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FORMULATION *IN-VITRO* EVALUATION, STUDY OF EFFECT OF HARDNESS ON BUOYANCY TIME OF GASTRO RETENTIVE FLOATING TABLETS OF ZIDOVUDINE USING NATURAL POLYMERS

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ABSTRACT

The purpose of present research was to develop and evaluate gastro retentive floating drug delivery system of an antiretroviral drug Zidovudine using natural polymers. The floating tablet of Zidovudine was prepared by direct compression method (effervescent method) by using natural polymers like *psyllium husk* powder, guar gum, xanthan gum. The results of pre-compression and post-compression parameters of all the formulated tablets were shown satisfactory results which complies with official limits. The compatibility study by FTIR confirmed that there is no interaction between the drug and the polymers used. The floating lag time and swelling index were found to be significantly increased with increasing concentration of the polymers. After the dissolution study of prepared Zidovudine floating tablet, it was concluded that the P4 formulation prepared with *Psyllium husk* powder shows better sustained release effect. The developed floating tablet of Zidovudine used to prolong drug release for more than 12 hrs, thereby improving bioavailability and better patient compliance.

KEY WORDS

Zidovudine, Gastro retentive floating drug delivery system, *Psyllium husk* powder, Xanthan gum, Guar gum and Sustained release.

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INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50 % of the drug delivery systems available in the market are oral drug delivery systems. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically

effective range needed for treatment, only when taken several times a day. This results in a significant fluctuation in drug levels. Recently, several technical advancements had introduced[1].

Gastro retentive systems or floating drug delivery systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[2].

The drug like Zidovudine appears most promising because it crosses the blood brain barrier and can be taken orally and in treaties they do not cause serious side effects. Zidovudine is the first approved compound for the treatment of AIDS; however the main limitation to therapeutic effectiveness of Zidovudine is its dose-dependent toxicity, short biological half-life and poor bioavailability. This limitation can be overcome by formulating gastro retentive drug delivery systems which retained in the stomach and help in continuously releasing the drug, thus ensuring optimal bioavailability[3].

MATERIALS AND METHOD

Materials

Zidovudine was obtained as gifts from Strides Arcolabs ltd, Bangalore. *Psyllium husk* was from a local market. Guar gum, Xanthan gum, Carbopol 940, PVP K-30, MCC, Hydrochloric acid, Sodium bicarbonate, Magnesium stearate, Talc all other diluents were used of analytical grade.

Method

The drug and all the excipients were passed through mesh # 40, weighed accurately, and mixed for 5 min, followed by lubrication, adding the weighed quantity of magnesium stearate and mixing. Effervescent floating tablets were prepared by direct compression technology using tablet punching machine. The drug, polymer, gas generating agent such as sodium bicarbonate, polyvinyl pyrrolidone, microcrystalline cellulose and lubricating agents are mixed geometrically and compressed by using round flat punches with hardness in the range of 4-7 kg/cm^2 to produce effervescent floating tablets.

In-vitro buoyancy study[4]

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remained buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of floatation *i.e.*, as long the dosage form remains buoyant is called Total Floating Time (TFT).

Swelling index[5,6]

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet. For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of 0.1N HCl. After each interval the tablet was removed from beaker and removed excess of 0.1N HCl by using filter paper and weighed again up to 12 hrs. Swelling index was calculated by using the following formula,

$$SI = \frac{Wt - W0}{W0} \times 100$$

Where, SI - Swelling index, Wt - weight of tablet at time t, W0 - initial weight of tablet.

Erosion Study[7]

The pre weighed tablets (W0) were placed in dissolution medium containing 0.1N HCl maintained at 37 ˚C. After 12 hrs, the tablets were withdrawn and dried in an oven at 105 ˚C and cooled to room temperature and weighed (We). The

percentage of erosion (E %) was calculated with the following formula.

$$E\% = \frac{W_0 - We}{W_0} \times 100$$

Where, W_0 = initial weight of the tablet, We = final weight of the tablet.

***In-vitro* drug release studies**[8]

Dissolution study was carried out for Zidovudine floating tablet to measure the release rate of drug from the dosage form. Dissolution medium: 900 ml of 0.1N HCl for 12 hrs.

Apparatus: USP type II (Paddle type for tablets)

Rotation speed: 75 rpm

Temperature: 37 ˚C ± 0.5 ˚C

Sampling time: Initially for 30 min, 1, 2, 4, 8 and 12 hrs.

RESULTS AND DISCUSSION

Pre-compression parameters

Pre-compression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include angle of repose, bulk density, tapped density, Haunser's ratio and Carr's index. Before formulation of tablets the drug and polymers were evaluated for all the above said parameters and it was found that all the observations were within the prescribed limits of IP.

Angle of repose of all the formulations was found to be ranging from 25.08 ± 0.61 to 28.92 ± 0.61, bulk density was found to be 0.43 ± 0.020 to 0.47 ± 0.022 g/cc, tapped density was in between 0.55 ± 0.019 to 0.61 ± 0.012 g/cc, Haunser ratio was found to be within 1.18 ± 0.02 to 1.27 ± 0.02 and Carr's index was found to be within 11.1 ± 0.21 to 14.98 ± 0.12 indicating compressibility of the tablet blend is excellent flow property.

Post-compression parameters

Prepared tablets were evaluated for weight variation and percentage deviation from the average weight is within the prescribed official limits (±5). The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch (8 mm) and the weight of the tablet (300 mg). The thickness of the batch from P1-P4, G1-G4 and X1-X4 was found to be 3.77 ± 0.14 to 4.26 ± 0.05 mm and hardness was found to be 4.50 ± 0.31 to 7.83 ± 0.60 kg/cm^2 thus tablets were having good mechanical strength. Friability is needed for tablets to withstand force of compression applied during the manufacture of tablets. The friability of all the formulated tablets of Zidovudine was found to be between 0.37 to 0.71 %. All the formulated tablets of Zidovudine were shown the % friability within the official limits. (*i.e.*, not more than 1%). The drug content of all the twelve formulations of Zidovudine floating tablets were found to be within the range of 99.19 ± 0.99 to 99.95 ± 0.74 % which were within the limits of USP specifications.

***In-vitro* buoyancy studies**

Buoyancy Studies were performed using 0.1N HCl at room temperature; the tablets were floated and remained buoyant without disintegration thus it, maintains its dimensional stability during floating. The formulation P1- P4 showed buoyancy within 67 sec was shown in the Figure No.1 and formulation G1-G4, X1 –X4 started to float within 285 sec and 186 sec. The gas generated by the sodium bicarbonate is trapped within the gel formed by the hydration of polymer and thus decreasing the density of the tablets. The formulation with *psyllium husk* powder showed better initial buoyancy than the other formulation. Table No.4 and Figure No.5 showed the results of buoyancy study. From the results it was observed that the buoyancy lag time was decreased with increasing polymer concentration. The formulation P1-P4 showed better floating time between 1.30 to 2.37 min and the formulation G1-G4 showed increased floating time of 1.37 to 6.15 min. All the formulation showed total floating time of more than 12 hrs except the formulation with xanthan gum which showed total floating time up to 12 hrs. From the results it was also observed that the floating lag time was increased as the hardness of the tablet increased. The formulation with hardness 4 kg/cm^2 (P1-P4) floated immediately but the tablet with hardness 6 kg/cm^2 (X1-X4) and 7 kg/cm^2 (G1-G4) the floating lag time was increased. High degree of

hardness resulting reduction of porosity of tablet and take more time to hydrate when contact with gastric fluids.

% erosion studies

The percentage matrix was eroded in the formulations P1-P4 were prepared with *psyllium husk* powder was in the range 6.52 ± 0.02 to 8.21 ± 0.02, G1-G4 formulations were prepared with guar gum was in the range of 6.31 ± 0.02 to 7.57 ± 0.03 and formulations X1-X4 were prepared with xanthan gum was in the range of 6.35 ± 0.04 to 8.53 ± 0.03 after 12 hrs were tabulated in the Table No.4 and Figure No.6.

% swelling index

Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structur e, hydrophilicity and ionization of the functional groups. Swelling is also a vital factor to ensure floating and drug dissolution. Swelling study was performed on all the batches of Zidovudine floating tablets for 8 hrs. Initially the index was found to rise due to the rapid water intake. This water intake makes the matrix swell and thus reduces the bulk density that is responsible for buoyancy. The swelling index of P1-P4 formulations was in the range of 147.33 ± 2.08 to 185.66 ± 3.51 %, G1-G4 was in the range of 130.56 ± 6.65 to 166.74 ± 3.05 % and X1-X4 was in the range of 144.33 ± 2.08 to 175.35 ± 2.16 %. Maximum swelling was seen with the polymers in the order of *Psyllium husk powder* > Xanthan gum > Guar gum. The results of swelling index were depicted in Table No.4 and Figure No.7.

From the results, it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces. Apparently, as swelling increases, drug release will be more diffusion-controlled or erosion-controlled for water soluble and water insoluble drugs, respectively.

***In-vitro* dissolution study of Zidovudine floating tablets**

In-vitro dissolution studies were performed for all the formulations using USP type II tablet dissolution apparatus employing paddle type at 75 rpm using 900 ml of 0.1N HCl as dissolution medium. The data for *in-vitro* drug release of formulations was shown in the Tables No.5-7 and Figures No.8-10. The drug release from all the formulations was varied according to the polymer concentration and the polymer used. The release of Zidovudine was decreased with increasing the concentration of *psyllium husk* powder, guar gum, xanthan gum. As the concentration of polymer increased, it causes increased viscosity of swollen matrix, which decreases water diffusion in to the core layer. The percentage of the drug released from the formulations P1, P2, P3, and P4 was found to be 96.07 ± 0.73 %, 93.85 ± 0.65 %, 90.58 ± 0.42 %, 82.12 ± 0.78 % respectively. The percentage of the drug released from the formulations G1, G2, G3, and G4 was found to be 94.27 ± 0.24 %, 91.83 ± 0.68 %, 86.41 ± 0.57 %, 83.96 ± 0.59 % respectively. The percentage of the drug released from the formulations X1, X2, X3, X4 was found to be 94.11 ± 0.59 %, 90.44 ± 0.43 %, 88.10 ± 0.24 %, 86.32 ± 0.67 % respectively. The results showed there is no burst effect on the prepared formulation and the tablet prepared with *psyllium husk* powder showed better controlled release than other polymers used.

Table No.1: Formulation design of Zidovudine floating tablets

S.No	Formulation Ingredients	Quantity taken in mg											
		P1	**P2**	**P3**	**P4**	**G1**	**G2**	**G3**	**G4**	**X1**	**X2**	**X3**	**X4**
1	Zidovudine	100	100	100	100	100	100	100	100	100	100	100	100
2	Psyllium husk	25	50	75	100	-	-	-	-	-	-	-	-
3	Guar gum	-	-	-	-	25	50	75	100	-	-	-	-
4	Xanthan gum	-	-	-	-	-	-	-	-	25	50	75	100
5	Carbopol 940	50	50	50	50	50	50	50	50	50	50	50	50
6	Sodium bicarbonate	20	20	20	20	20	20	20	20	20	20	20	20
7	PVP K-30	10	10	10	10	10	10	10	10	10	10	10	10
8	MCC	85	60	35	10	85	60	35	10	85	60	35	10
9	Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
10	Talc	5	5	5	5	5	5	5	5	5	5	5	5
11	Total weight	300	300	300	300	300	300	300	300	300	300	300	300

Table No.2: Pre-compression evaluation of tablet blend of Zidovudine

S.No	Formulation code	Angle of repose (θ)	Bulk density g/cc	Tapped density g/cc	Hausner's ratio	Carr's index %
1	P1	28.32±0.46	0.45±0.029	0.57±0.018	1.24±0.03	13.92±0.66
2	P2	25.2±0.81	0.45±0.026	0.60±0.010	1.26±0.03	14.58±0.32
3	P3	27.70±0.46	0.45±0.028	0.60±0.027	1.20±0.01	12.05±0.39
4	P4	28.32±0.84	0.46±0.037	0.61±0.012	1.25±0.02	12.76±0.28
5	G1	25.64±0.50	0.45±0.034	0.56±0.011	1.27±0.02	14.98±0.12
6	G2	25.71±0.40	0.43±0.020	0.58±0.038	1.19±0.07	11.60±0.19
7	G3	26.75±0.60	0.46±0.025	0.57±0.017	1.18±0.02	12.64±0.30
8	G4	28.92±0.67	0.44±0.026	0.59±0.024	1.23±0.05	14.59±0.29
9	X1	25.15±0.87	0.46±0.026	0.55±0.019	1.24±0.02	13.23±0.13
10	X2	25.08±0.61	0.44±0.034	0.60±0.013	1.23±0.03	12.74±0.07
11	X3	27.28±0.83	0.45±0.034	0.58±0.052	1.25±0.01	11.44±0.21
12	X4	25.54±0.72	0.47±0.022	0.55±0.026	1.2±0.03	11.1±0.21

Mean ± SD n=3

Table No.3: Post-Compression evaluation of Zidovudine floating tablets

S.No	Formulation code	Weight Variation (%)	Thickness**(mm)	Hardness** (Kg/cm^2)	Friability (%)
1	P1	0.0897±0.75	4.01±0.14	4.66±0.25	0.63
2	P2	0.041±0.78	4.0±0.10	4.58±0.37	0.57
3	P3	0.026±0.48	4.12±0.08	4.50±0.31	0.61
4	P4	0.042±0.43	4.26±0.05	4.66±0.25	0.69
5	G1	0.062±0.29	4.0±0.10	7.33±0.51	0.58
6	G2	0.074±0.65	3.77±0.14	7.33±0.40	0.37
7	G3	0.096±0.31	3.83±0.06	7.41±0.20	0.59
8	G4	0.015±0.27	3.87±0.09	7.83±0.60	0.65
9	X1	0.044±0.26	4.08±0.06	5.08±0.73	0.65
10	X2	0.027±0.61	3.92±0.03	6.41±0.49	0.57
11	X3	0.032±0.37	4.11±0.06	6.25±0.41	0.71
12	X4	0.077±0.48	4.05±0.10	6.41±0.37	0.60

Mean ± SD, *(n= 20), ** (n= 6)

Table No.4: Results of BLT, TFT, Drug content, Erosion studies and Swelling index

S.No	Formulation code	BLT in min	TFT in hrs	Drug Content* (%)	Erosion studies** (%)	Swelling index ** after 8 hrs (%)
1	P1	1.30	>12	99.35±0.59	8.21±0.02	147.33±2.08
2	P2	1.32	>12	99.54±0.88	7.79±0.06	158.42±1.15
3	P3	1.47	>12	99.49±0.71	7.2±0.01	170.26±4.72
4	P4	2.37	>12	99.53±0.86	6.52±0.05	185.66±3.51
5	G1	1.37	>12	99.46±0.80	7.57±0.03	130.56±6.65
6	G2	4.50	>12	99.73±0.75	7.36±0.06	147.66±5.13
7	G3	5.28	>12	99.71±0.77	6.89±0.01	155.37±3.05
8	G4	6.15	>12	99.69±0.66	6.31±0.02	166.74±3.05
9	X1	1.13	12	99.38±1.06	8.53±0.05	144.33±2.08
10	X2	1.45	12	99.19±0.99	8.11±0.03	153.66±1.52
11	X3	2.20	12	99.95±0.74	7.72±0.08	167.58±1.54
12	X4	4.45	12	99.53±0.77	6.35±0.04	175.35±2.16

Mean± SD *(n=20), **(n=3)

Table No.5: *In-vitro* release study of formulations P1-P4

S.No	Time in hour	% Cumulative drug release			
		P1	P2	P3	P4
1	0	0	0	0	0
2	0.5	12.56±0.87	10.83±0.39	10.59±0.53	10.92±0.31
3	1	21.43±0.61	18.02±0.21	22.02±0.71	17.24±0.83
4	2	44.01±0.19	40.29±0.57	39.74±0.93	29.27±0.65
5	4	65.02±0.89	61.91±0.56	52.88±0.37	51.68±0.52
6	8	77.77±0.88	75.25±0.59	72.15±0.27	70.13±0.57
7	12	96.07±0.73	93.85±0.65	90.58±0.42	82.12±0.78

Table No.6: *In-vitro* release study of formulations G1-G4

S.No	Time in hours	% Cumulative drug release			
		G1	G2	G3	G4
1	0	0	0	0	0
2	0.5	18.01±0.17	17.61±0.48	15.63±0.20	14.42±0.48
3	1	26.82±0.32	24.10±0.67	22.82±0.79	20.97±0.09
4	2	39.17±0.29	35.79±0.38	34.03±0.18	43.47±0.75
5	4	58.94±0.19	57.81±0.46	58.41±0.45	52.70±0.50
6	8	73.22±0.29	70.97±0.17	70.85±0.68	71.97±0.67
7	12	94.27±0.24	91.83±0.68	86.41±0.57	83.96±0.59

Table No.7: *In-vitro* release study of formulations X1-X4

S.No	Time in hrs	% Cumulative drug release			
		X1	X2	X3	X4
1	0	0	0	0	0
2	0.5	17.09±0.24	15.82±0.17	13.24±0.25	13.80±0.30
3	1	27.13±0.77	28.90±0.36	21.90±0.36	19.60±0.36
4	2	48.90±0.64	43.41±0.91	41.66±0.40	39.19±0.53
5	4	60.45±0.68	54.94±0.30	56.27±0.46	53.79±0.61
6	8	70.91±0.34	67.14±0.26	66.72±0.52	64.49±0.36
7	12	94.11±0.59	90.44±0.43	88.54±0.24	86.32±0.67

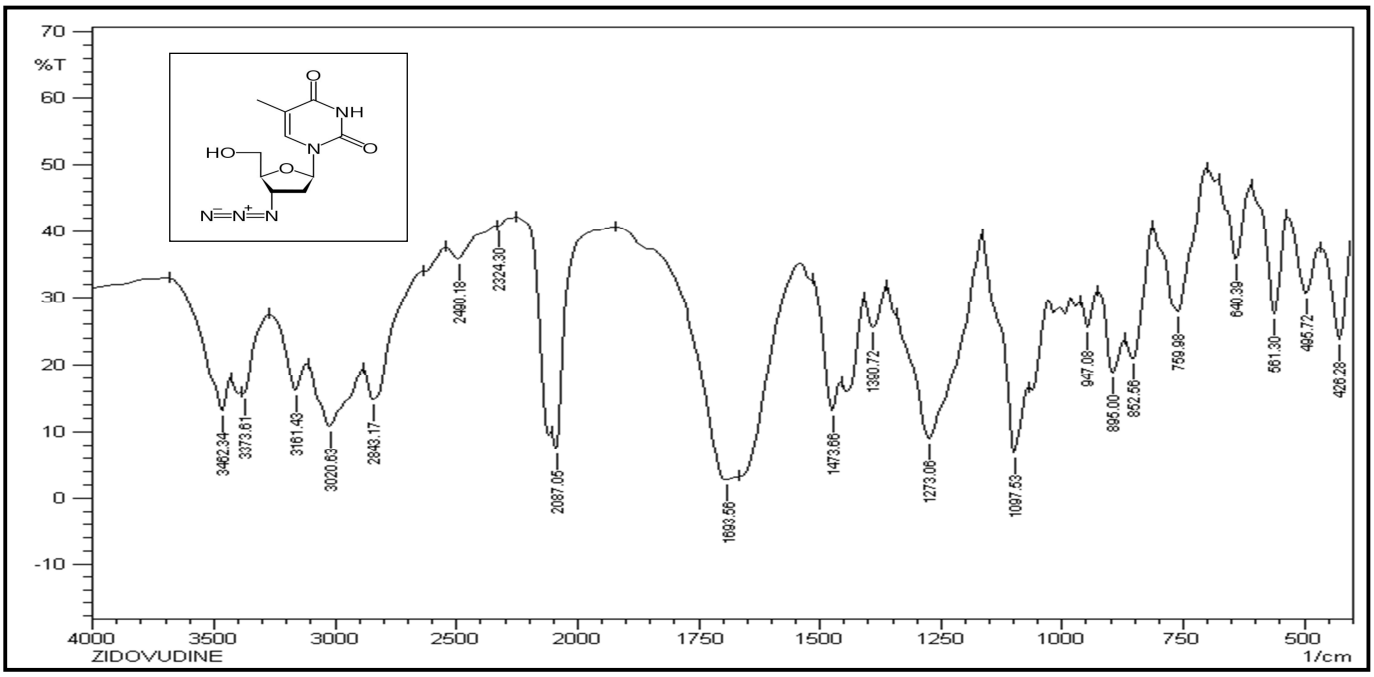


Figure No.1: FTIR Spectra of pure drug Zidovudine

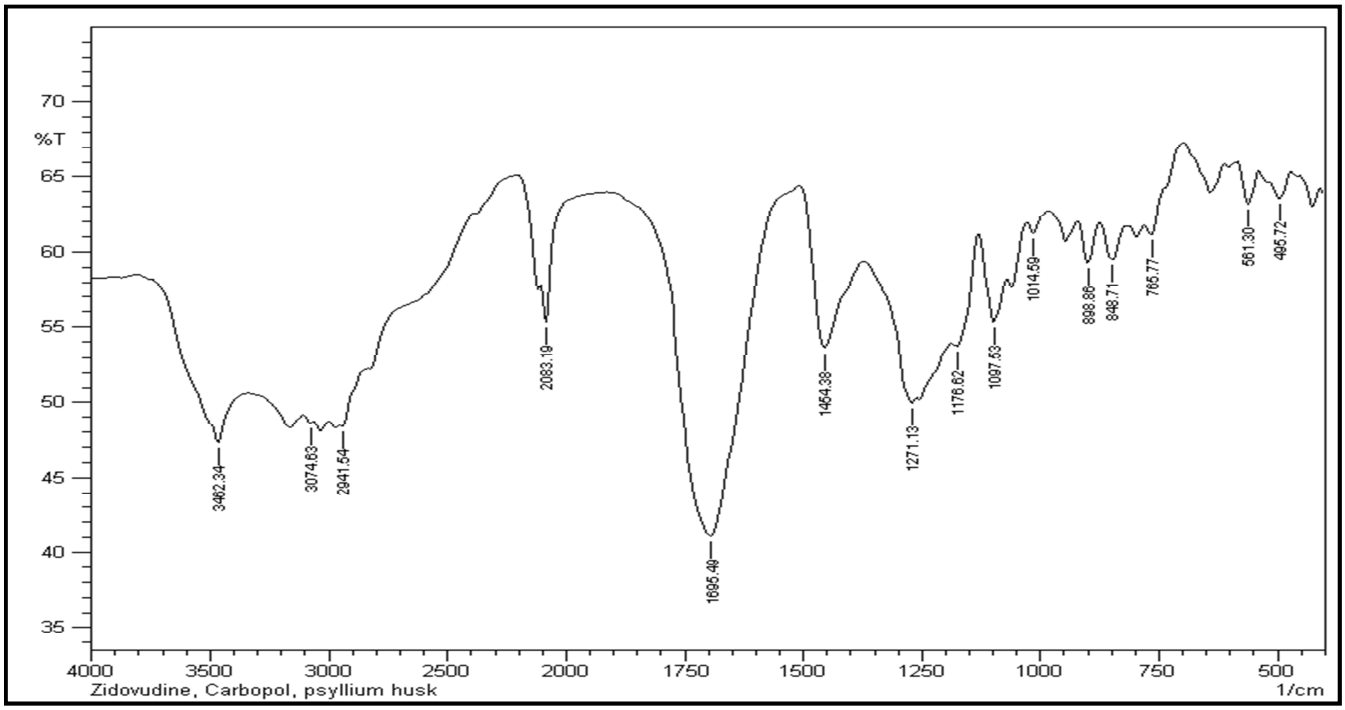


Figure No.2: FTIR Spectra of Zidovudine+Carbopol+*Psyllium husk* powder

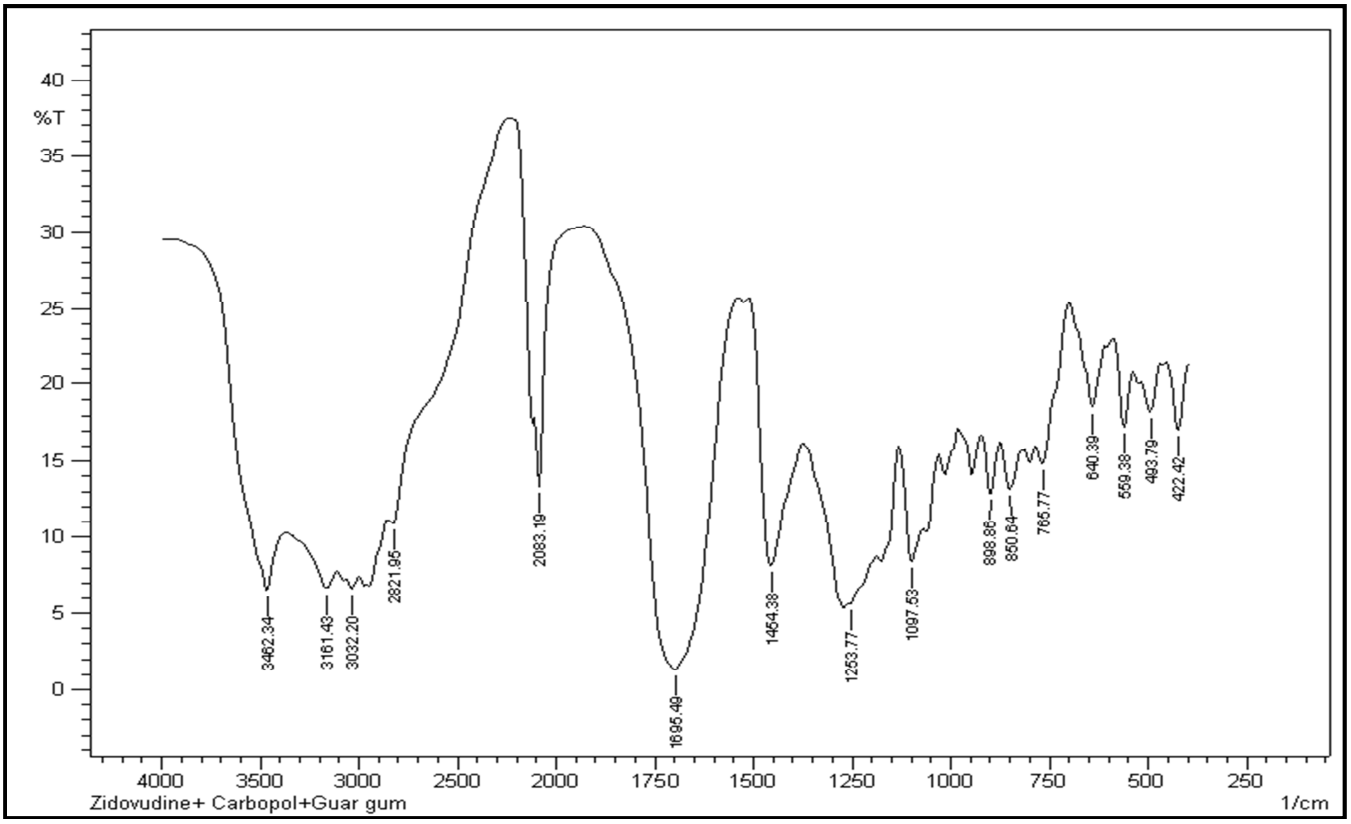


Figure No.3: FTIR Spectra of Zidovudine+Carbopol+Guar gum

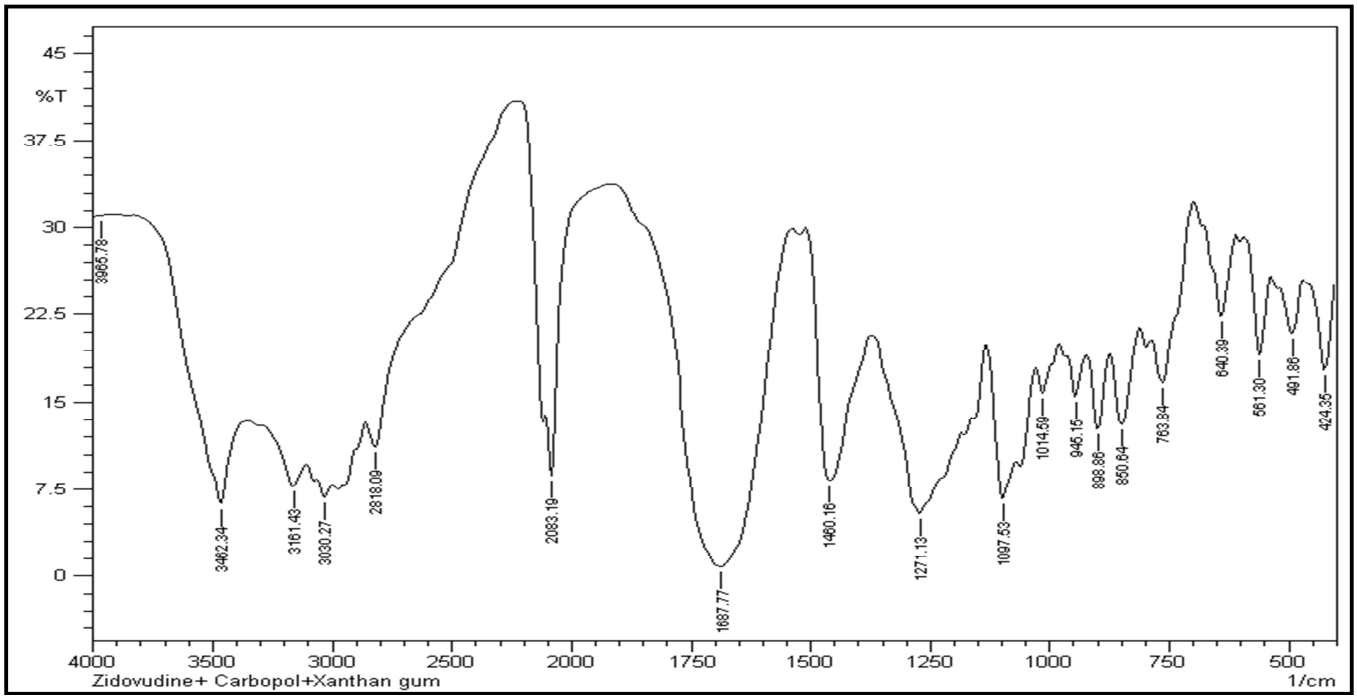
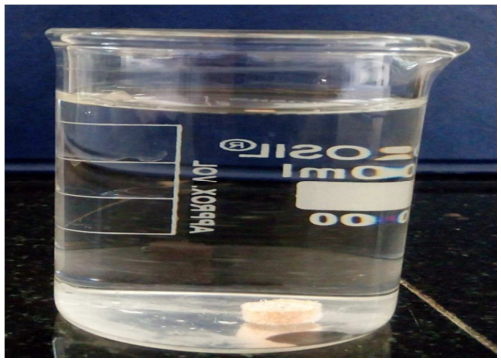
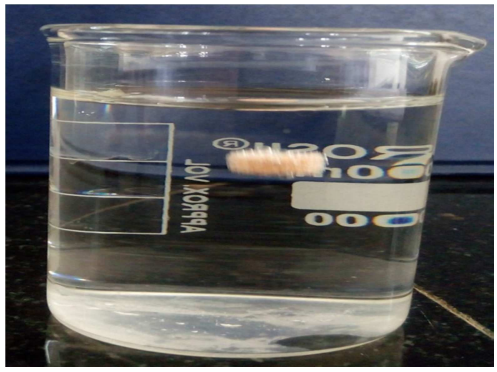


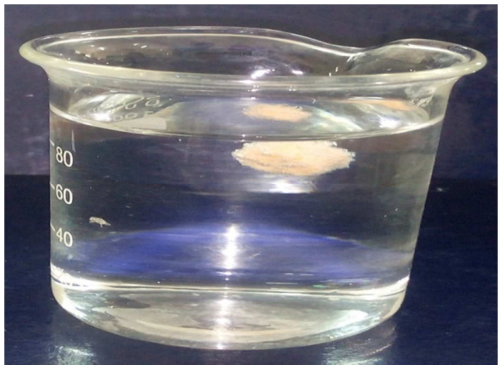
Figure No.4: FTIR Spectra of Zidovudine+Carbopol+Xanthan gum



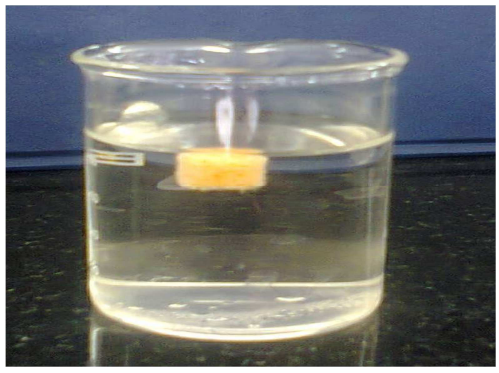
At initial time



Buoyancy at 67 Sec



BLT at 1.30 min



TFT at 12 hrs

Figure No.5: Buoyancy study of P4 optimized floating tablets of Zidovudine

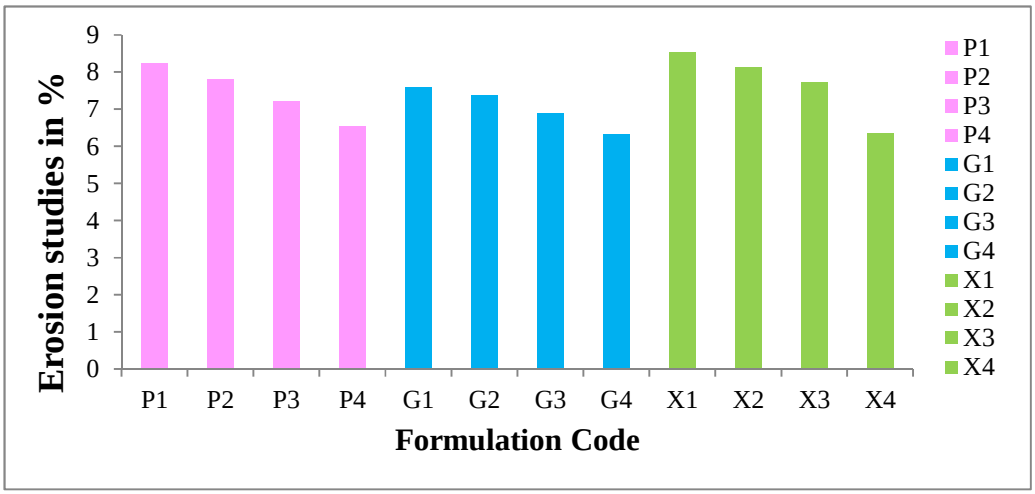


Figure No.6: Graphical representation of % erosion studies of different formulations

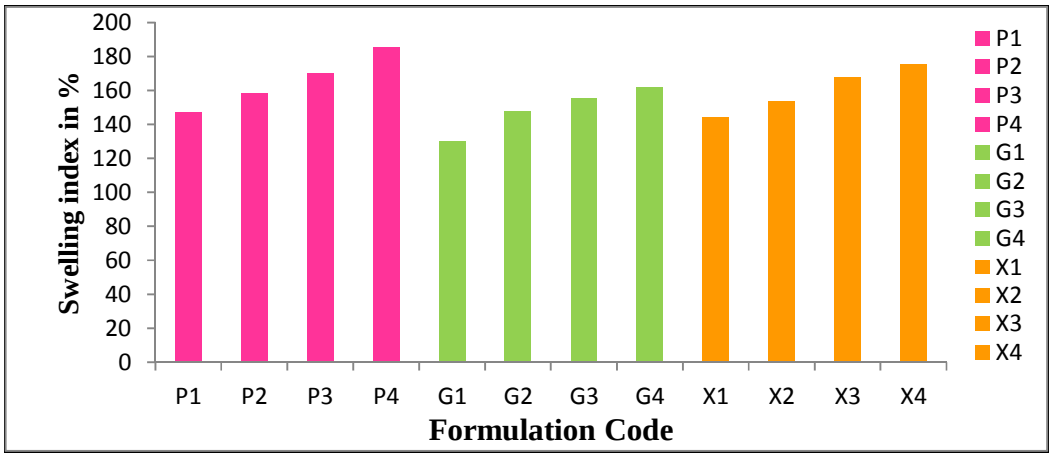


Figure No.7: Graphical representation of % swelling index of different formulations

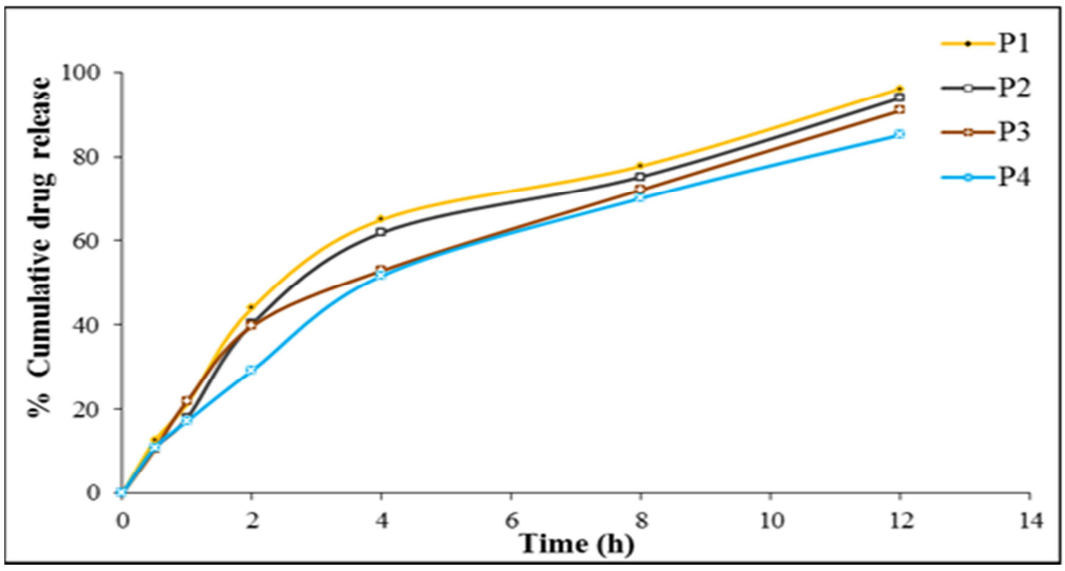


Figure No.8: *In-vitro* release profile of formulations P1 – P4

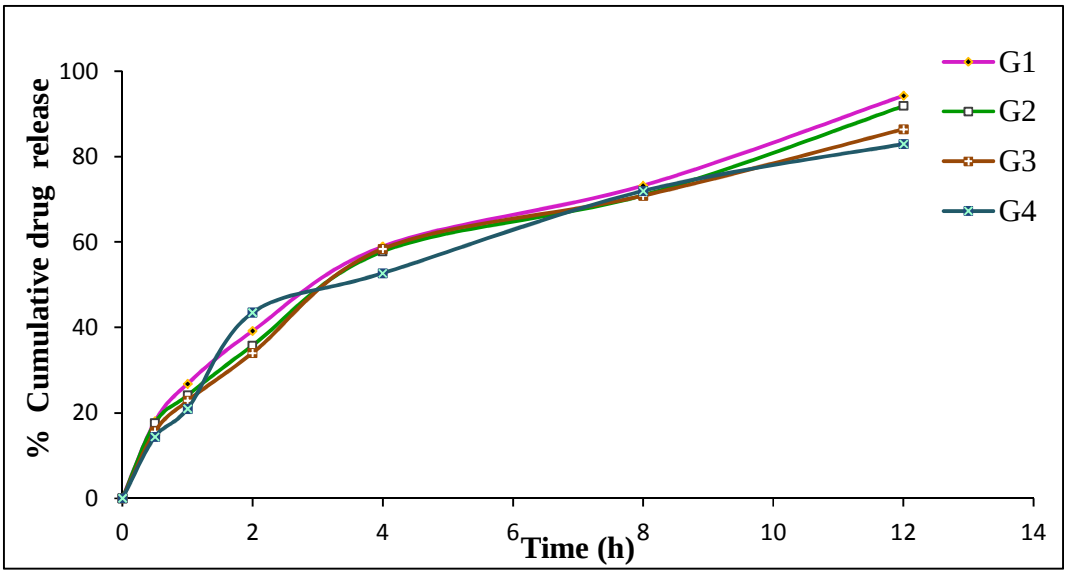


Figure No.9: *In-vitro* release profile of formulations G1 – G4

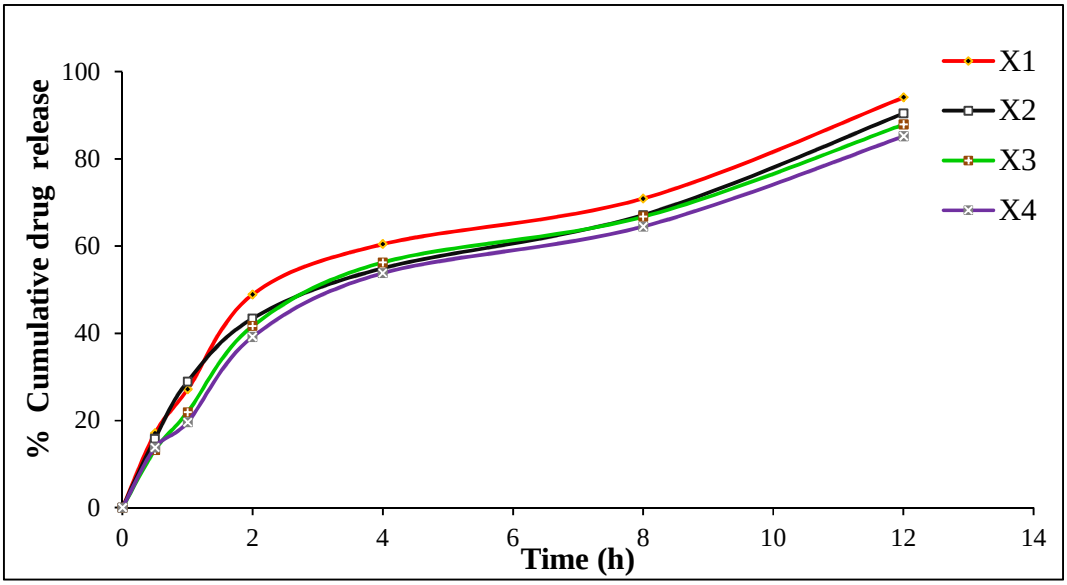


Figure No.10: *In-vitro* release profile of formulations X1 – X4

CONCLUSION

The effervescent based floating drug delivery system is a promising approach to achieve *in-vitro* buoyancy by using natural polymers. The *in-vitro* drug release studies revealed the drug release from the formulation depended upon the polymer concentration and the polymer used. The release of Zidovudine was decreased with increasing the concentration of *psyllium husk* powder, guar gum, xanthan gum. It concluded that the Zidovudine floating tablet of P4 optimized formulation has better potential of sustaining the drug release. From this study it was observed that % drug release was decreased with increase in the polymer concentration. The sustained drug release with better floating was achieved with natural polymers. The developed floating tablet of Zidovudine used to prolong drug release for more than 12 hrs, thereby improving bioavailability and better patient compliance.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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