ORIGINAL ARTICLE

# Design, Development, and Optimization of Novel Proniosomes for Enhanced Transdermal Delivery of Eprosartan Mesylate

**V. Sarovar Reddy[1], P. Anitha[1], D. Vasavi Devi[2], G.V. Sowmya Sree[1], S. Rahamathi[3], K. Nagalakshmi[4], B. Niveditha[5], A. Sushmitha[2], Shaik Yasmin[6], S. L. Manideep Royal[5]**

*[1]Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [2]Department of Pharmaceutical Analysis, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [3]Department of Pharmacology, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [4]Department of Pharmaceutical Chemistry, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [5]Department of Pharmacy Practice, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [6]Department of Pharmaceutics, Nirmala College of Pharmacy, Kadapa, Andhra Pradesh, India*

## Abstract

**Aim:** The present novelty in the fabrication work is preparation of proniosomal gel using eprosartan mesylate using coacervation phase separation technique. **Materials and Methods:** In the present work made, the formulations were prepared using drug along with excipients such as span 60, tween 80, lecithin, cholesterol, carbopol 934, alcohol, and glycerin. A total of six formulations on gels were prepared by coding EF1 to EF6. The drug and polymer interaction studies by Fourier transform infrared (FTIR) were carried before formulating the preparation composition. The gel formulations were evaluated for physicochemical evaluation such as scanning electron microscopy, percentage entrapment efficiency (EE), pH, rheological measurements, homogeneity, extrudability, spreadability, and *in vitro* drug release study. **Results and Discussion:** The formulation EF3 which was composed with drug, eprosartan mesylate 60 mg, lecithin 450 mg, cholesterol 100 mg, alcohol 0.5 mg, and carbopol 934 - 2% has shown optimum release in concentration independent manner. The *in vitro* drug release profile for formulation EF3 at 24 h was 98.43% and shown maximum drug release from the gel. The % EE was 89.43 ± 1.57, pH 7.04 ± 0.15, viscosity 35.46 (Pa S), and the shape, surface, and size characteristics of the optimized formulation EF3 were observed under a scanning electron microscope. The structure of the formed vesicle was studied by spreading as a thin layer on a glass slide. The images were taken using a Fujifilm Finepix F 40 fd 8.3 MP computer camera with a 3-inch optical zoom. **Conclusion:** Hence, prepared proniosomal gel of eprosartan mesylate could be promising drug delivery as they minimize the dose, overcome the side effects, simplify treatment regimen, and improve patient compliance.

**Key words:** Carbopol 934, *in vitro* drug release, lecithin, optimized formulation, transdermal, Tween 80

## INTRODUCTION

The novel drug delivery system should ideally fulfill two prerequisites which are first, it should deliver the drug at a rate directed by the needs of the body, till the period of treatment; second, it should channel the active ingredient of the formulation to the site of action.[1] In the past, drug delivery methods have been modified, with significant exploration of topical delivery routes. In the past decade, the delivery system was able to deliver the drugs which are poorly water soluble in nature (hydrophilic) as the skin uppermost layer consists of water as a component, and thus, they have suitable properties to be delivered through this

**Address for correspondence:**
Dr. P. Anitha, Department of Pharmaceutics,
Annamacharya College of Pharmacy, New Boyanapalli,
Rajampet - 516 126, Andhra Pradesh, India.
Phone: +91-9908344380.
E-mail: posina.anitha26@gmail.com

**Received:** 09-01-2024
**Revised:** 07-05-2024
**Accepted:** 26-05-2024

route to the systemic circulation. For hydrophobic drugs, there developed a requirement of permeability enhancement. Most of the drugs which are developed from contemporary drug delivery system are hydrophobic in nature which then requires delivering drugs in a modified form to enhance the bioavailability of the drug.[2]

The topical administration of drugs is gaining interest mainly not only for the local treatment of skin diseases but also for chronic diseases and it has been developed since a long time; the use of transdermal delivery for the systemic action is relatively new and increasingly used. The local side effects are the major problems, while the drug is administered topically. These are mainly cutaneous irritation, erythema, dryness, peeling, and scaling. Novel vesicular and particulate drug delivery systems have been proposed to reduce the side effects of drugs commonly used in topical treatment. The rapid development of transdermal delivery formulations in the last years is due to its ability to overcome certain problems of the conventional system of drug development.[3] The traditional transdermal drug delivery system (TDDS) is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. The adhesive of the TDDS is critical to the safety, efficacy, and quality of the product.[4,5] Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Transdermal delivery not only provides controlled, constant administration of the drug but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects.[5]

The major benefits of transdermal delivery could include enhanced efficacy of drug absorption, decreased incidence and severity of adverse events, enhanced patient compliance, and the multitude of benefits from administering drugs through a transdermal patch has contributed immensely to patient compliance and the patches are more convenient, less invasive, and less traumatic than intravenous (IV) delivery, multi-day administration is easily achieved with one application, patches are viable for drugs with high potency or short half-lives, as well as for patients unable to tolerate or achieve their individual "best dose" effect with oral or inhalation dosage forms, patches eliminate the need for the typical resources required for IVs and enhance safety by reducing the potential for disease transmission and the fear of injections is eliminated.[6]

The ideal properties of drug for TDDS which were the drug should not be irreversibly bound in the subcutaneous tissue, should possess a favorable oil: water partition coefficient. (Log P(octanol-water) between 1 and 4), irritation of skin layers should be avoided, drugs highly acidic or alkaline in solution are not suitable for transdermal delivery, the drugs should be stable when in contact with the skin, half-life of the drug should be 10 or less, substances having a molecular weight of <1000 units are usually suitable, melting point of the drug should be below 200°C, the solubility in both mineral oil and water should be >1 mg/mL, a saturated aqueous solution of the drug should have a pH value between 5 and 9, and the skin permeability coefficient should be $>0.5\times10^{-3}$ cm/h.[7-9]

Proniosomes are dry formulations of surfactant-coated carriers, which can be measured out as needed and rehydrated by brief agitation in hot water. Stability of dry proniosomes is expected to be more stable. Proniosome is derived from the niosomes. Proniosomes are converted to niosomes upon hydration. In release studies, proniosomes appear to be equivalent to conventional niosomes. The surfactants of spans and tweens of different grades to improve the formation of vesicles, stabilizers such as cholesterol and lecithin to prevent leakage of drug from formulation, and carriers such as maltodextrin, sorbitol were used to offer flexibility in surfactant activity.[10]

## MATERIALS AND METHODS

The proniosomal transdermal drug delivery of eprosartan mesylate was carried out using chemicals were brought eprosartan mesylate brought from Hetero Drugs, Hyderabad, Span 80 from LOBA CHEMIE, Mumbai; Tween 80 from Merck Specialties, Mumbai; Lecithin SD Fine, Mumbai; Cholesterol from Finar, Ahmedabad; Ethanol from SD Fine, Mumbai; Glycerol, from Fisher Scientifics, Mumbai; Propylene glycol, Carbopol 934P from LOBA CHEMIE, Mumbai; and Potassium dihydrogen phosphate, sodium hydroxide from Fisher Scientific, Mumbai.

### Preformulation studies[11,12]

In the present work, preformulation studies like compatibility studies between drugs - Excipients were carried out using Fourier transform infrared (FTIR) to confirm the absence of any possible chemical interaction between the drug and excipients, namely Span, Tween, Lecithin, and Cholesterol.

The pure drug eprosartan mesylate and a mixture of it with excipients such as Span, Tween, Lecithin, and Cholesterol were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000–400 $cm^{-1}$. The resultant spectra were then compared with Original Spectra and observe for any type of deviation from the original spectra.

## Fabrication of proniosomal gel

The proniosomal gel for eprosartan mesylate was fabricated using coacervation-phase separation method**.** Precisely weighed amounts of surfactant, lecithin, cholesterol, and drug were taken in a clean and dry wide-mouthed glass vial of 5.0 mL capacity and alcohol (0.5 mL) was added to it. After warming, all the ingredients were mixed well with a glass rod; the open end of the glass bottle was covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60–70°C for about 5 min until the surfactant mixture was dissolved completely. Then, the aqueous phase (0.1% glycerol solution) was added and warmed on a water bath till a clear solution was formed which was converted into proniosomal gel on cooling. The gel so obtained was preserved in the same glass bottle in dark conditions for characterization. Compositions of proniosomal gel formulations are given in Table 1.

All formulations, EF1 to EF6 were further prepared as proniosomal gels using carbopol 934. The proniosomal powder was dispersed in 2% carbopol 934 solution. This was further neutralized with few drops of 0.5% triethanolamine and few drops of 10% glycerin slowly with constant stirring to obtain proniosomal gel.[13]

## Characterization of proniosomal gel

The characterization of proniosomal transdermal gel of eprosartan mesylate was done using the following evaluation methods.

### *Scanning electron microscope (SEM)*

The shape, surface, and size characteristics of the optimized formulation EF3 were observed under a SEM. The structure of the formed vesicle was studied by spreading as a thin layer on a glass slide. The images were taken using a Fujifilm Finepix F 40 fd 8.3 MP computer camera with a 3-inch optical zoom.[14]

### *% Entrapment efficiency (EE)*

Percentage of EE has been determined by ultracentrifugation. The samples were centrifuged at 20,000 rotations/min for 3 h at 4°C in a centrifuge (REMI, Mumbai). The collected supernatant was diluted with phosphate-buffered saline solution and quantified using the ultraviolet spectrophotometer (Shimadzu, Japan). The percentage of EE was determined from equation.[15]

$$C_a - C_b/C_a \times 100$$

Where, $C_a$ = concentration of total drug, $C_b$ = concentration of free drug.

### *pH evaluation*

The pH of all formulations was determined by means of a pH meter (Elico) that is thinned out in double distilled water by laying it in contact with the gel.[16]

### *Rheological measurements*

Viscosity of gel was determined using a Brookfield Viscometer with spindle C50–1, (Model No. LVDVE, Brookfield Engineering Laboratories Inc., Middleboro, MA, USA), at 50 rpm for 50 s in triplicate.[16]

### *Spreadability, homogeneity, and extrudability[16]*

Spreadability was assessed along the basis of slide and swipe character of the gel. A modified method of introduction of 0.5 g gel between two glass plates of 2 cm diameter and on the upper glass plate a weight of 500 g was kept for 5 min. The diameter of gel spreading is increased and the % spread by area was determined by (A2/A1) × 100, where A1 is 2 cm and A2 is a final area after spreading. Through mere visual inspection, the homogeneity of the gels was observed. Extrudability of gels from a collapsible tube was set by weighing the weight in grams required to squeeze 0.5 cm ribbon of gel in 10 s.

### *In vitro drug release studies*

The *in vitro* drug release studies of proniosomal gel were carried out by means of treated cellophane membrane. *In vitro* release studies on proniosomal gel were performed using Franz-diffusion cell. The capacity of receptor compartment was 10 mL. The dialysis cellophane membrane was mounted between the donor and receptor compartment. A weighed amount of proniosomal gel was placed on one side of the membrane. The receptor medium was saline phosphate

**Table 1:** Composition of proniosomal gel using eprosartan mesylate

| S. No | Formulation Code | Span 60 (mg) | Tween 80 (mg) | Lecithin (mg) | Cholesterol (mg) | Alcohol (mL) |
|---|---|---|---|---|---|---|
| 1 | EF1 | 900 | - | 900 | 100 | 0.5 |
| 2 | EF2 | 900 | - | 900 | 200 | 0.5 |
| 3 | EF3 | 900 | - | 450 | 100 | 0.5 |
| 4 | EF4 | - | 900 | 900 | 100 | 0.5 |
| 5 | EF5 | - | 900 | 900 | 200 | 0.5 |
| 6 | EF6 | - | 900 | 450 | 100 | 0.5 |

buffer pH 7.4. The receptor compartment was surrounded by a water jacket to maintain the temperature at 37±1°C. Heat was provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid was stirred by a Teflon-coated magnetic bead fitted to a magnetic stirrer. At each sampling interval, 1 mL were withdrawn and were replaced by equal volumes of fresh receptor fluid on each occasion. Samples withdrawn were analyzed spectrophotometrically (Systronics-2200) at 238 nm. The release kinetics in the dissolution, data are fitted to four popular release models such as Zero order (Higuchi) Diffusion and (Peppa's and Korsemeyer) Erosion equations.[17,18]

## RESULTS AND DISCUSSION

### Preformulation studies

#### *Drug-polymer compatibility studies*

The development of a successful formulation depends only on suitable selection of excipients. Hence, the physical state of the drug, eprosartan mesylate using different excipients such as Span 60, Tween 80, lecithin, and cholesterol individually and the admixture of drug and excipients used were studied by FTIR to know the drug – polymer compatibility after interpretation. The IR Spectra data for pure drug eprosartan mesylate and pure excipients such as Span, Tween, Lecithin, and Cholesterol were tabulated in Tables 2 and 3. IR Spectra for pure drug eprosartan mesylate and a mixture of it with the excipients such as Span, Tween, Lecithin, and Cholesterol were represented in Figures 1-6.

#### *SEM*

Results eprosartan mesylate proniosomes are presented in (Tables 4-6), which indicated that vesicle formed with Span60 is smaller in size than vesicle formed with Tweens; this is due to greater hydrophobicity of Spans than Tweens. It is indicated that increasing in hydrophobicity decreases surface energy of surfactants resulting in smaller vesicle size. Size of vesicle was reduced when dispersion was agitated. The reason for this is the energy applied in agitation which results in breakage of larger vesicles to smaller vesicles. The

**Table 2:** IR spectra data for pure eprosartan mesylate, lecithin, and cholesterol

| S. No. | Pure eprosartan mesylate | | | Lecithin | Cholesterol | |
|---|---|---|---|---|---|---|
| 1 | 1783.57 | C=O Stretching | 3012 | C – H Stretching | 3398 | O – H Stretching |
| 2 | 3610.45 | C-OH Stretching | 2854 | C – H Stretching in $CH_2$ | 2935 | C – H Stretching |
| 3 | 1692.57 | C=N Stretching | 1620 | C=O Stretching | 1620 | C=C Stretching |
| 4 | 1212.91 | C-N Stretching | 1458 | C – H Deformed in $CH_2$ | 740,698 | C- C Stretching |
| 5 | 1532.14 | C=C Stretching | 1384 | C – N Stretching | - | - |

**Table 3:** IR spectra data for Span 60, Tween 80, and formulation EF3

| S. No. | Span 60 | | Tween 80 | | Formulation EF3 | |
|---|---|---|---|---|---|---|
| 1 | 3363, 3344 | O-H Stretching | 3483 | O-H Stretching | 3271 | NH Asymmetric Stretching |
| 2 | 3356, 3174 | C=C Stretching | 2924 | $CH_3$ Asymmetric Stretching | 2924 | CH Stretching Aromatic |
| 3 | 2920 | $CH_3$ Asymmetric Stretching | 2858 | $CH_2$ Symmetric Stretching | 2854 | $CH_2$ Symmetric Stretching |
| 4 | 2854 | $CH_2$ Symmetric Stretching | 1685 | C=O Stretching | 1735, 1651 | C=O Stretching |
| 5 | 1654 | C=O Stretching | 1639 | C=C Strecthing | 1539 | Aromatic $NO_2$ |
| 6 | 1365, 1273 | C=O Stretching and OH in Plane Bending Vibrations | 1111 | C– O –C Asymmetric Stretching | 1458 | $CH_2$ Bending |
| 7 | 1087 | C– O –C Asymmetric Stretching | 948,852 | CH Out of Plane Bending | 1195 | C – N Stretching |
| 8 | 925,883 | CH Out of Plane Bending | - | - | 1049 | C– O –C Stretching |
| 9 | - | - | - | - | 925,860 | C– O –C Asymmetric Stretching |
| 10 | - | - | - | - | 509 | O–C–N Deformation |

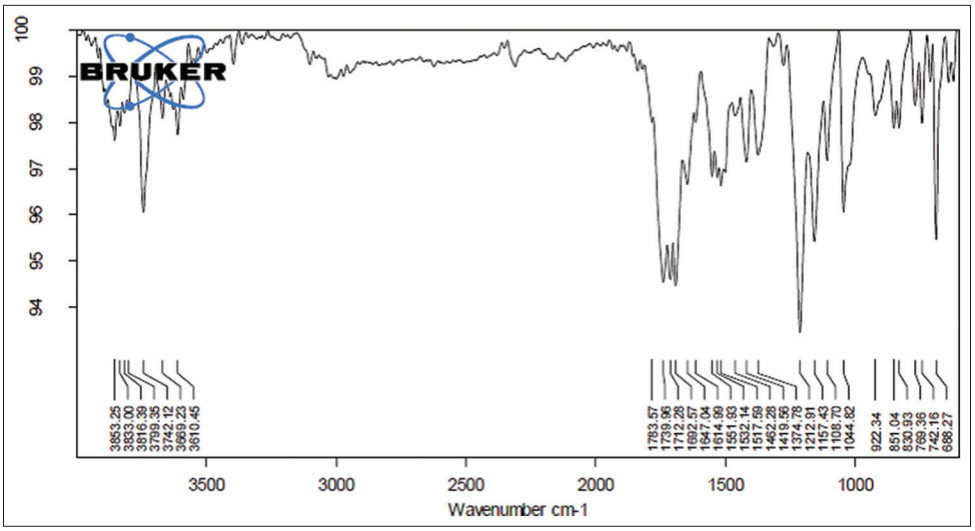


**Figure 1:** Fourier transform infrared spectra of pure eprosartan mesylate

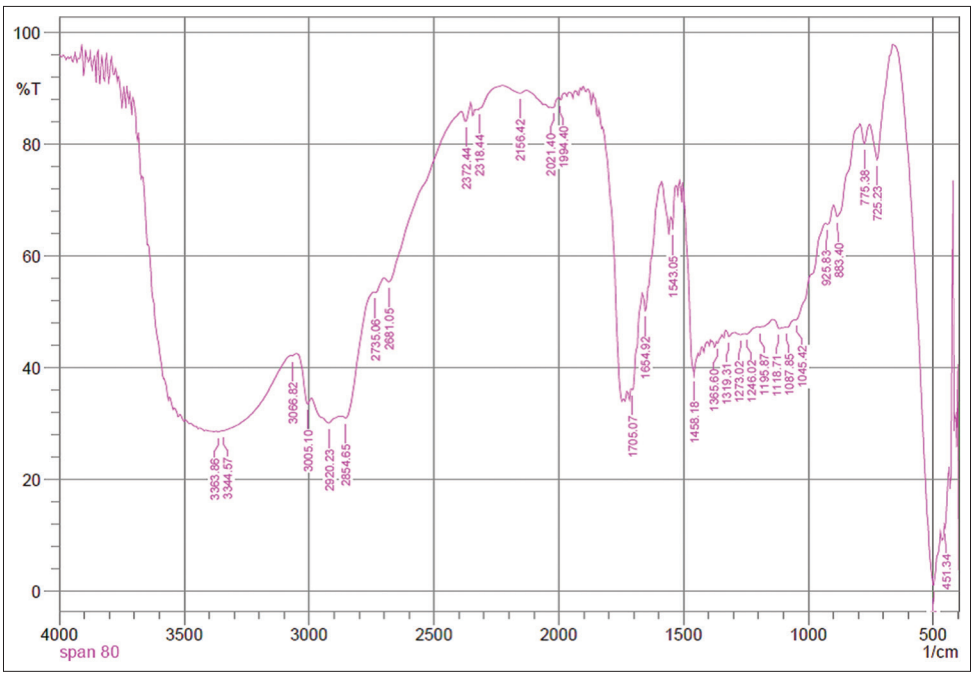


**Figure 2:** Fourier transform infrared spectra of pure Span 60

size range was found to be 326±20.02 nm to 580±10.45 nm. Surface morphological studies (SEM) revealed that the proniosome formed were spherical and homogeneous as shown in Figure 7.

### *Percentage EE, pH, viscosity, spreadability, homogeneity, and extrudability*

The prepared proniosomal gel was considered acceptable with no skin irritation and having a less vesicle size which facilitates their permeation. The prepared gels which are formulated were light in color with uniform appearance and texture with the absence of lumps. A gel with good spreadability takes less time to spread. The developed gel presented 90% spreadability with excellent extrudability. Viscosity is a significant factor for describing the gels as it affects the extrudability and release of drugs.

EE was found to be higher in the case of proniosomes prepared with Span60 than proniosome prepared with Tween80; this is due to fact that Span 60 is more hydrophobic than Tween 80, which acts as solid at room temperature and showed higher phase transition temperature (Tc), low HLB value, and long alkyl chain length and results are shown in Table 4.

### *In vitro drug release studies*

*In vitro* drug release studies were carried out in phosphate buffer (pH 7.4) for 24 h. The formulation EF1 formulated with cholesterol (100), lecithin (900), and span 60 (900) has

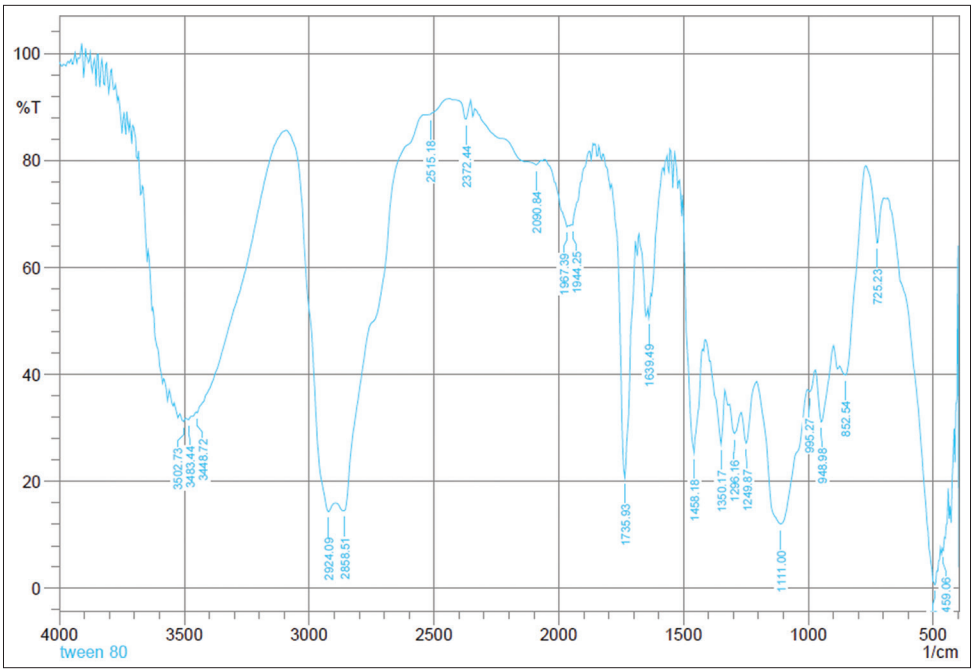


**Figure 3:** Fourier transform infrared spectra of Tween 80

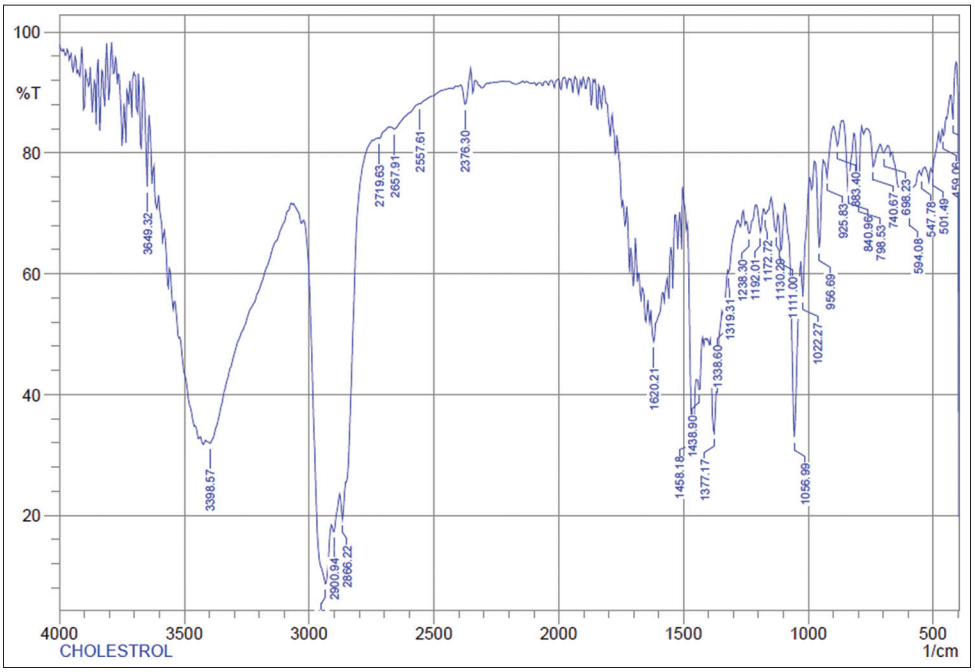


**Figure 4:** Fourier transform infrared spectra of cholesterol

shown release 96.24% at 24$^{th}$ h. The *in vitro* drug release plot has shown that the drug release followed zero-order kinetics, which was envinced from the regression value of the above-mentioned plot. Higuchi's plot has shown a regression value of 0.955, which indicated that diffusion mechanism influencing the drug release. To confirm this fact, Peppa's plot was drawn which has shown slope value of 0.686, which confirms that the diffusion mechanism involved in the drug release was of non-Fickian diffusion type.

The formulation EF2 formulated with cholesterol (200), lecithin (900), and span 60 (900) has shown release 92.32% at 24$^{th}$ h. This is due to those formulations which have higher cholesterol content (EF2 and EF5) are seen to have less drug release over a period of 24 h. Hence, increase in cholesterol ratio seems to result in a more intact bilayer and consequent reduction in permeability. The drug release was diffusion mediated and from Peppa's plot, it is confirmed that it is of non-Fickian.

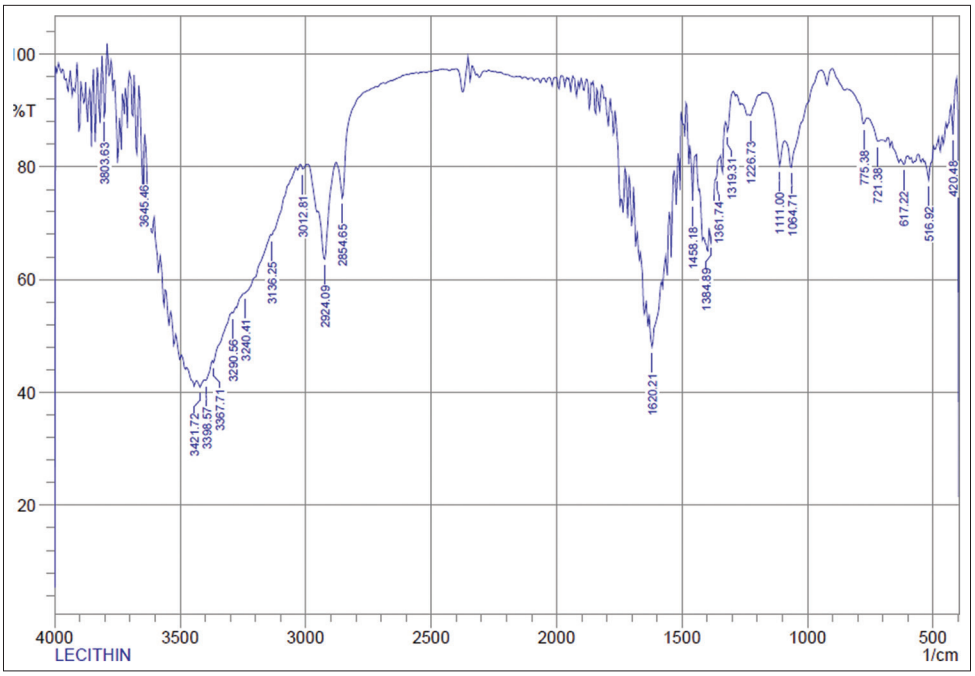


**Figure 5:** Fourier transform infrared spectra of lecithin

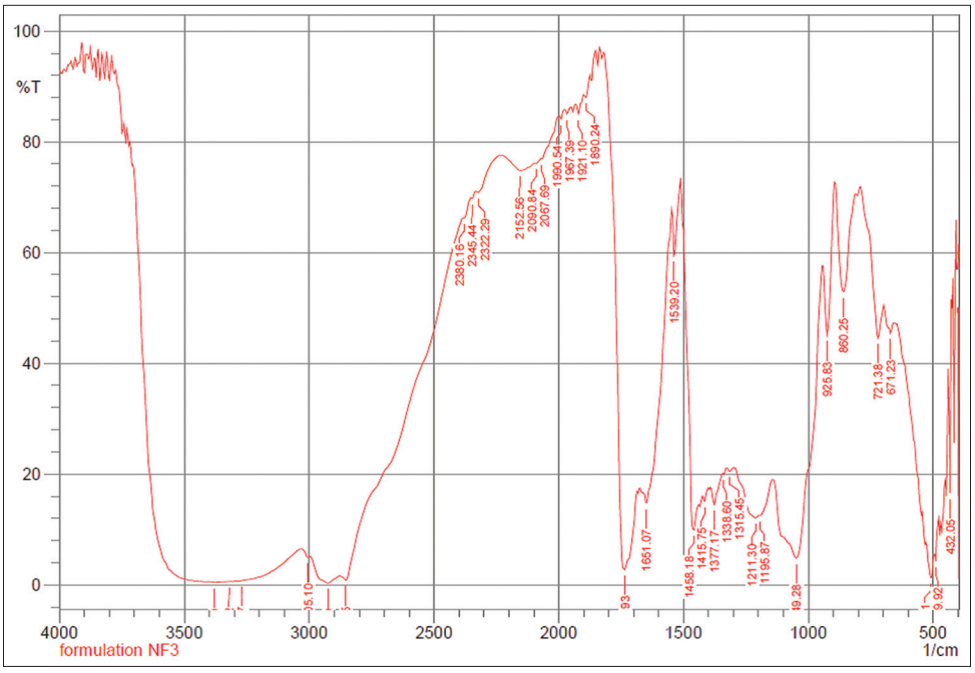


**Figure 6:** Fourier transform infrared spectra of formulation EF3

The formulation EF3 formulated with cholesterol (100), lecithin (450), and span 60 (900) has shown a drug release of 98.43% at 24$^{th}$ h. The drug release was diffusion mediated and it is non-Fickian type. Higuchi's plot has shown a regression value of 0.959, which indicated that diffusion mechanism influences the drug release. The drug release was diffusion mediated and from the Peppa's plot, it is confirmed that it is of non-Fickian type.

The formulation EF4 formulated with Cholesterol (100), Lecithin (900), and Tween 80 (900) has shown a drug release of 90.65% for 24 h. The *in vitro* drug release plot has shown that the drug release followed zero-order kinetics, which was envinced from the regression value of the above-mentioned plot. Higuchi's plot has shown the regression value of 0.952, which indicated that diffusion mechanism influencing the drug release.

To confirm this fact, Peppa's plot was drawn which has shown slope value of 0.705, which confirms that the diffusion mechanism involved in the drug release was of non-Fickian diffusion type.

**Table 4:** Characterization of proniosomal gel

| S. No. | F. Code | % entrapment efficiency | pH | Viscosity (Pa S) | Spreadability | Homogeneity | Extrudability |
|---|---|---|---|---|---|---|---|
| 1. | EF1 | 83.42±2.23 | 7.12±0.12 | 34.00 | Good | Fine | Yes, Maximum content |
| 2. | EF2 | 75.27±1.45 | 6.98±0.14 | 32.56 | Good | Fine | Yes, Maximum content |
| 3. | EF3 | 89.43±1.57 | 7.04±0.15 | 35.46 | Good | Fine | Yes, Maximum content |
| 4. | EF4 | 81.34±1.26 | 7.24±0.12 | 34.76 | Good | Fine | Yes, Maximum content |
| 5. | EF5 | 75.86±2.65 | 7.14±0.13 | 32.87 | Good | Fine | Yes, Maximum content |
| 6. | EF6 | 79.32±1.54 | 6.96±0.14 | 37.89 | Good | Fine | Yes, Maximum content |

**Table 5:** *In vitro* drug release profile for formulation EF1 to EF6 (Cumulative percentage)

| S. No. | Time in hours | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 10.12 | 9.12 | 14.12 | 8.32 | 9.98 | 6.92 |
| 2 | 2 | 17.31 | 16.24 | 22.36 | 18.24 | 12.54 | 15.32 |
| 3 | 3 | 26.54 | 20.21 | 30.26 | 22.32 | 15.87 | 17.34 |
| 4 | 4 | 29.32 | 24.32 | 32.21 | 26.21 | 18.97 | 18.32 |
| 5 | 5 | 32.12 | 28.28 | 34.65 | 30.21 | 20.87 | 20.32 |
| 6 | 6 | 35.12 | 32.54 | 38.45 | 33.21 | 24.78 | 23.34 |
| 7 | 7 | 40.65 | 36.25 | 40.25 | 38.1 | 28.97 | 28.54 |
| 8 | 8 | 43.26 | 38.54 | 44.62 | 40.24 | 31.43 | 32.43 |
| 9 | 9 | 46.15 | 40.65 | 48.26 | 43.65 | 35.76 | 36.24 |
| 10 | 10 | 50.36 | 45.54 | 50.24 | 48.24 | 37.21 | 38.12 |
| 11 | 11 | 55.69 | 47.24 | 53.12 | 52.32 | 39.21 | 40.32 |
| 12 | 12 | 58.32 | 50.24 | 57.45 | 54.36 | 42.76 | 42.43 |
| 13 | 13 | 61.54 | 54.2 | 61.2 | 58.14 | 44.32 | 45.32 |
| 14 | 14 | 65.24 | 58.32 | 64.21 | 60.24 | 46.76 | 49.21 |
| 15 | 15 | 69.25 | 61.1 | 68.41 | 63.3 | 49.21 | 52.76 |
| 16 | 16 | 71.65 | 64.36 | 71.54 | 68.32 | 51.76 | 54.36 |
| 17 | 17 | 76.23 | 68.32 | 75.24 | 71.6 | 54.76 | 56.23 |
| 18 | 18 | 79.21 | 70.21 | 79.1 | 74.25 | 56.87 | 58.32 |
| 19 | 19 | 81.32 | 73.1 | 81.36 | 78.21 | 61.65 | 61.12 |
| 20 | 20 | 85.65 | 79.32 | 84.21 | 80.3 | 66.87 | 63.23 |
| 21 | 21 | 88.21 | 82.31 | 88.45 | 82.12 | 69.65 | 65.32 |
| 22 | 22 | 90.25 | 86.21 | 91.26 | 84.21 | 72.43 | 68.32 |
| 23 | 23 | 92.65 | 89.32 | 94.23 | 88.24 | 76.87 | 72.32 |
| 24 | 24 | 96.24 | 92.32 | 98.43 | 90.65 | 83.76 | 85.32 |

The formulation EF5 formulated with Cholesterol (200), Lecithin (900), and Tween 80 (900) has shown the drug release of 83.76% at 24$^{th}$ h. The drug release was diffusion mediated and from Peppa's plot, it is confirmed that it is of non-Fickian type. The decrease in drug release is due to those formulations which have higher cholesterol content (EF2 and EF5) are seen to have less drug release over a period of 24 h. Hence, increase in cholesterol ratio seems to result in a more intact bilayer and consequent reduction in permeability.

The formulation EF6 formulated with Cholesterol (100), Lecithin (450), and Tween 80 (900) has shown the drug

**Table 6:** Diffusion characteristics for all formulations EF1-EF6

| S. No | Batch code | Regression for *in vitro* plot ($r^2$) | Regression for Higuchi's plot ($r^2$) | Slope for Peppa's plot (n) |
|---|---|---|---|---|
| 1 | EF1 | 0.933 | 0.955 | 0.686 |
| 2 | EF2 | 0.963 | 0.929 | 0.710 |
| 3 | EF 3 | 0.994 | 0.959 | 0.591 |
| 4 | EF 4 | 0.938 | 0.952 | 0.705 |
| 5 | EF 5 | 0.973 | 0.900 | 0.698 |
| 6 | EF 6 | 0.963 | 0.913 | 0.725 |

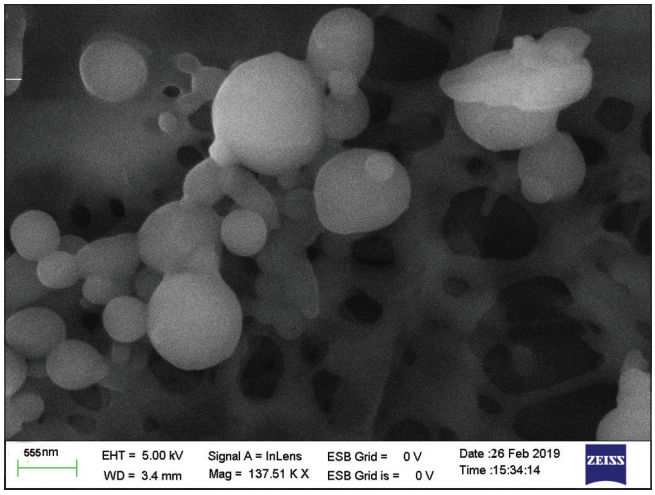


**Figure 7:** Scanning electron microscope analysis of EF3

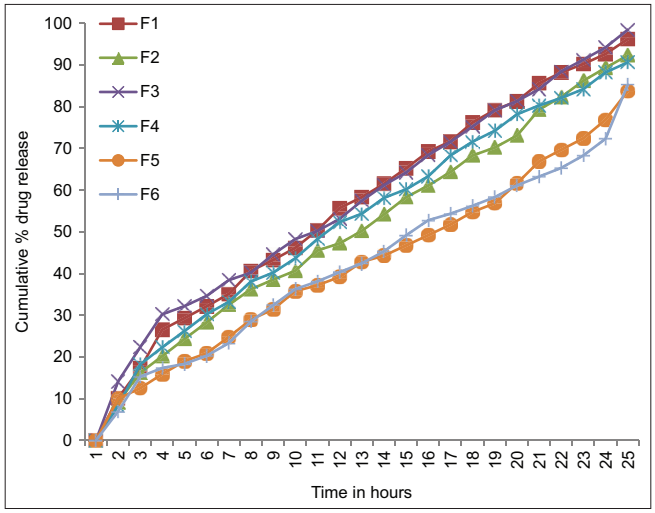


**Figure 8:** *In vitro* drug release profile for formulation EF1 to EF6

release of 85.32% at 24$^{th}$ h. The drug release was diffusion mediated and of non-Fickian type.

The *in vitro* release plots of all other formulations were suggestive of zero order release and are diffusion mediated which was envinced form the regression value Higuchi's plot. All the formulations undergo non-Fickian type of release which is confirmed from the slope values obtained from the Peppa's plot. All the results are shown in Tables 5 and 6, Figure 8.

## CONCLUSION

The selection, analysis, composition, fabrication, and evaluation of prepared topical transdermal gel focus on the results of present investigation revealed that all the excipients used did not interfere with the estimation of eprosartan mesylate at analytical wavelength 234 nm. Proniosomal transdermal gel of eprosartan mesylate was successfully fabricated using Coacervation Phase separation Technique. The prepared transdermal gel was evaluated for characterization techniques which show clear, smooth, uniform, and desired vesicle size with maximum drug release of 98.43% at 24$^{th}$ h by phosphate buffer, pH 7.4 as a dissolution medium. The formulation EF3 has shown optimum release in concentration-independent manner and holds promise for further extension of research as Higuchi's plot for the formulation revealed that the predominant mechanism of drug release is diffusion and Peppa's plot for the formulation revealed that the predominant mechanism of drug release is non-Fickian.

## REFERENCES

1. Lee SJ, McClements DJ. Fabrication of protein-stabilized nanoemulsions using a combined homogenization and amphiphilic solvent dissolution/evaporation approach. Food Hydrocoll 2010;24:560-9.
2. Li Y, McClements DJ. New mathematical model for interpreting pH-Stat digestion profiles: Impact of lipid droplet characteristics on *in vitro* digestibility. J Agric Food Chem 2010;58:8085-92.
3. Weiss J, Takhistov P, McClements DJ. Functional materials in food nanotechnology. J Food Sci 2006;71:R107-16.
4. Jain NK. Controlled and Novel Drug Delivery. Darya Ganj: CBS Publishers, and Distributors; 2002. p. 107.
5. Allen LV, Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. United States: Lippincott Williams and Wilkins; 2005. p. 275.
6. Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm 1998;172:33-70.
7. Finnin CB. Transdermal drug delivery-what to expect in the near future. In: Business Briefing: Pharm Technology.

Singapore: World Markets Research Centre; 2003. p. 192-93.
8. Franz TJ, Tojo K, Shah KR, Kydonieus A. Transdermal delivery. In: Kydonieus A, editor. Treatise on Controlled Drug Delivery. New York: Marcel Dekker; 1992. p. 341-421.
9. Chandrasekhar NS, Rani RH. Physicochemical and pharmacokinetic parameters in drug selection and loading for transdermal drug delivery. Indian J Pharm Sci 2008;70:94-6.
10. Gannu PK, Pogaku R. Nonionic surfactant vesicular systems for effective drug delivery-an overview. Acta Pharm Sin B 2011;1:208-19.
11. Sudhamani T, Priyadarisini N, Radhakrishnan M. Proniosomes-a promising drug carrier. Int J PharmTech Res 2010;2:1446-54.
12. Martin A, Swarbrick J, Cammarata A. Physical Pharmacy. 3rd ed. Philadelphia, PA: Lee and Febiger; 1991. p. 303.
13. Sambhakara S, Paliwala S, Sharmaa S, Singh B. Formulation of risperidone loaded proniosomes for effective transdermal delivery: An *in-vitro* and *in-vivo* study. Bull Fac Pharm Cairo Univ 2017;55:239-47.
14. Prajapati SK, Kumar S, Sahu VK, Prakash G. Proniosomal gel of flurbiprofen: Formulation and evaluation. J Drug Deliv Ther 2012;2:1-5.
15. Patil NH, Hardikar SR, Bhosale AV. Formulation development and evaluation of proniosomal gel of carvedilol. Int J Pharm Pharm Sci 2012;4:191-7.
16. Abdelbary G, El-Gendy N. Niosome-encapsulated gentamicin for ophthalmic controlled delivery. AAPS PharmSciTech 2008;9:740-7.
17. Kumar K, Rai AK. Development and evaluation of proniosomes as a promising drug carrier to improve transdermal drug delivery. Int Res J Pharm 2011;2:71-4.
18. Shoaib MH, Jaweria T, Merchant HA, Yousuf RI. Evaluation of drug release kinetics from Ibuprofen matrix tablets using HPMC. Pak J Pharm Sci 2006;19:119-24.

**Source of Support:** Nil. **Conflicts of Interest:** None declared.