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Design and Development of Lornoxicam Impregnated Dry Powder Based Liquid Crystals

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ABSTRACT

The objective of the present work was to fabricate dry powder precursors using GMO, which upon hydration forms cubic phase of lyotropic liquid crystal and it can be used for the fabrication of oral solid dosage forms. Dry powder precursor was evaluated for percentage yield, drug content, Fold scope microscopy, scanning electron microscopy, X-ray diffraction, viscosity and in vitro release behavior. The dry powder precursor was obtained by spray-drying method, with GMO, Lornoxicam and magnesium trisilicate. The drug content for optimized batch was92% and release kinetic was 96% (up to 12 hrs.)Surface morphology studies indicated the irregular shape of particles while polarizing light microscopy confirmsthat cubic phase forms upon hydration of powder precursor. The dry powder precursor of cubic phase was prepared in which drug release was entirely governed by the mesophases formed.

Keywords*: Liquid Crystalline powder precursor, Lornoxicam, Lyotropic, Oral drug delivery system.*

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INTRODUCTION

Glyceryl monooleate (GMO), an amphiphilic lipid self-associate to form sequential liquid crystalline mesophases, viz., lamellar, cubic and hexagonal when placed in an aqueous media [1,2].Being nontoxic, biodegradable and biocompatible it has found its utility in various delivery systems and routes of administrations. [3]Delivery system based on partially hydrated lamellar phase [4,5] hydrated cubic gel [6] cubic phase dispersionsand matrixhave been explored bymany researchers. Cubic phase coexists in equilibrium with the excesswater andbeing highly viscous has gained much attention for sustained release.[7,8]The sustained release may be due to slow drugsdiffusionor increased residence time in its solubilized form. Further, its isotropic nature, relative insensitivity to salts and solvents, robustness and resistance to physical degradation make it most preferred candidate for sustained drug delivery. However, design and development of cubic phase based palatable solid dosage form ofGMOhas limitations due to its intrinsic properties like stickiness and stiffness. Preparation of dry powder precursors, which can be quickly transformed into cubic phase *in situ,* will promote industrial application of the system. Recently, developed spray dried dry powder cubosomes by encapsulating monoolein using ternary (starch monoolein–water) and quaternary (dextran–monoolein –ethanol–water) systems.[9,10]

MATERIAL AND METHODS

Materials

Glyceryl mono-oleate (MONOGYL- 0100) was generousgift from Mohini Organics Pvt Ltd. Mumbai. Magnesium trisilicate (MTS) was gifted from Merck chemicals Pvt Ltd. Nashik (India).Lornoxicam was obtained as gift sample from Glenmark pharmaceuticals Ltd. Nashik (India). All other chemicals used were of analytical grade.

Preparation of powder precursor

Initially Glyceryl mono-oleate (GMO) was dissolved in sufficient amount of isopropyl alcohol and then MTS and Lornoxicam were dispersed in it. Total solid content of dispersion of all batches was 5.0%. The dispersion was further subjected to spray-drying (SPD E 111, Technosearch Instruments, Mumbai).

Samples of powder precursor were kept in desiccator at room temperature over silica gel for 12–24 h before being subjected to any further evaluation.

Table 1: Composition of powder precursor

Sr. no.	Batch	GMO (%)	Drug (%)	MTS (%)
1.	F1	1	0.5	0.5
2.	F2	1	0.5	1.0
3.	F3	1	0.5	1.5
4.	F4	1	0.5	2.0
5.	F5	1	0.5	2.5
6.	F6	1	0.5	3.0

Evaluation of powder precursor

Percent yield

The weight of powder precursor obtained after spray-drying was considered as observed yield and percent yield was calculated by using following formula:

$$\text{Percent yield} = \left(\frac{\text{Observed yield}}{\text{Theoretical yield}}\right) \times 100$$

Viscosity

A Brookfield digital viscometer, cone and plate type was used to determine viscosity of the formulations .The viscosity was measured at 5rpm after 30 sec, by using spindle no.64

Drug Content

0.5gm Lornoxicam impregnated dry powder based liquid crystals were weighed accurately. It was added in 100 ml volumetric flask containing 100 ml of PBS 6.8.Resultant solution was kept for sonication for 30 mins.For complete solubility of drug, the resultant solution was filtered .Absorbance of solution were determined at 376 nm and. Thus % assay was calculated.

Fourier Transform Infrared (FT-IR)

IR spectroscopy determined the molecular interaction between polymer and drug. Infrared spectra of drug, polymer, and physical mixture were obtained using FT-IR spectrophotometer (FT-IR 8400; Shimadzu Co Kyoto, Japan)

Polarized Light Microscopy (PLM)

Phase characterization of the formulations were performed by using Leica polarizing microscope equipped with f-601 camera

Scanning Electron Microscopy (SEM)

SEM was used to observe the morphological characteristics of powder precursor. Samples were mounted on a double-faced adhesive tape and sputtered with thin gold–palladium layer by sputter coater unit (VG Microtech, UK) and surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (Cambridge, UK) operated at an acceleration voltage of 10 kV.

***In Vitro* Dissolution study**

Drug release study of the powder precursor was carried out using USP 24 type II dissolution test apparatus (Electrolab TDT-08L, India). The dissolution test for each batch was performed in triplicate. The powder precursor was filled into the capsules. Capsules were placed in 900 ml of phosphate buffer (pH 6.8) maintained at temperature 37±0.5°C and stirred constantly at 100 rpm. Aliquots (5 ml) were withdrawn at pre-determined time intervals and replenished with fresh dissolution medium maintained at 37±0.5°C. The aliquots were assayed spectrophotometrically at 376 nm.

RESULTS AND DISCUSSION

Percent yield

The percent yields of different batches of powder precursors prepared by spray-drying are shown in Table no. 2. In case of batches (batch F1) with lower MTS content, sticking was observed on side wall of drying chamber. This sticking was attributed to incomplete adsorption of GMO on inadequate amount of MTS particles, resulting in lower yield. With increase in MTS content, yield was improved significantly, which may be attributed to uniform coating of GMO on MTS particles. The product thus obtained was found to be comparatively non-sticky one. Interestingly high density of MTS reduced the escaping tendency of the powder and increases the percent yield.

Table No.2: % yield of formulation batches.

Sr no.	Formulation Batches	% yield
1.	F1	67.5%
2.	F2	72%
3.	F3	80%
4.	F4	82%
5.	F5	91%
6.	F6	85%

Drug Content

Drug content of formulation batches has been tabulated as below in following table no.3.The drug content of the optimized Formulation (F5) was carried out in triplicate and average drug content was found to be of 92%.Hence uniformity of drug content was found to be satisfactory.

Table No.3: Drug contents of formulation batches

Sr. no	Formulation	Drug Content (%)
1.	F1	73%
2.	F2	79%
3.	F3	80%
4.	F4	88%
5.	F5	92%
6.	F6	88%

Fourier Transform Infrared (FTIR) Study.

FTIR studies were conducted to determine compatibility between drug and excipients. FTIR spectra and characteristic peaks of pure drug Lornoxicam, Drug and GMO mixture and formulation F5 were obtained respectively. FTIR spectra showed characteristic peaks at, C-H Aromatic at 3150-3050 cm^{-1}, C=O Ketone at 1725-1707 cm^{-1}, Sulfoxide at 1050 cm^{-1} and chloride at 785-550 cm^{-1}. All the characteristic peaks ofLornoxicam were found and no new bands were observed in the FTIR spectrum confirming no considerable interaction between the drug and all other excipients in formulation.

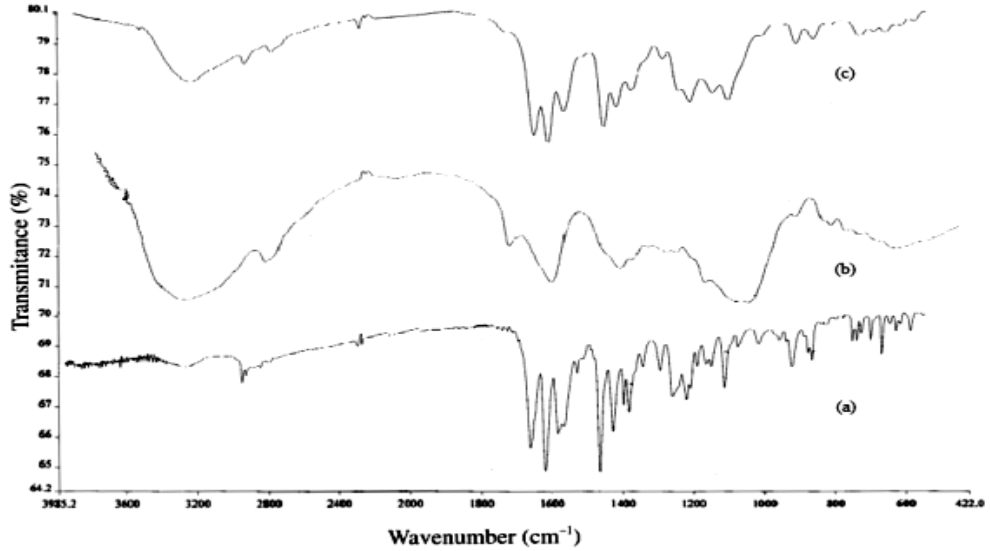

Fig 1. FT-IR Spectrum of: a) Drug b) Drug and GMO mixture c) Formulation batch F5

Rheological behavior

The effect of amount of MTS on the viscosity of hydrated powder precursor is shown in Table no.4. It was noted that as the amount of MTS in the powder precursor increased, viscosity increased linearly. The powder precursor with high amount of MTS (batch F5) had highest viscosity. With high content of MTS, GMO was completely coated on MTS. As a result, when such system was hydrated; it induced formation of cubic phase, having high viscosity. It was concluded that viscosity of the powder precursor was the function of amount of MTS.

Table No.4: viscosity of formulation batches.

Sr no.	Formulation	Viscosity (cp)
1.	F1	1.23
2.	F2	2.46
3.	F3	3.87
4.	F4	5.62
5.	F5	6.81
6.	F6	5.30

Saturation solubility studies

Pure drug lornoxicam showed the solubility of 0.023 mg/ml. In the saturation solubility study, it was found that the GMO based powder precursor increased the solubility of lornoxicam up to 7.73 times. Batch 5 showed the maximum saturation solubility of 0.178 mg/ml.

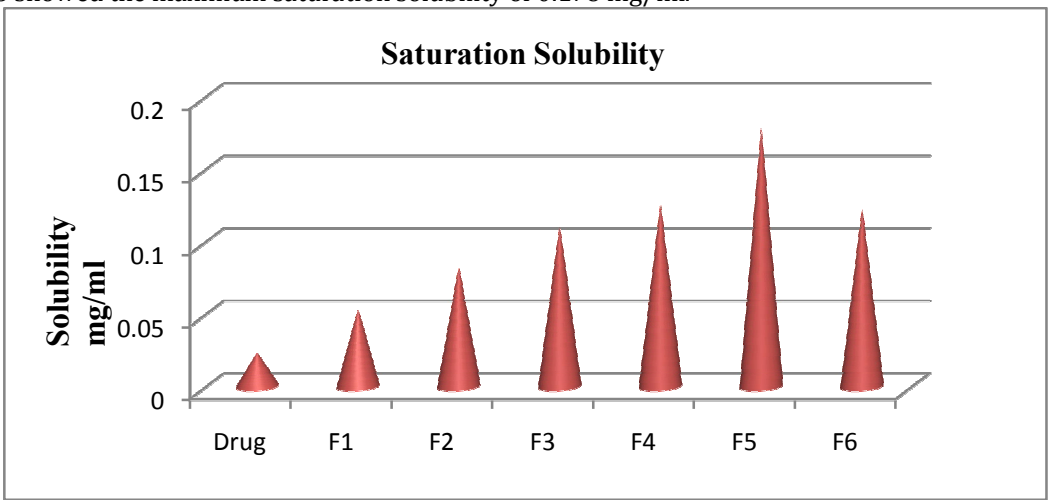

Fig 2: Saturation solubility of plain drug and its batches

Table.No.5. Saturation solubility of formulation batches

Sr no.	Formulation Batches	Saturation Solubility
1.	Drug	0.023
2.	F1	0.053
3.	F2	0.082
4.	F3	0.110
5.	F4	0.125
6.	F5	0.178
7.	F6	0.122

Differential Scanning Calorimetry (DSC)

The DSC thermogram of Lornoxicam showed a sharp melting endothermic peak at 218°C indicating crystalline nature of the drug. The optimized liquid crystalline powder precursor (LCPP) batch F5 showed no distinct melting endotherm peak for the drug. The formation of amorphous LCPP is attributed to the molecular interaction between drug and polymer. This indicates that the drug exists in the amorphous state in the LCPP powder. The disappearance of the sharp melting endotherm in the DSC scan of LCPP powder suggested that the drug has been converted to the amorphous form during the LCPP process successfully.

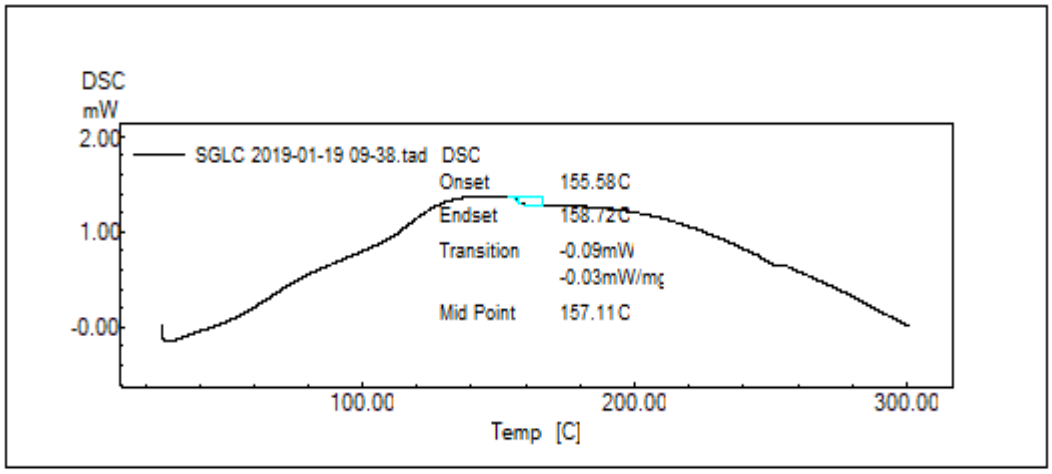

Fig 3: DSC study of powder precursor

Powder X-ray diffraction(XRD)

The Xray diffractogram of pure lornoxicam showed sharp multiple peaks, indicating the crystalline nature of the lornoxicam. It showed sharp peaks at diffraction angle (2θ) value of 13.13, 13.99, 15.20, 21.64, and 25.55 with intensity 723, 786, 408, 579, 318 respectively, whereas the LCPP (F5) diffractogram shows the (2θ) value 13.53, 14.02, 15.31, 21.76 and 25.18 with intensity 110, 47.5, 29.7, 38.5, 16.6 respectively. From the two spectra it was concluded that LCPP showed less intense peaks than pure lornoxicam due to conversion of crystalline drug into amorphous form.

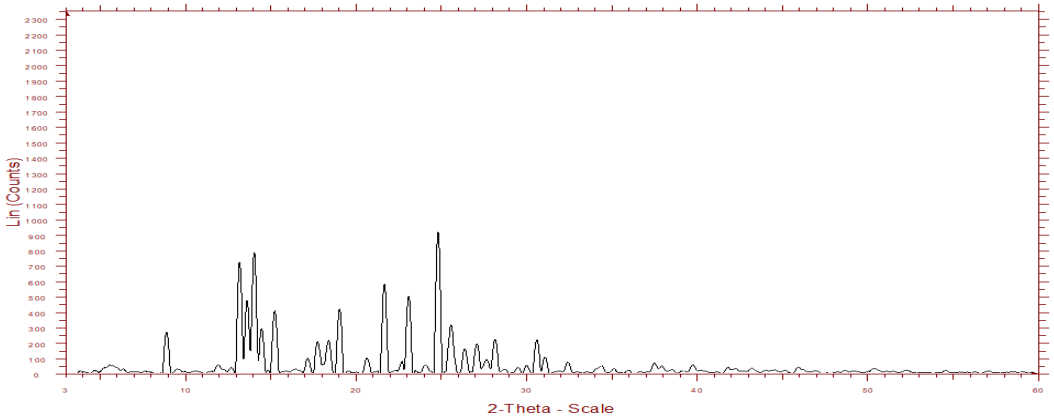

Fig 4: Powder X-ray diffraction of Purelornoxicam.

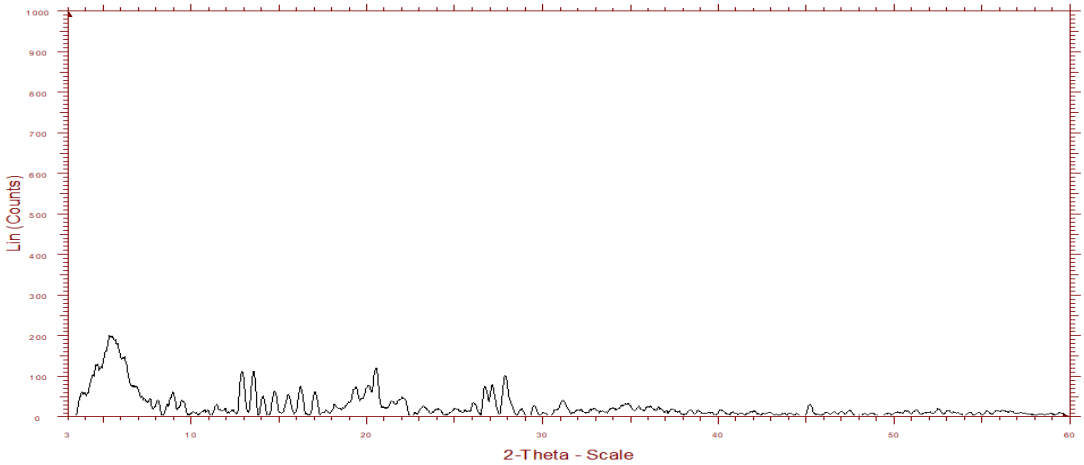

Fig 5: Powder x-ray diffraction of formulation batch F5.

Scanning Electron Microscopy (SEM)

The SEM microphotographs of batch F5 powder precursor showed that GMO had coated the entire dispersion of Lornoxicam and MTS and provided smooth texture to powder precursor. The small

semispherical powder particles had been packed together closely due to sticky nature of GMO leading to aggregation after spray-drying.

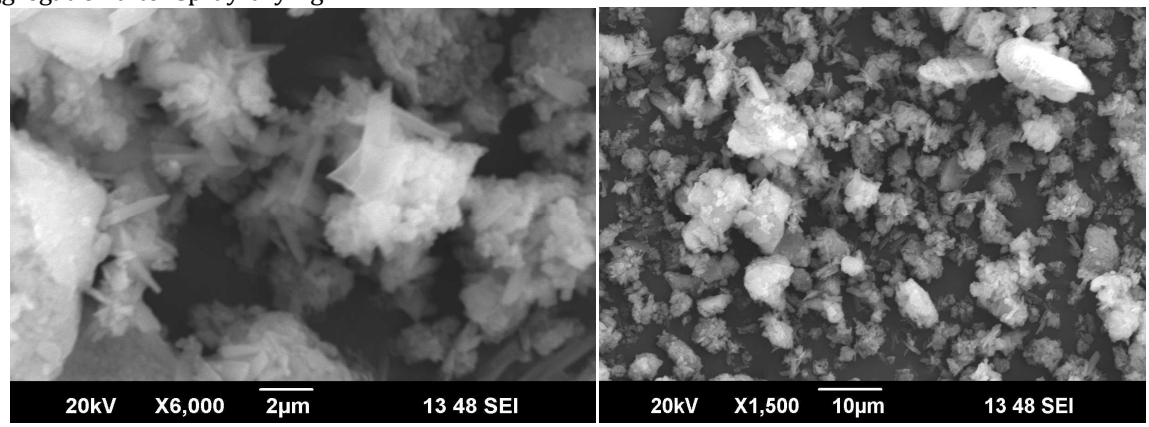

Fig 6:SEM images of formulation batch F5

Polarized Light Microscopy (PLM)

The phase identification of optimized batch F5 was studied by PLM. The obtained photomicrograph of optimized formulation shows the same image structure as the cubic phase.

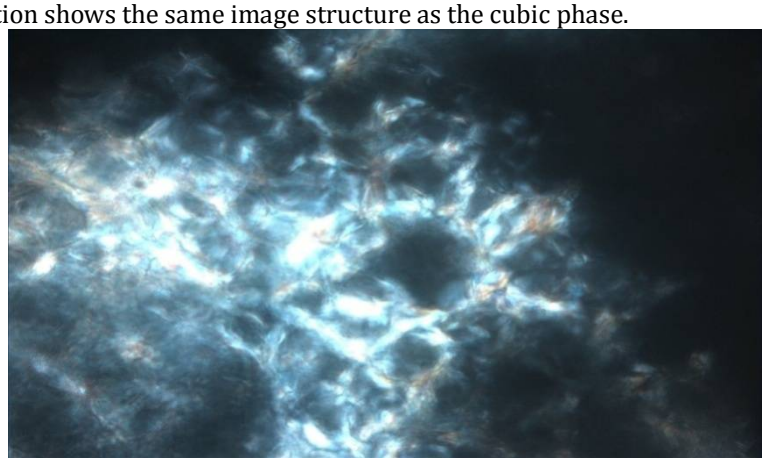

Fig 7: PLM image of cubic phase of formulation batch F5

***In- vitro* dissolution study of Liquid crystalline powder precursor**

The dissolution profile of powder precursor was shown in Table no.5. From dissolution data, plain lornoxicam drug showed poor dissolution profile in pH 6.8 phosphate buffer. The dissolution profile of all powder precursors or batches showed in between 69.49 % to 96.35 % for 12 hrs. at 37ºC ± 0.5ºC in pH 6.8 phosphate buffer F5 showed high dissolution profile which was 96.35 % for 12 hrs at 37ºC ± 0.5ºC in pH 6.8 phosphate buffer. Cumulative drug release of batches F1, F2, F3, F4, F5 and F6 in 12 hrswas found to be 69.49%, 71.20%, 77.11%, 87.76%, 96.35% and 88.76% respectively. Result indicates that, batch F5 shows high % release and sustained action.

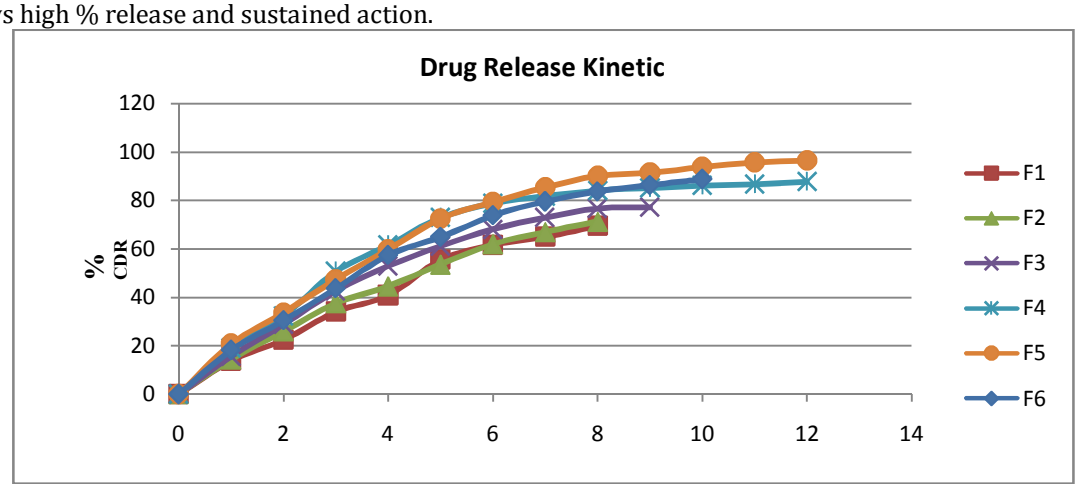

Fig 8: Drug release kinetics

DISCUSSION

With increase in MTS content, percent yield was improved significantly, which may be attributed to uniform coating of GMO on MTS particles. The drug content of the optimized Formulation (F5) was found to be of 92%. FTIR spectrum confirming no considerable interaction between the drug and all other excipients in formulation. It was concluded that viscosity of the powder precursor was the function of amount of MTS. Powder precursor increased the solubility of lornoxicam up to 7.73 times. DSC scan of LCPP powder suggested that the drug has been converted to the amorphous form during the LCPP process successfully. Powder X-ray diffraction(XRD) confirms conversion of crystalline drug into amorphous form. Polarized Light Microscopy of optimized formulation shows the same image structure as the cubic phase. In- vitro dissolution study of Liquid crystalline powder precursor indicates that, batch F5 shows high % release and sustained action.

CONCLUSION

The liquid crystalline powder precursor of lornoxicam with GMO and MTS (F5) showed a7.73-fold increase in the solubility and dissolution rate. This may be due to highly crystalline nature of lornoxicam converted into amorphous form successfully. A dry powder precursor of cubic phase had been fabricated. The SEM studies and image analysis demonstrated that the powder precursor was dependent on amount of MTS present in the powder precursor. Powder precursor formed cubic phase at faster rate and drug release was entirely governed by the mesophases formed. The Lornoxicam loaded powder precursor had presented more effective and prolonged anti-inflammatory and analgesic activity as compared to pure drug owing to sustained release of drug. The powder precursor thus prepared can be utilized for preparation of oral solid dosage forms such as tablet and capsule.

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