Reviewer's Comments

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS ALONG WITH ANTIEPILEPTIC DRUGS

Abstract

The objective of present study was to prepare and evaluate the mouth dissolving tablet of lacosamide using super disintegrant like Guar Gum, and other excipients like microcrystalline cellulose and mannitol in different concentrations by direct compressionmethod. Lacosamide has been shown to be an effective antiepileptic agent appropriate for epilepsy patients. Effect of different formulation variables; **asamount and type of polymer were 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 releasestudies were carried out for all formulations. All formulations**resultswere within**official limits.**Fast disintegration time obtained between 35sec. and 128 sec,was within official limit.**Different drug **release kinetic models**were applied for selecting batches**for** stability studies.These showed that there was no any significant change in residual drug content **in**mouth dissolving tablets. By the *in-vitro* disintegration, it is concluded that formulation prepared by Guar Gum (10%) showed**faster** disintegration time than **that of**MCC.**This indicates that the use of super disintegrants increases the release of drug from the formulation.** Therefore, it **can** be concluded that**such mouth dissolving tablets aresuitable delivery system for**lacosamide. **Thus; the objective of this study was achieved**. Thus, the "patient-friendly dosage form" especially for **pediatrics**, geriatrics, bedridden and non-cooperative patients, can be successfully formulated using this technology, **providing** faster and better drug release, thereby, improving the bioavailability of drug **compared** to **conventional** marketed formulations.

Keywords: Lacosamide, Epilepsy, Fast dissolving tablet, Superdisintegrants, Bioavailability, Pre-compression parameters, Post-compression parameters.

Introduction

Epilepsy is one of the most **common** central nervous system (neurological) disorders, resulting from stagesof **abnormal, excessive generation**of neuronal disturbances in the brain. Epilepsyis a brain disorder that is identifiedby chronic epileptic seizures. Epileptic **seizures result from** sudden repetitiveoccurrence of sensory disturbance, **causing**loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain.**About90% of epilepsy patients are found in developing countries.**

Causes of epilepsy

There are defined causes of epilepsy that are common in different age groups;

1. In neonatal period and early infancy, the most common causes are hypoxic–ischemic encephalopathy, CNS infections, trauma, congenital CNS abnormalities and metabolic disorder.

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Comment [D2]: Change the title as below

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF ANTIEPILEPTIC DRUG

Comment [D3]: Article is looking like the thesis. Article can be published only after suggested changes.

All minor phrasing, spelling and grammar mistakes are noted in the manuscript by red bold color

Comment [I4]: The (s) removed

Comment [D5]: Need spacing

Comment [I6]: (the) removed

Comment [I7]: Add "; as" instead of i.e

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Comment [I10]: Sentence modified into "amount and type of polymer" instead of "amount of polymer and type of polymer"

Comment [I11]: Were instead of was

Comment [I12]: Replace "i.e" by ; as Replace amount of polymer and type of polymer by "amount and type of polymer" Put "," after " was studied"

Comment [I13]: two words not one word

Comment [D14]: Need spacing

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Comment [I16]: "for all formulations" instead of "for all the formulation"

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Comment [D18]: Need spacing

Comment [D19]: Need spacing

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Comment [D21]: Arrange alphabetically

Comment [D22]: (1)Epilepsy and Seizure are not synonyms, they are pathologically and scientifically different. Patients might have seizures and still not epileptic. The author seems to be highly confused, so he has to identify this and fix it. He can simply describe the drug as antiseizure and not anti-epileptic, since anti-epileptics has different mode of action that is ...

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2. In late infancy and early childhood, the most common febrile seizures may be caused by CNS infections and trauma.

Pathophysiology of epilepsy

Seizures are paroxysmal manifestations **of cerebral cortex**. **Theyoccur**when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical**n**eurons. **Cell membraneinstability or its physiological changes in its adjacent supporting cells represent the main pathophysiology of seizures**.

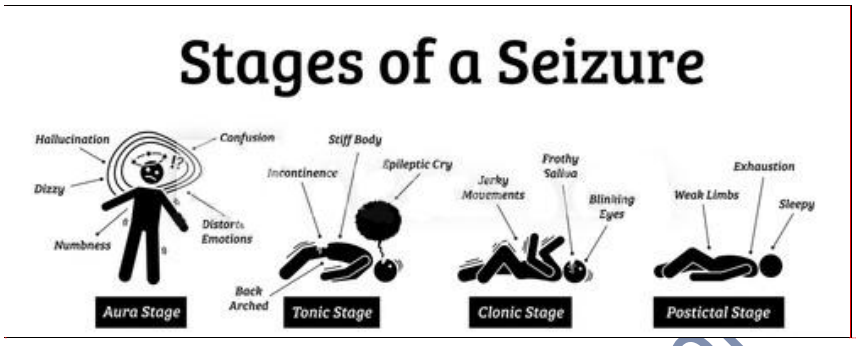

Fig.1 Stages of Seizure

Classification of seizures

1. Generalized Seizures

A. Absence seizures (formerly called petit mal)
B. Myoclonic seizures
C. Clonic seizures
D. Tonic seizures
E. Tonic clonic seizures (formerly called grand mal)
F. Atonic seizures (drop attacks)

2. Partial Seizures

A. Simple partial seizures (consciousness not impaired)

1. with motor symptoms
2. with sensory symptoms
3. with autonomic symptoms
4. with psychic symptoms

B. Complex partial seizures (with impaired consciousness)

l. simple partial seizures followed by impairment of consciousness
2. with impairment of consciousness at seizure onset

C. Partial seizures evolving to secondarily generalized seizures

1. simple partial secondarily generalized
2. complex partial secondarily generalized
3. simple partial evolving to complex partial evolving to generalized

Fast dissolving tablet

Although, tablets are themost commonly used dosage form because of **itssimplicity of**self-administration, **ease of preparation**, **and accuracy of dose delivery,however;pediatrics and geriatricsmay suffer difficulty in swallowing**(dysphasia) or chewing.

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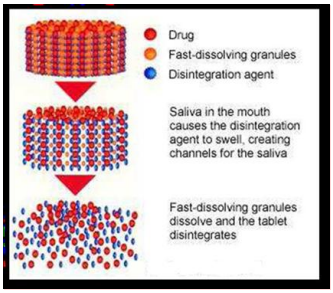

Fig. 2 Conceptual diagram of FDT

Need for Development of fast dissolving tablets FDTs:

Table 1. Patients related factors for development of FDTs

Taste masking	As large amount of drugs are unpleasant, fast disintegrating drugs usually contain medicament in a taste-masked form. The rapid disintegrating drugs break downing patient's oral cavity, thus, releasingactive ingredients which directly come in contact with taste buds.
Amount of Drug	As amount of the drug is an important parameter in the formulation of fast dissolving tablet i.e. an optimized amount should be taken during the formulation of these tablets, quantity of dose of the drug must be lesser than 400 mg forinsoluble drugs and less than 60 mg for solubledrugs.
Mouth feel	As good mouth feel considered as the important consideration in the formulation of FDT's. So it is important to note that ODT should leave minimal or no residue in the mouth after oral administration.
Sensitivity to environmental conditions	It should be kept in mind during the formulation of FDTs that they generally should show low sensitivity to environmental conditions such as humidity and temperature.
Hygroscopicity	Hygroscopicity is one the parameter that should be considered in FDT's as many orally disintegrating dosage forms loose physical integrity under standard conditions of temperature and humidity as they are hygroscopic.
Size of tablet	The size of the fast dissolving tablet should also consider as prior parameter to be considered. The easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and handle is difficult to reach.

Various effectiveness factors are as follows:

- Increased bioavailability and faster onset of action are major claim of these formulations.

Various Manufacturing and marketing factors are as follows:

- Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size.

Materials and Methods

Drug profile: Lacosamide

Synonyms: Erlosamide, Harkoseride, Lacosamida.

Chemical Structure:

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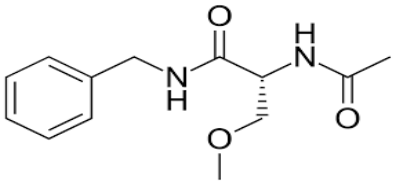
Comment [D29]: Since it is a research article no need of detail of used drug and other ingredients. In discussion section, illustrate about properties of ingredients affecting the results.

Comment [D30]: Please give justification for the use of this drug in this study. With proper references explain either this work is novel or not



Chemical Name: (2R)-N-benzyl-2-acetamido-3-methoxypropanamide
Molecular Formula: $C_{13}H_{18}N_2O_3$
Generic Name: Lacosamide
Molecular Weight: 250.298 g/mol
Category: Anti-epileptic Agents
Sub-category: Sodium channel Inhibitor
Percentage Purity: 98.0% - 101.0%
Description: Lacosamide is a white amorphous powder.
Solubility: Completely solubilize in Phosphate buffer of Saliva pH 6.8, sparingly soluble in water and slightly soluble in acetonitrile and ethanol.
Stability: Stable under ordinary conditions
pKa: 12.47
Log P: 0.728 (Octanol/Water)
Melting point: 140-146˚C
Storage: To be stored in well closed, away from heat and damp places.

Mechanism of action

- 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.

Absorption
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. It shows the reaching of peak plasma concentrations within 4hr after taking a single dose (100–800 mg).

Distribution
As Lacosamide is having low affinity to bound with plasma protein i.e. less than 15% and hence the risk of drug-drug interaction is very low. The volume of distribution of lacosamide is near about 0.8 L/kg.

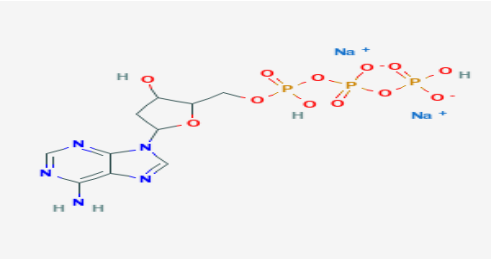
Elimination
The half-life of this drug was found to be near about 13 hr, allowing convenient BID dosing. The elimination process follows the first order kinetics which is described by the one compartment modelling. Lacosamide is mainly excreted by renal route

Formulations:
Lacosamide is a drug used in the treatment of partial onset seizures and diabetic neuropathic pain.Vimpat is the brand name of the lacosamide drug.

Polymer Profile

Guar gum

It is a natural occurring polymer, completely soluble in buffer, and is also approved by FDA for use as food additive. It has a formula of $C_{10}H_{14}N_5Na_2O_{12}P_3$



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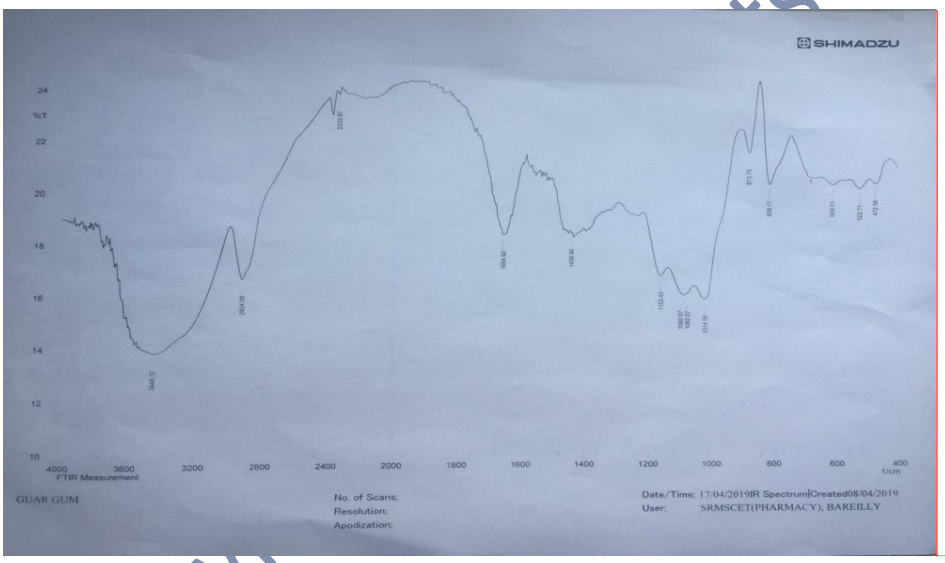

Fig 3FTIR range of Guar Gum

Table No1: Interpretation of FTIR spectra of Guar Gum

S.No.	Peak cm^{-1}	Groups
1.	3448	Ar-NH_2
2.	873	P=O-Ar Stretching
3.	522	P=O-Ar bending
4.	808	P-O-Ar stretching
5.	472	P-O-Ar Bending
6.	1014	C-O Acyclic ring
7.	2924	CH_2OH- Ar Stretching
8.	1654	N-H Bending
9.	1153	C-N

Comment [D31]: Since it is a research article no need of it
Simply write about materials and their source

Comment [D32]: Remove it

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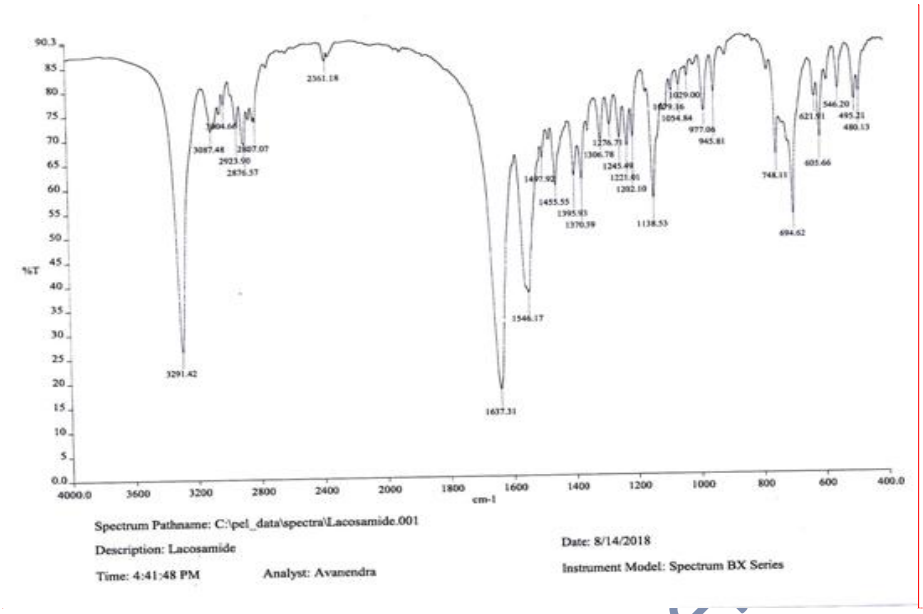

Fig 4 FTIR Spectra of Lacosamide

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Mannitol

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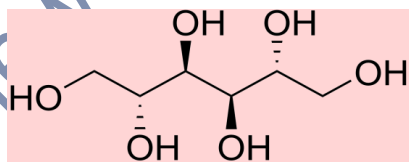
Mannitol is widely used as pharmaceutical excipients such as used as diluent in the formulation of tablet and capsule, used as sweetening agent in the mouth dissolving tablets mainly, used as a tonicity agent. Mannitol is extracted by the sugar fructose and its taste is as sweet as sucrose. Mannitol shows the cooling effect and hence helps in the masking of the bitter tastes.



Synonyms	D-Mannitol, mannite, manna sugar
IUPAC Name	(2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol
Molar mass	182.172 g·mol^{-1}
Appearance	White crystalline powder.
Odor	Odorless
Solubility	Soluble in alcohol; water.

Application in Pharmaceutical formulation:

- Mannitol is widely accepted excipients used in various pharmaceutical formulations.
- It is used as tablet diluent in different pharmaceutical formulations and since it is used in combination with moisture sensitive active ingredients because of its non-hygroscopic nature.

Stability and Storage Conditions:

Mannitol is stable when stored in a well closed amber colored container. It should also protect by variations in the environmental temperature.

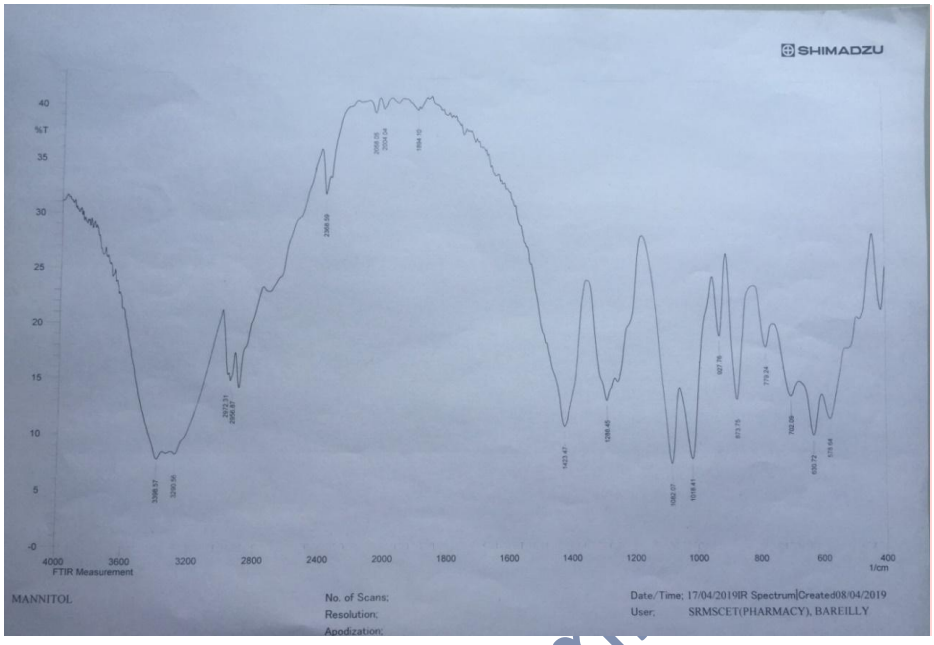


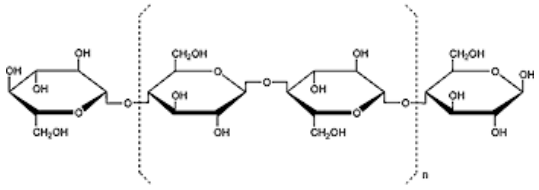
Fig 5 FTIR ranges of Mannitol

Table No: 2 Spectra showing wave no. of Mannitol

S.No.	Peak cm^{-1}	Groups
1.	3398	C-OH Aliphatic
2.	1288	C-C stretching
3.	2972	C-H stretching
4.	1423	C-O stretching

Microcrystalline cellulose: (Frone et al, 2011; Laka et al, 2007)

Microcrystalline cellulose is widely accepted excipients used as a disintegrants in the fast dissolving tablets and used as bulking agent in the food production.



Stability and Storage condition:

MCC is completely stable in nature, but it is one of the hygroscopic materials. Hence it should be stored in the well-closed container in a cool and dry place.

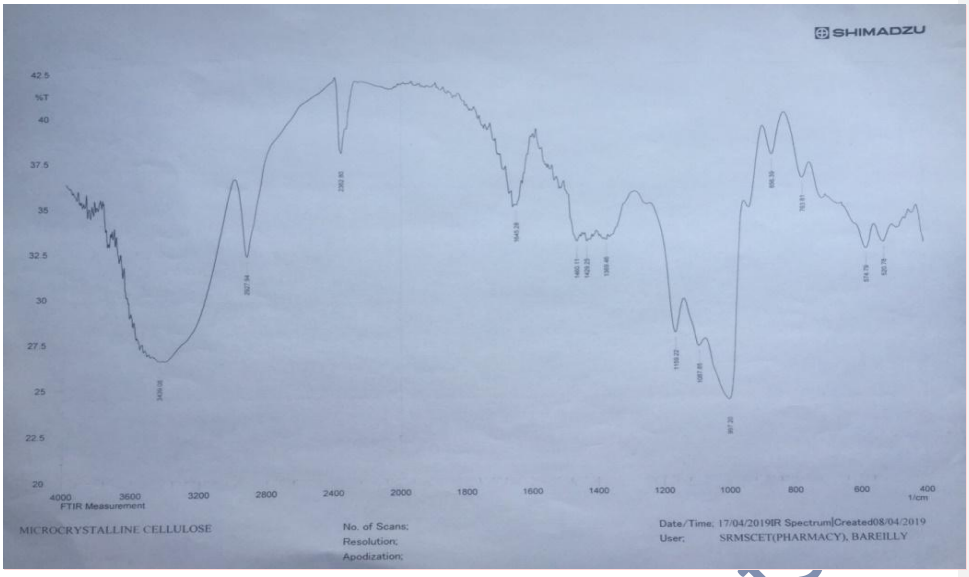


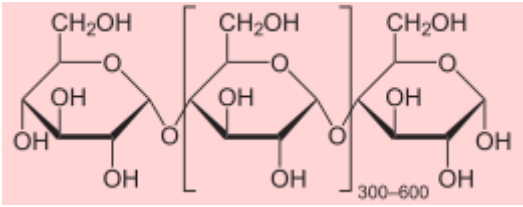
Fig 6 FTIR Spectra of MC

Table No 3: Interpretation of MCC by FTIR spectra

S.No.	Peak cm^{-1}	Groups
1.	2362	CH_2-OH
2.	2927	CHO aromatic
3.	1645	C-H stretching
4.	1460	C-OH Symmetric
5.	997	C-OH Asymmetric
6.	1159	C-O Stretching
7.	574	C-O-C bending
8.	763	C-C-O bending

Starch

Starch is one of the widely found substances which are stored in plants. Starch is widely accepted excipients have been very useful in tablet production due to their inertness, cheapness and utilization as fillers, binders, disintegrants and glidants. Starch is mainly used in the formulation of tablet as binders, and disintegrants.



Functional category of Starch:

- Glidant.
- Tablet and capsule diluent.
- Tablet and capsule disintegrants.

Application in Pharmaceutical formulation or Technology:

1. Starch is mostly or commonly used excipients in the tablet formulation.
2. It is used as food additive and is generally regarded as an essentially non-toxic and non-irritant material.

Stability and Storage Conditions:

Starch should be stored in an amber colored container & in a cool & dry place.

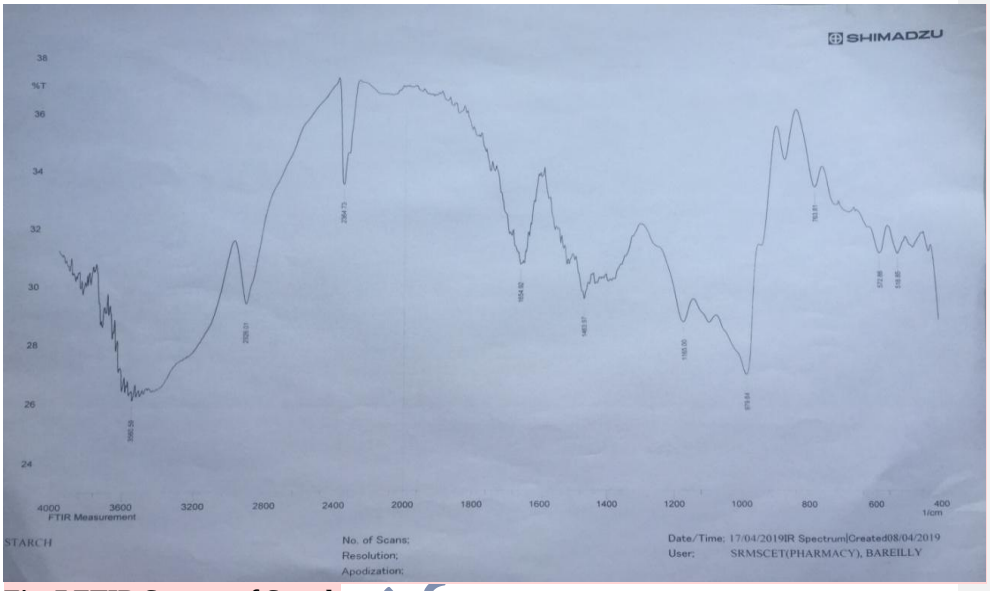


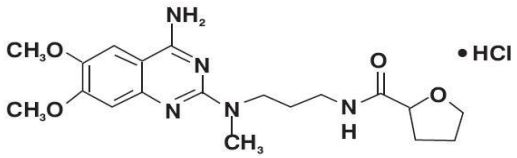
Fig .7 FTIR Spectra of Starch

Table No 4: Interpretation of Starch by FTIR spectra

S.No.	Peak cm^{-1}	Groups
1.	2364	CH_2-OH stretching
2.	1463	C-H_2 stretching
3.	1450	C-OH symmetric
4.	1165	C-O stretching
5.	979	C-OH Asymmetric
6.	763	C-C-O bending
7.	572	C-O-C bending

Talc

Talc is a mineral commonly occurring and consists of magnesium, silicon and oxygen. It is a substance mainly found in various cosmetic products such as baby powder, adult body powders and facial powders.



Chemical Name	Altalc, hydrous magnesium calcium silicate, hydrous magnesium silicate,
IUPAC Name	dioxosilane;oxomagnesium;hydrate
Molecular formula	$Mg_3Si_4O_{10}(OH)_2$
Molar weight	379.259 g/mol
Appearance	White to grayish-white very fine crystalline powder.
Density	2.70-2.80 g/cm^3
Melting point	900-1000 °C
Solubility	Freely soluble in water.

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Stability and Storage condition: Talc is very stable in nature and it can be sterilized by heating process at 160°C for not less than 1hour**,** it may also be sterilized by exposure to ethylene oxide or gamma irradiation. It should be stored in well closed container.

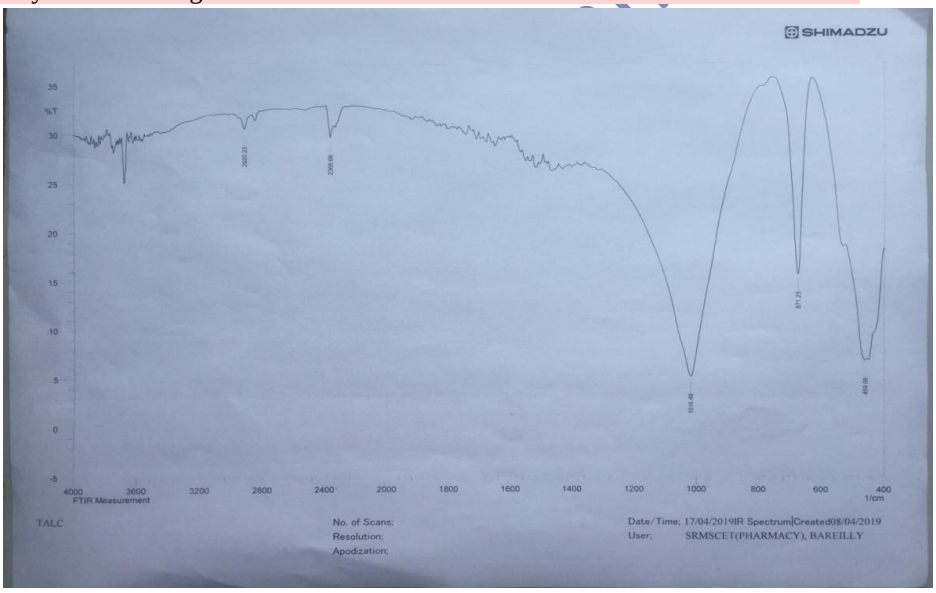


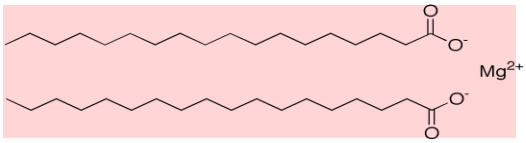
Fig 8 FTIR Spectra of Talc

Table No 5: Interpretation of Talc by FTIR spectra

S.No.	**Peak cm^{-1}**	**Groups**
1.	1016	C-O stretching
2.	1670	C=O stretching
3.	2920	N-H-bending
4.	2366	N-CH_3 stretching
5.	671	C-N bending
6.	650	O-CH_3

Magnesium Stearate

Magnesium stearate is the compound which is chemically produced having molecular formula Mg $(C_{18}H_{35}O_2)_2$. It consists of salt containing 2 anions of stearic acid and one magnesium cation.



Application in Pharmaceutical formulation

- Magnesium stearate is often used as an anti-adherentin the manufacture of medical tablets, capsules and powders.

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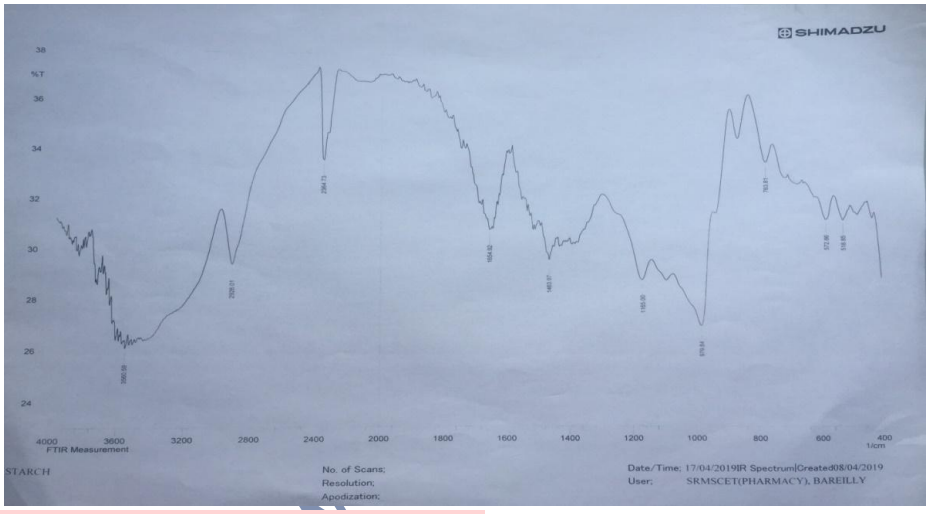


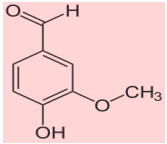
Fig.9 FTIR Spectra of Magnesium Stearate

Table No 6: Interpretation of Magnesium Stearate by FTIR spectra

S.No.	Peak cm^{-1}	Groups
1.	3380	O-H stretching
2.	3470	N-H stretching
3.	3080	C-H aromatic
4.	1740	C=O stretching
5.	1540	C=C aromatic

Vanillin

Vanillin is a widely used flavouring agent in tablet formulation to provide good feel. The molecular formula of vanillin is $C_8H_8O_3$



IUPAC Name	4-Hydroxy-3-methoxybenzaldehyde
Molecular formula	$C_8H_8O_3$
Molar mass	152.15 g mol^{-1}
Appearance	White crystalline form
Odor	Vanilla, Sweet, Balsamic, Pleasant
Density	1.056 g cm^{-3}
Melting point	81-83 °C, 354-356 K, 178-181 °F
Boiling point	285 °C, 558 K, 545 °F
Solubility **in** water	10 g dm^{-3}

Table No 7: List of equipments

S.No.	Name of instrument	Source
1	Fourier Transform Infrared Spectroscopy	IR Affinity 1, Shimadzu, Japan
2	UltravioletVisible Spectrophotometer	U.V. 1800, Shimadzu, Japan
3	Tablet compression machine	Rimek Mini- Press- I, Gujarat, India
4	Dissolution apparatus	TDT-08L, Electrolab, Dissolution Tester USP, Mumbai, India
5	Monsanto Hardness Tester	Vinsyst Technologies, Mumbai, India
6	VernierCaliper	Mitutoyo Corporation, China
7	Test Sieve (60)	Scientific Engineering Corp, Delhi.
8	Digital Balance	AW 120, Shimadzu Corporation, Japan

Comment [D36]: Remove it, no need

Comment [D37]: Please provide in details about how formuations were prepared.

Methodology

During development of any formulation; its exact analytical technique and its details are highly desirable, so for the same, firstly pure drug was studied for its characteristics and its standard curve was prepared.

Preparation of Lacosamide 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.

Results and Discussion

Comment [D38]: (1)Methods are presented in the results section, not the methodology section.
(2)Figures and tables are not referred to within the context of the research paper.
(3)Titles of figure 18 and figure 19 are the same, thereby the difference between both should be clarified within the caption.
(4)Figures should include standard deviation
(5)The author sometimes used the word “Fig.” and others he used “Figure”. He has to pick one and use it along the paper.
(6)On writing tables title, we do not write “Table no 1” we write “Table 1” directly.
(7)Table 12 comprising the dissolution test details, should be written in methodology in the paragraph form and not in table form within results.

Preformulation studies:

Identification of drug

Lacosamide was identified by several methods like infrared spectroscopy and ultraviolet spectroscopy.

Infrared spectrum:

In FTIR spectroscopy, firstly the pellets of KBr and drug were prepared and then examined under Shimadzu8400S (4000-400/cmIR spectrophotometer (Shimadzu, Japan).

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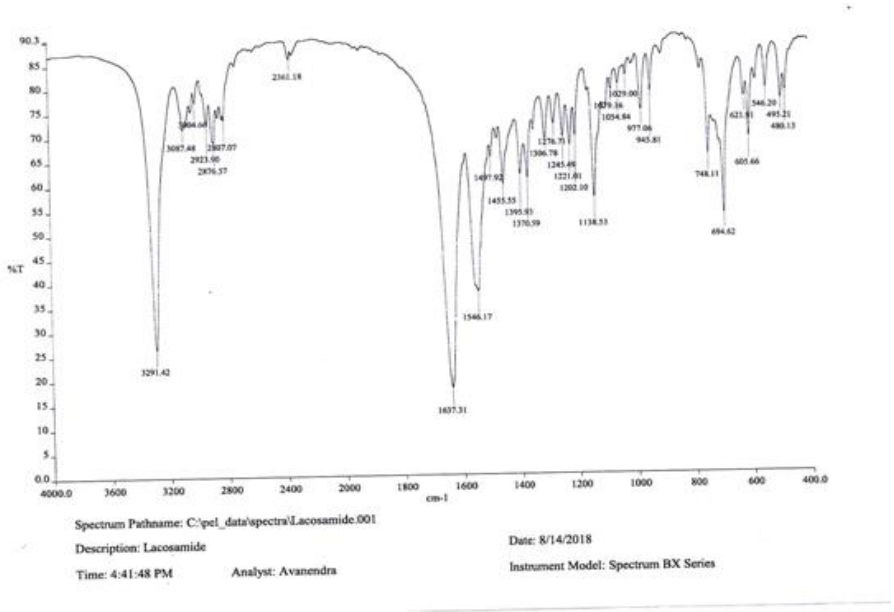

Figure 10: FTIR spectra of Lacosamide

Comment [D40]: Remove it, no need

Table No 8: Interpretation of FTIR spectra of Lacosamide

Comment [D41]: Remove it, no need

S.No.	Peak cm^{-1}	Groups
1.	$3400cm^{-1}$	O-H stretching
2.	$3300cm^{-1}$	N-H stretching
3.	$3040cm^{-1}$	C-H aromatic
4.	$1640cm^{-1}$	C=O stretching
5.	$1550cm^{-1}$	C=Caromatic
6.	$1540cm^{-1}$	N-H bending
7.	$1240cm^{-1}$	C-N stretching
8.	$1220cm^{-1}$	C-O stretching
9.	$1160cm^{-1}$	C-F stretching

Melting point determination:

The Lacosamide melting point can be measured by using thieles tube method. In this method 300 ml of heavy paraffin was filled in thieles tube, and the drug filled in a capillary tube of which one end is sealed with the help of flame, and was tied with the thermometer and was suspended in thieles tube filled with paraffin.

Table No 21: Melting Point of Lacosamide

Comment [D42]: No need of table for it

S.No.	Reported	Observed
1.	140-146ºC	145ºC

Solubility determination:

The solubility study of drug was performed in different solvent (e.g. Ethanol, Phosphate buffer pH6.8 etc).A known quantity of drug, i.e.10 mg was transferred in a series of different solvents having volume 5 ml in different test tubes.

Procedure:

The partition coefficient of drug (Lacosamide) was determined in solvent system: n-octanol/phosphate buffer pH (6.8). Accurately weighed quantity of drug (10 mg) taken in one stoppered glass vial containing 5 ml ofoctanol, 5ml of phosphate buffer was added to the vial.

Pw/o =(C aqueous / C organic)

Comment [D43]: Use Microsoft equation tool for it

Where,

C organic - Concentration of drug in organic phase.

C aqueous - Concentration of drug in aqueous phase.

Po/w - Partition coefficient of drug in oil in water system.

Pw/o - Partition coefficient of drug in water in oil system.

Same process was applied with n-octanol / distilled water system partition coefficient determination.

Methods of Analysis

Preparation of calibration curve:

The standard curve is prepared by preparing the stock solution of 100 mcg/ml by dissolving accurately weighed 5 mg of Lacosamide in 50 ml of Phosphate buffer pH-6.8 in a volumetric flask

1) Formula for preparing fast dissolving tablet using Guargum, Mannitoland MCC

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

2) Formula for preparing fast dissolving tablets using Guargum and increasing concentration of Mannitol

Ingredients (mg)	**Formulation code F2**
Lacosamide	50
Guar gum	10
Mannitol	110
Aspartame	4
Starch	20
Talc	4
Vanilline	q.s
Total weight (mg)	200

Method of preparation of fast dissolving tablets:

By Direct Compression Technique:

Tablets containing Lacosamide were formulated using various superdisintegrants like Guar gum, MCC in concentrations ranging from 5-10%. The tablets were prepared by direct compression method.

Procedure:

1. All the ingredients were passed through a sieve number 40 prior to mixing.
2. Lacosamide, MCC, Mannitol and the superdisintegrants were properly mixed for 30min in a suitable container to obtain a uniform blend. The blend was further lubricated with magnesium stearate and talc for 5min

Evaluation of fast dissolving tablets

Weight variation:

Weight variation was determined to know whether different batches of tablets have uniformity.

Table No 9: Weight variation specification

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

Tablet Thickness and Diameter:

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using VernierCalipers.

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Table No 10: Friability of different formulation

Comment [D44]: Add a single table having results of all evaluation parameters

S.No	Formulation code	Friability
1.	F1	0.42
2.	F2	0.49
3.	F3	0.58
4.	F4	0.55
5.	F5	0.56

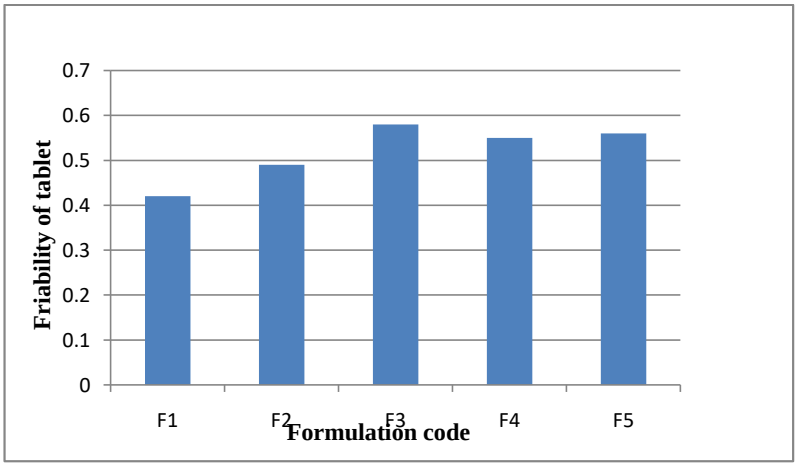

Figure 11: Friability of different formulation

Wetting time

Two circular tissue papers of 10 cm diameterwere placed in a petri dish having the sameinner diameter. 10 mL of phosphate buffersolution pH 6.8 containing a watersolubledye, was added to petri dish.

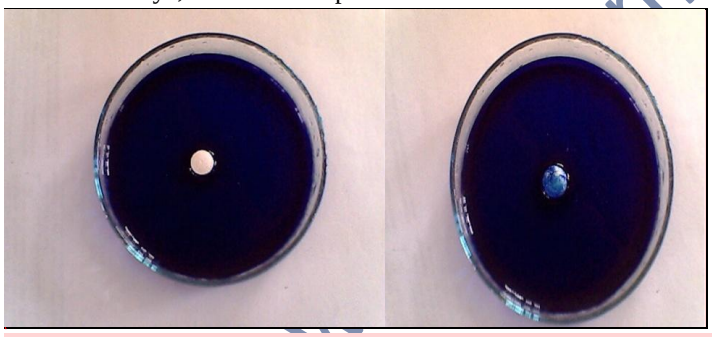

Figure 12Before wetting **Figure 13After wetting**

Comment [D45]: No need, remove it

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured.

R = 100 x [Wa – Wb] / Wb

Comment [D46]: Use Microsoft equation tool for it

Where, Wa = weight of tablet after absorption

Wb = weight of tablet before absorption

Figure 14Before Absorption **Figure 15After Absorption**

Comment [D47]: Remove it, no need

***In-vitro* dispersion time**

*In-vitro*dispersion time was measured by dropping a tablet into a Petri dish containing 10 ml of phosphate buffer solution pH 6.8 at 37±0.5^{0}C. Three tablets from each batch were randomly selected and tested.

TableNo 11: *In-vitro* dispersion time of different formulation

Comment [D48]: Add a single table having results of all evaluation parameters

S.No	Formulation code	*In-vitro* dispersion time (sec)
1.	F1	56.0±2.28
2.	F2	50.16±1.32
3.	F3	54.33±2.73
4.	F4	52.83±2.56
5.	F5	50.83±1.70

Mean ± S.D. (n=3)

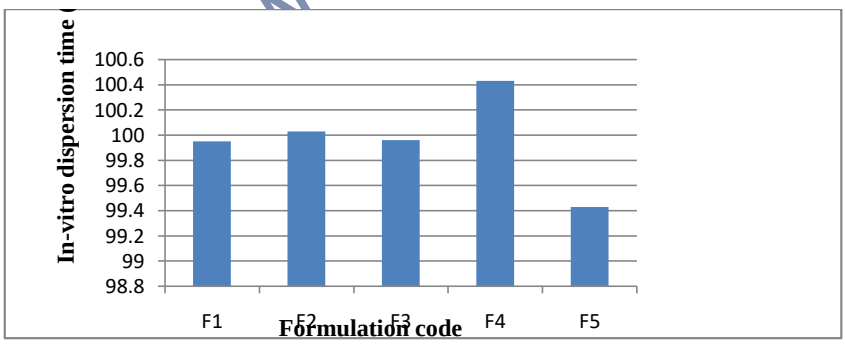

Figure 16*In-vitro* dispersion time of different formulation

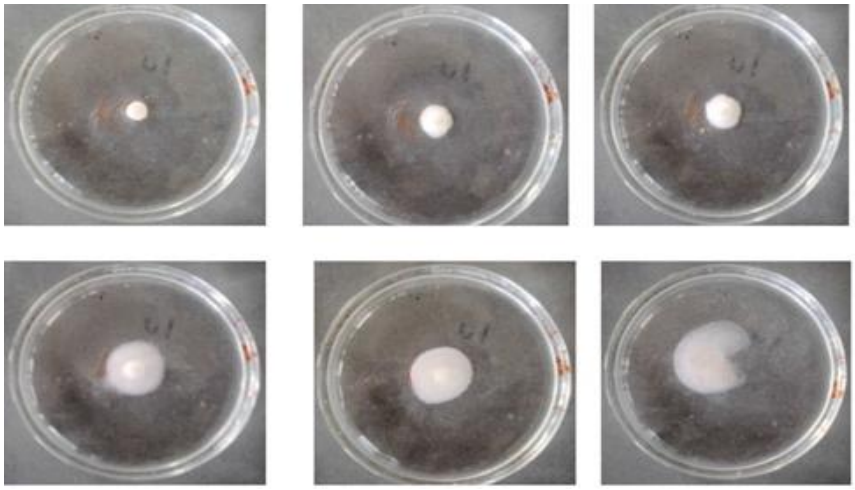

Figure 17*In-vitro* dispersion time

Dissolution Studies

The release rate of lacosamide from mouth dissolving tablets was determined using USP Dissolution Testing Apparatus II (Paddle type).

Table 12: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 13: Comparative cumulative drug release of different formulations

Comment [D49]: Remove it, no need Figure is sufficient for release study

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)

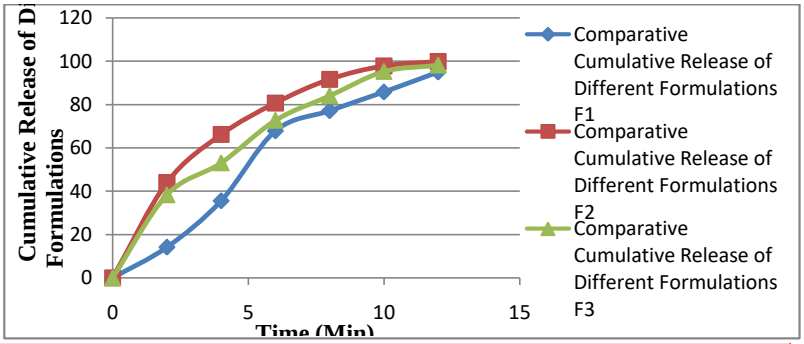

Figure 18Comparative study of cumulative release of different formulations

Comment [D50]: Arrange result of release study of all formulations in a single graph

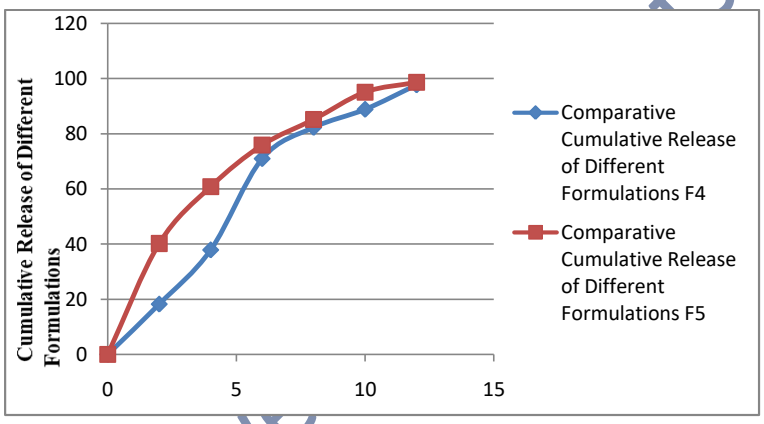

Figure 19 Comparative study of cumulativerelease of different formulations

Conclusion

The fast dissolving tablets were successfully prepared bydirect compression method of the Lacosamideusing superdisintegrants and the objective of this study was achieved. By the *in-vitro* disintegration, it is concluded that formulation preparedby 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 drugLacosamide. Therefore, it may be concluded that mouth dissolving tablet was suitable drug delivery system forLacosamide. Thus, the "patient-friendly dosage form" especially for pediatric, geriatric, bedridden, and non-cooperative patients, can be successfully formulated using this technology, and also provides faster and better drug release, thereby, improving the bioavailability of drug as compared to the conventional marketed formulation.The objective of present study was to prepare and evaluate the mouth dissolving tablet of Lacosamideusing Super disintegrants like Guar Gum, and Microcrystalline Cellulosein different concentrations by Direct Compression method.Lacosamide mouth dissolving tablets prepared were evaluated for Pre-compressional and Post compressional parameters. The Pre-compressional parameters evaluated are bulk density, true density, angle of repose and Carr's index. The various evaluation parameters are studied such as 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 (35sec to128 sec). Different drug release kinetics model were applied for selecting batches stability studies, showed that there was no any significant change in residual drug content mouth dissolving tablets.

Comment [I51]: Same as the abstract which is not acceptable

Comment [D52]: The author copied and pasted it from the abstract which is totally unacceptable. The conclusion has to be rewritten again. Since repetition is totally refused and non-academic.

Comment [D53]: Spacing needed

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Comment [D57]: Reduce the references upto 20 only

Add some latest references of 2015-2019

Please follow journal specifications for references like below-
Akhter S, Hossen MS, Salahuddin M, Sunny MA, Sathi FA, Islam MS. *In vitro* dissolution study of glimepiride from binary and ternary solid dispersion formulation. Univ J Pharm Res 2019; 4(5): 7-12.

Comment [D58]: References are not formatted within common format, every reference is written in a different way. This is a MAJOR CHANGE that has to be adjusted. Moreover, there is no indication in the text of the reference relevance. The author has to refer to referenced part by either number or author name and year.

Comment [D59]: Italic?

Comment [D60]: Superscript

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