International Journal of Research Publication and Reviews, Vol 3, no 4, pp 727-734, April 2022

WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

DEVELOPMENT AND CHARACTERIZATION OF FLOATING MICROSPHERES OF VALACYCLOVIR

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ABSTRACT

Oral drug delivery with floating microsphere preparation is nice option for the methodology expansion and upgrading purpose. Valacyclovir is given into conventional, immediate releasing preparations, the frequency of administration increased up to twice-thrice time for one day with larger dose because of shorter biological half-life. In such a case, the floating microsphere formulation will be beneficial than the immediate release dosage form as therapeutic level is maintained for an extended period of time, eliminating maxima in drug concentration commonly associated with multiple doses.All the formulations were shown satisfactory results. The obtained results stated that the natural polymer can be used for sustaining the release of 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 conventional tablet dosage form. 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 economic point of view. Conclusively, the formulation improves patient compliance, decreased dose frequency and will be useful in treatment strategy of *Herpes simplex* virus and *varicella zoster* virus.

Keywords: Microspheres, *DNA polymerase, Herpes simplex virus, gastrointestinal tract, enzymatic hydrolysis.*

1. INTRODUCTION

Oral delivery of drug is the greater part preferable route of drug-delivery due to easiness of administration, patient fulfillment and suppleness of formulation, etc. Beginning immediate release to site-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 swelling time for dosage form and controlled drug-release. Preparation remains buoyant in stomach content due to its lower density than that of gastric fluid. It is 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 gastrointestinal gut may be extremely short and high variable in certain circumstances. Gastric emptying of multi-particulate floating system would occur in consistent manner by way of reduced inter-subject variability in absorption. On every subsequent gastric emptying, deep-set particles will spread out over 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 short biological half-life of less 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.

Other advantages of floating microspheres are:-

- Bioavailability improved despite first pass effect since fluctuations in plasma drug concentration is avoided; a desirable plasma drug concentration is maintained by continuous drug-release.
- Site specific drug-delivery to stomach.

2. MATERIALS AND METHOD

A. MATERIALS

The drug, excipients, chemicals/ reagents and equipments used for various experiments are enlisted as follows:

Table 1: Materials and their source

S.No.	Material Used	Supplier
1.	Valacyclovir	Milan Distribution Private Limited, Mumbai
2.	Sodium Alginate	Qualikems
3.	Calcium Chloride	Qualikems
4.	Hydroxy propyl methyl cellulose (HPMC)	LOBA chemicals
5.	Chitosan	LOBA chemicals

3. EXPERIEMENTALS

A. PREFORMULATION STUDIES

a. **Physcialappreance**: The drug valacyclovir found to be white crystalline powder.

b. **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 Table 3.

Table: 2 Determination of Melting Point

Drug	Observation	Specification
Valacyclovir	172±1.46°C	170-172°C

a. **Determination of the Solubility:**

The results for the determination of the solubility of both drugs are shown in the Table 4.

Table: 3 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

c. **Determination of the Partition Coefficient:**

Table: 4 Determination of partition coefficient

Drug	Observation (LogP)	Standard (LogP)
Valacyclovir	-0.3±0.02	-0.3

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d. Analytical Method for Estimation of Valacyclovir:

Scanning of Val acyclovir:

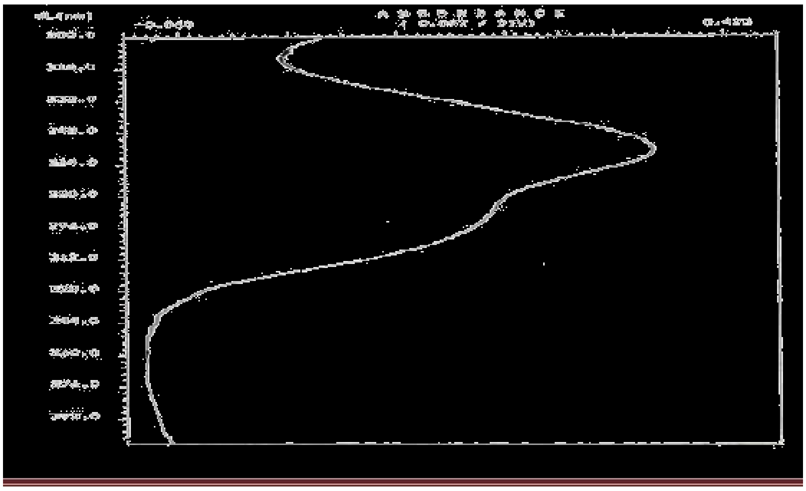

Figure:1 UV Spectra of Valacyclovir

The scanning of Valacyclovir was performed to determine the wavelength at which Valacyclovir absorb 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 solvent, under UV Spectrophotometer. The results of scanning of Valacyclovir are shown in the Table 6.

Table: 5Dilution 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±0.101
2	100 times (1 in 100 mL)	10	256.0	0.323±0.075
3	1000 times(1 in 1000 mL)	1	256	0.031±0.046

*All values are average of three determinations (n=3)

The results of scanning of Valacyclovir at 100, 10, 1 µg / mL showed that the solution of the 100 µg / mL has maximum absorbance at wavelength of 256 nm. This wavelength is selected as λmaxfor the determination of absorbance of different concentration of solutions.

e. 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 λmax of 256 nm. The results of absorbance of Valacyclovir solutions are shown in the Table 7.1.5.2.

Table: 6Data 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

*All values are average of three determinations (n=3)

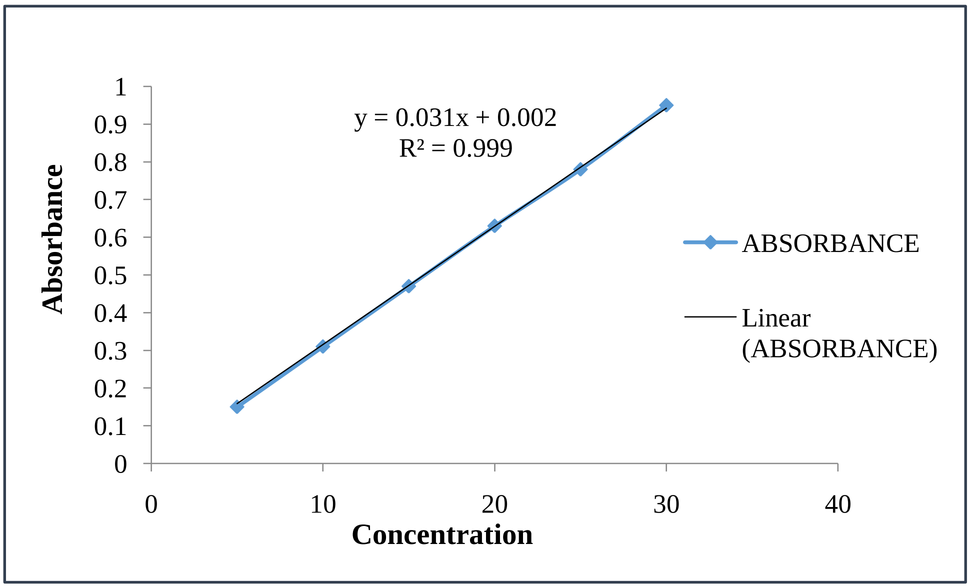

Figure: 2 Calibration curve of Valacyclovir at λmax of 256 nm

f. **Loss on drying:**

Table: 7 Loss on drying

S. NO.	Name of Drug	% Loss on drying	Specification (IndianPharmacopoeia, 2007)
1.	Valacyclovir	0.86±0.42%	NMT 0.9%

All values are average of three determinations (n=3)

B. FORMULATION OF VALACYCLOVIR MICROSPHERES:

Table: 8 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

C. EVALUATION OF VALACYCLOVIR MICROSPHERES:

a. **Micromeritics Studies of microspheres:**The results of the density of bulkiness and density of tapping were mentioned in 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.

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

Table: 9 Micromeritics Studies of Microspheres

Batch	Avg Microspheresize (± SD)	Bulk Density (± SD)	Tap Density (± SD)	Angle of Repose (± SD)	Compressibility Index (± SD)	Hausners ratio (± SD)
F1	291.46±8.3	0.298±0.010	0.522±0.005	25.15±1.04	13.81±0.24	1.15±0.04
F2	323.44±6.9	0.542±0.004	0.654±0.011	26.20±1.07	13.90±0.43	1.15±0.02
F3	356.88±8.6	0.526±0.012	0.636±0.007	25.12±1.10	12.65±0.19	1.13±0.03
F4	263.84±8.3	0.430±0.004	0.508±0.005	30.20±0.58	12.03±0.43	1.12±0.02
F5	327.65±7.5	0.482±0.008	0.528±0.013	25.06±1.41	13.71±0.44	1.14±0.05
F6	356.22±8.1	0.516±0.005	0.616±0.004	31.24±0.98	13.80±0.58	1.15±0.04

b. **Floating Behavior of microspheres:** Valacyclovir microsphere was dispersed in 0.1NHCl as simulate 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: 10 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.	F5	87.94±1.5

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

c. **Drug Content and Drug Entrapment efficiency:** Formulation F6 gave well 80.50±1.7 % drug content largest among the other formulations. The formulations has shown the percent drug content in between 48.14±0.9 to 80.50±1.7. All the batches has 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 used material.

Table: 11Percentage 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)

d. n-vitroRelease Profile Study of Formulated microspheres.

Table: 12 *In vitro* Cumulative Percent Drug Release Profile

S.No	Time	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	7.137±0.124	5.587±0.158	5.397±0.227	5.867±0.768	4.417±0.341	4.057±0.442
3	2	12.982±0.225	11.582±0.247	11.089±0.286	11.712±0.286	10.262±0.227	8.102±156
4	3	22.874±0.241	21.314±0.335	19.127±0.114	22.804±0.862	20.154±0.781	18.994±0.448
5	4	40.760±0.217	37.206±0.246	37.019±0.185	41.490±0.557	38.040±0.186	36.880±0.482
6	6	62.765±0.512	61.327±0.158	59.260±0.854	61.995±0.455	60.045±0.147	56.885±0.474

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

4. SUMMARY AND CONCLUSION:

Oral drug delivery with floating microsphere preparation is nice option for the methodology expansion and upgrading purpose.

Valacyclovir is given into conventional, immediate releasing preparations, the frequency of administration increased up to twice-thrice time for one day with larger dose because of shorter biological half-life.

In such a case, the floating microsphere formulation will be beneficial than the immediate release dosage form as therapeutic level is maintained for an extended period of time, eliminating maxima in drug concentration commonly associated with multiple doses.

- 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 non-sticky.
- All the formulations were shown satisfactory results.
- The obtained results stated that the natural polymer can be used for sustaining the release of 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 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 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 variable release with 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.

ACKNOWLEDGEMENT

The author is thankful to the management of Indore Mahavidyalaya, Indore, for providing necessary facilities to carry out the research work and heartily thankful to the co-authors for providing all the support and encouragement to carry out these studies.

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