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Niosomal Formulations and Characterization of Tenofovir Disoproxil Fumarate

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Abstract

In the current study, liposomal formulations of the antiretroviral drug tenofovir disoproxil fumarate (TDF) will be developed and evaluated for controlled distribution. By utilizing different non-ionic surfactants (span-20, span-60, and span-80) and cholesterol in different ratios to obtain improved drug permeability at the targeted site of action, which considerably lowers dosage frequency and hence improves patient compliance, niosomes were formed by ether injection. The efficacy of entrapment, vesicle size, zeta potential, and surface shape of the generated vesicles were evaluated by TEM and in-vitro release. According to the TEM findings, the niosomes produced were white, round, and had a defined interior aqueous area with uniform particle size. The composition F5, which contained cholesterol and span 60, was the most beneficial (2:1).

Introduction

Tenofovir Disoproxil Fumarate (TDF) is an antiretroviral drug that works by stopping the enzyme reverse transcriptase, which is needed for HIV-infected people to make viruses. It has been shown to be the best drug for treating HIV-1 and hepatitis B in people, either on its own or in combination with other drugs [1, 2]. The main problem with TDF therapy is that it only works about 25% of the time. This may be because it can't get through the biological membrane of the gastrointestinal tract [3], which helps the niosomal vesicular system grow [4].

Niosomes are made when non-ionic amphiphiles self-assemble in water to make closed bilayer structures [5, 6]. These structures can hold both hydrophilic and lipophilic drugs in an aqueous layer or in a vesicular membrane.

So, in this study, non-ionic surfactants (span-20, span-60, and span-80) and cholesterol were mixed in different amounts and used to try to make TDF-loaded niosomes. This was done using the ether injection method. This could lead to an easier way to give the drug, avoiding problems like low oral bioavailability and the side effects that come with it. It would also give the drug a controlled release of its effects.

Materials and Methods

Ranbaxy Laboratories Ltd. in Dewas, India, gave us a sample of Tenofovir Disoproxil Fumarate (TDF) as a gift.Loba Chemie Pvt. Ltd. in Mumbai, India, was used to get sorbitan monolaurate (span 20), sorbitan monosterate (span 60), sorbitan monooleate (span 80), and cholesterol.

Formulation of TDF-loaded niosomes

Table 1 shows how non-ionic detergents (span 20, span 60, and span 80) and cholesterol were mixed together in different amounts to make TDF-loaded niosomes. For each mixture, 20 ml of diethyl ether was mixed with the correct amount of non-ionic surfactant and cholesterol. Then, 10 mg of TDF was put into this fatty solution.

Table 1: Composition for Niosomes Preparation

Formulation code	Surfactant	Amount of surfactant (mg)	Cholesterol (mg)	Drug (mg)	Ratio (Surfactant: Cholesterol)
F1	Span 20	100	100	10	1:1
F2	Span 20	200	100	10	2:1
F3	Span 20	100	200	10	1:2
F4	Span 60	100	100	10	1:1
F5	Span 60	200	100	10	2:1
F6	Span 60	100	200	10	1:2
F7	Span 80	100	100	10	1:1
F8	Span 80	200	100	10	2:1
F9	Span 80	100	200	10	1:2

The resulting solution was put in a syringe and slowly injected through a 16-gauge needle into 10 ml of aqueous phase (phosphate 0 buffer solution PBS; pH 7.4) held in a beaker at 60 C to 0 65 C and stirred slowly. Diethyl ether vaporized as the lipid solution was slowly poured into the water phase. This caused niosomes to form. Ultracentrifugation (Remi C-24, Mumbai, India) at 4 C was used to separate the niosomes that had already been made [4].

Evaluation of TDF Entrapped Niosomes and Drug entrapment efficiency (% EE)

By ultracentrifuging 1 ml of the niosomal solution at 25,000 rpm for 2 hours in a cooling centrifuge at 4°C (Remi C-24, Mumbai, India), the amount of TDF that was wrapped up was found. The supernatant was removed from the niosomes, which were then washed twice with 1 ml of PBS pH 7.4 each time and centrifuged again for 1 hour. The amount of zaleplon that was trapped was found by using isopropanol to break up the separated vesicles. A 100 l sample of niosomes was mixed with 1 ml of isopropanol. The amount was brought up to 10 ml with PBS pH 7.4 and covered with parafilm to keep it from drying out. UV spectrophotometer (UV 1700 Pharm Spec, Shimadzu, Japan) at 291 nm was used to figure out how much of the drug was in the sample [5]. The following method can be used to figure out the % drug entrapment efficiency:

$$EE = \frac{(\text{Actual drug content})}{(\text{Theoretical drug content})} x\ 100$$

Vesicle size and zeta potential measurements

The vesicle sizes of all formulations ranged from 1.140.16m to 8.260.42m (Table 2). These sizes are suitable for oral administration. It was discovered that niosomes prepared with span 60 are greater in size than those prepared with span 20 and span 80. Span 60 contains a longer saturated alkyl chain, and it has been shown that surfactants with longer alkyl chains produce larger vesicles [10]. The zeta values for niosomal formulations were determined to be in the range of -23.901.86 mV to -28.140.12 mV (Table 2). The zeta potential of the niosome under investigation was found to be -23.901.86 mV, as illustrated in Figure 1. The results demonstrated that when the HLB values of the vesicles increased, the zeta values of the vesicles decreased.

Transmission electron microscopy (TEM)

The vesicles were identified and found to be in an almost perfect sphere-like shape with a smooth surface and a definite internal aqueous area (Figure 2). [6].

In-vitro drug release from niosomes

The membrane diffusion method was used to figure out how the drug inside niosomes was released in the lab. The 5 mg of TDF worth of niosoma was put in a glass tube that had a pre-soaked cellulose membrane covering it. This glass tube works as a donor compartment. The glass tube was put in a beaker with 100 ml of PBS pH 7.4, which served as a compartment for the receptors. Using a magnetic mixer, the temperature of the receptor medium was kept at 371000C, and it was stirred at 100

rpm. Samples of 5 ml were taken out at regular intervals, and the same amount of medium was added after each removal. The samples were looked at using spectrophotometry at 291 nm with PBS pH 7.4 as a blank. [7]

Results and Discussion

The entrapment efficiency of niosomes made from span 60 was found to be greater than that of those prepared from span 20 (Table 2). The formulation with span 80 had the lowest entrapment efficiency. This could be because:

(a) span 60 has the highest phase transition temperature (500C) compared to spans 20 (160C) and 80 (-120C), resulting in a high entrapment efficiency.

(b) Because span 60 has a longer saturated alkyl chain (C18) than span 20, it creates niosomes with greater entrapment efficiency. Span 60 and 80 have the identical head group, but span 80 has an unsaturated alkyl chain, which increases permeability and decreases entrapment [8, 9].

Vesicle size and zeta potential measurements

All formulations' vesicles ranged in size from 1.14 0.16 m to 8.26 0.42 m (Table 2). These measurements work well for oral delivery. Niosomes made with span 60 were found to be larger than those prepared with span 20 and span 80. It has been noted that surfactants with longer alkyl chains typically produce larger vesicles [10], and Span 60 has a longer saturated alkyl chain.

According to Table 2, the zeta values for niosomal formulations ranged from -23.901.86 mV to -28.140.12 mV.As illustrated in Figure 1, the zeta potential of the niosome under investigation was discovered to be -23.901.86 mV. The findings showed that as the HLB values of the surfactants increased, the zeta values of the vesicles moved in the direction of negativity [11].

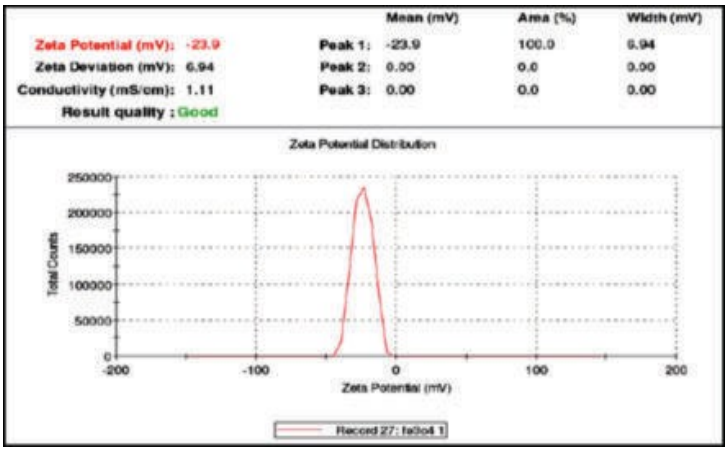

Figure 1: Zeta potential of niosomal formulation (F5). Transmission electron microscopy

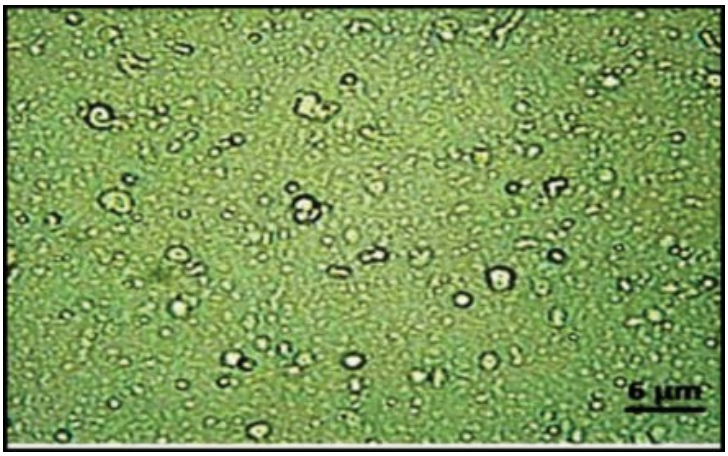

Figure 2: Transmission electron micrograph of niosomal formulation.

Table 2: Evaluation of niosomes

Formulation Code	Entrapment efficiency (%)	Vesicle size (µm)	Zeta potential (mV)	Q8h(%)
F1	77.05±1.65	1.14±0.16	-29.11±1.32	78.81±1.64
F2	82.16±1.29	2.34±0.99	-28.05±1.11	73.15±2.75
F3	76.21±0.23	1.89±1.26	-26.17±0.64	68.74±0.86
F4	91.02±2.13	5.64±1.32	-25.08±1.18	57.04±1.68
F5	92.46±1.62	6.09±2.11	-23.90±1.86	55.35±1.93
F6	90.04±3.15	5.97±1.95	-26.12±0.92	68.05±2.72
F7	88.76±2.18	7.01±0.27	-26.21±1.28	69.33±1.42
F8	81.04±0.56	8.26±0.42	-27.12±1.05	64.54±3.69
F9	76.08±2.11	7.75±1.24	-28.14±0.12	71.98±1.24

In-vitro drug release from Niosomes

Figure 3 shows that after 8 hours, the amount of drug released from the prepared niosomal vesicles in PBS with a pH of 7.4 ranged from 55.351.93% to 78.811.64%. When making niosomal mixtures with span 60 (2:1), the rate of release was slower than with span 20 and span 80. This can be explained by the fact that the rate of release from niosomes depends on the length of their alkyl chains [12, 13]. The Longer the chain, the slower the rate of release. It has been found that the niosomal formulas that release after 8 hours can be put in the following order: F1 > F2 > F9 > F7 > F3> F6 > F8 > F4> F5. Based on the results, it's clear that increasing the cholesterol molar ratio decreased the effects of the drug in niosomal preparations, which makes sense since cholesterol stabilizes membranes [14].

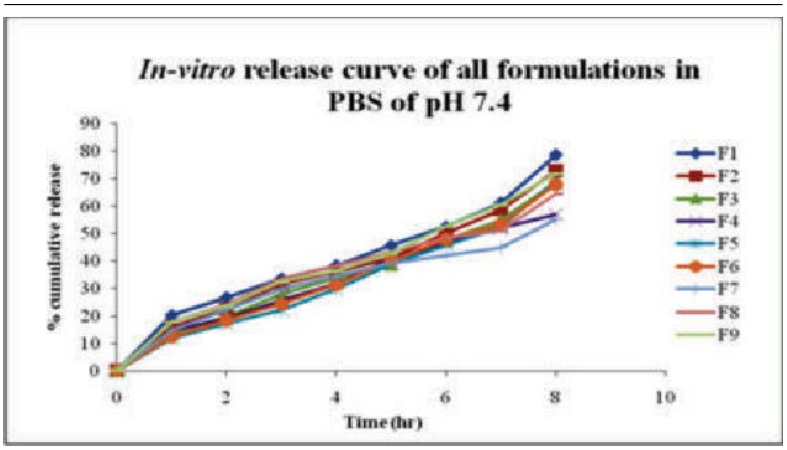

Figure 3: Drug release profile of TDF-loaded niosomes

Conclusion

When compared to other formulas, the best entrapment (92.461.62%) and slowest release after 8 hours (Q8h=55.351.93%) came from F5, which was made of span 60 and cholesterol (2:1). Niosomal formulations are more stable and have a lower rate of drug release. Based on these results, it seems likely that niosomes could be used to release TDF in a controlled way.

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