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FORMULATION AND EVALUATION OF GASTRO-RETENTIVE MUCOADHESIVE TABLETS OF ZIDOVUDINE

Kalasare Shweta N.*[1] and Deshpande Sanjeev V.[1]

[1]Padm. Dr. D. Y. Patil College Of Pharmacy, Akurdi, Pune-411044.

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***Correspondence for Author**
Kalasare Shweta N.
Padm. Dr. D. Y. Patil College Of Pharmacy, Akurdi, Pune-411044.

ABSTRACT

Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive oral drug delivery system prolongs the residence time, absorption and facilitates an intimate contact of the dosage form with the absorption surface. The aim of the present study was to develop mucoadhesive tablets of Zidovudine which were designed to prolong the gastric residence time after oral administration. Zidovudine is a pyrimidine nucleoside analogue active against HIV. Mucoadhesive tablets of Zidovudine were prepared by using different polymeric ratios of Polycarbophil, Carbopol 971G, Carbopol 934P and HPMC K4M. The tablets were evaluated for thickness, hardness, weight variation, swelling index, mucoadhesive strength, drug content uniformity, and in vitro drug release. Formulation of A9 which was formulated by using polymers Polycarbophil and HPMC K4M provided controlled release of Zidovudine over the period of 12 hrs. The cumulative % of drug release of formulation A9 was 97.01.

KEYWORDS: Mucoadhesion, Zidovudine, Oral controlled release, Evaluation parameters, functional polymers, drug delivery.

INTRODUCTION

Bioadhesion or mucoadhesion is generally the ability of the biological or synthetic material to "stick" to a mucus membrane resulting in an adhesion of material to tissue for a prolonged period of time.[1]

Approaches[2]

- Multiunit dosage forms

- Intragastric floating drug delivery system (IGFT)
- Sandwich – type polymeric delivery system, and
- Use of bioadhesive polymers.

Consideration for the formulation of sustained release dosage form[3]

- If the active compound has a long half-life (over 6 hrs.), it is sustained on its own. The biological half-life of Zidovudine is 3-5 hrs. in which is in desirable limit required for sustained release matrix tablet.
- The plasma protein binding also plays an important role while designing sustained release dosage form. Zidovudine has very low plasma protein binding which is about 30-38% which is desirable for sustained release dosage form.
- On the basis of protein binding we can say that Zidovudine is a good candidate for designing the sustained release dosage form.
- If the pharmacological activity of active compound is not related to its blood level then time releasing has no purpose.
- If the absorption of active compound involves an active transport then the development of time release product may be problematic.
- Finally, if the active compound has short half-life, it would require large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity, otherwise the risk is unwarranted and another mode of administration would be recommended.
- It is expected that "mucoadhesive delivery system" will bring the drug in the vicinity of absorption window and the rate and extent of Zidovudine will be expected to be increased. It is also expected that the increased plasma concentration (rate and extent) will be in the therapeutic window. This will reduce the dose of Zidovudine and treatment will be cost effective.
- Zidovudine is the drug of choice in the treatment of HIV Infection as the reverse transcripted enzyme inhibitor.
- In the present work, attempts are made in order to increase the rate and extent of absorption of Zidovudine by formulating it in a mucoadhesive delivery system. Reduced dose of the drug will decrease the development of the resistance and toxicity to Zidovudine.

MATERIAL AND METHODS

Materials

Zidovudine was received as a gift sample from Cipla ltd, Goa. HPMC K4M were obtained from Colorcorn pvt ltd. Goa, Polycarbophil, Carbopol 931P and Carbopol 71G were obtained from Lubrizol Mumbai, Magnesium Stearate and Talc S.D.Fine chem. Mumbai. All the reagents and chemical used were of analytical grade.

METHODS

FTIR SPECTROSCOPY

The combination spectra of the drug and polymer are shown the figure 8.3 which indicates that there is no interaction between Zidovudine and polymer when compared with infrared spectrum of pure drug as all functional group frequencies were present.

FORMULATION OF TABLET

Table No.1 all the ingredients were firstly weighed and mixed in mortar as the quantity given. The mixture was passed through the 60# Sieve and magnesium stearate, talc 1% was added and blended. The homogeneously blended mixture was compressed in Lab press with the 12 mm flat punch.

DIRECT COMPRESSION METHOD[4]

The tablets were formulated employing direct compression method using 12 mm flat-faced punches. It is the process by which tablets are compressed directly from mixtures of the drug and excipients without granulation.

The steps involved are as follows

EVALUATION PARAMETER

PRECOMPRESSION PARAMETER[5,6]

BULK DENSITY (DB): It is the ratio of total mass of powder to the bulk volume of powder.

It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by,

$$\text{Bulk Density} = \frac{\text{Mass}}{\text{Bulk volume}}$$

TAPPED DENSITY (DT): It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by,

$$\text{Tapped Density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

ANGLE OF REPOSE: The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane and it is given as, $\theta = \tan^{-1}\frac{h}{r}$

Where,

θis the angle of repose

h is the height in cm

r is the radius.

CARR'S INDEX (I): It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by,

$$I = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

POST COMPRESSION PARAMETERS[5,6]

THICKNESS & DIAMETER

Thickness and diameter of tablets were determined using Vernier calliper. Five tablets from each batch were used, and average values were calculated.

HARDNESS: The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in Kg / cm^2.

FRIABILITY (F)

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator.

The friabilator was operated at 25 rpm for four min. The tablets were weighed again (W_{final}). The percentage friability was then calculated by:

$$F = \frac{\text{Initial weight of tablet} - \text{Final weight of tablet}}{\text{Initial Weight of tablet}} \times 100$$

WEIGHT VARIATION TEST[7,8] 20 tablets of each formulation type were weighed individually using an electronic balance (0.01mg sensitivity). The average weight was calculated and individual tablet weight was compared with the average value and the deviation was recorded.

MUCOADHESIVE STRENGTH[9,10,11]

Mucoadhesive strength of the tablet was measured on the modified physical balance, the design used for measuring the mucoadhesive strength. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media 0.1N HCl pH 1.2, which was then placed below right side of the balance.Goat stomach mucosa was used as a model membrane and buffer media 0.1N HCl pH 1.2 was used as moistening fluid. The goat stomach mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The underlying mucous membrane was separated using surgical blade and washed thoroughly with buffer media 0.1N HCl pH 1.2. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in glass beaker. The beaker was filled with phosphate buffer media 0.1N HCl pH 1.2 up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments.The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established.A preload of 10 mg was placed on the slide for 5 min (preload time) to established adhesion bonding between mucoadhesive tablet and goat stomach mucosa.The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when mucoadhesive tablet was detached from the goat stomach mucosa. The weight of water required to detach mucoadhesive tablet from

stomach mucosa was noted as mucoadhesive strength in grams. From the mucoadhesive strength following parameter was calculated.

$$\text{Force of adhesion}(N) = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81$$

$$\text{Bond strength}\left(\frac{N}{m2}\right) = \frac{\text{Force of adhesion (N)}}{\text{Surface area of tablet (m2)}}$$

SWELLING INDEX[12]

Method: For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of buffer media. After each interval the tablet was removed from beaker and weighed again upto 8 hours. The swelling index was calculated using following formula.

$$\text{Swelling Index}(S.I.) = \frac{(Wt - Wo)}{Wo} \text{ X } 100$$

Where,

S.I. = Swelling index

W_t = Weight of tablet at time t

W_o = Weight of tablet before placing in the beaker

DRUG CONTENT UNIFORMITY[7,8]

Assay: 9 tablets were weighed and triturated. The tablet triturate equivalent to 100 mg of the drug was weighed accurately, dissolved in pH 1.2 buffer and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ml with simulated gastric fluid pH 1.2. Absorbance was read at 266 nm against the reagent blank, and the concentrations of Zidovudine in mcg/ml were determined by using the regression equation.

Drug content in mg/tablet = conc. µg/ml*dilution factor

% Drug content = drug content in mg*100/label claim.

IN VITRO DISSOLUTION STUDIES[13,14]

The In vitro dissolution study was carried out in USP Dissolution Test Apparatus, Type 2 (paddle type) 900ml of simulated gastric fluid pH 1.2 (without enzymes) was used as dissolution medium. The temperature of dissolution media was maintained at 37 ± 0.5 ^{O}C. The paddle rotation speed was kept at 50 rpm. One tablet at a time was weighed and taken for study. 5 ml of the sample was withdrawn at every 1-hour interval for 12 hours and the same volume was replaced with dissolution media. The sample withdrawn was diluted to suitable volume with simulated gastric fluid and the absorbance was recorded at 266nm using UV

spectrophotometer.Aliquots were withdrawn at 1 hr interval from a zone midway between the surface of dissolution medium and top of the rotating paddle not less than 1 cm apart. Suitable replacements with fresh medium were also made. Each sample solution was filtered through Whatman filter paper. The absorbance was measured after proper dilution with dissolution media at 266 nm for buffer pH 1.2 using spectrophometer. Drug concentrations in the samples were determined from standard curve.

KINETIC MODELING OF DRUG RELEASE[15]

All the nine formulation of prepared mucoadhesive tablets of Zidovudine were subjected to in-vitro release studies using Electrolab 08 dissolution apparatus (USP). The dissolution medium consisted of 900 ml of simulated gastric fluid pH 1.2 (without enzymes) for 12 hrs.

The results obtained in in-vitro release studies were plotted in different model of data treatment as follows

a) Cumulative percent drug released vs. time (zero order rate kinetics)
b) Log cumulative percent drug retained vs. time (First Order rate Kinetics)
c) Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
d) Logs of cumulative % release vs. log time (Peppas Exponential Equation.

RESULT

Table No.1: Mucoadhesive Tablet Formulation

Form. No.	INGREDIENTS (mg)							Total weight (mg)	Drug: Polymer Ratio (Drug:Polycarbophill:Carbopol971G:Carbopol934P:HPMCK4M)
	Zidovudine	Polycarbophil	Carbopol 971 G	carbopol 934 P	HPMCK4M	Mg. Stearate	Talc		
A1	200	-	150	-	50	05	05	410	1:0:0.75:0:0.25
A2	200	-	50	-	150	05	05	410	1:0:0.25:0:0.75
A3	200	-	100	-	100	05	05	410	1:0:0.5:0:0.5
A4	200	-	-	50	150	05	05	410	1:0:0:0.25:0.75
A5	200	-	-	150	50	05	05	410	1:0:0:0.75:0.25
A6	200	-	-	100	100	05	05	410	1:0:0:0.5:0.5
A7	200	100	-	-	100	05	05	410	1:0.5:0:0:0.5
A8	200	50	-	-	150	05	05	410	1:0.25:0:0:075
A9	200	150	-	-	50	05	05	410	1:0.75:0:0:0.25

Table No.2: Powder evaluation test results

Formulation No.	Angle of repose	Bulk density	Tap density	% Compressibility
A1	26.32 ^{o}	0.69	0.79	13.41
A2	26.92 ^{o}	0.67	0.71	6.84
A3	28.56 ^{o}	0.71	0.76	14.81
A4	26.72 ^{o}	0.70	0.74	10.25
A5	28.32 ^{o}	0.72	0.78	9.63
A6	28.64 ^{o}	0.77	0.86	12.35
A7	26.84 ^{o}	0.71	0.78	9.30
A8	26.56 ^{o}	0.73	0.79	20.25
A9	25.34 ^{o}	0.76	0.82	14.84

Table No.3: Tablet evaluation test results

Sr. no.	Form. No.	Hardness Kg/Cm^2 Mean ± S.D. (N=3)	% Friability	Thickness (mm) Mean ± S.D. (N=3)	Weight variation (mg) Mean ± S.D. (N=20)	% Drug Content (N=3)
1.	A1	5.3 ± 0.2	0.42	3.6 ± 0.1	410 ± 12	100.46
2.	A2	7.1 ± 0.2	0.33	3.7 ± 0.2	410± 17	99.70
3.	A3	6.4 ± 0.2	0.19	3.6 ± 0.2	410 ± 10	99.51
4.	A4	6.5 ± 0.2	0.33	3.6 ± 0.3	410 ± 15	99.62
5.	A5	6.2 ± 0.3	0.30	3.7 ± 0.3	410 ± 08	100.75
6.	A6	7.3 ± 0.1	0.23	3.7 ± 0.2	410 ± 15	98.90
7.	A7	6.8 ± 0.2	0.20	3.5 ± 0.2	410 ± 13	101.02
8.	A8	7.1 ± 0.2	0.25	3.6± 0.2	410 ± 17	100.41
9.	A9	7.3 ± 0.2	0.20	3.5 ± 0.1	410 ± 10	100.25

Table No.4: Swelling Test Result

Form. No.	TIME (hrs)									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
A1	0	14	23	46	49	56	58	59	60	61
A2	0	10	19	40	43	46	48	50	52	53
A3	0	12	21	42	45	50	52	53	54	55
A4	0	8	17	42	45	50	52	53	54	55
A5	0	11	22	46	49	54	56	57	58	60
A6	0	10	19	45	48	53	55	56	57	59
A7	0	16	28	50	53	58	60	61	62	63
A8	0	14	24	47	50	56	58	59	60	62
A9	0	18	31	52	55	60	62	63	64	65

Table No.5: Mucoadhesive strength of formulation

Formulation No.	Mucoadhesive Strength (gm) (N=3)
A1	14.35 ± 2.11
A2	15.26 ± 2.55
A3	16.40 ± 3.15
A4	11.45 ± 2.36
A5	12.65 ± 2.54
A6	13.34 ± 3.12
A7	15.86 ± 3.56
A8	16.45 ± 2.45
A9	17.80 ± 2.73

Table No.6: Dissolution Profile of oral mucoadhesive tablet formulation A1 to A5

Sr. No.	Time (hr)	% Cumulative Drug Released								
		A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1	18.2	16.81	10.51	8.94	15.21	10.41	7.31	4.33	6.84
3	2	30.09	24.2	25.94	18.05	31.09	22.42	15.25	6.26	10.28
4	3	42.54	27.31	34.57	24.73	43.14	26.03	24.31	8.14	16.2
5	4	47.7	33.57	40.51	31.13	49.51	32.54	32.34	12.87	19.85
6	5	56.23	39.24	45.9	37.22	52.25	37.29	39.6	16.84	24.23
7	6	64.59	45.2	51.13	48.27	64.41	43.41	43.01	26.87	29.84
8	7	69.03	52.91	58.78	49.25	68.86	48.67	48.46	49.01	39.05
9	8	77.34	56.49	63.01	56.88	75.81	55.93	56.42	50.78	55.22
10	9	81.57	62.83	68.88	65.51	82.86	59.46	65.84	58.46	69.51
11	10	86.09	68.16	72.29	69.89	85.92	67.36	74.65	66.84	85.45
12	11	89.03	73.81	77.44	77.81	89.01	83.71	82.86	76.86	92.89
13	12	92.31	84.55	85.89	89.81	92.19	90.06	90.02	84.11	97.01

Table No.7: Drug release kinetics of formulation (R-Value)

Formulation Code	Mathematical Models. (Kinetics)					
	Zero Order	First Order	Higuchi	Peppas		Best Fit Model
				r Value	n Value	
A1	0.9455	0.9769	0.9884	0.9976	0.6736	Peppas
A2	0.9818	0.9530	0.9632	0.9885	0.6670	Peppas
A3	0.9708	0.9737	0.9763	0.9874	0.7888	Peppas
A4	0.9967	0.9121	0.9351	0.9982	0.9144	Peppas
A5	0.9481	0.9756	0.9855	0.9909	0.7139	Peppas
A6	0.9897	0.8900	0.9316	0.9914	0.8255	Peppas
A7	0.9978	0.9126	0.9237	0.9979	1.0060	Peppas
A8	0.9597	0.8945	0.8275	0.9709	1.3833	Peppas
A9	0.9606	0.8026	0.8316	0.9764	1.1694	Peppas

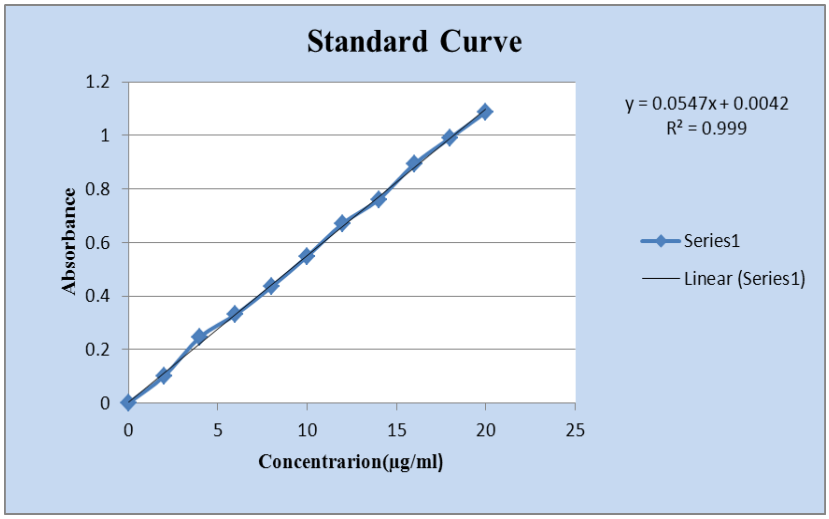

Fig.No.1: Standard curve of Zidovudine pH1.2

Table No.8: Stability Study: A9 Stored at 25^0C/60% RH.

Form. Code	Tested after time in days	Hardness (kg/cm^2)	% Friability	Mucoadhesive Strength (gm)	Drug release %
A9	20	7.3 ± 0.2	0.16	17.80 ± 3	97.01
	40	7.3 ± 0.2	0.16	17.60 ± 2	96.11
	60	7.3 ± 0.2	0.19	17.40 ± 2	96.97

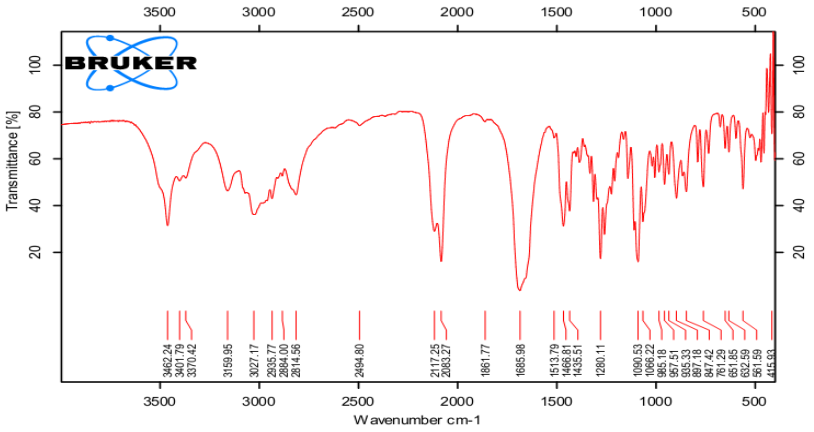

Fig.No.2: FTIR spectra of Zidovudine

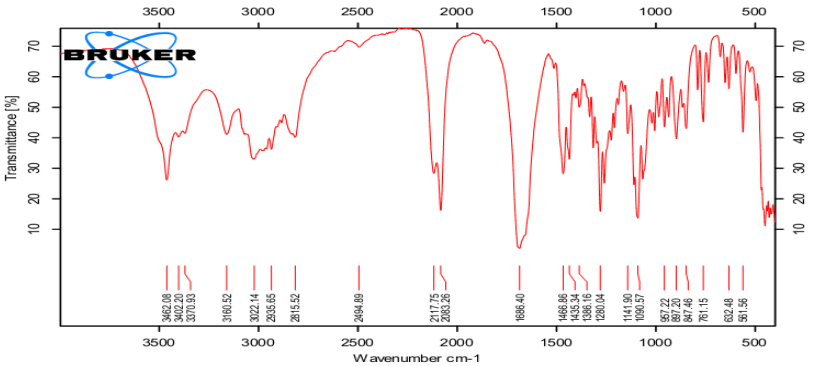

Fig.No.3: FTIR Spectra of Drug+Polymer

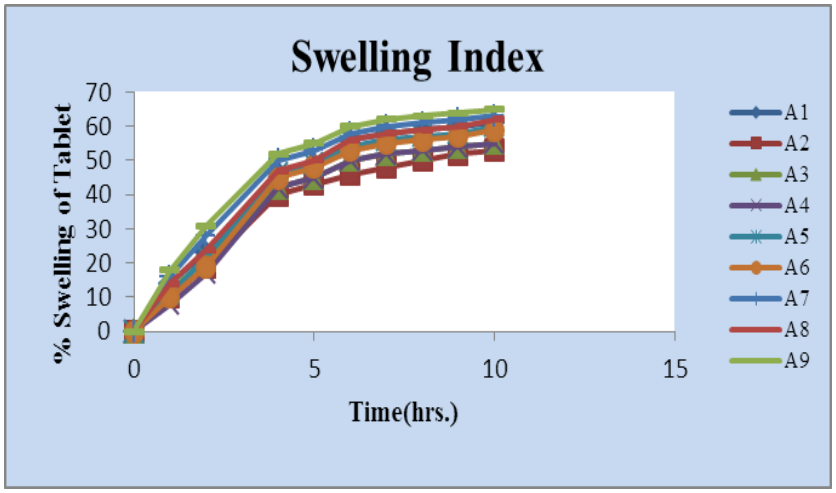

Fig.No.4: Percentage swelling Vs time of formulation A1 to A9.

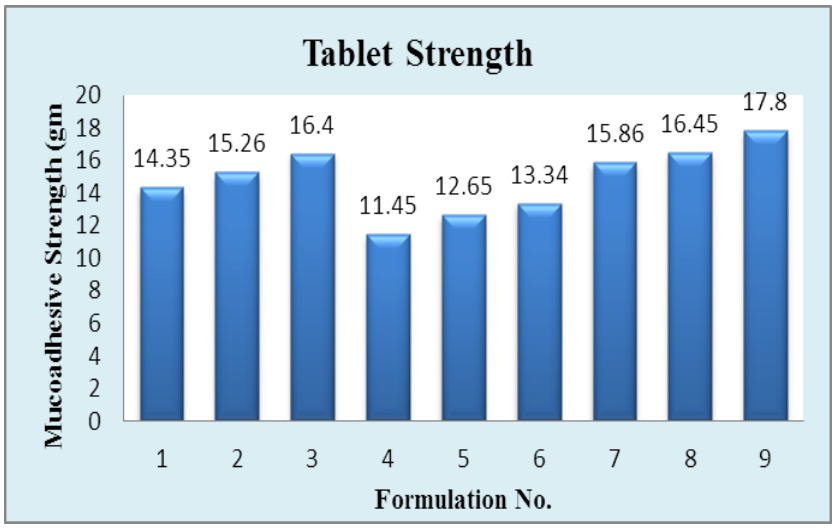

Fig.No.5: Mucoadhesive Tablet Strength.

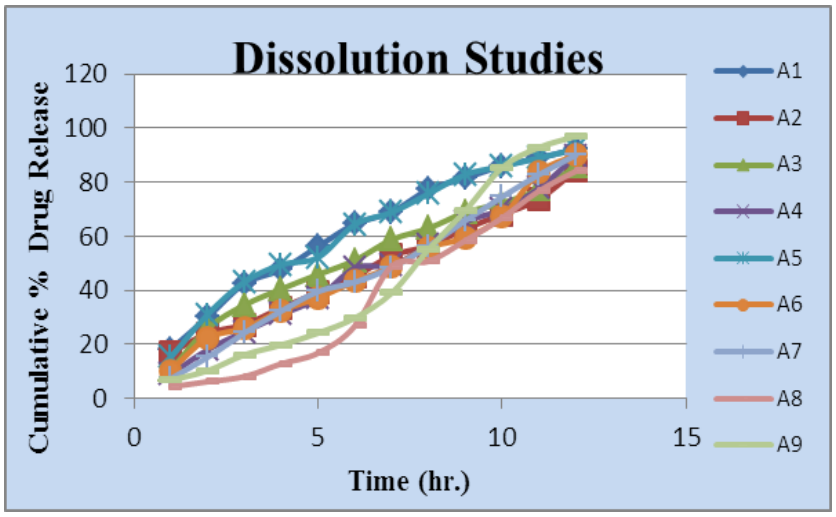

Fig.No.6: Dissolution test result A1 to A9.

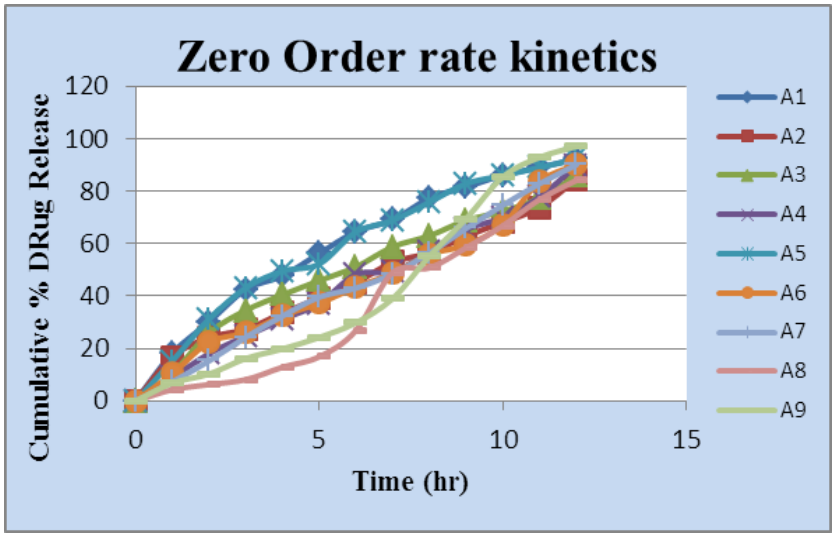

Fig.No.7: Zero Order rate kinetics.

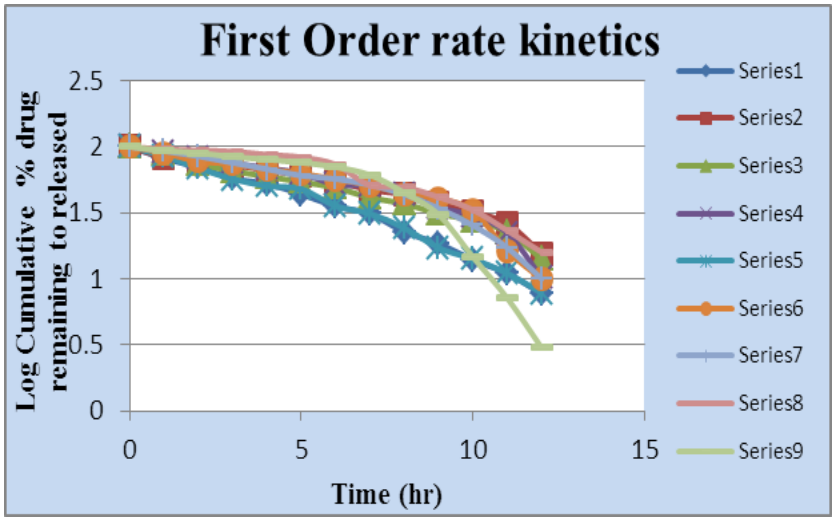

Fig.No.8: First Order rate kinetics

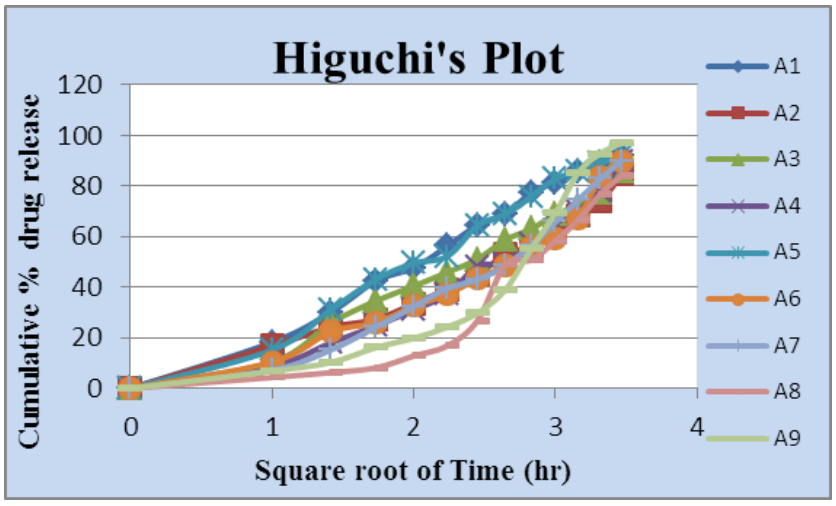

Fig.No.9: Higuchi's Plot.

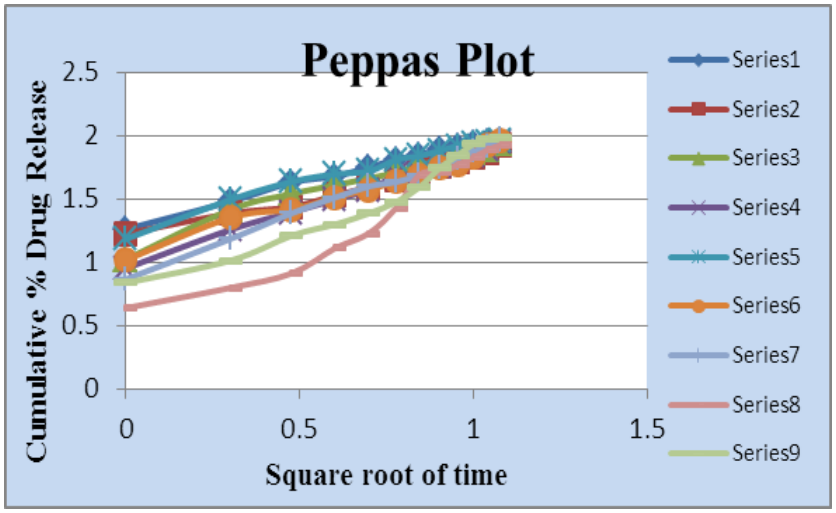

Fig.No.10: Peppas Plot.

CONCLUSION

All the prepared tablet formulations were found to be good without capping and chipping. As the amount of polymer in the tablets increases, the drug release rate, swelling index and mucoadhesion strength increases except for HPMC K4M. The designed formulations of Zidovudine stomach specific mucoadhesive tablets followed Peppas order release kinetics and A1 to A6 formulations followed Non-Fickian diffusion drug release mechanism while A7 to A8 formulations including optimized formulation showed Non-Fickian case II transport and zero order release rate. The formulation A9 was found to be of promising release. The A9 formulation containing Polycarbophil and HPMC K4M in the ratio 1:0.75:0.25 showed 97.01% cumulative drug release. It also showed good mucoadhesive strength 17.80 ± 2.73 gm and good swelling index 65% after 12 hrs.

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