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# PELLETIZATION OF LAMOTRIGINE SOLID DISPERSION FOR IMPROVED SOLUBILIZATION

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## ABSTRACT

Poorly solubility in water of many newly developed high-potential drugs is an obstacle in formulation development. The aim of this study was to increase the solubility of Lamotrigine which is a poorly soluble drug and comes under BCS class-II by using solid dispersion technique. Lamotrigine, PEG 4000 and PVPK-30 solid dispersion was prepared by solvent evaporation method and the formulation was characterized using stability studies, Fourier transform infrared spectroscopy (FTIR) and physical parameters. After checking the preformulation studies and getting satisfactory results pellets were formulated and evaluation was done. Drug entrapment efficiency was more than 98 % which indicates that the pellets formed are good possessing *in vitro* release of 94.89 & 92.30 % for $X_1$ & $X_2$ batches respectively.

**INTRODUCTION:** Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. It is not only existing drugs that cause problems but it is the challenge of medicinal chemists to ensure that new drugs are not only active pharmacologically but have enough solubility to ensure fast enough dissolution at the site of administration, often gastrointestinal tract [1].

It is estimated that 40% or more of new chemical entities (NCEs) being identified through combinatorial screening programs are poorly soluble in water, which is a critical determinant of oral bioavailability and solubility of many newly developed high-potential drugs is an obstacle in formulation development, in addition Biopharmaceutical Classification System (BCS) highlights dissolution as the rate-limiting step for oral absorption of class II and IV drugs [2].

Solubilization techniques include addition of a cosolvent, salt formation, prodrug design, complexation, particle size reduction, and the use of surface active agents, use of solvate and hydrates, polymorphs, hydrotrophy ,use of absorbents ,pH adjustment, solubilizing vehicles, etc. are the some other physico-chemical approaches to enhancing oral absorption of poorly water soluble drugs [1].

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs[1].Solid dispersions (SDs) traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs [3].

Lamotrigine is an antiepileptic drug which comes under BCS class II and causes lot of solubility problems. In order to increase the solubility of the drug solid dispersion was employed by using two polymers PEG 4000 and PVPK 30 and evaluation of solid dispersion mixture and pellets were formulated after getting satisfactory results.

In the present work, pellets of Lamotrigine were prepared by orifice-ionic gelation technique using

sodium alginate and calcium chloride. The formulated pellets of Lamotrigine were evaluated for the following parameters viz., particle size, entrapment efficiency, *in-vitro* drug release, rheology study, loose crystal surface [7].

**MATERIALS AND METHODS:** Materials: Lamotrigine drug was obtained as a gift sample from Cipla Ltd., and polyvinyl pyrrolidone, polyethylene glycol 4000, microcrystalline cellulose, lactose and methanol used were purchased from SD Fine Chemicals Ltd.

**Methods of preparation of Lamotrigine Solid Dispersion System:** Solid dispersions of Lamotrigine in PEG 4000, PVPK 30 were prepared with PEG 4000, PVPK 30, Lactose, Microcrystalline cellulose, as variables and maintaining the amount of Lamotrigine as constant. The methods used for the preparation of these solid dispersions was solvent evaporation method.[1]

**Solvent Evaporation Method:** The required amount of Lamotrigine and polymer and additives were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 45°C with continuous stirring to obtain dry mass. The dried mass was pulverized passed through 44 mesh sieve and stored in desiccator until used for further studies.

**TABLE 1: FACTOR & LEVELS IN THE DESIGN OF LAMOTRIGINE SOILD DISPERSIONS WITH TWO POLYMERS**

| Independent Variables | Ratio (2:2) | Ratio (4:8) |
|---|---|---|
| **PEG 4000** | 50 mg | 100mg |
| **PVPK 30** | 50mg | 100mg |
| **MCC** | 50mg | 200mg |
| **Lactose** | 50 mg | 200mg |

**Evaluation of Lamotrigine Solid Dispersion Systems:**

**Physical Appearance:** The two batches of Lamotrigine solid dispersions were evaluated for color and appearance.

**Determination of Lamotrigine content:** An accurately weighed amount of each preparation was dissolved in small volume of methanol and further diluted with methanol. The content of Lamotrigine was determined spectrophotometrically at 308nm using Perkin Elmer UV-visible spectrophotometer.

**Stability studies:** The stability studies were conducted on the drug substance packaged in a container closure system is the same as or simulates the packing proposed for storage and distribution. Stability studies on both the batches of solid dispersion were carried out by storing 1 gm of solid dispersions and excipients in an amber colored screw capped bottle at 40°C for a period of 4 weeks. The solid dispersions and excipients were visually examined for any physical change and drug content was estimated at the end of four weeks.

**Infrared spectroscopy:** The infrared spectra (IR) of Lamotrigine, PVPK30, PEG 4000, MCC, lactose, solid dispersions (1:2:2) and (1:4:8) were obtained using FTIR (Perkin Elmer 1600 Series). The IR spectrum was carried by KBr pellet method.

**Flow properties:** The flow properties of both solid dispersions (1:2:2) and (1:4:8) were checked by carrying out determining Carr's index and Angle of repose.

**Preparation of pellets by orifice ionic gelation technique:** Method used for preparation of pellets was orifice ionic gelation technique in which 5% sodium alginate solution was prepared in 50 ml water and 2% solid dispersion was added to the solution, then, separately prepared 10% calcium chloride solution (100 ml). To this solution added dispersed solution drop by drop by continuous stirring at less than 300 rpm. They are then oven dried for 6 hr at 60°C

**Characterization of Pellets:**

**Particle Size Determination:** Particle size analysis (Indian Pharmacopoeia. 1996) of the micropellets was done by sieving method using Indian Standard Sieves # 16, #22 and #30. Average particle size was calculated using the formula: -

$$davg = \frac{\sum dn}{\sum n}$$

Where, n=frequency weight, d= mean diameter.

**Determination of moisture content:** The formulations were subjected to moisture content study, by placing the micropellets at 60°C for 10 minutes in an IR moisture balance.

**Loose Surface Crystal Study (LSC):** This study was conducted to estimate the amount of drug present on the surface of the micropellets which may show immediate release in the dissolution media. 100mg of micropellets (# 22 sizes) were suspended in 100ml of phosphate buffer (pH 6.8), simulating the dissolution media. The samples were shaken vigorously for 15 min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 308nm. Percentage of drug released with respect to entrapped drug in the sample was recorded.

**Determination of Drug Entrapment Efficiency:** About 100mg of micropellets (# 22 sizes) were accurately weighed and dissolved in 25ml of Phosphate buffer (pH 7.4) for overnight and an aliquot from the filtrate was analyzed spectrophotometrically, after suitable dilution, using Perkin Elmer, at 308 nm. Reliability of the method was judged by conducting recovery analysis using known amount of drug with or without polymer. Recovery averaged 98.59± 0.50%. Drug content of every batch was determined for every size range of micropellets and the mean ± SD was calculated. Drug Entrapment Efficiency (DEE) was calculated according to the formula;

$$\%DEE = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

**Disintegration Studies:** Disintegration studies were performed in 0.1N HCl and simulated intestinal fluid in a rotating bottle apparatus. 5 pellets per vial were kept in 50 ml medium at 37°C and the vials were rotated at 25 rpm. The measured disintegration time was the time taken by the pellets to disintegrate into crystals, the polysaccharide being soluble and the drug insoluble in the disintegrating fluid.

***In vitro* Dissolution Study:** The USP Dissolution apparatus I (Electrolab) was used to study drug release from the micropellets. The dissolution parameters [ 100mg pellets ; 37± 2°C ; 100 rpm ; 1000ml of USP pH 1.2; n=3; coefficient of variation < 0.05] were maintained for two batches. 2ml of aliquot were withdrawn at specified intervals and after suitable dilution assayed by Perkin Elmer spectrophotometer at 308 nm.

**RESULTS & DISCUSSIONS:**

**Physical Appearance:** The Lamotrigine solid dispersions were prepared employing solvent evaporation method were fine powder.

**Determination of Lamotrigine Content Uniformity:** The drug content uniformity of formulations prepared was found to be 97.44±2.31

**Stability studies of two batches of Solid Dispersions:** Two batches of solid dispersions were considered for stability studies. Formulations were stored at 40°C as per ICH guidelines. These batches not showed any significant change.

**FT-IR Studies:** The Fourier Transform-Infra Red spectra (**Fig. 1 to 10**) of Lamotrigine, lactose, MCC, PEG 4000, PVPK30,solvent evaporation method (1:2:2),solvent evaporation method (1:4:8),sodium alginate, calcium chloride and Lamotrigine + sodium alginate + calcium chloride are given below and they show the characteristic peaks of individual Lamotrigine ,excipients and their mixture. The spectra showed no extra peaks. This is an indication that there is no interaction between Lamotrigine, excipients and their mixture.

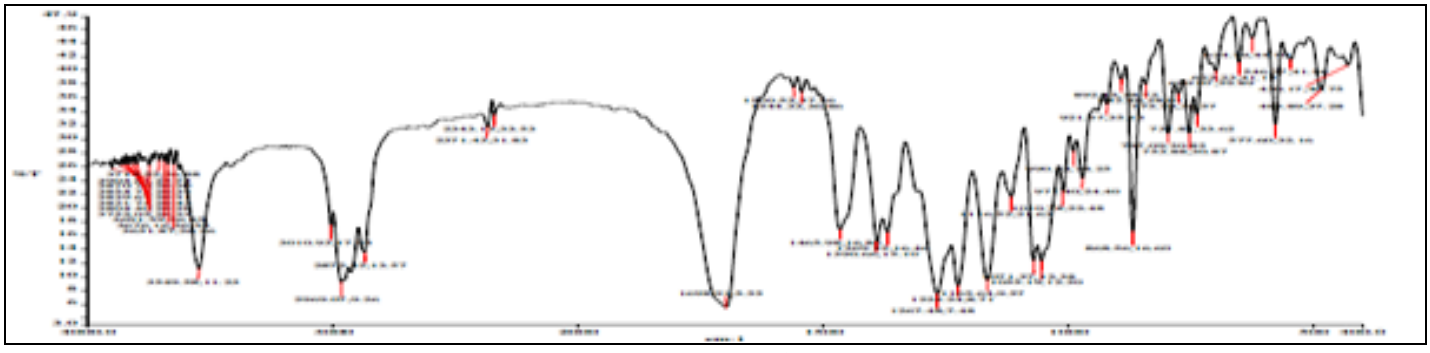

**FIG. 1: INDIVIDUAL SPECTRA OF LAMOTRIGINE**

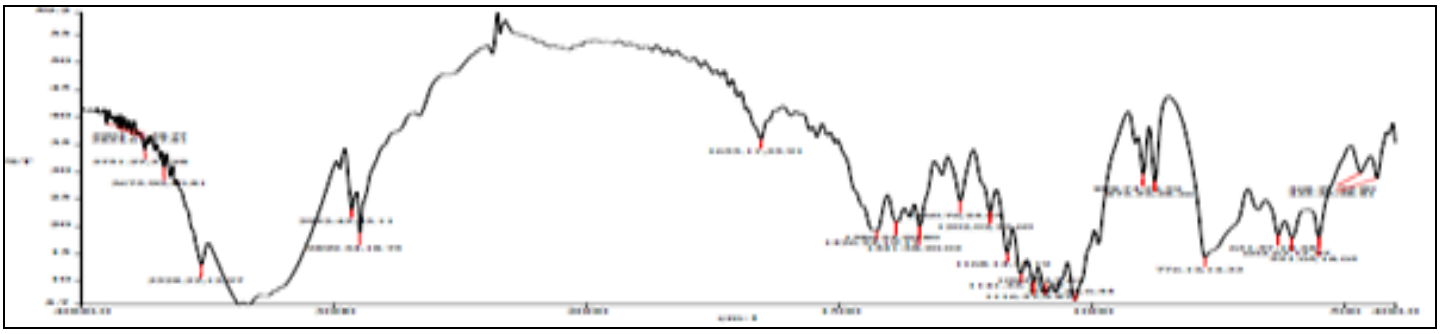

**FIG. 2: INDIVIDUAL SPECTRA OF LACTOSE**

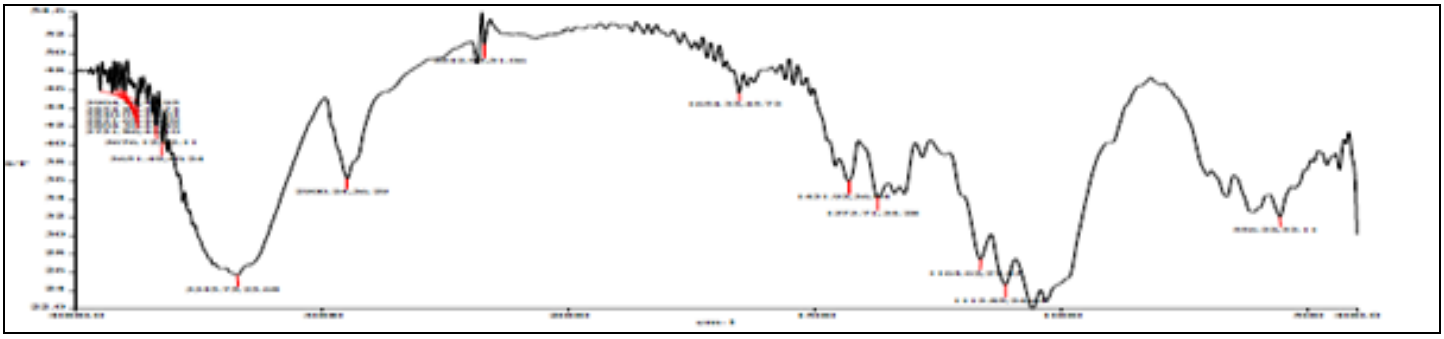

**FIG. 3: INDIVIDUAL SPECTRA OF MCC**

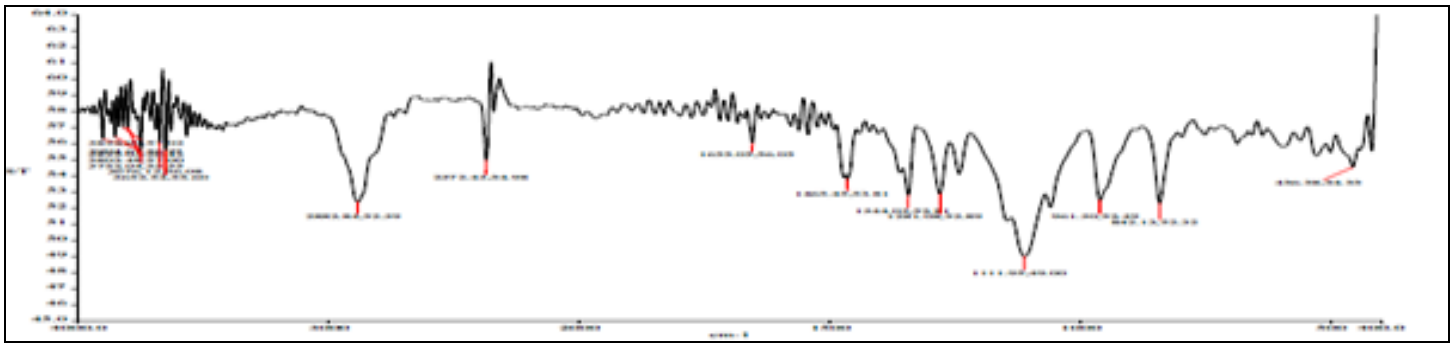

**FIG. 4: INDIVIDUAL SPECTRA OF PEG 4000**

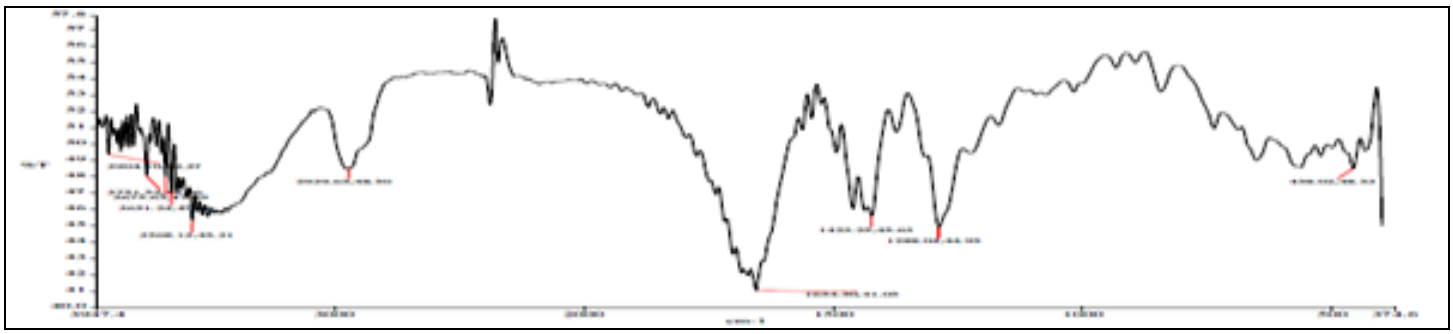

**FIG. 5: INDIVIDUAL SPECTRA OF PVPK 30**

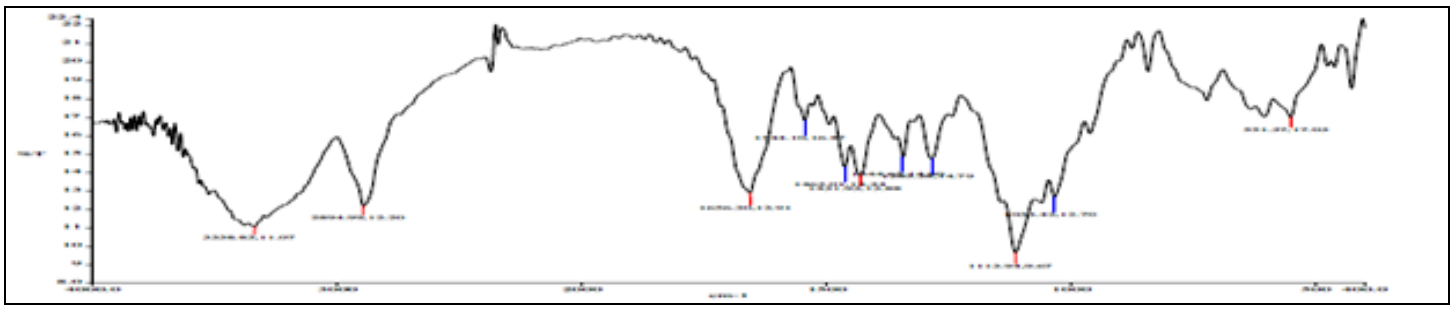

**FIG. 6: INDIVIDUAL SPECTRA OF SOLVENT EVAPORATION METHOD (1:2:2)**

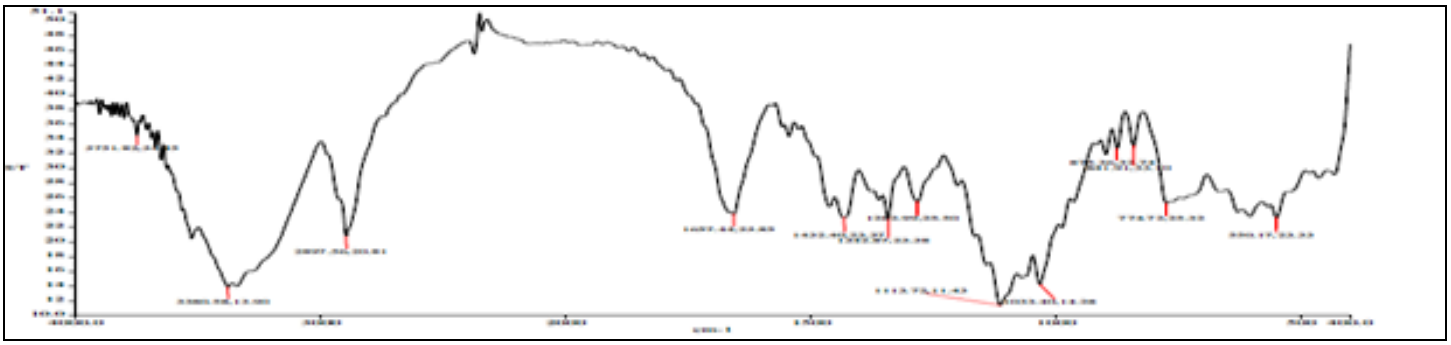

**FIG. 7: INDIVIDUAL SPECTRA OF SOLVENT EVAPORATION METHOD (1:4:8)**

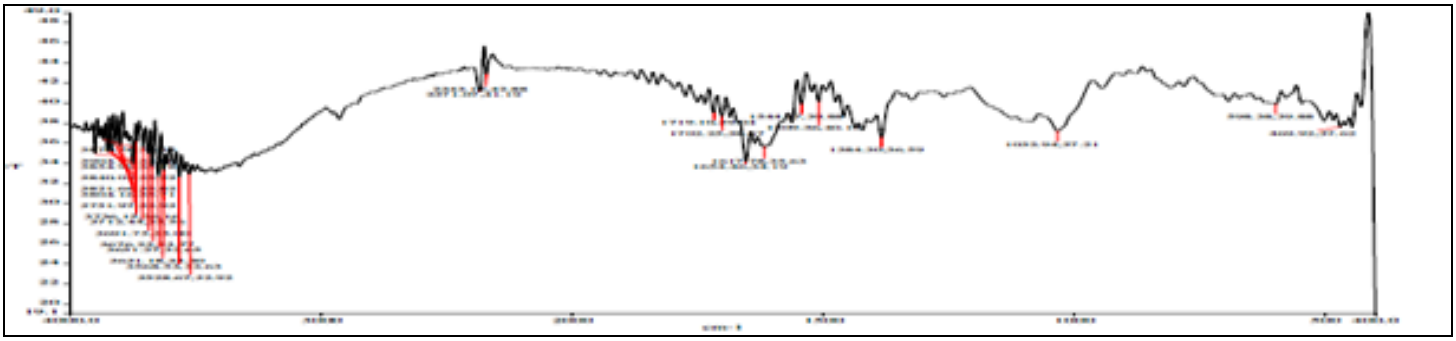

**FIG. 8: INDIVIDUAL SPECTRA OF SODIUM ALGINATE**

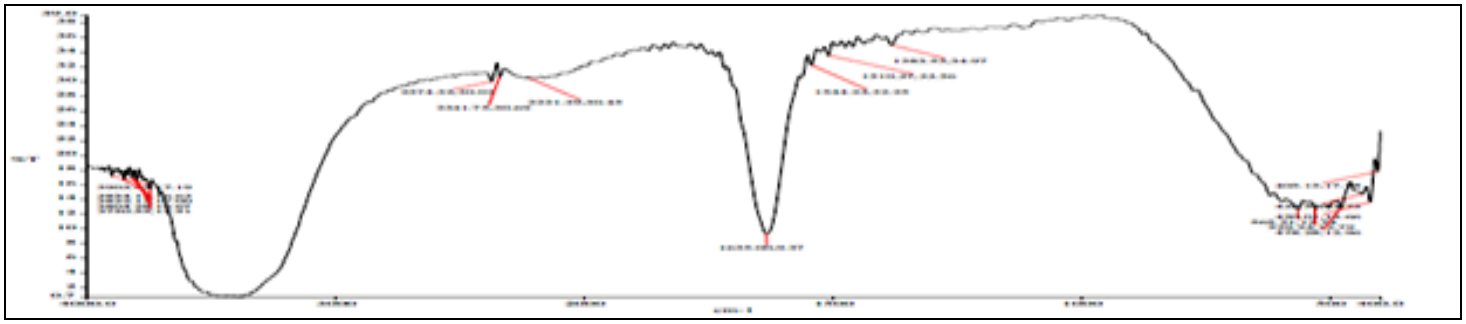

**FIG. 9: INDIVIDUAL SPECTRA OF CALCIUM CHLORIDE**

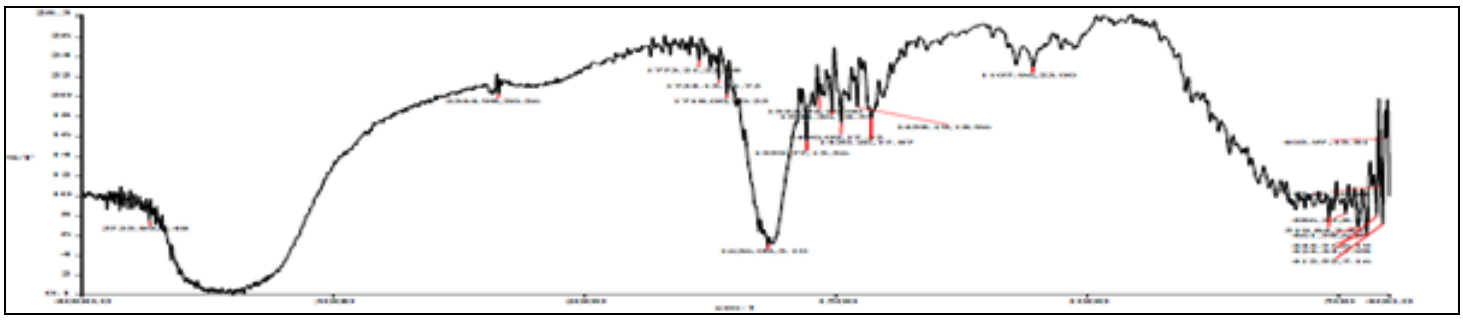

**FIG. 10: INDIVIDUAL SPECTRA OF LAMOTRIGINE+SODIUM ALGINATE + CALCIUM CHLORIDE**

**Flow properties:** The compressibility index values for the solid dispersions are 12.24 and 12.5. This indicates the powder blend has good flow property. The angle of repose values obtained for the solid dispersions are 19.99 and 20.07 which were good as per the flow chart. Thus the flow property was good and hence less lubricant would be required to compress the tablet (**table 2**).

**TABLE 2: EVALUATION OF FLOW PROPERTIES OF SOLID DISPERSION**

| BD* | TD* | Compressibility index (%) | Hausner's Ratio | Angle of repose (θ) |
|---|---|---|---|---|
| 0.60 | 0.69 | 12.24 | 1.13 | 19.99 |
| 0.62 | 0.71 | 12.5 | 1.14 | 20.07 |

BD*-Bulk density & TD*- Tapped density

**Evaluation parameters of pellets:** Drug entrapment efficiency of both the batches was good as shown in **table 3**. Loose surface crystal (LSC) study was an important parameter giving an indication of the amount of drug on the surface of the pellets without proper entrapment. With the increase in the copolymer concentration % LSC decreased significantly owing to high entrapment of drug in the dense network of polymers. As the drug was entrapped properly % LSC was less.

Low moisture content in all the pellets indicates the effectiveness of the optimized drying condition. Low moisture level ensures better stability of the drug in the pellets.

**TABLE 3 TABLE SHOWING EVALUATION PARAMETERS OF PELLETS**

| Batches | Drug entrapment efficiency (%±S.D.) | Loose surface crystal study | Moisture content | Disintegration test |
|---|---|---|---|---|
| **X1** | 98.59±0.50 | 3.66±0.29 | 1.48 ± 0.48 | 6.32±0.176 |
| **X2** | 98.41±0.21 | 3.61±0.21 | 1.44 ± 0.56 | 5.9±0.141 |

Results shown are the mean ± SD. n = 3 for disintegration study, entrapment efficiency and dissolution study

***In-vitro* release studies:** Drug release studies were carried out in gastric fluid, i.e., SGF. The drug release profiles were presented by plotting the amount of Lamotrigine released against time. **Table 4; figure 11** shows the results of release test of alginate-based pellets. Lamotrigine was released more rapidly and the release was more than (90%) within 30 min.

**TABLE 4 DISSOLUTION STUDIES OF PELLETS**

| Time (Hr) | Percent drug release ±S.D. | | |
|---|---|---|---|
| | X1 batch | X2 batch | Marketed |
| **0** | 0 | 0 | 0 |
| **5** | 17.20±0.5 | 16.23±0.65 | 9.08±0.11 |
| **10** | 29.30±0.7 | 29.26±0.47 | 23.08±0.56 |
| **15** | 45.06±0.77 | 44.18±0.44 | 37.50±0.62 |
| **20** | 63.66±0.78 | 61.02±0.5 | 55.20±0.66 |
| **30** | 94.89±0.7 | 92.30±0.55 | 82.30±0.40 |

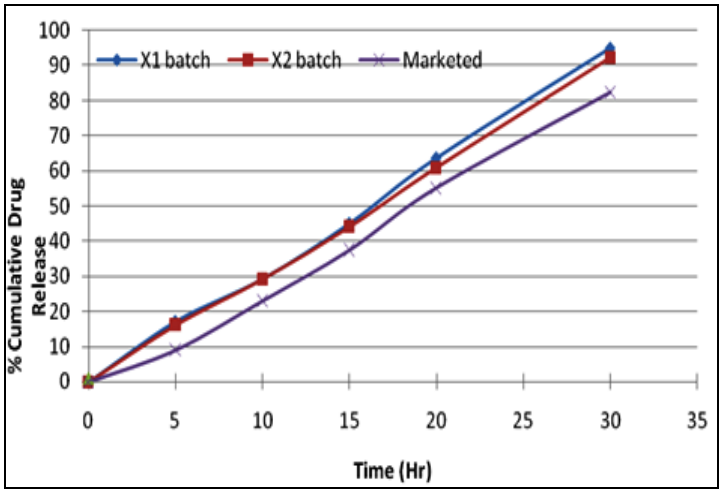


**FIG. 11: RELEASE PROFILE OF X1 AND X2 BATCH CONTAINING 50mg LAMOTRIGINE**

**CONCLUSION:** Solid dispersion technique increased the solubility of Lamotrigine was seen *in vitro* dissolution studies and also the use of two polymers increased the solubility of Lamotrigine. The flow property of solid dispersion was good so that it be can be easily formulated. The FTIR studies and stability studies indicated that there was no interaction between drug and the excipient.

The orifice ionotropic gelation technique employed for the preparation of pellets was simple, reproducible and produces beads of regular shape and size. The prepared beads were spherical in shape and discrete.

The drug entrapment efficiency of sodium alginate pellets was good which indicates that the drug was entrapped in and LSC also indicated that the drug was less on the surface and drug was efficiently entrapped.

*In vitro* release studies also shown more than 90% of the drug was released in 30mins which indicates that sodium alginate helps in release of the drug from the pellets.

**REFERENCES:**

1. Aleem MA, Dehghan MH, Rajesh BV. Solid Dispersion- An approach to enhance the dissolution Rate of Aceclofenac by Using 32 Factorial Design International Journal of Pharmaceutical Sciences and Research 2010; 1(12): 203-208.
2. Patidar K, Soni M, Sharma DK , Jain SK. Solid Dispersion: Approaches, Technology involved, Unmet need & Challenges .Drug Invention Today 2010; 2(7):349-357
3. Shinde SS, Patil SS, Mevekari FI, Satpute AS. An approach for solubility enhancement: solid dispersion .International Journal of Advances in Pharmaceutical Sciences 2010; 1:299-308
4. Chiou WL, Riegelmen S. Pharmaceutical application of solid dispersion system. Journal of Pharmaceutical Sciences 1971; 60:1281-1302.

5. James S, James CB. Enclyclopedia of pharmaceutical technology, Marcel Dekker, 2nd Ed, 1, 2467.
6. Amidon GL, Lennernas H, Shah VP, Crison JR.A theoretical base for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and in vivo bioavailability. Pharm. Res 1995 ; 12: 413-420
7. Rasala TM, Kale VV, Bhalekar MR, Avari JG. Formulation and Evaluation of Mucoadhesive Microcapsules of Diltiazem HCl and Diclofenac Sodium by Orifice-Ionic Gelation Method. International Journal of Pharmaceutics and Cosmetology (2010);1: 2-8
8. Prajapati SK, Tripathi P, Ubaidulla U, Anand V. Design and development of Gliclazide mucoadhesive microcapsules: *In vitro* and *In vivo* evaluation. AAPS Pharm SciTech 2008; 9(1):224-230
9. Ahmed MG. Formulation and evaluation of gastric mucoadhesive drug delivery systems of Captopril. Journal of Current Pharmaceutical Research 2010; 2(1): 26-32
10. Abbaspour MR, Sadeghi F, Garekani HA. Preparation and characterization of Ibuprofen pellets based on Eudragit RS PO and RL PO or their combination. International Journal of Pharmaceutics 2005; 303: 88-94
11. Shende AJ, Patil RR, Devarajan PV. Microemulsion of Lamotrigine for nasal delivery. International Journal of Pharmaceutical Sciences 2007; 69: 721-722
12. Yong CS, Yang CH, Rhee JD, Lee BJ, Kim DC, Kim DD, Kim CK, Choi JS , Choi HG. Enhanced rectal bioavailability of Ibuprofen in rats by Poloxamer 188 and menthol. International Journal of Pharmaceutics 2004; 269: 169–176
13. Ravichandran R. Nanoparticles in Drug Delivery: Potential Green Nanobiomedicine Applications. International Journal of Green Nanotechnology: Biomedicine 2009; 1: B108 - B130
14. Mali SL, Nighute AB, Deshmukh Vivek, Gonjari ID, Bhise SB. Microcrystals: For improvement of solubility and dissolution rate of Lamotrigine. International Journal of Pharmaceutical Sciences 2010; 2(2):515-521

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