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Research Article

**FORMULATION AND EVALUATION OF SINTERED MATRIX  
TABLETS OF LAMOTRIGINE**

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Telangana, India.**Abstract:**

*Extended release dosage form of lamotrigine with pH dependent solubility was formulated using sintering technique. In conventional immediate release tablet the pharmacokinetic profile shows peak concentration causing adverse effects and troughs causes breakthrough seizures. Hence the matrix tablets were prepared using controlled release natural and synthetic polymers such as HPMC K4M, HPMC K15M, HPMC K100M, acacia, guar gum and xanthan gum. The polymers were used in 1:2, 1:3, and 1:4 ratios and compressed by direct compression method. Dissolution studies were carried out in pH 6.8 buffer with 0.5% SLS. Relatively more extended release was observed with 1:4 ratio of polymer of HPMC K15M, HPMC K100, guar gum and xanthan gum. F15, F17, F18 formulations having 1:4 ratios of drug and polymer were found to comply with U.S.P specifications of controlled release. The lowest concentration of polymer 1:2 was selected for chemical sintering and percentage release profile was calculated. Formulae F3S, F5S, F6S were found to extend the release of the drug as that of formulae with higher concentration of polymers before sintering. F6S2 has found to show zero order kinetics with Higuchi release profile at lowest sintering time, complied with U.S.P specifications. Based on the study it can be concluded that sintering technique enhances the extended release of the drug with low concentrations of polymer and it would be a cost effective method.*

**Key Words:** Matrix Tablets, Natural and synthetic polymers, Sintering technique.**Corresponding author:****Dr. P. K. Lakshmi**

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## INTRODUCTION

### Oral Controlled Release Systems:

Oral drug administration has been the predominant route for drug delivery [1]. A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time [2, 3]. Controlled release systems can be influenced by physiological conditions such as motility, ions, pH and enzymes [4, 5]. Hydrophilic matrix systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective [6]. The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug then releases by dissolution, diffusion and/or erosion[7]. Matrix tablet is designed such that it releases its contents regarding first order kinetics or zero order kinetics due to special arrangement and combination of hydrophobic and hydrophilic polymers as an excipient to form a matrix. Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. The concept of sintering was applied for the fabrication of controlled-release matrix tablets and for the stabilization of the drug permeability of film coatings derived from various pharmaceutical lattices. Conventional sintering involves the heating of compact at a temperature below the melting point of the solid constituent in a controlled environment under atmospheric pressure. Variations in this method include heating in the presence of transient or stable liquid phases and under pressure (hot-pressing). Spark plasma sintering, microwave sintering, high frequency induction heat sintering are the more recent advances in sintering technologies [8, 9].

### MATERIALS AND METHODS:

Lamotrigine was purchased from RA Chem Pharma Ltd, Karaya gum, Guar gum, Xanthan gum, HPMC K4M, K15M and K100M was purchased from Otto Chemie Pvt Ltd, PVP K30, Ethyl Cellulose, and Magnesium stearate was purchased from SD fine Chemicals Limited.

### Analytical Methodology of LMG

Standard curve of LMG was performed in 6.8 pH buffer to quantify the samples by UV spectrophotometer. The solutions were analyzed at a wave length of 304.8 nm using a double beam spectrophotometer against phosphate buffer pH 6.8 as blank. Standard graph of drug in phosphate buffer pH 6.8 was constructed by taking concentrations ( $\mu\text{g/ml}$ ) on X-axis Vs absorbance (nm) on Y-axis [10].

### Drug Excipients Compatibility Study by FTIR

The spectrum analysis of pure drug and physical mixture of drug with excipients were subjected to IR spectral studies using FTIR spectrophotometer (FTIR 8400 S, Shimadzu, Japan) [11].

### Angle of Repose

Angle of repose was determined using funnel method. 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 ( $\theta$ ) was calculated using the following formula,

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

Where,  $\theta$  = angle of repose, r=radius of the pile, h=height of the pile

### Bulk Density

Bulk density is defined as mass of the powder divided by the bulk volume. Apparent bulk density ( $\rho_b$ ) was determined by pouring the blend in to graduated cylinder. The bulk volume ( $V_b$ ) and the weight of the powder (M) was determined. The bulk density was calculated using the formula

$$\rho_b = M/V_b$$

### Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a fixed time (100 tappings). The minimum volume ( $V_t$ ) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density ( $\rho_t$ ) was calculated using the formula

$$\rho_t = M/V_t$$

### Carr's Index:

Carr's index = (Tapped density - Bulk density)/Tapped density  $\times$  100.

The compressibility index (CI) and the Hausner's ratios (HR) were determined from the bulk and tapped densities according to the relationships.

### Hausner's Ratio:

It is the ratio of tapped density to bulk density. This is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Hausner's ratio} = \rho_t/\rho_b$$

$$\rho_t = \text{Tapped density } \rho_b = \text{Bulk density.}$$

### Formulation and Evaluation of LMG Matrix Tablets

All ingredients were triturated individually in a mortar and passed through #60 sieve. Then required quantity of all ingredients were weighed for a batch size of 50 tablets and mixed uniformly except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant. This uniformly mixed blend was compressed into tablets containing 25 mg drug using 6mm and 8mm flat face surface punches on a Rimek-1 rotary tablet machine by direct compression method.

Table1: Formula of Matrix Tablets of Lamotrigine

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Lamotrigine	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
HPMC K4M	50	-	-	-	-	-	75	-	-	-	-	-	100	-	-	-	-	-
HPMC K 15M	-	50	-	-	-	-	-	75	-	-	-	-	-	100	-	-	-	-
HPMC K100M	-	-	50	-	-	-	-	-	75	-	-	-	-	-	100	-	-	-
Acacia	-	-	-	50	-	-	-	-	-	75	-	-	-	-	-	100	-	-
Guar gum	-	-	-	-	50	-	-	-	-	-	75	-	-	-	-	-	100	-
Xanthan gum	-	-	-	-	-	50	-	-	-	-	-	75	-	-	-	-	-	100
Ethyl Cellulose	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
PVP K30	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

\*All the values are in mg. 0.5% of lubricants were added in all the formulation

#### Evaluation of LMG Matrix Tablets:

##### Weight Variation:

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percentage deviation from the average weight was calculated [12, 13, 14].

##### Thickness:

The thickness of tablet is measured by screw gauge. Tablet thickness should be controlled within a  $\pm 5\%$  variation of a standard value. The average thickness and standard deviation were reported.

##### Hardness:

The strength of the tablet is expressed as tensile strength (Kg/cm<sup>2</sup>). The tablet crushing load, which is the force required to break the tablet in to pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester) [12, 13].

##### Friability:

Friability of the tablets was determined using Roche Friabilator (Electrolab, India). Pre weighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. The friability (%F) is given by the formula, [15]

$$F\% = (1 - W_0/W)$$

Where, W<sub>0</sub> is weight of the tablets before test and W is the weight of the tablets after testing.

##### Assay:

Accurately weighed tablet powder mixture equivalent to 25mg of LMG was taken in 50ml volumetric flask. About 25ml of freshly prepared pH 6.8 buffer was added and sonicated for 15 min to dissolve the drug. The solution was made upto the volume with pH 6.8 buffer, which theoretically give 10mcg/ml solution. This was allowed to stand for 2hr. The supernatant was filtered. 2ml of aliquot was taken into another 50 ml volumetric flask and volume was made up with pH 6.8 buffer. This dilution gives 20 mcg/ml concentration whose

absorbance was obtained on a double beam UV spectrophotometer at 304.8 nm against blank pH 6.8 buffer. The drug content was calculated by comparison with the standard calibration curve.

##### Dissolution Study of Matrix Tablets:

*In-vitro* drug release of lamotrigine matrix tablets was determined using USP dissolution apparatus II (Paddle type) (Electrolab TDT- 0.8L). The dissolution test was performed using 900 ml of 6.8 pH buffer with 0.5% SLS at 37°C  $\pm$  0.5°C. The speed of rotation of paddle was set at 50 rpm. 5 ml samples were withdrawn at time points of 1hr, 2hrs, 4hrs, 6hrs, 8 hrs and the same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO-164 double beam spectrophotometer, Hyderabad, India) at a wavelength of 304.8 nm and drug release was determined from standard curve.

##### Sintering

The lower chamber of the dessicator was filled with acetone, closed and kept aside for saturation. After saturation of chamber, the compressed tablets were placed over a wire mesh which was kept above the lower chamber of the dessicator containing acetone. The dessicator was made airtight by closing the lid with the help of wax. The acetone vapours in the saturated dessicator enter the pores of tablets; solubilise the surface of the polymer particles which results in the fusion of particles thus bringing about sintering. At the end, the tablets were dried in an oven at 36°C temperature for 24 hour and then stored in a vacuum desiccators fused with calcium chloride until further use.

#### RESULTS AND DISCUSSION:

IR spectroscopic studies revealed that drug was compatible with all the excipients, optimized formula spectra shown in (Fig.1, 2)

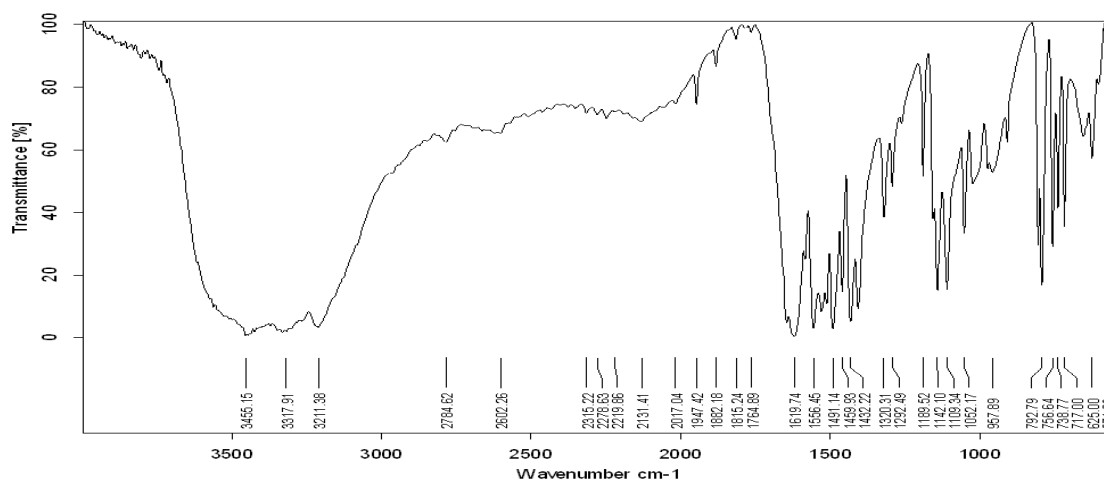


Fig 1: FTIR Spectra of Pure Drug LMG

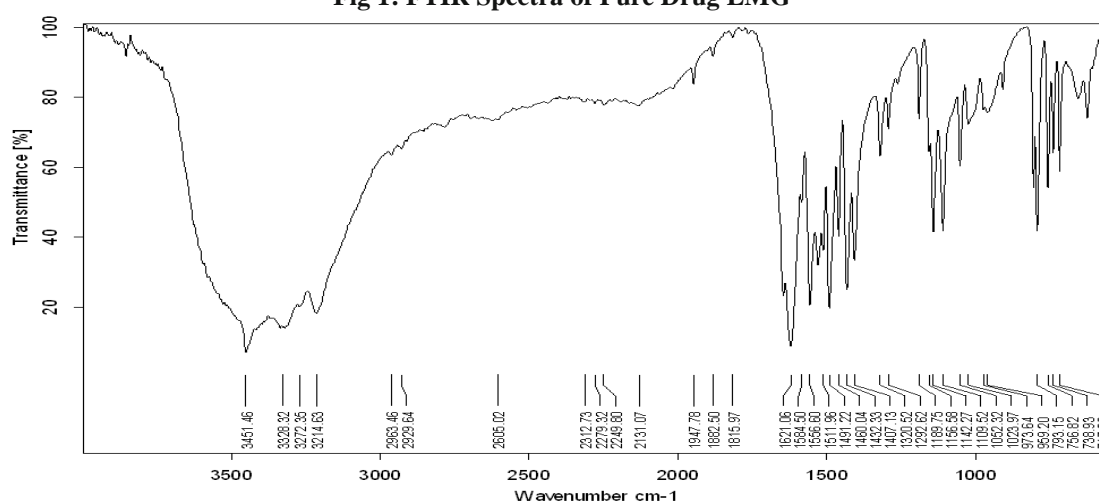


Fig 2: FTIR Spectra of LMG and Xanthan Gum

**Pre compression Parameters** The angle of repose of the powder blend of lamotrigine was in the range of  $27.5 \pm 0.92$  and  $31.8 \pm 0.80$  g/cm<sup>3</sup> showing that the powder blend was free flowing and can be used for direct compression. Bulk density was between  $0.409 \pm 0.01$  and  $0.605 \pm 0.01$  g/cm<sup>3</sup> and Tapped density was between  $0.5 \pm 0.01$  and  $0.670 \pm 0.01$  g/cm<sup>3</sup>. Hausner's ratio was between  $1.09 \pm 0.09$  and  $1.22 \pm 0.01$ . Compressibility index was between  $8.6 \pm 0.33$  and  $18.2 \pm 0.23$ . All the formulations showed good blend properties for direct compression and hence tablets were prepared by direct compression technology.

#### Evaluation of LMG Unsintered Tablets

##### Post Compression Parameters

Based on the pre-compression parameters of 1:2, 1:3, 1:4 ratios of drug and polymer formulations were selected for compression and evaluation tests were done.

The weight variation of 1:2 ratio formulations ranged between  $103 \pm 0.69$  to  $104 \pm 0.75$ , 1:3 formulations was  $128 \pm 0.65$  to  $129 \pm 0.89$  and 1:4 formulations was  $138 \pm 0.95$  to  $139 \pm 0.69$ . The hardness of the tablets was found to be  $4.1 \pm 0.11$  to  $4.5 \pm 0.44$  kg/cm<sup>2</sup> and friability was found to be below 1% indicating good mechanical resistance. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e.  $\pm 10\%$ . The drug content was found to be  $89.01 \pm 0.37$  to  $99.02 \pm 0.01\%$ , indicating uniform distribution of drug in the tablets [16].

##### In-vitro Evaluation of Tablets:

*In vitro* evaluation of the prepared tablets was done in pH 6.8 buffer with SLS for 1, 2, 4, 6, 8 hrs according to the specifications of U.S.P. All the formulations showed extended release as shown in the figures and were compared with the standard U.S.P values.

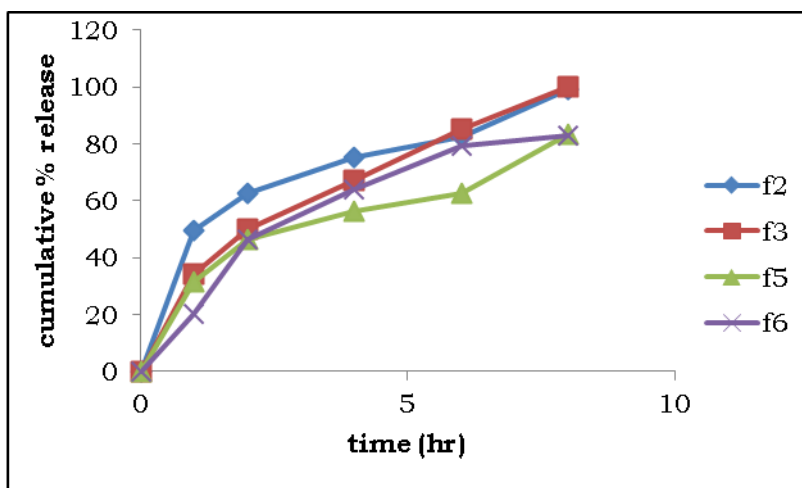


Fig 3: Percentage Release Profile of Unsintered Tablets Containing 1:2 Ratios of Drug and Polymer

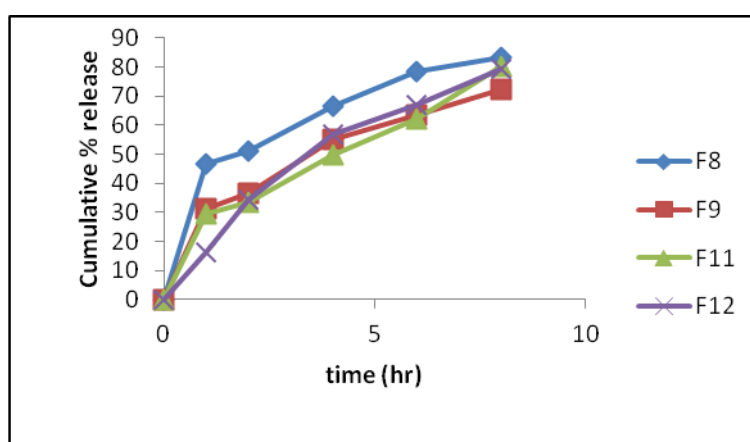


Fig 4: Percentage Release Profile of Unsintered Tablets Containing 1:3 Ratios of Drug and Polymer

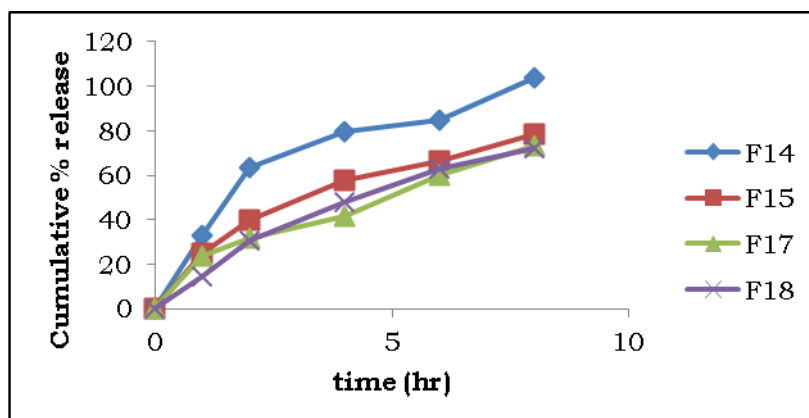


Fig 5: Percentage Release Profile of Unsintered Tablets Containing 1:4 Ratios of Drug and Polymer

#### Model Dependent Kinetic Study:

Among all the above formulations, F2, F8, F14 containing HPMC K15M was found to release the drug in zero order release kinetics and Higuchi release mechanism. This release profile was due to hydrophilic nature and swelling controlled mechanism by diffusion [17]. Dewan T Akhter et al also observed the extended release of drug by HPMC K15M in formulation of metformin hydrochloride extended release tablets. [18]

The formulations F3, F9, F15 containing HPMC K100M was found to show the release in zero order release kinetics with Higuchi release mechanism, the release profile was due to higher viscosity grade of HPMC (K100M) can strengthen the gel layer and retard the penetration of water into the dry matrix core resulting in decreased release of drug. [19] Doodipala N et al observed zero order release kinetics with Higuchi release mechanism with HPMC K100M in the

formulation of Levofloxacin matrix tablets. [20] The formulations F5, F11, F17 containing guar gum was found to show first order release kinetics with Higuchi model as guar gum swells in water and forms viscous colloidal dispersions or sols, this gelling property retards release of the drug from the dosage form. Guar gum showed release pattern that best fits Higuchi models in various studies. Deshmukh *et al* observed that the increased concentration of guar gum decreases the drug release. Increased gum concentration raises the swelling index value, thereby resulting in slow erosion of gelled layer which favored slow release of zidovudine from this viscous layer. Hence, there occurs diffusion through gel matrix coupled with erosion of matrix backbone mechanism for the drug release from guar gum based formulations. [21]

The formulations F6, F12, F18 containing xanthan gum was found to show zero order release kinetics with Higuchi mechanism as it shows high degree of swelling and small degree of erosion as a result of polymer relaxation. Mughal *et al* also has prepared sustained release tablets of propranolol

and obtained the same release profile as that of above mentioned formulations. [22]

The above results shows that all the formulations were releasing the drug in the sustained release manner and increase in polymer concentration extends the duration of release of the drug, so lowest concentration of the drug was selected and sintering technique was applied to improve the extended release of drug with low concentration of polymer.

Burst release was seen with the lowest drug: polymer (1:2) formulations the formulae F1 (HPMC K4M), F4 (karaya gum) due to low polymer concentrations as well as unmodified karaya gum rapidly hydrated and formed weak matrix systems which accounted for the 'burst' release as well as rapid release. [23] Hence F2, F3, F5, F6 formulations were studied further for sintering process and they are designated as F2S, F3S, F5S, F6S.

#### Evaluation of LMG Sintered Matrix Tablets

Tablets containing the polymer formulae F2S (HPMC K15M), F3S (HPMC K100M), F5S (Guar gum), F6S (Xanthan gum) were compressed and was subjected to chemical sintering for 1, 2, 3 hrs.

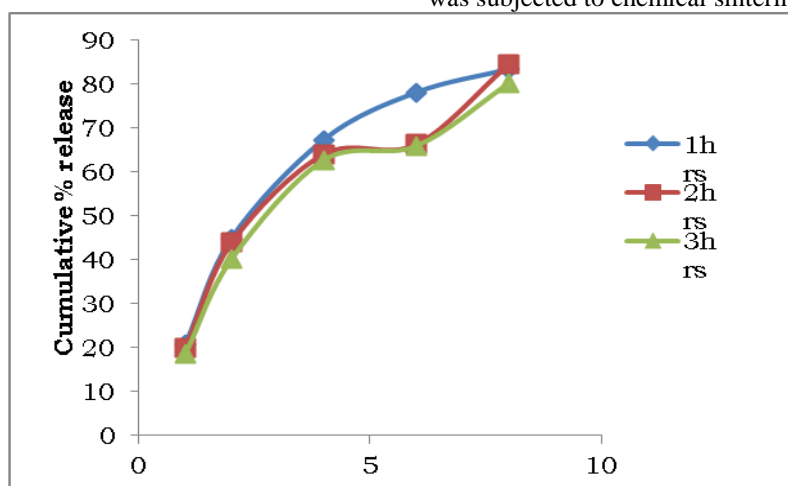


Fig 6: Percentage Release Profile of Sintered Tablets (F6S) Containing 1:2 Ratios of Drug and Polymer

Table 2: Model Dependant Kinetic Study for Optimized Sintered Tablets (F6S) Containing 1:2 Ratios of Drug and Polymer

Formulation	Zero order	First order	Higuchi	Korsmeyer peppas	n	Release Mechanism
	r	r	r	r		
F6S1	0.886	0.495	0.973	0.578	0.805	Anomalous transport
F6S2	0.896	0.562	0.97	0.478	0.892	Anomalous transport
F6S3	0.901	0.541	0.972	0.538	0.825	Anomalous transport

Model dependant kinetic study for optimized sintered tablets (F6S) containing 1:2 ratios of drug and polymer: Based on Correlation co-efficient values this formulation was found to show zero order release kinetics with Higuchi release profile. The release mechanism was anomalous transport.

### CONCLUSION

Sintered matrix tablet of lamotrigine were prepared and from the above study it can be concluded that by decreasing the concentrations of polymer and applying sintering technique may prove to be a cost effective method.

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