Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 30s (2025)
https://www.jneonatalsurg.com

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Formulation And Evaluation Of Lornoxicam Co – Crystal Tablet With Ibuprofrn Treatment Of Arthritis

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Cite this paper as: Sachin Suryawanshi, Dr. Garvita Joshi, Safiya bee, Narendra Gehalot, Dr. Vikash Jain, (2025) Formulation And Evaluation Of Lornoxicam Co – Crystal Tablet With Ibuprofrn Treatment Of Arthritis. *Journal of Neonatal Surgery*, 14 (30s), 535-558.

ABSTRACT

This study investigates the use of the solvent evaporation technique for developing co-crystals of Lornoxicam with Trimesic Acid (TA) to improve solubility, flowability, and drug release characteristics. Among the methods explored, solvent evaporation proved to be the most effective for producing co-crystals with enhanced physicochemical properties. Saturation solubility studies showed that while pure Lornoxicam had a solubility of 5.98 mg/mL, the co-crystal formulation LXM-TA CFIII achieved a 13.52-fold increase, indicating significant improvement. Crystals obtained through the solvent drop method demonstrated superior flow properties compared to those prepared via co-grinding or solvent evaporation. In vitro drug release studies revealed that pure Lornoxicam released 86.3% of its content within 360 minutes, whereas LXM-TA CFIII released up to 98.2%. This formulation followed a non-Fickian release mechanism, confirmed by a high regression value (R^2 = 0.999) and a release exponent (n = 0.793), indicating both diffusion and erosion-based release. In vivo testing on male albino mice showed that LXM-TA CFIII, administered at doses of 10, 20, and 30 mg/kg, led to dose-dependent improvements in protection and faster recovery times, with the 10 mg/kg dose offering the highest protective efficacy. Additionally, the role of electrolytes in matrix tablet formulation was evaluated. Sodium carbonate was identified as the most effective retardant for drug release. Formulation F14, containing an optimal level of sodium carbonate, demonstrated sustained drug release over 12 hours, supporting its use in twice-daily dosing. Overall, this research confirms the potential of cocrystallization and matrix modification techniques to enhance the bioavailability and therapeutic performance of poorly soluble drugs like Lornoxicam.

Keywords: *Lornoxicam, Co-crystal, Solvent evaporation, Trimesic acid, Solubility enhancement, Controlled drug release, Non-Fickian diffusion, Sodium carbonate*

1. INTRODUCTION

Arthritis, a chronic inflammatory condition affecting joints, causes pain, stiffness, and reduced mobility, significantly impacting patients' quality of life. Nonsteroidal antiinflammatory drugs (NSAIDs) remain the primary treatment option, but challenges such as poor solubility, gastrointestinal side effects, and limited bioavailability hinder their effectiveness. Lornoxicam, a potent NSAID belonging to the oxicam class, is widely used for its anti-inflammatory and analgesic properties but suffers from low aqueous solubility, which limits its therapeutic potential.

Co-crystallization, a crystal engineering technique, offers a promising solution by enhancing the solubility and dissolution rate of poorly soluble drugs without altering their pharmacological properties. When combined with ibuprofen—a commonly used NSAID with moderate solubility and a well-established safety profile—Lornoxicam may offer synergistic therapeutic effects for arthritis management. The co-crystal approach also allows for modulation of drug release behavior, improved stability, and better patient compliance. This study focuses on the formulation and evaluation of Lornoxicam-Ibuprofen co-crystal tablets aimed at enhancing the bioavailability and therapeutic efficacy of Lornoxicam in arthritis treatment. Various techniques such as solvent evaporation and co-grinding were employed to prepare co-crystals, which were then subjected to physicochemical characterization, solubility enhancement studies, in vitro dissolution testing, and in vivo efficacy assessments. The goal is to develop a stable, effective, and patient-friendly oral dosage form that offers improved pain relief and reduced dosing frequency.

istory of women with coagulation disorder and all women on anticoagulant therapy were the exclusion criteria for this study. All the antenatal women were willing to participate and signed the informed consent document was enrolled in the study. Demographic characteristics included age, booking status, area of residence, socioeconomic status, and gestational age at presentation were noted. Clinical characteristics including presenting complaints, fetal heart sounds (normal, reduced, and absent), and obstetric factors were

Experimental Work Materials and Methods

For this study, the manufacturer provided the best pharma grade materials available, which are listed in Table 1. The remaining chemicals and reagents are all analytical grade. Table 2 provides an inventory of the many instruments utilized in this piece.

Table 1: List of materials used

S. No.	Materials	Source
1.	Lornoxicam	A-Z Pharmaceuticals, Chennai
2	Benzoic acid	Sigma-Aldrich chemical Pvt. Ltd
3	Salicylic acid	Merck specialties Pvt. Ltd
4	Tartaric acid	Thermos Fisher Scientific India Pvt. Ltd.
5	Ethanol	ChangshuHongsheng fine chemical Co.Ltd.
6	Carboxymethyl Cellulose	Hi media laboratories Pvt. Ltd
7	Hydroxypropyl methylcellulose	Shasuun Pharmaceuticals Ltd, Pondy
8	Calcium carbonate	Shasuun Pharmaceuticals Ltd, Pondy
9	Magnesium carbonate	Shasuun Pharmaceuticals Ltd, Pondy
10	Sodium carbonate	Shasuun Pharmaceuticals Ltd, Pondy
11	Sodium bicarbonate,	Shasuun Pharmaceuticals Ltd, Pondy
12	Talc	Shasuun Pharmaceuticals Ltd, Pondy

Table 2: List of equipment's used

S.No.	Instruments	Company
1.	U.V-spectrophotometer	(UV-1700, Shimadzu Corporation, Japan
2.	FTIR spectrophotometer	Micro labs Agilent technologies Cary 630
3	Melting Point	DIGI MELT MP A161
4	PXRD	Bruker AXSD8
5	SCXRD	Bruker AXS Kappa Apex CCD diffractometer
6	Microscope	Olympus, BX 51- P
7	Dissolution test apparatus	Lab India DS-2000
8	pH meter	ELICO
9	Magneticstirrer	Remimotors, Ahmedabad.
10.	Waterbath	Singla Scientific Instruments, Ambala
11	Centrifuge	RemiC-24bl

12.	Hotair oven	Singla Scientific Instruments, Ambala
13.	Incubator shaker	Singla Scientific Instruments, Ambala
14.	Sonicator	DK instruments and chemicals
15.	Refrigerator	Samsung Electronics
16	Digital weighing balance	Shimadzu aux 220

Reagents: Various reagents, including pH 1.2 hydrochloric acid buffer, pH 6.8 phosphate buffer, 0.1N HCl, and 0.2M potassium chloride, were made in accordance with the experimental protocols. As per Indian Pharmacopeia (2010).

Preparation of novel multi-component crystal forms of Lornoxicam

Using the co-grinding method, solvent drop method, and solvent evaporation method in the stoichiometric ratio of drug and coformer (1:1) shown in figure, novel co- crystals was created for the current investigation.

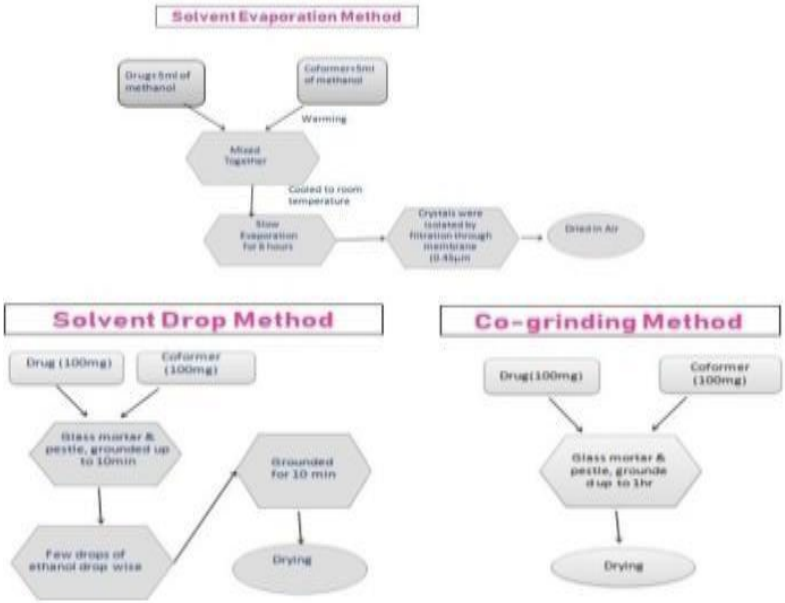

Fig 1:Preparation novel multi-component crystal forms of Lornoxicam by using solvent drop method, co-grinding method and solvent evaporation method

Preparation of LXM-BA CF-I (1:1) co-crystal by solvent drop method: After adding ethanol in small quantities and grinding for a further 10 minutes, Lornoxicam (LXM) and benzoic acid (BA) were combined in a glass motor and pestle. Then hold it till it dries.

Preparation of LXM-BA CF-II (1:1) co-crystal produced by co-grinding method: Benzoic acid (BA) and Lornoxicam (LXM) were both combined using a glass pestle and mortar, pounded for one hour and then left to dry.

Preparation of LXM-BA CF-III (1:1) co-crystal by solvent evaporation method: After being individually dissolved in 5 milliliters of ethanol and heated, Lornoxicam (LXM) and benzoic acid (BA) co-former were combined. After properly cooling the solution to ambient temperature, this was allowed to slowly evaporate for six hours. The crystals were separated via membrane filtering (0.45µm) and air drying.

Preparation of LXM-SA CF-I (1:1) co-crystal produced by solvent drop method: Salicylic acid (SA) as well as Lornoxicam (LXM) wasboth combined using a glass pestle and mortar and pounded for ten minutes. A little amount of ethanol was then added as a solvent and grounded once more for ten minutes, then left to dry.

Preparation of LXM-SA CF-II (1:1) by co-grinding method: Salicylic acid (SA) and Lornoxicam (LXM) were combined in a glass pestle and mortar, pounded for one hour, and then allowed to dry.

Preparation of LXM-SA CF-III (1:1) co-crystal by solvent evaporation method: Salicylic acid (SA) co-former and

Lornoxicam (LXM) were individually dissolved in 5 ml of ethanol while heated, then combined. After cooling the solution to ambient temperature, it was allowed to slowly evaporate for six hours. The crystals were separated by air drying after being filtered through a membrane with a thickness of 0.45 µm.

Preparation of LXM-TA CF-I (1:1) co-crystal by solvent drop method: Using a glass motor and pestle, Lornoxicam (LXM) and tartaric acid (TA) were crushed for ten minutes then add a small amount of ethanol (the solvent) dropwise and grind for an additional ten minutes then hold it till it dries.

Preparation of LXM-TA CF-II (1:1) co-crystal by co-grinding method: In a glass motor and pestle, Lornoxicam (LXM) and tartaric acid (TA) were combined, ground for one hour, and left to dry.

Preparation of LXM-TA CF-III (1:1) co-crystal by solvent evaporation method: In 5 milliliters of warm ethanol, the co-formers of tartaric acid (TA) and Lornoxicam (LXM) were separately dissolved and then combined. After cooling the solution to ambient temperature, it was allowed to slowly evaporate for six hours. The crystals were separated via membrane filtering (0.45µm) and air drying.

Formulation of Lornoxicam cocrystals controlled release matrix tablets: Using the direct compression method and electrolytes as rate retardants, a controlled release matrix tablet containing Lornoxicam and tartaric acid cocrystals was designed in this study. The dispensing space was kept at or below 25ºC and 30% relative humidity.

Procedure: Weigh all ingredients precisely, including the Lornoxicam-tartaric acid cocrystals. Each ingredient was then separately passed through sieve no. 60, and all ingredients were fully mixed by triturating for up to 15 minutes. After talc was added to the combined powder, it was thoroughly mixed once again in order to punch tablets using the direct compression method.

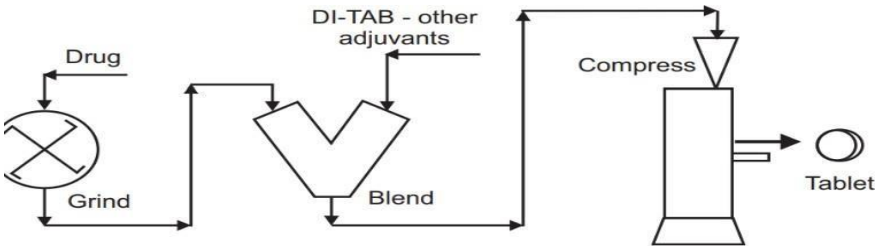

Fig.2: Direct compression method Table 3: Formulation of Lornoxicam-TA cocrystals controlled release tablets

S. No.	Ingredients	Amount of ingredients per tablet (mg/Tablet)																
		F	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1	Lornoxicam + TA cocrystals	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2	HPMC (50cps)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
3	Calcium carbonate	-	25	50	75	100	-	-	-	-	-	-	-	-	-	-	-	-
4	Magnesium carbonate	-	-	-	-	-	25	50	75	100	-	-	-	-	-	-	-	-
5	Sodium bicarbonate	-	-	-	-	-	-	-	-	-	25	50	75	100	-	-	-	-
6	Sodium carbonate	-	-	-	-	-	-	-	-	-	-	-	-	-	25	50	75	100
7	Lactose Monohydrate	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
8	Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Total Weight	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**

TA-Tartaric acid; HPMC-Hydroxypropyl methyl cellulose; F-Formulation without electrolyte; F1-F4- Formulations with calcium carbonate electrolyte; F5-F8- Formulations with magnesium carbonate electrolyte; F9-F12- Formulations with Sodium bicarbonate electrolyte; F13-16- Formulations with Sodium carbonate electrolyte; Q.S-Quantity Sufficient

Experimental Procedures Calibration of Drug by UV-Visible Spectrophotometry

a) Preparation of standard curve: After carefully weighing 100 mg of Lornoxicam in a 100 ml volumetric flask, the medication was solubilised in 20 ml of methanol. The previously described solution was further diluted then using distilled water, pH 6.8 phosphate buffer, and 0.1 N HCl up to 100 ml. The resulting solution was diluted up to 100 ml to create a 100 µg/ml stock solution. The absorbance of the solutions at 270 nm was measured using a twin beam UV visible spectrophotometer. Following the creation of the absorbance vs. concentration plot, a linear regression analysis was performed on the data using Microsoft Excel.

Characterizations of Lornoxicam multicomponent cocrystals: Co-crystals were characterized by FTIR, melting point, PXRD, SCXRD, electron microscopy, drug content, percentage yield, intrinsic solubility, *in-vitro*dissolution rate, and in vivo study

Fourier Transform Infrared Spectroscopy (FTIR): Using an FTIR spectrophotometer (Micro Labs Agilent Technologies Cary 630 FTIR), the FTIR spectra of the pure drug, coformers, and produced co-crystals are recorded. The wide spectrum was gathered in the same settings. Every spectra was produced by averaging three single scans that were gathered between 4000-400 cm-1.

Melting Point Analysis: Pulverize the crystalline material first. Pour the material into the capillary tube. Now lightly tap the capillary tube's sealed end against the porous plate. As an alternative, insert the tube's end into the tube tapper spaces on the Digi Melt's right edge and press the tube tapper button down. After the tube's bottom is filled with crystals, insert the tube into the Mel-Temp MPA161's slot behind the eye piece.

PXRD Analysis: It is a quick analytical method that can yield dimensions of unit cells and is mostly used to identify the phase of crystalline materials. In contrast to Lornoxicame and its respective conformers, such as benzoic acid, tartaric acid, andsalicylic acid, the generated multicomponent crystal formulations showed distinctive crystalline PXRD (BrukerAXSD8 Advance) patterns, suggesting the formation of novel solid phases.

Single Crystal X-ray Diffraction: Using Mo-Kα radiation (λ=0.71073 A°), X-ray diffraction datasets for compounds, LXM-BA-I, LXM-TA-I, and LXM-SA-I were gathered on a Bruker AXS Kappa Apex CCD diffractometer. The crystallographic data for the compounds has indicated the temperature at which the analysis was conducted. SHELXS-97 was utilized to solve all structures directly, and SHELXL-97 was used to refine them against F2 (Sheldrick, 2008). Using the difference Fourier map, the hydrogen atoms in carboxylic acid groups and amide groups involved in the synthesis of a salt or a co-crystal of LXM were located and refined isotopically. With an isotropic displacement value set to 1.2 times the Uq of the atoms they were linked to, all extra hydrogen atoms were geometrically inserted and refined.

Calculation of Percentage yield: Accurately weighed dried crystals were taken and percentage yield of them was calculated by the formula given below

$$Percentage\ yield = \frac{Practical\ yield}{Theoretical\ yield} \times 100$$

Drug content: Prepared supramolecular crystals (100 mg) were dissolved in 100 ml of distilled water, and the solution was subjected to adequate dilution with distilled water before being subjected to UV-visible spectrophotometric analysis at 270 nm to determine the drug concentration. The investigation was carried out three times.

Particle size and shape: Accelerated electrons illuminate an Olympus BX 51-P electron microscope. The light microscope's camera and image analysis software may count particles within preset size fractions to provide qualitative or semi-quantitative information on particle size and shape. The microscope can magnify particles up to 1000 times, allowing for precise measurements of particles as small as 1 µm in diameter. For full particle size distribution determination using light microscopy, a system with automated image analysis software must analyse many photos with many particles. Manual image analysis works well for small particle counts as there is no automated system.

Saturation solubility: Investigating the saturation solubility of Lornoxicam and produced co-crystals in triplicate using the methodology described by Higuchi and Connors was carried out. An excess amount of medication and produced Co-crystals were added to vials holding 10 milliliters of distilled water for the saturation solubility study. For four hours at room temperature, the vials were shaken in an incubator shaker at a rate of 100 shakes per minute. After passing the mixture through a membrane with a pore size of 0.45µm, the amount of medication dissolved was measured using spectrophotometry (Agilent Technologies Cary 60). Three duplicates of the study were conducted. **pH:** The vials holding 10 ml of distilled water were filled with an excess of medication and manufactured cocrystals, and they were shaken vigorously (100 agitations per minute) for two hours at room temperature. A digital pH meter is used to measure the pH of the formulated crystal formulations as well as the pure medication.

Evaluation of *In vitro* dissolution studies: A USP type 2 paddle dissolving apparatus with eight-station was used the study (Lab India, Model Disso 2000). The in vitro dissolution investigations were conducted in triplicate. 50 rpm, 37± 0.5^0C, and 900 mL of pH 6.8 phosphate buffer were used for the dissolution experiments. After a reasonable amount of time, 5 ml of the sample was removed, and each time, 5 ml of fresh medium was added. Without delay, the solutions underwent filtration

using a 0.45 mm membrane filter, were diluted, and the concentration of Lornoxicam was ascertained using spectrophotometry at the corresponding λmax of 270 nm.

Flow properties determination for Lornoxicam co-crystal controlled release (CR) tablet blend: Using a bulk density device, the bulk density (BD) and tapped density (TD) were examined in triplicate. BD and TD are used to assesss the Hausner's ratio (HR) and the Carr's index (%). Using the fixed funnel method, the angle of repose of the blend of Lornoxicam produced co crystal tablets was evaluated.

Evaluations of Lornoxicam controlled release co-crystal tablets: Every final batch underwent a variety of tests for quality assurance, including those for weight variation, thickness, hardness, drug content and friability.

In vitro dissolution: The dissolving experiments were performed using the USP Apparatus 2. Official procedures were adhered to, including the use of 900 mL of pH 6.8 phosphate buffer as the dissolving media at 50 rpm and 37±0.5°C. Samples were taken at pre-arranged intervals using a syringe with a pre-filter connected, and fresh fluid was also changed at that time. Sample absorbance at 270 nm was measured using a Lab India UV-3200 UV-Visible spectrophotometer. Every experiment was conducted in triplicate, and the mean ± SD was used to determine the outcome.

Release Kinetics: The dissolution data were statistically modeled using the Higuchi model, Peppas release model, zero order, and first order kinetics. The rate of drug release from a cocrystal tablet formulation was examined in this study. It was possible to determine the diffusion coefficient's n value and the regression analysis's r^2 value.

Table Release Kinetic Model of Lornoxicam co-crystal tablet Formulations

Kinetics	**Expression**
Zero order	Qo-Qt=kot
First order	logQt=logQ0+kt/2.303
Higuchi	$Q = k\sqrt{T}$
Korsemeyer Peppas	$Mt/M=KKPt^n$

Where Qt and Qo correspond to the amount of the drug present at the time t and initial quantity of the drug present at time t=0. Mt and M corresponds to quantity of drug present at the time t and at the infinite time respectively. Various other terms viz K0, KH, K1, and KKP related to the release constants obtained from the linear curves of zero-order, Higuchi model, first-order, and Korsemeyer–Peppas model, respectively

Table Interpretation of diffusion release mechanisms

Release Exponent (n)	**Release Mechanism**
<0.45	Fickian release (Case-I)
0.45<n<0.89	Non-fickian release (Anomalous)
0.89	Case-II transport
>0.89	Supercase-II transport

Physical Stability Studies: Accurately weighed samples (about 100 mg) of pure LXM and its multicomponent forms were deposited in loosely closed glass vials and stored in a stability room at 40C/75% RH as well as at ambient settings for six months before being evaluated for weight change, assay, and in vitro dissolution.

***In vivo* study**

Animals : Swiss Albino mice, Species : Wister, Gender : Male, Weight : 20-30gm,

Dose : 30.0 mg/kg/day, Duration: 1 month

a) ***Induction of seizure by Maximal electroshock seizure test:*** Total of 18 albino mice (20-30gm) will be used in this experiment. The mice will be randomly divided into three groups of six animals each (n=6)

b) ***Experimental Protocol:*** All the animals were divided into 3 groups (n=6)

Group I : Control (0.5% CMC with NS (0.9%)

Group II : Lornoxicam (30 mg/kg p.o)

Group III : Optimized LXM-TA Suspension formulation (10, 20, 30 mg /kg p.o)

c) Methodology: Experimental methodology for antiepileptic activity by maximal electroshock seizure test (MES) was explained in previous chapter 3.2.11 c.

d) Statistical analysis Data: All the data was expressed in Mean±SEM and statistically analysed byone way ANNOVA followed by multiple Dunnet's multiple "t" test as post hoc test is used, usingsoftware Graph pad prism 5 versions.

2. RESULTS AND DISCUSSION

Calibration of Lornoxicam (LXM) by UV- visible spectrophotometer: Essentially the straight-line relationship between two variables is looked at in a basic linear regression study. The calibration curve that was created using Beer Lambert's law for concentration ranges of 5 to 25 µg/ml in various media, including pH 1.2 (0.1 N HCl), distilled water, and pH 6.8 phosphate buffer. Plotting the absorbance against concentration data resulted in the calibration graphs, which were then subjected to linear regression analysis. The medication had shown linearity in the range of 5-25 µg/ml with a correlation coefficient of 0.998 in pH 6.8 phosphate buffer. This meium was chosen for additional study.

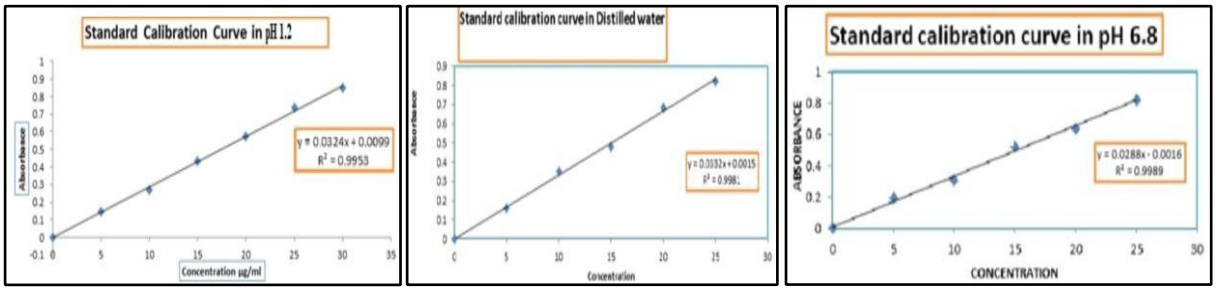

Figure Calibration curve and linear regression analysis of Lornoxicam in different mediums (pH 1.2, Distilled water, and pH 6.8 phosphate buffer)

Table Linear regression analysis of LXM

Buffer Medium	Linear Regression Analysis		
	R2	m	c
pH 1.2 (0.1 N HCl)	0.995	0.0324	0.001
Distilled water	0.998	0.0332	0.001
Phosphate buffer (pH 6.8)	**0.998**	**0.0288**	**0.008**

FTIR: A FTIR spectrophotometer (Micro Labs Agilent Technologies Cary 630) is used to record the FTIR spectra of individual drugs, excipients, and produced co-crystals. FT- IR spectroscopy is a highly effective method for characterizing and differentiating co- crystals from salts, particularly in the case of co-formers that are carboxylic acids. Every spectrum was produced by averaging three single scans that were gathered between 4000-400 cm^{-1}. FTIR spectra are shown in **Figures,** and interpretation values are listed in **Table.** A substantial C-H stretching at 2921.856 cm^{-1}, H-C=C stretching at 2846.875 cm^{-1}, C=C stretching at 1451.480 cm^{-1}, and C-O stretching at 703.932 cm^{-1} were all seen in the LXMBA CF1 instance.For the LXM-SA CF I demonstrated strong stretches at 3234.052 cm^{-1} for O-H, 2923.996 cm^{-1} for H-C=C, and 1711.901 cm^{-1} for C-O. In contrast, I demonstrated substantial O-H stretching at 3511.817 cm^{-1}, H-C=C stretching at 2931.893 cm^{-1}, C-O stretching at 1683.144 cm^{-1}, and C-O stretching at 1121.154 cm^{-1} in the LXM-TA CF I scenario. In a molar ratio of 1:1 (drug: co-former), the prepared co-crystals exhibit shifting values that suggest the production of a novel co-crystal solid phase.

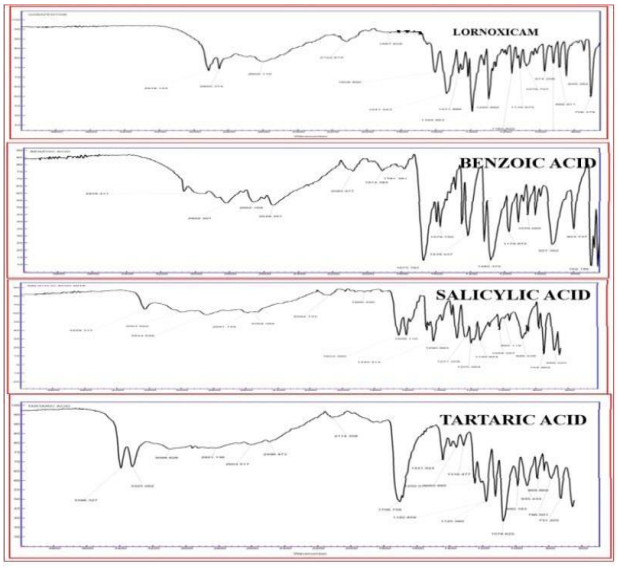

Fig FTIR Interpretation of pure Lornoxicam, Salicylic Acid, Benzoic Acid, and Tartaric Acid Table FTIR Interpretation of pure Lornoxicam, Salicylic Acid, Benzoic Acid, and Tartaric Acid

Drug substance	Wave number (cm^{-1})	Peak assignment
Lornoxicam (LXM)	3895.12	Acid OH Stretching
	2853	Amine N-H Stretching
	1195.992	C-N Stretching
	1541.543	Carbonyl COOH Stretching
Benzoic acid (BA)	2976.411	Alcohol O-H Stretching
	2822.301	C-H Stretching
	1685.787	C=O Stretching
	1475.537	Carbonyl COOH Stretching
	1290.376	C-O Stretching
Salicylic acid (SA)	3229.315	Alcohol (O-H Stretch, H- bonded)
	3013.240	Aromatic C-H Stretching)
	1662.964	Ketone(C-O Stretching)
	1612.282	C=C (phenolic) stretching
	1387.342	C=O (COO-) stretching
Tartaric acid (TA)	3396.327	Acid O-H Stretching
	3325.062	Alcohol (O-H Stretch, H- bonded)
	2970.358	Aromatic C-H Stretching
	1706.758	Ether (C-O Stretching)

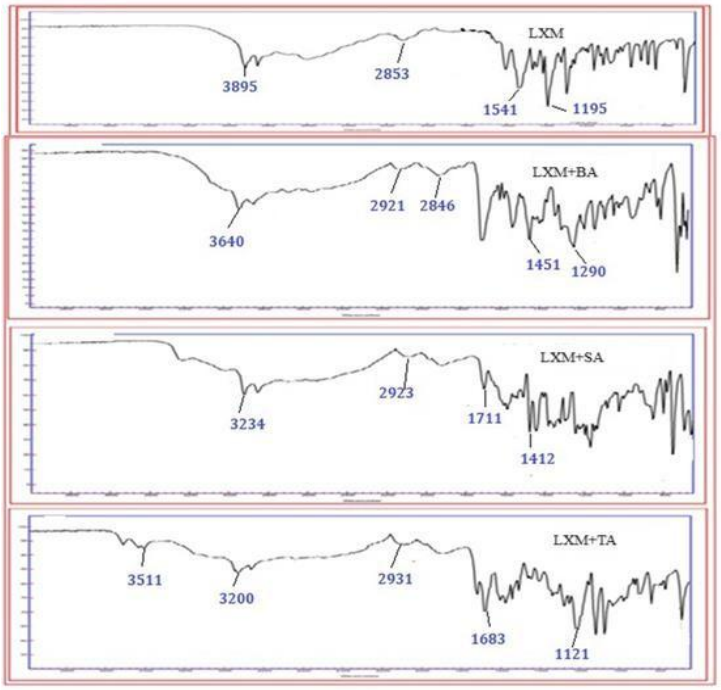

Fig FTIR Interpretation of prepared Lornoxicam co-crystal forms

Table FTIR Interpretation of prepared Lornoxicam co-crystal forms

Drug substance	-1	Peak assignment
Lornoxicam (LXM)	3895	Acid OH Stretching
	2853	Amine N-H Stretching
	1195	C-N Stretching
	1541	Carbonyl COOH Stretching
LXM-BA CF I	2921	Alcohol O-H Stretching (H-bonded)
	2846	H-C=C stretching
	1692	C=O Stretching
	1451	Carbonyl COOH Stretching
	1290	C-O Stretching
LXM-SA CF I	3234	Alcohol (O-H Stretch, H-bonded)
	2923	Aromatic C-H Stretching
	1711	C-O Stretching
	1412	C=C (phenolic) stretching
LXM-TA CF I	3512	Acid O-H Stretching
	2931	H-C=C stretching
	1683	C-O stretching
	1121	Ether (C-O Stretching)

Wave number (cm) Melting Point Analysis: It was done to investigate the prepared co-crystal formulations' thermal behavior in respect to their constituent parts. DigiMelt MPA161 was used to measure melting point values. Melting point values for the pure LXM medication were 162-166 °C, 121-123°C for benzoic acid, 157-159 °C for salicylic acid, and 170-172 °C for tartaric acid. As shown in Table, the observed melting point values for created co-crystals such as LXMBA CF show at 144-148 °C, while those for LXM-SA CF show at 165-170 °C and those for LXM-TA CF show at 178-184 °C.Co-crystal formulations had distinct melting points, and each individual component showed a separate melting transition. This indicates the formation of new solid phase in a molar ratio of 1:1.

Table Melting point analysis of drug, co-formers, and prepared co-crystals

S. No	Sample Code	Observed melting point (°C)
1	Lornoxicam (LXM)	162-166
2	Benzoic acid (BA)	121-123
3	Salicylic acid (SA)	157-159
4	Tartaric acid (TA)	170-172
5	LXM-BA CF III	144- 148
6	LXM-SA CF III	165-170
7	LXM-TA CF III	178-184

Lornoxicam (LXM); Benzoic acid (BA); Salicylic acid (SA); Tartaric acid (TA); CF IIISolvent Evaporation method

PXRD: An examination of powder X-ray diffraction (PXRD) can reveal the drug molecule's crystallinity. The unique co-crystals and the pure LXM drug's PXRD spectra were displayed. LXM-BA CF Ico-crystals demonstrated the major characteristic peaks of 2θ scattering angles at 7.92 , 15.07 , 17.03 , & 25.77 . LXM-SA CF I co-crystals demonstrated the major characteristic peaks of 2θ scattering angles at 6.17 , 7.90 , 11 , &18.6 . LXM-TA CF Icocrystals demonstrated the major characteristic peaks of 2θ scattering angles at 8.62 , 17.24 , 18.02 , & 20.47 . In all prepared co-crystals peaks represented also there in pure drug molecule and differ from co-former.LXM-TA CF Ishowed high degree of Crystallinity (87.10%) when compared to LXM-SA CF I(61.74%) andLXM-BA CFI (47.10%). Some additional peaks formed in prepared co-crystal forms when compared to pure LXM drug which represent the formation of new solid phases in a molar ration of 1:1 (drug:coformer).

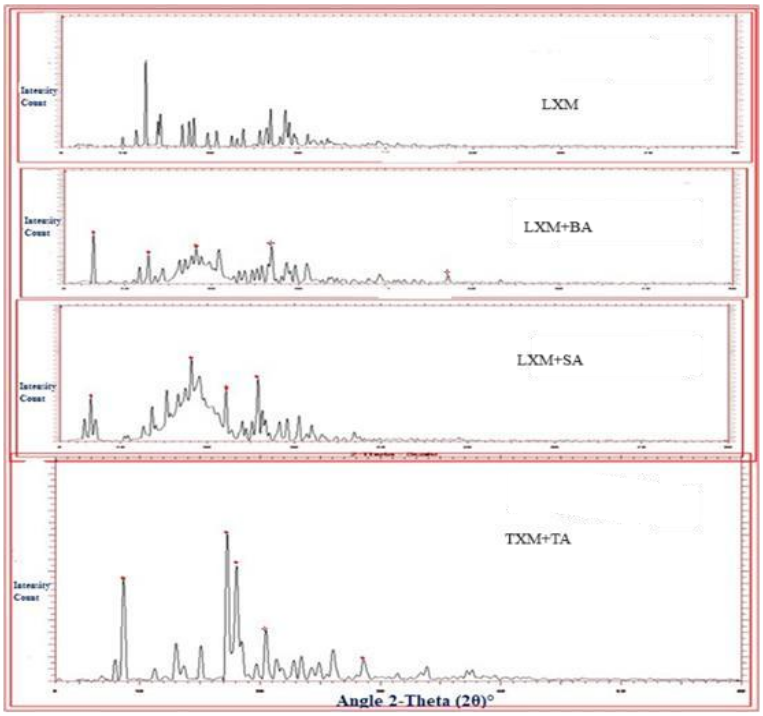

Fig. PXRD analysis of pure drug and prepared co crystals

Table PXRD analysis of pure drug and prepared co crystals

Formulation code	Peak Positions ($2\theta^0$)	d value Angstrom	Intensity Count	% Degree of Crystallinity (%Xc)
LXM	8.741	10.10819	1369	-
	17.412	5.0890	1720	
	18.167	4.8767	1660	
	20.641	4.2996	1432	
	26.357	3.3789	1006	
LXM-BA CF I	7.924*	11.149	108838	47.10
	15.071*	5.87401	3819	
	17.033	5.20139	6228	
	25.772*	3.45405	6131	
LXM-SA CF I	6.178*	14.29423	5206	61.74
	7.902	11.17879	1864	
	11.002*	8.03567	743	
	18.6	4.76657	1143	
LXM-TA CF I	9.626*	10.24274	825	87.10
	19.248*	5.13715	1204	
	21.023*	4.91798	947	
	24.479*	4.33326	414	

*New peaks formed; LXM-Lornoxicam; BA-Benzoic acid; SA-Salicylic acid; TA-Tartaric acid; CF-I- Solvent Evaporation

Single Crystal X-ray diffraction analysis (SCXRD): One molecule of benzoic acid and Lornoxicam in an asymmetric unit crystallizes in orthorhombic space group Pccn.

Lornoxicam is found in the crystal structure as zwitterions. The O-H•••O interactions that both phenolic and carboxylic and OH donors of 3HBA form with Lornoxicam result in a crown ether-like cyclic tetramer (synthons II, D=2.542 Å, θ=179°; synthons III, 2.673 Å, 176°). These tetramers are then joined by charge-assisted N+-H•••O- (2.701 Å, 153°) hydrogen bonds, creating a layered structure the Supporting Information for intra- and intermolecular N+-H•••O- hydrogen bonding using additional N-H donors from the ammonium group.

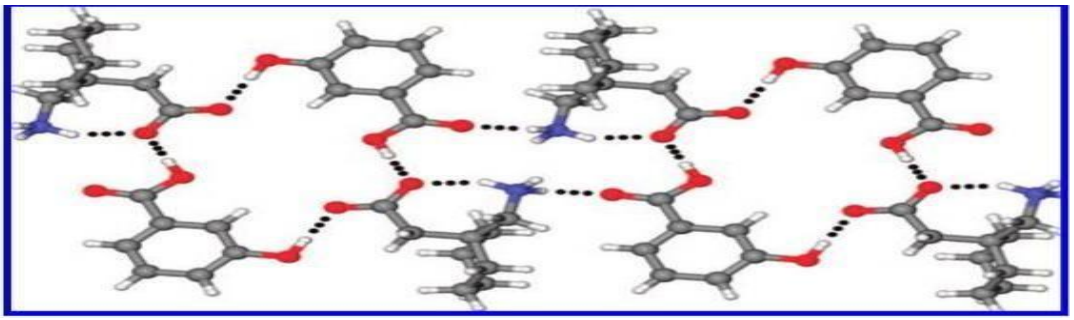

Fig. (a) Hydrogen bonding pattern in Lornoxicam-3HBA. Tetramers form between Lornoxicam and 3HBA through O-H···O- hydrogen bonds. These tetramers are connected by N^+-H···O- hydrogen bonds to form a layered structure. There is no proton transfer from 3HBA to Lornoxicam.

Two symmetry independent molecules of salicylic acid (monoclinic, P21/n) and Lornoxicam are present in each asymmetric unit. Proton transfer occurs between the basic carboxylate of Lornoxicam and the carboxyl group of salicylic acid. As seen, salicylic acid and Lornoxicam interact through ammonium carboxylate synthon I (2.948 Å, 147°; 2.842¯, 157°) and carboxyl carboxylate synthon II (2.551¯, 174°; 2.547¯, 173°). An intramolecular O-H•••O- (2.528 Å, 152°; 2.515 Å, 157°) hydrogen bonding involves a phenolic group.

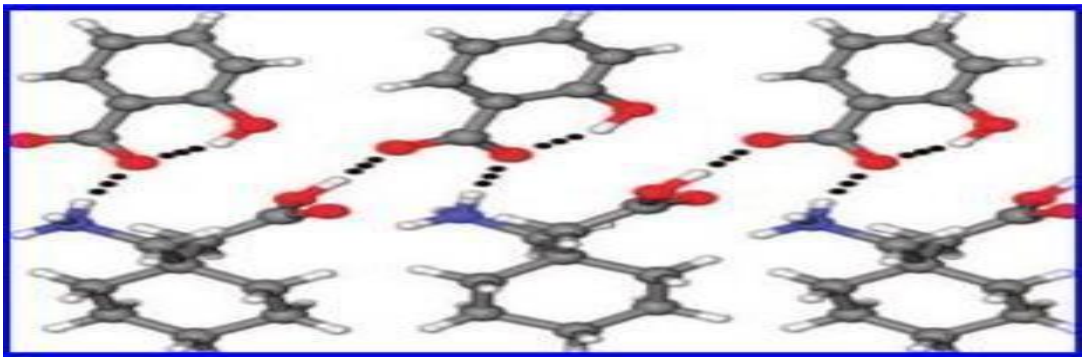

Fig. (b) The structure of the Lornoxicam-salicylic acid tape contains carboxylate synthons II and I as well as carboxylate synthons II and III. Proton transfer occurs between salicylic acid and the carboxylate of Lornoxicam.

Proton transfer from RS-tartaric acid to Lornoxicam's carboxylate takes place in the crystal structure. In the asymmetric unit of triclinic space group P1, one molecule of tartaric acid and one molecule of Lornoxicam crystallize respectively. Lornoxicam interacts with tartaric acid via phenolic O-H hydrogen bonds (2.815 Å, 147°) or carboxyl carboxylate synthon II (2.575 Å, 162°) to form a tetrameric motif. Charge- assisted N+-H•••O-(2.813 Å, 168°) hydrogen bonds that join these tetrameric motifs result in the formation of a layered structure. The hydrogen bonds between these layers are N+-H•••O-. Within the molecule, one of Lornoxicam's ammonium N-H donors mediates N+-H•••O hydrogen bonding.

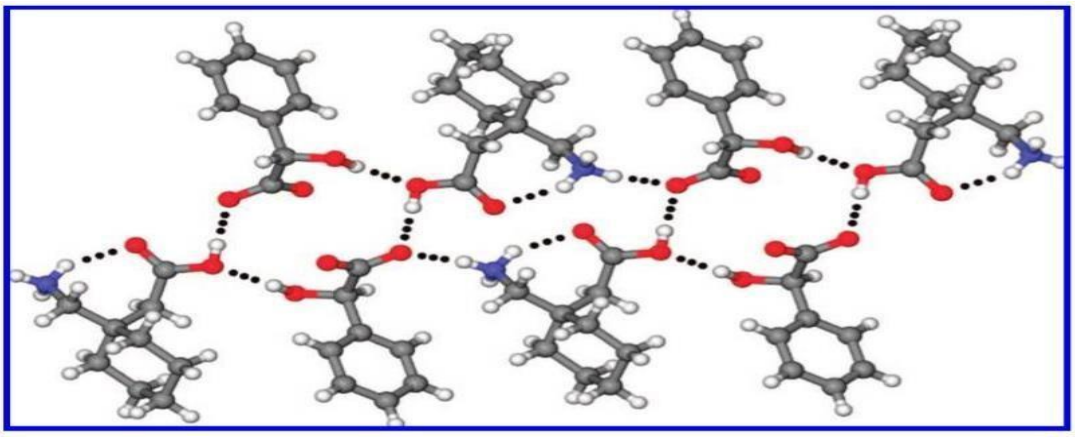

Fig.(c) In Lornoxicam-RS-tartaric acid, carboxyl-carboxylate synthon II and ammonium-carboxylate synthon I. Lornoxicam and RS-tartaric acid each consist of two molecules that form a tetramer, which is joined by N+-H•••O- hydrogen bonds. Proton transfer occurs between Lornoxicam and RS-tartaric acid.

Table Single Crystal X-ray diffraction analysis of co-crystal forms

Parameters	**LXM-BACFI**	**LXM-SACFI**	**LXM-TACFI**
Formula	C16H23NO5	C16H23NO5	C17H25NO5
Formula Wt.	309.35	309.35	323.38
Stoichiometric	1:1	1:1	1:1
Crystal System	Orthorhombic	Monoclinic	triclinic
Space Group	Pccn	P21/n	$P\bar{1}$

a (A˚)	12.828	10.582	6.113
b (A˚)	25.380	10.392	9.348
c (A˚)	9.5029	28.659	14.882
α (deg)	91	91	91
β (deg)	91	97.573	101.862
γ (deg)	91	91	91
Volume(A˚3)	3093.8	3130.6	811.9
Dcal ($g.cm^{-3}$)	1.328	1.313	1.324
Reflns collected	73414	67352	24635
Unique reflns.	3875	7815	4072
observed reflns	3586	6802	3890
Z	8	8	2
T (K)	85	85	85
R1	0.0371	0.0504	0.0426
W R2	0.0966	0.1248	0.1082
GOF	1.069	1.126	1.102

Drug content and percentage yield of Prepared Co-crystals: The percentage yield and content of drug of the manufactured multicomponent co- crystal formulations were assessed. When comparing the percentage yield of LXM-TA CF I (94.16%) and LXM-BA CF I (92.5%) to the other co-crystals shown**,** the results indicated high drug content in the case of LXM-TAC CF III (99.89) and LXM-BA CF III (99.24).

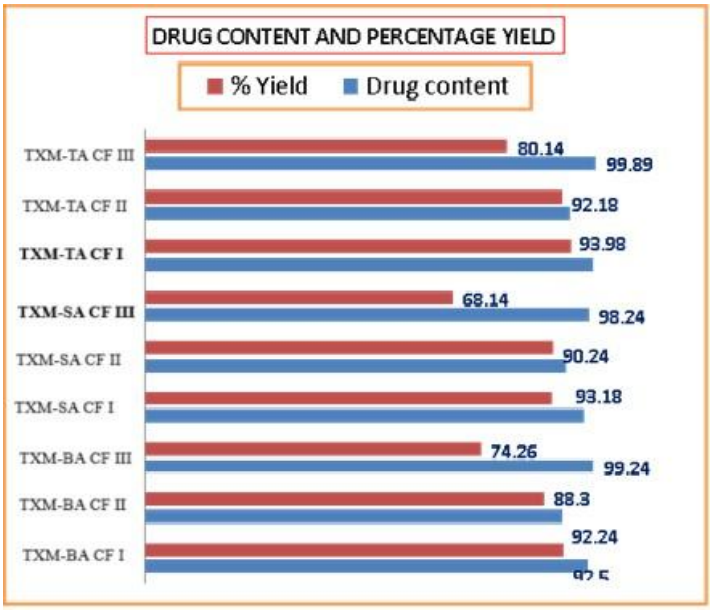

Fig Drug content and Percentage yield of prepared co-crystals

Intrinsic Solubility and pH: Saturation solubility analyses were performed on the generated co-crystal formulations that are of multicomponent and also the pure Lornoxicam. The results for the former showed a value of 0.598 mg/ml, the latter showed a high solubility value of 8.10, the latter showed a value of 7.85, and the latter showed a value of 5.45. When

compared to pure Lornoxicam, LXM-TA CF III shown 13.52 folds more solubility, LXM-SA CF III demonstrated 13.1 folds more solubility, and LXM-BA CF III demonstrated 9.6 folds more solubility.

The pH values that of the pure Lornoxicam solution at equilibrium were 6.7, 6.61 for the LXM-BA CF III solution, 4.88 for the LXM-SA CF II solution, and 2.82 for the LXM- TA CF II solution. When comparing saturation solubility studies, the co-grinding process used to manufacture LXM-TA CF II co-crystals yields the best results on comparison to other methods such as the solvent evaporation method andsolvent drop method

Table intrinsic solubility and pH of pure drug & prepared co-crystals in water at 25 °C

Drug substance	Solubility analysis		pH of solution at equilibrium
	mg/ml	No. of folds of elevation	
Lornoxicam (LXM)	0.598± 0.42	-	6.70
LXM-BA CF I	5.15 ± 0.15	9.1	4.26
LXM-BA CF II	3.83 ± 0.14	6.4	3.28
LXM-BACF III	**5.45 ± 0.19**	**9.6**	4.61
LXM-SA CF I	6.03 ± 0.11	10	3.35
LXM-SA CF II	5.65 ± 0.14	9.5	4.88
LXM-SA CF III	**7.85 ± 0.16**	**13.1**	3.15
LXM-TA CF I	6.55 ± 0.15	10.91	2.45
LXM-TA CF II	4.73 ± 0.17	8.8	2.31
LXM-TA CF III	**8.10 ± 0.19**	**13.52**	2.82

BA-Benzoic acid; LXM-Lornoxicam; TA-Tartaric acid; SA-Salicylic acid; CF-I-Solvent Evaporation; CFII-Solvent Drop method; CF-III Co-grinding method

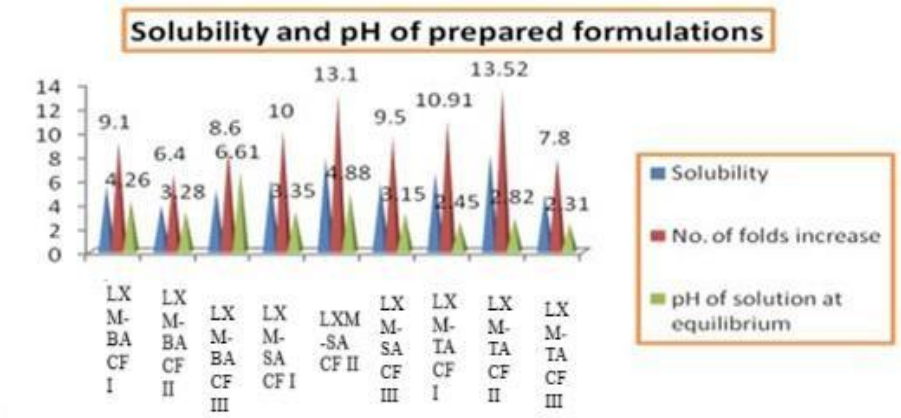

Fig Intrinsic solubility and pH of prepared co-crystal formulation

Particle size and shape: Morphological properties like particle size and shape was determined by using the electron Olympus microscope and findings represented in **Table.** The average particle size of LXM-BA CF in a range of 30.28 to 31.68 µm and cylindrical in shape, in case of LXM-SA CF in a range of 89.68to 94.08µm and cube shape, while in case of LXM-TA CF in a range of 26.24 to 29.84µm and rod shaped crystals are seen.

Table Electron Microscopy of pure drug and prepared co crystals

Formulation code	Average particle size (µm)	Shape of crystals
Pure LXM	29.28	Rod
LXM-BA CFI	31.68	Cylindrical
LXM-SA CFI	94.08	Cube
LXM-TA CFI	29.84	Rod
LXM-BA CFII	32.24	Cylindrical
LXM-SA CFII	92.24	Cube
LXM-TA CFII	28.12	Rod
LXM-BA CFIII	**30.28**	**Cylindrical**
LXM-SA CFIII	**89.68**	**Cube**
LXM-TA CFIII	**26.24**	**Rod**

LXM-Lornoxicam; SA-Salicylic acid; BA-Benzoic acid; TA-Tartaric acid; CF-I-Solvent Evaporation; CFII-Solvent Drop method; CF-III Co-grinding method

***In vitro* dissolution:** At the end of the 360th minute, the LXM pure drug released 86.3%, whereas the developed co-crystal products, such as LXM-BA CF I, LXM-BA CF II, and LXM-BA CF III, demonstrated drug releases of 97.7, 97.2, and 95.5%. CF I, CF II, and CF III in the LXM-SA example demonstrated drug releases of 95.2, 96.3, and 96.5%. On the other hand, LXM-TA I, II, and III indicate drug releases at the 360thminute release of 94.4, 95.4, and 98.3%. When compared to other co-crystals, the in-vitro drug release profile of LXM-TA CF III was higher (98.3%), as indicated by the results presented in and the drug release kinetic graphs displayed in **Figure.**

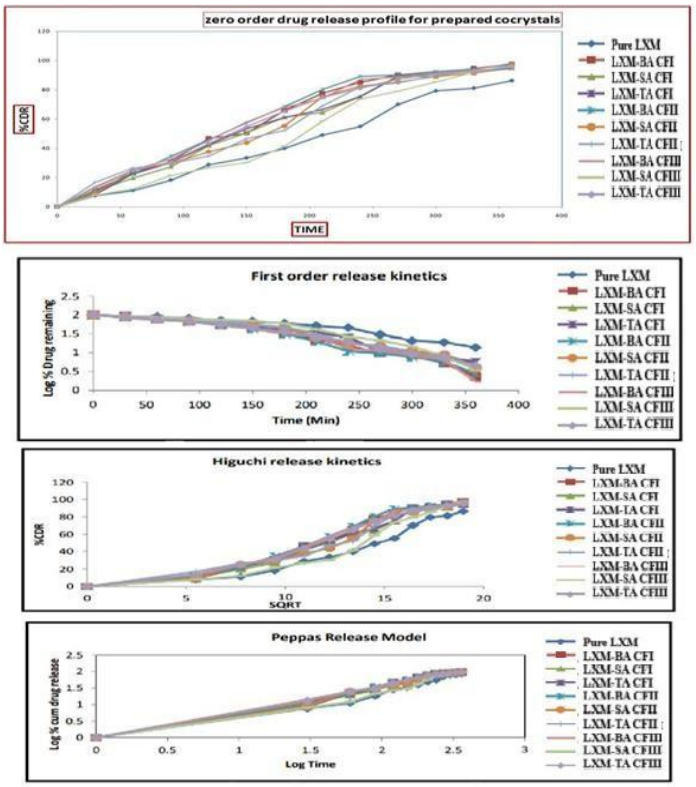

Fig. Release Kinetics of Lornoxicam pure drug and its co-crystal forms

Table Data *indicating In-vitro* dissolution of pure drug of Lornoxicam and that of its cocrystal forms in Phosphate Buffer pH 6.8

Time (min)	LXM pure	LXM-BA CFI	LXM-BA CFII	LXM-BA CFIII	LXM-SA CFI	LXM-SA CFII	LXM-SA CFIII	LXM-TA CFI	LXM-TA CFII	LXM-TA CFIII
30	7.7±0.14	11.3±0.15	10.2±0.14	14.1±0.42	10.8±0.43	9.1±0.16	8±0.12	8.6±0.13	16.9±0.28	**13±0.11**
60	11.2±0.26	23±1.13	22.5±1.19	25.2±1.19	19.7±0.52	25.2±0.29	12.2±0.18	22.5±1.10	26.6±0.42	**24.7±0.43**
90	18.3±0.11	31.1±1.15	34.7±1.18	33±1.20	27.5±0.75	29.7±1.13	21.4±0.43	30.2±1.11	29.7±1.09	**30.8±1.12**
120	28.9±1.19	46.9±0.21	46.1±1.16	45.3±1.28	41.9±1.18	37.8±1.14	26.9±0.55	42.5±1.13	35±1.11	**43.3±1.13**
150	33.5±2.11	50.3±1.24	57.5±1.15	58.1±1.17	50.6±1.29	43.9±1.16	30.3±1.09	53.3±1.15	46.7±1.13	**54.7±1.18**
180	40± 2.14	65.9±1.43	68.7±1.14	68.1±1.19	61.4±1.17	55.3±1.18	41.4±1.12	60.9±1.16	52.3±1.15	**65.3±1.17**
210	49.1±1.54	77.6±1.46	80.4±1.15	74.2±1.12	64.5±1.23	75.3±1.17	58.6±1.14	66.5±1.17	69.2±1.17	**74.8±1.16**
240	55± 1.53	85.1±1.49	89.3±1.23	87.2±1.14	75.4±1.43	82.6±1.4	73.7±1.18	75.4±0.18	82±1.19	**81±1.20**
270	70.1±1.25	90.2±1.54	90.4±1.26	88.9±1.15	88.8±1.17	85.3±1.15	79.1±1.17	89.3±1.19	84.8±1.21	**87.2±1.23**
300	79.3±1.28	91.5±1.34	92.5±1.42	91.7±1.21	89.1±1.21	89.2±1.21	85.5±1.19	90.8±1.22	89.9±1.24	**90.6±1.11**
330	81.2±1.36	94.7±1.22	94.3±1.13	93.6±1.15	91.4±1.18	91.4±1.13	92±1.0	92.6±1.25	93.2±1.26	**92.4±1.13**
360	86.3±1.45	97.7±1.23	97.2±1.11	95.5±1.14	95.2±1.16	96.3±1.14	96.5±1.23	94.4±1.29	95.4 ±1.29	**98.3±1.18**

LXM-Lornoxicam; SA-Salicylic acid; BA-Benzoic acid; TA-Tartaric acid; CF-I-Solvent Evaporation; CFII-Solvent Drop method; CF-III Co-grinding method

Preformulation Studies

Compatibility studies: It had been found during the drug and excipient compatibility testing that Lornoxicam is compatible with every excipient included in the formulation. The active medication is combined in a 1:1 ratio with each separate excipient. After being filled into sealed vials and kept in stability chambers with temperatures between 25±2ºC and 55±5% RH for 30 days, the samples were checked for any physical alterations. As a result, it was determined that the excipients selected for the formulations were compatible with the active ingredients in the pharmaceuticals. The blend's physical appearance remained unchanged, and the outcomes are shown in **Table.**

Table Compatibility studies of drug with excipients

S.No	Drug with Excipients	Initial color	Storage conditions25ºC/55 % RH at the end of 60th day
1	LXM-TA+HPMC	Colourless	Colourless
2	LXM-TA+MgCO3	Colourless	Colourless
3	LXM-TA+CaCO3	Colourless	Colourless
4	LXM-TA+NaHCO3	Colourless	Colourless
5	LXM-TA+Na2CO3	Colourless	Colourless

Flow properties: For the prepared formulation the bulk density values are in a range of 0.40 to 0.50 g/cc, tapped density values in a range of 0.49-0.58 g/cc, Compressibility index in a range of 11-15.98%, Hausner's ratio in the range of 1-12-1.19, and angle of repose values in a range of 22.44-33.69[1] all the limits in a range of good flow properties based on the findings represented in **Table.**

Table Flow properties results range for prepared co crystals

S. No.	Parameters	Results Range	Flow Property
1	Bulk density (g/cc)	0.40-0.50	**Good**
2	Compressibility index (%)	11-15.98	
3	Angle of Repose(°)	22.44-33.69	
4	Hausner's ratio	1.12-1.19	
5	Tapped density (g/cc)	0.49-0.58	

Table Flow properties determination of LXM-TA controlled release tablet blend

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index (%)	Hausner's ratio	Angle of repose (°)
F	0.50 ± 0.045	0.58 ± 0.04	13.56 ± 0.8	1.14 ± 0.09	33.69 ± 0.19
F1	0.46 ± 0.035	0.49 ± 0.08	11.01 ± 0.7	1.12 ± 0.05	24.57 ± 0.16
F2	0.47 ± 0.065	0.53 ± 0.08	12.11± 0.7	1.14 ± 0.07	25.52 ± 0.17
F3	0.43± 0.055	0.54± 0.05	15.98± 0.5	1.19 ± 0.05	31.43 ± 0.19
F4	0.45 ± 0.045	0.51 ± 0.09	11.58 ± 0.8	1.12 ± 0.09	22.44 ± 0.11
F5	0.44 ± 0.054	0.52± 0.07	14.68 ± 0.6	1.17 ± 0.06	24.54 ± 0.14
F6	0.40 ± 0.064	0.51 ± 0.08	15.0 ± 0.7	1.18 ± 0.07	30.85 ± 0.16
F7	0.42 ± 0.041	0.50 ± 0.11	14.48 ± 0.54	1.17 ± 0.12	24.52 ± 0.15
F8	0.45 ± 0.061	0.50± 0.14	13.0± 0.58	1.14± 0.14	25.12 ± 0.17
F9	0.40± 0.051	0.49 ± 0.12	16.64± 0.56	1.20 ± 0.13	30.24 ± 0.19
F10	0.46 ± 0.044	0.52 ± 0.09	11.58 ± 0.8	1.12 ± 0.08	22.44 ± 0.11
F11	0.44 ± 0.054	0.52± 0.07	14.68 ± 0.6	1.17 ± 0.06	24.54 ± 0.14
F12	0.42± 0.055	0.53± 0.05	15.88± 0.5	1.18 ± 0.05	31.23 ± 0.19
F13	0.42 ± 0.041	0.50 ± 0.11	14.48 ± 0.54	1.17 ± 0.12	24.52 ± 0.15
F14	0.45 ± 0.061	0.50± 0.14	13.0± 0.58	1.14± 0.14	25.12 ± 0.17
F15	0.43± 0.055	0.54± 0.05	15.98± 0.5	1.19 ± 0.05	31.43 ± 0.19
F16	0.45 ± 0.044	0.51 ± 0.09	11.58 ± 0.8	1.12 ± 0.08	22.44 ± 0.11

Mean ± SD (n=3); F-Formulation without electrolyte;F1-F4- Formulations with calcium carbonate electrolyte; F5-F8-Formulations with magnesium carbonateelectrolyte; F9-F12- Formulations with Sodium bicarbonate electrolyte; F13-16-Formulations with Sodium carbonateelectrolyte

Post Formulation: The weight variation, thickness, hardness, friability, dosage consistency, and dissolution profile of the tablets were all noted. In accordance with the 2006 United States Pharmacopoeia (U.S.P.) recommendations, the average weight was measured over 20 tablets. Using ten tablets, the hardness was measured using a Monsanto Hardness Tester. A maximum loss of 1% of starting weight was the acceptance criterion for each formulation, which was tested for friability across a sample of 20 tablets in a Roche Friabilator (U.S.P. 2006). For the ten tablets, the drug content percentage was also measured. Using a UV Spectrophotometer to analyze the materials, the dissolution profile was discovered. Electrolytes are used as rate retardants in the controlled release matrix tablets of Lornoxicam with HPMC. All the batches were evaluated for

post formulation parameters and results are represented in the **Table.**

Post formulation parameters of LXM-TA Controlled Release Tablets

F. Code	Average Weight*(mg)	Hardness** (kg/cm^2)	Thickness** (mm)	Friability*(%)	Drug Content** (%)
F	327±1.34	5.21±0.32	4.42±0.02	0.840	99.50±0.11
F1	324±1.84	5.1±0.24	4.12±0.01	0.812	100.3±0.13
F2	325±2.44	5.5±0.45	4.25±0.03	0.840	100.2±0.11
F3	327±3.72	5.7±0.46	4.32±0.03	0.831	99.82±0.12
F4	330±1.68	5.2±0.42	4.28±0.02	0.811	99.65±0.10
F5	325±2.52	5.5±0.45	4.27±0.02	0.652	99.95±0.11
F6	328±2.65	5.6±0.48	4.34±0.03	0.725	100.2±0.12
F7	326±2.75	5.1±0.24	4.42±0.04	0.845	100.5±0.11
F8	325±2.98	5.2±0.32	4.56±0.04	0.832	100.1±0.11
F9	327±1.29	5.4±0.43	4.65±0.05	0.840	99.80±0.12
F10	329±1.58	5.2±0.33	4.75±0.05	0.821	100±0.11
F11	329±2.88	5.5±0.46	4.84±0.06	0.832	100.1±0.11
F12	329±2.24	5.2±0.42	4.96±0.06	0.795	99.89±0.12
F13	328±2.84	5.3±0.44	4.98±0.07	0.823	100.2±0.12
F14	**330±2.65**	**5.0±0.22**	**4.12±0.01**	**0.542**	**100±0.11**
F15	326±2.85	5.4±0.43	5.12±0.07	0.822	99.98±0.12
F16	324±3.12	5.7±0.90	5.22±0.07	0.884	99.95±0.12

*All values are expressed as Mean ± SD, (*n=20; **n=10)*

***In-vitro* dissolution:** The polymer and concentration of the electrolytes used in the tablet production process can control the rate at which the medicine releases from the matrix tablets. Compared to other electrolytes such as magnesium carbonate, calcium carbonate, and sodium bicarbonate, sodium carbonate proved to be a more effective release rate retardant. **Table** displays the ideal batch formulation F14, which exhibited an optimal release pattern for upto 12 hours. Sodium carbonate in the ideal batch formulation F14, at the ideal concentration, works well and can be taken twice a day.

Release Kinetics: Zero order, Higuchi, first order, Korsmeyer, and Hixson-Crowell equations were used to investigate and describe the release mechanisms**.** In order to determine the drug release, the kinetic parameters for the in vitro release of LornoxicamTartaric acid CR tablets were examined. The kinetics model of Korsmeyer Peppa is followed by the ideal batch formulation (F14). For the F14 batch, the regression value was 0.989. The continuous diffusion channel lengths in all formulations result in a zero-order release rate and a non-Fickian drug release mechanism from swellable hydrophilic matrices.

146 ***a In-vitro*** **Dissolution data in pH-6.8 phosphate buffer for LXM-TA controlled release tablets**

TIME (hours)	Percentage Cumulative Drug Release (%CDR)								
	F	F1	F2	F3	F4	F5	F6	F7	F8
1	36.1±0.16	21.22±0.15	19.32±0.14	16.3±0.17	15.82±0.16	17.36±0.15	14.35±0.18	11.11±0.16	9.63±0.17
2	54.12±0.27	34.32±1.12	32.1±1.14	28.25±1.15	25.2±1.16	25.58±1.18	23.1±1.19	22.32±1.11	20.1±1.24
3	66.32±0.12	42.06±1.15	37.47±1.16	34.11±1.17	32.08±1.18	35.74±1.14	32.99±1.12	29.39±1.10	27.09±1.17
4	81.59±1.18	47.05±1.28	45.61±1.26	42.43±1.22	40.11±1.25	41.23±1.27	38.26±1.28	36.99±1.26	33.25±1.24
5	90.95±2.10	53.96±1.26	50.23±1.32	46.89±1.30	45.24±1.31	46.93±1.34	44.28±1.35	42.07±1.37	40.58±1.38
6	100.2±2.12	61.38±1.42	59.8±1.38	56.99±1.35	55.26±1.36	53.64±1.33	52.92±1.38	50.45±1.39	48.5±1.42
7	-	67.3±1.46	66.15±1.28	63.62±1.22	60.22±1.26	60.39±1.32	58.33±1.35	56.38±1.42	54.36±1.40
8	-	70.84±1.48	68.94±1.32	66.06±1.34	64.62±1.36	66.35±1.38	63.28±1.39	62.04±1.40	60.11±1.41
9	-	80.04±1.52	78.74±1.33	76.33±1.32	74.61±1.35	73.58±1.35	70.87±1.41	69.54±1.42	68.75±1.43
10	-	89.31±1.34	87.99±1.34	85.14±1.33	83.76±1.34	81.56±1.36	79.94±1.42	78.56±1.44	73.56±1.42
11	-	90.28±.28	91.21±1.35	93.17±1.34	90.79±1.33	89.12±1.35	88.01±1.40	86.25±1.45	82.69±1.44
12	-	95.57±1.22	92.37±1.32	96.26±1.35	93.04±1.31	92.65±1.38	93.27±1.42	95.05±1.46	94.12±1.45

(Mean ± SD); (n=3) ***b In-vitro*** **Dissolution data in pH-6.8 phosphate buffer for LXM-TA controlled release tablets**

TIME	Percentage Cumulative Drug Release (%CDR)							
(hours)	F9	F10	F11	F12	F13	F14	F15	F16
1	24.15±0.15	22.65±0.12	20.45±0.14	17.35±0.16	19.64±0.17	18.54±0.18	17.98±0.15	16.15±0.18
2	29.27±1.32	28.15±1.42	26.18±1.34	24±1.22	26.18±1.12	25.24±1.14	23.08±1.25	20.78±1.26
3	39.67±1.18	37.69±1.19	35.08±1.20	31.65±1.14	35.45±1.15	34.14±1.16	31.99±1.17	29.24±1.18
4	47.72±1.27	45.92±1.28	43.66±1.30	39.65±1.24	42.7±1.25	41.75±1.28	37.4±1.26	35.36±1.27
5	55.36±1.31	51.58±1.32	48.36±1,33	46.28±1,35	51.32±1.36	48.96±1.32	44.74±1.38	41.81±1.33
6	59.65±1.43	58.73±1.44	56.92±1.46	53.79±1.38	58.36±1.39	55.93±1.40	53.42±1.36	51.11±1.32
7	69.35±1.34	66.81±1.35	64.36±1.33	61.59±1.32	63.28±1.30	62.3±1.28	60.42±1.12	57.84±1.24
8	71.12±1.42	72.41±1.44	70.63±1.45	69.17±1.47	68.02±1.23	67.12±1.30	65.08±1.28	61.85±1.32
9	79.61±1.43	78.74±1.43	75.68±1.43	75.5±1.40	78.36±1.25	77.54±1.32	72.74±1.30	70.87±1.35
10	88.07±1.44	87.2±1.44	85.4±1.42	82.36±1.42	88.36±1.26	84.01±1.34	82.74±1.32	81.36±1.36
11	92.49±1.45	94.63±1.42	93.55±1.43	92.57±1.43	93.29±1.28	92.25±1.35	90.43±1.34	89.12±1.38
12	94.68±1.46	96.73±1.40	95.36±1.44	96.15±1.44	95.03±1.30	100±1.36	94.45±1.35	96.43±1.40

(Mean ± SD); (n=3)

Table Release kinetics for Lornoxicam Controlled Release Tablets

F. Code	Zero order		First order		Higuchi's		Peppa's		Hixson-Crowell		Release Mechanism
	% CDR Vs. Time		Log% Remaining Vs. Time		%CDR Vs. √T		Log% CDR Vs. Log T		Cube root % drug Remaining Vs. Time		
	K0	r2	K1	r2	KH	r2	n	r2	KHC	r2	
F	8.947	0.786	0.667	0.855	15.64	0.952	0.414	0.907	-0.494	0.995	Fickian
F1	8.012	0.960	0.227	0.917	28.24	0.991	0.594	0.994	-0.227	0.972	Non-Fickian
F2	7.951	0.968	0.210	0.940	28.24	0.979	0.633	0.993	-0.218	0.977	Non-Fickian
F3	8.058	0.984	0.237	0.865	28.95	0.963	0.707	0.993	-0.235	0.947	Non-Fickian
F4	7.876	0.987	0.206	0.908	28.40	0.959	0.725	0.994	-0.217	0.963	Non-Fickian
F5	7.732	0.983	0.195	0.916	27.69	0.968	0.682	0.994	-0.208	0.968	Non-Fickian
F6	7.692	0.989	0.194	0.892	27.80	0.956	0.748	0.996	-0.207	0.956	Non-Fickian
F7	7.696	0.995	0.200	0.842	28.04	0.944	0.827	0.996	-0.211	0.934	Non-Fickian
F8	7.509	0.996	0.184	0.835	27.51	0.936	0.875	0.996	-0.200	0.928	Non-Fickian
F9	8.046	0.963	0.226	0.930	28.40	0.984	0.591	0.985	-0.228	0.977	Non-Fickian
F10	8.162	0.975	0.251	0.879	28.99	0.976	0.623	0.985	-0.243	0.958	Non-Fickian
F11	8.049	0.982	0.231	0.888	28.77	0.968	0.658	0.985	-0.232	0.958	Non-Fickian
F12	8.038	0.991	0.232	0.862	29.00	0.956	0.720	0.988	-0.233	0.947	Non-Fickian
F13	8.113	0.980	0.234	0.902	29.04	0.968	0.671	0.989	-0.235	0.962	Non-Fickian
F14	**8.134**	**0.987**	**0.242**	**0.842**	**29.21**	**0.959**	**0.694**	**0.989**	**-0.277**	**0.828**	**Non-Fickian**
F15	7.857	0.992	0.211	0.884	28.30	0.952	0.706	0.981	-0.219	0.952	Non-Fickian
F16	7.833	0.995	0.220	0.818	28.40	0.935	0.753	0.978	-0.224	0.921	Non-Fickian

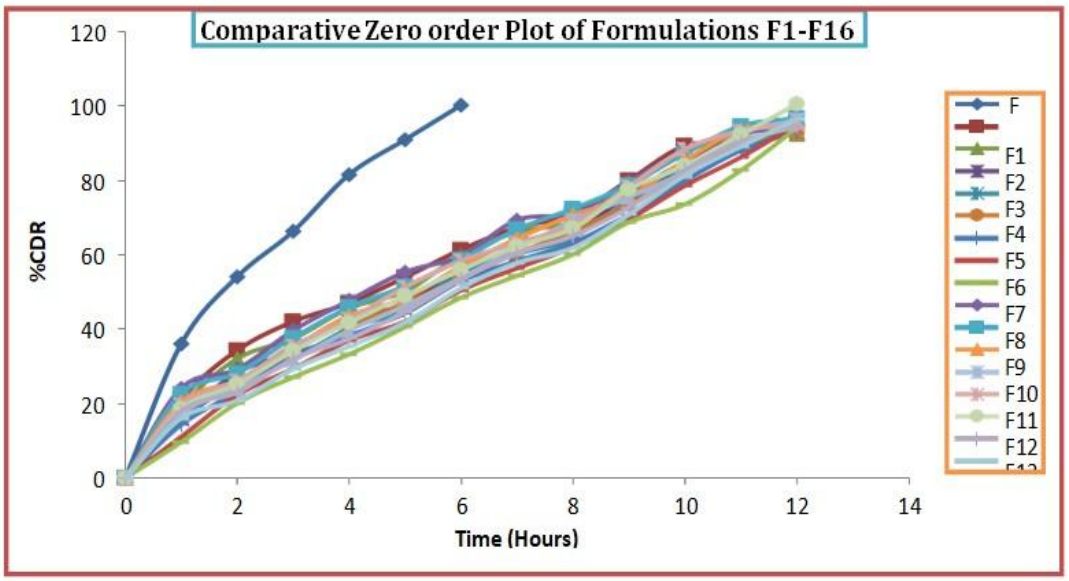

Fig. Zero order release kinetics in p^H 6.8 phosphate buffer For Lornoxicam controlled release tablets

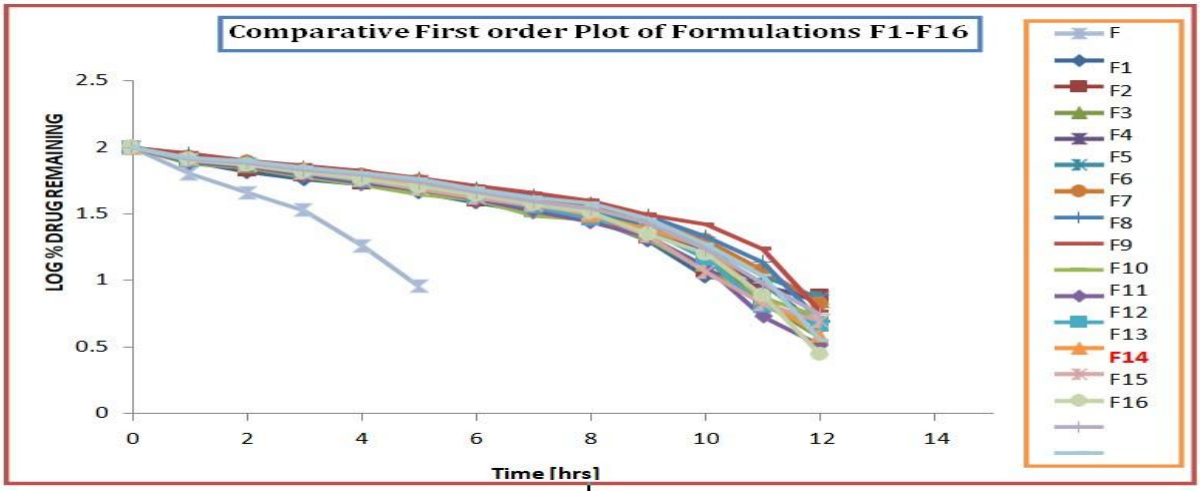

Fig.First order release kinetics in p^H 6.8 phosphate buffer For Lornoxicam controlled release tablets

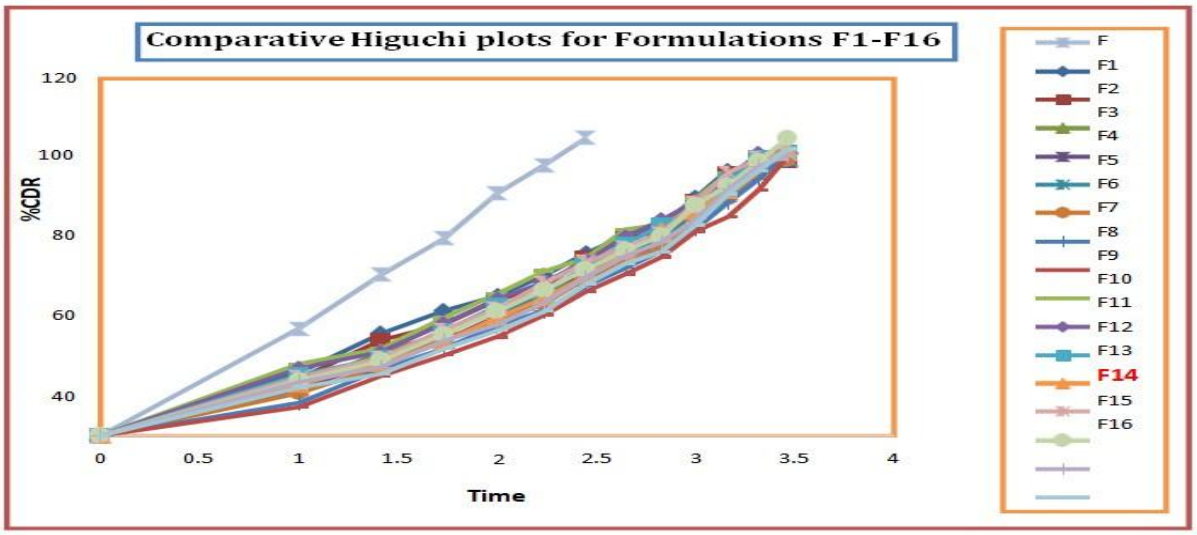

Fig.Higuchi's release kinetics in p^H 6.8 phosphate buffer For Lornoxicam controlled release tablets

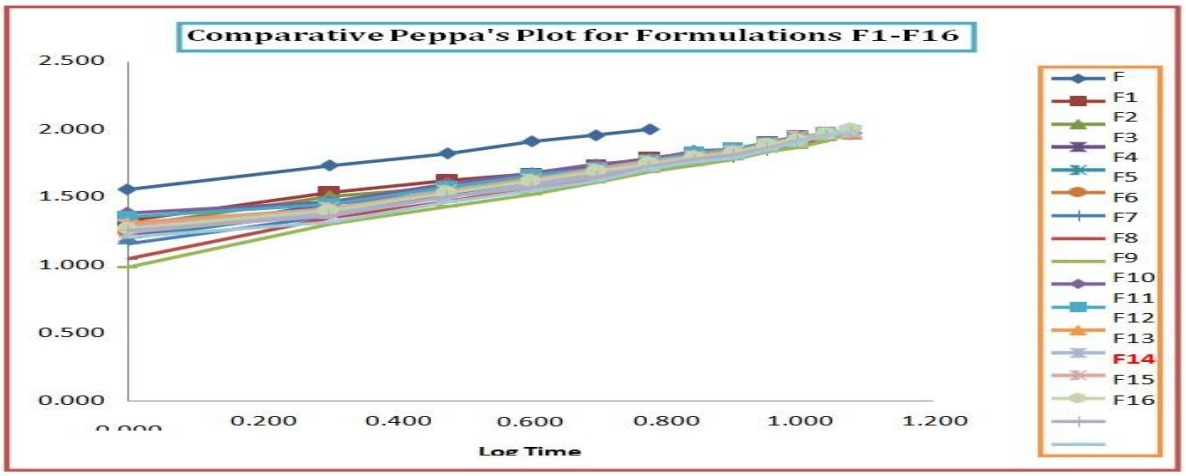

Fig.Peppa's release kinetics in p^H 6.8 phosphate buffer For Lornoxicam controlled release tablets

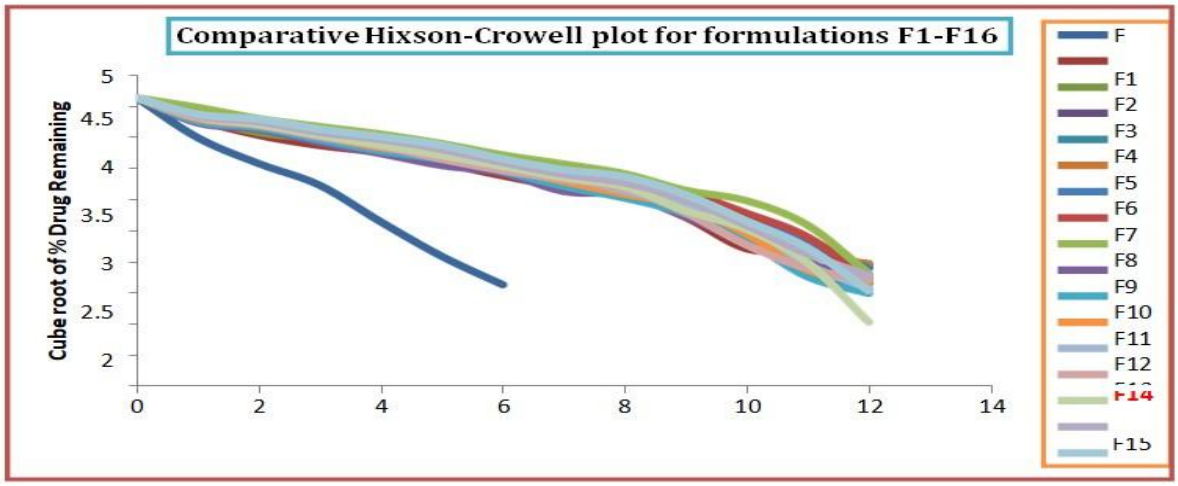

Fig.Hixson-Crowell kinetics in p^H 6.8 phosphate bufferfor Lornoxicam controlled release tablets

Similarity and difference factor: The difference factor, or f1, and the similarity factor, or f2, are two ways to express the fit factors. The two dissolution profiles to be deemed same and bioequivalent, f1 should be between 0 and 15 & f2 between 50 & 100. Using the similarity factor (f2) factor of around 87, the improved (F14) formulation's solubility profile is comparable to that of the innovator brand (NeurontinTM). However, applying the difference factor (f1)(2) to the innovator brand can likely be regarded as bioequivalent.

Table Comparative Dissolution Profile of Optimized Formulation [F14] with Marketed Product

Time [Min]	Marketed product [Neurontin]	Optimized Formulation F14	Similarity Factor F2	Difference FactorF1
0	0	0		
1	18.84±1.19	18.54±1.14		
2	28.23±2.14	27.24±1.09		
3	35.42±1.54	34.14±1.25	**87**	**2**
4	46.22±1.28	44.75±1.30		
5	55.86±1.36	54.96±1.44		
6	67.64±1.45	65.93±1.25		
7	72.48±1.22	72.36±1.11		
8	78.65±1.80	76.12±1.03		
9	80.12±1.37	79.54±1.79		
10	85.26±1.51	83.20±1.35		
11	92.16±1.26	91.25±1.51		
12	100.5±1.38	100.2±1.08		

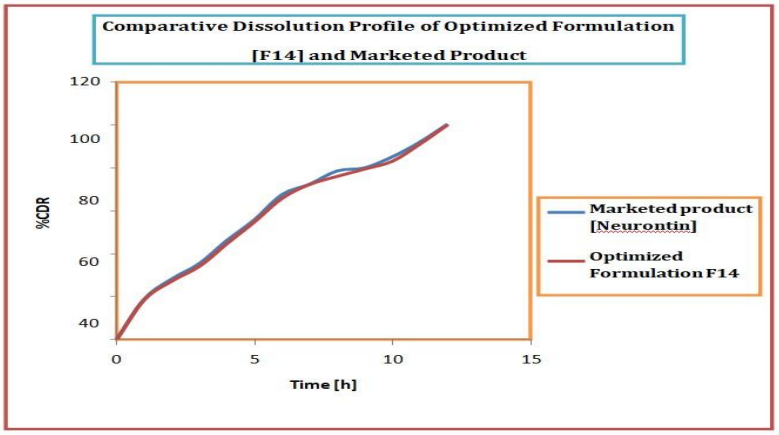

Fig. Comparative Dissolution Profile of the Optimized Formulation [F14] and Marketed Product

Physical Stability Studies: After three months of storage at 25˚C±2°C & 60±5% RH, the optimized (F14) blister packed formulations were assessed for physical appearance, average weight, drug content, hardness, and dissolution at predetermined intervals of time (1, 6, and 12 hours) for any potential changes. The results are provided in **Table.**Regarding the drug content, hardness, and dissolution of the F14 formulation, no physical changes has been noted. It was discovered that the chosen optimized F14 formulation was found to be stable.

Table Stability studies of the optimized formulation (F14)

Specification (Limits)	**Initial**	**1 Month**	**2 Months**	**3 Months**
Description	White - off- white	White - off- white	White - off-white	White - off- white
Average Weight (330 ± 10 mg)	330	330	332	334
Hardness NLT (5.0K.g/cm^2)	5.0	5.1	5.2	5.4
Dissolution of Best Batch **(F14)**	1st -- 18.54 6th - 55.93 12th -- 100	1st -- 17.54 6th -- 54.93 12th -- 99.83	1st -- 17.24 6th -- 54.26 12th -- 99.34	1st -- 16.34 6th -- 53.98 12th -- 99.13
Assay (99.9- 100.9 %)	100	99.96	99.94	99.92

3. CONCLUSION

This study confirms that the solvent evaporation method is highly effective for developing Lornoxicam co-crystals with significantly enhanced solubility and controlled drug release. The optimized LXM-TA CFIII formulation demonstrated over 13-fold solubility improvement and superior in vitro and in vivo performance, following a non-Fickian release mechanism. Sodium carbonate proved to be the most efficient electrolyte for sustaining drug release, with formulation F14 maintaining release over 12 hours. These findings suggest that co-crystallization, combined with electrolyte-based matrix systems, offers a promising strategy to improve the therapeutic efficacy and dosing convenience of poorly soluble drugs like Lornoxicam.

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