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TRANSDERMAL DRUG DELIVERY OF LAMOTRIGINE THROUGH LIPOSOME FOR CONTROLLED DRUG DELIVERY

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ABSTRACT
Liposomes, as the name indicates, they are little spherical shaped artificial vesicles prepared by using various phospholipids. With their hydrophobic, hydrophilic characters and smaller size, they actively deliver the drugs to site of action. The liposomal drug delivery system differs in their properties based on lipids composition, their preparation methods, size and surface charges. The selection of bilayer components determines the charge and fluidity of the vesicles. The permeable less stable bilayers of vesicles can be prepared using unsaturated phosphatidyl-choline species obtained from natural sources. The impermeable rigid bilayer structure is obtained using saturated phospholipids having long acyl chains. The aim of present study to prepare transdermal drug delivery of lamotrigine through liposome for controlled drug delivery.

KEYWORDS: Liposomes, Transdermal drug delivery, Lamotrigine.

INTRODUCTION
Epilepsy is a medical illness that affects the brain and is characterized by a persistent susceptibility to have epileptic seizures, as well as the neurobiological, cognitive, psychological, and social implications that are associated with this condition. This is because the seizures that are connected with epilepsy are unique to each individual and may often go undetected, which is why they need specific care.[1] An episode of momentary occurrence of signs or symptoms that are caused by aberrant, excessive, or synchronized neuronal activity of the brain is referred to as a seizure. The duration of the seizure may range from brief to an extended time of severe shaking.[2] Epilepsy is caused by biochemical processes at the cellular level that promote neuronal hyperexcitability. This activity is the intense electrical activity that underlies that condition. Any aberrations in the normal neuronal transmissions, beginning with a single enzyme-receptor malfunction and progressing to numerous important cortical and subcortical regions, are implicated in the generation of clinical seizures. The occurrence of seizures is caused by an extremely synchronized activation and prolonged firing of a group of neurons in the cortical region.[3] Seizures that are prevalent have a tendency to recur and do not have an immediate underlying cause. This is because they are caused by an abnormally high level of nerve cell activity in the cortex of the brain. In the early phases of epilepsy therapy, it has been discovered that many of the drugs that are presently being utilized, including intravenous formulations, are the least successful. Oral doses, which were formerly promising approaches for treatment ways but which were less effective in their therapeutic impact, are among the key formulations that are now being utilized for the treatment of epilepsy.[4] The skin in the human body is the outermost layer of tissue. When it comes to the look of their skin, people are quite sensitive. The skin is the biggest organ in the human body, both in terms of its weight and its number of surface areas. It weighs roughly 8% of the total body weight and has an area of approximately 16,000 square centimeters for an adult. The two most common varieties of skin are as follows: A thick and hairless substance that may be seen on the palms and soles of the feet in places that are often touched. It is hairy and thin, and it may be found all over the body.[5] The oral route is the most desired approach; nevertheless, oral administration is more likely to result in hepatic first pass metabolism, which necessitates a greater dosage of the medication. In addition, the inclusion of surfactants in lipid-based formulations is subject to severe limits due to the fact that they cause irritation to the stomach. Concurrently, the distribution of the medicine throughout the body might result in unavoidable adverse effects. Because of this, the non-invasive, non-painful, and non-irritating topical delivery of formulation is an alternative method that is associated with a number of benefits.[6] These benefits include the delivery of the drug to a specific site of action with reduced systemic toxicity, the avoidance of first pass metabolism and gastric irritation, the

increase in the release rate of the drug from the formulation in order to achieve better percutaneous absorption, and for a moment, topical application that is related to increasing bioavailability with a sustained release profile. A novel anticonvulsant with a profile similar to that of carbamazepine is able to modify aximal electroshock and reduce the duration of both electrically elicited and photic after-discharge. Lamotrigine is absorbed in the correct manner when taken orally and is entirely metabolized in the liver. In individuals who are taking phenytoin, carbamazepine, or phenobarbitone, the time it takes for it to reach its t½ is lowered to around 16 hours. Additionally, symptoms such as drowsiness, dizziness, diplopia, ataxia, and vomiting may be experienced. Within the context of comparative clinical studies, it has been discovered that lamotrigine is better tolerated than either carbamazepine or phenytoin. It is not documented that there is a negative influence on cognitive characteristics. There is a possibility that rash is a serious reaction, particularly in children, that requires withdrawal.[7] Lamotrigine is recommended as an additional treatment for the following types of seizures: partial seizures, number one generalized tonic-clonic seizures, and generalized seizures caused by Lennox-Gastaut syndrome. It is also advised for the process of conversion to medication monotherapy for individuals who are at least 16 years old and have partial seizures. they individuals are presently getting treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate at the moment since they are the single antiepileptic drugs (AEDs). In addition to the aforementioned, lamotrigine is also recommended for the maintenance treatment of bipolar I disorder. This medication is used to delay the onset of mood episodes (which can also include mania, hypomania, melancholy, and mixed episodes) in adults who are at least 18 years old and have been treated for acute mood signs and symptoms with fashionable therapy. Lamotrigine may perform cell sports that contribute to its effectiveness in a variety of circumstances; nevertheless, the specific method of movement of lamotrigine has not been completely explored. The effects of lamotrigine are similar to those of phenytoin and carbamazepine, despite the fact that they are chemically unrelated. Lamotrigine inhibits voltage-sensitive sodium channels, which stabilizes neuronal membranes and modulates the release of presynaptic excitatory neurotransmitters.[8] Lamotrigine may perform cell sports that contribute to its effectiveness in a variety of circumstances; nevertheless, the specific method of movement of lamotrigine has not been completely explored. The effects of lamotrigine are similar to those of phenytoin and carbamazepine, despite the fact that they are chemically unrelated. Lamotrigine inhibits voltage-sensitive sodium channels, which stabilizes neuronal membranes and modulates the release of presynaptic excitatory neurotransmitters. The aim of present study to prepare transdermal drug delivery of lamotrigine through liposome for controlled drug delivery.

MATERIAL AND METHODS

Determination of absorption maxima (λ_{max})

In order to identify the absorption maxima of the medication (lamotrigine), the drug solution will be scanned in a double beam UV spectrophotometer at wavelengths ranging from 200 to 400 nm. The dissolving media will be a solution of phosphate buffer with a pH of 7.4. In order to generate a solution with a concentration of 1000 µg/ml, the needed amount of medication, which was precisely weighed, was dissolved in 50 ml of dissolving medium that included Phosphate buffer with a pH of 7.4 in a volumetric flask that was 50 ml in size. This was accomplished by sonicating the mixture in a bath sonicator for a duration of 20 minutes. In order to get a solution with a concentration of 10 µg per ml, a volumetric flask containing 10 ml of methanol was used to dilute 1 ml of the resultant solution with a Phosphate buffer pH 7.4 solvent. Following this, the solution was diluted up to 100 ml using sonication for a duration of 20 minutes. A double beam ultraviolet spectrophotometer (Shimadzu, UV-1800, Shimadzu Corporation, Kyoto, Japan) was used to analyze the spectra of these solutions in the region of 200 to 400 nanometers wavelength.[9]

Preparation of calibration curve of Lamotrigine: As part of the preparation of the calibration curve for lamotrigine, the required quantity of 50 mg of the drug was accurately weighed and then dissolved in 50 ml of dissolution medium that contained phosphate buffer with a pH of 7.4 in a volumetric flask that was 50 ml in size. This was done with the assistance of sonication in a bath sonicator for a duration of 20 minutes in order to obtain a solution that contained 1000 µg/ml. In order to get a solution with a concentration of 100 µg per ml, a 10 ml portion of the resultant solution was taken and diluted with a Phosphate buffer pH 7.4 solvent by sonicating it for a duration of 20 minutes. In order to get concentrations of 5 µg / ml, 10 µg / ml, 15 µg / ml, and up to 40 µg / ml, respectively, from the solution that was made above, aliquots of 0.5 ml, 1.0 ml, 1.5 ml, and up to 4.0 ml were extracted and diluted with the appropriate solvent (Phosphate buffer pH 7.4) in volumetric flasks of 10 ml for a total of 10 ml. At a wavelength of 305 nm, the absorbance of each solution was measured independently for the phosphate buffer with a pH of 7.4. It was determined how much absorbance there was, and a standard curve was drawn between the absorbance and the concentration.[10]

Preformulation Study

Organoleptic properties*:* The organoleptic properties of drug such as color, odor and taste will be noted visually.

Microscopic examination: The microscopic examination of the drug sample was done to identify the nature / texture of the powder. The required amount of powder will spread on a glass slide and examine under phase contrast microscope and drug powder was crystalline in nature.

Solubility determination: Incremental method analysis was used to estimate the saturation solubility of the active pharmaceutical ingredient (API) for the medication lamotrigine in a variety of solvents. The precise amount of the medicine, which was fifty milligrams, was put on the conical flask, and the different solvents, which included distilled water, 0.1 N hydrochloric acid, phosphate buffer with a pH of 6.8 and phosphate buffer with a pH of 7.4, were each in their own burette. Slowly adding the solvent into the conical flask that contained the medication until the drug was completely dissolved, the flask was swirled continuously throughout the night at a temperature of 37±0.5C. Through the use of Whatmann filter paper with a pore size of 0.45µm, the samples were filtered. A determination of the drug's solubility was made by calculating the concentration in micrograms per milliliter (µg/ml) unit.[11]

The partition coefficient of the drug samples: It was determined by observing them in a mixed solvent of 100 milliliters that included n-octanol and phosphate buffer with a pH of 7.4. Inside of a separating funnel, 100 mg of the medication was introduced to 50 ml of each of the buffer phase and the n-octanol phase as well. After shaking the mixture for twenty-four hours, balance was finally achieved. Both mediums were separated, collected separately, and filtered after being separated. UV spectrophotometric analysis was used to assess the amount of active pharmaceutical ingredient (API) that was dissolved in an aqueous solution. Through the use of the following equation, the partition coefficient of API was determined by determining the percentage between the concentrations of the medication in organic and the amount of the buffer solution.

$\text{Log P}_{(\text{oct / pH 7.4})} = \text{Log } (C_{\text{noct}} - C_{\text{pH7.4}})$ equilibrium

Melting Point: The melting point of drug samples were obtained by pinch of drug material sample filled in capillary tube by manually. Capillary tube sealed from one end with a bunsen flame burner individually. The filled capillary tube was kept in melting point apparatus and identified the temperature at which the drug was starting to melt.

Drug excipient compatibility study: Infrared spectroscopy of drugs: The infrared spectroscopy technique was used in order to determine the functional group of the medication samples. Infrared spectroscopy was performed with the use of a Shimadzu IR Spectra photometer, as described in the following procedure. The wave number consisted of the distinctive peaks that were recorded. Through the use of the potassium bromide disc technique, the FTIR spectra of dried drug samples (Lamotrigine) were separately obtained by means of an FTIR spectrophotometer. After the drug sample was crushed, it was fully combined with a dried powder of potassium bromide material of IR grade. The weight ratio of the two substances was 3:1, which means that there were 9 mg of KBr for every 1 mg of drug. A hydrostatic press was used to apply pressure to the combination of materials for a period of five minutes at room temperature and the requisite humidity. The pressure used was ten tons. In order to measure the spectrum, the disc containing the sample was positioned within the sample holder. The spectra were recorded with a resolution of 4 cm, and the wave number ranges recorded were between 400 and 400 cm. It is useful for the design of dosage forms to conduct compatibility studies, often known as drug-excipient interaction studies. For the purpose of compatibility studies, the drug-to-excipient ratio is chosen and evaluated based on the realistic drug-to-excipient ratio that is present in the final product. The drug and the other excipients were weighed in a ratio of one to one, placed through sieve number forty, and well combined. Amber-colored glass vials were used to contain the mixture, and then gray rubber stoppers were used to halt the mixture before an aluminum seal was applied. The Fourier transform infrared (FTIR) spectrum of lamotrigine, which was recorded from a KBr pellet, is depicted in Figure 5.4. The spectrum reveals distinct infrared (IR) absorption bands that are attributed to the stretching of amine N - H (3450, 3314, 3212 cm-1), aromatic (C = C) stretching (1619 cm-1), and ortho-distributed aryl C - Cl stretching (1052 cm-1).[12]

Liposome formulations are prepared in the following manner: Through the use of a thin film hydration technique, the liposomes that carry the medicine lamotrigine will be created using a variety of lipohillic phospholipid molecules, such as cholesterol, soyalecithine, and others. The lipid film hydration technique was used in the manufacture of liposomes. via the use of a rotating vacuum evaporator that has been modified. The ratio of drug to SPC to CHOL was changed, and both the size of the vesicle and the efficacy of drug entrapment were investigated. In a nutshell, a combination of chloroform and methanol with a ratio of 2:1 contains a variety of drug types: To create a lipid film on the wall of a round bottom flask, the SPC method involves using a CHOL evaporator in a vacuum at a temperature of 400±0.50C. After that, the lipid film that was produced was hydrated with PBS (pH 7.4) for a duration of two hours at a temperature of 370±0.50C. Using a probe Sonicator, the preparation was sonicated at a temperature of forty degrees Celsius for three cycles of thirty seconds each, with a rest period of two minutes in between each cycle. In order to obtain liposomes, the formulation was homogenized using a high-pressure homogenizer for three cycles at a pressure of 15,000 pounds per square inch.[13]

Table 1: Formulation composition of liposomes.

S. No.	Formulation code	Drug (mg)	Soyalecithin (mg)	Cholesterol (mg)	Stirring Speed (rpm)
1	LL1	100	100	20	200
2	LL2	100	100	40	200
3	LL3	100	100	20	100
4	LL4	100	100	40	100

Evaluation of liposome: For the purpose of optimizing the optimal formulation, the generated liposomal formulation will be assessed using criteria such as zeta potential, entrapment efficiency, size and polydispersity index, and in vitro release research, amongst others.

Size of the vesicles and the distribution of their sizes: The crucial phenomenon of liposomes keeping a steady size and size distribution over an extended length of time is an important signal for the stability of liposomes. For the purpose of evaluating the surface morphology, size, and size distribution of liposomes, as well as conducting a major examination of the size and size distribution of the carriers, electron microscopy was used. A sample of the dispersion was diluted with distilled deionized water until it reached a ratio of 1:9. A zeta-sizer (Malvern Master Sizer, Malvern Instruments Ltd., Malvern, UK) was used in order to perform photon correlation spectroscopy, which allowed for the determination of the average vesicle size as well as the size distribution.[14]

Determination of Zeta potential: The zeta potential of prepared vesicular particles was the overall charge that was developed by particles as they acquired this charge in a certain medium. The zeta potential of liposome formulations was evaluated by means of photon correlation spectroscopy using a flow-through cell and a Zetasizer Nanoseries (Malvern Master Sizer, Malvern Instruments Ltd., Malvern, United Kingdom).

in-Vitro diffusion studies: For the purpose of determining the drug release of liposomes that included transdermal patch content, the dialysis technique was used in either a phosphate buffer solution with a pH of 7.4 or an artificial skin pH medium. The Franz diffusion cell that was created in the laboratory contained 35 milliliters of dissolving media. Prior to the experiment, the patch was stored within the receptor compartment, which was continually agitated at a speed of one hundred revolutions per minute and fastened with two clamps at each end. Both the donor compartment and the receptor compartment were kept in close proximity to one another, and the temperature was regulated at 37±0.5 degrees Celsius. For the purpose of preventing the dissolving media from evaporating, the receptor compartment was sealed securely. Teflon-coated magnetic bars that were driven from the outside were used to agitate the solution that was located on the receptor side. At regular intervals, five milliliters of fluid was removed from the receptor compartment using a pipette, and it was immediately replaced with five milliliters of new phosphate buffer with a pH measurement of 7.4. During the course of the experiment, samples were taken at predetermined intervals, and the same volume was subsequently replaced with new dissolving media.[15-16] Filtering the vesicle allowed for the determination of the quantity of drug that was entrapped inside it, and UV-Vis spectroscopy at 305 nm was used to quantify the amount of medication that was available. Calculation of percentage drug release was done using the formula.

$$\% \text{ drug release} = \frac{(\text{Conc. of drug (in mg)} \times \text{Volume of receptor compartment}) \times 100}{\text{Label claim (amount of drug in donor compartment).}}$$

RESULTS AND DISCUSSION

The absorbance of each solution was measured separately at 305 nm for Phosphate buffer pH 7.4. The absorbance was measured and standard curve was plotted between absorbance vs. concentration. Some of the organoleptic qualities of the medicine include its color, which is a pale cream tint, its odorlessness, and its taste, which is mildly bitter. It was necessary to conduct a microscopic inspection of the drug sample in order to determine the composition and consistency of the powder. In order to determine whether or not the medication powder is crystalline in form, the needed quantity of powder will be spread out on a glass slide and examined using a phase contrast microscope. Through the use of an optical microscope that is equipped with both an ocular micrometer and a stage micrometer, the average particle size (davg) of the medication will be accurately established. Unmilled lamotrigine was expected to have a particle size of 29.7 micrometers.

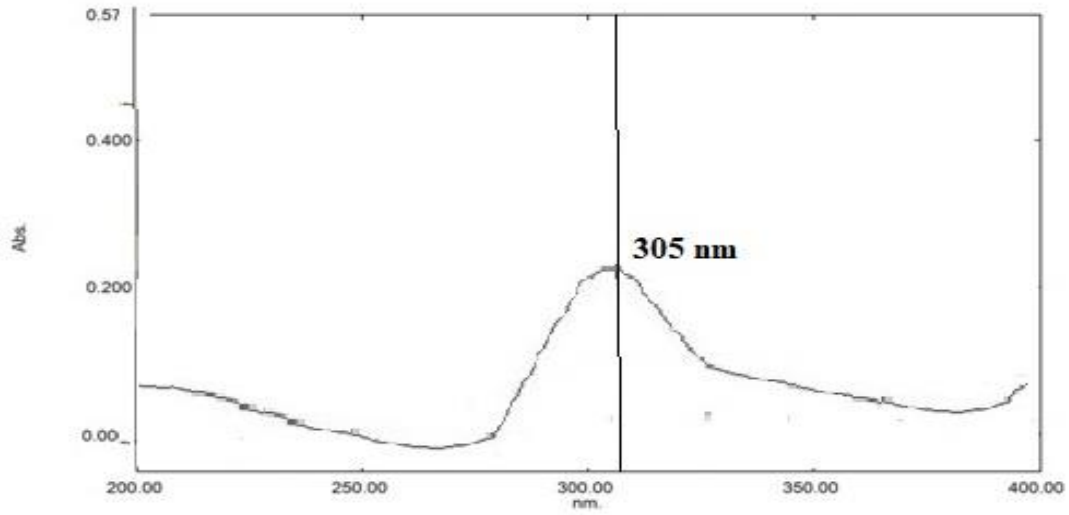

Figure 1: Absorption maxima (λ-max) of Lamotrigine in phosphate buffer pH 7.4 solution (10 µg/ml).

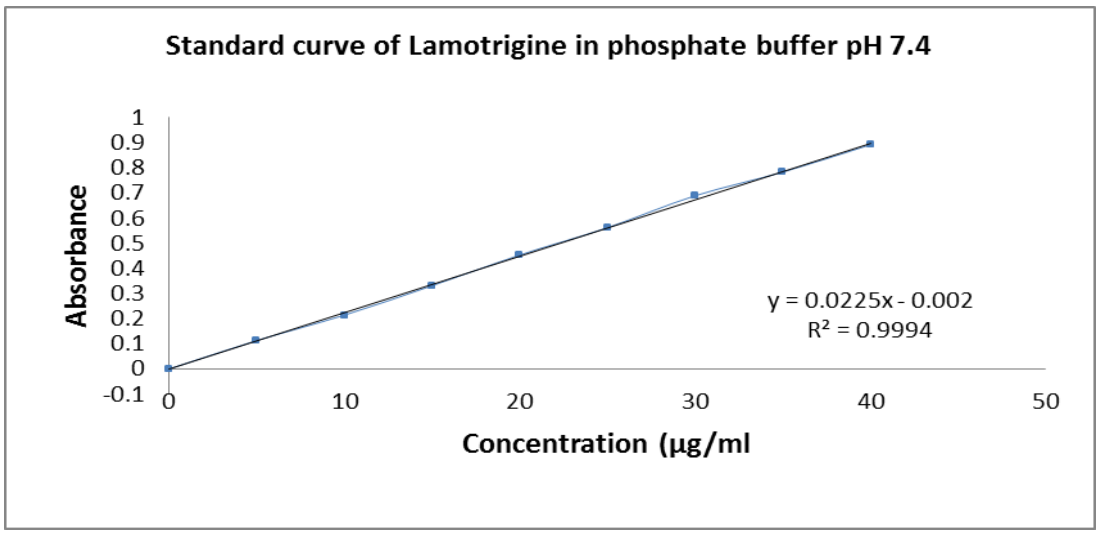

Figure 2: Standard curve of Lamotrigine in phosphate buffer pH 7.4 (305 nm).

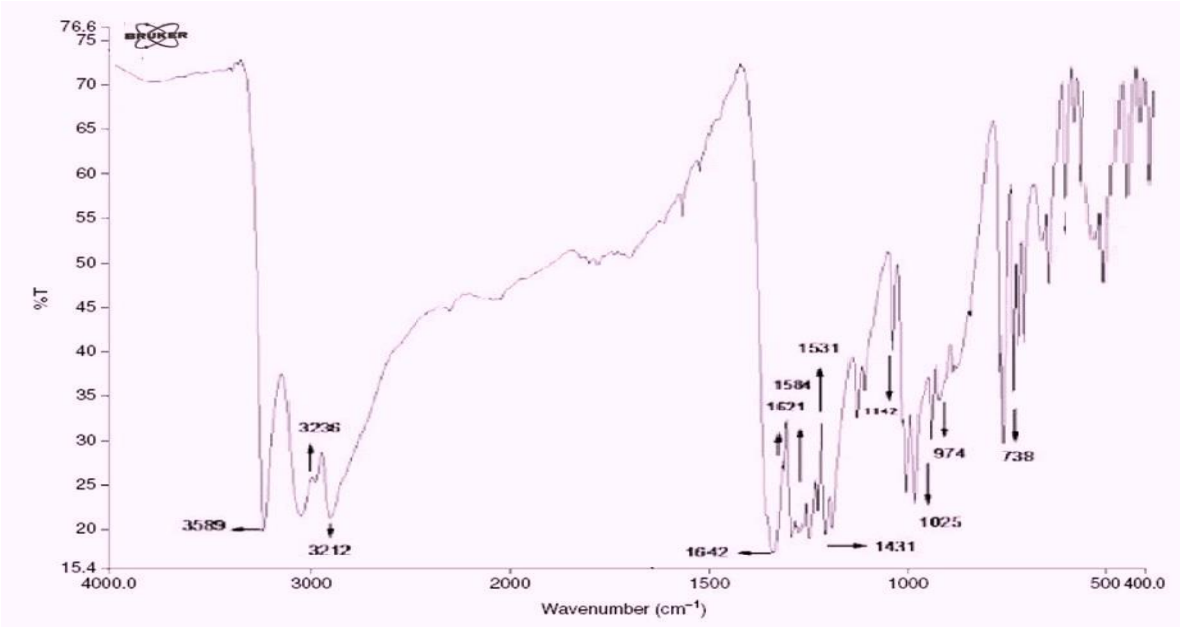

Figure 3: The I. R. Spectrum of lamotrigine drug and all excipients.

Incremental method analysis was used to estimate the saturation solubility of the active pharmaceutical ingredient (API) for the medication lamotrigine in a variety of solvents. Phosphate buffer pH 6.8 331.8±8.32 µg / ml, water 241.5±9.21 µg / ml, 0.1 N HCl 1089.0±27.91 µg / ml, and phosphate buffer pH 7.4 302.2±7.87 µg / ml were the sample concentrations used in this experiment. Lamotrigine was found to have a partition coefficient of 1.91, according to the findings. The melting point of drug samples was determined to be 181 degrees Celsius, with a standard deviation of 0.12 degrees Celsius. It is useful for the design of dosage forms to conduct compatibility studies, often known as drug-excipient interaction studies. For the purpose of compatibility studies, the drug-to-excipient ratio is chosen and evaluated based on the realistic drug-to-excipient ratio that is present in the final product. The drug and the other excipients were weighed in a ratio of one to one, placed through sieve number forty, and well combined. Amber-colored glass vials were used to contain the mixture, and then gray rubber stoppers were used to halt the mixture before an aluminum seal was applied.

Characterization of liposomes

The particle size distribution of lamotrigene containing liposomes assessed using zeta-sizer (Malvern Master Sizer, Malvern Instruments Ltd., Malvern, UK) showed an average particle size of 122.11±1.12 to 131.31±1.08 nm with double in layer and polydispersity index were 0.213±0.02 to 0.229±0.11. The size was analysed to be sufficiently small to penetrate the pores of stratum corneum. All liposomes containing lamotrigene formulations and their ionic interaction with the biological membrane, the zeta potential was analysed to be -20.12±1.02 to -23.91±1.01 mV. The zeta potential directly indicates the surface charge of the lipid nanocarrier. Thus the zeta potential of a stable dispersion of liposomes. The entrapment efficiency of all liposomes ranged between 63.05±0.8% to 83.17±1.04%. The maximum entrapment was found to be 83.17±1.04% for the liposome formulation LL3. The entrapment efficiency of liposomes was dependent on the concentrations of polymeric solution varied used for preparation of proposed formulation. Lamotrigene lioposomes are new dosage forms were created, and the in-vitro drug diffusion perfusion profile and release kinetics investigations were conducted. These were the main criteria, which were relevant in relation to the other physical properties, in order to validate the optimal formulation. The dissolving profile and the diffusion kinetic character of the dosage form were given significant consideration by these factors, which played an essential role. Following the in-vitro release performance, the dissolution data was acquired and then fitted to a variety of mathematical models. A number of mathematical models have been developed by a number of researchers, i.e.

Zero order (Cumulative % drug release versus time)
First order (Log cumulative % drug remaining versus time)
Korsemeyer-peppas model (Log cumulative % drug release versus log time)
Higuchi plot (Cumulative % drug release versus square root of time).

The in-vitro Release profile of liposomes was characterized for release percentage and release rate **k**. Release data within the linear range were selected and fitted to a zero-order mathematical model. $Q = C + kt$

Where Q is the release percentage at time t; k is the slope of the fitted linear equation and here represents release rate; and C is the intercept of the linear equation. T_{lag} is defined as the time of the start of drug release and calculated here from the fitted equation, setting Q=0.
$T_{lag} = - C / k$.

The linear equation is based on regression of at least three release data, and only correlation coefficient of over 0.99 is acceptable. The formulations TP4 showed the values of n> 0.5, followed Fickinan diffusion and supercase II transport mechanism. The value of t50% of TP4 was indicated more than 6 h and was retarded drug release upto 90% till 12h to get better controlled drug release profile. it was shown better controlled release mechanism of prepared drug delivery system.

Table 2: Particle size distribution of liposomes.

S. No.	Formulation code	Particle size (nm)	Layers	Zeta potential (mV)	PDI	Drug Entrapment (%)
1	LL1	122.11±1.12	Single	-20.12±1.02	0.226±0.11	63.05±0.8
2	LL2	124.13±1.04	Single	-20.21±1.11	0.226±0.08	68.32±1.2
3	LL3	130.11±1.09	Double	-22.24±1.04	0.229±0.01	65.12±1.2
4	LL4	131.31±1.08	Double	-22.78±1.08	0.228±0.07	71.86±1.1

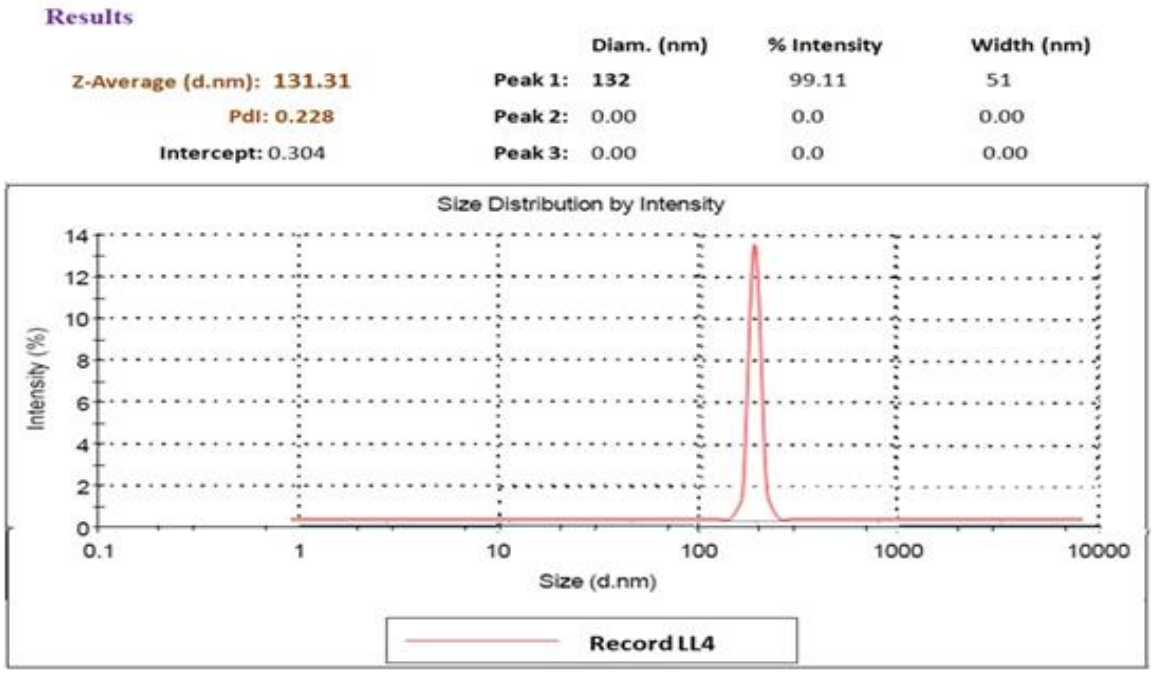

Figure 3: Particle size distribution & Polydispersity Index (PDI) of liposomes (LL4).

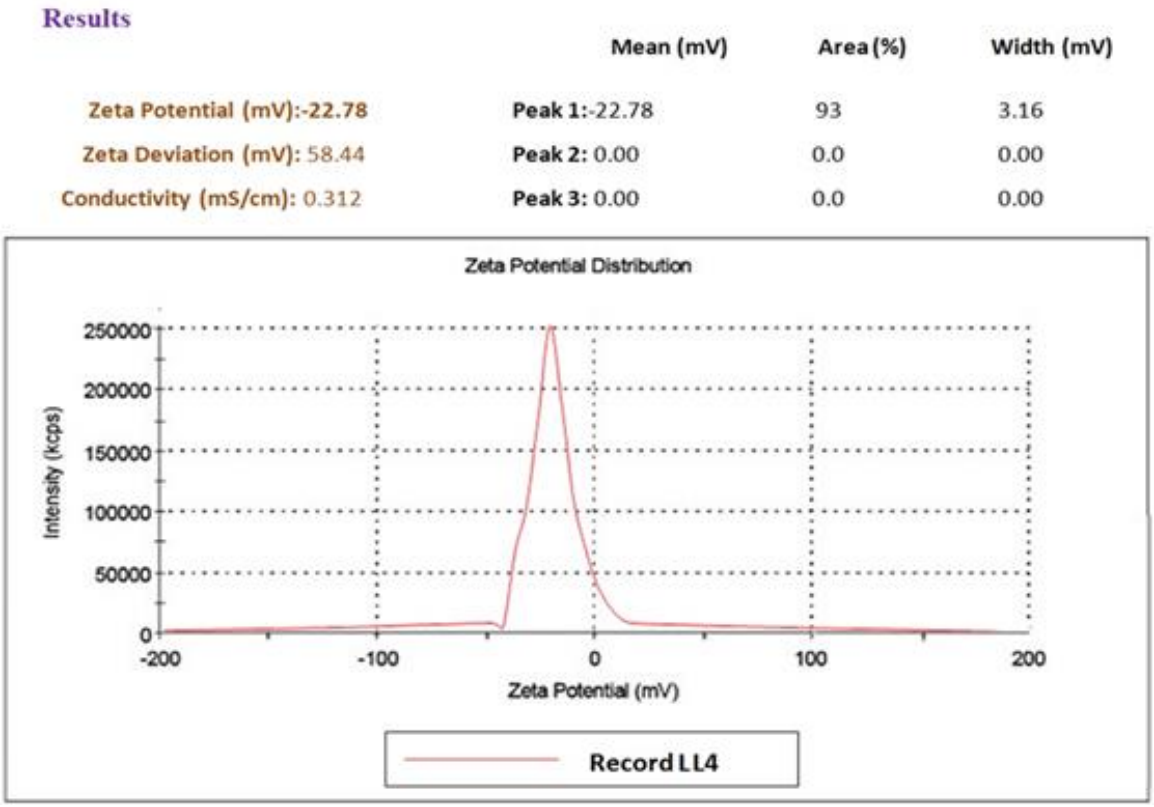

Figure 4: Zeta potential (mV) of liposomes (LL4).

CONCLUSION

Liposome vesicles seem to be potential carriers of different drugs that could be used for therapeutic applications. So many factors contribute to their success as drug delivery vehicles. Use of transdermal patches can evade many issues associated with oral drug delivery, such as first-pass hepatic metabolism, enzymatic digestion attack, drug hydrolysis and degradation in acidic media, drug fluctuations, and gastrointestinal irritation. The linear equation is based on regression of at least three release data, and only correlation coefficient of over 0.99 is acceptable. The formulations TP4 showed the values of n> 0.5, followed Fickinan diffusion and supercase II transport mechanism. The value of t50% of TP4 was indicated more than 6 h and was retarded drug release upto 90% till 12h to get better controlled drug

release profile. it was shown better controlled release mechanism of prepared drug delivery system.

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