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Formulation and In-Vitro Evaluation of Loxapine-Loaded Nanosuspension

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ABSTRACT

This study focuses on the development of a Loxapine nanosuspension aimed at enhancing the solubility of the drug. A comprehensive pre-formulation analysis, including UV and FTIR spectroscopy, confirmed compliance with USP standards and ruled out any interactions between Loxapine and the selected excipients. The nanosuspension was prepared using Nanoedge technology, which combines nanoprecipitation and high-pressure homogenization techniques. A 22 Central Composite Design (CCD) was employed to optimize the formulation, resulting in nine different formulations (NS1-NS9). The optimized nanosuspension (NS5) exhibited desirable characteristics, including a small particle size of 152.6 nm, a low polydispersity index (PDI) of 0.261, and a high zeta potential of -23.0 mV, indicating good stability. The drug content ranged from 88.50% to 95.83%, with entrapment efficiency between 78.12% and 92.26%. The NS5 formulation showed significant cumulative drug release of 95.65% over 60 mins, following first-order kinetics with an R2 value of 0.966. Stability studies further confirmed that the optimized formulation remained stable at room temperature. The study concludes that the Loxapine nanosuspension effectively enhances the solubility and dissolution rate of the drug, with the NS5 formulation being the most optimized, demonstrating excellent stability and uniformity.

Keywords: Nanosuspension, Loxapine, Solubility, Nanoedge, % Drug Release, % Drug content, Scanning Electron Microscopy.

INTRODUCTION

Nanosuspension[1-2]

Nanosuspension is favoured for compounds that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses. Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents. Hydrophobic drugs such as Atorvastatin, Famotidine, Simvastatin, Revaprazan, Aceclofenac are formulated as Nanosuspension. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. The Nanosuspensions can also be lyophilized or spray dried and the nanoparticles of a Nanosuspension can also be incorporated in a solid matrix.

Rationale for Nanosuspension [1-2]

- Preparing nanosuspensions is preferred for the compounds that are insoluble in water (but are soluble in oil) with high log P value.
- Conventionally the drugs that are insoluble in water but soluble in oil phase system are formulated in liposome, emulsion systems but these lipidic.
- Formulation approaches are not applicable to all drugs. In these cases nano suspensions are preferred.
- In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems. Nano suspensions are used as a formulation approach.

- Nano suspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose.

Benefits of Nanosuspension technology for poorly soluble drugs: [3-4]

1. Reduced particle size, increased drug dissolution rate, increased rate and extent of absorption, increased bioavailability of drug, area under plasma versus time curve, onset time, peak drug level, reduced variability, reduced fed/fasted effects.

2. Nanosuspensions can be used for compounds that are water insoluble but which are soluble in oil.

3. Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of the drug and thereby enhancing its absorption.

4. A pronounced advantage of Nanosuspension is that there are many administration routes for Nanosuspensions, such as oral, parenteral, pulmonary, dermal and ocular.

5. Nanosuspension has low incidence of side effects by the excipients.

6. Increased resistance to hydrolysis and oxidation, increased physical stability to settling.

7. Reduced administration volumes; essential for intramuscular, subcutaneous, ophthalmic use.

8. Finally, Nanosuspensions can provide the passive targeting.

MATERIALS AND METHODS

Pre-formulation studies [5-10]

- **Organoleptic properties:**

The sample of Loxapine was studied for organoleptic characteristics such as color, odour, taste and appearance.[5]

Determination of Loxapine Melting point:

Melting point of Loxapine was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate and average value was noted.[6]

Determination of Loxapine Solubility:

By placing an excess of the drug in a conical flask with 5ml of solvent, a solubility test is conducted. Following the addition of an excessive amount of the drug, the solution is held at room temperature for shaking in an orbital shaker (remi). Samples are taken. The samples were diluted accordingly with the same solvent after being filtered using Whatman filter paper, and their concentration was assessed using UV-VIS Spectroscopy.[7]

Drug-Excipients compatibility studies: [8]

Drug-excipient compatibility was performed to examine any feasible interactions linked with drug and other excipients in formulation.

• FTIR Spectroscopy

FTIR Spectroscopy is an analytical technique used to identify drug substances by monitoring the functional groups exist in the compound. FTIR spectra of Loxapine (pure) and its mixtures were done by using FTIR spectrometer (Bruker, Germany).The samples were mixed thoroughly with KBr and the spectrum was analyzed in resolution of 4/cm and frequency range of 4000 to 400cm^{-1}.

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Analytical method development for Loxapine Using UV spectroscopy [9-10]

a) Preparation of 6.8 pH Phosphate Buffer

Dissolve 6.8g of potassium hydrogen ortho phosphate and 0.9g of Sodium hydroxide in 1000ml Distilled water and pH was adjusted to 6.8 with dilute sodium hydroxide solution.

b) Preparation of Loxapine Standard Stock Solution (100µg/ml)

A Standard Stock solution of Loxapine was prepared by dissolving accurately weighed 10mg of Loxapine in 6.8 pH Phosphate buffer solution in a 100ml volumetric flask and the volume was made upto 100ml by using 6.8 pH Phosphate buffer solutions.

c) Determination of λ_{max} of Loxapine

From the standard stock solution 1ml was taken into 10ml volumetric flask. The volume was made upto 10ml with 6.8 pH Phosphate buffer solution. The resulting solution containing 10µg/ml was scanned between 200-400nm.The λ_{max} was found to be 250nm and used as analytical wavelength.

d) Calibration Curve of Loxapine

From the Standard stock solution (1000 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made upto 10 ml with 6.8 pH Phosphate buffer so as to get concentration of 5, 10, 15, 20, 25 µg/ml. The absorbance of the solution was measured at 250nm. This procedure was performed in triplicate to validate calibration curve. A calibration graph was plotted.

Design of Experiment and Optimization [11]

A CCD is an exploratory design, helpful in RSM, for building a quadratic model for response variables without requiring utilizing a whole 3-level factorial design. After carrying out the planned experiment is, rectilinear regression is utilized, at times repetitively, to get result.

During construction of this design Coded variables are often utilized. CCD has 5 levels such as -α, -1, 0, +1, + α, for parting various modes of parameters. A central composite design (2^2) was utilized to study the impact of two factors, i.e. PVP and Span 80 at various levels i.e. high (+1), and low (−1) to study their main and interaction effects, on the recognized critical parameters, i.e Particle Size, % Drug release. This design generates a total of 9 runs which were performed. The design matrix and responses to each experiment are obtained. The results were statistically analyzed using Sigmatech® software. To prevent any bias in the study all experiments were randomized and done according to run order [11].

Table 1: Experimental Variables

Independent variables	Dependent variables
A. PVP (X1)	Particle Size(Y1)
B. Tween 80 (X2)	% Drug release(Y2)

Table 2: Low and High Values of independent variables

Variable Index	Independent variable	Low	High
X1	PVP	25	75
X2	Tween 80	1	5

Table 3: Software generated Formulations

Ingredients	NS1	NS2	NS3	NS4	NS5	NS6	NS7	NS8	NS9
Loxapine (mg)	20	20	20	20	20	20	20	20	20
Poloxamer 188	1	1	1	1	1	1	1	1	1
PVP K30	25	75	25	75	50	25	75	50	50
Tween 80(ml)	2	2	4	4	3	3	3	1	5
Methanol	5	5	5	5	5	5	5	5	5
Water(ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Preparation of Nano suspension by Nanoedge Technology: [12]

Nanoedge technology is a combination of Nano precipitation and high-pressure homogenization techniques. The drug dissolved in suitable solvent. In another one beaker stabilizer and solvent which drug is insoluble. Drug and stabilizer different ratios were taken.

- Drug was dissolved in methanol.
- Stabilizer dissolved in water.

Nanoedge Technology was developed by Müller. The technology consists of two processes: precipitation of drug particles and their fragmentation by using high pressure homogenization. Generally, this technique includes mixing of two different solutions. The drug (loxapine 20mg) is dissolved in an organic solvent (methanol) which is miscible with water and forms the organic phase. And different concentrations of stabilizers i.e. poloxamer, PVPK30 & Span 80 are dissolved in the aqueous phase (Purified water) in which the drug is insoluble. Mixing these two solutions causes precipitation of drug particles. The last step of the process is high pressure homogenization at 1000RPM for 30min to allow the organic solvent to evaporate and get desired nanosuspensions.

Evaluation of Loxapine Loaded Nanosuspensions: [13-23]

1. Analysis of Average Particle size and Polydispersity index (PDI)

♠ **The droplet size/particle size** of the formulations generated by the CCD were measured by using Malvern Zetasizer. This instrument works generally by photon correlation spectroscopy, which measures scattering of light due to the Brownian motion in between the droplets or particles.

♠ Multiple light scattering effects were avoided during analysis by using a 10% diluted nanosuspension sample.

♠ **Polydispersity index** - The Surface charge and charge density of Nanosuspension droplets was determined using Malvern Zetasizer. If the PDI values of the oral nanosuspension formulations are less than 0.5, it indicates the homogeneity of the droplet size distribution as previously reported. Samples were considered to be polydisperse when the polydispersity index was higher than 0.2.

2. Zeta Potential: The Zeta potential of the selected formula of nanosuspension was measured by using 'Nano Brook 90Plus-zeta seizer (Brookhaven Instruments USA). Sample of the selected formula was placed in the electrophoretic cell and measured three times at 25 ±1° C, and the average values were calculated. Zeta potential gives information about the surface charge properties and furthers the long-term physical stability of the nanosuspension. To obtain an electrostatically stabilized nanosuspension, a minimum zeta potential of ± 30mV is required. In the case of a combination of electrostatic and steric stabilization, a minimum zeta potential of ± 20mV is desirable.

3. % Drug Content: To determine the drug content in the formulation, the percentage of drug incorporated/entrapped in each formulation was measured and calculate. Each 1 ml prepared nanosuspension sample was diluted with methanol and centrifuged at 3500 rpm for 30 minutes. After centrifugation, the supernatant clear layer was removed and filtered. The samples were measured at 240 nm using UV-VIS spectroscopy. Results were noted in triplicate and averaged.

4. In-Vitro Drug Release Studies: The in-vitro release of Loxapine nanosuspension was carried out in USP rotating basket dissolution apparatus. Employing the stirrer speed at 100 rpm and Phosphate buffer pH 6.8 as dissolution medium (900ml), at fixed time intervals 5 ml of the aliquot was withdrawn and same quantity was replaced by fresh buffer. The withdrawn samples were spectrophotometrically analysed at respective wavelength on Lab India UV3000+.

5. Scanning Electron Microscopy: The surface morphology of the raw materials and of the ternary systems was examined by means of JSM-6400 (Jeol, Japan) scanning electron microscope. The samples were previously fixed on a brass stub using double-sided adhesive tape and were then made electrically conductive by coating with a thin layer of gold and palladium alloy (180-200 Å) using a fine coat ion sputter (JEOL, fine coat ion sputter JFC-1100). The pictures were taken at an excitation voltage of 20 kV and magnification in the range of 118 to 245X.

6. Short Term Stability Assessment: These studies were conducted with optimized formulations. Taken the nanosuspensions in glass vials at a temperature of 4°C & 25°C. The samples were withdrawn at 0, 1, 5, 12, 20, 30 days for studying droplet size and drug content and it was noted down.

RESULTS AND DISCUSSION

Physicochemical Attributes of Loxapine:

- **Appearance:** The physicochemical characteristics, including color, odor, taste, and appearance, were assessed.

Table 4: Organoleptic properties

S.no	Test	Description
1	Colour	Pale yellowish powder
2	Odour	Odourless
3	Appearance	Crystalline Powder
4	Taste	Bitter taste

Melting point: It was determined to be 110°C, within the standard range reported in the literature.

Table 5: Melting Point of Loxapine

S.no	Pure drug	Reference range	Observed value
1.	LOXAPINE	109°C - 111°C.	110°C.

Results are expressed as mean + S.D, n = 3

- **Solubility studies**

At 250 nm the absorbance of the drug was measured and its highest solubility was determined in pH 6.8 Phosphate buffer.

Table 6: Solubility studies of drug in different solvents

S.no	Solvents	Solubility (mg/ml)
1	Water	0.003 ± 0.01
2	6.8 phosphate buffer	2.00 ± 0.01
3	Methanol	1.252 ± 0.01
4	Ethanol	0.25± 0.02
5	DMSO	20.01 ± 0.01

Results are expressed as mean ± S.D (n = 3)

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UV-Spectroscopic examination of drug:

Determination of λ max for Loxapine in pH 6.8 Phosphate buffer by UV:

Loxapine solution was analyzed spectrally between 200-400 nm, revealing a significant peak at 250 nm. This wavelength was chosen for detection in pH 6.8 Phosphate buffer due to its distinct and highest absorbance peak.

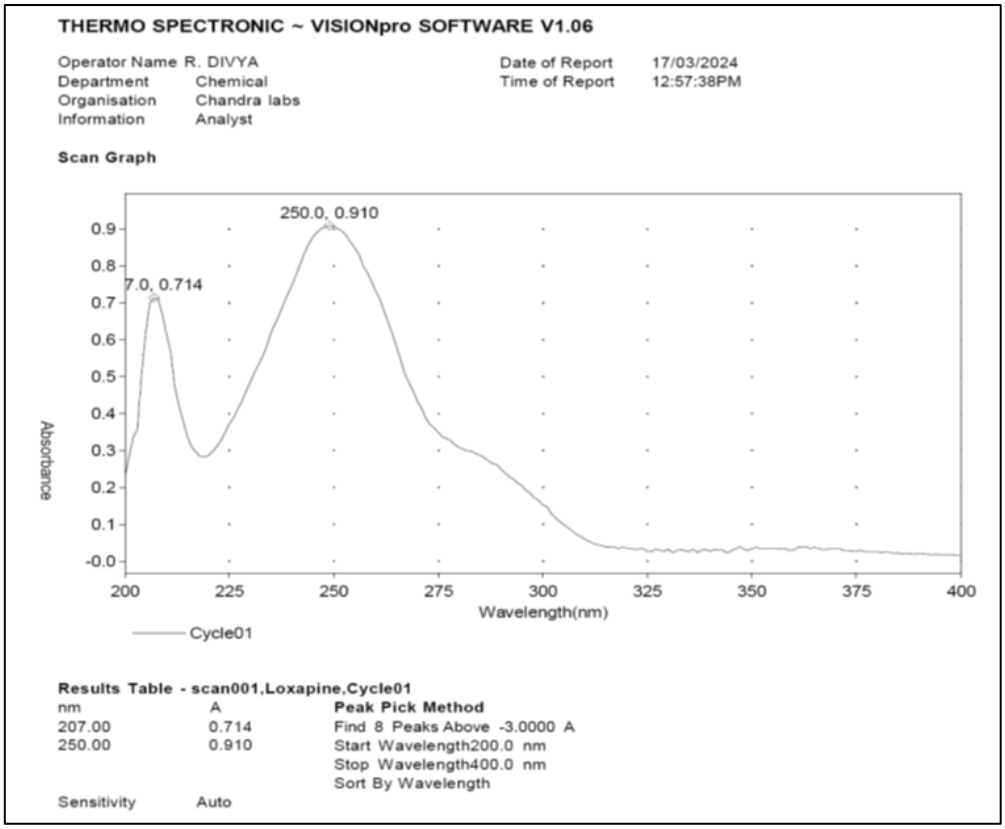

Figure 1: Spectra for Loxapine Wavelength optimization

Standard Calibration curve of Loxapine in pH 6.8 Phosphate buffer:

Table 7: Table showing absorbance values at multiple concentrations

Concentration (µg/ml)	Absorbance
5	0.145±0.012
10	0.248±0.022
15	0.372±0.014
20	0.490±0.047
25	0.614±0.018
30	0.772±0.081
35	0.941±0.042

All values are expressed as mean ± S.D (n = 3).

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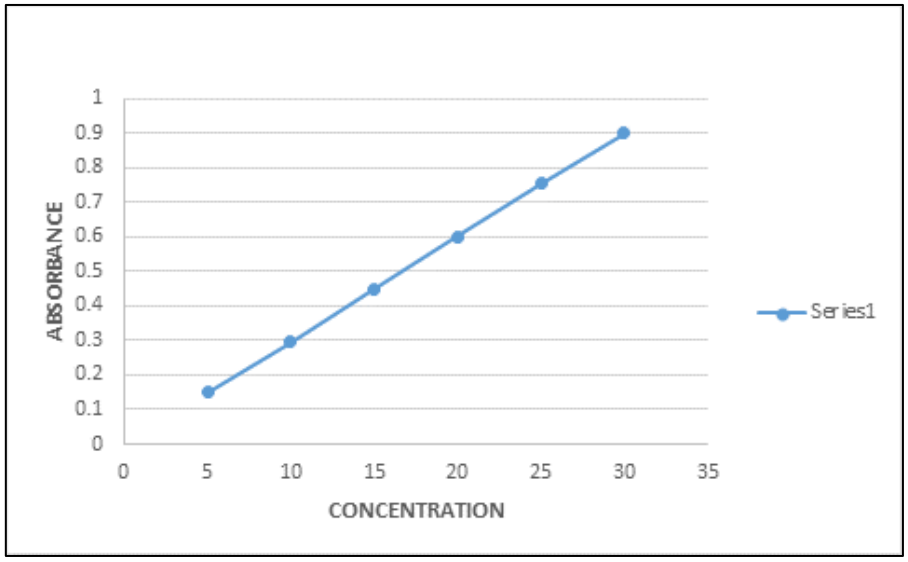

Figure 2: Calibration Curve Data of Loxapine In pH 6.8

Diluted sample solutions were analyzed at 250 nm, generating absorbance values. Standard graph was made where X-axis represented concentration. Y-axis represented absorbance, yielding a linear equation of

Y=0.0775x + 0.005 R^2Value Was Ascertained to be 0.9996.

FTIR REPORTS

Fourier Transform Infrared spectrophotometry (FTIR)

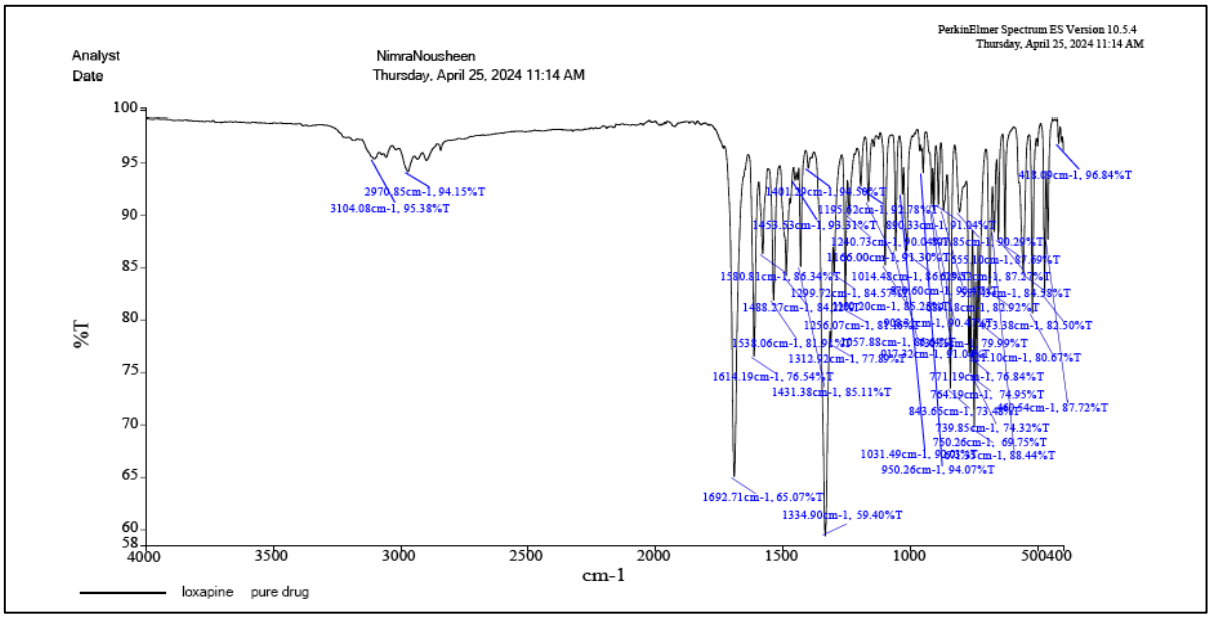

Figure 3: FTIR Spectra of Loxapine pure drug

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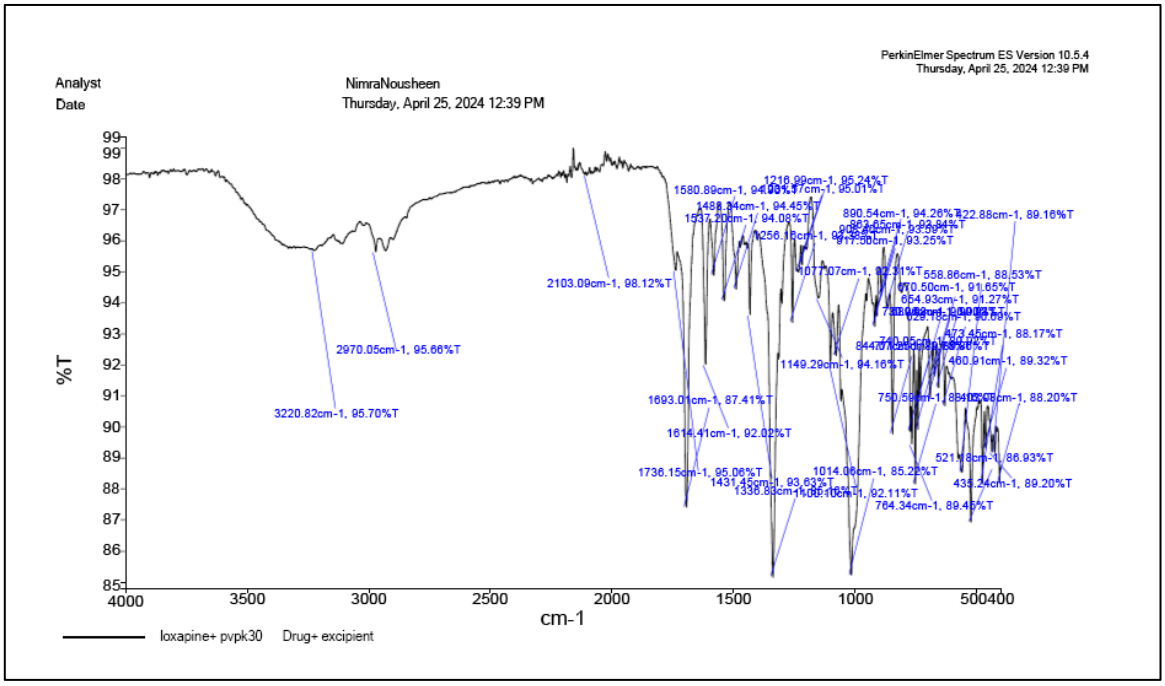

Figure 4: FTIR Spectra of Loxapine pure drug with PVPK30 excipient

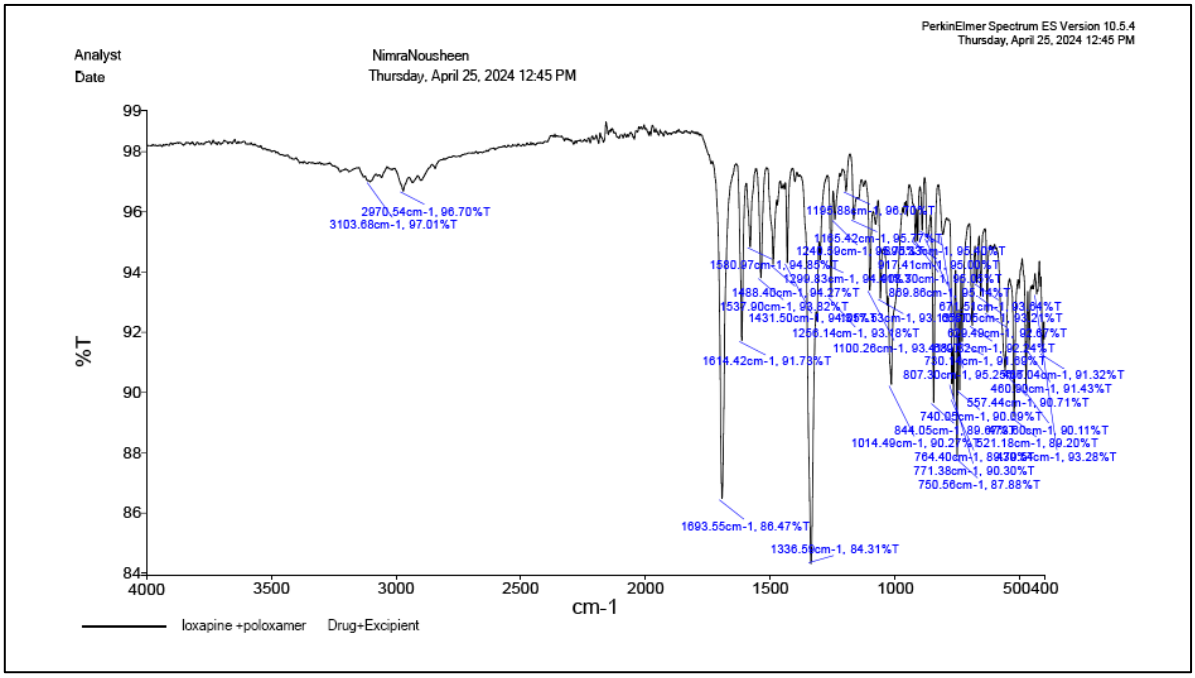

Figure 5: FTIR Spectra of Loxapine pure drug poloxamer excipient

Table 8: FTIR Interpretation

Characteristic peak	LITERATURE VALUES	OBSERVED VALUES		
		LOXAPINE Pure drug	Excipients	
			PVPK30	POLOXAMER
C=N	1640-1700	1692.71	1693.01	1693.55
C –N	1266-1330	1334.90	1336.83	1336.59
C-O	1250-1310	1256.07	1256.16	1256.14

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FTIR studies were performed to understand the compatibilities between the drug with different excipients. The figures above illustrate that the functional groups like **C═N** Stretching with the observation range of 1640-1700 has peaks at 1692.71 in pure drug, 1693.01 drug and excipient (PVPK30) and 1693.55 drug and excipient (Poloxamer). Similarly the functional group **C –O** Stretching has a peak range of 1250-1310 has peaks at 1256.07 in pure drug 1256.16 drug and excipient (PVPK30) and 1256.14 drug and excipient (Poloxaer). Similarly the functional group C-N Stretching has a peak range of 1266-1330 has peaks at 1334.90 in pure drug 1336.83 drug and excipient (PVPK30) and 1336.59 drug and excipient(poloxamer).The functional groups in both the pure drug and Excipient formulation are found. Hence it can be concluded that the pure drug is compatible with the excipients used in the study.

Evaluations:

1. Particle size & (PDI) analysis:

Particle size analysis revealed that NS5 had a 152.6 nm particle size and a PDI of 0.261, meeting oral nanosuspension stability criteria. In oral nanosuspension, a desirable PDI (Polydispersity Index) is <0.5, signifying excellent particle dispersion in the system.

Table 9:The Particle sizes and PDI values of all formulations

formulation	NS1	NS2	NS3	NS4	NS5	NS6	NS7	NS	NS9
P.Size (nm)	158.2	167.2	156.8	168.7	**152.6**	194.3	179.4	191.5	184.2
PDI	0.278	0.294	0.272	0.299	**0.261**	0.348	0.287	0.301	0.269

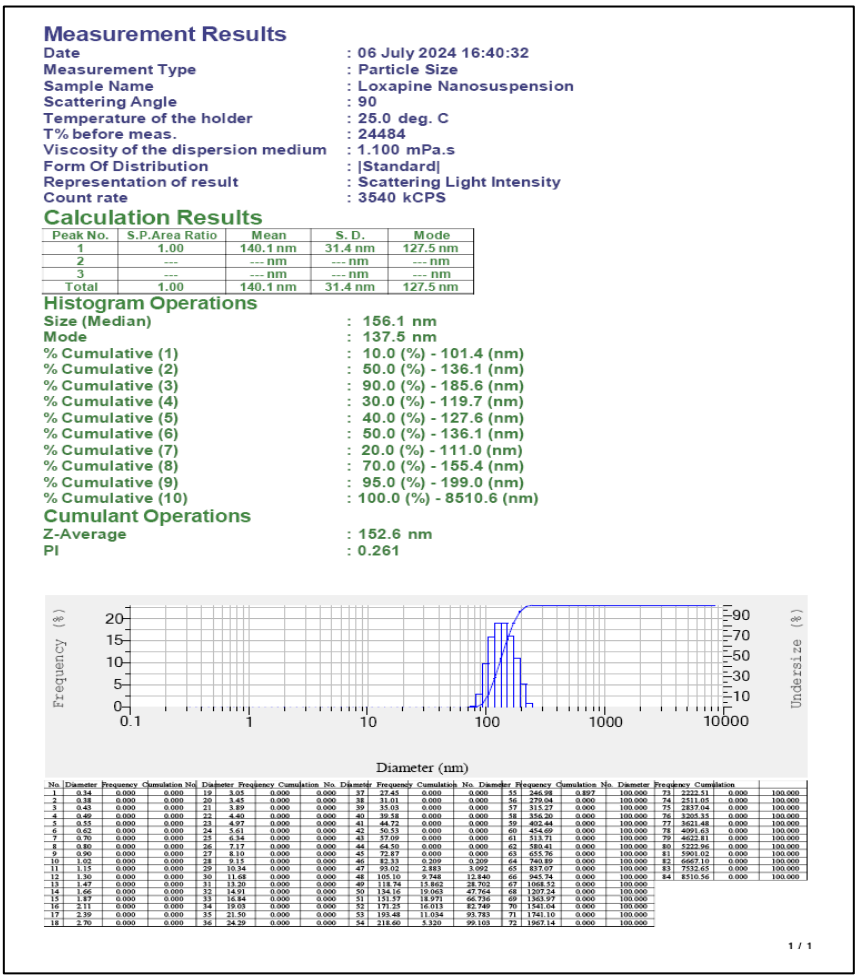

Figure 6: Average Particle Size & PDI of Optimized Formulation NS5

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2. Zeta Potential

The NS5 formulation displayed a high zeta potential value of -23.0 mV, signifying its stability as a nanosuspension. The zeta potential values of all the formulations is shown in the following table.

Table 10: Zeta Potential values of all formulations

formulation	NS1	NS2	NS3	NS4	NS5	NS6	NS7	NS	NS9
Zeta Potential (mV)	-18.7	-14.7	-18.6	-19.4	**-23.0**	-19.9	-20.6	-17.6	-21.8

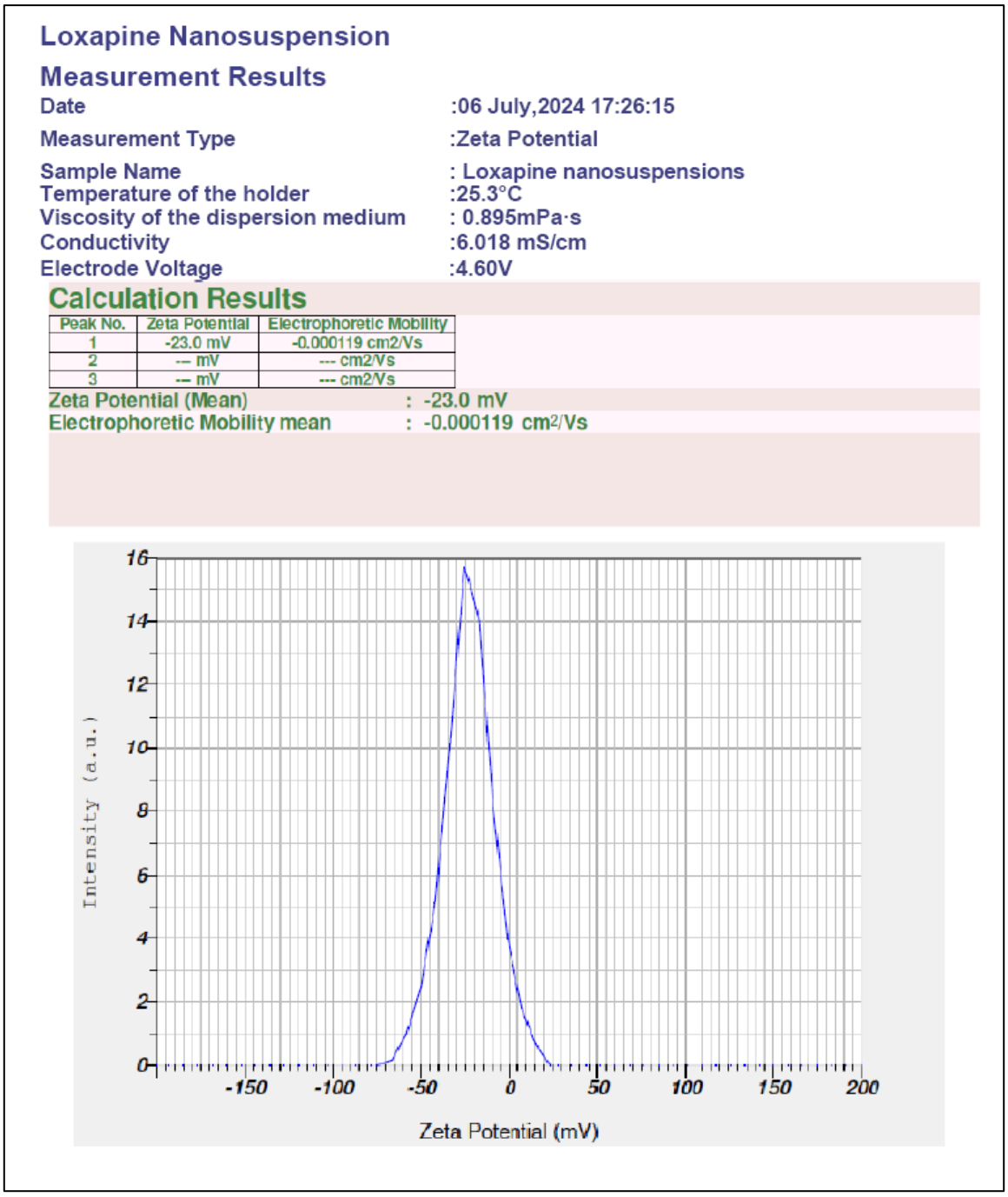

Figure 7: Zeta Potential of optimized formulation (NS5)

3.% Drug Content

Optimized formulation (NS5) had highest % drug content of about (95.83%) with NS4 (94.80%) being close to NS5's value.

Table 11: % Drug Content

Formulation	Drug content
NS1	91.75±0.46
NS2	91.02±1.20
NS3	93.51±0.66
NS4	94.80±0.65
NS5	95.83±0.82
NS6	88.58±1.50
NS7	89.33±1.17
NS8	92.33±0.86
NS9	91.16±1.32

The values are expressed as mean, + S.D (n=3)

Drug content: From the table, All the formulations drug content was found to be in the range of 88.50±1.50 to 95.83±0.82. NS5 formulation had highest % drug content of about (95.83%) with NS3 (93.51%) being close to NS5's value.

4. Invitro drug release studies:

Table 12: Dissolution data of Nanosuspension

Time in (min)	NS1	NS2	NS3	NS4	NS5	NS6	NS7	NS	NS9
0	0	0	0	0	0	0	0	0	0
10	14.28± 0.24	13.16± 0.28	8.24± 0.74	15.21± 0.62	20.87± 0.22	10.15± 0.27	10.25± 0.11	12.5±0. 24	14.2±0. 11
20	36.72 ±0.12	25.52± 0.16	20.79 ±0.25	28.33± 0.37	36.8 ±0.47	21.87± 0.59	24.23± 0.23	29.23± 0.35	28.11± 0.23
30	54.18± 0.25	44.47± 0.68	35.93± 0.65	45.92± 0.18	51.23± 0.84	45.23± 0.48	48.21± 0.71	45.23± 0.67	42.31±. 18
40	70.68± 0.68	59.16± 0.78	52.29± 0.38	62.29± 0.12	68.23± 0.69	61.23± 0.71	69.23± 0.26	64.23± 0.84	52.33± 0.45
50	84.89± 0.29	75.02± 0.48	72.29± 0.27	79.02± 0.26	85.23± 0.91	71.34± 0.28	76.77± 0.54	76.12±. 15	63.29± 0.29
60	90.68 ±0.45	88.7 ±0.56	87.41± 0.64	89.11± 0.58	95.65± 0.42	85.23± 0.88	82.28± 0.67	87.32± 0.22	81.6±0. 26

The values are expressed as mean, + S.D (n=3)

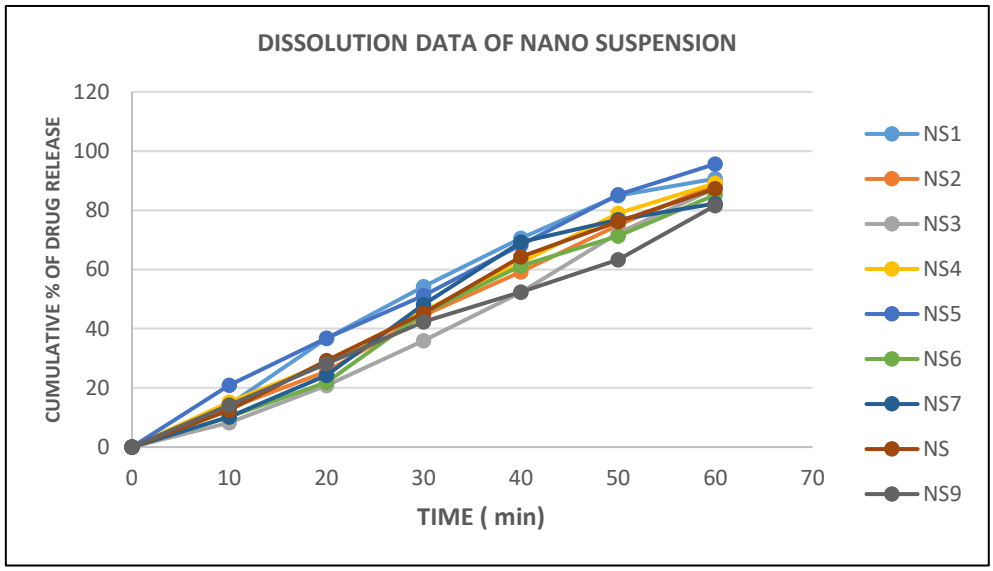

Figure 8: In-vitro drug release studies for NS1- NS 9

In-vitro dissolution studies of formulations NS1- NS 9 were carried out. It is observed that drug release from nanosuspension formulation markedly increased. The cumulative drug release, NS5 nanosuspension shows 95.65%, release at the end of the 60 min. It was observed that as the particle size increases, the release rate decreases, this is because smaller particles have a high surface area compared to their volume, and therefore the most of the drug will be at or near the particle surface and can be readily released.

Kinetic Release Models:

Table 13: Release kinetics for NS5

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	0.79665798	-0.01174906	9.31109973	0.97347738
Intercept	10.1729093	2.10129062	-7.71178269	0.07007621
R 2	0.95331135	0.96686554	0.97122453	0.98759184

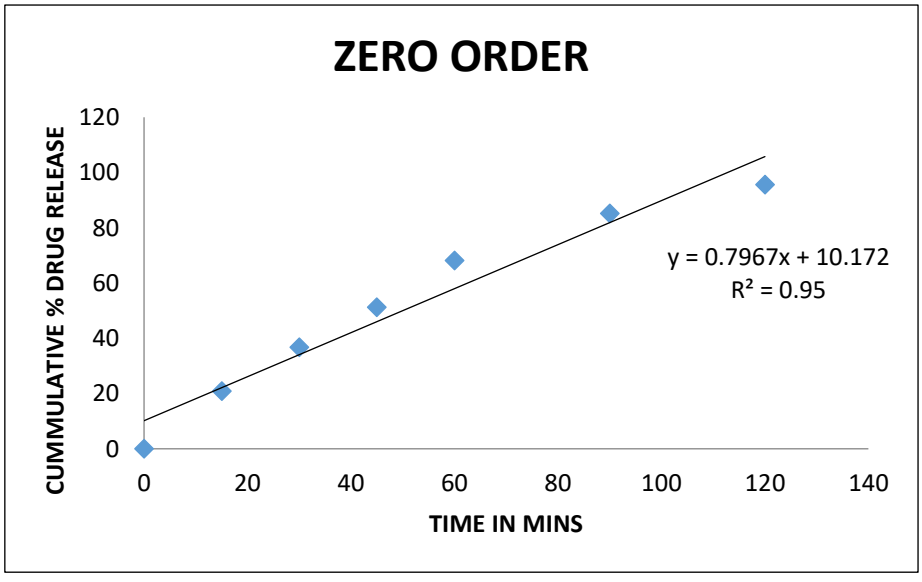

Figure 9: Zero order release graph for NS5

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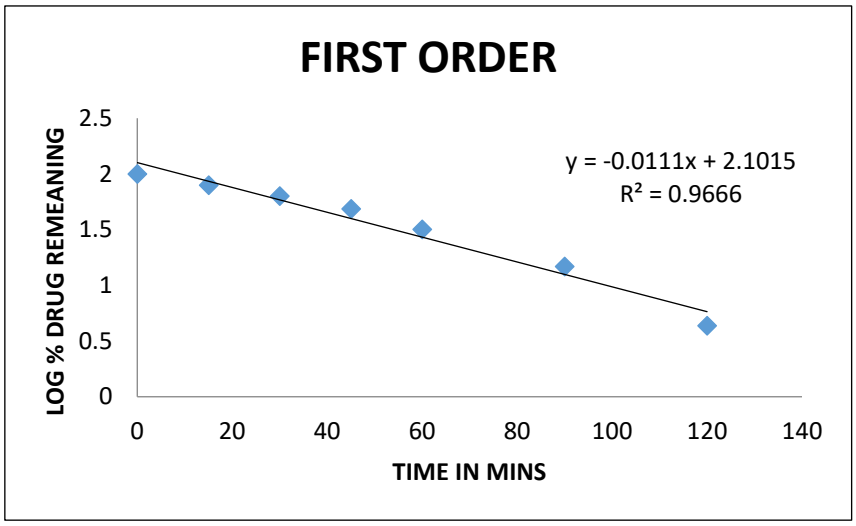

Figure 10: First order release graph for NS5

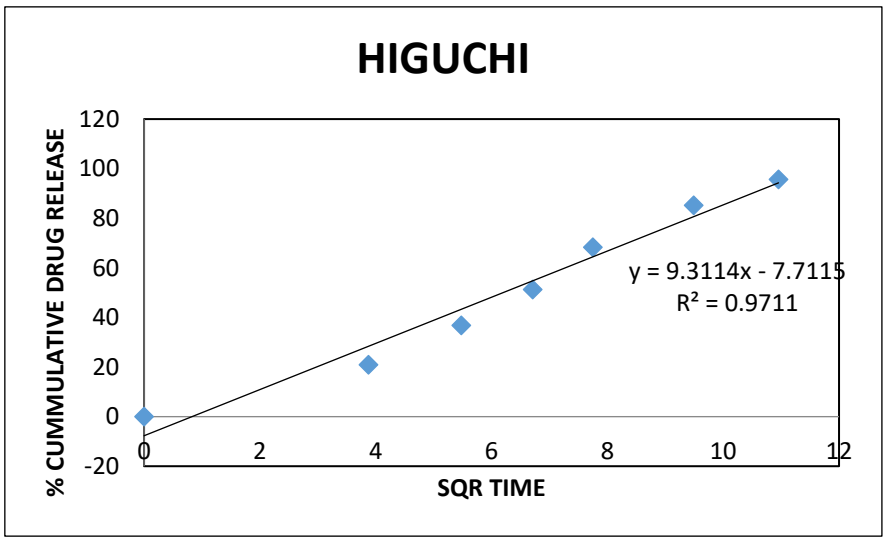

Figure 11: Higuchi model graph for NS5

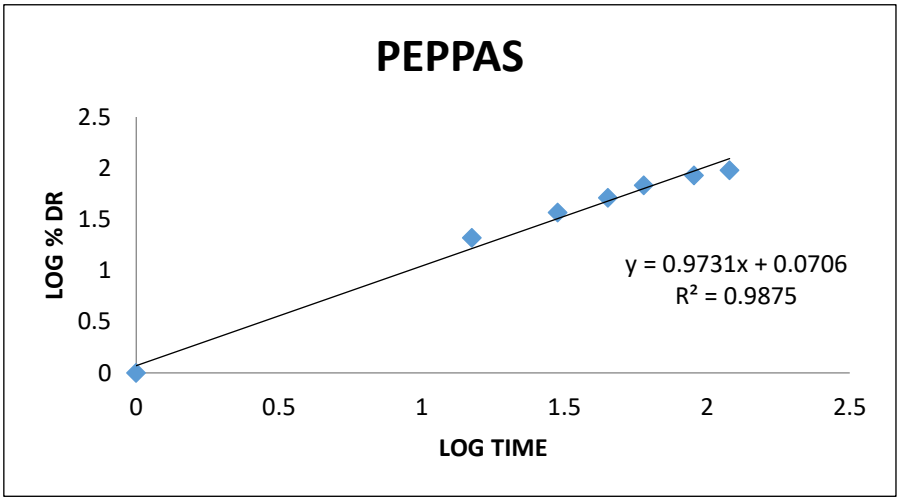

Figure 12: Peppas model for NS5

The kinetic release profile indicates that the kinetics of % DR data was fitted to the zero-order and 1st order. The profiles shows that the optimized formula NS5 followed first order kinetics (fig) with an R2 value of 0.966 which specifies that the drug release is dependent on concentration showed the log percent drug remained Vs time for first order kinetics.

5. Scanning Electron Microscopy Study

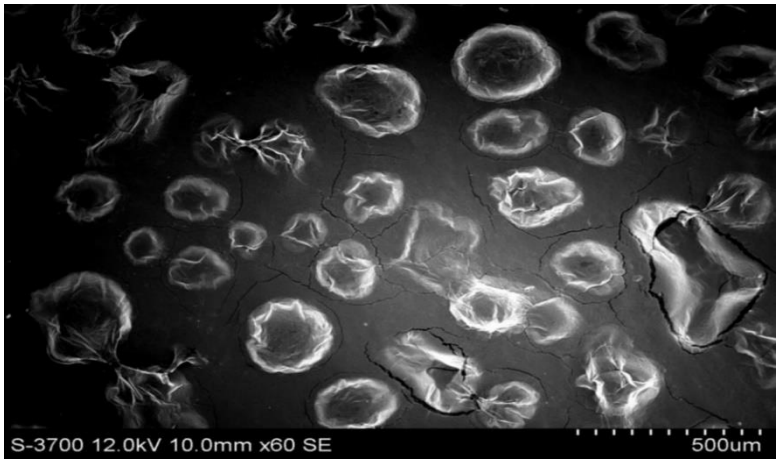

Figure 13: Scanning electron microscope image

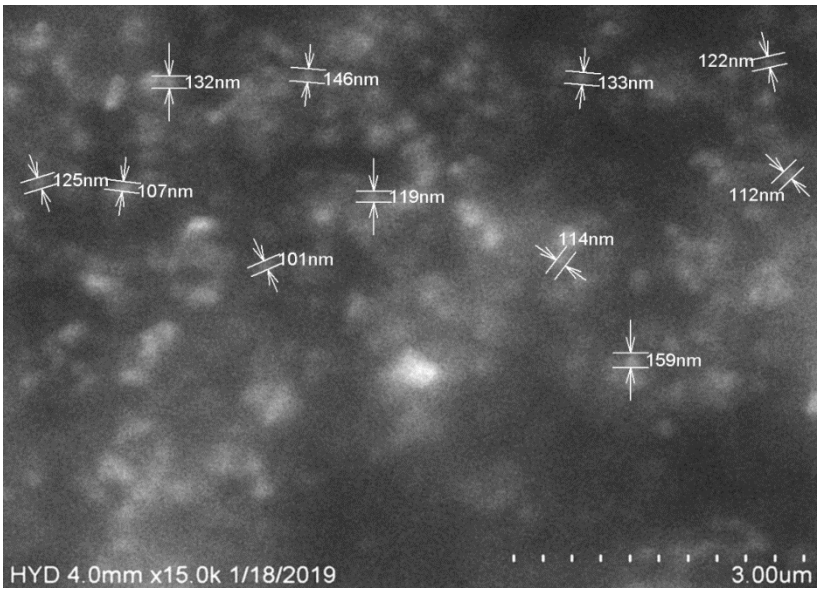

Figure 14: SEM image with Measurement

The optimized formula F3 demonstrated smooth, homogeneous particles in the nano range in SEM investigations (Figure 14) and the outcome is found to be satisfactory.

6. Short term Stability assessment of optimized nanosuspension

Loxapine NS-F5 was evaluated for stability in %Entrapment Efficiency and % *Invitro* drug release over 0, 1, 5, 12, 20, and 30 days and stored at temperatures of 4 and 25°C. Minimal changes were observed, indicating excellent stability.

Stability studies

Table 14: Short term stability study of optimized nanosuspension NS5

Number of Days	% Entrapment Efficiency at temperatures			% Drug release at temperatures		
	4±2ºC	25±2ºC	37±2ºC	4±2ºC	25±2ºC	37±2ºC
15	92.26	92.25	92.24	95.65	95.62	95.60
30	92.25	92.12	92.04	95.22	95.0	95.52
45	91.84	91.75	91.15	94.11	94.16	94.46
90	91.42	91.26	90.27	93.00	93.08	93.12

It is clear from the results obtained that the Nanosuspension have shown the minimum drug lost at refrigerated condition, and fairly high retention of drug was observed. At this low temperature condition % remaining drug entrapped and drug content was good over a period of 3 months. While, storage at higher temperatures 25±2ºC and 37±2ºC leads to less % remaining drug entrapped and drug content over a period of 3 months respectively. So it can be inferred from the above discussion that the Nanosuspension formulation should be stored at lower temperature to minimize the drug loss and increase the stability of drug.

CONCLUSION

Finally, it can be concluded from the results of present study that Nano suspension a challenging drug due to its low solubility. By utilizing different stabilizers and the nanoprecipitation method, we improved its solubility and dissolution properties. The drug and excipient compatibility was confirmed by FTIR studies. Nano suspension NS5, with small particle size of 152.6nm, low PDI (0.261) and a highly negative Zeta potential (-23.0mV), demonstrated excellent stability and uniformity. It also boasted a high Drug content of 95.83%, ensuring proper dosing. Most importantly, these Nano suspensions substantially enhanced Loxapine solubility and dissolution rates crucial for its therapeutic effectiveness. Nanosuspension NS5 following First order kinetics, emerged as the optimized formulation.

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