Formulation and Evaluation of Simethicone Nano Suspension

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***Abstract*- Simethicone, an anti-flatulent medication, is often formulated as a suspension for ease of administration. However, its limited solubility and slow dissolution rate can hinder its therapeutic efficacy. In this study, we aimed to develop and evaluate a simethicone nanosuspension to overcome these challenges and enhance its bioavailability.**

The nanosuspension was prepared using the precipitation method, with polyvinylpyrrolidone K30 (PVP K30) and sodium lauryl sulfate (SLS) identified as suitable stabilizers through compatibility studies. Various ratios of drug to stabilizer and drug to polymer were investigated, with the optimized batch (NS5) achieving a mean particle size of 258 nm and a zeta potential of -21.8 mV. Stability studies confirmed the formulation's robustness under different conditions.

In vitro dissolution studies revealed a remarkable 84 percent increase in drug release within 12 hours compared to a coarse suspension. Particle size reduction was identified as the primary factor contributing to this accelerated dissolution rate. These findings suggest that nano-precipitated simethicone nanosuspensions may offer superior therapeutic benefits over conventional formulations, highlighting their potential for enhanced bioavailability and improved patient outcomes.

***Index Terms*: Simethicone, anti-flatulent, nanosuspension, in vitro dissolution.**

I. INTRODUCTION

Materials at the nanoscale encompass a range of entities, including supramolecular structures, complexes, or composites, as well as devices or systems. It is anticipated that nanotechnology will yield substantial advancements in conventional discovery methodologies [1].

Nanotechnology has exerted a notable influence over the past decade, leading to the emergence of entirely new and unforeseen industries. Innovative drug delivery techniques have become a pivotal tool for the pharmaceutical sector in its endeavor to expand drug markets. These methods aim to elevate solubility, enhance oral bioavailability, increase surface area, expedite dissolution rates, and facilitate a quicker onset of therapeutic effects through the nano-sizing of pharmaceuticals [2].

Nanosuspension

In the past two decades, a new technology has been developed to enhance the dissolution of medications according to the Noyes–Whitney equation, resulting in accelerated breakdown processes. This advancement has led to higher dissolution rates, thereby facilitating delivery through various routes such as oral, topical, parenteral, or pulmonary administration [3].

Simethicone: Simethicone is classified as an anti-flatulent (anti-gas) medication. Its mechanism of action involves reducing the surface tension of gas bubbles present in the stomach and intestines, thereby facilitating their breakdown and the formation of larger bubbles. This process is believed to aid in the expulsion of gas through belching or passing flatus. Simethicone received approval from the FDA in 1952.

Chemically, simethicone is a blend of polydimethylsiloxane and hydrated silica gel. It exerts its effects primarily within the gastrointestinal tract (GIT) and is not absorbed into the bloodstream. The most commonly reported side effects associated with simethicone use include mild nausea, vomiting, and diarrhea.

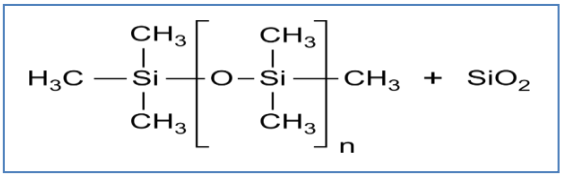


Figure 1: Chemical Structure of Simethicone

II. METHODS

Pre-formulation Studies

Pre-formulation refers to the systematic process aimed at enhancing a pharmaceutical product by evaluating its essential physical and chemical attributes. This endeavor involves a thorough examination of factors such as polymorphic forms, dissolution properties, and crystal structures to develop the most effective drug delivery system possible [4,5].

Employing pre-formulation parameters significantly enhances the likelihood of developing a pharmaceutical product that meets the criteria for acceptability in terms of adverse effects, efficacy, and stability. Concurrently, this approach establishes the foundation for enhancing the overall quality of medication products [6].

Physical Properties

i) Color and Nature

A minute quantity of the sample was transferred onto a white piece of paper, whereupon the powder was dispersed and visually inspected for examination.

ii) Odour

A minute amount of simethicone was utilized, and its odor was assessed through olfaction.

iii) Solubility

The solubility of simethicone was evaluated using the shake flask method in various solvents including distilled water, methanol, ethanol, acetone, chloroform, and pH 6.8 phosphate buffer. Each vial containing 10 mL of the chosen solvent was loaded with an excess amount of simethicone until the solution reached saturation.

iv) Melting Point

The melting range refers to the temperature span from the initial melting of the first particle to the complete melting of the last particle. Employing a melting point apparatus, the melting point of simethicone was ascertained [7].

v)……pH of the Solution

Utilizing a pre-calibrated pH meter, the pH of the freshly prepared solution was measured. The results of this analysis are presented in the results and discussion section.

Determination of Absorption maxima

The UV spectrum was obtained using a Double beam UV/VIS spectrophotometer from a solution containing 10 g/mL of the medication in 0.1N HCl. The solution was scanned over a range of 200-400 nm to acquire the spectrum.

Preparation of calibration curve

In a 100 mL volume of 0.1N HCl, 100 mg of pure simethicone was dissolved to create a stock solution. Subsequently, 10 mL of this stock solution was combined with 100 mL of 0.1N HCl (resulting in a concentration of 100 g/mL). From this mixture, 10 mL was extracted and further combined with 100 mL of 0.1N HCl (yielding a concentration of 10 g/mL). Next, a series of dilutions was prepared by diluting the solution with 0.1N HCl to achieve concentrations of 1, 2, 3, 4, and 5 g/mL of simethicone per mL of solution. A Double beam UV/VIS spectrophotometer was utilized to measure the absorbance of these dilutions at 266 nm, with 0.1N HCl used as the blank. Using concentration as the X-axis and absorbance as the Y-axis, a graph was generated, resulting in a linear relationship. The square of the correlation coefficient (R2) was calculated via least square linear regression analysis to assess the linearity of the standard curve **[8].**

FTIR Spectroscopy

The physical parameters of the physical mixture were contrasted with those of a frequently prescribed medication. Both samples were thoroughly blended with 100 mg of potassium bromide IR powder and subsequently compressed for 3 minutes under vacuum at 12 psi. The resulting spectra were then compared to ascertain any discernible differences [9].

NMR Spectroscopy

Nuclear Magnetic Resonance (NMR) is a spectroscopic technique employed to study the local magnetic fields surrounding atomic nuclei. In this study, NMR analysis was conducted using a JEOL 400 MHz spectrometer acquired in 1999 at CDRI Lucknow. The drug under investigation was dissolved in deuterated methanol and analyzed using NMR at a frequency of 300 MHz.

Mass Spectrometry:

In mass spectrometry, organic molecules are subjected to bombardment by either electrons or lasers, resulting in their conversion into highly energetic charged ions. A mass spectrum is then generated, depicting the relative abundance of these fragmented ions plotted against their mass-to-charge ratio. Mass spectrometry enables the precise measurement of the relative molecular mass (molecular weight) and facilitates the calculation of an exact molecular formula by identifying the positions at which the molecule undergoes fragmentation.

Drug –Excipient Compatibility Studies

The formulator can leverage this understanding of drug-excipient interactions to select suitable excipients. Such information is readily accessible for already-approved medications. However, for newly developed medications or excipients, pre-formulation scientists must generate the requisite data.

By Physical Observation:

The determination was carried out following the procedure detailed in the methodology section, as depicted in the table below.

Table 1: Physical Compatibility studies

S.NO.	TEST	OBSERVATION	INFERENCE
1.	Physical Compatibility	No change of color	These materials are compatible for formulation

Formulation Development

Nanosuspensions were formulated utilizing the nanoprecipitation technique. Initially, pure Simethicone and PVP K30 were dissolved in 1 ml of methanol at 40°C to yield a homogeneous organic solution. Subsequently, this prepared organic solution was slowly injected dropwise using a syringe into a 20 ml aqueous phase containing stabilizers (Sodium lauryl sulphate) under high-speed mechanical agitation at 6000 rpm to achieve the desired nano-dispersion.

The resulting nanosuspension was then magnetically stirred at 500 rpm at room temperature for a duration of 12 hours, facilitating the evaporation of the organic solvent. Complete evaporation of methanol was confirmed through a spectrophotometric method. To account for any loss, the volume was adjusted by adding triple distilled water while maintaining all other parameters constant [10,11]. The batches were prepared according to the formulation design in Table 2.

Table 2: Formulation Chart of Nanosuspension of simethicone

Formulation code	Drug (mg/ml)	PVP K30 (mg/ml)	Sodium Loren Sulphate (mg/ml)	Methanol (ml)	Water (ml)
SN1	60	6	3	1	20
SN2	60	6	6	1	20
SN3	60	6	30	1	20
SN4	60	18	3	1	20
SN5	60	18	6	1	20
SN6	60	18	30	1	20
SN7	60	30	3	1	20
SN8	60	30	6	1	20
SN9	60	30	30	1	20

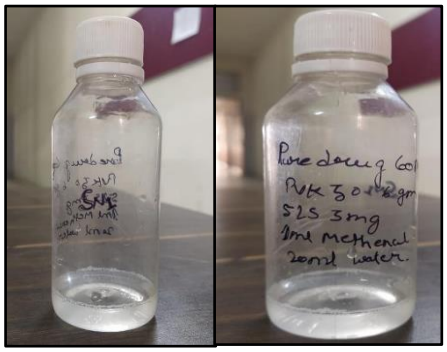


Figure 2: Picture of the Simethicone nanosuspension

Lyophilization and redispersibility of nanosuspensions

The Simethicone nanosuspension underwent a freezing and lyophilization process for a duration of 24 hours at 24°C utilizing a Decibel digital lyophilizer from India.

Upon completion of the lyophilization process, redispersibility was observed when the freeze-dried materials were reconstituted to their original volume using triple distilled water. Subsequently, solid-state characterization was conducted using the freeze-dried materials.

Evaluation of Nanosuspension

Particle Size and PDI

The mean particle size and polydispersity index of the produced nanosuspension were assessed using a Zetasizer instrument (Zetatrac, Microtrac, Japan). This device operates based on light diffraction principles, specifically employing photon correlation spectroscopy (PCS) [12].

Zeta Potential

Zeta potential is a metric that quantifies the electric charge present at the surface of particles, serving as an indicator of the physical stability of colloidal systems. A zeta potential exceeding 30mV typically suggests long-term electrostatic stability in aqueous dispersions. In this study, the zeta potential of the particles was determined using a Zetasizer device (Zetatrac, Microtrac, Japan) to measure their electrophoretic mobility [13].

Drug Content

A fraction of the manufactured nanosuspension (1 ml) was diluted in methanol and subsequently filtered through a 0.2 µm filter. The total drug content was then assessed using a UV spectrophotometer, with measurements conducted at the drug's lambda max wavelength [14].

Saturation Solubility

The resulting nanosuspension was transferred into a vial and left undisturbed for 48 hours while being stirred with a magnetic stirrer at 100 rpm. This process ensured that the solubility of the nanosuspension reached saturation. Subsequently, the nanosuspension was transferred into an Eppendorf tube and centrifuged for 30 minutes at 10,000 rpm. After appropriate dilution with dissolution media serving as a blank at the drug's lambda max wavelength, each sample was analyzed using three distinct methods. The saturation solubility was then estimated utilizing the calibration curve [15].

In-vitro Dissolution Study

In vitro dissolution studies were conducted using the USP 24 paddle apparatus (Electrolab TDP-06P) to assess dissolution characteristics. The selection of dissolution media was based on the specifications outlined in Table 3. To minimize foaming during the experiment, the dissolution medium was gently introduced into the dissolution vessel. The dissolution process was carried out at 37°C with a specified paddle speed. Nanosuspension equivalent to a therapeutic dose of the medication was added to the dissolution vessels. Samples of 5 mL each were withdrawn at intervals of 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours and subsequently filtered through a 0.2 µm syringe filter before being subjected to spectrophotometric analysis. Following each sampling, the dissolution vessel was replenished with 5 mL of fresh medium. These experiments were conducted thrice, and the average results obtained were documented [16].

Table 3: Dissolution conditions for nanosuspensions

S. No.	Dissolution Condition	Simethicone Nanosuspension
1	Volume of Dissolution media	250
2	Speed in RPM	50

3	Sampling Intervals	2, 4, 6, 8, 10, 15, 30, 45, 60 mins
4	Dose of drug	20 mg

Stability study

In compliance with ICH guidelines, the accelerated stability of the lyophilized nanosuspension was assessed over a period of 6 months at controlled conditions of 25 ± 2°C and 60 ± 5% relative humidity (RH). The lyophilized nanosuspension was encapsulated within firm gelatin capsules for storage purposes. Samples were withdrawn at specified intervals (0, 1, 3, and 6 months) and subjected to analysis for parameters including particle size, saturation solubility, and drug concentration [17].

III. RESULT

Pre-formulation Study

Description

The color, physical characteristics, taste, and odor of simethicone were meticulously observed, revealing results that aligned precisely with the specifications outlined in the Indian Pharmacopoeia (IP).

Table 4: Description of Simethicone

S.no.	Properties	As per I.P. specification	Observation
1	Colour	Light gray or white	Light gray or white
2	Physical nature	Viscous, translucent	Viscous, translucent
3	Taste	bitter	bitter
4	Odour	Bland, mild	Bland, mild

Drug Solubility Studies

The solubility of the drug was evaluated across various media, namely methanol, chloroform, distilled water, and phosphate buffer at pH 6.8. The results of the solubility studies are presented in Table 5, indicating that chloroform exhibits the highest solubility for the drug. Based on these findings, it can be deduced that simethicone demonstrates greater solubility in chloroform compared to the other solvents assessed.

Table 5: Drug Solubilities Study

S. No.	**Solvents**	**Solubility (mg/ml)**
1	Methanol	48.45
2	Phosphate buffer pH 6.8	29.73
3	Chloroform	55.24
4	Distilled water	7.35

Melting Point

The calculation was performed according to the procedures specified in the pre-formulation section outlined within the materials and methods section. Upon analysis, it was confirmed that the final product satisfies all prescribed criteria and requirements. The outcomes are shown in table 6.

Table 6: Melting point of Simethicone

S. No.	**Material**	**Melting point range**	**Result**
1	Simethicone	-57 °F	Complies

pH of the solution

The calculation was conducted following the procedures delineated in the pre-formulation section of the materials and methods section. The outcomes are shown in 7.

Table 7: pH of the solution

Material	Test	Specification	Observation
Simethicone	pH	6.3	6.4

Calibration Curve

Table 8: graph of Simethicone in 0.1N HCl (244 nm)

Concentration	Absorbance
0	0
0.1	0.145
0.2	0.156
0.3	0.203
0.4	0.296
0.5	0.379
0.6	0.445

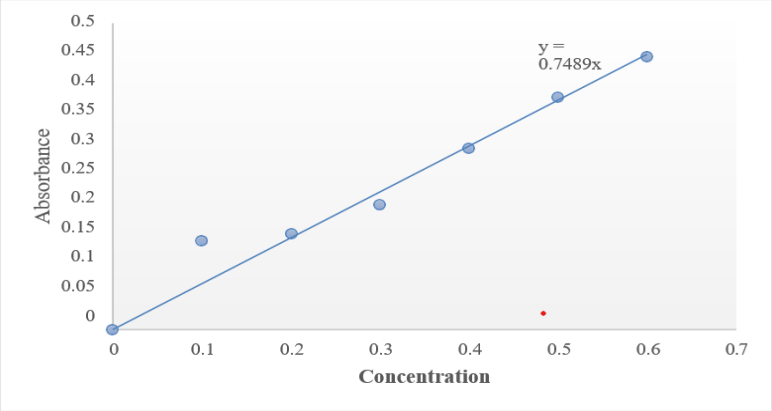


Figure 3: Calibration curve of Simethicone in HCl

FT-IR Spectrum

The FTIR spectrum of the simethicone drug was generated and is illustrated in Figure 4, displaying all the distinctive peaks characteristic of the medication. A summary of the interpretation of the FTIR spectrum is provided in Table 9.

Figure 4: FTIR Spectrum of Pure Drug Simethicone

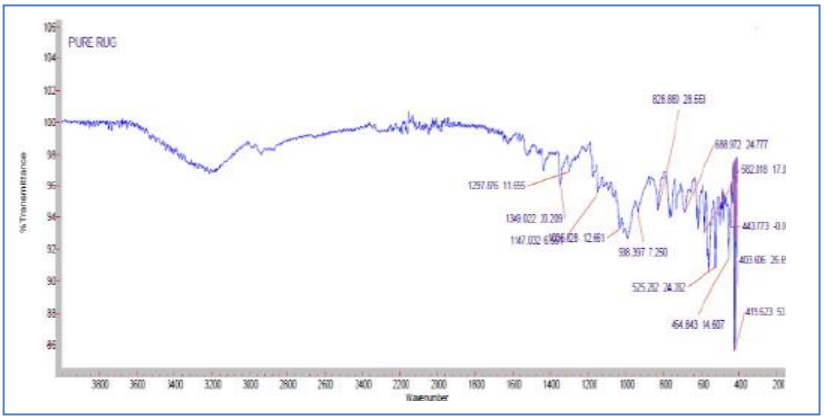


Table 9: Interpretation of Simethicone

S. No.	Observed peak (cm^{-1}) of sample drug	Inference
1	1297	O-NO_2 stretching
2	1147	C-O stretching
3	1349	CO-NH
4	1266	Aromatic pyridine tertiary amine

NMR Spectroscopy:

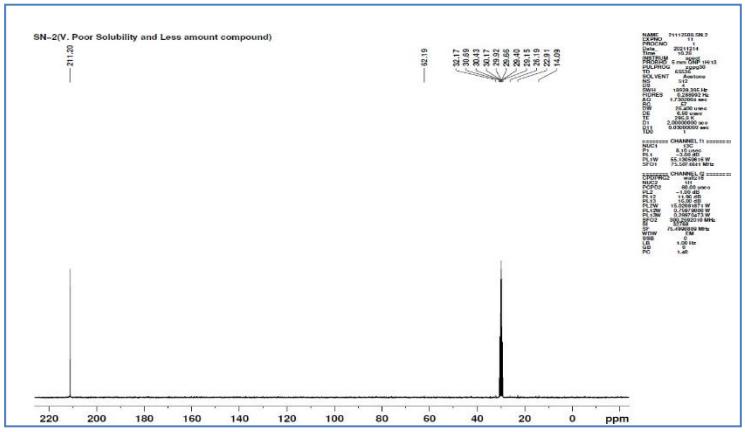


Figure 5: NMR Spectra of Drug

Compatibility Study

The investigation of drug-excipient interactions holds significance for multiple reasons, particularly concerning drug release from the formulation. To elucidate the physical and chemical relationship between the medication and the excipient employed, FTIR methods were employed.

Table 10: Drug – Excipients Compatibility Study Results

Drug + Excipients	Initial	After 1 month at		Compatible
		40°C/75% RH	60°C	
Drug	White amorphous powder	No change	No change	Yes
Drug + PVP K 30	White powder	No change	No change	Yes
Drug + SLS	White powder	No change	No change	yes

The analysis revealed a lack of chemical interaction between simethicone and the polymers utilized in this study. Figure 6 illustrates that the key peaks in the FTIR spectra of the drug-polymer mixture remained unchanged, indicating the absence of physical interactions resulting from the formation of bonds between the drug and polymer.

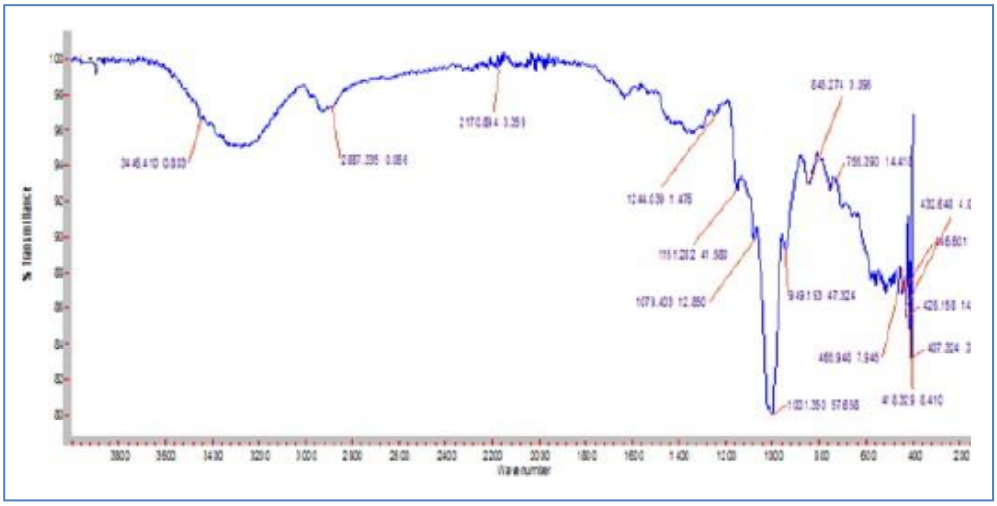


Figure 6: FTIR spectrum of Optimized formulation of nanosuspension

Formulation Development

Nanosuspensions of simethicone were prepared using a nanoprecipitation method. In all batches, the solvent-to-antisolvent ratio was maintained at 1:20, and the stirring speed was set at 6000 rpm for a duration of 8 hours. The resulting appearance of a bluish-white transparent colloidal nanodispersion serves as confirmation of successful colloidal nanodispersion formation.

Evaluation of Nanosuspension

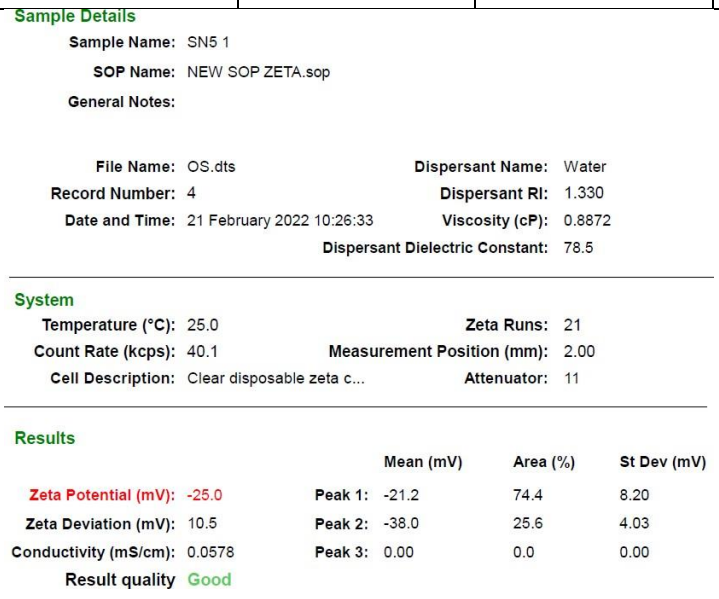
Particle size and Polydispersibility Index (PDI)

The particle size distribution plays a pivotal role in determining the in-vivo fate of nanosuspensions. As depicted in Table 11, the average particle size across batches SN1 to SN9 ranged from 205 nm to 524 nm. The maximum size observed was 524 nm in the SN2 batch. Notably, the improved formulation SN5 exhibited an average particle size of 207 nm, as illustrated in the accompanying figure.

The degree of particle size distribution is quantified by the polydispersity index (PDI), which ranged from 0.357 to 0.602 depending on the formulation variables. The lowest PDI value of 0.257 was recorded for formulation SN6, indicating a high level of particle size distribution homogeneity.

Table 11: Physicochemical Characterization of Simethicone Nanosuspensions

S.no.	Formulation code	PS (nm)	PI	ZP (mV)
1	SN1	556±3.99	0.373±0.21	-8.3±1.85
2	SN2	363±3.21	0.602±0.23	-13.5±1.98
3	SN3	237±1.95	0.414±0.19	-18.2±1.45
4	SN4	330±3.78	0.549±0.19	-16.5±1.99
5	SN5	258±2.76	0.549±0.20	-21.5±2.67
6	SN6	207±1.99	0.257±0.21	-25.8±2.87
7	SN7	309±3.21	0.566±0.23	-12.4±1.45
8	SN8	252±2.10	0.498±0.21	-18.5±1.09
9	SN9	230±3.04	0.567±0.22	-21.5±1.87



Sample Details

Sample Name: SN5 1
SOP Name: NEW SOP ZETA.sop
General Notes:

File Name: OS.dts
Record Number: 4
Date and Time: 21 February 2022 10:26:33
Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Dispersant Dielectric Constant: 78.5

System

Temperature (°C): 25.0
Count Rate (kcps): 40.1
Cell Description: Clear disposable zeta c...
Zeta Runs: 21
Measurement Position (mm): 2.00
Attenuator: 11

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-25.0			
Zeta Deviation (mV):	10.5	Peak 1:	-21.2	74.4	8.20
Conductivity (mS/cm):	0.0578	Peak 2:	-38.0	25.6	4.03
Result quality	Good	Peak 3:	0.00	0.0	0.00

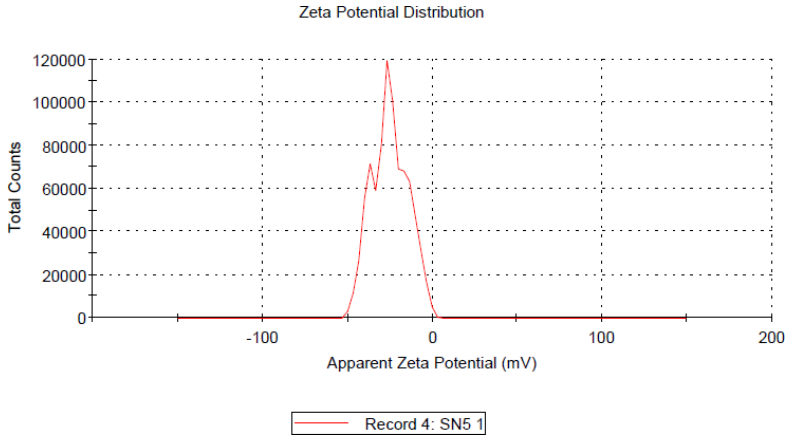


Figure 7: Zeta potential of the nanosuspension formulation SN5

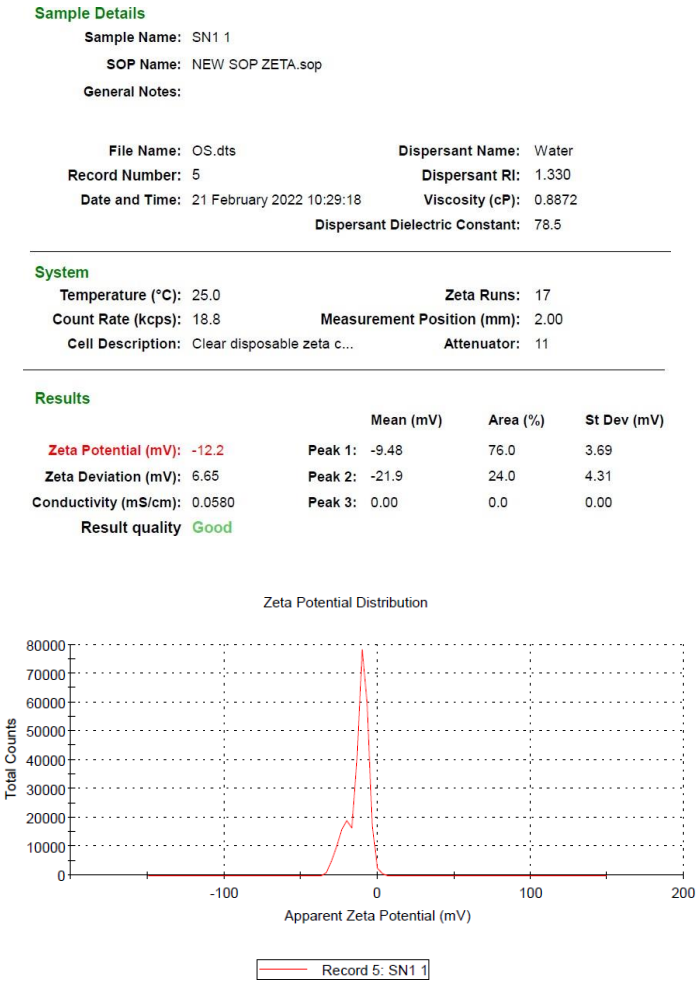


Figure 8: Zeta potential of the nanosuspension formulation SN1

Drug Content (DC):

The total drug content (DC) for the prepared batches is presented in Table 12. It is noteworthy that the DC values for all batches were satisfactory and exceeded 75%. This indicates that drug loss during the manufacturing procedure was minimal.

Table 12: Drug Content

S. No.	Formulation	Drug content (%)*
1	SN1	87.41

2	SN2	89.44
3	SN3	90.21
4	SN4	91.21
5	SN5	98.45
6	SN6	89.68
7	SN7	87.98
8	SN8	91.67
9	SN9	89.23

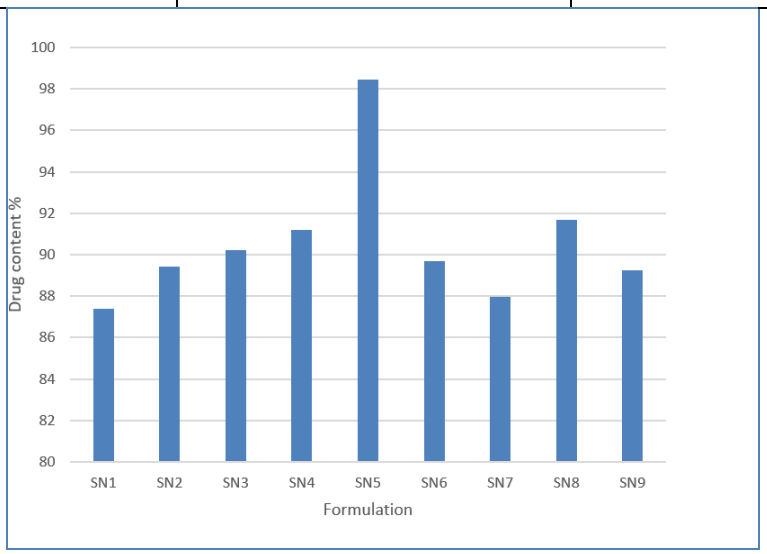


Figure 9: Drug Content of Nanosuspension Formulation

Saturated Solubility

The saturation solubility of an enhanced batch of simethicone nanosuspension and the pure drug were assessed, resulting in values of 102.9 g/ml and 1.205 g/ml, respectively. This demonstrates that the nanosuspension exhibited a saturation solubility approximately 100 times greater than that of the pure drug.

***In-Vitro* Drug Release**

The drug release from the optimized batch (SN5) reached 84 percent within a 12-hour period. This observation indicated that as the particle size decreases, there is an increase in medication release.

Table 13: Results of *in-vitro* drug release

S. No.	**Time**	**Optimized formulation SN5**	**Simethicone pure drug**
1	0.0	0.00	0.00
2	0.15	6.89	5.12
3	0.25	15.21	12.34

4	0.5	21.28	16.69
5	1.0	30.94	23.87
6	2.0	39.69	31.23
7	4.0	49.32	42.76
8	6.0	58.80	55.87
9	8.0	69.21	65.42
10	12.0	88.23	84.13

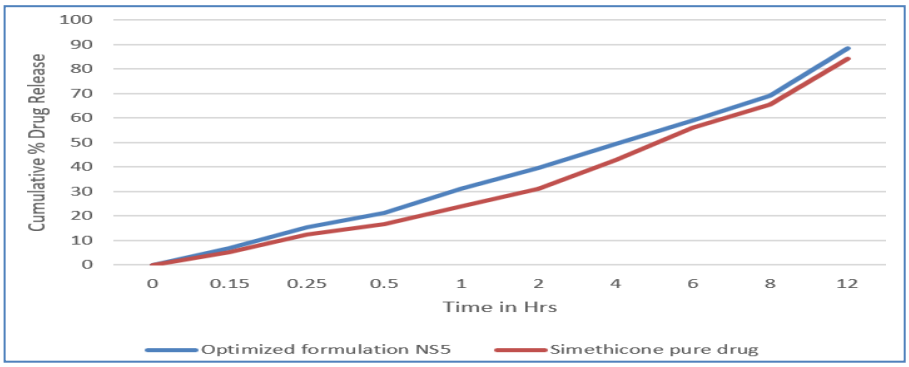


Figure 10: % Drug Release Compared with simethicone pure drug

Accelerated Stability Study

The results regarding mean particle saturation solubility, cumulative percentage drug release at 15 minutes, and percent w/w of drug content presented in Table 14 indicated a slight deviation in all parameters, with a negligible 5% bias that had no significant impact. Furthermore, the results obtained from the optimized batch before and after the stability investigation, conducted in accordance with the ICH guidelines, revealed only a minor change.

Table 14: Results of accelerated stability study of simethicone nanosuspension

Sr. No.	Storage condition	Time Period (months)	Evaluation Parameters		
			Mean Particle Size Mean ± SD	Saturation Solubility (µg/ml) Mean ± SD	Drug Content (%w/w) Mean ± SD
1	25°C ± 2°C and 60% ± 5% RH	0	238.0 ±2.56	76.25±1.42	99.46±1.06
2		1	243.2±2.86	76.07±1.86	98.43±1.08
3		2	252.1±2.64	75.59±1.56	97.91±1.11
4		3	250.2±2.65	75.43±1.43	97.88±1.09

IV. CONCLUSION

Nanosuspension is a technique that significantly enhances the effective surface area of drug particles, leading to a higher dissolution rate and improved bioavailability due to the vapor pressure effect. The initial phase of this study involved the preparation of simethicone nanosuspension using the precipitation method. Through compatibility studies using FTIR, PVP K30 and SLS were identified as the most suitable polymers for simethicone, demonstrating drug-excipient compatibility.

The second part of the research focused on the development and evaluation of a nanosuspension formulation of simethicone. Key parameters such as drug content, zeta potential, in-vitro drug release, and formulation stability were assessed. The findings highlighted the significant impact of the drug-to-stabilizer ratio (1:0.5) and the drug-to-polymer ratio (1:0.3) on particle size reduction.

The optimized batch (NS5) exhibited a mean particle size of 258 nm and a zeta potential of -21.8 mV, remaining stable under various conditions. Compared to coarse suspension, the optimized nanosuspension showed an 84 percent increase in dissolution rate within 12 hours (22 percent in 50 minutes), with particle formation being the primary factor contributing to this enhanced dissolution rate. Consequently, nanoprecipitated simethicone nanosuspension formulations hold potential therapeutic advantages over conventional formulations.

V. ACKNOWLEDGMENT

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