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FORMULATION AND EVALUTION OF FAST DISSOLVING TABLET OF SOLID DISPERSION OF LAMOTRIGINE

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ABSTRACT

Purpose: Lamotrigine belongs to biopharmaceutical classification systems; BCS class II (Low solubility & High permeability). In addition, it requires immediate therapeutic action as it is antiepileptic drug. Hence, the main objective of this study is to improve the solubility by solid dispersion technique and formulate it as fast dissolving tablets to avert the problems of swallowing and to provide rapid onset of action. **Method:** Lamotrigine solid dispersion was prepared by using solvent evaporation method and fusion method and formulated it into fast dissolving tablet by direct compression technique using different concentrations of Sodium Starch Glycolate, Cross Carmalose Sodium as superdisintegrants. **Result:** The tablets were evaluated for various parameters and the results were found to be satisfactory. **Conclusion:** The fast dissolving tablets containing solid dispersion prepared by solvent evaporation technique shows highest drug content. The optimized formulation shows more drug release than other formulation.

KEYWORDS: Solid dispersion, Superdisintegrants, Fast dissolving tablets, Solvent evaporation, Fusion.

INTRODUCTION

Lamotrigine was selected for the present work because it is BCS class II drug and has solubility problems. BCS class II (i.e., less water soluble) drugs require innovative approaches to reach a sufficiently high bioavailability when administered by oral route.[1-3]

Lamotrigine (LM) is an anticonvulsant drug used in the treatment of epilepsy, bipolar disorder and also acts as a mood stabiliser. Chemically unrelated to other anticonvulsants (due to LM being a phenyltriazine), LM has relatively few side-effects and does not require blood monitoring in monotherapy. LM is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). Peak plasma concentrations occur anywhere from 1.4 to 4.8 h following drug administration. This delay in the onset of action in spite of good bioavailability is because of its low aqueous solubility which is only 0.17 g/l. This may result in the delayed onset of action because of sub-therapeutic plasma drug levels and may also lead to therapeutic failure.[4-5]

Solid dispersions (SDs) refer to a system in which hydrophobic drug is dispersed in a hydrophilic matrix, in order to improve its dissolution properties and bioavailability. In SD, a drug can exist in an amorphous or crystalline form in hydrophilic polymeric carriers[3,6] such as polyethylene glycols (PEG), polyvinyl pyrrolidine K30 (PVP K30), urea, etc., which results in improved solubility and dissolution rates. The only preparation of solid dispersion is not sufficient as the formulation concern, it is always essential to convert solid dispersion into some suitable dosage form; hence in the present study it is decided to prepare fast dissolving tablets.

Fast dissolving tablets offer the convenience of a tablet with the ease of swallowing without a liquid. These dosage forms are of particular advantage in certain patients group such as children, elderly and psychiatric patients. In addition, patients suffering from dysphagia, motion sickness, repeated emesis, and mental disorders prefer these medications because they cannot swallow large quantity of water.[7-15]

The objective of the present research work was to formulate SDs of LM; two hydrophilic carriers were evaluated to determine their effect on solubility of LM; different methods were

then evaluated to select the best method of preparation of SDs. Furthermore, the SDs was formulated into fast-dissolving tablets and effect of formulation on the drug release of LM was studied.

MATERIAL AND METHODS

Active pharmaceutical ingredient- Lamotrigine was obtained as a gift from Hetero laboratories, Hyderabad. Hydrophilic polymers Polyethylene Glycol 4000 and Polyethylene Glycol 6000 were obtained from A.R. Chemicals, Hyderabad.

Excipients- Sodium starch glycolate, Croscarmellose, Magnessium Stearate, Aspartame, Talc, Microcrystalline cellulose were obtained from A.R. Chemicals, Hyderabad and all these were of analytical grade.

Analysis of Lamotrigine

The received sample of Lamotrigine was characterized according to different compendia methods and was found to be an odorless white fine powder.

Preparation of standard calibration curve of Lamotrigine

The calibration curve was plotted within the concentration range of 10-50 µg/ml of the Lamotrigine. Appropriate dilutions were prepared and absorbance was measured for each solution at 240 nm since maximum absorbance was observed at this wavelength. Graph was plotted for absorbance Vs concentration.

Preparation of Solid dispersion of Lamotrigine

Solid dispersion of drug and two different polymers was prepared by solvent evaporation method and fusion method in various ratios such as, 1:1, 1:2, 1:3, and 1:4. Solid dispersions prepared by solvent evaporation method S1, S2, S3, S4, S5, S6, S7, and S8. Solid dispersions prepared by fusion method or Melting method M1,M2,M3,M4,M5,M6,M7, M8.

Table 1: Formulation table of solid dispersion.

Sr. No	Ingredient	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	Lamotrigine	25	25	25	25	25	25	25	25
2	PEG 4000	25	-	50	-	75	-	100	-
3	PEG 6000	-	25	-	50	-	75	-	100

1. Preparation of Solid Dispersions by Solvent evaporation technique

The solid dispersions of Lamotrigine and carriers in various drug-to-carrier weight ratios were prepared by solvent evaporation method. Required amount of carriers was dissolved in q.s. of acetone in a beaker and Lamotrigine was added and mixed to dissolve. Then the solvent was allowed to evaporate. Solid Dispersions prepared were crushed, pulverized and sifted through sieve number #40 and stored in desiccators**.**

2. Preparation of Solid Dispersions by Fusion technique

Lamotrigine solid dispersions of all formulations were prepared by fusion method or melting method using different carriers in 1:1, 1:2, 1:3 and 1:4 (Drug: Carrier) proportions. Carrier was melted at 40 ºC. The drug was dispersed in the molten carrier and then kept aside for cooling. After solidification, the obtained SD was scraped off using a spatula. SDs were further subjected to milling in a mortar with pestle and passed through a 45 µm sieve before packing in an airtight container.

Evaluation of Solid Dispersion

Table 2: Pre compression parameters of Lamotrigine fast dissolving tablets (By Solvent Evaporation Method).

Formulation No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of Repose(^{0})
S1	0.352	0.441	20.18	1.22	29^0
S2	0.342	0.452	24.33	1.25	30^0
S3	0.348	0.442	21.26	1.25	27^0
S4	0.35	0.455	23.07	1.27	30^0
S5	0.346	0.452	23.45	1.22	27^0
S6	0.348	0.449	22.49	1.23	29^0
S7	0.352	0.451	21.95	1.25	30^0
S8	0.347	0.453	23.39	1.23	29^0

Table 3: Pre compression parameters of Lamotrigine fast dissolving tablets (By Fusion Method/Melting method)

Formulation No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of Repose(^{0})
M1	0.341	0.432	21.06	1.26	28^0
M2	0.332	0.461	27.98	1.31	29^0
M3	0.358	0.472	24.15	1.31	30^0
M4	0.361	0.486	25.72	1.34	27^0
M5	0.352	0.424	16.98	1.20	26^0
M6	0.368	0.447	17.67	1.21	28^0
M7	0.342	0.424	19.33	1.23	29^0
M8	0.317	0.432	26.62	1.36	28^0

Drug excipient compatibility studies

Fourier Transform Infra red Spectroscopy (FTIR) interpretation

To study the interaction between drug and polymers used in the preparation of solid dispersion, FT-IR Spectra of pure Lamotrigine and excipients were recorded.

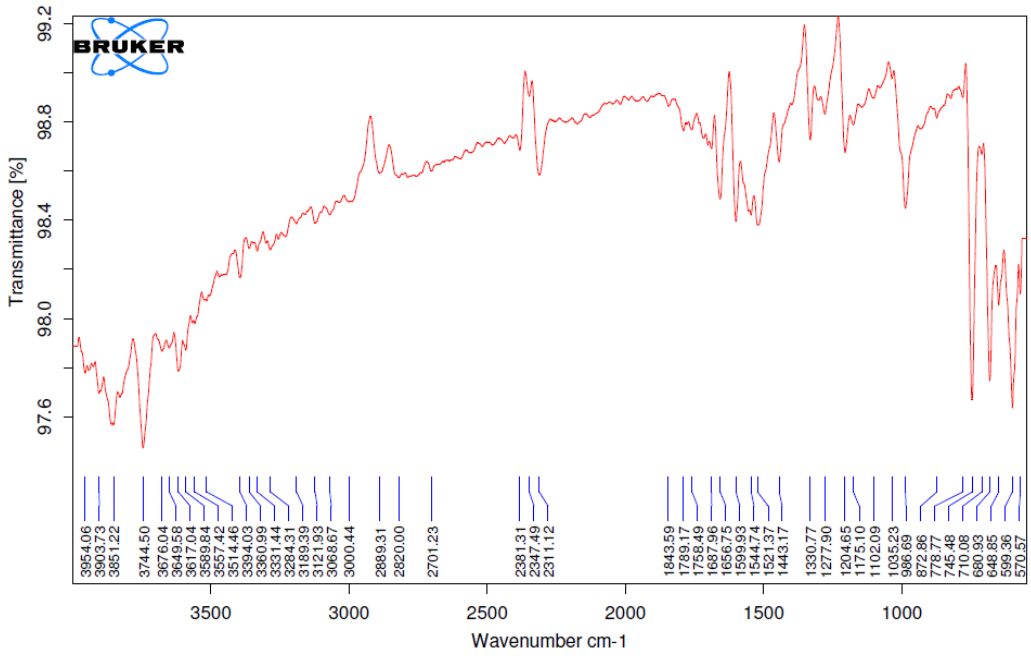

Figure 1: FTIR Spectra of Lamotrigine plain drug.

Table 4: Interpretation of FTIR spectrum of Lamotrigine pure drug

Sr. No.	Characteristic Peaks	Frequency range (cm^{-1})	Frequency (cm^{-1})
1	OH stretching	3500-3000	2972.18
2	OH Bending	1000-1500	1049.31
3	C-H stretching	3000-2500	2867.50
4	C=O stretching	2000-1500	1692.11

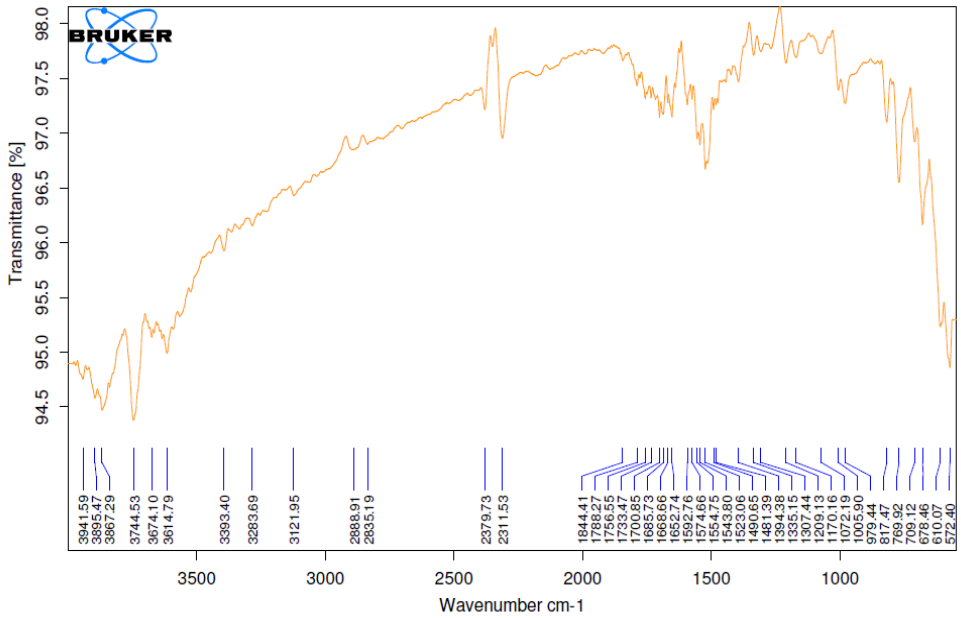

Figure 2: FTIR Studies of Physical mixture of drug and excipients.

Table 5: Characteristic Peaks for drug and excipients.

Sr. No.	Characteristic Peaks	Frequency range (cm^{-1})	Frequency (cm^{-1})
1	OH stretching	3000-2500	2916.84
2	OH Bending	1100-1070	1071.96
3	C=O stretching	2000-1500	1575.23

All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Lamotrigine and super disintegrant. It also confirmed that the stability of drug during microencapsulation process.

3. **Differential Scanning Colorimetry (DSC) -** Thermal analysis has been carried out for selected formulation containing LMT compared with the individual nanoparticles excipient. The powder sample (weighing about 5 mg) was sealed in aluminum pans hermetically, and subjected to a heating rate of 10 C/min, at range of 30 ^{0} –300 ^{0}C. In addition, N_2 was used as purging gas at rate of 40 ml/min. DSC scans of the samples have been recorded using differential scanning calorimeter (DSC- 60, Shimadzu, Japan) with Shimadzu software programs. Indium standard was utilized to calibrate the DSC temperature and enthalpy scale.

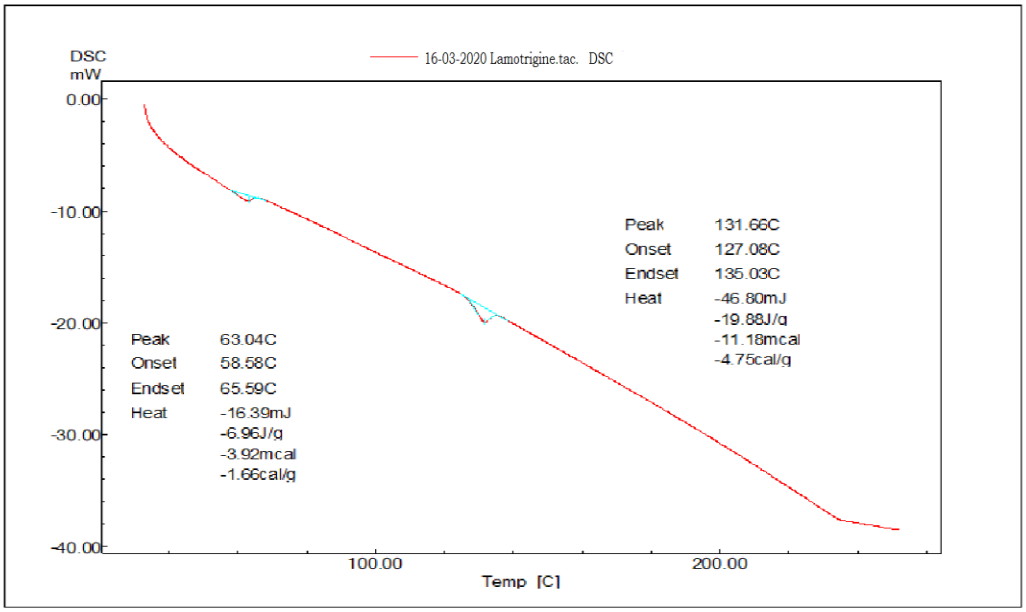

Figure 3: DSC of Lamotrigine.

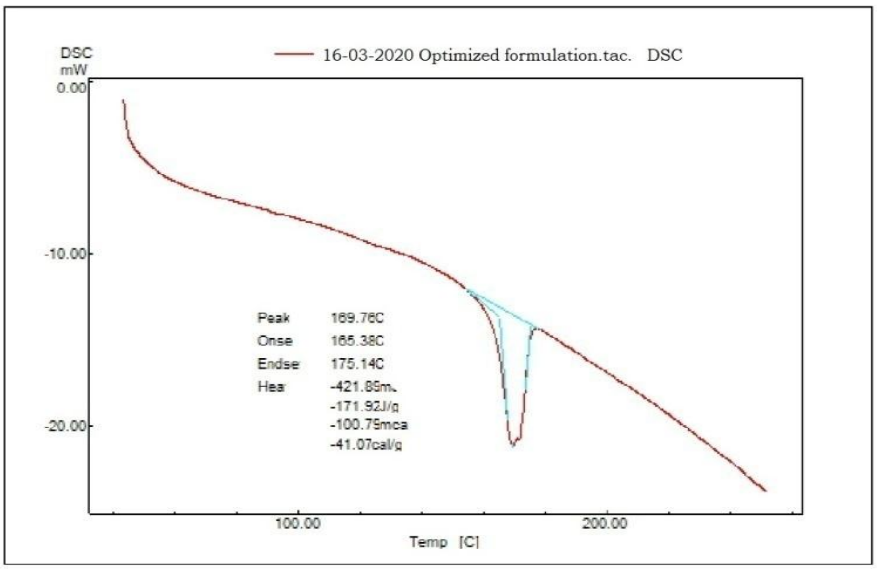

Figure 4: DSC of optimized formulation.

4. X-Ray Diffraction analysis

XRD analysis is based on constructive interference of monochromatic X-rays and a crystalline sample: The X-rays are generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample. The interaction of the incident rays with the sample produces constructive interference (and a diffracted ray) when conditions satisfy Bragg's Law ($n\lambda=2d \sin \theta$). This law relates the wavelength of electromagnetic radiation to the diffraction angle and the lattice spacing in a crystalline sample.

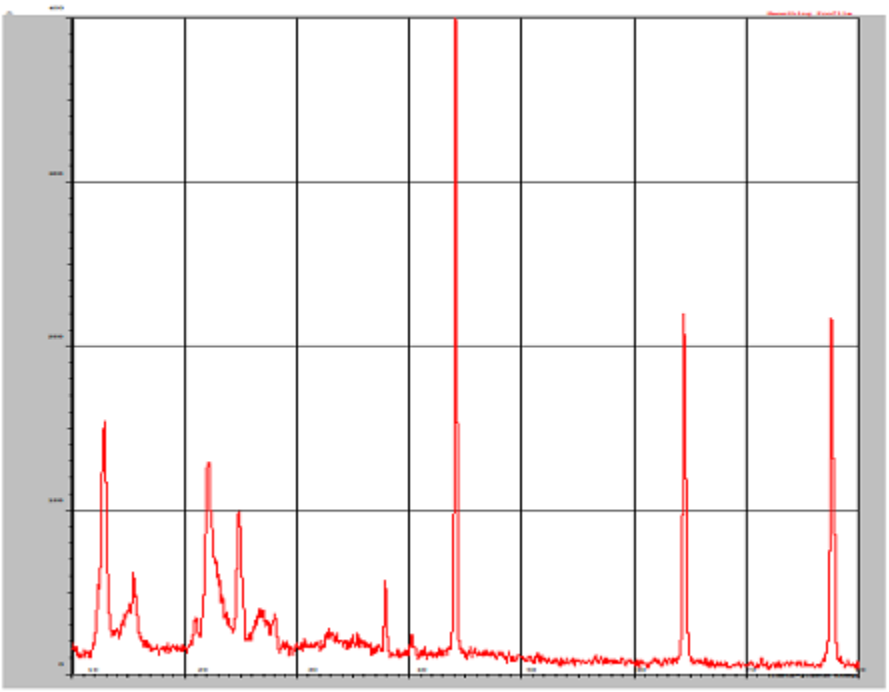

Figure 5: X-Ray Diffraction of Lamotrigine plain drug.

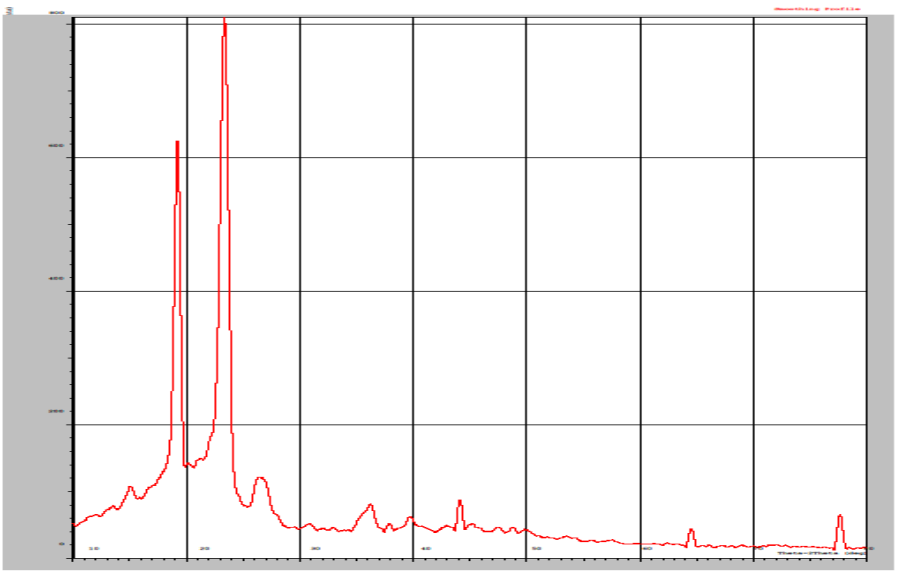

Figure 6: X-Ray Diffraction of optimized formulation.

Formulation of Fast dissolving tablet

Table 6: Formulation table of fast dissolving tablets

Sr. No	Ingredient	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	Solid dispersion complex	50	50	50	50	50	50	50	50
2	Sodium starch glycolate	5	10	15	20	-	-	-	-
3	Croscaramellose	-	-	-	-	5	10	15	20
4	Lactose	125	120	115	110	125	120	115	110
5	Aspartame	5	5	5	5	5	5	5	5
6	Magnesium stearate	3	3	3	3	3	3	3	3
7	Talc	2	2	2	2	2	2	2	2
8	Microcrystalline cellulose	10	10	10	10	10	10	10	10
	Total	200	200	200	200	200	200	200	200

Fast dissolving tablets of solvent evaporation solid dispersion and fusion or melt solid dispersion of Lamotrigine were prepared by direct compression. All the ingredints were passed through 60-mesh separately. Then the ingredients were weighed and mixed ingeometrical order and compressed into tablets of 200 mg using 8 mm round flat punches on 10-station rotary tablet machine (Rimek). Then fast dissolving tablet of solid dispersion prepared were subjected to post compression parameters like drug content, hardness, friability, weight variation, dissolution.

Table 7: Results of Evaluation parameters of tablets (Solvent evaporation technique).

Formulation No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
S1	200	3.15	5.10	0.25	94.85
S2	199	3.14	5.13	0.28	94.90
S3	201	3.12	5.21	0.30	95.87
S4	200	3.13	5.20	0.27	96.93
S5	198	3.17	5.18	0.31	94.58
S6	200	3.20	5.15	0.27	98.12
S7	200	3.19	5.21	0.29	97.78
S8	199	3.21	5.20	0.30	95.68

Table 8: Results of Evaluation parameters of tablets (Fusion technique).

Formulation No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
M1	200	3.12	5.12	0.24	92.85
M2	198	3.16	5.14	0.27	93.72
M3	200	3.14	5.23	0.26	89.83
M4	201	3.12	5.19	0.24	90.39

M5	197	3.19	5.17	0.30	89.82
M6	199	3.22	5.19	0.25	92.21
M7	201	3.16	5.23	0.26	94.87
M8	198	3.24	5.18	0.31	95.82

Dissolution studies

All the eight formulations of solid dispersion of solvent evaporation of Lamotrigine fast dissolving tablets were subjected to *in vitro* release studies; these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table 9: Drug release studies of all formulations.

Time	S1	S2	S3	S4	S5	S6	S7	S8
0	0	0	0	0	0	0	0	0
5	20.15	19.61	20.53	23.78	21.54	22.43	18.82	23.19
10	35.63	32.74	46.50	32.42	46.52	32.75	39.16	38.16
15	45.89	44.17	53.62	43.63	54.63	52.16	49.02	52.16
30	65.43	61.23	72.79	63.87	73.75	65.15	62.19	63.46
45	78.18	72.31	84.28	75.73	85.29	83.12	79.92	83.82
60	94.25	93.48	96.33	91.93	98.32	95.15	92.53	90.16

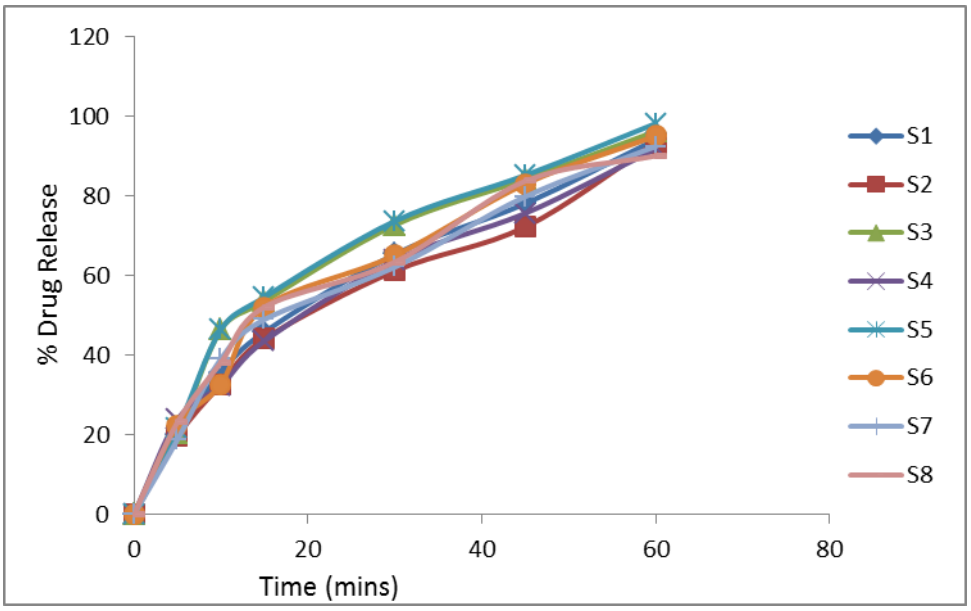

Figure 7: *In vitro* drug release of all formulations.

Comparison of optimized formulation with conventional marketed product

The optimized tablet formulation was compared with conventional marketed tablet for drug release profiles. This formulation fold faster drug release compared to the conventional commercial tablet formulation.

Table 10: Showing conventional marketed drug release with optimized formulation.

Time (mins)	S-5 Optimized formulation	Marketed tablet
0	0	0
5	21.54	19.24
10	46.52	40,16
15	54.63	51.67
30	73.75	68.13
45	85.29	79.32
60	98.32	86.73

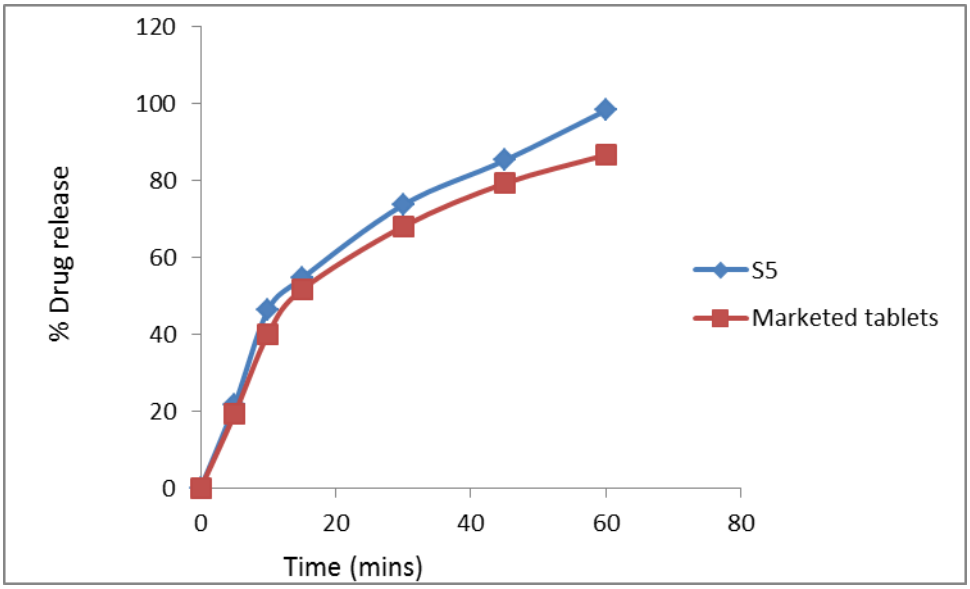

Figure 8: Drug release of optimized formulation and marketed tablet.

Stability Studies

There was no significant change in physical and chemical properties of the fast dissolving tablets of formulation S-5 after 90 days. Parameters quantified at various time intervals were shown.

Table 17: Stability studies of all formulations.

Formulation	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
S-5	25^0C/60%RH % Release	98.32	98.15	98.15	98.15	Not less than 85 %
S-5	30^0C/75% RH % Release	98.32	98.12	98.10	98.13	Not less than 85 %
S-5	40^0C/75% RH % Release	98.32	98.09	98.08	98.06	Not less than 85 %

Result: Lamotrigine is an anticonvulsant drug. In present study the attempts have been made to increase the dissolution of BCS class II drug Lamotrigine using polyethylene glycol 4000 and polyethylene glycol 6000 polymers by solvent evaporation and fusion or melt method of solid dispersion.

The formulation of solid dispersion prepared by both methods i.e. solvent evaporation S1, S2, S3, S4, S5, S6, S7, S8 and fusion or melt method M1, M2, M3, M4, M5, M6, M7, M8. Precompression parameters of all formulations were studied. After that, fast dissolving tablets were prepared by direct compression method. Postcompression parameters like weight variation, hardness, friability, thickness and drug content of all formulations were studied. Data of Drug content of the formulations containing solid dispersion prepared by solvent evaporation is greater than formulations containing solid dispersion prepared by fusion or melt method. Hence the formulations containing solid dispersion prepared by solvent evaporation i.e. S1, S2, S3, S4, S5, S6, S7, S8 were selected for *in vitro* drug release studies. Amongst all the formulations, S5 shows maximum drug release. So it is considered as optimized formulation. When S5 formulation was compared with marketed formulation, it gives highest percent drug release than marketed formulation.

S5 formulation was subjected to stability studies for three months at different temperature and RH conditions and was tested for its drug release. No significant change in drug release has been observed.

DISCUSSION

Lamotrigine was successfully formulated in fast dissolving tablets with desired characteristics. Solvent evaporation into aqueous solution thus may be a useful approach to produce tablets of poorly soluble drugs.

The aim of the present study was to develop an optimized formula for fast disintegrating tablet containing Lamotrigine. This medication is used alone or with other medications to prevent depression.

Pre-formulation studies it was decided to prepare fast dissolving tablets prepared by direct compression method. In the formulation of fast dissolving tablets, sodium starch glycolate, and crosscarmellose were used as super disintegrants.

Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed tablets were also evaluated for weight variation, hardness, friability, drug content, disintegration time, wetting time, in vitro drug release and stability studies.

In the above studies S-5 formulation showed promising results. It was further supported by FTIR analysis which showed that S--5 had no interaction with excipients. The stability studies were carried out for the optimized batch S-5 for 90days and it showed acceptable results. So S-5 formulation was considered as the optimized formulation.

Among all the prepared solid dispersions S5 was found to be optimized. The study shows that the dissolution rate of Lamotrigine can be enhanced to a great extent by solid dispersion technique using solvent evaporation method. Hence, Lamotrigine SSG, and croscarmellose systems could be considered for formulations of fast dissolving tablets of Lamotrigine. The fast dissolving tablets of Lamotrigine (S-5) was shown higher drug release when compared to other formulations. From above results it can be concluded that the Solid dispersion technique can be used to enhance the solubility, Dissolution rate and oral bioavailability of water insoluble drugs.

The optimized tablet formulation was compared with conventional marketed tablet for drug release profiles. This formulation fold faster drug release compared to the conventional commercial tablet formulation.

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