ORIGINAL ARTICLE

Accidental Formation of Eutectics during Crystal Engineering of Lamotrigine with Solubility Advantage and Drug Release Efficiency

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Abstract

Objective: Lamotrigine (LMG) is the Biopharmaceutical Classification System Class-II drug with hurdle in drug release and dissolution efficiency due to poor water solubility. The present investigation was aimed to improve the solubility and dissolution of LMG by crystal engineering by formation of cocrystals but which accidently turn toward eutectics formation. **Methods:** LMG was subjected to neat grinding with different Cocrystal Formers (CCF) to develop multicomponent crystalline system. The prepared multicomponent system was analyzed by Differential Scanning Calorimetry, Raman spectroscopy, and Powder X-ray Diffraction reveals the formation of multicomponent system. Improved dissolution was interpreted by comparative drug release study of tablet formulation of unprocessed drug and eutectics. **Results:** There was unplanned formation of eutectics of LMG-Ascorbic acid (LMG-AA) that was observed with improved drug solubility. LMG-AA eutectics showed enhanced solubility (651.61 ± 1.02 µg/ml) in comparison with pure drug (161.46 ± 0.86 µg/ml) and all remaining multicomponent systems formed with other CCF's. The LMG-AA eutectics showed comparatively better drug release than pure LMG tablet. LMG eutectics also showed significant improvement in flow properties and compressibility as compared to pure drug. **Conclusion:** Multicomponent LMG-AA eutectics although formed in unplanned way they effectively enhances the solubility of LMG serving the main purpose of the research work. It can be utilized efficiently for drug delivery due to its improved dissolution and better drug release.

Key words: Lamotrigine, Solubility, Dissolution, Crystal engineering, Eutectics, Cocrystal

INTRODUCTION

Lamotrigine (LMG) is broad spectrum drug used in the psychotherapeutics [Figure 1]. It is useful in the treatment of epilepsy, psychosis, and bipolar disorder. LMG is Biopharmaceutical Classification System (BCS) Class-II drug with very slight water solubility. The dose of LMG varies from 25 to 200 mg/day with existing solubility. LMG is broad spectrum antiepileptic drug from BCS Class-II. Low solubility of LMG restricts the flexibility in formulation development. The solubility enhancement of LMG reduces dose as there is improvement in drug release and can provide ease for formulation development.[1]

Cocrystallization is one of the important techniques in multicomponent crystal engineering. This approach is widely used for many drugs for improving solubility, dissolution, and drug release.[2] Cocrystals with pharmacological activity are considered as pharmaceutical cocrystals. Cocrystallization includes multicomponent crystalline modification.[3] In pharmaceutical cocrystals one of the components is Active Pharmaceutical Ingredient (API) and another is Cocrystal Formers (CCF). API and CCF are used in stoichiometric ratio to prepare pharmaceutical cocryastals.[4] CCF's are prepared by supramolecular synthon approach. These supramolecular

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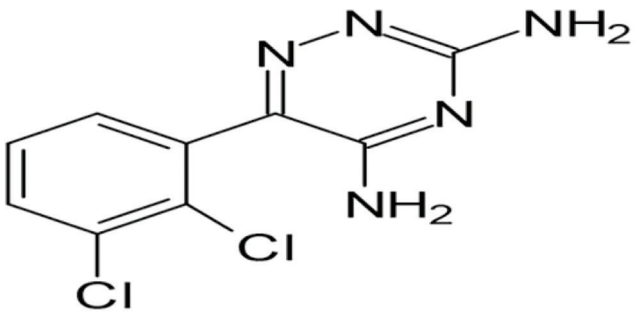

Figure 1: Structure of lamotrigine

synthons can be homosynthons or heterosynthons depending on hydrogen bonding between same or different functional groups of API and CCF.[5] The prominently used CCF's are solid carboxylic acids, amino acids, and their derivatives. Other than these the multiple compounds with potential of supramolecular synthon or hydrogen bonding potential can be used as CCF.[6] Formation of cocrystal is not necessary all the time for improvement of dissolution and flow properties, most the time crystal engineering also lead to formation of eutectics with enhanced solubility and flow properties.[7]

Crystal engineering involves multiple techniques such as neat grinding, solvent drop grinding, hot melt extrusion, cooling crystallization, antisolvent addition, and supercritical fluid technology which results formation of either cocrystals or eutectics. In all the techniques, the mechanism of solubility enhancement is hydrogen bonding between drug and CCFs. Cocrystallization is the crystal engineering technique so it has significant influence on flow properties. Cocrystallization additionally improves the micromeritic flow properties of the API too. Both cocrystals and eutectics often have better flow and compressibility than unprocessed API.[8]

Eutectics formed by neat grinding of API and CCF is also called as binary eutectics and generally have lower melting point than API which can be predicted by thermal analysis. Formation of eutectics takes place same as that of cocrystals by non-covalent interactions. Eutectics are also as stable as cocrystals and provide significant improvement in physicochemical properties. Recently, eutectics became an area of research interest due to its ease of scale up.[9]

MATERIALS AND METHODS

LMG was received as a gift sample from Wockhardt Ltd. Aurangabad. Ascorbic acid (AA) and all other coformers were procured from Research Fine Lab., Mumbai.

Preparation of multicomponent systems

Multicomponent systems of LMG were prepared by neat grinding technique using ten different CCF's. LMG and all ten CCF's were taken in 1:1 stoichiometric ratio and placed for neat grinding for 20 min at room temperature (28°C). After grinding for 20 min, the prepared cocrytals were subjected for different *in vitro* evaluations.[10]

Saturated solubility determination of LMG multicomponent systems

Saturated solubility method of Higuchi and Connors was used to determine the solubility of LMG multicomponent system. 10 ml water is taken in vials and multicomponent systems are added up to saturation kept on rotary shaker for 24 h. The concentration of LMG in resulting solution was analyzed by UV spectrometric analysis at 307 nm. The solubility of cocrystals was compared with unprocessed API.[11]

Differential scanning calorimetry (DSC) analysis of LMG eutectics

DSC analysis (Mettler Toledo) of LMG eutectics was performed to evaluate thermal behavior of the systems after crystallographic modification. The API/eutectics (2mg) were placed in hermetically sealed aluminum pans and then heated at a heating rate of 20°C/min from 50° to 300°C under constant purging dry nitrogen flow (20 ml/min), then thermograms of pure drug and LMG eutectics were comparatively analyzed.[12,13]

Eutectics evaluation by powder X-ray diffraction (PXRD)

Cocrystals with highest solubility were analyzed for PXRD. PXRD patterns of unprocessed drug, CCF, and eutectics were recorded at various 2θ values using Cu-kα radiation at scanning speed of 2°/min and a chart speed of 2°/2 cm/2θ.[14,15]

Raman spectroscopic analysis of eutectics

For distinguishing is the structural phase, Raman spectroscopic analysis was carried out. Raman spectroscopic technique is used to study vibrational, rotational, and other low frequency modes in a system. There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystal products. The analysis of drug, CCF, and LMG eutectics with the highest solubility was performed using Fourier Transform Raman spectrometer (Bruker RFS-27).[16]

Micromeritic properties of LMG and LMG eutectics

The prepared eutectics were evaluated for various powder characteristics such as bulk density and tapped density, Hausner's ratio, angle of repose, and compressibility index. Fixed funnel method was used to determine angle of repose.[17]

Formulation and evaluation of LMG and LMG eutectics tablets

The immediate release tablets of LMG and LMG-AA eutectics were prepared by direct compression technique [Table 1].

The prepared tablet formulations were evaluated for weight variation, friability, and hardness. Weight variation was evaluated with 20 tablets. The hardness was determined using hardness tester (Veego Ltd.), where the force required to break the tablet was determined in kg/cm^3. The friability of the tablets was determined using friabilator with 100 rotations for 4 min using ten tablets.[18] The percent friability of tablets was determined using following formula

% Friability = ([Initial wt of tablets- Final weight of tablets]/ Initial weight of tablets) × 100.

Comparative *in vitro* dissolution analysis of LMG and LMG eutectics tablets

The *in vitro* dissolution of LMG-AA eutectics tablets was compared to determine enhancement of drug release due to crystal engineering. USP apparatus type II (Veego Ltd.) was used for the analysis. The temperature was 37 ± 0.5°C and 900 ml distilled water was used as a dissolution medium. The study was performed with 50 rpm. 5 ml aliquot was withdrawn after each time interval of 10 min and fresh distilled water was added to maintain the sink condition up to 60 min. After filtration samples were absorbance was determined at λ max 307 nm using a UV 1800 spectrophotometer (Shimadzu). Drug release was calculated from the absorbance.[19]

Stability study of LMG eutectics tablets

Prepared tablets of LMG-AA eutectics were stored at 40 ± 2°C temperature and 75 ± 5% relative humidity in aluminum foil for 1 month. After 1 month, tablets were evaluated for assay (drug content), disintegration time, hardness, and friability.[20]

RESULTS AND DISCUSSION

Saturated solubility evaluation of LMG eutectics

Saturation solubility analysis of all ten multicomponent systems of LMG was carried out. The solubility of pure LMG in water was 161.46 ± 0.86 µg/ml at 25°C comparatively that there was almost four-fold increase in aqueous solubility of eutectics of LMG with AA (651.61 ± 1.02 µg/ml). The saturated solubility analysis of all ten multicomponent systems is shown in Table 2. In solubility analysis, it was found that the eutectics prepared with AA showed highest solubility as compared to multicomponent systems formed with other CCF's. This alteration in solubility is the desired effect obtained by crystal engineering and supramolecular hydrogen bonding between drug and CCF.[21]

DSC analysis of LMG eutectics

DSC thermograph analysis of pure drug, CCF, physical mixture (drug and CCF), and eutectics revealed the formation of new crystalline arrangement. The DSC thermogram LMG and AA showed the peak at 218.68°C and 193.12°C, respectively, while physical mixture and eutectics of LMG and AA showed peaks at 167.02°C and 149.65°C, respectively [Figure 2]. There is significant difference in DSC thermograms of LMG, AA, and LMG-AA after neat grinding which is the indication of formation of eutectics by non-covalent interactions between drug and CCF. Crystal engineering affect the physicochemical properties, so there is difference in melting points of pure drug and eutectics.

DSC thermogram confirms the accidental eutectics formation and not cocrystal as the melting point of eutectic is always less than pure drug and CCF while most of cocrystals have melting point in between drug and CCF.[22]

PXRD analysis

The comparative study of PXRD patterns of LMG, AA and LMG-AA eutectics showed that the LMG eutectics have non-significant difference in PXRD pattern with similar peaks of similar intensity and near about same 2θ values [Figure 3].

Table 1: Formulation of Lamotrigine and Lamotrigine-ascorbic acid eutectics tablet

Sr. no	Ingredients	Lamotrigine tablet (quantity in mg)	Lamotrigine-ascorbic acid eutectics tablet (Quantity in mg)
1	Lamotrigine/Lamotrigine eutectics (Equivalent to 100 mg Lamotrigine)	100	168.77
2	MCC-PH101	206	137.23
3	SSG	25	25
4	PVP-K-30	16	16
5	Magnesium stearate	3	3
	Total weight	350	350

In PXRD study, crystallinity of pure LMG is retained even after neat grinding with AA without significant difference in peaks and peak intensity. Similarity in the PXRD pattern of pure LMG and LMG-AA after neat grinding indicates there is no development cocrystal but still the changes in physicochemical properties is the result of formation of eutectics due to multicomponent crystal engineering.[23]

Table 2: Comparative solubility analysis of lamotrigine and lamotrigine eutectics

Drug/Cocrystal/Eutectics	Solubility (μg/ml)
Lamotrigine	161.46±0.86
Lamotrigine-Benzoic acid	302.25±0.75
Lamotrigine-Salicylic acid	288.30±1.21
Lamotrigine-Urea	199.45±1.10
Lamotrigine-Tartaric acid	194.00±0.90
Lamotrigine-Ascorbic acid	651.61±1.02
Lamotrigine-Cinnamic acid	189.68±1.13
Lamotrigine-Sodium acetate	197.80±1.34
Lamotrigine-Oxalic acid	224.44±1.50

Values are expressed as a mean±(*n*=3)

Raman spectroscopic analysis of eutectics

FT-Raman spectroscopy provides additional tool for prediction of cocrystal formation. Raman spectroscopic analysis of LMG analysis showed the prime peaks of C-C twisting at 143.613 cm^{-1}, NH_2 rocking at 371.32 and 473.16 cm^{-1}, C-C stretching at 1433.75 cm^{-1}, and C-H stretching at 3208.99 cm^{1} whereas in cocrystals NH_2 rocking slight shifted to 472.94 cm^{-1}, C-C stretching at 1434.22 cm^{-1}, and C-H stretching at 3081.25 cm^{-1}. FT-Raman spectra provide supportive characterization for formation of eutectics [Figure 4].

In FT-Raman spectroscopy all the significant peaks of LMG and AA observed even after neat grinding which indicates crystal engineering turn toward the formation of eutectics

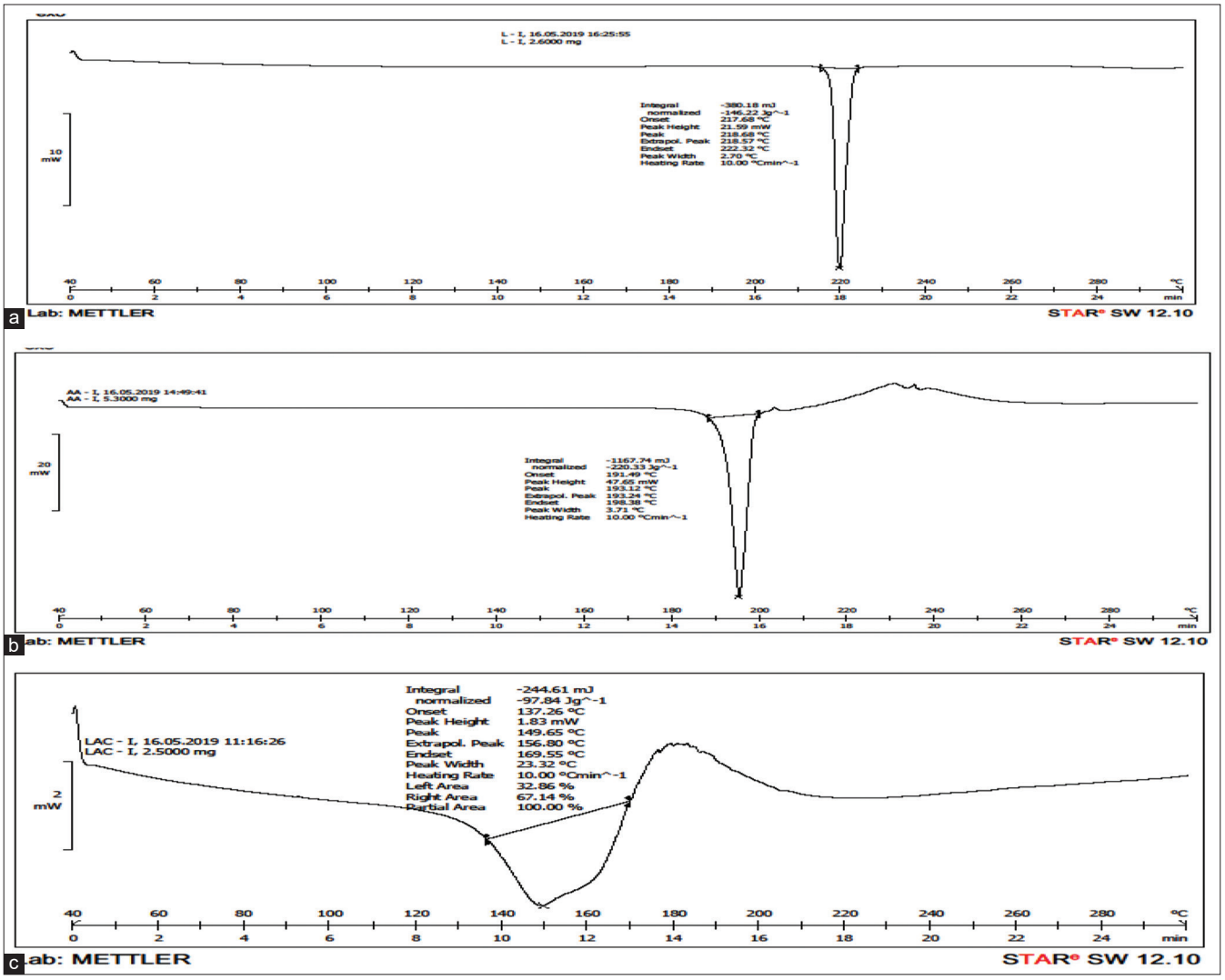

Figure 2: Differential scanning calorimetry thermograms of (a) lamotrigine (b) ascorbic acid (c) lamotrigine-ascorbic acid eutectics

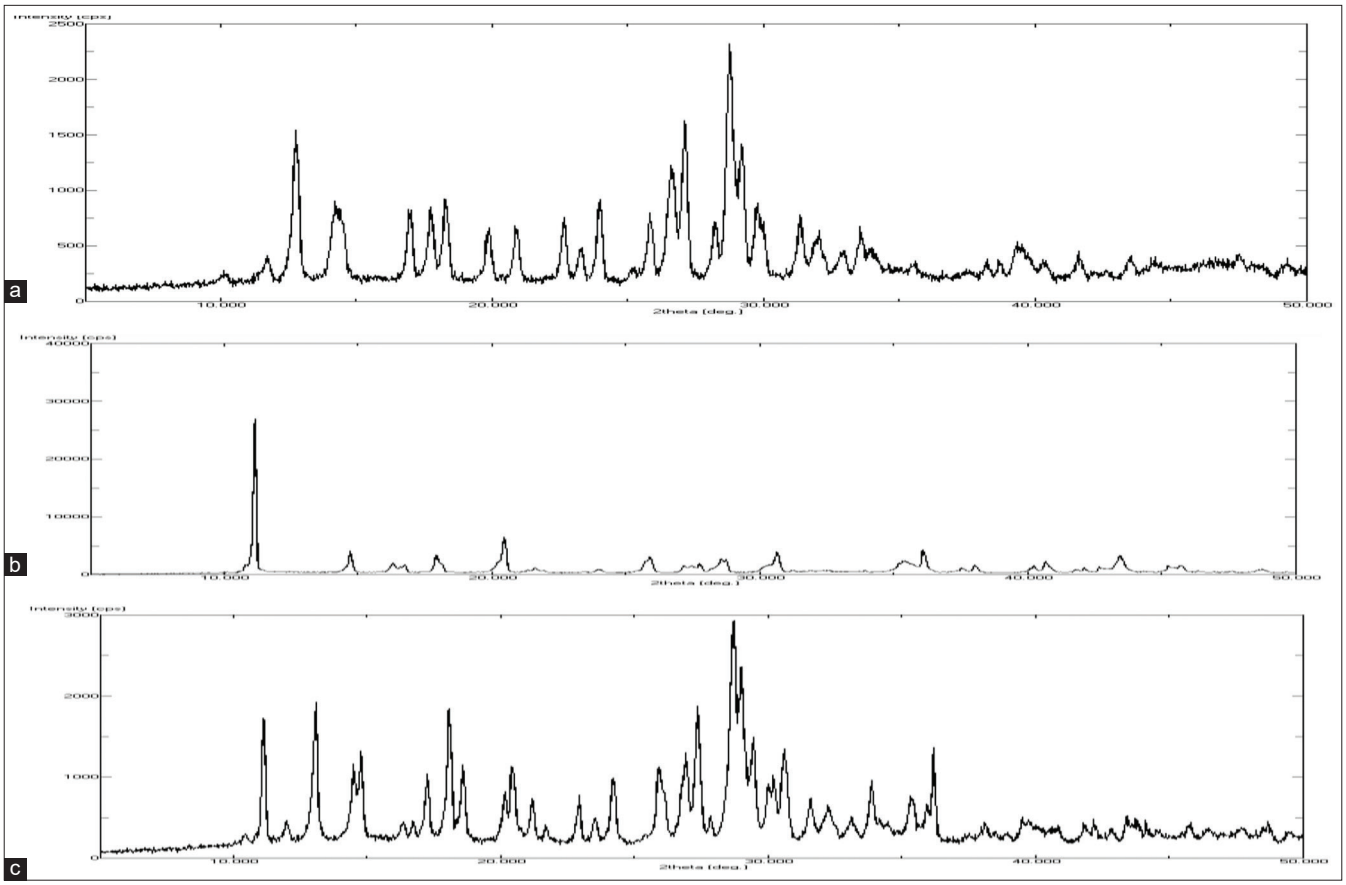

Figure 3: Powder X-ray diffraction patterns of (a) lamotrigine (b) ascorbic acid (c) lamotrigine-ascorbic acid eutectics

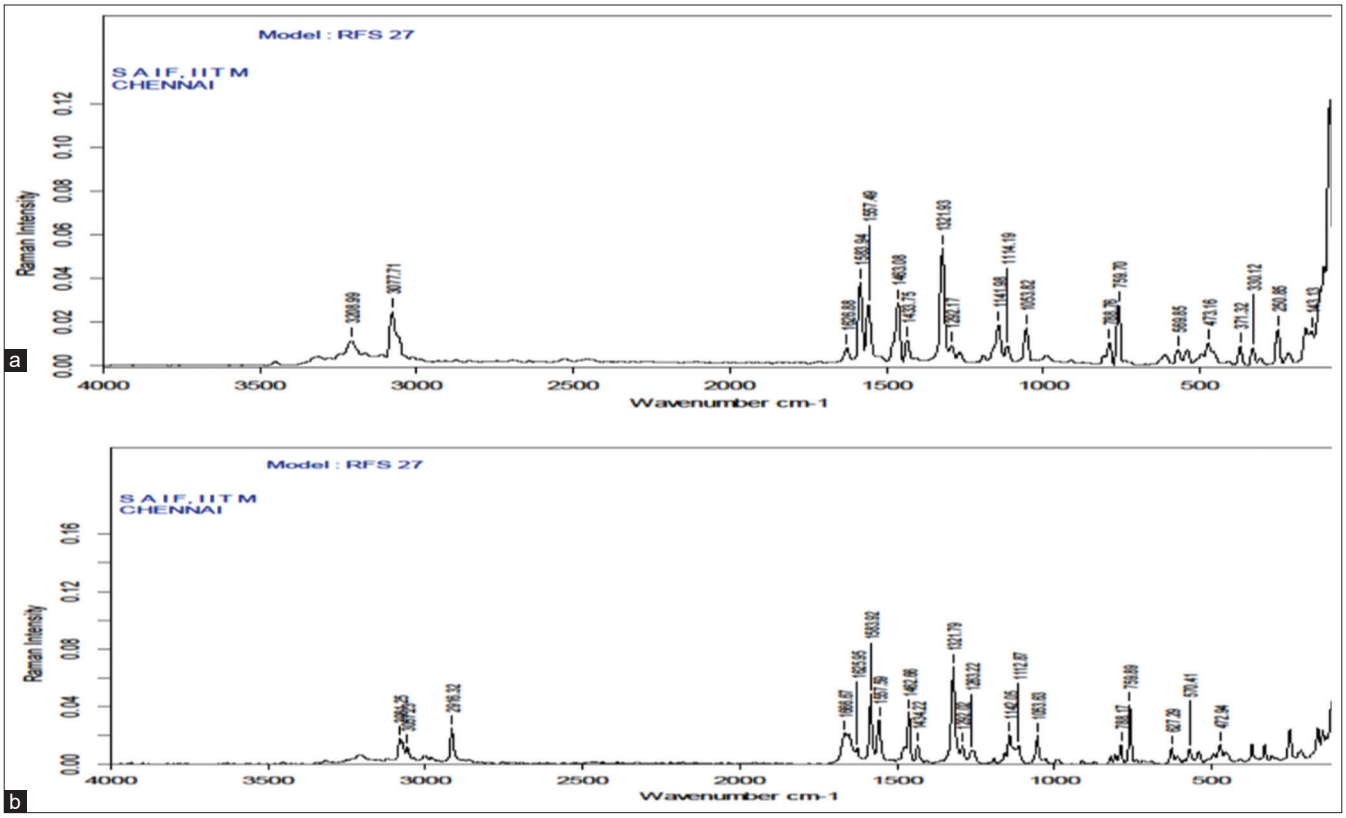

Figure 4: Raman spectra of (a) lamotrigine (b) lamotrigine-ascorbic acid eutectics mixture

Table 3: Comparative evaluation of micrometric properties of Lamotrigine and Lamotrigine-ascorbic acid eutectics

Properties	Angle of repose	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index	Hausner's ratio
Lamotrigine	45.56°	0.27	0.55	30.90	2.03
Lamotrigine-ascorbic acid eutectics	27.72°	0.46	0.77	19.29	1.23

Table 4: Evaluation parameters of Lamotrigine and Lamotrigine-ascorbic acid eutectics tablet

Batch	Thickness (mm)	Hardness (Kg)	*In vitro* DT (min)	%Friability
Lamotrigine tablet	5.01±0.05	1.8±0.5	11±1	0.68±0.30
Lamotrigine-ascorbic acid eutectics tablet	5.15±0.04	1.9±0.3	9±1	0.61±0.22

Values are expressed as a mean±(*n*=3)

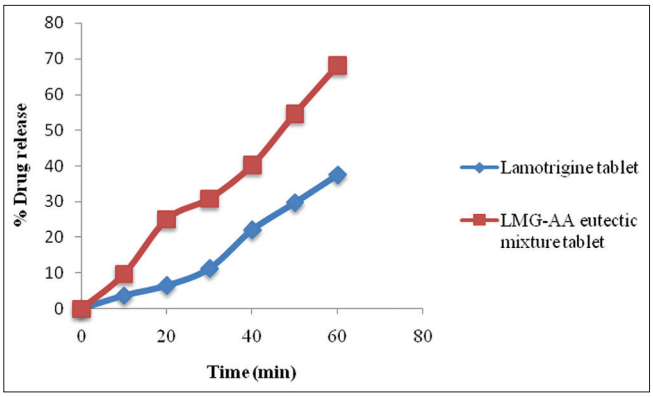

Figure 5: Comparative drug release of lamotrigine and lamotrigine-ascorbic acid eutectics tablets

rather than cocrystals. Cocrystal shows significant difference in Raman spectra which are not observed with eutectics.[24]

Micromeritic properties of LMG and LMG eutectics

Crystal engineering improves the flow and processing properties such as angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio as compared to pure drug. The pre-formulation characteristics of drug and eutectics are illustrated in Table 3. The physical interaction between drug and CCF during crystal engineering leads improvement in the flow properties of drug along with process ability for tableting. LMG-AA eutectics also showed improvement in powder flow characteristics as compare to pure LMG.[25,26]

Comparative evaluation of LMG and LMG eutectics tablets

LMG and LMG-AA eutectics tablets were evaluated for different parameters such as weight variation, hardness, disintegration time, and friability and all these parameters are summarized in Table 4. All the parameters were found within the limit.[27]

Comparative *in vitro* dissolution analysis of LMG and LMG eutectics tablets

In vitro dissolution analysis of immediate release tablets of LMG and LMG-AA eutectics was studied in distilled water. Pure LMG tablet releases 37.50 ± 0.81% drug while LMG-AA eutectics tablet releases 68.20 ± 0.98% drug at 60th min. This *in vitro* dissolution study indicates the significant contribution of multicomponent crystal engineering in solubility enhancement and drug release of LMG [Figure 5].[28]

Comparative *in vitro* dissolution study of tablet formulation of LMG and LMG-AA eutectics reveal the advantage of eutectics formation in solubility, drug release, and dissolution. LMG-AA eutectic tablet showed near about double drug release as compare to pure LMG tablet. This is the major advantage of eutectic formation by crystal engineering for poorly water soluble drugs like LMG. This increase in drug release ultimately improves the bioavailability and provides the scope to reduce the dose and decrease the load of metabolism and excretion.[29]

Stability study of LMG eutectics tablets

Stability study LMG eutectics tablets showed that there are no significant changes occur in evaluation parameters during the study period. The drug content was found to be 98.26 ± 0.51%. This indicates that tablets are stable at 40 ± 2°C temperature and 75 ± 5% relative humidity.[30]

CONCLUSION

The solubility limitation of LMG can be overcome by crystal engineering. The formation of eutectics with AA enhances solubility and ultimately improves drug release from dosage form. The crystal engineering also provides an ease for solid unit dosage forms with better flow and compressibility.

Development of dosage forms with the use of these eutectics is the efficient drug delivery approach for poorly water soluble drugs like LMG.

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