International Journal of Pharmaceutical Sciences and Drug Analysis

E-ISSN: 2788-9254
P-ISSN: 2788-9246
IJPSDA 2023; 3(1): 34-42
www.pharmacyjournal.info
Received: 21-10-2022
Accepted: 08-12-2022

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Formulation and evaluation of nasal mucoadhesive microemulsion of sumatriptan succinate

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Abstract
To formulate mucoadhesive microemulsion for nasal administration. The enhance rate of absorption, avoid first pass metabolism, reduce dose of drug and achieve systemic effect through the nasal route and evaluate the formulation for the following parameter, Clarity, pH Centrifugation, Particle size determination, Viscosity, Zeta potential, Electrophoretic mobility *In-vitro* mucoadhesion study, *In-vitro* drug diffusion study, Ex-vivo permeation study Histological study, Accelerated stability study, To evaluate optimized stability of formulation based on the above evaluation tests. The use of mucoadhesive systems as mucoadhesive microemulsion, provide a drug protection from enzymatic degradation and convert it in to gel and control the rate of clearance from the nasal cavity. Sumatriptan succinate from this mucoadhesive microemulsion was found to be fairly rapid, because it converts into gel inside the nasal cavity and increase the residence time and bioavailability of the drug. The mucoadhesive microemulsion may be a useful approach for the rapid- onset delivery of sumatriptan succinate during the emergency treatment of acute attack of migraine. SS is a 5-HT 1 receptor agonist used in the treatment of migraine. It is generally given by oral or parenteral routes, however, a substantial proportion of patient suffer severe nausea or vomiting during their migraine attack, which make oral treatment unsatisfactory. Moreover, SS has previously been shown to have a low oral bioavailability in human volunteers (15%) due to high first pass metabolism justifiesa need of nasal drug delivery.

Keywords: Sumatriptan succinat, microemulsion, nasal administration

Introduction
For systemic therapy, drugs are traditionally administered by oral and parenteral routes. The most desirable and convenient method of drug administration is the oral route and the most favored dosage form include tablets, capsules and solutions because of their ease of manufacture and administration. However in many instances, oral administration is unsuitable when the drug undergoes significant degradation in the gastrointestinal tract or is metabolized to a high degree via the first pass effect in the liver. Failure to systemically deliver selected compounds through the oral route led to research on alternative route of drug delivery. Lack of adequate absorption through the gastrointestinal tract was the single most predominant reason for such efforts. Researchers resorted to the parenteral route as an easy solution to the problem. Absorption through the intravenous route is not an issue and other parenteral routes such as intramuscular and subcutaneous provide satisfactory delivery of most drugs. But the parenteral route can be undesirable or impractical if a drug is intended for the treatment of chronic diseases. Therefore, an alternative route of administration would be preferred. For the past few decades, the transdermal route has been explored for a number of drugs, but its use is limited due to understandably low permeability of the skin to many drugs.

There has been significant interest in drug delivery via nonparenteral routes in recent years. Nonparenteral routes for drug delivery include nasal, buccal, pulmonary and transdermal routes. All these application routes are suitable for self administration. From a biopharmaceutical point view, the avoidance of first pass effects and a higher bioavailability compared to oral administration are to be mentioned. The nasal application is the only route of administration from this list of non-parenteral delivery systems.

Nasal drug delivery system
Nasal therapy known as “Nasaya Karma” has been recognized in Ayurvedic medicine since ages. However, the potential of nasal drug delivery was recognized in year 1992.

Conventionally the nasal route has been used for the delivery of drugs in the treatment of local diseases; however the last decade has recognized the.

Results and Discussion

Identification of drug

Identification of drug was carried out by UV spectroscopy, IR spectroscopy and by melting point determination.

UV Spectroscopy

The solution of SS was found to exhibit maximum absorption at 228 nm after scanning on the spectrophotometer which was reported as λmax in the literature. Thus the procured drug sample of SS complies with the reference spectra.

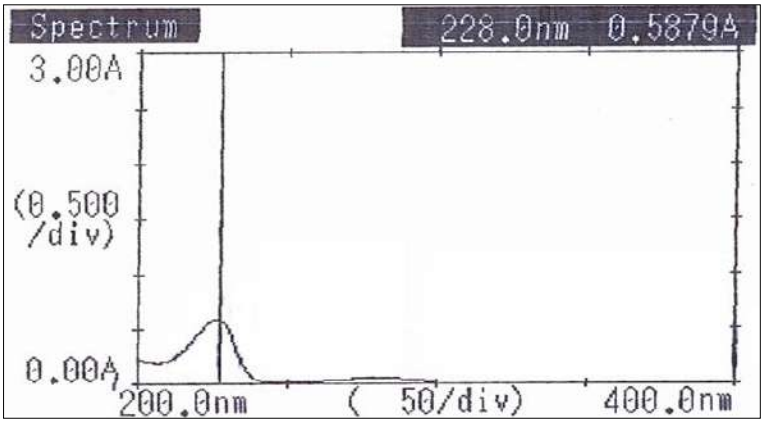


Fig 1: UV spectrum of SS.

IR Spectroscopy

Fourier transformed infrared (FTIR) spectra of SS was taken by using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 450 to 4000 cm $^{-1}$ and the resolution was 1 cm $^{-1}$. The obtained IR spectra of drug sample match with the standard IR spectra of SS.

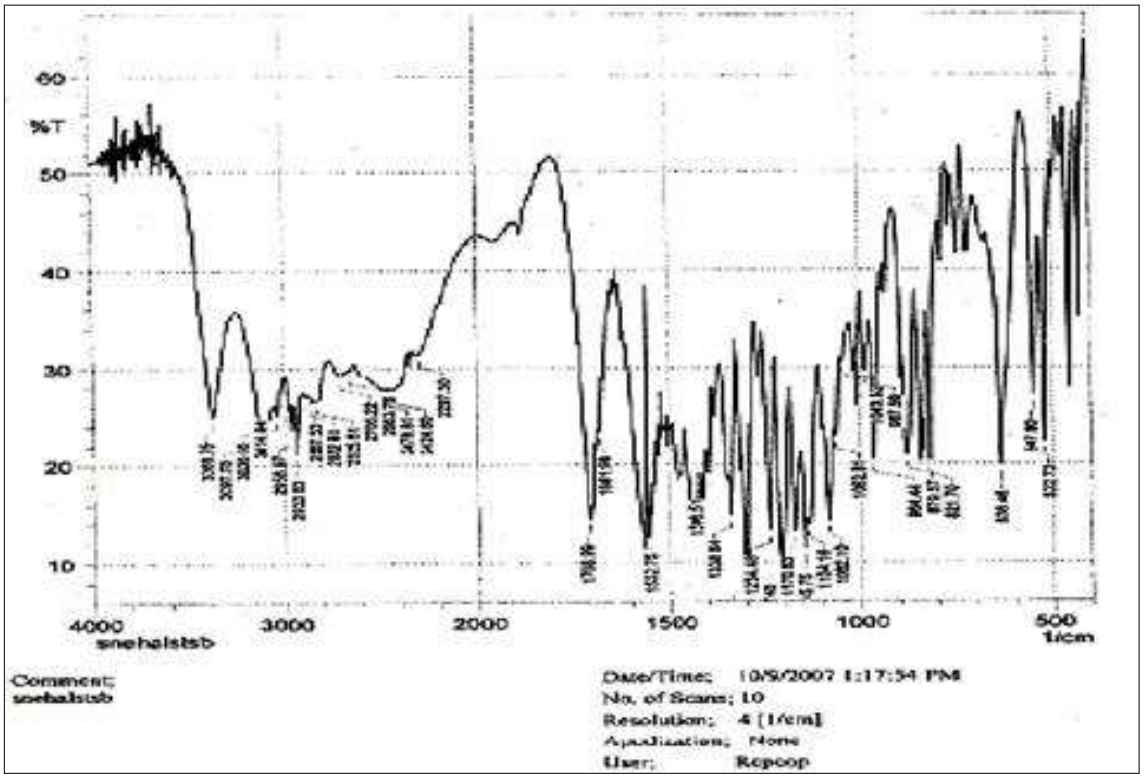


Fig 2: IR spectra of SS.

Determination of melting point

Melting point of SS was measured by using capillary method, showed melting range 164-167 °C.

Calibration curve of SS

Table 1: Standard calibration curve of SS in water

Sr. no.	Concentration (µg/ml)	Absorbance
1	1	0.168
2	2	0.298
3	3	0.426
4	4	0.558
5	5	0.724
6	6	0.848
7	7	0.963

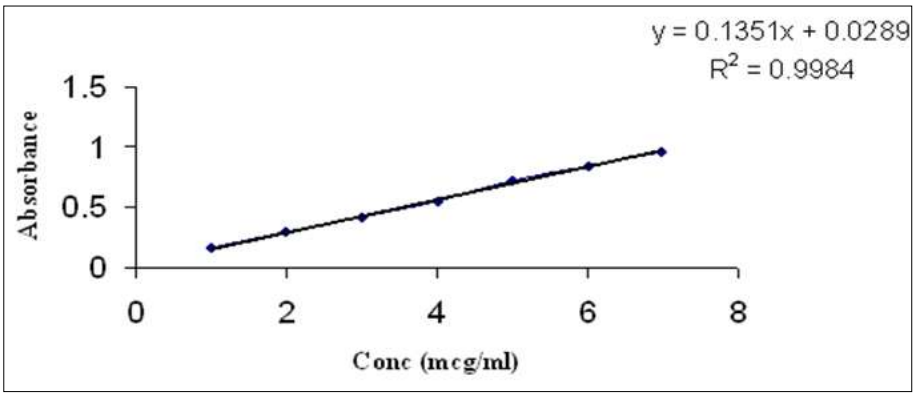


Fig 3: Calibration curve of SS in distilled water.

Table 2: Standard calibration curve of SS in pH 6.6 buffer

Sr. no.	Concentration (µg/ml)	Absorbance
1	1	0.177
2	2	0.323
3	3	0.474
4	4	0.653
5	5	0.778
6	6	0.977

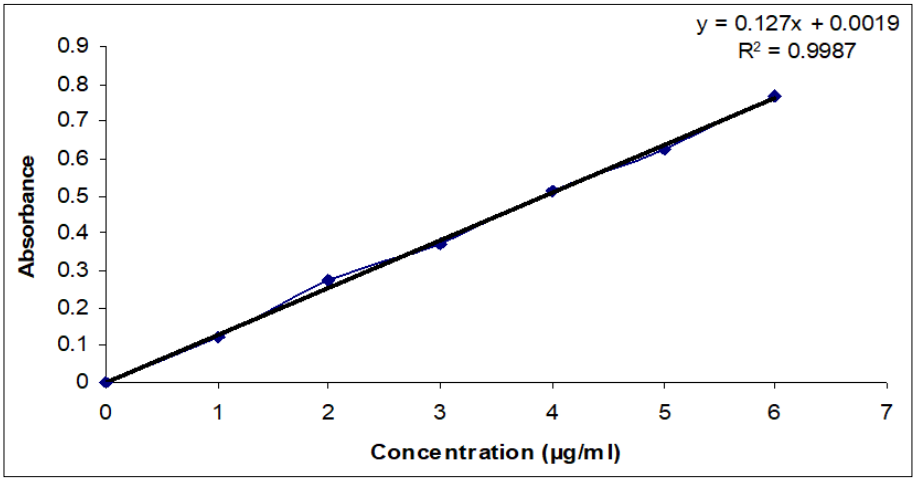


Fig 4: Calibration curve of SS in pH 6.6 buffer.

Table 3: Standard calibration curve of SS in methanol

Sr. no.	Concentration (µg/ml)	Absorbance
1	1	0.17
2	2	0.225
3	3	0.387
4	4	0.512
5	5	0.62
6	6	0.745
7	7	0.855
8	8	1.012

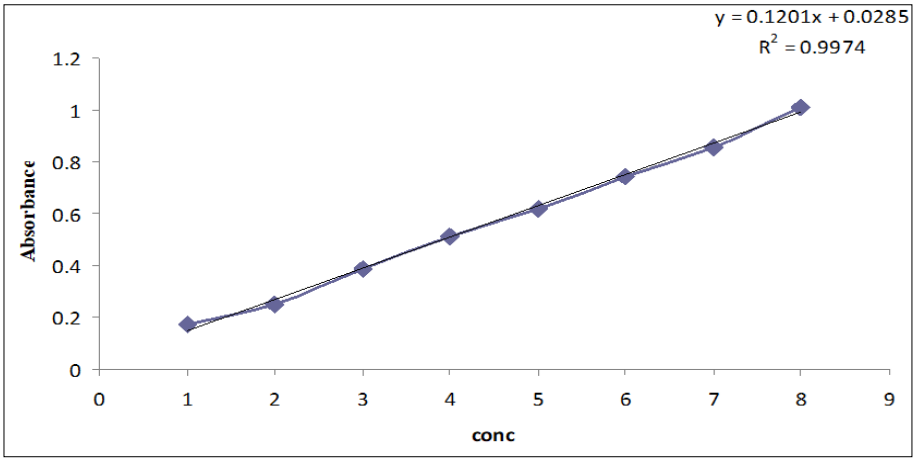


Fig 5: Calibration curve of SS in methanol.

Drug and polymer interaction study

Thin Layer Chromatography (TLC)

Drug excipients study was carried out by using TLC.

Results are shown in following table.

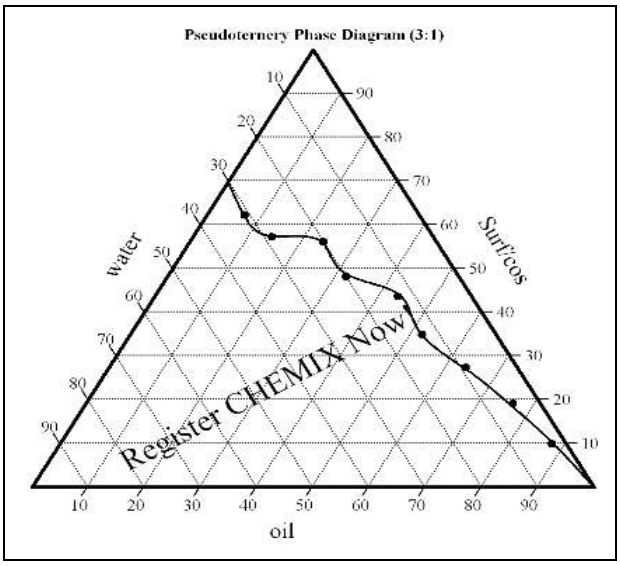
Table 4: R_f values of ingredients

Materials	R_f Value
SS	0.31
SS + Tween 80	0.33
SS + Span 80	0.30
SS+ n-butanol	0.32
SS+ IPM	0.31
SS+HPMCK4M	0.30

Standard R_f value of SS is 0.31 which was reported in literature. Results showed that R_f value of SS was 0.31 and other mixture of drug and polymers have no any major difference compare to standard R_f value of drug. So from TLC study it concludes that there was no interaction between drug and polymers.

Pseudoternary phase diagram

Phase behavior



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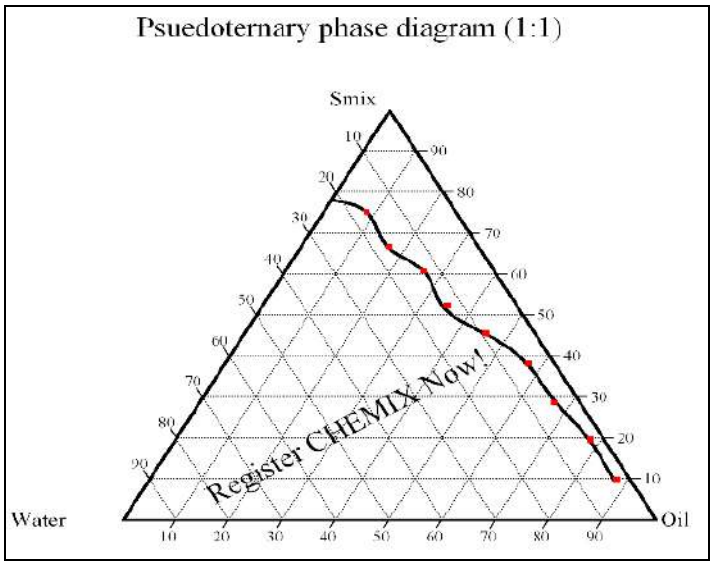

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The following figures represent the pseudoternary phase diagrams for microemulsions systems along with the ratios of surfactant and cosurfactant, as 1:1 and 3:1. Each of the vertices of triangle represents 100% of each of oil, water and surfactant and cosurfactant mixture (Smix). The change in the area of microemulsion region can be very well seen in the ternary phase diagram (fig 1 and fig 2) as the ratio of surfactant to cosurfactant was changed from 1:1 to 3:1. Render short chain alcohols useful for the preparation of microemulsions. Pseudoteranry phase diagram was plotted by using soft ware. (CHEMIX)

Identification of type microemulsion

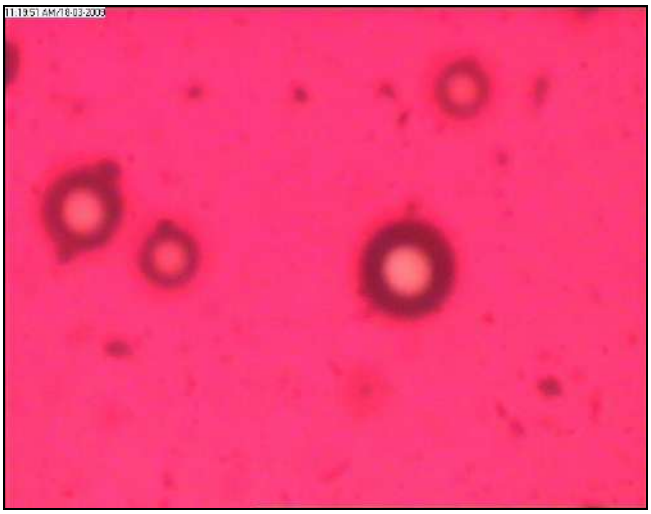

Fig 5: Photomicrograph of o/w type of microemulsion

From the image the type microemulsion was found to be o/w type. We used amaranth. which is water soluble dye. So the Background was found to be red and globule appears colorless.

Characterization of Mucoadhesive Microemulsion

Clarity

It observed visually, because microemulsions are clear and transparent

Dilutabilitys

The microemulsions formed were diluted in 1:10, and 1:100, ratios with double distilled water to check if the system shows any signs of separation.

pH

The pH of microemulsions found in the range of 4.5 to 6.5. The pH of optimized formulation MME3A was 5.3. This required for the nasal drug delivery.

Particle size

Particle size analysis was carried out by photon correlation spectroscopy with a Beckman N5 submicron particle size counter which can measure the size range from 5nm to approximately 3 µm. For size analysis approximately 0.1 ml Microemulsion is added to 10 ml double distilled water in order to obtain the optimum scattering intensity. Average particle size of optimized microemulsion (MME3A) was 38.78 nm, such particles are considered to be suitable for nasal administration.

		Diam. (nm)	% Intensity	Width (nm)
Z-Average (d.nm): 38.78	Peak 1:	71.21	100.0	69.83
PdI: 0.372	Peak 2:	0.000	0.0	0.000
Intercept: 0.947	Peak 3:	0.000	0.0	0.000
Result quality : Good				

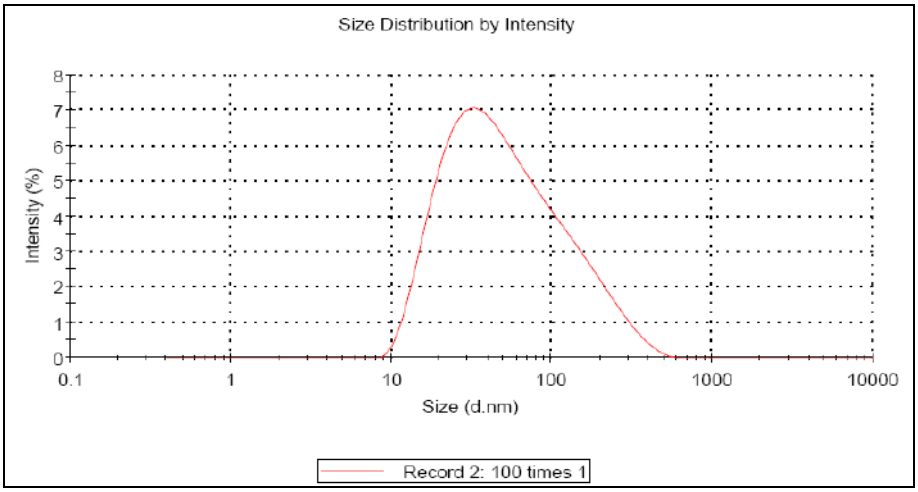

Fig 6; Particle size of MME3A

Zeta potential

Zeta potential of MME3A was -17.2 mv. The negative Zeta potential indicates that droplets of microemulsion having no charge that is system is stable. Zeta potential was determined by using Zetasizer. There was no charge on particles, so no flocculation of particles and microemulsion was stable.

Zeta Potential (mV):	-17.2				
Zeta SD (mV):	4.12		**Mean (mV)**	**Area (%)**	**Width (mV)**
Mobility (m²/Vs x10e-8):	-1.345	**Peak 1:**	-17.2	100.0	4.12
Mobility SD (m²/Vs x10e-8):	0.3233	**Peak 2:**	0.00	0.0	0.00
Wall Zeta Potential (mV):	-14.2	**Peak 3:**	0.00	0.0	0.00
Conductivity (mS/cm):	0.0366				

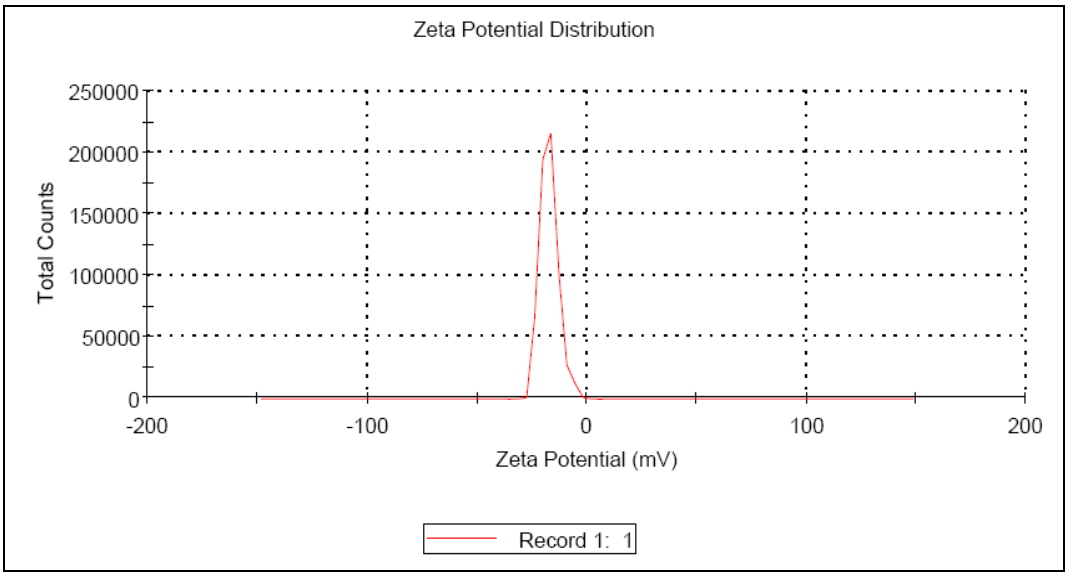

Fig 6: Zeta potential of MME3A

Viscosity

Viscosity of ME1 and ME2 (w/o) was less than ME3 and ME4 (o/w). Because the surfactant concentration in o/w was more than w/o. Surfactant used i.e. Tween 80 and Span 80 were highly viscous in nature. Viscosity of Tween 80 and Span 80 was 970-1080 cP and 425 cP respectively.

In case of w/o concentration of oil was more and viscosity of oil (IPM) was very less i.e. 5-6 cP, therefore viscosity of ME1 and ME2 was less. In case of MME3A and MME3B concentration of mucoadhsive polymer in MME3A was 0.05% and MME3B was 0.1%.

Therefore viscosity of MME3A was less than MME3B.

Table 5: Viscosity of SS loaded microemulsions

Formulations	Viscosity * (cP± SD)
ME1	130.2±0.16
ME2	147.6±0.55
ME3	202.1±0.19
ME4	191.3±0.12
MME3A	303.4±0.30
MME3B	385.2±0.18

Values expressed as Mean ± SD, n=3

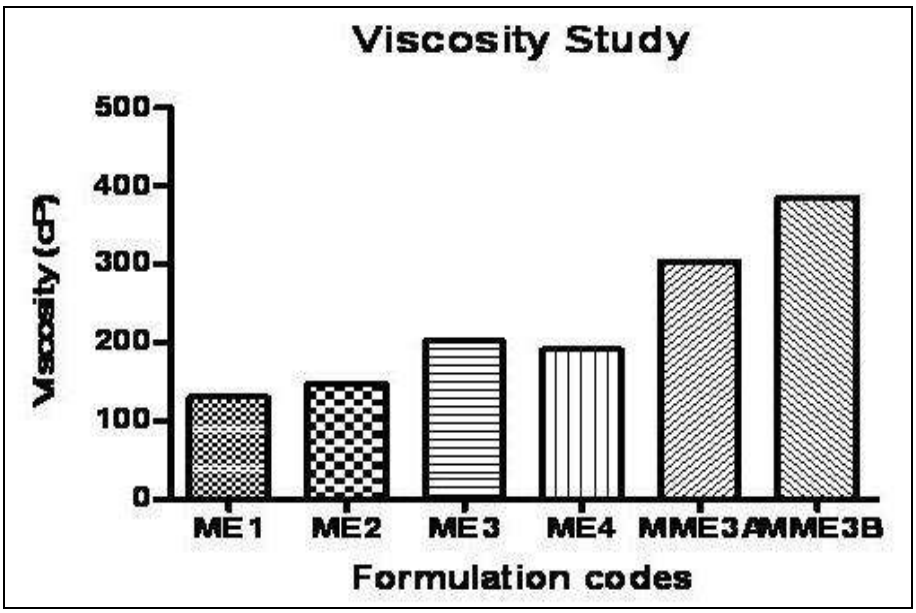

Fig 7: Graph of viscosity of microemulsions

Centrifugation

The microemulsion system was centrifuged at 3000 rpm for 15 minutes to determine whether the system shows signs of creaming or phase separation. The system was observed microscopically for appearance

Drug content of microemulsion

The drug content of formulation MME3A was 99.1%. Which was estimated by UV spectrophotometer at 228 nm.

Table 6: Percentage drug content of microemulsions

Sr. No.	Formulations	Drug Content (%)*
1	ME1	94.5
2	ME2	95.0
3	ME3	97.5
4	ME4	98.33
5	MME3A	99.1
6	MME3B	100.83

Statistical analysis

The data from different formulations were compared for statistical significance by one way analysis of variance (ANOVA). Differences were considered to be statistically significant because the P value ≤ 0.05.

***In-vitro* mucoadhesion study**

Mucoadhesion studies were carried out to ensure the adhesion of formulation to the mucosa for a prolonged period of time at the site of absorption. Results showed that, the nanoparticles adequately adhere on nasal mucosa. The ratio of the adhered nanoparticles was expressed as detachment stress in dyne/ cm^2. For all batches, the detachment stress was found to be 70-456 dyne / cm^2 Viscosity of ME1 and ME2 (w/o) was less than ME3 and ME4 (o/w). Because the surfactant concentration in o/w was more than w/o. Surfactant used i.e. Tween 80 and Span 80 were highly viscous in nature. Viscosity of Tween 80 and Span 80 was 970-1080 cP and 425 cP respectively. The detachment stress of o/w was also more because of high viscosity. In case of w/o concentration of oil was more and viscosity of oil (IPM) was very less i.e. 5-6 cP, therefore detachment stress was less. In case of MME3A and MME3B concentration of mucoadhsive polymer in MME3A was 0.05% and MME3B was 0.1.

Table 7: Detachment stress of SS loaded microemulsions

Formulations	Mucoadhesion * (dyne/cm^2 ± SD)
W/F	70.31±0.20
ME2	115.6±0.3
ME3	332.27±0.23
MME3A	346.484±0.25
MME3B	455.643±0.3

* Values expressed as Mean ± SD, n=3

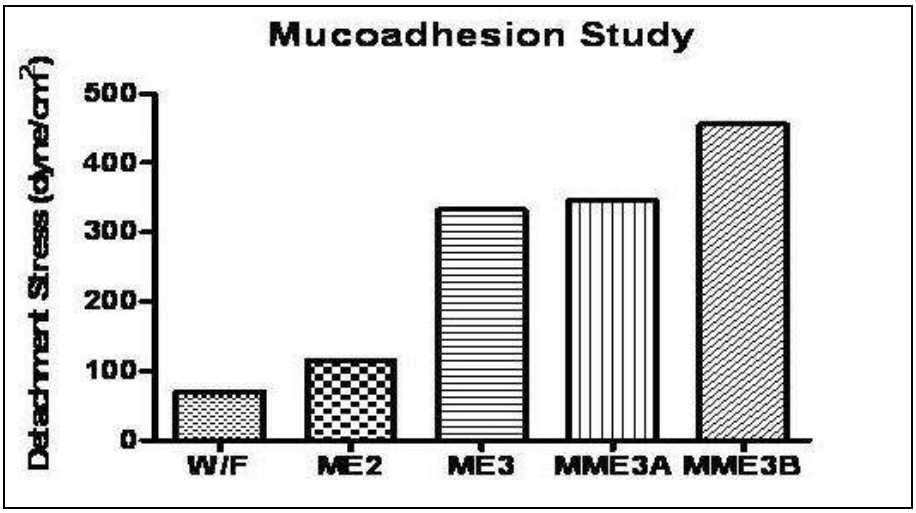

Fig 8: Graph of detachment stress of microemulsions

***In vitro* drug diffusion study**

Table 8: Drug diffusion data of microemulsions

Time (Min)	% Drug Release (Mean ± SD) *					
	ME1	ME2	ME3	ME4	MME3A	MME3B
05	3.89± 0.3	2.31±1.18	2.35±0.87	2.18±0.79	3.31±0.84	2.47±1.11
10	6.05±0.3	5.3±0.97	5.41±0.86	4.19±0.89	6.29±0.79	3.40±0.80
20	7.86±0.6	11.51±1.03	8.88±1.65	3.94±1.62	11.53±1.06	5.59±0.82
30	11.14±0.8	12.86±0.54	12.74±1.31	3.46±0.96	12.94±0.49	7.42±1.00
40	12.5±1.44	16.1±1.52	17.23±1.04	6.3±0.93	16.31±1.65	8.79±1.17
50	14.92±1.75	19.00±1.53	14.17±3.74	9.63±1.05	19.34±1.99	10.54±0.64
60	19.98± 1.19	26.18±1.09	17.00±1.67	13.46±1.95	26.43±0.93	14.33±0.98
90	25.70±2.34	31.69±1.32	20.38±1.11	17.27±1.22	38.44±1.39	20.31±1.95
120	41.53±2.49	34.18±0.83	35.06±1.45	19.89±1.39	47.51±2.16	35.63±1.26
150	57.62±1.79	37.94±1.15	47.5±3.0	41.6±0.86	56.52±0.73	44.34±1.67
180	61.09±2.00	42,93±1.63	62.66±2.91	60.83±2.48	79.48±1.98	73.29±1.58
210	82.13±2.35	71.3±2.19	82.53±1.77	81.36±2.12	90.89±1.44	78.56±0.98
240	91.45±0.87	90.04±1.68	92.10±1.61	86.61±1.39	97.74±1.00	89.31±1.2

Values expressed as Mean ± SD, n=3

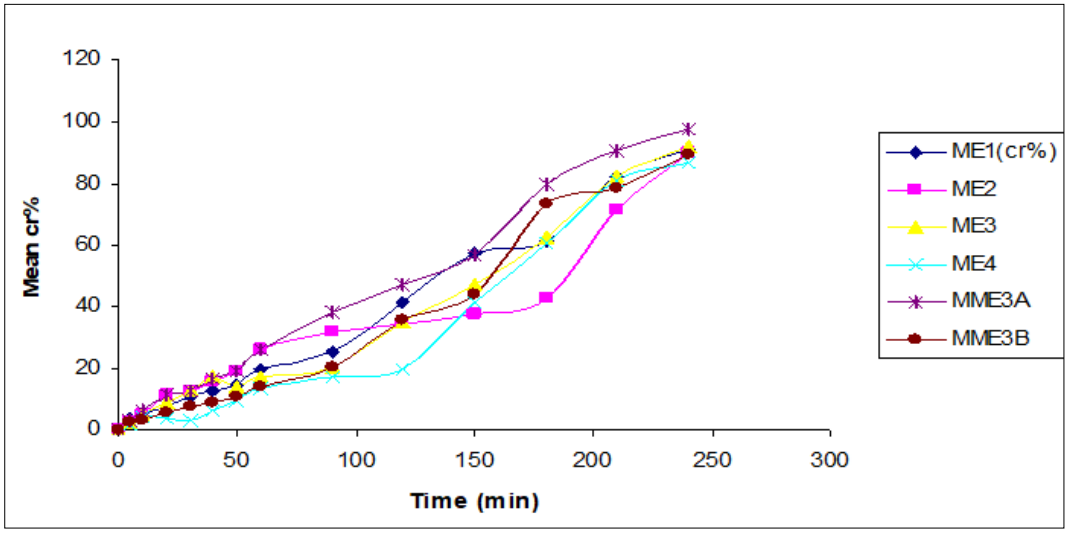

Fig 9: Release profile of SS from microemulsions.

***In-vitro* permeation study**

In vitro nasal permeability data shown in figure. The drug diffused at faster rate from microemulsion. The total percentage diffusion was much higher from the microemulsion system. After 4hrs of diffusion 97.74% of drug was diffused from microemulsion.

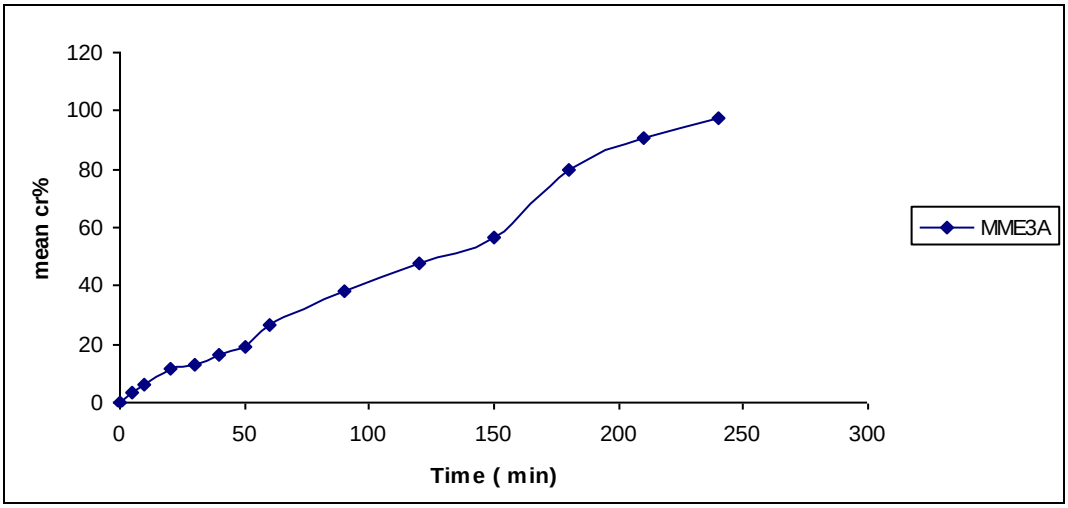

Fig 10: Ex- vivo permeation profile of SS through sheep nasal mucosa.

Histological study

It is necessary to examine histological changes in nasal mucosa caused by formulations, if it is to be considered for practical use. Histological studies shows control mucosa (normal nasal mucosa) stained with hematoxylin-eosin ("see Figure 20") and the effect of formulation on sheep nasal mucosa, 4 hours after applying the formulations ("see Figure 20a, 20b"). No change in mucosal structure was seen when treated with formulation MME3A as compared to the control

Table 9: Histopathological inference of Photomicrographs

Sr. No.	Histological findings	Formulations	
		PBS treated (A)	MME3A (B)
1	Degeneration of mucosa	-	+
2	Erosion of mucosa	-	+

No change, +: Very slight, +: Very Slight

The section of mucosa treated with formulation MME3A showed very slight degeneration of nasal epithelium along with very slight erosion. There was increased vascularity in basal membrane and superficial part of submucosa as compared with PBS-treated mucosa. There was no sign of remarkable destructive effect of formulations on the treated nasal mucosa.

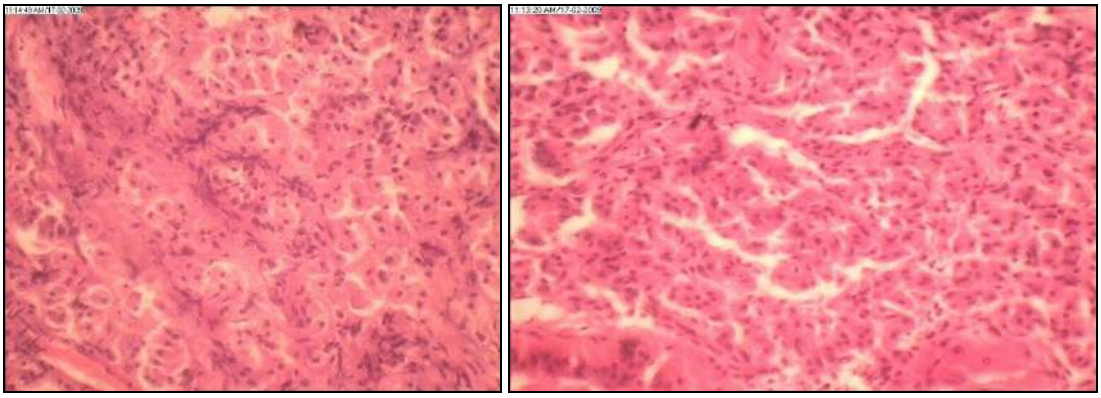

Fig 11: Microscopic image of normal nasal mucosa (control).

Microscopic image of MME3A treated nasal mucosa. Z

Stability of the microemulsions

Formulations showing optimum particle size and mucoadhesive strength was selected for stability studies. According to ICH guidelines, selected formulation (MME3A) was stored at 40^0C temperature and 75% relative humidity (RH) for a period of 3 months. Formulations were evaluated at periodical intervals of one month for particle size and microscopic appearance Evaluation parameters do not show any major difference and all are in acceptable limits.

Table 10: Evaluation parameter of stability batch after 3 months

Formulation Code	Parameters	Storage Time			
		0 month	1 month	2 month	3 month
MME3A	Particle size (nm)	37.45	38.23	39.8	38.14
	Microscopic appearance	Clear& transparent	Clear& transparent	Clear& transparent	Clear& transparent

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