JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

PREPARATION AND OPTIMIZATION OF PARACETAMOL LOADED NIOSOMES

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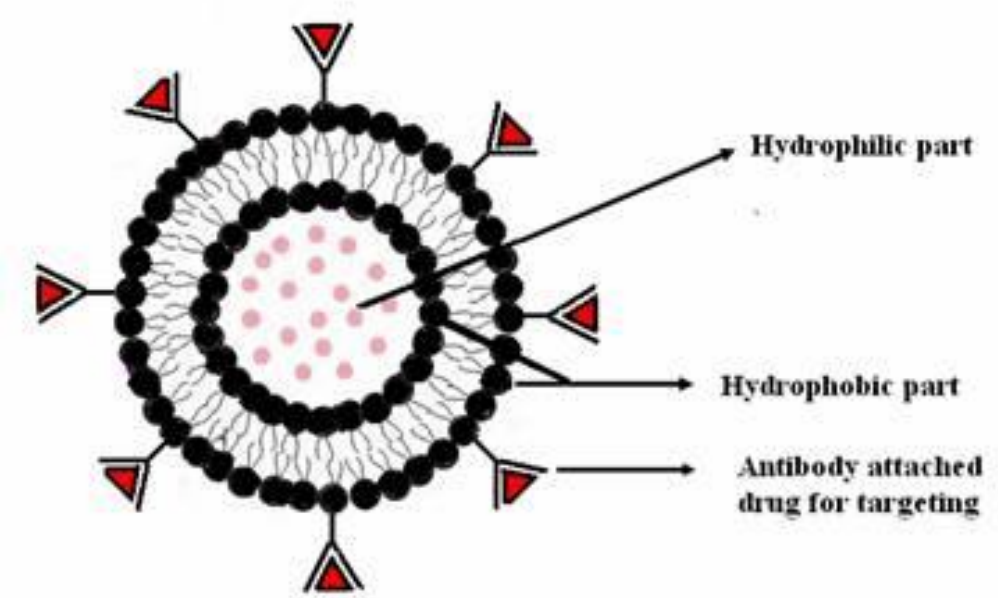
ABSTRACT:- The present study of Niosomes are one of the promising drug carriers that have a bilayer structure and are formed by self-association of nonionic surfactants and cholesterol in an aqueous phase. Niosomes are biodegradable, biocompatible, and nonimmunogenic. They have long shelf life, exhibit high stability, and enable the delivery of drug at target site in a controlled and/or sustained manner . the results revealed that the by optimization we can get better result in the release pattern of the drug. The present study demonstrated the successful preparation of Paracetamol niosomes and their evaluation. Formulation NSF-6 showed high entrapment efficiency (96.07%±0.35), particle size (4.22±0.47µm) and drug release (87.21%) over 80 h. Hence it was considered to be good niosomal formulation with greater bioavailability.

KEYWORDS: Matrix, Erosion, Evaluation, Sustained, Diffusion

INTRODUCTION: Controlled drug release and subsequent biodegradation are important for developing successful formulations. Potential release mechanisms involve: (i) desorption of surface-bound /adsorbed drugs; (ii) diffusion through the carrier matrix; (iii) diffusion (in the case of nanocapsules) through the carrier wall; (iv) carrier matrix erosion; and (v) a combined erosion /diffusion process. The mode of delivery can be the difference between a drug's success and failure, as the choice of a drug is often influenced by the way the medicine is administered. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature).



METHOD OF PREPARATION OF NIOSOMES

A. Ether injection method [13,14]

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm.

B. Hand shaking method (Thin film hydration technique)[14]

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.

Thermosensitive niosomes were prepared by Raja Naresh et al /i>[15] by evaporating the organic solvent at 60°C and leaving a thin film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

C. Sonication[14]

A typical method of production of the vesicles is by sonication of solution as described by Cable [32]. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

D. Micro fluidization[16]

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

E. Multiple membrane extrusion method [16]

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded polycarbonate membranes, which are placed in series for upto 8 through passages. It is a good method for controlling niosome size.

F. Reverse Phase Evaporation Technique (REV) [15]

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.

Raja Naresh *et al* [15] have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

G. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading) [17]

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.

H. The "Bubble" Method[18]

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and

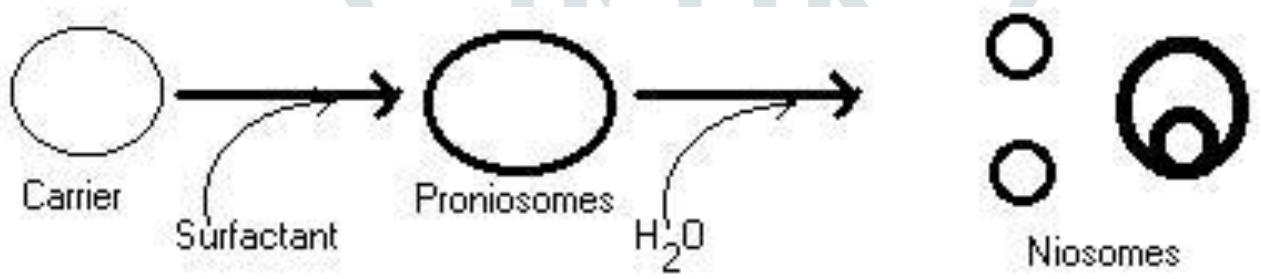
nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

I. Formation of niosomes from proniosomes [19]

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation.

T = Temperature.

Tm = mean phase transition temperature.



MATERIAL AND METHODS

Paracetamol drug was obtained from Lupin Pharmaceuticals Mandideep, India; Spans were obtained from NRI chemical STORE Bhopal (M.P) . Diethyl ether Methanol, potassium dihydrogen phosphate, sodium hydroxide was obtained from Govindpura drug market Bhopal. All ingredients used were of analytical grade.

PREPARATION OF NIOSOMES

Niosomes containing paracetamol were prepared by modified ether injection technique using nonionic surfactant (span 60, span 20) and cholesterol at different concentrations. Cholesterol and surfactant were dissolved in 6ml diethyl ether mixed with 2ml methanol containing weighed quantity of paracetamol. The resulting solution was slowly injected using micro syringe at a rate of 1ml/min into 15 ml of hydrating solution phosphate buffer (pH 7.4).The solution was stirred continuously on magnetic stirrer and temperature was maintained at 60-65ºC. As the lipid solution was injected slowly into aqueous phase, the differences in temperature between phases cause rapid vaporization of ether, resulting in spontaneous vesiculation and formation of niosomes. Different batches of niosomes were prepared in order to select an optimized formula as per general method described above and proportion of surfactant and cholesterol for the preparations of niosomes is given in Table 1 and optimized niosomal formula are given in Table 2.

CHARACTERIZATION OF NIOSOMES

1. DRUG ENTRAPMENT EFFICIENCY OF NIOSOMES

Entrapment efficiency of niosomes was determined by exhaustive dialysis method. The measured quantity of niosomal suspension was taken into a dialysis tube to which osmosis cellulose membrane was securely attached on one side. The dialysis tube was suspended in 100ml phosphate buffer (pH 6.8), which was stirred on a magnetic stirrer. The unentrapped drug was separated from the niosomal suspension into the medium through osmosis cellulose membrane. At every hour entire medium (100ml) was replaced with fresh medium (for about 9-12h) till the absorbance reached a constant reading indicating no drug is available in unentrapped form. The niosomal suspension in the dialysis tube was further lysed with propane-1-ol and estimated the entrapped drug by UV spectrophotometric method at 243nm. The entrapment efficiency was calculated using following equation.

$$\text{Entrapment efficiency} = \frac{\text{Amount of entrapped drug}}{\text{Total amount of drug}} \times 100$$

2. Drug content

Niosomes preparation equivalent to 40mg of Paracetamol 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 6.8). The absorbance was measured at 243nm and calculated drug content from the calibration curve.

4. Particle size and shape analysis

Particle size analysis was carried out using an optical microscope with a calibrated eyepiece micrometer. About 200 niosomes were measured individually, average was taken and their size distribution range and mean diameter were calculated. Further microphotographs of optimized niosomes were taken by using 9 megapixel Sony DSC-W110 digital camera. The histogram for particle size distribution and particle size are shown in Figure 1a, 1b and the microphotographs are shown in Fig. 2a, 2b.

5. In vitro release studies

The release of Paracetamol from niosomal formulations were determined using membrane diffusion technique [6-7]. The niosomal formulation equivalent to 40mg of Paracetamol was placedin a glass tube of diameter 2.5cm with an effective length of 8cm that was previously covered with soaked osmosis cellulose membrane, which acts as a donor compartment. The glass tube was placed in a beaker containing 100ml of phosphate buffer (pH 7.4), which acted as receptor compartment. The whole assembly was fixed in such a way that the lower end of the tube containing suspension was just touching (1-2mm deep) the surface of diffusion medium. The temperature of receptor medium was maintained at 37±10^{0}C and agitated at 100rpm speed using magnetic stirrer. Aliquots of 5ml sample were withdrawn periodically and after each withdrawal same volume of medium was replaced. The collected samples were analysed at 243 nm in

Double beam UV-VIS spectrophotometer using phosphate buffer (pH 6.8) as blank.

RESULT AND DISCUSSION

FORMULATION COMPOSITION OF NIOSOMES:

Table 1: composition of surfactant and cholesterol for preparation of niosomes

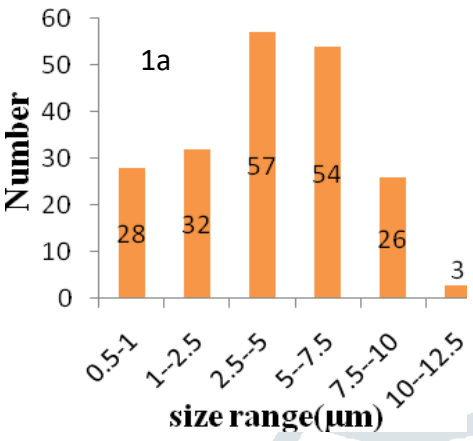
Sr. No	Code	Surfactant	Drug: Surfactant: Cholesterol	Weight taken (mg)		
				Drug	Surfactant	Cholesterol
1	NPF-1	S60	1:0.75:1	200	150	200
2	NPF-2		1:1:1	200	200	200
3	NPF-3		1:1.25:1	200	250	200
4	NPF-4	S20	1:0.75:1	200	150	200
5	NPF-5		1:1:1	200	200	200
6	NPF-6		1:1.25:1	200	250	200

Table 2: Optimized formula for the noisome preparation

Sr. No	Formula	NPF-3	NPF-6
1	Cholesterol	200mg	200mg
2	Span 60	250mg	-----
3	**Span 20**	**-----**	**250mg**
4	Paracetamol	200mg	200mg
5	Methanol	2ml	2ml
6	Diethyl ether	8ml	8ml
7	Phosphate buffer 7.4	15ml	15ml

EVALUATION OF NIOSOMES:

1. PARTICLE SIZE ANALYSIS:-



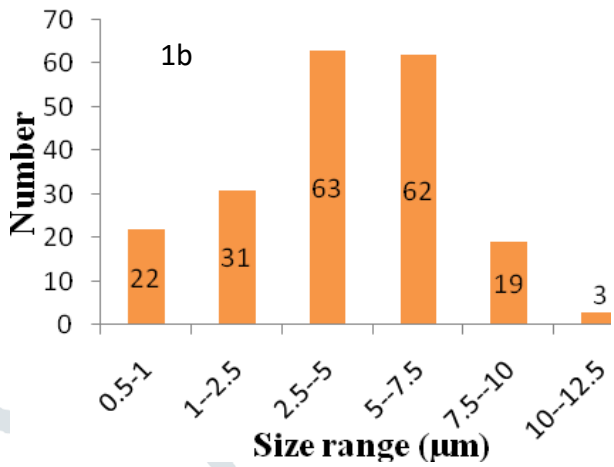


Table 3. Evaluation parameters of niosomes. (Mean ± S.D., n=3)

S. No	Formulation	Mean particle size µm±SD
1	NPF-1	4.83±0.35 µm.
2	NPF-2	4.50±0.49µm.
3	NPF-3	4.47±0.51 µm.
4	NPF-4	4.75±0.46µm
5	NPF-5	4.31±0.71µm.
6	NPF-6	4.22±0.47µm.

2. DRUG ENTRAPMENT EFFICIENCY:

Table 4: Drug entrapment efficiency of different formulation NPF-1 to NPF-6

S. No	Formulation	Entrapment efficiency
1	NPF-1	85.2%±0.51
2	NPF-2	87.2%±0.43
3	NPF-3	88.4%±0.46
4	NPF-4	94.02%±0.39
5	NPF-5	95.35%±0.28
6	NPF-6	96.07%±0.35

3. IN-VITRO DISSOLUTION STUDIES:-

Table 5: Dissolution data for different noisome formulation

Time	NPF-1	NPF-2	NPF-3	NPF-4	NPF-5	NPF-6
0	0	0	0	0	0	0
10	15	17	19	22	24	27
20	25	26	28	30	33	36
30	36	38	40	42	45	49
40	43	45	47	50	53	58
50	54	56	58	62	65	69
60	68	69	73	76	79	83
70	76	78	82	87	89	92
80	85.2	87.2	88.4	94.02	95.35	96.07

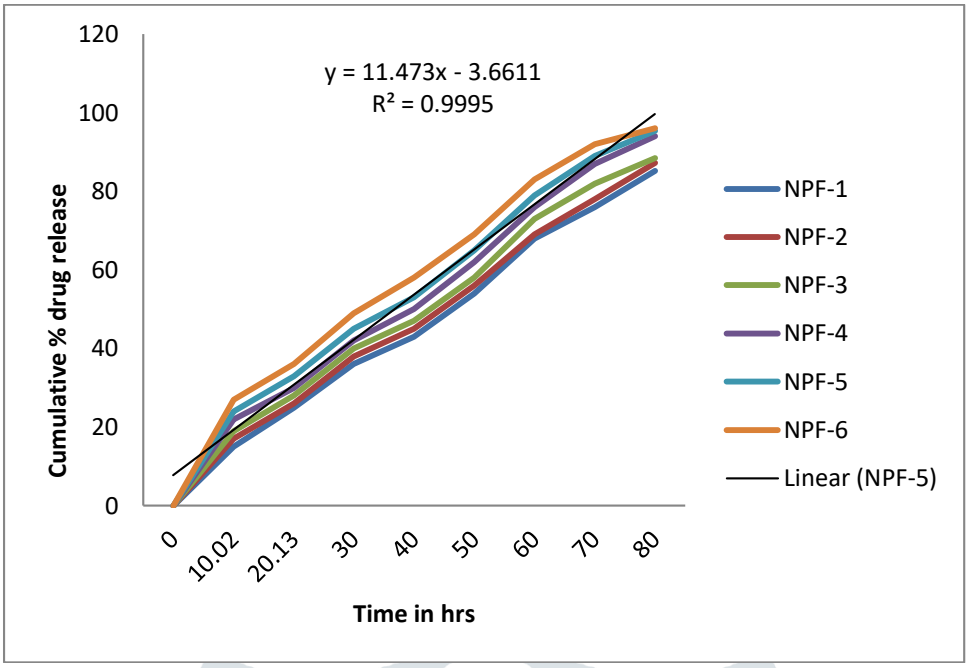


Fig no 3: cumulative % drug release of noisome formulation

SUMMARY AND CONCLUSION

SUMMARY:

Among the various methods, Modified ether injection method is widely used to prepare niosomes. The entrapment efficiency of niosomes prepared at varied concentration of surfactants: Paracetamol, keeping cholesterol concentration constant are shown in Table 1.

Drug content was determined for all niosomal formulations in triplicate. The drug content was found to be uniform with low SD and CV<2.The sizes of the niosomes are measured using an optical microscope with calibrated eyepiece micrometer. From each batch about 200 niosomes were measured for the diameter. The average vesicular size of niosomes of all the batches was measured in the range of 4.22±0.47µm to 4.83±0.35 µm. The result suggested that prepared were of uniform size and spherical in shape as shown in microphotographs Figures 1a, 1band 2a and 2b.

In all the niosomes prepared with spans, as the concentration of surfactant increased drug entrapment efficiency increased. The encapsulation efficiency of niosomes is governed by the ability of formulation to retain drug molecules in the aqueous core or in the bilayer membrane of the vesicles. Cholesterol improves the fluidity of the bilayer membrane and improves the stability of bilayer membrane in the presence of biological fluids such as blood/plasma. Among the spans, span 60 having high phase transition temperature (gel to liquid transformation) and having critical packing parameter (CPP) ranging from 0.5 to 1 entrap drug molecule without any cholesterol. The only drawback of span 60 vesicles was rapid leakage of drug from the vesicle because of high phase transition temperature. A small concentration of about 10-20% cholesterol was optimum to get stable vesicle by abolishing the phase transition temperature resulting in stable niosomes avoiding drug leakage. In Vitro drug release of various formulations of niosomes are shown in Figure 3.

CONCLUSIONS:

The present study demonstrated the successful preparation of Aceclofenac niosomes and their evaluation. Formulation NSF-6 showed high entrapment efficiency (96.07%±0.35), particle size (4.22±0.47µm) and drug release (87.21%) over 80 h. Hence it was considered to be good niosomal formulation with greater bioavailability.

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