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DESIGN AND CHARACTERIZATION OF ACYCLOVIR-LOADED NIOSOMES FOR TARGETED THERAPY AGAINST *HERPES SIMPLEX* VIRUS

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Abstract:

The present work aimed to formulate and evaluate niosomes of acyclovir for the treatment of ocular infections caused by Herpes Simplex Virus. Niosomes, composed of nano-sized multilamellar vesicles, offer enhanced drug delivery potential due to their ability to improve bioavailability, stability, and controlled release. Preformulation studies confirmed that acyclovir is a white, amorphous, odorless powder with solubility in water, phosphate buffer saline (pH 7.4), simulated tear fluid, and 0.1 N HCl, while being insoluble in methanol and ethanol. UV spectrophotometric analysis revealed a reproducible λmax at 254 nm with linearity in the concentration range of 2–10 µg/ml (r^2 = 0.996), confirming adherence to Beer–Lambert's law. Partition coefficient studies (value 1.53) indicated moderate lipophilicity, and IR spectroscopy authenticated the drug's structural integrity. Compatibility studies demonstrated no interference between drug and polymers. Niosomes were prepared using the thin-film hydration method with nonionic surfactants (Tween 20, Tween 80) and cholesterol, followed by sonication to achieve uniform vesicle size. Optimized formulations exhibited spherical, multilamellar vesicles with mean particle sizes ranging from 412–476 nm, polydispersity index of 0.181 ± 0.01, and high drug entrapment efficiency (92.63–98.83%). SEM analysis confirmed nanometer-sized vesicles with irregular surfaces. In vitro release studies showed biphasic release, with an initial burst attributed to surface-adsorbed drug, followed by sustained release up to 92.13%. Formulations incorporated into eye suspensions were clear, homogeneous, and stable, with pH maintained between 7.0–7.2. Stability testing was revealed minimal drug leakage under refrigerated conditions, while elevated temperatures increased leakage due to lipid bilayer degradation.

KEYWORDS: *Niosomes, Herpes Simplex, Acyclovir, Targeted Therapy, Stability*

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INTRODUCTION:

Acyclovir is an antiviral drug with a significant and highly specific activity against herpes virus and widely used in the treatment of various ocular disease[1]. It is used for the therapeutic purposes since long time. There is a major point of discussion that acyclovir is given by topical route in the form of ointment but the issue topical drug delivery is poor ocular drug bioavailability, pulse drug entry, systematic exposure due to the nasolacrimal drug drainage and poor entrance to the posterior segments of the eye iris lens diaphragm[2].

Currently there is no niosomal preparation of acyclovir in the market. The topical application of acyclovir is limited by poor ocular drug bioavailability, pulse drug entry, systemic exposure due to the nasolacrimal duct drainage and poor entrance to the posterior segments of the eye due to lens iris diaphragm, due to which it was chosen to formulate as the acyclovir loaded niosomes[3]. Niosomes have been used as ophthalmic delivery systems because they are able to penetrate into the corneal or conjunctival tissue by an endocytic mechanism. In this case acyclovir loaded niosomes may be advantageous over the topical ointment for the treatment of herpes keratitis[4].

We propose that niosomes loaded of acyclovir will lead to increase in duration of action as it interacts intimately with these extra ocular structures which would increase the concentration and residence time of the associated drug[5]. Moreover, niosomes has been recently been proposed as a material with a good potential for ocular drug delivery[6].

The rationale of this work is to develop niosomes loaded of acyclovir, which after ocular drug delivery provide local effects directly to the target site and also provide controlled drug release for a prolonged period of time which is very beneficial for the patients who are suffering from herpes keratitis disease[7].

Thus, our main aim is to develop niosomes loaded with acyclovir, and to study various process variables in its formulation, by evaluating various formulation and check it's *in-vitro* performance.

MATERIAL AND METHODS:

Methods of Formulation

Selection of surfactants for Niosomes: Nonionic surfactants are the main ingredient used in the structure of niosomes. These surfactants are incorporated into the lipid bilayer, forming polar defects which change the physical properties of the cell membranes. The tails of most surfactants are similar, consisting of a hydrocarbon chain, which can be branched, linear or aromatic. Surfactants having HLB values between 16 and 17 which correspond to polysorbate 20, was found to be most effective in increasing corneal permeability. Nonionic surfactants are preferred due to less irritation power which decreases in order of cationic > anionic > ampholytic > nonionic. Niosomes >10μm are suitable for drug administration to eye. Water-soluble surfactants like Tween 20, Tween 80, Cremophor EL and poloxamer 108 and so forth entrapped in niosomes an increased ocular bioavailability because surfactants act as penetration enhancers which can remove the mucus layer and break junctional complexes. Surfactants with an average alkyl chain length of C_{12}–C_{18} are suitable for the preparation of niosomes.

Formulation of Niosomes by thin film hydration method: The thin film hydration method is the most widely used technique for preparing niosomes. It involves dissolving surfactants and cholesterol in organic solvents, evaporating them to form a thin film, and then hydrating the film with an aqueous drug solution to produce multilamellar vesicles.

Preparation of Lipid Mixture: Surfactants tween 20 and cholesterol were weighed in appropriate ratios, than dissolved in a volatile organic solvent such as chloroform, methanol, or a mixture of both. The drug (if lipophilic) can also be dissolved in this organic phase.

Formation of Thin Film: The solution was placed in a round-bottom flask. The solvent was evaporated under reduced pressure at controlled temperature (usually 40–60 °C) using a rotary evaporator. This leaves behind a thin, dry lipid film deposited on the inner wall of the flask.

Hydration of the Film: The thin film is hydrated with an aqueous solution (phosphate buffered saline (PBS), pH 7.4). Hydration was typically carried out at a temperature above the phase transition temperature of the surfactant to ensure proper vesicle formation. Vortex was helped the lipid film peel off and form vesicles.

Formation of Multilamellar Vesicles (MLVs): Hydration process produced multilamellar niosomes (multiple concentric bilayers). These vesicles encapsulated acyclovir drug.

RESULT AND DISCUSSION:

Preformulation Study

The pure acyclovir drug was observed as white colored odorless amorphous powder. The pure acyclovir drug was soluble in water, 0.1 N HCl, Simulated Tear Fluid, Phosphate Buffer Saline (pH 7.4) and insoluble methanol and ethanol. Melting

point range of acyclovir was found as 248-252 ^{O}C. Acyclovir solution was scanned in the U.V. range of 200-400 nm using UV Visible spectrophotometer. The spectrophotometric method of analysis of acyclovir at λ_{max} 254.0 nm was found to be reproducible. The calibration curves of acyclovir were prepared in phosphate buffer solution pH 7.4, at λ_{max} 254.0 nm. The data were regressed to obtain the straight line. The correlation coefficient was observed 0.996.

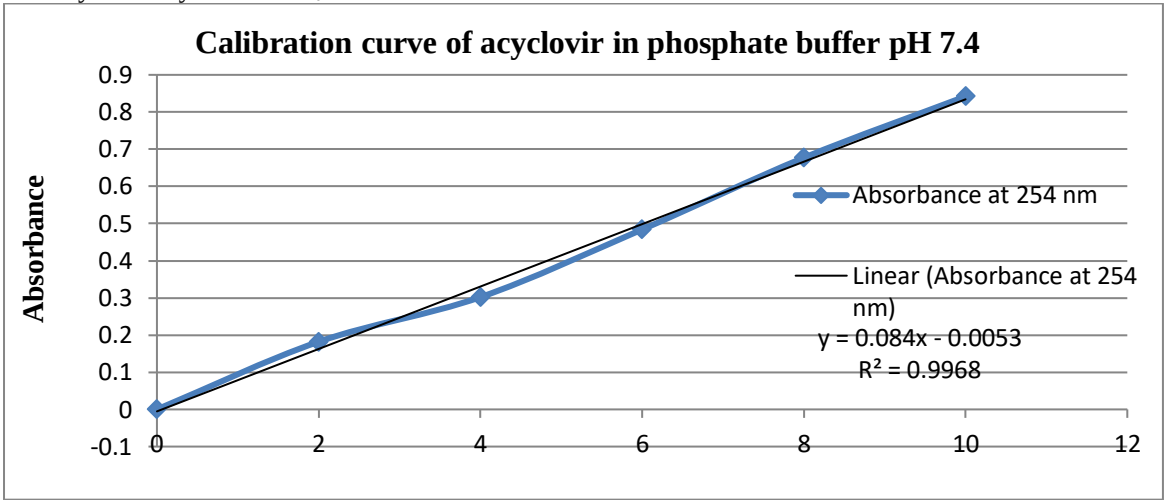

Figure 1: Calibration curve of acyclovir in phosphate buffer pH 7.4

Formulation of Niosomes

Selection of surfactants for Niosomes: Surfactants having HLB values between 16 and 17 which correspond to polysorbate 20 was found to be most effective in increasing corneal permeability. Nonionic surfactants are preferred due to less irritation power which decreases in order of cationic > anionic > ampholytic > nonionic. Water-soluble surfactants like Tween 20, Tween 80 and so forth entrapped in niosomes an increased ocular bioavailability because surfactants act as penetration enhancers which can remove the mucus layer and break junction complexes. Surfactants with an average alkyl chain length of C_{12}–C_{18} are suitable for the preparation of niosomes.

Formulation of Niosomes: The niosomes were effectively sediment on ultracentrifugation at 15,700xg for 90 min at 4°C. Optimized sonication time was 5 minutes of produced uniform vesicles size, hydration time from 30 to 45 min resulted in a higher percentage of drug entrapment. A speed of 100 rpm yielded a uniformly thin lipid film resulting in spherical vesicles on hydration. Lower and higher rpm produced thick films that formed aggregates of vesicles on hydration.

Table No. 1: Formulation of Niosomes

S. No.	Ingredients	F-1	F-2	F-3	F-4	F-5
1	Acyclovir (1 %) (mg)	100	100	100	100	100
2	Tween 20 (mg)	111	167	318	476	635
3	Cholesterol (mg)	100	100	100	100	100
4	Chloroform (ml)	20	20	20	20	20
5	Cholesterol: surfactant	1:1	1:1.5	1:1	1.1.5	1.2
6	(PBS) pH 7.4 (ml)	10	10	10	10	10

Characterization of formulated batches of Niosomes

Table No. 2: General Characterization of formulated batches of Niosomes

Batch code	Appearance	pH	% Drug entrapment ± S. D.	Viscosity (cps)	Vesicle size diameter (nm)	PDI
F1	Milky white	6.8	92.63 ± 0.59	3.083	452 ± 1.03	0.188 ± 0.01
F2	Milky white	6.7	95.72 ± 0.93	3.154	412 ± 1.03	0.189 ± 0.03
F3	Milky white	6.6	98.83 ± 0.90	3.231	454 ± 1.12	0.181 ± 0.01
F4	Milky white	6.9	94.11 ± 0.78	3.215	466 ± 0.92	0.181 ± 0.04
F5	Milky white	6.8	93.62 ± 1.01	3.532	476 ± 1.16	0.183 ± 0.03

Optical microscopy

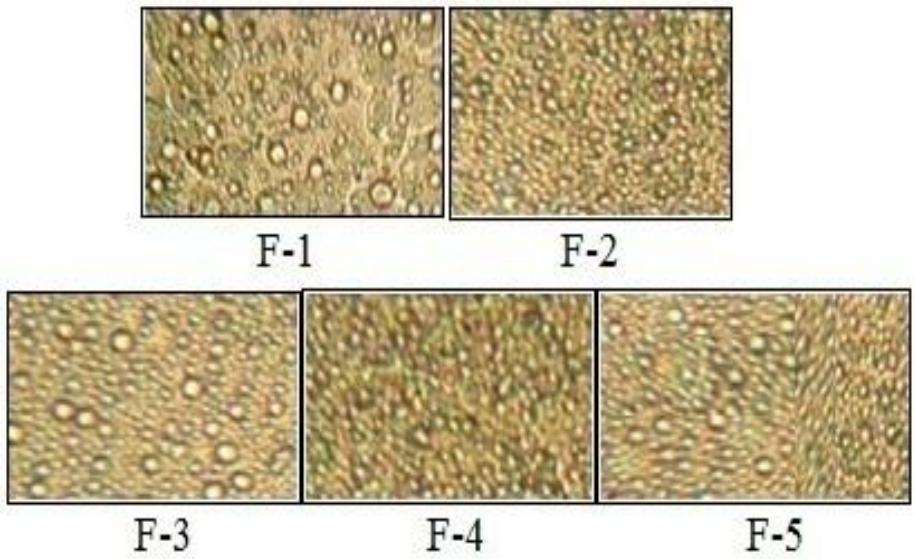

Figure 2: Optical microscopic photographs of all batches

Scanning Electron Microscopy (SEM): SEM analysis of optimized batch formulation F-3 was revealed that the prepared niosomes were nanometer size with irregular shape and surface was not smooth.

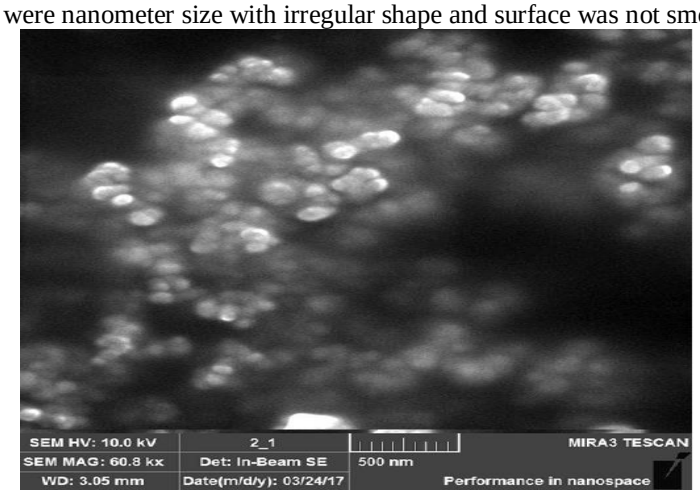

Figure 3: SEM analysis of optimized batch formulation F-3

Formulation of eye suspension incorporated niosome batches

Table No. 3: Formulation of eye suspension

S. No.	Name of ingredients	Role	Quantities
1	HPMC	Thickening agent	0.1 %
2	Boric acid	Buffering agent	0.1 %
3	Sodium chloride	Tonicity modifier	5 %
4	Sodium metabisulphate	Antioxidant	0.1 %
5	Benzalkonium chloride	Preservative	0.01 %
6	Sterile water	Vehicle	q. s.
7	Niosomes (F-3) eqiv. to acyclovir	Active Ingredient	3 %

Evaluation of Niosomal eye solution of Acyclovir

Table No. 4: Evaluation of Acyclovir Niosomal eye solution

Formulation code	pH	Clarity	Irritation Test	Viscosity(cps)
F-1	7.0	Clear	No irritation	564
F-2	7.1	Clear	No irritation	654
F-3	7.2	Clear	No irritation	776
F-4	7.0	Clear	No irritation	645
F-5	7.1	Clear	Irritating	554

7.5.1 *In-vitro* Release Studies of Niosome Formulation

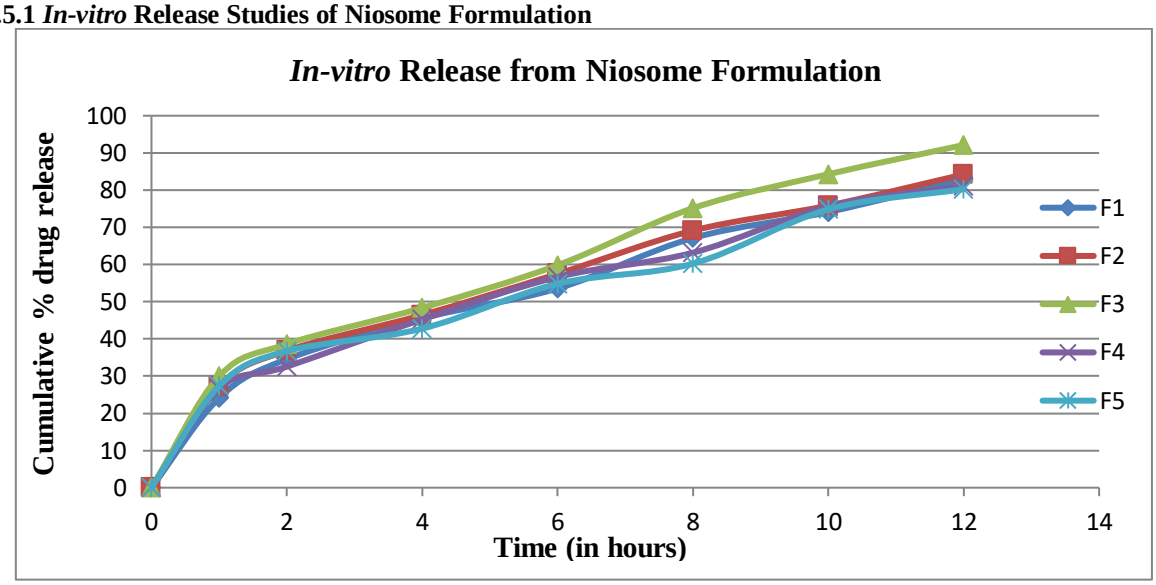

Figure 4: *In-vitro* Release from Niosome Formulation

Kinetics Modeling

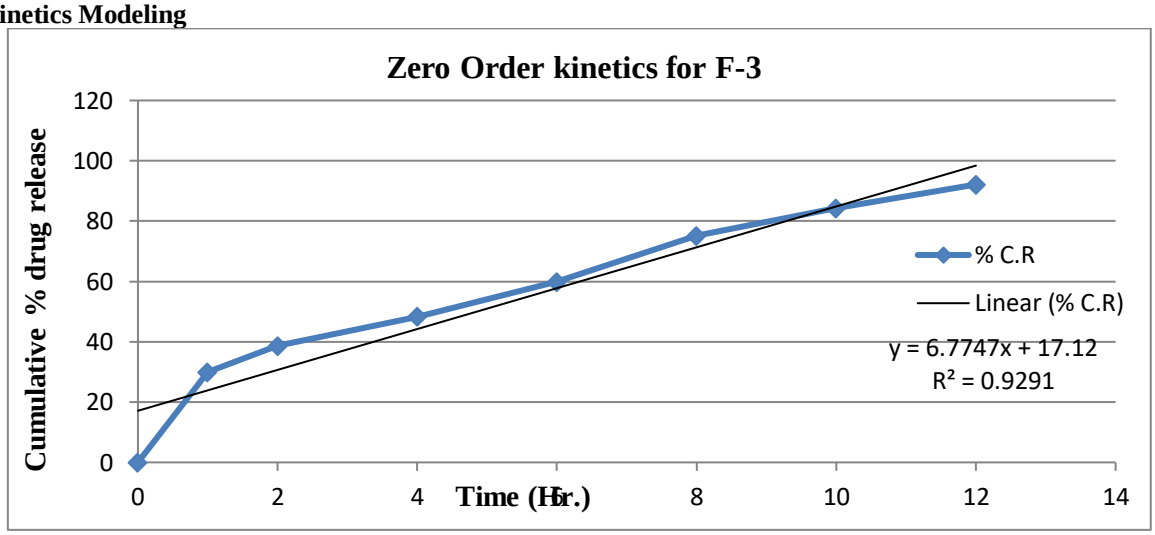

Figure 5: Zero Order kinetics for F-3

7.6.2 First order kinetic models

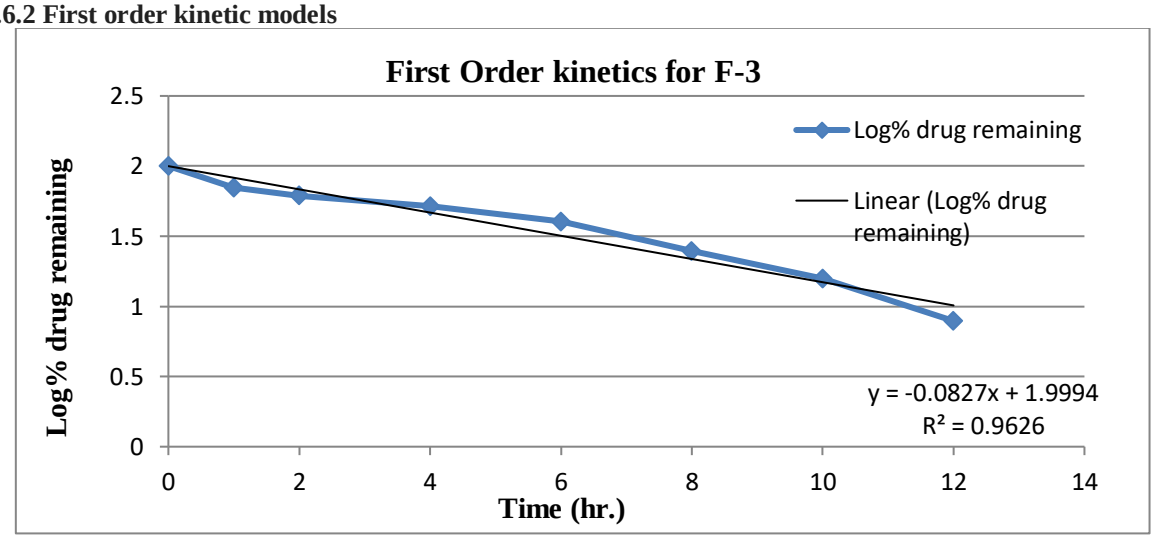

Figure 6: First Order kinetics for F-3

7.6.3 Higuchi model of kinetic

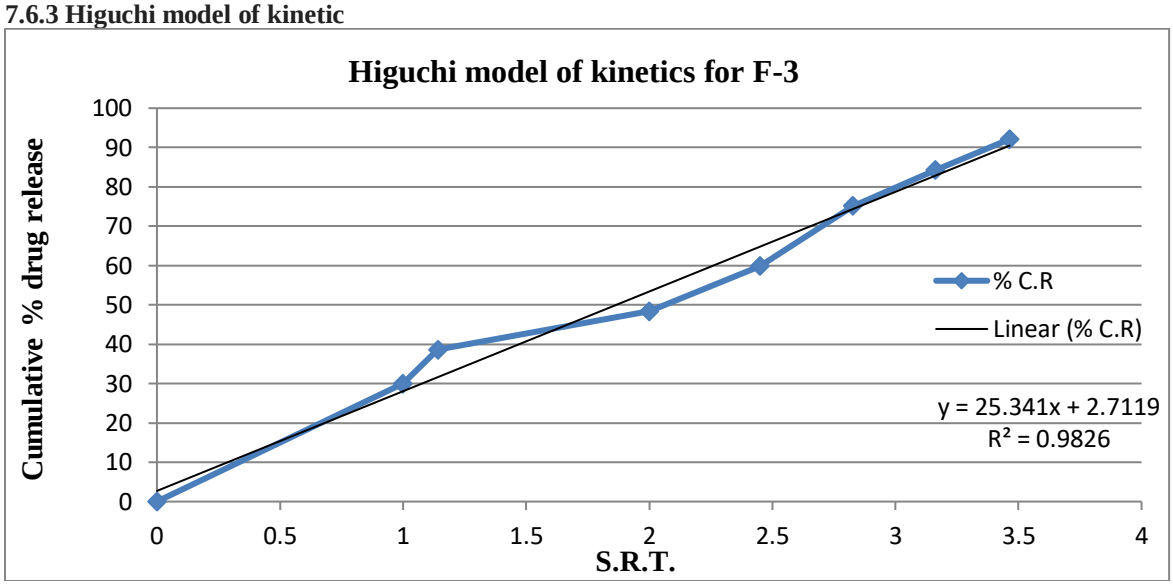

Figure 7: Higuchi model of kinetics for F-3

7.6.4 Korsmeyer- Peppas model of kinetic

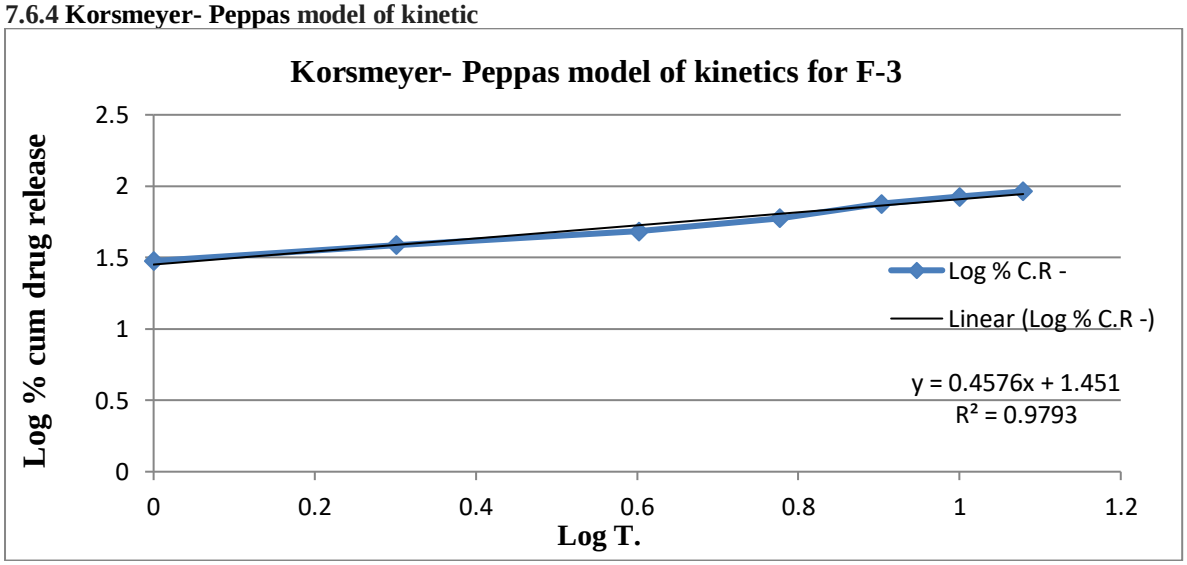

Figure 8: Korsmeyer- Peppas model of kinetics for F-3

Stability Studies

All formulations were kept in the stability chamber at specified temperature and humidity for one month. The chemical stability was assessed by the estimation of % drug remaining in the formulation; pH and physical stability was evaluated by monitoring any change.

Table No 5: Stability of acyclovir Niosomal eye solutions of at different conditions

Conditions	Evaluation Parameter	F-1	F-2	F-3	F-4	F-5
4° ± 2°C and 15 % RH	% Drug release	81.32 %	83.16 %	91.73 %	81.63 %	81.74 %
	pH	7.1	7.2	7.1	7.1	7.2
	Physical change	No	No	No	No	No
Ambient Temperature	% Drug release	82.92 %	84.22 %	92.13 %	81.11 %	80.27 %
	pH	7.0	7.1	7.2	7.0	7.1
	Physical change	No	No	No	No	No
40° ± 5°C and 75 % RH	% Drug release	83.42 %	84.73 %	91.78 %	80.11 %	79.73 %
	pH	7.1	7.1	7.0	7.1	7.0
	Physical change	No	No	No	No	No

CONCLUSION:

From the trial-and-error optimization design, drug loaded Acyclovir Niosomes were successfully evaluated. Preformulation study confirms purity of drug and compatibility of drug with excipients using FT-IR study. Span 60 was found significant with the experimental results. It was confirmed that the increasing the concentration of Tween 20 increases the deformability of niosomes. From characterization parameters and stability study, it was concluded that the formulation has acceptable morphology and particle size, no any chemical interaction and was stable at refrigerated condition respectively.

An extensive investigation is needed with reference to depth of penetration into the eye, determination of zeta potential and confirmation of configuration of phospholipids in lipid bilayer. There is a need to develop suitable formulation for commercial exploitation. Thus, the specific objective listed in the plan of work of this thesis were achieved namely design, characterization and release studies of acyclovir niosomal formulation.

CONFLICT OF INTEREST

There are no any conflicts of interests.

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