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FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM NANOEMULSION GEL

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ABSTRACT

Aim & objective: The aim of the study was to develop nanoemulsion gel for transdermal delivery of Losartan potassium to enhance its bioavailability. **Methods:** O/W Nanoemulsions were prepared by the spontaneous emulsification method. IPM was chosen as the oil phase, Tween 80, Transcutol-P were used as surfactant and cosurfactant respectively, on the basis of solubility studies and emulsification studies in the formulation of nanoemulsion. Pseudoternary phase diagrams were constructed to obtain the nanoemulsion region. Further optimized NE was incorporated into 0.5% Carbopol-934 to get a gel for improving convenience in superficial application of the drug. Drug loaded NE and NEG were characterized for particle size, viscosity, rheological behavior, thermodynamic stability studies. **Results:** The optimized formulation was compared to conventional gel formulation and it showed higher permeation rate *in-vitro* and *ex-vivo* which justifies the nanoemulsion gel to be a promising carrier for transdermal delivery of losartan potassium. **Conclusion:** The optimized formulation showed higher drug release of 90.2%, compared to conventional gel that released 68.2% release in about 9 hrs. The study suggested that nanoemulsion significantly enhanced bioavailability of transdermally applied Losartan potassium.

KEYWORDS: LP-Losartan Potassium, NE-Nanoemulsion, NEG- Nanoemulsion Gel.

INTRODUCTION

Hypertension is a chronic disease which required lifelong therapy. But most of antihypertensive drugs available today, showed extensive first-pass metabolism and low oral bioavailability which can be overcome by preparing it as Transdermal Drug Delivery Systems. It enhances the drug permeation through the skin which can be achieved by using chemical enhancers and various solvents. Use of chemical enhancers is limited for its chronic application as it causes irritation at the site of application. It is therefore desirable to develop a topical vehicle instead of chemical enhancers for formulating transdermal drug delivery system. Micro emulsion or Nanoemulsion technique proved to be one of the most promising techniques for enhancement of transdermal permeation of drugs.

Advantages of Transdermal Drug Delivery System
• It avoids GIT side effect, inactivation of drug by GIT enzymes, interaction of drug with food   and first-pass metabolism of drugs in GIT.
• It provides controlled and sustained release of the medicament.
• It improves the bioavailability of drug.
• It provides uniform drug plasma concentration.
• It improves the patient's compliance.

• It can be administered to non- responsive, unconscious and nauseating patient.
• It provides easy termination of drug in case of toxicity by removal of the formulation from the skin.

Losartan potassium, a potassium salt of 2-Butyl-4-chloro-1-[[2-(1H-tetrazol-5-yl)   [1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol, represents the first of a new class of orally active non-peptide angiotensin II (Type AT1) receptor antagonists employed in the management of essential hypertension. LP has high solubility and low permeability with only 32% of oral bioavailability.
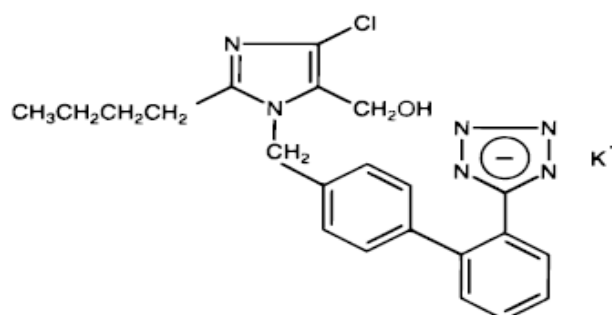

Fig. 1: Structure of Losartan potassium.

Nanoemulsion is a promising alternative to increase drug penetration of drug and targeting poorly soluble drugs, by increasing its absorption through the skin, better retention time of drug in the target area and eventually result in less side effects. Apparently, there have been researches on the antihypertensive drugs via transdermal route the bioavailability was 3.5 times higher than that of oral route which believed to be due to avoidance of first -pass metabolism. Besides that, nanoemulsion improves the permeation of drug through skin, which intergrades the interest of researchers. In addition, due to the small size of particles, more amount of drug is able to be incorporated in the formulation, which subsequently increases the thermodynamics towards the skin. Moreover, the drug affinity for partitioning increases permeation into the skin.

MATERIALS AND METHODS
Materials
Losartan potassium was a kind gift sample from Aurobindo pharma limited, Hyderabad, Telangana, India. Plurol Oleique cc (Polyglycerololeate), Cremophor RH 40, Capmul MCM (Glycerol mono dicaprylate) was received as gift samples from Abitec, India. Other chemicals like Oleic acid, Iso-propyl myristate, Ethanol, Propylene glycol, Span 20 (sorbitan-monolaurate), Span 80 (sorbitan-monooleate), Tween 20 (polyoxyethylene sorbitan monolaurate), Tween 80 (polyoxyethylene sorbitan monqoleate), Polyethylene glycol 400 (PEG 400), polyethylene glycol 600 (PEG 600), Olive oil, Castor oil and Methanol were from S.D Fine Chem, Mumbai. Carbopol 934 and Carbopol 940 were from Loba Chemie, Mumbai, Maharashtra, India. Transcutol P (Monoethyl ether of diethylene glycol) was from Abitec, India. Distilled water was used throughout the study and all other reagents used were of analytical grade.

MATERIALS AND METHODS
Solubility studies
The solubility of LP in oils, surfactants, and co-surfactants was measured using the shake flask method. An excess amount of LP was introduced into each excipient (2 ml) followed by sealing in vials and stirred for 48h at 30°C using a table top orbital Shaker (Eltek®India) to facilitate the solubilisation. Each vial was centrifuged at 15,000 rpm for 30 minutes using a research centrifuge (REMI) followed by the removal of undissolved drug by filtering through a membrane filter (0.45 µm*). Samples were suitably diluted with pH 6.8 phosphate buffer and drug concentration was obtained using a double-beam UV visible spectrophotometer (Lab India UV 3000+) at 234 nm using buffer as a blank. The experiment was repeated 3 times. The results were represented as mean values (mg/ml ± SD).

Emulsification studies
Screening of surfactants Different surfactants (span60&80, Tween 20&80) were screened for the emulsification ability of the selected oil phase. Surfactant selection was done on the basis of percentage

transparency and ease of emulsification. Briefly, 300 mg of the surfactants was added to 300 mg of the selected oily phase. The mixtures were gently heated at 50°C for the homogenization of the components. Each mixture, 50 mg, was then diluted with distilled water to 50 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield a homogenous emulsion. Emulsions were allowed to stand for 2 h and their percentage transparency was evaluated at 560 nm by a double-beam UV spectrophotometer using distilled water as a blank. Emulsions were furthermore observed visually for any turbidity or phase separation.

Screening of co-surfactants
Four co-surfactants were screened for nanoemulsion formulation, which include Transcutol P, PEG 400,PEG 600 and Ethanol. The screening of the co-surfactant was conducted on the basis of percentage transparency and ease of emulsification. Mixtures of 100 mg of the co-surfactant, 200 mg of the selected surfactants and 300 mg of the selected oil were prepared and evaluated for percentage transparency at 560 nm.

Construction of the ternary phase diagrams
On the basis of solubility and emulsification study Isopropyl myristate, Tween 80 and Transcutol-P were selected as oil, surfactant and co-surfactant, respectively. To determine the concentration of components in the existing range of the nanoemulsion, a pseudo-ternary phase diagram was constructed using an aqueous titration method at ambient temperature (25°C). The surfactant and co-surfactant were mixed in different volume ratios (1:1, 1:2, 1:3, 1:4, 4:1, 3:1 and 2:1). Oil and surfactant / co-surfactant (S_{mix}) were mixed thoroughly in different volume ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) and titrated with water by drop wise addition under gentle agitation. Slow titration with aqueous phase was done to each weight ratio of oil and Smix and visual observation was carried out for transparent and easily flowable o/w nanoemulsions. The proper ratio of one excipient to another in the nanoemulsion formulation was analyzed and the pseudo-ternary plot was constructed using TRIPLOT V14 software (version 4.1.0.2).

Preparation of Losartan potassium nanoemulsion
Accurately weighed (50 mg) of LP was added to oil in a beaker. The surfactant and co-surfactant were added to the oil mixture using a positive displacement pipette and magnetically stirred. The formulations were further sonicated (Sonica ultrasonic, 2000 MH, Spinotech Pvt Ltd, India) for 15 minutes and stored at room temperature for further studies.

Characterization of Nanoemulsion
Self emulsification time and Dispersability tests
The efficiency of dispersability was assessed using a USP II dissolution apparatus. Each formulation (0.5 ml) was added to 500 ml distilled water maintained at

37±0.5∘C, with paddle rotating at 50 rpm for gentle agitation. The *in vitro* performance of the formulations was visually assessed using the grading system as shown below.

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
Grade C: Fine milky emulsion that formed within 2 min.
Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Thermodynamic stability studies
1. Heating cooling cycle: Six Cycles between refrigerator temperature (4°C) and (45°C) with storage at each temperature for not less than 48 h was studied. Formulations, which were stable at these temperatures, were subjected to centrifugation test.

2. Centrifugation: Stable formulations were centrifuged at 3500 rpm for 30 min. Those formulations that did not show any phase separation were taken for the freeze thaw stress test.

3. Freeze thaw cycle: Three freeze thaw cycles between-21^0C and 25^0C with storage at each temperature for not less than 48 h was done for the formulations.

The formulations that passed the thermodynamic stability tests were selected for further studies.

Globule size and zeta potential determination
50 mg of the optimized nanoemulsion formulation was diluted with water to 100 ml in a flask, and gently mixed by hand. The droplet size distribution and zeta potential of the resultant emulsion was determined by laser diffraction analysis using a particle size analyzer (Horiba Scientific nanopartica, UK), that analyzes the fluctuations in light scattering due to Brownian motion of the particles. Light scattering was monitored at 25°C at a 90° angle.

Percent transmittance
The percent transmittance of the nanoemulsion was measured using UV-Visible double beam spectrophotometer using distilled water as blank at 560 nrn.

Viscosity
The viscosity of the samples was measured as such without dilution using a Brookfield viscometer (LVDV-II+P) fitted with an S-34 spindle at 25°C.

In vitro drug ·release studies
In-vitro drug release of LP from the nanoemulsion formulation was determined using Franz diffusion cell. Nanoemulsion equivalent to single dose (50 mg of LP) was placed in a donor compartment of diffusion cell. Receptor compartment was filled with pH 6.8 Phosphate buffer solution was stirred continuously at 350 rpm. The 'receptor and donor compartments were separated by Hi-media dialysis membrane 150 (molecular weight cut off 12000-14000 Dalton, pore size 0.4 nm). Samples were withdrawn at specific time intervals and an equal volume of medium was replaced to maintain sink condition. The samples were analyzed by the UV-Visible spectrophotometer at 234 nm to determine the concentration. The experiment was repeated thrice. Same procedure was repeated for the gel as well.

Preparation of LP Nanoemulsion gel
Nanoemulsion gels were prepared using three polymers namely carbopol-934, carbopol-940 & HPMC.

The appropriate quantity of polymers was dispersed into distilled water under constant stirring with glass rod, taking care to avoid the formation of indispersible lumps and allowed to hydrate for 24hrs at room temperature for swelling.

Nanoemulsion gels were prepared by incorporation of optimized nanoemulsion formulation containing drug into the respective gelling agents with constant stirring and sufficient quantity of propylene glycol was added. The dispersion was then neutralized using triethanolamine.

Evaluation of LP Nanoemulsion gel
pH
The pH of aqueous solutions (1%) of the gel was measured by a pH meter (Systronics, µ pH System 361) at 25°C±1^0C Studies were repeated thrice and results were described in mean±SD.

Spreadability
0.5 g test formulation was placed within a circle of 1 cm diameter pre marked on a glass plate over which a second glass plate was placed. A weight of 50 g was allowed to rest on the upper glass plate for 5 min. the increase in the diameter due to spreadability of the formulation was noted.

Drug content
Drug content was determined by UV-Spectrophotometer. 1gm formulation was accurately weighed, dissolved in 50 ml of phosphate buffer pH6.8, filtered and diluted if required. Absorbance was determined using a UV spectrophotometer. Studies were repeated thrice and results are described in mean±SD.

Drug -Excipient compatibility studies
Fourier transform infrared analysis (SHIMADZU) was conducted to study the drug excipient interactions.

Samples were scanned in the range from 400-4000 cm-[1]Thedrug excipients compatibility study was determined using Potassium bromide (KBr) pellet method and scanned in the range of 4000 cm-[1] to 400 cm-[1]The IR spectrum of the pure drug was compared to IR spectrum of optimized formulation to check for interaction.

RESULTS AND DISCUSSION
Solubility studies: As described in table 1, the solubility of LP was found to be highest in IPM as compared to other oils. Hence, IPM was selected as the oil phase. The drug was found to be more soluble in Tween[®]80 among surfactants and in Transcutol-P among Co-surfactants.

Table. 1: Solubility studies of LP in various excipients at 25°C.

Oil	Solubility (mg/ml)	Surfactant	Solubility (mg/ml)	Co-surfactant	Solubility (mg/ml)
Olive oil	41.03	Tween-80	61.04	Plurol oleiqe cc	21.03
Castor oil	12.6	Tween-20	86.6	Transcutol-P	93.47
Oleic acid	16.2	Span-60	33.07	Ethanol	39.02
IPM	79.8	Span-80	24.8	PEG-400	29.00
Capmul MCM	27.0	Cremophor RH-40	19.05	PEG-600	38.41

Emulsification studies
Screening of surfactants
Surfactants were selected based on their ability of ease of emulsification of oily phase and percent transmittance. IPM exhibited highest emulsification efficiency with Tween-80 (showed percent transmittance of 91.8% with 6 flask inversions) and Tween-20 (showed percent transmittance 86.3% with 19 flask inversions).

Table. 2: Screening of surfactants.

Surfactant	No.of flask inversions	% Transmittance
Tween-80	19	86.3
Tween-20	74	67.2
Span-60	6	91.3
Span-80	23	79.0

Screening of co-surfactants
Addition of a co-surfactant to the surfactant containing formulation was reported to improve dispersability and drug absorption from the formulation. Addition of a co-surfactant to the surfactant containing formulation was reported to improve transparency and drug permeation from the formulation. As depicted in the Table Transcutol P was selected as co-surfactants, due to high solubility of drug. Transcutol P was selected as co-surfactant as it exhibit high percentage transmittance with Tween-80 and IPM with less number of flask inversions.

Table. 3: Screening of Co-surfactants.

Co-surfactant	No.of flask inversions	% Transmittance
Transcutol-P	5	90.8
PEG-400	22	69.0
PEG-600	31	41.0
Ethanol	39	39.0

Construction of Pseudoternary phase diagram
Pseudoternary phase diagrams were constructed separately for each Smix ratio for getting o/w nanoemulsion regions. The area of nanoemulsion isotropic region changed slightly as the ratio of surfactant in Smix was increased. In the phase diagrams, the existence of large or small nanoemulsion region depends on the capability of the particular S_{mix} to solubilise the oil phase. The extent of solubilisation results in a greater area with the formation of more clear and homogenous solution. Phase diagrams were constructed for the following system

The ratio of surfactant to cosurfactant was very effective for a stable and an efficient nanoemulsion formation. The phase diagrams were constructed at surfactant/ co-surfactant ratios of 4:1,3:1,2:1,1:1,1:2,1:3,1:4(w/w). They were constructed using IPM as oil, Tween-80 as surfactant and Transcutol-P as co-surfactant in different ratios. The greater existence range of Nano emulsion region was found to be more for the formulation N5(2:1).
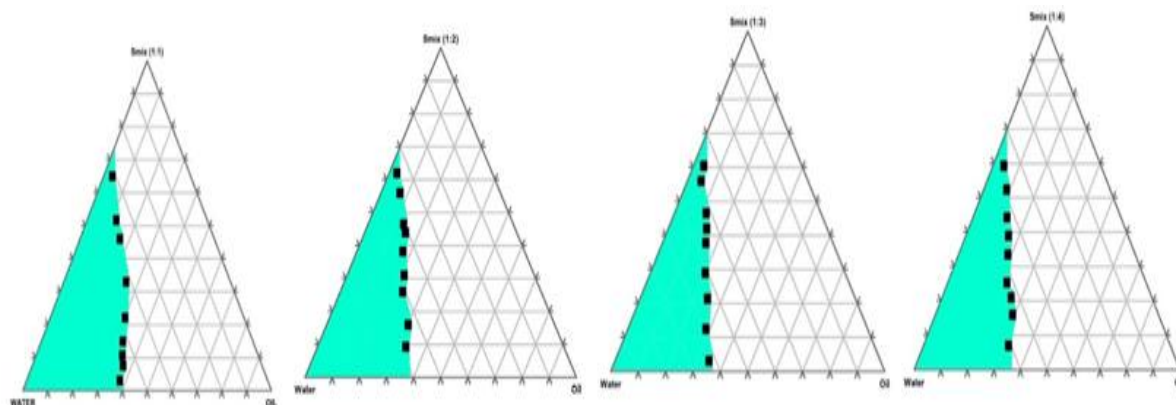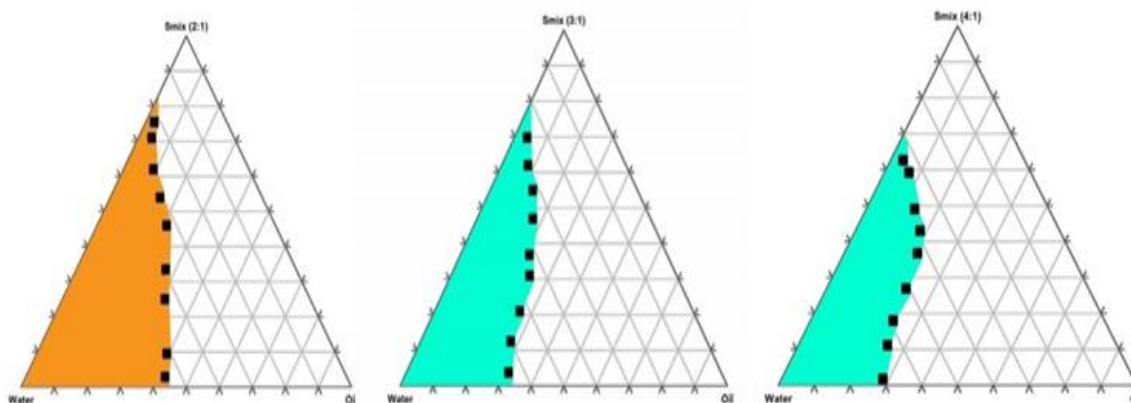
Fig. 2: Phase diagrams constructed using IPM ,Tween 80 and Transcutol P.

Table. 4: Percentage of Nano-emulsion region in formulation.

Formulation code (S_{mix} Ratio)	% of Nanoemulsion region
N1(1:1)	32%
N2(1:2)	27%
N3(1:3)	25%
N4(1:4)	25%
N5(2:1)	37%
N6(3:1)	31%
N7(4:1)	25%

Preparation of Nanoemulsion Formulations
For the preparation of drug loaded nanoemulsions, required amount of LP was dissolved in the oil phase. The required amount of mixture of surfactant and cosurfactant were added and double distilled water was then added drop wise drop till a clear and transparent liquid was obtained after ultrasonication. The prepared nanoemulsions were stored in the suitable container at ambient temperature. The composition of nanoemulsion formulations were shown in the next Table.

Fig. 3: Nanoemulsion.

Table-5 Composition of Nanoemulsion formulations

Formulation code (Oil:S_{mix})	Drug (mg)	Oil (mg)	Surfactant (mg)	Co-surfactant (mg)
F1 (1:1)	50	60	40	20
F2 (1:2)	50	60	80	40
F3 (1:3)	50	60	120	60
F4 (2:1)	50	120	40	20
F5 (3:1)	50	180	40	20

Characterization of Nanoemulsion
Nanoemulsion formulation with various surfactants and co-surfactants were evaluated for various physiochemical parameters like self-emulsification, viscosity, percent transmittance, thermodynamic stability studies. The results for the formulations are given in the Table-6 & Table-7.

Table. 6: Characterization of nanoemulsion.

Formulation	Self-emulsification time & dispersibility tests	Effect of dilution	Percentage transmittance	Viscosity (cp)	Drug content (%)
F1 (1:1)	Grade-A	Pass	97	31	93
F2 (1:2)	Grade-A	Pass	95	36	89
F3 (1:3)	Grade-B	Pass	81	41	85
F4 (2:1)	Grade-A	Pass	97	25	94
F5 (3:1)	Grade-C	Fail	75	38	89

Table. 7: Thermodynamic stability studies.

Formulation	Heating cooling cycle	Centrifugation	Freeze thaw cycle
F1 (1:1)	Pass	Pass	Pass
F2 (1:2)	Fail	Pass	Fail
F3 (1:3)	Fail	Fail	Fail
F4 (2:1)	Pass	Pass	Pass
F5 (3:1)	Fail	Fail	Fail

***In-vitro* drug release studies**

In vitro studies were performed to compare the release rate of the drug from the various nanoemulsion formulations all having the same quantity of LP (50 mg). Out of six formulations only two formulations had passed the stability studies. So, the drug release studies were carried out only to those two formulations. The release rate of F4 (96.1%) was found to be the best as compared to F1 (91.5%). From the results of *in vitro* drug release and thermodynamic stability studies, Formulation F4 was optimized and carried for further studies.

Fig. 4: Franz diffusion cell & magnetic stirrer.

Table-8 *In-vitro* drug release studies

Time (hrs)	% Drug Release	
	F1	**F4**
0	0	0
1	13.4±0.21	12.0±0.31
2	25.8±2.31	22.5±0.24
3	32.3±0.23	28.7±0.04
4	47.3±1.22	43.0±0.01
5	51.4±0.17	51.3±1.31
6	74.1±0.08	64.5±2.20
7	79.0±2.41	88.0±1.21
8	91.5±1.24	96.1±0.04

Globule size and zeta potential

Globule size and zeta potential were measured using Horiba Scientific nanopartica, optimized nanoemulsion had small average droplet diameter between 10nm. A small droplet sizes are very much prerequisite for drug delivery as the oil droplets tend to fuse with the skin thus providing a channel for drug delivery.

Polydispersity index (PI) is a measure of particle homogenicity and it varies from 0.0 to 1.0. The closer to zero the polydispersity value the more homogenous are the particles. Formulations showed PI 0.413 that indicates acceptable homogenicity.

Zeta potential of optimized Nanoemulsion formulation was found to be -40mV, indicates that the particles of nanoemulsions are negatively charged and stable. The particles are in a deflocculated and shall repel each other and impart physical stability to the system.
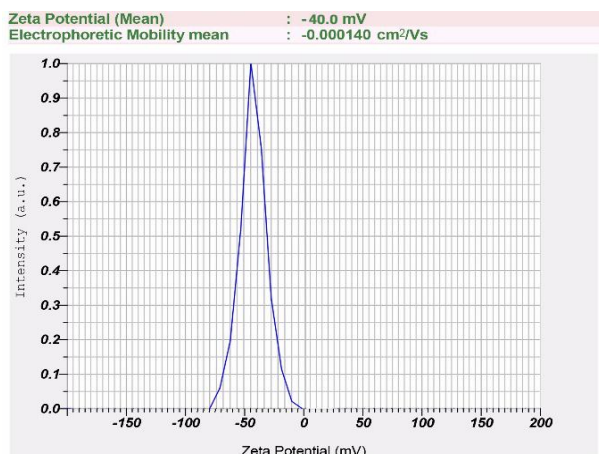

Fig. 5: Zetasizer.

Zeta Potential (Mean)   : -40.0 mV
Electrophoretic Mobility mean : -0.000140 cm^2/Vs
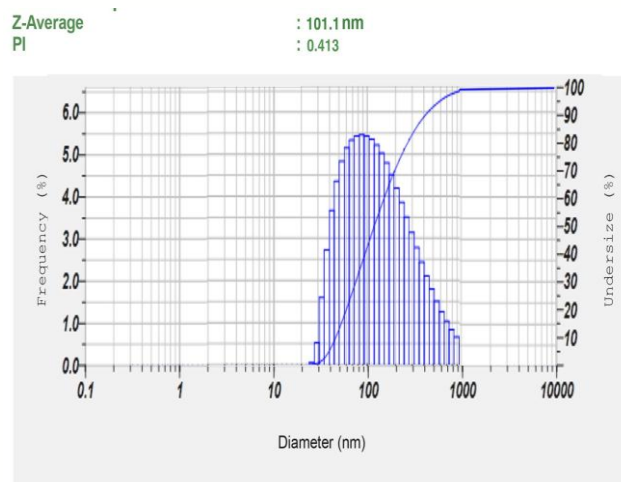
Fig. 6: Zetapotential.

Table. 9: Composition of LP Nanoemulsion based Gel.

Formulation code	LP w/w %	IPM w/w%	S mix w/w%	Water w/w%	S mix Ratio	Gelling agent w/w%
NG-1	1	5	45	50	2:1	Carbopol-940 (0.25%)
NG-2	1	5	45	50	2:1	Carbopol-940 (0.5%)
NG-3	1	5	45	50	2:1	Carbopol-934 (0.25%)
NG-4	1	5	45	50	2:1	Carbopol-934 (0.5%)
NG-5	1	5	45	50	2:1	HPMC-0.5%
NG-6	1	5	45	50	2:1	HPMC-1%

Evaluation of Nanoemulsion Gel
The pH of nanoemulsion-based gel ranged from 6.5-7.09 which are within the limit of the semisolid specification and at this pH the gel will be not irritant to skin. Spreadability is an important parameter for ease of application of topical formulation from a patient compliance point of view. The gel containing Carbopol-934 showed the highest spreadability while gel containing HPMC showed the lowest spreadability as shown in the below table. It was found that formulae showed pseudoplastic rheological behavior and the viscosity of the prepared gels at 50 rpm was shown in the table. The LP content was found to be ranged from $96.21\pm2.15\%$ to $98.66\pm1.47\%$ indicating uniform distribution of LP in formulation. Further it can be inferred that gelling process didn't affect the uniform distribution of LP.

Table. 10: Evaluation parameters.

Formulation code	pH (10%w/v in water)	Viscosity (cp) at 50 rpm	Spreadability (cm)	Drug content
NG-1	6.09±0.02	8429±111.2	3.2±0.03	97.57±0.88
NG-2	6.95±0.04	4270±117.4	3.1±0.11	98.12±2.36
NG-3	7.03±0.04	8310±170.5	3.6±0.012	98.45±1.45
NG-4	7.09±0.01	8334±135.1	3.4±0.06	98.66±1.47
NG-5	6.90±0.02	5222±125.4	2.7±0.04	96.85±1.47
NG-6	6.60±0.02	1730±123.2	2.6±0.05	96.21±2.15

***In-vitro* Drug release study:** Out of six formulations, the formulation NG4 containing carbopol-934 (0.5%) exhibited higher drug release compared to others.

Table. 11: *In-vitro* Drug release study of gel.

Time (hrs)	% Drug Release					
	NG-1	NG-2	NG-3	NG-4	NG-5	NG-6
0	0	0	0	0	0	0
1	15.6±0.21	14.7±0.25	12.6±2.11	10.1±1.56	9.0±0.51	6.7±0.21
2	23.0±1.22	21.4±1.65	16.8±0.38	15.5±1.22	14.8±1.22	14.2±0.34
3	30.5±0.68	29.2±1.47	23.2±0.41	22.1±2.33	22.3±1.32	20.3±1.25
4	43.1±2.31	36.2±2.45	31.3±1.22	32.0±0.25	34.8±1.32	31.3±2.17
5	49.6±1.55	45.2±2.66	41.4±2.31	43.8±0.14	45.3±1.12	41.6±3.11
6	54.1±1.13	60.8±1.48	57.1±0.29	62.2±0.52	54.3±0.30	48.2±0.01
7	61.8±2.32	66.6±0.36	63.4±0.41	76.7±1.24	61.3±0.21	55.2±0.56
8	76.4±1.24	72.7±2.35	71.2±2.41	84.6±0.36	67.6±0.22	61.6±1052
9	83.6±0.51	79.2±2.98	86.7±1.69	90.2±0.41	75.4±2.11	70.5±0.41
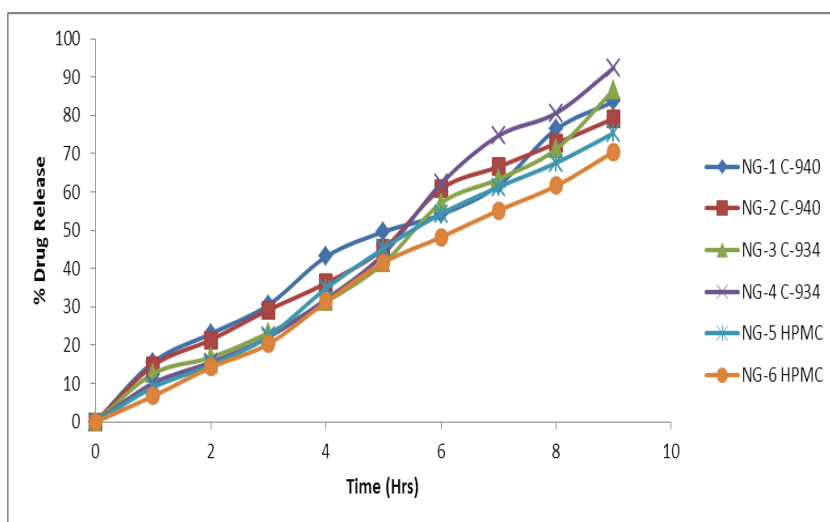
Fig. 7: Percent cumulative drug release of LP Nanoemulsion gel formulations.

Drug release comparison of nanoemulsion gel with conventional gel

In-vitro drug release of nanoemulsion gel containing carbopol-934(0.5%) was compared with conventional LP gel containing carbopol-934(0.5%). Results were represented in Table-11.

Table. 12: Drug release comparison of nanoemulsion gel with conventional gel.

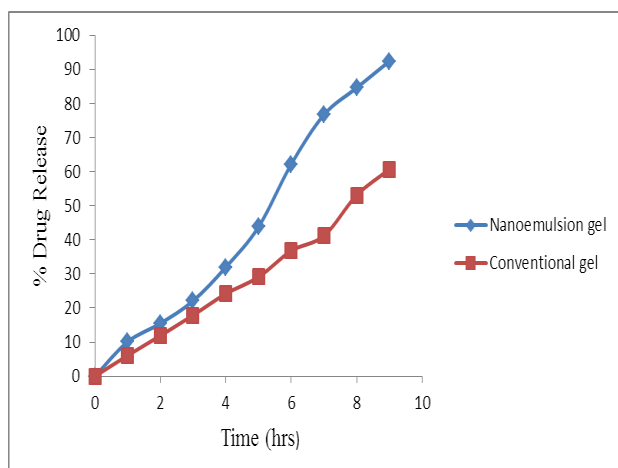| Time (hrs)	% Drug Release	
	Nanoemulsion gel	Conventional gel
1	10.1±1.56	6.1±0.21
2	15.5±1.22	11.9±1.22
3	22.1±2.33	17.9±2.30
4	32.0±0.25	24.2±0.40
5	43.8±0.14	29.1±1.01
6	62.2±0.52	36.8±1.42
7	76.7±1.24	41.2±0.54
8	84.6±0.36	53.1±0.21
9	92.4±0.41	68.2±2.36

Fig. 8: Percent cumulative drug release of LP gel and Nanoemulsion gel formulations.
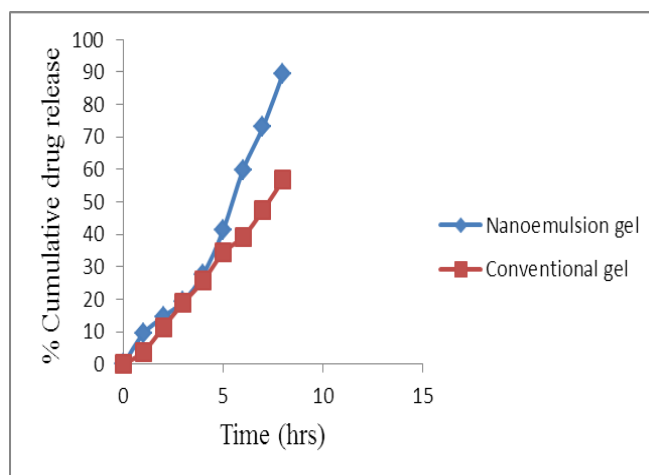

Fig. 10: *In-vitro* drug release of LP through excised rat skin.

Drug- Excipient compatibility studies

FTIR spectrums are mainly used to determine if there is any interaction between the drug and any of the excipients used. The presence of interaction is detected by disappearance of important functional groups of the drug. From the spectra of LP, LP loaded nanoemulsion gel, it was observed that all characteristic peaks of LP were present in the combination spectrum, thus indicating compatibility of the LP and polymer.
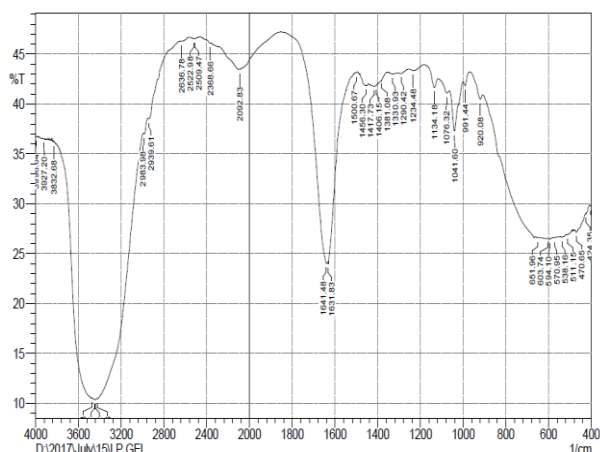

Fig. 9: FTIR spectra of LP nanoemulsion gel.

***Ex-vivo* skin permeation studies**

Ex-vivo skin permeation studies were performed to compare the release rate of the drug from the nanoemulsion gel as well as from conventional gel having the same quantity of drug (LP 50mg). The release rate of optimized nanoemulsion gel was found to be more as compared to conventional gel as shown in the figure.

Fig-11 Franz diffusion cell along with magnetic stirrer.

Permeation data analysis

Permeability parameters like a steady-state flux (Jss), permeability coefficient (Kp), and enhancement ratio (Er), were significantly increased in nanoemulsion gel as compared to conventional gel. The flux value was found to be 524.6±2.01 µg/cm^2/h of conventional gel in comparison to 1087.2±3.41 µg/cm^2/h. Permeability coefficient (Kp) and enhancement ratio (Er) of conventional and nanoemulsion gel are described in below table.

Table. 13: Permeation data analysis.

Formulation	Jss±SD (µg/cm^2/h)	Kp±SD (cm/h) *10^{-2}	Er
Conventional gel	524.6±2.01	1.04±0.14	-
Nanoemulsion gel	1087.2±3.41	2.17±1.23	2.086

The results indicated that higher permeability of drug through skin because of the presence of nanocarriers in the formulations. The flux of NEG is more than conventional gel formulation and provides prolonged drug release behavior as compared to nanoemulsion. Moreover, it can be thought that NEG excipients contain permeation enhancer like propylene glycol, which were also responsible for the increased permeation ability in comparison to the normal gel. Faster release of the drug from nanoemulsion and nanoemulsion gel could be due to small size of the droplet which permits faster release of the drug.

CONCLUSION

The results of this study indicated that nanoemulsion gel formulations of LP owing to nanosize have the potential to enhance their absorption without interaction or incompatibility between the ingredients. This nanoemulsion formed also showed an optimum particle size which could easily permeate through the stratum corneum layer of the skin and thus permeation could be enhanced along with solubility of the API. The optimized formulation was compared to conventional gel formulation and it showed higher permeation rate *in-vitro* and *ex-vivo* which justifies the nanoemulsion gel to be a promising carrier for transdermal delivery of losartan potassium. However it undergoes extensive first pass metabolism after oral administration. Approximately 65% of drug gets metabolized; leading to an absolute bioavailability of 32%. Therefore the transdermal route would be beneficial to improve its bioavailability by circumventing first pass metabolism.

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