International Journal of Pharma and Bio Sciences V1(2)2010

DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

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ABSTRACT

The present study in the development of Hydro dynamically Balanced Systems (HBS) of fenofibrate, a lipid regulating drug which are designed to increase the gastric residence time, thus prolonging the drug release. Hydroxy propyl methyl cellulose (HPMC) of different viscosity grades at three different drug to polymer ratios were used to prepare HBS by wet granulation technique. The prepared HBS tablets were evaluated in terms of their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content, swelling index, drug polymer interaction studies, *invitro* floating studies, *invitro* drug release and short term stability studies. The drug polymer ratio, viscosity grades of HPMC, different diluents and gas generating agents were found to influence the drug release and floating properties of the prepared HBS. The floating properties and drug release characteristics were determined for the prepared HBS in 0.1 N HCl dissolution media. All the HBS formulations showed good invitro floating properties with an optimum concentration of gas generating agent's sodium bicarbonate and citric acid. The rate of drug release decreased with increased polymer concentration. It was found that HPMC viscosity had significant impact on the drug release from the prepared HBS. Among the three viscosity grades of HPMC (K4M, K15M, K100M), HPMC K4M along with lactose as diluents was found to be beneficial in improving the drug release rate and floating properties . Regression analysis of drug dissolution profiles on the basis of Higuchi and Korsmeyer model indicated that diffusion is the predominant mechanism controlling the drug release. The drug polymer interaction studies indicated that there was no interaction . The short term stability study indicated that there was no much differences observed.

KEYWORDS

Fenofibrate, Hydrodynamically Balanced Systems, Hydroxy Propyl Methyl Cellulose, *Invitro* floating, Higuchi model , Korsmeyer model .

INTRODUCTION

For effective therapy or to improve therapeutic efficiency of the drug through improved bioavailability may overcome the absorption drawbacks associated with certain class of drugs. Drug delivery systems may overcome these drawbacks in some cases. Among the drug delivery systems, gastric oral floating drug delivery systems may be desirable especially when the bioavailability of the drugs reduces due to the pathophysiology of the patient. Prolonged gastric retention of the therapeutic moiety may offer numerous advantages, including improved bioavailability therapeutic efficiency and possible reduction of dose.[1-3]

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Floating drug delivery systems (FDDS) or hydrodynamically balance systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without effecting the gastric emptying rate. While the system is floating on the gastric contents the drug is released slowly at a desired rate from the system. After the release of drug residual system is empited from the stomach. This results in increase in the gastric residence time and a better control of fluctuation in plasma drug concentration. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non effervescent FDDS approach was attempted to release the drug from FDDS. These systems when reached to stomach, Co2 is liberated by the acidity of gastric contents and is entrapped in the jellified hydrocolloid. This produces an upward motion of the dosage form to float on the chime. The Co_2 generating components viz, sodium carbonate or calcium carbonate or citric acid and tartaric acid mixtures may be used.[4-7]

Fenofibrate is a fibric acid derivative. It is used in the treatment of high cholesterol and high triglyceride levels[8].It's bioavailability is about 44%. It is well adsorbed from the GIT. In the present work, an attempt has been made to formulate GFDDS of fenofibrate using hydroxyl propyl methyl cellulose of different viscosity grades in order to prolong the drug release, and to impart floating properties of the sustained release tablet formulations.

MATERIALS AND METHODS

Fenofibrate was obtaind as gift sample from Ranbaxy labs pvt. Ltd, Himachal Pradesh. Hydroxy propyl methyl cellulose K4M, K15M, K100M were obtained from colorcon asia Ltd, Goa. Microcrystalline cellulose, polyvinyl pyrolidone, sodium bicarbonate, citric acid, talc, magnesium stearate were procured from SD Fine chemical, Mumbai.

Procedure for preparation of HBS of fenofibrate

All the ingredients were accurately weighed, passed through sieve no. 60 and transferred to clean porcelain mortar except magnesium stearate and talc. PVP(3% w/v) binding solution is added to the powder mixture in small quantities, while mixing thoroughly after each addition until a coherent mass is formed. Then it is passed through sieve no.44 and the wet granules were spread on a paper and dried in hot air oven at 55^0C-60^0C for 30 minutes.

Tablets were compressed on a rotatory punching machine (Clit pilot press) using flat surfaced, round shaped punches of 9mm and 11mm diameter.

Evaluation of HBS of fenofibrate

Evaluation of fenofibrate granules

The flow properties of granules (before compression) were characterized in terms of angle of repose[9], tapped density, bulk density[10], Carr's index[11] and Hausner ratio.

Physical evaluation of fenofibrate floating tablets

Hardness test

The crushing strength (Kg/cm²) of tablets was determined by using Monsanto hardness tester. In all the cases, means of six replicate determinations were taken. The results are given in table-4

Friability test

This was determined by weighing 10 tablets after dusting, placing them in the friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated.

The results are given in table-4.

Uniformity of weight

The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation. The results are summarized in table-4.

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Uniformity of drug content

5 tablets were powdered in a glass mortar and 100 mg of powder was placed in a 100 ml stoppered conical flask. The drug was extracted with 0.1N HC1 with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 5 hour and filtered into 50 ml volumetric flask through cotton wool and filtrate was made up to the mark by passing more 0.1 N HCI through filter, further appropriate dilution were made and absorbance was measured at 291nm against blank. The results are given in table-4

Determination of swelling index[12]

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h. The swelling index (SI), expressed as a percentage, and was calculated from the following equation

$$SI = \frac{\text{Weight of tablet at time (t)} - \text{Initial weight of tablet} \times 100}{\text{Initial weight of tablet}}$$

***In vitro* floating studies:** *In vitro* floating studies were performed for all the eighteen formulations as per the method described by Rosa *et al*[13]. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT). The results are given in table-5

***In vitro* dissolution studies**

In vitro dissolution studies of HBS of fenofibrate were carried out using USP XXIII tablet dissolution test apparatus-Il (Electrolab), employing a paddle stirrer at 50 rpm using 900m1 of 0.1N HC1 at 37±0.5°C as dissolution medium. One tablet was used in each test. At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 291 nm using UV-Visible spectrophotometer after suitable dilutions. All the studies were conducted in triplicate.

The results of *in vitro* release profiles obtained for all the HBS formulations were fitted into four models of data treatment as follows

1. Cumulative percent drug released versus time (zero-order kinetic model).[14]
2. Log cumulative percent drug remaining versus time. (first-order kinetic model).[15]
3. Cumulative percent drug released versus square root of time (Higuchi's model).[16]
4. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).[17]

Stability studies

Short-term stability studies were performed at a temperature of 45° ±1°C over a period of three weeks (21 days) on the promising HBS tablet formulation F10. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in hot air-oven maintained at 45°±1°C. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and *in vitro* floating studies were performed to determine the drug release profiles, *in vitro* floating lag time and floating time. The data of dissolution and *in vitro* floating studies are shown in tables 11-13.

RESULTS AND DISCUSSION

In the present study, Hydrodynamically Balanced Systems of fenofibrate were prepared by using different viscosity grades of Hydroxy propyl methyl cellulose (HPMC), viz, K4M, K15M and K100M(4,000, 15,000 and 1,00,000cps respectively) at different drug to polymer ratio with or without gas generating agent like sodium

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bicarbonate and citric acid. Two different diluents used are lactose and MCC.

The weighed quantities of drug and polymers were mixed thoroughly in different ratios (1:0.2, 1:0.3 and 1:0.4) and HBS tablets were prepared by wet granulation method. The prepared HBS tablets were evaluated The prepared tablets of all the formulations were evaluated for precompression parameters like angle of repose, bulk and tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation buoyancy lag time, total floating time, *in-vitro* drug release.

Precompression parameters of fenofibrate granules

The formulations showed good flow property and compressibility index (Table 2). Angle of repose ranged from 23.13 to 35.13, Hausner ratio ranged from 0.056 to0.154 and the compressibility index ranged from 17.32 to28.78. The LBD and TBD of the prepared granules ranged from 0.421 to 0.561 and 0.547 to 0.642respectively. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property. Given in table 3.

Post compression parameters of fenofibrate tablets

Hardness and friability

The hardness of the prepared HBS of fenofibrate was found to be in the range of 4.0 to 5.5 kg/cm^2 and is given in table 5. The friability of all the tablets was found to be less than 1% i.e. in the range of 0.37 to 0.65 given in table 4.

Uniformity of weight

All the prepared HBS were evaluated for weight variation and the results are given in tables 4. The percent deviation from the average weight was found to be within the prescribed official limits.

Uniformity of drug content

The low value of standard deviation indicates uniform drug content in the tablets prepared as observed from the data given in table 4.

***Invitro* floating studies**.

In the initial HBS formulations of fenofibrate , formulation containing drug and different viscosity grades of HPMC with gas generating agent (F1 to F9), the floating lag time was found to be in between 80 seconds to 140 seconds and remained under floating conditions for 24hours.

Formulations containing lactose along with a gas generating agent sodium bicarbonate at varying concentrations has shown a floating lag time of 80 seconds to 98 seconds remained floating for 24 hours. HBS formulations containing MCC along with sodium bicarbonate at varying concentrations (F1, F2, F4, F5, F7,F8) the floating lag time was found to be in between 90 seconds to 140 seconds and remains under floating condition for 24 hours.

The floating lag time was found to be more in the formulations which contains less gas generating agent (sodium bicarbonate) in the HBS formulations which may be due to delayed swelling of the polymer.

It was observed that when an optimum concentration of sodium bicarbonate was used, there was a reduction in the floating lag time, where the dissolution medium was imbibed into the matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the formation and entrapment of CO_2 gas within the swollen gel, thus causing floating as the matrix volume expanded and its density decreased.

Reduction in the floating lag time was observed by the addition of citric acid along with sodium bicarbonate. Formulations F16, F17 and F18 containing combinations of gas generating agents at varying concentrations exhibited a floating lag time of 35 seconds, 25 seconds and 15 seconds respectively which may be due to the immediate formation of CO_2 gas that provides buoyancy.

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Hence it can be concluded that optimum concentration of sodium bicarbonate was found to achieve optimum *invitro* floating of HBS of fenofibrate.

Swelling index studies

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration. Swelling is also a vital factor to ensure floating and drug dissolution.To obtain floating , the balance between swelling and water acceptance must be restored [18-19].The swelling index of floating tablets of F1 to F18 is shown in Fig.1.

The HPMC grade also affects the swelling and hydration with considerably higher swelling index for HPMC K4M than HPMC K15M and K100M. HPMC K15M and K100M exhibited low swelling index, but there was no decrease in swelling rate. The reason for this appeared to be its high viscosity and high water retention property.Further, no significant effect of effervescents on swelling indices was observed. Swelling index values start decreasing when polymer erosion starts in the medium.

***Invitro* dissolution studies**

Invitro dissolution studies were performed for all the batches of HBS of fenofibrate using USP XXIII dissolution test apparatus-II at 50rpm, 900ml of 0.1N HCl used as dissolution media. The *invitro* drug release data was given in tables 6 to 8 and drug release profiles are shown in figure-2 to 7.

Formulations F1, F2 and F3 containing drug : polymer ratio 1:0.2, 1:0.3 and 1:0.4 prepared with HPMC K4M exhibited 93.87, 90.73 and 89.54% of drug release in 12 hours respectively and the data is given in table 6 and drug release profiles are shown in figure-2, 8-10.

Formulations F4, F5 and F6 containing drug : polymer ratio 1:0.2, 1:0.3 and 1:0.4 prepared with HPMC K15M exhibited 91.34,90.27 and 88.19% of drug release in 12 hours respectively and the data is given in table 7 and drug release profiles are shown in figure-3, 11-13.

Invitro drug release data for formulations F7, F8 and F9 are given in table 7 and drug release profiles are shown in figure-21, 31-33. The formulations F7, F8 and F9 were prepared with HPMC K100M in drug polymer ratios 1:0.2, 1:0.3 and 1:0.4 exhibited 90.71, 89.18 and 88.89% drug release rates in 12 hours respectively.

In the above results, it was observed that as the concentration of the polymers increased, there is a decrease in the drug release rates. An increase in polymer concentration causes increase in viscosity of the gel as well as the gel layer with longer diffusional path. This could cause a decrease in effective diffusion coefficient of the drug and a reduction in drug release rate.

Formulations containing higher HPMC viscosity grades have slower drug release rates when compared to formulations with lower HPMC viscosity grades i.e. formulations F1, F2, F3 containing HPMC K4M have showed the fastest and formulations F7, F8, F9 containing HPMC K100M showed the slowest drug release rates. The amount of drug released for a particular drug polymer ratio was found to be in the order of K4M > K15M> K100M.

Among the three viscosity grades of HPMC studied, HPMC K4M,K15M and HPMC K100M with a drug-polymer ratio of 1:0.4 has been selected to study the influence of excipient lactose on drug release rates (F3, F6, F9).

Formulation F10 containing lactose as diluent along with sodium bicarbonate and citric acid exhibited 99.19% of drug release in 12 hours whereas formulation F11 exhibited 96.03% of drug release in 12 hours.

Invitro release data of formulations F12, F13, F14 and F15 are given in tables 7-8 and dissolution profiles are shown in figure- 5-6, 17-22. These formulations containing drug and HPMC K15M

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and K100M along with lactose and a combination of gas generating agents sodium bicarbonate and citric acid exhibited a drug release of 96.99, 95.23, 94.59 and 90.29% in 12 hours. The addition of citric acid in these formulations did not influence the drug release rates.

The dissolution t_{50} and t_{90} values for all the HBS formulations of fenofibrate is given in table 9. The comparative effect of two different diluents on the release profiles of fenofibrate from the HBS formulations in terms of dissolution t_{50} and t_{90} values is shown in figure-26. It was observed that HBS containing MCC (t_{90} for F1=11.6 hours) exhibited shorter dissolution times when compared to formulations containing lactose (t_{90} for F3=12.2 hours).

Drug release kinetics

The *invitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, Higuchi and Korsmeyer models to ascertain the mechanism of drug release. The results of linear regression analysis of data including regression coefficient are summarized in table 10.

When the regression coefficient 'r' value of zero order and first order plots were compared, it was observed that the 'r' values of zero order were in the range of 0.990 to 0.999 whereas the 'r' values of first order plots were found to be in the range of 0.0830 to 0.0489 indicating drug release from all the formulations were found to follow zero order kinetics.

The good fit of the Higuchi model to the dissolution profiles of all the formulations suggested that diffusion is the predominant mechanism limiting drug release since the 'r' values of Higuchis plots were nearer to unity.

The *invitro* dissolution data as log cumulative percent drug release versus log time were fitted to Korsmeyer et al equation, values of the exponent 'n' was found to be in the range of 0.46 to 0.70 indicating that the drug release is by Non-Fickian diffusion mechanism.

Among the various formulations studies, HBS formulation F10 was considered as an ideal formulation which exhibited 90% of drug release in 10.0 hours (t_{90}) and floating lag time of 50 seconds with a floating time of 24 hours. Hence it is selected for further short term stability studies.

Stability studies

Short term stability study was performed for formulation F10 at 45±1^{0}C for 3 weeks (21 days). The samples were analysed for percent drug content, *invitro* floating ability and *invitro* drug release studies. The results are given in table 11 to 13. No appreciable difference was observed for the above parameters.

Drug – Polymer ratios for the preparation of HBS fenofibrate

Table1.
Preliminary trial formulation (for 1 tablet)

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fenofibrate	100	100	100	100	100	100	100	100	100
HPMC K4M	20	30	40	_	_	_	_	_	_
HPMC K15M	_	_	_	20	30	40	_	_	_

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HPMC K100M	_	_	_	_	_	_	20	30	40
MCC	50	50	_	50	50	_	50	50	_
Sodium bicarbonate	20	30	40	20	30	40	20	30	40
Lactose	_	_	50	_	_	50	_	_	50
Citric acid	20	_	_	20	_	_	20	_	_
Magnesium sterate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
PVP (3%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table-2.
Final formulation (for 1 tablet)

Ingredient (mg)	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Fenofibrate	100	100	100	100	100	100	100	100	100
HPMC K4M	60	80	-	-	-	-	90	108	125
HPMC K15M	-	-	60	80	-	-	-	-	-
HPMC K100M	-	-	-	-	60	80	-	-	-
Sodium bicarbonate	50	60	50	60	50	60	100	108	115
Lactose	50	50	50	50	50	50	50	50	50
Citric acid	20	-	20	-	20	-	70	75	80
Magnesium sterate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
PVP (3%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

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Table 3.
Precompression flow properties of granules of fenofibrate

Formulation code	Angle of repose (θ) in degrees	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner ratio (HR)
F1	28.13	0.486	0.614	18.12	0.154
F2	25.45	0.468	0.623	19.43	0.142
F3	28.67	0.431	0.591	22.10	0.065
F4	30.89	0.463	0.591	24.67	0.110
F5	24.34	0.521	0.632	17.32	0.146
F6	23.13	0.541	0.642	18.45	0.098
F7	28.15	0.561	0.632	21.78	0.141
F8	29.67	0.421	0.621	28.68	0.056
F9	30.90	0.458	0.581	25.90	0.078
F10	31.23	0.437	0.623	28.78	0.0121
F11	25.41	0.483	0.587	26.53	0.088
F12	24.58	0.510	0.610	21.32	0.112
F13	34.15	0.486	0.614	21.49	0.139
F14	30.96	0.483	0.606	20.44	0.128
F15	35.13	0.488	0.614	20.52	0.124
F16	28.73	0.468	0.578	19.03	0.140
F17	29.93	0.463	0.586	21.50	0.110
F18	30.96	0.453	0.547	17.17	0.141

Table 4.

Physical properties of HBS formulations F1 to F18

Formulation code	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation*(mg)	Percent drug content* ± SD
F1	9	2.64	4.5±0.5	0.41	216.95	98.32±0.21
F2	9	2.62	5.0±0.9	0.65	**216.85**	98.86±0.79
F3	9	2.90	4.5±0.3	0.43	236.95	99.59±0.37
F4	9	2.64	4.3±0.6	0.45	216.90	97.85±0.59
F5	9	2.63	5.0±0.8	0.49	216.75	97.94±0.91
F6	9	2.85	5.0±0.7	0.50	237.05	98.62±0.85
F7	9	2.60	5.1±0.3	0.52	216.95	99.47±0.99
F8	9	2.63	4.0±0.5	0.39	216.85	98.54±0.45
F9	9	2.83	4.0±0.9	0.37	237.00	99.47±0.67
F10	9	3.25	5.5±0.5	0.40	287.65	99.79±0.23
F11	9	3.60	5.2±0.2	0.38	297.75	98.95±0.89
F12	9	3.30	5.4±0.4	0.49	288.20	99.16±0.75

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F13	9	3.70	5.1±0.3	0.43	298.00	99.28±0.69
F14	9	3.55	5.3±0.1	0.45	288.15	99.65±0.47
F15	9	3.45	5.5±0.4	0.47	298.00	99.68±0.91
F16	11	5.00	4.5±0.6	0.49	417.45	99.89±0.89
F17	11	3.58	4.5±0.3	0.46	449.15	99.96±0.68
F18	11	3.72	4.5±0.5	0.51	478.50	99.80±0.27

Table 5.

***In vitro* floating of HBS of Fenofibrate**

Formulation code	Floating lag time (Seconds)	Floating time (hrs)
F1	120	24
F2	90	24
F3	80	24
F4	135	24
F5	100	24
F6	95	24
F7	140	24
F8	105	24
F9	98	24
F10	50	24
F11	75	24
F12	65	24
F13	80	24
F14	63	24
F15	78	24
F16	35	24
F17	25	24
F18	15	24

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Table 6.

***In Vitro* release data of HBS of Fenofibrate F1 to F6**

Sl. No.	Time (Hrs)	F1	F2	F3	F4	F5	F6
		Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD
1.	01	12.16±0.67	10.21±0.89	11.08±0.59	11.58±0.31	10.19±0.21	10.00±0.23
2.	02	18.47±0.47	16.74±0.17	15.88±0.22	19.98±0.29	19.96±0.19	18.91±0.31
3.	03	26.90±0.55	25.16±0.16	22.53±0.33	26.31±0.35	26.92±0.27	25.17±047
4.	04	34.96±0.76	33.75±0.25	29.81±0.51	32.07±0.47	33.09±0.57	30.28±0.56
5.	05	45.16±0.16	40.28±0.67	40.59±0.59	43.38±0.67	44.18±0.38	42.09±0.71
6.	06	55.62±0.62	48.23±0.23	52.81±0.40	51.93±0.85	51.88±0.43	51.42±0.63
7.	07	62.83±0.83	52.78±0.38	60.40±0.29	59.41±0.89	60.67±0.63	58.49±0.39
8.	08	70.83±0.53	60.33±0.33	65.15±0.57	66.88±0.79	65.13±0.13	64.19±0.91
9.	09	77.60±0.58	67.72±0.42	70.56±0.42	74.38±0.91	70.84±0.89	70.23±0.23
10.	10	81.65±0.23	75.35±0.35	76.37±0.37	79.91±0.58	78.97±0.73	77.09±0.85
11	11	85.88±0.88	83.83±0.37	81.98±0.29	84.16±0.99	83.88±0.85	82.00±0.79
12	12	93.87±0.89	90.73±0.73	89.54±0.33	91.34±0.87	90.27±0.47	88.19±0.63

*Average of three determinations

Table 7.

***In Vitro* release data of HBS of Fenofibrate F7 to F12**

Sl. No.	Time (Hrs)	F7	F8	F9	F10	F11	F12
		Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD
1.	1	10.19±0.23	10.97±0.18	10.28±0.21	12.32±0.59	11.79±0.56	13.99±0.58
2.	2	17.83±0.31	16.59±0.25	15.03±0.44	18.64±0.22	18.71±0.27	18.44±0.14
3.	3	23.69±0.47	24.34±0.39	20.86±0.51	28.36±0.33	27.93±0.35	24.95±0.24
4.	4	32.13±0.56	31.19±0.45	28.89±0.68	37.29±0.88	37.39±0.48	32.83±0.79

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5.	5	43.50±0.71	39.67±0.57	35.17±0.91	46.24±0.58	45.44±0.53	43.43±0.38
6.	6	51.91±0.63	45.15±0.67	41.17±0.71	58.48±0.69	56.73±0.76	56.35±0.53
7.	7	59.39±0.39	52.02±0.61	48.26±0.76	65.58±0.77	67.84±0.97	61.26±0.43
8.	8	66.77±0.91	60.02±0.73	58.69±0.69	75.05±0.49	79.15±0.68	71.96±0.87
9.	9	70.89±0.23	67.59±0.85	69.23±0.83	82.01±0.63	86.98±0.39	79.59±0.39
10.	10	76.77±0.85	75.74±0.69	75.36±0.89	90.42±0.19	90.17±0.11	85.23±0.58
11.	11	87.66±0.79	84.19±0.53	82.44±0.39	94.15±0.29	93.96±0.91	90.13±0.91
12.	12	90.71±0.63	89.18±0.91	88.89±0.78	99.19±0.23	96.03±0.55	96.99±0.17

*Average of three determinations

Table 8.

***In Vitro* release data of HBS of Fenofibrate F13 to F18**

Sl. No.	Time (Hrs)	F13	F14	F15	F16	F17	F18
		Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD
1.	1	13.59±0.52	12.72±0.19	13.59±0.71	18.70±0.27	18.57±0.37	18.52±0.49
2.	2	18.78±0.23	18.68±0.27	18.55±0.28	28.03±0.12	25.87±0.23	24.57±0.53
3.	3	26.45±0.39	27.81±0.39	25.00±0.17	34.07±0.29	33.04±0.81	32.14±0.36
4.	4	34.69±0.63	32.14±0.51	33.09±0.54	40.11±0.56	39.48±0.73	37.74±0.57
5.	5	44.49±0.56	46.38±0.87	40.66±0.44	50.96±0.76	49.50±0.18	48.77±0.69
6.	6	57.67±0.66	58.68±0.49	48.08±0.37	59.40±0.59	56.55±0.47	58.06±0.73
7.	7	65.07±0.18	65.11±0.93	54.19±0.83	68.56±0.71	67.12±0.38	65.71±0.89
8.	8	74.83±0.45	75.77±0.79	58.6±0.79	77.75±0.23	75.87±0.67	72.29±0.91
9.	9	83.86±0.49	84.56±0.68	66.69±0.83	84.13±.0.18	81.59±0.33	77.87±0.97
10.	10	89.19±0.58	89.47±0.54	74.59±0.97	90.43±0.53	88.10±0.27	83.88±0.95
11.	11	93.95±0.57	92.35±0.98	84.19±0.90	93.21±0.36	92.07±0.83	91.03±0.83
12.	12	95.23±0.63	94.59±0.62	90.29±0.68	97.69±0.18	96.65±0.69	95.89±0.33

*Average of three determinations

DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

Table19.

Dissolution t_{50} and t_{90} values of HBS of fenofibrate

Sl. No.	Formulation Code	t_{50}(hours)	t_{90}(hours)
1	F1	5.5	11.6
2	F2	6.5	11.8
3	F3	5.9	12.2
4	F4	5.7	11.9
5	F5	6	12
6	F6	5.8	12.4
7	F7	5.9	12
8	F8	6.6	12.1
9	F9	7.1.	12.3
10	F10	5.3	10
11	F11	5.5	10
12	F12	5.6	11.1
13	F13	5.5	10.3
14	F14	5.4	10.5
15	F15	6.3	11.9
16	F16	5.0	8.9
17	F17	5.3	10.6
18	F18	5.2	10.9

DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

Table 10.

Regression analysis data of formulations of fenofibrate

Batches		Zero Order	First Order	Higuchi's Equation	Peppas Equation
F1	r	0.9948	0.0651	0.9666	0.9021
	a	0.2447	6.7160	0.6794	0.2776
	b	0.1316	0.4821	0.0333	0.6271
F2	r	0.9990	0.0676	0.9670	0.9023
	a	0.3094	6.7364	0.6692	0.2887
	b	0.1355	0.4933	0.0339	0.6381
F3	r	0.9946	0.1667	0.9736	0.8904
	a	0.4673	7.6959	0.6113	0.2836
	b	0.1262	1.1917	0.0319	0.6159
F4	r	0.9962	0.0484	0.9711	0.9021
	a	0.3719	6.5387	0.6369	0.2776
	b	0.1337	0.3615	0.0338	0.6271
F5	r	0.9963	0.0830	0.9750	0.8955
	a	0.5064	6.9014	0.6019	0.2838
	b	0.1329	0.6138	0.0336	0.6234
F6	r	0.9967	0.1069	0.9722	0.8895
	a	0.0860	6.5410	0.7906	0.2747
	b	0.1338	0.3568	0.0330	0.6393
F7	r	0.9977	0.0484	0.9511	0.9809
	a	0.0860	6.5410	0.7906	0.2747
	b	0.1338	0.3568	0.0330	0.6393
F8	r	0.9992	0.0553	0.9632	0.8980
	a	0.2363	6.6091	0.6940	0.2820
	b	0.1358	0.4058	0.0338	0.6340
F9	r	0.9968	0.1124	0.9690	0.9036
	a	0.3111	7.1919	0.6640	0.2807
	b	0.1298	0.8116	0.0326	0.6249s
Batches		**Zero Order**	**First Order**	**Higuchi's Equation**	**Peppas Equation**
F10	r	0.9959	0.3838	0.9706	0.8937
	a	0.3521	8.9399	0.6475	0.2830
	b	0.1166	2.2641	0.0294	0.6073
F11	r	0.9906	0.3343	0.9679	0.8984
	a	0.2879	8.8883	0.6597	0.2832
	b	0.1147	2.1840	0.0290	0.6082
	r	0.9959	0.2684	0.9656	0.8856

DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

F12	a	0.2934	8.4352	0.6705	0.2801
	b	0.1211	1.7662	0.0304	0.6120
F13	r	0.9930	0.2998	0.9668	0.8879
	a	0.3057	8.6857	0.6609	0.2812
	b	0.1174	1.9907	0.0295	0.6079
F14	r	0.9908	0.2806	0.9667	0.8918
	a	0.2925	8.5818	0.6607	0.2807
	b	0.1171	1.9030	0.0295	0.6081
F15	r	0.9980	0.0555	0.9671	0.8764
	a	0.4745	6.6095	0.6260	0.2832
	b	0.1385	0.4079	0.0347	0.6278
F16	r	0.9906	0.3417	0.9822	0.8395
	a	1.0340	8.8640	0.4448	0.2782
	b	0.1230	2.2056	0.0315	0.5882
F17	r	0.9925	0.2865	0.9808	0.8427
	a	0.9745	8.5794	0.4659	0.2789
	b	0.1251	1.9279	0.0320	0.5928
F18	r	0.9934	0.2330	0.9811	0.8433
	a	0.9809	8.2117	0.4654	0.2786
	b	0.1284	1.6110	0.0328	0.5964

Table-11
Stability data of HBS formulation (F10) at 45±1°C

Sl. No.	Time in days	Physical charges	Mean ± SD (45 ±1°C)
1.	01	--	99.19±0.23
2.	07	No change	98.68±1.30
3.	14	No change	98.55±1.31
4.	21	No change	98.73±0.39

Table 12.
***Invitro* floating studies of formulation (F10)**

Sl. No.	Formulation code	Floating lag time (seconds)	Floating lag time (hrs)
1.	F10	50	24
2.	F10	50	24
3.	F10	50	24

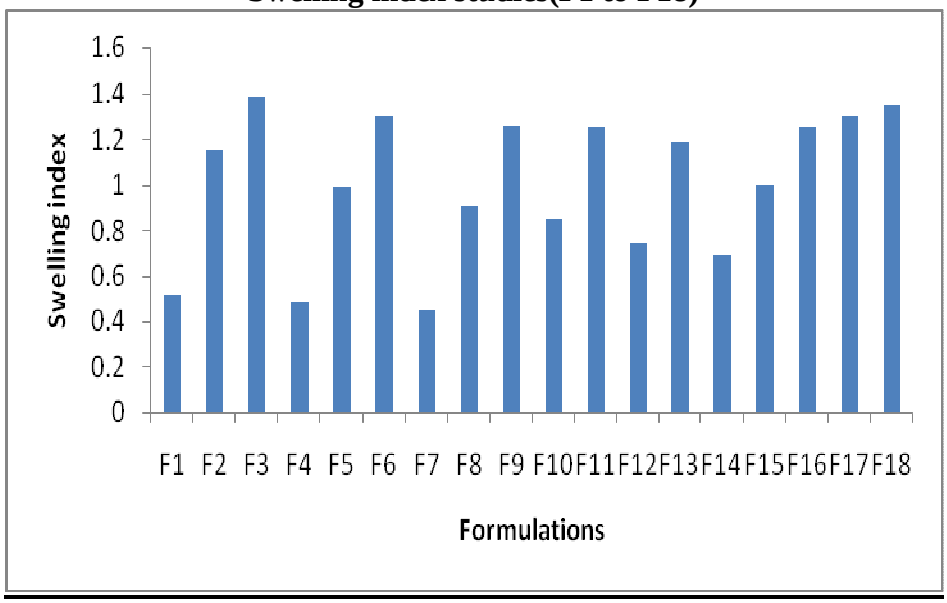
DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

Table 13
***In vitro* Release Data of the Formulation (F10)**

Sl. No.	Time (Hrs)	Cumulative * Percent Drug Released ± SD at 45±1°C	
		1st Day	21st Day
1.	01	12.32±0.59	11.98±0.79
2.	02	18.64±0.22	17.73±0.56
3.	03	28.36±0.33	27.89±0.65
4.	04	37.29±0.88	36.83±0.19
5.	05	46.24±0.58	45.93±0.27
6.	06	58.48±0.69	57.17±0.37
7.	07	65.58±0.77	64.89±0.45
8.	08	75.05±0.49	73.99±0.82
9.	09	82.01±0.63	80.89±0.15
10.	10	90.42±0.19	89.57±0.71
11.	11	94.15±0.29	93.67±0.63
12.	12	99.19±0.23	98.73±0.39

*Average of three determinations

Fig-1
Swelling index studies(F1 to F18)



DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

Fig-2
Cumulative Percent Drug Released Vs Time Plots (Zero Order) of formulation F1, F2 ,F3

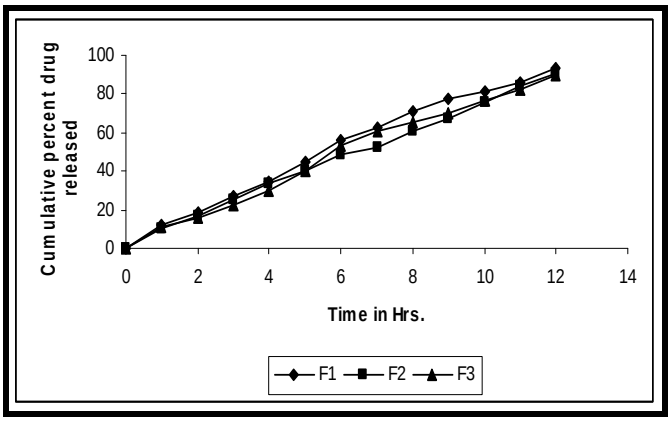


Fig-3
Cumulative Percent Drug Released Vs Time Plots (Zero Order) of formulation F4, F5 ,F6

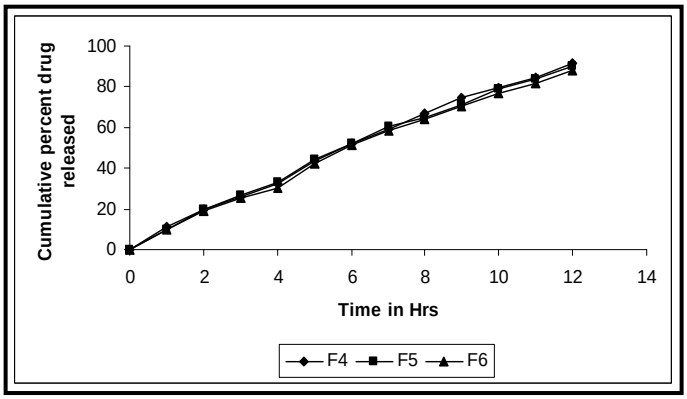
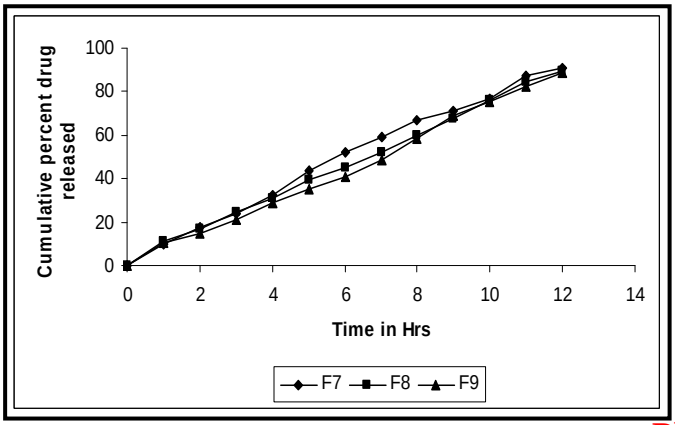


Fig-4
Cumulative Percent Drug Released Vs Time Plots (Zero Order) of formulation F7, F8,F9



DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

Fig-5
Cumulative Percent Drug Released Vs Time Plots (Zero Order) of formulation F10, F11, F12

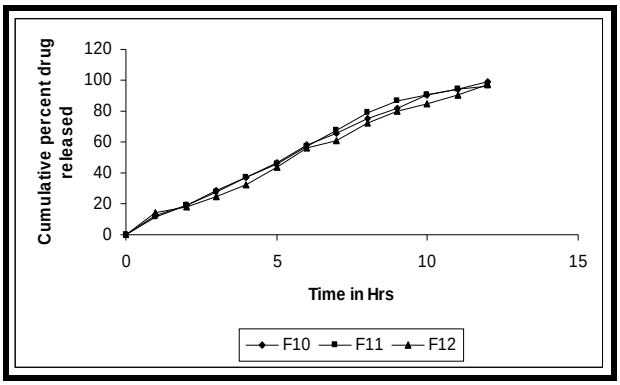


Fig-6
Cumulative Percent Drug Released Vs Time Plots(Zero Order) of formulation F13, F14, F15

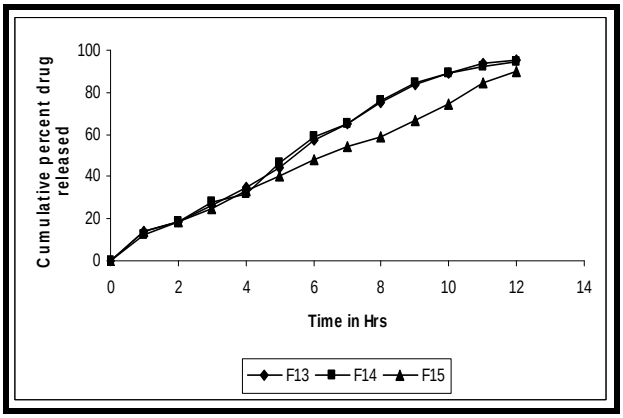


Fig-7

Cumulative Percent Drug Released Vs Time Plots(Zero Order) of formulation F16, F17, F18

DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

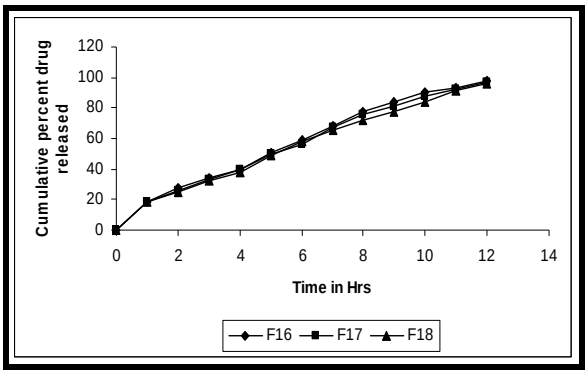


Fig-8

Log Cumulative Percent Drug Remaining Vs Time Plots(First Order) of formulation F1, F2, F3

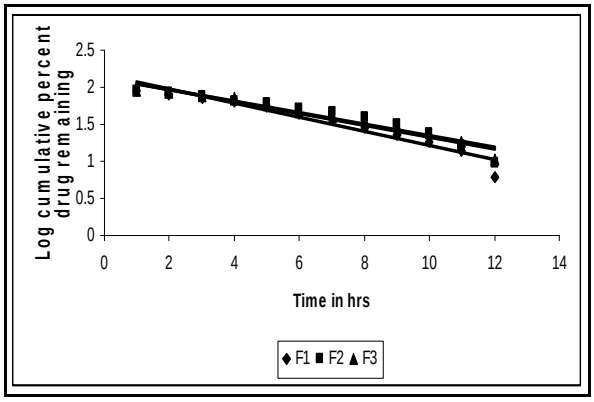


Fig-9
Cumulative Percent Drug Released Vs Square Root of Time(Higuchi's Plots) of formulation F1, F2 ,F3

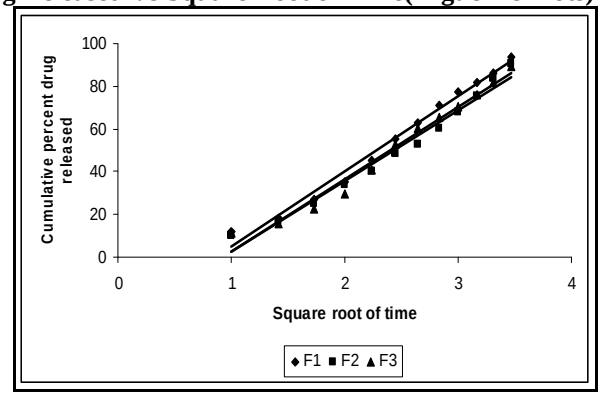


Fig-10
Log Cumulative Percent Drug Released Vs Log Time (Korsmeyer Plots) of formulation F1, F2 ,F3

DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

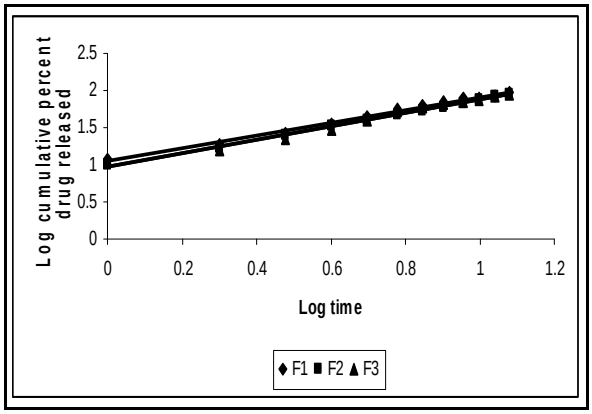


Fig-11
Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of formulation F4, F5 ,F6

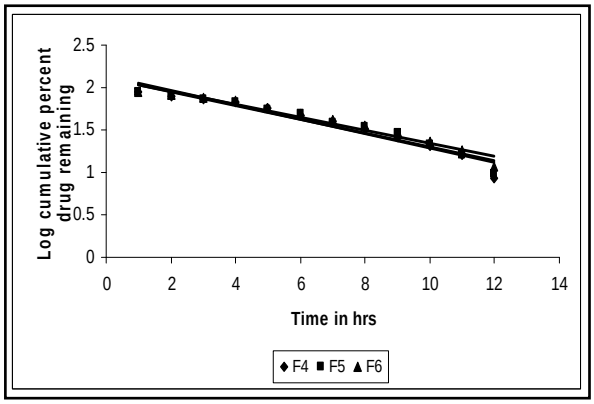
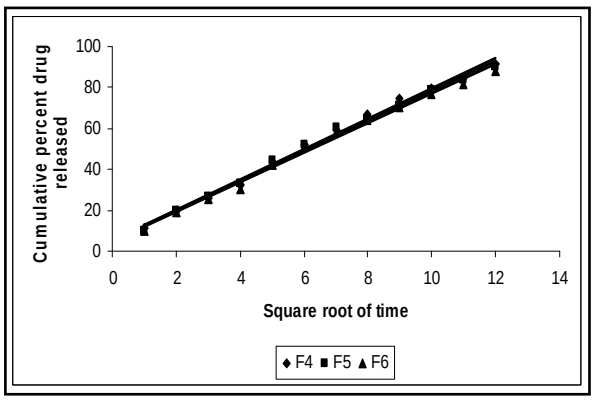


Fig-12
Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of formulation F4,F5, F6



DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

Fig-13
Log Cumulative Percent Drug Released Vs Log Time (Korsmeyer Plots) of formulation F4, F5, F6

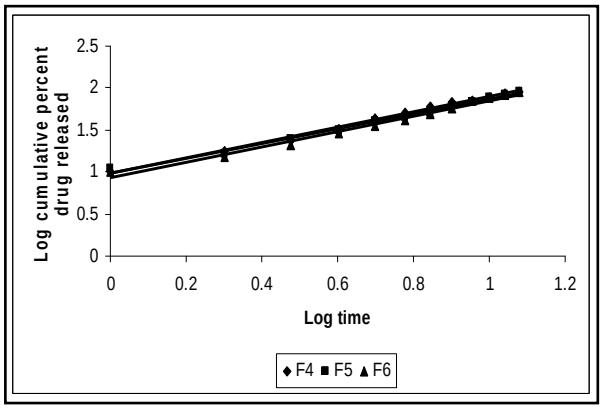


Fig-14
Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of formulation F7, F8, F9

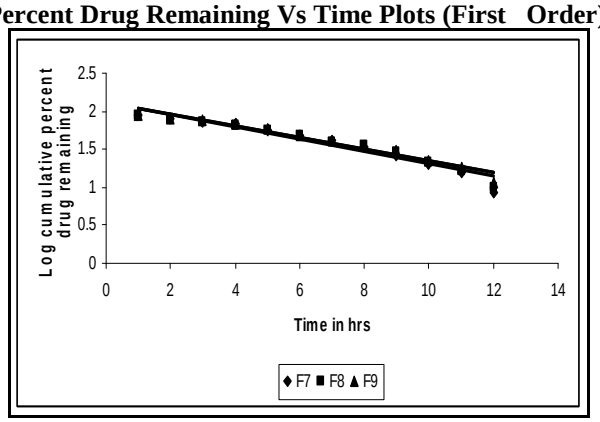
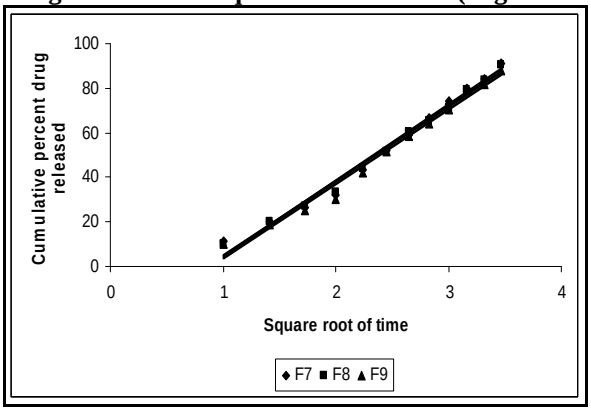


Fig-15
Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of formulation F, F8, F9



DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

Fig 16
Log Cumulative Percent Drug Released Vs Log Time(Korsmeyer Plots) of formulation F7, F8, F9

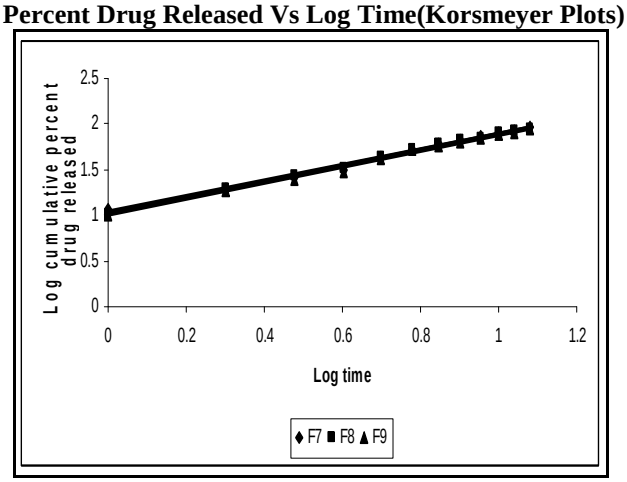


Fig-17
Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of formulation F10, F11, F12

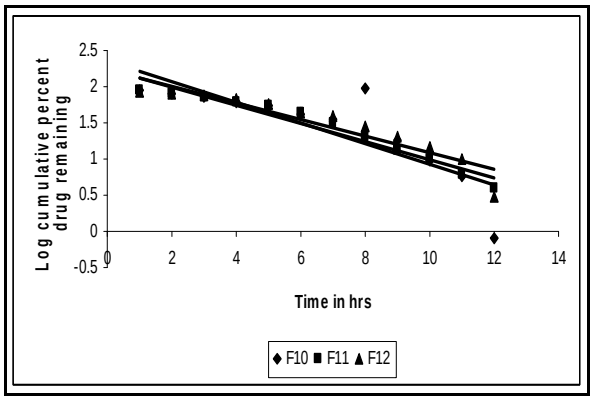


Fig-18
Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots)of formulation F10,F11, F12

DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

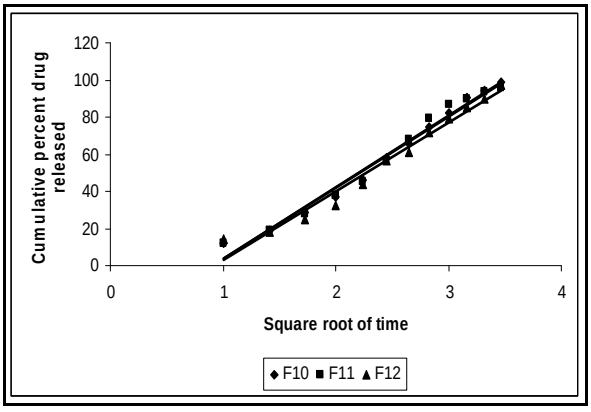


Fig-19
Log Cumulative Percent Drug Released Vs Log Time(Korsmeyer Plots)of formulation F10, F11, F12

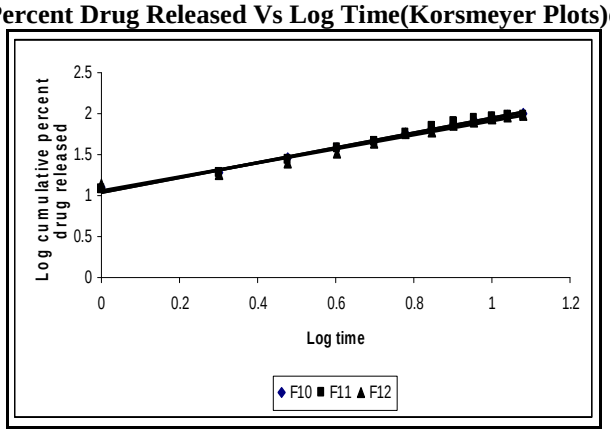


Fig-20
Log Cumulative Percent Drug Remaining Vs Time Plots(First Order) of formulation F13, F14, F15

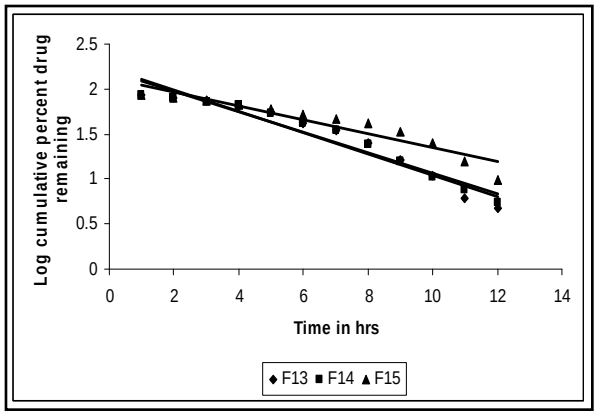


Fig-21
Cumulative Percent Drug Released Vs Square Root of Time(Higuchi's Plots) of formulation F13,F14, F15

DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

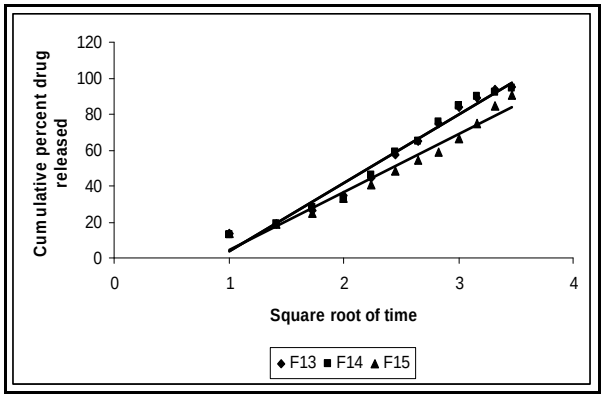


Fig-22
Log Cumulative Percent Drug Released Vs Log Time(Korsmeyer Plots) of formulation F13, F14, F15

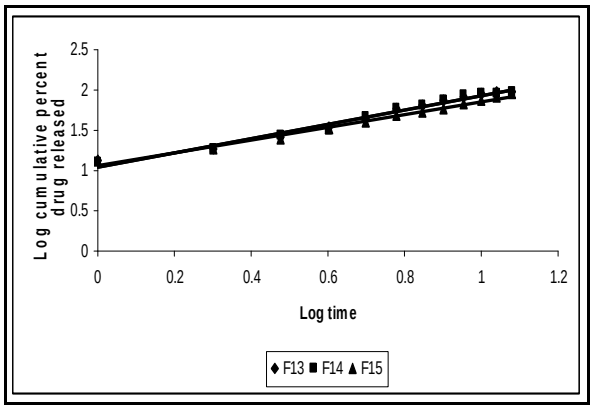
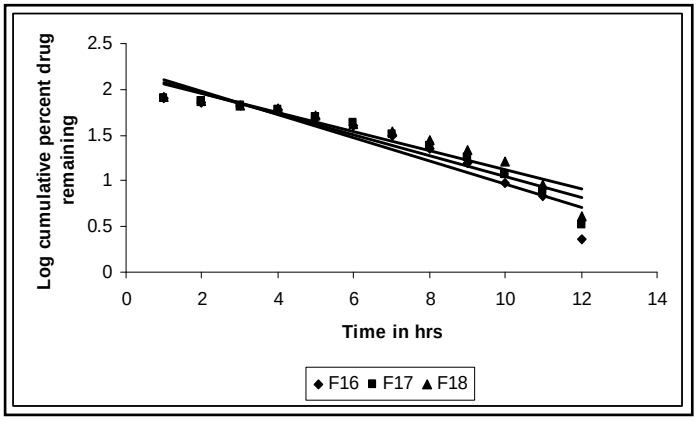


Fig-23
Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of formulation F16, F17, F18



DESIGN AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF FENOFIBRATE

Fig-24
Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of formulation F16, F17, F18

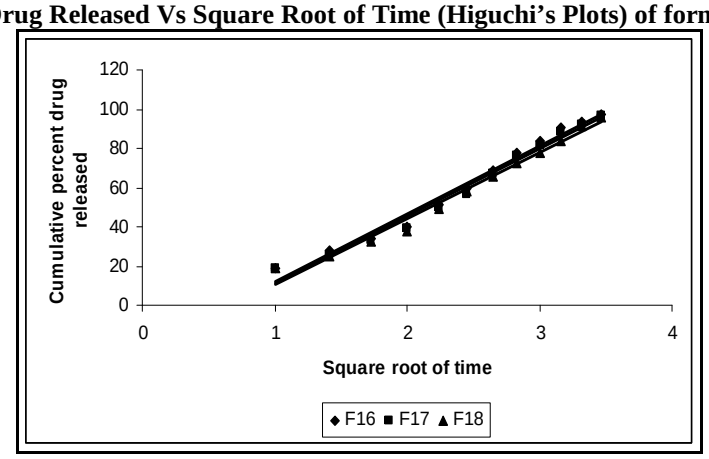


Fig-25
Log Cumulative Percent Drug Released Vs Log Time (Korsmeyer Plots) of formulation F16, F17, F18

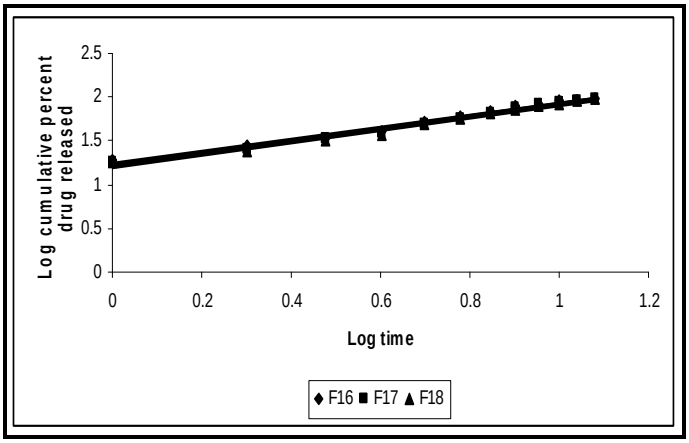


Figure-26: Dissolution t_{50} and t_{90} of HBS of fenofibrate (F1 to F18)

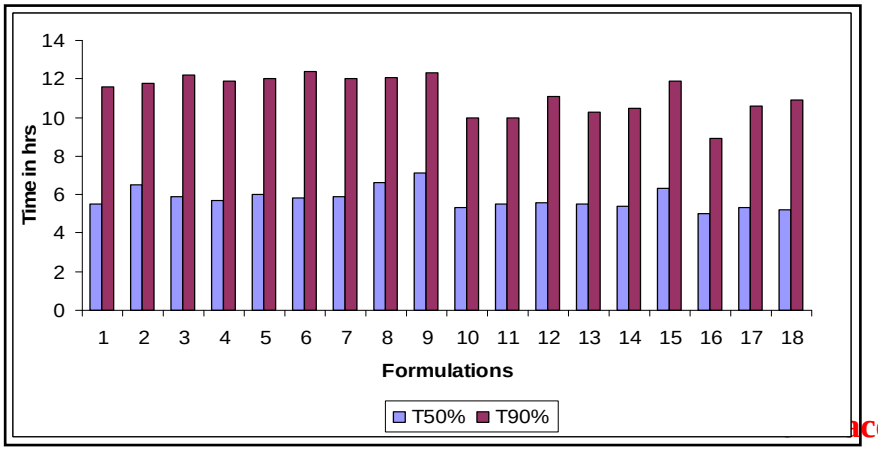


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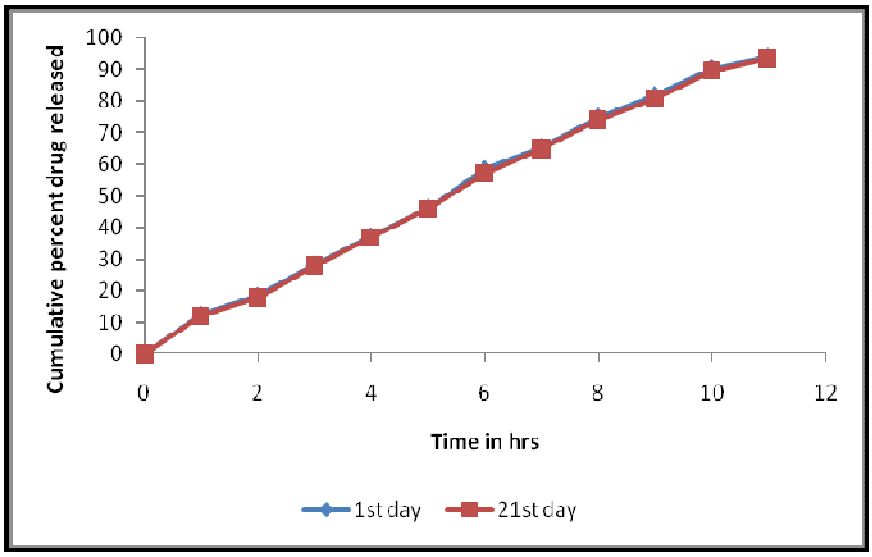
Figure-27:*In vitro* relaease profile of the formulation F10



CONCLUSION

The following conclusions can be drawn from the results obtained in this study:

- Hydrodynamically Balanced Systems offers a simple and practical approach to achieve increased gastric residence and to modify drug release profiles essential for sustained, site specific and localized drug action.
- The HBS of fenofibrate were developed by using different viscosity grades of HPMC by wet granulation technique. Lactose and MCC were used as diluents. Sodium bicarbonate and citric acid were used as gas generating agents either alone or in combination.
- All the prepared tablets prepared were found to be good without chipping, capping and sticking.
- The drug content was uniform and well within the accepted limits with low values of standard deviation indicating uniform distribution of drug within the HBS.
- The drug – polymer ratio, viscosity grades of HPMC, different diluents and gas generating agents were found to influence the release of drug and floating characteristics from the prepared HBS of fenofibrate.
- Polymer swelling is crucial in determining the drug release rate and is also important for flotation.
- The prepared HBS of fenofibrate showed excellent *invitro* floating properties. Addition of less quantity of gas generating agent sodium bicarbonate resulted in the reduction of floating lag time. Addition of citric acid to the HBS with sodium bicarbonate has produced a marked

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reduction in the floating lag time upto less than 15 seconds. All the HBS system have showed a floating time of 24 hours. The floating lag time is dependent upon the concentration of gas generating agent sodium bicarbonate and citric acid was found to achieve an optimum *invitro* floating.

- The *invitro* dissolution profiles of all the prepared HBS formulations of fenofibrate were found to extend the drug release over a period of 12 hours and the drug release decreased with increase in viscosity of polymer.
- Release of fenofibrate from most of the HBS formulations was found to follow zero order kinetics (0.990 to 0.999) and derived correlation coefficient 'r' (0.99) indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism controlling the drug release. When drug release data fitted to Korsmeyer equation, the values of slope 'n' (0.46 to 0.70) indicated that the drug release was by Non-Fickian mechanism.
- Among the various HBS formulations studied, formulation F10 containing drug-polymer ratio (1:0.6) prepared with HPMC K4M showed promising results releasing ≈ 90% of the drug in10.00 hours (T_{90}) with a floating lag time of 50sec and floating time of 24 hours has been considered as an ideal formulation and subjected to further short term stability studies.
- Optimized HBS of fenofibrate (F10) was found to be stable at 45^0C following a three week stability study.
- Finally, it may be concluded that this novel drug delivery system i.e HBS offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The HBS of fenofibrate provides a better option for increasing the bio availability and treating high cholesterol and high triglyceride levels by allowing a better control of fluctuations observed with conventional dosage forms..
- Formulation F10 appears suitable for further pharmacodynamic and pharmacokinetic studies to evaluate clinical safety of these HBS in suitable animal and human models.

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