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Formulation and Evaluation of Etodolac Oral Disintegrating Tablets

Thalla Sushma, Arsham Priyadarshini, Shravan Kumar Yamsani*
Department of Pharmaceutics, Vaagdevi College of Pharmacy, Kakatiya University, Warangal-506009, Telangana, India.
*For Correspondence – shravanyamsani@gmail.com

Abstract

Etodolac is a nonsteroidal anti-inflammatory drug, which result in inhibition of the enzyme cyclooxygenase (COX). The aim of this study is to formulate and evaluate oral disintegrating tablets (ODTs) of etodolac to achieve rapid dissolution, absorption and further improving the bioavailability of the drug. The oral disintegrating tablets were prepared by using Croscarmellose sodium, Sodium starch glycolate and Crospovidone by direct compression method. Taste masking was done by flavouring agents. Drug-polymer complex was then formulated into orally disintegrating tablets by direct compression by using different concentrations of superdisintegrants. Tablets were evaluated for weight variation, thickness, hardness, friability, drug content, *in vitro* disintegration time, wetting time, water absorption ratio, and *in vitro* dissolution studies. Total nine formulations were prepared (i.e. F1 to F9), out of which tablets with F9 formulation containing 9% crospovidone showed faster disintegration within 15.05 seconds.

Keywords: Superdisintegrants, etodolac, anti-inflammatory, and flavouring agents.

Introduction

Among the available pharmaceutical dosage forms, tablets are the most widely used dosage form because of their convenience in terms of self-medication, ease of administration, accurate dosage, compactness, good stability and ease of manufacturing. The elderly people would experience deterioration of their physiological and physical abilities like dysphagia (difficulty in swallowing). Pediatric patients may suffer from ingestion problems of their underdeveloped muscular and nervous system (1). In order to overcome this problem, a new drug delivery system has been developed known as Orally Disintegrating Tablets (ODTs). Orally Disintegrating Tablets are solid dosage form containing medicinal substances which disintegrates/dissolves rapidly upon contact with saliva. When these tablets are placed in the oral cavity, saliva penetrates into the pores causing rapid disintegration. These tablets are beneficial for the patients suffering from nausea and vomiting, those with mental disorders, bedridden and those who do not have easy access to water.

The U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

Recently, European Pharmacopoeia used the term 'Orodispersible tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing.

Orally disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, orodispersible tablets, rapi-melts, porous tablets, and quick dissolving tablet (2).

Materials and methodology

Materials

Etodolac was received as a gift sample from IPCA Laboratories Ltd., Mumbai. Sodium starch glycolate was procured from LOBA Chemie

Laboratory Reagents and Fine Chemicals, Mumbai. Croscarmellose sodium and crospovidone were procured as gift samples from Ranbaxy Laboratories Limited, Gurugram, India. Mannitol was procured Finar Chemicals Limited, Ahmedabad, India. Talc and magnesium stearate were purchased from the S D Fine-Chem Ltd., Mumbai. All other chemicals were of analytical grades.

Preformulation studies

Drug-excipient compatibility studies

Fourier Transform-Infrared Spectroscopic Studies : A Fourier Transform–Infrared Spectrophotometer (FTIR) was used to study the non-thermal analysis of drug-excipient (the binary mixture of drug: excipient 1:1 ratio) compatibility. Pure drug of Etodolac and drug with a physical mixture of F9 formulation (excipients) compatibility studies were performed. The spectrum of each sample was recorded over 100-4000 cm^{-1}.

Final Powder Blend : The powder blend of all formulations was evaluated for Bulk density, Tapped density, Compressibility index, Hausner ratio and Angle of repose.

A) Bulk Density : A 30 g of material was passed through a sieve no.25 to break up agglomerates and introduced into a dry 100 ml cylinder, without compacting, the powder was carefully levelled without compacting and the unsettled apparent volume (Vo) was read. The bulk density was calculated, in grams per ml, using the formula:

$$\text{Bulk Density} = (M) / (V_O)$$

Where

M = Total weight of the powder blend; V_0 = Bulk volume of the powder blend

B) Tapped Density *:* After carrying out the procedure as given in the measurement of bulk density, the cylinder containing the sample was tapped using a mechanical tapped density tester (Electrolab) that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement was less than 2% and then tapped volume (V_f) was measured to the nearest graduated unit. The tapped density was calculated, in grams per ml, using the formula:

$$\text{Tapped Density} = (M) / (V_f)$$

Where

M = Total weight of the powder blend; V_f = Tapped volume of the powder blend

C) Measures of Powder Compressibility : The Compressibility Index and the Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio, which are calculated using the following formula:

$$\text{Compressibility Index} = (Vr-Vo) * 100 / Vr$$

Where

Vr = Tapped density; Vo = Bulk density

D) Hausner Ratio : It is the ratio of bulk density to tapped density.

$$\text{Hausner Ratio} = Vo/Vr$$

Where

Vo = Bulk density; Vr = Tapped density

E) Angle of Repose : The fixed funnel method was employed to measure the repose angle. A funnel was secured with its tip at a given height (h) above a graph paper that was placed on a flat horizontal surface. The blend was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

$$\text{Angle of Repose } (\theta) = \tan^{-}1(h/r)$$

Where

h = height of pile; r = radius of the base of the pile; θ = angle of repose

Analytical method used in the determination of etodolac

Preparation of standard curve for etodolac : A standard stock solution of pure drug containing 100 mg of Etodolac/100 ml was prepared using 6.8 pH phosphate buffer. The working standards were obtained by dilution of the stock solution. The standard curves for Etodolac were prepared in a concentration range of 2-12 µg/ml at the selected wavelength of 225 nm. Their absorptivity values were used to determine the linearity. The solution was scanned and Beer-Lambert Law limit was obeyed in the concentration range of 2, 4, 6, 8, 10 and 12 µg/ml (figure 1).

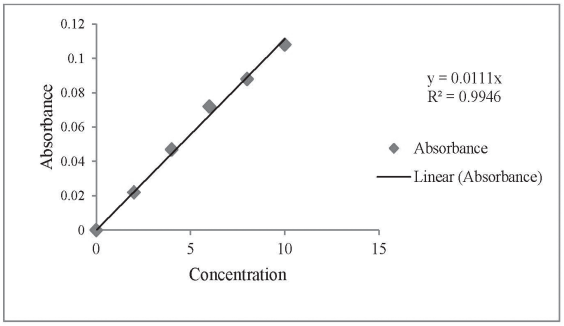

Fig. 1. Calibration curve of Etodolac

Formulation Design : Etodolac ODTs were prepared using direct compression technique. Different formulations of ODTs were designed to be prepared by direct compression technique using three super disintegrating agents (Crospovidone, Croscarmellose sodium and Sodium starch glycolate). Super disintegrating agents are varied with three different concentrations of 3, 6 and 9% respectively. Keeping all other ingredients constant, they are assigned with formulation codes in table 1.

Preparation Method : All the required ingredients were passed through sieve no. 40 to get uniform size particles and weighed accurately. The whole amount of Etodolac drug, sodium starch glycolate or croscarmellose or crospovidone, talc and flavour except lubricant were mixed in the increasing order of their weights in a mortar. To this mixture, talc and magnesium stearate were added. The final mixture was shaken manually for 5-10 minutes in a plastic bag. This powder was passed through the hopper of 16 station rotary tableting machine and punched into tablets using 9 mm s/c. The process is similar for all the formulations, which are prepared by direct compression technique.

Different quality control tests were performed for all the ODT formulations to check whether they have met the specifications given in USP along with other *in vitro* tests like wetting time and water absorption ratio.

Evaluation Parameters

- Weight variation test
- Thickness measurement
- Hardness and Friability
- Drug content uniformity
- Disintegration time
- Wetting time and Water absorption ratio
- *In vitro* dispersion time
- Dissolution test

Weight variation test : Twenty tablets were randomly selected from each formulation and their average weight was calculated by using an Electronic Balance (Shimadzu, AUX 220, Shimadzu Corp, Japan). Individual weight of each tablet was also calculated using the same and compared with the average weight. The mean ± S.D. was noted.

Thickness measurement : Randomly ten tablets were taken from each formulation and their thickness was measured using a Digital Vernier Caliper (Mitutoyo Corp, Kawasaki, Japan). Average thickness and standard deviation values were calculated. The tablet thickness should be controlled within a ± 5% variation of standard value.

Hardness : The tablet hardness of different formulations was measured using the Monsanto Hardness Tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures.

As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded and the zero force reading is deducted from it. Generally, a minimum hardness of 4 kg is considered acceptable for uncoated tablets. The hardness for ODTs should be preferably 1-3 kg.

Friability : This test is performed using a laboratory friability tester known as Roche Friabilator. Ten tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm (rotations per minute) dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were de-dusted and reweighed. Percentage loss of tablet weight was calculated:

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where

W_1 = Initial weight of the 10 tablets; W_2 = Final weight of the 10 tablets.

Drug content uniformity : Ten tablets were randomly selected, weighed and finely powdered and quantity of powder equivalent to one tablet was added to 100 ml of 6.8 pH phosphate buffer in a conical flask. Conical flasks were placed on a rotary shaker. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22 µ filter. The absorbance of the resulted supernatant solution was measured using UV-Visible Spectrophotometer at a wavelength of 225 nm against 6.8 pH phosphate buffer as blank. Concentrations were calculated with the help of standard graph and the total amount present in the formulation was calculated.

Disintegration time : Disintegration time is considered to be one of the important criteria in selecting the best formulation. *In vitro* disintegration time for ODTs was determined by using USP disintegration apparatus (Electrolab ED-2L, India) with 6.8 pH phosphate buffer as the disintegration medium. The medium was maintained at 37±0.5ºC. The time point at which tablet completely disintegrates is noted as disintegration time.

Wetting time : A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A water-soluble dye phenolphthalein was added to the petri dish. The dye solution is used to identify the complete wetting of the tablet surface (4). A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicates (n=6). The wetting time was recorded using a stopwatch.

Water absorption ratio (R) : The weight of the tablet before keeping in the petri dish was noted (W_b) using Shimadzu Digital Balance. The wetted tablet from the petri dish was taken and reweighed (W_a) using the same. The Water absorption ratio (R) was determined according to the following equation:

$$R = 100 (W_a - W_b) / W_b$$

Where

W_b = Weight before water absorption;
W_a = Weight after water absorption.

***In vitro* dispersion time :** *In vitro* dispersion time was measured by dropping a tablet in a beaker containing 100 ml of 6.8 pH phosphate buffer. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Dissolution test : The dissolution test was carried out using USP apparatus 2 (Paddle type). The stirring rate was 50 rpm. A 6.8 pH phosphate buffer and methanol (1:1) was used as dissolution medium (900 ml) and was maintained at 37±1^{0}C. Samples of 5 ml were withdrawn at predetermined intervals (2, 4, 6, 8, 10, 15, 20, 25 and 30 min), filtered and replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid wherever necessary and were analyzed for the Etodoloc at 225 nm by using UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

Results and Discussion

Oral disintegrating tablets of Etodolac were prepared by direct compression method using Crospovidone (CP), Croscarmellose sodium (CCS), and Sodium Starch Glycolate (SSG) as superdisintegrants. A total of 9 formulations (F1 to F9) were designed.

Construction of Calibration Curve : The study started with the construction of standard calibration curve. The λ_{max} of Etodolac in 6.8 pH phosphate buffer was scanned and found to have the maximum absorbance at 225 nm. The standard graph of Etodolac in 6.8 pH phosphate buffer was plotted by taking concentration ranging from 2-12 µg/ml and a good correlation was obtained with R^2 values of 0.994 respectively.

Precompression Parameters : The values of precompression parameters evaluated were found to be within the prescribed limits and indicated good free flowing property (table 3). Flow properties of the powder and resistance to the particle movement can be judged from the angle of repose. The values for an Angle of repose were found to be in the range of 28.12 to 30.35. The Carr's index of the prepared blends falls in the range of 16.26% to 19.08% and this is also supported by the Hausner's ratio values, which were in the range of 1.19±0.16 to 1.28±0.23. Hence, the prepared blends possessed good flow properties and these blends can be used for tablet manufacture.

Weight Variation Test : All the tablets were prepared under similar conditions. All the formulations exhibited white colour and odorless with a smooth surface. The average weight of the ODTs prepared by direct compression method was 291.12±0.39 to 300.01±0.09 mg.

Thickness Measurement : The thickness of all the formulations was within acceptable limits. The thickness of tablets was measured using a Digital Vernier Caliper. The thickness of tablets was found in between 3.05±0.10 to 3.15±0.09.

Hardness : The hardness of all the formulations was within acceptable limits. The hardness of tablets prepared by direct compression was 2.78±0.23 to 2.98± 0.39 kg/cm^2.

Friability : The friability of all formulations was found to be 0.41 to 0.68 and hence the tablets with lower friability may not break during handling on machines and or shipping. Various evaluated parameters for an oral disintegrating tablet formulation of Etodolac are shown in table 3 & 4.

Wetting Time : Wetting time of all the formulations was in the range of 08.39 to 25.02 seconds. ODTs of F9 formulation showed the least (08.39 sec) wetting time.

Water Absorption : Water absorption ratio of all the formulations was in the range of 12.77 to 30.56%. ODTs of F9 formulation showed the least (12.77%) water absorption ratio.

In vitro dispersion time: *In vitro* dispersion time of all the formulations were in the range of 18 to 38 seconds. ODTs of F9 formulation showed the least (18.56 sec) dispersion time.

Disintegration time*:* Disintegration time is very important for ODTs, which is desired to be less than 60 seconds for orally disintegrating tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in the buccal cavity, thus promoting bioavailability. The disintegration time of prepared ODTs was in the range of 15.05 to 32.41 seconds and the order is CP < SSG < CCS. Among all the formulations, the F9 formulation was prepared with Crospovidone in the concentration of 9% as disintegrant exhibit least disintegration time (15.05 sec). As the concentration of superdisintegrants in the formulations increased, the disintegration time was found to decrease.

Drug Content Uniformity : The drug content of all the formulations (F1 to F9) was found to be between 85.48 and 99.09%, which was within the acceptable limits. For most of the larger dose drugs in tablet form, the official potency range permitted is not less than 95% and not more than 105% of the labelled amount.

Dissolution Test : *In vitro* dissolution data of all the Etodolac ODT formulations are shown in table 5 and corresponding dissolution profile is shown in figure 2, 3 & 4. The F9 formulation exhibits the better dissolution profile than that of all Etodolac ODT formulations.

Drug-Excipient Compatibility Studies : The compatibility between the drug, polymer and excipients was compared by FTIR spectroscopy (Perkin Elmer). The FTIR spectrum of pure drug exhibits characteristic peaks at 3350, 1397, 889 and 2966 cm^{-1} due to N-H, C-O, C-N and C-H stretching respectively. The FTIR spectrum of optimized formulation (F9) showed characteristic peaks at 3351, 1422, 1042 and 2915 cm^{-1}. The presence of above peaks confirm undisturbed drug in the formulations. It was observed that there was no disappearance or shift in peak position of the drug in any spectra of drug and superdisintegrants, which proved that drug and superdisintegrants were compatible. The FTIR data interpretation of drug and optimized formulation was shown in table 6.

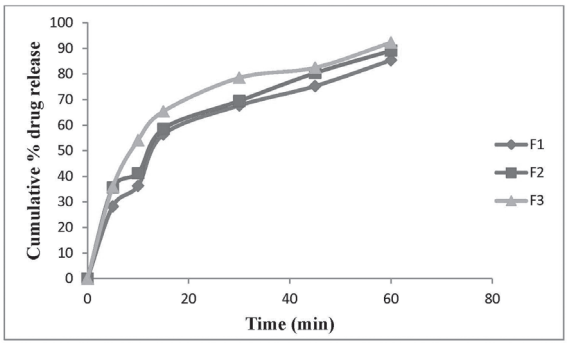

Fig. 2. Cumulative % drug release of Etodolac ODTs prepared individually varying concentrations of Superdisintegrating agents

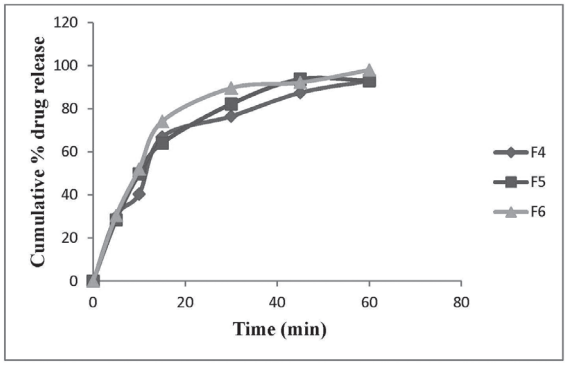

Fig. 3. Cumulative % drug release of Etodolac ODTs prepared individually varying concentrations of super disintegrating agents

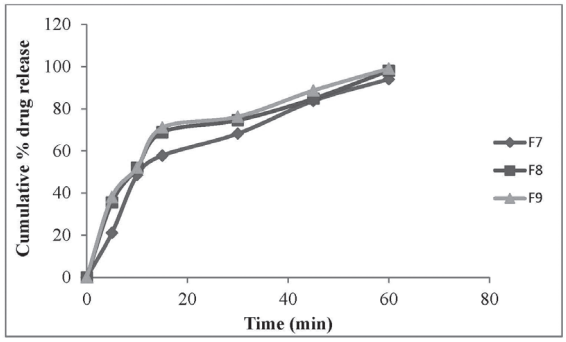

Fig. 4. Cumulative % drug release of Etodolac ODTs prepared individually varying concentrations of Superdisintegrating agents

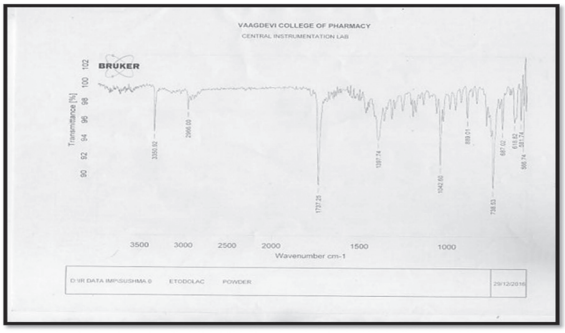

Fig. 5: FTIR studies of drug Etodolac

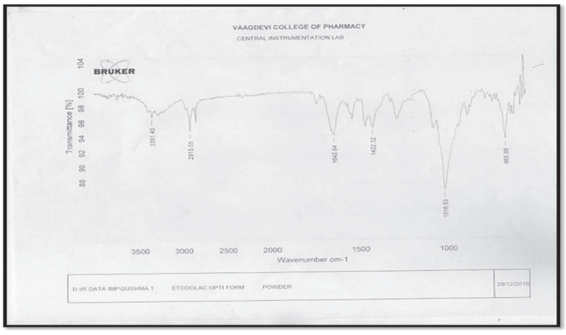

Fig. 6. FTIR studies of optimized formulation (F9)

Table 1. Formulation of Etodolac ODTs

Disintegrating Agents	Concentration (%)	Formulation Code
Sodium starch glycolate	3	F1
	6	F2
	9	F3
Croscarmellose sodium	3	F4
	6	F5
	9	F6
Crospovidone	3	F7
	6	F8
	9	F9

Table 2. Formula of ODTs Prepared by Direct Compression Method using Super Disintegrants Individually

Ingredients (mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etodolac	200	200	200	200	200	200	200	200	200
Sodium starch glycolate	3	6	9	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	3	6	9	-	-	-
Crospovidone	-	-	-	-	-	-	3	6	9
Mannitol	30	30	30	30	30	30	30	30	30
Talc	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1

Table 3. Preformulation Characteristics of Etodolac ODTs

Formulation Code	Bulk Density (g/c)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose
F1	0.425±0.15	0.527±0.25	1.19±0.16	16.75	28.98
F2	0.428±0.35	0.514±0.27	1.20±0.30	17.37	30.21
F3	0.429±0.22	0.521±0.29	1.28±0.22	18.46	30.19
F4	0.413±0.16	0.512±0.21	1.25±0.16	17.60	28.43
F5	0.417±0.37	0.515±0.28	1.22±0.26	18.71	30.35
F6	0.433±0.16	0.509±0.24	1.20±0.21	16.26	30.20
F7	0.423±0.50	0.519±0.30	1.20±0.25	18.32	28.12
F8	0.419±0.30	0.515±0.28	1.28±0.23	19.08	29.17
F9	0.411±0.28	0.509±0.29	1.24±0.22	18.44	28.17

Table 4. Evaluation Parameters of Etodolac ODTs

Formulation Code	Weight variation[a](mg)	Thickness[b] (mm)	Hardness[b] (kg/cm^2)	Friability[c] (%)	Drug content (%)
F1	298.05±0.62	3.10±0.10	2.92±0.30	0.59	85.48±0.45
F2	299.01±0.51	3.05±0.12	2.78±0.23	0.65	89.01±0.49
F3	297.03±0.61	3.15±0.09	2.95±0.21	0.58	92.27±0.23
F4	298.01±0.67	3.12±0.11	2.83±0.46	0.68	93.60±0.40
F5	291.12±0.39	3.13±0.16	2.85±0.42	0.41	95.70±0.30
F6	293.05±0.52	3.14±0.14	2.96±0.56	0.47	98.01±0.09
F7	295.25±0.45	3.05±0.10	2.93±0.36	0.56	94.05±0.45
F8	299.01±0.28	3.13±0.05	2.82±0.40	0.45	98.07±0.13
F9	300.01±0.09	3.12±0.07	2.98±0.39	0.58	99.09±0.11

a. Mean ± S.D., n = 20, b. Mean ± S.D., n = 6, c. Mean ± S.D., n = 10 tablets

Table 5. Formulation characteristics of Etodolac ODTs

Formulation code	Disintegrating time[a] (sec)	Wetting time[b] (sec)	Water absorption ratio[b] (%)	*In vitro* dispersion time[c] (sec)
F1	32.41±0.24	25.02±0.48	30.56±0.45	38.94±0.25
F2	29.94±0.56	19.23±0.33	24.66±0.50	34.22±0.55
F3	28.35±0.18	17.35±0.50	22.52±0.29	31.87±0.21
F4	24.25±0.55	18.25±0.12	20.85±0.28	30.51±0.78
F5	20.25±0.28	15.25±0.84	18.28±0.84	27.84±0.70
F6	18.47±0.65	12.47±0.25	16.18±0.22	25.54±0.80
F7	22.04±0.51	11.04±0.18	15.58±0.55	22.35±0.57
F8	17.48±0.22	10.48±0.55	14.32±0.88	21.14±0.74
F9	15.05±0.65	08.39±0.22	12.77±0.55	18.56±0.25

a. Mean ± S.D., n = 6, b. Mean ± S.D., n = 10, c. Mean ± S.D., n = 3

Conclusion

The anti-inflammatory effects of Etodolac result from inhibition of the enzyme cyclooxygenase (COX). This decreases the synthesis of prostaglandins involved in mediating inflammation.

Etodolac oral disintegrating tablets were prepared by direct compression method using Crospovidone, Croscarmellose sodium, and sodium starch glycolate as super disintegrants exhibited good preformulation properties.

Based on disintegration and dissolution results, formulation F9 was the best formulation with crospovidone from prepared ODT.

Oral disintegrating tablets of Etodolac were found to improve the versatility, convenience, and

Table 6. Cumulative % Etodolac released from ODTs containing varying concentrations of different Superdisintegrating agents individually

Formulation code	Time (minutes)					
	5	10	15	30	45	60
F1	28.26±0.18	36.31±0.19	56.36±0.10	67.68±0.32	75.27±0.27	85.40±0.12
F2	35.64±0.20	41.22±0.10	58.58±0.17	69.48±0.11	80.36±0.28	89.09±0.21
F3	35.87±0.17	54.12±0.31	65.37±0.11	78.48±0.39	82.48±0.09	92.27±0.13
F4	30.06±0.51	40.44±0.15	66.96±0.05	76.56±0.09	87.48±0.51	93.06±0.39
F5	28.44±0.09	49.81±0.30	64.08±0.07	82.2±0.27	93.78±0.34	93.05±0.37
F6	30.42±0.08	52.02±0.09	74.16±0.12	89.65±0.35	92.25±0.46	98.01±0.09
F7	21.18±0.43	48.52±0.12	57.78±0.27	68.22±0.13	83.73±0.22	94.05±0.15
F8	35.59±0.17	52.02±0.18	68.85±0.38	74.56±0.24	84.77±0.19	98.07±0.23
F9	38.07±0.13	52.06±0.30	71.05±0.31	76.25±0.18	88.65±0.01	99.09±0.11

Mean ± S.D., n = 3

Table 7. FTIR Studies of Etodolac pure drug and optimized formulation

PEAK OF FUNCTIONAL GROUPS {WAVELENGTH (cm^1)}				
IR SPECTRA	**N-H Stretching**	**C-O Stretching**	**C-N Stretching**	**C-H Stretching**
Etodolac	3350	1397	889	2966 (sp^3)
Optimized formulation (F9)	3351	1422	1042	2915

patient compliance leading to an enhanced approach for the administration of the drug.

The orodispersible tablets are particularly beneficial to the pediatric, geriatric, bedridden, and psychotic patients affected by dysphagia. These tablets get converted into a suspension with the salivary fluid in the oral cavity thereby showing rapid onset of action with improved bioavailability, better patient acceptance and offer better safety as compared to conventional oral dosage forms.

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