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STUDY OF IN VITRO KINETICS AND LIBERATION MECHANISM OF PENTOXIFYLLINE FROM COATED PELLETS AND COMPACTS BASED ON 2-HYDROXYETHYLMETHACRYLATE-BUTYL ACRYLATE COPOLYMER

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ABSTRACT

The influence of certain polymerous auxiliary materials upon the liberation kinetics and mechanism of pentoxifylline from peroral dosage forms has been followed. Solutions in organic solvents (R1, R2, R3) and water dispersions (E35, E36, E37) of the 2-hydroxyethyl methacrylate - butylacrylate (2-HEMA-BuA) copolymer containing the monomers as shown in various ratios, were being evaluated. Pellets were prepared from pentoxifylline coated by a layer of the polymers studied, with the subsequent production (by means of direct compression) of tablets containing 300 mg of the drug each. Release of pentoxifylline from the coated pellets and tablets has been determined by the dissolution test in accordance with the 4th edition of the Czechoslovak Pharmacopoeia. Using the Weibull and Higuchi functions parameters, the retarding ability of individual polymers was evaluated. Two mechanisms, viz. the formation of multiple unit tablets from coated pellets, and the app-

lication of a suitable polymer type, were observed as important factors related to the retarding effects in the dosage forms as prepared. Dispersion-type polymers were found as more suitable from the retardation viewpoints. From the parameters used in the evaluation of retardation, the mean drug liberation time (MLT) was found as the most advantageous one.

INTRODUCTION

One of the basic targets of recent pharmaceutical research is the qualitative enhancement of pharmacotherapy which is required to meet demands for high efficiency, specificity and safety. In addition to syntheses of new drugs, the pharmaceutical technology has a significant role in fulfilling these requirements, by formulating advanced drug generations (drug delivery systems) aside from conventional ones.

An important precondition in the implementation of the concept of controlled liberation and transportation (targeting) of drugs within the organism has been the progressive development observed in the field of polymer chemistry. Several authors have reviewed the problem area of utilization of synthetic polymers in the field of higher-generation drug development[1-4].

Among the synthetic polymers used for drug liberation control purposes from dosage forms designed for peroral application, certain types of Eudragit^{R} (Röhm Pharma GmbH., Darmstadt, FRG) have occupied a significant position. These synthetic polymers, in principle poly(meth) acrylates, are used both for film coating of small particles and tablets, and in the production of matrix-type tablets[5-7].

The Institute of Macromolecular Chemistry of the Czechoslovak Academy of Sciences (Prague, ČSSR) has prepared a series of copolymers based upon acrylate and methacrylate monomers, designed for use as drug liberation retar-

ding agents from solid dosage forms, designed for peroral application.

This work has been directed to the determination of the optimal dosage form and the comparison of production method and copolymer composition with respect to their retarding ability of liberation processes.

Pentoxifylline was selected as the model drug whose significance in the therapy of congestion disturbances has been steadily increasing. Its intervention with the blood rheological properties results in elimination of such disturbances, also in cases where the blood vessels already show advanced sclerosis, disabling the vasodilating effects of other vasodilatants. Any unwanted effects which could occur during therapy are limited to minimum if pentoxifylline is applied in the dosage form with controlled release[8].

EXPERIMENTAL

Materials

Pentoxifylline (manufacturer: Slovakofarma n.p., Hlohovec)
Polymers tested: Ethanolic solutions (R1, R2, R3) and aqueous dispersions (E35, E36, E37) of the 2-hydroxyethyl methacrylate-butylacrylate (2-HEMA-BuA) copolymer containing the monomers in the following ratios: 1:9; 2:8; 3:7 (manufacturer: Czechoslovak Academy of Sciences, Institute of Macromolecular Chemistry, Prague, ČSSR).

Preparation of pellets

Pellets were prepared from pentoxifylline and aqueous solution of gelatine using a pelletizer (laboratory fluid-mechanical instrument Mikropelet M 150)[9].

Preparation of coated pellets

Pellets having a mean diameter of 0.375 mm were coated with the polymers as shown above in a granulating pan; the volume of polymeric solution or dispersion used for coating was such that the coating weight would represent 22 % by weight of the coated pellets[10-12].

Preparation of tablets

Tablets containing 300 mg of the drug were prepared from the coated pellets by direct compression, using 50 MPa compaction pressure[5,12].

In vitro dissolution studies

Liberation of pentoxifylline under in vitro conditions from the dosage forms prepared was determined by the dissolution test in accordance with the 4th edition of the Czechoslovak Pharmacopoeia (rotating basket method, dissolution bakers containing 900 ml distilled water at 37 ± 0,5 °C). Dissolution fluid was stirred at 50 RPM. Dissolution aliquots were analysed spectrophotometrically at 274 nm after filtration. Absorbance followed Beer's law over the range of concentrations encountered[13,14].

Mathematical interpretation of experimental data

The dependence of the percentage of liberated drug upon time is shown

a) in diagrams No. 1 through 6 by the Weibull functions parameters[15,16]

$$f(t) = 1 - \exp\left[-\left(\frac{t}{\tau}\right)^{\beta}\right] \qquad (1)$$

where τ - time necessary for liberation of 63.2 % of the active ingredient present in the dosage form at the beginning of the liberation process into the dissolution medium; β - shape factor; MLT_w is the mean liberation time of the active ingredient from the dosage form used, calculated from the Weibull function[17,18]:

$$MLT_w = \frac{ABC}{M_0} \qquad (2)$$

where ABC is the area between the Weibull function curve and its asymptote; M_0 is the limit value of the Weibull function representing the total amount of drug liberated into the dissolution medium;

b) in diagrams No. 7 - 8 by the Higuchi equation [19,20]:

$$f(t) = k_H \sqrt{t} \qquad (3)$$

where k_H is a liberation rate constant.

Study of the dosage form microstructures

The surface and internal microstructure of coated pellets and compacts has been studied using evaluated microscopic pictures obtained with a JSM-35 C scanning electron microscope (JEOL,Tokyo, Japan) in the emission of secondary electrons at an accelerating voltage of 25 kV and a magnification of 1000x.

RESULTS AND DISCUSSION

Liberation kinetics

When parametrizing the time behaviour of drug liberation from the dosage form, the functional parameters or curve parameters, the so-called moments[21] may be used, based upon experimental data.

From the mathematic models applied in the description of pentoxifylline liberation from prepared dosage forms, the highest values of correlation between experimental and calculated data were found with the Weibull function and Higuchi's equation. The values of their parameters are shown in Tables 1 through 3.

The mean liberation time (MLT_w) was calculated from the Weibull function's regression data using the statistical moment method[22-23]. Application of statistical moments in the pharmacokinetics has been simultaneously described by Yamaoka et al., and Cutler[22,23]. Riegelman and Collier have used the statistical moment theory to determine the in vivo mean dissolution time [24].

Tanigawara et al., and Brockmeier et al. have used this new method to determine the in vitro mean dissolution time, thus introducing a suitable parameter applicable in

Table 1

PARAMETERS OF THE WEIBULL FUNCTION, DESCRIBING THE PROCESS OF PENTOXIFYLLINE LIBERATION FROM COATED PELLETS

Polymer	τ (min)	ß	MLT_w (min)	s (%)	i_k
R1	0.77	0.27	12.22	2.32	0.944
R2	0.87	0.24	27.26	4.23	0.875
R3	4.56	0.60	7.04	3.93	0.961
E35	14.77	1.17	14.00	1.28	0.999
E36	46.92	1.29	43.41	3.02	0.997
E37	7.42	0.62	10.75	1.02	0.998

Table 2

PARAMETERS OF THE WEIBULL FUNCTION, DESCRIBING THE PROCESS OF PENTOXIFYLLINE LIBERATION FROM COMPACTS

Polymer	τ (min)	ß	MLT_w (min)	s (%)	i_k
R1	49.13	1.13	47.01	3.11	0.993
R2	48.80	1.29	45.09	2.55	0.996
R3	73.14	1.12	70.10	4.54	0.988
E35	215.39	0.91	225.55	1.45	0.998
E36	307.81	0.79	351.53	0.88	0.999
E37	148.85	0.74	178.80	0.91	0.999

Table 3

PARAMETERS OF HIGUCHI'S EQUATION DESCRIBING THE PROCESS OF PENTOXIFYLLINE LIBERATION FROM COMPACTS

Polymer	k_H $\%.min^{-1/2}$	s (%)	i_k
R1	8.26	-	0.500
R2	8.82	7.01	0.701
R3	7.40	5.61	0.892
E35	4.09	2.33	0.959
E36	3.51	1.17	0.989
E37	4.45	-	0.500

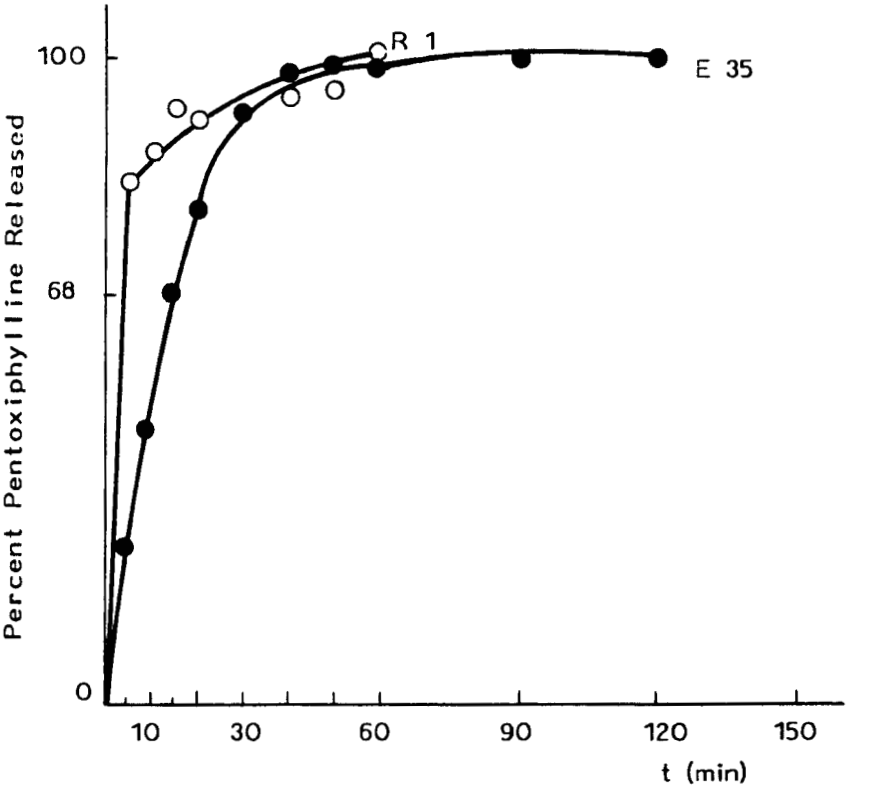

FIGURE 1

Liberation of pentoxifylline from coated pellets (according to Weibull)

Key: o Polymer R1

● Polymer E35

correlation studies of both the in vitro and in vivo type [17,18,25-28]. Comparing the values of the parameters τ, MLT_w and β as shown in Tables 1-2 it can be seen that the following rule is applicable:

$\beta = 1$	$\tau \approx MLT_w$	the liberation proceeds by first-order kinetics
$\beta > 1$	$\tau > MLT_w$	
$\beta < 1$	$\tau < MLT_w$	

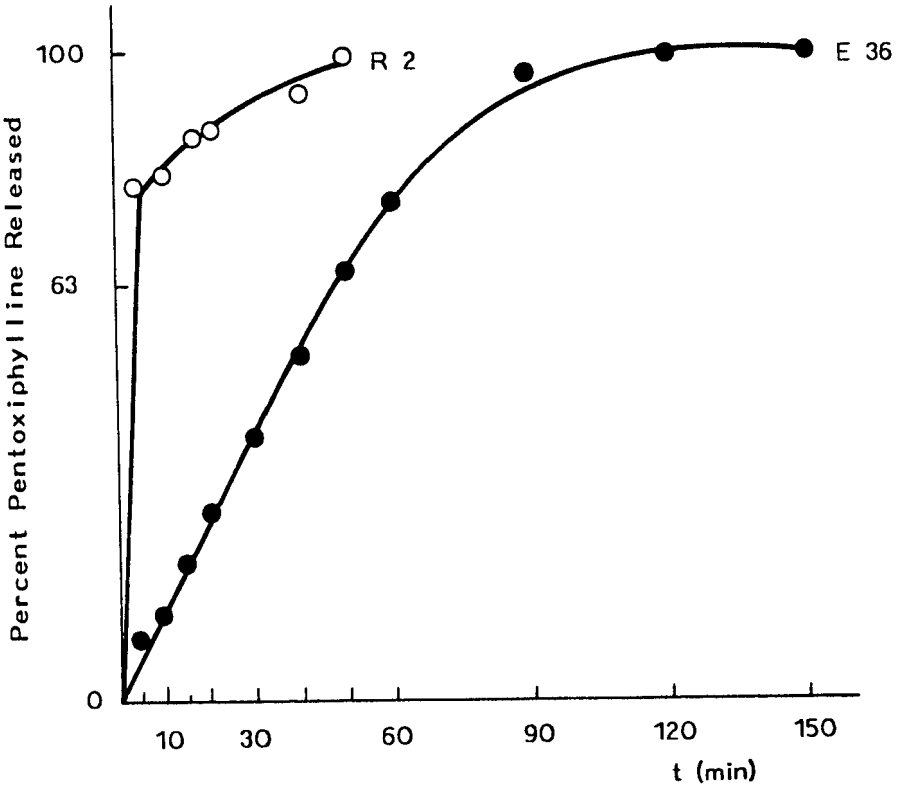

FIGURE 2

Liberation of pentoxifylline from coated pellets (according to Weibull)

Key: o Polymer R2

● Polymer E36

When evaluating the process of liberation, the MLT parameter can reliably replace the functional parameters, particularly if the liberation processes cannot be described by a known mathematical function.

The Higuchi equation describes the process of liberation from matrix systems[29]. Table 3 shows the values of the rate

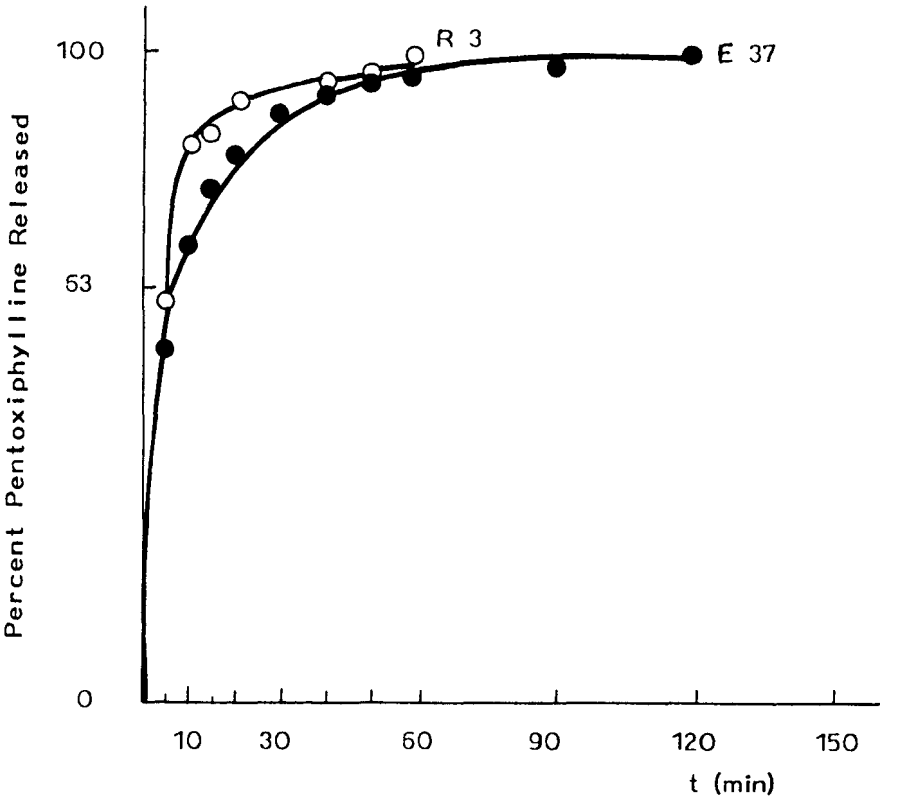

FIGURE 3

Liberation of pentoxifylline from coated pellets (according to Weibull)

Key: o Polymer R3

● Polymer E37

constant in Higuchi's equation for the liberation of pentoxifylline from compacts with matrix-type structures. However, the correlation of the experimental and regression data is lower here as compared to the Weibull function.

The time dependence of pentoxifylline liberation from coated pellets and compacts according to Weibull is shown in Fig. 1 through 6. The influence of the polymerization

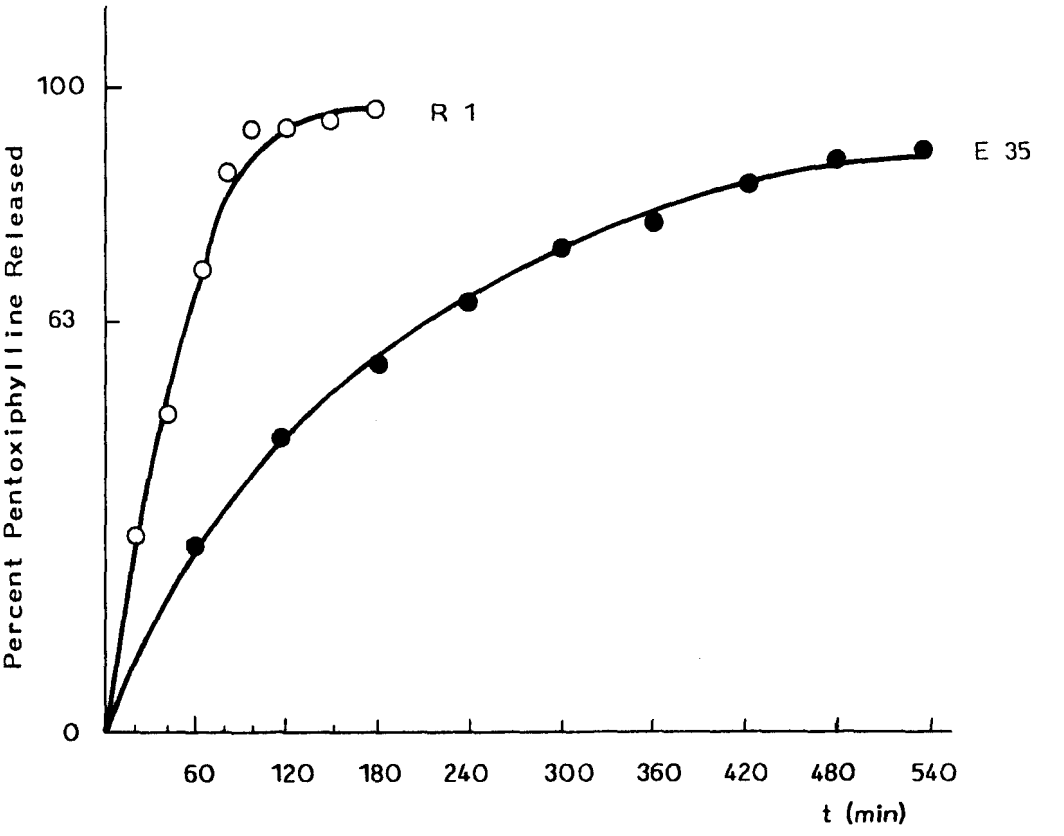

FIGURE 4

Liberation of pentoxifylline from tablets (according to Weibull)

Key: o Polymer R1

● Polymer E35

reaction used (solution or or radical emulsion polymerization) is obvious from these figures, as is the effect of the polymer type formed (solution or latex) upon the liberation retardation. The latex-type polymers are more favourable with respect to the requirement of liberation retardation.

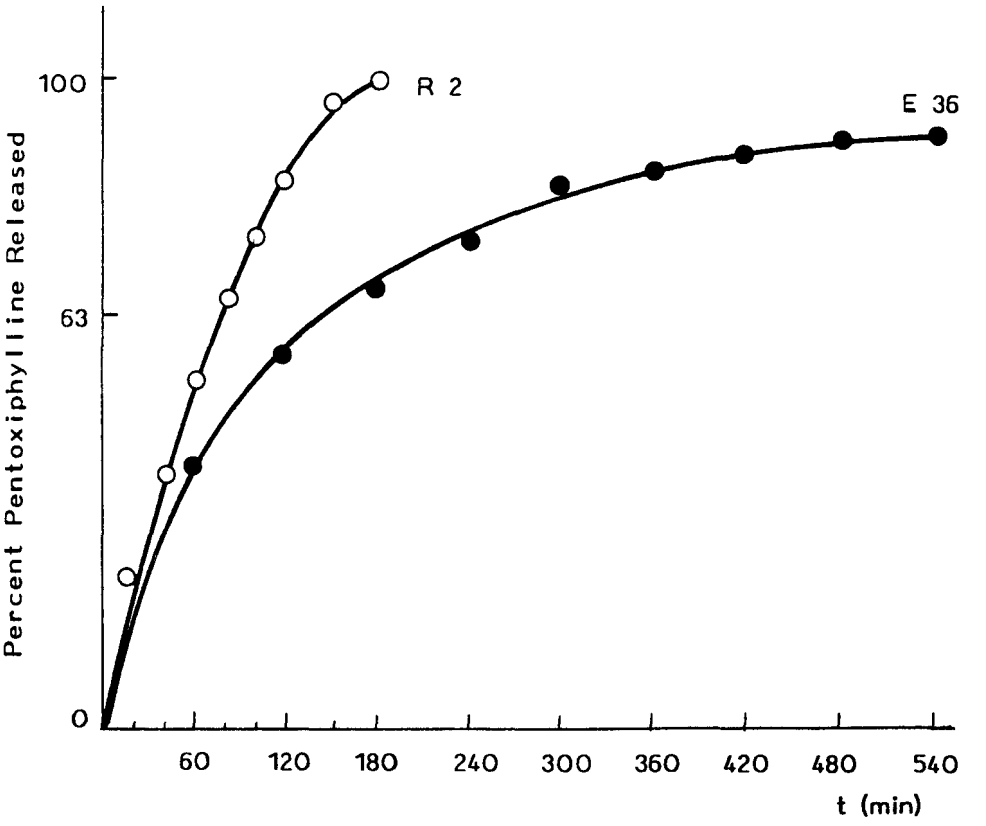

FIGURE 5

Liberation of pentoxifylline from tablets (according to Weibull)

Key: o Polymer R2

● Polymer E36

The pressing (compacting) of coated pellets into compacts is an important technological step resulting in a drug liberation slowdown by an approximate factor of 3 to 4, depending on the polymer type used.

The time dependence of pentoxifylline liberation from the compacts according to Higuchi is shown in Figs. 7-8 where the

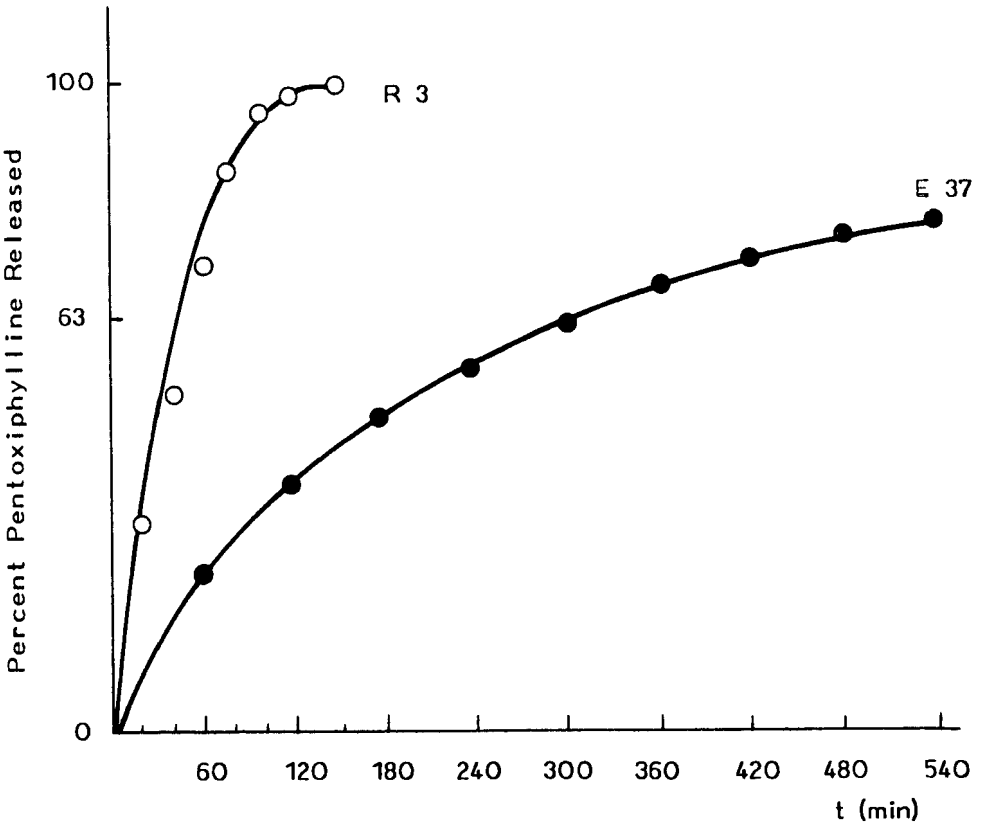

FIGURE 6

Liberation of pentoxifylline from tablets (according to Weibull)

Key: o Polymer R3

● Polymer E37

influence of the relative presence of monomers (2-HEMA, BuA) upon liberation can be compared. Slowest liberation was found in compacts prepared by compacting of pellets coated with R3 and E36 copolymers.

The mechanism of liberation

The scanning electron micropscopy (SEM) is an efficient tool when evaluating the dosage form morphology and thus the

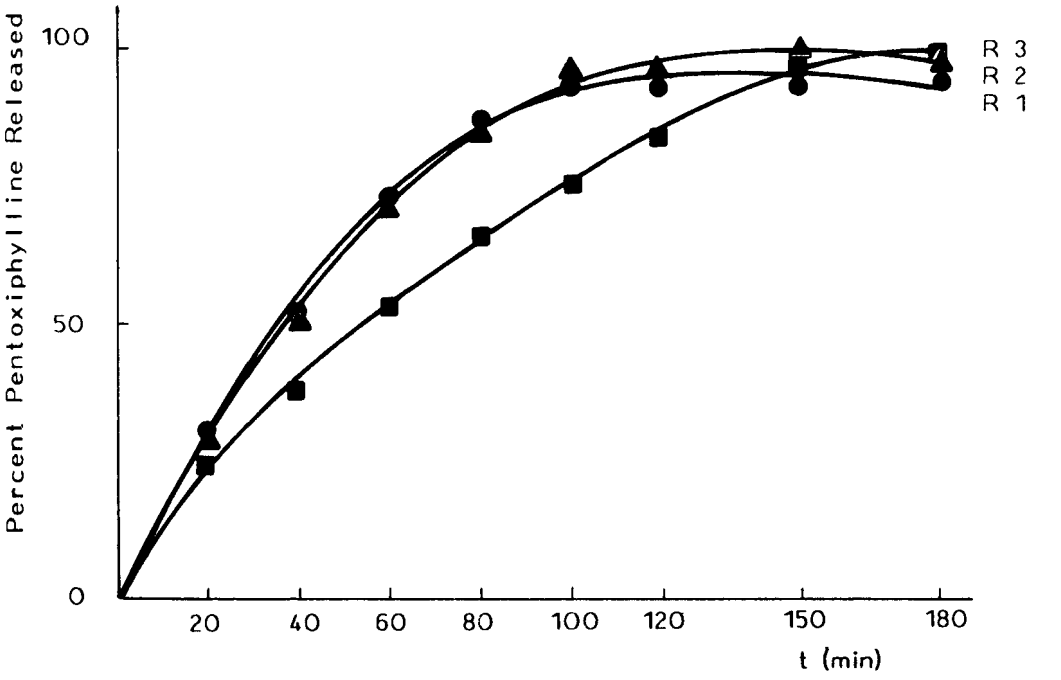

FIGURE 7

Liberation of pentoxifylline from tablets (according to Higuchi)

Key: ● Polymer R1
▲ Polymer R2
■ Polymer R3

drug liberation mechanism. Several authors have used this method as one of the important ones for qualitative evaluations of the prepared dosage forms of pentoxifylline[30-32].

Figs. 9 and 10 show SEM pictures of pellet su rfaces and cross-sections, prepared by coating with a solution polymer and a latex. Latexes used as coating material resulted in a higher quality of films with respect to homogenity and poro-

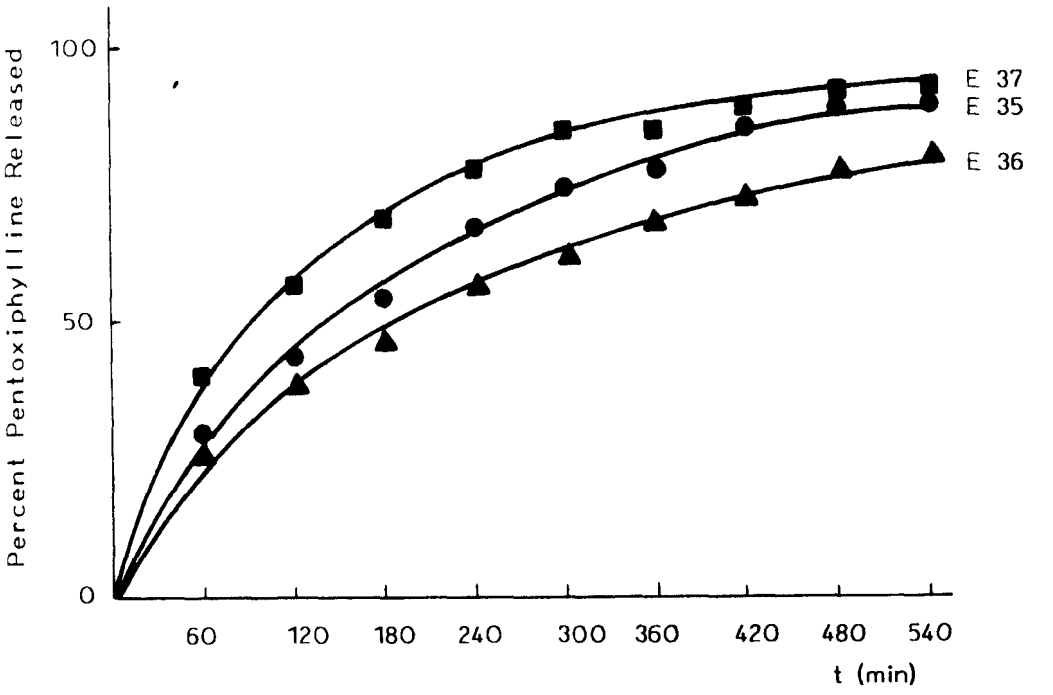

FIGURE 8

Liberation of pentoxifylline from tablets (according to Higuchi)

Key: ● Polymer E35
▲ Polymer E36
■ Polymer E37

sity of the coating. In this coating type the solvent showed less penetration into the pellet core as in the case of solution polymer coating; hence the boundary between coating and core was more distinctive.

The improved film-forming properties of latexes is a result of a different film-forming mechanism as compared with solution polymers. In latexes, ie. aqueous dispersions, coa-

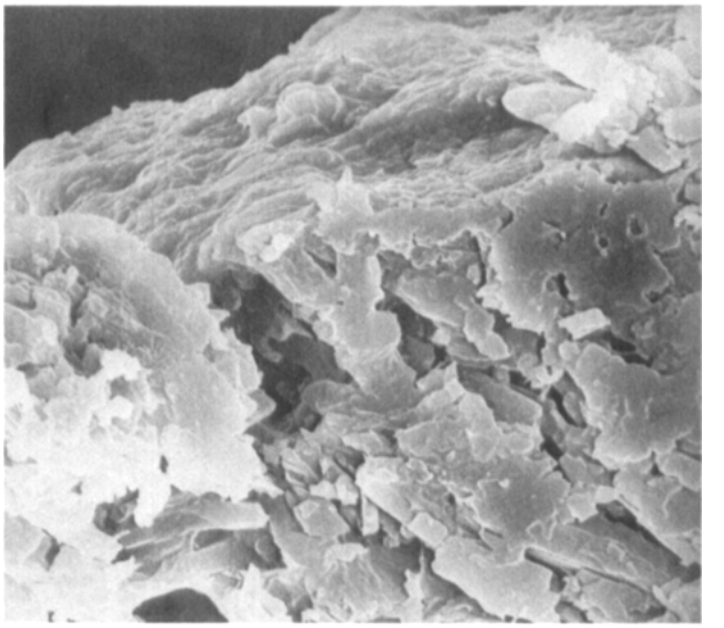

FIGURE 9

Surface and cross-section of a pellet containing solution polymer R3

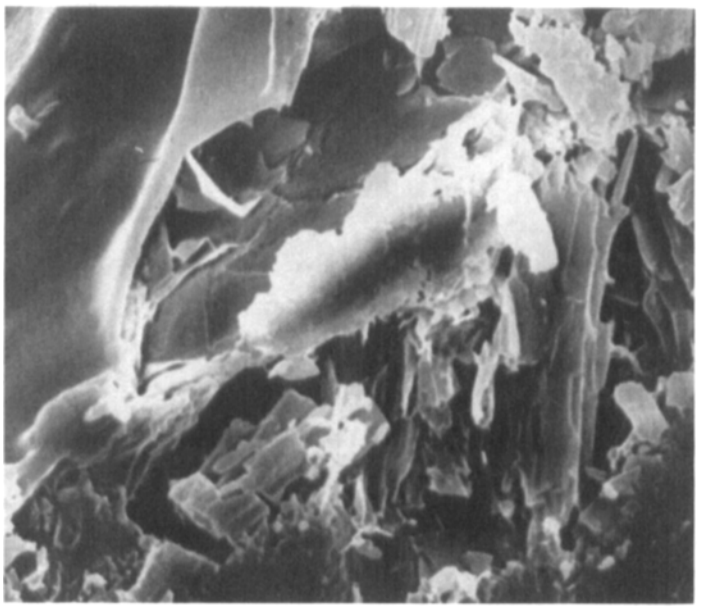

FIGURE 10

Surface and cross-section of a pellet containing latex polymer E37

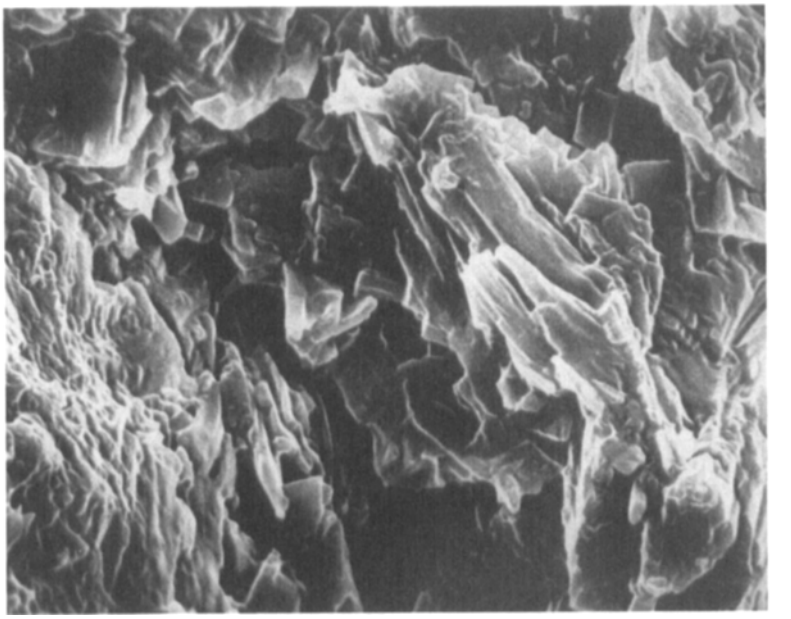

FIGURE 11
Cross-section of a compact containing solution polymer R2 before liberation of active drug component

lescence occurs in the latex particles in the course of water evaporation, which are consequently distorted and pasted together due to the strong capillary forces, resulting in the formation of a continuous compact film[33].

The different film morphology observed in pellets coated with latexes and solution polymers is in accordance with the differences found in the liberation profiles.

Figs. 11 through 14 show SEM photographs of compact surfaces and cross-sections both before and after liberation of the active drug substance. By compacting of coated pellets into the form of compacts, a matrix structure has been formed showing a large amount of voids and small channels. During dissolution, water penetrates through the channel system into

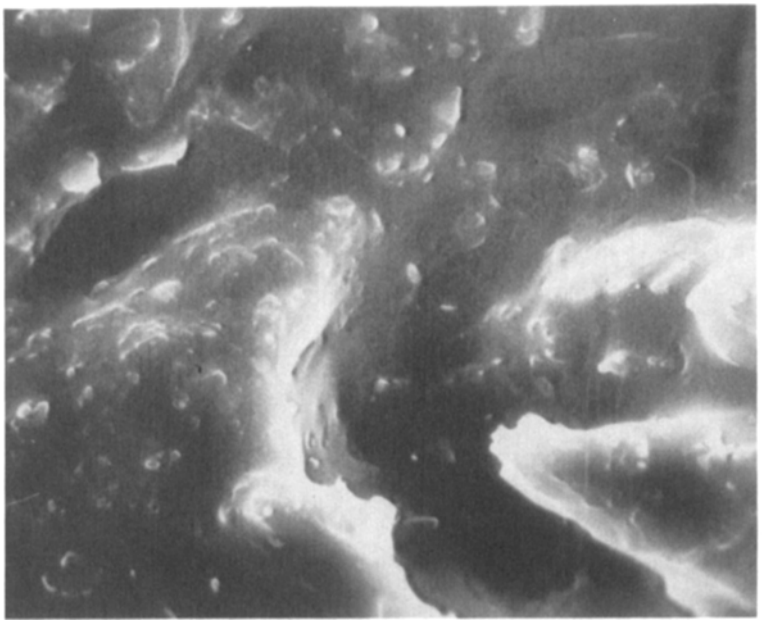

FIGURE 12
Cross-section of compact containing solution polymer R2 after liberation of the active drug component

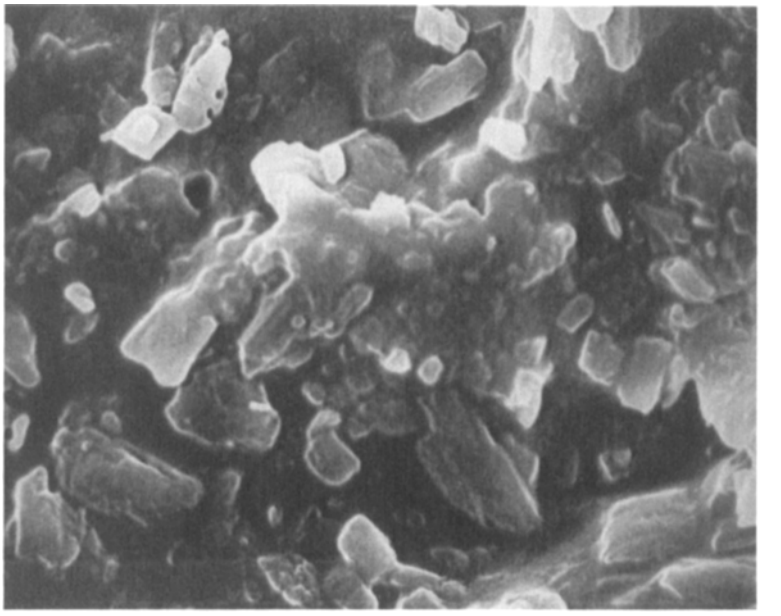

FIGURE 13
Surface of the compact containing latex polymer E35 before the drug liberation

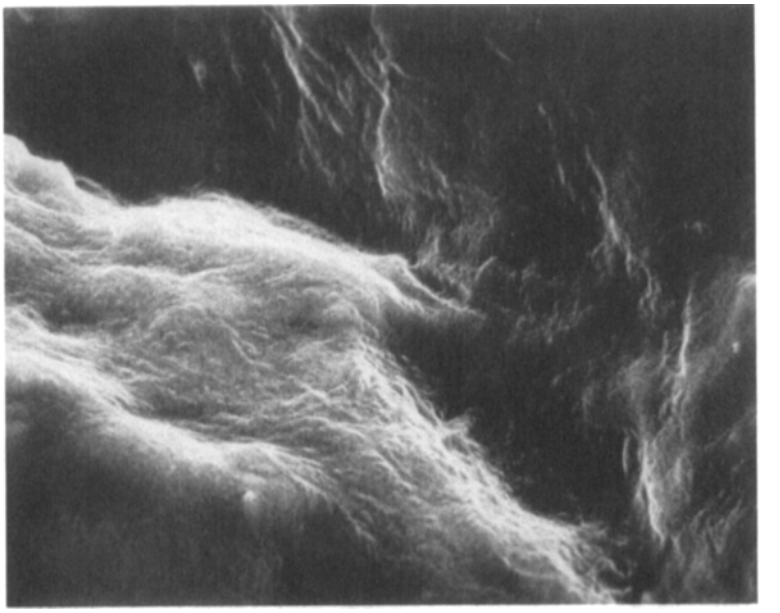

FIGURE 14
Surface of the compact containing latex polymer E35 after the drug liberation

the core of the compact, dissolving the drug substance gradually which diffuses into surrounding medium. The (HEMA) copolymer hydrophilic component undergoes hydration resulting in swelling of the polymer and the formation of a gel barrier; the drug permeates through this barrier at a lower rate than through water-filled voids and channels. If the HEMA contents of the copolymer exceeds a certain limit value (30 % for the latexes tested; the limit is higher for solution polymers), the intense swelling results in a disruption of the matrix structure and in the formation of cracks, thus accelerating the liberation process.

The drug liberation mechanism from acrylate matrix substances has been intensively studied by other authors as well[34,35].

CONCLUSION

Retardation of pentoxifylline liberation from the dosage forms as prepared was influenced by two mechanisms: by the formation of tablets from coated pellets, and by the application of the suitable type of polymer.

The retarding effect of dispersion-type polymers was higher as that of solution-type ones.

In both types, ie. solution (3:7), and particularly the dispersion polymers, the 2-HEMA-BuA ratio 2:8 has been shown as a suitable one from the viewpoint of retardation.

From parameters used for evaluation of the retarding ability of polymers used, the MLT_w value can be emphasized which, contrary to the τ value, is also depending upon the Weibull curve shape. Further advantage of the MLT_w value is its applicability for determinations of the measure of correlation of results obtained with in vivo liberation results.

The Higuchi equation was shown as a suitable means for description of liberation of pentoxifylline from tablets having a matrix-like structure, with the active ingredient probably being liberated by diffusion through matrix voids, even if the possibility of diffusion through the mat rix skeleton showing a high degree of swelling in aqueous medium cannnot be excluded.

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