Research Article

Formulation and Evaluation of Taste Masking Lornoxicam Oral Disintegrating Tablets

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ABSTRACT

Lornoxicam is a Non-steroidal anti-inflammatory drug with COX inhibiting property and belongs to the class of Oxicams. It is extremely bitter in taste. The purpose of this research was to develop a bitterless orally disintegrating tablet of poorly soluble drug like Lornoxicam. Taste masking was done by complexing Amberlite IRP-88 in different ratios. Three superdisintegrants like sodium starch glycolate, crospovidone, low substituted hydroxypropyl cellulose were used. Prepared tablets were evaluated for different properties like Drug content, hardness, friability, wetting time, water absorption ratio, disintegration time and invitro dissolution studies. The different formulations showed disintegration time between 39.46-52.40 seconds. Drug release showed between the range of 5 to 30 minutes. Among all the formulations, F9 with Low substituted hydroxy propyl cellulose at a concentration of 7% showed 98.73% drug release with in 30minutes. Thus F9 was considered as best among the other formulations. The tablets showed enhanced dissolution hence better patient compliance. Kinetic analysis(r^2) of release data based on best curve fitting method for selected ODT of Lornoxicam showed first order kinetics indicating that the drug release depends upon its concentration.

Keywords: Lornoxicam, Amberlite IRP-88, superdisintegrants, oral disintegrating tablets, disintegration time.

INTRODUCTION

Oral route of drug administration has wide accepted 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[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[4].

Unfortunately, majority of the drugs have a natural bitter taste that can create a burning feeling in the throat or in the mouth.

Various techniques have been developed to improve the taste of Bitter drugs like polymeric coatings strategies, complexation with cyclodextrins, ion exchange resins, salt formation, using liposomes, microencapsulation techniques and coating or granulation[5].

Lornoxicam (chlortenoxicam) was a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class and was used for the treatment of pain, inflammatory diseases of the joints, osteoarthritis, surgery, sciatica and other inflammations. The main objective of the present work is to formulate oral disintegrating tablets of Lornoxiam where in which its bitter taste is masked. Such taste masked formulations have been found to improve the patient compliance.

AMBERLITE IRP-88 resin was a weak acidic potassium form of cation exchange resin supplied as a dry powder. It was widely used as a tablet disintegrant and taste masking agent in oral dosage form of drug products. Amberlite IRP-88 was a potassium salt of cross linked polymer derived from methacryallic acid. Amberlite resin absorb water rapidly due to its high Hydrophilic nature and upon hydration, the resin particles swell.

MATERIALS AND METHODS

Materials

Lornoxicam was obtained from KP LABS Hyderabad. Amberlite IRP-88, Sodium starch Glycolate, Crospovidone, sucralose, Magnesium stearate, Sodium hydroxide, Microcrystalline Cellulose, Low substituted hydroxypropyl cellulose, Talc were obtained from KP LABS Hyderabad.

Methods

Preparation of drug resinate complex

The method used for masking the taste of lornoxicam was complexed with ion exchange resin such as polacrillin potassium (Amberlite IRP-88) as for the following procedure.

Step-I: Drug- resin complexes were prepared in the ratios of 1:1, 1:2, 2:1, respectively.

Step-II: Lornoxicam-resin complex was prepared by a simple aqueous binding process. The ion-exchange resin

particles were dispersed in a drug ethanol solution with a mass ratio under magnetic stirring until equilibrium state.

Step-III: The complexes were separated by filtration and washed with deionized water to remove unbound drug and other ions. The complexes were then dried in hot air oven for 4 hrs at 40 °C to constant mass and stored in a tight glass vial.

Step-IV: Then among the above complexes the best complex is selected based on Drug loading efficiency.

Drug and Excipient Compatibility by using FTIR

The interaction study between the drug and Amberlite IRP-88 in the ratio of 2:1 and L-HPC performed using FTIR. FTIR studies were conducted between drug- resinate complex and sodium starch glycolate, drug- resinate complex and crosspovidone. The pellets were prepared on KBR press. The spectra were recorded over the wave number range of 3500 cm^{-1}.

a) Standard calibration curve of pure lornoxicam

From the standard stock solution series of dilution were made to 2, 4, 6, 8, 10, 12, 14, 16, 18& 20µg/ml solution using phosphate buffer pH-6.8 and corresponding absorbance was measured at 376nm in a U.V spectrophotometer.

b) Characterization of complex for drug content

The drug resonated complex equivalent to 8mg of drug was stirred by using magnetic stirrer with 100ml of 6.8-phosphate buffer for 60min, till the entire drug leached out from complex. Then the solution was filtered through Whatmann's filter paper. Further the solution diluted with pH-6.8 phosphate buffer and the drug content was determined spectrophotometrically at 376nm.

Table 1: Characterization of complex for drug content

S.NO	Drug & Amberlite IRP-88 Ratio	% Drug Content in Complex
1	1:1	87.94
2	1:2	90.80
3	2:1	95.11

On the basis of above observations Drug & amberlite IRP-88 complex ratio 2:1 was finalized for further study due to high percentage drug content in the complex.

Evaluation of taste of drug-resinated complex

Taste of drug resonated complex was checked by time intensity method for this purpose five human volunteers were selected. In this method a sufficient quantity of sample was held in mouth for 10sec and volunteers were asked to evaluate the complex for taste. Bitterness levels were recorded immediately. Bitterness values are based on 0-3 scale.

3 - being – strong bitter

2 - being – moderate bitter

1 - being – slight bitter x threshold bitter

0 - being – tasteless

These volunteers were instructed not to swallow the granules, which were placed on the tongue. They were instructed to thoroughly gargle their mouth with distilled water, after the completion of the test.

Evaluation of the lubricated blend

The lubricated blend is evaluated for physicochemical characteristics like angle of repose (flow properties), bulk density, tapped density, compressibility index, hausner's ratio. The detail procedure for each of the test as given as below.

Angle of repose[11]

Flow properties of powders are important in the manufacture of tablets. Because non-uniform flow will result in variation in weight of the tablets, which intern affects the dose of the drug per tablet. It also creates problem of hardness during compression of tablets. It was measured by the fixed funnel method using the procedure as follows:

A glass funnel was selected to with a stem of 15-30 mm and fixed to the funnel stand; a graph paper was placed on table. Granules were allowed to flow to form a heap. The circumference of the heap was marked and measured the height of the pile using two rulers. The height was measured and noted it as (h). The area (πr^2) was determined, radius(r) was calculated and substituted in the formula ($\theta = \tan^{-1} h/r$) to obtain the angle of repose. Repeated the experiment twice more and average angle of repose can be calculated.

$$\text{Tan } \theta = h/r$$

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

Bulk density[11]

Weigh accurately 25 g of lubricated blend, which was previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V0). Calculate the apparent bulk density in gm/ml by the following equation.

Bulk density = Weight of powder/ Bulk volume

Tapped density[11]

Weigh accurately 25 g of drug, which was previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tap volume (V2) to the nearest graduated units. If the difference between the

two volumes is less than 2% then final the volume (V2). Calculate the tapped bulk density in gm/ml by the following equation.

Tapped density = Weight of powder / Tapped volume.

Carr's Index[12]

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below equation:

$$\text{Carr's index (\%)} = [(TD-BD) \times 100] / TD$$

Hausner's Ratio[12]

Hausner's Ratio is a number that is correlated to the Flowability of a powder. The formula for Hausner's Ratio is as below equation.

$$\text{Hausner's Ratio} = TD / BD$$

Table 2 : General composition of formulation prepared by direct compression method for single formulation (mg)

S. No	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	DRC(2:1) equivalent to 8 mg	32	32	32	32	32	32	32	32	32
2	SSG	6	8	10	-	-	-	-	-	-
3	CP	-	-	-	6	8	10	-	-	-
4	L-HPC	-	-	-	-	-	-	6	8	10
5	MCC	106	104	102	106	104	102	106	104	102
6	Sucralose	2	2	2	2	2	2	2	2	2
7	Mg.Sterate	2	2	2	2	2	2	2	2	2
8	Talc	2	2	2	2	2	2	2	2	2
9	Total weight(mg)	150	150	150	150	150	150	150	150	150

Evaluation of tablets

General appearance[14]

Five tablets from all batches were randomly selected and Organoleptic properties such as color, odor and shape were evaluated.

Thickness[14]

The thickness of five tablets for all batches was measured using vernier calipers. The diameter was also determined by using vernier calipers.

Hardness test[15]

Hardness of for five tablets for all the batches was tested using 'Monsanto' Hardness tester. The tester consists of a barrel containing a compressible spring held b/w two plungers. The lower plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is then forced against a spring by turning a thread bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force, which is a measure of hardness.

Weight variation test

Weighed 20 tablets selected at random and calculated the average weight. Then percentage deviation from the average was calculated.

Friability test[14]

The Roche friabilator was used for this test, this device subjects as number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm by dropping the tablets from a distance of six inches with each revolution. Normally, a preweighed 10 tablets are placed in the friabilator which is operated for 100 revolutions. The tablets are then dusted and reweighed.

Standards

Compressed tablets that lose less than 1% of their weight are generally considered acceptable.

***In-Vitro* Dispersion Time**[15]

In-vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of phosphate buffer pH 6.8 (simulated saliva fluid). The time for the tablet to completely disintegrate into fine particles was noted. Three tablets from each batch were randomly selected and *In- vitro* dispersion time was performed.

***In vitro* disintegration test**[12]

This test is performed to ensure disintegration of tablets in water. One tablet is introduced in to one tube of disintegration apparatus IP. The assembly is suspended in the beaker containing distilled water and the apparatus is operated until the tablet disintegrated.

Standards

The tablets must disintegrate less than 30 seconds when examined by the disintegration test for tablets.

Taste evaluation

Taste evaluation was done by a panel of 6 volunteers using time intensity method. One tablet was held in mouth for 10 seconds bitterness levels were recorded instantly and then at the end of 10seconds, 30seconds &

60seconds.

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.

Water absorption ratio[12]

Small piece of tissue paper folded twice was placed on a small petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then reweighed.

$$\mathbf{wateraborptionratio} = \frac{\mathbf{finalweight} - \mathbf{initialweight}}{\mathbf{initialweight}} * \mathbf{100}$$

Wetting time[12]

5 circular tissue papers of 10cm diameter were placed in a petridish containing water soluble dye methylene blue (w/v) solution 6ml. a tablet was carefully placed on surface. The time required for the developing color on the upper surface of the tablet is noted as "wetting time".

Drug content uniformity test

5 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100mg of drug was transferred to 100ml volumetric flask. Small quantity of pH-6.8 phosphate buffer is taken and sonicated for 30min. After Sonication filter it and volume is adjusted with pH-6.8 phosphate buffer to 100ml. The concentration was diluted to 10µg/ml and absorbance was observed at 376nm.

***In vitro* drug release**

In vitro dissolution study was performed in 900ml P^H 6.8 Phosphate buffer using USP type-II (paddle) apparatus at 50 rpm for 30 mins. (37±0.5^{0}C). Aliquots of the dissolution medium (5ml) were withdrawn at specific time intervals (0,5,10,15,20,25,30mins) and replaced immediately with equal volume of fresh medium. The samples were filtered and analyzed for drug content by measuring the absorbance at 376 nm. The drug concentration was calculated and expressed as cumulative % drug released.

RESULTS

Table 3: Pre-compression parameters

Formulation code	Angle of repose (Θ)	Bulk density	Tapped density	Carr's index (%)	Hausner's ratio
F1	24.32	0.289	0.321	12.03	1.11
F2	19.35	0.293	0.331	11.48	1.13
F3	21.06	0.285	0.324	14.46	1.14
F4	21.01	0.280	0.317	14.05	1.13
F5	21.16	0.283	0.325	12.96	1.15
F6	25.35	0.284	0.322	13.43	1.15
F7	23.32	0.284	0.323	12.03	1.13
F8	24.18	0.289	0.312	11.15	1.10
F9	23.12	0.280	0.320	11.98	1.10

Table 4: Post compression parameters

S. No	Formulation code	Weight Variation (mg)	Uniformity of Thickness (mm)	Hardness (kg/cm^2)	Friability %	Wetting Time (Sec)	Water Absorption Ratio	*In-vitro* Disintegration Time (sec)	*In-vitro* Dispersion Time (sec)	Drug Content (%)
1	**F1**	150	2.71	3.62	0.67	42.76	39.30	52.40	74.57	98.0
2	**F2**	149	2.73	3.79	0.33	35.52	37.16	50.71	72.74	99.1
3	**F3**	148	2.76	3.76	0.40	34.38	36.92	48.07	70.12	98.7
4	**F4**	149	2.83	3.84	0.60	34.19	38.64	51.81	71.71	98.57
5	**F5**	150	2.53	3.53	0.66	33.38	29.45	48.13	68.17	98.32
6	**F6**	148	2.65	3.96	0.53	31.46	27.10	42.19	66.12	99.15
7.	**F7**	149	2.79	3.43	0.46	38.66	38.01	48.19	70.17	98.4
8.	**F8**	148	2.68	3.36	0.40	33.72	35.31	41.91	65.18	98.2
9.	**F9**	150	2.88	3.71	0.47	32.65	33.71	39.46	63.16	99.9

Table 6: Dissolution parameters

Time (min.)	Cumulative % Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed preparation
0	0	0	0	0	0	0	0	0	0	0
5	35.73	50.48	52.53	50.43	53.48	69.65	71.86	73.82	74.85	50.21
10	42.34	53.41	54.02	55.62	57.38	78.83	77.53	78.36	81.93	64.53
15	45.27	61.53	64.35	63.38	63.66	85.73	82.53	83.48	92.3	68.85
20	47.38	64.38	72.38	68.12	70.73	88.83	83.72	84.85	94.23	75.92
25	48.16	66.52	74.87	72.83	76.92	90.52	85.25	87.98	96.35	84.86
30	52.83	71.29	77.83	78.51	79.16	92.35	93.35	94.83	98.73	85.88

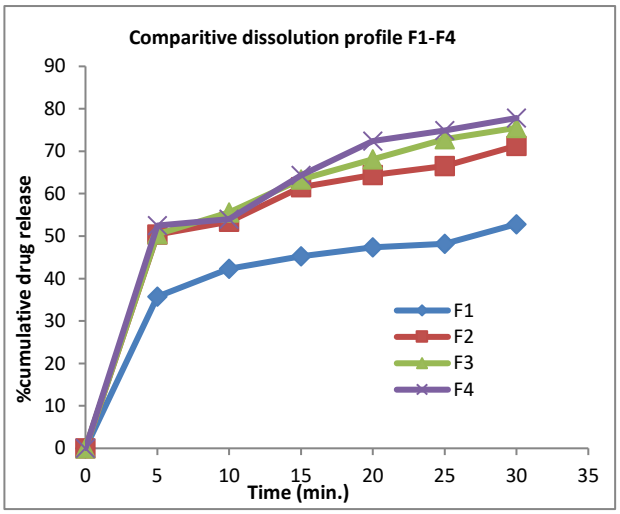

Figure 2: Comparative dissolution profiles F1-F4

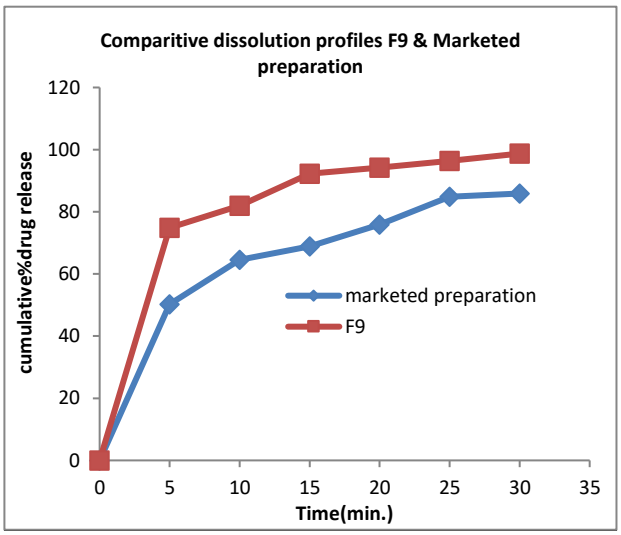

Figure 4: Comparative Dissolution profile F9 & Marketed Preparation

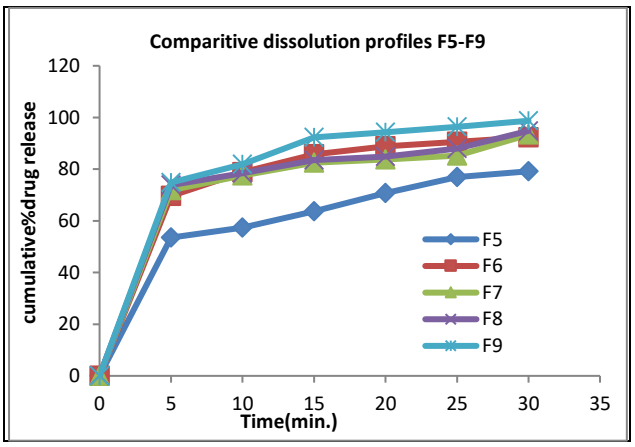

Figure 3: Comparative dissolution profiles F5- F9

Table 7: Different Dissolution kinetic parameters of optimized formulation F9.

Formulation code	Zero order R^2	First order R^2	Higuchi model R^2	Korsmeyer peppas R^2
F9	0.601	0.878	0.856	0.787

From the above observations Kinetic analysis (r^2) of release data based on best curve-fitting method for selected ODT of Lornoxicam the Drug release showed First order kinetics (R^2=0.878) indicated that the drug release depends upon its concentration.

SUMMARY AND CONCLUSION

In the present research investigation Amberlite IRP-88 (polacrillin potassium) was used as ion exchange resin for taste masking of the bitter drugs. The polymer was mixed with the drug in different ratio's i.e., drug: resin form 1:1, 1:2, 2:1. These drug-resinate mixtures were then

converted into granules. These granules were lubricated and used for compression as required. Results showed that the bitterness was masked with 2:1 ratio and the percentage drug content for 2:1ratio was found to be 95.11. The trail number F9 has high % cumulative drug release. FTIR studies showed that all the functional groups present in 2:1 ratio of drug-resin complex and that of final formula containing L-HPC along with drug-resin complex are same with that of the individual structures. Hence, they are compatible with each other.

The lubricated blends were characterized for Angle of repose, Bulk density, tapped density, Compressibility index & Hauser's ratio. All the formulations were shown good flow properties and good compressibility.

The compressed tablets were subjected to evaluation studies for the parameters like general appearance, thickness, diameter, and hardness, weight variation, wetting time, water absorption ratio, friability, *invitro* disintegration and dissolution tests respectively.

Drug Content uniformity studies were conducted for all the formulations and found satisfactory. For all the formulations the content uniformity was within 85% to 115 % limit only. *In vitro* dissolution studies showed a drug release up to 98.53% in 30 minutes, which was found to be better than a commercial product (85.83%).

Hence, from the present research investigation it was concluded that, the taste masking polymer i.e Polacrillin potassium have been proved to be useful as taste masking agent for bitter drug like Lornoxicam as well as super disintegrating agent.

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