RESEARCH ARTICLE

Preparation and evaluation of controlled release tablets of carvedilol

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The objective of the present investigation is to design and evaluate controlled release tablets of carvedilol, employing synthetic polymers like polyethylene oxides, of different molecular weights as release retarding materials and to select the optimized formulation based on the pharmacokinetics of carvedilol. Matrix tablets each containing 80 mg of carvedilol were formulated employing PEO N60 K, PEO 301, and PEO 303 as release-retarding polymers and β Cyclodextrin and HP β cyclodextrin as release modulators from the matrix. Carvedilol release from the formulated tablets was very slow. Hence the release was modulated with the use of cyclodextrins. The dissolution from the matrix tablets was spread over more than 24 hours and depended on the type of polymer, its concentration and the type of cyclodextrin used. All the matrix tablets prepared using polyethylene oxides showed very good controlled release over more than 24 hours. The matrix tablets prepared using HP β cyclodextrin showed a higher dissolution rate and gave a dissolution profile that was comparable to the theoretical sustained release needed for once-a-day administration of carvedilol. The drug release mechanism from the matrix tablets was found to be quasi Fickian mechanism.

Key words: *Carvedilol, controlled release, matrix tablets, polyethylene oxides*

INTRODUCTION

During the past 30 years, as expenses and complications involved in marketing new drug molecules have increased, with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on the development of controlled release drug delivery systems (CRDDS). The goal in designing CRDDS is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The use of controlled release (CR) formulations offers many potential advantages, such as, sustained blood levels, attenuation of adverse effects, and improved patient compliance. It is important, especially in the case of antihypertensive agents, to maintain constant blood levels, as otherwise, dose dumping may cause hypotension and subtherapeutic level may cause hypertension. Based on the physicochemical and biopharmaceutical properties carvedilol was selected as a drug candidate for the development of controlled release matrix tablet formulations.

In the present investigation, studies were undertaken for the design and development of oral controlled drug delivery systems of an antihypertensive drug, carvedilol, through tablets, using the matrix diffusion technique. Carvedilol is chemically (+)-1-(Carbazol-4-yloxy)-3-{[2-(o-methoxy phenoxy)ethyl]amino}-2-propanol and is an antihypertensive drug with a multiple action spectrum. It acts as a β receptor blocker,[1] and it also has vasodilating properties that are attributed mainly to its blocking activity at α_1 receptors. It is used in the treatment of mild-to-moderate hypertension and angina pectoris.[2]

Carvedilol is well absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism in the liver. Its absolute bioavailability is considerably low, that is, about 25%, and its plasma half-life is about 6 hours.[3] Moreover, it is desirable to develop a formulation that will improve the bioavailability as well as control the release of carvedilol. β cyclodextrin was used as a bioavailability enhancing agent.

Recently numerous hydrophilic polymers have been investigated, which are currently used in the design of complex controlled release systems. Among the hydrophilic polymeric materials used for the development of controlled drug delivery systems, polyethylene oxides

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(PEOs) are commanding good interest because of their low toxicity and pH-independent swelling and drug release properties.[4-6] Apicella A *et al.*[4] investigated the application of polyethylene oxides of different molecular weights in controlled release monolithic systems of etofylline. Zhang *et al.* [5] investigated the release mechanism of chlorpheneramine maleate from PEO matrix tablets, prepared by hot melt extrusion. Razaghi *et al.*[6] studied the release pattern of cyclobenzaprine HCl from the oral osmotic drug delivery systems containing water soluble polymer, PEO. Jamzad *et al.* [7] developed a controlled release dosage form of glipizide using PEO matrices and compared it with its hydroxypropyl methylcellulose (HPMC tablets). As PEOs are highly hydrophilic in nature, the involvement of water or moist granulation can make the process highly problematic, therefore, a dry process that produces acceptable powder characteristics and does not intervene with drug release characteristics would be desirable.[8] The direct compression technique, which is a dry process is also known to be a more economical process (i.e., less time, space, materials, labor, and fewer steps) than other techniques. In the present investigation the objective is to prepare directly compressed PEO matrix tablets for controlled release of carvedilol and to evaluate the tablets for *in vitro* drug release studies.

MATERIALS AND METHODS

Materials

Carvedilol and β cyclodextrin were kindly supplied by Orchid Healthcare (Chennai). Polyethylene oxides and microcrystalline cellulose (Avicel PH102) were obtained from Dow Chemicals Asia Pvt. Ltd., Mumbai. Talc and magnesium stearate were of pharmacopoeial grade and all other chemicals were of analytical grade and were used as received.

Preparation of matrix tablets

Different tablet formulations containing different grades of polyethylene oxides were prepared by the direct compression technique (Formulations F1 – F10, [Table 1]). All the ingredients were weighed accurately and passed through 40# mesh. The powder that passed through the mesh was blended well and required quantities of talc (glidant) and magnesium stearate (lubricant) were added. The tablets were compressed (9.0 mm diameter, flat punches without embossing) using a 16 station tablet compression machine (Cadmach, Ahmedabad, India). Each tablet contained 80 mg of carvedilol and other pharmaceutical ingredients, as listed in Table 1. Hardness and friability tests were conducted as in-process tests. Drug content estimation and *in vitro* drug release studies were done to evaluate the matrix tablets.

Estimation of carvedilol

An ultraviolet (UV) spectrophotometric method, based on the measurement of absorbance, at 241 nm, was developed and used for the estimation of carvedilol. The method obeyed Beer's law in the concentration range of 1 to 10 μg/mL, with good correlation coefficient (0.9997). When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and relative standard deviation (precision) were found to be 0.7 and 1.3%, respectively. No interference from the excipients used was observed.

Estimation of drug content in the matrix tablets

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 80 mg of carvedilol was taken into a boiling test tube and extracted with 4 × 10 ml quantities of methanol. The methanolic extracts were mixed and volume was made up to 50 mL with methanol. The solution was subsequently diluted with purified water and analyzed for carvedilol content by measuring absorbance at 241nm.

In vitro release studies

The *in vitro* dissolution studies were carried out using US Pharmacopeia (USP) apparatus type I (Tab-Machines, Mumbai, India) at 100 rpm. The dissolution medium consisted of 0.1 N hydrochloric acid for the first 2 hours and the phosphate buffer pH 7.4 from 3 to 24 hours (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by a diode array UV-visible spectrophotometer at 241 nm. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate, and the mean values of the percentage of drug released were plotted versus time.

Table 1: Compositions of carvedilol tablet formulations

Ingredients	Quantity in tablet (mg/tablet)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Carvedilol	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0
β cyclodextrin	-	-	-	-	80	80	80	-	-	-
HP β cyclodextrin	80	-	-	-	-	-	-	80	80	80
PEO N60K	-	50	-	-	50	-	-	50	-	-
PEO 301	-	-	50	-	-	50	-	-	50	-
PEO 303	-	-	-	50	-	-	50	-	-	50
Avicel PH 102	34	64	64	64	81	81	81	81	81	81
Talc	2	2	2	2	3	3	3	3	3	3
Mg. stearate	4	4	4	4	6	6	6	6	6	6
Total weight	200	200	200	200	300	300	300	300	300	300

Analysis of *in vitro* dissolution data

Data from the *in vitro* drug release were analyzed by different kinetic models like the zero order, first order, Higuchi[9] model, and the Korsmeyer-Peppas[10] model, in order to evaluate the kinetics and mechanism of carvedilol release from the matrix tablets. Statistical analysis by analysis of variance (ANOVA) was carried out to check the impact of the cyclodextrins/polyethylene oxides on the drug release from the matrix tablets.

RESULTS AND DISCUSSION

Matrix tablets each containing 80 mg of carvedilol could be prepared employing different grades of polyethylene oxide, using the direct compression method. Hardness of the tablets was in the range of 8-10 kg/sq.cm. Weight loss in the friability test was less than 0.4% in all the cases. All the matrix tablets prepared contained carvedilol within 100 ± 4% of the labeled claim. All the CR tablets were found to be nondisintegrating in water and aqueous acidic (0.1 N HCl) and alkaline (pH 7.4 Phosphate buffer) fluids. As such the prepared tablets were of good quality with regard to drug content, hardness, and friability. As the tablets were nondisintegrating in both acidic and alkaline fluids they were considered suitable for oral controlled release. Preliminary studies were conducted for selecting the diluent to be used and Avicel PH 102 was selected as the diluent, as it gave good cohesiveness when compressed with controlled release polymers.

Release parameters of the tablets are summarized in Table 2. Carvedilol release from the prepared matrix tablets was slow, spread over more than 24 hours, and depended on the grade of the controlled release polymer and type of cyclodextrin [Figure 1]. Among all the formulations, HP β Cyclodextrin gave greater release, with all the grades of polymer, and was found suitable for sustaining the release of carvedilol over 24 hours. As there are no sustained release tablets of carvedilol available in the Indian market, theoretical sustained release needed for carvedilol, for once-a-day (24 hours) administration, was calculated, based on its pharmacokinetics as suggested by Wagner[11] and the release profiles of the formulated tablets were compared with the theoretical sustained release needed, to select the optimized formulation. A once-a-day controlled release product of carvedilol should contain a total dose of 80 mg (initial-20.5 mg; maintenance dose-59.5 mg) and the drug should be released at a rate (K_0) of 2.475 mg/h. Based on these doses and release rate (K_0), an oral CR tablet of carvedilol should provide a release of 28.8% in 1 hour, 31.9% in 2 hours, 38.1% in 4 hours, 50.4% in 8 hours, 62.8% in 12 hours, and 100% in 24 hours. Matrix tablets formulated with PEO 301 (50 mg), HP β Cyclodextrin (80 mg), and MCC (F9) gave a release profile comparable to the theoretical sustained release needed for once-a-day (24 hours) administration of carvedilol [Figure 2]. The similarity factor (based on fit factor test) with theoretical profile was calculated and found to be 64.40, indicating good similarity.

To know the mechanism of drug release from these formulations, the data were treated according to first-order (log cumulative percentage of drug remaining versus time), Higuchi's[9] (cumulative percentage of drug released versus square root of time), and Korsmeyer's[10] (log cumulative percentage of drug released versus log time) equations, along with zero order (cumulative amount of drug released versus time) pattern. The release rate kinetic data (correlation coefficients) for all the equations can be seen in Table 2. When the data were plotted according to the zero-order equation, the formulations showed linearity with correlation coefficient values between 0.8838 and 0.9339. When the data were plotted according to the first-order equation, the formulations showed a fair linearity, with significantly higher correlation coefficient values than the zero order plots, (0.9351-0.9883) ($t = 5.8$ $P < 0.001$). First-order release rate constants for the tablets prepared with β CD and different grades of polyethylene oxides decreased from 0.0548 to 0.0538 with an increase in the molecular weight of the PEO. The same observation was found with HP β CD also. First-order release rate constants for the tablets prepared with HP β CD and different grades of polyethylene oxides decreased from 0.0734 to 0.0720, with an increase in the molecular weight of

Table 2: Release rate kinetics and correlation coefficients for zero order, first order, Higuchi, and Peppas models for carvedilol controlled release formulations

Formulation	Zero order plot		First order plot		Higuchi model	Peppas model	
	K_0	Correlation coefficient	K_1	Correlation coefficient	(Correlation coefficient)	Slope(n)	Correlation coefficient
F1	-	-	-	-	-	-	-
F2	1.3781	0.8838	0.0268	0.9351	0.9793	0.3265	0.9942
F3	1.3329	0.8892	0.0251	0.9353	0.9821	0.3429	0.9949
F4	0.3787	0.9070	0.0256	0.9446	0.9862	0.3788	0.9865
F5	2.0321	0.8982	0.0548	0.9648	0.9796	0.3318	0.9810
F6	2.0537	0.9132	0.0541	0.9749	0.9854	0.3509	0.9826
F7	0.0940	0.9221	0.0538	0.9752	0.9864	0.3749	0.9776
F8	2.3566	0.9189	0.0734	0.9794	0.9873	0.3759	0.9831
F9	2.3695	0.9331	0.0720	0.9883	0.9922	0.3931	0.9866
F10	2.4330	0.9339	0.0720	0.9839	0.9881	0.4195	0.9768

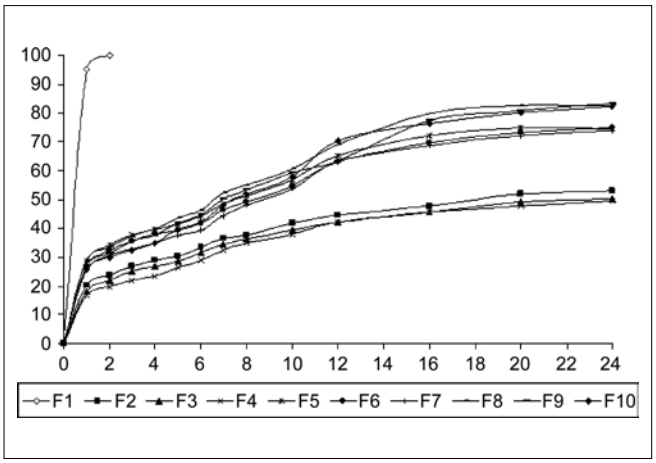

Figure 1: Drug release profiles of carvedilol matrix tablets

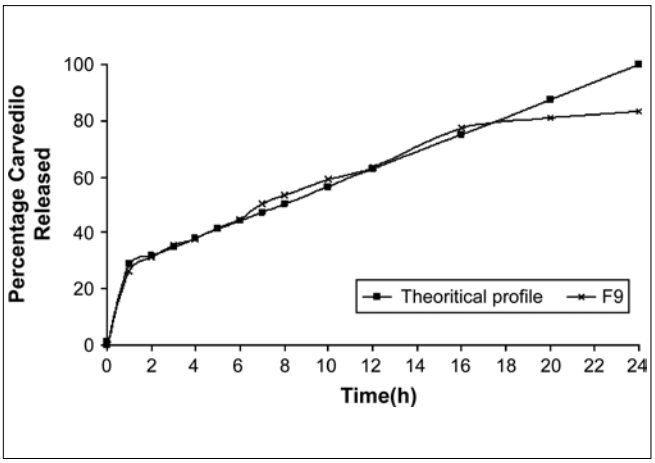

Figure 2: Comparative release profile of formulation F9 with theoretical release needed for carvedilol for oral CR administration

the PEO. When a two-way ANOVA test was done, it was found that in comparison to the matrix tablets prepared with β CD, matrix tablets prepared with HP β CD showed significantly faster release ($F = 22764$, $P < 0.05$). The difference among the polyethylene oxides was also statistically significant ($F = 29.769$, $P < 0.05$). The effect of β CD/HP β CD on the drug release from the matrix tablets was attributed to the solubility enhancement effect of these excipients. The release from the matrix tablets containing β CD/HP β CD (F5 – F10) showed a faster release than the other matrix tablets (F2 – F5).

Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of the drug from the dosage matrix into the dissolution fluid, depending on the concentration. As the concentration gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as the square-root kinetics or Higuchi's[8] kinetics. In this experiment, the *in vitro* release profiles of the drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity ($r = 0.9793$ to 0.9922). To confirm the diffusion mechanism, the data were fit into Korsmeyer *et al.*'s[9] equation. All the formulations showed good linearity ($r = 0.9768$ to 0.9949), with slope (n) values ranging from 0.3318 to 0.4195, indicating that diffusion was the dominant mechanism of drug release, with these formulations indicative of quasi-fickian diffusion. Similar results were observed by Basak and Lucas Mani[12] with matrix tablets of Ambroxol containing HPMC; they considered the n value of less than 0.5 to be indicative of quasi-Fickian diffusion mechanism.

CONCLUSIONS

1. Matrix tablets formulated employing different grades of polyethylene oxides as controlled release polymers and cyclodextrins as release enhancing agents are suitable for oral controlled release of carvedilol.
2. With the increase in the molecular weight of the PEO, the release rate constant was decreased irrespective of the type of cyclodextrin.
3. Once-a-day controlled release tablets of carvedilol could be formulated employing polyethylene oxides as release retardants and Avicel PH 102 as a diluent. Carvedilol release profile from these tablets was similar to the theoretical sustained release profile needed for once-a-day administration of carvedilol orally.
4. Quasi-Fickian diffusion was the drug release mechanism from all the formulated tablets.

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