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Original Article

DESIGN AND DEVELOPMENT OF CARVEDILOL GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEMS USING HYDROPHILIC POLYMERS AND *IN VITRO* CHARACTERIZATION

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ABSTRACT

Objective: The primary aim of the present examination was to create carvedilol phosphate floating tablets using factorial designs and for retention in the upper portion of the gastrointestinal (GI) tract to sustain the dissolution where the solubility of carvedilol phosphate is more in an acidic medium.

Methods: The floating tablets of carvedilol phosphate were ready to employ different concentrations and a combination of these polymers of Na-alginate, Carbopol 934P, and sodium carboxymethyl cellulose (NaCMC) with lubricants magnesium stearate by direct compression technique. In the present experiment, involved sodium bicarbonate and citric acid as a gas-producing agent. Fifteen formulations structured and judged for pre-compression components like the angle of repose, bulk and tapped density, Hausner's ratio, compressibility index, and post-compression factors are weight uniformity, hardness, drug content, friability, *in vitro* buoyancy, dissolution studies, and Fourier transforms infrared spectroscopy (FTIR).

Results: The drug released 90.02% in 12 h by combining NaCMC (7.5 mg) and Na-alginate (7.5 mg) in the formulation F14 towards the achievement of sustained release. Batch F14 selected as optimized, as provided desired zero-order release profile as well as floating lag time 20 s and total floating time>12 h, and the mechanism of drug release observed (n = 1.098, super case-II transport).

Conclusion: From the results fulfilled that all the preparation found to be within the pharmacopeia limits and was the best dosage form to treat moderate heart failure and hypertension. The *in vitro* dissolution profiles of all formulations placed into various kinetic models, the statistical parameters like slope, regression coefficient and intercept determined. The gastro-retentive dosage form to maintain the sustain drug delivery, which would improve the maximum therapeutic efficacy and patient compliance.

Keywords: Carvedilol phosphate, Gastroretentive dosage form, Factorial design, Direct compression method

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INTRODUCTION

The most ideal route of drug release is the oral route because of the patient compliance, simplicity of intake and flexibility in preparation, and so forth. Many of the drug delivery systems (DDSs) available in the market are oral drug delivery type dosage forms [1]. For, oral DDSs improved prompt release to site-specific drug delivery over a while. The perfect drug transport system holding the two key properties, a single dose or less dosing frequency for the entire term of therapy and the dosage form should discharge drug exactly at the site of activity and every single patient might want continuously a similar thing [2, 3]. A controlled release drug delivery system (CRDDS) administered by mouth takes on a wide reach of more varied circumstances, such as pH, agitation, intensity, and authorship of the GI fluids as it drives down the GI tract [4]. It has built the Extensive endeavors to invent oral CRDDS that are progressively expectable with concern to the drug release kinetics and which have expanded bioavailability. The absence of capacity to hold and confine the drug delivery system (DDS) inside the perfect locales of the GI tract and exceedingly factor nature of the gastric emptying procedure is for the evolution process prohibited by several physiological difficulties. A significant component, which may unfavorably influence the operation of an oral CRDDS, is the GI transit era. The absorption time through the GI transits in people, evaluated to be 8-10 h from mouth to colon, is usually short with impressive variation [2, 5].

Most of the drugs easily absorbed from all the parts of the GI tract while some occupied only from specific regions, mainly for their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, and because of the debasement of the drug by the microorganisms present in the colon [5, 6]. Subsequently, in examples where the medicament not absorbed consistently over the GI tract, the rate of drug ingestion may not be steady regardless of the DDS conveying the drugs at a steady rate into the GI fluids. More particularly, on occasions where a drug has a clear-cut 'absorption window', i.e., the drug absorbed only from specific parts of the stomach or upper portions of the small bowel, it may not be absorbed when administered in the course of a typical oral CRDDS. It is because in human gastric emptying time is comparatively brief, which normally gets about 2-3 h average time through the main absorption zone. Because of this form of the dosage form, the drug liberation may be inadequate at absorption locations leading to it diminished the capability of the administered dose. The drug should receive such type of 'absorption window' that an effective oral CRDDS should be destined not to transfer the drug at a controlled rate, but also to keep the drug in the stomach for a long period [7, 8].

A gastro retentive drug delivery system (GRDDS), which draws out the gastric retention time (GRT) progresses solubility and consequently enhances the bioavailability of drugs that are less dissolvable in an acute pH condition [9] carvedilol phosphate has a novel pharmacological profile. It blocks β1, β2, and α1 receptors, used in the management of high blood pressure, and as an adjunct to standard therapy in symptomatic heart failure and also produces vasodilation [10]. Carvedilol phosphate is a crystalline salt form with slightly more solubility and chemical stability than carvedilol; hence a controlled-release preparation is desirable which reduces patients' dosing regimen, improves patient compliance, improves the dissolution and hence bioavailability [11]. Carvedilol phosphate displays typical solubility activities in neutral or alkaline media, specifically, the solubility extended at pH 3 in the upper area of the GI tract [11, 12]. Due to its pH-dependent solubility, it is necessary to improve the absorption of the drug in the stomach to improve its absorption on that point, which makes carvedilol phosphate, a commendable candidate for

GRDDS. Steady-state plasma concentration of carvedilol vary between 22-160 mg/ml [13]. As compared to other systems with floating drug delivery systems (FDDS) the density of the gastric fluid is more than the FDDS so the dosage form remains buoyant in the stomach without interfering gastric emptying rate for a prolonged period [14]. The work was held out to plan and examine the floating dosage form of carvedilol phosphate as a model drug and had a goal that concluding batch preparation parameters should demonstrate prolong drug release. The improvement of the dosage form relies upon the chemical nature of the drug/polymers, matrix structure, pre-compression parameters (micromeritic properties), post-compression parameters, diffusion, release mechanism, and the *in vivo* condition. An endeavor cleared in this exploratory study to formulate floating tablets of carvedilol phosphate utilizing Carbopol 934P, NaCMC, and sodium-alginate. Rather than the ordinary and preliminary technique, utilizes a standard statistical tool design of investigations to look at the impact of formulation variables on the release properties. Huge scale production needs more simplicity in the formulation with the monetary and least expensive dosage form. The floating tablet formulation by the direct compression strategy is practically worthy in enormous scale creation. A factorial design utilized deliberately to inspect the drug release profile. Utilized the factorial design to research three independent variables (factors), i.e. the amounts of Carbopol 934P, NaCMC, and Na-alginate on the dependent variables [16].

MATERIALS AND METHODS

Materials

Acquired the gift sample carvedilol phosphate from the Unichem Laboratories Limited, Mumbai, India. Na-alginate and MCC purchased from Rankem Ltd., Delhi [12]. Carbopol 934P from NR chemicals limited, Mumbai and sodium carboxymethylcellulose procured from SD Fine Chemicals Ltd., Mumbai, India. Every other compound, for example, sodium bicarbonate, magnesium stearate, and citric acid obtained from SD Fine Chemicals Ltd., Mumbai, India [15, 16].

Estimation of lambda max

At first, 10 mg of the medicament gauged, and it dissolved in a little amount of methanol and built up to the volume in a 10 ml volumetric flask with pH 1.2 buffer solution to become a stock solution of 1000 µg/ml. 1 ml of it withdrawn and additionally diluted with the buffer solution to 10 ml in another 10 ml volumetric flagon to get a solution of concentration 100 µg/ml. From this solution of 100 µg/ml, 1 ml made up to a volume of 10 ml to get the solution of 10 µg/ml and this subsequent solution examined Spectro photometrically between 200-400 nm and the λ max of the scanned drug tracked out (fig. 1) [4, 24].

Preparation of calibration curve

A solution comprising 1 mg/ml of the unadulterated drug set up by solubilizing 100 mg of carvedilol in pH 1.2 buffer to create a 100 ml solution in a volumetric flask. The stock solution 100 µg/ml set up by withdrawing 10 ml of the above solution and diluted to 100 ml utilizing pH 1.2 buffer. From the of readied, 100 µg/ml stock solution, sequential dilutions set up by withdrawing 0.2, 0.4, 0.6, 0.8 and 1 ml which were a build-up to a volume of 10 ml each, in individual volumetric flasks to get the separate concentrations of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml and named appropriately. The calibration curve of carvedilol then recorded by scanning the respective sequential dilutions (2, 4, 6, 8, and 10 µg/ml) of the drug-using UV-Vis spectroscopy at a wavelength of greatest absorption in fig. 2 [4, 24].

Method of preparation

Altogether of the essential ingredients adequate for 20 tablets weighed precisely and thoroughly blended after passing through sieve no. 22 to acquire consistency. At first, the required quantity of the active constituent, i.e., carvedilol phosphate and the polymer (Na-alginate/Carbopol 934P/NaCMC/a combination of these polymers) counted accurately blended all together with one another than the specific measure of the effervescent substances NaHCO3 and citric acid inserted to the powder blend individually.

And so, the microcrystalline cellulose (MCC) was mixed uniformly with the blend, and then magnesium stearate mixed with the tablet mixture as a lubricant [15, 17]. The geometric dilution technique was used for the mixing of the contents. Tablets containing carvedilol phosphate equivalent to 15.7 mg compressed by using 6.0 mm diameter, circular tablet punches on a rotary compression machine containing 16-station at the hardness of 4 to 5 kg/cm^2 [18].

Table 1: Formulation composition of carvedilol phosphate

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Carvedilol phosphate	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.7
Carbopol 934P	5	-	-	10	-	-	15	-	-	20	-	-	7.5	-	7.5
NaCMC	-	5	-	-	10	-	-	15	-	-	20	-	7.5	7.5	-
Na-alginate	-	-	5	-	-	10	-	-	15	-	-	20	-	7.5	7.5
MCC	52.3	52.3	52.3	47.3	47.3	47.3	42.3	42.3	42.3	37.3	37.3	37.3	42.3	42.3	42.3
Sodium bicarbonate	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

note: (-) the particular excipient not utilized in the formulation

Table 2: Experimental design layout

Formulation code	X1	X2	X3
F1	-1	-	-
F2	-	-1	-
F3	-	-	-1
F4	-0.5	-	-
F5	-	-0.5	-
F6	-	-	-0.5
F7	0	-	-
F8	-	0	-
F9	-	-	0
F10	0.5	-	-
F11	-	0.5	-
F12	-	-	0.5
F13	1	1	-
F14	-	1	1
F15	1	-	1

note: (-) the particular excipient not utilized in the formulation

Experimental design

Experimental design utilized in the current investigation for the optimization of excipients concentration, such as the concentration of Carbopol 934P, NaCMC, and Na-alginate taken as X_1, X_2, and X_3. It represented the experimental design in table 2. Five levels for the concentration of polymers selected and coded as (-1=5%,-0.5=10%, 0=15%,+0.5=20%,+1=7.5%). Formulae for all the experimental batches were given in table 1 [15, 31].

Pre-compression parameters of Carvedilol phosphate granules

Bulk density

Bulk density evaluated by dividing the quantity of powder by cm^3 bulk volume. The previously passed powder around 50 cm^3, through a standard sieve no. 20, brought cautiously into a graduated cylinder containing 100 ml. At 2 s intervals, the cylinder was falling onto the hardwood surface three times from a height of 1 inch [19, 20]. Each formulation bulk density obtained by splitting the flock of the sample in grams by the final intensity of the sample obtained in the cylinder in cm^3. Its unit is in g/ml and esteemed by applying the equation given underneath [21].

$$\rho_b = M/V_0 \ldots\ldots (1)$$

Where,

M = mass of the powder,

V_0 = bulk volume of the powder.

Tapped density

It measured by dividing the total mass of powder by the tapped volume of the powder. By tapping the powder to a constant volume nearly 100 times, the tapped volumes evaluated, and the tapped density assessed by applying the equation given below. Its unit expressed in g/ml and the equation is presented below [19-21].

$$\rho_t = M/V_t \ldots\ldots (2)$$

Where,

M = mass of the powder,

V_t = tapped volume of the powder.

Angle of repose

The angle of repose has been set at the maximum angle possible between the surfaces of a pile of powder and horizontal plane. It is performed to determine the flow rate of the powder. The angle of repose can gauge the flow property of loose powder, θ. The angle of repose is the highest angle in between the horizontal plane and the heap of the powder surface. The unforced flow of powder to the die cavity from the hopper examined by the angle of repose of the powder blend and is a part of the rheological property. By the funnel method, the test done. Through the funnel hole which fixed vertically, the powder mass was permitted to fall to a plain paper that was proceeding on the horizontal surface that creates a mountain angle of powder on the paper. The angle of repose measured by dividing the top of the pile 'h' with radius 'r' by using the next equation [19-21].

$$\theta = \tan^{-1}(h/r) \ldots. (3)$$

Where,

θ = angle of repose,

h = height of the pile of powder (cm),

r = radius of the pile (cm).

Carr's Index

Carr's established a subordinate method of defining powder flow from densities. The compressibility percentage of powder was a direct computation of the powder arch potential or stability and bridge strength. This specifies the effortlessness with which it can induce a material to flow [19-21]. It limited in percentage and known by Carr's index. Carr's index determined by:

$$(\rho_t - \rho_b)/\rho_t * 100 \ldots. (4)$$

Where,

ρ_t = tapped density,

ρ_b = bulk density.

Hausner's ratio

The interactions of free-flowing powder are almost significant, so the value of bulk and tapped densities will be closer. If the particle is poorer flowing, the inter-particle interactions are also greater and it will detect a dispute between the bulk and tapped densities that will be detected more. In Hausner's ratio, these differences reflected and worked out by the following rules [18, 22].

$$\text{Hausner's ratio} = \text{(Tapped Density) / (Bulk Density)} \ldots. (5)$$

The value of Hausner's ratio of less than 1.2 shows the free flow and a value greater than 1.6 shows poor flow.

Post-compression parameters

Tablet thickness and diameter

For the size uniformity of tablets, the thickness and diameter of tablets are more substantive. The diameter and thickness of the tablet were estimated in Vernier caliper. They appear in mm [15, 18, 20].

Hardness

The hardness of a tablet determined by the hardness analyzer. Chipping or breakage of the table during storage, transit, and handling produce due to insufficient hardness. Hardness or tablet smashing strength is the power required to break down a tablet in a diametric compression. The force estimated in kg and the hardness of around 3-5 kg/cm^2 viewed as agreeable for uncoated tablets. From each formulation randomly, five tablets selected and each tablet hardness measured by using a Monsanto hardness tester. The unit of hardness is normally in terms of kg/cm^2 [17, 21, 22].

Friability

The weight reduction due to vibration and transport the friability test carried out rapidly in Roche friabilator. In this apparatus at first, 20 tablets weighed and kept in a drum which must catch on and rotating action. In this apparatus, the 20 tablets subjected to tumble from 6 inches height and the drum pivoted 100 rotations, then the tablets detached and weighted. The 20 tablets weight loss percentage estimated by using the below formula and presented in table 4. Mostly, thought to be an adequate USP limit is 0.5 to 1% [16, 19, 22].

$$f = (W_o - W/W_0) * 100 \ldots\ldots (6)$$

Where,

f = friability,

W_0 = initial weight,

W = final weight.

Uniformity of weight

This test is accomplished to keep up the consistency of the weight of every tablet, which ought to in the recommended range. The examination performed by picking out and weighing randomly 20 tablets and the mean weight is figured. Not over two of the distinct weights should diverge from the average weight by the above, then the percentage, demonstrated in table 4 and none should diverge by more than twofold the percentage. At last the standard and mean deviation were computed [19, 21, 22].

Uniformity of drug content

The criteria of the Pharmacopoeia depend on official test and assay methods. To find out the amount of the active ingredient available in the manufactured floating matrix tablets and to confirm the uniform strength of the tablets, the assay of the tablets was performed. Arbitrarily selected, formulated single tablets put in a 100 ml volumetric flask holding pH 1.2 buffer solution and the system was left undisturbed overnight. The

succeeding day, it measured the content of the solution in the conical flask using UV-Visible spectroscopy, which represents the tablet content in terms of carvedilol phosphate [21-23].

$$\text{Concentration} = \left(\frac{\text{Absorbance}}{\text{Slope}}\right) * \text{Intercept} \ldots\ldots\ldots (7)$$

$$\text{Drug content (mg)} = \text{Concentration} * \text{Dilution factor} \ldots\ldots\ldots (8)$$

$$\% \text{ Drug content} = (\text{Drug content/Label claim}) * 100 \ldots\ldots\ldots (9)$$

In vitro buoyancy determination

In the GRDDS the floating characteristics are essential, and GRDDS influenced in vivo behaviors of the DDSs. There will be no threshold value for the floating system to stay afloat under a physiological state of affairs due to the latter's complication. To quantify the lag time and duration of floating, the in vitro buoyancy achieved. The tumbler glass holding pH 1.2 buffer 100 ml into it, the tablets were placed. The floating lag time (tablet to pass from inside water to rise) and the entire floating time (tablet's floating duration) evaluated [18, 22, 24].

Drug excipients compatibility studies

The functional groups in the drug molecule determined by FTIR spectroscopy. In the sample, the electromagnetic radiation passing in between 400 cm^{-1} and 4000 cm^{-1}. Then in the sample, the molecules having bonds occupied by the electromagnetic radiation causing to turn or extend. The feature of the bond absorbing it is the wavelength of the radiation absorbed. In the current survey, the employed method was a potassium bromide pellet method. In a polybag, the dry powdered potassium bromide blended along with the sample. The blend then compacted by utilizing dies to form a disc. In the spectrophotometer, the spectrum was recorded after placing the disc [18, 22-24].

In vitro dissolution studies

But *in vitro* dissolution tests can be carried out, which will delineate the effects of variables on the kinetics and mechanism drug release from a dosage form. The exam will give a knowledge of how the dosage form will behave when subjected to *in vivo* studies. By using 8-station dissolution test apparatus (Lab India, Disso 2000) using a stirrer having a paddle (USP type II dissolution test apparatus) at a temperature of 37±0.5 ^{0}C at 50 rpm from the floating tablets the drug release considered. pH 1.2 (900 ml) buffer solution used as dissolution fluid. Through a filter (0.45 µm) the 5 ml of dissolution medium was getting back from the flask at various times interims and the same volume of the fresh dissolution medium substituted [15, 17, 20]. After reasonably diluted with a buffer solution, at 241 nm by utilizing a dual-beam UV-Visible spectrophotometer, the absorbance was estimated [24].

Drug release kinetics

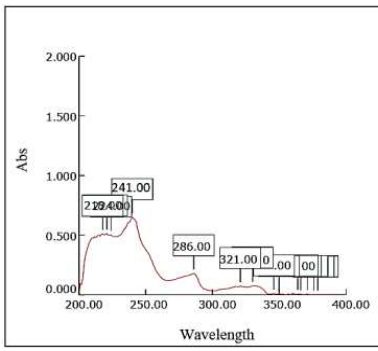
The release rate of the active ingredient is autonomous of its concentration depicts the zero-order rate equation [25]. The release rate of the active ingredient is concentration reliant portrayed by the first-order rate equation [26]. The fractional release of the drug exponentially linked to the release defines the Korsmeyer-Peppas power law equation [27]. The sack of drugs from the insoluble matrix as a square root of the fourth dimension-dependent method described the Higuchi method [28]. The medicament quits from the device wherever an alteration in surface area and diameter of particles or tablets portrays the Hixson-Crowell cube root law [29]. The log data of percentage drug discharged plotted against log time for various lots of matrix tablets characterizes the diffusion exponent 'n'. In fickian (case I) release the value of n indicates ≤ 0.45 but for non-fickian (anomalous) release>0.45 but<0.89, and in super case II category of the release specifies>0.89. The polymeric chain erosion commonly alludes to case II, and together diffusion and erosion-controlled drug delivery allude to anomalous transport (non-fickian) type delivery [30].

RESULTS AND DISCUSSION

Carvedilol phosphate floating matrix tablets prepared using (i) Na-alginate (ii) NaCMC and (iii) Carbopol 934P as matrix producers, and with sodium bicarbonate and citric acid as gas-producing agents (effervescent) through an aim of extending the GRT of carvedilol phosphate, (BCS Class II) a poorly water-soluble drug.

λ max and calibration curve

Calibration curves of carvedilol in phosphate buffer pH 1.2 solutions were built at λ max recorded 241 nm with a (Shimadzu Corporation, Kyoto, Japan) represented in fig. 1. Beer's law followed to construct the calibration curve was in the concentration range of 2-10 µg/ml. The standard graph of carvedilol was plotted according to the procedure, and its linearity appears. The standard graph of carvedilol demonstrated great linearity with an R^2 of 0.999, which indicates that it complies "Beer-Lambert's" law (fig. 2). The examination was done in triplicate [5, 24].



Instrument Performance
Model: UV-Vis Spectrophotometer
Number: 20-1650-01-0378
Spectral Bandwidth: 2.00 nm

Scan Spectrum Performance
Scan Range: 200.00 to 400.00 nm
Measure Mode: Abs
Interval: 1.00 nm
Speed: Fast
Data File: Untitled4.spd
Data Type: Original

Analyze Note
Analyzer:
Administrator
Sample Name: Carvedilol.

Wavelength	Abs
376.00	0.003
371.00	0.005
366.00	0.004
364.00	0.007
350.00	0.006
346.00	0.010
330.00	0.075
321.00	0.072
286.00	0.179
241.00	0.648
224.00	0.501
221.00	0.515
218.00	0.512

Fig. 1: Maximum absorbance (λ max) of carvedilol

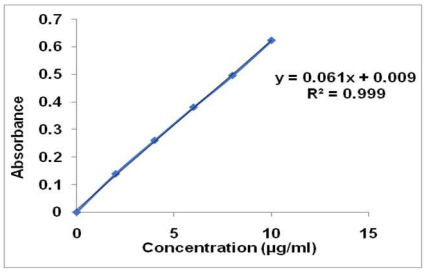


Fig. 2: Calibration curve of carvedilol in pH 1.2

Pre-compression parameters

The pre-and post-compression evaluations directed for both the formulations. The all formulations powder blend bulk and tapped density range is between 0.39±0.05 to 0.47±0.04 and 0.54±0.04 to 0.62±0.03. All formulations Carr's index and angle of repose values range are between 15.33±0.8 to 26.57±1.1 and 31.8±0.44 to 35.5±0.82, representing the prepared powder blend for direct compression nature are tolerable. The powder flow property again correlated with Hausner's ratio and the values set up between 1.16±0.02 and 1.34±0.02, representing a moderate flow displayed in table 3 [16, 22].

Table 3: Pre-compression parameters

Formulations	Bulk density*	Tapped density*	Carr's index*	Hausner's ratio*	Angle of repose*
F1	0.42±0.03	0.55±0.02	18.63±0.8	1.21±0.02	34.2±0.49
F2	0.41±0.02	0.54±0.04	19.07±0.7	1.22±0.04	35.5±0.82
F3	0.47±0.04	0.59±0.02	15.33±0.8	1.16±0.02	33.2±0.91
F4	0.43±0.06	0.58±0.05	20.86±1.5	1.25±0.05	32.4±0.53
F5	0.44±0.02	0.62±0.03	26.57±1.1	1.31±0.03	33.0±0.48
F6	0.39±0.05	0.57±0.02	24.03±0.9	1.34±0.02	32.1±0.63
F7	0.42±0.03	0.58±0.05	22.58±0.8	1.28±0.03	33.5±0.45
F8	0.45±0.05	0.61±0.03	21.22±0.9	1.26±0.02	32.1±0.64
F9	0.43±0.07	0.56±0.02	18.21±1.2	1.20±0.05	31.8±0.44
F10	0.45±0.03	0.58±0.03	17.41±1.4	1.19±0.04	32.6±0.57
F11	0.43±0.02	0.55±0.04	16.81±0.9	1.18±0.02	34.7±0.73
F12	0.45±0.03	0.57±0.02	16.05±0.8	1.17±0.03	33.5±0.92
F13	0.46±0.06	0.59±0.03	17.03±1.1	1.18±0.05	34.1±0.71
F14	0.41±0.07	0.58±0.05	24.31±0.8	1.31±0.02	35.2±0.43
F15	0.43±0.03	0.59±0.02	22.11±1.3	1.27±0.04	32.8±0.82

*entire data are stated as mean±SD; n= 3

Post-compression parameters

Carvedilol phosphate fifteen different formulations made by applying three different polymers at several concentrations separately and in combinations. By direct compression technique, all fifteen formulation batches were prepared and in table 4 the post-compression parameters given. The prepared tablet's thickness and hardness found between 2.7±0.92 to 3.3±0.98 mm and 3.5±0.20 to 4.2±0.27 kg/cm^2. The values of friability were found between 0.61±0.19% to 0.82±0.2%. The all the formulations friability values were found less than 1%, representing a satisfactory mechanical strength that means the tablets can tolerate the different cases of stress [15, 17]. The weight variation test for all formulated carvedilol phosphate tablets evaluated and every one of the tablets was discovered uniform weight having less standard deviation as compared to the prescribed Indian Pharmacopoeia limits of±7.5%. The drug content percentage of all the gastroretentive tablets were found in between 96.18±1.3% to 99.81±0.5% [21, 22].

Table 4: Post-compression parameters

Formulations	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)*	Uniformity of weight (mg)*	Assay (%)*
F1	3.1±0.81	3.5±0.20	0.61±0.23	100.1±1.09	97.39±1.1
F2	3.2±1.2	3.8±0.32	0.71±0.12	99.5±1.62	99.77±0.6
F3	3.3±0.98	3.6±0.63	0.68±0.2	98.7±1.75	98.52±1.1
F4	3.2±0.75	4.1±0.35	0.64±0.15	99.2±0.86	99.81±0.5
F5	3.1±0.59	3.63±0.76	0.72±0.22	99.4±1.2	98.98±0.9
F6	2.9±0.78	3.5±0.83	0.76±0.17	98.7±1.6	99.04±0.6
F7	2.9±0.5	3.5±0.23	0.77±0.14	98.2±1.34	97.26±0.9
F8	3.3±0.46	3.6±0.97	0.65±0.23	98.9±0.49	98.75±1.2
F9	2.8±1.6	3.8±0.43	0.69±0.21	99.7±0.79	98.88±0.8
F10	2.7±0.92	4.2±0.27	0.72±0.16	98.6±1.9	97.62±1.2
F11	3.2±0.86	3.7±0.81	0.69±0.18	99.2±0.96	98.18±0.8
F12	3.2±0.45	3.9±0.75	0.74±0.22	98.3±1.29	98.75±0.9
F13	2.9±0.7	4.18±0.41	0.62±0.17	97.32±1.05	96.18±1.3
F14	3.1±0.75	3.6±0.32	0.61±0.19	98.7±1.4	99.31±0.8
F15	3.3±0.62	4.1±0.54	0.82±0.2	98.79±1.26	98.82±1.1

*entire data are stated as mean±SD; n= 3

Table: 5 *In vitro* buoyancy properties of carvedilol phosphate

Formulations	Floating lag time (s)*	Total floating time (h)*
F1	80±2.5	9
F2	22±3.1	7
F3	18±2.4	>8
F4	85±2.6	7
F5	15±3.3	9
F6	12±2.2	10
F7	73±2.5	7
F8	16±2.8	10
F9	14±3.5	>12
F10	55±3.2	>12
F11	17±3.5	>12
F12	16±2.8	>12
F13	45±2.9	>12
F14	20±3.4	>12
F15	23±2.8	>12

*data are stated as mean±SD; n= 3

In vitro buoyancy determination

The lag time found in all formulations from 14 to 85 s and the data was shown in table 5. With the equal concentration of the gas-producing agent, all the formulations manufactured but the floating lag time was different because it depends on the amount and density of the polymer used [18, 22].

Drug excipients compatibility studies

The drug carvedilol phosphate floating tablets FTIR spectrum is presented in (fig. 3 and 4). The prominent peaks of carvedilol phosphate showed at 3341.97 cm^{-1}, 1501.83 cm^{-1}, 1453.70 cm^{-1}, 1252.44 cm^{-1}, 1213.74 $cm^{-1}$and 1098.32 cm^{-1}analogous to OH stretching, C=C stretching of the aromatic ring, C-N stretching and C-O stretching, respectively. The FTIR Spectrum of the pure drug indicates alike peaks closely resembling carvedilol phosphate floating tablets, which affirms that no interaction found between drug and polymers [24, 31].

In vitro dissolution studies

Spectrophotometrically drug scanned by using a double beam UV-Visible spectrophotometer between 200-400 nm and scanned drug λ max found at 241 nm. Among the initial three formulations F1 to F3 by comparing the drug release profiles, the enhanced percentage of drug release found in F1 then F2 and F3 because of F2 having NaCMC and F3 having Na-alginate respectively in equal quantity, which may be due to the role of Carbopol 934P in F1 (the drug release rates accelerated may be in the presence of cations). Although the Carbopol 934P is a highly cross-linked sustained release polymer, at pH 1.2 the drug released 96.89% in 4 h because not as much as pH 3 or larger than pH 12 the viscosity of Cabopol 934P diminished within the existence of strong electrolytes in F1. In the formulations F2 and F3, the formulation F3 drug release rate is slower than F2 for the accessibility of low concentration of electrolyte and high viscosity of Na-alginate and because of, less than pH 3 its solubility decreased in acidic aqueous solutions [32]. At below pH 2, due to the precipitation of NaCMC, the drug release found 94.06% in 4 h. In the next formulations (F4-F6), (F7-F9), (F10-F12) for the hike in the polymer concentration 10% the drug release decreased a bit and in (F10-F12) 20% polymer concentration applied and a release form kept similar. Then the two polymers, i.e., in F4 (Carbopol 934P) and F5 (NaCMC) the Na-alginate in formulation F6 could extend the release for an extended time (7 h). Likewise, formulations F9 and F12 were capable to run the drug release by using Na-alginate for a long time, i.e., for 10 h and>12 h, respectively. A minor change in the drug release % pattern of the F13 to F15 formulations was capable to continue the drug release for 12 h. By combining using Carbopol 934P and NaCMC in the formulation F13 having sustained release up to 12 h and had a drug release 95.01%. The drug released 90.02% in 12 h by combining NaCMC and Na-alginate in formulation F14 and drug released 93.04% in 12 h by combining Na-alginate and Carbopol 934P in formulation F15. In formulation F13, due to the addition of Carbopol 934P (which shows fast drug release characteristics) with NaCMC, it was observed that the drug release characteristics were pretty retarded (fig. 5). In formulation F14, the pace and extent of the drug release were found satisfactory, that's why it considered an optimized formulation [4, 15].

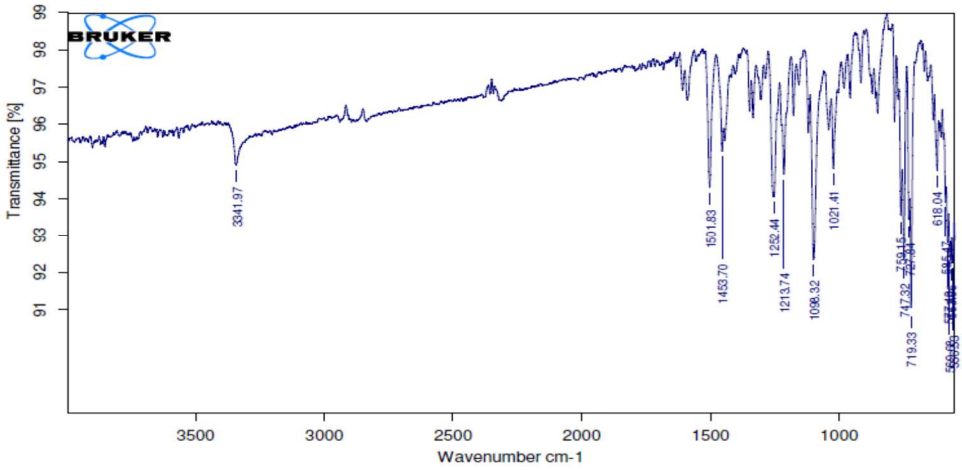


Fig. 3: FTIR spectrum of pure drug carvedilol phosphate

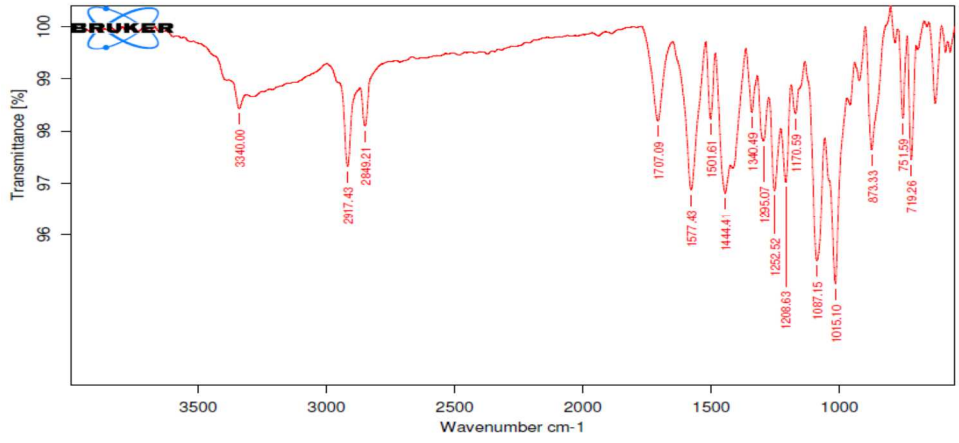


Fig. 4: FTIR spectrum of carvedilol phosphate best formulation

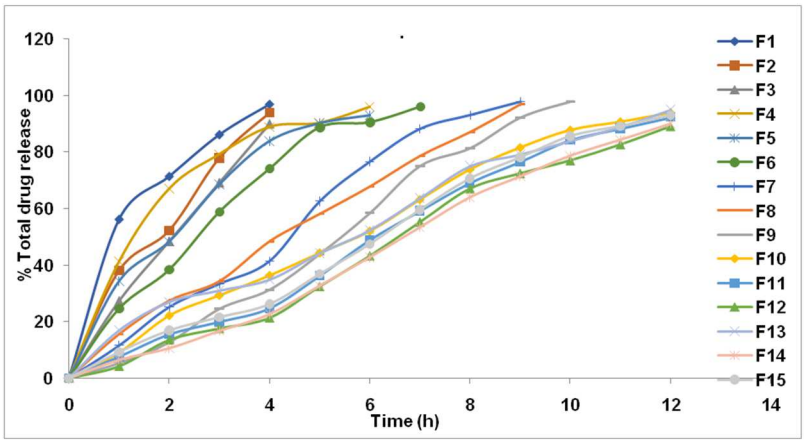


Fig. 5: Drug release of carvedilol phosphate GRDDS

Drug release kinetics

The release data, then incorporated into mathematical models such as a zero and first-order, Higuchi, Hixon-Crowell, and Korsmeyer-Peppas model, and the coefficients of regression results correlated. It was noted that the formulations F2, F3, and F7 to F15 followed the zero-order release and formulation F4, and F5 followed first-order release kinetics. The formulation F1 and F6 followed Higuchi release kinetic. Among all fifteen formulations, F14 selected as the best formulation. Then the release mechanism determined by the aid of the Korsmeyer-Peppas equation. The acceptable linearity was observed (R^2>0.948-0.999) for all fifteen developed formulations and the release exponent "n" varied from 0.457-1.324 that indicates F2 have fickian diffusion and F3, F5, F6, F8, and F13 followed by non-fickian diffusion. The remaining formulations F7, F9-F12, F14, and F15 followed the super case II transport release mechanism [33, 34].

Table 6: *In vitro* drug release kinetic studies

Formulations	Zero-order	First-order	Higuchi	Hixon crowell	Korsmeyer peppas	
	R^2					n
F1	0.994	0.092	0.997	0.976	0.995	--
F2	0.987	0.917	0.971	0.973	0.954	0.457
F3	1	0.927	0.99	0.967	0.999	0.824
F4	0.864	0.979	0.935	0.971	0.948	--
F5	0.937	0.985	0.975	0.981	0.98	0.493
F6	0.942	0.971	0.975	0.962	0.982	0.775
F7	0.977	0.954	0.97	0.976	0.987	0.922
F8	0.997	0.84	0.982	0.939	0.995	0.807
F9	0.99	0.843	0.964	0.939	0.995	1.324
F10	0.985	0.945	0.983	0.979	0.991	0.942
F11	0.985	0.94	0.963	0.973	0.986	1.023
F12	0.984	0.947	0.961	0.975	0.986	1.242
F13	0.987	0.913	0.966	0.965	0.975	0.592
F14	0.99	0.935	0.959	0.97	0.987	1.098
F15	0.984	0.934	0.958	0.969	0.982	0.919

Note: (--) the particular result doesn't originate in the formulation, (R^2 = regression coefficient), (n = release exponent)

CONCLUSION

In the present investigation, it has endeavored to get ready and assess the floating matrix tablets of carvedilol phosphate to prolong its GRT. Tablets formulated by direct compression strategy were observed to be serious with no chipping, capping, and sticking. The pre-compression parameters of all the prepared tablets were well within the demarcation lines, with the hardness values around 4 kg/cm^2 and variability below 1%, indicating a satisfactory mechanical strength. The appropriateness of rate impeding agent Na-alginate, NaCMC, Carbopol 934P, and gas creating agents such as sodium bicarbonate and citric acid has helped in the design and development of gastroretentive floating tablet formulations of carvedilol phosphate utilizing the factorial design. From the effects, it inferred that as the measure of polymer in the tablet formulation increases, the drug release rate decreases and both polymers can connect in the mix since don't interrelate with the drug which might be progressively useful in achieving the desired floating delivery of the drug for longer periods. It resolved that the optimized formulation kinetics followed super case II transport release, whereas the drug release mechanism behavior obtained Fickian, Non-Fickian diffusion and super case-II transport and zero, first and Higuchi release type, contained by the diffusion of low water-soluble drug through the fabrics and porous matrices. Based on evaluation parameters, the formulation F14 has determined as the optimized formulation; hence, for floating tablets of carvedilol phosphate, a poorly water-soluble drug these polymers (Na-alginate and NaCMC) discovered proper.

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AUTHORS CONTRIBUTIONS

From all 3 authors CH. Satyavanitook part in the practical work and Prasanta Kumar Mohapatra guided the entire project and writing of the manuscript. Satyajit Sahoo also helped to write the manuscript.

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CONFLICT OF INTERESTS

The authors have declared no conflict of interest.

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