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# DEVELOPMENT OF BIODEGRADABLE POLYMERS BASED FLOATING TABLETS CONTAINIG SITAGLIPTIN

**SHAUKAT S[1*], LATIF S[1], ZAMAN M[2], ARSHAD S[3] AND BATOOL N[1]**

1: Department of Pharmacy, Lahore College for Women University, Lahore, Pakistan

2: Department of Pharmaceutics, Faculty of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan

3: Faculty of Pharmacy, The University of Lahore, Pakistan

*** (Corresponding Author): Sumaira Shaukat: Email address: sumairapcw@yahoo.com**

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## ABSTRACT

**Purpose:** The purpose of current investigation was to prepare and evaluate the gastro retentive floating tablets of sitagliptin for the management of type II Diabetes Mellitus.

**Method:** The floating tablets of sitagliptin were prepared by wet granulation method. Six formulatins were prepared using different proportions of HPMC K4M & K15M. Sodium bicarbonate, citric acid and tartaric acid were used for effervascence. All the formulations were optimized on the basis of in vitro floating lag time, total floating time and in vitro drug release in 0.1 N HCl.

**Results:** The formulations showed good preformulation characteristics. FT-IR spectroscopy showed that no any significant interaction was developed between drug and excipients and results of DSC revealed that the nature of drug was not affected by other excipients. The floating tablets were floated within 90 seconds and they were floated for more than 12 hours. To analyze the release pattern of the drug the dissolution profiles were subjected to various mathematical models i.e zero order, first order, Higuchi, Hixson-Crowell and Korsemeyer Peppas model. The kinetic studies revealed that release of drug from the optimized formulation followed Korsemeyer Peppas model and the value of release exponent (n) showed that the mechanism of drug release was non fickian diffusion.

**Conlusion:** Finally it was concluded that both K4M and K15M has constructive influence on the drug release retadation, swellability and total byouncy time (TBT) of the floating tablets. Moreover both grades of HPMC were found suitable for the formulation of gastro-retentive drug delivery system of Sitagliptin.

**Keywords: Sitagliptin, Floa ting Tablets, HPMC K4M & K15M, Sodium Bicarbonate, Sustained Release**

**List of abbreviation: HPMC= Hydroxypropyl methylcellulose; MCC= Microcrystalline cellulose; NaHCO3= Sodium bicarbonate**

## INTRODUCTION

Gastro retentive dosage form can stay in stomach for prolonged time periods and release incorporated drug candidates to provide effective plasma concentration for longer period of time thereby ensure site specific release of drug in upper GIT for local & systemic actions (Kumar et al., 2012, Marinaganti et al., 2013). Floating drug delivery system retains the drug in stomach and it is a suitable approach for the drugs which are unstable and poorly soluble in alkaline media. This system has bulk density less than the gastric fluids and allows the dosage form to float immediately upon contact with gastric fluids. While the system is buoyant in the stomach, the drug is released slowly to give the sustained action. When drug is completely released from the system the residual is expelled out from the stomach (Arora et al., 2005). The low density may be achieved by entrapment of air or by using low density materials. Different swellable hydrophilic polymers like hydroxy propyl methyl cellulose have been utilized along with effervescent compounds like sodium bicarbonate and citric acid (Dongare et al., 2013). Carbon dioxide is generated that is entrapped in viscous hydrocolloid and produce an upward movement of the delivery system to maintain buoyancy (Basak et al., 2007). Diabetes mellitus is a chronic illness associated with hyperglycemia and disturbances in carbohydrate, fat and protein metabolism (Kumar et al.). Currently different types of oral hypoglycemics are recommended for the treatment of non-insulin dependent diabetes mellitus like sulphonylureas, metformin, alpha-glucosidase inhibitors, thiazolidinediones (Williams-Herman et al., 2010). Sitagliptin was taken as a model drug. It is an oral hypoglycaemic agent belongs to dipeptidyl – peptidase – 4 (DPP-4) inhibitor class. It is used for the treatment of non-insulin dependent diabetes mellitus either alone or in combination with other hypoglycaemics. Sitagliptin inhibits DPP-4 as this enzyme cause degradation of incretin hormones (GLP-1 & GIP). GLP-1 and GIP are released by intestines and their levels are increased after meal. When glucose level in blood is normal or elevated these hormones increase the production and release of insulin from beta cells of pancreas. GLP-1 also diminishes secretion of glucagon from alpha cells of pancreas thus reducing glucose synthesis by hepatic cells(Herman et al., 2006, Amori et al., 2007). The aim of current investigation was to design and optimize floating tablets of sitagliptin by wet granulation method and by using different proportions of HPMC K4M & K15 M. It is a swell able and hydrophilic polymer(Bravo et al., 2004, Rahman et al., 2011). It is a very suitable polymer to use as a retarding material in controlled release floating tablets because it is non-toxic and easy to handle(Rahman et al., 2011, Lee et al., 1999).

## MATERIALS AND METHODS

### Materials

Sitagliptin Phosphate was obtained as gift sample from CCL Pharmaceuticals Lahore, Pakistan. HPMC K4M, HPMC K15M, Microcrystalline cellulose, Magnesium stearate and Talc were procured from Unique Chem1icals Lahore, Pakistan. Sodium bicarbonate, Citric acid, Tartaric acid and Polyvinyl pyrrolidone K-30 were procured from Ali Baba Chemicals Lahore, Pakistan. All the reagents and materials were of analytical grade.

### Methods

### Preparation of Sitagliptin Floatable Tablets

The gastro retentive tablets of sitagliptin were formulated by conventional wet granulation method. Statistical approach namely central composite rotatable design was used for the design and optimization of floating tablets (Table 2 and 3). 6 out of 8 formulations were studies.

Sitagliptin, HPMC K15M, HPMC K4M, MCC, NaHCO3, citric acid and tartaric acid were mixed for 5min in a polythene bag and then passed through sieve # 40. In a beaker take enough ethanol to dissolve the poly vinyl pyrrolidone and make a solution. A sufficient volume of this granulating liquid was added in the powder mix to achieve granulation end point(Gavali et al., 2010). The wet mass was then passed through the sieve # 12. These granules were first dried at room temperature for 10min for evaporation of ethanol and then were dried at 45-55°C for 2 hours in tray dryer. Magnesium stearate and talc were introduced in the granules and compress them by using single punch compression machine (TDP, STC China)(Basak et al., 2007).

**Pre-formulation Studies**

**Melting Point**

Capillary tube method was employed for determination of melting point of sitagliptin. A small quantity of pure drug was placed into a capillary tube and attached it to the stem of thermometer and placed in a heating bath. Heat the bath slowly. The temperature when the powder started to melt and the temperature at which all the powder melted were observed(Sanghi and Tiwle, 2013).

**Estimation of Sitagliptin**

A suitable dilution of sitagliptin was prepared with 0.1N HCl. To measure the maximum UV absorbance, the UV spectrophotometer (UV 1601, Shimadzu) was run at the wavelength range of 300-220nm and maximum absorbance was obtained. The maximum absorbance ($\lambda max$) was found to be 267nm(Vadaliya et al., 2013).

**Excipient Compatibility Studies**

**Differential Scanning Calorimetery**

Thermal analysis was observed by using differential scanning calorimeter (SDT Q600, TA Instruments, USA). The pure drug, polymers and all the formulations (2-4mg) were heated from ambient temperature to 250°C with a uniform heating rate of 10°C per minute in sealed aluminium pans and nitrogen was used as purging gas(Sanghi and Tiwle, 2013).

**Pre-compression studies**

**Angle of Repose**

To study the flow properties of granules, angle of repose was calculated by fixed funnel method(Zaman et al., 2015a). In this method dry granules were poured from walls of funnel to form a conical pile in which its lower tip was 2-5 cm away from the hard surface. It is maximum angle between pile of granules and ground surface. It was measured by following formula

$$\theta = 1/\tan(h/r)$$

where h is height of the heap and r is radius of base of heap(Zaman et al., 2015a).

**Bulk Density**

A quantity of 2g of dry granules of each formulation was poured into a calibrated cylinder. It was measured by following formula(Zaman et al., 2015b).

**B.D = Wt of granules/ volume occupied by granules**

**Tapped Density**

2g of dry granules of each formulation were taken in calibrated measuring cylinder and these granules were subjected to conventional tapping method. Tap the cylinder until no change was observed in volume. It was measured by formula given below (Zaman et al., 2015b, Zaman et al., 2013).

**T.D = Wt of granules/ volume of granules after tapping**

**Compressibility Index (Carr's Index) (Zaman et al., 2015b)**

It is indication of flow ability of powder. In free flowing powder there is little difference between bulk and tapped density, therefore Compressibility index would be small while the poor flowing powder has a marked difference between bulk density and tapped density because of greater inter particle interaction. Therefore Carr's index would be bigger. It is named after the pharmacologist Charles Jelleff Carr. It was measured by following formula

$$C = 100 \times (1 - \rho_B / \rho_T)$$

Where C is Compressibility Index, $\rho_B$ is Bulk Density and $\rho_T$ is Tapped Density.

**Hausner Ratio (Zaman et al., 2015b)**

It is number which is associated to flow ability of granules or powder. It is named after engineer Henry H. Hausner. The ratio greater than 1.25 showed poor flow ability of granules or powder. It was measured by following formula

$$H = \rho_T / \rho_B$$

H is Hausner Ratio, $\rho_B$ is Bulk Density and $\rho_T$ is Tapped Density.

**Post-compression studies**

**Hardness**

Hardness of all the formulations was determined by Monsanto hardness tester (MHT 2020, Curio) (Zaman et al., 2015b, Thahera et al., 2012).

**Thickness and Diameter**

To check the uniformity of tablet size, thickness and diameter of all the formulations were determined by using vernier calipers (530, Mitutoyo, USA)(Thahera et al., 2012).

**Friability**

Friability test was performed to check the stability and integrity of tablet. Roche friabilator (Pharma test) is used for friability testing of all the formulations. Twenty tablets of each batch were weighed first and then place in rotating drum. They were rotated at 25rpm for 240 seconds. These tablets were reweighed. % loss of weight was measured by applying given formula(Zaman et al., 2015b).

**% friability = (initial wt- final wt)/initial wt x 100**

**Content Uniformity**

From each batch of prepared formulations, ten tablets were selected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred into 100ml volumetric flask. To this 100ml 0.1 N HCl was added and solution was then sonicated for 15 minutes & filtered through whatman filter paper. Suitable dilutions were prepared with 0.1 N HCl. Same concentration of standard was also prepared. The drug content was estimated by recording the absorbance at 267nmby using UV/Visible spectrophotometer(Kapoor and Patel).

**Weight Variation**

Twenty tablets from all the batches were taken randomly and were weighed individually. Average weight for all the formulations was calculated(Zaman et al., 2015a).

**Determination of Floating Parameters**

**In Vitro Buoyancy/ Floating Test**

One tablet from each batch was taken and placed in a beaker containing 100ml 0.1N HCl. The time taken by the tablet to appear on the surface of gastric fluid and float was termed as floating lag time and total time by which the tablet remained buoyant on the surface of gastric fluid is called total floating time(Padmavathy et al., 2011).

**Swelling Study**

One tablet from each formulation was weighed and put in a beaker having 200ml of distilled water. After one hour tablet was taken out from the beaker. The inflated tablet was reweighed. Repeat this procedure up to 12 hours. The %age gain of weight by each tablet was determined by following formula(Padmavathy et al., 2011)

**Swelling Index = [(Wt-Wo)/Wo] x 100**

Where Wt = Weight of the tablet at time t Wo = Weight of the tablet at time 0

**In Vitro Drug Release Studies**

USP Type II (Paddle) Dissolution Testing Apparatus (DL 0601, Curio, Pakistan) was used to carry out the in vitro drug release study. 0.1N HCl was used as dissolution medium. In all the vessels 900ml 0.1N HCl was taken. One tablet was added to each of three vessels. The paddle rotation was 100rpm and temperature was kept constant at 37°C. After a predetermined time interval 10ml sample was withdrawn and fresh medium was added to retain the volume of dissolution medium fixed and temperature was maintained at 37°C. After making suitable dilutions the absorbance was measured spectrophotometerically at a wavelength of 267nm against 0.1N HCl as a blank.

**Mechanism of Drug Release**

To study the mechanism of drug release from hydrophilic polymers, the in vitro release data of all the formulations was applied to kinetic models

including zero order, 1st order, higuchi model, hixoncrowell cube root and korsmeyer peppas model(Zaman et al., 2015a).

## RESULTS AND DISCUSSION

### Pre-formulation Studies

Pre-formulation is first step in development of new formulation. The melting point observed of the sampled drug was 215-217 °C. From UV Spectrum, the maximum absorption was found at the wavelength (λmax) 266.8nm(Kumar et al., 2012).

### Differential Scanning Calorimetery

The thermograms of pure drug (sitagliptin), pure polymers (HPMC K15M & HPMC K4M) and all the formulations were observed. The thermograms of pure drug showed a broad endothermic peak over a temperature range of 150 – 250 ºC and the peak point was 213.7 ºC which showed melting point of the pure drug. The thermograms of polymers showed a broad endothermic peak over a temperature range of 20 - 100 ºC and it was observed due to dehydration process [27]. These endotherms were also observed in formulations. The thermograms of formulations showed no any extra peak which revealed that there may be no any incompatibility between drug and polymer.

### Pre-compression studies

Granules were evaluated foe various parameters. Results revield that granules have good micromeritics properties resultes were calculated as mean±std (table).

### Post-compression studies

Tablets were prepared by wet granulation method and subjected to various studies. Results were satisfactory as there was no any single formulation falling beyond the limits described in the pharmacopoeias for related parameters (Table).

### Mathematical Modeling

Mathematical relations created using multiple linear regression analysis for the calculated responses including total bouncy time, swelling index and percentage drug release. Variables are expressed as equations 1 to 3.

$$\text{Total Bouncy Time} = 13.69 + 4.24\ X_1 + 2.34\ X_2 + 0.89\ X_1 X_2 \quad \text{.....1}$$

$$\text{Swelling Index} = 169.62 + 35.67\ X_1 + 28.77\ X_2 + 8.81\ X_1 X_2 \quad \text{.....2}$$

$$\%\ \text{Drug Release} = 30.77 - 24.24\ X_1 - 10.92\ X_2 - 7.33\ X_1 X_2 \quad \text{.....3}$$

### Response Surface Analysis

3-D and 2-D contour plots were plotted for TBT, swelling index and % drug release to show the impact of both variables on considered features.

### Total Bouncy time (Response 1)

Articulating the effect of HPMC K15M and HPMC K4M. Polynomial equation (1) showed that increase in $X_1$ could enhance the TBT. $X_2$ has relatively lesser effect on enhancing the TBT, both interacting factor $X_1X_2$ showed constructive effect that means simultaneous variation in both variables would be the cause of greater TBT. HPMC is the polymer that has the ability to swell excessively.

### Swelling Index (Response 2)

Uttering the association of $X_1$ and $X_2$ and their influence on swelling index. It is clear from the graphs that increase in both variables; especially in $X_1$ is increasing the SI. From polynomial equation 2, it was even clearer that mean of the dependent variable is a positive value which suggested that response is positive and both factors has a significant influence on the SI. $X_1$ with greater values in equation 2 described that it has more prominent effect on SI. Both grades of HPMC, K15M and K4M are Swellable polymer. Swellable polymers are extensively used in the formulation of sustained release polymer including gastro retentive matrix tablet. Result of the present study was the proof of their ability to form highly sustainable floating matrix tablets with the ability to deliver drug in the upper gastro intestinal track.

### % Drug release (response 3)

Results were indicating the influence of both $X_1$ and $X_2$ (equition 3) on the release of stiagliptin gastro retentive floating tablets. HPMC K15M and HPMC K4M were showing negative impact,

that mean increased in the concentration of polymer would be the cause of decrease in the relase of the drug. Same can be observed in the 3-D plot of the response presented from the equation it was cleaer that both interacting factors ($X_1X_2$) had negative impact on the response. Both polymers have sustianed effect and from the results it was observed that increase in concentration of both these variable would result in more drug retardation from the tablets.

**Table 1: Relation between coded and actual values of the factors**

| | |
|---|---|
| **-β** | $X_{min}$ |
| **-1** | $[(x_{max} + x_{min})/2] - [(x_{max} - x_{min})/2\alpha]$ |
| **0** | $[(x_{max} + x_{min})/2]$ |
| **+1** | $[(x_{max} + x_{min})/2] + [(x_{max} - x_{min})/2\alpha]$ |
| **+β** | $X_{max}$ |

**Table 2: Independent variables and their different levels used in formulation**

| Name | Variables | Xmin | Xmax | -β | -1 | 0 | 1 | +β |
|---|---|---|---|---|---|---|---|---|
| HPMC K15M | X1 | 50 | 150 | 29.2893 | 50 | 100 | 150 | 170.711 |
| HPMC K4M | X2 | 50 | 150 | 29.2893 | 50 | 100 | 150 | 170.711 |

**Table 3: Composition of tablets according to CCRD**

| Sr. No | X1 | X2 |
|---|---|---|
| 1 | 50 | 150 |
| 2 | 50 | 50 |
| 3 | 170.7107 | 100 |
| 4 | 100 | 29.28932 |
| 5 | 150 | 150 |
| 6 | 29.28932 | 100 |
| 7 | 150 | 50 |
| 8 | 100 | 170.7107 |

- **Net weight of the tablets was 580mg having constant quantities of Sodium bicarbonate (100mg), Citric acid (50mg), tartaric acid (50mg) PVP K30 (20mg) and Mg.stearate (5mg)**

**Table 4: Evaluation of dry granules**

| Batch Code | Angle of Repose (°) | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr's Index (%) | Hausner Ratio |
|---|---|---|---|---|---|
| F1 | 26.22±0.24 | 0.442±0.01 | 0.536±0.02 | 17.53±0.18 | 1.21±0.06 |
| F2 | 25.54±0.33 | 0.472±0.02 | 0.570±0.01 | 17.19±0.10 | 1.20±0.03 |
| F3 | 27.13±0.22 | 0.363±0.02 | 0.446±0.01 | 18.61±0.17 | 1.22±0.06 |
| F4 | 26.02±0.28 | 0.352±0.01 | 0.440±0.02 | 20±0.15 | 1.25±0.09 |
| F5 | 26.52±0.26 | 0.435±0.01 | 0.515±0.01 | 15.5±0.13 | 1.18±0.03 |
| F6 | 27.64±0.17 | 0.451±0.01 | 0.524±0.01 | 13.9±0.11 | 1.16±0.03 |

- **All the values were presented as mean±standard deviation (n=3)**

**Table5: Evaluation of Tablets**

| Batch Code | Hardness ($Kg/cm^2$) | Diameter (mm) | Thickness (mm) | Average Weight (mg) | Drug Content (%) | Friability (%) | Buoyancy Lag Time (sec) | Total Buoyancy Time (Hours) |
|---|---|---|---|---|---|---|---|---|
| F1 | 3.7±0.1 | 11.1±0.1 | 6.3±0.04 | 584±1.73 | 98.23±2.32 | 0.50±0.03 | 64±0.11 | 11.1±0.51 |
| F2 | 3.8±0.1 | 11.3±0.1 | 6.4±0.03 | 581±1.73 | 98.97±1.46 | 0.56±0.04 | 75±0.19 | 6±0.39 |
| F3 | 3.8±0.1 | 11.1±0.0 | 6.5±0.02 | 576±1.00 | 99.42±1.31 | 0.76±0.02 | 54±0.14 | 12.5±0.24 |
| F4 | 3.7±0.1 | 11.2±0.1 | 6.3±0.02 | 578±1.73 | 98.67±1.44 | 0.68±0.03 | 92±0.11 | 9±0.36 |
| F5 | 3.9±0.1 | 11.3±0.1 | 6.2±0.06 | 579±2.64 | 97.32±2.31 | 0.58±0.01 | 70±0.09 | 10±0.53 |
| F6 | 3.6±0.1 | 11.1±0.0 | 6.4±0.1 | 582±1.00 | 98.19±1.60 | 0.46±0.08 | 86±0.04 | 8±0.54 |

- **All the values were presented as mean±standard deviation (n=10)**

**Table 6: Swelling Index of all formulations**

| Time (Hours) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| 1 | 79 | 42 | 82 | 61 | 87 | 58 |
| 2 | 85 | 68 | 101 | 82 | 96 | 72 |
| 3 | 93 | 87 | 112 | 99 | 117 | 89 |
| 4 | 116 | 98 | 128 | 118 | 128 | 102 |
| 5 | 131 | 109 | 137 | 134 | 143 | 114 |
| 6 | 147 | 127 | 149 | 148 | 159 | 126 |
| 7 | 159 | | 153 | 169 | 165 | 138 |
| 8 | 163 | | 167 | 174 | 179 | 151 |
| 9 | 169 | | 171 | 185 | 187 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 10 | 177 | | 180 | | 198 | |
| 11 | 186 | | 189 | | 204 | |
| 12 | 199 | | 201 | | 212 | |

**Table 8: In vitro Drug Release Data**

| Time (Hours) | % Drug Release | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| 0.5 | 8.11 | 12 | 3.39 | 7.06 | 9.32 | 14.1 |
| 1 | 13.3 | 21.8 | 7.06 | 15.67 | 14.97 | 18.07 |
| 2 | 24.29 | 34.46 | 12.34 | 26.13 | 27.59 | 21.38 |
| 3 | 29.94 | 47.17 | 17.28 | 36.72 | 36.44 | 34.09 |
| 4 | 38.7 | 69.06 | 24.06 | 42.79 | 49.7 | 47.9 |
| 5 | 45.53 | 81.83 | 30.28 | 54.57 | 57.06 | 58.6 |
| 6 | 52.88 | 90.96 | 38.98 | 68.4 | 68.36 | 72.31 |
| 7 | 67.09 | | 47.59 | 72.88 | 72.17 | 80.93 |
| 8 | 74.85 | | 54.59 | 89.75 | 78.95 | 90.25 |
| 9 | 78.95 | | 63.77 | 91.66 | 81.21 | |
| 10 | 82.27 | | 73.02 | | 83.82 | |
| 11 | 89.12 | | 80.86 | | 89.61 | |
| 12 | 90.96 | | 82.76 | | 91.8 | |

**Table 9: Kinetic modeling of drug released from floating tablets of Sitagliptin**

| Formulations | Zero order | 1st Order | Hixson | Higuchi | Korsmeyer Peppas | | Best Fit Model | Drug release mechanism |
|---|---|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | $R^2$ | Value of 'n' | | |
| F1 | 0.9602 | 0.9629 | 0.9852 | 0.9112 | 0.9902 | 0.783 | Korsmeyer peppas | Non Fickian Transport |
| F2 | 0.9802 | 0.9444 | 0.9726 | 0.8775 | 0.9918 | 0.858 | Korsmeyer peppas | Non Fickian Transport |
| F3 | 0.9902 | 0.916 | 0.9456 | 0.798 | 0.9958 | 1.128 | Korsmeyer peppas | Super Case II Transport |
| F4 | 0.984 | 0.9432 | 0.9704 | 0.8782 | 0.9922 | 0.875 | Korsmeyer peppas | Non Fickian Transport |
| F5 | 0.867 | 0.9916 | 0.9961 | 0.9534 | 0.9829 | 0.643 | Hixson Crowell | Dissolution |
| F6 | 0.9799 | 0.9273 | 0.9565 | 0.8606 | 0.9845 | 0.904 | Korsmeyer peppas | Super Case II Transport |

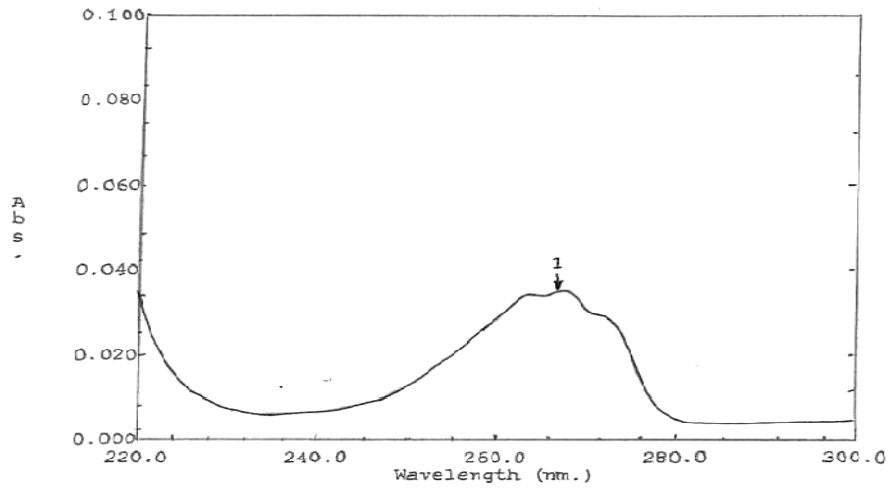


**Figure 1: Estimation of Sitagliptin**

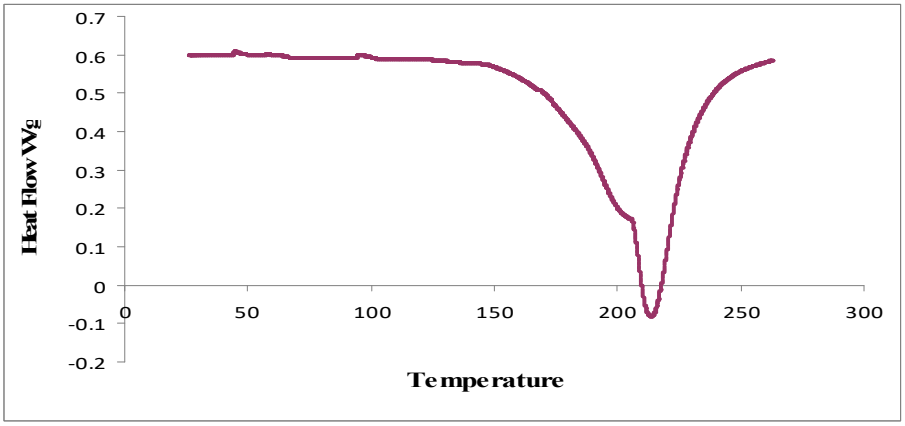


**Figure 3: DSC of Pure Drug (Sitagliptin)**

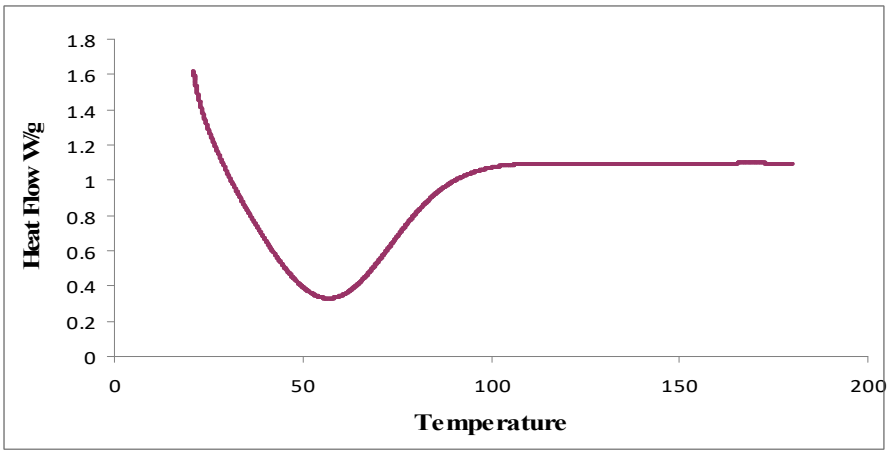


**Figure 4: DSC of HPMC K4M& K15M**

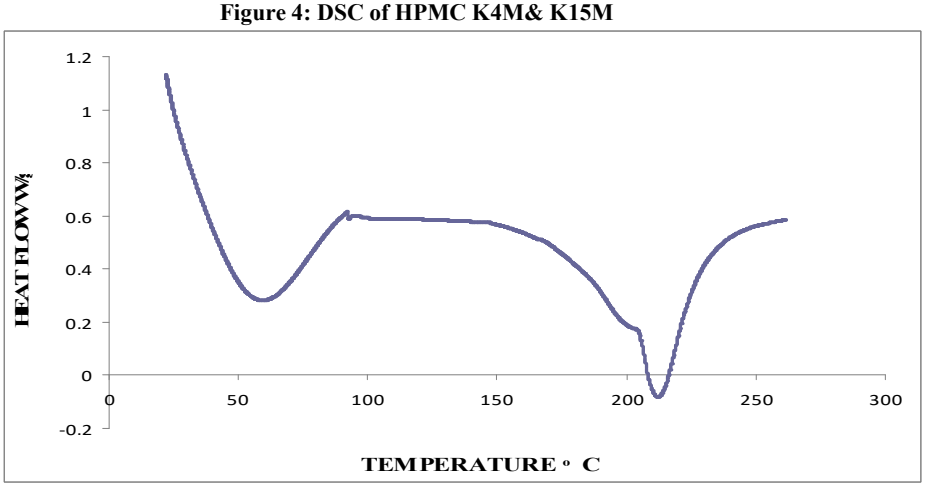


**Figure 5: DSC of F1**

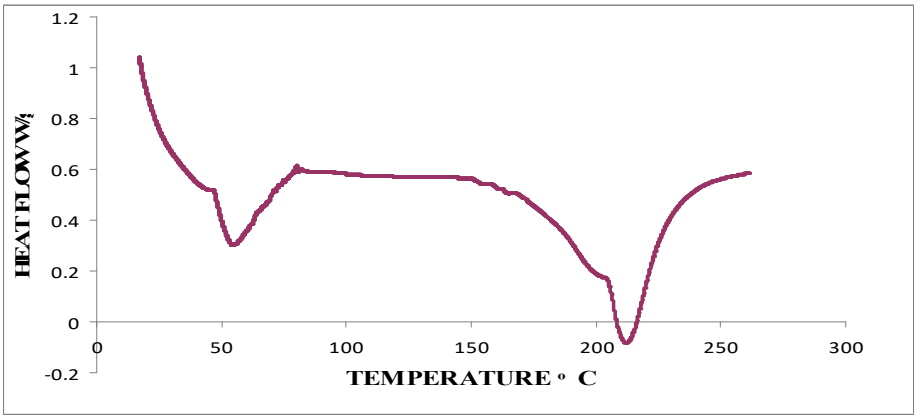


**Figure 6: DSC of F2**

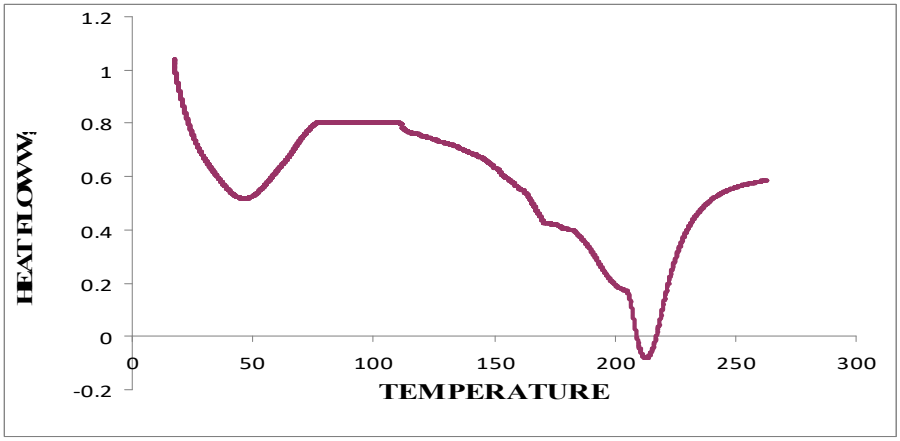


**Figure 7: DSC of F3**

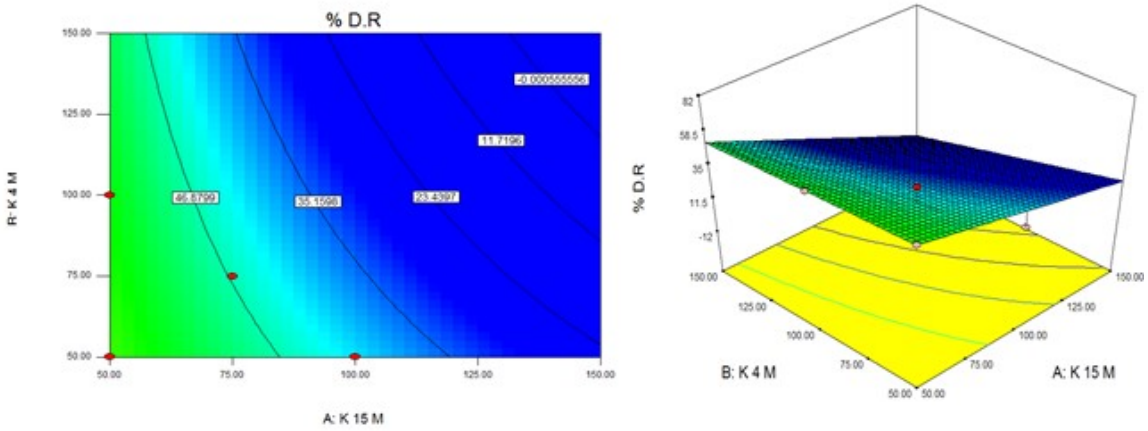


**Figure 8: Effect of HPMC K15M and HPMC K4M % drug release**

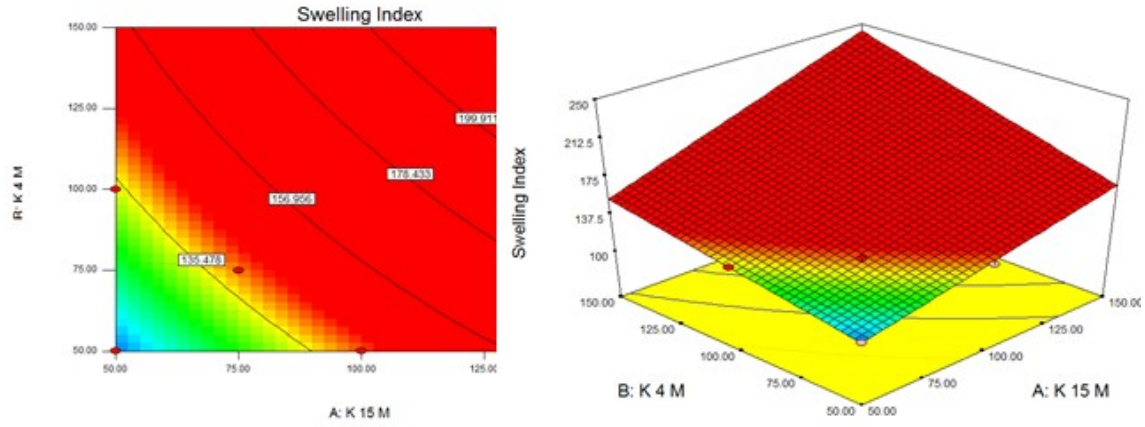


**Figure 9: Effect of HPMC K15M and HPMC K4M on swelling index**

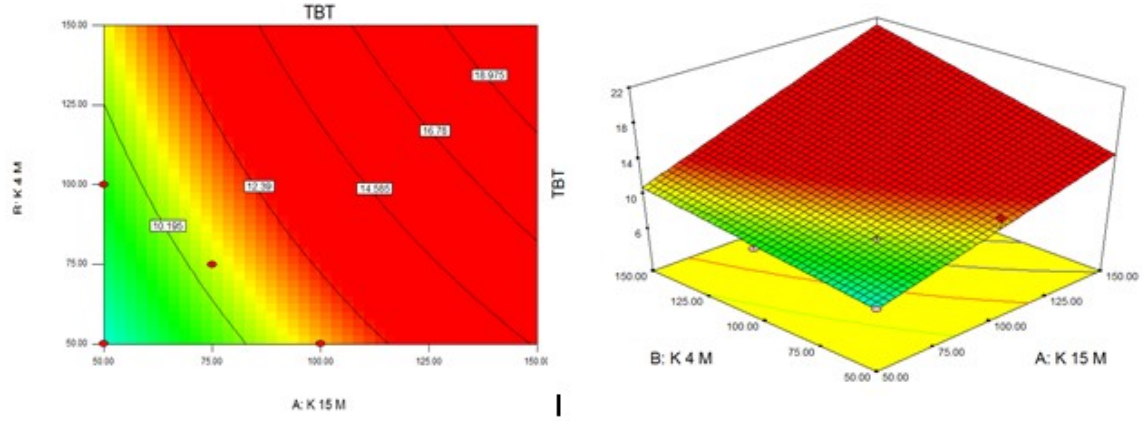


**Figure 10: Effect of HPMC K15M and HPMC K4M on TBT**

## DISCUSSION

The melting point of sitagliptin was determined by capillary tube method and it was 215°C. By using UV visible spectrophotometer maximum absorbance of sitagliptin was determined and it was observed at wavelength (λmax) 266.8nm. As observed in the thermogram of sitagliptin the melting transition was observed at temperature 213.7 ºC and the DSC scans of all formulations also showed melting endotherm at the same temperature which revealed that polymer did not affect the drug nature [16]. The thermograms of polymers showed endothermic peaks over a temperature range of 20-100 ºC that is due to dehyration process of polymers at this temperature range (Nayak et al., 2011). The angle of repose for all the six batches ranged from 25.54º to 27.64º, compressibility index ranged from 13.9 to 20, hausner ratio from 1.16 to 1.25. The dry granules of all the batches exhibited good flow properties. The hardness of all the six batches ranging from 3.6 kg/cm² to 3.9 kg/cm² which showed satisfactory mechanical strength. The thickness and diameter ranged from 6.2mm to 6.5mm and 11.1mm to 11.3mm respectively. The percentage loss in weight (friability) of all

the formulations ranging from 0.46% to 0.76% which complying pharmacopoeial specifications. The weight variation of 20 tablets ranging from 0.969% to 1.007% comply with specifications(Chavanpatil et al., 2005).

The floating lag time of all the batches ranged from 54 to 92 seconds. Floating lag time of formulations depends on amount of effervascent compounds (NaHCO3, citric acid & tartaric acid). The amount of gas generating agents were same for for all the formulations. So, all the six formulations exhibited satisfactory floating behaviour in 0.1N hydrochloric acid. Total buoyancy time depends on grade and concentration of hydroxy propyl methyl cellulose used. From all the formulations F1, F3 and F5 showed good total buoyancy time ranging from 10 to 12.5 hours. F1 contained HPMC K15M only while F3 & F5 contained high content of HPMC K15M and low content of HPMC K4M. F2, F4 and F6 formulations were disintegrated after 6, 9 and 8 hours respectively. In F2 formulation only HPMC K4M was used and F4 contained low content of hydroxy propyl methyl cellulose K15M and high content of hydroxy propyl methyl cellulose K4M. F6 contained equal amount of polymers but have high concentration of microcrystalline cellulose which cause disintegration of tablet(Kannan et al., 2010). The swelling index of all the formulations was estimated. As the time increased the polymer absorbed water due to its hydrophilic nature and swells. F1, F3 and F5 showed higher swelling index. F2, F4 and F6 showed low swelling index. This showed that by increasing the viscosity of polymer swelling index can be increased and vice versa(Kshirsagar et al., 2009). Dissolution studies for all the six batches were conducted by using USP dissolution apparatus II. After 12 hours period the cumulative percent release of F1, F3 and F5 was 90.96%, 82.76% and 91.8% respectively. The cumulative percent release of F2 was 90.96% after 6 hours, for F4 91.66% after 9 hours and for F6 90.5% after 8 hours which showed poor sustained effect. F1, F3 and F5 showed sustained effect of drug after 12 hours due to high content of hydroxy propyl methyl cellulose K15M polymer(Kannan et al., 2010).As the quantity of polymer increases sustained effect of the formulation increases (Garg and Gupta, 2010). The in vitro dissolution data of all the batches was fitted in different mathematical models like zero order, first order, Higuchi, Hixson Crowell and Korsemeyer Peppas models. The $R^2$ values for F1,F2, F3, F4 & F6 were best fitted in Korsemeyer Peppas model. The value of diffusion exponent (n) for F1, F2 and F4 were 0.783, 0.858 and 0.875 respectively ($0.45<n<0.89$) which is indication of drug release by non fickian (anomalous) diffusion thereby refers drug release by diffusion and erosion. The values of n for F3 and F6 were 1.126 & 0.904 ($n>0.89$) shows super case tranport II which describes the erosion of polymeric chain.

The $R^2$ value for F5 was best fitted in Hixson Crowell model which showed that the drug was released by dissolution.

## CONCLUSION

Gastro retentive floating tablets of sitagliptin phosphate were prepared successfully by wet granulation method using hydrophilic polymers hydroxy propyl methyl cellulose K15M & K4M and NaHCO3, citric acid and tartaric acid were used to generate effervescence. From F1-F6 batches, F1 formulation showed satisfactory buoyancy lag time and tablet was remained buoyant for 12 hours and released the drug in controlled manner. The other evaluation tests like hardness, weight variation, and friability were also according to specifications. The regression coefficient ($r^2$) value obtained from invitro release data of this formulation showed that it follows Korsemeyer Peppas model and mechanism of drug release was non fickian diffusion. F1 contained HPMC K15M as release retardant polymer and releases the drug slowly in controlled manner. So, on the basis of current investigation it was concluded that residence time of sitagliptin in the gastric fluids can be increased by formulating its floating tablets and rate of the drug release can be controlled by using HPMC K15M.

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**CONFLICT OF INTEREST**

All authors are agreeing to submit the article and they have no conflict of interest.

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