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Pharmaceutical Co-crystal in Improving Physicochemical properties of Lamotrigine

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ABSTRACT: The demand for fast dissolving tablet has been growing during the last decade especially for patients who require faster action. Lamotrigine is a triazene derivative having antiepileptic action pump sodium channel blocking. It has oral bioavailability of around 98% and half-life 21 to 25 hrs**.** One of the major hurdles for the Lamotrigine delivery is its low solubility which leads to limited bioavailability in the initial period. In the present study, an attempt has been made to improve its solubility by liquid assisted grinding using coformers. The molecular docking study and saturation solubility study was applied to find out the suitability of tested coformers. Both studies indicate suitability of ascorbic acid as a coformer to formulate a cocrystal. The highest affinity to Lamotrigine was shown by Ascorbic acid (interaction energy = -9.055 kcal/mol). The cocrystal was further incorporated into a tablet with superdisintegrants to have a fast-dissolving formulation which gave an instant action as highly required in epilepsy. The fast-dissolving tablets of Lamotrigine were prepared using Sodium starch glycolate, Crosspovidone as superdisintegrants by direct compression method. The prepared tablets were evaluated for various parameters like hardness, friability, disintegration time, drug-polymer interaction by FTIR studies, drug content and in-vitro drug release. The tablets prepared by direct compression method, demonstrated a hardness of 3.0 to 4.0 Kg/cm, percentage friability of 0.41 to 0.61 %, drug content uniformity was in 93.67 to 99.37%, and in vitro drug release showed 86.16%-98.40% within 10 min. The FTIR studies results reveal that there is no interaction between drug and any other formulation excipients. Stability study data revealed the robustness of the formulation as there was no any remarkable change in dissolution and physical characteristics. The results conclud the usefulness of fast dissolving tablets of Lamotrigine entrapped Ascorbic acid cocrystal with superdisintegrants Sodium starch glycolate and Crosspovidone. The formulation exhibit faster release, enhanced dissolution which not only with improved bioavailability but also fulfils the demand of immediate released dosage form in treatment of epilepsy achieving a goal of therapy.

Keywords: Co-crystal, Epilepsy, Fast dissolving tablet, Coformers, Molecular Docking study, Saturation solubility study, In-vitro inclined dissolution study.

I. INTRODUCTION:

Drug absorption from the GI tract can be hindered by a number of factors, the most prominent of which are the poor aqueous solubility and membrane permeability of drug. When an active substance is given orally, it must first dissolve into the gastric and/or intestinal fluids before it can permeate through the GIT and enter systemic circulation. As a result, there is a continuous demand in the field of improving the oral bioavailability and solubility of poorly water-soluble drugs [1].

The Biopharmaceutics classification system (BCS) is a scientific classification of a drug compound based on its solubility in water and intestinal permeability, which correlates in vitro dissolution and in vivo bioavailability of drug. Lamotrigine (LTZ) is BCS class II drug with low solubility and High permeability [2].

More than 40% of NCEs discovered in the pharma industry are practically water insoluble. Because these drugs are poorly water soluble and have slow absorption, they have inadequate and variable bioavailability as well as gastrointestinal mucosal toxicity. Techniques for improving solubility can be classified as physical, chemical, or other techniques such as Particle size reduction, nanonization, co-solvency, hydrotropy, pH adjustment, Solid dispersion, spray drying, inclusion complexation , cocrystalization has advantages over other solubility techniques such as it can modify solubility, permeability, melting

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point, dissolution , bioavailability, hygroscopisity, tablettability, physicochemical properties (physical and chemical stability etc.) of a chemical entity. The final characteristics of cocrystal such as purity, particle size and size distribution, and morphology are influenced by the cocrystallization method, and therefore its selection is of atmost importance. Several aspects must be taken into account when choosing the cocrystallization method. For example, API and coformer liability, solubility, stability, susceptibility to form polymorphs, solvates, or amorphous are some of the aspects to consider. Method scalability is also to be considered for industrial applications [3-7]

Cocrystallization of APIs can be achieved using different methods like solvent evaporation (solution cocrystallization), grinding method, anti-solvent addition, ultrasound assisted cocrystallization, slurry conversion method, liquid assisted grinding. supercritical fluid technology, coformer selection for an API is the most important aspect for designing and screening of cocrystals. The non-API component used as coformer should be non-toxic with no adverse side effects. Ideally, the cocrystal former should be included in the list approved by US FDA [8-10]

Hit and trial approach is mainly used with all types of coformers for an API and to confirm the structure of co-crystal. The major parameters to choose suitable co-formers are:-Supramolecular synthon approach, pKa Rule, Hansen solubility parameter, Cambridge structural database[11]

pKa Rule:

When the difference between pKa value of API and coformer (ΔpKa) ranges in negative values, there will be no proton transfer. Therefore, one can possibly expect cocrystal formation in such a case.The formation of salts or cocrystals can be predicted by determining the ΔpKa=[pKa (base)–pKa (acid)].A smaller ΔpKa value (less than 0) indicates the formation of cocrystals whereas higher value (more than 2 or 3) indicates the formation of salts

Hansen Solubility Parameter: Hansen solubility parameter approach measures the miscibility of drug and co-formers that are used for cocrystal production. The miscibility factor of the components in the solid state could give an idea about the cocrystal formation. The co-crystals synthesis success rate is improved by using the components which have similar miscibility. It is demonstrated that the two components should be miscible if total HSPs difference is <7MPa 0.5, otherwise immiscible. The another method estimates the miscibility of two components if the difference is <5MPa0.5 between two substances which are supposed to be co-crystal formation

Cambridge Structural Database (CSD):

The CSD is a reservoir for small molecule crystal structures. Researchers utilize single-crystal X-ray crystallography to decide the crystal structure of a compound. When the structure is comprehended yet in CSD researchers can look and recover from the database.

The researchers can utilize the CSD to contrast existing information and that got from crystal developed in their lab. The data can be likewise used to picture the structure in an assortment of programming, for example atom, powder cell and so on, this is especially significant for analytical reasons since it encourages the identification of stages present in a crystalline powder blend without the requirement for developing crystals.

The data gathered in the CSD for every passage can be considered in three classes. Firstly, there is a text based data containing the literature reference, chemical names and blueprints, some trial data about the crystal structure confirmation method and whatever other data that might be accessible for example molecule's uses, colour and shape of crystals and so on. Secondly, there is chemical structure data as a 2D structural illustration which is the premise of a great part of the advanced exploring procedure for the CSD framework. Thirdly, there is a crystallographic data, comprising of unit cell measurements and space group, and atomic coordinates. Finally, in this third class the genuine estimation of database lies [11,12]

The Pharmaceutical cocrystals are described as crystals which contain two or more distinct neutral molecules at a stoichiometric ratio and bond together through non-covalent bond interactions (eg. Hydrogen bonding, Van der Waals and pi-pi stacking interactions), where in as a minimum one of the additives is API and the others are pharmaceutically desirable ingredients. A pharmaceutical cocrystal constitutes API and benign substance called a coformer [13-15]

Lamotrigine is an antiepileptic drug is a member of the sodium channel blocking class it is a triazene derivative that inhibit voltage sensitive sodium channels leading to stabilization of neuronal membrane. It inhibit the glutamate release [16].

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II. MATERIAL AND METHODS:

Lamotrigine was gift sample from the MBH Raw Pharma, Mumbai (India). All other chemicals used are analytical grade.

2.1 Preparation of cocrystal: Drug and binary mixture of co-former in stoichiometric ratio (1:1) in mortar and pestle, these two components were mixed and ground for 45 min Grind this mixture for about 30-60 min using mortar and pestle with addition of ethanol drop by drop co-crystal was formed by liquid assisted grinding method. It was dried at ambient temperature and followed with storage of co-crystals in closed container to protect from light. The number of coformers screened were Ascorbic acid, Benzoic acid, Acetamide, Nicotinamide, Ascorbic acid, Salicylic acid, Urea, 4-Amino benzoic acid [17-19]

2.2 Determination of melting point: Melting point of the compounds were determined by using digital melting point apparatus.

2.3 Saturation solubility: The solubility was determined by dissolving excess quantity of pure drug and cocrystal in the 10 ml vials containing water, buffer pH 6.8, 0.1N Hcl. The vials were subjected to agitation on rotary shaker and allowed to stand for equilibrations for 24 hrs. diluted with water, pH6.8, and 0.1 N Hcl and analysed by UV spectrophotometer at 307nm, 307nm, 267 nm [20]

2.4 UV-Scanning of Lamotrigine:

In the spectrum of Lamotrigine ((10 µg/ml) is exhibited maximum absorbance (λ max) at 307 nm buffer pH 6.8.

2.5 Standard calibration curve of Lamotrigine in phosphate buffer pH 6.8 .

Lamotrigine was obtained by plotting the absorbance of standard solution against its concentration measured at 307nm.

2.6 Infra-Red Spectroscopy: Sample were subjected to FTIR studies for the purpose of characterization. The spectra of binary mixture was scanned between 4000 cm-1 to 400 cm-1 range

2.7 Screening of coformers by using molecular docking study: In this work, we developed virtual screening of coformers for Lamotrigine by employing molecular docking method. The 2D structure of Lamotrigine (Chem Spider ID: 3741) and coformer studies were downloaded in. molecular format from www.chemspider.com

All downloaded 2-D structures were converted to 3-D using Maestro 12.2 module using Ligprep of Schrodinger 2021-1 by adding polar hydrogen. All the compounds were then subjected to Docking and results obtained were recorded. The docking operations were repeated 5 times for each coformer. The parameters observed were the type and energy (Ei) of interactions

2.8 Formulation of mouth fast dissolving tablets of Lamotrigine cocrystal by 3^2 full factorial design. Weigh the accurate quantity of Lamotrigine cocrystal in an equivalent to drug dose (1:1) and all other ingredients were weighed and mixed. these mixed ingredients was directly compressed in to tablets. The quantity of all components is different the superdisintegrant are taken in low, medium and high concentration drug and coformer in equivalent ratio (1:1) were prepared using 12-station rotary tablet compression machine.

Table 1. Composition of factorial design formulation

Content Batches	Lamotrigine (Eq. wt. of cocrystal 25 mg of drug	Mg stearate	SSG	Cross-povidone	Mannitol	TOTAL WEIGHT
F1	42.2	2	15	25	115.8	200
F2	42.2	2	20	15	120.8	200
F3	42.2	2	20	25	110.8	200
F4	42.2	2	15	15	125.8	200
F5	42.2	2	20	20	115.8	200
F6	42.2	2	25	20	110.8	200
F7	42.2	2	25	25	105.8	200
F8	42.2	2	15	20	120.8	200
F9	42.2	2	25	15	115.8	200

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2.9 Evaluation of pre-compression parameter
Prior to compression, powder were evaluated for powder characteristic.

2.10 Evaluation of post compression parameter:
Thickness weight variation: The thickness of the tablets was measured using a Vernier Caliper. Five tablets were randomly selected from each formulation and thickness of each of these tablets was measured. The results are expressed mean ± standard deviation (SD).
Weight variation: Twenty tablet were selected at random and average weight was determined using an electronic balance (Shimanzu). Tablet were weighed individually and compared with average weight.
Hardness: Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester. The mean value and standard deviation for each batch were calculated.
Friability: The friability of tablets was measured using USP type Roche friabilator. Preweighed tablets were placed in plastic chambered friabilator attached to motor revolving at speed of 25 rpm for 4 min. The tablets were then reweighed, and percent weight loss was calculated using the following formula % friability = (initial weight – final weight) /initial weight)×100.
In vitro disintegration time: The tablet disintegration apparatus was used to determine in vitro disintegration time (DT) using buffer pH 6.8 at 37 ± 2º. The time taken by tablet for complete disintegration with no residue meaning in apparatus was recorded as mean ± SD.
In vitro drug release study : The drug release study were performed using the USP II dissolution test apparatus (ELECTROLAB INDIA DISSO TDT-08L) by use of paddle apparatus, The dissolution test was performed using media 900 ml of buffer pH 6.8 at temperature 37 ± 0.5º with rotation speed 50 rpm, About 5ml sample was collected at predetermined time interval 1 min and replaced with equal volume of fresh medium .This was continued for 10 min sample were then filtered through 0.45 membrane filter and analysed at 307 nm using 3200 double beam spectrophotometer (lab india)
Drug content: Twenty tablets were weighed and powdered. Powder equivalent to a single dose of Lamotrigine was weighed and dissolved in few ml of ethanol, diluted with buffer pH 6.8 and assayed for drug content at 307nm using 3200 UV-Double beam spectrophotometer (lab india)

III. RESULT AND DISCUSSION:

The four coformer were screened for potential cocrystal formation with lamotrigine by liquid assisted dry grinding method. Only ascorbic acid is selected for cocrystal preparation with Lamotrigine giving novel cocrystal form. The obtained Lamotrigine cocrystal was subjected to physicochemical evaluation and fast mouth dissolving tablet formulation.

3.1 Melting point: Its average melting point of Lamotrigine was determined by digital melting point apparatus and was found to be 216-218 ºC which is within reported range of melting point (216-218) indicates purity and identity of drug.
3.2 Organoleptic Properties [21]
The selected drug was examined as white, solid in nature and crystalline powder.
3.3 Solubility Study: Solubility of pure Lamotrigine in various medium: It was selected Lamotrigine has very low aqueous solubility. It was determined in distilled water,0.1 N HCl, and phosphate buffer pH 6.8. The Drug was found to be highly soluble in 0.1 N HCl. It was also soluble in ethanol, DMSO and low solubility in water and buffer pH 6.8, shown in Table

Table 2. Solubility of pure Lamotrigine in various medium:

Drug Lamotrigine	**Medium Water**	**Buffer pH 6.8**	**0.1 N HCl**
Solubility Reported (mg/ml)	0.17	0.15	4
Solubility found (mg/ml)	0.14	0.17	3.27

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3.4 Saturated solubility of cocrystal in different media:

The solubility of cocrystals was determined in distilled water, which buffer pH 6.8 and 0.1 N HCl.

3.5 Drug with Ascorbic acid cocrystal (molar ratio 1:1) was found to be highly soluble in Phosphate buffer pH 6.8, it was showed in table

The drug has shown pH dependent solubility as in following table

Table 3. Saturation solubility of LTZ in comparison to its cocrystals in different media

Sr. No.	Cocrystal	Solubility (mg/ml)		
	Sample name	**Water**	**Buffer pH 6.8**	**0.1 N HCl**
1	**Drug: Ascorbic acid (1:1)**	9.812	10.39	33.271
2	**Drug: Benzoic acid (1:1)**	1.445	0.8182	21.252
3	**Drug: Acetamide (1:1)**	0.7247	0.4258	29.467
4	**Drug: Nicotinamide (1:1)**	0.2142	0.3139	118.52

3.6 UV-Scanning of Lamotrigine:

- In the spectrum of Lamotrigine ((10 µg/ml) exhibited maximum absorbance (λ max) at 307 nm buffer pH 6.8 .

Standard calibration curve of Lamotrigine in phosphate buffer pH 6.8 [22]

The standard solution of Lamotrigine was prepared by diluting stock solution in the concentration with range of 2,4,6,8,10 µg/ml using phosphate buffer pH 6.8. The Standard calibration curve of Lamotrigine was obtained by plotting the absorbance of standard solution against its concentration at about307nm.

The standard solution of drug showed linear curve with correlation coefficient

(R2) of 0.998. The equation of the line is y = 0.038x - 0.003.

Table 4 Absorbance value of Lamotrigine in phosphate buffer pH 6.8

Sr. NO	CONC. (µg/ml)	ABSORBANCE
1	**0**	**0**
2	**2**	**0.076**
3	**4**	**0.137**
4	**6**	**0.225**
5	**8**	**0.307**
6	**10**	**0.378**

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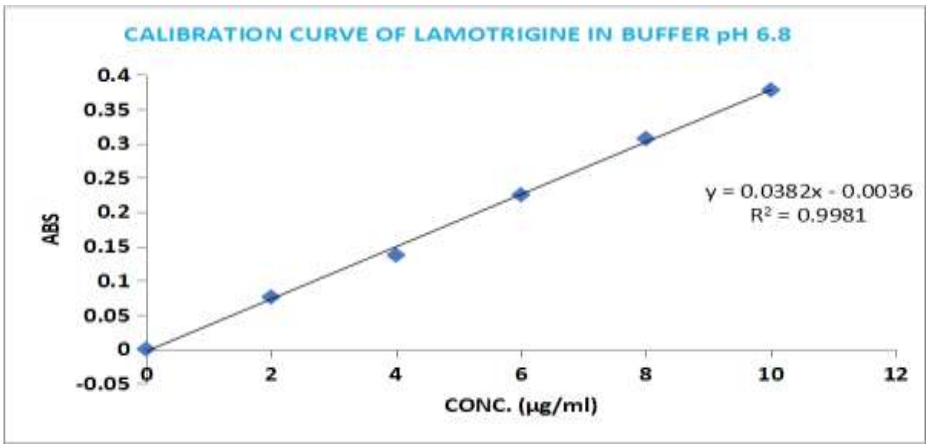

Fig1.Standard calibration curve of Lamotrigine in phosphate buffer pH 6.8

- **FTIR Spectrum for Identification of Pure Drug** [23,24]

The principal absorption peaks of Lamotrigine were observed wit functional group region indicates fingerprint region 3456.44 cm-1, 3332.99 cm-1, 3221.12 cm-1 (N-H Stretching) , 3212 cm-1(Aromatic C-H stretching), 624cm-1 (C-Cl stretching) ,1641.42 cm-1 (C=C stretching), 1440.83 cm-1 (C-C stretching) as Shown in figure.

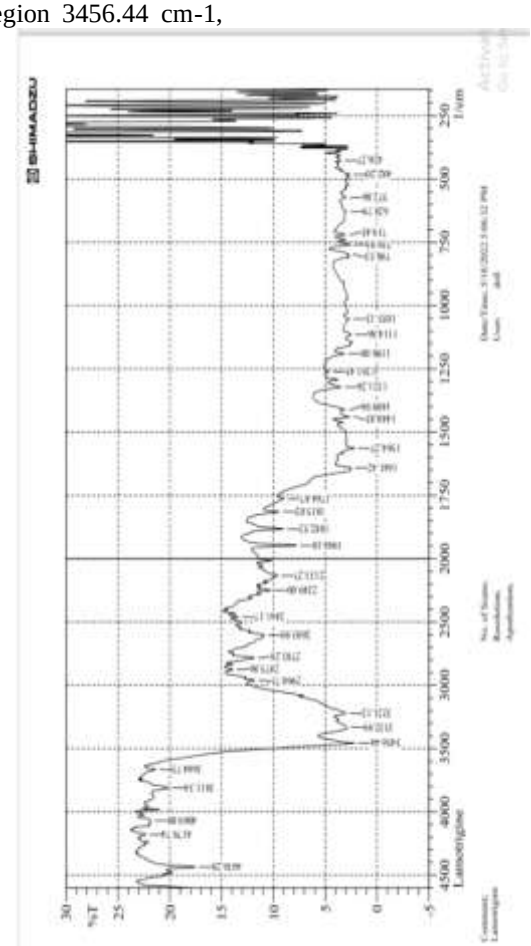

Fig 2. FT-IR spectra of pure Lamotrigine

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Table 5. FTIR spectrum characteristic peaks of Lamotrigine

Sr. No.	Functional group	Wave number cm-1	
		Actual value	Observed value
1	N-H stretching	3500 - 3300	3456.44 cm-1,3332.99 cm-1, 3221.12 cm-1
2	Aromatic C- H stretching	3300 – 2850	3212 cm-1
3	C-Cl stretching	785 – 540	628 cm-1
4	C=C stretching	1600 – 1475	1641.42 cm-1

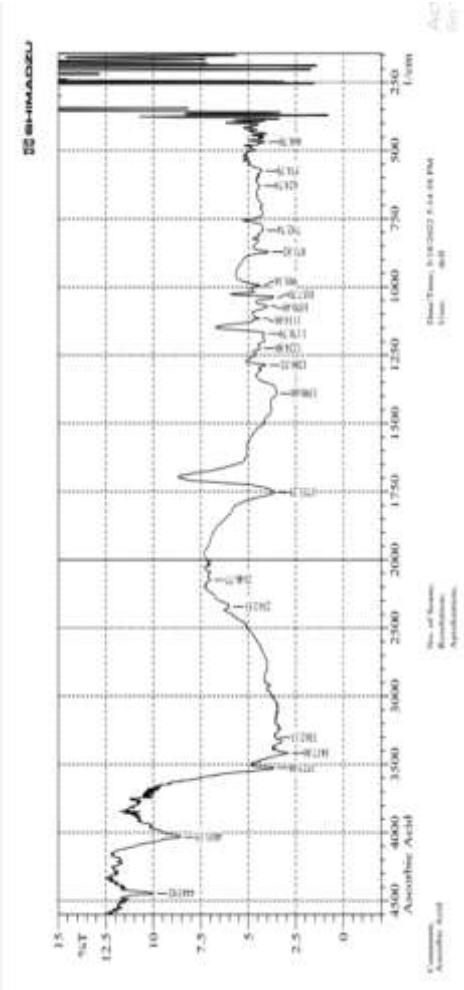

Fig.3. FT-IR spectra of pure Ascorbic acid

FTIR Spectrum for Identification of Pure Ascorbic acid [25]

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Table 6. FTIR spectrum characteristic peaks of pure Ascorbic acid

Sr. No.	Functional group	Wave number cm-1	
		Actual value	Observed value
1	Conjugation of C=C with C=O	1675	1674.19
2	Enol – Hydroxy stretching	1322	1322.17

- **FTIR Spectrum for Identification of Lamotrigine: Ascorbic acid (1:1)**

In the Lamotrigine: Ascorbic acid cocrystal, the bands of the Lamotrigine were shifted to 3452.58, 3331.07, 3217.27 cm-1(N-H stretching), respectively. The peak of 3212 cm-1 in Lamotrigine and the peak of 3212 cm-1 in cocrystal are for the C-H stretch. The C-Cl stretching up shifted from 628 cm-1 to the 738.74 cm-1.

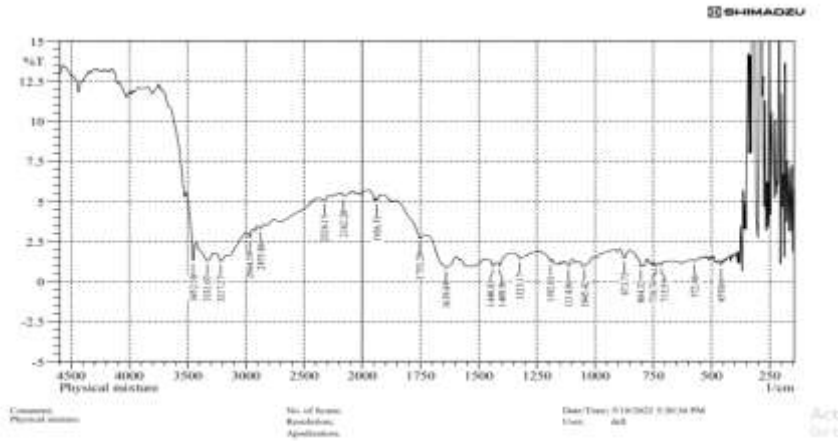

Fig 4. FT-IR spectra of Lamotrigine: Ascorbic acid (1:1).

Table 7. FTIR spectrum characteristic Lamotrigine: Ascorbic acid (1:1)

Sr. No.	Functional group	Wave number cm-1	
		Actual value	Observed value
1	N-H stretching	**3500 – 3300 cm-1**	3452.58 cm-1, 3331.07 cm-1, 3217.27 cm-1
2	Aromatic C- H stretching	**3300 – 2850 cm-1**	3212 cm-1
3	C-Cl stretching	**785 – 540 cm-1**	738.74 cm-1
4	C=C stretching	**1600 – 1475 cm-1**	1639.49 cm-1
5	Enol – Hydroxy stretching	**1322 cm-1**	1323.17 cm-1

3.9 Molecular docking study [26,27]

The molecule of Lamotrigine contains one dichlorophenyl aromatic ring, three nitrogen are hydrogen bond acceptor (HBA) and two amino group of triazine ring are hydrogen bond donors (HBDs), and hence, it is possible to form co-crystals with certain coformer. The coformer chosen in this work were Ascorbic acid, Benzoic acid, Nicotinamide, Acetamide. The results obtained for each coformer was listed in the table given below.

Molecular docking proved that all co-formers interacted with Lamotrigine, and the **highest affinity to Lamotrigine was shown by Ascorbic acid (interaction energy = -9.055kcal/mol). It showed one hydrogen bond, which is present between methoxy group of cyclic sugar with nitrogen of triazene ring of drug molecule**.

All the four co-formers showed interaction with the Lamotrigine. Hydrogen bond shows between COOH group of **Benzoic acid** and amino group of triazene ring of drug molecule with energy -6.87 Kcal/mol. Hydrogen bond shows between carboxy group of **Acetamide** and nitrogen of triazene ring of drug molecule with energy -5.725 Kcal/mol. Hydrogen bond shows between

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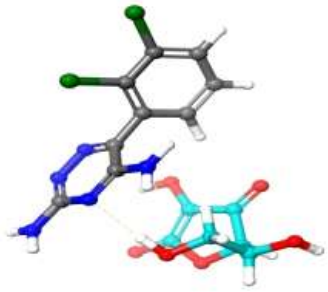
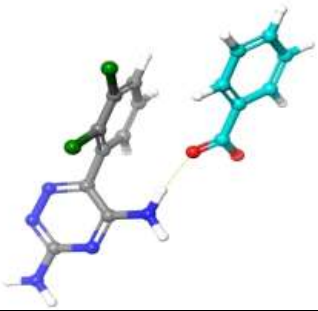
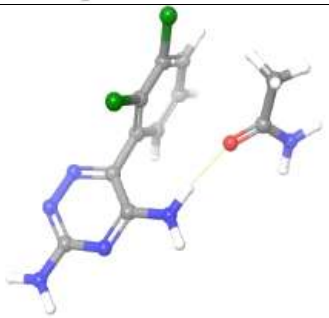
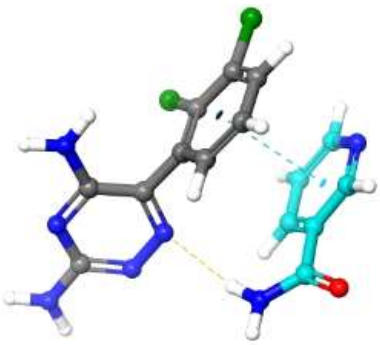
amino group of **Nicotinamide** and N of triazene ring of drug molecule, hydrophobic pi-pi interaction between the phenyl ring of nicotinamide and dichlorophenyl ring of drug molecule with energy -8.455 Kcal/mol. Ascorbic acid was chosen as a best co-former for solubility study based on the interaction energy.

Table 8. Molecular docking of lamotrigine with different coformer:

Name of coformer	Type of interaction	Interaction with Lamotrigine	Ei (Kcal/Mol)
Ascorbic acid	Hydrogen bond between Methoxy group of cyclic sugar with Nitrogen of triazene ring of drug molecule.		-9.055
Benzoic acid	Hydrogen bond between COOH group of benzoic acid and amino group of triazene ring of drug molecule		-6.87
Acetamide	Hydrogen bond between carboxy group of acetamide and Nitrogen of triazene ring of drug molecule.		-5.725
Nicotinamide	Hydrogen bond between NH2 group of iso nicotinamide and Nitrogen of triazene ring of drug molecule. Hydrophobic π-π interaction between the phenyl ring of iso nicotinamide and dichlorphenyl ring of drug molecule		-8.455

3.10. Formulation of Fast dissolving tablet [28]

The present study was aimed to prepare the fast-dissolving tablet of Lamotrigine. In this view the co-crystal and all excipients were subjected to direct compression and formulate the tablet This formulated tablet was give best results

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regarding dissolution and content uniformity. The coformer like Ascorbic acid, Benzoic acid, Acetamide were selected for study. The effect of type and ratio of coformer, type of excipient on release profile of drug was studied.

3.11. Preparation of fast dissolving Tablets of Lamotrigine cocrystal by direct compression Process:

Preparation of Lamotrigine Fast Dissolving Tablet: Fast dissolving tablets of Lamotrigine were prepared by direct compression technique, It was incorporated with equivalent weight of cocrystal powder containing drug and coformer ratio (1:1) Sodium starch glycolate, Crosspovidone and magnesium stearate. All the ingredients were weighed separately. These ingredients were then mixed in a geometrical order to compress into tablets of 200 mg individual weight, using a 12-station Rotary Tablet Compression machine [29].

A two factor three level factorial design (Design expert 13.0 software) was used for the formulation. The dependent variable are conc. of superdisintegrants SSG and Crosspovidone (15 mg, 20 mg and 25 mg). batches obtained are formulated and evaluated for optimization. The developed formulation were subjected to evaluation of various parameter which is precompression parameter and post compression parameter and their results are indicated

All formulation shows good flow properties which is the result of precompression parameter and the results of post compression showed that the formulated tablets were of uniform weight, thickness and hardness of 3.3 to 3.5kg/cm^2.The loss of friability was observed in range of 0.41 to 0.61% Thus by the results of hardness and friability studied it is confirmed that the tablets possess good mechanical resistance. The drug content in formulated tablet was observed between 93.67 to 99.37% which was within acceptable limits. The F3 batch was promising as it exhibited least disintegration time. The disintegration time was found to be decreased with increased concentration of superdisintegrants [30]

3.12. In-Vitro Dissolution Studies in Phosphate Buffer pH:

In vitro dissolution of fast dissolving tablet formulations was carried out by using dissolution test apparatus USP II (paddle type). The dissolution medium phosphate buffer pH 6.8 (900 ml) was maintained at 37ºC±0.5ºC. The speed of the stirrer was maintained at 50 rpm. A sample of 5ml was withdrawn by pipette at predetermined intervals of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 min. Same quantity of fresh dissolution medium equilibrated at 37ºC±0.5 ºC and replaced to maintain apparent sink conditions. The samples were assayed at 307nm λ max of drug by using Lab India UV spectrophotometer.

IN VITRO DISSOLUTION STUDY:

- **Fast dissolving tablets:**

Dissolution Study in Phosphate buffer pH 6.8
% Drug Release

In- vitro drug dissolution profile of all formulation is shown in Fig. and it was observed that percent dissolution release is increased successfully in cocrystals mixture tablets in comparison to marketed tablet. **Formulation F3 was showed cumulative percentage drug release profile (98.40%) in 8 min compared with marketed tablet (72.24%).** All formulations exhibit good release within 10 min in buffer pH 6.8, The results are comparable with marketed formulation [31].

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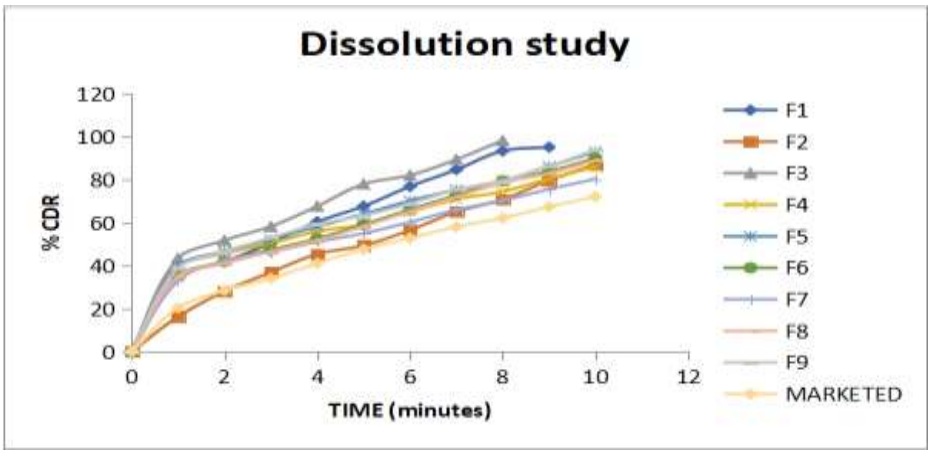

Fig.5. In vitro Dissolution Profile

Table 9. Dissolution Profile of fast dissolving tablet in Phosphate buffer pH 6.8

Cumulative % drug released (formulations)										
Time (Min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**Marketed tablet**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	35.43	16.22	43.50	39.59	39.93	35.13	33.19	35.17	38.97	20.392
2	41.96	28.03	51.89	45.74	46.80	41.88	42.38	41.08	46.62	28.46
3	50.50	36.95	58.35	50.47	52.30	47.38	46.39	46.56	53.10	34.05
4	60.42	45.37	67.73	55.98	58.31	52.59	51.08	51.77	59.29	41.18
5	67.72	49.47	78.08	59.23	64.12	59.18	55.11	58.36	63.42	47.67
6	76.95	56.58	82.19	65.18	70.23	66.11	60.28	65.29	68.93	52.90
7	84.77	65.11	89.54	70.99	75.37	72.87	66.07	72.05	75.38	58.13
8	93.48	70.89	98.40	74.56	79.61	79.55	70.44	78.73	79.58	62.25
9	95.26	79.77		80.56	86.32	83.92	75.66	83.10	86.39	67.46
10		87.26		86.16	93.17	90.15	80.44	89.17	94.05	72.24

Table 10. Precompression parameter.

Precompression parameter									
parameter	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Bulk density(gm/cm^3)	0.331 ±0.025	0.333 ±0.013	0.331± 0.011	0.334 ±0.014	0.336± 0.096	0.035± 0.060	0.333 ±0.052	0.032±0.034	0.034±0.038
Tapped density (gm/cm^3)	0.391 ±0.016	0.399 ±0.069	0.401± 0.093	0.408 ±0.094	0.418± 0.060	0.405± 0.065	0.410 ±0.063	0.409±0.097	0.409±0.097
Hausner's ratio	1.17± 0.057	1.19± 0.064	1.22±0.080	1.23± 0.095	1.24±0.065	1.22±0.090	1.23± 0.060	1.23±0.090	1.22±0.012
Compressibility index (%)	16.54 ±0.064	19.44 ±0.096	15.54± 0.064	18.36 ±0.068	19.70± 0.063	18.45± 0.032	18.50 ±0.050	18.80±0.060	18.53±0.040±
Angle of repose	29.90 ±0.030	26.98 ±0.065	25,50± 0.020	30.80 ±0.060	30.94± 0.012	18.75± 0.060	8.80± 0.014	18.80±0.014	31.20±0.079
Post compression parameter									

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parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Friability (%)	0.45±0.6	0.56± 0.5	0.41± 0.9	0.52±0.5	0.61±0.3	0.52 ± 0.5	0.42± 0.6	0.47 ± 0.8	0.49 ±0.4
Hardness(kg/cm^3)	3.5 ± 0.11	3.5 ± 0.11	3.0 ± 0.15	4.0 ± 0.20	3.0 ± 0.10	4.0 ± 0.21	3.5 ± 0.05	3.0±0.18	3.1± 0.12
Disintegration time (sec)	17±1.50	19±1.50	13±0.60	13±0.60	15±1	17±0.5	17±1.2	19. ±1	15±1.50
Drug content (%)	98.23± 0.15	96.45± 0.34	99.37 ±0.05	93.67± 0.21	95.73± 0.18	98.05 ±0.12	94.67± 0.20	97.17± 0.27	99.35±0.18

Table 11. Post compression parameter

IV. CONCLUSION:

- The cocrystal formation technique of Lamotrigine and Ascorbic acid has been successfully attempted with enhanced solubility and dissolution profile. The increased folds in dissolution rate of Lamotrigine has been observed
- Ascorbic acid and its cocrystal were observed using FTIR spectroscopy. The interaction change the molecular rearrangement results in to the formation of new crystal with modified physical properties such as melting point and solubility [32]
- Lamotrigine is BCS class II with low solubility and high permeability (0.17mg/ml at 25ºC)[33] due to presence of multifunctional moieties with both hydrogen bond donors and acceptors on the periphery of weak base(pka5.7). It also make the drug desirable for forming cocrystal and salt [34,35,] by use of liquid assisted grinding method Lamotrigine cocrystal possessing modified physicochemical properties were obtained and successfully fast dissolving tablet prepared with enhanced solubility observed.
- The molecular docking study has showed similar results and indicate suitability of Ascorbic acid.
- The directly compressible fast dissolving tablets of Lamotrigine cocrystal were develop with shorter disintegration time, low friability and greater release by using 3^2 full factorial design
- F3 formulation was found promising based on evaluation parameter, The marketed tablet showed 72.24 % drug release within 10 min in phosphate buffer pH 6.8, The drug and Ascorbic acid cocrystal tablet showed 98.27 % drug release within 10 min and the results are comparable with marketed formulation.
- When patient suffering from epileptic attack, then just place tablet in mouth which has pH 6.8 which results in fast and good release in mouth because of its pH dependent solubility and recurrent attack can be prevented.
- Overall results of the dissolution studies of formulation complies with the pharmacopeial standards as per USP monograph.

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