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Formulation and Evaluation of Etoricoxib Oro Dispersable Tablets by Direct Compression Method

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Abstract:*Oral disintegrating tablet (ODT) is defined as "A solid dosage form containing medical substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". The main aim of the present study is to formulate Etoricoxib oral disintegrating tablets. Etoricoxib is a selective COX-II inhibitor which acts by inhibiting the COX–2 enzyme and decreases the incidences of side effects associated with these agents. Conventional tablets of Etoricoxib are not capable of rapid action, which is required for faster drug effect onset and immediate relief from pain. Etoricoxib ODT's are prepared by direct compression method using Cross povidone, Cross carmellose sodium, Sodium starch glycolate and Calcium silicate as the super disintegrants. The prepared tablets were characterized for their hardness, weight variation, disintegration time, wetting time, tablet thickness, friability, and in vitro dissolution studies.DSC Studies were also performed. The ability of the tablet to release the drug faster depends on the concentration and type of super disintegrant. In this study the oral disintegrating tablets containing Cross carmellose sodium as the super disintegrant in the concentration of 10% shows better release of drug. About 98.6% of the drug was released in 10 mins from the tablets. Therefore, based on the physico chemical properties, in vitro drug release profile and mouth feel formulation F 10 containing 10% of Cross carmellose sodium is optimised as the best formulation. DSC study shows no drug excipient interaction.*

Keywords:*Etoricoxib, Oro-dispersable tablets, Direct compression method, Cross povidone, Cross carmellose sodium, Sodium starch glycolate, Calcium silicate*

I. Introduction

The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of administration, accurate dosage, versatility, self-medication and most importantly patient compliance. Therefore, oral solid dosage forms are more popular. Among the pharmaceutical dosage forms, the conventional tablets seem to be the most popular, because of ease of transportability and comparatively lower manufacturing cost [1]. The disadvantage of oral conventional dosage forms such as Dysphasia or difficulty in swallowing can be overcome by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration because they dissolve in saliva and does not require water for swallowing [2]. Recent advances in novel drug delivery system to enhance the safety and efficacy of drugs by administration of conventional tablets led to the development of oral disintegrating tablets. Administration is simple, as the tablet is placed in a mouth, and allowed to disperse or dissolve in the saliva, and swallowed [3].
United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medical substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue"[4]. The disintegration time for ODTs generally ranges from several seconds to about a minute.

The main aim of the present research is to formulate oral disintegrating tablets of Etoricoxib (Selective COX-II inhibitor) using varied concentrations of super disintegrants such as Crosspovidone, Cross Carmellose Sodium and Sodium starch glycolate.

II. Materials And Methods

Materials:-

The active ingredient Etoricoxib was received as a gift sample from Fleming Lab Ltd, Hyderabad. Microcrystalline cellulose received from SigachiChloro Chemicals Pvt Ltd, Hyderabad. Sodium starch glycolate, Cross Povidone and Cross carmellose sodium are the super disintegrants received as gift samples from Lincoln Pharmaceuticals Ltd, Ahemdabad. All the other ingredients used in the formulation are of pharmaceutical analytical grade.

Table 1: Formula for Etoricoxib Tablets:-

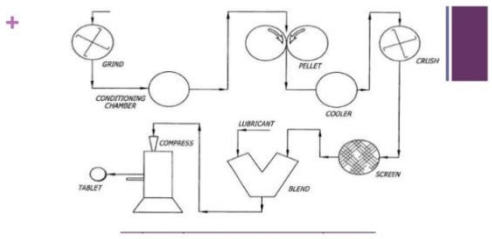
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Etoricoxib	100	100	100	100	100	100	100	100	100	100	100	100
Crosspovidone	5	-	-	-	7.5	-	-	-	10	-	-	-
CCS	-	5	-	-	-	7.5	-	-	-	10	-	-
SSG	-	-	5	-	-	-	7.5	-	-	-	10	-
Calcium silicate				5				7.5	-	-	-	10
MCC	70.00	70.00	70.00	70.00	68.75	68.75	68.75	68.75	67.50	67.50	67.50	67.50
Lactose	70.00	70.00	70.00	70.00	68.75	68.75	68.75	68.75	67.50	67.50	67.50	67.50
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
Aerosil	4	4	4	4	4	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Mg Stearate	2	2	2	2	2	2	2	2	2	2	2	2

Method:-

Direct Compression Method [6]:-

Etoricoxib oral dispersible tablets were formulated using direct compression method. The formulations are prepared using three different super disintegrants. Varied concentrations such as (5%, 7.5%, 10%) of each Super disintegrant were used in the preparation of the formulations.

The drug and all other excipients were sifted through ≠ 40 sieves separately and mixed thoroughly. The above blend was lubricated with magnesium sterate and the lubricated blend was compressed by using 8mm standard round faced punch on a16 station rotary tablet punching machine (Lincoln Pharmaceuticals Ltd, Ahemdabad).



Stepwise process for direct compression

III. Evaluation Of Tablets

A) Weight variation test [7]: 20 tablets were selected randomly from each formulation and their average weight was calculated using digital balance. All the 20 tablets were weighed individually and compared with the tablet meet USP specifications if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Pharmacopeial specifications for tablet weight variation

Average weight of tablets (IP)	Average o weight of tablets (USP)	Maximum % Difference allowed
Less than 80 mg	Less than 130 mg	10
80 mg-250 mg	130 mg-324 mg	7.5
More than 250 mg	More than 324 mg	5

B) Tablet Hardness[8]:-

Tablet hardness is termed as crushing strength and resistance to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping. This can be tested by using one of the following hardness testers [9] i.e. Monsanto hardness tester, Strong Cobb tester, Pfizer tester, Erweka and Varian tester.

C) Disintegration time[10]:-

The disintegration time of the tablet is the time taken for the tablet to break into small particles and was determined by using USP disintegration test apparatus. The limit for disintegration is not more than 3 times at 37˚c.

Procedure:-Six tablets were placed individually in each tube of disintegration test apparatus in which bath temperature was maintained at 37±0.5˚c and disc were placed on each tablets. The disintegration time of each tablet was noted.

D) Wetting time[11]:-

The wetting time of the tablets was measured by a simple procedure. A circular tissue paper of 10 cm diameter was placed in a Petri dish containing 10 ml of water containing Eosin blue. A tablet was carefully placed on the surface of tissue paper. The time required for developing blue colour on the upper surface of the tablet was noted as the wetting time.

E) Tablet thickness[12] :-

Randomly 10 tablets were taken from each formulation trail batch and their thickness was measured using digital Vernier callipers [13]. The individual tablet was placed between two anvils and sliding knob was rotated until the tablet was tightly fitted. The digital reading displayed was noted.

F) Friability[14]:-

It is used to measure the mechanical strength of tablets. Roche fribilator is used to determine the friability by following procedure.

Procedure: - Twenty tablets were weighed and placed in Roche Fribilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, de dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / initial weight) *100

G) In vitro dissolution studies[15]:-

Freshly prepared pH 7.4 phosphate buffer (900ml) was placed in each dissolution vessel of dissolution test apparatus (USP, II Paddle method). The tablets were placed in the dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5˚c and the paddle was rotated at 50 rpm. Five ml samples were withdrawn. The sample volume was immediately replaced with the same volume of fresh media as when as a sample was taken. The samples withdrawn were filtered, diluted and estimated spectrophotometrically[16] at 233 nm. Cumulative amount of the drug released at each interval was calculated by using standard graph of Etoricoxib.

IV. Results

Table2:-Physico-chemical parameters and in-vitro dissolution data of Etoricoxib ODT with 5 % super disintegrants

Parameter	F1 (mg)	F2 (mg)	F3(mg)	F4(mg)
Weight Variation*(mg)	200±0.92	201±0.91	200±0.92	201±0.92
Friability (%)	0.65	0.49	0.38	0.59
Hardness*(Kg/cm^2)	3.5±0.47	5±0.43	4.5±0.37	2.5±0.37
Thickness(mm)	3.26±0.92	3.18±0.23	2.18±0.62	3.24±0.94
Disintegration time*(Sec)	31±1.1	29±0.9	35±1.1	45±1.4
Wetting time*(sec)	47±1.5	43±1.3	46±1.4	57±1.8
Assay (%)	97.2±0.97	101.1±0.9	99.9±0.98	98.3±0.96
Dissolution Time* (min)				
5	91.8±1.5	90.69±1.2	70.2±0.9	60.3±1.5
10	97.2±1.6	96.7±1.6	85.7±1.1	70.4±1.3
15	98.5±1.6	96.8±1.6	87.6±1.4	77.7±1.6
20	99.8±1.2	98.2±1.5	94.3±1.3	76±1.5
25	100.4±0.8	98.6±0.8	96.3±1.5	75.8±1.2
30	101.1±0.7	101.5±0.8	100.9±1.2	85.4±1.6

Graph 1:- Cumulative % Drug release V_S Time profiles of Etoricoxib ODT prepared using F1 (CP), F2 (CCS),F3 (SSG), F4 (CS) in 2.5% concentration.

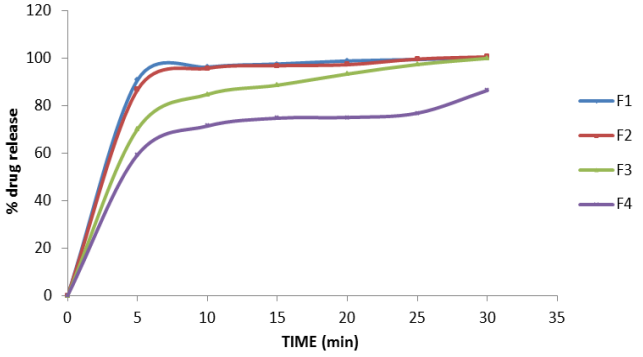


Table 3:-Physico-chemical parameters and in-vitro dissolution data of Etoricoxib ODT with 5 % superdisintegrants.

Parameter	F5(mg)	F6 (mg)	F7(mg)	F8(mg)
Weight Variation*(mg)	201±0.91	201±0.91	200±0.92	200±0.92
Friability (%)	0.90	0.74	0.70	0.65
Hardness(Kg/cm^2)	3.6±0.37	3±0.42	4±0.53	3.4±0.37
Thickness(mm)	3.44±0.34	3.37±0.45	3.18±0.2	3.27±0.62
Disintegration time (Sec)	33±0.7	22±0.5	25±0.9	40±1.4
Wetting time (sec)	34±1.3	33±1.2	39±1.4	50±1.7
Assay (%)	101.1±0.99	100.9±0.98	100.2±1.0	99.1±0.97
Dissolution Time (min)				
5	94.3±1.6	94.6±1.4	80.6±1.4	61.4±1.5
10	98.6±1.8	95.19±1.6	88±1.4	72.8±1.2
15	99.7±0.8	98.7±0.7	93.4±1.3	80.8±1.3
20	101.2±±0.7	101.5±0.8	100±0.9	86.1±1.1
25	101.4±0.8	102.1±0.7	101.±50.8	90.4±0.9
30	100.2±0.8	102.1±0.8	101.5±0.8	92.1±0.8

Graph 2:- Cumulative % Drug release V_S Time profiles of Etoricoxib ODT prepared using F5 (CP), F6 (CCS),F7 (SSG), F8 (CS) in 5% concentration.

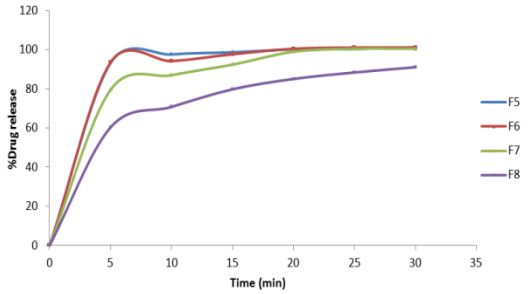
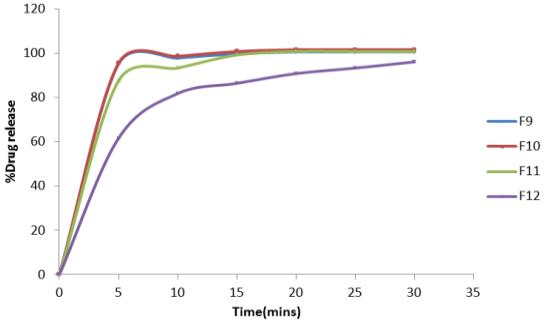


Table 4:-Physico-chemical parameters and in-vitro dissolution data of Etoricoxib ODT with 10 % superdisintegrants

Parameter	F9(mg)	F10 (mg)	F11(mg)	F12(mg)
Weight Variation*(mg)	200±0.92	200±0.91	200±0.92	200±0.92
Friability (%)	0.87	0.64	0.67	0.61
Hardness*(Kg/cm^2)	3.6±0.37	3±0.32	3.6±0.37	4±0.32
Thickness(mm)	3.36±0.59	3.32±0.25	3.41±0.25	3.26±0.63
Disintegration time (Sec)	20±0.7	15±0.4	21±0.5	26.8±1.1
Wetting time (sec)	21±1.2	20±1.1	29±1.3	43±1.9
Assay (%)	98.7±0.98	99.9±0.98	101.1±0.9	98.2±0.96
Dissolution Time* (min)				
5	96.2±1.6	95.5±1.5	88.6±1.2	62.6±1.5
10	98.8±1.5	98.6±1.7	94.3±0.9	82.8±1.3
15	100.7±1.5	100.8±0.9	100.2±0.8	85.4±0.9
20	101.6±0.9	101.6±0.8	101.8±0.9	91.8±0.8
25	101.6±-.8	101.6±0.8	101.8±1.2	94.3±1.1
30	101.6±0.9	101.6±0.8	101.8±0.9	95.1±1.8

Graph 3:- Cumulative % Drug release V_S Time profiles of Etoricoxib ODT prepared using F9 (CP), F10 (CCS), F11 (SSG), F12 (CS) in 10% concentration.



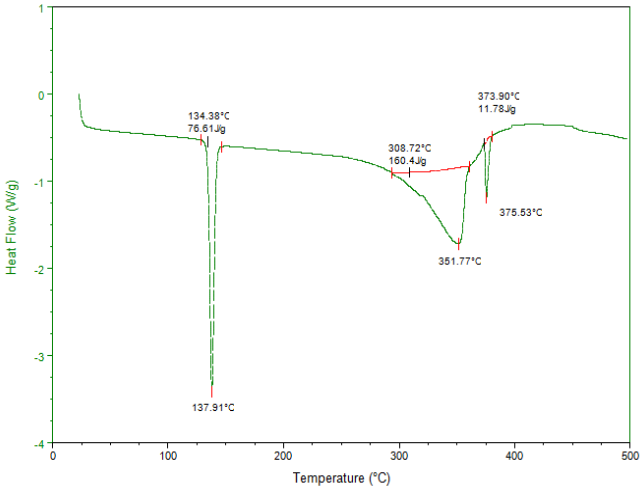
Differential scanning calorimetric study (DSC)

The DSC results shows sharp endothermic peak for the pure Etoricoxib at 137.91. Similar sharp endothermic peaks were observed in the formulations at almost similar temperatures. This clearly indicates that there is no drug excipient interaction. Table 5 shows the melting points of the pure drug and the formulations of Etoricoxib.

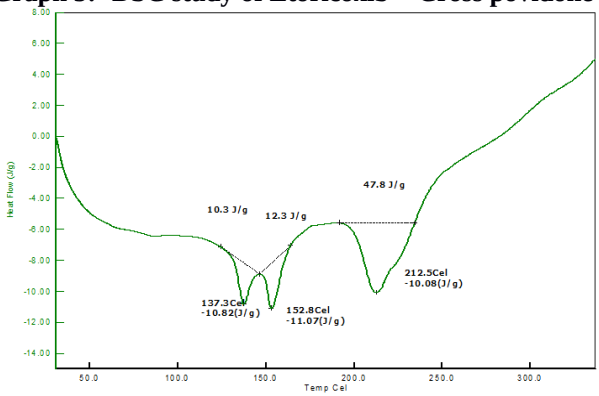
Table 5:- DSC melting points of the pure drug and the formulation of Etoricoxib

S.NO	FORMULATION	DSC MELTING POINT
1	Etoricoxib pure drug	137.91
2	SSG	135
3	CP	137.3
4	CCS	136.4
5	Calcium silicate	135.1

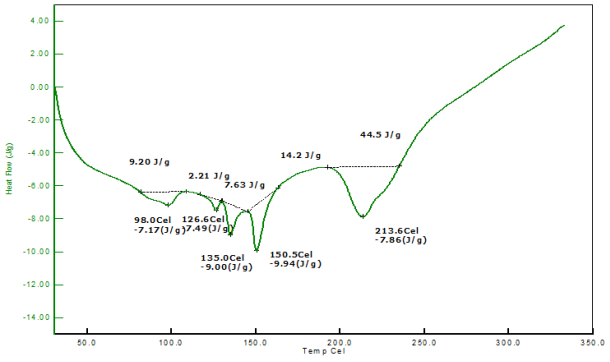
Graph 4:- DSC study of pure drug Etoricoxib



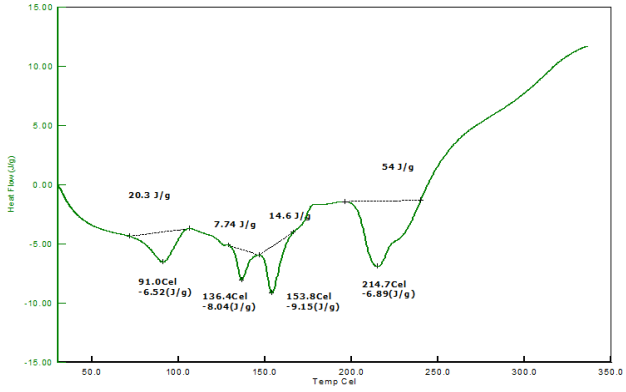
Graph 5:- DSC study of Etoricoxib + Cross povidone



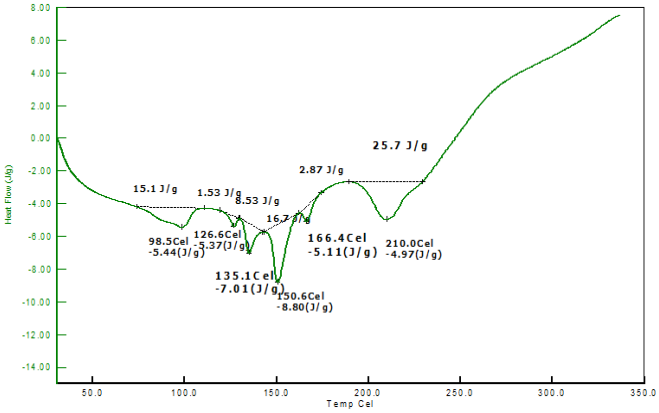
Graph 6:-DSC study of Etoricoxib + Sodium starch glycolate



Graph 7:- DSC study of Etoricoxib + Cross carmellose sodium



Graph 8:- DSC study of Etoricoxib + Calclium silicate



V. Discussion

Etoricoxib Oral dispersible tablets were developed with an aim to improve the patient's compliance. The formulations were developed with an objective to use by the paediatric and geriatric patients. The development was initiated with standard calibration curve using UV spectrophotometric methodsfor analysis of the drug. The UV spectrophotometric method was developed in 0.1N HCl at 233nm. The method shows linearity in the concentration range of 1-10µg/ml with a correlation coefficient of 0.998.

The Etoricoxib Oral disintegrating tablets were developed with different superdisintegrants such as Crosspovidone, Sodium starch glycolate, Cross carmellose sodium and Calcium silicate. 5% concentration was used in each formulation. The formulation prepared with Crospovidone, Sodium starch glycolate, Cross carmellose sodium and Calcium silicate releases 90 to 100% of the drug within 30mins. However DT was a little more in the above formulations. To improve the disintegration time and dissolution time, the formulations were prepared with increased concentrations (7.5% and 10%) of superdisintegrants, without any changes in the physico-chemical properties. The mouth feel of the formulations prepared with Sodium starch glycolate, cross carmellose sodium resulted smooth and fine particles, where as the formulations prepared with crosspovidone and calcium silicate yields particulate matter on the tongue. Based on the physico chemical properties, in vitro drug release profile and mouth feel formulation F 10 containing 10% of Cross carmellose sodium is optimised as the best formulation.DSC study shows no drug excipient interaction.

VI. Conclusion

Oral disintegrating tablets of Etoricoxib were successfully prepared by using different Superdisintegrants by direct compression method. The present investigations helped in understanding the effect of formulation process variables especially the concentration of different super disintegrants on the dispersion time and drug release profile. The rapid disintegration of Etoricoxib tablets formulated in this investigation may possibly help in administration of etoricoxib in a more palatable form without water, thus, the "patient-friendly dosage form especially for paediatric, geriatric, bedridden, and non-cooperative patients which makes it a promising candidate for further studies, including stability studies, on the way to achieving intraoral formulations.

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