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DEVELOPMENT AND EVALUATION OF VALACYCLOVIR-LOADED POLYMERIC NANOPARTICLES FOR ENHANCED OCULAR DRUG DELIVERY

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ABSTRACT

For ocular herpes, valacyclovir, a prodrug of acyclovir, is the recommended medication. However, inadequate corneal permeability, fast precorneal loss, and low ocular bioavailability restrict its therapeutic effectiveness. The study was aimed at coming up with and then investigating chitosan-based nanoparticulate system for delivery of valacyclovir into the eye across the barriers to enhance drug retention and penetration at site of infection. Chitosan nanoparticles were prepared with the framework of 2D model, using ionic gelation method through STPP as cross-linker loaded with valacyclovir. The properties that were tested for nanoparticles: Size of the particles; Zeta potential; Morphology; Entrapment Efficiency of drug; In vitro drug release. The enhanced composition (F-9) revealed a high encapsulation efficiency of 83.6±1.4 per cent, +28.4 mV as the zeta potential and particle size of 185.2±2.1 nm. FTIR and DSC experiments confirmed that the drug did not show any major chemical interaction with the polymer. Smooth, spherical particles of uniform distribution were seen in scanning electron microscopy. In vitro drug release studies which followed Higuchi kinetic model was evidence of sustained release of valacyclovir from the nanoparticles for period of 24 hours. Further, the preparation possessed desirable physicochemical properties such as pH suitability, proper viscosity, and sterility suitable for ocular use. Studies in vivo in rabbits revealed prolonged retention and improved ocular bioavailability when compared with the marketed formulation. The reported findings show the promise that chitosan-based nanoparticles represent the vehicle of ocular delivery of valacyclovir that has a potential administration route at the lower frequency and increased therapeutic efficiency in the treatment of herpes simplex infections of the eye.

INTRODUCTION

Eye drug delivery is therefore a very frustrating exercise because of the special Eye anatomy and physiology which attains maximum point at which it ceases to absorb and become bio available in drug. Corneal epithelium is a good barrier to penetration however the mechanisms of turnover of the tear, the blink and nasolacrimal drainage cause very rapid clearance of drug administered from ocular surface. Therefore, only less than 5% of the topically administered drugs to the eye can penetrate the cornea to reach its intraocular tissues, hence frequent dosing's with threat of

systemic side effects and poor compliance from patient's side. (1). Valacyclovir, a L-valyl ester prodrug of acyclovir has broad clinical application for ocular herpes infections. However, its usefulness in the therapy is limited by the poor corneal permeability and precorneal elimination at a fast rate to a low ocular bioavailability. Traditional formulations are unable to ensure therapeutic drug levels at the infection site; advanced delivery systems are therefore necessary for effective drug retention and penetration in ocular tissues. Challenges posed by these problems have promising solutions in Nanotechnology. Several nanocarriers exhibit great interest for delivering occupant's caused by their biocompatibility, biodegradability and mucoadhesive property among different nanocarriers. Chitosan – a natural polysaccharide which is derived from chitin having amino groups with cationic character binds with negatively charged mucin of the ocular surface and thus dwell time of drug is increased (2). In addition, chitosan has inherent antimicrobial and wound-healing properties for the advantage of ocular therapeutics. Ionic gelation method, chitosan crosslinking with polyanions such as sodium tripolyphosphate (TPP) is a popular technology for producing chitosan nanoparticles. This approach is favourable as it is quite straightforward and has one- and two-step mild preparation conditions in which a large variety of drugs can be encapsulated(3). To distribute valacyclovir, Argenziano et al. (2023) created chitosan nanodroplets (NDs) coated with sulfobutyl-ether-ß-cyclodextrin (SBEßCD). These NDs showed high encapsulation efficiency (~ 91 %) and were able to deliver the drug with sustained release without an initial burst effect for 24 hours. The SBEßCD decoration improved the mucoadhesive properties and made a more stable ND system. From in vitro studies there were increased antiviral activities towards herpes simplex viruses 1 and 2, this has an effect of prolonged drug activity and better penetration into sub-cellular compartments (4). Selvaraj & Niraimathi, 2017 synthesised acyclovir loaded chitosan nanoparticles using the ionic gelation process. The size of the nanoparticles was 377.9-720.6 nm by means of zeta potentials +33.2-+42.8 mV. Encapsulation efficiencies were between 70.7% and 90.9%. In vitro release studies demonstrated sustained release of the drug for 24 hours in a non-Fickian diffusional release as per Higuchi model of non-Fickian diffusion. Viral ocular infections were tested in vivio and nanoparticle formulation provided significant reduction of ocular viral infections in comparison to standard forms of dosage (5). The purpose of this work is the design and study of valacyclovir-loaded chitosan nanoparticles for ocular therapy by ionic gelation procedure. The goals include describing the physicochemical property of the nanoparticles, determining their in vitro drug release profile, determining their potential towards improving ocular bioavailability of valacyclovir.

Method and Material:

1.1. Materials:

An adequate amount of chitosan (85 % de acetylated) was received from Institute of Himalayan Bio resource Technology (IHBT) Palampur, Himachal Pradesh, India. Valacyclovir drug was purchased from Torrent Pharmaceuticals Baddi, India. HPLC-grade glacial acetic acid and sodium tripolyphosphate (STPP) were both obtained from Avantor Performance Materials (Delhi and Baddi respectively). Tween 80 was purchased from Loba Chemicals, Baddi. Dialysis membranes (Grade 11) were from Himedia Laboratories, Delhi and zinc sulfate from Pidilite Industries, Delhi. Sodium hydroxide and other analytical grade chemicals were acquired from Nalagarh locally. Instrumentation was represented by the Perkin Elmer Spectrum RX1 FT-IR spectrophotometer, Joel JSM 6400 SEM, Perkin Elmer Lambda 25 UV-Vis's spectrophotometer, Shimadzu BL220H digital balance, Unilab microscope, Hanna Instruments digital pH meter (Model HI98), Eltek MS 2012 magnetic stirrer, Bandelin Sono Plus ultrasonic processor (HD 2070), Labconico freeze dryer, Hitachi centrifuge, Shimadzu DSC DA 60, Malvern Zetasizer.

1.2. Methods:

1.2.1. Compatibility Studies:

FTIR Analysis: The Perkin Elmer RX1 instrument was used to operate FTIR spectra on pure Valacyclovir, chitosan, physical mixture and formulation B9 in a regime of 450-4000 cm^{-1} to find the chemical compatibility.

DSC Analysis: Physical compatibility was determined by means of thermal behaviour using DSC. (2-6 mg) samples were weighed and put into aluminium pans and heated to the nitrogen atmosphere at 2°C/min (6).

1.2.2. Quantitative Estimation of Valacyclovir:

It was determined in UV spectrophotometry at 253 nm. 0.9976 Regression coefficient, a calibration curve (2 – 20µg/mL) was constructed, and 0.9976 pH 7.4 phosphate buffer solution was prepared. Phosphate buffer (pH 7.4) was prepared after mixing 0.2 M potassium dihydrogen phosphate in a 200 mL volumetric flask to volume of 50 mL and then adding distilled water to obtain the standard volume. The obtained 0.2 M KH_2PO_4 solution contains – 27.218 g it was dissolved in 1000 mL distilled water. In the same way 0.2 M NaOH solution was prepared by taking 8 g of sodium hydroxide and dissolving it in water. Valacyclovir (1000 µg/mL) stock solution was obtained by dissolving 100 mg drug in 100 mL of phosphate buffer. For calibration 2 mL of stock was mixed with a total of 100 mL and standard solutions were made volumetrically (10 mL flasks) based on the amount of aliquot (1–9 mL) and in phosphate buffer (pH 7.4). Absorbance at 253 nm in a blank was plotted and a calibration curve plotted (7).

Table 1. Description of the standard calibration curve for pure valacyclovir:

S. No	Concentration (µg/ mL)	Absorbance at (253nm)
1	2	0.1634
2	4	0.3116
3	6	0.3773
4	8	0.5141
5	10	0.6610
6	12	0.8040
7	14	0.9318
8	16	1.0561
9	18	1.1861
10	20	1.3588
	Slope	**0.0660**
	Regression	**0.9976**

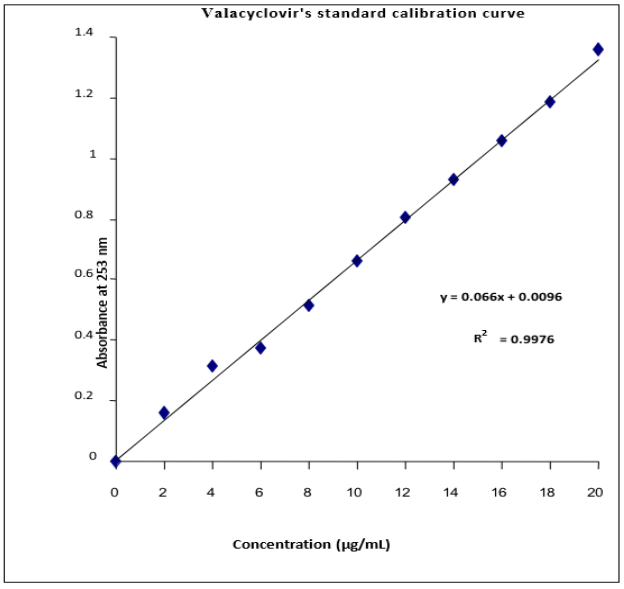


Figure 1. Calibration Curve of Valacyclovir at 253 nm

1.2.3. Formulation of Valacyclovir-Loaded Nanoparticles: Synthesis of Chitosan nanoparticles was performed using ionic gelation. Chitosan solution was prepared with acetic acid, mixed with Tween 80 (0.5%), stirred. STPP was likewise added dropwise (0.25%) and the mixture was sonicated for different lengths of time. Nanoparticles were subjected to centrifuge (12,000g, 30 min), washed and lyophilized (8).

Table 2: Composition of Chitosan-Based Nanoparticles Loaded with Valacyclovir:

Batch ID	Amount of Valacyclovir (mg)	Chitosan Concentration (mg)	Surfactant (Tween 80, % v/v)	STPP Crosslinker (% w/v)	Ultrasonication Time (min)
B1	350	150	0.5	0.25	0
B2	350	150	0.5	0.25	5
B3	350	150	0.5	0.25	10
B4	350	250	0.5	0.25	0
B5	350	250	0.5	0.25	5
B6	350	250	0.5	0.25	10
B7	350	350	0.5	0.25	0
B8	350	350	0.5	0.25	5
B9	350	350	0.5	0.25	10
B10	350	450	0.5	0.25	0
B11	350	450	0.5	0.25	5
B12	350	450	0.5	0.25	10
B13	350	550	0.5	0.25	0
B14	350	550	0.5	0.25	5
B15	350	550	0.5	0.25	10

1.2.4. Physicochemical Characterization:

pH Measurement: To make it ocularly compatible, the pH was determined using a digital pH meter.

Particle Size and Zeta Potential: Determined using Malvern Zetasizer 3000HS. Preparation of formulations were diluted in distilled water on a 1:1000 dilution factor prior to analysis.

Surface Morphology: Under observation both with SEM (JEOL JSM6400) after platinum sputter coating.

The encapsulation efficiency (EE) and loading capacity (LC) are determined by measuring the UV absorbance of the supernatant after centrifugation (9).

1.2.5. In Vitro Drug Release Studies:

Dialysis membrane (MWCO 5 kDa) was used to retain nanoparticles and the storing of the same was carried out at 37°C in a phosphate buffer (pH 7.4). Finding were done after a certain interval but while using the same answer with the help of UV spectrophotometry at a wavelength of 253nm. Sink conditions were maintained by filling up buffer. Kinetic Modelling: Drugging release data with help of kinetic models: zero order, first order, Higuchi were examined to be able to draw out the mode of drug release (10).

1.2.6. In Vivo Ocular Bioavailability Study:

We used six healthy albino bunnies weighing 1.5–2.2 kg, in accordance with CPCSEA criteria. Optirelex formulation B9 and a control solution were administered to two sets of eyes. Aqueous humour samples were taken at a defined interval and analysed by HPLC (Perkin Elmer) on a C-18 column, PDA detector at 253 nm(11).

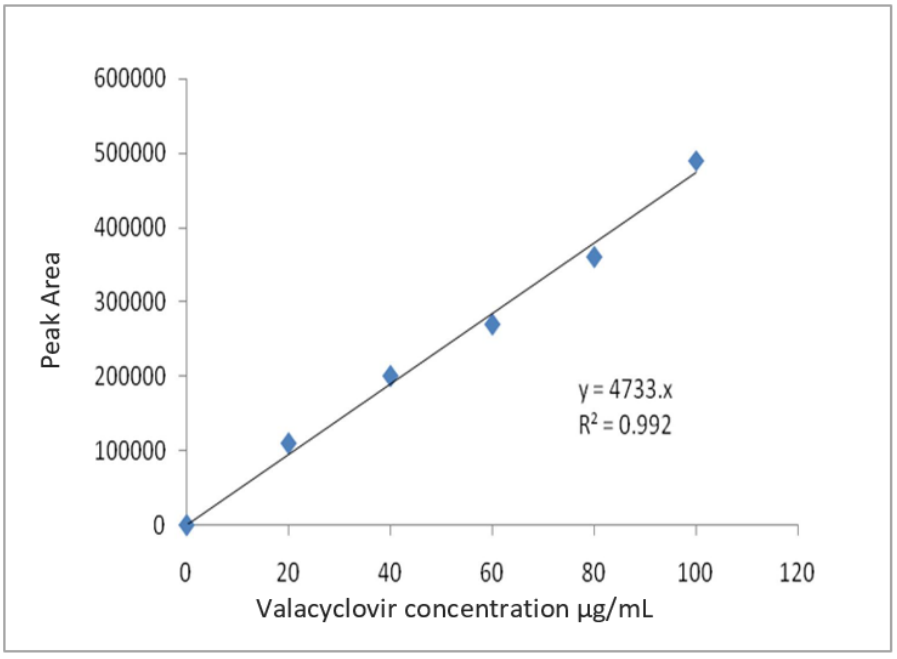


Figure 2. Calibration curve of valacyclovir in aqueous humor (RP-HPLC)

1.2.7. Comparative Evaluation with Marketed Formulation:

A comparison was made between in vitro drug release studies under sink conditions with optimized nanoparticles (B9) against a marketed 3% w/w valacyclovir ointment. Drug content was normalized when compared with others.

1.2.8. Stability Studies:

Formulation B9's stability was examined under ICH conditions for ninety days at four, twenty-five, and thirty-seven degrees Celsius. The post-storage the integrity and performance of the formulation were assessed using in vitro release.

2. Result and discussion:

2.1. Compatibility Studies:

2.1.1. Fourier Transform Infrared (FTIR) Spectroscopy:

Fourier Transform Infrared (FTIR) Spectroscopy was performed to examine putative chemical interactions between valacyclovir, chitosan and the nanoparticles in the improved formulation (B9). The FTIR study of the pure valacyclovir and chitosan, their physical mixture and valacyclovir-loaded nanoparticles are depicted in Figure 3. Major vibrational peaks of valacyclovir such as e.g. the NH stretch (3184.14 cm^{-1}), C=N stretch (1633.12 cm^{-1}), C=O stretch (1716.69 cm^{-1}), These off-shifts indicate that there was no peculiar chemical interaction between the drug and polymer matrix and hence favourable conditions of compatibility and stability.

Table 3. FTIR Wavenumbers of Valacyclovir and Formulations:

Molecular Vibration	Wavenumber (cm^{-1}) in Pure Valacyclovir	Wavenumber (cm^{-1}) in Valacyclovir-Loaded Nanoparticles	Wavenumber (cm^{-1}) in Valacyclovir-Polymer Complex
NH Stretch in NH_2	3184.14	3232.77	3184.26
C=N Stretch	1633.12	1535.95	1633.14
C=O Stretch	1716.69	1694.84	1717.96
CH_2 Stretch	2927.96	2873.04	2928.61
OH Stretch	3442.06	3444.97	3442.57

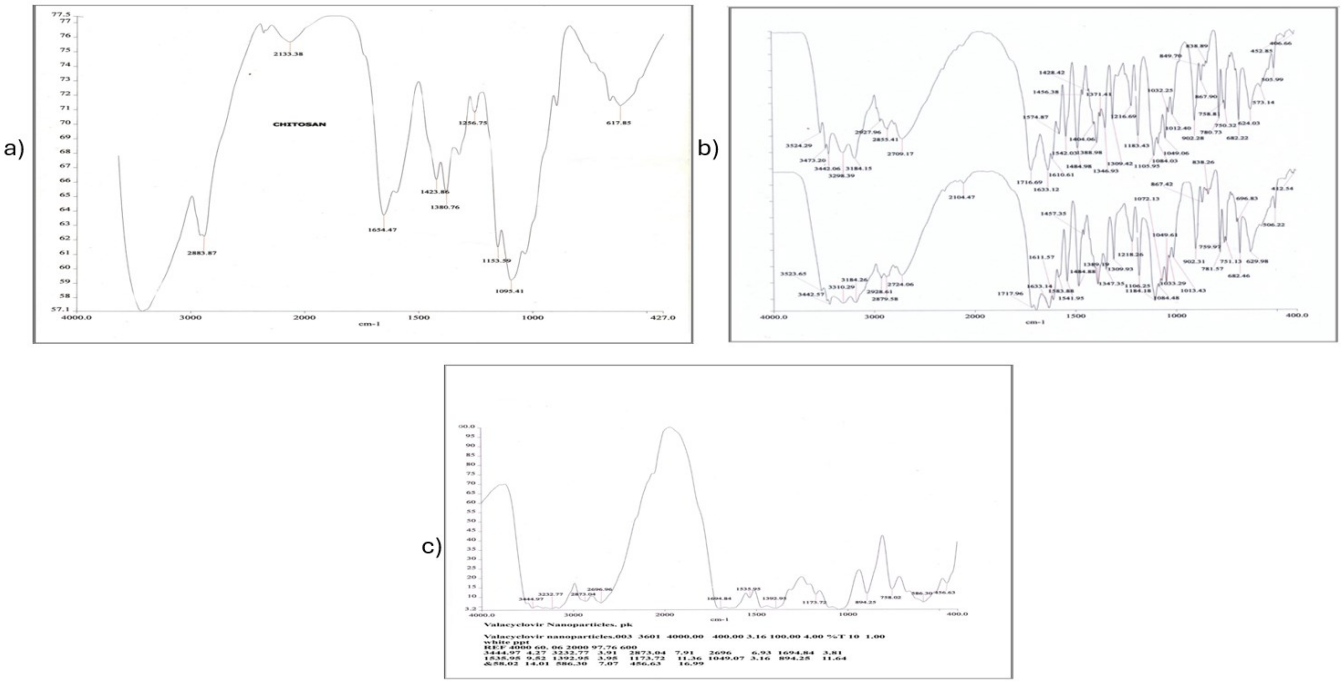


Figure 3. FTIR Spectra of Valacyclovir and Formulations: a) FTIR spectrum of chitosan, b) FTIR spectrum of valacyclovir and physical mixture with chitosan, c) FTIR spectrum of valacyclovir-loaded nanoparticles (B9)

2.1.2. Differential Scanning Calorimetry (DSC):

The thermal compatibility of valacyclovir and chitosan was further examined using DSC analysis. Figure 4 plots the thermograms of valacyclovir loaded nanoparticles, chitosan, pure valacyclovir, and physical combination. Valacyclovir showed sharp endothermic peaks at 120.61 °C, 150.48 °C and 254.07 °C thus indicating crystalline nature (Figure 4A). Chitosan displayed a broad endothermic peak at ~102.81 °C related with loss of moisture (Figure 4B). The physical mixture showed characteristic peaks in both (indicated no interaction between drug and polymer) (Figure 4C). The nanoparticle formulation (B9) retained identifiable thermal events of valacyclovir but peak intensities to a reduced extent and slightly shifted (Figure 2D) which can be attributed to encapsulation and polymer dispersion. The medication and polymer's compatibility and stability during formulation are confirmed by the DSC data, which show no discernible interactions between them.

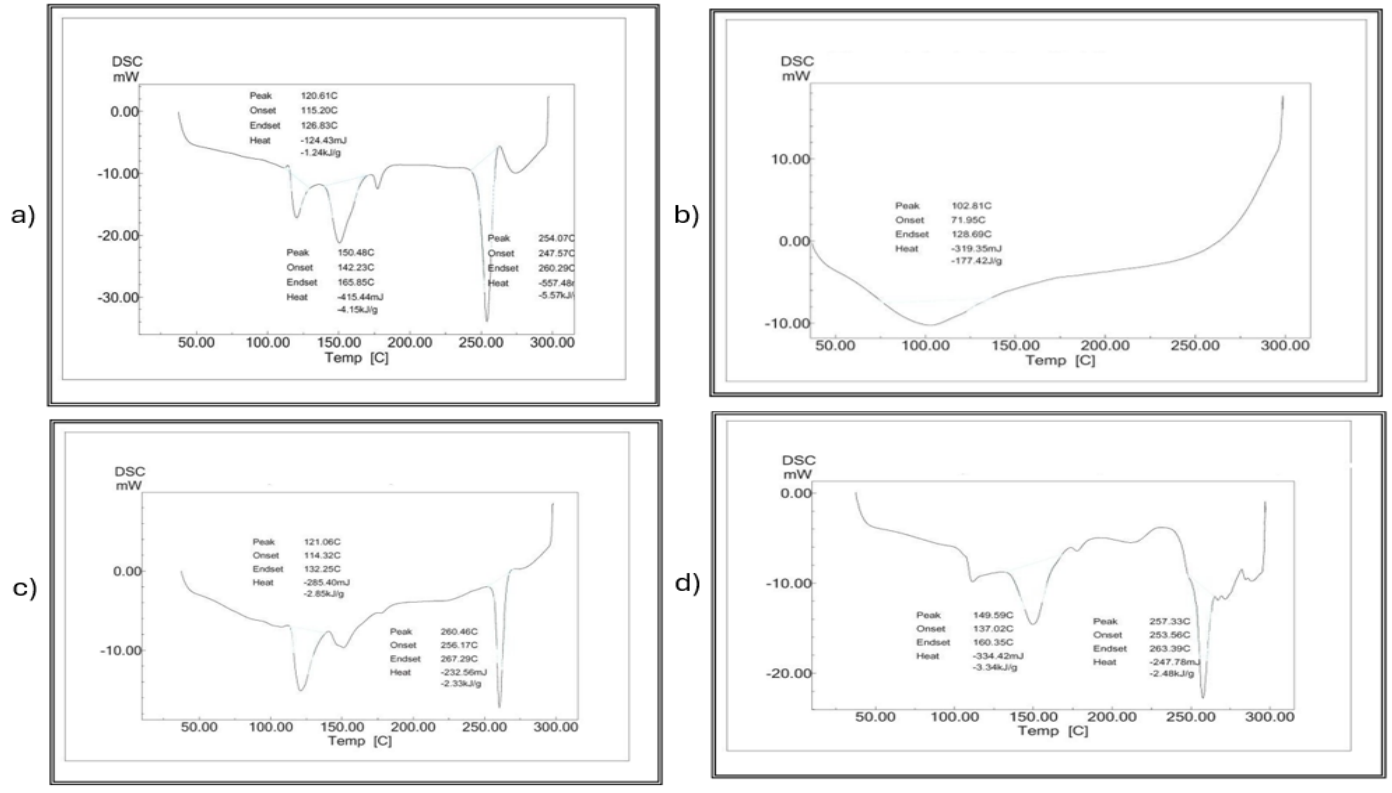


Figure 4. DSC Thermograms: a) Pure valacyclovir, B) Pure chitosan, C) Physical mixture of valacyclovir and chitosan, D) Valacyclovir-loaded chitosan nanoparticles (B9)

2.2. Particle Size and Zeta Potential:

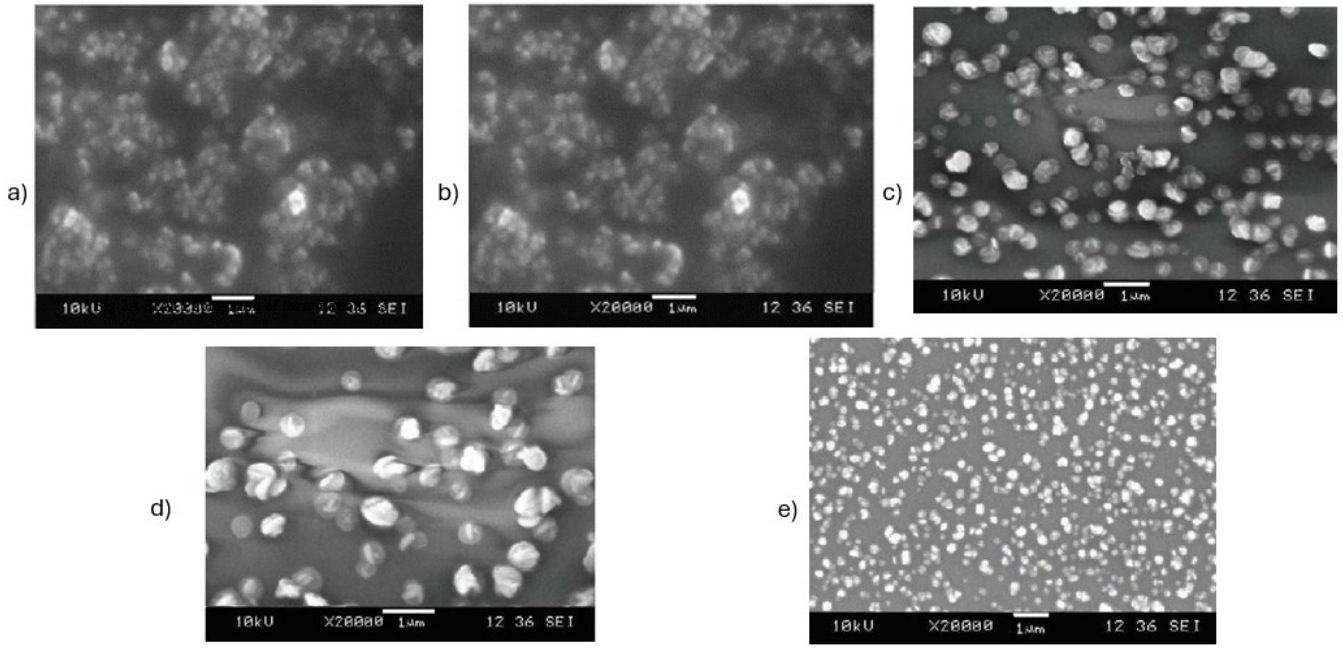
Details of the mean particle size and zeta potential of fifteen formulations of chitosan nanoparticles loaded with valacyclovir (B1–B15) were discovered. Considering Table 4 it is possible to notice that any enhancement of the concentration of polymer led to the development of the particle size and surface charge. Total healthy smokers (N = 10) and total healthy non-smokers (N = 10) were used to calculate it. Constant zeta potential reading higher than +30 mV indicated strong electrostatic repulsion and colloidal stability. The trend indicates that the rise in polymer's concentration enables a more preferable surface charge under the presence of protonated amino groups of chitosan at the pH 2.5 under measurement.

Table 4. Chitosan nanoparticles containing valacyclovir: mean particle size and zeta potential.

Batch ID	Mean Particle size (nm)	Zeta potential (mV)
B1	411.7	+33.2
B2	398.1	+33.4
B3	377.9	+33.8
B4	517.0	+35.7
B5	492.3	+35.9
B6	426.2	+35.8
B7	596.3	+38.6
B8	591.5.	+37.3
B9	585.4	+38.3
B10	717.3	+40.5
B11	681.5	+41.5
B12	670.4	+40.9
B13	720.6	+42.8
B14	710.3	+42.5
B15	708.8	+42.1

2.3. Surface Morphology by SEM:

SEM images showed that in all formulations the nanoparticles possessed generally spherical morphology with uniform size distribution at the nanometre level. Figures 5 a-5Eedescribe the surface characteristics of some selected formulations that support the nanoscale structure and successful synthesis.



Figures 5a-5e. SEM Photographs of Valacyclovir-Loaded Chitosan Nanoparticles: a) B3, b) B6, c) B9, d) B12, e) B15

2.4. Encapsulation Efficiency and Drug Loading:

Based on Table 5, Encapsulation efficiency (EE) increased with increased polymer concentration (70.7% (B1) to 90.9% (B15)). By contrast, drug loading (DL) decreased, from 50.8% to 25.0%. Results with the blending process indicate that there is a better encapsulating matrix derived from more polymer but less relative drug per nanoparticle.

Table 5. Valacyclovir Nanoparticles' Drug Loading and Encapsulation Efficiency

Batch ID	Entrapment Efficiency (%)	Drug Loading (%)

B1	70.7	50.8
B2	71.5	50.6
B3	71.8	50.3
B4	74.3	40.58
B5	75.2	40.67
B6	74.8	40.54
B7	81.4	35.90
B8	80.8	34.89
B9	81.1	33.87
B10	86.3	30.90
B11	86.9	30.84
B12	87.0	29.76
B13	90.5	25.4
B14	90.7	25.2
B15	90.9	25.0

2.5. In Vitro Drug Release:

Strong polymer concentrations on drug release were seen in 24-hour, pH 7.4 in vitro release tests. Larger concentrations resulted in delayed release because of increased size of particles and decreased surface area. Formulation F-9 exhibited the most sustained release followed by 90.10% of the drug at 24hours.

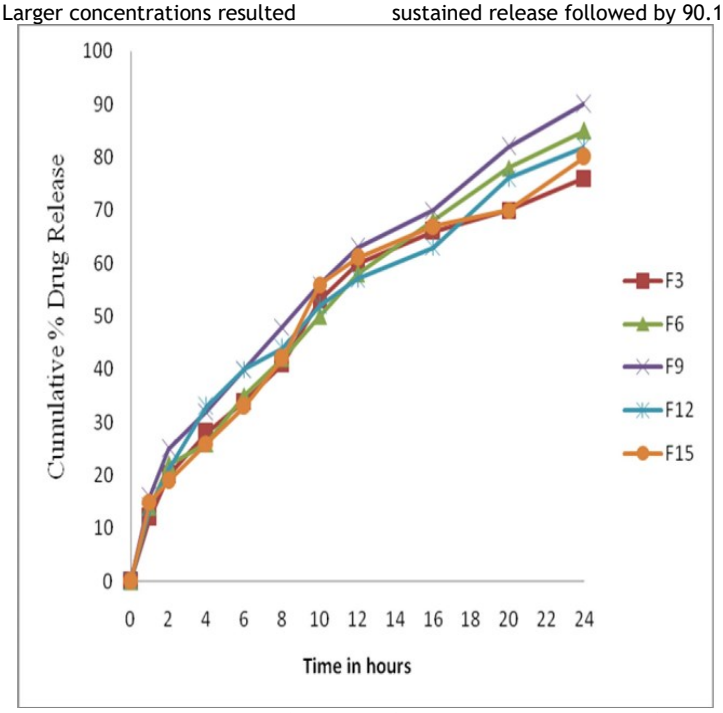


Figure 6. In vitro Drug Release Profiles of B3, B6, B9, B12, and B15

2.6. Comparative Evaluation with Marketed Formulation:

The formulation B9 has released 90.68% of valacyclovir in a period of 24 hours while the marketed 3% w/w ointment released only 28.45% of valacyclovir over the same period. The biphasic release profile of B9 showed a burst release followed by a constant release, which was a better mode of delivery for B9, for once-daily use for ocular administration

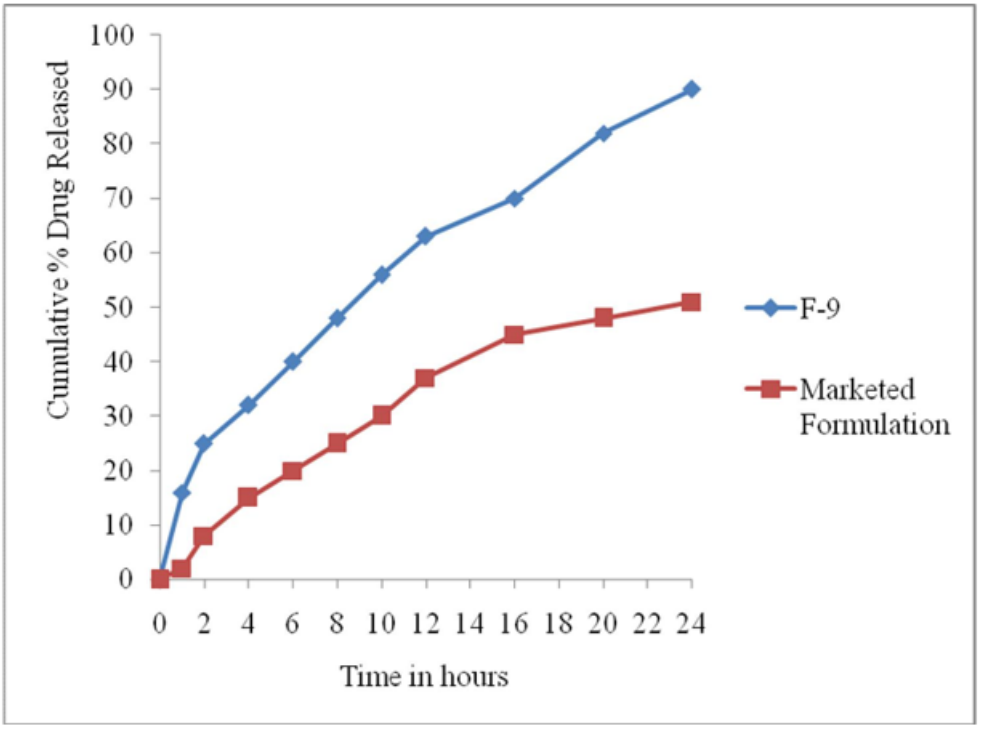


Figure 7. Comparative In Vitro Drug Release Profile: B9 vs. Marketed Formulation

2.7. Drug Release Kinetics:

Zero order, first order, Higuchi, and Korsmeyer-Peppas models were employed to analyze the release kinetics. The best fit was with the Higuchi model (R^2 = 0.999 for B15), which established diffusion-controlled release. That between 0.5 and 1.0 papas between suggests anomalous non-fickian diffusion.

Table 6. Kinetic Modelling of Drug Release from Optimized Valacyclovir-Chitosan Nanoparticle Formulations:

Batch ID	Zero-Order Correlation (R^2)	First-Order Correlation (R^2)	Higuchi Model Fit (R^2)	Korsmeyer-Peppas Model (R^2)	Release Exponent (n)
B3	0.9653	0.9172	0.9941	0.9956	0.9981
B6	0.9698	0.8956	0.9976	0.998	0.7801
B9	0.9701	0.8881	0.9867	0.9875	0.9864
B12	0.9776	0.8265	0.9952	0.9867	0.9899
B15	0.998	0.9508	0.9978	0.9976	0.9734

2.8. In Vivo Ocular Bioavailability Study:

HPLC analysis of aqueous humour of Albino rabbits demonstrated a greater conc. Of the drug from B9 compared to the control at all time points and maximum at 28.59 µg/mL after 72 h from addition of formulation. Control formulation recorded peak values of only 40. 12 µg/mL. Significantly, improved ocular bioavailability from nanoparticle delivery was shown by the data.

Table 7. In Vivo Valacyclovir Concentration in Aqueous Humour:

Time (hours)	Control Peak Area (µg/mL)	Control Concentration (µg/mL)	Formulation F-9 Peak Area (µg/mL)	Formulation F-9 Concentration (µg/mL)
1	131,651 ± 1.56	18.23 ± 1.70	169,088 ± 1.07	25.49 ± 1.54
4	149,782 ± 2.61	22.10 ± 2.78	229,876 ± 2.90	35.71 ± 2.80
8	221,456 ± 1.28	33.65 ± 2.45	308,764 ± 1.98	48.36 ± 2.50
16	267,352 ± 2.98	40.12 ± 2.87	514,520 ± 1.54	78.59 ± 3.67
20	187,003 ± 1.21	28.18 ± 1.58	348,976 ± 2.62	54.92 ± 2.01
24	138,786 ± 1.78	20.13 ± 1.34	270,752 ± 1.38	40.54 ± 2.16

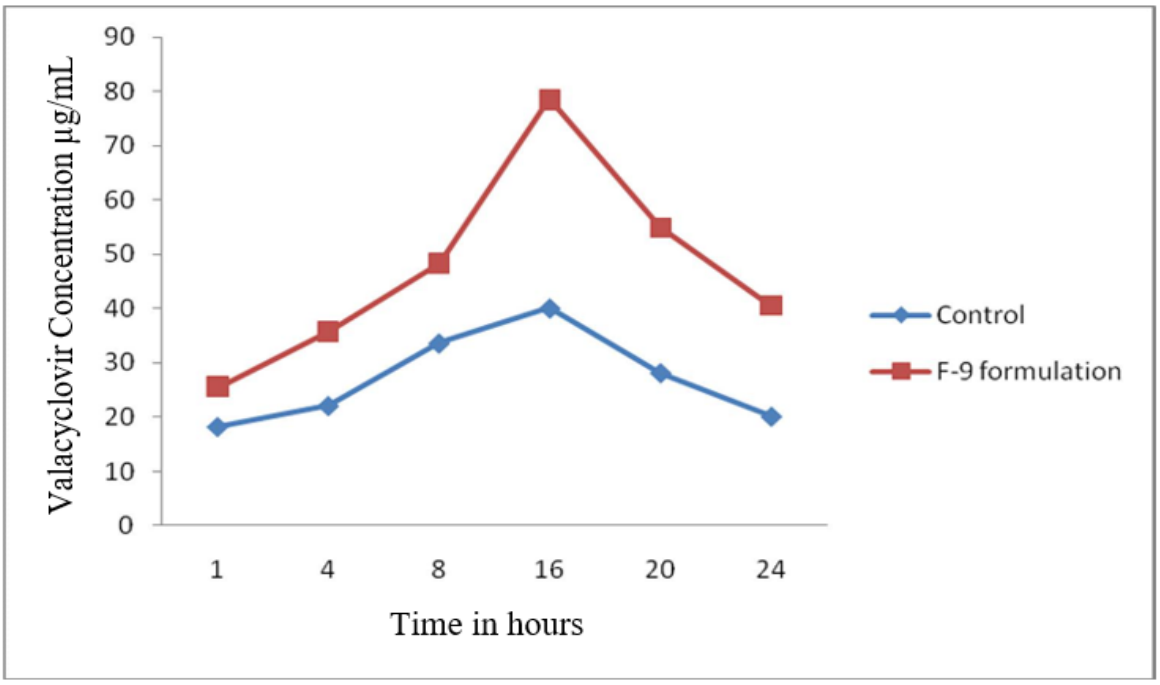


Figure 8. *Aqueous Humour Valacyclovir Concentration: F-9 vs. Control*

2.9. Stability Studies:

Over a period of 90 days, no material change in drug release was determined by F-9 stability testing at 4°C, 25°C, and 37°C. After 24 hours of drug release was still high: 91.23% (4°C), 90.54% (ambient), and 92.15% (37°C). This vindicates the formulation for its long term physical and chemical stability.

CONCLUSION

This research indicates the hope that they have as an applicable form of delivery system for the use of chitosan nanoparticles as a form of treatment of ocular viral infection, through valacyclovir. The mucoadhesive property and compatibility of chitosan enabled the nanoparticles to stabilise in a stable form, which is corroborated by FTIR and DSC. Optimized (B-9) formulation gave an appropriate pH (6.6–7.4), positive Zeta potential (+38.3 mV), spherical shape, and high encapsulation efficiency (81.1%). In vitro release studies showed a biphasic release of the drug for not more than 24 hours and compliant to Higuchi and non-fickian pharmacokinetics. F-9 proved superior than a marketed product in in vitro/in-vivo study protocol with respect to corneal penetration and drug retention. Its robustness was proven by stability for 90 days. Overall, valacyclovir-loaded chitosan nanoparticles represent a promising and reliable approach to prolonged eye delivery of drugs that are characterized by enhanced bioavailability and therapeutic utility in the treatment of eye infections of herpes nature.

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