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Research Article

Formulation and *in vitro* evaluation of floating pulsatile drug delivery system of Atenolol based on coated effervescent core

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ABSTRACT

Present research work attempts to design, formulate and optimize the floating pulsatile drug delivery system (FPPDS) intended to treat nocturnal hypertension. FPPDS was designed based on central reservoir system containing effervescent agent with rupturable coating and a buoyant layer on top of the coated core. This system consists of rapid release core that contains drug with disintegrants, osmogent (sodium chloride) and effervescent agent (sodium bicarbonate and tartaric acid) which was film coated by hydrophobic polymer Ethyl Cellulose(EC) with polyethylene Glycol(PEG) 6000 as a plasticizer for controlling membrane permeability to provide pulsatile drug release with the target lag time of 6 hours. This pulsatile release tablet was further press coated from one side with Sodium bicarbonate, HPMCK100 and Carbopol to produce buoyant layer for the high floating duration time and less floating lag time. Atenolol being absorbed in upper GI tract and used to treat chronological cardiovascular disease was used as a model drug. Total of 39 formulations were formulated and dissolution test were performed using USP type II at 50 RPM for 8 hours in 0.1N HCl. Results revealed that both coating composition were significant factors in affecting pulsatile lag time and cumulative percentage drug release. Similarly, HPMCK100 and sodium bicarbonate showed the significant role for determining floating lag time.

INTRODUCTION

All living organisms' physiological function follows a rhythm with varying frequencies that may range from seconds to seasons. Circadian rhythms are controlled by an inherited master clock network composed of the paired supra chiasmatic nuclei (SCN) that are situated in the hypothalamus and the pineal gland(Kalsbeek et al., 2006). The rhythmic activities of specific, so-called, clock genes, like per1, per2, per3, comprise the central timekeeping mechanism. Depending upon the length of the cycles, the mechanical rhythms are classified as circadian, ultradian,

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infradian, circannual and seasonal (Shidhaye, Lotlikar, Ghule, Phutane, & Kadam, 2010).

Pulsatile Drug Delivery Systems (PDDS) are designed according to the circadian rhythm of the body. These systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance and therapeutic efficacy. Pulsatile drug release is such a system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug is released from the device within the lag time.

Floating Drug Delivery System (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. FDDS itself is the most widely used technique for gastro retentive drug delivery system. The techniques used for FDDS are broadly divided as effervescent system (volatile liquid containing system, gas generating system) and non-effervescent system (colloidal gel barrier system, microporous compartment system, multiparticulate floating bead system, microballons system).

MATERIALS AND METHODOLOGY

Materials

Core material: Atenolol (IPCA laboratories), Lactose (fssai), HPMC K100 (DPB India), Crospovidone (Balaji Amines ltd, India), Sodium starch glycolate (Rosswell Industries), Sodium Lauryl Sulphate (Ginopol Godrej, India), Sodium bicarbonate (Ranbaxy laboratories, India), tartaric acid (fisher scientific), sodium chloride (fisher scientific), magnesium stearate (Spar Chem, India), Aerosil (Cobot sunmar ltd, India), Talc (NeelKanth Mine chem,India)

Coating material: Ethyl cellulose (Mehta Medicare Pvt. Ltd, India), PEG 6000 (India Glycols ltd, India) and methylene chloride (Gujraj Alkalis and chemical, India)

Buoyant layer: HPMC K100 (DPB, India), sodium bicarbonate (Ranbaxy laboratories, India), carbopol (Shree chem, India)

Methods of preparation of floating pulsatile drug delivery system (FPDDS)

Preparation of Rapid Release Core Tablet (RRCT) with Osmogent and Effervescent Agent

In order to optimize the rapid release core formulation for burst release, central composite design (CCD) was used taking two variables of two levels of weight. The variables were HPMC K 100 ranging from 10-30% and sodium bicarbonate and tartaric acid combination ranging from 5-25%. A total of 13 experiments named RRCT 1 to RRCT 13 were given by CCD which is given in Table 1

RRCT	Atenolol	Lactose	Crospovidone	HPMCK100	SSG	Sodium bicarbonate	Tartaric acid	Nacl	SLS	Magnesium stearate	Aerosil	Talc	Total
1	50	56.22	10	40	10	2.52	1.26	5	5	10	4	10	204
2	50	30	10	60	10	6.66	3.34	5	5	10	4	10	204
3	50	35	10	40	10	16.66	8.34	5	5	10	4	10	204
4	50	35	10	40	10	16.66	8.34	5	5	10	4	10	204
5	50	35	10	40	10	16.66	8.34	5	5	10	4	10	204
6	50	6.71	10	68.29	10	16.66	8.34	5	5	10	4	10	204
7	50	35	10	40	10	16.66	8.34	5	5	10	4	10	204
8	50	70	10	20	10	6.66	3.34	5	5	10	4	10	204
9	50	63.28	10	11.72	10	16.66	8.34	5	5	10	4	10	204
10	50	35	10	40	10	16.66	8.34	5	5	10	4	10	204
11	50	0	10	60	10	26.66	13.34	5	5	10	4	10	204

12	50	13.79	10	40	10	30.8	15.41	5	5	10	4	10	204
13	50	40	10	20	10	26.66	13.34	5	5	10	4	10	204
Opt RRCT	50	52.83	10	11.71	10	23.45	11.72	5	5	10	4	10	204

Table 1: Formulation of RRCT with effervescent agent

The formulation RRCT containing atenolol with osmogent and effervescent agent were prepared by direct compression method.

Preparation of the Pulsatile Release Tablet (PRT)

The optimized RRCT was produced and evaluated from Minitab 16 and this optimized RRCT was coated by hydrophobic polymer ethyl cellulose (EC) with channelling agent PEG 6000 to produce pulsatile drug release with lag time of 6 hours. In order to optimize the pulsatile release formulation in terms of predetermined lag time of 6 hrs., again two factors two variables CCD with EC concentration ranging from 2-9 mg per tab that is (0.98-4.41%)and PEG6000 value outlined range from 1-4 mg per tab (0.5- 1.96%) was used. A total of 13 experiments named PRT 1 to PRT 13 were given by CCD using Minitab 16 which is given in Table 2.

Experiment Number	Ethyl cellulose (mg per tab)	PEG 6000 (mg per tab)
PRT1	5.5	2.5
PRT2	5.5	0.38
PRT3	0.55	2.5
PRT4	2	4
PRT5	9	4
PRT6	5.5	2.5
PRT7	2	1
PRT8	5.5	4.62
PRT9	10.45	2.5
PRT10	9	1
PRT11	5.5	2.5
PRT12	5.5	2.5
PRT13	5.5	2.5

Table 2: Formulation of coating for pulsatile release

Preparation of the Floating Pulsatile Release Tablet (FPRT)

The floating-pulsatile release tablet was designed to comprise an optimized pulsatile release tablet with a top cover containing a buoyant layer. The buoyant layer included the different concentration of HPMCK100 M and sodium bicarbonate along with fixed concentration of Carbopol.

In order to evaluate and optimized floating lag time and floating time, two factors two variables CCD with HPMCK100 10-30 mg per tab and PEG6000 value outlined range from 5-30 mg was used. A total of 13 experiments named FPRT 1 to FPRT 13 were given by CCD using Minitab 16 which is given in Table 3.

Formulation Code	HPMCK100(mg)	Sodium Bicarbonate (mg)	Carbopol (mg)	Total (mg)
FPRT1	20	17	20	57.5
FPRT2	5.85	17.5	20	43.35
FPRT3	20	35.18	20	75.18
FPRT4	20	17.5	20	57.5
FPRT5	20	17.5	20	57.5
FPRT6	30	30	20	80
FPRT7	20	17.5	20	57.5
FPRT8	30	5	20	55
FPRT9	34.14	17.5	20	71.64
FPRT10	20	17.5	20	57.5
FPRT11	10	5	20	35
FPRT12	20	0	20	40

FPRT13	10	30	20	60

Table 3: Formulation of buoyancy layer

All the floating bi-layer tablets were prepared by using modified direct compression technique.

Evaluation of prepared dosage form

Analytical method development and validation

Analytical method was developed and validated by UV Spectroscopy method, for the quantification of Atenolol for floating pulsatile drug delivery system based on validation parameters linearity, specificity, accuracy, precision, robustness, limit of quantification and limit of detection as per ICH Harmonised Tripartite Guideline("ICH guidelines for Analytical Method Validation,").

Evaluation of Rapid Release Core Tablet (RRCT)

The tablets of each experiment were evaluated for their physicochemical parameters like weight variation, hardness, friability, average diameter, average thickness, assay and dissolution test.

Compatibility study of Atenolol with excipients

The compatibility study was carried by using FT-IR (Balpande, Raut, Umekar, & Kotagale, 2013; Chidambaram & Krishnasamy, 2014). FT-IR spectra were recorded on a FTIR spectroscopy using the instrument Agilent Cary 630 in the frequency range of 400-4000 cm^{-1}.

Weight variation

20 tablets were randomly sampled and their individual weight was taken in digital balance for determination of weight variation. Then average weight and its standard deviation were calculated.

Thickness and Diameter

10 tablets of each formulation were randomly sampled and their individual thickness and diameter was taken using digital vernier calliper for the determination of tablet thickness and diameter. The average thickness and average diameter and its respective standard deviation were calculated.

Hardness

For the determination of tablet hardness, 10 tablets were randomly sampled and their individual hardness was taken using digital hardness tester. The average hardness and its standard and its standard deviation were calculated.

Friability

For the determination of the friability, 20 tablets were randomly sampled and weight taken. These tablets were loaded in the friability tester and rotated for 100 revolutions. The weight of the tablet was retaken and friability was calculated.

Disintegration time test

In vitro disintegration test was carried out at 37 ± 2 ^{0}C in 900 ml of 0.1N HCl.

Assay

The assay of Atenolol tablet was determined as per BP2007.

***In vitro* Dissolution Test**

Dissolution study was carried out in USP dissolution apparatus II at 37 ± 0.5^o C and 50 rpm using 900 ml of 0.1 N HCL for 1 hour. 10 ml of sample was withdrawn at 10 minutes, 30 minutes and finally at 1 hour. Equal volume of fresh medium was replaced into the dissolution jar after each sampling. The withdrawn sample was subjected to filter and the filtered sample was then used for quantitative analysis using UV spectrophotometer.

Evaluation of Pulsatile Release Tablet (PRT)

Physicochemical characteristics of PRT

For PRT, physicochemical characteristics were evaluated for Average weight, Average thickness, Average diameter and Average Assay similarly as for RRCT.

Swelling index (water uptake study)

The percentage of water uptake of pulsatile release tablets was determined in 100ml of 0.1 N HCL (dissolution medium) maintained at 37^{0}C temperature placed in a beaker(PandeySharmila, 2010). At predetermined time intervals of half an

hour, the tablets were removed from dissolution medium, carefully blotted with tissue paper to remove surface water weighed and then placed back in the dissolution medium until the coating of the tablet rupture.

The swelling index was calculated as follows:

$$\text{Swelling Index} = \frac{weight\ of\ tablet\ at\ time\ t(Wt) - weight\ of\ dry\ tablet(Wo)}{weight\ of\ dry\ tablet(Wo)} * 100$$

***In vitro* dissolution test of PRT**

Dissolution study for PRT was carried out in USP dissolution apparatus II at 37 ± 0.5° C and 50 rpm using 900 ml of 0.1 N HCl for 8 hours. 10 ml of sample was withdrawn at an interval of an hour and equal volume of fresh medium was replaced into the dissolution jar after each sampling. The withdrawn sample was subjected to filter and the filtered sample was then used for quantitative analysis using UV spectrophotometer at 274 nm wavelength.

Evaluation of Floating Pulsatile Release Tablet (FPRT)

Physicochemical characteristics of FPRT

For FPRT, physicochemical characteristics were evaluated for Average weight, Average thickness, Average diameter and Average Assay similarly as for RRCT.

Floating time and Floating lag time:

The floating lag time (the period between placing FPRT in the medium and buoyancy) and floating time that is duration of FPRT in dissolution medium were determined by visual observation.

***In vitro* dissolution test**

Dissolution study for FPRT was carried out in USP dissolution apparatus II at 37 ± 0.5° C and 50 rpm using 900 ml of 0.1 N HCL for 8 hours. 10 ml of sample was withdrawn at an interval of an hour and equal volume of fresh medium was replaced into the dissolution jar after each sampling. The withdrawn sample was subjected to filter and the filtered sample was then used for quantitative analysis using UV spectrophotometer at 274 nm wavelength.

Data Analysis

Central composite Design, Response Surface Methodology and Statistical Analysis

Two factors two variable CCD and response surface methodology were used to investigate the influence of factors.

For PRT, the drug release profiles in terms of achieving lag time with different concentration of EC and channelling agent PEG6000 in the coating formulations were analyzed with the hypothesis that there is no significant effect in lag time with varying level of EC and PEG6000 in the coating solution, at 95% of confidence interval. The obtained lag time with various levels of EC and PEG 6000 were analysed by simple analysis of variance (one-way ANOVA).

Similarly, for FPRT, the floating lag time with different concentration of HPMCK100 and sodium Bicarbonate for the buoyant layer were analyzed with the hypothesis that there is no significant effect in floating lag time with varying level of HPMCK100 and sodium Bicarbonate in the buoyant layer, at 95% of confidence interval. The obtained lag time with various level of HPMCK100 and sodium Bicarbonate were analysed by simple analysis of variance (one-way ANOVA).

RESULT AND DISCUSSION

Evaluation of physiochemical properties of RRCT

Weight variation, hardness, thickness, diameter, friability and drug content of core tablets were determined for RRCT which is summarized in Annex I. The weight variation of all the formulations of RRCT was ranged within ± 7.5% of respective average weights. Average thickness, Average diameter, average hardness and average friability of all 13 RRCT formulation was 3.44 mm, 8.25mm, 4.27 kg/cm^2 and 0.37% respectively.

Compatibility study of drug-excipients

IR spectra of pure drug Atenolol and polymers HPMCK100 and Sodium Bicarbonate and their physical mixture in the ratio of 1:1 (Drug: Polymer) were observed after storing at 50°c in hot air oven for 4 weeks**.** IR Spectra was scanned and was overlaid upon the initial fresh samples which showed that the drug polymer mixture to be stable as shown in figure 1 and figure 2:

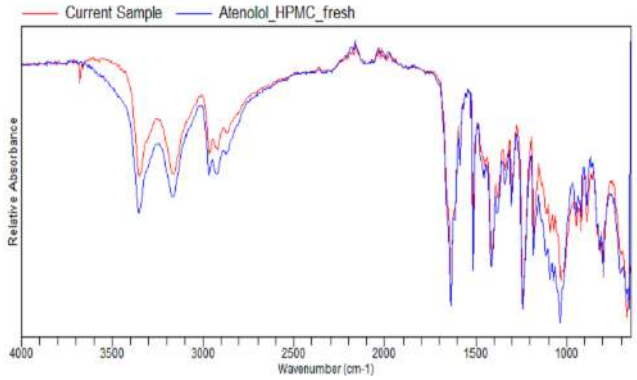

Figure 1: Overlaid spectra of 1:1 mixture of Atenolol and HPMC K 100 after charging in Oven for 1 month

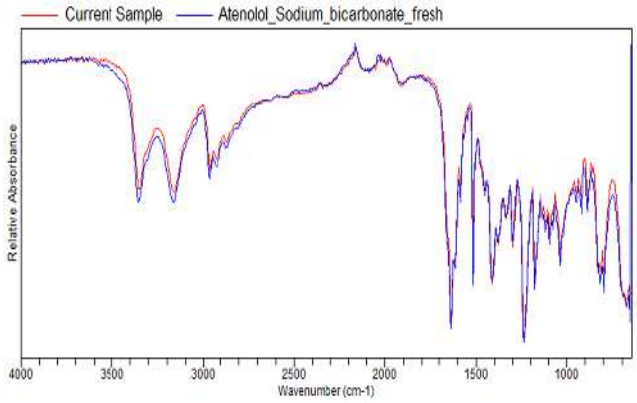

Figure 2: Overlaid spectra of 1:1 mixture of Atenolol and Sodium Bicarbonate after charging in Oven for 1 month

In vitro drug release of RRCT

In vitro drug release test of RRCT was carried out in 0.1 N HCL for 1 hour.

Effect of HPMCK 100 and Sodium bicarbonate: tartaric acid

The dissolution profiles of formulation of Rapid Release Core Tablet (RRCT) are shown in figure 3.

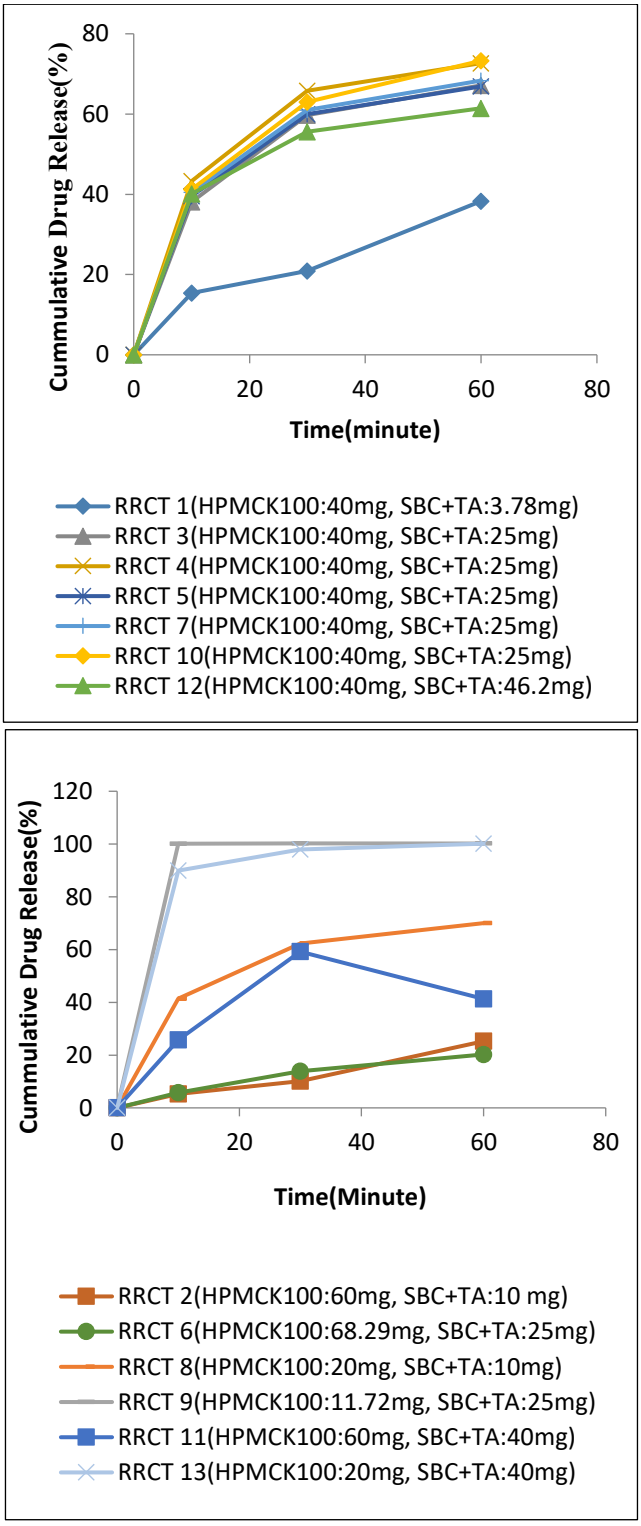

Figure 3: Effect of varying concentration of HPMC and Effervescent agent on drug release of RRCT

The result shows that increase in HPMC K100 decrease the drug release whereas increase in effervescent agent increase in drug release as in Krogel et al. (2009) research for chlorpheniramine

malaeate(Krögel & Bodmeier, 1999). In contact with water, HPMC K 100 form a viscous gel layer that will increase the diffusion path length but decrease the surface tension of the dissolution medium resulting in decrease of drug release(P. K. SHARMA, 2010). In contact with the dissolution medium, effervescent agent (sodium bicarbonate and tartaric acid) generate CO_2, which accumulates under the HPMC gel and results in its expansion and cause release of drug(Krögel & Bodmeier, 1999).

Central composite Design, Response Surface Methodology and Statistical Analysis of RRCT

Two factors two levels full factorial CCD with 4-star points and a central point with four replications resulting in a total of 13 experiments were used to optimize the coating formulation. Minitab 16 was used to find out the quadratic second order relationship mathematical model (equation 1) for drug release at 30 minutes with the intention of 100% drug release within 30 minutes for burst release after pulsatile coating:

Desired Drug release at 30 minutes = $-1.61X + 2.75Y - 0.0000075X^2 - 0.04176Y^2 + 0.01123XY + 72.34$

Where X= quantity of HPMC K100 (mg) per tab, Y= quantity of SBC+ TA (mg) per tab

Minitab 16 gave that optimum value for HPMC K 100 is 11.71mg/tab and Effervescent agent is 34.64 mg/tab for desired 100% drug release at 30 minutes as in figure 4. The optimized RRCT showed the drug release of 99.67% within 30 minute which was as expected. So, this optimized formulation was used for further study for Floating Pulsatile Drug Release system.

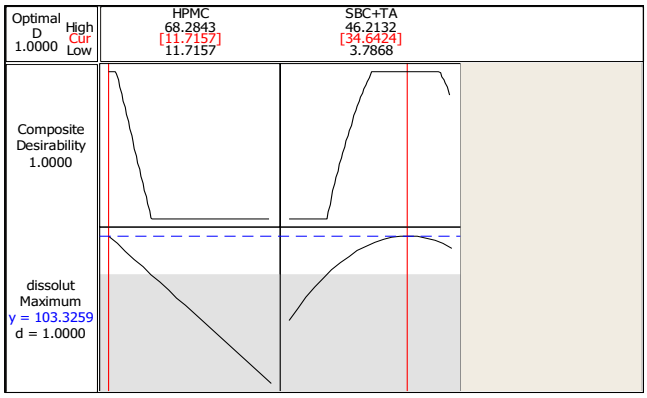

Figure 4: Optimization plot of rapid release core tablet

Evaluation of physiochemical properties of PRT

Weight variation, thickness, diameter and assay were determined for PRT which is summarized in Annex IV. The weight variation of all the formulations of PRT was ranged within ± 7.5% of respective average weights.

Swelling index study

Swelling index studies of all the 13-different pulsatile coated formulation were studied. It was observed that the tablet started to rupture from the edges of the tablet as similar to that observed during dissolution studies as in figure 5.

Figure 5: Pulsatile release tablet (PRT) after drug bursting and drug release

The result showed that higher ethyl cellulose levels retard the swelling index but increase the bursting time, irrespective of concentration of the PEG 6000 in the coating solution. This could be due to higher mechanical strength of the thicker coating, which requires a higher degree of swelling

(water uptake) for rupturing (Sungthongjeen, Sriamornsak, & Puttipipatkhachorn, 2008).

Thus, this study shows that the lag time of drug release from the pulsatile tablet can be increased by increasing the concentration or thickness of EC as it retards the water uptake due to its hydrophobic nature.

***In vitro* drug release of PRT**

In vitro dissolution test was carried out for all 13 formulations of Ethyl cellulose coated pulsatile release tablet in 0.1 N HCl for 8 hours. These 13 formulations were outlined by two factors two level CCD for optimizing the coating composition with independent variables that is EC and PEG 6000 and response on lag time (time at which burst release was seen).

Effect of varying concentration of EC and PEG 6000 on lag time

The results of the dissolution study of the experiments PRT 2,3,4,7,8,9 and 10 are given in figure 6 And the result of other formulation (PRT 1,5,6,11,12, and 13) showing desired pulsatile effect are given in figure 7.

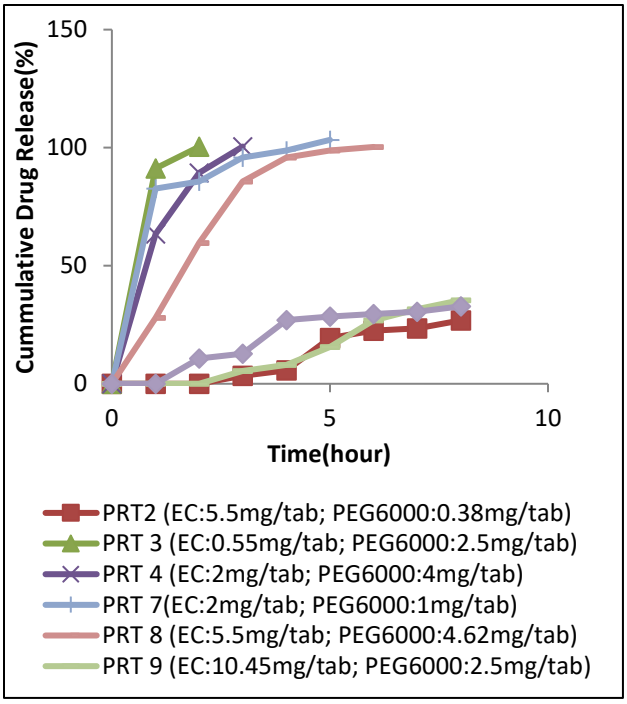

Figure 7: Dissolution profiles of experiments that showed pulsatile release near desired lag time

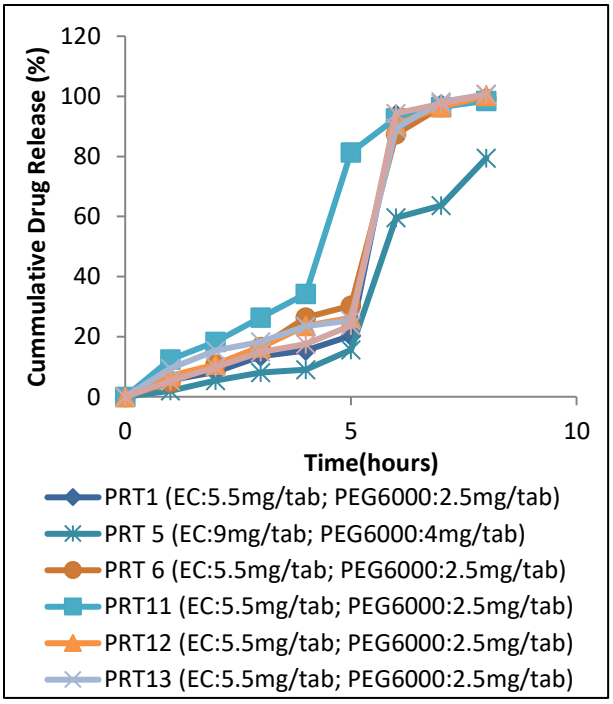

Figure 6: Dissolution profile of varying concentration of EC and PEG 6000 on PRT

All the formulation except the formulation PRT 3 as it had very less EC coating per tab; rupture from edges. When a PRT tablet is placed in dissolution media, the hydrophobic EC remain intact and does not dissolve whereas water soluble channelling agent PEG6000 gets dissolved by the media resulting in pore formation in uniform EC coating. From this pore, dissolution medium diffuses inside the inner core tablet. The core tablet contains osmogent Sodium Chloride, so on solvation of sodium chloride, creates a constant osmotic pressure difference between the core contents and the external environment to facilitate in imbibing the dissolution medium inside the core tablet. In the core tablet, the medium cause effervescent agent sodium bicarbonate and tartaric acid react, liberating CO_2. This gas creates a pressure for the outer coating of EC too rupture and drug release

instantly through the ruptured part. On hydration, all the disintegrant in tablet core swells and aids in increasing inner pressure. Finally, the release of the drug was completed, leaving the evacuated coating membrane(Krögel & Bodmeier, 1999; Rowe & Sheskey, 2009).

Since the four-identical formulation PRT 1,6, 12 and 13 showed the burst release with lag time of 6 hours, their coatingformulation EC: 5.5mg/tab and PEG 6000: 2.5 mg/tab was selected as optimized PRT for further study of floating character and floating pulsatile drug delivery system.

Central composite Design, Response Surface Methodology and Statistical Analysis of PRT

Two factors two levels full factorial CCD with 4-star points and a central point with one replication resulting in a total of 13 experiments were used to optimize the coating formulation. Minitab 16 was used to find out the quadratic second order relationship mathematical model (equation 2):

Z (lag time) = 1.5 X +1.82Y-0.1X^2 – 0.48 Y^2 + 0.1XY-2.0

Where X = concentration of EC mg/tab; Y = concentration of PEG 6000 mg/tab

If the values of independent variables that is X and Y are fed in equation 2, predicted value of the response (lag time) are obtained, which are shown in Figure 8:

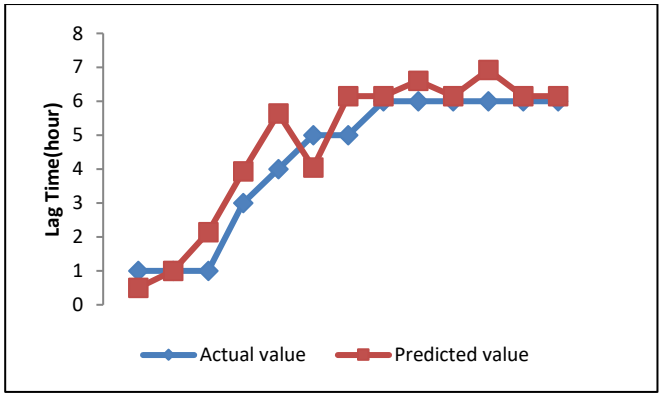

Figure 8: correlation of actual and predicted values

The correlation between the actual experimental response and the predicted response was analyzed using the regression equation and R^2 value was obtained as 0.90, which indicates that equation 2 is not so good model for the design which might be due to lack of robustness of the coating process.

The dissolution profile of optimized coating formulation (optimized PRT) is given in figure 9.

The dissolution profile of the optimised PRT showed that the dosage form was intact within 4th hour of the study then a crack gradually developed at the edges of the tablets with minimal release of the drug from the rupture edge till the 5th hour and at the end of 6 hour there was burst release of the drug resulting in more than 90% drug release in 6th hour. The predicted value from equation 2 is 6.45 hours.

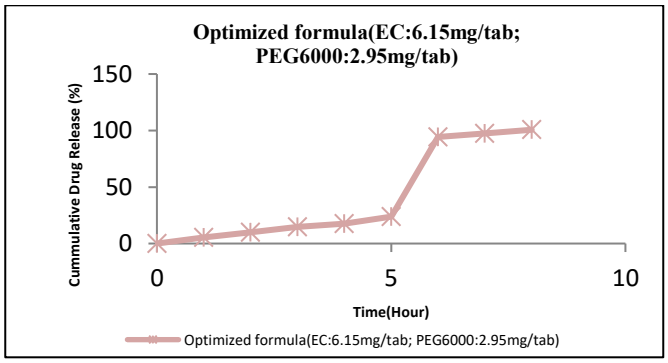

Figure 9: Dissolution profile of optimized coating formulation

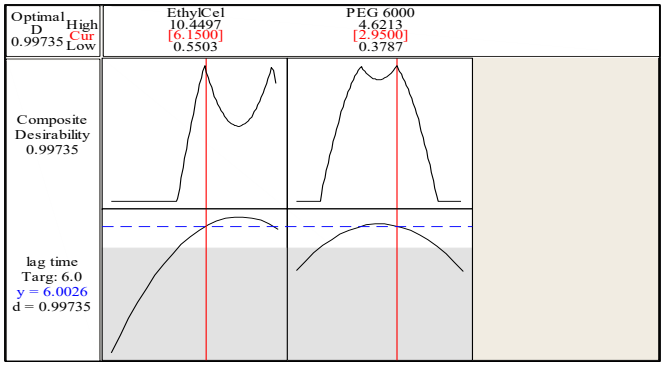

Figure 10: Optimization plot of pulsatile release tablet

The composite desirability of the optimum PRT is 0.99735 as shown in figure 10.

RESULT AND DISCUSION OF FPRT

Evaluation of physiochemical properties of FPRT

Weight variation, thickness, diameter, hardness and assay were determined for PRT. The weight variation of all the formulations of PRT was

ranged within ± 7.5% of respective average weights. The average hardness of all 13 formulations was 7.72 kg/cm^2.

***In vitro* drug release of FPRT**

In vitro dissolution test was carried out for all formulated floating pulsatile release tablet (FPRT) for 8 hours in 0.1N HCl for the evaluation of both floating and pulsatile drug release pattern. The dissolution results are summarized in Table 4.

Time (hrs)	FPRT 1	FPRT 2	FPRT 3	FPRT 4	FPRT 5	FPRT 6	FPRT 7	FPRT 8	FPRT 9	FPRT 10	FPRT 11	FPRT 12	FPRT 13	Optimized FPRT
1	6.23	5.44	4.75	5.19	6.22	6.89	5.49	6.26	5.33	4.88	8.01	4.74	7.45	5.34
2	9.41	8.55	8.2	9.48	9.89	10.54	9.62	10.74	9.26	8.38	12.31	7.89	11.51	8.72
3	12.26	11.72	12.31	14.61	14.18	13.7	13.5	14.09	12.37	14.11	15.42	12.19	16.22	14.35
4	17.3	18.41	17.12	18.3	17.62	19.22	17.8	19.64	17.54	18.89	20.7	18.06	20.01	18.01
5	24.89	25.47	24.87	25.31	23.47	25.08	22.72	26.13	24.38	24.22	26.03	23.41	25.93	23.22
6	91.45	93.82	90.27	92.61	89.54	92.18	88.63	92.71	91.85	90.63	93.52	90.26	91.77	92.49
7	98.32	100.4	97.26	99.1	97.4	100.2	95.38	99.19	98.71	97.61	99.61	98.36	98.55	97.38
8	100.7	100.5	100.2	101.3	100.1	100.3	99.61	101.1	100.3	99.87	100.2	100.4	100.6	99.58

Table 4: Dissolution studies of FPRT

Effect of increase in Hardness on lag time of pulsatile drug release:

The average hardness of all 13 formulation of PRT was about 4.27 kg/cm^2 whereas average hardness of 13 formulation of FPRT was 7.72 kg/cm^2. The increase in hardness was due to double compression of PRT for the press coated buoyant layer for floating effect. Interestingly increase in hardness results in the lag time of 6 hour of all FPRT; which was the desired lag time unlike previous same formulation PRT which showed lag time of 5 hours too.

This might be due to lesser porosity or increase in compactness of EC coating in tablet with higher hardness as it disturbs the water penetration and hindering in effervescent reaction for burst release causing delay in drug release(Krögel & Bodmeier, 1999).

Floating time and floating lag time

Figure 11: Floating pulsatile release tablet during dissolution

All 13-formulation showed similar drug release pattern and the EC coating rupture from edges, it can be concluded that the buoyant layer does not affect the drug release. It plays only significant role in floating time and floating lag time.

Although there is variation in floating lag time (The time taken for dosage form to emerge on surface of medium), there is no significant difference in floating time (duration of floating of tablet). All the formulation floating time exceed over 8 hours which is as desired result. This might be due to effect of buoyant layer as well as the CO_2 producing effervescent agent in core tablet that

makes it lighter and of less density(N. Sharma, Agarwal, Gupta, & Khinchi, 2011).

Central composite Design, Response Surface Methodolgy and Statistical Analysis of FPRT

Two factors two levels full factorial CCD with 4-star points and a central point with one replication resulting in a total of 13 experiments were used to optimize the minimum floating lag time. Minitab 16 was used to find out the quadratic second order relationship mathematical model (equation 3):

Y (Floating lag time): $1.49X - 0.45 Y - 0.022X^2 - 0.000079 Y^2 + 0.0065 XY + 0.67$…Equation 3

Where X = concentration of HPMC K 100(mg/tab), Y = concentration of Sodium bicarbonate (mg/tab)

From above Equation we can figure that increasing the concentration of sodium bicarbonate decreases lag time whereas increasing concentration of HPMC increases the floating lag time.

If the values of independent variables that is X and Y are fed in equation 3, predicted value of the responses are obtained which are shown in figure 12

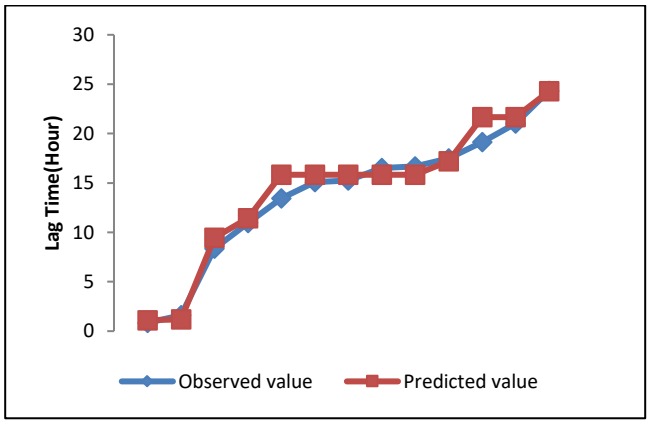

Figure 12: correlation of actual and predicted values of FPRT

Minitab 16 was used to optimize formulation with minimum amount of HPMC K 100 as well as sodium bicarbonate with composite desirability 1.0. Hence, an optimum formulation contains 5.85mg/tab HPMCK 100 and 15.47 mg/tabs sodium bicarbonate. The floating lag time of optimize formulation was 2.76 minute practically which is quite near to its predicted value 2.07 minute. The composite desirability of the optimized FPRT is 1.0 as shown in figure 13.

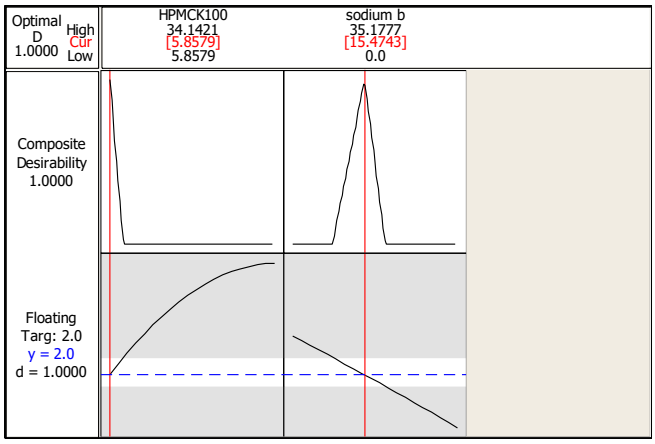

Figure 13: Optimization plot of buoyant layer of FPRT

CONCLUSION

All 13formulations showed similar drug release pattern and the EC coating rupture from edges, it can be concluded that the buoyant layer does not affect the drug release. All the formulation's floating time exceed over 8 hours which is as desired result and floating lag time of all formulation was below 25 minutes. Thus, combination of pulsatile and floating drug delivery system can be used for time and site-specific drug delivery system and can be a novel approach in addressing chronological disorder.

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