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Formulation and Evaluation of Lamotrigine Solid Dispersions

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ABSTRACT

The present study is an attempt to select the best possible inclusion complex formulation to formulate high porous mouth dissolving tablets of LMG using superdisintegrant such as sodium starch glycolate by sublimation technique.The precompression parameters of all formulations showed good flow properties and compressibility, so these can be used for tablet manufacture.The postcompression parameters of all formulations were determined and the values were found to be within IP limits.The various formulation of mouth dissolving tablet of high porous Lamotrigine inclusion complex were prepared using various concentration of subliming agent like as menthol and various concentration of superdisintegrant like as sodium starch glycolate and Crospovidone. And among the formulations prepared with various concentration of sodium starch glycolate, formulation N5 containing 19 mg of SSG and 15 mg Crospovidone showed complete release of drug in 9 min, was considered as best formulation.

Key words: Lamotrigine Pearlitol SD 200, β-cyclodextrin, Sodium Starch Glycolate , Aerosil 200.

Introduction

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs.[1] Various dosage forms administered orally, the tablets are the most preferred dosage form, because of its ease of manufacturing, Convenience in administration, accurate dosage and compactness. However, geriatric and paediatric patient experience difficulties in swallowing conventional tablets, which leads to poor patient compliance.[1-5]

Nearly 35% of the general population, especially the elderly patients and children suffer from Dysphagia or difficulty in swallowing, which results in high incidence of noncompliance and ineffective therapy. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mental ill, developmentally disabled, non co-operative patients and patients with reduced liquid intake plans or patients suffering from nausea. The swallowing problems are also common in some cases such as patients with motion sickness, sudden episodes of allergic attack or coughing and due to lack of water.[6-10]

That's why a method to improve patient's compliance has always attracted scientists towards the development of safer and new drug delivery systems. Among them, mouth dissolving drug delivery system (MDDS) have unique property of rapidly disintegrating, dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration.[11-15]

MATERIALS AND METHODS

Lamotrigine were obtained from Torrent Pharmaceuticals Ltd.,Gujrat India. Pearlitol SD 200, β-cyclodextrin, Sodium Starch Glycolate , Aerosil 200 were obtained from Strides Arcolab Ltd., Bangalore, India.

Methods of Preparation of inclusion complex

Inclusion complexes were prepared by different methods like physical mixture, kneading and co-evaporation method.

Physical mixture or grinding method:

Lamotrigine and β-Cyclodextrin were accurately weighed in different molar ratios viz. 1:1, 1:2, 1:3 and 1:5 separately. Then they were mixed and blended thoroughly by triturating in a mortar at 20ºC for about 10 minutes. The powder mixtures were then pulverized through sieve no.80 and stored in desiccator till further use.[15]

Kneading method:

The inclusion complex of drug with CD was prepared by wetting the physical mixture of LMG: β-CD in the different molar ratios viz. 1:1, 1:2, 1:3 and 1:5 in a mortar with methanol and water mixture (1:1, by volume). Then kneaded the wet mixture thoroughly with a pestle to obtain a paste like

consistency. The paste was then dried under vacuum at room temperature, pulverized by passing through sieve no. 80 and stored in a dessicator till further use. [17]

Co-evaporation method:

Lamotrigine and β-Cyclodextrin were accurately weighed in different molar ratios viz. 1:1, 1:2, 1:3 and 1:5 separately. Then lamotrigine was dissolved in methanol and β-cyclodextrin was dissolved in water. The two solutions were mixed, stirred for 6 hours at 40ºC and finally were dried at 40ºC for 24 hours. The dried complex was then pulverized by passing through sieve no. 80 and stored in a dessicator till further use.[73]

Inclusion complexes of LMG with β-CD prepared using compositions as given in Table 4.6.1.

Composition of LMG inclusion complexes

Inclusion complex composition	Method	Drug-β-CD ratio	Formulation Code
Lamotrigine: β-cyclodextrin	Physical mixture	1:1	N1
		1:2	N2
		1:3	N3
		1:4	N4
		1:5	N5
	Kneading method	1:1	N6
		1:2	N7
		1:3	N8
		1:4	N9
		1:5	N10
	Co-evaporation method	1:1	N11
		1:2	N12
		1:3	N13
		1:4	N14
		1:5	N15
		1:6	N16

Characterization of LMG Inclusion complexes [74]

Differential Scanning Calorimetry (DSC)

Approximately 2 mg of LMG, β-CD and inclusion complexes samples were taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging (atmosphere). The samples were scanned from 0-300ºC with the scanning rate of 10ºC rise/min using differential scanning calorimeter (DSC-60, Shimadzu, Japan).

Fourier Transform Infrared spectroscopy (FT-IR)

The samples of LMG, β-CD and inclusion complexes were prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FT-IR spectrophotometer.

Powder X-Ray Diffraction studies (XRD)

The powder XRD of the LMG, β-CD, and their inclusion complexes were recorded using an X-ray diffractometer. The scanning rate was 5º/min and diffraction angle (2θ) was 0 to 80º.

Scanning Electron Microscopy (SEM)

The external morphology of the sample LMG and LMG-β-CD inclusion complex was examined under a JSM-6400. The samples were previously fixed on a brass stub using double-sided adhesive tape and were then made electrically conductive by coating with a thin layer of gold and palladium alloy (180–200 Å) using a fine coat ion sputter (JEOL, fine coat ion sputter JFC-1100). The pictures were taken at an excitation voltage of 10 kV and magnification in the range of 100 to 1,500 X and 300 to 2,000 respectively.

Drug content:

An accurately weighed quantity of inclusion complex equivalent to 25 mg of LMG, was taken into a 100ml volumetric flask and dissolved in methanol and filtered through a whatman No. 1 filter paper. The filtrates were diluted suitably with 0.1 N hydrochloric acid (HCl) solution of pH 1.2. The content of LMG was determined spectrophotometrically at 267 nm against suitable blank using UV-visible spectrophotometer 1601, Shimadzu, Kyoto, Japan).

***In vitro* dissolution studies of LMG-β-CD complex:**

The quantity of inclusion complex equivalent to 25 mg of LMG, was placed in dissolution medium. The dissolution study of complex was conducted using dissolution testing apparatus II (paddle method) in 900 ml of 0.1 N hydrochloric acid (HCl) solution of pH 1.2 at 37±0.5ºC and at a speed of 50 rpm. Aliquots of 10 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 267 nm against suitable blank using UV-visible spectrophotometer(1601, Shimadzu, Kyoto, Japan).

Preparation of high porous mouth dissolving/disintegrating tablets:

Inclusion complex of LMG: β-CD (1:5 molar ratios) equivalent to 25 mg of drug prepared by kneading method were taken and mixed with directly compressible diluent, subliming agent, superdisintegrant and other excipients in a plastic container. Table 4.6.4 gives composition of the tablet formulation. Powder blend were directly compressed using 10.05 mm, round-shaped flat punch in a single station tablet compression machine (Cadmach, Ahmedabad, India).

	Ingredients(mg)						
Formulation code	**Inclusion complex**	**Pearlitol SD 200**	**Sodium starch Glycolate**	**Crospovidone**	**Menthol**	**Aerosil**	**Magnesium stearate**
N1	150	109	20	10	5	3	3
N2	150	105	14	15	10	3	3
N3	150	75	29	20	20	3	3
N4	150	84	15	15	30	3	3
N5	150	70	19	15	40	3	3
N6	150	69	15	10	50	3	3
N7	150	95	29	20	0	3	3
N8	150	129	20	10	0	3	3
N9	150	100	19	5	20	3	3
N10	150	100	14	10	20	3	3
N11	150	80	24	15	20	3	3
N12	150	80	24	20	20	3	3
N13	150	80	19	25	20	3	3
N14	150	70	24	30	20	3	3
N15	150	70	19	35	20	3	3
N16	150	100	24	10	20	3	3

Composition of mouth dissolving tablets of LMG inclusion complex

Characterization of inclusion complexes of LMG

Differential Scanning Calorimetric analysis

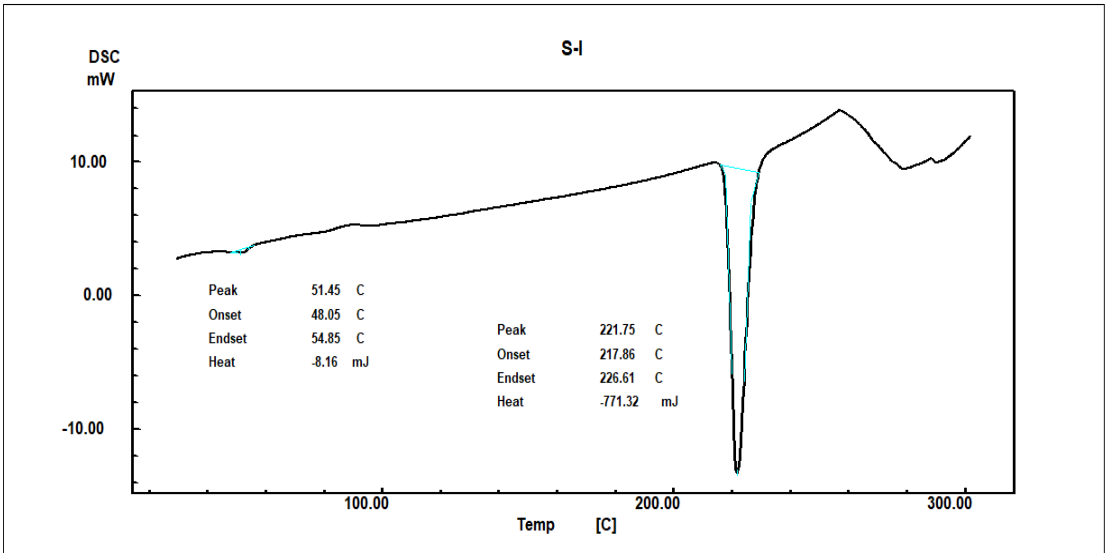
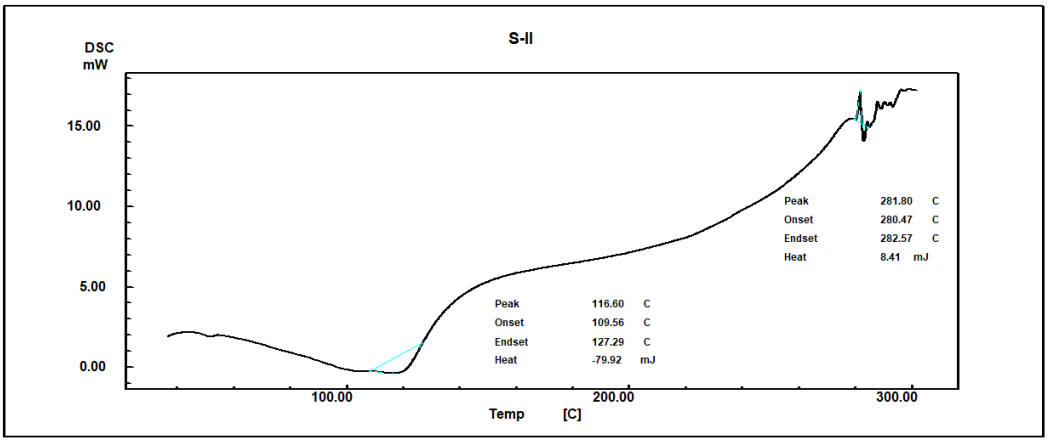
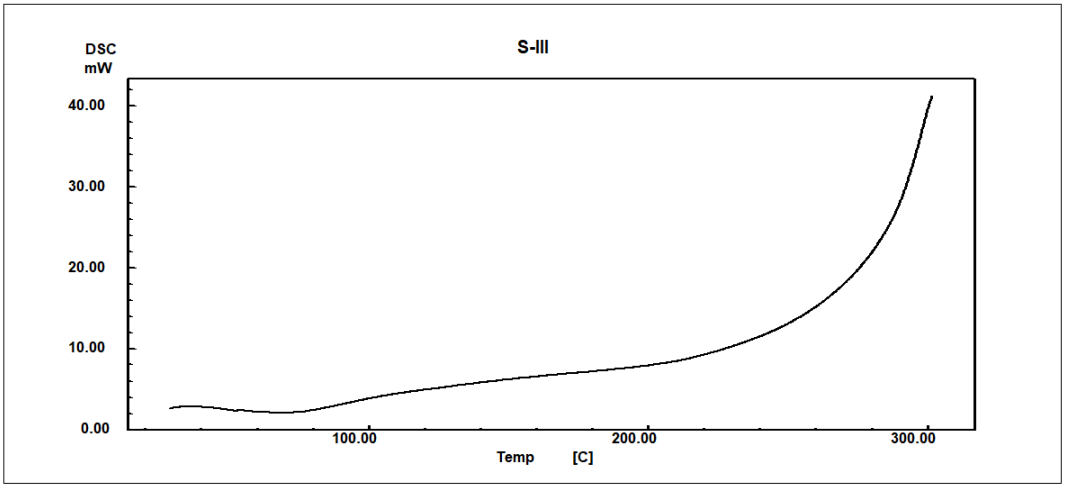


Figure 9: DSC thermogram of pure LMG

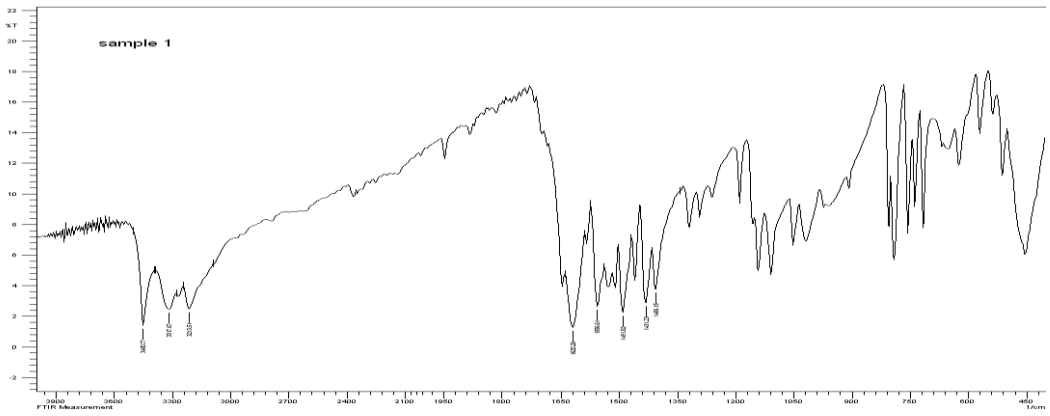


DSC thermogram of β-CD

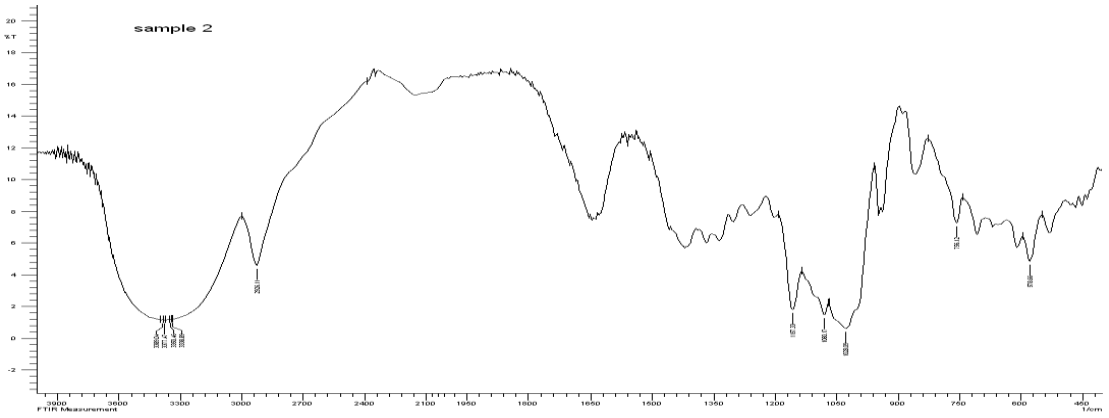


DSC thermogram of LMG: β-CD (1:5 molar ratios) inclusion Complex prepared by kneading method

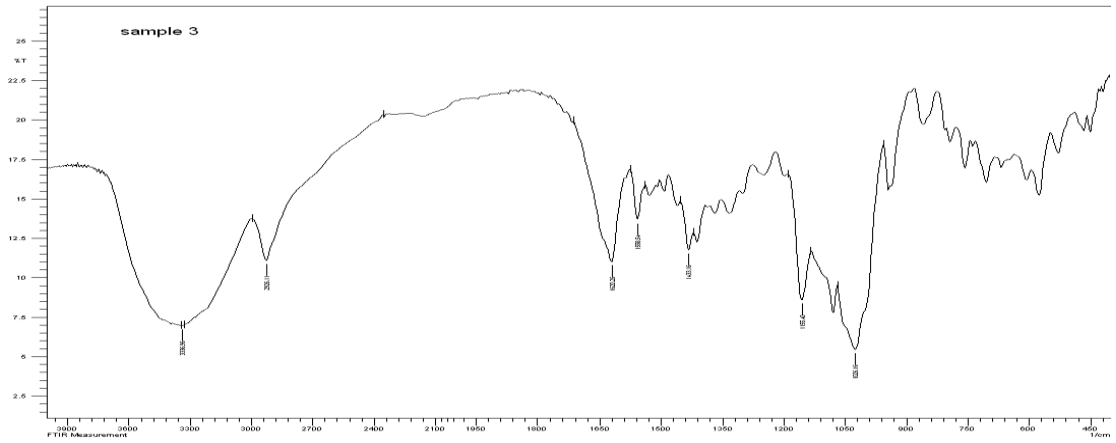
Fourier Transform Infrared spectroscopy



FT-IR spectra of pure LMG

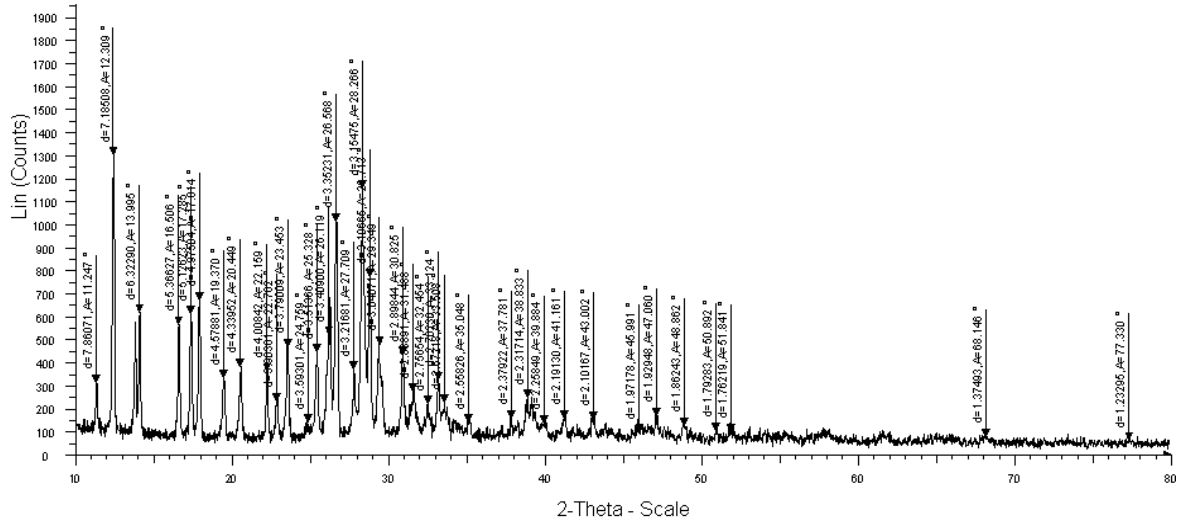


FT-IR spectra of β-CD

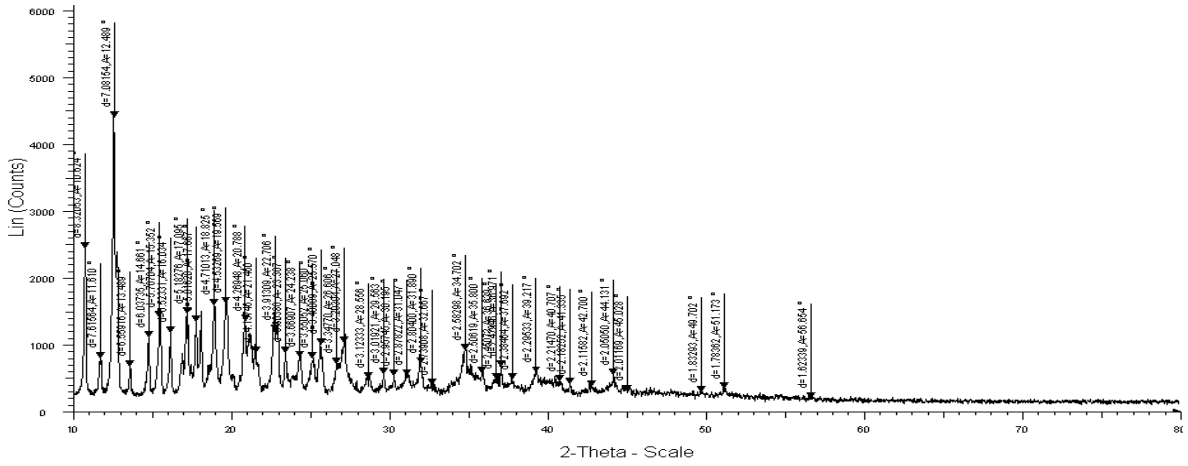


FT-IR spectra of LMG: β-CD (1:5 molar ratios) Complex prepared by kneading method

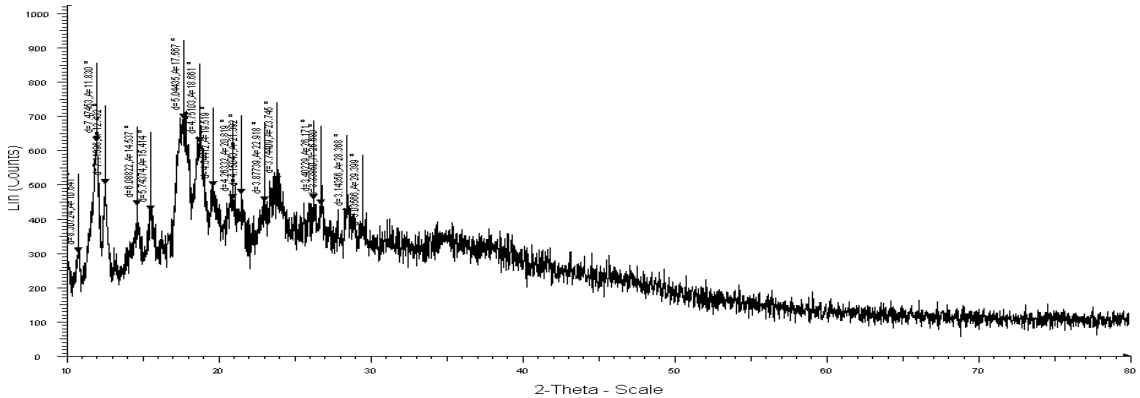
Powder X-Ray Diffraction studies



XRD pattern of pure LMG

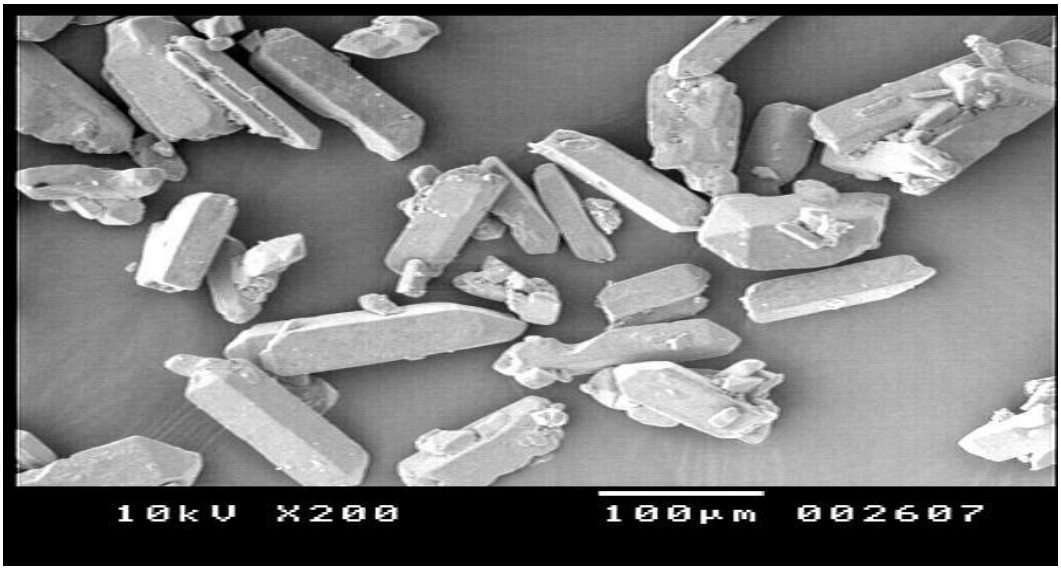


XRD pattern of β-CD

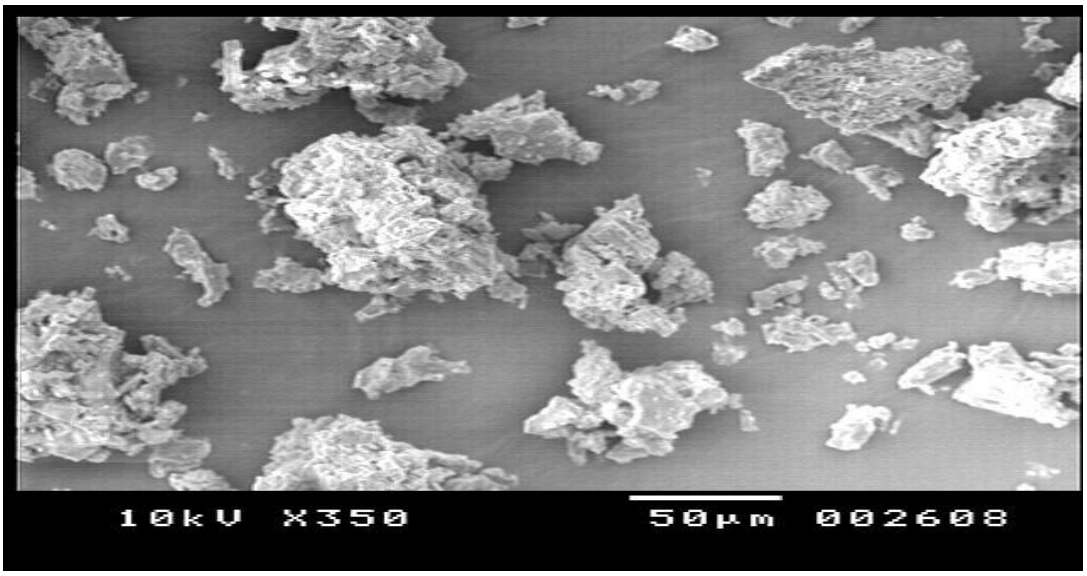


XRD pattern of LMG: β-CD (1:5 molar ratios) inclusion Complex prepared by kneading method

Scanning Electron Microscopy Studies



SEM images of pure LMG



SEM images of LMG: β-CD (1:5 molar ratios) inclusion Complex prepared by kneading method

CONCLUSION

Complex

The following conclusions were drawn from the inclusion complexation studies:

- The phase solubility studies of LMG in presence of β-CD showed a linear relationship of LMG and could be classified as A_L type.
- From the DSC, FT-IR, XRD, SEM, drug content and *in vitro* dissolution studies of LMG inclusion complexes it was concluded that the formulation K5 i.e., the inclusion complex of LMG with β-CD (1:5 molar ratio) prepared by kneading method is the best formulation.The present study is an attempt to select the best possible inclusion complex formulation to formulate high porous mouth dissolving tablets of LMG using superdisintegrant such as sodium starch glycolate by sublimation technique.
- The precompression parameters of all formulations showed good flow properties and compressibility, so these can be used for tablet manufacture.
- The postcompression parameters of all formulations were determined and the values were found to be within IP limits.

The various formulation of mouth dissolving tablet of high porous Lamotrigine inclusion complex were prepared using various concentration of subliming agent like as menthol and various concentration of superdisintegrant like as sodium starch glycolate and Crospovidone.

And among the formulations prepared with various concentration of sodium starch glycolate, formulation N5 containing 19 mg of SSG and 15 mg Crospovidone showed complete release of drug in 9 min, was considered as best formulation.

Accelerated stability study was carried out for selected formulations N1 and N16 which showed no significant difference in the drug content, disintegration time, hardness, friability and *in vitro* dissolution studies which confirms the stability of the product.

As a result of this study, it may be concluded that the inclusion complexation technique may be useful to improve solubility, dissolution rate and subsequently bioavailability of poorly soluble drug. The concept of formulating high porous mouth dissolving tablets of Lamotrigine inclusion complexes using superdisintegrants by sublimation technique offers a suitable and practical approach in serving desired objectives of faster disintegration and dissolution characteristics.

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