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Controlled release of cephalexin from double-layer tablets containing small proportions of acrylic resins

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Summary

This article reports the rates of dissolution of cephalexin from double-layer tablets made using various pressures and various proportions of two granulates, each containing a small percentage of Eudragit E or Eudragit RS. The variety of the dissolution profiles observed testifies to the potential of such formulations for controlled release of cephalexin.

Introduction

In recent years considerable effort has gone into the development of new excipients allowing controlled release of active principles from various dosage forms, the excipient most widely used for this purpose being polymers capable of forming various kinds of plastic matrix. Numerous mathematical models proposed to describe the release of the active principle from such matrices have recently been reviewed (Peppas, 1984; Peppas and Segot-Chieq, 1985), but few data have as yet been published regarding the influence of technological factors. This article reports the effectiveness of combinations of small proportions of the acrylic resins, Eudragit E and Eudragit RS, in controlling the release of cephalexin from double-layer tablets. The characteristics of Eudragit E and Eudragit RS have been extensively described (Lehmann, 1982, 1984). Cephalexin was chosen as the principle active agent because it is one of the microbial agents to which most attention has been paid as regards the development of controlled release formulations; the excipient used having included derivatives of cellulose (Hasegawa et al., 1980; Higashikawa, 1983), acrylic polymers (Kato et al., 1984) and lipid-based materials (Toyo Jozo Co., 1983; Shionogi Co., 1984). An important aspect of the work presented here was to evaluate the performance of low-excipient formulations, the interest for which stems from the large doses in which cephalexin is usually administered.

Materials and Methods

Formulation

Two granulates (one containing Eudragit E and the other Eudragit RS) were each prepared as follows.

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(a) Cephalexin (Antibioticos S.A., lot J-5142) was mixed with a 13.75% solution of the polymers in acetone, the proportions being calculated so that the final granulate would contain 5% of Eudragit E or 10% Eudragit RS. A small quantity of acetone was added when necessary to allow a mass suitable for granulation to be obtained.
(b) The paste was passed through a 1 mm sieve.
(c) The resulting granulate was dried for 2 h in a forced air oven at 25°C.
(d) Lubricant (1% of talc and 0.5% of magnesium stearate) was mixed in during 30 min in a Turbula mixer at 42 rpm.

Double-layer tablets containing various proportions of the two granulates were then punches under various pressures in a simple punch machine (Erweka) equipped with piezo-electric pressure sensors (Martinez-Pacheco et al., 1985). Table 1 lists the characteristics differentiating the 13 formulations tested. In all cases the dose of cephalexin was 500 mg per tablet.

Dissolution assay

Dissolution assays were performed on one tablet a time and triplicated for each formulation, the dissolution media being artificial gastric and enteric juices without enzymes according to the USP XXI Ed. The apparatus employed (Llabres et al., 1978) was of the flow-through type without accumulating reservoir and allowed the use of a pH gradient. Fig. 1 shows the changes in the pH of medium during the 3 course of dissolution tests. The concentration of cephalexin in samples taken from the dissolution tests was determined by direct spectrophotometry ($E^{1\%}_{1cm} = 211$ at 262 nm), preliminary experiments having shown that neither the acrylic resins or any other component of the formulation or dissolution media caused interference.

Percentages of drug dissolved were calculated as per Llabres et al. (1978) and curves of the percentage of drug dissolved against time were characterized by the parameters: D_{15}, D_{30}, D_{60}, D_{90} and D_{180} (referred to collectively below as the D_x), which represents the percentages of drug dissolved after 15, 30, 60, 90 and 180 min, respectively.

Experimental design

To evaluate a wide range of the two variables studied (upper punch pressure and the relative proportions of the two granulates) while keeping the number of experiments reasonably small, we used a central composite design (Cochran and

TABLE 1

DIFFERENTIAL CHARACTERISTICS OF THE 13 FORMULATIONS TESTED

Formulation	Percentage of the granulate containing Eudragit E	Upper punch pressure (MPa)
A	25	13
B	75	13
C	25	39
D	75	39
E	0	26
F	100	26
G	50	0
H	50	52
I	50	26
J	50	26
K	50	26
L	50	26
M	50	26

Dose of cephalexin was 500 mg/tablet.

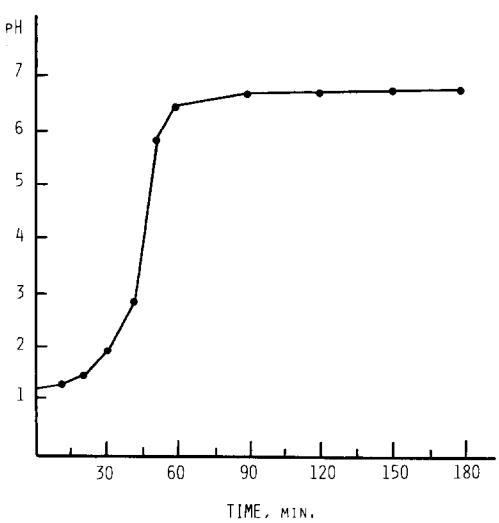

Fig. 1. Changes in the pH of the dissolution medium during testing.

Cox, 1957) with five levels of each of the two variables. The corresponding analysis of variance determined whether the D_x values exhibited linear and/or quadratic dependence on the independent variables and the lack of fit between the experimental data and the quadratic model implicit in the design. Significant terms were identified by estimating the corresponding confidence intervals. In order not to have use the orthogonalized values of variables, multiple linear regression of the D_x on the significant terms was used to estimate the coefficients of the response surfaces.

Results and Discussion

Table 2 shows the mean values of the D_x for each formulation, and Table 3 summarizes the corresponding analysis of variance. The empirically estimated dependence of the D_x values on P (the upper punch pressure in MPa) and %E (the percentage of the granulate containing Eudragit E) was as follows:

$$D_{15} = 72.75 + 0.40 \times \%E - 0.19 \times P$$

$$(r^2 = 0.9203;\ F = 57.76)$$

TABLE 2

PERCENTAGE OF CEPHALEXIN DISSOLVED AFTER 15, 30, 60, 90 AND 180 min OF TESTING (D_{15}, D_{30}, D_{60}, D_{90} AND D_{180})

Formulation	D_{15}	D_{30}	D_{60}	D_{90}	D_{180}
A	76.0	88.1	93.0	94.4	97.0
B	84.5	91.7	96.4	96.1	96.8
C	43.6	60.2	67.7	73.3	82.7
D	77.1	85.4	92.8	95.6	98.8
E	51.2	73.8	89.4	92.1	95.0
F	89.9	95.0	96.9	99.2	99.3
G	92.2	93.6	96.4	97.5	98.5
H	41.0	54.5	69.7	73.2	79.2
I	68.2	83.9	90.4	94.1	95.2
J	68.8	79.4	92.4	95.9	100.0
K	73.4	84.3	93.0	98.6	99.3
L	66.3	78.1	87.7	92.3	99.6
M	54.7	76.5	91.3	95.1	101.8

Each percentage is the mean of three determinations.

TABLE 3

ANALYSIS OF VARIANCE OF THE RESULTS

Source of variation	d.f.	Mean square				
		D_{15}	D_{30}	D_{60}	D_{90}	D_{180}
Linear terms	2	1374.7	717.3	372.7	263.1	116.4
%E		**	**	**	**	**
P		**	**	**	**	**
Quadratic terms	3	66.2	74.1	83.6	101.0	88.9
$\%E^2$		–	–	–	–	–
P^2		–	–	**	*	**
%E×P		–	*	**	*	**
Lack of fit	3	51.7	21.6	16.9	20.4	20.2 *
Error	4	10.7	11.1	4.4	6.5	1.4

* Significant at $P = 0.05$ level.
** Significant at $P = 0.01$ level.

$$D_{30} = 108.80 - 0.19 \times \%E - 1.55 \times P + 1.66 \times 10^{-2}\ (\%E \times P)$$

$$(r^2 = 0.8996;\ F = 25.87)$$

$$D_{60} = 110.53 - 0.29 \times \%E - 0.70 \times P - 1.27 \times P^2 + 1.67 \times 10^{-2}\ (\%E \times P)$$

$$(r^2 = 0.8959;\ F = 17.21)$$

$$D_{90} = 110.22 - 0.28 \times \%E - 0.46 \times P - 1.50 \times P^2 + 1.58 \times 10^{-2}\ (\%E \times P)$$

$$(r^2 = 0.8932;\ F = 16.73)$$

$$D_{180} = 108.63 - 0.24 \times \%E - 0.19 \times P - 1.46 \times P^2 + 1.25 \times 10^{-2}\ (\%E \times P)$$

$$(r^2 = 0.8654;\ F = 12.86)$$

Fig. 2 illustrates these response surfaces graphically.

Except in the case of D_{180}, none of the lack of fit contributions to the variances of the D_x values were significant, so that the corresponding response surfaces may be regarded as trustworthy.

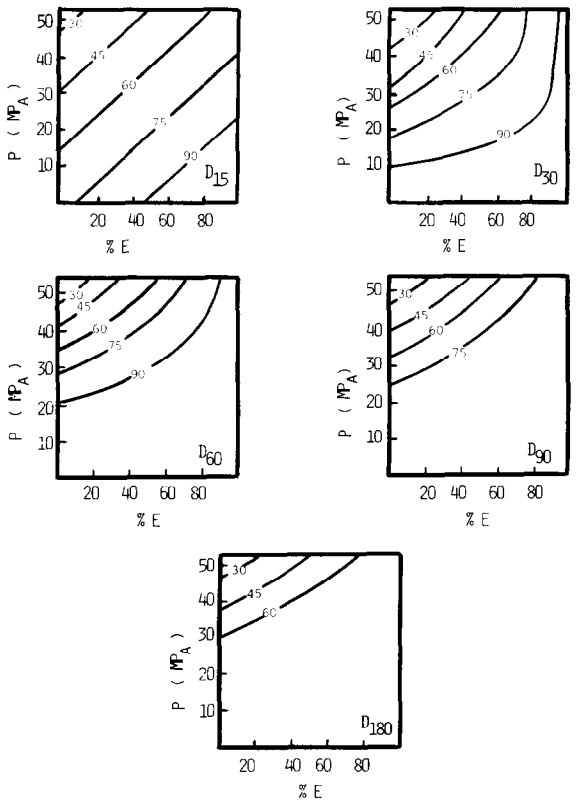

Fig. 2. Dependence of the cephalexin dissolution parameters D_{15}, D_{30}, D_{60}, D_{90} and D_{180} on upper punch pressure (P) and the percentage of the granulate containing Eudragit E (%E).

This contrasts with the results of other studies (Schwartz et al., 1973a and b). Except perhaps for D_{15}, all the response surfaces are complex, and taken together they are difficult to interpret as regards the separate contributions of the two granulates to cephalexin release, but two conclusions may nevertheless be confidently drawn. In the first place, the wide variety of dissolution profiles obtainable with values of the upper punch pressure and %E within the ranges studied implies (pending bioavailability data which we hope to obtain shortly) that such formulations offer great promise for the controlled-release of cephalexin. Secondly, dissolution profiles of all shapes may be obtained by varying the pressure used to punch tablets prepared with Eudragit RS alone, which simplifies the manufacture of tablets and allows the use of conventional presses. Finally, we wish to stress that such formulations contain just 11.5% of substances other than the active principle.

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