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RESEARCH ARTICLE

DESIGN AND EVALUATION OF TAZAROTENE LOADED LIPOSOME GEL FOR EFFECTIVE TREATMENT OF PSORIASIS AND ACNE

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ABSTRACT

Topical Tazarotene is a widely used drug in the topical treatment of Acne, Psoriasis and other skin disorders. Tazarotene synthetically produced retinoid commonly used in the treatment of acne. Tazarotene is a pro-drug of tazarotenic acid, a receptor-selective retinoid, which has shown efficacy in the treatment of these disorders. In the treatment of acne vulgaris, it has greater comedolytic activity than the currently available topical retinoids. In psoriasis, tazarotene normalizes keratinocyte differentiation, reverses keratinocyte hyperproliferation and has better anti-inflammatory effects than any of the currently available topical retinoids. But topical treatment with Tazarotene reported certain side effects. Approximately, 10 to 30% of patients experience peeling, dryness, irritation and burning with its use, mostly during the early weeks of therapy. Liposomal drug delivery strategies can play a pivotal role in improving the topical delivery by enhancing their dermal localization with a concomitant reduction in their side effects. Liposomes composed of Soya lecithin and cholesterol, with Tazarotene entrapped in the inner water compartment, were prepared by the simple mechanical method vortexing the phospholipid dispersion in water. Topical liposome gels will be prepared by incorporation of liposomes into a structured vehicle (1.5, 1.75 and 2 % Carbopol gel base). Also, corresponding hydrogels were prepared and drug release properties were investigated.

Keywords: Tazarotene, acne vulgaris, psoriasis, Liposomes

INTRODUCTION:

Acne is a disease that involves the oil glands of the skin. It is not dangerous, but can leave skin scars. Your skin has pores (tiny holes) which connect to oil glands located under the skin. The glands are connected to the pores via follicles - small canals. Sebum, an oily liquid, is produced by these glands. The sebum carries dead skin cells through the follicles to the surface of your skin. A small hair grows through the follicle out of the skin. Pimples grow when these follicles get blocked. In humans, when pimples appear they tend to do soon the patient's face, back, chest shoulders and neck. Acne develops when follicles get blocked and infected. Simply put - skin cells, sebum and hair can clump together into a plug, this plug gets infected with bacteria, resulting in a swelling. A pimple starts to develop when the plug begins to break down.[1-5] Psoriasis is regarded as an autoimmune disease in which genetic and environmental factors have a significant role. The name of the disease is derived from Greek word „psora" which means „itch". Psoriasis is a non-contagious, dry, inflammatory and ugly skin disorder, which can involve entire system of person. In this disease, the skin keeps scaling as flakes called psoriatic plaques due to rapid and excessive multiplication of epidermis cells which look like fishy skin & finally peels off as exfoliation.[6-10] Tazarotene is a pro-drug of tazarotenic acid, a receptor-selective retinoid, which has shown efficacy in the treatment of these disorders.[31-33] Liposomes are microscopic spheres with an aqueous core surrounded by one or more outer shells consisting of lipids arranged in a bilayer configuration. Liposomes are acceptable and superior carriers having ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. It also has affinity to keratin of horny layer of skin and can penetrate deeper into skin and hence give better absorption. Applied on the skin, liposomes may act as a solublizing matrix for poorly soluble drugs, penetration enhancer as well as local depot at the same time diminishing the side effects of these drugs. The liposome gel formulations could perform therapeutically better effects than the conventional formulations, as prolonged and controlled release topical dosage forms, which may lead to improved efficiency and better patient compliance.[20-25]

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MATERIALS AND METHODS:

MATERIALS:

Tezarotene is obtained as gift sample from Glenmark Pharmaceuticals Ltd; Soya lecithin was obtained from Natterman Phospholipid, Germany; Carbopol and Cholesterol were obtained from Qualigens Fine Chemicals, Mumbai; chloroform was obtained from S.D. Fine Chem. Ltd., Mumbai. All other chemicals & reagents used were of analytical grade.

Method of preparation of Tazarotene loaded liposomes[22,25,27]

Multi lamellar liposomes (MLV) consisting of Tazarotene were prepared using the thin film hydration method. Tazarotene, Soya lecithin, Cholesterol and α-tocopherol (1 % of lecithin) were dissolved in chloroform and a thin film lipid layer was obtained by evaporating the organic solvent (for 15min, at a definite temperature, at a definite Rotatory speed as given the table) using a Rotavapor and water jet vacuum. The obtained thin film layer was dried overnight in a vaccum oven to ensure complete removal of organic solvent. Then the lipid film was suspended in Phosphate buffered saline (PBS) (pH 7.4) by vortexing for 10 min, and was allowed to hydrate for 1h at 70°C, 90rpm. The liposomal suspension was then centrifuged 3000rpm for 30min. The settled liposomes were resuspended in PBS. Then this suspension was subjected for sonication for 15min to get small unilamellar liposomes (SUVs). Temperature was maintained at around 65°C. (**Note:- in each preparation. α-tocopherol (1 % of lecithin) was added as antioxidant during preparation to prevent the preparation from oxidation and to make it stable for long time)**

Batch No.	Lecithin (mg)	Cholesterol (mg)	Ratio of Lecithin and Cholestrol	Solvent volume (ml)	Rotatory speed (rpm)	Temperature (^{0}C)
L1	10	10	1:1	10	100	50^{0}C
L2	10	15	1:1.5	10	100	50^{0}C
L3	10	20	1:2	10	100	50^{0}C
L4	10	25	1:2.5	10	100	50^{0}C
L5	10	30	1:3	10	100	50^{0}C
L6	10	35	1:3.5	10	100	50^{0}C
L7	10	40	1:4	10	100	50^{0}C
L8	10	45	1:45	10	100	50^{0}C
L9	10	50	1:5	10	100	50^{0}C

Preparation of carbopol gel base[22,23]

Formula:

Carbopol 940: 2% w/w g
Triethanolamine: q.s.
Methyl hydroxy benzoate: 0.15 % w/w
Propyl hydroxy benzoate: 0.05 % w/w
Distilled water: 95.8 % w/w

Carbopol 940 was sprinkled slowly to 5 ml of water as medium and the medium was continuously stirred to get a uniform dispersion of carbopol. The other ingredients that are methyl hydroxy benzoate and propyl hydroxy benzoate were pre dissolved in separate portion of water (5 ml) and added to carbopol dispersion. Final volume was adjusted with water and pH brought to neutral by using the triethanolamine. This preparation was kept overnight, till the carbopol becomes uniform in texture and appearance and the air bubbles are removed. (With all the carbopol gels only distilled water should be used since the resin will react and precipitates with calcium salt in hard water).

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Incorporation of liposomes into gel base:

The drug loaded liposomes were incorporated into gel base (carbopol 940) in such a way that final formulation contained 1 % w/w (0.2 g /10ml liposomal suspension was levigated with 10 g of gel base) drug.

Characterization of Tazarotene loaded liposomes

Determination of the average size and size distribution in liposomes[18,19]

Average size and size distribution of liposomes was determined by microscopic method. Ocular micrometer was calibrated using a stage micrometer (0.01mm). About 10 µl of the liposomal formulation was placed on each microscopic slide and covered under a cover slip. The slide was placed on the stage of the binocular compound microscope and focused under 45X objective lens to observe the liposomes. Size of 150 liposomal vesicles was measured at different location on the slide. From the obtained results size distribution and average size of liposomal vesicles was determined.

Drug Entrapment Studies[20,22]

Separation of unentrapped drug from the prepared liposomes was carried out by mini column centrifugation method. Liposomal suspension (0.2 ml) was centrifuged at 2000 rpm for 3 min. Elutes containing drug loaded liposomes were collected and observed under optical microscope to ensure the absence of unentrapped drug particles. Appropriate amount of elute was digested with chloroform-methanol (2:1, v/v) and the clear solution thus obtained was analyzed spectrophotometerically (U.V./Visible spectrophotometer, Shimadzu-1700, Japan) for the drug content estimation at a λ max of ……nm. Studies were conducted in triplicate. Percent drug loading (PDL) for the prepared liposomes were calculated as –

$$PDL = \frac{EntarppedDrug(mg)}{TotalDrugLoaded(mg)} X100$$

Characterization of liposomal Gels

Gels were evaluated for their clarity, pH, viscosity, spread ability, skin irritation test, in vitro diffusion studies using standard procedure. All studies were carried out in triplicate and average values were reported.

Psychorheological Characteristic[23,24]

The Psychorheological Characteristic was checked for hair gel formulations (colour, clogging, homogeneity and texture).

Washability[21,22]

Formulations were applied on the skin and then ease and extent of washing with water were checked manually.

Extrudability study[20,21]

The hair gel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked.

Spreadability[17,19]

An important criterion for hair gels is that it must possess good spreadability. Spreadability is a term expressed to denote the extent of area to which the gel readily spreads on application to hairs. The therapeutic efficacy of a formulation also depends on its spreading value. A special apparatus has been designed to study the spreadability of the formulations. Spreadability is expressed in terms of time in seconds taken by two slides to slip of from formulation, placed between, under the application of a certain load. Lesser the time taken for the separation of two slides, better the spreadability. Two glass slides of standard dimensions (6×2) were selected. The hair gel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the hair gel formulation between the two slides was traced uniformly to form a thin layer. The weight was removed and the excess of the hair gel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied 50with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each hair gel formulation.

$$\text{Spreadability} = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec)
m = weight tied to the upper slide (20 grams)
l= length of glass slide (6cms).
t = time taken is seconds.

Determination of pH[20,23]

The pH of the hair gels were determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained.

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And constant reading was noted. The measurements of pH of each formulation were replicated two times.

Viscosity[22,24]

The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer. The viscosity was measured using spindle no. 6 at 10 rpm and 25^{0}C. The sufficient quantity of gel was filled in appropriate wide mouth container. The gel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the Viscometer.

Samples of the gels were allowed to settle over 30 min at the constant temperature (25 ±/1^{0}C) before the measurements.

In-vitro Drug Release Studies Using the Prehydrated Cellophane Membrane[22,23,24]

1. Preparation of cellophane membrane for the diffusion studies:

The cellophane membrane approximately 25 cm x 2cm was taken and washed in the running water. It was then soaked in distilled water for 24 hours, before used for diffusion studies to remove glycerin present on it and was mounted on the diffusion cell for further studies.

2. Diffusion Studies:

The in-vitro diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15mm internal diameter and 100mm height. The diffusion cell membrane was applied with one gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker containing neutralizing phthalate buffer, freshly prepared (pH 5.4)as a receptor base and the system was maintained for 2 hrs at 37± 0.5^o C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of 15, 30, 45, 60, 90, 120 min and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 257 nm using neutralizing phthalate buffer as blank=

Data Analysis via Drug Release Kinetics study

The results of in-vitro release profile obtained for all the formulations were plotted

in kinetic models as follows,

1. Cumulative of drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining to be absorbed versus time (First order model)
3. Cumulative amount of drug release versus square root of time (Higuchi model)
4. Log cumulative drug released versus log time (Korsmeyer-Peppas model)

Skin irritation test[22,23]

Gels should not produce skin irritation when applied topical drug delivery system. Hence, skin irritation study was performed. The skin irritation test was performed on healthy white rabbit of average weight 1.75 to 2.25 Kg. About 9 cm² area on the dorsal surface of the rabbits in each group was shaved and cleaned with spirit.

Rabbits were divided into three groups (n=3) as follows:

Group-I (control): There was no application on the surface of the rabbit skin.

Group-II (negative control): An aqueous solution of 1 ml containing 0.8% formalin soaked in 9 cm² cotton wool (standard irritant) was placed in the back of the rabbit as negative control. The cotton wool was secured firmly in the place with adhesive plaster.

Group-III (test): 1 ml of gel containing 10 mg of Tazarotene was applied to 9 cm² area on the dorsal surface of the rabbit. The visual inspection was observed for 3 days to check any evidence of skin irritation (sign of edema and erythrema). The scoring system of Draize et al was followed in grading the severity of the effect.

RESULT AND DISCUSSION

Characterization of Tazarotene loaded liposomes

Table 7.6: Determination of the average size and size distribution in liposomes:

Formulation code	Mean vesicles size (µm)
L1	2.51
L2	2.15
L3	2.43
L4	2.91
L5	2.66
L6	2.32
L7	2.56
L8	2.79
L9	2.88

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Drug Entrapment Studies:

Increase in the amount of Cholestrol enhanced the percent entrapment of drug, owing to its cementing effect on the membrane packing. The same would prevent drug leakage from the bilayer membranes leading to enhanced drug retention in liposomes.

Table 7.7:

Formulation code	Entrapment efficiency (%)
L1	81.66
L2	82.81
L3	83.51
L4	83.72
L5	83.95
L6	84.33
L7	84.67
L8	84.91
L9	85.41

7.4 Characterization of Tazarotene loaded liposomes Gels

Psychorheological Characteristic:

Formulation	Colour	Clogging	Homogenity	Texture
L1	White	Absent	++	Smooth
L2	White	Absent	++	Smooth
L3	White	Absent	++	Smooth
L4	White	Absent	++	Smooth
L5	White	Absent	+++	Smooth
L6	White	Absent	++	Smooth
L7	White	Absent	+++	Smooth
L8	White	Absent	++	Smooth
L9	White	Absent	++	Smooth

HOMOGENITY- EXCELLENT: +++, GOOD: ++, AVERAGE: +, POOR: -

Washability

Formulation	Washability
L1	++
L2	++
L3	++
L4	++
L5	++
L6	++
L7	++
L8	++
L9	++

EXCELLENT: +++, GOOD: ++, AVERAGE: +, POOR: -

Extrudability study

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Formulation	Extrudability
L1	++
L2	++
L3	++
L4	++
L5	++
L6	++
L7	++
L8	++
L9	++

EXCELLENT: +++, GOOD: ++, AVERAGE: +, POOR: -

Spreadability

Formulation	Spreadability (gcm/sec)
L1	12.61
L2	15.66
L3	14.51
L4	11.82
L5	16.23
L6	15.55
L7	11.67
L8	13.22
L9	14.31

Determination of pH

Formulation	pH
L1	6.7
L2	7.1
L3	7.4
L4	6.6
L5	6.9
L6	6.5
L7	7.3
L8	7.2
L9	6.8

Viscosity

Formulation	Viscosity (cps)
L1	2451
L2	2677
L3	2481
L4	2513
L5	2566
L6	2617
L7	2554
L8	2451
L9	2510

In-vitro Drug Release Studies

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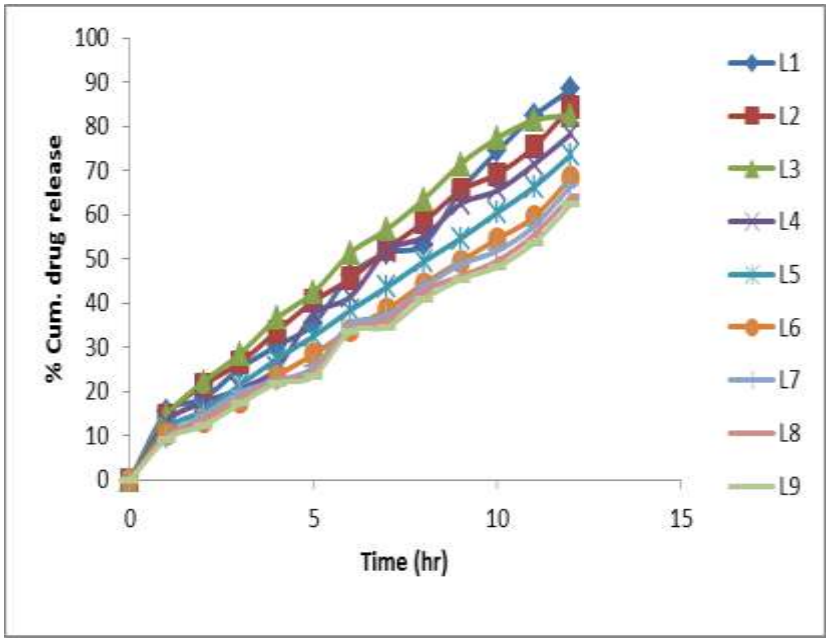
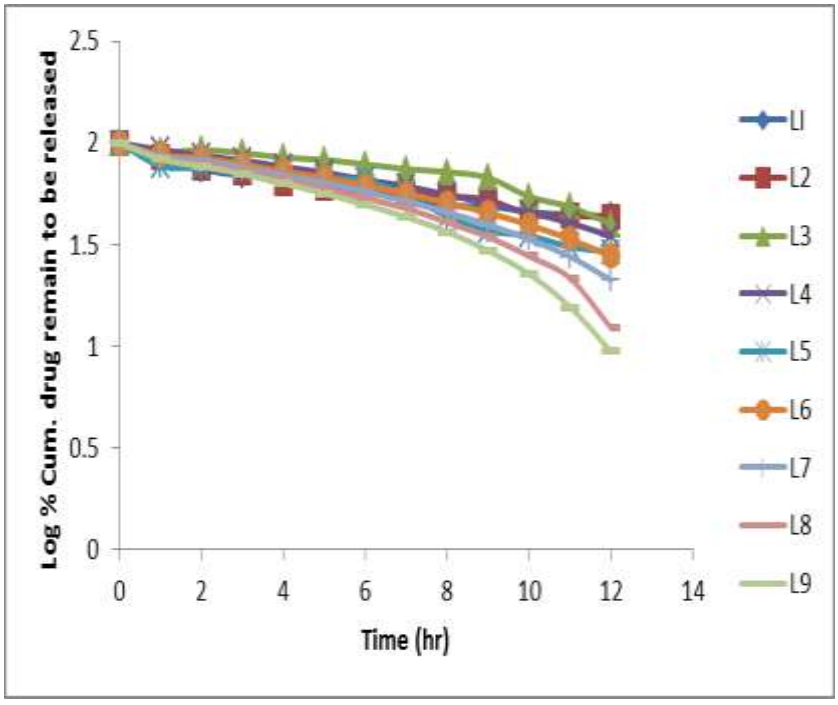
Release of drug from liposomes embedded into the gel base was significantly slower, which confirmed that encapsulation of drug into liposome resulted in a prolonged drug release rate. Lower release rate from liposome gel systems compared to basic liposome dispersion could be a result of the influence of the viscosity of the gel matrix followed by slower drug penetration.

Incorporation of cholesterol into the phospholipid bilayer affected the release rate of the encapsulated drug. By increasing the amount of cholesterol in the lipid phase, the release rate of the drug decreased, which could be related to the increased rigidity of the phospholipid bilayer, followed by its de-creased permeability for the encapsulated drug.

Zero order release kinetics graph



First order release kinetics graph



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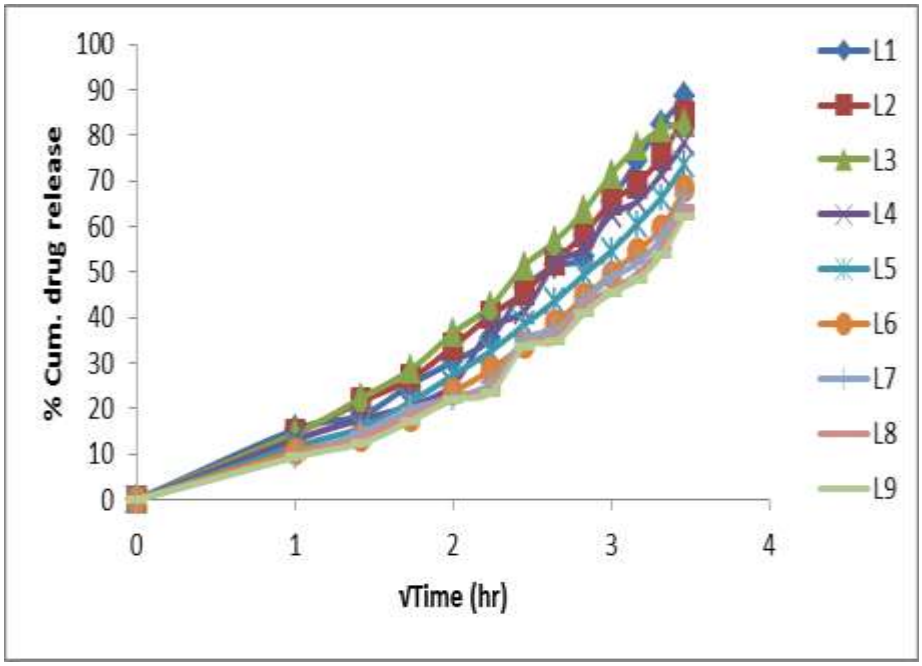
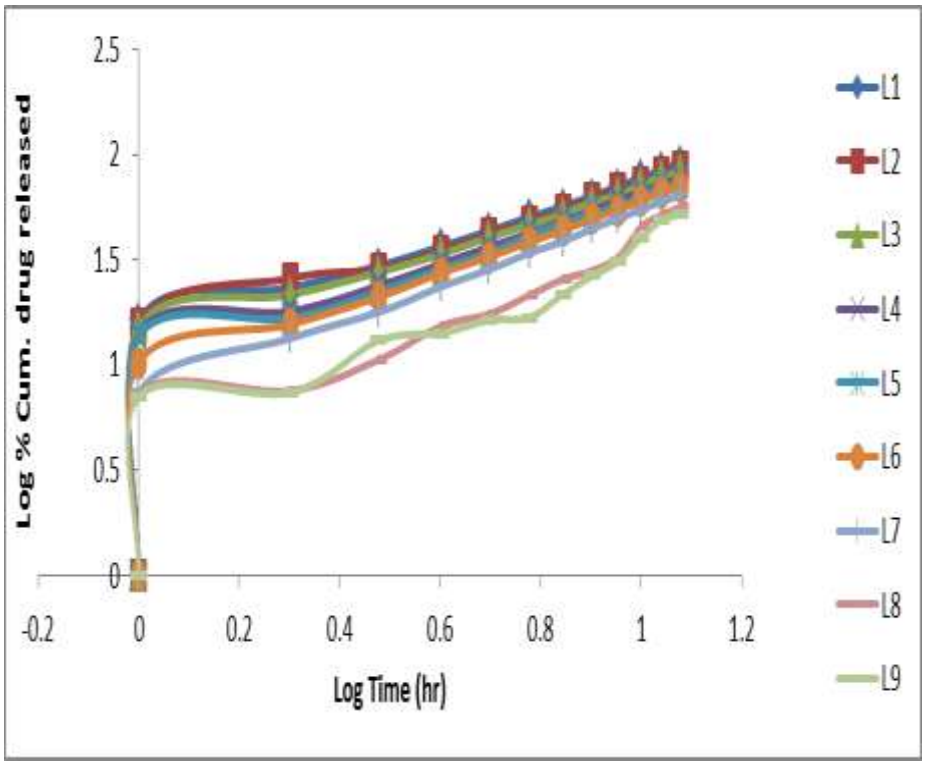
Higuchi matrix release kinetics graph



Peppas release kinetics graph



DRUG RELEASE KINETICS WITH MODEL FITTING:

These values of in-vitro release were attempted to fit into various mathematical models, plot of zero order, first order, higuchi matrix and peppas. These values were compared with each other for model fitting equation. Based on the highest regression values (r), the best fit model for all the formulations was Peppas. Further Korsmeyer and Peppas equation resulted into the values of n > 1, which appears to indicate that the release from the prepared microspheres was by Super Case II transport.

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Drug Release Kinetics with Model fitting (R^2)

Formulation code	Correlation coefficient of Model fitting (R^2)				'n' values for - Peppas	Best fit model
	Zero order	First order	Higuchi matrix	Peppas kinetics		
L1	0.9603	0.9627	0.9508	0.9859	2.2538	Peppas Model
L2	0.9714	0.8855	0.9298	0.9897	2.2386	Peppas Model
L3	0.9676	0.8844	0.9044	0.9873	2.2864	Peppas Model
L4	0.9544	0.8968	0.8822	0.9801	2.2167	Peppas Model
L5	0.9497	0.8921	0.8754	0.9868	2.2109	Peppas Model
L6	0.9186	0.8467	0.8317	0.9866	2.1168	Peppas Model
L7	0.9285	0.8165	0.8207	0.9825	2.2514	Peppas Model
L8	0.9226	0.8266	0.8116	0.9817	2.2813	Peppas Model
L9	0.9317	0.8349	0.8135	0.9869	2.2771	Peppas Model

Skin irritation test:

The liposomal gel formulation did not showed any irritation and erythema after 72 hours. This indicates better skin acceptability of Liposomal gels formulation

Table 7.5.2: Primary irritation study of Liposomal gel formulation

Formulation code	Irritation Score		
	Time of Application (Hours)		
	24	48	72
L1	0	0	0
L2	0	0	0
L3	0	0	0
L4	0	0	0
L5	0	0	0
L6	0	0	0
L7	0	0	0
L8	0	0	0
L9	0	0	0

CONCLUSION:

Topical formulations containing Tazarotene loaded liposomes embedded into Carbopol gel have been prepared and evaluated. Visual inspection showed that all Tazarotene liposomal gels were milky white homogenous gels. The present research work could be concluded as successful production of Liposomes using lecithin and cholesterol. The results of the characterization and

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evaluation established the suitability and compatibility of Tazarotene loaded liposomes gel. Further, developed liposome was meaningfully utilized for the topical delivery of anti-acne and Psoriasiatic drug Tazarotene. Lesser skin irritancy, greater occlusivity and slow drug release that observed with the developed Tazarotene – loaded Liposome-based topical gels would be advantageous over the commercial product. Improved drug stability and encapsulation of Tazarotene in the developed liposome had overcome the adverse effects of Tazarotene and would offer the efficacy in the treatment of psoriasis and acne and offer patient compliance. Production of Tazarotene -loaded liposome and its formulation as a topical gel could be a new, cost effective and commercially viable alternative to the commercial product.

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