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AN APPROACH FOR DESIGN AND CHARACTERIZATION OF NIOSOMES FOR CHLORPHENIRAMINE MALEATE

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ABSTRACT

Niosomes are vesicles composed of non-ionic surfactants, relatively nontoxic, more stable and inexpensive, an alternative and superior to liposome will be acts as a target drug delivery system/CDDS. The aim of the present investigation was to formulate niosomes and subject to evaluation of particle size, entrapment efficiency and *invitro* studies and study concentration of drug towards size of niosomes. Niosomes were prepared by the thin film hydration method by various using combinations of cholesterol and spans with tweens as surfactants in different ratios and diethyl ethyl as a solvent with antihistamine drug chlorpheneramine maleate. Formulation containing span 20 was found to be 10.58 in micron diameter. Span 20(20 mg of drug) gained size of 13.73µ in diameter and span 20(12 mg of drug) has got less in particle size of 5.44 µ in diameter in comparison to span 60 of 14.41microns. The formulation of niosomes within combination of span 20 and cholesterol in 1:1 ratio has 93.8 % PDE and in combination of tween 60 and cholesterol in 1:1 ratio was 95.94 % PDE. The *in vitro* diffusion study suggests that higher entrapment efficiency was related with slow release comparatively. The *in-vitro* drug release of 68 %was found to be for the extended period of time of 12 hrs of optimized one. Niosomes prepared from combination of span 60 is a promising approach to improve the bioavailability of chlorpheneramine maleate as antihistamine even for an extended period of time which showed good physicochemical properties with controlled drug release pattern, thereby improving the bioavailability of the drug with minimization of side effects due to

selective built up of drug concentration at site of action. The *in-vitro* diffusion study suggests that higher entrapment efficiency was related with slow release comparatively. The release pattern shown by these formulations were zero order and diffusion controlled mechanism.

KEYWORDS: Niosomes, Chlorpheneramine maleate, Spans and Tweens concentrations, Cholesterol, *in-vitro.*

INTRODUCTION

Niosomes **[**1] are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayers mainly composed of non-ionic surfactants and cholesterol. Niosomes can be used to deliver both hydrophobic and hydrophilic drugs via transdermal route. Although niosomes were tried for various routes, studies showed that an enhanced delivery of drugs was observed when niosomes were encapsulated. Niosomes increase skin penetration of drugs and it can act as local depot for sustained release of dermal active compounds. Surfactant is the core material for bilayers formation, but the bilayer of just the non-ionic surfactant is not strong enough to serve as host for the drug. So cholesterol having a steroidal rigid structure provides the required strength to the bilayer, despite of the fact that cholesterol itself is incapable of layer.

MATERIALS AND METHODS

Chlorpheniramine maleate was sample obtained from Research Lab, fine Chem. Industries, Mumbai. Span 60, Span 20, Span 80, Tween 60, from Research Lab fine Chem. Industries, Mumbai, Cholesterol, Diethyl ether, Disodium hydrogen phosphate, Potassium Dihydrogen phosphate from Virat lab, Hyderabad. Rota evaporator, Aditya Scientific, Hyderabad. UV-Visible Spectrophotometer, Shimadzu Corporation,Japan. All the ingredients used in the procedures were of analytical grade.

Standard calibration curve

20 mg of Chlorpheniramine maleate was dissolved in 10 ml of phosphate buffer solution of pH 6.8 and made up to 100 ml with buffer. From these stock solution different aliquots of 1, 2, 3, 4,5ml & 6ml were pipette out and made up to 10 ml with PBS pH 6.8. The absorbance of the solution was measured at 261 nm using UV-Visible spectrophotometer.

Preparation of Niosomes of Chlorpheniramine maleate by Rotary Evaporator Method [2]**.** Surfactant and cholesterol mixture is dissolved in 10 ml of diethyl ether in a round-

bottomed flask. The ethyl ether is evaporated under vacuum at room temperature in a rotary evaporator as discussed by Baillie et al. Upon hydration [3] for certain time in buffers solution the surfactant swells and forms niosomes. Swollen amphiphiles eventually fold to form vesicles.

Microscopy

The vesicle formation by the particular procedure was confirmed by optical microscopy in 400x resolution. The niosome suspension placed over a glass slide and fixed over by drying at room temperature, the dry thin film of niosome suspension observed for the formation of vesicles.

Entrapment efficiency [4,5]

Niosome entrapped chlorpheniramine maleate was estimated by ultracentrifugation method. The entrapment efficiency of niosomes was determined by ultra centrifuging the niosomal dispersions at 4,000 rpm for 30min.the clear supernatant was analyzed for chlorpheniramine maleate spectrophotometrically at ƛmax 261 nm and gave the amount of unentrapped drug. Amount of entrapped drug was obtained by subtracting amount of unentrapped drug from the total drug incorporated.

Entrapment efficiency = Amount of drug entrapped/Total amount of drug used ×100

Drug content of the niosomal preparations were determined by lysis method. Adequate amount of 50% n-propranolol was added to the niosomal dispersion and shaken well until all the vesicles were completely lysed. It was diluted suitably with distilled water and the absorbance was measured determined by UVspectrophotometer at ƛmax 261 nm.

Morphology

Morphology of niosomes-derived niosomes were studied under optical microscope. Niosomes prepared from niosomes were spherical in shape and composed of bilayered.

***In-vitro* drug release study [**6,7]

In vitro release pattern of niosomal suspension was carried out in dialysis bag method. 1.5 mg equivalent of 0.3 % of niosomal suspension was taken in dialysis bag and the bag was placed in a beaker containing 250 ml simulated fluid (pH 6.8phosphate buffer). The beaker was placed over magnetic stirrer and the temperature was maintained at 37 ± 0.5^{0C} . The amount of 3 ml samples were withdrawn periodically and were replaced by fresh phosphate buffer pH

6.8. The sink condition was maintained throughout the experiment until 12 hrs. The withdrawn samples were analyzed for drug content using U.V. spectrophotometer at λmax 261 nm by keeping phosphate buffer pH 6.8 as a blank.

Table 1: Formulation of niosomes

Formulation*code	Surfactants	Ratio (Surfactant:Cholesterol)
NS1	Span 20: Cholesterol	1:1
NS2	Span 20: Cholesterol	1:1
NS3	Span 60: Cholesterol	1:1
NS4	Span 60: Cholesterol	1:2
NS5	Span 60: Tween 60: Cholesterol	1:1:2
NS6	Tween 60: Cholesterol	1:1
NS7	Tween 60: Cholesterol	1:1

*Each formulation contains 20 mg of Chlorpheniramine maleate and 10ml diethyl ether, except NS2 contain 12 mg of drug only.

RESULTS AND DISCUSSIONS

Standard calibration curve: The absorbance of the solution was measured at 261 nm using UV-Visible spectrophotometer of different concentrations in micrograms per ml. A graph of Concentration vs. Absorbance was plotted and shown in fig no.1

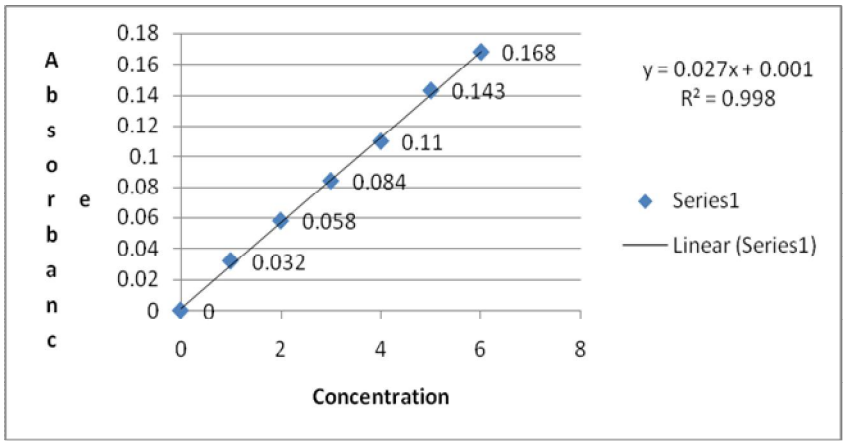

Fig 1: standard calibration curve of Chlorpheniramine maleate

Particle size determination

The prepared vesicles were studied under 400 x magnifications to observe the formation of vesicles. Some unevenness of vesicles that observed under the study may be due to drying process under normal environment condition. The photomicrograph of niosomes is shown in

the Figures. Based upon various preparations it was found to be an increase in HLB [8,9] value leads to be maximum in size of niosomes. Span 60 has 14.41 micron and span 20 was found to be 13.73 in micron diameter. Increase in size of niosomes was a function of dependent upon chain length of surfactant .As the length in carbon increases the size of niosomes also increases. The mean diameter of niosomes with tweens was in following order. Tween 60 > tween 80 > tween 40 > tween 20

Span 20 and span 40 have less in particle size in comparison to span 60.the mean size of niosomes increased with progressive increase in HLB value because surface free energy decreases on increasing hydrophobicity of surfactant.

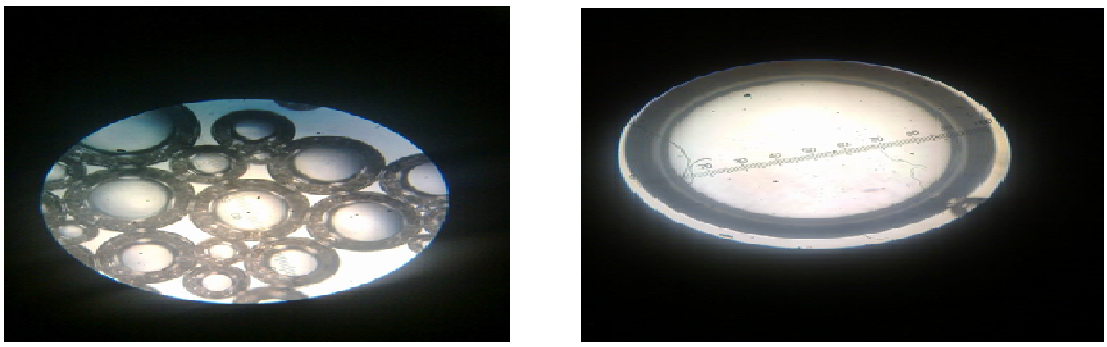

Fig no.2: photographs of niosomes

Also the results reveal that the niosomes prepared using span 60 is larger in size than niosomes prepared using span 40. Span 60 has a longer saturated alkyl chain compared to span 40 as mentioned previously and it was reported that surfactants with longer alkyl chains generally give larger vesicles. This would account for the higher entrapment efficiencies with span 60 niosomes.

Concentration of drug: As the concentration of drug is going to be less, ultimately it leads to decrease in particle size of niosomes. In NS2 formulation (12mg of drug) having only 5.44 micron in size compared to NS1 formulation of 13.73 micron in diameter (20mg of drug).

Table 2: Average particle size of Niosomes

Batch Code	NS1	NS2	NS3	NS4	NS5	NS6	NS7
Avg.Particle Size*	13.73±2.11	5.44±1.11	10.45±0.11	14.41±2.11	11.01±4.11	13.91±1.21	13.6±4.11

Each determination was carried out in triplicate. *Mean ± SD,n=3

Table 3:-Entrapment Efficiency of Drug (PDE)

Sample	Absorbance At 261 Nm	Concentration	Amount Of Drug	Entrapped Drug	Percent Drug Entrapped
NS1:E **UE**	0.536 0.036	12.739 6.172	1261.161 611.028	0.9328	93.28%
NS 2 : E **UE**	0.33 0.296	10.034 9.58	993.42 948.42	0.1030	10.3%
NS 3 : E **UE**	2.449 0.230	37.96046 8.720	3748.14 863.28	0.9060	90.6%
NS 4 : E **UE**	2.88 0.302	42.71 9.666	4228.29 956.939	0.8928	89.28%
NS 5 : E **UE**	0.694 0.202	41.082 8.353	4067.118 826.947	0.9250	92.50%
NS 6 : E **UE**	2.369 0.096	36.813 6.960	3644.487 689.04	0.9594	**95.94%**
NS 7 : E **UE**	0.933 0.880	17.953 6.750	1777.347 668.25	0.9142	91.42%

Each determination was carried out in triplicate.

Where E Means Entrapped

UE Means Unentrapped

The percentage drug entrapment was decreased in the order of NS6 >NS1 > NS5 > NS7.

In combination of span 20 and cholesterol in 1:1ratios was 93.8 PDE

In combination of span 60 and cholesterol in 1:2 ratios was 89.28 PDE

In combination of span 60 and cholesterol in 1:1 ratios was 90.6 PDE.

In combination of tween 60 and cholesterol in 1:1 ratios was 95.94 PDE

In combination of span 60, tween 60 and cholesterol in 1:1:1 ratios was 92.5 PDE

The spans having highest phase transition temperature provides highest entrapment for drug (16° for span 20, 42 °for span 40 and 53° for span 60).

Table 4: cumulative percent drug release profile of different niosome formulations

Sl. No	Time (12 Hrs.)	Cumulative percent Drug Release			
		Tween 80	Span 20	Span 40	Span 60
1.	1	4.16	**6.24**	5.200	4.68
2.	2	5.904	**8.856**	7.380	6.642
3.	3	7.5648	**11.347**	9.456	8.5104
4.	4	29.836	**44.755**	37.296	33.5664
5.	5	30.72	**46.08**	38.4	34.56
6.	6	33.536	**50.304**	41.92	37.728
7.	7	34.624	**51.936**	3.28	38.952
8.	8	36.48	**54.72**	45.6	41.04
9.	9	36.64	**54.96**	45.8	41.22

10.	10	43.84	**65.76**	54.8	49.32
11.	11	44.8	**67.2**	56	50.04
12.	12	45.36	**68.04**	56.7	51.03

HLB value of 14 to 17 was not suitable for niosomes and HLB value of 8.6 had maximum entrapment efficiency and said to be decreases from 8.6 to 1.7.

Maximum entrapment efficiency in order of following manner

Span 60 > span 40 > span 80 > span 20

After carrying out of invitro studies for period of 12 hrs drug release found to be 68.04 % from preparation containing span 20, tween 80 was 45.36%, span 40 has gained 56.7% and span 60 was 51.03%. In niosomal formulations, the experimental studies showed that the rate of drug release depends on the percentage of drug entrapment efficiency. From the results it was proved to be the higher chain length, lower release profile and in turn it also depends upon concentration of cholesterol content, once cholesterol has gained saturation the rate of release was found to be minimum due to disrupting bilayered structure of niosomes which totally makes loss of drug entrapment. The niosomal gel formulation showed controlled drug release due to the entrapment of drug in vesicles. From the results we can conclude that the drug was released from niosome by a zero order diffusion controlled mechanism.

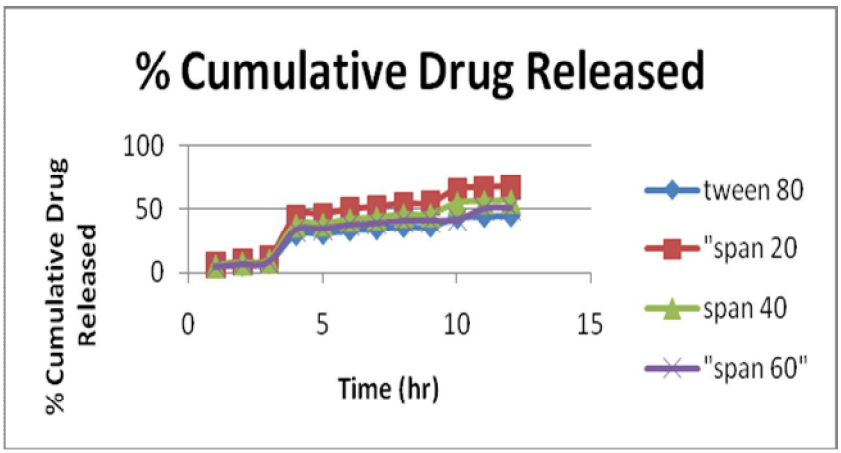

Fig 3: Drug release profile of various niosomes formulations

CONCLUSION

The main objective of this study was to design suitable noisome encapsulated drug delivery for chlorpheneramine maleate as a anti histamine. It has been concluded that noisome prepared from span 20 has much more entrapment efficiency as compare to tween 80 and span 40 has gained 2nd place. Finding of all this investigation conclusively demonstrate prolongation of drug release at a constant and controlled rate after encapsulation

of Chlorpheniramine maleate. This study suggests that niosomal formulation can provide consistent and prolonged release of drug from different niosomal formulations. It will lead to sustained action of the entrapped drug that minimizes the incidence of the side effects associate with frequent administration of the drug and potentiate the therapeutic effects of the drug. It shows that niosomal drug delivery system may and ideal be a promising carrier for the novel drug delivery system.

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