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Formulation and Evaluation of Mouth Dissolving Tablet of Lornoxicam Using Novel Natural Superdisintegrants.

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ABSTRACT

The present research is focused on development of mouth dissolving tablet of Lornoxicam using novel superdisintegrants from natural resources. The research is carried out to potentiate the use of natural excipients instead of synthetic ones. Lornoxicam B cyclodextrin complex is formed as it increases the solubility of drug and to mask the taste of drug while having many advantages such as improve dissolution, and bioavailability. Tablets were prepared using natural superdisintegrants like gum karaya, *Plantago ovata husk.* and synthetic superdisintegrants like Crospovidone, Kyron T-314, Croscarmellose Sodium. Tablet containing 6 % of gum karaya shows better results over the formulation containing synthetic or other natural superdisintegrants like *Plantago ovata husk.* The formulated tablet melts in mouth within fraction of seconds with promising release of drug. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy, acceptable taste and patient compliance. The accelerated stability study of batch (F2) revealed that no significant change in physical properties and could be considered as stable formulation even after 3 months.

Keywords: Gum karaya; Mouth dissolving tablet; Lornoxicam; Superdisintegrant.

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INTRODUCTION

Mouth dissolving tablet is choice of formulation over conventional tablet. The research is focused on development of mouth dissolving tablets using natural superdisintegrants. Both type of patients older and pediatrics always complaints about swallowing of tablet. Therefore novel mouth disintegrating tablet has many merits over conventional tablet. These tablets can be swallowed easily without water as it dissolves rapidly in saliva. Therefore It could be better formulation for mentally ill, the bed- ridden, and patients who do not have easy access to water. In addition to patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets first choice of preference over conventional tablet in the current market. [1,2,3,4,5,6,7,14]

Lornoxicam is a potent NSAID from the chemical class of oxicams. It is widely marketed in a number of European countries for the treatment of various painful conditions associated with inflammation. Lornoxicam is a potent inhibitor of both COX-1 and COX-2 enzymes. In contrast to the other oxicams, Lornoxicam has a very short half-life (approximately 4 hours as compared with >24 hours for the others) and is therefore especially suitable for short-term treatment. NSAIDs are medicines which are used to treat mild to moderate pain –from arthritis, bursitis, tendonitis, and sprains, as well as premenstrual cramps, headache, back ache, and minor injuries. Among various transmucosal available sites, buccal cavity mucosa was most convenient and also easily approachable site for the purpose of delivering the therapeutic agents for both local as well as systemic delivery.

Use of disintegrants is the basic approach in development of FDTs. Disintegrants play a major role in the disintegration and dissolution of FDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Synthetic superdisintegrants such as Kyron T- 314, Crospovidone, Sodium starch glycolate, Croscarmellose Sodium were used and compared with natural superdisintegrants such as *plantago ovata husk* and gum karaya. FDTs of Lornoxicam were prepared using all of these superdisintegrant, Lactose, MCC, Sodium Saccharin, magnesium stearate, talc were used as other agents. Unit tablet weight was maintained at 130 mg. FDTs were evaluated for various parameters.

Lornoxicam B cyclodextrin complex is formed as it increases the solubility of drug and having many advantages such as improve dissolution, and bioavailability. It increases the physicochemical stability of drugs and improves the shelf life of drugs.

The present study was focused on to develop mouth disintegrating tablet by using natural and synthetic superdisintegrants and comparative study was carried out. Mouth dissolving tablet was formulated by using natural and synthetic superdisintegrants. The comparative study was carried out between synthetic and natural superdisintegrants. The objective of the study was to potentiate the use of natural superdisintegrants over synthetic ones.

MATERIALS AND METHOD

The drug and B-cyclodextrin were obtained as gift sample from Glenmark Pharmaceuticals, Nasik and Wok hard Pharmaceuticals, Aurangabad. Crosscarmellose Sodium, crospovidone and sodium starch glycolate were purchased from S. D. Fine Chemicals Ltd, Mumbai. Kyron T-314 purchased from Micro labs, Banglore. *Plantago Ovata Husk* bought from Laxmi brand while gum karaya from Crystal Colloid, Mumbai.

FORMULATION

Preparation of Lornoxicam: β-cyclodextrin complex. [6,7]

Preparation of Lornoxicam: β-cyclodextrin complex (1:1) and (1:2) was prepared by kneading method. Both Lornoxicam and β-cyclodextrin were weighed separately. The pre-weighed quantity of cyclodextrin dissolved in minimum quantity of water. It triturated in glass morter using pestle. To this, the weighed quantity of Lornoxicam is added little until uniform slurry obtained. Kneading method also known as slurry complexation. The prepared slurry dried in hot air oven at 60^0C.After drying inclusion complex of Lornoxicam with β-cyclodextrin was kept in the dessicator until further use.

Table 1: Composition of different batches of mouth dissolving tablets of Lornoxicam.

Ingredient(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lornoxicam+β-Cd complex	24	24	24	24	24	24	24	24	24	24	24	24
Gum Karaya	4	6	-	-	-	-	-	-	-	-	-	-
Sodium Starch Glycolagte	-	-	4	6	-	-	-	-	-	-	-	-
Kyron T-314	-	-	-	-	4	6	-	-	-	-	-	-
Plantago ovata husk	-	-	-	-	-	-	4	6	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	4	6	-	-
Croscarmellose Sodium	-	-	-	-	-	-	-	-	-	-	4	6
Lactose	44	42	44	42	44	42	44	42	44	42	44	42
Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Sodium Saccharin	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total	130	130	130	130	130	130	130	130	130	130	130	130

Preparation of Lornoxicam fast dissolving tablets

Weighed quantity of Lornoxicam:β-cyclodextrin complex and different concentration of superdisintegrants (F1-F12) were passed through sieve no.#60. Drug complex and all excipients were added geometrically and mixed to obtain uniform mass of powder, which was directly compressed with 4.0mm flat faced punch (Rimek mini press II).

EVALUATION OF FAST DISSOLVING TABLETS [7,8,,9,10,11,12,13,14,15]

Appearance

Tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated**.**

Swelling index

Swelling index is the volume in millimeters that is occupied by 1 gm of drug or any adhering mucilage after it has swollen in an aqueous liquid for 4 h. The methods of studying swelling index for *plantago ovata husk*, Kyron T-314, crosscarmellose sodium, sodium starch glycolate, Crospovidone and Gum karaya were carried out as per BP specification. The swelling index of superdisintegrants is shown in figure 1.

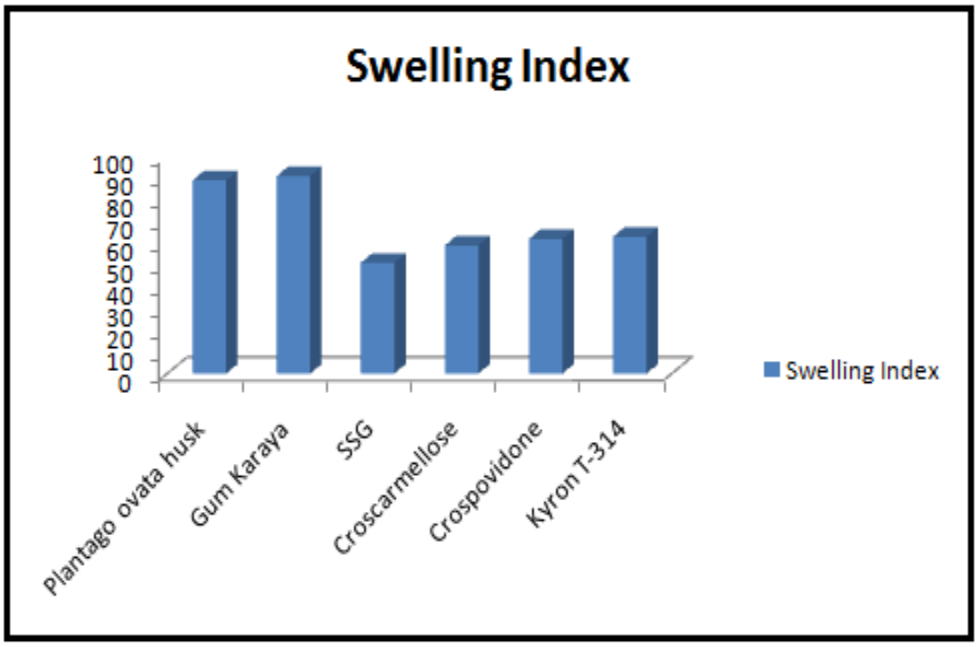

Figure 1: Swelling Index of Various Superdisintegrants

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted. The hardness was measured in terms of kg/cm.^{2} The hardness of all batches are described in (Table 2).

Weight variation

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. The percentage deviation was calculated and then compared with USP specifications. The weight variation of fast dissolving tablets was described in (Table 2).

Thickness

Thickness and diameter were measured using a vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually. The thickness of all batches are described in (Table 2)

Friability

Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. Friability of all batches described in table 21. The percentage friability of the tablets was measured as per the following formula,

Percentage Friability (%) = $\frac{\text{Initial weight}-\text{Final weight}}{\text{Initial weight}}$ X 100Wwetting time

A piece of tissue paper (10.75×12 mm) folded twice was placed in a petridish (d=6.5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for the upper surface of the tablet to become wet was noted as the wetting time of the tablet. Wetting time of all formulation are described in table 2.

Water absorption ratio

Test was done with the same procedure as that of wetting time. In this test initial weight of tablet was taken before placing on petridish. After complete wetting the wetted tablet was then weighed. Water absorption ratio, R was determined using the equation,

Water absorption ratio(R) = $\frac{Wa-Wb}{Wa}$ X 100

Where Wa is the weight of the before test and Wb is the weight of the tablet after water absorption. The water absorption ratio of all batches described in Table no.2.

***In -Vitro d*isintegration time (**Halakatti et al. 2010)

The disintegration time for all formulations was carried out using USP tablet disintegration test apparatus (ED 21, Electrolab, Mumbai). Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted. The disintegration time of all batches are described in table 3.

***In -Vitro* Dispersion time**

Tablet was added to 10 ml of phosphate buffer solution (pH 7.4) at 37±0.5°C. Time required for complete dispersion of a tablet was measured. The *in-vitro* dispersion time of all the formulations were shown in table no. 3.

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 20 mg of Lornoxicam was dissolved in 0.1N Hydrochloric acid (Methanolic) filtered, diluted the sample suitably and analyzed for drug content at 378 nm using UV-Visible spectrophotometer (UV 1700 Shimadzu, Japan). Drug content of all the formulations are shown in table 22.

***In-Vivo* Disintegration test**

This test was evaluated in human volunteers (After taking signed informed consent form) by placing a tablet on the tongue and immediately the time was recorded. They were allowed to move the tablet against the upper palate of the mouth with their tongue. The time required for the complete disintegration of orally disintegrating tablet in the oral cavity was recorded as *in-vivo* disintegration time. After testing, the content was immediately removed from the mouth, and the mouth was thoroughly rinsed with water. The *in-vivo* disintegration time of tablet were shown in table 22.

***In -Vitro* Drug release studies**

In vitro drug release studies of all the formulations were carried out using tablet dissolution test apparatus (USP paddle type II, TDT- 08 L Electro lab, Mumbai, India) at 50 rpm. 900ml of phosphate buffer pH 6.8 used as the dissolution media with temperature maintained at 37±1ºC. The test was carried out for 30 minutes Samples were withdrawn at different intervals, diluted suitably and analyzed at 378 nm for cumulative drug release using an ultraviolet visible spectrophotometer (UV 1700 Shimadzu, Japan). The study was performed in triplicate. The drug release study fast dissolving tablets were shown in table 23 and figure 2.

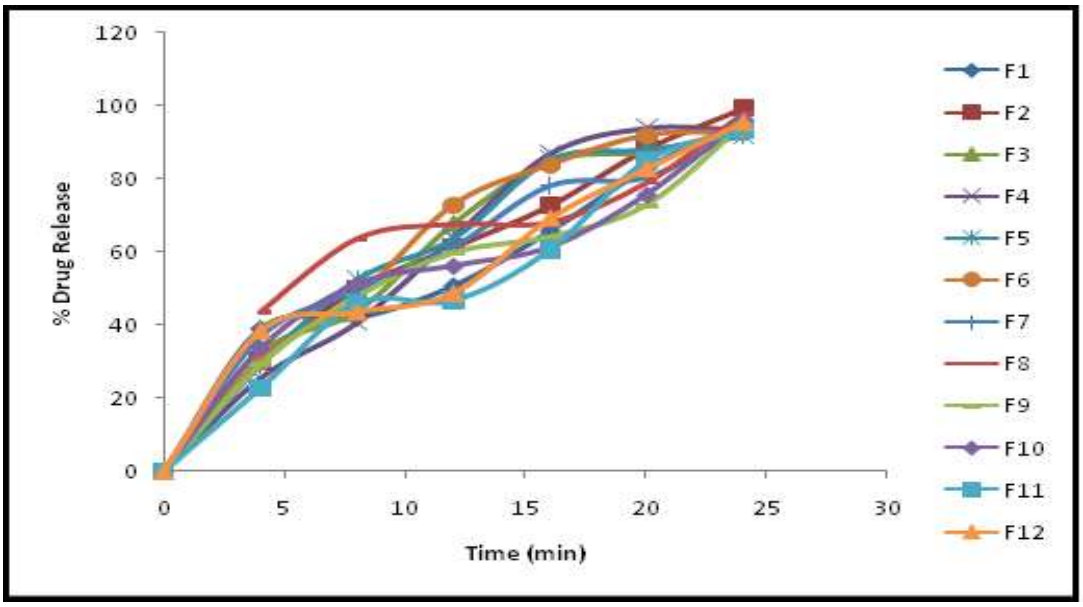

Figure 2: Dissolution Profile of Batch F1-F12

Accelerated stability study

Accelerated stability study was performed as per ICH guidelines on best batch F3 to determine the change in physical characteristics, dissolution study and disintegration time of tablets on storage at 45^{o}C and 75% relative humidity for 3 months. Every month the sample was withdrawn and to evaluated for change in weight of tablets, hardness, friability, *In vitro* disintegration time, uniformity of drug content and dissolution. The accelerated stability studies of fast dissolving tablets were shown in table.

RESULTS AND DISCUSSION

The use of novel natural superdisintegrants for formulation of mouth dissolving tablets is found to be most effective and economical as well. Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were avoided from the study as they are expected to cause an unacceptable feeling of grittiness in the mouth. The soluble diluents, mannitol was selected as a diluent because its advantages in terms of easy availability and negative heat of dissolution is considered. The formulated tablets were evaluated for uniformity of weight, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study.

Thickness of the formulations F1 to F12 varied from 3.0±0.017 to 3.3± 0.025 (mm). The hardness was uniformly maintained and it was found to be within 2.4± 0.14 to 2.8 ± 0.20kg/cm^2. These hardness values show the good mechanical strength of tablet. The friability was less than 1% in the entire formulations and the values obtained lies within to 0.38±0.03 to 0.65± 0.03 and found within range only. The lower limit of tablet weight was found to be 129.8± 2.88 and the upper limit was

found to be 131.8± 2.43. These limits are within range allowed as per IP 1996. The percentage drug content of all the tablets were found to be between 98.12±0.85 to 100.37±0.22, which was within the acceptable limits. The water absorption ratio of given tablets was found to be 51 ± 0.28 to 76 ± 0.14. The tablet containing Gum Karaya shows highest water absorption ratio and it is followed by formulation containing crospovidone. Formulation containing natural superdisintegrants Gum Karaya shows highest swelling index. As the concentration of disintegrants increases the disintegration time decreases. The rapid disintegration was seen in the formulation (F2) containing Gum Karaya as disintegrating agent. This is due to the rapid uptake of water from the medium, swelling and burst effect. The Disintegration time of the tablet was found to be in the range of 15±0.20 to 33±0.28 sec. The tablet containing 6 % of Gum Karaya as a superdisintegrants shows faster disintegration 15±0.20 sec while tablet containing 6% of crospovidone shows almost same result. Crospoviodne has low swelling efficiency, high water uptake capacity and spongy nature, which yield porous tablets that disintegrate in matter or fraction of seconds. Gum Karaya having fast wetting time 39±0.9 and cause swelling. The wetting time was found to be in the range of 39±0.9 to 60±0.23. The *in-vivo* disintegration time of the tablet was found to be 18 to 35 sec. The *in-vitro* dispersion time was found to be in the range of 21.04±0.23 to 39.06 ± 0.29. The lowest in vivo disintegration time was found to be in formulation F 10 having 6% of crospovidone while about same results are reported for formulation F2 having 6 % of Gum karaya. Increase in release of drug was found to be when concentration of superdisintegrants is increased from 4 to 6 % at the end of 24 min. Formulation (F2) prepared with Gum Karaya at 6 % concentration showed better release as compared to other formulations and selected for stability studies. The accelerated stability study of batch (F2) revealed that no significant change in physical properties and could be considered as stable formulation even after 3 months.

Table 2: Evaluation of mouth-dissolving tablets of Lornoxicam

Formulation	Weight variation (%)(±SD)	Hardness (kg/cm^2) (±SD)	Thickness (mm)(±SD)	Friability (%) (±SD)	Disintegration time(Sec) (±SD)
F1	130.7± 2.56	2.6± 0.26	3.2±0.018	0.65± 0.03	19±0.21
F2	131.2± 3.12	2.7± 0.15	3.3± 0.025	0.43± 0.02	15±0.20
F3	130.8± 1.35	2.5±0.25	3.2±0.016	0.52± 0.02	30±0.25
F4	131.5± 2.36	2.6± 0.23	3.1±0.017	0.63±0.04	26±0.35
F5	130.2± 1.89	2.6± 0.24	3.2±0.022	0.42±0.02	33±0.28
F6	130.6± 1.98	2.6± 0.21	3.2±0.018	0.38±0.03	19±0.20
F7	131.0± 2.87	2.7± 0.13	3.0±0.017	0.43±0.01	27±0.25
F8	129.8± 2.88	2.4± 0.14	3.1±0.019	0.55±0.02	24±0.23

F9	130.4±1.98	2.6± 0.14	3.2±0.016	0.59±0.01	17±0.24
F10	129.9±2.75	2.7± 0.27	3.0±0.023	0.60±0.02	16±0.20
F11	130.1±2.12	2.6±0.23	3.1±0.021	0.59±0.01	27±0.21
F12	131.8± 2.43	2.8± 0.20	3.0±0.022	0.46±0.03	25±0.32

Table 3: Evaluation Parameters of Tablets

Formulation	*In vitro* dispersion time (sec) (±SD)	Wetting time (Sec) (±SD)	Water absorption ratio (%) (±SD)	Drug Content (%) (±SD)	Cum% Drug Release (±SD)	*In vivo* disintegration time (sec)
F1	32.20±0.15	59±0.8	62±0.10	98.12±0.85	96.01±0.69	20±0.24
F2	21.04±0.23	39±0.9	76±0.14	99.58±0.36	99.21±0.35	18±0.31
F3	27.90±0.20	47±0.10	63±0.13	98.13±0.44	93.49±1.13	32±0.31
F4	26.32±0.24	48±0.12	72±0.10	100.2±0.12	94.66±0.96	29±0.20
F5	30.12±0.25	60±0.23	63±0.24	100.4±0.14	91.6±1.01	35±0.19
F6	33.05±0.23	52±0.26	61±0.21	98.22±0.28	92.61±0.60	23±0.29
F7	31.56±0.23	56±0.12	69±0.31	99.12±0.37	93.44±0.76	33±0.22
F8	33.08±0.31	49±0.14	70±0.25	100.22±0.47	97.74±1.07	28±0.23
F9	24.12±0.34	42±0.15	70±0.31	100.37±0.22	94.63±1.09	20±0.24
F10	22.18±0.25	39±0.23	73±0.26	98.24±0.32	96.09±1.73	17±0.18
F11	32.08±0.28	59±0.24	59±0.24	99.44±0.33	93.01±1.28	30±0.33
F12	39.06±0.29	51±0.19	51± 0.28	98.17.±41	95.35±1.73	26±0.26

Table 4: Dissolution studies of F1-F12

Formulation code	0	4	8	12	16	20	24
F1	0	33.9	41.88	50.71	65.8	82.99	96.69
F2	0	30.12	49.8	61.19	72.62	88.08	99.2
F3	0	32.5	43.72	67.75	84.87	87.4	93.49
F4	0	25.5	40.7	64.04	87.02	93.99	94.66
F5	0	29.12	52.44	63.65	85.2	87.96	91.00
F6	0	30.12	47.57	72.8	83.75	91.77	92.61
F7	0	36.85	49.36	61.26	78.08	80.38	93.44
F8	0	43.26	63.49	67.48	68.01	75.85	97.7
F9	0	29.12	47.65	59.65	63.99	72.67	94.63
F10	0	33.62	51.11	56.11	61.23	75.59	97.09
F11	0	22.74	45.88	46.71	60.57	84.57	93.01
F12	0	38.39	43.5	48.63	69.15	82.71	95.35

Table 5: Accelerated stability study of best batch F2 at 45ºC and 75% RH

Physical parameters	0 Days	30 Days	60 Days	90 Days
Weight Variation(mg)	131.2±3.12	131.72±1.12	132.09±1.11	132.17±1.09
Hardness (kg/cm^2)	2.7±0.17	2.7±0.13	2.6±0.28	2.6±0.24
Friability (%)	0.43±0.02	0.43±0.22	0.43±0.19	0.42±0.32
Disintegration Time (sec)	15.0±0.20	16.04±0.6	16.9±0.27	17.0±0.10
Drug Content (%)	99.58±0.36	99.43±0.11	99.42±0.28	99.12±0.21
Dissolution Test (%)	99.21±0.35	98.60±3.41	98.50±2.11	98.43±2.39

CONCLUSION

The formulation containing novel natural superdisintegrant successfully formulated mouth-dissolving tablets of Lornixicam with improved drug release profile. Among different excipients mannitol as diluent, magnesium stearate as a lubricant were used.

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