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Research Article

A SYSTEMIC APPROACH FOR THE FORMULATION OF FLOATING MICROSPHERES OF VALACYCLOVIR

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ABSTRACT

In present study valacyclovir, microsphere was prepared by ionic gelation technique. Valacyclovir HCl, having a short biological half-life of < 30 minutes (Acyclovir 1.5-2 h) and its rapid elimination from the body, is ideally suited to be delivered through floating multiunit dosage form. Six formulations with natural polymers were formulated and characterized for their micromeritic and other properties. The process induced the formation of microspheres with the incorporation efficiency of 98% to 99%. The effect of sodium alginate and xanthan gum concentration and conditions were evaluated with respect to entrapment efficiency, particle size, buoyancy studies, surface characteristics and in vitro release behaviours. The infrared spectroscopic study confirmed the absence of any drug-polymer interaction. Microsphere matrices showing spherical surface, which was confirmed by scanning electron microscopy study. The mean particle size and entrapment efficiency were found to be varied by changing various formulation parameters. The in vitro release profile could be altered significantly by changing various formulation parameters to give a prolonged release of drug from the microspheres.

INTRODUCTION

An effort is being finished to develop and characterize floating microspheres, which subsequent to oral administration might extend gastric residence time and increase drug bioavailability[1]. Oral delivery of the drug is the greater part preferable route of drug-delivery due to the easiness of administration, patient fulfilment and suppleness of formulation, etc. Beginning immediate release ofsite-specific delivery, oral dosage-forms have really progressed. Numerous difficulties have been faced in designing controlled release systems for better absorption and enhanced bioavailability. The principle of buoyant preparation offers an easy and sensible approach to achieve increased gastric dwelling time for the dosage form and controlled drug release[2]. Preparation remains buoyant in stomach content due to its lower density than that of gastric fluid. It is the sound accepted fact that it is difficult to predict the real In vivo time of release by way of solid, oral controlled release dosage forms. Thus drug absorption in the gastrointestinal gut may be extremely short and high variable in certain circumstances. Gastric emptying of the multiparticulate floating system would occur in a consistent manner by way of reduced intersubject variability in absorption[3]. On every subsequent gastric emptying, deep-set particles will spread out over a big area of absorption site, increasing the opportunity for drug-release and absorption. Valacyclovir, an antiviral used in the treatment of Herpes simplex virus and Varicella zoster virus, has a short biological half-life of fewer than 30 minutes. It is a prodrug of acyclovir intended for oral administration. Because of its short elimination half-life, it requires multiple dosing to achieve and maintain therapeutic levels.

MATERIALS AND METHODS

Valacyclovir obtained as a gift sample from Milan Distribution Private Limited, Mumbai, sodiumalginate and calcium chloride is obtained from Yarrow chemicals Mumbai, Hydroxypropylmethylcellulose (HPMC) obtained from Finar Scientific, Chitosan obtained from Acros scientific.

Analytical Method for Estimation of Valacyclovir

Determination of maximum wavelength (λmax) of Valacyclovir was done by preparing three different dilutions of stock solutions (1mg/ml) and scanned those dilutions under UV-Vis Spectrophotometer.

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Preparation of Calibration Curve of Valacyclovir in 0.1N HCl

Dissolved 50 mg of Valacyclovir in 50 mL of 0.1N HCl pH-1.2 (stock solution 1mg/ml e.g. e.g. 25 mg accurately weighed dissolved in 100 ml distilled water, then further diluted with solvent). The stock solution of Valacyclovir is diluted with solvent to make solution of 5, 10, 15, 20, 25 and 30 µg/ ml. The prepared solutions were then examined under UV-Vis Spectrophotometer at λmax of 256 nm for absorbance and then calibration curve is plotted between absorbance and concentration.

Loss on Drying

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified conditions. The test is carried out on a well-mixed sample of the substance**.**

Procedure

A glass-stoppered shallow weighing bottle was weighed that has been dried in an oven at 105°C for 3 hrs. After drying was completed, allowed it to cool to room temperature in a desiccator.1.0 g of the sample was transferred to the bottle, covered it and accurately weighed the bottle and the contents. The substance was dried by placing the loaded bottle in an oven at 105°C for 3 hrs. After drying was completed, allowed it to cool to room temperature in a desiccator before weighing. The bottle and the contents were weighed again (Table- 8.1.5).

$$\text{Loss on drying} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Drug Excipients Compatibility Studies [Infrared spectroscopy (IR)]

IR spectrum of any compound gives information about the group present in particular compound. IR transmission spectra were obtained using infrared spectrophotometer (Bruker). An infrared spectrum of the drug was taken using KBr pellets. A small quantity of drug was used for IR analysis. The pellets were placed in a holder and an infrared spectrum was taken. The scanning range was 400–4000 cm^{-1}; various peaks in the infrared spectrum were interpreted for the presence of the different group in the structure of the drug.

Preparation of Valacyclovir loaded Microspheres

The floating microspheres containing Valacyclovir were prepared by orifice ionic gelation technique. Sodium alginate alone or in combination with xanthan gum and the gas forming agent sodium carbonate was dispersed in the purified water to form a homogeneous polymer mixture. The drug, Valacyclovir was added to the polymer dispersion and mixed thoroughly on a magnetic stirrer to form a homogeneous dispersion. The gelation medium was prepared by dissolving calcium chloride in 2% glacial acetic acid. The homogenous alginate solution was extruded using 21G syringe needle into the gelation medium. The distance between the edge of the needle and surface of gelation medium was about 10cms. The gel microspheres formed were left in the solution with gentle stirring for 30 min at room temperature to improve mechanic strength. After that, microsphere was collected and washed with distilled water twice, dried at room temperature for 24 hr and stored in desiccators.[5,6]The composition and the conditions observed during the preparation of microspheres are showed in table no 1

Table1 Composition of Floating Microspheres of Valacyclovir

S. No.	Excipients	F1	F2	F3	F4	F5	F6
1.	Valacyclovir (mg)	500	500	500	500	500	500
2.	Sodium Alginate (mg)	500	1000	1500	250	500	750
3.	Xanthan Gum (mg)	-	-	-	250	500	750
4.	Sodium bicarbonate (%w/w)	50	50	50	50	50	50
5.	Calcium Chloride (%w/w)	10	10	10	10	10	10
6.	Acetic acid (%w/w)	1.5	1.5	1.5	1.5	1.5	1.5
7.	Drug: Polymer ratio	1:1	1:2	1:3	1:1	1:2	1:3

In-vitro drug release profile of formulated microspheres

The dissolution studies executed utilizing (type II) XXIV USP dissolution rate test apparatus in 0.1 N HCl for 2 hrs followed by pH 7.4 900ml dissolution media, at 50 rpm and 37 ± 1^0C temperature upto 12 hrs. Using Systronics UV-2203 U.V. Spectrophotometer double beam, 5ml of samples taken at different time gaps and 5ml of same dissolution medium added to uphold sink condition. Withdrawn aliquots diluted and analyzed spectrophotometrically at 256 nm. The percent release of Valacyclovir was calculated and agraph plotted against time.

Drug Release Kinetic Studies

To study the release kinetics and mechanism of release *in-vitro* release data was applied to kinetic models such as zero order (Cumulative % drug release vs. time), first order (Log Mean % drug unreleased vs. time), Higuchi (Mean % cumulative drug release vs. square root of time) and Korsmeyer-Peppas (Log mean % cumulative drug release vs. Log time) using Microsoft Excel software and the regression values (R^2) were calculated.

Accelerated Stability Studies of the optimized batch

The period of stability testing can be as long as two years, it is time-consuming and expensive. Therefore it is essential to devise a method that will help rapid prediction of long-term stability of the drug.

The accelerated stability testing is defined as the validated method by which the product stability may be predicted by the storage of the product under the condition that accelerates the change in defined and predictable manner.

Stability study of optimized formulation was carried out to determine the effect of formulation additives on the stability of drug and also to determine the physical stability of formulation (World Health Organization, 2006).

The stability study of formulations was carried out according to the ICH guidelines for zones III and IV. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 4 weeks by storing the samples in a stability chamber. At the end of 4 weeks, tablets were tested for drug content and disintegration time and *in-vitro* dissolution studies.

An adequate sample of batch F6was wrapped in aluminium foil and were stored at atemperature (40ºC) in a polyethene bag and a 75% relative humidity was maintained by placing them in a stability chamber. Samples were withdrawn at an interval of 7 days for 12 weeks and were studied for drug content and *in-vitro* dissolution studies.

Morphological Study using SEM

Formulation mounted directly on scotch double adhesive tape analyzed under scanning electron microscope SEM model XL-30, operated at 15K SEM thickness of 100% using FEI-Philips Analytical Electron microscope (Diya labs, Mumbai).

RESULTS AND DISCUSSION

Organoleptic Properties

The physical characteristic like organoleptic properties of drug sample was performed and it was found to be bitter in taste, the colour was white crystalline powder and was odourless. And hence the drug sample was found to be as per specifications

Table 2 Organoleptic properties of drug

S. No.	Test	Observations	Standard(90)
1.	Colour	white powder	White crystalline powder
2.	Taste	Bitter	Bitter
3.	Odor	odourless	odourless

Determination of Melting Point

The melting point of Valacyclovir was determined to check the purity of them. The melting point of the drugs was determined by using Digital melting point apparatus. The results of the observed melting point of the drugs are shown in the Table3

Table 3 Melting point

S. No.	Drug	Observation	Specification
1.	Valacyclovir	196.5-200.5^{0}C	196-200^{0}C

Determination of the Solubility

The solubility of Valacyclovir was determined to find the extent to which they were soluble in different solvents such water, 0.1 N HCl, Methanol, Ethanol, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4. The solubility of the drug in different solvent assists in identifying the proper release medium for *in-vitro* release studies. The results for the determination of the solubility of both drugs are shown in Table 4

Table 4 Solubility profile of drug

S. No.	Solvents	Solubility
1.	Distilled water	Freely soluble
2.	Methanol	soluble
3.	Ethanol	Slightly soluble
4.	0.1N HCl	Soluble
5.	PB pH 6.8	Soluble
6.	PBS pH 7.4	Soluble

Determination of the Partition Coefficient

Table 5

S. No.	Drug	Observation (LogP)	Standard (LogP)
1.	Valacyclovir	-0.3±0.02	-0.3

The partition coefficient observed was resembling with the standard values mentioned in the references

Scanning of Valacyclovir

UV Spectra As Shown In Figure 1 The scanning of Valacyclovir was performed to determine the wavelength at which Valacyclovir absorb a maximum of UV radiation when the solution of Valacyclovir was exposed to UV radiation. The scanning of Valacyclovir was done by placing solutions of different dilutions (100, 10, 1 µg / mL) of stock solution (1 mg/ml e.g. 25 mg accurately weighed dissolved in 100 ml distilled water, then further diluted with asolvent, under UV Spectrophotometer. The results of scanning of Valacyclovir are shown in Table 6. The results of scanning of Valacyclovir at 100, 10, 1 µg / mL showed that the solution of the 100 µg / mL has a maximum absorbance at a wavelength of 256 nm. This wavelength is selected as λ_{max} for the determination of absorbance of different concentration of solutions

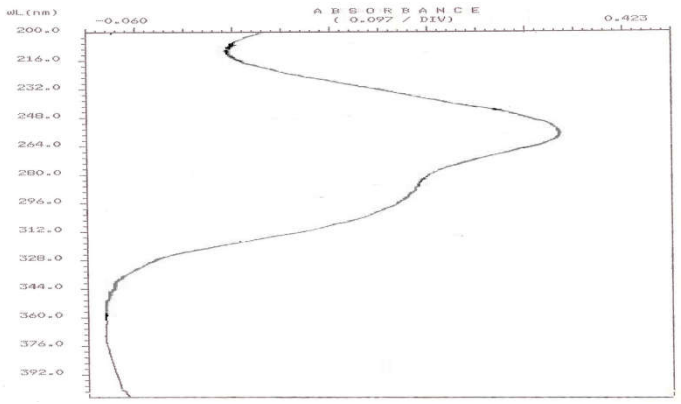


Figure 1

Table 6 Dilution data of stock solution for scanning of Valacyclovir

Sr. No.	Dilution of stock Solution of Valacyclovir (1 mg/mL)	Concentration (µg / mL)	Maximum Wavelength (λmax) (nm)	Absorbance
1	10 times (1in 10 mL)	100	256.5	1.871
2	100 times(1 in 100 mL)	10	256.0	0.323
3	1000 times(1 in 1000 mL)	1	256	0.031

Preparation of Calibration Curve of Valacyclovir by U.V Spectroscopy Method

The calibration curve of Valacyclovir in 0.1N HCl pH-1.2 was prepared to identify the linearity range of it. The calibration curve of Valacyclovir was prepared by examining the absorbance of valacyclovir solutions of 5, 10, 15, 20, 25 and 30 µg / ml in saline prepared from stock solution (1mg/ml e.g. e.g. 25 mg accurately weighed dissolved in 100 ml distilled water, then further diluted with solvent) under UV Spectrophotometer at λ_{max} of 256 nm. The results of absorbance of Valacyclovir solutions are shown in Table 7

Table 7 Data for preparation of Calibration Curve of Valacyclovir at λmax of 256 nm

Sr. No.	Concentration of Valacyclovir (µg / mL)	Absorbance ± SD (n=3)
1	5	0.157±0.007
2	10	0.315±0.006
3	15	0.471±0.004
4	20	0.630±0.009
5	25	0.783±0.006
6	30	0.951±0.008

Micromeritics Studies of microspheres

The results of the density of bulkiness and density of tapping were mentioned in the table. Bulkiness values were lies in 0.297 to 0.542 g/cm3 and density of tapping values lies in 0.508 to 0.654 g/cm3 i.e. less than 1.2, indicates good packing.

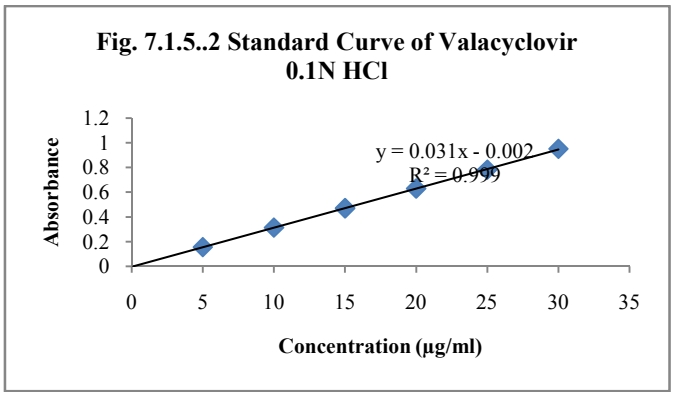


Figure 2 All values are average of three determinations (n=3).The results of calibration curve of Valacyclovir showed that curve is straight line with r^2 =0.999

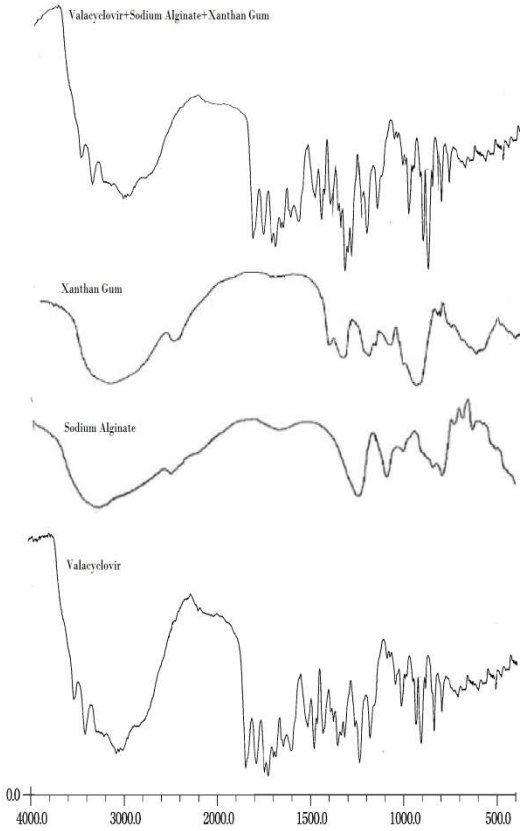


Fig 3 FTIR Spectra of Valacyclovir with Polymers

The values of Average particle size and angle of repose were lies in between 291.46 ±8.3 to 432.62 ±7.3, and 250-12° to 300-20°, respectively indicates acceptable particle size, flow property and also good packing ability

Table 8 Micromeritics Studies of Microspheres

Batch	Avgmicrosphere	Bulk Density	Tap Density	Angle of Repose	Compressibility Index	Hausner's ratio
F1	291.46±8.3	0.298	0.522	25.15°	13.81	1.15
F2	323.44±6.9	0.542	0.654	26.20°	13.90	1.15
F3	356.88±8.6	0.526	0.636	25.12°	12.65	1.13
F4	263.84±8.3	0.430	0.508	30.20°	12.03	1.12
F5	327.65±7.5	0.482	0.528	25.06°	13.71	1.14
F6	356.22±8.1	0.516	0.616	31.24°	13.80	1.15

Floating Behaviour of microspheres

Valacyclovir microsphere was dispersed in 0.1 HCl as simulated gastric fluid. Floating ability of different formulation was found to be differed according to sodium alginate and xanthan gum ratio. F1-F6 formulations showed floating ability (84.92-88.46%). F1-F3 formulations showed less floating ability (84.92-87.30%) as showed in Table-7.1.8.2 compared to F4-F6. The floating ability of microsphere is decreased by increasing the polymer ratio.

Table 9 Floating Behavior studies of Valacyclovir Microspheres

S. No.	Batch	% *In vitro* buoyancy
1.	F1	84.92±1.4
2.	F2	86.12±2.4
3.	F3	87.30±1.1
4.	F4	85.48±2.6
5.	F5	87.94±1.5
6.	F6	88.46±2.6

*All the values represent mean ± standard deviation (n=3)

Percentage recovery (i.e. Yield) of microspheres

Best % recovery was obtained for batch F6 - 96.47 %. Overall percent recovery of microspheres obtained was greater than 86%.

Table 10 Total Percent Yield of Valacyclovir Microspheres

S. No.	Batch	% Yield
1.	F1	86.46±1.2
2.	F2	88.37±1.8
3.	F3	90.41±2.7
4.	F4	82.62±2.3
5.	F5	88.54±1.7
6.	F6	96.47±1.3

*All the values represent mean ± standard deviation (n=3)

Drug Content and Drug Entrapment efficiency

Formulation F6 gave well 80.50±1.7 % drug content largest among the other formulations. The formulations have shown the percent drug content in between 48.14±0.9 to 80.50±1.7. All the batches have shown the percent drug efficiency in between 98.29±1.8 to 99.94±1.6. The F6 batch has shown 99.89±0.5 percent entrapment efficiency higher drug loading than other batches. It can be happened due to viscosity caused by the used material.

Table 11 Percentage Drug Content and Percent drug entrapment of microspheres

S. No.	Batch	% Drug Content	Entrapment Efficiency
1.	F1	48.14±0.9	98.29±1.8
2.	F2	68.40±3.6	99.32±1.2
3.	F3	79.25±1.9	99.38±0.7
4.	F4	49.62±2.6	98.77±1.5
5.	F5	71.72±1.4	98.94±1.6
6.	F6	80.50±1.7	99.89±0.5

*All the values represent mean ± standard deviation (n=3)

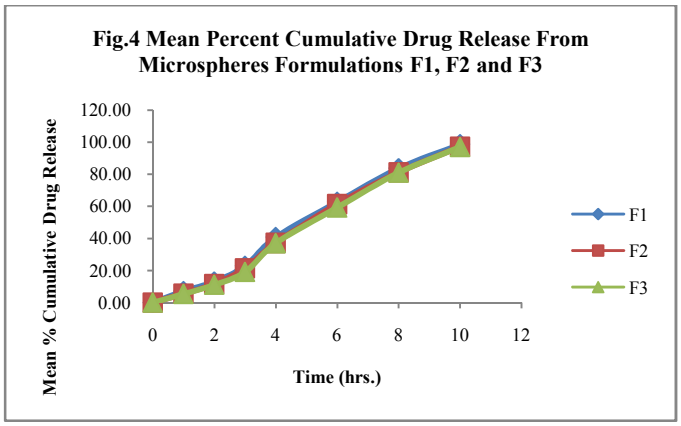
Drug entrapment efficacy slightly increases with increase in sodium alginate content and xanthan gum ratio in Microspheres. This is due to the permeation characteristics of polymers that could facilitate the diffusion of part of entrapped drug to surrounding medium during the preparation of Valacyclovir microspheres.

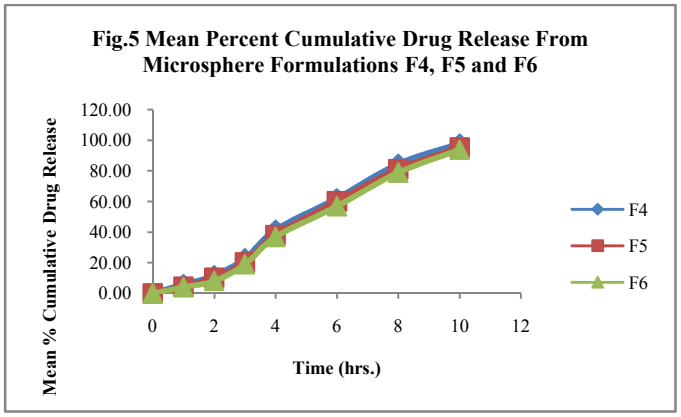
In-vitro Release Profile Study of Formulated microspheres

The results demonstrated that formulations (F1, F2, F3) showed Valacyclovir discharge speed in series of 96-98% when compared (F4, F5 and F6) demonstrated a Valacyclovir discharge speed from 93 -97% up to the duration of 10 hours. This denotes that if the quantity of rate retarding polymer raised, leads to retard discharge of drug. The synergistic effect was observed when the sodium alginate was combined with xanthan gum. Hence batch F6 indicates the better results than other prepared batches. Formulation F6 shown 93.77% cumulative drug release pattern.

Table 12 *In vitro* Cumulative Percent Drug Release Profile

S.No	Time	Percent Drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	7.137	5.587	5.397	5.867	4.417	4.057
3	2	12.982	11.582	11.089	11.712	10.262	8.102
4	3	22.874	21.314	19.127	22.804	20.154	18.994
5	4	40.760	37.206	37.019	41.490	38.040	36.880
6	6	62.765	61.327	59.260	61.995	60.045	56.885
7	8	83.726	81.127	80.962	84.456	81.006	78.846
8	10	98.659	97.107	96.953	97.689	95.239	93.779





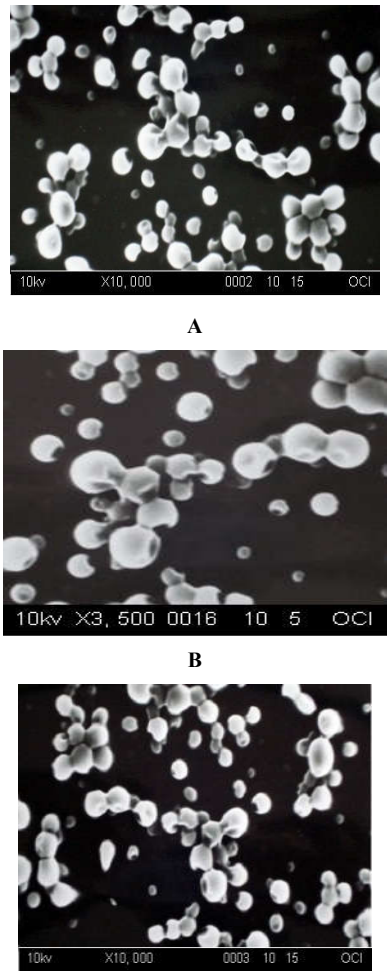


Figure 6 Morphological Study using SEM (Formulation F6)'

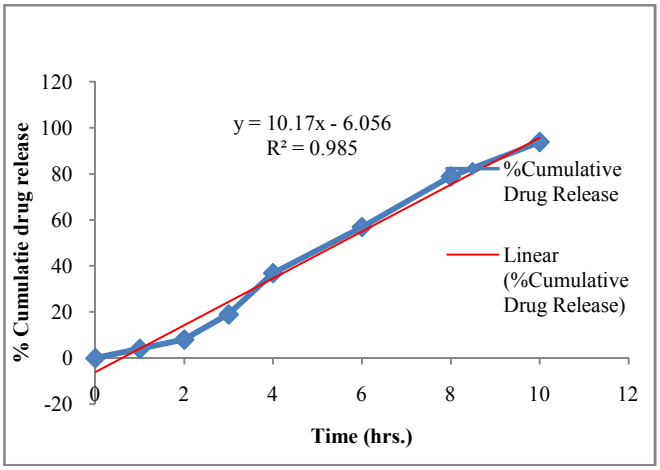
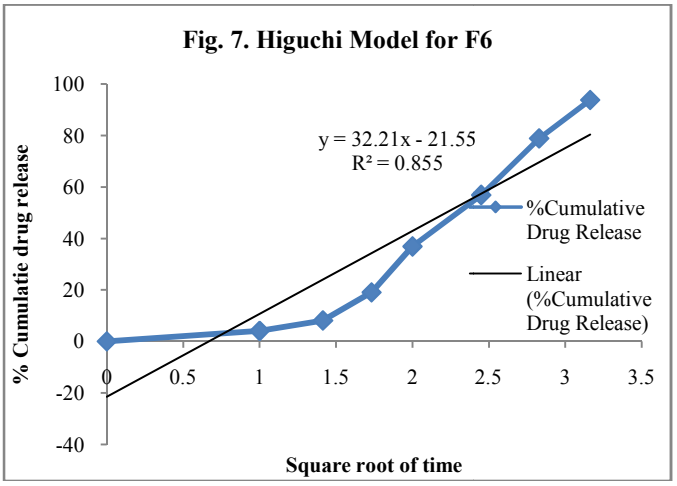
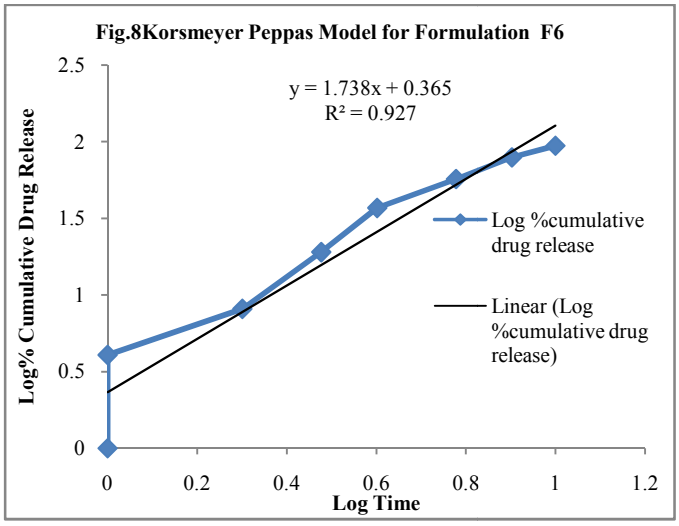


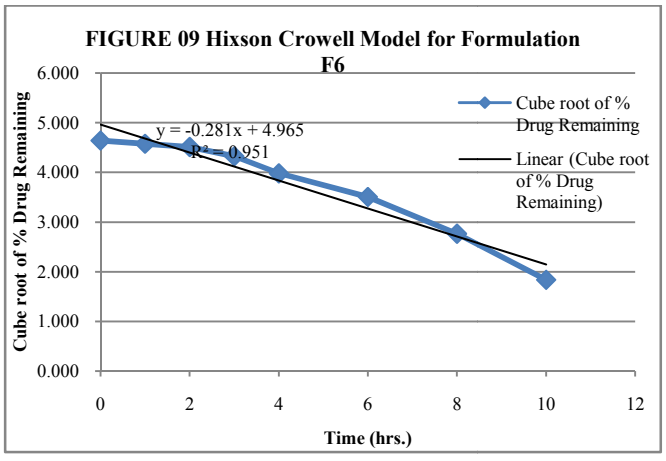
Table 13 Release Kinetic of F6

S. No	Time (hrs)	%Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	0	0	0	0	0	100	2	4.642
2	1	4.057	1	0	0.608	95.943	1.982	4.578
3	2	8.102	1.414	0.301	0.909	91.898	1.963	4.513
4	3	18.994	1.732	0.477	1.279	81.006	1.909	4.327
5	4	36.88	2.000	0.602	1.567	63.12	1.800	3.982
6	6	56.885	2.449	0.778	1.755	43.115	1.635	3.507
7	8	78.846	2.828	0.903	1.897	21.154	1.325	2.766
8	10	93.779	3.162	1.000	1.972	6.221	0.794	1.839

When the sodium alginate was combined with the natural gums is used for retarding drug discharge. The process of Valacyclovir liberates from matrix involve solvent diffusion into the matrix, polymer gelation, solubilization Valacyclovir and drug transfer along eddies of themedium.AS SHOWN IN FIGURE 4&5







Drug Release Kinetic Studies

The drug dissolution data was checked to discharge kinetics to check basis for medicament release by microspheres-

Table 14 R^2 Values for Different Kinetic models of F6

S.No.	Formulation	Models				
		Zero Order	First Order	Higuchi's	KorsmeyerPeppas	Hixson Crowell
1.	F6	0.985	0.896	0.855	0.927	0.951

The microspheres were subjected to *In-vitro* release studies by employing 0.1N Hydrochloric acid and the data was shown in Fig-7.1.8.5a-7.1.8.5.b. When the amount of drug release values were plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these microspheres followed zero order kinetics(Table-7.1.8.7 and Fig-7.1.8.7a) .To ascertain the mechanism of drug release from various microspheres, the plot of log% Released vs log time (Peppas plots) were drawn. The plots were found to be linear (Fig 7.1.8.7a-7.1.8.7.f). For the microspheres F6 the exponential coefficient values were found to be in between 0.855 and 0.985, indicating a fiction diffusion controlled release mechanism (Table-7.1.8.7.g). These results indicated that the release rate was found to decrease with increase in the concentration of coating material applied.

Accelerated Stability Studies

The microspheres from the selected and optimized batch F6 was studied for stability and kept under the accelerated conditions like raised temperature and moisture up to a period of three months. The results revealed no marked alterations in physical appearance and drug releasing properties.

Table 15 Drug Release From Formulation F6 After Stability Studies of Three Months

Time (Hours)	% Cumulative Drug Released			
	At 0 day	After 1st Month	After 2nd Month	After 3rd Month
0	0	0	0	0
1	4.012	3.892	3.782	3.743
2	7.982	7.752	7.712	7.692
3	18.874	18.644	18.604	18.584
4	36.76	36.53	36.49	36.47
6	56.765	56.535	56.495	56.475
8	78.726	78.496	78.456	78.436
10	93.659	93.429	93.389	93.369

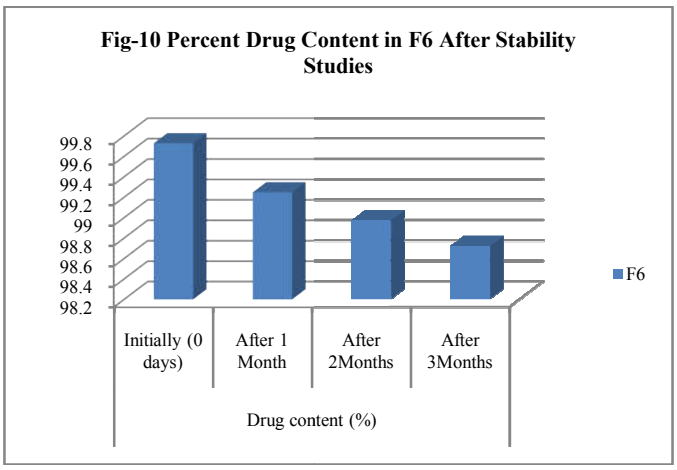
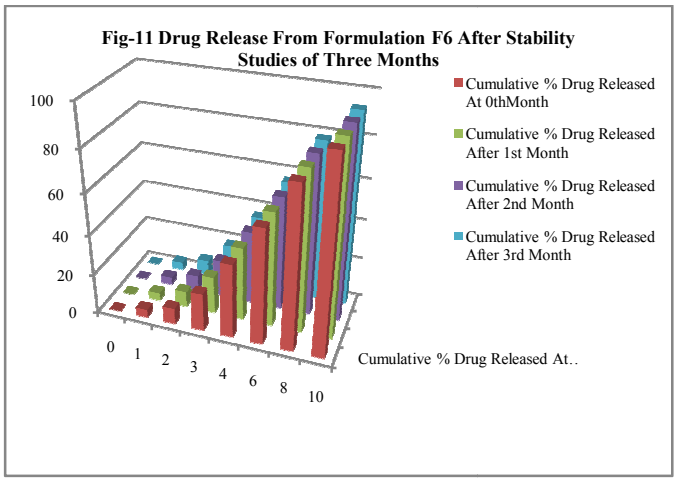


Table16 Percent Drug Content in F6 After Stability Studies

Optimized Formulation	Drug content (%)			
	Initially (0 days)	After 1 Month	After 2Months	After 3Months
F6	99.73	99.25	98.97	98.72



CONCLUSION

The microsphere of Valacyclovir was obtained utilizing orifice ionic gelation technique using xanthan gum and sodium alginate as a polymer with various ratios. The prepared microspheres were free-flowing and not sticky. All the formulations were shown satisfactory results. The obtained results stated that the natural polymer can be used for sustaining the release of the drug. In the above view of findings, it can be suggested that sodium alginate, when combined with the hydrophilic natural gums, shows the synergistic effects and hence can be utilized to prolong the release of Valacyclovir. The overall frequency of administration of a drug candidate like Valacyclovir was reduced as compared to the conventional tablet dosage form. The improved patient convenience might thus be obtained by the administration of such a dosage form with minimal blood level fluctuations. Among the different combinations of natural polymers and drug, many combinations were shown optimum results. The release retardant materials are cheap, readily available, safe, having wide regulatory acceptance and easy to handle for the economic point of view. It may beneficial to adopt such simple technology for the commercial manufacture of persistent release microspheres. Floating microspheres of Valacyclovir showed good entrapment efficiency with good buoyancy. The release was also prolonged. The formulation variables helped to incorporate different drug content with the variable release with the size of microspheres. Conclusively, the formulation improves patient compliance, decreased dose frequency and will be useful in treatment strategy of *Herpes simplex* virus and *varicella-zoster* virus.

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