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RESEARCH ARTICLE

Preparation and Evaluation of Nanostructured Mesalamine Niosomes with Different Concentrations of Non-Ionic Surfactant

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ABSTRACT

Introduction: Vesicular drug delivery system is currently the most cutting-edge area of pharmaceutical research. In terms of stability, niosomes are often superior to other vesicular systems like liposomes. Niosomes are a good method for delivering drugs to a particular site of action. **Objective:** The preparation and evaluation of Mesalamine niosomal dispersion using ether injection and thin film hydration techniques were the goals of this work. The niosomes formulation has tremendous promise and might be used in the future for its clinical implications for a variety of administration methods, making it a more effective formulation for treating diverse illnesses. Mesalamine has potent anti-inflammatory properties. **Materials and Methods:** In this study, non-ionic surfactants and cholesterol were used at various concentrations to produce niosomes containing dispersion utilizing the thin film hydration technique and the ether injection method. The created formulations were assessed using optical microscopy, zeta potential, *in-vitro* drug release, and other methods. **Results:** The ratio 2:1 of span 60 and cholesterol showed better results of the thin film hydration method. Hence, it was optimized as the final vesicle formulation. The results of the Fourier transform infra-red investigation showed that mesalamine did not interact with any of the excipients. As compared to the ether injection method niosomes forming by thin film hydration technique show the best and most promising results. **Conclusion**: The present study concluded that the thin film hydration technique was an optimized technique for the preparation of mesalamine niosomes than the ether injection method.

Keywords: Anti-inflammatory activity, ether injection method, mesalamine, niosomes, span 60, thin film hydration

INTRODUCTION

Over time, the study of pharmaceutical research has grown steadily and is now essential to maintaining our health and preventing disease. In recent decades, the vesicular delivery of drugs has gained great attention. Vesicular drug delivery systems are used largely for medication targeting by concentrating the drug's activity in the diseased or inflammatory tissue, area, or target organ through the use of different pharmaceutical carriers.[1] By regulating and maintaining the activity, the vesicular system-designed medication has given fresh life to previously used medications, enhancing their therapeutic efficacies.[2] Because of their unique advantages, niosomes, which are vesicular nanocarriers, have attracted a lot of attention as prospective drug delivery methods in recent years. They have amphiphilic molecule-based lamellar (bilayer) structures encased in an aqueous compartment.

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Surfactants are amphiphilic molecules with hydrophobic and hydrophilic groups that can self-assemble into a variety of geometries, such as micelles or a planar lamellar bilayer.[3] Niosomes are a better choice for industrial manufacture because they do not need particular conditions like low temperature or an inert atmosphere during preparation and storage.[4] Niosomal drugs help minimize a drug's toxicity but also improve a drug's bioavailability.[5,6] Chemical stability, biodegradability, biocompatibility, cheap cost of manufacture, ease of storage and handling, and low toxicity are the main goals in the development of niosomal systems.[7-10] As niosomes are osmotically active and stable, they may improve the payload's stability.[11,12]

Cholesterol is crucial for the formation of niosomes because it provides the vesicle its stiffness, but when it is given in excess, it also affects the vesicle's fluidity and the drug's permeability and penetration.[13] By raising the formulation's viscosity and hydrodynamic diameter, cholesterol prevents drug leakage from niosomal vesicles.[14-18] Non-ionic surfactants are preferable to anionic, amphoteric, or cationic surfactants in terms of stability, compatibility, and safety. Many different non-ionic surfactant types, such as span, tween, and Brij are being used.[19-21]

Mesalamine is an intestinal anti-inflammatory drug, an aminosalicylic acid derivative.[22,23] It acts by reducing inflammation of the colon topically by inhibiting the production of IL-1 and TNF-α, impeding the lipoxygenase pathway, scavenging free radicals and oxidants, and inhibiting NF-κB. Mesalamine goes through extensive first-pass metabolism.[24] Mesalamine formulations were initially developed to prevent Sulphasalazine's side effects while retaining efficacy.[25] According to the Biopharmaceutics Classification System, mesalamine has listed as a class IV medication and is usually prescribed to treat inflammation brought on by colon-related disorders like Crohn's disease and ulcerative colitis.[26] Both the oral and rectal routes are used to give the medication mesalamine. Patients with ulcerative colitis can be effectively put into and kept in remission by taking oral mesalamine compounds. Through local topical activity at the irritated mucosa, the drug has therapeutic effects.[27,28] The purpose of the current study is to describe niosomes containing mesalamine and phospholipids as vesicle-shaping agents by different two methods and to comment on in detail the comparison of niosomal dispersions.

MATERIALS AND METHODS

Materials

All the commercially available excipients, solvents such as span 60, tween 80, cholesterol, chloroform, diethyl ether, methanol, sodium chloride, and Potassium phosphate (Monobasic) were purchased from Research-Lab Fine Chem Industries, Mumbai. Drug Mesalamine was a gift sample by CTX Lifesciences.

Instrumentation

Ultraviolet-Visible (UV-Vis) Spectrophotometry is done by Shimadzu 1800 Software: UV-Probe. The Fourier transform infra-red (FTIR) Spectra were carried out on a shimadzu IR Affinity-ISCE. Transmission electron microscopy (TEM) is done by Carl Zeiss's model supra-5.

UV-Vis Spectrophotometry

Preparation of standard calibration curve and standard plot of Mesalamine in 0.1 N HCl:

Developing a mesalamine standard stock solution (in 0.1 N HCl) Mesalamine 10 mg was precisely measured and added to a volumetric flask with a 100 mL capacity. To make 100 g/mL of standard stock solution, it was dissolved and diluted with solvent until the desired strength was attained. Spectrophotometric scanning and determination of λmax of the drug were done. From the standard stock solution, 1 mL was pipetted out and diluted up to 10 mL using 0.1 N HCl and it was scanned between wavelengths 200–400 nm. For the Plotting of the calibration curve of Mesalamine from the standard stock solution, a series of dilutions were made by pipetting out 0.2, 0.4,

0.6, 0.8,1.0, and 1 mL of standard stock solution and diluting up to 10 mL by 0.1 N HCl to obtain 2, 4, 6, 8, and 10 ppm solution, respectively. Absorbance was measured at 232 nm by using UV-Vis Spectrophotometer.

Preparation of standard calibration curve and standard plot of Mesalamine in PBS 7.4:

Developing a mesalamine standard stock solution (in 7.4 PBS) Mesalamine 10 mg was precisely measured and added to a volumetric flask with a 100 mL capacity. To make 100 g/mL of standard stock solution, it was dissolved and diluted with solvent until the desired strength was attained. Spectrophotometric scanning and determination of λmax of the drug were done.

From the standard stock solution, 1 mL was pipetted out and diluted up to 10 mL using PBS 7.4 and it was scanned between wavelengths 200–400 nm. For the Plotting of the calibration curve of Mesalamine from the standard stock solution, a series of dilutions were made by pipetting out 0.2, 0.4, 0.6, 0.8, 1.0, and 1 mL of standard stock solution and diluting up to 10 mL by 7.4 PBS to obtain 2, 4, 6, 8, and 10 ppm solution, respectively. Absorbance was measured at 331 nm by using UV-Vis Spectrophotometer.

FT-IR Spectroscopy

The IR spectrum of pure drug and excipients along with a mixture of drug and excipients were recorded by FTIR and the compatibility of drug and excipients was checked by comparing the spectra.

Optimization of Niosomes

Before formulating a drug, optimization techniques are used in the pharmaceutical field. This is the initial phase in the process of using independent variables on process factors that may have an impact on the preparation and various niosomes characteristics.[29] The process of choosing the best variable from among various sets of variables is mathematical programming. During the manufacturing process, optimization was done to determine the drug's entrapment effectiveness and the niosome' particle size.[30]

Formulation of Niosomal Dispersion by Two Methods

By thin film hydration method

Surfactant, cholesterol, drug, and charge inducers are the vesicle-forming components and are solubilized in a round bottom flask having a volatile organic solvent.[31,32] The formation of a thin, dry film containing dissolved components is achieved by evaporating the organic solvent at room temperature using a Rotavap evaporator. Formations of niosomes are achieved by hydration and gentle agitation of the dried thin film with an aqueous phase.[33]

By ether injection method

Surfactant, cholesterol, the drug is solubilized in diethyl ether and slowly injected into an aqueous phase at 60°C using a 14-gauge needle, leading to the evaporation of the ether and forming single layered vesicles [Table 1].[34-37] Listed formulation of mesalamine niosomes by thin film hydration method and ether injection method.

Characterization of Niosomes

Visual appearance

A visual examination was carried out to establish the presence of niosomal dispersion. The use of clear containers for the niosomal dispersion allowed for the examination of turbidity, flocculation, and sedimentation.

Optical microscopy

Niosome suspension was diluted and dropped onto a glass slide. A cover slip was placed over

Table 1: Formulations of mesalamine niosomal dispersion by thin film hydration method and ether injection method

Formulation code	Drug (mg)	Surfactant	Surfactant: Cholesterol ratio (mg)
F1	100	Span 60	0.5:1
F2	100	Span 60	1:1
F3	100	Span 60	2:1
F4	100	Span 60	3:1
F5	100	Tween 80	0.5:1
F6	100	Tween 80	1:1
F7	100	Tween 80	2:1
F8	100	Tween 80	3:1

Different concentrations of surfactant: cholesterol of Mesalamine Niosomal formulation batches

the diluted niosome suspension, and an ordinary optical microscope was used to evaluate the average vesicle size and shape using a precalibrated ocular eyepiece micrometer.[38]

Vesicle morphology

TEM was used to examine the development and surface morphology of the niosomal vesicular structure at a scale of 50–200 nm.[19,39] Niosome diameter can also be determined via TEM.[40]

Entrapment efficiency

The unentrapped drug in the niosome formulation can be separated by centrifugation, gel filtration, or dialysis. The centrifugation procedure involves rotating a specific volume of niosomal dispersion at a specific speed for a specific period.[41] After that, the Eppendorf tubes should no longer contain the supernatant liquid. Re-centrifuge the settled product after re-suspending it, wash it twice to eliminate any remaining unentrapped drug with no void volume, and determine the total amount of free drug available by measuring absorbance at a specific wavelength using UV spectroscopy.[42]

Zeta potential

We need to perform zeta potential analysis to determine the colloidal characteristics of the formulation we created.[43] The dispersion of diluted Niosomes was measured using a zeta potential analyzer based on electrophoretic light scattering and the laser Doppler velocimetry method.[44,45] The charge on vesicles at 25°C and their mean zeta Potential values with standard errors of measurement were obtained directly from the measurements.

Differential scanning calorimeter (DSC) studies

The thermal behavior of mesalamine was investigated in a Perkin Elmer Pyres Diamond DSC in the United States at a heating rate of 10°C/min.[46] A precisely weighed sample (5 mg) was sealed in an aluminum pan and measured at a temperature range of 50–370°C. Equipment was standardized with zinc and indium before analysis.[47]

In-vitro drug release

In-vitro drug release studies are an alternative title to *in-vitro* diffusion studies. Diffusion cells and diffusion membranes are used in this investigation. The Franz diffusion cell is the most often utilized for the study.[48] A diffusion membrane was immersed in PBS has a pH of 7.4 for the course of the study, following the traditional diffusion study methods and the absorbance was measured by a UV spectrophotometer PBS 7.4 at 331 nm.

Stability

The stability of niosomes can be assessed by measuring mean vesicle size, size distribution, and entrapment efficiency during several months of storage at various temperatures.[49] The stability of niosomes is determined by UV spectroscopy.

RESULTS AND DISCUSSION

UV-Vis spectrum analysis of mesalamine showed the highest peak at 232 nm in [Figure 1], which is considered the maximum absorbance (λmax) for mesalamine in 0.1 N HCl. The highest peak at 331 nm observed in PBS pH 7.4 is given in [Figure 2]. Hence, this wavelength was selected for the calibration curve of mesalamine given in [Figures 3 and 4]. The concentration range of 2–10 ppm of mesalamine in 0.1 N HCl and PBS 7.4 was selected for the calibration curve. The

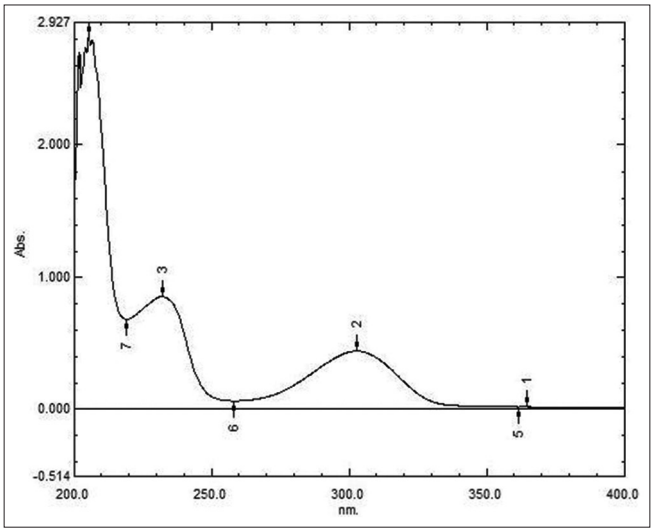

Figure 1: UV absorption spectrum of Mesalamine in 0.1 N HCl

value of R^2 was found to be 0.9995 in 0.1 N HCl and 0.9997 in PBS 7.4, indicating the relationship between drug concentration and absorbance was linear in the selected range.

The IR spectrum of pure drug and excipients along with the mixture of drug and excipients were recorded by FTIR of all the samples is represented in [Figure 5] along with spectrum peaks. All the characteristic peaks were found in the sample. The FTIR study concluded there was no interaction between Mesalamine and any of the excipients.

Entrapment efficiency was calculated by 8 formulations of both the methods given in [Table 2]. F3 formulation (2:1) using surfactant span 60 of thin film hydration method showed maximal entrapment efficiency as 88.2% and in Ether injection method is about 83.13%. The greater alkyl chain length of vesicles in span 60 makes their risen entrapment efficiency expected.

To observe the formation of vesicles, the manufactured vesicles were examined at a magnification of ×100. Some of the variations of the vesicles were seen throughout the investigation. [Figures 6 and 7] showed the photomicrographs of niosomes by both methods of the F3 formulation batch. Entrapment efficiency was obtained higher

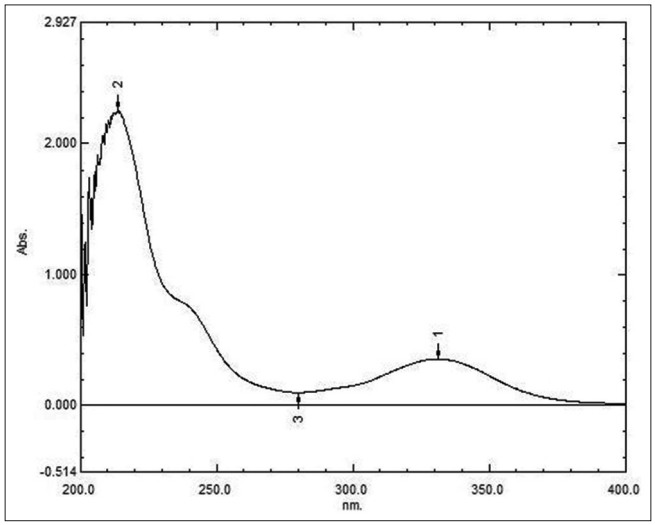

Figure 2: UV absorption spectrum of Mesalamine in PBS pH 7.4

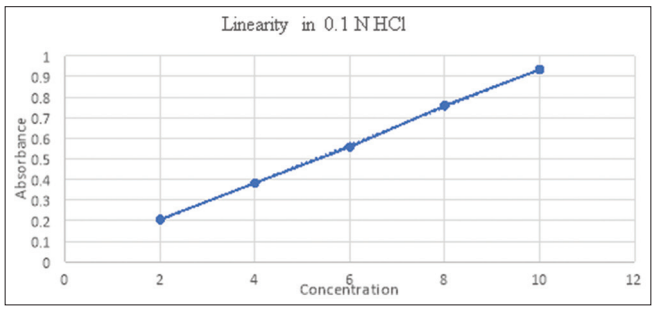

Figure 3: Calibration curve of mesalamine in 0.1 N HCl

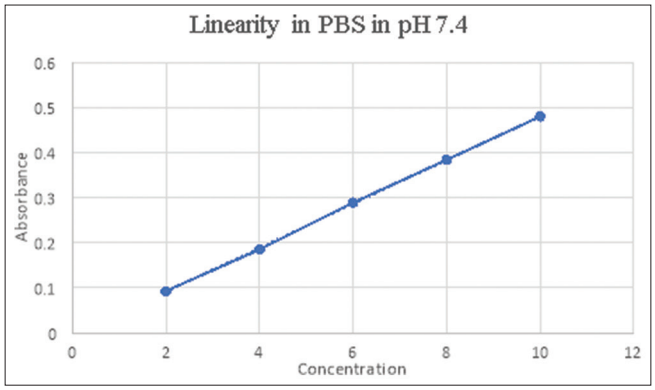

Figure 4: Calibration curve of mesalamine in PBS pH 7.4

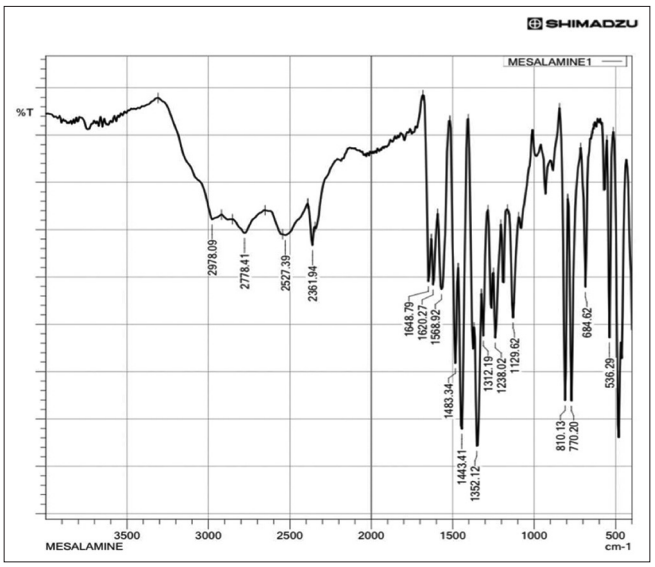

Figure 5: IR spectra of mesalamine drug and excipients

Table 2: Entrapment efficiencies of niosomal formulation

S. No	Formulation code	Entrapment efficiency (%) of the thin film hydration method	Entrapment efficiency (%) of the ether injection method
1	F1	75.55	69.85
2	F2	81.45	78.89
3	F3	88.2	83.13
4	F4	67.72	71.29
5	F5	76.64	70.11
6	F6	73.83	68.7
7	F7	67.72	63.54
8	F8	59.47	58.2

Entrapment Efficiency of mesalamine dispersion of different batches by thin film hydration method and ether injection method

in the F3 formulation batch due to this reason F3 batch becomes an optimized batch.

TEM images of the F3 formulation of both the dispersion show the formation of niosomal vesicles. The size of niosomes in the F3 batch of both the formulation was found to be nearly 100 nm which is in the good range. [Figure 8] showed that the niosomes prepared by ether injection method vesicles are overlapping to each other and also, they have poor vesicle morphology. Based on [Figure 9], the thin film hydration method showed more optimized results than the ether injection method.

Zeta potential provides knowledge about sample stability, expedites stability testing, lowers testing costs, and, shortens testing time. The Zeta potential of all formulations of both methods was determined by using Zeta-sizer. Among all formulations, the value of zeta potential of F3 formulation of niosomal dispersion by thin film hydration technique was found to be -37.8 mV which has good stability. The vesicle size, distribution, and zeta potential of the optimized formulation (F3) were determined by a third-party lab. The mean vesicular diameter of the optimized formulation F3 (thin film hydration method) containing the 2:1 ratio of surfactant (span 60): cholesterol concentration was showing the minimum mean vesicular diameter of 332.3 nm. Niosomal formulations with drugs added displayed broad transitions, which are prevalent in lipid mixtures and indicate good interactions among all the materials that make up the bilayers of niosomes. [Figure 10] showed that disappearance of Mesalamine's melting endotherm and a shift in the endotherms of the niosomes' surfactant bilayers on the DSC thermogram of loaded niosomes point to a possible interaction between Mesalamine and the bilayer components and could justify the

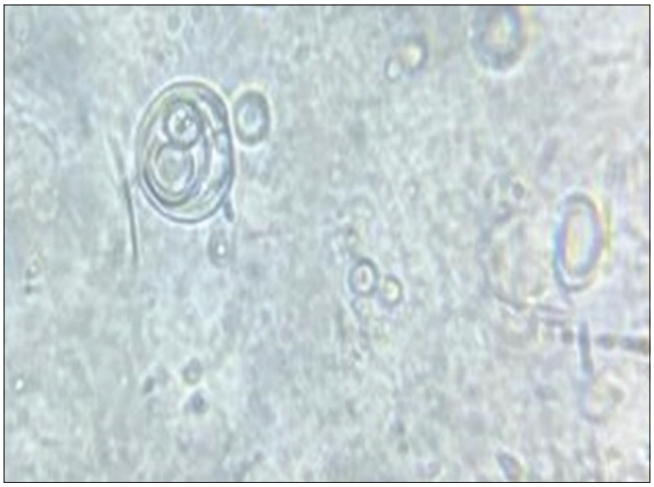

Figure 6: Photomicrograph of mesalamine niosomes (F3) by thin film hydration method

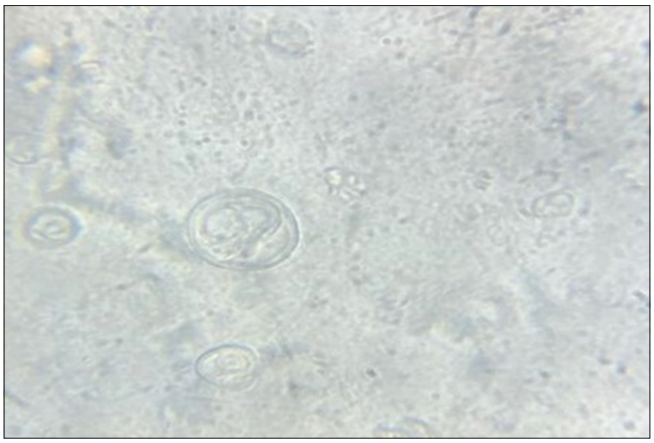

Figure 7: Photomicrograph of mesalamine niosomes (F3) by ether injection method

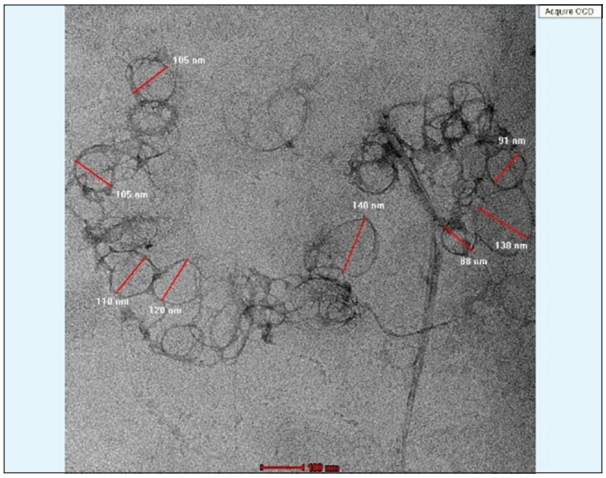

Figure 8: Transmission electron microscopy of mesalamine niosome (F3) by ether injection method

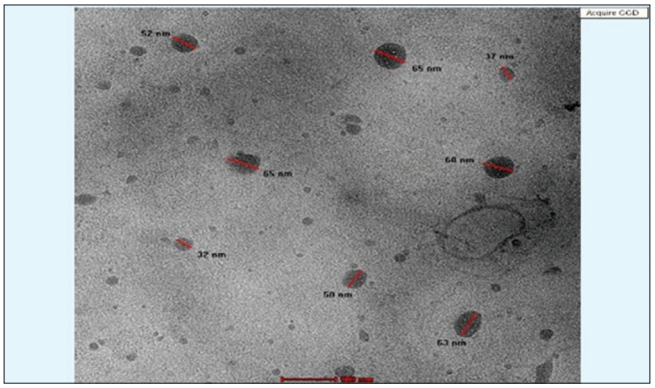

Figure 9: Transmission electron microscopy of mesalamine niosome (F3) by thin film hydration method

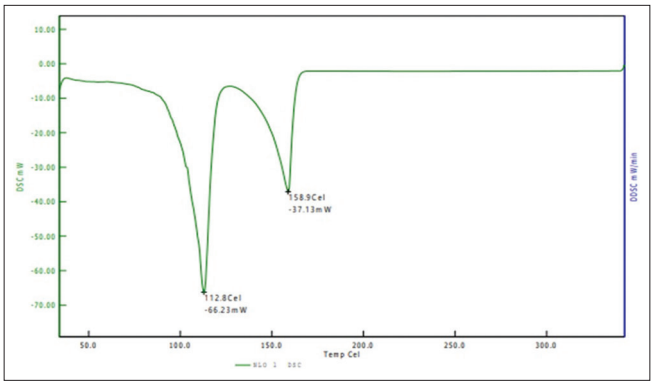

Figure 10: Differential scanning calorimetry of mesalamine dispersion of F3 batch by thin film hydration method

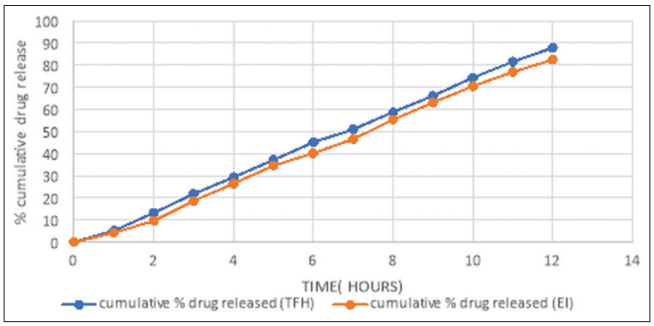

Figure 11: *In-vitro* drug release of mesalamine niosomal dispersion by both the methods

improved entrapment of Mesalamine drug in the optimized formulation.

Diffusion was used to carry out the *in-vitro* release of the F3 batch of both niosomal dispersions shown in [Figure 11]. The results of the studies demonstrated that the drug release rate is influenced by the percentage of drug trapping efficiency. In 12 h, F3-TFH demonstrated maximum trapping effectiveness and sustained release of 87.77%. It was discovered that the thin film hydration method had a greater order of drug release than the ether injection method. The *in-vitro* release data were merged into many releases kinetic models to assess the drug's release mechanism from the Niosomal dispersion of both methods. Excellent R^2 values are obtained in zero-order kinetics for both the F3-TFH and F3-EI batches listed in Table 3. As a result, zero-order kinetics establishes the niosomal dispersion of mesalamine.

The stability study of the niosomal dispersion was performed as per ICH guidelines. Freshly prepared niosomes dispersion was divided into groups and kept at specified storage conditions as per ICH guidelines. Samples were withdrawn periodically and tested for various evaluation parameters.

Table 3: R^2 values the mesalamine niosomal formulations from the drug release kinetic models

Kinetic models	F3-TFH	F3-EI
Zero order model	0.9993	0.998
First order model	0.9478	0.928
Korsmeyer-Peppas model	0.9245	0.8956
Hixson-Crowell model	0.9704	0.9763
Higuchi model	0.9204	0.9084

F3 formulation of thin film hydration method and ether injection method used for different drug release kinetic models

Table 4: Stability study of mesalamine niosomal dispersion

Formulation	F3-TFH (optimized batch)			
Storage condition	40°C±2°C/75% RH±5% RH			
Time interval (days)	0	30	60	90
In-vitro drug release (%)	87.77	86.63	86.40	86.16
Storage condition	Refrigeration (4±1°C)			
Time interval (days)	0	30	60	90
In-vitro drug release (%)	87.77	87.72	87.71	87.70

Refrigeration of mesalamine dispersion shows good stability. Stability study of mesalamine niosomal dispersion listed in Table 4.

Based on the comparative evaluation of both methods by various evaluation parameters such as entrapment efficiency, vesicle morphology, zeta potential, *in-vitro* drug release, etc., it was concluded that the thin film hydration technique was an optimized method for the preparation of mesalamine niosomes.

CONCLUSION

Anti-inflammatory diseases are treated with the drug mesalamine. Niosomes are non-ionic surfactant-based vesicles that are primarily generated by cholesterol and non-ionic surfactant incorporation as an excipient that may help in drug absorption. Thin film hydration and ether injection are two different methods used to generate mesalamine niosomal dispersion. Thin film hydration method prepared mesalamine niosomes shows promising results. Mesalamine niosome formulations have tremendous potential and will have clinical implications in the future.

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