Effect of Polymers and Gas Forming Agents on The Floating Tablets of Acyclovir & Zidovudine

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Abstract*— Acyclovir, a commonly prescribed antiviral medication for the treatment of HIV/AIDS, and Zidovudine prevent HIV from replicating in human cells. Because of this, they are nearly insoluble in water and other aqueous fluids, which presents difficult formulation and development issues. The goal of this work was to build and optimize Acyclovir floating drug delivery systems employing sodium bicarbonate as a gas-generating agent and xanthan gum as the polymer. Zidovudine tablets were made with various ratios of microcrystalline cellulose, magnesium state, talc, sodium bicarbonate, citric acid, lactose, carbopol 934, and HPMC K4M and K15M utilizing PVP K30. In the presence of the dissolution medium (0.1 N HCl), sodium bicarbonate was introduced as a gas producing agent, causing carbon dioxide to be produced. Citric acid and sodium bicarbonate together gave the required floating ability, hence this combination was chosen for the formulation. Hardness, friability, weight variation, homogeneity of drug content, swelling index, in vitro buoyancy, and in vitro drug release profile were assessed for every intended batch of formulations. Every formulation floated continuously on the dissolution medium for over 24 hours, with a floating lag time of one to three minutes. The acquired data showed that all formulations showed a dissolving behavior regulated by non-Fickain diffusion, and that drug release occurred via mixed order kinetics. These investigations indicate that the formulation offers regulated release of the medication and is kept in the stomach for extended lengths of time. Consequently, enhance the drug's therapeutic impact by raising its bioavailability. The current study comes to the conclusion that the formulation ZF2, which contains 100 mg of HPMC K4M and AF4 containing 150 mg of Xanthan gum had the maximum drug release in the shortest amount of time.

Index Terms- Acyclovir, HPMC, Xanthan gum, Zidovudine.

I. INTRODUCTION

A prolonged, predictable drug delivery system can be achieved by controlling gastric residence time (GRT). This has led to a great deal of research over the past ten years on sustained release dosage forms for drugs, with the goal of prolonging gastric emptying time (GET), which has been reported to be between two and six hours in humans in the fed state[1]. This has also increased interest in novel dosage forms that have both a mechanism for controlled drug release and controlled GI transit time, as evidenced by recent scientific patent literature[2]. Extended medication retention in the stomach shortens the gastric transit time. Research on gastric emptying rates has shown that controlled release dose forms taken orally can have two main negative effects: a short stomach residency duration and an irregular gastric emptying rate[3,4]. The short GIT residence time, drug degradation, and stomach emptying associated with the oral route are its primary drawbacks, making the drug delivery system unpredictable. System's stomach retention time can be extended by creating the Floating Drug Delivery System (FDDS)[5]. The most practical and widely used route of medication administration is oral ingestion[6]. It has a limited absorption window in the GI that is hampered by low bioavailability due to drug's incomplete release[7]. After being exposed to an aqueous media, HPMC absorbs water to form a gel that regulates the release of the medicine[8]. Zidovudine, a nucleoside analog reverse transcriptase inhibitor (NRTI), was the first antiretroviral medication authorized in the United States for use in the treatment of HIV/AIDS[9]. It considerably lowers the virus's ability to replicate in individuals, improving their health and immunity[10,11]. It can also be used to stop the spread of HIV, for example, from a woman to her child during childbirth or following a needlestick injury.

When used alone in HIV-positive patients, it reduces but does not completely stop HIV replication[12]. There is a window for Acyclovir absorption in the small intestine and duodenum. Merely 20% of the medicine is absorbed following oral delivery, with the remaining 80% being eliminated through the stool. It is possible to increase the bioavailability of Acyclovir after repeatedly administering tiny doses orally. These data suggest that extending the gastric residence time may improve the bioavailability of Acyclovir. Consequently, Acyclovir was chosen as a model drug in the design of a fixed-dose combination supplement (FDDS) to enhance its oral bioavailability, and Zidovudine floating tablets were designed for extended release and longer gastric retention time. The Zidovudine and Acyclovir floating tablets were made using a wet granulation technique.

Mechanism of Action[13]:
Zidovudine: Zidovudine is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis.

Acyclovir: Acyclovir triphosphate competitively inhibits viral DNA polymerase by acting as an analog to deoxyguanosine triphosphate (dGTP). Incorporation of acyclovir triphosphate into DNA results in chain termination since the absence of a 3' hydroxyl group prevents the attachment of additional nucleosides.

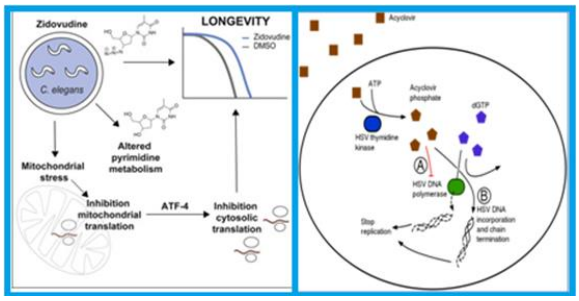

Fig 1: Mechanism of Action of Zidovudine & Acyclovir

Factors Affecting Gastric Retension[14,15]:
Numerous factors influence gastric retention time (GRT), including:

- Dose form size and shape
- Density
- Concomitant medication and food consumption
- Anatomical variables such as age, gender, body weight, posture, and illness conditions.
- An analog of guanine, Acyclovir is used to treat viral infections. Oral bioavailability has been found to be 10-20%, with a plasma elimination half-life of 1-2 hours[16].

Advantages of FDDS [17,18]:

- Sustained drug delivery: Because of their altered GRT, dosage forms of the HBS type stay in the stomach for a number of hours. The GRT's extension maintains the medication release pattern.
- HBS offers a superior substitute for preserving systemic drug concentrations within the therapeutic window.
- These systems offer a simple means of preserving a steady blood level that is easier to administer and result in greater patient compliance.
- Drugs with specific absorption sites in the stomach and upper intestine can be designed to deliver the medication to that particular place.

Drugs that are required to be formulated into gastro retentive dosage forms include[19]:

- Medications that act locally in the stomach
- Medications that are mostly absorbed there
- Medications with low solubility at alkaline pH.
- Medication with a limited absorption window.
- Both those that break down in the colon and
- Those that are quickly absorbed from the GI tract.

II. MATERIALS AND METHODS

Zidovudine was obtained as a gift sample from Emcure Pharma Pvt Ltd. Pune, HPMC was gifted by AstraZeneca Pvt. Ltd. Bangalore, 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.

Preparation Method of Floating Tablets:[20] Drug and polymers were mixed in a poly bag and the mixture was passed through a mesh No. 60. Granulation was done with a solution of PVP K30 in sufficient

isopropyl alcohol. The wet mass was passed through mesh No. 12. The wet granules were dried at 60º C for about 4 hours. The dried granules were sized by a mesh No. 18 and mixed with sodium bicarbonate, citric acid, magnesium stearate and talc. Granules thus obtained were compressed into tablets.

Table 1: FORMULATION TABLE

Ingredietns	ZF1	ZF2	ZF3	ZF4	AF1	AF2	AF3	AF4
Zidovudine	300 mg	300 mg	300 mg	300 mg	-	-	-	-
Acyclovir	-	-	-	-	400 mg	400 mg	400 mg	400 mg
HPMC K4 M	75 mg	100 mg	-	-	-	-	-	-
HPMC K15 M	-	-	75 mg	100 mg	-	-	-	-
Xanthan gum	-	-	-	-	25 mg	50 mg	100 mg	150 mg
Carbopol 934	20 mg	20 mg	20 mg	20 mg	-	-	-	-
Sodium aliginate	-	-	-	-	175 mg	150 mg	100 mg	50 mg
Sodium CMC	-	-	-	-	50 mg	50 mg	50 mg	50 mg
PVP K30	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Magnesium Stearate	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Talc	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Sodium Bicarbonate	80 mg	80 mg	80 mg	80 mg	150 mg	150 mg	150 mg	150 mg
Citric acid	20 mg	20 mg	20 mg	20 mg	-	-	-	-
Lactose	110 mg	105 mg	110 mg	105 mg	-	-	-	-
Microcrystalline Cellulose	20 mg	20 mg	20 mg	20 mg	-	-	-	-
Total weight	665 mg	665 mg	665 mg	665 mg	840 mg	840 mg	)	)

III. RESULT & DISCUSSION

Pre-Compressional Parameters:

The qualities and attributes of the powder blend are crucial in formulations. The prepared granules' powder blend qualities are displayed in Table 2. Particle size, shape, and adhesion propensity all affect bulk density, which in turn affects other qualities like dissolution, porosity, and compressibility. Good packing capacity of the powder mix is shown by the bulk density and tapped density, which were found to be between 0.650 ± 0.07 and 0.750 ± 0.02 gm/cm3 and 0.690 ± 0.02 and 0.926 ± 0.02 gm/cm3, respectively. Carr's index for the inter-particulate cohesive property was calculated using measurements of the angle of repose, and the effects of packing solids with bulk and tapping density on their shape were examined. The bulk and tapped density tests revealed that a powder's density is dependent on how its particles are packed, and that density varies as the powder solidifies. The degree of consolidation is specific to the powder, and the inter-particulate friction is correlated with the ratio of these densities. The percent compressibility ratio served as a flow index. Particle adhesion and cohesive forces influence flow characteristics. Carr's index values below 15% typically indicate strong flow qualities, while values above 25% suggest weak flow ability. The results showed that Carr's index ranged from 21.12 ± 0.03 to 28.22 ± 0.05. The powder column stability was assessed using Hausner's ratio approach, which also yielded an estimate of the flow characteristics. The results ranged from 1.10 ± 0.03 to 1.22 ± 0.04. Hausner's ratio was found to have a modest range, indicating high flow ability. To evaluate flow ability, other kinds of angular properties have been used. The powder's or granules' capacity to flow is indicated by their angle of repose. Angle of repose is appropriate for particles larger than 150 m. An angle of ≥400 indicates a poor flowing material, while

values ≤300 often suggest a free flowing substance. Granules had good flow qualities, as evidenced by the angle of repose of all the formulations, which ranged from 22.10 ± 0.08 to 30.21 ± 0.07.

Table 2: Precompressional parameters of all the Formulations

Formulations	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's Index	Hausner Ratio	Angle of repose (θ)
ZF1	0.680 ± 0.01	0.881 ± 0.05	24.10 ± 0.10	1.14 ± 0.02	22.10 ± 0.08
ZF2	0.710 ± 0.08	0.743 ± 0.02	28.22 ± 0.05	1.21 ± 0.04	30.21 ± 0.07
ZF3	0.750 ± 0.02	0.690± 0.02	21.17 ± 0.12	1.22 ± 0.04	25.12 ± 0.10
ZF4	0.650 ± 0.07	0.850 ± 0.07	24.14 ± 0.09	1.17 ± 0.02	23.40 ± 0.18
AF1	0.734 ± 0.07	0.914 ± 0.01	21.12 ± 0.03	1.10 ± 0.03	28.90 ± 0.12
AF2	0.651 ± 0.01	0.926 ± 0.02	22.28 ± 0.09	1.18 ± 0.05	24.99 ± 0.10
AF3	0.691 ± 0.07	0.898 ± 0.07	27.87 ± 0.01	1.11 ± 0.04	26.78 ± 0.17
AF4	0.710 ± 0.02	0.811 ± 0.04	21.56 ± 0.09	1.21 ± 0.10	27.11 ± 0.14

Post Compressional Parameters: Every formulation was assessed based on a number of factors, including hardness, diameter, and thickness. Table 3 displays all of the manufactured tablet formulations. It was observed that there was minimal variance in tablet thickness, indicating that the powder blends exhibited uniform behaviour during tablet compression and constant particle size.

Tablet thickness and diameter: Vernier calipers were used to measure the formulations, and the results indicate that neither will alter. The range of thickness was between 4.1 ± 0.03 and 4.9 ± 0.02.

Hardness: A Pfizer hardness tester was used to gauge the tablets' hardness. The hardness measured in cm^2 was between 4.1 ± 0.07 and 8.0 ± 0.04 Kg. Tablet porosity and density variations are reflected in tablet hardness, which influences the pace at which the tablet's surface penetrates the dissolving media and leads to distinct drug release patterns.

Weight Variation: The weight (mg) of each of 20 separate pills was obtained by dusting each tablet off and placing it in an electronic scale. The sample mean and % deviation of the weight data obtained from the tablets were examined. Table 3 displays the outcomes. Friability: The current investigation on tablets is within the allowed range, with a small fluctuation in friability due to variations in the compression force and overall weight. The kind of filler and moisture content of tablets also affect their friability. The results indicate that the friability ranges from 0.32 ± 0.080 to 0.67 ± 0.014, as indicated in Table 3.

Drug Content: The drug content ranged from 97.54 ± 0.11 to 99.89 ± 0.22, indicating good homogeneity across all produced formulations. The reading agrees with I P., indicating that the medication was evenly dispersed throughout the compressed tablet.

Table 3: Post-Compressional properties tablets

Formulations	Thickness (mm)	Diameter (mm)	Hardness (kg/cm2)	Friability (%)	Drug Content (%)
ZF1	4.2 ± 0.02	11.8 ± 0.06	7.4 ± 0.02	0.45 ± 0.016	97.70 ± 0.47
ZF2	4.4 ± 0.02	11.9 ± 0.08	6.9 ± 0.05	0.50 ± 0.020	98.12 ± 0.80
ZF3	4.1 ± 0.03	12.1 ± 0.06	7.9 ± 0.09	0.32 ± 0.080	99.10 ± 0.90
ZF4	4.3 ± 0.01	11.8 ± 0.09	8.0 ± 0.04	0.40 ± 0.054	98.78 ± 0.36
AF1	4.9 ± 0.02	12.1 ± 0.01	4.5 ± 0.02	0.52 ± 0.031	98.10 ± 0.32
AF2	4.7 ± 0.02	11.8 ± 0.02	4.2 ± 0.03	0.58 ± 0.054	97.54 ± 0.11

AF3	4.7 ± 0.01	12.0 ± 0.07	4.1 ± 0.07	0.64 ± 0.011	98.23 ± 0.12
AF4	4.7 ± 0.01	11.7 ± 0.02	4.8 ± 0.04	0.67 ± 0.014	99.89 ± 0.22

In-Vitro Buoyancy & Lag Time Study: Every formulation had a floating lag time of less than three minutes, and every formulation had a floating time length of up to twenty-four hours. The outcomes are shown in Figure 2 and Table 4. Because of the high concentration of gas producing agent, the tablet floated faster. According to certain findings, the total floating duration rose as the concentrations of HPMC K4M and Xanthan gum increased. This is because the matrices' higher gel strength prevents developed carbon dioxide from escaping, which lowers the density of the formulations. The drug release rate reduces with increasing polymer concentration in the tablet formulation, while the drug release increases with increasing concentration of gas producing agent (NaHCO3) and simultaneously decreases with floating lag time.

Table 4: *In-Vitro* Buoyancy & Lag Time Study:

Formulation codes	Floating lag time (min)	Floating time (hrs)
ZF1	2.3 min	24
ZF2	3 min	24
ZF3	2.3 min	24
ZF4	3 min	24
AF1	1 min	24
AF2	3 min	24
AF3	2.3 min	24
AF4	2 min	24

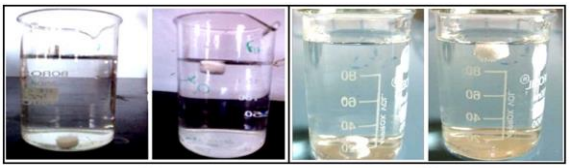

Fig 2: Floating tablets of (a) Zidovudine & (b) Acyclovir

InVitro Release Study:

Table 5: *Invitro* release data of FDDS of Zidovudine ZF1, ZF2, ZF3 & ZF4

Timings	ZF1	ZF2	ZF3	ZF4
0 hr	0	0	0	0
1 hr	14.00±0.51	15.13±0.45	10.23±0.11	12.23±0.89
2 hr	19.23±0.84	23.89±0.14	12.87±0.55	14.76±0.44
3 hr	27.78±0.16	31.54±0.71	16.77±0.41	17.52±0.14
4 hr	39.11±0.90	39.66±0.23	19.32±0.89	19.88±0.99
5 hr	43.25±0.89	47.23±0.19	21.63±0.34	22.41±0.13
6 hr	46.21±0.20	54.25±0.20	36.99±0.71	34.26±0.58
7 hr	53.22±0.54	59.67±0.48	44.45±0.12	47.88±0.15
8 hr	60.77±0.52	68.99±0.88	57.61±0.33	59.11±0.90
9 hr	76.58±0.13	87.55±0.87	67.43±0.56	66.96±0.52
10 hr	85.26±0.10	94.16±0.33	77.94±0.36	78.00±0.10
11 hr	94.17±0.53	96.97±0.13	89.23±0.51	91.55±0.20
12 hr	98.13±0.74	99.45±0.14	95.23±0.58	93.47±0.11

13 hr	-	-	99.35±0.44	97.29±0.70

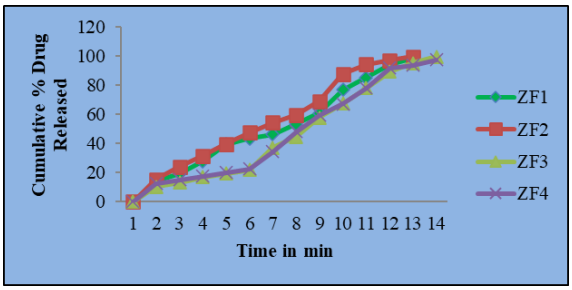

Fig 3: *Invitro* release curve of FDDS of Zidovudine ZF1, ZF2, ZF3 & ZF4

Table 6: *Invitro* release data of FDDS of Acyclovir AF11, AF12, AF13 & AF14

Timings	AF1	AF2	AF3	AF4
0 hr	0	0	0	0
1 hr	67.23 ± 0.11	42.90 ± 0.67	32.44 ± 0.78	26.15 ± 0.91
2 hr	79.87 ± 0.32	53.56 ± 0.90	44.92 ± 0.61	34.89 ± 0.13
3 hr	86.43 ± 0.88	67.10 ± 0.78	56.89 ± 1.87	43.11 ± 0.67
4 hr	100.00 ± 0.00	74.55 ± 0.11	64.11 ± 0.23	51.21 ± 0.36
5 hr	-	89.30 ± 0.89	75.51 ± 0.90	56.78 ± 1.02
6 hr	-	99.98 ± 0.13	84.94 ± 0.88	62.44 ± 0.34
7 hr	-	100.00 ± 0.00	95.17 ± 0.19	70.39 ± 0.73
8 hr	-	-	100.00 ± 0.89	78.55 ± 0.99
9 hr	-	-	-	85.80 ± 0.22
10 hr	-	-	-	98.00 ± 0.45
11 hr	-	-	-	100.00 ± 0.97

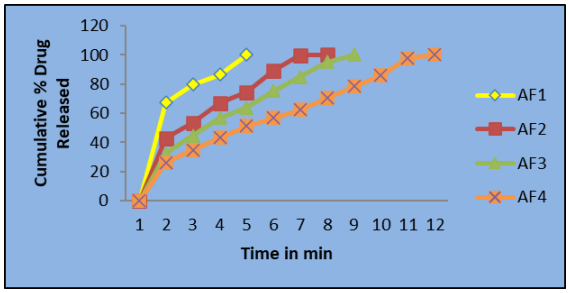

Fig 4: *Invitro* release curve of FDDS of Acyclovir AF1, AF2, AF3 & AF4

Table 7: Dissolution data of t50 and t90 values

Formulations	t50 (hr)	t90 (hr)
ZF1	6.30	10.40
ZF2	5.30	9.30
ZF3	7.30	10.50
ZF4	7.50	11.10
AF1	0.20	3.30
AF2	2.30	5.10
AF3	2.50	6.30
AF4	3.50	9.30

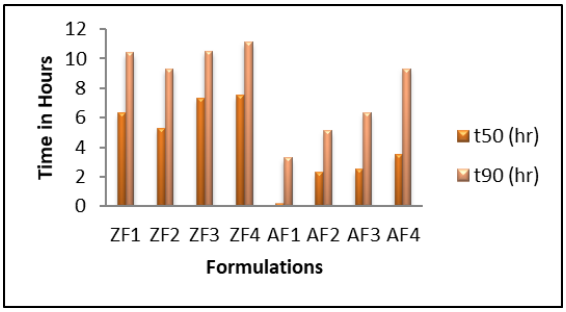

Fig 5: Dissolution graph of t50 and t90 values

CONCLUSION

Research has shown that Zidovudine and Acyclovir floating tablets can be created to lengthen the duration that the medication is in the stomach, boosting its bioavailability. It was discovered that every manufactured tablet formulation worked well without chipping or capping. For a number of post-compressional characteristics, including hardness, friability, thickness, weight variation, and content homogeneity, the formulated FDDS tablets produced good results.

The current study comes to the conclusion that the formulation ZF2, which contains 100 mg of HPMC K4M and AF4 containing 150 mg of Xanthan gum had the maximum drug release in the shortest amount of time. The drug release rate reduces as the amount of polymer in the tablet formulation grows, and the drug releases increase and the floating lag time decreases with the concentration of the gas producing agent (NaHCO3) increases. Xanthan gum and sodium alginate have improved the tablet's adherence and helped to keep it intact.

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