Original Research Article

Liposomal *Aloe vera* trans-emulgel drug delivery of naproxen and nimesulide: A study

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Abstract

Introduction: The present aim of this study was to formulate naproxen and nimesulide liposomal formulation for incorporation in *Aloe vera* transemulgel and to carry out *in vitro* and *in vivo* evaluation of the formulation. **Material and Methods:** *A. vera* gel was prepared and used as a gel base for formulation. Carbopol 934 is used as a gelling agent and Methyl paraben was used as a preservative for the formulation of the gel. Liposomes was formulated by using hydration method. The formulated naproxen and nimesulide liposomal formulation using *A. vera* trans-emul gel were evaluated for *in vitro* studies such as drug release, permeation study, and drug content and entrapment efficiency. Paw edema method in Wistar rats induced by carrageenan is used to study *in vivo* anti-inflammatory action. **Result:** From the *in vitro* studies such permeability drug release naproxen 65% (69.6), Nimesulide 65% (61.1), and commercial Nimsulide gel (60.82) at 240 min. *In vivo* data shows that formulated liposomal transemulgel formulation are superior in their efficacy compared to commercial and *A. vera* gel. The results are compared with the commercial formulations. **Conclusion:** From our results, it is concluded that the *A. vera* trans emul gel using nimesulide and naproxen liposomal formulation is stable and prepared gel base is effective for formulation with high drug release and drug content compared with commercial formulation with significant anti-inflammatory effect.

Key words: Aloe vera, drug release, emul gel, liposomes, naproxen, nimesulide, paw edema, peremeation studies

INTRODUCTION

One of the promising routes for drug administration is skin because of availability of large surface area. Transdermal delivery is the most promising route for selected drugs that are having many repercussions with oral and invasive administration.[1]

Nimesulide, a non-steroidal anti-inflammatory drug (NSAID). This NSAID is unique because of chemical structure and also due to its specific affinity to inhibit cyclooxygenase-2 (COX-2). It is administered oral route as well rectally route twice a day for a various type of inflammation and pain conditions. It has poor aqueous solubility because of this it is facing bioavailability problems *in vivo*.[2,3]

Naproxen, a NSAID, it is a nonselective COX-1 and COX-2 enzymes inhibitor. Naproxen can cause gastrointestinal problems, such as constipation, diarrhea, ulcers, and stomach bleeding unlike that of selective COX-2 inhibitor.[4]

Apart from the gastrointestinal problems, by mean of the oral route this selected NSAIDS, via, naproxen and nimesulide, which belongs poor soluble and high lipophilic category. This drugs are having poor aqueous solubility and hence they pose bioavailability problems *in vivo*.[5]

In order to avoid these disadvantages, the liposomal trans-emulgel formulations have been recommended as topical application, for the selected NSAIDS, via, naproxen and nimesulide.[6]

Liposomes were adopted as a promising delivery system because of its organized structure could accommodate hydrophilic as well as lipophilic drugs separately, depending on their solubility characteristics, in both the aqueous and lipid phases and prevent them from degradation.[7]

Due to the affinity of the keratin layer of the skin, it can also penetrate deeper into the skin therefore it gives better absorption.

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Access this article online

Quick Response Code:

Website: www.jpionline.org

DOI: 10.4103/2230-973X.147230

In the formulation of topical dosage forms, efforts are being made to use drug carriers that ensure increase in the localization, penetration of drug through or within the skin in order to improve the local action and diminish the systemic effects or to ensure sufficient percutaneous absorption of the therapeutic moiety.[8] Liposomes can act as a solubilizing matrix on Application of the skin, for poorly soluble drugs, due to penetration enhancer as well as local deposition at the same time decreases the side effects of these drugs. Topical liposome formulations can be more effective and decreases the toxicity that caused by conventional formulations.[9,10]

Many topical agents such as lotion, ointment, cream, which are widely used have various disadvantages. They have very sticky causing discomfort, less spreading coefficient, rubbing is need for application to the skin, and they show the problem of stability for formulation. Due to all this disadvantages gels are selected for both cosmetic as well as pharmaceutical formulation.[11]

In spite of several advantages of gels, a major drawback is with delivery of hydrophobic therapeutic moiety. So, emulgel based approach is used to overcome this drawback by this even a hydrophobic drug can be incorporated and delivered successfully using via gels.[12]

When emulsions and gels are combined then that dosage form is referred as emulgel. In fact, the presence of a gelling agent changes conventional emulsion into an emulgel in the water phase. These emulgel have various benefits over novel drug delivery systems as well as on conventional drug delivery systems in numerous aspects. The use of this emulgels can be studied in antifungal, inflammation and analgesics drugs.[13]

However, many natural compounds were not yet properly exploited for their pharmaceutical applications in liposomal trans-emulgel delivery of drugs. *Aloe vera* being naturally obtained product seems to be protective in nature to applied skin and also may itself reduce inflammation can deliver the drug effectively compared with the polymers that are synthetic in nature.[14] Partial use polymers or low concentration polymers may cause low toxicity associated with it if used for a long period.[15]

In this study, we formulate trans-emulgel using *A. vera* as aqueous base and dispersing liposomal drugs so that the effective delivery of drug through transdermal route can be achieved. *A. vera* gel, which is possessing anti-inflammatory activity and with the incorporation of liposomes we can obtain synergistic activity.[16]

The objectives of the present investigation include studies are to prepare selected drugs NSAIDS liposomal formulation. Incorporate the prepared liposomes (naproxen sodium and nimesulide liposomal formulation) into aloe gel. Evaluate naproxen sodium and nimesulide liposomal trans-emulgel formulation. We had performed various *in vitro* release studies and *in vivo* permeation studies through rat skin and evaluate efficacy of liposomal trans-emulgel against inflammation induced rat. The purpose was to deliver the liposomal trans-emulgel drug at controlled rate through the intact skin to increase the bioavalibity and inflammation control for long duration of time by reducing the toxicity of NSAID as much as possible. Followed by comparison of prepared liposomal trans-emulgel formulations using *A. vera* base and commercial formulation of an NSAID with marketed commercial formulations by using various *in vitro* and *in vivo* permeation through rat skin.

MATERIALS AND METHODS

Materials

Naproxen and Nimesulide, Carbopol 934, methyl paraben, Cholesterol, Lecithin, and carrageenan were obtained from Hi Media Labs Pvt. Ltd., Mumbai. Standard analytical grade were maintained for all chemicals.

Methods

Preparation of gel from aloe juice

The mucilage or pulp of *A. vera* leaf, which is free from any resinous content (the dark red resin has to be drain out by holding the leaf upside for several seconds until the resin drips out), has to be taken to prepare *A. vera* gel. Then the mucilage was washed repeatedly with pure water, since it is highly acidic finally washings with 0.1N sodium hydroxide (NaOH) solution increase the pH of Aloe pulp. By using a blender, the pulp is to be blended to obtain the juice. Then the juice is prefiltered for many times by using a cotton bed to remove any adhered rind. Then repeated subjection of the juice to the vacuum filtration produces a clear fluid. The Carbopol 934 (1%) is mixed with aloe juice to prepare *A. vera* gel by dispersion technique, were lump free mixture will be formed, and it allows free entrapped air upon standing. During the dispersion of juice to carbopol (jellifies under alkaline conditions), 0.5%w/w methyl paraben was added. Then 0.5 N NaOH solution was added drop wise until to form a gel. Finally the obtained gel was stored in air tight container to prevent any reactions.[17,18]

Preparation of liposome by hydration method

By using thin film hydration technique, multi lamellar liposomes consisting of drugs (Nimesulide and Naproxen), were prepared. As mentioned in the Table 1 the ratios of lipids composition, phospholipon and cholesterol, taken should be 9:1 and 9:3 respectively. So, that these ratios of lipids were finally used to retain 50% and 65% while preparing the drug emulgel. Here chloroform and methanol were used as organic solvents to evaporate the solvents. Initially the drug, lecithin and cholesterol were dissolved consecutively in chloroform and methanol (9:1) mixture to assure homogeneity. After thorough mixing in the organic solvent; the lipid layer is formed by removing the solvent. By means of rotary evaporation, the organic solvent should be removed yielding a lipid thin

Table 1: Formulation for preparation of nimesulide and naproxen emulgel

Name of the drug	Percentage of the lipid	Ratio of lipids (phospholipon:cholesterol) (g)				Solvent
		9:1		9:3		
Nimesulide	50	1.201	0.13	1.20	0.40	Chloroform
	65	1.58	0.17	1.58	0.52	Chloroform
Naproxen	50	1.201	0.13	1.20	0.40	Chloroform
	65	1.58	0.17	1.58	0.52	Chloroform

film on the sides of a round bottom flask. To remove organic solvent residual lipid film is thoroughly dried by placing the flask or vial on a magnetic stirrer at 37°C temperature. By Hydration process, the dry lipid film/cake is obtained which is accomplished simply by pouring an aqueous medium into the dry lipid and stirs it by using magnetic stirrer at 2000 rpm for 2 h. If the drug is water soluble first dissolve in aqueous phase and add into the lipid layer, but these drugs (Nimesulide and Naproxen) were insoluble in water and to be added them alone into the lipid layer.[19,20]

Incorporation of liposomes containing drugs into the gel

Under certain atmospheric conditions, at 25 rpm, Liposomes containing drugs (Nimesulide and Naproxen) were mixed into the prepared *A. vera* gel by using an electrical mixer.

In vitro evaluation studies

Weight of the gel

The juice has to be weighed to know how much amount of gel was formed from the measured volume of juice.

Microscopic analysis of liposomes

Prepared liposomal batches were monitored for their morphological attributes using optical light microscope (Bright field model, Leica DM2700M). Liposome suspension was stirred at 2000 rpm for 2 h in order to avoid the aggregation between particles.[21]

Measurement of pH

The gels pH was estimated by digital pH meter (Digital pH meter, Elico LI 120 model). 1 g of sample placed on a watch glass and surface pH was noted. The pH measurement of each formulation should be made in three copies and the averages of gels have to be presented.[22]

Viscosity

Brookfield viscometer (LVDV-E model) using spindle number 63 is used to determine the flow property of the formulation. Gels were filled in jar and attention should be there that spindle do not touch to the end of the jar when it was perpendicularly lowered by rotating the spindle in the gel, corresponding dial reading was noted at increasing shear rates 0.5, 1.0, 2.5 and 5 rpm. The opposite readings were noted down and average was calculated for these both readings. We can obtain the gel viscosity by multiplying the dial readings with the factors present in the Brookfield viscometer catalogues.[23,24]

Drug content

Weigh 1 g of gel and poured into a 100 ml of volumetric flask and to it add 50 ml phosphate buffer pH 7.4 and kept for 24 h in mechanical shaker (Single bros scientific). Then, filter the samples and dilute the samples with the same medium. By using ultraviolet (UV)-spectrophotometer (Shimadzu, UV-1700 model) at 262 nm, Absorbance of the solution has to be measured in the presence of blank.[25]

Drug entrapment efficiency

The liposome suspension was centrifuged at 5000 rpm for 15 min at 4°C temperature by using semi cooling centrifuge to separate the free drug. A supernatant is containing liposome in suspended stage and free drug in the wall of the centrifuge tube. The supernatant was collected and again centrifuged at 1500 rpm at 4°C temperature for 30 min. A clear solution of supernatant and pellet was obtained. The pellet containing only liposomes was re suspended in distilled water until further processing. The liposomes free from unentraped drug were soaked in 10 ml of methanol and then sonicated for 10 min. The vesicles were broken to release the drug, which were then estimated for the drug content. The absorbance of drug was noted at 260 nm. The entrapment efficiency was then calculated using the following equation.[26,27]

% Drug Entrapped (PDE) = (Amount of drug in sediment/Total amount of drug) × 100

In vitro permeation studies

For prepared gels, the diffusion studies (37°C ± 1°C) can be carryout in Franz diffusion cell (Aar Ger. Automation and Control Pvt. Ltd.,) to study the dissolution rates of gels through a cellophane membrane. 1 g of sample gel is taken in cellophane membrane, using 150 ml of phosphate buffer (pH 7.4) as the dissolution medium. A volume of 5 ml of each sample was withdrawn at regular intervals of time, that is, 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min and each sample was replaced again with fresh dissolution medium of equal volume. Then, by using phosphate buffer as blank, the drug content of samples were analysed by using UV spectrophotometer at 262 nm.[9] The flux (J) calculated by using the angular coefficient of a curve attained by plotting the time versus cumulative amount of the drug that is permeated. The permeability coefficient (Kp) was calculated from the below equation.[28]

$$K_{P} = J/C$$

Where, C is the initial amount of drug in the vehicle applied to membrane.

Fourier transformed infrared

The spectral measurements were performed using Thermo-IR 200 Fourier transformed infrared (FT-IR) spectrophotometer. Potassium bromide pellet method was employed. The film was finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and background spectrum was collected under identical conditions. From 16 single average scans collected each spectrum was derived in the range of 4000-400 cm^{-1} at the spectral resolution of 2 cm^{-1}. It is done to check whether there is any possible interaction with drug and polymer.[29]

Pharmacodynamic evaluation

Wistar rats for anti-inflammatory studies of either sex were used in the present study. Weights of the rats ranged from 160 to 210 g. All animals were maintained in groups of eight, each group containing five rats at 22°C ± 1°C with light/dark cycle of 12:12 h. They were adopted to laboratory conditions before 15 days of starting the experiment (930/PO/a/2006/CPCSEA).

Hind paw edema method

Antiinflammatory activity is was evaluated by using hind paw edema volume induced by carrageenan in rodents. Carrageenan (1%) was received by Group I, control group. *A. vera* gel and carrageenan is received by Group II. Commercial Nimsulide gel, followed by carrageenan is received by Group III. Group IV received naproxen 65% 9:3, followed by carrageenan. Group V received Nimesulide 65% 9:3 followed by carrageenan. Group VI received Nimesulide 65% 9:1 followed by carrageenan. By injecting carrageenan of 0.1 ml of 1% (w/v) to the left hind paw of the rats, induces the edema. *A. vera* gel, commercial Nimsulide gel, naproxen, and Nimesulide were applied before 30 min administration of carrageenan. Left hind paw ankle paw volume is measured. At intervals of 0 min, 1, 2, 3, and 4 h the paw volume was measured by plethysmometer using mercury displacement method.

Percent inhibition is calculated using paw edema of carrageenan control group compared with treated group.

$$\% \text{ Inhibition} = \frac{V_c - V_t}{V_c}$$

Where Vc is control group inflammatory increase in paw volume and Vt is test group inflammatory increase in paw volume.[29,30]

Statistical analysis

The data were expressed as mean ± standard error of the mean statistical analysis was performed by ANOVA test for multiple comparisons and $P < 0.05$ was a statistical significance.

RESULTS AND DISCUSSIONS

Physical appearance

All formulation is colorless with uniform consistency, homogenous texture and glossy appearance.

Morphology of liposomes

Microscopic pictures conform that formation of liposomes with bilayer lipid membrane entrapping drug. Naproxen 9:3 65% and Nimesulide 9:3 65% formulation is showing better liposomes than other formulation it's shown in Figure 1.

Fourier transformed infrared

Interpretation of cholesterol + naproxen + lecithin

Formulations of FT-IR spectra show all the major peaks of excipients, that is, primary alcohol 1022.34-1052.63, CDO 1211.04-1258.39, Aromatic CH 638.23-741.42, PDO stretch 1258.39-1390.48 from this we can justify that naproxen is stable within the formulation, without undergoing any physical interaction with the coexisting components.

Interpretation of cholesterol + lecithin + nimesulide

Nimesulide formulations of FT-IR spectra shows all the major peaks of its constituents individually that is, O-H 1335.93-1407.16, P-O stretch 1335.93-1407.16, Aromatic C H 600.46-662.9, indicating no physically interaction between these excipients. Thus, ensures the drug is stable within formulation it's shown in Figure 2.

Drug permeability studies

Table 2 summarizes the cumulative drug release the permeability study has been performed for all the formulations. Naproxen 50% (65.26 ± 0.24) shows slightly more drug release than Nimesulide 50% (63.55 ± 0.55) indicating the liposomes of naproxen are highly lipophilic and have enhanced permeability. Commercial Nimsulide gel (60.82 ± 0.88) the marketed formulation is showing only release which is less than all the prepared formulations, Nimesulide 65% (59.16 ± 0.28) is having less drug release than naproxen 65% (69.64 ± 0.24) these comparative diffusion profiles shown in Figure 3.

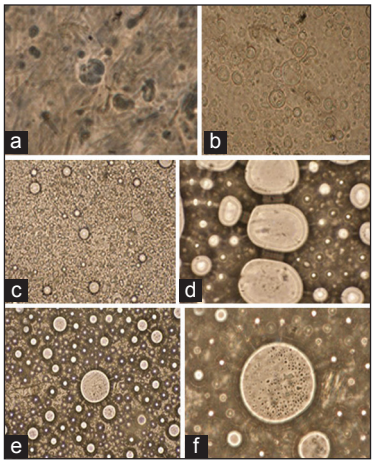

Figure 1: Microscopy of formulations: (a) Microscopy of naproxen 9:1 50% formulation. (b) Microscopy of naproxen 9:3 50% formulation. (c) Microscopy naproxen 9:3 65% formulation. (d) Microscopy of nimsulide 9:1 50% formulation. (e) Microscopy of nimsulide 9:350% formulation. (e) Microscopy of nimsulide 9:3 65% formulation

These formulations in turn show grater permeability than the drug solutions nimesulide and naproxen 41.04% ± 0.24%, 48.3% ± 0.88%. The diffusion profiles comparative are shown in Figure 4.

pH

The values of pH are shown in Table 3. Acidic nature of *A. vera* is due to the presence of acetyl mannan it is an Acidic constituent. The pH of *A. vera* emul gel was 8.23 nearly same as *A. vera* gel. Due to the acidic nature of Nimesulide, the pH was decreased to 7.56, followed by Naproxen formulation pH is 7.10 and this are suitable for transdermal applications.

Viscosity

Viscosity valve are shown in Table 3 from the observation *A. vera* gel is having more viscosity compared to emulgel due to its liquid consistence of the emulsion. And viscosity is unaffected by presence of Nimesulide naproxen liposomal formulations.

Flux and permeability coefficient

Flux and permeability coefficient of the formulations found to be more than the pure gels. Naproxen 9:3 65% (0.355), Nimesulide 9:3 65% (0.346), shows permeability coefficient of which is more than marketed formulations (0.307). Drug content results are shown in Table 3

Table 2: Percentage drug release of formulations in PBS 7.4 and drug solution

	Percentage drug release (mean ± SD)						
Time (min)	Nimesulide 50% (9:3)	Naproxen 50% (9:3)	Commercial Nimsulide gel	Nimesulide 65% (9:3)	Naproxen (9:3) 65%	Nimesulide solution	Naproxen solution
30	22.3±0.56	16.3±0.38	21.7±0.44	17.2±0.56	16.0±0.38	14±0.38	15.9±0.44
60	32.1±0.98	23.1±0.79	31.2±0.68	26.5±0.49	22.4±0.79	20.2±0.79	23.5±0.68
90	36.3±0.21	26.7±0.32	36.3±0.54	31.6±1.1	32.1±0.32	26.7±0.32	27.7±0.54
120	40.5±0.33	32.1±0.28	41.4±0.79	36.3±0.23	38.2±0.28	30±0.28	32.7±0.79
150	45.6±0.56	41.6±0.33	46.1±0.99	42.0±0.58	44.2±0.33	33.3±0.33	35.2±0.99
180	52.1±0.66	49.1±0.45	51.2±1.20	47.5±1.02	53.5±0.45	36.7±0.45	40.2±1.20
210	56.3±0.90	56.2±0.57	56.6±1.25	56.5±0.88	60.1±0.57	39.1±0.57	43.6±1.25
240	63.5±0.55	65.2±0.24	60.8±0.88	61.1±0.28	69.6±0.24	41.4±0.24	48.3±0.88

SD: Standard deviation, PBS: Phosphate buffer saline

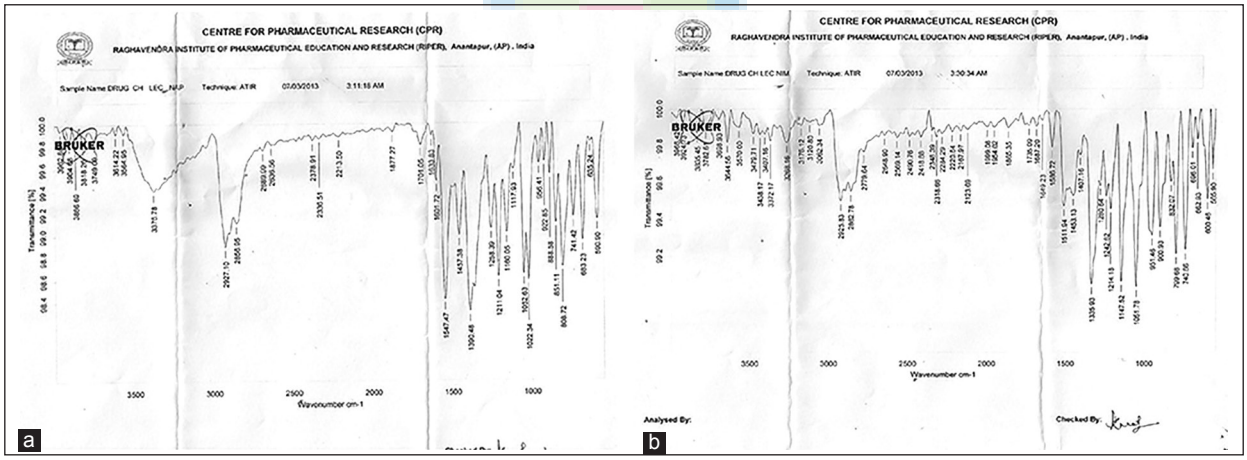

Figure 2: Fourier transformed infrared interpretations (a) Cholesterol + Naproxen + Lecithin. (b) Cholesterol + Lecithin + Nimesulide

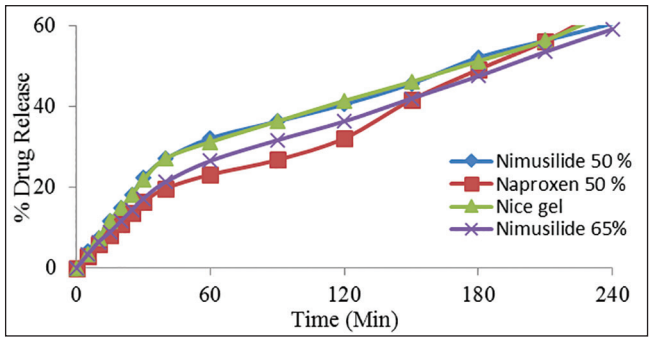

Figure 3: Graphical representation of % drug release of formulations in phosphate buffer saline 7.4

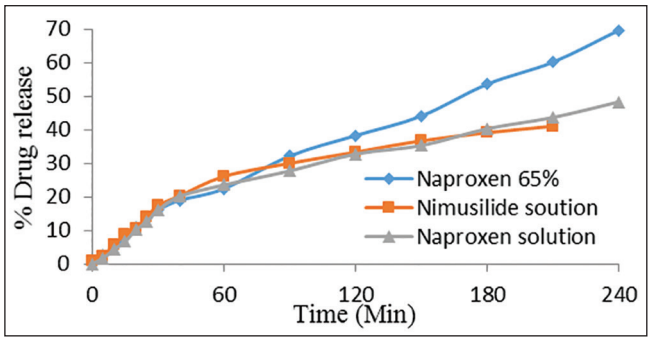

Figure 4: Graphical representation of % drug release of formuations and drug solution

Table 3: Evaluation parameters

Formulation (%)	Viscosity	pH	Percentage drug content	Flux	Permeability coefficient (×10^{-4})
Plain *Aloe vera* gel	70±0.16	8.53±0.27	—	—	—
Nimesulide 9:3 (50)	71±0.28	7.46±0.39	80.43±0.73	0.332	9.1
Nimesulide 9:3 (65)	73±0.54	7.52±0.64	81.90±0.56	0.333	9.2
Naproxen 9:3 (50)	65±0.48	6.98.±0.73	79.95±0.23	0.331	9.1
Naproxen 9:3(65)	68±0.22	7.10±0.15	80.47±0.65	0.332	9.1
Commercial Nimsulide gel	—	—	77.5±0.93	0.326	8.9
Naproxen solution	—	—	73.6±0.56	0.322	8.7

Table 4: Percentage inhibition of paw edema

Time	Group 1 (control)	Group 2 (plain *Aloe vera*)	Group 3 (commercial Nimsulide gel)	Group 4 (naproxen 9:3 65%)	Group 5 (nimesulide 9:3 65%)
0	0.38±0.029	0.36±0.028	0.33±0.025**	0.32±0.017***	0.32±0.024***
30	0.35±0.028	0.33±0.026*	0.32±0.021**	0.31±0.021***	0.30±0.031***
60	0.34±0.029	0.31±0.031**	0.30±0.032***	0.29±0.026***	0.28±0.021***
120	0.31±0.031	0.30±0.023	0.29±0.017*	0.27±0.023**	0.26±0.018***
180	0.30±0.037	0.29±0.017	0.27±0.022*	0.26±0.031**	0.24±0.032***
240	0.28±0.031	0.26±0.022*	0.25±0.026**	0.24±0.033***	0.23±0.027***

Valves are shown as Mean ± S.D. ($N = 6$). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ as compared with Group-1 (control)

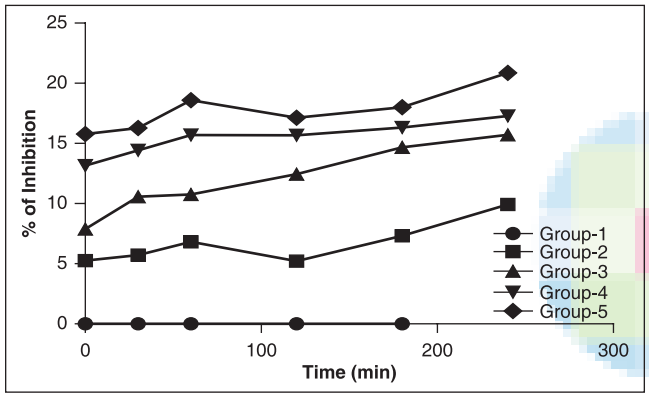

Figure 5: A plot of percentage inhibition of carrageenan induced rat paw edema

percentage of drug content is more compared with marketed formulations.

Anti-inflammatory studies

Statistical analysis shows that paw edema volume of the all formulations is significantly different compared to control group at all intervals of time except for *A. vera* emulgel at 0 and 120 and 180 min as shown in Table 4. Naproxen formulation show $P < 0.001$ at 0, 30, 60, 240 min. In this study, the percent inhibition was observed as $P < 0.001$ highest for the Nimesulide formulation at all intervals of time compared to marketed Nimesulide gel formulation shown in Figure 5. It is because of additive effect for Nimesulide and naproxen with *A. vera* which possesses mild anti-inflammatory effect. These suggest that *A. vera* has potential of gel base for transdermal drug delivery of Nimesulide and naproxen formulations. Liposomal formulation of these anti-inflammatory drugs cause sustain drug release compared to marketed formulations and More over emulgels increases the drug loading capacity of low hydrophobic of transdermal gels.

CONCLUSION

To ensure improved patient compliance in the coming years, topical drug delivery is the most promising route. *A. vera* trans-emul gel which is possessing mild anti-inflammatory activity and liposomes formulation of Naproxen and Nimesulide increase the solubility, permeability of this drugs followed by incorporation in *A. vera* trans-emul gel we had obtained synergistic activity and also effective delivery of drug through transdermal route had achieved. From the *in vitro* studies, Drug Content, Permeability coefficient, and effective drug release of naproxen 65% (69.6), Nimesulide 65% (61.1), commercial Nimsulide gel (60.82) at 240 min is observed indicating better drug release from Nimesulide formulations. Drug loading capacity of naproxen 65% 9:3(80%) and Nimesulide 65% 9:3 (81%) observed compared to commercial nimsulide gel (77.5%) indicating better content than marketed formulation. Our results are well supported by *in vivo* animal studies, which have been conducted on Wistar albino rats. Animal studies data revealed that prepares liposomal transemulgel formulation are superior in their efficacy compared to commercial and *A. vera* gel. Thus, it can be concluded that selected drugs via, naproxen and nimesulide are always better to formulate into NDDS than conventional formulations and well suitable for transdermal drug delivery by *A. vera* trans-emul gel.

ACKNOWLEDGEMENT

We Are thankful to the management of Sree Vidyanikethan College of Pharmacy, A. Rangampet, Tirupati, Andhra Pradesh, India for providing the necessary facilities to carry out the research work.

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How to cite this article: Venkataharsha P, Maheshwara E, Prasanna YR, Reddy VA, Rayadu BS, Karisetty B. Liposomal *Aloe vera* trans-emulgel drug delivery of naproxen and nimesulide: A study. Int J Pharma Investig 2015;5:28-34.
Source of Support: Nil. **Conflict of Interest:** None declared.