ejpmr, 2019,6(10), 460-475

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS CONTAINING ETORICOXIB USING NATURAL SUPER DISINTEGRANTS

Muhamed Rizvan Ebrahimkutty*[1], Shripathy D.[2] and Dr. A. R. Shabaraya[3]

[1]Research Scholar, M. Pharm (Department of Pharmaceutics), Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India.

[2]Assistant Professor, (Department of Pharmaceutics), Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India.

[3]Pricipal, HOD (Department of Pharmaceutics), Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India.

***Corresponding Author: Muhamed Rizvan Ebrahimkutty**

Research Scholar, M. Pharm (Department of Pharmaceutics), Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India.

Article Received on 13/08/2019 **Article Revised on 03/09/2019** **Article Accepted on 23/09/2019**

ABSTRACT

The present investigation was under taken with the objective of formulating fast dissolving oral films containing Etoricoxib using natural super disintegrant to enhance the convenience and compliance by the elderly and pediatric patients. Etoricoxib is a Non-steroidal anti-inflammatory drug (NSAID) belonging to COX II inhibitor class of drug. The oral films of etoricoxib was prepared by solvent casting method using Xanthan gum and Guar gum as a film forming agents, Plantago ovate as natural super disintegrating agent and PEG 400 as plasticizer. Nine formulations were prepared and were evaluated for physico-mechanical properties, *in-vitro* disintegration time and *in-vitro* dissolution studies. All formulated films showed the good physico-mechanical properties, in-vitro disintegration time. The formulation F3 showed better dissolution of 96.6% at the end of 14 minutes.

INTRODUCTION

FDOFs are useful in patients such as paediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anaesthetic for toothaches, oral ulcers, cold sores or teething. OTFs also have an established shelf-life of 2-3years, depending on the API but are extremely sensitive to environmental moisture.[2]

Ideal characteristics of oral films

- Should not be bitter and have quick onset of action.
- Should exhibit suitable tensile strength.
- Should not stick to the packing material and fingers.
- Should be ionized at pH of oral cavity.
- Dose up to 40mg can be incorporated.

Advantages

- No risk of chocking.
- Convenient and accurate dosing.
- No need of water for administration.
- Ease of swallowing for geriatrics and paediatrics.
- Easy transportation.
- Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability
- Convenient for dysphasic patients having difficulty in swallowing tablets and capsules.

Disadvantages

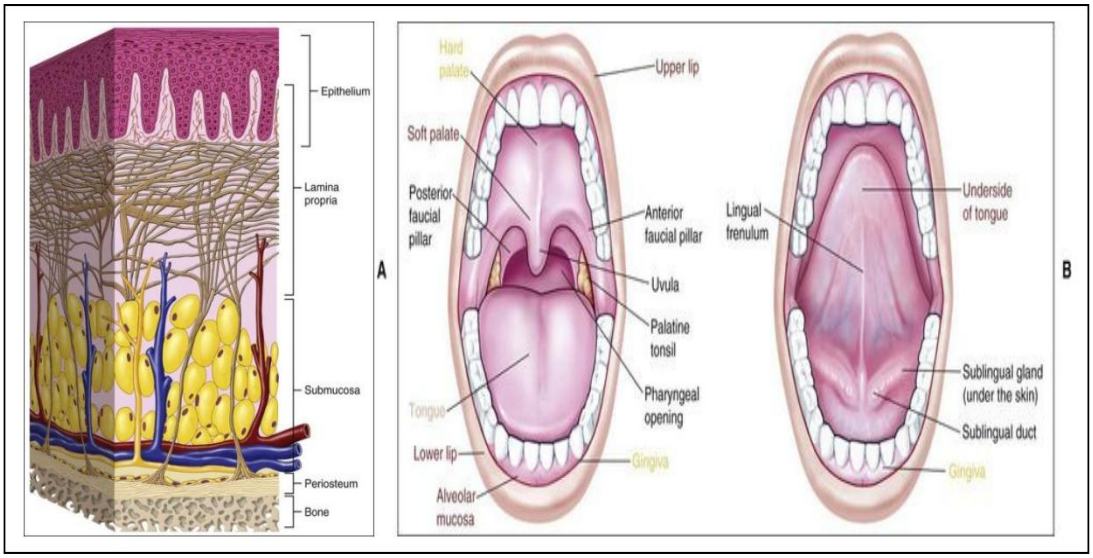
- Restriction of eating and drinking for some time after consumption of oral film.
- Only small dose of drug can be administered.
- Not suitable for drugs which irritate and are unstable at buccal pH.
- Packing requires special equipment. So, difficult to pack.[3]

Mechanism of action

The delivery system consists of a thin film of the size of a postage stamp, which is placed on the patient's tongue or mucosal tissue, where it instantly hydrates by absorbing saliva; the film then rapidly disintegrates and dissolves to release the drug for oral mucosal absorption. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment.

Overview of the Oral Mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer can be seen in figure 1.



Structure of oral cavity

The epithelium of the buccal mucosa is about 40- 50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 µm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, nonkeratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulphate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the socalled 'membrane coating granules' (MCG). When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200µm of the superficial layer.[4]

Composition of the formulation

Composition of the formulation of oral dissolving film (ODF) involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance and mouth feel etc. The excipients used formulations of oral dissolving film are given below as per their categories.

Composition of oral films

S. No	Name of the excipient	Quantity
1	Drug	1-30%
2	Film forming polymer	40-50%
3	Plasticizer	0-15%
4	Saliva stimulating agent	2-6%
5	Super disintegrating agent	2-8%
6	Sweetening agent	3-6%

Active Pharmaceutical Ingredient

A distinctive composition of the films contains 1 to 30% w/w of the active pharmaceutical ingredient. Always use low dose active pharmaceutical ingredient used because high dose of drug is difficult to incorporate in fast dissolving film. Micronized API is useful become it enhance the texture of film and provide improved

dissolution and uniformity in the fast dissolving film. A number of drugs can be used as fast dissolving oral film.

Film forming polymer

Water soluble polymers are used as film formers. The use of film forming polymers in dispersible films has attracted considerable attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good mouth feel effect and gives the mechanical property to the films. The disintegration rate of the polymers decreased by increasing the molecular weight of the polymer film bases. Some of the water-soluble polymers used as film formers are hydroxypropyl methyl cellulose (HPMC), Hydroxypropyl cellulose (HPC), pullulan, carboxymethyl cellulose (CMC), pectin, starch, polyvinyl acetate (PVA), and sodium alginate these polymers can be used alone or in combination to obtain the desired strip properties. They comprise the physical structure of the films, affording their integrity. The robustness of the strip depends on the type of the polymer and amount in the formulation. Polymers are selected not only for the physical characteristics of the films but also for the rate at which they dissolve. The dissolution rate of the dissolving polymer inversely related to the molecular weight of the polymer. In formulation at least 45% w/w of polymer should be present based on the total weight of the film.

Types of polymers used

Type of polymer	Example
Natural polymers	Starch, polymerized rosin, pullulan, sodium alginate, Guar gum, Pectin, gelatin, Xanthan gum and maltodextrins
Synthetic polymers	Polyvinyl alcohol, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, polyvinyl pyrrolidone, and hydroxy propyl cellulose

Plasticizer

It improves the flexibility of film and decrease the brittleness of the polymer film. The selection of plasticizers depends on the compatibility with polymer, method of formulation and the nature of solvent. Plasticizers such as glycerine, Polyethylene glycol, Propylene Glycol, Glycerol, castor oil, triacetin, triethylcitrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters can be added to the formulation to alter mechanical properties of final film. By lowering the glass transition temperature of the polymers more structurally pleasant, stronger and a flexible film can be prepared

Saliva Stimulating Agents

The rationale of employing saliva stimulating agents is to increase the rate of production of saliva that would be aid in the faster disintegration of the fast dissolving film formulations. The salivary stimulating agents activate the salivary glands to produce saliva that helps in the rapid disintegration of the films. Generally, acids which are used in the preparation of food can be utilized as salivary stimulations, like citric acid, malic acid, lactic acid, ascorbic acid etc. These are used alone or combination between concentration 2 to 6% w/w of the film. Sweeteners is also act and as salivary stimulating agents.

Sweetening Agents

Sweeteners have become the essential part of the food products as well as pharmaceutical products intended to be disintegrated to be disintegrated or dissolved in the oral cavity. Sweeteners are used to mask the bad odour and bitter taste of the drugs. Both type of sweetener is used natural and artificial sweeteners in the formulations and improves the palatability of the fast dissolving film i.e. Monosaccharide, Disaccharides and Polysaccharides can be used.[5]

Disintegrating agents

Disintegrating agents are added to FDF formulations to promote its breakup into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. Substances like microcrystalline cellulose, sodium starch glycolate, cross povidone and Ac-Di-Sol are used alone or in combination.

Mechanism of Disintegration by super-disintegrants

There are five major mechanisms for tablet disintegration as
follows:

- Swelling
- Porosity and capillary action (wicking)
- Deformation
- Enzymatic reaction
- Due to disintegration particle / particle repulsive force

By Swelling Action

In this mechanism, super-disintegrants swell when they comenin contact with water (e.g. starch).

By Capillary (Wicking)

In this mechanism, the disintegrants that do not swellfacilitate disintegration by their physical nature of lowcohesiveness and low compressibility. Thus, they provideporosity and capillaryaction for the penetration of liquid intothe bulk, rupture intra particulate bonds and cause thedisintegration.

By Deformation

In case of starch (such as potato starch and corn starch) arebelieved to be elastic in nature, but due to high compactionforce in case of tableting the elasticity deformed to plasticitywith energy rich potential. When these tablets are exposed toaqueous environment, the energy potential of deformedstarch grain will be triggered to cause disintegration.

Due to Disintegrating Particle / Particle Repulsive Force

Another mechanism of disintegration attempts to explain theswelling of tablet made with "nonswellable'' disintegrants.Researchers have proposed a particle repulsion theory basedonthe observation that non swelling particle also causedisintegration of tablets. The electric repulsive forcesbetween particles are the mechanism of disintegration andwater is required for it.

By Enzymatic Reaction

Enzymes present in the body also act as disintegrants. Theseenzymes dearth the binding action of binder and helps indisintegration. Due to swelling, pressure is exerted in theouter directionthat causes the tablet to burst or theaccelerated absorption of water leads to an enormous increasein the volume of granules to promote disintegration.[62]

Plantago ovata Seed Mucilage

Psyllium or Ispaghula is the common name, whose seeds areused commercially for theproduction of mucilage. Theseeds of Plantago ovata were soaked in distilled water for 48hours and then boiled for few minutes for complete release ofmucilage into water. The material was squeezed throughmuslin cloth for filtering and separating out the marc. Then,an equal volume of acetone was added to the filtrate so as toprecipitate the mucilage. The separated mucilage was dried inoven at temperature less than 60°. Mucilage of Plantago ovata has various characteristics like disintegrating, binding and sustaining properties.[62]

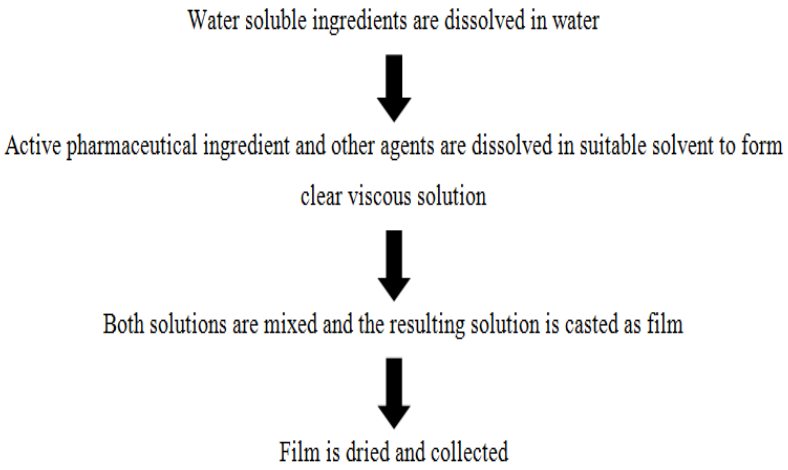
Methods of preparation of oral films

One or more of the following process can be used to manufacture the fast dissolving oral films.

Solvent casting method

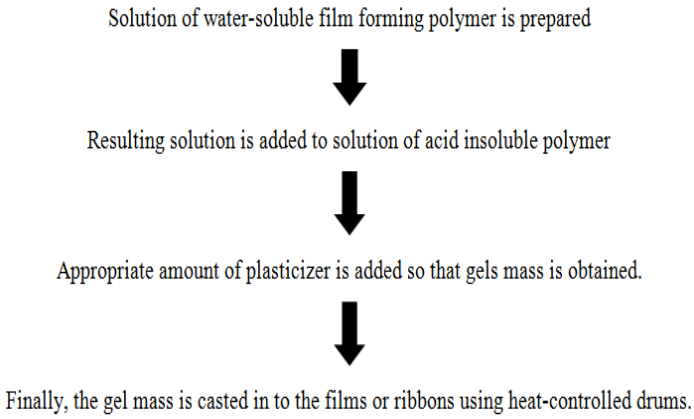
In solvent casting method Excipients are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally, solution is casted into the petri plate to form film and dried.

solution is casted into the petri plate to form film and dried.



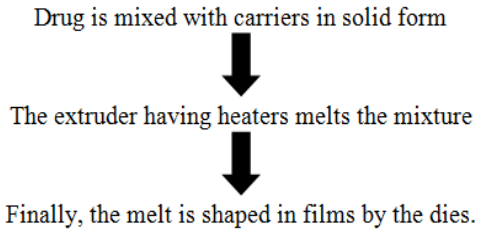
Semisolid casting

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. In semisolid casting method gel mass is casted in to the films or ribbons using heat-controlled drums. Gel mass is obtained by adding solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide. Acid insoluble polymers are cellulose acetate phthalate and cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.



Hot melt extrusion

In hot melt extrusion method firstly, the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder. The screw speed should set at 15rpm in order to process the granules inside the barrel of the extruder for approximately 3-4 min. The processing temperatures should be 80^0C (zone1), 115^0C (zone-2), 100^0C (zone-3) and 65^0C (zone-4). The extrudate then pressed into a cylindrical calendar in order to obtain a film.



Solid dispersion extrusion

In this method immiscible components are extruded with drug and then solid dispersions are prepared. Finally, the solid dispersions are shaped in to films by means of dies.

Rolling method

In rolling method, a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut into desired shapes and sizes.

Spray drying technique

A solvent system containing film former and other excipients are sprayed or coated on suitable carrier material, dried and peeled off to get the film.

The carrier materials used for film are glass, non-siliconized Kraft paper or polyethylene film.[6,7,8]

Classification of oral films[9]

There are three types of oral films:

1. Flash release
2. Mucoadhesive melt away wafer
3. Mucoadhesive sustained release wafers

Classification of oral films

Properties	Flash Release Wafer	Mucoadhesive Melt Away Wafer	Mucoadhesive Sustained Release Wafer
Area	2-8	2-7	2-4
Thickness	20-70	50-500	50-250
Structure	Single layer	Single or multi-layer	Multi-layer
Dissolution	Maximum 60 sec	Few minutes, forms gel	Maximum 8 to 10 hours
Application	Tongue	Gingival or buccal region	Gingival
Site of action	Systemic or local	Systemic or local	Systemic or local

COX-2 Inhibitors (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used for the treatment of arthritic conditions. Drugs in this heterogeneous class alleviate pain and inflammation by inhibiting cyclooxygenase-2 (COX-2). Cyclooxygenase-1 (COX-1) inhibition has traditionally been associated with increased gastrointestinal (GI) harm, whereas increased COX-2 selectivity has more recently become associated with greater risk of cardiovascular (CV) harm. When the entirety of data is considered, NSAIDs can be seen to exhibit a range of COX isoform selectivity, with all oral NSAIDs appearing to be associated with an increase in CV events.[10]

All NSAIDs must inhibit COX-2 to have any effect on inflammatory processes, NSAIDs are a chemically diverse group of medicines with significant heterogeneity in chemical structure and properties. They show substantial variation in selectivity for COX-2

overCOX-1, with this variable being best considered as continuous rather than simply dichotomous, where medicines are presented as either COX-2 selective or nonselective.[11]

The major therapeutic actions of NSAIDs are primarily enacted by their ability to block certain prostaglandins (PGs) synthesis through the cyclooxygenase enzymes (COX-1 and COX-2) inhibition. COX-1 produces prostaglandins and thromboxane A2 which control mucosal barrier in GI-tract, renal homeostasis, platelet aggregation and other physiological functions. COX-2 produces PGs that related to inflammation, pain and fever. COX-1 is expressed in normal cells, while COX-2 is induced in inflammatory cells. COX-2 inhibition most likely represents the desired effect of NSAIDs' anti-inflammatory, antipyretic and analgesic response; while COX-1 inhibition plays a major role in the undesired side effects such as GI and renal toxicities.[12]

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that arises more frequently in females than males, being predominantly observed in the elderly. RA primarily affects the lining of the synovial joints and can cause progressive disability, premature death, and socioeconomic burdens. The clinical manifestations of symmetrical joint involvement include arthralgia, swelling, redness, and even limiting the range of motion. Early diagnosis is considered as the key improvement index for the most desirable outcomes (i.e., reduced joint destruction, less radiologic progression, no functional disability).[13,14]

ETORICOXIB

Etoricoxib, a selective cyclooxygenase 2 (COX-2) inhibitor, is claimed to have greater gastrointestinal tolerability profile compared to conventional nonselective nonsteroidal anti-NSAID. It is used in various chronic inflammatory conditions such as osteoarthritis, gouty arthritis, and also in instances of acute pain.[15]

The oral bioavailability of Etoricoxib is not affected by food or high-fat meal, and thus, the drug can be administered with or without food. The most commonly reported adverse reactions in clinical trials were fatigue, dizziness, edema, upper respiratory tract infection, hypertension, diarrhoea, epigastric discomfort, heartburn, nausea, sinusitis, headache, and urinary tract infection.[16]

METHODOLOGY

Preformulation Studies

Preformulation testing is the first step in the rationale 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 testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be produced in large quantities. Hence, the following Preformulation studies were performed on the obtained sample of drug.

(1) Organoleptic characteristics
(2) Solubility
(3) Melting Point

- **Organoleptic Properties**

The colour, Odour and taste of the drug were characterized and recorded using descriptive technology.

- **Solubility Studies**

It is determined by dissolving drug substance in Water, 6.8 pH phosphate buffer and 1.2 pH 0.1N HCl. The solubility study was conducted by taking excess amount of the drug in 10 ml of solution. Then the samples were kept in the water bath shaker and agitated for 24 h at 37±0.5°C. The samples were filtered and suitably diluted. The samples were analyzed spectrophotometrically at λmax. The concentration of drug was determined using respective standard graph.[17]

- **Melting Point**

Melting point of Etoricoxib was determined by Thiel's tube method. Fine powder of Etoricoxib was filled in a glass capillary tube (sealed at one end). Capillary tube was tied to a thermometer and was placed in the Thiel's tube which was further placed on flame. The temperature at which the powder starts melting was noted.

Spectroscopic studies

Construction of Standard Calibration Curve for Etoricoxib[52]

The standard calibration curve for Etoricoxib was prepared using pH 6.8 phoshate buffer solution.

- **Preparation of 0.2 M sodium hydroxide**

8gm of sodium hydroxides dissolved in sufficient quantity of distilled water and it is made up to 1000ml with distilled water.

- **Preparation of 0.2 M potassium dihydrogen phosphate**

27.218gms of potassium dihydrogenphosphate is dissolved is dissolved in sufficient quality of distilled water and made up to 1000 ml with distilled water.

- **Preparation of 6.8 p^H phosphate buffer**

50 ml of 0.2 M potassium dihydrogen phosphate is taken in 200 ml volumetric flask and 22.4 ml sodium hydroxide is added and made up to 200 ml with distilled water.

Determination of λmax

Most of the drugs absorb light in UV wavelength region (200-400 nm) hence λmax was determined by using UV spectrophotometer. The solution containing 25µg/ml concentration of Etoricoxib was prepared in Phosphate buffer pH 6.8 and scanned over the range of 200-400nm against Phosphate buffer pH 6.8 as blank using double beam UV spectrometer. The wavelength at which

maximum absorbance of drug solution obtained in the graph was considered as λmax of the pure drug.

Preparation of Standard Stock Solutionand Standard Calibration Curve of Etoricoxib

100 mg of Etoricoxib accurately weighed and transferred into a 100 ml volumetric flask. It is then dissolved in 6.8 pH Phosphate buffer and the volume is made up to 100ml using phosphate buffer to get a solution concentration of 1000µg/ml as stock solution A. 5ml of stock solution A diluted with 100 ml phosphate buffer to get a stock solution B of 50µg/ml. Then further dilutions were made with same medium by pipetting out 1ml, 2ml, 3ml, 4ml and 5ml to get the solution concentration of 5,10,15,20 and 25µg/ml solution.

Drug excipeint compatibility study[18]

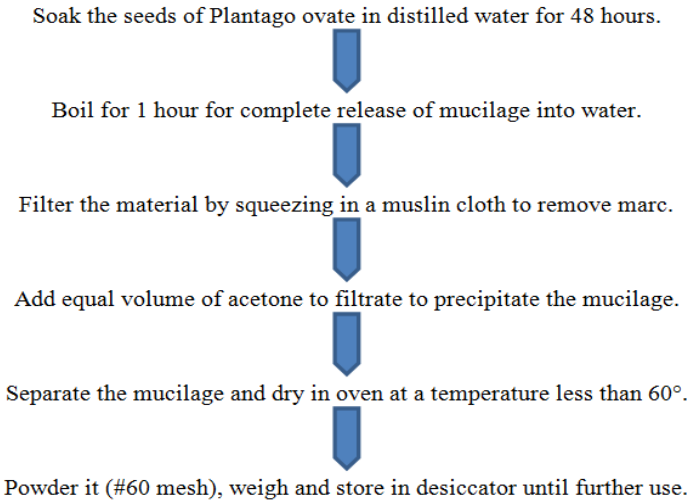
In the preparation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FTIR spectroscopy helps to confirm the identity of the drug and detects the interaction of the drug with the carriers. FTIR spectroscopy of pure drug (Etoricoxib), physical mixture of drug and polymers was carried out using FTIR to check the compatibility between drug and polymer. The FTIR spectra of the drug with polymers were compared with the standard FTIR spectrum of the pure drug.

Procedure

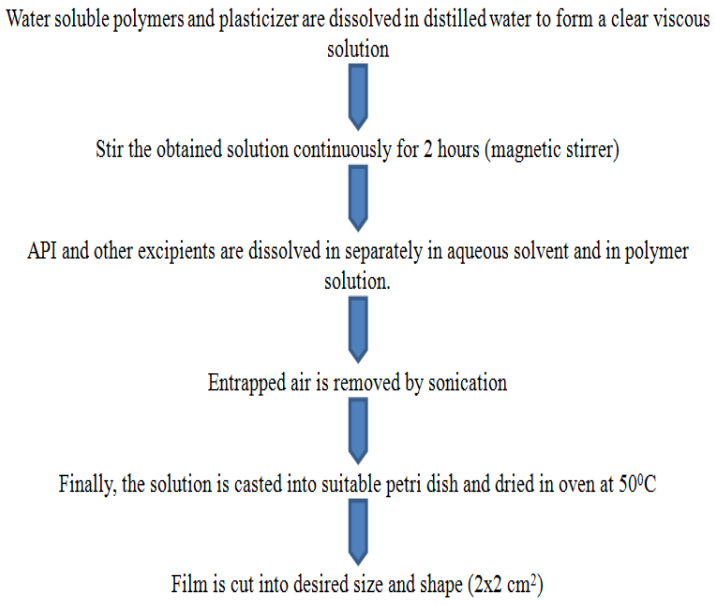
The pure drug, drug and polymer and physical mixture of drug, polymer and other excipients were prepared and scanned from 4000-400cm^{-1} in FTIR spectrophotometer. The IR Spectrum of pure Etoricoxib and Etoricoxib with polymers were recorded by FTIR spectrophotometer.

Extraction of plantago ovata mucilage[19,27]

Soak the seeds of Plantago ovate in distilled water for 48 hours.



Method of preparation oforal film of etoricoxib[21]



Formulation of fast dissolving film of etoricoxib
Calculation of amount of drug for one cast film: -

- Internal diameter of the Petri dish = 9cm
- Radius of the petri dish = 4.5cm
- Internal surface area of the petri dish = πr^2

= 22/7 X $(4.5)^2$
= 3.142 X 20.25
= 63.5 cm^2

- Surface area of one strip = 2cm X 2cm = 4cm^2
- 4cm^2 contains 15mg Etoricoxib
- 63.5 cm^2 contains = 240mg of Etoricoxib

FORMULATION DESIGN
Formulation of Etoricoxib oral film

Formulation code	Etoricoxib (mg)	XanthanGum (mg)	Guar Gum (mg)	Plantago ovate (mg)	PEG 400 (ml)	Citric Acid (mg)	Aspartame (mg)	Water (ml)
F1	240	500		20	0.5	80	80	q.s to 20
F2	240	500		30	0.5	80	80	q.s to 20
F3	240	500		40	0.5	80	80	q.s to 20
F4	240		500	20	0.5	80	80	q.s to 20
F5	240		500	30	0.5	80	80	q.s to 20
F6	240		500	40	0.5	80	80	q.s to 20
F7	240	250	250	20	0.5	80	80	q.s to 20
F8	240	375	125	30	0.5	80	80	q.s to 20
F9	240	125	375	40	0.5	80	80	q.s to 20

Evaluation of the prepared etoricoxib oral film
Evaluation of Oral filmis important in order to develop a drug product of high quality.

A. Weight measurement
Three individual batches of fast dissolving film of size (2cmX2cm) was weighed on anelectronic balance and the average weight and standard deviation was calculated.[20,23]

B. Thickness measurement
Thickness of the fast dissolving film was determined using a screw gauge. The thickness of each film at three different places was determined and standard deviation was also calculated.[23,24]

C. Drug content uniformity
Fast dissolving film size (2cm X 2cm) was cut into pieces and transferred to a Volumetric flask containing about 100ml of Phosphate buffer and dissolved. The solution then filtered and dilutions made and the absorbance measured against blank solution spectrophotometrically.[23,24]

D. Percentage Moisture Content
The percentage moisture absorption test was carried out to check the physical stability or integrity of the film at the humid condition. The moisture uptake by the films (n=3) was determined by exposing them to an environment of 75% relative humidity at room temperature for 1 day.[23,24]

$$\% = (W_1 - W^2) / W^2 \times 100$$

E. Surface pH
A pH electrode was used for this purpose. Oral film was slightly wetted with water. The pH measured by bringing electrode in contact with the surface of film. The procedure was performed in triplicate and average with standard deviation was reported.[24,25]

F. Tensile strength
The film size of 5cm X 2cm was selected for performing tensile strength test. The tensile strength apparatus has two clamps, the upper one is fixed and the lower is movable. The films sample was clamped between two clamps. The force at tearing and elongation were determined.[24,25]
Tensile strength = Break force/Cross sectional area of the film (cm^2)
Results were reported in N/cm^2units

G. Percentage elongation
The film size of 5cm X 2cm was selected for performing percentage elongation test. Percentage elongation was mainly based on tensile strength of films. Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement using the following formula.[24,25]

$$\text{Percentage elongation} = (L_f - L_o/L_o) \times 100$$

Where L_f is the final length and L_o is the initial length

H. Folding endurance
The film size of 4cm X 2cm was selected for performing the folding endurance test. Folding endurance measures the ability of patch to withstand rupture, higher the folding endurance lower was the film to rupture easily and vice versa. This parameter was determined by repeatedly folding the film at same place till it broke. The number of times the film could be folded at the same place without breaking/cracking give the value of folding endurance.[24,25]

I. *In-vitro* disintegration time
The disintegration time is the time when a film starts to break or disintegrate. The film size required for dose

delivery (2cm X 2cm) was placed on petri dish containing 10ml of pH 6.8 Phosphate buffer. The time required for breaking the film was noted as in-vitro disintegration time.[24,25]

J. *In-vitro* dissolution test

The dissolution study is carried out using USP type 1 apparatus at 37±0.5 ºc using 300ml of phosphate buffer Ph 6.8 as dissolution medium. The drug loaded film is placed in medium. The basket is set at 50 rpm.5ml samples were withdrawn at 0, 2, 4, 6, 8, 10, 12, 14, 16 minutes and replaced with fresh dissolution medium. The samples were filtered and analyzed spectrophotometrically.[26,27]

Stability studies

In order to determine the change in evaluation parameters like physical appearance stability studies of prepared SD will be carried out at accelerated storage conditions at temperature 40±2˚C and 75±5% RH in a humidity chamber for 6 month for the best formulation. Sample will be withdrawn after 90 days and evaluated for changes in physical appearance, drug content and *in-vitro* drug release profile.[26,27]

RESULTS

Preformulation studies of etoricoxib

Organoleptic property, Solubility and melting point of Etoricoxib

Properties	Reported		Observed	
Appearance	White Crystalline powder		White Crystalline powder	
Taste	Slightly bitter		Slightly bitter	
Odour	Odourless		Odourless	
Solubility	Water	0.033mg/ml	Water	0.029mg/ml
	6.8 pH phosphate buffer	0.99mg/ml	6.8 pH phosphate buffer	0.90mg/ml
	0.1 N HCl	3 mg/ml	0.1 N HCl	3mg/ml
Melting Point	127ºC-128ºC		131° C	
Identification (UV)	234nm		236nm	

a. Organoleptic evaluation

Organoleptic evaluation like general description, taste, odour and colour of Etoricoxib evaluated. It was found that Etoricoxib is odourless and crystalline powder.

b. Solubility study

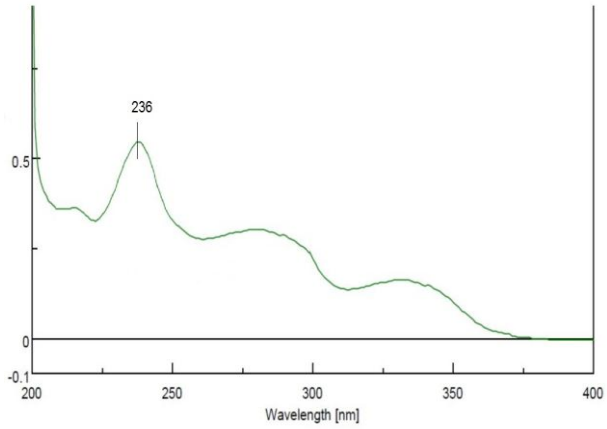
The study of Etoricoxib was carried out in water,6.8 pH phosphate buffer and 0.1 N HCl. The solubility of Etoricoxib in water was found to be 0.029mg/ml,in 0.1 N HCl was found to be3mg/ml, in 6.8 pH phosphate buffer was found to be 0.9 mg/ml. The results of solubility studies obtained were shown in Table.

c. Melting Point

The melting point of Etoricoxibwas determined by Thiel's tube method and melting point was found to be 131^0c which lies in the range of reported value of 127^0c - 128^0c.

Determination of λmax

The λmax was determinedby using UV spectrophotometer using6.8 pH phosphate buffer as medium. The drug solution of 25µg/ml prepared and absorbance measured in the U.V range of 200nm-400nm using 6.8 pH phosphate buffer. The absorbance ofdrug solution in 6.8 pH phosphate buffer showed the maximum absorbance peak at 236nm.



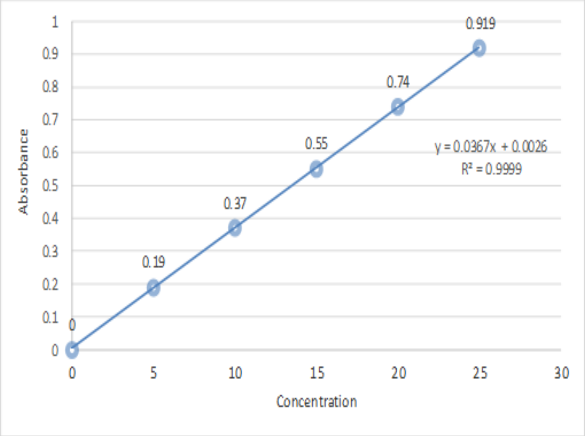
UV-Spectra of Etoricoxib

Standard Calibration Curve forEtoricoxib

Spectrophotometric absorbance data for standard curve of Etoricoxib in 6.8 pH phosphate buffer

Sl. No	Concentration (µg/ml)	Absorbance*
1	0	0
2	5	0.190±0.002
3	10	0.370±0.001
4	15	0.550±0.003
5	20	0.740±0.001
6	25	0.919±0.001

***** All the values represented are mean of 3 readings (n=3)

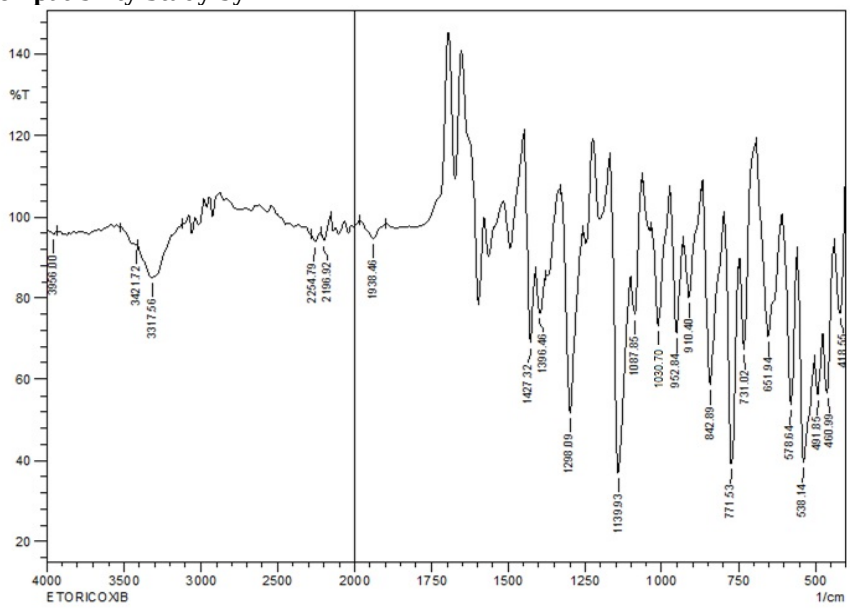


Standard curve of Etoricoxib

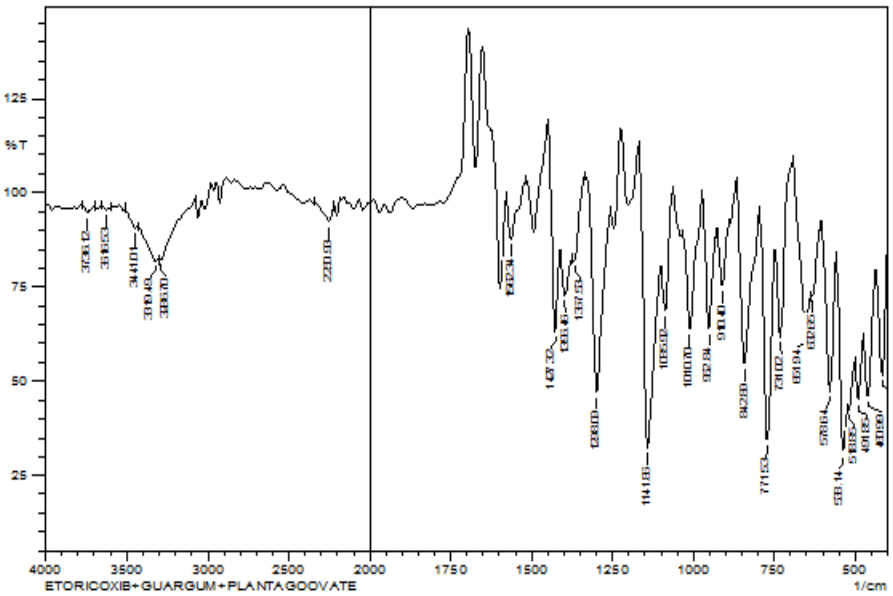
The drug solution of 5µg/ml -25µg/ml prepared in6.8 pH phosphate bufferand absorbance measured using UV spectrophotometer at theabsorption maximum (λ max) 236 nm. The obtained absorbance data is plotted against the concentration of drug solution. Absorbance value remained linear and obeyed Beer's Lamberts Law in the range of 0-25 µg/ml with the slope value of 0.0367 and R^2 value of 0.9999.

The drug absorbance at different concentration (µg/ml) in 6.8 pHPhosphate buffer are given in Table.

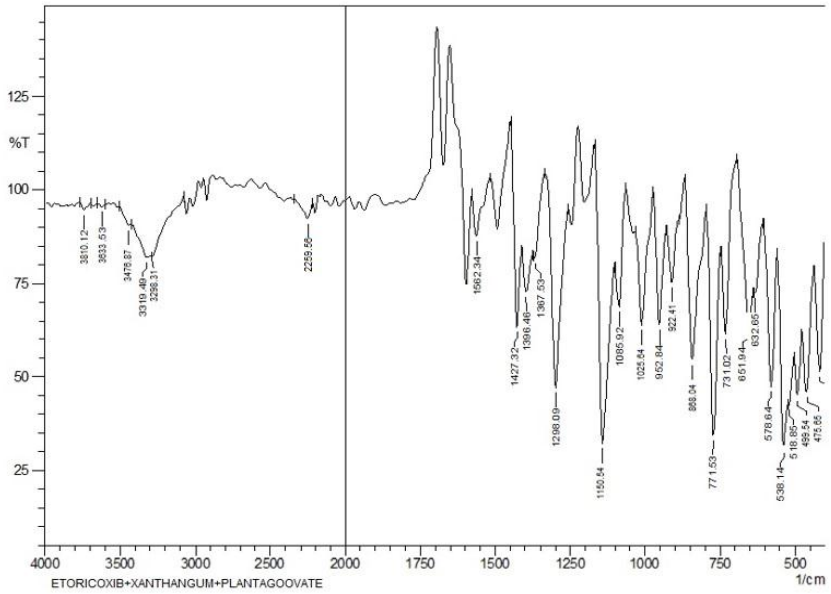
Drug Excipient Compatibility Study by FTIR



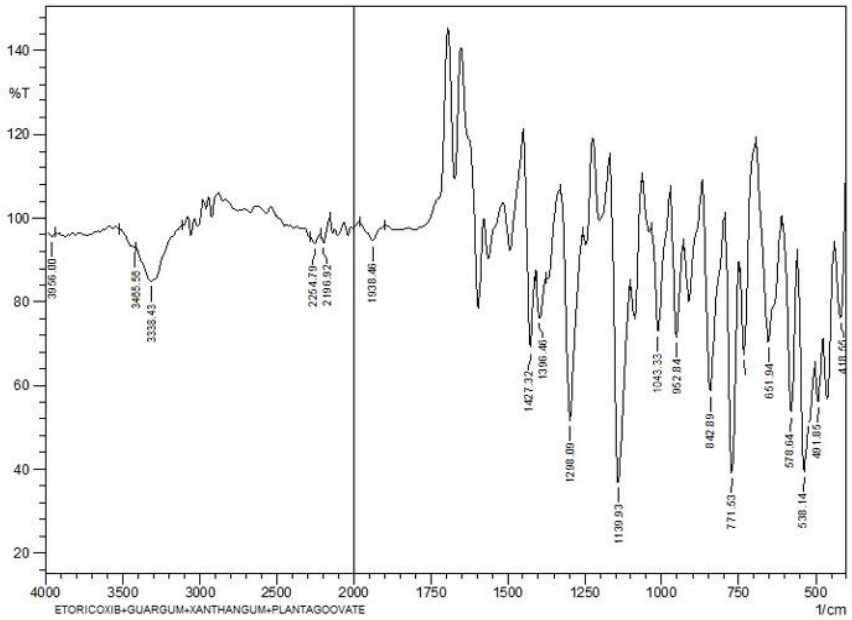
FTIR spectra of pure Etoricoxib



FTIR Spectra of Etoricoxib + Guar Gum + Plantago ovate



FTIR Spectra of Etoricoxib + Xanthan Gum + Plantago ovate



FTIR Spectra of Etoricoxib + Guar Gum + Xanthan Gum + Plantago ovate.

IR interpretation

Descriptions	Range (cm^{-1})	Etoricoxib	Etoricoxib + Xanthan Gum + Plantago ovate	Etoricoxib + Guar Gum + Plantago ovate	Etoricoxib + Xanthan Gum + Guar gum + Plantago ovate
C=N Stretching	2220-2260	2254.79	2259.56	2250.93	2254.79
S=O Stretching	1020-1060	1030.70	1025.64	1028.24	1043.33
C-Cl Stretching	550–850	651.94	651.94	651.94	651.94

Compatibility studies were performed using FTIR spectroscopy. The peaks obtained in the spectra of physical mixture correlates with peaks of drug spectrum. The FTIR of pure drug is characterized by C=N stretching at 2254.79 cm^{-1},S=O stretching at 1030.70cm^{-1} and C-Cl stretching at 651.94 cm^{-1}.

All the characteristic IR peaks related to pure drug Etoricoxib also appeared in the FTIR spectrum of drug mixed with polymer, so there was no chemical incompatibility between drug and polymer.

Characterisation of fast dissolving films containing Etoricoxib

Formulation code	Average weight (mg±SD*)	Thickness (mm±SD*)	Surface pH (*)	Folding endurance (*)	%Moisture content (%±SD*)
F1	62.20±1.74	0.070±0.003	6.86±0.04	220±14	1.28±0.13
F2	63.06±0.90	0.103±0.002	6.97±0.03	262±17	1.37±0.19
F3	63.90±1.58	0.130±0.013	7.15±0.04	249±41	1.40±0.12
F4	63.00±0.90	0.130±0.010	7.11±0.05	279±29	1.47±0.07
F5	68.10±2.00	0.170±0.009	6.96±0.05	257±09	1.71±0.07
F6	73.00±0.80	0.200±0.002	7.12±0.04	252±19	1.82±0.08
F7	58.90±0.35	0.134±0.039	6.81±0.09	261±26	1.35±0.01
F8	64.50±1.28	0.192±0.022	7.06±0.04	278±33	1.60±0.11
F9	65.20±2.07	0.186±0.075	6.95±0.14	247±14	1.67±0.10

* All the values represented are mean of 3 readings (n=3)

A) Weight variation

The weight of film is determined using digital balance and average weight of all film is given in table. All the films passed weight variation test as the standard deviation of percentage weight variation of the individual formulation was within pharmacopoeial limits of ±7.5%. It was formed to be in the range of **58.9±0.35** mg to **73±0.8**mg. Formulation F7 Showed lowest weight of **58.9±0.35** mg. Low concentration of super disintegrating agent may be the reason for lowest weight. Formulation F6 Showed highest weight of **73±0.8** mg and high concentration of super disintegrant in F6 may be the reason for highest weight. Hence, we can say that as the concentration ofsuper disintegrant increases, the weight of film also increase.

B) Thickness

Thickness of fast dissolving film depends on the concentration of polymer. Here the concentration of polymer kept constant. Hence, the thickness of fast dissolving film depends on the vary in concentration of the super disintegrant. Thickness all fast dissolving film was measured with micrometre screw gauge. The thickness of the fast dissolving film F1 to F9 varies from **0.07±0.003** mmto **0.20±0.002**mm. Formulation F1 showed lowest thickness of **0.07±0.003** mm and formulation F6 showed highest thickness of **0.20±0.002**. Low concentration of super disintegrant in F1 may be the reason for lowest thickness and highest concentration of thesuper disintegrant in F6 may be the reason for highest thickness. As a result of thickness measurement showed that as the concentration of super disintegrant increases, film thickness increases.

C) Percentage moisture content

The % Moisture content of films ranges from 1.28±0.13% to 1.82±0.08%. F6 showed high moisture content and F1 showed less moisture content.

D) Surface pH

The surface pH of the film F1 to F9 was ranging from **6.81±0.09** to **7.15±0.04** as shown in table. The surface film of all the film were uniform and within the range.

E) Folding endurance

Folding endurance measures the ability of patches to withstand rupture. Higher the folding edurance lower will be chances of film to rupture easily. The folding endurance of the film was determined by repeatedly folding a small strip at he the same place till it broke. Folding endurance of the film F1 to F9 ranges from **220±14** to **279±29**. Formulation F1 has lower folding endurance of **220±14** whereas formulation F4 had higher folding endurance of **279±29.**

Characterisation of fast dissolving films containing Etoricoxib

Formulation code	*In-vitro* Disintegration Time (Seconds±SD*)	Percentage Elongation (%±SD*)	Tensile Strength (N/cm^2 ± SD*)	Drug Content (%±SD*)
F1	51.6±2.50	27.1±0.9	1.53±0.05	94.9±0.65
F2	45.3±2.08	28.3±1.7	1.59±0.05	90.2±0.81
F3	40.3±3.20	37.7±0.9	1.53±0.10	93.9±0.80
F4	53.0±2.60	34.4±2.5	1.33±0.05	88.7±0.55
F5	49.3±1.50	39.4±0.9	2.02±0.05	95.8±1.05
F6	44.0±3.00	46.0±2.5	1.79±0.11	98.6±0.95
F7	51.3±3.00	32.1±0.9	1.72±0.05	90.6±1.30
F8	43.3±3.05	35.5±2.5	2.08±0.05	92.9±0.75
F9	41.0±1.70	38.3±1.7	1.79±0.11	87.0±0.65

***** All the values represented are mean of 3 readings (n=3)

F) Drug content

Drug content data study is shown in the table. The content uniformity for all the formulations prepared by using different concentrations of super disintegrant with polymer was found to be in the range of **87.06±0.65%** to **98.6±0.95%** which showed that there was uniform distribution of the drug in films of all formulation.

G) Tensile Strength

Tensile strength of the films F1 to F9 was ranging from **1.33±0.05 N/cm^2**to **2.08±0.05 N/cm^2** as shown in table. Formulation F4 showed minimum tensile strength of 1.33±0.05 N/cm^2 and formulation F8 showed maximum tensile strength of 2.08±0.05 N/cm^2.

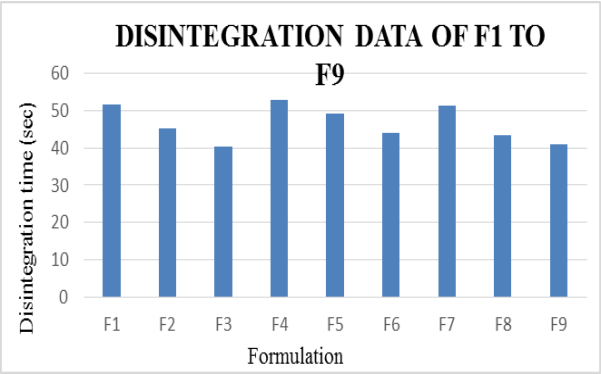
H) Percentage Elongation

The percentage elongation of the films F1 to F9 ranges from **27.1±0.9%** to **46±2.5%** and percentage elongation of all films was given in table.

Formulation F1 showed lowest percentage elongation of 27.1±0.9% and formulation F6 showed highest percentage elongation of 46±2.5%.

I) *In-vitro* Disintegration time

All the films are disintegrating rapidly. The disintegration time of the films F1 to F9 was found to be in the range of **40.3±3.2 seconds** to **53±2.6 seconds** as shown in table. Formulation F3 showed minimum *in-vitro* disintegration time **(40.3±3.2 seconds)** and formulation F4 showed maximum *in-vitro* disintegration time **(53±2.6 seconds).**

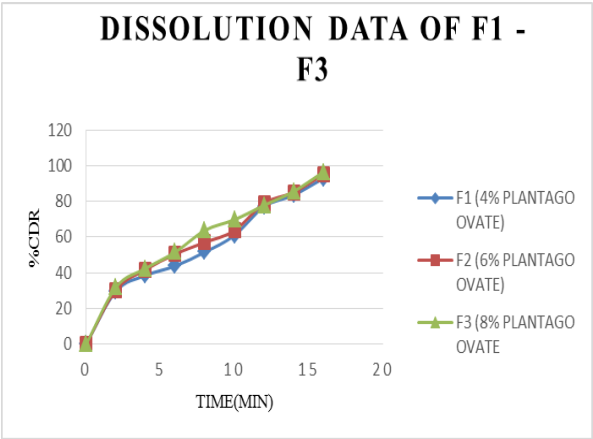


***In-vitro* Disintegration study of F1 – F9.**

J) *In-vitro* drug release study

***In-vitro* drug release study of F1 – F3.**

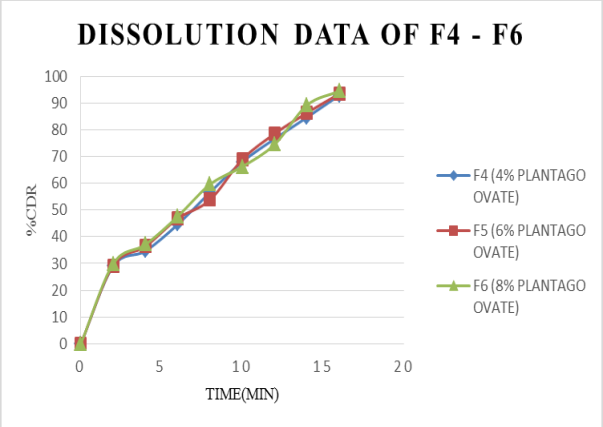
Time (min)	Percentage cumulative drug released		
	F1	F2	F3
0	-	-	-
2	29.60	30.32	31.85
4	38.50	41.79	42.44
6	43.80	50.50	51.56
8	51.60	57.07	63.80
10	61.02	63.70	69.80
12	77.19	79.03	77.90
14	83.66	85.20	85.70
16	93.02	95.16	96.60



***In-vitro* drug release study of F1 – F3.**

***In-vitro* drug release study of F4 – F6.**

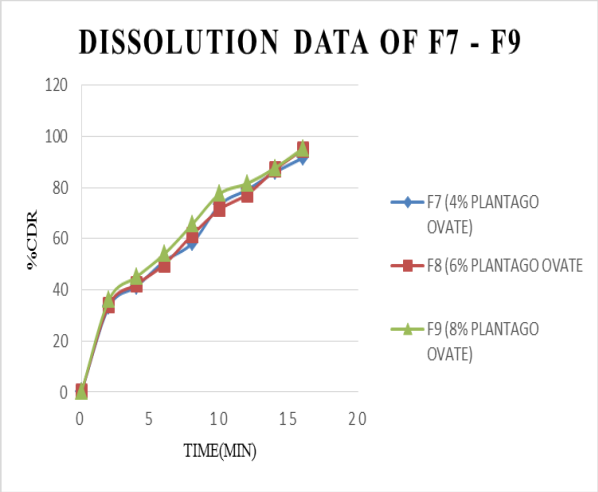
Time (Min)	Percentage cumulative drug released		
	F4	F5	F6
0	-	-	-
2	28.96	29.24	29.90
4	34.70	36.40	37.10
6	44.63	46.80	47.60
8	56.60	53.80	59.60
10	68.00	68.90	66.20
12	76.60	78.50	74.50
14	84.60	86.30	89.17
16	92.83	93.40	94.40



***In-vitro* drug release study of F4 – F6.**

***In-vitro* drug release study of F7 – F9.**

Time (min)	Percentage cumulative drug released		
	F7	F8	F9
0	-	-	-
2	33.41	34.20	36.24
4	41.50	42.25	45.20
6	51.30	50.10	54.13
8	58.30	61.50	65.60
10	73.30	71.60	77.70
12	79.30	77.50	81.70
14	86.15	87.15	87.80
16	91.70	95.02	95.40



***In-vitro* drug release study of F7 – F9.**

***In-vitro* drug release studies**

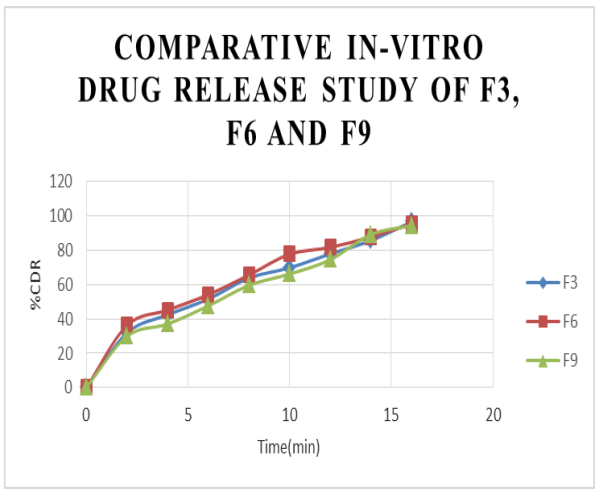
Formulation F3 (Xanthan Gum with 8% w/w Plantago ovate) which shows maximum drug release of **96.6%** at the end of 16 mins.

Formulation F6 (GuarGum with 8% w/w Plantago ovate) shows maximum drug release of **94.4%** at the end of 16 mins.

Formulation F9 (Combination of polymer with 8% w/w Plantago ovate) shows maximum drug release of **95.4%** at the end of 16 mins.

Comparative *In-vitro* drug release study of F3, F6 and F9.

Time (Min)	F3	F6	F9
0	-	-	-
2	31.85	36.24	29.90
4	42.44	45.20	37.10
6	51.56	54.13	47.60
8	63.80	65.60	59.60
10	69.80	77.70	66.20
12	77.90	81.70	74.50
14	85.70	87.80	89.17
16	96.60	95.40	94.40



Comparative *In-vitro* drug release study of F3, F6 and F9.

Comparative *In-vitro* drug releasestudy of F3, F6 and F9

The results show that the drug release depends on the concentration of natural super disintegrant and type of polymer used. Formulation F3 (Xanthan Gum with 8% w/w Plantago ovate) shows the highest rate of drug release (96.6%) at the end of 16 mins which is selected as the best formulation.

STABILITY STUDIES

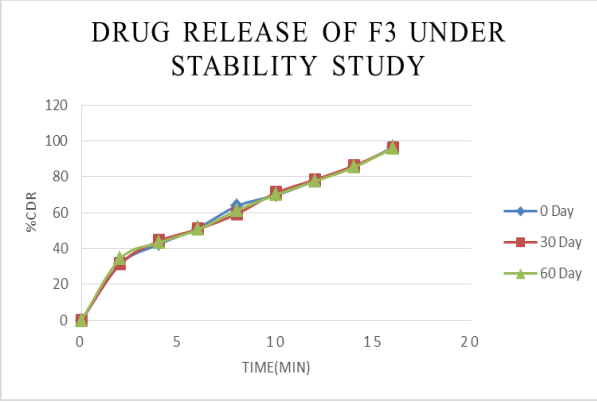
Stability study data of F3 (Xanthan gum with 8% w/w Plantago ovate)

Time (Months)	Appearance	Drug Content (%)
	*	*
Zero	Transparent	93.93
First	Transparent	93.33
Second	Transparent	94.14

* 40±2ºC and 75±5% RH

Drug release under Stability study of F3 (Xanthan gum with 8% w/w Plantago ovate).

Time (Mins)	%CDR 40±2ºC and 75±5% RH		
	0 Day	30 Day	60 Day
0	0	0	0
2	31.42	31.43	34.43
4	42.44	44.23	43.32
6	51.56	50.84	50.67
8	63.8	59.46	61.4
10	69.8	71.12	70.09
12	77.90	78.43	77.65
14	85.7	86.23	85.43
16	96.6	95.89	96.23



In-vitro dissolution study of F3 (Xanthan gum with 8% w/w Plantago ovate) under stability study

Short term accelerated stability study was performed on the F3 by storing the samples at 40±2ºC with 75±5% RH for 60 days. The samples were tested for any changes in appearance, drug content and *in-vitro* drug release studies at monthly intervals. F3 appeared to be transparent and showed drug content of 93.33% and

94.14% in first and second month respectively. Drug release studies conducted on F3 showed that there was no significant change as it released 95.89% and 96.23% at the end of 16 mins in first and second month respectively.

SUMMARY

Among all routes of drug administration, the oral route is one of the most favored routes, as it is more convenient, cost-effective, and ease of administration lead to high level of patient compliance. Drug delivery system being very eminent among pediatrics and geriatrics is orally disintegrating films (ODFs) or Fast dissolving films.

The concept of formulating and evaluating fast dissolving oral films of Etoricoxib using Plantago ovate as super disintegrant offers a suitable and practical approach of faster disintegration and dissolution characteristics.

The Etoricoxib is white powder and melting point of drug found 134^{o}c. The solubility study showed that drug is insoluble in water and freely soluble in 0.1N HCl and sparingly soluble in 6.8 pH phosphatebuffer.

Theλ maxvalue determined by analyzing drug concentration range 25µg/ml inpH 6.8 phosphate buffer by UV spectroscopy and maximum absorption of drug found to be at 236 nm.

The IR spectra of the Oral film compared with standard spectra of pure drug. The FTIR of pure drug is characterized by C=N stretching, S=O stretching and C-Cl stretching.

All the characteristic IR peaks related to pure drug Etoricoxib also appeared in the FTIR spectrum of mixed drug with polymers, so there was no chemical incompatibility between drug and polymer.

Total nine (F1, F2, F3, F4, F5, F6, F7, F8 and F9) Etoricoxib oral film prepared by solvent casting method.

Prepared Etoricoxib filmswas subjected to various evaluation parameters.

- Solubility of Etoricoxib in water was found to be 0.029mg/ml.Solubility of Etoricoxib in 6.8 pH Phosphate bufferwas found to be 0.99mg/ml. Solubility of Etoricoxib in 0.1N HCl was found to be 3 mg/ml.
- The drug content of Etoricoxib film was found to be in the range of 87.06±0.65% to 98.6±0.95%.
- The surface pH of the film F1 to F9 was ranging from 6.81±0.09 to 7.15±0.04.
- All the films passed weight variation test as the standard deviation of percentage weight variation of the individual formulation was within pharmacopoeial limits of ±7.5%. It was formed to be in the range of 58.9±0.35 mg to 73±0.8 mg.
- Thickness of the films F1 to F9 was found to be in the range of0.07±0.003 mm to 0.20±0.002 mm.
- Folding endurance of the film F1 to F9 ranges from 220±14 to 279±29. Formulation F1 has lower folding endurance of 220±14 whereas formulation F4 had higher folding endurance of 279±29.
- Tensile strength of the films F1 to F9 was ranging from 1.33±0.05 N/cm^{2}to 2.08±0.05 N/cm^2.
- The percentage elongation of the films F1 to F9 ranges from 27.1±0.9% to 46±2.5%.Formulation F1 showed lowest percentage elongation of 27.1±0.9% and formulation F6 showed highest percentage elongation of 46±2.5%.
- Disintegration time for the films was found to be in the range of 40.3±3.2 seconds to 53±2.6 seconds. Faster disintegration of film found in the F3 formulation containing Xanthan gum with 8% w/w Plantago ovate.

The *in-vitro* dissolution studies were carried out using USP Type-I Dissolution apparatus for up to 16 mins. Oral films of 4 cm^2 was placed in dissolution apparatus containing 300ml 6.8 pH phosphate buffer which was maintained at 37± 0.5°C and at a stirring speed of 50 rpm.

- The formulations F1 to F9 showed 91.7% to 96.6% drug release at the end of 15 mins. Rapid drug dissolution was observed in case of F3 containing Xanthan gum with 8% w/w Plantago ovate which released 96.6%. Slow drug dissolution was observed in F7 containing combination of polymer with 4% w/w Plantago ovate which released 91.7%.
- Short-term accelerated stability study was performed on the best formulations by storing the samples at 40±2^{0}C with 75±5% RH for 60 days. The samples were tested for any changes in drug content, and *in-vitro* drug release studies at monthly intervals. There were no significant differences found in the drug content and percentage cumulative drug release after stability study. This indicates that films are stable at storage condition.

CONCLUSION

The fast dissolving oral films containing Etoricoxib using natural super disintegrant was prepared successfully by solvent casting method. The FTIR spectral data indicates that there was no interaction between drug and the utilized polymers. All the polymers are compatible with the drug. 9 Etoricoxib oral films were prepared by solvent casting method. All the prepared Etoricoxib filmswere subjected to various evaluation parameters like spectroscopic studies Preformulation studies like solubility study, *in-vitro* drug release study etc. The *in-vitro* drug release was found to be in the range of 91.7% to 96.6% within 16min for Films containing etoricoxib prepared by solvent casting method. Short-term stability studies of the formulations indicate that there are no significant changes in the drug content, percentage drug dissolution parameter values after 60 days of storage at40±2 ºC with 75±5% RH.

REFERENCES

1. Nehal MD, Garima G, Pramod K. A Short Review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents". Adv in Bio Res., 2019; 5(6): 291-303.
2. Devender S, Pratik K. Update review on oral disintegrating film. IJCRT, 2018; 6(1): 2320-882.
3. Reena S. Buccal Drug Delivery System: A Review. IJPSRR, 2018; 50(1): 46-50.
4. Shahul H, Elango K. OralFast Dissolving Films-An Innovative Drug Delivery System. WJPPS, 2018; 7(11): 881-907.
5. Sharma P, Darwhekar G, Shrivastava B. An Overview About Novel Fast Dissolving Oral Films. IJDRA, 2018; 6(1): 1-7.
6. Prakruti M, Gangurde, Pranali V. Oral Film Technology: Challenges and Future Scope for Pharmaceutical Industry. IJPPR, 2015; 3(3): 184-203.
7. Irfan M, Sumeira R. Orally disintegrating films: A modern expansion in drug delivery system. SPJ., 2016; 24(1): 537-46.
8. Bilal M, Riaz T. Oral Films: A Comprehensive Review. ICPJ, 2016; 5(12): 111-17.
9. Chris W. Are All Oral COX-2 Selective Inhibitors the Same? A Consideration of Celecoxib, Etoricoxib, and Diclofenac. IJR, 2018; 1(1): 1-12.
10. Schmidt M, Lamberts M, Olsen A. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. Euro Heart J – CardioPharmaco, 2016; 2(2): 108-18.
11. Supakany W, Amaraporn W, Katie M. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. National Center for Biotechnology Information, 2018; 9(1): 143-50.
12. Quiang G, Xuiang W. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Research, 2018; 6(15): 1-14.
13. Cho S. Factors associated with time to diagnosis from symptom onset in patients with early rheumatoid arthritis. Korean J Internal Med., 2017; 1(1): 113-120.
14. Sukalyan S, Shathavisa M. Etoricoxib-induced toxic epidermal necrolysis: A fatal case report. IJP, 2018; 50(3): 139-42.
15. Raymond R, Arini S, Liana W. Pharmacokinetic equivalence study of nonsteroidal anti-inflammatory drug Etoricoxib. Clinical Pharmacology: Advances and Applications, 2018; 10(1): 43-51.
16. Francesco C, Silivia F, Umberto M, Francesca S, Paola M. Orodispersible dosage forms biopharmaceutical improvements and regulatory requirement. Drug discovery today, 2018; 23(2): 251-59.
17. https://www.pharmaguideline.com/2010/09/preparation-of-buffer-solutions.html
18. Lalith J. Formulation and evaluation of fast disintegrating tablets of etoricoxib by natural super disintegrant. AJPCR, 2011; 4(4): 236-353.
19. Shirsand SB, Sarasija S, Swamy D, Nagendra K. Plantago ovata mucilage in the design of fast disintegrating tablets. IJPS, 2009; 71(1): 41-45.
20. Devender S, Pratik K. Update review on oral disintegrating film. IJCRT, 2018; 6(1): 99-101.
21. Bhupendra N, Prashant D, Rajeev K. Preparation & evaluation of mouth dissolving film of pantoprazole sodium. WJPPS, 2014; 3(8): 1564-76.
22. Pallavi K, Pallavi P. Formulation and evaluation of fast dissolving films of elatriptan hydrobromide. IJCPR, 2017; 9(2): 59-63.
23. Jitender M, Vishal D, Pawan J, Formulation and evaluation of oral dissolving films of lisinopril. IJRPPS, 2016; 1(2): 34-38.
24. Kai B, Yvonne T, Kok K. Characterization of oral disintegrating film containing donepezil for Alzheimer disease. AAPS, 2012; 13(1): 134-42.
25. Takeuchi Y, Umemura K. Formulation design of hydroxypropyl cellulose films for use as orally disintegrating dosage forms. JDDST, 2018; 46(1): 93-100.
26. Santanu C, Madhusmruti K, Satya P. Comparative study on effect of natural and synthetic superdisintegrants in the formulation of fast dissolving tablets. IJGP, 2014; 2(1): 22-25.
27. Neeti A, Lalith S. Emergence of natural super disintegrants in orodispersible tablet: an overview. IRJP, 2013; 4(8): 33-37.