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Formulation, *In vitro* and *In vivo* Evaluation of Pioglitazone Hydrochloride - Effervescent Gastro Retentive Floating Hydrophilic Matrix Tablets.

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Abstract : Aim: Of this study was to formulate and evaluate an anti-diabetic agent, Pioglitazone HCl (PH) to an effervescent gastro retentive floating tablet (GRFT), which can extend its release up to 12 h in gastric pH. To determine the effect of combination of natural gums [sodium alginate (SA), sodium carboxy methyl cellulose (Na CMC), xanthan gum (XG) & guar gum (GG)] with semi-synthetic polymer, HPMC K100M in extending the release of PH up to 12 h in gastric pH. **Methods:** Drug- excipient compatibility studies were done by FT-IR studies. The effervescent PHGRFT was prepared by direct compression. All the formulations were evaluated for pre-compression (angle of Repose (θ), bulk density (BD), tapped density (TD), Carr's Index (CI) & Hausner's Ratio), post-compression (% wt variation, thickness, % friability, % assay, %swelling index and *in vitro* dissolution), *in vitro* buoyancy studies [floating lag time (FLT), total floating time (TFT) and matrix integrity (MI) up to 12 h], drug release kinetics determination. *In vivo* x-ray imaging studies in rabbits and accelerated stability studies in the final 10 cc HDPE package were conducted for the optimized formulation-F4. **Results:** FT-IR studies reveals that PH and the polymers used in the study are compatible. Pre & post-compression parameters were within the acceptable limits for all formulations. Drug release kinetics of formulation-F4(37.5% HPMC K100M and 12.5% GG) suggests it extends the drug release up to 12 h, with a better zero order release profile (as zero order, r^2=0.999). Drug release process is not predominantly by diffusion (as Higuchi r^2= 0.840); and the mechanism of diffusion is by super case-II transport (as Korsemeyer- Peppas, n=1.058). It is exhibiting FLT of 56 s, TFT and a better MI up to 12 h. Hence it is an optimized formulation. F4 batch passes the test for stability as per ICH guidelines. Hence, it was finally concluded that a better twice a daily PHGRFT was formulated and evaluated.

Key words: Pioglitazone HCl (PH), gastro retentive floating tablets (GRFT), hydroxy propyl methyl cellulose (HPMC K100M), sodium alginate (SA), sodium carboxy methyl cellulose (Na CMC), xanthan gum (XG), guar gum (GG), *in vitro* buoyancy studies, *in vivo* X-ray imaging studies.

Introduction:

Oral route is one of the most extensively utilized routes for administration of dosage forms. Drugs that have an absorption window in stomach or upper small intestine, have low solubility and stability at alkaline pH were suitable to convert as gastro retentive dosage forms (GRDF). GRDF significantly extend the period of drug release, and thereby decreasing the dosing frequency of drugs with shorter elimination half life ($t_{1/2}$ < 5h) and will increase patient's compliance.[1, 2] Various approaches for GRDF include: floating drug delivery system (FDDS), bio adhesive systems, swelling, expanding systems and high density systems.[3] FDDS has a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affected by gastric emptying rate. When the system is floating on the gastric fluids, the drug release will be extended from the system. Based on the mechanism of buoyancy, two different technologies for FDDS are effervescent systems and non-effervescent systems.[1-3] Effervescent systems contains carbonates (eg: sodium bicarbonate) and / or organic acids (eg: citric acid / tartaric acid) in their formulation to produce carbon dioxide (CO_2) gas when comes in contact with gastric fluids. The CO_2 gas entrapped in the matrix system, reduces its density and makes the system buoyant.[1-3] The non-effervescent systems are based on the mechanism of swelling of polymer or bio-adhesion to mucosal layer in gastro intestinal tract.[1-3] Pioglitazone Hydrochloride (PH) is an effective oral anti-diabetic agent that belongs to the thiazolidenones drug class and is widely prescribed in management of non-insulin dependent (type-2) diabetes mellitus.[4] It is poorly soluble in aqueous fluids and is majorly absorbed from stomach.[5] Dosage forms that are retained in the stomach would increase the oral bioavailability and efficacy of drugs, which are majorly absorbed from stomach.[6] PH has a short biological half-life of 3-7 h and is eliminated in the feces.[7] PH is to be administered in 2 to 3 doses of 15 to 45 mg per day.[8] Novel drug delivery systems (NDDS) such as floating mini tablets[9], floating tablets & microspheres[10] are effective in the better management of diabetes mellitus than conventional dosage forms. Therefore controlled release floating tablet formulations are needed for PH to prolong its duration of action and to increase its oral bioavailability and reduced dosing frequency. Natural gums like (kondagogu gum [11], Ghatti gum [12], gum olibanum[13], sodium alginate[14], sodium alginate and pectin[15], sodium alginate and chitosan[16] , HPMC and Xanthan gum[17], sodium alginate and xanthan gum[18]) in combinations or combination with semi synthetic polymers are promisingly extending the drug release in gastro retentive or stomach specific drug delivery systems. In this study an attempt was made to design floating tablets of PH using four natural gums (SA, Na CMC, XG and GG) in combination with a semi synthetic polymer, HPMC K100M as tablet matrix formers along with a gas generating agent, sodium bicarbonate by direct compression method.

Materials:

PH is a gift sample received from M/s Dr. Reddy's Laboratories, Hyderabad, India. Hydroxy Propyl Methyl Cellulose (HPMC K100M), Micro crystalline cellulose (Avicel PH 101) and Hydroxy propyl cellulose (HPC_{EXF}) were received as gift samples from Colorcon Asia Pvt. Ltd., Mumbai, India. Sodium alginate, sodium carboxy methyl cellulose, xanthan gum and guar gum were purchased from Arihant trading Co. Ltd., Bangalore. Magnesium stearate, sodium bicarbonate, talc and $BaSO_4$ were purchased from S.D. Fine-Chemicals Ltd., Chennai, India. All the excipients used in study are of analytical grade.

Methods:

Drug-excipient compatibility / FT-IR studies: FT-IR spectra of pure drug and drug: polymer (1:1) physical mixtures were recorded out, in the region of 400-4000 cm^{-1} at spectral resolution of 2 cm^{-1}, by the direct sampling method with isopropyl alcohol as solvent, using (Agilent technologies Cary 630 FT-IR, Japan) and the comparative FT-IR spectra were shown in (Figure 1).

Standard calibration curve:[19] 100 mg of PH pure drug was dissolved in 100 ml of 0.1 N HCl (stock solution-1000 µg/ml) and then placed in an sonicator for 10 min, from this 10 ml of solution was taken and the volume was adjusted to 100 ml with 0.1 N HCl (100 µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain the series of working dilutions containing 2, 4, 6, 8 and 10 µg/ml of PH solution. The working dilutions were analyzed at 269 nm by using a double beam UV-Vis spectrophotometer (Agilent technologies Cary 60 UV-Vis, Japan). The standard calibration curve was plotted by taking conc. on X-axis and absorbance on Y-axis.

Preparation of PHGRFT tablets: All the tablet batches were prepared by direct compression method, by keeping the amount of PH constant as 30 mg per tablet. The composition of other excipients is varied as mentioned in formulation table (Table 1).

Table 1: Formulation table of PHGRFT.

Ingredients*	F1	F2	F3	F4	F5	F6	F7
Pioglitazone HCl (PH)	30	30	30	30	30	30	30
HPMC K100M	75	112.5	150	112.5	112.5	112.5	112.5
Guar Gum (GG)	–	–	–	37.5	–	–	–
Xanthan Gum (XG)	–	–	–	–	37.5	–	–
Sodium Alginate (SA)	–	–	–	–	–	37.5	–
Sodium CMC (Na CMC)	–	–	–	–	–	–	37.5
Sodium bi carbonate	60	60	60	60	60	60	60
Micro Crystalline Cellulose (MCC)	99	61.5	24	24	24	24	24
HPC_{EXF}	30	30	30	30	30	30	30
Talc	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3
Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**

*All the ingredients are expressed as mg per tablet

Function of excipients: HPMC K100M is semi-synthetic controlled release (CR) polymer, SA, Na CMC, XG and GG are natural CR polymers, HPC_{EXF} is solid binder, micro crystalline cellulose (Avicel PH 101) is directly compressible diluent, magnesium stearate is lubricant and talc is glidant.

Procedure: PH and all other excipients excluding magnesium stearate and talc were co- sifted through Sieve No. # 40 (ASTM), blended in a poly bag for 10 min and lubricated with Sieve No. # 60 (ASTM) passed magnesium stearate and talc by mixing in the same poly bag, for additional 2–3 min. Tablets were compressed on a tabletting machine (Minipress by Clit, 10 stations, Chamunda Pharma Machinary Pvt. Ltd., India.) fitted with a 5 mm standard flat circular punches with an avg. wt. of 300 mg and avg. hardness of 6.0 kg/cm^2.

Pre-compression studies:[20-22] Directly compressible tablet blends of PHGRFT were evaluated by pre-compression studies [angle of Repose (θ), bulk density (BD), tapped density (TD) Carr's Index (CI) & Hausner's Ratio (HR)]. The consolidated results of pre-compression studies were tabulated in (Table 2).

Table 2: Pre-compression studies of PHGRFT.

F Code	Angle of repose (^{0})*	BD (gm/cc)*	TD (gm/cc)*	CI (%)*	HR*
F1	21.8 ± 0.15	0.38 ± 0.15	0.60 ± 0.08	36.7 ± 0.04	1.57 ± 0.07
F2	21.35 ± 0.12	0.37 ± 0.11	0.61 ± 0.12	39.34 ± 0.23	1.64 ± 0.11
F3	22.1 ± 0.23	0.36 ± 0.05	0.59 ± 0.15	38.9 ± 0.15	1.63 ± 0.11
F4	22.3 ± 0.14	0.35 ± 0.13	0.58 ± 0.02	39.6 ± 0.21	1.66 ± 0.21
F5	21.7 ± 0.22	0.36 ± 0.21	0.62 ± 0.03	40.0 ± 0.15	1.67 ± 0.08
F6	22.3 ± 0.15	0.37 ± 0.16	0.59 ± 0.14	37.2 ± 0.12	1.59 ± 0.13
F7	22.2 ± 0.13	0.38 ± 0.14	0.58 ± 0.06	34.5 ± 0.12	1.52 ± 0.07

*All the values are expressed as mean ± SD, where n=3

Post-compression studies:[23, 24] The wt. uniformity of tablets were determined by using an electronic balance (Shinadzu-BL-220H, Japan.), thickness was measured using a vernier calipers (Mitutoyo Corporation, Japan.), friability was carried out on Roche friabilator (M/s. Elite Scientific & Equipments, Germany.) and hardness was measured using a Monsanto hardness tester (Singla-Hardness tester, India.)

Estimation of PH in tablets:[25] Five tablets from each batch (n=3), were randomly selected and crushed in a mortar with pestle; the quantity of blend equivalent to 100 mg of PH was suspended in 100 ml of 0.1N HCl in a volumetric flask and sonicated for 2 min. The dispersion was filtered through 0.45µm membrane filter, suitably

diluted and analyzed by a double beam UV-Vis spectrophotometer (Agilent technologies Cary 60 UV-Vis, Japan) by measuring absorbance at 269 nm. The method obeyed Beer-Lambert's law in the concentration range of 2-10 µg/ml. When a standard drug solution was assayed repeatedly (n=6) the accuracy and precision were found to be 0.80 and 1.10 %, respectively. No interference from the excipients used was observed. The consolidated results of post compression studies are tabulated in (Table 3).

Table 3: Post-compression & *in vitro* buoyancy studies of PHGRFT.

F Code	Post compression parameters					Floating characteristics		
	Avg. Wt (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)#	Assay (%)*	FLT (S)*	TFT (h)*	MI (upto 12h)
F1	300.4 ± 0.12	6.32 ± 0.34	5.9 ± 0.26	0.59	99.98 ± 0.18	49 ± 0.51	Up to 8	-
F2	300.2 ± 0.22	6.21 ± 0.23	6.2 ± 0.25	0.68	100.21 ± 0.20	55 ± 0.22	Up to 12	+
F3	299.6 ± 0.24	6.14 ± 0.14	6.3 ± 0.21	0.58	99.67 ± 0.12	58 ± 0.63	Up to 12	+
F4	300.3 ± 0.31	6.18 ± 0.21	5.9 ± 0.23	0.59	100.32 ± 0.14	56 ± 0.70	Up to 12	+
F5	300.6 ± 0.21	6.17 ± 0.21	6.3 ± 0.13	0.62	100.65 ± 0.18	57 ± 0.83	Up to 12	+
F6	300.9 ± 0.23	6.34 ± 0.14	6.1 ± 0.20	0.59	99.89 ± 0.22	58 ± 0.52	Up to 12	+
F7	300.2 ± 0.26	6.21 ± 0.23	6.2 ± 0.25	0.68	100.21 ± 0.20	56 ± 0.24	Up to 12	+

*All the values are expressed as mean ± SD, where n=3 except for Avg. Wt. determination where n=10
Test for friability was performed for once on 10 tablets from each batch

Swelling index studies:[26] Of the tablet was measured by studying its weight gain. It was determined by placing the tablet in 100 ml beaker of 0.1N HCl and after 1,2,4,6 and 8 h tablet was withdrawn from beaker, blotted with tissue paper, to remove the excess water and weighed on the electronic balance (Shinadzu-BL-220H, Japan). It was performed in triplicate for each time point. Swelling index profiles of PHGRFT were shown in (Figure 2). It was calculated by using the formula below.

Swelling Index (SI) = $x\ 100$ *Equation 1*

In vitro buoyancy studies:[27] Was characterized by floating lag time (FLT), total floating time (TFT) and matrix integrity (MI) up to 12 h, as per the method described by (Rosa et al., 1994). Three tablets from each batch (n=3), were randomly selected. A tablet was dropped into 100 ml of 0.1 N HC1 in a beaker. The time required for the tablet to rise to surface and duration of time it constantly floated on medium were noted as FLT and TFT, respectively. During this study, whether the swollen matrix was intact or disintegrated was observed, to confirm the matrix integrity.The consolidated results of *in vitro* buoyancy studies are tabulated in (Table 3). *In vitro* floating images of PHGRFT, formulation-F4 was shown in (Figure 3).

In vitro dissolution studies: Three tablets from each batch, were randomly selected (n=3). In the USP-II (paddle) dissolution apparatus (Disso 2000, Labindia Analy. Inst. Pvt. Ltd., India.), each flask was filled with 900 ml of 0.1N HCl; speed of paddle was maintained at 50 rpm, the temperature was kept constant at 37^0C ± 0.5^0C. At time points 1, 2, 3, 4, 6, 8, 10 and 12 h, 5 ml of dissolution media was withdrawn, filtered through 0.45µm membrane filter, suitably diluted and analyzed at 269 nm using a double beam UV-Vis spectrophotometer (Agilent technologies Cary 60 UV-Vis, Japan). Each sample withdrawn was replaced with an equal amount of fresh 0.1 N HCl, to keep the volume constant. *In vitro* dissolution profiles of PHGRFT were shown in (Figure 4).

Drug release kinetics:[28-30] The *in vitro* drug release data of all batches were fitted into zero order, first order , Higuchi and Korsemeyer- Peppas models to ascertain the drug release kinetics. The drug release from the hydrophilic matrix whether depends on drug's concentration or not was explained by zero and first order models. Higuchi model describes whether the drug release is predominantly by diffusion or not. The Korsemeyer- Peppas model further explains the mechanism of diffusion. The respective models were defined by the equations below.

Zero order: $Q_t = Q_0 + K_0 t$ *Equation 2*
First order: $\log Q = \log Q_0 - K_1 t / 2.303$ *Equation 3*
Higuchi model: $Q_t = K_H t^{1/2}$ *Equation 4*

Korsemeyer -peppas model: $M_t/M\alpha = K\, t^n$ *Equation 5*

Where Q_t is the amount of drug dissolved at time, t; Q_0 is the initial amount of drug in the solution at time $t=0$, Q is the amount of drug remaining at time, t; M_t/M_α is the fraction of drug released at time, t and n is diffusion exponent. K_0, K_1, K_H and K refer to the rate constants of respective kinetic models. Drug release mechanisms based on n-values, for cylindrical shape, as per Korsmeyer - Peppas model, were tabulated in (Table 4). The consolidated drug release kinetic data of PHGRFT were tabulated in (Table 5).

Table 4: Drug release mechanisms for cylindrical shape in Korsmeyer - Peppas model.

Diffusion exponent (n)	Drug release mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous (non-Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

Table 5: Drug release kinetics data of PHGRFT.

Model	Parameter	F1	F2	F3	F4	F5	F6	F7
Zero order	r^2	0.982	0.992	0.990	0.999	0.991	0.993	0.990
First order	r^2	0.749	0.770	0.775	0.731	0.738	0.761	0.675
Higuchi	r^2	0.793	0.824	0.807	0.840	0.810	0.826	0.819
Krosmeyer-Peppas	r^2	0.971	0.980	0.982	0.999	0.988	0.984	0.993
	n	1.122	1.114	1.192	1.058	1.196	1.122	1.190

In vivo x-ray imaging studies: [31] *In vivo* residence time of optimized formulation F4's placebo (drug replaced with $BaSO_4$, a radio opaque marker) was studied by x-ray imaging studies in rabbit model. Three adult male New Zealand white strain, rabbits of one year old age and weighing approximately 2-2.5 kg were used for this study. The rabbits were fasted overnight before the start of the study. The tablets were administered through plastic tubing followed by flushing of 25–30 ml of water. During the entire study, the rabbits had free access to water only. X-ray images were taken using (Wipro Ge Dx300, SV diagnostic centre, Nethaji road, Tirupati, India) at before administration, 2nd, 6th, 8th, 10th and 12th h after the administration and are shown in (Figure 5). The protocol (SVCP/IAE/I-005/2015-16 dated on 15/02/2016) for *in vivo* study was approved by the institutional animal ethical Committee (IAEC) of Sree Vidyanikethan College of Pharmacy, Tirupati-517 102, Chittoor Dist. Andhra Pradesh, and is in accordance with guidance of committee for the purpose of control and supervision of experiments on animals (CPCSEA), Ministry of Social Justice and Empowerment, Govt. of India.

Accelerated stability studies: [32] Of the optimized formulation-F4, in final pack up to 6 months were carried according to International Conference on Harmonization (ICH) guidelines. 20 tablets were packed, labelled and sealed in 10 CC HDPE containers and placed in a humidity chamber (NSW-175, Narang Scientific work, India) maintained at 45°C ± 2°C and 75% ± 5% RH. At the end of every month up to 6 months, the samples were withdrawn and evaluated for post compression studies. The consolidated results of accelerated stability studies were tabulated in (Table 6). Comparative *in vitro* dissolution profiles of initial and accelerated stability samples were shown in (Figure 6). The chemical stability of drug in the 6M-accelerated stability sample of optimized formulation –F4; which will influence the *in vitro* and *in vivo* dissolution characteristics,[33] was investigated using FT-IR studies. The FT-IR spectra were recorded out in the region of 400-4000 cm^{-1} at spectral resolution of 2 cm^{-1}, by the direct sampling method with isopropyl alcohol as solvent, using (Agilent technologies Cary 630 FTIR, Japan).

Table 6: Accelerated stability studies data of PHGRFT optimized formulation-F4.

Time Interval	Post compression studies					Floating characteristics		
	Avg. Wt (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)#	Drug content* (%)	FLT* (S)	TFT* (h)	MI (upto 12h)
Initial	300.3 ± 0.31	6.18 ± 0.21	5.9 ± 0.23	0.59	100.32 ± 0.14	56 ± 0.70	Up to 12	+
1 Month	299.8 ± 0.21	6.23 ± 0.08	5.8 ± 0.12	0.61	100.12 ± 0.08	60 ± 0.09	Up to 12	+
2 Month	300.5 ± 0.08	6.21 ± 0.70	5.9 ± 0.13	0.64	100.24 ± 0.21	63 ± 0.11	Up to 12	+
3 Month	300.4 ± 0.70	6.13 ± 0.21	5.9 ± 0.21	0.66	99.64 ± 0.11	64 ± 0.12	Up to 12	+
6 Month	300.2 ± 0.62	6.12 ± 0.32	5.9 ± 0.21	0.71	99.98 ± 0.21	62 ± 0.12	Up to 12	+

*All the values are expressed as mean ± SD, where n=3 except for Avg. Wt. determination where n=10
Test for friability was performed for once on 10 tablets from each batch

Results & Discussion:

Drug-excipient compatibility / FT-IR studies: The FT-IR spectra of pure PH is characterized by 3364 cm^{-1} (N-H stretching amide), 3084 cm^{-1} (aromatic C-H stretching), 2928 cm^{-1} (aliphatic C-H stretching asymmetric), 1743 cm^{-1} (amide C = O stretching), 1616 cm^{-1} (C=C), 1460 cm^{-1} (ring C-N stretching), 1242 cm^{-1} (C-S stretching), 1084 cm^{-1} (aliphatic C-O-C) and 850 cm^{-1} (para disubstituted aromatic ring). The IR bands of pure drug and drug: polymer (1:1 ratio physical mixtures) shows no significant shifts or reduction in intensity of the FTIR bands. Hence there was no incompatibility problem between the drug and polymers used in the study. (Figure 1)

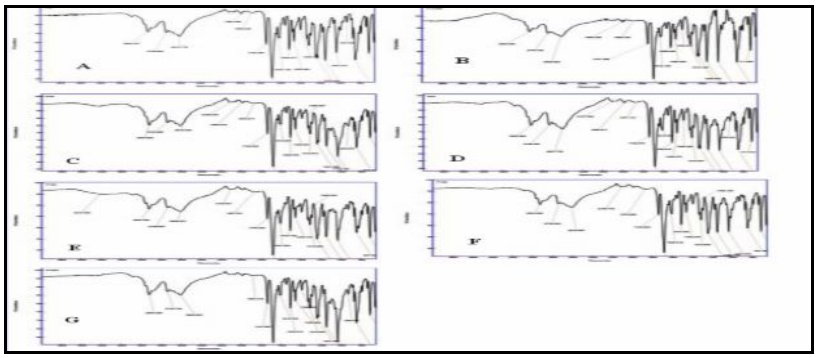

Figure 1: FT-IR spectra of A) PH; B) PH & HPMC K100M; C) PH & GG; D) PH & XG; E) PH & SA; F) PH & Na CMC and G) PH & HPC_{EXF}

Standard calibration curve: Is defined by a straight line equation, y=0.025x+0.002, following linearity with a regression (r^2 = 0.999). This method obeyed Beer's law in the concentration range of 1-10 µg/ml. Lower relative standard deviation (RSD) values ensured reproducibility of the method. As the excipients used in the study were not interfering and good % recovery indicates this method was suitable for the estimation of PH content and *in vitro* dissolution studies of formulations.

***Pre-compression studies*:** The angle of repose of all the PHGRFT blends are ranging between 21°.4' to 22°.3', CI and HR were found to be in the range of 34.5 to 40% and 1.52 to 1.67 respectively, indicating excellent flow properties and compressibility of the blends. (Table 2)

Post-compression studies: As the % wt variation of all batches is within ± 7.5% w/w, they passed the % wt variation test as per United States Pharmacopoeia-30, National Formulary-25(USP 30-NF 25). The thickness of tablets was found to be between 6.21 to 6.32 mm. The hardness of tablets was found to be between 5.9 to 6.33 kg/cm^2, indicating satisfactory mechanical strength. The % friability was NMT 1.0% w/w for all the formulations, which is an indication of good mechanical resistance to physical erosion of the tablet. As the % assay of all batches is within 95-105 %, they passed the content uniformity test as per USP 30-NF 25. (Table 3)

Swelling index (SI) studies: As the conc. of HPMC increases the SI increases, owing to the hydrophilic nature of this semi synthetic polymer.[33] When natural gums were combined with HPMC K100M, the SI of combined hydrophilic matrix was lesser, when compared to the formulations with HPMC K100M alone. Due to the combination of two different polymers; the swelling of combined matrix was depending on the hydration of both the polymers at the particular pH of the dissolution medium**.** Among the used four natural gums in combination with HPMC K100M, their effect on decreasing the SI of combined hydrophilic matrix is in the order; GG > SA > Na CMC > XG. (Figure 2)

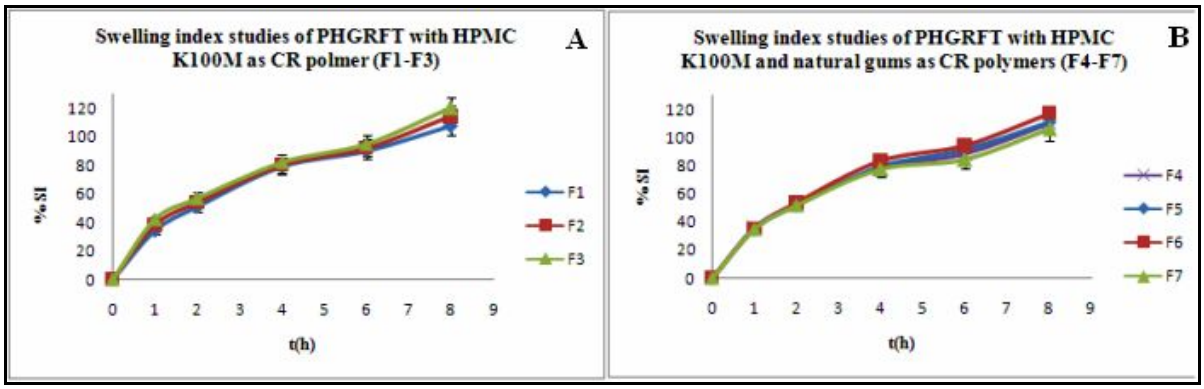

Figure 2: Swelling index profiles of A) PHGRFT with HPMC K100M as CR polymer (F1-F3); B) PHGRFT with HPMC K100M and natural gums as CR polymers (F4-F7)

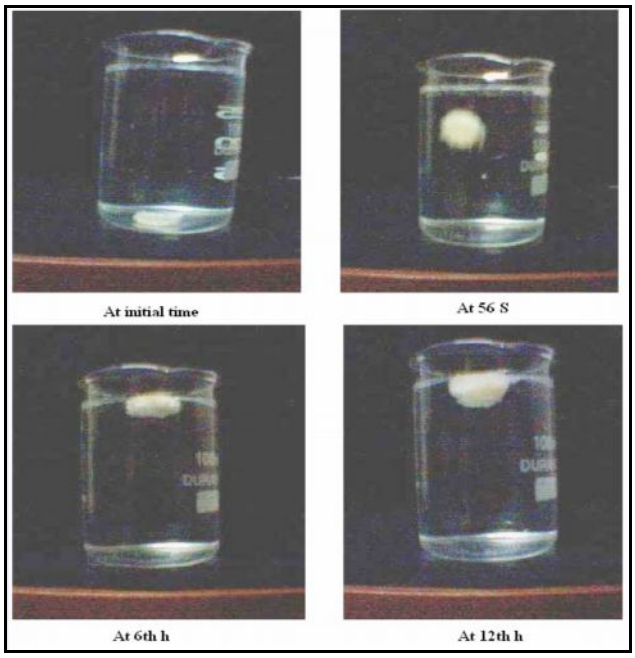

Figure 3: *In vitro* floating images of optimized PHGRFT formulation-F4.

In vitro buoyancy studies: The FLT was found to be NMT 2 min for all the formulations. Except F1 (25% HPMC K100M alone), other formulations were retaining their matrix integrity and TFT up to 12 h. (Table 3 & Figure 3)

In vitro dissolution studies: As the conc. of HPMC K100M increases, there is an increased viscosity of the gel matrix and decrease in the effective diffusion coefficient of the drug.[34] Other factors that may contribute to differences in drug release profiles include; differences in water penetration rate, water absorption capacity, polymer swelling and drug : polymer ratio.[35] Among all factors, drug : polymer ratio is important factor affecting the rate of drug release from the matrix, which has to be optimized.[36] The pH independent, zero order release profile of bio pharmaceutics classification system (BCS) class-II drugs (High Permeability, Low Solubility) like PH can be attained from the hydrophilic matrix systems, by combining the semi synthetic

polymers like, HPMC K100M with natural gums like (SA, Na CMC, XG and GG).[36] The combined matrix when exposed to gastric fluids, HPMC hydrates first to form a gel layer at the surface of the tablet, while the natural gums due to lesser hydration rate than HPMC remains insoluble. The resulting matrix system acts as a barrier for diffusion of poorly soluble drugs like PH and extends its release.[36] Formulation- F1 (12.5% HPMC K100M alone) cannot able to extend the release up to 12 h. All the formulations with natural gums in combination with HPMC K100M are extended drug release up to 12 h. The extended release exhibited by natural gums in combination with HPMC K100M was in the order; Na CMC > XG > GG > SA. Among all the batches, formulation-F4 (37.5% HPMC K100M and 12.5% GG) extends the release of PH up to 12 h with a better zero order release profile (r^2=0.999). (Figure 4)

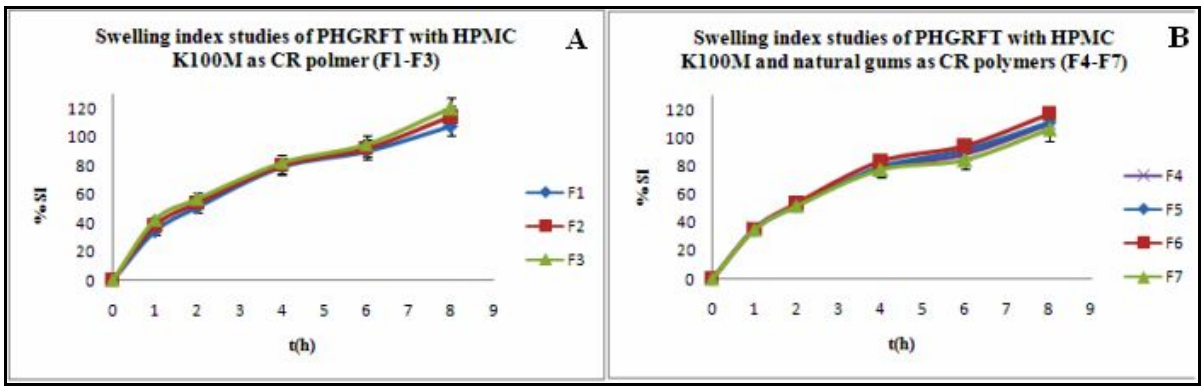

Figure 4: *In vitro* dissolution profiles of A) PHGRFT with HPMC K100M as CR polymer (F1-F3); B) PHGRFT with HPMC K100M and natural gums as CR polymers (F4-F7)

***Drug release kinetics*:** Among all the batches, formulation-F4, fitted best to the zero order kinetics (as zero order, r^2 = 0.999), indicating the drug release from the matrix does not depends on its conc. Drug release process is not predominantly by diffusion (as Higuchi, r^2= 0.840); and the mechanism of diffusion is by super case-II transport i.e. a combination of both diffusion and erosion (as Korsemeyer- Peppas, n=1.058). (Table 4)

In vivo x-ray imaging studies: X-ray images of a rabbit taken at before administration, 2nd, 6th,8th , 10th and 12th h after the administration of optimized formulation- F4's placebo (drug replaced with $BaSO_4$), indicates the optimized formulation-F4 was strong enough in withstanding repetitive gastric contractions and able to retain in gastric region up to 12 h. (Figure 5)

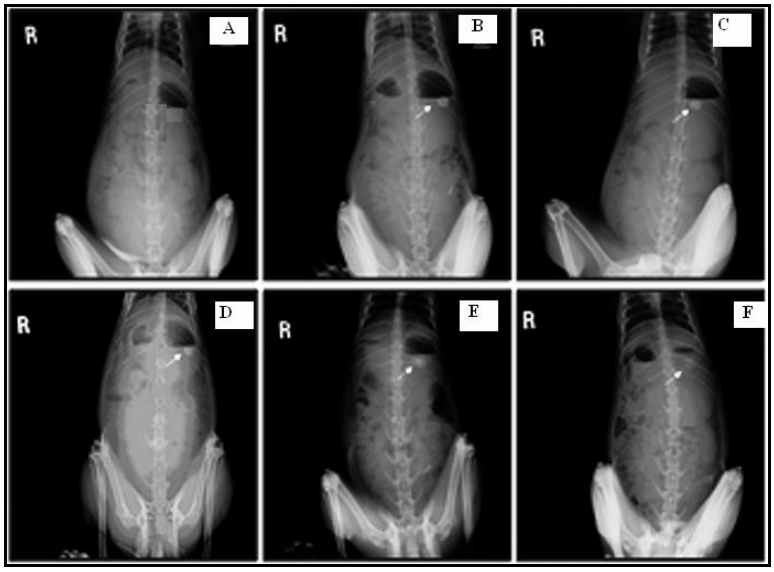

Figure 5: X-ray images of optimized PHGRFT formulation-F4 (placebo) in a rabbit model at A) Before administration, B) 2nd h, C) 6th h, D) 8th h E) 10th h and F) 12th h.

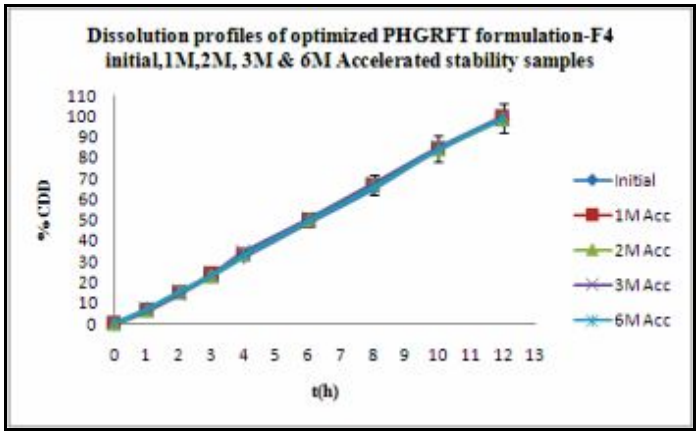

Figure 6: *In vitro* dissolution profiles of initial & 1, 2, 3 & 6M-Accelerated stability samples of PHGRFT optimized formulation–F4.

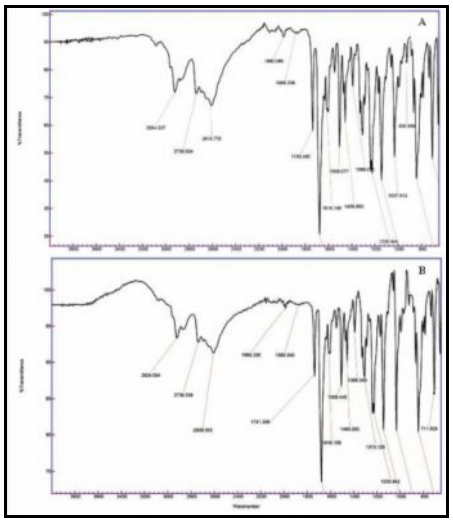

Figure 7: Comparative FT-IR spectra of A) Initial pure drug (PH) and B) 6M-Accelerated stability sample of optimized formulation–F4.

Accelerated stability studies: as there were no significant differences in post compression studies (wt. Variation, thickness, hardness, friability and in vitro dissolution studies) and floating characteristics (FLT, TFT & MI) of initial & accelerated stability samples of optimized formulation -F4, it passes the test for stability (Table 6 & Figure 6). Comparative FT-IR spectra in (Figure 7), reveals there is no significant change in the functional groups of the PH due to interaction with polymers and other excipients.

Conclusion:

In the view of above findings, effect of combination of natural gums (SA, Na CMC, XG and GG) with semi-synthetic polymer, HPMC K100M in extending the release of PH from its effervescent GRFT was better understood. It was further concluded that the optimization of the proportion of HPMC K100M: natural gum, had significant effect on extending the release profiles of PH. Among the four natural gums, GG in combination with HPMC K100M in the ratio 1:2 respectively forms a better matrix for the extending the release of PH in gastric pH up to 12 h. The formulation-F4 (37.5% HPMC K100M and 12.5% GG) extends the release of PH up to 12 h with a better zero order release profile (r^2=0.999), FLT of 56 s, TFT and a better MI up to 12 h. Hence it is an optimized formulation. A combination hydrophilic matrix design of this kind can serve as an alternative strategy for extending the release of other BCS class II drugs (High Permeability, Low Solubility) and their salt forms, which are having shorter elimination half-life ($t_{1/2}$ < 5 h).

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