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FORMULATION, DEVELOPMENT AND EVALUATION OF TAZAROTENE INVASOME GEL FOR TREATMENT OF TOPICAL DISEASE

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Abstract:
*In the tropics, infectious diseases that either occurs exclusively or more frequently in humid and subtropical climates are either more prevalent or more difficult to prevent or manage. A type of vesicular system called invasomes exhibits greater transdermal penetration than conventional liposomes. These vesicles' structures contain phospholipids, ethanol, and terpene, which provide the soft vesicles good transdermal penetration properties. These nanovesicles' ability to increase drug permeability into the epidermis while reducing absorption into the systemic circulation, hence restricting drug action within the skin layer, is one of its main advantages. In present study was to develop and characterize Tazarotene -loaded invasomal drug carrier systems. Different Formulations (F1 to F6) of invasomes were prepared and evaluated for average vesicle size, zeta potential and entrapment efficiency.*Drug content of Tazarotene incorporated invasomes gel for formulation TIG-1, TIG-2 and TIG-3 was found to be*97.85±0.32, 99.12±0.25 and 98.74±0.14 respectively. The maximum drug content was found in formulation TIG-2 (99.12±0.25), select as optimized formulation.When the regression coefficient values of were compared, it was observed that 'r^2' values of Higuchi was maximum i.e.0.994 hence indicating drug release from formulations was found to follow Higuchi kinetics.*

Key words: *Invasome,* Tazarotene *, Topical disease, Formulation, Evaluation*

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INTRODUCTION:

Infectious diseases that either occur uniquely or more commonly in steamy and subtropical regions are either more widespread in the tropics or extra tricky to prevent or control. The citizens who are the majority exaggerated by these diseases are frequently the poorest populations, whose residence is in remote, rural areas, urban slums or conflict zones. Neglected tropical diseases persevere under circumstances of scarcity and are intense approximately solely in poor populations in the developing world. The designation "tropical diseases" arise at no meticulous date and was slowly merge, as microorganisms came to be recognized as the underlying factor of diseases and had their broadcast mechanisms elucidate. In practice, the term is often taken to pass on to infectious diseases that flourish in burning, moist circumstances, such as malaria, leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, African trypanosomiasis, and dengue. A number of the organisms that grounds tropical diseases are bacteria and viruses, conditions that may be recognizable to the majority people as these types of organisms' grounds sickness common.

During current history, tropical areas of the world were more harshly exaggerated by infectious diseases in contrast to the mild world. Main reasons why infectious diseases can flourish in such regions can be establish in together environmental and biological factors that hold up high levels of biodiversity of pathogens, vectors and hosts, but also in social factors that weaken pains to manage these diseases [1]. Such infectious diseases are recognized just as tropical diseases and tropical medicine has come out as an significant regulation for their study.

Topical drug delivery can be defined as application of drug via skin to directly treat or cure the skin disorders. These topical drug delivery systems are generally used for local skin infection like fungal infection or where other route of administration is no suitable. It can penetrate deeper into skin and hence give better absorption. Topical application has no of advantages over the conventional dosage forms. In general, they are deemed more effective less toxic than conventional formulations due to the bilayered composition and structure. In the formulation of topical dosage forms, attempts has being made to utilize drug carriers that ensure adequate localization or penetration of the drug within or through the skin in order to enhance the local and minimize the systemic effects, or to ensure adequate Percutaneousabsorption. Topical preparation prevents the GI-irritation, prevent the metabolism of drug in the liver so as increase the bioavailability of the drug. Topical preparations give its action directly at the site of action. A gel is a two-component, cross linked three-dimensional network consisting of structural materials. The structural materials that form the gel network can be composed of inorganic particles or organic macromolecules, primarily polymers.

Invasomes are new, flexible vesicles that contain a combination of soy phosphatidylcholine (PC), terpenes, lyso PC, and ethanol, and have better skin penetration than liposomes. Invasomes, like liposomes, have the same structural elements as liposomes, but their structure includes terpene. Terpenes are hydrocarbon molecules that are recognized to be the main components of many plant essential oils. Terpenes generate deformable vesicles, which can improve the fluidity of the skin's lipid bilayers [2-5]. The capacity to permeate across skin layers boosts invasome activity, which works by disrupting lipid and intracellular protein connections by fluidizing the bilayer structure of SC lipids [6]. Invasomes are a kind of vesicular system that has better transdermal penetration than traditional liposomes.

These vesicles have phospholipids, ethanol, and terpene in their architectures, which provide the soft vesicles good transdermal penetration characteristics. The major benefits of these nanovesicles are their capacity to improve drug permeability into the epidermis while decreasing absorption into the systemic circulation, therefore limiting drug action within the skin layer.

Tazarotene, is 6-[2-(4,4-dimethylthiochroman- 6-yl)ethynyl] ethyl nicotinate,a member of a new generation of receptor-selective synthetic retinoids, indicated in the mild to moderate plaque psoriasis disease, acne vulgaris, and photoaging. Dermal safety studies have specified that tazarotene did not demonstrate photoallergic or phototoxic potential. However, the course of treatment which is usually prolonged (weeks or months) may lead to adverse reactions such as pruritus, burning/stinging, and erythema in a significant subset of users. These may often result in the interruption or discontinuation of the treatment regimen. Further, extremely low solubility limits tazarotene incorporation into an acceptable vehicle and its tolerability results in either discontinuation of treatment or poor compliance in patients. The aim of the present study was to develop and characterize Tazarotene -loaded invasomal drug carrier systems.

MATERIAL AND METHODS:

Material:

Tazarotene was obtained as a gift sample from Pharmaceutical Industries. Phosphotidylcholine, Terpene, Carbopol 934 was purchased from Sigma-Aldrich Chem, Germany. High purity 99.9% Ethanol were obtained from SD Fine chemicals, Mumbai, India. All other chemical and materials were of analytical grade. Triple distilled water was generated in house.

Methods:

Formulation Optimization of Tazarotene loaded Invasomes:

Tazarotene (10mg) was loaded in to invasomes by mechanical dispersion technique. Soya Phosphatidylcholine (0.25 to 0.75% w/v) was added to ethanol and vortexed for 5 minutes [7-8]. Drugand terpenes (0.25 to 0.75%) were added under constant vortexing, this mixture was sonicated for 5 minutes. Fine stream of Phosphate buffer saline (upto 10% w/v) was added with syringe under constant vortexing. It was vortexed for additional 5 minutes to obtain final invasomal preparation.

Table 1: Formulation optimization of Tazarotene loaded Invasomes

Ingredient (%)	F1	F2	F3	F4	F5	F6
Tazarotene (mg)	10	10	10	10	10	10
Phosphotidylcholine (%)	0.25	0.5	0.75	0.25	0.5	0.75
Terpenes (%)	0.25	0.25	0.50	0.50	0.75	0.75
Ethanol (ml)	5	5	5	5	5	5

Preparation of Gel Base:

Carbopol 934 (1-3% w/v -Invasome based gel formulation i.e. TIG-1 of 1% w/v, TIG-2 of 2% w/v, TIG-3 of 3% w/v) was accurately weighed and dispersed into double distilled water (80ml) in a beaker. This solution was stirred continuously at 800 rpm for 1 hour and then 10ml of propylene glycol was added to this solution [9]. The obtained slightly acidic solution was neutralized by drop wise addition of 0.05 N sodium hydroxide solutions, and again mixing was continued until gel becomes transparent. Volume of gel was adjusted to 100 ml and then sonicated for 10 min on bath sonicator to remove air bubbles. Final pH of the gel base was adjusted to 6.5. The same procedure was used to formulate Invasomes containing gel in which previously prepared Invasomes suspension was added. Invasomes preparation corresponding to 0.1% w/w of drug was incorporated into the gel base to get the desired concentration of drug in gel base.

Evaluation of Invasomes:

Entrapment efficiency:

Entrapment efficiency of Tazarotene Invasomes formulation was determined using centrifugation method [10]. The entrapment efficiency of acyclovir in invasomes vesicle was determined by ultracentrifugation, 10mL of invasomes formulation were collect in test tube. The amount of drug not entrapped in the invasomes was determined by centrifuging at 3,000 rpm and collect the supernatant, the supernatant layer was separated, diluted with water suitably and drug concentration was determined at 224 nm using UV spectrophotometer.

$$\%\ Entrapment\ Efficiency\ = \frac{Theroticaldrugcontent - Practicaldrugcontent}{\text{Therotical drug content}} \times 100$$

Vesicle Size:

Microscopic analysis was performed to determine the average size of prepared invasomes[11]. Formulation was diluted with distilled water and one drop was taken on a glass slide and covered with cover slip. The prepared slide was examined under trinocular microscopic at 400 X. The diameters of more than 150 vesicles were randomly measured using calibrated ocular and stage micrometer. The average diameter was calculated using the flowing formula.

$$AverageDiameter = \frac{\Sigma n.d}{\Sigma\ n}$$

Where n = number of vesicles; d = diameter of the vesicles

Evaluation of Invasomes containing gel:

Measurement of viscosity:

Viscosity measurements of prepared topical Invasomes based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm.

pH measurements:
pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the vesicles as long as covered by the vesicles. Then pH of selected formulation was measured and readings shown on display were noted [12].

Drug content:
Accurately weighed equivalent to 100 mg of topical Invasomes gel was taken in beaker and added 20 ml of methanol [59]. This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol. This solution was analyzed using UV-Spectroscope at λ_{max}351 nm.

Extrudability study:
Extrudability was based upon the quantity of the gel extruded from collapsible tube on application of certain load [13]. More the quantity of gel extruded shows better extrudability. It was determine by applying the weight on gel filled collapsible tube and recorded the weight on which gel was extruded from tube.

Spreadibility:
Spreadibility of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response. It was determined by method reported by Multimer *et al.,* [14]. An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan.To determine spreadibility, placing 2-5 g of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 10 cm upon adding 80 g of weight was noted. Good spreadibility show lesser time to spread.

$$Spreadibility\,(g.cm/\sec) = \frac{Weight\ tide\ to Upper\ Slide \times Lenth\ moved\ on\ the\ glass\ slide}{Time\ take\ nto\ slide}$$

***In-vitro* drug diffusion study:**
The *in-vitro* diffusion study is carried by using franz diffusion cell. Egg membrane is taken as semi permeable membrane for diffusion [15]. The franz diffusion cell has receptor compartment with an effective volume approximately 60 mL and effective surface area of permeation 3.14 sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm^2 size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32±0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell.

During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each sampling. The samples withdrawn are analyzed spectrophotometrically at wavelength of 351 nm.

RESULTS AND DISCUSSION:

In present study was to develop and characterize Tazarotene -loaded invasomal drug carrier systems. Different Formulations (F1 to F6) of invasomes were prepared and evaluated for average vesicle size, zeta potential and entrapment efficiency.The Average vesicle size was found to be in the range of 210.32±0.26 to 248.85±0.25, the minimum vesicle size was found in formulation F-4, 210.32±0.26 nm. The Entrapment efficiency of formulation F1, F2, F3, F4, F5 and F6 was found 65.45±0.45, 68.85±0.25, 67.74±0.36, 76.65±0.21, 70.12±0.14 and 68.85±0.35 percentage respectively.The maximum percentage entrapment efficiency was found to be in formulation F-4, 76.65±0.21 percentages.

Surface potential can play an important role in the behavior of Invasomes *in-vivo* and *in-vitro.* In general charged Invasomes were more stable against aggregation and fusion than uncharged Invasomes. The prepared gel at least rpm of 10 exhibited a viscosity of 3478±17 to3652±10cps that indicates that the formulation has the desired viscosity required for semisolid formulation for proper packaging. It was found that the viscosity decreases as the rotational speed of viscometer increased suggesting that greater the shearing the lower viscosity favours easy spreadability further confirmed by spreadability and rheological testing.

pH of prepared herbal Gel was measured by using digital pH meter. The pH of the Gel was found to be in range of 6.71±0.32 to 6.84±0.14which is good for skin pH. All the formulation of Gel was shown pH

nearer to skin required i.e. pH of IG1-6.72±0.25, 6.71±0.32 and IG3-6.84±0.14.

Spreadability plays considerable role in patient compliance and ensures uniform application of Gel to a larger area of the skin. The spreadability of the formulation TIG-2 was calculated as 11.23±0.15cm/sec. The low value of spreadability coefficient of the Gel was sufficient suggesting easy spreading and no signs of grittiness. The lower value of spreadability indicates the lesser work required to spread the Gel over the skin, which means formulation was easily spreadable by applying small amount of shear.

Drug content of Tazarotene incorporated invasomes gel for formulation TIG-1, TIG-2 and TIG-3 was found to be97.85±0.32**,** 99.12±0.25 and 98.74±0.14 respectively. The maximum drug content was found in formulation TIG-2 (99.12±0.25), select as optimized formulation.

When the regression coefficient values of were compared, it was observed that 'r^2' values of Higuchi was maximum i.e.0.994 hence indicating drug release from formulations was found to follow Higuchi kinetics.

Table 2: Entrapment efficiency and average vesicle size

Formulation Code	% Entrapment efficiency	Average vesicle size (nm)
F1	65.45±0.45	248.85±0.25
F2	68.85±0.25	235.65±0.32
F3	67.74±0.36	245.74±0.14
F4	76.65±0.21	210.32±0.26
F5	70.12±0.14	230.21±0.18
F6	68.85±0.35	246.65±0.24

Table 3: Characterization of optimized formulation of invasomes

Formulation .	Average vesicle size (nm)	% Entrapment efficiency	Zeta Potential (mV)
F-4	210.32±0.26	76.65	-33.12

Table 4: Characterization of Invasomesgel based formulation

Gel formulation	Viscosity (cps)	Ph	Drug Content (%)	Extrudability (g)	Spreadibility (g.cm/sec)
TIG-1	3652±10	6.72±0.25	97.85±0.32	165.58±0.36	12.25±0.21
TIG-2	3545±15	6.71±0.32	99.12±0.25	158.85±0.25	11.23±0.15
TIG-3	3478±17	6.84±0.14	98.74±0.14	152.25±0.14	10.15±0.14

Table 5: *In-vitro* drug release data for optimized formulation TIG-2

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	18.85	1.368	76.64	1.884
1	1	0	26.65	1.602	60.02	1.778
2	1.414	0.301	33.36	1.614	58.85	1.770
4	2	0.602	48.85	1.778	40.05	1.603
6	2.449	0.778	56.65	1.838	31.15	1.493
8	2.828	0.903	73.32	1.903	20.02	1.301
10	3.162	1	88.56	1.947	11.55	1.063
12	3.464	1.079	99.15	1.998	0.55	-0.260

Table 6: Regression analysis data of optimized gel formulation TIG-2

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
TIG-2	0.994	0.770	0.975	0.983

CONCLUSION:

Invasomes may be a promising delivery system for tazarotene when employed with the right formulations, according to the overall results of this research. Drug efficacy would enhance with an invasomal system. With appropriate drug loading, tazarotene could be successfully entrapped in invasomes. These results have been observed to enable more precise and localised pharmacological activity in the skin, offering a better solution to diseases related to the skin.

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