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Design And Development Of Mucoadhesive Acyclovir Tablet

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Abstract

Acyclovir, an antiviral medication commonly prescribed for the treatment of herpes simplex virus infections, is hindered by the limitations of conventional dosage forms, including the need for frequent dosing and poor patient compliance. To address these challenges, this study focused on the design and development of mucoadhesive tablets of acyclovir. These tablets were formulated using mucoadhesive polymers such as hydroxypropyl methylcellulose (HPMC) and Carbopol 934P, in combination with other excipients.Tablets were prepared by direct compression and measured for mucoadhesion strength and in vitro dissolution parameters. The index (n) in all four formulations examined varied between 0.5273 and 0.7116, demonstrating non-Fickian release behavior due to coupling diffusion or polymer relaxation, providing control and complete release for up to 12 hours. Both polymers have a significant effect on the mucoadhesion force, measured as the separation force of the prepared tablets from the sheep gastric mucosa. In addition to clarifying the effect of the two factors on various response variables, this study will also help in finding a suitable formulation with good mucoadhesive potency and controlled drug release. It is seen that with the development of acyclovir mucoadhesive tablets, it is completely released before the absorption window, thus solving the problem of incomplete release and the absorption is not stable due to the increase in the duration of the drug's residence in the intestine

Keywords: Acyclovir, Mucoadhesive Tablet, HPMC, Carbopol 934P, Drug Release.

INTRODUCTION

For systemic delivery, the oral route has become the preferred route of administration for many systemic drugs due to its ease of administration and patient compliance, and drug stores have been established that can determine and control the price of active drugs throughout the system. Promotion Delivery available. However, the most effective way to achieve the correct in vivo gastrointestinal (GIT) release time for oral administration is to control the intestinal residence time. Dosage forms with a longer retention time, commonly known as gastric retention dosage forms (GRDF).[1] When the drug is released. Therefore, they can delay drug therapy and increase patient compliance. This is particularly useful for the delivery of poorly soluble and insoluble drugs, favouring those absorbed in the upper intestines. Placement of GITs has many advantages, especially for drugs with window absorption and solubility issues. They may help improve oral administration of drugs with an "absorption window" by promoting the release of the drug long before the absorption window, thus increasing bioavailability. [2] Acyclovir, also referred to as acycloguanosine chemically (IUPAC name: 2-amino-1, 9-dihydro-9-[(2-hydroxyethoxy) methyl]-6H-purin-6-one), is used to treat HSV-2 infections as well as infections caused by the herpes simplex virus, including genital and cutaneous herpes, chicken pox (Varicella Zoster), and herpes zoster (shingles).1. At present, acyclovir is available for purchase as 200 mg capsules, 200, 400, and 800 mg tablets, and suspension for topical ointment, intravenous injection, and oral use. The most common dosage for oral acyclovir is five 200 mg tablets per day. Additionally, in immunocompetent patients with recurrent herpes simplex infections, long-term Acyclovir therapy (six months or more) is necessary.2. Many disadvantages of the currently prescribed conventional therapy include limited bioavailability (10–20%) following oral administration and very variable absorption. Additionally, there was a decrease in bioavailability with an increase in dose. Moreover, administration of the medication five times a day is necessary due to its 2.5-hour mean plasma half-life.[3]

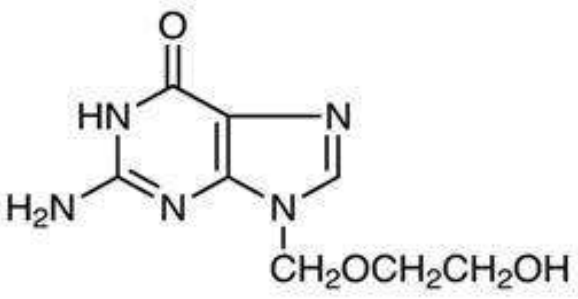


Fig-1: structure of Acyclovir

MATERIALS

Acyclovir is a gift sample from Cipla Ltd, Bangalore. Magnesium stearate was purchased from Himedia. Co., Mumbai. Carbopol 934P, microcrystalline cellulose, HPMC K100M was purchased from Loba chemie, Mumbai. Ltd. (a business entity under the banner of Avani Group of Industries). All reagents were used at analytical level. Present in table no 1. with amount in (mg).

Preparation of mucoadhesive tablets

Mucoadhesive formulations prepared using varying amounts of polymers (i.e. CP and HPMC K100M). MCC and the excipients were homogeneously blended and Add Drug then subsequently compressed into tablets.

(400mg, 10 mm diameter), using a single punch tablet compression machine.

Factorial design

A 2^2 full factorial design was constructed, where the amounts of CP (X_1) and HPMC K100M (X_2) selected as the factors. The levels of the two factors were selected on the basis of preliminary studies carried out before implementing the experimental design. Table 1 summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study.

Table. 1: Composition of tablets prepared by direct compression.

Ingredients	**F1**	**F2**	**F3**	**F4**
Acyclovir	200	200	200	200
Carbopol 934p	52	52	55	55
HPMC K100	77	80	77	80
Microcrystaliline cellulose	48	48	48	48
Magnesium sterate	4	4	4	4
Talc	q.s	q.s	q.s	q.s

Content uniformity: Two tablets from each formulation were powdered separately, and an amount equal to 100 mg of acyclovir was precisely weighed and extracted using an appropriate volume of 0.1 N HCl. Each extract was diluted appropriately and measured spectrophotometrically at 254 nm [4]

In vitro drug release studies

Using United States Pharmacopoeia (USP)-23 paddle procedures (Electrolab, TDT-06P Mumbai) and 0.1 N HCl as the dissolving medium at 50 rpm and 37°C ± 0.5°C, dissolution tests were conducted on all the produced formulations in triplicate. Every test sample was taken out in 0.5-mL aliquots at appropriate

intervals, and the volume was replaced with an equal volume of the simple dissolving media. At 254 nm, the samples underwent spectrophotometric analysis. [5]

Ex-Vivo mucoadhesion studies

The constructed bio-adhesion test apparatus was based on the operation of a double beam physical balance (Figure 1). The appropriate pan of a Vivo mucoadhesion studies steel cylinder suspended on a thin thread took the role of the physical balance. This entire setup was raised to allow room for a glass container underneath it, with roughly 0.5 cm of headroom remaining. One of the faces of a steel block was constructed with an upward projection. This was stored inside the glass container, which was positioned beneath the balance's right-hand setup. After that, the two sides were balanced.

Figure 1. Modified analytical balance used for the Mucoadhesion test.

Before the mucoadhesion evaluation research, the sheep mucus membrane was removed, cleaned (equilibrated at 37°C ± 1°C for 30 min in phosphate buffer saline solution), and securely knotted with the mucosal side facing upwards using a thread over the protrusion in the steel block. After that, the block was dropped into the glass container, which was kept at 37°C ± 1°C so that the buffer was just above the mucosal membrane's surface and kept it moist. This was then maintained beneath the balance's right-hand setup. After applying cyanoacrylate glue to adhere the tablet to the cylinder, the balancing beam was lifted. After that, a steady weight of 10 g was applied to the steel block for the duration of the 5-minute contact period. The next step was measuring the weight (in g) needed to separate the tablet from the membrane in order to determine

the mucoadhesive strength. This was done by adding weights to the left pan until the tablet detached from the mucosal surface [6,7]

Evaluation of powder blend

Angle of repose: Repose angle the funnel method was utilized to ascertain the angle of repose (Θ). A vertically adjustable funnel was used to pour the mixture through until the desired maximum cone height (h) was reached. The angle of repose was computed and the heap's radius (r) measured. Tan 0 = h/r where the angle of repose is 0.

Bulk density

Mass Density It was discovered what the loose bulk density (LBD) and tapped bulk density (TBD) were. A 10 ml measuring cylinder was filled with an appropriate amount of powder or granules from each formulation that had been gently shaken to break up any agglomerates that had formed. Following the observation of the initial volume, the cylinder was allowed to descend under its own weight at intervals of two seconds, falling to a hard surface from a height of 2.5 cm. The tapping was kept up till the loudness didn't change any more. We computed LBD and TBD using the formula below. LBD is the product of packing volume / weight of the grains or powder. TBD equals the tapped volume of the packaging / the weight of the grains or powder.

Compressibility Index

Index of Compressibility Carr's compressibility index was used to get the powder's compressibility index.

$$\text{Carr index } (\%) = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \times 100$$

Hausner Ratio

The Hausner Ratio A measure of the frictional force present in a moving powder mass is Hausner's ratio. The formula used to calculate it is as follows. Tapped density / Bulk density equals Hausner's ratio.[8]

Characterization of Mucoadhesive Tablets

Thickness

To determine thickness, five pills were randomly picked from each batch. The thickness of each tablet was measured using a screw gauge and reported in millimeters. The mean and standard deviation were calculated and published.

Weight Variation Test

1. Sample Selection: Randomly select a specified number of tablets from the batch. The number of tablets chosen for testing typically depends on the specifications outlined in regulatory guidelines or in-house quality standards.

2. Weighing: Weigh each individual tablet using a calibrated balance sensitive enough to detect small weight differences accurately. Record the weight of each tablet.

3. Calculation: Individually weighed with an electronic balance (Ohaus). The average weight was computed. The % difference from the average weight was given.

Hardness: The tablet's hardness determines its resistance to chipping, abrasion, and fracture during storage, transportation, and handling prior to use. The hardness of four randomly selected tablets from each batch was tested using a Monsanto Hardness tester and expressed in kg/cm'. The average mean and standard deviation were calculated.

Friability: The friability of tablets was determined using a Roche friabilator. The tablets should be thoroughly dedusted before testing. Six tablets were randomly selected from each batch, carefully weighed, and placed in the drum. Rotate the drum 100 times before removing the pills, weighing them again, and determining the percentage loss.

Calculations:

Calculate the percentage loss in weight using the formula:

$$\text{Friability (\%)} = \frac{\text{Initial Weight (W1)} - \text{Final Weight (W2)}}{\text{Initial Weight (W1)}} \times 100$$

In vitro disintegration time

The test was performed using disintegration apparatus. A tablet was placed in each of the six tubes of the apparatus and one perforated plastic disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was noted.

RESULTS AND DISCUSSION

The homogeneity of the weight and, consequently, content of the tablets is determined by the powder mixture's flow characteristics. Findings from the analysis of the powder blend's flow characteristics before direct compression are shown in Table 2.

Above following four formulations, the value of F1 formulation has higher dissolutiuon rate than other formulations.

Table. 2: Flow properties of powder blend

Batch	Angle of repose	Bulk density (gm/cc)	Tapped density (gm/cc)	Percent Compressibility	Hausner's ratio
F1	28.05	0.519	0.568	8.62	1.09
F2	30.18	0.611	0.742	17.65	1.21
F3	29.01	0.588	0.621	5.31	1.05
F4	33.06	0.654	0.764	14.39	1.16

The results of angle of repose, percent compressibility and Hausner's ratio ranged between 28.5 to 33.06;5.31 to 17.65 and 1.05 to 1.21 respectively. which indicate excellent flow properties.

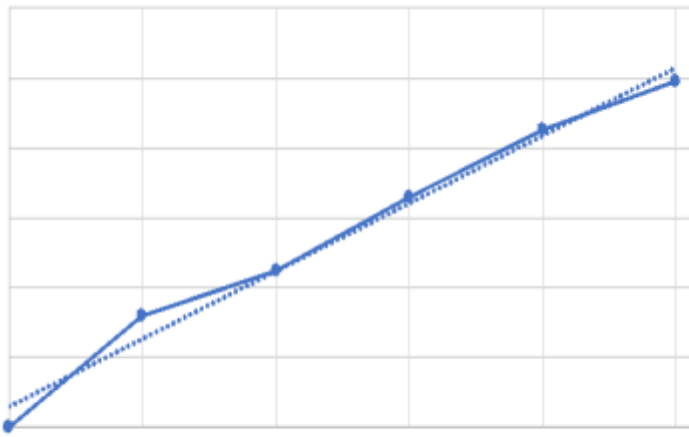
The results of evaluation of Acyclovir tablets prepared by are shown in Table .3. direct compression.

Table. 3: Results of evaluation of Acyclovir tablets prepared by direct compression.

Batch	**Thickness(mm)**	**Hardness (kg/cm^2)**	**Friability (%)**
F1	**4.9**	**5.3**	**0.690**
F2	**4.11**	**5.4**	**0.712**
F3	**4.3**	**5.1**	**0.613**
F4	**4.18**	**5.6**	**0.924**

All of the Acyclovir dispersible tablets had a smooth, glossy surface, were white, odorless, and circular in shape. They were made by both direct compression and wet granulation. Each formulation's thickness and hardness varied from 4.3 to 4.18 mm and 5.1 kg cm^2 to 5.6 cm^2, respectively All of the tablets' friability was found to be less than 1%, which is in line with IP friability requirements and validates the tablets' mechanical stability.

SR.NO	Concentration	Absorbance
1	0	0
2	5	0.032
3	10	0.0452
4	15	0.0659
5	20	0.0854
6	25	0.0994



Evaluation of formulations

Table 1. Factor combinations as per the chosen experimental design.

Batches code	**Variable level in coded Form**	
	X1	X2
F1	-1	-1
F2	1	-1
F3	-1	1
F4	1	1

Translation of code levels in actual units

Variable level	**Low (-)**	**High (+)**
XI = carbapolp 934p concentration %w/w	52	55
X2 = HPMC K100 Concentration %w/w	77	80

Table no1.Translation of coded value in actual unit

Dissolution Test Formulation:

F1 Formulation:

Time	Absorbance	Concentration ug/ml	Concentration 10 ug/ml	Concentration Mg/10ml	Concentration Mg/900ml	CDR	%CDR
30	0.010	0.974	9.74	0.00974	8.766	8.766	4.38
1	0.019	3.282	32.82	0.0328	29.52	29.52	14.76
2	0.026	5.076	50.76	0.0507	45.63	45.66	22.83
3	0.039	8.410	84.10	0.0841	75.69	75.740	37.87
4	0.047	10.461	104.61	0.10461	94.14	94.22	47.11
5	0.059	13.538	135.38	0.135	121.5	121.60	52.35
6	0.068	15.846	158.46	0.158	142.2	142.33	61.16
7	0.075	17.641	176.41	0.176	158.4	158.55	70.27
8	0.082	19.435	194.35	0.194	174.6	174.77	75.11
9	0.089	21.230	212.30	0.212	190.8	190.99	81.21
10	0.091	21.743	217.43	0.217	195.3	195.51	86.26
11	0.100	24.05	240.5	0.240	216	216.21	92.11

F2 Formulatiuon:

Time	Absorbance	Concentration ug/ml	Concentration 10 ug/ml	Concentration Mg/10ml	Concentration Mg/900ml	CDR	%CDR
30	0.028	5.58	55.8	0.0558	15.22	50.22	25.11
1	0.033	6.87	68.7	0.0687	61.83	61.88	35.02
2	0.048	10.71	107.1	0.1071	96.39	96.45	37.04
3	0.059	13.53	135.3	0.135	121.5	120.60	40.12
4	0.061	14.05	140.5	0.140	126	126.13	45.20

5	0.071	16.61	166.1	0.166	149.5	149.54	51.02
6	0.078	18.41	184.1	0.1984	165.6	165.766	60.114
7	0.083	19.69	196.9	0.196	176.4	176.58	75.14
8	0.085	20.20	202.0	0.202	181.8	181.59	81.52
9	0.090	21.48	214.8	0.214	192.6	192.80	85.02
10	0.095	22.76	227.6	0.227	205.3	204.59	88.12

F3 Formulation:

Time	Absorbance	Concentration ug/ml	Concentration 10 ug/ml	Concentration Mg/10ml	Concentration Mg/900ml	CDR	%CDR
30	0.020	3.53	35.3	0.0353	31.76	31.76	15.88
1	0.025	4.820	48.20	0.0482	43.38	43.41	21.07
2	0.038	8.153	81.53	0.08153	73.37	73.41	24.88
3	0.045	9.94	90.4	0.0994	89.46	89.541	30.08
4	0.057	13.02	130.2	0.1302	117.18	117.27	40.08
5	0.065	15.076	150.76	0.150	135	135.13	46.28
6	0.071	16.613	166.19	0.16613	149.4	149.55	50.02
7	0.015	17.64	176.4	0.1764	158.4	158.56	52.35
8	0.081	19.17	191.7	0.1917	171.9	172.07	65.80
9	0.089	21.23	212.3	0.2123	190.8	190.99	75.95
10	0.090	21.48	214.8	0.2148	192.6	192.8	82.66

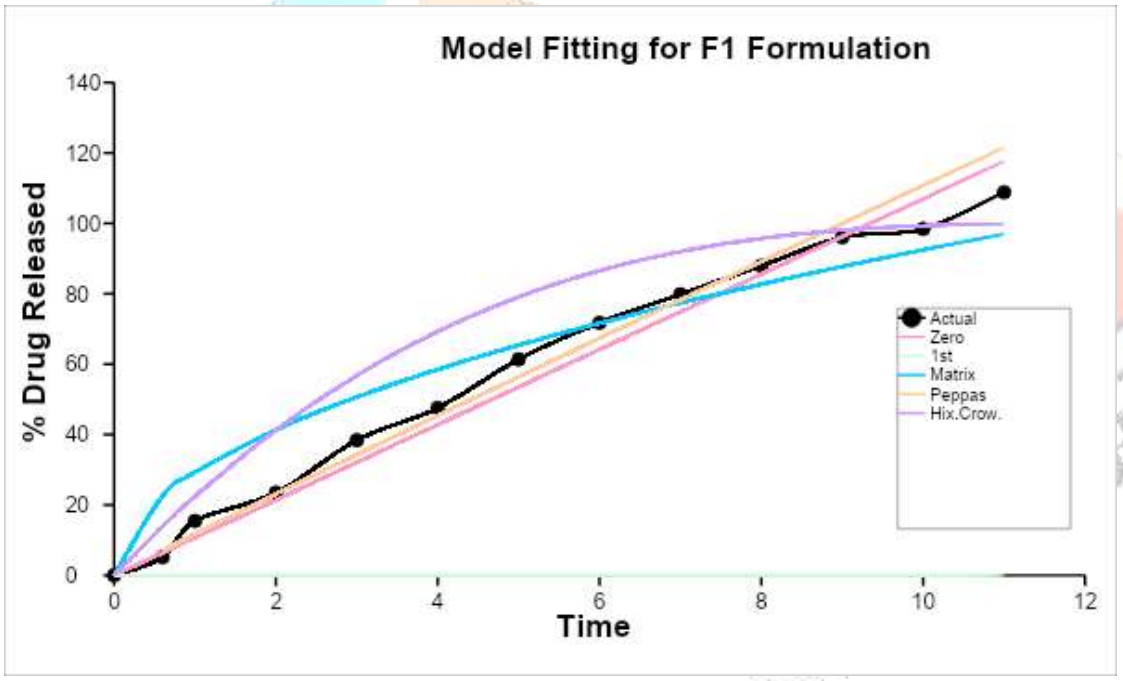
F4 Formulation:

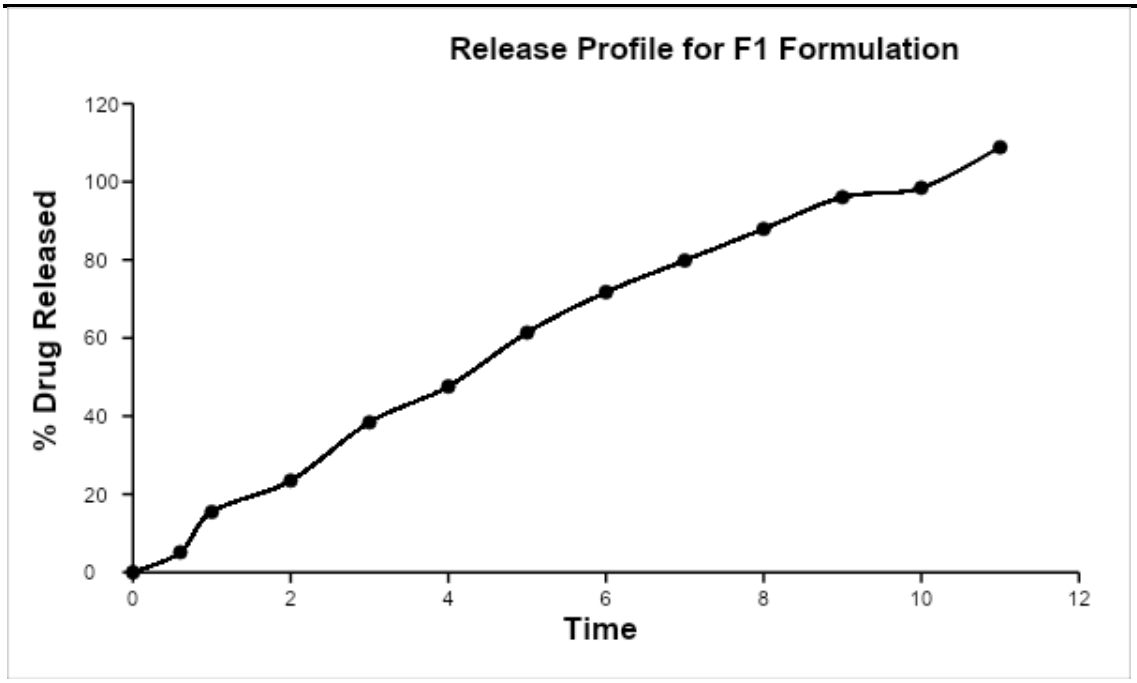
Time	Absorbance	Concentration ug/ml	Concentration 10 ug/ml	Concentration Mg/10ml	Concentration Mg/900ml	CDR	%CDR
30	0.05	-0.307	-3.07	-0.00307	-2.763	-2.763	-1.38
1	0.010	0.974	9.74	0.00974	8.766	8.76	4.38
2	0.018	3.025	30.25	0.03025	27.22	27.22	13.61
3	0.025	4.820	48.20	0.0482	43.38	43.41	21.70
4	0.038	8.153	81.53	0.08153	73.37	73.41	36.70
5	0.046	10.20	102.0	0.102	91.8	91.88	41.24
6	0.051	11.48	114.8	0.1148	103.32	103.42	47.04
7	0.055	12.51	125.1	0.12511	112.5	112.61	56.21
8	0.066	15.33	153.3	0.1533	137.7	137.82	67.08
9	0.075	17.641	176.4	0.1764	158.4	158.55	74.56
10	0.080	18.92	189.2	0.1892	170.1	170.27	78.22

RESULT :

F1 FORMULATION

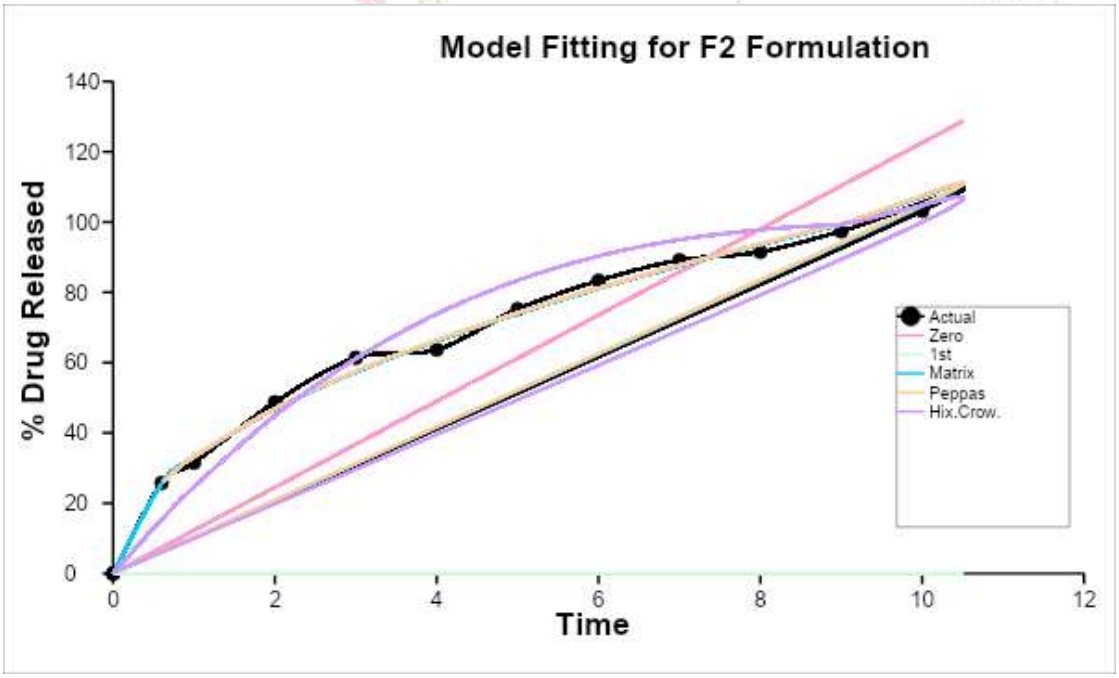
	R	k
Zero order	0.9883	10.6972
T-test	21.513	(Passes)
1st order	0.9823	#NUM!
T-test	#NUM!	#NUM!
Matrix	0.9582	29.2432
T-test	11.110	(Passes)
Peppas	0.9872	11.7781
T-test	20.540	(Passes)
Hix.Crow.	0.8817	-0.0813
T-test	6.198	(Passes)

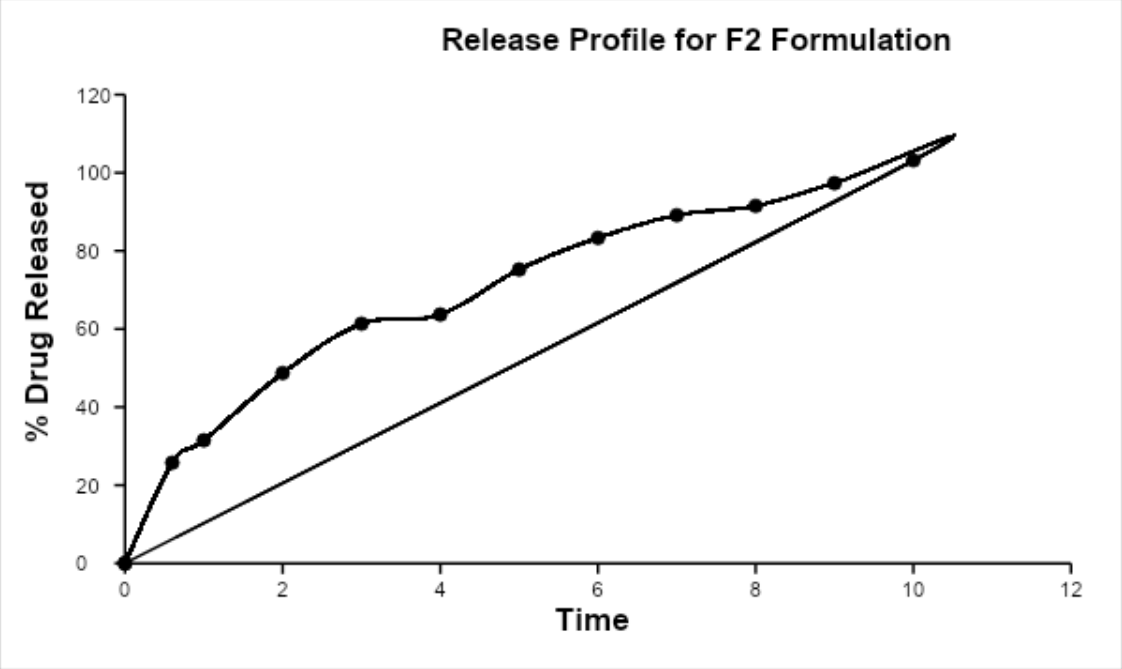




F2 FORMULATION

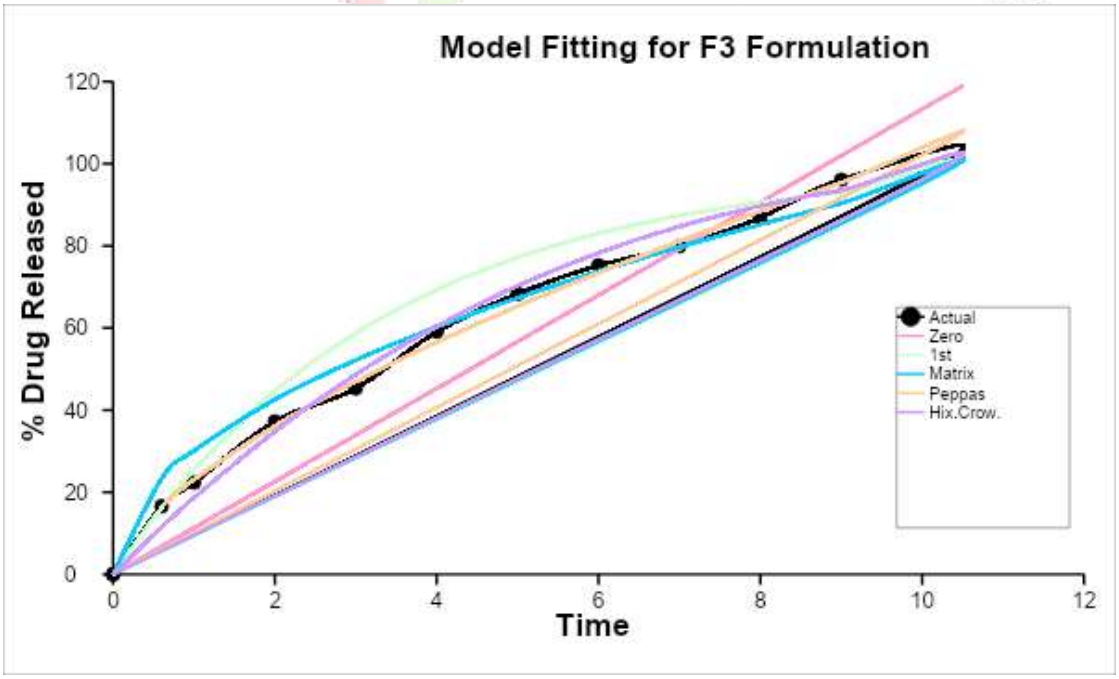
	R	k
Zero order	0.8582	12.2559
T-test	5.286	(Passes)
1st order	0.8562	#NUM!
T-test	#NUM!	#NUM!
Matrix	0.9979	33.0786
T-test	48.668	(Passes)
Peppas	0.9971	33.2112
T-test	41.358	(Passes)
Hix.Crow.	0.9068	-0.0901
T-test	6.801	(Passes)

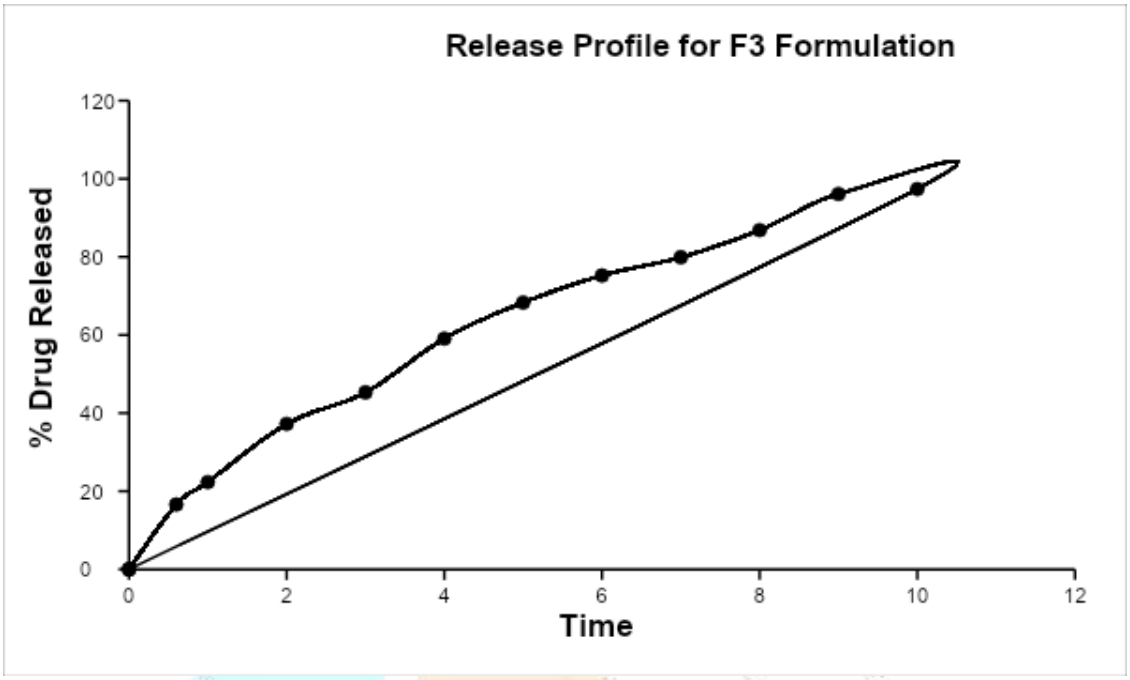




F3 FORMULATION

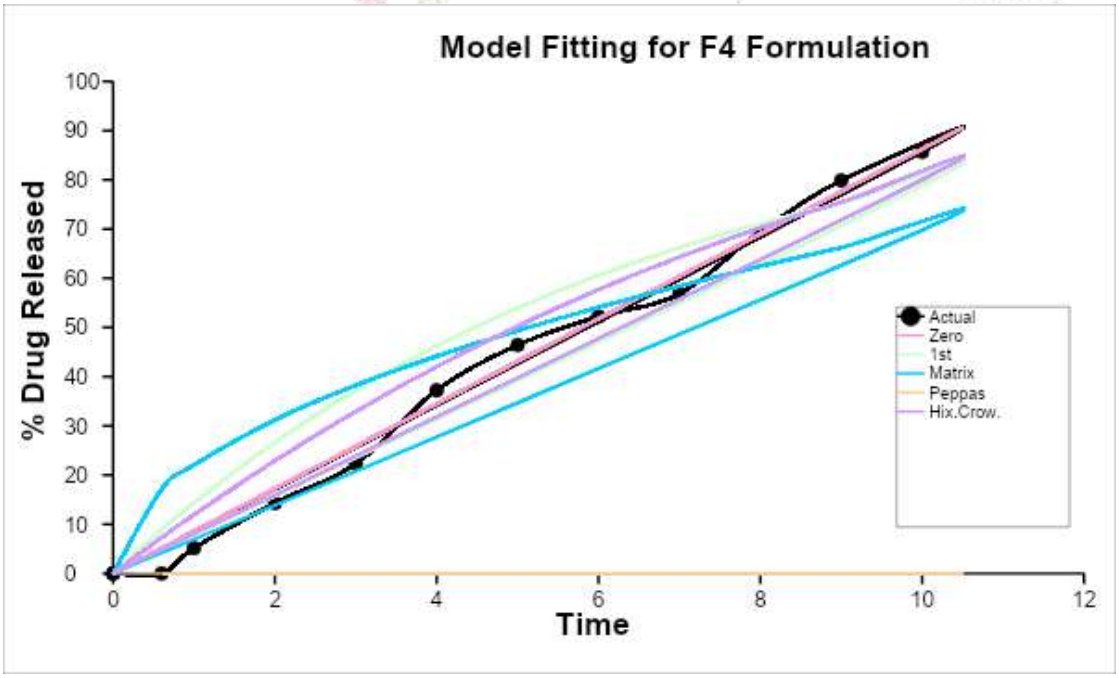
	R	k
Zero order	0.9454	11.3258
T-test	9.171	(Passes)
1st order	0.9474	-0.2954
T-test	9.365	(Passes)
Matrix	0.9902	30.1205
T-test	22.447	(Passes)
Peppas	0.9985	23.1011
T-test	57.476	(Passes)
Hix.Crow.	0.9901	-0.0664
T-test	22.256	(Passes)

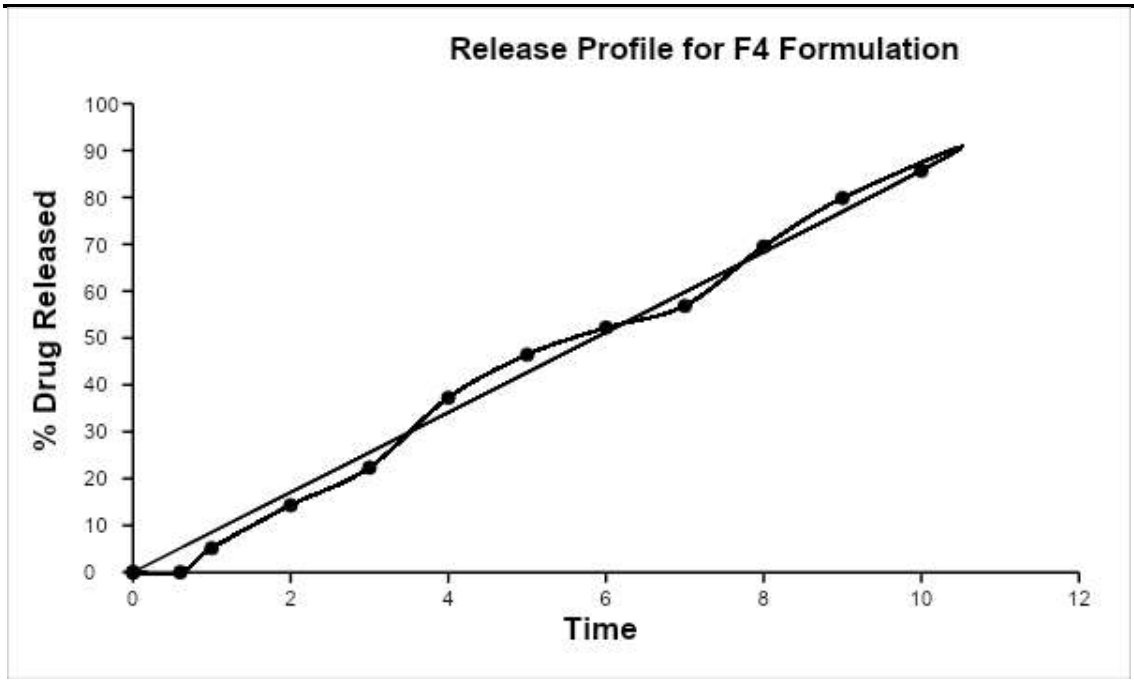




F4 FORMULATION

	R	k
Zero order	0.9951	8.6271
T-test	31.689	(Passes)
1st order	0.9513	-0.1552
T-test	9.756	(Passes)
Matrix	0.9157	22.0758
T-test	7.206	(Passes)
Peppas	0.9678	#NUM!
T-test	#NUM!	#NUM!
Hix.Crow.	0.9760	-0.0415
T-test	14.181	(Passes)





CONCLUSION

In summary According to this investigation, the produced acyclovir tablets may exhibit a regulated pattern of drug release thanks to the polymers Carbopol-934P and HPMC K 100M. This formulation's strong mucoadhesive strength is expected to lengthen its stay in the gastrointestinal system, ultimately increasing the amount of bioavailability. However, to achieve optimal mucoadhesion and release, the different amounts of the two polymers must be properly balanced. Conclusion: By creating mucoadhesive acyclovir tablets, the problem of incomplete drug release and irregular absorption can be resolved by lengthening the drug's retention period in the gastrointestinal tract. This ensures that the drug releases completely prior to the absorption window.

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