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Formulation and development of Oral Fast Dissolving Tablet Using etoricoxib

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Abstract

The basic objective of this study was to prepare oral fast dissolving tablet to achieve better patient compliance. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in such cases tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of action. Absorption of the drug is increased and first pass metabolism is reduced. The lowest disintegration time and high drug release was shown by KM3 formulation and selected as optimized formulation. From present study it can be concluded that bitter taste of Etoricoxib can be successfully masked with aspartame and solubility of Etoricoxib is increased using urea as hydrophilic carrier by kneading method. Well palatable and patient compliant Fast Dissolving Tablet can successfully prepared using Kneading method. The prepared optimized tablet showed quick disintegration as well as rapid dissolution as compared to marketed tablet. Thus, the Rapid Disintegrating Tablet of bitter drug having bitter taste and pleasant mouth feel can be successfully formulated.

Keywords- *Fast dissolving tablet, mouth-dissolving tablets, Orodispersible tablets, rapidmelts, porous tablets, quick dissolving, etoricoxib.*

INTRODUCTION

Many patients express difficulty in swallowing tablets and hard gelatine capsules, tending to non-compliance and ineffective therapy.[1] Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is orodispersible tablet.[1-4] Present review article focuses on recent trends of formulation and significance of Mouth Dissolving Dosage Forms and the technologies available for their manufacturing. Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. One important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in these wallowing of oral dosage forms. In absence of water there is inconvenience in swallowing conventional dosage forms such as tablet. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapidmelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva[6]. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some

drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics.[7] Their growing importance was underlined recently when European pharmacopoeia adopted the term " Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.[8] According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach in development of FDT is the use of superdisintegrant like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, thereby release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing fastdissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugarbased excipients, tablet compression, and disintegration addition .As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities. As per european pharmacopoeia, "Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed."[8]

MATERIALS AND METHODS

Materials

Etoricoxib was obtained from Cadila Healthcare Limited, Ahmedabad, India. Urea was purchased from Loba. Cheme. Pvt. Ltd, Akola. Cross Carmellose Sodium was obtained from Leben Laboratories Pvt. Ltd, Akola, India. Avicel PH 102 was obtained from Nicholas Piramal Health care Pvt. Ltd, Ahmedabad, India.

All other chemicals used in the study were of analytical grade.

Methods

Experimental:

1. CHARACTERIZATION OF ETORICOXIB

The drug was characterized according to following method.

1.1 Description

Nature: Amorphous

Color: White to off white powder

Melting point: 134-135°C

1.2 Solubility

Insoluble in water, sparingly soluble in ethanol.

1.3 Identification

1.3.1 By Ultraviolet absorption spectroscopy

The solution containing 10µg /ml of Etoricoxib in aqueous acid was scanned between 300 to 200nm.

Scanning of Etoricoxib in 0.1N Hydrochloric acid

The solution containing 10µg/ml of Etoricoxib in 0.1N hydrochloric acid was prepared and scanned over range of 200 to 300 nm against 0.1N hydrochloric acid as a blank using Shimadzu double beam UV spectrophotometer. The plot of absorbance against wavelength.

1.3.2 Reported FTIR spectrum of Etoricoxib

Etoricoxib was analyzed by Fourier Transform Infrared Spectroscopy (FTIR) using KBr disk method in the range of 4000-500 cm-1.

1.3.3 Characterization of powder blends of active pharmaceutical ingredient & excipients

The following preformulation studies were performed on the obtained sample of drug.

1. Bulk Density (Db)

Bulk density was determined by Weight of powder / Volume of powder before tapping.

2. Tapped Density (Dt)

Tapped density was determine by Weight of powder / Volume of powder after tapping

3. Angle of Repose (θ)

The friction forces in a loose powder can be measured by the angle of repose (θ).

$\tan(\theta) = h / r$

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

Where, θ is the angle of repose.

h is the height in cms

r is the radius in cms.

4. Carr's index (or) % compressibility

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt - Db}{Dt} * 100$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

5. Hausner ratio

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

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density and Db is the bulk density.

2. PREPARATION OF STANDARD CURVE IN 0.1 N HCL

100 mg etoricoxib was dissolved in 100ml of water. 10ml of the resulting solution was further diluted up to 100ml with 0.1 N HCL to make a stock solution of concentration 100µg/ml. Further serial dilutions were carried out with 0.1 N HCL to get drug concentration between 1 to 12µg/ml. The absorbances of the dilutions were measured against water as a blank at 234nm using Shimadzu double beam UV visible spectrophotometer. The plot of absorbance vs. concentration was plotted and was found to obey Beers Lambert's law in the range of 0 to 100 µg/ml. Data in this range was subjected to linear regression analysis. The plot for standard calibration curve of drug in 0.1N HCL.

3. DETERMINATION OF THRESHOLD CONCENTRATION OF THE DRUG THAT INDUCES BITTERNESS

This was carried out to determine threshold concentration of the drug that induces bitterness. 100mg of drug was dissolved in 100ml simulated salivary fluid to get the concentration of 1000 µg/ml. Further serial dilutions were

carried out to get drug concentration from 100 to 1000µg/ml. These solutions were tested *in vivo* to determine the minimum concentration that induces bitter taste.

4. DRUG-POLYMER INTERACTION STUDY

Pure Drug, urea,mixture of Drug+Urea were analyzed for interaction by Fourier Transform Infrared Spectroscopy (FTIR) using KBr disk method.

5. FORMULATIONS METHODS USED FOR FAST DISSOLVING TABLETS OF ETORICOXIB

5.1 Preparation of solid dispersion

The preparations of drug Etoricoxib-carrier Urea solid dispersion were prepared by physical mixture (PM), kneading (KN) and by fusion method (FM) techniques, in three molar rations (1;1, 1:2 and 1:3) which are described below in table;

Table 1:

Name of Method	Drug : Carrier Ratio	Solid Dispersion Code
Physical Mixture	1:1	PM1
	1:2	PM2
	1:3	PM3
Kneading Method	1:1	KM1
	1:2	KM2
	1:3	KM3
Fusion Method	1:1	FM1
	1:2	FM2
	1:3	FM3

Physical Mixture

Accurately weighed quantity of carrier was placed into a mortar. Then weighed quantity of drug was introduced slowly and triturate for 30 min. The ratio of drug and carrier in the ratio of 1:1.,1:3 and 1:5 were prepared by the modified technique.

Kneading Method

Accurately weighed quantity of carrier was placed into a mortar moistened with water and kneaded to the paste consistency. Then weighed quantity of drug was introduced slowly and kneaded for 30 min. During this process appropriate quantity of water was added to maintain suitable consistency. Finally the obtained paste was dried in an oven at 40 °C until the water was removed completely and stored in desiccators over fused calcium chloride.

Fusion Method

The accurately weighed amount of carrier urea was melted in a porcelain dish at 80-85oC in melted polymer . Calculated amount of Etoricoxib was added with thorough mixing for 1-2 minutes followed by quick cooling .The ratio of drug and carrier in the ratio of 1:1.,1:3 and 1:5 were prepared by the modified technique.

Table 2: Formulation Table

Ingredients(mg)	Formulation Code								
	PM1	PM2	PM3	KM1	KM2	KM3	KM1	KM2	KM3
Etoricoxib (equivalent to 60 mg)	120	180	240	120	180	240	120	180	240
Avicel PH 102	31	10.5	13	31	10.5	13	31	10.5	13
Mannitol	20	20	20	20	20	20	20	20	20
CCS (9%)	18	27	31.5	18	27	31.5	18	27	31.5
Aspartame	5	5	5	5	5	5	5	5	5
Aerosil(1%)	2	2.5	3.5	2	2.5	3.5	2	2.5	3.5
Mag. Stearate(1%)	2	2.5	3.5	2	2.5	3.5	2	2.5	3.5
Talc (1%)	2	2.5	3.5	2	2.5	3.5	2	2.5	3.5
Total Weight	200	250	320	200	250	320	200	250	320

6. EVALUATION OF TABLETS

Rapid dissolving tablets were evaluated for following parameters.

6.1 Drug Content

Ten tablets were taken and triturated in a glass mortar. The powdered tablet equivalent to 60 mg of drug was dissolved in a 900ml of 0.1 N HCL and the drug content was determined spectrophotometrically at 234 nm.

6.2 Hardness

Tablets require a certain amount strength or hardness and resistance to friability to withstand mechanical shock of handling in manufacturing, packaging and shipping. Hardness was measured using Monsanto hardness tester.

6.3 Friability

Friability was evaluated as the weight loss of tablets, tumbled in a friabilator (Roche) Dolphine, Pvt. Ltd., Mumbai) for 4 min at 25 rpm. The tablets then were dedusted, and the loss in weight caused by fracture or abrasion was recorded as percentage friability. The percentage friability was measured using the formula,

$$\%F = \{(W-Wo)/Wo\} *100$$

Where, % F = friability in percentage, Wo = initial weight of tablet, W = weight of tablet after test

6.4 Weight variation

For weight variation, 20 tablets were weighed individually. Average weight was calculated and individual tablet weights were compared to the average. All the tablets were found to pass the weight variation test.

6.5 Wetting time and Water absorption ratio

A piece of tissue paper folded twice was kept in a culture dish (i.d. 5.5 cm) containing about 6ml of purified water. A tablet having small amount of amaranth powder on the upper surface was placed on the tissue paper. Time required to develop red color on the upper surface of the tablet was recorded as a wetting time.The same procedure was repeated for determining water absorption ratio without using amaranth. The wetted tablet was then weighed and water absorption ratio, R, was determined according to following equation:

$$R= \{(Wa-Wb)/ Wb\}* 100$$

Where,

Wb = weight of tablet before study , Wa = weight of tablet after study.

7. TASTE EVALUATION OF TABLETS

7.1 *In-vitro* taste evaluation of tablets

Any substance, which is soluble in saliva will interact with taste buds, and can impart its taste. Therefore dissolution study of tablets was conducted in Phosphate buffer pH 6.8 for approximate estimation of release in human saliva before doing actual volunteer study. Tablet containing 60 mg of Etoricoxib was taken in a 25ml volumetric flask. To this, 10ml of Phosphate buffer pH 6.8 was added and was shaken for 60 seconds on mechanical shaker. The amount of drug released was analyzed spectrophotometrically at 234 nm.

7.2 In- vivo taste evaluation of tablets

Taste masking was evaluated using the stages and using time intensity method. For this study a panel of eleven healthy human volunteers was chosen, from whom informed consent was first obtained. The tablet containing 60 mg of Etoricoxib was held in the mouth for 10 sec. Bitterness was recorded immediately according to the bitterness intensity scale from 0 to 3, 3 being strongest, 2 being moderate, 1 being slight, 0.5 being threshold and 0 for no bitter taste. The readings were taken immediately and at several intervals over the period of 15 min. After study the mouth was rinsed well with water and waited for 1 hour before administering the next sample.

8. DISINTEGRATION TIME

For rapid dissolving tablets, drug formulation was intended to disperse rapidly (less than 1 min) in oral cavity, so that dose swallow easily. Hence the assessment of the disintegration profile of rapidly disintegrating tablet (RDT) was very important in the evaluation and the development of new formulation.

8.1 *In Vitro* Disintegration Study

Description of the Apparatus

The disintegration test apparatus used in the study .The apparatus consist of a glass beaker of capacity 1000 mL. This beaker was placed on magnetic stirrer (E) provided with a thermostat. The wire basket (B) has been positioned in a beaker with the help of support (D). It was positioned in an assembly in such a way that when beaker contains 900 mL of disintegrating medium, the basket will have only 6 mL of this medium. The assembly is provided with magnetic bead (C) which is rotating with speed 25 rpm.

Test Method

The disintegration test for Rapid Disintegrating Tablet was performed by using modified disintegration apparatus as shown in figure no.1. In this modified disintegration apparatus, first 900 ml of simulated salivary fluid was taken in a beaker. Basket was positioned in a beaker. The beaker was placed at 25 rpm and 37.5˚c. temperature. Then the tablet was dropped in the basket and the time required for complete disintegration of tablet was recorded using a stopwatch

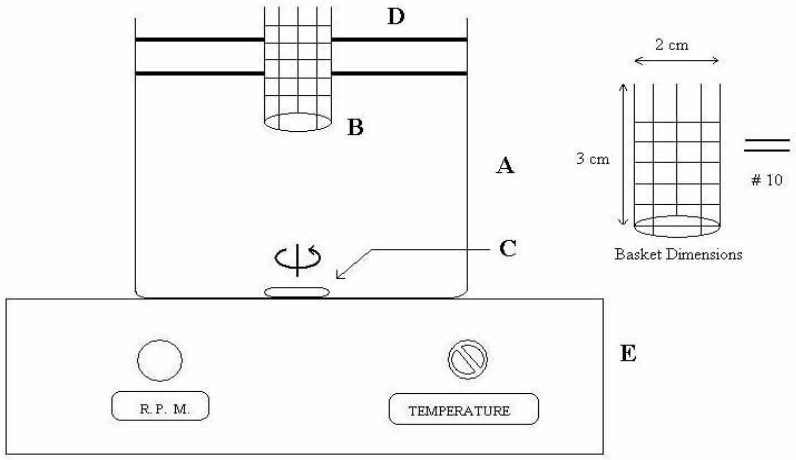

Fig. 1: Schematic representation of disintegration test apparatus

9. DISSOLUTION STUDY OF TABLETS

In vitro dissolution studies for rapid disintegrating tablets of different batches and marketed tablet were carried out in 900 ml 0.1 N HCL using USP type II (paddle) apparatus at 50 rpm and 37± 0.5°C temperature. Dissolution study of marketed tablet of Etoricoxib was done in a same way as that of the formulated tablet

10. STABILITY STUDIES OF TABLET FORMULATIONS75

The tablets were studied for stability at 40°C and 75% RH conditions for the period of three months. Each tablet was individually weighed and wrapped in an aluminium foil and packed in black PVC bottle and put at above specified conditioned in a heating humidity chamber for 3 months. After each month tablet samples were analyzed for the weight gain, drug content, disintegration time and in vitro drug release study

RESULT AND DISCUSSION

1. Analysis of Etoricoxib

1.1 Description

Nature : amorphous

Color : white to off white powder

Melting point : 134-135°C

1.2 Solubility

Insoluble in water, sparingly soluble in ethanol.

1.3 Identification by Ultraviolet absorption spectroscopy

Scanning of Etoricoxib in 0.1N Hydrochloric acid

The solution containing 10µg/ml of Etoricoxib in 0.1N hydrochloric acid was prepared and scanned over range of 200 to 300 nm against 0.1N hydrochloric acid as a blank using Shimadzu double beam UV spectrophotometer. The λmax was found to be 234 nm, which confirms to the reported value. The plot of absorbance against wavelength is shown in figure 2.

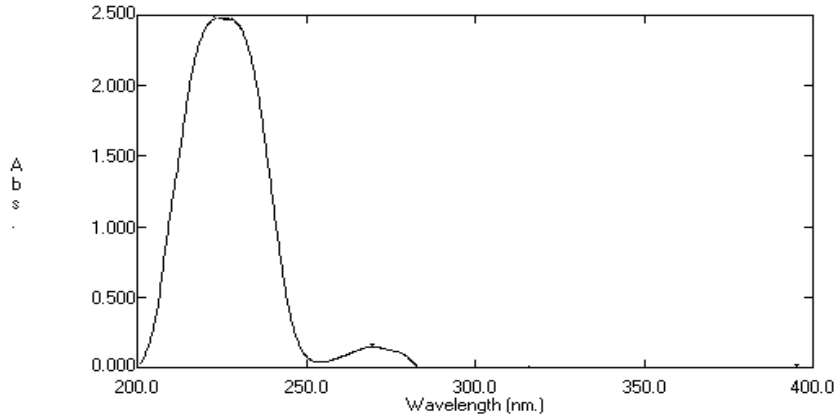

Fig. 2: **Scanning of Etoricoxib in 0.1 N hydrochloric acid**

FTIR spectrum of Etoricoxib

Etoricoxib was analyzed by Fourier Transform Infrared Spectroscopy (FTIR) using KBr disk method in the range of 4000-500 cm-1.

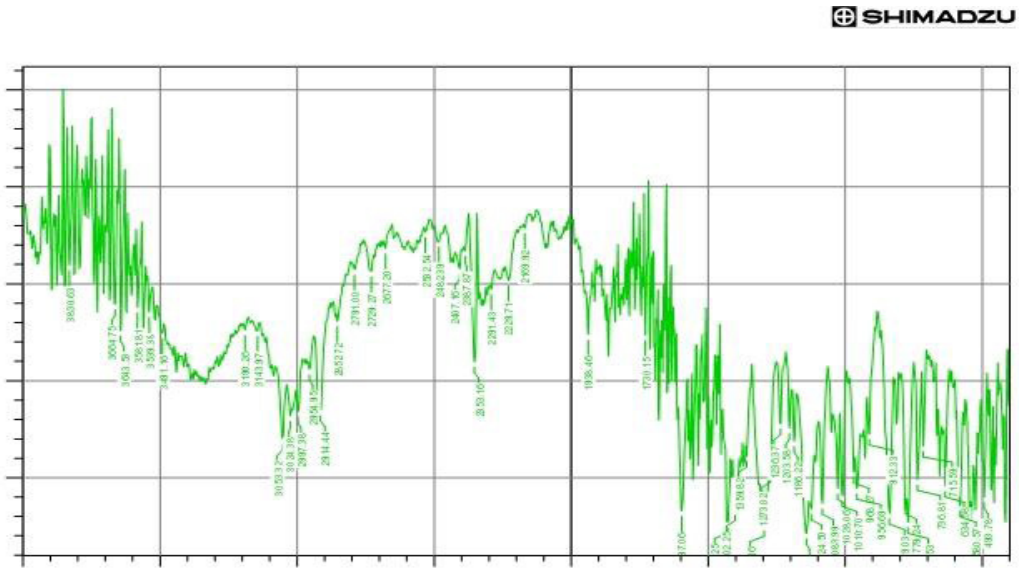

Fig. 3: FTIR spectrum of Etoricoxib

On the basis of Identification by UV spectroscopy, FTIR, organoleptic properties & other tests, it was concluded that the sample of Etoricoxib was pure. On the basis of characterization of the drug, it was concluded that the received drug sample from Cadila Healthcare limited, India. complies with the compendia specifications for identifications and other tests and was suitable for preparation of FDT.

2. EXCIPIENT COMPATIBILITY STUDY

The possible interaction between the drug and the urea was studied by FT-IR Spectroscopy.

FT-IR Spectroscopy

The possible interaction between the drug and the urea was studied by FT-IR spectroscopy. The FTIR spectra of pure Etoricoxib, urea and Etoricoxib with urea are as follows.

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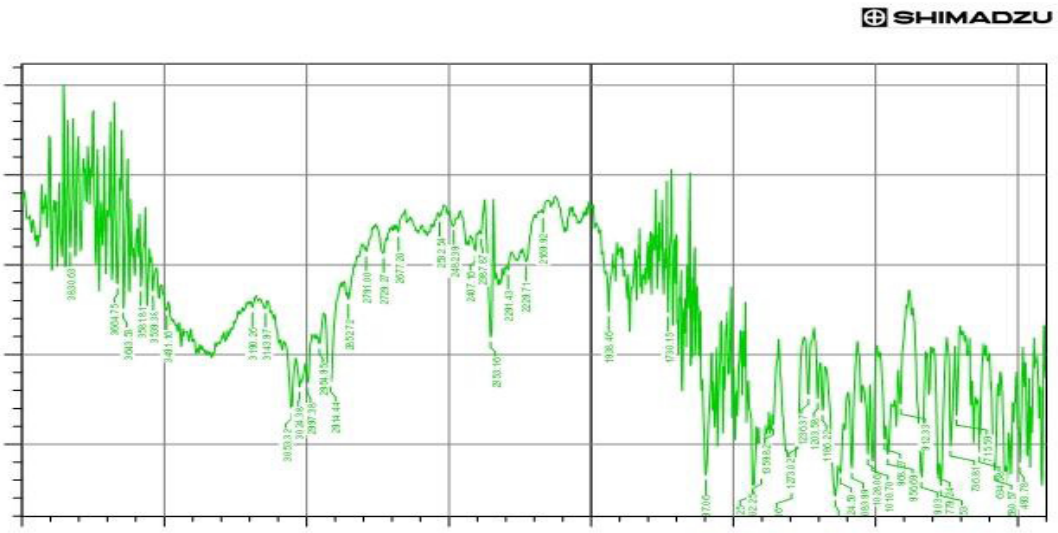


Fig. 4 : FTIR Spectrum of Etoricoxib

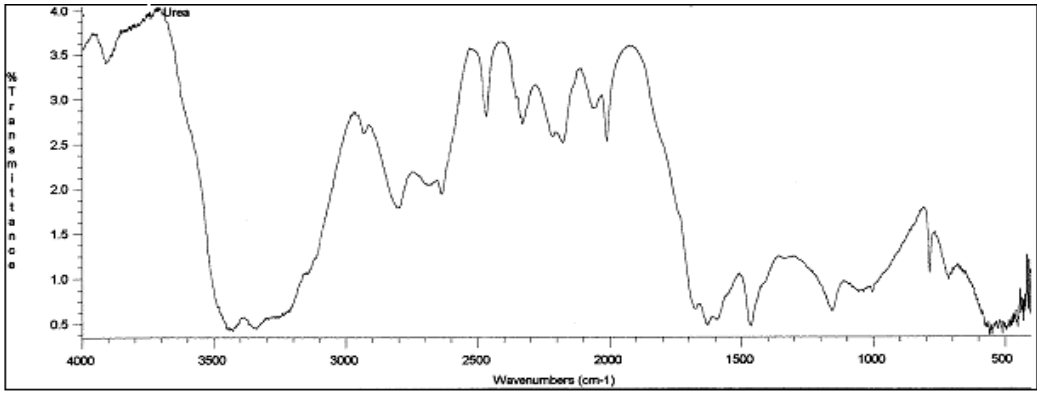


Fig. 5: FTIR spectum of Urea

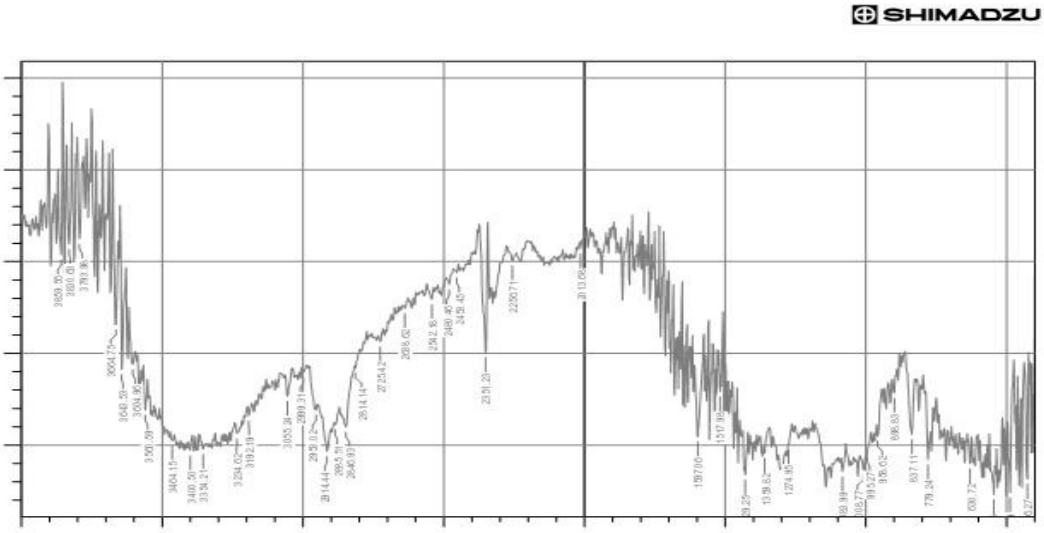


Fig. 6: FTIR Spectrum of Etoricoxib +Urea

The result shows that there is no incompatibility was seen in between the drug Etoricoxib and excipients used, as there is no significant change in the pattern of peaks of pure drug and physical mixture drug and excipients.

3. CONSTRUCTION OF CALIBRATION CURVE OF ETORICOXIB

Table 3: Absorbance of Etoricoxib Solutions of Different Concentrations in 0.1N HCL

Sr. No.	Concentration (µg/ml)	Absorbance at 234nm	S.D.
1	0	0	0
2	2	0.151	0.01
3	4	0.319	0.016
4	6	0.489	0.009
5	8	0.656	0.011
6	10	0.82	0.019
7	12	0.996	0.003

Each value represents mean (n=3) ± S.D.

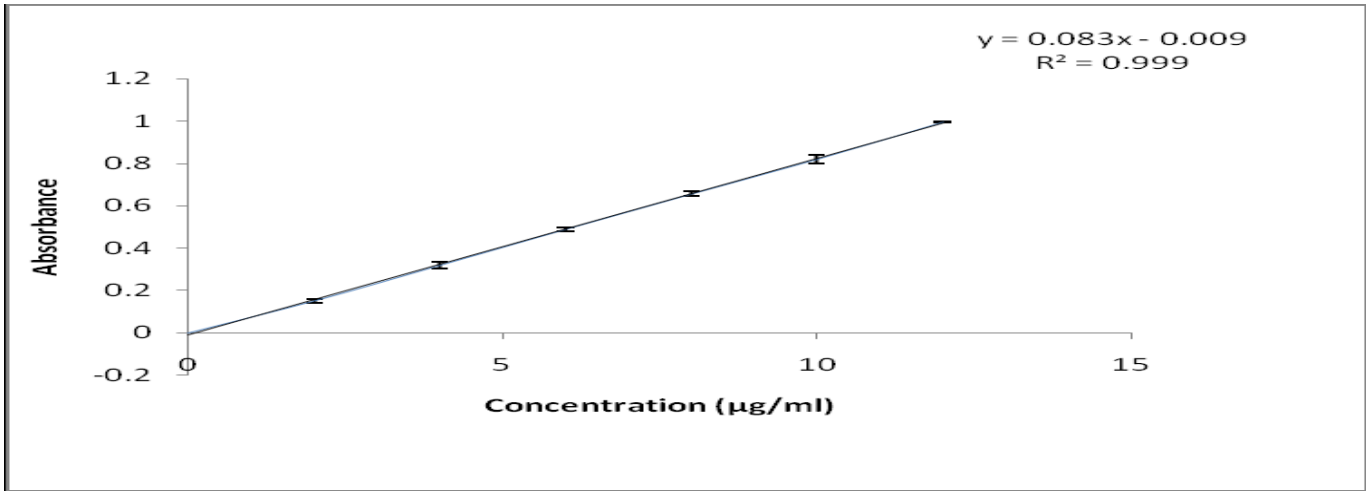


Fig. No. 7 Standard Curve for Etoricoxib

Correlation coefficient (R) = 0.999

Equation of regressed line; Y = 0.083X-0.009

Where,

X = value for concentration

Y = regressed value of absorbance

0.009 = slope of regressed line

4. CHARACTERIZATION OF POWDER BLENDS OF ACTIVE PHARMACEUTICAL INGREDIENT & EXCIPIENTS

Table 4: Preformulation Evaluation Parameters

Batch	Evaluation Parameters					
	Angle of Repose	**Bulk Density (g/cm3**	**Tapped Density (g/cm3)**	**Compressibility index (%)**	**Hausner's Ratio**	**Flowability**
PM1	**25.12+** (1.02)	**0.571+** (0.014)	**0.669+** (0.009)	**14.64±** (0.09)	**1.17±** (0.01)	Excellent
PM2	**26.35+** (1.0)	**0.586+** (0.009)	**0.684+** (0.008)	**14.32±** (0.1)	**1.16±** (0.01)	Excellent
PM3	**27.84+** (0.95)	**0.588+** (0.014)	**0.688+** (0.009)	**14.53±** (0.1)	**1.18±** (0.01)	Excellent
KM1	**24.21+** (0.98)	**0.579+** (0.019)	**0.674+** (0.01)	**14.09±** (0.1)	**1.16±** (0.01)	Excellent
KM2	**25.12+** (1.1)	**0.571+** (0.014)	**0.669±** (0.011)	**14.64±** (0.1)	**1.17±** (0.01)	Excellent
KM3	**26.45+** (1.05)	**0.582+** (0.015)	**0.682±** (0.015)	**14.3±** (0.1)	**1.16±** (0.009)	Excellent
FM1	**27.84+** (1.02)	**0.588+** (0.018)	**0.688±** (0.014)	**14.53±** (0.1)	**14.53±** (0.1)	Excellent
FM2	**26.35+** (0.96)	**0.586+** (0.019)	**0.684±** (0.01)	**14.32±** (0.1)	**1.16±** (0.012)	Excellent
FM3	**26.45+** (1.04)	**0.582+** (0.015)	**0.682±** (0.01)	**14.3±** (0.1)	**1.16±** (0.015)	Excellent

The angles of repose values given in table 7 for all the blends are 25-30 after the calculation. Thus all the blends were having excellent flow properties. The values of compressibility index of formulation blends of selected batches given in the table 7 shows that all the values ranged between 5-15%. This implies fairly properties for these blends.

5. EVALUATION OF TABLET CHARACTERISTICS

Table 5: Tablet Evaluation parameters

Sr. No	Parameters / Batches	Drug content (%)	Hardness	Friability (%)	Thickness (cm)	Diameter (cm)	Wetting time (sec)	Water absorption ratio (%)
1	**PM1**	**97.63** ± (0.02)	**3.83**± (0.26)	**0.66**± (0.01)	**0.42**± (0.01)	**0.81**± (0.01)	**11**± (0.031)	**170.27**± (0.04)
2	**PM2**	**99.3**± (0.067)	**3.66**± (0.288)	**0.65**± (0.01)	**0.51**± (0.011)	**0.82**± (0.011)	**13.2**± (0.044)	**166.46**± (0.003)
3	**PM3**	**99.99** ± (0.006)	**3.66**± (0.288)	**0.61**± (0.01)	**0.52**± (0.012)	**0.82**± (0.01)	**12.4**± (0.031)	**165.74**± (0.03)
4	**KM1**	**100.69**± (0.076)	**3.83**± (0.26)	**0.54**± (0.01)	**0.54**± (0.01)	**0.81**± (0.01)	**14.21**± (0.053)	**166.17**± (0.1)
5	**KM2**	**99.3**± (0.056)	**3.66**± (0.288)	**0.56**± (0.005)	**0.52**± (0.01)	**0.81**± (0.01)	**15.32**± (0.062)	**167.06**± (0.005)
6	**KM3**	**101.38**± (0.066)	**3.66**± (0.288)	**0.56**± (0.01)	**0.52**± (0.011)	**0.81**± (0.009)	**17.3**± (0.058)	**157.32**± (0.04)
7	**FM1**	**98.61** ± (0.036)	**3.83**± (0.26)	**0.59**± (0.01)	**0.42**± (0.01)	**0.82**± (0.01)	**16.23**± (0.027)	**160.62**± (0.12)
8	**FM2**	**100.69**± (0.1)	**3.83**± (0.26)	**0.60**± (0.005)	**0.52**± (0.01)	**0.82**± (0.01)	**18.4**± (0.002)	**154.11**± (0.007)
9	**FM3**	**99.99** ± (0.4)	**3.83**± (0.26)	**0.60**± (0.005)	**0.51**± (0.013)	**0.81**± (0.01)	**17.2**± (0.01)	**163.06**± (0.033)

Each value represents mean (n=3) ± S.D.

All Fast Dissolving Tablets from batches PM1 to FM3 were evaluated for tablet properties like friability, weight variation, drug content. Tablets passed all the tests. Friability, Weight variation and Content uniformity of all formulations were within acceptable limits

Table 6: Comparative Study of Disintegration Time with Different Methods and weight variation for individual batches

Sr. No.	Batch	*In vitro* disintegration time(sec.)	Weight variation(mg) (n=3)
0	0	0	------
1	**PM1**	**14.5**± (1.02)	**197.63** ± (0.26)
2	**PM2**	**16**± (0.1)	**248.63** ± (0.21)
3	**PM3**	**12.73**± (1.88)	**319.63** ± (0.26)
4	**KM1**	**17.32**± (1.45)	**198.63** ± (0.45)
5	**KM2**	**16.42**± (1.22)	**249.73** ± (0.36)
6	**KM3**	**13.14**± (0.76)	**319.63** ± (0.26)
7	**FM1**	**14.5**± (1.02)	**199.63** ± (0.26)
8	**FM2**	**17**± (0.1)	**249.63** ± (0.26)
9	**FM3**	**17.73**± (1.88)	**319.63** ± (0.31)
10	**M**	**18.4**± (0.077)	-----

M-Marketed Tablet

Each value represents mean (n=3) ± S.D.

The results of drug content, hardness, and % Friability, thickness, diameter, wetting time, water absorption ratio are given in table. The hardness of all these batches was in the range of 3.5-4 Kg/cm2. Such hardness range is enough to give mechanical indicates good Compressibility of blends. The value of friability for all these formulations was less than the limits of 1.0% which is given in the U.S.P. The friability found in these formulations shows a good strength of tablets to withstand abrasion during transportation and general handling.

6. TASTE EVALUATION OF TABLETS

Table 7: Release in Phosphate Buffer pH 6.8

SR NO.	BATCH	% RELEASE OF DRUG
1	**PM1**	**22.1**± (0.002)
2	**PM2**	**23.2**±. (011)
3	**PM3**	**23.6**± (0.02)
4	**KM1**	**25.1**± (0.1)
5	**KM2**	**23.2**± (0.003)
6	**KM3**	**19.3**± (0.02)
7	**FM1**	**20.1**± (0.01)
8	**FM2**	**24.3**± (0.03)
9	**FM3**	**23.6**± (0.1)

Each value represents mean (n=3) ± S.D.

Table 8: *In Vivo* Taste Evaluation of Tablets

Etoricoxib Tablet		Degree of bitterness after time					
		10 sec	1 min	2 min	5 min	10 min	15 min
Pure drug		3	2	2	2	2.5	2.5
KM3	Optimize Batch	0	0.1	0.15	0.11	0	0

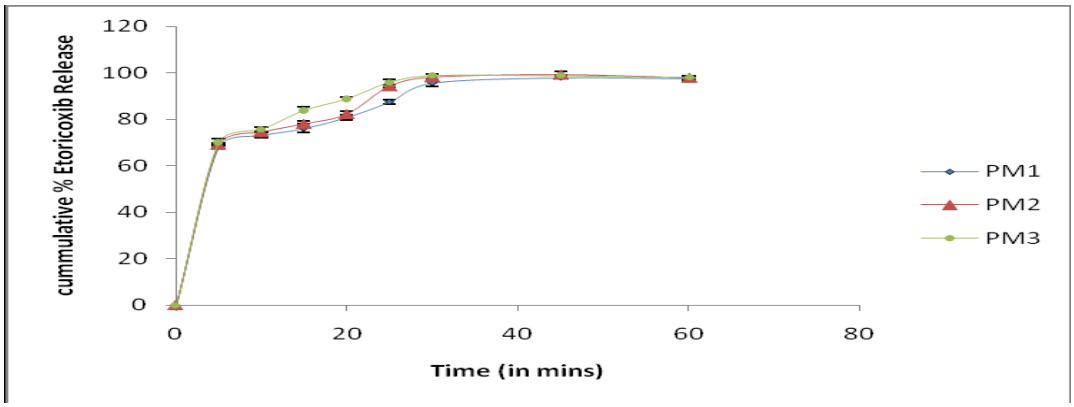
The bitterness intensity scale from 0 to 3,
3 being strongest,
2 being moderate, 1 being slight,
0.5 being threshold and
0 for no bitter taste

Any substance which is soluble in saliva will interact with taste buds, and can impart its taste. Therefore *in-vitro* taste evaluation study of the Fast Dissolving Tablet was done in the Phosphate Buffer PH 6.8 for approximate estimation of drug release in human saliva before doing actual volunteer study. This study shows that optimum batch KM3 having 1:3 (drug : Urea) ratio shows 19.3±0.02% of the drug release from the tablet in Phosphate Buffer PH6.8. The amount released was less than the amount that can induce bitterness.

7. *IN-VITRO* DISSOLUTION STUDIES

Table 9(a): Cumulative % Drug Released from Fast Disintegrating Tablet by Physical Mixture method at Different Time Interval

Sr. No.	Time (min)	Cumulative % drug released		
		PM1	PM2	PM3
1	0	0	0	0
2	5	**68.38±** (0.97)	**69.09±** (0.49)	**70.18±** (1.47)
3	10	**73.09±** (1.12)	**74.5±** (0.21)	**75.75±** (0.98)
4	15	**76.15±** (1.89)	**78.05±** (1.13)	**83.97±** (1.36)
5	20	**80.94±** (1.18)	**82.25±** (1.25)	**88.9±** (0.64)
6	25	**87.48±** (1.1)	**94.26±** (0.65)	**96.05±** (1.22)
7	30	**95.68±** (1.35)	**98.11±** (1.2)	**98.92±** (0.45)
8	45	**97.99±** (0.31)	**99.2±** (1.6)	**98.84±** (0.22)
9	60	**97.63±** (0.65)	**97.87±** (0.69)	**98.15±** (0.01)



Each value represents mean (n=3) ± S.D.

Fig. 8: Cumulative % Drug Released from Fast Disintegrating Tablet by Physical Mixture method

Table 9(b): Cumulative % Drug Released from Fast Disintegrating Tablet by Kneading method at Different Time Interval

Sr. No.	Time (min)	Cumulative % drug released		
		KM1	KM2	KM3
1	**0**	**0**	**0**	**0**
2	5	**69.59**± (0.41)	**69.76**± (0.52)	**75.5**± (0.54)
3	10	**75.25**± (0.47)	**75.37**± (0.53)	**80.05**± (0.31)
4	15	**79.04**± (0.89)	**79.46**± (0.31)	**89.76**± (0.94)
5	20	**85.95**± (0.15)	**89.15**± (0.93)	**99.96**± (0.51)
6	25	**94.91**± (0.62)	**96.79**±. (1.82)	**99.77**± (0.29)
7	30	**98.39**± (1.57)	**99.08**± (0.29)	**99.49**± (0.93)
8	45	**99.2**± (1.6)	**98.8**± (0.92)	**98.56**± (0.69)
9	60	**97.57**± (0.6)	**97.25**± (0.65)	**97.87**± (0.69)

Each value represents mean (n=3) ± S.D.

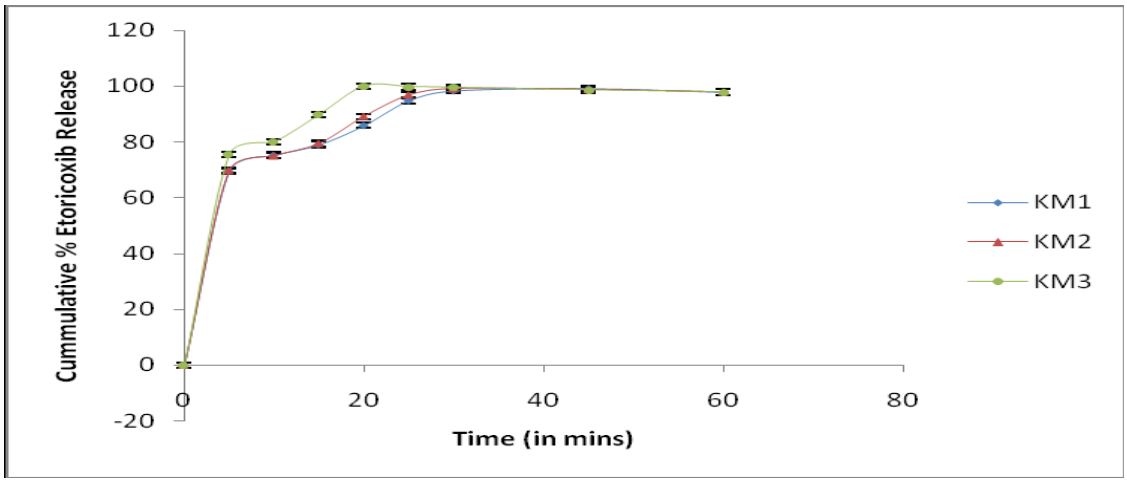


Fig. 9: Cumulative % Drug Released from Fast Disintegrating Tablet by Kneading method

Table 9(c): Cumulative % Drug Released from Fast Disintegrating Tablet by Fusion method at Different Time Interval

Sr. No.	Time (sec)	Cumulative % drug released		
		FM1	FM2	FM3
1	0	0	0	0
2	5	**66.91±** (1.72)	**69.26±** (1.28)	**70.18±** (1.47)
3	10	**71.83±** (1.24)	**75.37±** (0.46)	**75.42±** (0.91)
4	15	**74.37±** (1.65)	**79.92±** (0.71)	**85.21±** (1.09)
5	20	**81.39±** (1.85)	**90.38±** (1.22)	**89.07±** (0.46)
6	25	**88.06±** (1.3)	**97.56±** (1.09)	**96.05±** (1.22)
7	30	**95.68±** (1.35)	**99.08±** (0.29)	**98.92±** (0.45)
8	45	**97.99±** (0.31)	**98.8±** (0.92)	**98.84±** (0.22)
9	60	**97.63±** (0.65)	**97.87±** (0.69)	**98.15±** (0.01)

Each value represents mean (n=3) ± S.D

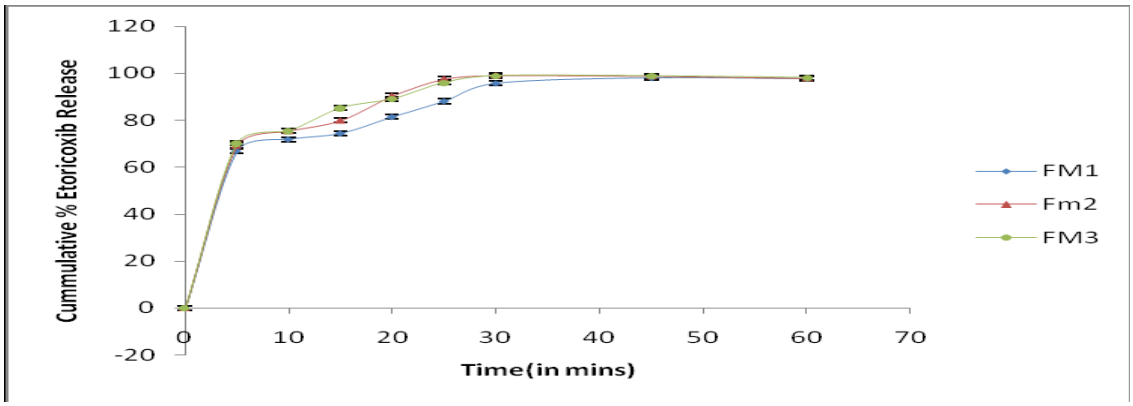


Fig. 10: Cumulative % Drug Released from Fast Disintegrating Tablet by Fusion method**.**

Table 10: Dissolution Profile of Marketed Etoricoxib Tablet

Time in min	Cumulative % release
0	0
5	**68.38** ± (0.97)
10	**76.88**± (0.084)
15	**83.68** ± (0.65)
20	**90.22** ± (1.38)
25	**99.34** ± (0.9)

Each value represents mean (n=3) ± S.D.

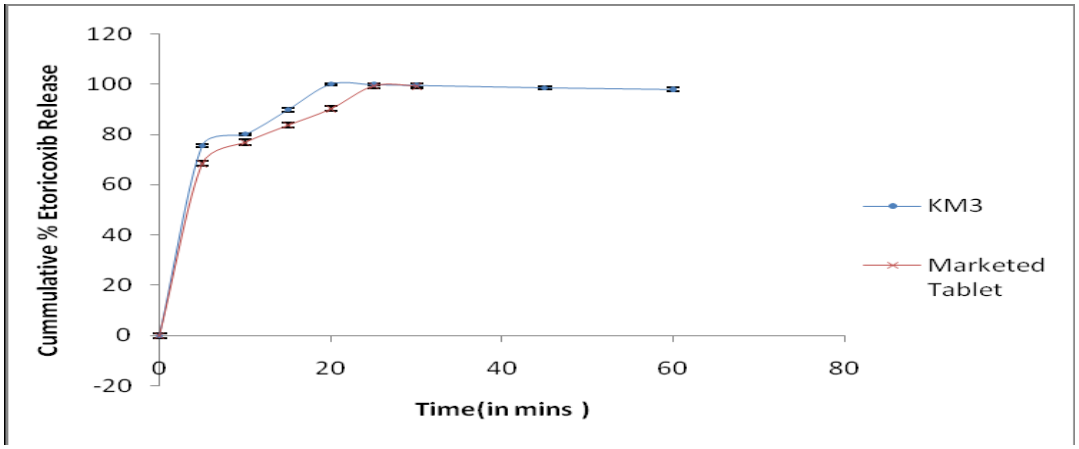


Fig 11: Dissolution profile of marketed Etoricoxib tablet

Physical mixture, Kneading, Fusion method were used for the preparation of Fast Dissolving Tablet it is well known fact that superdisintegrant and Hydrophilic Carrier i.e., Urea are the main constituents in the preparation of Fast Dissolving Tablet. Hence Urea was used in different ratios and superdisintegrant was used in fixed proportion. Mannitol was added in the sufficient quantity to maintains rapid disintegration. It offers and provides synergistic effect to improve hardness and disintegration. Wetting time for KM3 batch was 17.3±0.058 sec. and 13.14±0.76sec. respectively. Dissolution studies of the optimized tablet of batch KM3 reveled rapid release of drug (t90 for batch

KM3 is 15 mins.) as compared to marketed tablet wherein t90 around 20 mins. Disintegration time is a very crucial property of Fast Dissolving Tablet hence it is essential to determine exact disintegration time of Rapid Disintegration Tablet. In the present study disintegration time was evaluated by both methods.

1. In-vitro disintegration test *2.* In-vivo disintegration test.

The tablet having the sufficient hardness and the minimum disintegrating time the batch KM3 was selected as the optimized batches amongst all the 9 batches. These dosage forms include of water dispersible carrier material, which is impregnated with a unit dose of the pharmaceutical active agent. These formulations show significant difference in disintegration time as compared to marketed formulation. Hence these batches were selected as optimized batches. Sensory evaluation of optimized tablet proves better palatability. Also the tablet creates modern roughness in the mouth which get vanished within a short span without affecting compliance of the tablet.

Table 11: Similarity Factor

Time (mins)	Innovator	Test	Rt-Tt	(Rt-Tt)^2
5	68.38	75.5	7.12	50.6944
10	76.88	80.05	3.17	10.0489
15	83.68	89.76	6.08	36.9664
20	90.22	99.96	9.74	94.8676
25	99.34	99.77	0.43	0.1849
Σ	**418.5**	**445.04**	**26.54**	**192.7622**
Number of points		**8**		
F1	**6.34**			
F2	**65.01**			

Rt- Etoshine 60, Tt- KM3

Similarity analysis

Similarity factor were calculated from the *in-vitro* release profiles of both the formulation. The calculated value of KM3 was **65.01** (above 50) which clearly indicate indicated that the in-vitro release of KM3 were closely similar to that of marketed tablet release profiles.

Table 12: Parameters of Formulations at Time 0, 1, 2 and 3 Months of Stability Testing under 40°C and 75% RH.

Batch	Parameter	Months			
		0	1	2	3
KM3	**Weight gain (%)**	0	0.033	0.042	0.042
	Disintegration time(sec)	**13.73±** (1.88)	**13.70±** (1.03)	**13.75±** (1.06)	**13.75±** (1.01)
	Drug content (%)	**99.99±** (0.006)	**99.98±** (0.002)	**99.95±** (0.003)	**99.94±** (0.002)

Values shown in table are mean of three determinations.

Table 13: Stability Study of KM3 Tablet for Dissolution Pattern

Time (sec)	Cumulative % drug release			
	0 month	1 month	2 month	3 month
0	0	0	0	0
5	**75.5±** (0.54)	**74.2±** (0.052)	**74.3±** (0.32)	**74.2±** (0.25)
10	**80±** (0.31)	**80.4±** (0.22)	**79.5±** (0.42)	**79.6±** (0.35)
15	**89.76±** (0.94)	**89.2±** (0.012)	**89.4±** (0.14)	**89.2±** (0.1)
20	**99.96±** (0.51)	**99.9±** (0.1)	**99.5±** (0.1)	**99.5±** (0.1)
25	**99.77±** (0.29)	**99.7±** (0.02)	**99.7±** (0.1)	**99.6±** (0.1)
30	**99.49±** (0.93)	**99.49±** (0.9)	**99.49±** (0.9)	**99.5±** (0.1)

Values shown in table are mean of three determinations

Stability study was performed on optimized formulations KM3 results for weight gain, drug content, disintegration time and dissolution shows no appreciable change upto 3 months of accelerated stability studies.

Hydrophilic carriers were used to improve solubility of certain drugs having less solubility as BCS class II drugs. In this work, urea used in three different proportions i.e., 1:1,1:2,1:3. Drug compatibility study carried out by FTIR spectrophotometer. The results showed that drug and excipient were compatible. The powder blend was evaluated by determining bulk density, tapped density, compressibility index, hausner's ratio and Angle of repose. All values come within the specified limits and showed that it is suitable for direct compression . The evaluation tests like weight variation, hardness, friability, drug content, thickness, disintegration time, wetting time, water absorption ratio and *In- vitro* drug release studies were carried out. The lowest disintegration time and high drug release was shown by KM3 formulation and selected as optimized formulation.

CONCLUSION

From present study it can be concluded that bitter taste of Etoricoxib can be successfully masked with aspartame and solubility of Etoricoxib is increased using urea as hydrophilic carrier by kneading method. Well palatable and patient compliant Fast Dissolving Tablet can successfully prepared using Kneading method. The prepared optimized tablet showed rapid disintegration as well as rapid dissolution as compared to marketed tablet. Thus, the Rapid Disintegrating Tablet of bitter drug having better taste and pleasant mouth feel can be successfully formulated.

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