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DRUG RELEASE FROM MATRICES MADE OF POLYMERS WITH REACTING SITES

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SUMMARY

The release of drugs which may interact with the polymer matrix was studied. Salicylic acid and *p*-amino salicylic acid were chosen to avoid differences in diffusion coefficients. Solid dispersions of each of the two drugs were made with each of methacrylate copolymers, and compressed into tablets. Dissolution rate of a planar surface of these tablets showed a binding between the cationic methacrylate copolymer with each of two drugs, while the anionic copolymer interacts only with *p*-amino salicylic acid.

INTRODUCTION

Several workers (Schwartz et al., 1968) have reported the results of investigations regarding the factors influencing drug release from inert insoluble matrices. Higuchi (1967) claimed that the selection of the carrier has an ultimate influence on the dissolution characteristics of the dispersed drug. If the rate determining process is diffusion through the matrix, then the drug release can be described by Higuchi equation:

$$Q = \sqrt{\frac{DE}{\tau}(2A - EC_s)\,t}$$

where Q is the amount of the drug released per unit area of the disk exposed to the solvent, D is the diffusion coefficient of the drug in the solvent, E is the porosity of the matrix, τ is the tortuosity of the matrix, c_s is the solubility of the drug in the solvent, and t is time.

Theoretical considerations (Desai et al., 1966a) have shown that the release depen-

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dence remains linear with respect to $\sqrt{t}$ if reversible drug partitioning should occur, and a modified equation may be derived:

$$Q = \frac{DC_s}{\tau} [2A - C_s(E + K - KE)]^{1/2}$$

where

$$K = \frac{\text{drug in matrix phase}}{\text{drug in solvent}} \quad \text{at equilibrium}$$

The equation assumes equilibrium binding and takes into account the same factors included in first equation.

From the equation, the product of K and Ca (KCs) seemed to suggest that it is not an absolute factor, but that it is the partition coefficient in relation to solubility to be considered.

It was reviewed (Chien and Lambert, 1974) that, when high solubility was maintained the drug release pattern followed a $Q-t^{1/2}$ relationship (matrix controlled). Under this process the drug release profile was independent of the variation of the partition coefficient magnitude and insensitive to the change in solubility parameters. As the solubility in the elution medium was decreased, the drug release process shifted from matrix-controlled to partition-controlled and a Q–t (zero order) relationship was observed. The drug release profile was then a function of the partition coefficient of drug from the polymer matrix to the elution medium. A transition phase was also seen between the two processes.

It was also claimed (Roseman and Higuchi, 1970) that under certain conditions, the rate of diffusion from the surface of the matrix to the surrounding bulk solution makes a significant contribution to the total diffusional process. It was suggested (Haleblian et al., 1971) that possibly the rate of the solute transfer across the matrix–solution interface may control the release. Both reports, therefore, pointed out the possible existence of a partition-controlled model of drug release flux.

$$Q/t \propto k, \text{ and } k = c_s/cp$$

where Q/t is the drug released in time (t), k is the partition coefficient, c_s is the solubility of the drug in the solvent and c_p is its solubility in the polymer. The authors proposed that a constant release rate would be observed if the release of drug is controlled by either the rate of drug dissolution into the matrix, or the rate of solute transfer across the matrix–solution interface. With more solubility, the rate of partitioning of drug species across the matrix–solution interface may be considered as rate determining.

Critical examinations of physical models based upon the consideration of simultaneous equilibria and transport of all species in the system were made to approach to the understanding of release of interacting drug mixture (Singh et al., 1967), and of non-interacting drug mixture (Sjuib et al., 1972a and b) from inert matrices. Also a model (Sjuib et al., 1972b) was proposed to describe the release of a mixture of sulfadiazine and sulfapyridine from a polyethylene matrix into phosphate buffer as a reacting medium.

The present work deals with another situation in which the drug interacts with the polymer material of the matrix. Cationic and anionic methacrylate copolymers were chosen because they have reacting groups, and also, they are of a plastic nature forming perfect matrices. Salicylic acid and *p*-amino salicylic acid were chosen as the model drugs, to avoid differences in diffusion coefficients. This was based on the statement (Desai et al., 1966a) that the slope of the curve in the matrix-controlled mechanism would be inversely proportional to $\sqrt[6]{\text{mol. wt.}}$ and water was chosen as the eluting medium to avoid interactions with either the drug or polymer with different ions, and restrict the factors affecting the dissolution regimen to partition, diffusion and/or transfer phenomena.

MATERIALS AND METHODS

Materials

Cationic [1] and anionic [2] methacrylate copolymers, and analytical grades of salicylic acid and *p*-amino salicylic acid.

Preparation of solid dispersions

Alcoholic solutions of salicylic acid, pure amino-salicylic acid and each of the two copolymers were mixed, the alcohol was evaporated on a boiling water bath with continuous trituration until complete dryness. The mass was pulverized in a mortar to pass through sieve No. 30 [3], and kept in a desiccator until used.

Dissolution studies

The solid dispersions were made into tablets using a single stroke compression machine [4] to produce tablets weighing 220 mg ± 5%, 12 mm in diameter and of an average hardness of 5–6 kg using a Erweka hardness tester.

Tablets were fixed into melted beeswax on the top of test tubes, each of 15 mm in diameter. Each tablet was placed at a constant level 5 cm below the surface of 400 ml distilled water placed into 600 ml squat-form beaker, which was stirred at a constant speed of 100 rpm, using a constant speed Gallenkamp propeller, at 25 ± 1°C. At each time interval an aliquot of 1 ml was withdrawn and assayed spectrophotometrically [5] at 297 nm for salicylic acid and at 266 nm for *p*-amino salicylic acid.

Interaction of the salicylic acid and p-amino salicylic acid with polymers

A 400 ml solution containing 921.60 mg of salicylic acid and 707.04 mg of *p*-amino salicylic acid in distilled water was stirred with 300 mg of each polymer, using the previously mentioned stirrer at 100 rpm. The temperature of the solution was kept at 25 ± 2°C. At subsequent time intervals, an aliquot of the solution was withdrawn and analyzed spectrophotometrically.

The results are shown in Tables 1 and 2 and illustrated in Figs. 1–5.

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[1] Eudragit E granulate, Röhm Pharma GmbH, Darmstadt, G.F.R.
[2] Eudragit L_{90} granulate, Röhm Pharma GmbH, Darmstadt, G.F.R.
[3] B.P. 1969.
[4] Diaf. Copenhavn, Denmark.
[5] Unicam spectrophotometer sp. 500.

RESULTS AND DISCUSSION

From the aforementioned tables and figures it can be seen that the two polymers behave differently towards the two drugs. The cationic type interacted with both of salicylic acid and *p*-aminosalicylic acid with more or less the same pattern. Initially there is a sharp decline in the drug, followed by slight increments of the drug taken by the polymer.

With the anionic type, salicylic acid concentration was reduced very slightly, possibly by adsorption, while with *p*-amino salicylic acid the interaction was more pronounced indicating a possible reaction between the amino group of the drug and the anionic group of the polymer.

From Fig. 1, it was calculated that 300 mg of the cationic copolymer was found to interact with 350 mg of the salicylic acid. This means theoretically that with a ratio up to 54% of the drug in the matrix no free drug occurs $[(350 \times 100)/(300 + 350)]$, and the curves up to this ratio would show a lower curvature indicating (Desai et al., 1966b) bind-in or interaction of the drug and the polymer. Experimentally this was found to be the case. Matrix containing 10% of the drug does not show any release within the time of the experiment extending to 3 h. With a 20% ratio, the release of the drug starts after a short time-lag and proceeds with a slope of 0.036 mg/min$^{-1/2}$. With 40% and 50% ratios, the initial release is very slow increasing gradually with downward curvature confirming the strong binding between the acid drug and the cationic polymer. After the 45-min interval, the curve smooths upward to a linear function with slopes of 0.141 and 0.286 mg/min$^{-1/2}$ with 40% and 50% matrices, respectively. With 60% the picture changes and the release is initially high showing little excess of free drug. Afterwards, the release rate decreases and smoothly straightens to a linear curve very near in slope to that of 50% and with a matrix made of 80% drug, the initial release is higher decreasing gradually to a straight line with relatively higher slope.

On the same basis, 46.9 mg of *p*-amino salicylic acid was calculated to interact with 53.1 mg of the cationic copolymer and interestingly, the experimental results again corresponded to the theoretical calculations. The same types of curves described with salicylic

TABLE 1

DATA FOR THE SLOPE VALUES OF THE LINEAR FUNCTION FOR THE RELEASE OF SALICYLIC ACID AND *p*-AMINO SALICYLIC ACID FROM THEIR MATRICES AS A FUNCTION OF TIME

Drug	Methacrylate copolymer type	Slope of the curves of matrices made of the following drug percentages:					
		10	20	40	50	60	80
Salicyclic acid	cationic	–	0.036	0.141	0.286	0.270	0.800
	anionic	0.130	0.130	0.417	0.815	1.680	2.450
Para-amino salicylic acid	cationic	0.046	0.048	0.176	0.172	0.304	0.308
	anionic	0.128	0.180	0.264	0.288	0.292	0.616

TABLE 2

DATA FOR THE SLOPE/$\sqrt{}$CONC. VALUES FOR THE RELEASE OF SALICYLIC ACID AND *p*-AMINO SALICYLIC ACID FROM THEIR MATRICES

Drug	Methacrylate copolymer type	Ratio of slope/$\sqrt{}$conc. of the release of drug from matrices containing the following percentages:					
		10	20	40	50	60	80
Salicyclic acid	cationic	–	0.0080	0.0223	0.0405	0.0349	0.0895
	anionic	0.0411	0.0290	0.0660	0.1153	0.2130	0.2739
p-amino salicylic acid	cationic	0.0146	0.0107	0.0278	0.0243	0.0393	0.0344
	anionic	0.0405	0.0403	0.0418	0.0407	0.0377	0.0689

acid are shown, in this case the pronounced increase in the slope value occurs with the curve describing the release of *p*-amino salicylic acid from a matrix containing 60% instead of that for an 80% matrix shown with salicylic acid.

The anionic type and *p*-amino salicylic acid showed an interaction in the ratio of 68.3 mg of the drug to 300 mg of the polymer, corresponding to about 19% drug content. Release profile shows free drug with matrices containing more than 20%, proceeding

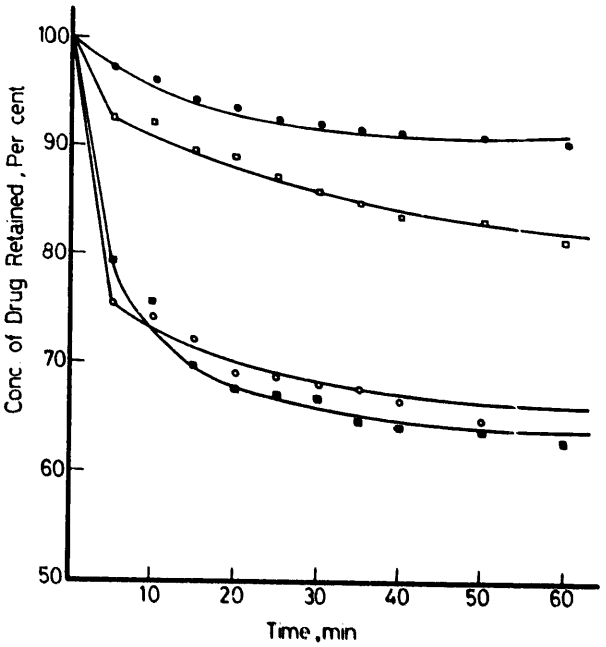

Fig. 1. Retained concentration of salicylic acid and *p*-amino salicylic acid in their aqueous solutions after the addition of 300 mg of each of the cationic and anionic methacrylate copolymer. Salicylic acid with the cationic polymer, ○, and the anionic polymer, ●, and *p*-amino salicylic acid with the cationic polymer, □, and anionic polymer, ■. 100% of salicylic acid concentration is 921.60 mg. 100% of para-amino salicylic acid concentrations is 707.04 mg.

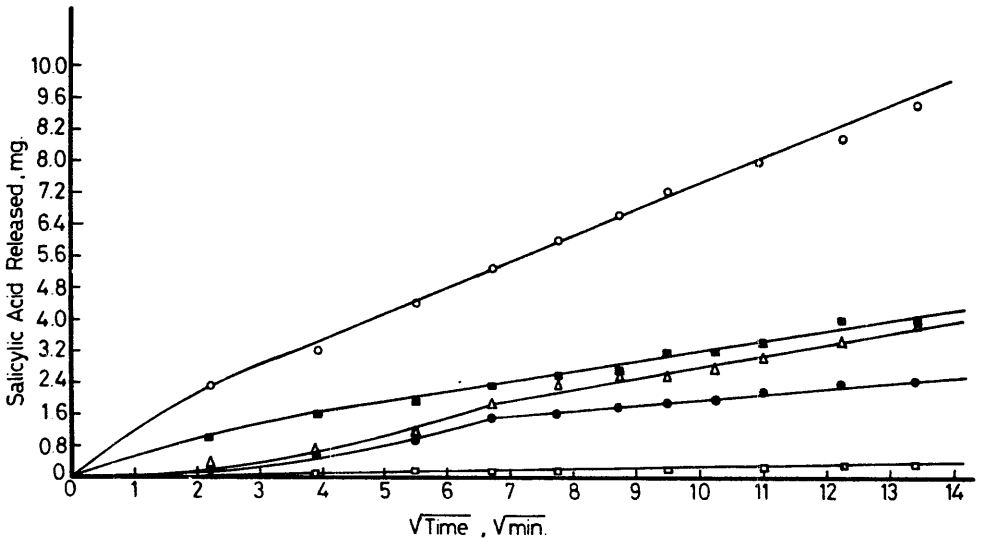

Fig. 2. Release profile of salicylic acid from its tablets made of solid dispersions with the cationic methacrylate copolymer of different ratios: □, 20%; ●, 40%; △, 50%; ■, 60% and ○, 80% of salicylic acid.

afterwards to a line function indicating a diffusion-controlled mechanism. These linear functions show a direct proportionality between the slope and square-root of concentration. This indicates that porosity of the matrix increases by the same factor as concentra-

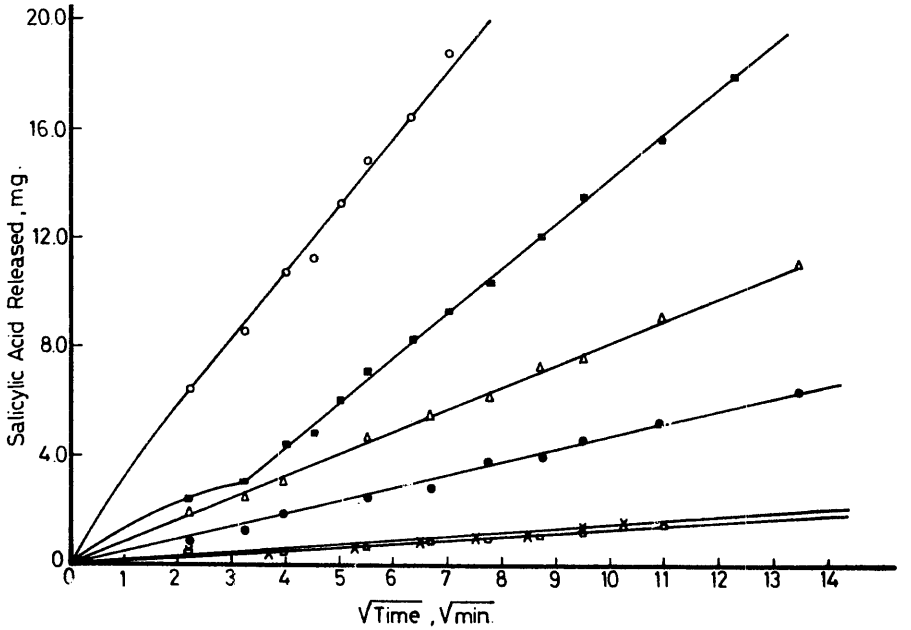

Fig. 3. Release profile of salicylic acid from its tablets made of solid dispersions with the anionic methacrylate copolymer of different ratios: ×, 10%; □, 20%; ●, 40%; △, 50%; ■, 60%; and ○, 80% of salicylic acid.

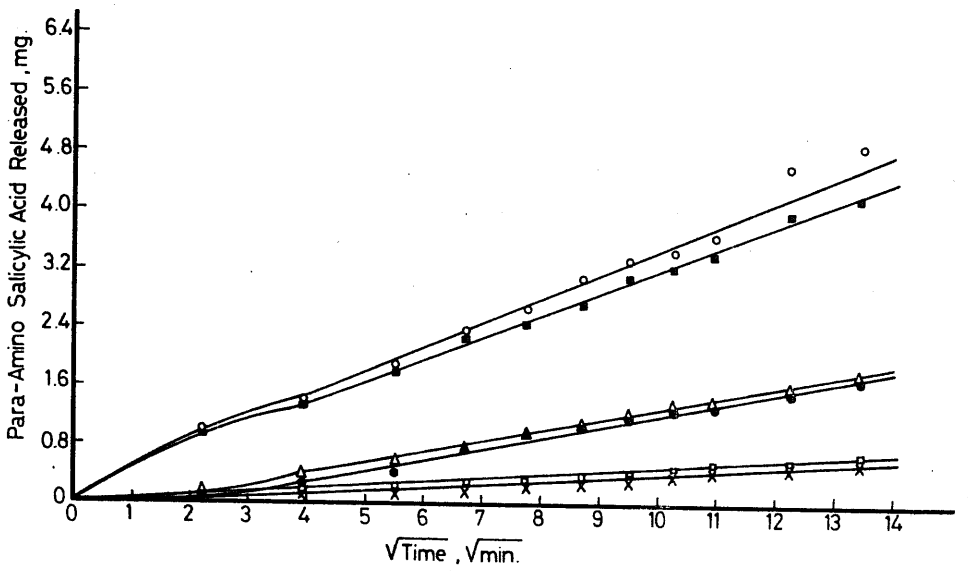

Fig. 4. Release profile of *p*-amino salicylic acid from its tablets made of solid dispersions with the cationic methacrylate copolymer of different ratios. ×, 10%; □, 20%; ●, 40%; △, 50%; ■, 60% and ○, 80% of *p*-amino salicylic acid.

tion, and the porosity is mainly dependent on the voids left after dissolution of drug particles (Desai et al., 1965). Such a relation is not valid in other 3 cases even with matrices made of salicylic acid and the anionic copolymer where there is no possible interaction and the profiles given show a perfect diffusion control up to a 50% ratio.

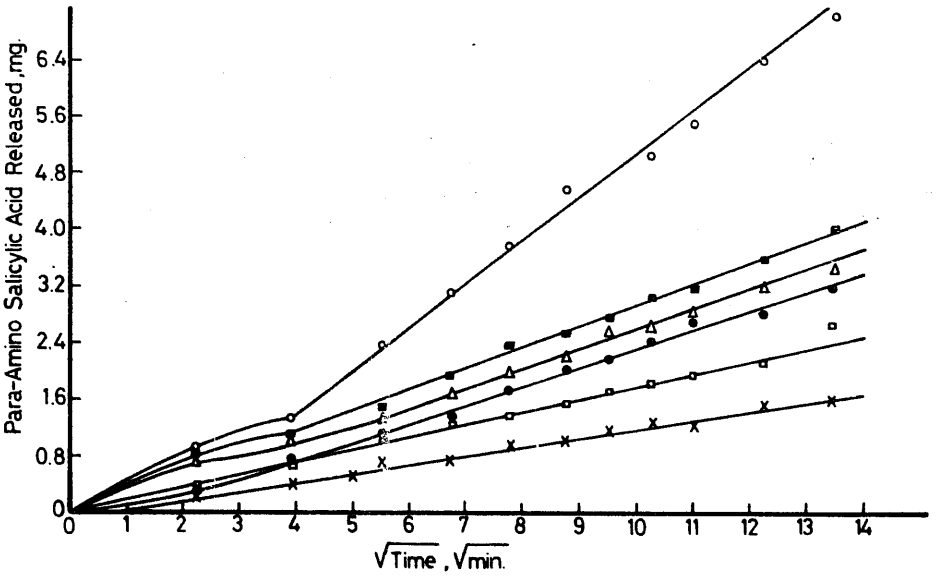

Fig. 5. Release profile of *p*-amino salicylic acid from its tablets made of solid dispersions with the anionic methacrylate copolymer of different ratios. ×, 10%; □, 20%; ●, 40%; △, 50%; ■, 60% and ○, 80% of *p*-amino salicylic acid.

When more drug was included into the matrix the polymer was unable to entrap or encapsulate all the drug particles and initially the release shows a higher rate.

Regarding the effect of solubility on the slope of the curve showing the relation between mg drug released and the square-root of time, the slope must be directly proportional to $\sqrt{C_s}$ where C_s is the saturated solubility of the drug. With matrices of low drug content, the experimental values of salicylic acid with respect to *p*-amino salicylic acid are less than the theoretical values showing a stronger binding between the salicylic acid and the polymer or higher dissociation tendency of *p*-amino salicylic acid complex with the polymer.

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