FORMULATION AND EVALUATION OF TRANSDERMAL EMULGEL OF EPILEPTIC DRUG

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Abstract: 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. Transdermal drugs significantly deliver molecules in a potent quantity that overcome the conventional problems of oral dosing. Antiepileptic drugs are generally available as tablets for oral administration, but this can pose problems for patients who are unable to consume medications orally. These patients may have difficulty in swallowing, may be in coma or may have gastrointestinal discomfort. Patient compliance may be a problem for those who cannot tolerate the taste of oral medications. Oral route is the majority ideal route close to patient execution; though, oral administration is additional prone to hepatic first pass metabolism required higher dose of drug. The transdermal emulgel ensures tolerable localization and dispersion of the drug by passable percutaneous absorption within the skin to enhance its local efficacy and/or through the skin to the circulation to polish its systemic effect.

Introduction: Skin is the outer tissue of the human body. People are very sensitive to appearance of their skin. Skin is the largest organ of human body in terms of weight and surface area both. It has about 8% of the body weight and of approximately 16, 000 cm2 area for an adult. Skin is a complex multi-layered tissue consists of a range of components including veins, capillaries, hairs, cells, fibers etc [1]. Skin has incredibly complex structure that consists of many components. multi-layered structure of skin made by different layers of Cells, fibers and other components and capillaries, veins and

nerves form huge networks inside this structure. Besides, hairs attach out from the inside of skin, plentiful fine hair furrows are spread over the surface of skin. Skin executes a extensive functions resulting from chemical and physical reactions inside these components [2]. Topical administration of drug is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Topical formulations apply a wide range of preparations, both cosmetic and dermatological, to their healthy or diseased skin. Topical drug delivery system has been used for centuries for the management of local skin disorders. It is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as a topical route [3]. Topical drug delivery system is defined as the application of a drug containing formulation to the skin to treat cutaneous disorders like acne or psoriasis with objective of effect of drug to the surface of the skin or within skin. There are two types of topical drug delivery products, External topicals and Internal topical [4-6]. The external topicals are spread, sprayed or dispersed on the tissues to cover diseased area, while the internal topicals are applied to mucous membrane orally, vaginally or on rectal tissues for local activity**.** These formulations may be solid, semisolid to liquid. Drug substances are rarely administered alone, but as part of a formulation, in combination with one or more nonmedical agents that provide diverse and specialized pharmaceutical functions. [7]**.** 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. Human skin is a large and easily accessible organ offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions. Human skin is a highly efficient self repairing barrier designed to keep the insides in and the outside out. Emulgel is emulsions, either of the oilin-water or water in oil type, which are gelled by mixing with a gelling agent. Emulgels are emulsions, may be oil-in-water or water-in-oil type, and gelled by mixing with a gelling agent. It is under major group of semisolid preparation, the use of transparent gels has prolonged widely both in cosmetics and in pharmaceutical preparations [8]. The USP defines, gels as semisolid systems containing either suspensions made up of either small inorganic particles, or large organic molecules interpenetrated by a liquid. Gel forms cross linked network, inwhich small drug particles captures and provides its release in a controlled manner. As mucoadhesive property of

system, it prolongs the contact period of medication over the skin 15. As biphasic liquid doses forms, emulsion is a controlled release system where entrapped, drug particles present in internal phase pass through the external phase to the skin and slowly get absorbed. The internal phases act as reservoir of drug, which slowly release drug in a controlled way through the external phase to the skin [9-10] Lamotrigine is a new anticonvulsant having carbamazepine-like profile: modifies aximal electroshock and decreases electrically evoked as well as photic after-discharge duration. Lamotrigine is properly absorbed orally and metabolized completely in liver. Its t½ is 24 hr, but is reduced to ~16 hr in patients receiving phenytoin, carbamazepine or phenobarbitone. Lamotrigine has been found to be higher tolerated than carbamazepine or phenytoin. Negative impact on cognitive characteristic isn't reported. Rash may be a severe response, specifically in kids, requiring withdrawal. Thus the aim of the proposed study is to develop lamotrigene loaded transdermal emulgel an effective substitute for the existing maintenance therapies used for controlling epileptic seizures. Conventionally, transdermal drug delivery research is usually restricted to low-dose, potent compounds with optimal physicochemical properties. Recently, though, more research laboratories are devoting considerable time and effort to the development of transdermal drug delivery systems for high dose compounds. There is therefore an unmet need for enhancement techniques with the potential of delivering high dose medications across the skin. This is the scientific basis upon which we embarked on the transdermal delivery of lamotrigene. The present investigation is to develop emulgel of lamotrigene drug with better-permeable, controlled and localized delivery via topical route [11].

Material and Methods:

Determination of absorption maxima (λ_{max}): The absorption maxima of drug (Lamotrigine) will be determined by scanning drug solution in double beam ultraviolet spectrophotometer between 200 to 400 nm wavelengths at dissolution medium (phosphate buffer pH 7.4) solution. Accurately weighed required quantity of drug 50 mg (Lamotrigine) was dissolved in 50 ml of dissolution medium containing Phosphate buffer pH 7.4 in 50 ml volumetric flask with the help of sonication in bath sonicator for 20 min to obtain 1000 µg/ml solution. From resulting solution take 1 ml and was diluted up to 100 ml with Phosphate buffer pH 7.4 solvent separately with sonication for 20 min to get

10 µg / ml solution with the help of methanol in 10 ml volumetric flasks. The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer (Shimadzu, UV-1800, Shimadzu Corporation, Kyoto, Japan).

Preparation of calibration curve of Lamotrigine: Accurately weighed required quantity of drug 50 mg (Lamotrigine) was dissolved in 50 ml of dissolution medium containing Phosphate buffer pH 7.4 in 50 ml volumetric flask with the help of sonication in bath sonicator for 20 min to obtain 1000 µg/ml solution. From resulting solution take 10 ml and was diluted up to 100 ml with Phosphate buffer pH 7.4 solvent separately with sonication for 20 min to get 100 µg / ml solution. From above prepared resulting solution of 100 µg / ml, withdrawn 0.5 ml, 1.0 ml, 1.5 ml upto 4.0 ml aliquots and diluted up to 10 ml with respective solvent (Phosphate buffer pH 7.4) in 10 ml volumetric flasks to get concentration of 5 µg / ml, 10 µg / ml, 15 µg / ml, upto 40 µg / ml respectively. 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 [12].

Preformulation studies of drug sample: Preformulation studies may carried out to standardize a spectrophotometric method of estimation for drug and to investigate any possible drug polymer interaction. Melting point determination, Determination of distribution coefficient, Drug polymer interaction was studied by carrying out Fourier Transform Infrared (FTIR) spectral studies etc.

Preparation of transdermal emulgel: The transdermal emulgel with drug in different combinations prepared by the high speed homogenization method. The oil phase of the emulsion was prepared by dissolving span 20 in nutmeg oil. The aqueous phase was prepared by dissolving tween 20 in distilled water and required weighed quantity of drug was dissolved in ethanol. Now all prepared both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70–80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature [13]. The obtained emulsion was mixed with the gel base (carbopol 940) in 1:1 ratio with gentle stirring to obtain the emulgel. The composition of different formulations has been discussed in **Table 1**.

Characterization of transdermal emulgel: The preparing systems evaluated with various parameters such as Organoleptic evaluation, physical evaluation of gel, determination of pH, spread ability, tube extrudability, viscosity, in Vitro diffusion studies, skin irritation study, drug release kinetic data analysis: The release data was fitted to various mathematical models.

Physical examination: The prepared emulgel formulations were inspected visually for their color, appearance and consistency and also tested for their appearance and presence of any aggregates.

Globule size and polydispersity index (PDI): GS and PDI were determination by mean droplet size and polydispersity index of the emulsions was determined by zetasizer by sending samples of formulation to centre.

Viscosity determination: The viscosity of the formulated batches was determined by using a brook field viscometer at 25°C. The sufficient quantity of gel base was filled in wide mouth jar separately and it should sufficiently allow dipping the spindle. Spindle was allowed to move freely into the emulgel and the reading was noted with RPM of the spindle was adjusted to 2.5 RPM.

Spreadability: Spreadability was determined as a ground glass slide is fixed onto the wooden block, while another upper glass slide having the same dimensions as that of the fixed ground slide is provided with a hook and placed on the ground slide. 2 g of emulgel were placed in between the glass slides and a weight of 1 kg was applied on the upper slide for 5 min to form a uniform film of the formulation between the slides. Excess of the formulation was scrapped off from the edges. The top plate was then subjected to a fixed weight of 100 g with the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7 cm was noted. A shorter interval indicates better spreadability. Spreading coefficient is determined by using the formula.

$S + m * l / t$

where, S = Spreadability,

m = Weight tied to upper slide, l = Length of glass slides,

t = Time taken to separate the slides completely from each other.

Drug content determination: One gram each of emulgel was taken and dissolved in methanol and sonicated for 1 h respectively. The resulting solutions were filtered with 0.45 µm filter to obtain clear solutions. The drug content was analyzed using a UV spectrophotometer method at 234 nm.

In-vitro permeation studies: In-vitro permeation studies of the developed emulgels were carried out using Franz-diffusion cell. The dialysis membrane (Himedia, thickness 0.025 mm) was cut into equal pieces (6 cm×2.5 cm) and soaked into distilled water for 12 h before use. The drug release studies of the lamotrigene emulgel was carried out in 10 ml of phosphate buffer pH 6.8 saline maintained at 37±2° with a magnetic stirrer with constant heating equipment. A sample of 2 ml of lamotrigene emulgel was placed in receptor compartment. Aliquot samples of 1 ml were withdrawn at the regular interval and replaced with same volume of fresh buffer. The aliquots were diluted with fresh media and amount of drug diffused through the membrane was measured by using U.V. spectrophotometer at the wavelength 234 nm against phosphate buffer (pH 6.8 saline) as the blank [14].

Results and Discussion

Analytical methods: The absorption maxima of drug (Lamotrigine) determined by scanning drug solution in double beam ultraviolet spectrophotometer between 200 to 400 nm wavelengths at dissolution medium (phosphate buffer pH 7.4) solution. The spectrums of Lamotrigine absorption maxima (λmax) shown in Figure 1 respectively. The absorbance was measured and standard curve was plotted between absorbance vs. concentration (Figure 2).

Preformulation studies of drug sample: Preformulation studies may carried out to standardize a spectrophotometric method of estimation for drug and to investigate any possible drug polymer interaction. Melting point determination, Determination of distribution coefficient, Drug polymer interaction was studied by carrying out Fourier Transform Infrared (FTIR) spectral studies etc. The organoleptic properties of drug such as color, odor and taste noted visually and results Pale cream-colored, odorless and bitter taste. The microscopic examination of the drug sample was done to identify the nature /

texture of the powder and drug powder was crystalline in nature. The solubility assessment of drug was determined by calculation of concentration µg/ml unit. The solubility of lamotrigine at water, 0.1 N HCl, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4 were 241.5±9.21, 1089.0±27.91, 331.8±8.32 and 302.2±7.87 respective;ly. The partition coefficient of drug was found to be 1.91. and melting point was 181°C ± 0.12. The FTIR spectrum for lamotrigine (recorded from a KBr pellet) is illustrated in Figure 3 and 4. Characteristic infrared (IR) absorption bands due to amine N - H stretching (3450, 3314, 3212 cm^{-1}), aromatic (C = C) stretching (1619cm^{-1}), and ortho-distributed aryl C - Cl stretching (1052cm^{-1}) were observed.

Characterization of transdermal emulgel: The prepared transdermal emulgel formulations were examined visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The emulgels were tested for homogeneity by visual inspection prior to the gels being filled into containers. The Formulation LTEG4 was best formulations among all the prepared formulations. The consistency of LTEG4 was excellent and the result is shown in Table 2. The globule size and polydispersity index (pdi) (Figure 5), viscosity, spreadability and drug content of prepared formulations also examined and the result concluded that LTEG4 was best formulation. This formulation LTEG4 was prepared emulgel with carbopol 940 (2g) as base, PVP, nutmeg oil for optimize globulate nature. The drug release profile and release kinetics are two important characteristics of the dosage forms, which play an important role for describing dissolution profile of dosage form. The dissolution data was obtained after in-vitro release performance, fitted to mathematical different models. The result of release data were computed in graph and release kinetic values were optimized. The formulations LTEG1 to LTEG8 showed the values of n> 0.5, followed Fickinan diffusion and supercase II transport mechanism (Figure 6-7). The value of t50% of LTEG4 is more than 15 h and showed better controlled release mechanism of praposed drug delivery system.

Summary and Conclusion: Skin is one of the most readily available organs on human body for topical management and is the major route of topical drug delivery system. Topical drug administration is a localized drug delivery system everywhere in the body during ophthalmic, vaginal, rectal and skin as topical routes. Emulsion as a dispersed

system, which consists of small droplets and well distributed in to immiscible vehicle. Emulgel ensures tolerable localization and dispersion of the drug by passable percutaneous absorption within the skin to enhance its local efficacy and/or through the skin to the circulation to polish its systemic effect lamotrigene drug The prepared emulgel formulations were examine visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The result concluded that LTEG4 was best formulation with carbopol 940 (2g), PVP, nutmeg oil. The drug release profile and release kinetics are two important characteristics of the dosage forms, which play an important role for describing dissolution profile of dosage forms with effective controlled release mechanism.

References

1. Kotta S, Khan AW, Ansari SH, Sharma RK, Ali J, “Anti HIV nanoemulsion formulation: Optimization and in vitro-in vivo evaluation,” Int. J. Pharm., 2014, 462, 129–134.
2. Iqbal M, Md S, Sahni J, Baboota S, “Nanostructured lipid carriers system: recent advances in drug delivery,” J. Drug., (Article in press), 2012.
3. Kaur A, Katiyar SS, Kushwah V, Jain S, “Nanomedicine: Nanotechnology,” Biology, and Medicine, (Article in press), 2017.
4. Choudhurya H, Gorainb B, Pandeya M, Chatterjeea LA, Senguptac P, Dasb A, Molugulua N, Kesharwani P, “Recent update on nanoemulgel as topical drug delivery system,” Journal of Pharmaceutical Sciences, (Article in press), 2017.
5. Cevc G, Vierl U, “Nanotechnology and the transdermal route: a state of the art review and critical appraisal,” J Control Release, 2008, 141, 3, 277–299.
6. Moser K, Kriwet K, Naik A, Kalia YN, Guy RH (2001) Passive skin penetration enhancement and its quantification in vitro, Eur J Pharm Biopharm, 52, 103–112.
7. Jain J, Bhandari A, Shah D, “Novel Carriers For Transdermal Drug Delivery: a Review,” Int J Pharm Appl Sci, 2010, 1, 62–69.

8. Gungor S, Erdal MS, Aksu B, “New Formulation Strategies in Topical Antifungal Therapy, Journal of Cosmetics,” Dermatological Sciences and Applications, 2013, 3, 56-65.

9. Kshirsagar NA, “Drug Delivery Systems,” Ind. J. Pharmacol, 2001, 32, S54-S61.

10. Arora R, Khan R, Ojha A, Upadhyaya K, Chopra H (2017) Emulgel: A Novel Approach for Hydrophobic Drugs, International Journal of Pharmacy and Biological Sciences, 2017, 7, 3, 43 – 60.

11. Sharma S, “Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes,” Pharmaceutical reviews, 2008, 6, 1-10.

12. Carolyn EH, Renee L, Bennett, Ishik C and Williams HB, “Activities of fluconazole and ketoconazole against ketoconazole susceptible and resistant candida albicans,” Antimicrobial and chemotherapy, 1988, 23, 209-212.

13. Chojnicka A, Sala G, Cornelus G, “The interaction between oil droplets and gel matrix affect the lubrication properties of sheared emulsion filled gels,” Food hydrocolloids, 2009, 23, 1038-1046.

14. Kullar R, Saini S, Sethi N, Rana AC, “Emulgel A surrogate approach for topically used hydrophobic drugs,” Int Journal Biol Sci, 2011, 117-128.

Table 1: Different transdermal emulgel formulations

Ingredient	**LTEG 1**	**LTEG 2**	**LTEG 3**	**LTEG 4**	**LTEG 5**	**LTEG 6**	**LTEG 7**	**LTEG 8**
Lamotrigene (mg)	100	100	100	100	100	100	100	100
Carbopol 934 (g)	0.5	1	1.5	2	0.5	1	1.5	2
Liquid	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5

paraffin (ml)								
Nutmeg oil (ml)	4	6	8	10	0	0	0	0
Tween 20 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Span 20 (ml)	1	1	1	1	1	1	1	1
Polyvinyl pyrrolidone (mg)	50	50	50	50	50	50	50	50
Ethanol (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 2: Physical characterization of various transdermal emulgel

	Formulations							
Parameters	**LTEG1**	**LTEG2**	**LTEG3**	**LTEG4**	**LTEG5**	**LTEG6**	**LTEG7**	**LTEG8**
Feel of application Skin	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Consistency	Poor	Good	Good	Excellent uniform	Good	Good	Good	Uniform
Extrudibility	Good	Good	Excellent	Excellent	Good	Good	Good	Average
Globule (Particle) size nm	151.11	147.14	137.17	134.11	141.84	131.04	117.08	104.27
Polydispersity index (PDI)	0.221	0.213	0.201	0.198	0.231	0.233	0.221	0.208
Viscosity (cps)	1434	1523	1579	1635	1634	1602	1589	1504
pH	6.22	7.21	7.13	7.11	7.02	7.11	7.73	7.01
Spreadability (g.cm/sec)	8.1	9.43	10.02	11.08	9.1	10.03	11.12	13.18
Drug Content (%)	98.31	98.11	98.19	99.32	99.01	99.21	99.27	99.03

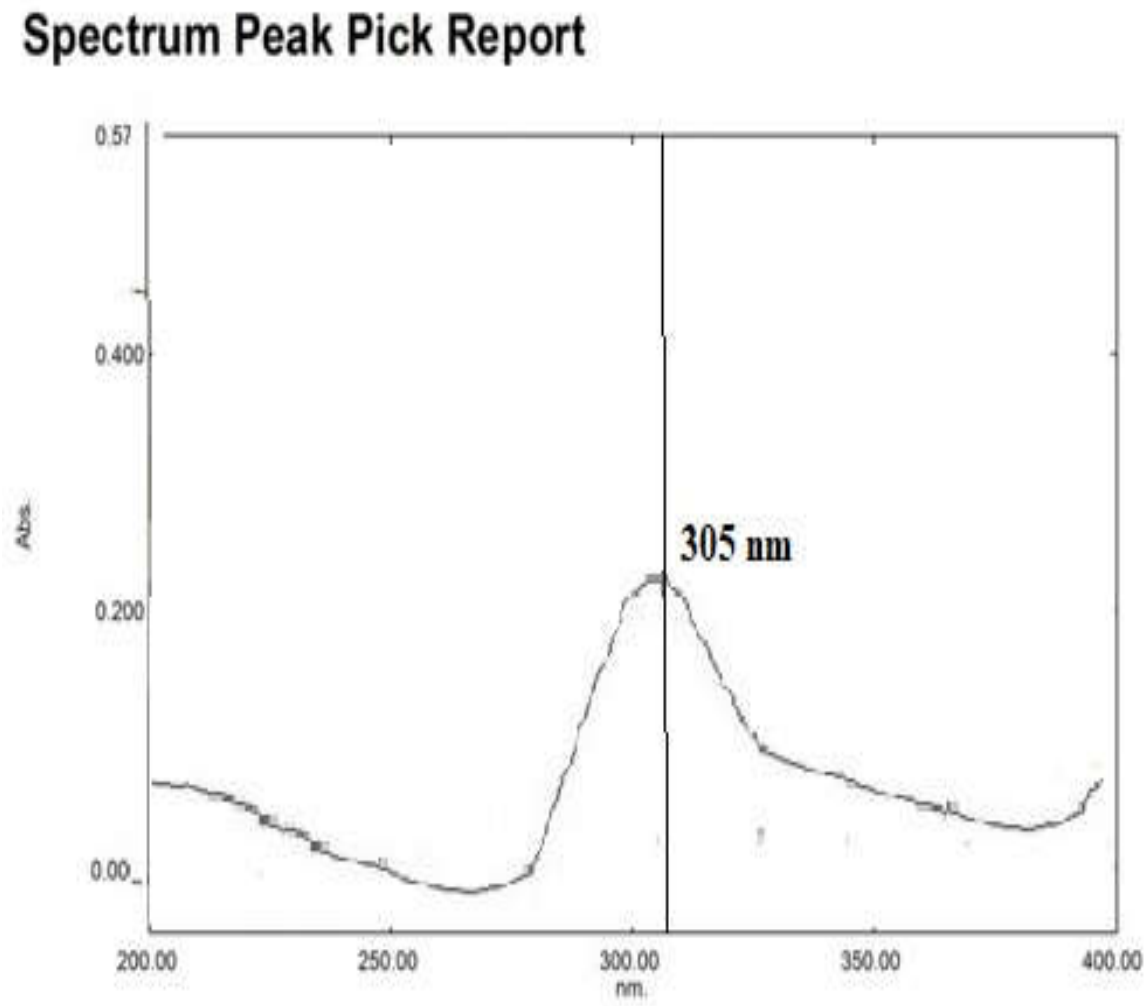

Figure 1: Absorption maxima (λ-max) of Lamotrigine in phosphate buffer pH 7.4 solution (10 µg/ml)

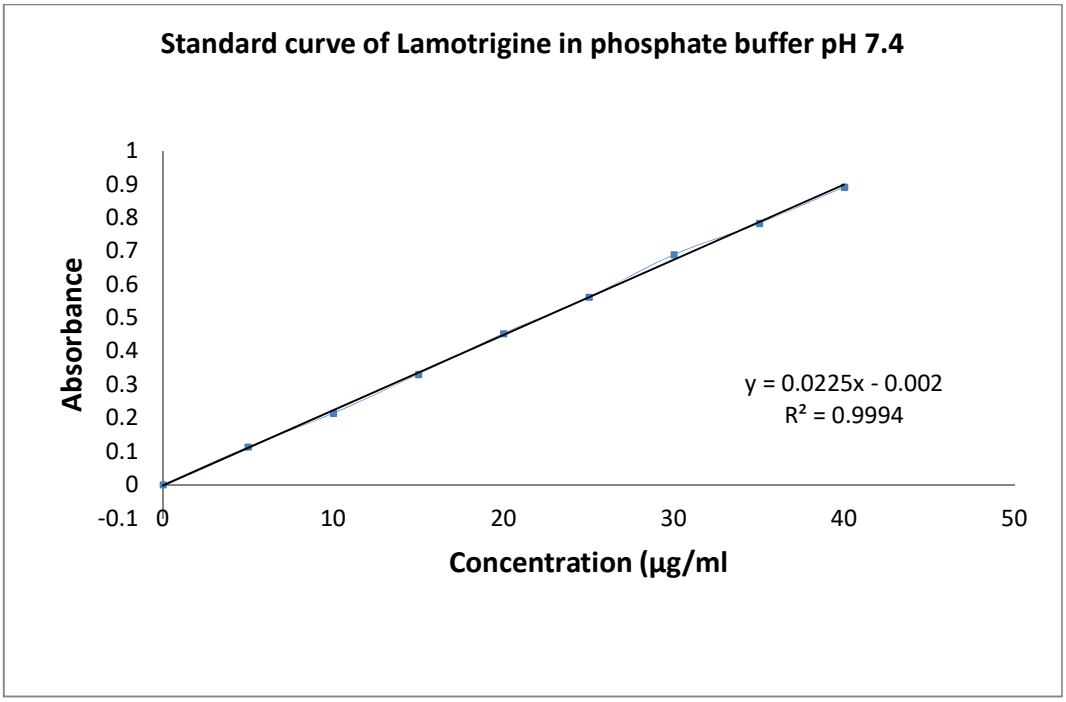

Figure 2: Standard curve of Lamotrigine in phosphate buffer pH 7.4 (305 nm)

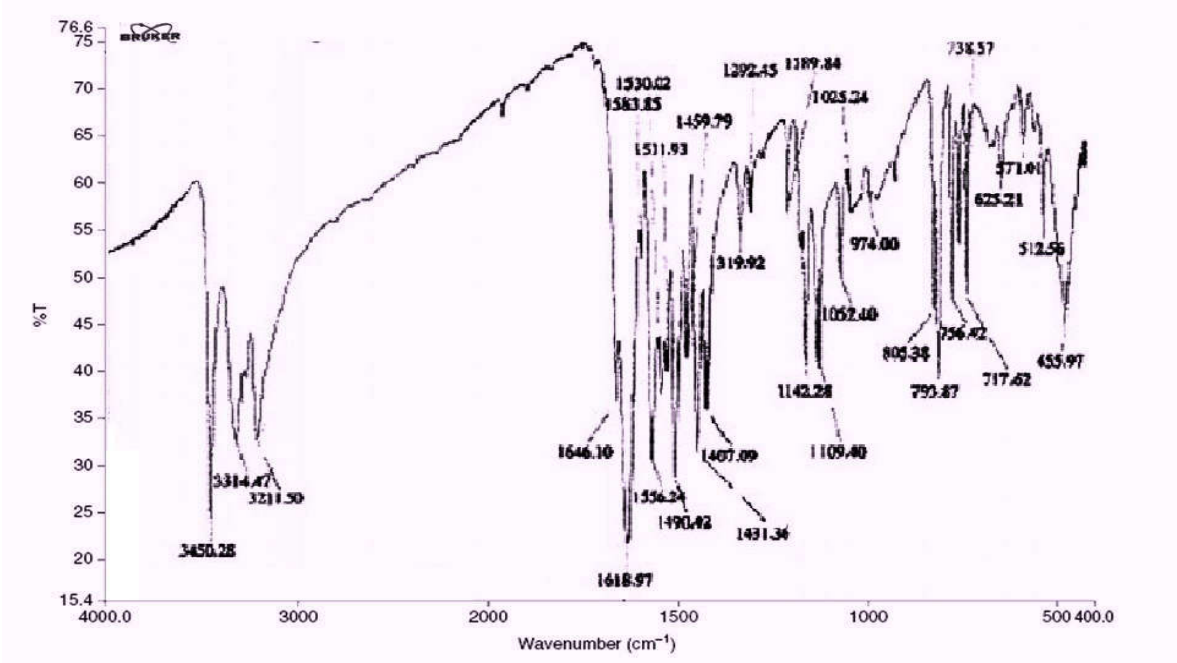

Figure 3: The I. R. Spectrum of Lamotrigine sample (S1)

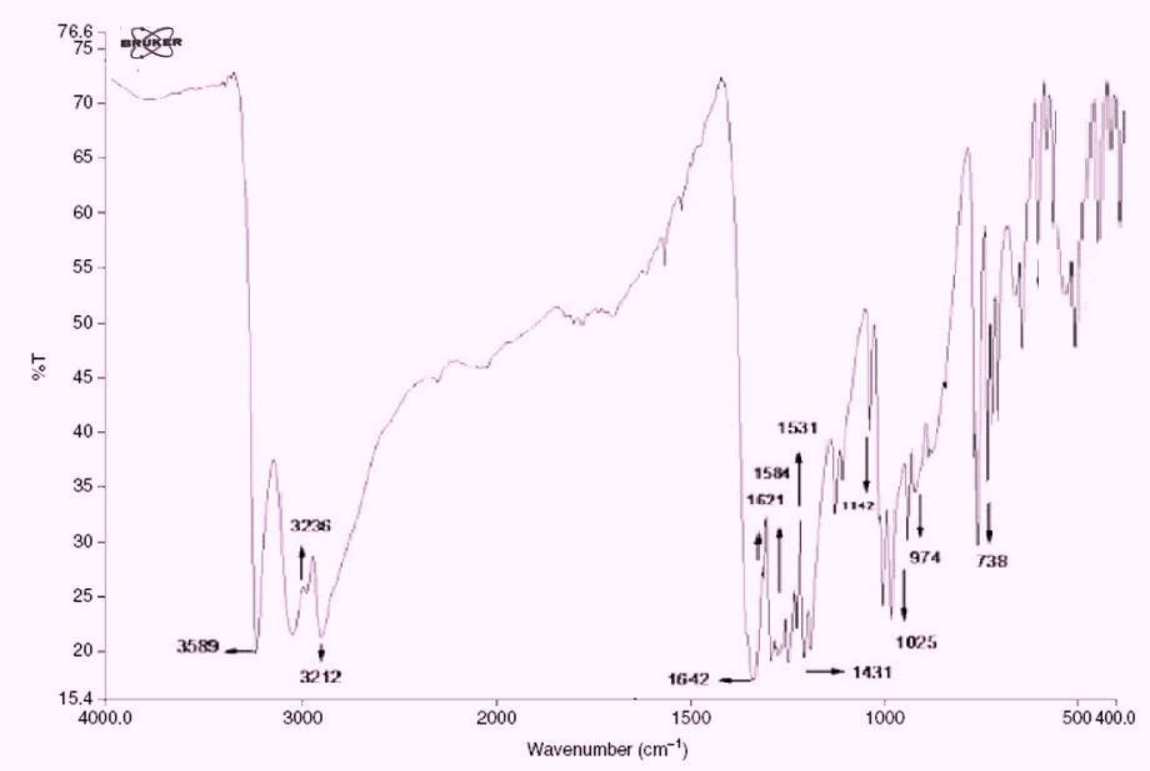

Figure 4: The I. R. Spectrum of Lamotrigine drug and all excipient (S2)

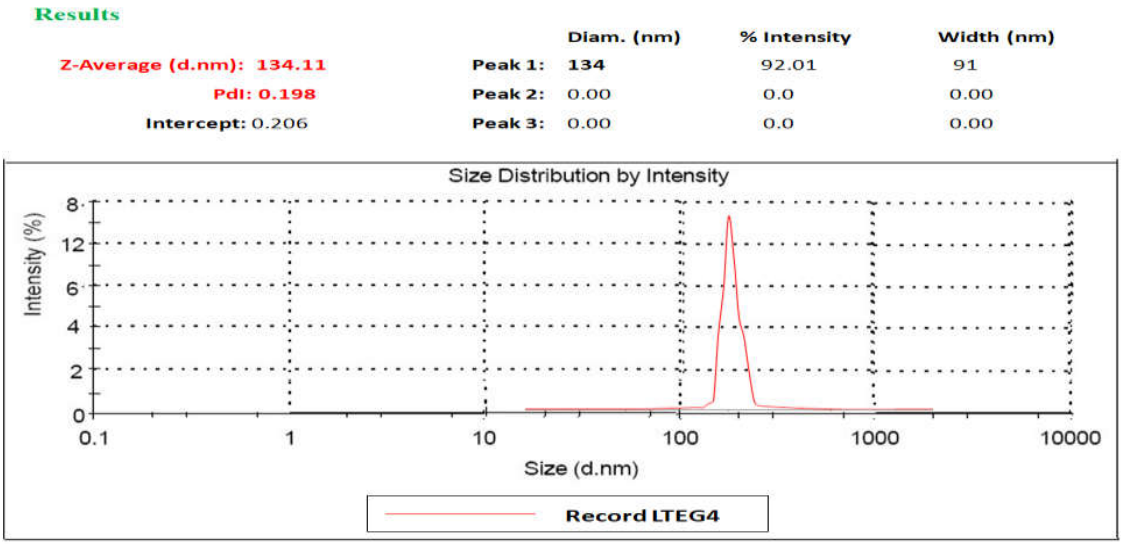

Figure 5: Determination of Globule (Particle) size and Polydispersity index (PDI) of formulations (LTEG4)

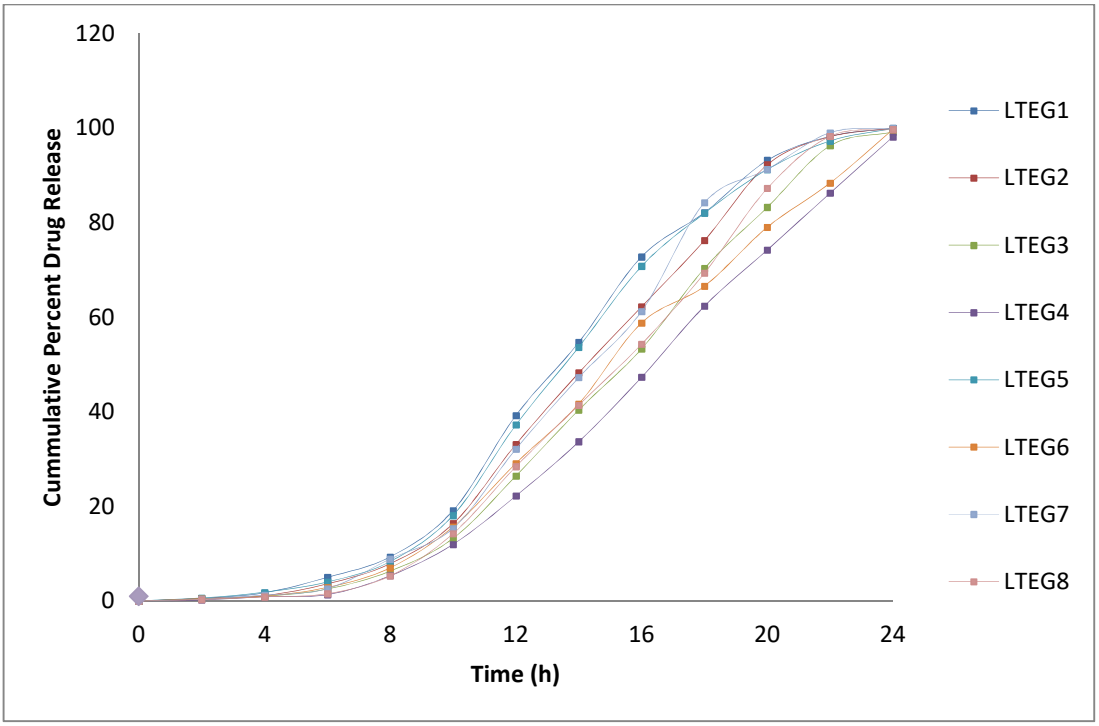

Figure 6: Zero-order plots for transdermal emulgel delivery system (LTEG1 to LTEG8)

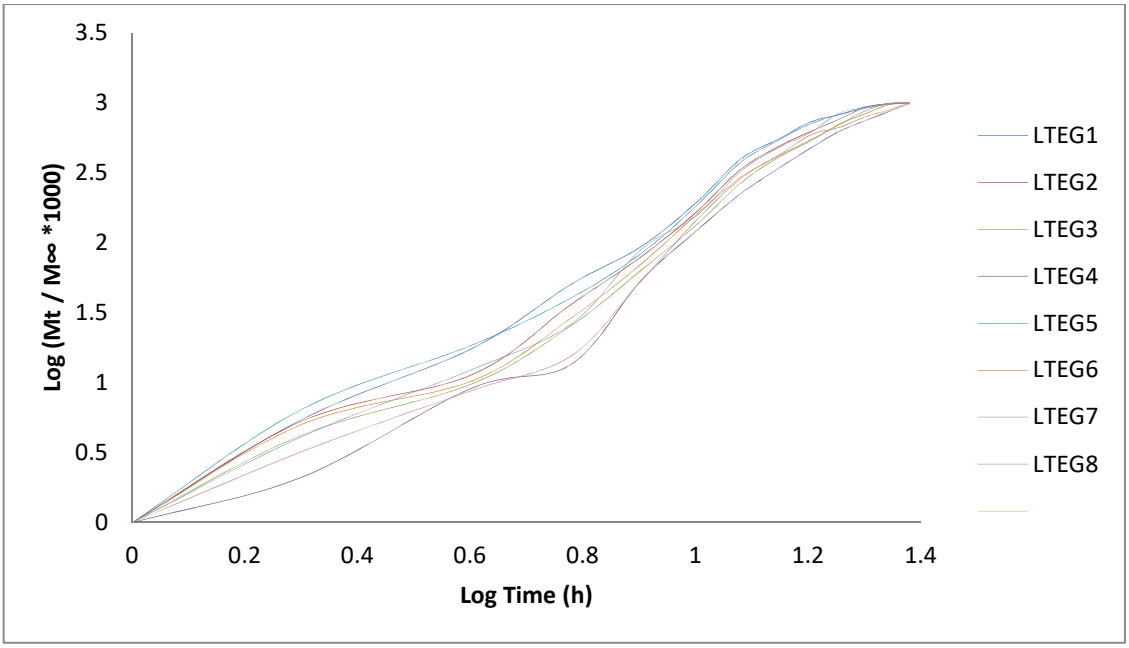

Figure 7: Korsmeyer's-Peppas plot for transdermal emulgel delivery system (LTEG1 to LTEG8)