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NIOSOMAL FORMULATION WITH ENHANCED ORAL BIOAVAILABILITY OF DICLOFENAC SODIUM

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ABSTRACT

The present research deals with niosomal suspension are formulated with diclofenac sodium. Niosome is a non-ionic surfactant-based vesicle. Niosomes have more penetrating capability then the previous preparations of emulsions. Niosomes are used to maintain drugs from any concentrations at target sites for a longer period of time (sustain effect) & even increase the bioavailability of the drug. The main aim of this study was to formulate niosomal suspension containing diclofenac sodium multilamellar vesicle (MLVs). Diclofenac sodium was encapsulated into niosomes through the film hydration method & different excipients like cholesterol, span-60 were used. When they were formulated as Niosomes it showed a sustained effect when evaluated in vitro. The different evaluation studies like particle size determination, vesicular entrapment, drug release profile, SEM studies and FTIR spectrum studies were done in the research & these tests were used as parameters to determine the optimized formulation and even the sustain release effect of the system.

INTRODUCTION:

Drug delivery systems are the means that carry drug to the desired parts of the body. They are liposomes like vesicles formed from the hydrated mixtures of cholesterol, charge inducing substance, and nonionic surfactant such as monoalkyl or dialkyl polyoxyethylene ether. Basically, these vesicles do not form impulsively. Thermodynamically stable vesicles form only in the presence of proper mixture of surfactants and charge inducing agents. Niosomes may be unilamellar or multilamellar depending on the method used to prepare them. The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle while the hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle while the hydrophobic drugs are embedded within the bilayer itself. The application of niosomal technology is widely varied and can be used to treat a number of diseases. One of the most useful aspects of niosomes is their ability to target vaccines and drugs to the reticulo-endothelial system. The reticulo-endothelial system (RES) preferentially takes up niosomal vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins, which mark the niosomes for clearance while delivering the cargo to the antigen presenting cells. Localization of drugs encapsulated in niosomes is utilized to treat tumors known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infection of the liver like leishmaniasis. Niosomes can also be utilized for targeting drugs to organs other than RES.

In this project, we have used diclofenac sodium. The behavior of niosomes in vivo is strongly depends on vesicles size, lipid composition, and lipid dose. In the absence of cholesterol, liposomes usually leak substantially when introduced intravenously. Diclofenac is used to relieve pain, swelling (inflammation), and joint stiffness caused by arthritis. Reducing these symptoms helps you do more of your normal daily activities. This medication is known as a nonsteroidal anti-inflammatory drug (NSAID). For diseases where diclofenac is used for a chronic period time, there is a lot of drug intake as because the plasma t1/2 of diclofenac is 1 to 2 hr, where approximately 65% is excreted in the urine and 35% in the bile as conjugates of unchanged diclofenac plus metabolites.

In the current research we have formulated the niosomes with diclofenac sodium with the help of thin film hydration techniques and different excipients like cholesterol, span-60 7 suitable solvent system were used & they were evaluated with different in-vivo evaluation studies like particle size determination, vesicular entrapment efficiency, SEM studies, drug release profile of the different formulation & FTIR spectrum studies of the formulations were performed. The aim of the current study is to determine optimized formulation and even the sustained release effect of the delivery system were determined by using the evaluation parameter results.

MATERIALS AND METHODS

Materials: The material like diclofenac sodium, cholesterol & span-60 were purchased from M.H Enterprise and all other chemicals were of analytical grade

Methods:

Formulation of niosomes:

The multilamellar vesicles containing diclofenac sodium was prepared by using thin film hydration technique. Initially, the cholesterol 150 mg, surfactant 50mg (span 60) & 50mg drug (other formulation was mentioned in figure 6) was dissolved in a little amount of chloroform (about 2-3 ml) and placed in a sonicator to form a homogenous solution. Meanwhile, diclofenac sodium was dissolved in ethyl alcohol (about 2-3ml) separately and placed in a sonicator for complete solubility of the drug. Later on the two mixture were mixed together again placed in a sonicator to form a homogenous clear solution. The organic solvents were slowly evaporated using rotary evaporator at 60°. This will form a very thin film of dry lipids on the inner surface of the round bottom flask. This layer was re-hydtrated with phosphate buffer saline (PBS) pH 7.4 up on continuous gentle shaking by hand, results in swelling of the surfactant layer. The dispersion was maintained for 2 hr at room temperature to allow the niosomes to form vesicles which entrap the diclofenac sodium as seen in table 1.

Separation of free drug:

The prepared MLV diclofenac sodium niosomes was separated from unentrapped diclofenac sodium ultracentrifugation at 6000 rpm for 1 hr using a centrifuge at ***2***°C the isolated particles were washed twice each with 10 ml phosphate buffer saline, and re-centrifuged again for 1 hr.

Evaluation of niosomes:

Niosomes formulation, after their formulation and processing for a specified purpose and characterized to ensure their predictable in-vitro performances There are several examples demonstrating the importance of proper selection of niosomes structure to optimize therapeutic effect. The characterization parameters for the purpose of evaluation could be classified as physical, chemical & biological categories. Physical charecterisation evaluates various parameters including size, shape, surface featurs, and drug release profile.

Determination of entrapment efficiency:

The amount of entrapped diclofenac sodium was determined by lysis of the vesicles with absolute ethanol. A 0.1 ml sample of niosomes was mixed with 5 ml of absolute ethanol and covered well with para-film to prevent evaporation. The solution then sonicated for 1m min in a sonicator to obtain a clear solution. The concentration of diclofenac sodium in absolute ethanol was determined spectrophotometrically at 277nm using UV spectrophotometer. Entrapment efficiency mentioned in table 2.

Table 1: Formulation table

Code	Drug: Cholesterol: Surfactant	Drug	Cholesterol	Surfactant
F1	1:1:1	50	50	50
F2	1:1.5:1	50	75	50
F3	1:2:1	50	100	50
F4	1:2.5:1	50	150	50

Table 2: Entrapment efficiency

Formulation code	Entrapment efficiency %
F1	79.0%
F2	74.0%
F3	68.0%
F4	52.0%

Figure 1: SEM images of optimized formulation

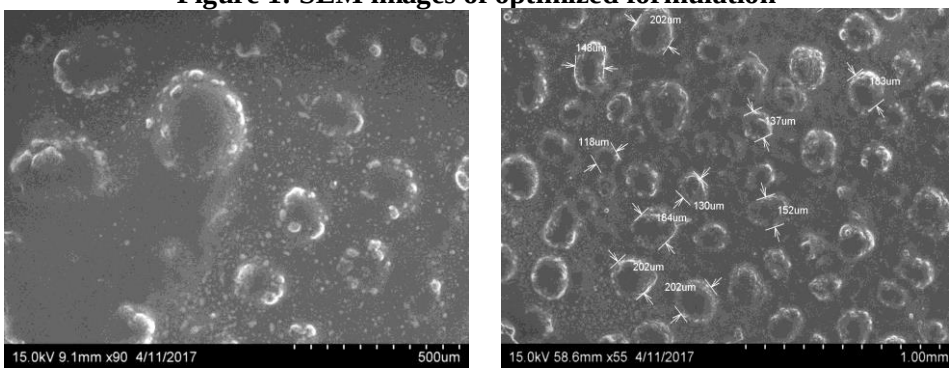


Figure 2: Microscopic images of Niosomes

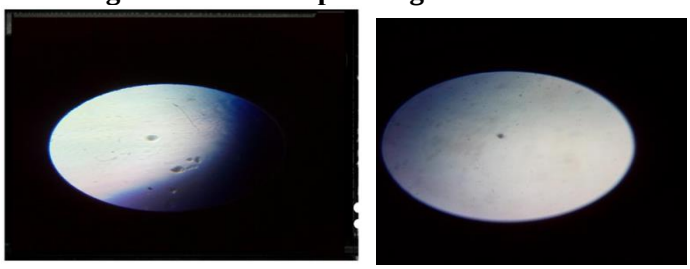
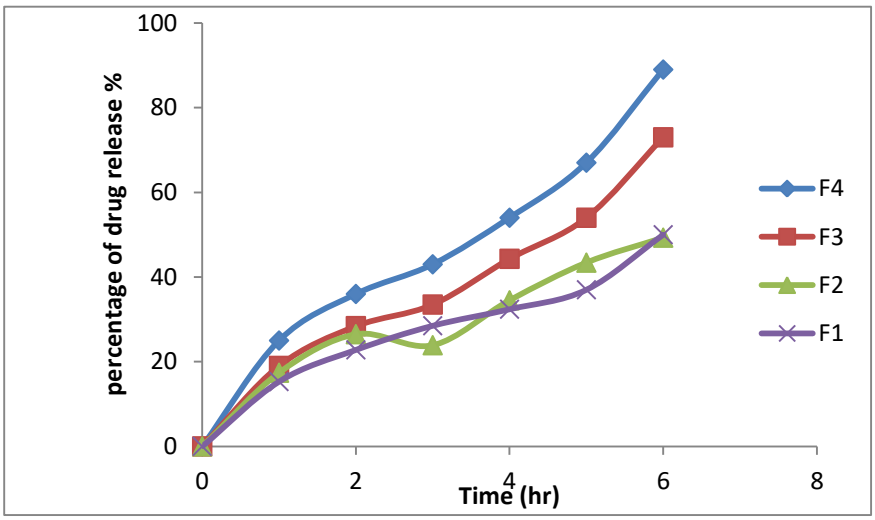


Figure 3: Graph of drug release



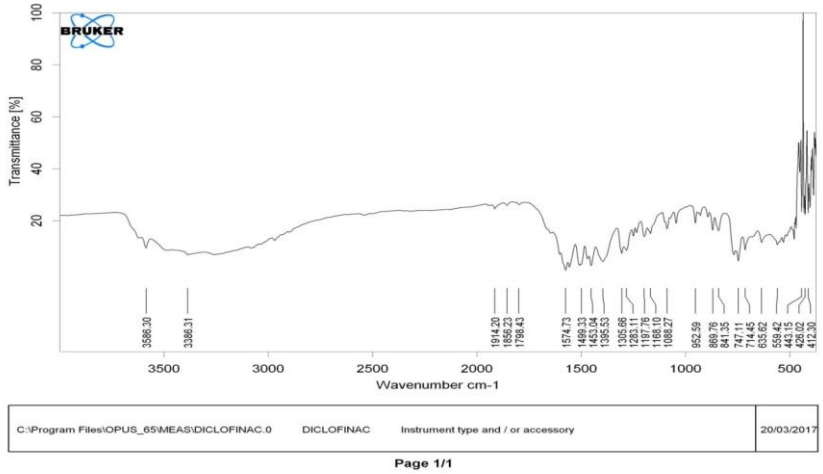


Figure 4: FTIR spectrum of Diclofenac sodium

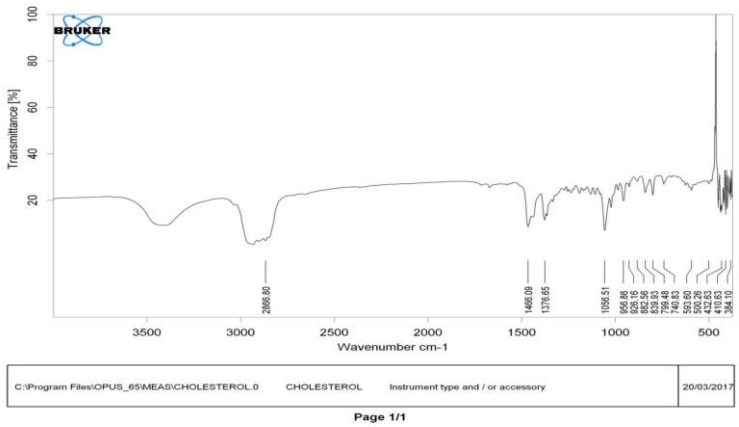


Figure 5: FTIR of Cholesterol

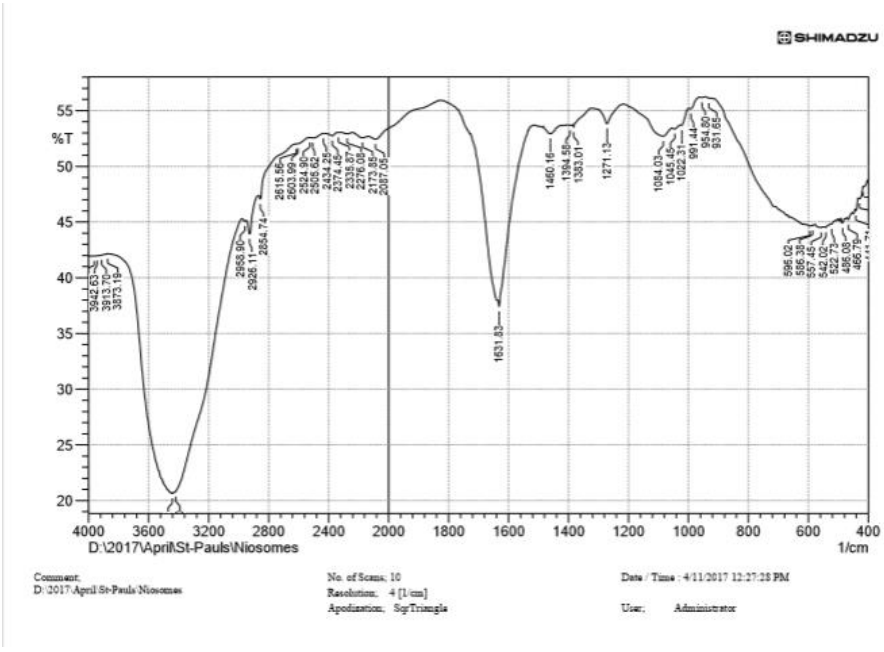


Figure 6: FTIR of optimized formulation

Vesicle morphology analysis:

The freshly formulated niosomes were observed under a calibrated eyepiece micrometer to analyze the particle size. The average was taken for their size distribution range and mean diameter were calculated by roughly about 100 liposomes individually. Even the morphology was studied by using SEM technique.

***In vitro* drug release studies:**

In vitro diffusion studies were carried out using Franz diffusion cell. Apparatus with a diameter of 25mm and a diffusional area of 4.90cm2.An egg membrane was isolated and soaked in pH 6.8 phosphate buffer solutions for 24hrs and was sandwiched between the lower cell reservoir and the glass cell top containing the sample and secured in place with a pinch clamp. The receiving compartment was filled with pH phosphate buffer. The system was maintained at 37C by magnetic heater resulting in a membrane surface temperature of 32oC stirred in the receiving medium to avoid diffusion layer effects. 2ml of receptor fluid were withdrawn from the receiving compartment at 15, 30, 45, 60, 120, 180, 240, 300, 360 minutes and replaced with 2ml of fresh solution. Samples were assayed spectrophotometrically for drug content at 277nm.

Scanning Electron Microscopy (SEM):

The SEM photographs of drug loaded vesicles of optimized formulation were obtained by scanning electron microscope (Jeol, JSM 6360 Aº) using platinum sputter technique.

RESULT AND DISCUSSION

The particle size of the niosome was determined by using microscopy studies and the particle size was found to 74.09 µm. The FTIR spectrum studies show no interactions between drug and polymers. The peaks of drug and polymer were found in the optimized formulation. In the SEM studies discrete particles were seen with no visible oil particles. Niosomes were found to be round and spherical. The diffusion studies were performed and the drug release percentage for the optimised formulation was found to be 89.01% for 8 hours.

Vesicle morphology study:

***Observation of niosomes under optical microscope*:**

The formulated niosomes were observed under an optical microscope and the particle were observed spherical in shape and surrounded by the of lipid layer. The microscopic images are shown in & graph of particle size is mentioned in Fig: 2

Drug release profile:

The formulation code of F4 was found to be significant because it has shown a percentage drug release of 89.01% over a period of 8 hours. The rate of drug release data obtained for diclofenac sodium was plotted according to different modes of formulated was shown in figure 3

FTIR Studies:

FTIR studies were conducted to determine the interactions between the drug and other materials used in the formulation of niosomes. The images of the graph of FTIR studies were mentioned in Figure 4, 5, 6.

CONCLUSION:

In the present research we have formulated diclofenac loaded niosome's using different lipids like cholesterol & surfactant. The SEM & microscopic studies have shown the decreased particle size in micron range for the liposomes. The absence of interactions between drug and polymer was confirmed by FTIR studies. The diffusion studies have shown sufficient release of drug from the delivery system. Hence, we can conclude by saying that niosomal formulation of the diclofenac sodium could be a better alternative to the conventional preparations available in the market.

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