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Research Article

PREPARATION & EVALUATION OF β-CYCLODEXTRINS INCLUSION COMPLEXES OF LORNOXICAM FOR SOLUBILITY ENHANCEMENT

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ABSTRACT

Lornoxicam is an Anti-Inflammatory Drug which has been widely used but is poorly water soluble. Thus, in the present, an attempt was made to enhance the water solubility by complexation with methyl-β-cyclodextrin to modify the physicochemical properties of Lornoxicam (LX) for solubility enhancement. Among these various Lornoxicam with β-CD inclusion complexes, K5 (1:5) formulations prepared by kneading method shows faster dissolution rate. The concept of formulating Fast Dissolving tablets of LX-β-CD inclusion complex using Effervescent agent i.e. Sodium bicarbonate, Citric Acid offers a suitable and practical approach of faster disintegration and dissolution characteristics. All formulations were evaluated for weight variation, thickness, hardness, friability, drug content uniformity, percent swelling index, *in vitro* dissolution study, their release kinetics and stability study. Drug and polymers were subjected to compatibility study using FT-IR spectroscopy, which suggests that, there was no interaction between drug and polymers and concluded that the drug, polymers and excipients were compatible to each other. From the *in-vitro* dissolution studies, a direct relationship of concentration of effervescent agent with drug release was found. F6 showed optimized release with 99.5% drug release at the end of 30 min, i.e. Immediate Release pattern. Further optimized formulation was subjected to stability testing for 2 months at Room temperature and 45°C/75RH.

Keywords: *Lornoxicam, Anti-inflammatory, Evaluation, Solubility*

1. INTRODUCTION

Oral route still remains the convenient route of drug administration in many diseases. But for the many drugs it can be problematic and inefficient mode of delivery for a number of factors. One of the important factors is aqueous solubility. Solubility and dissolution rate of the drugs are key determinants of its absorption behavior from gastrointestinal tract. Numbers of newly synthesized drug are poorly soluble in water. BCS class II (i.e., less water soluble) drug require innovative approaches to reach a sufficiently high bioavailability, when administered by oral route. Poorly water soluble drug can exhibit a number of negative clinical effects including potentially serious issues of inter-patient variability and subsequent erratic absorption following dosing to individual patients [1].

Lornoxicam is a new non steroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. Lornoxicam is a potent inhibitor of the cyclooxgenase enzymes, which are responsible for catalyzing the formation of prostaglandins (act as messenger molecules in the process of inflammation) and thromboxane from arachidnic acid [2]. Unlike some NSAIDS, lornoxicam's inhibition of cyclooxygenase does not lead to an increase in leukotriene formation, meaning that arachidonic acid is not moved to the 5-lipoxygenase cascade, resulting in the minimization of the risk of adverse events. One of the major problems with this has its very low solubility in GI fluid, which results in to poor bioavailability after oral administration. So there is a strong need to formulate Lornoxicam inclusion complex and also to formulate suitable dosage form like mouth dissolving/disintegrating tablet, to achieve reliable bioavailability and enhance patient compliance [3]. Hence, this work is planned to improve bioavailability of Lornoxicam by:

- Enhancing dissolution through complexation.
- Formulating the complex into mouth dissolving/ disintegration tablet using subliming agent and super disintegrant.

2. METHODOLOGY

2.1. Preformulation Studies

2.1.1. Identification and characterization of Lornoxicam

2.1.1.1. Determination of Melting point

Melting point of the drug was determined by taking small amount of Lornoxicam in a capillary tube closed at one end. The capillary tube was placed in a digital melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was noted.

2.1.1.2. Ultra-Violet Absorption Maxima

For the determination of absorption maxima, stock solution was prepared by dissolving 100 mg of accurately weighed Lornoxicam in 100 ml of methanol to get 1 mg/ml solution. Further 10 ml of this solution was pipetted into 100 ml of volumetric flask and diluted to 100 ml with methanol to get 100 µg/ml solution and scanned for the maximum absorbance in UV visible double beam spectrophotometer (Shimadzu 01618) in the range from 200 nm to 400 nm, using methanol solvent as a blank. The λ max of the Lornoxicam was found to be 376 nm [4].

2.1.1.3. Quantitative Estimation of Lornoxicam

For the preparation of calibration curve, stock solution was prepared by dissolving 10 mg of accurately weighed Lornoxicam in 10 ml of methanol to get 1 mg/ml solution. Further 1 ml of this solution was pipetted into 50 ml of volumetric flask and diluted to 50 ml with the same to get 20 µg/ml solutions. Aliquots of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ml of second stock solution was pipette out into 10 ml volumetric flasks to get concentration of 2 ,4, 6, 8, 10, 12, 14, 16,18 ,20 µg/ml. The volume was made up to the mark with the methanol. The absorbance of prepared solutions of Lornoxicam was measured at 376 nm against methanol as a blank [5].

2.1.1.4. Solubility analysis

Drug was added to 5 ml of different solvents i.e. Water, 0.5N HCl, 0.1N NaOH, Chloroform and Methanol in test tube at room temperature till saturation occurred. After that samples were filtered, appropriately diluted and analyzed at 376nm using UV-VIS spectrophotometer.

2.1.1.5. Partition coefficient

In order to determine the partitioning coefficient, water, n-octanol and the test substance were taken in a separating funnel and equilibrated with each other by slow shaking at a constant temperature and allowed to stand for 1 h and continued for 24 h. After 24 h these two phases i.e. water and oil were separated and analyzed at 376nm using UV- visible double beam spectrophotometer. Then the concentrations of the test substance in the two phases were determined by using the formulation.

2.1.1.6. Drug-excipient compatibility studies

A successful formulation of a stable and effective solid dosage form depends on careful selection of excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and not been used in formulation containing the active substance, the compatibility studies are of paramount importance. Compatibility of lornoxicam with β-cyclodextrin inclusion complex and with the respective polymers used in formulation of tablet, individual excipients and physical mixture of main formulation was established by Infrared Absorption Spectral Analysis (FT-IR). Any changes in the chemical composition after combining with the excipients were investigated with IR spectral analysis [6].

2.1.1.6.1. Fourier Transform Infra Red Spectroscopy

Approximately 2 mg of Lornoxicam, β -cyclodextrin and inclusion complexes samples were prepared in the form of KBr Pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FT-IR spectrophotometer.

2.2. Methods of preparation of Lornoxicam with β-cyclodextrin inclusion complex

Inclusion complexes were prepared by different methods like physical mixture, kneading and co-evaporation method.

2.2.1. Physical mixture or grinding method

Lornoxicam and β-cyclodextrin were accurately weighed in different molar ratios viz; 1:1, 1:2, 1:3 and 1:5 separately. Then they were mixed and blended thoroughly by triturating in a mortar at 20°C for about 10 minutes. The power mixtures were then pulverized through sieve no.80 and stored in desiccators till further use [6].

2.2.2. Kneading method

Here the inclusion complex of drug with β -CD was prepared by wetting the physical mixture in a mortar with a minimum volume of alcohol/water (1:1) and kneaded thoroughly with a pestle to obtain a paste, which was then dried under vacuum at room temperature, sieved through 80 no sieve and stored in a dessicator until further evaluation [7].

2.2.3. Co-evaporation method

Lornoxicam and β -cyclodextrin were accurately weighed in different molar ratios viz. 1:1, 1:2, 1:3 and 1:5 separately. Then Lornoxicam was dissolved in methanol and β-cyclodextrin was dissolved in water. The two solutions were mixed, stirred for 6 hours at 40°C and finally were dried at 40°C for 24 hrs. The dried complex was crush completely by passing through sieve no. 80 and stored in a dessicator till further use. Inclusion complexes of Lornoxicam with β -cyclodextrin prepared using composition as given in table 1.

2.3. Preparation of Fast Dissolving of tablet Lornoxicam and β-cyclodextrin inclusion complexes by Effervescent Technique

Inclusion complex of Lornoxicam: β-CD (1:5 molar ratio) equivalent to 48 mg of drug prepared by kneading method were taken using different concentration of sodium bicarbonate and citric acid as effervescence producing agent by effervescent technique. All the ingredients (except purified talc) were accurately weighed and sifted through # 44 mesh separately. The lornoxicam and diluents were mixed in small proportion in geometric order. The ingredients after sifting

through #44 mesh were thoroughly mixed. The tablets of weight 400 mg were prepared by directly compressed on a 10-station rotary tablet machine (Single punching Machine). Result was as shown in table 2 [8].

Table 1: Composition of Lornoxicam and β -cyclodextrin inclusion complexes

Inclusion complexes Composition	Method	Drug β -cyclodextrin Ratio	Formulation Code
Lornoxicam β -cyclodextrin	Physical mixture	1:1	P1
		1:2	P2
		1:3	P3
		1:5	P4
	Kneading Method	1:1	K1
		1:2	K2
		1:3	K3
		1:5	K4
	Co-evaporation Method	1:1	C1
		1:2	C2
		1:3	C3
		1:5	C4

Table 2: Preparation of fast dissolving of tablet Lornoxicam and β -cyclodextrin inclusion complexes by Effervescent Technique

Ingredients (mg)	Formulation batch					
	F1	F2	F3	F4	F5	F6
Drug: β -CD complex eq. to 8mg lornoxicam	48	48	48	48	48	48
Mannitol	399	299	289	269	249	239
Sod. Bicarbonate	10	20	30	50	70	80
Citric acid	20	20	20	20	20	20
Aspartame	5	5	5	5	5	5
Saccharine	5	5	5	5	5	5
Talc	3	3	3	3	3	3

2.4. Evaluation Parameters of Lornoxicam and β -cyclodextrin inclusion complexes

2.4.1. Preformulation Parameters:

2.4.1.1. Drug content

An accurately weighed quantity of Lornoxicam and β-cyclodextrin inclusion complexes equivalent to 8 mg of Lornoxicam was taken into a 100 ml volumetric flask and dissolved in 0.1M NaOH and filtered through a whatman no. 1 filter paper. The filtrates were diluted suitably with 0.1M NaOH solution. The content of Lornoxicam was determined spectrophotometrically at 376 nm against suitable blank UV-visible spectrophotometer [8].

2.4.1.2. In vitro dissolution studies of Lornoxicam- β-cyclodextrin complex

The quantity of Lornoxicam: β-cyclodextrin inclusion complexes (1:1, 1:2, 1:3, 1:5) was placed in dissolution medium. The dissolution study of complex was conducted using dissolution testing apparatus II (paddle method) in 900 ml of Phosphate Buffer solution of pH 6.8 at 37±0.5°C and at a speed of 100 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 376 nm using UV- visible spectrophotometer [9].

2.4.2. Evaluation of Lornoxicam and β-cyclodextrin inclusion complexes

2.4.2.1. Angle of repose

The angle of repose was determined by funnel method suggested by Newman angle of repose is determined by following formula:

$$\mathbf{Tan\Theta = h/r}$$

Where, θ = angle of repose
H= height of the cone
R= radius of the cone base

Table 3: Relationship between angle of repose (θ) and powder flow properties

Angle of repose (θ) (degrees)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

2.4.2.2. Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below [10]. It is expressed in gm/ml and is given by:
Bulk density= Bulk mass of powder/ Bulk volume of powder

2.4.2.3. Tapped Density

The tap density apparatus was set for 100 tabs and then the final volume (Vt) was measured and continue procedure till the two consecutive readings were equal [10].
Tapped density = Mass of powder/ Tapped Volume (Vt)

2.4.2.4. Carr's index or % compressibility

It indicates powder flow properties. It is expressed in percentage and is given by: [11].
% Compressibility= Dt- Db × 100/ Dt
Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Table 4: Relationship between %compressibility and flow ability

% Compressibility	Flow ability
5-15	Excellent
12-16	Good
18-21	Fair-Passable
23-35	poor
33-38	Very poor
>40	Very Very poor

2.5. Evaluation parameter of Fast Dissolving of tablet Lornoxicam and β-cyclodextrin inclusion complexes by Effervescent Technique

2.5.1. Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated [12].

2.5.2. Weight variation

Weighed 20 tablets were selected randomly and their average weight was calculated. None average weight deviates by more than the percentage and none deviates by more than twice that percentage [13].

Table 5: Weight variation specification as per IP

Average weight of tablet	% Deviation
80 mg or <	±10
More > 80 mg but < 250 mg	±7.5
250 mg or >	±5

Table 6: Weight variation tolerances for uncoated tablets as per USP XX- NF XV

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

2.5.3. Friability

Tablets were selected from each batch and placed in Roche friabilator and revolved at 25 rpm and equipment was run for 100 revolutions. Tablets were reweighed and after brushing of powder on surface of tablet, loss % was calculated [14].

$$\% \text{ Friability} = \frac{(\text{Initial weight- Final weight} \times 100)}{\text{Initial weight}}$$

2.5.4. Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The tablet to be tested was held between a fixed and a moving jaw and reading of the indicator adjusted to zero. The force applied to the edge of the tablet is gradually increased by moving the screw knob forward until the tablet breaks. The reading is noted from the scale which indicates the pressure required in kg or lb to break tablets. Tablet strength is expressed as tensile strength (kg/cm^2) [15].

2.5.5. Disintegration time

This test was performed on 6 tablets. For disintegration time, one tablet was placed in the centre of the Petri dish (internal diameter 10 cm) containing 10 ml of water and the time taken by the tablet to disintegrate completely was noted.

2.5.6. Wetting time

Five circular tissue papers were placed in a petridish of 10 cm diameter. Ten ml of water containing 0.5% eosin, a water-soluble dye, was added to the petridish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petridish at 25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicate of six. Wetting time was recorded using a stopwatch [16].

2.5.7. Water absorption ratio

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

$R = Wa-Wb/Wb\times100$

Where, Wa is weight of tablet after water absorption and Wb is weight of tablet before absorption [17].

2.5.8. Determination of drug content

Tablets (20) from each batch were randomly selected and powdered. An accurately weighed portion of the powder equivalent to about 100 mg of resulting powder was transferred to a 100 ml volumetric flask containing 70 ml of 7.4 pH phosphate buffer and dissolved completely. Then the volume was made up to 100 ml with buffer. It was shaken by mechanical means for 1h. After that it was filtered through a whatman filter paper. From this resulted solution 1 ml was withdrawn, diluted to 100 ml using buffer and absorbance was measured against blank at 376 nm [18].

2.5.9. In vitro dispersion time

10 ml of pH 6.8 phosphate buffer at 250C was placed in a petridish of 10 cm diameter. The tablet was then carefully placed in the center of the petridish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates of six tablet (n=6) and mean SD values were recorded [19].

2.5.10. In vitro Dissolution study

The dissolution study of Lornoxicam loaded FDTs was conducted using dissolution testing apparatus II (paddle method) in 900 ml of Phosphate Buffer solution of pH 6.8 at 37±0.5°C and at a speed of 100 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 376 nm using UV- visible spectrophotometer.

2.5.11. In vitro drug release kinetics

Equations to study drug release kinetics from dosage forms:

2.5.11.1. Zero Order (% R = kt)

This model represents an ideal release in order to achieve prolonged pharmacological action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets containing low soluble drugs.

2.5.11.2. First Order

Log (fraction unreleased) = kt/2.303

The model is applicable to hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

2.5.11.3. Matrix (Higuchi Matrix)

$$\% R = kt\ 0.5$$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

2.5.11.4. Peppas Korsmeyer Equation

$$\% R = ktn$$

$$log\ \% R = logk + nlogt$$

This model is widely used when release mechanism is well known or when more than one type of release phenomenon could be involved. The n" values could be used to characterize different release mechanisms.

Table 7: Release Kinetics Mechanism

Release Exponent 'n'	Drug Transport Mechanism	Rate as a function of time
0.5	Fickian Diffusion/Higuchi Matrix)	$t^{n-0.5}$
0.45< n=0.89	Non-Fickian Diffusion	t^{n-1}
0.89	Case – II Transport/Zero Order Release	Zero Order Release
Higher Release (n>0.89)	Super Case – II Transport	t^{n-1}

If n < 0.5, the polymer relaxation does not affect the molecular transport, hence diffusion is Fickian.

If n > 0.5, the solid transport will be non – fickian and will be relaxation controlled. [19].

2.6. Stability Studies

In any rational design and evaluation of dosage form for drug, the stability of the active component must be a major criterion in determining their acceptance or rejection.

Stability of a drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. Optimized formulation was selected and kept for stability studies. Formulations were packed in an aluminium foil and sealed tightly and studies were carried out for 90 days by keeping at

- Room Temperature
- $40^0C \pm 2^0C/75\%^{RH} \pm 5\%^{RH}$

Samples were withdrawn on 0th, 30th, 60th and 90th day and were analyzed for physical appearance and drug content.

The purpose of stability testing is to provide evidence on how the quality of a drug substances or drug product varies with time under the influence of a variety of environmental factors

such as temperature, humidity and light enabling recommend storage condition, re-test period and shelf-lives.

Generally the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

The International Conference on Harmonization (ICH) Guidelines titled "stability testing of new drug substances and product" describes the stability test requirements for drug registration application in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions.

3. RESULT AND DISCUSSION

3.1. Preformulation Studies

Lornoxicam is a yellow crystalline odourless powder.The melting point of Lornoxicam was found to be 228°C.

3.1.1. Determination of λ max

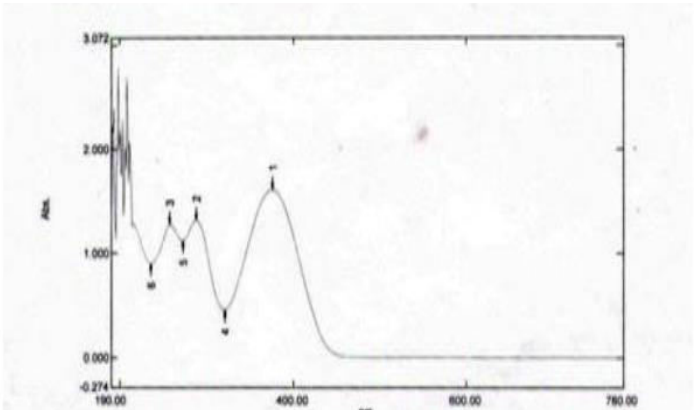

Fig.1: Absorption maxima of lornoxicam in 0.1 N NaOH

As shown in fig. 1, the maximum absorbance of lornoxicam was found to be 376 nm. Hence all further UV estimations were done at λmax 376 nm.

3.1.2. Solubility Analysis

According to the solubility data, lornoxicam drug is more soluble in methanol solvent when compared with other solvents i.e. distilled water, 0.5 N HCl, 0.1 N NaOH and Chloroform. Solubility profile of lornoxicam drug was recorded in Table 8.

Table 8: Solubility profile of lornoxicam

Dissolution media	Conc. (mg/ml)	Solubility
0.1 M NaOH	5.82	Slightly Soluble
Chloroform	5.45	Slightly Soluble
Methanol	2.76	Very Slightly Soluble
Acetonitrile	0.70	Very Slightly Soluble
Water	0.409	Insoluble

3.1.3. Partition coefficient

From the partition coefficient profile, more Lornoxicam concentration (µg/ml) was found to be in oil phase i.e. n-octanol than the water phase indicating that the drug is lipophilic in nature.

Table 9: Partition coefficient data of Lornoxicam

Phase	Absorbance	Conc. (mg/ ml)
water	0.015	0.0115
n-octanol	0.928	0.456

PO/W =C0 / CW

Partition coefficient was found to be 1.599

3.1.4. Quantitative estimation of drug

Table 10: Absorbance data for standard plot of Lornoxicam

Concentration	Absorbance
0	0
2	0.023
4	0.069
6	0.113
8	0.16
10	0.178
12	0.276
14	0.281
16	0.303
18	0.344
20	0.416

Absorbance was measured in a UV visible spectrophotometer at 376 nm against methanol as a blank. The absorbance so obtained was tabulated as in Table 10. Standard calibration curve was plotted and shown in Figure 2.

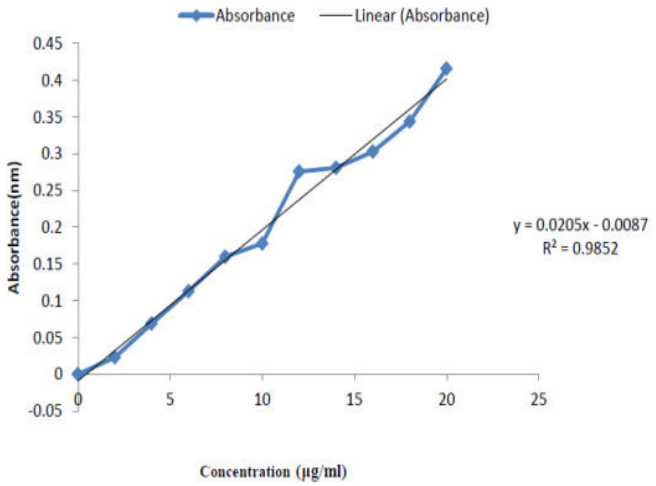

Fig. 2: Standard calibration curve of Lornoxicam

3.1.5. FT-IR of drug

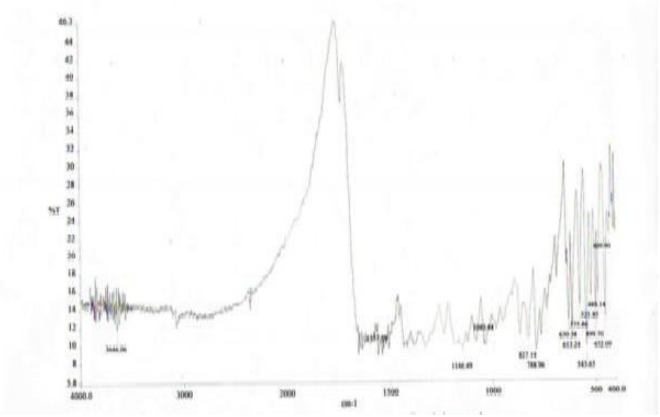

Fig. 3: FTIR Spectra of Lornoxicam

Table 11: FT-IR of Lornoxicam

Functional group	Wave number (cm^{-1})
N-H	3500-3100
C-Cl	785-540
-OH	3650
C-O	600
N-H (OPP)	827.14
S= O	1175

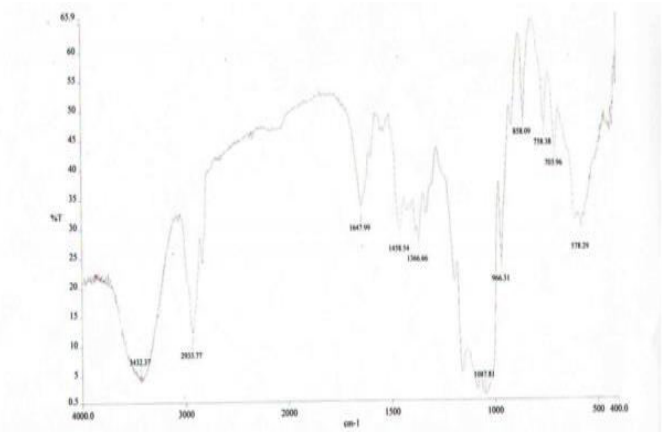

Fig. 4: FTIR Spectra of β-Cyclodextrin

Table 12: FT-IR of β-Cyclodextrin

Functional group	Wave number (cm^{-1})
C=C (benzene ring)	1446-1584
Aliphatic	1650
C-H	2920-2860
C-OH	3400(Strech) 1050(bending)
C-O	1200
C=O	875
=C-H	703 &735

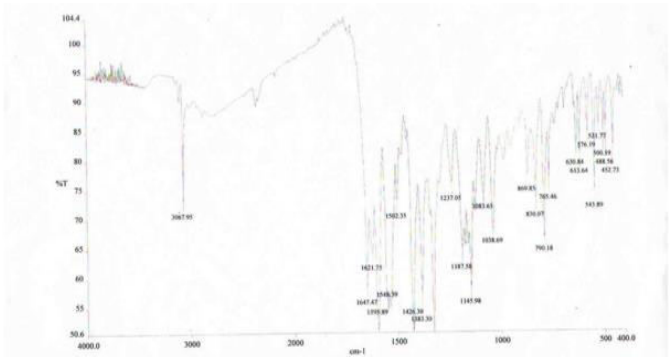

Fig. 5: FTIR Spectra of β-Cyclodextrin and lornoxicam

Table 13: FT-IR of Lornoxicam and β- cyclodextrin

Functional group	Wave number (cm^{-1})
N-H	3067.85
C=C (benzene ring)	1446-1584
Aliphatic	1650
C-OH	1050
C=O	875
N-H (OPP)	827.14
S= O	1175

3.2. Precompression Parameters

3.2.1. Angle of Repose

Angle of repose for physical mixtures was found to be ranging from 40.51° to 49.8° indicating poor flow properties of the physical mixtures.

3.2.2. Bulk density

The granules of different formulations were evaluated for loose bulk density and tapped bulk density which was found to be ranging from 0.434 to 0.476 g/ml and 0.606 to 0.714 g/ml respectively. The results were shown in Table 14.

3.2.3. Compressibility index (Carr's Index)

Compressibility index for physical mixture was found to be ranging from 26.7% to 35.7% for all the formulation batches indicating poor flow properties. The results were shown in Table 14.

3.2.4. Hausner's ratio

Hausner's ratio was found to be more than 1.25 for all the formulation batches indicating poor flow properties and results were shown in Table 14.

3.3. Post-Compression Parameters Of Lornoxicam β-Cyclodextrin Complex

3.3.1. Drug content estimation

The drug content in different Lornoxicam with β-CD inclusion Complex was highly uniform and was found to be ranging from 96% to 98.2%. Table 15 showed all values of drug content uniformity.

Table 14: Precompression Parameters of Lornoxicam-β-cyclodextrin complex

Formulation Batch	Angle of Repose (Θ)	Bulk Density (g/m)	Tapped Bulk Density (g/ml)	Carr's Index (%)	Hausner'sRatio
F1	40.51°	0.454	0.625	27.36	1.37
F2	42.3°	0.465	0.666	30.18	1.43
F3	47.7°	0.434	0.645	32.71	1.48
F4	41.1°	0.444	0.689	35.70	1.55
F5	40.4°	0.434	0.645	32.71	1.48
F6	46.88°	0.444	0.606	26.73	1.36
F7	49.8°	0.434	0.625	30.56	1.44
F8	47.7°	0.476	0.666	28.52	1.39
F9	41.5°	0.465	0.714	34.57	1.53

Table 15: Percentage drug contents inclusion complexes

Formulation code	Drug content (%)
P1	96.4
P2	98.2
P3	98.6
P4	97.3
K1	96
K2	98.2
K3	97.7
K4	99.08
C1	95.1
C2	98.2
C3	96.4
C4	98.6

3.3.2. In vitro dissolution studies of Lornoxicam with β-CD inclusion Complex

In vitro drug release study of the entire Lornoxicam with β-CD inclusion complex were carried out in phosphate buffer pH 6.8 from 0 to 30 min. In Physical mixture complete dissolution of inclusion complexes occurred more than 30 min. Complex P5 containing 1:5 molar ratios of drug and β-CD showed faster dissolution rate, about 98 % drug release was observed within 21 min. In case of kneading method complete dissolution of drug complexes occurred more than 30 min. Complex K5 containing 1:5 molar ratios of drug and β-CD showed faster dissolution rate, about 100% drug was released within 18 min. And in co-evaporation method complete dissolution of inclusion complexes occurred more than 30min. Complex C5 containing 1:5 molar ratios of drug and β-CD, showed faster dissolution rate, i.e. about 96% drug release in 21 min. So, among the different methods of preparation of inclusion complexes, kneading method was found to be most effective. Result were as shown in Table 14-17. Among these various Lornoxicam with β-CD inclusion complexes formulation K5 (1:5 molar ratio) prepared by kneading method shows faster dissolution rate.

Table 16: Comparisons of *in vitro* dissolution profile data of Lornoxicam with β-CD by Physical Method

Time (min)	Cumulative % drug release			
	P1	P2	P3	P4
0	0	0	0	0
5	14	16.9	29	25
10	19	26.6	49	55.6
15	25	46.8	63	76
20	54	58.8	77.5	98
25	66	77.5	100	
30	76	96		

Table 17: Comparisons of in vitro dissolution profile data of Lornoxicam with β-CD by Kneading Method

Time (min)	Cumulative % drug release			
	K1	K2	K3	K4
0	0	0	0	0
5	8.6	15.2	25.7	29
10	15.2	23.5	54.3	69.6
15	22.5	43.3	77.5	84.6
20	42.8	54.3	84.6	100
25	49.4	71.8	98	
30	69.2	87.2		

Table 18: Comparisons of *in vitro* dissolution profile data of Lornoxicam with β-CD by Co- Evaporation Method

Time (min)	Cumulative % drug release			
	C1	C2	C3	C4
0	0	0	0	0
5	7.7	10.8	14	23.5
10	14.7	20.5	25	54.3
15	38.9	43.3	49	71.8
20	49.9	55.6	77.5	98
25	69.6	71.8	96	
30	71	84.6		

3.3.3. Kinetic assessment of the in vitro release dissolution profile data of optimized complexes P4, K4, C4

In order to determine the release model which best describes the pattern of drug release, the *in vitro* release data were fitted according to zero order (cumulative amount of drug released vs. time), first-order (log cumulative percentage of drug remaining vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time) and Korsmeyer-peppas (log cumulative percentage of drug released vs. log time) kinetic models respectively. From the Table 18 Results of the release kinetic models showed that all the Formulation of P4, K4, C4 follows Zero Order which describes that the systems is independent of concentration. Regression value (r2) for all the three formulations was found to be in the range of 0.986 to 0.994 The zero-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsemeyer-Peppas equation. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of '*n*' gives an indication of the release mechanism n > 1.0 the release rate is independent of time and super case II transport.

Table 19: Optimization of *in vitro* dissolution profile data of optimized complexes by different method Physical, kneading and Co-Evaporation Method

Time (min)	Cumulative % drug release		
	P4	K4	C4
0	0	0	0
3	16.9	19	15.2
6	29	38.9	25.7
9	38.9	42.4	43.3
12	58.8	63	65.2
15	76	83.7	77.5
18	84.6	100	83.7
21	98		96

Table 20: *In vitro* dissolution kinetics of Lornoxicam and β- CD inclusion complexs

Formulation code	Zero-order (R2)	First order (R2)	Higuchi type (R2)	Korsemeyer-peppas release	
				(R2)	N
P4	0.994	0.813	0.913	0.94	1.38
K4	0.987	0.734	0.902	0.924	1.48
C4	0.986	0.91	0.918	0.94	1.43

3.4. Evaluation Parameters for Fast Dissolving Tablets of Lornoxicam: β-CD inclusion Complex

3.4.1. Thickness

Thickness of the developed formulations F1 to F6 varied from 2.9 ± mm to 3.2 ± mm in all the formulation which reveals that all the formulations showed uniform thickness. The results were recorded in Table 21.

3.4.2. Weight variation test

The percent weight variation for all formulations was shown in Table. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weight variation was found to be in the range of 399 to 401 indicates the uniformity of tablets with low standard deviation values.

3.4.3. Friability

The loss in total weight of the tablets due to friability was in the range of 0.68 ± % to 0.88 ± % in all the formulation and the friability value is less than 1% indicating that the friability is within the prescribed limits. This ensures that formulated tablets were mechanically stable. The results were shown in Table 21.

3.4.4. Hardness

Hardness of the developed formulations F1 to F9 varied from 3.5 to 4.1 kg/cm^2 in all the formulation indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling. The results were shown in Table 21.

3.4.5. Disintegration time

Disintegration time of the developed formulations F1 to F6 varied from 29 to 39 sec. On increasing the effervescent agent, reduction in the Disintegration time occur. The formulation F6 completely disintegrate only in 29 sec as shown in Table 21 [20].

3.4.6. Wetting time

Wetting time of the developed formulations F1 to F6 varied from 26 to 39 sec indicate that Wetting time reduce on increasing the effervescent agent. [19].

3.4.7. Water absorption ratio

Water absorption ratio is based on the concept of wicking nature of water towards the pore produced by Effervescent agent. Water absorption ratio of the developed formulations

F1 to F6 varied from 55% to 89%. From all the formulation F6 has high absorption ratio 89% was shown in Table 21 [21].

3.4.8. Drug content uniformity

The drug content in different tablet formulations was highly uniform and was found to be ranging from 96 ± % to 99.96 ± %. Table 21 showed all values of drug content uniformity and Fig represents the diagrammatic comparison of all the formulations [13].

3.4.9. In vitro dissolution profile data

In vitro drug release study of the entire Lornoxicam : β-CD loaded Fast Dissolving tablets formulations were carried out in phosphate buffer pH 6.8 from 0 to 30 min and Release of all formulations F1, F2, F3, F4, F5 and F6 are 94.6%, 96%, 97.3%, 98.2%, 97.7% and 99.5% respectively at the end of 30 min. This result suggests a direct relationship of concentration of Effervescent agent with drug release. Out of these F6 results shown optimized release was shown in Table 22. From the result, it was observed a significant effect of Effervescent agent i.e Sodium bicarbonate and Citric acid was observed. On increasing the Effervescent Agent, *in-vitro* release rate of Lornoxicam : β-CD FDts was increased [19].

3.4.10. Kinetic assessment of the in vitro release of Lornoxicam loaded FDTs of Formulations

In order to determine the release model which best describes the pattern of drug release, the *in vitro* release data were fitted according to zero order (cumulative amount of drug released vs. time), first-order (log cumulative percentage of drug remaining vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time) and Korsmeyer-peppas (log cumulative percentage of drug released vs. log time) kinetic models as shown respectively From the Table 23. Results of the release kinetic models showed that all the Formulation of F1, F2, F3, F4, F5, F6 follows Zero Order which describes that the systems is independent of concentration. Regression value (r2) for all the three formulations was found to be in the range of 0.986 to 0.994. The zero-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsemeyer-Peppas equation. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of '*n*' gives an indication of the release mechanism n > 1.0 the release rate is independent of time and super case II transport.

Table 21: Post compression Parameters for mouth dissolving tablets of Lornoxicam:β-CD inclusion complex

Evaluation	F1	F2	F3	F4	F5	F6
Thickness (mm)	3.1	3.2	3.1	2.9	3.1	3.1
Diameter (mm)	1.2	1.2	1.2	1.2	1.2	1.2
Hardness (kg/cm^2)	3.8	3.9	3.8	4.1	3.5	3.8
Friability (%)	0.84	0.41	0.83	0.82	0.42	0.82
Weight Variation (mg)	398.1	398.2	399.2	398	399.3	400
Wetting Time (sec)	37	34	33	39	33	26
Water Absorption Ratio (%)	55	68	70	74	81	89
Disintegration Time (sec)	35	38	36	39	31	29
In vitro Dispersion Time (sec)	58	38	36	39	31	29
Drug Content (%)	98.2	96	97.3	99.5	98.2	99.96

Table 22: *In vitro* dissolution profile data of mouth dissolving tablets Lornoxicam: β-CD using different concentration of Effervescent agent.

Time (min)	% Cumulative Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	7.7	10.8	14.7	12.6	23.5	29
10	20.5	25.7	38.9	42.4	36.7	43.3
15	38.9	42.4	58.8	66.1	46.8	55.6
20	54	58.8	71.8	77.5	69.6	74
25	77.4	84.6	85	87.2	83.2	92.5
30	94.6	96	97.3	98.2	97.7	99.5

3.5. Stability studies

Stability studies were conducted for the selected formulations of F6 at the 25°C or room temperature and 45°C/75% RH for a period of 60 days. The samples were withdrawn at every 15 days regular interval and analyzed for physical appearance and uniformity of drug content. The results obtained are shown in Table 24. There was no significant change observed in the physical appearance, hardness and uniformity of drug content which revealed that these formulations were found to be stable at the room temperature and 45°C/75% RH.

Table 23: *In vitro* dissolution kinetics of Lornoxicam: β CD loaded FDTs

Formulation code	Zero-order (R2)	First order (R2)	Higuchi type (R2)	Korsemeyer-peppas release (R2)	N
F1	0.983	0.72	0.830	0.999	1.35
F2	0.988	0.72	0.859	0.997	1.34
F3	0.986	0.876	0.859	0.979	1.35
F4	0.96	0.885	0.932	0.985	1.37
F5	0.99	0.813	0.93	0.949	1.291
F6	0.981	0.797	0.96	0.929	1.303

Table 24: Stability data of optimized formulation F6 stored at Room Temperature

Evaluation parameter	Time (days)				
	0	15	30	45	60
Physical appearance	+++	+++	+++	+++	++
Disintegration Time(sec)	29	29	29	30	31
Drug content (%)	99.6	99.4	99.6	99	98.6
In-vitro release (%)	99.5	99.2	99.4	98.2	98.9

Table 25: Stability data of optimized formulation F6 stored at 40 ºC/ 75 % RH

Evaluation parameter	Time (days)				
	0	15	30	45	60
Physical appearance	+++	+++	+++	++	++
Disintegration Time(sec)	29	29	30	31	31
Drug content (%)	99.6	99.2	99	98.6	98.2
In-vitro release (%)	99.5	98.2	98	97.7	97.5

+++ = Same as on zero day; ++ = Slight change in color

4. CONCLUSION

The present study is an attempt to select the best possible inclusion complex of lornoxicam with β-cyclodextrin to formulate fast dissolving tablets of lornoxicam. This paper describes a systematic development strategy to modify release pattern of lornoxicam by preparation of inclusion complex using β-CD to modify the physicochemical properties of Lornoxicam (LX), a non steroidal anti-inflammatory agent for solubility enhancement. An enhancement in the solubility and the dissolution rate can improve the oral bioavailability of such drugs, which further improves the therapeutic efficacy and patient compliance. FT-IR spectrum of pure and inclusion complex mixture of lornoxicam with β-cyclodextrin indicates compatibility between drug and polymers. All the prepared formulations were characterized for pre-compression parameters such as angle of repose, loose bulk density, tapped bulk density, carr's index, hausner's ratio and post-compression parameters such as tablet thickness, hardness, friability, drug content uniformity, percent swelling index, *in vitro* dissolution study and their release kinetics and stability study. From the *in vitro* dissolution studies of Lornoxicam: β-CD inclusion complex it was concluded that the formulation K5 i.e., the inclusion complex of (1:5 molar ratio) prepared by kneading method is the best formulation. *In vitro* study of all the formulations indicates that the formulation F6 is the best formulations among all the formulations and it shows the drug release in a manner of immediate release at the end of 30 min. Stability study of the optimized formulations indicates that the Fast dissolving tablets are stable at Room Temperature and 40ºC/75 RH.

This study conclude that since Lornoxicam is a poorly water soluble drug so an attempt was made to enhance the dissolution rate of LX, as it is a rate limiting step cause low Bioavailability. Inclusion complexation techniques are the most attractive processes to improve solubility of poorly soluble drugs. The concept of formulating Fast Dissolving tablets of LX- β-CD inclusion complex using Effervescent agent i.e. Sodium bicarbonate, Citric Acid offers a suitable and practical approach of faster disintegration and dissolution characteristics. After preparation of inclusion complex which helps to enhance the dissolution rate of LX. Among these various Lornoxicam with β-CD inclusion complexes K5 (1:5) formulation prepared by kneading method shows faster dissolution rate. Such significant enhancement in dissolution rate further causes faster onset of action which will helpful in case of reliving the pain. The LX- β-CD inclusion complex were subjected to pre-compression evaluation parameters such as angle of repose, loose bulk density, tapped bulk density, Carr's index and hausner's ratio. It was concluded from the results that the granules exhibited poor compressibility and flow property. After that the prepared FDTs tablets were subjected to various evaluation parameters such as tablet thickness, hardness, friability and drug content uniformity. From the obtained results it was concluded that the values of all formulations were determined and found to be within IP limits. Drug and polymers were subjected for compatibility study using FT-IR spectroscopy, which suggests that there, was no interaction between drug and polymers and concluded that the drug, polymers and used excipients were compatible to each other. From the *in vitro* dissolution study data and graphs, a direct relationship of concentration of Effervescent agent with drug release. Out of these F6 results shown optimised release with 99.5% drug release at the end of 30 min. On the basis of *in vitro* drug release, disintegration time formulations F6 were selected as a best formulation among all the six formulations. Proposed F6 FDTs was prepared and be a successful formulation as providing the promising release i.e. Immediate Release pattern and to analyze the mechanism of drug release from the polymeric matrices, *in vitro* drug release data were fitted to zero order, first order, higuchi release and korsemeyer-peppas model. From the study it was observed that the release of drug followed zero order release kinetics in all the formulations. From Peppa's plot the n value was found to be approximately 1.301, thus indicating super case II transport, it indicates that drug releases rate does not change over time. Accelerated stability study was carried out for selected formulations F6 which showed no significant difference in the drug content,

disintegration time, hardness, friability and *in vitro* dissolution studies which confirms the stability of the product.

5. REFERENCES

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