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RESEARCH ARTICLE

Statistical Optimization of Anti Platelet Drugs in Gastric Floating Tablets Formulation

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ABSTRACT

Floating drug delivery systems (FDDSs) promise to be satisfactory approach for prolonged gastric residence time of drug to improve solubility, lessen drug waste thereby enhances bioavailability (BA) for the drugs that are highly soluble in the lower pH condition. In this present research work, development and evaluation of gastric FDDS of selected three platelet aggregation inhibitors drugs were planned to enhance their BA and/or to minimize their potential side effects with better patient compliance. The three drugs were prasugrel hydrochloride, clopidogrel bisulfate, and dipyridamole which were selected based on their similar physic- chemical characteristics. All these three drugs belong to BCS Class-II (low solubility-high permeability) and exhibit pH-based solubility nature, greater at the lower pH conditions. As per reported literatures, combinational apply of a hydrophobic polymers and hydrophilic polymers well controls initial rapid drug release (DR) of highly soluble drugs. The DR from tablet formulation fabricated by melt granulation employing meltable hydrophobic polymer could be slower due to better uniform and rigid hydrophobic coating around the hydrophilic drug particles. Therefore, in this work, both hydrophilic HPMC K100M (HK100M) and hydrophobic meltable Compritol® 888 ATO (COM888) polymers were chosen in alone and combination to develop and evaluate FDDS of selected three drugs and investigated their individual and combined effects on DR of respective drugs from formulations.

Keywords: Floating drug delivery systems, gastric residence time, platelet aggregation inhibitors

INTRODUCTION

Controlled drug delivery system (CDDS) is devised to improve drug therapy that controls the release rate of drug and sustains its acting duration with/without targeted drug action. In recent times, diverse types of oral CDDS have been developed with different release mechanisms to enhance the bioavailability (BA) of drugs.

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Significant attempts have been made to design oral CDDS that exhibit more predictable drug release (DR) with increased BA of drugs. The majority of the drugs are absorbed well in all regions of the gastrointestinal tract (GIT) but some drugs are specifically absorbed well only in definite region of GIT that may be due to low permeability and/or low solubility, chemical instability, and microbial degradation of the drug in other regions of GIT. When a drug has its absorption window at the stomach or upper parts of the small intestine of GIT, then it may not be fully absorbed when administered as oral CDDS formulation due to short emptying

time (2–3 h) of the stomach that leads to crossing of formulation from the absorption window site. This leads to wastage of drug due to non-absorption of released drug and incomplete DR with diminished efficacy of drug dose.

Gastro-retentive drug delivery system is oral CDDS formulations with an ability to retain in the stomach of GIT which is aimed to enhance drug therapy with/without targeted drug action by extending gastric residence time (GRT) of formulation (Kawashima *et al*., 2000). The extension of GRT of formulation of a drug improves its solubility thereby enhances the BA and reduces wastage of drug that is soluble in low pH and slightly soluble in high pH. These systems are also effective for the stomach, proximal part of small intestine specific local drug delivery.

Floating Drug Delivery Systems (FDDS)

Among the various approaches, FDDS promises to be satisfactory for better gastric retention of drug formulations. FDDS is classified as follows based on the buoyancy mechanism of system (Abhishek *et al*., 2012).

1. Single Unit (SU) and Multi Unit (MU) Effervescent (EV) FDDSs
2. SU and MU Non-EV FDDSs
3. Raft Forming FDDS

MATERIALS AND METHODS

Prasugrel hydrochloride (PGHC) is a potent thieno-pyridine platelet aggregation inhibitor (PAI) drug indicated for ACS, POTE, MI, and CVA. It is a pro-drug converted into sulfhydryl active metabolite in the liver which irreversible binds to P2Y12- ADP platelet receptors thereby inhibits platelet activation and aggregation. It belongs to BCS Class-II with low solubility-high permeability and shows pH-based solubility, greater at the lower pH. The oral BA is 79% with approx T1/2–7 h (2–15 h). However, the potential side effect is bleeding including life-threatening fatal bleeding. It rapidly absorbs and metabolized with peak plasma concentrations of the active metabolite in 30 min post-dosing. This would provide a high concentration of active metabolite immediately after dosing and the patient is exposed to bleeding risk at peak levels of steady state and sustaining the DR is expected to minimize its potential bleeding risk by avoiding high concentrations of active metabolite immediate after dosing in maintenance therapy (Klaus, 2012).

The goal of the study is to fabricate and evaluate PGHC sustained-release (SR) gastric floating tablets (GFTs) to release the drug in highly soluble acidic stomach conditions in a sustained manner up to 8 h which is expected to minimize the potential bleeding side effect by avoiding high concentrations of active metabolite and improves BA. GFTs were prepared using HPMC K100M (HK100M) and Compritol® 888 ATO (COM888) polymers by EV procedure with melt granulation (MG) and direct compression (DC) techniques. NaHCO3 and microcrystalline cellulose were selected as EV agent and diluents, respectively.[1-10]

RESULTS AND DISCUSSION

Development and Evaluation of Hydrochloride Tablets

PGHC solubility studies result in distilled water, 4.5 pH AB, 6.8 pH PB buffer, and 0.1N HCl are presented in Table 1. The solubility of PGHC was found pH-dependent and freely soluble in 0.1N HCl

Micromeritic Properties

PGHC powder showed passable flow properties and PGHC formulation blends with diluent, glidant, and lubricant showed fair flow properties as per AR, CI, and HR values. The micromeritics of drug and selected batch of the formulation are tabulated in Table 2.

Table 1: PGHC solubility in different buffer mediums

S. No.	Buffer medium	Solubility (mg/ml)
1.	Distilled Water	18.46
2.	0.1N HCl	73.42
3.	pH 4.5 AB	0.61
4.	pH 6.8 PB	0.03

DE Compatibility Studies

FTIR spectra of PGHC and formulation blends were compared. The characteristic peaks (Al-Omari *et al*., 2015 and Rigobello and Steppe, 2016) wave numbers which are observed for the pure drug in the FTIR spectra [Figure 1] were also observed for formulation blend [Figure 2] with some slight peaks shifting signifies no interaction among drug and other excipients [Table 3]. The FTIR spectra of COM888 and HK100M are shown in Figures 1-4.

Table 2: Micromeritics of PGHC and selected batch blend

Parameters	Pure drug	PF9
AR (°)	42.61	33.42
CI (%)	22.44	18.36
HR	1.28	1.22

Formulation Development

PGBS GFT formulations were fabricated by EV technique with MG and DC alone and in combination by employing hydrophilic HK100M polymer and hydrophobic meltable COM888 polymer at diverse concentrations (20, 30, and 40% w/w) alone and in combination. The polymer's concentrations were decided based on the literature and trial and error. Combinational apply of a hydrophobic polymers and hydrophilic polymers efficiently controls initial rapid DR of highly soluble drugs (Pawar and Dhavale, 2014). Hence, mutually hydrophilic and meltable hydrophobic polymers were employed alone and in combination to study their individual and combined effects on DR.[10-23]

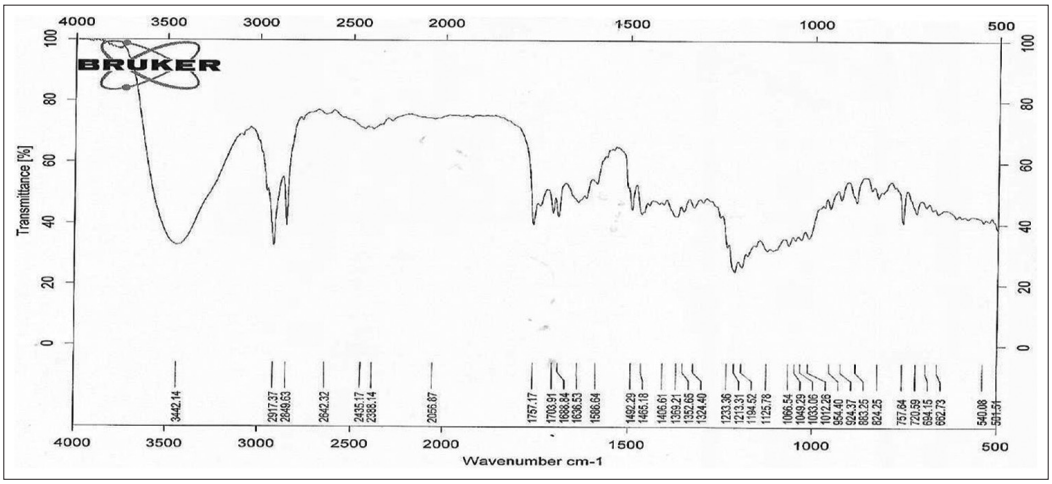

Figure 1: PGHC FTIR spectrum

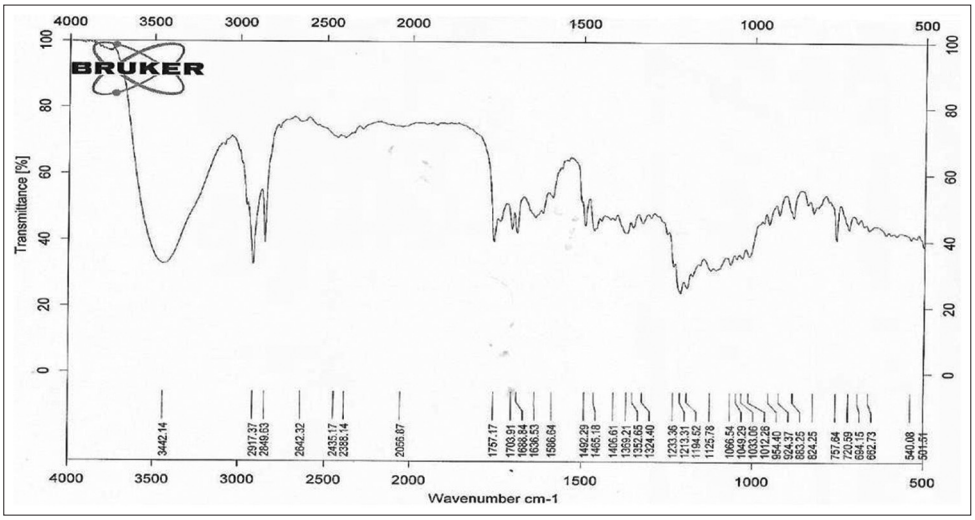

Figure 2: FTIR spectra of PGHC formulation blend with HK100M and **COM88**

GFTs Physical Characteristics

The results of physical characteristics of fabricated PGHC GFT formulations such as thickness, weight variation, hardness, and F (%) are shown in Table 4. Hardness was in between 4 and 5 (kg/cm^2), F <1% and weight deviation was in the limit for the fabricated tablets. PGHC GFTs drug content was in between 98 and 102\%. Therefore, all fabricated GFTs showed good quality and satisfied official specifications of pharmacopeia.

Table 3: Functional groups of PGHC and formulation blend

Functional groups	PGHC (WN)	Formulation blend (WN)
(–NH$^+$) stretching	2435.11	2435.17
(C=O); carboxylate stretching	1757.60	1757.17
(C=O); cyclopropylcarbonyl stretching	1688.72	1688.84
(C-H) bending	1492.64	1492.29
(C-F) stretching	1406.66	1406.61
(C-N) stretching	1352.61, 1325.02	1352.65, 1324.40
(C-O) stretching	1212.97, 1233.02	1213.31, 1233.36
(C-S) stretching	824.01, 757.36	824.25, 757.64

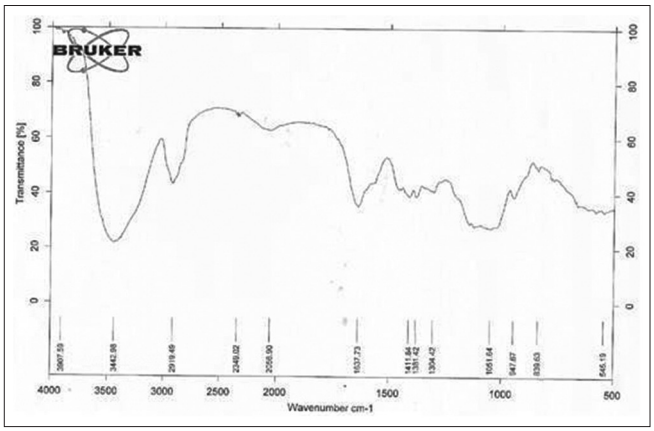

Figure 3: COM888 FTIR spectrum

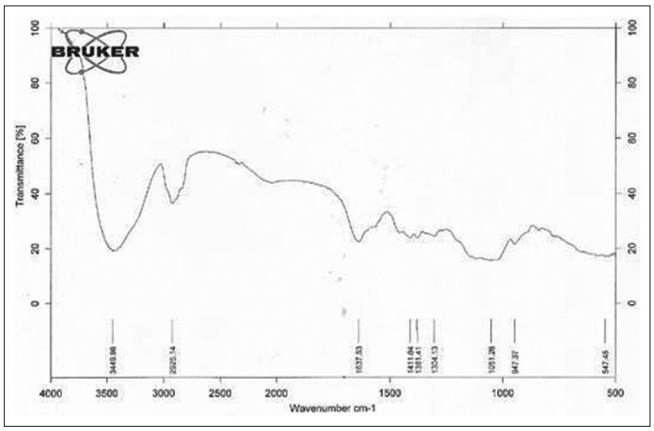

Figure 4: HK100M FTIR spectrum

GFTs Floating Properties

The PGHC GFT formulations *in-vitro* floating study results are shown in Table 5. NaHCO3 at 10% w/w was optimized as EV agent. CO2 generated in the formulations by NaHCO3 in acidic medium is trapped within the hydrogenated polymer gel which makes density of the formulation below 1 g/ml and leads to floatation/buoyant. PGHC GFTs formulations (PF1 to PF3) fabricated with COM888 did not show floating behavior due to the non-swelling nature of polymer that failed to entrap generated CO2. The FT of HKM100 and combinational PGHC GFTs formulations (PF4 to PF9) was observed in between 10 and >12 h with FLT was <2 min and showed better and desired floating characteristics. Pictures of PF8 formulation *in- vitro* floating study are shown in Figure 5.

In-vitro PGHC GFT formulations DR studies results in 0.1N HCl are shown as mean CDR in Table 5.

The *in-vitro* DR profiles of PF1, PF2, and PF3 formulations each had hydrophobic retardant and COM8888 are shown in Figure 6. The initial 1h DR was 39%, 26%, and 16% for PF1, PF2, and PF3 formulations, respectively. Formulation PF1 showed rapid/bust DR pattern in initial hours due to insufficient polymer concentration, in which COM888 was only 10 mg (20%) and almost 85% DR in 4 h. PF2 and PF3 formulations having 15 mg (30%) and 20 mg (40%) of COM888 showed 98% and 83% DR in 8 h from the respective formulations in controlled manner. However, these formulations did not show any floating characteristics.

In-vitro DR profiles of hydrophilic HK100M polymer GFT formulations are shown in Figure 7. The initial 1 h DR was 30%, 16%, and 13% for PF4, PF5, and PF6 formulations, respectively. PF4 formulation showed less sustained effect and may be as it has only 10 mg (20%) polymer concentration and sustained up to 6 h only. PF5 formulation with 15 mg (30%) sustained up to 8 h and released 87%

Table 4: Physical characteristics of PGHC GFTs

Formulation	Thickness (mm)	Average Weight (mg)	Hardness (kg/cm^2)	Friability (% w/w)	Assay (% w/w)
PF1	2.65±0.02	51.18±1.10	4.16±0.28	0.14	100.50±1.32
PF2	2.63±0.02	50.11±1.06	4.50±0.50	0.13	99.93±1.40
PF3	2.62±0.01	49.94±1.15	4.33±0.28	0.14	100.36±1.92
PF4	2.61±0.02	51.17±1.12	4.66±0.28	0.17	101.00±0.65
PF5	2.61±0.02	50.12±1.11	4.66±0.28	0.16	98.73±0.60
PF6	2.62±0.02	49.22±1.03	4.66±0.57	0.18	101.30±0.75
PF7	2.61±0.01	49.29±1.15	4.33±0.28	0.19	99.46±1.10
PF8	2.62±0.02	50.39±1.14	4.83±0.28	0.16	100.50±1.10
PF9	2.64±0.03	49.76±1.15	4.83±0.28	0.17	100.53±1.10

Table 5: PGHC GFTs *in-vitro* CDR data

Time (h)	Cumulative Percentage Drug Release (%w/w)								
	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
0.5	22.85	17.89	10.95	18.52	10.36	8.28	21.81	15.66	9.35
1	38.52	25.62	15.23	29.74	15.55	12.63	34.25	21.83	13.54
2	56.25	36.91	26.02	42.82	23.24	22.34	51.06	29.17	24.85
3	69.65	47.66	34.52	55.45	32.58	29.55	60.63	37.33	32.25
4	84.58	56.18	40.4	70.78	44.25	36.74	74.58	48.41	39.81
5	99.62	63.8	52.78	83.26	56.85	45.47	86.23	60.59	50.48
6		74.75	61.26	99.54	65.47	53.88	97.98	71.64	58.74
7		82.58	70.84		78.45	65.89		82.46	70.38
8		97.92	83.05		86.75	74.38		97.41	83.63

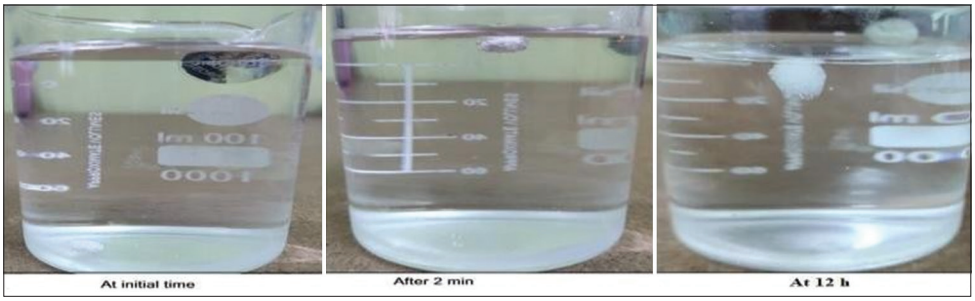

Figure 5: Pictures of PF8 formulation *in-vitro* floating studies

of drug. The DR from PF6 formulation containing 20 mg (40%) was moderate and released only 74% of drug at 8 h and futile to release complete drug. The formulations (PF4, PF5, and PF6) prepared with hydrophilic HK100M polymer showed better controlled retardation of DR than the hydrophobic COM888 polymer formulations (PF1, PF2, and PF3) at their defined respective concentrations as 83% DR in 8 h noted from 30% COM888 GFTs whereas only 74% DR was observed with 30% HK100M GFTs.

In-vitro DR profiles of PF7, PF8, and PF9 formulations each had blend of COM888 and HK100M are shown in Figure 7.3c. The initial 1 h DR was 34%, 22%, and 14% for PF7, PF8, and PF9 formulations, respectively. PF7 formulation showed rapid DR as it has only 5 mg (10%) COM888 and 5 mg (10%) HK100M polymer

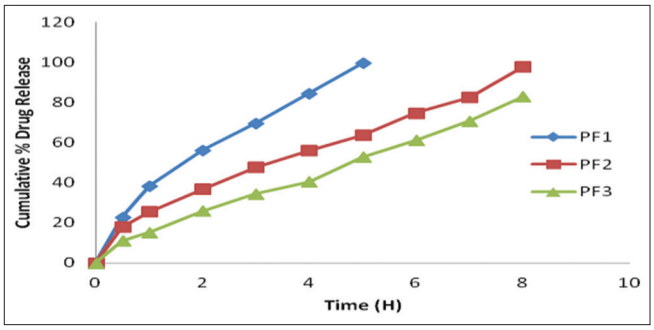

Figure 6: CDR profiles of COM888 PGBS tablet formulations

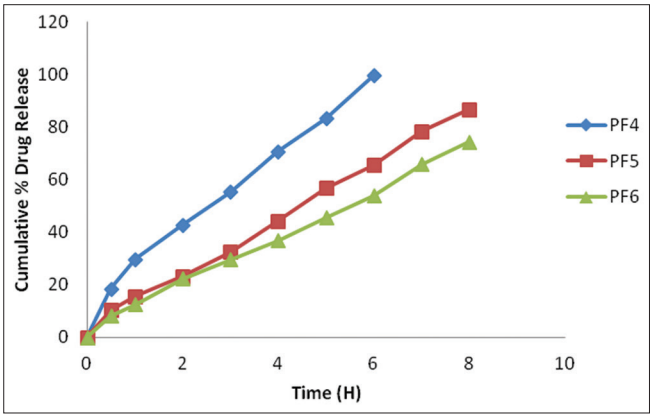

Figure 7: CDR profiles of HK100M PGHC GFT formulations

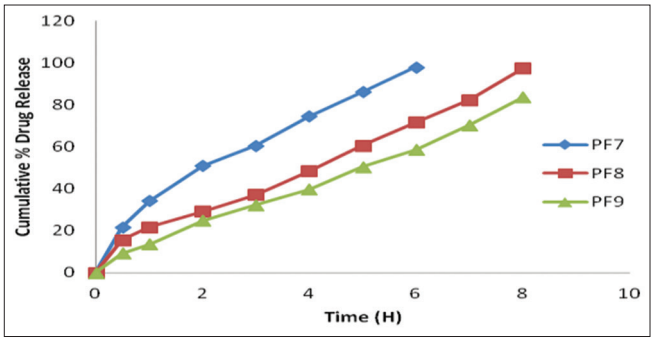

Figure 8: CDR profiles of COM888+HK100M PGHC GFT formulations 7.6.4DR Kinetic Modeling Studies

concentration and greater than 85% DR in 5 h may be due to insufficient polymers concentrations. PF8 formulation released 97% of drug at 8 h whereas DR from PF9 formulation was moderate and released only 84% of drug in 8 h. Formulation PF8 with 7.5 mg (15%) COM888 and 7.5 mg (15%) of HK100M polymer concentration showed better and desirable complete DR in 8 h with required floating characteristics. Hence, it was considered as an optimized formulation [Figure 8].

PGHC GFT formulations CDR data were subjected to assorted kinetic model equations. Zero and first-order analysis revealed all GFT formulations followed zero-order kinetics.[1-10]

GFT formulations release exponents (*n*) of Korsmeyer-Peppas were in between 0.550 and 0.776 representing non-fickian diffusion DR mechanism. The corresponding "r^2" values and zero-order rate constant (K0) with exponents (*n*) values are presented in Table 6 and DR kinetics plots of formulation PF9 are depicted in Figure 9.

The DR rate of PGHC GFT formulations was affected by polymer type and its concentration. As polymer concentration in formulations was increased, the DR was retarded. Moreover, increased content of hydrophobic polymer COM888 in combinational PGHC GFT formulations results in further retardation of DR may be due to slower penetration of dissolution medium into GFT as a result of increased lipophilic nature. Further, diffusion of medium into formulation was delayed by hydrophobic coating around the drug particles that lead to SR over extended period.[11-23]

Table 6: Kinetic modeling data of PGHC GFT formulations

Formulation	Regression coefficients (r^2)				Peppas "*n*" value	K0 (Percentage per h)
	Zero	First	Higuchi	Korsmeyer–Peppas		
PF1	0.9574	0.8208	0.9911	0.9916	0.649	18.16
PF2	0.9768	0.7644	0.9755	0.9987	0.550	10.81
PF3	0.9938	0.9335	0.9445	0.9902	0.698	9.687
PF4	0.9835	0.6980	0.9706	0.9971	0.602	15.30
PF5	0.9965	0.9310	0.9329	0.9811	0.722	10.60
PF6	0.9958	0.9556	0.9361	0.9967	0.754	8.86
PF7	0.9599	0.8505	0.9915	0.9947	0.575	14.94
PF8	0.9893	0.7637	0.9375	0.9735	0.563	11.08
PF9	0.9944	0.9142	0.9320	0.9939	0.748	9.74

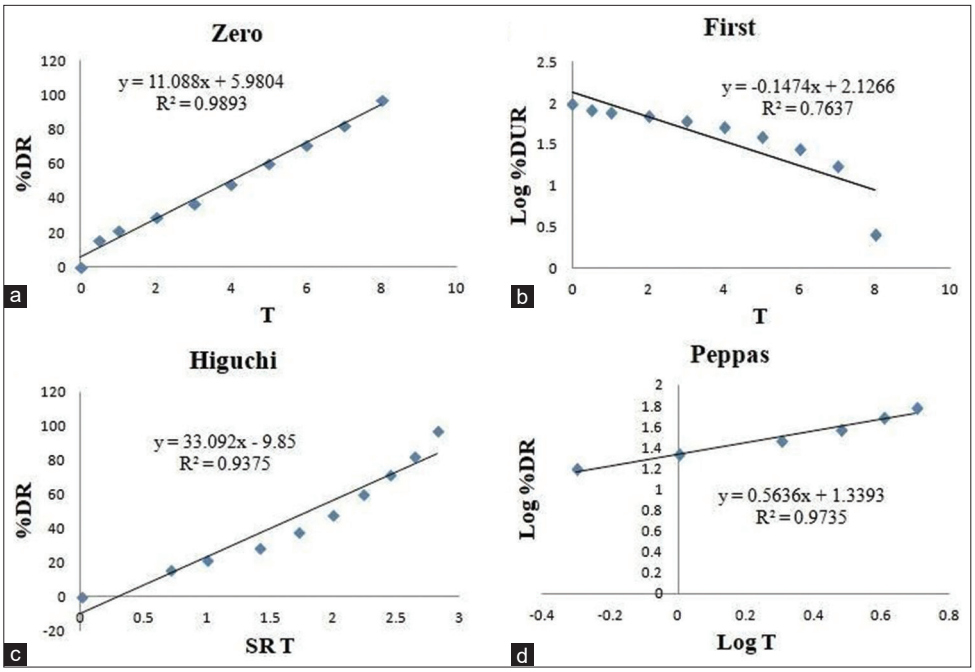

Figure 9: DR kinetic plots of PF8 formulation: (a) Zero-order, (b) first-order, (c) Higuchi, and (d) Korsmeyer–Peppas

CONCLUSION

FDDS promises to be satisfactory approach for prolonged GRT of drug to improve solubility, lessen drug waste thereby enhances BA for the drugs that are highly soluble in the lower pH condition. In this present research work, development and evaluation of gastric FDDS of selected three PAI drugs were planned to enhance their BA and/or to minimize their potential side effects with better patient compliance. The three drugs were PGHC, clopidogrel bisulfate, and dipyridamole which were selected based on their similar physic- chemical characteristics. All these three drugs belong to BCS Class-II (low solubility-high permeability) and exhibit pH-based solubility nature, greater at the lower pH conditions.

As per reported literatures, combinational apply of a hydrophobic polymers and hydrophilic polymers well controls initial rapid DR of highly soluble drugs. The DR from tablet formulation fabricated by MG employing meltable hydrophobic polymer could be slower due to better uniform and rigid hydrophobic coating around the hydrophilic drug particles. Therefore, in this work, both hydrophilic HPMC K100M (HK100M) and hydrophobic meltable Compritol® 888 ATO (COM888) polymers were chosen in alone and combination to develop and evaluate FDDS of selected three drugs and investigated their individual and combined effects on DR of respective drugs from formulations.

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