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FORMULATION AND EVALUATION OF PRONIOSOMAL GEL FOR DOXYCYCLINE

km saman Fatma[1*], Mrs. priyanka Maurya[2], Dr .Jai Narayan Mishra[3]

[1*]km Research scholar kailash institute of pharmacy and management, Gida Gorakhpur Uttar Pradesh
[2]Associate Prof. Dept of pharmaceutics, Kailash institute of pharmacy and management, Gida , Gorakhpur Uttar Pradesh
[3]Director kailash institute of pharmacy and management Gida Gorakhpur Uttar Pradesh

***Corresponding Author:** km Saman Fatma
***** Research scholar kailash institute of pharmacy and management, Gida gorakhpur Uttar Pradesh

Abstract
Proniosome gels' gives beneficial outcomes on degenerative joint sickness, there is a ton of interest in their utilization in transdermal drug conveyance frameworks. The reason for the ongoing review was to make and portray a proniosome of the NSAIDS drug, Doxycycline which might ship these prescriptions to the objective site all the more successfully and furthermore settle the issue with oral medicine organization. The viability of proniosome as another lipid for the effective dissemination of Doxycycline has been evaluated in the ongoing examination. By changing the convergence of phospholipids, cholesterol, Tween 60, and ethanol, and ph buffer7.4, proniosomes were upgraded. The plan of proniosome containing ethanol, cholesterol, and soy lecithin was moved along. Results: The best outcomes were gotten utilizing the F4 plan, which created round, unilamellar vesicles with a smooth surface when described. Proniosomes have been proposed as viable transporters for the skin organization of the medicine Doxycycline.

Keyword: Proniosomal gel, antifungal drug, topical drug delivery.

INTRODUCTION:

A solid micro biome can then decolonize when a few terrible microscopic organisms are hindered as a component of a microbiological way to deal with periodontal therapy.[1] Antimicrobial prescriptions can be directed in different techniques, including water system, washing, foundational organization, and nearby application utilizing supported and controlled conveyance gadgets. Through foundational conveyance, the antibacterial medication can arrive at all oral and periodontitis locales. [2,3] Antimicrobial sub gingival water system has had commonly sure outcomes when utilized in mix with high beginning medicine focuses in pockets. Negatives incorporate their little medication repository and water system frameworks' outstanding energy, which abbreviate the time expected for compelling drug fixation.. [4] On the grounds that early exploration on privately given antibiotic medication was promising, different anti-infection agents in a scope of various vehicles were likewise researched with an end goal to track down supported discharge conveyance procedures for periodontal treatment. Antimicrobial mixtures have been incorporated into gels, glues, films, strips, polymers, and filaments for nearby controlled drug discharge into periodontal pockets.[5] New vesicular prescription conveyance methods have altogether worked on in the area of

nanotechnology. These frameworks have been generally utilized for various applications, including drug focusing on, controlled delivery, and saturation increase of the meds

Proniosome is a water-solvent, surfactant-covered transporter framework that, when upheld by water, rapidly changes over into noisome [8].Its size is substantially more uniform and it looks like ordinary noisome. Subsequently, a proniosome might be a locally productive medication conveyance procedure for the treatment of periodontitis. When fluid dissolvable, like water, is added to proniosomes, which are anhydrate and free-streaming, they break down and make various lamellar noisome, a sort of suspension that is great for oral administration. Proniosomes have been demonstrated to be more powerful for neighborhood conveyance of medications, particularly lipid-solvent medications, than other conveyance frameworks including noisome, liposome, transferosomes, and Ethosomes.

By limiting the downsides of proniosome drug conveyance frameworks and having actual advantages such medication focusing on, it brings extensively more to the table. drug saturation expansion, controlled discharge, Minimal expense of plan, an extensive timeframe of realistic usability A more powerful pharmacological attack at a designated organ happens over the long run and results in expanded drug entrance.

Moreover, moves initiated to diminish actual security, for example, the combination of medication excipient, Programming interface, and medication, and the collection spilling of all excipient Extra benefits are its sans dry streaming structure, stockpiling sedimentation, and Greater dependability during disinfection and capacity, simple portion dissemination, and transport. Everybody upholds expanding bioavailability and remedial viability [9]. Simple to gauge, measurements, and disseminate poisonous; more steady away; liberated from microorganisms; increments bioavailability. Proniosomal gel is a straightforward, fluid vesicular bilayer lamellar gem. It is made by blending a non-ionic surfactant, lecithin, and cholesterol in dry proniosomes with a little measure of a gel-framing specialist or water.

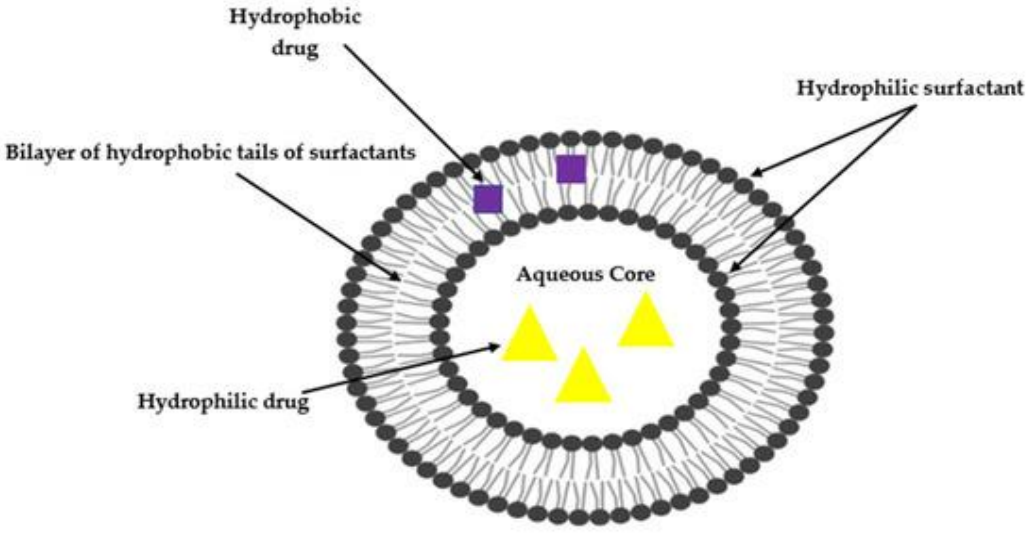


Fig 1. Structure for Proniosome

Also better than the Noisome are the Proniosomes. [11] Proniosomal drug conveyance framework: Proniosomes vary essentially from ongoing medication conveyance frameworks in that they capability as medication repository frameworks and have a proclivity for the objective situation because of their masterpiece of cholesterol and surfactant.[12]However, there are as yet significant issues with medicine conveyance by means of liposome and noisome.

Because of their synthetic and actual security, liposome are powerless to troubles such hydrolysis, oxidation, sedimentation, collection, and combination. Different issues incorporate sanitization, enormous scope assembling, and capacity issues. [13,14]

It is a dry, free-streaming detailing of a surfactant-covered transporter that might be momentarily rehydrated in steaming hot water or a cushion answer for make a multi-lamellar Noisome suspension that can be taken orally or controlled in other ways.[15] An enormous assortment of dynamic synthetic compounds might be moved utilizing these versatile conveyance strategies.[16]

There are two types of proniosomes based on the carrier and preparation method.

1. Liquid crystalline proniosomes:

- These proniosomes are designed as drug reservoirs for transdermal delivery and this patch consists of an aluminum foil as a backing material, and a plastic sheet is used. On the spherical plastic sheet, a Proniosomal gel is uniformly applied, and the nylon mesh is placed on top.

2. Dry granular proniosomes:

- Maltodextrin-based proniosomes: Maltodextrin serves as the carrier for proniosomes of this sort that likewise occur in a dry granular form.
- Sorbitol-based proniosomes: Sorbitol serves as the carrier for these proniosomes, which are in a dry state. They have a non-ionic surfactant coating that makes them easily dissolve in warm water.

ADVANTAGE

- ❖ Proniosomes provide several advantages, including ease of dosing, storage, transportation, and delivery.
- ❖ Proniosomes offer a solution to overcome issues related to physical stability such as fusion, sedimentation, and leakage during storage.
- ❖ Proniosomes enable drug delivery with improved bioavailability and reduced side effects.
- ❖ They can effectively encapsulate both hydrophilic drugs.
- ❖ The presence of non-ionic surfactants and phospholipids in proniosomes can act as penetration enhancers and aid in the distribution of the medication.
- ❖ They prevent the hydrolysis of encapsulated drugs, which can limit the shelf life of the dispersion.
- ➢ Not only do proniosomes offer a promising approach for drug delivery, but they can also enhance the recovery rate of the skin barrier.[16]

MATERIALS AND METHODS:

Doxycycline was politely provided by Yarrow Chemical Goods. In MUMBAI Central Drug House, we purchased soy lecithin. The lipid crystal-like was supplied by SDFCL Fine-Chem. Limited, the ethanol by Central Drug House, the Carbopole 934 by Carbopole 934, and the Triethanolamine by Central Drug House.

Coacervation Phase Separation Method

To do this, precisely gauged volumes of the medication, lipid stage, and surfactant were set in a spotless, dry glass vial with a wide mouth that could hold 5.0 ml, and 3 ml of liquor was likewise added. A glass bar was utilized to consolidate all the material completely. The glass vial was then warmed over a water shower at 60–70°C for about 5 minutes to completely dissolve the prescription in the surfactant combination. The open end of the glass vial was then secured with a lid to prevent dissolvable disaster. Then, until a workable arrangement was reached, the mixture was warmed over a water shower while containing 2 ml of the fluid stage phosphate support, pH 7.4.

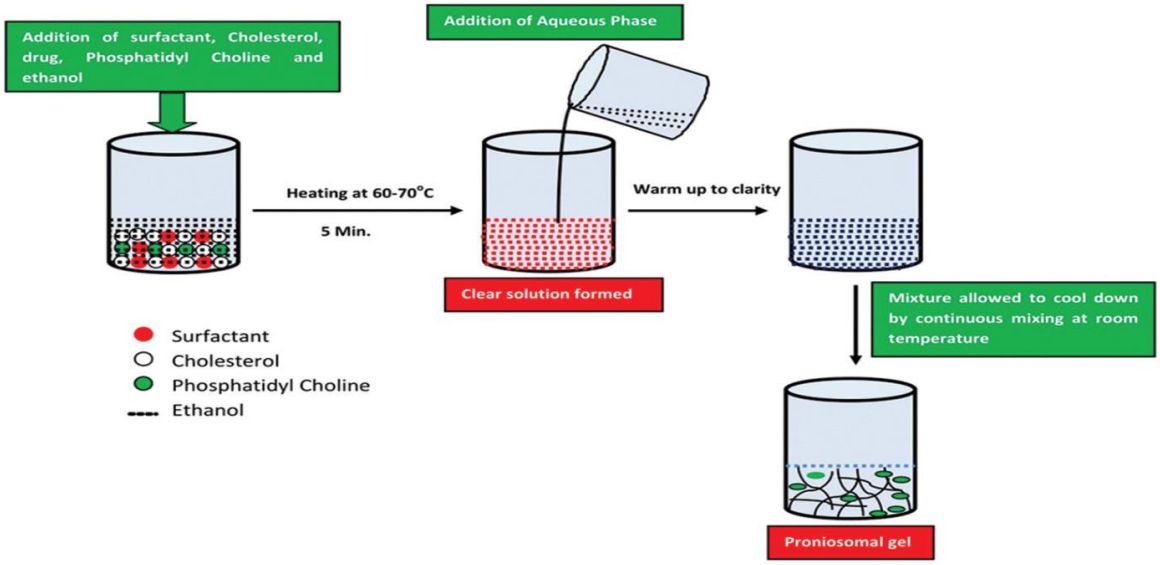


Fig . 2. Step in coacervation phase method

Table. 1 . Formulation Design

code	Doxycycline	Spane20	Spane60	Tween20	Tween60	cholesterol	Soyalecithine	Ethane	Ph buffer
F1	50mg	1.9mg	1.7mg	1.9mg	1.7mg	100mg	2.0mg	4ml	2ml
F2	50mg	2.0mg	1.7mg	2.0mg	1.7mg	100mg	1.9mg	3ml	2ml
F3	50mg	1.6 mg	1.7 mg	1.8mg	1.8mg	100mg	1.8mg	4ml	2ml
F4	50mg	1.8mg	1.8mg	1.8mg	1.8mg	100mg	1.8mg	3ml	2ml

preparation of Proniosomal gel

structure Proniosomal gels for Doxycycline Proniosomes were made using the coacervation stage partition technique F4 [17] with a couple of changes utilizing different Tween series surfactants. the parts of a few Proniosomal plans. The surfactant, cholesterol, and 3 ml of outright ethanol were consolidated in a receptacle before 50 mg of Doxycycline was added. The receptacle was then fixed with a cover to forestall dissolvable misfortune, and it was warmed in a water shower for five minutes at 55 to 60 degrees Celsius while being shaken to guarantee that the cholesterol had been all disintegrated. Subsequent to warming in the water shower for 3-5 minutes, ph support 7.4 2ml (55-60°C) was added to make an unmistakable or clear solution.[18] Until the scattering transformed into gel, the blend was permitted to cool at room temperature. All together work on ensuing characterization, the subsequent gels were kept in a similar shut receptacle.

METHODOLOGY:

Melting point: The USP procedure was used to ensure that the melting point was determined. The medication was put into a thin, cylindrical container in a little amount. The device for measuring the melting point was then placed into the container. The temperature inside the device was gradually raised, and both the temperature at which the medicine completely dissolved .

Determination of pH : A digital pH meter was used to determine the pH of Doxycycline.

Solubility studies: solubility is the new bond formation between the solute molecules and solvent molecules.

Determination of partition co-efficient: In an isolating pipe, 20 ml of n-octanol and 20 ml of phosphate cradle pH 7.4 were combined with the known dosage of Doxycycline. Then, two stages were allowed to equilibrate at 60-70^{0}C for 2 hours while being shaken intermittently. After vital deterioration, UV spectroscopic technology at λmax 363 nm did not completely seal the

centralization of medication in the watery stage and natural stage. The clear parcel coefficient was determined as the proportion of medication focus in each stage by the accompanying condition -
K p = Organic/ Caqueous
$O_{rganics}$ concentration of drug in organic phase A_{queous} is concentration of drug in aqueous phase

Fourier Transform Infra-Red (FTIR): A procedure used to get an infrared range of ingestion or outflow of a strong, fluid, or gas. At the point when IR radiation is gone through an example, some radiation is consumed by the example and a few goes through.

Evaluation of Doxycycline Proniosome
SEM: Examining Electron Microscopy, or SEM investigation, gives high-goal imaging valuable to assessing different materials for surface breaks, imperfections, impurities or erosion..

TEM: Transmission electron microscopy (TEM) is a microscopy strategy wherein a light emission is sent through an example to shape a picture.

Drug content: A particular amount (100 mg) of Proniosomal scattering was taken and broken up in 100ml of phosphate cradle of pH 7.4. The volumetric flagon containing scattering was shaken for 2hr on mechanical shaker to get total dissolvability of medication. This arrangement was separated and assessed spectrophotometrically at 248nm utilizing phosphate cushion (pH 7.4) as clear
***In vitro* release studies**: This study was performed by dialysis film strategy. Into 50ml container disintegration medium (100ml) was set. The container was put on an attractive stirrer at temp 37±5º. One finish of the dialysis layer was fixed in which liposome detailing was filled and fixed. The dialysis layer containing test was suspended in the medium from which 5ml of aliquots were removed at explicit time period which was promptly supplanted with same amount of new medium. The aliquots was estimated for how much medication by utilizing spectrophotometer.

Evaluation of Doxycycline Proniosomal gel:
Ph determination: The pH of the gel was determined by digital pH meter
Viscosity: Consistency is estimated utilizing a Swamp channel, a cone shaped molded pipe, fitted with a little drag tube on the base end through which mud streams under gravity head

Homogeneity and grittiness: proniosome gels set in straightforward measuring glasses were tried for homogeneity by visual investigation. It was likewise tried for their appearance what's more, presence of any totals. Proniosome gels were assessed minutely to actually take a look at the presence of any noticeable particulate matter.

Spreadability: One of the measures for an effective plan to meet the ideal characteristics is that it ought to have great Spreadability. It is the term communicated to mean the degree of region to which definition promptly spreads on application to skin or impacted part**.**

In vitro drug release of Proniosomal gel: Drug release was check by using diffusion cell with egg membrane.

RESULT AND DISCUSSION:
Pre formulation study:
Melting Point: The melting point of a drug lowering by cause an increase in its solubility in the SC and ultimately its permeation across the skin Normal melting point for Doxycycline201˚C.
Solubility: the solubility of Doxycycline found to be water, chloroform, ethanol, methanol Ether etc.

Table.2. Solubility studies are performed to determine the solubility of the drug in different solvent

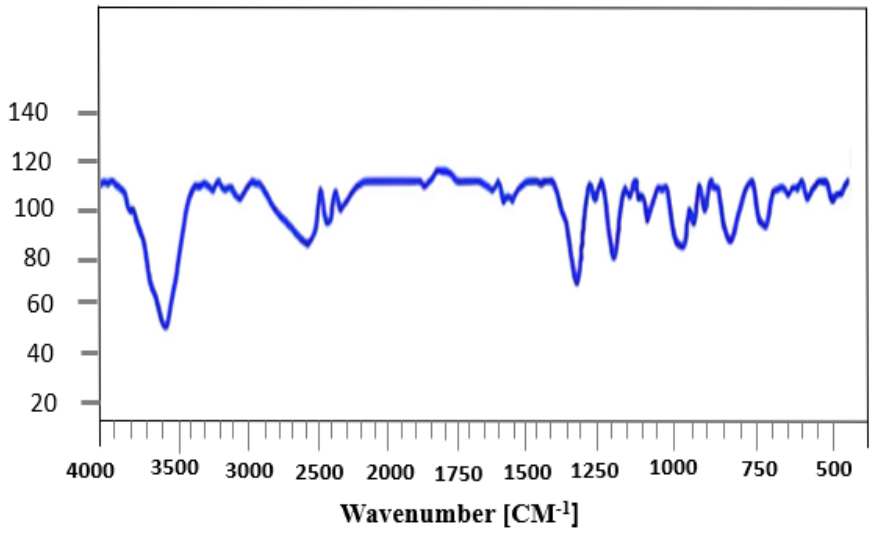
SNO	COMPOUND	SOLUBILITY
1	Chloroform	Insoluble
2	Water	Freely soluble
3	Ethanol	Freely soluble
4	Ether	Freely soluble
5	Buffer	Freely soluble

Partition coefficient:

In a solution with n-octanol and water, the Doxycycline partition coefficient is calculated. Shaking is used to combine the two phases in a separating funnel at a 1:1 volume ratio. Following separation, 10 milligram's of the medication are added to a mixture and shaken in the separating funnel for 5 minutes. The mixture is then allowed to sit undisturbed for 24 hours. The drug's partition coefficient, abbreviated "K O/W," is then determined by centrifuging the organic and aqueous phases and analyzing each one individually.

FTIR (FOURIER TRANSFORM INFRARED):

A. DRUG (DOXYCYCLINE)



FTIR (FOURIER TRANSFORM INFRARED)

Fig.3. Doxycycline

B. DRUG (DOXYCYCLINE)

Table no. 3. Doxycycline

Peak no.	Frequency cm^{-1}
1	3710
2	3222
3	2810
4	2500
5	1670
6	1423
7	1221
8	1125
9	1000
10	783
11	749

B. DOXYCYCLINE+LECITHIN

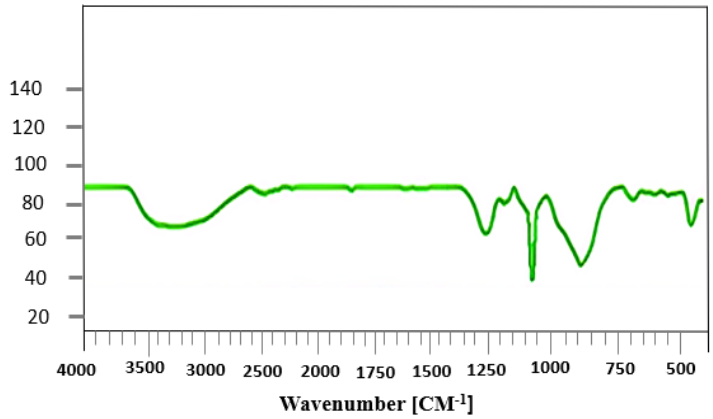


Fig.4. Doxycycline +lecithin

Table .4. Doxycycline+ lecithin

Peak no.	Frequency cm^{-1}
1	3422
2	3240
3	2838
4	2500
5	1970
6	1724
7	1249
8	980
9	749

C. DRUG+SPAN 20+TWEEN 20 + CHOLESTROL+ETHANOL+DW

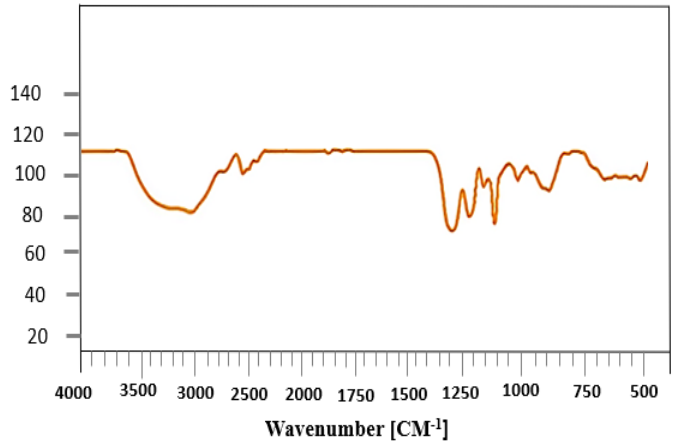


Fig.5 . Doxycycline+ span 20+tween 20 + cholesterol +ethanol+ DW

Table.5. Doxycycline+ span 20+tween 20 + cholesterol +ethanol+ DW

Peak no.	Frequency cm^{-1}
1	**3429**
2	**3231**
3	**1249**
4	**1145**
5	**770**
6	**560**

D. DRUG+SPAN 60+TWEEN 60 + CHOLESTROL+ETHANOL+DW

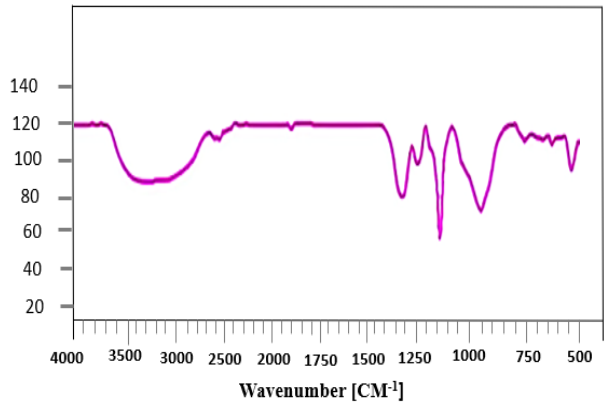


Fig no.6. Doxycycline+ span 60+tween 60 + cholesterol + ethanol+ DW

Table no .6. Doxycycline + span 60+tween 60 + cholesterol+ ethanol+ DW

Peak no.	Frequency cm^{-1}
1	3352
2	1248
3	1130
4	790
5	560

Evaluation Of Proniosomal

SEM: Scanning electron microscopy is a powerful imaging technique that may be used to examine the topography and morphology of a wide range of materials. It makes it possible to examine structures at the micro- and nanoscale and provides images with excellent depth of field.

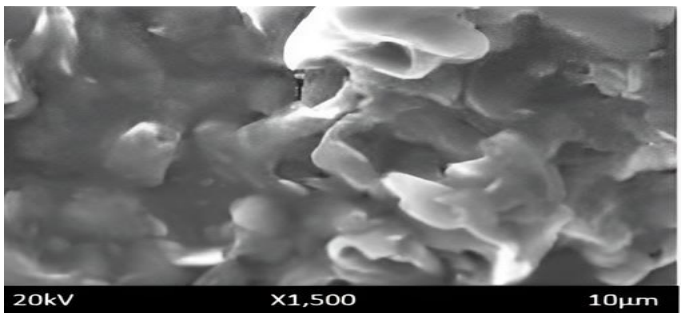


fig.7. Scanning electron microscopy for Proniosomal gel

TEM: A potent imaging method that enables high-resolution visualization of the internal structure and ultrafine features of specimens is transmission electron microscopy (TEM). It creates a picture by using an electron beam that is passed through an incredibly thin sample, revealing details about the sample's composition, morphology, and crystallography.

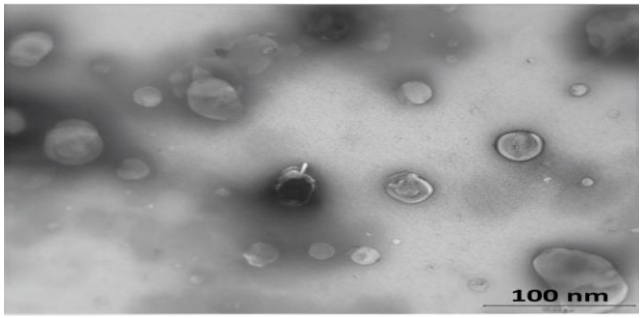


Fig.8. Trans electron microscopy for Proniosomal gel

Drug content: Proniosomes equivalent to 100 mg were taken in a standard volumetric flask. They were lyses with 50 ml ethanol by shaking for 15 min. The solution was diluted to 100 ml with methanol. Then 10 ml of this solution was diluted to 100 ml with saline phosphate buffer at certain pH 7.4.

In vitro release studies: In vitro drug: Doxycycline, which is a second-age antibiotic medication with wide range antimicrobial, antimalarial and mitigating exercises

Table no.7. In Vitro Drug Release

S NO	TIME INTERVAL OF PERCENTAGE YIELLD				
	Time	**F1**	**F2**	**F3**	**F4**
1	15 min	0.05	0.1	0.15	0.22
2	30min	0.13	0.2	0.29	0.37
3	45min	0.19	0.29	0.39	0.48
4	1 hours	0.26	0.36	0.46	0.55
5	2 hours	0.30	0.42	0.52	0.59
6	3 hours	0.32	0.47	0.55	0.61

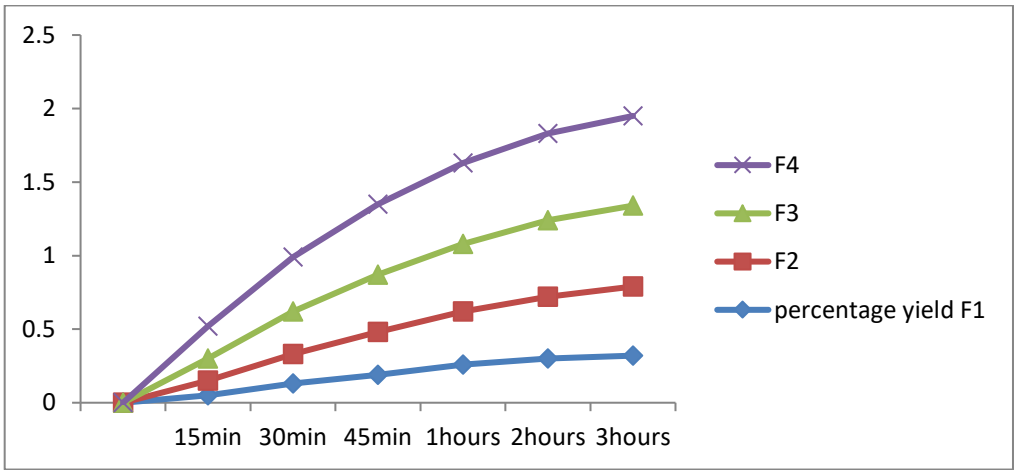


Fig. 9. Release profile of Doxycycline loaded Proniosome

Evaluation of Proniosomal gel

Ph determination: The pH of upgraded Proniosomal definition was viewed as 6.6 that suits the skin pH, showing skin similarity.

Viscosity: The thickness of the Proniosomal gels was not set in stone by Brookfield viscometer with axle no. 64, turned at 5 rpm for 5 min at 25 °C temperature. Viscosity of various formulated gels was found in the range of 234-275 centipoises

Homogeneity and grittiness: The liposomal gel was very smooth in texture.

Spreadability: The Spreadability study of the prepared gel was good.

In vitro drug release: In-vitro discharge study was performed by utilizing diffusion cell device and egg film. Egg film was isolated by putting the egg shell in combination of water and hydrochloric corrosive in which the shell is broken down to calcium chloride with bubbling of carbon dioxide. Prior to commencement of study. The egg film was absorbed phosphate cradle for 24 hours. Around 1g of Proniosomal gel was set in the benefactor compartment cylinder and spread over the egg film which was braced at the end of the cylinder. The acceptor compartment comprises of phosphate cradle (pH 7.4).

Table no.9. Drug Release Formulation

Time	F1
15 min	7.67
30min	31.45
45min	53.37
1 hours	66.81
2 hours	81.11
3 hours	87.32
4 hours	89.9
5 hours	91.3
6 hours	93.8
7 hours	97.2

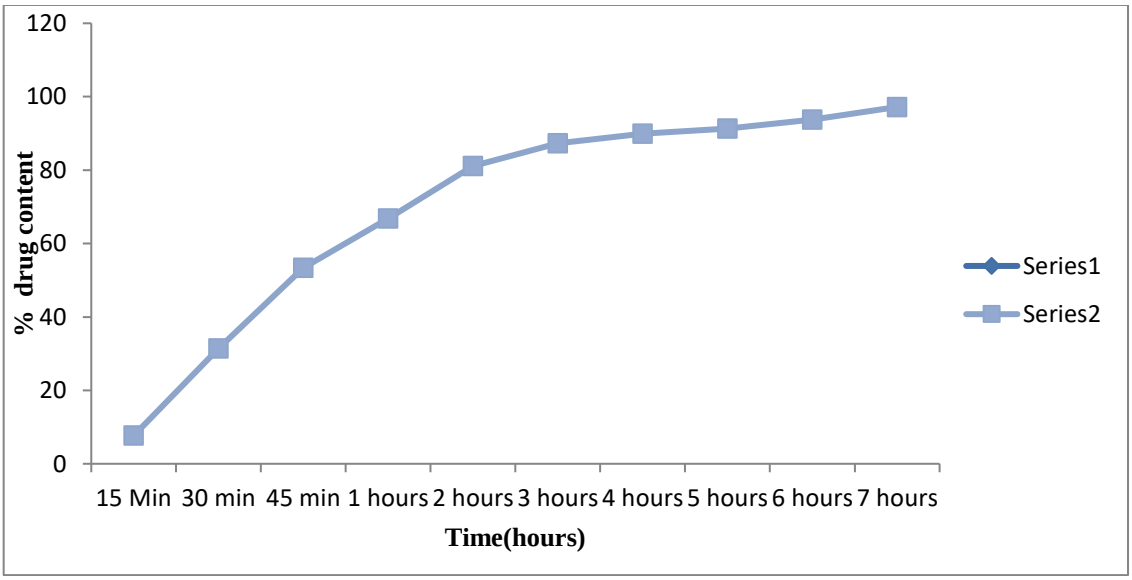


Fig no.10.drug release formulation

CONCLUSION:

As indicated by the discoveries, Doxycycline Proniosomal gel definitions might be utilized for transdermal organization of antifungal infection prescription. Noisome could be supplanted by the dry Proniosomal definition, which has impressive potential. Doxycycline Proniosomal gel has been made with drugs to upgrade treatments, lessen harmfulness, and lift adequacy in the therapy of issues .skin inflammation contamination, ophthalmic issues, and skin issues dermatology, immunization adjuvant, and disease treatment are fields where proniosome are progressively utilized on a more regular basis. Because of various revelations, the utilization of proniosome has prompted drug gathering at sickness destinations and decreased dissemination to delicate tissues. As another age of proniosome secrecy proniosome have been utilized in an assortment of remedial applications. proniosome with further developed drug conveyance to illness locales because of their capacity to remain available for use for delayed timeframes are progressively acquiring clinical acknowledgment.

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