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STUDIES ON SUSTAINED RELEASE IV: INERT MATRIX TABLETS OF SULFAMETHIZOLE, EMPLOYING POLYVINYL CHLORIDE AND CARBOXYPOLYMETHYLENE*

İlbeyi T. Ağabeyoğlu
Department of Pharmaceutical Technology
Faculty of Pharmacy
University of Ankara

A. Ü. Ecz. Fak.
Tandoğan
Ankara - TURKEY

ABSTRACT

An inert matrix type sulfamethizole sustained release dosage form is attempted, using polyvinyl chloride and carboxypolymethylene. The release obtained with the flow -through cell is lower than the target profile. With the rotating bottle apparatus, higher release rates were obtained, but based upon our previous findings, the latter method is considered not to be very realistic.

Upon the kinetic assessment of dissolution data, zero order, first order and Hixson-Crowell kinetics were found to give similar fits.

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INTRODUCTION

Sulfamethizole is a urinary antiseptic with a short biological half-life. In earlier work, we attempted to prepare a sustained release dosage form with this drug. Thus, polymethylmethacrylate was employed for preparing inert matrix tablets(1). In vitro and in vivo tests were conducted to assess its performance(1,2). In vivo tests done with eight human subjects showed that, although the blood levels were in the ballpark, a faster releasing product would be better. Matrix granule type dosage form was also considered. The results of in vitro dissolution tests showed that, the release profile was different from the target profile and overall release rates were quite high(3).

In this study, polyvinyl chloride and carboxypolymethylene as sustaining polymers were employed for preparing inert matrix tablets.

MATERIALS AND METHODS

The design parameters, the preparation of the tablets, testing, assay, dissolution tests and kinetic evaluation of dissolution data were as described previously(1). No initial dosage was incorporated into the tablets.

Polymers: Two grades of polyvinyl chloride was employed: PVC I was Vestolit S 7054 and PVC II was Vestolit E 7001 (both Chemische Werke, Hüls, FRG). CPM was Carbopol 934P, a pharmaceutical grade carboxypolymethylene (B.F. Goodrich, U.S.A.).

The composition of different formulations are shown in Table 1.

RESULTS

Formulation 36 was prepared with PVC I. In contrast to the others, this was compressed with a 20 mm die. In No. 37, the amount of polymer

TABLE 1. Formulations Used in the Study

Formulation	36	37	38	39	40	41
Sulfamethizole	450	450	450	444	443	443
PVC I	1350	150	-	-	-	-
PVC II	-	-	450	-	-	-
CPM	-	-	-	222	150	250
Lactose[a]	-	-	-	-	-	100
PEG 4000[a]	-	-	-	222	150	-
Ca CO_3[a]	-	-	-	-	-	50
Colloidal silica[b]	-	3	5	-	-	-
Mg Stearate[a]	-	6	10	14.5	-	9
PEG 6000[a] -PVP[c] (2:3)	-	-	-	-	30	-
Pressure[d]	-	4	5	1	1	1
Hardness[e]	-	10.6	21.1	26.8	27.5	>28

[a]E. Merck, FRG; [b]Aerosil 200, Degussa, FRG; [c]Kollidon 25, BASF, FRG; [d]tons/cm^2; [e]Strong-Cobb units.

was decreased and lubricants were added. No. 38 was prepared with PVC II.

Formulations 39-41 were prepared with CPM. In No.40, water soluble lubricants PVP-PEG 6000 were used. Since this tablet sticked to the punches, the lubricant was changed back to Mg stearate. Lactose was incorporated into the latter formulation to modify the release.

All these were compressed directly. The CPM formulations gave very good and hard tablets.

The release profiles of these formulations in both dissolution systems are shown in Figs 1 and 2.

The kinetic assessment of the dissolution experiments are given in Tables 2 and 3.

DISCUSSION

The matrix formation in formulations employing PVC, takes place by coalescing of the polymer particles under pressure. In this fashion, PVC I did not produce very hard tablets. The tablet surface could be scratched easily. PVC II however, produced better tablets in this respect. This may be due to lower particle size of this particular polymer.

Lowering the amount of PVC in the formulation increased the amount of drug released. Although the release profiles in the rotating bottle apparatus are in the ballpark, they are much lower in the flow-through cell. Based on previous data, we believe the latter dissolution system gives a more realistic picture(2). The rotating bottle can hardly maintain sink conditions and the agitation is somewhat unrealistic.

Zero order, first order and Hixson-Crowell kinetics seem to describe the data about equally well. Higuchi equtions for planar and spherical matrix release did not give very good fits (4).

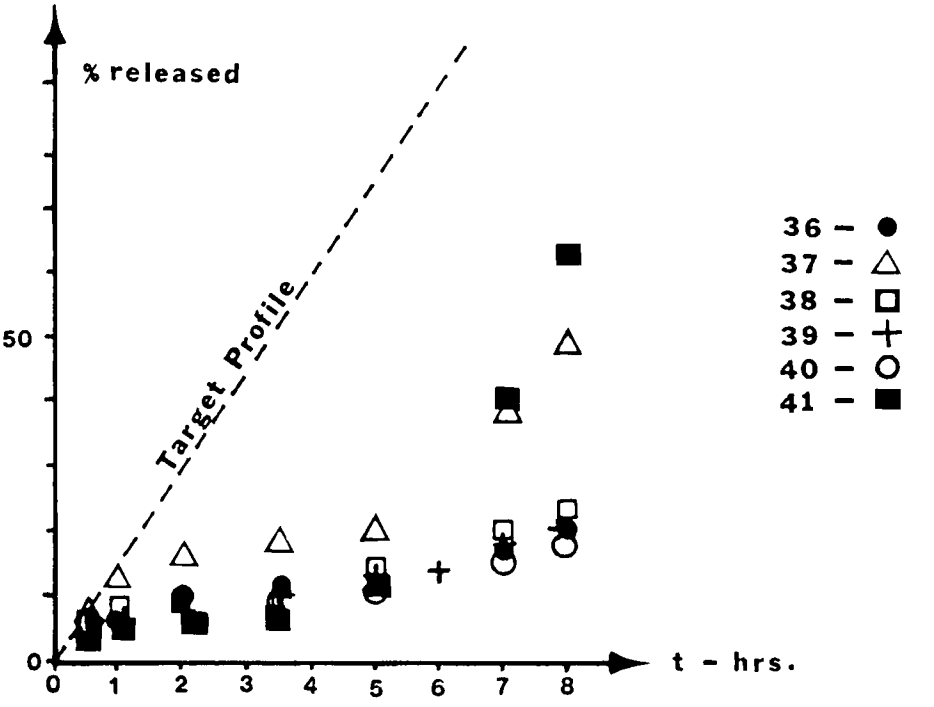

FIGURE 1. Release Profiles in Flow-Through Cell Dissolution System.

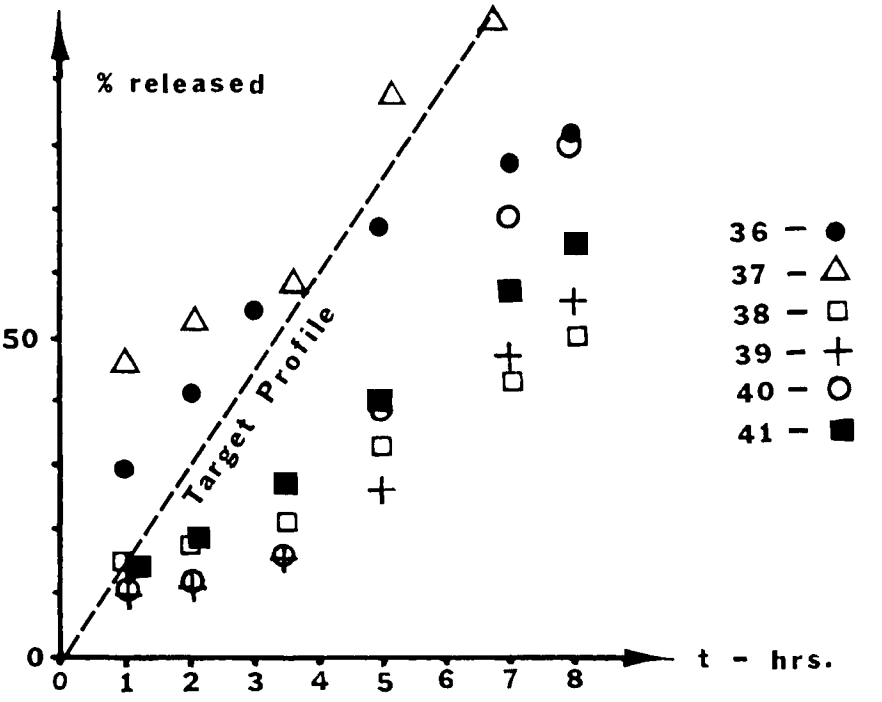

FIGURE 2. Release Profiles in Rotating Bottle Dissolution System.

TABLE 2. Kinetic Assessment of Release Data (Flow-Through Cell)[a]

Formulation No.		36	37	38	39	40	41
First Order	k_r[b]	2.05	6.82	2.49	2.15	1.84	11.1
	r^2[c]	0.959	0.861	0.959	0.930	0.939	0.758
Zero Order	k_r^o[d]	8.0	21.1	9.5	8.1	7.0	31.6
	r^2	0.962	0.893	0.962	0.937	0.940	0.819
Hixson-Crowell	rate[e]	0.830	2.56	1.00	0.864	0.740	4.02
	r^2	0.960	0.872	0.960	0.933	0.939	0.780
$Q \rightarrow \sqrt{t}$	slope	0.360	2.31	0.911	0.740	0.686	2.84
	r^2	0.916	0.811	0.917	0.885	0.904	0.702
Higuchi Eq.	slope[f]	2.74	19.6	3.67	3.06	2.50	3.51
	r^2	0.918	0.781	0.915	0.863	0.905	0.653
Tablet Area	cm^2	10.1	4.05	4.77	4.95	4.66	4.82
Flow Velocity	cm/min	2.0	1.9	1.9	1.6	1.7	1.6
Flow Rate	ml/min	6.2	6.0	6.1	5.0	5.4	4.9
Cell load	mg/cm^2	142	141	142	139	139	140

[a]For detailed description of kinetic models see Ref. (1); [b]$hr^{-1} \times 10^2$; [c]Coeff. of determination; [d]mg/hr; [e]$\times 10^3$; [f]$\times 10^5$.

TABLE 3. Kinetic Assessment of Release Data (Rotating Bottle)[a]

Formulation No.		36	37	38	39	40	41
First Order	k_r	18.9	33.6	7.93	10.8	21.6	13.0
	r^2	0.998	0.780	0.959	0.914	0.900	0.971
Zero Order	k_r^o	31.8	41.9	23.8	37.7	49.3	36.2
	r^2	0.975	0.870	0.972	0.943	0.943	0.993
Hixson-Crowell	rate	5.72	9.14	2.94	4.20	7.21	4.69
	r^2	0.996	0.809	0.964	0.924	0.918	0.981
$Q \rightarrow \sqrt{t}$	Slope	1.59	4.23	2.42	3.75	5.30	3.80
	r^2	0.997	0.804	0.919	0.873	0.878	0.960
Higuchi Eq.	Slope	86.5	156	25.0	33.9	86.2	48.3
	r^2	0.994	0.775	0.922	0.847	0.850	0.926
Tablet Area	cm^2	10.1	4.07	4.79	4.93	4.57	4.77

[a]Nomenclature as in Table 1.

Carboxypolymethylene produces tablets of almost excellent properties. Hardness and friabilities were very good. Formulations 39 and 40 gave similar and low release profiles, while that of 41 was relatively higher. Another problem arose at pH 7 to 7.5 of the dissolution fluids. At this pH the polymer, which is an acid itself, starts to neutralize and forms a gel. This swells considerably and the tablet loses its shape. The resulting release profile is thus quite different from the target profile, which is more apparent in the flow-through cell.

Based on previous in vitro and in vivo experience, it can be said that, the optimum release rates are not achieved with the given formulations. More formulation work needs to be done on these polymers.

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