

# FORMULATION DEVELOPMENT OF MOUTH DISSOLVING FILM OF ETORICOXIB FOR PAIN MANAGEMENT

## Abstract

Etoricoxib is a potent, orally active, highly selective COX-2 inhibitor that exhibits anti-inflammatory, analgesic, and antipyretic activities. The present research was undertaken to develop Mouth Dissolving Films of Etoricoxib to have rapid onset of action. Mouth Dissolving Film (MDF) is a better alternate to Oral disintegrating tablets due to its novelty, ease of use and the consequent patient compliance. Solubility enhancement and taste masking of Etoricoxib were the two challenges solved by formulating drug- inclusion complex with betacyclodextrin (BCD). MDF prepared by solvent casting etoricoxib-BCD complex along with HPMC as film forming polymer was found to possess desirable physico-mechanical properties. *In vitro* release of etoricoxib from MDF in simulated salivary fluid and 0.1 N HCl was more than 95% within 2 minutes. Taste masking and *in vivo* disintegration were in acceptable range as assessed by human volunteers. Etoricoxib MDF was further characterized by Differential Scanning Calorimetry, Powder X-ray Diffraction and by Scanning Electron Microscopy. The index of analgesia shown by Etoricoxib MDF was comparable to that of immediate release tablets (100% activity within 40 minutes) in animal studies. Conclusively the present study documents the development of a commercially viable formula for an MDF of Etoricoxib with rapidity in pain management.

## 1. Introduction

Rapid or fast dissolving oral thin film is becoming an increasingly popular drug delivery system because of its wide and varied benefits. On contact with saliva, it dissolves within a few seconds, without the need of water, making them particularly suitable for paediatric and geriatric patients. As most of the polymers used in mouth dissolving films (MDFs) are amorphous, dispersion of drug in polymer matrix aids rapid dissolution. These advantages enhance the patient compliance and make pharmaceutical manufacturer to invest money in change of the existing products in the market to MDFs [1].

Etoricoxib is a potent, orally active cyclooxygenase-2 (COX-2) specific inhibitor, indicated for pain and inflammation in osteoarthritis, in rheumatoid arthritis, in acute gouty arthritis; in chronic low back pain; in ankylosing spondylitis and in other acute and chronic musculoskeletal disorders; primary dysmenorrhoea and pain following dental surgery [2]. Etoricoxib is available as immediate release tablets of 30, 60, or 120mg [3]. It is a white to off-white powder bitter in taste. Etoricoxib is practically insoluble in water categorized to BCS class II (Low soluble, High Permeable). Its poor aqueous solubility and dissolution delays the rate of absorption [4]. Formulation of etoricoxib as MDF would improve its aqueous solubility along with fast dissolution of etoricoxib in mouth itself resulting in earlier drug absorption starting from oral cavity itself leading to rapid pain relief.

The main challenges of the present study were taste masking besides improving the aqueous solubility of the drug as medications that enter the oral cavity, irrespective of mode of administration viz. swallowing, sublingual or oral inhalation should have an acceptable taste. One of the major barriers that prevents patient from adhering to a prescribed medication regimen has been identified as the unacceptable taste of active pharmaceutical ingredients (APIs) in these dosage forms [5]. Taste has an important role in the development of oral pharmaceuticals, with respect to patient acceptability and compliance, and is one of the prime factors determining the market penetration and commercial success of oral formulations, especially in pediatric medicine [6].

Beta cyclodextrin (BCD) increases the aqueous solubility of many poorly soluble drugs by forming inclusion complexes with their polar molecules or functional groups. The resulting

complex hides most of the hydrophobic functionality in its interior cavity while the hydrophilic hydroxyl groups get exposed to the environment [7]. Also, the bitter taste of substances can be reduced, or even completely eliminated if they form inclusion complexes of sufficient stability with the selected cyclodextrin [8]. In the present study, this strategy of forming inclusion complexes of etoricoxib with BCD was investigated for taste masking as well as dissolution enhancement of the drug loaded in MDF. Although many studies have been reported on solubility enhancement and ODT of Etoricoxib [4, 9] oral thin films of Etoricoxib have not been formulated so far and hence our work is first of its kind.

## **2. Materials and Methods**

### *2.1. Materials.*

Etoricoxib was the gift sample obtained from Glenmark Pharmaceuticals Ltd, Navi Mumbai, India. Beta cyclodextrin (Kleptose), and Sucralose were generously gifted by Par pharmaceuticals, Chennai. Mixed fruit flavour 148691 and Bitter masking flavour 689796 were kindly offered by Apex Laboratories, Chennai. HPLC grade methanol and acetonitrile were procured from Fisher Scientific. Distilled de-ionized water was used for formulation and analytical studies. All other reagents and chemicals used were of analytical reagent grade.

### *2.2. Drug-Excipient Compatibility Study.*

FTIR spectra of pure drugs, polymers used and blends were recorded on KBr disk method using FTIR-8400S Spectrophotometer with IR solution software (Shimadzu, Japan) to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Technosearch Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400  $\text{cm}^{-1}$  using 20 scans with 4  $\text{cm}^{-1}$  resolution.

### *2.3. Preparation of inclusion complex.*

Etoricoxib/Betacyclodextrin inclusion complex at weight ratios (1g:1g) and molar ratio (1molar:1molar) were prepared by kneading method. Kneaded products were obtained by triturating Etoricoxib and betacyclodextrin in a glass mortar with the pestle by adding small volume of purified water. The slurry obtained was kneaded for 45 min and then dried in vacuum oven (Ketan Shivani Scientific Industries (P) Ltd, India) at 35°C. Dried complex was passed through ASTM (American Standards for Testing of Materials) sieve No: 60.

#### 2.4. Formulation of Etoricoxib MDF.

Mouth dissolving films of Etoricoxib was prepared by solvent casting method using both the types of drug inclusion complexes of BCD, the composition of which are given in Table 1.

TABLE 1: Formulation of Etoricoxib MDF.

<b>Batch code</b>		<b>EF-1</b>	<b>EF-2</b>
<b>S.No.</b>	<b>Ingredients</b>	<b>Quantity / film</b>	
1.	Etoricoxib-Betacyclodextrin complex	426.7 mg*	886.4 mg*
2.	Hypromellose(Hydroxypropyl methyl cellulose 15 cPs)	150 mg	150 mg
3.	Sucralose	50 mg	50 mg
4.	Mixed fruit flavour 148691	0.025 ml	0.025 ml
5.	Bitter masking flavour 689796	0.025 ml	0.025 ml
6.	Glycerin	65 mg	65 mg
7.	Distilled water to	5 ml	5 ml

\*Quantity equivalent to 30 mg of Etoricoxib in single dose MDF

EF-1- MDF with betacyclodextrin inclusion complex(1:1 g ratio);

EF-2- MDF with betacyclodextrin inclusion complex (1:1 molar ratio);

A homogenous solution of HPMC 15 cps was prepared by continuous stirring of the polymer solution in water. Sucralose, mixed fruit flavour, bitter masking flavour 148691 and glycerin were added to the above solution and stirred well. The solution was sonicated (Spinatex Pvt Ltd, Italy) and kept aside for the removal of air bubbles. Accurately weighed Etoricoxib - Betacyclodextrin inclusion complex was added to the above solution and mixed well. By using pipette, 5 ml of prepared uniform dispersion was carefully transferred to the Petridish (8 cm diameter) without air bubble and dried in microwave oven (Whirlpool, India) at 50°C for 45 min. Further the film was dried in vacuum oven (Ketan Shivani Scientific Industries (P) Ltd, India) at 35°C. The prepared film was carefully removed from the Petridish, checked for imperfections and was cut into small circular films of 3 cm diameter have an equivalent dose of 30 mg Etoricoxib per MDF. The samples were kept in butter paper and sealed with an Alu-Alu pouch.

#### 2.5. Evaluation of Etoricoxib MDF

Etoricoxib MDFs were evaluated for uniformity of weight (Shimadzu Electronic Balance, Japan), thickness of film (Dial gauge, Model: K17, accuracy 0.001 mm, Baker Precision measuring instruments, China), disintegration time (Digital tablet disintegration test apparatus,

model: VTD-AV, Veego instruments corporation, India), In vitro dispersion time, surface pH, folding endurance, water vapor permeability and mechanical properties[10,11].

#### *2.5.1. Uniformity of weight.*

Each film was individually weighed on analytical balance (Shimadzu Electronic Balance, Japan) and average weight of 3 films was found. A large difference in weight denotes the non-uniform distribution of drug in the film.

#### *2.5.2. Thickness of film.*

The thickness of the different films was measured using a calibrated dial gauge (Baker Precision measuring instruments, China) with an accuracy of 0.001 mm. Thickness was measured by placing each film between the anvil and the presser foot of the dial gauge in 5 different locations and the average thickness was calculated.

#### *2.5.3. In vitro dispersion time.*

*In vitro* dispersion time was measured by Petridish method. A film was dropped in culture dish of 8 cm in diameter, containing 10 ml of simulated salivary fluid. The mean *in-vitro* dispersion time of 6 films was determined [12].

#### *2.5.4. Surface pH.*

Either highly acidic or highly basic pH of MDF would cause discomfort on administration. To know the surface pH of the film, the film was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 30 sec. The surface pH was measured by means of pH paper placed on the surface of the swollen films. The average of 3 determinations for each formulation was found out.

#### *2.5.5. Folding endurance.*

Folding endurance was measured manually for the prepared films. A 7.07 cm<sup>2</sup> MDF was repeatedly folded at 180° angle of the plane at the same place until it breaks. The number of times the film could be folded at the same place without breaking was noted for 3 films of same batch [13].

### 2.5.6. Water vapor permeability.

Water vapor transmission rate (WVTR) of the film was measured by modified ASTM E96 method. The film was sealed on the top of a glass vial (4 ml) containing 2.5 ml of distilled water (100% RH; 3169 Pa vapor pressure at 25°C), which was placed in a desiccator at 25°C and 0% RH containing fused calcium chloride (0 Pa water vapor pressure). The vials are weighed every 24 hrs for 1 week. The amount of water vapor permeated through the films was determined from the weight loss [14, 15]. WVTR and water vapor permeability (WVP) was calculated using the formula

$$\text{WVTR} = \frac{\Delta w}{\Delta t} \times A$$

$$\text{WVP} = \frac{\text{WVTR} \cdot L}{\Delta p}$$

where WVTR is in g/h m<sup>2</sup>,  $\Delta w/\Delta t$  is rate of water gain in g/h, A is the exposed area of the film in m<sup>2</sup>, L is the mean thickness of film specimens in m, and  $\Delta p$  is the difference in partial water vapor pressure between the two sides of film specimens in Pa. The water vapor pressure on the high-stream side of the film was 3.169 kPa (i.e., saturated water vapor pressure at 25°C), while the low-stream side is assumed to be zero. Three replicates of the determinations were done.

### 2.5.7. Mechanical properties of films.

Mechanical properties of films were evaluated by Texture analyzer (TAXT plus, Stable Microsystems, UK; maximum load 50 kg).

#### a. Burst Strength.

Film burst strength is the force required to break or rupture the film, which is an indicator of the flexibility of the film. Burst strength of the film was studied using 5 mm spherical stainless steel ball probe (P / 5S) with the probe adapter which was connected to the load cell [16]. A circular strip film with an area of 7.07 cm<sup>2</sup> was placed in film supporting rig and moving probe reached the surface of the film with the pre test speed of 2.0 mm /sec. When the probe reached the surface of the film, probe speed was changed to 1.0 mm/sec test speed with the trigger load of 5g and the data were recorded.

*b. Tensile strength.*

Tensile strength of a film is an indicator of toughness of film [17]. Etoricoxib films were cut into specimens with a width of 20 mm and a length of 60 mm. Film thickness was measured by means of calibrated dial gauge with an accuracy of 0.001 mm at 5 different positions. Tensile strength of the film was determined with Tensile Grips (A/TG). The test film was fixed to the upper tensile grip and load cell was tared to zero weight. Upper tensile grip was moved to the preset distance of 25 mm and the test film was securely clamped to lower grip. The tensile force was gradually applied on the test film till the film broke. The parameters maintained were 1 mm/s pretest speed, 1mm/s test speed, in distance target mode [18].

Tensile strength was calculated using the formula

$$\text{Tensile Strength} = \frac{F_{\max}}{A_{\text{film}}}$$

where ' $F_{\max}$ ' is the maximum force at breakage ( N ) and ' $A_{\text{film}}$ ' is the initial cross sectional area of the sample ( $\text{mm}^2$ ). The data reported is the mean of 3 individual determinations.

% Elongation was calculated using the formula

$$\% \text{ Elongation} = \frac{L - L_0}{L_0} \times 100$$

Where ' $L_0$ ' is the initial gauge length of the specimen (mm) and ' $L$ ' is the length at the moment of rupture (mm).

Young's modulus was calculated using the formula

$$\text{Young's modulus} = \left( \frac{F_{\text{lin}}}{A_{\text{film}}} \right) \times \left( \frac{1}{\epsilon} \right)$$

Where ' $F_{\text{lin}}$ ' is the force at corresponding strain of the linear section (N), ' $A_{\text{film}}$ ' is the initial cross sectional area of the sample ( $\text{mm}^2$ ) and  $\epsilon$  is the corresponding strain.

*2.6. HPLC analysis.*

A HPLC method was used in determination of drug content of films and analysis of samples in drug release studies using HPLC (Waters 2695 series, USA, PDA Detector (Waters 2996 PDA,

USA) and an integrator (Empower). The mobile phase was a mixture of two in the proportion 60:40, the first one was the buffer of pH 2.5 prepared with 0.1% Di basic sodium phosphate, 0.1% Ammonium acetate and 0.1% Sodium pentanesulphonate filtered through 0.45 micron filter and the second one was Acetonitrile and Methanol mixed in the proportion of 20:20, sonicated and degassed for 10 minutes by using sonicator. The stationary phase was waters symmetry shield, C-18 column, 250 x 4.6 mm, 5 $\mu$ m, Waters, USA. The injection volume was 50  $\mu$ L and the flow rate was 1mL/min. The column was maintained at 25 $^{\circ}$ C and The effluent was monitored at 234 nm [19, 20].

### *2.7. Drug content and uniformity of dosage units.*

A film was taken in a 100mL volumetric flask and sonicated with 70 ml of methanol for 5 minutes after which the volume was made upto 100 ml with methanol. Then 1.0 mL of this solution was diluted to 100mL with 0.1N Hydrochloric acid which was filtered through 0.45 micron filter and diluted as required and the drug content was found out by HPLC analysis.

### *2.8. In vitro drug dissolution study.*

The dissolution studies were performed in 900 ml of simulated salivary fluid s well as 0.1 N Hydrochloric acid using Lab India DS8000 dissolution (paddle) apparatus (Lab India Instruments pvt Ltd, India) with autosampler at 37 $\pm$ 0.5 $^{\circ}$ C with paddle rotation speed at 50 rpm. The samples were collected through in built-in 10 micron filter which were diluted previous to HPLC analysis.

### *2.9. Evaluation of Taste masking and in vivo disintegration time.*

Taste masking was assessed by ten human volunteers from whom informed consent was obtained and they had participated in the test under the supervision of a clinician and the study protocol was approved by Institutional Ethical Committee - Ultra College of Pharmacy, Madurai (UCP/IEC/2013-2014/29). Volunteers were asked to rinse their mouth with a cup of water (200 ml) before the test and instructed to move the dose against the upper part of the mouth with the tongue without biting. They were also instructed to spit the contents, when the dose got disintegrated [21]. Volunteers were asked to rate the initial taste, after taste, mouth feel, flavour and overall acceptability of formulations as per the ratings given in Table 2.



TABLE 2: Taste evaluation reference table.

Parameters	Score				
	1	2	3	4	5
<b>Bitterness*</b>	Extremely bitter	Highly Bitter	Acceptable	Very slightly bitter	Not at all bitter
<b>Sweetness*</b>	Not at all sweet	Very slightly sweet	Acceptable	Highly sweet	Extremely sweet
<b>Mouth feel</b>	Very gritty	Gritty	Acceptable	Creamy	Very creamy
<b>Flavor</b>	Very unpleasant	Unpleasant	Acceptable	Pleasant	Very pleasant
<b>Overall acceptability</b>	Worst	Poor	Acceptable	Good	Very good

\*Parameter assessed for Initial taste and After bitterness

### 2.10. Differential scanning calorimetry (DSC).

The powdered sample (2-3 mg) of Etoricoxib, BCD, inclusion complex and dry mix of Etoricoxib MDF were hermetically sealed in aluminum pans and heated at a constant rate of 5°C/min, over a temperature range of 0–300°C. Thermogram of the samples was obtained using differential scanning calorimetry (DSC, Q20, TA Instruments, USA). Thermal analysis data were recorded using Universal Software. Indium standard was used to calibrate the DSC temperature and enthalpy scale. Aluminum pan with lid was used for all samples. An empty aluminum pan was used as reference.

### 2.11. Powder X-ray diffraction (PXRD).

The powder XRD patterns of Etoricoxib, BCD, inclusion complex, dry mix of Etoricoxib MDF and Etoricoxib MDF were obtained from an X-ray diffractometer (Rigaku MiniFlex 600, Japan) working with Cu-K $\alpha$  radiation and in 2 $\theta$  range of 10-90° at 40 kV and 15 mA. The scan duration time was 10 Deg. /min with step size of 0.020. The diffracted radiation from the samples passed through 1.25° divergence slit and 0.30 mm receiving slit.

### 2.12. Scanning electron microscopy (SEM).

SEM studies on Etoricoxib, BCD, drug-BCD inclusion complex and Etoricoxib MDF were done with the Scanning Electron Microscope (Tescan, Vega 3 SBH, Czech Republic). The samples

were mounted onto aluminum stubs using carbon double-sided tape, gold coated with a Sputter coater (Quorum sputter coater, SC7620, UK) and examined at an excitation voltage of 5 kV.

### 2.12. Evaluation of analgesic activity of Etoricoxib MDF in Wistar albino rats

The analgesic activity of the test solutions of etoricoxib formulations was evaluated by Tail Flick test in Wistar albino rats. The experimental procedures and protocols followed in the animal studies were reviewed and approved (Proposal No.UCP/IAEC/2012/064) by the Institutional Animal Ethical Committee (IAEC) of Ultra College of Pharmacy, Madurai constituted in accordance with the guidelines of the CPCSEA, Government of India Registration No: 890/ac/05/CPCSEA.

#### A. Experimental animals

Healthy Wistar Albino rats of either sex weighing 150-200g were used for the determination of analgesic activity of Etoricoxib MDF. The animals were housed comfortably in a group of five in a single clean polypropylene cage (internal dimensions 33.6cm×23.2 cm×15.4 cm,  $L \times W \times H$ ) with a metal frame lid on its top. They were housed in an environmentally controlled room (temperature  $24 \pm 1^\circ\text{C}$ ; relative humidity 30-70 %) under a 12-h light/dark cycle. The animals were fed on standard pelletized laboratory animal diet and tap water *ad libitum*. The animals were used after an acclimatization period of 7 days to the laboratory environment. Each rat was conditioned for 30 min in the restrainer before starting the experiment [22].

#### B. Tail flick test

The ventral surface of the tail of the animal (approximately 5 cm from the caudal end of the tail) was placed on the heating coil ( $45 \pm 2^\circ\text{C}$ ) of digital analgesiometer (Instruments and Chemicals Pvt Ltd, India) and the basal reaction times were noted. About 3-5 basal reaction times were noted for each rat at a gap of 5 min to confirm the normal behavior of the animal [23].

Based on previously available literature, the dose of etoricoxib was fixed as 10 mg /kg body weight [24]. Etoricoxib film and commercial tablets were dissolved in purified water and calculated equivalent dose was given to albino rats orally, using syringe and feeding needle. Tail flicking response of albino rats was observed for every 10 minutes for 1 hour. As the reaction time reaches 10 sec, it was considered as maximum analgesia and the tail was removed from the source of heat to avoid tissue damage. Analgesic activity was quantified by finding out the

relative increase in reaction time to the maximum response (10 sec – reaction time) which was calculated at each time interval using the formula given below.

Index of analgesia in % = [(Reaction time at a particular time interval of testing - Basal reaction time) / (10 - Basal reaction time)] X 100

### **3. Results and Discussion**

#### *3.1. Drug-Excipient Compatibility Study.*

IR spectra of Etoricoxib, BCD, Inclusion complex and dry mix of MDF are given in Figure 1. The FTIR spectrum of pure Etoricoxib drug showed characteristic peaks of aromatic C=C stretching at 1597.11 cm<sup>-1</sup>, 1562.39 cm<sup>-1</sup>, 1539.25 cm<sup>-1</sup> and 1492.95 cm<sup>-1</sup>. Prominent peaks at 1145.75 cm<sup>-1</sup>, 1084.03 cm<sup>-1</sup> indicate S=O stretching vibrations. C-Cl stretching vibration was denoted by the presence of peak at 775.41 cm<sup>-1</sup>. Absorption peak of C-H stretching vibration was observed at 2962.76 cm<sup>-1</sup> and (CH<sub>3</sub>) C-H stretching vibrations were observed at 1427.37 cm<sup>-1</sup>. Also C-H deformation peak was found at 850.64 cm<sup>-1</sup>. The obtained FTIR spectrum thus confirms the purity of the drug.

The FTIR spectrum of betacyclodextrin shows prominent peaks of O-H stretching vibration at 3375.54 cm<sup>-1</sup>. C-H stretching and C-O stretching vibrations were observed at 2962.11 cm<sup>-1</sup> and 1647.26 cm<sup>-1</sup> respectively. Absorption peaks of C-O-C stretching vibrations were located at 1249.91 cm<sup>-1</sup> and 1157.33 cm<sup>-1</sup>.

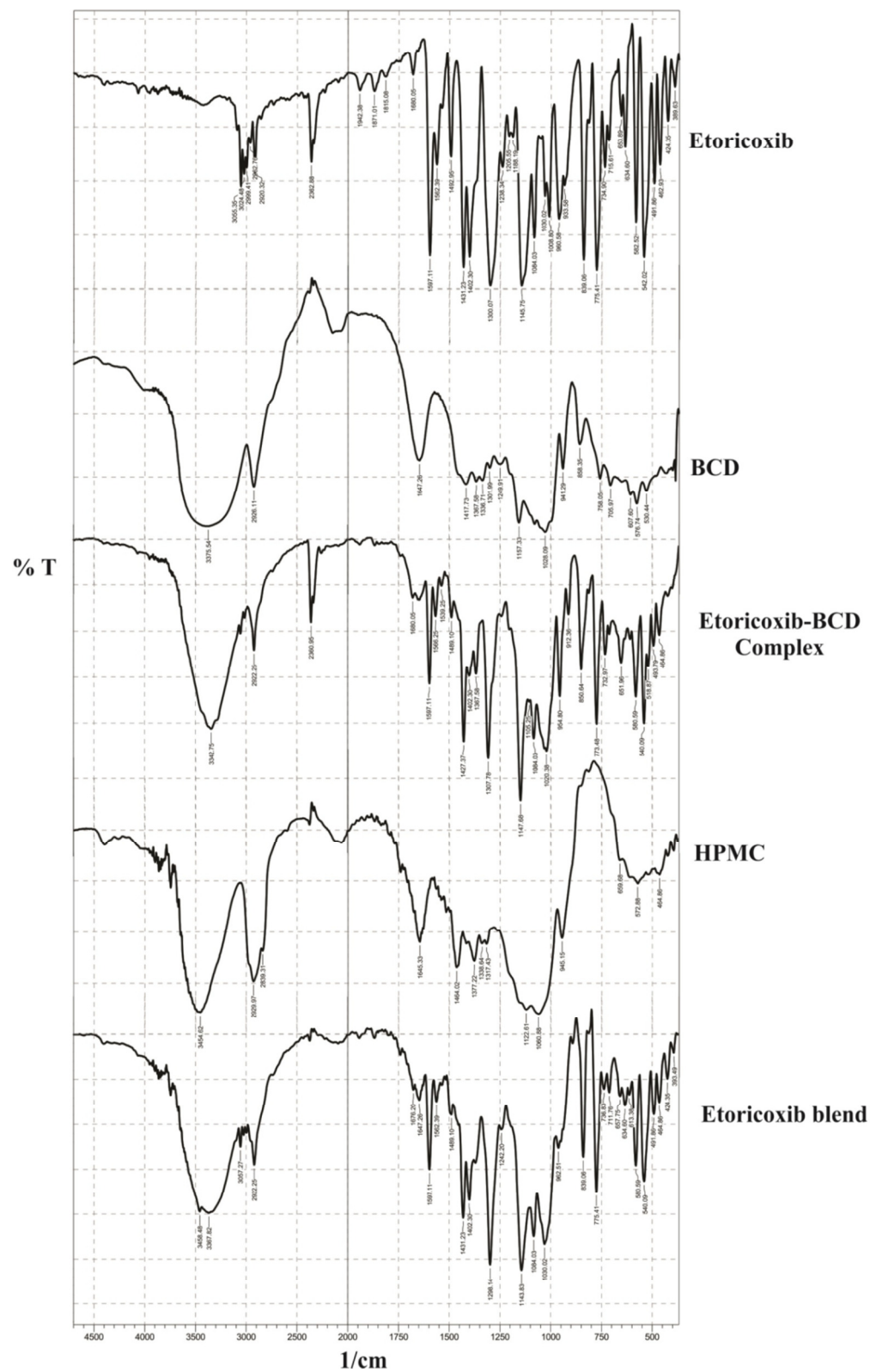


FIGURE 1: IR spectra of Etoricoxib, BCD, Inclusion complex and dry mix of MDF

The IR spectrum of Etoricoxib-betacyclodextrin complex bears the peaks corresponding to the Etoricoxib peaks as well as that of betacyclodextrin with no significant shift in the major peaks. The FTIR spectrum of dry mix of Etoricoxib MDF shows all the prominent peaks of Etoricoxib indicating the maintenance of identity of the drug and thus the stability of the drug in film [25].

### 3.2. Preparation of Etoricoxib MDF.

The drug-BCD complexes prepared in molar ratio and weight ratio of 1:1 were mixed with 3% w/v solution of HPMC 15cPs solution separately to obtain two formulations. The films were prepared by solvent casting method. The removal of Etoricoxib MDF with 1:1 molar ratio of betacyclodextrin inclusion complex from the glass substrate (petridish) was very difficult due to the presence of high solids content. So etoricoxib MDF formulated with 1:1 weight ratio BCD complex was used for further studies.

### 3.3. Evaluation of Etoricoxib MDF.

The physico-mechanical properties of Etoricoxib MDF prepared with 1:1 g/g drug:betacyclodextrin (EF-1) determined are presented in Table 3.

Table 3: Physical and mechanical characterization of Etoricoxib MDF (EF-1).

<b>Parameters</b>	
Weight (mg)	93.4 ± 1.66
Thickness (µm)	124.6 ± 3.68
Burst strength (N)	0.09 ± 0.001
Tensile strength (MPa)	4.0 ± 1.58
% Elongation	0.7 ± 0.24
Young modulus(MPa)	375.8 ± 3.03
Folding endurance	2 ± 1
Surface pH	7
Water vapor permeability (g. m/Pa h m <sup>2</sup> )x10 <sup>-7</sup>	17.8
<i>In vitro</i> dispersion time (sec)	34.6 ± 3.70
Disintegration time (sec)	8.5 ± 0.70

\*Values represent the mean ± S.D

#### 3.3.1. Appearance, weight and thickness.

The prepared films were homogenous, colourless, smooth and rough surface. The weight variation was found to be minimum as indicated by a small standard deviation of ± 1.66 mg. This

observation also shows the uniform distribution of the ingredients in MDF. The thickness shows a narrow range of 120.92 to 128.28  $\mu\text{m}$  further substantiating the above inference.

### *3.3.2. Mechanical Properties of film.*

Mouth dissolving films must be strong enough and ductile to prevent the rupture of the dosage form during processing, packing and during transit. The good burst strength and young modulus values of Etoricoxib MDF results indicate that Etoricoxib films are flexible and at the same time rigid enough to prevent the deformation of the dosage form.

Tensile strength, % Elongation and folding endurance results indicate that Etoricoxib MDF is slightly elastic and break at low force which might be due to the presence of high solid content [17].

Surface pH of the film is the neutral pH so that the films are safe to be used in buccal cavity without any problem of irritation and thus patient acceptance will not be affected. Water vapour permeability is a measure of ease of the moisture to pass through a material. The high water vapour permeability of Etoricoxib MDF would have been due to the presence of pores in MDF [14] which is also confirmed by SEM images as discussed in another following section.

### *3.4. In vitro dispersion time and Disintegration time.*

*In vitro* dispersion time of Etoricoxib MDF ranges from 31- 38 sec. The FDA recommends a disintegration time of 30 s or less for ODTs based on the USP disintegration test [26]. Etoricoxib MDF showed disintegration time of 8-9 sec and passes the limit for disintegration time.

### *3.5. Drug content and UOD.*

Drug content of Etoricoxib MDF was in the range of 99.0-100.6% implying uniform distribution of drug in the films.

### *3.6. In vitro drug release study.*

*In vitro* drug release studies of Etoricoxib MDF were carried out in simulated salivary fluid (SSF) and 0.1N Hydrochloric acid for 30 minutes. Etoricoxib MDF showed rapid and complete release profiles in both the media which correlates well with both disintegration time and *in vitro*

dispersion time. Dissolution profiles of Etoricoxib from MDF in SSF and 0.1N HCl are given in Figure 2a, 2b respectively.

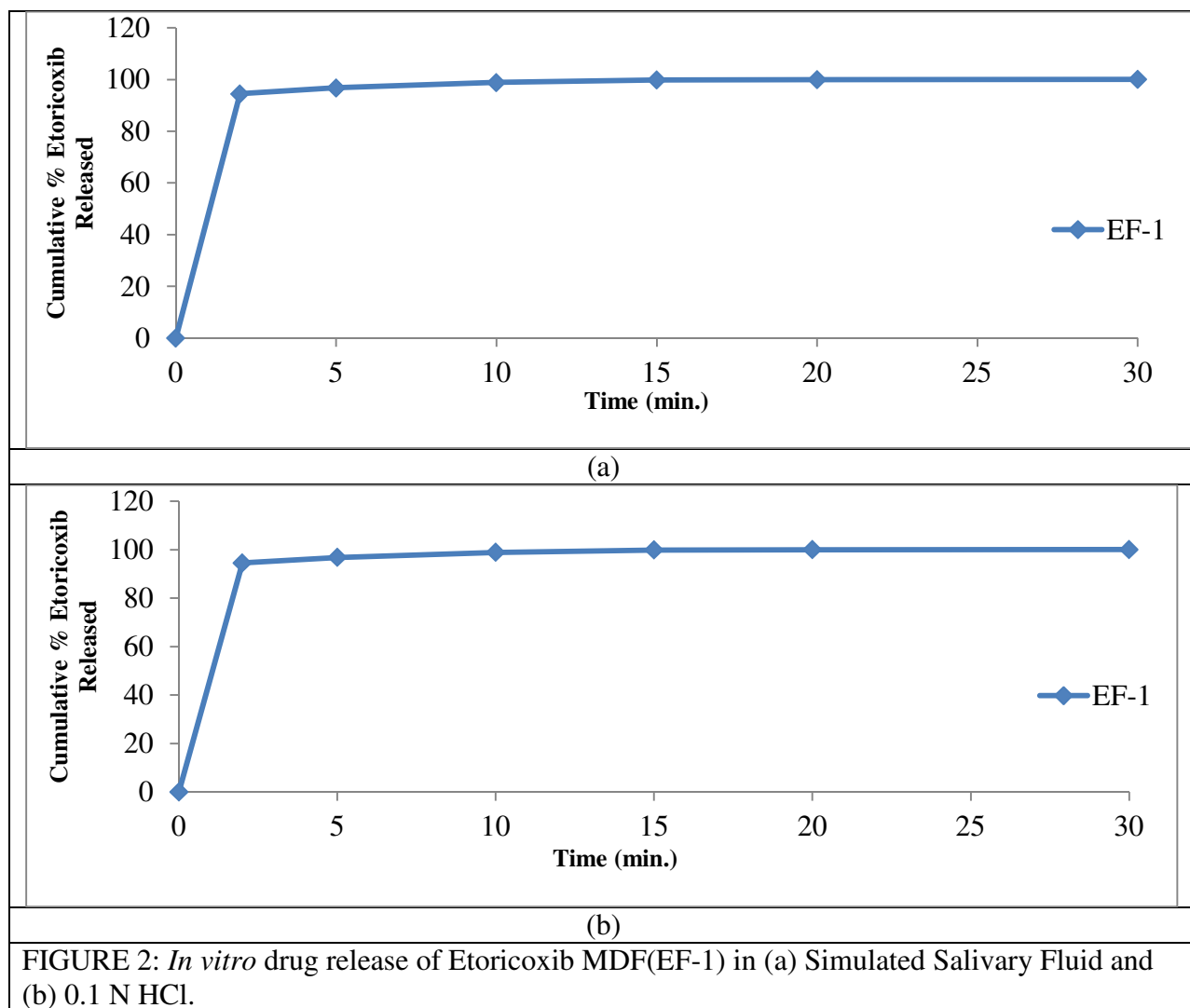


FIGURE 2: *In vitro* drug release of Etoricoxib MDF(EF-1) in (a) Simulated Salivary Fluid and (b) 0.1 N HCl.

### 3.7. Taste evaluation and *in vivo* disintegration time.

Results of *in vivo* disintegration time and palatability evaluation are presented in Table 4.

Results of *in vivo* disintegration time indicate that Etoricoxib MDF disintegrated within 30 seconds and well correlated with *in vitro* dispersion time and disintegration time. *In vivo* disintegration time of Etoricoxib MDF was 7.2- 8.4 sec which is even lower than the *in vitro* disintegration time suggesting the aided factor to be the pressing movement of tongue with the palate while keeping the film in position.

The results of taste evaluation study indicate that the taste masking of Etoricoxib could be achieved with complexation with betacyclodextrin. Although the dissolution of Etoricoxib MDF in SSF was rapid, the bitterness was not perceived by the volunteers as shown by the results. This is due to the fact that, Etoricoxib trapped in the inclusion complex formed with BCD was not exposed to taste buds during dispersion. The flavours also must have contributed to effective taste masking. The immediate dispersion and dissolution of MDF may produce rapid therapeutic action through faster drug absorption right from the buccal cavity.

Table 4: Taste evaluation by human volunteers.

<i>In vivo</i> disintegration time (sec)	Average score given by the Human volunteers			
	Initial observation			
	Bitterness	Sweetness	Mouth feel	Flavour
	4.6 ± 0.52	4.6 ± 0.52	4.7 ± 0.48	4.8 ± 0.42
7.8 ± 0.63	After 5 minutes			
	Bitterness	Sweetness	Overall acceptability	
	4.1 ± 0.30	4.6 ± 0.49	4.7 ± 0.46	

Values are given as Mean ± SEM (n=10).

Further, to characterize the inclusion complex and film, DSC and PXRD studies were carried out on drug, BCD, inclusion complex, film blend and films of Etoricoxib MDF.

### 3.8. Differential scanning calorimetry (DSC).

DSC of Etoricoxib MDF is presented in Figure 3. Melting of Etoricoxib in DSC starts at 137°C. DSC curve of Etoricoxib exhibited a broad endothermic peak at 147.15°C, starting at which is ascribed to drug melting [27]. DSC curve of betacyclodextrin exhibited a broad endothermic peak at 160°C, which is due to its dehydration of bound water.

DSC thermogram of Etoricoxib and Betacyclodextrin complex showed characteristic changes in melting endotherm and its enthalpy. Both the endothermic peaks were broadened, shifted to lower temperature with reduced intensity and enthalpy. This could be due to the possible interaction between Etoricoxib and betacyclodextrin and loss of crystallinity. Etoricoxib endotherm was shifted from 147.15°C to 118.61°C and betacyclodextrin endothermic peak



shifted from 160°C to 157.63°C. Enthalpy reductions observed were from 47.00J/g to 32.15J/g and from 872.3J/g to 33.03J/g for Etoricoxib and betacyclodextrin respectively.

Dry mix of Etoricoxib MDF blend retained the peak of betacyclodextrin at 157°C whereas the merged/broad peak start melting from 126.59°C and appeared as a peak at 141.71°C might be due to Etoricoxib in BCD complex and HPMC.

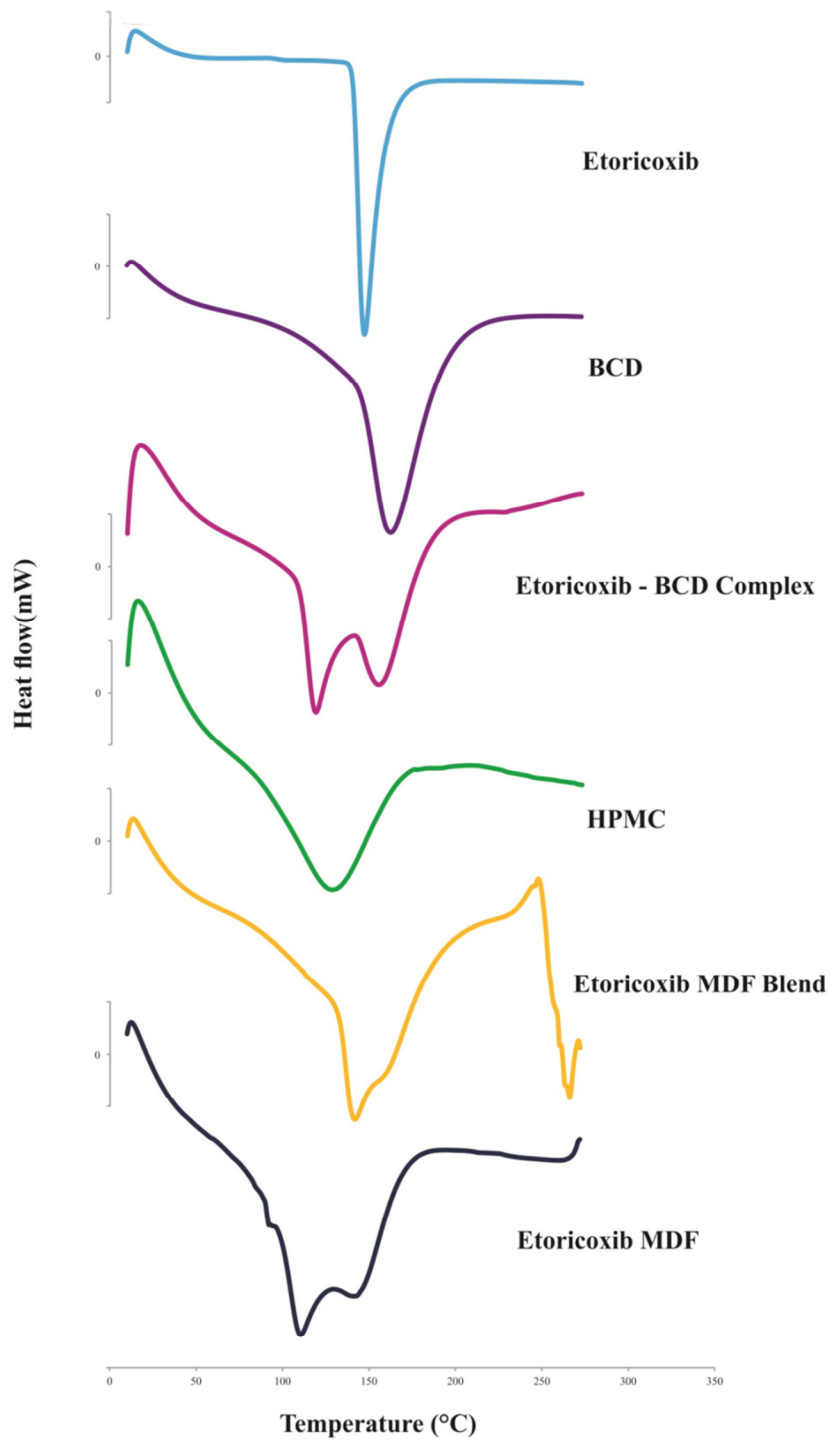


FIGURE 3: Differential scanning calorimetry profiles of Etoricoxib MDF.

DSC thermogram of Etoricoxib MDF showed endothermic peak of 135°C and 110.43°C are might be due to betacyclodextrin and Etoricoxib in BCD complex & HPMC respectively. Both the endothermic peaks were broadened, shifted to lower temperature with reduced intensity .This could be due to the possible interaction between HPMC and Etoricoxib BCD complex and further loss of crystallinity. A peak at 91°C indicates the loss of moisture in the sample.

### *3.9. Powder X-ray diffraction*

Powder X-ray diffractograms (PXRD) of etoricoxib, BCD, etoricoxib-betacyclodextrin complex, HPMC, etoricoxib-MDF dry mix and etoricoxib MDF are given in Figure 4. PXRD of Etoricoxib reveals many distinct reflections pointing to its highly crystalline nature. Various diffraction peaks of the drug crystals can be traced in the spectrum of the pure drug at 2θ values of 12.2, 12.8,13.4,15.9,16.9,18.5,19.7,20.4,21.5,23.1,24.0,24.4,26.7,28.7,29.6,30.2,31.1,31.6, 32.3,36.1, 39.6,43.4,45.5 and 47.2. The crystalline nature of BCD is also revealed by the PXRD of betacyclodextrin as shown by many distinct reflections. Various diffraction peaks of the drug crystals can be traced in the spectrum of the pure drug at 2θ values of 10.9,11.9,12.9,13.9,15.0,15.7,16.4,17.1,17.4,17.9,1.4,19.2,19.9,21.5,23.0,24.6,25.3, 25.9,27.4, 28.8,30.6, 31.3,32.2,35.1,36.2, 38.0,39.7,40.8, 42.8, 44.6,45.3 and 51.5.

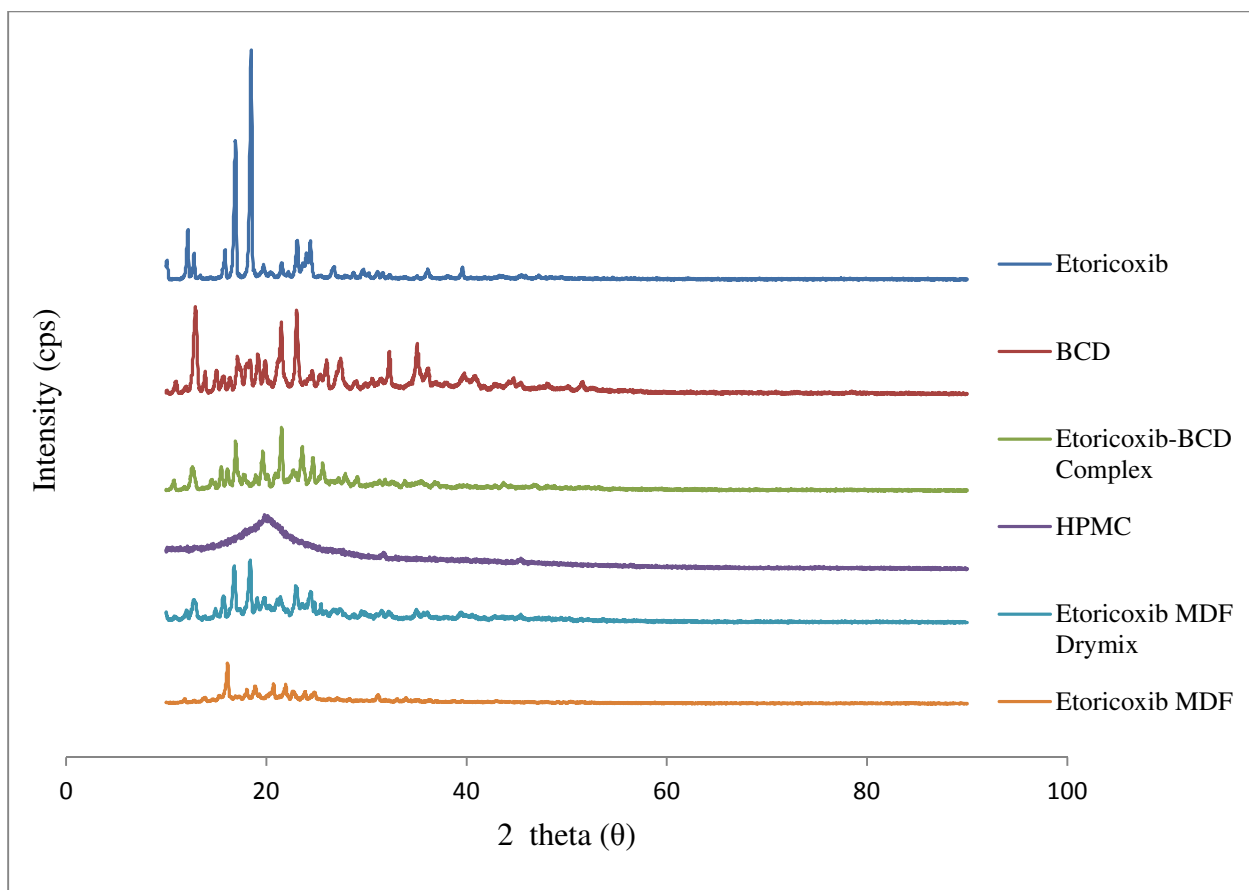


FIGURE 4: X-ray diffraction pattern of Etoricoxib MDF.

Prominent peaks at  $2\theta$  values of 18.5, 12.2, 15.7, and 24.4 are missing in the diffractogram of Etoricoxib-Betacyclodextrin complex. Intensity of peaks and peak heights are reduced at 16.9, 12.8, and 23.1. Reductions in peak intensity, shifts and absence of peaks, presence of new diffraction peaks, or a complete diffuse pattern might be related to possible change of crystallinity of the drug to amorphous form and/or complexation. An increase in peak width stands for the reduction in particle size [28, 29].

In PXRD of Etoricoxib film blend, new peaks are present along with that of drug which might be due to the crystalline excipients in blend composition. Absence of peaks, decrease in peak intensity and peak height of pure drug indicate reduction in drug crystallinity.

PXRD of Etoricoxib film shows drug peaks at  $2\theta$  values of 16.9 and 24.0 with decreased intensity. All the other peaks corresponding to the drug were absent in the diffractogram suggesting the loss of crystallinity of the drug.

### *3.10. Scanning electron microscopy (SEM).*

SEM images of etoricoxib, BCD, drug-BCD Inclusion complex and etoricoxib MDF are presented in Figure 4. SEM of etoricoxib exposes discrete, elongated flake-like structures with rough edges covered on their surfaces by fine particles. Some structures are large with parallelogram shape. It also reveals the hard and thick nature of the drug particles. In contrast, etoricoxib-BCD complex observed by SEM are soft and thin. Agglomerates of particles clumping to each other are present. The forms are different from both of the drug and BCD with reduced particles size. SEM of Etoricoxib-MDF shows the rough and uneven surface with circular pits with the absence of particles suggesting the presence of the drug in dissolved state in the polymer HPMC.

The results of DSC, XRD and SEM confirm the reduction in particle size of Etoricoxib in inclusion complex. They further ensure the loss of crystallinity when formulated as a film comprising amorphous HPMC.

### *3.11. Evaluation of analgesic activity of Etoricoxib MDF in Animal studies*

Analgesic activity of etoricoxib MDF was studied by tail flick test in Wistar rats. Results of tail flick test are presented in Table 5. Results were statistically analyzed by one way ANOVA, followed by the Tukey Kramer multiple comparison test using Graph pad InStat software.  $P < 0.001$  was considered extremely significant.

The statistical data showed that there is no significant analgesic activity for both etoricoxib MDF and commercially available immediate release tablets at 10 minutes when compared to control ( $P > 0.05$ ). But both formulations showed significant activity at 20 min when compared to the control ( $P < 0.01$ ). The results demonstrate the presence of the active therapeutic in the dissolved state leading to immediate absorption followed by fast analgesia greater than/comparable to that of IR tablets of etoricoxib. Thus better management of pain will be possible with the developed etoricoxib MDF.

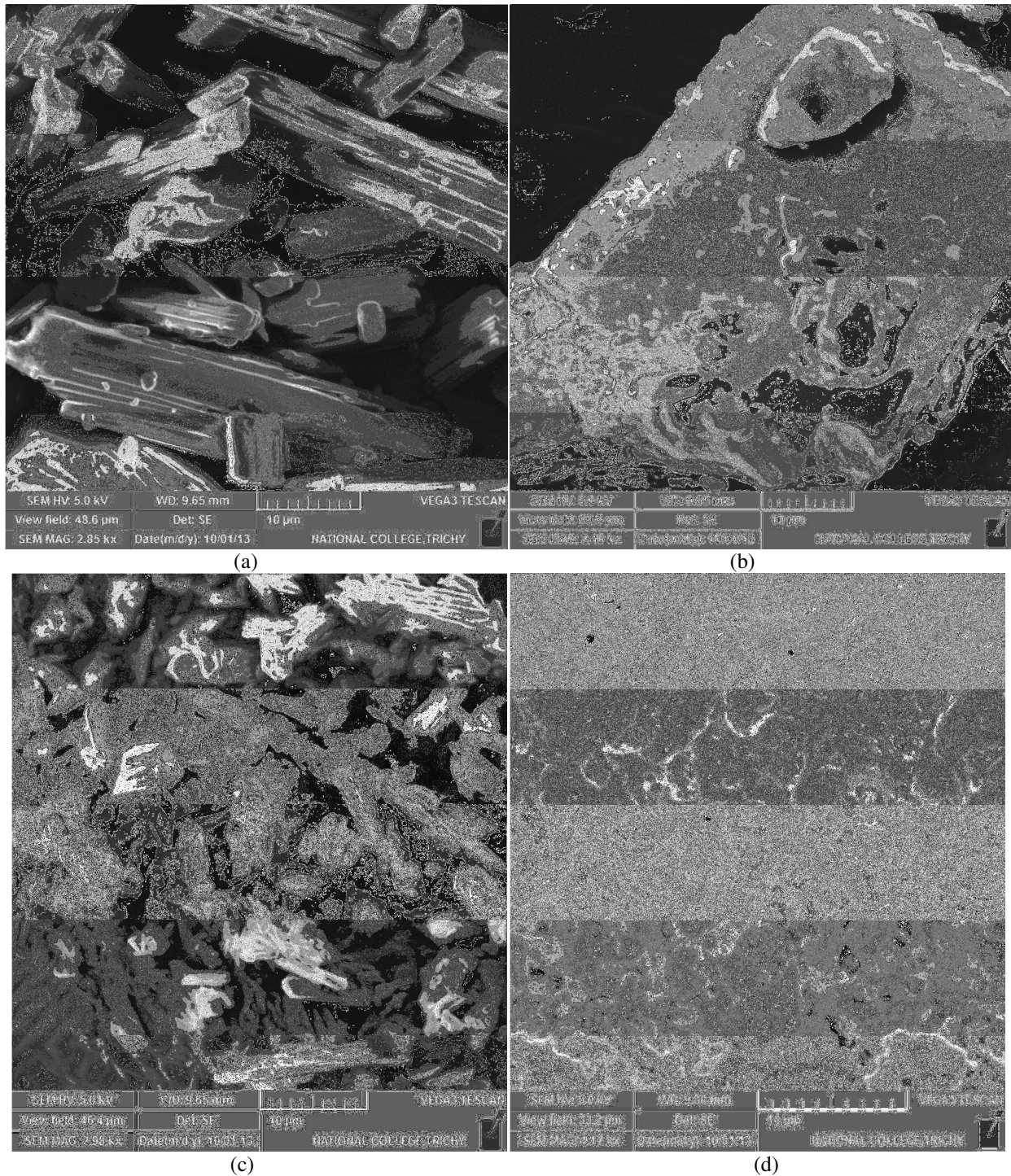


FIGURE 4: SEM images of (a) etoricoxib, (b) BCD, (c) etoricoxib-BCD Complex, (d) etoricoxib MDF.

Table 5: Evaluation of analgesic activity by Tail flick test (Reaction Time)

Treatment	Basal Reaction Time (Sec)	Reaction time (sec)				
		10 min	20 min	30 min	40 min	50 min
Control	1.26 ± 0.06	1.27 ± 0.11	1.22 ± 0.05	1.25 ± 0.09	1.27 ± 0.08	1.19 ± 0.04
Marketed IR Tablet	1.44 ± 0.31	1.44 ± 0.25 <sup>ns</sup>	3.16 ± 0.36 <sup>a</sup> (20%)	8.83 ± 0.35 <sup>b</sup> (86%)	10.17 ± 0.04 <sup>b</sup> (102%)	> 10 sec (>100%)
Etoricoxib MDF	1.26 ± 0.14	1.58 ± 0.28 <sup>ns</sup>	3.53 ± 0.26 <sup>a</sup> (26%)	8.85 ± 0.50 <sup>b</sup> (87%)	10.18 ± 0.16 <sup>b</sup> (102%)	>10 sec (>100%)

Values are expressed as mean ± SD (n = 3); <sup>a</sup> - P < 0.01; <sup>b</sup> - P < 0.001; <sup>ns</sup> = not significant when compared to control; Data were analyzed by using One-way ANOVA followed by Tukey Kramer multiple comparison test.

The values in the parentheses indicate the percentage increase in reaction time.

#### 4. Conclusion

To conclude, the developed Etoricoxib MDF with both enhanced dissolution and acceptable taste masking was achieved by forming inclusion complex with betacyclodextrin in 1:1g ratio. The cause for the improved dissolution of the drug has been shown to be particle size reduction of the drug in inclusion complex as shown by physical characterizations. DSC, PXRD and SEM studies also confirm the formation of inclusion complex and change in crystallinity. Etoricoxib MDF prepared possesses adequate mechanical strength and desired rapid disintegration which on administration will result in rapid therapeutic action and could be used as an alternate to the commercially available immediate release tablets resulting in improved patient adherence.

## 5. References

- [1] S. Gaisford, A. Verma, M. Saunders and P.G. Royall, "Monitoring crystallization of drugs from fast-dissolving oral films with isothermal calorimetry," *International Journal of Pharmaceutics*, vol. 380, pp. 105-111, 2009.
- [2] <http://www.medicines.org.uk/EMC/medicine/8734/SPC/Arcoxia+30mg>
- [3] A. Okumua, M. DiMaso and R. Löbenberg, "Computer simulations using GastroPlus™ to justify a biowaiver for Etoricoxib solid oral drug products," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 72, pp. 91-98, 2009.
- [4] A. Das, A.K. Nayak, B. Mohanty and S. Panda, "Solubility and Dissolution Enhancement of Etoricoxib by Solid Dispersion Technique Using Sugar Carriers," *ISRN Pharmaceutics*, vol.2011, pp. 1-8, 2011.
- [5] Z.Aynew, V. Puri, L. Kumar and A.K. Bansal, "Trends in pharmaceutical taste masking technologies: a patent review," *Recent Patents on Drug Delivery & Formulation*, vol.3, no.1, pp.26–39, 2009.
- [6] V. Anand, M. Kataria, V. Kukkar, V. Saharan and P.K. Choudhury, "The latest trends in the taste assessment of pharmaceuticals," *Drug Discovery Today*, Vol.12, no.5/6, pp. 257-265, 2007.
- [7] G. Tiwari, R. Tiwari R and K.A .Rai, Cyclodextrins in delivery systems: Applications. *Journal of Pharmacy & Bioallied Science*, vol.2, no.2, pp.72–79, 2010.
- [8] Szejtli J, Szente L. Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins. *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 61, pp. 115–125, 2005.
- [9] H.M. Patel, B.N. Suhagia, S.A. Shah, I.S. Rathod and V.K. Parmar, "Preparation and characterization of Etoricoxib- $\beta$ -cyclodextrin complexes prepared by the kneading method," *Acta Pharmaceutica*, vol.57, pp.351-359, 2007.
- [10] S.K. Yellanki, S. Jagtap and R. Masareddy, "Disso film: A novel approach for delivery of Phenobarbital; design and characterization," *Journal of Young Pharmacist*, vol.3, no.3, pp. 181-188, 2011.
- [11] P. Joshi, H. Patel, V.Patel and R. Panchal, "Formulation development and evaluation of mouth dissolving film of domperidone," *Journal of Pharmacy & Bioallied Science*, vol.4,



no.1, pp. S108–S109, 2012.

- [12] E.M. Janben, R. Schliephacke, A. Breitenbach and J. Breitreutz, “Drug-printing by flexographic printing technology-A new manufacturing process for orodispersible films,” *International Journal of Pharmaceutics*, vol. 441, pp. 818-825, 2013.
- [13] N.A. Nafee, N.A. Boraie, F.A. Ismail and L.M. Mortada, “Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride,” *Acta Pharmaceutica*, vol.53, pp. 199–212, 2003.
- [14] M.J. Akhtar, M. Jacquo, M. Jamshidian, M. Imran, E. Arab-Tehrany and S. Desobry, “Fabrication and physicochemical characterization of HPMC films with commercial plant extract: Influence of light and film composition,” *Food Hydrocolloids*, vol.31, pp. 420-427, 2013.
- [15] Y. Pranoto, C.M. Lee and H.J. Park, “Characterizations of fish gelatin films added with gellan and k-carrageenan,” *LWT-Food Science and Technology*, vol.40, pp.766-774, 2007.
- [16] L. Sievens-Figueroa, A. Bhakay, J.I. Jerez-Rozo et al., “Preparation and Characterization of hydroxypropyl methyl cellulose films containing stable BCS Class II drug nanoparticles for pharmaceutical applications” *International Journal of Pharmaceutics*, vol. 423, pp. 496- 508, 2012.
- [17] A.Q. Jun Low, J. Parmentier, Y.M. Khong et al., “Effect of type and ratio of solubilising polymer on characteristics of hot-melt extruded orodispersible films,” *International Journal of Pharmaceutics*, vol. 455, pp.138–147, 2013.
- [18] H.F. Brinson and L.C. Brinson, “Polymer Engineering Science and Viscoelasticity: An Introduction, In: Stress and Strain Analysis and Measurement,” New York: Springer Science + Business Media, LLC; pp.15-54, 2008.
- [19] M. Haque, S. Nasrin, M.M. Monir, M.M. Rahman and S. Chowdhury, “Method development and validation of RP-HPLC method of Etoricoxib in bulk and its tablet dosage forms,” *American journal of PharmTech Research*, Vol.2,no.6, pp.275-283, 2012.

- [20] S. Topalli, T.G. Chandrasekhar and M.M. Annapurna, "Validated RP- HPLC Method for the Assay of Etoricoxib (A Non-Steroidal Anti-Inflammatory Drug) in Pharmaceutical Dosage Forms," *CODEN ECJHAO, E-Journal of Chemistry*, vol.9, no.2, pp. 832-838, 2012.
- [21] S. Venkata Ramana Reddy , S. Dondeti, R. Manavalan and J. Sreekanth, "Palatability Evaluation Study of Oral Disintegrating Tablets by Human Volunteers," *International Journal of Pharma Sciences and Research*, vol.1, no.8, pp. 326-346, 2010.
- [22] M. Goyal, M. Ghosh, B.P. Nagor, D. Sasmal. "Analgesic and anti-inflammatory studies of cyclopeptide alkaloid fraction of leaves of *Zizyphus nummularia*," *Saudi Journal of Biological Sciences*, vol.20, no.4, pp.365–371, 2013.
- [23] S. K. Kulkarni, Hand Book of Experimental Pharmacology.3rd ed. Vallabh Prakashan. New Delhi, pp.123-124, 2009.
- [24] D.Mishra, G.Ghosh, P.S. Kumar and P.K.Panda, "An experimental study of analgesic activity of selective cox-2 inhibitor with conventional NSAIDs", *Asian Journal of Pharmaceutical and Clinical Research*, vol.4, pp.78 -81, 2011.
- [25] S.Y. Lin, C.H. Hsua and M.T. Sheub, "Curve-fitting FTIR studies of Loratidine / hydroxypropyl- $\beta$ -cyclodextrin inclusion complex induced by co-grinding process," *Journal of Pharmaceutical and Biomedical Analysis*, vol.53, pp.799-803, 2010.
- [26] FDA Guidance for Industry, Orally Disintegrating Tablets, 2008.
- [27] K.Shimpi, K.Mahadik, A.Takada, and A. Paradkar, "Application of Polyglycolized Glycerides in Protection of Amorphous Form of Etoricoxib during Compression," *Chemical & Pharmaceutical bulletin*, vol.55, no.10, pp.1448-1451, 2007.
- [28] A.H. Al-Marzouqi, H.M. Elwy, I .Shehadi and A. Adem, "Physicochemical properties of antifungal drug-cyclodextrin complexes prepared by supercritical carbon dioxide and by conventional technique," *Journal of Pharmaceutical and Biomedical Analysis*, vol.49, pp. 227–233, 2009.
- [29] Z. Aigner, O. Berkesi, G .Farkas and P .Szabo-Revesz, "DSC,X-ray and FTIR studies of a gemfibrozil/dimethyl-  $\beta$ -cyclodextrin inclusion complex produced by co-grinding," *Journal of Pharmaceutical and Biomedical Analysis*, vol.57, pp. 62-67, 2012.