Formulation design and *in vitro* characterization of gastroretentive floating acyclovir tablets

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Acyclovir is a thymidine kinase enzyme inhibitor used in the management of herpes zoster. Doses above 400mg exhibit poor bioavailability necessitating frequent administration to achieve the required therapeutic serum concentrations. This study aimed to design, formulate, and characterize floating tablets with enhanced bioavailability due to improved gastric retention time. The simplex lattice mixture design was employed to guide polymer proportions. Independent variables included polymers HPMC K100M, HPMC K4M, and Carbopol. The dependent variables were the floating lag time, total floating time and the cumulative drug release at 3, 6, and 8 hours, respectively. Formulation F2 exhibited the most desirable profile with a floating lag time and total floating time of 142 seconds and 14 hours, respectively and cumulative drug release at 3, 6, and 8 hours of 38.3%, 66.0% and 81.2 %, respectively. The findings indicate the feasibility of fabricating a commercially viable floating acyclovir tablet exhibiting extended gastric retention time and a controlled drug release profile.

Keywords: Acyclovir, gastroretentive floating; bioavailability; simplex lattice mixture design; controlled drug release; dissolution models

INTRODUCTION

Acyclovir, a synthetic deoxyguanosine analog, is the prototype viral thymidine kinase inhibitor.[1,2] It exhibits poor and unpredictable bioavailability owing to its low aqueous solubility (~2.5 mg/mL) and a narrow absorption window predominantly occurring in the stomach and proximal duodenum.[3,4] The drug exhibits a Biopharmaceutical Classification System (BCS) class III profile when administered in doses not exceeding 400 mg, above which it exhibits the properties of a BCS IV molecule with both poor solubility and permeability.[5]

A comprehensive review of the literature reveals that the oral bioavailability of acyclovir ranges between 15-30% .[1,6–8] The drug exhibits rapid elimination with the serum half-life being 1.5-3 hours (h) in adults and 3-4 h in neonates with unaltered renal function.[4] The oral dosage of the drug in adults with herpes zoster is extremely high (800 mg five times daily for 7-10 days).[2,9–13] The available dosage strengths in low- and middle-income countries are the 200 mg and 400 mg tablets, translating to a daily intake of 20 and 10 tablets, respectively. This high pill burden jeopardizes patient compliance as the disease prevalence is higher among the immunocompromised patients already on a cocktail of drugs including antiretrovirals, post-transplant medication and/or oncology drugs.[14]

Numerous approaches have been developed to address the poor bioavailability of drugs.[15–17] They include physical and or chemical modifications of the active ingredient as well as novel formulation approaches.[18,19] Formulation approaches may include improvement of drug solubility through particle size reduction, use of cosolvents or solubilizing agents, complexation with cyclodextrins, use of solid dispersions, among others.[20,21] In situations where poor bioavailability is attributable to extensive presystemic barriers to absorption, controlled drug release systems and the use of prodrugs have been successfully explored. The bioavailability of acyclovir may be significantly enhanced by prolonging the mean gastric residence time. This addresses the narrow absorption window that occasions limited absorption of the drug.[22] Further enhancement is achieved by controlling the rate at which the drug molecules are delivered to the absorption site, thus preventing saturation of the carrier proteins. Controlled

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release may be achieved using polymeric matrices that entrap the drug molecules and deliver them to the absorption site in an extended released fashion.[23]

Gastroretentive formulation approaches have been embraced in the last five decades for drug molecules exhibiting a narrow absorption window.[24–26] Current strategies include the use of high-density systems, floating systems, swelling or expanding devices, mucoadhesive systems or a combination of several of these approaches. This study aimed to design, develop, and characterize gastroretentive floating acyclovir tablets exhibiting desirable qualitative, quantitative, and pharmacokinetic properties It employed the design of experiment (DoE) approach to guide selection and variation of excipients to achieve an optimized pharmacokinetic profile.

MATERIALS AND METHODS

Materials

Acyclovir active pharmaceutical ingredient was a donation by Universal Corporation (Kikuyu, Kenya). Carbomer (Carbopol 934P), Hypromellose (HPMC K100M and HPMC K4M), sodium bicarbonate, polyvinylpyrrolidone (PVP), and magnesium stearate were procured from Research Lab Fine Chem Industries (Mumbai India). Analytical reagents, sodium hydroxide pellets, glacial acetic acid, and hydrochloric acid were availed by the Drug Analysis and Research Unit (DARU) of the School of Pharmacy, University of Nairobi, and were of analytical grade.

Preformulation studies

Identification of the active ingredient

The identity of acyclovir was established using Fourier-Transform Infrared (FTIR) spectroscopy employing the attenuated total reflectance over the range 500-4000cm^{-1}. The absorption peaks were matched with those of the spectra obtained from the reference standard under similar experimental conditions. The identity was further confirmed during the assay by High Performance Liquid Chromatography (HPLC) (model 1260, Agilent Technologies, California, USA) .[27]

Drug-excipient compatibility tests

The FTIR spectra of the pure drug substance and drug-excipient binary mixtures were obtained for the range 500-4000 cm^{-1} before and following storage for one month at accelerated conditions (40 °C, 75% RH) on a Shimadzu IRAffinity-1S spectrometer (Shimadzu, Carlsbad, CA, USA).[28] The resulting spectra were analyzed for peak disappearance, displacement, or any form of variation indicative of chemical and/or physical incompatibility.

Characterization of powder properties

The angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were determined to establish the flow properties of the powder blends. The tests were done in triplicate, and the average and standard deviation recorded. The funnel method was employed in the determination of tapped density.[27]

Design of Experiment (DoE)

The simplex lattice mixture design was applied.[29] Three independent factors were investigated: HPMC K100M(X_1), HPMC K4M (X_2), and Carbopol 934P levels. Their relative proportions in the formulation were varied as per the simple lattice mixture design model to a total polymer concentration of 180 mg. A total of ten combinations were randomly generated by the Design-Expert® software .[29,30] Five dependent variables were selected: floating lag time (Y_1), total floating time (Y_2) and cumulative drug release at 3 hours, 6 hours and 8 hours (Y_3, Y_4, and Y_5), respectively. The quantities of the other excipients were held constant in all the formulations. Table 1 details the actual composition of each formulation.

The ensuing data was analyzed using Design-Expert software (StatEase, Minneapolis, MN, USA). Response surface plots and contour plots were generated to detail the relationships graphically. The software was used to generate the optimized formulation with the objectives of minimizing the floating lag time, maximizing the floating time, and obtaining a controlled drug release profile with maximal cumulative drug release target being achieved at 8 hours.

Table 1: Composition (mg) of formulations in the simplex lattice mixture design

Formulation	Acyclovir	HPMC K100M	HPMC K4M	Carbopol 934P	$NaHCO_3$	PVP	Mg stearate	Total
F_1	200	180	0	0	110	45	5	540
F_2	200	0	180	0	110	45	5	540
F_3	200	0	0	180	110	45	5	540
F_4	200	120	60	0	110	45	5	540
F_5	200	60	120	0	110	45	5	540
F_6	200	0	120	60	110	45	5	540
F_7	200	0	60	120	110	45	5	540
F_8	200	120	0	60	110	45	5	540
F_9	200	60	0	120	110	45	5	540
F_{10}	200	60	60	60	110	45	5	540

Formulation of floating tablets

Ten batches comprising of varying ratios of the polymers as shown in Table 1 were prepared by direct compression employing a single punch tablet press (Inweka EP-1 GMBH Germany having a die diameter of 10 mm). The drug, polymers, $NaHCO_3$, and PVP were accurately weighed individually using a calibrated analytical balance (Sartorious Cubis II, GmbH, Goettingen, Germany) according to the DoE and passed through a mesh size 50 sieve to obtain a fine powder. The powders were blended for 15 minutes using a plastic container and a spatula employing the geometric mixing approach. Magnesium stearate was added and mixing continued for an additional 4 minutes. The resulting mixture was compressed to a target breaking force of between 60 and 80 N.

Post compression quality assurance tests

Tablet friability

The friability of the floating acyclovir tablets was established using the USP 2018 guidelines.[31]. Twenty tablets were randomly selected and dedusted. These were accurately weighed, and loaded into the tablet friability testing apparatus (Electrolab EF-2L, Electrolab PVT, Mumbai, India) set at 100 rotations (25 rpm for 4 minutes). The weight of the tablets was taken after removing any loose dust. Tests were done in triplicate. A value of less than 1% is deemed acceptable.[32,31] The friability was calculated as the percentage weight loss using the formula:

$$F\% = (W_1 - W_2)/W_1 * 100 \quad \text{Equation 1}$$

Where F, W1, and W2 represent percentage weight loss, initial weight, and final weight, respectively.

Tablet thickness and diameter

The thickness and diameter of ten randomly selected tablets were measured using a Vernier calliper SDN series (Baker Gauges PVT, Viman Nagar, Pune, India). The average values and standard deviation were calculated from the data obtained.

Tablet hardness test/crushing strength

The mechanical integrity of ten randomly selected tablets was established using a Schleuniger Pharmatron 6D tablet hardness tester (SpectraLab, Markham, ON, Canada).

Uniformity of weight test

From each batch, twenty tablets were randomly selected and their individual and total weights determined. The individual weights were compared to the average tablet weight. Compliance was achieved when the weights of no more than two tablets deviate from the average weight by >5% and >10% for a single tablet, according to pharmacopoeial specifications.[33,34]

Evaluation of drug release properties

Acyclovir calibration curve

To generate the calibration curve for acyclovir, 10 mg of the reference standard was accurately

weighed and transferred into a 100 mL volumetric flask. The powder was dissolved in 50 mL of freshly prepared 0.1N HCl and made up to a volume of 100 mL using the same solvent. The solution was sonicated for 15 minutes to homogenize at 37 °C and allowed to stand for 30 minutes. This yielded a stock solution containing 100 µg per mL. Serial dilutions were done to obtain concentrations of 2, 5, 8, 10, 15, 16 and 20 µg/mL. The absorbance of these solutions at 254 nm was determined using a Genesys 10 UV-Vis V4 spectrophotometer (Thermo Fisher Scientific, Leicestershire, UK). The tests were carried out in triplicate with the average and standard deviation being recorded.

Drug release properties and modeling of drug release profiles

The rate of dissolution of acyclovir was evaluated using USP apparatus 2 on a TrustE-14 model a dissolution tester (Electrolab PVT, Mumbai, India). The dissolution medium was 0.1 N hydrochloric acid (900 mL for each vessel) and the stirrer speed was set at 50 rpm. The bath temperature was 37±0.5 °C. Ten (10) mL aliquots of the fluid were drawn at 1, 2, 3, 4, 6 and 8 hours using automated sampling. Six samples were drawn at every instance. These were filtered using a 45 micron Whatman® filter membrane. After sample withdrawal, a similar volume of the dissolution media was added to the dissolution vessel. Samples were analyzed using UV spectroscopy at 254 nm and the average absorbance and standard deviation recorded.

Description of the dissolution profiles

The cumulative percentage of drug released was calculated at each sampling instant using the calibration curve generated earlier. The ensuing data was fitted to zero-order, first-order, Higuchi, and Korsemeyers-Peppas equations using the DDSolver Excel add-in (Microsoft Corporation, Redmond, WA.USA)[35–37]as follows:

Zero-order

$Q_t = Q_0 + K_0 t$ *Equation 2*

Where Q_t and Q_0 is the cumulative percentage of drug release at time t and time zero, respectively, and K_0 is the zero-order release constant.

First Order

$lnQ_t = lnQ_0 + k_1 t$ *Equation 3*

Where Q_t and Q_0 is the cumulative percentage of drug release at time t and time zero, respectively, and K_1 is the first-order release constant.

Higuchi model

$Q = K_H t^{0.5}$ *Equation 4*

Where Q is the cumulative drug release at time t and K_H is the Higuchi dissolution constant.

Korsemeyers-Peppas model

$Mt/M\infty = kt_n$ *Equation 5*

Where Mt/ M∞ refers to the fraction of drug dissolved at time t and k is the release constant while n is the drug release exponent that describes the mechanism of drug release.

The dissolution constants and R^2 for each model were recorded and the model with the highest R^2 values was selected.[38,39] The mechanism of drug release was determined from the value of *n* derived from the Korsemeyers Peppas equation.

Assay of acyclovir

The assay of the tablets followed the USP monograph for Acyclovir. The analysis was done using an Agilent 1260 HPLC system (Agilent Technologies, Santa Clara, CA, USA) fitted with an Xterra reversed-phase C18 5 µm (250×4.6 mm) column. The mobile phase was freshly prepared 0.02N glacial acetic acid. The operational parameters included an injection volume of 20 µL, a flow rate of 1.5 mL/min and a column temperature of 40 °C with UV detection at 254 nm. A system suitability test was carried out on six replications of the standard solution at a concentration of 0.1 mg/mL. Evaluation and quantification were done on Open Lab CD (EZ Chrom edition) Version A.04.07 ChemStation software (Agilent Technologies, santa Clara, CA, USA). The percentage label claim of acyclovir was determined using equation 6:

$L.C. = (R_u/R_s \times C_s/C_u)100$ *Equation 6*

Where L.C., R_u, R_s, Cs, C_u represent percentage label claim, the peak area of the test solution, the peak area of standard solution, the concentration of the standard solution and concentration of sample solution, respectively.

In vitro buoyancy test

In vitro buoyancy of the formulation was established by measuring the floating lag time and the total duration that they remain afloat. The test was performed in a volumetric flask containing 200 mL of 0.1 N HCl. A randomly selected tablet from each batch was placed in the flask and visually observed. The time taken for each tablet to float to the surface was recorded as floating lag time (FLT) while the total time duration during which the tablet remained afloat was recorded as the total floating time (TFT). The experiment was performed on six tablets per batch. The average time and standard deviation were computed.

Swelling index

Six tablets from each batch were accurately weighed and loaded into a volumetric flask containing 200 mL of 0.1 N HCl. The tablets were removed every hour and excess fluid removed using a blotting paper. Their weights were recorded, after which the tablets were placed back into the volumetric flask. Eight determinations were done.

The swelling index (SI) was calculated from the data using equation 7.

$SI = (W_t - W_0)/ W_0 \times 100$ *Equation 7*

Where SI is the swelling index, W_0 is the initial tablet weight and W_t is the tablet weight after time t.

Statistical analysis

The data obtained from these experiments was analyzed using the Software for Statistical and Data Science (Stata version 14, StataCorp LLC, College Station, TX, USA). Dissolution data was analyzed using DDSolver, while the effect of individual polymers and the combined effects on floating lag time (FLT), total floating time (TFT), and the cumulative drug release and the swelling index was determined using Design-Expert Software Version -12 StatEase. The significance level was set at an α value of <0.05.

Optimization of formulation

Optimization of the formulation was done in accordance with the target pharmacokinetic profile using the numerical optimization procedure. The concentration of the independent variables was kept within the range employed in the experimental design. It was found desirable to target a floating lag time of <180 seconds (s) as this minimal floating lag time reduces the risk of the dosage unit being expulsed from the gastric environment. Further, the maximum total floating time was set at 12 hours to enhance the controlled drug release profile. The target cumulative drug release profile was set as 30%, 60%, and 80% at 3, 6 and 8 hours, respectively. The highest desirability proposed by the Design-Expert was selected and the corresponding polymer composition used to fabricate the optimized formulation in triplicate.

RESULTS AND DISCUSSION

Identification of active ingredient

The FTIR spectrum of the active ingredient was concordant with that of the reference standard and that of the Reference Infrared absorption spectrum of acyclovir in the Japanese pharmacopeia.[40]

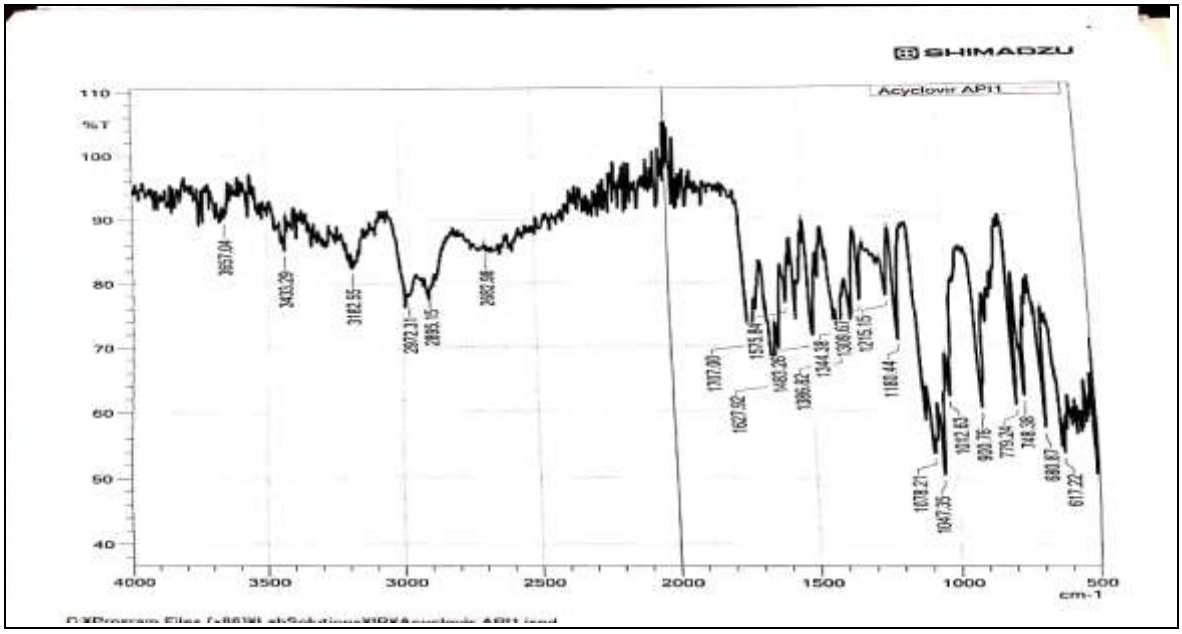

Figure 1: FTIR spectra of acyclovir active ingredient

The identity of the acyclovir was further confirmed during the quantitative analysis of the floating acyclovir tablets using HPLC. The retention times of the API and the standard were both 5.5 minutes under similar experimental conditions.

Drug excipient compatibility studies

The FTIR spectra of the binary mixtures did not reveal any incompatibilities at accelerated stability conditions (40 °C, 75%RH). All the principal peaks observed in the pure active substance were evident in the spectra of the binary mixtures.

Micromeritics of powder blends

It was established that Carbopol slightly improved the flow properties of the powder blends as evidenced by the pre-compression parameters; angle of repose, Carr's Index and Hausner's ratio for F3, F6, F7, F8, F9 and F10 in comparison with those of blends containing purely grades of HPMC. The pre-compression parameters of the powder blends are summarized in Table 2.

Post compression parameters

The direct compression of the powder blends yielded round and shiny flat plain tablets. All tablet batches complied with the USP specifications for uniformity of weight[34] and for friability. The thickness of the floating tablets was uniform for all batches (0.5 to 0.53 cm) where the minor differences may be attributed to the differences in polymeric proportions. The floating acyclovir tablets had a hardness of between 65 and 80N, which is consistent with the range of tablet hardness of other floating formulations in literature.[41,42] The compressibility of tablets varied between batches with lower compression pressures required to be proportional to the amount of Carbopol present. The post-compression experimental findings are enumerated in Table 3.

Table 2: Precompression characterization of powder blend properties

Formulation	Angle of Repose	Bulk Density*	Tapped Density*	Carr's Index %	Hausner ratio
F1	41.00	0.46	0.57	19.69	1.244
F2	41.32	0.41	0.51	21.25	1.267
F3	36.02	0.35	0.41	14.80	1.173
F4	40.40	0.41	0,53	22.43	1.280
F5	41.01	0.41	0.53	22.76	1.294
F6	39.22	0.38	0.44	14.28	1.160
F7	38.10	0.38	0.44	14.41	1.160
F8	40.10	0.41	0.48	15.62	1.190
F9	39.22	0.39	0.43	10.52	1.117
F10	39.80	0.40	0.51	20.99	1.266

*measured in g/cm^3

Table 3: Post compression characteristics of floating acyclovir tablets

Formulation	Breaking Force(N)	Average Friability (%)	Average Tablet Weight	Average Thickness(cm)
F1	69.6 ±3.1	0.743	545.25 ±7.5	0.50
F2	67.9 ±6.6	0.682	548.6 ±4.5	0.50
F3	73.6±3.7	0.392	536.3±7.8	0.53
F4	75.1±4.7	0.846	546.61±6.3	0.50
F5	70.6±3.7	0.631	550.37±4.1	0.50
F6	71.6±3.8	0.579	546.28±4.5	0.50
F7	75.3±3.8	0.842	551.02±4.6	0.51
F8	74.2±2.2	0.640	545.99±6.6	0.50
F9	76.15±2.6	0.538	547.525±4.1	0.51
F10	75.33±4.2	0.539	547.66±4.8	0.52

Buoyancy of floating acyclovir tablets

During the preliminary runs, it was determined that the proportion of polymer in the formulation had a significant effect on the floating lag time as insufficient polymer levels (24% w/w) failed to produce the gel viscosity required to entrap the carbon dioxide being generated resulting in continuous bubbling and failure to float (figure 2). Intermediate polymer proportions (27% w/w) yielded unstable floating behaviour with the tablet initially floating then sinking after reaching the surface of the fluid where the carbon dioxide was lost. These observations led to the selection of polymer levels of 33.33% w/w, which was used in the formulation of tablet batches F1-F10.

All batches achieved floatation within three minutes. The floating lag time ranged from 2.8-142 s with the shortest lag time being observed in F10, the ternary polymer blend. F2, with HPMC K4M as the sole polymer, had the longest floating lag time 142 s. Formulations containing Carbopol exhibited shorter floating lag times compared to those containing pure or binary blends the HPMC grades.

Figure 2: Continuous bubbling from a dosage unit containing 24% w/w polymer

The longer floating lag time observed for F2 could be attributable to the lower viscosity that

failed to entrap the carbon dioxide much earlier. F1, with HPMC K100 as the sole polymer, yielded sufficiently high gel viscosity to capture the gas produced hence the shorter floating lag time observed.

All formulations containing Carbopol had rapid floating times of less than 30 s. This observation may be attributed to the faster gelling of Carbopol owing to the high hydration rates, therefore, achieving rapid entrapment of the carbon dioxide produced. The binary blends containing Carbopol had floating lag time ranging between 3.86-6.15 s which could be explained by the varying viscosity of the resulting gels. The total floating time (TFT) ranged from 7 h (F3) to 48 h (F1). F3 containing pure Carbopol floated for only 7 hours with all the six tablets sinking to the bottom of the vessel, the matrix integrity of this batch was also not sustained with surface erosion being observed. The matrix integrity was maintained in all remaining nine batches. The buoyancy properties of the different batches are summarised in Table 4.

Table 4. Buoyancy properties of floating acyclovir tablets

Formulation	Average FLT[a] (s)	TFT[b] (hrs)
F1	40.0 ±3.2	48±2.0
F2	142 ±10.4	14±1.5
F3	30±0.9	7±1.0
F4	67±9.3	26±1.0
F5	120±6.4	12±0.4
F6	7±1.2	13±2.0
F7	3.86±0.3	14±0.5
F8	6.3±1.1	30±2.5
F9	2.37±0.3	14±1.5
F10	2.8±0.8	30±1.0

[a]Floating lag time; [b]Total floating time

Assay of acyclovir

All the batches complied with the USP 2019 specifications for assay (90%-110%). The acyclovir label claim ranged between 101.9 to 105.3%. Table 5 summarises the acyclovir assay results for the different batches.

Table 5: Acyclovir asay results (%) in floating tablet formulations (n=6).

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Avg. %	101.9	103.8	102.0	103.5	102.7	103.9	103.3	103.5	105.3	100.7
RSD %	1.50	1.92	0.95	1.20	1.08	0.89	0.04	1.45	1.03	0.68

Drug release characterization and modeling of dissolution profiles

The cumulative percentage of drug release for the formulations is shown in figure 3. Formulations containing HPMC K100M exhibited the highest extent of retardation for the release of acyclovir. Lower retardation effects were observed in formulations containing HPMC K4M except in F6. The lower retardation could be attributable to its lower viscosity in aqueous solutions in comparison with Carbopol 934 and HPMC K100M. The cause of the diminished release effect observed in formulation F6 was indeterminate. Carbopol 934 also had a lower retardation effect than HPMC K100M on drug release.

Combinations of the different polymers yielded higher retardation effects as evidenced by the drug release profiles of binary mixtures F4, F5, F6, F8, F9, and the ternary mixture F10 where the drug release was slower than for pure blends F1, F2 and F3. The drug release was found to be dependent on the viscosity of the polymers, where the more viscous HPMC K100M exhibited pronounced retardation effects compared to HPMC K4M that has a lower viscosity. HPMC K100M and HPMC K4M exhibit a gel viscosity of 100,00 centipoise (cPS) and4000 cPS in a 5% w/v aqueous solution at 37 °C.[43]

Modelling of drug release kinetics

All the formulations exhibited zero-order drug release kinetics where a constant amount of the drugs was released per unit time. The predominant drug release mechanism was Super case II except for formulations F2 and F5 that exhibited a non-Fickian drug release mechanism. Table 6 details the drug release kinetics of all the formulated batches.

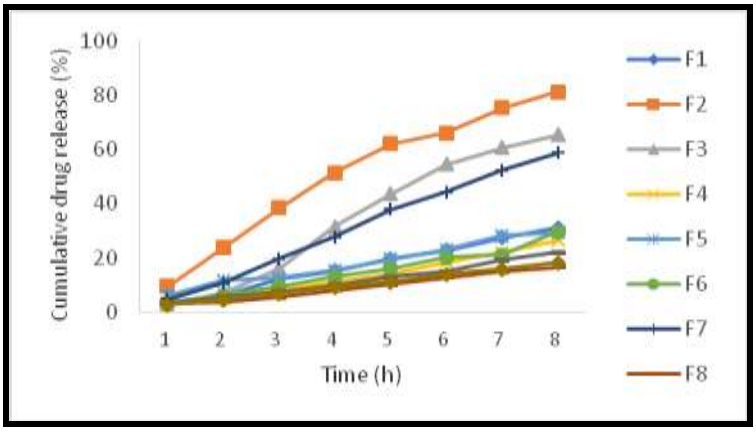

Figure 3: Cumulative drug release profile for floating acyclovir tablets in 0.1N HCl

Table 6: Kinetics modelling of acyclovir release from floating acyclovir tablet matrices

	Zero order		First Order		Higuchi		Korsemeyers-Peppas			RM[a]
	K_0	R^2	K_1	R^2	K_H	R^2	k_{KP}	R^2	n	
F1	3.879	0.9950	0.045	0.9868	9.601	0.8002	3.689	0.9968	1.028	SC II
F2	10.161	0.9686	0.18	0.9671	26.154	0.8640	14.992	0.9799	0.832	NF
F3	9.897	0.9789	0.111	0.8790	18.884	0.6962	5.179	0.9681	1.256	SC II
F4	3.334	0.9846	0.034	0.9605	7.153	0.7424	2.149	0.9932	1.201	SC II
F5	3.355	0.9839	0.045	0.9677	9.246	0.8760	5.516	0.9787	0.808	NF
F6	7.406	0.9747	0.037	0.9595	7.769	0.7632	2.788	0.9773	1.101	SC II
F7	3.619	0.9972	0.095	0.9447	18.867	0.7627	5.786	0.9951	1.128	SC II
F8	12.101	0.9851	0.022	0.9815	4.883	0.7997	2.056	0.9846	1.009	SC II
F9	9.382	0.9913	0.029	0.9836	6.190	0.7921	2.418	0.9925	1.052	SC II
F10	10.990	0.9981	0.025	0.9963	5.352	0.8181	2.340	0.9979	0.988	SC II

*RM = Release mechanism; SC II = Super case II; NF = Non Fickian

Swelling index

Formulation F3 exhibited the highest swelling index of all the formulations, and it achieved a swelling index of 370.07±18.8 % by the eighth hour. These findings are consistent with other studies where Carbopol was used in gastroretentive formulations. The high swelling index can be attributed to its high hydration rate. The matrix integrity was sustained up until the sixth hour, after which the cylindrical shape of the tablet was distorted. Formulation F2 containing HPMC K4M had the lowest swelling index of all the formulations. The tablets then started eroding from the surface with a swelling index of 46% being observed at the end of the eight hours. The tablet size attained (12 mm) was above the diameter of the pylorus and thus it could avoid peristaltic removal of the tablet from the stomach thus achieve gastroretention.

The swelling indices for F1, F4, F5, F6, F7, F8, F9 and F10 were 126, 167, 119,158,167,179,157 and 170 % respectively. The matrix integrity of these formulations remained intact throughout the eight hours, with slight distortions being observed for formulations F7 and F9 that contained high proportions of Carbopol. Figure 4 shows a comparison of the relative tablet size in the dry and wetted state. The swelling indices are illustrated in figure 5.

Figure 4: Photograph of batch F8 acyclovir floating tablets in the dry (right) and wetted (left) state after eight hours in 0.1N HCl.

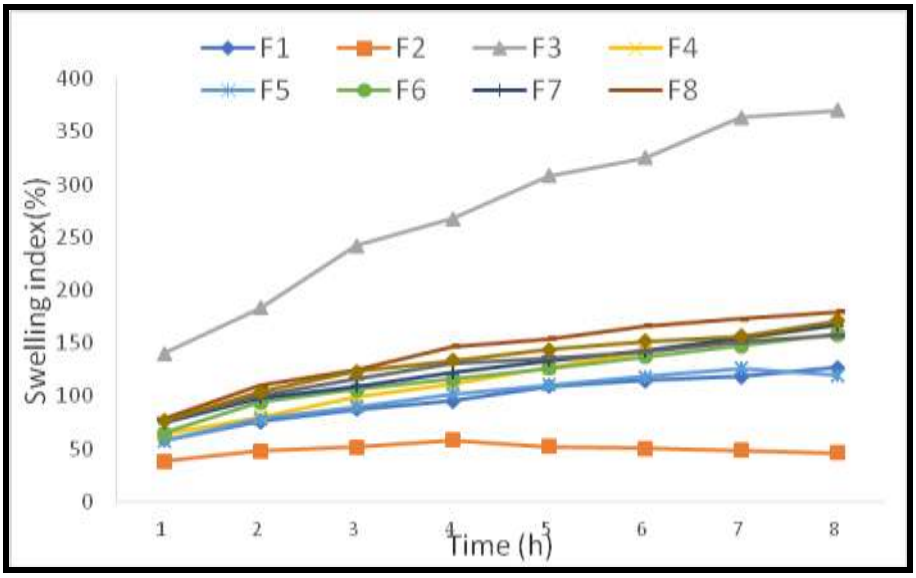

Figure 5: Graphical representation of swelling indices of acyclovir tablets in 0.1N HCl as a function of time

Statistical analysis

The data obtained was keyed into Design-Expert. The analysis was conducted to determine the model that best described the relationship between the input variables and the selected outcomes based on the regression coefficient and a significant p-value. Floating lag time (FLT) and the total floating time (TFT) were best described by a quadratic model. The mathematical expressions for the two are given in the equations8 and 9. With respect to the equations 8 and 9, the coefficients $\beta_2>\beta_1>\beta_3$ indicate that component X_2 (HPMC K4M) produced tablets with the longest floating lag time. Coefficients β_{13} and β_{23} were negative inferring to a synergistic effect in lowering the floating lag time. The main component prolonging the total floating time was found to be component X_1 (HMPC K100M).

Cumulative drug release also best fitted the quadratic model as shown in equations 10, 11 and 12. From the equations, HPMC K100M had the highest retardation effect which can be attributed to the high viscosity of the gel formed. In contrast, HPMC K4M had minimal retardation effect. Carbopol, when combined with HPMC, tended to further improve the retardation as evidenced by the higher values of the interaction coefficients. The contour plots and 3D response surface graphs for all dependent variables are shown in figures 6 through figure 10.

$$FLT = 38.89X_1 + 141.33X_2 + 36.34X_3 - 160X_1X_3 - 360X_2X_3 \quad \text{Equation 8}$$

$$TFT = 48.57X_1 + 13.57X_2 + 7.14X_3 - 53.68X_1X_2 - 26.68X_1X_3 + 385.75X_1X_2X_3 \quad \text{Equation 9}$$

$$Y_3 = 12.51X_1 + 34.97X_2 + 18.44X_3 - 59.29X_1X_2 - 38.22X_1X_3 - 52.58X_2X_3 \quad \text{Equation 10}$$

$$Y_4 = 24.95X_1 + 60.12X_2 + 56.78X_3 - 94.33X_1X_2 - 117X_1X_3 - 114.41X_2X_3 \quad \text{Equation 11}$$

$$Y_5 = 33.62X_1 + 74.02X_2 + 69.06X_3 - 114X_1X_2 - 142.39X_1X_3 - 121.53X_2X_3 \quad \text{Equation 12}$$

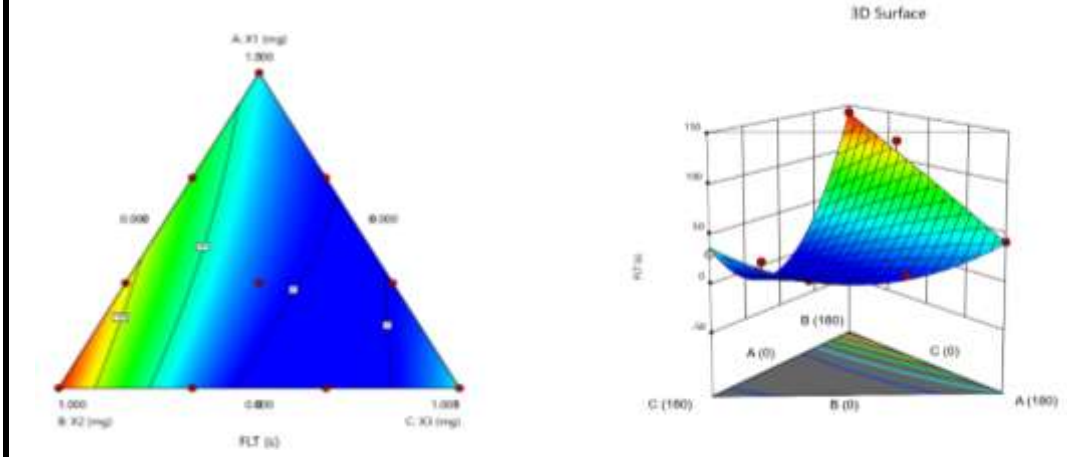

Figure 6:Contour plots and 3D plots for floating lag time (Y1)

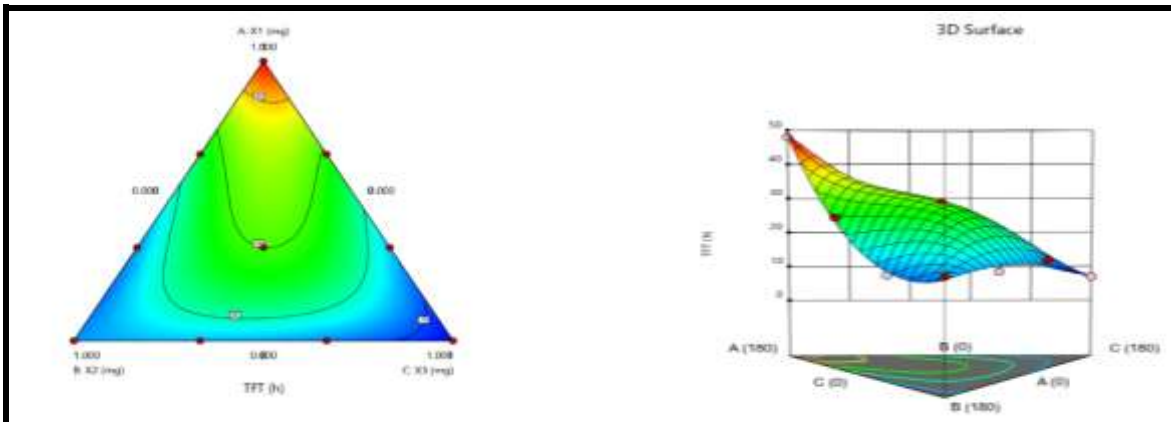

Figure 7: Contour plots and 3D plots for total floating time (Y2)

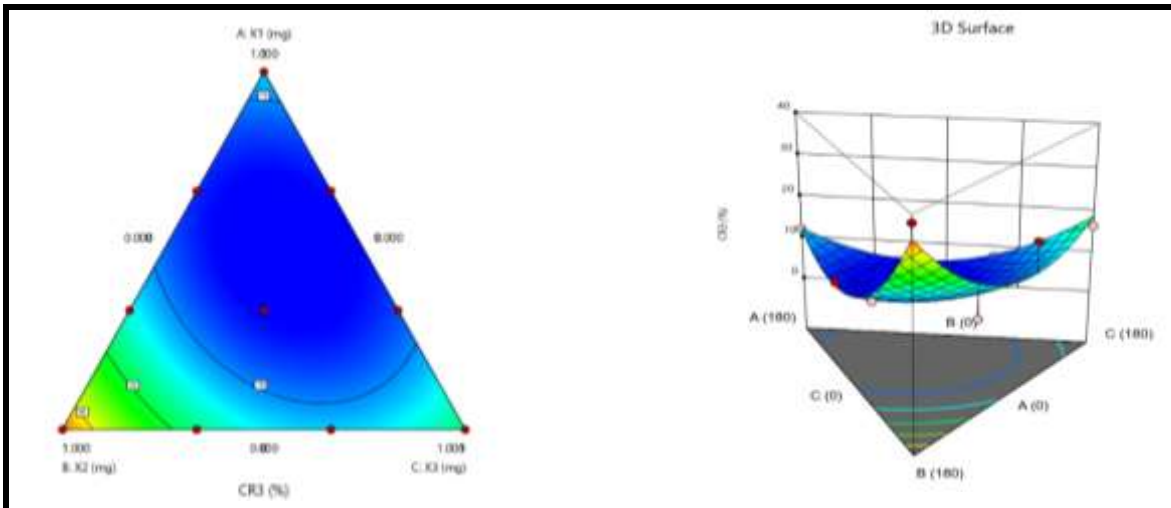

Figure 8: Contour plots and 3D surface plots for Cumulative drug release 3h (Y3)

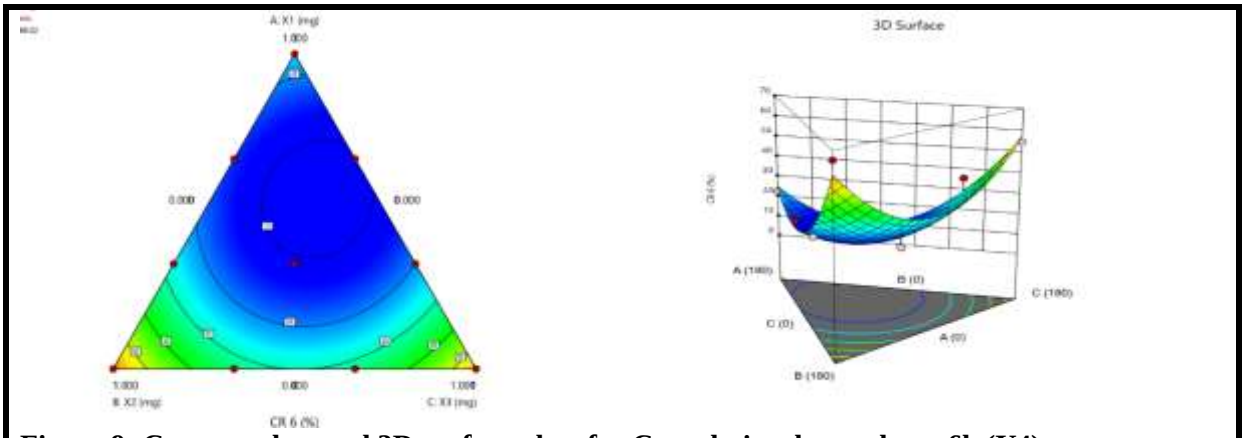

Figure 9: Contour plots and 3D surface plots for Cumulative drug release 6h (Y4)

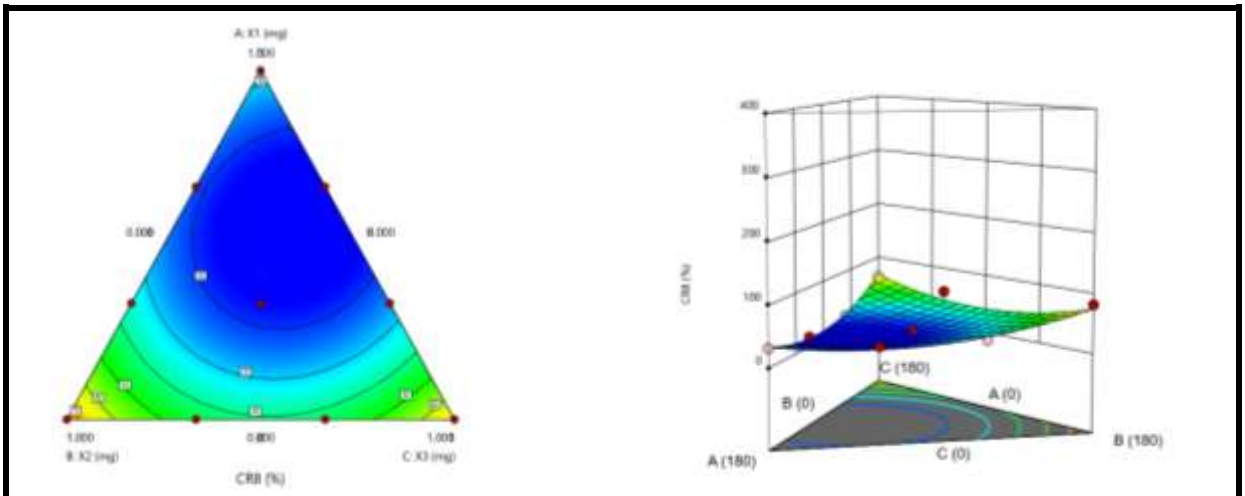

Figure 10: Contour plots and 3D surface plots for Cumulative drug release 8h (Y5)

Formulation optimization

The desirable characteristics of acyclovir gastroretentive formulations included low floating lag time, total floating time enough to last till most of the drug has been released, and a complete drug release by around twelve hours. The best desirability obtained on analysis of the various dependent variables on Design-Expert was 0.8 and corresponded to a formulation fitting that of F2, a pure blend containing HPMC K4M. This desirability index was deemed acceptable to guide the achievement of the desired product parameters. This formulation was thus considered to be the optimized batch that would ensure the optimality of the targeted pharmacokinetic parameters. Analysis of the tablets reformulated with the proposed optimized formula yielded a model predictive value of 90%, 92%, 85%, 95%, and 97% for floating lag time, total floating time, cumulative drug release at 3, 6 and 8 hours, respectively. The model predicts 100% drug release at approximately 10 hours.

CONCLUSION

Gastroretentive floating tablets of acyclovir sodium were successfully formulated using a simple lattice mixture design. The buoyancy, controlled release, and swelling properties envisioned in the experimental design were achieved. The study findings indicate that formulating acyclovir tablets with prolonged floating times and achieving a controlled drug release profile is feasible. Such formulations could result in decreased frequency of dosing, potentially improving patient compliance and treatment outcomes.

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