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Research

Formulation and evaluation of etoricoxib oral disintegrating thin films

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Abstract

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablets/capsules. Etoricoxib is a selective COX-2 inhibitor used to relieve moderate post-surgical dental pain as a short-term treatment and inflammatory and painful symptoms of various forms of arthritis. Although oral disintegrating tablets have an advantage of administration without choking and fast disintegration; the disintegrated materials contained in them are insoluble and remain until swallowing. In such cases formulation of oral disintegrating thin films was advantageous. In the present work, oral thin films of Etoricoxib were designed with a view to enhance patient compliance by solvent casting method. In the solvent casting method, Croscarmellose sodium (2, 4 and 6 % w/w), Crospovidone (10 and 15% w/w) as super disintegrants were used in different concentrations with Gelatin, Poly vinyl alcohol as a film forming base for the formulation of oral disintegrating thin films of Etoricoxib by solvent casting method. The prepared formulations of films were evaluated for film thickness measurement, folding endurance study, *in-vitro* disintegration time, *in-vitro* drug release pattern (in 6.8pH Buffer). Drug content, Short-term stability (40°C/ 75% RH for 3 months) and drug-polymers interaction study (IR spectroscopy). Among all the formulations, the formulation(F8) prepared by 4% Crospovidone show good drug release(99.27%).

Keywords: Croscarmellose sodium, Crospovidone; Etoricoxib; oral disintegrating thin films.

INTRODUCTION

The oral route is one of the oldest routes which are used for conventional and novel drug delivery. The main reason for this route being the highly preferred is ease of administration. FDFs, a new drug delivery system for the oral delivery of the drugs, was developed in late 1970's based on the technology of the transdermal patch. These were developed as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms [1]. Some problems are associated with the OFDF like they are sometime difficult to carry, storing and handling (friability and fragility), these are prepared using the expensive lyophilisation method.[2,3] To overcome these problems oral films were developed, which are very popular now a days. The concept of oral film was come from confectionary industry.[4,5] Orally fast-dissolving film rapidly disintegrates and dissolves to release the medication for oromucosal and

intragastric absorption.[6] It is possible to have more than one type of arthritis and knowing what you have can help in treating your symptoms. Gout, which can occur with osteoarthritis (OA) or autoimmune, inflammatory forms of arthritis, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), results when uric acid builds up and forms crystals that are deposited in joint tissue. It causes sudden, severe pain, swelling and tenderness, usually in the big toe, but it also can occur in the feet, ankles, hands, knees, wrists, elbows or other joints. It's typically in only one joint, but chronic gout can affect multiple joints.[7] Etoricoxib, 5-chloro-6_-methyl-3 [4-(methyl sulfonyl) phenyl]-2, 3_–bypyridine, is a highly selective second generation cyclooxygenage-2 (COX-2) inhibitor administered orally as an analgesic and nonsteroidal anti-inflammatory analgesic drug that has shown some improved efficacy versus traditional NSAIDs.[8]

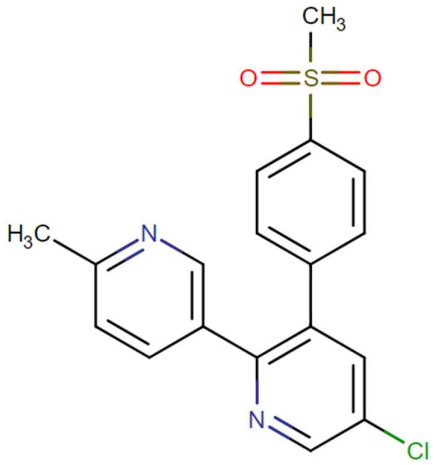

Fig 1: Structure of Etoricoxib[13]

It is used in the treatment of rheumatoid arthritis, osteoarthritis, postoperative dental pain, chronic back pain, and acute gout.[9,10] Moreover, recent studies evidenced its efficacy in patients with ankylosing spondylitis.[8] But it's very low aqueous solubility and poor dissolution can cause formulation problems and limit its therapeutic application by delaying the rate of absorption and the onset of action.[9,12]

Materials & methods used

Etoricoxib API was procured from Matrix Pvt. Ltd. Hyderabad, HPMCk15, Croscarmellose sodium, Citric acid and Sucrose was procured from S.D FINE CHEMICALS, Tween 80 from INR chem. Mumbai, PEG-6000 from Hi Media lab. Pvt. Ltd. Mumbai, Crospovidone from Signet Chemical Corp., Mumbai.

Formulation of oral disintegrating thin films of etoricoxib

From the preliminary physical observation of the films prepared the best compositions were used for the incorporation of Etoricoxib. HPMCk15, TWEEN 80 polymers was dissolved in water with continuous stirring. Calculated amount of Etoricoxib was dissolved in the polymeric solution, after complete dissolution of the drug; propylene glycol-6000 (plasticizer) was added and stirred to form a homogeneous solution. The solution was casted onto mercury substrate then kept in hot air oven at 40ºC for 24 hrs. The film thus formed was cut into size of 2 cm diameter. Each film contains 4 mg of Etoricoxib. The oral disintegrating thin films of Etoricoxib were prepared by solvent casting technique employing mercury as substrate. The Odt films were prepared using polymers like HPMCk15, TWEEN 80. propylene glycol-6000 is used as plasticizer. The calculated amount of polymer was dispersed in three forth volume of with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. The calculated amount of Etoricoxib was incorporated in the polymeric solutions after levigation with required volume of PEG. The solution was casted on to mercury substrate then kept in hot air oven at 40^0c. The films were punched in to size 2cm diameter containing 4mg of Etoricoxib. By carrying out the trial and error method different concentrations of film forming polymers were used like :HPMCk15, TWEEN 80 . It has been found that 4.5%of HPMCk15, 3.5% of TWEEN 80 shows better films. Which these concentrations of films were prepared by dissolving different quantities of film forming polymers in 10 ml of water.

NOTE: With the same procedure the films of 4.5% HPMCk15, 3.5% TWEEN 80 were prepared with out the super disintegrating agents named as Fm , Fn respectively.

Table 1: Formulation details of Etoricoxib Oral disintegrating thin films

Formulation	Etoricoxib (mg)	$HPMC_{k15}$	Tween 80	Cros carmellose sodium	Cros povidone (mg)	Sucrose (mg)	Citric Acid (mg)	Trusil Flavor (mg)	PEG-6000 (mg)
Fm	60	4.5	--	--	--	4	4	8	30
F1	60	4.5	--	2	--	4	4	8	30
F2	60	4.5	--	4	--	4	4	8	30
F3	60	4.5	--	6	--	4	4	8	30
F4	60	4.5	--	--	10	4	4	8	30
F5	60	4.5	--	--	15	4	4	8	30
Fn	60	--	3.5	--	--	4	4	8	30
F6	60	--	3.5	--	10	4	4	8	30
F7	60	--	3.5	2	--	4	4	8	30
F8	60		3.5	4	--	4	4	8	30
F9	60	--	3.5	6	--	4	4	8	30
F10	60	--	3.5	--	15	4	4	8	30

Evaluation of odt dissolving oral thin films
Post formulation studies
The etoricoxib odt films were evaluated for the following properties

a) Physical appearance and surface texture
b) Weight uniformity
c) Thickness uniformity
d) Folding endurance
e) Surface pH
f) In vitro disintegration time
g) Drug content uniformity
h) In vitro drug release
i) Drug Release kinetics

RESULTS AND DISUSSIONS

In the present study, an attempt has been made to formulate and evaluate odt films of Etoricoxib by solvent casting method using Crospovidone and CCS as super disintegrants.

Solubility

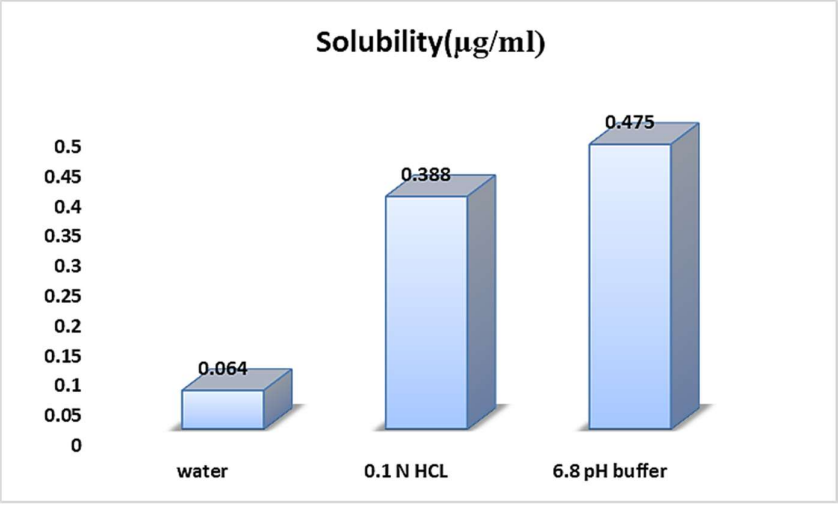

Fig 2: Graphical representation of Etoricoxib Solubility studies

From the above conducted solubility studies in various buffers we can say that 6.8 pH buffer solution has more solubility when compared to other buffer solutions.

Flow properties of the pure drug

Angle of repose	24.02
Bulk density	0.46
Tapped density	0.54
Carr's index	13.33
Hausner's ratio	1.12

Uv spectrum of Etoricoxib

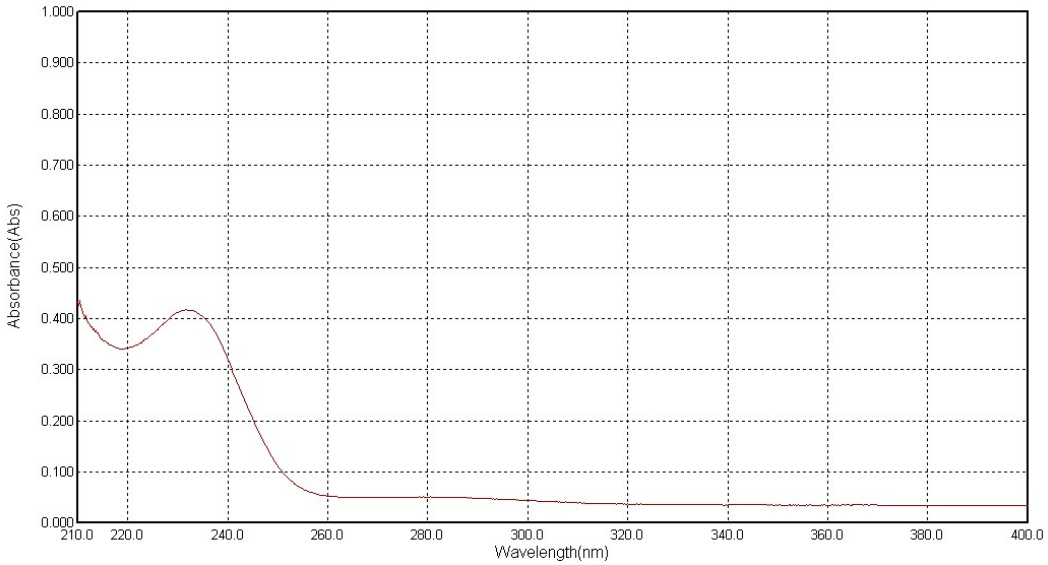

Fig 3: Absorption maxima of Etoricoxib in 6.8 pH buffer

Standard calibration curve of etoricoxib in 6.8 ph buffer

Standard calibration curve of Etoricoxib was drawn by plotting absorbance vs concentration. The λmax of Etoricoxib in 6.8 pH buffer was determined to be 233 nm as shown in Fig. The absorbance values are tabulated in Table. Standard calibration curve of Etoricoxib in the Beer's range between 0-50 µg/ml is shown in Fig.

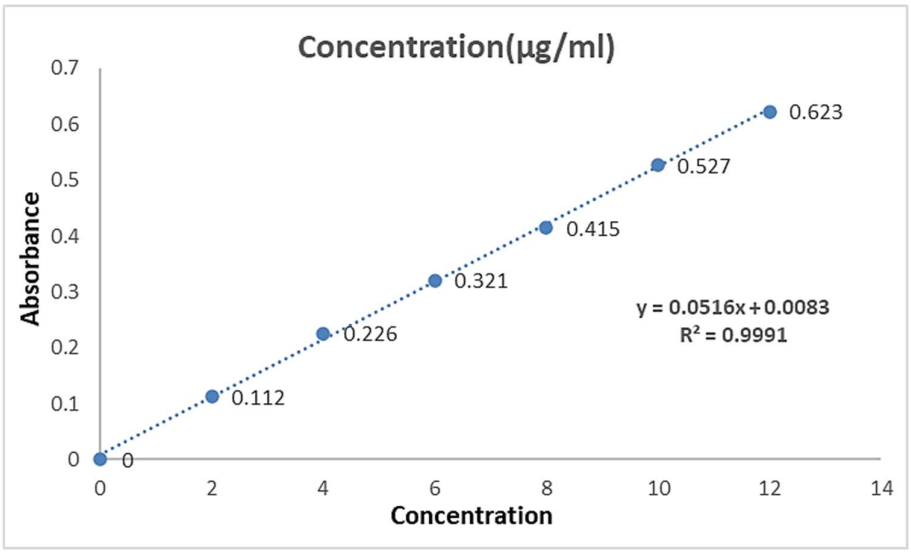

Fig 4: Standard calibration curve for Etoricoxibin 6.8 pH bufferat λmax 233 nm.

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

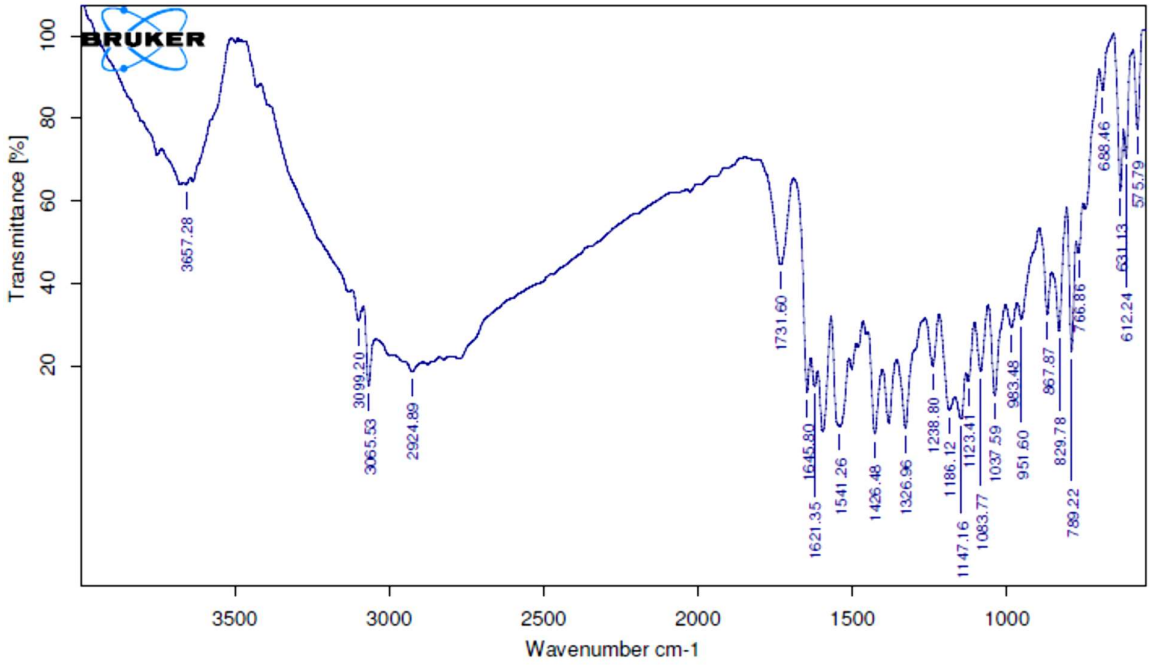

Fig 5: I.R. Spectra of pure drug

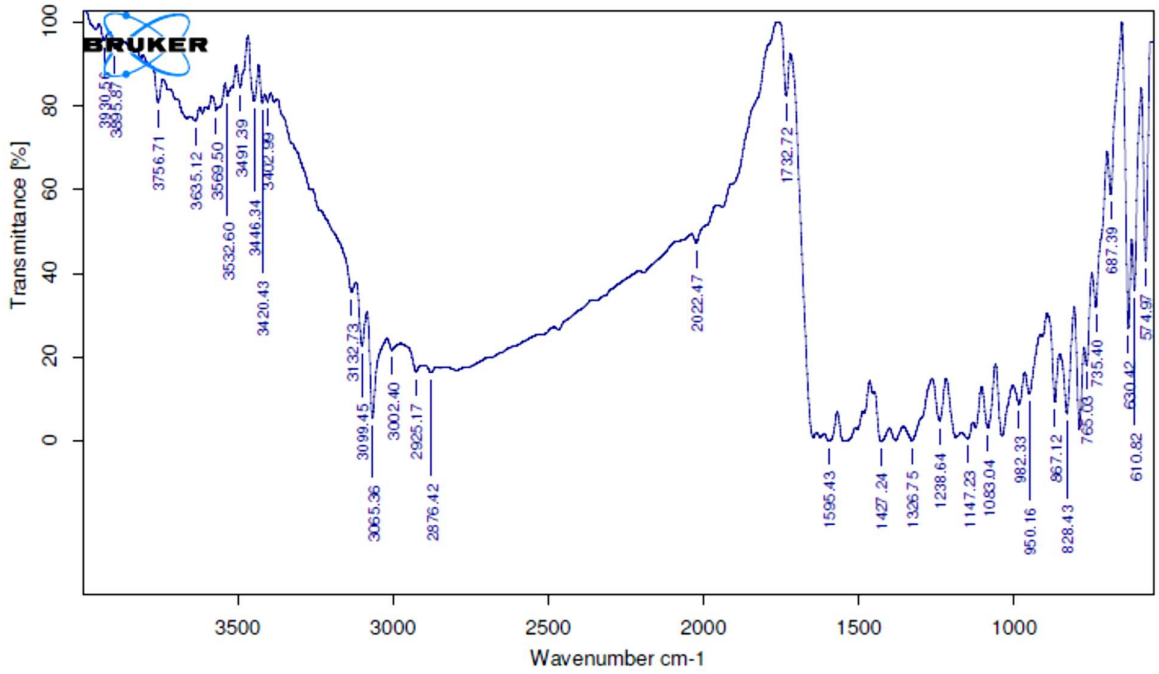

Fig 6: I.R. Spectra of optimized formulation

Evaluation of oral disintegrating thin films formulations

Physical appearance and surface texture of films

These parameters were checked simply with visual inspection of films and by feel or touch. The observation suggests that the films are having smooth surface and they are elegant enough to see.

Formulation Code	Avg. Weight (mg) ± SD, n=3	Avg. Thickness (mm) ± SD, n=3	Avg. Folding Endurance ± SD, n=3
Fh	62.97 ± 0.12,	0.135+0.124	262 + 1.674
F1	64.35±0.28	0.142 ± 0.021	281 ± 2.340
F2	66.89±0.31	0.143 ± 0.011	284 ± 2.640
F3	68.25±0.21	0.157 ± 0.012	265 ± 1.000
F4	64.14±0.38	0.162 ± 0.013	275 ± 1.730
F5	67.27± 0.41	0.168 ± 0.007	279 ± 1.000
Ft	50.36 ± 0.24	0.124+ 0.005	266+ 1.253
F6	73.58±0.11	0.172 ± 0.011	261 ± 3.310
F7	48.96±0.32	0.131 ± 0.021	269 ± 2.000
F8	52.45±0.23	0.130 ± 0.018	272 ± 3.460
F9	54.78±0.41	0.140 ± 0.017	265 ± 1.000
F10	75.35±0.22	0.171 ± 0.018	294 ± 2.000

Table 2: Evaluation of Odt films of Etoricoxib.

Formulation Code	Avg. Drug Content Uniformity (%) ± SD, n=3	Avg. In Vitro Disintegration (sec) ± SD, n=3	Avg. Surface pH ± SD, n=3
Fh	94.55 ± 0.253	76.21 ± 0.253	6.67± 0.154
Ft	97.56 ± 1.443	72.43 ± 0.165	6.89 ± 0.122
F1	97.78 ± 0.925	15.33 ± 0.171	6.76 ± 0.153
F2	98.14 ± 1.539	8.10 ± 0.435	6.00 ± 0.100
F3	96.15 ± 0.369	12.50 ± 0.591	6.46 ± 0.115
F4	94.25 ± 1.056	17.76 ± 0.151	6.23 ± 0.152
F5	96.98 ± 1.396	11.86 ± 0.151	6.66 ± 0.152
F6	95.35 ± 1.396	15.10 ± 0.479	6.06 ± 0.153
F7	98.95 ± 1.545	11.00 ± 0.100	6.83 ± 0.057
F8	97.78 ± 1.175	8.53 ± 0.151	6.06 ± 0.152
F9	94.02 ± 1.001	12.93 ± 0.057	6.33 ± 0.152
F10	97.41 ± 0.350	14.41 ± 0.076	6.76 ± 0.152

In-Vitro Dissolution Study

The *in-vitro* drug release study of mouth dissolving films from each batch (Fh,Ft , F1 to F10) was carried out in 6.8 pH Buffer solution for 30 mins and the values are shown in Table. The plot of % Cumulative drug release V/s time (mins) were plotted and depicted as shown in Fig.

Time (min)	Fh	F1	F2	F3	F4	F5	Ft	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0	0	0
5	34.95	65.42	**57.14**	56.93	58.45	52.27	36.87	54.78	56.87	58.45	42.95	65.42
10	43.31	69.37	**67.49**	68.86	64.94	65.96	42.08	59.85	60.98	64.94	57.31	69.37
15	51.72	73.07	**74.04**	72.13	70.51	71.97	50.36	64.19	65.39	70.51	66.72	73.07
20	59.05	79.19	**79.19**	79.78	77.93	80.05	57.16	70.69	72.68	77.93	72.05	79.19
25	62.66	86.83	**88.06**	86.53	83.50	84.34	63.76	79.71	82.96	83.50	81.66	86.83
30	70.26	93.75	**99.34**	92.79	94.82	91.68	68.48	89.61	93.06	94.82	88.26	93.75

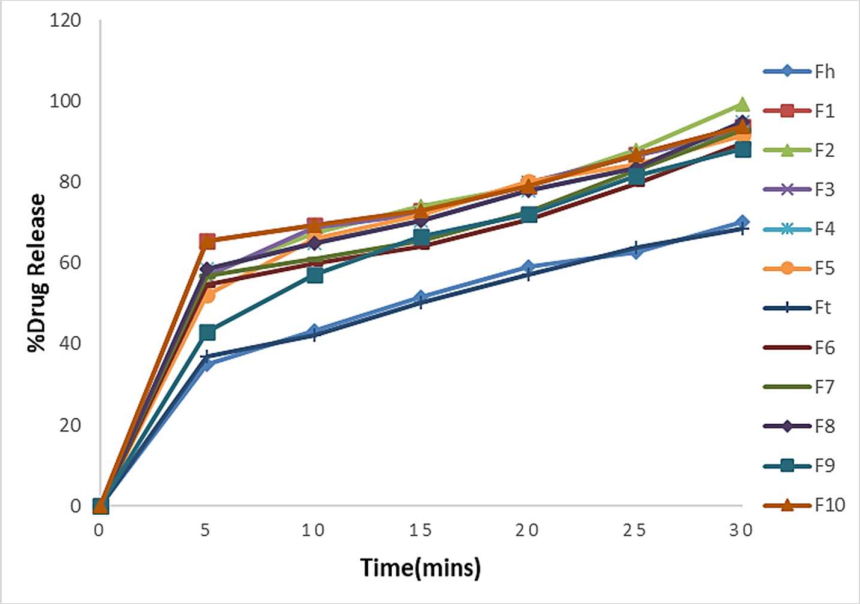

Fig 7: *Invitro* drug release profile for (F1-F10)

Drug release kinetics of etoricoxib
Zero order release kinetics

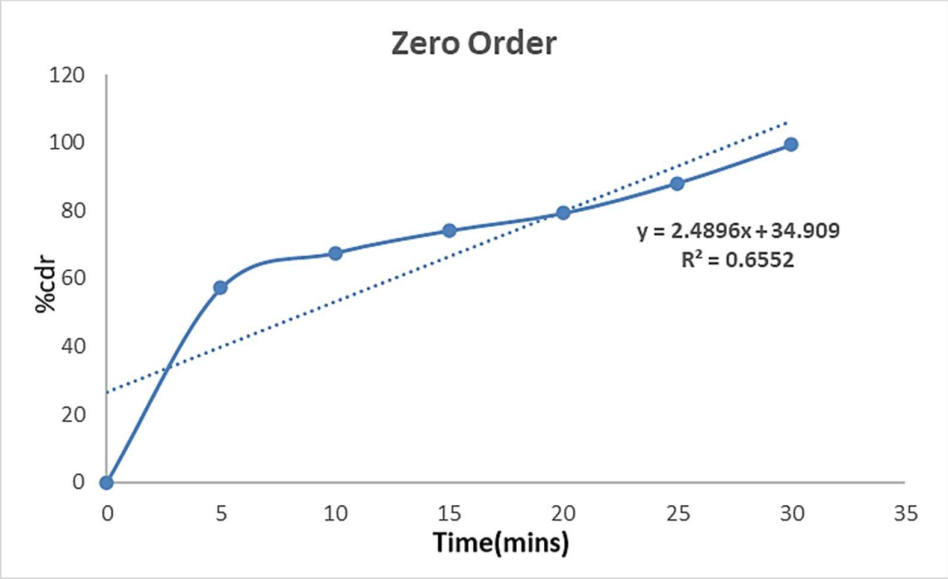

Fig 8: Zero order release profile for best formulation

First order release kinetics studies

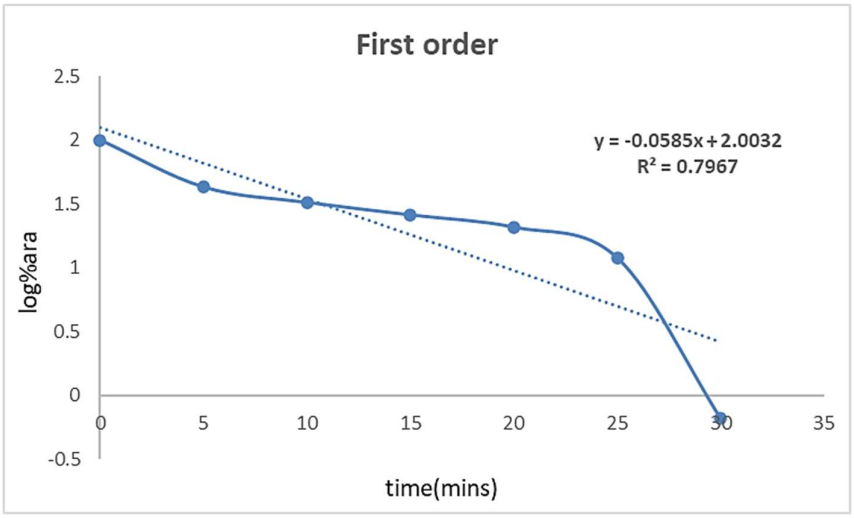

Fig 9: First order release profile for best formulation

The invitro dissolution data for best formulation F2 were fitted in different kinetic models i.e, zero order, first order. Optimized formulation F2 follows first order.

Stability studies

The selected formulations was evaluated for stability studies which was stored at 40ºC at 75%RH tested for 3month and were analyzed for their physical parameters, In vitro dispersion time and drug content at 1 month interval. The residual drug contents of formulations were found to be within the permissible limits which was estimated by seeing drug content uniformity.

Table 3: Stability data of F_2 formulation

Time in months	Formulation F_2 stored at 40^0c/ 75% RH		
	Physical appearance	*In-vitro* Dispersion time	% Drug content
1	+++	7.89	98.95
2	+++	8.24	98.78
3	++	8.48	97.36

Summary

In the present study Oral disintegrating drug delivery system of Etoricoxib were successfully developed in the form of oral disintegrating thin films which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increase bioavailability. Oral disintegrating thin films of Etoricoxib were prepared by using Crospovidone and CCS as super disintegrants. Formulations were evaluated for percent drug content, Surface pH, Folding endurance, Weight uniformity, Thickness, disintegration time, *in-vitro* drug release studies and characterized by FT-IR. The *in-vitro* disintegration time (DT) of best formulation was found to be within 8.10 ± 0.151sec. The maximum increase in the dissolution rate was found with 4% CCS (F2) 99.34% in 30min. On the basis of release data and graphical analysis formulations F2 having 4% w/w of CCS showed good immediate release profile and followed by higuchi release kinetics. The stability study conducted as per the ICH guidelines for 3months and the optimized formulation F2 were selected for stability study. After storage, the formulation F2 was subjected to drug content, Physical appearance, *In-vitro* Disintegrating time. The statistical analysis of the parameters drug content, after storage at 40^0C/75 % RH for three months showed no significant change in drug content and *in-vitro* Dissolution time was observed even after the evaluation for 3 months.

CONCLUSION

In the present work, oral disintegrating thin films of Etoricoxib were prepared by solvent casting method using super disintegrants such as Crospovidone and CCS. Etoricoxib has poor solubility but its bioavailability is limited and hence this method is useful for improving its bioavailability of the drug. The dispersion time of films were reduced by super disintegrants like Crospovidone and CCS.

From the findings obtained, it can be concluded that: FT-IR studies revealed that there is no chemical interaction between Etoricoxib and the excipients used in the study. The prepared film containing Etoricoxib was clear and colourless. Formulated films gave

satisfactorily result for various physico-chemical evaluation of films like physical appearance, and surface texture, weight uniformity, thickness uniformity, folding endurance, surface pH, drug content uniformity, In vitro disintegration time, In vitro drug release The low values of standard deviation for average weight and drug content of the prepared films indicate weight and drug content uniformity within the batches prepared.

Based on *in-vitro* dispersion time, formulation F2 that is with 4% CCS were approximately 7-10sec and show good % cumulative drug release 99.34% in 30min. Short-term stability studies of promising formulation indicated that there is no significant change in drug content and in vitro dispersion time. From the present study, it may be concluded that the Oral disintegrating thin films of Etoricoxib can be prepared by Solvent casting method using super disintegrants CCS was found to be the best among the two super disintegrants. At 4% w/w of CCS with 4.5% HPMC-$_{k15}$ concentration level it showed the least dispersion time of 8.10± 0.151sec and the highest release of more than 99.34% of the drug in 30 min.

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