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Development of Multilayered Niosomal Transdermal Patch of Lamotrigene Drug

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Abstract: Niosomes are self-assembled vesicular nanocarriers obtained by hydration of synthetic surfactants and appropriate amounts of cholesterol or other amphiphilic molecules. Just like liposomes, niosomes can be unilamellar or multilamellar, are suitable as carriers of both hydrophilic and lipophilic drugs and are able to deliver drugs to the target site. Furthermore, niosomal vesicles, that are usually non-toxic, require less production costs and are stable over a longer period of time in different conditions, so overcoming some drawbacks of liposomes. The transdermal route of drug administration ensures systemic delivery of drug by applying a drug formulation onto intact and healthy skin thus ensuring sustained drug release and bypass of first-pass metabolism. Thus the aim of the study is to develop antiepileptic drugs loaded niosomal transdermal patchas an effective substitute for the existing maintenance therapies used for controlling epileptic seizures. The transdermal route for the treatment eliminates major side effects of oral medication and showed better effect. This also bypasses the liver metabolism of drug for maintaining the plasma concentration in blood for longer period of time.

Keywords: Niosomes, vesicular nanocarriers, synthetic surfactants cholesterol or other amphiphilic molecules. liposomes, unilamellar, multilamellar hydrophilic, lipophilic drugs, target site.

1. Introduction

The niosome properties are specifically dictated by size, shape, and surface chemistry which are able to modify the drug's intrinsic pharmacokinetics and eventual drug targeting to the areas of pathology. Niosomal carriers are suitable for the delivery of numerous pharmacological and diagnostic agents. According to this statement it must be pointed out that an emerging paradigm for the design of effective nanocarriers is the modification of physico-chemical parameters to influence the drug delivery and targeting. This approach has the advantage that high drug concentrations can be localized at the site of action, minimizing systemic absorption, thus reducing systemic side effects. On the other side, transdermal drug delivery uses the skin as an alternative route for the drug towards the systemic circulation. This drug delivery route shows several advantages over the conventional oral and parental routes such as: avoidance of the risk and inconvenience of intravenous therapy (non invasive), avoidance of first pass hepatic metabolism (avoiding the deactivation by digestive and liver enzymes), which leads to an increase of drug bioavailability and efficacy, no gastrointestinal degradation (pH, enzymatic activity, drug interactionwith food, beverages and other orally administered drugs), alternative to oral administration when such route is unsuitable (e.g., vomiting and diarrhea). However, transdermal drug delivery shows the major disadvantage of a low penetration rate through the skin. Actually, only limited number of drugs can be formulated as transdermal delivery systems due to the functions of the stratum corneum (SC), which provides the main barrier to permeation [1]. Skin penetration through stratum corneum is also a great concern to the researchers for the systemic activity of the transdermal delivery. The topical drug delivery offers a direct accessibility to the skin as a target. The semisolid preparations transparent gel has expanded both in cosmetics and in pharmaceutical preparations. Drugs are administered topically for their action at the site of application, or for systemic effects. The topical drug delivery system is normally used where the others system of drug administration not succeed or it is mainly used in fungal infection [2]. The 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. Transdermal patches can be tailored and developed according to the physicochemical properties of active and inactive components, and applicability for long-term use [3]. Multilayer transdermal patches consist of a drug reservoir layer and an adhesive layer where drug release is controlled over a period of time. A temporary protective layer and a permanent backing laminate are included in multilayer systems. Multi- layer patches are used to deliver pain medication, drugs that encourage smoking

cessation, and hormone therapy; drug delivery can be prolonged for up to seven days **[4].** Polymers employed in transdermal patch formulation have various functions, such as matrix formation, drug delivery rate control, pressure sensitive adhesives, backing laminates, and protective drug release liners. They should be biocompatible with the skin, and should render a constant and effectual supply of the drug throughout the delivery period advertised by the manufacturer. Polymer selection is critical in the design of a polymer matrix because the polymer affects the release properties of the drug, the adhesion/cohesion balance, and the stability of the product and its compatibility with other product constituents and the skin of the recipient. Several polymers used in transdermal patch matrix formation are described below **[5]**. The proposed work is based on drug loading to niosomal transdermal patches for overcoming the frequent dosing and lower bioavailability complications associated with conventional therapy. The formulation will be prepared by thin film hydration method. Niosomes are nanometre size hydrated vesicles composed of non-ionic lamellar lipid bilayer posing an amphiphilic infrastructure. The drug gets encapsulated within the amphiphilic system of the biodegradable and biologically compatible carrier system.

2. Material and Methods

Preparation of Niosomes formulations: The niosomes containing lamotrigine drug were prepared by thin film hydration method with non-ionic surfactant Span 60 and various lipohillic phospholipid molecules i.e. Soyalecithin, cholesterol etc. Niosomes were prepared by all materials were weighed and dissolved together in the round bottom flask containing methanol-chloroform mixture of ratio 2:1 together with glass beads. The round bottom flask is connected to a rotary vacuum evaporator and then vacuum was applied. During the preparation the vacuum was applied to completely remove the solvents until the complete dried solid thin film was developed in the wall of the flask. The resulting lipid film was then hydrated with PBS (pH 7.4) for 2 hours at 37°±0.5°C. The preparation was sonicated at 40°C in 3 cycles of 30 sec. and rest of 2 minutes between each cycle by using probe sonicator. The obtained niosome dispersion was sonicated using probe sonicator for 20 min to decrease the particle size. The formulation was homogenized at 15,000 psi pressure in 3 cycles using high-pressure homogenizer to get niosomes.

Characterization of Niosomes formulations:
Determination of vesicle size and size distribution: The important phenomenan of maintaining constant size and size distribution for a prolonged period of time important indication for stability of niosomes. Electron microscopy was used for the assessment of surface morphology, size and size distribution of niosomes significant analysis of size and size distribution of the carriers. The sample of dispersion was diluted to 1:9 with distilled deionized water. The average vesicle size and size distribution was determined by photon correlation spectroscopy using zeta-sizer (Malvern Master Sizer, Malvern Instruments Ltd., Malvern, UK).

Determination of Zeta potential: The zeta potential of prepared vesicular particles was the overall charge develops by particles acquires in a particular medium. The awareness of the zeta potential of a preparation can help to calculate the outcome of the preparation during the in vivo assessment and to assess the stability of colloidal systems. Zeta potential of niosomes formulations were assessed by photon correlation spectroscopy using Zetasizer Nanoseries (Malvern Master Sizer, Malvern Instruments Ltd., Malvern, UK) using a flow-through cell.

Formulation of niosomal transdermal patch: The obtained niosomes were stored under normal room temperature and transdermal patches were prepared using solvent casting method. The transdermal films containing lamotrigene were formulated by using different polymeric combinations of Poly vinyl alcohol and Poly vinyl pyrrolidone.

Preparation of casting solutions: The films were prepared by method reported by Prabhu, *et al* as solvent casting method. The polymer mixture was prepared by dissolving weighed quantities of polymers in water. The drugs were dissolved in methanol as solvent, which added to the prepared polymeric solution with Propylene Glycol 400 (10% w/v) as plasticizer and Tween 80 (5% v/v) were added respectively. The solution of mixture (20 ml) was poured into Petri plates, kept it in the hot air for drying.

Preparation of transdermal patches: The optimized prepared niosomal formulation (1 ml) was thoroughly mixed to polymer mixture of casting solution to form a homogeneous mixture with thermostable heating mantle at 60°C. The solution of poymer mixture (20 ml) was poured into Petri plates containing mercury as base, kept it in the hot air for drying upto 24 h for solvent evaporation. The patches were removed by peeling and cut into

square dimension of 2 cm × 2 cm (4 cm^2). These patches were kept in desiccators for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers.

Characterisation of niosomal transdermal patch:
Physical appearance: The physical appearance of transdermal patches was visually inspected for its color, clarity, flexibility, and smoothness.
Thickness: The thickness of transdermal patches was measured using screw gauge at different sites of the various formulations and average measurement of triplicate readings was taken.
Weight uniformity: The weight variation of patch was obtained by weighing of three patches randomly selected from the batch of formulation. Each batch and the average weight of formulation were calculated. The individual weight should not deviate significantly from the average weight of formulations.
Flatness: The longitudinal strips of each patch were cut from the centre and both sides by blade. The length of each strip and variation in length of patch was measured. It was identified the non-uniformity in flatness as measured % constriction, So the 0% constriction was considered to be equivalent to 100% flatness.
Folding endurance: The Folding endurance test of patch was carried out by folding the patch at the same point upto "n" number of times, till it may broken. This parameter was conducted to identify the efficiency of plasticizer and the strength of the patch, while using various ratios of polymers. This test was carried out in three times.

Tensile strength: The tensile strength of the prepared patches was determined for identifying mechanical strength by using Instron universal testing instrument (model F. 4026) with a 5 kg load cell. The prepared patch strips as declared dimension should be free from air bubbles were hold between two clamps at a distance of 3cm. The patches were pulled at top clamps with a rate of 100 mm/min force and patch elongation were measured at the time of film broken. Experiment was done in triplicate manner for each film. The tensile strength and percentage elongation were computed as given formulae.

Tensile strength is computed from the following equation:
Tensile strength = Break force / Initial cross sectional area of the sample (mm2)
Percentage elongation can be obtained by following equation:
% Elongation at break = Increase in length / Original length × 100
Swelling ratio: The effect of polymer combination during application was performed by swellability of the patch. The swelling properties of transdermal patches were found by keep in double distilled water in petri dish, and identified swelling nature of patch upon contact with water for specified time. The increase weight of the each patch was determined at specific time intervals until a constant weight was observed. The degree of swelling (S%) is calculated using the formula given below.
S (%) = Wt – Wo / Wo x 100
Where, S= percent swelling, W_t= weight of patch at time t, W_o = weight of patch at time zero.

Surface pH: The surface pH of the patches was measured using method discussed by Bottenberg et al. The patches were kept in 0.5 ml double distilled water and allowed to swell for 1 h. The surface pH of prepared patches was calculated by combined glass electrode at the surface of the patch for 1 minute.

Percentage drug content: The drug content was determined for identified the specific quantity of drug presence in prepared patch. Patch (2 cm2) was cut into pieces and keep into a 100 ml volumetric flask containing 100 ml phosphate buffer pH 7.4 for 24 hours with occasional shaking. After shaking, filtered and prepared suitable dilution with phosphate buffer pH 7.4. The blank was prepared with drug-free patch. The solutions were observed by UV spectrophotometer at wavelength 305 nm for lamotrigene.

Percentage moisture content: The transdermal patch was introduced to a desiccator at room temperature containing activated silica for one day. The patches were repeatedly weighed the next day for constant weight was attained. The patches were weighed and kept in desiccators at room temperature for 24 h, the films were weighed and the percent moisture uptake was calculated using the formulae given below (5):
Percentage moisture uptake = [Final weight - Initial weight / Initial weight] × 100……(5)

Water vapour transmission rate: The water vapor transmission rate was observed by using conical flasks of equal diameter as transmission cells. These transmission cells were washed thoroughly and dried in an oven. The anhydrous calcium chloride (1g) was placed inside each flask. The prepared transdermal patches of each formulation were fixed over the brim of cell with the help of adhesive material. The complete transmission cells

were weighed and kept in closed desiccators containing saturated solution of potassium chloride to maintain 84% relative humidity. The cells were weighed after time interval i.e. 6, 12, 24, 36, 48 and 72 h. Water vapor transmission rate was expressed as the number of grams of moisture gained/cm2/h. The amount of water vapour transmitted was found using equation (6):
Water vapour transmission rate = [Final weight - Initial weight / Initial weight] × 100…(6)

In-Vitro diffusion studies: The drug release study of niosomes semisolid content was studied by dialysis method in phosphate buffer pH 7.4 solution or artificial skin pH medium using laboratory prepared Franz diffusion cell. Before experiment, the cellophane membrane was washed in the running water and then soaked in distilled water for 24 h to remove glycerine present on membrane. The dialysis bag was dipped into the receptor compartment containing 35 ml of dissolution medium and stirred continuously at 100 rpm. The 2 ml niosomes containing samples were kept on dialysis bag which was screwed with two clamps at each end. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.5°C. The receptor compartment was closed to prevent evaporation of the dissolution medium. The solution on the receptor side was stirred by externally driven teflon coated magnetic bars. At predetermined time intervals, 5 ml of solution from the receptor compartment was pipette out and immediately replaced with fresh 5 ml phosphate buffer pH 7.4. Samples were withdrawn at regular time intervals, and the same volume was replaced with fresh dissolution medium. The amount of drug entrapped in the vesicle was then determined by filtering it and the drug content was determined using UV-Vis spectroscopy at 305 nm. Calculation of percentage drug release was done using the formula:
% drug release = (Conc. of drug (in mg) x Volume of receptor compartment) x 100
Label claim (amount of ~~drug in donor compartment).~~

Kinetic study models:
Zero order release kinetics: Zero order release kinetics refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with low-soluble drugs and other delivery systems. In its simplest form, zero order release can be represented as:
$Q = Q0 + K0\ t$ Eq. 1
where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q0 is the initial amount of drug in solution (it is usually zero), and K0 is the zero order release constant. The plot made was cumulative % drug release vs time (zero order kinetic models).

First order release kinetics: The rate laws predicted by the different mechanisms of dissolution both alone and in combination, have been discussed by Higuchi.
$\text{Log } C = \text{Log } C0 - kt / 2.303$ Eq. 2
where, C0 is the initial concentration of drug and K is first order constant. The equation in resemblance to the other rate law equations, predicts a first order dependence on the concentration gradient (i.e. Cs - Ct) between the static liquid layer next to the solid surface and the bulk liquid.

3. Summary and Conclusion

Niosomes have valuable effect over the conventional liposomes with transdermal route of drug administration. Such formulations ensures systemic delivery of drug by applying a drug formulation onto intact and healthy skin thus ensuring sustained drug release and bypass of first-pass metabolism. Transdermal drugs significantly deliver molecules in a potent quantity that overcome the conventional problems of oral dosing. So, the development of antiepileptic drugs loaded niosomal transdermal patchas have better effect over existing therapies used for controlling epileptic seizures. The transdermal route for the treatment eliminates major side effects of oral medication and showed better effect. The proposed niosomal transdermal patch were Flexible, smooth, opaque, non sticky in nature. The patches LNTP4 and LNTP6 formulations having an intermediate concentration of PVA and PVP were found to be having the satisfactory results. This ability to retain the structural integrity helps the patch to be retained over the skin surface for a longer time without breaking. It was concluded that the tensile strength decreases as the increase of Polyvinyl pyrrolidone polymer due to the anti nucleating effect of PVP. All prepared formulations due to the pore forming nature of PVP polymer. Polyvinylpyrrolidone leaches out during preparation of patches from membrane casting, leaving pores typically from 1 to 10 µm. All the formulations which is skin pH and no skin irritation were showed. The values of water content, water uptake and water vapour transmission of formulations was found with the increase in PVP concentration due to its anti-nucleating effect. The in-vitro permeation release of prepared patches with hydrophilic polymer PVA: PVP showed good amount

of cumulative drug release. The proportion of PVP with PVA is responsible for better cumulative release among the formulations. High hydrophilicity of polymers resulted in increase in absorbion of water and incresase in percentage swelling resulting in the more release of drug from the patches. The data was further treated as per the following equation for confirming the Koresmeyer-Peppas model, Where, Mt / Mα, was the fractional release of drug, Mt is the amount released at time t, Mα is the total amount of drug contained in the transdermal film, t is the release time, K is a kinetic constant and the diffusional release exponent indicative of the release mechanism. The formulations LFT4 showed the values of n>0.5, it means drug permeation followed Fickian diffusion. The LFT4 formulations was subjected to the in-vivo Studies for testing their Pharmacokinetic and Pharmacodynamic effects.

Table 1: Formulation composition of lamotrigene loaded niosomal transdermal patches

F. code	**PVA (mg)**	**PVP (mg)**	**Plasticizer (Propylene Glycol 400) % W/V**	**Penetration Enhancers (Tween 80) % W/V**	**Methanol (ml)**	**Water (ml)**
LFT1	600	400	10	5	10	20
LFT2	600	400	10	5	10	20
LFT3	600	400	10	5	10	20
LFT4	600	400	10	5	10	20
LFT5	600	400	10	5	10	20
LFT6	600	400	10	5	10	20

Table 2: Characterization of niosomal transdermal patches

S. No.	**F. code**	**Flexibility**	**Smoothness**	**Transparency**	**Stickness**
1	LNTP1	Flexible	Smooth	Opaque	Non sticky
2	LNTP2	Flexible	Smooth	Opaque	Non sticky
3	LNTP3	Flexible	Smooth	Opaque	Non sticky
4	LNTP4	Flexible	Smooth	Opaque	Non sticky
5	LNTP5	Flexible	Smooth	Opaque	Non sticky
6	LNTP6	Flexible	Smooth	Opaque	Non sticky

Table 3: Characterization of niosomal transdermal patches

F. code	**Thickness (mm)**	**Weight Variation (mg)**	**Folding Endurance**	**Percentage Elongation (%mm2)**	**Tensile Strength N/mm2**	**Swellability (%)**
LFT1	0.26±0.03	32.66±1.165	77-84	89±0.02	4.79±0.23	16.97± 0.43
LFT2	0.22±0.02	32.23±1.154	75-80	93.74±0.15	5.86±1.18	18.32 ± 0.39
LFT3	0.25±0.03	31.33±1.155	86-91	101± 0.100	6.69±0.23	22.42 ± 0.57
LFT4	0.23±0.01	30.33±1.156	98-99	109± 0.02	9.13±0.13	28.63 ± 0.54
LFT5	0.27±0.01	31.60±0.144	79-80	94± 0.02	5.93±0.13	19.18 ± 0.58
LFT6	0.24±0.02	31.32.±1.154	93-97	108± 0.03	9.66±1.18	23.43 ± 0.49

Table 4: Characterization of niosomal transdermal patches

F. code	**Surface pH**	**Drug Content**	**Moisture Content(%)**	**Percentage Moisture uptake (%)**	**Moisture Vapour Transmission (gm/cm^2/24 hour)**

LF T1	5.5 ± 0.13	74.21± 1.2	4.96±0.14	4.99±0.27	5.87×10^{-3}
LF T2	5.5 ± 0.14	79.78± 1.1	4.89±0.17	4.93±0.37	4.97×10^{-3}
LF T3	5.8± 0.12	71.23± 0.3	4.15±0.13	4.83±0.36	4.27×10^{-3}
LF T4	5.7 ± 0.12	79.13± 1.1	3.28±0.18	3.89±0.38	3.77×10^{-3}
LF T5	5.5 ± 0.14	77.21± 0.74	4.62±0.13	4.87±0.26	4.47×10^{-3}
LF T6	5.6 ± 0.14	80.08± 1.07	3.63±0.13	4.67±0.25	4.17×10^{-3}

Results

		Diam. (nm)	% Intensity	Width (nm)
Z-Average (d.nm): 126.11	**Peak 1:**	**121**	91.08	79
PdI: 0.213	**Peak 2:**	0.00	0.0	0.00
Intercept: 0.262	**Peak 3:**	0.00	0.0	0.00

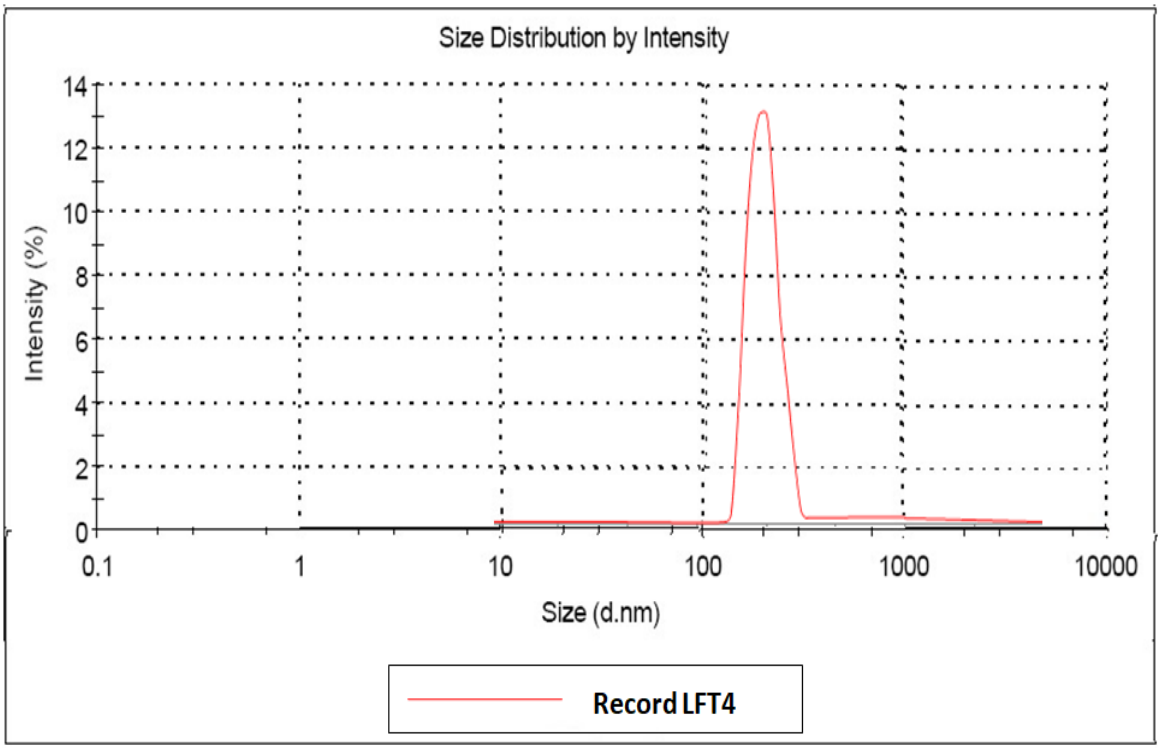

Figure 1: Particle size distribution & Polydispersity Index (PDI) of niosomal transdermal patch formulation (LFT4)

Results

	Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): -23.11	**Peak 1:** -23.11	98	3.21
Zeta Deviation (mV): 67.11	**Peak 2:** 0.00	0.0	0.00
Conductivity (mS/cm): 0.278	**Peak 3:** 0.00	0.0	0.00

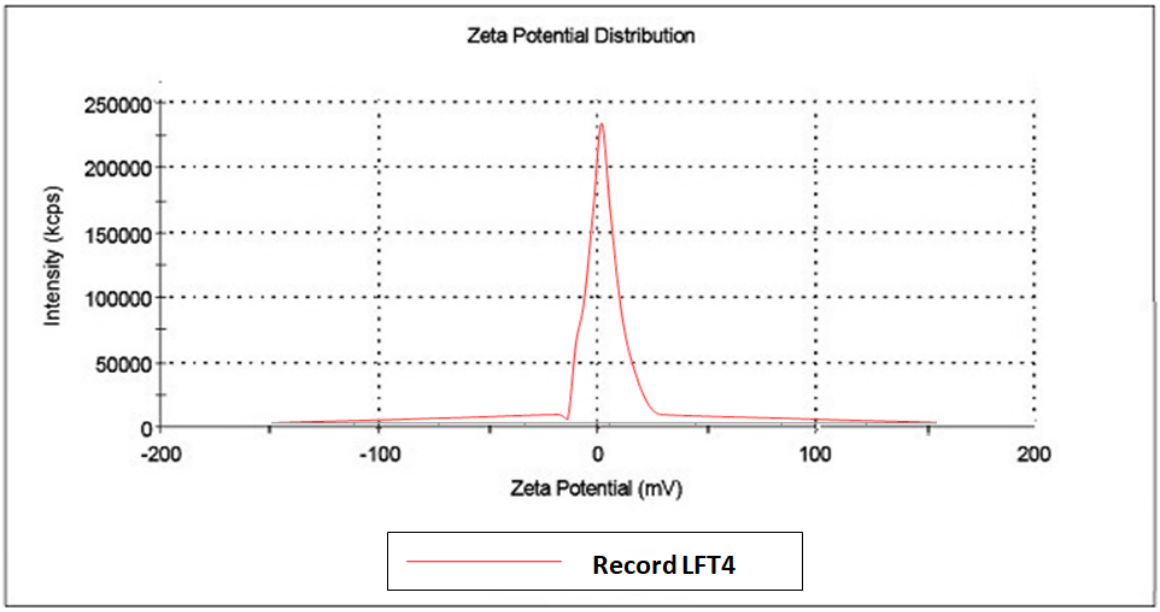

Figure 2: Zeta potential (mV) of niosomal transdermal patch formulation (LFT4)

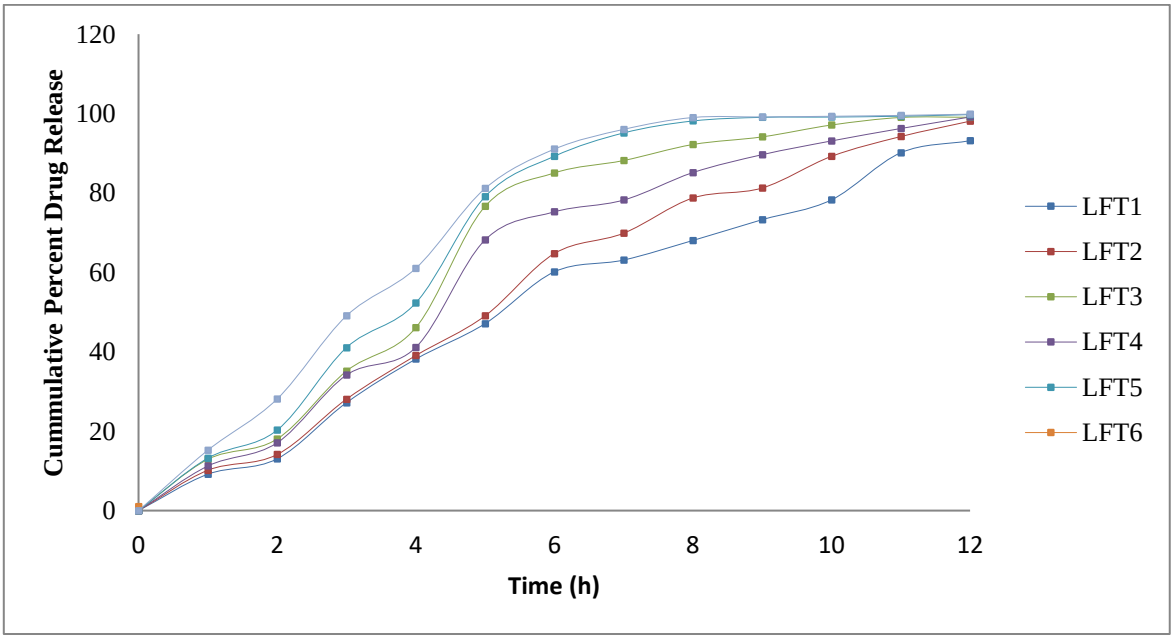

Figure 3: Zero-order plots of niosomal transdermal patch formulation (LFT1 –LFT6)

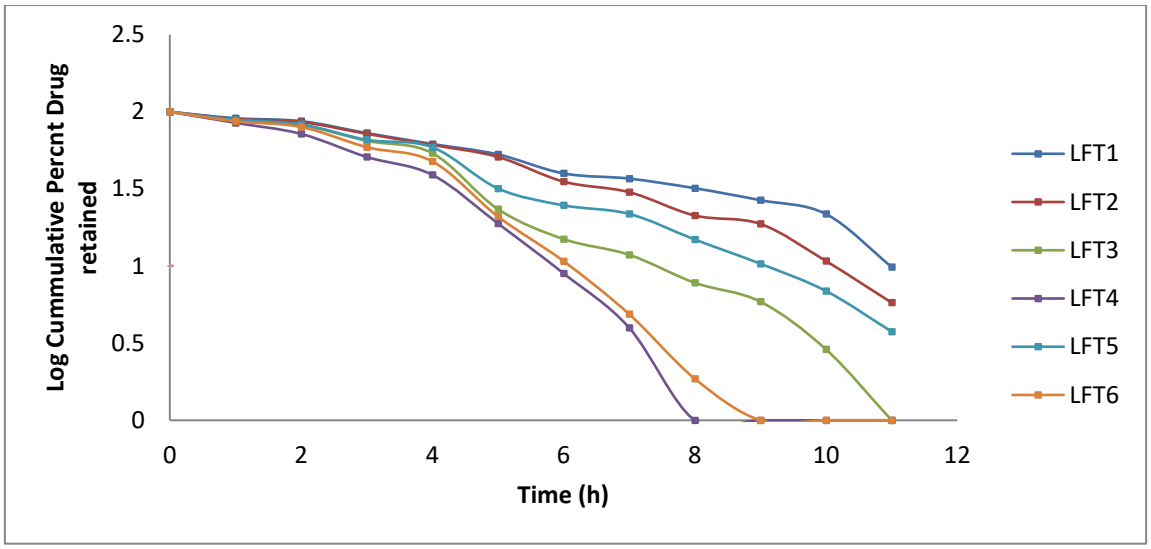

Figure 4: First-order plots of niosomal transdermal patch formulation (LFT1 –LFT6)

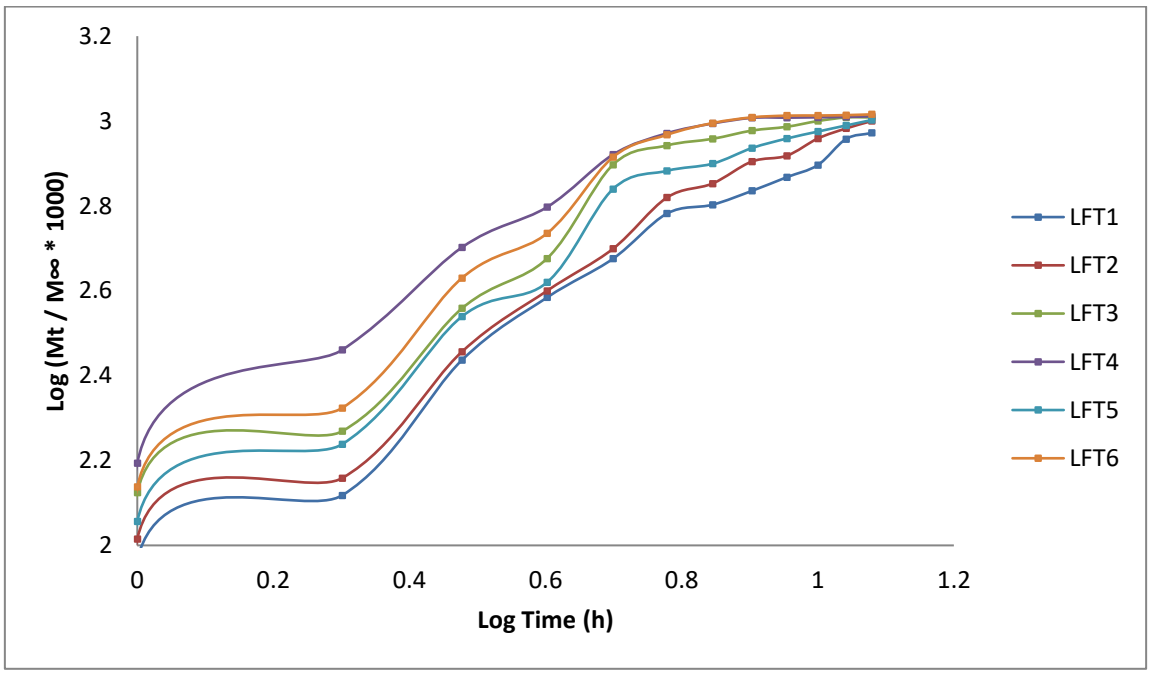

Figure 5: Korsmeyeyr's Peppas plots of niosomal transdermal patch formulation (LFT1 –LFT6)

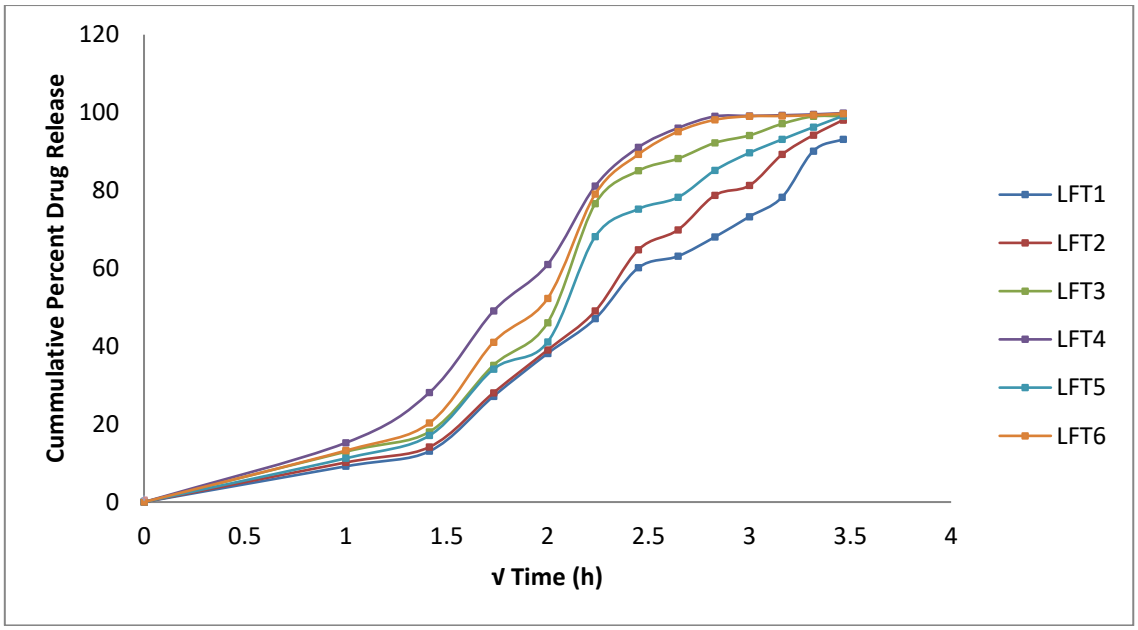

Figure 6: Higuchi plots of niosomal transdermal patch formulation (LFT1 –LFT6)

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