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PREPARATION AND EVALUATION OF CONTROLLED RELEASE OF CARVEDILOL

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ABSTRACT
The aim of present investigation is preparation, characterization and evaluation of oral controlled release matrix tablets of Carvedilol in order to improve efficacy and to reduce the side effects. Tablets were prepared by direct compression method using different polymers like Ethyl Cellulose, HPMC K100M, Sodium Alginate and Chitosan. The tablets were evaluated for pre-formulation characteristics, post compression parameters, drug content and *in-vitro* dissolution release studies. *In-vitro* dissolution studies were carried out for 8 hrs and the results showed that among the nine formulations F5 showed good dissolution profile to control the drug release respectively. The stability studies were carried out according to ICH guideline which indicates that the selected formulation F5 was stable. In conclusion the results suggest that the developed matrix tablets of Carvedilol could perform therapeutically better than conventional dosage form, leading to improved efficacy and better patient compliance.

KEYWORDS: Carvedilol, polymers, direct compression technique, *in vitro* drug release studies, stability studies.

INTRODUCTION
Controlled-release (CR) formulations have been introduced into drug therapy with two main purposes: to reduce the number of single doses per day improving patient compliance of treatments and to decrease the fluctuations of plasma levels, in order to obtain better therapeutic efficacy and lower toxicity.[1,2] There are many controlled-release pharmaceutical systems currently known, ranging from monolithic matrices, membrane reservoirs, erodible polymers, to the more technologically complex and sophisticated pH independent formulations, ion exchange resins, osmotically, and geometrically modified systems.[3,4] Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner by dissolution control as well as diffusion controlled mechanisms.[5]

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery systems of existing drug molecules to maximize their therapeutic action, patient compliance and protection. Patient protection is equally important in the case of antihypertensive agents, because if constant blood levels are not maintained, it results in dose dumping which leads to hypotension. Controlled release formulations help to maintain constant blood levels.[6] Carvedilol, an anti-hypertensive agent is a nonselective β-adrenergic blocking agent with α1-blocking activity which is rapidly and extensively absorbed following oral administration; with absolute bioavailability of approximately 25- 35% due to a significant degree of first-pass metabolism and its plasma half-life is about 6h.[7]

MATERIAL AND METHODS
Materials
Carvediol, Ethyl cellulose, HPMC k100M, Sodium Alginate, Chitosan, Microcrystalline cellulose, Magnesium state and talc were purchased form AR Chemicals, Hyderabad, India.

Methods
Analytical Methods
Preparation of standard curve of Carvediol
Preparation of 0.1 N HCl
8.5 ml of concentrated HCl dissolved in 1000 ml of distilled water.

Preparation of standard curve of Carvediol in 0.1 N HCl
For the standard graph, Carvediol 10mg was accurately weighed and dissolved in 10ml of 0.1 N HCl. From the stock solution (1mg/ml), different concentrations of Carvediol- 10, 20, 30, 40 and 50mcg/ml were prepared and made up to volume with distilled water. The absorbance's, which were found, are given in Table No.1 and the graph plotted of concentration Vs absorbance is shown in Fig no.1

Preparation of 6.8 phosphate buffer
28.80 gm of Disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate were dissolved in 1000 ml of water.

Preparation of standard curve of Carvediol in 6.8 pH
For the standard graph, Carvediol 10 mg was accurately weighed and dissolved in 10ml of 6.8 phosphate buffer. From the stock solution (1mg/ml), different concentrations of Carvediol- 10, 20, 30, 40 and 50mcg/ml were prepared and made up to volume with distilled water. The absorbance's, which were found, are given in Table No.2 and the graph plotted of concentration Vs absorbance is shown in Fig no.2

Drug - excipient compatibility studies
Drug excipient compatibility studies were accomplished to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were defined to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were defined to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.[8]

Formulation Development

Table 3: Formulation of Controlled Release tablets of Carvedilol.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Carvediol	25	25	25	25	25	25	25	25
HPMC K100 M	50	100	-	-	-	-	-	-
Ethyl cellulose	-	-	50	100	-	-	-	-
Chitosan	-	-	-	-	50	100	-	-
Sodium Alginate	-	-	-	-	-	-	50	100
Microcrystalline Cellulose	120	70	120	70	120	70	120	70
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Total wt	200	200	200	200	200	200	200	200

Preparation method
Different matrix embedded formulations of carvediol were prepared by direct compression method using varying proportion of polymers either alone or in combination. The ingredients were passed through a 44 mesh sieve. Calculated amount of the drug, various polymers and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 6-mm flat-faced punches at a compression force required to produce tablets of about 7–8 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Post compression parameters

Weight variation
Prepared 20 tablets were selected from each batch and separately weighed. After that average weight of tablets were calculated.

Thickness
Twenty tablets were unsystematically selected from each batch and the thickness was determined by using vernier caliper.

Hardness
The hardness of the tablets was measured by utilizing Pfizer hardness tester. It is expressed in kg/cm. 3 tablets were unsystematically chosen and hardness of the tablets were determined.

Friability
Twenty tablets were weighed and located in the Roche friabilator, which was then conducted for 25 rpm for 4 min. After revolution dosage forms were redusted and reweighed.

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,
% F = friability in percentage
Wo = Initial weight
W = Final weight

Content Uniformity
Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg carvedilol. The weighed quantity of powder was dissolved into 100 ml of 6.8 phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at nm using reagent blank.

***In- Vitro* Release study**
In-vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution bowls 900 ml of Standard buffer 0.1 N HCl for 2 hr and followed by pH 6.8, and the temperature was maintained at 37±5. From that 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and the volume was adjusted with buffer.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile**.** The prepared Matrix tablets of carvedilol were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 90 days.

RESULTS AND DISCUSSION

Preparation of standard curve of Carvedilol

Standard curve of Carvedilol was determined by plotting absorbance V/s concentration at nm. Using solution prepared in ethanol, buffer pH 1.2, pH 6.8 at 214 nm. And it follows the Beer's law.

Table 1: Calibration curve of Carvedilol in 0.1 N HCl.

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	10	0.126
3	20	0.234
4	30	0.348
5	40	0.457
6	50	0.569

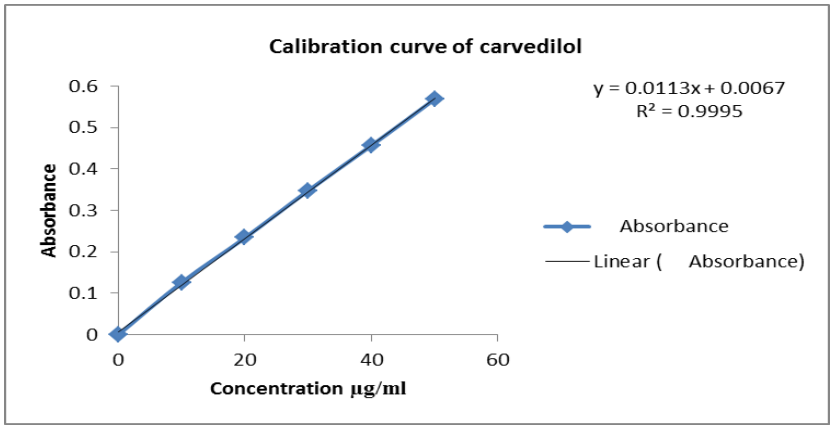

Fig-1: Calibration curve of Carvedilol in 0.1 N HCl.

Table 2: Calibration curve of Carvedilol in 6.8 phosphate buffer.

S. No	Concentration (µg/ml)	Absorbance
1	0	0
2	1	0.176
3	2	0.327
4	3	0.474
5	4	0.639
6	5	0.758

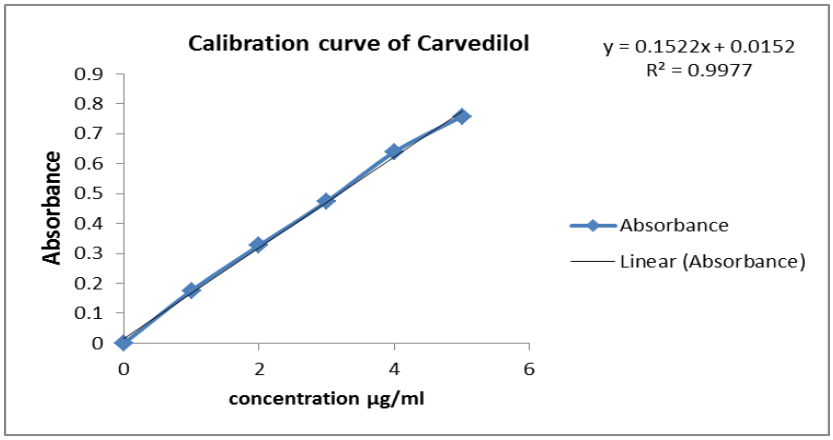

Fig-2: Calibration curve of Carvedilol 6.8 phosphate buffer.

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

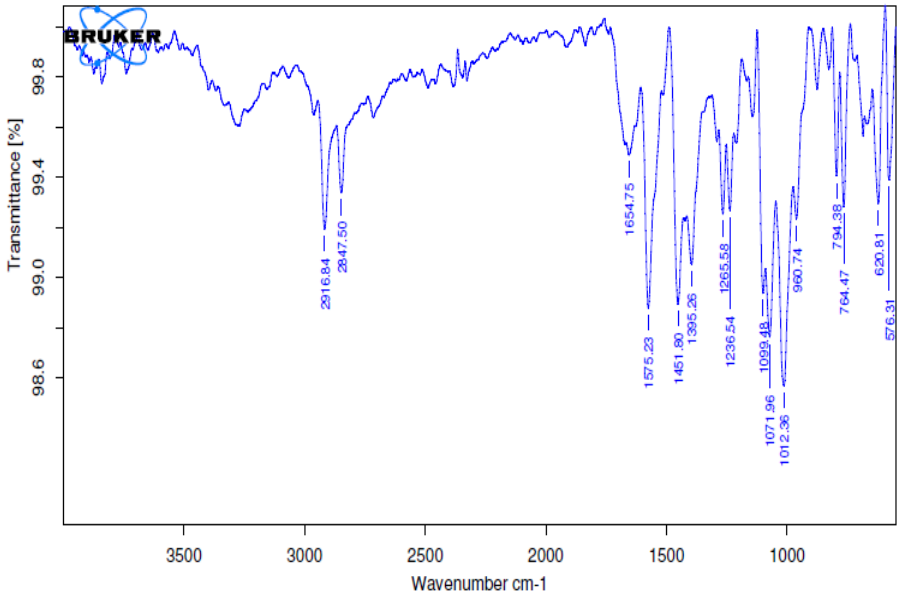

Fig-3: FT-IR Sample for Carvedilol.

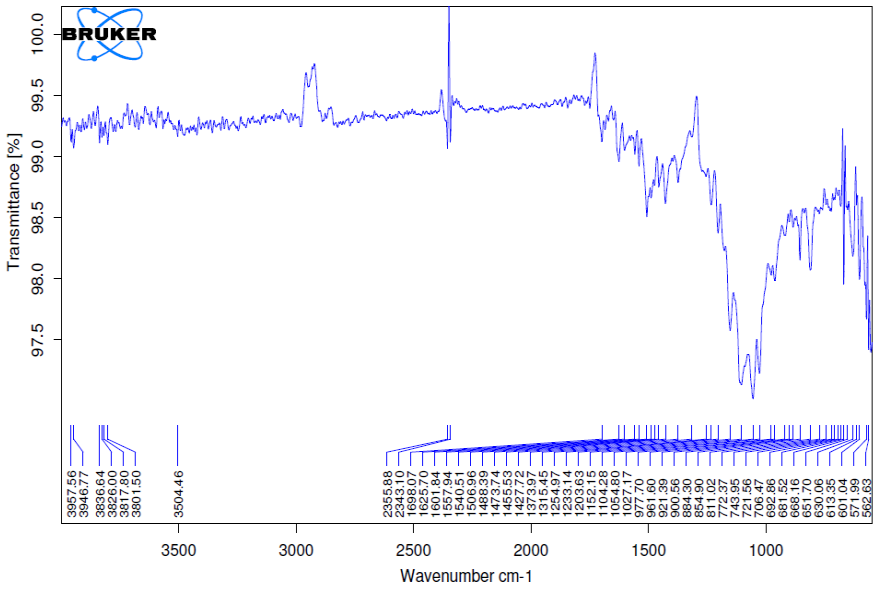

Fig-4: FT-IR Sample for Optimized Formulation.

Evaluation studies

Pre compression parameters

The prepared Carvedilol tablet blends were evaluated for angle of repose, bulk density, tapped density and compressibility index.

The bulk densities of the tablet blends were found to be in the range of 0.556 to 0.523 gm/ml and the tapped density ranged from 0.660 to 0.632 gm/ml. The flow characteristics of the tablets blend were assessed by determined their angle of repose. The values of compressibility indexes were in the range of (15.75 to 18.26%) and angle of repose varied from (28º to 31º) signifies reasonably good flow properties of the tablet blends for all the formulations thus ensuring homogenous filling of dies. The Hausner's ratio of all formulation blends was found to be less than 1.2 indicates better flow properties.

Table 5: Evaluation parameters of Carvedilol.

F. No	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of Repose (0)
F1	0.556	0.660	15.75	1.18	28^0
F2	0.529	0.638	17.08	1.20	29^0
F3	0.531	0.643	17.41	1.21	31^0
F4	0.528	0.646	18.26	1.22	27^0
F5	0.548	0.650	15.69	1.18	28^0
F6	0.545	0.648	15.89	1.18	29^0
F7	0.523	0.632	17.24	1.20	30^0
F8	0.550	0.655	16.03	1.19	28^0

Post compression parameters

Weight variation

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 3.12mm to 3.29 mm.

Hardness

The measured hardness of tablets of each batch ranged between 4.18 to 4.25 kg/cm^2. This ensures good handling characteristics of all batches.

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for F1 to F8 was found to be between 94.13% and 98.84% of Carvedilol it complies with official specifications.

Table 6: Results of Pre compression parameters.

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	399	3.12	4.18	0.29	98.19
F2	397	3.24	4.22	0.27	97.82
F3	401	3.15	4.25	0.30	95.35
F4	398	3.17	4.19	0.28	95.16
F5	400	3.29	4.23	0.24	98.84
F6	398	3.22	4.18	0.29	96.23
F7	395	3.19	4.21	0.24	95.71
F8	396	3.20	4.19	0.23	94.13

***In-vitro* Dissolution Study**

All the formulation of prepared matrix tablets of carvedilol were subjected to *in-vitro* release studies, these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

Table 7: *In-vitro* release data of tablet F1 to F8.

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	25.65	23.50	26.41	23.40	28.30	26.72	26.50	25.22
2	35.20	33.72	30.85	29.72	32.42	35.63	31.15	32.81
3	41.28	42.70	40.28	32.70	41.18	40.92	38.65	39.90
4	52.62	56.65	51.27	49.65	50.90	52.65	48.23	53.41
5	60.74	65.38	62.32	52.38	63.82	61.25	59.95	65.50
6	78.56	73.72	71.63	68.72	73.86	73.12	72.82	74.84
7	81.68	85.09	82.75	80.09	84.82	80.19	81.84	83.90
8	93.62	95.25	96.90	91.25	98.14	91.16	92.32	93.25

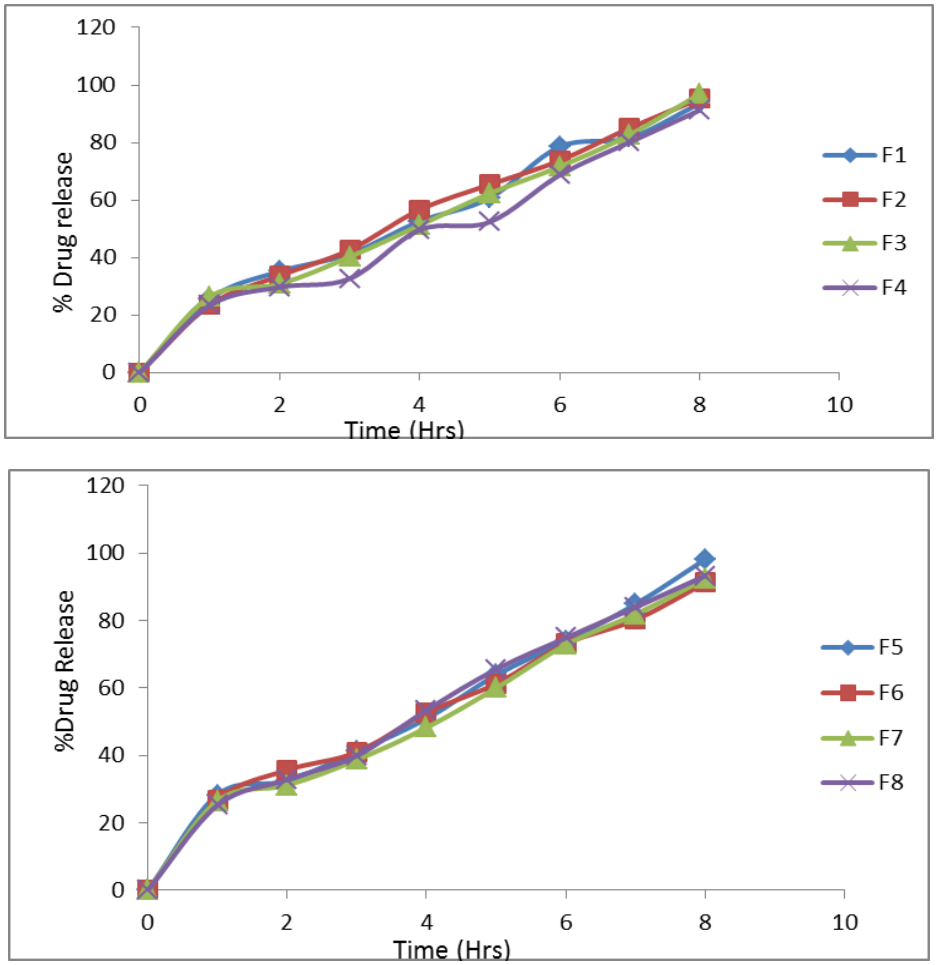

Fig-5: *In-vitro* drug release studies of (F1-F8) Formulations.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-5 after 3 months. Parameters quantified at various time intervals were shown.

Table 8: Results of stability studies of optimized formulation F5.

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	25^0C/60%RH % Release	98.14	98.02	97.18	96.25	Not less than 85 %
F-5	30^0C/75% RH % Release	98.14	97.18	97.26	96.39	Not less than 85 %
F-5	40^0C/75% RH % Release	98.14	97.54	96.15	96.39	Not less than 85 %

CONCLUSION

The present study was undertaken with an aim to formulate and evaluate Carvedilol controlled release tablets using different polymers as release retarding agents. Pre formulation study was carried out and all the parameters were found within the specification. Hence different batches of Carvedilol were prepared using selected excipients. Powders were evaluated for bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. Various formulations of controlled release tablets of Carvedilol were prepared by using different polymers viz, HPMC K100M, Ethyl cellulose and Sodium alginate and Chitosan in different proportions and combinations by direct compression technique. The tablets were evaluated for physical parameters, *in vitro* release study and stability studies. All formulations were found to be within the specifications of official pharmacopoeias and/or standard references. *In-vitro* release indicated that the formulation F5 had better dissolution profile along with controlled action as compare to other formulations. Stability study was conducted on tablets of Batch F5 stored at room temperature, 40^0C, and 2-8^0C for one month. Tablets were evaluated for hardness, friability, *in-vitro* release profile and drug content. No significant changes were observed in any of the studied parameters

during the study period (3 months), thus it could be concluded that formulation was stable.

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