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Formulation and Characterization of Nano Particle Loaded Ocular Drug Delivery System

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Abstract
Acyclovir is a antiviral drug that has broad-spectrum action against Gram- negative as well as Gram Positive pathogens. The purpose of the present investigation was to design, optimize and evaluate Acyclovir -loaded solid lipid nanoparticle (SLN) gel and Acyclovir loaded nano-structured lipid carriers (NLCs) to treat eye infections. Acyclovir loaded SLN and NLC were prepared by the emulsification solvent evaporation method and hot homogenization method. Stearic acid was used as solid lipid and poloxamer 188 as surfactant in SLN and olive oil as liquid lipid, stearic acid as solid lipid and tween 80 as surfactant. Optimization of nano formulation was done by Box Behnken Design using Design Expert Software 12. Lipid (X1), Surfactant (X2), Co surfactant (X3) were the independent variables and particle size and % entrapment efficiency (EE) were dependent variables in SLN, and Lipid ratio (X1), surfactant (X2), homogenization cycle (X3) were the independent variable and particle size, entrapment efficiency and % drug release were dependent variable in NLC formulations. The optimized Acyclovir -loaded SLN and NLC were further incorporated into Chitosan (LSNG and L-NLCG). A total of 9 batches (LSNG1 to LSNG9, L-NLCG1-L-NLCG9) were prepared by varying the concentration of Chitosan from 0.05% w/v to 0.25% w/v. LSNG8 and L-NLCG8 were selected as an optimized batch based on their gelling capacity and viscosity. In vitro and ex vivo studies of LSNG8 and LNLCG8 showed drug release for a prolonged period of time. Furthermore, the HET-CAM test revealed that the formulation is non-irritant and thus can be well tolerated when instilled in the eye. Therefore, LSNG8 and L-NLCG8 can offer improved management of microbial growth.
Keywords: Acyclovir, SLN, NLC, HET-CAM, Box-Behnken

Eyes have long been regarded as the doorway to the human soul because of their complex and distinctive nature. The human eye is divided into two parts, the anterior and posterior

segments, which can be further subdivided [1]. Each of these main categories has a subset of eye disease disorders. These include conjunctivitis, glaucoma, blepharitis, cataracts, and diabetic retinopathy, which are all diseases that affect the eye's anterior segment, as well as age-related macular degeneration and diabetes [2].

A pharmaceutical expert has found it difficult to transport drugs to the eye because of the eye's distinctive structure, which makes it difficult for drug molecules to enter the desired region. More than 90% of all ophthalmic medications on the market are eye drops. In contrast, they wash away from the eye, resulting in limited ocular bioavailability (less than 5%) following topical treatment through several elimination pathways [3]. Complex penetration barriers, including the corneal barrier, blood aqueous barrier and blood retinal barrier (BRB), also play a role in this process. Tissue turnover and drainage, protein binding, absorption into the bloodstream and enzyme breakdown, are all involved in this elimination process [4].

Optimal medication concentration at the site of action in the eye is difficult to achieve and maintain with ocular drug administration. There have been numerous attempts to extend the duration of drug exposure to the ocular surface after topical treatment, including ointments, eye drop solutions, gels, and implants. The amount of time that the cornea is in contact with these formulations has been lengthened. However, because of impaired vision and low patient compliance, they have not yet been widely embraced [5].

1.1 ANATOMY OF THE EYE

To create a successful drug delivery system, it is essential to comprehend the ocular anatomy and properly understand the obstacles associated with ocular drug delivery.

The human eye is a doorway to the phenomenon of vision because of its exquisite design and functionality. One inch is the diameter of the eyeball, which has a spherical form. This complex has a wide variety of components that operate in concert to improve vision. The layers and internal structures of the human eye have a specific purpose. The next paragraphs provide an in-depth explanation of each eye part.

One of the most essential parts of a human eye is the anterior segment which includes the cornea, conjuctival tissue and ciliary body; the pupil; the anterior chamber; the anterior fluid; the lens and trabecular meshwork. The vitreous fluid, the retinal pigment epithelium (RPE), the choroid and the optic nerve are also included in this segment (Figure 1.1) [1].

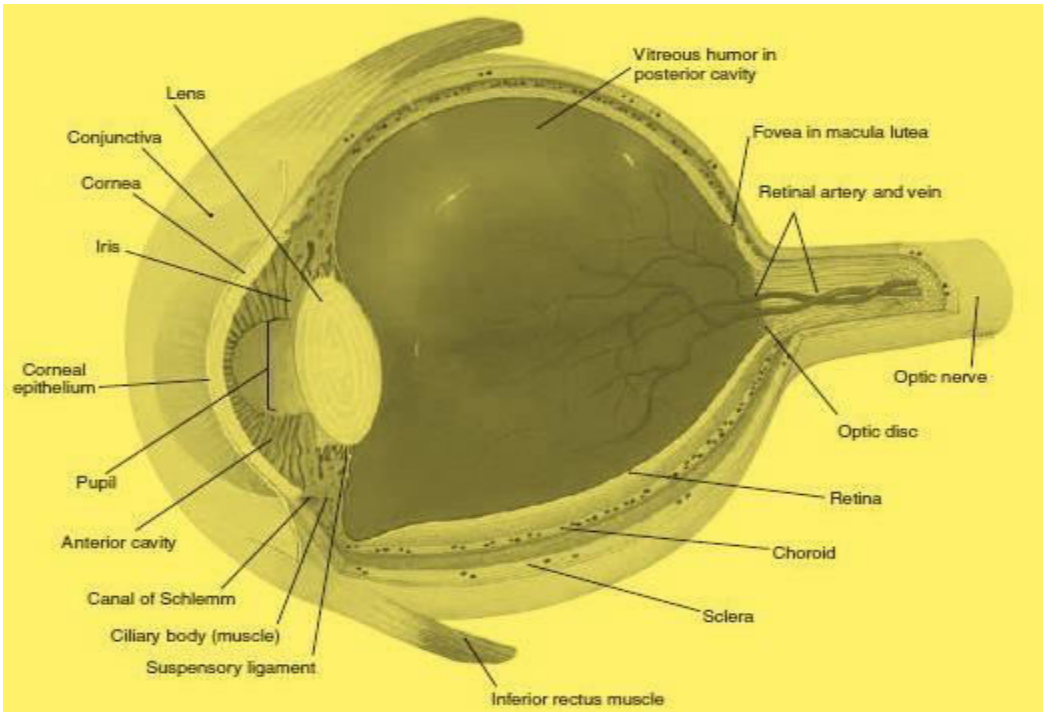


Fig. 1.1: Anatomy of Eye

1.1.1 Cornea

The cornea is the outermost layer of the eye's a vascular ocular system, which is clean and transparent. When it comes to corneal anatomy, there are a total of five primary layers. The outermost layer of the cornea is the corneal epithelium [9]. Endothelium and the Bowman's membrane are among the other layers [1]. The main determinant of medication concentration in aqueous humour is corneal permeability. The epithelium acts as a rate-limiting barrier to transcorneal drug diffusion for the majority of hydrophilic medicines. [10]. In order to keep lipophilic medications from being absorbed, the hydrophilic characteristic of the stroma functions as a barrier. [10]. A hydrophobic molecule can't diffuse through the corneal stroma because of the presence of charged and well-organized hydrophilic collagen [11].

1.1.2 Conjunctiva

Sclera and eyelids are lined by the conjunctiva, an eyelid-lining membrane that is transparent and thin. Goblet cells and non-keratinized stratified epithelium make up the stratified epithelium. When it secretes mucus, it stops bacteria from entering and lubricates the eyes [1]. The conjunctiva is 17 times larger than the cornea in human eyes. The conjunctiva is more able to absorb the medication because of this. As a result, medicines pass through the conjunctiva more easily than they can the cornea. It is still not significant because the conjunctiva has blood capillaries and lymphatics, which means that a large amount is lost to systemic circulation, thereby decreasing the overall bioavailability of the ophthalmic medicine [12].

1.1.3 Iris

The iris is a thin, round, contractile veil that lies between the cornea and the lens. The iris is a diaphragm of changeable size that serves to control the quantity of light that enters the eye by adjusting the size of the pupil. It is the eye's iris, which is coloured (shades may vary individually like blue, green, brown, hazel, or grey) [13].

1.1.4 Pupil

Although the pupil appears to be the "centre" of the eye, it is actually an aperture in the iris that allows light to enter the eye. The pupillary reflex controls the size of the pupil and, as a result, the amount of light entering the eye (also known as the "light reflex").

1.1.5 Ciliary Muscle

In the central layer of the eye, schlemm's canal is regulated by the ciliary muscle, a ring of

striated smooth muscles. Both the parasympathetic and sympathetic nervous systems innervate the muscle. The lens curvature can be changed by contracting and relaxing the ciliary muscle. Ciliary Muscle relaxed and Ciliary Muscle contracted are the two states that exist at any given time in the process of focusing on distant things (This enables the eye to focus on near objects).

1.1.6 Aqueous Humor

Aqueous humor is a transparent liquid, which fills the eye's posterior and anterior chambers of the eye. For the cornea, aqueous humor is an essential source of nourishment since it must be clear to allow light to pass through. It has a pH of 7.2, which is nearly 15 times higher than the plasma's ascorbate content. Its primary role is to supply nutrition, remove waste from non-vascular tissues, and maintain the convex shape of the cornea by controlling intraocular pressure [14].

1.1.7 Lens

A narrow clear capsule houses the lens, which is a transparent structure. Ciliary muscles encircle the eyeball, which is placed behind the pupil. It aids in the refraction of light entering the eye (which first refracted by the cornea). In order to create a picture on the retina, the lens utilizes light. When a person is looking at a distant object, the shape of the lens changes. The ciliary muscles contract and relax to change the lens shape, a process known as accommodation.

1.1.8. Vitreous Humor

Nearly two-thirds of the eye's surface is taken up by the vitreous humor (also known as the vitreous body). It is a translucent jelly-like substance in the chamber behind the lens of the eye. The hyaloid membrane is an albuminous fluid encased in a fragile, translucent membrane.

1.1.9. Sclera

Collagen fibers make up the sclera, the white part of the eye that is both opaque and elastic [1]. Because diffusion across sclera is essentially a matter of transport over an aqueous medium of proteoglycans or leaky gaps in the collagen network rather than diffusion across cellular membranes, sclera is more permeable to solutes such as hydrophilic substances than the cornea and conjunctiva [12].

Lipid Drug Conjugate (LDC)

Lipophilic medicines can be included into SLNs. Only very powerful hydrophilic medicines that are efficacious at low concentrations (e.g., LHRH or EPO) can be stably incorporated into the solid lipid matrix due to portioning effects during the manufacture process [38,39]. The so-called LDC nanoparticles with drug loading capacities of up to 33% were produced at the turn of the millennium to circumvent this constraint [40].

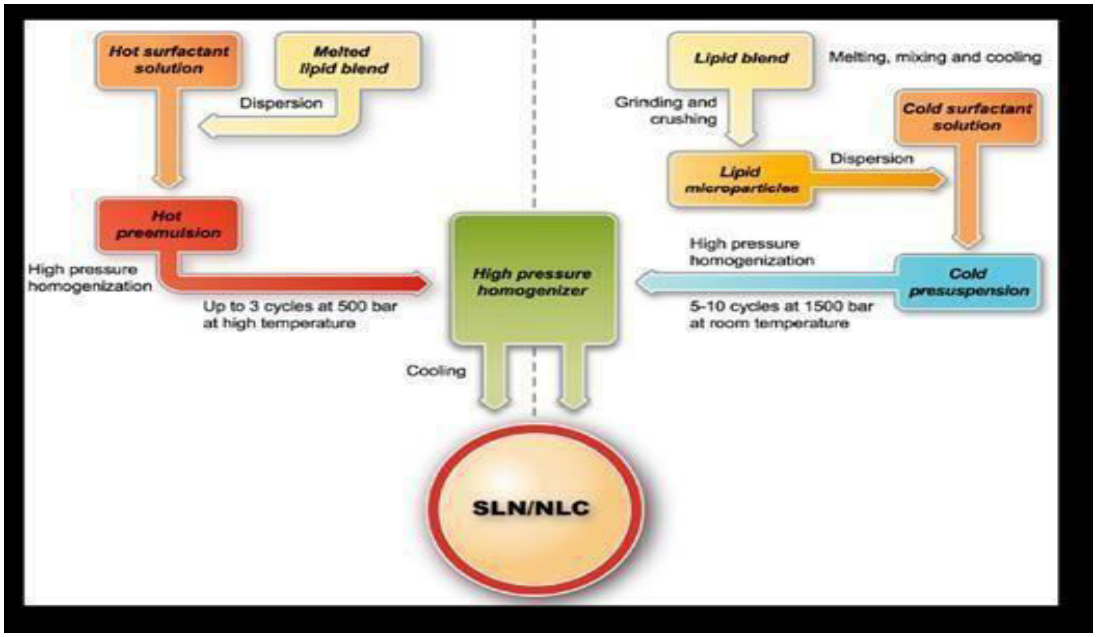
1.2 METHODS OF PREPARATION OF SLNs/NLCs

1.2.1 Homogenization at high pressures

To prepare SLNs/NLCs, high pressure homogenization (HPH) has developed as an effective and reliable approach. High pressure homogenizers (100-2000 bar) force a liquid through a small gap with high pressure. The fluid reaches at a speed of 1000 kilometers per hour (620 miles per hour) in a short period of time. Submicron- sized particles are broken apart by extremely high shear stress and cavitation forces. Homogenizers have no trouble with lipid content in the range of 5% to 10%. It has been possible to homogenize lipid nanodispersions with concentrations as high as 40% [41].

- Hot Homogenization

Homogenization is commonly done at temperatures over the lipid's melting point. To make a pre-emulsion from the drug-loaded lipid melt and the aqueous emulsifier phase, a high-shear mixing apparatus is employed (both at the same temperature). SLNs/NLCs are formed when the heated o/w emulsion cools, causing the lipid to crystallize and precipitate (Figure 1.6).



1.3 OPTHALMIC INFECTION

Bacteria are the most common culprit of eye infections in the globe. Contact lenses, trauma, surgery, ageing, dry eye, chronic nasolacrimal duct blockage, and past ocular infections all contribute to ocular infection (Figure 1.8) [54]. Many forms of ocular infections, including conjunctivitis, keratitis, endophthalmitis, blepharitis, orbital cellulitis, and dacryocystitis, are caused by bacteria. It is estimated that conjunctivitis costs the U.S. economy and society millions of dollars each year due to the widespread nature of the disease. In chronicity, the disease can damage not only the conjunctiva but also surrounding tissues such as the eyelid and may pose a risk for various extra or intraocular infections. Infectious conjunctivitis is caused by around 50–70 percent of the time by bacteria. There can be bacterial conjunctivitis in newborns, as well as in youngsters and the elderly. [55]. Eye lash loss can be caused by blepharitis, an infection of the eyelids. It is possible that the infection will spread to other parts of the eye. [56]. Corneal blindness is a significant cause of corneal infection and keratitis. In addition, if caught early enough, the infection might proceed to endophthalmitis.

4.1 PREFORMULATION STUDIES

Preformulation studies are an important foundation tools in the development of both active pharmaceutical ingredients (API) and drug product. They influence

- Selection of the drug candidates itself, Selection of the formulation components,
- The physicochemical parameters of new drug substances,
- Development of analytical methods and,
- Compatibility of drug substances with common excipients.

4.2.1 Drug Characterization

Acyclovir was characterized by various tests of identification.

4.2.1.1 Physical Appearance

Physical appearance of Acyclovir was evaluated by various Organoleptic properties, like color, odor, melting point etc.

4.2.1.2 Determination of Melting Point

DSC method was used to determine the melting point of Acyclovir. The melting point was recorded and compared with the literature value.

4.2.1.3 Solubility Profile

The equilibrium solubility of Acyclovir was studied in various solvents. A small excess quantity (approximately 25mg) was taken with 10ml of each investigated solvents in 25ml volumetric flask at room temperature (25°C). Increment of drug was added to each conical flask until undissolved particles were seen even after equilibration for 8 hrs with intermittent shaking. The supernatant liquid was analyzed spectrophotometrically for the drug dissolved until two successive readings of analysis were constant. In the following, the solubility of drug in a variety of solvents is examined and summarized.

4.2.1.4 UV/VIS Spectroscopy analysis

Absorbance maxima of the drug is recorded by the UV/VIS Spectrophotometer in the 0.1N HCl buffer pH 1.2 with wavelength scanning of drug sample in 1cm cell from 200 to 400 nm.

4.2.1.5 FTIR Spectral Analysis

The IR absorption spectra of the nanoparticulate formulation were recorded using FT-IR spectroscopy. Sample was analyzed using KBr disc, was obtained using the IR Prestige 21 instrument (Shimadzu Corp, Kyoto, Japan). A disc was formed by grinding the sample with KBr (1:10) and 4 mm/s scanning at a resolution of 2 cm/1 over a range of wave numbers from 4700 to 350 cm^{-1} was used.

5.1 DRUG CHARACTERIZATION

5.1.1 Pre-Formulation Study

5.1.1.1 Physical Appearance and Properties

Table 5.1: Properties of Acyclovir

Description	Acyclovir
Colour	White to white pale
Odour	Odourless
Molecular formula	C17H19F2N3O3
Molecular weight	351.35g/mol
Hygroscopicity	Non-Hygroscopic

5.1.1.2 DSC of Pure Acyclovir

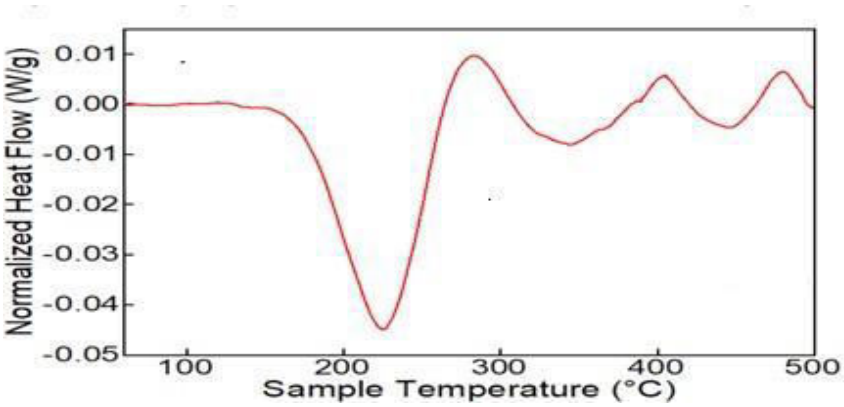


Fig. 5.1: DSC of Pure Acyclovir

The melting point of pure Acyclovir was clearly seen in the endothermic peak at 240^0C (Figure 5.1).

5.1.1.3 Solubility

The solubility of drug in a variety of solvents was examined and summarized in Table 5.2 and Figure 5.2.

Table 5.2: Solubility Study of Acyclovir

S. No.	**Solvents**	**Solubility of** Acyclovir **at 25° C**
1	Chloroform	Very soluble
2	Ethyl acetate	Freely soluble
3	Methanol	Freely soluble
4	Dimethyl Formamide	Soluble
5	Water	Sparingly Soluble
6	0.1 N HCI	Slightly Soluble
7	7.4 Phosphate Buffer	Slightly Soluble
8	6.8 Phosphate Buffer	Slightly Soluble

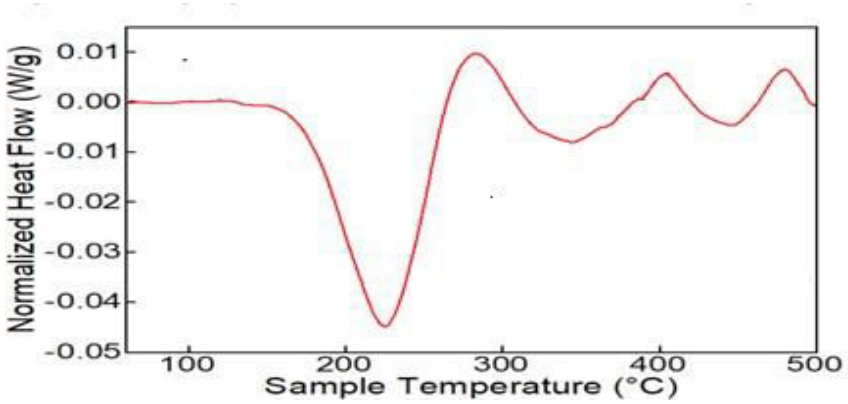


Fig. 5.2: Solubility of Drug in Various Solvents

5.1.1.4 UV/Vis Spectra of Acyclovir

Wavelength scanning of drug in 1 cm cells from 200 to 400 nm to was done to access the absorbance maxima of the drug. During this study the samples was found same absorbance maxima at 281nm (Figure 5.3).

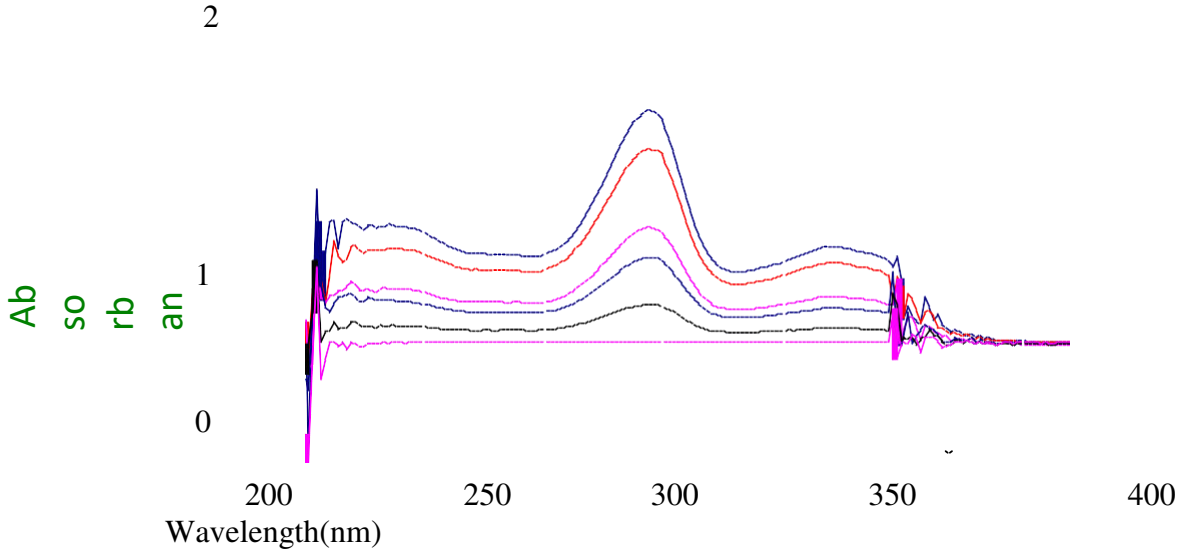


Fig.5.3: UV Spectra of Acyclovir

5.1.1 Determination of melting point:

The melting point of drug was found to be 256.4ºC. The reported melting point of drug Acyclovir is 256- 257^{0}C. Thus drug was identified as Acyclovir and found to be pure.

5.1.2 Fourier transform infrared spectroscopy analysis:

Identification of acyclovir was done by the FTIR Spectroscopy. The FTIR spectra was shown in figure

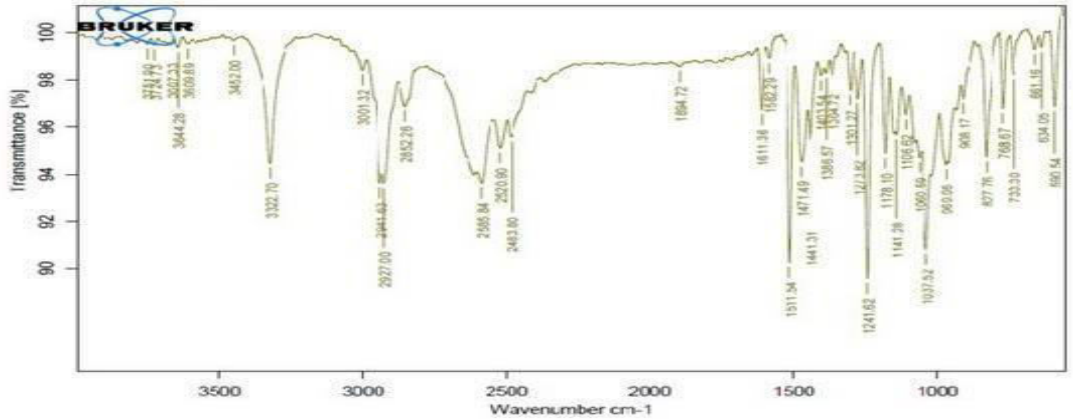


Fig 5.1 FTIR Spectra of acyclovir

Interpretation of FTIR spectra

Wave no cm^{-1} Reference	Sample	Indication	Inferences
1601.73	1683.81	NH Stretch	Primary Amines
1244.75	1244.13	C-H	Halogen group(Chlorine)
1319.51	1338.64	C-H in plane deformation	Alkane
3318.58	3545.38	O-H Stretch	Hydroxyl
1428.27	1417.27	C=H-	Alkene
1200.07	1338.38	-F	Halogen group (Flourine)

5.1.1 Standard Curve of Acyclovir in Various Mediums

The standard curve of Acyclovir was prepared in 0.1N HCl, in phosphate buffer pH 6.8, phosphate buffer pH 7.4 at 281nm. And the results are summarized in Table 5.4, Table 5.5, Table 5.6 and the curves are depicted in fig. 5.6, fig. 5.7, fig. 5.8 respectively.

Table 5.4: Standard Curve of Acyclovir in 0.1N HCl at 281nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.2145
3	4	0.4258

4	6	0.6457
5	8	0.8547
6	10	1.0291

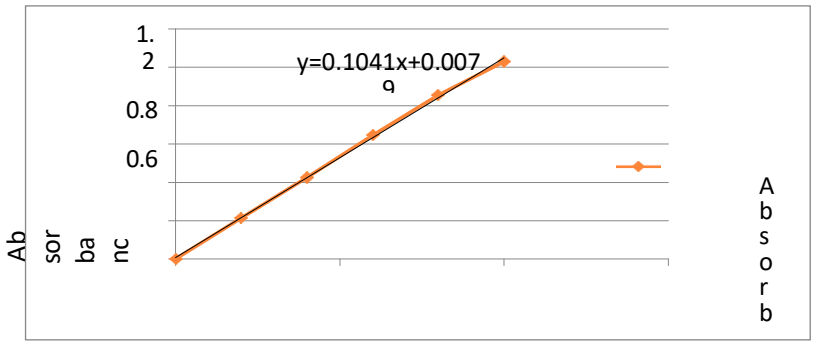


Fig. 5.6: Calibration Curve of Acyclovir in 0.1N HCl at 281nm Table 5.5: Standard Curve of Acyclovir in Phosphate Buffer pH 6.8 at 281 nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.1848
3	4	0.356
4	6	0.5352
5	8	0.7532
6	10	0.9291

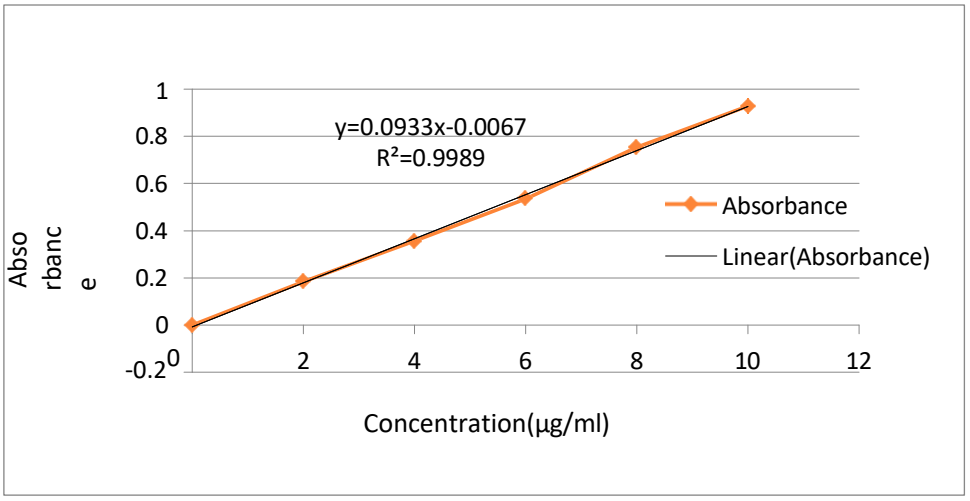


Fig. 5.7: Calibration Curve of Acyclovir in Phosphate Buffer pH 6.8 at 281nm

S.No	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.134
3	4	0.233
4	6	0.343
5	8	0.464
6	10	0.585

Table 5.6: Standard Curve of Acyclovir in Phosphate Buffer pH 7.4 at 281 nm

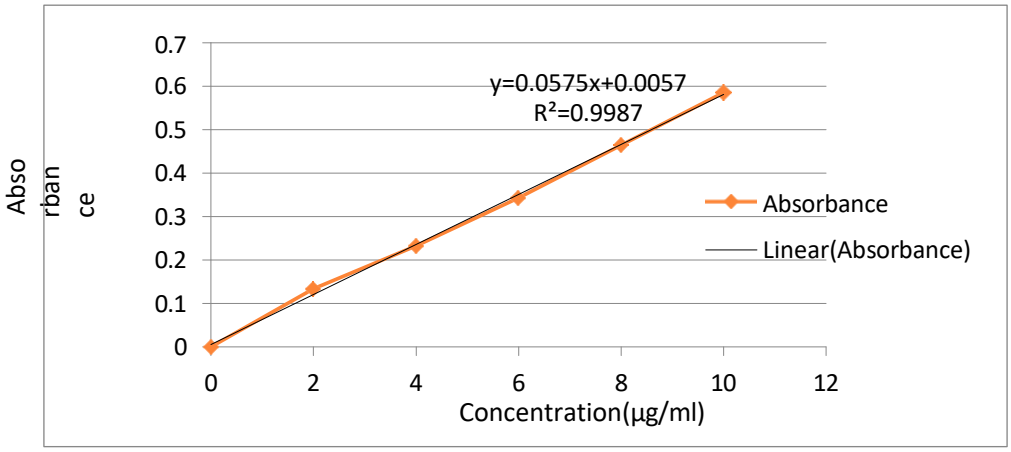


Fig. 5.8: Calibration Curve of Acyclovir in Phosphate Buffer pH 7.4 at 281nm

Conclusion FTIR and DSC measurements were used to verify that drugs, lipids, and polymers had no major physical or chemical incompatibility. Development Optimization of Acyclovir Loaded SLN Gel for Ophthalmic Drug Delivery. Different solid lipids such Compritol 888 ATO, Precirol ATO 5, GPS, Cetyl palmitate and Stearic acid were investigated as potential nanoparticle precursors from literature research. As the solubility of drug in various lipids was analyzed at an elevated temperature. It was found that Acyclovir shows maximum solubility 115 ±8.01 mg/ml in Stearic acid. The solubility of the Drug and lipid in the different solvents such as dichloromethane, ethanol, acetone, and methanol was taken into consideration while selecting a solvent, (Mean SD, n=3) the dichloromethane had the maximum solubility 600 mg/ml (P=0.05). Thus, Stearic acid (lipid) and Dichloromethane (solvent) were used for further studies. Particle size and entrapment efficiency were used to determine the best surfactant to use in the development of nanoparticles utilizing six different surfactants such as Poloxomer 188, Tween 20, Tween 60, Tween 80, Span 60 and Span 80, and Stearic acid (SA) as the lipid. . It was found that Poloxomer 188 shows minimum particle size and maximum entrapment efficiency as 212±7.04nm and 70.11±2.84, respectively. A Box-Behnken design was used to optimize the L- SNs using the Design- Expert 12 programme, Stat-Ease Inc., (Minneapolis, USA). Total solid lipid (X1), Surfactant (X2), and Co-surfactant (X3) were examined separately as

three independent variables. The dependent responses of particle size (Y1) and entrapment efficiency (Y2) were investigated. The design included a total of 15 experiments, each with a different centre point. Linear, 2-factor interaction (effects and interactions), and quadratic models were compared to find the most accurate prediction power.

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