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FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LORNOXICAM

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ABSTRACT

Lornoxicam is a non steroidal anti-inflammatory drug with analgesic properties. The purpose of this study was to develop a taste masked oral disintegrating tablet of poorly soluble Lornoxicam by direct compression technique with β-cyclodextrin (BCD) complexes using various super disintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium. Prepared tablets were evaluated for different properties like drug content, hardness, friability, disintegration time and in vitro dissolution study. The different formulations showed disintegration time between 22 to 58 s. Drug release showed time between the ranges of 8 to 20 min. Among all the formulations, L6 showed 99.85% drug release within 8 min. Thus, L6 was considered best among the other formulations. The stability study was conducted as per the ICH guidelines and the formulations were found to be stable, with insignificant change in hardness, drug content and disintegration time. The tablets showed enhanced dissolution hence better patient compliance.

KEYWORDS

Lornoxicam, β-cyclodextrin, Super disintegrants, Oral disintegrating tablet and Disintegration time.

INTRODUCTION

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. [1]

More than 50% of pharmaceutical are administered orally for several reason and undesirable taste is one of the formulation problem encountered with such oral products.[2] Taste of pharmaceutical product is important parameter in governing compliance. Thus taste masking of oral pharmaceutical has become important tool to improve patient compliance and the quality of treatment especially in pediatrics.[3] In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a

FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LORNOXICAM

stable complex. The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Vander Waals forces are mainly involved in inclusion complexes.[4]

β-cyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. Strong bitter taste of carbapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin. The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma, beta cyclodextrin.[5]

Lornoxicam is a non-steroidal 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 cyclo-oxygenase enzyme). Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract.[6] 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 it into oral disintegrating tablet.

MATERIALS AND METHODS

Lornoxicam was gift sample from Sunpharma industries Ltd, Vadodara. Sodium starch glycolate, crospovidone, croscarmellose sodium, β-cyclodextrin, directly compressible mannitol (Pearlitol SD 200), microcrystalline cellulose (MCC, PH-102) and aspartame were obtained as a gift sample from Osaka Pharmaceutical Pvt. Ltd, Vadodara. All the other chemicals used were of analytical reagent grade.

(i) Preparation of complex of Lornoxicam with β-cyclodextrin

A mixture of lornoxicam and β-cyclodextrin was ground in a glass container and a minimum amount of water was added. The mixture was stirred for 5 min and dried at 60°C in the vacuum oven. After drying inclusion complex of lornoxicam and β-cyclodextrin was obtained.

(ii) Characterization of complex for drug content

Drug content was determined by dissolving 25 mg of complex in suitable quantity of 0.1N HCl and analyzed 1mL of appropriately diluted sample at 376 nm using UV-vis spectrophotometer, Shimadzu 1700 (Table 1).

Table 1
Drug content of prepared complex

Serial No.	Drug BCD ratio	%drug content in complex*
1	1:1	76.04 ± 0.83
2	1:2	35.62 ± 0.49
3	1:3	26.34 ± 0.93

*Results are the mean of 3 observations ± SD

On the basis of these observations Drug BCD ratio 1:2 was finalized for further study.

FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LORNOXICAM

(iii) Preparation of tablets containing a complex of Lornoxicam with β-cyclodextrin

Tablet containing 4 mg of lornoxicam was prepared by direct compression method. Drug β-cyclodextrin complex equivalent to 4 mg was taken and pass through the # 20. Diluents, superdisintegrants, sweetener and flavor were passed through # 40. All above ingredients were mixed and blended properly. Magnesium stearate was passed through # 40 and mixed properly with above blend. Powdered lubricated blend was compressed into tablet by 12 station Cadmach single rotary compression machine using 8 mm round flat punches.

Table 2

Composition of Lornoxicam oral disintegrating tablets

Ingredients	Formulations and their excipients (mg)								
	L1	L2	L3	L4	L5	L6	L7	L8	L9
Drug BCD complex equivalent to 4mg of drug (1:2)	11.23	11.23	11.23	11.23	11.23	11.23	11.23	11.23	11.23
Sodium starch glycolate	5	10	15	-	-	-	-	-	-
Croscarmellose Sodium	-	-	-	5	10	15	-	-	-
Crospovidone	-	-	-	-	-	-	5	10	15
Avicel PH 102	64.27	59.27	54.27	64.27	59.27	54.27	64.27	59.27	54.27
Perlitol SD 200	108.5	108.5	108.5	108.5	108.5	108.5	108.5	108.5	108.5
Flavor Mint	1	1	1	1	1	1	1	1	1
Aspartame	6	6	6	6	6	6	6	6	6
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200	200

EVALUATION PARAMETERS OF LORNOXICAM ORAL DISINTEGRATING TABLETS

(i) Weight Variation

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet was determined from the collective weight. [7]

(ii) Hardness and Friability

Hardness is the tensile strength of tablets expressed in kg/cm^2, which was determined using Monsanto Hardness Tester. Preweighed sample of tablets was placed in the friabilator (Roche friabilator), and operated for 100 revolutions. Tablets were dusted and reweighed. The test complies if tablets not loose more than 1% of their weight.

(iii) Wetting time

A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The time

FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LORNOXICAM

required for complete wetting of the tablet was then recorded. [11]

(iv) Disintegration Time

Disintegration time for ODT was determined using USP disintegration apparatus using SSF (pH 6.2, 900 ml at 37°C) as the disintegrating medium. To comply the test all tablets should disintegrate within 30 sec as per new USFDA guidelines. [10]

(v) Content Uniformity

Ten tablets were weighed and powdered, 4 mg equivalent of lornoxicam weighed and dissolved in suitable quantity of 0.1N HCl. Solution was filtered, diluted and analyzed for drug content.

(vi) In vitro Drug Release

In vitro dissolution study was performed in 900ml 0.1N HCl using USP type II (paddle) apparatus at 50 rpm for 20 minutes (37 ± 0.5°C). Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10, 15 and 20 min) and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 mm membrane filter disc and analyzed for drug content by measuring the absorbance at 376 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved.

(vii) Stability study

The stability study of formulations was carried out according to the ICH guidelines for zones III and IV. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 4 weeks by storing the samples in a stability chamber. At the end of 4 weeks tablets were tested for hardness, drug content and disintegration. In-vitro dissolution was carried out for selected formulation.

RESULT AND DISCUSSION

β-cyclodextrin was chosen for the taste masking of the lornoxicam. Drug BCD complexes (DBC) (Taste masked complex) were prepared by the kneading method. DBC in the ratio of 1:2 gave the best result and it showed drug content 35.62 ± 0.49%. Nine formulations L1 to L9 were prepared using various excipients and three different superdisintegrants (croscarmellose sodium, crospovidone and sodium starch glycolate) in different concentrations. The values of the pre-compression parameters evaluated were within prescribed limit and indicate good flow property (Table 3).

Table 3

Pre-compression parameter of powder blend used in the direct compression technique with BCD complex

Formulation	Angle of Repose (θ) (±SD) (n=3)	Compressibility (±SD) (n=3)	Hausner's ratio (±SD) (n=3)
L1	18.25 ± 0.15	14.17 ± 0.12	1.15 ± 0.12
L2	21.63 ± 0.18	15.61 ± 0.15	1.21 ± 0.08
L3	20.45 ± 0.09	14.89 ± 0.13	1.17 ± 0.14
L4	17.12 ± 0.23	16.11 ± 0.11	1.14 ± 0.15
L5	19.35 ± 0.16	15.08 ± 0.08	1.19 ± 0.10

FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LORNOXICAM

L6	15.08 ± 0.11	13.41 ± 0.17	1.12 ± 0.06
L7	18.21 ± 0.17	14.52 ± 0.15	1.22 ± 0.16
L8	19.58 ± 0.10	15.71 ± 0.09	1.18 ± 0.07
L9	14.51 ± 0.18	11.92 ± 0.12	1.16 ± 0.09

Note: Values in parenthesis are standard deviation (± SD)

ODT were prepared by direct compression and evaluated for hardness, weight variation, friability, content uniformity, wetting time and disintegration time. The % drug content was found in the range of 99.35% to 101.31% which shows good content uniformity. Wetting time was found in the range of 43 to 73 s. Hardness was found between 3.1 to 3.5 kg/cm^2 which indicate good mechanical strength. Friability was found below 1% indicating good resistance against mechanical shear. (Table 4)

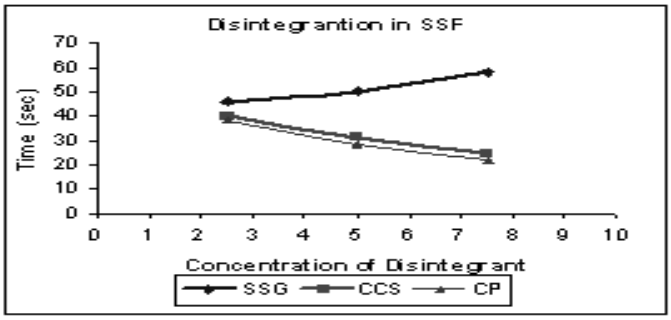
Table 4
Post-compression parameters

Formulation	Hardness (kg/cm^2) (±SD) (n=3)	Friability (%) (n=6)	Drug Content (%) (±SD) (n=10)	Disintegration time (s) (n=6)	Wetting Time (s) (n=3)	Wt Variation (mg) (±SD) (n=20)
L1	3.1 ± 0.09	0.31	99.52 ± 1.50	46	59	200.78 ± 1.51
L2	3.5 ± 0.12	0.32	101.31 ± 0.89	50	62	201.21 ± 2.23
L3	3.2 ± 0.16	0.21	100.21 ± 1.82	58	73	199.79 ± 2.18
L4	3.2 ± 0.17	0.53	100.35 ± 2.00	40	55	200.51 ± 2.31
L5	3.1 ± 0.11	0.28	99.90 ± 0.51	31	51	200.72 ± 1.23
L6	3.4 ± 0.07	0.39	100.25 ± 1.45	25	45	202.51 ± 2.08
L7	3.3 ± 0.12	0.32	99.35 ± 0.82	38	53	201.82 ± 1.92
L8	3.5 ± 0.18	0.29	98.95 ± 0.35	28	49	200.24 ± 2.89
L9	3.4 ± 0.14	0.36	100.07 ± 0.92	22	43	201.12 ± 1.35

Note: Values in parenthesis are standard deviation (± SD)

The most important parameter that needs to be optimized in the development of orally disintegrating tablets is the disintegration time. In the present study disintegration time was found in the range of 22 – 58 s. It is observed that the disintegration time of the tablets decreased with the increasing level of croscarmellose sodium (CCS) and crospovidone (CP) whereas it is increased with increasing level of sodium starch glycolate (SSG). As increase in the level of SSG, it produces viscous gel layer which might have formed a thick barrier to further penetration of the disintegration medium and hindered the disintegration of the tablet contents.[9]

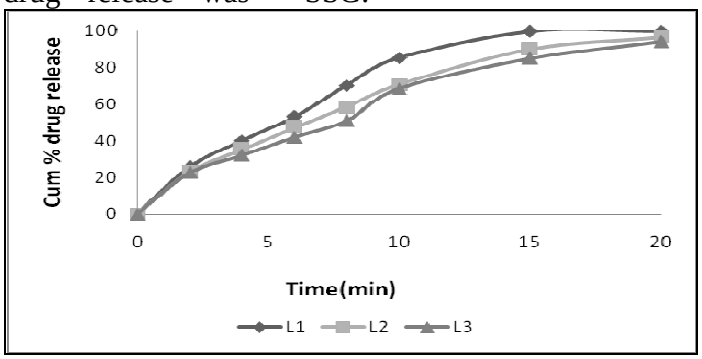
FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LORNOXICAM



Graph 1: Effect of concentration of sodium starch glycolate, crosscarmellose sodium and crospovidone on disintegration time

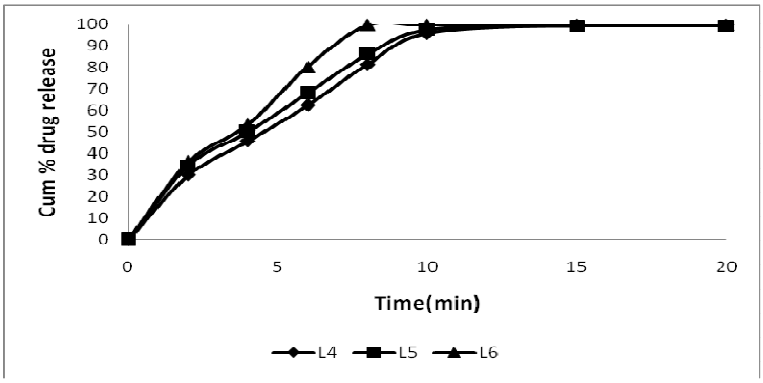
Dissolution process mainly depends on the wetting followed by disintegration of the tablets; the measurement of wetting time may be used as another confirmative test for disintegrating tablets. In the wetting time study, the wetting time was rapid in CP followed by CCS and SSG. It was observed that as the concentration of CCS and CP is increased, time taken for wetting was reduced. However for SSG as the concentration increased, time taken for wetting also increased (Table 4).

Effect of concentration of disintegrants was shown in graph 2 – 4. It indicates that time required for drug release from formulation was decreased with increasing in concentration of CCS and CP. However, time required for drug release was increased with increasing in concentration of SSG. The rapid increase in dissolution of lornoxicam with increase in CCS may be due to rapid swelling and disintegration[12] of the tablet into apparently primary particles. However; tablets prepared with SSG disintegrate by rapid uptake of water followed by rapid and enormous swelling[12] in to primary particle, but more slowly due to the formation of viscous gel layer by SSG. CP exhibits high capillary activity and pronounced hydration, with little tendency to gel formation,[12] and disintegrate the tablets rapidly but into larger masses of aggregated particles.[8] So it is anticipated that CCS gives better disintegration and thus better dissolution property compared to CP and SSG.

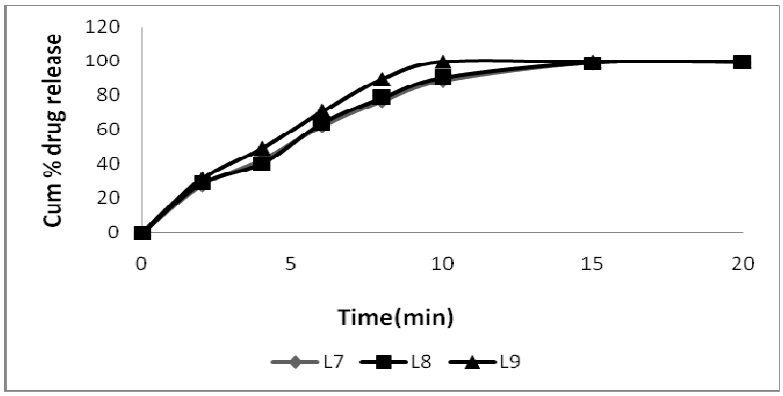


Graph 2: Dissolution profile of different sodium starch glycolate formulations

FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LORNOXICAM



Graph 3: Dissolution profile of different croscarmellose sodium formulations



Graph 4: Dissolution profile of different crospovidone formulations

The Stability study for all formulation according to ICH guidelines at 40°C/75%RH showed that formulations are stable after 4 weeks as there is no significant change in the hardness, disintegration time and drug content (Table 5).

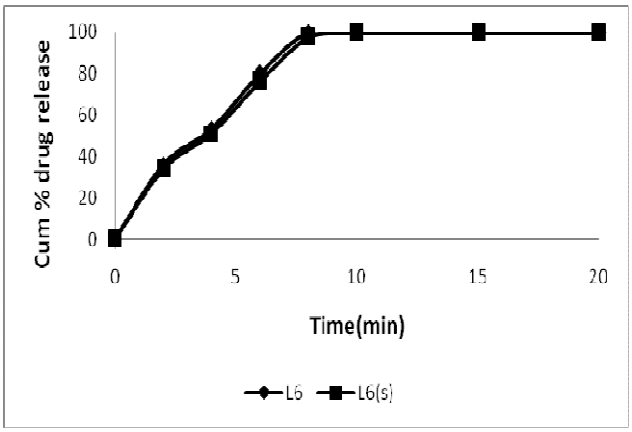
Table 5
Stability data

Formulation	Hardness (kg/cm^2) (±SD) (n=3)	Disintegration time (s) (n=6)	Drug Content (%) (±SD) (n=6)
L1	3.3 ± 0.04	48	99.02 ± 0.53
L2	3.1 ± 0.15	51	100.67 ± 1.52
L3	3.6 ± 0.18	62	100.23 ± 1.29
L4	3.2 ± 0.14	42	99.52 ± 2.31
L5	3.5 ± 0.06	35	98.98 ± 1.03

FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LORNOXICAM

L6	3.2 ± 0.11	27	100.03 ± 0.80
L7	3.6 ± 0.13	38	99.20 ± 1.43
L8	3.1 ± 0.09	31	98.53 ± 1.38
L9	3.2 ± 0.12	24	99.63 ± 1.05

Among all formulations, L6 formulation is considered as better as it gives disintegration time 25 s which fulfills official requirement (< 30s, as per USFDA guideline) for oral disintegrating tablets and % cumulative drug release was 99.85% within 8min which is the least time among all formulations. Dissolution Profile of L6 formulation after stability period of 4 week did not showed any variation in drug release which indicates formulation was stable.



Graph 5: Dissolution profile of L6 formulation (initial and after stability)

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 β-cyclodextrin in 1: 2 ratios masked the bitter taste of drug. Overall results suggested that L6 formulation containing crosscarmellose sodium in 7.5% concentration was better and satisfy all the criteria of ODTs.

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