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Original Article

FORMULATION AND EVALUATION OF COMPRESSION COATING FLOATING TABLETS OF CARVEDILOL PHOSPHATE ONCE DAILY DOSE

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ABSTRACT

Objective: The rationale for the study was to develop a once-daily dose of immediate as well as a gastro-retentive form of carvedilol phosphate by compression coating floating technique.

Methods: In the presented study the core tablet was containing half the quantity of the drug formulated as floating drug delivery using different controlled release polymers blend in various proportions like ethyl cellulose, carbopol, hydroxypropyl methylcellulose (HPMC) K4, K15, and K100 by direct compression method. Outer coat layer was formulated with rest of the drug with the blend of different super disintegrants in various proportions like crospovidone, croscarmellose sodium (CCS), sodium starch glycolate (SSG) for the immediate release of the drug. Both the immediate and controlled formulation was separately formulated from sf1 to sf9 and f1 to f9 respectively. Based on the evaluation parameters finally, formulation F1 to F9 were formulated by applying compression coating floating method. These formulations were characterized for their tablet density, disintegration time, floating lag time, *in vitro* drug release, drug-excipients interaction and accelerated stability studies etc.

Results: The result revealed formulation sf9 containing SSG of 15% was able to 97.2% of drug release within 15 min towards the achievement of immediate release. Similarly, the formulation f9 containing 0.5:0.5:4.5 ratios of ethyl cellulose, carbopol and HPMC K15 was able to 95.3% of drug release within 16h. From compressed coat tablets batches of F1 to F9, based on the dissolution data F9 was considered as an optimized formulation which was able to release 48.6% of drug release within 15 min and cumulatively controlled the release up to 96.4% for 16 h, followed zero-order kinetics and Higuchi pattern.

Conclusion: The results obtained in this research work clearly indicated that the compression coating floating tablet of carvedilol phosphate was the best dosage form for the treatment of hypertension. Results of the evaluation of prepared batches indicate that the batch F9 is a promising formulation for both a quick onset of action as well as gastro-retentive dosage form to maintain the constant drug action which would improve the maximum therapeutic efficacy and patient compliance.

Keywords: Carvedilol phosphate, Gastro-retentive form, Compression coating, Floating drug delivery, Immediate release

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INTRODUCTION

Carvedilol phosphate is the drug of choice in the treatment of hypertension and congestive heart failure. Carvedilol phosphate is a class II drug which has low solubility and high permeability, practically insoluble in water, have a slow onset of action and poor bioavailability [1]. Therefore it could not be ideal to be given in an emergency clinical situation like hypertension and heart failure. For better therapeutic effect, immediate and prolonged duration of action both is needed. The purpose of this research was to first dissolute and release the drug immediately for a quick onset of action and then to maintain the dosage form of control over a period of time. So this research is designed with a dual approach such as compression coating technique, where the core would be a gastro-retentive floating tablet and the coating material is to provide a quick onset of action. Hurdles in such formulation were identified as the low solubility, high permeability of carvedilol phosphate, which caused the poor oral bioavailability. Due to its poor bioavailability, it exerts strong effects on the performance of drug and leads to the necessity to give a higher dose for attaining required pharmacological action, which may cause serious side effects like gastric irritation. Therapy should be individualized according to patient response to attain maximum therapeutic response with minimal dose. Drug which is practically insoluble in gastric fluid and having high permeability through the stomach but due to its solubility limitations, in the gastric fluid it could not enter into the systemic circulation [2, 3]. Whereas in the small intestine the drug is soluble but cannot permeate through the membrane due to its permeation limitation [4]. To improve bioavailability and to reduce dosing frequency, a suitable formulation was required with a controlled rate towards the treatment of hypertension and congestive heart failure.

In the present study, the compression coating, floating tablets of carvedilol phosphate were designed and developed from that coat layer causes immediate release and coat with controlled layer polymers using a hydrophilic polymer, hydroxypropyl methyl-cellulose (HPMC K100, K15 and K4) and ethyl cellulose, in combination with carbopol to release for a prolong duration. The compression coating floating tablet may overcome all above limitation which may exhibit benefits to improve the bioavailability, therapeutic efficacy with reduction of side effects. This would be benefit towards the treatment of severe hypertension with prolonged drug action [5-7].

Carvedilol phosphate is a non-selective beta blocker indicated in the treatment of mild to moderate congestive heart failure (CHF). It blocks beta-1 and beta-2 adrenergic receptors as well as the alpha-1 adrenergic receptors [8]. It is a weakly basic drug, with low solubility in alkaline pH. It is available as odorless, crystalline powder. Carvedilol phosphate is more than 98% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol phosphate is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 liter, indicating substantial distribution into extravascular tissues.

Carvedilol phosphate is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. Demethylation and hydroxylation at the phenol ring produce three

active metabolites with b-receptor blocking activity. The 4-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol phosphate for b-blockade. Less than 2% of the dose was excreted unchanged in the urine. The metabolites of carvedilol phosphate is excreted primarily via the bile into the fecal [9-11].

MATERIALS AND METHODS

Materials

Carvedilol phosphate was obtained as a gift sample from Yarrowchem Products, Mumbai. Lactose was purchased from Suvidhinath Laboratories, Baroda. HPMC different grades were purchased from Loba Chemie Ltd, Mumbai. Crospovidone, croscarmellose sodium (CCS), sodium starch glycolate (SSG) were purchased from Hetero Pharma Ltd., Hyderabad. Sodium bicarbonate, microcrystalline cellulose (MCC) were purchased from Qualigens Fine Chemicals, Mumbai. Ethyl cellulose and carbopol were purchased from Finar Chemicals Ltd, Ahmadabad, India. All other ingredients used were of analytical grade.

Methodology

Preparation of carvedilol phosphate core controlled-release tablets

The core layer of 350 mg obtained from different polymeric mixtures of different ratios was taken. The inner core tablets were prepared by using direct compression method. A powder mixture of carvedilol phosphate, HPMC K100, K15, K4, ethyl cellulose, carbopol, citric acid, sodium bicarbonate and lactose ingredients were dry blended for 20 min followed by the addition of magnesium stearate and talc. The mixture was then further blended for 10 min. 350 mg of resultant powder blend was manually compressed using 8 mm punch diameter as mentioned in table 1.

Table 1: Composition of carvedilol phosphate floating tablets (f1-f9)

Batch code	Drug: polymer ratio	Polymer ratio
f1	1:3	0.5:0.5:2 (Ethyl cellulose: carbopol: HPMC K4)
f2	1:5	0.5:0.5:4 (Ethyl cellulose: carbopol: HPMC K4)
f3	1:7	0.5:0.5:6 (Ethyl cellulose: carbopol: HPMC K4)
f4	1:1.25	0.5:0.5:0.25 (Ethyl cellulose: carbopol: HPMC K100)
f5	1:1.5	0.5:0.5:0.5 (Ethyl cellulose: carbopol: HPMC K100)
f6	1:1.75	0.5:0.5:0.75 (Ethyl cellulose: carbopol: HPMC K100)
f7	1:3	0.5:0.5:2 (Ethyl cellulose: carbopol: HPMC K 15)
f8	1:5	0.5:0.5:4 (Ethyl cellulose: carbopol: HPMC K 15)
f9	1:5.5	0.5:0.5:4.5 (Ethyl cellulose: carbopol: HPMC K 15)

Preparation of carvedilol phosphate immediate release tablets as a coating material

The coat layer of 100 mg obtained from different polymeric mixtures of different ratios were taken. A powder mixture of carvedilol phosphate, MCC, lactose, SSG, crospovidone and CCS were dry blended for 20 minutes followed by addition of magnesium stearate. The mixture was then further blended for 10 min. 100 mg of resultant powder blend was manually compressed with 6 mm punch diameter to obtain the coat tablet for preliminary studies as mentioned in table 2.

Table 2: Composition of immediate release tablets for coat materials (sf1-sf9)

Batch code	Drug: polymer ratio	Polymer ratio to total blend
sf1	1:0.25	Crospovidone(5%)
sf2	1:0.5	Crospovidone(10%)
sf3	1:0.75	Crospovidone(15%)
sf4	1:0.25	Croscarmellose sodium(5%)
sf5	1:0.5	Croscarmellose sodium(10%)
sf6	1:0.75	Croscarmellose sodium(15%)
sf7	1:0.25	Sodium starch glycolate(5%)
sf8	1:0.5	Sodium starch glycolate (10%)
sf9	1:0.75	Sodium starch glycolate (15%)

Preparation of carvedilol phosphate compression coating floating tablets

Coating material containing 50% equivalent of the drug was placed in the die cavity of 9 mm punch diameter. The core tablet was then placed in the centre of the die cavity, which was filled with the remainder of the coat formulation and compressed. Based on preliminary trials on the carvedilol phosphate compression coating floating tablets, formulation of F1 to F9 were designed and evaluated for the release profile of both immediate release and for controlled release profile of carvedilol phosphate.

Evaluation tests for compression coating floating tablets

Compression coating floating tablets were separated into immediate release (IR) and sustained release (SR) layer. Assays were performed for both IR and SR layers separately. To each of the layer, the following estimation procedure was carried out.

Pre-formulation studies

The following pre-formulation studies were performed with carvedilol phosphate dry blend with formulation components.

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose 'θ'. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by the fixed funnel and free-standing cone method. An accurately weighed 5 g powders of carvedilol phosphate were carefully poured into the funnel with its tips about 2 cm height (h) until the apex of the conical heap formed to be just reached the tip of the funnel [12]. The mean diameter (r) and height were calculated and the angle of repose (θ) was calculated by using formula $\theta = \tan^{-1}(h/r)$.

Bulk density and tapped density

A quantity of 5 gm of carvedilol phosphate, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder of the tapped density apparatus maker of Campbell electronics, Mumbai. The initial volume was observed and the cylinder was allowed to hit a height of 2.5 cm at 2 s intervals until there were no further changes in volume. Both bulk density (Db) and tapped bulk density (Dt) were determined.

Carr's index (I): It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I = (Dt - Db/Dt)100$$

Where 'Dt' is the tapped density and 'Db' is the bulk density of the powder.

Hausner's ratio

This indicates the flow properties of the powder and measured by the ratio of tapped density to the bulk density.

Physical evaluation tests

The tablets were tested for post-compression quality control tests like hardness, friability, weight variation, disintegration test, tablet thickness and *in vitro* buoyancy studies.

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand the mechanical shock of handling in manufacture, packaging and also in shipping. The hardness was tested for 6 tablets from each formulation batch using Monsanto hardness tester [13].

Friability testing

Friability is the tendency for a tablet to chip, break or crumble following compression. Tablets need to be hard enough so that they do not break up in the bottle but friable enough to disintegrate in the gastrointestinal tract. As specified in the United State Pharmacopoeia (USP) weight variation test was run by taking 10 tablets. The weight (W1) of those tablets was determined before re dusted prior to weighing. The tablets were then placed in a test drum of friability tester 'FR1000' of Copley Scientific, Mumbai, India and allowed to rotate for 100 times. The tablets were reweighed (W2) having first removed accumulated dust to them. The result was calculated in terms of % weight loss by utilizing the following formula.

$$\text{Friability (\%)} = \frac{W1 - W2}{W1} \text{x } 100$$

The maximum weight loss not less than 1% be normally acceptable [14].

Swelling studies

Sustained released dosage forms were weighed individually (w_1) and placed separately in petri dishes containing 4 ml of medium. At regular interval viz. 0.5, 1, 2, 3, 4, 5h the dosage forms were removed from the petri dishes and excess surface water was removed by using filter paper. The dosage forms were reweighed (w2) and swelling index (SI) was calculated by using following formula [15].

$$SI = \frac{w2 - w1}{w1}$$

Where w_1 was the initial and w_2 was the final weight of the tablet.

Tablet density

Tablet density (ρ) is an important parameter for floating tablets. The tablet floats when its density is less than that of gastric fluid (1.004 g/cc). The tablet density was determined by using following formula [16].

$$v = \pi r^2 h$$

$$\rho = \frac{m}{v}$$

Where v = volume of the tablet (cc); r = radius of the tablet (cm); h = crown thickness of the tablet (mm); m = mass of the tablet.

Disintegration test

To test for disintegration time, one tablet was placed in each tube, and the basket rack was positioned in a 1-liter beaker of the medium at 37±2 °C. The standard motor driven device was used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Perforated plastic discs were placed on top of the tablets [17].

***In vitro* buoyancy and total floating time studies**

The *in vitro* buoyancy was determined by floating lag time. Formulated tablets of each batch were placed in a 100 ml beaker containing 0.1N HCl and the time required for the each table to rise to the surface was determined as floating lag time. The total floating time of granules in each batch was also recorded [18].

***In vitro* drug release studies**

In vitro dissolution studies were performed in a USP XXIII dissolution test apparatus, type II (paddle method) (Disso 2000, Lab India, India) at 37±0.5 °C and with a paddles rotation speed of 50 rpm. The compression coating floating tablets were placed into 900 ml of 0.1 N HCl solution (pH 1.2) as the dissolution medium. The tablets were placed in 316 stainless steel sinkers which kept them in sink condition during the dissolution study. Dissolution studies were carried out in triplicate. 10 ml aliquots of samples were collected at 1h interval up to 16 h. They were filtered and estimated for carvedilol phosphate release using UV-visible spectrophotometer at 241 nm. At each time of withdrawal, 10 ml of fresh medium was replaced into the dissolution flask. The concentrations were calculated using the standard calibration curve prepared using 0.1N HCl as a solvent. The cumulative percentage of carvedilol phosphate released from compression coating floating tablets was calculated [19].

Release kinetic study

To study the release kinetics, the data obtained from *in vitro* drug release studies were plotted in various kinetic models as follows:

1. Zero-order: Cumulative % of drug released versus time;

2. First order: Log cumulative % of drug remaining versus time;

3. Higuchi: Cumulative % of drug released versus square root of time; and

4. Korsmeyer–Peppas: Log cumulative % of drug released versus log time.

The linearity of the plots was obtained from the values of regression coefficient (R^2). The model with the highest linearity (R^2 value approaching unity) was chosen as the best fit kinetic model [20].

Accelerated stability studies

Short-term accelerated stability testing was carried out according to ICH guidelines considering 40±2 °C/75±5% relative humidity (RH) in a stability chamber for a period of 6 mo. The compression coating floating tablets of optimized formulation was subjected to stability chamber at a minimum of three-time points, including the initial, intermediate and final time points (e. g., 0, 3, and 6 mo). At the end of 3rd and 6 mo of the tablets exposed to stability chamber were again analyzed for their physical appearance, assay (%) and *in vitro* drug release profile at 1st,2nd, 12th and 16th h [21].

RESULTS AND DISCUSSION

Micromeritic properties of the pre-compressed powder blend

Micromeritic properties of pre-compressed powder blend were evaluated and cited in table 3. The angle of repose found to be within the limit of 20.34±0.04 to 29.88±0.24. Bulk density was found between 0.105 to 0.129 g/cc and tapped density was between 0.112 to 0.162 g/cc. The result cited in the table indicated good flow as it varied from 20 to 30. In addition to that, carr's index was found to vary from 11.84 to 31.41, which indicated good compressibility.

Physical characterization of carvedilol phosphate tablets with floating polymers

Physical characterization of carvedilol phosphate tablets formulated with floating polymers was evaluated and displayed in table 4. The hardness of tables ranged from 3.8 kg/cm^2 to 4.3 kg/cm^2. During the study, it observed that a formulation having HPMC grades of low viscosity has a low swelling index as compared to higher viscosity grades of HPMC. As per US pharmacopoeia, the maximum percentage friability should not exceed 1%. The prepared tablets lie within the acceptable and passed the friability test ranged from 0.33

to 0.44. All the tablets have shown excellent uniform thickness and no such variation was found. All the tablets have shown acceptable tablet densities between 0.968 to 0.996 g/cc, which were less than that of gastric fluid (1.004 g/cc), resulting in all of them to float. Drug content study of prepared batches at various concentrations with the drug has shown majorly drug content in between 90-94%.

Table 3: Evaluation of pre-compression parameters

Batch code	Angle of repose (X±SD)	Bulk density(g/cc) (X±SD)	Tapped density(g/cc) (X±SD)	Hausner's ratio	Compressibility index (Carr's index)
f1	20.34±0.04	0.114±0.03	0.134±0.04	1.17	14.92
f2	21.32±0.12	0.106±0.02	0.122±0.03	1.15	13.11
f3	20.42±0.08	0.105±0.03	0.127±0.01	1.21	17.32
f4	20.52±0.6	0.129±0.02	0.148±0.03	1.14	12.83
f5	20.47±0.22	0.122±0.03	0.154±0.02	1.26	20.78
f6	24.28±0.34	0.135±0.02	0.162±0.01	1.2	16.66
f7	23.56±0.4	0.134±0.01	0.152±0.03	1.13	11.84
f8	25.28±0.26	0.107±0.02	0.156±0.02	1.45	31.41
f9	29.88±0.24	0.129±0.03	0.152±0.02	1.17	15.13

Data are represented as mean(X)±standard deviation (SD), n=3

Evaluation of *in vitro* buoyancy and total floating time

Lag time and total floating time were performed visually. The evaluation of prepared floating tablet batches have shown that batches f1, f2, f4, f5, f7, f8, were having a lag time between 36-80 s and total floating time between 14-23 h and batches f3, f6, f9 were having lag time between 112-155 seconds and total floating time between 21-27 h. This study suggested that as the quantity of HPMC increased in the formulation, lag time and total floating time of tablet increased. The f9 batch was selected in order to produce tables with good gel strength, entrapping carbon dioxide gas, imparting stability and persistent buoyancy up to 27 h.

Table 4: Post compression studies of carvedilol phosphate tablets formulated with HPMC K4 (f1-f3), K100 (f4-f6) and K15 (f7-f9)

Batch code	Weight variation (mg) (X±SD)	Hardness (kg/cm²) (X±SD)	Friability (%) (X±SD)	Thickness (mm) (X±SD)	Density (g/cc)	Swelling index	Lag time(s) (X±SD)	Floating Time(h) (X±SD)	Drug Content (%) (X±SD)
f1	346±0.2	3.9±1.01	0.34±0.02	3.46±0.6	0.974	8.26	36±6	16±3	90±1.24
f2	351±0.5	3.8±1.04	0.33±0.03	3.3±0.8	0.982	26.33	40±8	18±1.6	91±2.46
f3	348±0.5	3.9±1.05	0.33±0.05	3.5±0.9	0.996	45.5	125±6	23±2.4	92±1.48
f4	344±0.5	4.3±1.02	0.44±0.11	3.48±0.5	0.968	8.6	80±4	14±2.6	90±1.54
f5	348±0.2	3.9±0.8	0.42±0.2	3.57±0.7	0.976	18.36	65±7	16±1.8	91±1.65
f6	348±0.6	4.2±0.9	0.37±0.12	3.6±0.5	0.985	26.2	155±4	21±0.6	92±1.74
f7	352±0.4	4.1±1.17	0.43±0.16	3.42±0.8	0.979	8.60	52±6	23±0.8	92±1.82
f8	351±0.6	4.1±1.25	0.42±0.08	3.7±0.4	0.986	18.36	56±9	22±0.9	93±1.42
f9	349±0.4	3.8±1.1	0.35±0.1	3.8±0.8	0.989	26.2	112±8	27±1.4	94±1.84

Data are represented as mean(X)±standard deviation (SD), n=3

Dissolution studies of carvedilol phosphate tablets with floating polymers

The formulated batches f1 to f9 were subjected to drug release studies in dissolution media of 0.1N HCl. The formulation f1-f3 those containing drug and HPMC K4, the maximum amount of the drug was released in f2 of 91.3% in 8h. Among the f4-f6 containing K100, the maximum amount of the drug was released in f4 of 90.5% in 6h. Similarly in f7–f9, containing K15, the maximum amount of the drug was released in f9 of 95.3% in 16 h as displayed in table 5. From these studies, based on drug release profile and duration of release, batch f9 was selected as the best batch.

Table 5: % Release of drug formulated with floating polymers

Dissolution medium	Time (h)	f1	f2	f3	f4	f5	f6	f7	f8	f9
		HPMC K4			HPMC K100			HPMC K15		
0.1N HCL	1	26.1	28.2	29.5	15.2	17.1	18.2	16.6	5.6	3.6
	2	38.2	35.5	36.5	26.6	28.2	29.1	22.5	12.6	9.8
	3	49.1	48.1	47.2	40.5	65.5	68.2	33.5	18.5	15.3
	4	69.3	69.3	66.2	65.5	72.5	78.3	46.6	28.5	21.2
	5	77.2	75.5	77.3	79.5	83.2	84.1	56.2	36.5	29.8
	6	80.2	81.1	88.2	90.5	90.2	90.1	65.3	42.5	37.2
	7	91.2	86.2	89.2	--	--	--	75.5	50.5	43.1
	8	--	91.3	91.1	--	--	--	82.5	60.2	54.2
	10	--	--	--	--	--	--	90.5	75.2	68.3
	12	--	--	--	--	--	--	--	85.2	78.6
	14	--	--	--	--	--	--	--	92.5	89.6
	16	--	--	--	--	--	--	--	--	95.3

The physical characterization of carvedilol phosphate tablets formulated with super disintegrants

Physical characterization of carvedilol phosphate tablets formulated with super disintegrating polymers was evaluated and displayed in table 6. The hardness of tables ranged from 3.1 kg/cm^2 to 3.3 kg/cm^2. The disintegration times for prepared batches have shown 36 to 87 seconds. During the study, it observed that a formulation having increased super disintegrates concentration has less disintegration time. All the prepared tablets lie within the acceptable and passed the friability test ranged from 0.42 to 0.77. Drug content study of prepared batches at various concentrations with the drug has shown majorly drug content in between 95-98%. The sf9 batch was selected in order to produce a tablet with faster disintegrating within 36 s.

Table 6: Post compression studies of carvedilol phosphate tablets formulated with crospovidone (sf1-sf3), CCS (sf4-sf6) and SSG (sf7-sf9)

Batch code	Weight variation (mg) (X±SD)	Hardness (kg/cm^2) (X±SD)	Friability (%) (X±SD)	Disintegration (seconds)(X±SD)	Drug content (%) (X±SD)
sf1	100±0.79	3.1±0.2	0.56±0.12	87±3	95±1.82
sf2	108±0.98	3.2±0.2	0.43±0.3	68±5	96±1.44
sf3	107±0.69	3.1±0.2	0.43±0.02	44±12	95±1.47
sf4	101±0.67	3.3±0.2	0.54±0.01	63±9	95±1.64
sf5	105±0.21	3.2±0.2	0.42±0.21	55±8	96±1.32
sf6	96±0.1	3.1±0.2	0.77±0.12	43±7	98±1.24
sf7	101±0.67	3.2±0.2	0.53±0.14	54±15	95±1.28
sf8	104±0.21	3.2±0.2	0.62±0.22	48±8	96±1.46
sf9	99±0.1	3.1±0.2	0.65±0.16	36±4	98±1.78

Data are represented as mean±standard deviation (SD), n=3

The dissolution studies of tablets formulated with super disintegrants

The formulated batches sf1 to sf9 were subjected to drug release studies in dissolution media of 0.1N HCL. The formulation sf1-sf3 those containing drug and crospovidone, the maximum amount of the drug was released in sf3 to 92.2% in 20 min. Among the sf4-sf6 containing CCS, the maximum amount of the drug was released in sf4 of 92.4% in 20 min. Similarly in sf7-sf9 containing SSG the maximum amount of the drug was released in sf9 of 97.2% in 15 min as displayed in table 7. From these studies based on drug release and time to disintegrate, batch sf9 was selected as the best batch.

Table 7: % drug release of tablets with different concentrations of super disintegrants

Dissolution medium	Time (Min)	sf1	sf2	sf3	sf4	sf5	sf6	sf7	sf8	sf9
		Crospovidone			CCS			SSG		
0.1N HCL	5	18.2	19.2	20.52	19.8	20.1	22.1	23.1	25.2	30.5
	10	48.3	48.1	68.2	66.5	65.2	68.2	59.2	64.5	67.34
	15	76.1	68.3	82.1	83.1	82.2	82.1	90.2	95.5	97.2
	20	85.5	87.1	92.3	92.4	92.1	92.2	--	--	--
	25	90.2	90.2	--	--	--	--	--	--	--

Drug release study of compression coating floating tablet in dissolution apparatus

For confirmation and optimization of compression coating floating tablet, the individual batches f1-f9 for controlled release formulation as core tablet and powder blend as per sf1 to sf9 for immediate release were formulated as F1 to F9 and evaluated for release of carvedilol phosphate in a dissolution medium of 0.1N HCl. Immediate release profile was studied at 5, 10, 15, 20, 25 min respectively and cumulatively calculated for controlled release profile in 1 h to 16 h. From the above studies, it was concluded that the release rate of F9 has shown a steady immediate release within 15 min similar to that of an individual batch of sf9 and the concentration became more flatter with a continuous release for 16h similar to that of an individual batch of f9. The graphical release pattern is displayed in fig. 1.

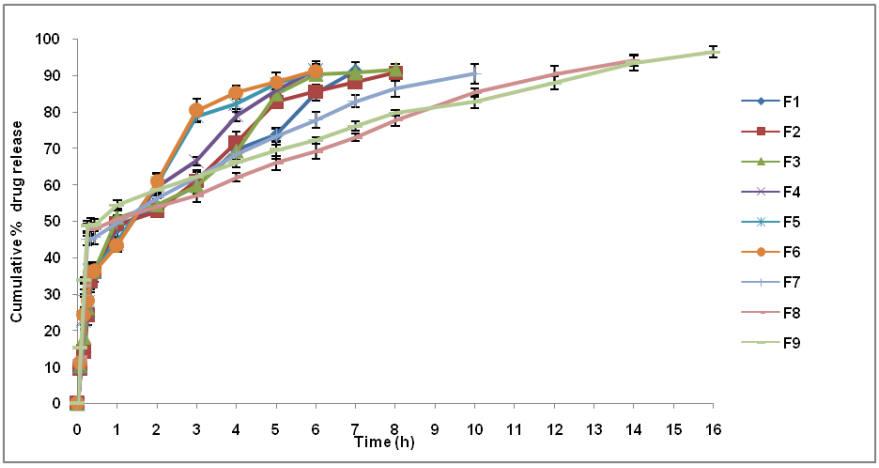

Fig. 1: *In vitro* dissolution study of all formulations (F1-F9), (Data are represented as mean±SD, n=3)

Drug release study of reproduced batches of the best batch

Further to confirm the release pattern and to observe the reproducibility of the best batch again five trial batches of F9 were compressed (T1 to T5) and their release profile was studied. The average release of these five batches and their standard deviations was plotted in fig. 2. From the above studies, it was concluded that the release rate was maintaining immediate release as well as a controlled release for continuously up to 16 h, which were reproducible and predictable in nature.

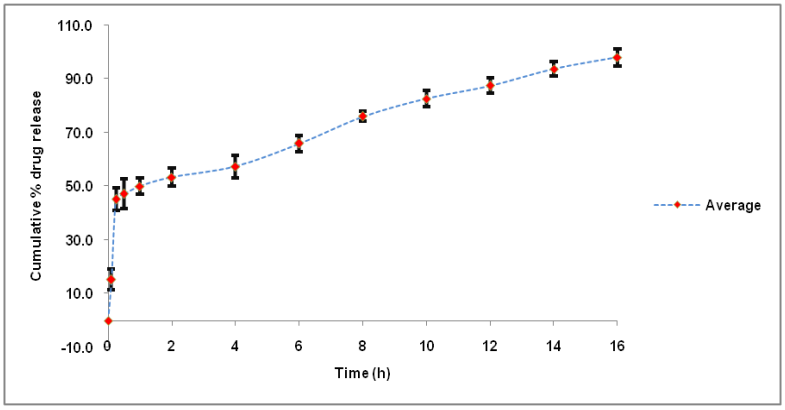

Fig. 2: Average cumulative % drug release of compression coating floating tablets (T1–T5) with error bars, n=5

Drug-excipients interaction studies

Drug-excipients interaction studies were performed using FTIR spectrophotometer. The FTIR spectra for the formulation and pure drug are shown in fig. 3-5.

Characteristics peaks obtained for the pure drug correlated well with that of the formulation peaks. These indicated that the drug was compatible with the formulation components and there ware no chemical interactions between the drug and excipients used.

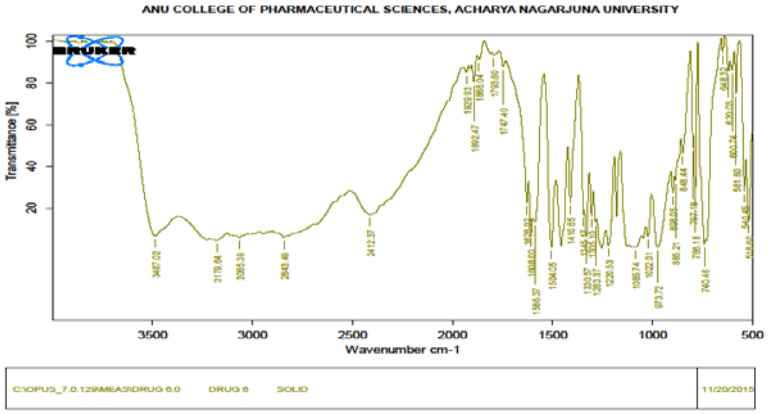

Fig. 3: IR Spectrum for carvedilol phosphate

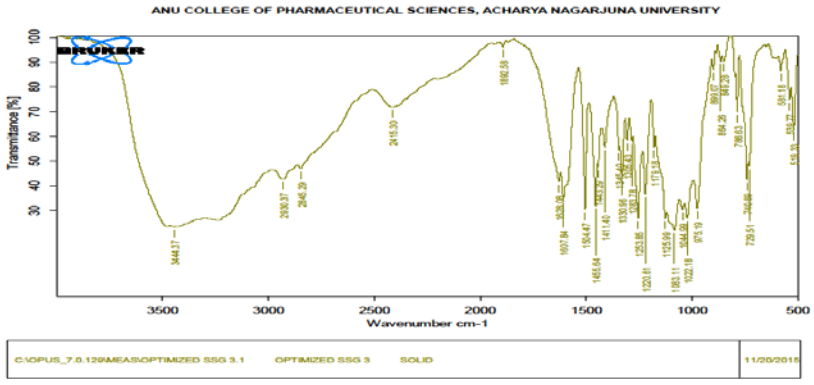

Fig. 4: IR Spectrum for carvedilol phosphate with HPMC K15 optimized formula

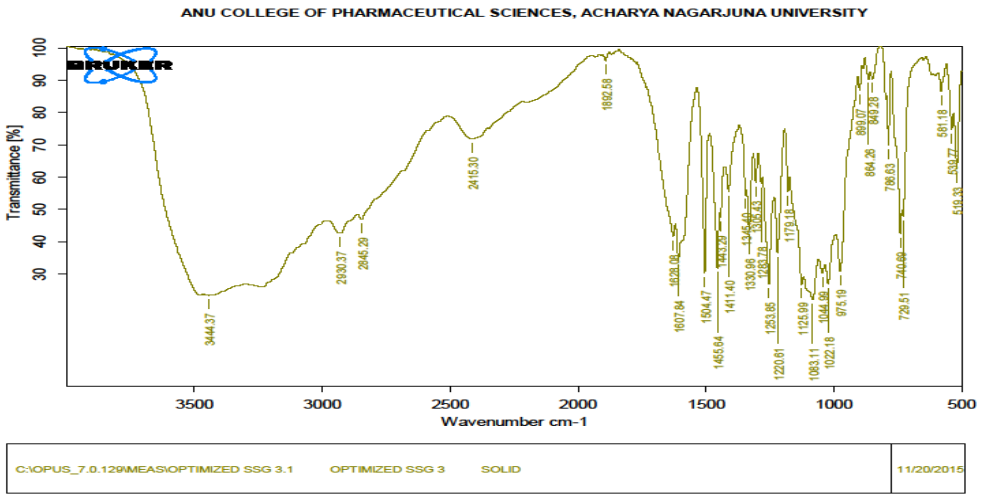

Fig. 5: IR Spectrum for carvedilol phosphate with SSG optimized formula

Table 8: Accelerated stability studies report of compression coating floating tablet

Period	Dissolution (%)				Assay (%)	Appearance
	1st h	2nd h	12th h	16th h		
Initial (0 mo)	50.4±1.2	53.5±2.3	87.9±2.6	96.4±1.7	96.2±3.2	Off white
Intermediate (3 mo)	50.8±1.8	52.4±3.1	84.6±1.7	94.5±1.4	95.3±2.3	Off white
Final (6 mo)	51.3±1.4	54.1±3.2	87.7±1.5	95.6±2.1	95.4±2.4	Off white

Data are represented as mean±SD, n=3

Accelerated stability study of best batch

The accelerated stability study report revealed that the formulation has not undergone any physical or chemical degradation during the period. There was no significance change in the *in vitro* drug release and drug assay as shown in table 8.

Pharmacokinetic report

The kinetic summary from fig. 6 to fig. 9 revealed that carvedilol phosphate extended-release tablets followed zero-order kinetics as the regression coefficients approached unity, indicating that the drug release was independent of drug concentration.

The Higuchi plots also has shown good linearity, indicating that the drug release was proportional to the square root of time and the drug was released at a slower rate.

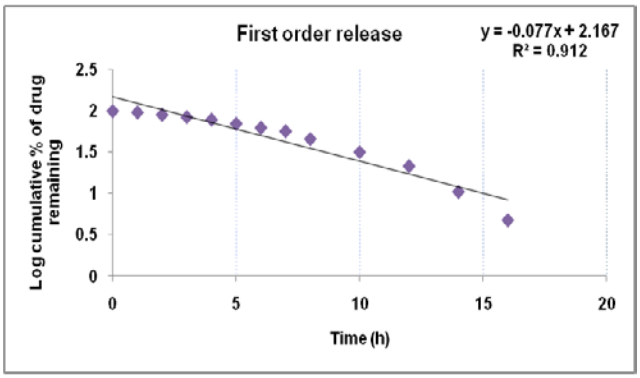

Fig. 7: First order drug release of carvedilol phosphate in f9

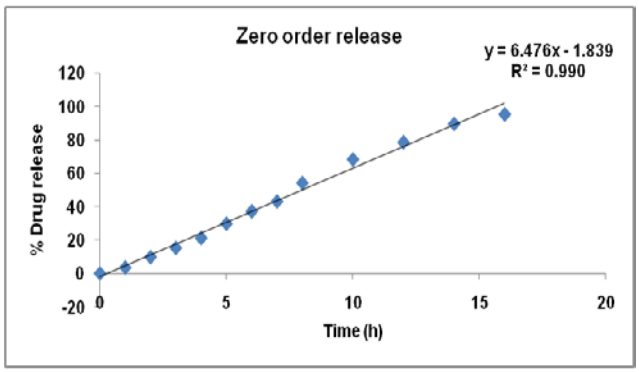

Fig. 6: Zero order drug release of carvedilol phosphate in f9

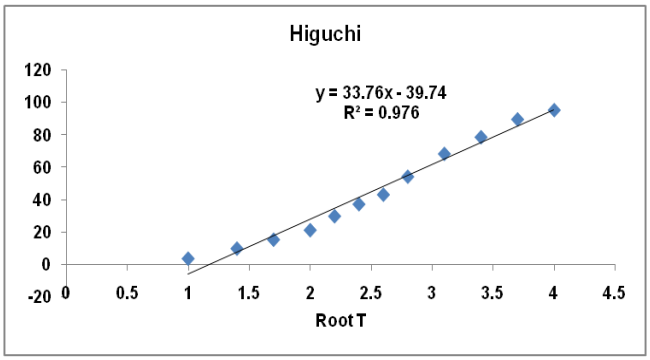

Fig. 8: Higuchi graph of drug release of carvedilol phosphate in f9

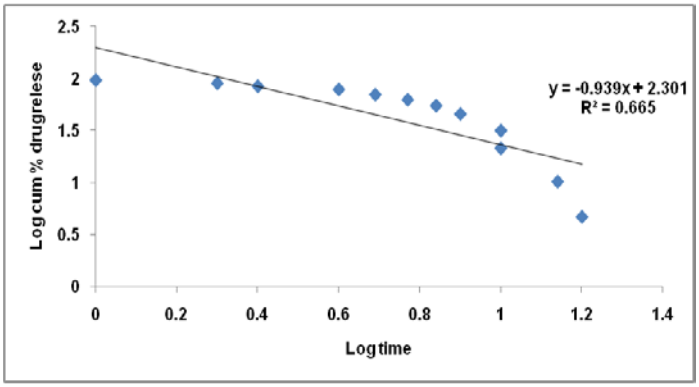

Fig. 9: Peppas graph of drug release of carvedilol phosphate in f9

CONCLUSION

During this study, both immediate release and controlled release tablets of carvedilol phosphate were formulated by designing compression coating floating drug delivery system. Among formulated batches based on performance with respected to buoyancy, log time, release pattern F9 was selected as a best formula. For the better onset of action, immediate release coat has provided dissolution within 15 min and the controlled release floating core tablet has shown a buoyancy time of 36s with total floating time for 16h. The newly developed tablets also have shown both pre-compression and post-compression characters within expectable limits. There were no formulation problems associated with the optimized batch of carvedilol phosphate compression coating floating tablets. The tablets also passed the short-term accelerated stability studies, indicating that the physical and chemical stability of the product. The compression coating floating tablet was the best dosage form for the treatment of hypertension because it was reported the constant drug action which was needed the entire day and it would improve maximum therapeutic efficacy with patient compliance.

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AUTHORS CONTRIBUTION

Experimental design, guidance for the project and writing of this manuscript was done by Subhranshu Panda. Second author Ch. Surya Kumari supported to draft manuscript design and correction of data. Third author G. Puniya performed the experiments, analysed spectra and interpreted the result.

CONFLICT OF INTERESTS

All authors have none to declare

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