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FORMULATION, DEVELOPMENT AND *IN-VITRO* EVALUATION OF ORODISPERSIBLE TABLETS OF LAMOTRIGINE

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ABSTRACT

The aim of the present work is to formulate and develop orodispersible tablets of lamotrigine using different super disintegrating agent by direct compression method. The objective of the study is to increase rapid onset of action of lamotrigine in treatment of epilepsy. The orodispersible tablets of lamotrigine were prepared by diect compression method using different concentration of sodium starch glycolate, crosscarmellose sodium, crospovidone, polyplasdone, indion. The tablet were evaluated for various parameters and results were found to be satisfactory. Total 15 formulations were prepared out of which f13, has shown good results.

KEYWORDS: Lamotrigine, oraldispersible Tablets, Direct compression, Sodium starch Glycolate, Indion.

INTRODUCTION

Oral drug delivery through is the most common and preferred route of drug administration both for solid and liquid dosage forms. However, solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance at site of administration, and most importantly the patient compliance. Tablets and capsules are popular solid dosage forms. However, many people face difficulty in swallowing tablets and hard gelatin capsules, called dysphasia. It has been found that this problem has been encountered in all groups of patient, but especially with pediatric and geriatric populations. Specially in the case of pediatric, geriatric patients, these conventional dosage forms result in high incidence of noncompliance and ineffective therapy with respect to swallowing, or any mentally retarded persons. Orodispersible tablets are also called as orally disintegrating tablets, mouth-dissolving tablets, rapid-dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets. Recently, European Pharmacopoeia has used the term orodispersible tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 min before swallowing. United States Pharmacopoeia has also approved these dosage forms as orodispersible tablets. Thus, orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. It offers several advantages with respect to its stability, administration without water, accurate dosing, easy manufacturing, small packaging size, and handling.Its ease of administration in the population especially for pediatric, geriatric, or any mentally retarded persons makes it a very popular dosage form. Due to the presence of super disintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action. Since the absorption is taking place directly from the mouth, so, bioavailability of the drug increases. Drugs present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is becoming popular day by day due to its numerous advantages.

Advantages

They are easy to consume and as such are convenient for such patients as "the elderly, stroke victims, bedridden patients, patients affected by renal failure, and patients who refuse to swallow, such as pediatric, geriatric, and psychiatric patients";

- increased bioavailability (rapid absorption) due to pregastric absorption;
- don't require water to consume and thus suitable for "patient compliant for disabled, bedridden patients, and for travelers and busy people who do not always have access to water";
- good mouth feel;
- improved safety due to low risk of choking or suffocation during oral administration.

Disadvantages

- cost-intensive production process;
- lack of physical resistance in standard blister packs;

- limited ability to incorporate higher concentrations of active drug.

Limitations of ODTs

• These tablets usually have insufficient mechanical strength i.e. hence, careful handling required.
• These tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Challenges to Develop ODTs

• Rapid disintegration of tablet.
• Avoid increase in tablet size.
• Have sufficient mechanical strength.
• Minimum or no residue in mouth.
• Protection from moisture.
• Good package design.
• Compatible with taste masking technology.
• Not affected by drug properties

MATERIALS

Lamotrigine, Sodium starch glycolate, Crosscarmellose, Crospovidone, Indion, Polyplasdone, Mannitol, Micro crystalline cellulose, Aspartate, Talc, Magnesium, Stearate Aerosil are received from Himedia laboratories.

METHODS

Preparation of Orodispersible by using direct compression

In the direct compression method of tablet production, dry ingredients are thoroughly mixed and then compressed into tablets. This eliminates the drying steps associated with the wet granulation method. It also reduces the higher costs involved in wet granulation including increased equipment, labor, time, process validation and energy expenditure. As a result, direct compression is both efficient and economical, well suited to the production of high quality tablets, which exhibit hardness, low friability and excellent dissolution rates. As an added benefit, direct compression can improve the physical and chemical stability of tablets as compared to wet granulation (Bolhius and Lerk, 1973).Direct compression demands the use of excipients with strictly defined properties. Kerry has designed a range of excipients specifically to meet the requirements of the direct compaction process and your needs. The formuation of lamotrigine orodispersible tablets is given in table no 1.

EVALUATION METHODS

Pre-compression studies

Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

Db = M/ Vb

Where,
M is the mass of powder
Vb is the bulk volume of the powder.

Tapped Density (Dt)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

Dt = M / Vt

Where,
M is the mass of powder
Vt is the tapped volume of the powder.

Table 1: Formulation of lamotrigine orodispersible tablets 100mg.

c	Composition (mg)	Batch code														
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}
1	Lamotrigine	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
2	SSG	4	6	8	---	---	---	---	---	---	---	---	---	---	---	---
3	CCS	---	---	---	4	6	8	---	---	---	---	---	---	---	---	---
4	CPD	---	---	---	---	---	---	4	6	8	---	---	---	---	---	---
5	PPD	---	---	---	---	---	---	---	---	---	4	6	8	---	---	---
6	Indion	---	---	---	---	---	---	---	---	---	---	---	---	4	6	8
7	Mannitol	52.5	50.5	48.5	52.5	50.5	48.5	52.5	50.5	48.5	52.5	50.5	48.5	52.5	50.5	48.5
8	MCC	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
9	Aspartame	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
10	Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
11	Aerosol	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
12	Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Angle of Repose (Ɵ)
The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane tan(Ɵ) = h / r
Ɵ = tan-1 (h / r)
Where,
Ɵ is the angle of repose.
h is the height in cm, r is the radius in cm.

Carr's index (or) % compressibility
It indicates powder flow properties. It is expressed in percentage and is give by,
I=Dt - Db / Dt×100
Where,
Dt is the tapped density of the powder
Db is the bulk density of the powder.

Hausnerratio: It is an indirect index of ease of powder flow. It is calculated by the following formula.
Hausner ratio=Dt /Dv
Where,
Dt is the tapped density,
Db is the bulk density.
Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post-compression Studies
Hardness Test
Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester.
It is expressed in kg/cm2.

Weight variation
20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

Friability (F)
Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed.

Invitro Dissolution studies: Invitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min.

In-vitro disintegration test: 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 drug release - Release of the drug in vitro, was determined by estimating the dissolution profile, USP 2 Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, phosphate buffer (PH 6.8) (900 ml) was used as a dissolution medium.

Friability testing: The crushing test may not be the best measure of potential behaviour during handling and packaging. The resistance to surface abrasion may be a more relevant parameter. Friability of each batch was measure in "Electro lab friabilator". Ten preweighed tablets were rotated at 25 rpm for 4 min, the tablets were then re weighed and the percentage of weight loss was calculated. Rapidly Disintegrating Property To evalutae the tablets for their rapid disintegration properties, following tests were carried out.

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

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

In-vitro disintegration test: 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.

Differential scanning calorimetry, or DSC, is a Thermoanalytical technique in which the difference in the amount of heat required to increase the Temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned. The technique was developed by E. S. Watson and M. J. O'Neill in 1962, and introduced commercially at the 1963 Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy. The first adiabatic differential scanning calorimeter that could be used in biochemistry was developed by P. L. Privalov and D. R. Monaselidze in 1964 at Institute of Physics in Tbilisi, Georgia. The term DSC was coined to describe this instrument, which measures energy directly and allows precise measurements of heat capacity.

Applications

Differential scanning calorimetry can be used to measure a number of characteristic properties of a sample. Using this technique it is possible to observe fusion and crystallization events as well as glass transition temperatures T_g. DSC can also be used to study oxidation, as well as other chemical reactions.

Glass transitions may occur as the temperature of an amorphous solid is increased. These transitions appear as a step in the baseline of the recorded DSC signal. This is due to the sample undergoing a change in heat capacity; no formal phase change occurs.

As the temperature increases, an amorphous solid will become less viscous. At some point the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature (T_c). This transition from amorphous solid to crystalline solid is an exothermic process, and results in a peak in the DSC signal. As the temperature increases the sample eventually reaches its melting temperature (T_m). The melting process results in an endothermic peak in the DSC curve. The ability to determine transition temperatures and enthalpies makes DSC a valuable tool in producing phase diagrams for various chemical systems.

Fourier transform infrared spectroscopy (FTIR) is a technique which is used to obtain an infrared spectrum of absorption or emission of a solid, liquid or gas. An FTIR spectrometer simultaneously collects high spectral resolution data over a wide spectral range. This confers a significant advantage over a dispersive spectrometer which measures intensity over a narrow range of wavelengths at a time.The term Fourier transform infrared spectroscopy originates from the fact that a Fourier transform (a mathematical process) is required to convert the raw data into the actual spectrum. For other uses of this kind of technique,

Advantages

There are three principal advantages for an FT spectrometer compared to a scanning (dispersive) spectrometer.

1. The multiplex or Fellgett's advantage. This arises from the fact that information from all wavelengths is collected simultaneously. It results in a higher Signal-to-noise ratio for a given scan-time for observations limited by a fixed detector noise contribution (typically in the thermal infrared spectral region where a photodetector is limited by generation-recombination noise). For a spectrum with m resolution elements, this increase is equal to the square root of m. Alternatively, it allows a shorter scan-time for a given resolution. In practice multiple scans are often averaged, increasing the signal-to-noise ratio by the square root of the number of scans.
2. The throughput or Jacquinot's advantage. This results from the fact that in a dispersive instrument, the monochromator has entrance and exit slits which restrict the amount of light that passes through it. The interferometer throughput is determined only by the diameter of the collimated beam coming from the source. Although no slits are needed, FTIR spectrometers do require an aperture to restrict the convergence of the collimated beam in the interferometer. This is because convergent rays are modulated at different frequencies as the path difference is varied. Such an aperture is called a Jacquinot stop. For a given resolution and wavelength this circular aperture allows more light through than a slit, resulting in a higher signal-to-noise ratio.
3. The wavelength accuracy or Connes' advantage. The wavelength scale is calibrated by a laser beam of known wavelength that passes through the interferometer. This is much more stable and accurate than in dispersive instruments where the scale depends on the mechanical movement of diffraction gratings. In practice, the accuracy is limited by the divergence of the beam in the interferometer which depends on the resolution.

Another minor advantage is less sensitivity to stray light, that is radiation of one wavelength appearing at another wavelength in the spectrum. In dispersive instruments, this is the result of imperfections in the diffraction gratings and accidental reflections. In FT instruments there is no direct equivalent as the apparent wavelength is determined by the modulation frequency in the interferometer.

RESULTS AND DISCUSSIONS

Table 2: In-vitro- pre compression studies.

Batch code	Bulk Density kg/cm^2	Tapped density kg/cm^2	Carr's Index %	Hausners ratio	Angle of Repose θ
F1	0.453±0.005	0.546±0.005	17.03	1.205	18.22
F2	0.440±0	0.543±0.005	18.968	1.234	18.26
F3	0.493±0.005	0.553±0.015	10.849	1.121	18.45
F4	0.463±0.005	0.556±0.011	16.720	1.200	18.33
F5	0.473±0.005	0.553±0.015	14.466	1.169	18.12
F6	0.440±0.010	0.550±0.010	20	1.250	18.23
F7	0.450±0.010	0.563±0.015	20.071	1.251	18.11
F8	0.466±0.015	0.553±0.025	15.732	1.186	18.22
F9	0.463±0.020	0.550±0.020	15.818	1.187	18.26
F10	0.456±0.015	0.563±0.015	19.005	1.234	18.19
F11	0.460±0.020	0.553±0.015	16.817	1.202	18.17
F12	0.480±0.020	0.553±0.015	13.200	1.152	18.18
F13	0.440±0	0.550±0	20	1.250	18.10
F14	0.463±0.020	0.546±0.005	15.201	1.179	18.19
F15	0.476±0.015	0.563±0.015	15.452	1.182	18.82

Table 3: In-vitro post compression studies.

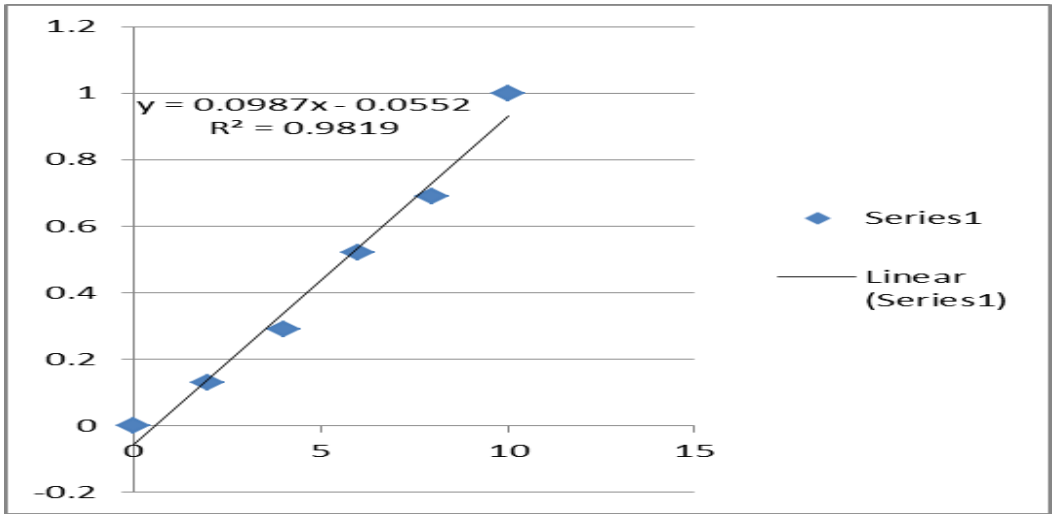
Batch Code	Weight – variation mm	Hardness kg/cm^2 n=3	Friability %	Thickness mm n = 3	Disintigration sec n=3
F1	100±1.015	2.5	0.5	3.10	17.58
F2	100±1.011	2.5	V.S	3.11	18.45
F3	100±1.252	2.5	0.6	3.12	19.21
F4	100±1.447	2.8	0.8	3.10	18.20
F5	100±1.888	2.7	0.9	3.16	18.36
F6	100±1.531	2.5	0.5	3.14	18.44
F7	100±1.356	2.7	0.8	3.15	19.33
F8	100±1.860	2.8	0.9	3.18	18.55
F9	100±0.786	3	0.6	3.11	19.33
F10	100±0.768	2.6	0.7	3.21	20.45
F11	100±1.302	2.2	0.9	3.19	18.33
F12	100±1.269	2.7	0.8	3.11	15.23
F13	100±1.215	2.5	0.7	3.12	15.00
F14	100±1.118	2.6	0.8	3.11	19.33
F15	100±0.940	2.8	0.6	3.15	19.52

Table 4: Invitro dispersion time of all formulations.

Batch code	Invitro dispersion time		
	6.8buffer	0.1N HCL	WATER
F1	9.66±0	12.33±0.577	4.33±0.661
F2	16.66±0	24.33±1.52	6.11±2.309
F3	9.66±0.577	8.33±0.577	5.66±0
F4	8.66±0.577	18.33±0.577	25.33±6.429
F5	42.66±5.033	42.66±5.033	26.33±5.773
F6	29.33±0	36±2	26.33±5.773
F7	18±0	22.33±0.577	33±1.295
F8	8±1.732	8.33±0.577	5.33±0.572
F9	6.33±1.73	6.66±0.577	6±1
F10	6.33±0	8.331±0.527	6±1
F11	39.33±0	11±0	14.33±0.041
F12	51±2.645	13.33±0.577	18±2
F13	4.33±0.661	5.66±0.577	9.33±1.527
F14	20.33±0	8.33±0.568	11.33±3.785
F15	37.66±4.509	14.33±3.055	22±3.464

Table 5: calibration curve of lamotrigine.

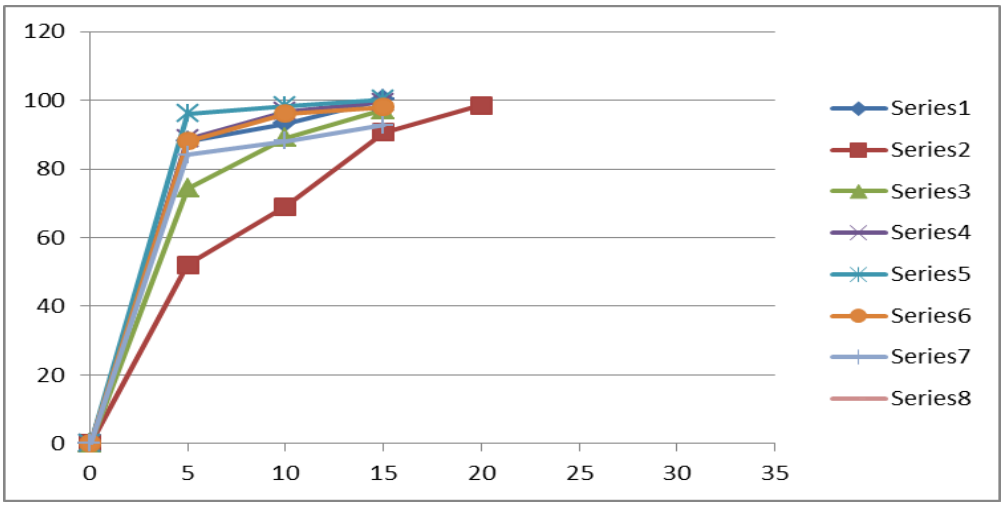
Concentration µg/ml	Absorbance
2	0.13
4	0.29
6	0.52
8	0.69
10	1



Graph 1: Calibration standard graph.

Table 6: Invitro drug release of formulations F1 to F8.

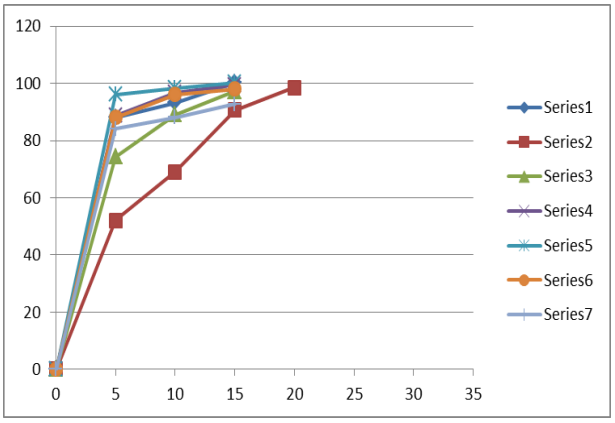
Sl. no	Time min	Batch code							
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1	5	76%	81%	89.2%	92.93%	94.40%	96.30%	91.46%	94.24%
2	10	98.3%	87.4%	99.0%	95.06%	95.22%	98.42%	97.44%	96.06%
3	15	99.05%	98.33%	99.7%	99.73%	99.22%	100.04	100.29%	99.54%
4	20	---	---	---	---	---	---	---	---
5	25	---	---	---	---	---	---	---	---
6	30	---	---	---	---	---	---	---	---



Graph 2: In vitro drug release of formulations F1 to F8.

Table 7: Invitro drug release of formulations F9 to F15.

Sl. no	Time min	Batch code						
		F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}
1	5	88.13%	52%	74.30%	88.69%	96.08%	88.06%	84.12%
2	10	93.27%	69%	89.06%	96.72%	98.28%	96.09%	88.06%
3	15	100.27%	90.73%	97.16%	99.54%	100.34%	98.03%	92.72%
4	20	---	98.44%	---	---	---	---	---
5	25	---	---	---	---	---	---	---
6	30	---	---	---	---	---	---	---



Graph 3: In vitro drug release of formulations F9 to F15.

Table - 8: Solubility results of all formulations.

	Solubility		
	6.8buffer	0.1N HCL	WATER
Lamotrigine	FS	SS	SS
CM1	VS	VS	VS
CM2	VS	VS	VS
CM3	VS	VS	VS
F1	VS	VS	VS
F2	VS	VS	VS
F3	VS	VS	VS
F4	VS	VS	VS
F5	VS	VS	VS
F6	VS	VS	VS
F7	VS	VS	VS
F8	VS	VS	VS
F9	VS	VS	VS
F10	VS	VS	VS
F11	VS	VS	VS
F12	VS	VS	VS
F13	VS	VS	VS
F14	VS	VS	VS
F15	VS	VS	VS

DSC of lamotrigine (Drug)

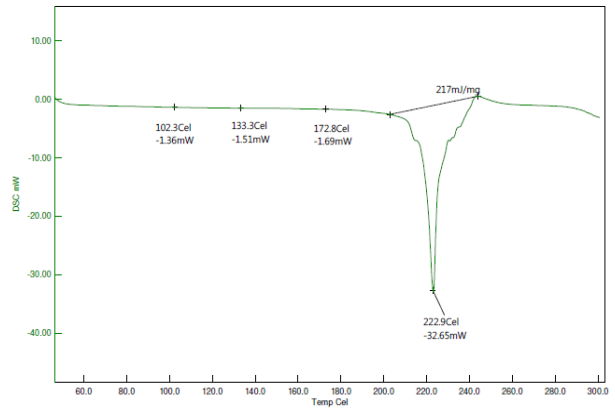


Figure1: DSC of lamotrigine (Drug).

DSC of F6

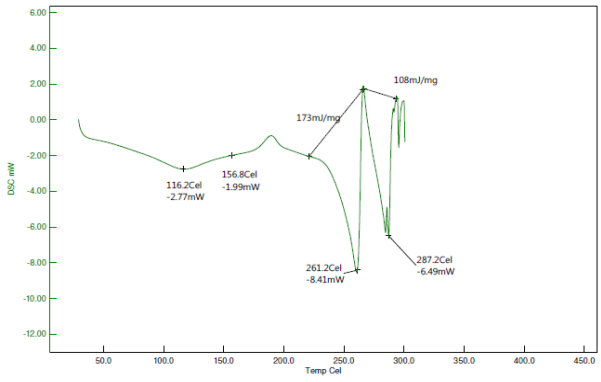


Figure-2: DSC of F6.

DSC of F13

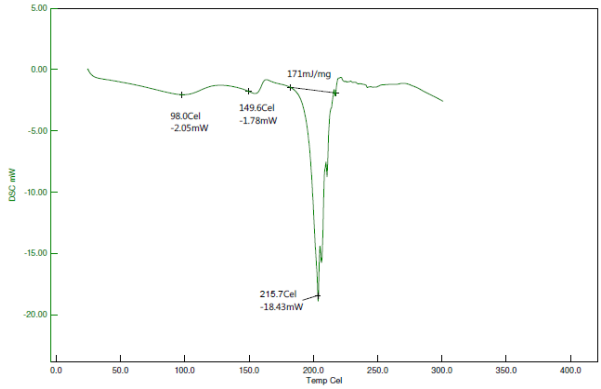


Figure 3: DSC of F13.

FTIR of lamotrigine(Drug)

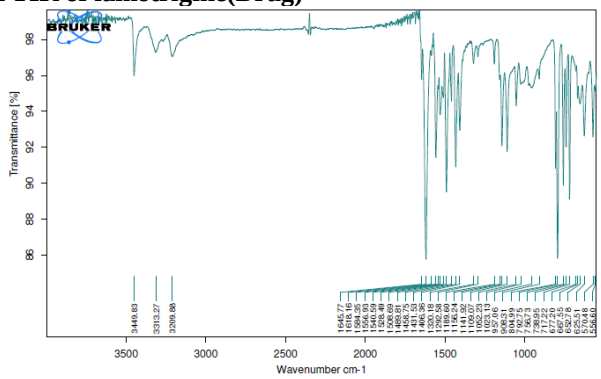


Figure 4: FTIR of lamotrigine(Drug).

FTIR of Indion

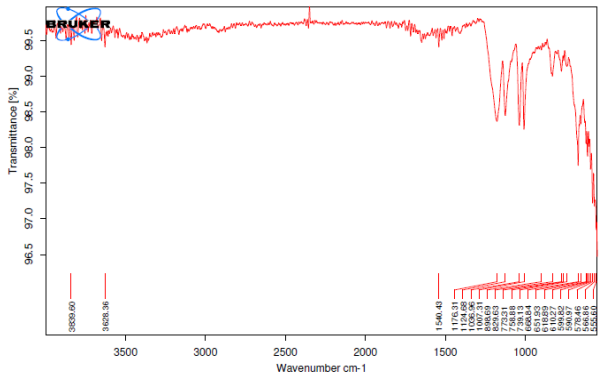


Figure 5: FTIR of Indion.

FTIR of Polyplasdone

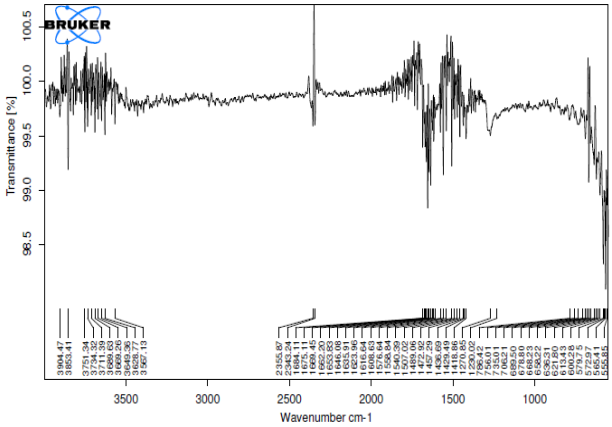


Figure 6: FTIR of Polyplasdone.

FTIR of Crosspovidone

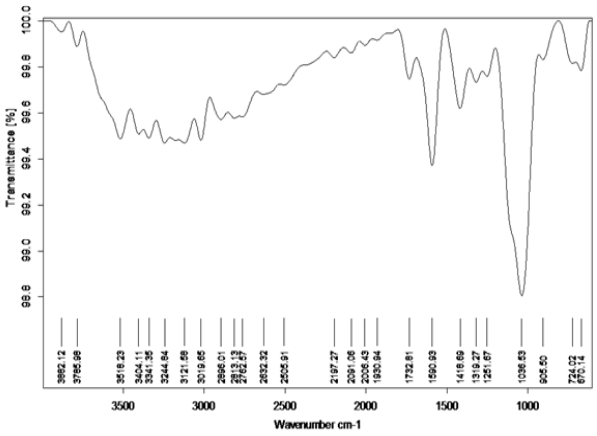


Figure 7: FTIR of Crosspovidone.

Micro-cellulose crystalline

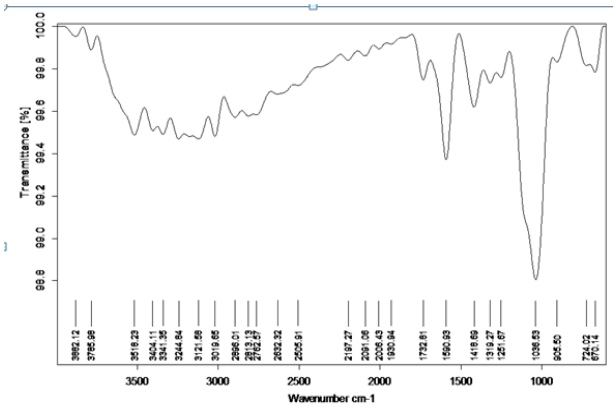


Figure 8: Micro-cellulose crystalline.

FTIR of Formualtion containing Polyplasdone

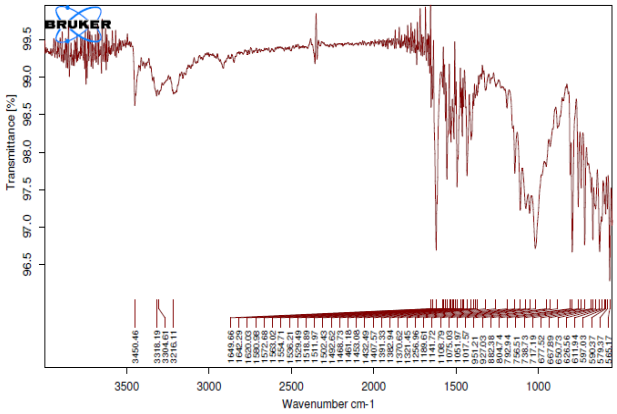


Figure 9: FTIR of Formualtion containing Polyplasdone.

FTIR Formualation containing Sodium starch glycolate

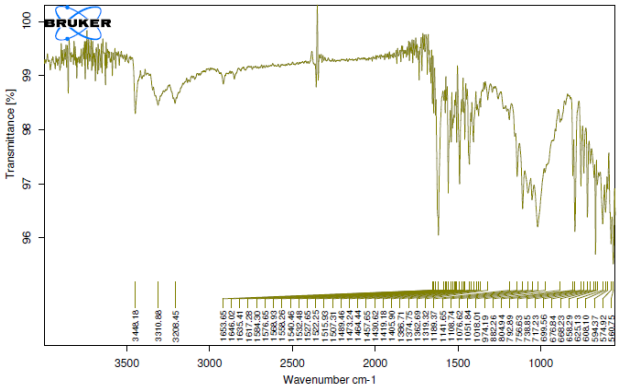


Figure 10: FTIR Formualation containing Sodium starch glycolate.

FTIR Formualion containing Crosscarmilose

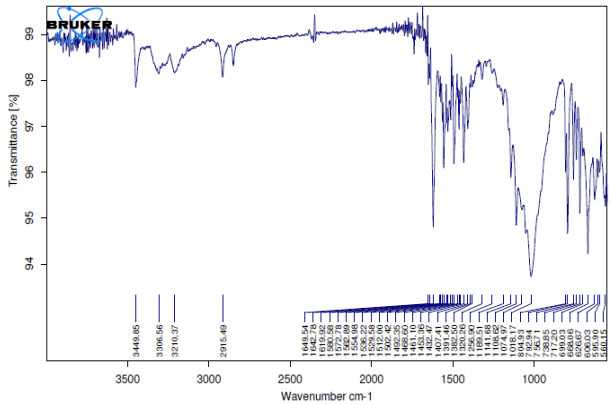


Figure 11: FTIR Formualion containing Crosscarmellose.

FTIR Formualtion containing Crosspovidone

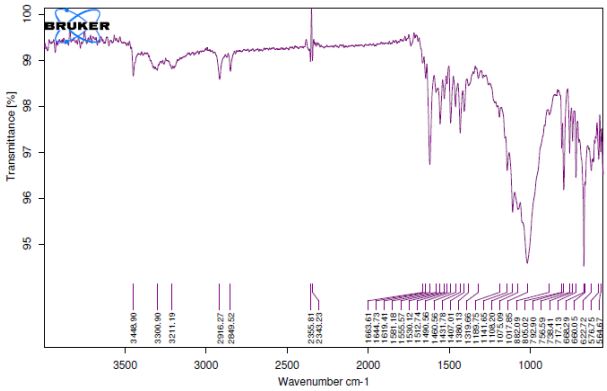


Figure 12: FTIR Formualtion containing Crosspovidone.

FTIR Formualation Containing Indion

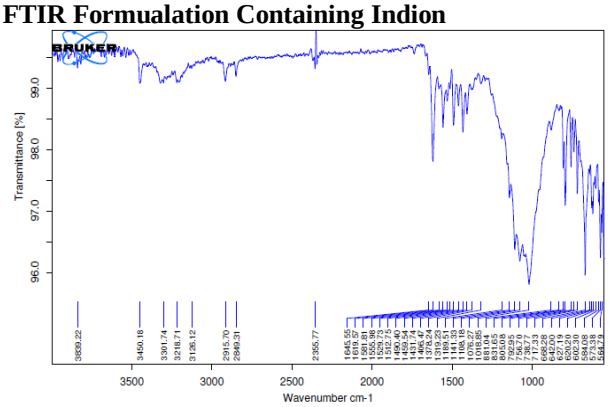


Figure 13: FTIR Formualation Containing Indion.

CONCUSION

Orodispersible tablets of lamotrigine using different superdisintegrating agents in different concentration by direct compression method were formulated,evaluated and the results are found to be satisfactory.F6 and F13 formulation have shown good result in all aspects where has F13 found to be best formulation from the prepared formulation depending upon DSC Analysis.

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