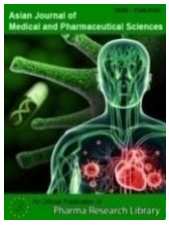

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Formulation and evaluation of microparticle controlled release solid dosage form of Remogliflozin

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A B S T R A C T

Encapsulation of medicaments in vesicular organization can be expected to prolong the availability of the medicaments in the systemic circulation and hence augment penetration into objective tissue and diminish toxicity. Proniosome formulations are minute lamellar arrangements of alkyl or dialkyl polyglycerolnon-ionic surfactant, cholesterol and hydrophilic carrier molecule. On hydrolysis they generate unilamellar or multi-lamellar noisome vesicles that leads to better drug delivery. Proniosomes enter in the human body, they are recognized as the foreign bodies and easily taken up by the mononuclear phagocytic cells. HIV is present in mononuclear phagocytic cells of infected patient, so proniosomes represent suitable carriers for targeting anti-HIV drugs to the infected cells. The present study was undertaken to formulate pronoisome carrier system for antiviral drug Lamivudine by slurry method using commonly available surfactants like span 20, span 40, span 60, span 80, tween 20, tween 40, tween 60 and tween 80. A total of 16 formulations were prepared to achieve the encapsulation of Lamivudine in vesicular carrier system.The mean vesicle size of proniosome derived vesicles in case of charge inducer incorporated formulations were in the range of 131.8 ±8.45 to 178.8 ±6.87 respectively. In case of the formulations without charge inducer the size of drug loaded formulations were in the range of 129.1±15.808 to 176.2±9.735 respectively.Zeta potential of the proniosomal formulations were found in range of -33.0 ±1.17 to -44.3 ±1.74 for charge inducer and -2.23±0.521 to 32.5±0.833 in the formulations without charge inducer.

Keywords: Lamivudine, Niosomes, Proniosomes, Surfactants, Charge inducer etc

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C o n t e n t s

1. Introduction

The novel drug delivery systems are the carriers which maintain the drug concentration in therapeutic range for longer period of time and also, in addition, may deliver the content to the site of action if so desired as per requirements [1]. Niosomes are unilamellar or multilamellar microscopic vesicles, formed on admixtures of nonionic surfactant and cholesterol with subsequent hydration in aqueous media can entrap both hydrophilic and lipophilic drugs, either in aqueous region or in vesicular membrane made of lipid materials with size ranging from 10 to 1000 nm in size[2,3]. Liver can act as depot for many drugs where niosomes containing drugs may be taken up and broken down by lysosomal lipase slowly to release the free drug and re-enter the circulation. Hence niosomes are slowly degraded providing a more sustained effect. Proniosome formulations are minute lamellar arrangements of alkyl or

dialkyl polyglycerolnon-ionic surfactant, cholesterol and hydrophilic carrier molecule[4,5].

Drugs regularly used for the management of the retroviral infection mostly exist as conventional dosage forms[6]. The main shortcoming of these dosage forms are non specific or non targeting delivery of the drug in the site of action. Drug delivery systems by means of colloidal particulate carriers such as liposomes, niosomes have distinct advantages over conventional dosage forms because the particles can act as drug containing reservoirs, and modification of the particle composition or surface can adjust the drug release rate and/or the affinity for the target site[7,8].

Acquird immune deficiency syndrome (AIDS) is the most common problem throughout the world because of rapid increase in the number of victims. After entering the body of the host, the HIV activates the enzyme called reverse transcriptase[9]. The RNA genome of the virus undergoes reverse transcription, leading to the synthesis of double-stranded complementary DNA[10]. Hence in the present research Lamividine proniosomes were formulated and evaluated to target the release of drug at the site of infection.

2. Materials and Methods

Materials

The drug Lamivudine was purchased from Drugs India LTD, Hyderabad., Cholesterol, Maltdextrin, Tweens and Spans was purchased from Himalaya Scientifics, Nellore, APAll the other chemicals and reagents used were of analytical grade and purchased from Hi media Laboratories, SD Fine chemicals and Merck, Mumbai.

Methods

Pre-formulation Studies:

Preformulation studies like fundamental characterization studies (Organoleptic properties, melting point, solubility, and pH) and spectroscopic studies (UV and IR) were performed on Lamivudine drug sample.

Formulation Methodology:

Concentration and process optimization:

The concentrations of nonionic surfactant and cholesterol were optimized to develop the stable dosage form with different nonionic surfactants (spans and tweens) at150, 200, 250 and 300µM concentrations with anequal ratio of cholesterol. Although vesicles were formed in all concentrations, the encapsulation efficiency was found tobeverylessexceptat300µMratio.Thus300:300µMratioofsurfactant:cholesterolwaspreferredforpresentformulation.Theprocess-relatedvariables like speed of rotation of flask, hydration medium and hydration time were optimized by trial and error method. Lamivudine proniosome preparation: Proniosome formulations were prepared by the slurry method. The slurry method is comparatively simple and is mostly useful for the carriers which are not dissolving in organic solvents. In brief, accurately weighed amounts of lipid mixture (500µM) comprising of surfactant and cholesterol, with 5µM DCP were dissolved in 4ml chloroform. The drug was dissolved in 6ml methanol and the result ant solutions were transferred to a 250ml round bottom flask having malto dextrin carrier. Additional chloroform: methanol solution was added to form slurry in the case of inferior surfactant loading. The flask was attached to a rotary flash evaporator to evaporate solvent at 100-150rpm, a temperature of 60°C, and a reduced pressure of600mmHg until the mass in the flask had become a dry, free flowing product. After ensuring the complete removal of solvent, the resultant materials were further dried over night in a desiccator under vacuum at room temperature[11,12]. This dry preparation is referred to as 'proniosomes' and was used for preparations and for further study on powder properties. These proniosome granules were stored in a tightly closed container at refrigerator temperature until further evaluated. The composition of different batches of Lamivudine proniosomal formulations are represented in Table 1.

Characterization of Lamivudine proniosome formulations

Preparation of proniosomes

The proniosomal powder was transformed to noisome vesicles by hydrating with phosphate buffer (pH7.4) at 80°C by means of vortexingusingvortexmixer for 2min. The niosomal dispersion was placed over a glassslide and thevesicleformationwasobservedunderopticalmicroscope.Thereresultantniosomaldispersion was subsequently subjected to evaluation of zeta potential, vesicle size, Sized is tribution, Encapsulation Efficacy and morphology as per the procedure.

Drug content

Lamivudine content in proniosomes was obtained by an UV spectrophotometric method. Niosomes obtained from proniosomal formulation containing 10mg Lamivudine was taken into a standard volumetric flask. The vesicles were destructed with 50ml propane-1-ol by shaking and 1ml of the mixture subsequently diluted with phosphate buffer pH 7.4. The absorbance was measure dspectrophotometrically against blank at 267 nm[13].

Dissolution study

Dissolution is the procedure of extracting the active pharmaceutical ingredient out of the solid pharmaceutical dosage form matrix into solution with in the GIT. Dissolution study is an in-vitro method that describe showan active pharmaceutical ingredient is take out of a solid dosage form.

The dissolution studies were carried out according to the US Pharmacopeia (USP) type Iapparatus (basket method). The Lamivudine proniosome formulations corresponding to 10 mg Lamivudine were filled into hard gelatin capsule. The dissolution medium was 900m l0.1NHCl/ phosphate buffer solution (pH6.8)in six dissolution jars to maintain sink conditions. The capsules were placed in basket and immersed in dissolution medium. The stirring speed was 50rpm, and the temperature was maintained at 37°C±0.5°C. The samples (3 ml) were withdrawn atfixed time intervals using a syringe and passed through 0.2µm membrane filter [14].

Withdrawn samples from dissolution jars were replaced by fresh medium. The Lamivudine content was evaluated by UV spectrophotometer at 267nm. The cumulative percentage of Lamivudine release from formulation was plotted as a function of time.

Osmotic shock studies

The consequence of osmotic shock on optimized pronoisome formulations was evaluated by incubating of niosomal suspensions obtained from proniosomes in media of diverse tonicities. The formulation was divided into three parts incubated with hypotonic (0.5%NaCl), isotonic (0.9% NaCl), and hypertonic solutions (1mol/ Lsodium iodide solution) for 3 hours. Then the changes in the vesicle size in the formulations were observed.[15]

Scanning electron micro scopy (SEM)

The exterior characteristics of the proniosome powder and maltodextrin was examined by scanning electron microscope (JSM 6390LA, Jeol, Tokyo, Japan). Each sample was smearedon a small piece of adhesive carbon tape which was fixedon abrass stub and subjected to gold coating using sputtering unit for 10 sec at 10mA of current. The gold coated samples were placed in chamber of SEM and images were recorded.[16]

Fouriertrans form infrared (FT-IR)spectroscopy

FTIR spectra of pure Lamivudine, surfactants, cholesterol, maltodextrin,blankproniosomeformulation(CBPF7)andopti mizedproniosomeformulation (LVC 7) were obtained using FT-IR spectrophotometer (FTIR-6300, Jasco, Japan) by the usual KBr pellet method to scrutinize the interactions between drug and excipientsin formulation. The scanning range was 4000-400cm−1 at ambient temperature. The smooth in the IR spectra and the base line correlation procedures were applied.[17]

Differential scanning calorimetry

The physical nature of Lamivudine in optimized proniosome formulation was evaluated by performing differential scanning calorimetry analysis of pure Lamivudine, maltodextrin, tween60, cholesterol and formulation (LVC 7). The DSC thermograms of the samples were gained by a differential scanning calorimeter (DSC6000, Perkin Elmer). Each sample was held in an aluminum pan and then crimped with an aluminum cover. All the five samples were scanned at 10°C/min from 30 to 400°C under a nitrogen purgeat 20 mL/min.[18]

Stability study

Physical stability study was carried out to investigate the degradation of drugfrom proniosome during storage. The optimized pronoisome formulation with the composition of tween 60 and cholesterol in 250:250 µM ratio with 5µM DCP was divided into 3sets of samples. The samples were sealed in glass vials and stored at (2-8°C) in refrigerator, room temperature 25±2°C and 45±2°C for a period of 3 months. Samples were withdrawn at definite periods of time and analyzed for vesicle size,% drug remaining and percent drug entrapment.[19]

Table 1: proniosomal formulations without charge inducer

S. No	Formulation code	Surfactant used	300µM surfactant	300µM Cholesterol	Maltodextrin
01	LV1	Span20	83.30µl	98 mg	500 mg
02	LV2	Span40	101.64 mg	98 mg	500 mg
03	LV3	Span60	106.66 mg	98 mg	500 mg
04	LV4	Span80	109µl	98 mg	500 mg
05	LV5	Tween20	273.90µl	98 mg	500 mg
06	LV6	Tween40	390.22µl	98 mg	500 mg
07	LV7	Tween60	312.5µl	98 mg	500 mg
08	LV8	Tween80	314.14µl	98 mg	500 mg

#Drug content used 25mg per batch, LV-drug loaded proniosome formulations.

Table 2: Composition of Lamivudine proniosomal formulation with charge inducer

S.No	Formulation code	Surfactant used	300µM Surfactant	300µM Cholesterol	DCP	Maltodextrin
1	LVc1	Span20	83.30µl	98 mg	3 mg	400 mg
2	LVc2	Span40	101.64 mg	98 mg	3 mg	400 mg
3	LVc3	Span60	106.66 mg	98 mg	3 mg	400 mg
4	LVc4	Span80	109µl	98 mg	3 mg	400 mg
5	LVc5	Tween20	273.90µl	98 mg	3 mg	400 mg
6	LVc6	Tween40	390.22µl	98 mg	3 mg	400 mg
7	LVc7	Tween60	312.5µl	98 mg	3 mg	400 mg
8	LVc8	Tween80	314.14µl	98 mg	3 mg	400 mg

#Drug content used 30mg per batch, LVc-Charge inducer added drug loaded proniosome formulations.

3. Results and Discussion

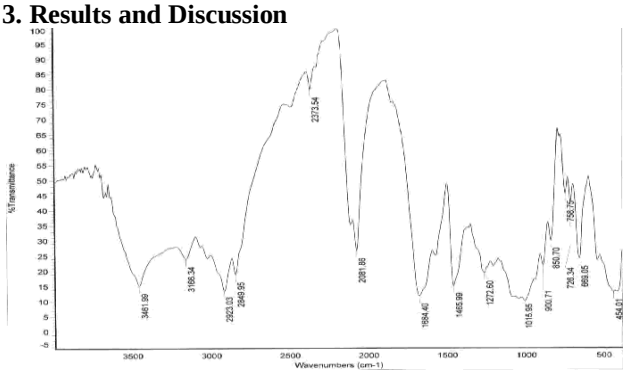


Figure 1: FT-IR Spectra of pure Lamivudine

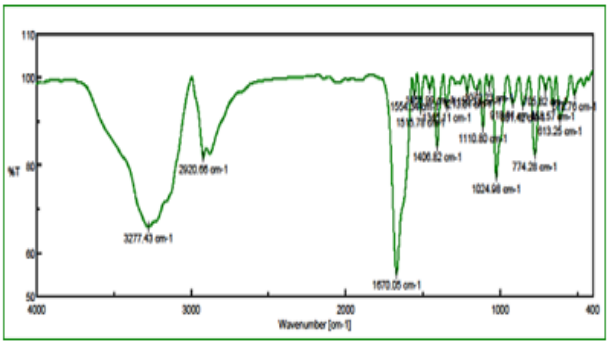


Figure 2:FT-IR Spectra of Lamivudine with cholesterol

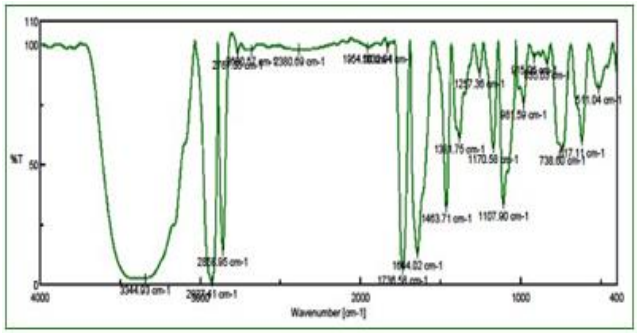


Figure 3: FT-IR Spectra of Lamivudine with maltodextrin

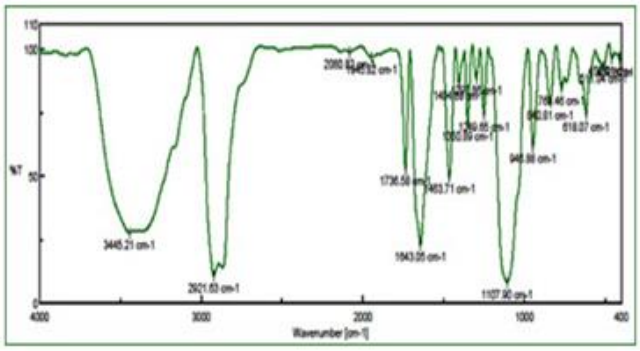


Figure 4: FT-IR Spectra of Lamivudine with Span

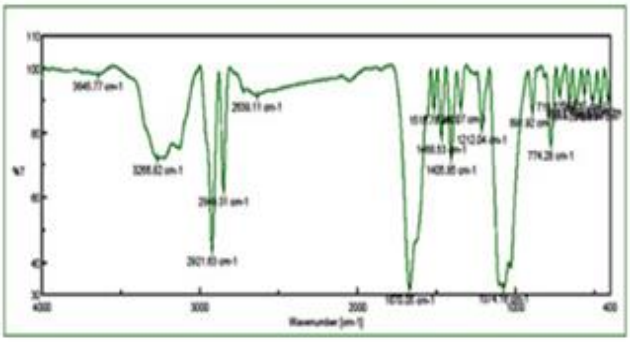


Figure 5: FT-IR Spectra of Lamivudine tween

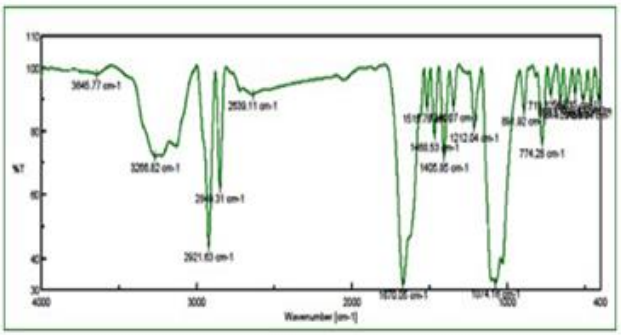
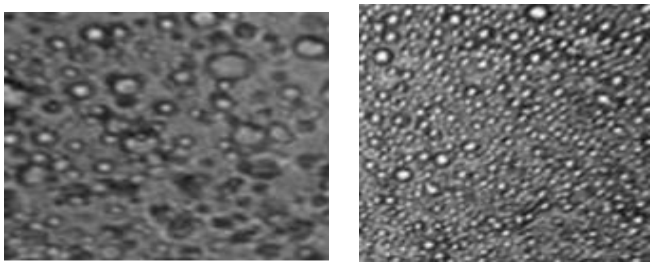


Figure 6: FT-IR Spectra of Lamivudine with DCP



LV6 **LV7**

Figure 7: Optical photomicrograph of various batches of proniosome

Table 3: Encapsulation efficiency of various pronoisome formulations

Formulation code	%Drug Encapsulated	Formulation code	%Drug Encapsulated
LV1	42.72 ±2.727	LVC1	45.38 ±1.924
LV2	61.02 ±2.555	LVC2	63.62 ±1.541
LV3	68.73 ±1.740	LVC3	70.72 ±2.479

LV4	33.49 ±0.978	LVC4	35.13 ±1.404
LV5	64.80 ±2.807	LVC5	68.38 ±2.395
LV6	72.27 ±2.491	LVC6	77.32 ±2.113
LV7	80.24 ±1.886	LVC7	85.02 ±1.560
LV8	49.47 ±0.919	LVC8	57.59 ±2.025

Table4: Drug content of Lamivudine proniosomal formulations

Formulation code	Drug content	Formulation code	Drug content
LV1	100.17 ±0.766	LVC1	99.03 ±0.245
LV2	99.58 ±0.474	LVC2	99.94 ±0.652
LV3	99.32 ±1.082	LVC3	99.19 ±0.854
LV4	99.95 ±0.578	LVC4	100.13 ±1.234
LV5	99.16 ±1.524	LVC5	99.04 ±0.573
LV6	99.93 ±0.541	LVC6	99.01 ±0.949
LV7	99.54 ±1.125	LVC7	99.67 ±0.963
LV8	100.04 ±0.769	LVC8	99.03 ±0.245

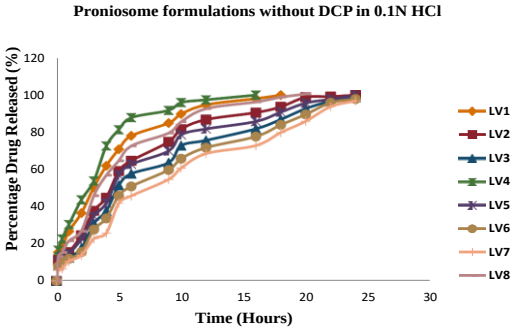


Figure 8 : *In-vitro* Lamivudine release plot of proniosome formulations without DC Pin 0.1N HCl

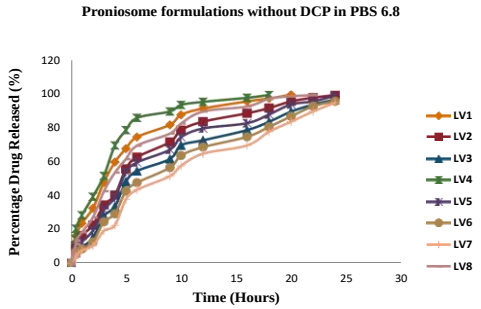


Figure 9: In-vitro Lamivudine release plot of proniosome formulations without DC Pin PBS 6.8

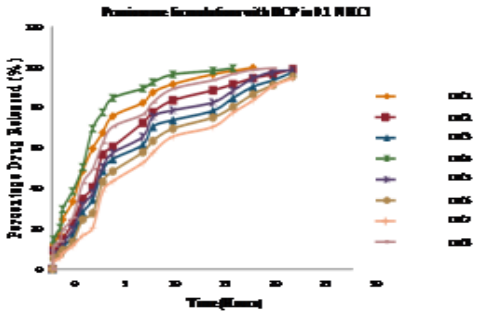


Figure 10: In-vitro Lamivudine release plot of proniosome formulations with DCPin0.1 N HCl

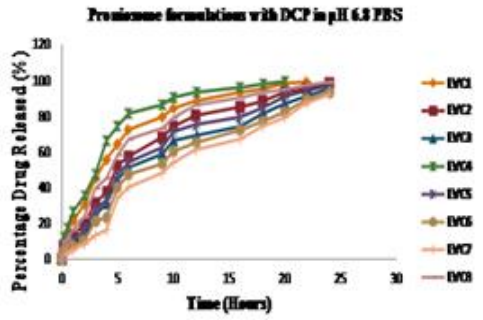


Figure 11: *In-vitro* Lamivudine release plot of proniosome formulations with DCP in PBS pH 6.8

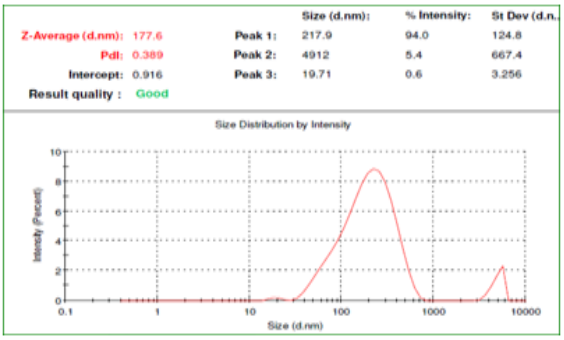


Figure 12: Vesicle size, size distribution report of optimized proniosome LVC-7

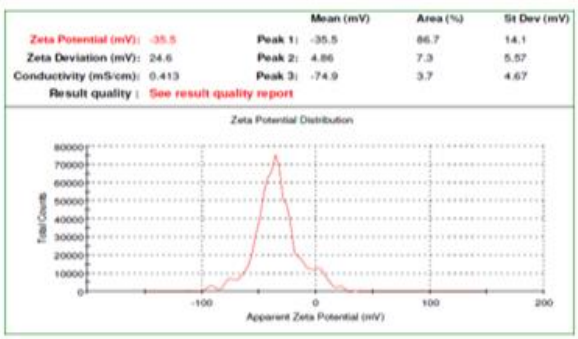


Figure 13: Zeta potential reports of optimized proniosome LVC 7

Table 05: Effect of osmotic shock on Lamivudine proniosome formulations

Formulation	Average Vesicle size			
	PBSpH7.4	Hypertonic1 mol/LNaI	Isotonic 0.9% NaCl	Hypotonic 0.5%NaCl
LV7	171.4 ±6.047	Shrunk	176.2 ±10.627	197.4 ±15.615
LVC7	175.0 ±5.122	Shrunk	182.7 ±8.059	203.0 ±10.104

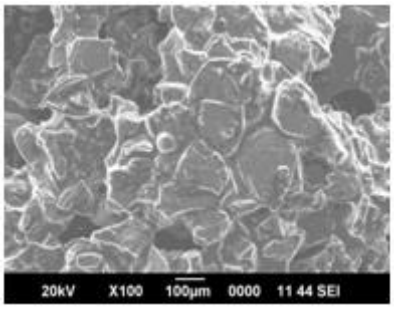


Figure 14: SEM image of optimized proniosome formulation LVC7

Table 06:Stabilitystudydataofoptimizedproniosomeformulation

Temperature	RefrigeratorTemperature2-8°C			Room Temperature25±2°C			Elevated Temperature45° ±2°C		
Sampling period	**1 month**	**2 months**	**3 months**	**1 month**	**2 months**	**3 months**	**1 month**	**2 months**	**3 months**
Percentage Drug retained	99.23 ±0.89	98.71 ±0.80	98.55 ±1.17	98.56 ±0.81	98.12 ±0.72	97.69 ±0.98	98.66 ±0.92	95.13 ±1.35	90.98 ±1.45
Percentage drug Encapsulated	84.69 ±1.14	84.07 ±1.45	83.16 ±1.24	83.39 ±0.81	81.89 ±1.18	80.08 ±1.40	80.52 ±1.57	73.42 ±1.63	68.02 ±2.03
Vesicle Size	178.63 ±7.16	182.5 ±8.18	188.97 ±8.91	182.97 ±8.91	189.67 ±7.83	196.83 ±11.95	189.67 ±12.24	202.63 ±17.38	224.4 ±18.04

Discussion

Pre formulation studies:

The results of pre formulation studies like organoleptic properties, particle size analysis, solubility studies, partition coefficient and FT-IR spectrum were proved the characteristic sofpureantiretro viral drug Lamivudine. From the result of drug excipient compatibility study, the chosen excipients did not show any characteristic changes. The FT-IR spectrum of all physical mixtures showed the characteristic peaks of Lamivudine, thus confirming that no reaction of drug occurred with the excipients of the physical mixture.

Formulation of Lamivudine proniosome formulations:

The formulation of proniosomes by slurry method was found to be more convenient and the hydration of proniosome had taken short period of time (2 minutes at 80°C) in vortex mixture. The convenience during hydration of proniosome is due to the more surface area of the surfactant–lipid film that occurs over the water-soluble carrier particle maltodextrin.

Characterization of Lamivudine proniosome formulations: Most of the optical microscopy images of proniosome derived niosome vesicles are multilamellar, discrete and spherical with sharp boundaries without much aggregation. Some irregularities that monitored under the microscopic study may be due to drying process under ordinary environ mental condition.

The size of proniosome derived vesicles were found to be inacceptable limit. The mean vesicle size of proniosome derived vesicles is presented in table. In case of charge inducer incorporated formulations the size of and the drug loaded formulations were in the range of 131.8 ±8.45 to 178.8 ±6.87 respectively. In case of the formulations without charge inducer the size of drug loaded formulations were in the range of 129.1±15.808 to 176.2±9.735 respectively. The liaison observed between blank and drug loaded formulations has been attributed the role of drug encapsulation in vesicle size. The noisome vesicles produced from span proniosomes were extremely statistically significant (P=0.0001<0.05) smaller insize than the vesicles produced from tween proniosomes [20]. Among the 16 proniosome formulations niosomes were of bigger size (178.8 nm ± 6.87) in the case of tween 40 based charge inducer incorporated proniosomes. The smaller vesicles produced from span formulations might be due to low HLB value, higher hydrophobicity, and low surface energyofspanseriessurfactants.Furthermoreincreasingalkylchainlengthandhydrophilicityofsurfactantsmayincreasethe vesicle size of proniosomes.

4. Conclusion

Presently proniosomes have been studied by investigators as a preference of oral drug delivery system for antiretroviral drugs to provide a better oral bioavailability considering, targeted delivery, minimize the adverse effects, prolonged release of the niosome encapsulated medicaments through biological membrane and the stability of them.The Lamivudine novel proniosome drug delivery system represent a significant improvement in all evaluation parameters. To summarize the above mentioned outcomes, water soluble drug Lamivudine was fruitfully incorporated into proniosomes.

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