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FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF LACOSAMIDE

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Keywords:

Dysphagia, Spray drying, Taste masking, Formulation development, Disintegration, Optimization

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ABSTRACT: Lacosamide is an antiepileptic bitter drug used to treat partial onset seizure. The aim of the work was to mask the taste of lacosamide and then formulation and evaluation of tablet. Taste was masked using spray dryer. Oral disintegrating tablet was prepared using 3 superdisintegrants Sodium starch glycolate, Crosscarmellose sodium and Polyplasdone XL10. Out of these polyplasdone showed quick disintegration. The 3^2 factorial experimental design was applied to optimize response variable disintegration time and drug release. Tablet from optimized batch (F9) disintegrate within 27 seconds with 99.38% drug release.

INTRODUCTION: The oral route is chosen as the most convenient route for drug administration. But one important drawback of such dosage forms is 'Dysphagia' or difficulty in swallowing. This is seen to afflict nearly 35 % of the general population. This disorder is also associated with a number of conditions like:

- Parkinsonism
- Motion sickness
- Unconsciousness
- Elderly patients
- Children
- Mentally disabled persons, uncooperative
- Unavailability of water

QUICK RESPONSE CODE

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US Food and Drug Administration Centre for drug evaluation and Research (CDER) defines, in the 'Orange Book' an ODT as " a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

Taste masking by Microencapsulation: Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with a polymeric material or film.

Types of microencapsulation include:

1. Air suspension coating
2. Coacervation phase separation
3. Spray drying
4. Spray congealing
5. Solvent evaporation
6. Pan coating
7. Interfacial polymerization etc. of these processes, first four are mostly used techniques for achieving taste masking [1].

Spray Drying: Spray dryers are widely used in pharmaceuticals and biochemical processes. Spray drying provides a fast and economical way of removing solvents and producing highly porous fine powders. Spray drying can produce highly porous and fine powders that dissolve rapidly. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This then mixed with active ingredients and compressed into tablets.

This taste masked powder collected from spray dryer and used for formulation, development and evaluation of oral disintegrating tablet [2].

MATERIALS AND METHODS

Characterization of Drug: Characterization of collected sample was done by checking its physico-chemical properties such as its colour, taste i.e. either tasteless or bitter, its chemical properties i.e. ionic nature then its solubility in various solvents such as water, methanol, ethanol, HCl and 6.8 pH buffer. Melting properties of Lacosamide was analyzed by two methods i.e. melting point apparatus and differential scanning apparatus which indicate its purity by comparing with reported value. FTIR characterization of Lacosamide indicates its presence of characteristic functional group in the compound which gives structural identification of the drug by comparing it with reported values.

Development of Analytical Method for Lacosamide by UV-spectroscopy [3]:

Determination of λ_{max} of Lacosamide: Lacosamide was accurately weighed and dissolved in 6.8 pH phosphate buffer and 0.1 N HCl to make concentration 1mg/ml. UV spectrum was recorded over the wavelength range 200- 400 nm.

Validation of UV-spectroscopic Analytical Method:

Linearity: Various drug concentrations (300-1000 µg/ml) in distilled water were prepared and the absorbance was measured at 257 nm. For the standard curve, 100 mg of Lacosamide was accurately weighed and dissolved in 100 ml of water to make stock solution of concentration 1000 mcg/ml. Further serial dilutions were carried out with water to get drug concentrations 300 to 900 µg/ml. The absorbance of dilutions was measured against distilled water as a blank at 257 nm using double beam UV/Visible spectrophotometer. The plot of absorbance Vs concentration was plotted and subjected to linear regression analysis. Drug was found to obey Beer Lambert's law in the concentration range of 300-900 µg/ml. A standard plot of absorbance v/s concentration of drug in µg/ml was plotted. Correlation coefficient and regression equation were obtained from the calibration curve. Similarly linearity was checked in 6.8 pH phosphate buffer and 0.1 N HCl.

Precision: For checking method precision, a standard solution of Lacosamide of concentration 500 µg/ml was prepared and the absorbance was recorded in 6 replicates. From the data obtained standard deviation (SD) and % RSD were calculated. The process was repeated for a solution of the same concentration in 0.1 N HCl. For checking intraday variability, three solutions of concentration 300, 450, 600, 750 & 900µg/ml in distilled water and 0.1 N HCl were prepared and the absorbance of each solution was measured three times in a day. For checking inter day variability, absorbance of above solutions were measured for three successive days.

Accuracy: To check the accuracy of the method, recovery studies were carried out at three different levels. A standard marketed tablet of Lacosamide was used. The tablet powder was dissolved in water and 0.1 N HCl separately, filtered and the solution was diluted to make concentration of 600µg/ml. To this tablet solution, a standard solution of Lacosamide of concentration was added to produce three solutions of concentrations 300, 600 & 900µg/ml. The absorbance of each solution was measured and concentration was estimated from the regression equation. Percent recovery was calculated from the data obtained.

LOD & LOQ: These were determined as per standard procedures.

Taste Masking of Lacosamide:

Determination of threshold bitterness concentration of Lacosamide [4]: A panel of ten healthy human volunteers (age 20-25) was selected. A series of solutions of Lacosamide in phosphate

buffer of pH 6.8 of concentrations 50, 100, 150, 200 and 250 μg/ml were prepared. The volunteers held 10 ml of each solution in oral cavity for 30S and rated the taste on a scale from 0 to 4 (0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness). Rinsing the mouth by distilled water and a gap of 30 min was given before next higher concentration was tasted. Based on the opinion of the volunteers, threshold bitterness concentration of lacosamide was judged.

Selection of Method for Taste Masking of Lacosamide: In order to achieve more pleasant dosage forms, various masking techniques have been described in the literature. The simplest method is to add flavors or sweeteners. However, in most cases, these are rather limited and may not be effective enough to mask the unpleasant taste of some drugs. A number of more useful approaches have been tried, including capsule formulations, absorption to ion-exchange resin, microencapsulation with various polymers, and inclusion complexes with cyclodextrin. In recent days, taste masking by coating with water-insoluble polymers or pH-dependent water-soluble polymer, is becoming more popular. Release of drug from coated polymer is pH dependent. So, selection of taste masking method was primarily focused coating of drug with pH dependant polymer by spray drying. Spray drying is widely used for the preparation of the microspheres. Spray drying is widely used in pharmaceutical processing as it requires only a one step process and can be easily controlled and scaled up.

Selection of Polymer [5]: Eudragit E100 is a polymethacrylate with pH dependant solubility, specifically used for taste masking. It is insoluble at and above pH 5. So the polymer is expected to keep intact in buccal cavity (pH 5.8 to 7.5) with good taste masking, but dissolve quickly in stomach (pH 1-3) without influencing the dissolution or bioavailability of the drug

Compatibility Study of Lacosamide with Selected Polymer: Compatibility of Lacosamide with that selected resin Eudragit E100 was evaluated by using FTIR spectroscopy. For compatibility study equal proportion of Lacosamide with that of Eudragit E100 was kept for different conditions such as at room temperature, accelerated 40°C/75RH and freeze condition. All kept mixture was checked by FTIR spectroscopy for first, second and third month.

Preparation of Microspheres: The microspheres were prepared by spray - dying technique. The spray drying was performed by spray dryer Labultima (Lu-222). The different drug – polymer ratios used for various microsphere formulations are 1:1 to 1:5. The polymer solution was prepared by adding given quantity of polymer to the solvent (Dichloromethane). The given quantity of drug was added to the polymer solution and the resulting mixture was spray – dried. Inlet and outlet temperature were 70 & 50 respectively. Feed pump flow rate was 1.2 ml/min. Aspirator level was 75 psi (5 Bar) and vacuum was 200 mm Wc.

Evaluation of Microspheres:

***In-vitro* Evaluation of Bitter Taste of Microspheres:** Microspheres equivalent to 50mg of lacosamide were placed in a volumetric flask with 25 ml phosphate buffer pH 6.8 and stirred for 5 min. The mixture was filtered, and the filtrate was analyzed for Lacosamide concentration at 257nm by uv – visible spectrophotometer (Jasco) and that was compared with the threshold value.

Infrared Spectroscopy: Infrared (IR) spectroscopy was conducted using Fourier transform IR (FTIR) spectrophotometer (FT/IR-4100 Jasco Tokyo, Japan.) and the spectrum was recorded over the region 400–4,000 cm–1 for the Lacosamide and polymer microsphere.

Drug Loading and Entrapment Efficiency: The drug loading and entrapment efficiency were determined by UV – visible spectrophotometer. The microspheres equivalent to dose of the drug were stirred with 100 ml 0.1 N HCL. The drug concentration was determined at 257 nm. The drug loading and entrapment efficiency were calculated using the following equations.

Drug loading (%) = (weight of drug in microcapsules / weight of microcapsules) ×100

Drug entrapment efficiency = (weight of drug in microcapsules / weight of drug fed initially) ×100

Drug Release Study: The drug release studies were performed by USP Type I dissolution test apparatus (TDT-082-Electrolab, Mumbai, India). Microspheres equivalent to 8 mg of OSH were filled in hard gelatin capsule shell size '0'. 900 ml of 0.1 N HCl was used as dissolution medium. The temperature and speed of the apparatus were maintained at 37±0.5°C and 50 rpm, respectively. The samples were withdrawn at predetermined time interval and analyzed for drug concentration at 257 nm by UV-Visible spectrophotometer after filtration. The readings were taken in triplicate.

Formulation Development of Orodispersible Tablets (ODT):

Preformulation Studies:

Selection of Other Excipients [6]: For the formulation of ODT various superdisintegrant were selected such as sodium starch glycolate, cross carmellose sodium and Polyplasdone. Microcrystalline cellulose was selected as bulking agent because of its good compressibility, good flowing properties, good solubility in water, and a pleasant taste. Magnesium stearate was used as lubricant. ODTs of Lacosamide were prepared using one of these superdisintegrants, microcrystalline cellulose, magnesium stearate, steveoside sweetener and peppermint flavor.

Selection of Superdisintegrant: Lacosamide ODT were prepared according to the formula given in Table. A total number of 9 trial batches (T1-T9) were prepared; all the ingredients were passed through 60 mesh sieve separately and collected. The ingredients were weighed and mixed in a geometrical order. First MCC, superdisintegrant, sweetener and flavor were mixed together. 3 different superdisintegrants at three concentrations were used. Drug polymer complex was then added and was mixed for10–15 min. The prepared blend was lubricated by using magnesium stearate for 2 min. The mixture blends of all the formulations were subjected to pre-compression parameters like angle of repose, bulk density, tapped density, % compressibility. The tablets were then compressed by direct compression using 12 mm size punches to get a tablet of approx. 400 mg weight and hardness was set between 4 to 5 kg/cm^2. The prepared orodispersible tablets were evaluated for content uniformity, hardness, friability, weight variation, dissolution and disintegration.

TABLE 1: FORMULATION OF DIFFERENT BATCHES OF LACOSAMIDE ODT (SCREENING OF SUPERDISINTEGRANTS)

Ingredients (mg)	Formulations								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
DPC	300	300	300	300	300	300	300	300	300
MCC	40	40	40	40	40	40	40	40	40
SSG	20	40	60	-	-	-	-	-	-
CCS	-	-	-	20	40	60	-	-	-
Polyplasdone XL 10	-	-	-	-	-	-	20	40	60
Mg. Stearate	8	8	8	8	8	8	8	8	8
Steveoside	20	20	20	20	20	20	20	20	20
Flavor	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total (Approx.)	400	400	400	400	400	400	400	400	400

*DPC (Drug polymer complex) contain the 50mg of Lacosamide.

Compatibility Study:

Compatibility Study by FTIR Spectroscopy [7]: Preformulation study was carried out with potential formulation excipients to determine drug-excipients compatibility. Excipients included such as superdisintegrants used, microcrystalline cellulose, steveoside, magnesium stearate and pippermintflavour. Lacosamide was uniformly mixed in 1:1 ratio with the excipient and the mixture was placed in sealed glass vials. Lacosamide alone was also kept in a similar manner to serve as control. Vials were kept at room temperature and 40^{o}C/75% RH. After 30 days samples were observed for physical changes and possible drug-excipient interaction using FTIR spectroscopy.

Compatibility Study by UV-spectroscopy: Preformulation study was carried out with potential formulation excipients to determine drug-excipient compatibility. Excipient studied included superdisintegrants used, microcrystalline cellulose, steveoside, magnesium stearate and pippermintflavour. Lacosamide was uniformly

mixed in 1:1 ratio with the excipient and the mixture was placed in sealed glass vials. Lacosamide alone was also kept in a similar manner to serve as control. Vials were kept at room temperature and 40°C/75% RH. After 30 days samples were observed for % recovered and possible drug-excipient interaction using UV spectroscopy.

Full Factorial Experimental Design [8]: A 3^2 randomized full factorial design was used for optimization of lacosamide tablets. The design was also applied to study the effect of concentration of polyplasdone XL 10 and microcrystalline cellulose on physicochemical characteristics of tablets. The amount (%) of superdisintegrant polyplasdone XL10 (X_1) and the amount of microcrystalline cellulose (X_2) were selected as independent variables, in this study. These two factors were evaluated, each at 3 levels. The actual units of higher, middle and lower levels of factor X_1 were 5%, 10% and 15%, and for factor X_2 were 5%, 7.5% and 10%. The coding was +1, 0 and -1, respectively for higher, middle and lower levels of each factor. The dependant or response variables included disintegration time (Y_1) and drug release (Y_2).

TABLE 2: FORMULATION OF DIFFERENT BATCHES OF LACOSAMIDE ODT

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
DPC	300	300	300	300	300	300	300	300	300
Polyplasdone XL 10	20	20	20	40	40	40	60	60	60
Microcrystalline cellulose	20	30	40	20	30	40	20	30	40
Mg. Stearate	8	8	8	8	8	8	8	8	8
Steveoside	20	20	20	20	20	20	20	20	20
Flavor	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total (Approx)	400	400	400	400	400	400	400	400	400

Evaluation of Tablet Blend [9, 10]:

Micromeritics Properties: Bulk density and tapped density were determined using a bulk density apparatus.

Density Studies: Density is another property that provides characterization of the Flowability of powders. The tapped density of a powder provides a relationship between the degree of the compaction and the flow properties. The distribution of inter particle pore sizes determine the tapped density of powder. If a powder has a low bulk density and there is large difference between the bulk and tapped densities, it usually does not have good flow properties because of the interlocking of non-isometric and highly textured particles present in powder. From tapped density studies, one can also get an indication of the compressible nature

Bulk Density: An accurately weighed quantity of blend was taken. The volume occupied by it was noted as Vo. Bulk density was calculated using following equation

$$\text{Bulk density} = M/Vo$$

Where, M = Mass of test sample Vo = Initial unsettled volume.

Tapped Density: An accurately weighed quantity of blend was taken and introduced in a 100 ml graduated cylinder. Cylinder was tapped mechanically (USP 1 Tap Density Tester) by raising the cylinder and allowing into the drop under its own weight that provides a fixed drop of 14 ± 2 mm at a normal rate of 300 drops per minute. The cylinder was tapped 1250 times initially and measured the tapped volume. Tapped density was calculated using following equation

$$\text{Tapped density} = M/Vt$$

Where, M= Mass of test sample Vt = final tapped volume

Flow Properties: Angle of repose, compressibility index and Hausner ratio were evaluated as per methods described in USP.

Angle of Repose: For determining angle of repose a funnel was mounted on a stand at a fixed height and a fix weighed quantity of each blend was poured through the funnel. The height and the base diameter of the pile was noted and angle of repose was calculated as

$$\text{Angle of repose} = \tan^{-1} (\text{height}/ 0.5 \text{ base})$$

TABLE 3: FLOW PROPERTIES CORRESPONDING TO ANGLE OF REPOSE

Flow character	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

Compressibility Index and Hausner Ratio: In the recent years compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The basic procedure to calculate the compressibility index and Hausner ratio involves measuring the bulk volume (V_0) and final tapped volume (V_f). A 250 ml volumetric cylinder with 100 gm of the material is used for this purpose. The calculations are done as:

$$\text{Compressibility index} = 100\ (V_0 - V_f)/\ V_0$$

$$\text{Hausner ratio} = (V_0)/\ V_f$$

TABLE 4: FLOW PROPERTIES CORRESPONDING TO COMPRESSIBILITY INDEX AND HAUSNER RATIO

Flow character	Compressibility index (%)	Hausner ratio
Excellent	<10	1.00-1.11
Good	11-15	1.12-1.18
Fair	16-20	1.19-1.25
Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-37	1.46-1.59
Very, very poor	>38	>1.60

Evaluation of Tablets [11, 12, 13]:

Hardness: Five tablets from each batch were selected and hardness was measured using Monsanto hardness tester to find the average tablet hardness.

Friability (%F): Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability.

$$\%F = 1 - (\text{loss in weight}/\ \text{initial weight}) \times 100$$

Weight Variation: Weight variation was calculated as per method descried in Indian Pharmacopoeia. 20 tablets were weighed individually and the average weight is calculated.

The requirements are met if the weights of not more than 2 of tablets differ by more than the percentage listed in **Table 5** and no tablets differ in weight by more than double that percentage.

TABLE 5: LIMITS FOR WEIGHT VARIATION

Average weight of tablet (mg)	Percentage difference allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 or more	5

Uniformity of Content: Five tablets were selected randomly and powdered. A quantity of this powder corresponding to 50 mg of Lacosamide was dissolved in 100 ml of 0.1 N HCl, stirred and filtered. Absorbance of this solution was measured at 257 nm using 0.1 N HCl as blank and content of Lacosamide was estimated.

Disintegration Time: Many reports suggest that conventional disintegration apparatus may not give correct values of disintegration time for ODT. The amount of saliva available in the oral cavity is very limited (usually less than 6 ml) whereas the conventional DT apparatus uses a large amount of water with very rapid up and down movements. MDT is required to disintegrate in such small amount of saliva within a min without chewing the tablet. In a simplest method to overcome this problem, 6 ml of phosphate buffer of pH 6.8 was taken in a 25 ml measuring cylinder. Temperature was maintained at 37±2°C. A Tablet was put into it and time required for complete disintegration of the tablet was noted.

Wetting Time: A Petri dish containing 6 ml of distilled water was used. A tissue paper folded twice was kept in the dish and a tablet was placed on it. A small quantity of amaranth red color was put on the upper surface of the tablet.

Time required for the upper surface of the tablet to become red was noted as the wetting time of the tablet.

Dissolution Studies: Dissolution test was carried out using USP Type II dissolution test apparatus at 37±2°C and 50 rpm speed. 900 ml of 0.1 N HCl was used as dissolution medium. Aliquot equal to 10 ml was withdrawn at specific time intervals and amount of lacosamide released from tablets was determined.

Stability Studies: Stability studies for the optimized formulations were carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions. Stability studies were carried out as per the ICH guidelines. The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40 ± 2°C/ 75 ± 5 % RH. A control Sample was placed at an ambient condition. Both test and control samples were withdrawn at the end of 0, 30, 60 and 90 days and evaluated for active drug content, disintegration time and *in-vitro* drug release.

RESULT AND DISCUSSION:

Characterization of Lacosamide: Characterization of drug was done by following methods.

- Physico-Chemical Properties
- Melting Point Determination
- FTIR Spectroscopy

Physicochemical Properties:

Color: White to off white

Taste: Bitter (metallic)

Solubility: Soluble in ethanol, methanol, 0.1N HCl and slightly soluble in water. The solubility of Lacosamide in water was found to be 27mg/ml, therefore, Lacosamide can be considered to be a sparingly soluble drug as per I.P.

The partition coefficient of Lacosamide is high thus indicating that compound is hydrophillic.

pH Dependent Solubility:

TABLE 6: SOLUBILITY OF LACOSAMIDE AT DIFFERENT PH WAS FOUND TO BE AS FOLLOWS

Sr. no.	pH	Solubility
1	1.2	28.162 mg / ml
2	4.6	25.912 mg / ml
3	6.8	27. 215 mg / ml
4	7.4	27. 561 mg / ml

Melting Point Determination: Melting point determination was done by using Thieles tube (capillary method) which shows melting at 140°C and by DSC method °C (as shown in **Fig. 1**) which comply with the reported value.

Reported Value: 135-145°C

Observed Value: 140°C (By Capillary Method)

: 141°C (By DSC Analysis)

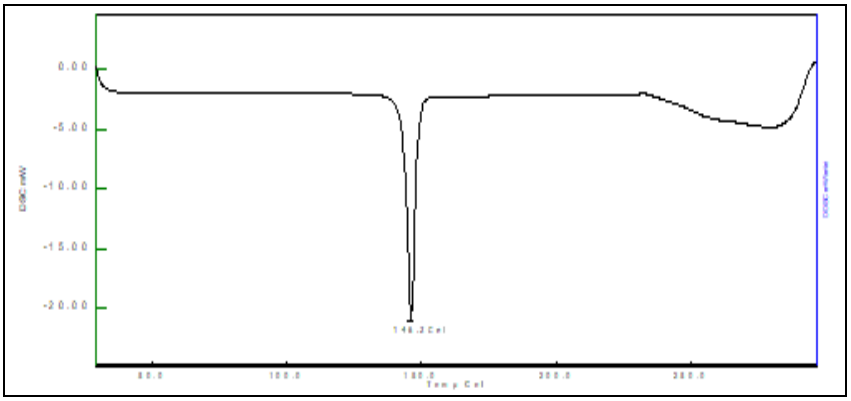

FIG. 1: DSC GRAPH OF LACOSAMIDE

FTIR of Lacosamide: For characterization of pure lacosamide the FTIR studies were carried out. The observed characteristic peaks of functional group have been shown in **Table 7** and the refractogram of pure lacosamide is shown in **Fig. 2** and **3** which comply with the reported data.

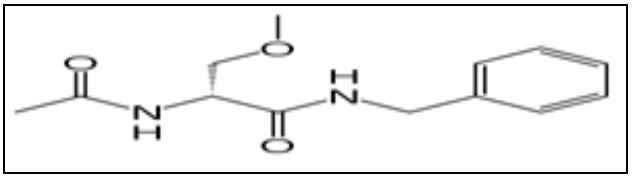

FIG. 2: CHEMICAL STRUCTURE OF LACOSAMIDE

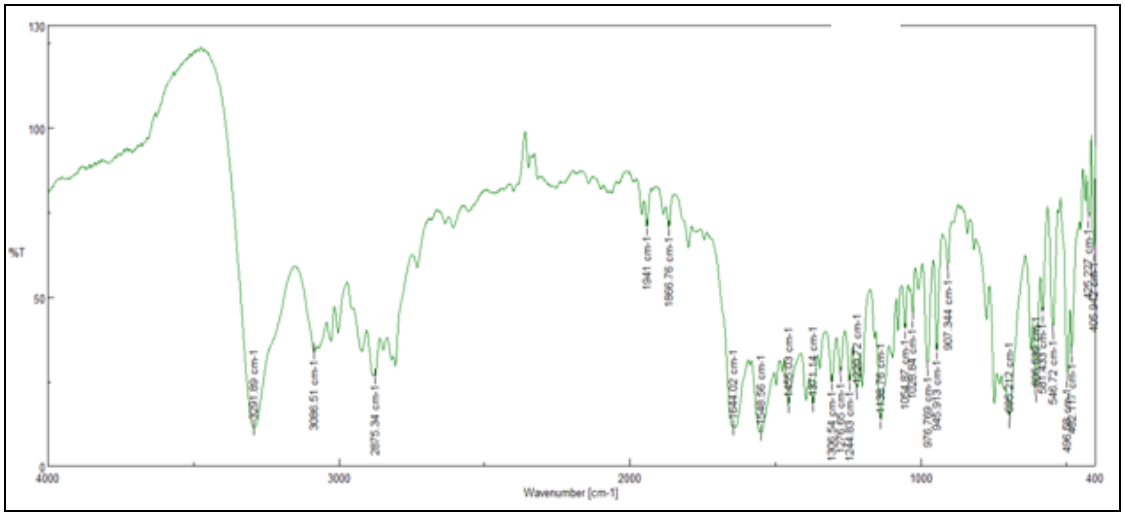

FIG. 3: FTIR OF PURE LACOSAMIDE

TABLE 7: IR FREQUENCIES OF LACOSAMIDE

Sr. no.	Functional group	Observed frequency	Range (cm^{-1})
1	C-C stretch ring aromatics	1548	1600-1545
2	C=C-C Aromatic ring stretch	1450	1510-1450
3	C-C Aromatic	3086	3110-3070
4	N-H Primary, secondary amine	695	910-665
5	C-H Aromatics	3086	3100-3000
6	Amide	1644	1680-1630

Development of Analytical Method for Lacosamide by UV Spectroscopy:

Preparation of Standard Stock Solution and Determination of λ max of Lacosamide: Standard lacosamide 100 mg was weighed and transferred to 100 ml volumetric flask and dissolved in water. The flask was shaken and the volume was made up to the mark with water to give a solution containing 1000 mcg per ml. Appropriate dilutions were prepared for drug from the standard stock solution and the solutions were scanned in the wavelength range of 200 to 400 nm. For the standard solution analytical concentration range was found to be 300 to 900 mcg / ml. The λ_{max} of lacosamide in distilled water and 0.1 N HCl were found to be 257 nm as shown in **Fig. 4** and **Fig. 5.**

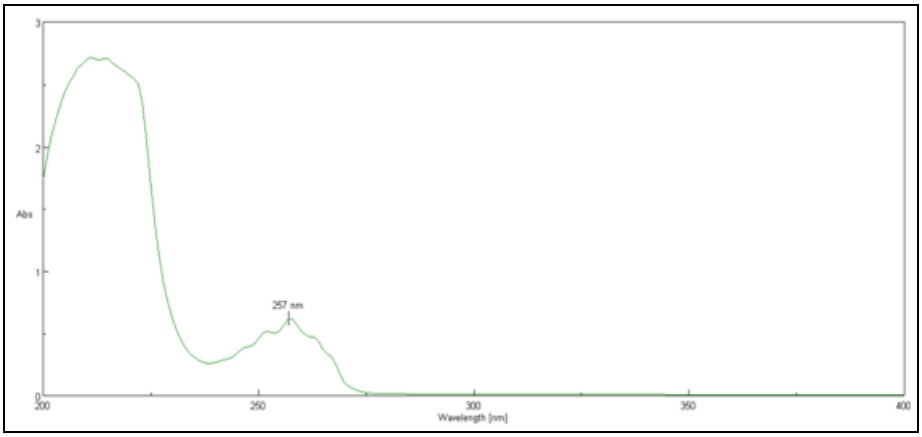

FIG. 4: SCAN OF LACOSAMIDE IN WATER

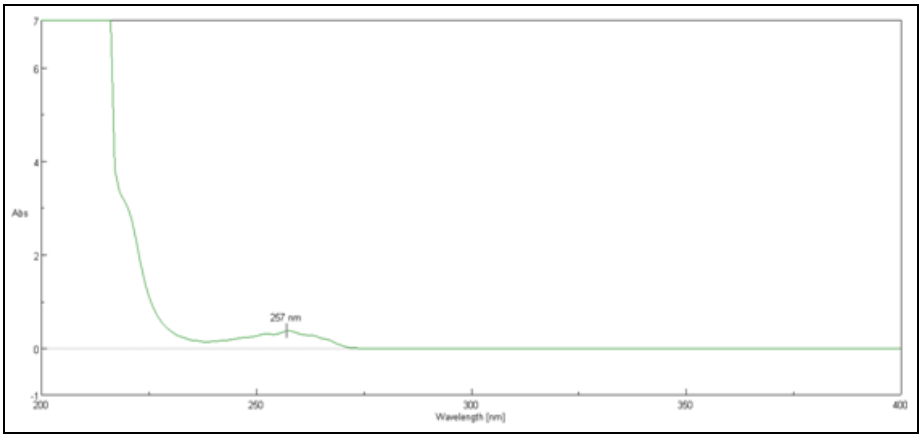

FIG. 5: SCAN OF LACOSAMIDE IN 0.1 N HCL

Validation of UV-spectrophotometric Analytical Method:

Linearity:

Preparation of Standard Calibration Curve in Distilled Water and 0.1N HCl: Calibration curve was constructed in distilled water and 0.1N HCl as per the said procedure which was in the range of 300 - 900 µg/ml for distilled water and 500 – 900 µg/ml for 0.1N HCl which obeys Beer's law. The high values of regression coefficients were 0.999 and 0.995 respectively as shown in Figure 6 & 7 which estimated the linearity of relationship between concentration and absorbance.

TABLE 8: CALIBRATION CURVE OF LACOSAMIDE IN DISTILLED WATER

Sr. no.	Concentration (mcg/ml)	Absorbance
1	300	0.2433
2	450	0.3542
3	600	0.4808
4	750	0.5930
5	900	0.7071

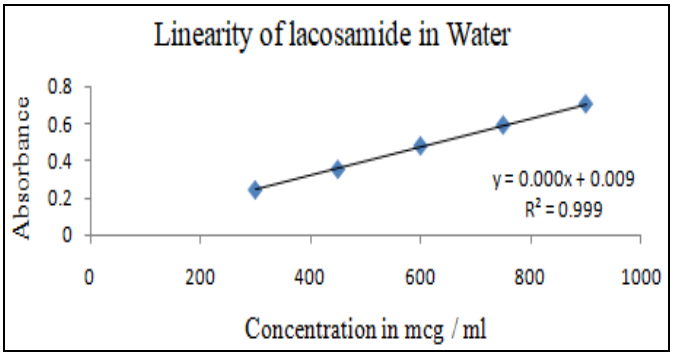

FIG. 6: CALIBRATION CURVE FOR LACOSAMIDE IN WATER

TABLE 9: CALIBRATION CURVE OF LACOSAMIDE IN 0.1N HCL

Sr. no.	Concentration (mcg/ml)	Absorbance
1	500	0.368
2	600	0.9753
3	700	0.5573
4	800	0.6141
5	900	0.7303
6	1000	0.7803

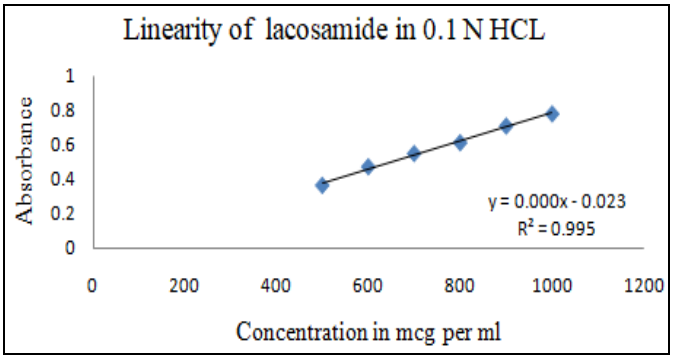

FIG. 7: CALIBRATION CURVE OF LACOSAMIDE IN 0.1N HCL

Precision: Precision was carried out to check whether the developed method is precise or not and it was done as per the given procedure and % RSD was calculated.

From the data presented in **Table 10, 11** and **12**; %RSD values for the method intra and inter day variability were less than 2% and good reproducibility of the results was observed which indicate that the method was precise for detection of Lacosamide.

TABLE 10: PRECISION OF METHOD

Solvent	Distilled water	0.1 N HCL
Mean of 6 absorbance	0.551317	0.551967
Standard deviation (SD)	0.006598	0.002356
% Relative standard deviation (RSD)	1.196	0.426

TABLE 11: INTRADAY VARIABILITY

Concentration µg/ml	Absorbance Mean	Standard deviation SD	% RSD
Distilled Water			
700	0.551317	0.002383	0.432
800	0.624967	0.009107	1.456
900	0.706196	0.002712106	0.382
0.1 N HCl			
700	0.551967	0.002356	0.426
800	0.614742	0.0032889	0.535
900	0.71215	0.00678699	0.9516

TABLE 12: INTERDAY VARIABILITY

Concentration µg/ml	Absorbance Mean	Standard deviation	% RSD
Distilled Water			
700	0.547383	0.0069878	1.526
800	0.614878	0.01342	0.211
900	0.707157	0.0056688	0.792
0.1 N HCl			
700	0.54845	0.0067802	1.236
800	0.62126	0.006085	0.966
900	0.718883	0.008519	1.184

Accuracy: Recovery studies were carried out using solutions of Lacosamide at three different levels in distilled water and 0.1 N HCl. The amount of drug recovered was shown in **Table 13** and **14**. The concentration recovered was within ±2% to the true value which concluded the method was accurate.

TABLE 13: RECOVERY STUDIES LACOSAMIDE IN DISTILLED WATER

Parameters	Level of recovery		
Concentration µg/ml	300	600	900
Mean absorbance	0.2530	0.4858	0.7340
Concentration recovered	304.95	595.92	906.23
Mean % recovery	101.65	99.32	100.69

TABLE 14: RECOVERY STUDIES OF LACOSAMIDE IN 0.1 N HCL

Parameters	Level of recovery		
Concentration µg/ml	300	600	900
Mean absorbance	0.2385	0.4832	0.7342
Concentration recovered	298.125	601.2	914.94
Mean % recovery	99.375	100.20	101.66

Limit of Detection (LOD): Limit of detection is the minimum quantity of the drug which can be detected by the method. LOD was found to be 1.3 µg/ml for detection of lacosamide in water and 1.24 µg/ml for detection of Lacosamide in 0.1 N HCl.

Limit of Quantification (LOQ): Limit of quantification is the minimum quantity of the drug that can be quantified by the method. LOQ was found to be 5 µg/ml in water and 4.5 µg/ml in 0.1 N HCl. Thus the UV-Spectroscopic analytical method was found to be linear, precise and accurate. The method could detect and quantify Lacosamide in concentration as low as 5 µg/ml.

Taste Masking of Lacosamide: Spray drying technique was used for the taste masking of Lacosamide by coating the drug with Eudragit E 100 polymer because it requires only a one step process and can be easily controlled and scaled up. Eudragit EPO was used as a taste masking agent because it dissolves at a pH of less than five. Therefore, it does not dissolve in the buccal cavity (pH 5.8-7.4) and keeps the coated drug intact to produce good taste masking, but the polymer dissolves in the stomach (pH 1-3) to release the drug.

Determination of Threshold Bitterness Concentration of Lacosamide: Threshold bitterness concentration is the minimum concentration at which bitterness starts to appear and continues to provoke after 30s.

In this study it was observed that most of the volunteers rated 200µg/ml as the threshold bitterness concentration for Lacosamide (as shown in **Table 15**).

From the literature it was concluded that the taste masked form of the drug should not release more than or equal to 200 µg/ml of the drug in mouth for satisfactory taste masking.

TABLE 15: DETERMINATION OF THRESHOLD BITTERNESS CONCENTRATION

Volunteer	Concentration Of Drug (µg/ml)				
	50	100	150	200	250
1	0	0	1	1	2
2	0	0	1	1	2
3	0	0	0	1	2
4	0	0	0	1	2
5	0	0	0	1	2
6	0	0	0	1	2

(0: No Bitterness, 1: Threshold bitterness, 2: Bitter, 3: Moderate bitterness, and 4: Strong bitterness)

Evaluation of Microspheres:

***In-vitro* Evaluation of Bitter Taste of Microspheres (Taste Masking Evaluation):** The prepared microspheres were evaluated for *in-vitro* taste masking in 10 ml phosphate buffer pH 6.8. The drug release from 1:1, 1:2, 1:3 and 1:4 drug-polymer ratio microspheres were greater than the bitter taste recognition threshold value of Lacosamide. While excellent taste masking was achieved by 1:5 drug-polymer ratio with drug release lesser than the bitter taste threshold value of Lacosamide. Hence 1:5 ratio was selected as the taste masked microsphere.

Infrared Spectroscopy: It was found that there was no interaction of polymer with the drug.

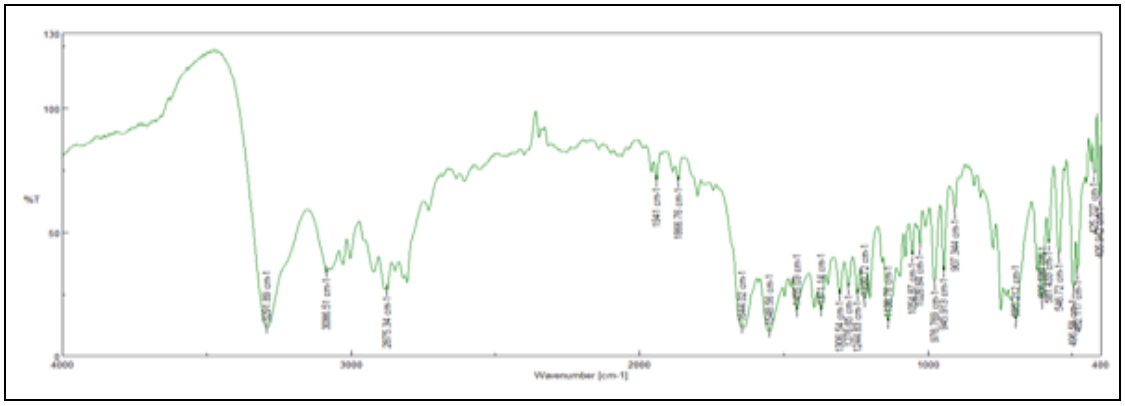

FIG. 8: FTIR OF PLAIN DRUG

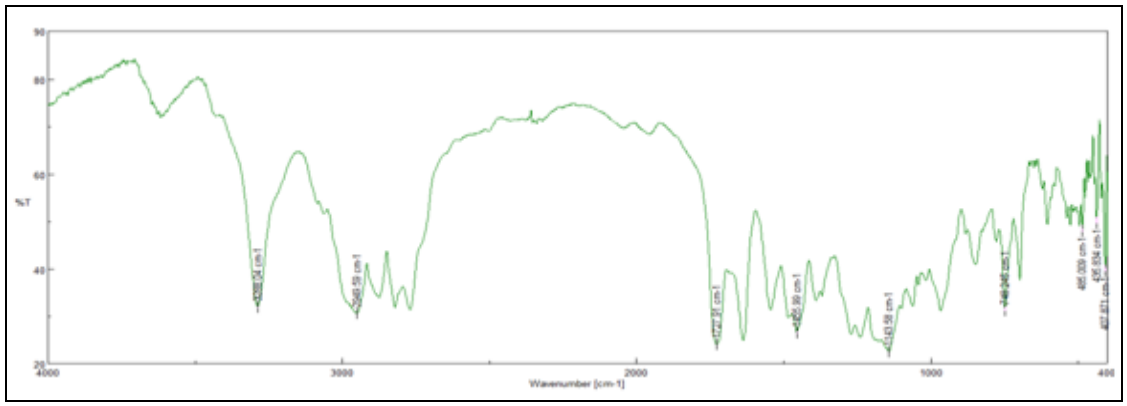

FIG. 9: FTIR OF DRUG-POLYMER MICROSPHERE

Drug Loading and Entrapment Efficiency: The entrapment efficiency of microcapsules was found to be 82.8% with a drug loading of 55.5 %. The low entrapment efficiency could be due to a smaller portion of small and light particles which escaped through the exhaust of the spray dryer during the

spray-drying process. The entrapment efficiency of the microspheres may be further improved if the loss of particles through the exhaust of the spray dryer apparatus can be prevented.

Drug Release Study: Figure shows the dissolution profiles of Lacosamide microspheres in 0.1N HCl and purified water. The dissolution profiles showed that Lacosamide microspheres dissolved more than 50% within 5 min 0.1N HCL but only 0.56% within 20 min in purified water. These results suggested that after being coated by eudragit E100, Lacosamide was released hardly in saliva but quickly in gastric juice. This method was therefore conclude to mask the bitter taste of lacosamide without reducing its dissolution or absorption of drug in gastrointestinal tract.

Formulation Development of Orodispersible Tablets (ODT): For the formulation of ODT trials batches various superdisintegrant were used such as sodium starch glycolate, cross carmellose sodium and Polyplasdone XL 10. Polyplasdone XL 10 showed lowest disintegration time therefore selected as a superdisintegrant. Microcrystalline cellulose was selected as bulking agent because of its good compressibility, good flowing properties, good solubility in water, and a pleasant taste. Microcrystalline cellulose can also increase the porosity of tablets thus promoting capillary action. It was observed that increase in the concentration of MCC led to decrease in disintegration time at concentration less than 10%.

Compatibility Study by FTIR Spectroscopy: Physical mixtures of Lacosamide with selected excipients were kept at room temperature and at 40°C/75% RH for 30 days in sealed vials. FTIR spectra of these samples were recorded to investigate any possible interactions. It was found that there was no interaction of the excipients with the drug at both normal and accelerated storage conditions. The characteristic peaks of Lacosamide were not affected as shown in **Fig. 10.**

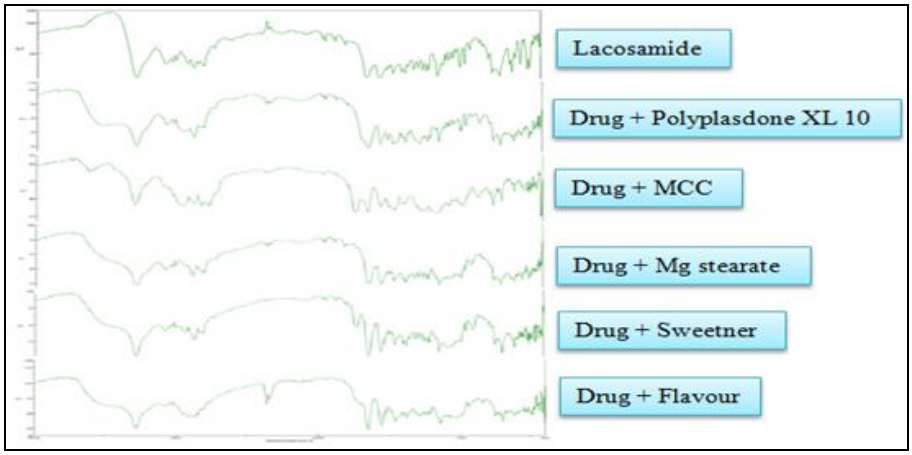

FIG. 10: COMPATIBILITY OF LACOSAMIDE WITH ALL EXCIPIENTS BY FTIR

Formulation of Lacosamide ODT: Formulation of Lacosamide ODT was done according to the formula given in **Table 2**. Total 9 different formulations were prepared as per the procedure given earlier.

Optimization: To study the effect of independent variables on responses Design Expert 8.0 software was used. Experimental design layout developed for 9 possible batches of lacosamide ODT. Out of the various models such as Linear, 2FI, Quadratic and Cubic which fit well was suggested by software and was tested for analysis of variance (ANOVA). Regression polynomials were calculated for the individual dependent variables and then contour plots and 3D surface graphs were obtained for each individual dependent variable.

Mathematical models were generated for each individual dependent variable or response (R) and expressed as equation 1-2. X_1 and X_2 are the main effects which represent the average result of changing one factor at a time from its low to high value and X_1 X_2 are interaction terms show how the response changes when 2 factors are simultaneously changed. Nonlinearity is investigated by polynomial terms X_1^2 and X_2^2**.**

TABLE 16: EXPERIMENTAL DESIGN LAYOUT OF LACOSAMIDE ODT

Run	FC	Coded levels of variables		Disintegration Time (Sec.) (Y_1)	% Drug release (Y2)
		Factor X_1 (Polyplasdone)	Factor X_2 (MCC)		
1	F1	-1	-1	227	89.1
2	F2	-1	0	193	92.32
3	F3	-1	1	166	96.71
4	F4	0	-1	147	97.11
5	F5	0	0	122	98.23
6	F6	0	1	113	99.42
7	F7	1	-1	94	97.25
8	F8	1	0	67	98.94
9	F9	1	1	27	99.38

Effect of Formulation Variable on Disintegration time: Disintegration becomes an important parameter to be studied as appropriate disintegration behavior of ODT. Formulation F9 containing highest concentration of polyplasdone (15%) and highest concentration of MCC (10%), showed lowest disintegration time.

On applying factorial design, the linear model was suggested by software and found to be significant with model F value of 234.59, p value <0.0001 and R^2 value of 0.9874 which implied that model was significant. There was only 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob> F" less than 0.05 for each term was obtained which indicated that every model term was significant. In this case X_1, X_2, were significant model terms. The model for response Y_1 (Disintegration time) is as follows:

$$Y_1 = +128 - 66.33(X_1) - 27.00(X_2) \ldots\ldots (1)$$

Above equation (eqn.1) indicates that X_1 (concentration of Polyplasdone) and X_2 (concentration of MCC) has negative effect on disintegration time. That is disintegration time of the tablet decreased with an increase in concentration of polyplasdone and concentration of MCC. However effect of X_1 is more significant than X_2. Effect of X_1 and X_2 can be further explained by contour plot and response surface plot as shown in **Fig. 11.**

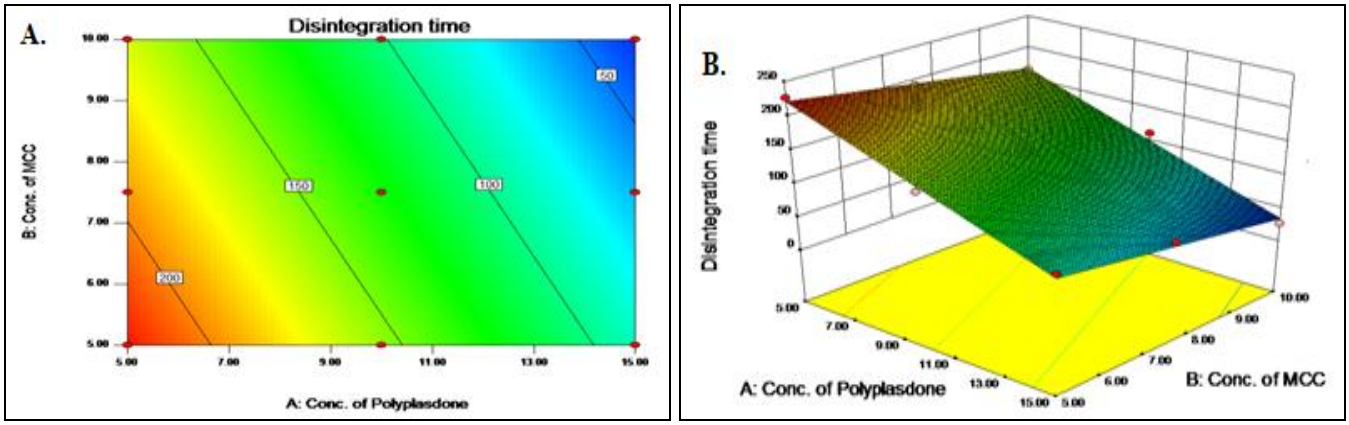

FIG. 11: TWO DIMENSIONAL CONTOUR PLOT (A), THREE DIMENSIONAL (3D) RESPONSE SURFACE PLOTS FOR RESPONSE Y1 (B)

Effect of Formulation Variables on Drug Release: Lacosamide ODT formulations were subjected for *in-vitro* dissolution studies. Drug release data obtained from all batches (F1-F9) is tabulated in **Table 17**. The cumulative percent of lacosamide released as function of time is shown in **Fig. 12.**

TABLE 17: *IN-VITRO* CUMULATIVE % DRUG RELEASE FROM LACOSAMIDE ODT

Time (Min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	35.98	38.49	46.59	52.97	56.83	60.11	67.78	70.69	73.67
4	81.29	85.85	91.82	92.33	93.59	96.3	95.51	95.17	97.41

6	82.49	88.68	94.13	95.77	96.3	97.54	98.53	98.17	98.78
8	88.65	92.01	95.9	96.14	98.12	99.26	97.11	98.56	99.19
9	89.10	92.32	96.71	97.11	98.23	99.42	97.25	98.94	99.38

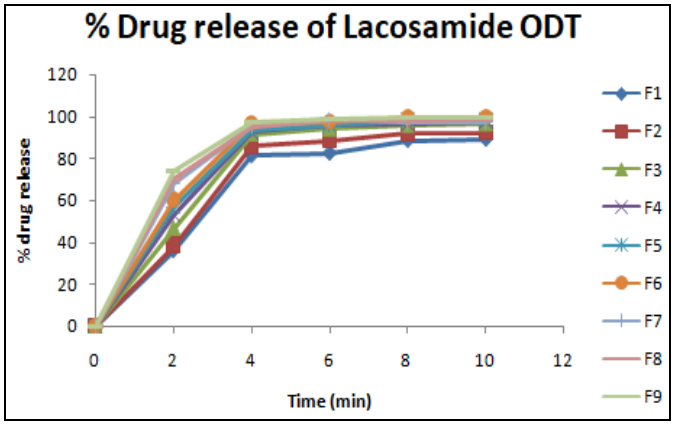

FIG. 12: COMPARATIVE CUMULATIVE % DRUG RELEASES FROM LACOSAMIDE ODT

The % cumulative drug released from all batches **Table 17** was used for optimization. On applying factorial design, the quadratic model was suggested by software and found to be significant with model F value of 23.64, p value <0.012 and R^2 value of 0.9753 which implied that model was significant. And there was only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob> F" less than 0.05 for each term was obtained which indicated that every model term was significant. In this case X_1, X_2, X_1^2, X_2^2 were significant model terms. The model for response Y_2 (percentage drug release) is as follows;

$$Y_2 = +98 + 2.84\ (X_1) + 2.01\ (X_2) - 1.37(X_1\ X_2) - 2.70\ (X_1^2) - 0.13(X_2^2) \ldots\ldots (2)$$

Above equation (eqn. 2) indicates that X_1 (concentration of polyplasdone) and X_2 (concentration of MCC) have positive effect on release of drug and drug release rate appeared to increase with an increasing amount of factor X1 (concentration of Polyplasdone) and factor X2 (concentration of MCC). However effect of X_1 is more significant than X_2.Effect of X_1 and X_2 can be further explained by contour plot and response surface plot **Fig. 13.**

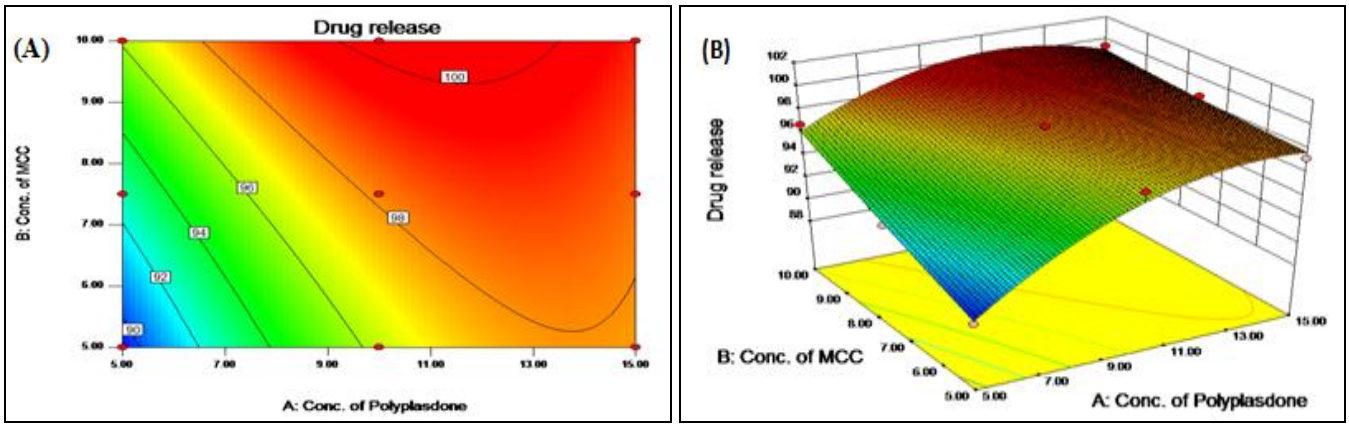

FIG. 13: TWO DIMENSIONAL CONTOUR PLOT (A), THREE DIMENSIONAL (3D) RESPONSE SURFACE PLOTS FOR RESPONSE Y_2 (B)

Optimization of Formulation: The 3^2 factorial experimental design was applied to optimized response variable Y_1 and Y_2. Formulation which shows optimum disintegration with desired drug release is to be selected as optimised formulation. Batch F9 tablets disintegrate within 27 seconds with 99.38% drug release. So it was considered as optimized and used for further evaluations.

Evaluation of Tablet Blends: The twelve tablet blends prepared were analyzed for various micromeritics and flow properties. Values of compressibility index were less than 18.5. Hausner ratio was between 1 and 1.17. Angle of repose was less than 30°. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The outcomes of these parameters indicated excellent flow properties and the blends were suitable for direct compression.

TABLE 18: EVALUATION OF PHYSICAL PROPERTIES OF TABLET BLENDS

Formulation	Bulk density (gm/ml)±SD [a]	Tapped density (gm/ml)± SD [a]	Hausner ratio	Compressibility index (%)	Angle of repose (degree) [a]
F1	0.594±0.0084	0.7258±0.008	1.221886	18.16	30.84±0.66
F2	0.6164±0.006	0.7564±0.009	1.227125	18.49	32.40±0.287
F3	0.5921±0.0055	0.7258±0.008	1.225806	18.41	34.39±0.674
F4	0.629±0.0062	0.7826±0.009	1.244197	17.07	32.99±1.072
F5	0.6388±0.0065	0.7826±0.009	1.22511	18.15	33.34±0.240
F6	0.6569±0.0068	0.7965±0.010	1.212513	17.52	32.06±0.607
F7	0.6716±0.0071	0.7665±0.010	1.141304	12.38	31.44±0.264
F8	0.7200±0.0082	0.8258±0.011	1.146944	12.81	28.64±0.564
F9	0.6809±0.0101	0.7759±0.009	1.139521	12.24	28.56±0.531

[a]Values expressed as average ± S.D. (n=3)

Evaluation of Tablets: All twelve formulations were evaluated for various quality control tests as per I.P. and the results were shown in **Table 19.** The observed results indicate that all the values obtained are within the range.

TABLE 19: PHYSICAL EVALUATIONS OF TABLET FORMULATIONS

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm) ±SD [a]	12.11 ±0.01	12.13 ±0.02	12.14 ±0.04	12.19 ±0.03	12.10 ±0.06	12.11 ±0.05	12.35 ±0.07	12.41 ±0.04	12.41 ±0.05
Weight variation	P*	p	p	p	p	p	p	P	P
Hardness (kg/cm^2) ±SD [a]	4.62 ±0.12	4.50 ±0.10	4.31 ±0.06	3.96 ±0.05	4.66 ±0.1	4.50 ±0.04	4.23 ±0.08	4.12 ±0,04	4.01 ±0.05
Friability (%) ±SD [a]	0.81 ±0.05	0.83 ±0.06	0.79 ±0.08	0.74 ±0.05	0.7 ±0.09	0.75 ±0.06	0.77 ±0.05	0.75 ±0.08	0.73 ±0.05
Disintegration time (sec) ±SD [a]	227 ±1.2	193 ±1.5	166 ±1.0	147 ±2.0	122 ±1.8	113 ±2.0	94 ±1.0	67 ±1.5	27 ±1.0
Wetting time (sec) ±SD [a]	221 ±1	185 ±2	145 ±2	141 ±1	111 ±2	98 ±2	91 ±1	64 ±2	23 ±1
%Water absorption ratio	98	96	99	98	97	98	95	99	100
Content uniformity(%) ±SD [a]	97 ±0.24	99 ±0.65	98 ±0.43	98 ±0.29	97 ±0.91	99 ±0.72	98 ±0.07	99 ±0.17	99 ±0.63

[a]Values expressed as average ± S.D. (n=3) *P = passes

Stability Studies: Stability studies for the optimized formulations were carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions. The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity condition of 40 ± 2^{o}C/ 75 ± 5 % RH. A control Sample was placed at an ambient condition. Both test and control samples were withdrawn at the end of 0, 30, 60 and 90 days and evaluated for active drug content, disintegration time and *in-vitro* drug release.

TABLE 20: STABILITY STUDIES OF OPTIMIZED F9 BATCH

Temperature Conditions	Disintegration time (seconds) ±SD [a]	% Drug Release ±SD [a]	%Drug Content ±SD [a]
First month			
Ambient	27±0.26	98.53±0.36	99.23±0.26
40^{o}C/ 75% RH	25±0.34	98.32±0.65	99.39±0.34
Freeze	29±0.28	99.01±0.34	99.48±0.54
Third month			
Ambient	29±1.06	98.06±0.95	98.97±0.66
40^{o}C/ 75% RH	28±0.85	98.03±0.78	98.92±0.32
Freeze	29±0.28	99.01±0.34	99.48±0.43

[a]Values expressed as average ± S.D. (n=3)

CONCLUSION: Taste masking was successfully carried out by spray drying technique using eudragit E100 polymer. Oral disintegrating tablet of lacosamide was prepared and evaluated.

Formulation containing highest concentration of polyplasdone (15%) and highest concentration of MCC (10%), showed lowest disintegration time.

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REFERENCES:

1. Kaur T, Gill G, Kumar S and Gupta GD: Mouth dissolving tablets: a novel approach to drug delivery. International J of Current Pharmaceutical Research 2011; 3(1): 1-7.
2. Stavras F, Partheniadis I and Nikolakakis I: Formulation of taste masked orodospersible famotidine tablets by sequential spray drying and direct compression – Bitterness Evaluation Journal of Drug Delivery Science and Technology 2023; 81(4): 104290.
3. Ravisankar P, Navya CN, Pravallika D and Sri DN: A review on step-by-step analytical method validation. IOSR J Pharm 2015; 5(10): 7-19.
4. Sohi H, Sultana Y and Khar R: Taste masking technologies in oral pharmaceuticals, recent development and approaches. Drug DevInd Pharm 2004; 30: 429-448.
5. Hu X, Li Y, Zhang E, Wang X, Xing M, Wang Q, Lei J and Huang H: Preparation and evaluation of orally disintegrating tablets containing taste-masked microcapsules of berberine hydrochloride. AAPS Pharm Sci Tech 2013; 14(1): 29-37.
6. Rowe R: Handbook of pharmaceutical excipients, Ninth edition 2020; 221-228.
7. Dourado D: Thermal analysis as a useful tool in drug-excipient compatibility studies. The Impact in Pharmaceuticals Products Biomedical Journal of Scientific and Technical Research 2019; 22(3): 16634-16636.
8. Patil MG, Kakade SM and Pathade SG: Foemulaton and evaluation of orally disintegrating tablet containg tramadol hydrochloride by mass extrusion technique. Journal of Applied Pharmaceutical Science 2011; 1(6): 178-181.
9. Gita Chaurasia: A review on pharmaceutical preformulation studies in formulation and development of new drug molecules. International Journal of Pharmaceutical Sciences and Research 2016; 7(6): 2313-2320.
10. Lachman L, Lieberman H and Kanig L: The theory and practice of Industrial Pharmacy 2003; 3: 293-294.
11. Mohd A, Sodiyal N and Patil S: A review on Evaluation of tablet International Journal of Research in Engineering and Science 2022; 10(4): 79-82.
12. Taymouri S, Mostafavi A and Talabaki H: Formulation and evaluation of taste-masked oral disintegrating tablet containing tolterodine-loaded montmorillonite Research in Pharmaceutical Sciences 2023; 18(5): 528–540.
13. IP 2010 vol I 187-198.

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