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Original Research Article

Design and Evaluation of Gastro Retentive Floating Multi Unit Dosage Form of Valacyclovir Hydrochloride

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Abstract: Valacyclovir hydrochloride (VCH), is L-valyl ester prodrug of acyclovir. VCH degrades in intestinal fluid. The objective of investigation was to develop floating mini-tablets of VCH to localize the drug at upper part of GIT, for improved absorption. The tablets were prepared by wet granulation method, using HPMC K_4M, HPMC $K_{15}M$ and HPMC$K_{100}M$ as release retarded polymers and sodium bicarbonate as gas forming agent. The each dose of tablet was compressed with 50 mg of 14 mini-tablets, equivalent to 320 mg of VCH. The tablets were evaluated for post compression parameters includes hardness, weight variation, content uniformity, friability, *in vitro* buoyancy and *in vitro* dissolution studies were performed. DSC studies were used to reveal the drug-excipient interaction. The data obtained from the *in vitro* release study was fit to various kinetic models to explain the release profile of the drug. Formulation F6 containing HPMC K_4M and HPMC $K1_{00}M$ showed minimal floating lag time and remained float throughout dissolution period, while prolong the drug release of 99.51% up to 8 h, following zero order kinetics.
Keywords: Valacyclovir hydrochloride, gastro retentive floating mini tablet, polymers.

INTRODUCTION

Floating drug delivery systems (FDDS) have been developed for drugs that act either locally in the stomach or absorbed from it, for those drugs that are either poorly soluble at alkaline pH or unstable in the intestinal or colonic environment [1-4]. These systems help in completely releasing the drug in the vicinity of the absorption window to enhance bioavailability. Several approaches that are currently made to prolong gastric retention time include, floating drug delivery systems, swelling and expanding systems, bioadhesive systems, high density systems and other delayed gastric emptying devices [4-9].

Most of the floating systems previously reported are single unit systems such as tablets and capsules. Multiple unit floating drug delivery systems, such as pellets or mini-tablets, show several advantages over monolithic ones, which include avoiding all or nothing emptying, more predictable drug release kinetics, less chance of localized mucosal damage and administration of units with different release profiles or containing incompatible substances [10, 11]. Mini-tablets offer an alternative for pellets because of their relative ease of manufacturing. In addition, they offer dosage forms of equal dimensions and weight with smooth regular surface that could be obtained in a reproducible and continuous way. Mini-tablets could be either filled into hard capsules or compacted into bigger tablets. These systems can reduce the chances of gastric irritation and inter subject variability in absorption by uniformly distributing in the stomach [12].

Valacyclovir hydrochloride (VCH), is the L-valyl ester prodrug of acyclovir. VCH is chemically stable along the acidic pH side, while it degrades in alkaline medium through a base-catalyzed pseudo-first-order kinetics. The degradation of the VCH progress faster in intestinal fluid. VCH is nearly completely converted to acyclovir and L-valine by first-pass intestinal and/or hepatic metabolism [13]. VCH is having 55% oral bioavailability with 30 mins biological half-life. After metabolism, VCH is converted to acyclovir, has half-life of 2-3 h. Acyclovir is absorbed slowly and incompletely from the human gastrointestinal tract. Hene, it is a suitable candidate for floating delivery systems. But, previously Uphadhyay *et al*., 2014 [14] reported the sustained release matrix tablets of VCH by prolonged gastric retention with the aid of floating and swelling mechanisms. Therefore, the floating mini tablets of VCH are more beneficial than the single unit system as it avoids 'all or nothing' phenomenon. Further, to localize the drug at upper part

of GIT, for improved absorption and oral bioavailability.

The objective of present investigation was to develop floating multi unit tablets of VCH by using hydrophilic polymers. The prepared tablets are evaluated for Physico-chemical parameters and characterize the drug release kinetics.

MATERIALS

Valacyclovir hydrochloride was obtained as a gifted sample from Wockhardt laboratories, Ahmadabad, India. HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ were purchased from Merck, Mumbai, India. Microcrystalline cellulose (Avicel pH 102), cross povidone, sodium bicarbonate, magnesium stearate, talc and hydrochloric acid were obtained from SD Fine Chemicals, Mumbai, India. All the reagents used were analytical grade.

METHODS

Preparation of Valacyclovir hydrochloride mini-tablets by wet granulation technique

Floating mini tablets of VCH were prepared by wet granulation method. Composition of mini-tablet formulations is showed in Table 1. All the ingredients were weighed, and mixed using the geometric dilution technique except magnesium stearate. The mixture was granulated using isopropyl alcohol. Polyvinyl pyrrolidone (PVP) was added as a binder to the granulating solvent by 5%. The obtained dough mass was passed through #12 sieve to prepare the granules. The granules were dried at 60^0C in the thermostatic hot air oven. Dried granules were passed through #25 sieve. Magnesium stearate and talc were then added as 2%. Mini-tablets, weighing 50 mg, were obtained using a single punch tablet press fitted with a 4 mm diameter concave punch. Each dose comprised 14 mini-tablets which are equivalent to 320 mg of VCH.

Evaluation of the pre-compression parameters of powder mixtures

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, and Carr's index and Hausner's ratio.

Evaluation of the post-compression parameters of VCH mini-tablets

Compressed mini-tablets were characterized for weight variation, crushing strength, thickness and friability as follows:

Weight variation of mini-tablets

The weight variation test was conducted by weighing 20 randomly selected mini-tablets individually. The average weight and standard deviation were calculated.

Thickness

The thickness of ten randomly selected mini-tablets from each formulation was measured with a Vernier caliper scale. The average and standard deviation were reported.

Hardness and friability

Crushing strength of tablet was determined by Monsanto tester (Campbell Electronics, India) hardness tester. Friability test was carried out using Roche friabilator (Erection instrument & engineering, Ahmedabad, India). Ten tablets were weighed and subjected to the combined effect of attrition and shock by utilizing a plastic chamber. The friabilator was operated for 100 revolutions (4 min, 25 rpm). The tablets were dedusted and re-weighed to calculate the percentage of friability.

In vitro Buoyancy studies

The *in-vitro* buoyancy was determined by the method described by Rosa *et al* [15]. For this purpose, the tablets were placed in a 100 mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and floating duration of the tablets was determined by visual observation.

Drug content

Ten tablets were finely powdered; quantities of the powder equivalent to 100 mg of VCH accurately weighed, transferred to a 100 mL volumetric flask containing 100 mL of 0.1N HCl of pH 1.2 and allowed to stand for 5 h with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with 0.1N HCl of pH 1.2. The solution was suitably diluted and the absorption was determined by UV-Visible spectrophotometer at 255 nm [16].

In vitro drug release studies

Fourteen mini-tablets containing 320 mg of VCH were placed in 900 mL 0.1 N HCl as a dissolution medium and was maintained at 37± 0.5^oC. Drug release was performed using a USP type II apparatus at 50 rpm for 8 h. Aliquots of 5 mL were withdrawn at specified intervals of time, filtered and replenished with 5 mL fresh dissolution medium. Samples' absorbance was measured at wavelength of 255 nm after suitable dilution. The studies were performed in triplicate. The cumulative % of VCH released was calculated at each time interval.

Mathematical modeling of drug release

The *in vitro* drug release profiles were subjected to different kinetic models (zero-order, first-order, Higuchi, and Korsemeyer-Peppas kinetic models) to explain the release kinetics for floating mini-tablets [17]. The best model of fit was evaluated using the correlation coefficient values (R^2). Further, the Korsemeyer-Peppas model was employed in the analysis of *in vitro* drug release behaviour to distinguish

between competing release mechanism. If a value of 'n' ≤ 0.5, indicates the Fickian release mechanism. The value of 'n' between 0.5 and 1 is an indication of non-Fickian release mechanism (both diffusion controlled and swelling controlled). When, 'n' ≥ 1, it is case-II transport and this involves polymer dissolution and polymeric chain enlargement or relaxation [18, 19].

Differential scanning calorimetry (DSC)

The incompatibility study was performed by using DSC 4000 (Perkin Elmer, USA) model. Samples of drug, optimized formulation were heated in hermetically sealed aluminum pans over temperature range of 10˚C – 300˚C at a constant rate of 10˚C/min under nitrogen purge.

RESULTS AND DISCUSSION

DSC studies

The thermal properties of the drug and the mixture of drug and excipients are used to assess the interaction among different components of the formulations. The DSC thermogram of pure drug VCH showed a sharp endothermic peak at a temperature of 133.67°C and it was corresponding to its melting point range (Figure 1). In optimized formulation, the drug showed an endothermic peak at 132.03°C. It indicates the there was no interaction between the drug and the excipients used in the formulation.

Pre-compression parameters of powder mixtures

The angle of repose of the powder mixture for all formulations (F1–F9) ranged from 25.18^{o} to 31.21^{o} indicating excellent flow properties. Hausner's ratios and compressibility indices ranged from 1.14 to 1.79 and 13.16% to 15.87%, respectively. The results of flow properties are within the acceptable range for granules. The values of compressibility indices, further confirmed the good compressibility of the prepared granules. The values are represented in Table 2.

Post-compression parameters for mini-tablets

The prepared mini-tablets were evaluated for physical parameters and showed in Table 3. Concerning appearance, the mini-tablets were white in colour with smooth surface in both sides and no visible cracks were observed. The mean diameter of mini-tablets was 4.0± 0.0 mm while mean thickness ranged from 2.7 to 3.6 mm. Mean hardness was in the range of 5.6 to 6.2 kg/cm^2 indicating that the mini-tablets are of sufficient strength to withstand physical abrasion. The percentage friability for all formulations was less than 1%, which is an indication of satisfactory mechanical resistance of the mini-tablets. The mini-tablets showed no evidence of capping, cracking, cleavage or breaking after being removed from the friabilator. The percentage of mean drug content (14 mini-tablets) ranged from 95.7-99.49%, which met the standard pharmacopoeial requirements (90-110%).Since the mixtures of powders used were free flowing, the obtained mini-tablets were of uniform weight due to uniform die fill. The mean weight of mini tablets was 50.09± 0.65 mg, (n= 20). The USP specification is generally ±10% for tablets weighing 130 mg or less. This means that no difference was observed in the weight of individual mini-tablets from the labeled weight indicating uniformity of weight.

***In vitro* buoyancy test**

All the formulations were tested for floating properties like floating lag time and total floating time. All the batches showed good *in vitro* buoyancy. The floating time of tablets were 8 h with a floating lag time of less than one min.

***In vitro* drug release,**

In vitro drug release study was performed using dissolution test apparatus at 50 rpm using 900 mL of 0.1N HCl maintained at 37±0.5ºC as the dissolution medium. The percentage drug release profile was showed in Figure 2. The formulations F1, F2, F3 were prepared using combination of HPMC K_4M and HPMC $K_{15}M$. The formulation F1 has released the total drug in 5 h, whereas F2 and F3 have released the total drug content in 6 h.

The formulations F4, F5, F6 were prepared using combination of HPMC K_4M and HPMC $K_{100}M$. The formulations F4, F5 have released the total drug content in 7 h and F6 has shown the drug release of 99.51% in 8 h.

The formulations F7, F8, F9 were prepared using combination of HPMC $K_{15}M$ and HPMC $K_{100}M$. The formulations have shown the percentage drug release of 95.04%, 91.48%, and 88.59% respectively in 8 h.

The drug release from floating matrix tablets was sustained for a prolonged period of time due to the viscous nature of the HPMC matrix through which drug diffuses. HPMC K_4M helped to increase the drug release within 8 h and maintained the integrity and buoyancy of the tablets formed but floating lag time decreased with increased concentration. The increased drug release from floating matrix tablets with high concentration of HPMC K_4M and HPMC $K_{15}M$ compared to the floating matrix tablets containing its smaller amount may be due to matrix erosion in the former and swelling diffusion and a slight erosion mechanism in the latter. However, the matrix containing a high viscosity grade of polymer with large molecular mass mainly results in swelling properties with little erosion and *vice versa*. Integrity and floating properties of floating matrix tablets were thus maintained.

Kinetics of drug release profiles

The *in vitro* dissolution data was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer- Peppas models to ascertain

the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4. It was observed from the data that all formulations have displayed zero order release kinetics in the range of 0.850 to 0.989. The values of R^2 of formulations for Higuchi's equation was found to be in the range of 0.919 to 0.992, which shows that the data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from 0.255 to 0.501 that shows Fickian and non Fickian diffusion mechanisms.

Comparative studies of the optimized formulation (F6) and marketed immediate release tablet

The optimized formulation (F6) is compared with the marketed immediate release tablet of Valacyclovir hydrochloride. The marketed tablet has shown the % drug release of 99.52% in 2hs where as the optimized formulation (F6) showed the % drug release of 99.51% in 8h. The results are showed in Figure 3.

Table–1: Formulation composition of Valacyclovir hydrochloride floating mini-tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Valacyclovir Hydrochloride	320	320	320	320	320	320	320	320	320
HPMC K_4M	120	80	40	120	80	40	-	-	-
HPMC $K_{15}M$	40	80	120	-	-	-	120	80	40
HPMC $K_{100}M$	-	-	-	40	80	120	40	80	120
$NaHCO_3$	78.4	78.4	78.4	78.4	78.4	78.4	78.4	78.4	78.4
Cross povidone	21	21	21	21	21	21	21	21	21
Magnesium stearate	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
Talc	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
MCC	107	107	107	107	107	107	107	107	107
Total weight	700	700	700	700	700	700	700	700	700

Table–2: Pre-compression parameters of prepared granules

Formulation	Angle of repose	Compressibility index (%)	Hausner's ratio
F1	25.18	14.42	1.16
F2	31.21	14.28	1.16
F3	27.42	13.02	1.14
F4	25.45	15.23	1.16
F5	28.46	15.87	1.18
F6	25.66	15.67	1.16
7F	27.21	14.23	1.79
F8	29.03	14.28	1.16
F9	28.36	13.16	1.15

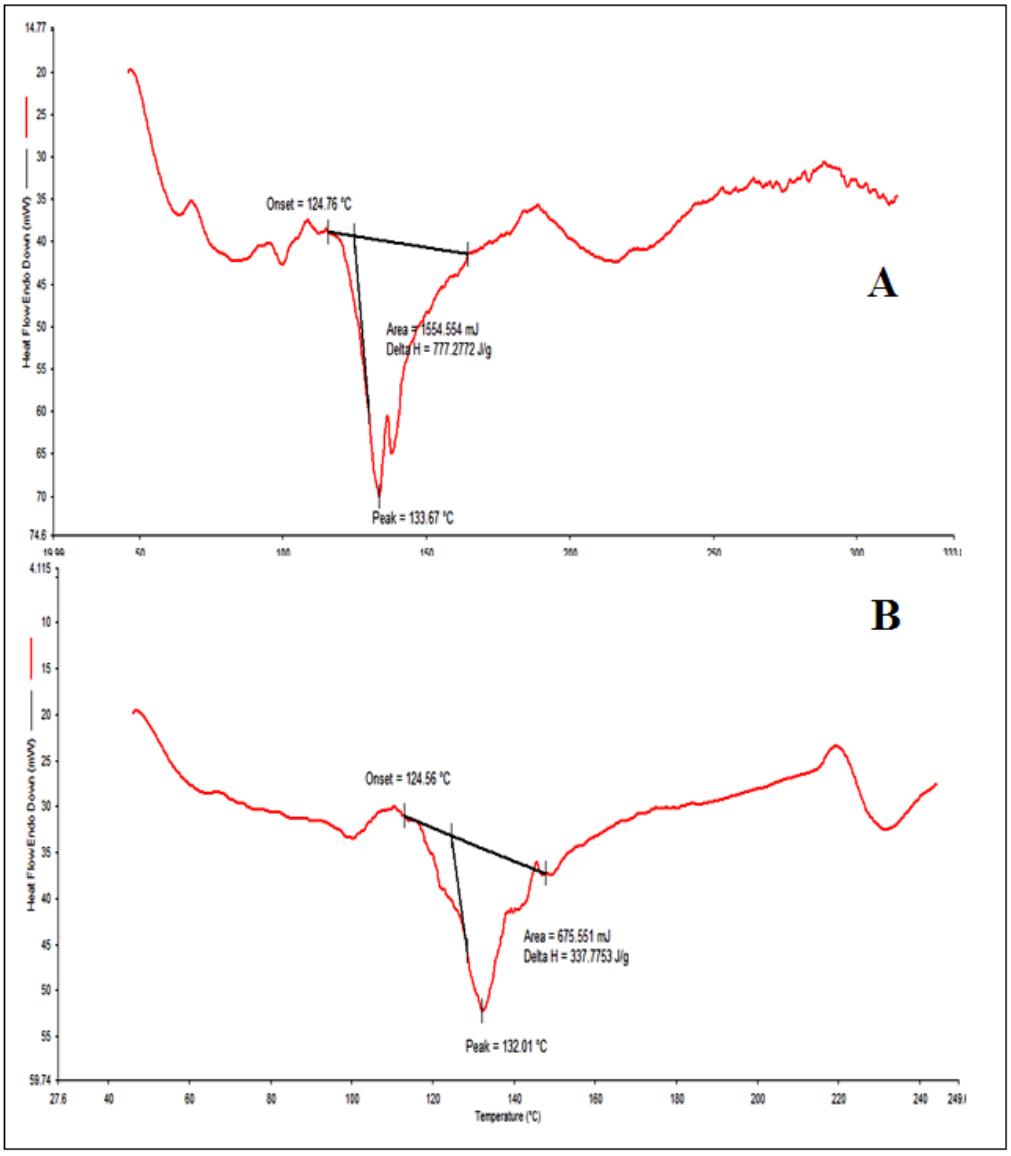
Table–3: Post-compression parameters of Valacyclovir hydrochloride floating mini-tablets

Formulation	Weight variation (mg)[a]	Hardness (kg/cm^2)[b]	Thickness (mm)	Friability (%)	Assay (%)[a]
F1	50.15 ±0.8	6.2 ± 0.2	2.9	0.21	98.30
F2	49.31 ±0.2	5.7 ± 0.2	2.7	0.36	99.08
F3	50.10 ±0.3	5.6 ± 0.4	3.1	0.24	98.61
F4	50.36 ±0.2	5.8 ± 0.9	3.2	0.25	98.29
F5	49.55 ±0.5	6.1 ± 0.4	2.9	0.12	98.02
F6	50.35 ±0.9	5.8 ± 0.2	3.4	0.38	98.96
F7	50.28 ±1.2	5.9 ± 0.2	2.8	0.19	95.70
F8	50.87 ±1.3	6.2 ± 0.3	3.6	0.16	99.08
F9	49.91±0.5	5.6 ± 0.8	3.2	0.28	99.49

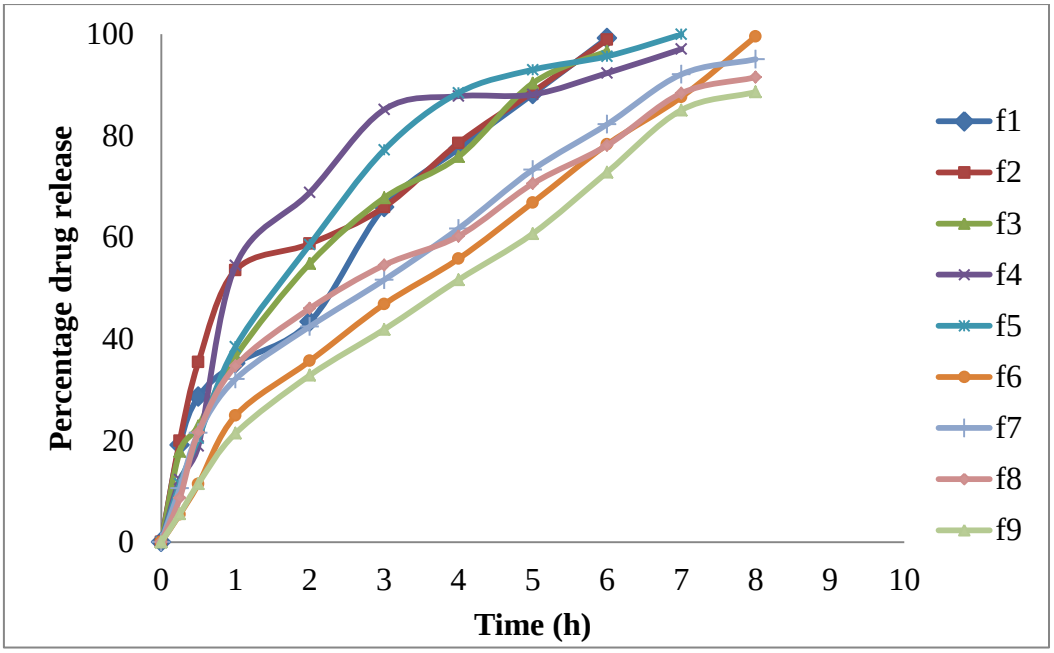
(a- n=20, b – n=6; mean±SD)

Table-4: Correlation coefficient (R^2) and release exponent (n) values of valacyclovir floating mini tablets by different kinetic models

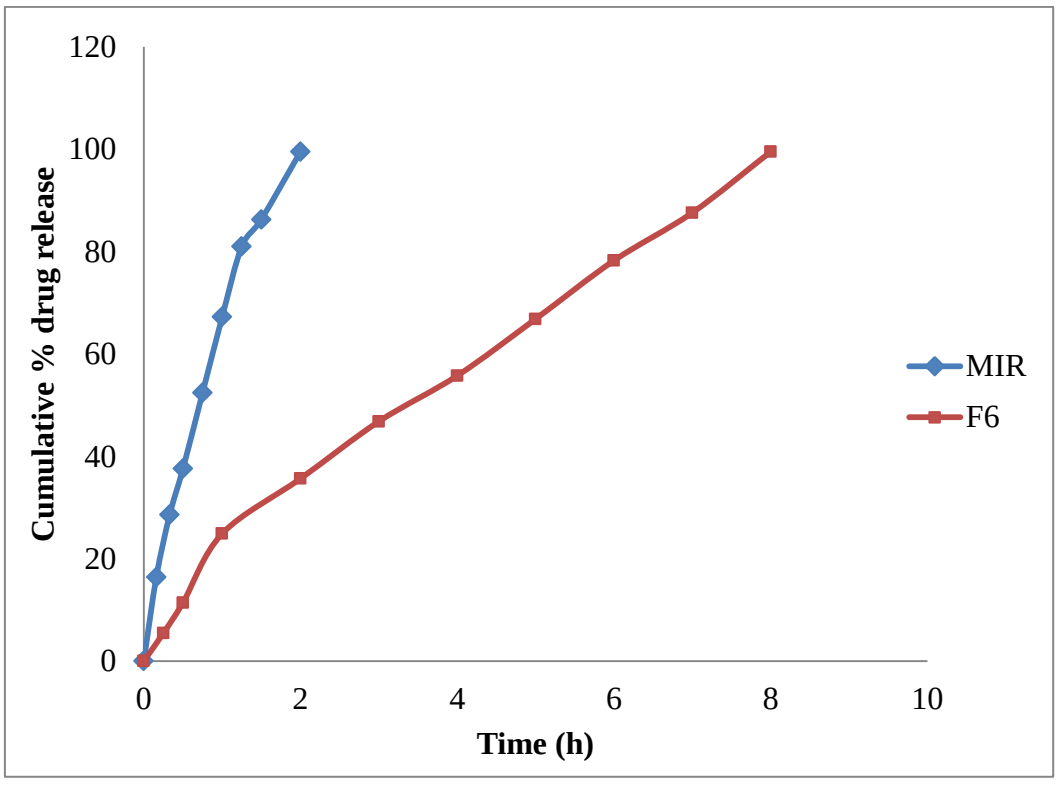
Formulation	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	R^2				N
F1	0.927	0.896	0.984	0.980	0.501
F2	0.914	0.949	0.991	0.993	0.436
F3	0.870	0.911	0.976	0.963	0.534
F4	0.767	0.970	0.919	0.901	0.240
F5	0.850	0.863	0.964	0.964	0.450
F6	0.989	0.704	0.974	0.987	0.524
F7	0.959	0.946	0.991	0.985	0.341
F8	0.935	0.967	0.992	0.958	0.282
F9	0.986	0.953	0.973	0.993	0.255



Fig−1: DSC thermograms of A) pure drug and B) optimized formulation of Valacyclovir hydrochloride floating mini-tablets



Fig−2: In vitro drug release profiles of Valacyclovir hydrochloride floating min-tablets (mean±SD, n=3)



Fig−3: Comparative study of the optimized formulation (F6) and marketed immediate release tablet

CONCLUSION

VCH mini tablets were successfully prepared with polymers like HPMC K_4M, HPMC $K_{15}M$, HPMC $K_{100}M$ and $NaHCO_3$ as gas generating agent. DSC gave confirmation about the purity of the drug and showed no interaction between drug and the polymers. All the prepared tablet formulations were found to be good without capping and chipping. The formulated tablets showed compliance for various physiochemical parameters. According to the results obtained, formulation (F6) offered best VCH controlled release along with floating lag time 21 s and total floating time >8 h. Data obtained from kinetic treatment revealed F6 formulation follows zero-order and the drug release follows non-fickian diffusion mechanism. The marketed immediate release tablet of Valacyclovir hydrochloride is compared with the optimized formulation (F6).

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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