Formulation and Evaluation of Ganciclovir Floating Controlled Drug Delivery System

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ABSTRACT

INTRODUCTION: Oral controlled release dosage form has been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. One of the most feasible approaches for achieving a prolonged predictable drug delivery profile is floating drug delivery system (FDDS) which prolongs the gastric residence time and increases the overall bioavailability of the dosage form.

MATERIALS AND METHODS: In this study the Ganciclovir is formulated as a floating tablet. 4 formulations were prepared. In each formulation drug concentration remains the same and excipient concentration was varied. Direct compression method was used for the formulation. Different polymers such as HPMC K 15, HPMC K 100, MCC were used with other standard excipients. Sodium bicarbonate was used as effervescent agent . The prepared powder blend was evaluated for its preformulation characteristics viz, true density, bulk density, compressibility index, angle of repose, Hausner's ratio.The physical characters of tablet were evaluated viz, hardness, friability, weight variation, thickness, drug content, swelling study, floating time and in vitro dissolution analysis.

RESULTS AND DISCUSSION: The results of preformulation study showed that the prepared powder blend had good flow property and packaging ability. The results of hardness and friability

test revealed that all the twelve formulation F1 to F4 showed good mechanical strength and complied with pharmacopoeial specifications. Optimized formulation F3 showed a drug release of **97.55±1.53** % and a floating lag time of 2.92 min and total floating time of >15 h clearly complies with the standard values. Overall results showed that the formulation satisfies the parameters necessary for a good floating drug delivery system.

CONCLUSION: The results of the present study clearly stipulate the feasibility to develop Ganciclovir in the form of gastroretentive drug delivery system with prolongation of gastric retention time and controlled drug release.

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

INTRODUCTION

Pharmaceutical dosage forms are the physical nature or form in which the drug is administered into the human body. There are many dosage forms which include tablet, capsule, pill, powder, mixture, syrup, cream, injections, suppositories etc. The different dosage forms are administered into the body via different routes of administration which includes oral, parenteral, transdermal etc. Among this oral route is considered as the most important route due to its ease of administration. Conventional drug administration has many disadvantages like less bioavailability, drug leakage etc. To avoid these disadvantages, novel drug delivery methods were developed. A drug delivery system refers to the technologies or methods which are used to present the drug at the site of action and release the drug in a predetermined rate which last for the specified time intervals. 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. Dosage forms that can be retained in the stomach are called GRDDs. GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site. Floating systems was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. FDDS are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach without affecting the gastric emptying rate for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration[1,2,3].

Ganciclovir is a class of medications called antivirals. It is used to treat - cytomegalovirus infections (CMV), retinitis, colitis, and esophagitis in AIDS patients and other immunocompromised individuals, and to prevent and treat CMV disease in transplant patients Physician's Desk Reference (2000).It is usually taken with food three to six times a day. Ganciclovir is a synthetic analogue of 2′-deoxy-guanosine[4,5].

MATERIAL AND METHODS

Material

Ganciclovir was used as the API and obtained as a gift sample from Sigma-Aldrich. HPMC K15 M and HPMC K100M , Sodium bicarbonate, Magnesium stearate and microcrystalline cellulose were purchased from Trivandrum Scientific Supplies. All the reagent; chemical and solvent used were of analytical grade

Methods

Preformulation Study[6,7]

Preformulation is the study that focus on the different physicochemical properties of drug that may interfere the performance of drug and dosage form development. It is the first step in the development of dosage form. The main aim of preformulation studies is to develop a stable, effective and safe dosage form by establishing kinetic rate profile of dosage form and by ensuring compatibility of drug .with other excipients

Physicochemical properties and identification of drug

Identification of drug by IR Spectroscopy

For the identification of given drug the IR spectra of drug sample (Ganciclovir) was compared with the standard IR spectra of pure drug

Physicochemical properties of drug

General appearance: Drug was tested for colour, odour and taste

Solubility of drug:

Solubility test was conducted to determine its solubility in the dissolution medium and other solvent

Drug –excipient compatibility

IR spectroscopy method was used for carried out drug –excipient compatibility study .FT-IR spectra of pure drug and drug + HPMC were recorded .Characteristic peaks of pure drug were compared with peaks of drug + HPMC

Precompression parameters of powder blends[8,9]

1. Bulk and Tapped density

10gm of powder was weighed. Weighed amount of given powder was introduced into 100ml measuring cylinder. After transferred of powder into a measuring cylinder the initial volume was observed for bulk density and then cylinder was tapped continuously until no further change in volume was observed . Record the final volume for tapped density. Then bulk and tapped density were calculated by using the given formula:

BULK DENSITY = WEIGHT OF POWDER / INITIAL VOLUME

TAPPED DENSITY = WEIGHT OF POWDER / TAPPED VOLUME

2 . Carr's index

Carr's index is also known as compressibility index. It is significant number that can be obtained from bulk and tapped density. The compressibility of raw material and blend was determined by Carr's compressibility index by using given formula

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

3. Hausner's ratio

The Hausner's ratio is a number that indicates flowability of a powder. Hausner's ratio is calculated by given equation

Hausner's ratio = Tapped density / Bulk density

4. Angle of repose

Maximum angle possible between the surface of a pile of powder and the horizontal plane are refer as angle of repose. Angle of repose used to measured frictional force leads to improper flow. Funnel stand method was used for determined the angle of repose. The average value is taken and angle of repose was calculated by using the given equation

$\tan \theta = h/r$

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

Where θ = Angle of repose

h = height of the heap

r = radius of the heap ϖ

Compression of Tablet

Floating tablets of Ganciclovir were prepared by direct compression method using different ingredient. Ganciclovir and other ingredient were passed through sieve no# 40 individually. According to different formulation required amount of ingredient was weighed by using digital balance. Drug ,HPMC K15M ,HPMC K100M, MCC, MCC and sodium bicarbonate were blended geometrically in mortor and pestle and then powder blends were lubricated with magnesium stearate. Final mixing was done by using poly bag. The punching machine dye was adjusted to get 400mg tablet with hardness 10-12 kg/cm2. Tablets were collected and evaluated.4 formulations of (F1 to F4) floating tablets of Ganciclovir were prepared using variable concentration of HPMC K1M & HPMC K100M as shown in table.

Post Compression Parameter Evaluation 10-13

The prepared floating tablets were evaluated for general appearance, thickness, hardness, friability, weight variation, In vitro buoyancy ,In vitro dissolution studies , and short term stability study.

General appearance

Organoleptic properties (General appearance) of tablet is the first most important quality for the acceptance of tablet. Its play a major role for the consumer acceptance. Prepared tablets were evaluated for organoleptic properties (colour, odour, taste and shape)

Thickness

6 tablets from each formulation were randomly selected and thickness was measured by using vernier calipers and then average value was calculated

Hardness

Hardness of tablet refer to the ability of a tablet to withstand for mechanical shocks. Hardness testing is used to test the breaking point of tablet. 6 tablets were taken from each formulation. Hardness of tablet was determined by using Pfizer hardness tester. Hardness was expressed in Kg/cm2 .

Friability

Roche friabilator was used for the determination of friability and it is expressed in percentage. 20 tablets were taken, initially weighed (W initial). Preweighed selected tablets were placed in the friabilator which revolves at 25 rpm (100 revolutions) for 4 min. Then tablets were removed from the chamber de-dusted and weighed again (W final). The % friability was then calculated by

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

Weight variation

20 tablets were taken from each formulation randomly and weighed individually. Average weight was calculated and percentage deviation from the average weight was determined by using given formula.

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

In vitro buoyancy/ floating study

In-vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing 0.1N HCl.The time taken for the tablet to rise to the surface and float was floating lag time and the duration of time the dosage form constantly remained on the surface of medium was determined as total floating time (TFT)

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

In vitro dissolution studies of cimetidine floating tablets were carried out by using USP type II apparatus (paddle type). Dissolution vessel was filled with 900ml 0.1 N HCL pH 1.2 and then temperature of the medium was adjusted to 37 ± 0.5^0C. Rotational speed of paddle was set at 50 rpm and then one tablet was introduced in each dissolution vessel .10ml solution were withdrawn from the dissolution vessels at every hour for 12 hrs and the samples were replaced with 10ml fresh dissolution medium. Absorbance of this solution was measured at 218 nm using a UV spectrophotometer.

RESULTS AND DISCUSSION

Solubility Analysis

Solubilty analysis of the drug sample has been carried out. Drug is found to be soluble in 0.1 N HCl, Water, Dimethyl –sulfoxide. The results are shown in the Table 2.

Melting Point determination

Melting point is within the standard range of 250˚C which shows pure drug Ganciclovir is free from impurities. The results are shown in the Table 3.

Drug-polymer interaction studies

Fourier transform infrared spectroscopy (FTIR) studies

FT-IR spectrum of pure drug and drug-excipient mixtures were taken. All the major bands present in the spectrum of the pure drug are also seen in the spectrum ofdrug- polymer mixture with negligible changes in their position. Thus it is clearly showed that there was no interaction between the drug and excipients. The results are shown in the Figure 1,Figure 2 , Figure 3 and Table 4.

Differential Scanning Calorimetry (DSC) Studies

The DSC thermograms of pure drug and the drug-excipient mixture showed that the endothermic peak corresponding to the melting point of pure drug was prominent in all the drug excipient mixture and, it is clear that there was no interaction between the drug and the polymers and the drug was existed in its unchanged form as shown in the Figure 4, Figure and Figure 6.

Evaluation of floating tablets

Preformulation studies

The Powder blend of all these formulations showed good flow property which was indicated by angle of repose 23.27± 0.1551 to 26.63± 0.1310 , bulk density 0.3421±0.0847 g/ml

to 0.4908±0.0680g/ml, tapped density 0.4504±0.0079 g/ml 0.5502±0.0015g/ml, Hausner‟s ratio 1.51 to 1.89 and carr's index 17.72 % to 22.04 %, as shown in the Table 5.

Postcompression studies

Ganciclovir floating tablets were prepared by direct compression technique using HPMC (K15M, and K100M), sodium bicarbonate, microcrystalline cellulose and magnesium stearate. Total 4 formulations were prepared. The formulated tablets were white color, biconvex and round shaped without any scoring on any sides. All the tablets were elegant in appearance. Hardness of all the formulations were found to be in the range of 10.40± 0.061 to 11.94± 0.036 Kg/cm2, thickness 3.63± 0.061 to 4.01± 0.053 mm, friability less than 1% 0.26± 0.03 to 0.38± 0.02 and weight variation within the acceptable limits as per I.P, 394.59± 1.11 to 409.73 ± 0.097 mg. The percentage drug content of all the formulations was found to be within the limits of 95% to 110%. 99.38± 8.37 to 100.58 ± 9.8 % .The results of the physical characteristics of floating tablets are shown in Table 6.

In vitro buoyancy studies

All the 4 formulations were subjected to buoyancy studies. The floating lag time ranges from 1:19 min:sec to from 2:92 min:sec. The total floating time ranges from 12 : 37 hrs: min to 15.00 hrs: min. By this buoyancy studies results it can be concluded that the batch containing moderate combination of HPMC K 1 M5 and K 100 M polymer showed good floating lag time when compared to other batches.. The buoyancy of the tablet varies from polymer to polymer which is governed by both the swelling of the hydrocolloid upon contact with the dissolution fluid and the presence of voids in the centre of the tablet. The results are shown in Table 7

Swelling studies

The swelling indexes for all the prepared formulation (F-1 to F-4) are shown in table 8. Swelling indexes have a direct relationship on tablet floating. Due to the rapid water intake, initially the index was found to rise. This water intake makes the tablet swell and thus reduces the bulk density that is responsible for buoyancy. The total floating time hence, depends on the decrease of bulk density. The formulation having a lower total floating time was found to have a decreasing order of swelling index. On the other hand, an increasing order of swelling index was observed for formulations having higher total floating time. The swelling index of all the prepared formulations at 1 hour ranges from 100.68 ± 2.62 to 117.61± 1.08 %. The results are shown in Table 7**.**

In vitro release studies

The invitro drug release studies of 4 formulations were carried out. The formulations F 2, showed a drug release upto 9 hours. The formulation F 4 showed a drug release upto 10 hours. The formulations F 1and F 3 showed a drug release upto 12 . Formulation F 4 showed the lowest drug release of 91.22± 2.41 at 10 hours. Formulation F 3 showed the highest drug release of 97.55± 1.53 at 12 hours.From this it is clear that a combination containing HPMC K 15 M and HPMC K 100 M (4:5) showed a better release characteristics. The results are shown in Table 8.

Formulation

Table 1: Formulation of Ganciclovir Floating tablets

Ingredients	F1	F2	F3	F4
Ganciclovir (mg)	250	250	250	250
HPMC K 15 M(mg)	10	20	30	40
HPMC K 100 M(mg)	12.5	25	37.5	50
Sodium bicarbonate(mg)	40	40	40	40
MCC(mg)	84.5	62	39.5	17
Magnesium stearate (mg)	3	3	3	3
Total weight/tablet	400	400	400	400

Solubility Analysis

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

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

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

Evaluation of floating tablets

Preformulation studies

Table 5: Precompression parameters of designed formulations

Formulation code	Bulkdensity[&] (mg/mL)	Tapped density[&] (mg/mL)	Carr'sindex (%)	Angleofrepose[&]	Hausner's ratio
F1	0.3927±0.0222	0.4701±0.0072	18.45	23.27±0.1551	1.89
F2	0.4908±0.0680	0.4504±0.0079	22.04	26.63±0.1310	1.53
F3	**0.4472±0.0091**	**0.4725±0.0044**	**17.72**	**24.62±0.0978**	**1.51**
F4	0.3421±0.0847	0.5502±0.0015	19.41	23.48±0.1524	1.66

Postcompression studies

Table 6: Postcompression parameters of designed formulations

Formulation code	Thickness[@] (mm)	Hardness[@] (kg/cm)	Weight variation[#] (mg)	Friability[$] (%)	Drug content[@] (%)
F1	3.66±0.092	10.86±0.077	394.59±1.11	0.31±0.06	99.38±8.37
F2	3.63±0.061	11.94±0.036	408.21±1.23	0.28±0.03	99.87±6.68
F3	**4.00±0.027**	**10.40±0.061**	**409.73±0.97**	**0.26±0.03**	**100.58±9.82**
F4	4.01±0.053	11.48±0.031	403.5±0.99	0.38±0.02	99.54±9.66

In vitro buoyancy studies

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	2:43	12:37
F2	1:39	14:67
F3	**2:92**	**15:00**
F4	1:19	14:99

Swelling studies

Table 8: Swelling Index of gastroretentive floating tablets

Formulation code	Swellingindex(%)atdifferenttimeinterval				
	2 hr	4 hr	6 hr	8 hr	12 hr
F1	50.64±4.98	63.32±1.94	74.66±5.75	84.45±6.09	101.80±3.12
F2	50.80±7.65	82.49±4.23	80.53±7.98	80.13±4.79	100.68±2.62
F3	**71.40±1.72**	**62.01±5.38**	**84.93±1.84**	**85.68±5.89**	**117.61±1.08**
F4	65.63±1.42	76.80±1.49	72.88±7.76	80.74±5.02	114.69±2.50

In vitro release studies

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

Time (H)	F1	F2	F3	F4
1	17.36±1.60	19.50±1.75	**18.46±2.41**	18.81±1.94
2	20.32±2.06	28.95±1.78	**20.16±1.95**	20.50±1.70
3	31.02±2.03	35.50±1.96	**39.73±1.63**	33.06±2.16
4	46.82±2.18	45.25±1.79	**44.15±1.83**	41.35±2.44
5	54.86±2.48	57.54±1.53	**59.98±2.39**	53.13±2.35
6	69.42±1.72	69.11±2.13	**62.85±2.12**	61.44±2.21
7	72.09±2.21	72.56±2.03	**70.49±1.67**	74.24±2.11
8	79.79±2.40	85.16±2.42	**76.80±2.35**	78.80±2.16
9	80.20±2.45	94.03±2.05	**82.24±1.51**	83.94±1.51
10	89.88±2.33		**89.05±1.95**	91.22±2.41
11	90.01±1.97		**94.83±2.11**	
12	93.84±1.99		**97.55±1.53**	

Drug-polymer interaction studies

Fourier transform infrared spectroscopy (FTIR) studies

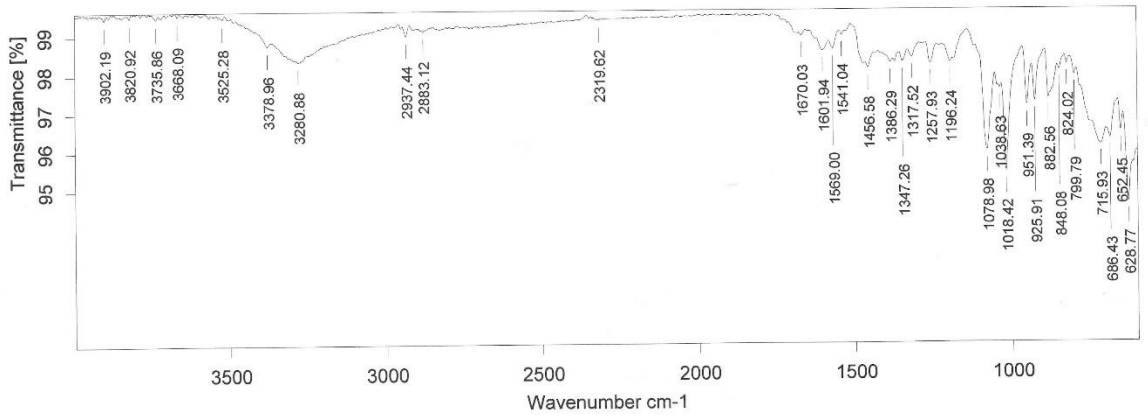

Figure 1: FTIR Spectrum of Ganciclovir

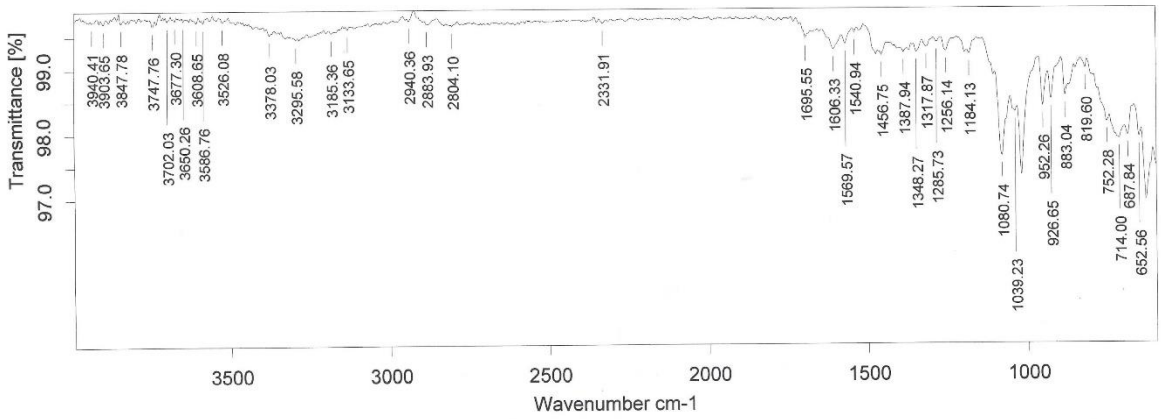

Figure 2: FTIR Spectrum of Ganciclovir + HPMC K 15

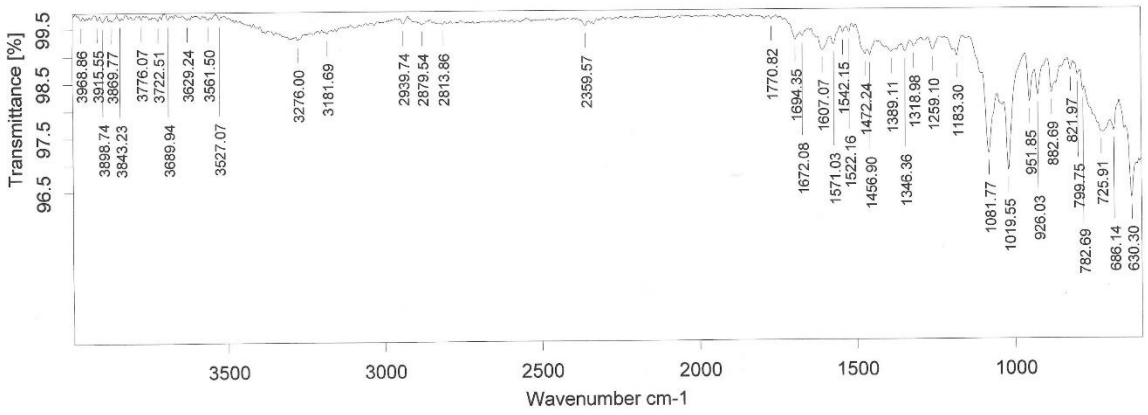

Figure 3: FTIR Spectrum of Ganciclovir + HPMC K 100

Differential Scanning Calorimetry (DSC) Studies

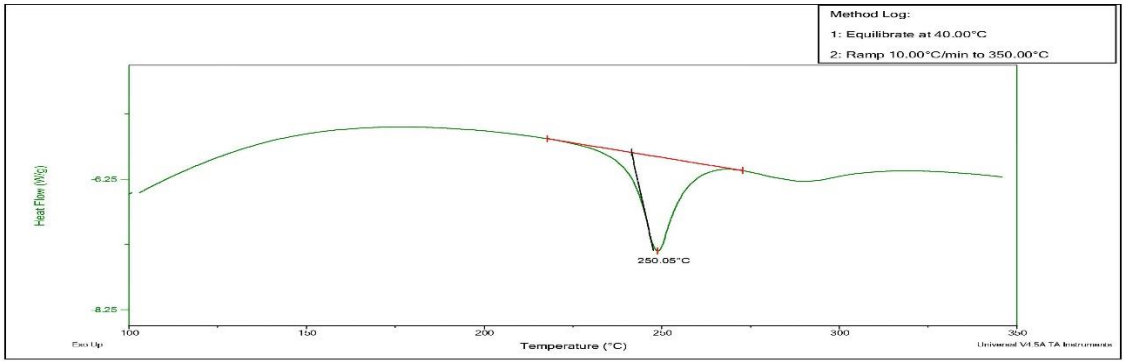

Figure 4: DSC of Ganciclovir

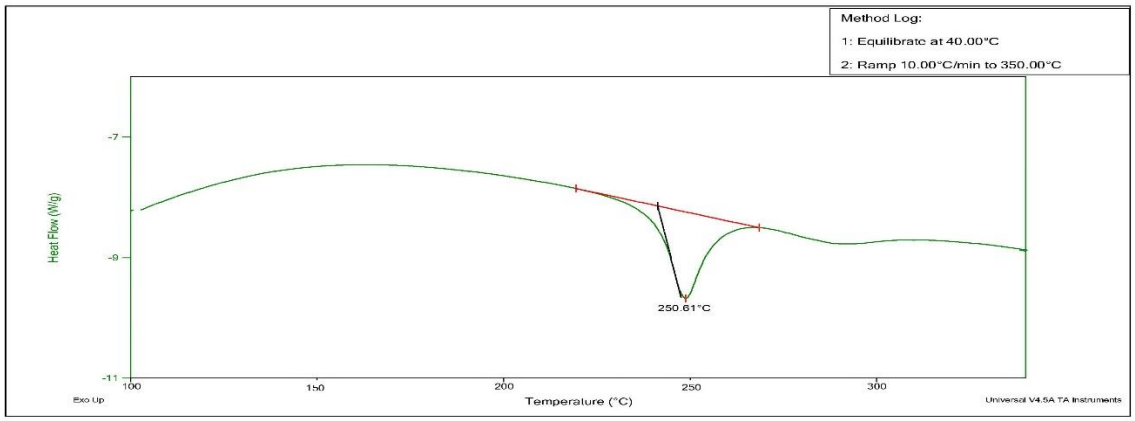

Figure 5: DSC of Ganciclovir + K 15

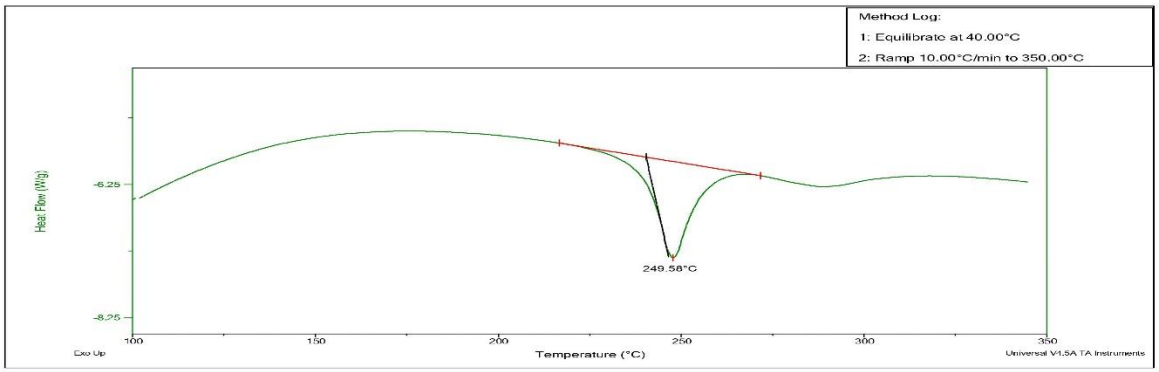

Figure 6: DSC of Ganciclovir + K 100

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 12.3 to 15 hours with controlling the release rate throughout the time. Formulation F 3 which contains both HPMC K 15M and HPMC K 100 M in the ratio 4:5 showed highest release of **97.55±1.53 at** 12 hours .By considering swelling index, floating properties, pre compression and post compression evaluation and release rate, F 3 was selected as the best among the 4 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 investigate the pharmacokinetic parameters related to bioavailability and clinical trial investigations which may prove that Gastroretentive type formulation can be safely administered orally with improved therapeutic efficacy.

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