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Formulation And Evaluation Of Etoricoxib Oro Dispersible Tablets

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Abstract: An attempt has been made for the development of Orodispersible tablet of Etoricoxib by direct compression method.Sodium starch glycolate, Crospovidone, Croscarmellose, and Ludiflashwere used as a Superdisintegrants for the formulation. Twenty formulation having Superdisintegrants at different concentration (3, 6, 9, 12 %) level were prepared using microcrystalline cellulose as a direct compressible vehicle. The prepared batches of tablets were evaluated for Tablet weight variation, content uniformity, hardness, friability. Effects of Superdisintegrants on wetting time, dispersion time, and in vitro release also have been studied in 0.01Hcl buffer medium. Tablet containing Croscarmellose sodium (9%) showed excellent in vitro dispersion time and drug release as compared to other formulation. After the color and flavor optimization study formulations F18 shows short dispersion time (18sec) with maximum drug release in 15 min. FT-IR & DSC studies revealed that there was no physico-chemical interaction between Etoricoxib and Superdisintegrants. It is concluded that Oro dispersible Etoricoxib tablets could be prepared by direct compression method using Croscarmellose sodium as Superdisintegrants. Stability study of F18 formulation showed no significant changes in tablet properties.
Keywords: Etoricoxib, Superdisintegrants, Oro dispersible tablets, drug release.

Introduction

The oral route of administration is the most important method of administering drugs for systemic effects .Tablets and capsules is most widely used dosage form because of its convenience in terms of ease of administration, accurate dosage , self-medication, versality and patient compliance[1,2].

However many patients, particularly pediatric and geriatric and bedridden patients have difficulty in swallowing or chewing solid dosage forms which lead to poor patient compliance.[3,4] This disorder is also applicable to number of pathological conditions including schizophrenic, Parkinson's disease, neurological disorders, Motion sickness, Unconsciousness, Mentally disabled persons.[5,6] Recent advances in novel drug delivery systems (NDDS) aim to develop dosage form of drug for easy administration and to improve patience compliance. One of such approach leads to development of Oro dispersible tablets /disintegrating tablets (ODTs) .[7,8] Oro dispersible tablets dissolve or disintegrate in oral cavity within a minute without the need of water or chewing. Advantages of this dosage form include convenience of administration, patient compliance, accurate dosing as compared to liquids, good stability, easy portability, rapid onset of action ,ability to provide advantages of liquid medication in the form of solid dosage form, ideal for pediatric and geriatric patients and rapid dissolution/absorption of the drug.[9,10]

Some drugs are absorbed from the oral cavity as the saliva passes down into the stomach and in such cases, bioavailability of drug is significantly greater than those observed from conventional tablet & capsule dosage form.[11] ODTs also beneficial for developmentally disabled patients with persistent nausea, those with conditions of motion sickness, sudden episodes of allergic attack and patients who do not have ready access to water.[12]

Etoricoxib (ET), 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine, a effective and selective COX-2 inhibitor administered orally as an anti inflammatory and analgesic properties and is having bitter taste.[13] Etoricoxib is used for a variety of acute and chronic inflammatory diseases such as arthritis, postoperative dental pain, chronic low back pain, acute gout, primary dismonorrea and spondylitis.[14] Etoricoxib is practically insoluble in water and poor dissolution give rise to difficulties in the formulation of dosage form ,etoricoxib very low aqueous solubility limits its therapeutic application.[15]

In the present study an attempt has been made to prepare Oro dispersible tablets of etoricoxib and to study the effect of different Superdisintegrants on the tablet disintegration and dissolution rate as well as to improve the patient compliance .

Materials And Methods

Materials:

Etoricoxib was a gift sample from Fleming Lab Ltd. Croscarmellose sodium, Sodium starch glycolate; Crospovidone was procured from AVEB chemicals Ltd. FDC red, Sunset yellow was procured from Aurobindo Pharma Ltd., Hyderabad. Aspartame and flavours (Ranbaxy, New Delhi, India) were obtained. All other ingredients used were of analytical grade.

Preparation of Orodispersible tablets

Oro dispersible tablets containing 60 mg of etoricoxib were prepared by direct compression method and the various formula compositions used in the study are shown in [Table 1&1a]. The drug and all other excipients were sifted through a 40 mesh sieve and mixed thoroughly .The above blend was pre lubricated with aerosol and lubricated with magnesium stearate and talc .The prepared powder blends was compressed (8 mm diameter, standard round flat faced punches) using multiple punch tablet compression machine (Cadmach Machinery Ltd., Ahmedabad, India). All the tablets were stored in airtight containers for further study.

Table 1. Composition of Etoricoxib ODT tablets

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
Etoricoxib	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Crosspovidone	6				12				18				24			
CCS		6				12				18				24		
SSG			6				12				18				24	
Ludiflash				6				12				18				24
MCC	62	62	62	62	59	59	59	59	56	56	56	56	53	53	53	53
Lactose	62	62	62	62	59	59	59	59	56	56	56	56	53	53	53	53
Aspartame	1	1	1	1	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	4	4	4	4
Talc	3	3	3	3	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	2	2	2	2
Total weight	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 1a. Composition of Etoricoxib ODT tablets with flavor &coloring agent

Ingredients(mg)	F17	F18	F19	F20
Etoricoxib	60	60	60	60
CCS	18	18	18	18
Citric acid	2	2	2	2
Menthol	1	1	1	1
Aspartame	1	1	1	1
Orange	5	5		
Banana			5	5
FDC Red No.40	2		2	
Sunset Yellow		2		2
MCC	51	51	51	51
Lactose	51	51	51	51
Aerosil	4	4	4	4
Talc	3	3	3	3
Mg.Stearate	2	2	2	2
Total wt	200	200	200	200

Evaluation of Etoricoxib oro dispersible tablets

Tablet Hardness

Tablet hardness is defined as the forced applied across the diameter of the tablet in order to break the tablet .The etoricoxib oro dispersible tablets hardness was measured by using Monsanto hardness tester. From each batch the crushing strength of ten tablets with known weights were recorded in kg/cm^2. [16]

Friability

Previously weighed 20 tablets from each batch were taken in Roche friabilator (Roche friabilator, Pharma labs, Ahmedabad, India) where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus.After100 revolutions tablets were recovered. The tablets were then made free from dust and the total remaining weight was recorded .Friability was determined as the percentage loss in weight of the tablets. [17]

$$\text{Percentage friability} = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Initial weight}}$$

Weight Variation Test

Twenty tablets were randomly selected from each batch and their average weight (W_A) was calculated using digital balance. All 20 tablets were weighed individually (W_I) and compared with average weight of tablets and Percent weight variation of each tablet was calculated as follows .[18]

$$\text{Percentage weight variation} = (W_A - W_I) \times 100 / W_A$$

Thickness

Randomly selected ten etoricoxib oro dispersible tablets from each batch were used for thickness determination. Thickness of each tablet was measured by using digital Vernier Caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations, with standard deviations.[19]

Drug content

Ten tablets were taken and powdered; powder equivalent 60mg of etoricoxib was weighed and dissolved in 100 ml of 0.01N HCl buffer. Soluion was filtered, suitably diluted and the drug

content was analyzed by using UV-Visible Spectrophotometer (Elico, India) at 233 nm. Each measurement was carried out in triplicate.[20]

Wetting Time

Circular tissue papers of 10cm diameter were placed in a Petridish (with internal diameter 6.5cm) containing 10.0 ml of water containing amaranth a water soluble dye. A tablet was carefully placed on the surface of tissue paper. The time required for develop red color on the upper surface of the tablet was noted as the wetting time.[21]

In -Vitro Disintegration time

Disintegration time of etoricoxib oro dispersible tablets was measured in 900ml of 0.01N HCl buffer using USP tablet disintegration test apparatus (Electrolab, India) without disk at room temperature. The disintegration time of six tablets was recorded and average was reported.[22]

In -Vitro Drug Release:

In vitro drug release studies were carried out using USP dissolution apparatus type II (Electrolab, Mumbai, India) at 37 ± 0.5ºC. The dissolution test was performed using 900 ml of 0.01N hydrochloric acid buffer pH 1.2 at 50 rpm. The samples (5ml) were withdrawn at predetermined intervals (5min) and replaced with an equal volume of buffer. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.01N hydrochloric acid. The drug release at different time intervals was measured using an UV spectrophotometer (Elico, Ahemadabad, India) at 233 nm. The dissolution study was performed in triplicate.[23]

Flavor, color and mouth feel optimization

To assess the color, flavor and mouth feel effect of prepared Etoricoxib Orodispersible tablets; different age group healthy volunteers were employed. The evaluation test was performed according to the guidelines and the reports of the volunteers were recorded.[24]

Drug excipients compatibility study

Infrared spectrum of etoricoxib and formulations with the Croscarmellose sodium, Sodium starch glycolate, Crospovidone, Ludiflash was analyzed on Fourier transform infrared spectrometer (FTIR) using KBR dispersion method. The pellets were scanned over a wavelength range of 400 to 4,000 cm-1 .

DSC studies also performed to investigate the physical state of the drug in the tablets and to know the interactions of drug with Superdisintegrants in the formulation. Thermal properties etoricoxib and the formulation were evaluated by Differential scanning calorimetry (DSC) . The analysis was performed at a rate 5^0C min-1 from 500 ^{0}C to 2000 ^{0}C temperature range under nitrogen flow of 25 ml min.

Stability study

Etoricoxib oro dispersible tablets were formulated and accelerated stability studies were carried out as per ICH guidelines. The prepared Etoricoxib oro dispersible containing Croscarmellose sodium (9%) F18 was selected for stability study on the basis of in vitro dispersion time and drug dissolution studies. The oro dispersible tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month. The samples were analyzed for its hardness, drug content, friability and In vitro dispersion time.[25,26]

Results And Discussion

The physicochemical characterizations of different batches of Etoricoxib oro dispersible tablets are given in (Table 2-3).

The thickness of the ODTs tablets were ranged between 3.16±0.09 to 3.32±0.25 mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 199±0.92 to 202±0.92. All the tablets passed weight variation test as the percentage weight variation was within the pharmacopoeial limits (7.5%). Hardness of all the prepared ODTs tablets was found to be satisfactory .The hardness were ranged from 3.0±0.32 4.0±0.43 kg/ cm^2. The percentage friability of all the formulations was ranged from 0.45 % to 0.75 %. In the present study, the percentage friability for all for formulations was within the prescribed limits, indicates the tablets possess good mechanical strength. The percentage of drug content for F1 to F16 was found to be in between 98.2±0.97 to 100.1±0.9 of Etoricoxib it complies with official specification. Wetting time of the tablets were ranged 18±0.9 to 56±1.8 sec and disintegration time were 46±1.4 to 09±0.7 sec which indicated fast wetting and disintegration of tablet formulations in mouth. The cumulative percentage of the drug released

determined by dissolution was ranging from 74.7±1.6 to 100.5±0.9% after 15min as shown in figure 1.1-1.5. Superdisintegrants at different concentration level (3, 6, 9 and 12% w/w) were used to assist disintegration.

Table 2 : Physico chemical properties of Etoricoxib ODT tablets

Formulation code	Hardness (kg/cm2)	Thickness (mm)	% Friability	Weight variation
F1	3.5±0.37	3.26±0.82	0.75	201±0.92
F2	4.0±0.43	3.28±0.23	0.59	200±0.91
F3	3.5±0.37	3.18±0.62	0.48	202±0.92
F4	3.5±0.37	3.24±0.74	0.49	201±0.92
F5	3.5±0.37	3.24±0.34	0.45	199±0.91
F6	3.0±0.32	3.27±0.45	0.53	200±0.91
F7	4.0±0.43	3.28±0.2	0.63	201±0.92
F8	3.5±0.37	3.17±0.62	0.55	202±0.92
F9	3.5±0.37	3.26±0.59	0.64	201±0.92
F10	3.0±0.32	3.32±0.25	0.57	200±0.91
F11	3.5±0.37	3.31±0.25	0.51	201±0.92
F12	3.0±0.32	3.16±0.63	0.64	199±0.92
F13	3.0±0.32	3.16±0.09	0.54	200±0.91
F14	3.5±0.37	3.18±0.25	0.65	201±0.92
F15	4.0±0.43	3.22±0.15	0.54	199±0.92
F16	3.5±0.37	3.19±0.21	0.63	201±0.92

Table3:Physico chemical properties of Etoricoxib ODT tablets

Formulation code	% Drug content	Disintegration time	Wetting Time
F1	98.2±0.97	32±1.1	48±1.5
F2	100.1±0.9	30±0.9	42±1.3
F3	99.4±0.98	34±1.1	45±1.4
F4	97.3±0.96	46±1.4	56±1.8
F5	100.1±0.99	23±0.7	35±1.3
F6	99.9±0.98	21±0.5	32±1.2
F7	99.2±1.0	26±0.9	38±1.4
F8	98.1±0.97	39±1.4	49±1.7
F9	99.7±0.98	19±0.7	22±1.2
F10	99.9±0.98	15±0.4	20±1.1
F11	100.1±0.9	20±0.5	28±1.3
F12	97.2±0.96	20±0.9	42±1.9
F13	100.1±0.99	14±0.8	21±1.2
F14	99.6±0.98	09±0.7	18±0.9
F15	99.3±0.98	16±0.8	25±0.8
F16	98.7±0.97	22±1.2	36±1.8

The formulation prepared with lower concentration of Sodium starch glycolate, Crospovidone, Croscarmellose sodium and ludiflash yields rapid disintegration and dissolutions. However DT was a little more in the lower concentrations of Superdisintegrant formulations. To improve the disintegration time, the formulations were prepared with increased concentrations of Superdisintegrants such as 6, 9 and 12%. Increased concentrations of Superdisintegrants improved the disintegration time without any changes in the physico-chemical properties. All formulations had disintegration time of less than 46 second. Among the four Superdisintegrants we have used, Croscarmellose sodium showed maximum efficiency. The mouth feel of the formulations prepared with Sodium starch glycolate, Croscarmellose sodium is resulted smooth and fine particles where as the formulations prepared with Crospovidone, yields particulate matter on the tongue. Formulation F10 containing 9% w/w

Croscarmellose sodium showed the optimum disintegration time of 15±0.4. Formulation F10 was selected for further color and flavor optimization study. Sweetener aspartame was used along with citric acid and menthol.

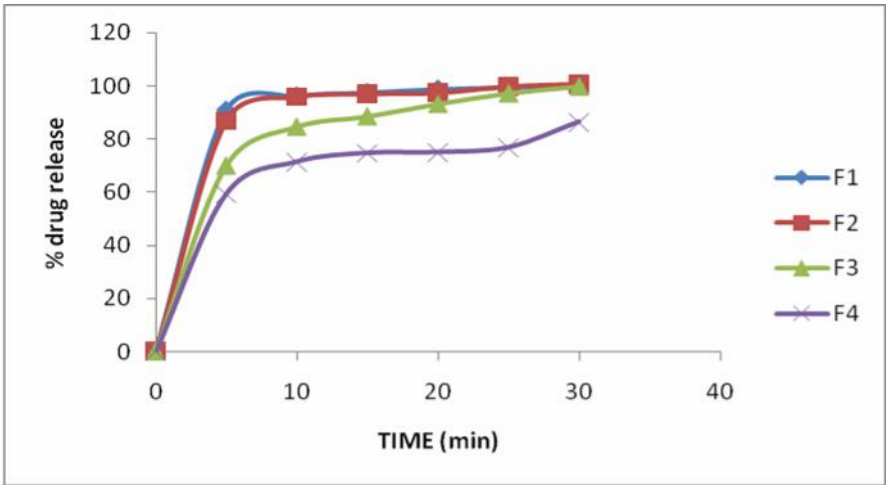

Fig 1.1 Comparative release profile of formulation F1 to F4

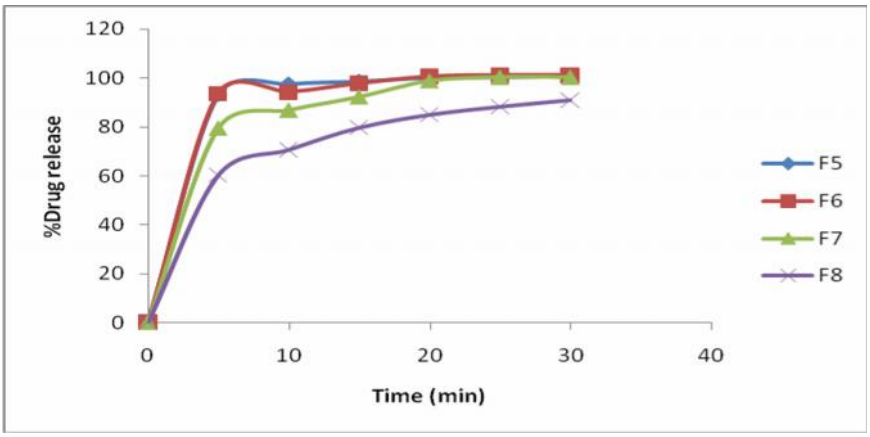

Fig 1.2 Comparative release profile of formulation F5 to F8

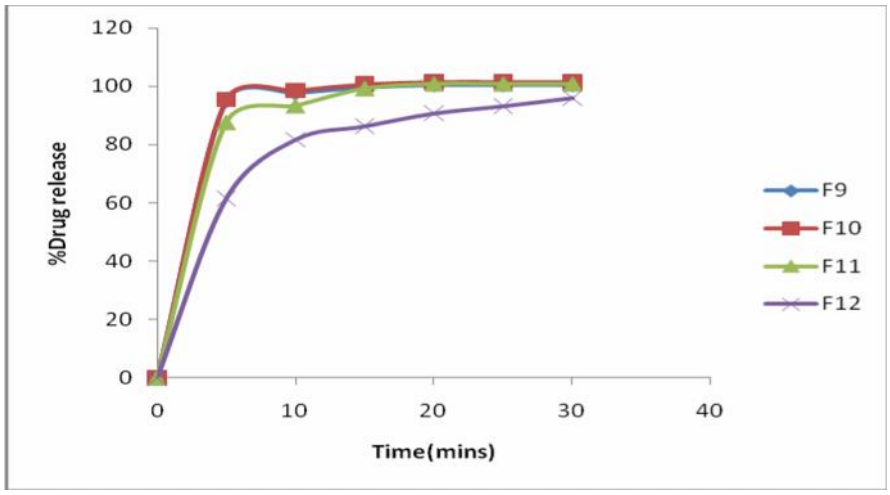

Fig 1.3 Comparative release profile of formulation F9 to F12

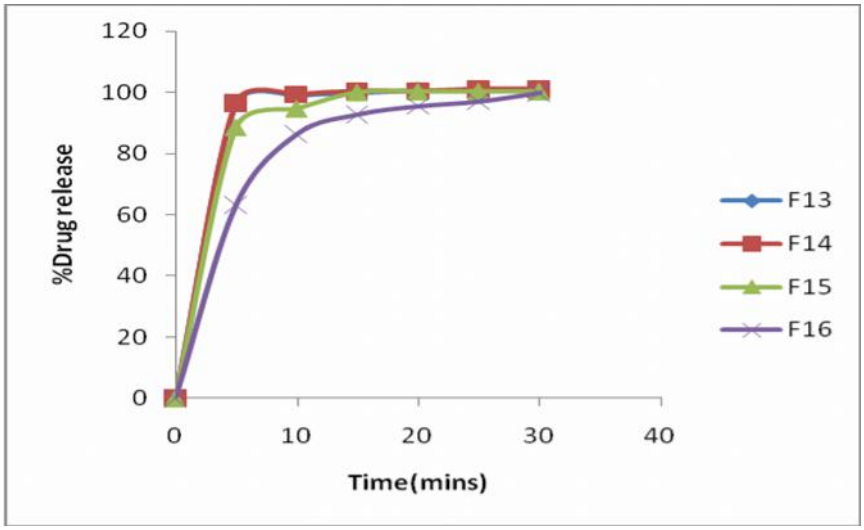

Fig 1.4 Comparative release profile of formulation F13 to F16

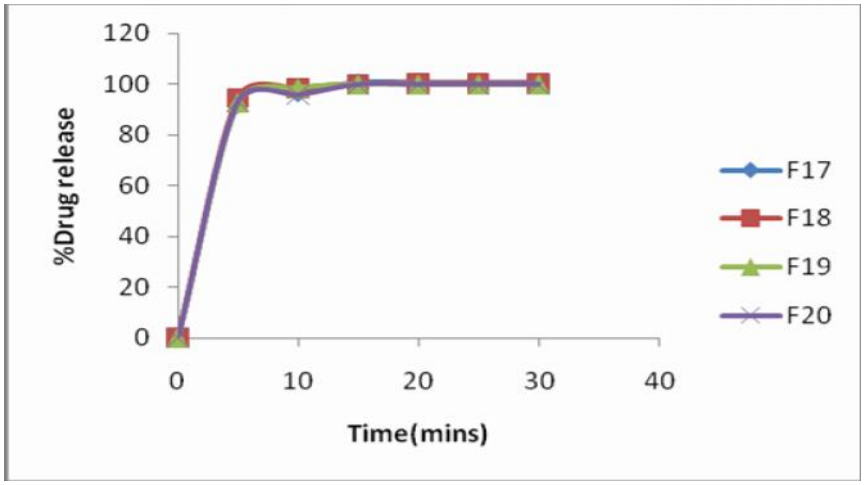

Fig 1.5 Comparative release profile of formulation F17 to F20

Table4:Physico chemical properties of Etoricoxib ODT tablets for color & flavor optimization

Parameter	F17	F18	F19	F20
Weight Variation (mg)	201±0.92	201±0.92	200±0.91	202±0.92
Friability (%)	0.54	0.65	0.54	0.63
Hardness (Kg/cm^2)	3±0.32	3.5±0.37	4±0.43	3.5±0.37
Thickness (mm)	3.26±0.59	3.32±0.25	3.31±0.25	3.16±0.63
Disintegration time (Sec)	22±1.2	18±1.1	19±1.1	16±0.9
Wetting time (sec)	23±1.4	25±1.5	24±1.4	26±1.5
Assay (%)	100.2±0.99	100.1±0.9	99.4±0.98	99.6±0.98
Taste/mouth feel	Good	Excellent	Average	Average

Different flavoring agents such as banana, orange, were incorporated into the formulations prepared with Croscarmellose sodium (9%) and aspartame as sweetener. There is no significant change was observed in the physico-chemical properties (Table4). In-vivo taste and flavor evaluation was performed on the prepared tablets at different time intervals. The formulations prepared with Croscarmellose sodium -Aspartame-Orange flavored scored excellent during in-vivo evaluation. The tablets were incorporated with FDC Red No.40, Sunset yellow lake as coloring agents. In the color identification most of the people in the age group of 50-60 years likes FDC

Red No.40. People in the age group of 25-30 years like Sunset yellow lake (Data not shown). The optimized formulations F18 contain 9 % Croscarmellose sodium with orange flavor & Sunset yellow exhibited least disintegration time (18sec) and faster drug dissolution (100% in 15min) will lead to enhance the patience compliance.

FT-IR results revealed that there was no significant difference in the peaks of etoricoxib and Superdisintegrants in ODTs tablets compared to pure etoricoxib as shown in figure 2.1-2.2. It was found that there was no interference to the drug with excipients and Superdisintegrants used in the formulations.

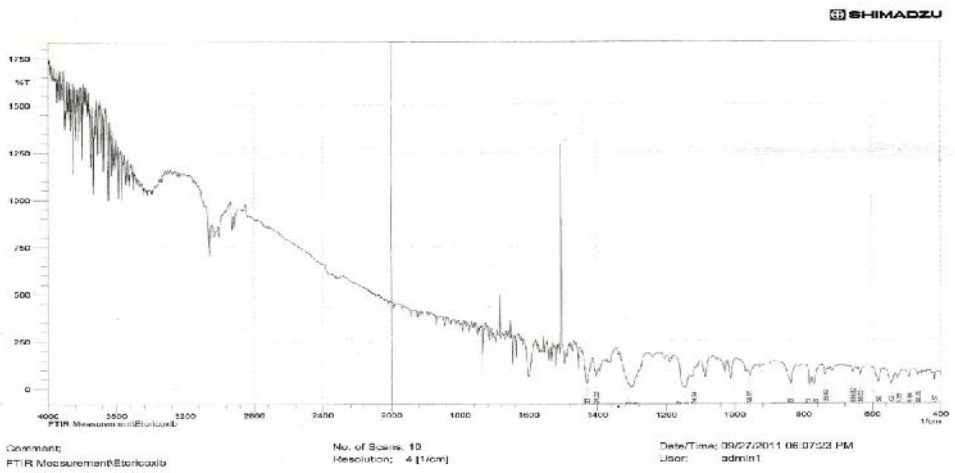

Fig 2.1. FTIR spectra of pure drug Etoricoxib

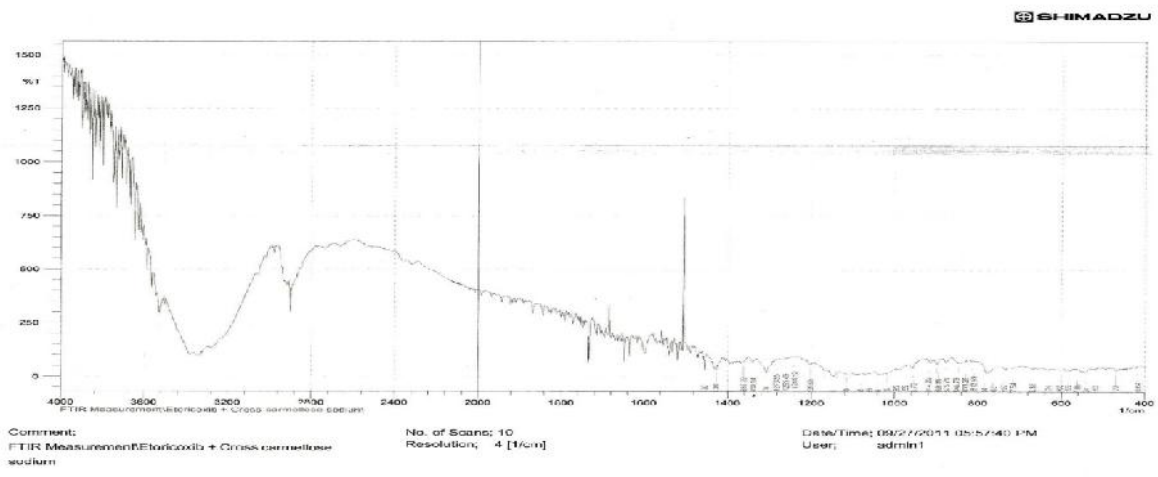

Fig 2.2. FTIR spectra of Etoricoxib + Cross carmellose sodium

Pure powdered etoricoxib showed a melting endotherm at 137.91^{0}C, and Superdisintegrants in different formulation also showed their identical peaks at defined temperature range as shown in figure 3.1-3.5. Presence of all peaks indicates that all ingredients are compatible with drug and there is no incompatibility between the selected Superdisintegrants and ingredients.

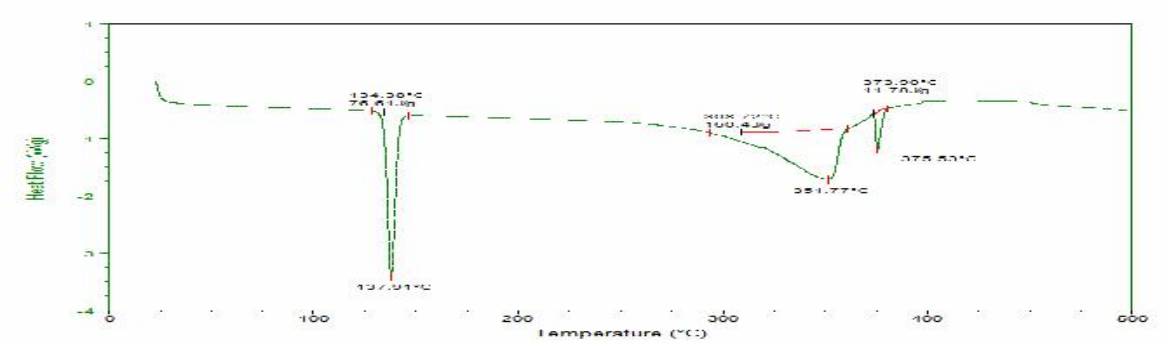

Fig 3.1. DSC study of Pure Drug Etoricoxib

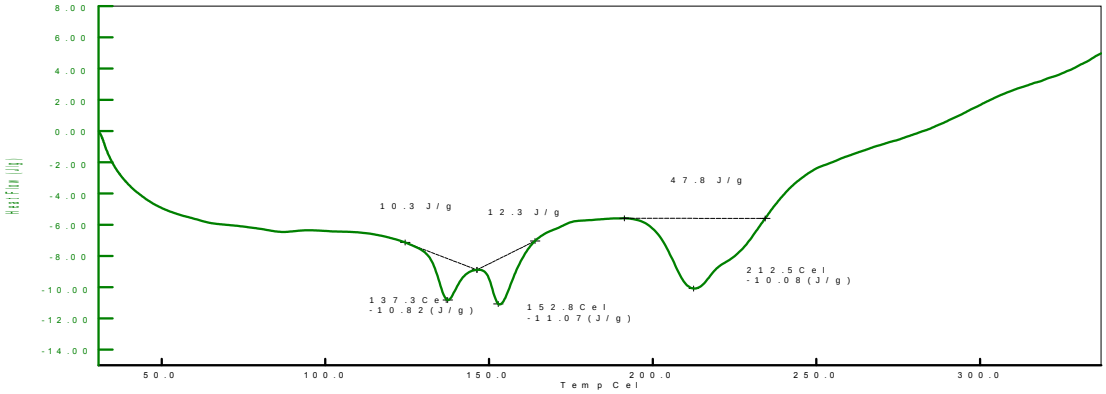

Fig 3.2. DSC study of Etoricoxib + Crosspovidone

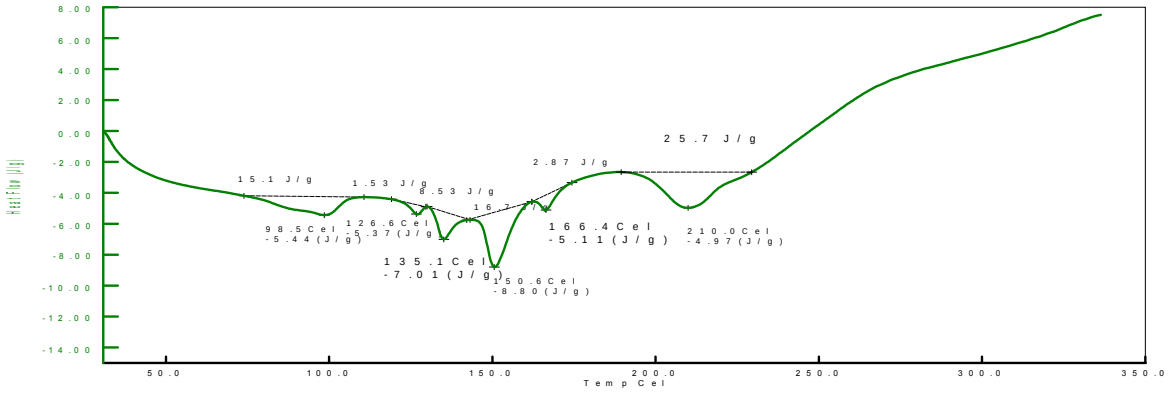

Fig 3.3. DSC study of Etoricoxib + Cross carmellose sodium

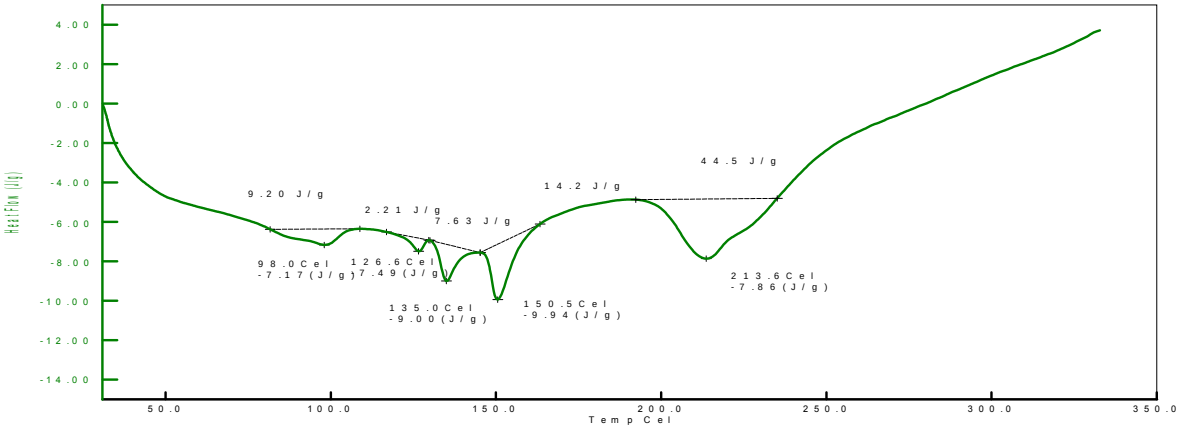

Fig 3.4. DSC study of Etoricoxib + Ludiflash

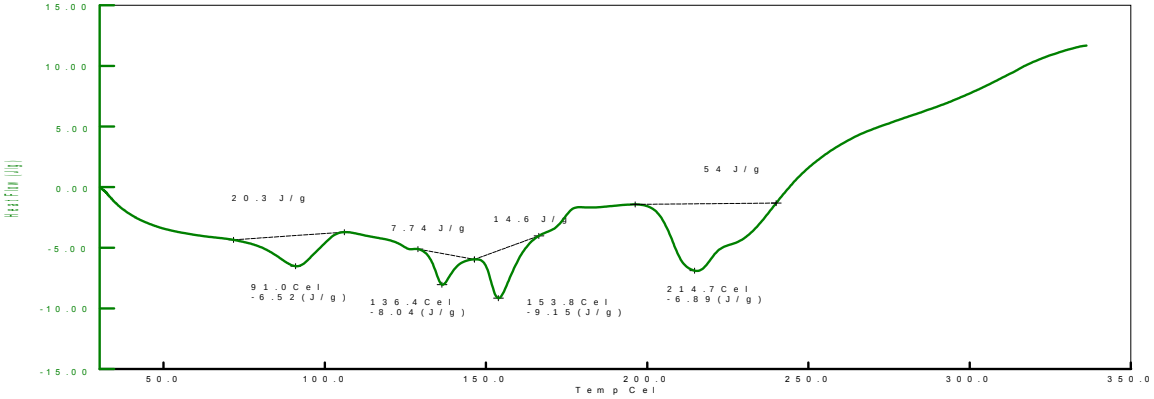

Fig 3.5. DSC study of Etoricoxib + Sodium starch glycolate

Stability studies performed on batch F18 as per ICH guidelines for 90 days at 40°C±2°C / 75% RH±5%. The etoricoxib oro dispersible tablets did not show any significant change in physicochemical parameters and other tests. Thus, it was found that the oro dispersible tablets etoricoxib (F18) were stable under short-term storage conditions for at least 3 months.

Table 5 : Stability study results

Formulation code	Stability period	Hardness	Friability %	Drug content	Disintegration time
F18	0	3.5	0.65	100.1	18
	30 Days	3.5	0.71	99.7	20
	60 Days	3.7	0.79	98.7	21
	90 Days	4.0	0.86	97.9	23

Conclusion

Oro dispersible tablets of etoricoxib were successfully prepared with different Superdisintegrants by direct compression method .The present investigations were helped in understanding the effect of concentration of different super disintegrants on the dispersion time and drug release profile. An overall result indicates that formulation F18 contain 9 % Croscarmellose sodium with orange flavor exhibited optimium disintegration time and faster drug dissolution will lead to enhance the patience compliance. FTIR & DSC studies revealed the compatability between etoricoxib and Superdisintegrants of the developed ODTs tablets. The stability studies were carried out according to ICH guideline and selected F18 formulation were stable at 40°C/75% RH up to 3 months. Taste masked oro dispersible tablets of etoricoxib formulated in this investigation may possibly help in administration of etoricoxib in a more palatable form without water.

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References

1. Chein Y W; Oral Drug Delivery and Delivery Systems. 2nd ed, New York: Marcel Dekker; 1992.
2. Anupama kalia, shelly khurana, neena bed. Formulation and evaluation of mouth dissolving tablets of oxcarbazepine.International journal of pharmacy and pharmaceutical science, 2009; 1(1):12-23
3. Seager H. Drug-delivery Products and the Zydis Fast-dissolving Dosage Form. J Pharm Pharmacol 1998; 50:375-382.
4. Velmurugan, Sundar Vinushitha "Oral Disintegrating Tablets: An Overview" International Journal of Chemical and Pharmaceutical Sciences , Vol.1 (2),2010,
5. Kaur T, Bhawandeep G, Sandeep K, Gupta G D; Mouth dissolving tablets: a novel approach to drug delivery.Int J Curr Pharm Res. 2011;3(1):1-7.
6. P.M. Dandagi : V.S. Mastiholimath ; S.A. Srinivas A.P. Gadad: A.M. Godbole, S.P. Hiremath, S.T. Bhagawati. Orodispersible Tablets: New-fangled Drug Delivery System-A Review" Indian J. Pharm. Educ. Res.2005; 39(4) : 177-181
7. Chang RK, Guo X, Burnside BA and Cough RA. Fast dissolving tablets. Pharm. Tech. 2000; 24:52-58.
8. Dobetti L. Fast-melting tablets: Developments and technologies. Pharma. Tech. 2001; (Suppl.): 44-50.
9. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. Eur. J. Pharm. Sci. 2002; 15: 295-305.
10. Bradoo R, Shahani S, Poojary S, Deewan B, Sudarshan S. Fast Dissolving Drug Delivery Systems. JAMA India 2001; 4(10): 27-31
11. Leon Lachman, Herbert A, Lieberman, and Joseph LK. The Theory and Practice of Industrial Pharmacy 1991; 3: 325-326.
12. .P.M. Dandagi : V.S. Mastiholimath ; S.A. Srinivas A.P. Gadad: A.M. Godbole, S.P. Hiremath, S.T. Bhagawati. Orodispersible Tablets: New-fangled Drug Delivery System-A Review" Indian J. Pharm. Educ. Res.2005; 39(4) : 177-181
13. P. Leclercq and M. G. Malaise, Etoricoxib (Arcoxia), Rev. Med. Liege 59 (2004) 345–349.
14. Leclercq P., Malaise M. G.: Etoricoxib (Arcoxia). Rev. Med. Liege (2004), 59 (5), 345–49.
15. Agrwal NGB and Porras AG (2001). Dose proportionality of oral etoricoxib, A Highly selective COX-2 inhibitor, in healthy volunteers. J. Clin. Pharmacol., 41: 1106- 1110.
16. Sahithya Chowdary,S Velmurugan,Santosh giri.Formulation evaluation of sustain release matrix tablets of Stavudine.Inter continental journal of pharmaceutical science .2012, 1: 9-17. 17.
17. Leon Lachman, Herbert A, Lieberman, and Joseph LK. The Theory and Practice of Industrial Pharmacy 1991; 3: 325-326.
18. S.Velmurugan, B.Deepika, K.Naga Raju "Formulation and *in vitro* evaluation of buccal tablets of Piroxicam, International Journal of ChemTech Research. 2010; 2(3):1958-1968, 2010.
19. P.D. Chaudhari, S. P. Chaudhari, S. D. Lanke *et.al. Indian J Pharm Educ Res.,* 41(4), 319-328(2007).
20. Indian Pharmacopoeia. 4th Ed, Ministry of Health and Family Welfare, Govt. of India. The controller of publications, New Delhi, 1996, pp. A-54.
21. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. Eur J Pharm Sci, 2002; 15: 295-305
22. Simone SS, Peter CS, Fast dispersible ibuprofen tablets, European Journal of Pharmaceutical Sciences, 2002;15: 295–305.
23. In vitro dissolution. The United States pharmacopoeia, United States pharmacy convention, inc., Asian edition, 2000; 1941- 1943
24. World Medical Association Declaration of Helsinki. 1964. Ethical principles for medical research involving human subjects. Adopted in the 18th WMA General Assembly and subsequent amendments
25. P.A. Swamy, S.H. Areefulla, S.B. Shrisand, S. Gandra and B. Prashanth, 2007. Ind. J. Pharm. Sci. 2007; 69(6): 836-840.
26. S. Malke, S. Shidhaye and V.J. Kadam, Ind. J. Pharm. Sci. 2007; 69(2): 211-214.

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