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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF LAMOTRIGINE USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

The objective of the presented research work was to develop and evaluate fast-dissolving oral film containing solid dispersion of lamotrigine (LM) for improvement of its water solubility, dissolution and oral bioavailability by avoiding the first pass metabolism, providing faster onset of action and avoidance of problem of seizures. First, physical mixture, solid dispersion (SDP) of LM were prepared with PEG 4000, PVP K-90 (as hydrophilic polymeric carrier) in 1:1, 1:2 and 1:3 by using conventional method. The prepared SDP were analyzed for all the physical parameters, drug: carrier interactions like FTIR. Solid dispersions showed a better solubility compared to the pure drugs and among all the other formulations 1:3 ratios shows high % enhancement of solubility i.e. 270.52% and therefore 1:3 ratios were found to be superior and were used for further formulation development. Oral fast dissolving films prepared by solvent casting method using water and 95% ethanol as solvents and HPMC as film forming polymer. PEG 400 was the selected plasticizers, Superdisintegrants such as croscarmellose sodium (CCS) and sodium starch glycolate (SSG) alone and also in combinations was incorporated to achieve the aim. The prepared films were evaluated for the drug content, weight variation, film thickness, disintegration time, folding endurance, percentage of moisture content and *in vitro* dissolution studies. Among all, the formulation F3 was found to be best formulation which releases 96.65±0.65% of the drug within 15 min and disintegration time is 1.37 min. which was significantly high when compared to other formulation. Stability studies were carried out for optimized formulation F3 at 40±2^{o}C temperature and 75±5% relative humidity for a period 3 months. The % assay of film was found to slightly decrease at higher temperature. Based on the results, it was concluded that fast-dissolving oral film contained SDP of drug may provide the merits of faster onset of action, avoidance of extensive first-pass metabolism, enhanced bioavailability, and improved patient compliance for the delivery of poorly water-soluble drug such as lamotrigine.

Key words: Epilepsy, Lamotrigine, Solid dispersion, Oral fast dissolving film, Superdisintegrants.

INTRODUCTION:

Lamotrigine (LM) is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder (Barbosa *et al.*, 2003). 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 also acts as a mood stabilizer (Rogawski and Löscher, 2004). LM is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). Common oral dosage is 25mg/day (dose/solubility ratio ≥250 ml; class II drug according to the Biopharmaceutics Classification System). 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. Delivery of poorly water-soluble drugs by the oral route has been difficult due to insufficient amount of drug dissolved for absorption from the gastrointestinal tract (Teofilo *et al.*, 2007). Although, there are number of formulation strategies have been employed to enhance the dissolution rate of poorly soluble drugs such as particle size reduction, modification of crystal habits, salts formation, complex formation with cyclodextrin, use of surfactants, solid dispersions (SDP), fast-dissolving oral films (FDFs), lipid-based formulations, and prodrug approaches (Shah *et al.*, 2008; Siddiqui *et al.*, 2011). Preparation of SDP is a better approach for improving drug solubility because it is easier to produce and more applicable SDP (Park, 2014; Srinarong *et al*., 2010; Yin *et al*., 2012) refer to a system in which hydrophobic drug is dispersed in a hydrophilic matrix, in order to improve its dissolution properties and bioavailability. In SDP, a drug can exist in an amorphous or crystalline form in hydrophilic polymeric ca 2011rriers (Shah et al., 2010; Shah et al., 2009) such as polyethylene glycols (PEG), polyvinyl pyrrolidine K30 (PVP K30), urea, etc., which results in improved solubility and dissolution rates. Fast-dissolving dosage forms were initially prepared for providing substitute to conventional solid dosage forms to achieve better patient compliance (Naziya *et al.*, 2013). In addition, fast-dissolving oral films (FDFs) showed a great potential over other dosage forms for the delivery of poorly soluble drugs since they provide distinct advantages including rapid disintegration and dissolution in the oral cavity thus increase bioavailability with faster onset of action and avoidance of first-pass effect (Figueroa *et al*., 2012). Due to

high permeability of oral mucosa, it allows direct access of drug to the systemic circulation and avoids the first pass metabolism (Chaudhary *et al.*, 2013). FDFs represent an advantageous dosage form, especially for geriatric and pediatric patients (Choudhary et al., 2012; Cilurzo et al., 2010).

MATERIALS AND METHODS

Materials

Lamotrigine was obtained as a gift sample from Aurobindo Pharma Limited, Hyderabad. HPMC was procured from Qualikems fine chem Pvt Ltd Vadodhara. PEG400, sodium starch glycolate, croscarmellose sodium was obtained from S.D fine chemicals limited, Mumbai. Citric acid, ethanol was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid, KH_2 PO_4, NaoH was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Standardization of lamotrigine by UV-Visible spectrophotometry

Preparation of stock solution: Stock solution 1000µg/ml LM was prepared in phosphate buffer pH 6.8 solutions. This solution was suitably diluted with buffer solution to obtain a concentration of 10µg/ml. The resultant solution was scanned in the range of 200-400 nm using UV double beam spectrophotometer (Labindia 3000+, Mumbai).

Standard calibration of *lamotrigine*: From stock solutions of LM 1 ml was taken and diluted up to 10 ml. from this solution 0.5, 1.0, 1.5, 2.0 and 2.5 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with Phosphate buffer pH 6.8, gives standard drug solution of 5, 10, 15, 20, 25µg/ ml concentration, absorbance was measured at 224nm.

Optimization of drug: polymer ratio

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method.

Preparation of physical mixture

All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixtures of drug with carrier PEG 400 and PVP K-90 was prepared in different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 400 and drug: PVP K-90 ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 85 and was stored in desiccator for 2-6 hrs to carry out further

analysis. The prepared physical mixture was subjected to spectrophotometric method.

Preparation of solid dispersion of LM

For the preparation of lamotrigine-PEG 400 and lamotrigine-PVP K-90 solid dispersion by conventional method, PEG 400 and PVP K-90 was weighed and melted at 58°C (±1°C) and a measured amount of Lamotrigine was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 10mg of lamotrigine - PVP K-90 powder (containing 10mg of Lamotrigine and 30mg of PVP K-90) and was used for further investigations. Percentage solubility enhancement given in Table 1

Table 1 Results of % solubility enhancement

S. No.	% solubility enhancement						
	Drug: PEG 400			Drug: PVP K-90			
Absorbance	1:1	1:2	1:3	1:1	1:2	1:3	Pure Drug
	0.133	0.148	0.225	0.243	0.200	0.257	0.095
% Solubility Enhancement	140.00	155.78	236.84	255.78	210.52	270.52	----

Formulation development of oral film of LM

Solvent casting technique

Drug (lamotrigine) containing fast dissolving films were fabricated by the solvent casting method (Senthilkumar and Vijaya, 2015). The optimized amount of HPMC was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm * 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use. Formulations were prepared using HPMC K15, PEG-400, SSG and CCS at different drug: polymer ratios. The compositions of the formulations were shown in table 2.

Table 2 Formulation of Lamotrigine oral fast dissolving films

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
API Equivalent to 300 mg	480	480	480	480	480	480
HPMC	400	600	800	400	600	800
Glycerin	-	-	-	-	-	-
PEG-400	100	100	100	100	100	100
SSG	100	150	200	-	-	-
CCS	-	-	-	100	150	200
Aspartame	25	25	25	25	25	25
Citric acid	50	50	50	50	50	50
DM water qs to (ml)	30	30	30	30	30	30

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 films present whole plate = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug = 25×12 = 300mg
- The amount of drug added in each plate was approximately equal to 300mg.

Evaluation

The formulations were evaluated by the following tests [Kumar et al., 2005; Nagar et al., 2012; Prabhu et al., 2012; Nafee et al., 2003).

Thickness

Randomly 10 films were selected and thickness was measured using vernier calliper at three different places.

Weight variation

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Drug content analysis

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 224nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work. The film of (4.15cm^2) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.

In vitro dissolution study

The *in vitro* dissolution test was performed using the USP dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5°C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Lamotrigine was determined using UV-Visible spectrophotometer at 224nm. The results were presented as an average of three such concentrations.

Stability studies

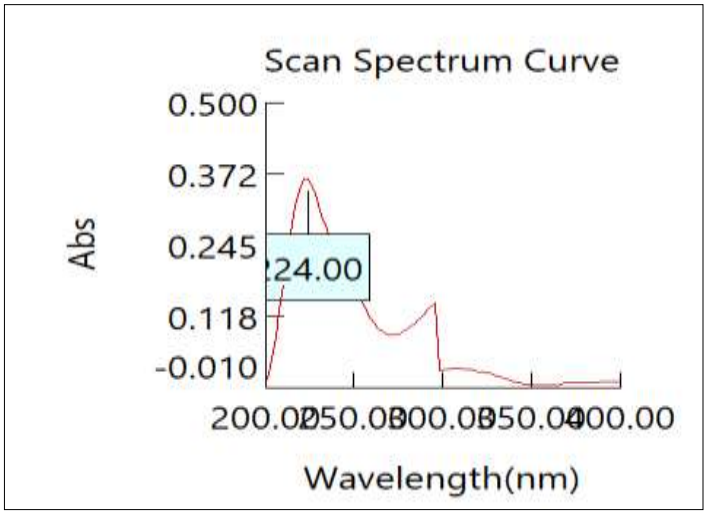
Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2^{o}C temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method.

RESULTS AND DISCUSSION

Solubility of LM was freely soluble in 0.1 N NaOH, sparingly soluble in 0.1N HCl, water and chloroform, soluble in methanol/ ethanol, slightly soluble in 6.8 pH phosphate buffers. λ_{max} of LM was found to be 224 nm by using U.V. spectrophotometer (Labindia-3000+). The calibration curve of olanzapine was found to be linear in the concentration range of 5-25µg/ml at 224 nm Fig. 1& 2. The general appearance, assay, weight variation and thickness of all the films were within acceptable limits Table 3. The results for tensile strength, folding endurance, disintegrating time and % of moisture were shown in Table 4. Tensile strength value of optimized formulation (F3) was 0.754±0.074kg/cm^2 and folding endurance was more than 100. The formulations containing

SSG were showing good results compared to CCS. The assay values of all the formulations were ranging from 95.65±0.32to 99.45±0.25%. The disintegration time was ranging between 1.37±0.15 to 2.45±0.14 min. The final formulation shows better drug release (96.65±0.65%) compared to other formulation within 15 min (Table 5). Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2ºC temperature and 75±5% relative humidity for a period 3 months. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time Table 6.

Figure 1 Determination of λ_{max} of LM



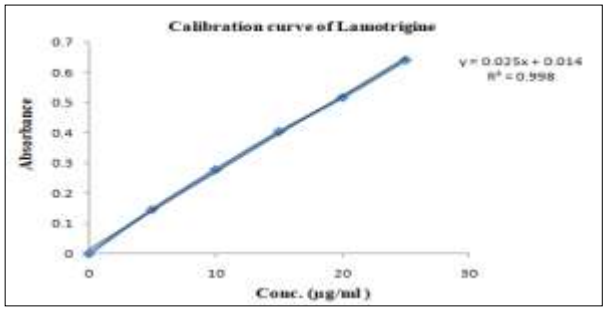


Figure 2 Calibration Curve of LM in Phosphate buffer pH 6.8 at 224 nm

Table 3 Result of general appearance, thickness, weight variation and % assay

Formulation code	General Appearance	Thickness (µm)	Weight (mg)	(%)Assay
F1	Translucent	110±2	173±4	98.56±0.32
F2	Translucent	115±5	175±5	97.85±0.45
F3	Translucent	120±4	188±4	99.45±0.25
F4	Translucent	119±6	165±2	98.45±0.56
F5	Translucent	123±4	175±3	96.65±0.41
F6	Translucent	125±3	169±4	95.65±0.32

Table 4 Result of folding endurance, disintegrating time, tensile strength &% of moisture content

Formulation code	Folding endurance	Disintegration time (min.)	Tensile strength (kg/cm^2)	Moisture Content (%)
F1	145±4	2.25±0.25	0.665±0.045	1.45±0.25
F2	148±6	2.10±0.21	0.632±0.065	1.32±0.32
F3	165±2	1.37±0.15	0.754±0.074	0.65±0.12
F4	165±4	2.56±0.20	0.658±0.032	1.22±0.15
F5	178±5	2.45±0.14	0.678±0.041	1.36±0.21
F6	165±6	2.32±0.11	0.710±0.025	1.41±0.32

Table 5 Results of *In-Vitro* release study of optimized formulation F3

S. No.	Time (Min.)	Cumulative % Drug release
1.	1	32.25±0.45
2.	2	49.87±0.32
3.	5	65.58±0.48
4.	10	88.98±0.45
5.	15	96.65±0.65

Table 6 Characterization of stability study of optimized film (F3)

Characteristic	Time (Month)			
	Initial	1 Month	2 Month	3 Month
% Assay*	99.12±0.12	98.95±0.23	98.23±0.45	98.12±0.32

***Average of three determinations (n=3)**

CONCLUSION

Preparation of SDP of the lamotrigine using conventional method with PVP-K30 up to 1:3 (drug to polymer ratio) found to remarkably increase the aqueous solubility of lamotrigine. Results of evaluation parameters of optimized and validated lamotrigine oral fast dissolving films revealed good mechanical strength, uniformity of content, optimum surface pH, faster disintegration time, almost complete drug dissolution or release and good stability up to three months. Thus it can be concluded that lamotrigine fast dissolving films could be commercially exploited for the treatment of seizures using lamotrigine with merits of faster onset of action, avoidance of extensive first pass metabolism, low dosage regimen, enhanced bioavailability and improved patient compliance.

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