

Orodispersible tablets of Lamotrigine: preparation and evaluation

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ABSTRACT

The aim of the present research was to prepare orodispersible tablets of Lamotrigine for applications in epilepsy and convulsion related problems. Fast action onset is highly desirable in the control of this type of disease condition. All tablets were prepared by solid dispersion method using mannitol and synthetic superdisintegrants like Explotab, Cross Povidone and Micro Crystalline Cellulose. The different powder blends were evaluated for pre-formulation parameters. Effect of superdisintegrants on wetting, disintegration and dissolution parameters was studied. The tablets were evaluated for various parameters like wetting time, hardness, friability, drug content, disintegration and in vitro dissolution. Tablets with Explotab have shown good disintegrating features, also the dispersion not showing any bitter taste; indicate the capability of Vanilla used, as taste masking agents. Almost more than 99% of drug was released from the formulation(F4) within 27 min. Tablets have shown no appreciable changes with respect to physical appearance, drug content, disintegration time, and dissolution profiles.

Keywords: *Lamotrigine, Solid Dispersion, Explotab, MCC, Cross Povidone, in-vitro dissolution.*

1. INTRODUCTION

Difficulty in swallowing (dysphasia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. The concept of orodispersible drug delivery system emerged from the desire to provide patient with conventional mean of taking their medication. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva [1]. In order to achieve an acceptable palatability, the addition of flavors or sweeteners is added to mask the taste [2].

Lamotrigine is an antiepileptic agent shown to be effective in the adjunctive treatment for refractory partial seizures and generalized seizures. It works by inhibiting voltage dependent sodium channels, resulting in decreased release of the excitatory neurotransmitters glutamate and aspartate [3]. It has an elimination half-life longer than 24 h so once or twice daily dosing is possible in all patients. Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 h following drug administration. Lamotrigine has a bitter taste. It is very slightly soluble in water (0.17 mg/ml at 25°C) [4].

Mouth-dissolving/disintegrating tablets (MDDDS) have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. Therefore, these dosage forms have lured the market for a certain section of the patient population which includes dysphagic, bed ridden, psychic, and geriatric and pediatric patients. Mouth dissolving/disintegrating tablets (MDDTs) are also called as “fast-

dissolve”, “fast-melt”, “rapidly disintegrating”, “quick-melt”, “quick-dissolve”, “crunch-melt”, “bite-dispersible”, “orally disintegrating”, and Orodispersible tablets. Drugs without any bitter taste, having dose lower than 20mg, small to moderate molecular weight, good stability in water and saliva, partially non ionized at the oral cavities pH, and having ability to diffuse and partition into the epithelium of the upper GIT (log p>1, or preferably>2) are ideal candidates to formulate as MDTs. Various approaches used for preparation of MDT include Freeze-drying, Moulding, Compression moulding, Heat moulding, No vacuum lyophilization, Sublimation Phase transition process, Mass extrusion Three-dimensional Printing (3DP), Spray drying Cotton Candy Process, Direct compression, Melt Granulation. Use of disintegrants is the basic approach in development of MDTs. Disintegrants play a major role in the disintegration and dissolution of MDT. It is essential to choose a suitable disintegrant, in an optimum concentration to ensure quick disintegration and high dissolution rates [5].

Therefore, it is necessary to develop a formulation which releases the drug in an immediate release manner. Thus Lamotrigine orodispersible tablets would become promising candidate for management of epilepsy and convulsion.

Thus, the present study reveals a novel attempt to formulate FDT of antiepileptic drug Lamotrigine by using solid dispersion method and to clarify effect most commonly used superdisintegrants like, Sodium starch glycolate, Cross Povidone and Micro Crystalline Cellulose on disintegration and dissolution profile of tablets.

Lauryl sulphate was purchase from S.D Fine Chem. Ltd. Mumbai. Cross Povidone was purchased from Balaji Chemicals Ltd. Surat.

2. EXPERIMENTAL SECTION

2.1. Materials

Lamotrigine was received as gift samples from Torrent Pharma Ltd., Mehsana. Explotab, Mannitol, MCC and Sodium

2.2. Preparation of Lamotrigine Orodispersible tablets

Solid dispersion containing Lamotrigine and carrier in mannitol were prepared by melt solvent method. Solid dispersion of drug with mannitol was prepared by melt solvent method. In this method Lamotrigine was dissolved in acetone and the solution was incorporated into the melt of mannitol at 165°C by pouring into it.

It was kept in an ice bath for sudden cooling. The mass was kept in the desiccators for complete drying. The solidified mass was scrapped, crushed, pulverized and passed through 80# (mesh sieve). All the solid dispersion was preserved in well closed glass container until use.

The compositions of various formulations along with formulation codes are summarized in Table 1.

Solvent Method: Physical mixture of two solid components is dissolved in a common solvent and then the solvent is usually removed by evaporation under reduced pressure at varying temperatures. The choice of solvent and its removal rate is critical to the quality of the dispersions. A mixture of solvent may also be used. Freeze-drying and spray drying can also achieve the solvent removal. This method is also called co-precipitation. Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs such as Ketoprofen, spironolactone, nifedipine, so as to consequently improve their bioavailability [6].

2.3. Characterization of powder blends of active pharmaceutical ingredient and excipients

2.3.1. Angle of repose

Angle of repose was determined using funnel method [7]. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following formula:

$$\theta = \tan^{-1} \frac{h}{r}$$

2.3.2. Bulk density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density (ρ_b) was calculated using following formula [7],

$$\rho_b = \frac{M}{V_b}$$

2.3.3. Tapped density

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The minimum volume (V_t) occupied in the cylinder and weight of the blend was measured. The tapped density (ρ_t) was calculated using following formula [7],

$$\rho_t = \frac{M}{V_t}$$

2.3.4. Hausner's ratio (H)

This is an indirect index of ease of powder flow. It is calculated by the following formula [7],

$$H = \frac{\rho_t}{\rho_b}$$

Where ρ_t indicates the tapped density; ρ_b indicates the bulk density.

2.3.5. Compressibility index or Carr's Index:

The simplest method of measurement of free flow of powder is compressibility. An indication of the ease with which material can be induced to flow is given by compressibility index (I) which is calculated as follows [7],

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Where ρ_t indicates the tapped density; ρ_b indicates the bulk density.

2.4. Evaluation of Lamotrigine orodispersible tablets

2.4.1. Hardness

The prepared tablets hardness was measured by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2 [8].

2.4.2. Friability

Ten tablets were weighed collectively and placed in the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively [8].

2.4.3. Weight variation

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. The percentage deviation was calculated and then compared with USP specifications [8].

2.4.4. Thickness

The thickness of the prepared tablets was analyzed by vernier calipers and the average was calculated [8].

2.4.5. Wetting time

A piece of tissue paper folded twice was placed in a small Petridis (internal diameter of 5 cm) containing 6 mL of distilled water. A tablet was placed on the paper, and the time required for complete wetting of the tablet was measured [9].

2.4.6. Drug content

Twenty tablets were powdered; powder equivalent to 50 mg of Lamotrigine was accurately weighed and transferred into a 100 mL volumetric flask. Then, the volume was made up to 100 mL with 0.1N HCl. The diluted solution was analyzed for the Lamotrigine content by a UV-spectrophotometer (UV-1700 Shimadzu Corporation, Japan) using 0.1N HCl as a blank at 267 nm. The filtrate contained the drug within the standard plot range.

2.4.7. In vitro dispersion time

One tablet was placed in a beaker containing 10mL of Acidic buffer pH 1.2 at $37 \pm 0.5^\circ\text{C}$ and the time required for complete dispersion was determine [10].

2.4.8. In vitro disintegration time

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of $37^\circ \pm 2^\circ\text{C}$ and time taken for the entire tablet to disintegrate completely was noted [11].

2.4.9. In vitro dissolution study of tablets

The prepared Orodispersible tablets were subjected to in vitro dissolution studies using an 8 station USP (TYPE II) dissolution apparatus (Electro Lab, TDT-O8L, Mumbai). The

dissolution studies were carried out in 900 mL of 0.1N HCl at $37 \pm 0.50^\circ\text{C}$. The speed of the paddle was set at 50 rpm. Sampling was done every 3 minutes interval. For each sample, 5 mL of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. The samples withdrawn were analyzed in the UV spectrophotometer at 267 nm.

2.4.10. Stability studies

The optimized formulation was subjected for two month stability study according to ICH guidelines. The selected formulations were packed in aluminum foils, which were closed tightly in wide mouth bottles. They were then stored at Room

Temperature $40^\circ\text{C} / 75\% \text{RH}$ for 2 months and evaluated for their permeation study [12].

2.4.11. FTIR studies

Pure drug, and optimized formulation (F4) were subjected for FTIR analysis using Fourier transformer infrared spectrophotometer (8600, Shimadzu Corporation, Japan). The samples were prepared on KBr-press (Spectra Lab, India) and scanned over wave number range of 4000 to 400 cm^{-1} . Spectra were analyzed for drug polymer interactions and functional groups.

Table 1. Composition of orodispersible tablets of Lamotrigine.

No	Drug	Mannitol	Cross Povidone	Explotab	MCC	Corn Starch	Magnesium Stearate	SLS	Vanilla
	mg	mg	Mg	Mg	Mg	mg	Mg	mg	Mg
F1	50	37	2	–	–	1	1	3	6
F2	50	33	6	–	–	2	1	3	6
F3	50	37	–	2	–	1	1	3	6
F4	50	33	–	6	–	2	1	3	6
F5	50	37	–	–	2	1	1	3	6
F6	50	33	–	–	6	2	1	3	6

* MCC : Micro crystalline cellulose; SLS: Sodium lauryl sulphate

3. RESULTS SECTION

3.1. Evaluation of Micrometric Properties of precompression powder blend

The micrometric properties of precompression powder blend such as of bulk density, tapped density, Angle of repose, compressibility index, Hausner's ratio were studied. The overall results were shown in Table 2. The value of bulk densities and tapped densities of various formulation were found to be in the range of 0.39 to 0.51 (g/mL) and 0.45 to 0.60 (g/mL) indicates good packing characteristics. The Hausner's ratio of the powdered was in the range of 1.13 to 1.25 and the compressibility index (Carr's Index) of the formulation fall in the range of 12% to 16% shows excellent flow properties of granules which were further confirmed by determining the angle of repose, it is in the range of 25° to 27° which indicates good flow properties.

3.2. Tablets evaluation

The results for tablets evaluation are given in Table 3. As the results obtained from Table 2 indicate that the material was free flowing, tablets were obtained of uniform weight due to uniform dye filling and appropriate punch size. Hardness of tablets was between 3.5 - 4.0 kg/cm^2 for all the formulation, showing optimum hardness for orodispersible tablet. The thickness was found in the range of 2.10 - 2.14 mm . The test for friability of all the tablets formulation lies in the range of 0.16 - 0.32% which shows good mechanical resistance of the tablet. The weight variation study shows that there was uniform distribution of the drug in tablets of all formulation and were in the range of 98 ± 1.5 - $103 \pm 3.6\%$. The drug content was found to be 98.26 - 99.87% which was within the acceptable limits.

The most important parameter for orodispersible tablets is the disintegration time and wetting time. Wetting time is related to

core material of tablet and hydrophobicity of components. Wetting time is used as an indication the ease of tablet disintegration in oral cavity. There is good relation between wetting time and disintegration time. The disintegration time is shorter with quick wetting properties at the core of tablets. The wetting time/dispersion time decreases with increase in the concentration of superdisintegrants. It was observed that as the concentration of superdisintegrants increases disintegration time decreases. Explotab when came in contact with water it quickly wicks water into the tablet through capillary action to create internal pressure that disintegrates tablet. MCC and Cross Povidone with longer wetting time result in slower disintegration of tablets.

3.3. FTIR studies

The FT-IR spectra of pure drug and optimized formulation (F4) were taken for the characterization studies Figure 1-2 The comparison of the IR spectrum of the formulation F4 with that of pure drug revealed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. There was no chemical interaction between drug and excipients.

3.5. In vitro release study

The *in vitro* dissolution characteristics of Lamotrigine orodispersible tablets are shown Figure 3. Based on the In vitro release profile of drug formulations of F1 to F6, the formulation TF4 a showed better drug release, which was achieved by increasing the concentration of the superdisintegrant Explotab. The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium. Hence formulation F4 was selected for further stability studies.

3.6. Stability Studies

The selected formulation F4 was subjected to accelerated stability studies for 60 days at Room Temperature 40°C / 75% RH, in vitro permeation study was performed on every week and showed negligible change in permeation profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content as shown in Figure 4.

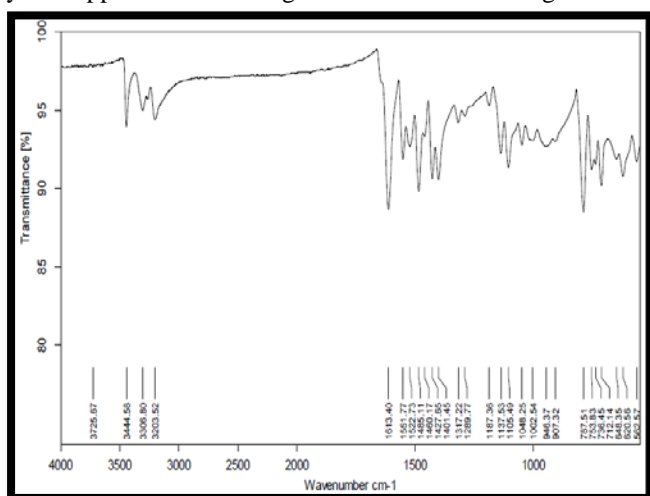


Figure 1. FTIR spectra of Lamotrigine.

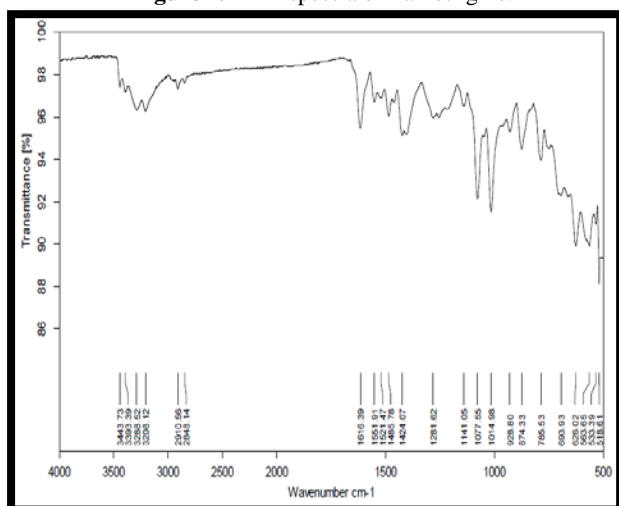


Figure 2. FTIR spectra of formulation F4.

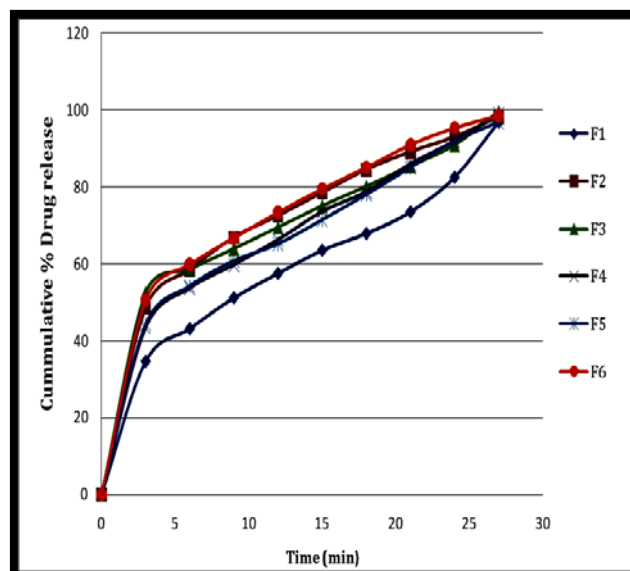


Figure 3. In vitro dissolution profile of formulation F1 to F6.

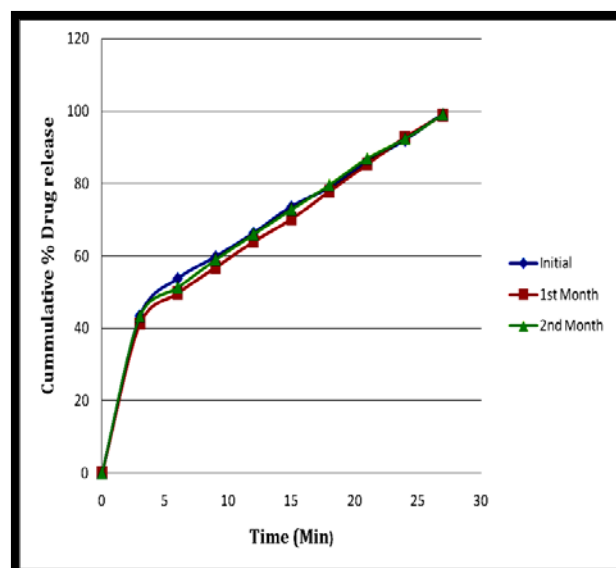


Figure 4. In vitro dissolution and assay profile for stability test F4.

Table 2. Characterization of precompression powder blend.

Batch no	Angle of repose (θ)	Bulk density(g/mL)	Tapped density(g/mL)	Carr's Index (%)	Hausner's ratio
F1	26.11	0.3976	0.4506	13.32	1.13
F2	25.67	0.4328	0.5410	12.54	1.25
F3	29.94	0.4473	0.5244	17.23	1.17
F4	24.62	0.5189	0.6020	16.01	1.16
F5	27.55	0.4983	0.5750	15.39	1.15
F6	22.67	0.4500	0.5464	21.42	1.21

Table 3. Evaluation parameters of the prepared Lamotrigine FDT.

Batch no	Hardness (kg/cm ²)	Friability (%)	Weight variation (mg)	Thickness (mm)	Wetting time(sec)	Drug content (%)	Dispersion Time (sec)	Disintegration Time (sec)
F1	3.5	0.20	98±1.5	2.13	30	98.45	42	29
F2	3.6	0.28	99±0.3	2.12	28	99.5	38	25
F3	4.2	0.16	98±0.3	2.11	31	99.26	39	27
F4	3.2	0.19	100±0.8	2.10	24	99.87	35	23
F5	3.8	0.32	100±0.9	2.14	30	98.81	43	30
F6	4.0	0.25	103±3.6	2.11	29	98.26	37	24

4. CONCLUSIONS

The study demonstrates shows the preparation of orodispersible Lamotrigine tablets containing its solid dispersion by using mannitol as a carrier. The polymer and superdisintegrant used in the solid dispersion and its concentration had significant

effect on the *in vitro* dissolution of the drug. The formulated tablets showed rapid *in vitro* drug dissolution and dissolution efficiency within 27 min. The developed tablets will be therefore able to produce a rapid onset of drug action with reasonable cost.

5. REFERENCES

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