

Formulation and In vitro Evaluation of Floating Tablets of Antiretroviral Drug: Acyclovir

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ABSTRACT:

The drug Acyclovir widely prescribed as antiviral drug used for the treatment of HIV/AIDS, practically insoluble in water and aqueous fluids and as such it possesses challenging problems in its formulation and development. The purpose of the present work was to design and optimize floating drug delivery systems of acyclovir using Xanthan gum as the polymer and sodium bicarbonate as a gas generating agent. The tablets were prepared by wet granulation method. All the designed eight batches of formulations were evaluated for hardness, friability, weight variation, drug content uniformity, swelling index, in vitro buoyancy, and in vitro drug release profile. All formulations had floating lag time in the range of 2-5 min and constantly floated on dissolution medium for more than 24 hrs. The obtained results revealed that, release of drug was by mixed order kinetics & in vitro release data were also subjected to Higuchi's equation, the r values of all the formulations were 0.9674 and above which indicates that the drug release was by Higuchi's mechanism. The formulations were also treated to Peppas's plots, found fairly linear and the regression values of all the formulations indicating a dissolution behavior controlled by Non Fickian Diffusion. The stability studies were conducted as per ICH guidelines were found stable.

From these studies it can be concluded that, the formulation retained for longer periods of time in the stomach and provides controlled release of the drug. Hence improve the therapeutic effect of the drug by increasing its bioavailability.

KEYWORDS: Acyclovir, Gastro retentive drug delivery, Xanthan gum

I. INTRODUCTION:

During the last decade, many studies have been performed concerning the sustained release dosage form of drugs, which have aimed at the prolongation of gastric emptying time (GET). The GET has been reported to be from 2 to 6 hours in humans in the fed state. Accordingly, when a

sustained release dosage form is administered orally, sufficient bio-availability and prolongation of the effective plasma level occasionally can't be obtained. Also reflected in the recent scientific patent literature, an increased interest in novel dosage forms which possesses not only a mechanism for controlled release of the drug but also controlled GI transit time [1].

In present situation, the AIDS is causing more threatens, AIDS is not a disease, it is the damage done to immune system by the infection of HIV [2]. Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups [3]. 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 significant fluctuations in drug levels [4].

Oral ingestion is the most convenient and commonly used method of drug delivery [5]. Which has narrow absorption window in GI restricted by poor bioavailability because of incomplete release of drug [6].

Drugs that are required to be formulated into gastro retentive dosage forms include [7]:

- Drugs acting locally in the stomach.
- Drugs that are primarily absorbed in the stomach.
- Drugs that are poorly soluble at alkaline pH.
- Drugs with a narrow window of absorption.
- Drugs rapidly absorbed from the GI tract and
- Drugs that degrade in the colon.

Advantages of FDDS:

- Sustained drug delivery: HBS type dosage forms remain in the stomach for several hours due to their modified GRT. Prolongation in the GRT sustains the drug release behaviour [8]
- Hydrodynamically balanced controlled release drug delivery systems provides a better

alternative for maintenance of systemic drug concentrations within the therapeutic window.

- These systems provides an easy way of maintaining constant blood level with an ease of administration and better patient compliance.
- Site specific drug delivery: Drugs having absorption sites in the stomach and upper parts of the intestine can be formulated to target the drug to the specific site [9].
- Drugs like furosemide which has absorption mainly in the stomach followed by duodenum can be developed into monolithic floating systems which prolongs the GRT and thereby increase the bio availability. Misoprostol has been developed into bilayer floating capsule for prevention of gastric ulcers caused by non steroidal anti-inflammatory drugs [10].

Limitations:

- The major disadvantage of floating systems is requirement of a sufficiently high level of fluids in the stomach for the drug delivery [7]. However, this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
- The dosage form should be administered with a minimum of glass full of water (200-250 ml).
- Floating system is not feasible for those drugs that have solubility or stability problems in gastric fluids.
- The drugs, which are absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are not desirable candidates.
- Some drugs present in the floating system causes irritation to gastric mucosa.

Physiology of Stomach [11]

- The stomach is a J shaped dilated portion of the alimentary tract situated in the epigastric,

umbilical and left hypochondriac regions of the abdominal cavity. Its size varies with the amount of food it contains. The volume is 1.5 l or more in adult and after food has emptied a 'collapsed state' is obtained with a resting volume of only 25-30 ml. The stomach consists of fundus, body and antrum; pylorus is a sphincter present in between the most terminal antrum and duodenum. The fundus and body store food temporarily, secrete digestive juices and propels chymes, a milky mixture of food with gastric juices, to the antrum. The antrum grinds and triturates food particles and regulates the secretion of the hydrochloric acid as well as the emptying of food.

Factors Affecting Gastric Retention: Gastric retention time (GRT) is affected by several factors which include [12-13]:

- a) size and shape of the dosage form
- b) density
- c) concomitant intake of food and drugs
- d) biological factors like age, gender, posture, body weight and disease states.

Anatomy of Stomach: The stomach is divided into three anatomical regions: fundus, body and pylorus or antrum. The proximal stomach consists of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying [14]. The fundus adjusts to increased volume during eating by relaxation of fundal muscle fibers. The fundus also exerts a steady pressure on the gastric contents, pressing them towards the distal stomach. To pass through the pyloric wall into the small intestine, particles should be of the order of 1-2mm. As in figure-1

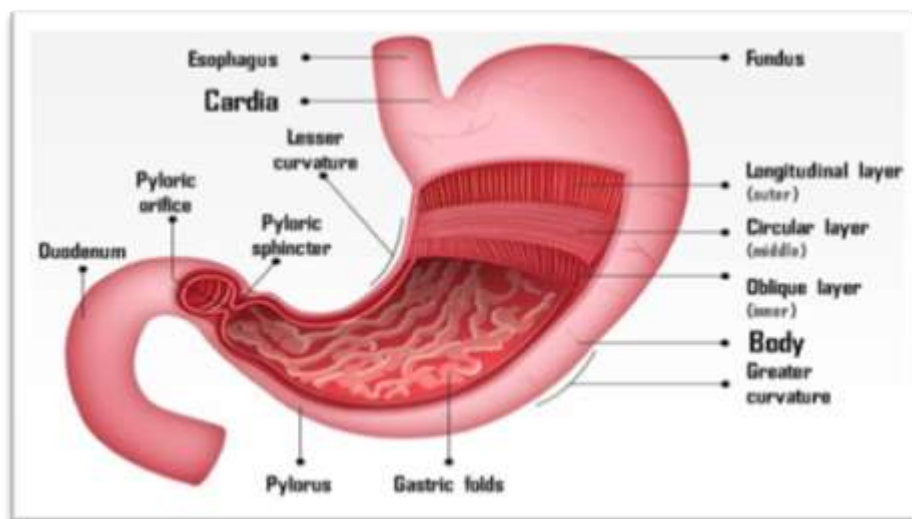


Figure 1: Anatomy of stomach

Acyclovir is a guanine analogue used in the treatment of viral diseases. The reported oral bioavailability is 10-20% with a plasma elimination half life of 1-2 h [15]. Acyclovir has its absorption window in the duodenum and small intestine. After per oral administration, only 20% of the drug is absorbed with the remaining 80% of the drug excreted in the feces. After repeated per oral dosing of small amounts of acyclovir the bioavailability can be enhanced. These facts indicate that increasing gastric residence time may enhance bioavailability of acyclovir. Therefore, acyclovir was selected as a model drug for the design of a FDDS with a view to improve its oral bioavailability.

II. MATERIALS AND METHODS:

Acyclovir was obtained as a gift sample from M/s Modern Laboratories Pvt. Ltd., Indore, Xanthan gum was gifted by Hi Media Chem. Pvt.

Ltd. Mumbai and other chemicals & reagents were of SD fine chemicals provided by college.

2.1 Preparation of Floating tablets of Acyclovir

[16,17]: According to the present invention, the FDDS includes a swelling agent PVP, gas generating component generated by sodium bicarbonate, swelling controlled by xanthan gum, which acts both as swellability and a release controlling agent. The gas generating component sodium bicarbonate contacts with gastric fluid to generate carbon dioxide that gets entrapped within the hydrated gel matrix of the swelling composition. Sodium bicarbonate (NaHCO₃) was incorporated in the formulation in such a way that when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage form. Magnesium stearate and talc as lubricant and glidant, all the formulations shown in table 1.

Ingredients	AF1	AF2	AF3	AF4	AF5	AF6	AF7
Acyclovir	400	400	400	400	400	400	400
Xanthan gum	25	50	75	100	125	150	175
Sod aliginate	175	150	125	100	75	50	25
Sod CMC	50	50	50	50	50	50	50
PVP K30	25	25	25	25	25	25	25
Sod bicarbonate	200	200	200	200	200	200	200
Mg Stearate	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10
Total weight	895	895	895	895	895	895	895

Table 1: Composition of Different Acyclovir formulations (in Mg)

III. RESULTS AND DISCUSSION:

3.1. Pre-Compressional Parameters:

The characteristics of granules are most important to formulation therefore most universally measured. These basic measurements of the granulations have been utilized to develop the manufacture of many successful pharmaceutical dosage forms. Table 2 shows the powder blend properties of Xanthan gum prepared granules. Bulk density depends on particle size, shape and tendency of particles to adhere together, may influence compressibility, porosity, dissolution and other properties.

The bulk density and tapped density of powder blend was found between 0.582 ± 0.02 to 0.734 ± 0.07 gm/cm³ and 0.691 ± 0.03 to 0.926 ± 0.02 gm/cm³, which indicates good packing capacity of powder blend. For inter particulate cohesive property, Carr's index was evaluated with angle of repose measurements and studied for the effects of geometry of packing solids with bulk and tapped density.

The measurements of bulk density and tapped density found that density of a powder depends on particles packing and density changes

as the powder consolidates. The degree of consolidation is unique to the powder and ratio of these densities is related to inter particulate friction. This ratio, percent compressibility, was used as an index of flow. Adhesive/cohesive forces of particles are related to flow behaviors. Values of Carr's index below 15% usually show good flow characteristics and above 25% indicate poor flow ability. Carr's index was found to be between 19.93 ± 0.07 to 27.87 ± 0.01 . Hausner's ratio method used to evaluate stability of powder column and to estimate the flow properties, it was found between 1.10 ± 0.03 to 1.27 ± 0.05 . Low range observed of Hausner's ratio which indicates good flow ability. Other different types of angular properties have been employed to assess flow ability. The angle of repose indicates the flow ability of the powder/granules. Angle of repose is suited for particles >150 m. Values ≤ 300 generally indicate the free flowing material and angle of ≥ 400 indicates a poor flowing. The angle of repose of all the formulations were found to be within the range of 22.43 ± 0.18 to 31.12 ± 0.13 which showed that, granules were of good flow properties.

Formulations	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's Index	Hausner Ratio	Angle of repose (θ)
F1	0.734 ± 0.07	0.914 ± 0.01	21.12 ± 0.03	1.10 ± 0.03	28.90 ± 0.12
F2	0.651 ± 0.01	0.926 ± 0.02	22.28 ± 0.09	1.18 ± 0.05	24.99 ± 0.10
F3	0.582 ± 0.02	0.646 ± 0.03	21.34 ± 0.04	1.23 ± 0.01	22.43 ± 0.18
F4	0.691 ± 0.07	0.898 ± 0.07	27.87 ± 0.01	1.11 ± 0.04	26.78 ± 0.17
F5	0.685 ± 0.01	0.691 ± 0.03	19.93 ± 0.07	1.24 ± 0.04	31.12 ± 0.13
F6	0.723 ± 0.03	0.710 ± 0.02	22.09 ± 0.10	1.27 ± 0.05	29.19 ± 0.18
F7	0.710 ± 0.02	0.811 ± 0.04	21.56 ± 0.09	1.21 ± 0.10	27.11 ± 0.14

Table 2: Pre compressional parameters of all the Formulations

3.2 Post compressional Parameters of Prepared Tablets:

Acyclovir floating tablets were prepared by wet granulation method and were evaluated for average weight, thickness, hardness, friability and drug content.

3.2.1 Average Weight, Tablet Thickness, Diameter, Hardness and Friability:

All the formulations were evaluated for various parameters like thickness; diameter and hardness. All the prepared tablets formulations F1 to F7 shown in Table 3, it was found that there was no much variation in thickness of tablets; it showed that powder blends was consistent in particle size and uniform behavior during tablet compression.

Thickness and diameter of tablets of all formulations were measured by vernier caliper and there will be no any change in thickness and diameter of tablets respectively. Thickness was in range of 4.7 ± 0.01 to 4.9 ± 0.02 . The hardness of tablets was measured by Pfizer hardness tester. The hardness was in range of 4.1 to 4.8 Kg/cm². Tablet hardness reflects differences in tablet density and porosity, which showed results in difference release patterns of the drug by affecting the rate of penetration in the dissolution medium at the surface of the tablet.

Weight Variation: The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance.

The weight data from the tablets were analyzed for sample mean and percent deviation. The results are showed in table 3. **Friability:** The present study of tablets is within the limit and the slight variation in seen in friability because of the variation in

compression force applied and its total weight. The friability of tablets also depends on type of filler and moisture contents present in it. The friability was found to be in the range of 0.51 ± 0.086 to 0.67 ± 0.014 shown in Table 3.

Formulations	Average weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm ²)	Friability (%)
F1	893 ± 0.02	4.9 ± 0.02	12.1 ± 0.01	4.5 ± 0.02	0.52 ± 0.031
F2	891 ± 0.03	4.7 ± 0.02	11.8 ± 0.02	4.2 ± 0.03	0.58 ± 0.054
F3	894 ± 0.01	4.6 ± 0.01	11.9 ± 0.01	4.4 ± 0.05	0.61 ± 0.021
F4	892 ± 0.02	4.7 ± 0.01	12.0 ± 0.07	4.1 ± 0.07	0.64 ± 0.011
F5	891 ± 0.01	4.8 ± 0.03	11.9 ± 0.05	4.7 ± 0.05	0.51 ± 0.086
F6	892 ± 0.01	4.9 ± 0.02	11.8 ± 0.03	4.5 ± 0.03	0.54 ± 0.065
F7	894 ± 0.01	4.7 ± 0.01	11.7 ± 0.02	4.8 ± 0.04	0.67 ± 0.014

Table 3: Post-Compressional properties of Acyclovir tablets

3.2.2 Drug Content and Swelling Index Study:

The drug content and swelling index (water up take) studies were carried out for all the prepared formulations, the results are shown in Table 4.

Drug Content: Drug content was in range of 97.54 ± 0.11 to 99.89 ± 0.22 , which reflects good drug content uniformity in all the prepared formulations. The reading complies as per I P. which indicates drug was uniformly distributed throughout the tablet compressed.

Swelling Index Study: Swelling of tablet is also a vital & important factor to ensure floating. To obtain floating balance between swelling and water acceptance must be restored. Tablets composed of polymeric matrices, when they come in contact

with water, build a layer of gel around the tablets core. This gel layer governs the release of drug. Swelling is important because the gel barrier is formed by water permeation.

Swelling index results study showed that, the order of swelling in these polymers indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymer was achieved up to 24 hrs and then gradually decreased due to erosion. The swelling of polymers used in these tablets could be determined by water uptake of the tablets. The complete swelling was achieved by the end of 24 hrs. The % of swelling index was in the range of 56.12 ± 0.27 to 68.77 ± 0.19 , values are given in Table 4.

Formulations	Drug content (%)	Swelling index
F1	98.10 ± 0.32	62.90 ± 0.45
F2	97.54 ± 0.11	60.11 ± 0.15
F3	98.77 ± 0.18	63.51 ± 0.41
F4	98.23 ± 0.12	66.10 ± 0.27
F5	99.44 ± 0.17	59.70 ± 0.12
F6	98.11 ± 0.34	56.12 ± 0.27
F7	99.89 ± 0.22	68.77 ± 0.19

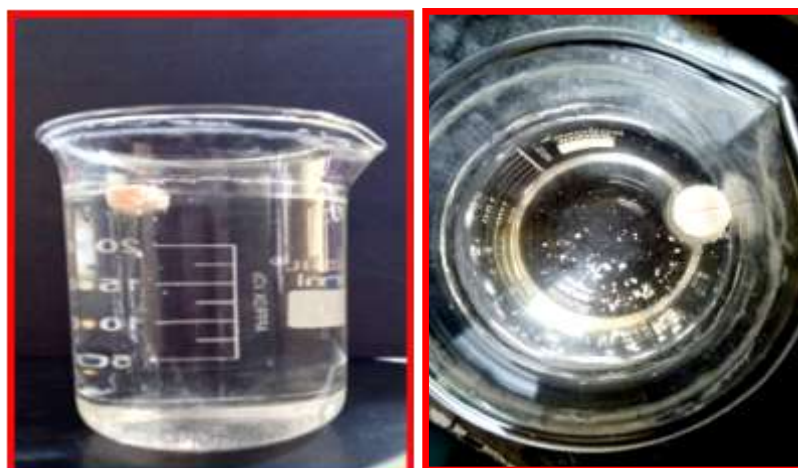
Table 4: Physico-chemical properties of Acyclovir tablets

3.2.3 In-Vitro Buoyancy and Lag Time Study: The floating lag time shown in figure.2 for all the formulations were found to be less than 2.3 minutes, The floating time duration shown in figure.2 was found to be up to 24 hrs in all formulations. The tablet floated with less lag time due to high concentration of gas

generating agent. It was observed that paddle speed affected the floating properties of tablet. However, some results revealed that, as the concentration Xanthan gum increased, total floating time increased, this is because of increased gel strength of matrices, which prevents escape of evolved carbon dioxide from matrices, leading to decreased

density of the formulations. The outermost hydrophilic polymer hydrates and swells and a gel barrier were 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, thus maintaining the integrity of the dosage form. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results concluded that linear relationship exists between swelling process and viscosity of polymer. So the presence of optimum amount of Xanthan gum and

Sodium bicarbonate are important in achieving good floating time and minimum floating lag time. Incorporation of sodium bicarbonate helps to produce carbon dioxide gas which entrapped inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and dosage form starts to float. As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent increases, the drug release increases and at the same time floating lags time decreases.



Side view Top view

Figure.2: In-vitro Buoyancy Study

Formulation codes	Floating lag time (sec/min /hrs)	Floating time (hrs)
F1	1 min	24
F2	3 min	24
F3	1.3 min	24
F4	2.3 min	24
F5	2.3 min	24
F6	1.3 min	24
F7	2 min	24

Table 5: Floating ability of various Acyclovir tablets

3.2.4 In-Vitro Release Study:

Timings	AF1	AF2	AF3	AF4
1 hr	67.23 ± 0.11	42.90 ± 0.67	39.99 ± 0.89	32.44 ± 0.78
2 hr	79.87 ± 0.32	53.56 ± 0.90	48.56 ± 0.14	44.92 ± 0.61
3 hr	86.43 ± 0.88	67.10 ± 0.78	58.99 ± 0.89	56.89 ± 1.87
4 hr	100.00 ± 0.46	74.55 ± 0.11	67.11 ± 1.89	64.11 ± 0.23
5 hr		89.30 ± 0.89	78.53 ± 0.98	75.51 ± 0.90
6 hr		99.98 ± 0.13	87.22 ± 0.55	84.94 ± 0.88
7 hr			98.99 ± 0.91	95.17 ± 0.19
8 hr				100.00 ± 0.89

Table 6: In-vitro release data of FDDS of Acyclovir AF1, AF2, AF3 & AF4

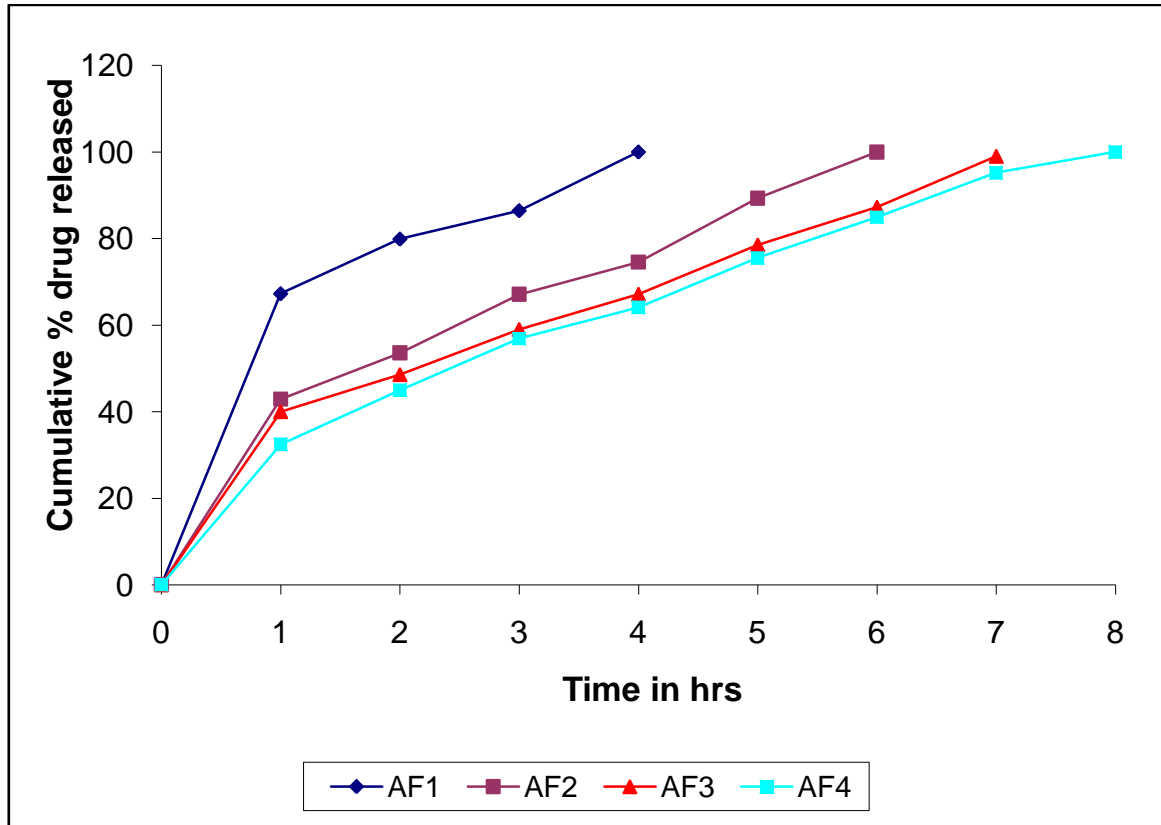


Figure 3: In-vitro release data of FDDS of Acyclovir AF1, AF2, AF3 & AF4

Timings	AF5	AF6	AF7
1 hr	30.01 ± 0.73	28.47 ± 0.19	29.15 ± 0.91
2 hr	37.68 ± 1.54	36.90 ± 0.27	36.89 ± 0.13
3 hr	49.97 ± 0.90	41.67 ± 0.79	47.11 ± 0.67
4 hr	56.55 ± 0.61	48.88 ± 1.89	54.21 ± 0.36
5 hr	64.66 ± 0.22	57.90 ± 0.62	64.78 ± 1.02
6 hr	71.88 ± 0.43	64.77 ± 0.44	71.44 ± 0.34
7 hr	80.12 ± 0.65	76.61 ± 1.01	78.39 ± 0.73
8 hr	99.97 ± 0.76	87.28 ± 0.36	85.55 ± 0.99
9 hr		99.38 ± 0.76	94.80 ± 0.22
10 hr			100.00 ± 0.97

Table 7: In vitro release data of FDDS of Acyclovir AF5, AF6, AF7 & AF8

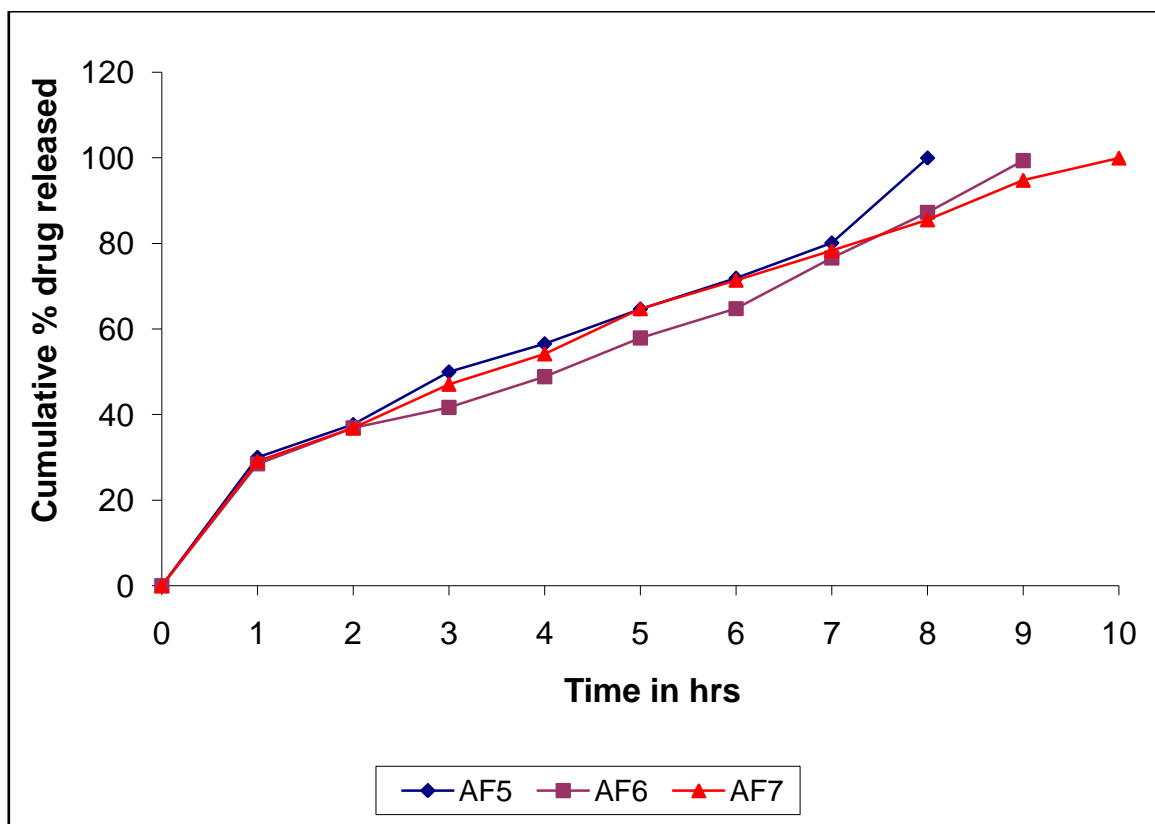


Figure.4: In vitro release data of FDDS of Acyclovir AF5, AF6, AF7 & AF8

Formulation code		Zero order	1 st order	Higuchi	Korsmeyer
AF1	r	0.9843	-0.9981	0.9870	0.9873
	A	57.165	1.700	35.305	1.817
	B	10.487	-0.1915	31.290	0.2835
AF2	r	0.9979	-0.9507	0.9891	0.9882
	A	30.225	1.997	0.05405	1.610
	B	11.431	-0.1715	39.430	0.4714
AF3	r	0.9955	-0.8565	0.9867	0.9844
	A	26.948	2.267	-0.2556	1.570
	B	12.276	-0.2433	35.706	0.4662
AF4	r	0.9964	-0.9395	0.9960	0.9973
	A	25.334	2.116	-8.267	1.497
	B	9.759	-0.1718	38.034	0.5705
AF5	r	0.9892	-0.9892	0.9731	0.9832
	A	19.796	1.965	-10.829	1.440
	B	9.235	-0.08864	35.418	0.5543
AF6	r	0.9925	-0.9409	0.9674	0.9722
	A	16.828	2.033	-13.997	1.400
	B	8.676	-0.09698	34.595	0.5619
AF7	r	0.9983	-0.9407	0.9936	0.9930
	A	22.418	2.092	-9.895	1.425
	B	7.966	-0.1240	33.885	0.5574

Table.8: Linear regression analysis data

'r'=Regression co-efficient
 'A'= Intercept
 'B'= Slope

Formulations	t ₅₀ (hr)	t ₇₀ (hr)	t ₉₀ (hr)
AF1	0.21	1.20	3.40
AF2	1.50	3.10	5.05
AF3	2.04	4.20	6.20
AF4	2.30	4.35	6.30
AF5	3.05	5.55	7.30
AF6	4.02	6.30	8.20
AF7	3.40	5.50	9.30

Table.9: Dissolution of t₅₀, t₇₀ and t₈₅ values of various formulations

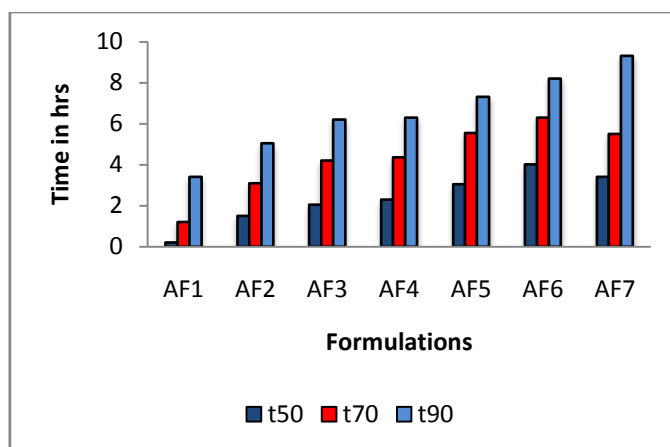


Figure.5: Dissolution of t₅₀, t₇₀ and t₈₅ values of various formulations

3.2.5 Stability Studies:

The most promised formulations were selected stability studies. Three month stability studies were performed as per ICH guidelines at a temperature of $45^{\circ} \pm 1^{\circ} \text{C}$ over a period of three month on the promising Floating tablet formulations F7 Sufficient number of tablets (10) were packed in aluminium packing and kept in stability chamber maintained at $45^{\circ} \pm 1^{\circ} \text{C} / 75 \pm 5 \% \text{RH}$ for 3 months. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and in-vitro floating studies were performed to determine the drug release profiles, the estimation of drug contents and data of dissolution and in-vitro floating studies are shown in tables 10 and 11.

Sl no	Time in days	Physical changes	Mean \pm SD (45°C)
1.	01	--	99.44 \pm 0.10
2.	30	No Change	98.25 \pm 0.18
3.	60	No Change	98.19 \pm 1.09
4.	90	No Change	98.12 \pm 1.52

Table-10: Stability studies of Formulation AF7

Sl. No.	Time (Hrs)	Cumulative*percent drug released \pm SD	
		45 \pm 1 ^o C	
		1 st Day	90 th Day
1.	01	17.23 \pm 0.12	16.23 \pm 0.08
2.	02	26.13 \pm 0.67	25.14 \pm 0.45
3.	03	31.20 \pm 1.05	30.01 \pm 0.41
4.	04	47.56 \pm 0.21	46.77 \pm 1.10
5.	05	58.98 \pm 0.13	57.11 \pm 0.76
6.	06	66.78 \pm 1.23	64.88 \pm 1.45
7.	07	76.67 \pm 0.34	74.89 \pm 0.14
8.	08	86.19 \pm 1.19	85.39 \pm 0.19
9.	09	96.65 \pm 0.22	95.90 \pm 0.75
10.	10	98.08 \pm 0.27	97.12 \pm 1.77

Table.11: InVitro release data of the stability formulation AF7

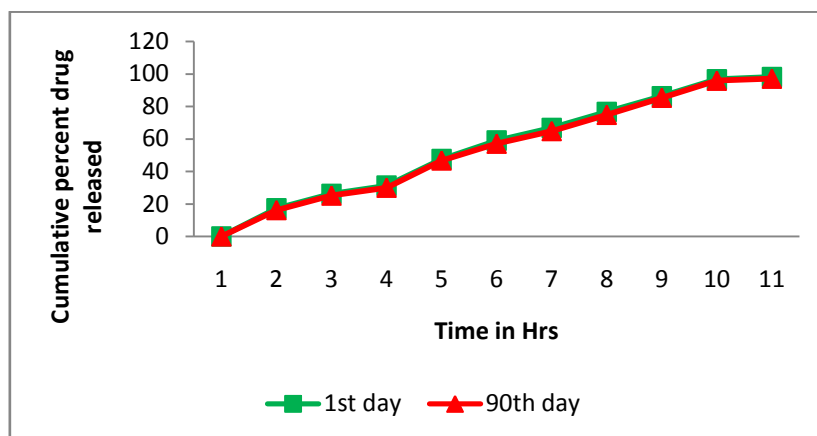


Figure.6: InVitro release data of the stability formulation AF7

IV. CONCLUSION:

From study it is evident that, floating tablets of Acyclovir can be developed to increase gastric residence time and thereby increasing its bioavailability. Further detailed investigations are required to establish efficacy of these formulations and fix the required dose, all the prepared tablet formulations were found to be good without capping and chipping. Formulated FDDS tablets gave satisfactory results for various post-

compressional parameters like hardness, friability, thickness, weight variation and content uniformity.

As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent (NaHCO₃) increases the drugs releases increases and at the same time floating lag time decreases. Sodium alginate and Xanthan gum has given extra adhesion property and helped to maintain the integrity of the tablet. Swelling index has a significant effect on the drug release. Short

term stability studies of formulation F7 indicates there are no significant changes in the drug content and dissolution parameter value at stable at 45°C and 75% RH for a period of 3 Months.

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