Drug Development and Industrial Pharmacy, 2011; 37(7): 855–867

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2010.546404

informa
healthcare

RESEARCH ARTICLE

Optimization of acyclovir oral tablets based on gastroretention technology: Factorial design analysis and physicochemical characterization studies

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Abstract

The purpose of this research was to prepare a floating drug delivery system of acyclovir. Floating matrix tablets of acyclovir were developed to prolong gastric residence time and increase its bioavailability. The tablets were prepared by direct compression technique, using polymers such as hydroxypropylmethylcellulose 4000, Compritol 888. Sodium bicarbonate was used as a gas-generating agent. A 3^2 factorial design using the Design Expert Software (version 7.1.6) was applied to optimize the drug release profile systematically. The amounts of hydroxypropylmethylcellulose 4000 (X_1) and Compritol 888 (X_2) were selected as independent variables and the percentage drug released in 1 (Q_1), 6 (Q_6), and 12 (Q_{12}) h as dependent variables. The results of factorial design indicated that a high level of both hydroxypropylmethylcellulose 4000 (X_1) and Compritol 888 (X_2) favors the preparation of floating controlled-release of acyclovir tablets. Also, a good correlation was observed between predicted and actual values of the dependent variables chosen for the study. By fitting the data into zero-order, first-order, and Higuchi models, we concluded that the release followed Higuchi diffusion kinetics. Storage of the prepared formulations at 40°C/75% relative humidity for 3 months showed no significant change in drug release profiles and buoyancy of the floating tablets. We can conclude that a combination of hydroxypropylmethylcellulose 4000, Compritol 888, and sodium bicarbonate can be used to increase the gastric residence time of the dosage form up to 12 h. These floating tablets seem to be a promising gastroretentive drug delivery system.

Keywords: Acyclovir, floating time, gastroretentive, factorial design, HPMC, Compritol, bioavailability

Introduction

Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability (Brijesh & Avani, 2004) of the drugs that are having site-specific absorption from the stomach or upper part of the small intestine. Therefore, different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems (Whitehead et al., 1998), swelling and expanding systems (Menon et al., 1994; Santus et al., 1997), floating systems (Deshpande et al., 1996; Deshpande et al., 1997; Zhao et al., 2009), and delayed gastric emptying devices (Chawla & Bansal, 2003). Based on the mechanism of buoyancy, two distinctly different technologies, that is noneffervescent and effervescent systems, have been utilized in the development of Floating Drug Delivery Systems (FDDS). The effervescent system utilizes matrices prepared with swellable polymers and effervescent components (Sungthongjeen & Sriamornsak, 2008), for example sodium bicarbonate and citric acid or stearic acid. The matrices are fabricated such that in the stomach carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. In noneffervescent FDDS, the drug is mixed with a gel-forming hydrocolloid,

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(Received 02 October 2010; revised 01 December 2010; accepted 03 December 2010)

which swells on contact with the gastric fluid after oral administration and maintains relative integrity of shape and a bulk density of less than unity (Junyaprasert & Pornsuwannapha, 2008) within an outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms (Singh, 2000; Monica et al., 2009)

This attribute allows them to remain float on the surface of the gastric content for a longer period of time without affecting the rate of emptying (Singh, 2000). Thus, for the development of a floating matrix drug delivery system, selecting a suitable polymer with a bulk density of less than 1 g/cm^3, forming a cohesive gel barrier and the ability to dissolve slowly enough to retain the drug over a longer period of time is representing a challenge (Strübing et al., 2008).

Drugs of many pharmacological groups satisfy these criteria and can be used to fabricate gastroretentive tablets. Acyclovir (ACV) requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for gastroretentive formulation (Gromova et al., 2007).

ACV, 9-(2-hydroxy) ethoxymethylguanine, is used as an antiviral agent and is especially active against herpes simplex virus and zoster herpes. ACV is administered intravenously, locally, and perorally. For peroral administration, ACV is produced as tablets (200 mg) that are recommended to be taken five times per day. It has been noted that not more than 20% of the ACV is absorbed. However, the daily therapeutic dose is attained by taking 400 mg tablets 12 times or 800 mg tablets 5 times. According to the US FDA, the time for reaching the maximum concentration of ACV in blood plasma is 1.5–1.75 h. The biological availability of ACV is only 10–20% and decreases with increasing dose. The half-elimination period for constant kidney function is 2.5–3.3 h. ACV readily penetrates into tissues, organs, and biological fluids of an organism, including brain, kidneys, lungs, liver, muscle, saliva, uterus, vaginal lining, vaginal secretion, cerebrospinal fluid, and herpetic bladder contents. Blood plasma proteins bind 9–33% of ACV. ACV is eliminated from healthy individuals primarily with the urine. It can be concluded from the literature that the effective absorption zone of ACV is the duodenum and, possibly, the upper section of the small intestine adjoining it. Considering that ACV has several side effects, fabricating a gastroretentive drug form (GRDF) would solve the problem of increased bioavailability without increasing the dose in the drug form and also reduce the number taken to 1–2 per day (Gennaro, 2005).

In a previous study (Junyaprasert & Pornsuwannapha, 2008), the hollow microspheres were developed to extend the gastric retention time of ACV. The hollow microspheres that can float on gastric fluids would provide more time for ACV absorption at the absorption zone of the intestinal region. It is expected that as the fraction of the hollow microspheres gradually pass down to the intestinal region where they are soluble, the loaded drug starts to dissolve and is absorbed into the systemic circulation. As a result, a sustained release formulation of this drug may be achieved and the drug can be efficiently delivered, thereby improving absolute bioavailability, reducing the frequency of the drug administration, and raising patient compliance.

In this study, HPMC 4000 was used as a swelling as well as a release-retarding polymer. Compritol 888 ATO, a hydrophobic matrix-forming polymer to minimize the hydration rate of the matrix and variability in the release profiles, was used in combination with HPMC 4000. Formulations were optimized with 3^2 factorial design for desired acceptance criteria. Characterization of the prepared tablets included: physical evaluation (drug content, thickness, and hardness), *in vitro* floating studies, *in vitro* release experiments, differential scanning calorimetry (DSC), IR spectroscopy for the drug, polymers, and 1:1 physical mixtures. Effect of storage on their release behavior was also investigated. This investigation applied a systematic balance between floating lag time (FLT), floating duration, and *in vitro* drug release for the development of gastroretentive dosage forms of ACV suitable for a twice daily formulation with improved bioavailability.

Materials and methods

Materials

ACV and hydroxypropylmethylcellulose 4000 (kindly supplied by Pharco Pharm Company, Alexandria, Egypt), Compritol 888 ATO (Gattefosse, St Priest, Cedex, France), sodium bicarbonate and magnesium stearate (El-Nasr Pharmaceutical Chemicals Co., Egypt) were used. All chemicals were of analytical grade.

Methods

Preparation of ACV floating matrix tablets

ACV, HPMC 4000, and Compritol 888 ATO were passed through sieve No. 80 separately. The drug, polymer, and other ingredients were blended thoroughly using a mortar and pestle for 10 min to obtain a homogeneous mixture. The powder blend was then lubricated with magnesium stearate (1% w/w) for additional 3 min and this lubricated blend was compressed into tablets using 12 mm flat-face round tooling on a single punch tablet machine (Erweka, GmbH, Frankfurt, Germany). The compression force was adjusted to obtain tablets with hardness in range of 4–5.5 kg.

In vitro evaluation of the prepared tablets

Drug content

Tablets were separately finely ground in a mortar. Each tablet was allowed to dissolve in 100 ml 0.1 N HCl (Srivastava & Ridhurkar, 2005; Barhate et al., 2009; Tadros, 2010). Aliquots were filtered and assayed spectrophotometrically (UV-Spectrophotometer, JENWAY 6305, England) at 255 nm for ACV content.

Tablet thickness

The thickness of 10 tablets was measured using a micrometer (Moore and Wright Ltd. Britain Tool, Factory Sheffield, UK). The mean thickness and standard deviation (SD) were calculated.

Hardness test

The crushing strength (Kg) of 10 individual tablets was determined using Erweka hardness tester (type TB24, Erweka, GmbH, Heusenstamm, Germany).

Factorial design

A 3^2 randomized factorial design was used in this study and two factors were evaluated, each at three levels; experimental trials were performed at all nine possible combinations. The percentage of HPMC 4000 (X_1) and Compritol 888 ATO (X_2) was selected as independent variables while Q_1, Q_6, and Q_{12} (i.e., drug release after 1, 6, and 12 h, respectively) were selected as dependent variables. The formulation layout for the factorial design batches (F_1–F_9) is shown in Table 1.

The resulting data were fitted into Stat Ease, Inc. (Minneapolis, MN) Design Expert 7.1.6 software (Design Expert, 2008) and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of HPMC 4000 and Compritol 888 ATO on dependent variables.

Tablet weight was not constant because that would require the use of diluents for weight adjustment, which in turn may have caused variation in release profile. Thus, we did not alter the amount of diluents in the formulation to nullify any effect due to change in the proportion of diluents (Gambhire et al., 2007).

All batches contained 400 mg ACV, 60 mg sodium bicarbonate, and 6 mg magnesium stearate. X_1 and X_2 are the amounts of HPMC 4000 and Compritol 888 ATO in percentage, respectively.

In vitro floating studies

The *in vitro* buoyancy was determined by FLT using the method described by Gambhire et al. (2007). The tablets were placed in a 100 ml beaker containing 0.1 N HCl and the time required for the tablet to rise to the surface was determined as FLT, floating time (FT) was also recorded, which is the duration of time the dosage form to constantly remain on surface of medium.

In vitro dissolution studies

The release rate of ACV from floating tablets ($n = 3$) was determined. The dissolution test was performed using United States Pharmacopoeia (USP) dissolution apparatus type II (paddle), 900 ml of 0.1 N HCl, at 37°C ± 0.5 and 100 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at the appropriate time for 12 h (Tadros, 2010), and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 255 nm (Dhaliwal et al., 2008; Junyaprasert & Pornsuwannapha, 2008) using UV/visible double-beam spectrophotometer.

Kinetic modeling of drug release

Kinetics of ACV released from the prepared formulations was examined based on the magnitude of correlation coefficients obtained after application of zero-order, first-order (Gibaldi & Feldman, 1967; Wagner, 1969), and Higuchi diffusion models (Higuchi, 1961; Higuchi, 1963), and the model with the highest correlation coefficient was considered to be the best model.

Differential scanning calorimetry

DSC (SDT Q 600 V20.5, TA Instrument, USA) was performed to study the thermal behavior of drug alone, polymers (HPMC 4000 and Compritol ATO 888), and physical mixture. The instrument comprises calorimeter (DSC

Table 1. Formulation and evaluation of batches in full factorial design.

	Variable levels in coded form				
Batch code	X_1	X_2	Q_1 ± SD	Q_6 ± SD	Q_{12} ± SD
F1	−1	−1	38.51 ± 0.23	98.10 ± 1.21	98.10 ± 1.95
F2	−1	0	33.67 ± 0.78	85.31 ± 2.02	99.90 ± 0.88
F3	−1	1	24.32 ± 2.22	78.20 ± 0.32	99.90 ± 0.45
F4	0	−1	20.71 ± 1.98	72.10 ± 1.45	97.33 ± 0.23
F5	0	0	20.67 ± 1.93	70.72 ± 0.87	95.80 ± 1.11
F6	0	1	19.50 ± 0.54	68.90 ± 2.76	94.93 ± 0.91
F7	1	−1	15.21 ± 0.89	68.70 ± 0.97	93.21 ± 2.11
F8	1	0	11.40 ± 2.13	50.31 ± 2.91	90.40 ± 0.21
F9	1	1	9.87 ± 0.29	40.30 ± 0.65	89.20 ± 1.98
Coded values	Actual values**				
	X_1	X_2			
−1	50	50			
0	100	100			
1	150	150			

*All batches contained 400 mg of acyclovir. SD is standard deviation of three determinations. **The amount of HPMC 4000 (mg) X_1 and the amount of Compritol (mg) X_2.

60), flow controller (FCL 60), thermal analyzer (TA 60), and operating software (TA 60). The samples were heated in sealed ceramic pans under nitrogen flow (25 ml/min) at a scanning rate of 10°C/min from 24°C ± 1 to 300°C. Empty ceramic pan was used as a reference (Immordino et al., 2004).

Fourier transform infrared (FT-IR) spectroscopy

IR spectroscopy was conducted using a Perkin Elmer spectrum RXIFT-IR system (Perkin Elmer Instruments, USA) and the spectrum was recorded in the wavelength region of 4000–500 cm^{-1}. The procedure consisted of dispersing a sample (ACV, Compritol ATO 888, HPMC 4000, and the physical mixture) in KBr and compressing into discs by applying a pressure of 5 t for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded. All spectra were collected as an average of three scans.

Effect of storage on floating behavior and release profile

To determine the change *in vitro* release profile and floating behavior upon storage, the prepared formulations were exposed to the accelerated stability studies (40 ± 2°C and 75 ± 5% RH) for a period of 3 months in stability chamber (Fukuda et al., 2006; Dasharath et al., 2007; Patel et al., 2009). Samples were taken and evaluated for change *in vitro* drug release pattern and floating behavior. For each determination, duplicate runs were made.

In vivo floating experiment (X-ray photographing)

The experiment was performed on a healthy nonsmoker male subject (35 years old, body weight 75 kg, height 165 cm) who was not on any medication. The study followed the ethics for treatment of human volunteers according to the guidelines of the Ethical Committee of Alexandria University Hospital. After ensuring that the subject understood the aim of participation in the study, he signed an informed consent.

The method used was previously mentioned by Patel et al. (2009) and Tadros (2010). To make the selected formula X-ray opaque, 100 mg of the drug was replaced with barium sulfate and all other ingredients were kept constant. This amount was determined experimentally to allow X-ray visibility but not to hinder tablet buoyancy. After overnight fasting, the volunteer was on a low calorie food. Half an hour later, a barium sulfate-loaded tablet was given to every subject with 200 ml of water. At different time intervals (0, 1, 3, and 5 h postadministration of tablets), the volunteer was exposed to abdominal X-ray imaging in a standing position (Genesis 50, Josef Betschart AG, Brunnen, Switzerland).

A radiograph was taken just before the administration of the tablet, at zero time, to ensure the absence of radioopaque material in the stomach. The distance between the source of X-rays and the subject was kept constant for all images . Thus, the observation of the floating tablet movements could be easily noted.

Results and discussion

Results of preliminary screening

Hydrocolloids of natural or semisynthetic origin are commonly used for the development of gastric floating matrix devices. Floating matrix systems containing HPMC 4000 as the matrix-forming excipient begin to swell and form a gel layer with entrapped air around the tablet core after contact with gastric fluid, whereas this gel layer controls the drug release (Patel et al., 2007).

The evaluation results for *in vitro* drug release showed that HPMC 4000 alone was unable to retard the drug release after 4 h and that was in agreement with previous work (Patel et al., 2007). Although the tablets with HPMC 4000 were able to float for more than 8 h, the drug was released completely within 4 h. To study the effect of various drug release modifiers from the tablets, three batches were formulated using PVP K30, PEG 4000, and Compritol 888 ATO (glyceryl behenate). From the *in vitro* release study, Compritol 888 ATO was found to be the most effective in retarding the drug release and it has been used for the preparation of controlled-release formulations since it possesses some interesting characteristics, such as chemical inertness against other materials and excellent flow properties. Several studies have been carried out on the *in vitro* release from matrices comprising hydrophobic and hydrophilic components, lipids may be suitable in this way as release modifiers for incorporation into cellulose matrices (Kiortsis et al., 2005; Li et al., 2006; Barakat et al., 2009). To evaluate the combined effect of HPMC 4000 and Compritol 888 on the drug release from the floating tablets, a full factorial design was used.

Evaluation of the prepared tablets

Table 2 shows the different characteristics of the prepared tablets. The assayed content of the drug in various formulations varied between 97.25 and 101.56%. The tablet weights varied between 566 and 766 mg and the hardness varied between 4 and 5.5 kg (average hardness 4.8 kg) and thickness between 4.12 and 4.40 mm (average thickness 4.22 mm). Thus, the physical parameters of the compressed matrices were within control.

In vitro floating studies

The preliminary batches prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas-generating agent in order to aid floating of tablets. The sodium bicarbonate induces CO_2 generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml, and the tablet becomes buoyant (Gutiérrez-Sánchez et al., 2008; Garg & Gupta, 2009); 10% sodium bicarbonate was used to achieve optimum *in vitro* buoyancy (Sungthongjeen & Sriamornsak, 2008; Boldhane & Kuchekar, 2009). Further increase in concentration of sodium bicarbonate does not show any significant effect

on floating behavior. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release (Gambhire et al., 2007; Tadros, 2010).

The hydrophobic polymer Compritol 888 ATO, having low density, was tried for floating controlled release. The tablets prepared with Compritol 888 ATO only were found to sink within 1 h, with complete drug release in 2 h. But the tablet formulation did not swell because the CO_2 generated by the interaction between 0.1 N HCl and sodium bicarbonate did not get entrapped; thus, this formulation failed to float the tablet and a combination of both HPMC 4000 and Compritol 888 ATO was used.

Figure 1 shows a system containing sodium bicarbonate as a gas-forming agent dispersed in hydrogel matrix. After reacting with hydrochloride acid, carbon dioxide bubbles evolved on the surface of tablets caused its floating for more than 12 h *in vitro*.

All the factorial design batches showed good FLT in 0.1 N HCl, ranging from 35 to 160 sec (Table 2. The tablets remained buoyant throughout the duration of the dissolution studies. As the amount of HPMC 4000 in the matrix was increased from 50 to 100 and 150 mg, the FLT was found to increase as polymer may need more time to be wetted with hydration medium. In case of formulations F_1, F_2, and F_3, the FLT was much lower (35, 60, and 90 sec, respectively) and accompanied with rapid disintegration and loss of mass integrity that could be due to lower amount of HPMC 4000, which was insufficient to form the gel layer required to entrap the generated CO_2.

In vitro dissolution studies

In vitro dissolution studies were performed on nine formulations. Formulation F_1 was found to disintegrate within 6 h, while formulations F_2 and F_3 were found to disintegrate within 8 h. This can be attributed to the low level of HPMC 4000 due to which the gel layer had comparatively poor strength and hence could not sustain the larger amount of gas generated. Formulations F_4, F_5, and F_6 showed 68.9–72.1% release in 6 h and 94.93–97.33% release in 12 h, whereas in formulations F_7, F_8, and F_9, the drug release in 6 h was found to be in the range of 40.31–68.9% and 89.2–93.21% release in 12 h, respectively. High HPMC 4000 contents result in a greater amount of gel being formed. This gel increases diffusion path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug; as a result, reduction in drug release was obtained (Garg & Gupta, 2009), also, the hydrophobic properties of Compritol 888 retard the drug release from the prepared formulations.

Table 2. Formulation characteristics of batches.

Batch code	Total weight of tablet (mg)	Hardness (kg)	Thickness (mm)	Floating lag time (seconds)	Floating time (hours)	Matrix integrity
F1	566 ± 0.007	4.0 ± 0.011	4.12 ± 0.043	35	12	–
F2	616 ± 0.054	4.3 ± 0.076	4.14 ± 0.012	60	12	±
F3	666 ± 0.013	4.5 ± 0.005	4.22 ± 0.000	90	12	±
F4	616 ± 0.034	4.8 ± 0.000	4.12 ± 0.004	120	12	+
F5	666 ± 0.005	5.2 ± 0.004	4.22 ± 0.066	120	12	+
F6	716 ± 0.056	5.0 ± 0.005	4.28 ± 0.004	140	12	+
F7	666 ± 0.034	4.9 ± 0.087	4.24 ± 0.064	120	12	+
F8	716 ± 0.077	5.0 ± 0.000	4.32 ± 0.033	150	12	+
F9	766 ± 0.064	5.5 ± 0.003	4.40 ± 0.076	160	12	+

(–) sign indicates loss of mass integrity.

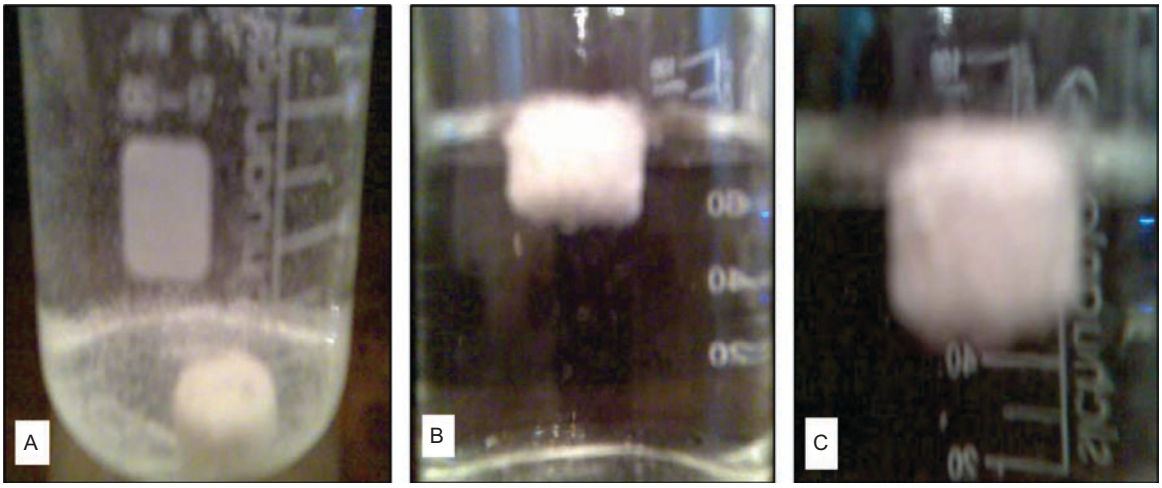

Figure 1. Photographs of a floating matrix tablet floating in the artificial gastric fluid 0.1 N HCl (A: 0 h, B: after 30 s; and C: after 12 h).

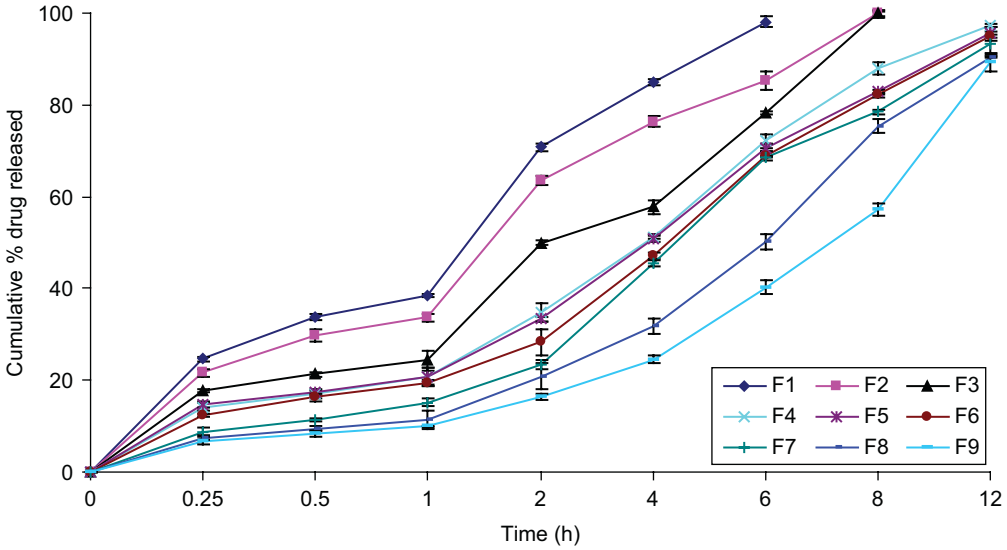

Figure 2. Release profile of acyclovir (ACV) from 32 factorial designs.

The data demonstrated that both X_1 and X_2 affect the drug release. It is concluded that a high level of both HPMC 4000 (X_1) and Compritol 888 ATO (X_2) favors the preparation of controlled-release tablets of ACV in terms of desired release profile. An increase in the concentration of HPMC 4000 or Compritol 888 ATO decreases the rate of release of ACV from matrix. Release profile of ACV from 3^2 factorial designs is illustrated graphically in Figure 2.

Factorial design

A 3^2 full-factorial design was constructed to study the effect of the amount of HPMC 4000 and Compritol 888 ATO on the drug release from floating ACV tablets. The dependent variables chosen were Q_1, Q_6, and Q_{12} (i.e., drug release after 1, 6, and 12 h, respectively). A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X^2{}_1 + b_{22}X^2{}_2 \quad (1)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and *bi* (b_1, b_2, b_{12}, b_{11}, and b_{22}) is the estimated coefficients for the factor X_i (X_1, X_2, X_1X_2, X_{12}, and X_{22}). The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors change simultaneously. The polynomial terms (X_{12}, X_{22}) are included to investigate nonlinearity (Boldhane & Kuchekar, 2009).

The dissolution profile for nine batches showed a variation (i.e., initial 1 h release ranging from 9.87% to 38.51%, drug released after 6 h ranging from 40.3% to 98.1% and drug released after 12 h ranging from 89.2% to 99.9%). The responses of formulation prepared by 3^2 factorial designs are indicated in Table 1. The data clearly indicate that the Q_1, Q_6, and Q_{12} values are strongly dependent on the selected independent variables. The fitted equations relate the response Q_1, Q_6, and Q_{12} to the transformed factor. The polynomial equations can be used to draw conclusions after considering the sign and magnitude of the main effect signify the relative influence of each factor on the response.

Table 3. Summary of results of regression analysis for responses Q_1, Q_6, and Q_{12}.

	Q_1 (after 1 h)	Q_6 (after 6 h)	Q_{12} (after 12 h)
R^2	0.9235	0.9232	0.9070
Adjusted R^2	0.8981	0.8976	0.8760
Predicted R^2	0.7998	0.8129	0.7389
Adequate precision	15.311	16.127	13.015

Regression equations of fitted model

Q_1 (after 1 h) = 21.53 – 10.00 × A – 3.45 × B

Q_6 (after 6 h) = 70.59 – 17.05 × A – 8.58 × B

Q_{12} (after 121 h) = 95.22 – 3.88 × A – 0.92 × B

where A is the amount of HPMC 4000 and B is the amount of Compritol 888 ATO.

Normal probability plot of the residuals (difference between the actual and predicted values) was a straight line and showed a normal distribution of the error. All residuals were within the limit (±3.5) with no externally studentized residuals detected. Furthermore, a plot of residuals versus the predicted values was structureless indicating that the assumption of constant variance was satisfied. Therefore, ANOVA could be used as a tool for the detection of main effects.

All the polynomial equations were found to be statistically significant ($P < 0.01$), as determined by ANOVA. It could be deduced that the effect of HPMC 4000 concentration was the main effect as seen from its higher regression coefficient (–10.00, –17.05, and –3.88), but as a general pattern both HPMC 4000 and compritol 888 ATO concentartion have a negative effect on response, that is increasing their concentration decrease % of drug released.

Table 3 showed summary of results of regression analysis for responses Q_1, Q_6, and Q_{12}. The 'Pred R-Squared' of all responses were in reasonable agreement with the 'Adj

R-Squared.' 'Adequate Precision' measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The ratio of 15.322, 16.127, and 13.015 in case of Q_1, Q_6, and Q_{12}, respectively, indicate an adequate signal. This model can be used to navigate the design space.

Figures 3–5 show the plot of the percentage of HPMC 4000 (X_1) and the percentage of Compritol 888 ATO (X_2) versus Q_1,Q_6, and Q_{12} (% released), respectively. The plot was drawn using Stat-Ease Design Expert 7.1.6. The data demonstrate that both X_1 and X_2 affect the drug release (Q_1, Q_6, and Q_{12}).

Figures 6–8 show correlation plots between the observed and the predicted values of Q_1, Q_6, and Q_{12}.The linear correlation plots drawn between the predicted and the observed responses indicate excellent fitting of the model ($P<0.001$).

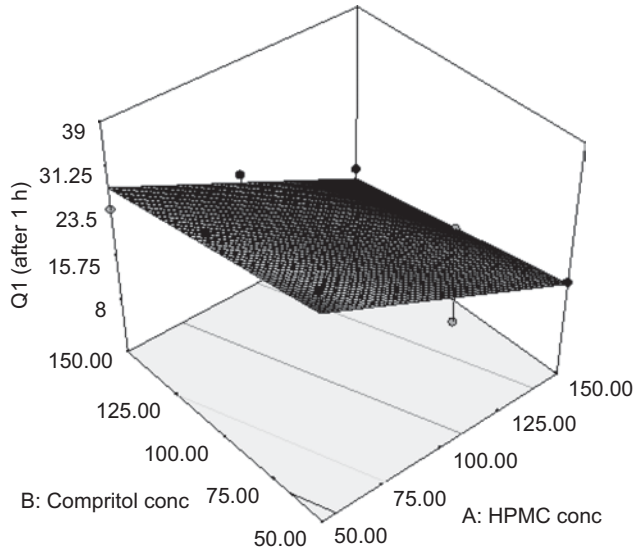

Figure 3. Response surface plot showing the influence of HPMC 4000 and Compritol on Q_1.

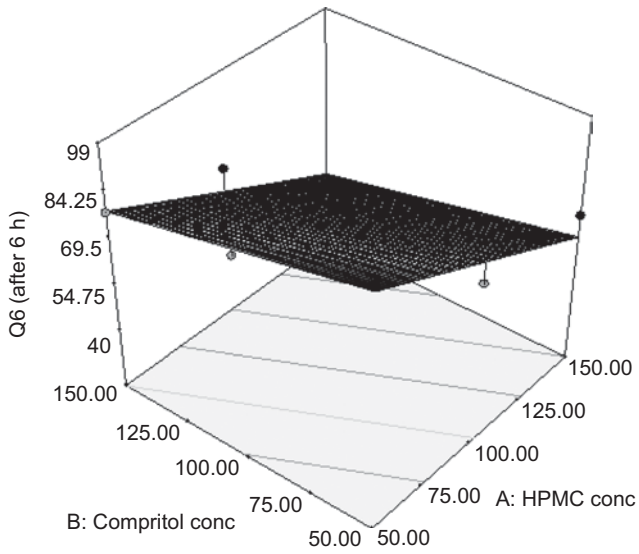

Figure 4. Response surface plot showing the influence of HPMC 4000 and Compritol on Q_6.

Kinetic modeling of drug release

In case of controlled- or sustained-release formulations, diffusion, swelling, and erosion are the three most important rate-controlling mechanisms. Formulations containing swelling polymers show swelling as well as diffusion mechanism because the kinetics of swelling includes relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to a rubbery state (Monica et al., 2009).

To determine the mechanism of release of drug from different formulae, the release data were analyzed using the linear regression according to

zero-order kinetics

$$C_t = C_0 - K_t \quad (2)$$

first-order kinetics

$$\mathrm{Log}\, C_t = \mathrm{Log}\, C_0 - K_t / 2.303 \quad (3)$$

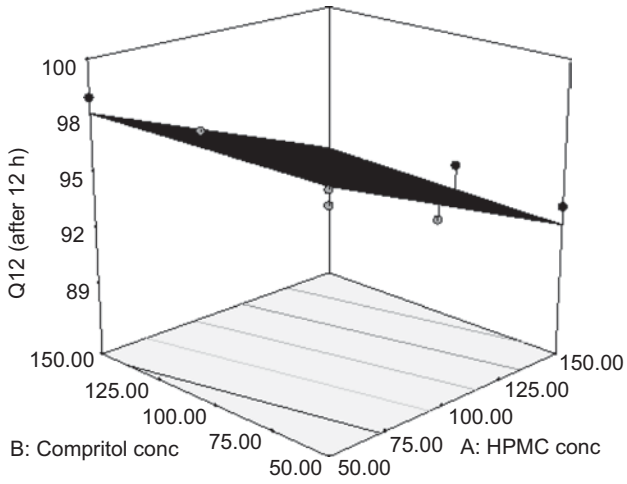

Figure 5. Response surface plot showing the influence of HPMC 4000 and Compritol on Q_{12}.

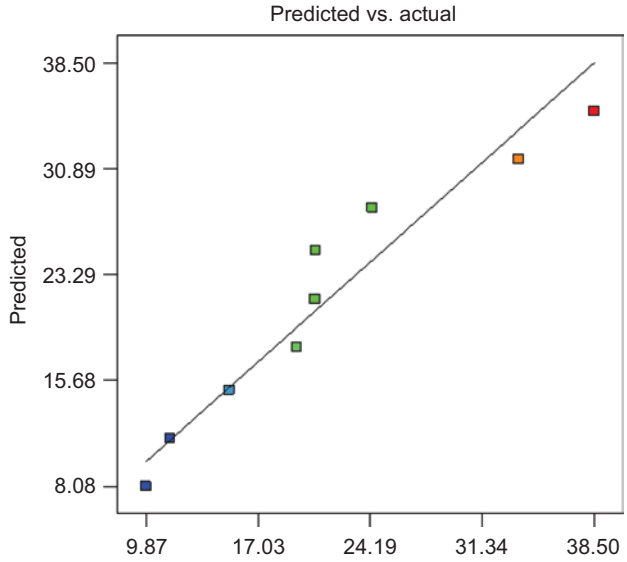

Figure 6. Linear plots between observed and predicted values of Q_1.

And also according to the simplified Higuchi diffusion model;

$$Q/A = 2C_0(A/2\pi)^{1/2} t^{1/2} \quad (4)$$

where Ct is the concentration at time (t) and Co is the initial drug concentration.

Q is the amount of drug released per unit area (A) exposed after time (t).

The correlation coefficient (r) was determined in each case, from which mechanism of release was predicted.

The kinetic parameters (obtained using the above equations) were given in Table 4. Based on the correlation coefficient, the results of kinetic study showed

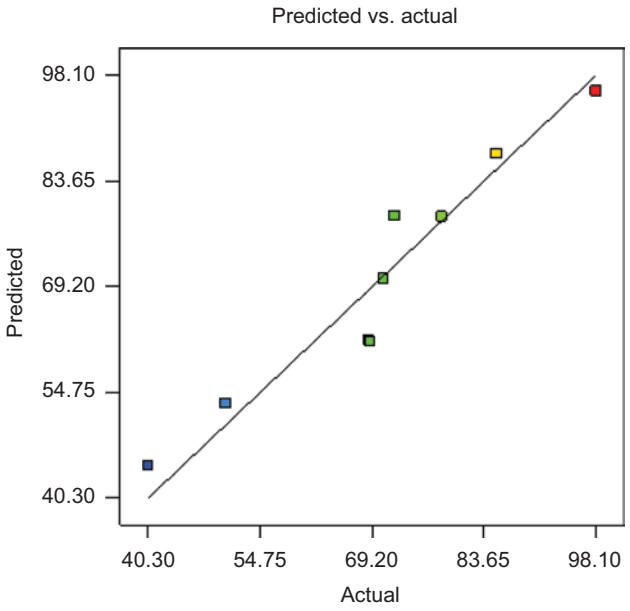

Figure 7. Linear plots between observed and predicted values of Q_6.

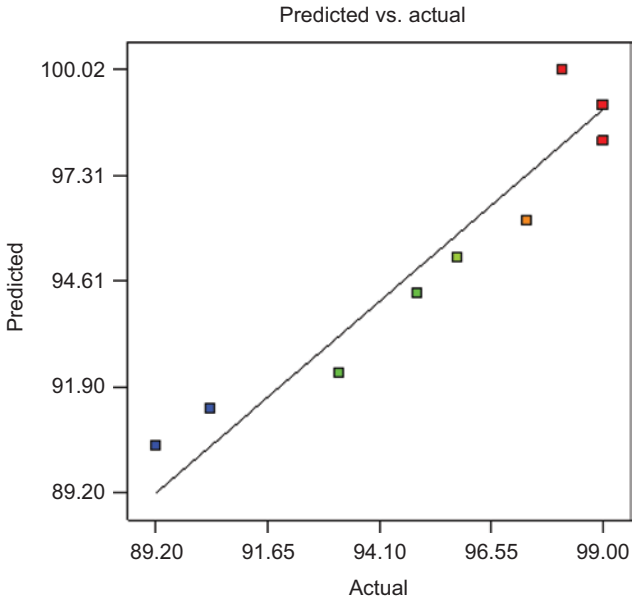

Figure 8. Linear plots between observed and predicted values of Q_{12}.

Table 4. Kinetic parameters of the release data of ACV from different formulations.

	Linear regression analysis using correlation coefficients according to				Kopcha parameters		
Formula code	Zero-order	First-order	Higuchi model	Mechanism of release	A	B	A/B
F1	0.9278	0.9807	0.9887	Diffusion	49.2571	3.4069	14.458
F2	0.9342	0.8839	0.9895	Diffusion	43.3825	2.883	15.047
F3	0.9747	0.8449	0.9880	Diffusion	30.0435	0.99625	30.1567
F4	0.9683	0.9836	0.9921	Diffusion	23.168	1.85334	12.5006
F5	0.9709	0.9869	0.9939	Diffusion	23.8097	1.31181	18.1502
F6	0.9758	0.9875	0.9901	Diffusion	20.2882	2.3195	8.7468
F7	0.9778	0.9865	0.9911	Diffusion	12.8466	4.74491	2.70744
F8	0.9687	0.9742	0.9901	Diffusion	9.0273	4.95875	1.82048
F9	0.9469	0.9362	0.9945	Diffusion	7.30758	4.37567	1.67005

Table 5. Comparison of experimental results with predicted responses of the effervescent floating tablet formulations.

	Composition						
Formulation	X_1 (mg)	X_2 (mg)	Response variables	Predicted value	Experimental value	Residual*	%Bias**
C_1	120.01	145.81	Q_1 (%)	14.367	15.88	1.51	10.5
			Q_6 (%)	55.601	53.98	−1.62	2.91
			Q_{12} (%)	92.824	95.77	2.593	3.17
C_2	64.44	128.70	Q_1 (%)	26.66	25.93	−0.73	2.74
			Q_6 (%)	77.49	74.66	−2.83	3.65
			Q_{12} (%)	97.45	98.46	1.01	1.04
C_3	133.41	85.64	Q_1 (%)	15.84	17.77	1.93	12.18
			Q_6 (%)	61.36	59.33	−2.03	3.31
			Q_{12} (%)	92.89	90.76	−2.13	2.29

*Residual = Actual (experimental) value− predicted value. **Bias = [predicted value− experimental value/predicted value] × 100.

that the best fit was achieved with Higuchi model for the prepared formulations, which indicated that drug release mechanism from floated tablets contain HPMC 4000 as main matrix component, was diffusion. Similar result was observed in many literatures (Ritger & Peppas, 1987; Siepmam & Peppas, 2001; Barakat et al., 2009).

It is known that the drug release from HPMC matrices is controlled for water-soluble drugs by diffusion through the gel layer or, for poorly soluble drugs, by erosion of the outer polymer chains. Therefore, the kinetics of swelling is important, because the gel barrier is formed with the water penetration. Hydroxypropylmethylcellulose hydrogels have several important characteristics that play an essential role in drug diffusion including swelling ratio and specific mesh or pore size. Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure,

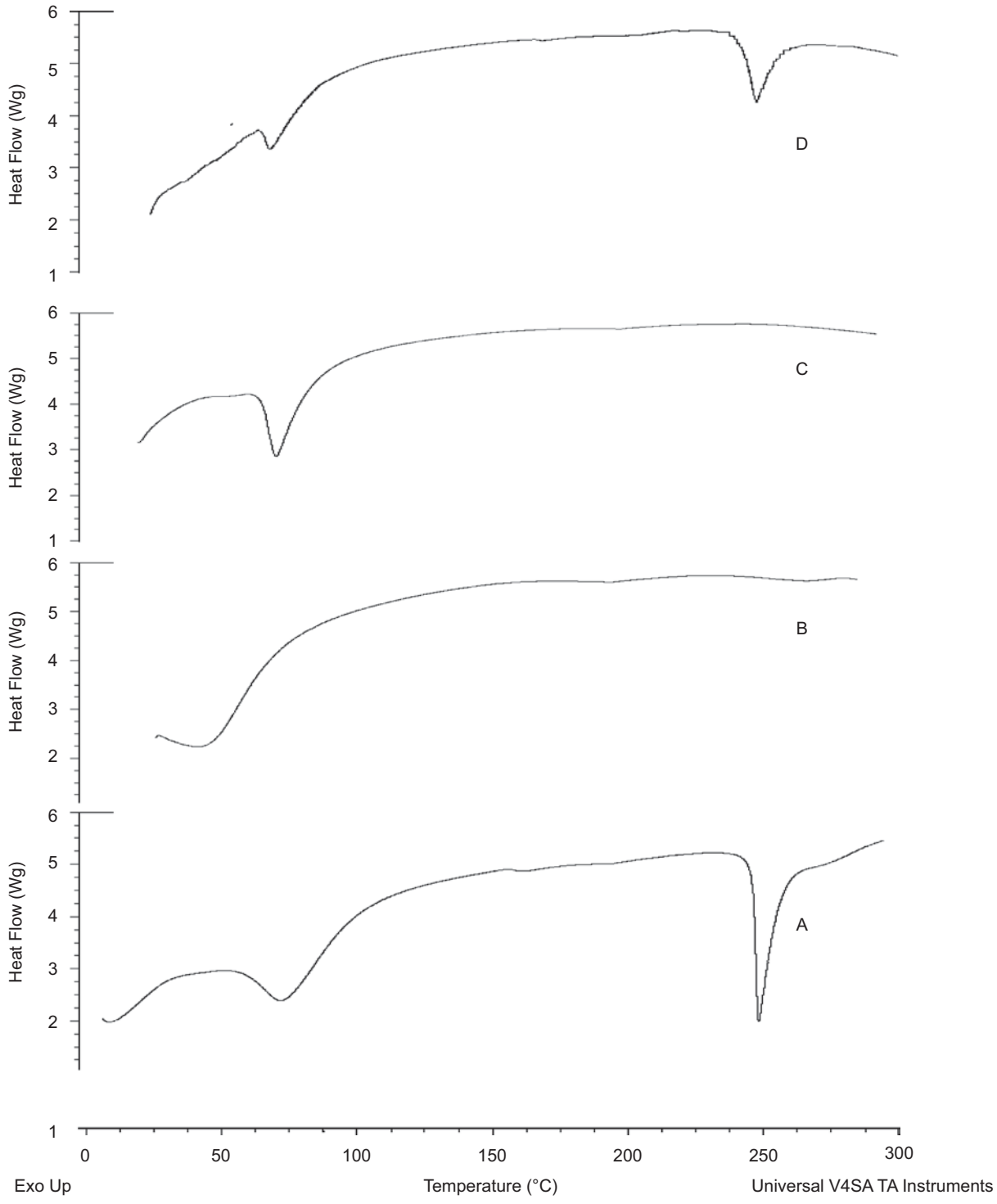

Figure 9. DSC thermogram of drug (A), HPMC (B), Compritol 888 ATO (C), and physical mixture (D).

hydrophilicity, and ionization of the functional groups. The pore size is the space available for drug transport. The drug characteristics are as important as those of the gel. The size, shape, and ionization of the drug affect its diffusion through the gel layer (Sasa et al., 2000).

Furthermore, the predominance of diffusion was confirmed by treating the release data with the empirical equation proposed by Koppcha (1991)

$$M = A t^{1/2} + B \quad (5)$$

In the above equation, M is the cumulative percent of drug released at time *t*. A and B are diffusion and erosion terms, respectively. According to this equation, if A/B ≥ 1, then diffusion prevails, while for A/B ≤ 1, erosion predominates (Koppcha et al., 1991; Chengsheng et al., 2006; Mayur et al., 2007) .The values of diffusion and erosion terms obtained using Kopcha equation were presented in Table 4. In all preparations, diffusion coefficient A was greater than erosion coefficient B, giving A/B>1, demonstrating that diffusion of drug was the rate-limiting step of its release from the prepared tablets.

Validation of optimized formulations/check point analysis

Three checkpoint formulations (C_1–C_3) were evaluated to validate model ability to predict response; the experimental values of the responses were compared with that of the anticipated values, and the prediction error for the three responses variables was found to be varying between 1.04 and 12.18.

Table 5 lists the composition of the checkpoints, the predicted and experimental values of all the response variables, and the percentage error in prognosis. A good agreement existed between the predicted and the actual values of % drug released after 1 (Q_1), 6 (Q_6), and 12 h (Q_{12}).

Differential scanning calorimetry

Figure 9 shows the DSC of ACV, HPMC 4000, Compritol 888 ATO, and physical mixture. There are two main peaks for ACV: The first is endothermic peak starting at 68.33°C and ending at 90.25°C, with peak maximum at 84.14°C, which is related to water (Stulzer et al., 2009) and the

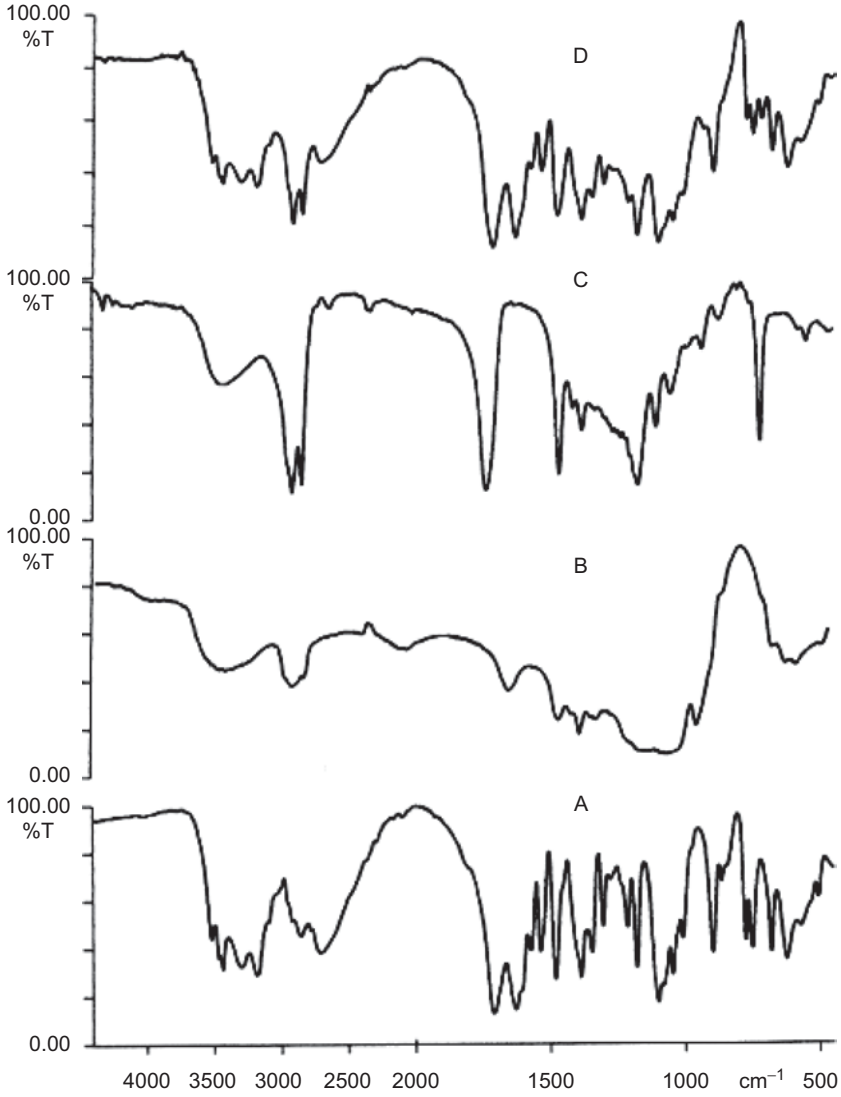

Figure 10. IR spectra of acyclovir (A), HPMC (B), Compritol 888 ATO (C), and physical mixture (D).

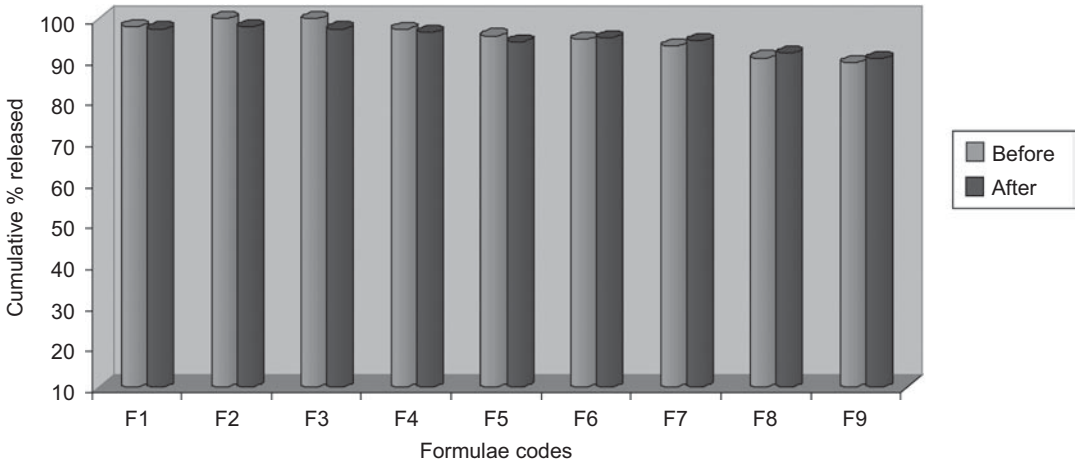

Figure 11. Effect of storage on release pattern of ACV from different formulae.

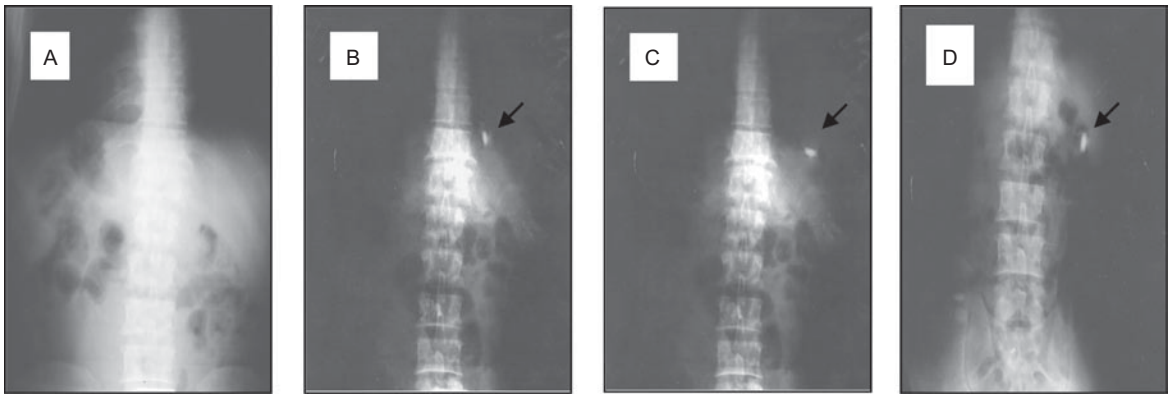

Figure 12. X-ray photographing of floating tablet at 0 h (A), 1 h (B), 3 h (C), and 5 h (D).

second peak starting at 250.63°C and ending at 257.63°C, with peak maximum at 252.49°C, due to melting of ACV (Lund, 1994).

The characteristic peak of ACV fusion appears in the thermogram of both pure drug and physical mixture did not reveal any obvious interaction.

FT-IR spectroscopy

The IR spectra for HPMC 4000, Compritol 888 ATO, and physical mixture are shown in Figure 10. The main absorption bands of ACV are broadband at 3500 cm^{-1} due to (NH, OH), C = O stretching at 1600 cm^{-1}, CH-aliphatic stretching at 2950 cm^{-1}, and CH-aromatic stretching at 3050 cm^{-1}, the characteristic peaks of pure ACV have appeared in physical mixture, without any markable change in their position, indicating no chemical interaction between drug and polymer used. This was in accordance with the results obtained from DSC studies, as mentioned earlier.

Storage studies

Effect of storage on the release pattern of different formulae kept at 40°C ± 2 and 75 ± 5% RH for a period of 3 months is shown in Figure 11.

No change in drug release profile was observed in all formulae, revealing good stability under the storage conditions. Concerning the effect of storage on floating behavior, it could be observed during *in vitro* release experiment that all formulae come to surface in less than 4 min and remain floated over 12 h revealing good FLT and FT, respectively.

Evaluation of gastric retention using X-ray imaging

Figure 12 showed the gastric retention of ACV floating tablet in one volunteer. The *in vivo* buoyancy of tablet was confirmed by X-ray imaging at different time intervals after ingestion of tablet containing $BaSO_4$. The behavior of the floating tablet in the volunteer stomach was observed using a radiographic imaging technique. The tablet seen in stomach of the volunteer till 5 h showed the confirmation of buoyancy of the floating tablets.

Conclusion

The effervescent-based floating drug delivery is a promising approach to achieve *in vitro* buoyancy by using gel-forming polymer HPMC 4000 and gas-generating agent, sodium bicarbonate. Combination of HPMC 4000 and Compritol 888 ATO has resulted in minimal variation in drug release. A systematic study using a 3^2 full-factorial design revealed that by selecting a suitable composition of HPMC 4000 and Compritol 888 ATO, the desired

dissolution profile could be achieved. The optimized formulation gives the best result in terms of the required lag time and floating duration of 12 h and can successfully be employed as twice daily oral controlled-release drug delivery system.

Short FLT and higher percentage release of the formulation is likely to increase its residence time in the stomach, and eventually, improve the extent of bioavailability. However, appropriate balancing between various levels of the two polymers is imperative to acquire desirable controlled-release pattern and floating.

Declaration of interest

The authors reported no conflict of interest

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