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STUDIES ON SUSTAINED RELEASE II: IN VIVO PERFORMANCE OF THE INERT MATRIX SULFAMETHIZOLE TABLET, EMPLOYING POLYMETHYLMETHACRYLATE

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

A.Ü.Ecz.Fak.
Tandoğan
Ankara - TURKEY

ABSTRACT

The in vivo performance of the developed sustained release preparation was assessed on eight subjects. Based upon urinary excretion rates, in vivo data supported previous in vitro dissolution test results. An overall release/excretion rate of 32.6 mg/hr was obtained. The blood levels were assayed for intact drug and were fit to a three exponential equation employing the program AUTOAN. First order release rate constant of 1.33 hr^{-1} was calculated, but the fits were not very satisfactory Although the blood levels were in an acceptable range, it is concluded that a faster releasing dosage form would be more appropriate This might require however, switching to another dosage form.

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INTRODUCTION

Sulfamethizole is a sulfonamide used in therapy as a urinary antiseptic. Its biological half-life is quite short (about 1.3 to 2.4 hrs.)(1-3), which urged us to prepare a sustained release dosage form. Feasible design parameters were calculated as follows: Sustaining and corrected initial doses 450 mg and 135 mg respectively; zero order release rate 67.5 mg/hr or first order release rate constant 0.15 hr^{-1}; dosage interval 8 hrs., and the designed blood level 40-10 μg/ml. Two such unit doses are to be taken at each dosing.

In a previous study (4), we had given the details of the formulation work and in vitro dissolution results. Extensive kinetic assessment of such data and a preliminary blood profile check on a single subject enabled us to conclude that, the target formulation might have been achieved. In vivo testing of the final formulation (No:35), employing human subjects is the main purpose of this communication.

METHODS

Subjects : Eight healthy human volunteers were employed. Their ages were from 26 to 50. Subject 2 was a female. These were the same subjects used for the determination of the oral pharmacokinetics of sulfamethizole in the earlier part of the study (1,3).

Protocol : After an overnight fast, the subjects were given two units of the prepared inert matrix tablets with 200 ml of water. No food was allowed for three hrs., but 100 ml of water was given to the subjects every hr during this period. 0.1 to 1 ml blood samples were obtained from fingertip punches. Samples were taken at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6 and 8 hrs. At this point, another and similar dose was given and blood samples were taken at 9 and 10 hrs. Urine samples were collected at 2 hr intervals up to 12 hrs and another one to 24 hrs. No urine was collected from one of the subjects.

Assay: Bratton-Marshall procedure was employed for all the samples(5). The calibration equation obtained was as follows:

$$C = 5.54\ S\ A \qquad (1)$$

where C is the blood concentration in μg/ml; S is the dilution factor and A is the absorbance read from the spectrophotometer at 547 nm.

Pharmacokinetic Assessment : Blood concentrations were evaluated with the computer program AUTOAN (6) on an Amdahl 470V/6 system.

RESULTS AND DISCUSSION

The blood levels obtained with the test formulation are shown in Fig. 1. As can be seen, the blood levels stay mostly within the programmed level of 40-10 μg/ml. The area under the curve within the dosage interval were calculated with the trapezoidal rule and appear in Table 1.

Average blood level within the dosage interval was calculated by dividing the area under the curve by the former. The mean of all subjects such values gave us 28.4 μg/ml. This is a reasonable result and is in compliance with the target values.

The sustained release blood level C for a one compartment model drug-such as sulfamethizole-is described by a three expunential equation (7):

$$C = A_1 e^{-k_d t} + A_2 e^{-k_a t} + A_3 e^{-k_r t} \qquad (2)$$

where the As are the coefficients and the ks are the rate constants for disposition, absorption and drug release respectively. This equation assumes that the drug is released from the sustained release dosage form with first order. Upon the fitting runs of our data with AUTOAN, the program itself determined that the best fit within its 18 models was Eq.(2). So, the final fits were computed according to this model. The resulting in vivo release rate constants(kr) are given in Table 1 together with the goodness of fits(r^2). At first sight, it is seen that the mean first order release rate constant is far above from the aimed value. However, the 95% confidence interval and the coefficient of variation for this value is also high. The r^2s for individual subject fits are somewhat less than satisfactory.

In our earlier work(3), the plasma peak of sulfamethizole was determined to take place between 0.43 to 1.91 hrs. Theoretically, at constant blood level the excretion rate of a drug by urine should

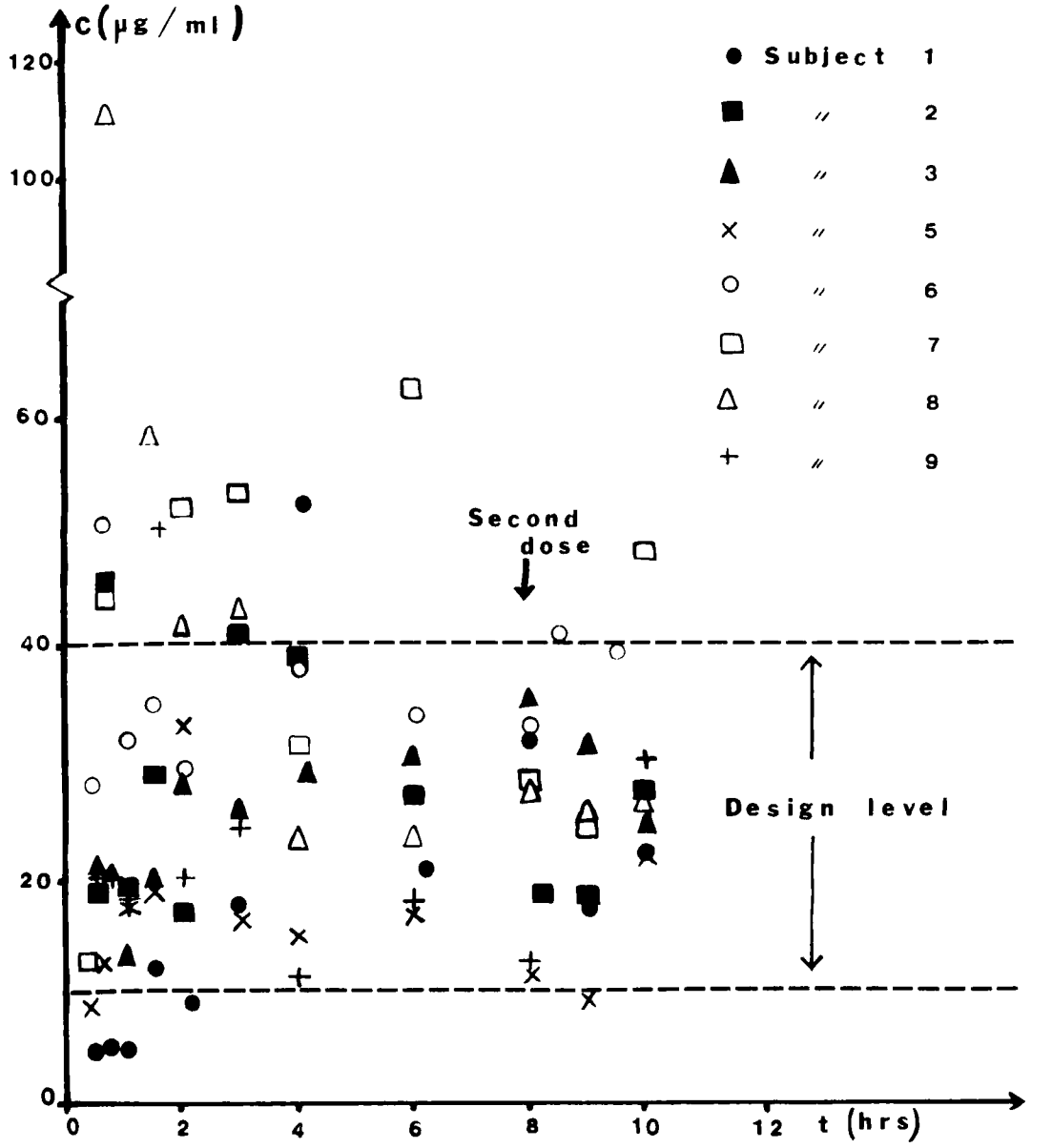

FIGURE 1. Blood levels of the subjects with the sustained release dosage form.

TABLE 1 : Pharmacokinetic Parameters

Subject	$AUC_{o \rightarrow \tau}$ [a]	$\bar{C}$ [b]	k_r [c]	r^2 [d]
1	188	23.4	0.375	0.843
2	232	28.4	0.695	0.883
3	215	26.6	0.0638	0.944
5	133	16.6	0.165	0.883
6	265	33.0	1.00	0.856
7	353	43.8	2.91	0.914
8	295	36.6	5.27	0.696
9	149	18.8	0.178	0.858
Mean	229	28.4	1.33	
C.I. [e]	± 62	± 7.6	± 1.53	

[a] Area under the curve, determined by the trapezoidal rule (μg.hrs/ml). [b] Average blood level within the dosage interval in μg/ml; [c] First order release rate constant calculated by AUTOAN. [d] Coefficient of determination of the AUTOAN fit; [e] 95% confidence interval.

also be constant. The excretion rates of subjects during the 12 hr. period are given in Fig.2. Excluding the first two hr. urine sampling period for equilibration, the excretion rates for the remaining data points were averaged for each subject and are shown in Table 2. It is seen that, the intra-subject variations are high, but inter-subject variation is quite reasonable. The overall excretion rate for seven subjects is 65.0 mg/hr This is half as much as the target value, since

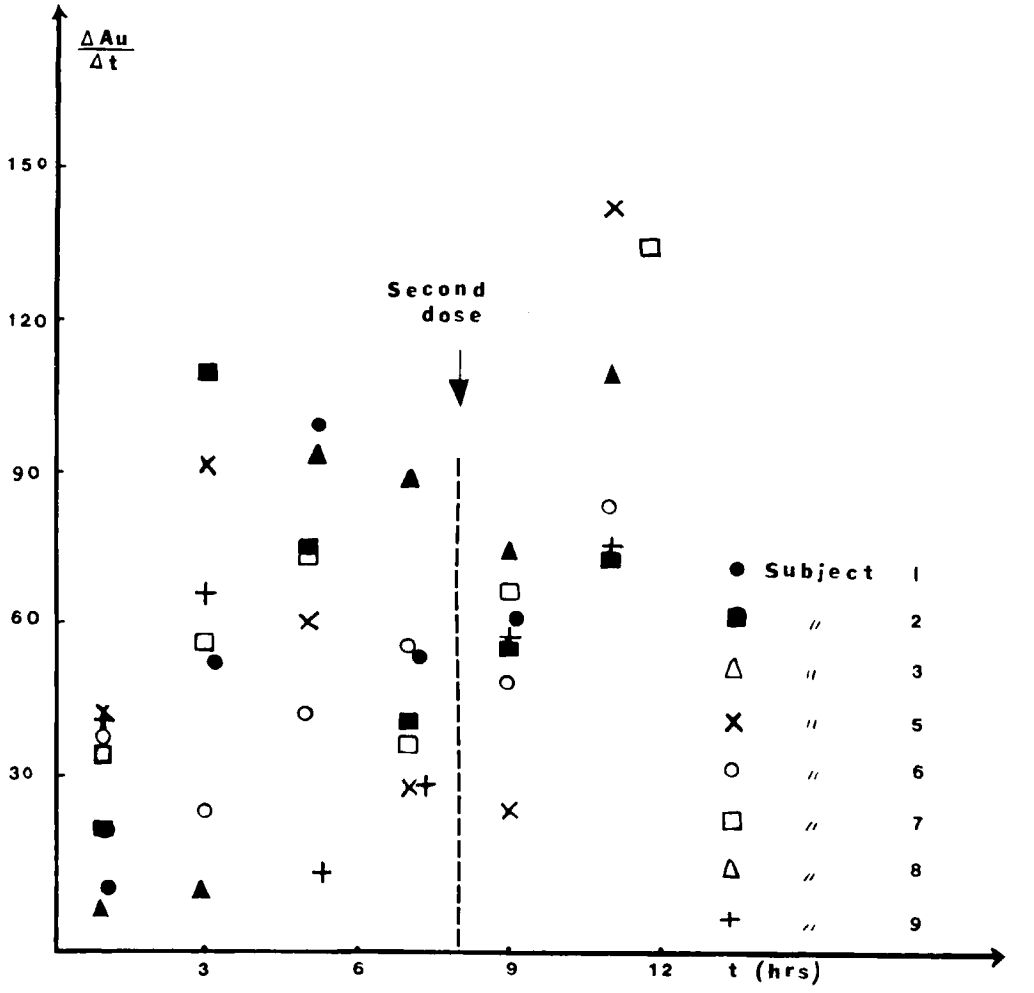

FIGURE 2. Urinary excretion rates of the subjects with the sustained release dosage form.

TABLE 2 : Assessment of Urine Data

Subject	Mean Excretion Rate[a]	SD[b]	CV[c]
1	67.7	22.9	33.9
2	71.1	26.0	36.6
3	75.3	39.5	52.5
5	69.2	49.6	71.6
6	50.9	22.2	43.7
7	73.4	37.1	50.5
9	47.4	27.3	57.7
Mean	65.0		
SD[b]	11.2		
CV[c]	17.2		

[a] mg/hr; [b] Standart deviation; [c] Coefficient of variation in %.

two units are administered for each dosing. That gives a release rate of 32.5 mg/hr/tablet. Incidentally, in the first part of the study(4), this very formulation gave a release rate of 32.6 mg/hr in the flow through-cell dissolution test. In this instance, urinary excretion rates and in vitro dissolution test results confirmed each other very well. Although the blood levels look acceptable, the first order in vivo release rate constants do not seem conclusive. It is apparent that the product should be formulated, so that the release rate is higher. With the inert matrix type tablet, it is doubtful whether a faster release could be achieved. Another type of dosage form, such as inert matrix granules, can possibly be more useful, and will be investigated by the author in subsequent work.

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