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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF NIOSOMAL GEL OF TAZAROTENE FOR TREATMENT OF PSORIASIS

Dr. Vivek Jain, Raghuraj Lovanshi*, Anwar Iqbal Khan

NRI Institute of Pharmacy, Bhopal, Madhya Pradesh, India

ABSTRACT

Aim of the current work was to prepare and characterize Tazarotene encapsulated niosome, incorporated in to a appropriate dermatological base and assess its comparative effectiveness in the cure of dermal infections. Drug encapsulated niosomes was formulated by thin film hydration method using different ratio of drug, cholesterol and surfactant ratio. Vesicular carriers were characterized for vesicle shape and size, drug entrapment efficiency, and in-vitro diffusion study. Vesicular size, zeta potential and drug entrapment efficiency of the optimized niosomes were determined. Microscopic examination suggests niosomes to be multilamellar vesicles with smooth surface. In-vitro diffusion study demonstrated that the drug diffused from optimized batch (F1) niosomal gel was found 95.69%. Optimized formulations were subjected for stability studies carried out at 4.0℃ ± 0.5 ℃ and 28 ± 0.5℃ for 28 days. There was no important variation found in physical appearance, average particle size and % drug content of niosomes gel.

Keywords: Niosome, Gel, Tazarotene, Psoriasis, In-vitro diffusion.

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Correspondence

Raghuraj Lovanshi * ✉ raghurajlovanshi@gmail.com
Address - NRI Institute of Pharmacy, Bhopal, Madhya Pradesh, India

INTRODUCTION

Tazarotene is a topically prescribed retinoid sold in the form of cream or gel. Tazarotene is approved medication for curing of acne, psoriasis and sun damaged (photodamage) skin. Psoriasis is one of the chronic inflammatory skin disorders that might significantly affect the quality of the life that person affected. There are numbers of treatments present for psoriasis and among all these therapies tazarotene is generally used in patients affected by psoriasis [1].

Niosomes are constructed as lamellar structures comprises of cholesterol and non-ionic surfactants. Niosomes possesses amphiphillic bilayer in which polar heads arranged outside and inside so vesicle could be filled with hydrophilic drug while nonpolar bilayer is formed hydrophobic drug can be entrapped [2].

To produced niosomes various choices of nonionic surfactants are available e.g. Crown ethers, polyglycerol alkyl ethers, glucosyldialkyl ethers, ester-linked surfactants, polyoxyethylene alkyl ethers, Tweens and Spans [3]. Niosomes composed of nonionic surfactants were prepared with that type of drug having no charge, mild to use and relatively nontoxic [4]. Niosome is a very useful tool for drug targeting for different parts or organs of body such as skin[5], brain, liver[6], lung ocular systems[7], tumor[8] etc. Niosomes improves the bioavailability and Permeation, provides Controlled and sustained release of drugs [9]. Niosomes are also applicable to protect drug from biological enzymes and acids so the stability of the drug increased. Inadequacy in performance of conventional formulations could be overcome by developing novel formulation that diminishes side-effects and possessed maximum desirable effects. Thus, Niosome were prepared that improves skin permeation, deposition and released slowly in controlled manner [10].

MATERIALS AND METHODS

Pure sample of Tazarotene was obtained from Euphoria Healthcare Pvt. Ltd. Mumbai as gift samples along with their analytical reports. Carbopol 934p and Propylene Glycol procured from S. D. Fine Chem. Ltd., Mumbai and Cholesterol from Ash Chemie India, Thane. Disodium Hydrogen Phosphate, Di potassium Hydrogen Orthophosphate and Sodium Chloride also purchased from S. D. Fine Chem. Ltd., Mumbai. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

Characterization of Drug

Physical evaluation: It the tests performed on the basis of sensory characters e.g. - odor, taste, appearance, habitat of the drug.

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Solubility: The drug solubility was identified by dissolving definite quantity of drug (10 mg) in the 10ml volumetric flask separately and added 1ml of the solvent (ethanol, water, 0.1N HCL, methanol, Chloroform, 0.1N NaOH and 7.4 pH buffer) shake dynamically and set aside for some time. The solubility of drug was noted down in different solvents at ambient temperature.

Melting point: Some quantity of powdered drug was filled into a fused capillary tube. This drug filled tube was put in the melting point apparatus filled with castor oil. Castor oil temperature was increased gradually and noted the temperature on which the drug powder get melt.

Partition coefficient: Taken well cleaned and dried separating funnel, then transferred the octanol/ water system (50:50, 20 ml) as sufficient quantity in separating funnel and added the 1 gm drug in it. Shaked the funnel continuously until the drug was distributed in both phases. Then placed the funnel on stand for settle both phases. After that taken both phases in beaker separately and calculated the drug amount present in both phases.

Determination of pH (1% w/v solution in water): weighed accurately 100 mg of the drug was taken and dissolved in 100 ml of water with sonication and filtered. Filtrate was checked for pH by standard electrode.

λ max Determination: drug was accurately weighed 10 mg, taken in 10 ml of volumetric flask dissolved in 7.4 pH buffer solution of 10 ml. The formed solution was 1000µg/ml and from this solution 1 ml pipette out and transfer into separate 10 ml volumetric flask and make up the volume with 7.4 pH buffer solutions and prepared desired dilutions range of 5-25 µg/ml concentration. The drug spectrum was scanned between 200-400 nm range of U.V. spectrophotometer (Labindia-3000+). The photometric spectrograph peak point shows maximum absorbance of Tazarotene wave length was shown in figure:

FTIR spectroscopy: Infra - red spectrum has an important role to identify the structural information of the compound. The infra red wave length region known as Near Infra-red from 0.8 µ to 2.5 µ and Far infra-red region exist from 15 µ to 200 µ.

Formulation Development

Tazarotene Loaded Niosomes

Different specified ratios was used as shown in table of lipid mixture combined with surfactant (span 40) and Cholesterol to formulate niosomes by thin film hydration method. Lipid mixture with span 40 and Cholesterol and drug were dissolved in chloroform 10ml separately. This properly dissolved, solution was filled in 100 ml round bottom flask, solvent was evaporated by rotary evaporator under low pressure and elevated temperature of 55-65°C. A thin film formed underneath wall of the round bottom flask, film was hydrated with 20 ml of Phosphate buffer saline pH 7.4, by rotating flask for 1 h, at 55-65°C on the rotary evaporator. To attain niosomal dispersion including both entrapped and free drugs of different size, hydrated niosomes kept in bath sonicator for 20 min. Formed niosomes were subjected for evaluation then dried by freeze drying.

Evaluation of Tazarotene Loaded Niosomes

Vesicle size determination: particle size analyzer was used to analyze vesicle size.

Entrapment efficiency: estimation of Tazarotene in niosomes was done by ultra-centrifugation method. Measure the whole volume of the niosomes suspension then 2 ml of this formulation was pipette out and transmitted to centrifuge tube, then diluted with distilled water to mark up 5 ml and centrifuged at 2000 rpm for 20 minutes. Undissolved drug was separated out from the formulation by centrifugation. Ultra centrifugation method was applied to separate Niosomes at 20,000 rpm for 30 minutes. Recovered supernatant and sediment volume was measured. Distilled water was used to dilute Sediment upto 5ml. Estimation of the unentrapped drug was analyzed in supernatant by spectroscopic method.

Transmission Electron Microscopy: it was used to know surface morphology. TEM sampling was prepared by the sample drop was put on a carbon-coated copper grid then after 15 min, 1% phosphor tungustic acid solution was applied to negatively stained. The copper grid was subjected for air dry and observed in transmission electron micro scope.

Preparation of carbopol gel base: accurately weighed 0.5 g of Carbopol 934 was dissolved to disappear in water with vigorous stirring then stand aside for 24 hours to swell properly, obtained clear 0.5%

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carbopol gel. To maintain gel consistency glycerin (2ml) was added. Similar, preparation was prepared using 1 and 2% carbopol.

Preparation of niosomal gels: unentrapped drug was removed by centrifugation to taken equivalent to 1g of niosomes formulation dissolved in 10ml of ethanol. Formulation was separated into supernatant and sediment, supernatant was decanted out and settled niosome formulation was included into the gel. The niosomal incorporation of into gels was done by mechanical mixing at 25 rpm for 10 minutes. Three different conc. of gel at 0.5, 1 and 2% w/w was prepared optimized preparation was incorporated in these.

EVALUATION OF GELS

Determination of pH:

Accurately weighed 50 gm of formulated niosomal gel was shifted in beaker (10ml) and measured it's pH by digital pH meter. Ideal value of pH should be 3-9 for the topical formulations for skin infection treatment.

Spreadability: for the determination of Spreadability a modified apparatus was suggested. Slip and drag characteristics was used to obtained spreadability. The modified apparatus was composed of two glass slides slips over, the lower slid was fixed on wooden plate and upper slid was joint by a hook to equilibrium. The Spreadability formula:

$$S = ml/t$$

Where, S = spreadability
m = weight in upper slide pan
t = time spend to specific distance travelling
l = distance traveled

The mass and length kept steady and't' was identified practically. Spreadability of each preparation was obtained in triplicate and mean values are presented as result.

Measurement of viscosity: Brook Field viscometer's T-Bar spindle combined with a helipath stand was measured the viscosity with accurate readings. The viscosity of gels was measured by using a T-bar spindle (T-95). The factors affect the viscosity e.g. pressure, temperature and sample size and all that were maintained throughout the process. The helipath T- bar spindle was stirred up and down obtaining viscosities at digits of points beside the path. The torque interpretation was for all time greater than 10%. Within 60 sec five readings was taken, mean reading achieved the final viscosity.

Drug content: 1 gm. of each gel preparations was dissolved in ethyl alcohol (100ml). Serial dilutions method was applied to prepare suitable aliquots of various concentrations. After filtration, the absorbances of aliquots were taken at 351 nm. Using linearity equation and the calibration curve drug content was calculated.

In-vitro diffusion study: Franz diffusion cell was used for in-vitro drug release study. Artificial dialysis membrane was put between donor and receptor compartments. Receptor compartment was occupied with phosphate buffer (pH 7.4, 24 ml) and the donor section was filled with Niosomal gel equivalent to 500 mg of tazarotene. The diffusion cell was put at 37±0.5°C with slow stirring of 50 rpm. Aliquots of 5-5 ml were withdrawn time to time from receiver section through side tube and analyzed membrane diffused drug by UV-Visible spectrophotometer.

Statistic treatment of in-vitro release data: the values obtained by release studies was quantitatively analyzed by mathematical formulas easily that express results of the diffusion study as a function of dosage forms characteristics are used.

RESULT AND DISCUSSION

Tazarotene is well known and prescribed retinoid category drug which is sold as a creams or gels, also approved for cure of acne, psoriasis and photo-damaged skin. Chemically, these are oxygenated derivatives of 3,7-dimethyl-1-(2,6,6-trimethylcyclohex-1-enyl) nona-1,3,5,7-tetraene.

Preformulation studies were performed; physical observations realized that the tazarotene is odorless and tasteless light yellow powder soluble in chloroform, acetone, DMSO and phosphate buffer pH 7.4 and freely soluble in ethanol and methanol, observed melting point was 95-96 oC. patition coefficient value was 0.84, mean pH value 6.9 was obtained. Maximum absorbed web length was 351nm (fig. no. 2) obtained using UV- visible spactro-photometer also calibration curve was constructed with r2 value of 0.999 (as shown in fig. no. 3).

From the FT-IR data of the physical mixture it was observed that functional groups of tazarotene structure remain unchanged with their peak

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intensities. It was understood (by fig. no. 10) that drug and excipients was not interacted, it was facilitated to further proceeding for preparation of vesicular drug delivery system. Preformulation studies reported that the formulation of niosomes of Tazarotene can be prepared with appropriate methods.

Drug encapsulated total six formulations (F1 – F6) of niosomes was prepared by thin film hydration method using various ratios of drug, cholesterol and surfactant ratio. Optimized Vesicular carriers were characterized for vesicle size, and shape, drug entrapment efficiency and in-vitro diffusion study, found satisfactory. Microscopic examination suggests niosomes to be multilamellar vesicles with smooth surface. But on the basis of vesicle size and entrapment efficiency, formulation F-2 was optimized and further incorporated in 0.5%, 1.0% and 2.0% carbopol gel.

All niosomes incorporated Gel formulations (F-2(0.5), F-2(1.0) and F-2 (2.0)) were evaluated for pH, Spreadability, viscosity and drug content and formulation F-2(0.5) was optimized. Optimized formulations F-2(0.5) was further evaluated in-vitro diffusion study demonstrated that the drug diffused from optimized batch F-2(0.5) niosomal gel was found to be 95.69%. Diffusion study data was presented as Zero order and First Order kinetics with R2 value 0.936 and 0.936 respectively.

Optimized preparations were subjected for stability studies at 4.0℃ ± 0.5 ℃ and 28 ± 0.5℃ for 28 days. There was no variation observed in physical appearance, mean particle size and % drug content of the niosomal gel.

CONCLUSION

The enhanced delivery of tazarotene using niosomes can be ascribed to an interaction niosomes and skin lipids. The drug release deeply into the skin and transdermal absorption of drug may due the fusion of niosomes with skin lipids and drug releases occurs at various points along the penetration pathway. It was concluded that niosomes loaded with Tazarotene gel formulation possessed prolonged action and it will be developed successfully against the dermal infections.

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EXPERIMENTAL FIGURE AND TABLE

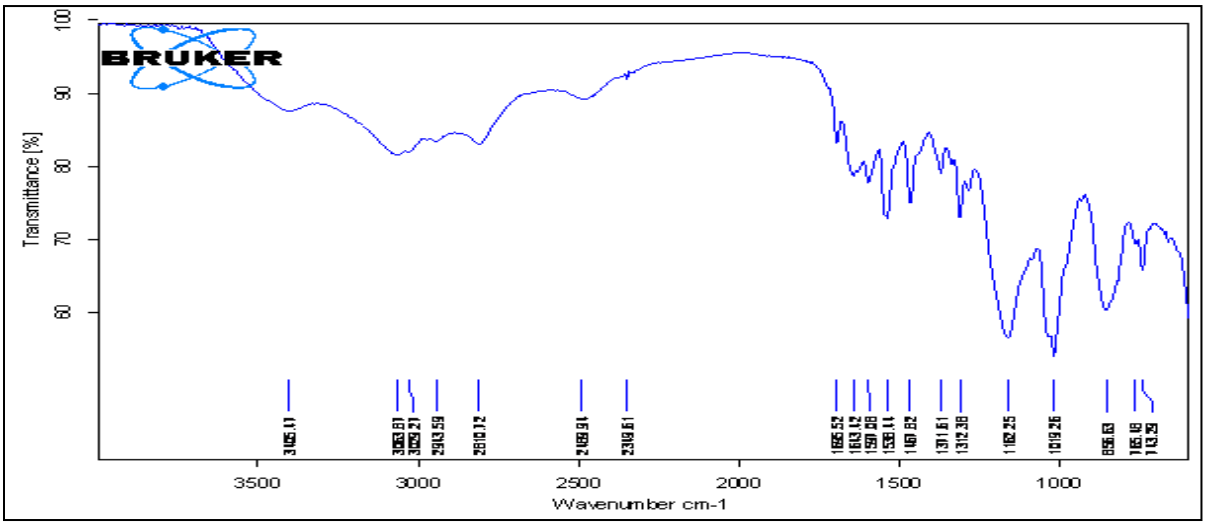

Figure 1: FT-IR Spectrum of Pure Drug (Tazarotene)

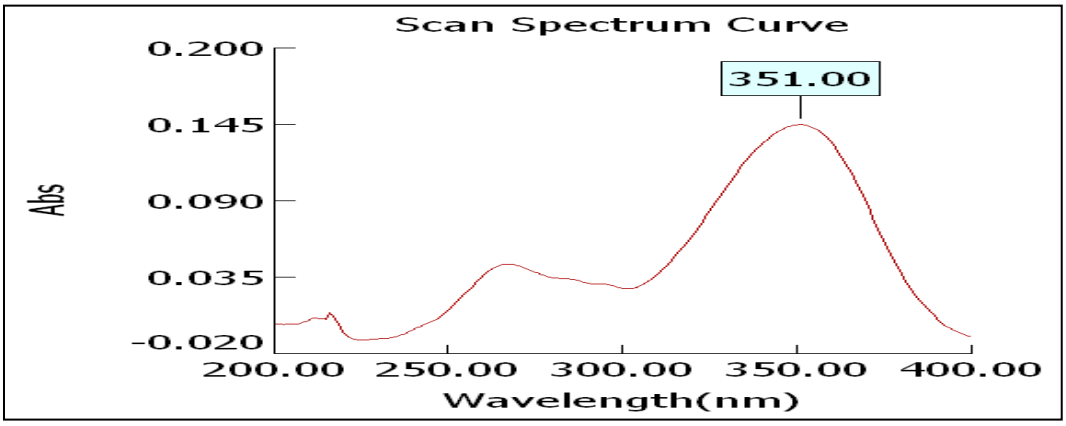

Figure 2: Wavelength maxima of tazarotene in phosphate buffer pH 7.4

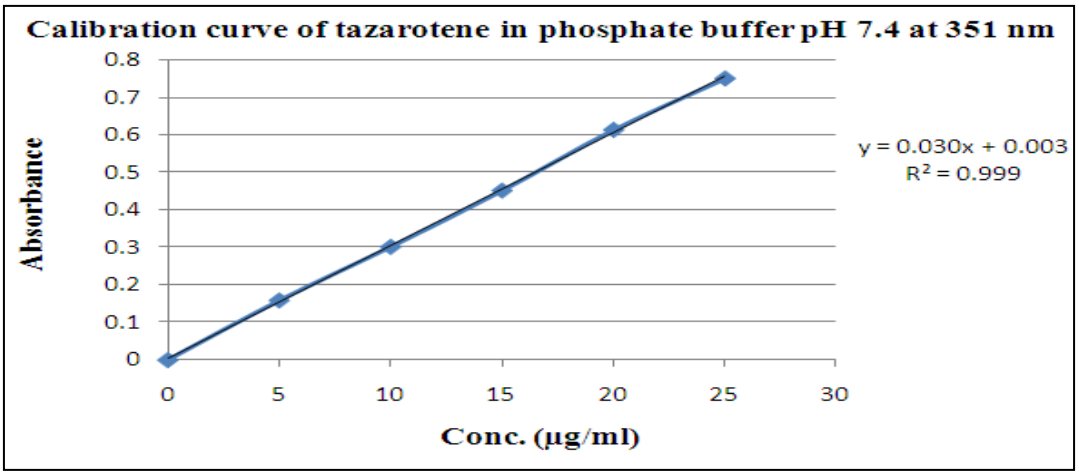

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Figure 3: Calibration curve of tazarotene in phosphate buffer pH 7.4 at 351 nm

Table no. 1: Composition of niosomes by varying amount of lipid

Components	Formulation code					
	F1	F2	F3	F4	F5	F6
Drug (mg)	100	100	100	100	100	100
Span 20 (mg)	50	100	150	200	250	300
Phosphatidylcholine	50	50	50	50	50	50
Cholesterol (mg)	10	20	30	40	50	60
Chloroform (ml)	10	10	10	10	10	10
PBS (7.4) (ml)	20	20	20	20	20	20

Table 1: Evaluations of niosomes for vesicle size and entrapment efficiency

Formulation	Vesicle Size (nm)	Entrapment efficiency (%)
F-1	230.56 ±4.56	65.65±0.25
F-2	223.40 ±5.69	81.78±0.45
F-3	242.56 ±6.98	76.69±0.85
F-4	270.569±7.45	72.65±0.75
F-5	285.658±8.98	68.98±0.45
F-6	295.658±7.45	60.25±0.56

Table No. 2: Results of niosomes gel formulations

Code	Drug content (%)	pH	Spreadability (Gm.cm/sec.)	Viscosity (cps)
F-2(0.5)	99.25 ±0.027	7.0±0.021	23.75±0.075	6589±32
F-2(1.0)	98.68 ± 0.021	7.2±0.040	24.08±0.042	6895±24
F-3(2.0)	96.56 ± 0.017	7.3±0.060	20.75±0.059	72587±25

Table no. 3: *In-vitro* drug release data for optimized formulation F-2(0.5)

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
1	1.000	0.000	20.250	1.306	98.694	1.994
2	1.414	0.301	38.690	1.588	98.412	1.993
3	1.732	0.477	55.650	1.745	98.255	1.992
4	2.000	0.602	69.960	1.845	98.155	1.992
6	2.449	0.778	85.650	1.933	98.067	1.992
8	2.828	0.903	95.690	1.981	98.019	1.991

*Average of three readings

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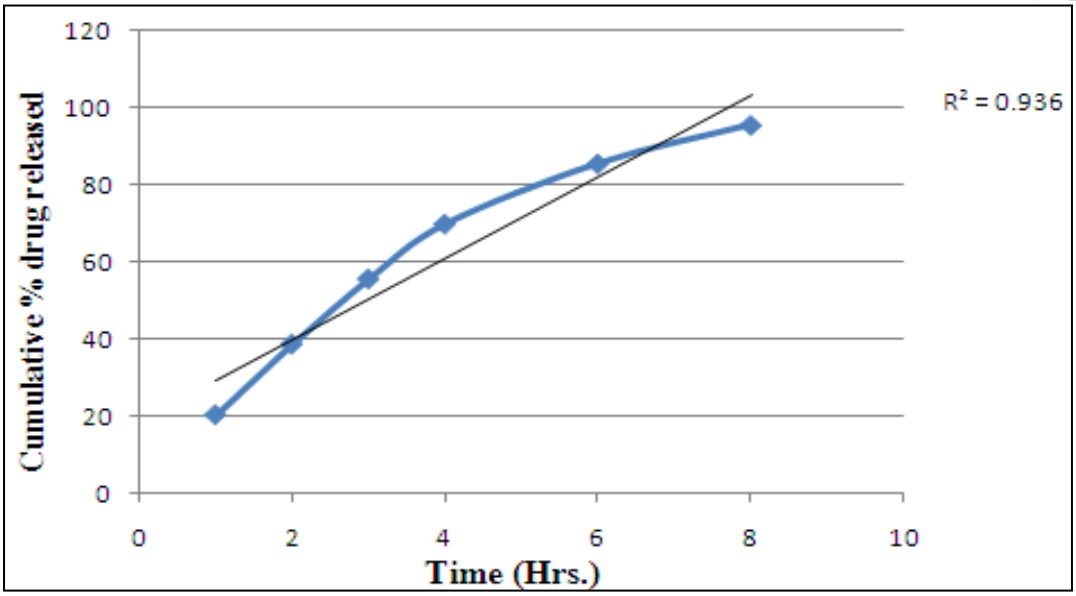

Figure 4: Cumulative % drug released Vs Time

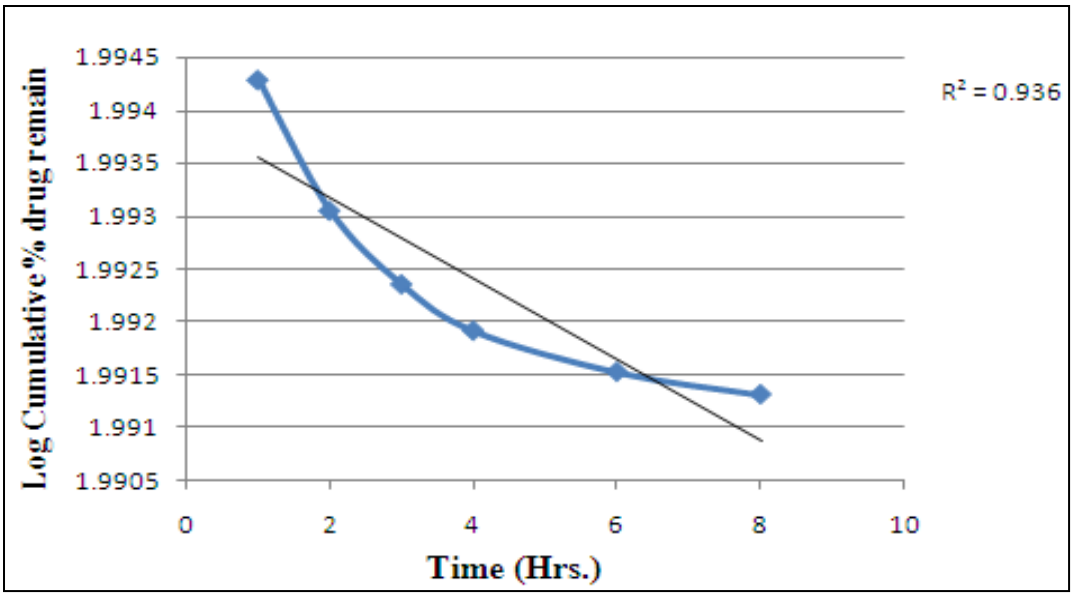

Figure 5: Log cumulative % drug remaining Vs Time

Table 4: Regression analysis data of niosomes gel formulation

Batch	Zero Order	First Order
	R^2	R^2
F1	0.936	0.936