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Formulation and Evaluation of Mesalamine Niosomes

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ABSTRACT

The goal of this study was to use the ether injection approach to create and characterize mesalamine-loaded niosomes. The kind and concentration of surfactant were changed to create a total of sixteen formulations using the ether injection technique. The drug content, entrapment effectiveness, loading capacity, and drug release characteristics of every formulation were assessed. Based on assessment criteria, formulation FMN9 made using the ether injection method demonstrated 96.53 percent entrapment efficiency, 97.65 percent drug content, and a particle diameter of roughly 377.8 nm. Its zeta potential value was 31.8 mV, which indicated greater stability. According to in-vitro release trials, FMN9 had the highest level of drug release out of all the formulations towards the end of 24 hours, at roughly 97.45 percent, demonstrating a sustained release pattern. The super case 2 transport mechanism was demonstrated by drug release kinetic measurements of the improved formulation (FMN9), which followed zero order release and had an R2 value of 0.997. The findings suggest that the investigated Mesylamine loaded niosome (FMN9) has the potential for prolonged drug release and may function as an exciting vehicle for Mesylamine drug delivery.

INTRODUCTION:

Drug targeting is a phenomenon in which a drug is absorbed into the body and distributed so that the majority of the drug only interacts with the target tissue at the cellular or subcellular level. To obtain a desired pharmacological response at a chosen location without undesired interactions at other sites is the goal of medication targeting [1, 2]. In cancer chemotherapy and enzyme replacement therapy, this is very crucial. Medicine delivery to receptors, organs, or any other particular area of the body where one intends to administer the drug only is known as drug targeting. The second strategy uses cellular carriers (erythrocytes and lymphocytes), macromolecules, liposomes, niosomes, microspheres, nanoparticles, antibodies, and nanoparticles to deliver the medicine to the target area [3, 4]. New drug delivery systems have been created as a result of recent developments, and they have the potential to completely change the way we take medications and provide a range of therapeutic advantages.

Any drug delivery system's objective is to quickly attain and then maintain the appropriate drug level by delivering a therapeutic dose of the medication to the right location in the body. The optimum drug delivery system directs the active ingredient entirely to the site of action and disperses the medication at a rate determined by the body's requirements during therapy. No medication delivery technology now in use can accomplish all three objectives. The targeted drug delivery system succeeds in delivering the medication to the right place, but it is unable to predictably manage the drug's release kinetics [5, 6].

When Paul Ehrlich looked into a drug delivery system that would direct medications to sick cells, he launched the age of development for targeted delivery in 1906. Immunoglobulins, serum proteins, synthetic polymers, lipid vesicles (liposomes), microspheres, erythrocytes, reverse micelles, niosomes, pharmacosomes, and other carriers were used to deliver drugs to the target organ or tissue. Few drug carriers from among the several types of carriers made it to the point in clinical trials where phospholipid vesicles shown great promise for efficient drug delivery to the site of action. The components of these carriers, known as niosomes, can be used as parts of biological membranes since they are physiologically inert and free from any antigenic, pyrogenic, or allergic responses. Drugs contained in liposomes and niosomes did not activate under physiological circumstances or have any negative side effects [7, 8].

A protein binding capacity of 20 to 30, mesalamine has a half-life of five to seven hours and is utilised as an anti-inflammatory. Mesalamine is quickly and nearly fully absorbed when

taken orally as a tablet, however less of the medicine reaches the distal small intestine and colon. Orally administered mesalamine act within the lumen of inflamed bowel and is partly absorbed into systemic circulation. niosomes can alter the metabolism of a drug; these can also prolong the circulation and half–life of a drug so that the side effects of the drug can be decreased.

MATERIALS AND METHODS:

Mesylamine was obtained as a gift sample from Vital Healthcare Pvt Ltd., Vapi. Oleic acid, Tween 80, isopropyl alcohol (IPA), and HPMC K100M were obtained from Chemdyes Corporation, Vadodara. All other chemicals used were of laboratory reagent grade.

I) UV-SPECTROSCOPY: Accurately weighed mesalamine drug (10 mg) was dissolved in 10 ml volumetric flask containing methanol. Then volume was adjusted upto the level with sufficient quantity of methanol. This gave the concentration of 1000 µg/ml. It was diluted to 100µg/ml. Further, different aliquots were prepared with the stock solution. These aliquots were analyzed spectrophometrically (Shimadzu, UV-1800, Japan). [9]

Preparation of Standard Curve: Mesalamine (10 mg) was accurately weighed and dissolved in 100 ml volumetric flask containing hydrochloric acid buffer (0.1N HCl, pH 1.2) and simulated gastric fluid (SGF, pH 6.8, pH 7.4) individually. To get a 100 µg/ml concentration in the buffer medium of pH 1.2, pH 6.8 and pH 7.4 volume was maintained upto level separately.

This stock solution was used to prepare further standard solution of the drug. From the standard stock solution, different aliquots 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8and 2.0 ml were taken from different buffer pH and volume made up to 10 ml with each buffer pH 1.2, pH 6.8and pH 7.4 individually in volumetric flask to produce2, 4, 6, 8, 10, 12, 14, 16 18 and 20 µg/ml respectively. The solutions were filtered (Whatman filter paper # 41) and absorbance was measured at 220 nm using a double beam UV-spectrophotometer (Shimadzu, UV-1800, Japan).

II) FT-IR ANALYSIS: FTIR spectrum investigation was carried out to confirm the compatibility of pure drug mesalamine with different excipients which was used for preparation of optimized mesalamine loaded mucoadhesive beads. The KBr discs of pure mesalamine, polymers (span 80, span 60, tween 80, tween 60) and powdered mesalamine

brads were prepared and scanned in an FTIR spectrophotometer (Shimadzu IR Affinity, Japan) at 4000-500 cm-1 wave number. [10, 11, 12]

III) PREPARATION OF NIOSOME: The weighed amount of non-ionic surfactant (Span 80, Tween 80, Tween 60 and Span 60) was taken along with cholesterol and dissolved in 6 mL of diethyl ether which was mixed with 2 mL of methanol previously containing weighed quantity of drug. Then the resulting solution was slowly injected using micro syringe at the rate of 1 mL/min into 10 mL 7.4 pH phosphate buffer. Then, the solution was stirred continuously with magnetic stirrer and the temperature was maintained at 60-65 °C. The difference in temperature between the phases caused vaporization, resulting in the formation of niosomes [13, 14].

Table 1: Formulation of niosomes by ether injection method

Formulation	Drug	Cholesterol	Surfactant	Drug: Cholesterol: Surfactant
FMN1	100 mg	100 mg	Span 60 (50 mg)	1:1:0.5
FMN2	100 mg	100 mg	Span 60 (100 mg)	1:1:1
FMN3	100 mg	100 mg	Span 60 (200 mg)	1:1:2
FMN4	100 mg	100 mg	Span 60 (300 mg)	1:1:3
FMN5	100 mg	100 mg	Tween 60 (50 mg)	1:1:0.5
FMN6	100 mg	100 mg	Tween 60 (100 mg)	1:1:1
FMN7	100 mg	100 mg	Tween 60 (200 mg)	1:1:2
FMN8	100 mg	100 mg	Tween 60 (300 mg)	1:1:3
FMN9	100 mg	100 mg	Span 80 (50 mg)	1:1:0.5
FMN10	100 mg	100 mg	Span 80 (100 mg)	1:1:1
FMN11	100 mg	100 mg	Span 80 (200 mg)	1:1:2
FMN12	100 mg	100 mg	Span 80 (300 mg)	1:1:3
FMN13	100 mg	100 mg	Tween 60 (50 mg)	1:1:0.5
FMN14	100 mg	100 mg	Tween 60 (100 mg)	1:1:1
FMN15	100 mg	100 mg	Tween 60 (200 mg)	1:1:2
FMN16	100 mg	100 mg	Tween 60 (300 mg)	1:1:3

IV) EVALUATION AND CHARACTERIZATION OF NIOSOME

i) Microscopic Evaluation of niosomes: Morphology was determined for all the sixteen formulations using projection microscope with 10×magnification. The photo micrographic picture of the preparation was obtained from the microscope by using a digital SLR camera [15, 16].

ii) Drug Entrapment efficiency of niosomes: The niosomal suspension in the dialysis tube was further lysed with propane-1-ol and estimated the entrapped drug by UV spectrophotometric method at 274nm. The entrapment efficiency was calculated using following equation.

$$\% \text{ Entrapment efficiency} = \frac{(\text{Weight of initial drug} - \text{Weight of free drug})}{\text{Weight of initial drug}} \times 100$$

iii) Drug Content: Niosomes preparation equivalent to 100mg of mesalamine was taken into a standard vol flask. Then they were lysed with100ml of propane-1-ol by shaking. Then 1ml of this was subsequently diluted with phosphate buffer (pH 7.4). The absorbance was measured at 274nm and calculated drug content from the calibration curve.

iv) Mean Particle Size and Polydispersibility Index: Mean particle sizes of all empty niosomes formulation and drug loaded niosomal formulations were determined by using optical microscopy. The results of mesalamine loaded noisome were shown in results and discussion part.[17]

v) Zeta potential (ζ): A dynamic light scattering (DLS) zeta potential analyzer (Zetasizer nano series, Malvern Instruments, United Kingdom) measured the zeta potential of niosomes in six repeated intervals by monitoring the count rate of about 3,000 kcps of particles. In short, 10-20 µl of niosome suspension and 3 ml of distilled water were mixed together. About 1 ml of the diluted niosome solution was then filled into the cuvette in DLS zeta potential analyzer.

vi) Differential Scanning Calorimeter (DSC) Studies: The thermal behavior of mesalamine was studied in Perkin Elmer, Pyris Diamond DSC, USA at a heating rate of 10°C /min. Accurately weight sample (5mg) was sealed in an aluminium pan and measurement was performed at a heating range of 50- 370°C. Before analysis, equipment was standardized with zinc and indium. [18]

Vii) *In-vitro* Drug Release Studies of Niosomes: Membrane diffusion was used to study the in-vitro drug release analyses of the niosomal formulation. The cellophane membrane was used to create the in-vitro diffusion cell, which is a semi-permeable membrane. A test tube with both ends open, a temperature-controlled magnetic stirrer, and a beaker make up the diffusion cell. A treated cellophane membrane was used to seal one end of the test tube as a semi-permeable membrane, leaving the other end accessible for the addition of the niosomal formulation. The diffusion medium was 100 cc of freshly made phosphate buffer saline pH 7.4 adjusted at 37 °C 0.5 °C. The open end of the test tube was used to place the 5 ml niosomal formulation on the cellophane membrane within the diffusion cell. Freshly made 100 ml of phosphate buffer with a pH of 7.4 was utilised as the diffusion medium. It was positioned within the beaker so that the lower surface of the cellophane membrane made contact with the buffer. Using a magnetic stirrer, the buffer solution temperature was maintained at 37 °C 0.5 °C during the research period. To keep the volume constant, aliquots (5 ml) of the medium were periodically taken out and replaced with fresh pH 7.4 buffer diffusion media (sink condition). At 254 nm, the samples were analysed spectroscopically to determine the amount of mesalamine. [19, 20]

RESULTS AND DISCUSSION

Determination of Absorbance Maxima (λmax): The mesalamine dissolved in methanol and diluted to give solution of 10 µg/ml which was spectrophotometrically analyzed at UV range. Solution gives peak at 241 nm as shown in tabletre 1. Thus, this wavelength was selected as λmax for the further study.

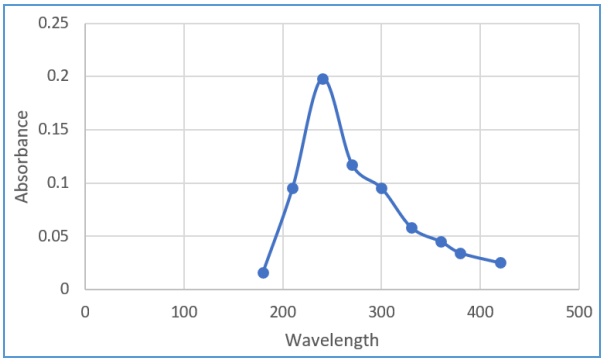

Figure 1: UV Spectra of Mesylamine in methanol

Preparation of Standard Curve: The stock solution of mesalamine was diluted with either hydrochloric acid buffer (0.1N HCl, pH 1.2), SGF pH 6.8, pH 7.4 to get a concentration

range of 2 to 20µg/ml of mesalamine. The absorbance was measured at 241 nm and calibration curve of mesalamine was plotted between absorbance and concentration for the3 different buffers solutions was shown in Figure 2, 3 and 4. The data were subjected to linear regression and the correlation coefficient was found to be 0.9999 for pH 1.2, 0.995 for pH 6.8 and 0.9943 for pH 7.4. Thus, the value of correlation coefficient indicates that the concentration range of 2 to 20 µg/ml of mesalamine obeys beer's lambert law.

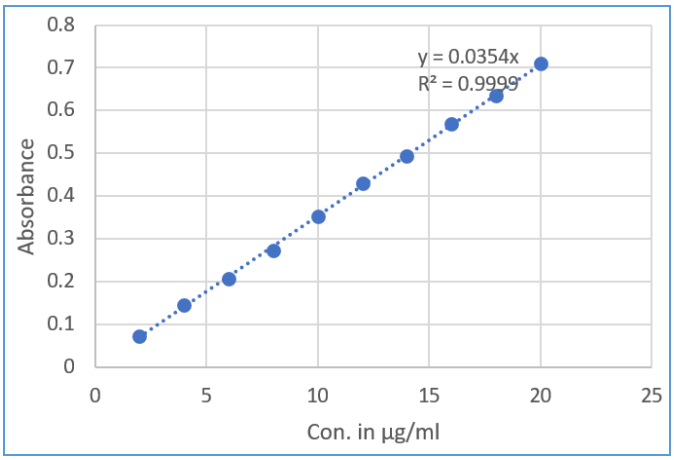

Figure 2: Standard Plot of Mesylamine in 0.1N HCl at 241 nm

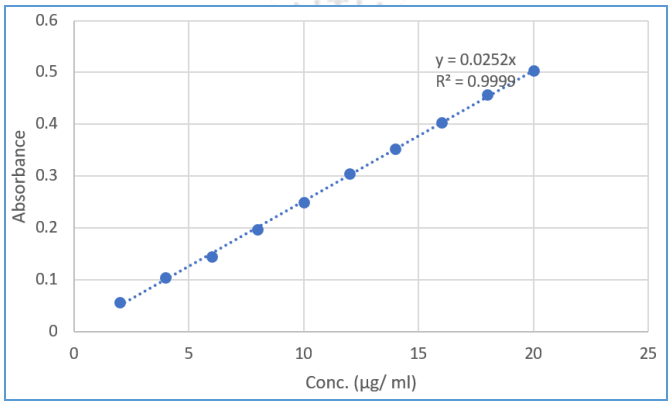

Figure 3: Standard plot in SGF pH 6.8

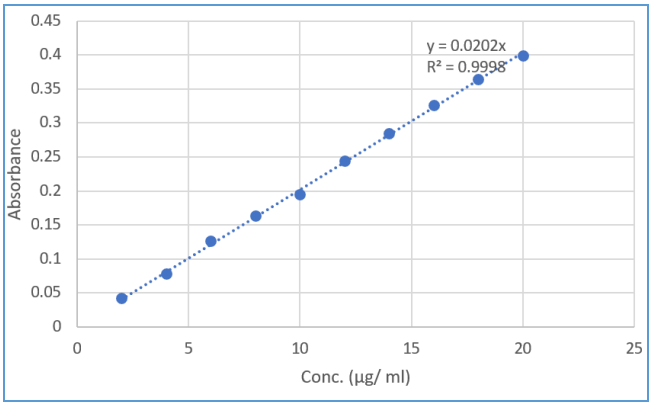

Figure 4: Standard Plot of Mesylaminein SGF pH 7.4

Compatibility Study by FTIR:

FTIR Spectra of Drug: The IR spectrum of the sample obtained was performed according to the material and methods referred to in the procedure and complied with the reference norm IR spectrum of Mesalamine. Test drug IR spectra exhibit identical characteristic peaks. The IR spectrum of the sample drug is shown in Figure 5.

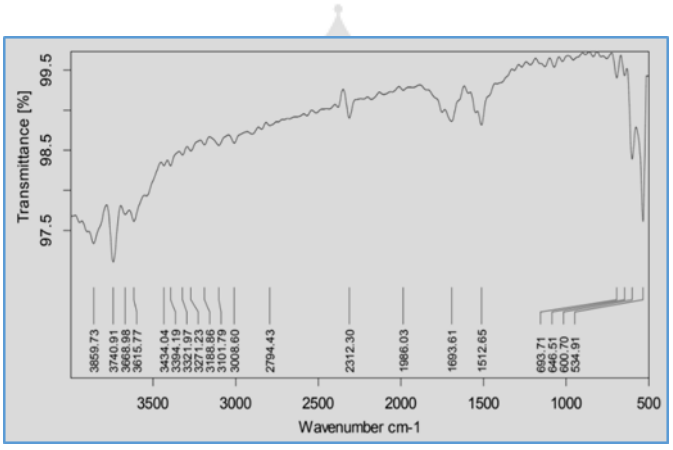

Figure 5: IR spectra analysis of Mesylamine (Sample)

FTIR Spectra of Drug with Surfactant: To evaluate the compatibility of the drugs and excipients, FTIR spectra have been registered. The research was conducted according to the technique referred to in the material and methods in the section. The FTIR Spectra are represented in figure 6.

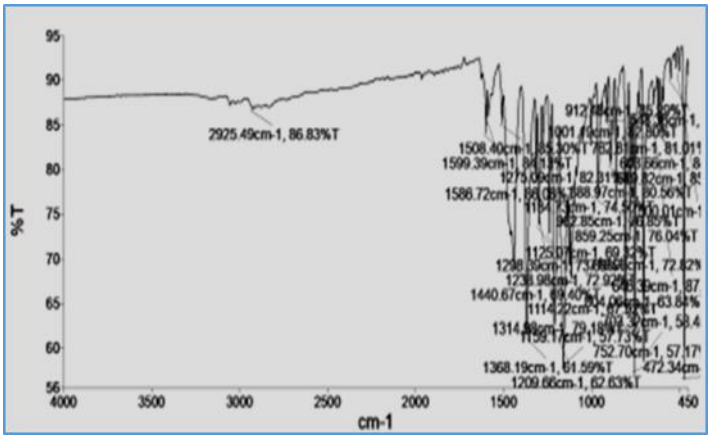

Figure 6: FT-IR spectra of Mesylamine with surfactant

FTIR spectra of the Mesylamine, showed characteristic C-N, C-O, C-H, C=O(ester) stretching bands at 1025.20 cm^{-1}, 1728.04 cm^{-1}, 2046.77 cm^{-1}, 3076.50 cm^{-1}, 3644.49cm^{-1}, 3734.39cm^{-1} respectively. The compatibility of drugs with physical mixture of drug (s) & span 60, cholesterol. The characteristic C = O stretching band was observed at 1728.04 cm^{-1} in the FTIR spectra of Mesylamine, which is in line with the recorded values. The findings showed no chemical activity and improvements occurred in the drug's FTIR spectra and different surfactants alone or in combination with both excipients exhibiting drug compatibility.

FORMULATION DEVELOPMENT: As mentioned in the procedure earlier, niosomes were prepared using the Ether Injection Method. Sixteen formulations of mesylamine niosomes were prepared using surfactants (Span 60, 80 and tween 60, 80) along with a constant value of cholesterol (100 mg) and a constant drug mesylamine (10 mg), as shown in Table 1.

CHARACTERIZATION AND EVALUATION OF PREPARED NIOSOME:

Morphological Study: The Optimized Formulations Optical Microscopic Imaging (FMN3, FMN6, FMN9 and FMN12) showed that most vesicles were spherical in shape, as shown in Figure 7 and figure 8. Compared to the other niosomal formulations, niosomes prepared using Span 60 were bigger in scale. This can be because high drug entrapment vesicles are wide and the mean size of niosomes increases proportionally with the decrease in surfactant value of Hydrophilic-Lyophilic Balance (HLB).

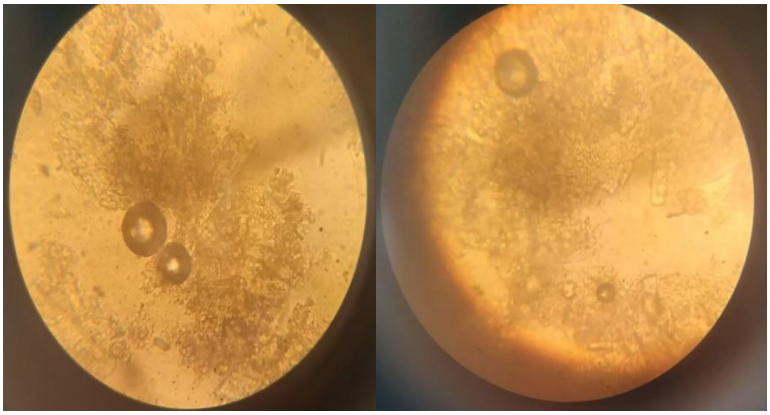

Figure 7: Morphology of formulation FMN3(Left) and FMN6 (Right)

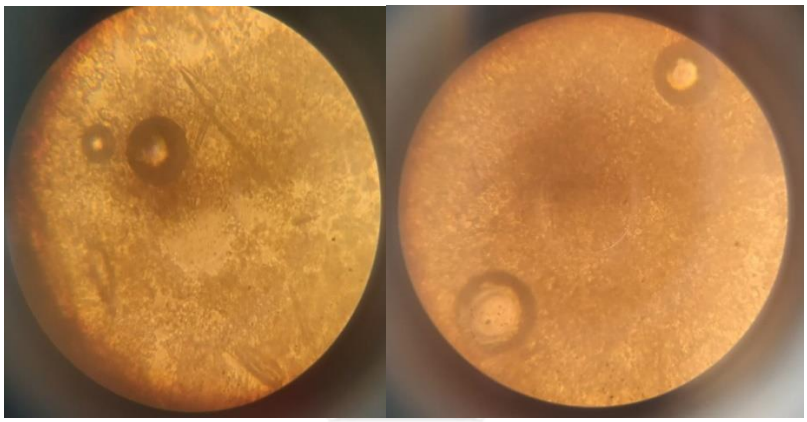

Figure 8: Morphology of formulation FMN9 (Left) and FMN12 (Right)

Drug Content Analysis: The mean percent drug content in microemulsion formulations (FMN-1 to FMN-16) was found to be respectively, (84.43 ± 0.13, 75.65± 0.13, 96.81± 0.35, 87.21± 0.12, 91.54± 0.15, 95.98± 0.34, 92.21± 0.21, 85.64± 0.20, 97.65± 0.22, 87.76± 0.19, 91.76± 0.21, 96.99± 0.12, 87.41± 0.15, 90.32± 0.08, 93.73± 0.32, 92.72± 0.55). FMN-9 was exhibited 97.65± 0.22% higher drug content than other formulations in figure 9.

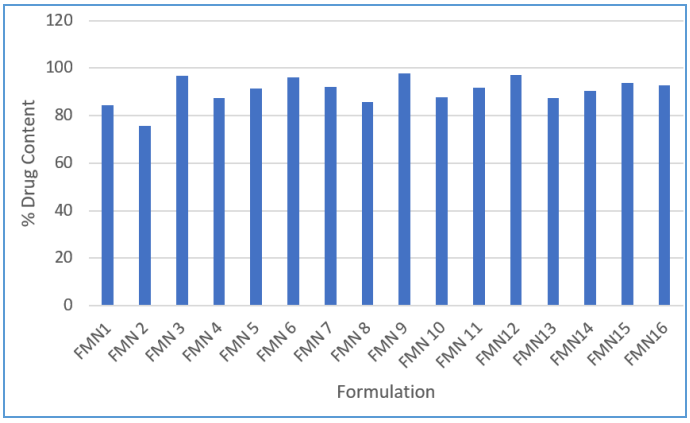

Figure 9: % Drug content of niosomal formulation

Entrapment Efficiency: The trapping efficacy of the niosomal formulations was calculated by the process of centrifugation. The entrapment efficiency is influenced by factors such as the HLB value and the surfactant's phase transition temperature. The efficiency of entrapment is improved by low HLB and high transition temperature. FMN-9 demonstrated maximum entrapment efficiency among all the formulations compared to other formulations, as shown in Figure 3.14. This was due to its low HLB value and the high temperature of the transition. In the bilayer membranes, cholesterol has the potential to reinforce the leaking room. Increased cholesterol content begins to disturb the normal bilayer structure above a certain level, thus reducing drug capture.

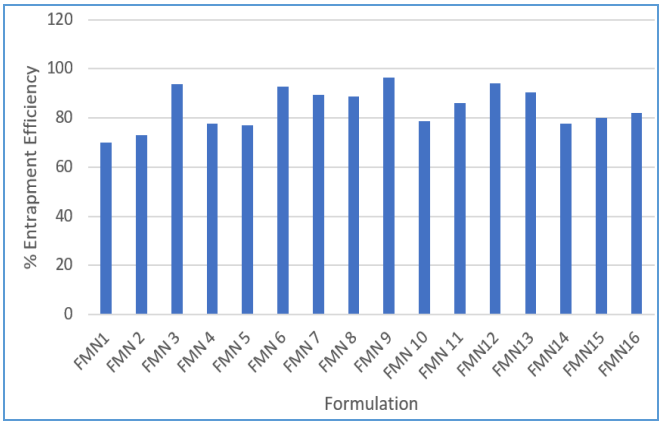

Figure 10: % Entrapment Efficiency of Niosomal formulation

Mean Particle size and Poly dispersity Index: The mean vesicular diameter of the optimized formulation was evaluated by using Malvern instrument. The mean vesicular diameter of the optimized formulation FMN9 containing the 1: 1:3 ratio of drug: Cholesterol: surfactant concentration was showing the minimum mean vesicular diameter of 432.5 nm.

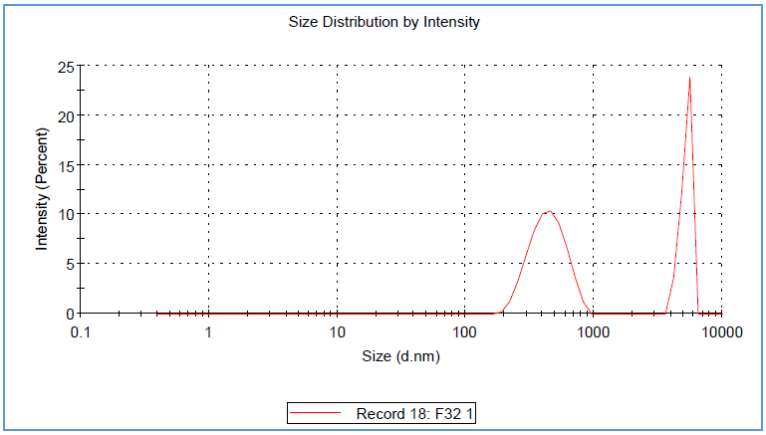

Figure 11: Particle size distribution of formulation FMN9

Zeta potential: The optimized formulation was characterized for zeta potential value in order to reveal the stability of the formulation. The zeta potential value for the optimized formulation was found to be −31.8mV. The zeta potential of the optimized formulationFMN9 containing the 1: 1: 3 ratio of drug: Cholesterol: Span80concentration was showing the highest zeta potential of−31.8 mV. A higher zeta potential was an indicator of a stable colloidal system.

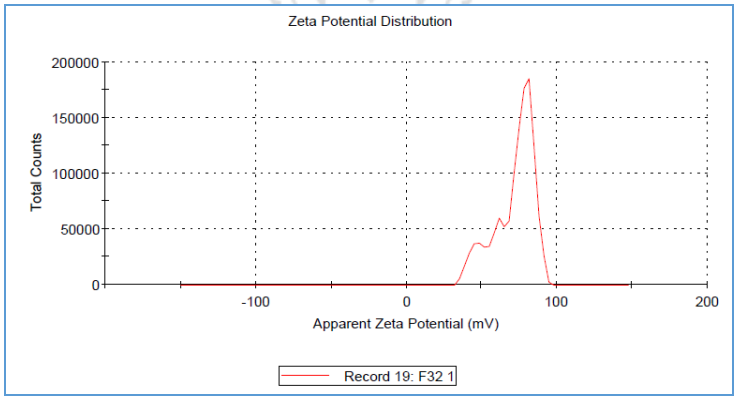

Figure 12: Zeta potential of Formulation FMN9

***In vitro* Drug Release of Niosomes:** The *in-vitro* release of all sixteen niosomal formulations produced was carried out using the method of diffusion. The studies showed that the drug release rate depends on the percentage of the efficiency of drug trapping. Formulation (FMN9), i.e. equimolar ratio of cholesterol and surfactant (Drug/ Cholesterol /Span 80 / 1:1:3) among all sixteen established formulations, showed maximum trapping efficiency and sustained drug release of 81.34% in 12 hours. Hence, the order of drug release was found to be Span 80 > tween 80 > Span 60 > tween 60. The *in vitro* release profile of all developed formulations of niosomes of Mesalymine as shown in the Fig 13-16.

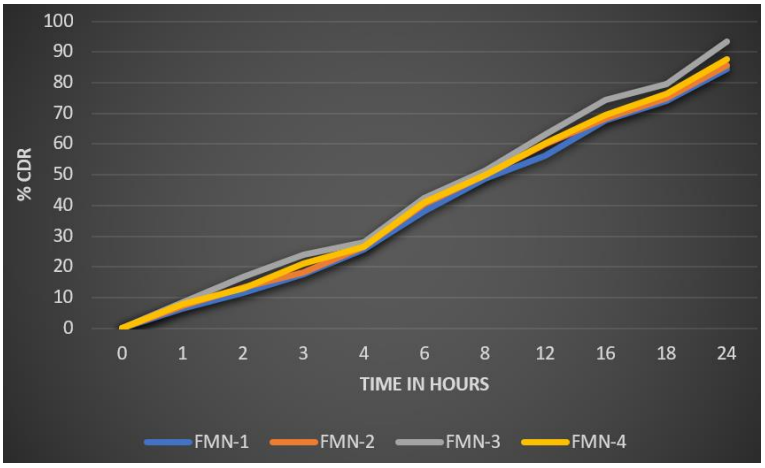

Figure 13: Cumulative drug release of niosomes of Mesalymine (FMN1-FMN4)

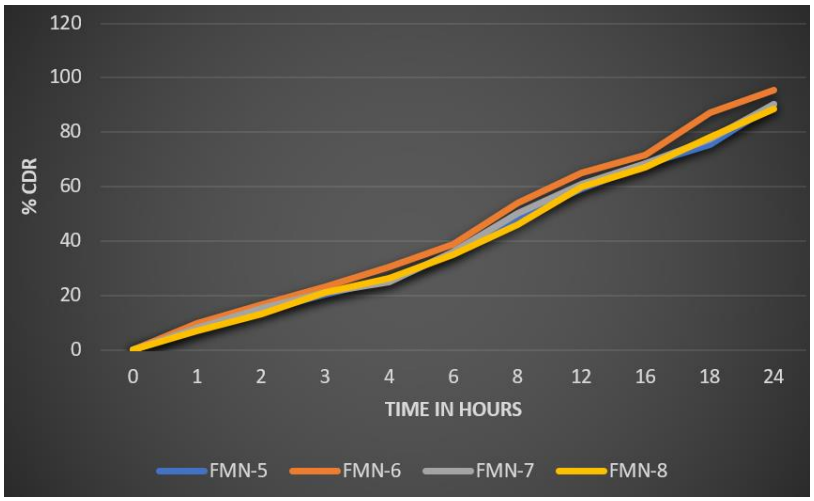

Figure 14: Cumulative drug release of niosomes of Mesalymine (FMN5-FMN8)

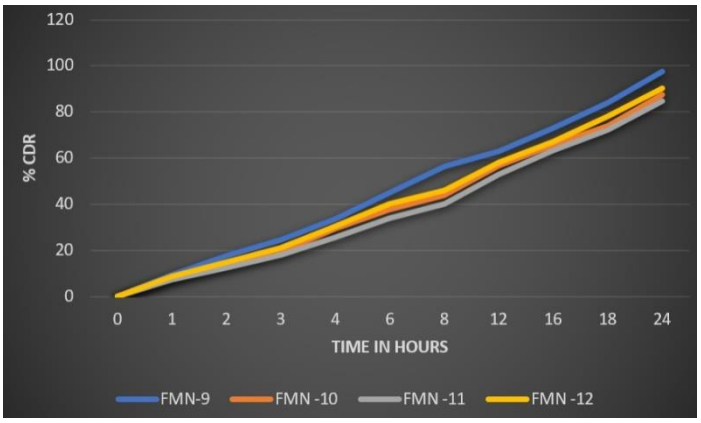

Figure 15: Cumulative drug release of niosomes of Mesalymine (FMN9-FMN12)

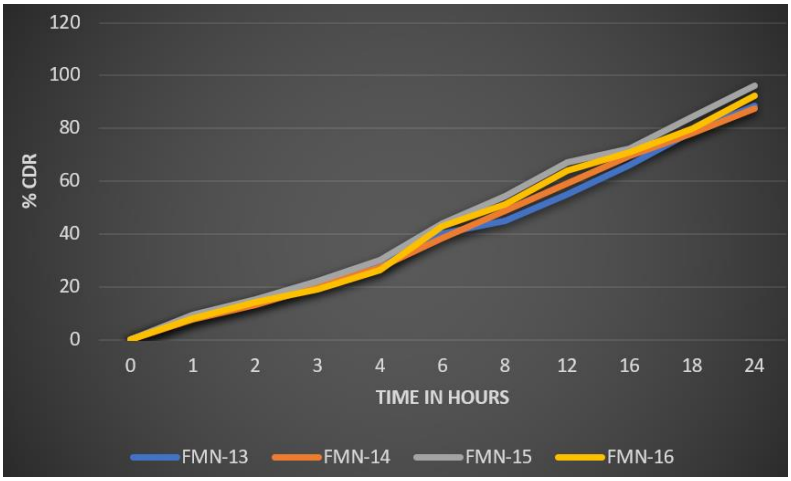

Figure 16: Cumulative drug release of niosomes of Mesalymine (FMN1-FMN4)

In vitro release kinetics: In vitro release kinetics data was sown in Table 2. The results shown that formulation FMN3, Span 60 with cholesterol follows zero-order kinetics. Calculation of Higuchi's correlation coefficient confirms that drug release was proportional to the square root of time indicating that drug release from niosomes was diffusion controlled. The n value from the Korsmeyer-Peppas model for release Mesylamine from niosomal formulation was 0.66 which confirms the Non-Fickian type diffusion.

Table 2: In-vitro drug release kinetics of FMN9 formulation

Formulation	Higuchi R^2	Korsmeyer-Peppas		Zero order		First order		Release Mechanism
FMN9	0.997	0.998	0.66	0.976	8.32	0.765	0.162	Non Fickian

STBILITY STUDIES: Storage under refrigerated condition showed greater stability with 94.85% of drug content at the end of three months, whereas storage under room temperature at 40 °C ± 2 °C / R-H 70 % ± 5% showed drug content of 95.45%, 94.67%, and 86.87% at the end of three months.

Table 3: Stability Studies

Temperature	Amount of drug retained % after months			
	Initial	**I**	**II**	**III**
Refrigeration (4 ± 1 °C)	100	97.42	96.65	95.45
Room Temperature	100	96.97	95.49	94.67
40 ± °C RH-70± 5%	100	88.98	87.67	86.87

CONCLUSION:

Mesalamine is an amino salicylic acid derivative and intestinal anti-inflammatory used to treat ulcerative colitis. Additionally, the terminal elimination half-life is 15 hours. Based on assessment criteria, formulation FMN9 made using the ether injection method demonstrated 96.53 percent entrapment efficiency, 97.65 percent drug content, and a particle diameter of roughly 377.8 nm. Its zeta potential value was 31.8 mV, which indicated greater stability. According to in-vitro release experiments, the formulation with the highest quantity of medication released relative to the others displayed a sustained release pattern. The improved formulation FMN9's drug release kinetic tests indicated super case II transport mechanism and zero order release with an R2 value of 0.997. Hence, the present study concluded that the formulation FMN9 shows better activity than the Mesylamine plain.

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