ORIGINAL RESEARCH

Formulation and optimization of chronomodulated press-coated tablet of carvedilol by Box–Behnken statistical design

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Objective: The primary objective of the present investigation was to formulate and optimize chronomodulated press-coated tablets to deliver the antihypertensive carvedilol at an effective quantity predawn, when a blood pressure spike is typically observed in most hypertensive patients.

Experimental work: Preformulation studies and drug excipient compatibility studies were carried out for carvedilol and excipients. Core tablets (6 mm) containing carvedilol and 10-mm press-coated tablets were prepared by direct compression. The Box–Behnken experimental design was applied to these press-coated tablets (F1–F15 formula) with differing concentrations of rate-controlling polymers. Hydroxypropyl methyl cellulose K4M, ethyl cellulose, and K-carrageenan were used as rate-controlling polymers in the outer layer. These tablets were subjected to various precompression and postcompression tests. The optimized batch was derived both by statistically (using desirability function) and graphically (using Design Expert® 8; Stat-Ease Inc). Tablets formulated using the optimized formulas were then evaluated for lag time and in vitro dissolution.

Results and discussion: Results of preformulation studies were satisfactory. No interaction was observed between carvedilol and excipients by ultraviolet, Fourier transform infrared spectroscopy, and dynamic light scattering analysis. The results of precompression studies and postcompression studies were within limits. The varying lag time and percent cumulative carvedilol release after 8 h was optimized to obtain a formulation that offered a release profile with 6 h lag time, followed by complete carvedilol release after 8 h. The results showed no significant bias between predicted response and actual response for the optimized formula.

Conclusion: Bedtime dosing of chronomodulated press-coated tablets may offer a promising alternative to control early morning hypertensive increase.

Keywords: Box–Behnken, carvedilol, chronotherapy, hypertension, optimization, press coating

Introduction

Circadian variation in the severity and onset of many diseases over a 24-h period is well known.[1–3] Chronobiology shows that in most people, both normotensive and hypertensive, blood pressure (BP) rises rapidly in the early morning hours, the time when most individuals wake and begin their days, ie, 6 am–10 am, due to increased secretion of catecholamines and increased plasma renin activity during the night.[4] Specifically, the "dippers" type of hypertensives that constitute approximately two-thirds of all hypertensives show a drop in BP during the night and an increase during early morning hours. Takeda et al have also described that cardiovascular organs are

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35

closely related to circadian rhythm, and that an increased incidence of myocardial infarction, cerebral infarction, atrial fibrillation, stroke, and heart attack have been observed due to early morning surges in blood pressure.[5]

Conventional slow-release (SR) medications formulated to ensure a near-constant drug concentration may not provide for spurts of increased drug concentration in order to control hypertension during these critical times. Conventional once-daily extended-release drugs usually sustain drug concentration over the 24-h dosing interval. Although this profile offers safe and effective BP lowering, this static pattern of drug release is not tailored to meet time-specific physiologic variations in BP.[6]

Clearly, in drug design, the notion that "one size fits all at all times" is not correct. This 24-h rhythm in disease risk in addition to evidence of the effect of 24-h rhythm on drug pharmacokinetics, effects, and safety constitutes the rationale for chronotherapy as a pharmacotherapy approach. One alternative to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are likely to be most effective and/or best tolerated. Chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules and a drug-delivery system to synchronize drug concentrations to rhythms in disease activity.[7]

Hence, the rationale of chronotherapy for hypertension is to deliver the drug in higher concentrations during the early morning postawakening period, when BP is highest, and in lesser concentrations in the middle of a sleep cycle, when BP is low. Thus, night-time antihypertensive medication that is more specific for the early morning surge of BP in addition to 24-h BP control would be useful for the prevention of cardiovascular events in hypertensive patients.

Many approaches have been investigated in chronotherapy for hypertension, such as Verelan® PM (chronotherapeutic oral drug absorption system for verapamil) (Elan Drug Technologies, King of Prussia, PA) and Covera-HS® (controlled-onset extended release verapamil) (Alza Corporation, Mountainview, CA) that provide control of hypertension according to circadian pattern.[8,9]

In the present work, we examined the drug carvedilol, a beta-adrenergic blocker without intrinsic sympathomimetic activity that is safe and effective for treating hypertension, left ventricular dysfunction, and heart failure. The drug's half-life is 6–10 h and it is extensively metabolized by first-pass metabolism.[10] There are currently no reports of any marketed formulations of carvedilol for chronotherapy that address early morning surges in BP.

The approach selected was a press-coated tablet (ie, tablet-in-tablet design), which is a time- and rate-controlled drug-delivery device. This consists of an inner immediate release core tablet containing the drug and an outer layer consisting of various rate-controlling polymers, which slowly swell and erode during the requisite lag time. This press-coated approach offers several benefits, including that it is simple, versatile, has a solvent-free coating, and economical at the production scale compared to other pharmaceutical platform technologies which have been reported for such pulsatile drug delivery.[11–13] Recently, TIMERx platform technology with an erosion mechanism has been developed to achieve chronotherapeutic delivery of oxymorphone.[14]

In this work, we attempted to formulate and optimize chronomodulated press-coated tablets of carvedilol for administration at bedtime with a 6-h lag time for modulation of rapid release of carvedilol during morning hours.

Press-coated tablets consist of (i) an inner core tablet containing carvedilol, croscarmellose (superdisintegrant) PVP K-30 (dissolution-enhancing agent) since carvedilol is a biopharmaceutics classification system (BCS) class II drug and (ii) an outer coat layer containing hydrophilic polymers hydroxypropyl methylcellulose (HPMC) K4M, k-carrageenan, and hydrophobic polymer ethylcellulose (EC). These components simultaneously control the rate of swelling and erosion of the outer coat until the desired lag time has been achieved.[15–18] The ratio of hydrophilic polymers that affects the lag time, ie, the amount of HPMC K4M, EC, and K-carrageenan in the outer layer, were selected based on screening experiments. This ratio was confirmed using computer-aided optimization using a three factors, three-level, Box–Behnken experiment design (BBD) with constraints on lag time and percent cumulative carvedilol release after 8 h.

Materials and methods
Materials

Carvedilol was obtained as a gift from Symed Labs, Ltd (Hyderabad, India). Microcrystalline cellulose (Avicel PH101; Thrien Enterprise, Ahmedabad, India), polyvinyl pyrrolidone K30 (PVP K 30) as dissolution enhancer (Kollidon 30; Signet Chemical Corporation, Mumbai, India), Croscarmellose sodium as superdisintegrant (Astron Chemicals, Ahmedabad, India), talc as glidant (Best Pharma, Ahmedabad, India), magnesium stearate as lubricant (Chemdyes Corporation, Vadodara, India) and Brilliant Blue as a coloring agent (Suvidhinath Laboratories, Vadodara, India) were used for preparation of the core tablet. HPMC K4M as the

rate-controlling hydrophilic polymer (Signet), ethyl cellulose (Signet) as the rate-controlling hydrophobic polymer, and K-carrageenan as the thin gel-forming polymer (Mayur Corporation, Mumbai, India) were used in the outer coat layer.

All other ingredients and reagents were of analytical grade and were used as received.

Preformulation studies
Drug-excipient compatibility studies
Fourier transform-infrared spectroscopy
Infrared spectra were acquired using the potassium bromide pellet technique on a Shimadzu Fourier transform-infrared (FT-IR) WQF 520 Spectrophotometer (Shimadzu, Tokyo, Japan) in the wavelength region of 4000 to 500 cm^{-1}. The procedure consisted of dispersing a sample (drug alone, mixture of drug and excipients, or formulation) in potassium bromide, and compressing the sample into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. Spectra were obtained for the three pellets.

Differential scanning calorimetry
Dynamic light scattering (DSC) analysis of (a) pristine carvedilol, (b) tablet triturate of the core tablet without carvedilol, and (c) core tablet powder triturate were carried out on DSC Model 60 calorimeter (Shimadzu) at a temperature range of 500°C–3000°C at the rate of 200°C per min. These spectra were analyzed for possible interactions in the thermal peaks of the drug peak.

Micromeritic properties
The angle of repose of carvedilol and the formulation mixture of the core tablet was determined by the fixed funnel method.[11] The loose bulk density and tapped bulk densities were determined using a density apparatus (Metalab Industries, Mumbai, India). Carr's index (%) and the Hausner's ratio were also calculated.[19]

Formulation of an optimized carvedilol core tablet (OCT)
Based on preliminary laboratory studies, the formulation for the core tablets was optimized using different concentrations and types of diluents, disintegrant, and binders as shown in Table 1.

Core tablets were prepared by direct compression. All ingredients were passed through a sieve No 120 and then accurately weighed on an electrical balance (Shimadzu). carvedilol (6.25 mg/tablet), Avicel PH101 (65.56% w/w), croscarmellose (7.5% w/w), and PVP K 30 (15.6% w/w)

Table 1 Formula table for optimized core tablet of carvedilol

Sr no	Ingredients	Quantity per tablet (mg)	Category
1	Carvedilol	6.25	Drug
2	Microcrystalline cellulose (MCC)	52.45	Directly compressible filler
3	Polyvinyl pyrrolidone (PVP K 30)	12.50	Dissolution enhancer
4	Croscarmellose sodium	6.00	Superdisintegrant
5	Magnesium stearate	0.80	Glidant
6	Talc	1.60	Lubricant
7	Brilliant blue	0.40	Color
	Total weight	80 mg	

were mixed in geometric proportions and blended in a Rolex Double Cone Blender (DSPL Ltd, Mumbai, India) for 30 min.

Magnesium stearate (1% w/w) and talc (2% w/w) were added to the mixture and mixed for 10 min. Brilliant Blue (0.5% w/w of tablet blend) was used as the coloring agent in the core for easy visibility of tablet disintegration after coat rupture. Tablets were compressed within 6 mm of concave-faced SS punches on a Shemdew 18-station Tablet Compression Machine (Shemdew, Mumbai, India). Hardness was adjusted to 4 kg/cm^2 using a Monsanto hardness tester (Shimadzu).

Experiment design
Initial screening trials were carried out to evaluate the formulation and processing of press-coated tablets. Variations in the quantities of hydrophilic and hydrophobic polymers affect the lag time and percent carvedilol release.

Table 2 Presentation of Factors and factor levels investigated in Box–Behnken experimental design

Independent factors	Unit	Levels		
		Low	middle	high
		−1	0	1
X_1 = amount of HPMC K4M in outer coat	mg	115.2	126	136.8
X_2 = amount of ethyl cellulose in outer coat	mg	92	100	108
X_3 = amount of K-carrageenan in outer coat	mg	12.8	14	15.2
Responses (dependent factors)				
Y_1 = lag time at which tablet ruptured	h			
Y_2 = percent cumulative carvedilol release after 8 h	%			

Abbreviation: HPMC, hydroxypropyl methylcellulose.

When an admixture of HPMC, K4M, and ethylcellulose were used as the rate-controlling polymer in the outer coat, premature release of carvedilol occurred. One reason may be that pores created in the outer layer did not adequately control water penetration up to the core. To overcome this problem of premature drug release, a natural gelling agent such as K-carrageenan was added; this chemical forms a viscous layer in the outer coat and prevents premature release of carvedilol. K-carrageenan was selected as the third polymer for the outer layer to control erosion.

Based upon the discussed preformulation studies, three independent variables, X_1 = amount of HPMC K4M, X_2 = amount of EC, and X_3 = amount of K-carrageenan were selected at three levels (low, medium, and high). Y_1 = lag time in h and Y_2 = percent cumulative carvedilol release after 8 h were selected as dependent factors.

A three-factor, three-level BBD was used to explore quadratic response surfaces and construct second order polynomial models using Design Expert 8 (Version 8.0.7.1; Stat-Ease Inc, Minneapolis, MN).[20]

The number of experiments (N) required for the development of BBD is defined as

$$N = 2k(k - 1) + Co,$$

where k is number of factors and Co is the number of central points.

Since there are three factors, three levels, and three center points, the number of runs according to the above equation is $N = 2 \times 3(3 - 1) + 3 = 15$ runs. The 15 experiments included the use of three center runs, which were necessary to avoid singularity and to verify any change in the estimation procedure.[21]

This design is suitable for exploration of quadratic response surfaces and for construction of second-order polynomial models, thus helping to optimize the process by using a smaller number of experimental runs (15 runs). This is more feasible than normal three-level three-factor (3^3) full factorial design (27 runs).

The model is of the following form:

$$Y = b_0 + b_1X_1 + b_3X_2 + b_3X_3 + b_4X_1X_2 + b_5X_1X_3 + b_6X_2X_3 + b_7X_1{}^2 + b_8X_2{}^2 + b_9X_3{}^2 + E,$$

where Y is the selected response, b_0–b_9 are the regression coefficients, X_1, X_2, and X_3 are the factors studied, and E is an error term.

For statistical calculations, the variables X_i were coded as x_i according to the following relationship:

$$x_i = \frac{X_i - X_0}{\delta X},$$

where x_i is the coded value of the ith test variable, X_i the uncoded value of the ith test variable, X_o the value of X_i at the center point of the investigated area, and δX is the step change value.[22]

Formulation of carvedilol press-coated tablet[15]

The previously prepared 6-mm core tablets were press-coated with different coating blends as per a previously outlined experimental design (Table 3).

All three ingredients of the outer layer were first passed through sieve No 120, weighed for 30 tablets, and mixed using a mortar and pestle to obtain a uniform powder blend. A powder blend equal to half the total weight of the outer layer for the tablet was weighed accurately and transferred into a 10.00-mm die cavity and compressed once. Next, the core tablet was centrally placed on the coat layer and the remaining half of the outer layer powder blend was added into the die and again compressed in 10-mm concave shaped SS punches using the 10 station tablet compression machine (057-01 GMP model; Riddhi Trading, Ahmedabad, India). Tablet hardness was adjusted to a uniform 6–8 kg/cm^{2} using a Monsanto hardness tester to obtain uniform press-coated tablets.

Tablets were stored in an air-tight container in a dry location until further evaluation. In case of capping, the hardness of the tablet may be increased approximately up to 9–10 kg/cm^{2}.

Evaluation of carvedilol core tablet and press-coated tablet

Content uniformity of powder blend for core tablet and press-coated tablet

The powder blend for the core tablet and all formulations of the press-coated tablet were tested for carvedilol content uniformity.[22] Six samples of powder blend or six tablets equivalent to 6.25 mg of carvedilol were withdrawn from different sites. Each sample was transferred to individual 50-mL volumetric flasks; 30-mL of methanol was then added and the sample was sonicated in an ultrasonicator (D Compact; EIE instrument Pvt Ltd, Ahmedabad, India) for 30 min. The volume of the resulting slurry was then increased to 50 mL using methanol. This solution was filtered through Whatmann filter paper No 42. Absorbance of the filtrate was measured at 243 nm using a double-beam UV spectrometer (Specord 205; Analytic Jena, Jena, Germany) after appropriate dilution. In this manner, the content of carvedilol was measured.

Table 3 Presentation of 15 experiments (F1–F15) with coded values and actual values for factor levels for the Box–Behnken experimental design

Formula code	Coded levels			Amount for outer coat layer per tablet			Total weight of outer layer mg
	X_1	X_2	X_3	X_1 = amount of HPMC K4M mg	X_2 = amount of EC mg	X_3 = amount of K-carrageenan mg	
F1	1.00	1.00	0.00	136.8	108	14.8	259.6
F2	0.00	−1.00	1.00	126	92	15.2	233.2
F3	0.00	1.00	−1.00	126	108	12	246
F4	−1.00	0.00	−1.00	115.2	100	12	227.2
F5	0.00	0.00	0.00	126	100	14.8	240.8
F6	−1.00	1.00	0.00	115.2	108	14.8	238
F7	0.00	0.00	0.00	126	100	14.8	240.8
F8	1.00	0.00	−1.00	136.8	100	12	248.8
F9	0.00	1.00	1.00	126	108	15.2	249.2
F10	0.00	−1.00	−1.00	126	92	12	230
F11	1.00	0.00	1.00	136.8	100	15.2	252
F12	0.00	0.00	0.00	126	100	14.8	240.8
F13	−1.00	0.00	1.00	115.2	92	15.2	222.4
F14	1.00	−1.00	0.00	136.8	92	14.8	243.6
F15	−1.00	−1.00	0.00	115.2	92	14.8	222

Abbreviations: EC, ethylcellulose; HPMC, hydroxypropyl methylcellulose.

Physicochemical characterization of tablets

The thickness and diameter of the tablets was determined using a digital micrometer screw gauge (Mitutoyo Corporation, Kawasaki, Japan). Hardness of the tablets was determined using a Monsanto hardness tester. The friability of these tablets was determined using a Friabilator (Friabilator USP EF-2; DBK Instruments, Mumbai, India). Weight variation of the core tablets and press-coated tablets was carried out using the official method of IP 2010.[23] Disintegration time of core tablets was determined using the Disintegration Tester USP (Model 40TDA01, DBK Instruments, Mumbai, India).

Determination of tensile strength (T) for press-coated tablets

Tensile strength is defined as the stress needed to fracture a tablet by diametric compression. Tensile strength is described by Fell and Newton in the equation:

$$\text{Tensile strength} \, (T) = \frac{2P}{\pi DT},$$

Table 4 Result table of micromeritic properties

Parameters	Carvedilol (mean ± SD)	Powder blend (mean ± SD)	Inference
Angle of repose	32.54 ± 0.28	34.07 ± 1.23	Good
Carr's index %	20.26 ± 1.06	18.98 ± 3.2%	Fair
Hausner's ratio	1.254 ± 0.017	1.23 ± 0.12	Fair

Abbreviation: SD, standard deviation.

where P is the fracture load that causes tensile failure of a tablet of diameter D cm and thickness T cm. The fracture load (kg) of individual tablets was determined using a Monsanto hardness tester using the procedure of Brook and Marshal.[24] Mean values of fracture loads were used to calculate T values.

Swelling index for press-coated tablet

Tablets made from each formulation blend were randomly selected. Individual tablets (W_1) were placed in petri dishes containing 10 mL of phosphate buffer, pH 6.8. After 24 h, these tablets were carefully removed from petri dishes and excess water was removed using filter paper. Swollen tablets were reweighed (W_2), and the swelling index[25] of each tablet was calculated using the equation:

$$\% \, \text{swelling index} = \frac{W_1 - W_2}{W_1} \times 100.$$

In vitro dissolution testing of carvedilol core tablet

Carvedilol is rapidly absorbed throughout the gastrointestinal tract. Our press-coated tablet is formulated to disintegrate and release the drug in the upper part of the small intestine.[26] Hence, in vitro dissolution was carried out in pH 6.8 phosphate buffer to simulate gastrointestinal tract conditions. Since carvedilol is a BCS class II drug, to facilitate complete dissolution, 1% sodium lauryl sulfate was added to the dissolution medium.[27]

Table 5 Physicochemical characterization of tablet

Formula	Hardness kg/cm² (mean ± SD)	Thickness mm (mean ± SD)	Avg weight (mean ± SD)	% friability	% content of carvedilol loaded (mean ± SD)
Core tablet	4.2 ± 2.54	3.752 ± 0.45	79.5 ± 2.01	0.82	99.98 ± 1.23
F1	8.5 ± 1.20	4.946 ± 2.30	340 ± 1.23	0.49	100.34 ± 0.45
F2	9.0 ± 0.80	4.567 ± 1.45	313 ± 4.55	0.42	99.89 ± 1.23
F3	8.2 ± 0.78	4.346 ± 3.15	327 ± 3.44	0.10	99.56 ± 0.67
F4	8.0 ± 1.23	4.156 ± 0.75	308 ± 2.44	0.32	98.97 ± 2.34
F5	8.0 ± 1.25	4.567 ± 2.45	320 ± 4.55	0.56	99.87 ± 1.34
F6	8.5 ± 0.23	4.667 ± 0.68	318 ± 3.55	0.94	101.23 ± 0.56
F7	8.4 ± 0.45	4.560 ± 0.25	320 ± 3.74	0.10	99.78 ± 2.31
F8	8.5 ± 0.56	4.667 ± 2.67	328 ± 2.54	0.15	99.78 ± 1.23
F9	9.0 ± 0.34	4.683 ± 1.45	329 ± 4.53	0.10	100.23 ± 0.78
F10	8.5 ± 0.27	4.500 ± 3.67	310 ± 3.56	0.05	99.56 ± 3.23
F11	8.5 ± 0.45	4.584 ± 2.67	332 ± 4.56	0.05	100.34 ± 0.12
F12	8.5 ± 0.56	4.523 ± 3.78	321 ± 1.25	0.10	101.23 ± 0.23
F13	8.4 ± 0.56	4.167 ± 0.56	302 ± 3.44	0.11	99.88 ± 1.23
F14	8.8 ± 0.34	4.545 ± 6.45	324 ± 3.45	0.51	100.34 ± 0.45
F15	8.0 ± 0.68	4.367 ± 3.45	302 ± 3.22	0.11	101 ± 0.89

Dissolution of six tablets was evaluated using a USP Dissolution Apparatus II (Paddle Apparatus TDL 08 L; Electrolab, Mumbai, India). The dissolution bath was maintained at 37°C ± 0.5°C at 50 rotations per minute (RPM) for 2 h. Next, 5-mL samples were withdrawn at 15, 30, 45, 60, 90, and 120 min time points. The volume withdrawn was replaced with 5 mL of fresh 6.8 pH phosphate buffer. The withdrawn solution was immediately filtered using Whatmann Paper No 42, diluted, and the concentration of carvedilol in the sample was determined by measuring UV absorbance at 241 nm. In this manner percent cumulative carvedilol release was calculated.

Lag time and in vitro dissolution testing of press-coated carvedilol tablet

In vitro drug release studies were conducted for all formulations using the USP Dissolution Test Apparatus II, Paddle type, at 37°C ± 0.5°C at 50 RPM.

Previous studies reported that there are different patterns for gastric movement and transit time during sleep and that gastric residence time and small intestinal transit time of radio labeled tablets were found to be extended after night dosing.[28] The average gastric emptying time for oral tablets was found to be approximately 5 h at nighttime dosing,

Table 6 Swelling index, tensile strength and lag time of press coated tablets

Formula	% swelling index (mean ± SD)	Tensile strength (MPa)	Lag time in hours (mean ± SD)
F1	61.76 ± 1.2	1.108	7.2 ± 0.52
F2	75.72 ± 1.3	1.255	5.8 ± 0.34
F3	63 ± 1.5	1.26	5.6 ± 0.66
F4	34.74 ± 0.5	1.226	5.4 ± 0.45
F5	42.19 ± 0.5	1.116	6.6 ± 0.32
F6	68.24 ± 0.76	1.16	5.9 ± 0.44
F7	63.13 ± 2.00	1.173	6.4 ± 0.54
F8	68.93 ± 3.9	1.146	6.2 ± 1.23
F9	62.61 ± 4.00	1.224	6.1 ± 0.54
F10	47.1 ± 3.00	1.189	5.6 ± 0.66
F11	57.53 ± 0.45	1.167	7.4 ± 0.65
F12	69.47 ± 0.55	1.211	6.7 ± 0.43
F13	69.54 ± 3.42	1.284	5.6 ± 0.34
F14	62.35 ± 2.44	1.233	7.2 ± 1.23
F15	69.54 ± 0.54	1.167	5.8 ± 0.45

Table 7 Factors with coded levels and responses obtained in BBD

Formula	X_1	X_2	X_3	Y_1 = lag time in h	Y_2 = percent cumulative carvedilol release after 8 h
F1	1	1	0	7.2	97.26
F2	0	−1	1	5.8	99.51
F3	0	1	−1	5.6	103.63
F4	−1	0	−1	5.4	100.01
F5	0	0	0	6.6	99.26
F6	−1	1	0	5.9	99.34
F7	0	0	0	6.4	94.47
F8	1	0	−1	6.2	105.81
F9	0	1	1	6.2	96.10
F10	0	−1	−1	5.6	108.91
F11	1	0	1	7.4	95.68
F12	0	0	0	6.7	98.21
F13	−1	0	1	5.6	96.10
F14	1	−1	0	7.2	102.05
F15	−1	−1	0	5.8	101.13

Table 8 ANOVA summary of all responses

Fitted model	Y_1 (quadratic model)		Y_2 (linear model)	
	F value	P value	F value	P value
Model	31.42	0.0007	7.7320	0.0047
X_1-HPMC	168.540	<0.0001	0.341	0.5713
X_2-EC	1.500	0.2752	4.469	0.0582
X_3-K-carrageenan	29.040	0.0030	18.386	0.0013
X_1X_2	0.120	0.7431		
X_1X_3	12.000	0.0180		
X_2X_3	1.920	0.2245		
X_1^2	4.212	0.0954		
X_2^2	6.797	0.0478		
X_3^2	57.751	0.0006		
Lack of fit	0.82	0.5899	1.04	0.5821
	R-squared	0.9826	R-squared	0.6783
	R-squared pred	0.8291	R-squared pred	0.5906
	Adj R-squared	0.9514	Adj R-squared	0.5906

Abbreviations: ANOVA, analysis of variance; EC, ethyl cellulose; HPMC, hydroxypropyl methyl cellulose.

which is greater than morning dosing of the tablet.[28] These results have been attributed by Kumar et al to alterations in the periodicity of the fasting migrating myoelectric complex at night.[29,30] Hence, it may be concluded that sleep plays a major role in GI transit time.

Our press-coated carvedilol tablets have been synchronized for time release and mimic the pattern of gastrointestinal transit time during sleep. Thus, dissolution was conducted in 900 mL 0.1 N hydrochloric acid (1.2 pH) for 5 h and subsequently in 900 mL 6.8 pH phosphate buffer containing 1% sodium lauryl sulfate for 3 h. The average percent cumulative carvedilol release was then calculated. The lag time after which tablet rupture was observed was also noted.

Result and discussion
Preformulation studies
Drug excipient compatibility studies
The characteristic peaks of carvedilol observed at 2919.34 cm^{-1} were for C-H stretching vibrations, 1502 cm^{-1} for N-H bending, 1216 cm^{-1} for O-H bending and C-O stretching, and 3342 cm^{-1} for O-H bending. These peaks were present in all four carvedilol spectra with varying core tablet excipients.

Table 9 Criteria for an optimized batch to be achieved

Response	Target of response	Weight factor
Y_1 = lag time	6 h	+++++
Y_2 = % drug release at the end of 8 h	100%	+++

Table 10 Optimized formula for outer layer of press-coated tablet with coded levels and transformed values

Variables	Coded level	Actual amount in outer layer mg	Desirability
X_1 = amt of HPMC K4M	−0.70	115.63	1
X_2 = amt of EC	−0.72	93.12	1
X_3 = amt of K-carrageenan	0.22	13.33	1
Y_1 = predicted lag time	6 h		1
Y_2 = predicted percent cumulative carvedilol release after 8 h	100%		1

Abbreviations: EC, ethyl cellulose; HPMC, hydroxypropyl methyl cellulose.

Since these peaks were found to be unchanged in different drug and excipients mixture, carvedilol is physically compatible with the excipients used.

In the DSC study, a characteristic endothermic peak of carvedilol was observed at 115°C for pristine carvedilol (A) as well as core tablet containing carvedilol (C). The thermal peak of excipient in the core tablet did not interact with the drug peak at 115°C. This result rules out any possibility of drug excipient interaction during compression, which may change the crystalline structure of carvedilol.

Micromeritic properties
For direct compression, materials must have good flow and compacting properties. Values for the angle of repose between 31–35° are believed to indicate good flow property. A Hausner's ratio of less than 1.19–1.25 and Carr's index of 16–20 indicates fair flow.[19]

Carvedilol as well as the prepared formulation mixtures showed good flow properties as measured by values of angle of repose, Carr's index, and Hausner's ratio.

Physicochemical characterization of tablets
The core tablet's average hardness was 4 kg/cm^2, which is desirable, since the tablets undergo further processing in a

Table 11 Comparison of predicted and actual response

Response term	Predicted response (h)	Actual response (h)	% bias
Y_1 = lag time	6	6.09	−1.5
Y_2 = percent drug release at the end of 8 h	100	100.03	−0.03

Note: % bias = [(Predicted response − actual response)/predicted response] × 100.
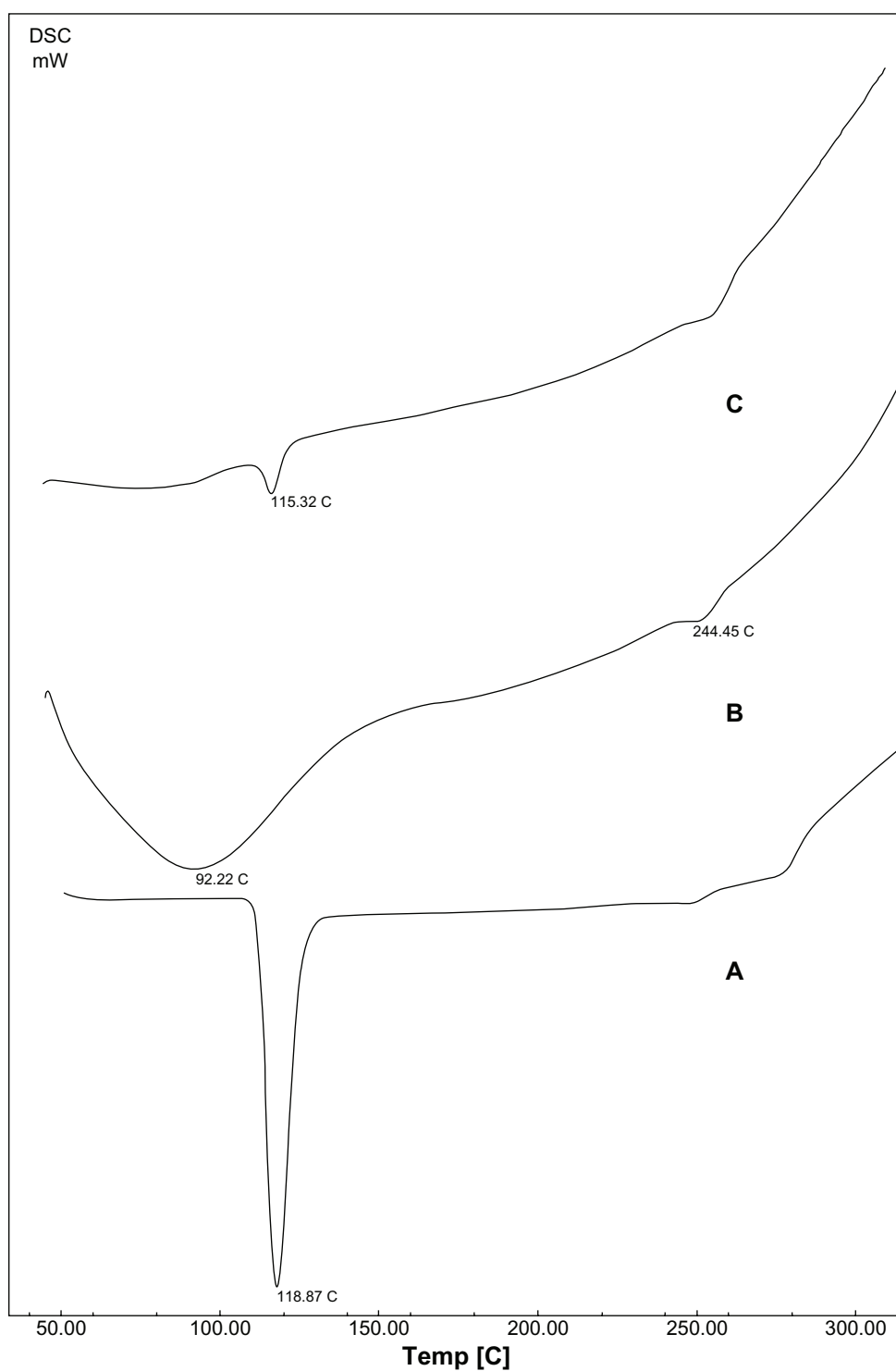
Figure 1 Overlay spectra of DSC scan of (**A**) pristine carvedilol (**B**) core tablet without carvedilol (**C**) carvedilol core tablet.

second compression cycle. The average thickness was also in a desirable range.

Press-coated tablets based on all the different formula had hardness in the range of 8–9 kg/cm², which was acceptable.

Capping was observed in tablets made using formulas F1, F8, F9, and F11, and this was resolved by increasing hardness up to 10 kg/cm².

The average disintegration time was 10.33 s, which is desirable for a core tablet designed to disintegrate immediately after
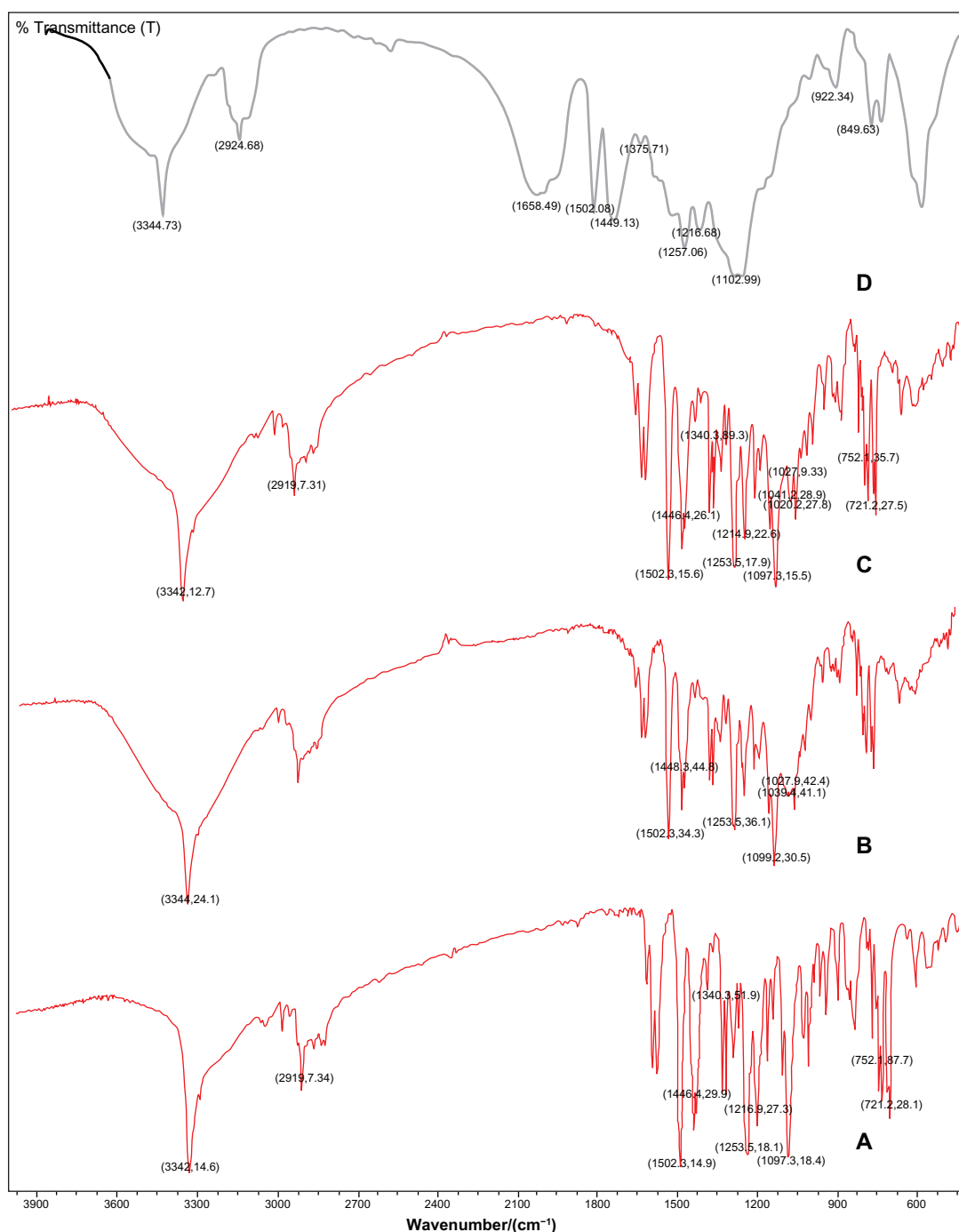
Figure 2 Combined FTIR spectra for (**A**) pristine carvedilol (**B**) carvedilol + MCC (1:1) (**C**) carvedilol + crosscarmellose sodium (1:1) (**D**) carvedilol + PVP K 30 (1:2).

a lag time. It was found that the increased hardness did not have a significant effect on the disintegration time of tablets.

Tablets from all formula passed the weight variation test as per IP 2010.[22] A few tablets were found to deviate from average weight, but within IP limits.

The results of friability were found to be less than 1%, which indicates that these tablets are of sufficient physical strength to withstand mechanical abrasion during transportation.

Swelling index and tensile strength

All tablets were found to have good radial tensile strength. The swelling index ranged from 34%–74%. All tablets possessed sufficient swelling capacity due to HPMC K4M

Figure 3 Photographic image of press coated tablet by Digital camera (Canon, Japan).
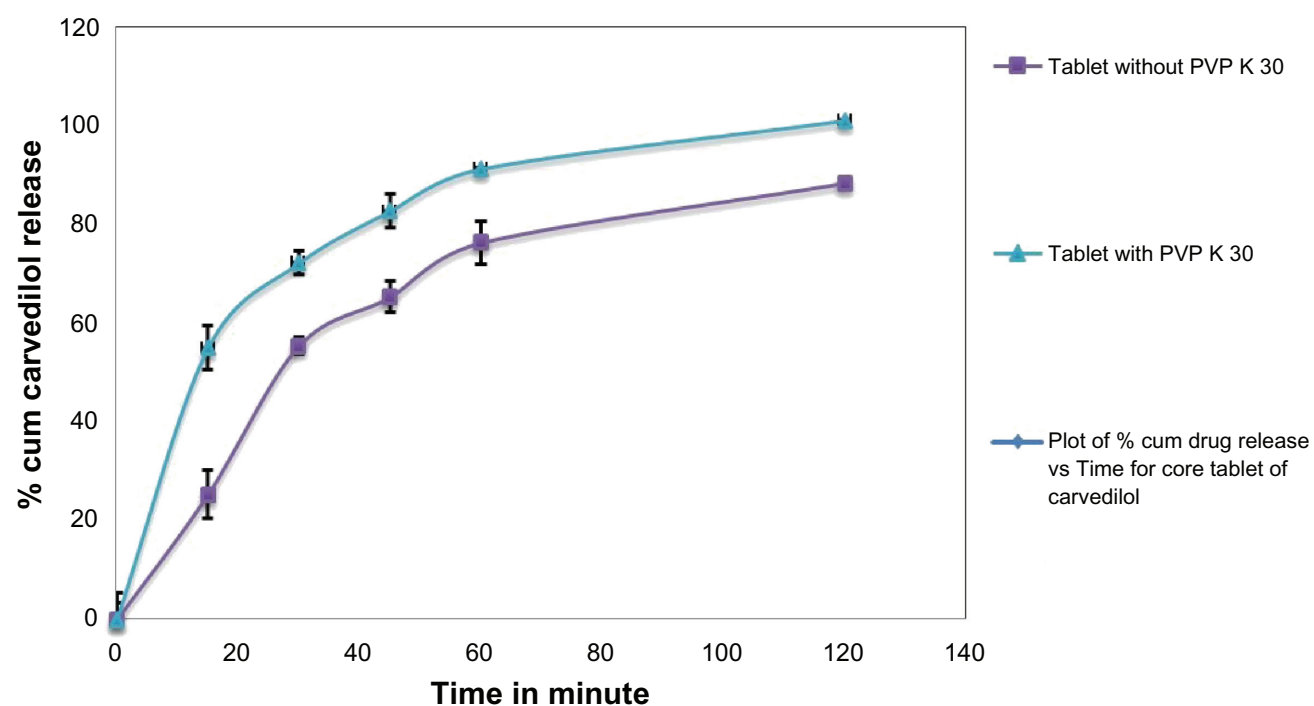
Figure 4 Plot of % cum release of carvedilol from core tablet vs time in min for tablet containing PVP K 30 and without PVP K 30.
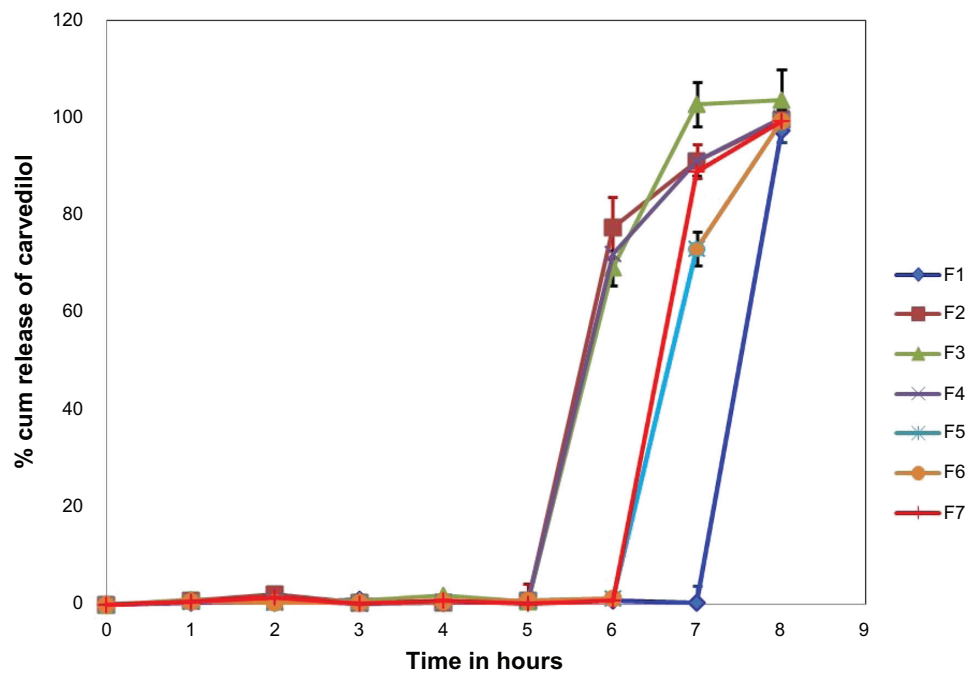
Figure 5 Plot of % cum release of carvedilol vs time in hours for F1–F7 formula of press coated tablets.

in the coat, which allows controlled erosion during the lag time.

In vitro study of optimized carvedilol core tablet

More than 70% of the carvedilol was dissolved in 45 min, and at the end of 2 h, 100% release was observed, which is desirable for a core tablet. PVP K 30 was used to increase the

dissolution of carvedilol in phosphate buffer since carvedilol is a BCS class-II drug.

Lag time and in vitro study of press-coated tablet

All press-coated tablets showed pulsatile release with distinct lag time, during which the dissolution medium reaches the core after eroding or rupturing the outer layer.
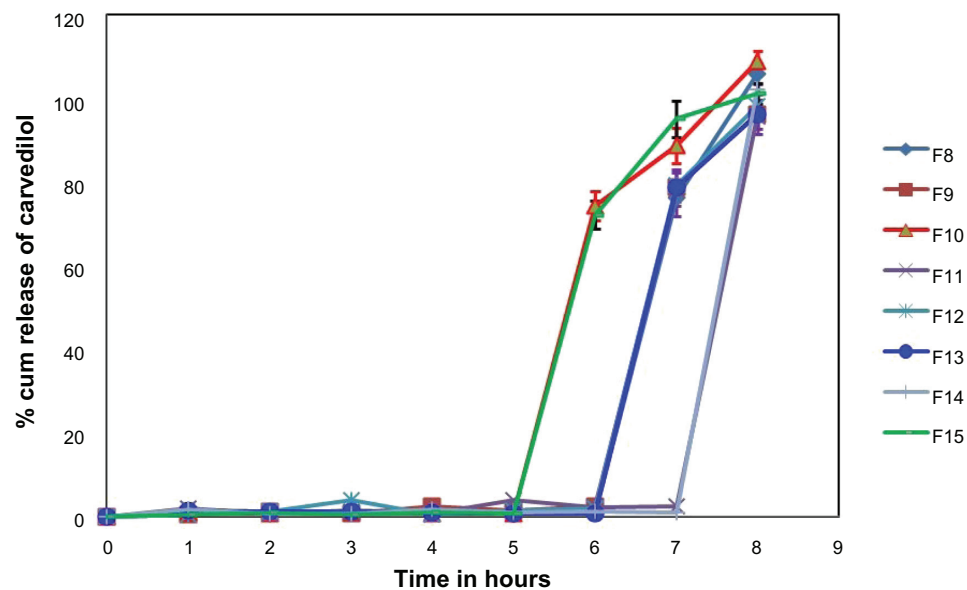
Figure 6 Plot of % cum release of carvedilol vs time in hours for F8–F15 formula of press coated tablets.
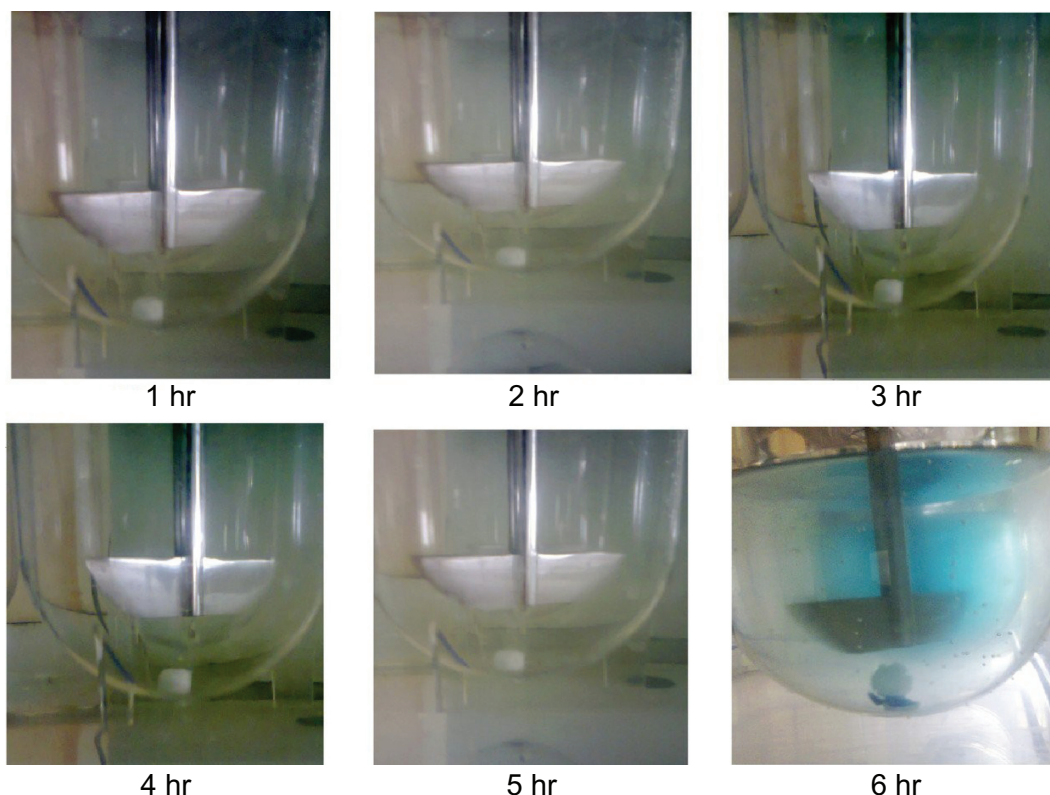
Figure 7 Images of dissolution of press coated tablet at 1–6 hr by Digital camera (Canon, Japan).

The release of carvedilol after 8 h was found to vary, which was further optimized for 100% release. The lag time was of varying range from 5.4 to 7.4 h, which was further optimized to obtain the desired lag time of 6 h. The effect of various polymers was also determined by statistical analysis.

Statistical optimization

Targeted response parameters were statistically analyzed by applying one-way analysis of variance (ANOVA) at a 5% significance level and the significance of the model was estimated using Design Expert 8. Individual parameters were evaluated using Fisher's F-test. A mathematical relationship between
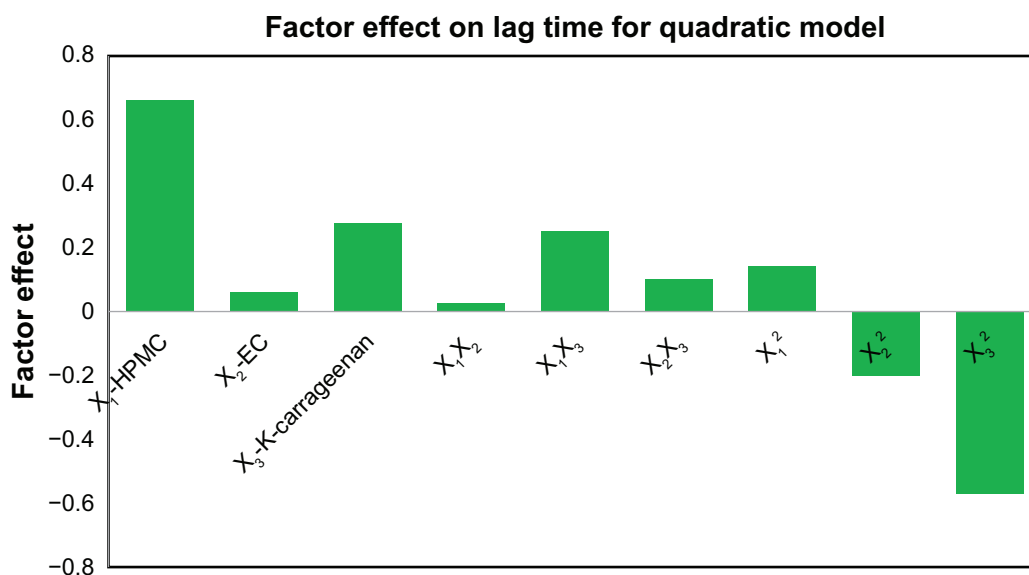
Figure 8 Evaluation of various factors on lag time.

Factor effect on % carvedilol release for linear model
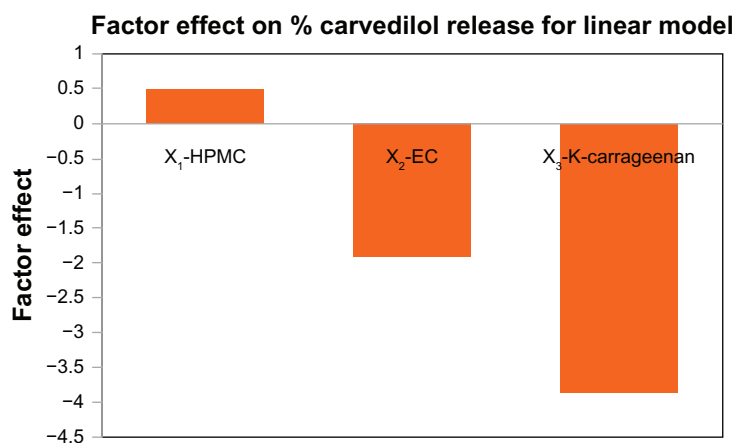
Figure 9 Evaluation of various factors on % cum carvedilol release after 8 hours.

factors and responses were generated using multiple linear regression analysis. This was used to determine the levels of factors which yield optimum dissolution responses. [30,31,32]

The Y_1 response, ie, lag time followed a quadratic model, and Y_2 response for all formulations followed a linear model since the P-values for ANOVA were less than 0.05.

Lack of fit is an undesirable characteristic for a model. If the model does not fit the data well, the test will show a significant lack of fit. For a well-fitted model, lack of fit will be insignificant ($P > 0.10$).

In our case, lack of fit was insignificant, soothe model fits the data generated. The R-squared values were also found to be 0.9826 and 0.6783, which is desirable.

These equations represent the quantitative effect of variables (X_1, X_2, and X_3) and their interactions on the response Y. Coefficients with more than one factor term and those with higher order terms represent interaction terms and quadratic relationships, respectively. A positive sign represents a synergistic effect, while a negative sign indicates an antagonistic effect.
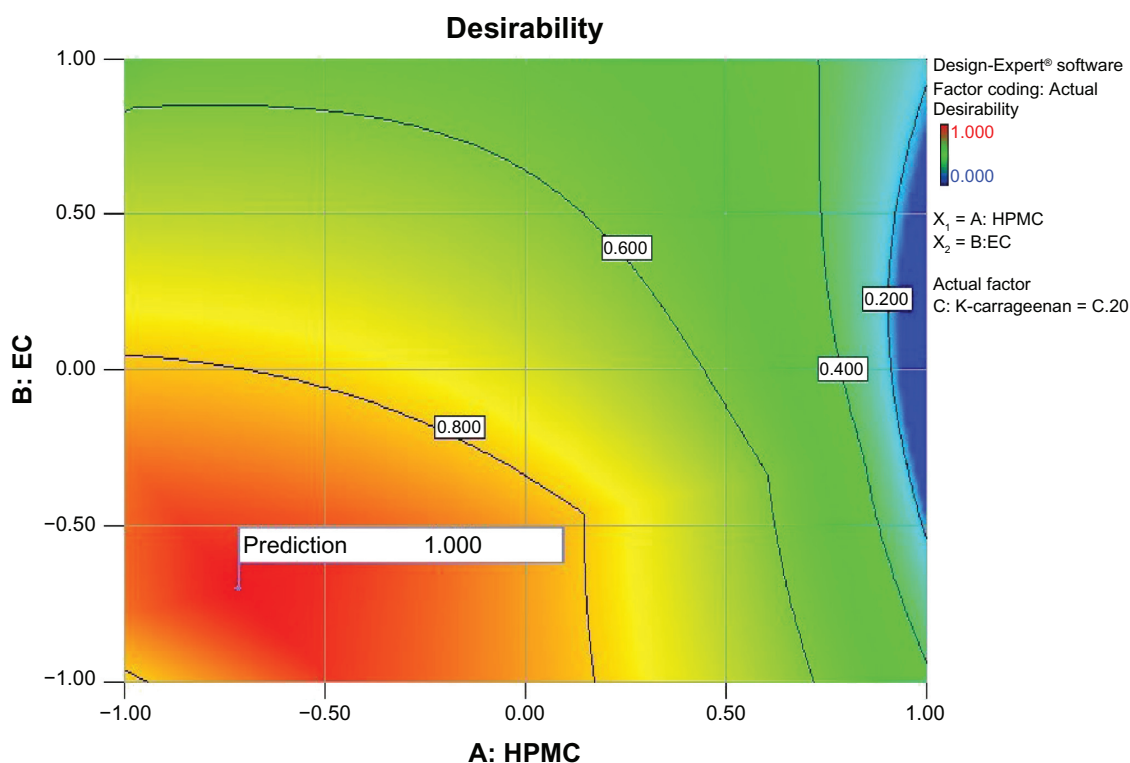
Desirability

Figure 10 Contour plot of optimized batch with target desirability.
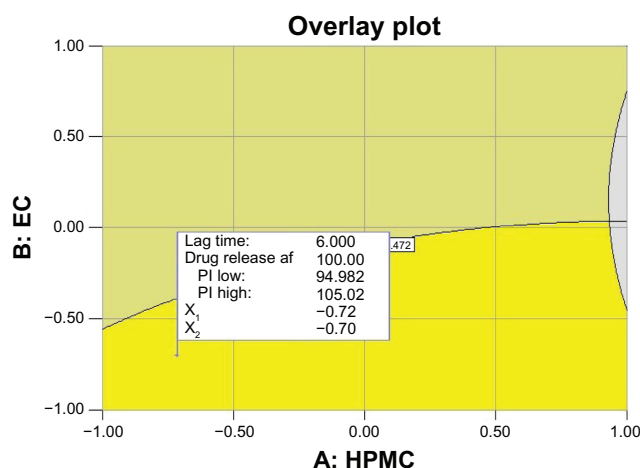
Figure 11 Overlay plot of all response contours showing optimum region for the press coated formulation.

Quadratic model equation for Y_1

$$Y_1 = 6.5 + 0.66X_1 + 0.062X_2 + 0.28X_3 - 0.025X_1X_2 + 0.25X_1X_3 + 0.10X_2X_3 + 0.15X_1^2 - 0.20X_2^2 - 0.57X_3^2$$

Linear model equation for Y_2

$$Y_2 = 99.83 + 0.5X_1 - 1.91X_2 - 3.87X_3$$

Prediction of factor effect and interaction on Y_1 and Y_2 responses[35]

ANOVA analysis of Y_1 showed that coefficients b_1 and b_3 and interaction coefficient b_5 had significant effect with F value of 168.54 ($P \leq 0.0001$), 19.01 ($P = 0.0030$), and 12.00 ($P = 0.0180$), respectively.

From this generated data, we can hypothesize that as the concentration of HPMC and K-carrageenan increases in outer layer of this press-coated tablet, lag time also increases.
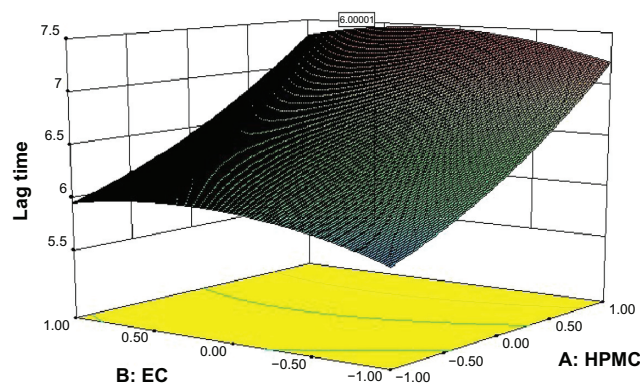
Figure 12 Response surface graph showing optimized formula for response Y_1 at different level of HPMC and EC keeping K-carrageenan at constant level.
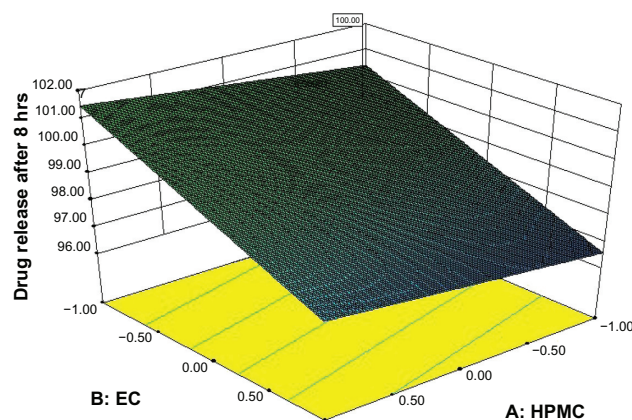
Figure 13 Response surface graph showing optimized formula for response Y_2 at different level of HPMC and EC keeping K-carrageenan at constant level.

The combined effect was also observed for both polymers on lag time.

For Y_2 coefficients, b_3 had significant effect with F value 18.36 ($P = 0.0013$). There is negative effect of K-carrageenan on percent cumulative carvedilol release at the end of 8 h. This indicates K-carrageenan retarded drug release.

Search for optimized formula by desirability

The desirability function helps us to predict the optimum levels for independent variables. This function searches for a combination of factor levels that jointly optimize a set of responses by satisfying the requirements for each response in the set.

Optimization was accomplished by obtaining the individual 'desirability' (d) for each response, combining individual desirabilities to obtain the combined or composite desirability (D), and finally by maximizing the composite desirability and identifying the optimal factor settings. The measured responses were transformed to a dimensionless desirability (d) scale. The scale of the desirability function ranges between d = 0, for a completely undesirable response to d = 1 for a fully desired response above which further improvements would have no importance.

After the individual desirabilities were calculated for each response, they were combined to provide a measure of composite desirability of the multi-response system. This measure of the composite desirability is the weighted geometric average of the individual desirabilities or the responses. The optimized formula using transformed values of variables was prepared and evaluated for the in vitro dissolution test and lag time.

The predicted response was compared with actual and the percent bias was determined.[34] The bias for predicted

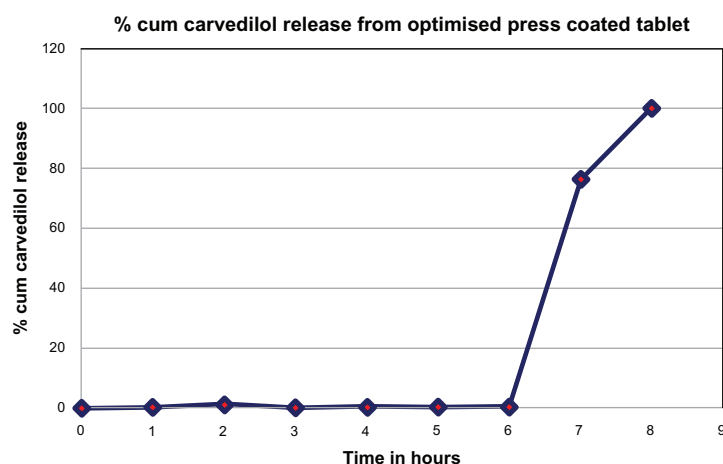**% cum carvedilol release from optimised press coated tablet**

Figure 14 Plot of % cum drug release vs time in hours for optimized batch.

versus observed responses was acceptable, which is desirable. The results were found to be within the acceptable limit and indicate the successful optimization of this formulation of carvedilol press-coated tablets.

Conclusion

The formulation and optimization of press-coated tablet of carvedilol was successfully conducted.

Preformulation studies indicated that the carvedilol obtained was pure and there was no drug interaction, which was confirmed using DSC and FTIR. Carvedilol core tablets and press-coated tablets of all formulas according to BBD passed the precompression and postcompression evaluation tests. Since the gastric emptying time differs while sleeping, we simulated the conditions during sleep at night.

The dissolution of press-coated tablet was conducted for 5 h in stomach condition and afterwards in phosphate buffer, pH 6.8.

The release profile of our formulation of carvedilol press-coated tablets exhibited a time lag, a period without significant drug release, followed by a rapid and complete release phase. We observed that press-coated tablets swelled due to water penetration in outer layer and after the lag time, the tablet ruptured into two layers exposing the core tablet which disintegrated within minutes to give excellent release of carvedilol. PVP K 30 increased the dissolution of carvedilol in phosphate buffer, pH 6.8.

From our statistical analysis, we found that the amount of HPMC K4M and K-carrageenan had a positive effect on lag time, while the K-carrageenan had a positive effect on percent cumulative carvedilol release at the end of 8 h. We observed that the amount of HPMC and K-carrageenan increased the lag time with increased concentration. Observed responses

for the optimum formulation were in close agreement with predicted values, indicating excellent predictability of the optimization procedure.

We conclude that chronomodulated drug delivery using a press-coated approach may be a promising alternative in controlling early-morning hypertension surge, when administered at bedtime to patients suffering from hypertension. However, the in vivo assessment of lag time and drug release in humans must be further investigated to determine the efficacy and behavior of the optimized formulation.

Surveys showed that most of the doctors in many countries were unaware of the chronobiologic behavior of the hypertension and that ultimately decrease chances of the effective treatment of hypertensives patients. Thus, the need is to bring down chronotherapeutic formulation in clinical practice to increase the efficacy of drug. This formulation can be a promising formulation if it is preclinically and clinically assessed for its efficacy and may reduce the chance of early morning incidences of heart failure.

The technology used for the preparation of press-coated tablet of carvedilol is a relatively simple manufacturing process which can be easily adopted in industrial units on a commercial scale.

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(Kherva, Gujarat, India) for infrared and differential scanning calorimetry analysis of samples, respectively.

Disclosure

The authors declare no conflicts of interest in this work.

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