ISSN 2581 – 4303

Available Online at www.ijpba.info
International Journal of Pharmaceutical & Biological Archives 2018; 9(3):151-156

RESEARCH ARTICLE

Formulation and Evaluation of Controlled Release Tablet of Lamotrigine

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Received: 25 May 2018; Revised: 27 June 2018; Accepted: 20 July 2018

ABSTRACT

Controlled drug delivery can be defined as delivery of the drug at a predetermined rate and/or to a location according to the needs of the body and disease states for a definite time period. Controlled release drug administration means not only the prolongation of the duration of drug delivery, similar to the objective in sustained release and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. Oral controlled release drug delivery system is one that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a pre-determined period throughout the course of GI transit.

Keywords: Controlled release tablet, lamotrigine, mixed solvency, solid dispersion

INTRODUCTION

Together with the permeability, the solubility behavior of drug is a key determinant of its oral bioavailability. There have always been drugs for which solubility has presented a challenge for the development of a suitable formulation for oral administration. Solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for a desired pharmacological response. At present, only 8% of new drug candidates have high solubility and permeability. The aqueous solubility of drugs is often a limiting factor in developing the most desirable dosage forms.

Product development scientists often encounter significant difficulties in solving the problem of poor water solubility of drug candidates in the development of pharmaceutical dosage forms. Slow absorption rate results in an erratic and variable profile of drug level. As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility. Water insolubility can postpone or completely halt new drug development and can prevent the much-needed reformulation of currently marketed products.

Solubility

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature, and in the qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent.

Mixed solvency approach[3]

Melted PEG-4000, PEG-6000, PEG-8000 (temperature <100°C), and melted urea (M.P.: 132-135°C) dissolves diclofenac sodium (M.P.: 283°C). This shows that melted PEGs and urea act as a solvent for diclofenac sodium. Melted ibuprofen (M.P.: 78°C) dissolves diclofenac sodium (M.P.: 283°C), salicylic acid (M.P.: 159°C), and niacinamide (M.P.: 132°C) which again shows that melted ibuprofen acts as a solvent for diclofenac sodium, salicylic acid, and niacinamide, respectively.

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Additives may either increase or decrease the solubility of a solute in a given solvent. The
effect of an additive depends very much on the influence; it has on the structure of water or its ability to compete with the solvent water molecules.

Maheshwari proposed the concept of mixed solvency. He is of the opinion that all substances have solubilizing power and all substances whether liquids, solids, or gases may enhance the solubility of poorly water-soluble drugs. It is the increase in solubility of poorly soluble drugs by the addition of more than one solubilizing agent. Use of these agents in combination may enhance the solubility of poorly soluble drugs by the miraculous synergistic effect in addition to the additive effect.[2]

Solid dispersion[6]

Definition of solid dispersions[7]

Dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method.

A solid dispersion is a system in which the concentration of the drug is in excess of its saturation solubility at room temperature. The excess drug separates as a solid phase which is dispersed in the vehicle in crystalline or amorphous forms.

The advantageous properties of solid dispersions

1. Particles with improved wettability- a strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability.
2. Particles with higher porosity - the increased porosity of solid dispersion particles also hastens the drug release profile.
3. Drugs in the amorphous state - poorly-water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state because no energy is required to break up the crystal lattice during the dissolution process.

Methods for preparing for solid dispersion[8]

Hot melt method

In this method, the drug is mixed with the carrier and heated slightly above the melting point of the highest melting solid until a clear liquid is formed. The liquid is allowed to solidify and subsequently pulverized into a powder of a particular sieve size range usually 125–250 IM. The method is advantageous for compounds which do not undergo significant thermal degradation.

The main disadvantages of the melt method are thermal degradation, sublimation, and polymeric transformation which can affect the physicochemical properties of the drug including its rate of dissolution.

Solvent method[4]

In this method, the drug and the carrier both are dissolved in a common solvent, and then the solvent is evaporated under vacuum to produce a solid solution. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods. The temperature used for solvent evaporation usually lies in the range of 23 + 6.5°C. The solvent can also be removed by freeze-drying.

Hydrotropic solid dispersion[9]

This method is similar to the common solvent method. The only difference is that here hydrotropic solubilization technique is employed to solubilize the poorly water-soluble drugs. There are various hydrotropic agents that can be used as a hydrophilic career for the hydrotropic solid dispersion. At first, a concentrated solution of the hydrotropic agent is prepared in water by the application of heat. The drug is added to this clear and concentrated solution with the aid of stirring or any other type of mechanical agitation and solvent; water is removed simultaneously by slight heating. When this converted to very viscous mass, it is dried in an oven at about 60°C. Then, it is triturated and passed through the desired sieve. The disadvantage of this technique is only that it cannot be applied to heat labile drugs.

Maheshwari prepared a hydrotropic solid dispersion of paracetamol a poorly-water soluble drug employing urea as a hydrotropic agent. Here urea played the role of hydrotrope as well as water-soluble career, so it precludes the use of organic solvent in the process. This formed hydrotropic solid dispersion showed a marked increase in dissolution rate of paracetamol.

Method of preparation[10]

Preparation of calibration curve in ethanol, methanol, and demineralized water

50 mg of lamotrigine was accurately weighed and transferred to 100 mL volumetric flask. The drug was dissolved by addition of 20 mL methanol, ethanol, and demineralized water, and volume was made up to 100 mL with methanol, ethanol, and demineralized water so as to obtain a stock solution of 500 Ig/mL. Appropriate dilutions from the stock solution were made with methanol, ethanol, and demineralized water in the concentration range of 10–50 Ig/ml. The absorbances of the resulting drug solutions were observed at 306 nm against the reagent blank (methanol). The data are recorded in Table 1 and Table 2 graphically represents in Figure 1 and Figure 2.

Preparation of solid dispersion of lamotrigine[8]

For the preparation of solid dispersions, accurately weighed polymer mixture consisting of Eudragit RS, RL, and PVP K-30 was dissolved in absolute ethanol to get a clear solution. The quantity of PVP K-30 and total amount of Eudragit (Eudragit RS + Eudragit RL) was kept constant in which Eudragit RL was varied from 10% to 50%. Accurately weighed amount of drug was dissolved in the polymer solution and stirred on a magnetic stirrer at room temperature for 4–6 h. After evaporation of solvent, the residue was transferred to a glass plate and dried in an oven at a temperature of 50°C for 24 h. After complete drying, solid dispersions were crushed and triturated using a glass pestle mortar and passethroug# 60 and stored in a closed glass container.

In tablets, the amount of solid dispersion (300 mg), talc (3 mg), and Aerosil (3 mg) was kept constant 7.2.6. Preparation and evaluation of lamotrigine controlled release tablet formulation (optimization batches).

The solid dispersion blend of lamotrigine was compressed into a tablet using 10 mm flat punches on a single punch tablet machine (Pharmaceutical Machinery Mfg. Works) and evaluated for following parameters: Weight variation, hardness, friability, assay, and *in vitro* drug release profile. The results of these tests are reported in Tables 2 and 3.

Evaluation of micromeritic properties of solid dispersion

- Bulk density
- Tapped density
- Compressibility index (CI)
- Hausner's ratio
- Angle of repose

Bulk density[1]

Accurately weighed, 5 g solid dispersion was filled in a 50 mL graduated cylinder and its unsettled volume after three tapping from 1 inch height, V_i

Table 1: Absorbance data for calibration curve of lamotrigine in methanol at 306 nm

Concentration (µg/mL)	Absorbance
0	0
10	0.286
20	0.546
30	0.845
40	1.139

Table 2: Absorbance data for calibration curve of lamotrigine in demineralized water at 306 nm

Concentration (Pg/mL)	Absorbance
0	0
10	0.241
20	0.483
30	0.727
40	0.981
50	1.271

Table 3: Relationship of compressibility index (CI) and Hausner's ratio with powder flow[1]

% Compressibility	Hausner's ratio	Flowability
<10	1.00–1.11	Excellent
11–15	1.12–1.18	Good
16–20	1.19–1.25	Fair to
21–25	1.26–1.34	Passable
26–31	1.35–1.45	Poor
32–37	1.46–1.59	Very poor
>38	1.60	Very, very poor

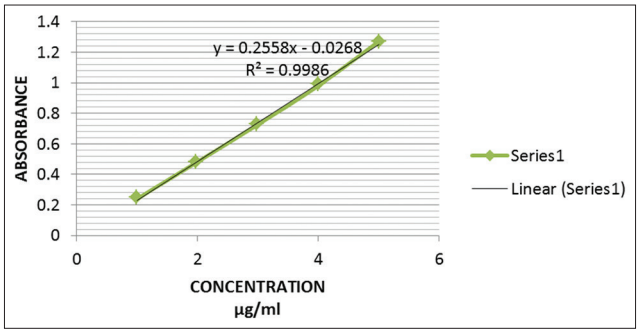

Figure 1: Calibration curve of lamotrigine in methanol at 306 nm

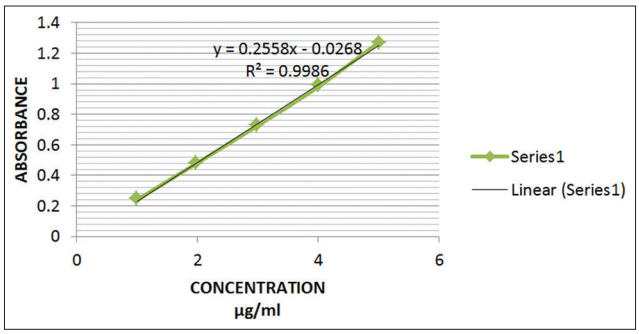

Figure 2: Calibration curve of lamotrigine in deminreized water at 306 nm

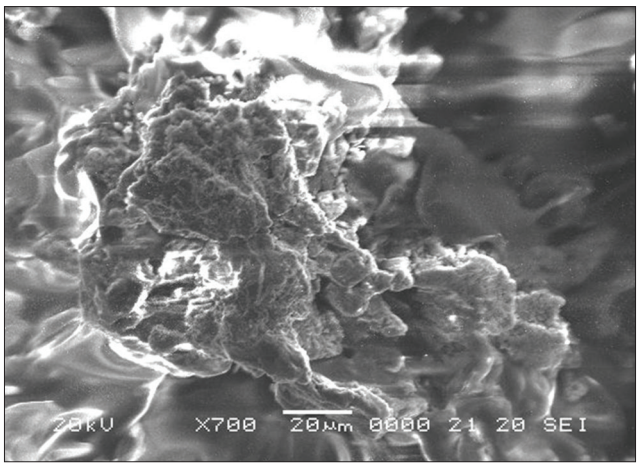

Figure 3: Scanning electron microscopy photograph of lamotrigine drug sample

was noted. The bulk density was calculated by the following formula.

Bulk density (D_o) (in g/cc) = M/V_i

Where, M = Mass of powder taken (in g), V_i= Apparent volume (in cc).

***Tapped density*[10]**

Accurately weighed, 5 g solid dispersion was filled in a 50 mL graduated cylinder. The cylinder was manually tapped on a wooden surface for 500 times, and the tapped volume V_i was noted. Tapping was continued further for an additional 750 times and the tapped volume, V_f was noted. The difference between the two tapping volumes was <2%, so V_f was considered as a tapped volume. The tapped density was calculated by the following formula.

Tapped density (D_f) (in g/cc) = M/V_f

Where, M = weight of sample powder taken (in g), V_f = Final tapped volume (in cc)

***CI and Hausner's ratio*[1]**

The CI and Hausner's ratio are measures of the propensity of the powder to be compressed. Carrs index is the measures of inter-particulate interactions. In a freely flowing powder, such interactions are less significant and bulk densities and tapped densities are closer in value. For a poorly flowing powder, there are frequently greater inter-particulate interactions and therefore a greater difference in the bulk density and tapped density.

Hausner's ratio = Vi/Vf

***Angle of repose*[1]**

A glass funnel was held in place with a clamp on ring support over a plate. The height of the funnel through which the solid dispersion blend was passed, fixed relative to the base. Approximately 5 g of solid dispersion blend was transferred into the funnel. The powder was allowed to flow from the funnel. The height of the pile and the radius of the base (r) were measured. The angle of repose was calculated using the following formula.

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

Where, h = height of pile, r = radius of the base of the pile, θ = angle of repose.

Preparation and evaluation of lamotrigine controlled release tablet formulation

The solid dispersion blend of lamotrigine was compressed into tablet using 10 mm flat punches on a single punch tablet machine (Pharmaceutical Machinery Mfg. Works).

Preliminary trial batches of controlled release tablet formulation were evaluated for following parameters.

- Weight variation
- Hardness

- Friability
- Assay
- *In vitro* release profile

Weight variation[5]

A total of 20 tablets were individually weighed and then their average weight was calculated. The average weight was compared with the individual tablet weights, and the weight variation was calculated.

Hardness[1]

The hardness of the prepared tablets was determined using Monsanto tablet hardness tester.

Characterization of solid dispersion (predicted optimized formulation)

Powder X-ray diffraction studies

The powder X-ray diffraction spectra of lamotrigine prepared solid dispersions and the physical mixtures were obtained using RU-H3R, Horizontal Rotaflex rotating anode X-ray generator instrument, and Rigaku (Rigaku International Corporation, Tokyo). The sample was spread on a graticule and pressed in such a way that sample did not fall on keeping the graticule in a vertical position. The graticule was placed in the sample holder and exposed to CuKα-radiation (40 KV and 50 MA), 2θ = 50–500 at a scanning speed 30/min and step size 0.040 2θ. The X-ray diffractograms of lamotrigine, physical mixture, and solid dispersion so obtained.

The crystalline nature of the drug lamotrigine was clearly demonstrated by the characteristic XRD pattern with peak appearing at 12.21, 12.25, 13.60, and 13.64 2θ values. Furthermore, the XRD diffraction patterns of solid dispersion and physical mixture gave sharp and intense peaks and are thus easily comparable with that of lamotrigine. It is observed that the numbers of peaks in case of solid dispersion are less than in physical mixture. Furthermore, there is a reduction in the intensities of the characteristic peaks in case of solid dispersion. This suggests that the degree of amorphousness in solid dispersion is more.

Scanning electron microscopy (SEM)[11]

SEM was used to investigate solid state physical structure of the prepared solid dispersion. SEM photographs of lamotrigine, its physical mixture with solubilizing agents and its solid dispersions were obtained using a scanning electron microscope model JEOL JSM 5600 with accelerating voltage from 0.5 to 30 KV. SEM photographs are shown in Figure 3.

SEM photographs of pure lamotrigine in Figure 3 show characteristic shaped structures, indicating the crystallinity of lamotrigine. These characteristic shaped structures can also be seen along with other structures of solubilizing agents in photographs of the physical mixture in Figure 3. However, in photographs of solid dispersion, there are no distinguishable characteristic shaped structures of lamotrigine in Figure 3. This suggests the total miscibility of lamotrigine within the carrier.

In vitro release profile

The *in vitro* drug release studies of the tablets were performed using a dissolution test apparatus (USP 24 Type II, Model TDT6P) with the peddle rotating at 50 rpm in dissolution media maintained at 37±0.5°C. The dissolution media used were 0.1 N HCl/pH 6.8 buffer (1000 mL). The media were 750 mL of 0.1 N HCl for 2 h then for the remaining intervals 250 mL of trisodium phosphate buffer was added to adjust the pH to 6.8. 10 mL aliquots of dissolution media were withdrawn at suitable time intervals and replaced with the same volume of fresh dissolution media after each withdrawal. Aliquots were filtered through Whatman filter paper no. 5

Table 4: Solubility of lamotrigine in different mediums

Solvent	Solubility (mg/mL)	Solubility (% w/v)	Description
Demineralized water	0.18	0.018	Very slightly soluble
0.1 N Hydrochloric acid (pH 1.2)	2.75	0.275	Very slightly soluble
Phosphate buffer (pH 6.8)	0.36	0.036	Very slightly soluble
Ethanol	0.59	0.059	Very slightly soluble

and then the absorbance of samples was measured at 306 nm (267 nm in case 0.1 N hydrochloric acid) against the corresponding reagent blank.

RESULTS

The solubility studies of lamotrigine were carried out in demineralized water, 0.1N hydrochloric acid, ethanol and buffer (PH 6.8). The excess drug was added gradually to 5 mL of each solvent contained in 10 mL glass vials and shaken on a mechanical shaker (orbital flask shaker, Khara instrument Pvt. Ltd., Delhi) at room temperature for 12 h so that equilibrium solubility can be achieved and solutions were allowed to equilibrate for 24 h. Then, the solutions were transferred into centrifuge tubes and centrifuged at about 2000 rpm for 5 min and filtered through Whatman filter paper no. 5. Aliquots of the filtrate were suitably diluted. The diluted solutions were analyzed at 306 nm (267 nm in case 0.1 N hydrochloric acid) against the reagent blank. The results are recorded in Table 4.

CONCLUSION

The main aim of the present research study was to explore the possibility of employing the mixed-solvency technique in the formulation of a poorly water-soluble drug. Immediate release dosage forms of lamotrigine provide rapid dissolution results with a rapid increase in blood plasma levels after each dosing, which causes adverse effects. Lamotrigine exhibits a decrease in solubility with increasing pH. The second objective of the present research work was to formulate the solid dispersion of lamotrigine and to develop its controlled release tablet (to reduce the side effects). Tablet formulation comprises solid dispersion of lamotrigine with solubility modifiers and release controlling polymers, which would exhibit a significantly similar release rate throughout the GI tract, irrespective of the pH of the environment.
In the pre-formulation studies, solubilities of the drug were determined. The solubilities of lamotrigine in demineralized water, 0.1 N HCl, phosphate buffer of pH 6.8, and ethanol were found to be 0.018%, 0.27%, 0.036%, and 0.063%, respectively.

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