Development and pharmacokinetic evaluation of osmotically controlled drug delivery system of Valganciclovir HCl for potential application in treatment of CMV retinitis

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Abstract

Valganciclovir HCl (VGH) is the widely used drug for the treatment of Cytomegalovirus (CMV) retinitis infection with an induction dose of 900mg twice a day and a maintenance dose of 900mg. This required dose of the drug also leads to multiple side effects due to repeated administration. The research was highlighted to develop, formulate, optimize and evaluate Single-Core Osmotic Pump (SCOP) tablet of VGH with the dose of 450mg to reduce dosing frequency and associated side effects. . The decrease in dose also minimize the hepatic and nephrotic load. The optimized batch of formulation was subjected to comparative *in vitro* and *in vivo* evaluation. The tablet core composition is the primary influencer of the drug delivery fraction in a zero-order, whereas the membrane characteristics control the drug release rate. *In-vivo* pharmacokinetic studies revealed that the newly developed osmotic formulation has controlled zero-order release for 24 hours with a single dose of 450mg while the marketed formulation requires twice administration within 24 hours to maintain the plasma concentration in the therapeutic window. The developed formulation can be the promising option for the treatment of CMV retinitis with the minimum dose and dosing frequency.

Introduction

Cytomegalovirus (CMV) infection is the common opportunistic infection and a leading cause of death in patients with the Acquired Immunodeficiency Syndrome (AIDS). It may present in various clinical forms, including retinitis, colitis, pneumonitis, esophagitis, and encephalitis (Tan, 2014). If untreated, CMV retinitis is invariably progressive, leading to retinal necrosis, loss of vision, and accounting for at least 70% of all intraocular infections in patients with AIDS. Till now there are three agents (Ganciclovir, Foscarnet, and Cidofovir) approved in the United States for the treatment of cytomegalovirus retinitis (Tseng & Foisy, 1996). VGH is the prodrug of Ganciclovir, is well absorbed from the gastrointestinal tract as well as quickly metabolized in the intestinal wall and liver to Ganciclovir (Cvetković & Wellington, 2005). Ganciclovir is a synthetic guanine derivative active against CMV and is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). VGH is an L-valyl ester (prodrug) of Ganciclovir that exists as a mixture of two diastereomers that increases the bioavailability of Ganciclovir by 10 fold as compared to Ganciclovir dosage forms. Conversion of diastereomers takes place to Ganciclovir by intestinal and hepatic esterases (Vaziri et al. 2014).The oral route has been the most accepted route for the ailment of various disorders from ancient times. Immediate-release formulations lead to rapid release and rapid excretion and therefore lacking in controlling the right plasma concentration of a drug with disadvantage of smaller duration of action (Ahmed, 2015). Hence the controlled release formulations are preferred for maintaining the adequate plasma concentration and to facilitate patient compliance by minimizing dosing frequency (Bhusal et al., 2016). Injections of Ganciclovir into the vitreous body are effective, but due the short half-life of the drug weekly injections are required to maintain therapeutic levels. Daily intravenous therapy is associated with substantial cost, inconvenience, and risk of catheter-related complications. As the patient requires long-term venous access patient is at high risk of sepsis which may lead to serious complications like endophthalmitis, retinal detachment, and vitreous hemorrhage. The presence of an indwelling catheter and the time required to infuse these medications may also have a negative impact on the quality of life (Teoh et al., 2012).

Biodegradable polymers have been the focus of extensive research because of the potential for long- term unattended therapy and site-specific drug administration. However, drug release kinetics from polymers exhibits complex drug release due to changes in the polymer phase properties during degradation, resulting in drastic changes in drug diffusivity and permeability (Jana et al., 2021). Majority of per oral dosage form falls within the category of the matrix, reservoir, or osmotic system. Osmotic systems utilize the principle of pressure for the delivery of medicine (Chourasiya et al. 2013). There is a large potential for osmotic drug delivery systems because of their unique advantages, over other types of dosage forms. The accuracy and predictability of drug release from osmotic pumps is evident from the fact that these have been used for determining the pharmacokinetic and pharmacodynamic properties of new or existing drug molecules during the early drug development stages (Keraliya et al., 2012). The dosing frequency of conventional VGH tablet is 900mg twice a day induction and 900 mg tablets, once a day as a maintenance dose with a half-life (4.08 ± 0.76 hours). This high dose leads to major side effects like hematologic toxicity, impairment of fertility, mutagenicity, carcinogenicity, fetal toxicity and acute renal failure (Humar, 2005). The intention behind the present research was to develop an oral osmotic pump that can provide controlled delivery of drug up to 24 hours with prospects of better therapy, reduce dose burden, avoid potential side effects and achieve patient compliance with once-daily dosing in chronic treatment. The objective in formulating such a system is to deliver under zero-order kinetics, the maximum drug fraction over a fixed duration. The sustained-release delivery system for the treatment of cytomegalovirus retinitis was developed to achieve a longer-lasting therapeutic effect and to avoid intravitreous injections and surgical procedures. The target of product development was to develop an osmotic delivery system that can deliver VGH in a controlled manner and which will be independent of environmental pH, agitation, and other conditions encountered in the gastrointestinal tract. Since, the osmotic gradient controls the flux of water through the membrane and into the core, which successively controls the speed of drug delivered from the tablet (Bathool et al. 2012; Dasankoppa et al. 2013).

Materials And Methods

Materials

VGH was obtained as a free sample from Wockhardt Research Centre, Aurangabad (M.S), India, and lactose monohydrate was obtained from DFE Pharma, India. Povidone K-90 was procured from BASF, Ahmadabad, India, Colloidal silicon dioxide from Evonik, Mumbai, India Caprylocaproyl polyoxyl-8 glycerides from Gattefosse, Mumbai, India Magnesium stearate from Mallinckrodt New Delhi, India, Cellulose Acetate from Eastman Chemicals Ltd., Singapore, Hydroxypropyl Cellulose from Nippon Soda, Tokyo, Japan and polyethylene glycol from Clariant Chemicals India Limited, Vadodara, India. Isopropyl alcohol and acetone were purchased from Lee chang, Bengaluru, India and Merck, Bengaluru, India respectively.

Experimental animals

The beagle dogs were used as experimental animals from the animal house facility of Wockhardt Research Centre, Aurangabad. Throughout the experimental period, the animal room temperatureand relative humidity will be maintained at 22-250C and 40 to 70% RH respectively. Animalswere kept in 12 hours light and 12 hours of darkness in the experimental room. Animal experiments were performed with the protocol approved by animal ethical committee.

Drug-Excipient Compatibility study by Differential Scanning Calorimetry (DSC)

DSC analysis of the drug and the physical mixture of the drug and excipients was carried out using a DSC (Mettler SATR SW 9.30, India) under the inert atmosphere maintained by purging with nitrogen. VGH and excipients were kept together at 25°C/60%RH and 40°C ± 2°C/75% ± 5% RH for 4 weeks. DSC analysis was carried out at a scanning (heating) rate of 10°C min-1. Thermograms of drug and physical mixture were compared for compatibility (Pekamwar et al. 2021).

Micromeritic properties of tablet blend

The Tablet blend was subjected to micrometric evaluation to determine the flow properties and compressibility of the blend. Bulk density, tapped density, angle of repose, Hausner's ratio, and compressibility (Carr's) index was determined (Gadade et al., 2017).

Preparation of VGH osmotic tablets

The osmotic tablets were prepared by wet granulation method. The osmotic delivery system consists of a drug, hydrophilic polymer, and an osmotic agent. The proposed extended-release formulation for VGH 450mg is developed for once a day dosing. In the formulation, VGH, Povidone (kollidon K90) & Lactose monohydrate were collected and sifted through #20 ASTM using a vibratory sifter (Electrolab, Mumbai). Before the start of wet granulation slurry (Binding agent) was prepared by mixing Labrasol, Isopropyl alcohol & Purified water (Table 1). The sifted blend was collected and transferred to Rapid Mixer Granulator (Saral Engineering Company, Gujrat) and the granulation was carried out by the slow addition of slurry to the bed of the granules. Once the granulation is finished the mixture was collected and passes through the vibratory sifter (#12 Sieve). Granules were dried using a fluidized bed dryer (make and name) for 60 min at 60^{o}C to achieve the LOD of 1 to 2.0%. Dried granules were sifted through #20 mesh sieve. Retained lumps were milled through Co-mill with 40G screen (Screen no. 1016). Milled granules were collected and mixed with the granules initially passed through #20 mesh sieve. Granules were collected and loaded into the double cone blender. Extra-granular ingredient magnesium stearate was weighed as per yield and sifted through sieve #60 ASTM and blended with the dried granules in double cone blender for 3 min at 23 ± 1 RPM. Lubricated granules were collected and shifted for the compression process. Compression was done by using Rotary Compression Machine (Cadmach, Ahmadabad) with 12.00 mm, round, plain, and beveled edge punches. Temperature and relative humidity during compression was maintained at NMT 25°C and NMT 50% respectively (Gundu et al. 2020; Kulshrestha et al. 2013; Xin et al., 2014).

Table 1
Composition of Valganciclovir HCl (VGH) tablet

S. No.	Ingredients/Grade	As such	After Assay calculation
		mg/tablet	mg/tablet
	Intra-granular		
1	Valganciclovir HCl	496.3	535.19
2	Povidone (kollidon K90)	110	110
3	Lactose monohydrate (DCL11)	73.7	34.81
	Binder		
4	Labrasol®	14	14
5	Purified water	q.s.(30%)	q.s.(30%)
6	Isopropyl alcohol	q.s.(70%)	q.s.(70%)
	Extra-granular		
7	Colloidal silicon dioxide (Aerosil 200)	3	3
8	Magnesium stearate	3	3
	Core Tablet Weight	700	700

Tablet coating

Seal coating was done using suitable polymers using the different compositions as enlisted in Table 2. Isopropyl alcohol (Solvent) was taken in a stainless steel container. PEG 400 andHydroxypropyl Cellulose (Nisso HPC SSL) was added to the solvent with continuous (45 min) stirring until it was completely dissolved to obtain a transparent solution. Seal coating was performed in a perforated coating pan till the desired weight was achieved. Extended-Release (ER) coating solution was prepared by using Acetone, Polyethylene Glycol (PEG) 6000, Hydroxypropyl methylcellulose (HPMC) cellulose acetate, and purified water (Table 2). A solvent mixture of Acetone & Purified water was taken in a suitable stainless steel container. PEG 6000 and HPMC 3cps were added to the above mixture with continuous stirring. To the above mixture, cellulose acetate was slowly added and stirred for 1 hr to get a transparent solution. Tablets were coated with an extended-release coating solution to gain the desired weight. Thereafter, tablets were dried in a coating pan for 10 minutes at 45 ± 5°C. All the process parameters for seal coating and ER coating are given in Table 3 (Shirsat, 2017; Patil et al., 2016).

Table 2
Seal coating and Extended Release (ER) Coating Composition

Seal Coating Composition				**ER Coating Composition**		
Sr.No.	Ingredients	% w/w	mg/tablet	Ingredients	% w/w	mg/tablet
1	Core tablet	–	700	Seal coated tablet	–	721
2	Hydroxypropyl Cellulose (Nisso HPC SSL)"	90.5	19	Cellulose Acetate CA 398 – 10	93	40
3	Polyethylene glycol 400	9.5	2	Polyethylene glycol 6000	7	3
4	Isopropyl alcohol (95%)	–	q.s.	Acetone (90%)	–	q.s.
				Purified water (10%)	–	q.s.
	Total Weight Gain (%w/w)	**3**		**Total Weight Gain (%w/w)**	**6**	
	Seal coated tablet weight (mg)	**721**		**ER coated tablet weight (mg)**	**764**	
	–	–				

Table 3
Seal coating and Extended Release (ER) Coating Composition

Parameters	Seal Coating	ER Coating
Inlet Temp. (^oC)	45.0–50.0	35.0–40.0
Exhaust Temp. (^oC)	40.0–45.0	27.0–33.0
Bed Temp. (^oC)	35.0–40.0	27.0–33.0
Pan Speed (RPM)	10–15	10–15
Spray Rate (RPM)	5–12	5–10
Atomization (kg/cm^2)	0.9–1.1	0.90–1.10

Laser drilling

ER coated tablets were drilled using a laser drilling machine (Control Micro System, USA) with one drill (orifice) on one side of tablets with an orifice size of 0.5, 0.6, and 0.7 ± 0.05mm as it is one of the independent variables in a factorial design.

Factorial design and optimization

Response surface methodology was carried out for the optimization of the prepared formulation. Design Expert (Stat-Ease Inc., Minneapolis, version 11) software was used to perform factorial design. A 2^4 factorial design was applied for VGH tablet formulation. The effect of different independent factors was studied using the response surface methodology (Table 4) (Patel et al., 2016).

Table 4
Details of design layout for Valganciclovir HCl (VGH) Extended Release (ER) tablets

B. No	Factor 1	Factor 2	Factor 3	Factor 4
	A:Povidone (kollidon K90) mg	B:Cellulose Acetate % ratio	C:Polyethylene glycol 6000 % ratio	D:Orifice diameter mm
VGH1	120	94	6	0.6
VGH2	90	91	3	0.7
VGH3	90	91	3	0.5
VGH4	150	91	3	0.7
VGH5	150	91	9	0.7
VGH6	90	97	9	0.5
VGH7	90	97	3	0.5
VGH8	90	97	3	0.7
VGH9	90	97	9	0.7
VGH10	150	97	9	0.7
VGH11	90	91	9	0.7
VGH12	120	94	6	0.6
VGH13	120	94	6	0.6
VGH14	150	97	3	0.5
VGH15	150	97	3	0.7
VGH16	150	91	3	0.5
VGH17	150	91	9	0.5
VGH18	150	97	9	0.5
VGH19	90	91	9	0.5
VGH20	120	94	6	0.6

Evaluation of Osmotic tablets

Osmotic tablets were evaluated for different physicochemical evaluations. Uniformity of weight, Friability, and Hardness of the tablet was evaluated. Uniformity of weight was studied using 20 tablets. .From the average weight the variation was determined. The Friability of VGH osmotic tablets was evaluated using a Friability tester(Electrolab, Mumbai, India). For the Friability test, ten formerly weighed tablets were placed friability taster and rotated for100 revolutions in 4 min (25 rpm). The hardness of the tablet was evaluated using a hardness tester (Erweka, Germany) (Kumar et al., 2017).

In vitro **dissolution and drug release kinetics**

The *in vitro*dissolution study was carried out using USP dissolution apparatus at 37 ± 0.5°C. Phosphate buffer pH 7.4 was added used as a dissolution medium. In vitro dissolution was studied for 24 hours. After each time interval, 15ml of aliquots were withdrawn and filtered through 0.45 µm nylon filters. After suitable dilutions, drug release was calculated from absorbance determined by UV spectrophotometric analysis. Different kinetic models were applied to study release kinetics and data analysis was done using (DD solver, 1.0 (Trial version), Nanjing, China) (Pudjiastuti et al., 2020).

Comparative In vitro **dissolution of optimized formulation and marketed preparation**

In vitro drug release analysis of the optimized batch of osmotic pump tablet of Valganciclovir HCl (VGH-12) was comparatively studied with marketed formulation (Valcyte®). Phosphate buffer pH 7.4 was used as dissolution media.

Dissolution analysis byScanning Electron Microscopy (SEM) and Hydration study

The dissolution of the optimized formulation (VGH 12) of the osmotic pump tablet was analyzed by Scanning Electron Microscopy (SEM) with 1000X magnification. To check the permeation of solvent through semi-permeable cellulose acetate coating membrane and subsequent hydration of the core part of tablets at different time interval hydration study was done. Samples were withdrawn at different dissolution time intervals as a whole tablet and the further tablet was cut with a sharp blade into two half portions. Images were captured and labeled for all these samples to depict hydration of core and drug release though drilled coating orifice (Geetha et al., 2009) .

In-vivo **pharmacokinetic study**

A pharmacokinetic study was carried out on beagle dogs (male/female) (weight 10-12kg) of age 2–4. Six dogs were used for test formulation whereasthree dogs were used for reference formulations. Animals were housed under the controlled condition at 22ºC ± 3ºC and 30 to 70% RHwith a 12 h in light and 12 h in dark. A standard diet with free water access was provided to dogs Dogs were fasted for 18 h. VGH ER tablets 450mg OROS tablets (Test product) were administered once (450mg single dose) to each dog by oral route and blood samples were collected from the cephalic vein. Approximately 0.7ml sample was withdrawnfrom the cephalic vein before drug administration and at 1, 3, 5, 8, 10, 12, 15, 18, 21, and 24 hrs after administration of VGH tablet. Whereas Valcyte® tablets 450 mg (Reference Product) were administered two times a day (450mg dose at 12 hours interval) to each dog orally and blood samples were collected. After centrifugation, drug content in plasma samples was analyzed using the LC-MS-MS method (Elshafeey & Sami, 2008).

An analytical method for the determination of VGH in dog plasma

The liquid chromatography-tandem mass spectrometric (LC-MS-MS) method was found suitable for the estimation of VGH in the form Ganciclovir (the active metabolite of VGH) in dog plasma. Transferred accurately 50 µL of dog plasma study sample to 1.5 mL centrifuge tube containing 400 µL of acetonitrile and vortex it for 1 min. Add 50 µL of IS (Internal Standard) solution, vortex, and centrifuged for 5 min at 10000 rpm and transferred the supernatant to an autosampler vial and inject on LC-MS-MS (Table 5) (Rhee et al., 2008).

Table 5
Parameters for in vivo analytical method development (LC-MS)

Parameters	Chromatographic Specifications	Parameters	Mass Spectrometric specifications	
			Valganciclovir HCl	Ganciclovir
Stationary Phase	Zorbax SB C18, 75 x 2.1 mm, 3.5µm with guard column	MRM transition (amu)	355.4 > 152.2	256.3 > 152.0
Mobile Phase	Mixture of Buffer : Organic mixture (20:80; v/v)	Declustering potential (Volts)	50	24
Organic mixture	Acetonitrile: Methanol (95:5; v/v)	Entrance potential (Volts)	12	6
Flow rate	0.3 mL/min	Collision energy (Volts)	19	16
Auto-injector temperature	5 ± 1ºC	Collision cell exit potential (Volts)	13	15
Column temperature	30 ± 1ºC	Dwell time (msec)	300	300
Injection volume	5 µL	-	-	-
Run time	3.5 min	-	-	-
Detector	Triple quadrupole mass spectrometer	-	-	-

Stability study

For stability study, theosmotic tablets were packed in a blister pack with a forming laminate of PVC and aluminum lidding foil and were kept at 40˚C ± 2˚C & 25˚C ± 2˚C with 75% ± 5% and 60% ± 5% of RH respectively (Gupta et al., 2010).

Results And Discussion

Drug excipient stability study by DSC

DSC thermograms of drug and physical mixture of drug and excipient were compared analyzed for compatibility (Fig. 1). In DSC analysis no significant changes were found in both DSC thermograms of pure drug and for mixtures of drug and different excipients, this indicates that the formulation blend is stable. The peak temperature value of VGH in the DSC thermogram was 177.99^{0}C. DSC thermograms of physical

mixtures of all the excipients with Valganciclovir HCl showed peak value in the range of 173.10^{0}C to 177.03^{0}C. This insignificant change in DSC values shows the compatibility of the drug with excipients (Kaushik & Pathak, 2016).

Micromeritic properties

The preformulation characteristics indicate the optimum flow properties of the tablet blend. The angle of repose for all the 20 formulations, formulated was between 27.68–28.10 is the indication good flowability of all the tablet blends. Similarly, the results of densities, Hausner's ratio and compressibility index also support the conclusion of optimum flow properties of tablet blends (Table 6) (Maheshwari et al., 2018).

Table 6
Micromeritic properties of tablet blends of all 20 batches of Valganciclovir HCl (VGH)

B.No	Angle of Repose* (°)	Bulk Density* (g/cm3)	Tapped Density*(g/cm3)	Compressibility* Carr's Index	Hausner's ratio
VGH1	27.75 ± 0.14	0.458 ± 0.03	0.523 ± 0.02	13.48 ± 0.02	1.18 ± 0.01
VGH2	27.88 ± 0.13	0.464 ± 0.01	0.515 ± 0.01	13.42 ± 0.01	1.22 ± 0.01
VGH3	27.95 ± 0.11	0.450 ± 0.03	0.526 ± 0.03	13.52 ± 0.02	1.15 ± 0.03
VGH4	27.98 ± 0.15	0.455 ± 0.03	0.525 ± 0.04	13.41 ± 0.05	1.13 ± 0.04
VGH5	27.78 ± 0.20	0.462 ± 0.04	0.525 ± 0.03	13.38 ± 0.04	1.08 ± 0.05
VGH6	27.82 ± 0.11	0.452 ± 0.03	0.523 ± 0.02	13.49 ± 0.03	1.14 ± 0.02
VGH7	27.68 ± 0.12	0.464 ± 0.04	0.529 ± 0.01	13.46 ± 0.03	1.15 ± 0.01
VGH8	28.1 ± 0.23	0.454 ± 0.05	0.520 ± 0.02	13.52 ± 0.03	1.17 ± 0.05
VGH9	27.87 ± 0.11	0.452 ± 0.06	0.519 ± 0.03	13.46 ± 0.02	1.20 ± 0.06
VGH10	27.9 ± 0.12	0.460 ± 0.04	0.515 ± 0.02	13.45 ± 0.04	1.16 ± 0.08
VGH11	27.81 ± 0.15	0.466 ± 0.02	0.523 ± 0.04	13.44 ± 0.03	1.13 ± 0.03
VGH12	27.95 ± 0.15	0.458 ± 0.02	0.526 ± 0.02	13.45 ± 0.03	1.14 ± 0.04
VGH13	28.01 ± 0.18	0.450 ± 0.03	0.522 ± 0.03	13.48 ± 0.02	1.15 ± 0.03
VGH14	27.75 ± 0.11	0.460 ± 0.01	0.530 ± 0.05	13.49 ± 0.03	1.17 ± 0.03
VGH15	27.96 ± 0.09	0.455 ± 0.05	0.528 ± 0.04	13.44 ± 0.05	1.13 ± 0.05
VGH16	27.92 ± 0.14	0.468 ± 0,05	0.515 ± 0.03	13.45 ± 0.03	1.18 ± 0.04
VGH17	27.99 ± 0.12	0.457 ± 0.03	0.522 ± 0.05	13.50 ± 0.02	1.20 ± 0.03
VGH18	27.88 ± 0.11	0.456 ± 0.06	0.525 ± 0.06	13.48 ± 0.02	1.15 ± 0.02
VGH19	27.89 ± 0.15	0.465 ± 0.07	0.524 ± 0.03	13.45 ± 0.01	1.17 ± 0.01
VGH20	27.95 ± 0.14	0.458 ± 0.04	0.528 ± 0.03	13.46 ± 0.01	1.19 ± 0.04
Values are expressed as mean ± S.E.M; n = 3					

Preparation and evaluation of VGH osmotic tablets

The variation in tablet evaluation parameters like weight, diameter, thickness, friability and hardness were within the limit (Table 7). These within the limit parameters indicates the optimized execution of tableting process involving mixing, granulation, compression and coating.

Table 7
Evaluation parameters of Valganciclovir HCl (VGH) osmotic pump tablets

B. No	Weight (mg)	Diameter (mm)	Thickness (mm)	Drug content (%)
VGH1	805 ± 5	11.36 ± 0.02	7.85 ± 0.03	101.20 ± 1
VGH2	802 ± 6	11.35 ± 0.02	7.89 ± 0.02	99.28 ± 2
VGH3	803 ± 4	11.34 ± 0.01	7.86 ± 0.01	102.50 ± 1
VGH4	810 ± 3	11.33 ± 0.01	7.83 ± 0.01	98.65 ± 1
VGH5	802 ± 5	11.38 ± 0.02	7.81 ± 0.03	99.86 ± 1
VGH6	800 ± 7	11.35 ± 0.03	7.83 ± 0.02	100.35 ± 2
VGH7	799 ± 6	11.32 ± 0.02	7.78 ± 0.02	97.45 ± 0.05
VGH8	802 ± 8	11.3 ± 0.02	7.8 ± 0.03	98.76 ± 1
VGH9	804 ± 6	11.36 ± 0.01	7.83 ± 0.02	99.12 ± 0.05
VGH10	798 ± 9	11.34 ± 0.01	7.85 ± 0.03	101.5 ± 0.05
VGH11	795 ± 5	11.35 ± 0.03	7.78 ± 0.02	102.86 ± 1
VGH12	802 ± 7	11.35 ± 0.02	7.75 ± 0.02	99.57 ± 0.05
VGH13	795 ± 4	11.37 ± 0.02	7.86 ± 0.03	98.32 ± 2
VGH14	809 ± 4	11.35 ± 0.03	7.88 ± 0.01	100.98 ± 1
VGH15	807 ± 3	11.37 ± 0.02	7.83 ± 0.01	101.14 ± 0.05
VGH16	804 ± 9	11.32 ± 0.02	7.85 ± 0.02	98.24 ± 1
VGH17	803 ± 7	11.35 ± 0.02	7.81 ± 0.01	99.10 ± 0.01
VGH18	798 ± 9	11.38 ± 0.02	7.83 ± 0.02	100.32 ± 0.05
VGH19	802 ± 5	11.35 ± 0.03	7.86 ± 0.01	99.67 ± 1
VGH20	804 ± 8	11.34 ± 0.02	7.83 ± 0.03	99.16 ± 2
Values are expressed as mean ± S.E.M; n = 3				

Optimization of formulation

A full factorial design was used in response surface modeling and optimization wherein the data was interpreted using Design Expert Software Version 11.0.5.0, Stat-Ease, Inc. USA. The study facilitated in identifying the critical variables influencing dissolution. Factor C (PEG 6000), followed by Factor B (Cellulose acetate % ratio) and FactorA (PVP k-90) were found to be the major factors in influencing the dissolution profile. The regression equation obtained for percent drug release at 2h, 5h, 11h, and 20h for coded factors are given as follows

Percent drug release at 2h (acid stage) = + 11.81 – 1.06*A-2.44*B + 6.06*C-1.06*AC-2.44*BC……..Eq. 1

Percent drug release at 5h (Buffer stage) = + 64.31-0.8125*A-2.44*B + 9.69*C-1.31*AB-1.44*AC……Eq. 2

Percent drug release at 11h (Buffer stage) = + 82.38 – 1.25*A-1.87*B + 7.50*C-0.250*D + 0.00*AB + 0.625*AC-0.125*AD 0.250* BC + 0.375* CD + 0.875* ABC + 0.7500 * ACD……..Eq. 3

Percent drug release at 20h (Buffer stage) = + 94.87 − 0.750*B + 2.75*C + 0.375*D-1.63*BC-0.750*BD……Eq. 4

In the above equation, positive sign indicates a directly proportional result whereas a negative sign indicates an inversely proportional result. Graphical analysis was carried out using Contour and Response surface plots (Fig. 2) (Mohamed et al., 2020; Tuntikulwattana et al., 2010).

It was found to influence PEG6000, CA 398 − 10 on response dissolution at 2 h and 5h whereas PEG6000 was found to demonstrate a higher impact on the dissolution profile followed by CA 398 − 10 at 2h and 5h. Povidone K-90 was found to have the least effect on the response

whereas orifice diameter didn't demonstrate any effect on dissolution at 2h and 5 hr. PEG6000 was found to be directly proportional to the drug release at 2hr and 5h. Factors B and C was found to have significant interaction at 2h and 5h respectively. PEG6000 was found to have a significant effect affecting dissolution at 11 hr and 20h, whereas Povidone K-90 and orifice diameter demonstrated less impact on drug release at showed relatively less influence on the response at 11h and 20h. PEG 6000 was found to be directly proportional for drug release at 11h and 20h whereas CA 398 – 10 was found to be inversely proportional for dissolution at 11h and 20h (Narayanan et al., 2017).

P-values for the response were found to be less than 0.0500 indicate model terms are significant whereas values greater than 0.1000 indicate the model terms are not significant the results recorded showed VGH 12 was the optimized formulation (Jagtap et al., 2018).

Analysis of Variance (ANOVA)

Analysis of variance for VGH ER tablets DOE batches is given in Table 8. The Model F-value of 81.04,37.26,33.50 and 43.37 implies the model is significant for the percent drug release at 2h (acid stage), percent drug release at 5h (Buffer stage), percent drug release at 11h (Buffer stage), and percent drug release at 20h (Buffer stage) respectively (Edavalath et al., 2011).

Table 8
Analysis of Variance (ANOVA) for Valganciclovir HCl Extended Release (ER) tablets Design Of Experiment (DOE) batches

Response	Source	Sum of Squares	df	Mean Square	F value	p-value	Remarks
Percent drug release at 2h(acid stage)	Model	814.31	5	162.86	81.04	< 0.0001	significant
	Residual	26.12	13	2.01			
	Cor Total	850.95	19				
Percent drug release at 5h (Buffer stage)	Model	1667.81	5	333.56	37.26	< 0.0001	significant
	Residual	116.37	13	8.95			
	Cor Total	6920.20	19				
Percent drug release at 11h (Buffer stage)	Model	1013.25	11	92.11	33.50	< 0.0001	significant
	Residual	19.25	7	2.75			
	Cor Total	3654.55	19				
Percent drug release at 20h (Buffer stage)	Model	183.50	5	36.70	43.37	< 0.0001	significant
	Residual	11.00	13	0.8462			
	Cor Total	200.55	19				

In vitro **dissolution and release kinetics**

All 20 factorial batches were subjected to dissolution studies. The *in vitro* drug release of the batches isgraphically presented in Fig. 3. Zero-order, First order, Korsmeyer-Peppas, Higuchi, and Hixon–Crowell kinetic models were applied to drug release data. Develop an elementary osmotic pump tablet formulation (OROS® Technology based), designed to deliver the VGH active substance in a controlled manner over the period of 24 hours. The system deploys an osmotic gradient across a semi-permeable membrane for the delivery of the active substance in a controlled manner with zero order release kinetics. The core tablet is surrounded by semi-permeable membrane coat (extended release coat), which acts as a rate controlling membrane. The resulting membrane is substantially permeable to both water and dissolved solutes, and the drug release from these systems was found to be caused primarily by osmosis with simple diffusion playing a minor role. It was found that release kinetics of the drug followed zero-order kinetics for batches VGH-1, VGH-12, VGH13, and VGH-14 with R^2 between 0.9961 to 0.9997. None of the batches followed the first-order kinetics and Higuchi model whereas, batches VGH-4, VGH-5, VGH-10, VGH-14, VGH-15, VGH-16, VGH-17, VGH-18 followed Korsmeyer Peppas model and batches VGH-2, VGH-3, VGH-6. VGH-7. VGH-8. VGH-9, VGH-11, VGH-19 followed Hixon–Crowel model (Tables 9 and 10) (Yadav et al., 2013; Bhanushali et al., 2009).

Table 9
Release kinetics of batches Valganciclovir HCl (VGH) 1 to 10

Trials	Unit	VGH-1	VGH-2	VGH-3	VGH-4	VGH-5	VGH-6	VGH-7	VGH-8	VGH-9	VGH-10
Zero Order	K0	4.8790	5.8090	5.7230	4.2566	4.6754	5.7707	5.5634	5.5070	5.9250	4.5176
	R2	0.9997	0.9126	0.9284	0.9896	0.9886	0.8839	0.9260	0.9046	0.8763	0.9852
First order	K	0.0828	0.1301	0.1237	0.0648	0.0734	0.1313	0.1159	0.1161	0.1400	0.0702
	R2	0.9330	0.9743	0.9690	0.9152	0.8911	0.9790	0.9657	0.9730	0.9773	0.8911
Korsmeyer Peppas	n	0.9860	0.6508	0.6841	1.1658	1.1969	0.6302	0.7142	0.6793	0.6153	1.2283
	KKP	5.0704	15.0740	13.5680	2.6938	2.7150	15.8440	12.1580	13.2370	16.9350	2.4043
	R2	0.9997	0.9876	0.9861	0.9971	0.9987	0.9727	0.9717	0.9660	0.9750	0.9984
Higuchi	KH	18.2360	22.3060	21.9080	15.7172	17.2410	22.2130	21.2360	21.0980	22.8400	16.6230
	R2	0.8804	0.9665	0.9567	0.8229	0.8168	0.9562	0.9336	0.9375	0.9616	0.8068
Hixon–Crowell	KHc	0.0235	0.0348	0.0333	0.0189	0.0214	0.0353	0.0316	0.0317	0.0375	0.0204
	R2	0.9633	0.9933	0.9901	0.9439	0.9264	0.9945	0.9874	0.9893	0.9953	0.9250

Table 10
Release kinetics of batches Valganciclovir HCl (VGH) 11 to 20

Trials	Unit	VGH-11	VGH-12	VGH-13	VGH-14	VGH-15	VGH-16	VGH-17	VGH-18	VGH-19	VGH-20
Zero Order	K0	6.0970	4.9506	4.9911	4.0828	4.2583	4.0952	4.5361	4.4550	6.1119	4.8086
	R2	0.8313	0.9961	0.9976	0.9790	0.9835	0.9852	0.9774	0.9784	0.8013	0.9992
First order	K	0.1550	0.0859	0.0602	0.0600	0.0642	0.0608	0.0699	0.0681	0.1598	0.0806
	R2	0.9785	0.9416	0.9011	0.9011	0.9009	0.9097	0.8741	0.8792	0.9793	0.9316
Korsmeyer Peppas	n	0.5669	0.9389	0.9837	1.2560	1.2328	1.2200	1.2980	1.2928	0.5409	0.9938
	KKP	19.8690	5.8543	5.2192	2.0080	2.2388	2.2290	1.9894	1.9825	21.3710	4.8913
	R2	0.9686	0.9975	0.9977	0.9956	0.9975	0.9976	0.9980	0.9986	0.9631	0.9992
Higuchi	KH	23.6280	18.5570	18.6578	14.9710	15.6470	15.0680	16.6250	16.3288	23.7558	17.9700
	R2	0.9636	0.8917	0.8791	0.7919	0.8017	0.8072	0.7875	0.7885	0.9612	0.8786
Hixon–Crowell	KHc	0.0412	0.0243	0.0243	0.0177	0.0188	0.0179	0.0203	0.0199	0.0425	0.0229
	R2	0.9960	0.9707	0.9590	0.9302	0.9318	0.9380	0.9098	0.9141	0.9942	0.9616

Comparative In vitro **dissolution of optimized formulation and marketed preparation**

Dissolutions were carried out to check the release profile of the marketed innovator sample which is available as immediate-release dosage against optimized osmotic formulation tablets (VGH 12) were subjected to *in-vitro* dissolution studies. In the case, marketed innovator sample (Valcyte® IR tablets) complete release was observed within one hour because of the immediate release dosage form. Whereas osmotic developed VGH formulation shows zero-order drug release until 24 hours (Fig. 4) (Wang et al. 2018). Comparative *in vitro* dissolution study shows that the drug release from marketed formulation show peak plasma concentration within an hour but at the same time due to the short half-life of the drug (4 hrs.) we can expect its immediate excretion so to maintain effective plasma concentration up to 24 hours repeated administration of tablet is required. The formulated osmotic release drug delivery system shows drug release up to 24 hours with a single dose of 450mg (Ning et al., 2011).

Dissolution analysis by Scanning Electron Microscopy (SEM) and Hydration study

To investigate the effect of ER coating of coated tablets the SEM images were captured before and after dissolution (Fig. 5). Hydration study at different time intervals during the dissolution of the osmotic tablet is shown in Fig. 6 (Shahi et al., 2012). Dissolution analysis from SEM

and hydration study shows that significant porosity has resulted due to the leaching of water-soluble additive i.e. PEG 6000 during dissolution (Suryadevara et al., 2014).

An in-vivo **pharmacokinetic study in dog plasma**

A simple and rapid liquid chromatography/tandem mass spectrometry (LC-MS) method was developed and applied for estimationconcentration of VGH levels in dog plasma after administration of VGH extended-release tablets (450 mg) and Valcyte® Immediate-Release Tablets (450mg). Valganciclovir is get converted in vivo to Ganciclovir so, the concentration of Ganciclovir was monitored instead of VGH in dog plasma.The liquid chromatography-tandem mass spectrometric (LC-MS) developed method was found suitable for the estimation of Ganciclovir (the active metabolite of Valganciclovir) in dog plasma. The developed method was successfully employed to support the pharmacokinetic study of VGH formulations in dogs. Study of *in vivo* plasma concentration in two groups of beagle dogs reveals that the group administered with marketed formulation with immediate release required repeated dosing to maintain therapeutic concentration up to 24 hours while the group administered with formulated osmotic formulation showed continuous zero-order drug release for 24 hours with only 450mg of dose and this study is presented in Table 11 and Fig. 7. A pharmacokinetic study in beagle dogs provides the significant outcomes of controlled release of VGH from prepared osmotic tablets up to 24 hours with single-dose while marketed tablets require repeated administration in 24 hours. The prepared formulation provides sufficient drug release for 24 hours with 450 mg of dose. These significant results with prepared formulation reduce the dosing frequency of VGH in the treatment CMV retinitis and also reduce associated side effects (N. Li et al., 2019; Y. Li et al., 2019; Banerjee et al., 2016).

Table 11
Pharmacokinetic parameters summary of VGH osmotic tablets vs Valcyte® IR tablets

Product	**Valganciclovir HCl ER tablets 450mg (Osmotic)**	**Valcyte® tablets 450mg (Immediate Release)**		
Analyte	Ganciclovir Conc (µg/mL) measured in dogs	GanciclovirConc (µg/mL) measured in dogs		
Parameter	Single dose (0–24 hrs)	First dose (0–12 hrs)	Second dose (13–24 hrs)	Cumulative average results (0-24hrs)
C_{max}(µg/mL)	7.120 (0.707)	12.342 (2.352)	11.510 (0.631)	12.559 (2.090)
T_{max}(h)	8.000 (0.000)	1.000 (0.000)	1.000 (0.000)	1.000 (0.000)
AUC(µg.h/mL)	58.415 (9.242)	37.903 (6.644)	31.983 (1.951)	68.167 (6.925)
$T_{1/2}$ (h)	2.838 (1.214)	1.444 (0.042)	1.106 (0.014)	1.106 (0.014)
C_{max}: Maximum plasma concentration, T_{max}: Time required to achieve maximum plasma concentration, AUC:Area Under Curve, $T_{1/2}$:: Plasma half life				

Stability study of optimized batch

The optimized tablet batch of VGH was subjected to stability study and then it was found therewere no significant changes in tablet evaluation parameters (Table 12). Stability study showed that there were no significant changes in physical description, assay and drug release during both accelerated as well as long term stability study at different temperature and humidity conditions (Hashem et al., 2020).

Table 12 Stability data VGH osmotic pump tablets 450 mg (VGH 12)

Sr.no.	Tests	Specification	Initial	40˚C ± 2˚C & 75 % ± 5% RH				25˚C ± 2˚C & 60 % ± 5% RH		
				1M	2M	3M	6M	3M	6M	12M
1	Description	Transparent/Translucent White round biconvex tablet with preformed passageway at the center of the tablet	NC	NC	NC	NC	NC	NC	NC	NC
2	Assay (%)	NLT 90% & NMT 110%	101.1	99.8	100	100.0	98.2	101	99.8	99.2
3	Dissolution (% drug release)									
	Acid stage									
	2 hr	NMT 15%	10	9	10	10	11	9	9	10
	Buffer stage									
	5 hr	Between 20% -35%	25	25	24	25	23	25	28	27
	11 hr	Between 45%- 60%	53	54	56	53	52	51	55	51
	20 hr	NLT 85%	97	97	95	97	96	99	100	98
	M:Month, NC: No Change, RH: Relative Humidity, NMT: Not More Than, NLT: Not Less Than									

Conclusion

The *In vitro* release data of prepared osmotic formulation of VGH fitted to various kinetic models like Zero order, First order, Korsmeyer–Peppas, Higuchi, and Hixon–Crowell and it showed that optimized osmotic pump tablets follow zero-order release kinetics. The *In vivo* study comparing pharmacokinetic parameters of VGH ER tablets 450mg (Osmotic) and Valcyte® tablets 450mg (Immediate Release) carried out in beagle dog reveals that the formulated osmotic drug delivery system significantly maintains the plasma concentration of drug within the therapeutic window over 24 hours with once a day dosing. In conclusion, the formulated osmotic extended-release tablet can be the better option with a minimum dose for the treatment of CMV retinitis with less associated side effects due to reduced dose and dosing frequency.

Declarations

Ethical statement

Ethics approval and consent to participate

All animal experiments were approved by Animal Ethical Committee of Wockhardt research center, Aurangabad. All institutional and national guidelines for the care and use of laboratory animals were followed.

Consent for publication

Not applicable

Availability of data and materials

The data or analysis during the current study will be made available on request by corresponding author.

Competing interest

The authors don't have any competing interest

Funding

Authors did not received any funding.

Author's contributions

Author RG performed the complete research work. Author SP guided for the proposed research work. The result analysis and interpretation is done by author SS. Author DK and DG contributed for writing and editing of manuscript. All the authors approved the manuscript for submission.

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Figures

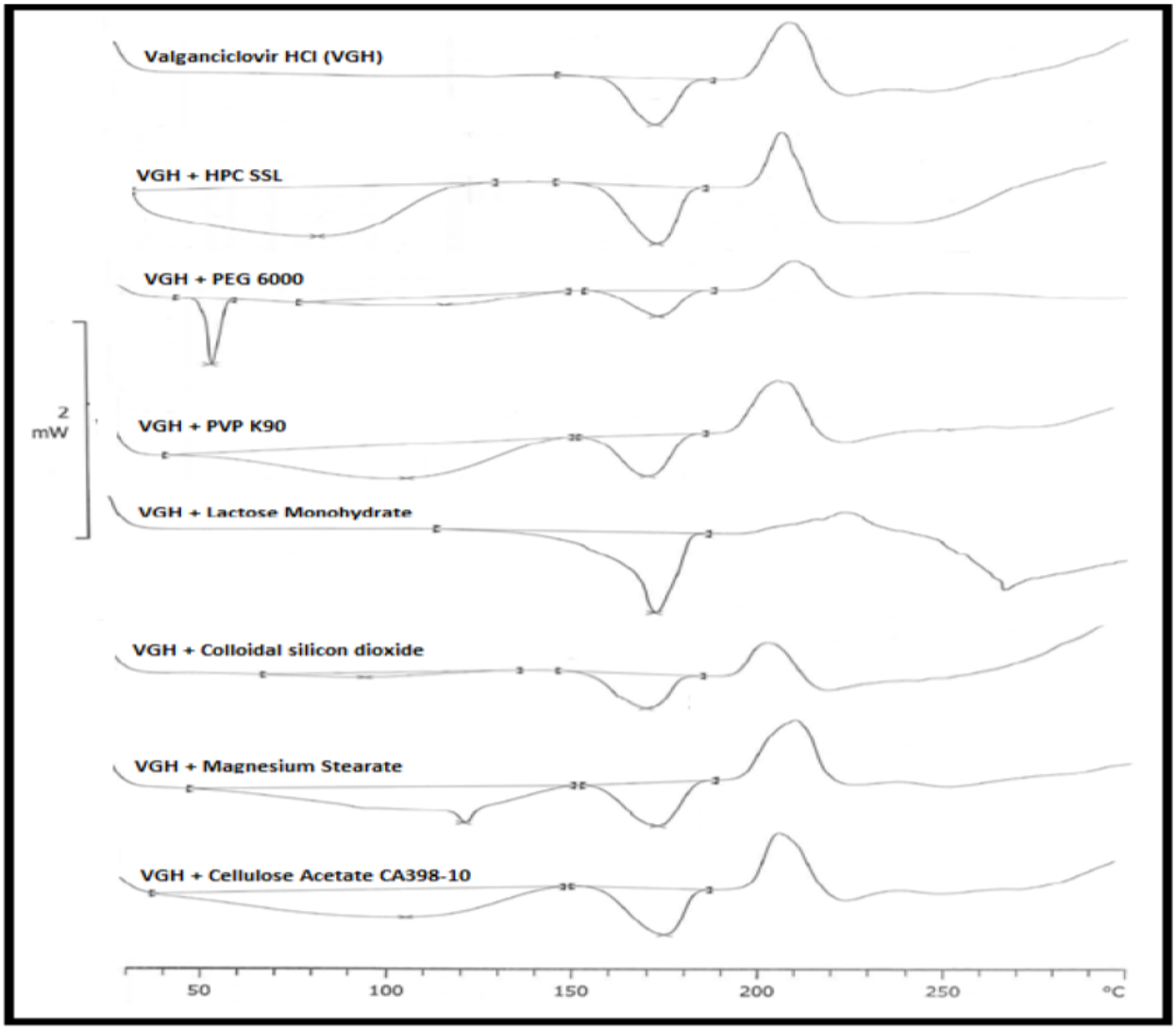


Figure 1

Differential Scanning Calorimetry (DSC) peaks of the pure drug and the mixture of drug and excipients

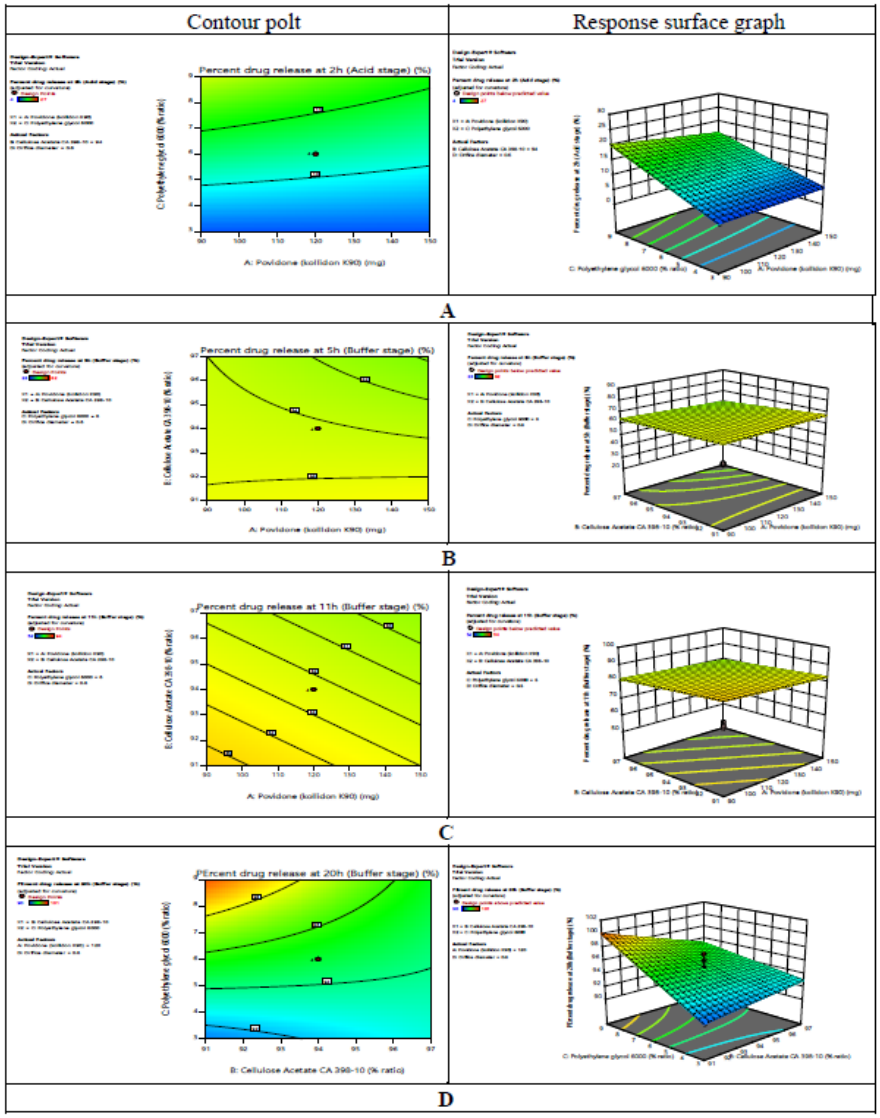


Figure 2

Percent drug release at 2h (Acid stage), 5h, 11h, 20h (Buffer stage) showing Contour plot and Response surface graph

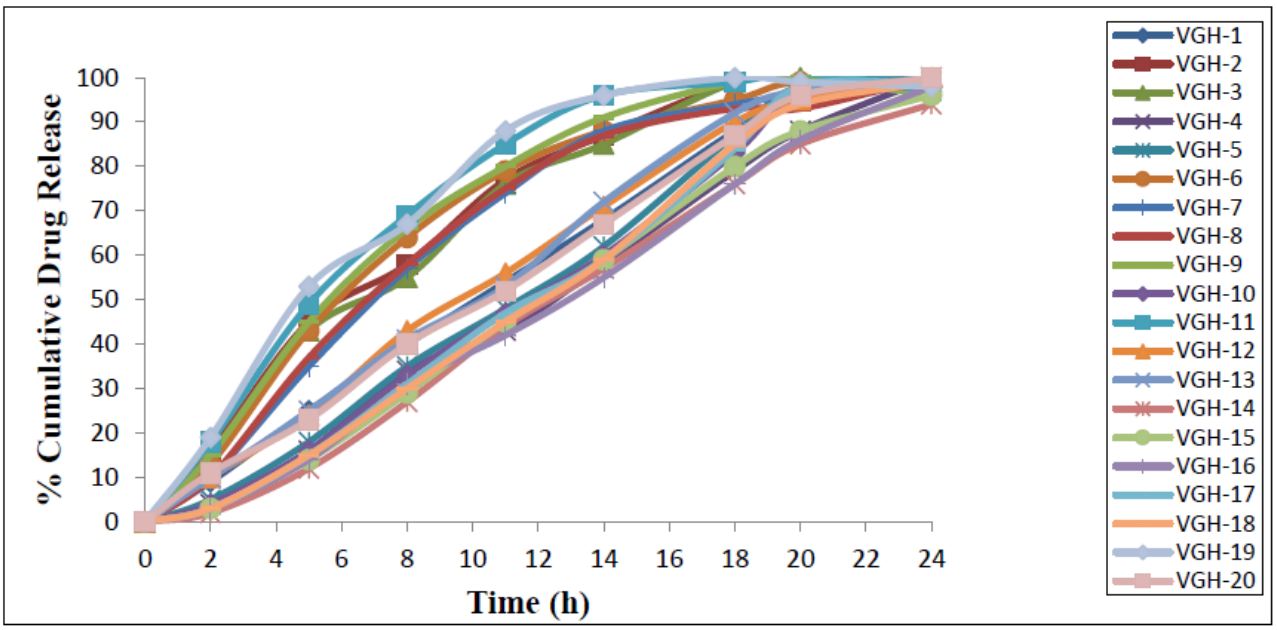


Figure 3

Drug release kinetics of DOE batches VGH-1 to VGH20

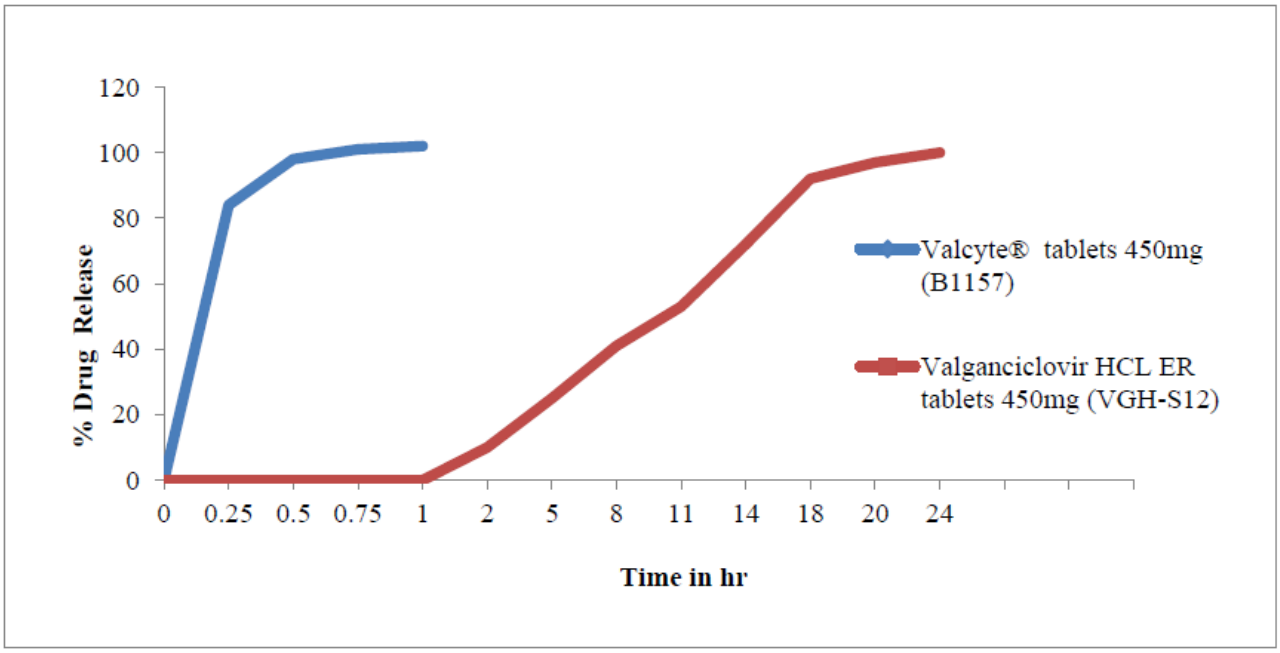
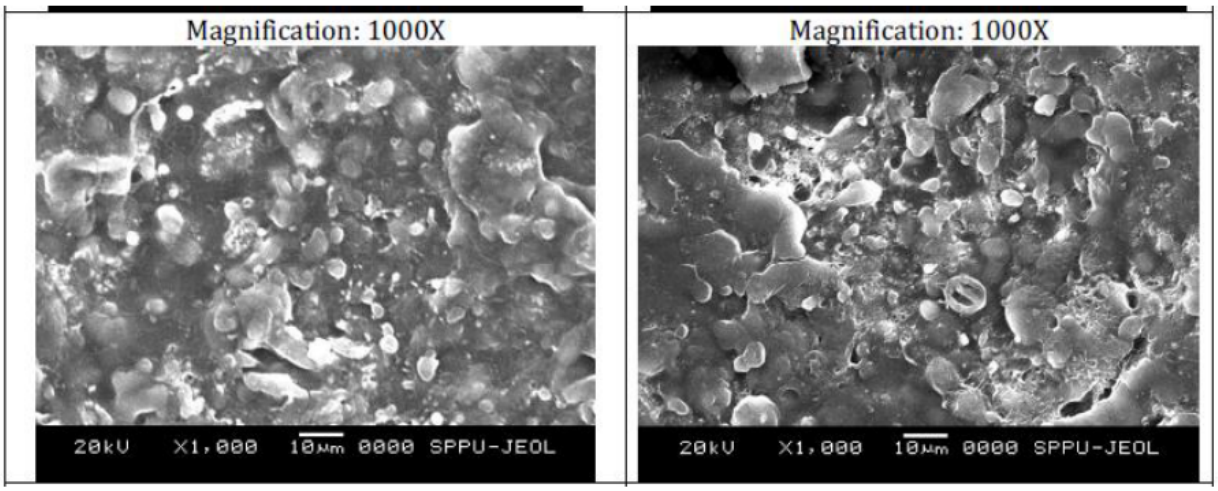
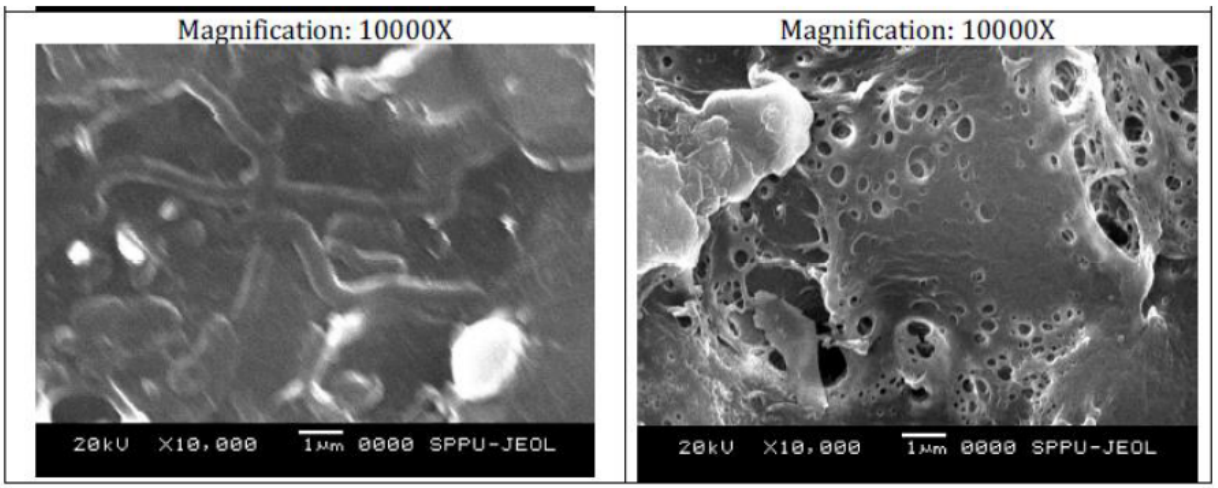


Figure 4

Comparative % drug release of optimized Valaganciclovir HCl osmotic tablet (VGH 12) and Valcyte® IR tablets



(A) Initial Dissolution



(B) After dissolution

Figure 5

Dissolution analysis of Valganciclovir HCl optimized osmotic pump tablet (VGH 12) by Scanning Electron Microscopy (SEM)

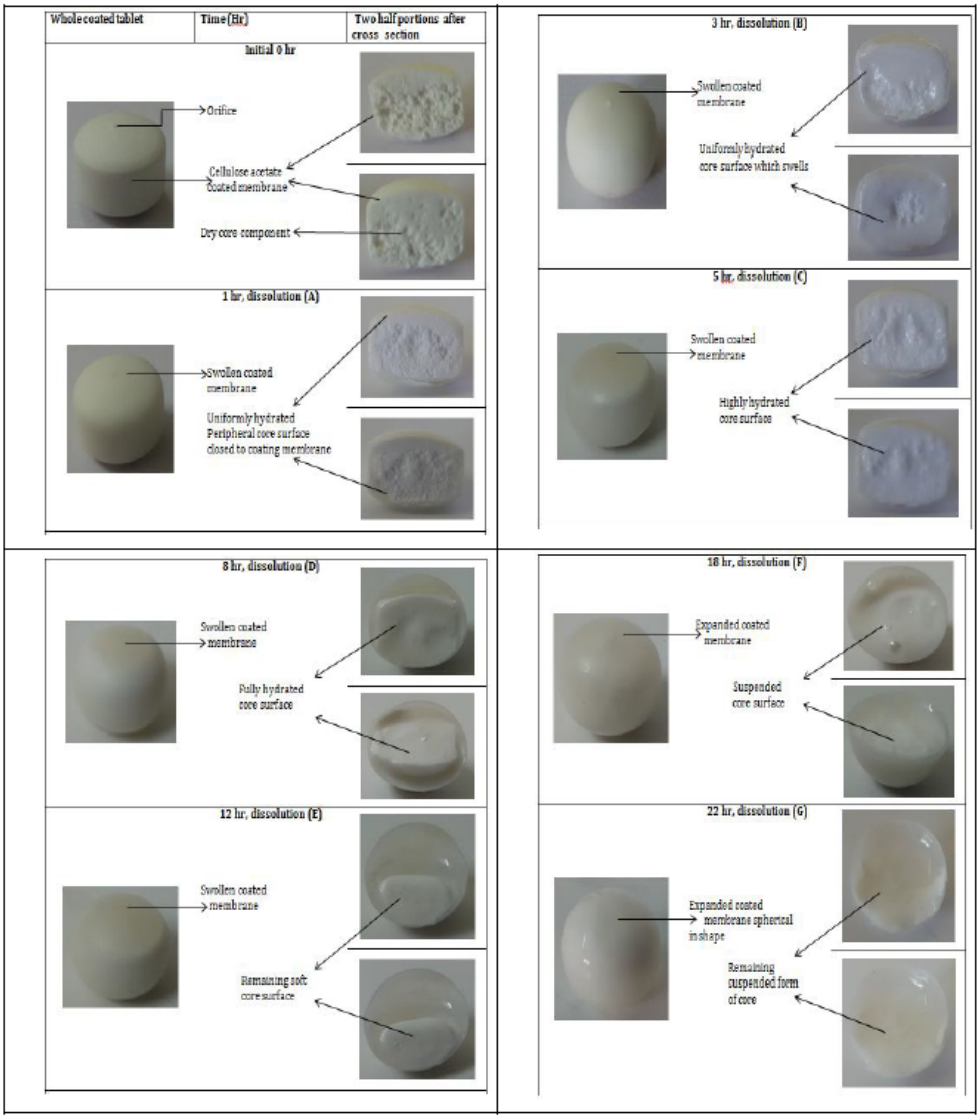


Figure 6

Valganciclovir HCl (VGH -12) coated tablets after exposure to the dissolution buffer: Tablets were measured after 1 hr (A), 3 hr (B), 5 hr (C), 8hr (D) 12hr (E), 18hr (F) and 22hr (G)

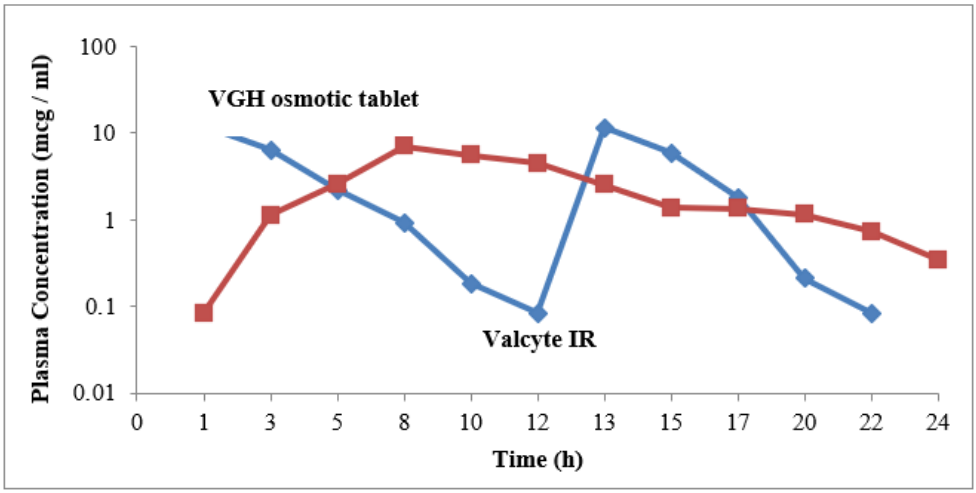


Figure 7

Comparative mean plasma concentration of optimized Valganciclovir HCl osmotic tablet (VGH 12) and Valcyte® IR tablets

Supplementary Files

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- GraphicalAbstract.png