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Effect of Cholesterol Concentration on Simvastatin Encapsulated Niosome Containing Span 60 and Span 80 as Surfactant

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ABSTRACT

Niosomes are a novel drug delivery system, where the drug is encapsulated in a bilayered vesicle of Non-ionic surfactant. Simvastatin is origin chemically by fermentation from Aspergillus terreus. It actsas an Antihyperlipidemic. It hydrolyzes to create beta, delta, and dihydroxy acid, which structurally resembles HMG-CoA. Thus, for HMG-CoA reductase, hydrolyzed simvastatin competes with HMG-CoA. To improve in-vitro and well-in-vivo release and increase bioavailability, simvastatin niosomes are used. After the evaluation, it may be hypothesized that a formulation having a higher concentration of cholesterol may alter the physicochemical properties and in vitro release of the encapsulated drug molecule. It was also found that the formulation with half the concentration of cholesterol than the surfactant may give a smaller particle size of the vesicle system. Thus, it can be concluded that cholesterol has a significant effect on niosomes.

KEYWORDS: *Niosome, cholesterol, Simvastatin, span 60 and span 80*

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1. INTRODUCTION

The Novel drug delivery system have been played an important role for the delivery of various drugs, for getting the best therapeutic efficacy, controlled and sustained drug release of new as well as pre-existing drugs [1,2]. Noisomes are vesicular systems that can improve the bioavailability of the active pharmaceutical ingredient [3,4]. The encapsulated drug material gives a better therapeutic effect for a prolonged period of time with controlled release [5,6]. Niosome (non-lipoidal modified release system) also improves patient compliance as well as less adverse effects[7,8]. The bilayers of niosomes were composed of the non- ionic surfactants [9]. The drug encapsulated in the bilayers acts as a depot from which control release is obtained thus the pharmacological effect of the prepared formulation is enhanced [10,11]. The clearance of drug molecules from blood circulation can also be delayed by noisomes. The bilayer structure of the niosome helps to protect the drug from gastric intestinal irritation. Niosome only acts at the target site [12, 13]. While niosomes and liposomes share similar structures, niosomes' bilayer is composed of non-ionic surfactants rather than phospholipids [14, 15]. Their structure is lamellar. They could have one or more lamellar segments [16, 17]. Aspergillus terreus is fermented to produce simvastatin [18–20]. For the treatment of hyperlipidemia, it works well. Simvastatin hydrolyzes to creates beta, delta and dihydroxy acid, which structurally resembles HMG-CoA (hydroxylmethylglutaryl CoA) [21, 22]. Thus, for HMG-CoA reductase, hydrolyzed simvastatin competes with HMG-CoA [23]. As a result of interfering with this enzyme, it lowers the amount of cholesterol and decreases the creation of the precursor (mevalonic acid) of cholesterol [24, 25].Due to poor water solubility, it follows BCS class II and has first-pass metabolism thus resulting in low bioavailability (5%) [26]. The dosing frequency increases due to the short biological half-life (3 hrs), which causes fatigue, headache, rash, and GIT-

related adverse effects. [27, 28]. Most formulations exist as immediate release type of drug delivery system, which gives immediate drug release just after the disintegration for particular formulations [29]. In such a type of preparation, the drug plasma concentration may alter due to the alteration in dissolution either increasing or decreasing, so the effect of the drug is also altered [30].

The aim of this project is to find out the effect of varying cholesterol concentrations on the encapsulation efficiency, stability, and release profile of simvastatin in niosomes formulated with Span 60 and Span 80 as surfactants. The study seeks to optimize the cholesterol content to enhance the therapeutic efficacy of simvastatin-loaded niosomes for potential applications in targeted drug delivery.

2. MATERIALS AND METHODS

Materials

I have received a gift sample of Simvastatin from SUN PHARMACEUTICALS, GURGAON. The Cholesterol, Span 60 and Span 20 were purchased from Sdfcl, Fine Chemical Ltd. Mumbai. Analytical grade solvents and reagents were utilized in this research [31].

Method of preparation of Simvastatin noisome:

The simvastatin niosome was formulated by the handshaking method. In this method, selected surfactant and Cholesterol was solubilised in a suitable volatile organic solvent such as Chloroform, diethyl ether, or methanol in round bottom flask [32]. After this the organic phase was evaporated at 20°Cby the aid of a rotary vacuum evaporator for deposition of solid material as a thin layer on the surface of the round bottom flask [33]. The obtained dried film was further rehydrated by using an aqueous medium with agitation at 0-60°C, which formulated multilamellar-type niosomes [34].

Table 1 Composition of formulations

S. No	Formulation code	Span60/Span80: Cholesterol
1	F1	Span 60 (1:1)
2	F2	Span 60 (2:1)
3	F3	Span 60 (3:1)
4	F4	Span 60 (1:3)
5	F5	Span 80 (1:1)
6	F6	Span 80 (2:1)
7	F7	Span 80 (3:1)
8	F8	Span 80 (1:3)

Characterization of Simvastatin niosomes

Particle size

By using Photon Correlation Spectroscopy and Nanoplus-3 Zeta Sizer, the morphological properties of the synthesized niosome, such as particle size, polydispersity index (PDI), and zeta potential, were assessed (Japan). A He-Ne laser was used to analyse each formulation after it had been appropriately diluted and placed in a thermostatic chamber at 25^0C [35–37].

Entrapment efficiency

The entrapment efficiency of different formulations of niosomes was analyzed by centrifugation method. 1 ml of niosomal formulation was centrifuged after that the supernatant was collected and diluted with 7.4 pH buffer. Then absorbance of the diluted sample was taken by UV- Spectroscopy at 234 nm. The concentration of the free drug was calculated. After that, the % entrapment efficiency (EE %) was calculated with the formula given as below [38].

$$\%EE = [ED \div TD] \times 100$$

Where:
ED= Amount of Entrapped Drug
TD= Amount of Total Drug

In vitro drug release profile

In vitro drug release studies of niosomal formulation and API of simvastatin (0.25% CMC) were done by dissolution apparatus [39]. The API and niosomal formulation (1ml) were placed separately in 0.1N HCL, and pH 6.8 and pH 7.4 buffers were filled in the basket [40]. The buffer solution was agitated with the help of a magnetic stirrer at 50 rpm and the temperature was maintained at 37± 5 ºC[41,42]. Different aliquots of the 5 ml sample were withdrawn after a fixed time

interval and the same volume was added simultaneously in the medium [43]. The absorbance of each sample was taken at 234 nm by using a UV- Spectrophotometer. [44].

3. RESULT AND DISCUSSION

Preformulation study:

The pure drug sample (simvastatin) was found to have comparable physical properties and a melting point (135–138ºC) to those indicated in official monographs. The calibration curve of Simvastatin was prepared in methanol. The obtained data was regressed to achieve straight line equation. The R^2 value of methanol was obtained 0.996 and it shows good linearity. The solubility of Simvastatin was described in table 2-

Table 2 Solubility of Simvastatin in Different Solvents

S. No.	Solvent	Solubility (g/ml)
1	Methanol	Freely Soluble
2	Phosphate buffer pH 7.4	Sparingly Soluble
3	Phosphate buffer pH 6.8	Sparingly Soluble
4	1.2 N HCl	Sparingly Soluble
5	Water	Insoluble

Particle Size:

The Size of the various niosomal formulations prepared by using Span 60 and Span 80 with Changed concentrations of cholesterol was analyzed by Zeta sizer and obtained results from the study are shown in Table 1.2. The mean vesicular size of F2 and F6 formulations , containing span 60 and Span 80 with cholesterol concentration in 2:1 in both formulations were found to be smaller 225.41 and 261.4 nm respectively in comparison to others, which shows that the niosome containing a half concentration of cholesterol than surfactant having smaller particles size. The results show that the lower concentration of cholesterol than surfactant may produce niosome of smaller size but on the other hand, the particle size was increased in both formulations F4 and F8 upon increasing the cholesterol concentration.

This might be due to the amphipathic nature of cholesterol. Cholesterol inserts itself in the bilayer membrane and increases the chain length bilayer. It also reinforces the non-polar tail of non-ionic surfactant. In low concentrations cholesterol is closely packed to surfactant monomers which reduces the size of vesicles. On the other hand, the increased concentration of cholesterol having lipophilic properties (log P=7.02) and decrease in nonionic surfactant results increase in the hydrophobicity nature of the bilayer membrane of niosome vesicles.

Table 3 Particle size of different niosomal formulations

S. No	Formulation code	Span60/Span80: Cholesterol	Size (nm)
1.	F1	Span60 (1:1)	559.1
2.	F2	Span60 (2:1)	225.41
3.	F3	Span60 (3:1)	582.31
4.	F4	Span60 (1:3)	375.6
5.	F5	Span80 (1:1)	472.8
6.	F6	Span80 (2:1)	261.4
7.	F7	Span80 (3:1)	302.3
8.	F8	Span80 (1:3)	317.6

Poly dispersity index (PDI):

The niosomal formulations including Span 60 had **a** polydispersity index of 0.286, 0.152, 0.368, and 0.285, while Span 80 had polydispersity indices of 0.291, 0.166, 0.238, and 0.214, in that order. From all the formulations it was found that formulation F2 and formulation F6 having Span 60/ Span 80 and Cholesterol ratio 2:1gives lower PDI in both cases 0.152 and 0.166 and these values were < 1, which indicates that these formulations have better homogeneity than other formulations. From the obtained result it can also be hypothesized that on further increasing the cholesterol concentration in formulations F4 and F8 there was a slight decrease in the PDI.

Table 4 Poly dispersity Index niosomes

S. No	Code of Formulations	Span60/Span80: Cholesterol	PDI
1	F1	Span60 (1:1)	0.286
2	**F2**	**Span60 (2:1)**	**0.152**
3	F3	Span60 (3:1)	0.368
4	F4	Span60 (1:3)	0.285
5	F5	Span80 (1:1)	0.291
6	**F6**	**Span80 (2:1)**	**0.166**
7	F7	Span80 (3:1)	0.238
8	F8	Span80 (1:3)	0.214

% Entrapment Efficiency:

The entrapment efficiency of different formulations is shown in Table 1.4. The formulations F2 (Span 60: cholesterol, 2:1) and F7 (Span 80: cholesterol, 3:1) showed better entrapment efficiency. Upon increasing the cholesterol concentration in both cases (Span 60/ Span 80: Cholesterol, 1:3) the entrapment efficiency was decreased. This may occur due to the increase in bilayer membrane rigidity with an increase in cholesterol concentration which leads to disruption of the bilayer structure of vesicles and thus the total number of bilayers decreases which also decreases the entrapment efficiency of the drug in niosomes. Cholesterol has a greater affinity to packed in the bilayer of the vesicles so a higher amount of cholesterol competes with active molecules and decreases the percentage of drug entrapped in the niosomes.

Table 5Percentageentrapment efficiency of niosomes

S. No	Formulation code	Span60/Span80: Cholesterol	% Entrapment efficiency *
1	F1	Span 60 (1:1)	71.17±2.91
2	F2	Span 60 (2:1)	85.72±2.10
3	F3	Span 60 (3:1)	77.69±2.05
4	F4	Span 60 (1:3)	73.67±3.73
5	F5	Span 80 (1:1)	74.23±1.72
6	F6	Span 80 (2:1)	75.57±1.19
7	F7	Span 80 (3:1)	81.44±3.83
8	F8	Span 80 (1:3)	71.17±2.91

*Values expressed are mean ± SD where n=3

In-vitro release:

Table 6 Percentage cumulative release of different formulations in pH 6.8 buffer

S. No	Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	**0**	0	0	0	**0**
2	0.25	2.85±5.60	14.05±4.39	5.79±4.62	**0.86±3.67**	12.32±6.45	3.26±2.42	6.09±8.53	**2.93±2.18**
3	0.50	20.12±4.40	25.25±8.79	17.72±1.36	**14.11±6.82**	27.83±7.41	12.15±2.42	19.61±7.23	**9.16±3.33**
4	1.00	32.21±3.23	38.18±7.99	32.72±1.24	**22.76±8.03**	40.76±8.53	25.98±9.16	35.07±8.53	**21.61±7.85**
5	2.00	45.17±10.44	50.24±3.22	42.37±2.15	**42.67±4.90**	51.10±7.99	38.83±8.38	48.59±7.61	**37.61±4.36**
6	4.00	59.77±6.24	60.58±4.39	55.53±3.72	**56.35±3.20**	64.89±8.44	49.69±9.16	60.18±7.61	**50.95±4.36**
7	6.00	70.04±5.52	74.37±1.22	66.93±5.41	**66.04±1.22**	74.37±8.79	64.51±7.39	71.77±5.46	**63.40±5.48**
8	12.00	83.17±3.66	85.57±3.66	78.33±5.41	**78.16±0.00**	83.85±7.99	75.38±7.78	81.44±4.10	**74.96±3.77**
9	24.00	87.57±3.26	90.74±4.22	85.35±4.47	**83.35±2.12**	85.57±7.61	80.32±6.40	85.30±3.61	**79.40±5.48**

Percentage Cumulative release of different formulations at pH 6.8 buffer

The results of the In- vitro release study of prepared niosomes in pH 6.8 buffer are shown in Table 1.5. The in-vitro release of the formulation containing span 60 and span 80 with cholesterol reveals that when the concentration of Cholesterol

increases (from 1 ratio to 3), in both cases the release decreases in comparison to the lower concentration of cholesterol. The reason behind decreasing drug release may be the membrane stabilizing property of the cholesterol which can enhance the rigidity of bilayers of this delivery system.

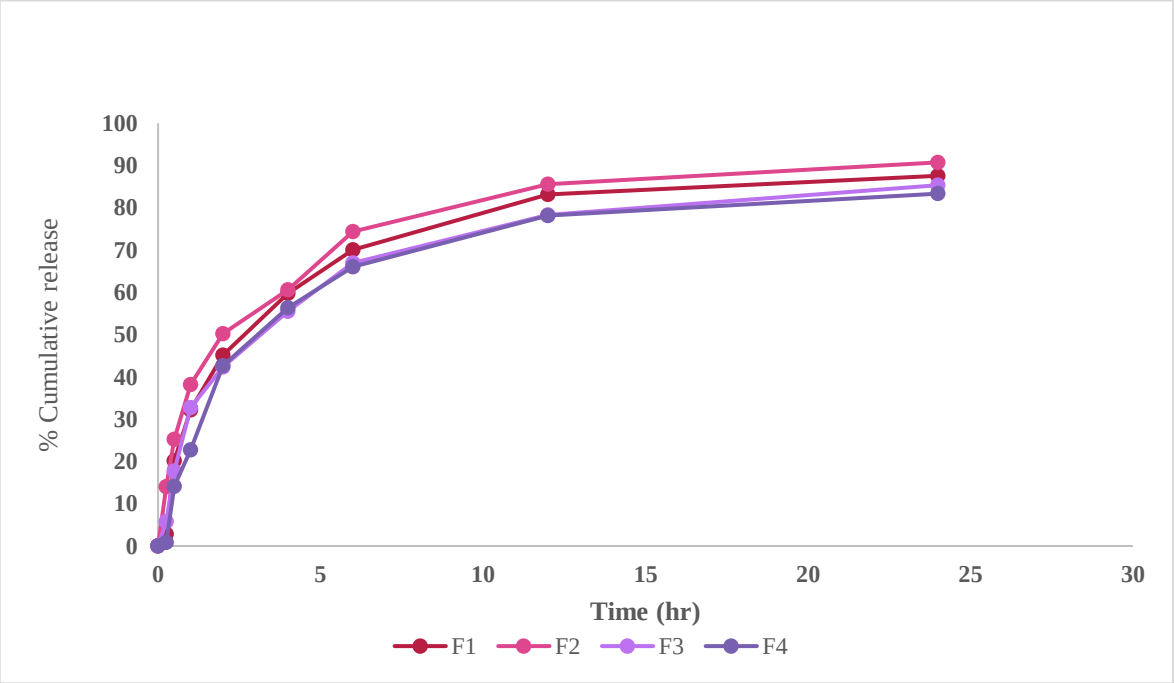

Figure 1 % Cumulative release of niosomal formulations conatining span 60 with cholesterol at pH 6.8 buffer

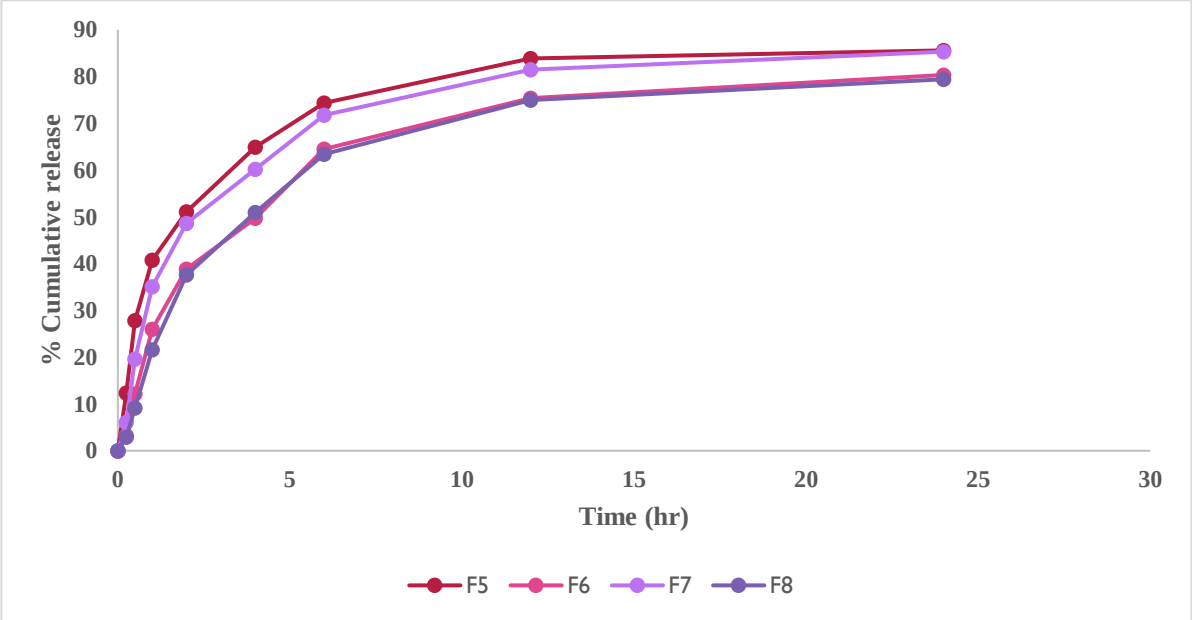

Figure 2% Cumulative release of niosomal formulations containing span 80 with cholesterol at pH 6.8 buffer

Release Kinetics:

To study the mechanism of the effect of Cholesterol concentration on Simvastatin encapsulated Niosome Containing Span 60 and Span 80 as surfactant data was fitted to various release models i.e. Higuchi square root of time and Korsmeyer-Peppas equations. Linearity was observed in the drug release plot with the Higuchi model as a regression coefficient (R^2) was found to be higher than 0.9544 for formulation (F2), and except it remaining formulation F1, F3-F8) was followed Higuchi model and their (R^2) was found 0.9326, 0.9277, 0.9361, 0.9219, 0.9337, 0.9319 and 0,9388 respectively. This indicates that these formulations followed Fick's law of diffusion. The release exponent (n) value for F2 was found to be 0.3602, which shows fickian diffusion.

Table 7: In Vitro release kinetics of all formulations

Parameter	Formulations							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Zero-order	0.6462	0.6437	0.6715	0.6587	0.5751	0.6785	0.6127	0.6782
First order	0.8487	0.8747	0.8667	0.8323	0.7628	0.8293	0.8029	0.8209
Higuchi	0.9326	0.9153	0.9277	0.9361	0.9219	0.9337	0.9319	0.9388
Peppas	0.8024	0.9544	0.8978	0.766	0.9034	0.8918	0.8743	0.9138
n value	0.5768	0.3602	0.4889	0.757	0.3589	0.5897	0.4782	0.6342
k value	3.8545	4.694	4.0463	3.2144	4.7059	3.5975	4.1837	3.4258

In this research article, we prepared eight formulations (F1-F8) these formulations F1, F3, F4, F5, F6, F7, and F8 followed the Higuchi model and shown diffusion mechanism. The F2 formulations follow the Korsmeyer-Peppas model and show a Fickian mechanism.

4. CONCLUSION

The study is based on the formulation of simvastatin niosome by changing the cholesterol concentration as the formulation variable. The investigation concluded that the higher cholesterol content increases the particle size due to the increase in hydrophobicity of the bilayer of vesicles, which alters the properties of the vesicular membrane. On the other hand, the entrapment efficiency and release also decreased upon increasing the concentration of cholesterol. Thus, cholesterol has significant effects on the characteristics of the niosomal formulations.

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Conflict of interest
None

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