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Original Article

FORMULATION AND EVALUATION OF SUSTAINED-RELEASE FLOATING MATRIX TABLETS OF VALGANCICLOVIR HYDROCHLORIDE

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ABSTRACT

Objective: The present study aimed to formulate and evaluate the formulated sustained-release floating matrix tablets of valganciclovir hydrochloride to produce a stable and bioavailable dosage form.

Methods: The tablets were prepared using hydrophilic and hydrophobic polymers such as ethyl cellulose, Hydroxy-propyl methylcellulose (HPMC), and Povidone. The formulations were subjected to evaluation characteristics such as drug content, hardness, friability, floating lag time, total floating time, and *In vitro* drug dissolution studies.

Results: The formulation composition and method of manufacturing are novel for this particular active moiety and robustness was assessed using a central composite design. All the formulation trials exhibited more than 90% of drug release in 12 h duration, with a floating lag time of more than 11 h, and drug content was found more than 90% across the batches. The hardness and friability profiles were found to be uniform across the batches. The preliminary evaluation confirms the received drug is pure and FTIR results show that the drug and excipients are compatible. The hardness and friability profiles were found consistent across the batches. All the formulation trials of central composite design have shown more than 90% of drug release in 12 h duration, with a floating lag time of more than 11 h, and drug content was found more than 90% across the batches.

Conclusion: The formulated valganciclovir hydrochloride sustained release floating matrix tablets showed an increased GRT with a sustained release for 12 h, thereby allowing a better window for absorption and consequently improving the drug's therapeutic effect.

Keywords: Gastroprotective, Valganciclovir hydrochloride, AIDS, DOE

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INTRODUCTION

Human cytomegalovirus (CMV) earns its name from the characteristic cytomegalic appearance of intranuclear inclusions in infected cells, an appearance first described in 1881. As a member of the Herpesviridae family, human herpes virus 5 (HHV 5), or CMV, is a double-stranded DNA virus capable of a wide spectrum of diseases in humans [1].

Among many anti-viral drugs, valganciclovir hydrochloride is a potent antiviral agent that has been approved for the treatment of cytomegalovirus diseases like CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS) and for the prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplantation. Valganciclovir hydrochloride is the L-monovaline ester of ganciclovir and is a stable prodrug of ganciclovir with improved absorption. Valganciclovir hydrochloride is described in detail in United States patent No. 6,083,953 [2].

Oral administration is the most versatile, convenient, and commonly employed route of drug delivery for systemic action. Indeed, for controlled release systems, the oral route of administration has received more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes [3]. There has been considerable research over the last decade on the possibility of controlled and site-specific delivery to the GIT by controlling the gastrointestinal transit of orally administered dosage forms using gastro retentive drug delivery system (GRDDS). Such GRDDS possess the ability to retain the dosage forms in the gastrointestinal tract (GIT) particularly in the stomach for a long period [4]. GRDDS perfectly increases the drugs' gastric retention times and their bioavailability increases [5]. Gastric retention systems are such systems that increase the gastric retention time of the dosage form at the stomach and upper parts of the small intestine and are suitable for the drugs having site-specific absorption from the above sites [6]. gastro retentive drug delivery systems (GRDDS) are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. are preferred as they are economical and have improved patient compliance and they are advantageous for drugs absorbed from the stomach [7]. To formulate a successful gastroprotective drug delivery system various technologies developed until now, i.e., high density (sinking), floating, bio-or mucoadhesive, expandable, super porous hydrogel, magnetic systems, etc [8]. Floating dosage forms may be made as tablets or capsules by using appropriate excipients and including gas-generating agents, which give the dosage form buoyancy in gastrointestinal fluids [9]. The present study aimed to formulate and evaluate the formulated sustained release floating matrix tablets of valganciclovir hydrochloride to produce a stable and bioavailable dosage form.

MATERIALS AND METHODS

Materials

Valganciclovir HCl (99.98% purity), Magnesium stearate, and talc were obtained as a gift sample from Strides pharma., Bangalore, India. Microcrystalline cellulose, Ethyl cellulose, and Povidone-k-30 were obtained from Stabicon Life Sciences, Bangalore India. Sodium bicarbonate and colloidal silicon dioxide are obtained from Shilpa Medicare, Dabaspete, India.

Methodology

Melting point evaluation

The melting point of an organic solid can be determined by introducing a tiny amount into a small capillary tube, attaching this to the stem of a thermometer centered in a heating bath, heating the bath slowly, and observing the temperatures at which melting begins and is complete [10].

Solubility test

In general, the solubility test for the drug valganciclovir was performed by using various solvents, which include distilled water,

ethanol, dimethyl sulfoxide (DMSO), methanol, ethanol: water (1:9), and isopropyl alcohol.

Construction of calibration curve

The 100 mg of Valacyclovir Hydrochloride was dissolved in 100 ml of 0.1N HCl. A series of dilutions containing 5,10,15,20 and 25 µg/ml of drug per ml of solution were prepared. The absorbance of the above dilutions was measured at 254 nm by using a UV-spectrophotometer. The graph was plotted by taking concentration on the X-axis and absorbance on the Y-axis which gives a straight-line linearity of the standard curve was assessed from the square of correlation coefficient (R2), which was determined by least-square linear regression analysis [11].

Drug-excipient compatibility study

Compatibility studies were carried out to know the possible interactions between valacyclovir HCl and the excipients used in the formulation. Physical mixtures of drugs and excipients were prepared to study the compatibility using the FTIR. The investigations were carried out to denote the changes in the chemical composition of the drug after combining it with the excipients.

Drug content

10 tablets were dissolved in 0.1N Hcl solution at room temperature and absorbance was taken at 254 nm by using a UV spectrophotometer to determine the amount of valganciclovir hydrochloride [12].

Formulation of valganciclovir hydrochloride tablets

Wet granulation method

All the materials are dispensed as per BOM. Valganciclovir hydrochloride and sodium bicarbonate are sifted through #40mesh (step 1). The Hydroxypropyl methylcellulose (HPMC K15M), ethyl cellulose, and microcrystalline cellulose (MCC) are sifted through #30mesh (step 2). Step 1 and Step 2 are blended manually in a 2 kg polybag for 5 min (Step 3). The dispensed binder is dissolved in the required quantity of purified water by using a remi stirrer at optimum rpm. The step 3 is transferred to RMG.

Table 1: Mixing parameters monitored during the process

Parameter	Impeller rpm	Chopper rpm	Time in min	LOD @105 °C
Dry mixing	150.00	off	5.00	4.5
Binder addition	150.00	750.00	30.00	NAP
Kneading	150.00	750.00	2.00	NAP

Note: The amount of water consumed for granulation is 25 gm (12.5%).

Table 2: Drying parameters monitored during process

S No	Time in min	Inlet temp (°C)	Airflow (cfu)	Product temp (°C)	LOD @105 °C
1	Initial	50.00	75.00	21.80	NAP
2	After 20	65.00	75.00	24.40	7.80
3	After 30	65.00	65.00	27.30	6.50
4	After 40	50.00	55.00	28.80	5.60
5	After 45	50.00	50.00	30.70	4.40
6	After 50	50.00	50.00	31.20	4.00

The dried granules are milled with a 1.0 mm grated screen at 900rpm using a co-mill, the milled granules are sifted through #12 mesh (step 4). Talc and colloidal silicon dioxide are passed through #60mesh, then added for step 4 and blended manually for 2 min (step 5). The magnesium stearate is passed through #60 mesh, then added for step 5 and blended manually for 5 min.

Compression parameters

The 15 mm size and plain concave punch are used for compression.

***In vitro* drug dissolution studies**

In vitro release studies of the prepared formulations were carried out using USP Dissolution test apparatus II. A 900 ml of 0.1 N HCl solution was used as dissolution medium which is maintained at a temperature of 37±0.5 °C and the paddle was rotated at 50 RPM. Aliquots of 5 ml each of the dissolution media were withdrawn using a syringe fitted with a prefilter at appropriate time intervals and immediately replaced with 5 ml of fresh medium maintained at 37±0.5 °C. The absorbance of samples was measured at 254 nm after suitable dilutions with the medium using a UV Spectrophotometer.

Determination of floating lag time and total floating time

The floating lag time (FLT) is the time taken for a tablet to rise on a medium surface, and the total floating time (TFT) is the floating duration that a tablet remains on the surface. To determine the floating lag time, tablets were put on 100 mL of 0.1 N HCL in a beaker, and the time is required for a tablet to rise on the surface was measured. Then, the duration of each formulation that remained on the surface was determined as total floating [13].

RESULTS AND DISCUSSION

Melting point

The melting point is determined using the capillary tube for valganciclovir hydrochloride to ensure the received drug is pure and has the same chemical entity. The melting point was found 164 °C, which is matching with the theoretical range [14].

Solubility analysis

The solubility of valganciclovir hydrochloride is performed using different solvents and in a mixture of solvents. As per the information provided in the US patent, valganciclovir hydrochloride has shown maximum solubility in 0.1N Hcl solution [2].

Table 3: The solubility profile of valganciclovir hydrochloride

Solvent	Solubility status
0.1N Hydrochloric acid	Freely soluble
Water	Sparingly soluble
Phosphate Buffer of pH at 7.4	Sparingly soluble
Methanol/DMSO	Slightly soluble

Determination of λmax

From 0.1N Hcl with valganciclovir working standard solution, 5 ml was pipette out into a 10 ml volumetric flask, and the volume was made up to the mark with 0.1N Hcl to prepare a concentration of 50µg/ml. Then the sample was scanned in a UV spectrophotometer in the range 400-200 nm using 0.1N Hcl as a blank and the wavelength

corresponding to maximum absorbance (λmax) was found to be 254 nm. The obtained absorbance maximum was found similar to the theoretical value determined by multiple researchers [15].

Drug-excipient compatibility

FT-IR study was carried out to check any possible interactions between the drug and the Inactive ingredients. Pure drug was mixed with Inactive ingredients with respect ratio which is proportional to the formulation composition and checked for any interaction present. The major FTIR peaks of the drug were retained in the FTIR physical mixtures. The study results revealed that no major interaction between the selected drug and inactive ingredients.

Formulation development

The formulation of sustained-release floating matrix tablets of valganciclovir hydrochloride is carried out using dry granulation and direct compression techniques in the initial stages. However, due to hardness and friability issues the wet granulation method is adopted and the formula is optimized using different binders and controlled-release polymers. To study the robustness of formulation, the design of experiment (DOE) trials was carried out by using a central composite design. The F1 and F10 are the control formulations used as bracketing controls in the design of experiment (DOE) trials.

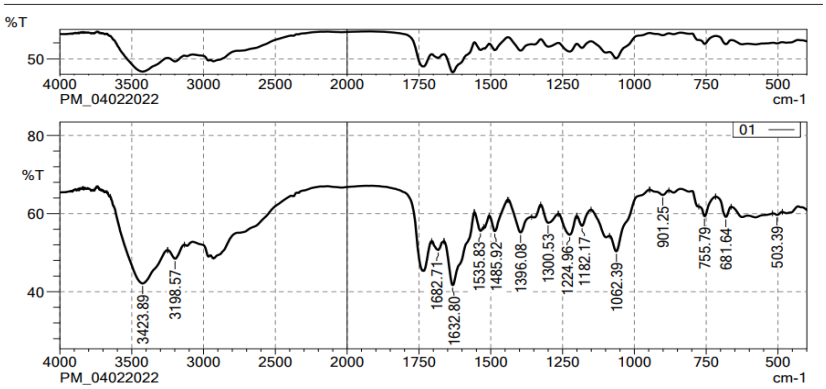

Fig. 1: FTIR spectra for valganciclovir hydrochloride

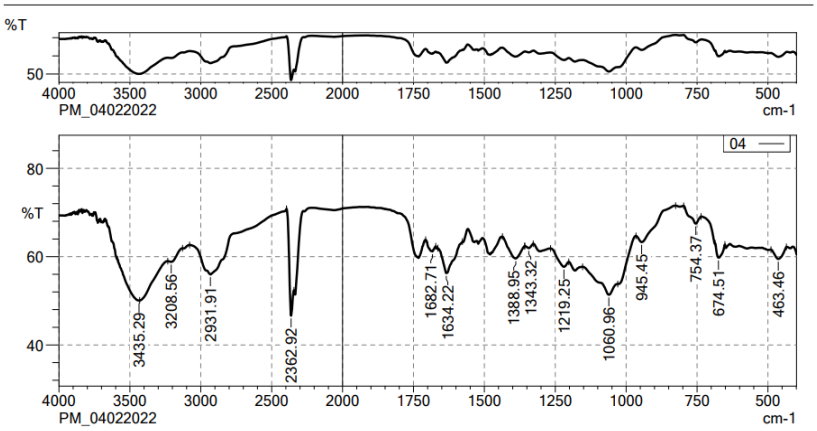

Fig. 2: FTIR spectrum of valganciclovir hydrochloride and hydroxy propyl methyl cellulose

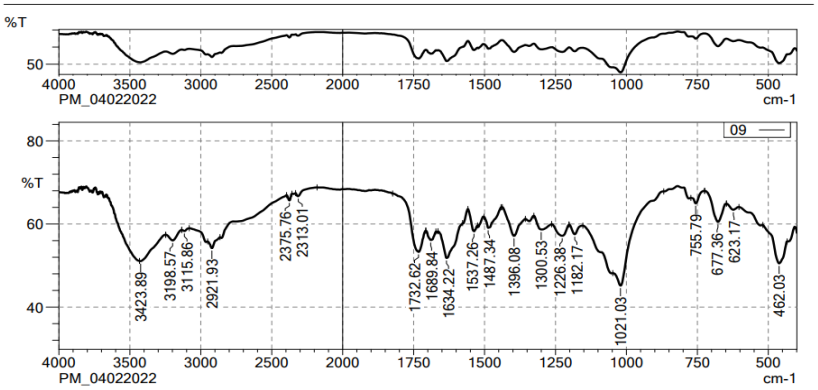

Fig. 3: FTIR spectrum of valganciclovir hydrochloride and all inactive ingredients

Table 4: Formulation with central composite design

Formulation with central composite design						
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Valganciclovir hydrochloride (mg/tab)	450.00	450.00	450.00	450.00	450.00	450.00
Microcrystalline cellulose (mg/tab)	88.00	87.68	88.32	87.36	88.64	86.00
Povidone K 30 (mg/tab)	16.00	16.32	15.68	16.00	16.00	16.00
Ethyl cellulose (mg/tab)	32.00	32.00	32.00	32.64	31.34	32.00
HPMC K15 (mg/tab)	100.00	100.00	100.00	100.00	100.00	102.00
Sodium bicarbonate (mg/tab)	96.00	96.00	96.00	96.00	96.00	96.00
Colloidal silicon dioxide (mg/tab)	4.00	4.00	4.00	4.00	4.00	4.00
Talc (mg/tab)	6.00	6.00	6.00	6.00	6.00	6.00
Magnesium stearate (mg/tab)	8.00	8.00	8.00	8.00	8.00	8.00
Total (mg)	800.00	800.00	800.00	800.00	800.00	800.00

Table 5: Formulation with central composite design

Formulation with central composite design						
Ingredients	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Valganciclovir hydrochloride (mg/tab)	450.00	450.00	450.00	450.00	450.00	450.00
Microcrystalline cellulose (mg/tab)	90.00	86.08	89.92	87.84	88.16	88.00
Povidone K 30 (mg/tab)	16.00	16.00	16.00	16.00	16.00	16.00
Ethyl cellulose (mg/tab)	32.00	32.00	32.00	32.00	32.00	32.00
HPMC K15 (mg/tab)	98.00	100.00	100.00	100.00	100.00	100.00
Sodium bicarbonate (mg/tab)	96.00	97.92	94.08	96.00	96.00	96.00
Colloidal silicon dioxide (mg/tab)	4.00	4.00	4.00	4.00	4.00	4.00
Talc (mg/tab)	6.00	6.00	6.00	6.00	6.00	6.00
Magnesium stearate (mg/tab)	8.00	8.00	8.00	8.16	7.84	8.00
Total (mg)	800.00	800.00	800.00	800.00	800.00	800.00

Hardness and friability evaluation profiles for formulations of central composite design

The hardness is tested with an erweka hardness tester and friability is tested with Roche friability apparatus. The results were found consistent across the batches. The hardness profile was found more stable enough to withstand the friability and to provide a controlled release profile from all the batches of central composite design. The assay results were found uniform across the formulation batches.

Table 6: Hardness, friability, and drug content profiles

Formulation	Hardness (Newton)	Friability (%)	Assay (mg/tab)
F1	201.04±3.92	0.00	97.00-103.00%
F2	204.71±5.18	0.00	
F3	197.39±3.91	0.00	
F4	203.16±6.67	0.00	
F5	200.98±6.39	0.00	
F6	207.44±5.36	0.00	
F7	196.38±3.71	0.00	
F8	201.25±3.84	0.00	
F9	202.68±7.80	0.00	
F10	210.37±4.75	0.00	
F11	206.43±6.63	0.00	
F12	204.27±3.44	0.00	

Note: (mean±SD n=3)

Table 7: Dissolution profiles for formulations of central composite design

Time in min	60 min (% CDR)	120 min (% CDR)	240 min (% CDR)	480 min (% CDR)	720 min (% CDR)
F1	12.04±1.58	22.26±3.06	37.22±2.85	78.95±4.55	97.21±4.02
F2	11.87±2.42	22.01±3.63	35.52±3.52	76.25±3.25	96.20±3.29
F3	12.82±2.85	23.45±2.89	38.23±2.25	78.88±4.02	96.11±2.98
F4	12.11±1.62	23.20±4.15	37.55±3.65	76.23±3.85	94.21±3.55
F5	13.62±4.21	25.16±3.55	39.50±4.22	79.21±2.62	98.44±4.14
F6	11.20±3.24	21.04±4.06	36.22±5.03	77.89±3.07	95.01±3.78
F7	13.22±2.02	24.70±4.25	35.34±3.45	75.09±4.01	96.23±3.33
F8	12.52±2.63	23.07±2.41	36.89±3.61	77.22±3.96	96.23±5.06
F9	13.21±2.86	26.21±3.33	37.86±2.88	77.95±3.77	96.74±3.87
F10	12.50±3.01	21.08±3.97	36.45±3.24	77.04±4.54	95.26±3.64
F11	13.12±2.41	23.56±3.45	37.89±3.85	78.62±4.14	98.63±2.73
F12	13.02±1.21	22.79±2.33	36.87±3.71	77.50±2.10	96.55±3.98
Average	12.60	23.21	37.13	77.57	96.40
% SD	0.70	1.57	1.18	1.27	1.28

Note: *The % standard deviation is considered from an average of 12 batches and from each batch 6 tablets are tested for dissolution (mean±SD, n=6).

Dissolution profile for formulations of central composite design

The formulation design is made from the theoretical aspect of the central composite design to evaluate the robustness of the formulation composition. The functional excipient povidone K 30 is varied between+2% to-2% from the target concentration to evaluate the hardness and friability profile. The HPMC K15, magnesium stearate, and ethyl cellulose are varied between+2% to-2% to evaluate the release profile of valganciclovir hydrochloride sustained release floating matrix tablets. The release profile was found to be exceptional across the batches. The formulated tablets have shown sustained release over 12 h by releasing>90% drug. This indicates minor variation in composition from the control formulation has no impact on the release profile thereby product quality. High concentration of polymer influences the formation of swollen mass that restricted the rate of diffusion into the matrix, which may result in retardation the drug release (16). As per the reference quoted here, the same observation was found with our formulation, which has high polymer content (F6).

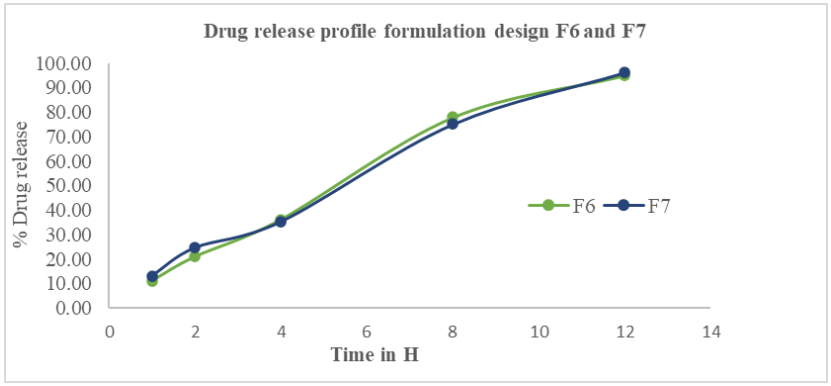

Fig. 4: Dissolution profile for HPMC K15 variable composition

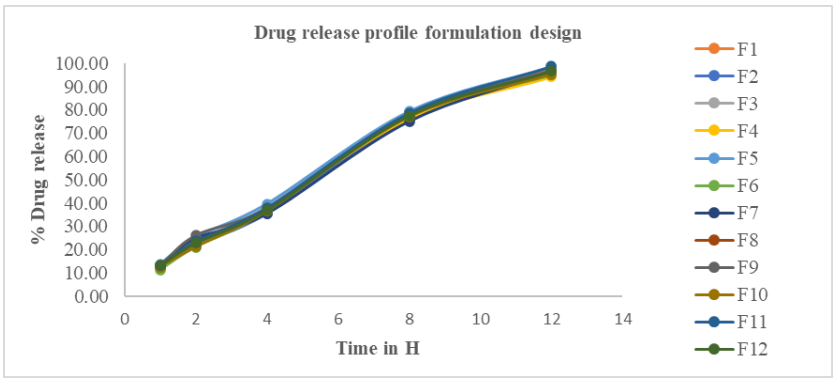

Fig. 5: Dissolution profile for formulation DOE

Dissolution profile on process optimization

The formulation is carried out to study the robustness of process design by varying the critical process parameter of binder addition rate to±1 min and the release profile is evaluated; the analytical results were found that there is no meaningful difference observed in the release profiles when comparing target formulation. However, the binder addition rate is not impacting the quality of the product but it's considerably increasing the drying time for 10-15 min; hence the addition rate should be maintained to avoid loss of time.

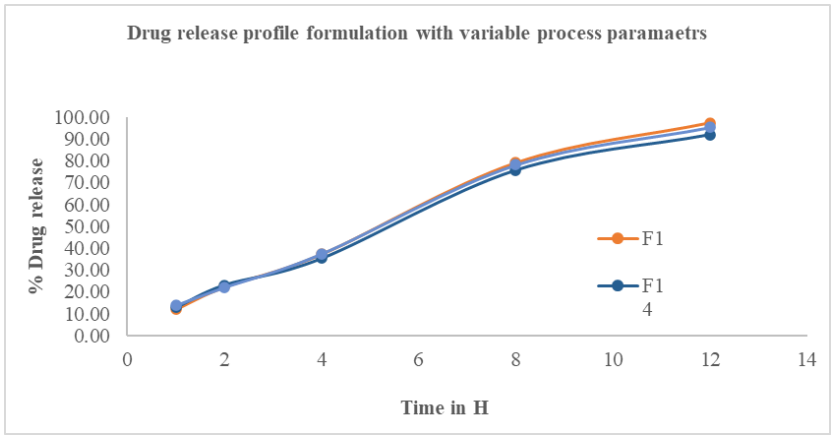

Fig. 6: Drug release profile formulation with variable process parameters

Determination of floating lag time and total floating time

The tablets were prepared by effervescent technique using sodium bicarbonate as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution of a medium (0.1N Hcl). The gas generated is trapped and protected within the gel, formed by the hydration of the polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1 g/ml, the tablet becomes buoyant (17). The effect of sodium bicarbonate on buoyancy of the tablets was evaluated by using it at 2 different level but since difference is minimal, no major difference has been observed. The selected concentration of sodium bicarbonate is more enough to provide the required buoyancy. The floating lag time and total floating time were tested for all the formulations and all formulations showed consistent total floating time with sustained release profile. The total floating time is found>11 h across the batches and it is a reflection of tablets floating time in an acidic media, which mimics the stomach pH and environment. The total floating time is comparable to the dissolution release profile with respective formulations of central composite design.

Table 8: Floating lag time and floating time for formulations of central composite design

Formulation	% Release at 12 h*	Floating lag time (s)	Total floating time (h)
F1	97.21±4.02	38.00	>11.00
F2	96.20±3.29	57.00	>11.00
F3	96.11±2.98	102.00	>11.00
F4	94.21±3.55	86.00	>11.00
F5	98.44±4.14	45.00	>11.00
F6	95.01±3.78	64.00	>11.00
F7	96.23±3.33	147.00	>11.00
F8	96.23±5.06	123.00	>11.00
F9	96.74±3.87	41.00	>11.00
F10	95.26±3.64	109.00	>11.00
F11	98.63±2.73	89.00	>11.00
F12	96.55±3.98	65.00	>11.00

Note: (*mean±SD n=6)

CONCLUSION

The preliminary evaluation has been made to confirm the purity of valganciclovir hydrochloride. A series of formulation trials has been conducted and the parameters are evaluated. The valganciclovir hydrochloride is more soluble in 0.1N Hcl solution and FTIR confirms drug and excipients are compatible. The in-process parameters like compressibility index, and flow properties were found ideal by looking towards the results of friability and hardness. The dissolution profile found no meaningful difference across the batches of composition and process robustness trials. This indicates the minor change in critical material and process attributes has no major impact on product quality. The optimized formulation is reproducible and consistent enough to indicate the robustness of process parameters and formulation composition.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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