenac 100 mg

Time in Minutes	Absorbance of Standard Tablet	Absorbance of Raw material
45 minutes	0.246	0.343

Wave length 273nm

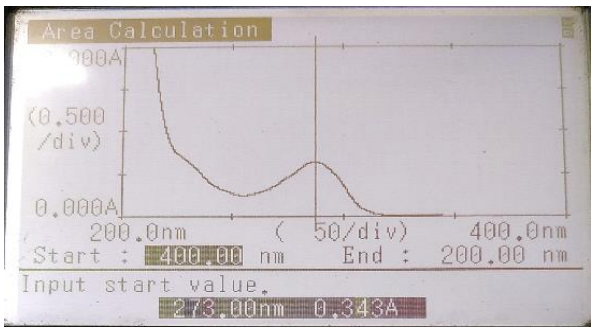


Fig. UV spectrum of Aceclofenac Raw Material

The above result is showing :
When standard tablet of aceclofenac tested then result obtained 82.5% (table: 7.2.2) while we added piperine with aceclofenac then result becomes more better or increases the release drug concentration in different formulations (table 7.2.3).

CONCLUSION-

Aceclofenac tablet which is used like NSAID but due to this drug being of BCS class II, its solubility is less but permeability is high so Due to this, it is not very effective so to enhance its effect, added piperine which contributes our role as a bioavailability enhancer and facilitator.

What does piperine do?

Piperine may inhibits certain liver enzymes like CYP3A4, which can metabolise aceclofenac and increase their solubility, making them more bioavailable and more effective. It was demonstrated that while aceclofenac was not able to exert its therapeutic effect, when it combined with piperine the effect of the drug was somewhat increased or even provided better relief or effective results to patients.

S.No.	Formulations	Weight Variation	Hardness	Friability	Disintegration Time
1	F1	0.3526 ± 5%	3.0	0.28%	4 min
2	F2	0.3578 ± 5%	3.5	0.31%	4.5 min
3	F3	0.3493 ± 5%	3.0	0.29%	4 min

This suggests that this formulation should be submitted to future analysis in relation to other findings.

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