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FORMULATION AND EVALUATION OF FILM FORMING GEL CONTAINING AYCLOVIR NIOSOMES

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ABSTRACT

Acyclovir is anti-viral drug used for treatment of various viral skin infection. In the present study film forming gel loaded with acyclovir Niosome was formulated. Acyclovir being BCS class 3 drug has less permeability that's the reason to formulate drug Niosome. The Niosome are prepared by thin film hydration method using cholesterol and varying concentration of surfactant span 60(1:1, 1:2, 1:3). The solvent used here is chloroform. The evaluation tests for Niosome like Particle size analysis, *In-vitro* permeation study, and entrapment efficacy are performed. Film-forming gel was prepared by using pH sensitive gelling agent like Carbopol. PVP and PVA as film forming agents, the triethanolamine is used for neutralization. Various evaluation tests are performed. Among Niosome formulation the F1(1:1) was found to be best contributing to optimum vesicles size of 824nm, highest *in vitro* permeation of 86.16±0.45% after 8hr and satisfactory entrapment of drug. Gel was also subjected to physical examination, drying time, pH, Spreadability, extrudability, film thickness, *In-vitro* release profile evaluation parameter. The gel shown satisfactory physical properties, *In-vitro* permeation after 6hr was found to be 57.19±0.26%, drying time of the film also aids in patient compliance. So the Niosome prepared by using the acyclovir, cholesterol, span 60(1:1:1) gave best results and gel prepared by Carbopol 934 as gelling agent with PVP and PVA as film formers produced expected outcome.

KEYWORDS: Acyclovir, Viral skin infection, Niosomes, Film-forming gel, *In-vitro* permeation, Film hydration method.

INTRODUCTION

Herpes simplex virus (HSV) is a common infection with two types: HSV-1, causing oral symptoms, and HSV-2, linked to genital symptoms. While not life-threatening, it can worsen if untreated. Diagnosis involves physical exams and swab tests. Symptoms like blisters, lesions, and eye infections often lead patients to seek treatment to alleviate severity and duration.[1] The skin, covering about 2 square meters and receiving one-third of the body's blood flow, is the most accessible organ. Drugs are administered through the skin for either topical treatment of skin conditions or transdermal absorption into systemic circulation.[2] The film-forming system is a novel alternative to traditional topical and transdermal formulations. It creates a film on the skin after application, containing both the drug and excipients. As the solvent evaporates, a film forms, which can either be a solid polymeric matrix for sustained drug release or a liquid film absorbed into the skin.[3] Film-forming gels create a thin, transparent film on the skin, offering a more aesthetically pleasing alternative to traditional semisolid products. They are non-sticky, adhere well, and provide sustained drug release, reducing reapplication frequency. The film forms as the volatile components evaporate, leaving a residue on the skin.[4] Niosomes are non-ionic surfactant vesicles with bilayer structures that can encapsulate both hydrophilic and lipophilic drugs. They are made from various surfactants, including non-ionic types like Tweens and Spans, cationic surfactants like Cetrimide, and anionic ones like sodium dodecyl sulfate, combined with cholesterol. Spans are particularly favored for commercial use due to their safety and widespread use as emulsifiers in food and pharmaceuticals.[5] Acyclovir, chemically known as 2-

amino-1,9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one, is used to prevent and treat infections caused by Herpes simplex (HSV) and Varicella-Zoster virus (VZV). As an antiviral agent, it integrates into viral DNA, inhibiting synthesis. Converted to acyclovir triphosphate by enzymes, it blocks DNA replication and viral replication. This synthetic purine nucleoside analog inhibits HSV-1, HSV-2, and VZV both in vitro and in vivo.[6] Acyclovir's oral absorption is dose-dependent and variable, with bioavailability ranging from 10% to 30%. Oral use can also cause side effects like nausea, diarrhea, rash, and headache. To address these issues, efforts have focused on developing a transdermal formulation for prolonged systemic delivery.[7] Topical acyclovir (ACV) faces challenges due to low transdermal penetration and poor solubility. To enhance its efficacy, strategies like chemical modification, liposomes, and nanoparticles have been explored. This experiment focuses on formulating a film-forming gel with Carbopol as a gelling agent, incorporating acyclovir-loaded Niosomes, to improve the treatment of Herpes simplex and other viral infections.[8]

MATERIALS AND METHODS

Materials: Acyclovir, Polyvinyl alcohol, Polyvinyl pyrrolidine, span 60, Tween 80 and cholesterol, Methanol, carbopol934, Triethanolamine.

Methods

Preformulation studies[9,10]

A. Organoleptic properties

Using descriptive terms, the color, order, and taste of Acyclovir were assessed and noted.

B. Determination of melting point

The melting point of acyclovir was determined using the capillary method. A small amount of acyclovir was placed in a capillary tube, which was then inserted into an electrically operated melting point apparatus. The temperature at which the drug melted was recorded, and the measurement was repeated three times to calculate the average value.

C. Solubility

To determine the solubility of acyclovir, the drug was dissolved in water and phosphate buffer at a pH of 6.8. An excess amount of acyclovir was added to 10 mL of the solution. The mixture was then stirred at 37.0°C for 12 hours using a water bath shaker. After stirring, the sample was filtered and subjected to spectrophotometric analysis. The resulting data was used to construct a graph for calculating the concentration of acyclovir.

2. Determination of λ max of Acyclovir in PBS pH 6.8

A standard stock solution of acyclovir was prepared by dissolving 100 mg of acyclovir in 100 mL of phosphate-buffered saline (PBS) with a pH of 6.8. Further dilution was performed by taking 10 mL of this stock solution and diluting it to 100 mL with PBS pH 6.8. The diluted solution was then scanned using a UV-Visible spectrophotometer to determine the maximum absorbance (λ max).

3. Preparation of standard plot of Acyclovir in PBS pH 6.8

The UV spectrophotometric estimation method was used to prepare a standard plot for acyclovir. Initially, 100 mg of acyclovir was dissolved in PBS with a pH of 6.8, and the volume was adjusted to 100 mL to achieve a concentration of 1000 µg/mL. This solution was labeled as Stock A. From Stock A, 10 mL was pipetted and diluted to 100 mL with PBS pH 6.8, resulting in a concentration of 100 µg/mL, and labeled as Stock B. Aliquots of Stock B (0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL, and 1 mL) were then pipetted and diluted up to 10 mL with PBS pH 6.8 to obtain concentrations of 2 µg/mL, 4 µg/mL, 6 µg/mL, 8 µg/mL, and 10 µg/mL, respectively. The absorbance values of these solutions were recorded against PBS pH 6.8 as the blank.

FORMULATIONS OF ACYCLOVIR CONTAINING NIOSOME[5,11]

The niosomal formulations were prepared by using the thin film hydration method. Precise amounts of drug (60 mg), non-ionic surfactant (Span 60), and cholesterol were dissolved in an adequate volume of chloroform to produce a clear solution. The resulting solution is transferred into a 1000 ml rotary evaporator flask and evaporated under vacuum (20-25 mm Hg) at 60°C ± 2°C, with a rotation speed of 60 rpm, to create a uniform thin dry film. The flask is then removed from the bath and allowed to cool to room temperature. The thin film was hydrated with 10 ml of PBS (pH 6.8) containg 2%W/V Tween 80 while gently rotating the flask at 50 rpm and maintaining a temperature of 60°C ± 2°C. Subsequently, the mixture was sonicated with a probe sonicator for 5 minute.

CHARACTERIZATIONS OF ACYCLOVIR CONTAINING NIOSOMES

1. Particle size

The vesicle size and size distribution of prepared niosome was determined by using high polarizing microscope. The slide of niosome was prepared and coverslip placed for analysis.

2. Estimation of entrapment efficiency[11]

The entrapment efficiency of the formulations was assessed by centrifuging 1 ml of the suspension diluted to 10 ml with distilled water at 15,000 rpm for 60 minutes at 4°C, using a high-speed cooling centrifuge. This process separated the niosomes from the unentrapped drug. The concentration of free drug in the supernatant was measured at 252 nm with a UV-Visible Spectrophotometer after appropriate dilution. The percentage of drug entrapped in the niosomes was then calculated using the specified formula. Drug entrapment = (Total drug - Drug in supernatant liquid) / Total drug X 100.

3. *Invitro* diffusion study[11]

The *Invitro d*rug release pattern was studied using a cellophane membrane. After separating the non-entrapped drug, the niosomal preparation was placed in an open ended glass tube with one end covered by the cellophane membrane, forming the donor compartment. This tube was then placed in a beaker containing 100 mL of phosphate buffered saline (PBS) at pH 6.8, which served as the receptor compartment. The temperature of the receptor medium was maintained at 37±2°C, and the medium was agitated using a magnetic stirrer at 100 rpm. At predetermined time intervals, 5 mL samples were collected from the receptor compartment and immediately replaced with an equal volume of fresh PBS pH 6.8 to maintain sink conditions. The collected samples were analyzed spectrophotometrically at 252nm using a UV-Visible spectrophotometer.

FORMULATIONS OF ACYCLOVIR NIOSOMES CONTAINING FILM FORMING GEL[12,13]

Film-forming gel were prepared by using Carbopol 934 and hydrated in water for 2 hours, and then niosomes were added to the gel base. A solution of polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) was dissolved in distilled water by heating and stirring until homogeneous. This solution was then mixed with the Carbopol gel. Ethanol, PEG 400, and propyl paraben were added and stirred to ensure uniformity. The gel was neutralized with triethanolamine (TEA) and the volume adjusted to 30g with distilled water. The formulation was stored at 4°C for 24 hours before evaluation. Finally, the properties of the film-forming gel containing acyclovir niosomes were assessed.

CHARACTERIZATIONS OF ACYCLOVIR CONTAINING FILM FORMING NIOSOMAL GEL

a. Physical appearance[14]

The prepared gel formulations were examined for the properties such as clarity, homogeneity, texture and for the presence of foreign particles.

b. Determination of pH[15,16]

The gel pH is determined by dispersing 2.5g of gel in the 25 ml of distilled water and pH meter was used for examination.

c. Determination of viscosity[12]

The Brookfield viscometer used for the determination of viscosity. 10g of gel placed in the beaker and spindle(s-64) was immersed in gel. The spindle rotation was 15 rpm used to determine the gel viscosity.

d. Spreadability[4]

To assess the spreadability, around 1 gram of the gel was positioned between two glass slides of identical dimensions (20 cm x 20 cm). A weight of 1000 grams was applied to the upper glass slide, facilitating the spreading of the gel. After one minute, the weight was lifted, and the diameter of the spread area was recorded.

e. Extrudability[4]

The gel formulations were contained in standard collapsible aluminum tubes, which were subsequently sealed at the end through crimping. The weights of these tubes were documented. The tubes were positioned between two glass slides, and a weight of 1 kg was applied on top of the slides before removing the cap. The extruded gel was collected and weighed, and the percentage of gel extruded was calculated and recorded.

% Extrudability =Initial weight of the tube (g) - Extruded weight (g)/100 Initial weight of the tube (g)× 100

f. drying time[4]

ne gram of gel was spread in a petri dish and placed in a 37°C in hot air oven to dry and form a film. The drying time and film-forming ability were recorded.

g. Film thickness[4]

The film's thickness was measured using a screw gauge. After calibrating the pointer to zero, the film was placed on the anvil, secured, and the measurement was recorded.

h. Drug content[11]

The drug content in the gel was determined by weighing a 10 mg portion of the gel, transferring it to a 100 mL volumetric flask, and adding n-Octanol to disrupt the vesicles. The volume was adjusted to 100 mL with phosphate buffer (pH 6.8) and filtered. From the filtered solution, 5 mL was transferred to a 50 mL flask, and the volume was adjusted with phosphate buffer. The solution was analyzed for drug content using a UV-Visible spectrophotometer.

***i. In-vitro* permeation study[11]**

1g of gel was placed in Franz diffusion apparatus and cellophane membrane used as barrier. Phosphate buffer 6.8 placed in receiving compartment. 1ml aliquotes withdrawn every 1 hr analyzed using UV-Visible spectrophotometer.

RESULTS AND DISCUSSION

1. Pre-formulation studies of drug acyclovir

Organoleptic evaluation

Organoleptic properties like physical appearance, color, odour and of Acyclovir were evaluated. It was found that Acyclovir is a white amorphous powder which is odorless in nature.

Solubility study

Acyclovir was found to be sparingly soluble in water and completely soluble in 6.8 pH phosphate buffer.

Melting point

The melting point of Acyclovir was carried out and found that the drug melted at 256.5°C temperature which is in the reported range of 255°C and thus was within the reported literature limits indicating that the drug is pure.

Standard curve of acyclovir in phosphate buffer of pH 6.8

The absorbance values of pure Acyclovir at different concentration ranges (0.2-1.0 ug/ml) in the PBS (6.8 pH) are scanned at 252 nm.

CHARACTERIZATION OF ACYCLOVIR NIOSOMES

Surface morphology study

The surface morphology of niosome was studies by using optical microscope. Fig no. 01 demonstrates the surface morphology of acyclovir loaded niosomes which indicates the vesicles are where small and round shape.

Average particle size and size distribution

The average particle size of the niosomes were analyzed using High Polarizing Microscopy.

Entrapment efficacy

The entrapment efficacy of the niosomes was analyzed using the centrifugation method, The efficacy ranged from 69-75%, with formulation F3 having the highest drugentrapment compared to F1 and F2.

***Invitro* drug diffusion study**

The *in vitro* diffusion study of all three formulations was conducted using a Franz diffusion cell, with cumulative drug release data. The data showed linear drug release up to 8 hours, with the highest release observed in F1 compared to F2 and F3. Since Acyclovir is hydrophilic and struggles to pass through the skin's lipophilic barrier, the niosomal formulation enhances drug permeability, sustaining its action in the body for a longer period.

Table No. 01: Preformulation studies of Acyclovir.

PROPERTIES	REPORTED		OBSERVED
Odour	Odourless		Odourless
Melting point	256.5 °C		255.6 °C
Appearance	White amorphous powder		White amorphous powder
identification	253 nm		252 nm
Solubility	Water	1.22 -1.6mg/ml	1.2mg/ml
	Phosphate buffer 6.8	2.4mg/ml	2.3mg/ml

Table No. 02: Calibration data of Acyclovir in phosphate buffer of pH 6.8.

Sl No.	Concentration (µg/ml)	Absorbance*
1	0	0
2	2	0.1733±0.0165
3	4	0.355±0.0134
4	6	0.424±0.0456
5	8	0.5737±0.0247
6	10	0.68571±0.0248
7	12	0.8375±0.0145
8	14	0.9594±0.0275

***All values are represented as mean of 3 readings (n=3)**

Table No. 3: Average particle size of Niosome formulations.

SI. No.	Formulation code	Particle size(nm)*
1	F1	824
2	F2	936
3	F3	919

***All values are represented as mean of 3 readings (n=3)**

Table No. 04: The entrapment efficacy of the niosomal formulation.

Formulation code	Entrapment efficacy (%)
F1	70.3
F2	72.06
F3	74.03

Table No. 05: *In Vitro* drug diffusion profile study of different formulation.

TIME (HRS)	%CDR*		
	F1	F2	F3
0	0	0	0
1	16.25±0.26	15.24±0.34	16.25±0.42
2	25.37±0.15	23.94±0.28	25.37±0.39
3	34.46±0.31	32.12±0.17	34.46±0.26
4	46.94±0.18	43.34±0.34	46.94±0.23
5	57.76±0.24	51.24±0.26	57.76±0.24
6	68.34±0.34	62.91±0.29	66.31±0.19
7	77.64±0.26	71.78±0.51	74.85±0.28
8	86.16±0.18	83.84±0.94	84.16±0.45

***All values are represented as mean of 3 readings (n=3)**

Table No. 6: Physical appearance of niosomal gel.

Formulation Code	Colour	Clarity	Homogeneity	Texture	Foreign particles
F1	White	++	Good	Smooth	-

Turbid- +
Clear- ++
Very clear- ++

Table No. 7: Various evaluation parameter of Film;forming gel.

pH	Viscosity(cps)	Spreadability (cm)	Extrudability (%)	Film Thickness(mm)	Drying time (min)
5.6±0.23	17,370±0.94	6.8±0.073	88.34±0.152 %	0.015	12.08

IN- VITRO PERMEATION STUDY

Table No. 8: In-vitro drug permeation release profile of niosomal film forming gel.

Time (hrs)	%CDR*
0	0
1	15.170.13
2	24.480.26
3	33.69±0.42
4	40.08±0.35
5	48.41±0.18
6	57.19±0.26

***All values are represented as mean of 3 readings (n=3)**

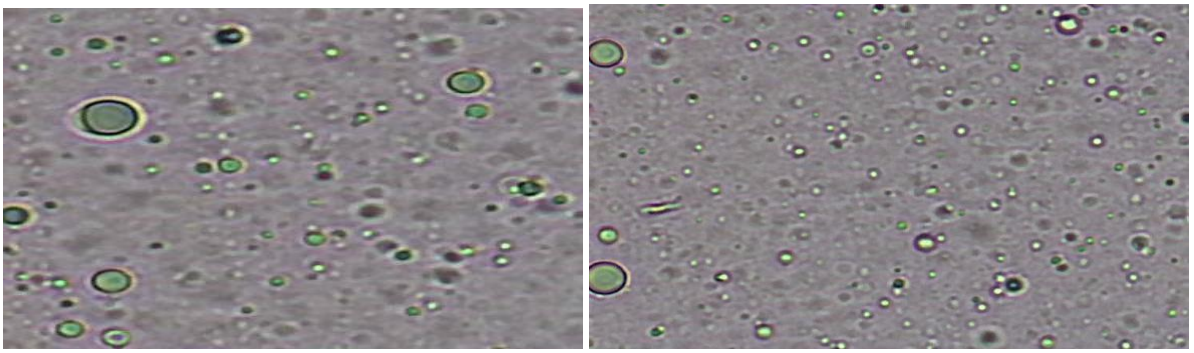

Fig. No. 01: Optic microphotograph of Niosome vesicles.

CONCLUSION

The formulation of a film-forming gel containing Acyclovir niosomes using the Film Hydration method ensured rapid drug release. Preformulation studies met reported standards, and FTIR analysis showed no interaction between the drug and polymers. Three niosomal preparations with varying concentrations of Cholesterol and Span 60 were evaluated for vesicular size, entrapment efficacy, and drug release, with F1 identified as the ideal formulation due to its vesicular size and drug permeability. The F1 niosomal gel, prepared with Carbopol, PVP, and PVA, showed satisfactory physical properties, good viscosity, and film thickness, and a pH of 5.6 ± 0.23, compatible with skin. Extrudability was excellent, and in vitro release studies showed optimal drug release after 6 hours.

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CONFLICT OF INTEREST
We declare that we have no conflict of interest.

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