

FORMULATION AND *IN VITRO* EVALUATION OF FLOATING TABLETS OF PSYLLIUM HUSK & TRAGACANTH USING SITAGLIPTIN PHOSPHATE AS A MODEL DRUG

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Abstract: A novel floating controlled release drug delivery system of Sitagliptin phosphate was formulated in an effort to increase the gastric retention time of the dosage form and thereby increased drug bioavailability. The tablets were prepared by wet granulation method using psyllium husk and tragacanth gum as a release retarding polymers and sodium bicarbonate as a gas generating agent. All the designed nine batches of floating tablets were evaluated for physical characteristics viz. weight variation, thickness, content uniformity, hardness, floating capacity, swelling studies. All formulations had floating lag time of less than 1 min and constantly floated for 12 h except F₁, F₂ and F₇ (that dissolved completely in 8 h or less than 8 h). *In vitro* drug release studies were carried out for 8 h and release mechanism was further evaluated by linear regression analysis, F₉ composed of 30% Psyllium Husk, 10% tragacanth gum and 18% sodium bicarbonate sustained the drug release for longer period. The formulations followed first order kinetics, Higuchi drug release kinetics with diffusion as the dominant mechanism of drug release and the release exponent ranged (0.452-0.635) indicating that the drug release from all formulations was by non-Fickian diffusion mechanism. The prepared floating tablets of STP (F₉) might be a promising drug delivery system with sustained release action and improved bioavailability.

Keywords: Sitagliptin phosphate, floating tablets, psyllium husk, tragacanth, release kinetics, sustained release

For efficient drug delivery oral route is still considered the most favorable route owing to its formulation flexibility, good patient compliance and simplicity of administration (1). These conventional delivery systems meant for producing abrupt drug release offer many complications in therapy such as short half-life drugs poses multiple dosing problems and plasma drug fluctuations specifically for lower therapeutic index drugs could be dangerous (2). The unavoidable drug concentration fluctuations may result in under medication or over-medication as the steady state concentration (C_{ss}) values decrease or increase beyond the therapeutic range (3, 4). Additionally, as the drug gets passed through the absorption window of the gastrointestinal tract, mainly for the slow release dosage forms, it becomes useless, as body fails to absorb it (5).

In past decade, a number of novel drug delivery techniques have revolutionized the medication

methods with added benefits. These novel systems aim to reduce drug dosing frequency but still maintain therapeutic blood levels for longer period of time. Additionally, these novel adopted techniques carry the active pharmaceutical ingredient to the target organ thus minimizing possible side effects. However, the absorption of drug is often insufficient due to physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release so gastro-retentive approach is an alternate to tackle this problem (6).

Through gastro retentive approach, the dosage form will persist in the gastric region for longer time period, extending the gastric residence time of drugs. Extended gastric retention increases drug absorption/bioavailability, decreases drug waste, and increases its solubility that is otherwise least soluble in high pH milieu. Besides, it is also appro-

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appropriate for delivering drug locally to the stomach and small intestine (7).

The approaches of drug delivery, like conventional dosage forms rely heavily on excipients that directly or indirectly affect the rate of drug release. In recent times, isolated and highly purified plant based additives demand replacing synthetic additives with natural ones. These natural additives offer many benefits over synthetic ones i.e. are inert, non-toxic, less expensive, biodegradable and commonly available but such excipients are very often less predictable. Ispaghula husk (dried seed coat of *Plantago ovata*) and tragacanth gum (from *Astragalus gummifer*) a mixture of both water soluble and insoluble polysaccharides have been used as matrixing agents in modified release dosage forms owing to their swelling features upon hydration (8).

Sitagliptin phosphate (STP) is novel oral anti hyperglycemic drug used to treat type-II diabetes mellitus. It competitively inhibits the enzyme dipeptidyl peptidase-4. This enzyme breaks down the incretins glucagon-like peptide-1 (GLP-1) and Gastric inhibitory polypeptide (GIP) gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal (9).

The objective of the present study was to design and optimize the floating tablets of STP by wet granulation method using different ratios of psyllium husk, tragacanth gum and sodium bicarbonate. Magnesium stearate was also added. The dose of STP was 100 mg. Hence, to maintain the

bioavailability and to reduce the frequency of drug administration floating tablets were prepared.

MATERIALS AND METHODS

Materials

Sitagliptin phosphate monohydrate was gift sample from Neon Chemicals (Pvt) Ltd. Psyllium husk was purchased from Qarshi Industries (Pvt) Ltd. Tragacanth (Sigma-Aldrich), isopropyl alcohol (Merck), sodium bicarbonate (Sigma-Aldrich), magnesium stearate (Merck). Reverse osmosis was used to obtain water. All the chemicals utilized were of analytical grade and were used as such without further processing.

Methods

Preparation of Sitagliptin phosphate floating tablets

Floating tablets of STP were obtained by wet granulation using psyllium husk and tragacanth as a release retarding agents and sodium bicarbonate was used as gas generating agent. STP, psyllium husk, tragacanth, sodium bicarbonate were passed through sieve # 40 and all ingredients mixed well for 10 min and then isopropyl alcohol was added drop wise to make the wet mass of granules. After remixing for 5 min, the granules were passed through sieve # 16 and dried at 40°C for 1 h and dried granules were further passed through sieve # 40 (10). Magnesium stearate was added as a lubricant and dried granules were compressed under 15 kN force on ZP-19 rotary press with 7 mm round flat punches. In this study, 9 formulations of 100

Table 1. Formulations of Sitagliptin phosphate floating tablet using various concentrations.

Formulation code	Ingredients (mg)					Total weight (mg)
	STP	PSH	TRG	SBC	MST	
F1	100	25	75	15	5	220
F2	100	50	50	15	5	220
F3	100	75	25	15	5	220
F4	100	25	75	30	5	235
F5	100	50	50	30	5	235
F6	100	75	25	30	5	235
F7	100	25	75	45	5	250
F8	100	50	50	45	5	250
F9	100	75	25	45	5	250

STP, PSH, TRG, SBC and MST corresponds to Sitagliptin phosphate, psyllium husk, tragacanth gum, sodium bicarbonate and magnesium stearate, respectively

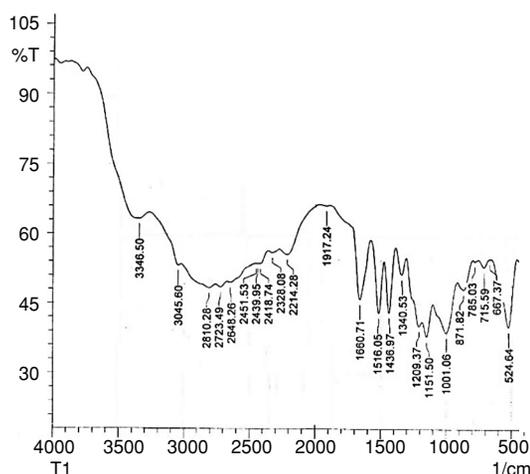


Figure 1a. FTIR spectrum of Sitagliptin

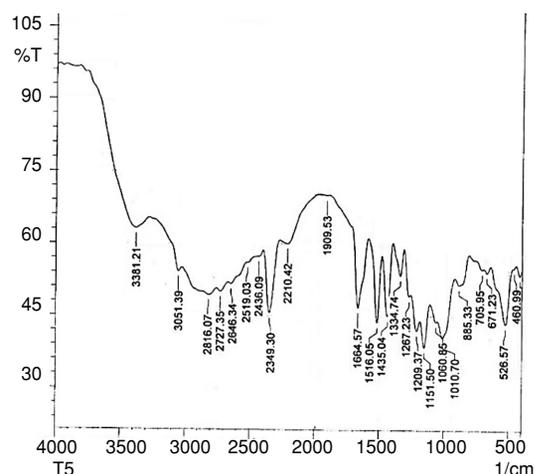


Figure 1b. FTIR spectrum of the formulation containing Sitagliptin and all excipients

mg of STP were prepared using various proportions of polymers as shown in Table 1.

Characterization of floating tablets

Fourier transform infrared analysis

The interactions between drug and rate controlling polymers were studied by FTIR spectroscopy. Disks for FTIR analysis were prepared by mixing drug/polymers with KBr (2/mg sample in 200/mg KBr). The prepared disks were then examined in FTIR spectroscope at the resolution of 2 cm⁻¹ with scanning range of 4000-400 cm⁻¹ (6).

Flow properties of granules

Following parameters of prepared granules were measured to assess the powder rheology.

Determination of bulk density, tapped density

Weighed quantity of (50 g) was added into a graduated cylinder and bulk density was found by measuring the volume occupied by powder. Then, the cylinder containing known amount of powder was subjected to tapping for about 1 min on a balanced surface until constant volume was obtained (11).

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Volume of powder before tapping}}$$

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Volume of powder after tapping}}$$

Angle of repose

The powder was poured through the funnel on the horizontal surface to form a cone. Height and radius of formed cone was measured and angle of repose was calculated by using following equation (12).

$$\tan \theta = \frac{\text{Height}}{\text{Radius}}$$

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

For good flowing properties, angle of repose should be less than 30°.

Powder compressibility

To measure the compressibility of powder, Carr's index and Hausner's ratio was calculated by using following formulas (12).

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Physicochemical characterization of tablets

All the relevant compressed tablets tests such as thickness, weight variation, friability, content uniformity, crushing strength, buoyancy and swelling index tests were performed (9).

Hardness, friability test and tensile strength

Hardness Tester was determined using Monsanto type hardness tester. All the tests were performed in triplicate. Friability was determined by randomly selected 20 tablets, de-dusted, weighed accurately and placed in a friability apparatus and run for 4 min with 25 rpm. Friability for all the formulations (F₁-F₉) was calculated using equation. Where w₁ represent matrix initial weight and w₂ denotes weight after test, and x is indication of the percent weight loss.

$$x = \frac{w_1 - w_2}{w_1}$$

The tensile strength of the tablets from all batches was calculated using the crushing strength data in addition to the thickness and diameter using a formula, where F = force in Newton (N), D = diameter of the tablet (mm), T = thickness of the tablet (mm).

$$T_s = 2F/\pi DT$$

Weight variation test

Uniformity of weight was determined by using electronic balance to understand the extent of regularity among dosage units, the variation was determined using a formula where w_a = average weight of the tablet and w_o = theoretical weight of the tablet.

$$\% \text{ age difference} = 100 - [(w_o - w_a/w_o) \times 100]$$

Swelling index

From all the formulations, one tablet was weighed accurately (W_i) and 200 mL of 0.1 N HCl (pH 1.2). At regular intervals, tablets were withdrawn; excess surface liquid was removed using filter paper and reweighed and swelling index was determined with the following equation.

SI = Swelling Index, W_i = Weight of the tablets prior to test and W_f = Weight of the tablets subsequent to test

$$SI = \{[W_f - W_i]/W_i\} \times 100$$

In-vitro buoyancy studies

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed by placing one tablet from each formulation in 200 mL of 0.1 N HCl (pH 1.2) poured in 250

mL beaker. The temperature of simulated gastric fluid was maintained at $37 \pm 0.5^\circ\text{C}$ in a water bath during the whole study period (12 h). The time difference between the introductions of dosage form in 0.1 N HCl and when it started to float was calculated (floating lag time). Moreover, the time during which the dosage form remained buoyant (total floating time) was also determined.

In-vitro drug release studies

In-vitro drug release study for all the formulations (F_1 – F_9) was carried out using dissolution apparatus, having beaker with capacity to accommodate 900 mL simulated gastric fluid 0.1 N HCl (pH 1.2), equipped with type-II paddle apparatus at 100 rpm with medium temperature of $37^\circ\text{C} \pm 0.5^\circ\text{C}$. Samples of 5 mL were withdrawn at pre-determined time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h and replenish the same with equal volume of fresh medium. The samples were filtered, suitably diluted with fresh dissolution medium and analyzed at 271 nm using a Shimadzu UV-1700 double beam UV/Vis spectrophotometer. The determinations were performed in triplicate (13).

Kinetic modeling of drug release

To analyze the mechanism of drug release from the floating tablets, the *in vitro* dissolution data of the formulations were fitted to the zero order, first order, Higuchi model and Korsmeyer- Peppas mode (14, 15).

RESULTS AND DISCUSSION

The prepared floating tablets were evaluated for hardness, friability, uniformity of weight, unifor-

Table 2. Rheological evaluation of powder blend of formulations (F1-F9).

Formulation Code	Bulk Density	Tapped Density	Angle of Repose	Carr's Index	Hausner's Ratio
F1	0.64	0.76	30.54	15.79	1.19
F2	0.61	0.70	26.57	12.82	1.15
F3	0.60	0.67	21.80	10.26	1.11
F4	0.66	0.80	30.54	17.50	1.21
F5	0.58	0.67	26.57	13.64	1.16
F6	0.61	0.74	31.8	18.18	1.22
F7	0.66	0.79	26.57	16.67	1.20
F8	0.59	0.68	32.21	13.64	1.16
F9	0.66	0.73	29.25	9.52	1.11

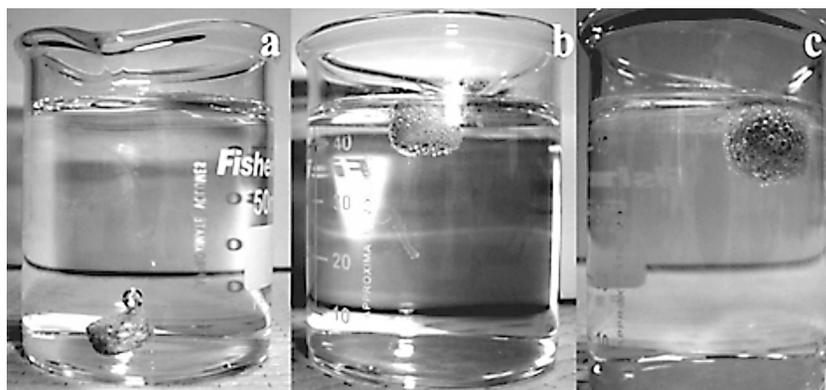


Figure 2. F_9 lag time in simulated gastric fluid at (a) time $t = 0$, (b) $t = 4$ seconds, (c) $t = 12$ h

mity of drug content, swelling index, floating lag time, *in vitro* buoyancy behavior, *in vitro* dissolution and drug-polymer interaction.

Fourier transform infrared analysis

FTIR spectrum of STP showed characteristic absorption bands at 3324 cm^{-1} (NH_2), 3050 cm^{-1} (aromatic C–H stretching), 1636 cm^{-1} (amide C=O group), 1064 cm^{-1} (terminal amine) and 1018 cm^{-1} (C–F) which remain unchanged in the entire formulations (Fig. 1a and 1b) while a characteristic absorption band was observed at 2349.30 cm^{-1} (Fig 1b) that showed the strong stretching of CO_2 (O=C=O group). However, this data showed that there was no major change in the properties of the drug, when mixed with polymers and other excipients (16, 6).

Flow properties of granules

Prepared granules from each formulation were subjected to different rheological parameters in order to assess the flow properties and the values were shown in (Table 2). The Hausner's ratio was within the range of 1.11–1.22 showing good flow characteristics. The Carr's index was also determined to divulge inter-particulate cohesive properties. The values were found in acceptable range of 9.52–18.18. Furthermore, flow characteristics were examined by measuring angle of repose and values were found to be 21.8–32.21 that also showing excellent powder flow. Hence, it was proved that prepared granules have shown good rheological characteristics (11).

Physicochemical characterization

Content uniformity of all the formulations showed promising results and weight variation was

within official limits (85–115%) for all the formulations (F_1 – F_9) (USP30-NF27, 2007). The data of friability test for all the batches (F_1 – F_9) was less than 1%. The data from weight variation test was uniform, which indicate that mixing of drug and excipients was proper (Table 2a and b). Hardness and tensile strength was in the range of 9.20–16.18 and 2.09–3.88 kg/cm^2 respectively and demonstrating outstanding mechanical strength (Table 3a and b).

In vitro buoyancy studies

Excellent buoyancy lag time was observed for all formulations as all the tablets started to float before 1 h and observed floating lag time ranged 4.0 to 50.3 seconds. Total floating time of all experimental formulations (F_1 – F_9) was also determined, F_1 , F_4 and F_7 dissolved before 8 h. While other formulations remained buoyant in dissolution media for more than 12 h (Fig. 2).

The formulations maintained their matrix integrity for more than 12 h except F_1 , F_4 and F_7 . The result shows that the total floating time for the formulations was more than 12 h irrespective to the amount of sodium bicarbonate whereas floating lag time decreased with increasing amount of sodium bicarbonate. The amount of carbon dioxide produced was exclusively proportional to the quantity of sodium bicarbonate in the tablet. Decrease in floating lag time of the formulations can be attributed to the availability of an increased amount of carbon dioxide as the quantity of sodium bicarbonate was increased, being entrapped in the formed gel to give rapid buoyancy (10).

Swelling studies

Polymers formed a polymeric gel layer on contact with simulated gastric fluid, and this gel layer is

Table 3a. Post-compression evaluation parameters of Sitagliptin floating matrix tablets.

Evaluation parameters	F1	F2	F3	F4	F5
*Drug Content in mg/tablet (%RSD)	99.63 ± 0.81 (0.81)	97.27 ± 1.24 (1.28)	98.47 ± 1.75 (1.78)	98.80 ± 0.66 (0.66)	98.00 ± 1.42 (1.45)
†Weight Variation in mg (Difference)	219.99 ± 0.18 (0.00%)	219.75 ± 1.40 (0.11%)	219.53 ± 1.31 (0.21%)	234.72 ± 1.21 (0.12%)	235.11 ± 1.28 (0.05%)
†Friability (%)	0.89	0.68	0.32	0.81	0.62
†Crushing Strength (kg/cm ²)	15.4 ± 1.51	16.18 ± 1.03	9.24 ± 0.53	14.28 ± 0.93	15.00 ± 1.39
†Tensile Strength (kg/cm ²)	3.62 ± 0.37	3.84 ± 0.22	2.20 ± 0.13	2.89 ± 0.19	3.13 ± 0.19
*Thickness (mm)	3.84 ± 0.02	3.84 ± 0.03	3.83 ± 0.02	4.46 ± 0.03	4.47 ± 0.03
*Diameter (mm)	7.02 ± 0.02	7.02 ± 0.02	7.01 ± 0.01	7.01 ± 0.01	7.02 ± 0.01
£Buoyancy Lag Time (s)	50.3	49.7	19.0	13.0	24.3
£Total Buoyancy Time (h)	< 4.0	> 12	> 12	< 7	> 12

*n = 10, †n = 20, £Average of n = 3

Table 3b. Post-compression evaluation parameters of Sitagliptin floating matrix tablets.

Evaluation parameters	F6	F7	F8	F9
*Drug Content in mg/tablet (%RSD)	97.42 ± 0.35 (0.36)	98.40 ± 1.01 (1.03)	97.57 ± 0.83 (0.85)	96.90 ± 1.23 (1.27)
†Weight Variation in mg (Difference)	235.12 ± 0.94 (0.05%)	250.56 ± 1.54 (0.22%)	250.54 ± 2.03 (0.22%)	250.48 ± 1.99 (0.19%)
†Friability (%)	0.38	0.84	0.40	0.36
†Crushing Strength (kg/cm ²)	9.20 ± 0.59	10.88 ± 1.17	16.28 ± 0.76	13.60 ± 0.57
†Tensile Strength (kg/cm ²)	1.85 ± 0.14	2.09 ± 0.24	3.16 ± 0.23	2.60 ± 0.10
*Thickness (mm)	4.48 ± 0.03	4.73 ± 0.04	4.74 ± 0.03	4.74 ± 0.02
*Diameter (mm)	7.02 ± 0.02	7.01 ± 0.01	7.02 ± 0.02	7.02 ± 0.02
£Buoyancy Lag Time (s)	6.3	9.7	18.7	4.0
£Total Buoyancy Time (h)	> 12	< 12	> 12	> 12

*n = 10, †n = 20, £Average of n = 3

Table 4. Fitness of release parameters to mathematical models.

Formulation	Zero Order		First Order		Higuchi's		Korsmeyer Pepas		
	k ₀	R ²	k ₁	R ²	k _H	R ²	k _p	R ²	N
F ₁	0.137	0.991	-0.005	0.973	4.029	0.978	0.047	0.926	0.529
F ₂	0.133	0.987	-0.004	0.961	3.832	0.996	0.051	0.993	0.487
F ₃	0.129	0.959	-0.004	0.972	3.749	0.991	0.043	0.970	0.523
F ₄	0.124	0.974	-0.004	0.956	3.704	0.967	0.038	0.798	0.588
F ₅	0.125	0.986	-0.003	0.957	3.644	0.973	0.035	0.889	0.536
F ₆	0.135	0.981	-0.003	0.996	3.912	0.989	0.021	0.943	0.622
F ₇	0.136	0.993	-0.005	0.816	4.035	0.975	0.030	0.857	0.635
F ₈	0.133	0.995	-0.004	0.992	3.803	0.973	0.081	0.905	0.452
F ₉	0.134	0.968	-0.003	0.987	3.852	0.980	0.035	0.950	0.531

thought to govern the drug release from matrices, thus affect the kinetics of drug release. Due to hydrophilic nature of polymers swelling index increased with time as shown in Figure 3. Various

formulations showed different swelling index. The formulations containing larger quantity of low viscosity polymer tragacanth (3.4 Pas) used in F₁, F₄ and F₇ swelled around 6 h where chain relaxation

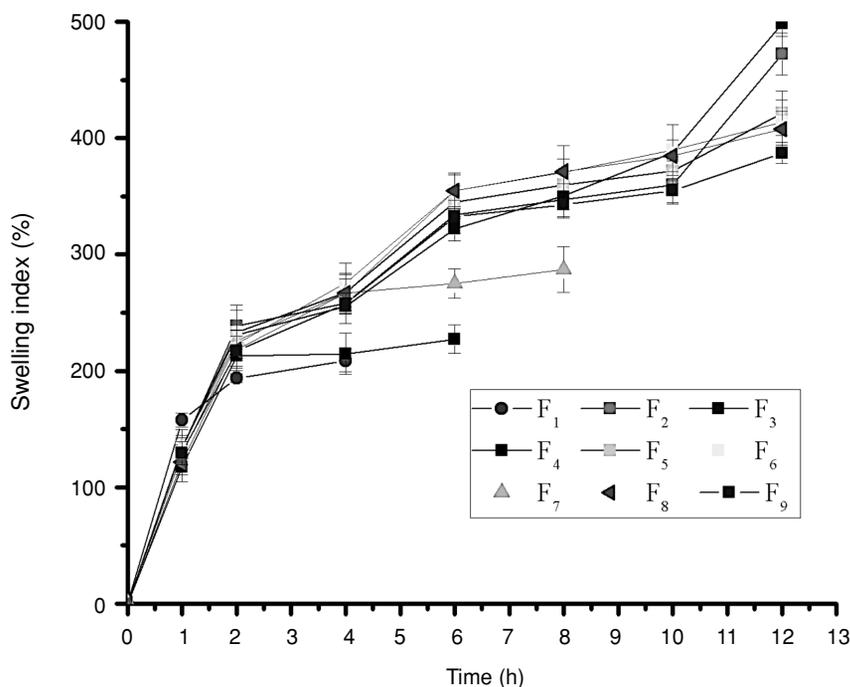


Figure 3. Results of the swelling index studies of F₁ to F₉ formulations

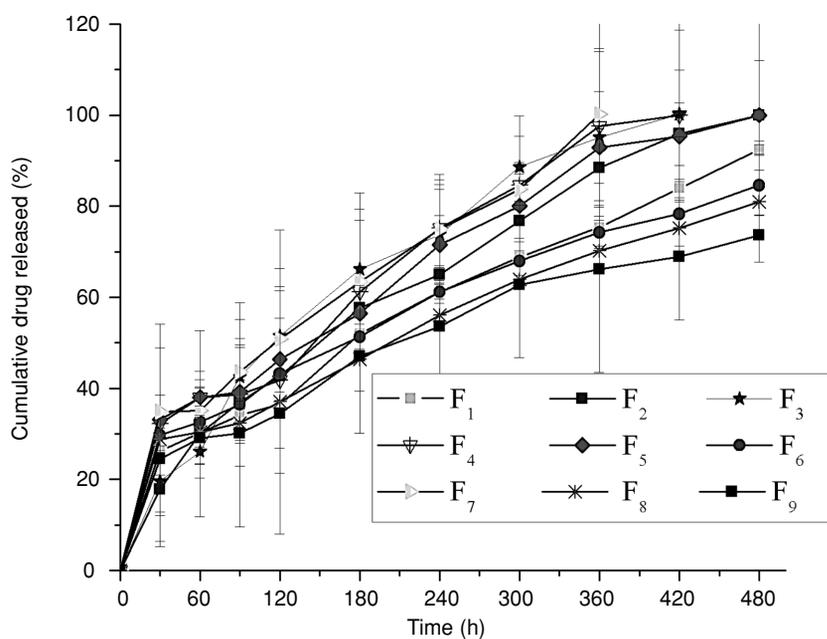


Figure 4. *In-vitro* dissolution profile of formulations (F₁-F₉), presented as cumulative drug release vs. time

caused decrease in swelling index. While high viscosity and larger quantity of psyllium husk used in other formulations lead to the high swelling index up to 8 h, which indicated direct relationship between the viscosity of polymeric matrices and the swelling index (10).

***In vitro* drug release studies**

The drug release profile for matrix system (F_1 – F_9) loaded with STP was studied for 8 h as shown in Figure 4. The percentage of drug released from F_1 was 30% in the initial 30 min and almost complete drug release was observed in less than 6 h and no residue was left for tablets. This behavior was attributed to inadequate concentration of psyllium husk in matrix; similar low sustaining results have been reported for tragacanth (17). In F_2 equal amount of psyllium husk and tragacanth were used (50 mg/tab), 25% initial drug release was seen in 30 min while 80% release was seen at end of 6 h and at the end of study complete release was noted. Formulation F_3 with maximum amount of psyllium husk (75 mg/tab) and lowest amount for tragacanth (25 mg/tab) released the drug in 7 h. It may be seen that with increase in psyllium husk quantity the retardation properties of formulation was directly affected. Similar results have also been reported previously, psyllium husk showed prompt swelling and gelling property so it was suggested a suitable candidate for matrix systems (18).

Formulation F_4 , F_5 and F_6 differed from F_1 , F_2 and F_3 only in sodium bicarbonate quantity that was doubled i.e., 30 mg instead of 15 mg. F_4 released the drug faster i.e., 80% of drug released in less than 4 h but eroded completely in 5 h. F_5 formulation sustained the drug release for 8 h while 81% of drug was released from F_6 after 8 h (19, 20). In formulation F_7 , F_8 and F_9 the quantity of sodium bicarbonate was further increased i.e. 45 mg/tab. From F_7 , the drug release was faster and 86% of drug was released in 5 h and almost all the drug was released in 6 h. The F_8 formulations release 86% of drug after 8 h. From formulation F_9 the drug release was controlled and after 8 h, only 73% drug was released. Formulation F_9 containing psyllium husk (75 mg) and tragacanth (25 mg) showed promising dissolution with desired floating properties. From the results it was clear that the release rate was controlled for formulations containing low level of tragacanth and higher level of psyllium husk i.e. F_3 , F_6 and F_9 compared with other formulations (21). Therefore, required release rate of drug can be obtained by manipulating the composition of tragacanth and psyllium husk.

Kinetic modeling of drug release

The *in vitro* dissolution data was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4. Analysis of the drug release data as per zero order and first order kinetic models indicating that the formulations followed first order kinetics and different *in-vitro* dissolution parameters such as dissolution rate constant (K). Plots of percent release versus time (Higuchi plots) were found to be linear with the range of 0.96 to 0.99 indicating diffusion as the release mechanism. In the analysis of release data as per Korsmeyer-Peppas equation, the release exponent "*n*" was in the range 0.452-0.635 indicating non-fickian diffusion as the release mechanism (21, 22).

CONCLUSION

In recent past natural polymers have attracted attention of formulation scientists in design of novel drug delivery systems owing to their biodegradable nature, less environmental concerns and most importantly its acceptance and safety in human beings. Outcomes of the studies showed a direct relation between Psyllium Husk concentration and drug release rate i.e. higher the polymer concentration and delayed the release of drug. On the other hand inverse relation was observed between formulation floating lag time and sodium bicarbonate concentration i.e. with increase in sodium bicarbonate floating lag time of formulations decreased. Therefore, it can be concluded that psyllium husk along with tragacanth might be used to develop sustained release floating tablets of STP by integrating suitable amount of sodium bicarbonate for gas generation.

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