FORMULATION AND EVALUATION OF *TABLET IN CAPSULE* DEVICE - A NOVEL APPROACH FOR THE MANAGEMENT OF PAIN WITH GI PROTECTION

A dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600 032.

in partial fulfilment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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DATE:

This is to certify that the dissertation entitled **"Formulation and Evaluation of *Tablet in Capsule* Device - A Novel Approach for the Management of Pain with GI Protection"** submitted by the candidate bearing **Reg. No. 26108307** for The Tamil Nadu Dr. M.G.R. Medical University examinations.

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DEDICATED TO EXCALIBURS' 10

LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
NC	No Change
ASTM	American Standards for Testing Materials
KF	Karl Fischer
HDPE	High Density Poly Ethylene
Hr	Hours
Min	Minute
Sec	Seconds
RH	Relative humidity
PP	Polypropylene
GIT	Gastro intestinal tract
C_{max}	Maximum concentration
C_{min}	Minimum concentration
SLS	Sodium lauryl sulphate
Cc	Cubic Centimeter
Kp	Kilopond
USP	United States Pharmacopoeia
BP	British Pharmacopoeia
JP	Japanese Pharmacopoeia
ml	Millilitre
SD	Standard deviation
mg	Milligram
RS	Reference Standard
ER	Extended Release
IR	Immediate Release
NSAIDs	Non Steroidal Anti Inflammatory Drugs
COX	Cyclooxygenase
OA	Osteoarthritis
RA	Rheumatoid arthritis

CONTENTS

Introduction

INTRODUCTION

SOLID ORAL DOSAGE FORMS

Historically, the most convenient and commonly employed route of drug delivery has been by oral ingestion.[1] Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. It is considered as the most natural, uncomplicated, convenient and safe route.[2]

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are the most widely preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparison to some other dosage forms, and also provide means of accurate dosing. They can be mass produced with robust quality controls and offer different branding possibilities by means of colored film coating, different shapes, sizes or logos.[3]

Capsules are solid dosage forms in which drug is enclosed within either a hard or soft soluble shell. The shells are generally made up of gelatin. The capsules may be regarded as the container drug delivery system for powder and non powder filling such as tablets, capsules and pellets.[4]

Advantages of Solid Oral Dosage Forms [5]

- They are the most stable dosage form with respect to their physical, chemical and microbiological attributes.
- Provide an accurate, stable dose with greatest precision and least content variability, easy to use, handle and to be carried by the patient.
- They are attractive and elegant in appearance.
- The manufacturing cost of tablets is low as compared to other dosage form and their manufacturing speed is also quite high.
- The packaging and shipping of tablets is comparatively easy and cheap.

- The unpleasant taste and odor of medicament(s) can be easily masked
- The incompatibilities of medicament(s) and their deterioration due to environmental factors are less.
- They are more suitable for large scale production.
- Their identification is probably the easiest because of variety of shapes and colors.
- They are formulated with certain special release profile products such as enteric or delayed release products.
- They are the lightest and most compact dosage form.

Disadvantages of Solid Dosage Forms[5]

- Drugs that are amorphous in nature or have low density character are difficult to be compressed into tablet.
- Hygroscopic drugs are not suitable candidate for compressed tablets.
- Drugs having poor wetting properties, slow dissolution profile and high optimal gastro intestinal absorption are difficult or impossible to formulate as a tablet.
- Drugs having bitter taste and objectionable odor require special treatment like coating or encapsulation which may increase their production cost.
- Some drugs which preferably get absorbed from the upper part of GIT may cause bioavailability problem in tablet dosage form.
- Capsules cannot be used for extremely soluble materials such as potassium chloride, potassium bromide.
- Capsules cannot be used for highly efflorescent or deliquescent fill materials.

Method of manufacturing of solid dosage forms

Tablets [3]

Different types of tablet formulations are available, which could be broadly classified based on route of administration such as tablets for oral, sublingual delivery, buccal delivery, rectal delivery or vaginal delivery and formulation characteristics such as immediate release tablets, effervescent tablets, melt-in-mouth or fast dissolving tablets, delayed release or

extended release tablets. In all the cases, the general manufacturing process, machinery used for preparation of tablets and materials used are similar.

TYPES OF TABLET MANUFACTURING [3]

The tablet manufacturing process can be broadly classified as

- Direct compression
- Granulation

Direct compression [3]

Direct compression is used when a group of ingredients can be blended, placed onto a tablet press and made into a perfect tablet without any of the ingredients having to be changed. Powders that can be blended and compressed are commonly referred to as ***directly compressible*** **or as** ***direct-blend formulations.*** The inherent physical properties of the individual filler materials are highly critical, and minor variations can alter flow and compression characteristics, so as to make them unsuitable for direct compression.

The most widely used direct compression fillers are cellulose derivatives (e.g. microcrystalline cellulose), saccharides (e.g. lactose and mannitol), mineral salts (e.g. Dicalcium phosphate, calcium carbonate) and partially pregelatinized starch.

Granulation [3]

Granulation is an agglomeration process to improve the flow, density and compressibility of particulate material by size enlargement and densification. Granulation can be achieved by the use of binder solution (wet granulation) or dry binder (dry granulation).

Wet granulation [3]

When powders are very fine, fluffy, will not stay blended, or will not compress, then they must be granulated. *Wet massing* is the process of adding a solution to a blended powder and mixing for a predetermined period of time at a given mechanical speed. Once the process is complete, the wet mass is milled, spread on trays dried in a tray dryer. The formed granules are

milled and compressed. Examples of wet granulation methods include fluid bed, high shear, pelletization techniques, such as extrusion spheronization and spray drying.

Dry granulation [3]

Dry granulation (roll compaction or slugging) involves the compaction of powders at high pressures into large, often poorly formed tablets or compacts. These compacts are then milled and screened to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of heat and moisture in the processing. Dry granulations can be produced by extruding powders between hydraulically-operated rollers to produce thin cakes that are subsequently screened or milled to give the desired granule size.

Table 1.1: Granulation Methods[3]

Method	Advantage	Limitations
Direct compression	Simple, economical process, No heat or moisture, so good for unstable compounds.	Not suitable for all API, generally limited to lower dose compounds, Segregation potential, expensive excipients
Wet Granulation	Robust process, reduce elasticity problems, wettablity, reduced segregation potential.	Expensive, Time and energy consuming, Specialized equipment, Stability issues.
Wet Granulation (Non Aqueous)	Vacuum drying technique, Suitable for moisture sensitive API	Expensive equipment, solvent recovery issues, needs organic facility, health and environmental issues.
Dry Granulation	Eliminates exposure to moisture and drying	Dusty procedure, slow process, not applicable for all API

MANUFACTURE OF CAPSULES [5, 6]

Immediate-release or Altered release hard gelatin capsules require the following common operations.

- Rectification i.e. body-end downward orientation
- Separation of caps from bodies
- Dosing of Fill Material (Powder or Non powder filling)
- Replacement of caps and ejection of filled capsules
- Finishing includes de-dusting and polishing.

Hard gelatin capsule dimensions and filling capacities [7]

CAPSULE SIZE	000	00el	00	00 LQ	0el	0	1	2	3	4
WEIGHT										
Average Weight (mg)	158	130	123	132	107	99	76	61	48	38
tolerance	± 10	± 10	± 7	± 4	± 7	± 6	± 5	± 4	± 3	± 3
CAPACITY										
Volume Capacity (ml)	1.37	1.02	0.95	0.95	0.77	0.68	0.48	0.36	0.27	0.20
density of dosing powder						Weight Capacity (mg)				
0.6 g/ml	822	612	570	570	462	408	288	216	162	120
0.8 g/ml	1096	816	760	760	616	544	384	288	216	160
1.0 g/ml	1370	1020	950	950	770	680	480	360	270	200
1.2 g/ml	1644	1224	1140	1140	924	816	576	432	324	240
OVERALL CLOSED LENGTH										
(mm)	26	25.4	23.4	23.4	23.4	21.6	19.4	17.6	15.7	14.3
tolerance	± 0.3	± 0.3	± 0.3	± 0.3	± 0.3	± 0.3	± 0.3	± 0.3	± 0.3	± 0.3
(inches)	1.024	1	0.921	0.921	0.921	0.85	0.764	0.693	0.618	0.563
tolerance	± 0.012	± 0.012	± 0.012	± 0.012	± 0.012	± 0.012	± 0.012	± 0.012	± 0.012	± 0.012
INDIVIDUAL LENGTHS (CAP & BODY)										
CAP (mm)	12.9	12.94	11.8	11.8	11.9	10.85	9.85	8.8	8	7.2
tolerance	± 0.35	± 0.5	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35
BODY (mm)	21.9	22.38	20.1	20.1	20	18.45	16.4	15.15	13.45	12.1
tolerance	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35	± 0.35
CAP (inches)	0.508	0.509	0.464	0.464	0.468	0.427	0.388	0.346	0.315	0.283
tolerance	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014
BODY (inches)	0.862	0.881	0.791	0.791	0.787	0.726	0.646	0.596	0.529	0.476
tolerance	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014	± 0.014
EXTERNAL DIAMETER										
CAP (mm)	9.94	8.58	8.56	8.56	7.66	7.65	6.96	6.39	5.85	5.33
BODY (mm)	9.55	8.25	8.23	8.23	7.35	7.35	6.63	6.12	5.60	5.08
CAP (inches)	0.391	0.338	0.337	0.337	0.302	0.301	0.274	0.252	0.23	0.21
BODY (inches)	0.376	0.325	0.324	0.324	0.289	0.289	0.261	0.241	0.22	0.2
Recommended Storage Conditions:			59°-77°F / 15°-25°C				RH 35-65%			

Extended Release Formulation [8]

The formulated solid oral dosage form when administered reaches the absorption site and ends with its elimination in the original or modified form, through the normal channel of excretion. Hence in order to prolong the residence of drug in the body, dosing interval can be extended either by

- Altering the release rate of a dosage form to retard the rate of absorption (k_a)
- Slowing down of biotransformation rate
- Manipulating the drug molecule to reduce the rate of elimination(k_{el})

Retarding the absorption rate in designing drug product provides well controlled drug concentration in blood stream. It is also necessary to take into account the physiological constraint of a finite residence time at the absorption site as in case of GI transit time.

Factors involved in slowing the absorption rate [9]

- Route of administration
- Vasoconstriction
- Dissolution rate
- Decreased solubility
- Particle size and surface area
- Slowing the disintegration and dissolution rate
- Polymerization
- Viscosity and nature of vehicle
- Esterification

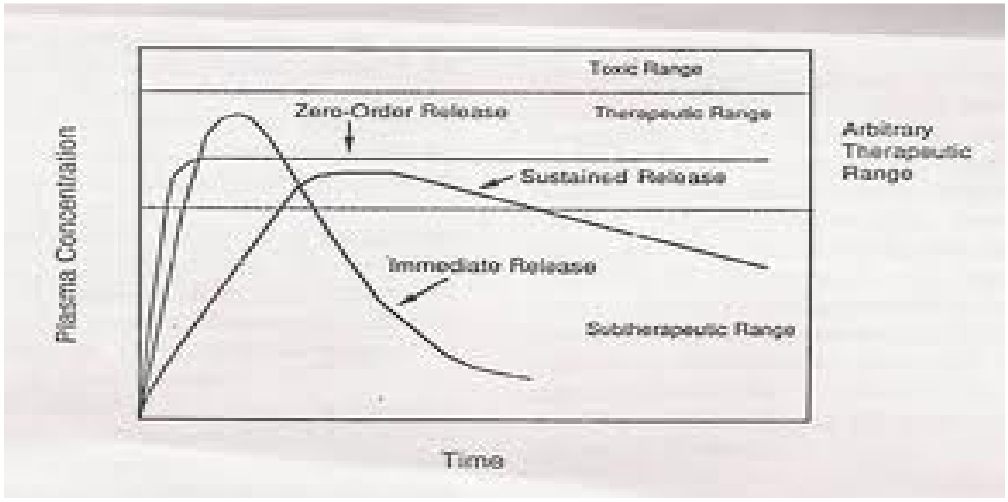


Fig 1.1: Blood profiles

- An ideal dosage regimen in the drug therapy of any disease immediately attains the desired therapeutic concentration of drug in plasma or at the site of action and maintains it as a constant for the entire duration of treatment.[9]
- Administration of drug by conventional drug delivery systems does not maintain blood levels of drug within the therapeutic range for extended periods of time and associated with saw-tooth kinetic pattern.[6]
- The goal of any extended release dosage form is to maintain therapeutic levels of the drug for an extended period of time.[9]
- In extended release system, the amount and rate of drug release are determined by the physiological/therapeutic needs of the body and therefore provides physiologically, therapeutically based drug delivery system.[6]

Terminology [4]

There are several terms used interchangeably for modified release dosage forms viz., controlled release, programmed release, prolonged release or sustained release, extended release, timed release, slow release, delayed release, repeat action, long acting, repository dosage forms etc.

Modified Release

They are designed to modify the rate, the place or the timing of drug release and not absorption. The dosage forms are coated or uncoated.

Controlled Release

Controlled release systems provide a release profile predominantly controlled by the design of the system.

Prolonged Release or Sustained Release

These dosage forms only prolong the therapeutic blood or tissue level of the drug for an extended period of time that is not possible with conventional preparations.

Extended Release

Pharmaceutical dosage forms that release the drug slower than normal manner

Slow Release

Preparations formulated for the purpose of avoiding toxicity associated with peaking effect.

Delayed Release

These preparations release the drug after a “time delay” or after the tablet has passed through one part of the GI tract into another. All enteric coated tablets are delayed release tablets but not all delayed release tablets are enteric coated, because enteric- coated tablets release the drug rapidly once they reach the intestine and it cannot provide sustained therapy.

Repeat Action Tablet

In this one part of the tablet releases in the stomach, another part releases in the intestine. The release depends upon gastric emptying. It is an alternative to sustained release. Here multiple dose of a drug is retarded at a period interval.

Long Acting

They are used to encompass those drugs with an inherently long pharmacological effect because of their pharmacokinetic properties. Hence it can be seen that sustained release systems simply prolong the drug release, and hence plasma drug levels for an extended period of time, whereas controlled release systems control the release rate and the duration of actions.

Advantages of Extended Release Products [4, 9, 10]

- Decreased local and systemic side effects.
- Reduced gastrointestinal irritation.
- Better drug utilization.
- Reduction in the total amount of drug used.
- Minimum drug accumulation and chronic dosing/improved efficiency in treatment.
- Optimized therapy.
- More uniform blood concentration.
- Reduction in fluctuation in drug level and hence, more uniform pharmacological response.
- Improved patient compliance.
- Less frequent dosing
- Reduced night time dosing
- Reduced patient care time.

Disadvantage of Sustained Release Products [4, 9, 10]

- Dose dumping
- Reduced potential for accurate dose adjustment
- Need for additional patient education.
- Stability problems.

- Possible reduction in systemic availability.
- Increased variability among dosage units.
- Slow absorption may delay the onset of activity
- Unpredictable and often poor *in vitro, in vivo* correlations
- Reduced potential for dosage adjustment
- Increased potential for first pass clearance and poor systemic availability
- Effective drug release period is influenced and limited by GI residence time for oral controlled release formulations.

Rationale for extended-release dosage forms [10]

Increase in time interval required between doses. This provides a reduction in the total number of doses required per day. Reduction in fluctuation of drug blood levels about the mean. A controlled release dosage form decrease the drug concentration's fluctuation by,

a) Reducing the blood levels(C_{max}) thus potentially reducing dose related adverse effects
b) Increasing the minimum plasma concentration (C_{min}) thereby increasing efficacy if a threshold concentration is required. The plasma concentration stays within therapeutic range that is "therapeutic occupancy time".

Potential bioavailability problem of extended release products [10]

The potential problems inherent in oral extended-release dosage forms related to

- Interaction between the rate, extent and location that the dosage form release the drug
- The regional differences in GI tract physiology.

Characteristic That Makes a Drug Unsuitable For Extended- Release Formulation [10]

- Short elimination half-life,<2 hr
- Long elimination half-life, >8 hr
- Narrow therapeutic index
- Large doses
- Poor absorption
- Active absorption

- Low or slow solubility
- Time course of circulating drug different to that of pharmacological effect
- Extensive first-pass clearance

Extended release mechanism [3, 6]

The various systems under this category are

- Dissolution controlled systems
- Diffusion controlled systems
- Dissolution and diffusion controlled systems
- Ion exchange resin drug complexes
- Slow dissolving salts and complexes
- pH dependent formulations
- Osmotic pressure controlled systems
- Hydrodynamic pressure controlled systems

Design and fabrication of controlled drug delivery systems [6]

The majority of oral controlled release systems rely on dissolution, diffusion, or a combination of both mechanisms, to generate slow release of drug to the GI tract. Based on the data of drug candidate such as dose, rate constant for absorption and elimination, some elements of metabolism, physical and chemical properties one can estimate a desired release rate for the dosage form, the quantity of the drug needed and a preliminary strategy for the dosage form to be utilized.

- **Diffusion systems** [6]

  In these systems the release rate of drug is determined by its diffusion through a water insoluble polymer. There are two types of diffusion devices.

  - Reservoir devices
  - Matrix devices

Matrix devices [11]

Depending upon the mechanism by which the rate controlling element controls diffusion such systems can be classified into five categories.

- Hydrophobic Matrices (Plastic matrices)
- Lipid Matrices
- Hydrophilic Matrices
- Biodegradable Matrices
- Mineral Matrices

Hydrophilic matrices [12]

A hydrophilic matrix tablet is the simplest and most cost-effective method of fabricating an extended release solid oral dosage form. A typical ER matrix consists of a drug, one or more water swellable hydrophilic polymers and excipients such as fillers, binders, glidant and lubricant.

Mechanism of drug release from the matrix

- When the matrix tablet is exposed to an aqueous solution or gastrointestinal fluids, the surface of the tablet is wetted and the polymer hydrates to form a jelly-like structure around the matrix called as 'gel layer'. This process is termed as glassy to rubber state transition of the polymer surface layer.
- The gel layer grows with time as more water permeates into the core of the matrix, increasing the thickness of the gel layer and providing a diffusion barrier to the drug.
- As the outer layer becomes fully hydrated, the polymer chains become completely relaxed leading to disentanglement and erosion from the surface of matrix.
- Water continues to penetrate towards the core of the tablet, through the gel layer until it has been completely eroded.
- Soluble drugs are released by this combination of diffusion and an erosion mechanism, erosion is the predominant mechanism for insoluble drugs.

Impact of the formulation and process variables on the drug release from extended release matrix systems

Formulation variables

- Drug particle size
- Drug: polymer ratio
- Polymer type
- Fillers
- Polymeric excipients

Process variables

- Compression force.
- Tablet shape.
- Tablet size.

REGULATORY CONSIDERATION IN CONTROLLED RELEASE PRODUCTS [13]

FDA regulation of oral controlled-release drugs governing bioequivalence and *in vitro–in vivo* correlations for controlled-release products requires the following pharmacokinetic evaluations,

- Relative bioavailability following single dose
- Relative bioavailability following multiple doses
- Effect of food
- Dose proportionality
- Unit dosage strength proportionality
- Single-dose bioequivalence study (experimental versus marketed formulations at various strengths)
- *In vivo–In vitro* correlation
- Pharmacokinetic/Pharmacodynamic (PK/PD) relationship.

In general, for drugs in which the exposure–response relationship has not been established or is unknown, applications for changing the formulation from immediate release to controlled release requires demonstration of the safety and efficacy of the product in the target patient population. When a drug is developed as a controlled-release dosage form, additional studies to characterize its absorption, distribution, metabolism, and excretion characteristics are recommended.

IMMEDIATE RELEASE TABLETS [6]

Immediate release tablets are designed to disintegrate and release the drug in absence of any controlling features such as coating or other formulation technique

Disintegrants are used to ensure that, when a tablet is ingested, it breaks down quickly in the stomach. Rapid disintegration is a necessary step in ensuring that the active ingredients are bioavailable and readily absorbed. This is especially important for immediate release products where rapid release of drug substance is aimed at. The proper choice of disintegrants and its consistency of performance are critical to formulation development of immediate release tablets. Some superdisintegrants are Croscaramellose sodium, Crospovidone, L-HPC (Low Substituted hydroxypropyl ether of cellulose), Sodium Starch Glycolate.[6]

TABLET IN CAPSULE DOSAGE FORM[14]

Tablet in capsule is a multifunctional and multiple unit system, which contains versatile mini-tablets in a hard gelatin capsule.

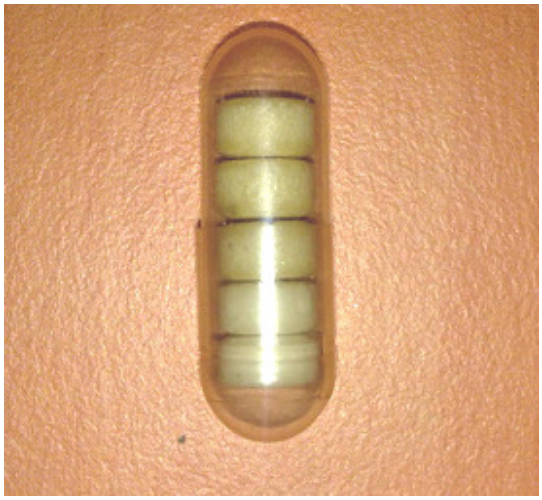
It can be developed by preparing Rapid-release Mini-Tablets, Sustained-release Mini-Tablets, Pulsatile Mini-Tablets, and Delayed-onset Sustained-release Mini-Tablets, each with various lag times of release and encapsulating in a capsule.

The system can be designed to contain rapid and delayed release mini-tablets of two different or similar drugs. Two tablets in a capsule is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release drug delivery in which one tablet in the capsule is immediate release as initial dose and second is maintenance dose.

Biphasic delivery system can be achieved in this dosage form and it can produce the rapid onset of release for those drugs that need prompt appearance of therapeutic effect, followed by an extended release phase at a constant rate. When a simple constant rate of drug release does not entirely satisfy the therapeutic objective, the quick/ slow drug delivery system can be opted to achieve it. The nature of tablets and number of tablets to be filled depends on the formulator and the objective of the drug delivery system.

Fig 1.2: Tablet in Capsule System

Source: Raghevendra Rao et al 2011 **[43]**



Objective

OBJECTIVE OF THE WORK

1. To formulate a combination dosage form of Aceclofenac Extended Release Tablet 200 mg and Misoprostol Immediate Release Tablet 200 mcg enclosed in Size '0' elongated Hard Gelatin Capsules.
2. Preformulation study shall be taken up to decide on the Drug – Excipient compatibility of Aceclofenac and Misoprostol individually .[15]
3. A compact Aceclofenac Extended Release Tablet 200 mg shall be prepared by using varying grades of Hydrophilic polymer HPMC and Ceolus KG 1000 (Microcrystalline cellulose).
4. The dissolution profile of Aceclofenac ER tablets for a period of 12 hr and mechanism of drug release from the ER tablet shall be determined.[16]
5. A Misoprostol Immediate Release Tablet 200 mcg shall be prepared by direct compression method.
6. In process Quality Control Checks like Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio, Angle of Repose for the blend/granules and Uniformity of weight, Thickness, Hardness, Friability, Disintegration Time shall be measured for tablets of every formulation trial.
7. Accelerated Stability Study of the combination product enclosed in capsule packed in 60cc HDPE Bottle and 33mm PP Child Resistant Cap, Induction sealed with 1 g of 6 g/yard cotton as dunnage, shall be determined at the end of 40 ±2°C /75±5% RH 3rd Month and the following shall be used as raiders for evaluation while comparing with Initial.
    - Appearance
    - Assay
    - Thickness
    - Friability
    - Hardness
    - Dissolution
    - Disintegration Time

Rationale

RATIONALE BEHIND THE FORMULATION

- Aceclofenac therapy is effective, well-tolerated, widely accepted and of considerable value to both the patient and physician in the management of inflammatory pain.[17]
- It is prescribed for both acute and chronic inflammatory and degenerative disease such as osteoarthritis, rheumatoid arthritis with low incidence of side-effects.[18]
- Advancing age is the powerful risk factor for osteoarthritis and rheumatoid arthritis.
- NSAID for chronic use places patients at a risk for serious Gastroduodenal complications and in particular geriatric patients.[19]
- Misoprostol is the only drug indicated for prevention of NSAID induced gastropathy.[20]
- Combination of Aceclofenac and Misoprostol tablets in a simple Tablet in Capsule dosage yields added advantage.
- It offers advantage in terms of Safety, Patient compliance, Ease of manufacturing and as Chronopharmacotherapy with maximum therapeutic effect and minimum side effects.[16]

Literature Review

LITERATURE REVIEW

Literature pertaining to the drugs

Anil Pareek et al.[21] compared the efficacy and safety of Aceclofenac control release (CR) tablets with conventional Aceclofenac tablets in patients with knee osteoarthritis (OA). This was a double-blind, double-dummy, randomized, parallel group multi-centric study conducted at 6 centers. It was observed in the study that patients on Aceclofenac group consumed more tablets of ranitidine as compared to patients on Aceclofenac-CR group indicates higher incidence of gastrointestinal adverse events. The results suggested that Aceclofenac-CR formulation was found to be effective and safe while offering practical advantage of once daily administration.

Ballinger AB et al.[22] performed a study involving patients receiving NSAID. The study states that many NSAID associated ulcers that bleed or perforate have been asymptomatic until the time of presentation. It concluded that Misoprostol is the best choice for NSAID induced Gastroduodenal damage and it is superior to all other drugs in prevention of gastric damage. It also reveals that prophylactic treatment should be considered in at-risk patients.

Davey PJ et al.[23] conducted a study that considered the cost effectiveness of Misoprostol prophylaxis for Nonsteroidal Anti-Inflammatory Drug induced gastrointestinal damage, using data from the Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial which involved 8843 patients receiving continuous NSAID therapy for the control of Rheumatoid arthritis. This study concluded that cost effectiveness of Misoprostol prophylaxis in long-term Nonsteroidal Anti-Inflammatory Drug therapy such as arthritis.

Dooley M et al.[24] conducted a meta-analysis of 13 comparisons with Diclofenac, Naproxen, Piroxicam, Indomethacin, Tenoxicam or Ketoprofen in 3574 patients, and preliminary details of a comparison with 10 other NSAIDs in 142,776 patients. Aceclofenac reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis, and is similar in efficacy to Ketoprofen, Diclofenac, Indomethacin and Tenoxicam in these patients. Data from in vitro studies indicate properties of particular interest with respect to cartilage matrix effects and selectivity for cyclo-oxygenase-2and it is evident that Aceclofenac is well tolerated with improved GI tolerability relative to other NSAIDs.

Fred E Silverstein et al.[25] performed 6-month randomized, double-blind, placebo-controlled trial including 8843 men and women with mean age of 68 years receiving continuous therapy with any of 10 specified NSAIDs for control of symptoms of rheumatoid arthritis. The study revealed that serious upper gastrointestinal complications including perforation, obstruction, and bleeding, in older patients with rheumatoid arthritis were reduced by 40% among patients receiving Misoprostol compared with those receiving placebo.

George V Papatheodoridis et al.[26] studied that *H. pylori* infection almost doubled the risk of upper gastrointestinal bleeding among NSAID users after adjustment for other risk factors for bleeding. *H. pylori* infection was diagnosed by serum antibodies and CagA seropositivity. It was diagnosed by enzyme-linked immunoassay.

Gérard Thiéfin et al.[27] assessed the prevalence of gastroprotective agent prescription in patients treated with Nonsteroidal Anti-Inflammatory Drugs in France to analyze the determinants of this prescription. This study concluded that gastroprotection is still largely underprescribed in patients at risk of gastrointestinal Nonsteroidal Anti-Inflammatory Drug complications in France. And in geriatric population, half of Nonsteroidal Anti-Inflammatory Drug users above 65 years are prescribed with gastroprotective agents.

Jay L Goldstein et al.[20] reviewed the current approaches in prevention of NSAID-induced Gastropathy and economic implications of NSAID-induced Ulceration. It states that Misoprostol is the only drug currently indicated for the prevention of NSAID-induced gastropathy. The review concluded that increasing proportion of elderly, inherently at-risk patients in the population, increased savings can be realized with the use of a GI-protective NSAID such as Diclofenac/misoprostol combination.

Lemmel EM et al.[17] conducted a pan-European study involving 23407 patients with pain due to various inflammatory or degenerative rheumatic diseases was undertaken in Austria, Belgium, Germany and Greece, to evaluate overall pain relief and satisfaction with Aceclofenac therapy. The study concluded that Aceclofenac was considered by patients to be a highly efficacious treatment with excellent and fast analgesic activity that was maintained throughout the study period. Patient satisfaction compliance of Aceclofenac therapy was found to be 90% at the end of the study.

Li J et al.[28] studied that Misoprostol, a PGE_2 receptor agonist that is utilized clinically as an anti-ulcer agent and signals through the protective PGE_2 EP_2, EP_3, and EP_4 receptors, would reduce brain injury in the murine middle cerebral artery occlusion-reperfusion (MCAO-RP) model. These findings suggest a novel function for Misoprostol as a protective agent in cerebral ischemia acting via the PGE_2 EP_2 and/or EP_4 receptors.

Plosker GL et al.[29] studied that the combined formulation of Diclofenac/Misoprostol provides effective relief of pain and inflammation, with a 2- to 3-fold lower incidence of NSAID-associated gastroduodenal ulcers than Diclofenac monotherapy. This study also included pharmacoeconomic studies of co-prescribed Misoprostol with NSAIDs, the most favourable results with the combined formulation of Diclofenac/Misoprostol appear to be in patients at high risk of developing NSAID-associated gastroduodenal ulcers such as elderly with rheumatoid arthritis or osteoarthritis.

Literature pertaining to the formulation

Afsar C Shaikh et al.[30] developed sustained release tablets of Aceclofenac by wet granulation using hydrophilic polymers HPMC K100 and HPMC K15. *In vitro* dissolution studies were performed using 0.1 N Hydrochloric acid pH 1.2 and phosphate buffer pH 6.8. The kinetics of the release process of drug in the selected formulation was studied using Higuchi and Korsmeyer-Peppas models. Results indicated that formulation of sustained release tablet of Aceclofenac containing HPMC K100 as retarding agent fulfills all the requirement of sustained release tablet.

Ahmed A Bosela et al.[31] developed a multifunctional multiple unit system for programmable release for combined administration of rapid and delayed release minitablets of Famotidine with timed release tablets of Ketorolac in novel tablet- in- capsule dosage form. Famotidine was included as two mini tablets one release rapidly and other after a lag time of 6 hours. For Ketorolac the water soluble tromethamine salt was used to develop mini tablets providing a pulse of drug release after 1 hour with the other mini tablet providing sustained drug release after a lag time of 4 hours. This combination provides sustained analgesic effect of Ketorolac with sustained gastric protection of Famotidine.

Basak SC et al.[32] formulated and studied controlled release HPMC matrix tablets of Propranolol hydrochloride. The matrix tablets were prepared with HPMC K4M and fulfilled all the official requirements of tablet dosage forms. The *in vitro* drug release was measured in

aqueous solutions for a period of 12 hours using 1.2 pH buffer for first hour and pH 7.5 buffer for the rest of periods. The drug release was within the limits of USP requirements.

Bin Li et al.[33] developed a programmed drug delivery from a novel system, which contains a water-soluble cap, impermeable capsule body, and two multi-layered tablets. In this study the multi-layered tablets formulation prepared was filled within the capsule body and sealed with the water-soluble cap. Sodium alginate and HPMC E5 were used as the candidate modulating barrier material. This study investigated the effect of types of barrier materials, weight of barrier layer, tablets hardness, location of tablets in capsule, and bulking agent on release profiles.

David Chen et al.[34] formulated the sustained-release solid dispersion of Misoprostol using Ammonio Methacrylate copolymer Eudrgit RS, RL. The solid dispersion matrix formed by the copolymer protects Misoprostol from being degraded by water so that the stability of Misoprostol is improved. The formulated dispersion found to release Misoprostol slowly by diffusion from the copolymer matrix and give sustained effect. This revealed that Misoprostol–Eudragit dispersion can be used in a powder form, filled in capsules, or compressed into tablets for sustained delivery of Misoprostol.

James L Ford et al.[35] studied the release rate of Promethazine hydrochloride from HPMC tablet matrices. The results stated that rate of release was controlled predominantly by drug-polymer ratio and the viscosity of the polymer. It concluded that lowest viscosity HPMC produced higher release rates than other HPMC polymers. The Molecular size of the polymers did not produce much influence on rate of release.

Jigar Mehta et al.[36] developed and validated the *in vitro* dissolution method with HPLC analysis for Misoprostol in formulated dosage form. The study finalized that paddle at 50rpm stirring speed, deaerated water dissolution medium with volume 500mlas per very low content of the drug substance and drug product.

Karali TT et al.[37] studied that stability of Misoprostol oil is significantly improved in HPMC dispersion. The results states that below 30% relative humidity (approximately 2% water) the Misoprostol degradation were found to be minimum when it is in the form of 1:100 HPMC dispersion.

Oth M et al.[38] developed a Bilayer floating dosage unit to achieve local delivery of Misoprostol, at the gastric mucosa level. The unit was a capsule consisting of a floating layer maintaining the dosage unit buoyant upon the gastric content and a drug layer formulated to act as a sustained-delivery system. HPMC was used to make hydrophilic matrix. The present study also revealed that the use of a large capsule increases the gastric residence time, as it impedes passage through the pylorus opening. Gamma-Scintigraphic studies were used for evaluations.

Indiran Pather S et al.[39] took an effort to reduce production costs by direct compression of theophylline and ethyl cellulose. This method enabled to sustain the release of a therapeutic dose of theophylline over a 12 hr period. The study states that Theophylline to ethylcellulose ratio and the tablet hardness were found to influence the rate of drug release. The study concluded that the rate of drug release can be altered by changing the ratio of theophylline to ethylcellulose and by adjusting the compression force used to prepare the tablets.

Patil Dinesh et al.[40] developed a multifunctional and multiple unit system containing Propranolol hydrochloride sustained release pellets and Flunarizine dihydrochloride immediate release mini tablet in a hard gelatin capsule for synergistic effect in migraine and hypertension. *In vitro* dissolution study was performed separately. Propranolol hydrochloride sustained release pellets in pH 1.2 phosphate buffer for 1.5 hours followed by testing in pH 6.8 buffer at 4,8,14 & 24 hours and Flunarizine dihydrochloride immediate release tablets separately in different medias 0.1 N HCl, pH 4.5, 6.8 and water at 60 minutes.

Raghavendra Rao NG et al.[41] develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers HPMC, Karaya gum and Carrageenan. The effect of polymer concentration and polymer blend concentration were studied by employing different ratios of polymers. The *in vitro* release study was performed in 0.1 N Hcl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The results showed that 20% HPMC K15M and 80% of carageenan release the drug which follows Zero order kinetics and was comparable with release rate of the marketed product.

Punna Rao Ravi et al.[42] formulated the oral controlled release matrix tablets of Lamivudine using HPMC as the retardant polymer. The effect of various formulation factors such as polymer proportion, polymer viscosity, and compression force on the in vitro release of drug was studied. *In vitro* release studies revealed that the increase in polymer proportion and viscosity grade and increase in compression force was found to decrease the rate of drug

release. Formulations containing 60% HPMC 4000 cps were found to show good initial release and extended the release up to 16 hrs while tablets containing 80% HPMC 4000 cps and 60% HPMC 15 000 cps showed a first-hour release of 22% but extended the release up to 20 hours.

Raghavendra Rao NG et al.[43] developed a system comprises of different doses of immediate release tablets and sustained release tablets of Montelukast sodium contained in a HPMC capsule. Two immediate release and three sustained release tablets were used to obtain different drug release rates. *In vitro* evaluation showed that the drug contained in the immediate release tablets dissolved within the first 45 min, and the drug contained in the sustained release tablets formulated using HPMC released over a period of 10 to 12 hrs. The study states that this multiparticulate delivery system offers chronotherapeutic advantage in nocturnal asthma.

Shinichiro Tajiri et al.[44] developed two types of extended-release tablets of cevimeline simple matrix tablets and press-coated tablets and assessed their potential as extended-release dosage forms. The results showed that simple matrix tablets could not sustain the release of cevimeline while the press-coated tablets showed a slower dissolution rate compared with simple matrix tablets and the release curve was nearly linear. The results concluded that cevimeline was constantly released from the press-coated tablets in the gastrointestinal tract and the steady-state plasma drug levels were maintained in beagle dogs.

Santanu Ghosh et al.[45] developed matrix tablets for oral controlled release of Aceclofenac using various viscosity of hydrophilic polymer HPMC in two different proportions and ethyl cellulose and Guar gum were prepared by wet granulation method. *In vitro* dissolution studies were performed for 0-12 hrs. The dissolution medium was phosphate buffer 7.5. It was found that the *in vitro* dissolution profile of Aceclofenac is almost similar with that of marketed product. The kinetics of the release process of drug in the formulations were studied using different dissolution models. The finalized formulation followed Higuchi model.

Syed Azeem Hyder et al.[46] attempted to increase the rate of dissolution of Rupatidine by using superdisintegrants CMC, crospovidone and alginic acid. 3^2 full factorial design was used to investigate the joint influence of 2 independent variables: amount of selected superdisintegrant crospovidone and hardness of the tablets. The results of multiple linear regression analysis revealed that the dependent variables disintegration time and drug release at 0.5h values are strongly dependent on the selected independent variables.

Sharma et al.[47] developed a mouth dissolving tablets of Domperidone containing camphor and crospovidone by direct compression technique. A 3^2 full factorial design was used to investigate the joint influence of two formulation variables, amount of camphor and crospovidone. The results suggested that tablets should be prepared using an optimum concentration of camphor and high concentration of crospovidone

Shivakumar HN et al.[48] formulated a pH-sensitive tablet in capsule system intended to approximate the Chronobiology of nocturnal asthma and for site specific release to the colon. Drug-loaded core minitablets were produced by wet granulation procedure using alcoholic solution of PVP K 30 as a binder and coated using Eudragit S-100 to produce the pH sensitive minitablets. The studies showed that a Eudragit S-100 coat weight of 10% weight gain was sufficient to impart an excellent gastro resistant property to the tablets for effective release of the drug at higher pH values.

Umesh D Shivhare et al.[49] formulated sustained release once daily tablets of Aceclofenac by wet granulation using carboxy polymethylene polymer. *In vitro* dissolution studies were performed using phosphate buffer 6.8. Formulations containing Carbopol 971P and Carbopol 974P were found to release the drug in sustained manner upto 24 hour. Different dissolution models were applied to evaluate drug release mechanism and kinetics and the hydrophilic matrix tablets formulated.

Ying-huan Li et al.[14] developed a multifunctional and multiple unit system, which contains different mini-tablets such as Rapid-release Mini-Tablets, Sustained-release Mini-Tablets, Pulsatile Mini-Tablets, and Delayed-onset Sustained-release Mini-Tablet in a hard gelation capsule, each with various lag times of release. Based on the combinations of mini-tablets, multiplied pulsatile drug delivery system, site-specific, slow/quick, quick/slow, and zero-order drug delivery system could be obtained. Nifidipine was used as the model drug.

Literature pertaining to the excipients

Hardy IJ et al.[50] studied modulation of drug release kinetics from HPMC matrix tablets using PVP. The study presents a simple, cost effective and elegant solution for achieving a range of predictable release profiles from linear to bimodal for a water-soluble drug (Caffeine) form HPMC matrices through the inclusion of PVP. Mechanistic studies using gel rheology, excipient dissolution and near infrared microscopy are presented which shows the modulation of drug release.

Harris Shoaib M et al.[51] studied the evaluation of drug release kinetics from Ibuprofen matrix using HPM**C.** Different dissolution models were applied to evaluate drug release mechanism and kinetics. The drug release data fit well to the Higuchi expression. Drug release mechanism as a complex mixture of diffusion, swelling and erosion.

Khanvilkar KH et al.[52] studied the effects of use of a mixture of two different grades of HPMC, apparent viscosity and tablet hardness on drug release profiles of extended-release matrix tablets. A 2(3) full factorial design was used. Dissolution studies were performed in USP apparatus I and $t_{50\%,}$ t_{lag} values are used for evalution of matrix tablets. The study concluded that within the viscosity range studied (12,000-19,500 cps) an HPMC mixture of two viscosity grades can be substituted for another HPMC grade if the apparent viscosity is comparable. And the drug release is diffusion-controlled and depends mostly on the viscosity of the gel layer formed.

Melanie Dumarey et al.[53] studied the influence of microcrystalline cellulose properties on the roll compaction process. Four dissimilar MCC grades were selected for study. It confirmed that the particle size increase caused by roll compaction is highly responsible for the tensile strength decrease of the tablets. The evaluation of the full factorial design shows that the Ceolus KG-1000 resulted in tablets with higher tensile strength and shorter disintegration time, compared to the other MCC grades.

Mira Jivraj et al.[54] studied that many formulation scientists ranked microcrystalline cellulose as the most useful filler for direct compression. It reveals that the popularity ascribed to its excellent compactibility at low pressures, high dilution potential and superior disintegration properties. This study concluded that as a result of its low bulk density, microcrystalline cellulose has a high dilution potential.

Obae K et al.[55] made attempt to fractionate microcrystalline cellulose particles of Avicel® PH-101 and Ceolus® KG-801 into four sieve fractions by using an air-jet sieve and to disclose effects of morphology of the particle on tablet tensile strength. It increased with an increase in the ratio of L:D for particles (L- length: D- width). KG grade consists of a larger number of rod-shaped particles than PH grade, giving significantly higher compressibility than PH grade. It also revealed that the hardness of tablets made of the KG grade is about 1.5 times higher than that of the standard PH grade, but both tablets can be disintegrated easily within the same

short period once they come in contact with water. This study concluded that the high compressibility of KG grade enables to improve the tensile strength of tablets.

Ranjani V Nellore et al.[56] developed model extended-release matrix tablet formulations for Metoprolol tartrate. Different grades of HPMC K4M, K15M, K100M and K100LV were used. Three granulation processes were employed for the preparation of tablets. In vitro drug release testing was performed in pH 6.8 phosphate buffer using USP apparatus type II at 50 rpm. The study results suggested that HPMC K100LV can be used as the hydrophilic matrix polymer and fluid-bed granulation as the process of choice for further evaluation of critical and non-critical formulation and processing variables.

Takumi Magome et al.[57] compared the tableting properties of Ceolus KG-1000 with other microcrystalline cellulose products in roller compaction using an acetaminophen formulation. In this comparison Microcrystalline cellulose products used were Ceolus KG 1000, Ceolus KG 802, and Ceolus PH 101. Roller compaction was done at 15 kN 30 kN and 50kN. When the roller compaction force increased, the tablet hardness decreased with other grades while tablets with KG-1000 could only keep around 50 N that is considered as practically required hardness.

Profiles

MARKETED FORMULATIONS [58-62]

ACECLOFENAC

TRADENAME	STRENGTH	DOSAGE FORM	MANUFACTURER
Indian brands			
Valus –A	100mg	Tablet	Glenmark
Aroff	100mg	Film coated tablet	Unichem
Fastanac SR	200mg	Sustained release tablet	Lupin
Aceclo	200mg	Sustained release FC tablet	Aristo
Zerodol CR	200mg	Controlled release tablet	IPCA
Zynac	150mg/ml	Injection	Zydus
International brands			
Preservex	100mg	Film coated tablets	Almirall ltd
Airtal	100mg	Tablet	Highnoon
Bristaflam	100mg	Oral powder	Bristoll Mayer Squibb

COMBINATION PRODUCTS OF ACECLOFENAC

TRADE NAME	COMBINATION AND STRENGTH	DOSAGE FORM	MANUFACTURER
Altra day	Aceclofenac 200mg, Rabeprazole 20mg	Spantules	Inventia
Altraflam-P	Aceclofenac 100mg , Paracetamol 500mg	Tablets	Ranbaxy
Peale	Aceclofenac 1.5%w/w , Methyl Salycilate 105w/w, Oleum lini 3% w/w, Menthol 5% w/w, Capsaicin 0.01%w/w, Benzyl alcohol 1% w/w	Gel	Cadila

MISOPROSTOL

TRADE NAME	STRENGTH	DOSAGE FORM	MANUFACTURER
Indian Brands			
Misoprost	Misoprostol 25, 100, 200mcg	Tablet	Cipla
Prestakind	Misoprostol 200mcg	Tablet	Mankind
Misolast	Misoprostol 200mcg	Tablet	FDC
International brands			
Cytotec	Misoprostol 200mcg	Tablet	GD Searle LLC
Cyprostol	Misoprostol 200mcg	Tablet	Idis
Gymiso	Misoprostol 200mcg	Tablet	HRA Pharma
Apo-Misoprostol	Misoprostol 100, 200mcg	Tablet	Apotex
Misotrol	Misoprostol 200mcg	Tablet	Sanofi Aventis

COMBINATION PRODUCTS OF MISOPROSTOL

TRADE NAME	COMBINATION AND STRENGTH	DOSAGE FORM	MANUFACTURER
Arthotec	Misoprostol 200mcg, Diclofenac 50, 75mg	Tablet	GD Searle LLC
Artene	Misoprostol 200mcg, Diclofenac 150mg	Tablet	Merck
Misonac	Misoprostol 200mcg, Diclofenac 50, 100mg	Tablet	Ordain Health care

DRUG PROFILE[63-70]

Drug name : Aceclofenac

Chemical name : [[[2-[(2, 6-Dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid.

Synonym : Aceclofenaco,Aceclofenacum,aceclofenakas

CAS number : 89796-99-6

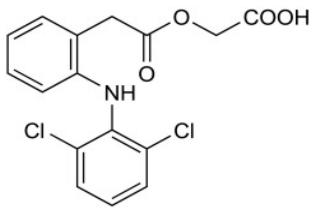
Mol.formula : $C_{16}H_{13}C_{l2}NO_4$

Mol.weight : 354.2

Melting point : 149° to 150° C

Origin of substance : Synthetic

Structure :



Category : Non Steroidal Anti-Inflammatory Drug

Solubility : It is practically insoluble in water, soluble in alcohol, freely soluble in Acetone and dimethyl formamide.

Proprietary names : Airtal, Barcan, Biofenac, Difucrem, Falcol, Gerbin, Preservex, Sanein.

CLINICAL PHARMACOLOGY

Mechanism of action

Aceclofenac relieves pain and inflammation through a variety of mechanisms and in addition exerts stimulatory effects on cartilage matrix synthesis.

Anti-Inflammatory activity

The anti-inflammatory effects of Aceclofenac have been shown in both acute and chronic inflammation. It inhibits various mediators of pain and inflammation including,

- **PGE2 via cyclooxygenase inhibition** (COX-1 & COX-2) after intracellular metabolism to 4- hydroxy-aceclofenac and Diclofenac in human rheumatoid synovial cells and other inflammatory cells.
- **IL-1β, IL-6 and tumor necrosis factor** in Human Osteoarthritic Synovial cells and human articular chondrocytes.
- **Reactive oxygen species** (which plays a role in joint damage) has also been observed in patients with osteoarthritis of knee.
- **Expression of cell adhesion molecules** (which is implicated in cell migration and inflammation) has also been shown in human neutrophils.

Stimulatory effects on cartilage matrix synthesis

Aceclofenac stimulates glycosaminoglycan synthesis in human osteoarthritic cartilage by inhibition of IL-1β and suppresses cartilage degeneration by inhibiting IL-1β mediated promatrix metalloproteinase production and proteoglycan release.

PHARMACOKINETICS

Absorption

Aceclofenac is absorbed rapidly and completely after oral administration. Peak plasma concentrations are reached approximately 1-3 hours after an oral dose. The presence of food does not alter the extent of absorption of Aceclofenac but the absorption rate is reduced.

Distribution

Aceclofenac is highly protein bound (~99.7%). The plasma concentration of Aceclofenac was approximately twice that in synovial fluid and multiple doses of drug in patients with knee pain and synovial fluid effusion. The volume of distribution is approximately 30L.

Metabolism

Aceclofenac is metabolized into a major metabolite, 4- hydroxy Aceclofenac and to a number of other metabolites including 5-hydroxy Aceclofenac, 4- hydroxy Diclofenac, and 5-hydroxy Diclofenac. These other metabolites account for the fate of approximately 20% of each dose of Aceclofenac.

Excretion

Renal excretion is the main route of elimination of Aceclofenac with 70-80% of the administered dose found in the urine, mainly as the glucuronides of Aceclofenac and its metabolites. Of each of dose of Aceclofenac, 20% is excreted in the faeces. The plasma elimination half-life of the drug is approximately 4 hours.

Indications

Aceclofenac is indicated for the relief of pain and inflammation associated with Rheumatoid arthritis, Osteoarthritis and in Ankylosing spondylitis.

Contraindications

Aceclofenac should not be administered to patients hypersensitive to Aceclofenac or other NSAID's, or patients with history of Aspirin or NSAID's related allergic and to patients with anaphylactic reactions or with peptic ulcers or GI bleeding, moderate of severe renal impairment.

Drug interactions

Drug interactions associated with Aceclofenac are similar to those observed with other NSAID's. Aceclofenac may increase plasma concentrations of Lithium, Digoxin and Methotrexate, increase the activity of anti coagulants, inhibit activity of Diuretics, enhance Cyclosporine Nephrotoxicity and precipitate convulsions when co administered with Quinolone antibiotics. The co-administration of Aceclofenac with other NSAID's or corticosteroids may result in increased frequency of adverse events.

Adverse drug reactions

Aceclofenac is well tolerated with most adverse events being minor and reversible and affecting mainly the GI system. Most common events includes dyspepsia, and abdominal pain, dizziness, vertigo, pruritis, rash and dermatitis have been reported with Aceclofenac, but the incidence of these events is less than 5%. Increased blood urea nitrogen and blood creatinine level have been reported with Aceclofenac treatment. As with other NSAID's, Aceclofenac can elevate circulating levels of hepatic enzymes.

Dose and Administration

The usual dose of Aceclofenac is 100mg given orally twice daily. There is some evidence that the dose of Aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100mg be used.

Over dosage

There are no human data available on the consequences of Aceclofenac over dosage. The symptoms could be nausea, vomiting, stomach pain, dizziness, somnolence, and headache.

Therapeutic Uses

Aceclofenac is used in

- Osteoarthritis
- Rheumatoid arthritis
- Ankylosing spondylitis
- Dental pain
- Postoperative pain
- Dysmenorrhoea
- Acute lumbago
- Musculoskeletal trauma
- Gonalgia (knee pain)

Drug name : Misoprostol

Chemical name : (11α,13E)-11,16-Dihydroxy–16–methyl–9–oxoprost–13–en–1–oic acid methyl ester

Synonym : Misoprostolum, Mizoprostol

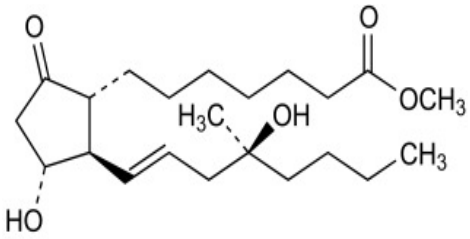
CAS number : 59122-46-2

Mol.formula : $C_{22}H_{38}O_5$

Mol.weight : Average: 382.5341
Monoisotopic: 382.271924326

Origin of substance: Synthetic

Structure :



(11*R*, 16*S*)-Form

Categories : Anti-Ulcer Agents
Oxytocics
Nonsteroidal Abortifacient Agents
Prostaglandins

Solubility : Water-soluble, Viscous liquid

Proprietary names : Cytotec, Arthrotec (with Diclofenac), Napratec (with Naproxen)

CLINICAL PHARMACOLOGY

Mechanism of action

The significant Cytoprotective actions of Misoprostol are related to several mechanisms. These include,

- Increased secretion of bicarbonate,
- Considerable decrease in the volume and pepsin content of the gastric secretions,
- It prevents harmful agents from disrupting the tight junctions between the epithelial cells which stops the subsequent back diffusion of H+ ions into the gastric mucosa,
- Increased thickness of mucus layer,
- Enhanced mucosal blood flow as a result of direct vasodilatation,
- Stabilization of tissue lysozymes/vascular endothelium,
- Improvement of mucosal regeneration capacity, and
- Replacement of prostaglandins that have been depleted as a result of various insults to the area. Misoprostol has also been shown to increase the amplitude and frequency of uterine contractions during pregnancy via selective binding to the EP-2/EP-3 prostanoid receptors.

PHARMACOKINETICS

Absorption : Misoprostol is extensively absorbed. Approximately 88% of a dose is absorbed.

T_{max} : 12 ± 3 min

Half life : Misoprostol, less than 30 min, Misoprostol acid 20 min

Volume of distribution : Approximately 6.6 L/kg

Metabolism : It undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs.

Protein binding : 85% (the free acid of Misoprostol)

Route of Elimination

Excreted mainly via urine as its dimer and tetramer (65%) and some in faeces (15%) . Excretion is mainly in the form of metabolites but little as the unchanged drug. After a single oral dose of Misoprostol to nursing mothers, Misoprostol acid was excreted in breast milk.

Indications

- Treatment of ulceration (duodenal, gastric and NSAID induced) and prophylaxis for NSAID induced ulceration.
- Misoprostol is indicated for the medical termination of an intrauterine pregnancy, used alone or in combination with Methotrexate, as well as the induction of labour in a selected population of pregnant women with unfavourable cervices.
- Misoprostol is used for the prevention, treatment of serious postpartum hemorrhage.

PHARMACODYNAMICS

Misoprostol is a prostaglandin E1 (PGE1) analogue used for the treatment and prevention of stomach ulcers. When administered,

- Misoprostol stimulates increased secretion of the protective mucus and increases mucosal blood flow, thereby increasing mucosal integrity.
- Misoprostol seems to inhibit gastric acid secretion by a direct action on the parietal cells through binding to the prostaglandin receptor.
- The activity of this receptor is mediated by G proteins which normally activate adenylate cyclase. The indirect inhibition of adenylate cyclase by Misoprostol may be dependent on guanosine-5'-triphosphate (GTP).

Dosage and administration

The recommended adult oral dose of Misoprostol for reducing the risk of NSAID-induced gastric ulcers is 200 mcg four times daily with food. It should be taken for the duration of NSAID therapy as prescribed by the physician. It should be taken with a meal, and the last dose of the day should be at bedtime.

Adverse reactions

Gastrointestinal adverse events such as diarrhoea and abdominal pain, the incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding co-administration of Misoprostol with magnesium-containing antacids. Gynecological disorders

such as spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%), Postmenopausal vaginal bleeding.

Warnings

Misoprostol administration to pregnant women can cause abortion, premature birth, or birth defects, Uterine rupture. It should not be taken by pregnant women to reduce the risk of ulcers induced by NSAID. It should not be used for reducing the risk of NSAID-induced ulcers in women of childbearing potential unless the patient is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, Misoprostol may be prescribed if the patient

- Has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- Is capable of complying with effective contraceptive measures.
- Has received both oral and written warnings of the hazards of Misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- Will begin Misoprostol only on the second or third day of the next normal menstrual period.

Precautions

Caution should be employed when administering Misoprostol to patients with pre-existing cardiovascular disease. Women of childbearing potential using Misoprostol to decrease the risk of NSAID-induced ulcers should be told that they must not be pregnant when Misoprostol therapy is initiated, and that they must use an effective contraception method.

Special precautions

- Adjustment of the dosing schedule in renal impaired patients is not routinely needed, but dosage can be reduced if the 200mcg dose is not tolerated.
- There were no significant differences in the safety profile of Misoprostol in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

EXCIPIENT PROFILE[53, 55, 57, 71-73]

MICROCRYSTALLINE CELLULOSE[72]

Nonproprietary Names

BP, JP : Microcrystalline cellulose

PhEur : Cellulosum microcristallinum

USP-NF : Microcrystalline cellulose

Synonyms

Avicel PH, Celex, cellulose gel, Celphere, Ceolus KG, Crystalline Cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.

Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

Functional Category

Adsorbent, Suspending agent, Tablet and Capsule diluent, Tablet disintegrant.

Applications in Pharmaceutical Formulation

As a binder/diluent in oral tablet and capsule formulation in both wet-granulation and direct-compression processes.

Table 7.1: Application of Microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluents	20–90
Tablet disintegrant	5–15
Tablet binder/diluents	20–90

Table 1.2: Typical Properties of MCC

Angle of Repose	Density(g/cm^3)			Flowablity	Melting Point ° C	Moisture content
	Bulk	Tapped	True			
49°	0.337	0.478	1.512-1.668	1.41g/s	260-280	< 5%w/w

Solubility : Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.

Incompatibilities

Cellulose acetate is incompatible with strongly acidic or alkaline substances. Cellulose acetate is compatible with the following plasticizers diethyl phthalate, polyethylene glycol, triacetin, and triethyl citrate.

Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Uniqueness of *Ceolus* KG 1000[71, 73]

- Distinguished by its rod-form particle configuration which aids inter-particle cohesion when compression force is applied, resulting in twice the compactibility of conventional MCC.
- This enables tablets of equivalent hardness to be produced with lower compression force and less excipient than would conventionally be required.
- Posses the largest L/D ratio when compared to other grades KG-1000: 3.5, KG-802: 2.8, PH-101: 1.8
- The particles are porous, rounded composites of multiple micro-rods. The result is an unparalleled combination of compressibility and flowability.
- Heightened efficiency in direct-compression tableting with gravity feeder
- Decreased capping
- Enhanced tabletting efficiency

The advantages of ***Ceolus KG*** 1000 are [73]

- Smaller tablet size make large-dose drugs without increasing tablet size, and to make small, easy-to-swallow tablets for seniors
- Tabletting at low compression force enables tabletting of drugs which are sensitive to loss of activity due to heat generated during compression
- Reduced tablet breakage and fragmentation improves productivity by lowering production loss

HYPROMELLOSE[72]

Nonproprietary Names

BP, USP : Hypromellose

JP : Hydroxypropylmethylcellulose

PhEur : Hypromellosum

Synonyms

Benecel MHPC, E464, hydroxypropyl methylcellulose, HPMC, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, Tylopur.

Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

Functional Category

Coating agent,film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Applications in Pharmaceutical Formulation

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

Table 7.3: Application of Hypromellose

Concentration	Application
2-5%	Tablet binder
2-20%	Film-coating material
10-80%	Matrix extended release tablet

Table 7.4: Typical Properties of Hypromellose

Acidity/Alkailinity (1% w/w aq.solution)	Ash	Density(g/cm^3)			Melting Point ° C	Moisture content
		Bulk	Tapped	True		
pH 5.5-8	1.5-3	0.341	0.557	1.326	225-230	Depends on RH and temperature

Solubility

- Hypromellose is soluble in cold water
- It is also soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol
- Practically insoluble in chloroform, ethanol (95%), and ether

Specific gravity **:** 1.26

Viscosity of Hypromellose Grades

2% w/v aqueous solutions of Hypromellose are measured at 20 °C

Table 7.5: Viscosity of different grades of Hypromellose

Nominal Viscosity of HPMC in mPa s				
K100 LV CR	**K4 CR**	**K15 CR**	**K100M CR**	**E50**
80-120	3000-5600	11250-21000	80000-120000	50

Stability and Storage Conditions

Solutions are stable at pH 3–11. Aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents.

STEARIC ACID[72]

Nonproprietary Names

BP, JP, USPNF : Stearic acid

PhEur : Acidum stearicum

Synonyms

Cetylacetic acid, Crodacid, E570, Edenor, Emersol, Hystrene, Industrene, Kortacid 1895, Pearl Steric, Pristerene, stereophonic acid, Tegostearic.

Chemical Name and CAS Registry Number

Octadecanoic acid [57-11-4]

Functional Category

Emulsifying agent, Solubilizing agent, Tablet and Capsule lubricant.

Applications in Pharmaceutical Formulation

Stearic acid is widely used in oral and topical pharmaceutical formulations.

It is mainly used in oral formulations as a

- Tablet and capsule lubricant, binder, in combination with shellac as a tablet coating.
- In topical formulations, stearic acid is used as an emulsifying and solubilizing agent in the preparation of creams.
- Stearic acid is used as the hardening agent in glycerin suppositories.

Table 7.6: Application of Stearic acid

Use	Concentration (%)
Ointments and creams	1–20
Tablet lubricant	1–3

Table 7.7: Typical Properties of Stearic Acid

Acid Value	Density (g/cm^3)			Melting Point ° C	Moisture content	Saponification value
	Bulk	Tapped	True			
200-212	0.537	0.571	0.980	554	No Water	200-220

Solubility: Freely soluble in benzene, carbon tetrachloride, chloroform, and ether, soluble in ethanol (95%), hexane and propylene glycol, practically insoluble in water.

Specific surface area: 0.51–0.53m^2/g

Stability and Storage Conditions

Stearic acid is a stable material, an antioxidant may also be added to it. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

- Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents.
- Insoluble stearates are formed with many metals, ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salt.
- Incompatible with naproxen, Stearic acid has been reported to cause pitting in the film coating of tablets coated using an aqueous film-coating technique, the pitting was found to be a function of the melting point of the stearic acid.

CROSPOVIDONE[72]

Nonproprietary Names

BP, USPNF : Crospovidone

PhEur : Crospovidonum

Synonyms

Crosslinked povidone, E1202, Kollidon CL, Kollidon CL-M, Polyplasdone XL, Polyplasdone XL-10, polyvinylpolypyrrolidone, PVPP, 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Functional Category

Tablet disintegrant.

Applications in Pharmaceutical Formulation

- Crospovidone is used as tablet disintegrant and dissolution agent at concentration 2-5%
- Crospovidone can also be used as a solubility enhancer

Table 7.8: Typical Properties of Polyplasdone XL

Acidity/alkalinity	Density		Moisture content
	Bulk	Tapped	
pH 5-8	0.213	0.273	Maximum sorption 60%

Solubility

Practically insoluble in water and most common organic solvents.

Stability and storage conditions

Crospovidone is hygroscopic, and should be stored in cool and dry place

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

COLLOIDAL SILICON DIOXIDE[72]

Nonproprietary Names

BP : Colloidal anhydrous silica

PhEur : Silica colloidalis anhydrica

USPNF : Colloidal silicon dioxide

Synonyms

Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, Wacker HDK.

Chemical Name and CAS Registry Number

Silica [7631-86-9]

Functional Category

Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

Applications in Pharmaceutical Formulation

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics and food products.

- To improve the flow properties of powders in a number of processes such as tableting
- To stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.
- In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles.
- As a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.
- Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate.
- Colloidal silicone dioxide is also used as an adsorbent during the preparation of wax microspheres
- As a thickening agent for topical preparations
- Used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

Table 7.9: Application of Colloidal Silicon dioxide

Use	Concentration (%)
Aerosols	0.5–2.0
Emulsion stabilizer	1.0–5.0
Glidant	0.1–0.5
Suspending and thickening agent	2.0–10.0

Table 7.10: Typical Properties of Colloidal silicon dioxide

Acidity/alkalinity 4%w/v aq. dispersion	Density(g/cm^3)		Flowablity (% CI)	Refractive index
	Bulk	Tapped		
pH 3.5-4.4	0.029-0.042	0.04	35.52%	1.46

Particle size distribution: 7–16 nm.

Solubility : Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid, soluble in hot solutions of alkali hydroxide, forms a colloidal dispersion with water.

Specific gravity : 2.2

Specific surface area : 200–400m^2/g

Stability and Storage Conditions

Colloidal silicon dioxide is hygroscopic. It should be stored in a well-closed container.

Incompatibilities

Incompatible with diethylstilbestrol preparations.

ISOPROPYL ALCOHOL[72]

Nonproprietary Names

BP, USP : Isopropyl alcohol

JP : Isopropanol

PhEur : Alcohol isopropylicus

Synonyms

Dimethyl carbinol, IPA, Isopropanol, Petrohol, 2-propanol, sec-propyl alcohol.

Chemical Name and CAS Registry Number

Propan-2-ol [67-63-0]

Functional Category

Disinfectant, Solvent.

Applications in Pharmaceutical Formulation

- Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations primarily as a solvent in topical formulations
- It is used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation
- 70% v/v aqueous solution is used as a topical disinfectant

Typical Properties

Antimicrobial activity: isopropyl alcohol is bactericidal, at concentrations greater than 70% v/v and it is a more effective antibacterial preservative than ethanol (95%).

Auto ignition temperature : 42.5°C

Boiling point : 82.4°C

Dielectric constant : D20 = 18.62

Explosive limits : 2.5–12.0% v/v in air.

Flammability : flammable.

Flash point : 11.7°C (closed cup), 13°C (open cup). The water azeotrope has a flash point of 16°C.

Freezing point : 89.5°C

Melting point : 88.5°C

Moisture content : 0.1–13% w/w for commercial grades

Refractive index

- n_D^{20} = 1.3776
- n_D^{25} = 1.3749

Solubility

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone, insoluble in salt solutions. Forms an azeotrope with water, containing 87.4% w/w isopropyl alcohol.

Specific gravity : 0.786

Vapor density (relative) : 2.07 (air = 1)

Vapor pressure

- 133.3 Pa (1mmHg) at -26.1°C
- 4.32 kPa (32.4 mmHg) at 20°C
- 5.33 kPa (40 mmHg) at 23.8°C
- 13.33 kPa (100 mmHg) at 39.5°C

Viscosity (dynamic) : 2.43 mPa s (2.43 cP) at 20°C

Stability and Storage Conditions

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, sodium chloride, sodium sulfate and other salts sodium hydroxide.

DISEASE PROFILE[18, 74-77]

OSTEOARTHRITIS

Osteoarthritis (OA) represents failure of the diarthrodial (movable, synovial-lined) joint. It is also erroneously called as degenerative joint disease. OA is primarily a disease of cartilage that reflects a failure of the chondrocyte to maintain proper balance between cartilage formation and destruction. This leads to loss of cartilage in the joint, local inflammation, pathologic changes in underlying bone, and further damage to cartilage triggered by the affected bone.

According to the American College of Rheumatology, OA may be of

- **Idiopathic**
  - Localized (spine, knee, hip, hands, feet, elbow, shoulder, and other joints)
  - Generalized (involving 3 or more joints)
- **Secondary**
  - Trauma
  - Developmental and congenital diseases (dysplasia etc.)
  - Metabolic diseases (gout etc.)
  - Endocrine disorders (diabetes, hypothyroidism etc.)
  - Calcium deposition diseases (pyrophosphate, hydroxyapatite etc.)
  - Other bone and joint diseases (rheumatoid arthritis etc.)
  - Neuropathic (Charcot) arthropathy
  - Septic arthritis

Epidemiology

OA is the most common joint disease of humans. Among the elderly, knee OA is the leading cause of chronic disability in developed countries. Some 100,000 people in the United States are unable to walk independently from bed to bathroom because of OA of the knee or hip.

- In older individuals, hip OA is more common in men, while OA of interphalangeal joints and the thumb base is more common in women. Similarly symptomatic knee OA is more common in women than in men

- Racial differences exist in both the prevalence of OA and the pattern of joint involvement. The Chinese in Hong Kong have a lower incidence of hip OA than whites. OA is more frequent in Native Americans than in whites. Interphalangeal joint OA and especially hip OA are much less common in South African blacks than in whites in the same population
- Age is the most powerful risk factor for OA. In a radiographic survey of women 45 years, only 2% had OA, between the ages of 45 and 64 years, however, the prevalence was 30% and for those 65years it was 68%.
- The prevalence of clinician-diagnosed arthritis is estimated at 46 million in the United States and is projected to increase to nearly 67 million by 2030, of which 25 million are expected to report arthritis related activity limitations.

Incidence

The overall incidence of hip or knee OA is approximately 200 per 100,000 person-years. Approximately one-half million symptomatic new cases of OA are estimated to occur annually in the United States.

Risk Factors for OA

- Age
- Repetitive stress, e.g. Vocational
- Female sex
- Obesity
- Race Congenital/developmental defects
- Genetic factors Prior inflammatory joint disease
- Major joint trauma
- Metabolic/endocrine disorders

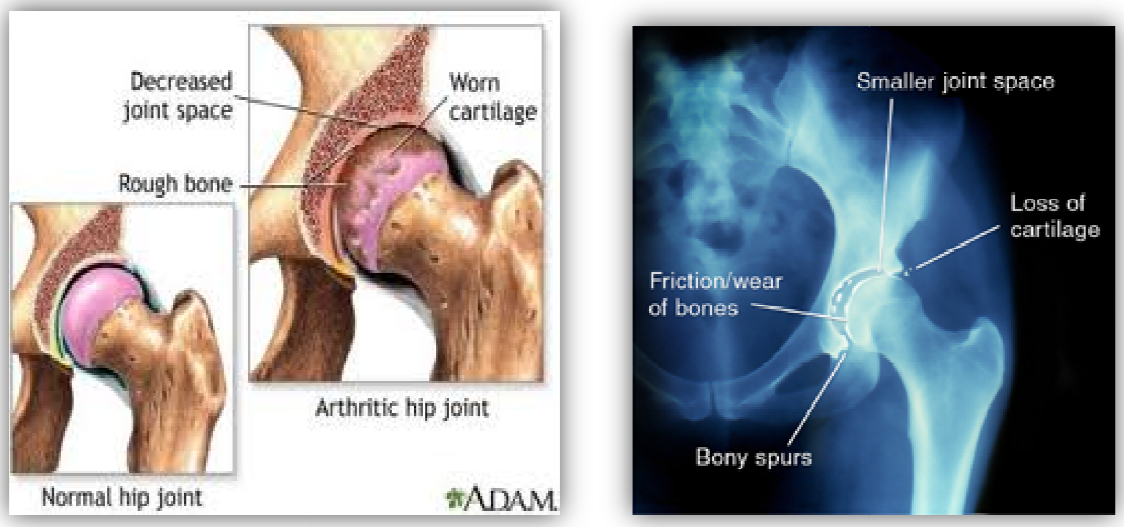


Fig 8.1: Normal and osteoarthritic joint

Fig 8.2: Normal cartilage and osteoarthritic cartilage

Developmental Stages of Osteoarthritis

1. **Destruction of the cartilage**
    - Proteolytic damage to the cartilage matrix
2. **Inflammation of the synovial membrane**
    - Fibrillation and erosion of the cartilage surface and release of degradation products from the synovial fluid
3. **Remodeling of subchondral bone**
    - The synovial cells consume the degradation products. Production of inflammatory proteases and cytokines.

Physiopathology of Osteoarthritis

The physiopathology of OA is not completely understood, but progress is being made.

- Under normal conditions, the components of the cartilage matrix are gradually replaced. Chondrocytes are the cells responsible for this metabolism, in which synthesis (anabolism) and destruction (catabolism) are balanced in a coordinated way
- When this process is altered, a series of changes occurs in the morphological and biomechanical characteristics of cartilage that make it fail to perform its function.
- Protease inhibitors and anti-inflammatory cytokines participate in the anabolic process, where the final aims are the formation of the extracellular matrix and cell proliferation.
- Pro-inflammatory cytokines and proteases participate in the catabolic process, which results in the destruction of the cartilage matrix and a reduction of cell proliferation.

Signs and Symptoms

Nearly all patients have pain in the affected joints, with the hands, knees, and hips being the most common locations with motion, but pain in late disease can occur with rest.

- Joint stiffness resolves with motion; recurs with rest
- Joint stiffness with or without joint enlargement
- Crepitus, a crackling or grating sound heard with joint movement that is caused by irregularity of joint surfaces may be present
- Limited range of motion that may be accompanied by joint instability

- Late-stage disease is associated with joint deformity

Diagnosis

In general, the disease can be detected because of its clinical and radiological signs. Some of the methods used to detect the clinical manifestations of osteoarthritis include:

- Measuring pain using Huskisson's Visual Analogue Scale, **WOMAC** (Western Ontario and McMaster Universities) **Osteoarthritis Index**
- Measuring functional status
- Joint-fluid aspiration
- Radiology
- Other tests include: Nuclear Magnetic Resonance (NMR), Ultrasound, Bone Gammagram, CT scan, Arthroscopy.
- A system of Radiographic Grading of osteoarthritis is also used. It was developed by Kellgren and Lawrence and is key in current radiological assessment of osteoarthritis.

Table 8.1: Grades of Osteoarthritis

Grade	Classification	Description
0	Normal	No characteristic symptoms of osteoarthritis
1	Doubtful	Indications of Osteophytes Significance doubtful
2	Minimal	Definite Osteophytes
3	Moderate	Moderate narrowing of joint space
4	Severe	Joint space very narrow, with Subchondral-bone sclerosis

Treatment

The most common symptom associated with OA is pain, which leads to decreased function and motion. Pain relief is the primary objective of medication therapy

Non Pharmacologic Measures

Non pharmacologic therapy is the foundation of the pharmaceutical care plan and should be initiated before or concurrently with pharmacologic therapy.

- Reduction Of Joint Loading
- Patellar taping
- Thermal modalities
- Exercise
- Wedged insoles/orthoses
- Diet

Pharmacologic Therapy

Drug therapy for OA today is palliative, no pharmacologic agent has been shown to prevent, delay the progression of, or reverse the pathologic changes of OA in humans. It includes the following,

- NSAID and Acetaminophen
- Glucocorticoid injection
- Intraarticular Injection Of Hyaluronan
- Opioids
- Rubefacients/Capsaicin
- Orthopedic surgery
- Glucosamine, Chondroitin Sulfate
- Cartilage regeneration

Recommended drug treatment starts with acetaminophen ≤4 g/day and topical analgesics as needed. If acetaminophen is ineffective, NSAIDs may be used, often providing satisfactory relief of pain and stiffness.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. The characteristic feature of RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution.

The potential of the synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in joint integrity is the hallmark of the disease.

Epidemiology

- The prevalence of RA is approximately 0.8% of the population.
- The disease is three times more common in women. In people ages 15 to 45 years, women predominate by a ratio of 6:1. The sex ratio is approximately equal among patients in the first decade of life and in those older than age 60 years
- Rheumatoid arthritis is six times more common among dizygotic twins and non-twin children of parents with rheumatoid factor-positive erosive rheumatoid arthritis when compared with children whose parents do not have the disease
- If one of a pair of monozygotic twins is affected, the other twin has a 30 times greater risk of developing the disease.

Etiology

The cause of RA remains unknown. It has been suggested that RA might be a manifestation of the response to an infectious agent in a genetically susceptible host. The factors that initiate the inflammatory process are unknown.

- Chronic inflammation of the synovial tissue lining the joint capsule results in the proliferation of this tissue. The inflamed, proliferating synovium characteristic of rheumatoid arthritis is called Pannus.
- This Pannus invades the cartilage and eventually the bone surface, producing erosions of bone and cartilage and leading to destruction of the joint.

Pathophysiology

In rheumatoid arthritis, this no longer can differentiate self from non-self tissues and attacks the synovial tissue and other connective tissues. Most patients with rheumatoid arthritis form antibodies called Rheumatoid Factors.

- Rheumatoid factors have not been identified as pathogenic, nor does the quantity of these circulating antibodies always correlate with disease activity.
- Seropositive patients tend to have a more aggressive course of their illness than do seronegative patients.
- Immunoglobulins can activate the complement system and other inflammatory mediators such as T-cells (helper and killer),TNF, IL-1, IL-6, IL-4,IL-5, IL-10 results in activation of cytokines which are directly toxic to tissues, and cytokines, which stimulate further activation of inflammatory processes.

The end results of the chronic inflammatory changes are variable. Loss of cartilage may result in a loss of the joint space. The formation of chronic granulation or scar tissue can lead to loss of joint motion or bony fusion called Ankylosis. Laxity of tendon structures can result in a loss of support to the affected joint, leading to instability or subluxation. Tendon contractures also may occur, leading to chronic deformity.

Clinical Presentation of Rheumatoid Arthritis

Symptoms

- Joint pain and stiffness of more than 6 weeks' duration
- May also experience fatigue, weakness, low-grade fever, loss of appetite
- Muscle pain and afternoon fatigue may also be present.
- Joint deformity is generally seen late in the disease
- Morning stiffness of greater than 1hr duration is an almost invariable feature of inflammatory arthritis and may serve to distinguish it from various Noninflammatory joint disorder.

Signs

Tenderness with warmth and swelling over affected joints usually involving hands and feet. Distribution of joint involvement is frequently symmetrical. Rheumatoid nodules may also be present.

Extraarticular Manifestations

RA is a systemic disease with a variety of extraarticular manifestations occurs due to rheumatic factors

- Rheumatoid Nodules
- Vasculitis
- Pulmonary Complications
- Ocular Manifestations
- Cardiac Involvement
- Felty's Syndrome
- Osteoporosis secondary to rheumatoid involvement

Seronegative Inflammatory Arthritis

Although rheumatoid arthritis may have a negative rheumatoid factor titer, a number of other systemic inflammatory arthritic conditions exist including psoriatic arthritis, ankylosing spondylitis, and arthritis associated with inflammatory bowel disease. These conditions often tend to be less aggressive than what is typically seen with rheumatoid arthritis.

Diagnosis

- No tests are specific for diagnosing RA.
- Rheumatoid factor (RF) detectable in 60% to 70%.
- Anticyclic citrullinated peptide (anti-CCP) antibodies have similar sensitivity to RF (50% to 85%) but are more specific(90% to 95%) and are present earlier in the disease.
- Elevated erythrocyte sedimentation rate and C-reactive protein are markers for inflammation.
- Normocytic normochromic anemia is common as is thrombocytosis
- Synovial fluid analysis (Joint fluid aspiration) confirms the presence of inflammatory arthritis. The fluid is usually turbid, with reduced viscosity, increased protein content, and a slightly decreased or normal glucose concentration with 2000/μL with more than 75% polymorphonuclear leukocytes.
- Radiographic evaluation(Joint radiography) used to determine the extent of cartilage destruction and bone erosion produced by the disease.

- ^{99m}Tc Bisphosphonate bone scanning and magnetic resonance imaging, may be capableof detecting early inflammatory changes.

Treatment

Treatment of rheumatoid arthritis is a multifaceted approach that includes pharmacologic and Nonpharmacologic therapies. It is aimed at relieving pain and inflammation and maintaining and preserving joint function.

Non Pharmacologic Therapy

- Rest
- Occupational therapy
- Physical therapy
- Use of assistive devices
- Weight reduction
- Surgery
- Tenosynovectomy, tendon repair, and joint replacements are surgical options for patients with RA, such management is reserved for patients with severe disease.

Pharmacologic Therapy

- Nonsteroidal Antiinflammatory Drugs as a result of the capacity of these agents to block the activity of the COX enzymes and therefore the production of prostaglandins, prostacyclin, and thromboxanes, they have analgesic, anti-inflammatory, and antipyretic properties
- A disease-modifying antirheumatic drug (DMARD) include Methotrexate, Hydroxychloroquine, Sulfasalazine, and Leflunomide and biologic agents that have disease-modifying activity include the anti-TNF drugs (Etanercept, Infliximab, Adalimumab), the IL-1 receptor antagonist Anakinra, the costimulation modulator Abatacept, and Rituximab, which depletes peripheral B cells.
- Less frequently used DMRDS are D-Penicillamine, gold (including Auranofin), Minocycline
- Glucocorticoid Therapy Low-dose Prednisone (7.5 mg/dl)
- Immunosuppressive Therapy with Azathioprine, Leflunomide, Cyclosporine, and Cyclophosphamide.

Materials and Methods

MATERIALS AND METHODS

Table 9.1: List of materials and their applications in formulation

S.No	Name of the material	Manufacture/ Supplier	Use in formulation
1	Aceclofenac	Schwitz biotech	Active Ingredient
2	Misoprostol	Fagron GmbH & Co	Active Ingredient
3	HPMC K4M	Dow Colorcon	Hydrophilic polymer
4	HPMC K100M CR	Dow Colorcon	Hydrophilic polymer
5	HPMC K100 LV CR	Dow Colorcon	Hydrophilic polymer
6	HPMC E50	Dow Colorcon	Hydrophilic polymer
7	HPMC K15 M CR	Dow Colorcon	Hydrophilic polymer
8	Microcrystalline Cellulose (Ceolus KG 1000)	Asahi Kasei, Japan	Diluent
9	Microcrystalline cellulose (Vivapur Type 102)	JRS Pharma	Diluent
10	Stearic acid	Cognis, Germany	Lubricant
11	Crospovidone	ISP Technologies	Disintegrant
12	Colloidal Silicon Dioxide (Cabosil)	Cabot Sanmar	Glidant
13	Isopropyl alcohol	Rankem	Solvent

Table 9.2: List of Instruments/Equipments used

S.No	Instruments/Equipments	Manufacturer
1	Mixer with Sigma blade	Lumix® food processor
2	ASTM Sieve No. 40 (425µm)	Electro Pharma
3	ASTM Sieve No. 30 (600µm)	Electro Pharma
4	ASTM Sieve No. 60 (250µm)	Electro Pharma
4	Moisture Analyzer	OHAUS MB 45
5	Tap density tester USP I	Electrolab ETD-1020
6	Friabilator USP	Electrolab EF-1W
7	Analytical balance	OHAUS adventurer
8	Top loading balance	Essae Teraoka Limited (Model DS 450cw)
9	Disintegration Apparatus	Electrolab ED-2L
10	Dissolution apparatus	Electrolab India
10	16 station single Rotary compression machine	Cadmach, Ahmedabad, India
11	Hardness tester	Dr.Schleuniger Pharmatron model 5Y tablet tester
12	Vernier caliper	Mitutoyo

METHODOLOGY

PREFORMULATION STUDIES [5]

Preformulation studies is the first step in the rational development of dosage forms of a drug substance, It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

Drug-Excipient Compatibility Study

The drug and the excipients chosen for the formulation were screened for compatibility by physical and assay methods.

Physical Compatibility Study [15]

The physical compatibility studies were conducted to provide valuable information in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and the excipients, taken in 2 ml glass vial and kept at 40±2°C/75±5% RH. Any change in colour of the physical mixture was observed visually.

Compatibility Study by Assay and Water Content

Assay and Water by KF can be used to investigate the Drug-excipient interactions.

PREPARATION OF BUFFER SOLUTIONS

Preparation of 0.1N Hydrochloric Acid (1.2pH) [70]

8.5 ml of the hydrochloric acid was taken and dissolved in water and made upto 1000 ml to get 0.1N hydrochloric acid.

Preparation of Phosphate buffer solution (6.8pH) [70]

50 ml of 0.02 M Potassium dihydrogen phosphate was taken in a 200 ml volumetric flask. 22.4 ml of 0.02 M sodium hydroxide solution was added and the volume was made up to 200 ml using distilled water.

Preparation of 1% sodium lauryl sulphate [45]

1 g of sodium lauryl sulphate was dissolved in 100 ml of distilled water.

STANDARD PLOT FOR ACECLOFENAC

Standard plot in 0.1 N Hydrochloric Acid Buffer pH 1.2 [30]

100 mg of Aceclofenac was weighed and dissolved in 10ml of methanol and made up to 100 ml with 0.1 N Hydrochloric Acid buffer pH 1.2 to get a concentration of 1mg/ml. From the stock solution 10ml was taken and diluted to 100 ml to get a concentration of 100 mcg/ml. The above solution was further diluted with 0.1N Hydrochloric acid buffer pH 1.2 to get a concentration of 2, 4, 6, 8 and 10 mcg/ml. The absorbance of the resulting solutions was measured at 275 nm using UV-Visible spectrophotometer taking 0.1 N HCl as blank.

Standard plot in Phosphate Buffer pH 6.8 [30]

100 mg of Aceclofenac was weighed and dissolved in 10 ml of methanol and made up to 100 ml with phosphate buffer pH 6.8 to get a concentration of 1mg/ml. From the stock solution 10 ml was taken and diluted to 100 ml to get a concentration of 100mcg/ml. The above solution was further diluted with phosphate buffer pH 6.8 to get a concentration of 2, 4, 6, 8 and 10 mcg/ml. The absorbance of the resulting solutions was measured at 275 nm using UV-Visible spectrophotometer taking pH 6.8 phosphate buffer as blank.

PRECOMPRESSION STUDIES OF DRUG AND BLEND

Flow Property Measurements [5]

The flow properties of powders are critical for an efficient tabletting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. The flow property measurements include Bulk Density, Tapped Density, Compressibility index, Hausner's ratio and Angle of Repose. The flow property measurements of drug and blend were determined to select the type of granulation technique to be carried out for the formulation.

a) Bulk Density (ρ_b) [78]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$\rho_b = M / V_b$$

Where, **M** and V_b are mass of powder and bulk volume of the powder respectively.

b) Tapped Density (ρ_t) [78]

It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 500 times using Tap Density tester USP I and the volume attained is the tapped volume. It is expressed in g/ml and is given by

$$\rho_t = M / V_t$$

Where, **M** and V_t are mass of powder and tapped volume of the powder respectively.

c) Angle of Repose (θ) [78]

The flow properties were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose (θ), the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug and the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\theta = \tan^{-1}(h/r)$$

Where, **h** = height of pile in cm, **r** = radius of pile in cm.

d) Carr's Index (or) % Compressibility [78]

It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and is given by

$$CI = \frac{\rho_t - \rho_b}{} \times 100$$

$$\rho_t$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

e) Hausner's Ratio [78]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$HR = \rho_t / \rho_b$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

Table 9.3: Scale of flowability[79]

Flow property	Angle of Repose(θ)	Compressibility Index (%)	Hausner's Ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very Very poor	>65	>38	>1.60

f) Water determination by Karl Fischer Titration[79]

Four tablets were powdered in a mortar and it was taken as analyte. The Karl Fischer reagent was added from automated burette and the endpoint was determined electrometrically. At the endpoint of the titration a slight excess of the reagent cause the flow of current which was measured in microamperes.

$$H_2O + I_2 + SO_2 + 3C_5H_5N + CH_3OH \longrightarrow 2C_5H_5N.HI + C_5H_5NH.SO_4CH_3$$

Formulation Development

FORMULATION DEVELOPMENT

FORMULATION OF IMMEDIATE RELEASE BLEND OF MISOPROSTOL

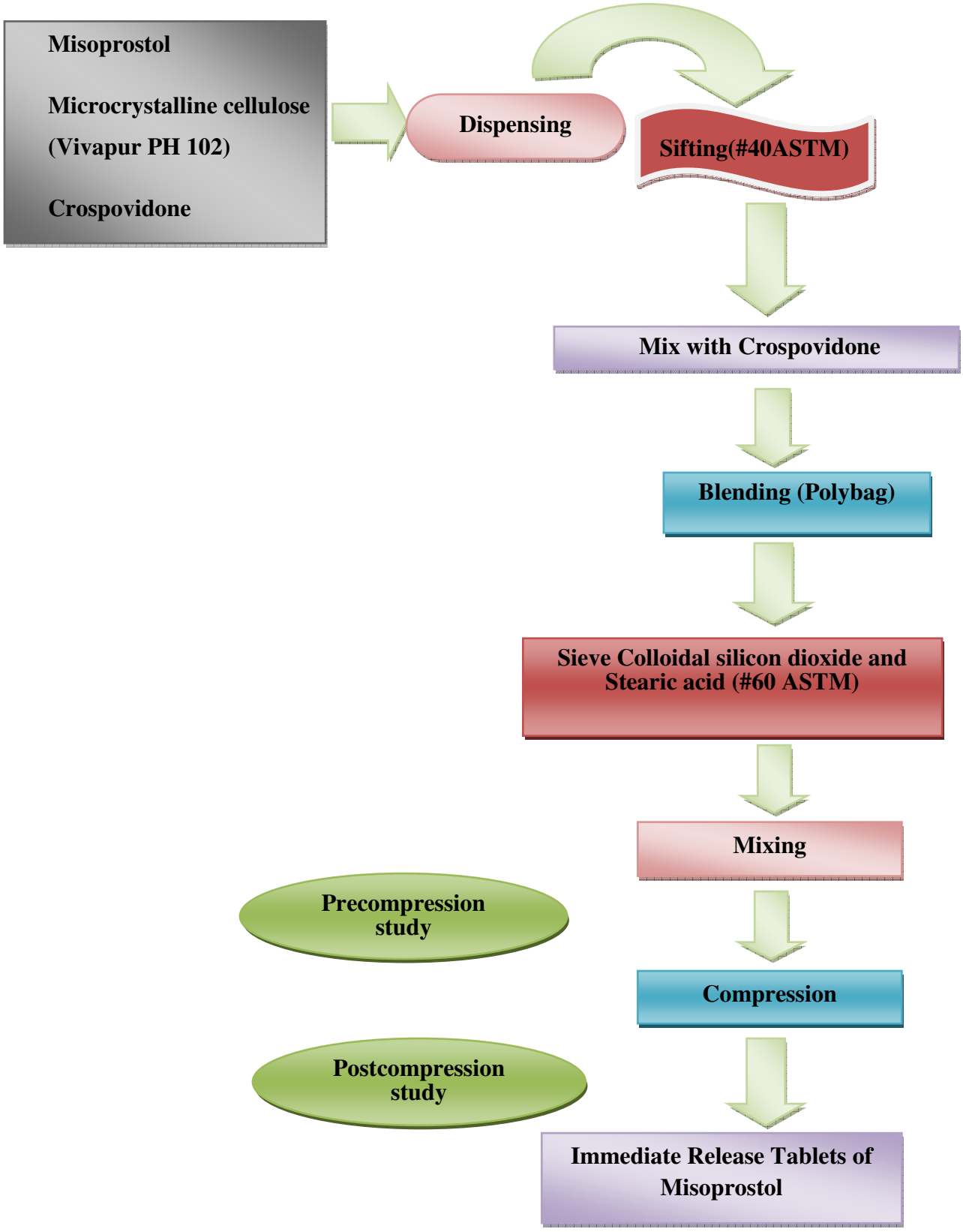
The immediate release tablets of Misoprostol were prepared by direct compression technique.[47] Crospovidone was used as the superdisintegrant (2%, 3% and 4% concentrations). The blends were compressed by 16 station tablet compression machine using 6.25mm round concave punches.

Table10.1: Composition of Immediate Release Blend

S.No	Ingredients	mg/ tablet		
		M 1	M 2	M 3
1	Misoprostol	20	20	**20**
2	Microcrystalline cellulose	100.75	99.50	**98.25**
3	Crospovidone	2.5	3.75	**5.00**
4	Colloidal silicon dioxide	0.5	0.5	**0.5**
5	Stearic acid	1.25	1.25	**1.25**
Total		125.00	125.00	**125.00**

The immediate release tablet of Misoprostol was formulated and optimized. The optimized formulation was used for the final filling in the capsule.

Flowchart for formulation of Misoprostol immediate release (IR) tablets



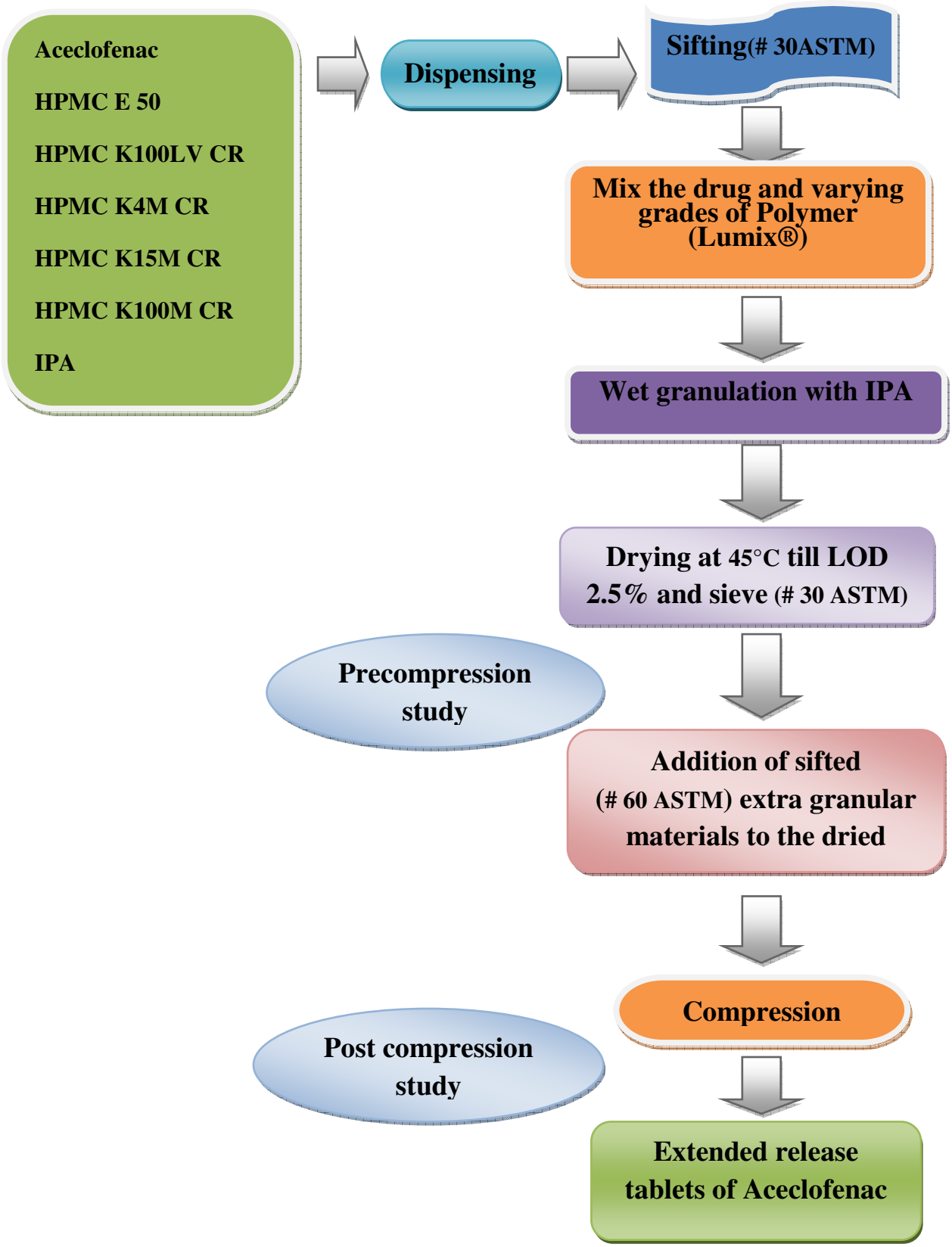
FORMULATION OF ACECLOFENAC EXTENDED RELEASE TABLET

The extended release granules were prepared by Non aqueous wet granulation technique. Different grades of hydrophilic polymer HPMC such as HPMC E50, HPMC K100LV CR, HPMC K4M CR, HPMC K15M CR and HPMC K100M CR were used in different ratios. The tablets were compressed by 16 station compression machine using 17 X 4.5mm caplet punch tooling. The optimized batch of extended release tablets were finally filled in the capsule along with the optimized batch of Misoprostol.

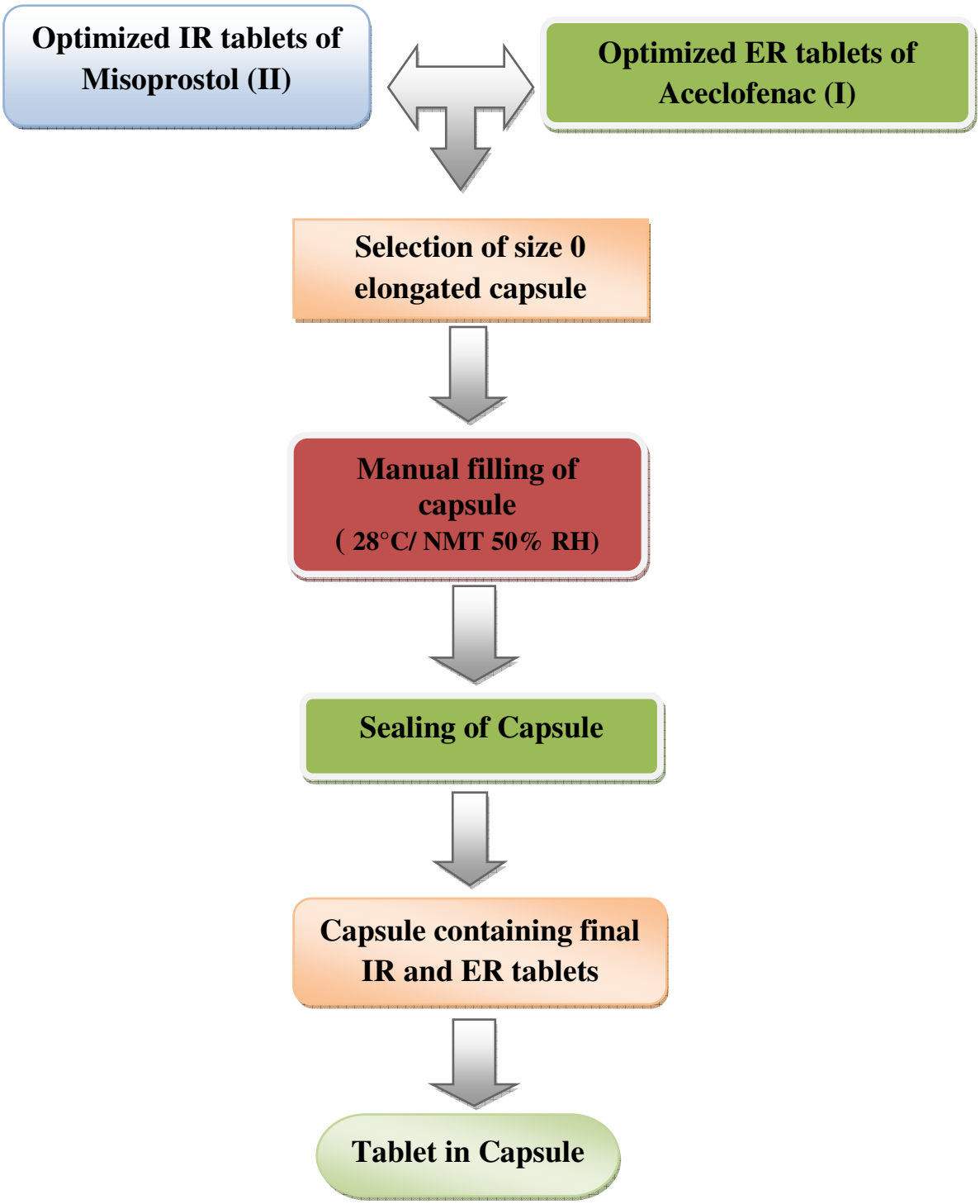
Table 10.2: Composition of Aceclofenac Extended Release Tablets

S.No	Ingredients	mg / tab							
		A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**
Intra granular Part (330 mg)									
1	Aceclofenac	200	200	200	200	200	200	200	**200**
2	HPMC E 50	130	-	-	-	-	65	50	**40**
3	HPMC K100LV CR	-	130	-	-	-	65	80	**90**
4	HPMC K4M CR	-	-	130	-	-	-	-	**-**
5	HPMC K15M CR	-	-	-	130	-	-	-	**-**
6	HPMC K100 M CR	-	-	-	-	130	-	-	**-**
7	IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	**q.s**
Extra granular Part (70 mg)									
1	MCC(Ceolus KG 1000)	62	62	62	62	62	62	62	**62**
2	Stearic acid	8	8	8	8	8	8	8	**8**
Total weight (mg/tab)		400.00	400.00	400.00	400.00	400.00	400.00	400.00	**400.00**

Flowchart for formulation of Aceclofenac Extended Release Tablets



Flowchart for final Tablet in capsule formulation



POST COMPRESSION STUDIES

1. PHYSICAL PARAMETERS

a) General appearance

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters are shape, colour, presence or absence of odour and taste were evaluated visually.

b) Uniformity of Weight [70]

Twenty tablets were selected at a random and weighed individually. The average weight was calculated. The percentage deviation of tablets was calculated and compared with the standard specifications.

Table 10.3: Uniformity of Weight[70]

S.No	Average weight of a tablets	% Deviation
1	80 mg or less	±10
2	80-250 mg	±7.5
3	More than 250 mg	±5

c) Thickness [30]

The thickness was measured to determine the uniformity of size and shape. Thickness of the tablets was measured using vernier caliper.

d) Hardness [70]

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations was determined using Dr. Schleuniger Pharmatron model 5Y tablet tester. It was expressed in kp.

e) Friability [70]

Friability of the prepared formulations was determined by using Roche friabiltor. Pre- weighed sample of tablets was placed in the friability tester, which was then operated for 25 revolutions for 4 min, tablets were dedusted and reweighed. The friability of the tablets was calculated using the formula mentioned below.

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets X 100}}{\text{Initial weight of the tablets}}$$

2. DRUG CONTENT

MISOPROSTOL [70]

Instrumentation

A liquid chromatography consisting of an isocratic pump, a fixed volume injector loop UV-Visible Spectrophotometer detector and data management software.

Chromatographic Conditions

- **Column** : Stainless steel column 25 X 4.6 mm
- **Column packing** : Endcapped ODS bonded to porous silica
- **Column temperature** : 40° C
- **Flow rate** : 0.75 ml/min
- **Wave length** : 200nm
- **Injection volume** : 10µl

Reference Solution

0.2 % w/v solution of Misoprostol RS in acetonitrile.

Mobile Phase

Mixture of 45 volumes of acetonitrile, 55 volumes of water and 0.05 volume of 2.45 % w/v solution of orthophosphoric acid.

Preparation of Test Solution

Twenty tablets were selected randomly and ground. The equivalent of 10 mg of Misoprostol was weighed and dissolved in 5 ml of acetonitrile.

Procedure

- Standard solution and test solution were filtered through 0.45 µ membranes filter.
- The standard solution in five replicate and test solution in duplicate were injected into the chromatograph.
- Content of the Misoprostol as mg/ tablet was calculated using the formula

$$C_t = C_s (r_t / r_s)$$

Aceclofenac [49]

Three tablets were crushed and powder containing 200 mg of Aceclofenac was dissolved in 100 ml of methanol. The solution was passed through a whatman (No. 1) filter and analyzed by UV Visible Spectrophotometer at 275 nm after sufficient dilution with suitable medium (0.1N HCl and pH 6.8 Phosphate buffer).

3. *IN VITRO* DISINTEGRATION STUDIES FOR IR TABLETS [5]

The disintegration time was determined using disintegration test apparatus. The tablets were placed in each of the six tubes of the basket. The assembly was suspended in water maintained at a temperature of 37°C ± 2°C and the apparatus was switched on. The time taken to disintegrate the tablets completely was noted.

4. *IN VITRO* DISSOLUTION STUDIES

Misoprostol Tablets [36]

The release of Misoprostol was determined using USP Type II paddle dissolution apparatus under sink condition. 500ml of de-aerated water was used as dissolution medium at a temperature of 37°C ±0.5°C. The paddle was stirred at a speed of 50 rpm. The release studies were carried out for 30 min. 10 ml of sample was withdrawn at regular intervals of 10 min and the percentage of drug dissolved were determined using HPLC method.

Chromatographic conditions

- **Column :** ODS 1 column of dimensions 100 X 4.6mm
- **Column temperature:** 40° C
- **Flow rate :** 0.75 ml/min
- **Injection volume:** 500µl
- **Wavelength:** 200nm

Mobile Phase

The mobile phase is a mixture of acetonitrile, purified water and 24.5 g/l solution of orthophosphoric acid in the ratio of 55 : 45 : 0.05 v/v/v respectively.

Standard Solution

0.4 µg/ml solution of Misoprostol prepared using mobile phase and subsequently diluted to appropriate concentration with dissolution medium.

Procedure

The standard and sample solutions were filtered using whatman filter No.1 and injected into the chromatograph for the determination of percentage drug release at different time points.

Aceclofenac tablets [45]

The dissolution rate of Aceclofenac ER tablets prepared were studied using USP type II dissolution test apparatus employing paddle stirrer, using 0.1N hydrochloric acid for first 2 hours and phosphate buffer pH 6.8 further as dissolution fluids. In each test one tablet, a speed 100 rpm rotations and a temperature of 37°C ± 1°C were employed. A 10 ml aliquot of dissolution medium was withdrawn at different time interval suitable diluted and assayed by UV Visible spectrophotometer at 275 nm. The percentage of drug dissolved at various time intervals 2, 4, 6, 8, 10, 12 hrs was calculated and plotted against time.

5. EVALUATION OF *IN VITRO* RELEASE KINETICS [51]

To study the *in vitro* release kinetics of the ER tablets, data obtained from the *in vitro* dissolution study of optimized formulation were plotted in various kinetic models.

Zero order equation

The zero order release kinetics can be obtained by plotting cumulative % drug released Vs time (hours). It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C = K_0 t$$

Where, K_0 = Zero order constant in conc. / time

t = Time in hours

First order equation

The graph was plotted as log % cumulative drug remaining Vs time in hours.

$$\text{Log } C = \log C_0 - Kt/2.303$$

C_0 = Initial drug concentration

K = First order constant

t = Time in hours.

Higuchi kinetics

The graph was plotted with % cumulative drug released Vs square root of time.

$$Q = Kt^{1/2}$$

K = Constant reflecting design variable system (Differential rate constant)

t = Time in hours.

The drug release rate is inversely proportional to the square root of time.

Hixson and Crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and Crowell erosion equation. The graph was plotted by cube root of % drug remaining Vs Time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t$$

Q_t = Amount of drug released at time t

Q_0 = Initial amount of drug

K_{HC} = Rate constant for Hixson Crowell equation

Korsmeyer – Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs log time.

$$M_t/M_\alpha = Kt^n$$

Where, **M_t/M_α =** Fraction of drug released at time t

t = Release time

K = Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

n = Diffusional exponent indicative of the mechanism of drug release.

Table 10.3: Evaluation of *in vitro* release kinetics[51]

Zero-order reaction	% Cum. drug release	Time (hours)
First order reaction	Log % cum. drug remaining	Time in hours
Higuchi kinetics	% cum. drug release	Square root of time
Korsmeyer-Peppas equation	Log cum.% of drug release	Log time
Hixon and crowell erosion equation	Cube root of % drug remaining	Time in hours

The n value obtained is used to characterize different release mechanisms for cylindrical shaped matrices.[51]

Table 10.4: Diffusion exponent and its mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

6. STABILITY STUDY [49]

Stability study of optimized formulation of tablet in capsule was carried out according to ICH guidelines. Accelerated stability study of encapsulated formulation can be performed by packing 30 units of capsules in 60cc HDPE Bottle and 33mm PP Child Resistant closure with induction seal liner and 1 g per bottle of 6 g/yard Cotton as dunnage. Then these bottles are kept at and 40°C ±2ºC/75±5% RH. The samples were withdrawn at 1st, 2nd and 3rd month and analyzed for the following raiders,

- Thickness
- Assay
- Disintegration for IR tablets only
- Dissolution

Results and Discussion

RESULTS AND DISCUSSION

The present investigation was to formulate tablets for immediate release of Misoprostol and extended release of Aceclofenac enclosed in a capsule for pain management with GI protection. The drug-excipient study was conducted to reveal the excipient compatibility with the drug. The physical and chemical compatibility of drug and excipients are given in Table 11.1 and 11.2.

PREFORMUALTION STUIDES

Drug -Excipient Compatibility Study

Table 11.1: Drug– Excipient Compatibility

S.No	Drug-Excipient	Ratio	Initial		Appearance
			Assay %	WC	
1	MI-MCC Type 102	1:1	97.29	4.75	White powder
2	MI-Crospovidone	1:0.25	98.90	3.81	White powder
3	MI-Cabosil	1:0.25	96.58	2.79	White powder
4	MI-Stearic acid	1:0.25	98.05	1.25	White to off white powder
5	AC-MCC KG 1000	1:0.5	98.05	4.32	White powder
6	AC -HPMC E50	1:0.5	96.07	3.12	White powder
7	AC-Stearic acid	1:0.25	99.30	0.10	White to off white powder

Table 11.2: Drug– Excipient Compatibility (Accelerated Stability Studies)

S.No	Drug-excipient	40± 2° C/75±5% RH-2W			40± 2° C/75±5% RH-4W		
		Assay%	WC	Appearance	Assay%	WC	Appearance
1	MI-MCC PH 102	93.0	3.90	NC	96.0	4.62	NC
2	MI-Stearic Acid	95.0	0.81	NC	93.0	1.14	NC
3	MI-Colloidal silicon dioxide	94.0	2.43	NC	94.0	2.56	NC
4	MI-Crospovidone	91.0	3.68	NC	97.0	3.77	NC
5	AC-MCC KG 1000	95.0	3.75	NC	95.7	4.21	NC
6	AC-HPMC E50	96.08	2.78	NC	94.03	3.00	NC
7	AC-Stearic acid	97.0	0.05	NC	95.0	0.07	NC

NC- No change, WC- Water content, MI- Misoprostol, AC- Aceclofenac

Inference

The excipients were found to be compatible with the drug.

STANDARD PLOT FOR ACECLOFENAC

The concentration and absorbance for Aceclofenac in 0.1N HCl (pH 1.2) and Phosphate buffer (pH 6.8) at wavelength 275 nm was measured using UV Visible Spectrophotometer. The results are given in Table 11.3.

Table 11.3: Standard plot for Aceclofenac

S. No	Concentration (mcg/ml)	Absorbance at λ_{275nm}	
		pH 1.2	pH 6.8
1	0	0	0
2	2	0.024	0.061
3	4	0.049	0.122
4	6	0.074	0.187
5	8	0.097	0.243
6	10	0.125	0.302

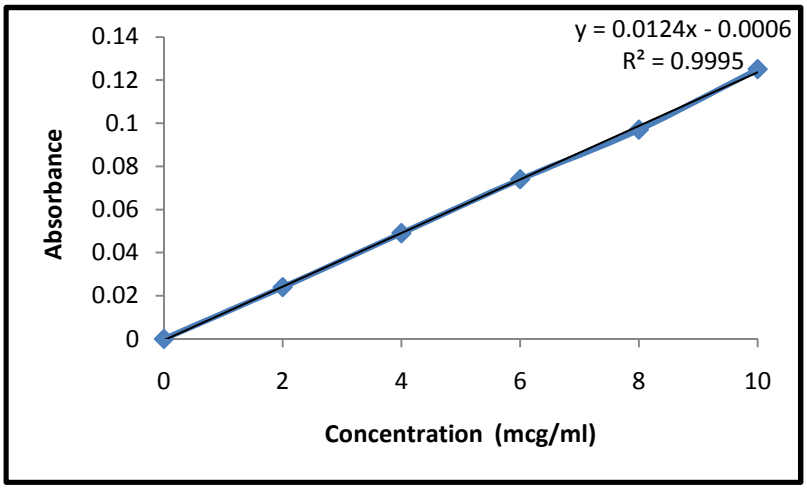


Fig 11.1: Standard plot of Aceclofenac in pH 1.2

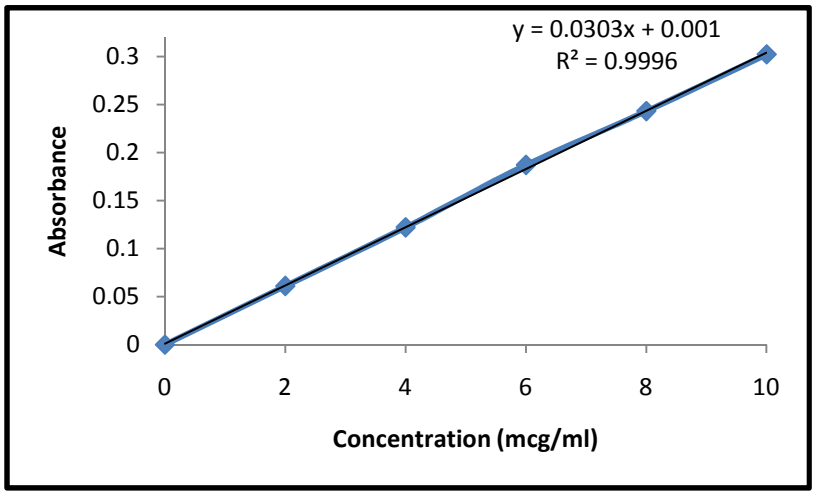


Fig 11.2: Standard plot of Aceclofenac in pH 6.8 Phosphate Buffer

EVALUATION OF IR FORMULATION

PRECOMPRESSION STUDY

The drug and the formulated blends were evaluated for precompression parameters. The results are given in Table 11.4.

Table 11.4: Precompression study of drug and formulated blends

Drug and Formulation	Bulk Density g/cm^3 *	Tapped Density g/cm^3 *	Compressibility index (%)*	Hausner's Ratio*	Angle of Repose (Degree)
MI	05848± 0.0091	0.6754 ± 0.0072	13.42 ± 0.4430	1.15 ± 0.0072	21.50
M1	0.4987± 0.0078	0.5361 ± 0.0056	8.52 ± 1.02	1.09 ± 0.01	22.36
M2	0.5018± 0.0021	0.5590 ± 0.018	10.24 ± 1.75	1.11 ± 0.0220	23.45
M3	**0.4863± 0.0143**	**0.5317 ± 0.0025**	**8.53 ± 2.62**	**1.09 ± 0.0280**	**23.05**

*** Mean ± S.D (n = 3)**

The bulk density of the IR blends ranged from 0.4863 to 0.5018 g/cm^3 and the tapped density ranged from 0.5317 to 0.5590 g/cm^3. The compressibility index of the IR blends ranged from 8.52% to 10.24% and Hausner's ratio ranged from 1.09 to 1.11.The angle of repose of the IR blends ranged from 22.36 to 23.45. The formulated blend shows good flow property so direct compression was employed.[70] The IR blends were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and Angle of Repose.[79]

POST COMPRESSION STUDY FOR TABLETS

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in Table 11.5

Table 11.5: Uniformity of weight of the formulated tablets

Formulation	Uniformity of weight (mg) *
M1	125.28±0.3382
M2	125.36±0.4852
M3	**125.58±0.5263**

*** Mean± S.D (n=20)**

The tablets comply with the test for uniformity of weight.[70]

TABLET THICKNESS

The thickness of the formulated tablets is given in Table 11.6

Table 11.6: Thickness of formulated tablets

Formulation	Thickness (mm) *
M1	3.114±0.0219
M2	3.112±0.0109
M3	**3.114±0.0308**

*** Mean± S.D (n=5)**

The tablets possess uniform thickness.

HARDNESS

The hardness of the formulated tablets is given in Table 11.7

Table 11.7: Hardness of formulated tablets

Formulation	Hardness (kp) *
M1	5.16±0.0547
M2	5.18±0.0457
M3	**5.17±0.0358**

*** Mean± S.D (n=5)**

All the formulated tablets showed sufficient mechanical strength to resist the transportation and handling.

FRIABILITY

The friability of the formulated tablets are given in Table 11.8.

Table 11.8: Friability of formulated tablets

Formulation	% Friability
M1	0.34
M2	0.42
M3	**0.40**

The percentage friability of all the formulations was within the acceptable limits.[70]

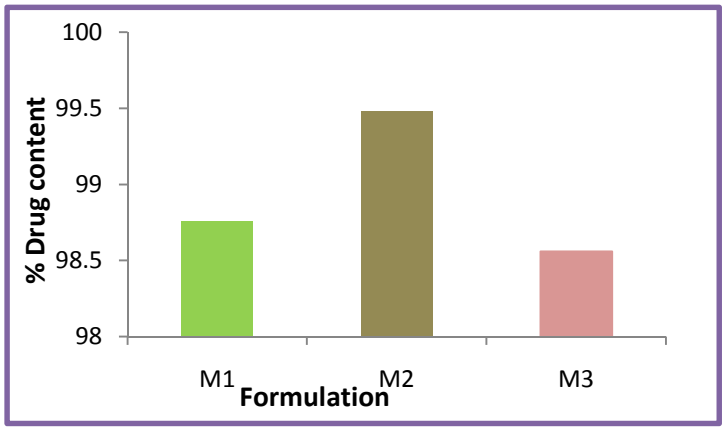
DRUG CONTENT

The drug content of the IR tablets is given in the Table 11.9.

Table 11.9: Drug content of formulated IR tablets

Formulation	% Drug Content
M1	98.76 ± 0.1300
M2	97.48 ± 0.0100
M3	**98.56**± 0.1201

Fig 11.3: Drug content of IR tablets



DISINTEGRATION TIME

The disintegration time of the IR tablets is given in the Table 11.10.

Table11.10: Disintegration time of IR tablets

Formulation	Disintegration time (minutes)
M1	8.50 ± 0.012
M2	4.29 ± 0.0004
M3	**2.10** ± 0.0020

Fig.11.4: Disintegration time of IR tablets

The disintegration time of the IR tablets ranged from 2.10-8.50 minutes. All the tablets disintegrated within the Pharmacopoeial limits.[70] The disintegration time of the IR tablets containing 4% Crospovidone was found to have faster disintegration among the formulated IR tablets.

***IN VITRO* DISSOLUTION STUDY**

The *in vitro* dissolution of immediate release formulations of Misoprostol are given in the Table 11.11.

Table11.11: *In vitro* Dissolution study of IR formulation of Misoprostol

Time (Min)	Cumulative % drug release		
	M1	M2	M3
0	0	0	**0**
10	20.39±0.7112	30.35±1.22	**60.28±0.7**
20	48.38±0.6515	60.78±1.988	**85.02±0.5178**
30	69.99±1.5076	73.49±1.817	**98.94±0.4564**
40	78.42±0.7616	87.52±0.4659	
50	87.81±0.9269	98.27±0.3463	
60	96.95±0.5162		

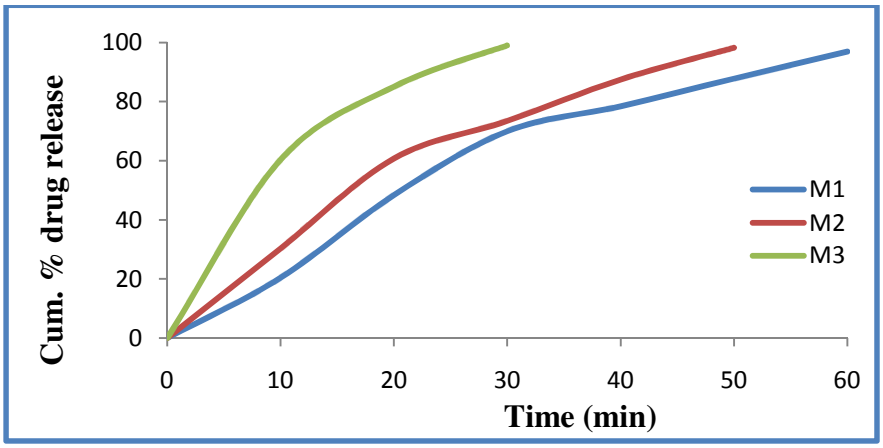


Fig.11.5: *In vitro* Dissolution study of IR tablets of Misoprostol

The formulation M3 containing 4% of Crospovidone released the drug faster when compared to M1 and M2 formulations. The formulation M3 released 98.94% of Misoprostol at the end of 30mins. Therefore formulation M3 was optimized and selected for filling in capsule.

EVALUATION OF ER FORMULATION

PRECOMPRESSION STUDY

The drug and the formulated blends of ER formulation were evaluated for precompression parameters.

The results are given in the Table 11.12.

Table11.12: Precompression study of drug and formulated blends

Drug and formulation	Bulk density g/cm^{3} *	Tapped density g/cm^{3} *	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (Degree)
AC	0.6511± 0.0012	0.8326± 0.0010	21.79 ± 0.0907	1.27 ± 0.0000	37.99
A1	0.5916± 0.0018	0.7682± 0.0023	22.99 ± 0.5831	1.30 ± 0.0000	32.45
A2	0.5886± 0.002	0.7693± 0.0011	23.48 ± 0.3329	1.30 ± 0.0057	33.06
A3	0.589± 0.0024	0.7711± 0.0019	23.62 ± 0.4635	1.31 ± 0.0057	32.12
A4	0.5880± 0.0024	0.7689± 0.0011	23.54 ± 0.1563	1.31 ± 0.0058	34.36
A5	0.5883± 0.0025	0.7695± 0.0013	23.55 ± 0.1674	1.30 ± 0.0057	31.58
A6	0.5898± 0.0009	0.7696± 0.0006	23.37 ± 0.2271	1.31 ± 0.0058	32.10
A7	0.5894± 0.0001	0.7708± 0.0057	23.52 ± 0.7000	1.31 ± 0.01525	33.42
A8	0.5897± 0.0019	0.7705± 0.0024	23.47 ± 0.1053	1.30 ± 0.0057	33.36

*** Mean± S.D (n=3)**

The bulk density of the formulated blends ranged from 0.5880 to 0.5916 and tapped density ranged from 0.7682 to 0.7711. The compressibility index ranged from 22.99 to 23.62 and Hausner's ratio ranged from 1.30 to 1.31. The Angle of repose ranged from 31.58 to 34.36. The formulated blends did not show adequate flow properties for compression.[79] Hence Non aqueous wet granulation method was employed. The formulated ER granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and Angle of Repose. The results are given in the Table 11.13

Table11.13: Precompression study of Extended release granules

Formulation	Bulk density g/cm^3	Tapped density g/cm^3	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (Degree)
A1	0.5852± 0.0046	0.7316± 0.0009	20.0 ± 0.6560	1.24± 0.0115	25.25
A2	0.5889± 0.0018	0.7395± 0.0008	20.35 ± 0.3000	1.25 ± 0.0057	25.12
A3	0.5912± 0.0011	0.741± 0.0008	20.21 ± 0.2402	1.25 ± 0.0057	24.29
A4	0.5905± 0.0056	0.7393± 0.0004	20.11 ± 0.862	1.25 ± 0000	23.22
A5	0.5906± 0.0005	0.7392± 0.0004	20.09 ± 0.0400	1.25 ± 0000	22.78
A6	0.5916± 0.0008	0.7414± 0.0011	20.19 ± 0.2371	1.25 ± 0.0057	25.11
A7	0.5904± 0.0003	0.7405± 0.0015	20.25 ± 0.1404	1.25 ± 0.0000	26.0
A8	**0.5911± 0.0006**	**0.7328± 0.0048**	**19.32 ± 0.6178**	**1.23 ± 0000**	**27.26**

The bulk density of the ER granules ranged from 0.5852 to 0.5916 g/cm^3 and the tapped density of ranged from 0.7316 to 0.7410 g/cm^3. The compressibility index of the ER granules ranged from 19.32 to 20.35% and Hausner's ratio ranged from 1.23 to

1.25. The Angle of Repose of the ER granules ranged from 22.78 to 27.26. The formulated granules shows good flow property.[79]

POST COMPRESSION STUDY

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in Table11.14.

Table 11.14: Uniformity of Weight

Formulation	Uniformity of weight (mg) *
A1	400.33 ±0.4723
A2	400.06±1.3848
A3	400.35±0.5060
A4	400.65±1.7588
A5	400.06±0.9147
A6	400.49±0.7427
A7	400.49±0.8312
A8	**400.31±0.7053**

*** Mean± S.D (n=20)**

The tablet complies with the test for uniformity of weight.[70]

TABLET THICKNESS

The thickness of the formulated tablets is given in table11.15

Table 11.15: Thickness of formulated tablets

Formulation	Thickness (mm) *
A1	4.12±0.0001
A2	4.11±0.0055
A3	4.12±0.0055
A4	4.11±0.0055
A5	4.12±0.0084
A6	4.12±0.0055
A7	4.12±0.0070
A8	**4.11±0.0055**

*** Mean± S.D (n=5)**

The tablets have uniform thickness.

HARDNESS

The hardness of the formulated tablets is given in Table11.16.

Table11.16: Hardness of formulated tablets

Formulation	Hardness (kp) *
A1	6.1±0.0707
A2	6.1±0.0894
A3	6.12±0.8367
A4	6.1±0.1000
A5	6.1±0.1414
A6	6.1±0.0707
A7	6.1±0.0707
A8	**6.12±0.0447**

*** Mean± S.D (n=5)**

All the formulated tablets showed sufficient mechanical strength to resist the transportation.[70]

FRIABILITY

The friability of the formulated tablets is given in Table 11.17.

Table 11.17: Friability of formulated tablets

Formulation	% Friability
A1	0.45
A2	0.31
A3	0.61
A4	0.52
A5	0.49
A6	0.63
A7	0.60
A8	0.55

The percentage friability of all formulations was within the acceptable limits.[70]

DRUG CONTENT

The drug content of formulated tablets are given in table 11.18.

Table 11.18: Drug content of formulated tablets

Formulation	Drug content %
A1	98.78
A2	97.42
A3	95.75
A4	96.59
A5	99.54
A6	98.21
A7	98.03
A8	98.27

All the formulations are within the acceptable limits.[70]

IN VITRO DISSOLUTION PROFILE OF ER TABLETS[40]

The *in vitro* dissolution study of the formulated ER tablets is given in table 11.19.

Table11.19: *In vitro* dissolution Profile of ER tablets A1-A8

TIME (HR)	A1	A2	A3	A4	A5	A6	A7	A8
0	0	0	0	0	0	0	0	**0**
2	20.69± 1.6934	13.81± 0.7806	27.6± 0.4585	23.02± 1.0219	26.48± 0.5300	7.24± 0.5474	11.25± 1.3741	**9.14± 0.1938**
4	55.52± 1.3714	38.58± 1.1104	38.67± 1.3708	34.2± 0.4546	31.62± 1.2400	40.28± 0.7708	35.68± 0.7489	**20.69± 0.4906**
6	73.94± 0.9610	52.4± 1.1655	48.96± 0.6401	43.52± 0.3608	38.48± 0.6530	71.17± 1.3357	61.02± 0.6411	**47.97± 0.3046**
8	88.91± 0.4220	68.26± 1.5928	58.92± 0.8882	50.82± 0.2344	43.35± 0.8411	83.2± 0.7530	77.44± 0.5079	**63.25± 0.2541**
10	98.55± 0.5996	92.41± 0.7427	61.57± 1.0064	57.44± 1.0228	44.33± 1.0944	94.16± 0.9932	86.12± 0.3929	**85.27± 0.2381**
12	-	98.43± 0.4062	69.43± 0.7155	61.8± 0.9528	48.87± 1.0953	97.93± 0.7219	97.41± 0.8251	**98.1± 0.1890**

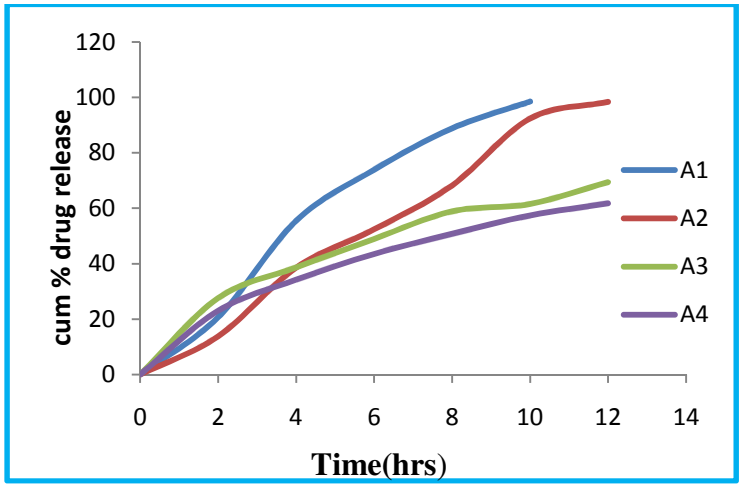


Fig11.6: *In Vitro* Drug Release of ER Formulation A1-A4

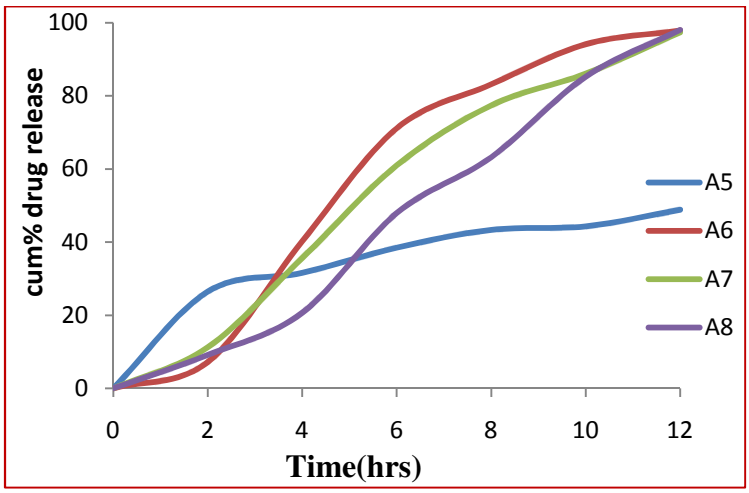


Fig11.7: *In Vitro* Drug Release of ER Formulation A5-A8

The results of *in vitro* dissolution study of ER tablets showed that the formulation A8 containing HPMC E50 40 mg and HPMC K100 LVCR 90 mg showed ideal release of the drug in 12 hours. Other formulations of ER not meeting the objective.

***IN VITRO* RELEASE KINETICS**

The values obtained from *in vitro* dissolution of Aceclofenac Extended release tablets were fitted to kinetic models. The results are given in table 11.18 and fig.

Table 11.20: *In vitro* release kinetics of Aceclofenac ER tablets

Time (Hr)	% Cum Drug Release	% Cum Drug Remaining	Log % Cum Drug Remaining	Square root of time	Log time	Log % cum drug release	Cube root of % drug remaining
0	0	100	2	0	0	0	4.6415
2	9.14	90.86	1.9583	1.4142	0.3010	0.9609	4.4956
4	20.69	79.31	1.8993	2	0.6020	1.3157	4.2964
6	47.97	52.03	1.7162	2.4494	0.7781	1.6809	3.7332
8	63.25	36.75	1.5652	2.8284	0.9030	1.8010	3.3246
10	85.27	14.73	1.1682	3.1622	1	1.9307	2.4513
12	98.1	1.9	0.2787	3.4641	1.0791	1.9916	1.2385

Determination of drug release mechanism of extended release tablets

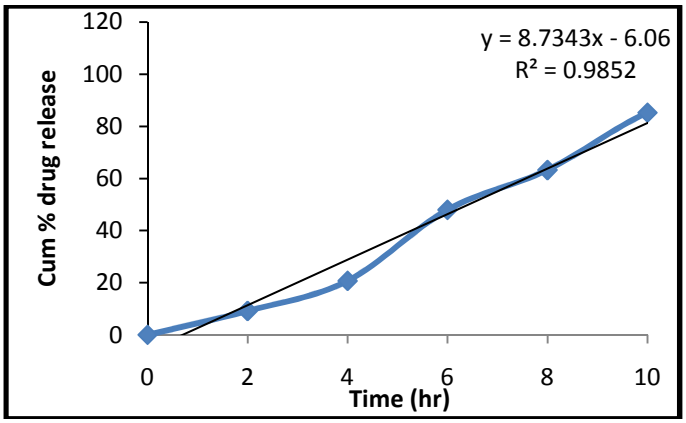


Fig 11.8: Zero order release kinetics plot

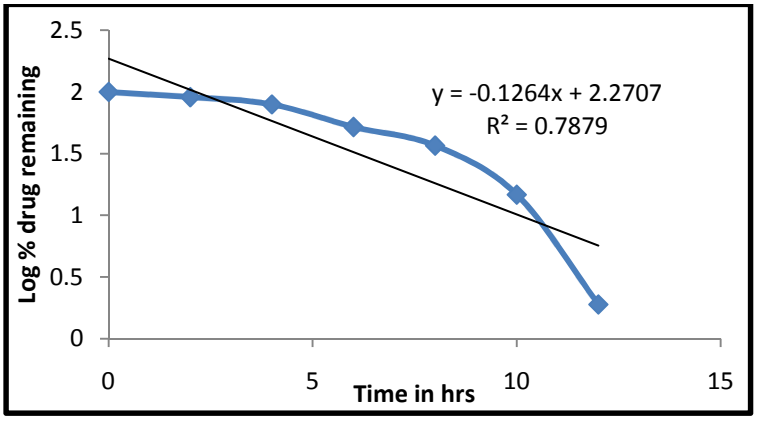


Fig 11.9: First order release kinetics plot

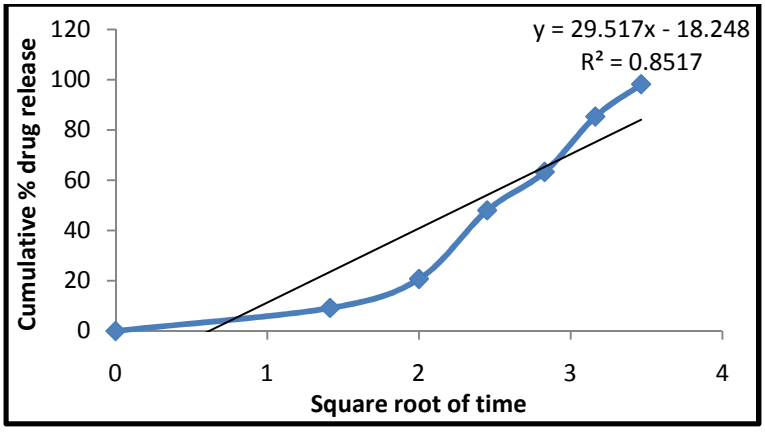


Fig 11.10: Higuchi Release Kinetics plot

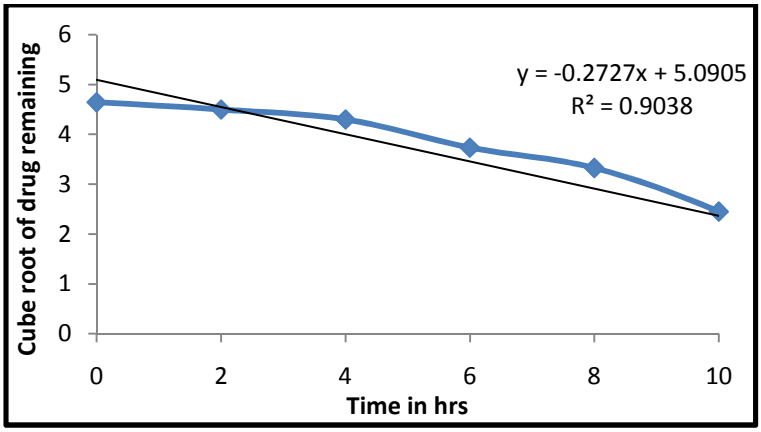


Fig 11.11: Hixon Crowell Release Kinetics plot

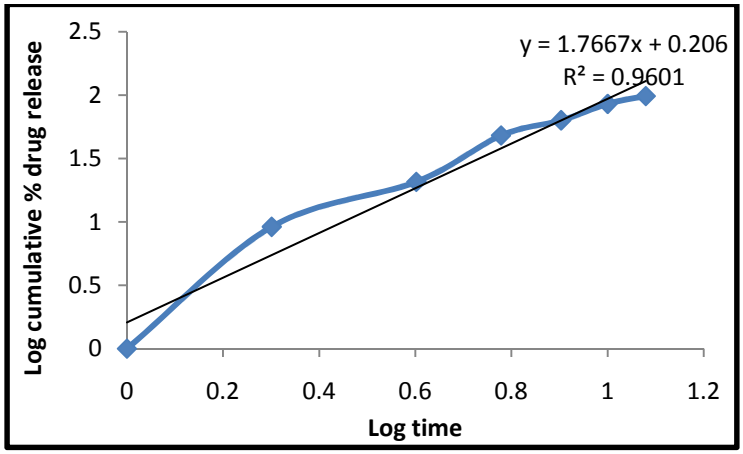


Fig 11.12: Korsemeyer Peppas release kinetics plot

Table11.21: R^2 values of various Kinetic Models

Kinetic Model	R^2 Value
Zero order release kinetics	**0.985**
First order release kinetics	0.787
Higuchi release kinetics	0.851
Hixon Crowell release kinetics	0.903
Korsemeyer Peppas release kinetics	0.960

The kinetic parameters revealed that release data of optimized formula A8 showed r^2 value of 0.985 which is close to 1, indicating that release of drug follows **zero order kinetics** and the release is independent of concentration.

STABILITY STUDY

The optimized tablets were subjected to stability studies and the results are given in Table 11.22 to 11.25

Stability study of physical parameters of the optimized formulations

Table 11.22: Misoprostol

Parameter	Initial	1st month	2nd month	3rd month
Uniformity of weight (mg)*	125.58± 0.5263	125.21± 0.3796	125.02± 0.5225	124.99± 0.4083
Thickness(mm)**	3.114± 0.0308	3.11± 0.0054	3.11± 0.0054	3.11± 0.0044
Disintegration Time (min)	2.10± 0.0152	2.23± 0.1369	2.18 ± 0.1158	2.21 ± 0.0790
Water content of finalized formulation	4.72	5.16	5.37	5.62

*** Mean± S.D (n=20), ** Mean± S.D (n=5)**

Table 11.23: Aceclofenac

Parameter	Initial	1st month	2nd month	3rd month
Uniformity of weight (mg)*	400.31± 0.7053	400.12± 0.6462	400.32± 0.4348	400.35± 0.503
Thickness(mm)**	4.11± 0.0055	4.11± 0.0054	4.11± 0.0083	4.11± 0.0054
Water content of finalized formulation	4.82	5.46	5.67	5.8

*** Mean± S.D (n=20), ** Mean± S.D (n=5)**

Table 11.24: Assay and Dissolution profile of formulated Misoprostol tablets

Time Interval	Drug content (%)	Cumulative % release At the end of 30 min
Initial	98.56	98.94± 0.4564
1st month	98.45	98.15± 0.3793
2nd month	97.32	97.74 ± 0.3610
3rd month	97.14	98.11± 0.2553

Table 11.25: Assay and dissolution profile of formulated Aceclofenac tablets

Time Interval	Drug content (%)	Cumulative % release with respect to Time(hr)		
		2	**6**	**12**
Initial	98.27	9.14± 0.1938	47.97± 0.3046	98.1± 0.1890
1st month	97.33	9.23± 0.3291	48.43± 0.646	98.13± 0.6241
2nd month	96.87	9.38± 0.3824	47.09± 0.3906	97.82± 0.6614
3rd month	96.54	9.45± 0.2714	47.87± 0.319	98.08± 0.5035

Summary and Conclusion

SUMMARY AND CONCLUSION

A Tablet in Capsule device containing Aceclofenac ER tablet and Misoprostol IR tablet for Pain Management with Gastro protection was formulated. Rationale of combining a NSAID and a prostaglandin analogue was well justified and the design of drug delivery system was made simple by encapsulating two different tablets (Aceclofenac and Misoprostol) in single capsule and it offers advantage in terms of GI protection, Patient Compliance and Chronotherapeutics.

- Aceclofenac extended release tablet 200mg was formulated using various grades of hydrophilic polymer such as HPMC E50, HPMC K100 LV CR, HPMC K4M CR and HPMC K15M CR as release retardant to prolong the release for 12 hr .
- Misoprostol Immediate release tablet 200mcg was formulated using Crospovidone as superdisintegrant at 2%, 3% and 4%.
- Formulation characteristics such as precompression and postcompression studies of the developed formulations were carried out separately as per standard procedures.
- The tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter, friability and drug content.
- *In vitro* dissolution studies for both the tablets were conducted separately.
- Aceclofenac ER formulation A8 was optimized based on the ideal release upto 12 hr
- The optimized Aceclofenac formulation followed Zero order release kinetics
- Based on the disintegration time Misoprostol IR formulation M3 was optimized
- The optimized formulations of Aceclofenac A8 and Misoprostol M3 were used for filling in size 0 elongated capsules.
- The stability studies under accelerated conditions of 40± 2°C /75±5% RH was found to be satisfactory.

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