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In vitro/in vivo correlations of sustained-release coated multiparticulate formulations of doxazosin ☆

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Abstract

Sustained-release coated multiparticulates of doxazosin were prepared by layering the drug onto nonpareil seeds and then coating these drug-layered beads with a rate-controlling membrane made from a mixture of ethylcellulose (EC) and hydroxypropylcellulose (HPC). The in vitro doxazosin release rates were dependent on the external medium and increased with the ratio of HPC/EC in the final coat. The in vivo doxazosin release rates in beagle dogs and in healthy humans were linearly dependent on the HPC/EC ratio in the final coat. Although drug exposure after administration of the multiparticulate formulations was reduced compared to an immediate-release control preparation, there was good correlation between the initial in vitro and in vivo release rates.

Key words: In vitro-in vivo correlation; Multiple-unit dosage form; Sustained-release dosage form; Coating

1. Introduction

Multiparticulate sustained-release dosage forms have several advantages over a single unit dosage form such as a tablet (Follonier and Doelker, 1992). First, multiparticulate dosage forms afford the means for easily combining two or more active agents as well as the flexibility of combining two or more different release profiles. Thus, the drug release rates can be tailored for a specific application. Second, different dosage strengths can be easily obtained with the same formulation by adjusting the number of multiparticulates filled into a capsule. Furthermore, incompatible components or drugs can be combined in the same dosage form by isolating them with barrier coatings. Third, multiparticulate dosage forms also have a reduced potential for toxicity. Since the dose is distributed over multiple units, there is reduced risk of systemic toxicity due to dose-dumping. Also, after the capsule shell dissolves, the individual units are dispersed in the gastrointestinal tract which may reduce the

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risk of local irritation. Finally, compared to a single unit, multiparticulates have advantageous gastrointestinal transit characteristics. These include predictable gastric emptying and less dependence on the fed vs fasted state (Davis, 1985). These characteristics may lead to lower intra- and inter-subject variability.

Both single-unit and multiparticulate controlled-release dosage forms have several medical and marketing advantages (Thombre, 1991). These have led to the development of several commercially important sustained-release and enteric-coated formulations (e.g., Procardia XL®, Cardizem SR®, Cardizem CD®, Novafed®, and Theodur®).

An important step in the characterization of a controlled-release dosage form is to establish an in vitro-in vivo correlation. Such a correlation can help to rationally develop and optimize formulations, to predict the effect of formulation or process changes, and to allow performance-based specifications to be set for the drug product (Skelly et al., 1990). In most cases, however, only the in vitro characteristics are well studied as a function of the formulation and manufacturing variables. The in vivo characterization is limited to a few variables because of the time and cost of conducting appropriate studies. Furthermore, in some cases, the in vitro-in vivo correlations can be complex due to the effect of enzymes, site-specific absorption, pathophysiological effects, polarity of the drug molecule, and site-specific enzyme carrier transport. Further complications might be introduced in man given the intrinsic differences in the physiology and absorptivity of the gastrointestinal tract in the animal model vs humans (Dressman, 1986). Therefore, a correlation between the in vitro and in vivo performance of sustained-release multiparticulates is particularly desirable.

In this paper, we report the effect of a systematically varied formulation parameter on the in vitro and in vivo characteristics of sustained-release doxazosin multiparticulates. The dosage form consists of nonpareil seeds layered with doxazosin mesylate and then coated with a polymeric film-coat of a mixture of hydroxypropylcellulose (HPC) and ethylcellulose (EC). The release rates were studied as a function of the ratio of HPC/EC in the coat.

2. Materials and methods

Sustained-release coated multiparticulates of doxazosin mesylate were fabricated by the procedure shown schematically in Fig. 1. Confectioner's nonpareil seeds (no. 18/20 mesh, Ingredient Technology Corp., Pennsauken, NJ) were sprayed with a 95:5 (w/w) ethyl alcohol/water mixture containing doxazosin mesylate in a 10% solution of 35:65 (w/w) HPC (Aqualon, Wilmington, DE)/EC (10 cP, Dow Chemicals, Midland, MI) that served as the binder. The coating was done

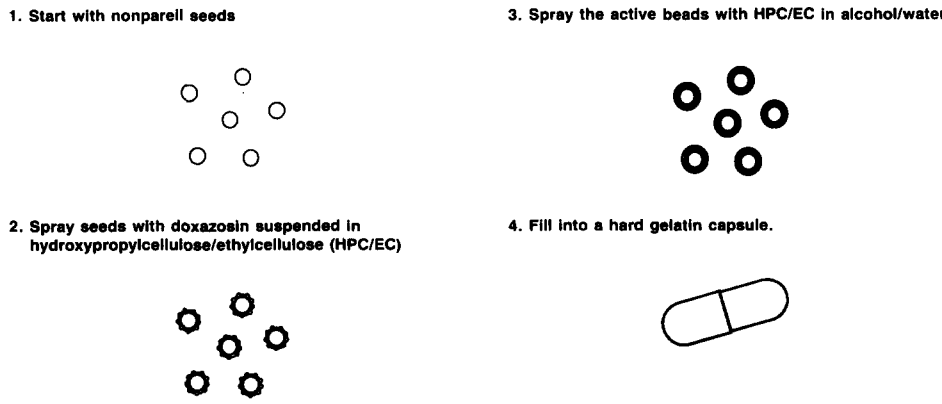


Fig. 1. Schematic for the preparation of sustained-release doxazosin multiparticulates.

in a CF-Granulator (Vector-Freund, Marion, IA). These drug-layered beads were then sprayed with a 10% solution of HPC/EC in 95:5 ethyl alcohol/water, and dried overnight at 55°C. The dried beads were lubricated and a quantity corresponding to a 2 mg dose of doxazosin were filled in a no. 4 hard gelatin capsule using a Zanazi LZ-64 encapsulation machine with a pellet filling option. The formulations were designated A–E (Table 1), depending on the ratio of HPC/EC in the final coat.

The surface of the uncoated, drug-layered, and coated multiparticulates, both before and after exposure to water was examined using a scanning electron microscope (Joel 840 SEM). In vitro drug release profiles in simulated gastric fluid without enzymes (SGN) and in simulated intestinal fluid without enzymes (SIN) were determined with unencapsulated multiparticulates containing 2 mg doxazosin using standard USP dissolution methodology (Apparatus 1, rotating baskets, 50 rpm, 37°C, and 1000 ml of medium). The doxazosin samples were assayed by an HPLC method.

Pharmacokinetic studies with the multiparticulate formulations and an immediate-release control formulation were conducted in one of two sets of four beagle dogs ($n = 4$) dosed in a cross-over fashion. The control formulation and the formulation designated C was dosed in both sets of dogs ($n = 8$). The dogs were fasted overnight prior to dosing, and food was withheld for 4 h after dose administration. Blood samples were withdrawn at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 h post-dose, and the resulting plasma samples were stored at −20°C until assayed for doxazosin.

An open, single dose, four-way cross-over study in humans was conducted to evaluate the rate and extent of doxazosin absorption from an immediate-release control and from the sustained-release doxazosin multiparticulates. Six normal male volunteers were dosed with the 1 mg control formulation and three 2 mg test preparations (B–D). There was a minimum of 5 days between doses. All subjects were fasted 12 h prior to drug administration and for the first 4 h following drug administration. The washout period between treatments was at least 5 days. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h post-dose, and the resulting plasma samples were stored at −20°C until assayed by HPLC (Fouda et al., 1988).

Table 1
Key to formulations

Formulation designation	Hydroxypropylcellulose/ethylcellulose ratio in the final coat	% coat relative to the core
A	35:65	6
B	30:70	6
C	25:75	6
D	20:80	6
E	15:85	6

The drug absorption kinetics in dog and man were obtained from the plasma concentrations of doxazosin according to the following equation (Wagner and Nelson, 1964):

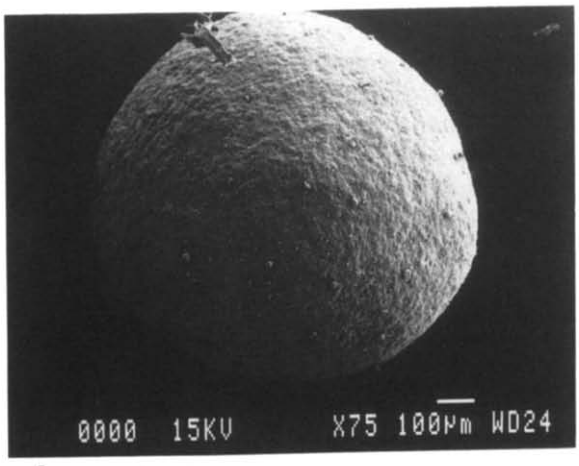
$$\frac{(X_A)_T}{(X_A)_\infty} = \frac{C_T + K\int_0^\infty C\,dt}{K\int_0^\infty C\,dt} \quad (1)$$

where $(X_A)_T$ is the cumulative amount of drug absorbed into the systemic circulation after time T, $(X_A)_\infty$ denotes the amount of drug ultimately absorbed, C is the drug concentration at time t, and K represents the apparent first order elimination rate constant of the drug from the body. The Wagner-Nelson equation is strictly applicable to drugs following the one-compartment model and has the advantage that although it does not tell us about the extent of drug absorption, no assumption is made regarding absorption kinetics.

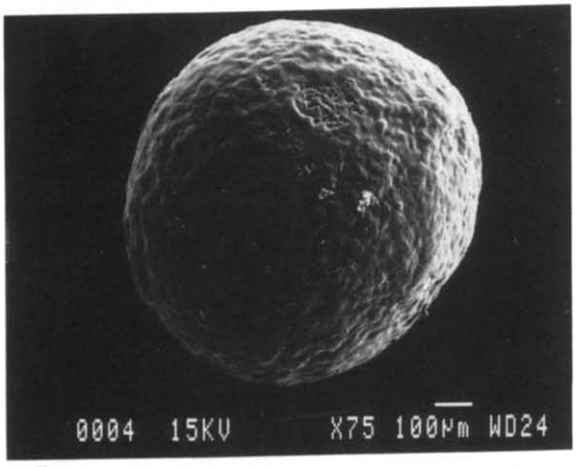
3. Results and discussion

3.1. Scanning electron micrographs

Scanning electron micrographs of a nonpareil seed (A), a doxazosin mesylate-layered multiparticulate (B), and a coated multiparticulate (C) (Fig. 2) show the uniformly spherical shape of the multiparticulates. Fig. 3 shows the membrane surface of formulation C after exposure to water.



A



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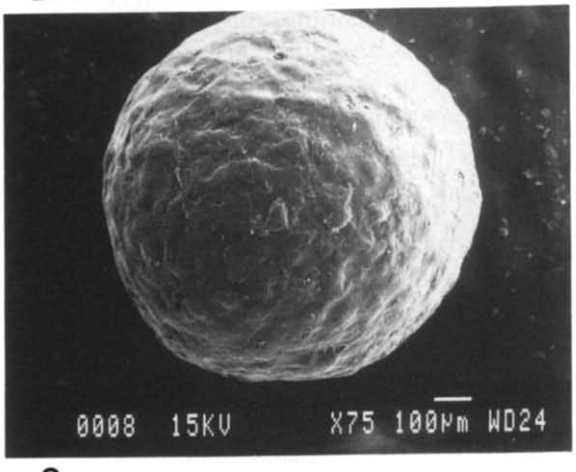
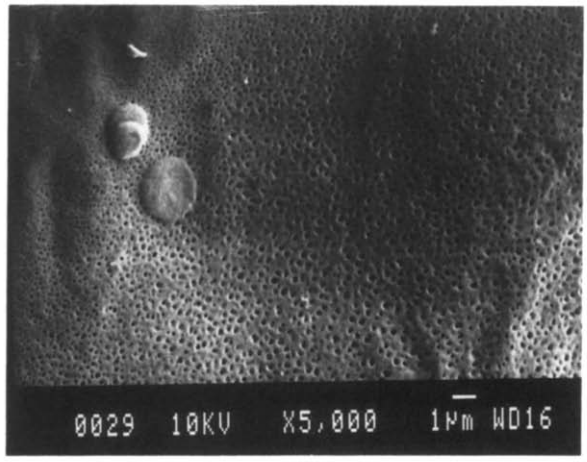
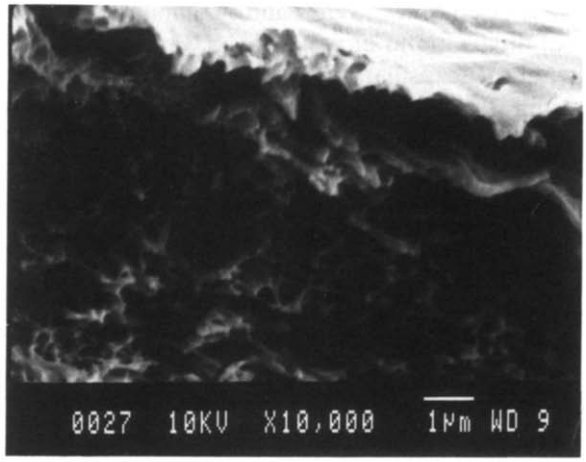


C

Fig. 2. Scanning electron micrographs at 75× magnification of: (A) a nonpareil-seed; (B) a doxazosin layered multiparticulate; (C) a doxazosin layered, coated multiparticulate.



A



B

Fig. 3. Scanning electron micrographs of the membrane surface of formulation C: (A) before exposure to water (×5000 magnification); (B) after exposure to water (×10000 magnification).

The final coat of this formulation contained 25% HPC by weight relative to EC. The submicron-sized pores seen on the surface at 5000× magnification were not present initially but were formed after exposure of the coating to water. Thus, the network of pores was likely formed by leaching of the water-soluble HPC from the membrane coat. This observation coupled with the external medium-dependent doxazosin release characteristics observed with the multiparticulates (discussed later) support the diffusive

release of doxazosin through a porous membrane barrier. Thus, the multiparticulates can be considered as a reservoir device with a drug-containing core surrounded by a rate-controlling membrane.

3.2. Drug release profiles

Doxazosin release profiles from the multiparticulate formulations in SGN (Fig. 4) and in SIN (Fig. 5) show that the release rates increased with the proportion of HPC relative to EC in the final coat. Although the individual formulations maintained their rank order, it was also interesting to note that formulations B and C released at a slower rate in SIN compared to SGN while formulations D and E released more rapidly in SIN compared to SGN. These differences are probably due to the pH-dependent and chloride ion concentration-dependent aqueous solubility of doxazosin (Fiese, personal communication; 1987).

3.3. In vivo characterization

The time course of plasma doxazosin concentrations (normalized to a 2 mg dose) in fasted beagle dogs given the doxazosin preparations is shown in Fig. 6. Compared to the control formulation, the peak plasma doxazosin levels occurred later and were progressively lower with the sustained-release preparations A–E. The doxazosin exposure as measured by the AUC(0–30 h) values was progressively lower with the sustained-release preparations A–E and ranged from 84 to 5% of the control. Table 2 summarizes the calculated pharmacokinetic parameters for doxazosin in dogs.

In fasted human volunteers, the plasma doxazosin profiles showed a similar trend (Fig. 7), viz., the peak doxazosin concentrations (C_{max}) were lower and occurred later (T_{max}) with the sustained-release preparations (B–D) compared to the control formulation. As was the case in the study in dogs, the relative bioavailability of the sustained-release preparations in humans was reduced (79 to 26%). Table 3 summarizes the calculated pharmacokinetic parameters for doxazosin in humans.

3.4. Correlations between in vitro and in vivo performance

The in vitro release rates were calculated from the initial slopes of the release profiles in SGN

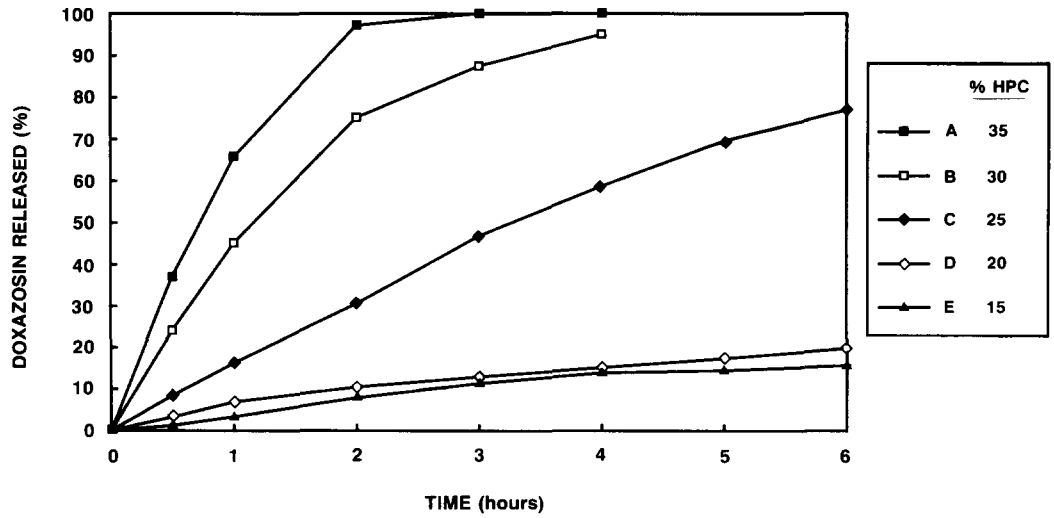


Fig. 4. Multiparticulate doxazosin. Dissolution in simulated gastric fluid (without enzymes); rotating baskets, 50 rpm, 37°C, $n = 3$.

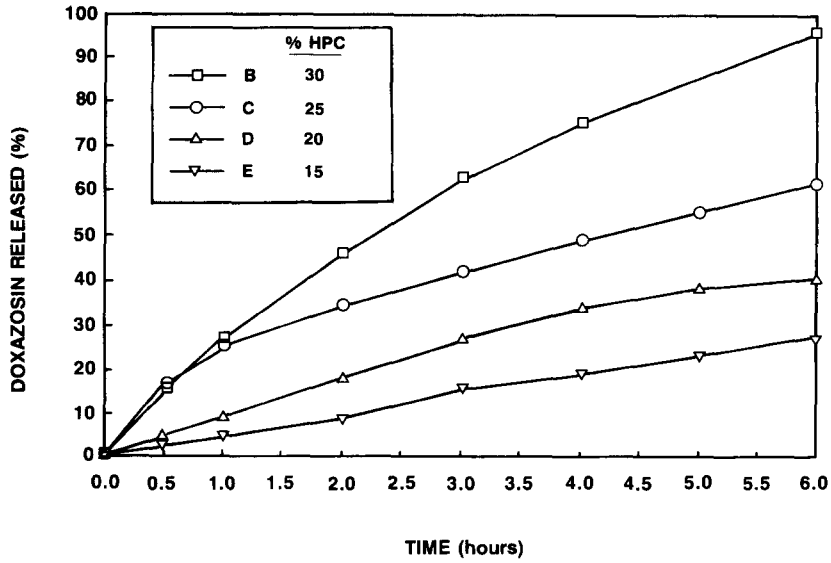


Fig. 5. Multiparticulate doxazosin. Dissolution in simulated intestinal fluid (without enzymes); rotating baskets, 50 rpm, 37°C, $n = 3$.

and SIN, and the in vivo release rates were calculated from the initial slopes of the absorption profile by a Wagner-Nelson analysis. Although the calculated rates represent doxazosin release over a very broad range of conditions in vitro and include species-related differences in vivo, a consistent trend and a good rank-order correlation was seen with the formulations (Fig. 8).

The in vivo release rates, calculated as described above, were also found to be correlated with a formulation variable, viz., the proportion of HPC initially present in the final coat (Fig. 9).

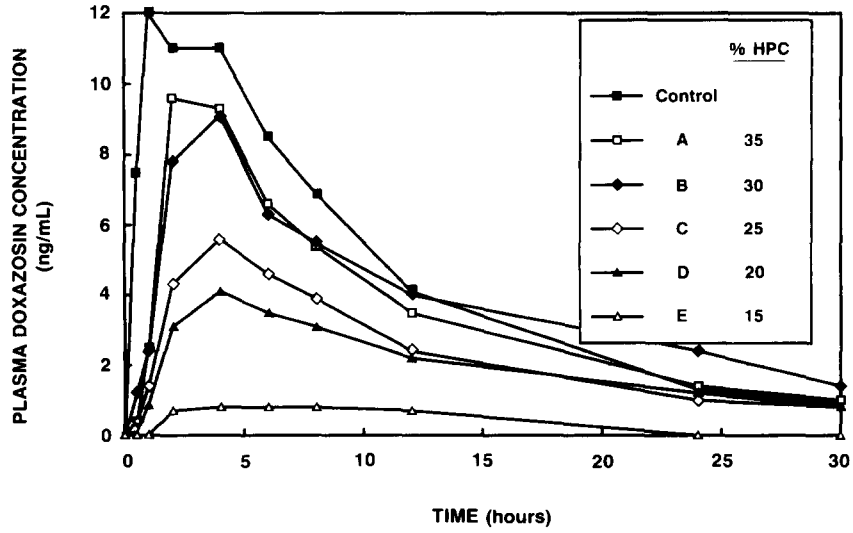


Fig. 6. Multiparticulate doxazosin. Normalized plasma doxazosin levels in fasted dogs.

Table 2
Pharmacokinetics of doxazosin formulations (1 mg) in beagle dogs

Form	Dog set no.	C_{max} (ng/ml)	T_{max} (h)	AUC (0–30) (ng h ml^{-1})	Relative BA (%)
Control	1	15.0 (6.0)	2.0 (1.4)	144 (17)	100
Control	2	13.0 (2.0)	1.9 (1.4)	128 (32)	100
Control	1 and 2	14.0 (4.0)	1.9 (1.4)	136 (25)	100
A	2	10.0 (1.0)	3.0 (1.2)	108 (25)	84
B	1	9.6 (4.4)	2.7 (1.2)	120 (39)	83
C	1 and 2	6.0 (2.0)	4.3 (2.0)	70 (21)	51
D	1	4.1 (1.8)	3.5 (1.0)	60 (21)	42
E	1	0.8 (0.2)	4.5 (2.5)	7.6 (2.2)	5

Numbers in parentheses are standard deviations. Relative bioavailability (BA) was calculated based on the ratio of mean AUC(0–30) values.

These data were well represented by a linear model with a slope of 0.044 mg h^{-1} (% HPC)$^{-1}$.

The lower and 'flatter' plasma concentration profiles of doxazosin in dogs and in humans given the test formulations indicate a slow release of doxazosin compared to the immediate-release control. It also appears that the absorption was significantly slowed after 4–6 h in dogs and after 6–8 h in humans. In this time period, the multiparticulates are expected to have just reached the colon. The reduced relative bioavailability is most

Table 3
Pharmacokinetics of doxazosin formulations in normal human volunteers

Form	Dose	C_{max} (ng/ml)	T_{max} (h)	AUC(0–24) (ng h ml^{-1})	Relative BA (%)
Control	1 mg	11.0 (2.2)	1.3 (0.3)	103 (26)	100
B	2 mg	12.0 (5.0)	4.5 (1.7)	161 (66)	79 (32)
C	2 mg	5.0 (1.7)	6.0 (1.8)	75 (24)	38 (18)
D	2 mg	3.3 (1.2)	4.8 (1.3)	49 (15)	26 (16)

Numbers in parentheses are standard deviations. Relative bioavailability (BA) was calculated as the mean of individual relative bioavailabilities.

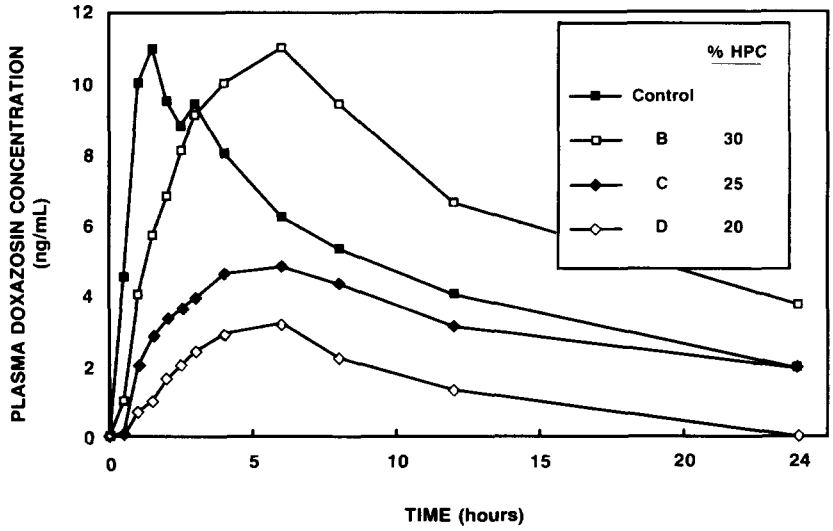


Fig. 7. Multiparticulate doxazosin. Normalized plasma doxazosin levels in fasted humans (1 mg control vs 2 mg test formulation).

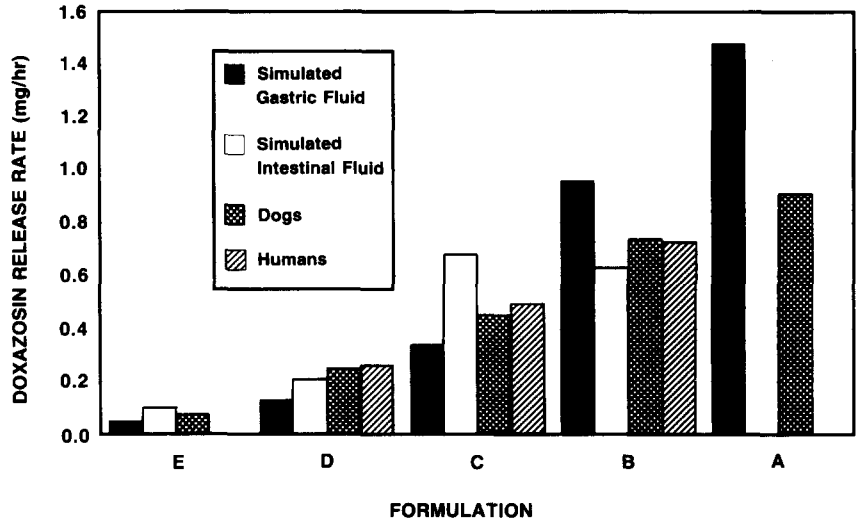


Fig. 8. Relationship between the initial in vitro release rates and the initial in vivo release (absorption) rates.

likely not due to poor absorption, since it has been previously shown by an intubation study in man that doxazosin can be absorbed throughout the gastrointestinal tract (Barr et al., 1987). Thus, it appears that the physiological conditions such as lack of water, higher pH, and lower permeability that are present in the colon prevent or significantly reduce drug release from these preparations. It is also possible that doxazosin is released from the multiparticulates but is not available for

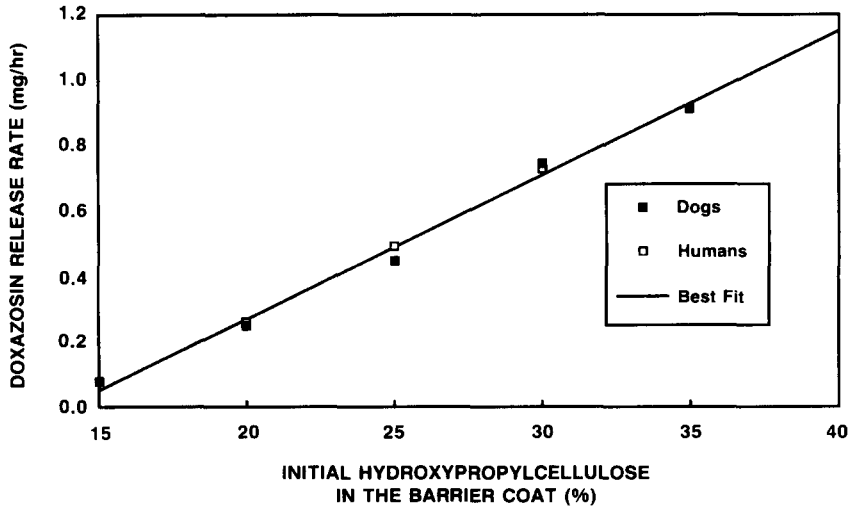


Fig. 9. Relationship between the in vivo release (absorption) rate and the proportion of hydroxypropylcellulose in the coat.

absorption at the gastrointestinal wall because of possible compaction in the feces or other mass-transfer barriers.

4. Conclusions

In this study, we have shown that sustained-release doxazosin multiparticulates can be prepared by layering the drug onto a substrate and then coating with a barrier of HPC/EC. The surface porosity of the membrane coat after exposure to water and the in vitro release rate characteristics of this dosage form are dependent on the proportion of HPC in the final coat. The in vitro release profiles from these formulations were dependent on the external medium.

The pharmacokinetics of sustained-release doxazosin multiparticulates were studied in fasted beagle dogs and in fasted healthy humans as a function of the HPC/EC ratio in the final coat. Although the bioavailability of the test preparations was reduced relative to an immediate-release control formulation, the initial release rates were well correlated to each other and to the HPC/EC ratio.

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