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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF VALGANCICLOVIR HYDROCHLORIDE BY USING NATURAL AND SYNTHETIC POLYMERS

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Abstract:
The present study focuses on the formulation and evaluation of sustained release matrix tablets of Valganciclovir Hydrochloride (VH) using both natural and synthetic polymers to enhance therapeutic efficacy and patient compliance. Various formulations were prepared utilizing different concentrations of Hydroxypropyl Methylcellulose (HPMC), Xanthan Gum, and Karaya Gum as matrix-forming agents. The pre-compression parameters including bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose were evaluated and found within acceptable limits, indicating good flow properties. Post-compression studies, such as hardness, thickness, friability, weight variation, and drug content, were also within pharmacopeial standards, confirming the uniformity and mechanical integrity of the tablets. In-vitro drug release studies were carried out for 12 hours using USP dissolution apparatus. Among all formulations, batch VH4 demonstrated a sustained and controlled drug release profile, achieving 99.14% drug release at the end of 12 hours, thereby considered the optimized formulation. This study concludes that a combination of natural and synthetic polymers can effectively control the release of Valganciclovir Hydrochloride, providing a promising approach for sustained drug delivery.
Keywords: *Valganciclovir Hydrochloride, HPMC, Xanthan Gum and Karaya Gum*

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1. INTRODUCTION:

Out of the many routes of administration available, the oral route remains the most popular dosage form among patients as it is easy to administer, carry around, formulation design flexibility, cost-effectiveness, causes minimal discomfort for many patients, and least sterility restrictions during manufacturing. Most of the newly discovered drugs are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems.[1]

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitro Glyn' and made under license by Key Corp. in Florida.
Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.
The above factors need serious review prior to design [2-8].

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of pharmaceutical technology. It excludes complex production procedures such as coating and Palletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e.hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane-controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water-soluble drugs [9-10].

List of Materials Used

Valganciclovir Hydrochloride Provided by SURA LABS, Dilsukhnagar, Hyderabad.

HPMC K 15 Degussa India Ltd. (Mumbai, India)

Xanthan Gum Merck Specialities Pvt Ltd, Mumbai, India

Guar gum Merck Specialities Pvt Ltd, Mumbai, India

PVP K30 Signet chemical corporation, Mumbai

Talc Shakti Chemicals, Mehsana, India.

Mg stearate Merck Specialities Pvt Ltd, Mumbai, India

MCC Merck Specialities Pvt Ltd, Mumbai, India

List of Equipment's used

Name of the Equipment	Manufacturer
Weighing Balance	Sartourius
Tablet Compression Machine (Multistation)	Lab Press Limited, India.
Hardness tester	Monsanto, Mumbai, India.
Vernier callipers	Mitutoyo, Japan.
Roche Friabilator	Labindia, Mumbai, India
Dissolution Apparatus	Labindia, Mumbai, India
UV-Visible Spectrophotometer	Labindia, Mumbai, India

METHODOLOGY:

Formulation development of Sustained release Tablets:

All the formulations were prepared by Direct compression method. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Valganciclovir Hydrochloride.

Procedure:

1) Valganciclovir Hydrochloride and all other ingredients except Mg stearate and Aerosil

were individually passed through sieve no ≠ 40.

2) Valganciclovir Hydrochloride, MCC, and polymer mix thoroughly than add the binder solution mix properly up to 15 min.
3) Dry the above mixture at 65-70ºC by using dryer.
4) After completion of drying the mixture is passed through sieve no ≠ 22.
5) The powder mixture was lubricated with Mg stearate and Talc.
6) Finally go for compression.

Table 7.1: Formulation of Sustained release tablets

Ingredients	VH1	VH2	VH3	VH4	VH5	VH6	VH7	VH8	VH9
Valganciclovir Hydrochloride	100	100	100	100	100	100	100	100	100
HPMC K 15	50	75	100	-	-	-	-	-	-
Xanthan Gum	-	-	-	50	75	100	-	-	-
Guar gum	-	-	-	-	-	-	50	75	100
PVP K30	20	20	20	20	20	20	20	20	20
Talc	15	15	15	15	15	15	15	15	15
Mg stearate	10	10	10	10	10	10	10	10	10
MCC	255	230	205	255	230	205	255	230	205
Total weight	450	450	450	450	450	450	450	450	450

Flow property

Table No.7.2 The flow property of powder blend

Flow property	Angle of repose	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

7.4.2 Post Compression parameters

Weight variation test

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight 250 mg so the % deviation was ±5 %.

Table 7.3 IP standards of uniformity of weight

S. No.	Average weight of tablet	% of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	5

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss (F) was calculated by the following formula.

F =100 (W0-W)/W0

Where W0 = Initial weight, W = Final weight

Hardness test

The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.

Thickness test

The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter.

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

***In vitro* drug release studies**

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCL, p H 6.8 Phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	1, 2, 3, 4, 5, 6, 7, 8, 9,10 ,11 and 12hrs.
Temperature	--	37°C ± 0.5°C

Procedure:

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The media was allowed to equilibrate to temp of 37°C ± 0.5°C. Tablet was placed in the vessel and apparatus was operated for 2 hours. Then 0.1 N HCL was replaced with pH 6.8 phosphate buffer and process was continued up to 24 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5ml media was added to maintain the sink condition. Withdrawn samples were analyzed at 271 nm wavelength of drug using UV-spectrophotometer.

7.5 Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

8. RESULTS & DISCUSSION:

The present study was aimed to develop sustained release tablets of Valganciclovir Hydrochloride using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Valganciclovir Hydrochloride were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 251 nm and 254 nm respectively.

Table 8.1: Observations for graph of Valganciclovir Hydrochloride in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
2	0.124
4	0.236
6	0.346
8	0.459

10	0.574

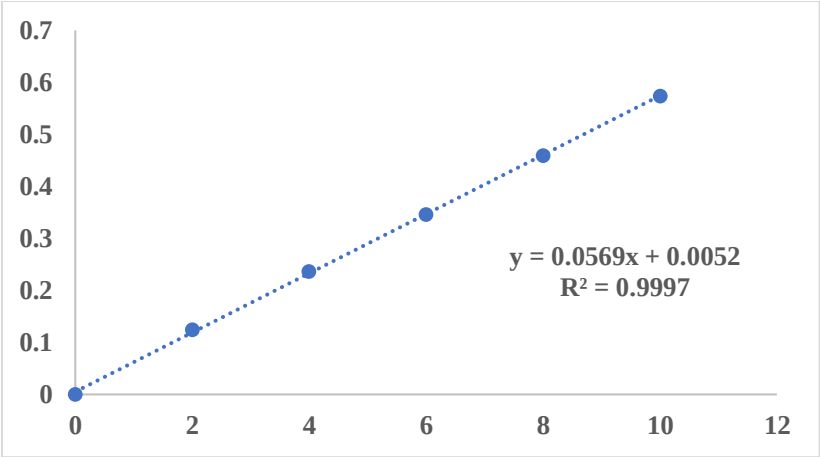

Fig 8.1: Standard curve of Valganciclovir Hydrochloride

Table 8.2: Standard graph values of Valganciclovir Hydrochloride at 254 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.127
4	0.242
6	0.359
8	0.477
10	0.591

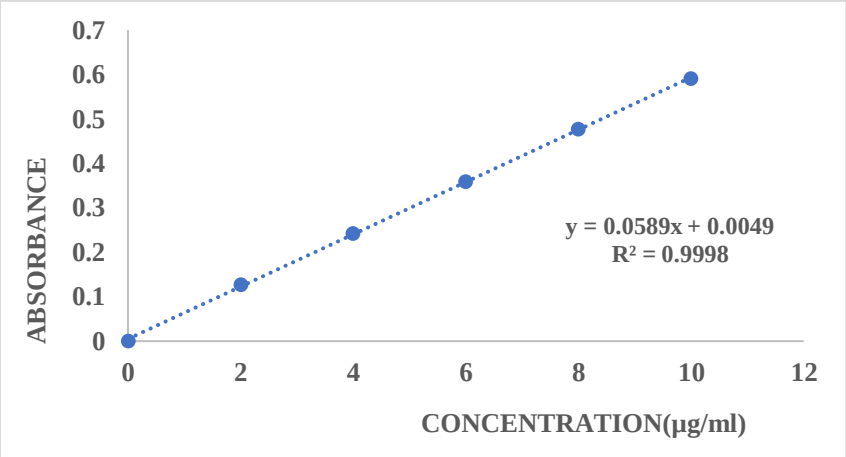

Fig 8.2: Standard curve of Valganciclovir Hydrochloride

Pre formulation parameters of powder blend

Table 8.3: Pre-formulation parameters of Core blend

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
VH1	26.45±0.6	0.54±0.02	0.65±0.04	16.92±0.04	1.2±0.07
VH2	25.12±0.51	0.48±0.09	0.57±0.05	15.78±0.05	1.18±0.06
VH3	27.08±0.47	0.58±0.01	0.69±0.05	15.94±0.01	1.18±0.04
VH4	28.12±0.35	0.56±0.03	0.66±0.02	15.15±0.02	1.17±0.05
VH5	25.24±0.52	0.53±0.02	0.65±0.05	18.46±0.09	1.22±0.07
VH6	25.33±0.48	0.54±0.05	0.64±0.04	15.62±0.05	1.18±0.08
VH7	27.7±0.42	0.52±0.09	0.64±0.02	18.75±0.09	1.23±0.06
VH8	26.8±0.35	0.56±0.04	0.67±0.08	16.41±0.00	1.19±0.05

VH9	25.01±0.21	0.49±0.05	0.57±0.06	14.03±0.01	1.16±0.02

All the values represent n=3

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The tapped density of all the formulations powders has good flow properties. The compressibility index of all the formulations was found to be below 16.19 which show that the powder has good flow properties. All the formulations have shown the Hausner ratio below 1.19 indicating the powder has good flow properties.

Quality Control Parameters for tablets:

Tablet quality control tests such as weight variation, hardness, friability, thickness and drug release studies in different media were performed on the compression tablet.

Table 8.4: *In vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
VH1	448.28	4.12	0.36	3.56	98.76
VH2	451.36	4.37	0.22	3.48	99.44
VH3	447.22	4.25	0.18	3.51	97.39
VH4	450.47	4.08	0.12	3.44	99.25
VH5	455.88	4.29	0.34	3.61	99.71
VH6	446.34	4.34	0.28	3.59	98.34
VH7	449.86	4.38	0.39	3.44	101.29
VH8	447.25	4.19	0.27	3.49	97.52
VH9	451.47	4.22	0.36	3.52	99.33

Drug content:

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 97.39 – 101.29 %.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits

***In Vitro* Drug Release Studies**

Table 8.5: Dissolution Data of Valganciclovir Hydrochloride Tablets

TIME	CUMULATIVE % OF DRUG RELEASE								
	VH1	VH2	VH3	VH4	VH5	VH6	VH7	VH8	VH9
0	0	0	0	0	0	0	0	0	0
1	26.23	21.41	22.36	18.12	20.54	17.36	27.54	24.02	16.82
2	35.35	28.65	29.25	37.64	26.22	28.55	32.11	28.53	21.59
3	48.09	35.53	33.13	43.20	32.13	34.12	41.56	35.41	26.15
4	52.69	44.25	39.52	49.56	38.28	43.69	48.37	38.57	28.23
5	58.41	49.57	46.87	56.43	44.74	49.11	53.64	44.98	34.69
6	63.58	51.45	53.71	59.01	51.44	58.82	59.21	47.61	38.87
7	74.29	62.62	58.97	68.57	55.52	63.17	63.95	56.57	45.53
8	81.14	67.95	63.72	74.91	59.39	69.43	72.41	62.11	52.26
9	89.16	71.41	75.46	79.41	64.62	75.89	79.89	65.76	57.34
10	92.17	74.54	79.78	84.72	76.54	82.47	84.42	69.43	62.22
11	96.33	82.75	86.01	87.02	81.63	89.21	88.27	77.04	71.01
12	97.22	96.81	97.46	99.14	96.74	98.58	93.41	86.81	83.61

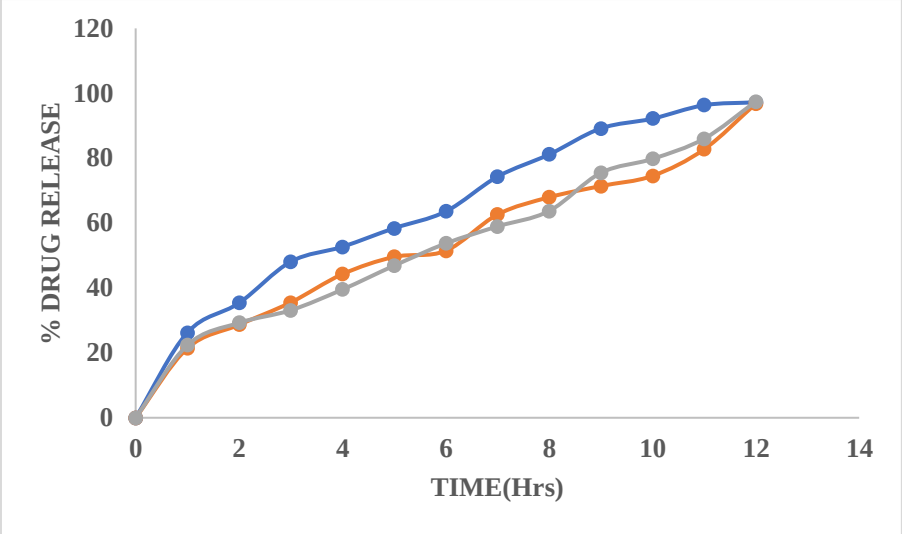

Fig 8.3: Dissolution profile of Valganciclovir Hydrochloride (VH1, VH2, VH3 formulations)

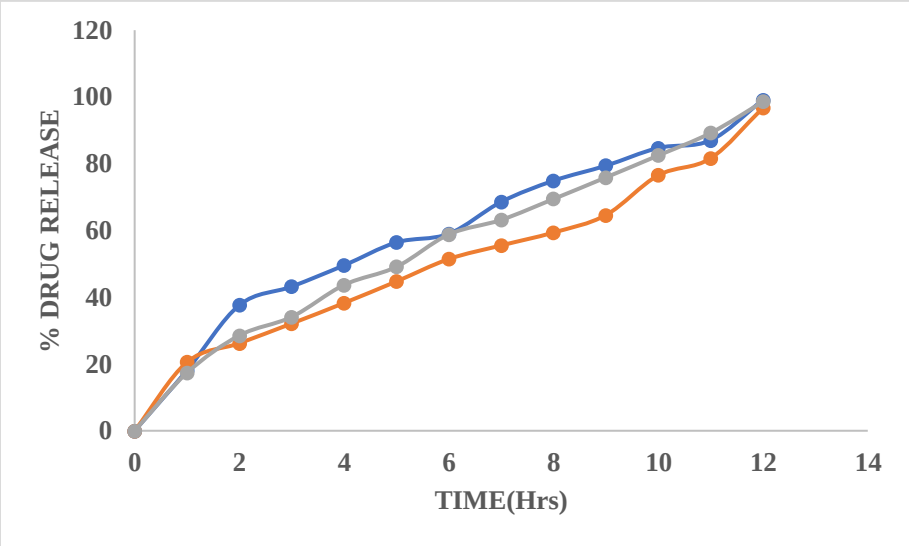

Fig 8.4: Dissolution profile of Valganciclovir Hydrochloride (VH4, VH5, VH6 formulations)

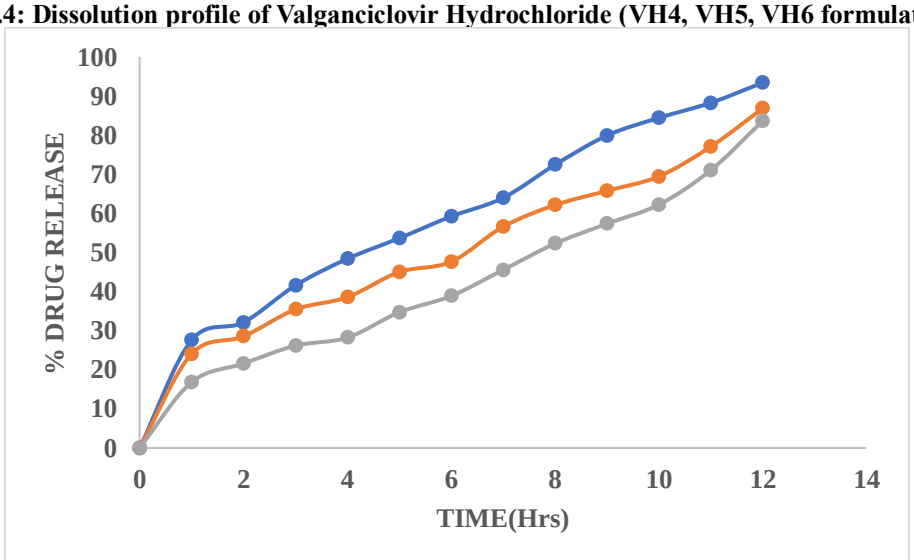

Fig 8.5: Dissolution profile of Valganciclovir Hydrochloride (VH7, VH8, VH9 formulations)

The formulations prepared with HPMC K 15 showed good retardation capacity of drug release (97.46 %) up to 12 hours in concentration 100mg whereas high concentrations (retard the drug release up to 12 hours.

The formulations prepared with Xanthan Gum showed good retardation capacity of drug release (99.14%) up to 12 hours in concentration 50 mg whereas high concentrations (retard the drug release up to 12 hours.

The formulations prepared with Guar gum showed good retardation capacity of drug release (93.41%) up to 12 hours in concentration 50mg whereas high concentrations (retard the drug release up to 12 hours.
Hence from the above dissolution data it was concluded that VH4 formulation was considered as optimized formulation because good drug release (99.14 %) in 12 hours.

Table 8.6: Release Kinetics:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
18.12	1	1.000	1.258	0.000	1.913	18.120	0.0552	-0.742	81.88	4.642	4.342	0.299
37.64	2	1.414	1.576	0.301	1.795	18.820	0.0266	-0.424	62.36	4.642	3.966	0.676
43.2	3	1.732	1.635	0.477	1.754	14.400	0.0231	-0.365	56.8	4.642	3.844	0.798
49.56	4	2.000	1.695	0.602	1.703	12.390	0.0202	-0.305	50.44	4.642	3.695	0.947
56.43	5	2.236	1.752	0.699	1.639	11.286	0.0177	-0.248	43.57	4.642	3.519	1.123
59.01	6	2.449	1.771	0.778	1.613	9.835	0.0169	-0.229	40.99	4.642	3.448	1.194
68.57	7	2.646	1.836	0.845	1.497	9.796	0.0146	-0.164	31.43	4.642	3.156	1.486
74.91	8	2.828	1.875	0.903	1.400	9.364	0.0133	-0.125	25.09	4.642	2.928	1.714
79.41	9	3.000	1.900	0.954	1.314	8.823	0.0126	-0.100	20.59	4.642	2.741	1.901
84.72	10	3.162	1.928	1.000	1.184	8.472	0.0118	-0.072	15.28	4.642	2.481	2.160
87.02	11	3.317	1.940	1.041	1.113	7.911	0.0115	-0.060	12.98	4.642	2.350	2.291
99.14	12	3.464	1.996	1.079	-0.066	8.262	0.0101	-0.004	0.86	4.642	0.951	3.691

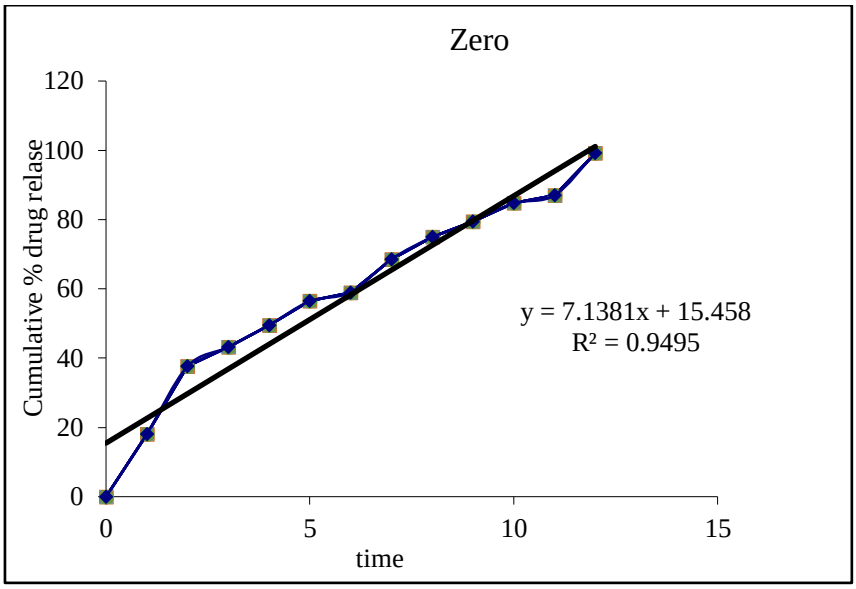

Figure 8.6: Zero order release kinetics graph

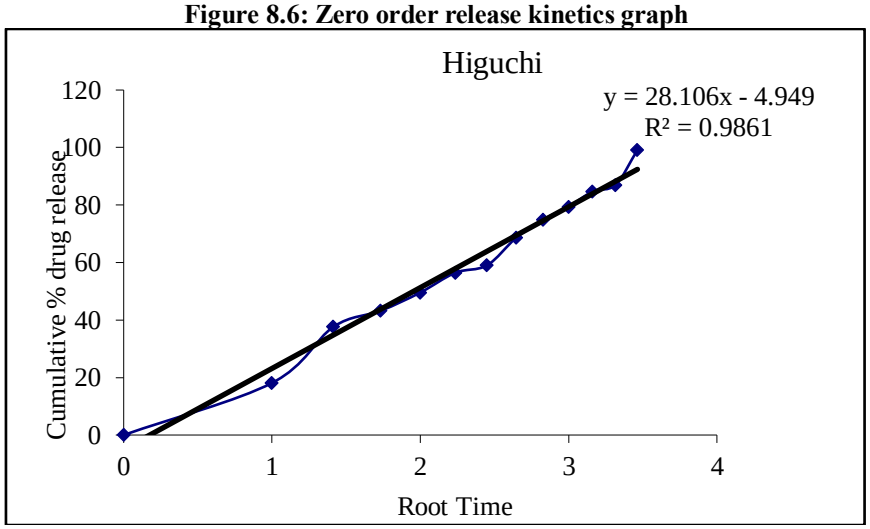

Figure 8.7: Higuchi release kinetics graph

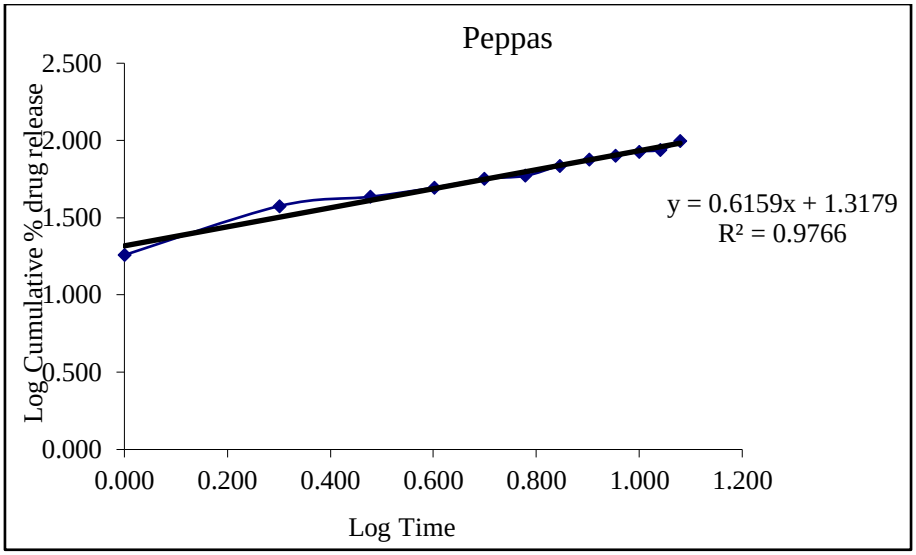

Figure 8.8: Peppas release kinetics graph

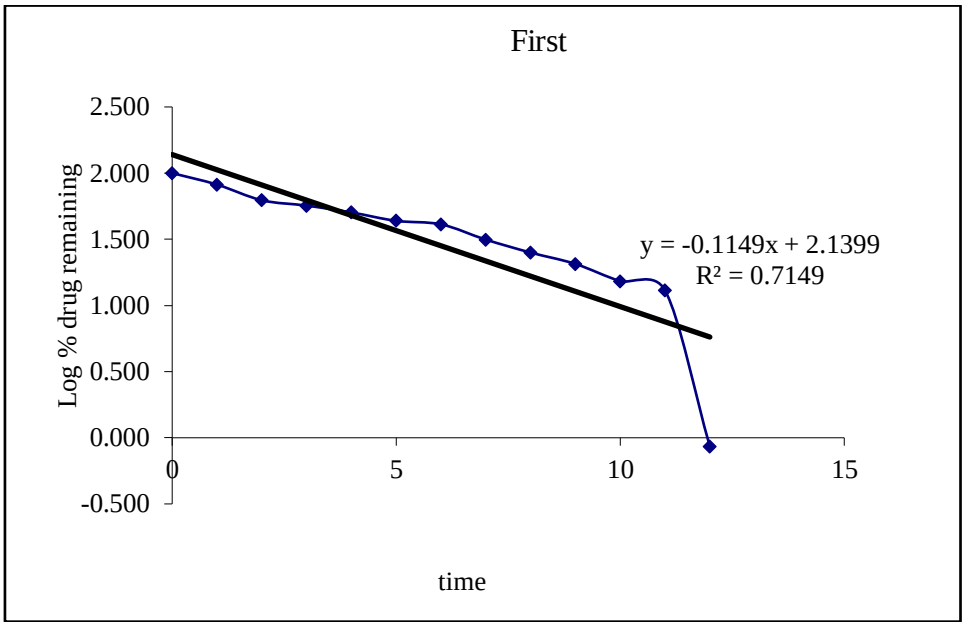

Figure 8.9: First order release kinetics graph

Optimised formulation VH4 was kept for release kinetic studies. From the above graphs it was evident that the formulation VH4 was followed Higuchi release kinetics mechanism.

Drug – Excipient compatibility studies

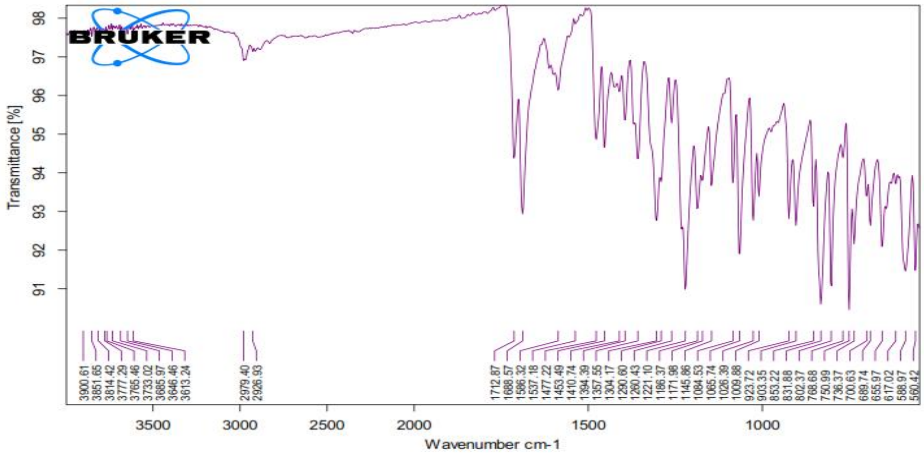

Figure 8.10: FT-TR Spectrum of Valganciclovir Hydrochloride pure drug

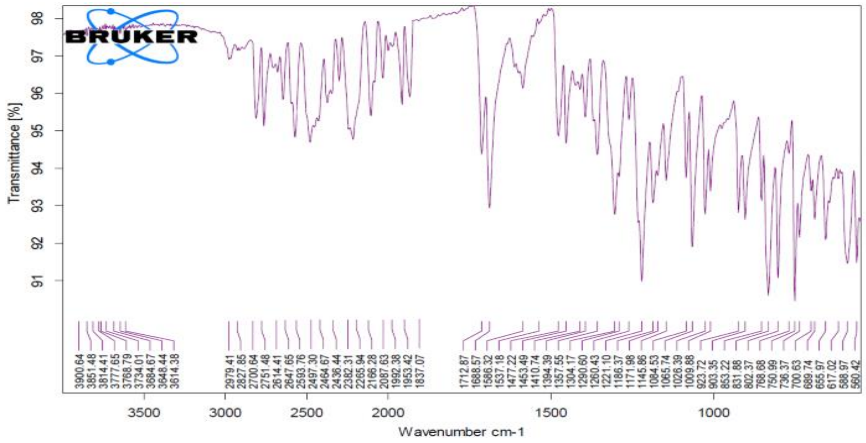

Figure 8.11: FT-IR Spectrum of Optimized Formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Valganciclovir Hydrochloride is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

9. CONCLUSION:

The present study focused on the formulation and evaluation of sustained release matrix tablets of Valganciclovir Hydrochloride using both natural and synthetic polymers. All pre-compression and post-compression parameters of the prepared formulations were found to be within the acceptable limits as per Indian Pharmacopoeia (IP) standards, indicating good flow properties and tablet integrity. Among the various formulations developed, VH4 emerged as the optimized formulation, demonstrating a sustained and controlled drug release of 99.14% over a 12-hour period. This sustained release profile suggests that VH4 can effectively maintain therapeutic drug levels for an extended duration, potentially improving patient compliance and treatment efficacy. Overall, the study successfully highlights the potential of using a combination of natural and synthetic polymers in developing an efficient sustained release drug delivery system for Valganciclovir Hydrochloride.

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