e-ISSN: 2248-9126
Vol 10 |Issue 1| 2020 |1-8. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

DEVELOPMENT AND CHARACTERIZATION OF EFFECTIVE TOPICAL FORMULATION FOR ADAPALENE LOADED INVASOMES FOR ACNE MANAGEMENT

Monika Targhotra, Madhu Gupta*

Department Of Pharmaceutics, Delhi Pharmaceutical Sciences and Research University, PushpVihar Sec- 3, New Delhi, India.

ABSTRACT

The model retinoid adapalene was formulated in a novel invasomal dispersion as a topical drug delivery system for transport of the active pharmaceutical ingredient (API) into hair follicle orifices. In this study, we investigate the preparation of Adapalene loaded invasomes by mechanical dispersion technique with different ratio of terpenes added as penetration enhancers. The formulation was characterized for particle size, zeta potential, entrapment efficiency and drug release properties. This dispersion is then incorporated into HPMC gel to prepare as a invasomal gel formulation properties. The resultant formulation invasomal gel was evaluated for drug content, pH, spread ability, viscosity *in vitro* drug release, skin permeation and rheological behavior. The TEM photograph revealed that the carrier systems are spherical in shape. The particle size analysis indicated that the size of vesicles increased with increasing the amount of terpenes in the vesicles: the size of invasomes containing 0.5 % Terpene A formulation was 132.5±0.56 nm, while the size of in vasomes containing 1.5% terpenes was 159.2±0.32. The entrapment efficiency of Adapalene loaded invasomes ranged from (40-80%). Prepared gel was inspected under black and white background and was found very clear and without any aggregates. After all evaluation it can be concluded that Adapalene invasomal gel could increase the drug permeability across the membrane and fast release of the drug could be achieved successfully.

Keywords: Acne, invasomes, penetration, terpenes, formulation, topical delivery.

INTRODUCTION

Acne is a complex disease with multifactorial pathogenesis and considerable variation in severity. The occurrence of acne in the people increases with age and approx. 22% patients suffers from acne lesions at 13 years whereas 68% at 16 years of age. [1]The rate of occurrence of acne lesion in boys was observed only 40% at 12 years but increased rate up to 95% rate at the age of 16 years with maximum occurring rate between 17-19 years [2-3]. Acne is a disease of the sebaceous follicles, mainly pilosebaceous unit situated in different areas like face, neck, chest, upper back and upper arms. Pilosebaceous unit mainly consist of sebaceous gland along with the small hair follicles. It results from the interaction of few factors comedogenesis, excessive sebum production, proliferation of propionibacterium acnes, inflammation.

There are 3 types of cane based on lesions- Mild acne consist of whiteheads and blackheads, Moderate includes papules and pustules whereas Severe acne or Nodulystic acne leads to scarring [4].Treatment options differ with the stage and strength of the disease. According to the severity, acne can be classified as mild, moderate, or severe. First choice of treatment for acne is basically topical treatment which used as a monotherapy in mild forms of acne, or in combination with systemic treatment in moderate and severe cases. A topical retinoid is used as a first line treatment ,topical antibiotic such as clindamycin or erythromycin can be used if inflammation occurs to enhance the efficacy [5-6]. Benzoyl peroxide has strong effective antimicrobial activity, is somewhat anti-inflammatory but has only extremely mild anticomedogenic effects [7-9]. Oral antibiotics are

Corresponding Author:-**Madhu Gupta** Email: madhugupta98@gmail.com

indicated for the management of moderate and severe acne, acne that is resistant to topical treatment and acne that covers large parts of the body surface. *P. acnes* is highly sensitive in vitro to a number of antimicrobial agents of different classes, including macrolides, tetracyclines, penicillins, clindamycin, aminoglycosides, cephalosporins, trimethoprim, and sulfonamides. Light/photodynamic therapy (PDT) UVA and/or UVB phototherapy mainly not used widely in patients with acne. Blue light radiation results in improvement of acne lesions when compared with benzoyl peroxide [10].Topical drug delivery system, mainly localized drug delivery sytem and preparations mainly applied to the skin surface. They act as protectant, lubricant and exert physical effect on the skin surface [11]. Penetration enhancer results in the promotion of drug transport through the skin barrier. A number of mechanisms are involved to increase penetration enhancement. The polar head group of lipid interacts with the enhancers results in the increment of penetration across the skin. As a result packaging order of lipids are changed with lipid -lipid head group interactions which source the facilitation of the distribution of hydrophilic drugs [12].

Invasomes are novel vesicular carriers which are made up of unsaturated soybean lecithin (with high % PC), small amount of ethanol, and small amount of a mixture of terpenes (cineole, citral, and d-limonene, essential oils) [13].

Low T_m, ofunsaturated phospholipids, lead to the formation of nano carriers as liposomes. Terpenes are used to impart deformability to the carrier. Terpenes are used as penetration enhancer, ultimately enhance the fluidity of stratum corneum and which simultaneously results in the increase of fluidity in vesicle bilayers [14]. Previous studies supported that terpenes have shown to be a good enhancer for number of drugs like nicardipine [15] lorazepam, clonazepam, haloperidol [16], nicardipine, carbamazepine, tamoxifenetc [17]. Increased penetration of lipophilic drugs accounts as there is increase in the partition coefficient into the stratum corneum/ vehicle and it results in proportionally increase in the solubility of the enhancer [18-21].. Ethanol results in fluidization of the vesicles bilayers in the same mode as it fluidizes the Stratum corneum lipid bilayers.

Adapalene is a third-age topical retinoid basically utilized in the treatment of mellow moderate skin break out. Unthinkingly, adapalene ties to explicit retinoic corrosive atomic receptors (gamma and beta) and retinoid X receptors yet does not tie to the cytosolic receptor protein. Despite the fact that the precise method of activity of adapalene is obscure, it is proposed that topical adapalene may standardize the separation of follicular epithelial cells bringing about diminished microcomedone development [22].

With all the above aspects in mind the present work was aimed at investigating the potential of Invasomes as Penetration enhancer Vesicles (PEVs) contain in adapalene as topical drug delivery systems for the treatment of acne vulgaris so as to increase the contact time of the drug with site of application reduce the number of application and better patient compliance.

MATERIALS AND METHODS

MATERIALS

Adapalene was a kind gift sample obtained from Swapnroop Drugs & Pharmaceuticals (Maharashtra , India). Peppermint oil was purchased from Central Drug House Pvt. Ltd. (Delhi, India). Eucalyptus oil and HPMC E-15 was purchased from Molychem, Mumbai.. Soya lecithin, ethanol, triethanolamine were purchased from Central Drug House Pvt. Ltd. (Delhi, India). All were obtained from Central Drug House Pvt. Ltd., New Delhi, India. Urea and ethanol were ordered from Merck, India. All chemicals utilized in the research work were of analytical grade.

METHOD

Preparation of Invasomes

Invasomes were prepared by Mechanical dispersion techniquewith previously reported technique with minor alteration [23]. Invasomes were formulated with the concentrations of soya lecithin (3%w/v) and ethanol (10%v/v). Drug (Adapalene 0.1%w/v) and Terpenes or mixtures of terpenes (TERPENE A- peppermint oil and TERPENE B- eucalyptus oil) in varying concentrations (from 0.2-1.5%w/v) were dissolved in ethanolic phospholipid solution. To obtain a clear solution mixture obtained was vortexed and sonicated for 5 min. Phosphate buffer saline (PBS) (pH: 6.8) was added to the solution by a syringe under constant vortexing. The vortexing was continued for an additional 5 min [23]. The most suitable preparation is used for further studies and termed as TERPENE A – Peppermint oil and TERPENE B – Eucalyptus oil.

Characterization

The prepared formulations were characterized by different parameters like vesicle size and size distribution, morphology and others.

Transmission electron microscopy (TEM)

The morphology of optimal invasomal dispersion was examined by transmission electron microscopy(TEM). A drop of vesicle dispersion was applied to a carbon film-covered copper grid and stained with 0.1% phosphotungstic acid. Then, samples were examined with a Hitachi H-7500 transmission electron microscope (Hitachi Ltd., Tokyo, Japan) at an accelerating voltage of 80 Kv [24].

Particle size and Zeta potential

The mean diameter of adapalene loaded invasomal dispersion was measured by photon correlation

spectroscopy (PCS) using a particle sizer (NICOMP 3000 PSS sizing system) at a fixed angle of 90◦ at 25 ◦C [24]. The measurements were obtained using a He–Ne laser of 633 nm and the particle size analysis data were evaluated using the volume distribution.

Entrapment efficiency

The entrapment efficiency of adapalene loaded invasomal dispersion was directly determined by ultrafiltration method using centrifugal filter tubes using (Remi, Rm-12c, India). Briefly, 1ml of adapalene-loaded invasomaldispersion was placed into a centrifugal filter tube which was centrifuged at 15,000 rpm for 15 min at 4ºC in two cycles to separate the unentrapped drug. The absorbance of the drug was noted by spectrophotometrically at 230 nm (Shimadzu Corp. 81195, Uv-1800, Toshvin Analytical) [23]. The amount of incorporated drug was calculated as a result of the initial drug minus free drug. The entrapment efficiency of adapalene in invasomaldispersion were calculated according to the following equation-

$$\text{Entrapment efficiency} = \frac{\text{Total drug-free drug}}{\text{Total drug}} \times 100$$

Formulation and Characterization of Gel

Preparation of invasomes incorporated gel

Promising invasomal dispersion (formulation prepared by mechanical dispersion method containing different Tepenes). Formulations of invasomes prepared using different terpenes containing adapalene equivalent to 0.1 % w/w was incorporated into the gel base composed of HPMC E-15 (2% w/w)

Propylene Glycol (10 % w/w)and Triethanolamine in sufficient quantity wasadded subsequently to the aqueous dispersion with co tinuous stirring.The gel was sonicatedfor 30 minutes on bath sonic ator and kept overnight to remove air bubbles [23].

Physical Characteristics and pH determination

The prepared gel was examined for clarity, color, and the presence of foreign particles [26].Weighing2.5 g of gel and was mixed in 25 ml of distilled water. The pH of the dispersion was measured by using a digital pH meter (Eutech Instruments, Ph Tutor, India) [26].

Drug content

The drug content of the prepared gel was carried out by dissolving 10 mg of the gel in 100 ml volumetric flask and volume was made up to 50 ml with of phosphate buffer pH 6.8. The content was filtered through Whatman filter paper No. 41. 5 ml of above solution was taken into a 25 ml volumetric flask. The content of Adapalene was determined at 230 nm against blank by using the Shimadzu UV/visible spectrophotometer. (Shimadzu Corp. 81195, Uv-1800) [26].

Spreadability

An excess of gel sample 1 gm was placed between two glass slides and a 150g weight was placed on slides for 5 minutes to compress the sample to a uniform thickness. The time required to separate the two slides was taken as a measure of spreadability. It was calculated using the formula [23]

$$S = \frac{ML}{T}$$

Where, S = Spreadability.

M = Weight tide to upper slide.

L = Length moved on the glass slide.

T = Time taken to separate the slide completely from each other

The therapeutic efficiency to the formulation is depending on its Spreadability values.

Rheological properties

The viscosity of invasomal gel was measured by a Brookfield viscometer (Brookfield Engineering Laboratories Inc. Rheo2,8, India) at 37 ºC [26].

Homogeneity

All developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates [26].

Extrudability

Extrudability is an empirical test for the measurement of force required to extrude the material from tube containing gel. The invasomal gels were filled into collapsible tubes and the extrudability of the formulation was tested. Extrudability was carried out by Pfizer hardness tester. 15g of gel was filled in aluminum tube and plunger was adjusted to hold the tube properly. Pressure of 1 Kg/cm^2 was applied for 30 sec and the mass of gel extruded was measured. This procedure is repeated at three equidistance places of tube [23].

***In vitro* drug release**

In vitro drug release of entrapped drug from formulations was studied by employing dialysis tube diffusion techniques with slight modification. Control bags were prepared and tested with the dispersions. Dialysis bag consist of 1mgof drug in it. Dialysis bag were tightly enclosed with the help of threads. The dialysis bag was hung inside a beaker with the aid of a glass rod in order that the portion of the dialysis sac with the formulation dipped into the buffer solution.1 ml of sample was taken into a dialysis tube (MWCO 10000, Sigma) and placed in a beaker containing 20 ml of PBS (pH 6.8) for a period of 12 hrs which was tied at both ends and placed in separate beaker. The beakers were assembled above a magnetic stirrer in order to have continuous stirring at 100rpm and maintained constant temperature, 32±1 °C. One ml of sample was withdrawn intermittently

(1h,2h,3h,4h,5h,6h,7h,8,h,10h,12h,24h) and was replaced with same volume of solvent mixture in receptor compartment and assayed for drug content by measuring the absorbance at 230 nm against a reagent blank, using the UV spectrophotometer (Shimazdu Double beam UV spectrophotometer) [23].

***In vitro Skin* permeation Studies**

Abdominal skin section of male wistar rat was prepared and permeation studies were performed using Franz diffusion cell. Effective surface area of cell was 1.0 cm^2 and has a receptor volume of 7.5 ml. Donor compartment was applied with invasomal preparation and 7.5 ml of pH 6.8 phosphate buffer maintained at 37ºC was used as receptor medium. Aliquot amounts were withdrawn and replaced by fresh media to maintain sink condition. Samples were analyzed by using double beam UV spectrophotometer [23].

RESULTS AND DISCUSSION

Preparation of invasomes

As a new type of vesicle structured drug carrier, invasomes showed the characteristics of good flexibility, high entrapment efficiency, satisfactory permeability, and reliable stability, which enabled the delivery of drugs into deeper skin layers and/or the systemic circulation. In the present work, invasomes containing phospholipid (3% w/v), 0.2 - 1.5% w/v of the terpene (Peppermint oil and eucalyptus oil) and 10% w/v ethanol were prepared by mechanical dispersion technique shown in Table 1 in order to accentuate the penetration of adapalene. Invasomal dispersion was found to be easy to prepare and composed mainly of phospholipids, ethanol, and terpene compounds commonly found in pharmaceutical preparations.

Particle size and shape

The different invasomal preparations Table 1were respectively measured by PCS. The particle size and zeta potential were respectively shown in Table 2. The average size of all the formulations located between 120 and 270 nm. The particle size analysis indicated that the size of vesicles increased with increasing the amount of terpenes in the vesicles: the size of invasomes containing 0.5 % Terpene. A formulation was 132.5±0.56 nm, while the size of invasomes containing 1.5% terpenes was 159.2±0.32. Similarly with the Terpene B formulation 0.2% Terpene was 176.4±0.64 , while the size of invasomes containing 0.5% B Terpene was 265.8±0.67.The results of particle size on different formulations are shown in the (Table 2). The zeta potentials of all the formulations are about in the range of -25mV to -55mV. Even though a high zeta potential can provide an electric repulsion. It was reported an increase in concentration of terpenes in vesicles resulted in increase in negative surface charge. Wherein invasomes containing 1.0% TA2 terpenes possessed a surface charge of -55.8mV and 0.5% TB2 terpenes possessed -52.5mV. It has been reported that negatively charged vesicles promoted permeation of drug. Negative charge may be imparted due to the presence of ethanol. The results of zeta potential on different formulations are shown in the Table 2.

The TEM imaging of invaosmal preparation is shown inFigure 1. The particle size of invasomal preparation from TEM image accords with that from that from PCS. The imaging showed that preparation exhibited a spherical shape and had a narrow size distribution Visualisation of vesicle morphology by transmission electron microscopy (TEM) revealed the predominance of spherical shaped vesicles. The vesicles were unilamellar with spherical shape as shown in the **Figure 1.**

Entrapment Efficiency

Entrapment efficiency is a direct commentary on the ability of drug to integrate with lipoidal content to form particles of suitable integrity .The entrapment efficiency for all formulations adapalene loaded invasomes systems was in between the range of 40- 80% Table 2. The entrapment efficiency was least found with (41.23±0.18) for the formulation TB1 and least concentration of terpene TB2 (0.1%w/v) showed maximum entrapment (84.42±0.24%) as compared to rest of the formulations. Due to the lipophilic nature of the drug, it gets intercalated into the lipid layer. Entrapment efficiency was found to be influenced by hydrophilicity of drug and terpene added and concentration of terpene added. The results of entrapment efficiency on different formulations are shown in the Table 2.

Invasomal Gel

To facilitate topical application, fluid dispersions which are obtained when the lipid content is low, can be incorporated into a gel base which does not induce dissolution or aggregation of carriers. All optimized formulations were incorporated into HPMC E-15 gel.

Invasomal gel was prepared with the incorporation of HPMC E-15, TA2 & TB2 selected on the basis of lesser particle size, high entrapment efficiency and gel. This invasomal gel formulation was evaluated for appearance, pH, viscosity, drug content, *in vitro* drug release.

Prepared gel was inspected under black and white background and was found very clear and without any aggregates. The gel showed occlusive nature, occlusive effect enhances penetration of active drug and improves efficacy as shown in the Table 3.

Prepared gel was inspected under black and white background and was found very clear and without any aggregates. The pH values of all prepared formulations were ranged between 6.40- 6.84 as shown in the Table 4 namely significant to evade the skin irritation following application of the gel. The gel showed occlusive nature,

occlusive effect enhances penetration of active drug and improves efficacy.

Drug content of the invasomal gel was determined using ultraviolet spectrophotometer and range from 82.98±0.7 to 84.65±0.5 % as shown in the Table 4. The drug was consistently dispersed during the formulation and with minimal drug loss while formulating invasomal gel. The results of drug content on different formulation as shown in the Table 4.

Spreadability characterized as the degree of region to which the gel promptly spreads on application to the skin and the influenced zone. The aftereffects of spreadability on various plan as appeared in the Table 4.

Homogeneity of a topical formulation gives the idea about the consistency, stability and elegance of the final product. Incorporation of propylene glycol as a humectant and HPMC E-15 as the gelling agent contributed towards the good homogeneity. The result of prepared formulations on Homogeneity are as as shown in Table 5.

The result of prepared formulations on Rheological properties are as as shown in (Table 5). Gels with a high consistency may not extrude from tube whereas, low viscous gels may flow quickly & hence suitable consistency is required in order to extrude gel from the tube, extrudability of gel was found to be good. The result of prepared formulations on Extrudability are as as shown in Table 5.

The enhanced plan was chosen dependent on the criteria of achieving the most extreme estimation of entrapment efficiency; minimizing the particle size. The formulation TA2 &TB2 was found to fulfill requisites of an optimized formulation. These two formulations were selected for *in vitro* drug release studies.

These two formulations were selected for the preparation of invasomal gel formulation incorporation with HPMC E-15.

In this way, it is presumed that dependent on the information of in vitro investigations of TA2 and TB2 appear to be better.

Evaluation of *in vitro* drug release from encapsulated invasome was done by dialysis method. The *in vitro* release behavior of the free adapalene-loaded conventional invasomal gel, and marketed formulation is summarized in the cumulative percentage release shown in Figure 2. The drug release rate of invasomal gel and marketed formulation is often comparable. The discharge rate of the medication was most astounding for the free medication release rate of while the rate of release from marketed formulation was less than that of invasomal gel. The release of gel formulation was found to be of gel TA2, TB2 and marketed gel formulation as 44.78±3.22%, 52.45±3.34%, 79.28±2.98%. The rapid initial phase may be accounted to the leached drug in the dispersion medium, whereas subsequent slower release may be due to slow and controlled diffusion of drug through the layer. As expected, quantitative drug diffusion across the dialysis membrane as measured for different formulations was slower as compared to the marketed solution. This result was probably due to the release-retarding effect of the polymeric matrix of gelling agents. The *in vitro* release profile of invasomal gel depicted as shown in the Table 6 and Figure 2.

The *in vitro* skin permeation profile shows that invasomes formulation (TA2 AND TB2) presents maximum flux value, (45.31±2.12%, 59.24±1.14) which was less than the marketed formulation (78.63±1.69) through rat skin. Penetration was resolved regarding the mean combined sum diffused at each inspecting point for a period of 24 h. The explanation behind this better execution of invasomes is that it contains phospholipids as well as ethanol and terpenes. Terpenes are considered as potent penetration enhancers, and they have been shown to upgrade the percutaneous retention of hydrophilic and lipophilic medications. The nearness of ethanol and terpenes construct the molecules deformable and may also serve as penetration enhancers.

The saturation improving impact of invasomes has been clarified by making permeable to the skin corneum lipid bilayer structure, thus disturbing the organization of stratum corneum lipids. These phenomena, i.e. an increased deformability of particles and a disorganized stratum corneum bilayer structure, are thought to facilitate the penetration of invasomes.The effect of variables such as phospholipid, ethanol and terpene on flux is shown in Table 7. The enhanced detailing was chosen dependent on the criteria of accomplishing the most extreme estimation of flux and entrapment efficiency; minimizing the particle size. The formulationTA2and TB2 was found to fulfill requisites of an optimized formulation. The *in vitro* skin permeation profile of invasomal gel depicted as shown in the Table 7 and Figure 3.

Table1. Composition of invasome as pevs

S.No	Formulation code	Drug(%w/v)	Soya lecithin (%w/v)	TERPENE A & B (%w/v)	Ethanol (%v/v)
1	TA1	0.1	3	0.5	10
2	**TA2**	**0.1**	**3**	**1.0**	**10**
3	TA3	0.1	3	1.5	10
4	TB1	0.1	3	0.2	10
4	**TB2**	**0.1**	**3**	**0.5**	**10**

Table 2. Characterization of invasomes

Formulations	Zeta potential (mV)	Vesicle size± SD(n=3) (nm)	Entrapment efficiency %(n=3)
TA1	-31.2mV	132.5±0.56	41.23±0.18
TA2	**-55.8** mV	**210.9±1.01**	**75.48±0.06**
TA3	-41.8mV	159.2±0.32	49.51±0.36
TB1	-30.5mV	176.4±0.64	41.22±0.34
TB2	**-52.5 mV**	**265.8±0.67**	**84.42±0.24**
TB3	-28.6mV	123.2±0.65	51.66±.76

Table 3. Physicochemical characteristics of gel

Physicochemical characteristics of gel	Observations
Appearance	White
Odour	Characteristic
Clarity	Clear

Table 4. Drug content, pH, spreadability of invasomal gels

Formulation	Drug content ±SD (n=3)	pH	Spreadability(g.cm/sec)
TA2	82.98±0.7	6.22±0.02	21.99
TB2	84.65±0.5	6.25±0.04	17.89

Table 5. Extrudability, homogeneity, viscosity of invasomal gel formulation

Formulation	Extrudability (gm/cm^2)	Homogeneity	Viscosity (cps)
TA2	Good	Good	8527
TB2	Excellent	Good	13698

Table 6.*In vitro* release of invasomal gel and marketed formulation

Time (hrs)	Cumulative % Release of gel TA2	Cumulative % Release of gel TB2	Cumulative % Release of marketed formulation
1	09.38±1.09	09.92±1.12	15.63±1.19
2	12.52±1.34	11.67±1.87	27.66±1.45
3	15.19±1.56	17.55±1.45	35.14±1.76
4	19.08±1.87	22.57±1.76	43.13±2.12
5	22.16±2.02	27.41±2.12	51.09±2.43
6	27.89±2.27	31.62±2.22	64.24±2.56
8	33.88±2.34	35.64±2.45	**79.28±2.98**
10	39.34±2.33	40.96±3.02	---
12	41.80±3.11	45.38±3.12	---
24	**44.78±3.22**	**52.45±3.34**	---

Table 7. *In vitro* skin permeation of both invasomal gel & marketed formulation

Time (hrs)	Cumulative % permeation TA2	Cumulative % permeation TB2	Cumulative % permeation of marketed formulation
1	7.97±1.02	8.06±1.09	10.70±1.34
2	11.51±1.12	10.24±1.16	22.43±1.45
3	14.23±1.23	13.87±1.26	29.98±1.67
4	17.42±1.45	16.18±1.29	36.98±1.89
5	18.88±1.56	18.46±1.32	44.73±2.22
6	21.77±1.65	20.95±1.45	52.69±2.34
8	25.44±2.02	24.82±2.12	64.93±2.48
10	29.57±2.12	32.22±2.24	**78.63±1.69**
12	34.79±2.32	43.31±2.48	----
24	**45.31±2.12**	**59.24±1.14**	----

Fig1. Tem image of adapaleneinvasomes

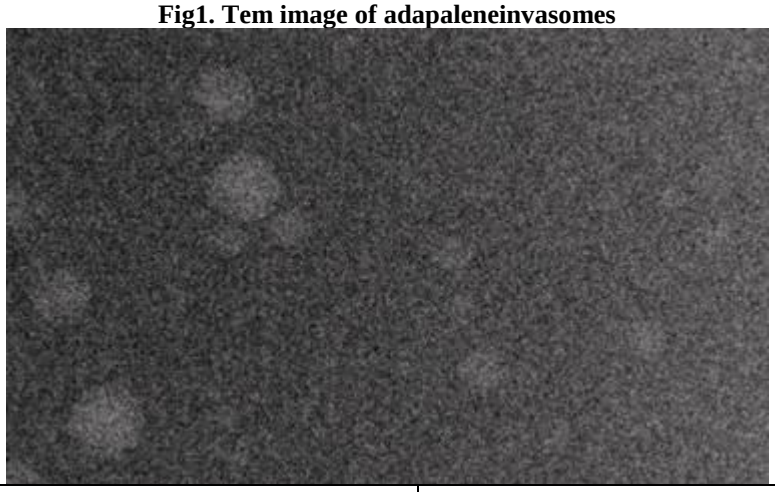


Fig 2. *In vitro* release of both invasomal gel & marketed formulation

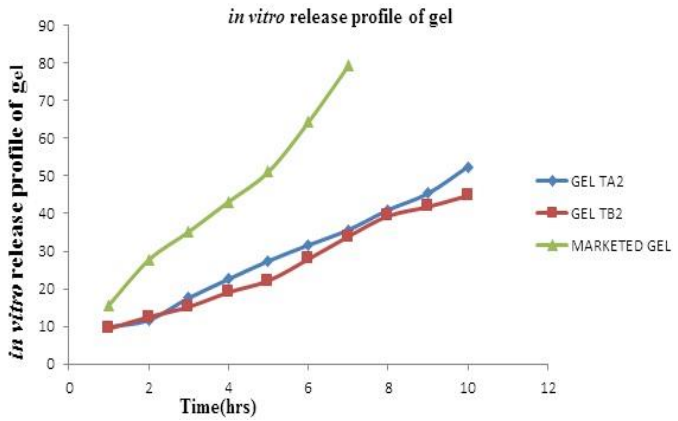
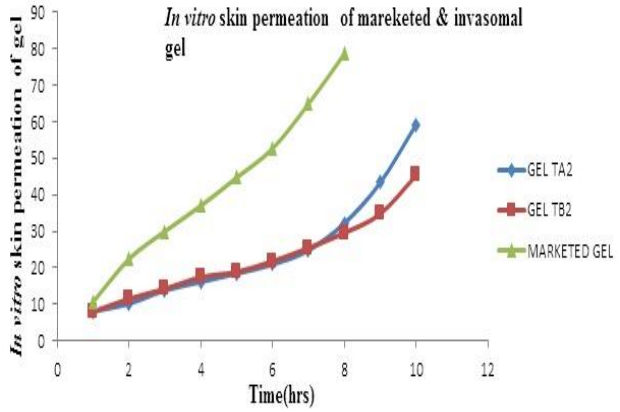


Fig 3. *in vitro* skin permeation of both invasomal gel & marketed formulation



CONCLUSION

Recently, invasomes have been studied by many researchers as a choice of topical or transdermal drug delivery system to provide better oral bioavailability consideration, high penetration property of the invasome encapsulated agents through biological membrane and their stability. The present formulation study on adapalene is an attempt to prepare invasomal drug delivery system and evaluate its in vitro performance. The formulations were prepared with different ratios of terpene. An ideal or best formulation of invasome is said to be one that gives high entrapment efficiency. With all the above aspects in mind the present work was aimed at investigating the potential of invasomal formulation contain in adapalene as topical drug delivery systems for the treatment of acne vulgaris so as to increase the contact time of the drug with the skin, reduce the number of application and better patient compliance. So in this work an attempt has been made to provide invasomes based topical drug delivery.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

REFERENCES

1. Rademaker M, Rademaker M, Garioch JJ, Simpson NB. Acne in schoolchildren: no longer a concern for dermatologists. *BMJ*, 298(6682), 1989, 1217-1219.
2. Dreno B. Recent data on epidemiology of acne. *Ann DermatolVenereol*, 137, 2010, S49-51.

3. Ghodsi SZ, Orawa H, Zouboulis CC. Prevalence, severity, and severity risk factors of acne in high school pupils: a community-based study. *J Invest Dermatol*, 129, 2009, 2136-2141.
4. Raza K, Talwar V, Setia A, Katare OP. Acne: An understanding of the disease and its impact on life. *International Journal of Drug Development & Research*, 4(2), 2012, 0975-9344.
5. Gollnick H, Cunliffe WJ, Berson D. Management of acne: a report from a global alliance to improve outcomes in acne. *J Am AcadDermatol*, 49, 2003, S1–37.
6. Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatr*, 118, 2006, 1188–1199.
7. Fulton J, Farzad-Bakshandeh A, Bradley S. Studies on the mechanism of action of topical benzoyl peroxide and vitamin A acid in acne vulgaris. *J CutanPathol*, 1, 1974, 191–200.
8. Hughes B, Norris J, Cunliffe W. A double blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. *ClinExpDermatol*, 17, 1992, 165–168.
9. Chalker DK, Shalita A, Smith JG, Swann RW:A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. *J Am AcadDermatol*, 9, 1983, 933–936.
10. Borelli C, Merk K, Plewig G, Degitz K. Laser und PDT TherapiebeiAkne. *Hautarzt*, 56(11), 2005, 1027–32.
11. Reddy GSC, Reddy BA, Jotish M, Pranitha CN, Suryadevara H. Organogels- a review.*Int. J. Pharm. Tech*, 2011, 584-602.
12. Walker RB, Smith EW. The role of percutaneous penetration enhancers. *Adv drug delivery*, 18, 1996, 295-301.
13. Verma DD: Invasomes-novel topical carriers for enhanced topical delivery: characterization and skin penetration properties, PhD thesis. Philipps-University Marburg, Marburg/Lahn 2002.
14. Cornwell PA, Barry BW, Stoddart CP, Bouwstra JA. Wide-angle X-ray diffraction of human stratum corneum: effects of hydration and terpene enhancer treatment. *J Pharm Pharmacol*, 46, 1994, 938–950.
15. Krishnaiah YS, Satyanarayana V, Bhaskar P. Enhanced percutaneous permeability of nicardipine hydrochloride by carvone across the rat abdominal skin. *Drug DevInd Pharm*, 29, 2003, 191–202
16. Puglia C, Bonina F, Trapani G, Franco M, Ricci M. Evaluation of in vitro percutaneous absorption of lorazepam and clonazepam from hydroalcoholic gel formulations. *Int J Pharm*, 228, 2001, 79–87.
17. El-Kattan AF, Asbill CS, Kim N, Michniak B. The effects of terpene enhancers on the percutaneous permeation of drugs with different lipophilicities. *Int J Pharm*, 215, 2001, 229–240.
18. Williams AC, Barry BW. Terpenes and the lipidprotein- partitioning theory of skin penetration enhancement. *Pharm Res*, 8, 1991, 17–24.
19. Williams AC, Barry BW. The enhancement index concept applied to terpene penetration enhancers for human skin and model lipophilic (oestradiol) and hydrophilic (5-fluorouracil) drugs. *Int J Pharm*, 74, 1991b, 157–168.
20. Cornwell PA, Barry BW, Bouwstra JA, Gooris GS. Modes of action of terpene penetration enhancers in human skin; differential scanning calorimetry, smallangle X-ray diffraction and enhancer uptake studies. *Int J Pharm*, 127, 1996, 9–26.
21. Moghimi HR, Williams AC, Barry BW. A lamellar matrix model for stratum corneum intercellular lipids. V. Effect of terpene penetration of the matrix. *Int J Pharm*, 146, 1997, 41–54.
22. Irby CE, Yentzer BA, Feldman SR. A review of adapalene in the treatment of acne vulgaris. *J Adolesc Health*, 43, 2008, 421-424.
23. Lakshmi PK, Mounica V, Manoj KY, Prasanthi D. Preparation and Evaluation of CurcuminInvasomes. *International Journal of Drug Delivery*, 6, 2014, 113-120.
24. Kumar A, Parthiban S, Kumar S. GP:Formulation and evaluation of transdermal proniosomal gel for glipizide. *European Journal of biomedical and Pharmaceutical Sciences*, 3(5), 2016, 368-374.
25. Jain AK, Jain A, Garg NK, Jain A, Jain SA, Tyagi RK, Agrawal GP. Adapalene Loaded Solid Lipid Nanoparticles Gel: An Effective Approach for Acne Treatment. *Colloids and Surfaces B: Biointerfaces*, 2014.
26. Dubey A, Prabhu P, Kabrawala H, Gupta V. Niosomal gel of Adapalene: Its formulation, physicochemical properties and evaluation for mild-acne. *Advances in Biomedicine and Pharmacy*, 2(1), 2015, 22-31.