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STUDIES ON SUSTAINED RELEASE XI: LIPID GRANULES OF SULFAMETHIZOLE

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ABSTRACT

The aim of this study was to prepare a sustained release granule of sulfamethizole, employing hydrogenated castor oil (Cutina HR). After the dosage form design was made, different formulations were prepared as granules by the fusing technique. The granules manufactured were analysed with sieves between 0.5 and 1 mm openings. The fractions obtained were tested for dissolution rate for a period of seven hours with fluids of varying pHs with the continuous flow-through cell apparatus.

Upon the kinetic evaluation of dissolution data, it was seen that the target release rates were achieved. The results showed that,

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the drug release rates increase with increasing amounts of PEG 4000 added to the formulations; up to a certain percentage. No increase beyond this point was noticed.

The drug release rates mostly followed zero-order and modified Hixson-Crowell kinetics.

INTRODUCTION

Studies have been carried out previously to prepare sustained release matrix type dosage forms of sulfamethizole, a urinary tract antiseptic with a short biological half-life (1-3). Polymethylmethacrylate, polyvinyl chloride, and carboxpolymethylene have been employed as sustaining materials and it was concluded that, the granule type of dosage form would be better suited for this purpose. Polymethylmethacrylate and cellulose acetate phtalate was employed as polymers for the preparation of sustained release sulfamethizole granules (4). The results showed that, these polymers were not suitable for achieving the desired release rates.

Hydrogenated castor oil (Cutina HR) was used in this study as the sustaining material for this purpose.

MATERIALS

Assay

The assay was done as in our previous work (1). The UV peaks of the drug were at 269 nm for pH 1.2; 277 nm for pHs 2.5 and 4.5; and 261 nm for pHs 7.0 and 7.5.

Chemicals

Sulfamethizole (FAKO Pharmaceuticals, Turkey), Hydrogenated castor oil (Cutina HR,Henkel), PEG 4000 (Merck), Polysorbate 20 (Merck).

Apparatus

pH meter (Orion 701), spectrophotometer (Pye-Unicam , SP8-100), flow-through cell (Desaga), sieves (Erweka), microscope (Nikon SK-E).

TABLE 1: The Formulations Used In The Study

FORMULATIONS (mg)	F1	F4	F5	F6	F7	F8
Sulfamethizole	450	450	450	450	450	450
Hydrogenated castor oil	200	100	100	100	100	100
PEG 4000	-	100	50	130	180	300

METHODS

Design Parameters

The target values for the dosage form to achieve, were calculated form the pharmacokinetic parameters of the drug and were as follows (1,5,6):

Initial dose	:	135 mg
Sustaining dose	:	450 mg
Zero-order release rate	:	67.5 mg/hr
First order release rate constant	:	0.15 hr^{-1}
Dosage interval	:	8 hrs
Sustained plasma concentration	:	40-10 µg/ml

The values are based on the administration of two units per dose.

Preparation Of The Formulations

All the formulations in the study appear in Table 1. They were all prepared by fusing (7,8). Hydrogenated castor oil and PEG 4000, if present, was melted over water bath. Sulfamethizole was added to this melted mass and mixed thoroughly. This mixture was removed from the heat and screened through a 1.25 mm sieve, when its temperature was close to the congealing point. Since the solubility of the drug was high at pH 1.2, the initial dose portion was not added to the formulations in this study and only the sustaining part was used throughout.

TABLE 2: The Calibration Data of Sulfamethizole [a]

PARAMETERS[b]	WAVELENGTH (λmax)		
	261 nm pH 7-7.5	269 nm pH 1.2	277 nm pH 2.5-4.5
Slope	14.7(± 0.6)	20.6 (± 0.9)	13.9 (± 0.1)
Intercept	-0.603 (±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 calibrations equations are as follows:

Conc (μg/ml): Slope x Absorbance + Intercept

c: Coefficient of determination.

d: Standart deviation of the regression.

Particle Size Analysis

The formulations prepared were sieve analysed and the 0.5 to 1 mm fractions were tested for dissolution. In order to properly evaluate the release kinetics, particle size analysis was carried out microscopically and the surface areas were determined (9). An average of 500 particles from each formulation was counted and the mean particle size was determined.

Dissolution Rate Tests

Flow-through cell dissolution apparatus was employed for this purpose. The procedure was as given in our previous study (1). USP simulated gastric and intestinal fluids were used without the enzymes and 0.02 % polysorbate 20 added to bring the surface tension to about 45-50 dyne/cm for mimicking the in vivo value (10,11).

Kinetic Assesment of Dissolution Data

The program DISSOL, written for such kinetic analysis was used to evaluate the data (1,12-18).

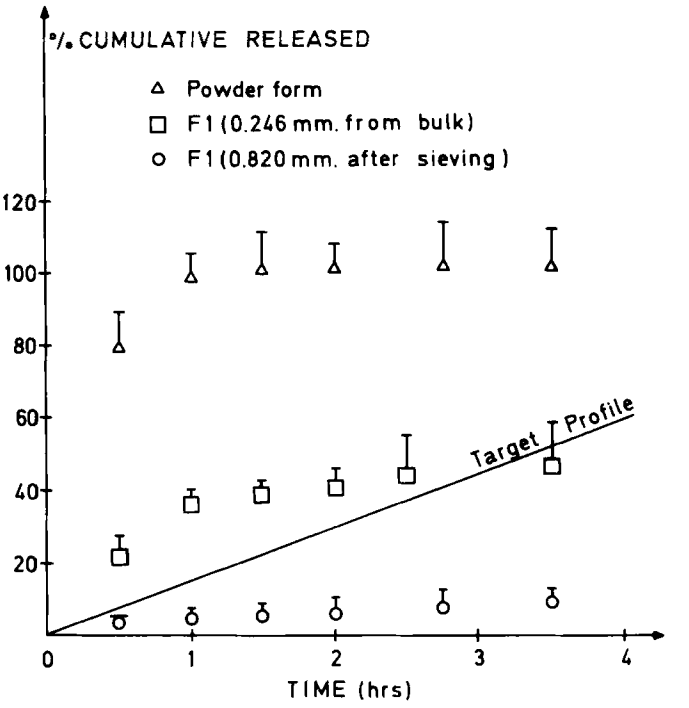

Figure 1: Initial dissolution profiles
(Bars represent 95 % confidence intervals)

RESULTS

The calibration data at different pHs appear in Table 2(1).

The dissolution profiles of the drug itself and the various size fractions of the formulations at different pHs are given in Fig.1.

The particle size analysis results of the formulations prepared are given in Table 3. The log probability plot of two of the formulations are seen in Fig.2.

The dissolution profiles of the formulations appear in Fig.3. The kinetic assessment of the dissolution data are given in Table 4.

TABLE 3: The Results of Particle Size Analysis of Formulations

Formulations	The Number of Granules/ Unit Dose	Mean Diameters of Granules (mm)			Surface Area/ Unit Dose (cm^2)		
		d_{ln}	d_{vn}	d_{vs}	d_{ln}	d_{vn}	d_{vs}
F1	3952	0.794	0.820	0.846	78.9	83.4	88.8
F4	4257	0.800	0.817	0.834	85.6	89.2	93.0
F5	3060	0.756	0.777	0.798	54.9	58.0	61.2
F6	3754	0.727	0.752	0.777	62.5	66.7	71.2
F7	4126	0.730	0.769	0.776	69.0	76.6	78.0
F8	4275	0.730	0.753	0.786	71.5	76.9	82.9

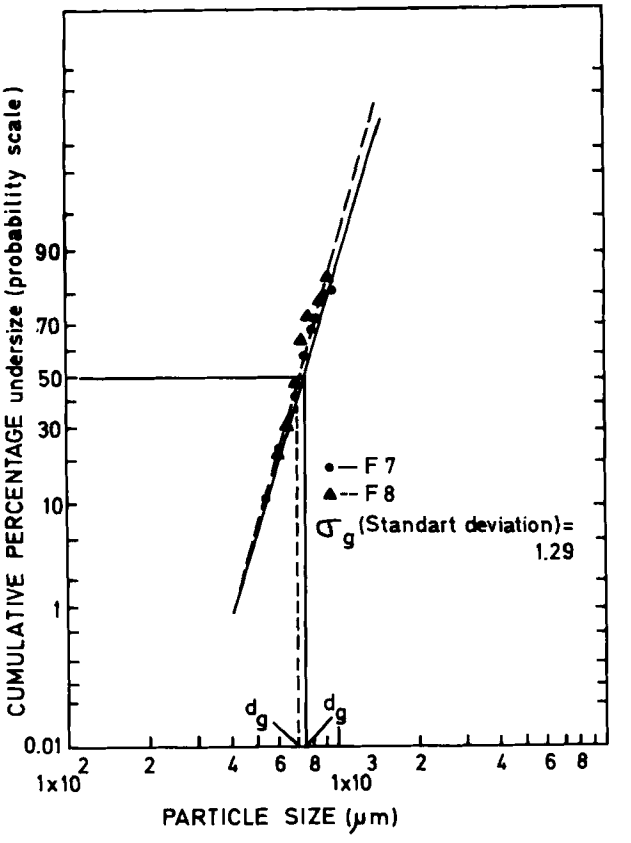

Figure 2: Log-probability plot of formulations F7 and F8

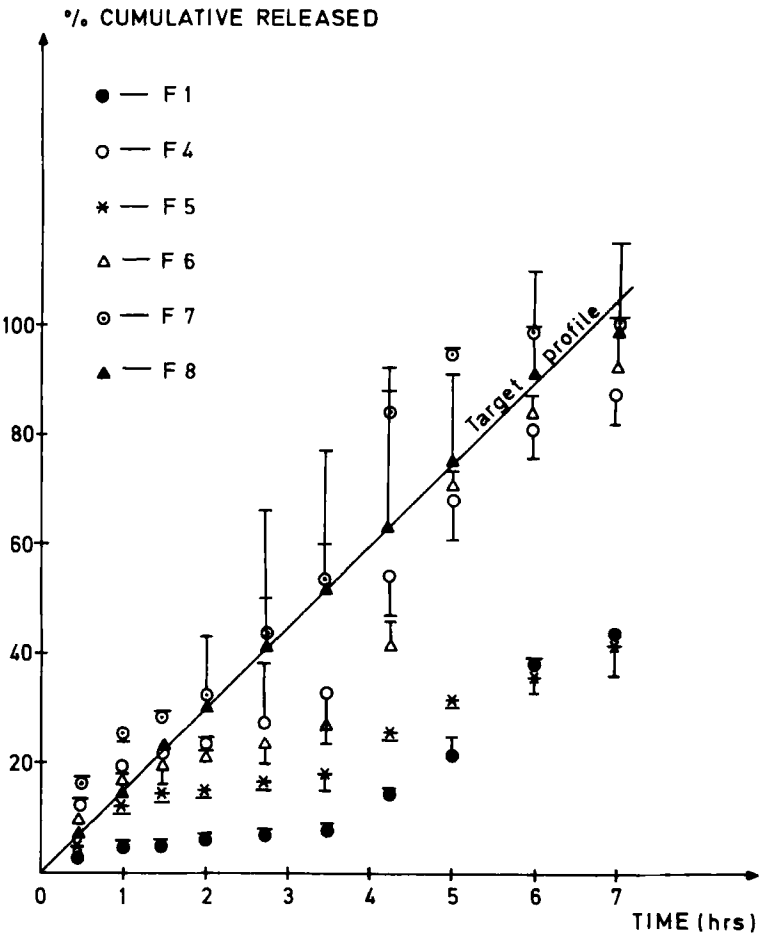

Figure 3: Dissolution profiles of the formulations
(Bars represent 95 % confidence intervals)

DISCUSSION

PEG 4000 was employed as the porosity agent to increase the drug release rate. It could be adjusted by varying the amounts of wax and PEG 4000.

The release rate increased in proportion to the amount of PEG in the formulation (Fig.2) (19). On the other hand, as seen in F7 and F8, increasing PEG beyond a certain value has no effect on drug release.

TABLE 4: The Kinetic Assessment of Release Data [a]

KINETICS		FORMULATIONS					
		F1	F4	F5	F6	F7	F8
Modified Hixson - Crowell [b]	a	1.00	0.925	0.695	0.989	1.12	1.16
	b	2.55×10^{-4}	7.86×10^{-4}	1.46×10^{-4}	8.36×10^{-4}	1.75×10^{-3}	1.27×10^{-3}
	r^2	0.813	0.871	0.926	0.827	0.900	0.981
RRSBW [c]	T	1260	317	1261	320	167	257
	B	1.03	1.03	0.735	1.10	1.39	1.28
	r^2	0.794	0.853	0.922	0.802	0.862	0.962
First Order [d]	k_r	0.0810	0.288	0.0777	0.346	0.846	0.375
	r^2	0.835	0.895	0.952	0.825	0.879	0.877
Zero Order [e]	k_r^o	28.0	54.9	23.7	58.7	67.7	60.3
	r^2	0.866	0.947	0.963	0.911	0.934	0.996
Hixson - Crowell [f]	k	3.20×10^{-4}	1.03×10^{-3}	3.88×10^{-4}	1.08×10^{-3}	1.88×10^{-3}	1.19×10^{-3}
	r^2	0.846	0.920	0.956	0.864	0.926	0.942
$Q \rightarrow \sqrt{t}$ [g]	k	4.93×10^{-3}	2.93×10^{-3}	1.73×10^{-2}	5.05×10^{-2}	7.09×10^{-2}	4.67×10^{-2}
	r^2	0.752	0.882	0.909	0.827	0.919	0.965
Higuchi (Heterogen. Pellet) [h]	m	1.14×10^{-4}	8.27×10^{-4}	1.34×10^{-4}	9.30×10^{-4}	1.94×10^{-3}	1.04×10^{-3}
	r^2	0.720	0.855	0.892	0.789	0.890	0.842
Erodible Sphere [i]	k'_2	4.11×10^{-4}	1.17×10^{-3}	3.55×10^{-4}	1.34×10^{-3}	2.26×10^{-3}	1.41×10^{-3}
	r^2	0.846	0.920	0.956	0.864	0.926	0.942
Erodible Cylinder [i]	k"	5.90×10^{-4}	1.52×10^{-3}	5.08×10^{-4}	1.70×10^{-3}	2.52×10^{-3}	1.77×10^{-3}
	r^2	0.851	0.929	0.958	0.879	0.935	0.965
Erodible Slab [i]	k'"	1.10×10^{-3}	2.03×10^{-3}	8.78×10^{-4}	2.17×10^{-3}	2.51×10^{-3}	2.24×10^{-3}
	r^2	0.866	0.947	0.963	0.911	0.934	0.996

Footnotes for TABLE 4.

[a] Summary of output obtained from the program DISSOL (1); [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 (12); [c] T value stands for the time for 63.2 % release of the drug, and B is a shape factor (13); [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 (16,17); [i] the rate constants k',k" and k"' are obtained according to Hopfenberg (18).

With formulations F7 and F8, values very close to the target (67.5 mg/hr.) were obtained. F8 was considered as the better of these two, since its fit to zero-order was better.

Fits to matrix kinetics was in general good. Constant release rates (zero order kinetics) was also obtained with a number of formulations.

CONCLUSION

Sustained release granules of sulhamethizole with the designed release rate of 67.5 mg/hr was obtained, using hydrogenated castor oil as matrix material. In this way, it seems probable to employ the very short acting drug sulfamethizole with longer dosage intervals. An in vivo study, testing this formulation on 12 subjects has been carried out with excellent results (20). That is the subject of our next publication in this series.

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