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Formulation and invitro evaluation of mucoadhesive microspheres of valacyclovir

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ABSTRACT

In the present work, mucoadhesive microspheres of valacyclovir using Sodium alginate along with Carbopol 934 and HPMC K100 as copolymers were formulated to deliver valacyclovir via oral route. The results of this investigation indicate that Ionotropic gelation method can be successfully employed to fabricate valacyclovir microspheres. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymer used. Analysis of drug release mechanism showed that the drug release from the formulations followed the best fit higuchi's model of drug release diffusion mechanism and follows zero oreder kinectics. Based on the results of evaluation tests formulation coded VM3 was concluded as best formulation.

Keywords: Valacyclovir, Sodium alginate and HPMC K100

INTRODUCTION

The oral route for drug delivery is the most popular, desirable, and most preferredmethod for administrating therapeutically agents for systemic effects because it is a natural, convenient, and cost effective to manufacturing process.Oral route is the most commonly used route for drug administration. Although different route of administra- tion are used for the delivery of drugs, oral route remain the preferred mode. Even forsustained release systems the oral route of administration has been investigated the mostbecause of flexibility in designing dosage forms. Present controlled release drug delivery systems are for a maximum of 12 hoursclinicaleffectiveness.Such systems are primarily used for the drugs with shortelimi-nationhalf life.

AIM OF THE STUDY

The aim of the study is to formulate and evaluate mucoadhesive microspheres of valacyclovir by using different polymers Sodium alginate, HPMC K100M and Carbopol 934 in different ratios.

METHODOLOGY

Preparation of microspheres

All the formulations were prepared by orifice ionic gelation method. The compositions of different formulations are given in Table No: .The microspheres were prepared as per the procedure

given below and the aim is to prolong the release of drug.

Procedure

Valacyclovir and all other polymers were individually passed through sieve no ≠ 60.The required quantities of Sodium alginate and the mucoadhesive polymer were dissolved in purified water to form a homogenous polymer solution. The Drug, Valacyclovir was added to the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually drop wise into calcium chloride (4 % w/v) solution through a syringe with a needle of size no. 22. The added droplets were retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce the spherical rigid microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 45^0C for12 hours.

Table No :1 Composition of different formulations

Formulation code	DRUG: POLYMER Ratio	POLYMER Ratio
VM1	1:1	Sodium Alginate : HPMC K 100 (3:1)
VM2	1:2	Sodium Alginate : HPMC K 100 (3:1)
VM3	1:2.5	Sodium Alginate : HPMC K 100 (3:1)
VM4	1:3	Sodium Alginate : HPMC K 100 (3:1)
VM5	1:1	Sodium Alginate : Carbopol 934 (3:1)
VM6	1:2	Sodium Alginate : Carbopol 934 (3:1)
VM7	1:2.5	Sodium Alginate : Carbopol 934 (3:1)
VM8	1:3	Sodium Alginate : Carbopol 934 (3:1)

RESULTS AND DISCUSSION

Drug excipient compatibility studies

The From the IR spectral data of ideal formulation F3,it is clearly evident that there were no interactions of the drug .

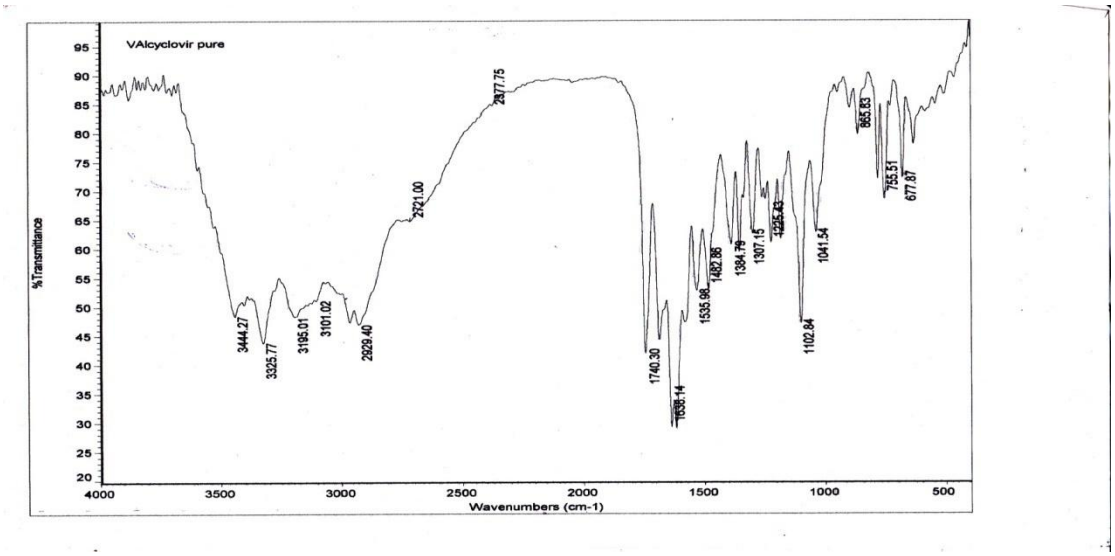

Figure No 1:FTIR Spectra of valacyclovir pure drug

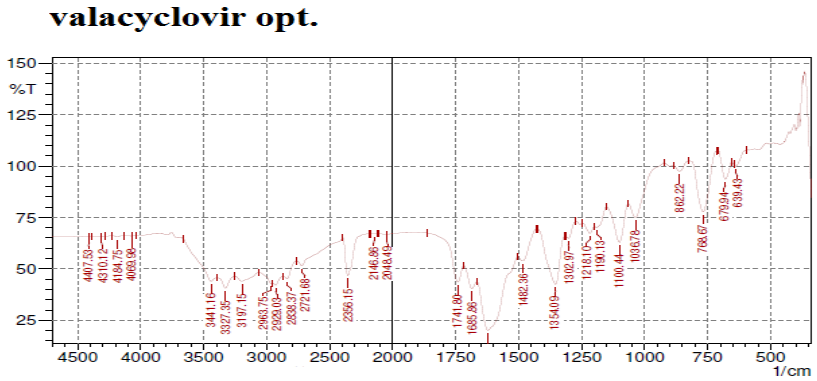

Figure No 2:FTIR Spectra of valacyclovir optimized formulation

Evaluation and characterisation 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 79.9 to 84.9% for microspheres containing sodium alginate along with carbopol 934 as copolymer and 82.1 to 88.8% for microspheres containing sodium alginate along with HPMC K100 as copolymer. The percentage yield of the prepared microspheres is recorded in Table --2 and displayed in Figures --3.

Drug entrapment efficiency

Percentage Drug entrapment efficiency of valacyclovir ranged from 72.1 to 84.66% for microspheres containing sodium alginate along with carbopol 934 as copolymer and 77.9 to 85.6% for microspheres containing sodium alginate along with HPMC K100 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. The % drug entrapment efficiency of the prepared microspheres is displayed in Table --2, and displayed in Figure --4-.

Tale no: 2 Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	%Drug entrapment efficiency
1	**VM1**	82.1	77.9
2	**VM2**	85.4	79.3
3	**VM3**	86	85.2
4	**VM4**	88.8	85.6
5	**VM5**	79.9	72.1

6	**VM6**	81.2	78.7
7	**VM7**	84.6	82.3
8	**VM8**	84.9	84.6

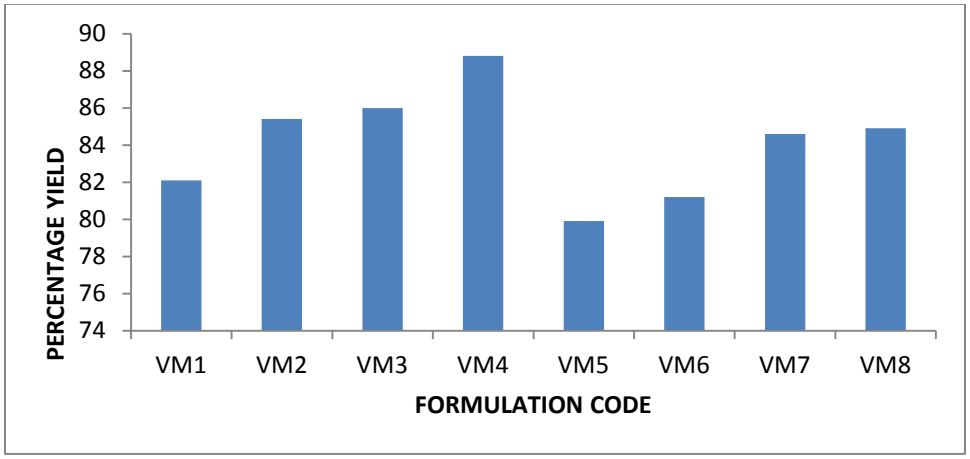

Fig no:3 Graphical representation of percentage yield of formulations VM1 - VM8

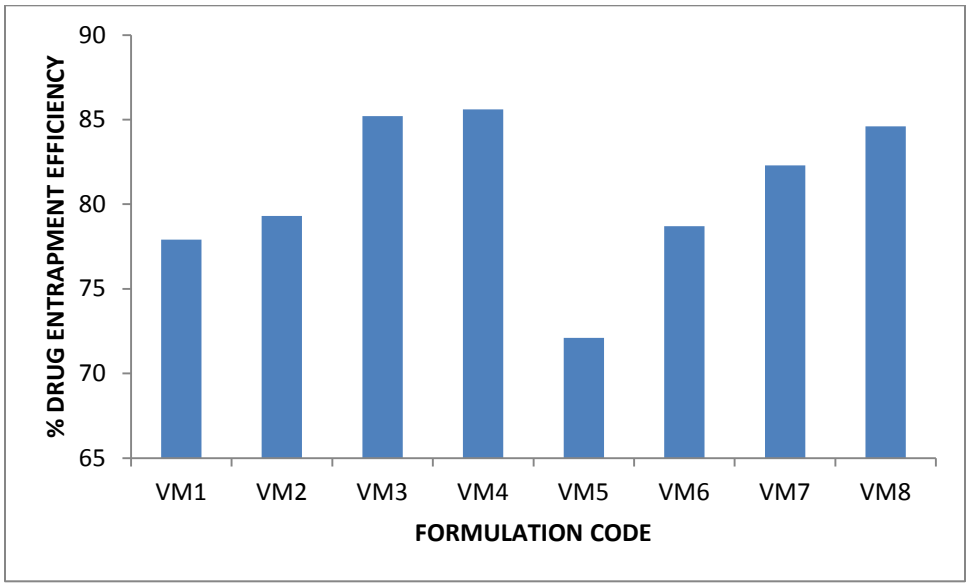

Fig no:4 Graphical representation of percentage drug entrapment efficiency of formulations

VM1 - VM8

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 625µm to 648µm, and microspheres containing sodium alginate along with HPMC K100 as copolymer had a size range of 548µm to 612µm. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.Table 3: Average Particle Size analysis for formulation VM1- VM8

Formulation code	Average particle size(µm)
VM1	548
VM2	554
VM3	568
VM4	612
VM5	625
VM6	633
VM7	645
VM8	648

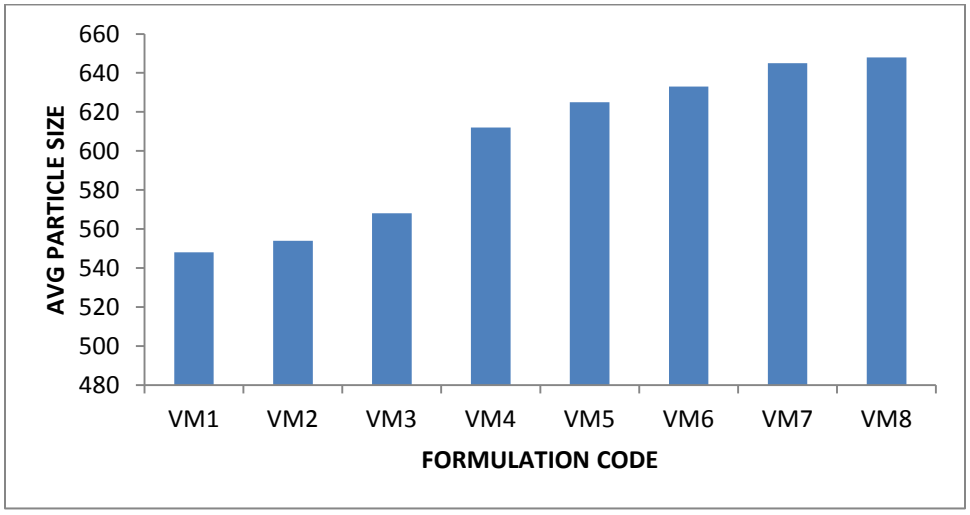

Fig:5 Graphical representation of average particle size for formulations VM1- VM8

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,0.1 N HCl. The results of the in-vitro dissolution studies of formulations VM1-VM8 shown in table no.4-- The plots of Cumulative percentage drug release Vs Time. Figure --6 shows the comparison of % CDR for formulations VM1- VM8.

The formulations VM1, VM2, VM3 and VM4 containing Sodium alginate along with HPMC K100 showed a maximum release of 80.74, 82.31 % at 8 hours, 85.62 % and 83.40 % at 12 hours respectively.

The formulations VM5, VM6, VM7 and VM8 containing Sodium alginate along with carbopol as copolymer showed a maximum release of 75.51,72.80,70.11 and 64.48 % at 12 hours respectively.

The formulation VM3 Sodium alginate along with HPMC K100 showed a maximum release of 85.62 % at 12 hours.

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. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.

Table no:4 In-Vitro drug release data of valacyclovir microspheres containing sodium alginate along with HPMC K100 as copolymer.

TIME (hrs)	Cumulative Percent Of Drug Released			
	VM1	VM2	VM3	VM4
0	0	0	0	0
1	15.08	12.60	10.82	10.78
2	29.70	28.01	22.62	21.07
3	32.68	34.80	30.96	28.86
4	39.54	40.68	38.84	34.10
5	44.25	47.13	43.17	45.42
6	51.36	53.69	50.80	56.62
7	72.74	76.82	62.26	67.71
8	80.74	82.31	72.18	70.92
10	--	--	80.11	79.21
12	--	--	85.62	83.40

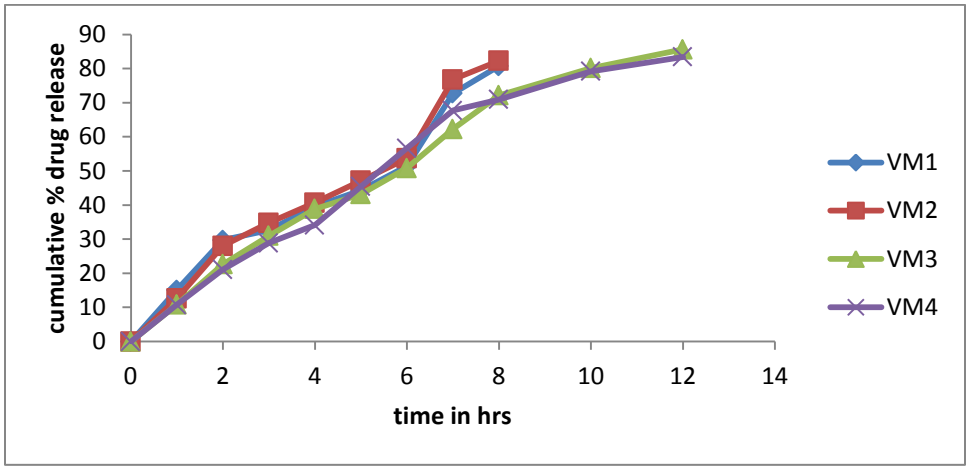

Fig no:6 Comparison of In-Vitro drug release profile of valacyclovir microspheres containing sodium alginate along with HPMC K100 as copolymer

Table no: 5 In-Vitro drug release data of valacyclovir microspheres containing sodium alginate along with Carbopol as copolymer

TIME (hrs)	Cumulative Percent Of Drug Released			
	VM5	VM6	VM7	VM8
0	0	0	0	0
1	9.70	9.61	8.20	8.29
2	15.62	12.07	12.60	11.04
3	22.40	22.46	20.34	18.79
4	36.16	28.60	28.00	26.55
5	43.80	36.90	34.31	36.50
6	50.91	47.22	45.52	43.64
7	55.40	55.07	55.61	54.52

8	61.82	58.09	57.70	58.30
10	68.70	66.58	65.98	62.66
12	75.51	72.80	70.11	64.48

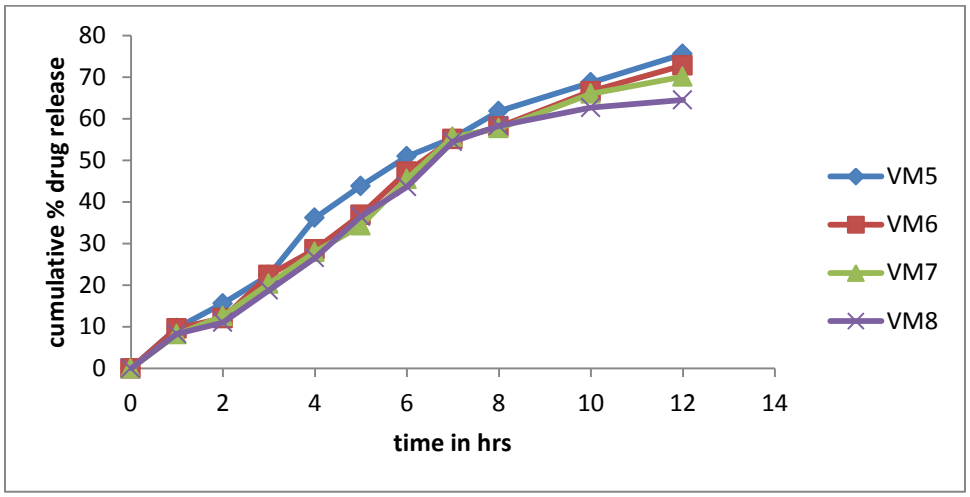

Fig no:7 Comparison of In-Vitro drug release profile of valacyclovir microspheres containing sodium alginate along with carbopol 934 as copolymer

In-vitro drug release kinetics

Table no: 6 Release Kinetics For Vm3 Formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.344124041	-0.07153207	27.17639657	1.297433521
Intercept	6.492800512	2.048856387	-11.4399498	0.693252508
Correlation	0.986189189	-0.98825520	0.977030397	0.871493489
R 2	0.972569117	0.976648342	0.954588397	0.759500902

Zero order kinetics

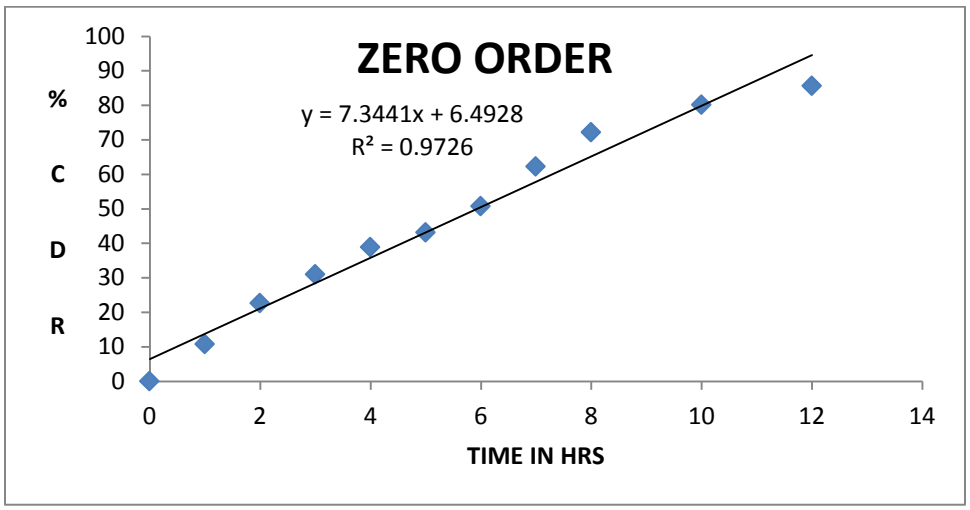

Fig no:8 Zero order kinetics graph

First order kinetics

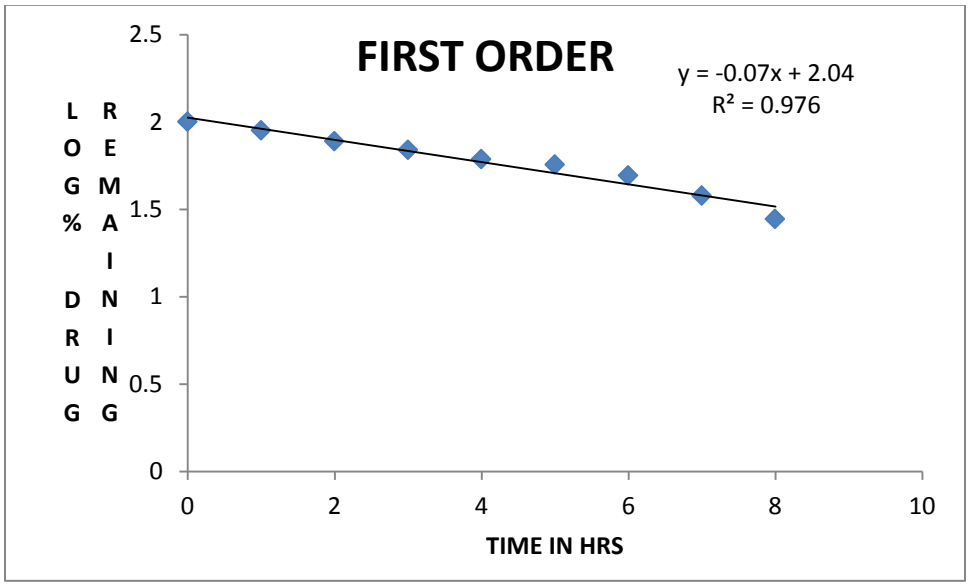

Fig no:9 First order kinetics graph

Higuchis plot

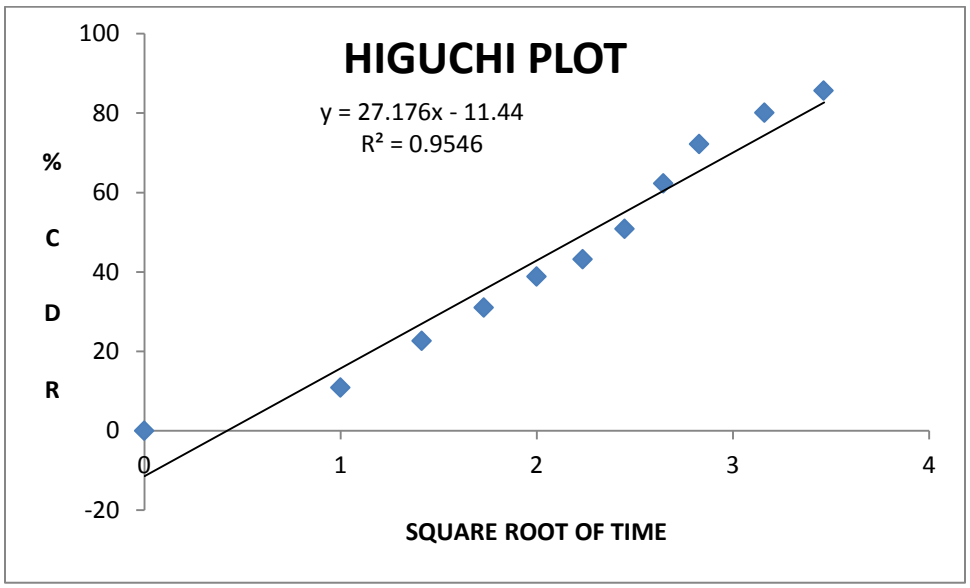

Fig no:10 Higuchis plot

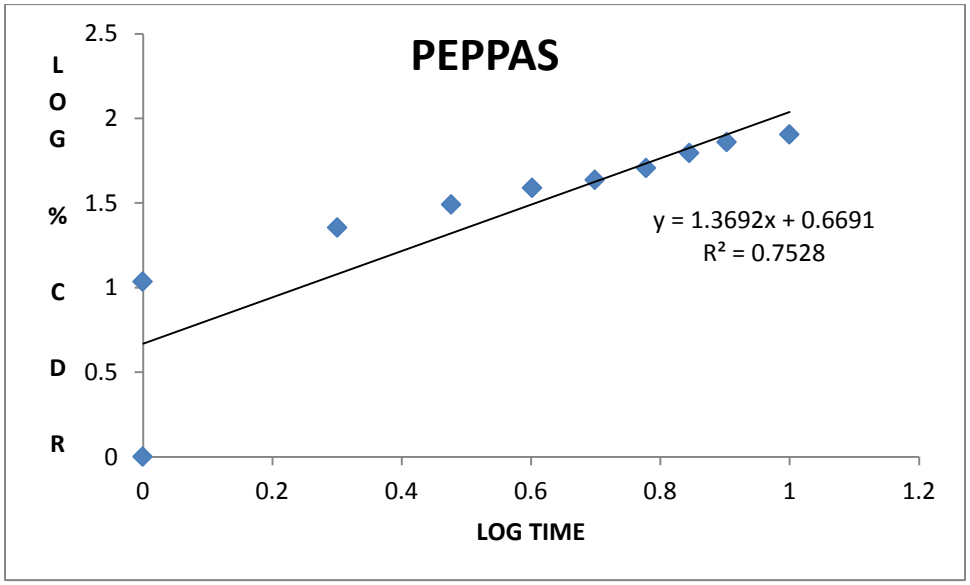

Fig no:11 peppas plot

Release kinetics studies of the prepared formulations

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table --. The coefficient of determination (R2) was used as an indicator of the best fitting for each of the models considered. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows first order kinetics which is dependent on concentration and Higuchis model along with diffusion mechanism which leading to the conclusion that a release

mechanism of drug followed combination of diffusion and spheres erosion.

DISCUSSION

Micromeritic studies revealed that the avg particle size of the prepared microspheres containing sodium alginate along with carbopol 934 as copolymer had a size range of 625µm to 648µm, and microspheres containing sodium alginate along with HPMC K100 as copolymer had a size range of 548µm to 612µm. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size. The *invitro* drug release decreased with increase in the polymer and copolymer concentration.The formulation VM3 Sodium alginate along with HPMC K100 showed a maximum release of 85.62 % at 12 hours.

CONCLUSION

In the present work, mucoadhesive microspheres of valacyclovir using Sodium alginate along with Carbopol 934 and HPMC K100 as copolymers were formulated to deliver valacyclovir via oral route. Micromeritic studies revealed that the avg particle size of the prepared microspheres containing sodium alginate along with carbopol 934 as copolymer had a size range of 625µm to 648µm, and microspheres containing sodium alginate along with HPMC K100 as copolymer had a size range of 548µm to 612µm. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size. The *invitro* drug release decreased with increase in the polymer and copolymer concentration.The formulation VM3 Sodium alginate along with HPMC K100 showed a maximum release of 85.62 % at 12 hours. Analysis of drug release mechanism showed that the drug release from the formulations followed the best fit higuchi's model of drug release diffusion mechanism and follows zero oreder kinectics.Based on the results of evaluation tests for mulation coded VM3 was concluded as best formulation.

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