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A controlled release matrix using a mixture of hydrophilic and hydrophobic polymers

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Summary

A mixture of acrylic resin and carboxymethyl cellulose was used for the preparation of a matrix in an attempt to modify the release rate of propranolol HCl. The dissolution data indicate that it is possible to prepare a dosage form from these polymers capable of delivering the drug at constant rate (zero-order release).

During the past two decades, hydrophilic polymers and especially celluloses have been extremely popular in controlling the release rate of soluble drugs from solid dosage forms. The ease of compression, their ability to accommodate large amounts of drugs and the minimum influence of the processing variables on the release rates are the main reason for their popularity (Alderman, 1984; Ranga, 1988).

More recently, hydrophobic polymers, such as acrylic resins, have been used for the preparation of controlled release formulations since they possess some very interesting characteristics, i.e., excellent flow properties and weight uniformity. Drug content uniformity has also been observed with tablet formulations (McGinty et al., 1983; Efentakis et al., 1990).

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The purpose of this study was to investigate the effect of a mixture of two polymers (a hydrophilic, sodium carboxymethyl cellulose, and a hydrophobic Eudragit RS 100) on the release rate of a water-soluble drug, such as propranolol HCl. The release of the drug from four basic types of formulations was studied and evaluated.

The acrylic resin Eudragit RS 100, obtained from Rhom Pharma (Darmstadt, Germany), was powdered in ball mill and sieved through a 300 mm sieve. The product was then blended with propranolol HCl (provided by ICI), Carboxymethyl cellulose, (NaCMC, produced by FMC) and magnesium stearate (BDH) for 5 min in a blender. The formulations prepared contained varying amounts of materials in the proportions shown in Table 1. The powder mixture was compressed to prepare tablets 500 mg using the direct compression technique on an instrumented single-punch tabletting machine (Korch-Erwena).

The ratio between the diameter and the thickness of cylindrical tablets was between 0.7 and 0.9.

TABLE 1

The formulations used in the study

	Formulations (%)			
	I	II	III	IV
Propranolol HCl	32	32	32	32
Eudragit RS 100	50	17	33.5	–
NaCMC	17	50	33.5	67
Magnesium stearate	1	1	1	1

The hardness level was 8 kg as measured in the Schleuniger-2 hardness tester.

Dissolution measurements were carried out in a USP dissolution test apparatus, paddle method, using 1000 ml of a pH 7.2 phosphate buffer (USP) or in dilute hydrochloric solution (USP) pH 1.2 at 37.5 °C, rotated at 50 or 100 rpm (see Table 2). Propranolol HCl samples were taken hourly over an 8 h period and immediately replaced with an equal volume of test medium.

The samples were analyzed spectrophotometrically at 289 nm using a Perkin Elmer Lambda series spectrophotometer. All experiments were performed in triplicate and the average value was recorded. The mixture of NaCMC/RS 100 and the drug exhibited good flow properties and weight uniformity. By altering the ratio of NaCMC/RS 100, it was possible to increase or decrease the rate of drug release (Fig. 1). Increased release of the drug was observed as the content of Eudragit RS 100 was increased. This was probably due to the fact that as Eudragit RS 100 erodes from the swollen matrix the greater penetration which occurs through the exposed surface results in a faster release of the drug. The phenomenon was more profound in formulation I, where the content of Eudragit RS 100 is 50% of the mixture or alternatively the highest among the formulations. This was more intense when a pH 7.2 medium was used, than for pH 1.2. In both cases the release of the drug was completed in less than 4 h.

Three preparations, with hardness of 2.3, 4.6 and 8 kg respectively, were tested, but no effect on the release rate was observed. Afterwards, the hardess used in this study was established at 8 kg. The stirring speed appears to influence the dissolution rate; with an increase of agitation speed

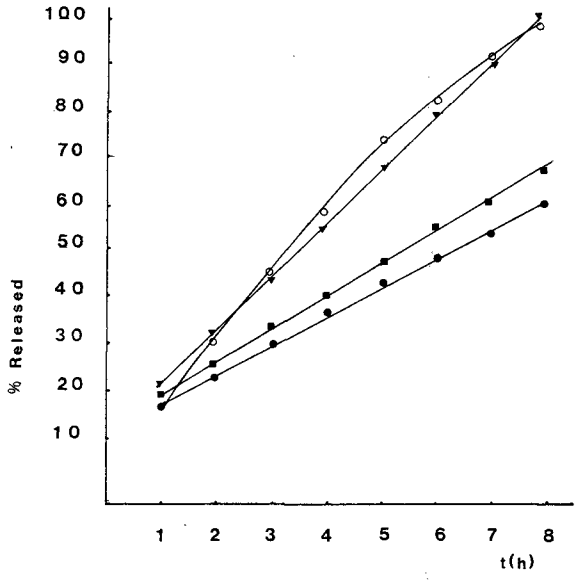

Fig. 1. Drug release profiles of propranol HCl from tablets containing different ratio Eudragit RS 100/NaCMC. A1 (■), A3 (▼), A4 (●), A5 (○).

from 50 to 100 rpm, a faster erosion of the matrix was observed and the release rate of the drug was increased (Fig. 2). The pH also appears to influence the release rate. An increase of the pH of

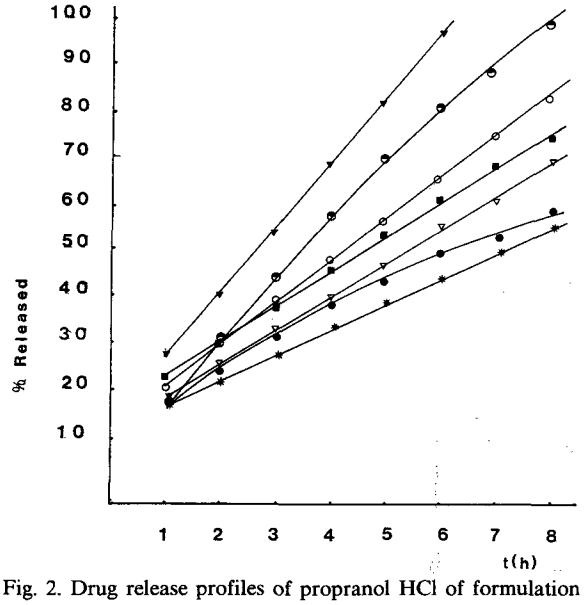

Fig. 2. Drug release profiles of propranol HCl of formulation II, under different conditions. A1 (▽), A2 (◓), A6 (■), A7 (▼), A8 (*), A9 (○), A10 (●).

TABLE 2

Estimated values of slope, intercept and correlation coefficient following regression of dissolution data

Formulation	Matrix	Slope	Intercept	r^2
Ia	[a]	–	–	–
Ib	[a]	–	–	–
IIa	A1	0.112	11.961	0.999
IIb	A2	0.200	4.50	0.993
IIIa	A3	0.198	9.032	0.998
IVa	A4	0.100	11.571	0.996
IVb	A5	0.195	9.463	0.986
IIa_1	A6	0.125	15.821	0.999
IIb_1	A7	0.239	12.133	0.999
IIa_{43}	A8	0.148	11.924	0.999
IIa_{25}	A9	0.092	11.465	0.999
IIa_{60}	A10	0.100	13.212	0.993

[a] Release of the drug was completed in less than 4 h.
a, pH of the medium 1.2; b, pH of the medium 7.2; a_1, b_1, stirring speed was 100 rpm instead of 50 rpm; a_{43}, a_{25}, temperature of the medium 43 and 25 °C, respectively; a_{60}, storage for 100 days at 60 °C.

the medium from 1.2 to 7.2 resulted in an increase of release rate which was probably due to an increase in erosion rate of NaCMC (Baveja et al., 1987) (Fig. 2). Further, the influence of temperature of dissolution medium on the release rate was examined and it was found that increased temperatures resulted in increased release rates of the drug from the matrix (Fig. 2).

Finally, the effect of storage at higher temperatures was studied. Tablets from formulation II were stored for 100 days at 45 and 60 °C. The dissolution data showed almost no effect for tablets stored in 45 °C, while those stored at 60 °C showed significant changes and slower release rate (Fig. 2).

In Table 2 the estimated values of slope, intercept and correlation coefficient following regression of dissolution data are listed from the different formulations and under different conditions. The values of correlation coefficient (r^2) were higher than 0.993, except for formulation IVb. The linearity of the relationship and the resulting high correlation suggests that the drug is released according to zero-order kinetics, within the specified time period.

The results of this study indicate that the matrices consisting of these two polymers exhibit the above-mentioned characteristics that would allow them to be used in the formulation of solid controlled release peparations of water soluble drugs since they can release them at a constant rate (zero-order release).

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