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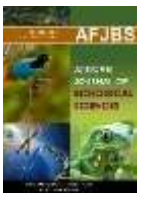

PREPARATION AND EVALUATION OF GANCICLOVIR FLOATING TABLET

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Abstract

INTRODUCTION: Over the past three decades, oral controlled release dosage forms have been created due to their significant therapeutic benefits, including simplicity of administration, patient compliance, and formulation flexibility. Floating drug delivery system (FDDS) is one of the most practical methods for generating a prolonged predictable drug delivery profile since it extends the stomach residence period and boosts the dosage form's overall bioavailability..

MATERIALS AND METHODS: The Ganciclovir is used in this trial was manufactured as a floating tablet. Three formulations were made. Drug concentration is constant in each formulation whereas excipient concentration varies. The formulation employed the direct compression method. Other common excipients were combined with other polymers, including HPMC K 15, HPMC K 100, and MCC. Effervescent agent was sodium bicarbonate. The prepared powder blend's preformulation properties, including true density, bulk density, compressibility index, angle of repose, and Hausner's ratio, were assessed. Hardness, friability, weight fluctuation, thickness, drug content, swelling study, floating time, and in vitro dissolution analysis were all examined as physical characteristics of the tablet.

RESULTS AND DISCUSSION: The preformulation study's findings demonstrated that the powder blend's good flow characteristics and packing potential. All 3 formulations (F1 to F3) demonstrated good mechanical strength and complied with pharmacopoeial standards, according to the findings of the hardness and friability test. The improved formulation F3 met the standards with a drug release of 94.03±.2.05 %, a floating lag time of 1.39 min, and a total floating time of >14 h. Overall findings indicated that the formulation meets the criteria needed for an effective floating medication delivery system..

CONCLUSION: The findings of this study clearly demonstrate the viability of creating a drug delivery system for ganciclovir that prolongs the time the drug is retained in the stomach while allowing for regulated release.

Keywords: Ganciclovir, Floating time, Floating tablets, Swelling index

Introduction

The physical shape or nature in which a pharmaceutical is given to a patient is known as a dose form. Tablet, capsule, pill, powder, combination, syrup, cream, injections, suppositories, and many other dosage forms are available. The various dose forms are injected into the body via a variety of delivery methods, such as transdermal, parenteral, and oral. Due to its simplicity of administration, the oral route is regarded as the most significant method among these. Traditional drug administration has a number of drawbacks, including lower bioavailability and drug leakage. Innovative drug delivery strategies were created to overcome these drawbacks. When a medicine is presented at the site of action and released at a specific pace over a set period of time, this is referred to as a drug delivery system. The oral route is increasingly being employed to deliver therapeutic drugs since it is simple to administer and has a cheap cost, which results in high patient compliance. Oral medication delivery methods make up more than half of all drug delivery systems on the market. GRDDs are dosage forms that can be retained in the stomach. By constantly releasing the drug for a lengthy time before it reaches its absorption site, GRDDSs can enhance the controlled delivery of medications with an absorption window. In 1968, Davis published the first description of floating systems. FDDS is a useful method for increasing the drug's bioavailability by extending the stomach residence period. FDDS are low density systems that can float over the stomach's contents and stay there for a while without slowing down the stomach's rate of emptying. The medicine is released slowly at the prescribed pace while the apparatus floats over the contents of the stomach, increasing GRT and minimising fluctuations in plasma drug concentration[1,2,3].

Ganciclovir belongs to the group of drugs known as antivirals. It is used to prevent and treat CMV illness in transplant recipients as well as to treat cytomegalovirus infections (CMV), retinitis, colitis, and esophagitis in AIDS patients and other immunocompromised people (2000). Typically, it is taken three to six times per day with food. A synthetic counterpart of 2′-deoxyguanosine is ganciclovir[4,5].

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Material and Methods

Material

The API, ganciclovir, was received as a free sample from Nacto Pharma. Trivandrum Scientific Supplies provided the HPMC K15 M and HPMC K100 M, sodium bicarbonate, magnesium stearate, and microcrystalline cellulose. All of the chemicals, solvents, and reagents utilised were of analytical quality**.**

Methods

Preformulation Study[6,7]

Preformulation is the study that focuses on the various physicochemical characteristics of drugs that may obstruct the development of dosage forms and drugs. It is the initial stage in the creation of the dosage form. Preformulation studies determine the kinetic rate profile of the dosage form and ensure that the medication is compatible with additional excipients in order to generate a stable, effective, and safe dosage form.

Physicochemical properties and identification of drug

Identification of drug by IR Spectroscopy

The IR spectra of the drug sample (Ganciclovir) were compared with the standard IR spectra of pure medicine for the purpose of identifying the specific medication.

Physicochemical properties of drug

General appearance: The drug's colour, odour, and taste were evaluated.

Solubility of drug:

To ascertain its solubility in the dissolution medium and other solvent, a solubility test was performed.

Drug –excipient compatibility

For the drug-excipient compatibility investigation, IR spectroscopy was utilised. FT-IR spectra of the pure drug and the drug + HPMC were acquired. Characteristic peaks of the pure drug were compared with peaks of the drug + HPMC. For the same, differential scanning calorimetry is also used.

Precompression parameters of powder blends[8,9]

1. Bulk and Tapped density

The powder, 10gm, was measured. A measured quantity of the provided powder was added to a 100ml measuring cylinder. Powder was placed into a measuring cylinder, and the initial volume was measured for bulk density. After that, the cylinder was continuously tapped until no more volume change was seen. Keep a record of the tapped density's final volume. Then, using the provided formula, bulk and tapped density were computed.

BULK DENSITY = WEIGHT OF POWDER / INITIAL VOLUME

TAPPED DENSITY = WEIGHT OF POWDER / TAPPED VOLUME

2 . Carr’s index

Compressibility index is another name for Carr's index. The amount that can be collected from bulk and tapped density is significant. Using the provided formula, Carr's compressibility index was used to determine the compressibility of the raw material and mix.

Carr’s index (%) = {(tapped density)- (bulk density)/ (tapped density}×100

3. Hausner’s ratio

A measurement of a powder's flowability is the Hausner's ratio. Equation is used to compute Hausner's ratio.

Hausner’s ratio = Tapped density / Bulk density

4. Angle of repose

Angle of repose is the largest angle that can be formed between the top of a pile of powder and the horizontal plane. Incorrect flow results from using the angle of repose to measure frictional force. The angle of repose was calculated using the funnel stand method. Using the provided equation, the average value is taken, and the angle of repose is determined**.**

$\tan \theta = h/r$

$\theta = \tan^{-1} (h/r)$

Where θ = Angle of repose

h = height of the heap

r = radius of the heap ϖ

Compression of Tablet

Ganciclovir floating tablets were created utilising the direct compression method and several ingredients. Each ingredient was individually processed through sieve number 40, including the Ganciclovir. A computerised balance was used to weigh the necessary number of ingredients for each mixture. In a mortar and pestle, the following ingredients were geometrically combined: drug, HPMC K15M, HPMC K100M, MCC, MCC, and sodium bicarbonate. The powder blends were then lubricated with magnesium stearate. Using a plastic bag, the final mixing was completed. Using an adjusted punching machine, 400 mg tablets with a hardness of 10–12 kg/cm2 were produced. Tablets were gathered and assessed. As indicated in table 1, 3 different formulations of Ganciclovir floating tablets (F1 to F3) were created using varying concentrations of HPMC K1M and HPMC K100M.

Table 1: Formulation of Ganciclovir Floating tablets

Ingredients (mg)	F1	F2	F3
Ganciclovir	250	250	250
HPMC K15M	20	0	20
HPMC K100M	0	25	25
Sodium bicarbonate	40	40	40
Microcrystalline Cellulose	87	82	62
Magnesium stearate	3	3	3
Total Weight/ tablet	400	400	400

Post Compression Parameter Evaluation [10-13]

The manufactured floating tablets underwent evaluations for their overall look, thickness, hardness, friability, weight fluctuation, in vitro buoyancy, in vitro dissolution investigations, and short-term stability testing.

General appearance

The first most crucial factor in a tablet's adoption is its organoleptic qualities (general look). It is very important for consumer approval. Organoleptic characteristics of prepared pills were assessed (colour, odour, taste and shape)

Thickness

Vernier callipers were used to measure the thickness of 6 randomly chosen tablets from each formulation, and an average value was then calculated.

Hardness

The ability of a tablet to withstand mechanical shocks is referred to as its hardness. The breaking point of a tablet is examined using a hardness test. Six pills from each formulation were taken. Pfizer's hardness tester was used to measure the tablet's hardness. The unit of hardness was Kg/cm^2.

Friability

The friability was assessed using the Roche friabilator, which is given as a percentage. 20 pills were taken; they were weighed originally (W initial). Selected tablets that had been preweighed were put in the friabilator, which rotated for 4 minutes at a speed of 25 rpm (100 revolutions). The tablets were then taken out of the chamber, cleaned, and weighed once again (W final). Next, the% friability was determined using the formula

F= {(W initial)- (W final)/ (W initial)}×100

Weight variation

20 tablets were randomly selected from each formulation and weighed separately. Utilizing the provided formula, the average weight was derived, along with the % deviation from the average weight.

% deviation ={(Average weight – initial weight) /Average weight} X 100

In vitro buoyancy/ floating study

All of the formulations were subjected to in-vitro buoyancy tests. In a 100 ml beaker with 0.1N HCl, the tablets from each formulation that were randomly chosen were retained. Total floating time (TFT) is the formula used to calculate how long a dosage form stays continuously on the surface of a medium. Floating lag time is the amount of time it takes for a tablet to rise to the surface and float.

Swelling Study

The weight gain of a dosage unit was used to assess its swelling behaviour. The swelling index of the tablets was determined by placing them in the dissolving device's basket with the dissolution liquid at $37\pm.5^0$C. After two, four, six, eight, and up to twelve hours, each dissolution basket containing a tablet was taken out, blotted with tissue paper to remove any extra water, and

weighed on an analytical scale. The experiment was performed in triplicate for each time point, and the swelling index was calculated

In vitro dissolution studies

Utilizing USP type II equipment, in vitro dissolution experiments of cimetidine floating tablets were performed (paddle type). The dissolution vessel was filled with 900ml of 0.1 N HCL solution with a pH of 1.2, and the medium's temperature was then set to 37±.5^{0}C. One tablet was added to each dissolving vessel after the paddle's rotational speed was set to 50 rpm. Every hour during 12 hours, 10ml of solution was taken out of the dissolving containers, and samples were then replaced with 10ml of brand-new dissolution media. Using a UV spectrophotometer, the solution's absorbance at 218 nm was determined.

RESULTS AND DISCUSSION

Solubility Analysis

An analysis of the drug sample's solubility has been done. Drug is discovered to be soluble in water, dimethyl sulfoxide, and 0.1 N HCl. Table 2 displays the outcomes.

Table 2: Solubility analysis of Ganciclovir

Solvent	Solubility
0.1 N HCl	Very soluble
Water	Very soluble
Dimethyl-sulfoxide (DMSO	Very soluble
Phosphate buffer pH 6.8	Freely soluble

Melting Point determination

Melting temperature is within the typical range of 250 °C, proving that Ganciclovir is a clean medicine and free of contaminants. Table 3 displays the outcomes.

Table 3: Melting point determination of Ganciclovir

Melting point of sample in literature	Melting point of sample experimented determine
250^{o}C	250^{o}C ± 1

Drug-polymer interaction studies

Fourier transform infrared spectroscopy (FTIR) studies

Pure drugs and drug-excipient combinations' FT-IR spectra were collected. With only minor modifications in their positions, all the major bands visible in the spectrum of the pure drug are likewise present in the spectrum of the drug plus polymer mixture. The lack of

interaction between the medicine and excipients is therefore amply demonstrated. The findings are displayed in Table 4, Figure 1, Figure 2, and Figure 3.

Table 4 FTIR analysis of Ganciclovir

Sl.No.	Functional Group	Frequency (cm-1)
1	NH2(stretching)	3358.25
2	N-H(Stretching)	3151.61
3	C-H(Stretching)	33048.47
4	C-H(Stretching)	2734.24
5	C=O(Stretching)	1628.39
6	C=N(stretching)	1530.73
7	C=N(bending)	1328.10
8	C-O-C(stretching)	1220.37

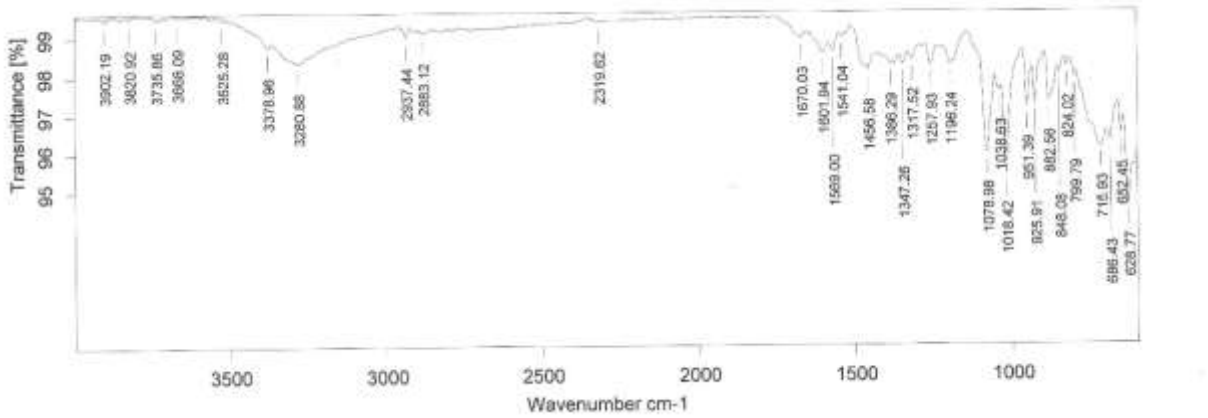

Figure 1: FTIR Spectrum of Ganciclovir

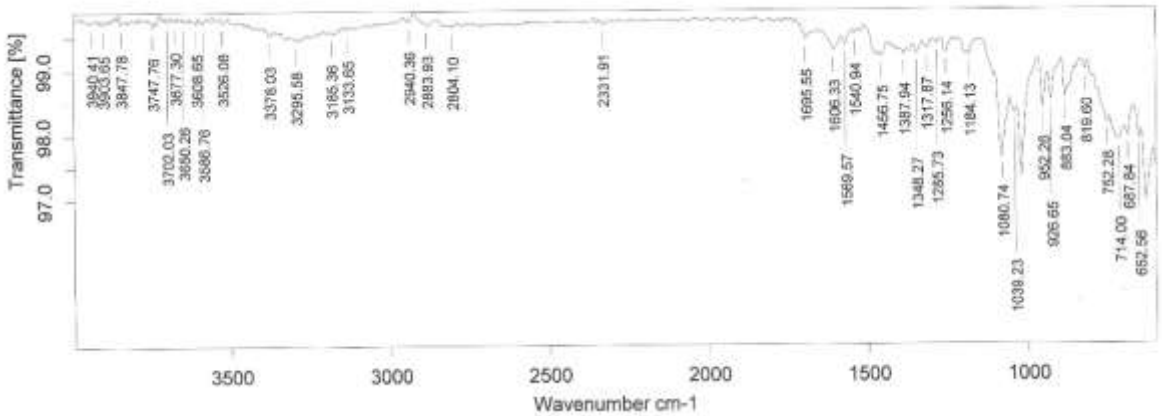

Figure 2: FTIR Spectrum of Ganciclovir + HPMC K 15

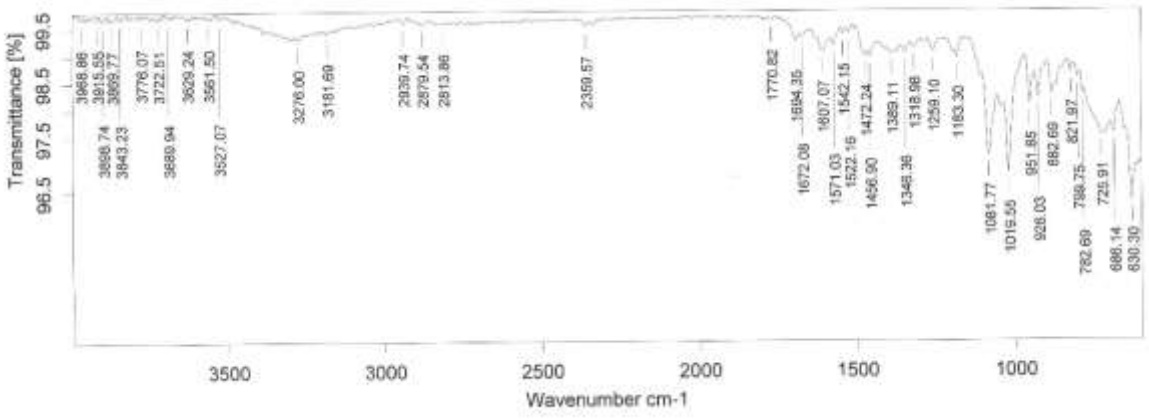

Figure 3: FTIR Spectrum of Ganciclovir + HPMC K 100

Differential Scanning Calorimetry (DSC) Studies

It is evident from the DSC thermograms of the pure drug and the drug-excipient mixture that there was no interaction between the drug and the polymers and that the drug existed in its unchanged form, as shown in Figures 4, 5, and 6. The endothermic peak that corresponds to the melting point of the pure drug was prominent in all of the drug-excipient mixture.

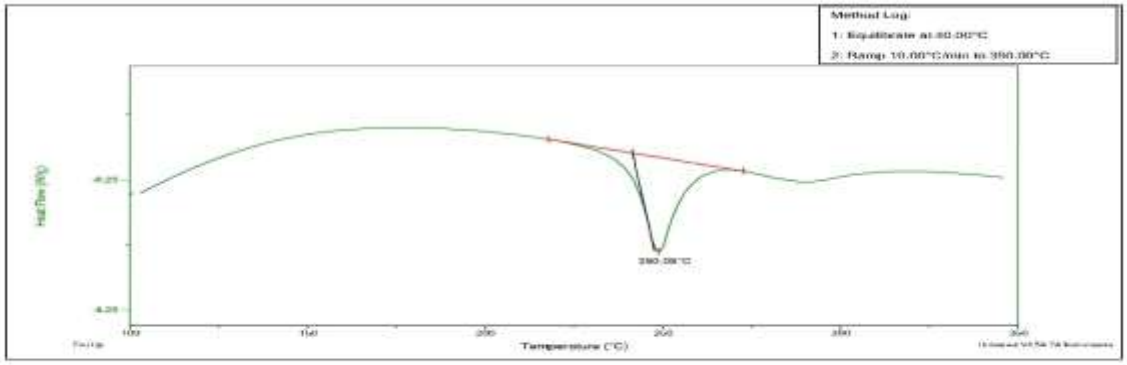

Figure 4: DSC of Ganciclovir

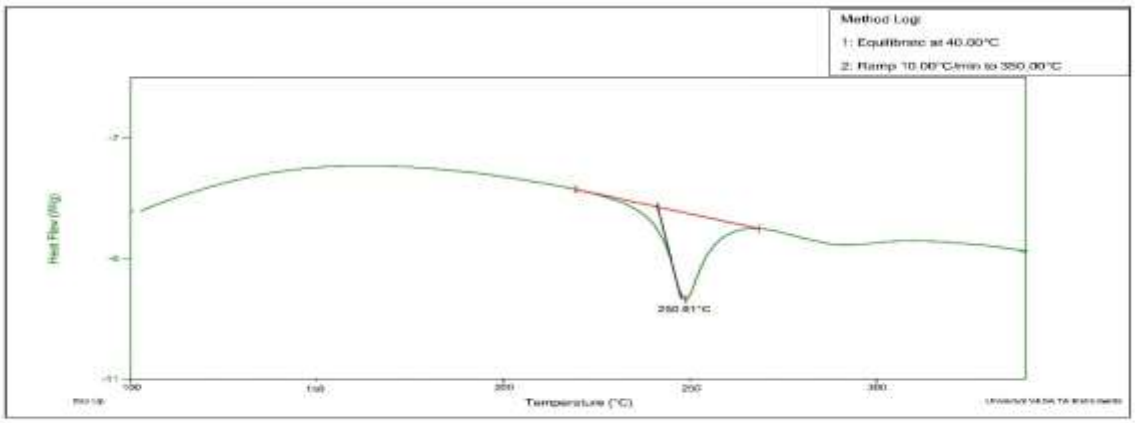

Figure 5: DSC of Ganciclovir + K 15

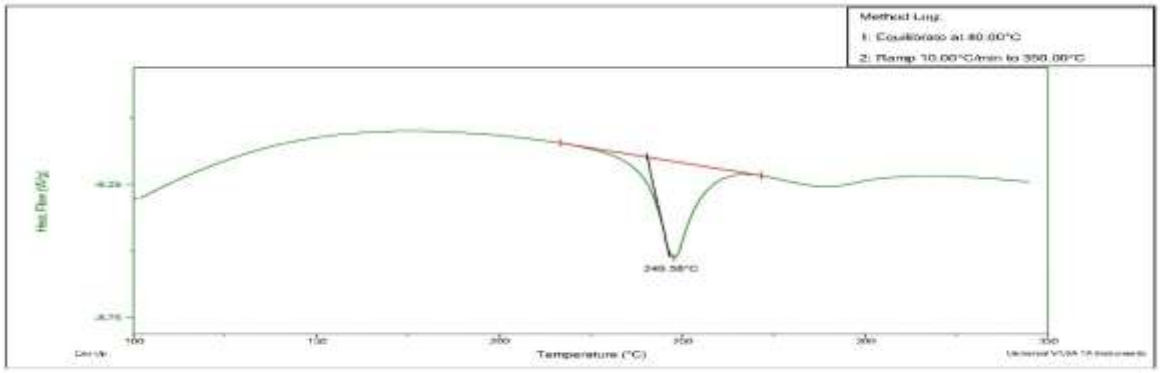

Figure 6: DSC of Ganciclovir + K 100

Evaluation of floating tablets

Preformulation studies

The bulk density ranged from 0.3969±.0196 g/ml to 0.4961±.0.0020 g/ml, the tapped density ranged from 0.4504±.0079 g/ml to 0.5347±.0057 g/ml, Hausner's ratio ranged from 1.44 to 1.97, and the Carr's index ranged from 18.47% to 21.76 %, angle of repose ranged from 24.49± 0.0098 ˚ C to 24.97± 0.1391 ˚ C for the powder blend of all three formulations, as shown in Table 5.

Table 5: Precompression parameters of designed formulations

Formulation code	Bulkdensity (mg/mL)	Tapped density (mg/mL)	Carr'sindex (%)	Angle of repose	Hausner's ratio
F1	0.4961±0.0020	0.4664±0.0093	18.47	24.97±0.1391	1.44
F 2	0.3969±0.0196	0.5347±0.0057	21.76	24.49±0.0998	1.97
F 3	0.4908±0.0680	0.4504±0.0079	22.04	26.63±0.1310	1.53

Postcompression studies

Sodium bicarbonate, microcrystalline cellulose, magnesium stearate, and HPMC (K15M and K100M) were used to make ganciclovir floating tablets using the direct compression method. There were 4 formulations created in total. The tablets were round, biconvex, and white in colour without any scoring on the sides. Each tablet had a refined appearance. All of the formulations were found to have hardness between 10.53±0.014 and 11.94±0.036 kg/cm2, thickness between 3.54±0.094 and 3.91±0.075 mm, friability between 0.13±0.07 and 0.28±0.05 %, and weight variation between 395.65±1.37 and 408.21±1.23 mg, which was within acceptable I.P. ranges. All of the formulations' percentage drug content was determined to fall between the ranges of 98.71± .41 to 99.87 ± 6.68 % .Table 6 indicated the results.

Table 6: Postcompression parameters of designed formulations

Formulation code	Thickness (mm)	Hardness (kg/cm)	Weight variation mg)	Friability (%)	Drug content (%)
F1	3.54±0.094	10.97±0.036	400.66±1.07	0.28±0.05	98.71±2.41
F2	3.91±0.075	10.53±0.014	395.65±1.37	0.13±0.07	99.49±6.30
F 3	3.63±0.061	11.94±0.036	408.21±1.23	0.28±0.03	99.87±6.68

In vitro buoyancy studies

Studies on buoyancy were conducted on all 3 formulations. The floating lag time is between 1:44 and 2:49 seconds. The whole floating time is between 13:14 and 14:68 hours and minutes. According to the findings of this buoyancy study, the batch comprising K100 M polymer alone or combination displayed a good floating lag time in comparison to other batches. The expansion of the hydrocolloid upon contact with the dissolving fluid and the presence of cavities in the tablet's centre control the buoyancy of the tablet, which varies from polymer to polymer. The outcomes are displayed in Table 7.

Table 7: Floating lag time and total floating time of designed formulations

Formulation code	Floating lag time (min:sec)	Total floating time (hrs:min)
F1	1:44	13:14
F2	2:49	14:68
F3	1:39	14:67

Swelling studies

Table 8 displays the swelling indices for all the developed formulations (F-1 to F-3). Swelling indices and tablet floating are directly related. The index originally was observed to increase as a result of the quick water consumption. The tablet swells as a result of the water intake, which lowers the bulk density, which affects buoyancy. Therefore, the reduction in bulk density determines the overall floating time. It was discovered that the formulation with the smaller total floating time had a decreasing order of swelling index. On the other hand, formulations with a longer total floating duration showed a rising order of the swelling index. All of the produced formulations' swelling indices at one hour range from 100.68± 2.62 to 114.35± 0.44 %.

Table 8:Swelling Index of gastroretentive floating tablets

Formulation code	Swellingindex(%)atdifferenttimeinterval				
	2 hr	4 hr	6 hr	8 hr	12 hr
F1	63.77±6.54	75.47±1.06	86.02±7.59	97.66±1.79	100.91±0.16
F2	53.01±5.71	83.22±2.64	81.31±2.98	84.33±1.58	114.35±0.44
F3	50.80±7.65	82.49±4.23	80.53±7.98	80.13±4.79	100.68±2.62

In vitro release studies

Three formulations underwent investigations on the release of drugs in vitro for upto 9 hours., Formulation F 3 had the maximum drug release of 94.03± .2.05 %. It is evident from this that a mixture consisting of HPMC K 15 M and HPMC K 100 M had better release characteristics. Table 9 presents the outcomes.

Table 9: Percentage of *in vitro* drug release profiles for the formulations

Time (H)	F1	F2	F3
1	19.02±1.40	19.83±1.58	19.50±1.75
2	29.57±1.80	23.47±1.60	28.95±1.78
3	39.20±1.26	33.24±1.50	35.50±1.96
4	43.91±1.96	42.17±1.13	45.25±1.79

5	51.79±1.01	56.25±1.22	57.54±1.53
6	63.14±1.67	63.24±1.41	69.11±2.13
7	72.33±1.41	72.70±1.92	72.56±2.03
8	78.90±1.60	79.97±1.01	85.16±2.42
9	93.19±1.11	93.93±1.37	94.03±2.05

Conclusion

Gastro retentive floating tablets of Ganciclovir were prepared using polymers HPMC K 15 M and HPMC K 100 M. All the formulations were able to float from 13.14 to 14.68 hours with controlling the release rate throughout the time. Formulation F 3 which contains both HPMC K 15M and HPMC K 100 M showed highest release of **94.03±2.05 at** 9 hours .By considering swelling index, floating properties, precompression and postcompression evaluation and release rate, F 3 was selected as the best among the 3 formulations. However, in vivo test is required for final selection of formulation. The results of the present study clearly stipulate the feasibility to develop Ganciclovir in the form of gastreretentive drug delivery system with prolongation of gastric retention time and controlled drug release. The future studies may be extended to inverstigatethe pharmacokinetic parameters related to bioavailability and clinical trial investigations which may prove that Gastroretentive type formulation can besafely administered orally with improved therapeutic efficacy.

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