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Formulation and Characterization of Mouth Dissolving Tablet of Antiepileptic Drug using Natural Superdisintegrants

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ABSTRACT

MDTs is regarding as a good candidates for the patients with persistent nausea, who are traveling, or who have little or no access to water. The objective of present research work was to prepare and evaluate the mouth dissolving tablet of Lacosamide using Super disintegrants like Guar Gum, and other excipients like Microcrystalline Cellulose and Mannitol in different concentrations by Direct Compression method. Lacosamide has been shown to be an effective antiepileptic agent appropriate for the epilepsy patients. Effect of different formulation variables i.e. amount of polymer and type of polymer was studied on release profile and other characteristics. The mouth dissolving tablets were prepared by single punch machine using powder blend of superdisintegrant and Lacosamide. Post-compression parameters like Hardness, weight variation, friability, *In-Vitro* dispersion, Drug content uniformity and *In-vitro* drug release studies were carried out for all the formulation. All the Formulations gave the result within the official limits. The prepared mouth dissolving tablet shows the properties of fast disintegration time (28 sec to 47 sec) within official limit. By the *in-vitro* disintegration, it is concluded that formulation F2 prepared by Guar Gum (10%) showed the fast disintegration time than the MCC. Therefore, it may be concluded that mouth dissolving tablet was suitable choice for delivery system of Lacosamide.

Keywords: Lacosamide, Mouth dissolving tablets, Superdisintegrants, Guargum, microcrystalline cellulose, Direct compression method, Antiepileptic drug.

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1. INTRODUCTION

Tablet is the very commonly used dosage form because of the important advantages such as simplicity of self-administration, easy to prepare, can be deliver in the accurate dose.[1] In pediatric and geriatric patients, the solid dosage forms shows a difficulty in swallowing (dysphagia) or chewing, and it is one of the limitations of solid dosage forms.[2]

FDTs is regarding as a good candidates for the patients with persistent nausea, who are traveling, or who have little or no access to water. As according to the United States Food and Drug Administration (USFDA), the FDT is defined as the solid dosage forms which contains the active pharmaceutical ingredient, which break down rapidly usually within a seconds when taken in the mouth. These tablets are also known as fast dissolving tablets, fast melting tablets.[2]

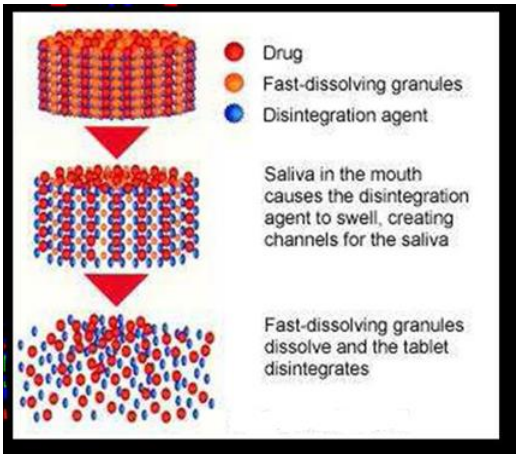

Fig 1: Conceptual diagram of FDT

Lacosamide is an antiepileptic drug used to treat seizures and this drug is structurally unrelated to other anticonvulsant drugs. Lacosamide works in a very unique way and it shows 2 pathways of mode of action: [3, 4]

- It works by selectively enhancement of slow inactivation of voltage gated sodium channels, and helps in the stabilizing of the hyperexcitable neuronal brain membranes and also inhibits the neuronal firing.
- As other antiepileptic drugs works by fast inactivation of the sodium channels and hence this lacosamide drug is having its unique mode of action.
- This drug also acts on the receptor i.e. collapsing response mediator protein- 2(CRMP-2), however, its expression is altered in epilepsy and other neurodegenarative diseases.

Lacosamide is administered by oral route and shows the complete absorption of the drug with having no first pass metabolism. In-vivo studies show that lacosamide is having 100% bioavailability. The absorption rate and extent are not affected by food intake. The volume of distribution of lacosamide is near about 0.8 L/kg. The metabolite of lacosamide is O-desmethyl metabolite which is not having any pharmacological activity. The enzymes involved in the metabolism process is CYP isoenzyme 2C19 which is mainly responsible for the formation of the O-desmethyl metabolite, although in vitro data suggest that also CYP3A4 and CYP2C9 may be involved. The half-life of this drug was found to be near about 13 hrs, allowing convenient BID dosing. Lacosamide is mainly excreted by renal route.

2. MATERIALS AND METHODS

2.1. Materials:

Lacosamide was obtained from Jubilant Chemsys (Research and development) Noida, India, Guargum was obtained from CDH (Central Drug House) Ltd, New Delhi-11002 (India), Microcrystalline Cellulose was obtained from Loba Chemie Ltd., Mumbai, India, All other reagents and chemicals used were of analytical grade.

2.2. Methods:

2.2.1. Determination of λ_{max} of Lacosamide and preparation of calibration curve

The standard curve of lacosamide is prepared by firstly preparing the stock solution of 100 mcg/ml. The stock solution was prepared by taking accurately weighed 5 mg of drug (Lacosamide) and dissolve in the 50 ml of phosphate buffer of pH 6.9 in a volumetric flask. From the above prepared stock solution, different dilutions such as (2, 4, 6, 8, 10, 12 mcg/ml) were prepared and the absorbance at which calibration curve has to be obtained was scanned at **206 nm** in UV Spectrophotometer. After taking the absorbance, the calibration curve was prepared by taking the concentration on X-axis and absorbance on Y-axis.

2.2.2. Formulation of Mouth Dissolving Tablets

Initially pure drug (Lacosamide) and all polymers (Guargum, Microcrystalline cellulose & Mannitol) were taken together and screened through sieve having mesh size # 60 and co grind in a mortar and pestle. Then lubricant & glidant are added in the mixture after passing through sieve of mesh size # 60 to improve the flow properties. Then the mixture is thoroughly mixed. Then the prepared mixture was compressed into tablet to prepare 200 mg convex faced tablet by using 8mm round punches on multipunch tablet compression machine.

Table 1: Formulation of Lacosamide mouth dissolving tablets

Ingredients (mg)	Formulation code				
	F1	F2	F3	F4	F5
Lacosamide	50	50	50	50	50
Guar gum	10	10	20	-	-
Mannitol	100	110	100	100	110
Microcrystalline cellulose	10	-	-	20	10
Aspartame	4	4	4	4	4
Starch	20	20	20	20	20
Talc	4	4	4	4	4
Magnesium stearate	2	2	2	2	2
Vanilline	q.s	q.s	q.s	q.s	q.s
Total weight (mg)	**200**	**200**	**200**	**200**	**200**

2.2.3. Evaluation of powder blends (pre-compression):

2.2.3.1. Angle of repose:

Angle of repose is one of the evaluation parameters for study the flow properties of powder. This analysis can be done by using funnel method in which funnel used and kept vertically at 6.3 cm height. Then the powder is poured by the upper side and closing the end of funnel with the help of thumb until powder is completely filled in the funnel. After pouring powder completely, the pile was formed by which radius of the heap can be measured and then the angle of repose was calculated by the following formula. [5, 6]

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

Where h is the height of pile and r is the radius of the base of the pile.

2.2.3.2. Bulk density (B_D):

This is one of the preformulation parameters to be studied before going to the formulation. This type of analysis is studied for improving the flow properties. Bulk density is the ratio of total mass of the powder to the bulk volume of the powder. This can be determined with the help of the cylinder in which weight powder (passed through standard sieve # 20) is poured into the cylinder and initial weight was noted. This initial volume is called the bulk volume. Then the bulk density can be measured by the following formula i.e,

Db = M/ Vb. It is expressed in g/ml.

Where, M = mass of powder

Vb = bulk volume of the powder.

2.2.3.3 Tapped density (T_D):

This is analysis parameter to study the flow properties. It is the ratio of total mass of the powder to the tapped volume of the powder. The tapped density can be determined by tapping the powder for 750 times and then tapped volume was noted and if the difference between these 2 volumes i.e. initial as well as after tapping volume is less than 2%, If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. 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.

2.2.3.4. Compressibility index and hausner ratio:

These are the analysis for the determination of the flow properties of powder. It is expressed in percentage and is give (Table 2)

I = (Dt – Db)/ Dt x100

Dt: tapped density of the powder

Db: bulk density of the powder.

Table 2: Relationship between % compressibility and flow ability [7, 8]

% Compressibility	Flow ability
5-10	Excellent
12-16	Good
18-21	Fair Passable
23-25	Poor
33-38	Very Poor
<40	Very Very Poor

2.2.4. Evaluation of Lacosamide fast dissolving tablets (Post compression):

All the tablets were evaluated for different parameters such as weight variation, hardness, friability, disintegration time, wetting time, drug content, water absorption ratio and *in vitro* dissolution.

2.2.4.1. Weight variation:

This is one of the tests for the evaluation of the tablets in which 20 tablets are taken randomly from the batch and then weighed individually, to check the weight variation. Then the weight variation is calculated by calculating the difference between average and individual weight.

Weight variation specification as per I.P.

Table 3: Weight variation specification as per I.P [9, 10]

Average Weight of Tablet	% Deviation
80 mg or less	±10
80 mg to 250 mg	±7.5
250 mg or more	±5

2.2.4.2. Friability:

This test is very important to study to check the effects of the shocks and friction during transportation. It checks the tablet chipping or any break of the tablet. Roche friabilator is used to test the friability of the tablet. 'This friabilator helps to measure the effect of abrasion or shock by keeping the 20 tablets in the plastic chamber that revolves at 25 rpm at a distance of 6 inches with each revolution. Initially the weight was measured before keeping the tablets in friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weight [11]

F = Wt initial–Wt final / Wt initial x 100

2.2.4.3. Disintegration time:

This is the evaluation parameter to determine the time to break the tablet in the oral cavity so to measure the drug action. The disintegration time can be calculated by placing the 6 tablets in each tube of the apparatus having 6 tubes. This apparatus contains the distilled water at 37ºC±2ºC was used as a disintegration media. Then the time to break the tablet was noted which determines the action of the drug.

2.2.4.4. Wetting time: [12]

This is very important to determine in case of mouth dissolving tablets which depends on the inner structure of the tablet as well as hydrophilicity of the excipient. The water penetration rate determines the wetting time which depends on the hydrophilicity of the powders.

dl/dt = r¡cosq/ (4hl)

Where l is the length of penetration, r is the capillary radius,

! is the surface tension,

h is the liquid viscosity,

t is the time,

q is the contact angle.

2.2.4.5. Water absorption ratio:

The weight of the tablet before keeping in Petri-dish was noted (Wb). Fully wetted tablet from the Petri-dish was taken and reweighed (Wa). The water absorption ratio R can be determined according to the following formula:

R= (Wa-Wb)/Wa×100

2.2.4.6. Drug content:

Ten tablets from each formulation were powdered. The powder equivalent to 100 mg of Lacosamide was weighed and dissolved in suitable amount of methanol and volume was made up to 100 ml with phosphate buffer (pH 6.8). The solution was sonicated for 5 min. Then solution was filtered through Whatman filter paper and then suitable dilution was prepared and it was analyzed at 206 nm by UV spectrophotometer.

2.2.4.7. *In vitro* release study:

This test is conducted for the prepared fast dissolve tablets for a period of 12 min using a six-station USP type II (paddle) apparatus at 37°C and 50 rpm speed. The sampling of ODT's was done after every 2 min interval in which 5 ml of the sample was withdrawn and replaced with fresh medium to maintain the volume constant. Then the absorbance was measured in UV spectrophotometer at λ max 206nm.

3. RESULTS AND DISCUSSION

3.1. Characterization of blend for fast dissolving tablets:

The data for evaluation of powder blends of rapidly disintegrating tablets of Lacosamide are shown in Table 4. The pre-compression parameters values were within limits and indicated good free flowing property. The angle of repose was in the range 26.84±0.48 to 28.93±0.59 indicating good flow property. The compressibility index was in the range of 13.38±0.26 to 15.38±0.29. The Bulk and Tapped density were in the range of 0.43±0.01 to 0.44±0.01 and 0.51±0.01 to 0.52±0.01 respectively.

Table 4: Evaluation of powder blends (Pre-formulation study)

S.No.	Formulation Code	Angle of repose	Bulk Density	Tapped Density	Carr's Index
1.	F1	28.93±0.59	0.44±0.01	0.52±0.01	15.38±0.29
2.	F2	27.15±0.52	0.44±0.01	0.52±0.01	15.28±0.16
3.	F3	27.77±0.45	0.43±0.01	0.51±0.01	13.38±0.26
4.	F4	26.84±0.48	0.44±0.01	0.51±0.01	15.38±0.29
5.	F5	27.74±0.50	0.43±0.01	0.52±0.01	14.92±0.85

All the readings are expressed as mean ± standard deviation (n=3)

3.2. Evaluation of Lacosamide fast dissolving tablets:

Mouth dissolving tablets of Lacosamide were prepared by direct compression method using Guargum as a superdisintegrant, Microcrystalline cellulose as a disintegrant and mannitol serves as diluent in Table 1. The preparation of mouth dissolving tablets using superdisintegrants has proven to be highly effective and commercially convenient. They were taken in various ratios to find the optimum concentration of the superdisintegrants required to yield formulation providing least wetting time, minimum disintegration time and get maximum drug release. The superdisintegrants were used alone as low as 10% to as high as 20% in fast dissolving formulations to improve dissolution of Lacosamide. Five formulations were designed including the formula without superdisintegrant. The data obtained from post compression parameters such as hardness, friability, uniformity of weight, drug content, wetting time, disintegration and water absorption ratio are shown in Table 3.

Table 3: Evaluation parameters of mouth dissolving tablets of Lacosamide

Formulation code	Thickness	Hardness	Disintegration time (sec)	Weight variation
F1	3.67±0.045	4.0±0.002	47	200
F2	3.75±0.065	3.91±0.204	28	202
F3	3.72±0.048	3.83±0.258	38	200
F4	3.74±0.049	3.90±0.201	30	200
F5	3.73±0.040	3.80±0.204	37	202

Table 4: Evaluation parameters of mouth dissolving tablets of Lacosamide

Formulation code	Friability %	Wetting time (sec)	Water absorption ratio (%)	Drug Content (mg%)
F1	0.42	3.53±2.59	55.81±1.47	99.95±0.70
F2	0.49	3.48±2.42	60.32±1.45	100.03±1.14
F3	0.58	3.54±1.47	59.93±1.90	99.96±1.18
F4	0.55	3.52±2.50	62.22±1.35	100.43±0.90
F5	0.56	3.27±2.26	68.50±2.24	99.43±1.20

The drug content of all the prepared tablets was in the range of 99.43±0.90 to 100.43±0.90%. Hardness of the tablets was found to be in the range of 4.0±0.002 to 3.80±0.204 kg/cm^2.

Tablet hardness difference is an indication of tablet density and porosity variations. It has been presumed that these differences influence the rate of penetration of the dissolution fluid at the surface of the tablet which consequently affects the release pattern. Uniformity of weight was found to be in the range of 200 to 202 mg which is complying with USP specifications within an acceptable range of ±5%. The friability of the formulated tablets was

less than 1% which was in the range of 0.42 to 0.58% in Table 3. The capacity of the disintegrant to swell in the presence of little amount of water is governed by water absorption ratio and wetting time. Determination of wetting time is an important confirmative test for mouth dissolving tablet evaluation as the dissolution profile of a tablet depends on its wetting prior to disintegration. The wetting time for all the prepared tablets was in the range of 3.27±2.26 to 3.54±1.47 sec. The wetting time decreased with increase in the level of guargum (10-20%). The lowest wetting time was observed for F2 containing 10% guargum as superdisintegrant. The water absorption ratio was found to be in the range of 55.81±1.47 to 68.50±2.24 %. The disintegration time of all the formulated tablets was between 28 to 47sec, this was found to be well within the acceptable limit for fast dissolving tablet (< 3 min.).

3.3. *In vitro* dissolution study:

The release rate of Lacosamide from mouth dissolving tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution medium used was 900 ml of phosphate buffer pH 6.8 which was maintained at 37±0.5^{0}C. The paddle speed was kept at 50 rpm throughout the study. Five ml of samples was withdrawn at every 2 minutes interval and diluted to 10ml then 5ml of fresh dissolution media maintained at the same temperature was replaced. The samples were analyzed spectrophotometrically at 206 nm using phosphate buffer pH 6.8 as blank. The raw dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals.

Table 5: Details of Dissolution Test:

S.No	Requirement	Specification
1.	Apparatus	USP Type II
2.	Volume of medium	900 ml
3.	Temperature	37±0.5^{0}C
4.	Paddle Speed	50 rpm
5.	Dissolution medium used	6.8 phosphate buffer
6.	A liquid taken at each time interval	5 ml

Table 6: Comparative Cumulative Drug Release of Different Formulations

S. No	Time (Min)	Comparative Cumulative Release of Different Formulations				
		F1	F2	F3	F4	F5
1.	0	0	0	0	0	0
2.	2	15.15±0.73	18.96±0.73	28.34±1.26	18.21±0.67	20.21±0.77
3.	4	29.53±0.32	35.14±0.39	40.08±0.32	35.85±0.31	42.85±0.40
4.	6	44.79±0.96	50.71±0.50	52.7±0.77	48.93±0.49	60.90±0.50
5.	8	60.09±0.73	62.64±0.57	64.05±0.95	56.24±0.31	72.20±0.55
6.	10	74.74±0.44	78.80±0.37	76.25±0.50	78.8±0.81	84.10±0.27
7.	12	92.94±0.69	99.86±0.54	90.17±1.14	92.66±0.47	95.66±0.50

[a]Mean ± S.D.(n=3)

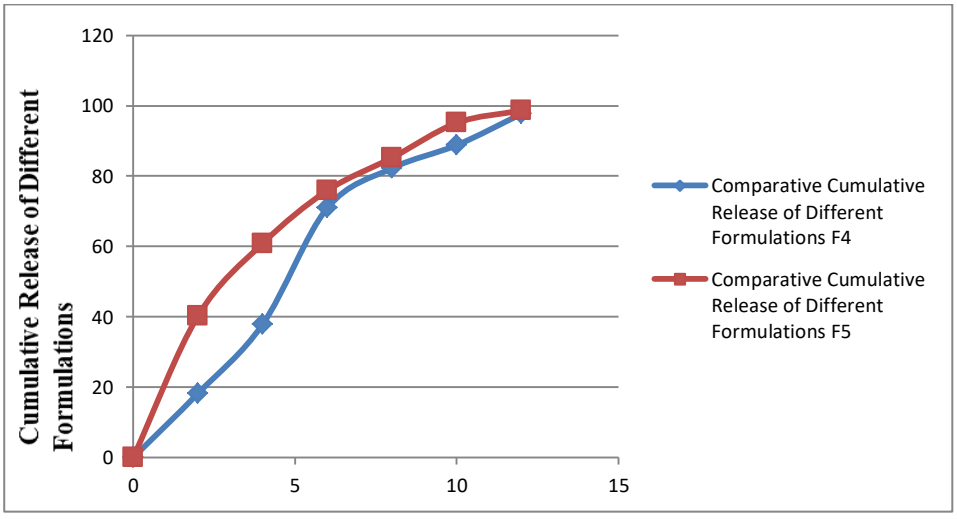

Figure 1: Comparative Study of Cummulative Release of different Formulations

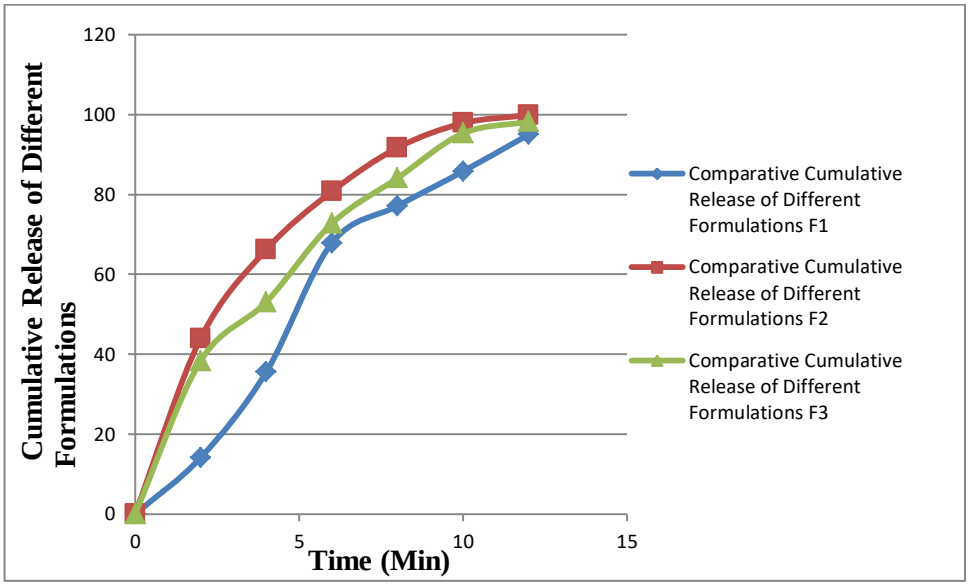

Figure 2: Comparative Study of Cummulative Release of different Formulations

4. CONCLUSION

The fast dissolving tablets of lacosamide were successfully prepared by direct compression method by using superdisintegrants and the objective of this study was achieved. By the *in-vitro* disintegration, it is concluded that formulation F2 prepared by Guar Gum (10%) showed the fast disintegration time than the MCC.

So it represent that the use of superdisintegrants, it increases the release of the drug Lacosamide. Therefore, it may be concluded that mouth dissolving tablet was suitable drug delivery system for Lacosamide.

Thus, the fast dissolving tablets are successfully prepared for the patients who are suffering from difficulty of swallowing or dysphagia, the patients mainly for paediatric, geriatric, or the patients who have no access of water, and also provides faster and better drug release, thereby, improving the bioavailability of drug as compared to the conventional marketed formulation.

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