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FORMULATION & EVALUATION OF LAMOTRIGINE NANOSUSPENSION WITH STUDY OF CRITICAL QUALITY ATTRIBUTES (CQA)

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ABSTRACT

Solubility of a drug can be a limiting factor for its formulation into a suitable dosage form & it influences the effectiveness of a drug to a large extent. Nanosuspensions are defined as the sub-micron colloidal dispersions of pure drug particles stabilized by surfactants. Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features & unique advantages. Lamotrigine Nanosuspension was prepared using emulsification-solvent diffusion method with overcoming limiting factor. All the formulations were subjected to in-vitro evaluation & the statistically optimized one was used for stability, scanning electron microscopic & differential scanning calorimetric studies. By virtue of the submicron particle size & distinct physicochemical properties, nanosuspension has the potential ability to tackle many formulation & drug delivery issues typically associated with poorly water & lipid soluble drugs. Lamotrigine undergoes extensive hepatic metabolism upon oral administration & its absorption is affected in the presence of food. This study was aimed to develop nanosuspension of Lamotrigine & investigate its formulation characteristics. The application of nanosuspensions in different drug delivery systems such as oral, ocular, brain, topical, buccal, nasal & transdermal routes are currently undergoing extensive research.

KEYWORDS: Lamotrigine, Nanosuspension, QBD, Epilepsy, CQA, Technology

Advancement.

1. INTRODUCTION

1.1. Introduction to Nanosuspension

Nanosuspension is described as finely dissipated solid prescription particles in liquid vehicle. It is characterized as "finely scattered strong medication particles in a fluid vehicle, settled by surfactants, for one or the other oral & skin use or parenteral & aspiratory organization, with diminished molecule size, prompting an expanded disintegration rate & consequently improved bioavailability".[1,2,3] Atom gauge in Nanosuspension stretches out in area of 200 & 600nm. Dissipating of drug Nanocrystals in liquid media prompts "Nanosuspension". Dispersing media can be water, liquid plans or non-watery media (e.g., Liquid Polyethylene Glycol (Stake), Oils).[4,5] Nano suspensions properties that connect with one's consideration are.

• Speed up & drenching dissolvability of medicine.
• Improved normal execution.
• Simplicity of produce & scale-up.
• Long haul actual relentlessness.
• Adaptability.
• Expansion in oral maintenance.
• Improved estimations proportionality.[7,8]

1.2. Methods of Nanosuspension Preparation

There are numerous strategies for readiness of Nanosuspensions. Presently the current procedures utilized for readiness are of two classifications.[9,10,11]

A. Bottom-up Technology
B. Top-down Technology

- High pressing factor Homogenization (DissoCubes)
- Media processing (Nanocrystal or NanoSystems)
- Homogenization in non-watery media (Nanopure)
- Combined precipitation & homogenization (Nanoedge)
- Nano jet innovation
- Emulsification-dissolvable dissipation method
- Hydrosol strategy
- Supercritical liquid technique

- Dry co-pounding
- Emulsion as format
- Micro emulsion as format

1.3. Introduction of Epilepsy

Epilepsy is a persistent non transmittable infection of the cerebrum that effects around 50 million individuals around the world. It is described by repetitive seizures, which are brief scenes of compulsory development that may include a piece of the body (incomplete) or the whole body (summed up) & are once in a while joined by misfortune of cognizance & control of gut or bladder work.[12,13,14]

Treatment of Epilepsy[15]

Sr. No.	Class of Drug	Examples
1	Barbiturates	Phenobarbitone
2	Deoxy barbiturate	Primidone
3	Hydantoin	Phenytoin
4	Iminostillbene	Carbamazepine
5	Succinimide	Ethosuximide
6	Aliphatic Carboxylic Acid	Valproic acid
7	Benzodiazepine	Clonazepam
8	Phenyl triazine	Lamotrigine
9	Cyclic GABA analogues	GABApentine
10	Newer Drugs	Zonisamide

2. MATERIALS & METHODOLOGY

2.1. List of Materials

List of Materials

Ingredient	Source
Lamotrigine (mg)	Torrent Pharmaceutical Ltd., Ahmedabad
PVA (mg)	Laboratory Sulab Reagent, Vadodara
PVP K-30 (mg)	Laboratory Sulab Reagent, Vadodara
Tween-80 (ml)	Laboratory Sulab Reagent, Vadodara
Pluronic-F68 (mg)	Colorcon Pvt. Ltd., Goa
Acetone (ml)	Laboratory Sulab Reagent, Vadodara
Water (ml)	Prepared in laboratory by Distillation

2.2. List of Equipment

List of Equipment

Instruments	Specifications
Digital Weight Balance	US-300
Electrical Weight Balance	Shimadzu AUW220 D
U.V Visible Spectro photometer	UV-1700, Shimadzu Corporation.
Particle size Analyzer	Zetasizer Nano series
Cooling Centrifuge	Remi Instrument's Pvt. Ltd., C-24 BL
Magnetic Stirrer	Remi Equipment's Pvt. Ltd.
pH Meter	PM100, Welltronix
FT-IR Spectrophotometer	Shimadzu corporation
Lyophilizer	CAT NO -137
Differential Scanning Calorimeter.	Mettler Toledo DSC 822e
Laser diffraction particle size analyzer	Malvern Mastersizer
Supercritical Particle former	Thar Instruments
Transmission Electron Microscope	Philips, Tecnai 20

2.3. Methods for Study[16,17,18,19,20]

1. Preformulation study of Drug (Lamotrigine)

a. Organoleptic characteristics of Lamotrigine API

b. Melting Point Determination

c. Solubility Analysis

d. Saturation solubility of Lamotrigine API

e. Identification & determination of Wavelength Maxima (λ_{max})

f. Preparation of Calibration Curve of Lamotrigine API

g. Confirmation of Lamotrigine API by FT-IR & DSC study

h. Particle size analysis of Lamotrigine API

i. Drug-polymer Compatibility study by FT-IR & DSC study

2. Preparation of Lamotrigine Nanosuspension by Co-solvent method

3. Selection of Formulation & Process Variables by Preliminary Trial Batches of Lamotrigine Nanosuspension.

a. Selection of stabilizer type

b. Selection of stabilizer concentration

c. Selection of organic phase type & its volume

d. Selection of Stirring Speed &/or time

4. Particle size of optimized batches of Lamotrigine Nanosuspension

5. Risk Assessment for Critical Quality Attributes (CQAs) as per preliminary trial batch to identify formulation & process variables affecting Lamotrigine Nanosuspension Quality

6. Characterization of Lamotrigine Nanosuspension

a. % Entrapment efficiency

b. % Drug content

c. % Saturation solubility studies

d. Stability Study of optimized formulation

2.4. Preparation of Lamotrigine Nanosuspension

Lamotrigine Nanosuspension was prepared using Solvent Precipitation Method. The Lamotrigine drug was first dissolved in Acetone (Organic Phase). The PVA & PVP K30 (Stabilizers) were dissolved in Water (Aqueous Phase). The organic phase was injected drop wise with the help of syringe into the aqueous phase with magnetic agitation at 1500-2000 rpm for 60 minutes. After magnetic agitation, the solvent is then removed by air drying (Solvent Evaporation).[21,22,23,24]

3. RESULT AND DISCUSSION

3.1. Preformulation of Drug

Preformulation study mostly generates data which are useful to develop stable dosage forms that can be mass-produced for manufacturer.

3.1.1. Organoleptic Characteristics of Lamotrigine

Physical examination was done to check organoleptic characteristics of drug like color, odour & physical appearance of pure drug.

Organoleptic Characteristics

Parameter	Observed Result
Colour	White powder
Odour	Odourless
Appearance	White crystalline powder
Taste	Bitter

3.1.2. Determination of Melting Point of Lamotrigine

Melting point of Lamotrigine was evaluated by capillary method.

Table 4: 1 Melting point of Lamotrigine

Drug Name	Standard Value	Observed Value
Lamotrigine	216-218°C	214-216 °C

Melting point was carried out to determine purity of sample. Drug sample has melting point

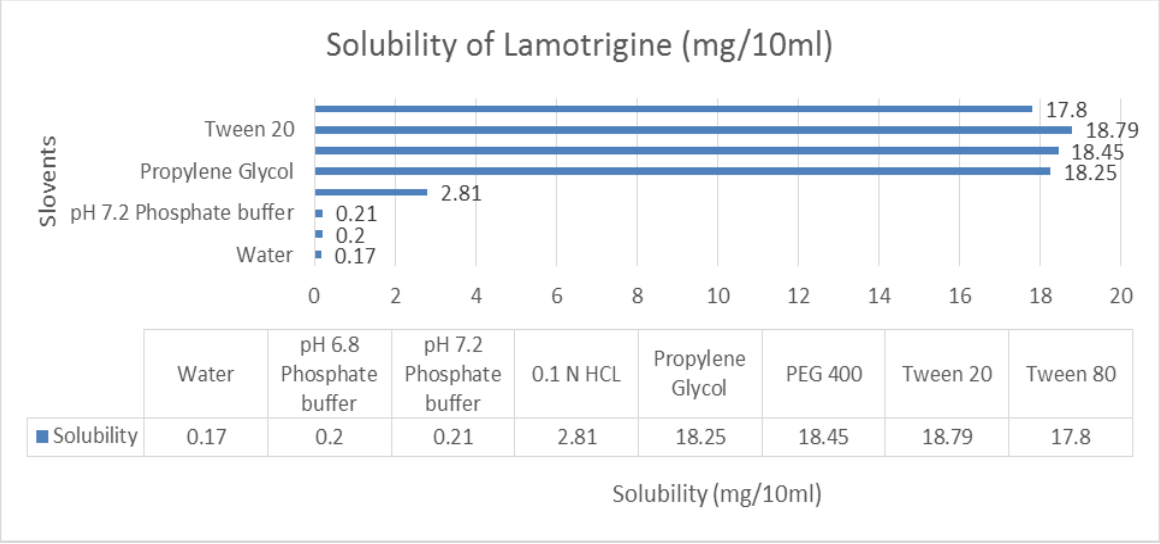
of 214-216°C which was in range & indicate purity of sample as Lamotrigine.

3.1.3. Solubility study of Lamotrigine

Six different commonly used non-volatile solvents i.e., Water, 0.1 N HCL, pH 6.8 Phosphate buffer, PEG 400, polysorbate 20, polysorbate 80, propylene glycol (PG) were used to carry out solubility studies of Lamotrigine. Saturated solutions of Lamotrigine were prepared by adding excess drug to vehicles & shaking on shaker for specific period of time under constant vibration. After this period solutions were filtered, diluted with distilled water & analyzed by UV-spectrophotometer at wavelength of 307 nm. Solvents with greater ability to solubilize drug was selected for formulation of nanosuspension for enhanced release.

Solubility of Lamotrigine

Sr. No.	Solvents	Solubility	Interpretation
1.	Water	0.17	Insoluble
2.	pH 6.8 Phosphate buffer	0.20	Insoluble
3.	pH 7.2 Phosphate buffer	0.21	Insoluble
4.	0.1 N HCL	2.81	Slightly Soluble
5.	Propylene Glycol	18.25	Freely Soluble
6.	PEG 400	18.45	Freely Soluble
7.	Tween 20	18.79	Freely Soluble
8.	Tween 80	17.80	Freely Soluble



Solubility of Lamotrigine

3.1.4. Saturation Solubility of Lamotrigine

Immersion solvency study was done by planning soaked arrangement of medication in water & investigating them by utilizing spectrophotometer. Immersed arrangement was set up by adding abundance measure of medication to water & allow it to remain to accomplish

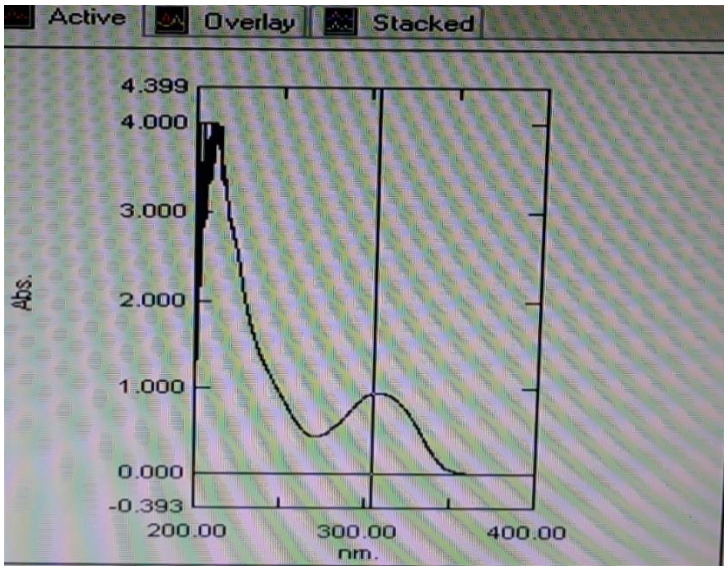
harmony state (e.g., by shaking, mixing) for explicit season of period.

Saturation solubility of Lamotrigine

Sr. No.	Solvent	Saturation Solubility (mg/mL)
1.	Water	0.19

3.1.5. Identification of Wavelength Maxima (λ_{max}) of Lamotrigine

Weigh 100mg of Lamotrigine & dissolved in sufficient amount of methanol & make up volume up to 100 ml by using Phosphate buffer pH 7.4. Take 1ml of this solution was pipette out in separate volumetric flask & diluted with phosphate buffer pH 7.4 & subjected for UV scanning in range 200-400 using UV Visible Spectrophotometer.



λmax Spectrum for Lamotrigine

Wavelength$_{max}$ (λ_{max}) of Lamotrigine

Drug Name	Actual λ_{max}	Observed λ_{max}
Lamotrigine	308nm	307nm

3.1.6. Preparation of Calibration Curve for Lamotrigine

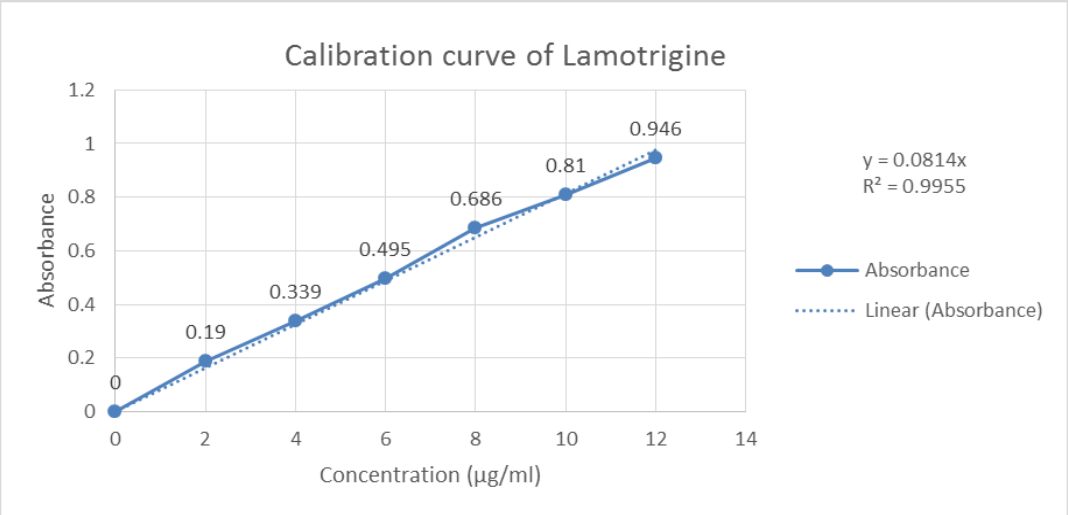
Sample Preparation of Stock & Standard solutions for Lamotrigine

Primary stock solution (1mg/ml of lamotrigine in Methanol) was prepared. Secondary stock was prepared using phosphate buffer pH 7.4 to produce 100 µg/ml. From secondary stock solution calibration curve standards (2, 4, 6, 8, 10 & 12 mcg/ml) were prepared using phosphate buffer pH 7.4. From calibration curve standards, 10 µg/ml was scanned over range 200-400 nm using UV Visible Spectrophotometer to determine its λ_{max}. Peak was observed at

307 nm for Lamotrigine. Absorbance was measured for all calibration curve standards at 307 nm & linear graphs was plotted between concentrations versus absorbance.

Calibration curve of Lamotrigine

Sr. No.	Concentration (mcg/ml)	Absorbance
1	0	0
2	2	0.19
3	4	0.339
4	6	0.495
5	8	0.686
6	10	0.81
7	12	0.946



Calibration curve of Lamotrigine in phosphate buffer 7.4

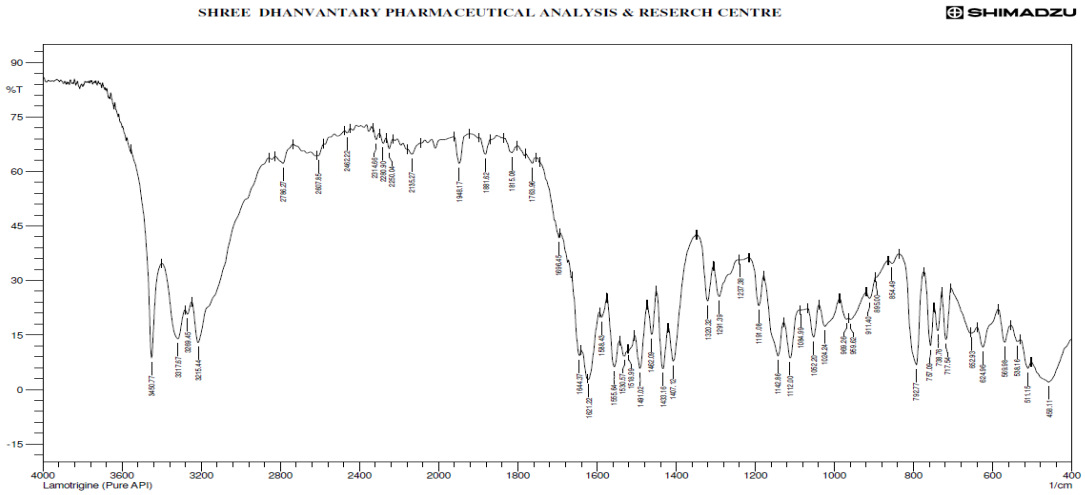
Summary Report of calibration curve for Lamotrigine

Parameters	Lamotrigine
Wavelength (λ_{max})	307
Beer's limit (µg/ml)	0-50
Correlation coefficient (R^2)	0.9987
Slope	0.0791
Obeys Beer law in conc. range of 0-50 µg/ml	
R^2 value shows linearity	

Calibration curve for drug was obtained by using 0-50 µg/mL solution of Lamotrigine in acetone. Calibration curve shows Regression equation (y) = 0.0814x & Correlation coefficient (R^2) = 0.9987.

3.1.7. Identification of Drug- Lamotrigine by FT-IR Spectroscopy

KBr IR disc was prepared using 1mg of Lamotrigine on Hydraulic Pellet press which was scanned of 4000-400 cm^{-1} are in FT-IR & obtained IR Spectrum was compare with reference spectrum of Lamotrigine.



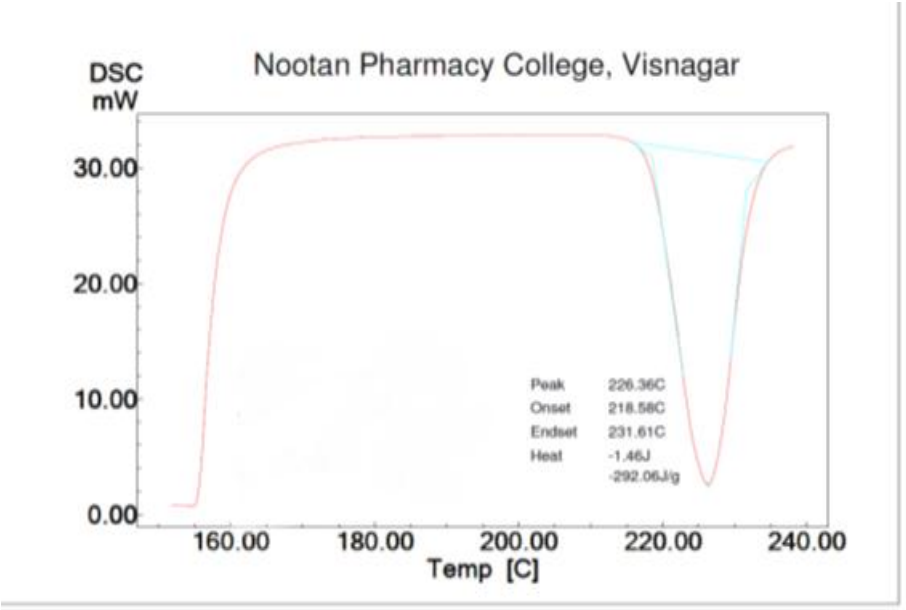
Identification of Lamotrigine by IR Spectrum

Above figure shows IR spectrum of Lamotrigine. All major peaks of Lamotrigine drug were observed at wave numbers 3451 cm^{-1} (N-H aromatic), 3212 cm^{-1} (C-H aromatic)' 1630 cm^{-1} (C=N), 1292 cm^{-1} (C-N), 1556 cm^{-1} (C=C aromatic), 1052 cm^{-1} (C-CL), 738 cm^{-1} (*o* substituted benzene), 756, 793 & 805 cm^{-1} (*m* substituted benzene) were observed which confirms identity & purity of drug.

Obtained FT-IR spectrum compiles with standard data which further confirms Drug identity & purity**.**

3.1.8. Identification of Drug Lamotrigine by DSC

Thermal analysis of Drug Lamotrigine was studied employing differential scanning calorimetry which was done to check drug for Liquid-solid compact formulations.



DSC graph of Lamotrigine

3.1.9. Particle Size Analysis of Pure Drug Lamotrigine

Particle size of drug was studied by using Zeta Sizer or Malvenizer Instrument.

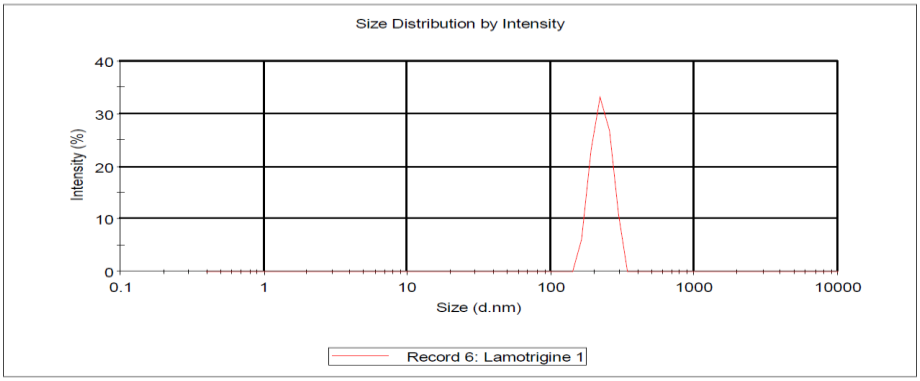
System

Temperature (°C):	25.0	**Duration Used (s):**	500
Count Rate (kcps):	1.3	**Measurement Position (mm):**	4.65
Cell Description:	Glass cuvette with square aperture	**Attenuator:**	9

Results

			Size (d.nm):	% Intensity	Width (d.nm):
Z-Average (d.nm):	425.1	**Peak 1:**	227.3	100.0	35.91
PdI:	0.695	**Peak 2:**	0.000	0.0	0.000
Intercept:	0.942	**Peak 3:**	0.000	0.0	0.000

Result quality : Refer to quality report

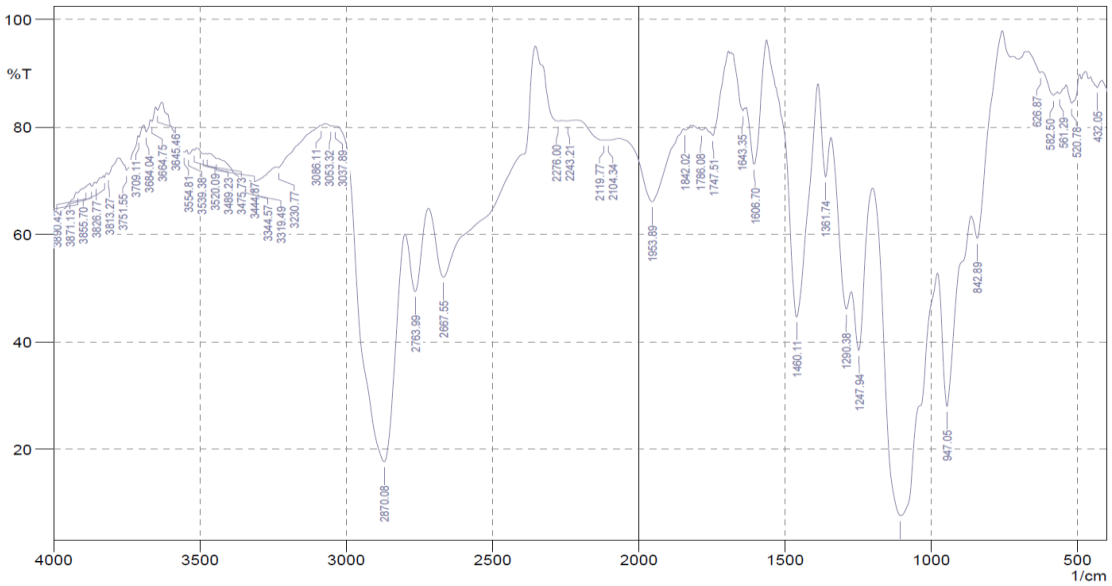


Particle Size Analysis of Pure Drug Lamotrigine

3.1.10. Drug-Excipients Compatibility Studies by FT-IR

KBr IR disc was prepared using Lamotrigine & mixture on Hydraulic Pellet press was scanned 4000-400 cm^{-1} region in FT-IR & obtained IR Spectrum was compared with reference spectrum of Lamotrigine.

FT-IR graph of Lamotrigine Formulation



Identification of Compatibility of Lamotrigine with formulation by IR Spectrum

Type of Vibration	Observed Wave Number (Cm^{-1})	
N-H stretching	3444.87	The obtained FT-IR spectrum compiles with standard data which further confirms Drug identity, purity & compatibility.
C-H stretching	3319.49	
C=C stretching	1608.70	
C-N stretching	1290.38	
C-CL stretching	1052.49	
C=N stretching	1643.35	

Figures shows IR spectrum of Lamotrigine. All major peaks of Lamotrigine drug were observed at wave numbers 3451 cm^{-1} (N-H aromatic), 3212 cm^{-1} (C-H aromatic), 1630 cm^{-1} (C=N), 1292 cm^{-1} (C-N), 1556 cm^{-1} (C=C aromatic), 1052 cm^{-1} (C-CL), 738 cm^{-1} (*o* substituted benzene), 756, 793 & 805 cm^{-1} (*m* substituted benzene) were observed which confirms identity & purity of drug. Obtained FT-IR spectrum compiles with standard data which further confirms Drug Excipient compatibility.

3.2. Selection of Formulation & Process Variables by Preliminary Trial Batches of Lamotrigine Nanosuspension

Lamotrigine Nanosuspension were prepared by Solvent Precipitation Method. Prepared Nanosuspensions were found to be turbid & stable. No visible sedimentation noticed atleast for period of 3 days. Prepared Lamotrigine Nanosuspension were evaluated for drug content & entrapment efficiency.

3.2.1. Priliminary Trial batches

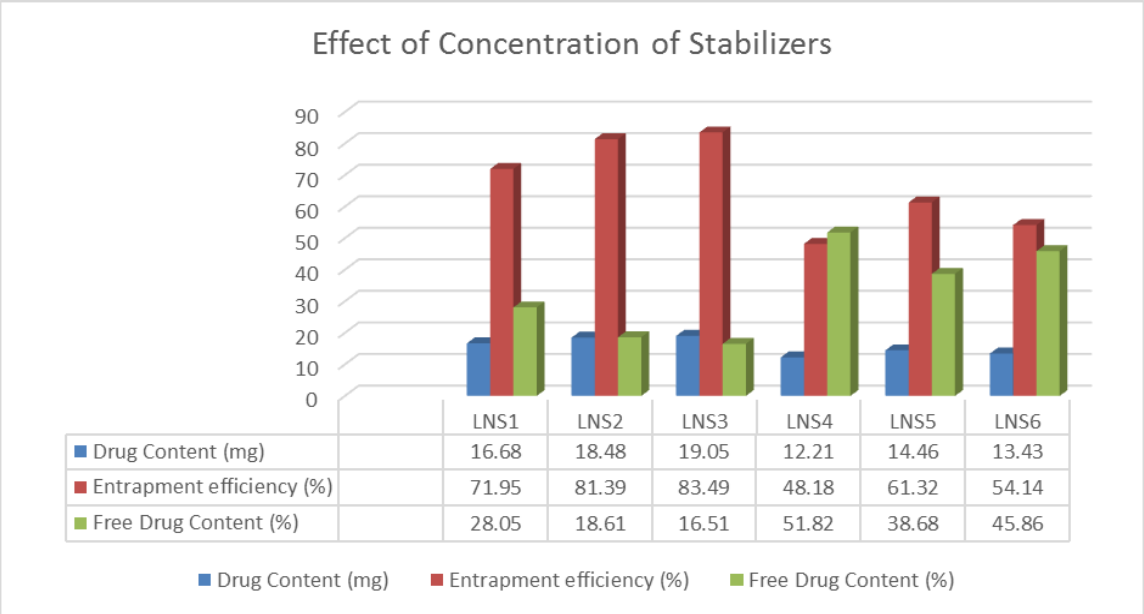
3.2.2. Preliminary Selection of Stabilizer Concentration

Preliminary Selection of Stabilizer Concentration for Lamotrigine Nanosuspension

Batch	Type of Stabilizer	Stabilizer Concentration	Type of Organic Phase (ml)	Sweetener (Asparate) (mg)	Volume of Organic Phase (ml)	Water (ml)	Stirring Speed (R.P.M.)	Stirring Time (mins)
Preliminary Selection of Concentration of Stabilizers								
LNS1	Pluronic F- 68: TWEEN 80	2:1	Acetone	2	5	30	1500	60
LNS2	Pluronic F- 68: TWEEN 80	3:1	Acetone	2	5	30	1500	60
LNS3	Pluronic F- 68: TWEEN 80	4:1	Acetone	2	5	30	1500	60
LNS4	PVP K30: TWEEN 80	2:1	Acetone	2	5	30	1500	60
LNS5	PVP K30: TWEEN 80	3:1	Acetone	2	5	30	1500	60
LNS6	PVP K30: TWEEN 80	4:1	Acetone	2	5	30	1500	60

Characterization of Trial batches (LNS1 – LNS9) for Lamotrigine NS

Batch No.	Drug Content (mg)	Entrapment efficiency (%)	Free Drug Content (%)
Effect of Concentration of Stabilizers			
LNS1	16.68	71.95	28.05
LNS2	18.48	81.39	18.61
LNS3	19.05	83.49	16.51
LNS4	12.21	48.18	51.82
LNS5	14.46	61.32	38.68
LNS6	13.43	54.14	45.86



Effect of Concentration of Stabilizers

Nanoparticulate DDS often employ stabilizers. In absence of suitable stabilizer, high surface energy of particles in nano-range can aggregate to form larger particles, thereby rendering formulation unstable. Main function of stabilizer is to wet drug particle completely in order to inhibit agglomeration with another particle. It provides stearic or ionic barriers by way of which inter-particulate interactions in nanosuspensions are prevented. However, concentration of stabilizer in Nanosuspension must be optimum. PVA has been found to be very effective stabilizer for Nanoparticles produced by various methods. PVA or Polyvinyl Alcohol has both hydrophobic & hydrophilic parts liken acetate & hydroxyl groups respectively. These help in getting absorbed & oriented at interface. In fact, effectiveness of PVA in reducing interfacial tension is such that it even promotes to maintaining low particle size of Nanoparticles. Even surfactants like Pluronic F-68 & Tween80 have been utilized for reducing interfacial tension at surface of nanoparticles. Hence, LNS2 & LNS3 have been selected as optimized batches.

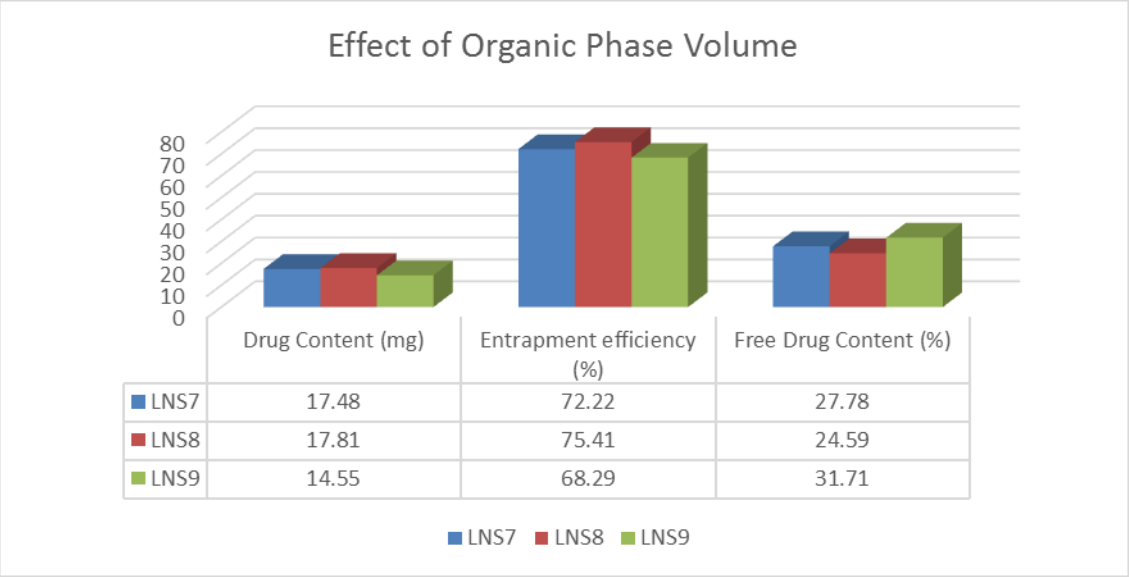
3.2.3. Preliminary Selection of Organic Solvent Volume

Preliminary Selection of Organic Solvent Volume for Lamotrigine Nanosuspension

Batch	Type of Stabilizer	Stabilizer Concentration	Type of Organic Phase (ml)	Volume of Organic Phase (ml)	WATER (ml)	Stirring Speed (R.P.M.)	Stirring Time (mins)
Preliminary Selection of Organic Phase Volume							
LNS7	Pluronic F- 68: TWEEN 80	3:1	Acetone	5	30	1500	60
LNS8	Pluronic F- 68: TWEEN 80	3:1	Acetone	10	30	1500	60
LNS9	Pluronic F- 68: TWEEN 80	3:1	Acetone	20	30	1500	60

Characterization of Trial batches (LNS7 – LNS9) for Lamotrigine Nanosuspension

Batch No.	Drug Content (mg)	Entrapment efficiency (%)	Free Drug Content (%)
Effect of Organic Phase Volume			
LNS7	17.48	72.22	27.78
LNS8	17.81	75.41	24.59
LNS9	14.55	68.29	31.71



Effect of Organic Phase Volume

Organic solvents are often employed in formulation of nanoparticles by variety of techniques. However, since many organic chemicals can be hazardous in nature, acceptability of organic solvent being employed in formulation must be kept in mind with respect to its toxicity potential & ease of its removal from formulation. Solvents such as ethanol, isopropanol, ethyl acetate, butyl lactate, acetone & triacetin & benzyl alcohol are some which are considered to be acceptable & thus employed in formulation. Hence, LNS8 has been selected as optimized batch. One of most important things to be kept in mind while utilizing organic solvents is their miscibility with water. More solvent is miscible & readily diffusible with water, more effective will be formation of nanosuspension.

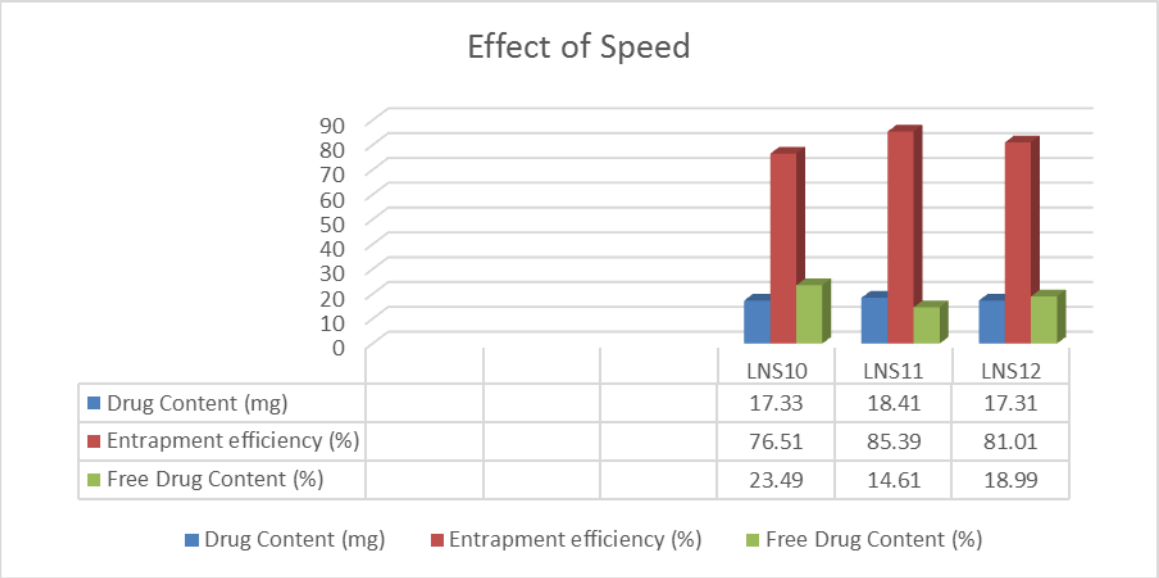
3.2.4. Preliminary Selection of Stirring Speed (RPM)

Preliminary Selection of Speed (RPM) for Lamotrigine Nanosuspension

Batch	Type of Stabilizer	Stabilizer Concentration	Type of Organic Phase (ml)	Volume of Organic	Water (mL)	Stirring Speed (R.P.M.)	Stirring Time (Mins)
Preliminary Selection of Speed (R.P.M.)							
LNS10	Pluronic F- 68: TWEEN 80	3:1	Acetone	5	30	1000	60
LNS11	Pluronic F- 68: TWEEN 80	3:1	Acetone	5	30	1500	60
LNS12	Pluronic F- 68: TWEEN 80	3:1	Acetone	5	30	2000	60

Characterization of Trial batches (LNS10 – LNS12) for Lamotrigine Nanosuspension

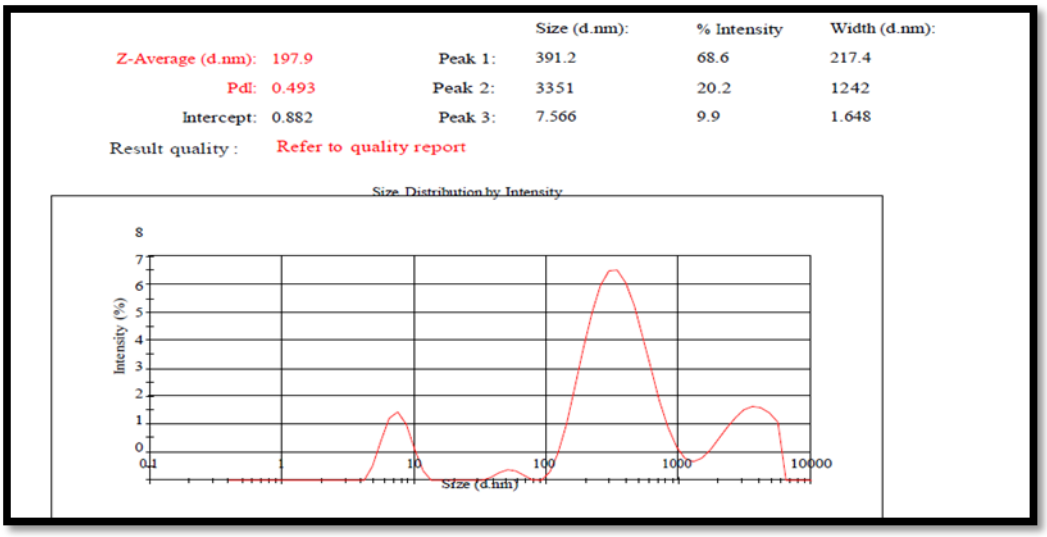
Batch No.	Drug Content (mg)	Entrapment efficiency (%)	Free Drug Content (%)
LNS10	17.33	76.51	23.49
LNS11	18.41	85.39	14.61
LNS12	17.31	81.01	18.99

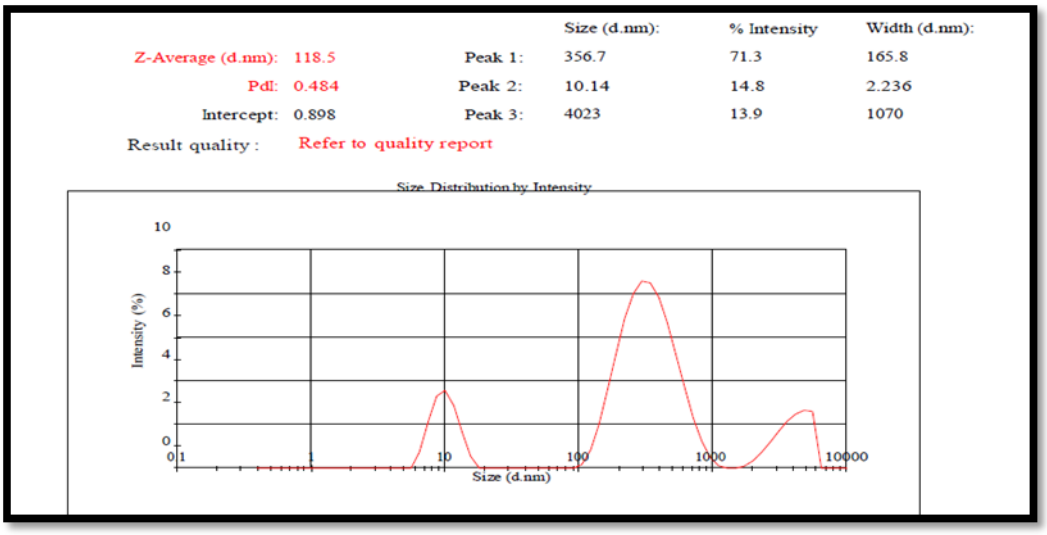


Effect of Speed

Stirring speed is also important formulation variable. It has been observed that on average, increasing speed of stirring leads to reduction in particle size towards Nano sized range. However, it has been noted that operating instruments at high-speed conditions is not always optimum & average speed has to be maintained. This is because higher agitation speeds often lead to formation of huge amount of foam in suspension which often leads to early separation of solid nanoparticles from aqueous medium. As result, this can lead to ineffective size reduction & insufficient formation of Nanosuspension. Hence, LNS11 & LNS12 have been selected as optimized batches.

3.3. Particle size of optimized batches of Lamotrigine Nanosuspension





Pure drug used for study was characterized by relatively large particles as reported. Nanosuspension prepared after emulsification & solvent evaporation may decrease in particle size when compared to pure drug particles which may have positive effect on drug dissolution rate as per Noyes-Whitney equation. Hence decrease in particle size will have significant effect in drug solubility & dissolution characteristics.

3.4. Risk Assessment of Critical Quality Attributes from Preliminary trial Batches to Develop QbD Approach

CQAs are categorized in high, medium & low risk parameters based on knowledge space to check influence of formulation & process parameters. Usually, high risk parameters are considered important for Design of Experiments (DoE) as they are having more effect than

others & need to be in accepted multivariate ranges.

Risk assessment to identify variables affecting drug product quality

Drug Product CQA's	Drug: Stabilizer Ratio	Volume of Internal Phase	Agitation Speed
Drug Content	High	Low	Medium
Entrapment Efficiency	High	Low	Medium
Particle Size	High	Medium	High
Drug Release	High	Low	Medium

3.5. Stability Study of LNS10 for 1 Month

Stability Study of LNS10 for 1 Month

Parameter	Optimized Lamotrigine Nanosuspension			
	Room Temperature			
	0 Day	10 Day	20 Day	30 Day
% E.E.	83.62	85.48	85.21	84.91
% CDR	93.84	92.43	91.68	91.57

4. CONCLUSION

Drug Nanosuspension is portrayed as finely dispersed solid medicine particles in liquid vehicle. It is characterized as finely scattered solid medication particles in a fluid vehicle, settled by surfactants for one or the other oral & skin use. Atom gauge in nanosuspension reach out in area of 200 & 600 nm.

Lamotrigine is an antiepileptic medication of Phenyltriazine class, utilized for the treatment of halfway seizures. It is an essential medication with an inherent solvency of 0.017 mg/ml & goes through broad hepatic digestion upon oral organization. It is a white pale cream shaded powder having pKa 5.7. So, tranquilizes with lower solvency can be defined as nanosuspension that can improve the disintegration of Lamotrigine & thus the bioavailability.

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