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TO INVESTIGATE THE EFFECT OF SPAN 60 AND SPAN 80 POLYMER ON RELEASE RATE OF SIMVASTATIN NOISOME IN COMPARISON WITH PURE SIMVASTATIN

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ABSTRACT: The main objective of the present study was to develop and evaluate the simvastatin noisome using different grades of nonionic surfactants. It was hypothesized that niosomes would increase in vitro release of simvastatin in comparison to the API Mumbai. Niosome were prepared by thin-film hydration method and evaluated for particle size, entrapment efficiency, PDI, and in vitro release. The different niosomes shows various mean particle size, but Span 60 containing Niosomes have higher particle size than Span 80. Both optimized formulations of Span 60 and Span 80 have particle size 225.40 and 261.4. The PDI, entrapment efficiency of these optimized formulations was found to be 0.153, 0.167 and 85.72 ± 2.10, 81.44 ± 3.83, respectively. Niosomes prolonged the release of Simvastatin and provided a sustained release pattern. From the current study, it may be concluded that formulation F2 containing 2:1 (Span 60: Cholesterol) and F8 containing 1:3 (Span 60: Cholesterol) were found to be high % of entrapment efficiency and desired sustained release of simvastatin. Span 60 is a better non-ionic surfactant for preparation of noisome in comparison to Span 80, and niosomal drug delivery system of simvastatin is a simple and effective approach to produce nanoparticles of poorly water-soluble drug to enhance the release. These niosomes will probably reduce the frequency of administration of Simvastatin.

INTRODUCTION: Niosome is the vesicular system formed from the self-assembly of a hydrated nonionic surface-active agent, which can enhance the bioavailability of the drug; thus, the encapsulated drug provides therapeutic action in a controlled manner for a long period of time [1]. Niosomes increase the pharmaceutical profile of API, improve patient compliance, and reduce the side effects of drug [2].

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Niosomes are composed of the bilayer of non-ionic surface active agent, in which medicament is encapsulated; thus noisome acts as a depot from which drug release in a controlled manner.

The therapeutic activity of the drug may improve [3, 4]. Delay clearance of drug molecule from blood circulation. The bilayer protects the drug from gastric, biological, or enzymatic environment. Niosome also restricting the effect to target cells. Structurally noisome are similar to the liposome but in the case of noisome the bilayer is made up of non – ionic surfactant rather than the phospholipids [5]. Niosomes are lamellarin structure. They may be lamellar or multilamellar [6, 7]. Simvastatin is derived synthetically from fermentation products of *Aspergillus terreus* [8].

It is used to treat hyperlipidemia. Simvastatin, when hydrolyzed, produces beta, delta, dihydroxy acid, which is similar to HMG – CoA (Hydroxyl methyl glutaryl CoA) in structure. So hydrolyzed simvastatin competes with HMG – CoA for HMG – CoA reductase. Thus the quantity of mevalonic acid reduces which is the precursor of cholesterol due to interference with this enzyme, and level of cholesterol decreases [9]. Being a BCS class II drug simvastatin shows poor water solubility.

First pass metabolism is a major problem that results in low bioavailability (5%) [10]. The biological half-life is 3 h, so dose repetition is required, which may cause various adverse effects such as gastrointestinal complaints, fatigue, headache, and rash. Simvastatin may cause a minor increase in serum creatine phosphor kinase, which may be associated with myopathy [11].

On the other hand, all the formulations of simvastatin are available in the immediate release drug delivery system .this system shows instant drug release due to rapid disintegration. These formulations fluctuate the drug plasma level due to fast increase and decrease in dissolution, which results in loss of effect of drug and increase in effects [12].

MATERIALS AND METHODS:

Materials: Simvastatin was obtained from Sun pharmaceuticals, Gurgaon. Cholesterol Span 60 and Span 20 were purchased from SDFCL, fine chemical ltd. Mumbai. All other reagents and solvents used were of analytical grade.

Methods:

Formulation of Niosomes: Multi lamellar niosomes of Simvastatin were prepared by handshaking method. In this method, a mixture of vesicles forming ingredients of different grade non-ionic surfactants and cholesterol were dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask.

The organic solvent was removed at room temperature (20 °C) using a rotary vacuum evaporator, with the deposition of a thin layer of the solid mixture on the wall of the flask. The dried surfactant film rehydrated with an aqueous phase at 0-60 °C with gentle agitation. This process formed typical multi-lamellar niosomes.

Characterization of Simvastatin Niosomes:

Particle Size and Poly-Dispersity Index (PDI): The simvastatin niosomes were characterized for morphology viz. particle size and PDI. The average particle size and PDI of niosomes were evaluated by photon correlation spectroscopy zeta sizer nanoplus-3 (Japan). All the samples were appropriately diluted and analyzed by using 1ml cuvette in a thermostatic chamber at 250C using a He-Nelaser.

Entrapment Efficiency: 1.0 ml of niosomal formulation was taken and centrifuged at rpm 10000 to separate niosomes from non-entrapped. The supernatant was collected and diluted with a 6.8 pH buffer. Then absorbance was taken at 234 nm by the UV Spectrophotometer. The percentage of drug entrapment efficiency (EE %) was calculated by using the following formula.

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

Where, EE% is the percent entrapment efficiency, and ED is the amount of entrapped drug.

***In-vitro* Release Profile:** *In-vitro* release was studied using a dialysis membrane were investigated using dissolution apparatus. Niosomal formulations (1 ml) and API were placed in the donor compartment of K.C cell, and the acceptor compartment was filled with pH 6.8 buffer. The temperature of the receptor medium was maintained at 37 ± 5 ºC and agitated at 50 rpm speed using a magnetic stirrer. Aliquots of 5 ml sample were withdrawn periodically, and after each withdrawal, same volume of medium was replaced. The collected samples were analyzed at 234 nm in a Double beam UV-VIS spectrophotometer.

RESULTS AND DISCUSSION:

Pre formulation study: The physical appearance and melting point of the drug Simvastatin sample under investigation was found to be the same as that of the official reports. UV- VIS estimation of simvastatin was done by UV- VIS spectrophotometer. The calibration curve was prepared in methanol. The data was regressed to obtain a straight line. The R^2 value was found to be 0.996 in methanol, indicating good linearity. The solubility of simvastatin was determined in aqueous and organic solvents. It was found to be freely soluble in methanol, sparingly soluble in Phosphate buffer of pH 7.4, pH 6.8, and 1.2N HCl, or insoluble in water.

TABLE 1: SOLUBILITY OF SIMVASTATIN IN DIFFERENT SOLVENT SYSTEM

S. no.	Solvent	Solubility
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 particle sizes of the various developed formulations containing Span 60 were determined by Zeta sizer and found to be 559.2, 225.40, 582.3, 375.7 nm. It was clearly observed from the result, as shown in **Table 2** that the mean vesicle size of the formulations containing Span 80 was found to be 472.7, 317.6, 302.2, 261.4 nm, which shows that the niosomes containing Span 80 having a smaller particles size than Span60. This might be due to the higher hydrophobicity of Span 80 than Span 60. The decrease in surface free energy with increasing in hydrophobicity of Span 80 also contributes to particle size reduction.

TABLE 2: PARTICLE SIZES OF NIOSOMES CONTAINING SPAN 60

S. no.	Formulation Code	Span60:Cholesterol	Size (nm)
1	F1	Span 60 (1:1)	559.2
2	F2	Span 60 (2:1)	225.40
3	F3	Span 60 (3:1)	582.3
4	F4	Span 60 (1.3)	375.7

TABLE 3: PARTICLE SIZES OF NIOSOMES CONTAINING SPAN 80

S. no.	Formulation Code	Span80:Cholesterol	Size (nm)
1	F5	Span 80 (1:1)	472.7
2	F6	Span 80 (2:1)	317.6
3	F7	Span 80 (3:1)	302.2
4	F8	Span 80 (1:3)	261.4

Polydispersity index: The polydispersity indexes of the different formulations containing Span 60 were found to be 0.287, 0.153, 0.369, and 0.286, respectively. Formulation F2 having PDI 0.153 < 1, which shows better homogeneity of sample than other formulations.

TABLE 4: POLYDISPERSITY INDEXES OF NIOSOMES CONTAINING SPAN 60

S. no.	Formulation Code	Span60:Cholesterol	PDI
1	F1	Span 60 (1:1)	0.287
2	F2	Span 60 (2:1)	0.153
3	F3	Span 60 (3:1)	0.369
4	F4	Span 60 (1.3)	0.286

The polydispersity indexes of the different formulations containing Span 80 were found to be 0.290, 0.239, 0.215, and 0.167, respectively. Formulation F2 having PDI 0.167< 1, which shows better homogeneity of sample than the other formulations.

TABLE 5: POLYDISPERSITY INDEXES OF NIOSOMES CONTAINING SPAN 80

S. no.	Formulation Code	Span80:Cholesterol	PDI
1	F5	Span 80 (1:1)	0.290
2	F6	Span 80 (2:1)	0.239
3	F7	Span 80 (3:1)	0.215
4	F8	Span 80 (1:3)	0.167

TABLE 6: % ENTRAPMENT EFFICIENCY OF NIOSOMES CONTAINING SPAN 60

S. no.	Formulation Code	% Entrapment efficiency*
1	F1	71.17 ± 2.91
2	F2	85.72 ± 2.10
3	F3	77.69 ± 2.05
4	F4	73.67 ± 3.73

*Values expressed are mean ± SD where n=3

Entrapment efficiency: The entrapment efficiency of formulations containing Span 60 were given in **Table 6** in which F2 shows better entrapment efficiency. The entrapment efficiency of formulations containing Span80 were given in **Table 7.** F8 shows better entrapment efficiency.

TABLE 7: % ENTRAPMENT EFFICIENCY OF NIOSOMES CONTAINING SPAN 80

S. no.	Formulation Code	% Entrapment efficiency*
1	F5	73.93 ± 4.31
2	F6	74.23 ± 1.72
3	F7	78.57 ± 1.19
4	F8	81.44 ± 3.83

*Values expressed are mean ± SD where n = 3

% Cumulative release of niosomal formulations containing Span 60 at pH 6.8: *In- vitro* release of niosomal formulations in pH 6.8 buffer is given in table 8. The *in-vitro* release of F2 formulation is found to be 14.05 ± 4.39 at initial 15 min and 90.74 ± 4.22 at 24 h, which is better than the other formulations, so F2 formulation considered as optimized formulation among all the rest formulations containing Span 60 on the basis of better particle size, entrapment efficiency, and *in-vitro*-release.

TABLE 8: % CUMULATIVE RELEASE OF NIOSOME FORMULATIONS CONTAINING SPAN60 AT PH 6.8

S. no.	Time (h)	% Cumulative release			
		F1	F2	F3	F4
1	0	0	0	0	0
2	0.25	0.86±3.67	14.05±4.39	5.79±4.62	2.85±5.60
3	0.50	14.11±6.82	25.25±8.79	17.72±1.36	8.12±4.40
4	1.00	22.76±8.03	38.18±7.99	22.72±1.24	12.21±3.23
5	2.00	42.67±4.90	50.24±3.22	32.37±2.15	28.17±10.44
6	4.00	56.35±3.20	60.58±4.39	45.53±3.72	49.77±6.24
7	6.00	66.04±1.22	74.37±1.22	56.93±5.41	63.04±5.52
8	12.00	78.16±0.00	85.57±3.66	68.33±5.41	67.17±3.66
9	24.00	83.35±2.12	90.74±4.22	79.35±4.47	73.57±3.26

*Values expressed are mean ± SD where n=3

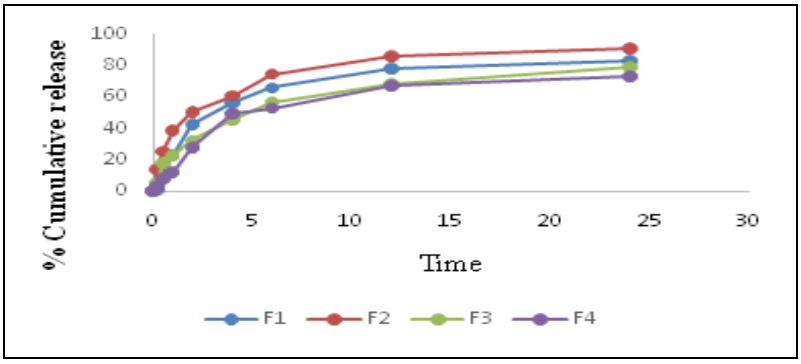

FIG. 1: % CUMULATIVE RELEASE OF NIOSOME FORMULATIONS AT PH 6.8

The *in-vitro* release of F8 formulation is found to be 12.32 ± 6.45 at initial 15 min and 85.57 ±7 .61at 24 h, which is better than the other formulations, so F8 formulation considered as optimized formulation among all the rest formulations containing Span 80 based on better particle size, entrapment efficiency, and *in vitro*-release.

TABLE 9: % CUMULATIVE RELEASE OF NIOSOME FORMULATIONS CONTAINING SPAN80 AT PH 6.8

S. no.	Time (h)	% Cumulative release			
		F5	F6	F7	F8
1	0	0	0	0	0
2	0.25	2.93±2.18	0.26±2.42	3.09±8.53	12.32±6.45
3	0.50	9.16±3.33	3.15±2.42	15.61±7.23	27.83±7.41
4	1.00	21.61±7.85	12.98±9.16	31.07±8.53	40.76±8.53

5	2.00	37.61±4.36	25.83±8.38	43.59±7.61	51.10±7.99
6	4.00	50.95±4.36	38.69±9.16	58.18±7.61	64.89±8.44
7	6.00	63.40±5.48	49.51±7.39	67.77±5.46	74.37±8.79
8	12.00	74.96±3.77	64.38±7.78	74.44±4.10	83.85±7.99
9	24.00	79.40±5.48	75.32±6.40	80.30±3.61	85.57±7.61

*Values expressed are mean ± SD where n=3

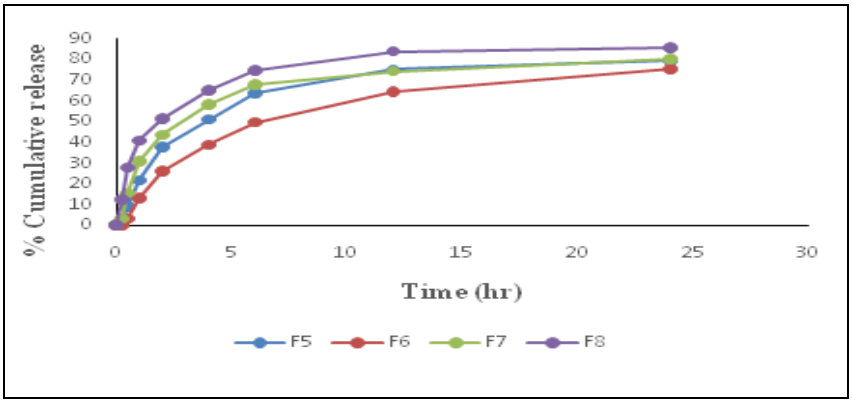

FIG. 2: % CUMULATIVE RELEASE OF NIOSOME FORMULATIONS AT PH 6.8

Niosome formulations (F2 and F8) at pH 6.8 buffer are shown in **Fig. 3**. In pH 6.8, the percent drug dissolved of the formulation F2 (14.05 ± 4.39%) and F8 (12.32 ± 6.45) increased as compared to the simvastatin powder (9.95 ± 3.11%) at the first 15 min of dissolution. Formulation F2 and F8 showed 90.74 ± 4.22 and 85.57 ± 7.61% release respectively within 24 h, which is better than the release of API *i.e.*, 59.27 ± 2.99.

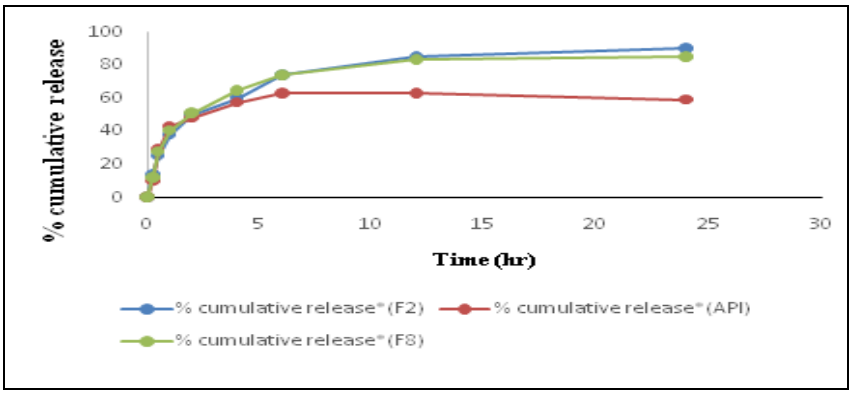

FIG. 3: % CUMULATIVE RELEASE OF F2, F8 AND API OF SIMVASTATIN AT PH 6.8

TABLE 10: % CUMULATIVE RELEASE OF F2, F8 AND API OF SIMVASTATIN AT PH 6.8

S. no.	Time (h)	% cumulative release*(F2)	% cumulative release*(F8)	% cumulative release*(API)
1	0	0	0	0
2	0.25	14.05±4.39	12.32±6.45	9.95±3.11
3	0.5	25.25±8.79	27.83±7.41	29.04±6.22
4	1	38.18±7.99	40.76±8.53	42.99±5.66
5	2	50.24±3.22	51.10±7.99	48.19±2.28
6	4	60.58±4.39	64.89±8.44	57.61±3.11
7	6	74.37±1.22	74.37±8.79	63.24±0.86
8	12	85.57±3.66	83.85±7.99	63.01±2.59
9	24	90.74±4.22	85.57±7.61	59.27±2.99

*Values expressed are mean ± SD where n=3

CONCLUSION: An effort was made to formulate the simvastatin niosomes to get better in vitro release. From the comparative study of the experimental result, it may be concluded that formulation F2 containing 2:1 (Span 60: Cholesterol) and F8 containing 1:3 (Span 60: Cholesterol) were found to be high % of entrapment efficiency and desired sustained release

of simvastatin. The particle size of simvastatin niosomes was obtained in nanosize, ranges (225.40 nm and 261.4 nm), which demonstrated that our prepared niosomes are in optimum size. The dissolution of nanosized simvastatin was significantly enhanced when compared with pure simvastatin. On the other hand, it may observed that both the optimized formulations containing different non-ionic surfactant showed different particle size, PDI, entrapment efficiency, and *in-vitro* release. When both optimized formulation compared, it revealed that the Span 60 having better release than the Span 80. Thus, we conclude that the Span 60 is a better non-ionic surfactant for the preparation of noisome in comparison to the Span 80 andniosomal drug delivery system of simvastatin is a simple and effective approach to produce nano particles of poorly water-soluble drug to enhance the release.

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