Proniosomal Gel: Formulation and Charecterization of an Antifungal Drug (Butenafine Hcl) Loaded Proniosomes for Topical Delivery

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Received: 9 December 2019 Accepted: 1 January 2020 Published: 15 January 2020

Abstract

The present proniosomal gel investigation was aimed to minimize the adverse effects associated with present topical butenafine hydrochloride formulations and made to enhance its bioavailability and sustained release by novel proniosomal drug delivery system. Butenafine hydrochloride is an allylamine class of advanced antifungal drug. Which mainly recommended to treat long term topical fungal infection. Proniosomes were prepared by slurry method using different concentrations of non-ionic surfactant (span and tween) and evaluated various parameter like surface morphology, entrapment efficiency, drug content, viscosity, drug content, in-vitro

Index terms— butenafine hydrochloride, fungal infection, proniosomes, slurry method, in-vitro diffusion studies, antifungal activity

1 Introduction

he main target of drug therapy is to provide therapeutic amount of drug concentration to proper site in the body to produce desired therapeutic efficacy. Now a days in the field of pharmaceutical industries are put great efforts towards the prefabrications of existing drugs and their delivery systems, to break the problem related to poor solubility, Author ?: Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B.G Nagara, Mandya-571448, Karnataka, India. e-mail: rajustyle28595@gmail.com stability, toxicity, bioavailability, dosage problem etc. 1 Topical administration is a preferable route for direct, local therapy, in that it is Non-invasive and is directly applied to the invading site and reduces systemic adverse effects. However, it is not possible to use all types of drugs (antifungal drugs) through transdermalroute. 2 The drawbacks of topical antifungal formulation such as cream, lotions, spray etc. may include difficult to apply in deep dermatophytic infections, inadequate amount leads poor response, inability to apply difficult to reach area such as natal cleft, low effectiveness, redness of skin, stinging and burning sensations as side effects. 3 Various attempts have been made to improve the skin permeation of drugs like use of permeation enhancers, electroporation, microneedles, needleless injection, thermophoresis, etc. But these methods damaging the protective barrier function of the skin and may cause irritation or other skin problems. 4 Hence, to overcome the problems associated with topical antifungals formulations, this study is intended to formulate novel drug delivery system such as Proniosomal gel for topical administration with model anti-fungal drug, in order to enhance skin permeation as well as to sustain the drug release for prolonged period of time. 5 There are many novel drug delivery systemshave been investigated by pharmaceutical scientists to fulfil these criteria and considerations for topical delivery of drugs. In that nanocarrierssuch asProniosomescan make their way easily to hair follicles and they may show accumulation between corneocytes, skin having high lipid content so it can easily combining with lipidic layer, Proniosomes also have the capability to control/sustain the drug release, which reduces the side effects and dosing frequency of drugs. ? Proniosomes reduces the physical stability problems of niosomes such as fusion, aggregation, leaking on storage.

? It also controls hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

? The entrapment of both hydrophilic and hydrophobic drugs can be done easily by this vesicular system. 8 ? Sustained and controlled release of drugs can be done due to depot formation.

? More stable and Ease of use. ? It leads to ease the transportation, better size distribution and storage uniformity of dose.

? These formulations are biodegradable, biocompatible and non-immunogenic to the body. 9 Butenafine hydrochloride is a synthetic benzylamine antifungal agent. It is indicated for the topical treatment of the following dermatologic infections: Interdigital Tinea pedis (athlete's foot), Tinea corporis (ringworm) and Tinea cruris (jock itch) due to E. floccosum, Tinea mentagrophytes, T. rubrum, and T. tonsurans, tinea (pityriasis) versicolor due to M. furfur. 10 Butenafine Hcl is a synthetic antifungal agent that is structurally and pharmacologically related to allylamine antifungals. The exact mechanism of action has not been established, but it is suggested that butenafine's antifungal activity is exerted through the alteration of cellular membranes, which results in increased membrane permeability, and growth inhibition. Butenafine is mainly active against dermatophytes and has superior fungicidal activity against this group of fungi when compared to that of terbinafine, naftifine, tolnaftate, clotrimazole, and bifonazole. It is also active against Candida albicans and this activity is superior to that of terbinafine and naftifine. Butenafine also generates low MICs for Cryptococcus neoformans and Aspergillus fumigatus as well. 11 The aim of the current study was to develop a topical formulation which would be effective against transdermal fungal infection as well as overcome the drawbacks of current topical/ oral therapy. The butenafine hcl loaded proniosomal gel formulation is prepared by slurry method with some modifications. The formulations are evaluated for its vesicle size, entrapment efficiency (EE), viscosity, spreadability, skin permeation, and stability.

2 II.

3 Materials and Methods

Materials and sources: Butenafine hydrochloride were supplied as a gift sample by Glenmark Pharmaceuticals Ltd. Mumbai. Cholesterol and soya lecithin were purchased Yarrow chem products, Mumbai, India. Span-60, Tween-60 were purchased from SD fine Chem. Ltd. Mumbai, India, Chloroform and Ethanol Merck Specialties PVT. LTD. All other chemicals and reagents used were of analytical grade and were used without further purification.

4 Methods:

Characterization of drug and other excipients: Characterisation was done by Fourier transfer infrared spectroscopy (FT-IR) (Make: Brukers alpha t-series, Software: Opus) of butenafine hydrochloride and other was performed.The drug and excipients were kept in 1:1 ratio at 5°C in refrigerator to observe any reaction which may take place between drug and excipients. The mixtures of samples were analysed by FT-IR after one month along with standard drug and excipients as the reference.

5 Procedure for preparation of proniosomes

The current proniosomes were prepared by adopting slurry method using maltodextrin as carrier. The composition of different proniosome formulation were prepared by using various non-ionic surfactants and cholesterol in different molar ratios and drug is represented in Table-01. The solvent such as chloroform and ethanol (2:1) were used to dissolve ingredients. The physical mixtures and solvent were mixed thoroughly in the beaker using sonicator/ glass rod. Then, an accurately weighed amount of maltodextrin was added slowly to above resultant solution with continuous stirring to obtain slurry, otherwise it forms clump mass because maltodextrin was water soluble. Additional quantity of solvent was added to form slurry, in case of lower surfactant loading. The obtained solution was immediately transferred to round bottomed flask and attached to rotary flask evaporator to evaporate solvents at temperature 45± 2ºC, 60-70 RPM and reduced pressure 600-700mm of Hg respectively. After complete removal of solvent from the flask, thin layer of proniosomes was obtained. Then, further dried overnight in a desiccator (containing cacl 2 / silica) under vacuum at room temperature to get dry, free-flowing proniosomal powder. The obtained proniosomes was stored in a tightly closed container at 4ºC until further evaluation. The composition of different proniosomal formulations were represented in Table -01.

Proniosomes were transformed into niosomes by hydrating using phosphate buffer (pH 6.8), the niosomes were sonicated twice for 2 min. usinga sonicator. These niosomes were used in the formulations of gels. 12

6 Preparation of butenafine hydrochloride proniosomal gel

Butenafine hydrochloride proniosomal gel was prepared by using 1% w/w of Carbopol-940 as a gel base. Carbopol-940 was soaked overnight in 100ml distilled water then mixed with niosomal suspension and required quantity of preservatives (methyl/ propyl paraben) were added.Triethanolamine was added drop wise to the formulation for an adjustment of required skin (pH5.8-6.0) and also to obtain gel at required consistency. The prepared butenafine hcl. proniosomal gel was stored in the refrigerator until further evaluation studies. 13 The photomicrography was carried out using optical microscope. A dry Proniosomes were hydrated using saline buffer pH 6.8, then

drop of suspension were mounted on glass slide and observed under the microscope with magnification of 40X for morphological observation. The photomicrograph of the preparation obtained from the optical microscope by using a digital SLR camera.

7 ii. Morphology study by Scanning electronic microscopy (SEM)

The sample of proniosomes is placed in an evacuated chamber and scanned in a controlled manner by an electronic beam. The dried proniosomes were mounted on to stubs by using double-sided adhesive carbon tape. Then proniosomes were analyzed after gold sputtering to yield a gold film of 30 nm thickness. In the SEM (Joel, JSM-5600LV, japan), interaction between electronic beam and vesicles produces a variation in the physical phenomenon that can be obtained in the form of images. These obtained images usedfor surface characteristics. 14 iii. Particle size analysis Particle size analysis was carried out using optical microscope. The optical microscope was fitted with a stage micrometer to calibrate the eyepiece micrometer. A dry Proniosomes were hydrated usings a line buffer pH6.8 or NaCl then drop of suspension were transferred onto a clean glass slide and observed under the microscope. Before placing the cover slip sample was dispersed uniformly with the help of a brush, size of 100 niosomes from the batch were measured in terms of eyepiece division. 15

8 b) % Entrapment efficiency

To determine the % EE, 20mg of Proniosomes were taken in beaker and was dissolved in 20ml of cosolvents of Ethanol and buffer pH 5.8. The free butenafine hydrochloride was separated from proniosomes by ultra-centrifugation (Eppendorf centrifuge 5430 R) at a speed of 14000 RPM for 30-45 min. at 4 0 C. after centrifugation 1ml of supernatant was taken and observed at 223nm using UV spectrophotometer (shimadzu-1800), to determine the amount of free drug in the formulations. 16

9 c) Viscosity and pH studies

Viscosity of the prepared proniosomal gel is evaluated by using Brookfield viscometer (model-DV2TRVTJ0) with spindle No. RV-07(7) at 100 rpm. 100 g of the proniosomal gel was taken in a beaker and the spindle was dipped in it. The viscosity of gel was measured at temperature of 25°C. The readings of 03 were taken for average ofsamples then calculate the viscosity.

The pH of each formulation was measured using a calibrated digital pH meter. The readings were taken for average of 3 samples. The normal range of topical gel pH is 5.5-8 respectively. 17

10 d) Spreadability

For the determination of spreadability, excess of sample was applied between the two glass slides and was compressed to uniform thickness by placing 1000 gm weight for 5 min. Weight (50 gm) was added to the pan. The time required separating the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spreadability (S). The standard range of gel spreadability is 8.4-15gm.cm/sec. respectively. 18 Spreadability (g.cm/s) (S) = M×L/T Where M = weight tied to upper slide, L = length moved on the glass slide, T= time taken.

11 e) In-vitro drug release studies i. Method for egg membrane preparation

The contents of egg shells were removed and then it was dipped in the dilute hydrochloric acid (0.1N) for 30 min. The egg membrane was separated manually and washed thoroughly with distilled water. 19 ii. Drug release studies

In vitro release studies were carried out using Franz diffusion cells with a receptor compartment volume of 20 mL and an effective diffusion area of 3.14 cm 2 . Egg membrane was used as diffusion membrane. A predetermined amount of gel containing proniosomes was placed on the donor compartment and 20ml of freshly prepared phosphate buffer of pH 5.8 is placed in receptor compartment. The receptor medium was continuously stirred using magnetic stirrer at37±0.5ºC. At predetermined time intervals, 0.1 mL samples were withdrawn from the receiver compartment and replaced with an equal volume of fresh buffer. The collected samples were analyzed at 223 nm by using UV spectrophotometer. 20 f) In-vitro antifungal studies 9.75gm of Potato dextrose agar was taken in a 250 mL conical flask and dissolved in 250 mL of distilled water. The medium was sterilized in an autoclave at 15 lbs for 30 min. After sterilization, the medium was kept aside at room temperature. Then medium was poured into sterilized Petri dishes to get 3-4 mm depth uniformly in front of laminar airflow unit. After solidification, a loop of diluted suspension culture (Candida albicans) in nutrient broth was added on to the surface of solidified agar and was spread homogeneously with the help of L shape rod. After stabilization of culture, Gels of known concentration along with pure drug were fed into the petridish with the help of sterile disk. Then Petri dishes were incubated for 48 h at 37 °C. After incubation the zone of inhibition was measured. 21

12 g) Stability studies of the most satisfactory formulation

Optimized formulations of butenafine loaded proniosomal gel were subjected to accelerated stability testing as per ICH guidelines for short term and placed in a screw capped glass container and stored at ambient humidity conditions and temperatures 40°C (75 ± 5RH) for a period of 30 days. The samples were analyzed for physical appearance, pH, drug content, and in vitro drug release at regular interval of 30 days. 22 IV. Particle size has increased with increase in concentration of polymer, with constant drug load and concentration of other agents. However, size was reduced with increase in concentration of surfactant and mean size of particles depends upon on the rotational and temperature of the rotavapor. The results of particle size of each formulations were found to be 33.85-40.03?m and tabulated in table no. 02.

13 Result and Discussion

14 b) % Entrapment efficiency

Entrapment efficiency was found to increase with increase in polymer (cholesterol) Concentration. Increase in size of proniosomes with increase in concentration of polymer and drug has resulted in increase in drug entrapment efficiency and also improves the stability of the bilayer membrane of the vesicles. Cholesterol decreases leakage of drug molecule from bilayer vesicle structure and also provides spherical smooth surface to the bilayer vesicles.

Entrapment efficiency of proniosomes formulations ranged from 64.41% to 79.87%. niosomes formed from span 60 proniosomal gel exhibits higher EE than other surfactant formulations (i.e. span 40, tween 60). Span 60 is solid at room temperature and have highest phase transition. Span 60 is having the same head group with different alkyl chains and might lower the HLB value and thus increases the EE of the drug. Formulation F3 containing span 60: cholesterol in 1:2 ratio showed highest EE (79.87%) and tabulated in table no. 02.

15 c) pH and Viscosity

The pH values exhibited by gels are tabulated in table no. 03 and found in range of 5.40 to 6.11 at 25 0 C which is physiologically acceptable range for topical preparations.

The viscosity of the proniosomal gels were found in range 8920-14400 at 25 0 C, as concentration of Carbopol used in all the formulations is same (1%). The results of viscosity of each formulation were tabulated in table no. 03. when using spindle no. 07 respectively.

16 d) Spreadability studies

Spread ability of the different proniosomal gel formulations were determined and tabulated in table no. 03.The spread ability range of gel were found to be 16.40-22.19 gm.cm/sec.

17 e) In-vitro drug release studies of the proniosomal gel

The release studies were carried out for all the butenafine hcl loaded formulations. The formulation which shows the percentage of drug release maximum at 30 hrs. was considered as optimum. The percentage drug release of all prepared formulation is compared with optimized formulation (F3 The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F1-F9 could be best expressed by first order equation as the plots showed highest linearity (R 2 :0.340-0.395), then zero order release kinetics (R 2 :0.977-0.997).The release data of the optimal batch showed F3 value of 0.997 and 0.395 for the zero order and first order respectively. The formulations were observed to yield correlations with Higuchi model i.e. R 2 =0.994 thus indicating the diffusion mechanism. The 'n' values obtained Korsmeyer-peppas model of F-3 was 0.443 which indicates that drug release swelling and mechanism of release was Anomalous (non-Fickian) diffusion. The in-vitro antifungal activity of formulation was studied by cup plate method. Results of the in-vitro antifungal activity are shown in table-06. The zone of inhibition is more observed in butenafine hcl loaded proniosomal gel formulation (F3) compared to other formulation and pure drug was taken as a standard. The marketed product (Butop-1% cream) showed less zone of inhibition compared to optimized proniosomal gel formulation (F3). From the experimental outcome, it was concluded that prepared proniosomes gel formulation exhibited promising antifungal activity. The stability studies of the formulation were carried out according to ICH guidelines. The optimized formulations i.e. (F3) were subjected to stability studies @ 40°C (75 ± 5RH) for a period of 30 days. The physical stability was assessed by the pH, drug content, and % invitro drug release. The stability studies showed that there were no significant changes in the abovementioned response variables. Thus, it can be concluded that the drug was found to be stable on storage.

18 Conclusion

Result of the present study indicates that prepared butenafine loaded proniosomes gel formulation is an alternative route for transdermal drug deliveryto treat fungal infection. Proniosomes were prepared by slurry method using different concentration of cholesterol, surfactants, and soya lecithin etc. The prepared proniosomes were evaluated for % entrapment efficiency, spreadability, viscosity and % drug content. The values obtained were found to be

satisfactory and complies with standard range. The in-vitro drug release was found to increase with increase in cholesterol (polymer) concentration and decreased with increase in surfactant concentration. In that F3 formulation exhibited highest drug release (75.46%) compared to other formulations over a period of 30 hours. The in-vitro antifungal activity study was concluded that proniosomal gel formulation with drug (F3) shows better zone of inhibition than the other formulations and marketed product. Stability studies demonstrated there was no significant variation in pH, drug content and % in-vitro drug release and found to be stable at the end of storage period (30days).From the above experimental data, it can be concluded that the transdermal delivery of butenafine Hcl loaded proniosomal gel formulations can be used in the future for treatment of fungal infection with improved bioavailability. [1] [2] [3]

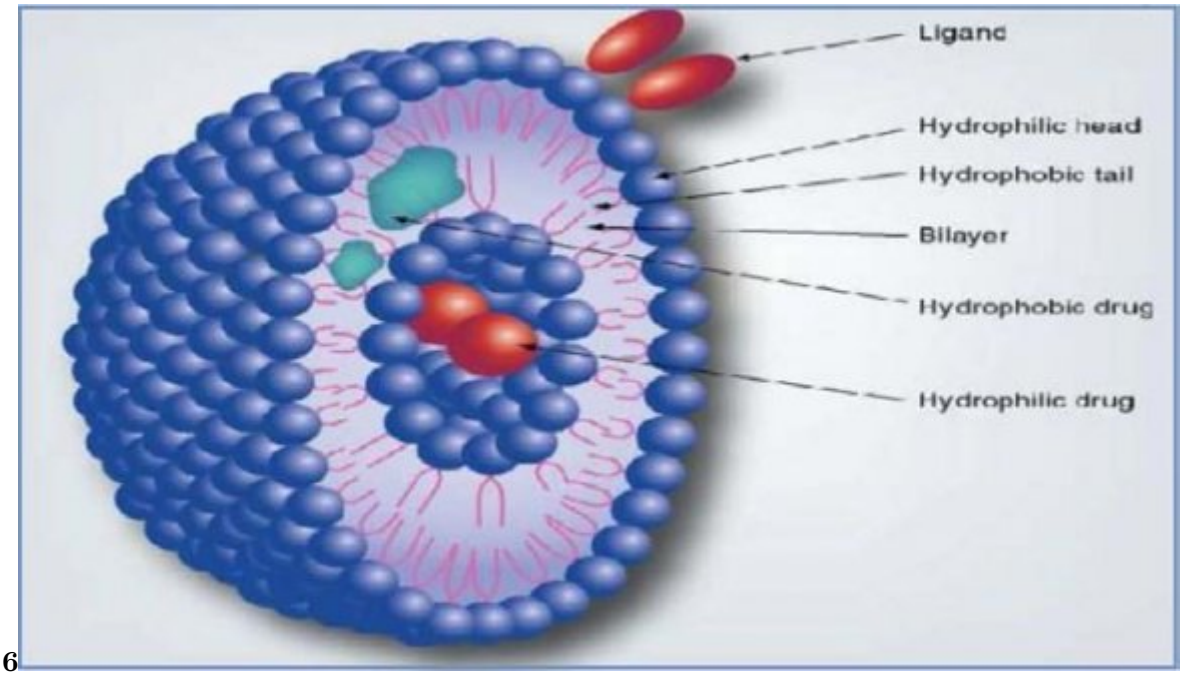

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Figure 1: 6

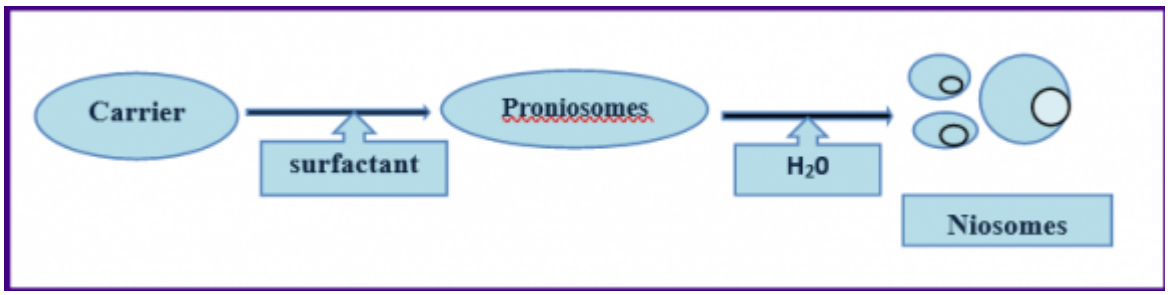

Figure 2:

[1]Proniosomal Gel: Formulation and Charecterization of an Antifungal Drug (Butenafine Hcl) Loaded Proniosomes for Topical Delivery

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[3]Proniosomal Gel: Formulation and Charecterization an Antifungal Drug (Butenafine Hcl) Loaded Proniosomes for Topical Delivery

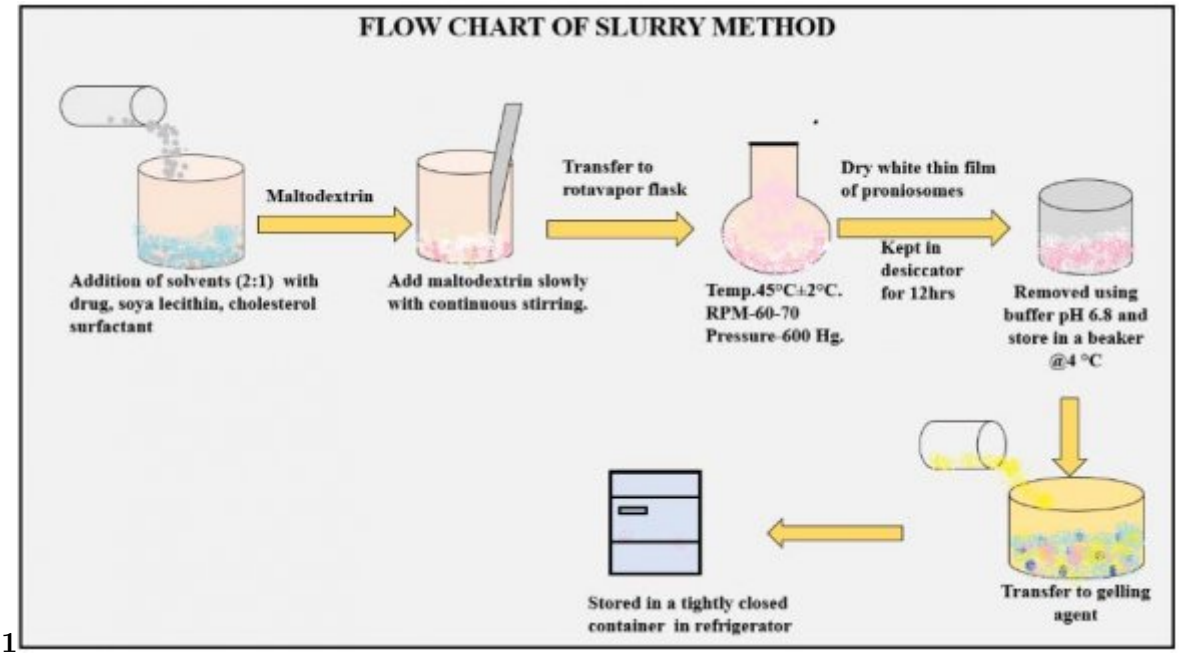

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Figure 3: Figure 1 :

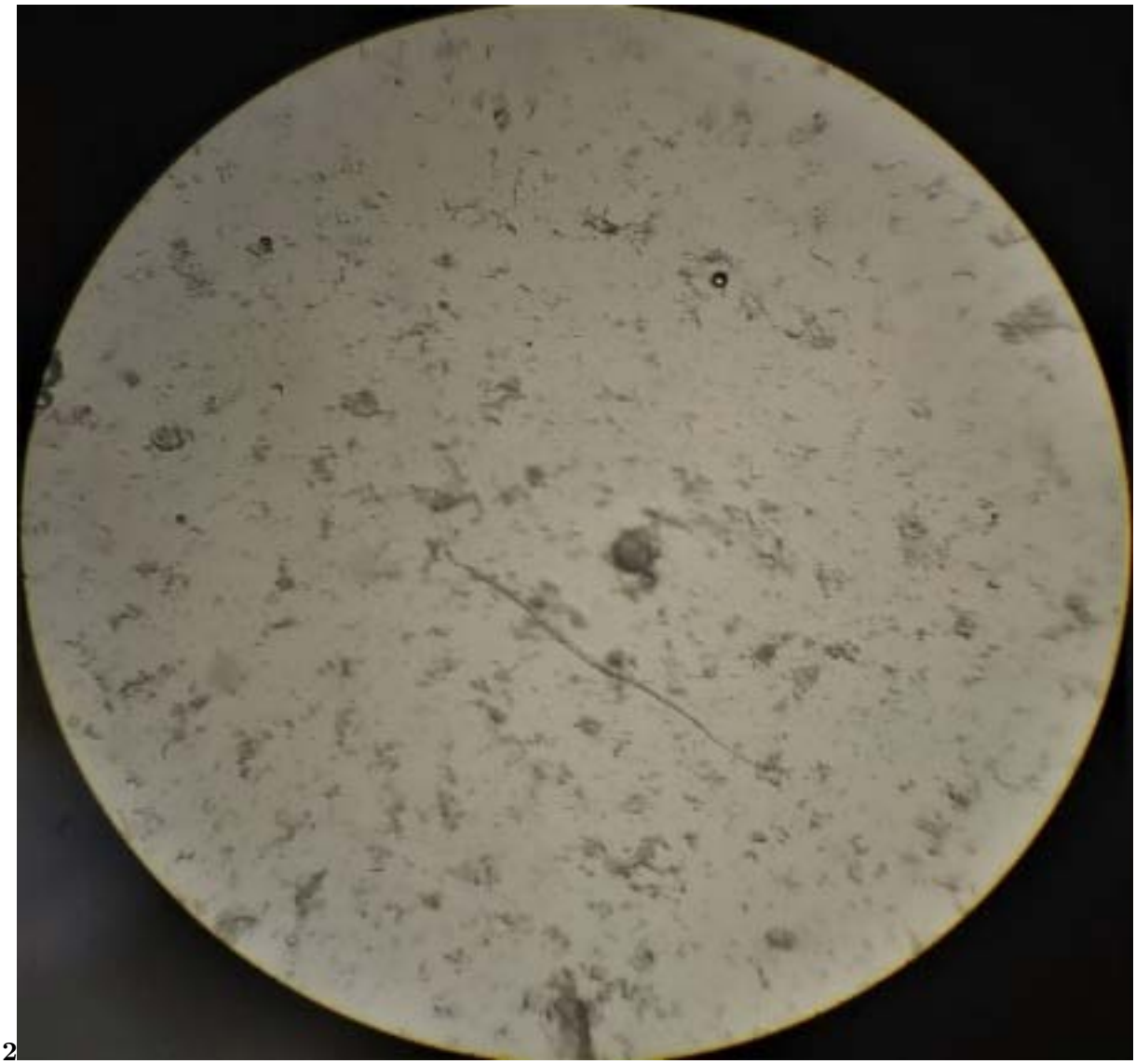

Figure 4: Figure 2 :

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Figure 5: Figure 3 :Figure 4 :

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Figure 6: Figure 5 :

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Figure 7: Figure 6 :

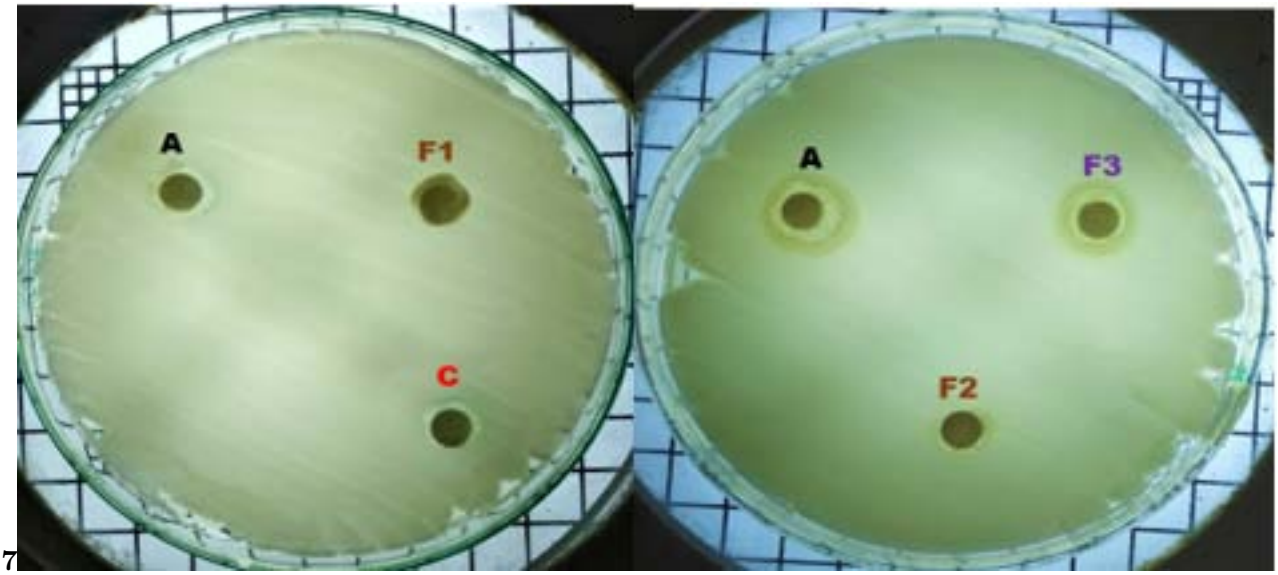

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Figure 8: Figure 7 :

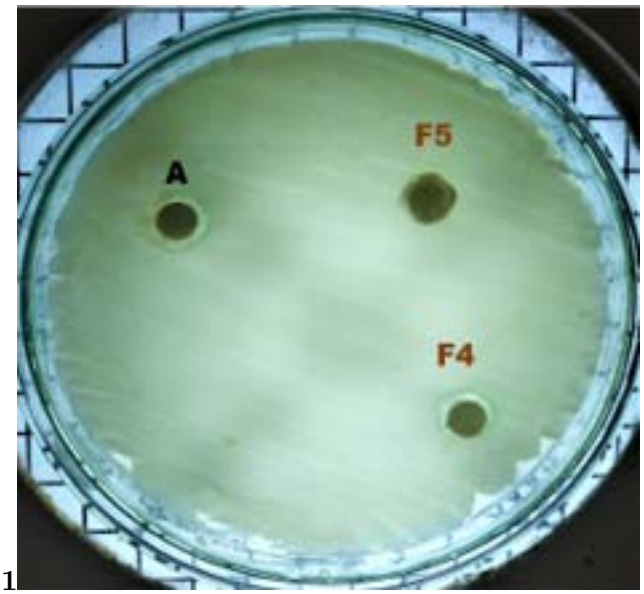

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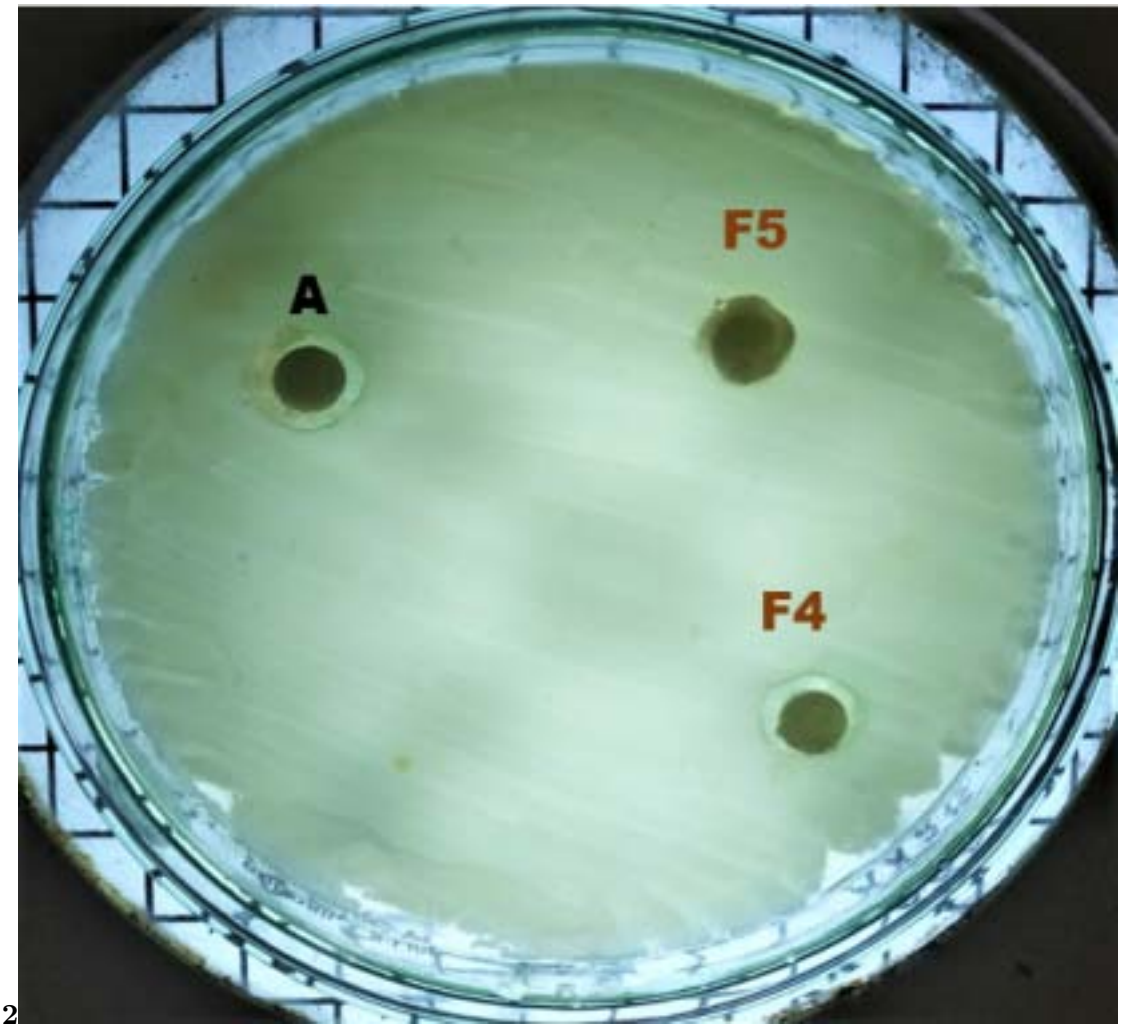
Figure 9: Figure 9 :Figure 10 :Figure 11 :



12

Figure 10: Figure 12 :

1

Excipients							
Formulation code		Drug Bute-nafine Hcl (mg)	Soya lecithin (mg)	Maltodextrin (mg)	*Surfactants (mg)		*Cholester (mg)
					Span 40	Span 60	tween60
	PF1	20	100	500	100	-	-	100
	PF2	20	100	500	200	-	-	100
	PF3	20	100	500	100	-	-	200
	PF4	20	100	500	-	100	-	100
	PF5	20	100	500	-	200	-	100
	PF6	20	100	500	-	100	-	200
	PF7	20	100	500	-	-	100	100
	PF8	20	100	500	-	-	200	100
	PF9	20	100	500	-	-	100	200

*Surfactant: cholesterol-(1:1), (2:1), (1:2) ratios respectively.
Solvents: -Chloroform: Ethanol (2:1)-PF1-PF9
III. Evaluation Studies of Proniosomal Gel

[Note: B a) Characterization of Proniosomes i. Photomicrography]

Figure 11: Table 1 :

2

SL. NO.	FORMULATION	VESICLE PARTICLE SIZE (µm)	% ENTRAPMENT EFFICIENCY
1	F1	35.69 ± 1.56	69.01 ± 2.71
2	F2	34.15 ± 1.45	71.34 ± 1.21
3	F3	40.03 ± 0.14	79.87 ± 1.93
4	F4	36.60 ± 1.81	64.41 ± 3.10
5	F5	34.74 ± 2.11	70.53 ± 1.58
6	F6	38.81 ± 0.56	72.32 ± 2.17
7	F7	33.85 ± 1.54	73.87 ± 3.89
8	F8	35.15 ± 2.21	65.37 ± 0.98
9	F9	37.80 ± 2.92	77.64 ± 1.89

Figure 12: Table 2 :

3

FORMULATION	MEAN pH	VISCOSITY (CPS)	SPREADABILITY (gm.cm/sec)
F1	5.69±0.04	8,920±0.02	17.40
F2	5.55±0.02	9,960±0.01	21.27
F3	5.97±0.02	13,960±0.03	16.76
F4	5.84±0.04	10,920±0.01	18.80
F5	5.40±0.03	11,680±0.04	22.19
F6	5.47±0.02	12,360±0.03	17.25
F7	6.11±0.01	9,800±0.05	21.26
F8	6.00±0.02	13,360±0.02	19.03
F9	5.93±0.01	14,400±0.01	16.40

Figure 13: Table 3 :

4

). The prepared

Figure 14: Table 4 :

5

Formulation	Zero order kinetic	First order kinetics	Higuchi's model	Korr'speppas Model	n value
F1	0.991	0.373	0.989	0.916	0.416
F2	0.989	0.382	0.986	0.929	0.412
F3	0.997	0.395	0.994	0.985	0.443
F4	0.985	0.377	0.991	0.929	0.426
F5	0.983	0.371	0.987		0.404
F6	0.994	0.366	0.991	0.983	0.422
F7	0.945	0.369	0.990	0.920	0.397
F8	0.977	0.340	0.981	0.918	0.401
F9	0.995	0.393	0.993	0.984	0.441

Figure 15: Table 5 :

6

SL.NO.	FORMULATION	ZONE OF INHIBITION (mm)
1	Pure drug	18±0.04
2	Marketed product (butop-1%)	12
3	F1	-
4	F2	3
5	F3	16
6	F4	8.5
7	F5	-
8	F6	9.5
9	F7	-
10	F8	7.6
11	F9	14.5

Figure 16: Table 6 :

7

Sampling Interval (days)	pH	Storage condition 40 0 C±20C /75% RH±5%RH Drug content	% in-vitro Drug release
0	5.97±0.02	99.13±2.13	75.46±0.62
30	5.93±0.01	98.91±1.12	74.78±0.91
V.			

Figure 17: Table 7 :

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