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Research Article

FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLET OF ETORICOXIB USING NATURAL SUPERDISINTEGRANTS

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ABSTRACT

The objective of the present investigation was to prepare fast disintegrating tablets of Etoricoxib by direct compression using isolated mucilage of *Plantago ovata* and gelatinized starch as a natural superdisintegrants. The tablets were evaluated for weight variation, mechanical strength, *in vitro* disintegration time, wetting time, water absorption ratio, and drug release characteristics. Hardness and friability data indicated good mechanical strength of tablets. FTIR studies indicated no interaction between drug and excipients. The results of *in vitro* disintegration time indicated that the tablet disintegrates rapidly within 37.49 to 17.45 seconds. Dissolution study revealed faster release rate of Etoricoxib from the tablets as compared to pure drug tablets devoid of superdisintegrants. Gelatinized starch was found to be more beneficial than that isolated mucilage of *Plantago ovata* .

Keywords: Etoricoxib, Gelatinized starch, *Plantago ovata* mucilage, Direct compression, Fast disintegrating tablet.

INTRODUCTION

Recently, European pharmacopoeia (5.0, 2005) adopted the term "Orodispersible Tablet" as a tablet to be placed in the mouth where it disappears rapidly before swallowing, stating a maximum disintegration time of 3min as determined in a conventional disintegration test apparatus[1].

Orodispersible tablets are also known as Quick dissolves, Fast melts, Fast dissolving, Fast disintegrating, Rapid dissolve or Orally dissolving tablets. Their characteristics advantage such as administration without water anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water. The benefit in terms of patients compliance rapid onset of action, increase bioavailability and good stability, make these tablets popular as a dosage form of choice in the current market[2].

Etoricoxib(5-chloro-2[6-methyl pyridin-3-yl]-3-[4-methyl sulfonyl phenyl]pyridine) is a novel, selective second generation cyclo-oxygenase -2 inhibitor administered orally as an analgesic and anti-inflammatory drug that is used for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. Etoricoxib can be categorized as a class II drug according to the biopharmaceutical classification system. These drugs are poorly water soluble but once dissolves they are easily absorbed over the gastrointestinal membrane[3].

Various natural substances gum karaya, modified starch and agar have been used in the formulations of mouth dissolving tablets. Mucilage of natural origin is preferred over semi-synthetic and synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and non-toxic in nature. In the present investigation, the preparation and evaluation of fast disitegrating tablets by using different concentrations of natural superdisintegrants that is *plantago ovata* husk and *gelatinized starch* was studied. The reasons for selection of *plantago ovata* husk because it's high swelling index[4]. Mucilage of *plantago ovata* has various characteristics like binding, disintegrating and sustaining properties[5]. Hence, in present study, mucilage of *plantago ovata* was used to develop fast dissolving tablets of Etoricoxib. The objective of present work was to develop fast dissolving Etoricoxib tablet by direct compression method and to study the effect of functionality differences of natural superdisintegrant *plantago ovata* mucilage on the tablet properties.

MATERIAL AND METHODS

Materials

Etoricoxib was obtained as a gift sample from Cadila Healthcare Ltd, Ahmadabad, Isapgol husk (Plantago Ovata) procured from local market, Lactose anhydrus, Sodium saccharine, Microcrystalline cellulose (PH101), Magnesium Stearate and Talc were purchased from S.D. Fine Chemicals, Mumbai.

Methods

Isolation of mucilage

Mucilage was isolated by soaking seeds of *plantago ovata* in water (20-30 times) for at least 48 hrs, boiled for 2 hrs subsequently mucilage was released into the water completely. With the help of the muslin cloth the mucilage was squeezed out and separated from seeds. The mucilage collected and precipitated using 3 times of 95% ethanol. Collected mucilage was dried in the oven at 50-55°. Dried mucilage was scraped and powdered using pestle and mortar. Powder was sieved using mesh no.100[6].

Preparation of gelatinized starch[7]

10gm of corn starch was added into 40ml of distilled water and was heated with continuous stirring till the uniform paste is obtained. Then to this paste 60ml of boiling distilled water was added and the resulting paste was stirred for 15min and spread uniformly over the slab and was kept for drying in the hot air oven at 45^{0}C for 12Hrs.The resulting thin films of gelatinized starch was scrapped out, and powdered with the help of mortar and pestle. This powder was then passed through # no 100 and stored at 40^{0}C, in air tight container until use.

Characterization of drug and excipients

Fourier transform infra red spectroscopy (FTIR)

FTIR spectra of pure Etoricoxib and physical mixture of drug and excipients were recorded on Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400- 4000 cm^{-1} at spectral resolution of 2cm^{-2} and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu. The spectrums are shown in Fig 1,2, and 3,4,5 and 6.

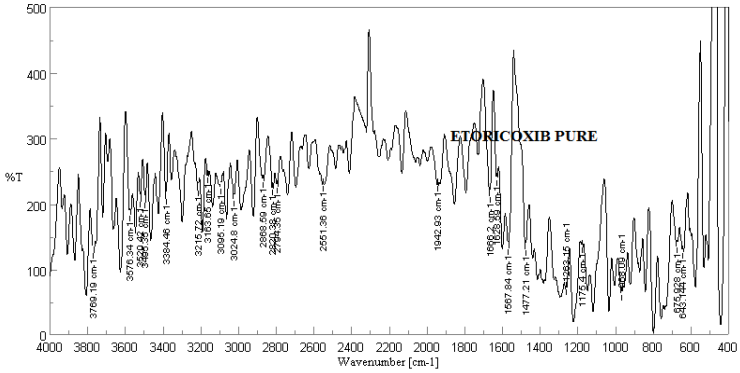

Fig. 1: FTIR of Etoricoxib Pure

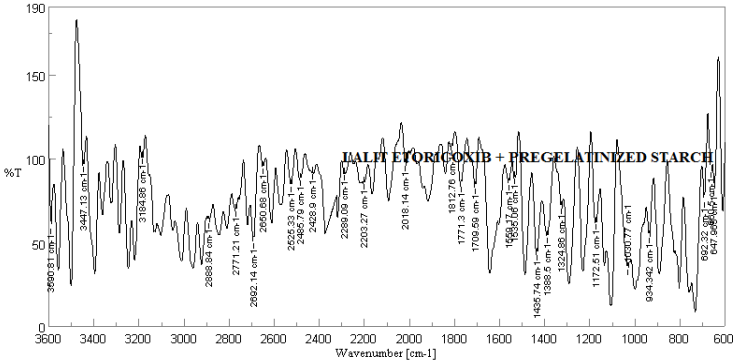

Fig. 2: FTIR of Etoricoxib + Pregelatinized starch

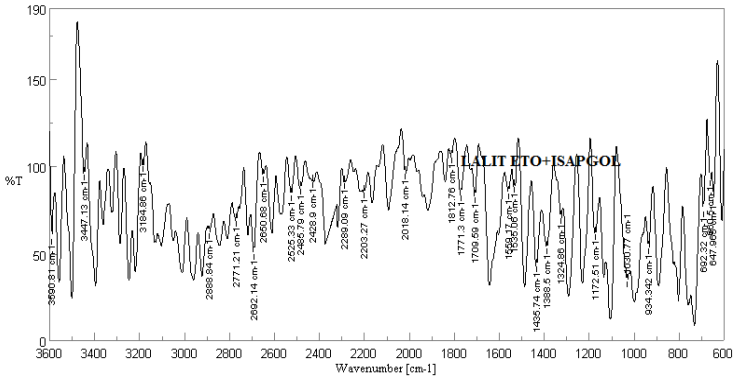

Fig. 3: FTIR of Etoricoxib + Isapgol mucilage

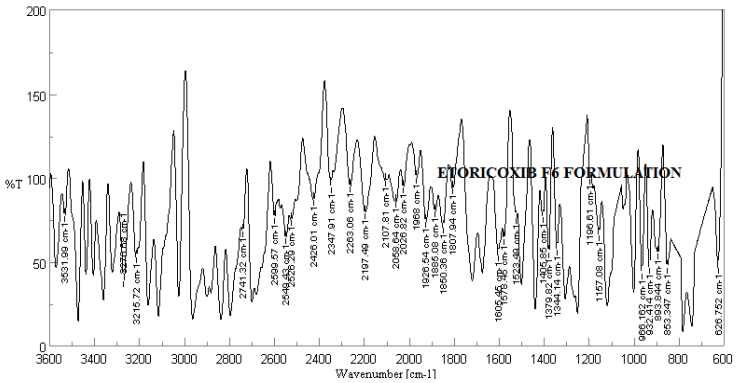

Fig. 4: FTIR Etoricoxib F6 formulation

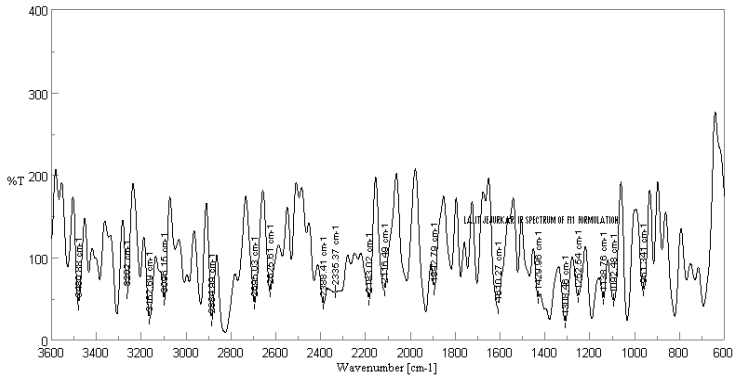

Fig. 5: FTIR F10 formulation

Preparation of tablet

Etoricoxib, Sodium Saccharin, Microcrystalline cellulose, Lactose anhydrous were shifted through sieve #100 separately and admixed together by means of geometrical mixing for about 15min to make a uniform blend.

Magnesium Stearate and Talc both have passed through sieve #100 separately and mixed with the above blend for sufficient time usually 5-7 min .The powder blend was evaluated for various flow properties as follows[8,9] and observations were reported in Table No.1.The resulting uniform blend of composition per tablet as mentioned in Table-2 were directly compressed using a 10mm, round, flat faced tooling to make the tablet of said compression specifications as mentioned in Table-3, using 10 station ……machine. The tablet press setting was kept constant across all formulations.

Evaluation of powder blend

Prepared powder blend was evaluated for the bulk density, tapped density, angle of repose, compressibility index and Hausner ratio[8,9] and results were shown in table no.1.

Table 1: Evaluation of Powder blend

Formulation Code	Evaluation Parameters					
	Angle of Repose	Bulk Density(gm/cm³)	Tapped Density(gm/cm³)	%Compressibility Index	Hausner Ratio	Flowability
F1	26⁰33′	0.50	0.53	5.66	1.06	Excellent
F2	25⁰03′	0.51	0.54	5.55	1.05	Excellent
F3	25⁰87′	0.52	0.55	5.45	1.05	Excellent
F4	25⁰31′	0.51	0.54	5.55	1.05	Excellent
F5	25⁰12′	0.50	0.53	5.66	1.06	Excellent
F6	25⁰24′	0.52	0.55	5.45	1.05	Excellent
F7	25⁰92′	0.50	0.53	5.66	1.06	Excellent
F8	25⁰49′	0.51	0.54	5.55	1.08	Excellent
F9	25⁰12′	0.52	0.55	5.45	1.05	Excellent
F10	25⁰72′	0.50	0.53	5.66	1.06	Excellent
F11	25⁰76′	0.50	0.53	5.66	1.06	Excellent

Table 2: Design of Etoricoxib Orodispersible tablet

Tablet Ingredients	Formulation Code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Etoricoxib	60	60	60	60	60	60	60	60	60	60	60
Microcrystalline cellulose	75	75	75	75	75	75	75	75	75	75	75
Sodium Saccharin	6	6	6	6	6	6	6	6	6	6	6
Lactose	150	147	144	141	138	135	147	144	141	138	135
Gelatinized Starch	-	-	-	-	-	-	3	6	9	12	15
Isapgol Mucilage	-	3	6	9	12	15	-	-	-	-	-
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6	6	6	6
Total	300	300	300	300	300	300	300	300	300	300	300

Evaluation of fast disintegrating tablets

Q.C tests for fast dissolving tablet of all formulations were performed and the average values were calculated. Weight variation was determined by weighing 20 tablets individually the average weight and percent variation of each tablet was calculated. Hardness was determined by taking six tablets from each formulation using a Pfizer Hardness tester and the average of it was determined.

Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche Friabilator) which was rotated for 4min at 25 rpm. After dusting the total remaining mass of tablet was recorded and the percent friability was calculated. Results are shown in table no 3.

Drug Content

Three tablets were powdered and drug equivalent to 60mg was weighed and transferred into a 100ml volumetric flask and diluted up to 60ml using Methanol. Subsequently the solution in the vol.flask was filtered and 1ml of solution diluted suitably and analyzed at 284nm using UV-Visible spectrophotometer (Shimadzu 1601). The

drug content of the sample was estimated from their standard curve. Results are shown in table no 3.

Wetting time and water absorption ratio (R) [10]

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time.Water absorption ratio (R) was then determined according to the following equation:

$$R = 100 \times (w_a - w_b) / w_b$$

Where; w_b and w_a were tablet weights before and after water absorption, respectively, Results shown in table no. 4.

In Vitro Dissolution Study

USP type II (Paddle) apparatus was used and paddle was allowed to rotate at 50 rpm. Hcl 0.1 N (900 ml) was used as a dissolution medium. Determination of amount of drug dissolved from tablets was carried out by UV 1601 spectrophotometer at 234.4 nm. Results shown in Fig: 6

Table 3: Evaluation of tablets

Formulation code	Evaluation Parameters					
	Hardness (Kg/cm^2) Mean(n=5)±S.D	Thickness (mm) Mean(n=5)±S.D	%Friability	Disintegration Time (in Sec) Mean(n=5) ± S.D	Weight Variation (mg) Mean(n=20) ±S.D	%Drug Content Mean(n=3)±S.D
F1	4 ± 0	4.98 ± 0.06	0.44	92.47±0.83	299.25±2.17	99.23±0.17
F2	4.2 ± 0.2	4.98 ± 0.09	0.53	37.49±0.28	301.65±1.78	100.17±1.21
F3	4 ± 0	4.98 ± 0.05	0.64	35.17±0.93	299.50±2.44	99.38±0.45
F4	4 ± 0	4.93 ± 0.02	0.72	33.43±0.39	302.50±2.05	100.31±0.29
F5	4.2 ± 0.2	4.95 ± 0.03	0.83	30.91±0.19	300.25±1.60	100.29±0.78
F6	4 ± 0	4.83 ± 0.04	0.89	28.83±0.79	299.15±1.82	99.11±0.48
F7	4.2 ± 0.2	4.96 ± 0.07	0.42	33.53±0.89	299.65±0.92	99.25±0.15
F8	4 ± 0	4.87 ± 0.08	0.55	27.56±0.47	300.85±1.27	99.13±0.67
F9	4 ± 0	4.98 ± 0.06	0.59	19.97±0.78	301.14±0.79	100.19±0.13
F10	4.2 ± 0.2	4.89 ± 0.04	0.71	18.49±0.29	302.25±2.05	100.13±0.11
F11	4 ± 0	4.98 ± 0.03	0.81	17.47±0.65	300.21±1.87	100.21±0.16

Table 4 : Tablet Evaluation Parameters

Formulation Code	Evaluation Parameters	
	Wetting Time (in Sec)	Water Absorption Ratio
F1	24.94	60.72
F2	23.79	67.43
F3	21.57	71.67
F4	18.51	75.22
F5	17.94	85.94
F6	16.54	94.53
F7	22.56	69.53
F8	20.23	75.47
F9	17.72	78.47
F10	15.60	100.31
F11	14.05	105.05

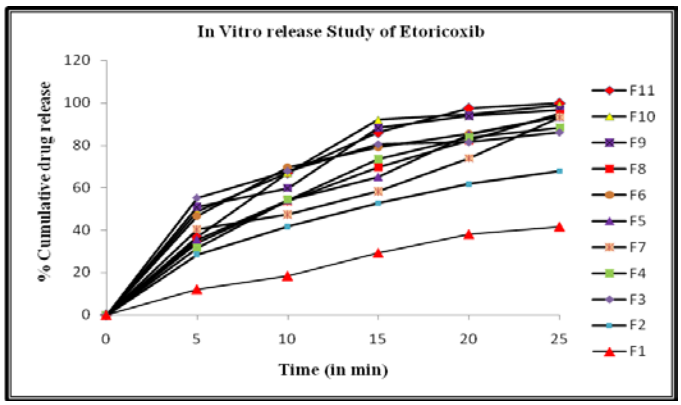

Fig. 6: In vitro drug release study of Etoricoxib Orodispersible tablet

RESULT AND DISCUSSION

The present work was aimed to formulate and evaluate fast disintegrating tablets of Etoricoxib by direct compression method using *gelatinized starch* and *plantago ovata* mucilage as natural superdisintegrants. The results obtained by evaluating the powder blends of drug and excipients are shown in Table 1. The angle of repose <30° indicates free flowing material and >40° with poor flow properties[9]. Values for angle of repose were found in the range of $25^0 03'$ to $26°33'$ showing that the blend of powder was free flowing and can be used for direct compression.

The value for %Carr's index was in between 5.45-5.66, indicating that all the batches of powder blends were having excellent compressibility. Hausner ratio was ranging from 1.05-1.08 (< 1.25) indicating good compressibility[8].The results for evaluation of

different batches of Etoricoxib prepared by direct compression method are shown in Table 3. Weight variation was satisfied by all the batches for uncoated tablets as per United States Pharmacopoeia[11]. One of the primary requirements of immediate release preparation is faster disintegration. It is well known to formulation scientists that the tablets with higher crushing strength show longer disintegration time. Since mechanical integrity is of paramount importance in successful formulation of fast

disintegrating tablets, hence the hardness of tablets was determined and was found to be 4Kg/cm^2 and was kept undisturbed throughout the work for all the batches. Friability was observed between 0.44 to 0.89%, which were below 1% indicating sufficient mechanical integrity and strength of the prepared tablets. Thus, hardness and friability data indicates good mechanical resistance of tablets. *In vitro* disintegration time for different batches of gelatinized starch and *plantago mucilage* was 33.53 to 17.47 seconds and 37.49 to 28.83 seconds respectively. The tablet formulations without superdisintegrants showed highest values of 92.47 seconds for *in vitro* disintegration time. The drug content of all the formulations was in the range of 99.11- 100.31%.Wetting time was determined to get idea of wetting lag time before disintegration and results are shown in table 4. As the concentration of superdisintegrants increases the wetting time decreases, this might be due to fast water absorption by superdisintegrants. The wetting time of gelatinized starch containing tablets (F7-F11) was ranging between 22.56 to 14.05 seconds and that of plantago mucilage batches (F2-F6) was between 23.79 to 16.54. Plantago mucilage batches require more time to wet as compare to gelatinized starch batches. Also the water absorption ratio (Table 4) increases as the concentration of superdisintegrants increases and was found to be more for F7-F11 (69.53-105.05) as compare to F2-F6 (67.43-94.53). These results indicate the high hydrofilicity of gelatinized starch than plantago mucilage. Due to this the disintegration time of F7-F11 is lower than F1-F6. The disintegration might be due to the penetration of water into the pores of tablet which leads to the swelling of superdisintegrants and create enough hydrodynamic pressure for quick and complete disintegration of the tablet. The cumulative percentage drug release from pure drug (F1), gelatinized starch batches (F7- F11) and plantago mucilage tablets (F2- F6) formulation is shown in (Fig 6). It was observed that at the end of 25 min, only 41.55 % drug was released from F1 while it was between 93.09 to 99.79% in case of gelatinized starch batches and between 67.89-93.59% for plantago mucilage batches (Fig: 2). Thus the release rate of Etoricoxib was significantly enhanced by gelatinized starch batches as compare to plantago mucilage batches due to their low disintegrating time.

CONCLUSION

The present work was aimed to formulate the fast disintegrating tablet of Etoricoxib by using two natural superdisintegrants plantago mucilage and gelatinized starch respectively. The results from in vitro disintegration time, in vitro release study, wetting time and water absorption ratio showed that gelatinized starch is more beneficial than the plantago mucilage. Thus it can be concluded that natural superdisintegrant based more cheap, fast disintegrating tablet of Etoricoxib would be quite effective in treatment of Rheumatoid Arthritis providing quick onset of action.

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