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A Pharmaceutical Composition Comprising A Liposomal Formulation Of Efavirenz, Its Preparation And Application Thereof

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ABSTRACT
In many countries, Efavirenz is the primary non nucleotide reverse transcriptase inhibitor for first-line antiretroviral therapy. It is an orally active antiviral drug that is specific for human immunodeficiency virus type 1 (HIV-1). Its effectiveness is due to its lengthy half-life, which ranges from 52 to 76 hours after numerous doses. The medication is poorly soluble in water. One of the most difficult difficulties for formulation scientists in the research sector will be the oral delivery of poorly soluble drugs. We intended to investigate effective encapsulation of efavirenz (EFV, which is one of the powerful (ARVs) using varied mass ratios of crude soybean lecithin and cholesterol, since the liposome is the most clinically successful DDS and yet is often investigated for ARVs delivery.

Keywords: *antiviral, DDS, Efavirenz, ARVs, poorly soluble drug*

1. INTRODUCTION

Acute immune deficiency syndrome and the human immunodeficiency virus HIV/AIDS is one of the most lethal and life-threatening infectious illnesses that plagues the world's population.[1] According to the U.n., approximately 36.9 million people worldwide, including 1.8 million children, are living with HIV/AIDS (UNAIDS 2019). As of 2017, an estimated 21.7 million people across the world were receiving antiretroviral therapy (ART) (UNAIDS 2019). Patients infected HIV are often treated with HAART, which incorporates the administration of several antiretroviral drugs on a regular basis. Unfortunately, this medication is only used for the short-term treatment and effective control of the virus, and it merely slows the virus's reproduction within infected cells, increasing patients' quality of life (Gupta and Jain 2010).

In HAART regimens, three main categories of antiretroviral (ART) medications are proposed: non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, and HIV integrase inhibitors. These include nevirapine, efavirenz (EFA), etravirine, rilpivirine, saquinavir, indinavir, ritonavir, raltegravir. Various drug delivery methods are used to administer HIV medicines in a regulated and targeted way, enhancing drug bioavailability and resident duration at target locations, and therefore improving HIV patients' quality of life. These medicines are less expensive and have less dosage dumping issues.

The ARTs, on the other hand, have a limited oral bioavailability and are metabolised by cytochrome P450 (CYP). Chemical modification of pre-existing entities, reduction of vesicle size using high pressure homogenization, colloidal mill, and development of novel delivery systems such as self-nano emulsifying drug delivery systems, solid-lipid nanoparticles, nanosponges, and liposomes to improve the efficacy of ART drugs are some of the methodologies used to overcome these drawbacks. Liposomes are tiny vesicles made up of one or more lipid bilayer spheres that are separated by water or an aqueous buffer compartment. They are utilised as carriers for enhancing medication solubility, bioavailability, stability, and targeting because of their biphasic characteristics, variety in design, and composition. Amphotericin B, silymarin, fenofibrate, dapsone, budesonide, and artemisinin have all been utilised as carriers in liposomes.

Water-soluble medicines in the central core, lipid-soluble drugs in the membrane, and peptides and small proteins at the lipid-aqueous interface are all possible compartments for pharmaceuticals carried by liposomes. Efavirenz is a nonnucleoside reverse transcriptase inhibitor (NNRTI) that is one of the most commonly used in first-line antiretroviral therapy (ART) and is indicated as a preferred option in adult treatment recommendations [16]. Its chemical name is (4S)-6-chloro-4-(cyclopropylethynyl)-1, 4-dihydro-4-(cyclopropylethynyl)-1, 4-dihydro-4-(cyclopropylethynyl)-1,4-dihydro (trifluoromethyl) 1-benzoxazin-2-one, -2H-3 (Figure 1). The absorption of orally administered medicines from the gastrointestinal (GI) tract determines their bioavailability; It is a poor water soluble BCS class-II medication with a low aqueous solubility of 6.2 g/ mL. The medication has limited oral absorption and bioavailability (40-45 percent) and considerable inter-subject variability due to its high lipophilicity (log P=5.4) and hence poor water solubility.

2. MATERIALS

Table no. 1:- List of Materials

Sr.no	Ingredient	Specification/ Grade	Manufacture/Supplier
1.	Efavirenz	Research Grade	Yarrow Chem Products. Mumbai.
2.	Soya lecithin	Research Grade	Himedia laboratories Pvt. Ltd. Mumbai
3.	Cholesterol	AR	Cosmochem Pvt. Ltd
4.	Chloroform	AR	Cosmochem Pvt. Ltd
5.	Methanol	AR	Lobachem Pvt. Ltd. Mumbai
6.	PEG 6000	AR	Lobachem Pvt. Ltd. Mumbai
7.	Potassium Dihydrogen Phosphate	AR	Lobachem Pvt. Ltd. Mumbai
8.	Sodium hydroxide	AR	Merck specialties Pvt. Ltd

Optimization of Analytical Method:

1. Determination of λmax of Efavirenz

UV spectrum of Efavirenz was carried out in methanol and 0.1 N HCL by dissolving 100mg drug in 100 ml methanol to get conc. of 1mg/ml (1st Stock Solution) and further dilutions were made with mentioned solvent. From that 1ml diluted to 100ml to get 10ug/ml (2nd Stock Solution). A solution of 10ug/ml was kept in Quartz cell of path length 10nm. The UV spectrum was recorded using double beam UV-visible spectrophotometer in the wavelength range of 400-200 nm using methanol as blank and λmax was determined.

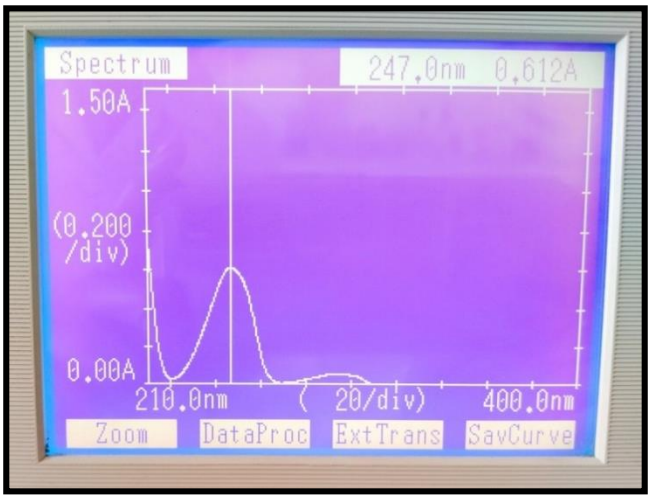


Figure no. 1:- UV spectra of Pure Drug Efavirenz

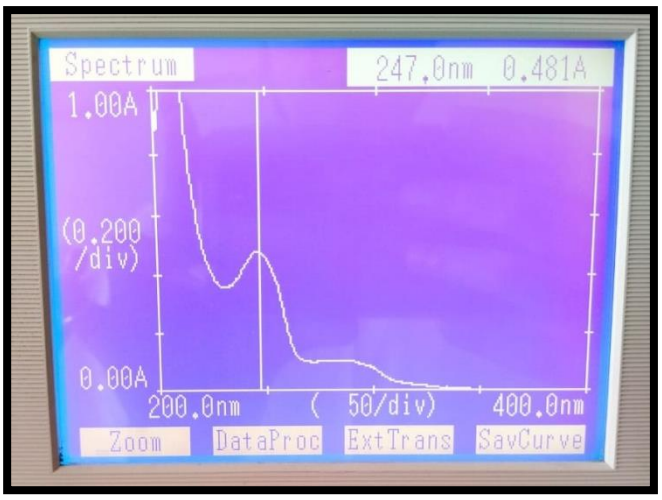


Figure 2:- UV spectra of Efavirenz in 0.1 N HCL

2. Standard calibration curve of Efavirenz

Accurately weighed quantity of 100mg Efavirenz was transferred in 100 ml of Volumetric flask, dissolved in solvent (Methanol & 0.1 N HCL) and volume made up to those solvent to obtain first stock solution was diluted up to 100ml by using solvent (Methanol & 0.1N HCL) to obtain 2nd stock solution (10ug/ml). This stock was suitably diluted with solvent (Methanol & 0.1 N HCL) to obtain range of 1-10ug/ml and absorbance was recorded at 247nm in Methanol & 0.1 N HCL using UV spectrophotometer. The linear correlation was obtained between absorbance and concentration. The calibration curve is shown in figure.1 and absorbance of different concentration of Efavirenz is shown in table.no. 2

Sr.no.	Conc (ug/ml)	Absorbance 247nm	Absorbance 247nm
		Methanol	0.1N HCl
1	0	0.000	0.000
2	1	0.072	0.142
3	2	0.124	0.199
4	3	0.175	0.267
5	4	0.236	0.323
6	5	0.284	0.384
7	6	0.349	0.452
8	7	0.411	0.511
9	8	0.476	0.569
10	9	0.532	0.635
11	10	0.601	0.684

Table no. 2:- Data for Calibration curve of Efavirenz

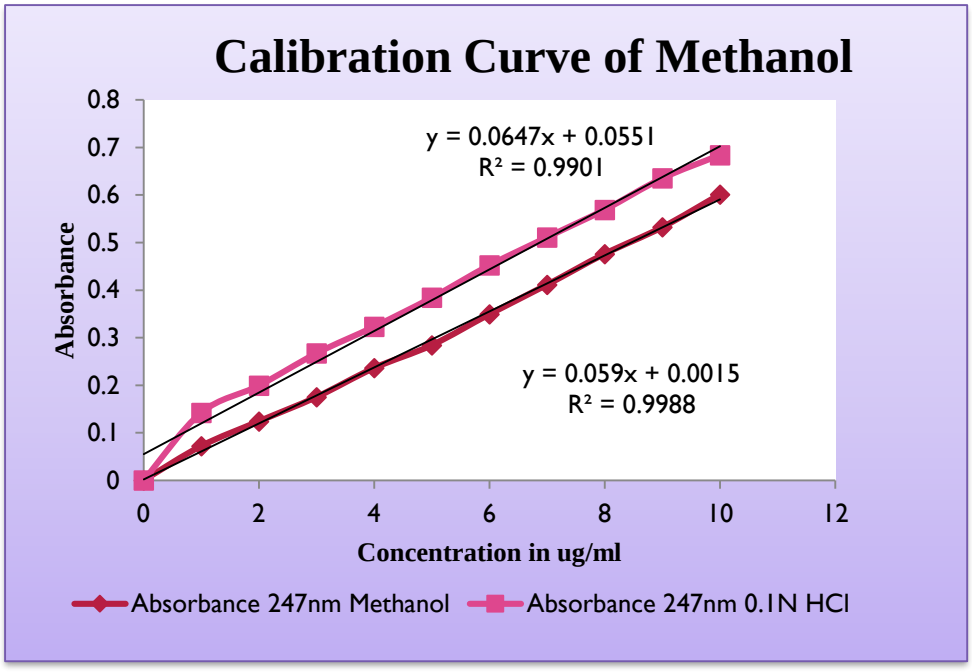


Figure no.3:- Standard calibration curve of Efavirenz

Preparation of Efavirenz liposomes by using thin film hydration technique:-

The liposomes were made utilising a Rotary Evaporator Instrument and a thin film hydration process. The various Efavirenz formulations were developed as described in table 8.13. Weigh the medication, cholesterol, and soya lecithin dissolved in 2 mL methanol and 3 mL chloroform precisely. A 250ml round bottom flask was used to hold this solution. The flask was rotated at 200 rpm for 30 minutes in a thermostatically regulated water bath at 400°C under vacuum of 900 mm Hg in a rotating flash evaporator. This technique gradually eliminated the organic solvent until a very thin film of dry lipids formed on the flask's inner surface. The thin film layer was created and stored in a desiccator at room temperature (22-30°C)

overnight. The dry lipid film was progressively hydrated with 10 mL Phosphate buffer 7.4 and swirled for 2 hours, yielding a milky white suspension. Centrifugation at 3000 rpm for 30 minutes is performed on the formulation. Efavirenz liposomes were obtained, and they were further considered for characterization before being stored in a tightly sealed container for later assessment.

The 2^2 factorial design was used to optimise the formulation and process variables. A 2^2 factorial design is a type of study that allows researchers to assess two interventions in one sample. It is desirable to generate an appropriate pharmaceutical formulation in the lowest amount of time possible while employing the fewest amount of man-hours and raw resources possible. The 2^2 factorial design was used to optimise the formulation and process variables. A 2^2 factorial design is a type of study that allows researchers to assess two interventions in one sample. It is desirable to generate an appropriate pharmaceutical formulation in the lowest amount of time possible while employing the fewest amount of man-hours and raw resources possible.

Batch Code	**X_1**	**X_2**
F1	-1	-1
F2	+1	-1
F3	-1	+1
F4	+1	+1

Table no 3:- Formulation batch by 2^2 factorial designs

Variable	**-1**	**+1**
(X_1)Soya lecithin : Cholesterol	5.5 : 4.5	7.5 : 2.5
(X_2) PEG 6000	1%	2%

Table no. 4:- 2^2 factorial design with actual values and coded levels of variables

3. EVALUATION OF LIPOSOMES

1. Particle Size determination

Particle sizes of prepared liposomes were determined by using HORIBA SZ-100 for Windows [Z Type] Ver2.40. The instrument was operated under temperature 25.2°C and dispersion medium viscosity was kept 0.892mPa.s. The particle size of liposomes was determined by using scanning electron microscope. Reported mean value of particle size shown at figure no. 4.

2. Zeta Potential

Zeta Potential was preferably done under temperature 25.1°C and dispersion medium viscosity was taken 0.893 mPa.s with the help of HORIBA SZ-100 for Windows [Z Type] ver2. 40. Reported Mean value of Zeta Potential is shown at figure no. 5.

3. Determination of Entrapment Efficiency percentage

A milky white suspension was obtained by gradually hydrating the dried lipid film with 10 mL Phosphate buffer 7.4 and swirling it for 2 hours. On the formulation, centrifugation at 3000 rpm for 30 minutes is used. Efavirenz liposomes were obtained, and they were then categorized before being deposited in a sealable glass container for sustainability advancement. Reported in figure no. 6.

$$\textbf{Entrapment Efficiency Percentage} = \frac{\textbf{Entrapped drug}}{\textbf{Total drug}} \times 100$$

4. Determination of Percentage Yield

The liposomes that had been created were collected and weighed. The total amount of medicine and components used to make liposomes was separated by that of the weight of the measurements. Reported in figure no. 7.

$$\textbf{Percentage yield (\%)} = \frac{\textbf{Actual weight of product}}{\textbf{Total weight of Drug and Excipient}} \times 100$$

5. Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to investigate morphology and surface properties. By scattering liposomes on one side of the double adhesive stub, the sample for SEM analysis was prepared. The stub was taken and fine gold dust was applied to it. Scanning Electron Microscopy (JEOL and Tokyo, Japan JS/m-6360) was used to examine the liposomes at Pune University's Physics Department. The SEM is shown in figure no. 8.

6. FTIR Spectroscopy

The Infra-Red Fourier Transform on a Schimadzu Fourier Transform Infrared spectrophotometer, KBr powder was used to record spectroscopy of mixtures. Scans were obtained at a speed of 2mm/sec with a resolution of 4cm-1 over a region of 4500-400 cm-1 while the device was operated under dry air purge. The scans were examined for the presence of drug primary peaks, drug peak shifting and masking, and the formation of additional peaks as a result of polymer interaction. Figure no. 9 show the FT-IR spectra of polymer and complex formulation.

7. Differential Scanning Calorimetry

Formulation was done on Perkin Elmer 4000 equipment using differential scanning calorimetry. Thermographs were made by heating 1 mg samples in aluminum pans at 100°C/min in a nitrogen environment (flow rate 20ml/min) from 30°C to 350°C. PYRIS Version-11.0.0488 software was used to analyse the data for origin in order to determine the onset temperature (T onset), peak temperature (T peak), and endset temperature (T endset) of the endothermic peak. Figure no. 11 illustrates the DSC curve.

8. In – Vitro Drug Release Studies

USP equipment type I Rotating Basket apparatus was used for the in vitro dissolution investigation. In the receptor chamber, 900ml of 0.1 HCL was used to conduct the release investigations. The medium was equilibrated at 370.5°c and the apparatus was built at 30 revolutions per minute. Liposomes pass through the membrane and into the medium in the receptor chamber. Aliquots of 2 mL were obtained from the receptor chamber medium under sink conditions, diluted appropriately, and the absorbance was measured every 6 hours. After that, the samples were compared to a blank of fresh media using a UV spectrophotometer (Shimadzu Model UV 1700).

Figure no. 4:- USP Dissolution Apparatus Type I Rotating Basket apparatus

Observation for Evaluation of Parameter of Efavirenz liposomes:

Percentage Entrapment Efficiency and Percentage Yield of Different Formulation of Liposomes:-

Sr.no	Batches	% Entrapment Efficiency	Percentage Yield
1.	F1	76.23	86.77
2.	F2	80.05	76.05
3.	F3	85.25	80.6
4.	F4	91.28	71.86

Table no. 5:- %EE and Percentage Yield of Liposomes

Observation of Evaluation Parameters

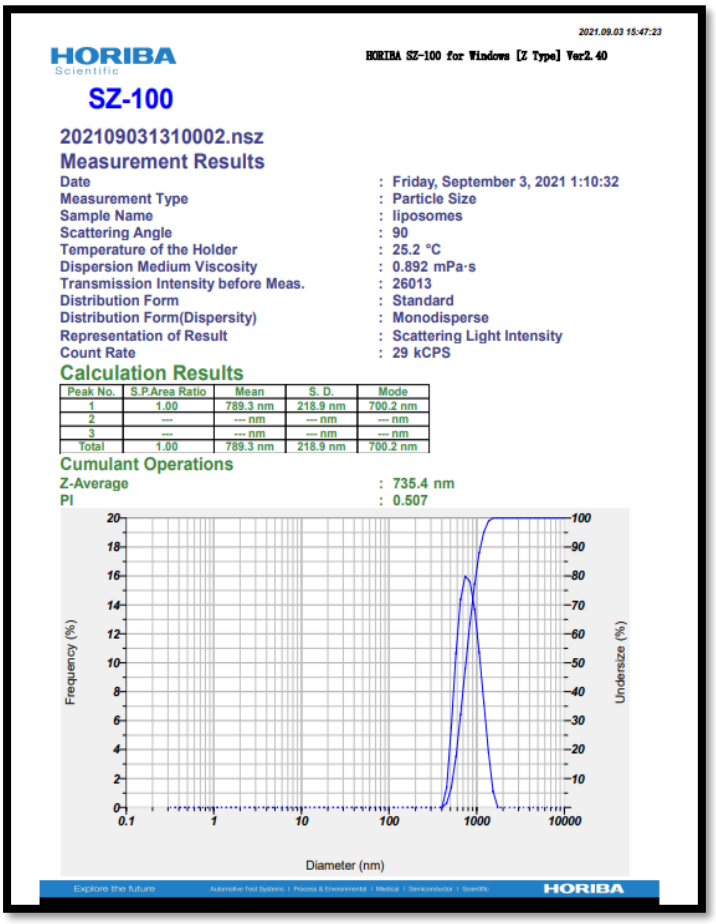


Figure no.5:- Particle size determination of F4 Formulation

Zeta Potential of Liposomes

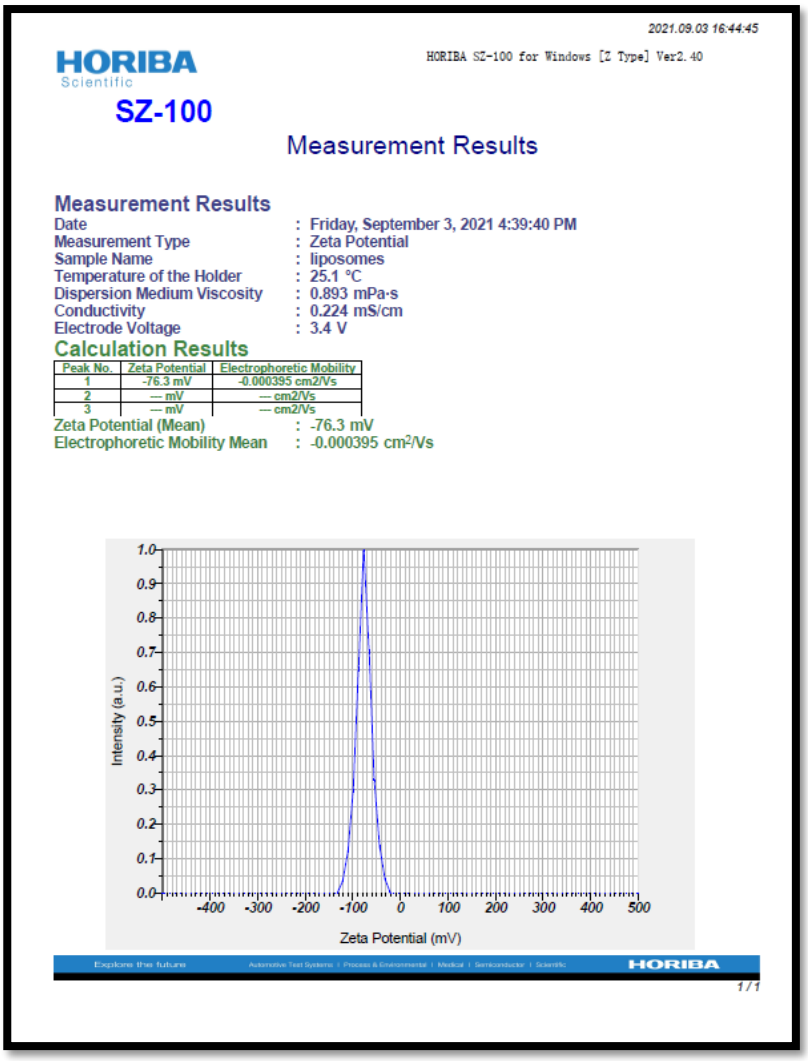


Figure no. 6:- Graphical presentation of Zeta Potential of F4 formulation

Entrapment Efficiency % of Different Formulation of Liposomes

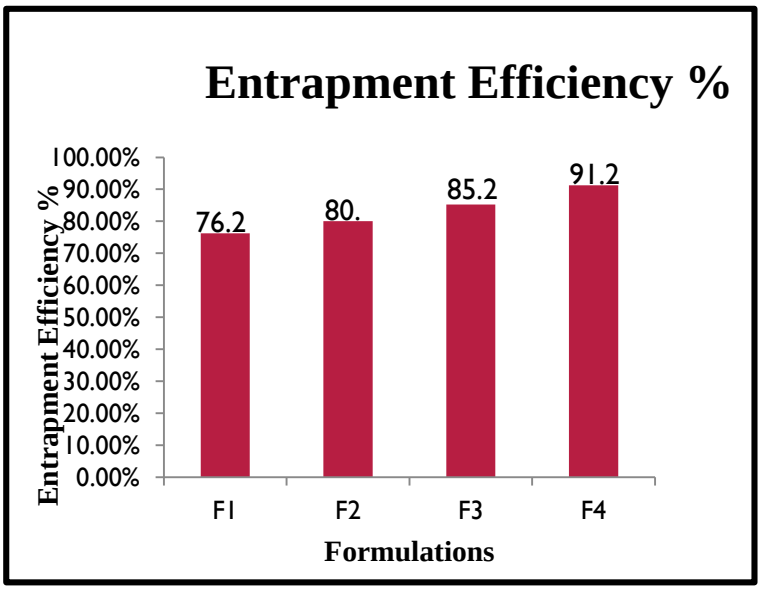


Figure no. 7:- Graph of Entrapment Efficiency %

Percentage Yield of Different Formulations of liposomes

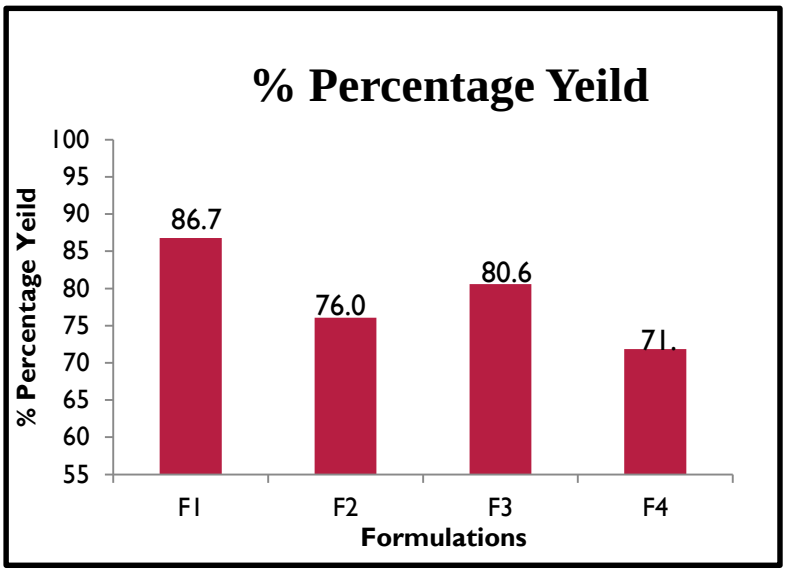


Figure no. 8:- Graph of % Percentage Yield

Scanning Electron Microscopy:

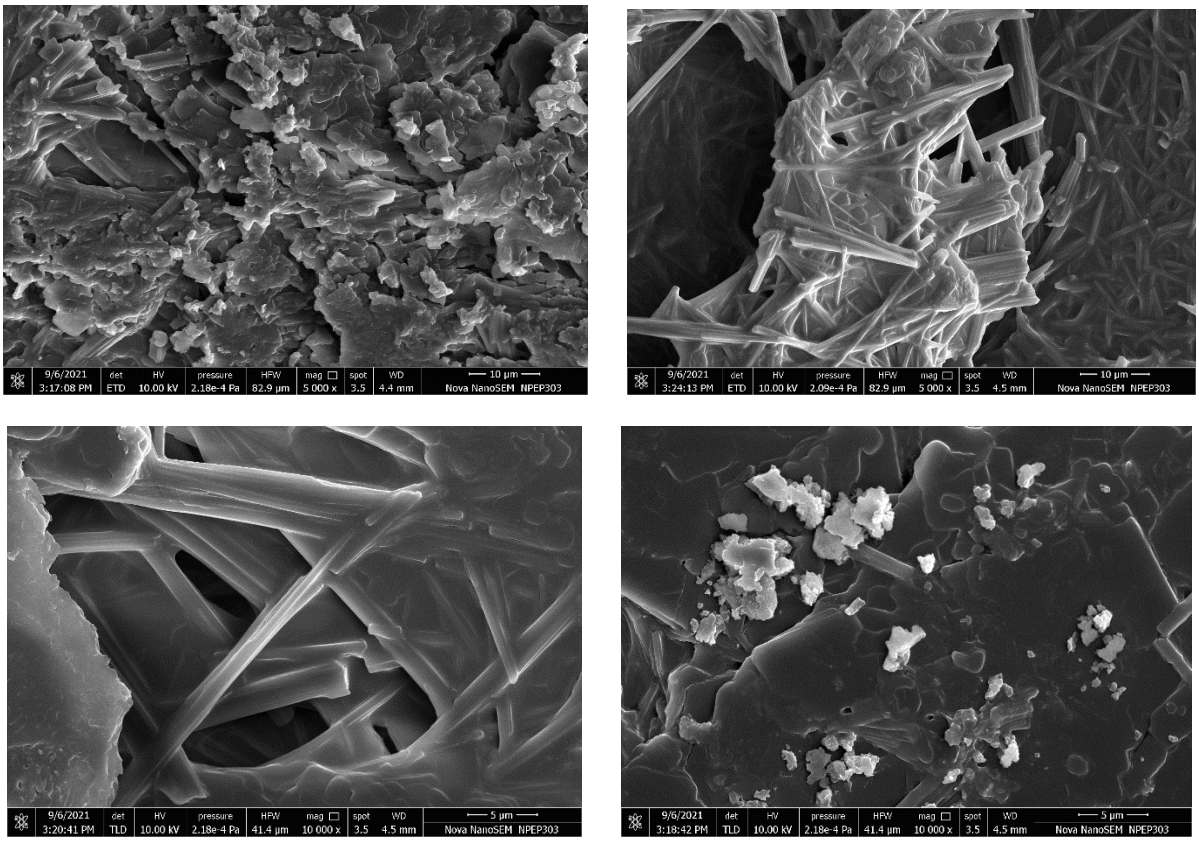


Figure no. 9:- Structure and Topography of Liposomes

Fourier Transform Infrared Spectroscopy of Formulations

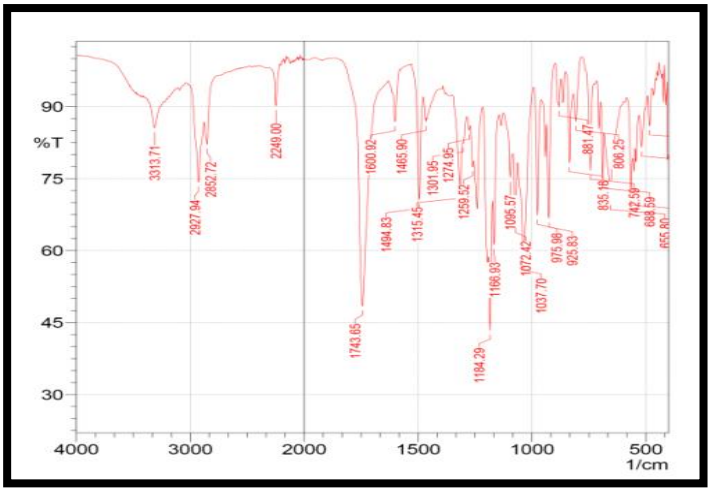


Figure no. 10:- FTIR Spectra of F4 Formulation

Differential Scanning Calorimetry

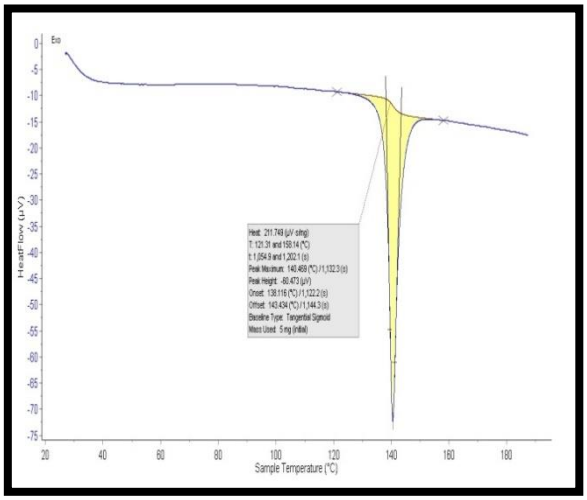


Fig.11 DSC Thermogram of Pure drug

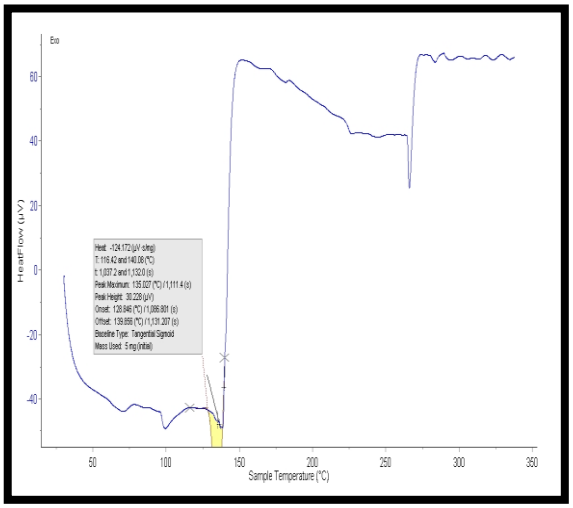
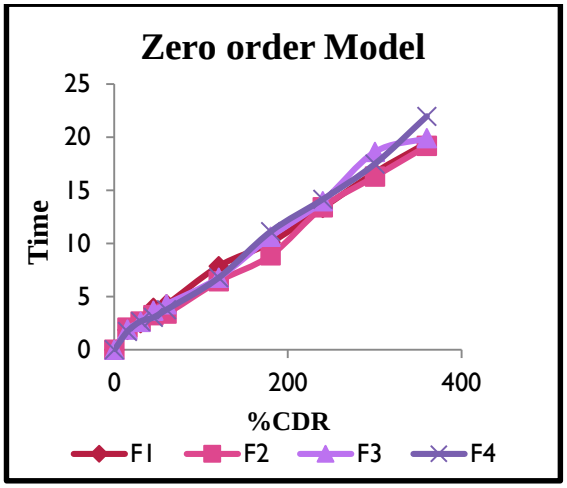


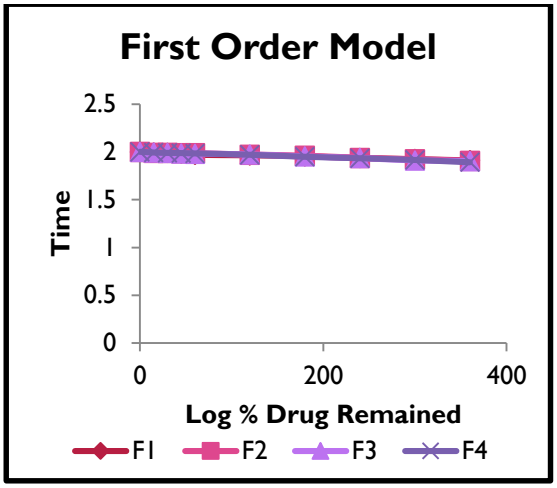
Fig. 12 DSC Thermogram of Formulation

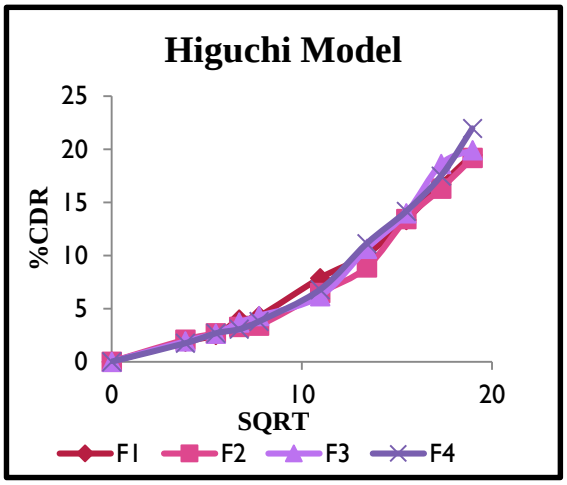
In Vitro Drug Release Study

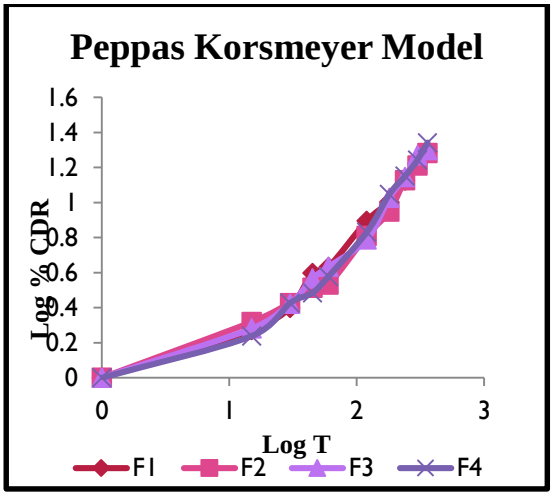
Sr.no	Batch	Zero order	First order	Higuchi Model	Korsmeyer Peppas Model	
		R^2	R^2	R^2	R^2	N
1	F1	0.9951	0.9776	0.9553	0.9116	0.5341
2	F2	0.9932	0.9919	0.9275	0.8901	0.5181
3	F3	0.9899	0.9749	0.9318	0.9136	0.5385
4	F4	0.9967	0.9942	0.9278	0.8793	0.5522

Table no. 6 :- Kinetic assessment of drug release from liposome formulation









Accelerated Stability Study

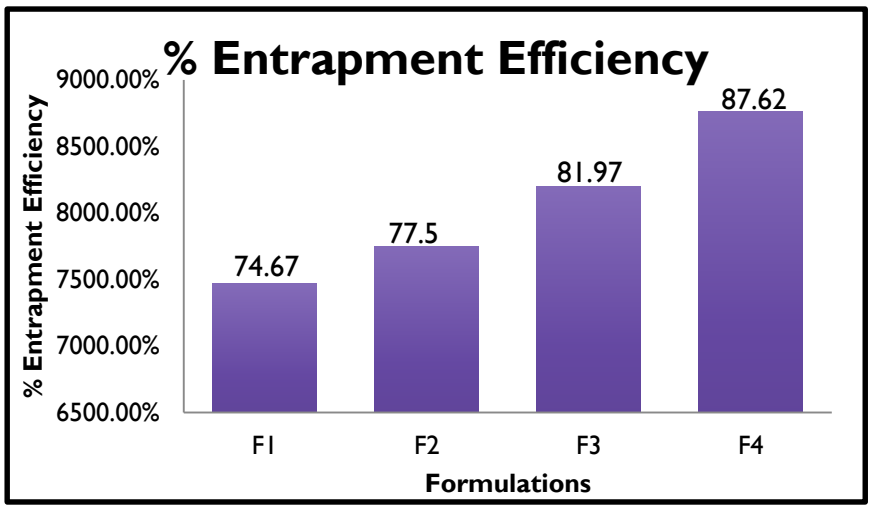


Figure no. 13:- Graph of Entrapment Efficiency % of formulation after 30 days

4. RESULT AND DISCUSSION

Particle Size Determination: Using the Horiba SZ-100 for Windows [Z Type] Ver 2.40, the mean particle diameter of the formulation was calculated. Figure no. 4 shows that the average particle size for the formulation is 789.3 nm.

Zeta Potential: One of the key factors that mediates inter-particle interaction is the zeta potential. The zeta potential of Efavirenz liposomes was determined using the Horiba sz-100, and the results revealed that the Efavirenz liposomes have a high zeta potential value, as shown in the Fig.no. 5.

Entrapment Efficiency: Fig. no. 6 show that the liposomes' entrapment efficiency ranges from 76.23 percent to 91.28 percent. The F4 formulation had the maximum entrapment efficiency of 91.28 percent, while the F1 formulation had the weakest entrapment efficiency of 76.23 percent. All other formulations had nearly identical entrapment efficiency. According to these findings, drug entrapment efficiency improves when the concentration of Soya Lecithin and the polymer PEG 6000 increases.

Percentage Yield: Different formulas' percentage yields (F1, F2, F3, F4) were calculated and determined to be 86.77 percent, 76.05 percent, 80.3 percent, and 71.86 percent, respectively. The formulations of all four Efavirenz liposome formulations are shown in figure no. 7.

Scanning Electron Microscopy: The morphological structures of the formed liposomes were examined by SEM analysis. Figure no. 8 shows the liposomal formulation microphotographs that were obtained. The PEG-based formulation exhibited a slightly dense aggregation of dense crystal particles, as well as actually slightly fused, film-like, fluffy, and porous particulates that were completely smooth and had a higher surface area of the solid-state particles. This will almost certainly increase the chances of the medicine colliding with hydrophilic transporters. Overall, the microphotographs showed that the drug's wetting action, in combination with the carriers, created small pore capillaries, which aided the drug's solubility and resulted in a quicker dissolving rate.

FTIR: The FTIR of F4 Formulation showed characteristic peaks at wave numbers were N-H strong stretching at 3313.71cm^{-1}, C=O Stretching at 1745.58 cm^{-1}, C=C stretching at 1462.04 cm^{-1},C-F stretching at 1184.29 cm^{-1}, C≡C stretching at 2249.00cm^{-1} and C- Cl stretching at 658.59 cm^{-1},C-O stretching at 1039.63.42cm^{-1}, C-H stretching at 2927.94cm^{-1}, C-C Strong Stretching at 1442.75 cm^{-1} and O-H stretching at 2852.72cm^{-1} which corresponds with standard stated as per literature survey as represented in figure no. 9.

Differential Scanning Calorimetry (DSC): The DSC study of optimized formulation was done. The DSC thermogram of drug showed a characteristics endothermic peak at 128.84°c indicating the drug sample get melted. The consequent peak at 139.85°c indicate the drug remains present in more percentage in its amorphous form and in range of 250-300 crystalline form is present as represented in figure no.11.

In Vitro Drug Release Study: The in-vitro release data for formulations F1, F2, F3, and F4. For formulations F1, F2, F3, and F4, the cumulative percent drug release after 6 hours was determined to be 19.47 percent, 19.18 percent, 19.9 percent, and 21.97 percent, respectively. The lowest drug release was 19.18 percent for the F2 formulation, while the maximum drug release was 21.97 percent for the F4 formulation, according to the findings.

Kinetic model for drug release: Formulation F1, F2, F3, and F4 diffusion studies were carried out for 6 hours in 0.1N HCL dissolving medium using a USP Type I apparatus at 100 rpm and 37°C. Models such as the Zero-order model, First-order model, Higuchi's (Matrix) model, and Peppas Korsmeyer model were used to determine the release kinetics of the formulation. The regression coefficient (R2) and release exponent were combined to find the best-fitting model (n). F4 used a zero-order release methodology, while F2 and F4 used a first-order release model. Table no.6 shows the regression coefficient (R2) and release exponent (n) for each formulation. To define the release mechanism, the n value obtained from the Peppas Korsmeyer model was compared to the standards listed in table no.6. The formulation follows the Non-Fickian release since the values of n were more than 0.5 and less than 1.

Accelerated Stability Studies: The Efavirenz liposomes were submitted to accelerated stability testing for days on all formulations at elevated temperatures of 40°C, room temperature, and 75 percent relative humidity, with the results shown in Figure no. 12. Any changes in particle size and entrapment effectiveness percent were seen in liposomes. At the end of 30 days, the liposomes' colour and entrapment efficiency percent had not changed much. According to the stability results, all of the formulations were stable for 30 days.

5. CONCLUSION

The goal of the research was to improve and evaluate the liposomal drug delivery technology for antiviral drugs. The major goals of the research were to increase the solubility of Efavirenz and create a liposomal drug delivery system for Efavirenz to release the medicine for a longer amount of time in the gastrointestinal tract (GIT).

Thin film hydration with a Rotary Evaporator Instrument can be used to successfully manufacture efavirenz liposomes. Liposomes were formed using different concentrations of lipid and cholesterol.

• Preformulation tests such as organoleptic properties and pure drug melting point Efavirenz's partition coefficient and all polymers meet official requirements, showing drug and polymer purity. All analytical parameters, including the determination of max, the standard calibration curve, and the creation of UV Spectrophotometric technique, were found to be significant and within acceptable limits.

• Drug entrapped efficiency ranged between 76.23 and 91.28 percent, indicating that drug dosage should be taken into account. The results of SEM tests for liposome surface characterisation. The PEG-based formulation produced slightly laminated, film-like, fluffy, and porous particles that were smooth and had an enhanced surface area of the solid-state particles. This will almost certainly increase the chances of the medicine coming into contact with hydrophilic carriers. Overall, the microphotographs showed that the drug's wetting action, in combination with the carriers, created micropore capillaries, which aided the drug's solubility and resulted in a faster dissolving rate. Using the Horiba SZ-100 for windows [Z Type] Ver 2.40, the mean particle diameter of the F2 formulation was calculated. For the F2 formulation, the average particle size and zeta potential were found to be 789.3 nm and 76.3 mV, respectively.

• No additional subsequent peak is found in the FTIR study, indicating that there is only a physical connection between the medication and the phospholipid and no chemical interaction. A DSC analysis of the optimised formulation was carried out. The DSC thermogram of the drug revealed a distinctive endothermic peak at 128.84°c, indicating that the drug sample melted. The subsequent peak at 139.85°c indicates that the drug is still present in amorphous form in greater proportions, with a crystalline form present in the range of 250-300.

• In-vitro drug release was carried out utilising a USP Type I apparatus and 0.1 N HCL as a medium, with the results revealing that drug release was regulated for up to 6 hours. F4 used a zero-order release model, while F2 and F3 used a first-order release model and showed Non-Fickian diffusion.

• All formulations of Efavirenz liposomes were tested over 30 days at increased temperatures of 40°C, room temperature, and 75 percent relative humidity. After 30 days, there was no discernible change in the liposomes' colour or entrapment efficiency percent. The formulation was shown to be stable after 30-day stability tests.

The assessment investigations found that the higher the content of cholesterol and soya lecithin, the more rigid the bilayer will be and the better the controlled release of medicine will be. As a result, the formulation combination was discovered to be the best for providing better regulated release, and the liposomal formulation of Efavirenz would be a good way to get a more uniform release profile.

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