RESEARCH ARTICLE

Design and Development of Carvedilol Floating Pulsatile Drug Delivery System

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Abstract

Objective: The current study's objective is to develop and evaluate floating pulsatile delivery systems (FDT) for carvedilol. Carvedilol, non-selective α, β-receptor blocking agent. It is indicated for the treatment of moderate heart failure and hypertension.

Methods: The rapid-release core tablets were formulated using various concentrations of superdisintegrants such as croscaramellose sodium and crospovidone. The optimized pulsatile release tablets were prepared by using different grades of HPMC) at different concentrations. Dry-coated tablets were prepared by using a combination of a pulsatile layer and a rapid-release layer. 3^2 randomized full factorial designs were applied to optimize the buoyant layer composition. The amount of HPMC K100M (X_1), and sodium bicarbonate (X_2) were chosen as independent variables. Floating lag time (Y_1), and total floating time (Y_2) were chosen as dependent variables. Nine formulations were designed and are evaluated for pharmaceutical product performance.

Results: Findings indicate that all formulations meet the acceptance criteria, and kinetic modeling was applied to the *in-vitro* dissolution profiles.

Conclusion: The best formulation (F_6) contained 80 mg of HPMC K100M and 25 mg of sodium bicarbonate and showed promising results for obtaining desired floating parameters (Floating lag time 4.4 mins; Total floating time 14.3 hours) and may produce patient compliance by means of reducing dosing frequency and provide chronotherapy for effective management of morning surge of hypertension.

Keywords: Carvedilol, Superdisintegrants, Sodium bicarbonate, HPMC K100M, 3^2 full factorial.

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Introduction

Oral administration is the most convenient, commonly used route for both conventional and new drug delivery systems and the preferred route of drug delivery for systemic action. In long-term therapy for treating chronic disease conditions, Immediate Release formulations must be administered in multiple doses. However, when administered orally, many therapeutic agents are subjected to extensive presystemic elimination by gastrointestinal degradation and/or first-pass hepatic metabolism, resulting in low systemic bioavailability and, shorter duration of therapeutic activity and formation of inactive or toxic metabolites.[1]

The pulsatile drug delivery systems are beneficial for drugs having chronopharmacological behaviour. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e. a zero-order release, is not desired. The release of the drug as a pulse after a lag time (period of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. The types of pulsatile drug delivery systems are capsular, osmotic, single, and multiple-unit systems based on the use of soluble or erodible polymer coatings, rupturable membranes, pH-induced, and externally regulated systems.[2]

The human body has many built-in rhythms known as biological clocks. Broadly, these can be classified as ultradian, circadian, and infradian. Ultradian cycles are shorter than a day, e.g., the time a nerve impulse takes to be transmitted. Circadian cycles last about 24 hours, e.g. sleeping and waking patterns. Infradian cycles are longer than a day, e.g., the menstrual cycle. The gastroretentive pulsatile drug delivery system is useful for drugs with pH-dependent solubility, poor bioavailability in the gastrointestinal tract (GIT), and a narrow absorption window. These considerations led to the development of oral pulsatile release dosage forms possessing gastric retention capabilities.[3-6]

Carvedilol is a non-cardioselective alpha1- beta-adrenergic blocking agent with no intrinsic sympathomimetic activity and weak membrane-stabilising activity. The alpha 1-adrenergic blocking activity of CV causes vasodilation and reduces peripheral vascular resistance. At higher doses, calcium channel-blocking activity also observed. It is most effective in the management of hypertension, angina pectoris, moderate heart failure of ischemic or cardiomyopathic origin, and left ventricular dysfunction with

myocardial infarction. It has a narrow absorption window, i.e., the upper part of the GIT. Therefore, a good candidate for gastroretentive dosage form. However, fluctuations of drug concentration in plasma may occur, resulting in side effects or a reduction in drug concentration at the receptor side. As the drug is effective when the plasma fluctuations are minimized, therefore sustained-release dosage form of carvedilol phosphate is desirable. The short biological half-life of drug (7 hours) also favors the development of sustained-release formulations.

The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the sustained oral delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability Thus, there is a need to maintain carvedilol phosphate at its steady-state plasma concentration. Hence, the study was carried out to formulate and evaluate the floating dosage form of carvedilol phosphate as a model drug and aimed that final batch formulation parameters should show prolonged drug release.

Hence, this research work attempts to formulate floating tablets of carvedilol phosphate using HPMCK 100M and sodium bicarbonate. Instead of normal and trial methods, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.[7]

The rationale for the development of an appropriate formulation is to provide the drug at the right time, i.e., early morning. The formulation has a rapid-release core tablet of carvedilol with superdisintegrants. The core was press-coated by the layer of polymer to impart pulsatile release and finally, on the top, a buoyant layer was added for gastric retention. The formulation was evaluated for its properties (*in-vitro* buoyancy studies).

Materials and Methods

Materials

Carvedilol (CAS No: 72956-09-3) was a gift sample procured from Maxter Pharma Pvt Ltd, India. Crospovidone croscaramellose sodium was procured from National Scientifics, Guntur. Other excipients were procured from Loba Chemie Ltd, Mumbai.

Formulation of core tablets

The inner core tablets were prepared by using the wet granulation method. Different preliminary batches of core tablets were taken to fix concentrations of superdisintegrant in the tablets. The formula for the core tablets is presented in Table 1 Lactose, drug (Carvedilol) mixed well in poly bag for 10 minutes. The binder solution was poured over the dry mix, mixed, and processed to obtain granules (#10). The granules were subjected drying in oven at 60^{0}C, and dried granules passed through # 30. Superdisintegrants and magnesium stearate were mixed to the above blend for 5 minutes in a polybag. The blend was subjected to compression using 8, 8-station rotary tablet punching machine (RIMEK Minipress) using 8 mm circular punches and the same hardness was used for the required number of tablets.

Table 1: Formulae for the Preparation of Carvedilol Rapid Release Core Tablets

Name of Ingredients	*Quantity of Ingredients per each tablet (mg)*					
	R_1	R_2	R_3	R_4	R_5	R_6
Carvedilol	3.125	3.125	3.125	3.125	3.125	3.125
Lactose	68.375	68.075	67.775	68.375	68.075	67.775
Croscaramellose sodium	1.3	1.6	1.9	-	-	-
Crospovidone	-	-	-	1.3	1.6	1.9
Sucrose	1	1	1	1	1	1
Povidone	2	2	2	2	2	2
Aerosil	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium Stearate	0.7	0.7	0.7	0.7	0.7	0.7
Total Weight	80	80	80	80	80	80

Table 2: Experimental design layout for Floating Pulsatile Tablets

Formulation Code	X_1	X_2
F_1	+1	0
F_2	0	+1
F_3	0	0
F_4	-1	+1
F_5	-1	-1
F_6	+1	+1
F_7	+1	0
F_8	0	0
F_9	-1	0

Preparation of Floating pulsatile release tablets

A selected three-level, two-factor experimental design (3^2 factorial design) describes the proportion in which the independent variables HPMC K100M and sodium bicarbonate were used in the formulation of carvedilol phosphate floating pulsatile release tablets. The amount of HPMC K100M (X_1), and sodium bicarbonate (X_2) were chosen as independent variables. Floating lag time-FLT (Y_1), and total floating time-TFT (Y_2) were chosen as dependent variables. Nine formulations were developed as per 3^2 factorial design. The experimental design layout is presented in Table 2. The three levels for HPMC K100M (X_1) are -1 = 60, 0 = 70, +1 = 80 (All the quantities expressed in mg). The three levels for Sodium bicarbonate (X_2) are -1 = 15, 0 = 20, +1 = 25 (All the quantities expressed in mg).

Dry coated tablet was prepared by placing 50% of the pulsatile release layer in the appropriate die and a rapid release core tablet (RRCT) layer was placed on it and then the

Table 3: Post-Compression Parameters for Core Tablets

Formulation Code	*Hardness (kg/cm^2)*	*Thickness (mm)*	*Friability (%)*	*Average Weight (mg)*	*Drug Content (%)*	*Disintegration Time (sec)*
R_1	3.55 ± 0.07	2.9 ± 0.02	0.84 ± 0.01	80 ± 0.14	97.5 ± 0.12	245 ± 5
R_2	3.7 ± 0.05	3.1 ± 0.06	0.67 ± 0.02	80 ± 0.21	98.23 ± 0.2	235 ± 3
R_3	3.62 ± 0.11	3.0 ± 0.03	0.71 ± 0.01	79 ± 0.17	98.75 ± 0.17	210 ± 7
R_4	3.7 ± 0.16	2.9 ± 0.06	0.82 ± 0.01	80 ± 0.19	99.21 ± 0.08	193 ± 2
R_5	3.7 ± 0.04	3.0 ± 0.05	0.84 ± 0.01	80 ± 0.08	98.22 ± 0.04	150 ± 3
R_6	3.9 ± 0.04	2.9 ± 0.03	0.86 ± 0.02	80 ± 0.21	98.74 ± 0.02	121 ± 2

remaining quantity of the pulsatile release layer was added in the cavity, so as to cover the RRCT and finally compressed using rotary tablet compression machine. In-process quality control (IPQC) tests were performed on the acquired tablets. Finished tablets were transferred to airtight, light-resistant containers for storage and subsequent processing.[8]

Evaluation of Carvedilol floating pulsatile tablets (FPT)

Hardness

It was carried out with the help of a monsanto tablet hardness tester.[9]

Friability/ Durability

Twenty tablets were weighed and noted as W_0 cumulatively (Initial weight). The pills were then dedusted with a Roche Friabilator, Mumbai for 4 minutes at a speed of 25 rpm, and weighed again recorded as (W). The following equation was used to obtain the percentage of friability (%Friability ≤1).

$$\text{Friability (\%)} = (W_0 - W)/W_0 \times 100$$

Assay

About 20 tablets were chosen and ground in an impartial manner. The 100 mg of carvedilol powder was weighed and added to a volumetric flask with 15 mL of methanol. The solution was filtered through the Whatman filter paper. From this 1-mL of solution was withdrawn and diluted to 10 mL. Again, from this 1-mL solution was withdrawn and diluted to 10 mL. The resulting solution absorbance was measured at 241 nm using a UV-visible spectrophotometer (Analytical UV Double beam -2800, Baroda).

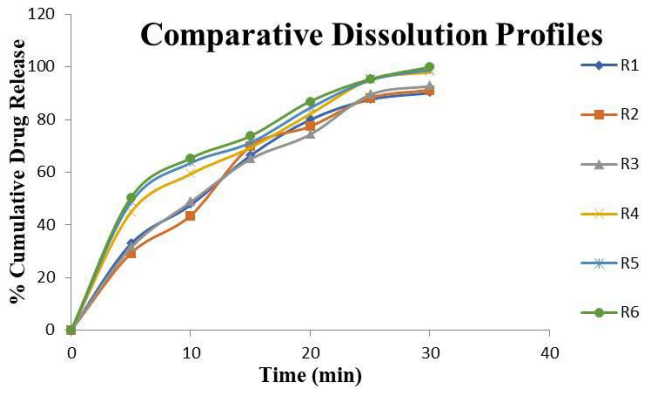

Figure 1: Comparative Dissolution Profiles

Thickness

It was measured with the help of verinier calipers.[10]

In-vitro Dissolution Study

Carvedilol FPT was analyzed for drug release study utilizing a Lab-India USP type-II tablet dissolution test apparatus (Labindia Tablet dissolution Apparatus DS 8000, Navi Mumbai) and 900 ml of 0.1 N Hydrochloric Acid in accordance with the official method. Using a UV-visible spectrophotometer, samples' absorbance was measured at 241 nm and the data was subjected to kinetic modeling.[7,11]

In-vitro Buoyancy Studies

The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.[7]

Results and Discussion

Evaluation of Core Tablets

Results for hardness, friability, drug content, and *in-vitro* disintegration are shown in Table 3. In all of the formulations, the hardness test indicated good mechanical strength, whereas the friability was less than 1%, indicating that the tablets had good mechanical resistance. The *in-vitro* disintegration times for the formulations varied from 123 to 250 seconds. It was observed that when crospovidone was used as a disintegrant, the tablets were disintegrated within a short time due to the easy and high swelling abilities wicking action of crospovidone as compared to croscarmellose sodium. For the development of the pulsatile release study, disintegration time had to be short to obtain the burst effect. The drug content was found to be high (99.21 ± 1.78) and uniform in all of the tablet formulations. It ranged from 97.45 ± 1.23 to 99.21 ± 1.78 and was uniform in all tablet formulations.

The rapid increase in the dissolution of carvedilol with an increase in croscarmellose sodium may be attributed to the rapid swelling and disintegration of the tablet. Crospovidone exhibited capillary activity (wicking) and pronounced hydration with little gel formation tendency and rapidly disintegrated the tablet. Formulation R_6 showed satisfactory hardness, % drug content, the lowest disintegration time, and high drug release. So R_6 was considered the optimized formulation and taken for further studies. The dissolution data for the core tablet are as shown in Figure 1.

Table 4: Post-Compression Parameters for Floating Pulsatile Tablets

Formulation Code	*Hardness (kg/cm²)*	*Thickness (mm)*	*Diameter (mm)*
F_1	5.85 ± 0.37	4.9 ± 0.17	10.01 ± 0.01
F_2	5.78 ± 0.28	4.86 ± 0.08	10.03 ± 0.03
F_3	5.75 ± 0.28	4.81 ± 0.14	10.02 ± 0.02
F_4	5.68 ± 0.6	4.71 ± 0.26	10.01 ± 0.01
F_5	5.63 ± 0.27	4.62 ± 0.24	10.02 ± 0.005
F_6	5.87 ± 0.24	4.95 ± 0.06	10.03 ± 0.02
F_7	5.78 ± 0.16	4.86 ± 0.21	10.01 ± 0.008
F_8	5.72 ± 0.13	4.78 ± 0.13	10.04 ± 0.01
F_9	5.66 ± 0.35	4.66 ± 0.12	10.01 ± 0.004

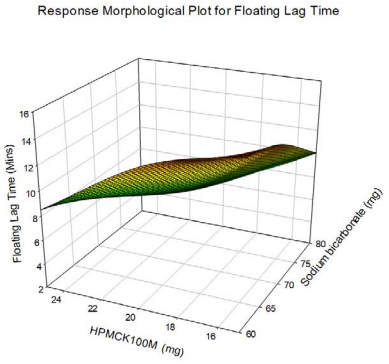

Figure 2: Response Surface Morphological Plot for Floating lag time (Y_1)

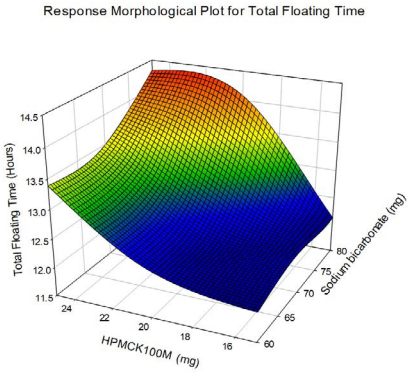

Figure 3: Response Surface Morphological Plot for Total floating time (Y_2)

Evaluation of Floating Pulsatile Release Tablets

Results for drug hardness, thickness, diameter, floating lag time, and total floating time are given in Table 4. On the basis of defined constraints for each independent variable, the Design Expert Software version 11 automatically generated the optimized formulation. The experiments were performed and the responses were obtained. The independent and corresponding dependent variables' results are presented in Table 5. Response surface morphological (RSM) plots for dependent variables, i.e., floating lag time (Y_1) and total floating time (Y_2) were constructed and the same were presented as Figures 2 and 3.

Table 5: Kinetic Parameters

Formulation	*X_1 (HPMC K100M, mg)*	*X_2 (Sodium bicarbonate, mg)*	*Y_1 (FLT, Min)*	*Y_2 (TFT, Hour)*
F_1	80	20	6.5	14.08
F_2	70	25	7.1	13.49
F_3	70	20	8.4	12.51
F_4	60	25	8.5	13.39
F_5	60	15	15.1	12.01
F_6	80	25	4.4	14.32
F_7	80	15	10.1	12.13
F_8	70	15	13.4	12.21
F_9	60	20	13.09	12.30

Figure 2 illustrates that when the amount of HPMC increases, there is a decrease in floating lag time, and when the amount of sodium bicarbonate increases, there is a decrease in floating lag time.

Figure 3 illustrates that when the amount of HPMC increases, there is a decrease in floating time, and when the amount of sodium bicarbonate increases, there is a decrease in floating time. The software generated the optimized formulation and predicted the response based on the constraint. Based on the desirability (0.918) formulation containing 80 mg of HPMC K100M, 25 mg of Sodium bicarbonate (F_6) was considered as an optimized formulation.

Conclusion

The lag time of drug release from the floating pulsatile release formulation can be readily modulated by varying the HPMC K100M concentration and sodium bicarbonate in the outer barrier layer. From the experimental findings, it can be concluded that floating pulsatile tablets of carvedilol can give efficient therapy by reducing dose and dosing frequency and provide chronotherapy for effective management of the morning surge of hypertension. Finally, it may be concluded that a floating pulsatile drug delivery system offers a valuable dosage form for the treatment of hypertension.

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