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Preparation and *in vitro* Evaluation of Polylactic Acid Microspheres Containing Lamotrigine

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The aim of this study was to prepare and evaluate polylactic acid microspheres containing lamotrigine. Microspheres were prepared by solvent evaporation method using methylene chloride solvent. The influence of formulation factors (stirring speed, polymer: drug ratio, stabilizer: drug ratio) on particle size, encapsulation efficiency and *in vitro* release characteristics of the microspheres were investigated. The yields of preparation and the encapsulation efficiencies were high for all formulations. Particle size changed by changing the polymer:drug ratio or the stirring speed of the system.

Key Words: Lamotrigine, Polylactic acid, Microspheres, Controlled release.

INTRODUCTION

In mental illness, the main cause of failure of oral dosage form is patient non-compliance. Drug adverse effects and pessimistic tendency about the likelihood of improvement of disease and difficulty in remembering the dose are the main reasons for not taking their medication. The other problems with oral conventional drug therapy are incidences for relapse with violence, suicide or extremely psychotic behaviour after withdrawal of anti psychotic drug. Lamotrigine is an antipsychotic drug and is used mainly in the management of mental illness and it is also used in the treatment of various forms of epilepsy[1,2]. Depot formulation can be the only way to solve all these problems. Such medication is very useful in overcoming the problem of patient non-compliance and minimizes the incidence and severity of adverse side effect as with oral tablet dosage form[3]. Microspheres are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability or stability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance[3,4].

Polylactic acid is a biodegradable polymer. It is nontoxic and its ultimate degradation product d-lactic acid is completely eliminated from the body. The polymer also possesses the strength and mechanical properties required for processing into a variety of forms, such as drug and capsulation and matrix systems[5].

The aim of this study is to prepare polylactic acid microspheres containing lamotrigine to achieve a controlled drug release profile suitable for parenteral administration. First, we investigate some formulation variables (polymer type, polymer: drug ratio, stirring speed) to obtain spherical particles. The yield of production, particle size distribution, encapsulation efficiency, surface properties and lamotrigine release rate from microspheres was then investigated. Later influences of formulation variables on the microsphere properties were examined, microsphere formulations suitable to achieve our goal were determined.

EXPERIMENTAL

Polylactic acid and lamotrigine were obtained from Torrent research center, Ahamdabad, India and polyvinylpyrrolidone was purchased from E. Merck (India) Pvt. Ltd. Other reagents and chemicals used were of analytical grade.

Solubility measurement: Lamotrigine in excess amount was added to 15 mL of dissolution medium (aqueous solution pH =7.2) in a 20 mL bottle maintained at 37 ± 0.5 ºC and shaken in a constant temperature water bath for 48 h. At appropriate time intervals samples of the solution were taken out from the bottle, filtered (0.45 µm pore size) and diluted to 100 mL. The samples were assayed spectrophotometrically (Shimadzu UV 160 A) for drug content at 268 nm. Calibration curve was used to determine the amount of drug dissolved.

Preparation of microspheres: Microspheres of lamotrigine drug were prepared by solvent evaporation technique[6,7].

Different amounts of polymer (180, 300, 420, 540 and 600 mg) of polylactic acid were dissolved in 10 mL of methylene chloride by using a magnetic stirrer. Powdered lamotrigine (60 mg) was dispersed in the polymer solution. The resulting dispersed solution was then poured into the mixture of different amounts of polyvinyl pyrrolidone (1.0, 1.5, 2.0, 2.5 and 3.0 g) and sodium chloride in 50 mL distilled water in a cylindrical vessel (10 cm inside diameter and 14 cm height) and a mechanical stirrer with a blade (6 cm diameter) (RW 20 DZM, IKA, Germany) for continuous stirring. The process was continued for 3 h, until methylene chloride evaporated completely. Polymer: drug ratio and stirring rate (2000 and 3000 rpm) of the system were changed to obtain spherical particles. After the complete evaporation of methylene chloride, the microspheres formed were collected by filtration through vacuum and washed 4-5 times with 50 mL distilled water and dried at room temperature for 24 h.

All microsphere formulations were prepared 3 times to check the reproducibility of the results.

Microspheres were dried at room temperature, weighed and the yield of microsphere preparation was calculated using the formula:

$$\text{Yield (\%)} = \frac{\text{Amount of microspheres obtained (g)}}{\text{Theoretical amount (g)}} \times 100$$

Shapes and surface characteristics of the microspheres were investigated and photographed using scanning electron microscope (SEM; Jeol JSM-6400, Japan). The particle size was determined by optical versamet-2 microscope, Union Optical Co. Ltd. The particle size distribution of the microspheres obtained from various formulations was also determined.

Entrapment efficiency of the microspheres: Microspheres were crushed and powdered by using a mortar and pestle. 100 mg of this powder was taken and extracted in 100 mL of methanol. The solution was filtered and an aliquot of 2 mL was withdrawn from this solution, diluted to 50 mL with methanol and assayed spectrophotometrically to determine the lamotrigine content of the microspheres.

***In vitro* release studies:** The dissolution rate of pure drug and the drug release rate from the microspheres were studied at pH 7.2 using the paddle method[8] under sink conditions. Accurately weighed samples of lamotrigine microspheres were added to dissolution medium and kept at 37 ± 0.5 °C. After particular time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. After suitable dilution, the samples were analyzed spectrophotometrically at 268 nm. The kinetics data obtained from release rates were also evaluated.

Statistical analysis: The data obtained from the particle size, encapsulation efficiency and release rate determination studies of lamotrigine microspheres were analyzed statistically with one-way ANOVA and t-test by using SPSS (Windows 9.0).

RESULTS AND DISCUSSION

Solvent evaporation method was used to prepare lamotrigine microspheres. Methylene chloride as a solvent, poly vinyl pyrrolidone as an stabilizer and sodium chloride was added to avoid leaching effect. Various formulations with different polymer: drug ratios and different stabilizer: drug ratio were tried, stirring speed was also changed to obtain spherical particles. When polymer: drug ratio was too low (1:1, w/w) no spherical particles were obtained (at 2000 and 3000 rpm). These results show that the amount of solid and viscosity of the inner phase play an important role in the preparation of microspheres. The increased amount of the polymer ensures the formation of spherical particles while the amount of the drug and volume of the solvent remains constant. However, when polymer: drug ratio was (10:1), the shapes of particles were irregular at 2000 rpm, because at this concentration of the polymer the stirring speed was not fast enough to disperse the inner phase. When the stirring speed was raised to 3000 rpm in the above polymer drug ratio (10:1) spherical particles with good surface characteristics were obtained. Two scanning electron micrographs of the microspheres prepared, are shown, using polymer: drug ratio 10:1 at 2000 rpm (Fig. 1) and at 3000 rpm (Fig. 2).

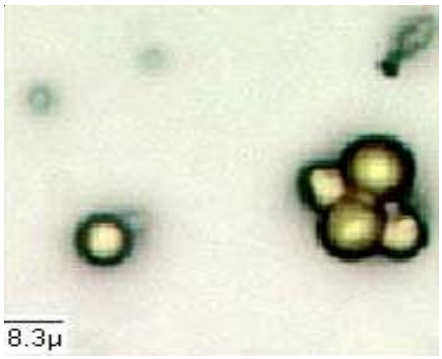

Fig. 1. Scanning electron micrographs of microspheres of formulation 5 at 2000 rpm

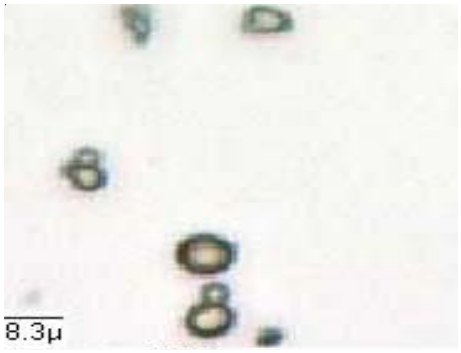

Fig. 2. Scanning electron micrographs of microspheres of formulation 5 at 3000 rpm

Effect of process variables on microsphere properties: Polylactic acid microspheres were prepared at different stirring rates (2000 rpm, 3000 rpm), with various polylactic acid: drug ratios (Table-1) and with stabilizing agent polyvinylpyrrolidone (PVP) at concentrations of 2, 3, 4, 5 and 6 % w/v, sodium chloride 5 % as leaching agent in the external phase (Table-2).

TABLE-1
VARIOUS POLYMERS:DRUG RATIO FOR THE FORMULATION OF MICROSPHERES

Polymer:Drug ratio	Formulation No
3:1	1
5:1	2
7:1	3
9:1	4
10:1	5

TABLE-2
DRUG ENTRAPMENT OF MICROSPHERES (FORMULATION NO 5) AT VARIOUS CONCENTRATION OF POLYVINYL PYRROLIDONE (PVP) SOLUTION

S. No.	Concentration of PVP solution (%)	% Drug loading
1	2	35.00
2	3	42.00
3	4	46.00
4	5	58.34
5	6	50.00

Drug entrapment of microspheres (formulation no 5) at 5 % concentration of PVP solution was found to be 58.35 % (Table-2 and Fig. 3). Dissolution studies were carried out for all the formulations (1-5) at pH 7.2. Formulation no 5 (drug: polymer ratio 10:1) showed 99 % release rate at 3000 rpm (Fig. 5) and 97 % release rate at 2000 rpm (Fig. 4).

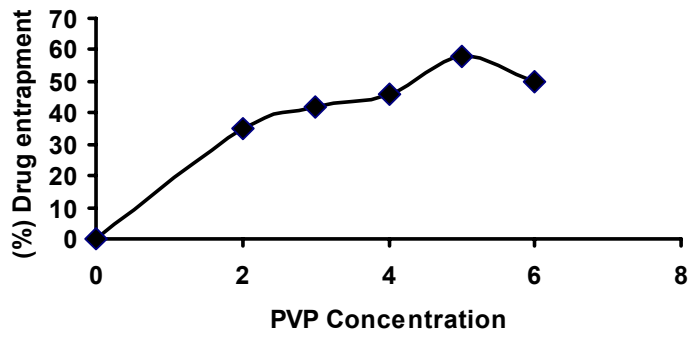

Fig. 3. Effect of PVP concentration on per cent drug entrapment

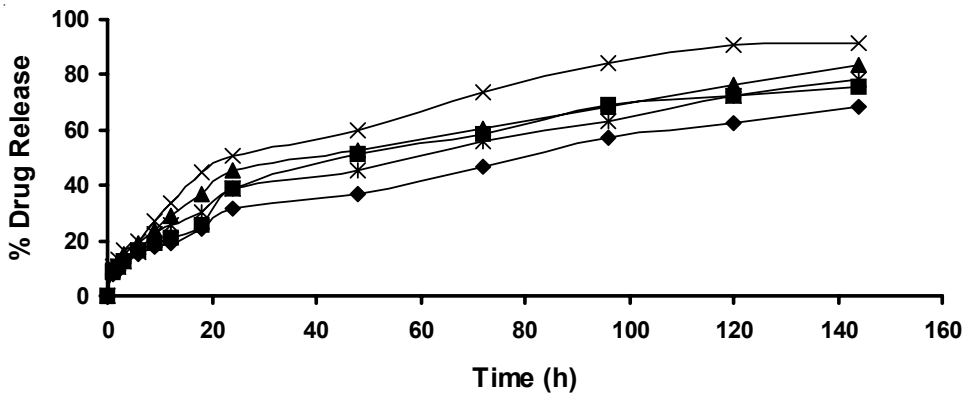

Fig. 4. *In vitro* release of formulation no's 1, 2, 3, 4 and 5 of lamotrigine from polylactic acid microspheres (pH 7.2) at 2000 rpm

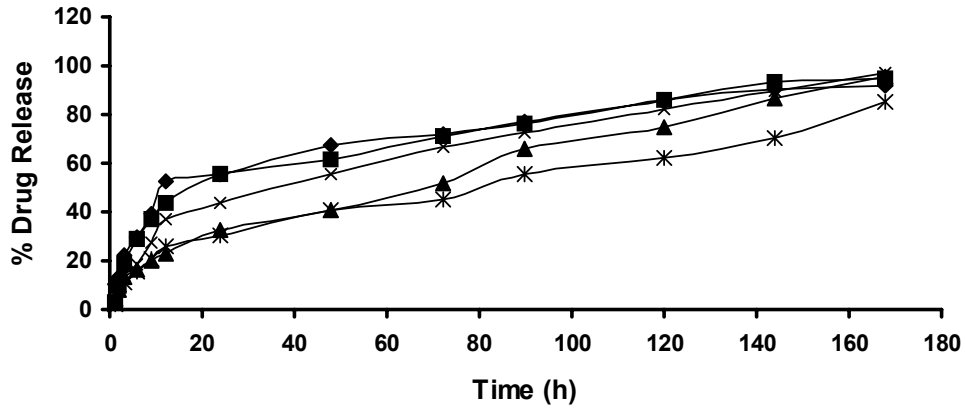

Fig. 5. *In vitro* release of formulation no's 1, 2, 3, 4 and 5 of lamotrigine from polylactic acid microspheres (pH 7.2) at 3000 rpm

Drug release rates from polylactic acid microspheres were affected by polymer: drug ratio, stabilizer: drug ratio and stirring speed of the system. The release rates of lamotrigine increased as polymer: drug ratio increased. As the concentration of PVP raised up to 5 %, the drug entrapment also increased. As the concentration of PVP was increased more than 5 %, the drug entrapment decreased due to the interaction of PVP with dichloromethane layer of polylactic acid.

The release rate increased as stirring speed increased. The release rate was approximate 97 % when stirring rate was 2000 rpm and it was increased to 99 % when stirring speed was 3000 rpm.

Conclusion

Lamotrigine microspheres were prepared successfully using solvent evaporation method. Polymer:drug ratio, stabilizer:drug ratio and stirring speed of the system were important to obtain spherical particles with smooth surfaces. The yields of preparation and encapsulation efficiencies were very high for all microspheres obtained. Changing the ratio of polymer, stabilizers and leaching agent (sodium chloride) the entrapment efficiency and release rate of lamotrigine was also affected. Microsphere formulation showing controlled release without initial peak levels was achieved. These microspheres can assure reduced dosing frequency, decreased side effects and better patient compliance.

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