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FORMULATION AND EVALUATION OF TASTE MASKING LORNOXICAM ORAL DISINTEGRATING TABLETS

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ABSTRACT

Recent development in Oral disintegration tablets have brought convenience in dosing to elderly and children who have trouble in swallowing tablets. The purpose of the present research was to prepare taste masking Oral disintegrating tablets of poorly soluble Lornoxicam by direct compression technique using Kyron T-114(cation exchange resin) as a taste masking agent. With in various ratios the Drug-resin ratio of 1:3 was found to offer best taste masking. The superdisintegrants used in formulation are Crosscaramelose Sodium, Sodium Starch Glycolate and Cross Povidone. Among these Cross Povidine showed better drug release. The tablets were evaluated for hardness, friability, weight variation, wetting time, disintegration time and uniformity of content. Optimized formulations were evaluated for *in vitro* dissolution test. Amongst all the formulations F-011 was found to be most successful tablets prepared by this technique had disintegration time of 7 sec and % CDR 93.80 within 30 min. Hence, this approach can be utilised for taste masking of bitter pharmaceutical ingredients leading to improved patient compliance.

KEYWORDS

Lornoxicam, Kyron T-114, Superdisintegrants, Direct Compression Technique and Oral Disintegration Tablets.

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INTRODUCTION

Oral route of drug administration have wide acceptance and hence up to 50-60% of total dosage forms are administered orally. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules. However one of the limitations of

these dosage forms for some patients is the difficulty to swallow. This difficulty in swallowing or dysphagia is currently affecting 35% of general population. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as when water is not available. For these reasons tablets that can easily dissolve or disintegrate in the oral cavity have attracted a great deal of attention[1].

Oral disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people[2]. 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 DT of 3 min as determined in a conventional disintegration test apparatus. ODT are also known as quick dissolves, fast melts, fast dissolving, fast disintegrating, rapid dissolve or orally dissolving tablets.

The bitter taste of the drugs which are orally administered often contributes to patient non-compliance in taking medicines, especially for children and elderly. Unfortunately, majority of the drugs have a natural bitter taste that can create a burning feeling in the throat or in the mouth. In particular, a bitter taste can decrease the patient compliance and thus reducing an effective pharmacotherapy[4].

Various techniques have been developed to improve taste like polymeric coatings strategies, complexation with cyclodextrins, ion exchange resins, salt formation, using liposomes, microencapsulation techniques and coating or granulation[5]. Kyron T-114(cation exchange resin) is mostly used as a taste masking agent derived from croslinked polymer of methacrylic acid. Strong bitter taste of Famotidine was masked with drug resin ratio of 1:2; this approach can be used for taste masking of bitter pharmaceutical ingredients and can make eligible to formulate mouth disintegrating dosage form.

Lornoxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. The mode of action of Lornoxicam is partly based on inhibition of prostaglandin synthesis (inhibition of the cyclooxygenase enzyme). Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract. Lornoxicam is very bitter in taste. Therefore to provide this drug in a more accessible and patient compliant form, in the present study an attempt has been made to mask its bitter taste and formulate in to oral disintegrating tablet.

MATERIAL AND METHODS

Material

Lornoxicam was obtained as a gift sample from KORES (INDIA) LIMITED; Navi Mumbai. Polyacrylic acid (kyron T-114) was a gift sample from Corel Pharma Chem, Ahmedabad. Sodium starch glycolate, Cross carmellose sodium, and Lactoe Monohydrate (SN 21) were obtained from DFE Pharma, Germany. Cross povidone was obtained from Nanhang Industrial, China. Sucralose was from Unisweet (ZIBO) Ltd, China. Lemon Flavour was from Givaudan, Switzerland. Colloidal Silicon Dioxide was from Wacker Chemie, Germany. Magnesium stearate was from Mayfield Heights, Ohio. All the other chemicals used were of Analytical grade.

Method

Preparation of drug-resinate complex

The method used for masking the taste of Lornoxicam A was complexation with ion exchange resins such as Polyacrylic acid (Kyron T-114), as per the following procedure:

Step I: Drug and resin were accurately weighed in required ratio.

Step II: Then slurry of resin was made in sufficient quantity of demineralised water and stirred for half an hour at 500rpm, in order to allow the polymer structure to swell uniformly.

Step III: Then drug was added slowly under stirred condition to Step II.

Step IV: The drug resin mixtures were then continuously stirred for 8 to10hrs at 500 to 600rpm and the volume was made up to 100ml.

Preparation of drug-resinate granules & Lubrication

After drug-resin mixtures were stirred for required time, the drug-resinates were thoroughly washed with demineralized water for several times then filtered by using Whatman's filter paper and dried. The powdered drug-resinate particles are wetted, made into damp mass. Then passed through sieve no-16 and dried at 60°C for 30 minutes. The dried granules are again passed through Sieveno-16 over sieveno-44 to obtain uniform granules. These dried granules were lubricated with the suitable excipients and used for the compression of the Lornoxicam Orally disintegrating tablets. Form Trail No. F001 to F005, Trail No. F003 is considered for the further development as the taste is found good with the F003. Next several trails were made to finalize the suitable Disintegrant as shown in the Table No.1. After finalization of the suitable concentration of the Polyacrylic acid (Kyron T-114) and the suitable disintegrating agent, several trails were taken with sweeteners and finally flavor to further improve the acceptance of the Lornoxicam Orally disintegrating tablet dosage form as shown in the Table No.1.

EVALUATION PARAMETERS

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BRUKER FTIR instrument. Approximately 1mg of sample were mixed with 100mg of spectroscopic grade KBr Pellets, samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Pre-compression studies of fast dissolving tablets

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$D_b = M / Vb$$

Where, M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$D_t = M / Vt$$

Where, M is the mass of powder

Vt is the tapped volume of the powder.

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\tan \theta = h/r$$

Therefore $\theta = \tan^{-1} h/r$

Where θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

Carr's compressibility index (%) = $[(D_t - D_b) \times 100] / D_t$

Where D_t is the tapped density

D_b is the bulk density

Hauser's ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = D_t / D_b$$

Where, Dt is the tapped density,

Db is the bulk density.

Post compression studies of Lornoxicam oral disintegrating tablets

Tablet thickness test

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using a Vernier calipers.

Weight variation test[6]

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of tablet hardness[6]

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test[6]

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

Disintegration Time

The USP device to test disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is positioned in 1 liter beaker of distilled water at 37± 2ºC, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Taste evaluation

Taste evaluation was done by a panel of 6 volunteers using time intensity method.1 tablet was held in mouth for 10 seconds bitterness levels were recorded instantly and then at the end of 10seconds, 30seconds & 60seconds. Bitterness levels are again noted and recorded and compared with F005 formulation which is not having the taste masking agent. The data was presented as shown in the Table No.4.

Mouth feel

The same human volunteers participated in taste evaluation test, were asked give their opinion about the feeling of dosage form in the mouth and the data was presented as shown in Table No.4.

Assay

The assay of the proposed method was ascertained by performing assay of the standard drug with reference to the sample drug. 10 tablets of marketed sample were taken and crushed. Average weight is recorded (a). Equivalent weight to average weight is weighed and taken in to 100ml volumetric flask. Small quantity of ph 7.4 phosphate buffer is taken and sonicated for 30 minutes. after sonication filter it and the volume is adjusted with 7.4 phosphate buffer to 100ml.the concentration was diluted to 10mcg/ml and the absorbance was observed at 376nm.and the % purity of the drug was calculated using the formula

% Purity = Test absorbance X Dilution factor X Labelclaim

Standard absorbance

Drug content uniformity

5 tablets were taken randomly and individual tablet was taken in a 100ml volumetric flask. Small quantity of pH 7.4 phosphate buffer is taken and sonicated for 30 minutes. After sonication filters it and the volume is adjusted with pH 7.4 phosphate buffer to 100ml. The concentration was diluted to 10mcg/ml and the absorbance was observed at 376nm. All the formulations were analysed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated.

In vitro dissolution studies

In vitro dissolution of Lornoxicam fast dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Lab India ds2800) employing a paddle stirrer at 50 rpm using 900 ml of pH 7.4 phosphate buffer at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specified intervals of time (5, 10, 15, 20, 30 min respectively) and analyzed for drug content by measuring the absorbance at 376nm.The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Lornoxicam released was calculated and plotted against time.

RESULTS AND DISCUSSION

Excipient Compatibility study

The possible interaction between the drug and the ion exchange resin was studied by FT-IR Spectroscopy.

FT-IR Spectroscopy

The possible interaction between the drug and the polymers was studied by FT-IR spectroscopy. In FTIR spectra similar peaks were obtained for pure Lornoxicam and Lornoxicam with kyron T-114 indicating that there are no physical or chemical interactions between drug and excipients the spectra is as follows:

FORMULATION OF LORNOXICAM ORAL DISINTEGRATINGTABLETS

Orodispersible tablets were prepared using Lornoxicam and Kyron T-114 complexes which were prepared by Physical mixture method, variable concentrations of superdisintegrants and other excipients.

Table No.1: Composition of all the trails taken during the development of the taste masked Lornoxicam Orally Disintegrating Tablets

S.No	Ingredients	F-001	F-002	F-003	F-004	F-005	F-006	F-007	F-008	F-009	F-010	F-011
1	Lornoxicam	8	8	8	8	8	8	8	8	8	8	8
2	Kyron T-114	8	16	24	32	-	24	24	24	24	24	24
3	Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
4	LACTOSE SN21	128	120	112	104	136	97	97	97	91	91	91
5	SSG	-	-	-	-	-	15	-	-	-	-	-
6	CCS	-	-	-	-	-	-	15	-	-	-	-
7	CP	-	-	-	-	-	-	-	15	15	15	15
8	SUCRALOSE	-	-	-	-	-	-	-	-	2	4	4
9	LEMON FLAVOUR	-	-	-	-	-	-	-	-	-	-	2
10	AEROSIL	4	4	4	4	4	4	4	4	4	4	4
11	MG-STERATE	2	2	2	2	2	2	2	2	2	2	2
Total tablet weight (mg)		150	150	150	150	150	150	150	150	150	150	150

SSG = Sodium starch glycolate; **CCS =** Cross carmellose sodium;
CP = Cros povidone.

Table No.2: Results of flow properties of different formulations of the Lornoxicam

Parameters / Batch No	**Angle of repose (θ)**	**Bulk density (g/cc)**	**Tapped Density (g/cc)**	**Compressibility index**	**Hausner's ratio**
F-001	19.35	0.293	0.331	11.48	1.13
F-002	24.32	0.289	0.321	12.03	1.11
F-003	21.06	0.285	0.324	14.46	1.14
F-004	21.01	0.280	0.317	14.05	1.13
F-005	25.35	0.284	0.322	13.43	1.15
F-006	21.16	0.283	0.325	12.96	1.15
F-007	23.32	0.284	0.323	12.03	1.13
F-008	19.11	0.285	0.312	11.82	1.15
F-009	24.12	0.293	0.324	11.23	1.13
F-010	24.18	0.289	0.312	11.15	1.10
F-011	23.12	0.280	0.320	11.98	1.10

Table No.3: Thickness, Diameter, Hardness, Friability, weight variation & *In vitro* disintegration time

Parameters / Batch No	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%w/w)	Weight variation (mg)	*In vitro* disintegration time
F-001	3.9 ± 0.04	10.02	5.4 ± 0.5	0.421	146 ± 2	45
F-002	3.9 ± 0.03	10.01	5.5 ± 0.5	0.480	148 ± 2	52
F-003	3.9 ± 0.02	10.01	5.4 ± 0.5	0.453	147 ± 2	55
F-004	3.9 ± 0.02	10.02	5.5 ± 0.5	0.465	147 ± 2	53
F-005	3.9 ± 0.03	10.01	5.7 ± 0.5	0.458	148 ± 2	48
F-006	3.9 ± 0.05	10.02	5.8 ± 0.5	0.455	152 ± 2	15
F-007	3.9 ± 0.05	10.02	5.8 ±0.5	0.456	151 ± 2	12
F-008	3.9 ± 0.04	10.02	5.5 ± 0.5	0.476	153 ± 2	7
F-009	3.9 ± 0.05	10.01	5.7 ± 0.5	0.468	152 ± 2	7
F-010	3.9 ± 0.04	10.01	5.7 ± 0.5	0.476	149 ± 2	7
F-011	3.9 ± 0.03	10.02	5.8 ± 0.5	0.477	152 ± 2	7

Table No.4: Taste evaluation & Mouth feel for best formulation

Trail. No	Volunteer. No	Bitterness	Mouth feel
F-011	1	a	++
	2	a	++
	3	a	++
	4	a	++
	5	a	++
	6	a	++

a = absent, ++ indicates more pleasant feeling.

Table No.5: Formulation of Drug-resin complex ratio and its % Drug release

S.No	Drug-resin complex ratio	% Drug release
1	1:1	85.20
2	1:2	84.8
3	1:3	85.25
4	1:4	75.10

Note: On the basis of these observations Drug-kyron ratio 1:3 was finalized for further study.

Table No.6: *In-Vitro* Drug Release Data of formulation F-01 to F-11 & Market sample

Time in min	Cumulative % drug release										
	1:1	1:2	1:3	1:4	1:0	Drug-kyron T114 ratio (1:3) and Different SDs					
	F-01	F-02	F-03	F-04	F-05	F-06	F-07	F-08	F-09	F-10	F-11
5	45.33	44.8	44.8	40.10	48.02	45.35	45.50	46.10	45.50	44.50	47.10
10	55.90	54.15	52.10	45.10	58.02	56.90	56.10	57.50	58.00	56.25	56.89
15	63.31	62.10	60.10	55.10	65.08	64.8	63.10	65.10	66.00	67.25	66.15
20	68.76	66.10	67.10	60.10	72.91	75.10	79.10	80.15	81.20	81.28	82.15
30	85.20	84.8	85.25	75.10	92.50	88.10	90.00	91.15	92.25	90.10	93.80

Table No.7: Comparative dissolution profiles for F-011 and Marketed Sample

S.No	Formulation F-11	Market Sample
1	47.10	50.10
2	56.89	61.00
3	66.15	68.00
4	82.15	75.10
5	93.80	85.25

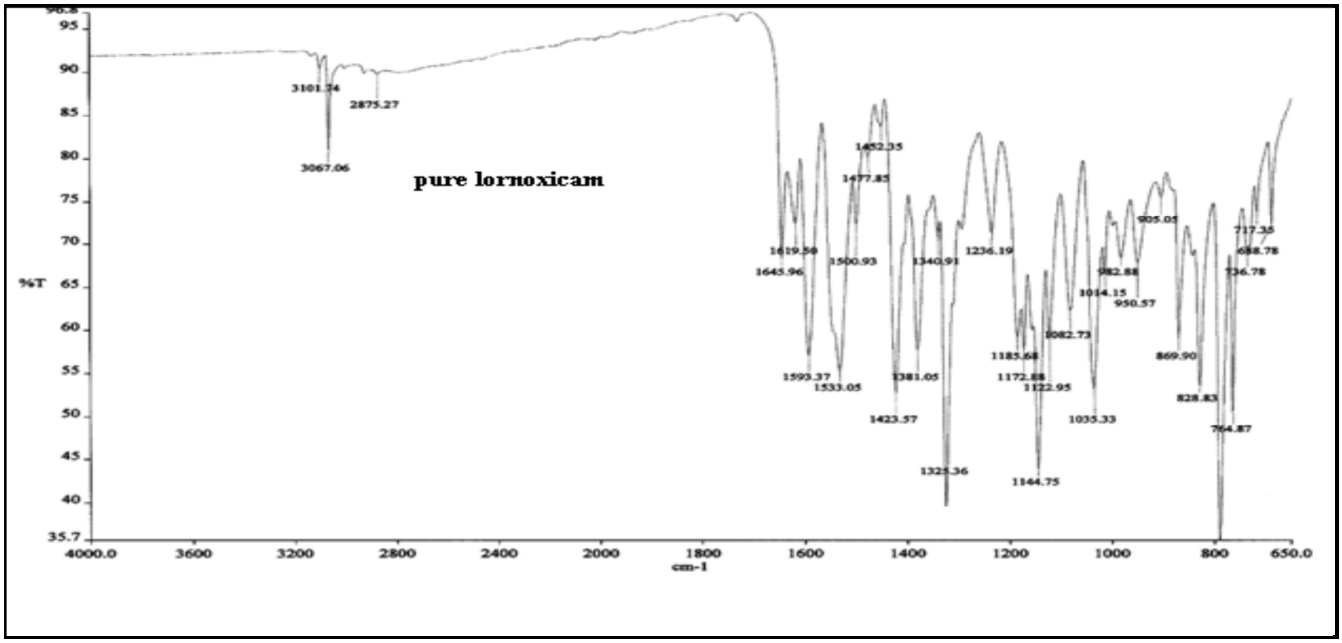

Figure No.1: FT-IR Spectra of Pure Loroxicam

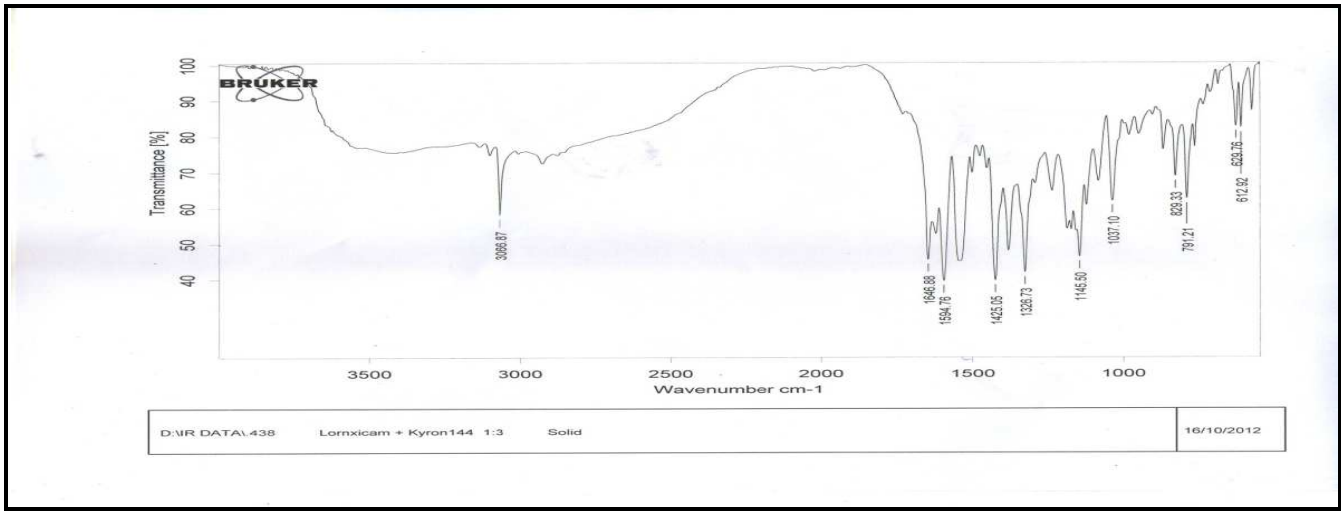

Figure No.2: FT-IR Spectra of Lornoxicam and Kyron T-114

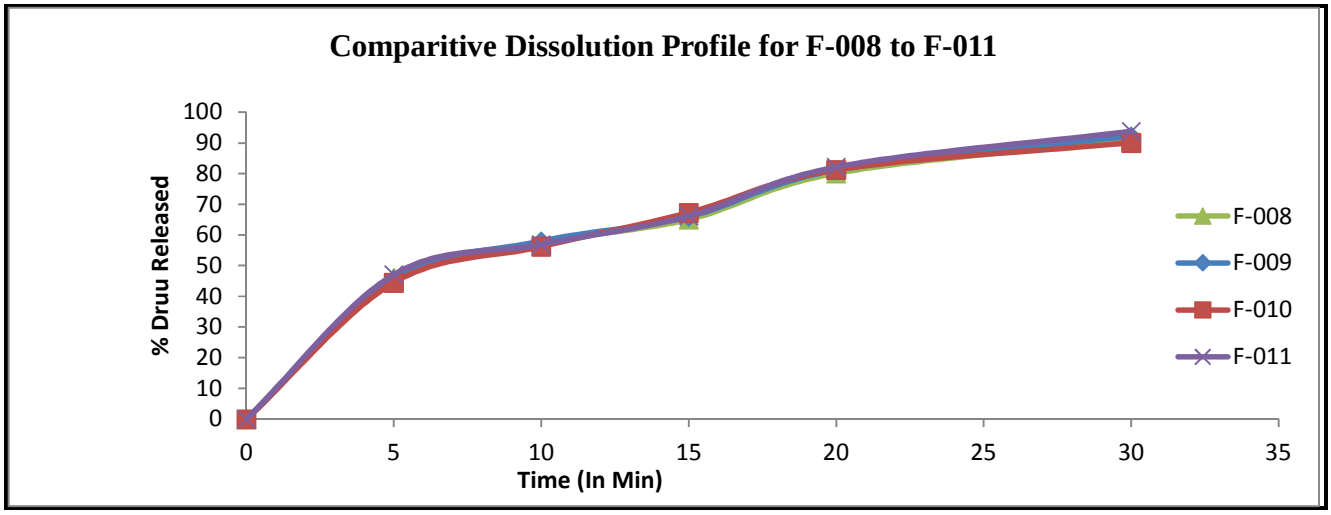

Figure No.3: Comparative Dissolution profiles for Cross povidone formulation

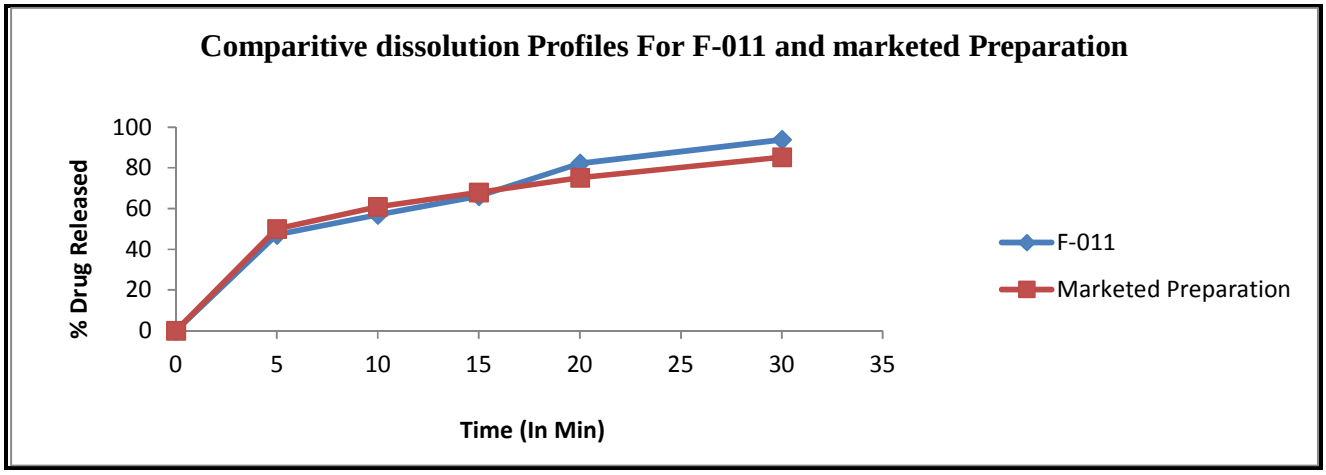

Figure No.4: Comparative dissolution profiles for F-011 and marketed preparation

CONCLUSION

One of the problems encountered in the preparation of ODTs of Lornoxicam was the bitter taste of the drug. Results suggested that by complexing drug with Kyron T-114 in 1: 3 ratios masked the bitter taste of drug. Overall results suggested that F-011 formulation containing crosspovidone in 10% concentration was better and satisfy all the criteria of ODTs and the *In vitro* dissolution studies showed a drug release up to 93.8% in 30 minutes, which was found to be better than a commercial product (85.25%).

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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