DEVELOPMENT AND EVALUATION OF NIOSOMAL GEL CONTAINING ACYCLOVIR FOR ENHANCED SKIN PENETRATION

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ABSTRACT:

Niosomes enhance drug permeation into skin by distorting membrane properties of stratum corneum, and it fuses with upper layer of skin. They also showed drug deposition in different skin layers and A niosomal gel formulation of acyclovir for enhanced topical delivery, aimed at improving its therapeutic efficacy and bioavailability for the treatment of viral diseases. Specifically, it seeks to optimize the formulation parameters to achieve maximum drug encapsulation, stability while ensuring safety and minimizing skin irritation. Acyclovir used for preparation of niosomal gel including preformulation studies and evaluated for Particle size, Zeta potential, drug content, Viscosity, Spreadability, Stability studies etc.

KEYWORDS*: Acyclovir, Niosomal gel, preformulation studies, Stability studies.*

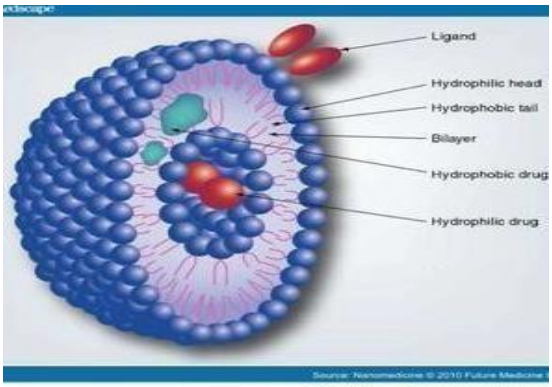
INTRODUCTION

NIOSOMES

Niosomes are lipid-based vesicular membranes or aqueous layers that may enclose hydrophilic and lipophilic medicines. Niosomes or commonly known as non-ionic surfactants are used widely as an alternate carrier to liposomes. They have comparable physical properties. Niosomes enhance drug permeation into skin by distorting membrane properties of stratum corneum, and it fuses with upper layer of skin. They also showed drug deposition in different skin layers. Niosomes when used in topical drug delivery system act as penetration enhancers, serve as local storehouse for sustained release of drug, increase solubility of poorly soluble drugs, and act as rate-limiting membrane barrier for controlled delivery systems. [(1)]They are made of amphiphilic components that enable them to encapsulate both hydrophilic and hydrophobic drugs.[(2)] These amphiphilic molecules make a bilayer as the membrane of vesicles that can help them be monolayer (having just one bilayer) or multilayer (having several bilayers and creating concentric spheres) based on the synthesis method. To have stable vesicles and improve other properties, some non-ionic surfactants, cholesterol, or their derivatives have been used in the synthesis. Niosomes revealed lower toxicity, allowing for regulated delivery and the release of loaded active compounds with beneficial properties to give a moisturising and tanning effect to the skin. [(3)]

Structure Of Niosomes

The niosome are circular bilayer structure of non ionic surfactant, surfactant which must having ability to form micelle. When surfactant concentration are goes above the critical micelle concentration (CMC) then it forms micelles in formation, but non-ionic surfactant has ability to form circular bilayer structure instead of micelles. The size of the niosome structure is variable from 10 to 1000 nm and they are categorized as small unilamellar



vesicles (SUV), large unilamellar vesicles (LUV), and multilamellar vesicles (MLV).[4]

Structure of niosomes

Niosomes present a structural similarity to liposome and hence, these are able to represent as alternative kinds of vesicular systems with respect to liposomes. These are believed to be better carriers for drug delivery as compared to liposomes due to various issues like cost, stability at pH variations, sterilization, etc. The drug encapsulation efficiency of these systems increases with increment in the concentration as well as lipophilicity of surfactant. Niosomes can perform as drug 11 depots and these are able to release the drugs in a controlled manner.

These also behave like liposomes in vivo and to prolong the circulation of encapsulated drugs, varying the organ distribution of the carrier system as well as the metabolic stability [5]. Niosomes are able to modify the plasma clearance kinetics, tissue distribution, drug metabolism and cellular interaction of the drug molecules. These may be employed as vehicles for poorly absorbable drug molecules to develop the novel drug delivery system. Delivery of various kinds of drug molecules can be possible using niosomal systems like oral, topical, parentral, ophthalmic, targeting, etc. Niosomes are able to improve the bioavailability of the encapsulated drug molecules through crossing the barrier of gastrointestinal tract (GIT) by transcytosis of 'M cells' of Peyer's patches in the intestinal lymphatic tissues. Several drugs also encapsulated within the niosomes for the delivery through the transdermal route to enhance the drug permeation and the therapeutic efficacy [6].

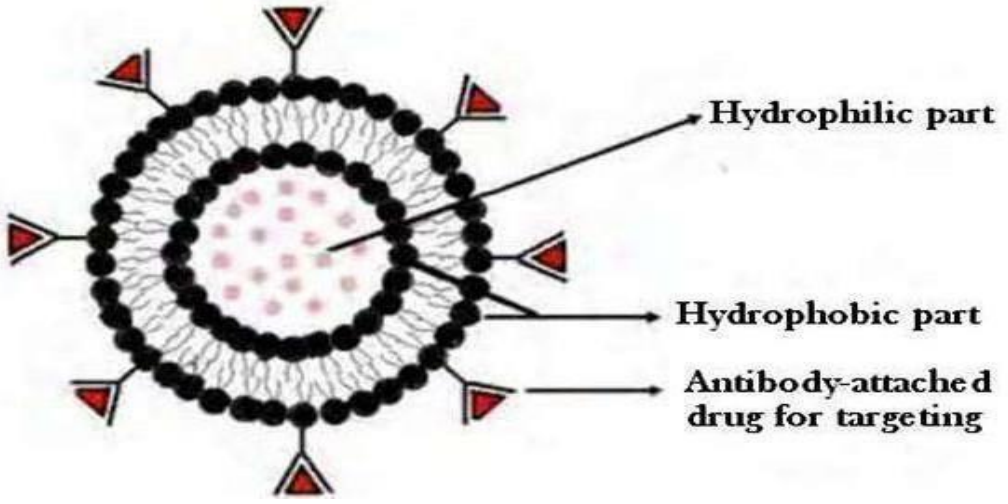


Figure : Drug targeting through the use of linkages to niosome via antibody

Classes of niosomes

On the basis of vesicle sizes, niosomes can be classified into three categories:

a) Small Unilamellar Vesicles (SUV, vesicle size: 0.025-0.05 μm)

b) Multi-lamellar Vesicles (MLV, vesicle size: > 0.05 μm)

c) Large Unilamellar Vesicles (LUV, vesicle size: >0.10 μm).

Advantages of niosomes [7]

The potential advantages of niosomes are presented below:

- Simple methods are required for the formulation of niosomes. Even large–scale production can be possible.
- Since the niosomal structure presents position to accommodate hydrophilic, lipophilic and amphiphilic drug moieties, these can be employed for a variety of drug molecules.
- Niosomes displays the flexibility in their structural features (i.e., composition, size and fluidity) and can be intended in relation to the preferred situation.
- Niosomes enhance the therapeutic potential of the drug molecules by protecting from the biological environment as well as restricting influences to the target cells, thus lowering the clearance of the drugs.
- Niosomes perform as a depot for releasing the drug molecules slowly and present controlled release of drug molecules.
- Niosomes enhance the stability of the encapsulated drugs at various pH.
- Niosomes enhance the oral bioavailability of various drugs.
- Niosomes are osmotically active as well as stable at various pH environments.
- Niosomes can improve the skin penetration of drug molecules through topical administration. Niosomes are able to reach the site of action through oral, parenteral and topical routes.

Formulation design

Topical gel may include the following components:

A) Gel forming agent or polymer

B) Drug Substance

C) Penetration Enhancers

A) Gel forming agent or Polymer

Different classes of polymeric materials have been used to achieve rate controlled drug delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer [8]. The following criteria should be satisfied for a polymer to be used in a topical system:

- Molecular weight, chemical functionality of polymer must allow diffusion and release of the specific drug.
- The polymer should permit the incorporation of a large amount of drug.
- The polymer should not react, physically or chemically with the drug. The polymer should be easily manufactured and fabricated into the desired product and inexpensive.
- The polymer must be stable and must not¬ decompose in the presence of drug and other excipients used in the formulation, at high humidity conditions, or at body temperature.
- Polymers and its degradation products must be nontoxic.

B) Drug Substance

Drug Substance plays a very important role in the successful development of a topical product. The important drug properties that effect its diffusion through gels as well as through skin are as follows[9].

- **Physicochemical properties**

- Drug should have a molecular weight of less than 500 Daltons.
- Drugs highly acidic or alkaline in solution are not suitable for topical delivery.
- Drug must have adequate lipophilicity.

- A saturated aqueous solution of the drug should have a pH value between 5 and 9.
    - **Biological properties**
- The drug should not be directly irritated to the skin.
- Drugs, which degrade in gastrointestinal tract or are inactivated by hepatic first pass effect, are suitable for topical delivery.
- Tolerance to the drug must not develop under the near zero order release profile of topical delivery.

The drug should not stimulate an immune reaction in the skin. Drugs which have to be administered for a long time or which cause adverse effects to non-target tissue can also be formulated for topical delivery [10].

C) Penetration Enhancer

Penetration enhancers (also called accelerants or sorption promoters) are defined as substances that are capable of promoting penetration of drugs into skin, or their permeation through skin, by reversibly reducing the skin barrier resistance. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis, and into the blood circulation. The skin behaves as a passive barrier to the penetrant molecule [11]. The stratum corneum provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption.

Application of gels [12]

Application of gels in Pharmaceutical and cosmetic industry:

- Gels are applied directly to the skin, mucus¬ membrane or the eye to provide local action.
- They acts as long acting forms of drug injected¬ intramuscularly or implanted into the body.
- Gelling agents are useful binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid, and suppository bases.
- Cosmetically gels have been employed in wide variety of products, including shampoos, fragrance products, dentifrices, skin and hair care preparations.
- Gel products containing anti-inflammatory steroids are used to treat inflammations of scalp because this is an area of the body where creams and ointments are too greasy for patient acceptance.
- Gels have better potential as a vehicle to administer drug topically in comparison to ointment, because they are nonstick, requires low energy during formulation, are stable and have aesthetic value [13].

EXPERIMENTAL WORK

Organoleptic Properties

Organoleptic properties of Acyclovir were observed by visual observation. The organoleptic studies of Acyclovir like general appearance like color, odor, state, etc. were observed.

Solubility study

Qualitative solubility of Acyclovir in different solvents was determined according to USP NF, 2007. Approximately 1 mg of Acyclovir was weighed and transferred into a 10 ml test tube and dissolved in the respective solvents (1 ml each of methanol, ethanol, DMSO, chloroform and water) [20].

Melting Point

Melting point was analyzed by open Capillary method using Thiele's tube. Few quantity of the Acyclovir was placed in a thin walled capillary tube 10-15 mm long, about 1mm inside diameter, and closed at one end. Liquid paraffin oil was filled in the thieles tube and placed in the contact of flame. The capillary was suspended into the thiele's tube and heat the sample slowly; thermometer was attached to check the temperature. The temperature at which the sample starts to melt was taken as the melting point of the sample [21,22].

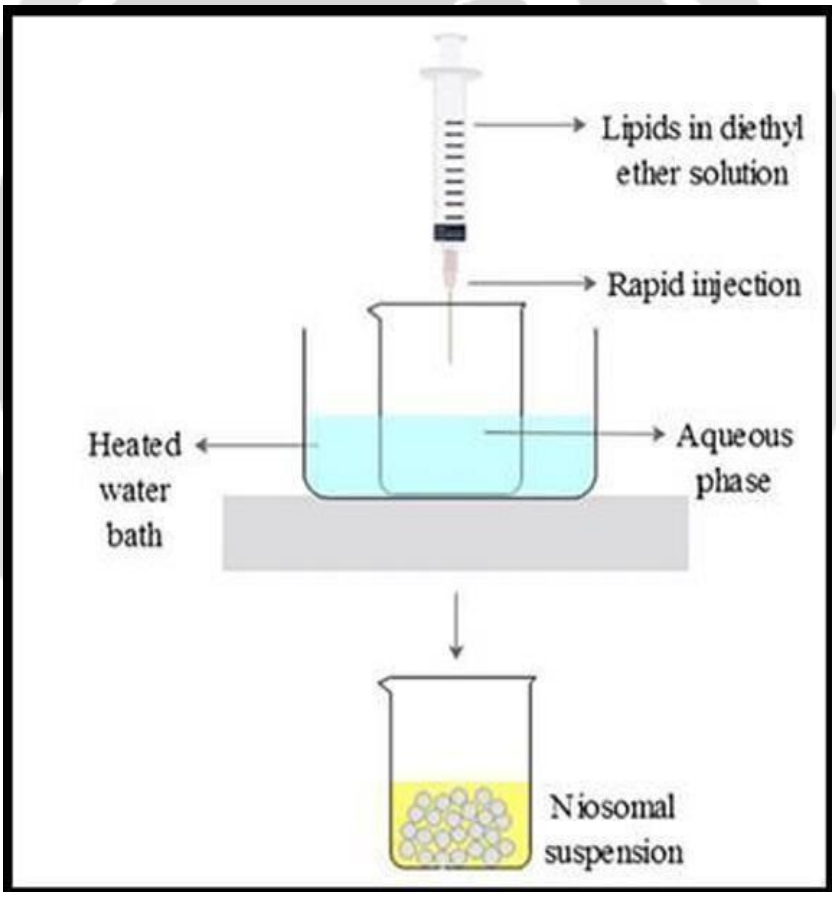
Preparation of Niosomes

This method uses a solution of surfactant that is made by mixing the surfactant (Span80/Tween80) in diethyl ether. This mixture is then added into warm water or an aqueous medium (containing the drug or therapeutic entity) by

means of an injection having a 14 gauge needle (This is done very slowly as diethyl ether is highly flammable). The aqueous medium is maintained at a temperature of 60° Celsius. Single layered vesicles are then formed by vaporizing the ether. The size of these vesicles or particles ranges from 50 to 1000 µm depending on the conditions of preparation used [23].

Formulation composition of Niosomes

Type of formulation	F1	F2	F3	F4	F5
Acyclovir	1 gm	1 gm	1 gm	1 gm	1 gm
Cholesterol	200 mg	200 mg	200 mg	200 mg	200 mg
Tween 80	50 mg	100 mg	150 mg	200 mg	250 mg
Buffer	10 ml	10 ml	10 ml	10 ml	10 ml
Diethyl ether	2 ml	2 ml	2 ml	2 ml	2 ml



Niosome preparation by ether injection method

Preparation of niosomal loaded gel of acyclovir

Acyclovir niosomes was added directly into gel base and make up the volume 50 ml by adding water [24]. Ingredients along with their quantities used in formulation of gel are shown in table

Composition of niosomal loaded gel of acyclovir

Composition	F1	F2	F3	F4	F5
Acyclovir niosomes (gm)	1.5	1.5	1.5	1.5	1.5
Carbopol 940 (gm)	0.5	1.0	1.5	2.0	2.5
Methyl paraben (gm)	0.25	0.25	0.25	0.25	0.25
Triethanolamine (ml)	1	1	1	1	1
propylene glycol (ml)	15	15	15	15	15
Water	q.s	q.s	q.s	q.s	q.s

RESULTS AND DISCUSSION

Physicochemical parameters of drug

Organoleptic properties

Organoleptic Character Of acyclovir

Drug	Characteristics	Observed
Acyclovir	Odour	Odourless
	Colour	White
	Appearance	crystalline powder
	State	Solid

An evaluation of the API's organoleptic qualities, including Appearance, color, odor, and state, was conducted. Acyclovir was discovered to have a white color to it when tested. Acyclovir has an odorless and has a solid state, according to research conducted on it. Acyclovir exhibited the same appearance, color, odor and state as the I.P. requirements for these characteristics.

Solubility study

Solubility of acyclovir in various solvent

Drug	Name of solvent	Solubility
Acyclovir	Water	Slightly soluble
	Ethanol	Freely soluble
	Methanol	Freely soluble
	Chloroform	Soluble
	DMSO	Freely soluble

The solubility of Acyclovir was determined in various non-volatile or volatile liquid vehicles shown in Table 5. From the results, it was observed that the drug is freely soluble in Dimethyl sulfoxide, ethanol and methanol and soluble in chloroform.

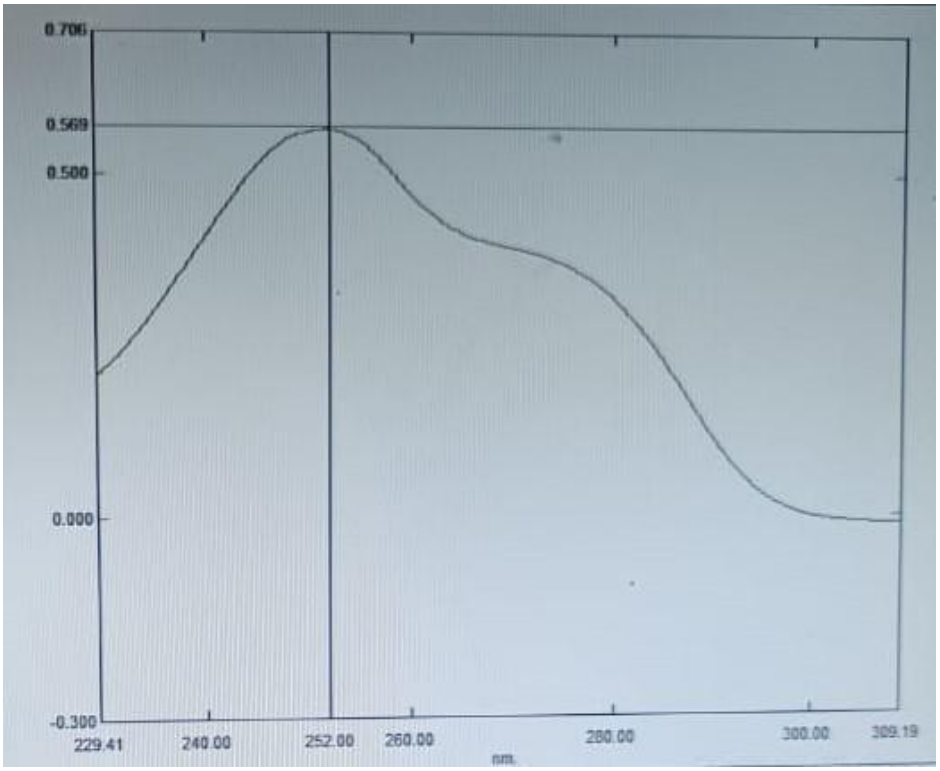
Melting point

Melting point of Acyclovir

Drug	Observed	Reference
Acyclovir	257°C	256°C-260°C

The capillary method is used to determine the melting point of a substance. The melting point of the Acyclovir was found to be 257ºC, which is well within the limits of the drug specification.

Lambda max Acyclovir



Lambda max of Acyclovir: UV absorption maxima

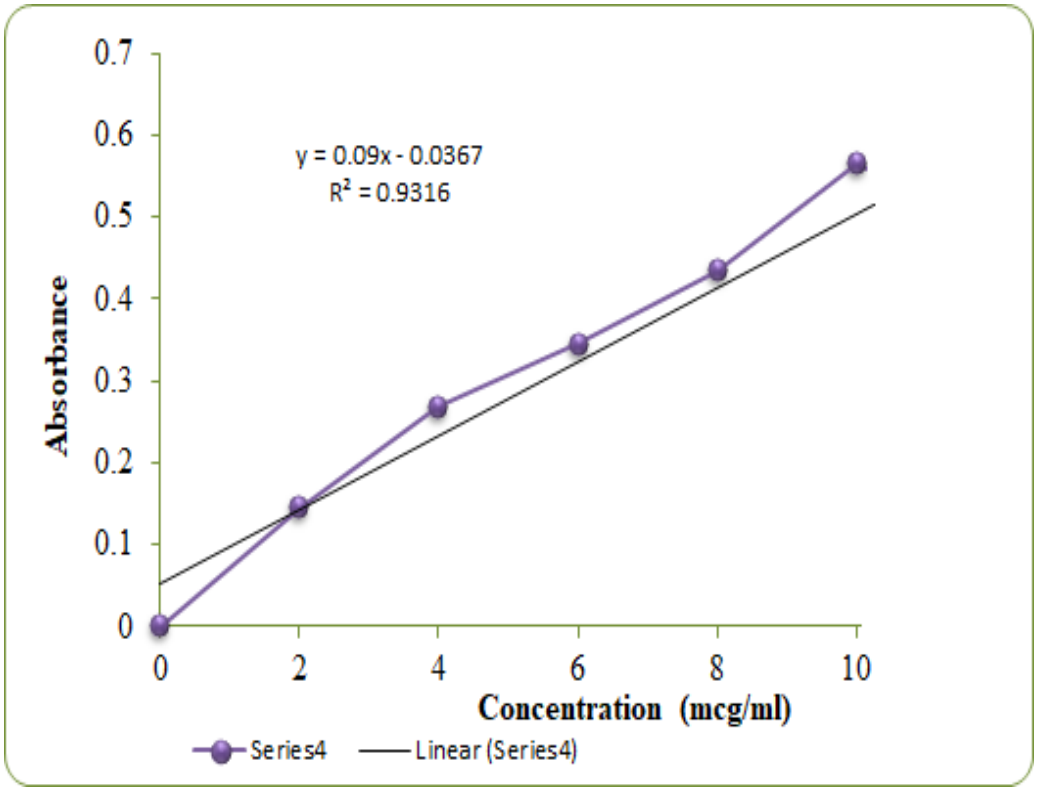
Sr no	Drug	UV absorption maxima (Lambda max)
1	**Acyclovir**	252 nm

Double beam UV visible spectrophotometer (Shimadzu- 1700) was used to determine the lambda max (absorption maxima) of a substance. The lambda max of the Acyclovir was found to be 252 nm. This is well within the limits of the drug specification.

Calibration curve and linearity of Acyclovir

Calibration curve

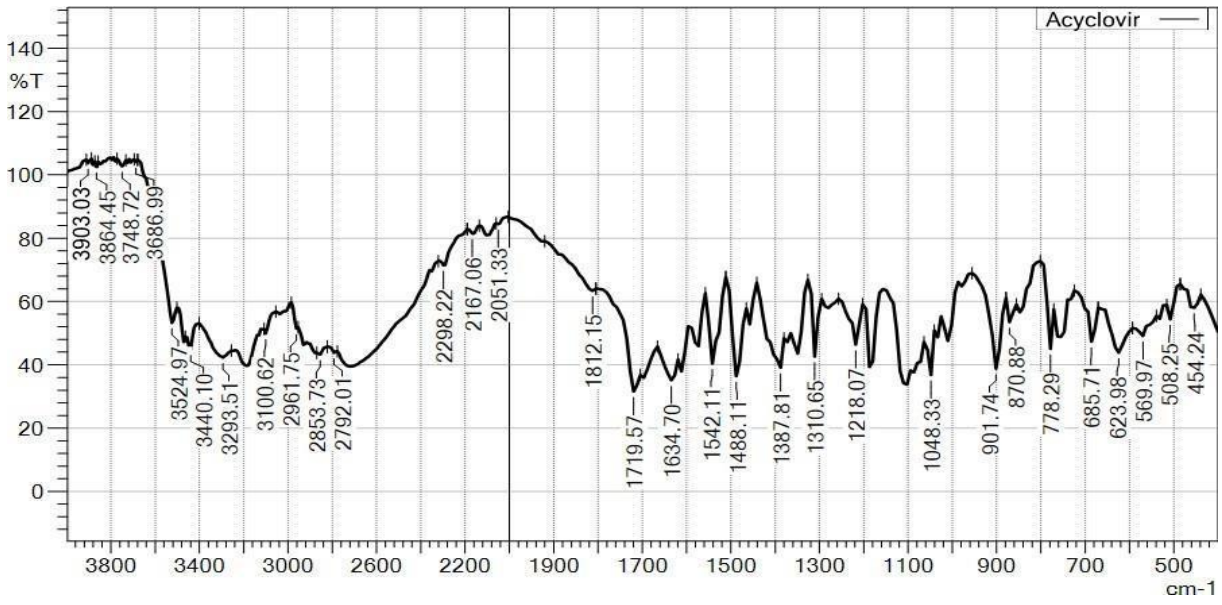
Sr. No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.145
3.	4	0.269
4.	6	0.345
5.	8	0.435
6.	10	0.565



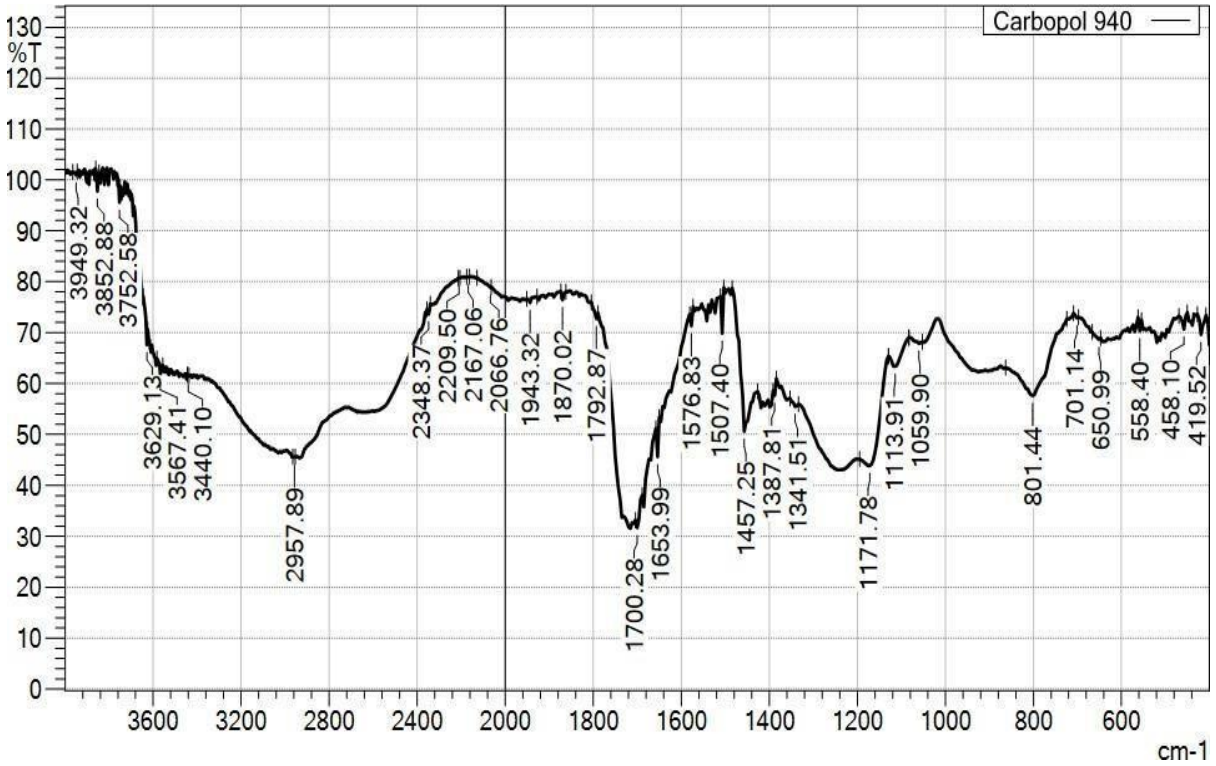
Calibration curve of Acyclovir

The linearity of the proposed method was established by least squares linear regression analysis of the calibration curve. The regression equation for Acyclovir was obtained by plotting absorbance versus concentration of Acyclovir in the range of 2-12 µg/mL. Six points calibration curve were obtained in a concentration range from 2-12 µg/ml for drug. The response of the drug was found to be linear in the investigation concentration range and the linear regression equation was y = 0.058x + 0.017 with correlation coefficient R^2 = 0.993.

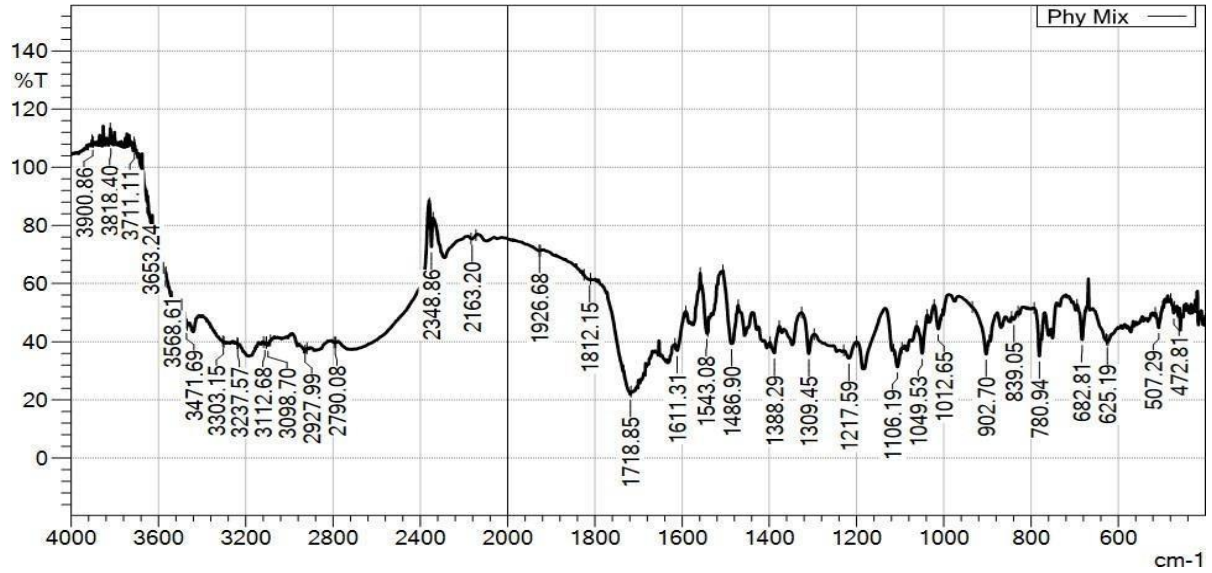
Functional group identified by Fourier transform infrared (FTIR) study



FTIR Spectrum of acyclovir



FTIR Spectrum of Carbopol 940



FTIR Spectrum of physical mixture of acyclovir with Carbopol 940

The peaks obtained in the spectra of drug and polymers mixtures correlates with each other. This indicates that the drug was compatible with the formulation components. IR studies indicated no interaction between drug and polymers.

The standard band frequency of the acyclovir is show in the Table.

Standard band frequency acyclovir

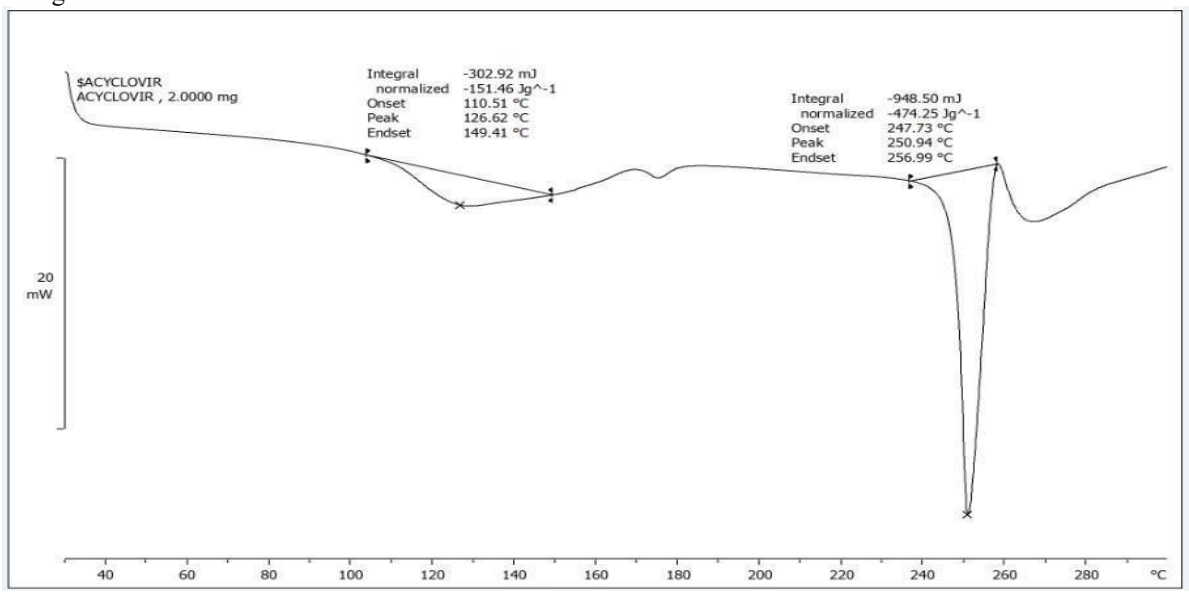
Wave number in cm $^{-1}$	Characteristic
1900	C=H
1650 - 1580	N-H bending
1600 - 1400	Aromatic C=C
1400 - 1000	Stretching C-N bending
1373	C-F
1049	S=O

The spectra obtained from the physical mixture show that all the principal peaks are at or around the requisite wave number of pure drug. Thus, it may be inferred that there was no chemical interaction between drug and polymer and the purity and integrity of drug was maintained in the physical mixtures.

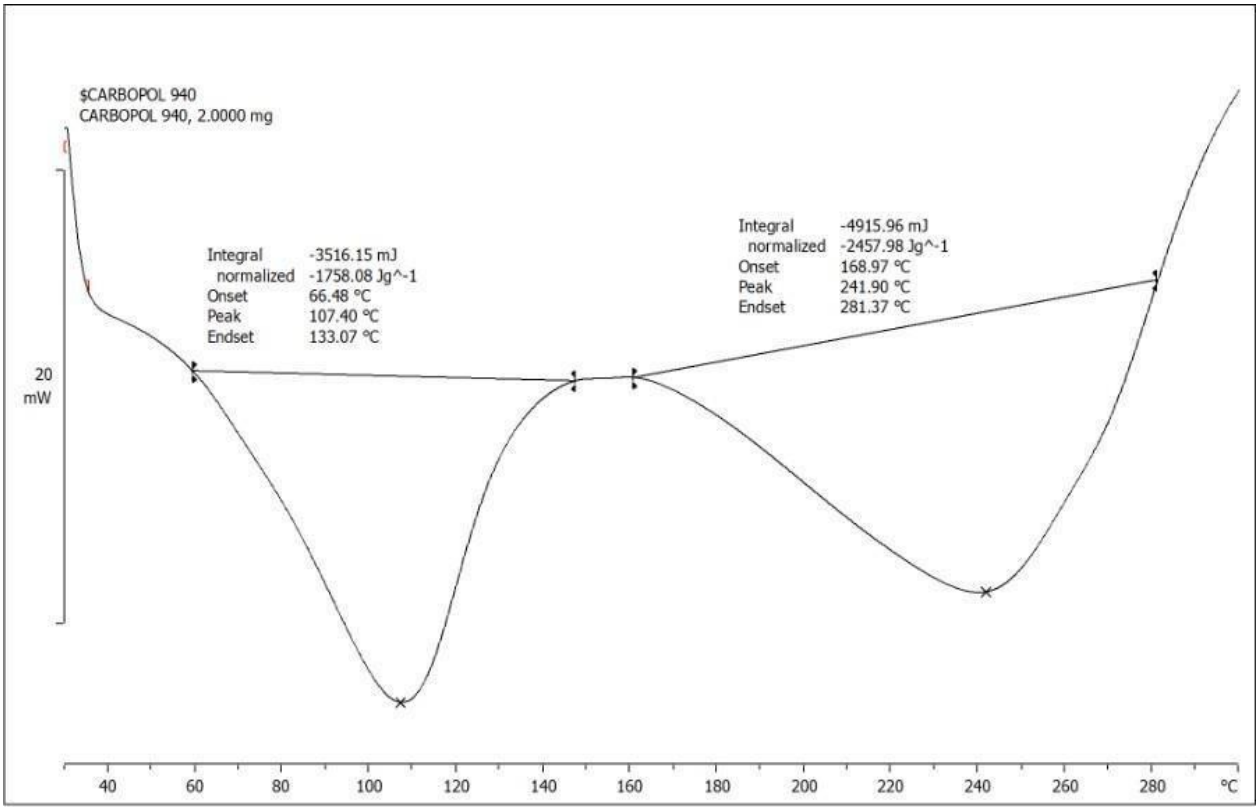
Drug excipient compatibility study

DSC thermal analysis:

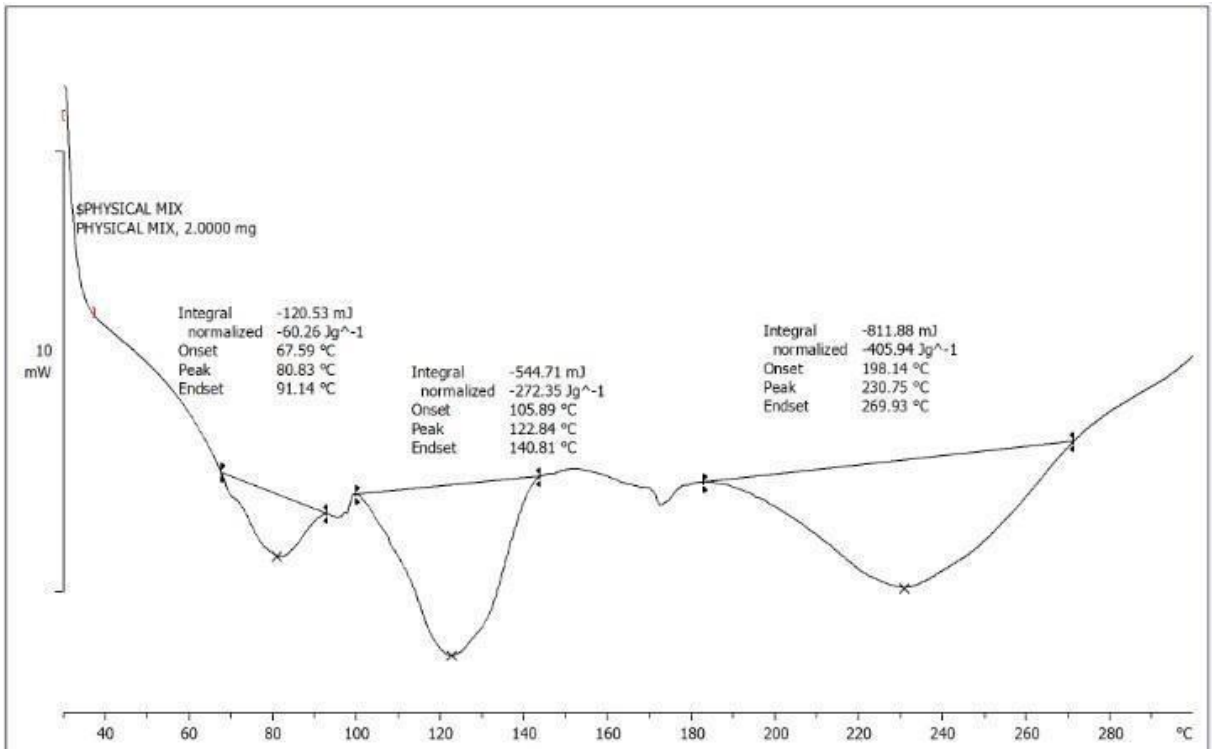
The interactions between acyclovir and polymers were determined by DSC studies and results were represented in Figure.



DSC thermogram of acyclovir



DSC thermogram of Carbopol 940



DSC thermogram of physical mixer of acyclovir with Carbopol 940

Values of evaluation parameters of developed gel

Batch no	pH of gel	Homogeneity	Spreadability (g. cm/sec)	Drug content
F1	7.1± 1.5	Very good	3.49 ± 0.20	99.81 ± 0.50
F2	7.5± 0.5	Very good	6.9 ± 0.30	99.45 ± 0.20
F3	7.3± 1.0	Good	4.19 ± 0.42	98.25 ± 0.35
F4	7.2± 1.5	Good	5.1 ± 0.38	98.75 ± 0.10
F5	7.4± 1.0	Very good	7.5 ± 0.18	99.15± 0.20

Percent drug content in all five formulation was in range 98.25-99.81%, indicating homogeneity. pH of all formulations was found neutral (7.1-7.5). The spreadibility was found to be in the range of 3.49-7.5 g cm/s.

Viscosity of niosomal loaded gel

Viscosity at different angular velocity

Angular velocity (Spindle 60)	Viscosity (cps)				
	F1	F2	F3	F4	F5
10 rpm	2744 ± 2.05	2927 ± 4.25	3615 ± 3.5	4144 ± 2.15	4648 ± 1.15
20 rpm	2705 ± 4.25	2890 ± 4.0	3595 ± 4.6	4100 ± 2.35	4605 ±1.90
30 rpm	2650 ± 3.15	2870 ± 3.5	3560 ± 4.15	4050 ± 2.90	4580 ± 1.35
40 rpm	2600 ± 1.99	2810 ± 3.3	3505 ± 4.35	4005 ± 3.25	4530 ± 2.20
50 rpm	2620 ± 2.45	2725 ± 4.0	3430 ± 3.90	3985 ± 3.05	4495 ± 2.00

In vitro Permeation study

Permeation studies with synthetic membranes were performed for 6 hours. The results of the amount of niosomes acyclovir gel permeated (%) through the silicone membrane and skin are shown in Table 14. Formulation F5 was selected for viscosity studies based on the physicochemical characterization of gel and drug content. After the 6 hrs the group F5 show good permeability i.e. 40.61 ± 1.37 which shows that the greater the viscosity of gel more permeability through the membrane.

Sr no	Time (hr)	Niosomal gel (% Cumulative release)
1	**0**	**0**
2	**1**	27.78±0.41
3	**2**	32.42±1.24

4	**4**	35.76±1.51
5	**6**	40.61±1.37

Stability studies

Stability of a drug in a dosage form at different environmental conditions is important as it determines the expiry date of that particular formulation. Changes in the physical appearance, color, odor, taste or texture of the formulation indicate the drug instability. Among the niosomes Formulation, Formulation F5 was selected for stability studies based on the physicochemical characterization of gel and release characteristics.

Stability studies of acyclovir niosomes gel formulation F5

Time (Days)	**25º C±2º C and 60 ± 5% RH**		**40º C±2ºC and 70 ±5% RH**	
	Viscosity	**pH**	**Viscosity**	**pH**
0	1431± 3.5	6.7 ± 0.5	1431± 3.0	6.7 ± 1.0
30	1433± 8.5	6.8 ± 1.0	1435± 5.5	6.9± 0.5
45	1435± 6.5	6.9 ± 0.5	1440± 4.0	7.0± 1.5
60	1439± 12.0	7.1 ± 1.5	1443± 5.0	7.1± 0.5
90	1441 ± 5.5	7.3 ± 1.0	1445± 4.5	7.5± 1.0

Formulation were found to be stable, both physically and chemically, for a period of 3 months at accelerated stability conditions (25º C±2º C and 60 ± 5% RH) and (40º C±2º C and 70 ±5% RH). Evaluation parameters including viscosity and pH studies were not altered significantly. Results of assay and other evaluation criteria at periodic time points of stability studies are summarized. The result of accelerated stability studies of gel formulation is shown in above table. No major changes were observed.

CONCLUSION

In the present study, the findings revealed that the process variables critically affect the formulation of niosomes with regard to drug loading and need to be carefully controlled. Niosomal formulations containing acyclovir were successfully prepared with surfactants like Tween 80, and carbopol by ether injection method. The evaluation parameters revealed acyclovir niosomes shows reduced particle size distribution with better drug content. Niosomes has negative surface charges which indicate excellent stability.

In permeation studies of niosomal gel were carried out in modified Franz diffusion cell using cellophane membrane which inferred that % cumulative release was 40.61±1.37 of the initial dose in 6 h. It was confirmed that niosomes showed sustained drug release as compare to plain drug solution. The formulations produced good spreadability.

The niosomal formulation through topical route could be a useful dosage form to reduce the undesirable side effects associated with oral route. Niosomes play vital role in improving photostability of drug. From the research findings, it can be concluded that acyclovir was successfully integrated into niosomal gel by ether injection method for topical application in the treatment of acne. The current Study evaluated the achievements and hurdles in the development of suitable topical formulations for the delivery of Acyclovir drug in the treatment of skin disease.

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