International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Issue 3, 2011

Research Article

DEVELOPMENT AND CHARACTERIZATION OF LAMOTRIGINE ORODISPERSIBLE TABLETS: INCLUSION COMPLEX WITH HYDROXYPROPYL B CYCLODEXTRIN

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Received: 07 April 2011, Revised and Accepted: 09 May 2011

ABSTRACT

The present study aimed at preparing Orodispersible tablets of lamotrigine by forming inclusion complex with hydroxypropyl β-cyclodextrin (HPβCD) employing kneading method. The complex was compressed into tablets along with superdisintegrants such as Kyron T-314, Sodium starch glycolate, Indion 414, Croscarmellose sodium and crospovidone in different concentration. Bitter taste of drug is successfully masked by HPβCD complex and is also useful to enhance the solubility which was confirmed by phase solubility analysis. Orodispersible tablets were characterized by Fourier Transform Infrared (FTIR) Spectroscopy, Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction Analysis (PXRD). The prepared tablets were evaluated for weight variation, thickness, hardness, friability, *in vitro* dispersion time, wetting time, *in vitro* disintegration time, drug content and *in vitro* drug release. *In vitro* dispersion time decreases with increase in concentration of all superdisintegrants. Result revealed that F6 had shown short dispersion time with maximum drug release in 12 minutes. Formulation containing higher concentration of Indion 414 decreases disintegration time (22.71 sec) and optimize the drug release (99.09% in 12 minutes).

Key words: Orodispersible tablets, Lamotrigine, Direct compression, Inclusion complex.

INTRODUCTION

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric populations, as well as other patients who prefer the convenience of easily swallow able dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva[1].

Lamotrigine [6-(2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine] is an antiepileptic agent shown to be effective in adjunctive treatment for refractory partial seizures and generalized seizures. It works by inhibiting voltage dependent sodium channels, resulting in decreased release of the excitatory neurotransmitters glutamate and aspartate[2]. It has an elimination half-life longer than 24 hr so once or twice daily dosing is possible in all patients[3]. Lamotrigine has a bitter taste. It is very slightly soluble in water (0.17 mg/ml at 25°C) [4].

Bitter taste of drug and solubility becomes hurdles for formulating orodispersible tablets (ODT) hence there is strong clinical need to explore any technique to enhance its solubility and simultaneously by masking of taste. β-cyclodextrin is known to form inclusion complexes with many drugs by enclosing drug molecule either partially or completely within their cavities. Drug β-cyclodextrin complexes are reported to influence the solubility, dissolution rate and to mask the bitter taste[5]. β-cyclodextrin has also been used to solubilize and increase the absorption of poorly water-soluble drugs delivered via the buccal mucosa. cyclodextrin, especially HPβCD, is widely used in the pharmaceutical field owing to their high aqueous solubility and ability to stabilize drug molecules[2, 6, 7].

Most commonly used methods to prepare ODT are freeze-drying/lyophilization, tablet molding and direct compression. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva in to the cost-intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug. Molded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern. The main advantages of direct compression are low manufacturing cost and high mechanical integrity of tablets. Therefore, direct compression appears to be a better option for manufacturing the tablets[8].

The object of this study was to formulate lamotrigine ODT using direct compression technique and to clarify the effect of different superdisintegrants like Kyron T-314, Sodium starch glycolate (SSG), Indion 414, Croscarmellose sodium (CCS) and Crospovidone (CP) on the disintegrating and dissolution properties of tablets.

MATERIALS AND METHODS

Lamotrigine and crospovidone were received as gift samples by Torrent Pharmaceuticals Ltd., Ahmedabad. Hydroxypropyl β cyclodextrin was generously donated by Gangwal Chemicals; Mumbai. Kyron T-314 was obtained as a gift sample from Corel Pharma Ltd., Ahmedabad. Indion 414 was obtained as a gift sample from Ion-Exchange resin of India, Mumbai. Microcrystalline Cellulose was obtained as a gift sample from Asahi-Kasei Chemicals, Japan. Croscarmellose Sodium was obtained as a gift sample from Maruti Chemicals, Ahmedabad. Sodium starch glycolate was obtained as a gift sample from S. Zhaveri Pharmakem Ltd., Mumbai. All other chemicals/solvents used were of analytical grade.

Phase solubility studies of lamotrigine with HPβCD[2]

Phase solubility studies were carried out in distilled water according to method described by Higuchi and Connors. Constant amount of lamotrigine (50 mg) that exceeded its solubility was added to 25 ml of aqueous solutions of HPβCD in various molar concentrations (2-20 mM). Then the suspensions were shaken on the rotary shaker at 25ºC for 3 days. The samples were filtered, diluted and the concentration of lamotrigine was determined spectrophotometrically at 306 nm. The apparent 1:1 stability constant was calculated from the phase solubility graph using the following equation,

$$Ks = \frac{Slope}{S_o(1\text{-}Slope)}$$

Where, So is the solubility of lamotrigine in absence of HPβCD.

Gibbs free energy of transfer ($\Delta G tr^o$) of lamotrigine from pure water to aqueous solution of HPβCD was calculated using the equation,

$$\Delta Gtr^{o} = -2.303\ RT \log \left(\frac{S_0}{S_S} \right)$$

Where, So/Ss is the ratio of the molar solubility of lamotrigine in aqueous solution of HPβCD to that of the pure water.

Preparation of lamotrigine inclusion complex with HPβCD by kneading method[9]

Lamotrigine and HPβCD in 1:1 ratio were taken. HPβCD and small quantity of distilled water was added in mortar with trituration to get slurry like consistency. Then slowly drug was incorporated into the slurry and trituration continued further for 15 min. Slurry was further air-dried at 40ºC for 24 hours, pulverized and passed through sieve No. 100 and was stored in a dessicator over fused calcium chloride.

Preparation of lamotrigine orodispersible tablets

The amounts of complex equivalent to 50 mg of drug, diluents, superdisintegrant and sweetener were passed through sieve no 60. All the above ingredients were properly mixed together (in a plastic container). Talc and magnesium stearate were passed through mesh number 80, mixed, and blended with initial mixture in a plastic container followed by compression of the blend. The tablets were prepared by direct compression method using 4 mm flat punches on a 10 station rotary compression machine. Formulation codes (F1-F10) used in the study is shown in the Table 1.

Table 1: Composition of lamotrigine orodispersible tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Amount of complex equivalent to 50 mg of lamotrigine	100	100	100	100	100	100	100	100	100	100
Kyron T-314	2.5	5	---	---	---	---	---	---	---	---
SSG	---	---	2.5	5	---	---	---	---	---	---
Indion 414	---	---	---	---	2.5	5	---	---	---	---
CCS	---	---	---	---	---	---	2.5	5	---	---
SP	---	---	---	---	---	---	---	---	2.5	5
MCC	114.5	112	114.5	112	114.5	112	114.5	112	114.5	112
Spray Dried Mannitol	25	25	25	25	25	25	25	25	25	25
Aerosil	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2
Aspartame	2	2	2	2	2	2	2	2	2	2
Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Characterization of lamotrigine orodispersible tablets

FTIR studies

Pure drug, inclusion complex and optimized formulation (F6) were subjected for FTIR analysis using Fourier transformer infrared spectrophotometer (8600, Shimadzu Corporation, Japan). The samples were prepared on KBr-press (Spectra Lab, India) and scanned over wave number range of 4000 to 400 cm^{-1}. Spectra were analyzed for drug polymer interactions and functional groups.

DSC Studies

The optimized complexes were subjected to differential scanning calorimeter equipped with an intra cooler (NETZSCH, DSC 200PC, Japan). Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples (Pure drug, inclusion complex and F6) were sealed in aluminum pans and heated at a constant rate of 10ºC/ min over a temperature range of 20-250ºC. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 10 ml/min.

PXRD studies

The PXRD patterns of pure lamotrigine and all binary systems of lamotrigine with HPβCD were recorded using X-ray diffractometer (X-pro Pan analytical, Phillips, Mumbai, India) with a copper tube anode over the interval 5-70º $2\theta^{-1}$. The operation data were as follows: generator tension (voltage) 40 kV; generator current 30 mA; scanning speed $2^{o}min^{-1}$.

Evaluation of lamotrigine orodispersible tablets

Hardness[10]

The prepared tablets hardness was measured by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Thickness and diameter[10]

Thickness and diameter of prepared tablets were tested by vernier callipers and the average was calculated.

Weight variation[10]

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. The percentage deviation was calculated and then compared with USP specifications.

Friability[10]

Ten tablets were weighed collectively and placed in the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

Wetting time[11]

A piece of tissue paper folded twice was placed in a small petridish (internal diameter of 5 cm) containing 6 ml of distilled water. A tablet was placed on the paper, and the time required for complete wetting of the tablet was measured.

Water absorption ratio[11]

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the tissue paper. The wetted tablet was weighed. The test was done in triplicate. The water absorption ratio(R) was determined according to the following equation

$$\text{Water absorption ratio (R)} = \frac{W_a - W_b}{W_a} \times 100$$

Where, Wa is the weight of the tablets before the test and

Wb is the weight of the tablet after water absorption.

Drug content[12]

Twenty tablets were powdered; powder equivalent to 50 mg of lamotrigine was accurately weighed and transferred into a 100 ml

volumetric flask. Then, the volume was made up to 100 ml with 0.1N HCl. The filtrate was collected and diluted with sufficient amount of 0.1N HCl till the concentration of the drug lies with in the standard plot range. The diluted solution was analyzed for the lamotrigine content by UV-spectrophotometer (UV-1700 Shimadzu Corporation, Japan) using 0.1N HCl as a blank at 267 nm.

***In vitro* dispersion time[11]**

One tablet was placed in a beaker containing 10 ml of phosphate buffer of pH 6.8 at 37 ± 0.5°C and the time required for complete dispersion was determined.

***In vitro* disintegration time[13]**

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted.

***In vitro* dissolution study of tablets[4]**

The prepared orodispersible tablets were subjected to *in vitro* dissolution studies using an 8 station USP (TYPE II) dissolution apparatus (Electro Lab, TDT-08L, Mumbai). The dissolution studies were carried out in 900 ml of 0.1N HCl at 37 ± 0.5°C. The speed of the paddle was set at 50 rpm. Sampling was done every 2 minutes interval. For each sample, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. The samples withdrawn were analyzed in the UV spectrophotometer at 267 nm.

Stability studies[13]

Stability studies were carried out at 25°C ± 2°C / 60 % RH ± 5 % and 40°C ±2 °C / 75 % RH ± 5 % for a period of 30 days with selected formulations by storing the samples in stability chamber (Lab-Care, Mumbai).

RESULTS AND DISCUSSION

Phase solubility studies of lamotrigine with HPβCD

The phase solubility graph for the complex formation between lamotrigine and HPβCD is shown in Fig. 1.

The plot showed that the drug solubility increased with increase in the concentration of HPβCD. According to Higuchi and Connors, the phase solubility profile can be considered as A_L (linear) type. The slope calculated was 0.252 which is less than 1, thus 1:1 stoichiometry was suggested. The value of the stability constant was found to be 576 M^{-1}. The stability constant between the range of 100 and 1,000 M^{-1} is considered as an ideal value, smaller value indicate weak interaction between drug and cyclodextrin, while larger value indicate incomplete drug release from the inclusion complex. The line equation from the linear regression analysis for the system was y=0.252x + 0.594. The obtained values of ΔGr^o are shown in Table 2. The negative values of calculated Gibbs free energy transfer indicated the spontaneous solubilization of lamotrigine in aqueous solution of HPβCD.

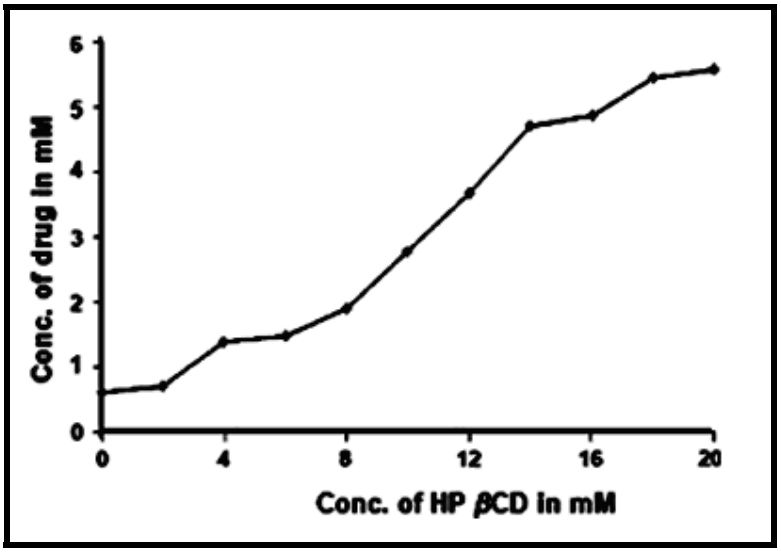

Fig 1: Phase solubility diagram of lamotrigine with HPβCD

Table 2: ΔGtr^o for solubilization process of lamotrigine in aqueous solutions of HPβCD at 25°C

Concentration of HPβCD (mM)	ΔGtr^o (KJ/mol) at 25°C	Concentration of HPβCD (mM)	ΔGtr^o (KJ/mol) at 25°C
2	-0.42	12	-4.52
4	-2.07	14	-5.11
6	-2.26	16	-5.19
8	-2.86	18	-5.47
10	-3.79	20	-5.54

Physico-chemical evaluation of tablets

The results of physicochemical evaluation of tablets are given in Table 3-4. As the material was free flowing, tablets were obtained of uniform weight due to uniform die filling. Hardness of tablets was between 2.1-2.5 kg/cm^2 for all the formulations. The thickness was found in range of 6.09-6.41 mm. Diameter of all tablets was between 4.12- 4.25 mm. Friability was found in between 0.18-0.84%. The friability value below 1% was an indication of good mechanical resistance of the tablet. The drug content was found to be 98.23-99.98% which was within the acceptable limits.

The most important parameter that is needed to optimize during the development of orodispersible tablets is disintegration time. Wetting time is related to inner structure of tablet and hydrophobicity of components. Dispersion time is used as an indication from the ease of tablet disintegration in buccal cavity. There is a good relationship between dispersion time and disintegration time (Fig 2). The disintegration time is shorter with quick wetting properties at the core of the tablets. The wetting time/dispersion time decreases with increase in the concentration of superdisintegrants. It was observed that as the concentration of superdisintegrants increases water absorption ratio increases and disintegration time decreases. Indion 414 and CCS when comes in contact with water it quickly wicks water into the tablet through capillary action to create internal pressure that disintegrates tablet. Kyron T-314, SSG and CP have swelling tendency with a longer wetting time results in slower disintegration of tablets.

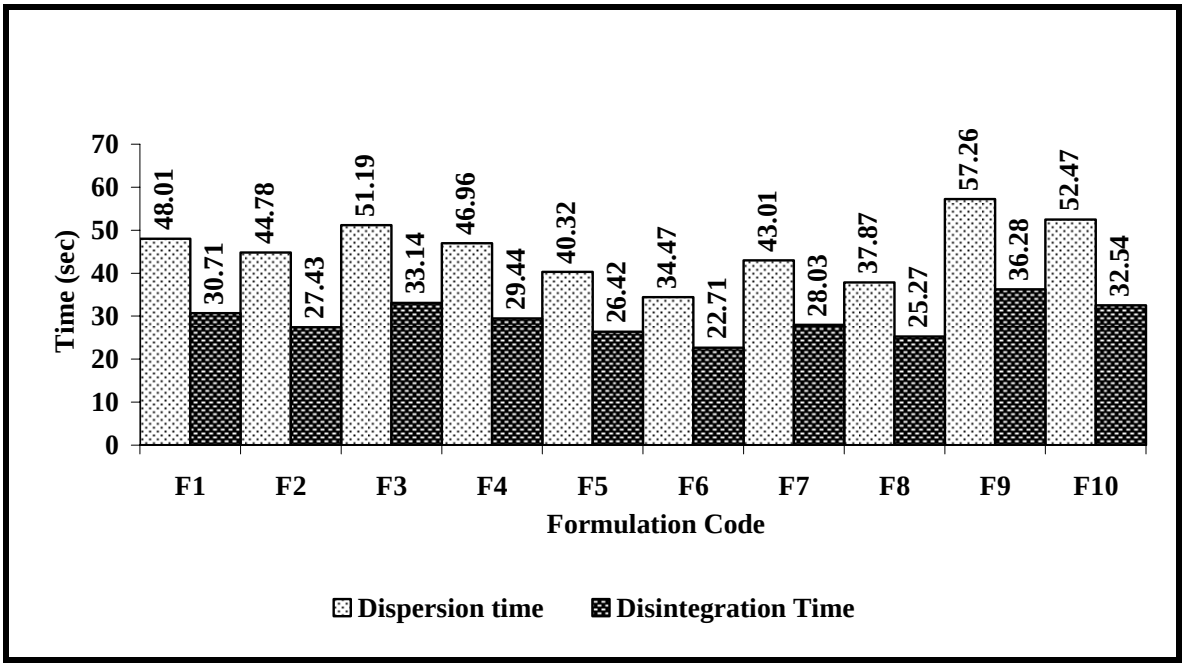

Fig. 2: Comparison between dispersion time and disintegration time

Table 3: Physico-chemical evaluation of tablets

Formulation Code	Hardness test (Kg/cm²) (±SD), n=3	Friability (%), (±SD), n=10	Weight variation(%), (±SD), n=20	Thickness (mm) (±SD), n=4	Diameter (mm), (±SD), n=3
F1	2.2 ± 0.14	0.39 ± 0.29	1.37 ± 0.22	6.21 ± 0.04	4.23 ± 0.04
F2	2.1 ± 0.11	0.43 ± 0.17	1.73 ± 0.69	6.26 ± 0.05	4.15 ± 0.07
F3	2.5 ± 0.18	0.18 ± 0.45	1.94 ± 0.18	6.09 ± 0.03	4.23 ± 0.04
F4	2.3 ± 0.14	0.84 ± 0.12	1.41 ± 0.33	6.23 ± 0.07	4.25 ± 0.09
F5	2.4 ± 0.14	0.27 ± 0.43	1.62 ± 0.43	6.41 ± 0.02	4.15 ± 0.06
F6	2.2 ± 0.15	0.28 ± 0.49	1.33 ± 0.01	6.15 ± 0.02	4.12 ± 0.06
F7	2.1 ± 0.16	0.51 ± 0.21	1.72 ± 0.32	6.26 ± 0.08	4.22 ± 0.05
F8	2.4 ± 0.11	0.74 ± 0.25	1.38 ± 0.16	6.18 ± 0.09	4.14 ± 0.04
F9	2.2 ± 0.15	0.36 ± 0.47	1.22 ± 0.11	6.41 ± 0.03	4.25 ± 0.01
F10	2.1 ± 0.12	0.18 ± 0.53	1.71 ± 0.37	6.18 ± 0.05	4.19 ± 0.03

Table 4: Physico-chemical evaluation of tablets

Formulation Code	Drug content (%) (±SD), n=4	Wetting time (sec) (±SD), n=4	Water absorption ratio (%) (±SD), n=4	Dispersion time (sec) (±SD), n=4	Disintegration time (sec) (±SD), n=4
F1	99.08 ± 0.35	49.33 ± 0.17	76.16 ± 1.16	48.01 ± 0.43	30.71 ± 0.51
F2	99.78 ± 0.74	45.64 ± 0.45	78.81 ± 1.43	44.78 ± 0.68	27.43 ± 0.93
F3	99.85 ± 0.38	53.63 ± 0.72	72.54 ± 1.58	51.19 ± 0.83	33.14 ± 0.51
F4	99.98 ± 0.72	49.39 ± 0.14	75.25 ± 1.29	46.96 ± 0.27	29.44 ± 0.93
F5	99.33 ± 0.45	42.47 ± 0.38	84.43 ± 1.67	40.32 ± 0.39	26.42 ± 0.47
F6	98.23 ± 0.23	36.06 ± 0.15	86.54 ± 1.23	34.47 ± 0.54	22.71 ± 0.32
F7	98.59 ± 0.67	45.14 ± 0.63	81.23 ± 1.84	43.01 ± 0.32	28.03 ± 0.68
F8	99.58 ± 0.71	40.25 ± 0.29	83.78 ± 1.66	37.87 ± 0.76	25.27 ± 0.24
F9	98.73 ± 0.29	58.88 ± 0.72	70.06 ± 1.18	57.26 ± 0.17	36.28 ± 0.15
F10	99.63 ± 0.62	53.94 ± 0.17	73.63 ± 1.39	52.47 ± 0.81	32.54 ± 0.83

FTIR studies

The FT-IR spectra of pure drug, inclusion complex and optimized formulation (F6) are taken for the characterization studies. As the shifts in the positions of major functional groups of the lamotrigine and HPβCD are observed in the IR spectrum of inclusion complex, it suggests that there is strong physical interaction (peak intensities were smoothened and disappeared) between drug and polymer.

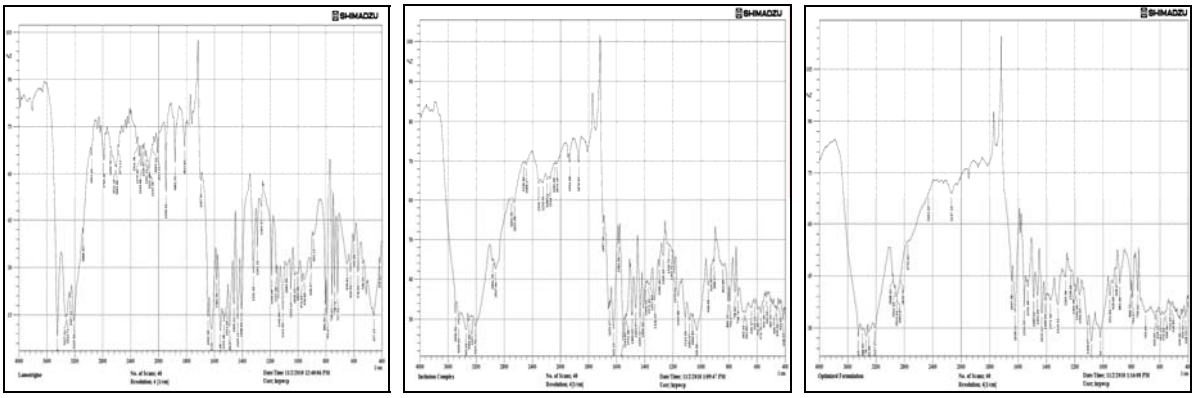

Fig 3: Comparison between FTIR spectra of (a) Lamotrigine (b) Inclusion complex and (c) Optimized formulation

DSC studies

In the DSC thermogram of optimized formulation (F6) the melting point of the drug was decreased from 87.55°C to 84.71°C. For the inclusion complex the peak of HPβCD was shifted from 83.33°C to 84.44°C indicating strong physical interaction of the drug and polymer in optimized formulation.

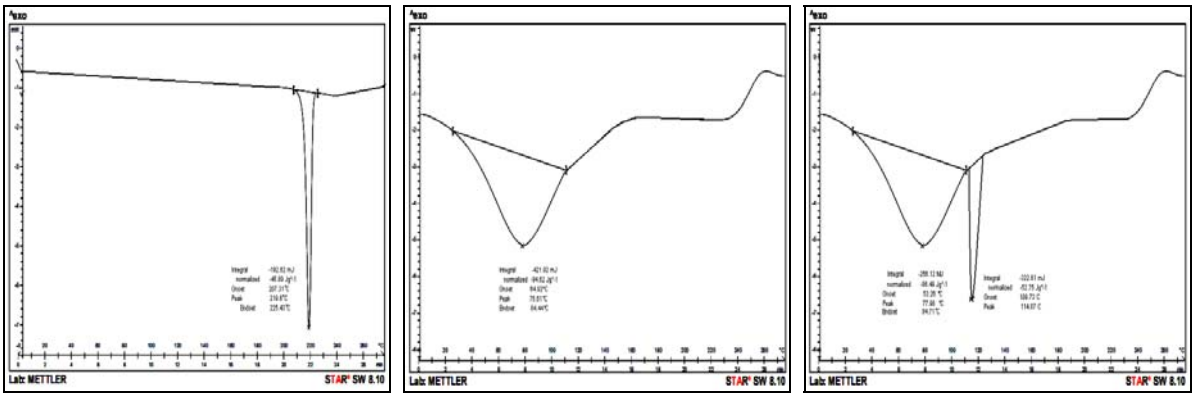

Fig 4: Comparison between DSC thermograms of (a) Lamotrigine (b) Inclusion complex and (c) Optimized formulation

PXRD studies

The PXRD of drug, polymer, inclusion complex and optimized formulation showed sharp and intense peak in the case of pure drug and polymer. The peaks are totally decreased which are almost smoothened with the decreased intensity. These suggest that the crystalline nature of the drug that changed in to amorphous.

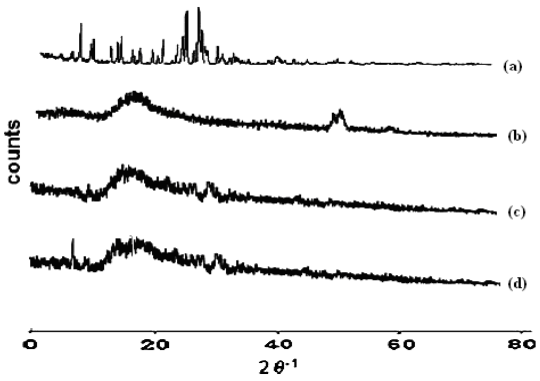

Fig 5: Comparison between PXRD spectra of (a) Lamotrigine (b) HPβCD (c) Inclusion complex and (d) Optimized formulation

***In vitro* release study**

Formulations F1, F3, F5, F7 and F9 which contains 1% superdisintegrants releases 81.93%, 77.47%, 89.01%, 85.17% and 74.22% drug respectively at the end of 10 min (Fig 6). An increase in the drug release was observed when 2% superdisintegrants used in formulations. Formulations F2, F4, F6, F8 and F10 releases 87.81%, 80.74%, 99.63%, 95.16% and 77.78% at the end of 10 min in 0.1N HCl respectively (Fig 7). The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium.

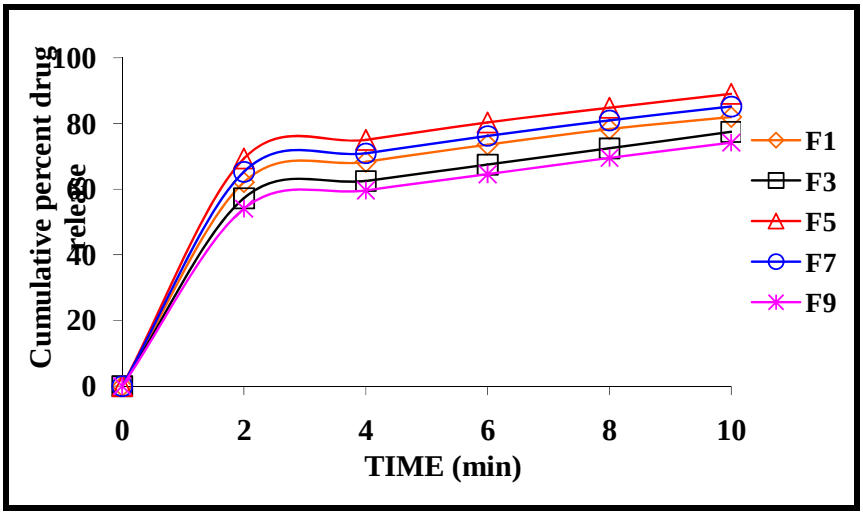

Fig. 6: Effect of 1% superdisintegrants on release rate of lamotrigine

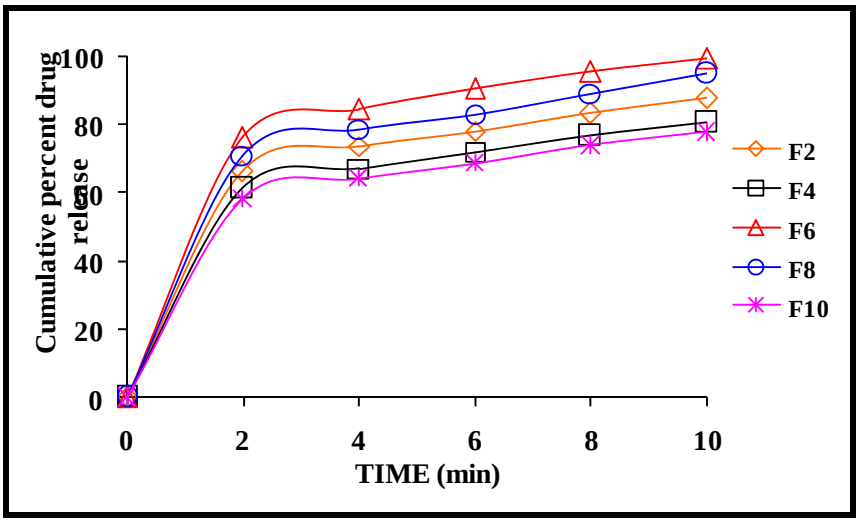

Fig. 7: Effect of 2% superdisintegrants on release rate of lamotrigine

Stability studies

The stability studies were carried out for selected tablets at 25°C ± 2°C / 60 % RH ± 5 % and 40°C ±2 °C / 75 % RH ± 5 % for a month. The orodispersible tablets were evaluated by their drug content, wetting time, water absorption ratio, dispersion time, disintegration time and *in vitro* drug release. The studies indicated that, there were no significant changes found in the tablet properties.

CONCLUSION

HPβCD has been used to solubilize and increase the absorption of poorly water-soluble drugs delivered via the buccal mucosa. Lamotrigine has bitter taste hence approach like HPβCD complex was successfully used to mask the bitter taste and used to enhance the solubility which was confirmed by phase solubility analysis. The comparative study of several superdisintegrants yielded a conclusion that Indion 414 and croscarmellose sodium at 2% concentration are suitable for the preparation of lamotrigine orodispersible tablets which will satisfy all the criteria and official limits.

ACKNOWLEDGEMENT

The authors are grateful to Torrent Pharmaceutical Ltd., Ahmedabad, India for providing gift sample of Lamotrigine. The authors would like to acknowledge the Principal, N.E.T Pharmacy College, Raichur, India for providing facilities during research.

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