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FORMULATION AND EVALUATION OF LAMOTRIZINE ORODISPENSIBLE TABLETS

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Abstract:

The aim of the present study was to develop and optimize oral disintegrating tablets of model drug (Lamotrizine) to give quick onset of action by rapidly disintegrating in a few seconds without the need of water with better patient compliance. In such cases, bioavailability of drug is significantly greater and adverse event is reduced than those observed from conventional tablet dosage form. By performing compatibility studies by IR spectrophotometry, no interaction was confirmed. Oral disintegrating tablets were formulated by direct compression method and evaluated by UV-Visibile spectrophotometer. Standard calibration curve prepared to determine the drug content in the prepared tablets. Prior to compression, the blend of drug and excipients were evaluated for flow properties such as Angle of repose, Bulk density, Tapped density, % Compressibility, and Hausner ratio. All the formulation showed excellentproperties. Oral disintegrating tablets were prepared by direct compression technique using CADMACH 16 station tablet punching machine, equipped with round flat punches of 8 mm diameter. Post compression evaluation of prepared oral disintegrating tablets were carried out with the help of different pharmacopoeial and non-pharmacopoeial (industry specified) tests. The shape and color of all the formulations were found to be circular and white in color. The thickness was found to be uniform in specific formulations. The hardness and friability are also within the permitted limits. Dissolution of tablets was carried out. The crospovidone used formulation gave the more dissolution profile compared to other superdisintegrants.

Keywords: *Lamotrizine, UV-Visibile spectrophotometer , superdisintegrants, crospovidone*

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INTRODUCTION:

Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance [1]. One such approach was oral dispersible tablets which has gained acceptance and popularity in the recent time. Oro - dispersible tablet provides a convenient means of administrating drugs, particularly to pediatrics and geriatric patients, more importantly they can be taken without water for oral drug administration. Several pharmaceutical industries prepared oro - dispersible tablets by direct compression technique by selecting suitable superdisintegrants. Direct compression technique offers important advantages such as increased output, reduced cost, less machinery and improved drug stability when compared to the wet granulation method [2].

Lamotrigine is an anticonvulsant medication used to treat epilepsy and bipolar disorder. In bipolar, it is used to treat acute episodes of depression, rapid cycling in bipolar type II, and prevent recurrence in bipolar type I[3]. Common side effects include sleepiness, headache, vomiting, trouble with coordination, and rash. Serious side effects include lack of red blood cells, suicide, Stevens-Johnson syndrome, and allergic reactions. There are concerns that use during pregnancy or breastfeeding may result in harm. Lamotrigine is a phenyltriazine, making it chemically different from other anticonvulsants. It appears to increase the action of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system and decrease voltage-sensitive sodium channels [4].

The present research work has been carried out with an aim to formulate Lamotrizine orally disintegrating tablets with superdisintegrants like crospovidone, croscaramellose sodium and sodium starch glycolate in different concentrations

MATERIALS AND METHOD:

Chemicals Required:

Cefuroxime axetil, Mannitol, Microcrystalline cellulose, crospovidone, Magnesium stearate, Sodium starch glycolate.

Apparatus Required:

Balance, sieves, tapped density tester, mixer granulator, mechanical stirrer, dryer, compression meachine, vernier calipers, hardness tester, disintegration apparatus, stability chambers, phmeter and dissolution

API Characterization

A. Organoleptic evaluation

Organoleptic characters like color, odor, and taste of drug were observed and recorded using descriptive terminology.

B. Analytical evaluation

Calibration Curve of Lamotrizine in 0.1N Hcl[5]

Preparation of Stock solution

Stock I: 100mg of the drug was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in sufficient quantity of buffer and volume was made up to the mark with 6.8 Phosphate buffer to get a 1000 µg/ml solution. This was the standard stock solution containing 1 mg/ml of model drug. (Stock I).

Stock 2: From above stock 1 solution 10ml was taken and make up with 6.8 Phosphate buffer to 100ml and this was 100 ppm concentration solution.

Preparation of the calibration curve

From the stock II solution proper dilutions were made to 10 ml volumetric flasks and were diluted with 6.8 Phosphate buffer up to the mark to obtain concentration of 1, 2, 3, 4 and 5µg/ml respectively. Absorbance of each solution was measured at 243 nm. The Standard curve preparation was performed. The absorbances on x-axis were plotted against the concentrations on y-axis and r^2 value was obtained.

Pre-Formulation Studies

I. FT-1R Studies [6]

The IR absorption spectra of the Lamotrizine drug and with different superdisintegrants, natural gums and excipients were taken in the range of 4000-450 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powdered and dried potassium bromide .These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due presence super disintegrants and excipients.

Formulation Planning

Oro dispersible tablets containing 6.25mg of Lamotrizine were prepared with a total tablet weight of 150mg. By conducting the thorough literature survey, the excipients were selected and an attempt was made to produce Oro dispersible tablets.

General formula

Different superdisintegrants croscarmellose sodium, crospovidone, Sodium starch glycollate in the concentration range of 3- 7.5%.. Microcrystalline cellulose (Avicel PH102) was selected as the filler or diluent, owing to its multiple functionalities as binder, disintegrant, compressibility and flowability. Out of the various grades available, the granular form - Avicel PH102 was selected for direct compression purpose, because it had been already reported to provide lower crushing strengths and shorter disintegration times. To improve flow property of the blend magnesium stearate (1.5%) and aerosil (1%) as glidant and lubricant were incorporated, magnesium stearate also decreases the hardness of tablets without affecting the disintegration time.

Formulation of different batches

The main aim of the present study was to formulate different batches using three various superdisintegrants and other ingredients in varying concentrations. So, different batches of formulations were planned accordingly. According to that F1, F2, F3 (with Crospovidone-3%, 5%, 7.5%), F4, F5, F6 (with Crosscaramellose-3%, 5%, 7.5%), F7, F8, F9 (with Sodium starch glycollate-3%, 5%, 7.5%).

Table 1: Formulations of Different Batches (F1-F9)

Formulations Code									
Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Lamotrizine	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Crospovidone	4.5	7.5	11.25	------	------	-------	------	------	-----
Croscarmellose sod.	------	------	------	4.5	7.5	11.25	------	------	-----
SSG	------	-----	----	-------	------	-----	4.5	7.5	11.25
MCC 102	qs	Qs	qs	Qs	qs	qs	qs	qs	Qs
Vanillin	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Mannitol	30	30	30	30	30	30	30	30	30
Magnesium stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation of Tablet Blends:

Pre-compression parameters:

1. Angle of repose [7]

A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

2. Bulk density and tapped density [8]

Apparent Bulk density (gm/ml) of the drug was determined by pouring (preseived 40-mesh) gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density was calculated by following formula.

Tapped densities the drug was determined by pouring gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. In USP TAP DENSITY TESTER, Tap density is measured in 500taps, 750 taps & 1250taps with drop/time-299-302. Volume occupied by the sample after tapping were recorded and tapped density was calculated.

3. Measures of Powder Compressibility (Carr's compressibility index) [9]
Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density.

4. Hausner ratio [10]
Hausner's ratio provides an indication of the degree of densification which could result form vibration of the feed hopper. A lower value of indicates better flow and vice versa.

Method of Formulation [11]:
Direct compression method.
The model drug (Lamotrizine) is thoroughly mixed with the super disintegrants and then other excipients are added to the mixer and passed through the sieve (sieve no. 40). Collected the powder mixer, blended with magnesium stearate (pre sieved through sieve no. 60), the powder blend is subjected to drying for removal of moisture content and then subjected the blend for tablet compression by using Round and flat faced punches in CADMACH 16 punches tablet punching machine. Punches of 8 mm diameter were used for compression. Tablet of 150 mg was prepared by adjusting hardness and volume screw of compression machine properly.

Post compression tests:
1. Organoleptic properties of tablets
Organoleptic properties such as taste, color, odour, were evaluated. Ten tablets from each batch were randomly selected and tested for taste, color, odour and physical appearance**.**

2. Uniformity of Thickness [12]
The thickness of individual tablets of 6 numbers were measured with vernier calipers, it permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within ± 5% variation of standard value.

3. Hardness [13]: The tablet hardness of different formulations was measured using the Monsanto hardness tester for 6 tablets. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge on the barrel to indicate the force. The force of fracture is recorded and the zero force reading is deducted from it. Generally, a minimum hardness of 5 - 7 kg/cm^2 is considered acceptable for uncoated tablets.

4. Weight Variation Test [13]
Twenty tablets from each batch were weighed with electronic digital balance and average weight was determined. Then individual tablets were weighted and individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Standard deviation was calculated. Using this procedure weight variation range of all the batches were determined and recorded.

5. Friability [14]
The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Thirty three tablets (6.600gms.) were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$\% \textbf{ Friability} = \frac{\textbf{Loss in weight}}{\textbf{Initial weight}} \times \textbf{100}$$

Where,

W1 = Initial weight of the 33 tablets before testing.

W2 = Final weight of the 33 tablets after testing.

Friability values below 1% are generally acceptable.

% Friability of tablets less than 1% is considered acceptable. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1 - 0.9%).

6. In vitro Disintegration time [15]
The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications.

I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 0.1N Hcl as dissolution medium maintained at 37^0±2C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the 0.1N Hcl maintained at 37±2c. The time in seconds taken for complete disintegration of the tablet with no palpable mass

remaining in the apparatus was measured and recorded.

7. Drug Content Uniformity [16, 17]

Assay

Twenty tablets were selected randomly and powdered. A quantity of this powder corresponding to one tablet was dissolved in 100 ml of 0.1N Hcl, stirred for 15 min and filtered. 1 ml of the filtrate was diluted to 100 ml with 0.1N Hcl. Absorbance of this solution was measured at 243nm using 0.1N Hcl as blank and content of drug was estimated.

8. *In vitro* Dissolution studies [18]:

Dissolution of the tablet of each batch was carried out using USP type II apparatus (ELECTRO LAB) using paddles at 50 rpm. As per the official recommendation of IP 500ml of 0.1N Hcl used as dissolution medium and the temperature of the medium was set at 37 ± 0.5 ^{0}C. 5 ml of sample was withdrawn at predetermined time interval of 5min., 10min., 15min., 20min, 30min, 45mins and 60mins. And same volume of fresh medium was replaced. The withdrawn samples were analyzed by an UV-visible spectrophotometer at 243 nm using 0.1N Hcl solution as blank solution.

The drug content was calculated using the equation generated from standard calibration curve. The % cumulative drug release was calculated.

Table 2: Summary of general dissolution conditions

Sl. No.	Parameter	Specifications
1.	Dissolution medium	6.8 pH Phosphate buffer
2.	Temperature	37±0.5^{o}c
3.	Rotation speed	50 rpm
4.	USP Type II	Paddle
5.	Volume withdrawn	5 ml
6.	λ_{max}	243 nm

RESULTS AND DISCUSSION:

RESULTS

Table 3: Organoleptic characteristics of the drug

Characteristics	Results
Colour	White to off white powder

Table 4: Calibration Curve of Lamotrizine with 6.8 Ph Phosphate Buffer

Concentration	Absorbance
0	0
1	0.084
2	0.165
3	0.249
4	0.330
5	0.445

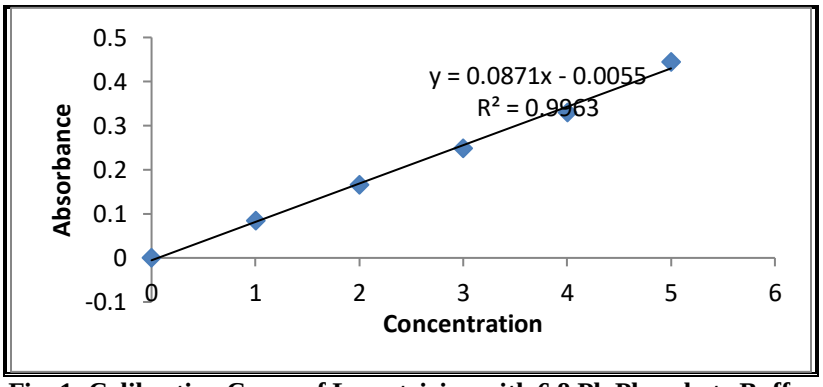

Fig .1: Calibration Curve of Lamotrizine with 6.8 Ph Phosphate Buffer

Drug-excipients Compatibility studies

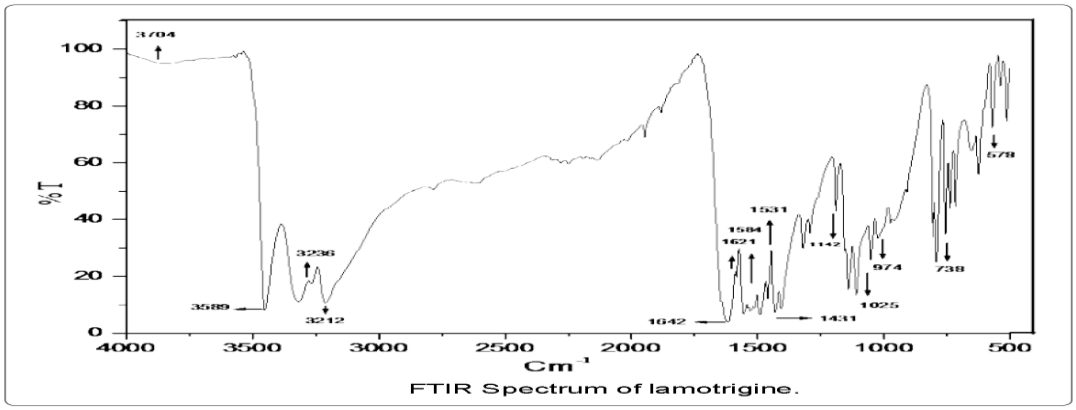

Fig .2: FT-IR spectra of Lamotrizine

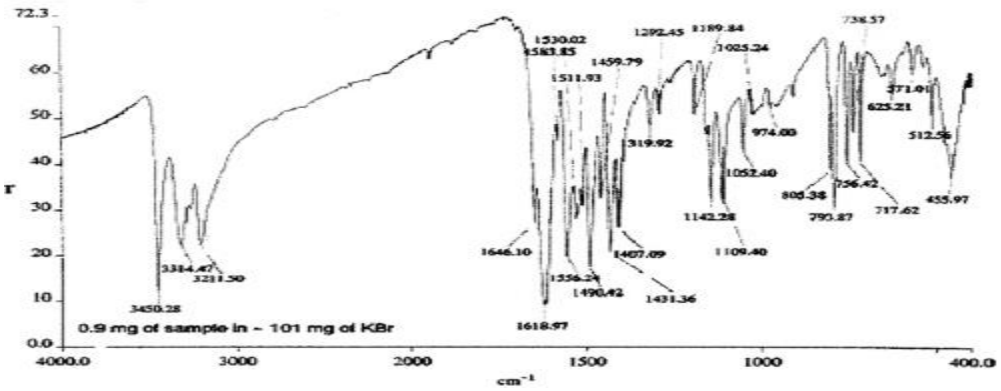

Fig .3: FT-IR spectra of Lamotrizine final formulation

Table 5: Evaluation of tablet blend for formulations (F1 – F9)

Formulation	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner ratio	Compressibility index (%)	Angle of repose
F1	0.42	0.48	1.14	12.50	26.09
F2	0.39	0.45	1.15	13.33	27.16
F3	0.35	0.41	1.17	14.63	25.57
F4	0.44	0.50	1.14	12.00	26.38
F5	0.42	0.47	1.12	10.64	28.94
F6	0.45	0.51	1.13	11.76	24.64
F7	0.38	0.43	1.13	11.63	29.10
F8	0.40	0.45	1.13	11.11	27.69
F9	0.46	0.52	1.13	11.54	25.18

Table 6: Evaluation of Immediate Release Tablets for formulations (F1 – F9)

Formulation	Hardness(kg/cm^2)	Friability(%)	Weight (mg)	Thickness(mm)
F1	3.2	0.35	151	2.20
F2	3.0	0.32	148	2.21
F3	3.4	0.36	150	2.16
F4	3.6	0.34	151	2.11
F5	3.2	0.38	150	2.19
F6	3.5	0.40	148	2.13
F7	3.0	0.37	152	2.20
F8	3.3	0.32	151	2.18
F9	3.5	0.41	149	2.14

Table 7: Evaluation of Immediate Release Tablets for formulations (F1 – F9)

Formulation	Disintegration time(sec)	Drug content (%)
F1	17	97.80
F2	14	99.05
F3	10	98.12
F4	5	99.10
F5	4	99.48
F6	2	98.16
F7	32	97.45
F8	24	98.16
F9	20	99.09

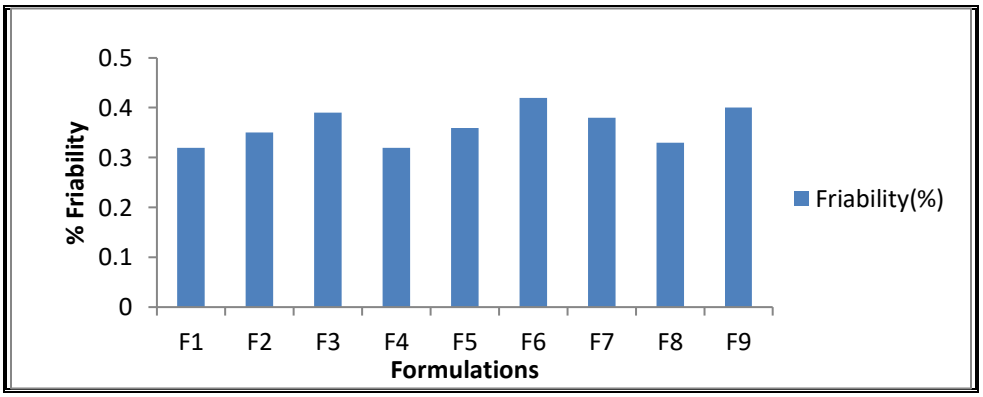

Fig .4: Bar graph comparison friability for formulations (F1- F9)

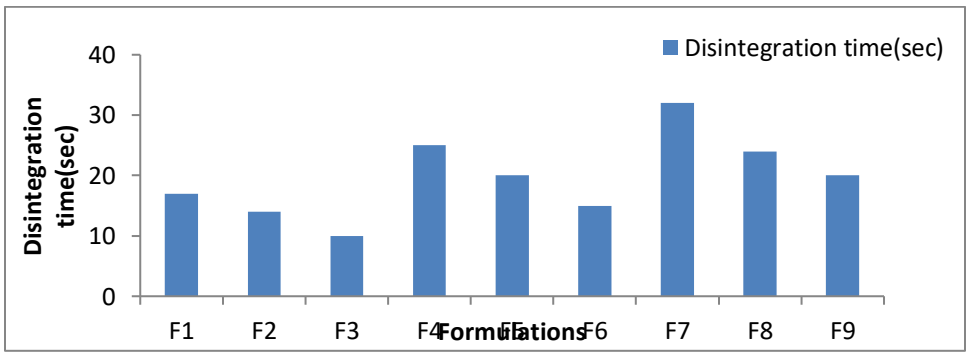

Fig .5: Bar graph comparison between Disintegration time for formulations (F1- F9)

Table 8: Cumulative % drug release for formulations (F1 – F9)

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	19	21	13	21	33	69	28	29	28
10	32	34	22	45	64	99	40	43	45
15	40	45	52	52	83	99	62	67	60
30	51	53	76	63	98	98	74	81	78
45	67	70	99	85	98	98	83	89	82
60	80	94	99	98	98	98	89	98	99

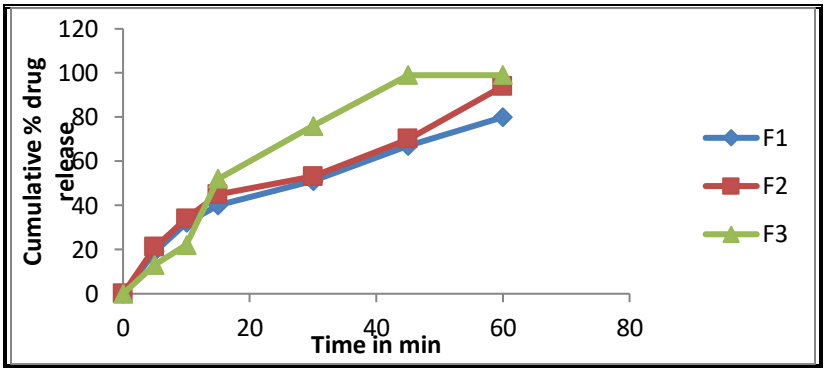

Fig .6: Linear graph comparison between cumulative % drug release for formulations (F1- F3)

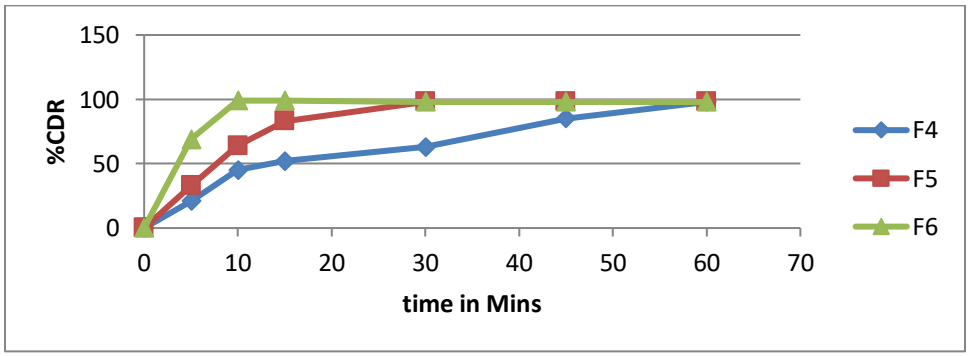

Fig .7: Linear graph comparison between cumulative % drug release for formulations (F4 - F6)

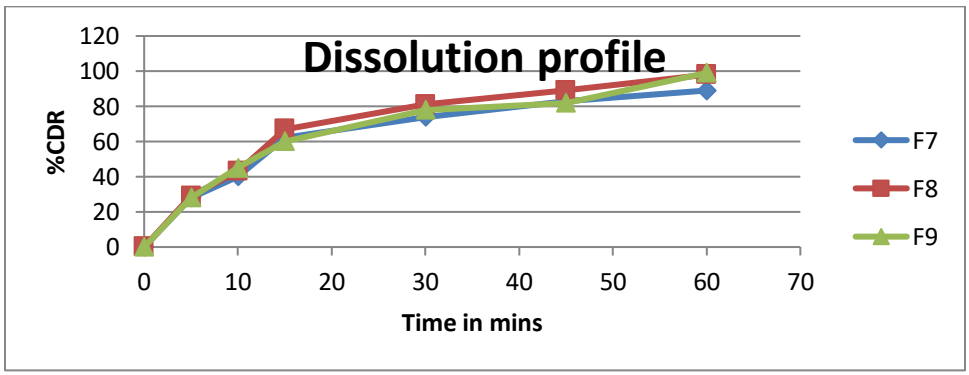

Fig .8: Linear graph comparison between cumulative % drug release for formulations (F7- F9)

Table 9: Stability studies of optimized formulation at room temperature

Time	Colour	Cumulative % drug release ± St.D.	Drug content ± St.D.
First day	White	96.20± 0.91	96.20±0.55
30 days	White	95.84 ± 0.23	96.01±0.72
60 days	White	99. 06 ± 0.62	95.62±0.65
90 days	White	98. 92 ± 0.31	95.20±0.98

Stability Studies of Lamotrizine Optimized Formulation:

The optimized formulation of Lamotrizine (F6) were subjected to short-term stability testing by storing the microspheres at room temperature 25°C/60%RH.

Results from stability studies indicate that the formulated ODT are stable for a period of 3 months under room temperature i.e., 30˚C temp and 65±5% RH. There were no remarkable changes were observed during the period of storage.The optimized formulation of Lamotrizine (F6) were subjected to accelerated stability testing by storing the microspheres at accelerated temperature 40°C/70%RH.

DISCUSSIONS

I. API Characterization

i. Organoleptic properties

An organoleptic property such as color was evaluated and the results are within the standards, shown in (Table.).

ii. Analytical evaluation (Determination of λ_{max})

The absorption wavelength maximum was found to be at 243 nm.

Pre-Formulation Studies

FTIR spectral data

The FT-IR represents the peaks of the Lamotrizine functional groups. These peaks were not affected, they were prominently observed in IR-spectra of Lamotrizine along with super disintegrants, simple disintegrants and other excipients. The spectral details of the drug and the excipients are shown in (Figure.). There was no difference in the position of the absorption bands, hence providing evidence for the absence of any chemical incompatibility between pure drug with the excipients.

Pre- Compression Parameters

1. Angle of repose

All the formulations prepared by direct compression method showed the angle of repose less than 25, which reveals excellent flow property.

2. Bulk density, Tapped density, Hausner ratio, Compressibility index

The bulk density and tapped density for all formulation (F1 – F9) varied from 0.35 - 0.46 gm/cm^3 and 0.41 - 0.52 gm/cm^3 respectively. The results of carr's consolidate index or % compressibility index and hausner's ratio for the entire formulation (F1 – F9) blend range from 11.11-14.63 and 1.12-1.17 respectively, shows fair flow properties. The results are shown in the (Table.).

POST COMPRESSION PARAMETERS

1. Organoleptic properties

All the tablets show similar color, odour, taste and physical appearance. There is no impact of superdisintegrants in their organoleptic properties. **2.**

Hardness test

By using the superdisintegrants, the hardness values ranged from 3.0-3.5 kg/cm^2 for formulations (F1-F9)

3. Weight variation test

The entire tablet passes weight variation test, as the average % weight variation was within the Pharmacopeial limit - 7.5%. It was found to be 148mg -152 mg. The weight of all the tablets was found to be uniform with less deviation.

4. Friability test

The friability values were found to be within the limit 0.32-0.41 (0.5 - 1%). The above evaluation parameter showed no significant difference between F1-F9 formulations.

5. *In-vitro* Disintegration test

Disintegration test carried out in modified dissolution apparatus, Results shows the formulations with 3%, 5%, 7.5% of SSG having high disintegrating time as 32, 24, 20 sec. The disintegration time of F1, F2, F3 with 3%, 5%, 7.5% CP formulations is 17, 14, 10 sec respectively and is almost better than F4, F5, F6, F7, F8, F9 formulations and comparative profile

6. Drug content uniformity

The concentration of the drug in all the formulations with superdisintegrants was found to be 97.45 – 99.48%. It was within the IP limits. The results of drug content of all batches are shown in

7. *In-vitro* Dissolution studies

Dissolution is carried out in USP apparatus type-2 apparatus at 50rpm in 900ml dissolution media (0.1N HCL) for 60 minutes. At the end of 30 minutes almost total amount of the drug is released (i.e. 98%), from the formulation prepared by the direct compression method with 7.5% croscaramellose sodium.

CONCLUSION:

The above results suggest that the formulated oral disintegrating tablets of Lamotrizine exhibited good physical parameters and rapidly disintegrating without affecting the release profile and is very effective in case of elderly and pediatric patients. The overall results indicated that formulation F6 with croscarmellose sodium (7.5%) had a higher edge compared to other formulations containing superdisintegrants. They satisfy all the criteria for oral disintegrating tablets. This direct compression process is simple, reproducible and robust to prepare orally disintegrating tablets of Lamotrizine.

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