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COMPARATIVE SOLUBILITY STUDY OF CYCLODEXTRINS (B- CD AND HPB- CD) AND ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF LORNOXICAM BY USING TERNARY COMPLEXATION

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Keywords:

Cyclodextrins, Lornoxicam, Poloxamer 407, Ternary complex, Solubility, Dissolution

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ABSTRACT: The present investigation aimed to provide an approach for the solubility and bioavailability enhancement by Comparative solubility of cyclodextrins with Lornoxicam **(**LXM) by forming ternary Inclusion complexation (TIC). The phase-solubility and saturation solubility studies were executed in the existence of β-CD, HP-βCD and polymers. The drug/CD complexes were formulated and characterized further to confirm complex formation using DSC and FTIR. The solid dispersions (SDs) were formulated using double hydrophilization and accessed using FT-IR, DSC, and *in-vitro* testing. The equilibrium phase solubility and saturation solubility study for both binary and TIC showed a more significant solubility enhancement of LXM-HP β-CD- poloxamer-407(PXM 407) than LXM-β-CD. The FT-IR and DSC analysis confirmed the formation of a TIC amongst LXM-HP-βCD-PXM 407. The TIC demonstrated a higher Complexation Efficiency (CE) and stability constant than binary. The drug dissolution rate (DR) profile showed significant drug release from developed TIC and improved DR to a greater extent. From comprehensive study findings, it can be stated that employing the TIC of LXM-HP β-CD with PXM 407 might be a pragmatic choice to augment the LXM's solubility and Drug release.

INTRODUCTION: The numerous innovative drug candidates with minimal aqueous solubility and dissolution kinetics have risen significantly over the last decades. As a result, high throughput and combinatorial screening techniques are used during drug discovery and development.

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Escalating the oral bioavailability of low water-soluble drugs or substances in pharmaceutical innovation remains one of the most challenging issues [1]. The poor water solubility of these therapeutic compounds remains the primary barrier in forming formulations for new chemical entities and generics.

When the solubility profile of these molecules is improved, any drug that must be absorbed can be available at the target site in the form of an aqueous solution [2]. The oral route is the most convenient and extensively used in drug distribution due to its simplicity and great patient compliance.

Poorly water-soluble medications may also require high dosages to attain the desired therapeutic plasma concentrations after oral delivery [3-4]. Nearby, 70% of modern medicine compounds need a strong candidate to improve oral bioavailability and solubility since they have poor water solubility [5]. Over 80% of orally administered drugs, from which 40% have poor water solubility, in a more severe scenario for R&D drug candidates showed that 90% failed due to solubility concerns [6]. It is now difficult for formulation scientists to develop a novel formulation using such moieties. But solubility is one of the most important aspects in achieving the optimum systemic concentration of the drug required to induce the desirable therapeutic action [7].

As solubility is a crucial factor in formulation development, numerous techniques, such as salt formation, solubilization, and reduction in particle size, have frequently been used to improve the solubility, DR, and, subsequently, the oral bioavailability of such drugs [8]. All of these methods, though, have their limitations. Not all medications with poor solubility can be more soluble by salt formation. When co-solvents or surfactants are employed to speed up the dissolution process, problems arise. Drug solubility increases as their particle size are reduced, but hydration and flow properties are influenced [9].

Several poorly soluble medications have been explored to augment their solubility and dissolution rate utilizing a class of cyclic oligosaccharides termed cyclodextrins (CDs). Furthermore, various modified-release formulations have been widely used to alter the drug release (DR) pattern. To circumvent the limitations of the present technology, CD binary complexes comprising poorly water-soluble drugs can be adopted [10]. However, the utilization of CD is constrained in a wide range of circumstances because foreign compounds entirely or partially adhere inside the CD cavity. The physicochemical properties of the host and foreign molecules, the ease at which the foreign molecules can enter the CD cavity. Stoichiometry, therapeutic dosage, and CD toxicity significantly influence this modification. CDs raise the formulation's cost, toxicity, and weight by 4-10 folds, restricting their use in solid dosage forms. As a result, CDs in solid oral forms are limited to drug dosages of less than 200 mg having good complexation capabilities [11-12]. Adding small quantities of water-soluble polymers to the system, which improves the solubilization efficiency using smaller portions of CD, is described as "ternary complexation," frequently utilized to enhance the complexation between drugs and CDs. Because of the drug's development, these findings are synergistic in solubilization: CD refers to water-soluble polymer TIC [13]. Water-soluble polymers can interact with poorly water-soluble drugs, CD, and drug: CD complexes. Adding water-soluble polymers in drug-CD complexes improves bioavailability, resulting in a nearly 80% decrease in the quantity of CD required. In the presence of an aqueous phase, these polymers promote the hydrophilicity of the particles, resulting in higher solubility and DR [14]. The impending shortcomings of the drug: CD binary complexes can be overcome by developing ternary complexation. Lornoxicam (LXM), a non-steroidal anti-inflammatory medication, is frequently prescribed to alleviate the symptoms of pain and inflammation in individuals with arthritis. It is a BCS-II compound with limited solubility and strong permeability. It is insoluble in water, and its absorption rate in the GI tract usually governs the oral absorption rate. It is tough to dissolve in the upper GI fluid owing to its very poor aqueous solubility (0.03850.01 mg/ mL) at room temperature, which reduces bioavailability and inhibits its sanative implementation and onset of action [15].

The present research was conducted to address the issues regarding LXM solubility, dissolution rate, and absorption. Due to the potential benefits of TIC over binary complexes, the present study explored the development of a double hydrophilization TIC using the stable and cost-effective axillary substance Polaxomer-407 (PXM 407). The current research emphasizes the comparative solubility study between two distinct cyclodextrins (β-CD and HP-βCD) to increase the efficiency of drug complexation, solubility, bioavailability, and stability.

MATERIALS AND METHODS:

Materials: Lornoxicam (gift) was kindly donated by Alkem laboratory, Mumbai, Hydroxy-Propyl β-Cyclodextrin was procured from Alkem

Laboratories, Mumbai, and Cadila Pharmaceutical Ltd gifted β-Cyclodextrin. Ahmedabad, poloxamer 407 was procured from Cadila Pharmaceutical Ltd. Ahmedabad. All the other excipients and solvents utilized were of analytical grade.

Methods:

Saturation Solubility Studies: Three solvents were used to evaluate the LXM's saturation solubility: 0.1N HCl, double-distilled water (DDW), and phosphate buffer solution (PBS pH 7.4). The 3 conical flasks filled with 10 mL of each solvent were laden with the excess amount of LXM and shaken for 72 h at 37℃ and 100 rpm in a rotary shaker (Remi, India). The samples were subjected to centrifugation (R8C, Remi, India) at 4000 rpm for 20 min, filtered, and then analyzed after proper dilution (if necessary) under a UV spectrophotometer (Jasco V-530, Japan) at 380 nm to determine the amount of drug in the filtrate [16].

Phase Solubility Studies of LXM: The phase solubility study was executed according to the methods documented by Higuchi and Peppas [17-18]. A series of molar concentrations ranging from 3 to 15 mM for β-CD and HP- β CD were synthesized successfully. Excessive LXM was added to 25 mL of an aqueous solution comprising β-CD and HP-βCD in a series of 100 mL conical flasks.

The solutions were agitated in a rotating shaker for 7 days at 100 rpm (Remi in India). The aliquots were collected, filtered through a Millipore and estimated LXM content was using UV visible spectroscopy (Jasco V-530, Japan). The phase solubility graph was developed by plotting the molar concentration of LXM versus β- CD & HP-βCD concentration. The following equations were utilized to estimate the stabilization constant, CE, and drug: carrier ratio.

$$Ks=slope / SO (1-slope)……. (1)$$

$$CE= [Drug-CD] / [CD] = Slope/ 1-slope…… (2)$$

$$D: CD= 1: [1+1/CE]….. (3)$$

Selection of Optimized Concentration of an Auxiliary Substance (Polaxomer 407): Auxiliary material (PXM -407) at concentrations between (0.04-0.8% w/v) was employed in experiments here on equilibrium solubility of LXM and plotted against the amount of medication dissolved to estimate the CE and stability constant (Ks). From the findings obtained, PXM 407 was utilized for further ternary inclusion complex formation.

Preparation of SD by Double Hydrophilization Approach: The hydrophilized SD of LXM with HP- βCD was prepared in a stoichiometric ratio of 1:4, adopting two distinct strategies described in the subsequent section.

Solvent Evaporation Technique: Accurately weighed 0.092 gm of Lornoxicam, HP-βCD (1.37 gm), and PXM 407 (1 gm) were dissolved in DDW under continuous stirring with the gradual addition of ammonia solution. The solvent was drained at decreased pressure in a rotary vacuum evaporator tuned to 450℃ to acquire a slurry. The resulting slurry was collected and dried (45℃ for 3 h), pulverized and sieved through sieve #85 for further use.

Lyophilization Technique: The Lornoxicam, HP β- CD (1375 mg) and PXM 407 (1000 mg) were precisely measured by using a digital weighing balance and dissolved in the DDW with continuous shaking for 24 h using a rotary shaker before the gradual addition of 25% ammonia solution to produce a translucent liquid. The previously obtained solution was placed in a 1000 mL beaker and refrigerated (-45℃) overnight, being further lyophilized for 48 hours in a freeze dryer (-45℃) and secondary drying at ambient temperature.

Characterization of the Hydrophilized SDs:

Differential Scanning Calorimetry (DSC): A DSC (Shimadzu DSC 60) was employed to establish the thermal analysis of pure LXM and its SD. For the calibration of the instrument, an indium standard was used. The 3-5 mg sample was weighed precisely before being placed in a DSC non-hermetic aluminium pan with a volume of 50 µL and a thickness of 0.1 mm. The empty pans were utilized as a reference point. In contrast, the loaded pans were enclosed with an aluminium cover pressurized over them and scanned from 50 to 300℃ at a thermal output of 10℃/min under a continuous stream of dry nitrogen was employed to purge the sample at a rate of 20 mL/min.

Fourier Transform Infrared Spectroscopic (FT-IR) Analysis: FT-IR (Jasco V-530 FT-IR-4100, Japan) was employed to discover the chemical interactivity between the polymers and the drug in

the TIC. The samples of pure LXM, HP β- CD, PXM 407, and solid inclusion complex (3 mg each) were precisely weighed, combined with IR-grade potassium bromide (50 mg), compacted into discs, and examined on an (FT-IR- 8400S, Shimadzu, Japan). The scanning was done at a resolution of $1cm^{-1}$ in 400- 4000 cm^{-1}.

***In-vitro* Dissolution Test:** *In-vitro* dissolution of the solid TIC was done using the powder dispersion method. The 30 mg pure LXM and SDs were perfectly weighed and subjected to disso-testing. The dissolution studies were carried out in 900 mL 0.1N HCl buffer pH 1.2 at 37 ± 0.5℃ using a rotary paddle at 100 rpm. At predetermined time intervals, 1 mL sample was withdrawn, filtered via a membrane filter (0.45-µm), and examined under UV at 380 nm. The Sink condition was sustained by substituting an equal volume of dissolution media after each sample extraction.

RESULTS:

Saturation Solubility Studies in Different pH Conditions: The LXM's saturation solubility was evaluated in several pH solutions and DDW. The findings demonstrated that LXM was rarely soluble in any selected media. It was proven that LXM has pH-dependent solubility with higher solubility in a PBS pH 7.4 than 0.1N HCl. The saturation solubility results in the present investigation are consistent with those reported by Yarraguntla and the team[19]. The data from saturated solubility is summarized in **Table 1** and depicted in **Fig. 1.**

TABLE 1: SATURATION SOLUBILITY DATA OF LXM

Sr. no.	Solvents	Solubility (µg/ mL)
1	0.1N HCl (pH 1.2)	0.094
2	DDW	0.20
3	PBS pH 7.4	0.66

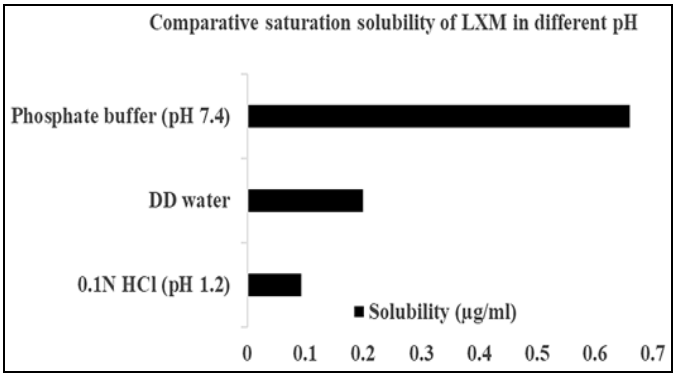

FIG. 1: pH-DEPENDENT SOLUBILITY PROFILE OF LXM

Phase Solubility Studies of LXM:

Comparative Phase Solubility Studies of LXM in the Presence of β-CD & HP-Bcd: The determination coefficients (r^2) for the phase solubility of the two CDs were 0.974 for the β-CD and 0.986 for the HP-βCD. Due to the r^2 value being less than 0.999, these are referred to as Ap-phase illustrations. The positive linearity deviations pointed to the emergence of the complexation that might dissolve greater amounts of the guest substances *via* non-inclusion complexion. Such higher-order complexation among LXM and CDs give rise to these complex aggregates. The assumption suggested LXM interacts more strongly with HP-βCD was validated by the estimated higher CE values for HP-β-CD compared to β-CD [20-21]. Previous research has discovered that Vander Waals attraction forces, hydrophobic interactions, H-bonding, electrostatic forces, and the releasing structural distortion are tangled in the complexation process amongst CD and the guest with low-polarity organic compounds [22-26]. The comparative phase solubility profile of LXM with β-CD and HP-β-CD in DDW are shown in **Fig. 2** and selected the HP-β-CD for the ternary complexion study.

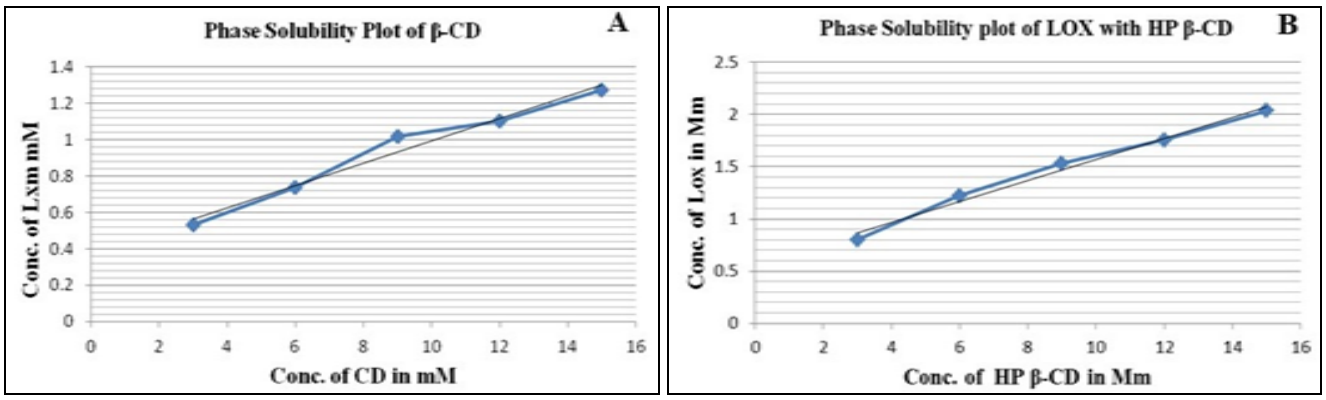

FIG. 2: PHASE SOLUBILITY PLOT OF LXM IN (A): B-CD SOLUTION; (B): HP B-CD SOLUTION

Selection of Optimized PXM 407 Concentration: The PXM 407 at the optimal concentration was selected, and LXM equilibrium solubility experiments were performed with a concentration of 0.1-0.8% w/v. However, there was no increment in LXM solubility after raising the PXM 407 concentration beyond 0.4%, despite the significant variation in the values. Consequently, a concentration of 0.4% PXM 407 was employed to develop SD. The following **Fig. 3** illustrates investigations of LXM's equilibrium solubility in the presence of the PXM 407 (0.4-0.8% w/v).

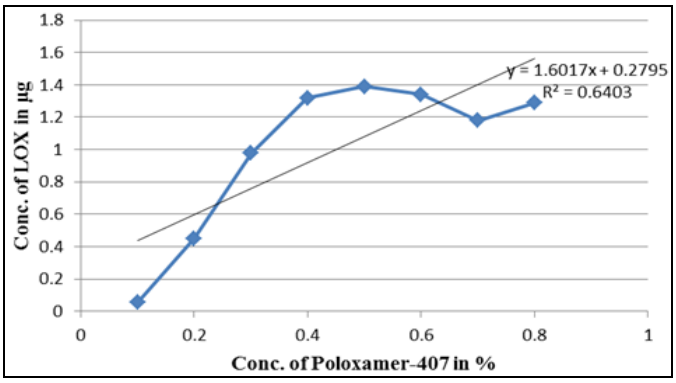

FIG. 3: SOLUBILITY PLOT OF LXM WITH PXM 407

Phase Solubility Studies of LXM plus HP β-CD with PXM 407: A synergistic effect on LXM solubility was reported in PXM 407 and HP -βCD. The solubility profile of LXM in the aqueous phase was higher when HP- βCD with auxiliary substances were introduced together than alone. The stability constant Ks values of a single hydrophilized complex (LXM-CD & LXM-HP-βCD) were 267 min^{-1}& 315 min^{-1}, indicating a fragile and unstable interaction between the two components. Ternary hydrophilized complexes increased their Ks value to 349 min^{-1}. The greater the Ks value, the more stable the complex of LXM-HP-βCD-PXM 407 was compared to single hydrophilized complexes. The high Ks value for the TIC indicated that LXM interacted with the cavity of HP-βCD. PXM, an auxiliary molecule, can establish a network with the outer surface of HP-βCD and with LX- HP- βCD, facilitating co-complex development [27].

The Complexation Efficiency (CE) for binary with β-CD, HP-βCD, and TIC (LXM+ HP-βCD+ PXM 407) was discovered to be 0.064, 0.1, and 0.33, respectively. The increased CE value for the TIC is due to PXM 407, which aids in complex formation [28]. The ternary system (1:4) utilized substantially lower CD than the binary systems (1:16 and 1:11), but it still exhibited a huge upsurge in solubility.

The ternary system (1:4) used substantially less CD than the binary systems (1:16 and 1:11), but there was still a significant increase in solubility with the ternary system. These findings suggested that using the TIC of LXM-HP-βCD-PXM 407 probably leads to considerable reductions in the total weight of the final dosage form. According to our findings, the TIC improved LXM solubility more than the binary system. **Table 2** compares the phase solubility patterns of LXM for single and double hydrophilization SDs. **Fig. 4** depicts the phase solubility graph of LXM in HP-βCD and PXM 407.

TABLE 2: COMPARATIVE DATA SHOWING THE PHASE SOLUBILITY OF SDs

S. no.	Solid Dispersion	Complexation efficiency (CE)	Stability Constant Ks (min^{-1})	Drug: CD Ratio
1	LXM: β-CD	0.064	267 min-1	1: 16
2	LXM: HP β-CD	0.1	315min^{-1}	1:11
3	LXM: HP β-CD-PXM 407	0.33	349 min-1	1: 4

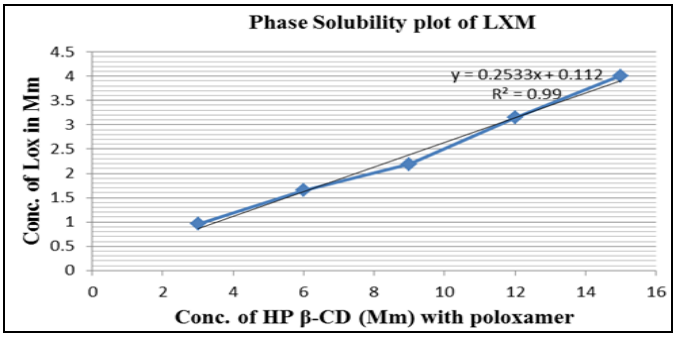

FIG. 4: PHASE SOLUBILITY OF LXM IN HP B-CD-PXM-407

Solubility Studies of SDs in Comparison with Pure LXM: The solubility of the ternary complexation was accessed in aqueous, acidic and alkaline media. Compared to pure LXM, the SD of LXM demonstrated solubility enhancements of 10.5-fold, 3.63-fold, and 20.12-fold in DDW, PBS pH 7.4, and 0.1N HCl (pH 1.2), respectively. The inclusion of PXM 407 as an auxiliary component in the TIC contributes to LXM solubility by reducing the surface tension between LXM and DDW.

Table 3 demonstrated the comparative solubility of LXM-SD containing and pure LXM in various pH conditions, whereby LXM-SD explored the higher solubility in all solutions than that of pure drug. Zafar A *et al.* discovered a similar pattern of solubility improvement using a TIC system incorporating PXM 407 as an auxiliary component [29]. **Fig. 5** illustrates the comparative solubility enhancement of LXM SD.

TABLE 3: SOLUBILITY STUDIES OF SDS AT DIFFERENT PH CONDITIONS

S. no.	pH	Saturation solubility of LXM (µg/ mL)	LXM- SD solubility (µg/ mL)	Fold enhancement in solubility
1	0.1N HCl (pH 1.2)	0.094	1.9	20.12
2	DDW	0.20	2.1	10.5
3	PBS pH 7.4	0.66	2.4	3.63

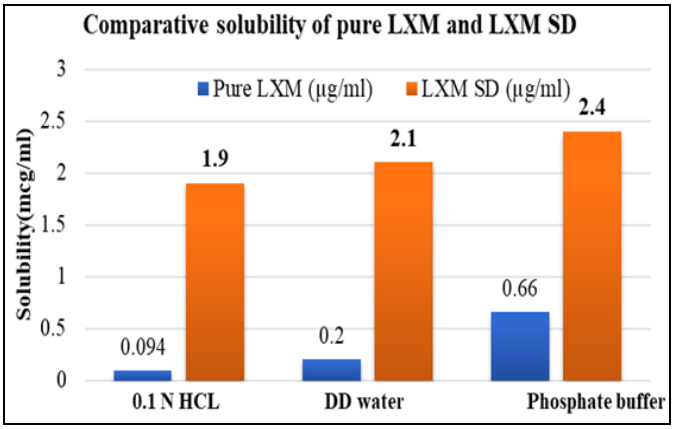

FIG. 5: COMPARATIVE SOLUBILITY OF THE PURE LXM AND LXM SD

DSC of SD in Comparison with Pure LXM: Thermal analysis helps indicate the existence of an interaction between two components. When guest molecules are introduced into the CD cavity, their melting, boiling, and sublimation points frequently shift/disappear.

LXM DSC thermograms **Fig. 6A** demonstrated a standard anhydrous crystalline drug at 223.3°C, corresponding to its melting point.

The sharp endothermic peak for LXM disappeared entirely in the DSC curves of the LXM-HP-βCD-PXM 407 SD **Fig. 6B**, indicating the development of a realistic LXM hydrophilized inclusion complex with HP-βCD.

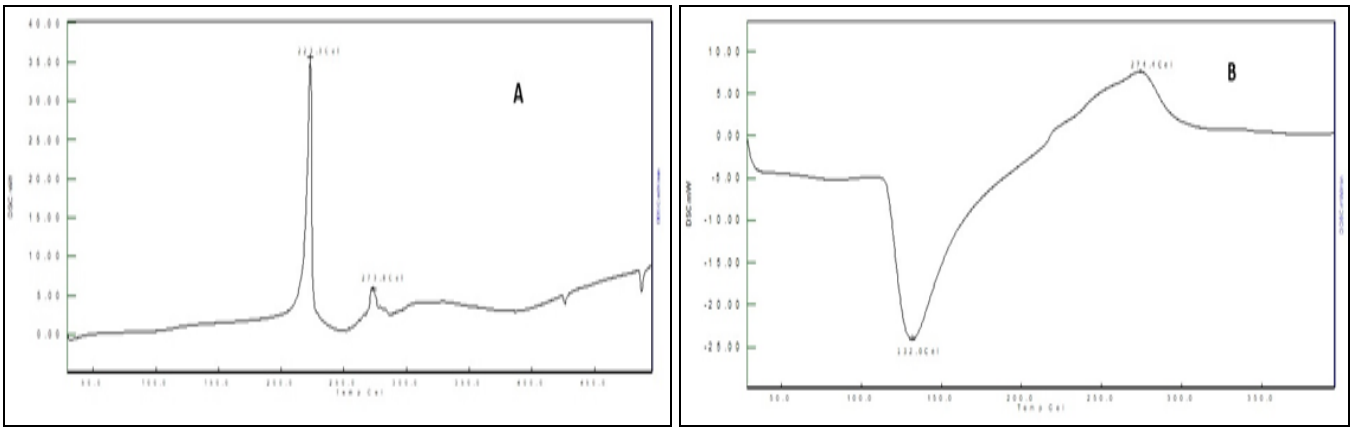

FIG. 6: DSC THERMOGRAM OF A: PURE LXM AND B: SD OF LXM

FT-IR of SD in Comparison with Pure LXM: The FT-IR spectra of a double hydrophilized SD of LXM **Fig. 7D** showed significant shifting in the stretching vibrations of pure LXM **Fig. 7A**. Due to the inclusion complexion of the pure LXM and the dissociation of intermolecular hydrogen bonds, spectra of the TIC showed slight shifting of the O-H band of LXM and C-O stretching band of PXM 407 slightly shifted towards a shorter wavelength, confirming the existence of interaction with the drug HP-βCD. In an aspect of PXM 407, the C-O peak (1145 cm^{-1}) shifted at 1105 cm^{-1}, whereas in SD, the O-H band of LXM (3400 cm^{-1}) shifted to a shorter wavelength at 3284 cm^{-1}.

The absence of the absorption peak at 1088 cm^{-1} in SD might arise afterthe coexistence of the C-O group with other bands, indicating a strong interaction and overall development of the SD with HP-βCD and PXM 407.

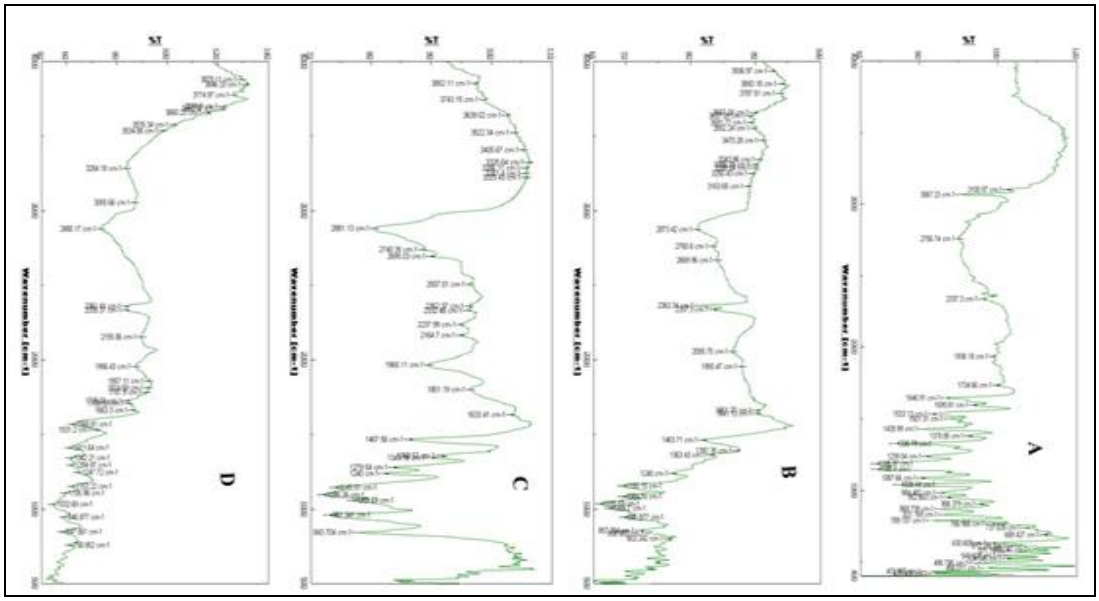

FIG. 7: FT-IR SPECTRA'S A): LXM; B): HP B-CD; C): PXM -407, AND D): LXM- SD

***In-vitro* Dissolution test:** In the *in-vitro* dissolution testing, LXM-SD (91.65% DR) demonstrated much higher than pure LXM (30.91% DR). A significant increase in DR from the double hydrophilization complex was accountable for development of water-soluble complexes. The solubilization effect of carriers can also contribute to a marked increase in LXM dissolution rates from SDs, as well as the alteration of crystalline LXM to afree-flowing powder which increases the DR associated with the ternary system [30]. The complexation between HP β-CD and LXM produced an amorphous form with improved solubility, which was the cause of the higher release associated with the ternary system. In combination with HP β-CD, the PXM 407 significantly increased the rate at which LXM dissolved by lowering the surface tension between LXM and the dissolution media [31]. These comprehensive findings suggested that complexation poorly soluble drugs with HP-βCD and PXM 407 can be a precise approach for increasing solubility along with DR. **Fig. 8A** and **8B** represent the percent cumulative DR of LXM-SD in comparison with pure LXM.

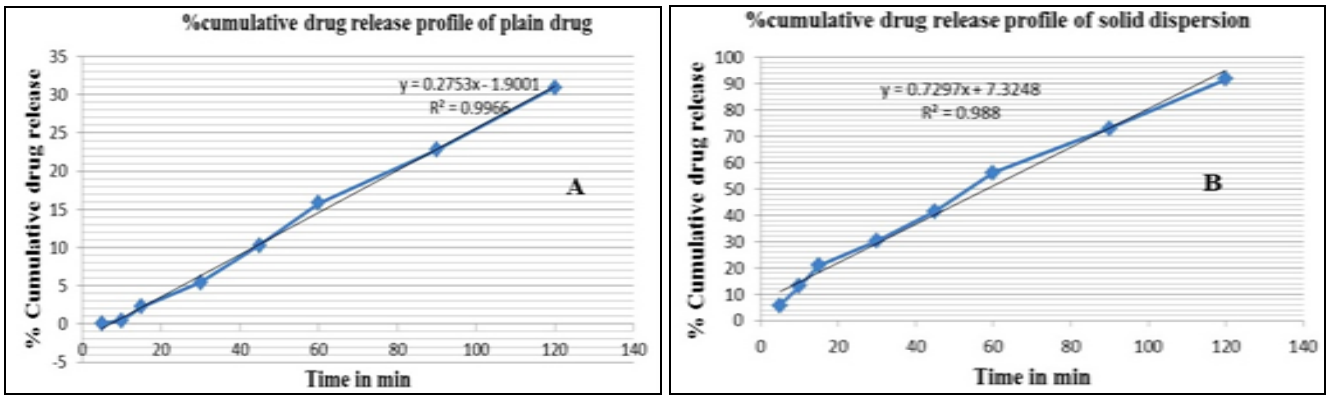

FIG. 8: PERCENT CUMULATIVE DR PROFILE OF A): LXM; B): LXM-SD

DISCUSSION: Modern anti-inflammatory drugs in the market have sparked a phenomenal deal of controversy. They have been demonstrated to be ineffective/harmful in certain instances. Owing to CD's capability to bind to organic and non-organic molecules, its application in pharmaceuticals and cosmetics has surged significantly over the past few decades. The utilization of functional excipients can minimize volatility while simultaneously boosting solubility and membrane permeability. Numerous drugs have indeed been discovered to benefit from CDs' physical, chemical, and biological aspects. As a result, the drugs used in the investigation exhibited increased bioavailability and decreased toxicity. It exerted a significant impact on both synthetic and organic

chemicals. They belong in the inner cone because of their 3D structure and hydrophobic carbon backbones. Inclusion complexes for NSAIDs and other drugs with low water solubility might house on CDs with their acetyl and dimethyl groups altered and possess remarkably varied solubility and DR characteristics (such as acetyl and hydroxypropyl). It could be attributed to the fact that CD is a natural chemical that is cost-effective and simple to explore in the research literature. Since, β-CD is less soluble than the other two CDs, it is safe to consume up to 5mg/kg daily. The swine's buccal mucosa has deteriorated its outer cellular membrane; as a result, irrespective of that, β-CD and its synthetic counterparts had traditionally been regarded believed to be innocuous. The *in-vitro* investigations have demonstrated the safety of developed formulations based on CDs.

Solubility and permeability are critical parameters for exploiting drug absorption and therapeutic efficacy. Balanced lipophilicity and hydrophilicity of drugs play a vital role in penetrating it in the bloodstream or other tissues. The lipophilicity of aromatic moieties may differ due to the presence of aromatic rings and different substitutions. Several investigational studies demonstrated that Hydrophilic polymers (predominantly HP-βCD) significantly enhanced the aqueous solubility of NSAIDs (flurbiprofen and diclofenac) and reported the association between the solubility, increased bioavailability and anti-inflammatory activities. The interaction between l-arginine with drugs and CDs leads to salt formation, Hydrogen bonding, and electrostatic interactions. The data suggested that the attributes of HP-βCD and L-amphiphilic arginine may be combined to create supramolecular three-component structures that can improve the complexation, solubility, and regulation of DR of the NSAIDs-CD complexes.

CONCLUSION: Modern anti-inflammatory drugs in the market have sparked a terrific controversy associated with their poor solubility, bioavailability and dissolution rate; one of them is LXM. Therefore, the present investigation conducted a Comparative solubility study of cyclodextrins (β-CD and HP-βCD) and enhancement of solubility and dissolution of LXM using TIC. The comprehensive data obtained from the present study confirmed that the LXM could interact with the CDs, including complexity in the aqueous phase depending on the pH, method of preparation, and selection of an effective auxiliary substance. The double hydrophilized ternary SD of LXM-HP-βCD-PXM-407 was best compared to the binary mixture of LXM- β-CD. The study determined significant improvement in CE and greater Ks values for HP-βCD than β-CD. The HP–βCD was required to be slightly more concentrated than the β-CD due to its lower drug: carrier ratio, which reduces cytotoxicity and manufacturing expenses. Studies on DSC, FTIR, and in-vitro dissolution supported the effectiveness of the selected approach. Additional product development using prepared SDs should be explored to achieve clinical relevance. The results obtained justified using PXN as a pragmatic choice of polymer to improve LXM's solubility and the DR using the ternary composition strategy.

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