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STUDIES ON SUSTAINED RELEASE III: MATRIX GRANULES OF SULFAMETHIZOLE

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ABSTRACT

Polymethylmethacrylate and cellulose acetate phtalate has been employed for the preparation of matrix sustained release sulfamethizole granules. The effect of various adjuvants on the release profile is also investigated. It is seen that, this type of sustained release is suitable for high values of release rate in contrast to inert matrix type tablets. The kinetics of release is not zero order, but RRSBW distribution seems to give better fits. Cellulose acetate phtalate warrants further work in such formulations; possibly with the concurrent employment of other polymers.

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INTRODUCTION

Sustained release products are designed to bring the blood level of a drug immediately to therapeutic concentrations by means of an initial dose portion and then sustain this level for a certain predetermined time with the maintenance portion (1). In order to achieve this, the drug release from the dosage form has to be the rate limiting step and the drug has to be released with a predesigned rate. The order of release has theoretically to be zero.

The release kinetics of sustained release products has been studied by various researchers. These have been summarized in previous reports (2-4).

Hopfenberg also derived equations describing the release from spherical and cylindirical matrices and from slabs (5).

With regards to dissolution, there are several different, but well known proposed models (4,5).

RRSBW distribution has also been applied to dissolution data with good results (6-8).

In this study, the release data have been applied to these kinetic equations with the aid of a program written for this purpose (9).

Sulfamethizole has been used in this study as a model drug with a very short biological half-life. The design parameters for a sustained-release product for this drug has been carried out according to Krüger-Thiemer et al. (10) and Robinson et al. (11,12). The resultant target design parameters are as follows (2,3):

Initial dose: 135 mg

Maintenance dose: 450 mg

Zero-order release rate constant: 67.5 mg/hr

First-order release rate constant: 0.15 hr^{-1}

Dosage interval: 8 hrs.

Plasma concentrations: 10-40 μg/ml

These are based on the proposition that two units are to be used for each dosing.

In this study, we have attempted to achieve sustained release by granule matrices. Since we were mainly interested in sustaining the release, we did not prepare any initial dose portion.

MATERIALS

The following materials and equipments were used:

Chemicals: Sulfamethizole (Ayerst, through FAKO İlaçları A.Ş., Turkey), polysorbate 80 (Atlas Europol), polymethylmethacrylate (PMM I and PMM II) (Eudragit RLPM and RSPM, Röhm Pharma), cellulose acetate phtalate (CAP) (Kodak), talc (BDH), dimethicone (Dow Corning).

Apparatus: pH meters (Orion 701, Beckman H4), spectrophotometer (Pye-Unicam SP 8-100), continuous flow through cell, peristaltic pump (both Desaga), sieves (Erweka), microscope with camera attachment (Nikon S-KE), programmmable calculator (TI 58-C), microcomputer with Microsoft BASIC-80 interpreter (Altos ACS 8000-2E).

METHODS

Formulations Prepared: The composition of different formulations employing various polymers and ingredients are shown in Table 1:

TABLE 1. The Formulations Used in the Study[a]

Formulations	47	48	49	50	51	52	52/A	52/B	53	56
Sulfamethi-zole	450	450	450	450	450	450	450	450	450	450
PMM I	25									
PMM II		25	41.2	29.5	32	22.6	55	33.6		
CAP										20.7
Talc				50						
Lactose					200					
Mg Stearate						45	90	90		45
$CaCO_3$									100	
Total Weight	475	475	491.2	529.5	682	521	562.6	595	583.6	515.7
Mean Granule Diam.[b]	0.730	0.703	1.02	0.873	0.841	0.960	0.851	0.840	0.736	0.907
Surface Area[c]	64.8	77.6	80.4	82.1	91.0	81.7	61.8	74.0	60.3	64.7

[a]Amounts are in mg; [b]mn; [c]cm^2/unit dose.

The ingredients were mixed in a mortar in powder form by geometric dilution. The binder polymer solution was added dropwise, until the mass had a consistency of a paste. It was then screened through a no. III sieve (1.75 mm opening) and dried in a blow-through incubator at 40°C. It was rescreened through a no. IV sieve (1 mm opening). Coating was carried out twice in formulations 49 and 52/A and three times in formulation 52/B.

Determination of the Mean Granule Size: Particle size analysis of the granules were carried out by the microscopic method. Single layers of granules were formed in a silicone fluid. Approximately 100 to 120 particle diameters were measured and the mean was taken (13).

Calibration Curves of Sulfamethizole: Series of standart solutions of the drug was prepared in various dissolution mediums of different pH s. The absorbances were read at the λ_{max} values determined previously. The concentrations were plotted versus absorbances and the regression line was calculated with the method of least squares.

Dissolution Rates: The dissolution rate of the drug from the granules prepared was determined by the continuous flow-through cell (column method). Artificial gastric and intestinal fluids of pH 1.2 to 7.5 were employed (USP XX). No enzyme was incorporated in these dissolution mediums, but 0.05 % polysorbate 80 was added to bring the surface tension to about 45-50 dyne/cm, which mimics the in vivo situation. The dissolution tests were carried out for a period of 8 hrs. with the following scheme: 0-1 hrs. pH 1.2; 1-2 hrs. pH 2.5; 2-3.5 hrs. pH 4.5, 3.5-5 hrs. pH 7 and 5-8 hrs. pH 7.5. The

flow rate was 6 ml/min. An open flow-through system was employed and the collected fluids were assayed for the drug content after suitable dilutions. All the runs were done in triplicate. The amount and percent dissolved was calculated from the absorbances using the calculator and microcomputer programs written for this purpose.

The percent released versus time data so obtained was assessed for the kinetics of release and dissolution. A program (DISSOL)(9) written just for this purpose was employed. The data was tested according to 10 different release and dissolution kinetics.

RESULTS AND DISCUSSION

The parameters of the linear calibration equations obtained at different wavelengths are given in Table 2:

TABLE 2. Calibration Data[a]

Parameters[b]	Wavelength (λ_{max})		
	261 nm.	269 nm.	277 nm.
Slope	14.7 ($\pm$ 0.6)	20.6($\pm$0.9)	13.9($\pm$0.1)
Intercept	-0.603($\pm$ 0.453)	-	-
r^2[c]	0.998	0.985	1.00
S_r[d]	0.266	0.831	0.124

[a]The values within the paranthesis are 95 % confidence intervals.

[b]The calibration equations are as follows:

Conc. (μg/ml) = slope x Absorbance + Intercept.

[c]Coefficient of determination; [d]Standart deviation of the regression.

The mean diameters of the prepared granules appear in Table 1. The surface areas for a unit dose (450 mg) of the granules also appear in the same table.

The release/dissolution profiles of the various formulations are seen in Figs. 1 and 2. The results of the kinetic assessment of the release data appear in Table 3.

Upon checking the results, it is immediately seen that, the release rates are far above optimum. This obviously results from the high specific surface area of the granules. The type of polymethylmethacrylate, which has higher solubility, releases the drug more than that of the low solubility type, which is what is expected. The addition of lactose lowers the release rate more than the addition of talc.

Increasing the amount of Mg stearate lowers the rate, but doubling the amount of polymethylmethacrylate at this point does not have much effect.

Best suppression of release was obtained with cellose acetate phtalate which however was still above the target value. We believe, this polymer is a good candidate for further research in this respect. Since it dissolves in the intestinal fluid, it might be combined with other polymers with necessary formulation changes.

The shape of the dissolution curve in Fig. 1 is far from being ideal. It is seen that, the pattern of release is nowhere zero order. This is substantiated with very low coefficients of determinations for that kinetics.

Although the granules preparad were of matrix type, the kinetic result did not give very good fits to either homogeneous

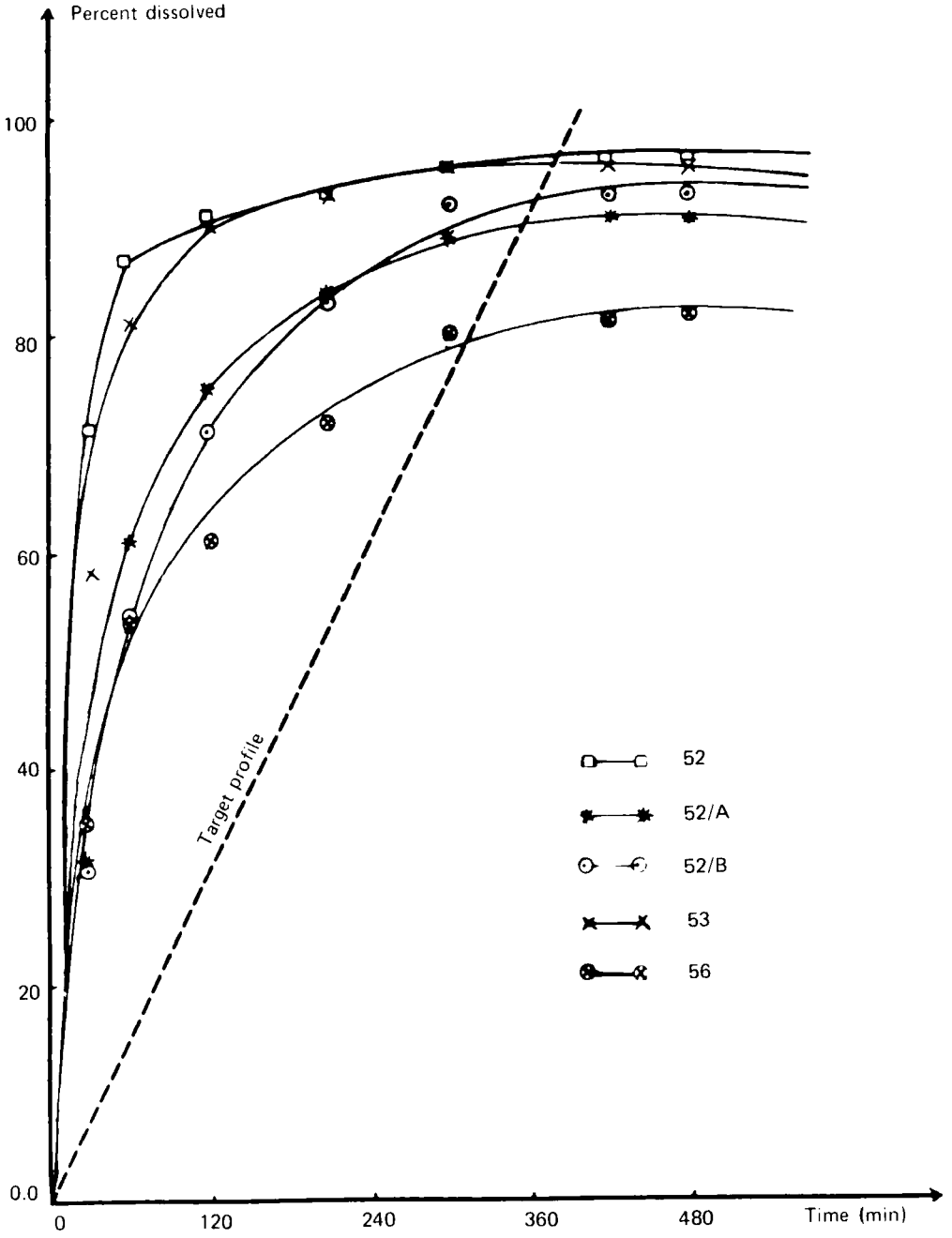

Fig. 1 The release/dissolution profiles of the various formulations.

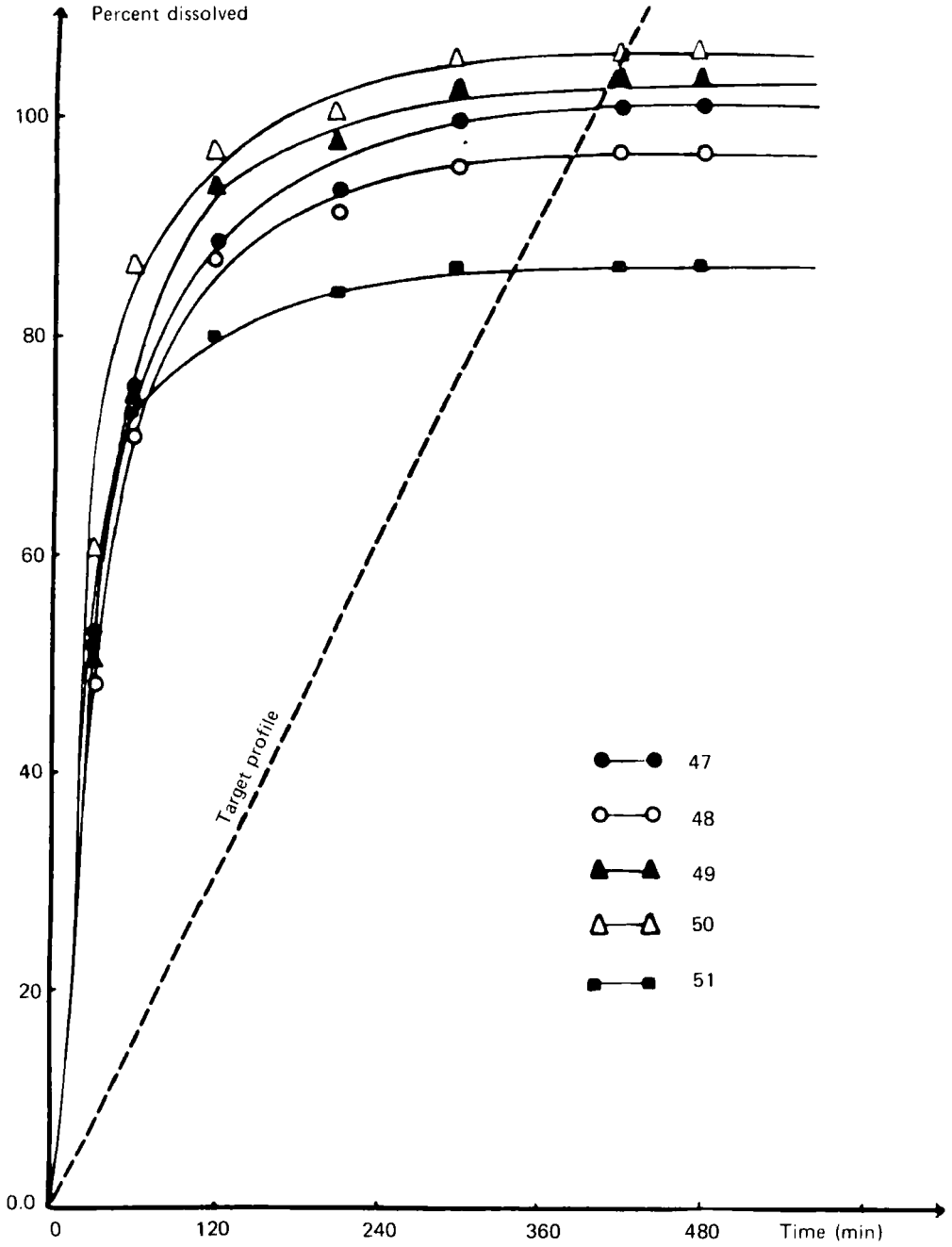

Fig. 2 The release/dissolution profiles of the various formulations.

TABLE 3. The Kinetic Assessment of Release Data[a]

KINETICS		FORMULATIONS				
		47	48	49	50	51
Modified Hixson Crowell[b]	a	0.497	0.429	0.524	0.473	0.244
	b	1.85×10^{-3}	1.09×10^{-3}	2.01×10^{-3}	1.41×10^{-4}	3.67×10^{-4}
	r^2	0.984	0.935	0.970	0.970	0.831
RRSBW[c]	T	45.5	47.6	45.9	38.0	39.5
	β	0.804	0.581	0.823	0.857	0.306
	r^2	0.967	0.962	0.991	0.960	0.851
First Order[d]	k_r	0.918	0.344	0.822	1.24	0.122
	r^2	0.946	0.890	0.985	0.920	0.675
Zero Order[e]	k_r^o	22.3	22.4	23.2	18.8	1.36
	k^2	0.681	0.639	0.624	0.594	0.547
Hixson-Crowell[f]	K	0.768	0.614	0.777	0.828	0.453
	r^2	0.957	0.814	0.904	0.918	0.633
$Q \rightarrow \sqrt{t}^q$	k	0.153	0.100	0.100	0.0992	0.0622
	r^2	0.809	0.775	0.962	0.729	0.622
Higuchi (Heterogen. pellet)[h]	m	2.4×10^{-3}	0.00194	2.45×10^{-3}	0.00255	0.00126
	r^2	0.927	0.829	0.869	0.858	0.666
Erodible Sphere[i]	k'	1.47×10^{-3}	9.46×10^{-4}	1.45×10^{-3}	1.48×10^{-3}	4.21×10^{-4}
	r^2	0.958	0.814	0.904	0.918	0.633
Erodible Cylinder[i]	k''	1.34×10^{-3}	1.02×10^{-3}	1.35×10^{-3}	1.26×10^{-3}	4.99×10^{-4}
	r^2	0.895	0.770	0.831	0.833	0.611
Erodible slab[i]	k'''	8.28×10^{-4}	8.29×10^{-4}	8.60×10^{-4}	6.98×10^{-4}	5.02×10^{-4}
	r^2	0.681	0.639	0.624	0.594	0.547

TABLE 3. (continued)

KINETICS		FORMULATIONS				
		52	52/A	52/B	53	56
Modified Hixson Crowell[b]	a	0.212	0.509	0.571	0.310	0.420
	b	3.67×10^{-4}	8.61×10^{-4}	1.06×10^{-3}	7.08×10^{-4}	4.84×10^{-4}
	r^2	0.900	0.897	0.958	0.877	0.969
RRSBW[c]	T	9.14	91.1	96.8	25.2	97.9
	β	0.311	0.622	0.708	0.429	0.516
	r^2	0.929	0.923	0.973	0.909	0.972
First Order[d]	k_r	0.220	0.242	0.306	0.258	0.220
	r^2	0.824	0.845	0.896	0.780	0.934
Zero Order[e]	k_r^o	10.2	27.2	31.5	15.5	25.7
	k^2	0.582	0.655	0.748	0.548	0.837
Hixson-Crowell[f]	K	0.619	0.496	0.524	0.609	0.453
	r^2	0.746	0.788	0.859	0.706	0.912
$Q \rightarrow \sqrt{t}$[g]	k	0.0962	0.132	0.0931	0.172	0.110
	r^2	0.710	0.788	0.870	0.685	0.924
Higuchi (Heterogen. pellet)[h]	m	1.97	1.46×10^{-3}	1.58×10^{-3}	1.92×10^{-3}	1.27×10^{-3}
	r^2	0.742	0.838	0.887	0.716	0.934
Erodible Sphere[i]	k'	5.55×10^{-4}	8.20×10^{-4}	9.99×10^{-4}	7.01×10^{-4}	9.64×10^{-4}
	r^2	0.746	0.788	0.859	0.706	0.912
Erodible Cylinder[i]	k''	5.68×10^{-4}	9.72×10^{-4}	1.17×10^{-3}	7.48×10^{-4}	9.12×10^{-4}
	r^2	0.704	0.756	0.835	0.666	0.897
Erodible slab[i]	k'''	3.78×10^{-4}	1.01×10^{-3}	1.17×10^{-3}	5.75×10^{-4}	9.51×10^{-4}
	r^2	0.582	0.655	0.748	0.548	0.837

Footnotes for TABLE 3.

[a] Summary of output obtained from the program DISSOL(9); [b] For this kinetics, the a parameter is associated with the shape of the dissolution curve and the b parameter is an apparent dissolution rate constant (3,4); [c] T value stands for the time for 63.2 % release of the drug, and β is a shape factor (7,8); [d] k_r is the first order release rate constant; [e] k_r^o is the zero order release rate constant; [f] K is the dissolution rate calculated from the Hixson-Crowell plot for sink conditions (14,15); [g] k is the rate constant obtained from the slope of the linear regression of cumulative amount released per unit area versus square root of time; [h] m is a rate constant obtained from the plot of the Higuchi equation for heterogenous pellets (16); [i] the rate constants k', k'' and k''' are obtained according to Hopfenberg (5).

or heterogeneous matrix release equations (16). The only exceptions are formulations 49 and 56. The former was granulated with polymethylmethacrylate solution, and after drying, was also coated with the same polymer solution. The latter was granulated with CAP solution. These two formulations gave somewhat good fits for matrix kinetics.

Some of the formulations do show apparent first order fits, but the goodness is far from being ideal.

Best fits were obtained with RRSBW distribution. This equation seems to be able to describe these data better than the others. Modified Hixson-Crowell equation (4,5) follows behind. Other kinetic fits, like the Higuchi equations and the erosin from spheres, cylinders and slabs did not give satisfactory results at all. In general, the kinetic treatment did not give any new information.

In this study, we tried to use the same polymers employed in a previous study(2). In that study, we had prepared an inert matrix type tablet. Upon comparison, it is immediately seen that, matrix granules release the drug at a higher rate. We plan to continue this work with other polymers.

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REFERENCES

1. P. G. Welling, M.R. Dobrinska, in "Sustained and Controlled Release Drug Delivery Systems", J.R. Robinson, ed., Marcel Dekker, Inc., New York and Basel, 1978, p. 631.
2. İ. T. Ağabeyoğlu, Drug Dev. Ind. Pharm., submitted (1984).
3. İ. T. Ağabeyoğlu, "The Biopharmaceutical Design and Realization of a Sustained Release Sulfamethizol Dosage Form", Thesis for Assoc. Prof., Coll. Pharm., Univ. Ankara, Ankara, 1978.
4. İ. T. Ağabeyoğlu, "A New Equation in Sustained Release Kinetics and a Computer Program for Kinetic Calculations", Presented at National Pharmaceutical Congress, Istanbul, 1981.
5. H.B. Hopfenberg, "Controlled Release Polymeric Formulations", D.R. Paul, F.W. Harris, eds., Amer. Chem. Soc. Press, Washington D.C., 1976, p. 26.
6. M.O. Vaizoğlu, Acta Pharm. Fenn., 90, 63(1981).
7. F. Langenbucher, J. Pharm. Pharmacol, 24, 979 (1972).
8. F. Langenbucher, Pharm. Ind., 38, 472 (1976).
9. İ. T. Ağabeyoğlu, "DISSOL: A BASIC Microcomputer Program for the Kinetic Assessment of Dissolution Data", to be published.
10. E.Krüger-Thiemer, S.P.Eriksen- J.Pharm. Sci., 55, 1249 (1966).
11. J.R. Robinson, S.P. Eriksen, J. Pharm. Sci., 59, 1796 (1970).
12. J.R. Robinson, S.P. Eriksen, J. Pharm. Sci., 55, 1254 (1966).

13. A.H. Edmunson, "Advances in Pharmaceutical Scienses", Vol.II., H.S. Bean, A.H. Beckett, J.E. Carless, eds., Academic Press, New York, 1967, p. 94.

14. A.W. Hixson, J.H. Crowell, Ind. Eng. Chem., 23, 923 (1931).

15. A.W. Hixson, J.H. Crowell, Ind. Eng. Chem., 23, 1002 (1931).

16. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).