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Formulation and *In-Vitro* Characterization of Acyclovir Floating Matrix Tablets: A Factorial Design Study

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ABSTRACT

The objective of present study was to develop controlled release floating matrix tablets of Acyclovir using combination of release retarding polymers: hydroxypropyl methylcellulose (HPMC K15M CR) and polyethylene oxide (Polyox WSR 303) for treatment of herpes infections using direct compression technique. The influence of type of polymer and its concentration on the drug release from prepared floating tablets was investigated using a 3^2 factorial design. Independent variables selected were concentration of Polyox WSR 303 (X_1) and HPMC K15M CR (X_2) while dependent variables were percentage cumulative drug release at 3, 9 and 12 h (Q_3, Q_9, and Q_{12}). Analysis of variance (ANOVA) and multiple regression analysis showed significant effect on Q_3, Q_9, and Q_{12}. Formulations also contained sodium bicarbonate ($NaHCO_3$) and anhydrous citric acid as floating agent, polyvinyl pyrrolidone (PVP K30) as dry binder and microcrystalline cellulose (MCC, Avicel PH 102) as diluent. The floating tablets were evaluated for their floating lag time (FLT), floating duration, hardness, friability, weight variation, and *in-vitro* drug release, dissolution efficiency and accelerated stability study. F2 with Polyox WSR 303 (50 mg) and HPMC K15M CR (15 mg) gave best results. Stability study revealed optimized formulation F2 to remain stable. A controlled release floating matrix tablet of Acyclovir was successfully prepared by using Polyox WSR 303 and HPMC K15M CR.

INTRODUCTION

The oral bioavailability of many drugs is limited by their unfavorable physicochemical characteristics or absorption in well defined part of the gastrointestinal tract (GIT) referred as 'absorption window'. Most of the conventional oral drug delivery systems have shown some limitations related to fast gastric emptying time. When the absorption window is in the upper part of the GIT, a prolonged residence time of the drug product in the stomach would help in making absorption more reliable (Davis et al., 2005). Various approaches have been investigated to increase the retention of oral dosage form in the stomach, including floating systems, swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices (Singh et al., 2000). Among the various approaches explored to prolong the gastric residence time of drug products, floatation is frequently studied as mechanism for obtaining the gastroretention of dosage forms (Reddy et al., 2002). Floating systems are of two types: effervescent systems, consisting generation of carbon dioxide gas upon contact with gastric fluids, and non effervescent systems. The latter systems can be further divided into four subtypes, including hydrodynamically balanced systems, microporous compartment systems, alginate beads and hollow microspheres or microballons (Seth et al., 1984; Harrigan et al., 1977; Whitehead et al., 1996; Kawashima et al., 1992). Acyclovir is a guanine analogue used orally for the treatment and prophylaxis of initial and recurrent episodes of genital and labial herpes, for the treatment of herpes zoster and varicella (chickenpox) in immunocompetent individuals (Fiddian et al., 1984). Also safety and efficacy of Acyclovir in management of herpes simplex virus in pregnancy is well documented (Glaxo Wellcome Inc., 1999). The reported absolute oral bioavailability of Acyclovir is 10-30% in humans (AHFS Drug Information., 2004) with a plasma elimination half life of 2.5- 3.3 h and its oral dosage forms must be administered five times during 24 h, leading to the patient incompliance (Tao et al., 2009). Capacity limited as well as passive paracellular diffusion absorption mechanism for Acyclovir has been suggested indicating increased absorption with increase in contact

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time of drug solution with gut surface (Lewis et al., 1986; Kagan et al., 2008). Therefore, many attempts have been made to develop Acyclovir gastroretentive systems using different approaches (Groning et al., 1998; Tavakoli et al., 2012; Dias et al., 2009; Dhaliwal et al., 2008). Hydrocolloids of natural or semi synthetic origin are commonly used for the development of gastric floating matrix devices. Floating matrix systems containing hydroxypropyl methylcellulose (HPMC) as the matrix forming polymer swell and form a gel layer with entrapped air around the tablet core after contact with gastric fluid, this gel layer controls the drug release (Nur et al., 2000). Addition of non-ionic polymers to HPMC has been shown to slow dissolution rate and retardation to the release profiles.

This retardation has been attributed to a stronger gel layer of the resultant matrix, reducing the diffusion and erosion rate characteristics of the gel layer. Non-ionic polymer polyethylene oxide (Polyox) is the fastest hydrating water-soluble polymer among the hydrophilic polymers. The inclusion of Polyox in HPMC matrices could be beneficial in cases where slower initial drug release is required or when a shift in mechanism of drug release is desirable (Gusler et al., 2004). Polyox is an inherently dissipative polymer and non-ionic surfactant of great scientific and technological interest for a wide variety of applications, many of which depend on the properties of the polymer in aqueous solution.

Inherently dissipative polymers are co-polymers with a high degree of resistivity. Polyox is one of the most important polymers used in pharmaceutical formulations, mainly because of its non toxicity, high water solubility and swelling ability, insensitivity to the pH of the biological medium and flexibility during dosage form production. Polyox shows excellent flowability and can be used as an excipient for direct compression, whereas these tablets are characterized by a low friability and high crushing forces at low compression forces during the tabletting process.

It was expected that the good flowability properties of Polyox would be able to compensate the deficient flowability properties of Acyclovir. Also it has been shown that the higher molecular weight Polyox swells to a greater extent and tends to form, upon hydration, a stronger gel, which is less liable to erosion, if compared to the lower molecular weight Polyox (Maggi et al., 2002). Also lactose, other promising directly compressible excipient with superior compression properties was not a selected on the grounds of its reported incompatibility with Acyclovir (Monajjemzadeh et al., 2009).

The objective of the present study was the design and *in-vitro* evaluation of more promising Acyclovir effervescent floating tablets based on: (i) release retarding gel forming polymers, hydroxypropyl methylcellulose (HPMC K15M CR) and Polyox WSR 303 to combine drug diffusion and polymer erosion drug release mechanisms and (ii) a gas former like sodium bicarbonate ($NaHCO_3$). Also obvious advantages of low cost and simple direct compression technique outweighing other established methods were taken into consideration.

MATERIALS AND METHODS

Materials

Acyclovir was a kind gift from Alkem Laboratories Ltd. (Mumbai, India). Hydroxypropyl methylcellulose (HPMC K15M CR), Polyethylene oxide (Polyox WSR 303) and microcrystalline cellulose (MCC, Avicel PH102) were obtained from Colorcon Asia Pvt. Ltd. (Goa, India) as gift samples. Polyvinyl pyrrolidone (PVP K30) from Signet Pharma (Mumbai, India) and Sodium bicarbonate from Wockhardt Ltd., (Aurangabad, India). All other chemicals were of standard pharmaceutical grade or analytical grade.

Drug excipients compatibility study

Interactions in dosage forms can give rise to changes in the chemical nature, solubility, absorption and therapeutic response of drugs. Therefore, during the formulation of new drugs or the reformulation of existing products, the study of the interaction between drug and excipients in the solid state is an important stage.

Differential scanning calorimetry

In this study DSC thermograms of pure drug in 1:1 combination (physical mixture), individually with each of the excipients i.e. HPMC K15M CR, Polyox WSR 303 and PVP K30 were recorded and compared with that of pure drug using DSC TA60 WS Thermal Analyser (Shimadzu, Kyoto, Japan). The system was calibrated with a high purity sample of Indium. Heating rate used was 20°C over a temperature range of 70 - 300°C. Peak transitions and enthalpy of fusion was determined for the samples using TA60 integration software.

Fourier transform infra-red (FTIR) spectroscopy

The pure drug Acyclovir and a mixture of drug with HPMC K15M CR, Polyox WSR 303 and PVP K30 were triturated separately with infrared grade KBr in the ratio of 1:10 in porcelain mortar pestle and corresponding samples were scanned over a wave number range of 4000–400 cm^{-1} with diffraction reflectance scanning technique using Prestige 21 (Shimadzu, Kyoto, Japan) with IR Resolution software.

Factorial design experiment

Floating matrix tablets of Acyclovir were prepared based on 3^2 factorial design. The independent variables were Polyox WSR 303 concentration (X_1) and HPMC K15M CR concentration (X_2). The levels of formulation variables were selected based on preliminary studies. For X_1, selected high, intermediate and low levels were 40, 50 and 60 mg whereas same for X_2 were 15, 25 and 35 mg respectively. On the other hand, percentage cumulative drug release after 3 (Q_3), 9 (Q_9) and 12 (Q_{12}) h were the response parameters as the dependant variables. Table 1 shows the composition of factorial batches. In this study, fixed amount of sodium bicarbonate (90 mg) and anhydrous citric acid (20 mg) were used as gas forming agent to aid floating. PVP K30 (25 mg) was selected as dry binder considering its widespread

acceptability. Magnesium stearate (5 mg) and talc (5 mg) were used as lubricant and flow promoter and final tablet weight was maintained constant to 500 mg with MCC PH 102.

Table. 1: Composition of factorial design formulations of Acyclovir floating tablets.

Ingredients (mg/tablet)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acyclovir	200	200	200	200	200	200	200	200	200
Polyox WSR303	40	50	60	40	50	60	40	50	60
HPMC K15M CR	15	15	15	25	25	25	35	35	35
PVP K30	20	20	20	20	20	20	20	20	20
Sodium bicarbonate	90	90	90	90	90	90	90	90	90
Anhydrous citric acid	20	20	20	20	20	20	20	20	20
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
MCC PH102	105	95	85	95	85	75	85	75	60

Acyclovir floating tablet preparation

Tablets containing 200 mg of Acyclovir were prepared according to design depicted in Table 1, by direct compression. The respective powders, namely Acyclovir, release retarding polymers (HPMC K15M CR and Polyox WSR 303), a gas forming agent ($NaHCO_3$), and citric acid anhydrous, binder PVP K30 were passed through 40#, separately.

Mixing of powders was carried out using a pestle and mortar for 20 min. Talc and magnesium stearate passed through 60# and then added to mixed powders. Mixing was continued for another 3 min. Finally, 500 mg of each mixture were weighed and fed manually into the die of rotary tablet compression machine Labpress (Cip Machinery, Ahmadabad, India) equipped with flat faced punches (11.0 mm) to produce desired tablets. The hardness of the tablets was adjusted to 5 kg/cm^2 using a Monsanto hardness tester (Monsanto Chemical, St. Louis, MO).

***In- vitro* characterization of tablets**

Tablet weight variation

Twenty tablets were randomly selected and accurately weighed. Results were expressed as mean values ± SD.

Tablet thickness

Vernier caliper (For-bro Engineers, Mumbai, India) was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values ± SD.

Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (500 mg) was extracted in 100 mL of 0.1N HCl. The solution was filtered through a Whatman filter paper (Grade1, 11um). The drug content was determined by Double beam UV spectrophotometer Pharm Spec 1700 (Shimadzu, Kyoto, Japan) at a wavelength of 255.50 nm after a suitable dilution with 0.1 N HCl.

Tablet friability

Ten tablets were randomly selected and placed in the drum of Roche friability tester (V Scientific, Bombay, India). The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated by Eq. (1).

$\% F=(W_0-W)/W\times 100$.....Eq. (1)

Where, F=friability

W_0=initial weight of tablets

W=final weight of tablets

Tablet floating behaviour

The time the tablets took to emerge on the water surface (floating lag time) and the time the tablets constantly float on the water surface (duration of floating) were evaluated in a dissolution vessel of dissolution tester Disso 2000 (Labindia, Bombay, India) filled with 900 ml of 0.1 mol/L HCl, pH 1.2; maintained at 37±2°C, paddle rotation speed 50 rpm. The measurements were carried out for each series of tablets in triplicate.

Drug release testing

The drug release studies were carried out using the USP Type II dissolution testing apparatus Disso 2000 (Labindia, Bombay, India). The dissolution vessels were filled with 900 ml of 0.1 mol/L HCl, pH 1.2, maintained at 37 ± 2°C, paddle rotation speed was 50 rpm.

The samples were taken at preselected time intervals and were analysed at 255.50 nm spectrophotometrically after suitable dilution using Pharm Spec 1700 (Shimadzu, Kyoto, Japan). Cumulative percentage drug release was calculated using PCP Disso V3 Software (Poona College of Pharmacy, Pune, India) with use of calibration curve.

Dissolution efficiency

The dissolution efficiency of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain limit, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It was calculated by the Eq. (2) using PCP Disso V3 software (Poona College of Pharmacy, Pune, India).

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100 \quad \text{.....Eq. (2)}$$

Where, y is the drug percent dissolved at time t.

Kinetics of drug release

To describe the kinetics of the drug release from the floating matrix tablets, mathematical models such as zero-order, first-order, Higuchi, Hixon–Crowell and Koresmeyer-peppas were used (Higuchi T et al., 1963; Korsmeyer RW et al., 1983). The drug release data was evaluated by model- dependent (curve fitting) method using PCP Disso version 3.software (Poona College of Pharmacy, Pune, India) and model with the highest correlation coefficient was considered to be best model.

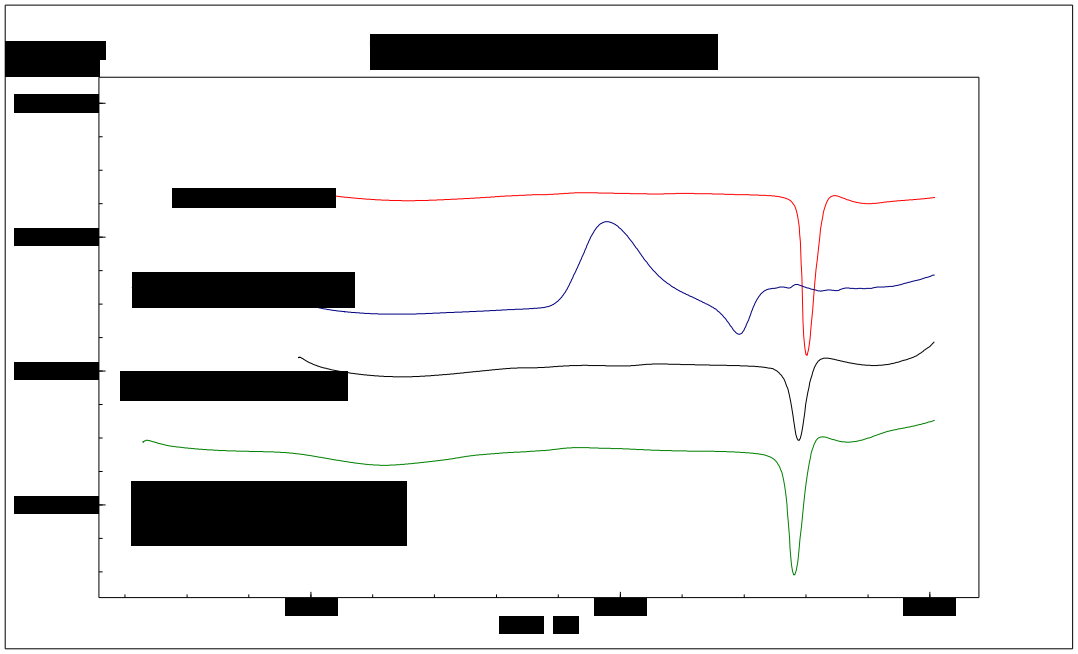

Fig. 1: DSC thermograms of pure Acyclovir and Acyclovir with various formulation excipients.

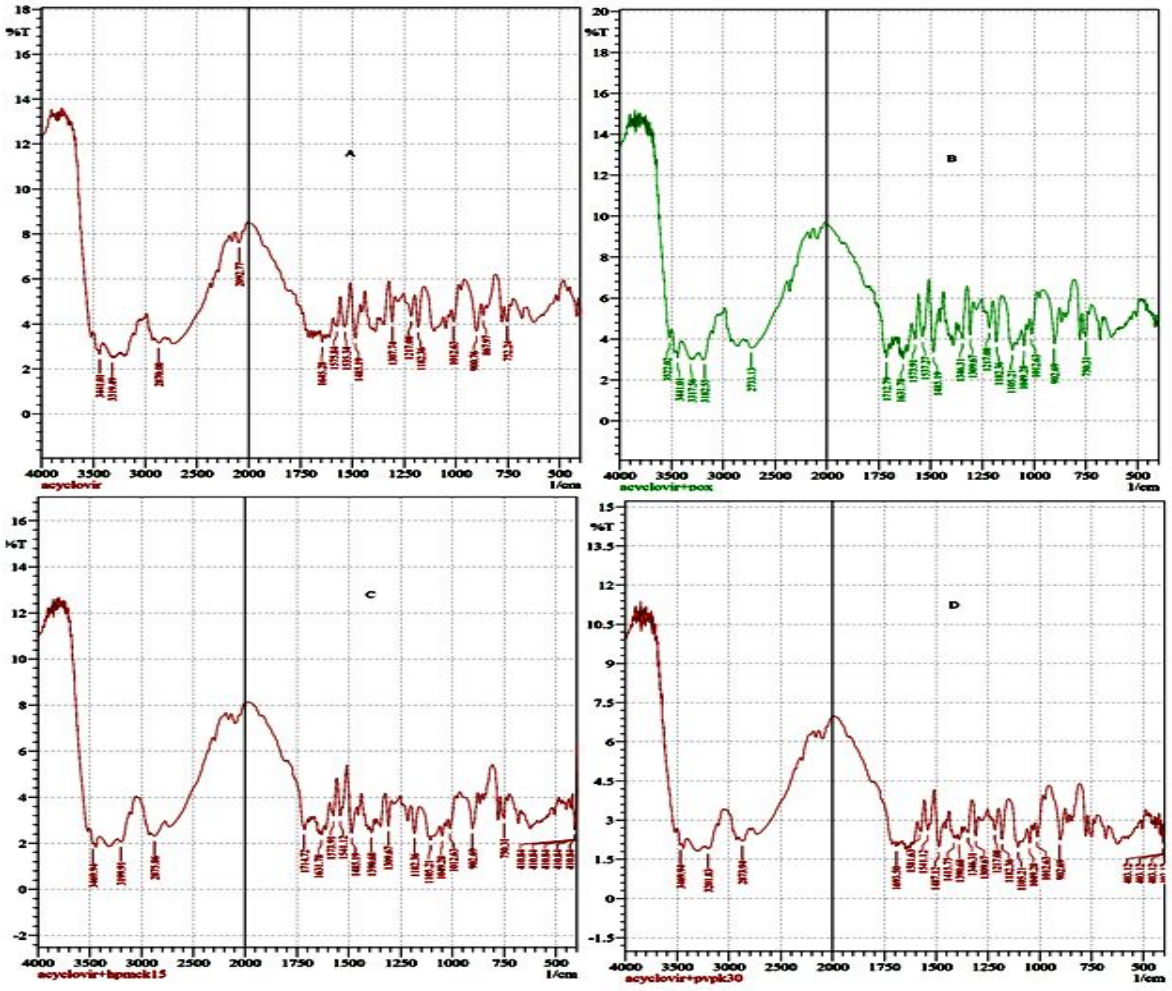

Fig. 2: FTIR spectrophotograms of (A) Acyclovir and physical mixture of Acyclovir, (B) with Polyox WSR 303, (C) with HPMC K15M CR and (D) with PVP K30.

Statistical analysis of data

Traditional designing of the pharmaceutical formulations are based on time consuming approach of changing one variable at time which does not take into consideration the joint effect of independent variables. The factorial design can serve as an essential tool to understand the complexity of the pharmaceutical formulations. The results can be expressed either as simple linear or second order polynomial equation to statistically evaluate the responses obtained after experiments. A 3^2 factorial design was selected or the two factors were evaluated at three levels. Polyox WSR 303(X_1), HPMC K15M CR (X_2) were selected as independent variables and Q_3, Q_9, Q_{12} were the dependent variables. The data obtained were treated by Design expert version 7.1.6 software (Stat Ease Inc., Minneapolis, USA) and analysed statistically applying one way analysis of variance (ANOVA) for differences in average of data. Differences between formulations were considered to be significant at $p < 0.05$. The data was also subjected to 3-D response surface methodology to study the interaction of dependent variables.

Stability studies

The optimized formulation (F2) was packed in aluminium foil and subjected to stability studies as per ICH guidelines, 40°C ± 2°C/75% RH ± 5% RH (Thermolab) (ICH Q1A (R2)). Samples were withdrawn at time intervals of 1, 2 and 3 month. The samples were evaluated for appearance, hardness, friability, assay and *in-vitro* release profile.

RESULTS AND DISCUSSION

Drug-excipients compatibility study

Differential scanning calorimetry

Obtained DSC thermograms of pure drug Acyclovir and Acyclovir in 1:1 physical mixture with each of different formulation excipients viz. HPMC K15M CR, Polyox WSR 303 and PVP K30 are compiled in Fig 1. Summary of thermal parameters of DSC study of Acyclovir in combination with each of the formulation excipients and the changes that occurred with characteristic endothermic peak of Acyclovir is provided in Table 2. From DSC thermogram (Fig 1) it is clear that the thermograms of the mixtures containing Acyclovir in combination with HPMC K15M CR, Polyox WSR 303 and PVP K30 exhibit all the thermal features of the individual components. The DSC analysis shows no change in endothermic peak of Acyclovir indicated that there was no drug‑excipient incompatibility/interaction.

Table. 2: DSC parameters of Acyclovir in combination with excipients.

Drug + Excipient	Sample weight (mg)	Range drug (°C)	T_{peak} (°C)	Heat of fusion (ΔH)
Pure Drug	2.790	257.89-265.09	260.37	-130.30
HPMC K15M CR	4.270	252.82-261.19	256.00	-81.90
PEO WSR303	4.100	231.78-244.55	238.39	-44.19
PVP K30	4.630	253.66-262.06	257.73	-48.27

Fourier transform infra-red (FTIR) spectroscopy

Fig 2 shows the FTIR spectrums of the pure drug Acyclovir, physical mixture of Acyclovir individually with Polyox WSR 303, with HPMC K15M CR, and with PVP K30. No predominant drug interaction was detected. Although, there were some mild interactions in the wave number 3600-3200 cm^{-1} and 1500-800 cm^{-1}. The region 3600-3200 cm^{-1} is a stretching region of the functional group N-H, C-H of aromatic ring (3100–3000 cm^{-1}), O-H (3200 cm^{-1}) and C-H of alkenes (3100–3000 cm^{-1}) and C-H of alkane (3000 cm^{-1}). The region 1500–800 cm^{-1} is the stretching region of the functional group C-OH of alcohol (1400–1075 cm^{-1}). In the region 1500–800 cm^{-1}, the weak drug interaction was noticed at 1307.74, 900.76 cm^{-1} in case of Acyclovir mixtures with HPMC K15M CR, Polyox WSR 303 and PVP K30.

Physicochemical characteristics of tablets

Controlled release Acyclovir floating tablets were developed using release retarding gel forming polymers like HPMC K15M CR in combination with Polyox WSR 303 and a gas forming agent like $NaHCO_3$. The selection and incorporation of microcrystalline cellulose in the designed systems imparted superior flow and enhanced powder compaction in direct compression. Also overall tablet swelling was increased due to synergistic effect of celluloses (MCC and HPMC). Moreover, it was proved that microcrystalline cellulose is capable of swelling in contact with aqueous fluids as simulated gastric fluid leading to an increase in the water uptake capacity, porosity of the matrix and consequently would enhance floating abilities (Garg et al., 2009). Recent study characterized the influence of the tablet hardness on the floating lag time and the diltiazem hydrochloride release and concluded that tablet hardness had no or little effect on the drug release profile but was a determining factor with regard to buoyancy of the tablets (Gambhire et al., 2007).

Increasing the hardness (>5-6 kg/cm^2) would possibly lead to prolongation of the floating lag time by affecting the rate of the tablet penetration by the dissolution medium. Based on these conclusions, the hardness of the floating tablets was adjusted, in the current work, to 5 kg/cm^2. The physicochemical properties of the tablets are summarized in Table 3. The thickness of all tablet batches ranged from 4.98 ± 0.07 to 5.17 ± 0.11 mm. All the tablet formulae showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The weight of the tablets ranged from 502.4±0.9 to 512.3±1.2 mg. All the prepared formulae meet the USP requirements for weight variation tolerance (United States Pharmacopeia., 2004). Drug uniformity results were found to be good among different batches; the percentage of drug content ranged from 97.30% to 103.20%. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance.

Floating lag time and duration

The investigated gastric floating systems employed $NaHCO_3$ as a gas forming agent dispersed in combination with

anhydrous citric acid in a hydrogel matrix made up of HPMC K15M CR and Polyox WSR 303. These fabricated matrices upon arrival in the stomach entrapped carbon dioxide gas liberated by the acidity of the gastric contents in the jellified hydrocolloid. A decrease in specific gravity caused the dosage form to float. The *in-vitro* testing revealed the ability of most formulae to maintain buoyant for more than 12 h (Table 3). This suggested that the gel layers, formed by the investigated polymers, were strong enough to efficiently entrap generated gas bubbles. The possible increase in tablet porosity due to MCC made it float on the test medium (0.1 N HCl) for this extended period of time. The extended residence time of drug in stomach could cause increased absorption due to the fact that the duodenum is the main absorption site for Acyclovir. Progressive decline in floating lag time in case of batches F1 through F3 can be attributed to increasing concentration of gel forming polymers resulting in fast formation of CO_2 bubble entrapping membrane. Further batches F4 through F9 shows general pattern of increased floating lag time which may due to initial resistance provided by strong and rigid gel barrier on tablet surface to water permeation in core tablet necessary for formation of sufficient CO_2 bubble. Thus it may be inferred that optimum concentration of gelling polymers is necessary for low FLT and too high concentration may result in increase in FLT.

Drug release studies

The *in-vitro* drug release from tablet of all formulation was performed in triplicate using USP apparatus II (paddle method) using 0.1 N HCl as a dissolution media for 12 h time period and the obtained results are summarized in Fig 3. Depending upon type and concentration of the investigated polymers in the current study, variable drug release profiles were successfully tailored. The influence of HPMC K15M CR and Polyox WSR 303 combination concentration on the release of Acyclovir from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5°C was shown in Fig 3. It is clear that all formulae succeeded in controlling the rate of drug release for 12 h. However, the drug release rate was dependent on the type and concentration of the investigated polymer. Obtained drug release can be considered as combination effect of swellable / non erodible system characteristics of HPMC and a swellable / erodible principle (Polyox). The degree of retardation of the drug release rate from formulations was a function of HPMC K15M CR and Polyox WSR 303 concentrations. Increase in Polyox WSR 303 concentrations resulted in decreased cumulative Acyclovir release. But the pattern seen from batches containing low (F1 through F3), intermediate (F4 through F5) and high (F6 through F9) level concentrations of HPMC K15M CR contained increased *in-vitro* drug release with HPMC K15M CR level. The reason may be inherent hydrophilicity of HPMC K15M CR at low concentrations was more predominant factor in controlling Acyclovir release than its barrier gel properties. The higher viscosity of HPMC K15M CR and Polyox WSR 303 would promote the formation of highly viscous gels upon contact with aqueous fluids. This would promote retardation of the drug release rate. In a parallel line, Siepmann and Peppas (Siepmann et al., 2001) suggested that the drug release from HPMC matrices is sequentially governed as follows: (i) At the beginning, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. (ii) Due to the imbibition of water, HPMC swells resulting in dramatic changes of polymer and drug concentrations and increasing dimensions of the system. (iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradients. (iv) With increasing water content, the diffusion coefficient of the drug increases substantially. It is worth to note that no burst effect was observed with any formulations. This was due to the successful inclusion and selection of concentration of PVP K30 as dry binder in formulae. PVP K30 was included in formulae taking into consideration the fact that the gel layer, which controls the drug release rate, needs some time to become effective. Another reason may be, as suggested by Kulkarni and Bhatia (Kulkarni et al., 2009), the higher HPMC K15M ratio can effectively reduce the burst drug release by conversion of gel-like networks surrounding these matrices into strong surface barriers upon contact with aqueous media Taking into consideration the objective of the work, achieving a compromise between excellent floating behavior (very short floating lag time and prolonged floating duration) and controlled drug release characteristics, formula F2 was chosen for further stability study.

Dissolution Efficiency

The dissolution efficiency of all factorial design formulations were found between 29.75-50.52% for 0.1N HCl at 12 h. The variation pattern of dissolution efficiency with the formulation was shown in Fig 4.

Drug release kinetics

Drug release kinetics involves drug release mechanism and drug release rate. In present study the dissolution results were analyzed by PCP Disso Version 3.0 software to study the kinetics of drug release. The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion, but in addition, other processes like relaxation of the polymer chains, which influences the drug release mechanism, are also important. This process is described as non-Fickian or anomalous diffusion. Release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains. The thermodynamic state of the polymer and the penetrant concentration are responsible for the different types of the diffusion. A third class of the diffusion, Case II diffusion is a special case of non-fickian (Peppas et al., 1985). A simple, semiempirical equation can be used to analyze data of controlled release of water-soluble drugs from polymer matrices Eq. (3). This equation predicts the mechanism of diffusional release.

$$\frac{M_t}{M_\infty} = bt^n \text{.....} \mathbf{3}$$

Where, M_t is amount of the released drug at time t, M_∞ is the overall amount of the drug (whole dose), b is the constant incorporating structural and geometric characteristics of the controlled release device, and n is the release exponent indicative of the drug release mechanism. For tablets of a known geometry (in this case a slab) n = 0.5 means Fickian diffusion, 0.5 <n< 1.0 non-Fickian diffusion, and n=1.0 Case II diffusion. Results obtained after fitting dissolution data to different models are shown in Table 4. The 'n' values (release exponent) were found to be between 0.48 to 0.81, indicating non-fickian diffusion or anomalous transport. It's clear that most of the factorial design formulations followed matrix dissolution mode.

Reported fact is matrices containing higher molecular weight Polyox; seem to drive the release mechanism toward a combination of swelling and diffusion, while polymer erosion seems to play a minor role in controlling drug delivery from this kind of devices. The passage of a water soluble drug through hydrated gel layer around the matrix tablet is approximately dependent on the square root of time (Shah et al., 1993).

$$Q_t = kt^{1/2} \text{…… ……..} \mathbf{4}$$

Where, Q_t is the amount of the released drug in time t, k is the kinetic constant, and t is time. Many times this Eq. (4) is useful for the determination of the drug release rate. The release rate constants 'k'from Eq. (4) for the tested tablets is shown in Table 4.

Statistical Analysis

`A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses obtained with performed 3^2 factorial design experiments.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_{12} + b_{22} X_{22} \text{ ……} \mathbf{5}$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i (b_1,b_2,,b_{12},b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The Q_3, Q_9 and Q_{12} for the nine formulations of design showed a wide variation. The data clearly indicated that the Q_3, Q_9 and Q_{12} values are strongly dependent on the selected independent variables. The fitted regression equations in terms of coded factors relating the responses Q_3, Q_9 and Q_{12} are shown below Eq. (6-8)

$$Q_3 = 27.91 - 4.29X_1 - 3.58X_2 + 2.76X_1X_2 - 3.21X_1^2 + 1.07X_2^2 \text{Eq. ..} \mathbf{6}$$
(r^2=0.9661)

$$Q_9 = 50.78 - 3.02X_1 - 11.32X_2 + 1.85X_1X_2 + 0.065X_12 + 6.71X_22 \text{..Eq....} \mathbf{7}$$
(r^2=0.9953)

$$Q_{12} = 61.74 - 6.77*X_1 - 11.95*X_2 + 1.27*X_1*X_2 - 0.015*X12 + 5.15*X22$$
(r^2=0.9622)…**8**

The information the equation conveyed was the basis to study the effects of variables. The regression coefficient values are the estimates of the model fitting. The high r^2 value indicated adequate fitting of the quadratic model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative.

Both the variables (Polyox WSR 303 and HPMC K15M CR) showed negative coefficient in case of responses Q_3, Q_9 and Q_{12} denoting increase in concentration of any of polymers decreases cumulative release at 3, 9 or 12 h from formulated polymeric matrix.

ANOVA study

Evaluation and interpretation of research findings are important and the p-value serves a valuable purpose in these findings. ANOVA for the dependent variables Q_3, Q_9 and Q_{12} was shown in Table 5. The coefficients of X_1 and X_2 were found to be significant at $p<0.05$, hence confirmed that both the variables have significant effect on the selected responses. Overall both the variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 7.1.4 software.

Response Surface Plots

The quadratic model obtained from the regression analysis was used to build a 3-D graphs in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots presented in Fig 5 to observe the effects of independent variables on the response studied such as Q_3, Q_9 and Q_{12} respectively. The response surface plots showed that various combinations of independent variables X_1 and X_2 may satisfy any specific requirement (i.e. maximum drug release up to 12 h) while taking into consideration of various factors involved in dosage form.

Stability Study

The results obtained for accelerated stability study of formulation F2 are presented in Table 6. The results of the accelerated stability studies revealed no significant change in the physicochemical parameters. Drug content remained more than 100 % for 3 months. Therefore the formulation F2 can be considered stable.

Table. 3: Physiochemical properties of prepared floating matrix tablets.

Batch Code	Avg. Wt (mg)	Friability (%)	Drug content (%	Thickness (mm)	FLT (sec)	Floating duration (h)
F1	505.4±1.4	0.33±0.03	99.60±1.19	5.17±0.11	14±0.60	>12
F2	507.7±1.3	0.40±0.06	98.37±0.95	5.01±0.05	9.73±0.46	>12
F3	502.1±1.7	0.18±0.03	101.80±1.13	5.1±0.03	7.40±0.43	>12
F4	512.3±1.2	0.13±0.05	99.50±0.86	4.98±0.07	24.67±0.50	>12
F5	506.5±1.3	0.22±0.02	99.90±1.12	5.12±0.06	18.7±0.55	>12
F6	503.2±1.1	0.31±0.05	102.70±1.10	5.04±0.02	16.22±0.90	>12
F7	509.4±1.5	0.18±0.12	103.20±1.23	5.09±0.04	32.71±1.01	>12
F8	507.4±1.5	0.27±0.04	97.30±0.90	4.99±0.03	21.15±0.75	>12
F9	502.4±0.9	0.15±0.06	102.20±0.50	5.00±0.01	14.62±0.59	>12

* All values are expressed as mean ± SD, n = 3

Table. 4: Kinetic Model fitting data for factorial formulations.

Formulation Code	R^2					n	k
	Zero Order	1st order	Matrix	Peppas	Hixson Crowell		
F1	0.9674	0.9890	0.9781	0.9952	0.9961	0.6918	15.3133
F2	0.9917	0.9921	0.9541	0.9945	0.9965	0.8059	8.7049
F3	0.9638	0.9728	0.9721	0.9857	0.9836	0.6463	15.7039
F4	0.9274	0.9859	0.9864	0.9790	0.9784	0.5486	18.1898
F5	0.9261	0.9809	0.9915	0.9868	0.9684	0.5547	14.0693
F6	0.9572	0.9890	0.9817	0.9937	0.9814	0.6874	9.5676
0.54440	0.9293	0.9788	0.9876	0.9822	0.9680		13.7744
F8	0.8844	0.9576	0.9905	0.9764	0.9389	0.4849	15.8813
F9	0.9501	0.9814	0.9759	0.9827	0.9738	0.6600	9.5821

*R^2, n, k: Values of Correlation coefficient, Release exponent and Release rate constant for different kinetic models of drug release

Table. 5: Combined ANOVA table for response Q_3, Q_9 and Q_{12}.

Response	Source	Sum of Squares	DF	Mean Square	F Value	P Value	Model Significant/ Non significant
Q_3		240.79		48.16	17.12	0.0205	
Q_9	Model	927.79	5	185.56	126.95	0.0011	
Q_{12}		1191.65		238.33	15.26	0.0241	
Q_3		110.60		110.60	39.31	0.0082	
Q_9	X_1	54.66	1	54.66	37.40	0.0088	
Q_{12}		274.86		274.86	17.60	0.0247	
Q_3		76.83		76.83	27.31	0.0136	
Q_9	X_2	769.31	1	769.31	526.33	0.0002	
Q_{12}		857.29		857.29	54.88	0.0051	
Q_3		30.53		30.53	10.85	0.0459	significant
Q_9	X_1X_2	13.76	1	13.76	9.42	0.0546	
Q_{12}		6.45		6.45	0.41	0.5662	
Q_3		20.55		20.55	7.30	0.0736	
Q_9	$(X_1)^2$	8.54E-003	1	8.540E-003	5.78E-003	0.9442	
Q_{12}		4.50E-004		4.50E-004	2.88E-005	0.9961	
Q_3		2.29		2.29	0.81	0.4336	
Q_9	$(X_2)^2$	90.05	1	90.05	61.61	0.0043	
Q_{12}		53.05		53.05	3.40	0.1626	
Q_3		8.44		2.81	-	-	-
Q_9	Residual	4.38	3	1.46			
Q_{12}		46.86		15.62			
Q_3		249.23		-	-	-	-
Q_9	Core Total	932.17	8				
Q_{12}		1238.51					

Table. 6: Stability study of optimized formulation F2.

Tests	Limits	Initial	1 Month	2 Months	3 Months
Appearance (Description)	No change	Off white , circular, 11mm flat faced tablet	Off white , circular, 11mm flat faced tablet	Off white , circular, 11mm flat faced tablet	Off white , circular, 11mm flat faced tablet
Assay (%)	95.0%-105%	101.60±	101.52±	101.44±	100.40±
Cumulative Release (%)	After 3h	18.94±1.20	18.80±1.54	18.65±0.90	18.47±0.56
	After 9h	60.29±0.96	60.10±0.82	59.95±0.60	59.73±0.40
	After 12h	82.65±0.75	82.61±0.60	82.45±0.86	82.21±0.60
Hardness (Kg/cm^2)	No Significant change	5.1±0.123	5±0.160	5±0.240	5±0.260
Friability (%)	<1%	0.45±0.0.5	0.44±0.06	0.45±0.05	0.45±0.06

*****All values expressed as mean± SD, n = 3

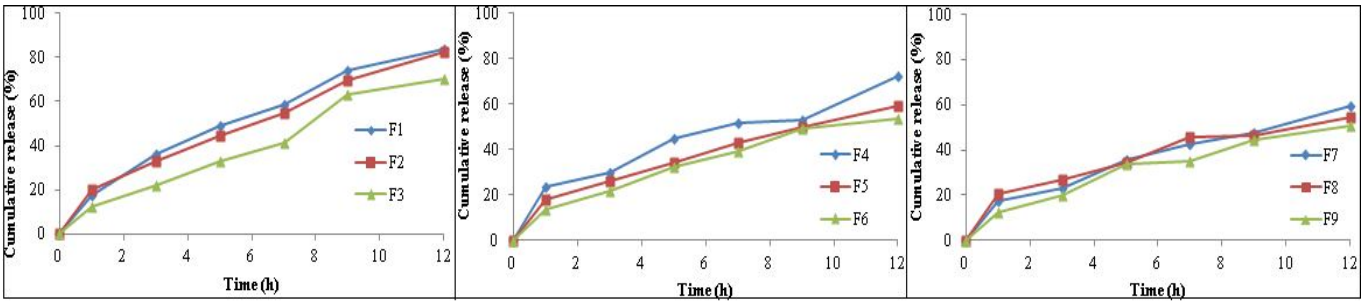

Fig. 3: *In-vitro* drug release of different factorial design formulations (F1-F9).

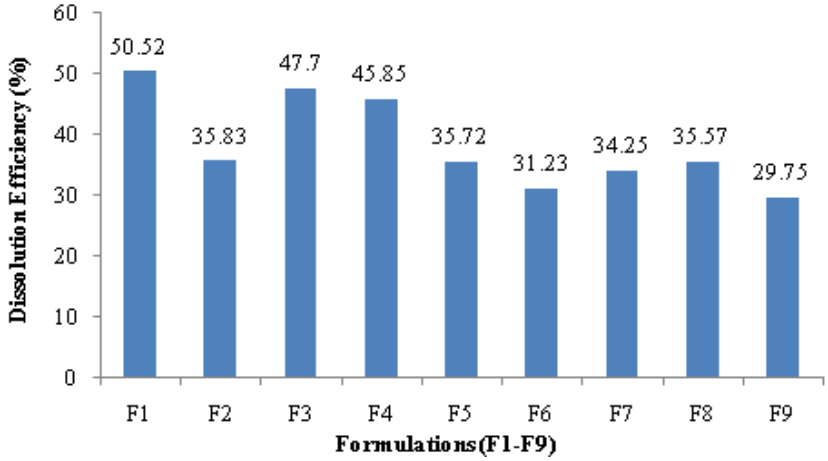

Fig. 4: Dissolution efficiency of factorial design formulations for 12h.

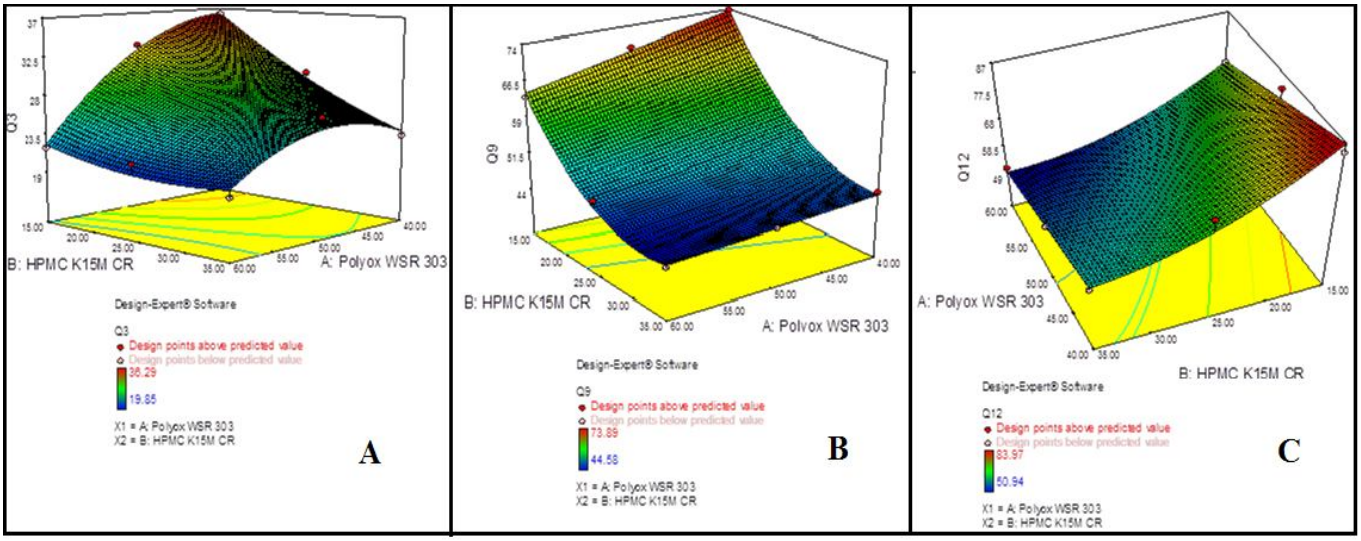

Fig. 5: Response surface plots for responses (A) Q_3, (B) Q_9 and (C) Q_{12}.

CONCLUSION

In present study controlled release floating matrix tablet of Acyclovir was successfully prepared utilizing direct compression technique. The formulation components i.e. Acyclovir, HPMC K15M CR, Polyox WSR 303 and PVP K30 were found to be compatible as analyzed by DSC and IR studies. Selected independent variables utilized in 3^2 factorial design viz. Polyox WSR 303 (X_1) and HPMC K15M CR (X_2) amount were able to effectively control drug release from formed hydrophilic matrix. All factorial designed formulations possessed excellent physicochemical characteristics and met with pharmacopoieal standards for weight variation, friability and drug content. Also excellent floating behavior was observed with FLT below 1 min and floating duration greater than 12 h. The optimized formulation F2 was found to remain stable as per ICH stability criteria. Finally, it is concluded that controlled release floating matrix tablet of Acyclovir was successfully prepared by using Polyox WSR 303 and HPMC K15M CR and thus it is a promising approach for the

treatment and prophylaxis of initial and recurrent episodes of genital and labial herpes.

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