Formulation and evaluation of floating pulsatile released tablets of Fenoterol

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ABSTRACT

Present study was perform to develop a floating pulsatile released formulation of fenoterol. To develop such formulation, it is necessary to reduce the disintegration time to obtain burst effect therefore rapid release core tablets (RRCT) were prepared. RRCT tablet (F3) was compression-coated with HPMC K4M, HPMC K15M and HPMC K100M (P1-P9). HPMC K100M (Batch P7-P9) shows the lag time of 4 hours then follow the sigmoidal release pattern with 100% drug release at 10th hr. As the concentration of the HPMC K100M coating increases from 140 to 180 mg the lag time extended to 4.5hr and then follow the delayed release profile with the 100 % drug release at the 12th hr. On this basis, formulation P9 was selected as the best formula. P9 formula containing 100mg of FEN core tablet compression- coated with HPMC K100M was formulated with different floating compositions. Floating composition containing pulsatile release tablets formula P9 tablet were evaluated for floating lag time and floating time and formula N2 was found to be best. Drug release profile for final formulation F3P9N2 shown a lag time of 4 hr and 100% drug release in 12 hr. For pulsatile release tablet of fenoterol optimized batch F3P9N2 was selected for stability testing, it was seen that there are no significant changes in drug release profile for the batches stored at different conditions of temperature and humidity. From the results it is concluded that the pulsatile release tablet we prepared could achieve a rapid release after lag time of 4hr with the relatively low variability.

Keywords: Floating tablets, Pulsatile release, Fenoterol, HPMC, Compression-coating.

INTRODUCTION

Now a day development of chronotherapeutic formulations and specifically to time controlled release dosage forms in order to achieve the maximum drug concentration inthe plasma at the

peak time of the symptomatology[1]. The major disadvantage of these systems reclines in achieving long residence time which is desired for diseases needing morning medication[2]. Pulsatile drug delivery systems are characterized by two release phases, a first phase with no or little drug being released, followed by a second phase, during which the drug is released completely within a short period of time after the lag time. The release can be either time or site controlled. The release from the first group is essentially determined by the system, while the release from the second group is primarily controlled by the biological environment in the gastrointestinal tract. With conventional pulsatile release dosage forms, the highly variable nature of gastric emptying process can result *in vivo* variability and bioavailability problems. To overcome this, novel/conceptual approach termed as "floating pulsatile drug delivery system" was developed[3].

The floating pulsatile concept was thus applied to increase the gastric residence of the dosage form having lag phase followed by a burst release in either stomach or distal part of small intestine[4].

A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in upper GIT after a defined time period of no drug release. A pulsatile drug delivery that can be administered at bedtime but releases drug in early morning would be a promising chrono-therapeutic system [5].

The system consists of three different parts, a core tablet, containing the active ingredient, an erodible outer shell, and a top cover buoyant layer. One layeris for buoyancy and the other for drug pulsatile release. The pulsatile release system with various lag times was prepared by compression with different erodible polymeric layers (press-coated systems) as described previously. Ideally, the novel system could result in a floating dosage form with a prolonged gastric residence time and in a pulsatile dosage form, in which the drug is released rapidly in a time controlled fashion after rupturing of the coating [6].

Despite significant improvements in the diagnosis and management of asthma over the past decade, as well as the availability of comprehensive and widely-accepted national and international clinical practice guidelines for the disease, asthma control in Canada remains suboptimal. Poor asthma control contributes to unnecessary morbidity, limitations to daily

activities and impairments in overall quality of life [7]. The pharmacologic agents commonly used for the treatment of asthma can be classified as controllers (medications taken daily on a long-term basis that achieve control primarily through anti-inflammatory effects) and relievers (medications used on an as-needed basis for quick relief of bronchoconstriction and symptoms). Controller medications include ICSs, leukotriene receptor antagonists (LTRAs), LABAs in combination with an ICS, long-acting muscarinic receptor antagonists (LAMAs), and biologic agents including anti-IgE therapy and anti-IL-5 therapy[8]. Reliever medications include rapid-acting inhaled beta$_2$-agonists and inhaled anticholinergics. Allergen-specific immunotherapy may also be considered in most patients with allergic asthma, but must be prescribed by physicians who are adequately trained in the treatment of allergies.

MATERIALS AND METHODS

Fenoterol (FEN) was procured from Prextor India International Surat. Crospovidone, Cross Carmellose Sodium, Sodium starch glycolate and microcrystalline cellulose were used of Qualigens, India. HPMC K4M, HPMC K15M, HPMCK100M, Sodium Bicarbonate and Magnesium stearate and Talc were procured from LOBA ltd.

Preparation of Calibration Curve

Calibration curve of FEN was prepared spectrophotometrically based on UV absorption at λ_{max} 275 nm in 0.1N HCl for the quantitative estimation of drug. Stock solution of 100µg/ml was used to prepare diluents of 2 to 20 µg/ml concentration using 0.1N HCl and absorbance was measured at λ_{max} 275nm by a UV spectrophotometer. Calibration curve of FEN was prepared using concentration vs absorbance data [9].

Precompression characterization of drug excipients blend

Angle of Repose[10-11]

The angle of repose of powdered drugs was measured by funnel method. A funnel was fixed at 2.5cm height on a burette stand and 25g powdered blend of FEN with excipients was passed individually through the funnel making a pile. A circle was drawn across the pile to calculate the radius. Height of the pile was determined using two scale one vertical and one horizontal touching the tip of the pile. The angle of repose was calculated by using equation:

$$\text{Tan } \theta = H / R \text{ (or)} \quad \theta = \tan^{-1}(H / R)$$

Where, H and R are the height and radius of the pile.

Bulk density (BD)[12]

25g of FEN blend was weighed and transferred into 50ml measuring cylinders without tapping during transfer the volume occupied by blend was measured. Bulk density (Db) was calculated by following formula:

$$BD = m/Vo$$

Where, m : Mass of the blend, Vo : Untapped Volume

Tapped density (TD)[12]

25g of FEN blend were weighed and taken into graduated measuring cylinders. Initial volume occupied by drugs blends was noted down. Then cylinder was subjected to 200 taps in tapped density tester according to USP. Tapped density was calculated using the tapped volume and mass of powdered drugs using following formula:

$$TD = m/Vi$$

Where, m : Mass of the blend, Vi : Tapped Volume

Compressibility Index (Carr's index)[12]

The Compressibility Index of the powder blend of FEN was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \text{X } 100$$

Determination of Hausner ratio[12]

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

Hausner Ratio=Tapped density/Bulk density

Preparation of floating pulse release tablets[13-14]

A pulsatile–floating drug delivery system consists of three different parts, a core tablet, containing the active ingredient, an erodible outer shell, and a top cover buoyant layer. Floating pulsatile release tablet of FEN was prepared by compression with different composition ratio of erodible coating (press-coated systems). Rapid release core tablet (RRCT) of FEN was first prepared and optimized. RRCT was then press coated with polymers in two steps to formulate Pulsatile release tablet (PRT). Finally PRT were compressed with effervescent floating layer to prepare floating pulsatile released tablets (FPRT).

Preparation of the Rapid Release Tablet (RRCT)[15]

Core tablets containing Fenoterol were prepared by using direct compression method. All the ingredients were passed through 60# mesh sieve separately and collectively. Different preliminary batches of core tablets were prepared by mixing all ingredients with different superdisintegrants. Powder mixture of FEN, Crospovidone, crosscarmellose sodium, Sodium Starch Glycollate and MCC were dry blended for 20min followed by addition of magnesium stearate. The mixtures were then further blended for 10 min and resultant powder blend was compressed using rotary tablet machine (Cadmach Machinery, Ahmedabad, India) with a 6mm punch and die to obtain the core tablet containing 25mg of FEN. For the above batches disintegration study was conducted from which optimized batches were selected and only that batch was conducted for further study (Table 1).

Preparation of Pulsatile Release tablet (PRT)[16]

The optimized RRCT (F3) was taken as core for the preparation of PRT. For dry coating of F3 formulation 250mg coatings of HPMC K4M, Na CMC, HPMCE14 and Magnesium stearate

were used with two steps: In the first 125mg coatings were filled into the die (11.8mm in diameter), followed by RRCT placed in the center of die, and slightly pressed to fix the coatings around and under the core, and then the rest of the coatings were filled and compressed (Table 2).

Preparation of Floating pulsatile release tablets (FPRT)[16]

On the basis of drug release profile of PRTs best formula composition (F3P9) was selected for the preparation of FPRT (Table 3). Floating tablets were prepared by placing 50% of pulsatile release layer in 11.8 mm die and optimized RRCT was placed on it. Further remaining quantity of pulsatile release layer was added in cavity so as to cover the RRCT and finally pre-compressed it with lower compression pressure (hardness, 3-4 kg/cm^2) by using single punch tablet machine. The weighed amount (100 mg) of floating layer powder composition was kept on pre-compressed tablet (PRT) in die, and then finally compressed it to give certain hardness (6-7 Kg/cm^2). The total weight of each FPRT tablet was adjusted to 400mg.

Table 1: Composition of Rapid release core tablet of FEN

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fenoterol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Crospovidone	3.0	4.0	**5.0**	-	-	-	-	-	-
Cross Carmellose Sodium	-	-	**-**	3.0	4.0	5.0	-	-	-
Sodium starch glycolate	-	-	**-**	-	-	-	3.0	4.0	5.0
MCC	89 .5	88.5	**87.5**	89 .5	88.5	87.5	89 .5	88.5	87.5
Magnesium stearate	4.0	4.0	**4.0**	4.0	4.0	4.0	4.0	4.0	4.0
Talc	1.0	1.0	**1.0**	1.0	1.0	1.0	1.0	1.0	1.0
Total Tablet weight	100	100	**100**	100	100	100	100	100	100

Table 2: Composition of Pulsatile release tablets

Ingredients (mg)	P1	P2	P3	P4	P5	P6	P7	P8	P9
HPMC K4M	90	100	110	-	-	-	-	-	**-**
HPMC K15M	-	-	-	90	100	110	-	-	**-**
HPMCK100M	-	-	-	-	-	-	90	100	**110**
MCC	105	95	85	105	95	85	105	95	**85**
Magnesium stearate	5	5	5	5	5	5	5	5	**5**
Total Tablet weight	200	200	200	200	200	200	200	200	**200**

Table 3: Compositions of the Buoyant Layer

Ingredients (mg)	N1	N2	N3
HPMC E15LV	40	**50**	60
Sodium Bicarbonate	20	**20**	20
Citric acid	10	**10**	10
Lactose	30	**20**	10
Total weight	100	**100**	100

Evaluation of floating pulsatile release tablet

Hardness (Kg/cm^2) of RRCT and FPRTs were determined by Monsanto hardness tester. Friability is the measure of tablet strength. RRCT and FPRT formulations (20) were weighed and placed in the Roche Friabillator that revolves at 25 rpm for 4 minutes dropping the from a distance of six inches with each revolution. After operation the tablets were de-dusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable [17]. The % friability was then calculated by the following formula:

$$F = \frac{\text{Initial Weight - Final weight}}{\text{Initial weight}} \text{ X } 100$$

FPRT formulations (20) were individually weighed, calculated the average weight, and compared the individual tablet weights to the average. The maximum percentage difference allowed is 5% for average weight of tablets more than 250mg. Total 10 tablets were weighed and powder equivalent to 2.5 mg of FEN was weighed and dissolved in 0.1N HCl then filtered through Whatman filter paper. Solution was analysed for FEN content by UV Spectrophotometer at 275 nm using 0.1N HCl as blank[19-20].

USP disintegration test apparatus was used to determine the disintegration time of RRCT formulation. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing 0.1N HCl at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted [21]. Floating time of the prepared formulations were determined using USP paddle apparatus at a speed of 50 rpm in 900ml of 0.1N HCl solution at 37 ± 0.2^0c for 24 hours. The time during which the dosage form remains buoyant (floating duration) was measured [22].

Dissolution studies on PRT & FPRT tablet of FEN was performed under gastric conditions. Test was performed using the USP dissolution apparatus type II at 50 rpm. A tablet containing 2.5mg of FEN was placed in the dissolution vessel containing 900mL of 0.1N HCl maintained at 37±0.5^{0}C. At predefined time intervals, samples from the dissolution medium were withdrawn, filtered and concentration of FEN was determined spectrophotometrically at λ_{max}275nm [23].

Stability studies were performed to determine the changes on the final formulation at different storage conditions. In present study the selected formulation (F3P9N2) exposure up to 3 months stability studies as per ICH guidelines which recommend a temperature of 40±2^{0}C, a relative humidity of 75±5% and period of 3 months for accelerated stability studies. However, the stability was also assessed at at 25±2^{0}C with 60±5% relative humidity. The sampling time was kept at 1, 2 and 3 months. The studies were performed using stability chamber (Thermo Lab, Mumbai). Changes in the appearance and drug content of the stored films were investigated during the period and after 3 month [24].

RESULTS AND DISCUSSION

Calibration curve was prepared in 0.1N HCl at 275nm and linearly regressed. The correlation coefficient for standard curves was found to be very near to one which indicates good co-linear correlation between concentration 2-10 µg/ml (Table 4 and Fig. 1). Hence, drugs are following Beer Lambert Law in the above range (Table 6.5).

Table 4:Calibration curve of FEN at 275nm

Concentration (µg/ml)	2	4	6	8	10
Absorbance	0.0912	0.1878	0.2696	0.3564	0.4524

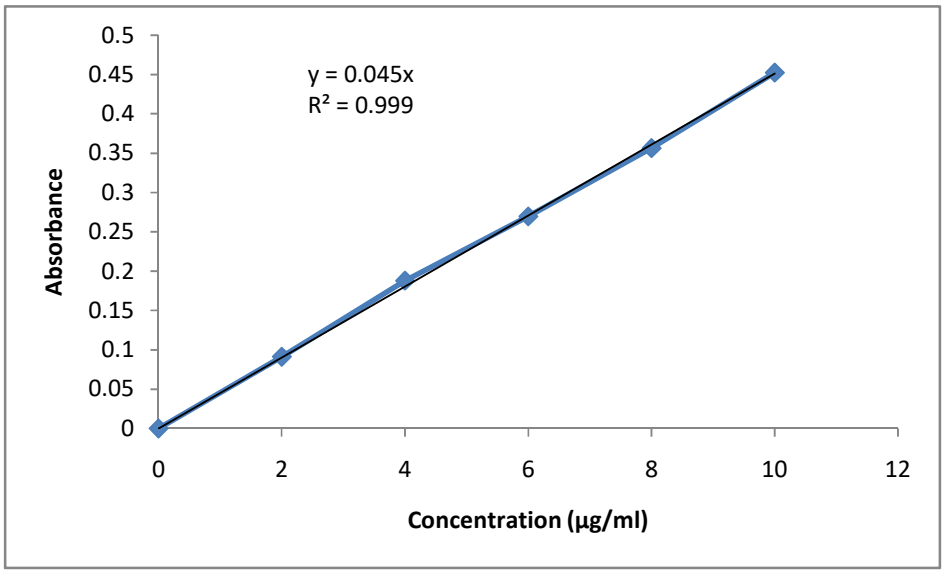

Fig. 1: Calibration curve of FEN at 275 nm

Core tablet (RRCT) of FEN was prepared and evaluated for various parameters. On the basis of different studies F3 formula for core tablet was selected for further studies. Pulsatile release tablets containing F3 RRCT was evaluated for hardness, friability, weight variation and in vitro drug release. Formulation P9 was found to be most suitable to include in final formulation of FPRT.

Precompression evaluations were done to ensure the flow properties of the powder blend. The powder blend's good flow properties will yield the tablets of desired quality and ease the tableting process. The bulk density of all formulations ranges from 0.36g/cm^3 to 0.45g/cm^3. The tapped density of all the formulations ranges from 0.45g/cm^3 to 0.56g/cm^3. The angle of repose of all formulations was found in a range of 25˚.5' to 29˚.6'. It was evident from the results that the powder blends of all formulations posses' good flow. The compressibility index of all the formulations ranges from 8.69 to 30.35. The Hausner's ratio for powder blends of all formulations ranges from 1.09 to 1.43. It was observed from the results that the powder blends of all formulations have good flow properties except for formulations (F1, F2 and F7) (Table 5, 6 & 7).

Table 5: Pre-compression characterization of RRCT blend

Formula Code	PARAMETERS				
	Angle of Repose (θ)	BD (g/ml)	TD (g/ml)	CI (%)	HR
F-1	28.2	0.36	0.49	26.53	1.36
F-2	25.5	0.39	0.56	30.35	1.43
F-3	28.1	0.39	0.48	18.75	1.23
F-4	29.6	0.42	0.46	8.69	1.09
F-5	25.7	0.4	0.46	13.04	1.15
F-6	27.2	0.38	0.45	15.55	1.18
F-7	27.1	0.41	0.53	22.64	1.29
F-8	27.8	0.39	0.46	15.21	1.17
F-9	27.4	0.45	0.54	16.66	1.2

Table 6: Pre-compression characterization of PRT blend

Formula Code	PARAMETERS				
	Angle of Repose (θ)	BD (g/ml)	TD (g/ml)	CI (%)	HR
P-1	29.6	0.42	0.46	8.69	1.09
P-2	25.7	0.39	0.56	30.35	1.43
P-3	27.2	0.38	0.45	15.55	1.18
P-4	27.1	0.41	0.53	22.64	1.29
P-5	27.8	0.39	0.46	15.21	1.17
P-6	27.4	0.45	0.54	16.66	1.2
P-7	25.4	0.38	0.45	15.55	1.18
P-8	26.3	0.39	0.46	15.21	1.17
P-9	26.1	0.38	0.47	19.14	1.23

Table 7: Pre-compression characterization of buoyant layer blend

Formula Code	PARAMETERS				
	Angle of Repose (θ)	BD (g/ml)	TD (g/ml)	CI (%)	HR
N-1	28.2	0.36	0.49	26.53	1.36
N-2	25.5	0.40	0.46	13.04	1.15
N-3	28.1	0.39	0.48	18.75	1.23

The tablets obtained after compression were evaluated on various parameters to determine their quality and to ensure that the resultant product meets all necessary criteria's required for the fast dissolving tablets. The hardness for tablets of all the formulations was found to be less than 3 kg/cm^2. Friability below 1% was an indication of good mechanical resistance. The results indicate that the friability for tablets of all formulations was below 1%and hence passes the test. The weight variation for tablets of all formulations was found to be within the range of 7.5%. The results indicate that all tablets of each formulation were of uniform weight (Table 8 & 9).

The thickness for RRCT tablets of all formulations was found to be 1.6 to 2.2mm. The thickness for FPRT tablets of all formulations was found to be 4.0 to 4.2mm. It was observed that the disintegration time for formulation varied from 21 to 44 second. It was observed that when crosspovidon was used as disintegrates, tablet was disintegrate within short time due to easy and high swelling ability of crosspovidon as compared to CCS and SSG. It is observed that

disintegration time of tablet decreased with increased in concentration of crosspovidon, CCS and SSG (Table 9).

The drug contents for tablets of all the formulations ranges from 95.46% to 98.84%. The drug content was analyzed at 275 nm (Table 9). Floating behavior of tablet depends on added fillers in buoyant layer. Tablets containing lactose and 50% HPMC E15LV floated earlier than tablets prepared with the lesser or higher concentrations of HPMC E15LV. In addition, lactose has higher water solubility, resulting in faster water uptake of medium into tablet. N2 formulation was used for further investigation (Table 10).

Table 8: Post-compression evaluation of Rapid release core tablet

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (Kg/cm$^{2)}$	2.8	2.7	**2.8**	3.1	2.9	2.9	3	2.8	2.7
(%) Weight variation	2.2	2.2	**0.8**	2.6	1.5	1.8	0.8	1.4	2.5
Thickness (mm)	1.6	2	**1.8**	2.2	2	2	1.9	1.8	2
Friability (%)	0.68	0.66	**0.62**	0.67	0.66	0.62	0.68	0.65	0.63
% Drug Content	95.2	98.84	**98.84**	98.15	98.02	98.26	97.58	98.18	98.37
Disintegration Time (Sec)	36	26	**21**	44	31	24	30	28	25

Table 9: Post compression characterization of PRT

Parameter	P1	P2	P3	P4	P5	P6	P7	P8	P9
Hardness (Kg/cm^2)	3.4	3.4	3.2	3.5	3.8	4.4	3.2	3.6	**4.3**
Friability (%)	0.4	0.37	0.35	0.46	0.38	0.32	0.45	0.38	**0.31**
Uniformity of weight (mg)	394	398	398	402	398	398	399	404	**399**

Table 10: Post compression evaluation of FPRT

Parameter	N1	N2	N3
Hardness (Kg/cm^2)	6.6	**6.8**	7.2
Thickness (mm)	4	**4.2**	4.2
Friability (%)	0.72	**0.54**	0.65
Uniformity of weight (mg)	496	**498**	496
Floating Lag Time (sec)	54	**26**	45
Floating Time (hr)	10	**12**	17

In vitro drug release from FPRTs was carried out in 0.1N HCl. Formulation P9 was found to be most suitable to include in final formulation of FPRT on the basis of 98.28% drug release in 12hr. It was observed that HPMC K100M shows the lag time of 4 hr then follow the sigmoidal release pattern with 100% drug release at 10hr. As the concentration of the HPMC K100M coating increases from 140 to 180mg the lag time extended to 4.5 hr and then follow the delayed release profile with the 100 % drug release at the 12 hr. From above discussion it was cleared that HPMC K4M and HPMC K15M cannot be used to develop a successful pulsatile drug delivery system. Only FPRT tablets of optimized batch (F3P9N2) were evaluated for in vitro drug release profile which was found to be 98.15% in 12hr (Table 11 and 12 and Fig 2 & 3).

Table 11: Dissolution study of PRT

Time (hr)	**% Drug Release**								
	P1	P2	P3	P4	P5	P6	P7	P8	**P9**
0.5	0	0	0	0	0	0	0	0	**0**
1	0	0	0	0	0	0	0	0	**0**
2	0	0	0	0	0	0	0	0	**0**
4	6.26	5.42	5.15	6.88	5.3	5.64	5.22	6.84	**2.56**
6	35.86	30.26	27.65	31.35	34.38	28.53	35.37	32.4	**28.58**
8	68.42	76.14	61.36	74.45	70.9	69.54	75.57	71.68	**68.8**
10	99.88	98.65	86.23	99.42	100.3	91.48	95.61	96.52	**90.36**
12			98.68			97.12			**99.85**

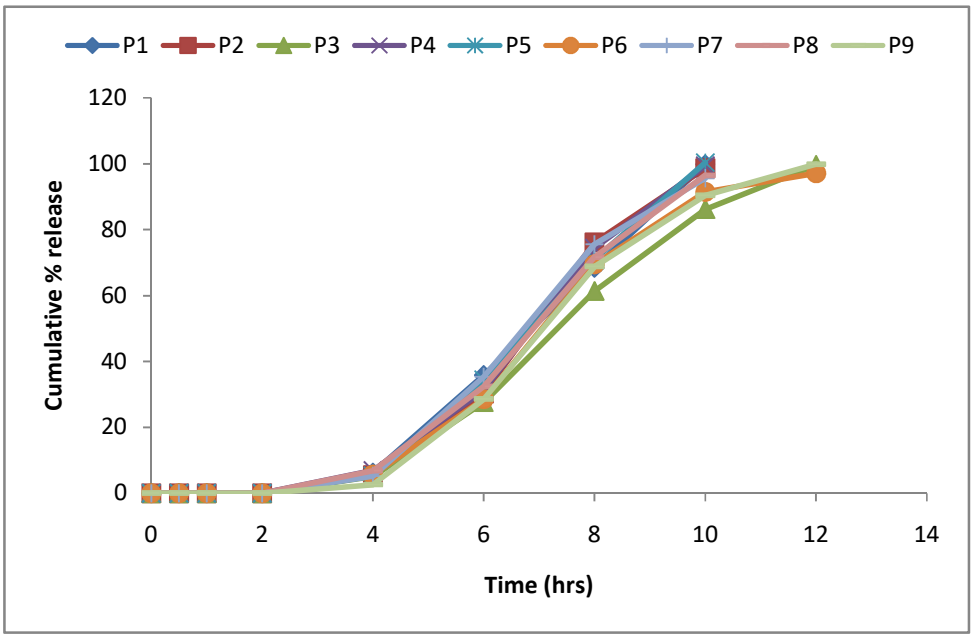

Fig 2: Cumulative % FEN release from Pulsatile release tablets (P1-P9)

Table 12. *In vitro* release profile of optimized floating pulsatile release tablets (F3P9N2)

Time (hr)	0.5	1	2	4	6	8	10	12
Cumulative % drug release	0	0	1.05±0.16	2.56±0.68	30.58±1.82	71.86±3.44	88.36±4.65	97.85±5.28

Value represent mean ± SD (n=3)

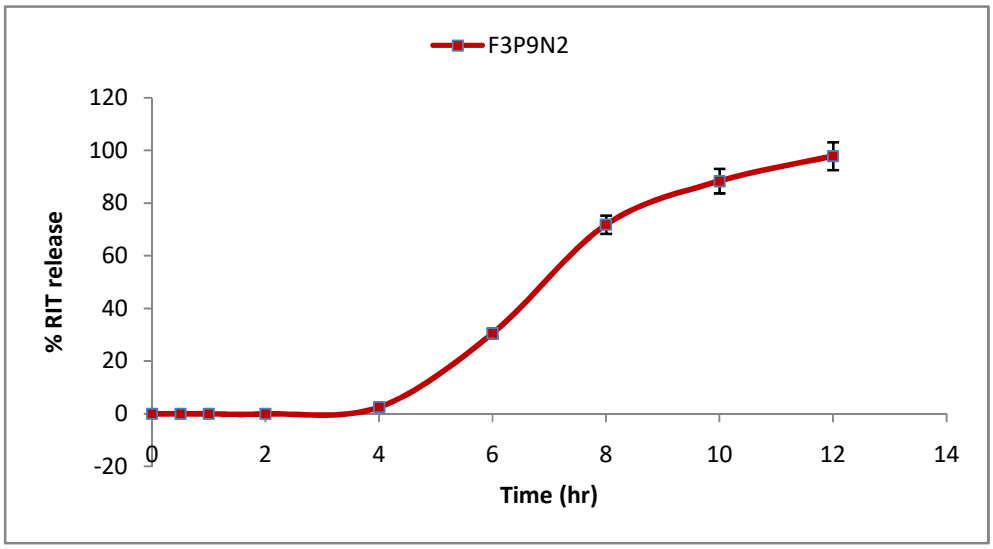

Fig 3: Cumulative % FEN release from floating pulsatile release tablets

It was found that the percent drug content after a period of 3 months for FEN was 99.42±1.3% at 25±2^{0}C & 60±5%. On the other hand it was 99.29±1.6% at 40±2^{0}C & 75±5% (Table 13). Stability studies on final formulation demonstrated its stabile at 25^{O}C and at higher temperature and humidity conditions.

Table 13: Stability studies at different conditions

Storage Conditions	Observations on storage for Drug content (%) (F3P9N2)			
	Initial	1 months	2 months	3 months
25±2^{0}C and 60±5%	100	99.92±4.6	99.76±3.3	99.42±1.3
40±2^{o}C and 75±5%	100	99.82±3.7	99.63±3.1	99.29±1.6

Values are mean± SD (n=3)

CONCLUSION

The present work was based on the floating pulsatile drug delivery of FEN. The core containing crosspovidone disintegrate the tablet within short time due to easy and high water penetration ability of as compared to Cross Carmellose Sodium and Sodium starch glycolate. The PRT containing the buoyant material, such as HPMC E15LV, $NaHCO_3$, and citric acid achieved a satisfactory buoyant force in vitro, whereas the floating onset time was less than 1 min. The pulsatile releasing mechanism of PRT is based on the exploitation of the peculiar interaction between hydrophilic polymeric coating and the aqueous gastrointestinal fluids.

The in vitro release profiles of FEN from pulsatile release tablet prepared using HPMC K100M as retarding polymer are characterized by a predetermined lag time (4 hr), the duration of which depends on the kind and amount of the polymeric layer applied on the cores as well as type of superdisintegrant in core tablet. The developed system offers a simple and novel technique for pulse release of drugs. From the results, it is concluded that the pulsatile release tablet we prepared could achieve a rapid release after lag time of 4hr with the relatively low variability.

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