Original Article

Novel Formulation for Facial Acne using Liposomal Gel Containing Lipid Soluble Naphthoic Acid Derivative

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ABSTRACT

The first line therapies in many acne diagnoses include application of retinoic acid derivatives for improvement in acne severity. Though, it has been observed that, current available formulations are sensitive to skin and requires to be applied after repeated time to prolong the action of the medicament at the local layers. To overcome this major downside, in the present investigation the Adapalene (AD) being entrapped into the lipid layers of the liposomes (LUVs) to provide the sustain release and also to bypass the main adverse effect of the retinoic acid derivatives of being toxic if absorbed into blood stream. **Aim:** To prepare and evaluate the liposomal adapalene for sustain release effect and entrapment into skin layers. **Materials and Methods:** To prepare the LUVs by film hydration method various lipid polymers are being utilised like DMPG, DPPG, HSPC, and cholesterol. Prepared LUVs were optimized on the basis of particle size, entrapment efficiency. The batch with highest entrapment efficiency (66.18%) and particle size range of 1000nm was further incorporated into (5%) HPMCk4M gel to avail the application compliance in the patient. This formulation was studied for viscosity, pH, Drug content, Spreadability study, *in vitro* drug release pattern of the dosage form, *ex-vivo* skin retention study in the layers of skin. **Results:** The result of the *in-vitro* release study showed only 28% of drug release which is beneficial for follicular delivery as well as sustained release of the AD. **Conclusion:** This can be concluding that, AD liposomal gel can be potential solution to the adverse reaction of the current marketed formulation with insights of providing low frequency of application and improved skin health in the acne prone patients.

Key words: Liposomal gel, Adapalene, *Ex-vivo* skin retention study, % entrapment efficiency, *in-vitro* drug release study.

INTRODUCTION

Dermatological preparation has acquired momentum in the world of pharmaceuticals, Acne is one of the common skin conditions that has affected the psychological behaviour of all age groups.[1-4] Acne lesions develop from the sebaceous glands and all the therapies are targeted to treat the infection at the pilosebaceous region.[5,6] There are main four underlying mechanisms thought to be involved in the genesis of acne: An abnormal explosion of keratinocytes present in pilosebaceous regions, high sebum release, infection due to *P. acnes*, and inflammatory response to antigens and cytokines.[7-12]

Retinoids are known to provide anti-inflammatory and comedolytic activity, as well as stabilizes keratinization. Hence, its potential application in the first-line therapy of acne is due to its efficacious comedolytic activity at a micro-comedones level that inhibits further progress of the lesions. However, their tolerance to irritation which is the prime side effect of these formulations is subjective to patient compliance. Even though it is utilized in topical preparations, it tends to pass the stratum corneum which further reported producing erythema and desquamation into the skin layers. This not only creates the secondary lesions but also

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produces pigmentation and acne flare.[13-16] Yet all the retinoids have been reported to show skin irritation and sensitization while treatment span, most frequently redness, dryness, burning, soreness.[17] To eradicate these adverse effects various Pharmaceutical approaches have been employed to achieve the dermal deposition of the Retinoids as shown in Figure 1.

Liposomes are similar to biological membranes, which can incorporate water-soluble and lipid-soluble moiety in their vesicular structure. Since 1960, liposomes have amassed their application in skin delivery systems.[18] The recent investigations have supported their augmented drug efficacy and reduced skin irritancy profile of the molecule.[19] The dermal deposition of the drug can be achieved by preparing the Large Unilamellar Vesicles (LUV) (20-100nm). This route can circumvent the Trans epidermal pathway and diminish the systemic toxicity of the drug.[20,21] The fluidity of the liposomal formulation, one of the major drawbacks has been overcome by incorporation of the liposome colloidal solution into the gelling system of Hydroxy Propyl Methylcellulose (HPMC) k4M grade polymer. The 3 D polymer matrix can integrate the liposomal formulation along with the free drug.[22,23] So here in the present experimental work, Adapalene (AD) has been utilized for the preparation of liposomal formulation and evaluated for various parameters to provide scientific background for utilizing as the sustained follicular delivery system.

MATERIALS AND METHODS

Materials

Adapalene was purchased from Sigma-Aldrich Chemicals, Ltd, Bangalore. Other phospholipids such as Di myristol phosphatidylcholine (DMPC), Di palmitoyl phosphatidylcholine (DPPC), Di myristol phosphatidyl glycerol (DMPG), hydrogenated soy phosphatidyl choline (HSPC), were obtained from Lipoid, Germany. Cholesterol and other excipients were obtained from ACS chemicals, Ahmedabad, which is of Analytical grade and used as received.

Methods

Drug excipient interaction study by FTIR

To analyze the critical drug-excipient interaction excipient and drug has been studied by Fourier transform infrared spectroscopy (FTIR). The pellet used for the IR study was potassium bromide and it was performed in the range of 4000-400 cm^{-1}. (FTIR-8300, Shimadzu Co., Kyoto, Japan).

Selection of lipid and drug ratio

AD liposomes were prepared by taking three Primary lipids i.e. DMPC, DPPC, and HSPC. The ratio of primary lipid with DMPG has also been varied and Entrapment of the maximum amount of drug has been optimized. The attributes like the stability of liposomal solution and polydispersity index with entrapment of drug have been chosen to provide the basis of the formulation.

Preparation of liposomes[24]

The AD liposomes were prepared by conventional thin-film hydration method using a rotatory vacuum evaporator, as per Table 2. A lipid mixture of primary and secondary lipids in the ratio of 1:10 has been selected as per Table 1. The mixture of lipids was been solubilised into 5ml of Chloroform ($CHCL_3$/Methanol (2:1v/v). Attach the flask to a rotary film evaporator and allow it to evaporate for 15 min at 55°C until all the liquid has evaporated and a thin film of lipid has been deposited on the wall. Remove residual solvent by subjecting flask to high vacuum at room temperature for at least an hour. After releasing the vacuum, add 5 ml of D.W and glass beads and again and rotate for 30 min at the same speed for producing liposomes containing suspension. Allow this suspension to stand for 2hr at room temperature for further process.

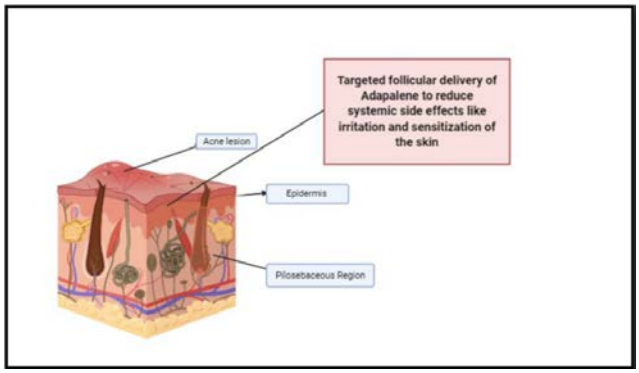

Figure 1: Liposome as follicular delivery.

Table 1: Selection of primary lipid ratio for liposome formulation.

Batch. No	(DMPC:DMPG) (9:1)	(DPPC: DMPG) (9:1)	(DMPC+DPPC: DMPG) (9:1)	(HSPC: DMPG) (9:1)
1	1:4	1:10	1:5:5	1:5
2	1:6	1:10	1:7:3	1:10
3	1:8	1:12	--	--
4	1:10	--	--	--

Table 2: Formulation of liposomes.												
MOLAR RATIO (AD: DMPC: DPPC : DMPG:CHOLESTEROL)												
Ingredients	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12
(AD)	1	1	1	1	1	1	1	1	1	1	1	1
DPPC	--	--	--	--	5	10	3	10	12	--	--	--
DMPC	4	6	8	10	5	--	7	--	--	--	--	--
DMPG	1	1	1	1	1	1	1	1	1	1	1	1
CHOL.	1	--	--	--	--	--	--	--	--	--	--	1

Characterization of liposomal formulation[25]

FT-IR study for Drug- Excipient Compatibility

One of the requirements for the selection of suitable excipients or carriers for pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out using Fourier Transformed Infrared (FT-IR) spectrophotometer to confirm the absence of any possible chemical interactions between the adapalene and Excipients like DPPC, DMPC, DMPG, MPEGDSPE and Cholesterol. Infra-red spectroscopy was carried out by potassium bromide pellet method. The pellet was scanned from 4000-400 range in a spectrophotometer. (FTIR-8300, Shimadzu Co., Kyoto, Japan).

Spectrophotometric Estimation of AD

Adapalene in quantity of 5 mg was dissolved in 1 ml of Dimethyl sulfoxide (DMSO) then make up the volume up to 50 ml by Methanol as solvent. The resultant solution was stock solution from which different dilutions in the range of 1-10µg/ml has been prepared and evaluated at 314nm wave length in UV-Visible spectrophotometry.

Percentage Entrapment efficiency of liposomes

After size reduction using probe sonicator (10 cycles of 15 sec with 15 sec interval with 230W energy), the liposomal suspension has been centrifuged for 5 min at constant temperature of 5°C at the speed of 2000rpm, which allows the free drug to get separated from liposomal solution. The absorbance of the drug was noted at 314 nm by UV spectroscopy. The entrapment efficiency in percentage was then calculated using equation described below:

$$\% \text{ Entrapment efficiency} = \frac{\text{Entrapped drug}}{\text{Total drug}} \times 100$$

Scanning Electron microscopy

The liposome of Adapalene of batch L10 was used for performing scanning electron microscopy using JSM- IT 100 In Touch Scope (JEOL IT100 with cold stage assembly) instrument. For sample preparation the usage of cold stage assembly is utilized since the liposomes were in solution form. The measurement of particle size of liposomal solution was kept in sample holder and the procedure was conducted at −14°C.

Table 3: Optimization of gelling (polymer) agent.			
Batch code	%carbopol 940	% HPMCK4M	% HPMC E 50
F1	0.5	0.5	--
F2	1.0	1.0	--
F3	1.5	1.5	--
F4	1.0	--	2.5
F5	1.5	2.5	--
F6	--	5.0	--

Particle size analysis

The size of liposome formulation (batch L10) was measured by dynamic light scattering with a Malvern Zetasizer (Malvern Instruments, Malvern, UK). Liposome suspension was added to the sample cuvette and then cuvette was place in Zetasizer. Sample was allowed to stabilize for two minutes and reading was measured.

Development of liposomal gel

HPMCK4M was kept for swelling overnight in concentration of 5% in distilled water, as per Table 3. Prepared liposomal solution was added to gelling agent with gentle stirring for some period. Then prepared gel was evaluated for various properties.[26-49]

Characterization of optimized batch of liposomal gel

pH measurement of gel

The pH of final formulation was measured using electronic pH meter. The calibration of pH meter was done by using standard Phosphate buffer of known pH 7.4. The measured values were noted for evaluation.

Viscosity of gel

The apparent viscosity of the gel formulation was carried out using brook field viscometer with spindle number 4 at 1.5rpm. The observations are noted for evaluation of the fluidity of the gel.

Drug content of gel

The drug content of the gel was performed using Methanol: DMSO mixture which was used to dissolve the drug for UV spectroscopic determination. The weighed quantity of the gel (100mg) was dissolved in the system of methanol and DMSO. Then solution was checked for its absorbance at 314nm in the UV visible spectrometer. The observations were evaluated for total drug content of the prepared gel.

Spreadability study of liposomal gel[8]

The Spreadability study should be carried out to denote the ideal spreading efficiency of the formulation which corresponds to its therapeutic efficacy also. It can be determined by various methods; while here it has been performed using wooden block and glass slide. Which was supposed to reflect the weight require to slide the upper glass slide from lower slide, placed 2gm of gel in between. Spreadability was then calculated by using the formula:

$$S = M.L / T$$

Where, S = Spreadability
M = Weight tide to the upper slide
L = Length of a glass slide
T = Time taken to separate the slide completely from each other

In vitro drug release study of optimized batch

Liposomal gel of Adapalene was taken (3gm) in dialysis bag (13000 - 14000Mo. Wt. cut off) having length of 7.5cm which is sealed in both sides by thread and suspended in 50ml phosphate buffer solution of pH 5.0. 2 ml of fluid was withdrawn from the beaker after 1, 2, 3, 4, 5, and 24 hr. Interval and replaced with 2 ml of fresh solution of PBS pH 5.0. The samples were analysed in UV spectrophotometer at a wavelength of 314 nm and the concentration of Adapalene in each sample was determined from a standard curve.

Ex-vivo skin retention study of gel

Goat skin obtained from slaughter house was washed thoroughly and stored well in phosphate buffer for some period of time. Then skin was cut into circular piece of 12.56 cm^2 area. Then this Circular piece of skin was attached on the vertical Franz diffusion cell having phosphate buffer pH 5.5 in receptor compartment. Accurately weighed 3gm of liposomal gel having liposomes of Adapalene was placed on donor compartment. 2 ml sample aliquots were withdrawn at 1 hr. time interval up to 5 hr. There after sample was withdrawn after 24 hr. After removal of skin from Franz diffusion cell, liposomal gel retained on skin was collected and dissolved in 10ml solvent mixture (9:1-methanol: DMSO). Stratum corneum was removed by stripping the skin surface with adhesive tape. Tape used to strip was cut into pieces and soaked in solvent for 2 hr. Skin surface was also cut into pieces and soaked for 2 hr. Then these solutions were measured for amount of drug retained, spectrophotometrically at wave length of 314nm.[26]

Stability study of optimized batch

Stability study was performed to investigate the leak out or degradation of the drug during storage. Liposomal gel of adapalene of optimized batch (L10) were sealed in10-mlglass jar and stored at refrigeration temperature (2-8°C) and room temperature(25±2°C) for a period of 1 month. After one month drug content of the gel was determined by spectroscopic estimation.

RESULT AND DISCUSSION

FT-IR study for Drug- Excipients Compatibility

The study has revealed that, no any specific incompatibility has been observed with the FT-IR study as shown in Figure 2, which allows the preparation of the formulation with lipids and drug. It also demonstrated that, lipid polymers can conjugate with the AD without any chemical degradation which is the prime concern of the formulation.

Spectrophotometric estimation of AD

It provides the base for the further estimation of drug content into the formulation, also will be utilised in measuring the properties of the formulation like *in-vitro* release pattern as well as *ex-vivo* skin retention study. The

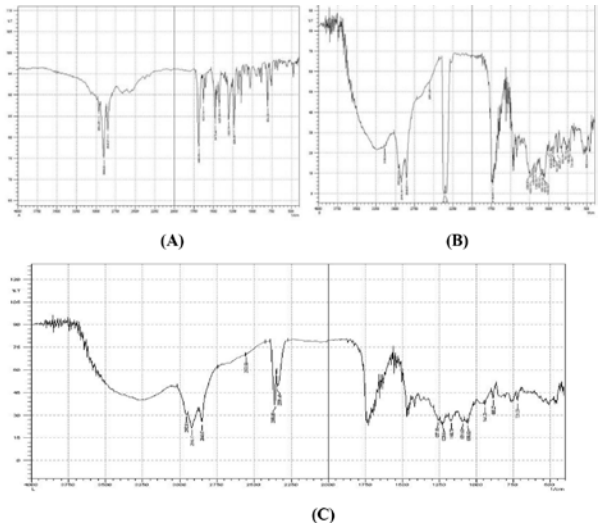

Figure 2: (A) FT-IR of AD (B) FT-IR of Excipients (C) FT-IR of AD+ Excipients.

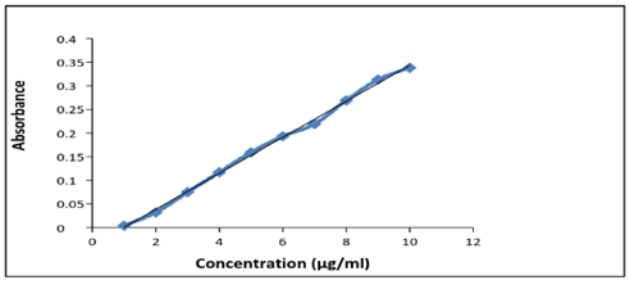

Figure 3: Standard calibration curve of AD at 314nm.

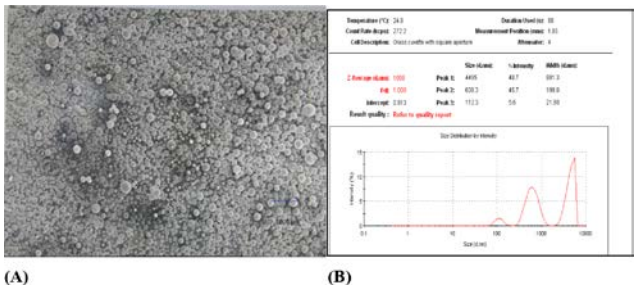

Figure 4: (A) SEM Image of Liposome (B) Particle size analysis of liposome formulation.

Table 4: Entrapment efficiency of liposomes.

	Quantity of Excipients (Molar ratio)											
Ingredients	**L1**	**L2**	**L3**	**L4**	**L5**	**L6**	**L7**	**L8**	**L9**	**L10**	**L11**	**L12**
Adapalene	1	1	1	1	1	1	1	1	1	1	1	1
DPPC	--	--	--	--	5	10	3	10	12	--	--	--
DMPC	4	6	8	10	5	--	7	--	--	--	--	--
DMPG	1	1	1	1	1	1	1	1	1	1	1	1
CHOL.	1	--	--	--	--	--	--	--	--	--	--	1
MPEGDSPE	--	--	--	--	--	--	--	1	1	--	--	--
HSPC	--	--	--	--	--	--	--	--	--	10	5	10
%E.E	20	22.6	54	56.4	62.3	57.5	64.6	61.6	40	66.18	20	63.18

standard graph obtained at 314nm is as shown in the Figures 3, 4.

Estimation of Percentage Entrapment efficiency of liposomes

The highest Percentage Drug Entrapment is observed in L10 formulation (Table 4). Here it is estimated that, HSPC and DMPG as lipid has shown greater entrapment efficiency as compared to other lipids.

Particle size analysis

Particle size studies have shown the correlation between drug retention into the skin layers. Here the formulation has achieved the particle size range of LUVs so that the probability of the drug being stored in the skin layers will be enhanced. Thus, allowing the formulation to provide sustain release of the medication which is further studied in *in-vitro* release study with marketed formulation.

Estimation of pH, Viscosity, Spreadability, Drug Content of gel

Liposomal gel formulation shows adequate pH, Viscosity and Spreadability suitable for skin environment and ideal drug content to be released at the follicular region.

In vitro drug release study of gel

Release study of liposomal gel was carried out in dialysis bag and it is compared with marketed formulation (Deriva Ms) with microspheres in it. (Table 6) (Figure 5). The data clearly indicate the sustain release pattern of the formulation, hence, it shows only 30% release at the 6 hr. time duration which allows the formulation to deposited in the skin layers for longer duration of time. Without being absorbed into the systemic circulation. This is the prime adverse reaction of the current marketed formulation.

Table 5: pH, viscosity, Spreadability of gel.

Batch code	Viscosity (Cps)		pH	Spreadability (gm.cm/sec)	Drug content
	30 rpm	6o rpm			
F1	700	900	5.5	5.3	90
F2	1100	1000	5.6	6.4	92
F3	1300	1375	5.6	6.6	91
F4	1600	1400	6.2	7.2	90
F5	2000	1800	5.7	7.9	91
F6	3200	3000	5.8	8.1	90

Skin retention study of gel

The prepared liposomal formulation is suspected to give localization effect hence it can be used for retention of drug into the skin layers. Almost 89.24% of drug was found to be accumulated in dermis and epidermis layer. This has been confirmed by performing spectrophotometric evaluation of the solution present in accepter compartment from the Franz diffusion

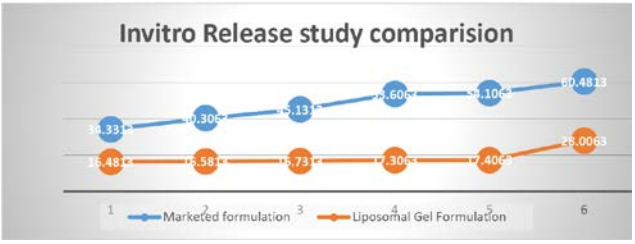

Figure 5: *In-vitro* release Pattern of formulation to Deriva MS.

Table 6: Comparison with marketed formulation.

Time (Hr.)	%CPR	
	Marketed formulation (Deriva MS)	Batch L10
1	34.3313	16.4813
2	40.3063	16.5813
3	45.1313	16.7313
4	53.6063	17.3063
5	54.1063	17.4063
24	60.4813	28.0063

Table 7: Result of skin retention study.

Result of *ex-vivo* skin retention study	% Drug
Drug present in gel	7.92%
Drug retained in skin layers	89.24%
Drug permeated from skin layers	2.84%

cell. Liposomal encapsulation of adapalene shows drug reservoir effect in skin and drug was found to be accumulated in dermis and epidermis layer. The results are suggestive that adapalene skin permeation and retention between the layers of skins are indicative of the drug retention at application site. This is ultimately reduce the systemic circulation and thus opted for suitable targeted delivery of the drug.

Stability study of optimized batch of liposomal gel

Estimation of drug content after one month stability study shows that at room temperature 75% drug was remained unchanged and around 17% drug was degraded. Whereas drug content after one month stability study at 2 to 8°C was found to be 90.6%. This result indicates that formulation was found stable at 2 to 8°C for one month. Therefore the preferred storage condition of present formulation is 2 to 8°C

CONCLUSION

There are several studies of anti-acne molecules have been reported using various vesicular deliveries. The efficacy of current novel dosage forms is high as compared to conventional dosage forms. The present investigation focuses on development of topical liposomal gel of adapalene. For liposome preparation two primary lipids HSPC and DMPG were used to prepare liposomes of Adapalene by lipid hydration method. These liposomes have shown properties which can be optimum for follicular targeting of the drug. Adapalene being the third-generation retinoid, most prescribed for acne and acne lesions. The available marketed product with microspheres formulation shows systemic toxicity and dermal irritation and photosensitization due to systemic absorption. This liposomal formulation having particle size of 100nm is optimum for topical application. Further it shows greater entrapment efficiency, as it is lipid soluble in nature. The liposomal formulation was further incorporated into 5% gel of HPMCk4M. The prepared final formulation was optimized for viscosity and other gel parameters like Spreadability, pH, and drug content. The invitro drug release studies and *ex-vivo* skin retention study as per Table 7 shows retentive properties of the formulation. The current investigation point out targeting prospective and promotes retention potential of the formulation in epidermis tissue. The comparative retention study of the marketed formulation and prepared formulation shows distinctive properties of the formulation. Hence, it can further be utilised for the decrease in the systemic side effect for secondary lesion production. The developed liposomal gel established ideal therapeutic response, improved therapeutic efficacy, and negligible diffusion through epidermis with an intervention of the insignificant side effects.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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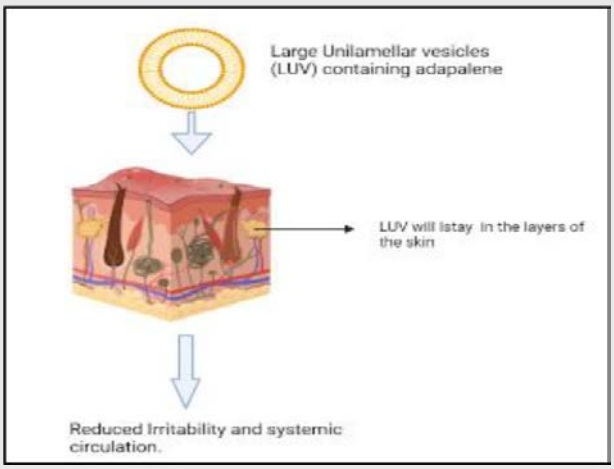
PICTORIAL ABSTRACT



SUMMARY

The skin being the most common organ for delivering drugs in various disease conditions has identified from several years. Here, in the case of Acne vulgaris, the commonly known as the puberty out break often leads to the most complicated treatment path with use of retinoids. The targeting to the follicular deliveries are more of the concern with various novel deliveries, hence liposomal gel can be promising for obtaining the follicular target in acne vulgaris.

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