Original Article

# Lamotrigine Novel Cocrystals: An Attempt To Enhance Physicochemical Parameters

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## Abstract

Background: Cocrystals are defined as multiple component structures whose components interact through non-covalent interactions. Cocrystals can enhance other essential properties of the APIs.

Aim: The current research work focuses on formulating and evaluating novel co-crystals of Lamotrigine anti-epileptic drug (BCS-II)

Methods: The Cocrystals of Lamotrigine drug with different cocrystals formers like Saccharin sodium, 4-Hydroxy benzoic acid, and Methyl paraben used with molar ratios (1:1) were prepared by solvent drop method, co-grinding method, and solvent evaporation method.

Results: The results signify the establishment of intermolecular interaction within the cocrystals. In the novel cocrystals, Lamotrigine was determined to be engaged in the hydrogen bond interaction with the complementary functional groups of Saccharin sodium, 4-Hydroxy benzoic acid, and methyl paraben. Compared with the pure Lamotrigine flow properties for prepared co-crystal by using solvent evaporation method crystals are showing excellent flow properties. LTG-SAC CF I, LTG-HBA I, and LTG-MP III showed 49.6 folds, 7.4 folds, and 3.36 folds improved solubility respectively. The dissolution test showed that the LTG-SAC CF I, LTG-HBA I, and LTG-MP III cocrystals exhibited a 1.09-fold, 1.08-fold, and 1.07-fold higher dissolution rate than the pure Lamotrigine.

Conclusions: LTG-SAC CF I, LTG-HBA I, and LTG-MP III cocrystals showed modification in the chemical environment, intermolecular interactions were established, improved flow properties with enhanced intrinsic solubility and in-vitro dissolution rate than pure drug.

**Keywords:** Lamotrigine; Cocrystals; Antiepileptic; Solubility enhancement; Dissolution enhancement

## 1. INTRODUCTION

Dissolution and solubility are generally considered to be the rate-determining step of weakly water-soluble medicines after oral absorption, among all the physicochemical characteristics of the active moiety. In order to achieve adequate oral absorption, method selection for increasing solubility and dissolving rate is critical. Among the many approaches, pharmaceutical cocrystals appear to be the most promising option for improving the active moiety's physicochemical properties such as solubility, melting point, dissolution, and stability [1,2].

Pharmaceutical co-crystals are solids that are neutral crystalline single phase materials composed of two or more different molecular and or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts [3]. If at least one of the co-former is an API and other is pharmaceutically acceptable, then it is recognized as a pharmaceutical co-crystal [4].

Co-crystals contain two or more components which are held together by supramolecular synthons. In order to obtain co-crystals, functional groups capable of forming supramolecular hetero or homosynthons should be present in the API and coformer [5].

Lamotrigine, 3, 5diamino -6-(2,3-dichlorophenyl)-1,2,4-triazine has been used for the treatment of seizures and bipolar disorder, chemical structure of Lamotrigine represented in [Figure 2]. Lamotrigine is an anti-epileptic agent and mood stabilizer. The physiologic effect of Lamotrigine is by means of decreased central nervous system disorganized electrical activity which belongs to BCS class-II drugs [6]. The major trouble with this drug is low water solubility (0.17mg/ml at 25 $^0$C) which displays low solubility in gastrointestinal fluids [7] The co-crystallization method is a good choice since it gives the active molecule with required physicochemical properties [8,9]

In the present investigation, three coformers containing the carboxyl group, shown in (Figure.2) are preferred to form cocrystal with Lamotrigine. Specifically, cocrystals of LTG with Sodium Saccharin, 4-Hydroxy Benzoic acid and Methyl Paraben were synthesized by the Co-grinding, Solvent drop and solvent evaporation technique [10]. For the novel cocrystals, structural characterization was done by powder x-ray diffraction (PXRD), infrared spectroscopy (FT-IR), differential scanning Calorimetry (DSC), 1H liquid FT-NMR, and scanning electron microscopy (SEM) [11]. In vitro evaluations were done by aqueous solubility and in vitro dissolution drug release and these were compared with the parent drug molecule.

## 2. MATERIALS AND METHODS

### 2.1. Materials

Lamotrigine was a gift sample from A-Z pharmaceuticals at Chennai. Benzoic Acid were purchased from the Sigma-Aldrich chemical Pvt. Ltd; Saccharin sodium were purchased from Hi-media laboratories Pvt. Ltd. Methyl paraben were purchased from Hi-media laboratories Pvt. Ltd. Double distilled water was used throughout the research. Other solvents are used for analytical grade.

### 2.2. Synthesis of novel Lamotrigine cocrystals

Novel cocrystals of Lamotrigine were synthesized by three methods like co-grinding, solvent drop and solvent evaporation technique [12-15] flow process of synthesis of co-crystals represented in (Figure 2)

#### 2.2.1. Solvent drop method:

The cocrystals are produced by a molar ratio of 1:1; Lamotrigine and coformers were taken in glass motor and grounded up to 10 min with help of pestle. Then add solvent (ethanol) few drops in drop wise and again grounded for 10 min and keep it for drying in the air, [13] represented in (Figure 3).

#### 2.2.2. Co-grinding method:

The cocrystals are produced by a molar ratio of 1:1; Lamotrigine and co-former were taken in glass motor and pestle and grounded up to 1 hr. and keep it for drying in the air [14] represented in (Figure 3).

#### 2.2.3. Solvent evaporation method:

Lamotrigine and co-former were dissolved separately in 5 ml of ethanol with warming and mixed together. Solution was cooled to room temperature and kept for slow evaporation for 6 h. the crystals were isolated by filtration through a membrane (0.45µm) and dried in the air [15] represented in (Figure 3).

### 2.3. Characterization of Cocrystals

The synthesized cocrystals were evaluated for preliminary structural properties, flow properties, intrinsic solubility and *invitro* dissolution studies [16] flow process of characterization of cocrystals represented in (Figure 4).

#### Structural Properties

#### 2.3.1. Fourier transforms infrared spectroscopy analysis (FTIR)

FTIR spectra of pure LTG, SS, 4-HBA, MP and synthesized cocrystals like LTG-SAC, LTG-4-HBA, and LTG-MP is recorded using Micro labs Agilent technologies Cary 630 containing DLATGS detector with 2 cm−1 spectral resolution. Then, 2–4 mg of each sample was placed on the sample cell and each spectrum was derived from average of 3 singles scans collected in the region 4000-400 cm$^{-1}$ [17].

#### 2.3.2. Powder X-ray diffraction analysis (PXRD)

Crystalline structure alterations of LTG and novel cocrystals were analyzed by utilizing powder XRD diffractometer. Each sample of the pure drug, co-formers, and the cocrystals were placed in the sample holder then scanned by utilizing Philips Xpert MPD diffractometer with Cu target X-ray tube source which was operated at 30 kV and 15 mA for 2 scan axis. Maintaining a 5–65° scan range with 0.02° of step width and 10.00°/min scan speed [18].

#### 2.3.3. Liquid FT-NMR analysis

$^1$H liquid FT-Nuclear Magnetic resonance spectra for pure drug, co-formers, and the cocrystals is recorded by utilizing 400 MHz FT-NMR spectrometer (JNM-ECZ 400S) USINF TMS as an internal standard. Each sample was dissolved in deuterated dimethyl sulfoxide (DMSO-d6) for analysis and operated at 400 MHz frequency [18].

### 2.3.4. Differential scanning Calorimetry analysis (DSC)

The thermal behaviour of the samples was analysed by utilizing differential scanning Calorimetry. Each sample (3–5 mg) of pure drug, co-formers, and novel cocrystals were scanned by using NETZSCH DSC 204 Calorimetry. Each sample (3-5 mg) was placed in sealed non-hermetic aluminum pans and were heated at scanning rate of $10^{o}c\ min^{-1}$ over the temperature range of 0- $300^{o}c$ under dry nitrogen purging (10 ml /min) [19].

### 2.3.5. Electron microscopy

Morphological changes between the pure drug LTG and the novel cocrystals were analyzed with electron microscopy. It is a special type of microscope having a high resolution of images. Electron microscope use signals arising from the interaction of an electron beam with the sample of obtain information about structure, morphology and composition. The electron gun generates the electrons. Two sets of condenser lens focus the electron beam on the specimen and then into a thin light beam. To move electrons down the column, an accelerating voltage (mostly between 100kV- 1000kV) is applied between tungsten filament and anode. The specimen to be examined is made extremely thin at least 200 times thinner than those used in optical microscope [20].

### 2.3.6. Percentage yield

The dried crystals were weighed and percentage yield of the prepared cocrystals were calculated by using the following formula [21].

$$\text{Percentage yield} = \frac{\text{Practical yield (mg)}}{\text{Theoretical yield}} \times 100 \qquad \text{(Equation 1)}$$

### 2.3.7. Drug content:

For the determination of drug content, prepared supramolecular crystals (100mg) were dissolved in 100 ml distilled water and the solution was analyzed spectrophotometric at 270 nm (Agilent technologies cary 60 UV Vis) for drug content, after sufficient dilution with distilled water [22].

## 2.4. FLOW PROPERTIES

### 2.4.1. Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved cocrystals into a graduated cylinder via a large funnel and measure the volume and weight. Bulk density was expressed in g/cc [23].

$$\text{Bulk density} = \frac{\text{Weight of crystals}}{\text{Bulk volume of cocrystals}} \qquad \text{(Equation 2)}$$

### 2.4.2. Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of cocrystals and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed [24].

$$\text{Tapped density} = \frac{\text{Weight of crystals}}{\text{Tapped volume of cocrystals}} \qquad \text{(Equation 3)}$$

### 2.4.3. Angle of repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder into a conical heat on a level, flat surface and measure the included angle with the horizontal [23-25]

$$\theta = \tan^{-1}(h/r) \qquad \text{(Equation 4)}$$

Where, h= Height of the heap
r = Radius of the heap

### 2.4.4. Carr's Index (CI)

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index

$$CI = \frac{(T_D - B_D)}{T_D} \times 100 \qquad \text{(Equation 5)}$$

Where $T_D$ = Tapped density $B_D$ = Bulk density

### 2.4.5. Hausner's Ratio

It indicates the flow properties of the powder and ratio of tapped density to the bulk density of the powder or granules [23-25]

Hausner's Ratio = Tapped density / Bulk density (Equation 6)

## 2.5. IN VITRO EVALUATION

### 2.5.1. Intrinsic solubility

Intrinsic solubility analysis was conducted in triplicate; the equilibrium method [37] was utilized for determining the intrinsic solubility of pure drug LTG, cocrystals LTG-SAC, LTG-4-HBA and LTG-MP. An excess amount of each sample was placed in vials with caps containing 10 ml of distilled water. These solutions were sonicated for 15 min and were placed in a water bath shaker for 48 h with a rotating speed of 100 rpm at 30 ± 1 °C. The supernatant solution was filtered through 0.45μm filters. This filtrate was diluted with methanol and the drug concentration was determined by utilizing UV-Spectrophotometer (Agilent technologies cary 60 UV vis) at 270 nm [26]

### 2.5.2. PH of solution at equilibrium

An excess quantity of prepared cocrystals was placed in the vials containing 10 ml distilled water. The vials were agitated in incubator shaker (100 rpm) for 2 hours at room temperature. The pH of prepared crystal formulations and pure drug are measured in digital pH meter [27].

### 2.5.3. In vitro dissolution study:

The *in vitro* dissolution studies were carried out in triplicate using eight-station USP type 2 (Paddle method) dissolution apparatus (Lab India, Model Disso 2000). Dissolution studies were carried out using 900 ml of pH 1.2 (0.1N HCl) acidic buffer. The paddles were rotated at 100 rpm. by maintaining 37 ± 0.5 °C throughout the study. 5 ml of aliquot was collected at 10, 20, 30, 40, 50, and 60 min by replacing with fresh dissolution medium. Collected aliquots were filtered through a 0.45μ filter; the filtrate was diluted and estimated for drug concentration using UV-Spectrophotometer (Agilent technologies cary 60 UV vis) at 270 nm [28].

## 2.6. RELEASE KINETICS

The matrix systems were reported to follow the peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into zero order, first order, higuchi matrix and peppas. In this by comparing the r-values obtained, the best-fit model was selected [29-32]

### 2.6.1. Zero Order Kinetics

$$Qt = Qo + Ko\ t \qquad \text{(Equation 6)}$$

Where,
Qt = Amount of drug dissolved in time t,
Qo = Initial amount of drug in the solution
Ko = Zero order release constant.

### 2.6.2. First Order Kinetics

$$\text{Log } Qt = \log Qo + K1t/2.303 \qquad \text{(Equation 7)}$$

Where,
Qt = Amount of drug released in time t,
Qo = Initial amount of drug in the solution
K1 = First order release constant.

### 2.6.3. Higuchi Model

$$Qt = K_H \times t\ 1/2 \qquad \text{(Equation 8)}$$

Where,
Qt = Amount of drug released in time t
$K_H$ = Higuchi dissolution constant.

### 2.6.4. Peppas Release Model

$$Mt / M\infty = K.tn \qquad \text{(Equation 9)}$$

Where,
Mt / M∞ = Fraction of drug release,
K= Release constant,
t = Drug release time and
n = Diffusion release exponent

## 3. RESULTS AND DISCUSSION

### 3.1. Fourier transforms infrared spectroscopy (FTIR)

Alterations of intermolecular interactions in comparison to parent molecules can be studied using FTIR. (Figure 5) shows the FTIR spectra of starting materials and novel cocrystals. For LTG, the characteristic peaks corresponding to amine N-H Stretch and C-H Stretch are assigned at 3310.70, 3207.51 cm-1 For SAC, a sharp peak appeared at 3530.64 cm-1 was assigned to C=O stretch and a broad multiple peaks at 3248.89 cm-1 was ascribed as O-H stretching. For 4-HBA, a characteristic O-H stretch peak was assigned at 2663.21 cm-1 and a broad multiple peaks corresponding to C=O stretch at 1675.60 cm-1. For MP, a characteristic O-H Stretch peak was assigned at 3284.49 cm-1 and a broad multiple peaks corresponding to C=C Stretch at 1585.01 cm-1, represented in figure 5 These are the main functional groups that are responsible for hydrogen bond formation.

FTIR analysis LTG-SAC cocrystals showed the shift in the N-H, and C-H stretch peak position of parent molecule from 3310.70, and 3207.51 cm-1 to strong O-H stretching at 3485.07 cm-1, C=C stretching at 1623.01 cm-1. LTG-4HBA cocrystals showed the shift in N-H, and C-H stretch peak position of parent molecule from 3310.70, and 3207.51 cm-1 to strong O-H stretching at 2663.21 cm-1 , C=C stretching at 1637.49 cm-1. LTG-MP cocrystals showed the shift in N-H, and C-H stretch peak position of parent molecule from 3310.70, and 3207.51 cm-1 to strong O-H stretching at 3283.87 cm-1, C=O stretching at 1669.06 cm-1, represented in (Figure 5). The similar shifting values are indicating formation of novel co-crystals indicating a similar type of interaction.

### 3.2. Powder X-ray diffraction analysis (PXRD)

Along with the DSC, powder X-ray diffraction (PXRD) analysis has the ability to determine the Crystallinity of the drug molecule. PXRD spectra of the starting materials and the novel cocrystals were shown in (Figure 6). LTG-SAC cocrystal showed the major characteristic peaks of 2ɵ scattering angles at 12.625o, 17.599o, 18.141o, 20.751o, and 26.854o which were absent in the drug molecule and differ from co-former. LTG-4HBA cocrystal showed the major characteristic peaks of 2ɵ scattering angles at 18.065o, 18.441o, 18.72o, 18.989o, 22.055o, and 25.768o which are new for LTG and differ from 4HBA. LTG-MP cocrystal showed the major characteristic peaks of 2ɵ scattering angles at 17.248o, 18.023o, 8.626o, 18.447o, and 20.479o, represented in figure 6. Which are new for LTG and differ from MP

### 3.3. 1H liquid FT-NMR analysis

Alteration in the chemical environment can be readily detected through the chemical shift in NMR spectrum. The Novel cocrystals, LTG-SAC, LTG-4HBA, and LTG-MP showed the co-existence of resonance peaks from the starting materials with significant chemical shift indicating the new phase generation. A solvent peak (DMSO-d6) at $\delta = 2.6$ can be detected in the starting materials and the co-crystals. Plain LTG showed the proton peaks at $\delta = 3.77$, 6.372, 6.690, 7.341, 7.360, 7.428, 7.448, 7.686, 7.703, and 7.706, in which 6.372 and 6.690 are assigned to protons of two amine groups which are considered to be the main characteristic groups that involved in hydrogen bond interaction. LTG-SAC cocrystals showed a major peak shift in these amine groups to 6.369 and 6.694 respectively. Whereas, LTG-4HBA cocrystals exhibited the chemical shift in these amine groups to 6.372 and 6.696 respectively. In case of LTG-MP cocrystals showed a major peak shift in these amine groups to 6.378 and 6.699 respectively. All the proton peaks assigned were clearly indicated in (Figure 7).

### 3.4. Differential scanning calorimetry (DSC)

DSC experiments were carried out to study the thermal behavior of the prepared co-crystal formulations in relation to individual components. DSC study of pure LTG drug shows sharp endothermic peak at 217.12 °C, while in case of pure Saccharin shows at 230.52°C, Hydroxy Benzoic acid shows at 214.98 °C and in case of Methyl paraben shows sharp endothermic peak at 134.47 °C. DSC study of prepared co-crystal formulations like LTG-Saccharin CF I shows sharp endothermic peak at 257.35 °C while in case of LTG-Benzoic acid CF I shows at 234.56°C and in case of LTG-Methyl paraben CF I shows sharp endothermic peak at 175.32°C, represented in (Figure 8). The thermal profile of co-crystal formulations was distinct, with a different melting transition seen with either of individual components. This indicated the formation of novel crystal phase in a molar ratio 1:1. The single endothermic transition indicates the absence of any unbound or absorbed solvent or water and also demonstrates the stability of the phase until the melting point.

### 3.5. Electron microscopy

Electron microscopy pictures are clearly indicating that small rod like co-crystals are high in solvent evaporation method crystals and degree of crystalline more when compared to the other method like solvent drop method and co grinding method. In case of solvent drop method reduction in size and LTG-SAC II co-crystal had shown uniform block like while in LTG-MP II had shown flake like crystals. In case of co-grinding method reduction in size and degree of crystalline less, LTG-HBA had shown small rod like co-crystals, LTG-MP III flake like crystals are observed and LTG-SAC II co-crystal had shown uniform block like crystals, represented in (Figure 9).

### 3.6. Percentage yield

For prepared cocrystals formulations like LT-HBA CF III (94.43%) and LTG-SAC CF III (93.28%) both are showing high percentage yield compared to other cocrystals formulations, represented in (Figure 10).

### 3.7. Drug content:
The prepared multicomponent co-crystal formulations are evaluated for drug content. In case of LT-SAC CF I (98.72) and LTG-HBA CF I (98.32) both are showing high drug content compared to other cocrystals formulations, represented in (Figure 10)

### 3.8. Measurement of flow ability
Lamotrigine and prepared co-crystals formulations were assessed by fixed funnel method for determination of angle repose. The solvent evaporation method crystals (LTG-SAC CF I, LT-HBA CF I and LT-MP CF I) are showing excellent flow properties while compared to solvent drop method crystals (LTG-SAC CF II, LT-HBA CF II and LT-MP CF II) and co grinding method crystals (LTG-SAC CF III, LT-HBA CF III and LT-MP CF III), results represented in (Table 1). While in case of solvent drop method the prepared crystals are showing good flow properties and in case of co-grinding method passable flow properties.

### 3.9. Intrinsic solubility
The prepared multicomponent co-crystal formulations and pure Lamotrigine were evaluated for intrinsic solubility analysis in case of pure Lamotrigine showed 0.154 (mg/ml), LT-SAC CF I showed high solubility values7.642, while in case of LTG-HBA CF I showed 1.129, in case of LT-MP CF III showed 0.512. In case of LT-SAC CF I showed 49.6 folds solubility increases LTG-HBA I showed 7.4 folds solubility increases and LT-MP III showed 3.36 folds solubility increases compared to pure Lamotrigine, results represented in (Table 2 and Figure 11)

### 3.10. pH of solution at equilibrium
The pH of pure Lamotrigine solution at equilibrium showed at 6.7, while in case of LTG-SAC CF I solution showed at 6.4, LT-HBA CF I solution showed at 4.4 and LT-MP CF I solution showed at 6.4. By comparing saturation solubility analysis and pH, LTG-SAC CF I co-crystal by using the solvent evaporation method is giving optimum results while compared to other methods like solvent drop method and co-grinding method results represented in (Table 2 and Figure 11).

### 3.11. In vitro dissolution Studies in pH 1.2 (0.1 N HCl)
LTG pure form releases 91.34% at the end of 60th minute. While in case of prepared co-crystal formulations like LTG-SAC CF I, II and III showed drug release at the end of 60th minute are 99.89%, 98.68% and 97.54%. In case of LTG-HBA CF I, II, and III showed drug release at the end of 60th minute are 98.89%, 98.69% and 97.18%. While in case of LTG-MP CF I, II, III showed drug release at the end of 60th minute are 98.28%, 96.98% and 95.78%. The drug release profile high in LTG-SAC CF I (99.89%) at the end of 60th minute, represented in (Figure 12).

### 3.12. Release kinetics
The release kinetics were done for prepared co-crystal formulations, in case of zero order the regression value high for LTG-SAC CF I (0.989) compared to other cocrystal formulations. While in case of peppa's release kinetics LTG-SAC CF I showed high regression value (0.998) and release exponent showed 0.691 represented in (Table 3), so LTG-SAC CF I formulation was selected as optimized and optimized formulation following non Fickian release mechanism.

## 4. CONCLUSION
The novel cocrystals of Lamotrigine showed a new characteristic of powder X-ray diffraction, thermogram of differential scanning Calorimetry, proton-NMR spectra, and electron microscopy. These results signify the establishment of intermolecular interaction within the cocrystals. In both the novel cocrystals, Lamotrigine was determined to be engaged in the hydrogen bond interaction with the complementary functional groups of Saccharin sodium, 4-Hydroxy benzoic acid and Methyl paraben. Compared with the pure Lamotrigine flow properties for prepared co-crystal by using solvent evaporation method crystals are showing excellent flow properties. LT-SAC CF I, LTG-HBA I and LT-MP III showed 49.6 folds, 7.4 folds, and 3.36 folds improved solubility respectively. The dissolution test showed that the LT-SAC CF I, LTG-HBA I and LT-MP III cocrystals exhibited 1.09-fold, 1.08-fold and 1.07-fold higher dissolution rate than the pure Lamotrigine in pH 1.2 acidic buffer respectively. Modification in the chemical environment, Intermolecular interactions established within the cocrystals, improved flow properties, Enhanced intrinsic solubility and invitro dissolution rate than pure drug.

Despite the fact that much study has been done on cocrystals, the majority of the literature has focused on innovative cocrystal synthesis and its alteration in physicochemical parameters; there is a lack of information on co-former selection and their impact on the biological system. As a result, the current study found that GRAS amino acids, which pose little risk to the biological system, are a good choice as a co-former in cocrystal production. These amino acids are good hydrogen bond acceptors and donors due to their zwitter ionic potentialities. Sodium Saccharin, 4-Hydroxybenzoic acid, and Methyl paraben were used as co-formers in this work to demonstrate the formation of Lamotrigine cocrystals. The spectral data of the parent molecule is compared to the Cocrystal structure modification, suggesting the intermolecular interaction established within the cocrystals. The effect of co-crystallization in improving physicochemical characteristics was proven in solubility tests. In addition, the results of the solubility analysis match those of the in vitro dissolution research. However, in the present investigation, the Pharmacokinetic parameters of the cocrystals like Cmax and AUC

have not been covered and will be taken up in our next publication. The results clearly show that co-crystallization modifies the chemical structure, improves solubility, and improves dissolution of LTG.


## ACKNOWLEDGMENTS:

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## CONFLICTS OF INTEREST:

No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

## APPENDIX

## ABBREVIATIONS

LTG: Lamotrigine; SAC: Saccharin Sodium; 4-HBA: 4-Hydroxy Benzoic acid; MP- Methyl Paraben; CF-Cocrystal Formulation; LTG-SAC CFI- Lamotrigine-Saccharin crystal formulation I; LTG-HBA CFI-Lamotrigine-Hydroxy Benzoic acid crystal formulation I; LTG-MP CF I- Lamotrigine-Methyl Paraben crystal formulation I; FT-IR: Fourier transform infrared spectroscopy; DSC: Differential Scanning Calorimetry; PXRD: Powder X-ray diffraction; 1H NMR: 1H-Nuclear Magnetic Resonance; EM: Electron Microscopy; GRAS-Generally Regarded as Safe; CDR: Cumulative Drug Release

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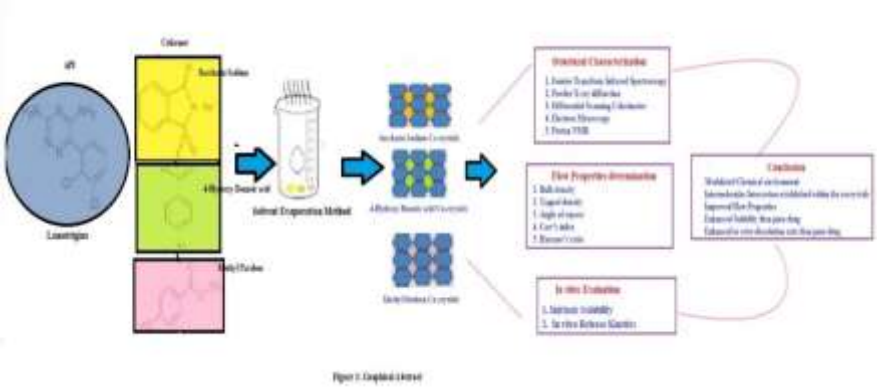


**Figure 1**- Graphical Abstract

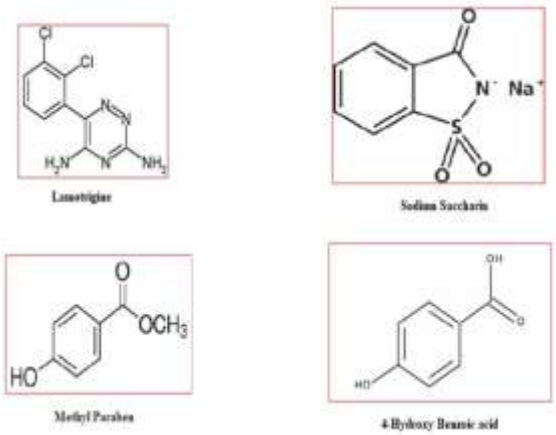



**Figure 2-** Molecular structures of pure Lamotrigine (LTG), Sodium Saccharin (SAC), 4-Hydroxy Benzoic acid (4HBA) and Methyl Paraben (MP)

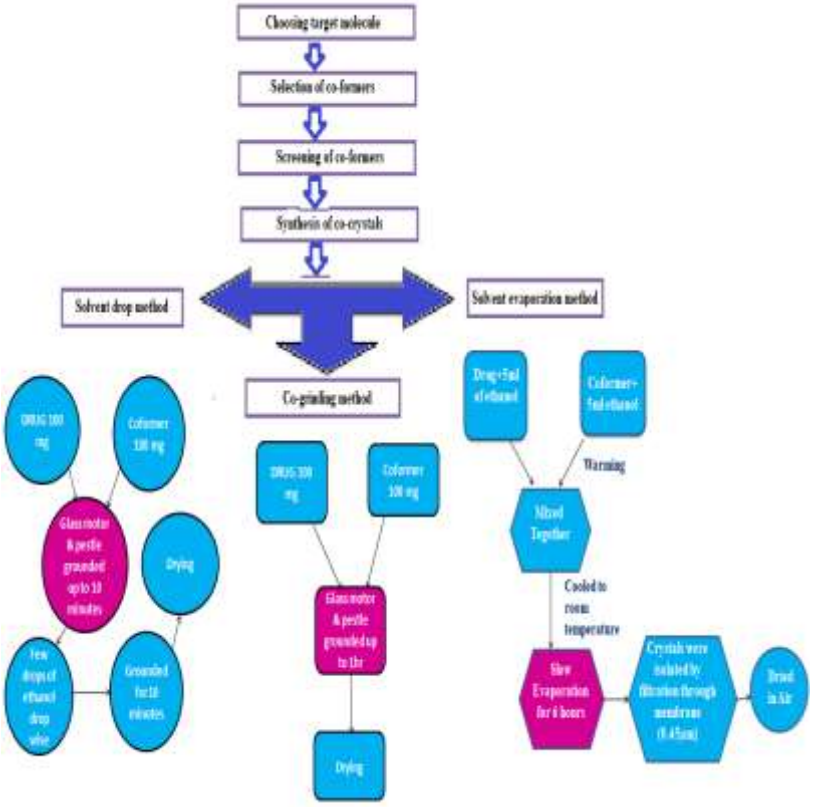



**Figure 3-** Flow process for synthesis of co-crystals

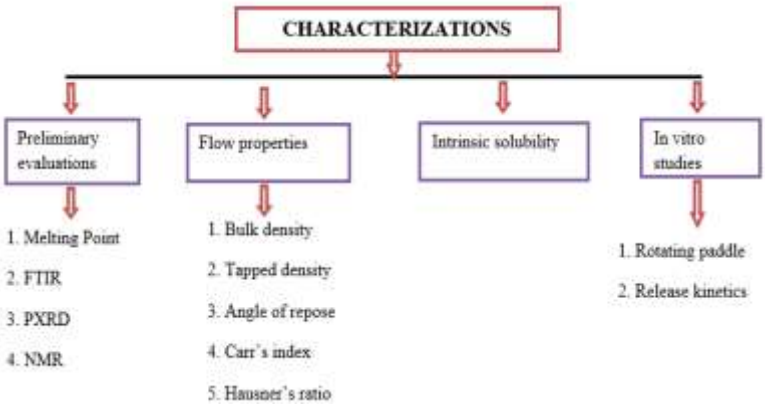



**Figure 4-** Flow process of characterizations of co-crystals

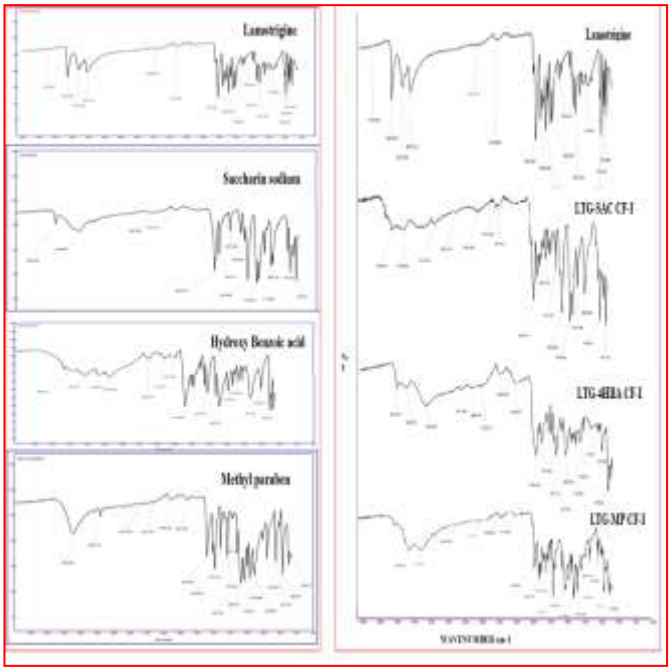



**Figure 5-** FTIR of pure Lamotrigine, Saccharin Sodium, Hydroxy Benzoic Acid, Methyl Paraben and synthesized co crystals like LTG-SAC CFI, LTG-HBA CFI, and LTG-MP CF I

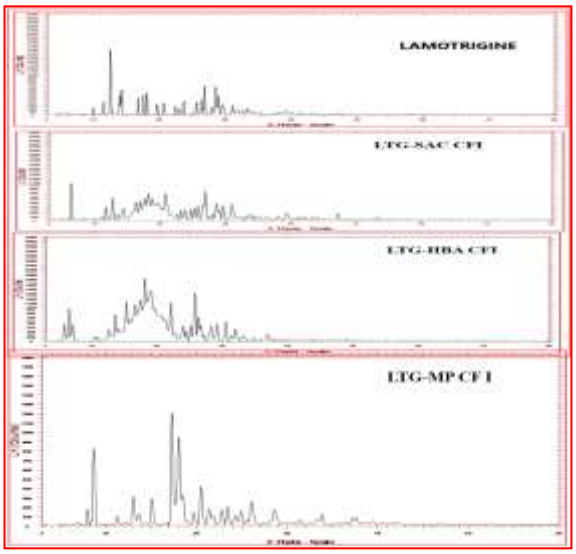



**Figure 6-** PXRD analysis of pure Lamotrigine and synthesized co crystals like LTG-SAC CFI, LTG-HBA CFI, and LTG-MP CF I

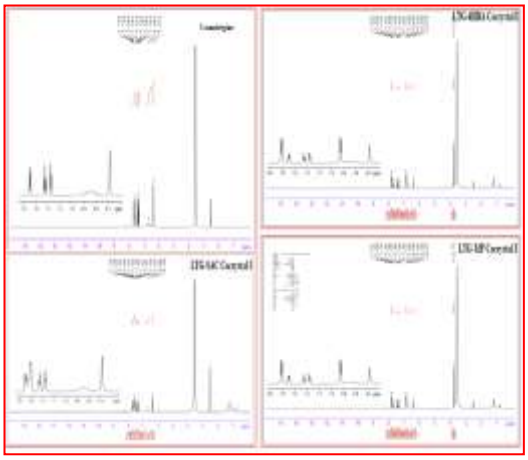


**Figure 7-** NMR spectra of pure Lamotrigine and synthesized co crystals like LTG-SAC CFI, LTG-HBA CFI, and LTG-MP CF I

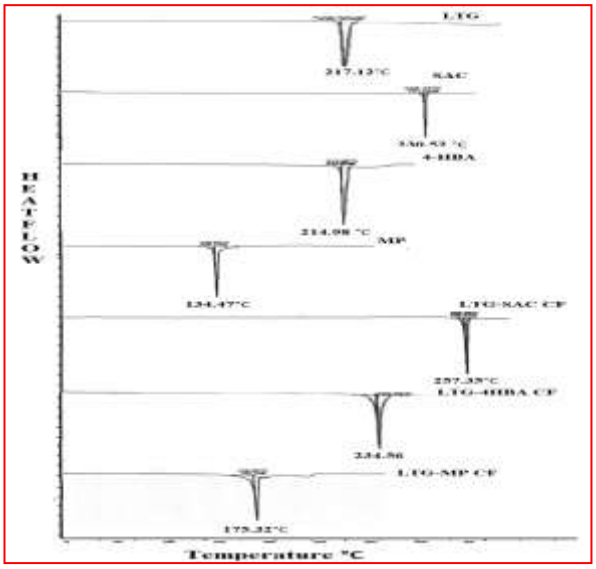
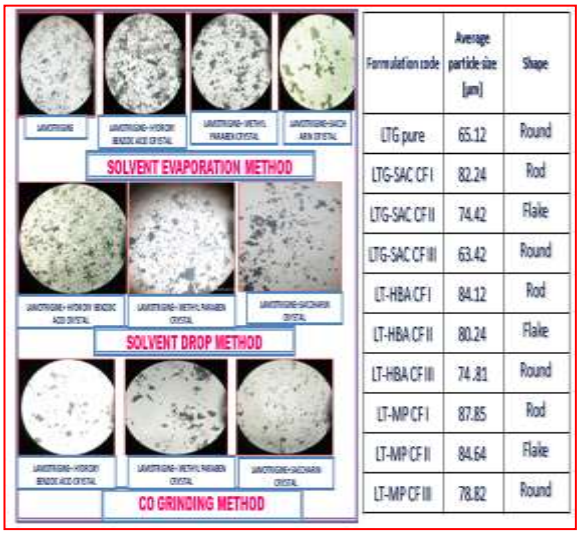



**Figure 8-** DSC melting endotherm peak values of pure forms of drug and synthesized co crystals




| Formulation code | Average particle size [µm] | Shape |
|---|---|---|
| LTG pure | 65.12 | Round |
| LTG-SAC CF I | 82.24 | Rod |
| LTG-SAC CF II | 74.42 | Flake |
| LTG-SAC CF III | 63.42 | Round |
| LT-HBA CF I | 84.12 | Rod |
| LT-HBA CF II | 80.24 | Flake |
| LT-HBA CF III | 74.81 | Round |
| LT-MP CF I | 87.85 | Rod |
| LT-MP CF II | 84.64 | Flake |
| LT-MP CF III | 78.82 | Round |

**Figure 9-** Electron microscopy pictures (10X) of prepared co-crystal formulations by solvent evaporation, Solvent drop, and Cogrinding methods

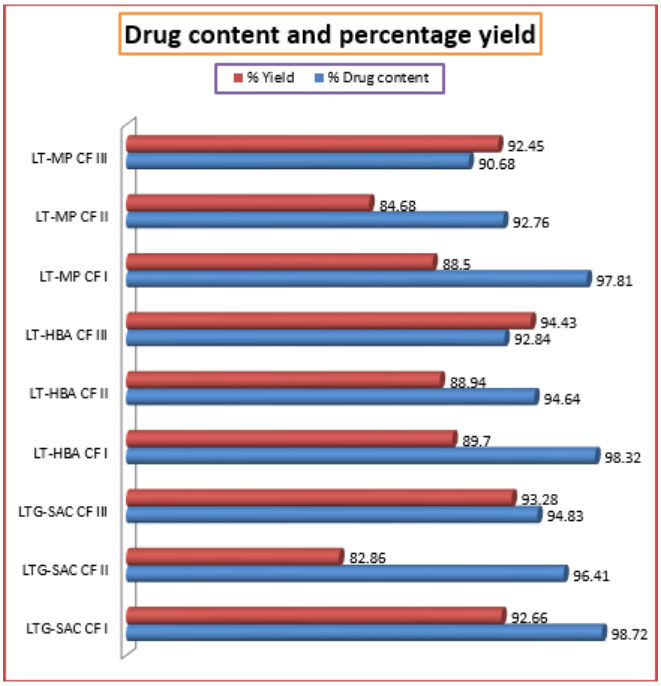



**Figure 10-** Drug content and Percentage yield of prepared co-crystal formulations

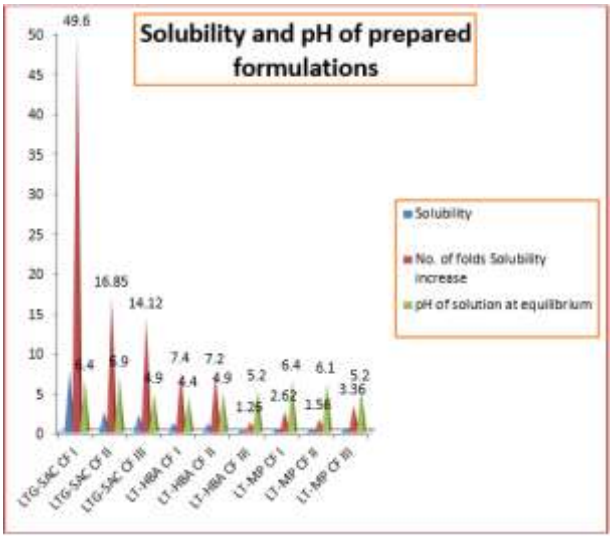



**Figure 11-** Solubility and pH of prepared co-crystal formulations

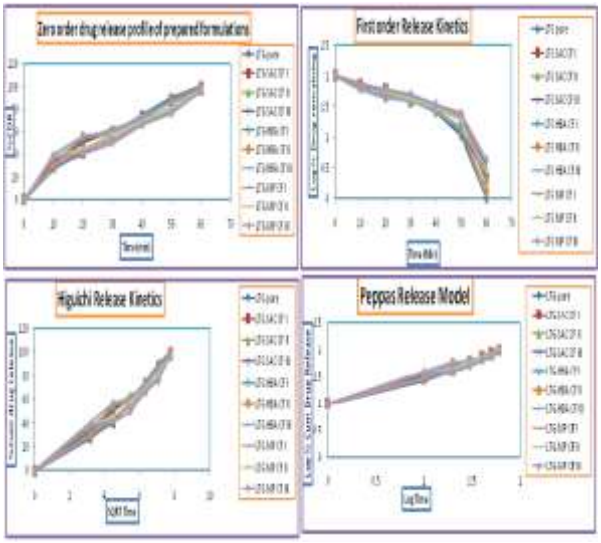



**Figure 12-** Release kinetics of Lamotrigine prepared co-crystal formulations

**Table 1-** Flow properties of pure drug and prepared co-crystal formulations

| Formulation code | Bulk density | Tapped density | Compressibility index | Hausner's ratio | Angle of repose | Flow properties |
|---|---|---|---|---|---|---|
| LTG pure | 0.51 ± 0.045 | 0.59 ± 0.04 | 13.56 ± 0.8 | 1.15 ± 0.09 | 34.69 ± 0.19 | Passable |
| LTG-SAC CF I | 0.45 ± 0.055 | 0.50 ± 0.07 | 10.00 ± 0.6 | 1.11 ± 0.04 | 24.58 ± 0.15 | Excellent |
| LTG-SAC CF II | 0.48 ± 0.065 | 0.54 ± 0.08 | 11.11± 0.7 | 1.12 ± 0.07 | 26.52 ± 0.17 | Good |
| LTG-SAC CF III | 0.44± 0.055 | 0.53± 0.05 | 16.98± 0.5 | 1.20 ± 0.05 | 30.43 ± 0.19 | Passable |
| LT-HBA CF I | 0.44 ± 0.044 | 0.50 ± 0.09 | 12.58 ± 0.8 | 1.13 ± 0.08 | 23.44 ± 0.11 | Excellent |
| LT-HBA CF II | 0.43 ± 0.054 | 0.51± 0.07 | 15.68 ± 0.6 | 1.18 ± 0.06 | 25.54 ± 0.14 | Good |
| LT-HBA CF III | 0.42 ± 0.064 | 0.50 ± 0.08 | 16.0 ± 0.7 | 1.19 ± 0.07 | 31.85 ± 0.16 | Passable |
| LT-MP CF I | 0.43 ± 0.041 | 0.51 ± 0.11 | 15.48 ± 0.54 | 1.18 ± 0.12 | 25.52 ± 0.15 | Excellent |
| LT-MP CF II | 0.44 ± 0.061 | 0.51± 0.14 | 14.0± 0.58 | 1.15± 0.14 | 26.12 ± 0.17 | Good |
| LT-MP CF III | 0.41± 0.051 | 0.50 ± 0.12 | 17.64± 0.56 | 1.21 ± 0.13 | 31.24 ± 0.19 | Passable |

(N=3 ± S.D); LTG-Lamotrigine; LTG-SAC CF-Lamotrigine-Saccharin Sodium Crystal Formulation; LT-HBA CF-Lamotrigine- 4 Hydroxy Benzoic acid Crystal Formulation; LT-MP CF- Lamotrigine- Methyl Paraben Crystal Formulation

**Table 2-** Solubility and potential conversion of multicomponent forms in solubility studies performed in water at 25 °C

| Drug substance | Solubility analysis | | pH of solution at equilibrium | Conversion during experiment (Assessed by PXRD and DSC) |
|---|---|---|---|---|
| | mg/ml | No. of folds increase | | |
| Lamotrigine (LTG) | 0.154 ± 0.19 | - | 6.7 | Yes (LTG hydrate) |
| LTG-SAC CF I | 7.642 ± 0.15 | 49.6 | 6.4 | Yes (LTG hydrate) |
| LTG-SAC CF II | 2.541± 0.14 | 16.85 | 6.9 | Yes (LTG hydrate) |
| LTG-SAC CF III | 2.16 ± 0.19 | 14.12 | 4.9 | Yes (LTG hydrate) |
| LT-HBA CF I | 1.129 ± 0.11 | 7.4 | 4.4 | Yes (LTG hydrate) |
| LT-HBA CF II | 1.103 ± 0.14 | 7.2 | 4.9 | No |
| LT-HBA CF I III | 0.182 ± 0.16 | 1.26 | 5.0 | No |
| LT-MP CF I | 0.395 ± 0.15 | 2.62 | 6.4 | No |
| LT-MP CF II | 0.233 ± 0.17 | 1.56 | 6.1 | No |
| LT-MP CF III | 0.512 ± 0.19 | 3.36 | 5.0 | No |

(N=3 ± S.D); LTG-Lamotrigine; LTG-SAC CF-Lamotrigine-Saccharin Sodium Crystal Formulation; LT-HBA CF-Lamotrigine- 4 Hydroxy Benzoic acid Crystal Formulation; LT-MP CF- Lamotrigine- Methyl Paraben Crystal Formulation

**Table 3-** Release kinetics of prepared co-crystal formulations

| F. CODE | ZERO ORDER %CDR Vs TIME | | FIRST ORDER Log% Remaining Vs TIME | | HIGUCHI'S %CDR Vs √T | | PEPPA'S Log% CDR Vs Log T | | Release mechanism |
|---|---|---|---|---|---|---|---|---|---|
| | K0 | $r^2$ | K1 | $r^2$ | KH | $r^2$ | n | $r^2$ | |
| LTG PURE | 1.726 | 0.984 | 0.104 | 0.6151 | 10.56 | 0.764 | 0.73 | 0.996 | Non-Fickian |
| LTG-SAC CF I | 1.674 | 0.989 | 0.056 | 0.8379 | 10.25 | 0.764 | 0.691 | 0.998 | Non-Fickian |
| LTG-SAC CF II | 1.620 | 0.951 | 0.051 | 0.7924 | 9.968 | 0.746 | 0.5417 | 0.986 | Non-Fickian |
| LTG-SAC CF III | 1.598 | 0.956 | 0.046 | 0.8214 | 9.795 | 0.744 | 0.572 | 0.985 | Non-Fickian |
| LTG-HBA CF I | 1.780 | 0.984 | 0.089 | 0.668 | 10.49 | 0.772 | 0.729 | 0.989 | Non-Fickian |
| LTG-HBA CF II | 1.679 | 0.962 | 0.060 | 0.7956 | 10.50 | 0.780 | 0.627 | 0.972 | Non-Fickian |
| LTG-HBA CF III | 1.646 | 0.936 | 0.050 | 0.859 | 10.46 | 0.783 | 0.573 | 0.969 | Non-Fickian |
| LTG-MP CF I | 1.596 | 0.977 | 0.054 | 0.734 | 9.939 | 0.785 | 0.629 | 0.978 | Non-Fickian |
| LTG-MP CF II | 1.599 | 0.958 | 0.048 | 0.813 | 9.971 | 0.771 | 0.518 | 0.947 | Non-Fickian |
| LTG-MP CF III | 1.532 | 0.959 | 0.043 | 0.7911 | 9.706 | 0.797 | 0.581 | 0.878 | Non-Fickian |

(N=3 ± S.D); LTG-Lamotrigine; LTG-SAC CF-Lamotrigine-Saccharin Sodium Crystal Formulation; LT-HBA CF-Lamotrigine- 4 Hydroxy Benzoic acid Crystal Formulation; LT-MP CF- Lamotrigine- Methyl Paraben Crystal Formulation