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## Research Article

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### Formulation Development and *In-vitro* Evaluation of Valacyclovir Bioadhesive Microspheres

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#### ABSTRACT

In the present work, bioadhesive microspheres of Valacyclovir using Sodium alginate along with Carbopol 934, Carbopol 971, HPMC K4M as copolymers were formulated to deliver Valacyclovir via oral route. The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Valacyclovir microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an “all-aqueous” system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range of 512-903µm and are suitable for bioadhesive microspheres for oral administration. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The *in-vitro* drug release decreased with increase in the polymer and copolymer concentration. Based on the results of evaluation tests formulation coded T<sub>4</sub> was concluded as best formulation. The optimized Formulation microspheres were packed in hard gelatin capsule shells.

**Keywords:** Valacyclovir, Microspheres, Carbopol Polymers

#### ARTICLE INFO

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## 1. Introduction

The oral route for drug delivery is the most popular, desirable, and most preferred method for administering therapeutically agent for systemic effects because it is natural, convenient, and cost effective to manufacturing process. Oral route is the most commonly used route for drug administration. Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. Even for sustained release systems the oral route of administration has been investigated the most because of flexibility in designing dosage forms. Present controlled release drug delivery systems are for a maximum of 12 hours clinical effectiveness. Such systems are primarily used for the drugs with short elimination half life

### Oral Controlled Release Dosage Form:

The treatment of acute diseases or chronic illnesses has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems [2,3].

### Advantages of Controlled Drug Delivery System:

- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady-state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization drug enabling reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction personal time to dispense, administer and monitor patients.

### Disadvantages of Controlled Drug Delivery System:

- Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first-pass metabolism, increased in stability, in sufficient residence time for complete release, site specific absorption, pH dependent solubility etc. Poor in vitro- in vivo correlation. Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patients and thus, increased risk of toxicity.

- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- Higher cost of formulation.

### Microspheres:

For many decades, medication of an acute disease or a chronic disease has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption leads to the concept of controlled drug delivery systems [4-5]. The word new or novel in the relation to drug delivery system is a search for something out of necessity. An appropriately designed sustained or controlled release drug delivery system can be major advance toward solving the problem associated with the existing drug delivery system. The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while Temporal delivery refers to controlling the rate of drug delivery to the target tissue [6]. Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is beset with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable motility and relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [7].

## 2. Materials and Methods

**Preparation of 0.1N HCl (pH 1.2):** Take 8ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water

### Determination of $\lambda_{max}$ :

Stock solution (1000 $\mu$ g/ml) of Valacyclovir was prepared in methanol. This solution was appropriately diluted with 0.1N HCl (pH 1.2) to obtain a concentration of 10 $\mu$ g/ml. The resultant solution was scanned in the range of 200nm to 400nm on UV-Visible spectrophotometer. The drug exhibited a  $\lambda_{max}$  at 269nm.

### Preparation of Standard Calibration Curve of Valacyclovir:

- 10 mg of Valacyclovir was accurately weighed and dissolved in 10ml of methanol (Stock Solution – I) to get a concentration of 1000 µg/ml.
- From the stock solution- I, 1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.
- From the stock solution- II, aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 2 to 10µg/ml. The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 269nm against reference solution 0.1N HCl (pH 1.2).

**The Linear Regression Analysis:** The linear regression analysis was done on Absorbance points. The standard calibration curve obtained had a Correlation coefficient of 0.998 with of slope of 0.028 and intercept of 0.004.

### Method of Preparation

#### Ionotropic gelation method:

Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, Valacyclovir (100mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried.

#### Characterization of microspheres:

##### Percentage yield:

The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

##### Drug entrapment efficiency:

Microspheres equivalent to 15 mg of the drug Valacyclovir were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres. The powder was transferred to a 100 ml volumetric flask and dissolved in 10ml of methanol and the volume was made up using simulated gastric fluid pH 1.2. After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 269 nm.

### Particle size analysis:

Samples of the microparticles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1 unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 Microparticles sizes were calculated under 45 x magnifications.

### Swelling study:

Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2. The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance.

### Evaluation of Mucoadhesive property:

The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of goat stomach mucous were mounted on to glass slides with cotton thread. About 20 microspheres were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test, when the test apparatus was operated, the sample is subjected to slow up and down movement in simulated gastric fluid pH 1.2 at 37°C contained in a 1-litre vessel of the apparatus.

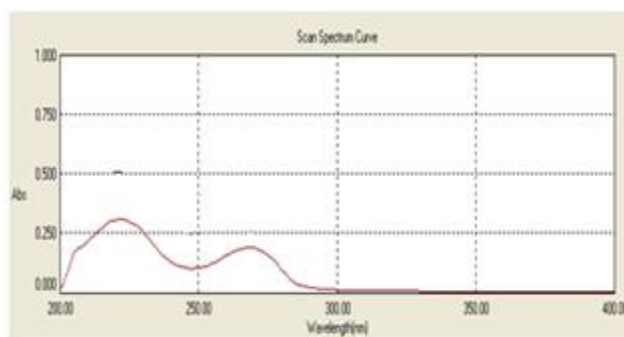
### In-vitro drug release study:

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.50°C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml). A quantity of accurately weighed microspheres equivalent to 15mg Valacyclovir each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 269nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment.

## 3. Results and Discussion

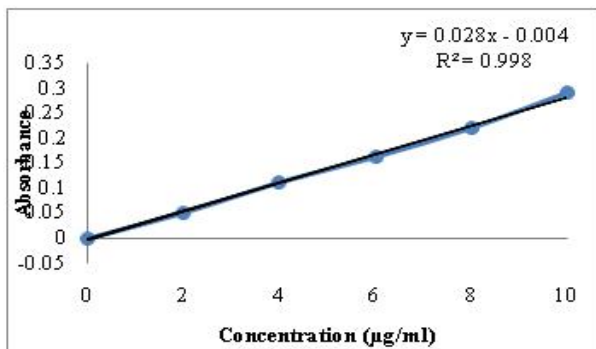
### Determination of max

A solution of 10µg/ml of Valacyclovir was scanned in the range of 200 to 400nm. The drug exhibited a max at 269nm in simulated gastric fluid pH 1.2 and had good reproducibility. Correlation between the concentration and absorbance was found to be near to 0.998, with a slope of 0.028 and intercept of 0.004.



**Figure 1:** UV Spectrum of Valacyclovir in simulated gastric fluid (pH 1.2)

**Calibration curve of Valacyclovir in simulated gastric fluid pH 1.2:** Table 6.1 shows the calibration curve data of Valacyclovir in simulated gastric fluid pH 1.2 at 269nm. Fig. 6.2 shows the standard calibration curve with a regression value of 0.998, slope of 0.028 and intercept of 0.004 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 2-10µg/ml.



**Figure 2:** Standard graph of Valacyclovir in simulated gastric fluid pH 1.2

**Evaluation and characterization of Microspheres Percentage Yield**

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of 80 to 88% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 62.22 to 87% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 80 to 87.5% for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The percentage yield of the prepared microspheres is recorded in Table 6.3 and displayed in Figures 6.7 to 6.9.

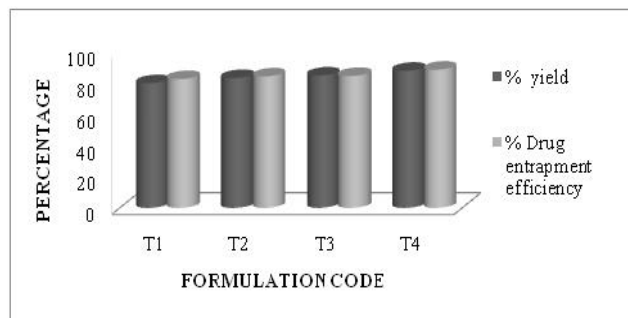
**Drug Entrapment Efficiency**

Percentage Drug entrapment efficiency of Valacyclovir ranged from 82.66 to 88.66% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 53.2 to 76.66% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 66.73 to 79.2% for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency.

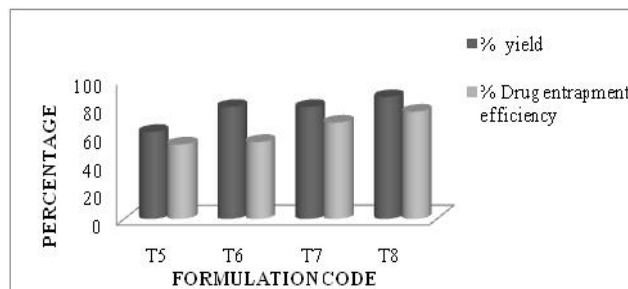
**Particle Size Analysis**

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing

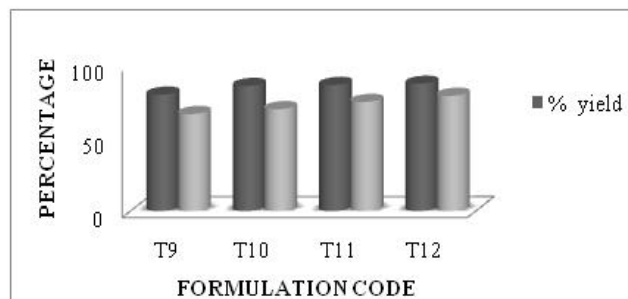
sodium alginate along with carbopol 934 as copolymer had a size range of 512µm to 826µm, microspheres containing sodium alginate along with carbopol 971 as copolymer exhibited a size range between 517µm to 834µm and microspheres containing sodium alginate along with HPMC K 4 M as copolymer had a size range of 664µm to 903µm.



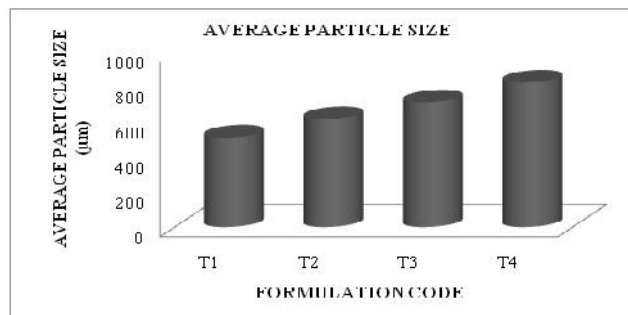
**Figure 3:** Comparison of % Yield and % drug entrapment efficiency microspheres containing sodium alginate along with carbopol 934 as copolymer.



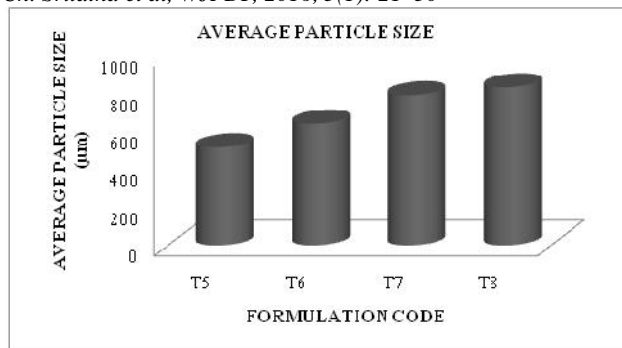
**Figure 4:** Comparison of % Yield and % drug entrapment efficiency microspheres containing sodium alginate along with carbopol 971 as copolymer



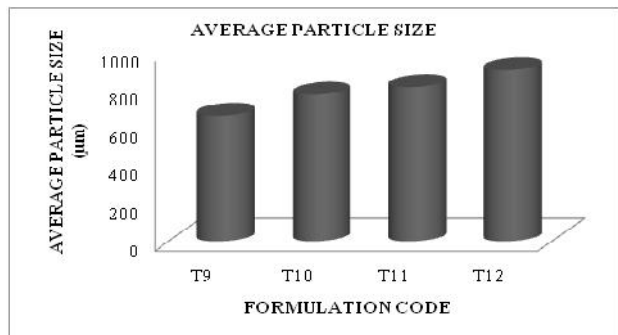
**Figure 5:** Comparison of % Yield and % drug entrapment efficiency microspheres containing sodium alginate along with HPMC K 4 M as copolymer



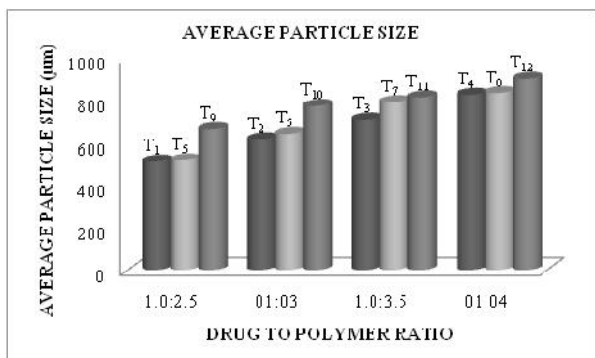
**Figure 6:** Average particle size of microspheres containing sodium alginate along with carbopol 934 as copolymer



**Figure 7:** Average particle size of microspheres containing sodium alginate along with carbopol 971 as copolymer



**Figure 8:** Average particle size of microspheres containing sodium alginate along with HPMC K 4 M as copolymer



**Figure 9:** Comparison of average particle size of prepared microspheres

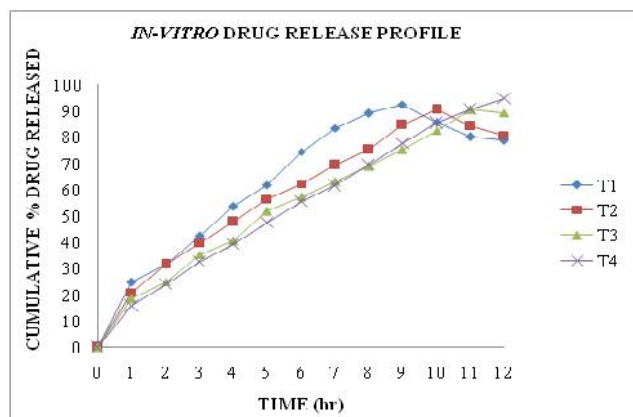
The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swellability is an important characteristic as it affects muco adhesion as well as drug release profiles of polymeric drug delivery systems. Swellability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swellability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table 6.16 that with an increase in polymer concentration, the percentage of swelling also increases. Thus we can say that amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 28 to 85% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 24 to 64% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 31 to 85 for microspheres

containing sodium alginate along with HPMC K 4 M as copolymer. The percentage of swelling of the prepared microspheres is displayed in Fig. 6.16 to 6.18. The effect of drug to polymer ratio on percentage swelling is displayed in Figure 6.19.

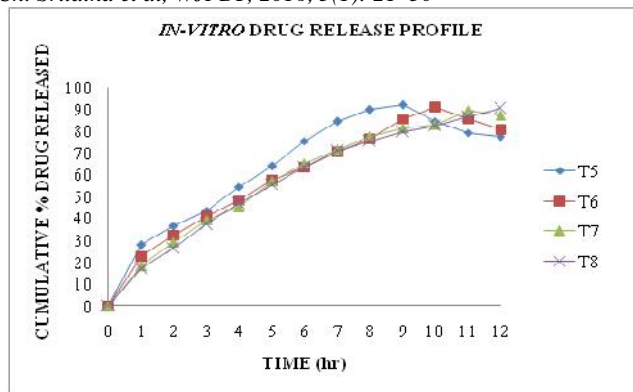
**In-Vitro Drug Release Studies**

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2. The results of the in-vitro dissolution studies of formulations T1 to T4, T5 to T8 and T9 to T12 are shown in table no.6.18 to 6.20. The plots of Cumulative percentage drug release Vs Time. Figure 6.24 shows the comparison of %CDR for formulations T1 to T4, figure 6.25 for formulations T5 to T8 and figure 6.26 for formulations T9 to T12. Korsmeyer-Peppas plots of Valacyclovir microspheres formulations T1 to T12 are displayed in figures 6.27 to 6.30. The formulations T1, T2, T3 and T4 containing Sodium alginate along with Carbopol 934 as copolymer showed a maximum release of 92.66% after 9 hours, 90.66% after 10 hours, 90.6% after 11 hours and 94.66% after 12 hours respectively.

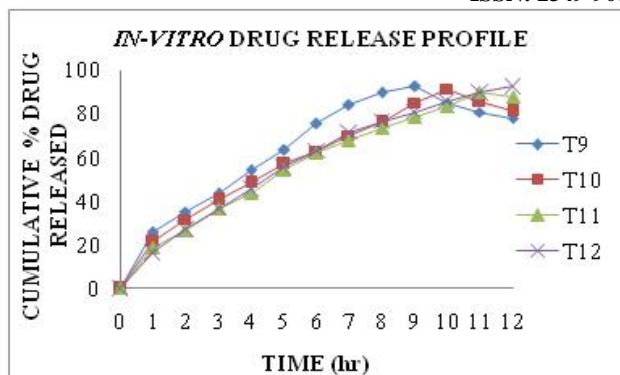
The formulations T5, T6, T7 and T8 containing Sodium alginate along with Carbopol 971 as copolymer showed a maximum release of 92.22% after 9 hours, 91.33% after 10 hours, 89.55% after 11 hours and 90.66% after 12 hours respectively. The formulations T9, T10, T11 and T12 containing Sodium alginate along with HPMC K 4 M as copolymer showed a maximum release of 92.6% after 9 hours, 91.3% after 10 hours, 90% after 11 hours and 92.44% after 12 hours respectively. This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling control release mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.



**Figure 10:** Comparison of In-Vitro drug release profile of Valacyclovir microspheres containing sodium alginate along with carbopol 934 as copolymer



**Figure 11:** Comparison of In-Vitro drug release profile of Valacyclovir micro spheres containing sodium alginate along with carbopol 971 as copolymer



**Figure 12:** Comparison of In-Vitro drug release profile of Valacyclovir micro spheres containing sodium alginate along with HPMC K 4 M as copolymer

**Table 1:** Prepared formulation of Bio-adhesive Microspheres

S.No	Formulation code	Drug:polymer ratio	Polymer ratio
1	T <sub>1</sub>	1:2.5	Na alginate:Carbopol 934 (1.5:0.5)
2	T <sub>2</sub>	1:3	Na alginate:Carbopol 934 (2:1)
3	T <sub>3</sub>	1:3.5	Na alginate:Carbopol 934 (2.5:1)
4	T <sub>4</sub>	1:4	Na alginate:Carbopol 934 (3:1)
5	T <sub>5</sub>	1:2.5	Na alginate:Carbopol 971 (1.5:0.5)
6	T <sub>6</sub>	1:3	Na alginate:Carbopol 971 (2:1)
7	T <sub>7</sub>	1:3.5	Na alginate:Carbopol 971 (2.5:1)
8	T <sub>8</sub>	1:4	Na alginate:Carbopol 971 (3:1)
9	T <sub>9</sub>	1:2.5	Na alginate:HPMC K 4M (1.5:0.5)
10	T <sub>10</sub>	1:3	Na alginate:HPMC K 4 M (2:1)
11	T <sub>11</sub>	1:3.5	Na alginate:HPMC K 4 M (2.5:1)
12	T <sub>12</sub>	1:4	Na alginate:HPMC K 4 M (3:1)

Concentration (µG /ML)	Absorbance
2	0.051
4	0.110
6	0.163
8	0.221
10	0.290

**Table 3:** Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	Drug Content (mg)	% Drug entrapment efficiency
1	T <sub>1</sub>	80	12.40	82.66
2	T <sub>2</sub>	83.33	12.66	84.4
3	T <sub>3</sub>	85	12.70	84.66
4	T <sub>4</sub>	88	13.29	88.66
5	T <sub>5</sub>	62.22	8.07	53.2
6	T <sub>6</sub>	80	8.25	55
7	T <sub>7</sub>	80	10.33	68.86
8	T <sub>8</sub>	87	11.5	76.66
9	T <sub>9</sub>	80	10.01	66.73
10	T <sub>10</sub>	86	10.5	70
11	T <sub>11</sub>	86.66	11.25	75
12	T <sub>12</sub>	87.5	11.88	79.2

**Table 4:** Particle size data of T1

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
200-300	250	9	2250	512 $\mu\text{m}$
300-400	350	13	4550	
400-500	450	17	7650	
500-600	550	29	15950	
600-700	650	32	20800	
		n=100	nd=51200	

**Table 5:** Particle size data of T2

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
300-400	350	15	5250	617 $\mu\text{m}$
400-500	450	13	5850	
500-600	550	18	9900	
600-700	650	12	7800	
700-800	750	28	21000	
800-900	850	14	11900	
		n=100	nd=61700	

**Table 6:** Particle size data of T3

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
400-500	450	10	4500	711 $\mu\text{m}$
500-600	550	12	6600	
600-700	650	18	11700	
700-800	750	27	20250	
800-900	850	33	28050	
		n=100	nd=71100	

**Table 7:** Particle size data of T4

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (D)	FREQUENCY (N)	ND	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
500-600	550	6	3300	826 $\mu\text{m}$
600-700	650	12	7800	
700-800	750	16	12000	
800-900	850	32	27200	
900-1000	950	34	32300	
		n=100	nd=82600	

**Table 8:** Particle size data of T5

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
200-300	250	8	2000	517 $\mu\text{m}$
300-400	350	12	4200	
400-500	450	18	8100	
500-600	550	29	15950	
600-700	650	33	21450	
		n=100	nd=51700	

**Table 9:** Particle size data of T6

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
300-400	350	12	4200	642 $\mu\text{m}$
400-500	450	11	4950	
500-600	550	15	8250	
600-700	650	14	9100	

700-800	750	31	23250	
800-900	850	17	14450	
		n=100	nd=64200	

**Table 10:** Particle size data of T7

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
400-500	450	6	2700	792 $\mu\text{m}$
500-600	550	10	5500	
600-700	650	8	5200	
700-800	750	19	14250	
800-900	850	26	22100	
900-1000	950	31	29450	
		n=100	nd=79200	

**Table 11:** Particle size data of T8

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
500-600	550	6	3300	834 $\mu\text{m}$
600-700	650	11	7150	
700-800	750	13	9750	
800-900	850	33	28050	
900-1000	950	37	35150	
		n=100	nd=83400	

**Table 12:** Particle size data of T9

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
400-500	450	18	8100	664 $\mu\text{m}$
500-600	550	19	10450	
600-700	650	18	11700	
700-800	750	21	15750	
800-900	850	24	20400	
		n=100	nd=66400	

**Table 13:** Particle size data of T10

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
400-500	450	8	3600	774 $\mu\text{m}$
500-600	550	12	6600	
600-700	650	10	6500	
700-800	750	17	12750	
800-900	850	24	20400	
900-1000	950	29	27550	
		n=100	nd=77400	

**Table 14:** Particle size data of T11

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
500-600	550	8	4400	814 $\mu\text{m}$
600-700	650	14	9100	
700-800	750	17	12750	
800-900	850	28	23800	
900-1000	950	33	31350	
		n=100	nd=81400	



**Table 15:** Particle size data of T12

PARTICLE SIZE RANGE ( $\mu\text{m}$ )	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE ( $\mu\text{m}$ )
600-700	650	2	1300	903 $\mu\text{m}$
700-800	750	3	2250	
800-900	850	35	29750	
900-1000	950	60	57000	
		n=100	nd=90300	

#### 4. Conclusion

In the present work, bio adhesive microspheres of Valacyclovir using Sodium alginate along with Carbopol 934, Carbopol 971 and HPMC K4M as copolymers were formulated to deliver Valacyclovir via oral route. Details regarding the preparation and evaluation of the formulations have been discussed in the previous chapter. From the study following conclusions could be drawn:

The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Valacyclovir microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an “all-aqueous” system, avoids residual solvents in microspheres. Other method utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used. Micro meritic studies revealed that the mean particle size of the prepared micro spheres was in the size range of 512-903 $\mu\text{m}$  and are suitable for bio adhesive microspheres for oral administration. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The in-vitro drug release decreased with increase in the polymer and copolymer concentration. Based on the results of evaluation tests formulation coded T4 was concluded as best formulation.

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