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STUDIES ON SUSTAINED RELEASE I : THE BIOPHARMACEUTICAL DESIGN AND PRODUCTION OF AN INERT MATRIX TYPE SULFAMETHIZOLE TABLET, EMPLOYING POLYMETHYLMETHACRYLATE*

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ABSTRACT

An inert matrix type sustained release tablet of sulfamethizole is attempted. Sustained release dosage form design parameter values were first calculated. Thirteen different formulations were prepared using polymethylmethacrylate as the sustaining polymer. Release and dissolution profiles were determined by the flow-through cell and the rotating bottle apparatus. Experimental results were fitted to several different kinetic equations using a computer program

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written for this purpose. Results of the final formulation showed that the goal was achieved.

INTRODUCTION

Sustained release products bring the blood level of a drug to therapeutic concentrations as soon as possible and then maintain this level for a certain period of time(1,2). These first release a certain amount of drug from the "initial dose" portion of the dosage form to attain the desired blood level, then release the drug with a gradual, but at a predetermined rate from the "sustaining dose" portion, so that the designed level is maintained for the proposed dosage interval. In this fashion, these products enable a more consistent and better therapy (3). Naturally, such products are in consideration for drugs with a short biological half-life.

Among the many different sustained release forms, inert matrix type is a special model. In this from, the drug is trapped in an insoluble, spongy and porous polymer structure (1,3-5). As the matrix progressess down the gastro-intestinal tract, the drug is leached by the G.I. fluids. The remaining and undissolved polymer matrix,which still has almost the same physical shape, is disposed with faeces. We worked on such an inert matrix tablet in this study.

The biological half-life of sulfamethizole, which is used as a urinary antiseptic, was reported to be 1.3 hrs(6). In a study done by the author, the oral pharmacokinetics of this drug was carried out on ten subjects(3,7). Parameters like absorption rate constant

(k_a), disposition rate constant(k_d), clearance(Cl), apparent distribution volume(V_{darea}), time for plasma peak(t_p) and area under the plasma concentration- time curve(AUC), etc. were determined.

THEORETICAL

Release Kinetics From Sustained Release Dosage Forms : Theoretically, optimum release kinetics from a sustained release product should be of zero order(1,8-10).Such a release can be shown as follows:

$$W = W_o - k_r^o t \qquad (1)$$

where, W is the amount remaining to be released at time t; W_o is the maintenance dose and k_r^o is the zero order release rate constant(10). If first order release prevails, then,

$$W = W_o e^{-k_r t} \qquad (2)$$

where, k_r is the first order release rate constant(8). It must be pointed out however, that first order release is not theoretically suitable for sustained release and apparently acceptable results can be obtained in actual practice with a relevely large drug reservoir.

Higuchi first developed the kinetic equations for release from inert matrices(11). The cumulative release per unit area, Q, versus time t, from a planar surface is determined with the following equation :

$$Q = \sqrt{DC_s(2A-C_s)\, t} \qquad (3)$$

where, D is the diffusion coefficient of the drug in the diffusion medium; A is amount of drug per unit volume of the matrix; and C_s is the solubility of the drug in the matrix material.

If the matrix is heterogeneous; i.e. the drug is insoluble in the matrix polymer, a slightly different equation results:

$$Q = \sqrt{\frac{DC_s \in}{\tau}(2A - \in C_s)\, t} \qquad (4)$$

Here, $\in$ is the porosity of the matrix. τ is the tortuosity factor, which denotes the extra path to be taken by the diffusing drug molecules around the matrix particles. Its value is supposed to be around 2 to 3(11). In this case however, D and C_s are the diffusion coefficient and solubility in the dissolution medium.

Higuchi also developed equations for three dimensional drug release from spherical pellets. For homogeneous pellets;

$$1 - 3\left(\frac{a'}{a_o}\right)^2 + 2\left(\frac{a'}{a_o}\right) = \frac{6DC_s}{A\, a_o^2}\, t = Bt \qquad (5)$$

and for heterogeneous pellets, the right hand side of Eq(5) becomes

$$\frac{6DKC_s}{\tau\, a_o^2}\, t = B't \qquad (6)$$

The terms D, C_s, A and τ are as in Eqs.(3) and (4). a_o is the initial radius and a' is the radius of the unleached portion at time t of the pellet and K is the reciprocal of the density of the drug. On the other hand,

$$\text{Fraction of drug remaining in the pellet} = \left(\frac{a'}{a_o}\right)^3 \qquad (7)$$

Eqs.(3) and (4) show square root of time relationship, while the plot of the left hand sides of Eqs(5) and (6) versus time give a straight line passing through the origin.

Hixson and Crowell defined the dissolution rate of a single crystal under sink conditions as follows(12,13).

$$W_o^{1/3} - W^{1/3} = K_4 t \qquad (8)$$

The Ws are as in Eq.1 and K_4 includes a shape and a density factor. Assuming spherical particles and if the density is ρ, the dissolution rate can be calculated from K_4 as follows(14):

$$\text{Diss.rate} = 0.619\ \rho^{2/3}\ K_4 \qquad (9)$$

Parameters of the Flow-Through Cell : Parameters affecting the dissolution in a flow-through cell has been thoroughly investigated by Langenbucher(15). If the flow rate of the dissolution medium through the cell is Q, then the linear velocity of the fluid flow is,

$$Q_A = Q/A \qquad (10)$$

where A is the crosssectional area of the cell. The amount of drug to be dissolved per unit area of the cell is called the cell load and given as

$$m_A = m/A \qquad (11)$$

where m is the total dose within the cell.

The Pharmacokinetics of Sustained Release Dosage Forms : When a sustained release product is used orally, the resultant compartmental model is as follows:

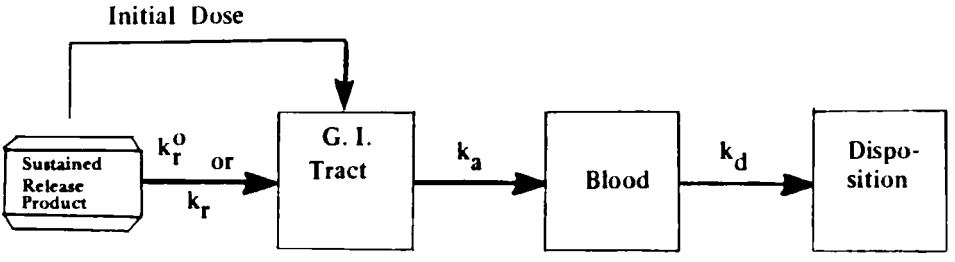

FIGURE 1. Sustained Release Compartmental Model.

The pharmacokinetics of such a model has been carried out by various authors(10,16,17). In fact, the multiple dosing regimen and the method of calculating the relevant design parameters have also been investigated(8-10,18). In this study, we carried out such calculations for sulfamethizole, employing the pharmacokinetic parameters for this drug, which were determined by the author in a previous study(3,7). The resultant design parameters of a sustained release product for this drug are as follows :

D_s (Sustaining dose) : 450 mg.

D_1^{corr} (Initial dose) : 135 mg.

k_r^o (Zero order release rate): 67.5 mg/hr.

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

τ (Dosage interval) : 8 hrs.

C (Sustained blood level) : 40-10 μg/ml.

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

MATERIALS AND METHODS

Preparation of the Tablets : The tablets were prepared either by direct compression of after wet granulation. A 13 mm diameter hand press was employed for compression[a]. Wet granulation was carried out in a mortar and the mass was screened through a 2 mm sieve and dried in an incubator at 40°C. The granules or powder mixtures were assayed for drug content just before compression and the necessary amounts for correct dosage were compressed.

[a]Specac, U.K.

The initial dose portion of the final formulation (No. 35) was prepared by wet granulation using simple syrup as the binder. The granules so obtained was layered on the sustaining portion and compressed together.

The composition of the formulations prepared are shown in Table 1.

Two derivatives of polymethylmethacrylate were employed as the matrix material. They are termed PMM I[b] and PMM II[c] respectively. The are very similar with regards to chemical structure, but differ only in the number of hydrophilic groups on the side chain (19-23), and are insoluble in water.

Assay : All assays were carried out spectrophotometrically on the UV range for sulfamethizole content. 269 nm was used for pH 1.2 samples; 277 nm for pHs 2.5 and 4.5; and 261 nm for pHs 7 and 7.5.

Hardness : A Strong-Cobb apparatus was employed for the determination of the hardness of the tablets.

Dissolution Test : All the formulations prepared were tested for dissolution rate with two apparatuses :

a- Flow-Through Cell : A commercial flow-through cell with a peristaltic pump was employed[d]. The flow rate was 5 to 6 ml/min. Since the diameter of the cell is 2 cm, this corresponds to a fluid velocity of 1.5 to 2 cm/min. An open system was used. Dissolution media was artificial gastric and intestinal fluids without enzymes and the pHs adjusted according to the following scheme: 0-1 hrs,

[b]Eudragit RLPM; [c]Eudragit RSPM, Röhm Pharma, FRG; [d]Desaga, FRG.

TABLE 1. Formulations Used in the Study[a]

Group	I			II			
No.	11	12	13	21	22	23	24
Sulfa-methizole[b]	460	460	444	444	444	444	443
PMM I	46 10.2	40 17.4	44 22.5	11.5	26	10	26,6
PMM II	46 10.2	-	-	11.5	-	-	-
Lactose[c]	-	-	142	-	-	-	222
Talc[d]	61.3	10	-	4.4	-	-	-
Colloidal Silica[e]	3.1	2.5	3.2	-	-	2.2	3.5
Mg stearate[c]	6.2	5.4	6.6	4.4	10	4.6	7.3
Pressure[f]	5	2	5	1	1	1	2
Hardness[g]	21.1	23.8	28	11.1	9.4	9.4	25

[a]Amounts are in mg; [b]Fako İlaçları A.Ş., Turkey; [c]E.Merck, FRG; [d]BDH, UK; [e]Aerosil 200, Degussa, FRG; [f]tons/cm^2; [g]Strong - Cobb units.

TABLE 1. continued

Group	II	III					
No.	25	31	32	33	34	35	
						Sust.	Init.
Sulfa-methizole	443	460	460	443	444	443	136
PMM I	10.8	230	460	200	200	200	-
PMM II	-	230	-	-	-	-	-
NaCl	25	-	-	25	25	25	50
Sucrose[h]	-	-	-	-	-	-	37.8
Colloidal Silica	-	4.6	4.6	3	3	3	-
Mg stearate	5	9.2	9.2	7	6	7	2.1
Pressure	1	2	5	3	3	2	0.25
Hardness	10.4	18.9	24	9.2	14.7	13.8	

[h]Türkiye Şeker Fabrikaları, Turkey.

pH 1.2; 1-2 hrs, pH 2.5; 2-3.5 hrs, pH 4.5; 3.5-5 hrs, pH 7.0 and 5-8 hrs, pH 7.5. 0.05 % polysorbate 80 was incorporated into dissolution media to bring the surface tension similar to those of the gastro-intestinal fluids.

b- Rotating Bottle : A home-made apparatus similar to that of NF XIV was employed. Cylindiral bottles of 105 ml capacity was mounted radially on a disk of about 30 cm in diameter. Six such bottles were put on each side of the disk. This was mounted on a shaft and put in a thermostated and agitated water bath. It was rotated from outside at a speed of 28(±1) rpm with a variable speed motor[e]. 70 mls of dissolution fluid was used. It was replaced with fresh fluid at the end of each sampling period.

Dissolution fluids and procedures were similar to that of the flow-through cell.

All the dissolution runs were carried out in quadruplicate.

Kinetic Assessment of Dissolution Data : A program was written in FORTRAN IV for the kinetic assessment of the dissolution data (3, 24). Direct experimental results (absorbances, volumes of the dissolution samples, dosage, etc.) were input. The program first calculates the percent dissolved and then fits these to several release and dissolution models and prints the values of various kinetic parameters, together with goodness of fits.

Blood Assays : Bratton-Marshall procedure was employed for the determination of sulfamethizole concentrations in blood (25).

[e]Erweka AR 400, FRG.

RESULTS

In formulation No. 11, PMM I and PMM II are used in the ratio of 1:1. The powder mixture was granulated with 12.5 % solution of both of the polymers in acetone-isopropyl alcohol(40:60). The polymers were present both in the powder mixture and as a binder. Talc was also present as a filler. Formulation No. 12 was similar, but PMM II was omitted to increase the release rate. In formulation 13, lactose was employed instead of talc.

Formulation 21 was prepared by granulating the drug powder directly with the polymers' solution mentioned above. In formulations 22 and 23, only PMM I was employed. In No. 22, binder solution was sprayed with a spray gun. In No. 24, lactose was added. Sodium chloride was employed in formulation 25, instead of lactose.

Direct compression was the method employed in formulation 31. PMM I and II were used in the ratio of 1:1. In No. 32, only PMM I was employed. In formulation 33, the amount of polymer was decreased to less than half and NaCl was added. No. 34 is essentially the same as No. 33, but the drug particles were less than 37 μm in size (those that pass through a 400 mesh sieve, USP XVIII).

The results of the dissolution experiments are given in Tables 2 and 3. These are obtained from the printouts of the computer program output. The parameters of dissolution and the coefficient of determinations obtained for four kinetic models are submitted in these tables.

TABLE 2. Release and Dissolution Parameters (Flow-Through Cell)[a].

Group		I			II			
Formulation No.		11	12	13	21	22	23	24
First Order	k_r[b]	2.21	2.85	3.32	3.72	4.15	6.19	3.67
	r^2	0.952	0.923	0.946	0.936	0.947	0.940	0.953
Zero Order	k_r^o[c]	8.70	11.2	11.4	13.4	14.0	19.4	12.9
	r^2	0.957	0.932	0.954	0.948	0.956	0.957	0.960
Hixson-Crowell	rate[d]	0.899	1.16	1.29	1.47	1.60	2.33	1.44
	r^2	0.953	0.926	0.949	0.940	0.950	0.946	0.955
$Q \rightarrow \sqrt{t}$[e]	slope	0.969	1.30	1.28	1.56	1.66	2.32	1.37
	r^2	0.899	0.860	0.896	0.886	0.898	0.884	0.908
Higuchi Eq.[g]	slope[f]	2.94	4.81	0.638	6.99	8.63	1.62	7.37
	r^2	0.899	0.865	0.897	0.862	0.893	0.872	0.904
Tablet Area	cm^2	4.04	3.95	4.06	3.81	3.81	3.80	4.27
Flow Rate	ml/min	5.81	6.0	5.0	5.9	5.9	5.6	5.5
Flow Velocity	cm/min	1.85	1.90	1.58	1.86	1.88	1.77	1.76
Cell Load	mg/cm^2	143	149	135	141	135	137	139

[a] r^2s are coefficinets of determination; [b] $hr^{-1} \times 10^2$; [c] mg/hr; [d] $\times 10^3$; [e] Eq.(3) or (6); [f] $\times 10^5$; [g] Eq.(5) or (6).

TABLE 2. continued

Group		II	III				
Formulation No.		25	31	32	33	34	35
First Order	k_r	5.76	5.68	5.06	6.92	6.45	8.51
	r^2	0.936	0.926	0.925	0.936	0.903	0.967
Zero Order	k_r^o	19.3	19.7	16.9	21.5	20.9	32.6
	r^2	0.951	0.943	0.943	0.955	0.928	0.980
Hixson-Crowell	rate	2.22	2.21	1.95	2.60	2.46	3.42
	r^2	0.941	0.932	0.932	0.943	0.912	0.972
$Q \rightarrow \sqrt{t}$	slope	2.25	1.67	1.57	2.26	2.16	3.11
	r^2	0.876	0.879	0.870	0.898	0.845	0.942
Higuchi Eq.	slope	13.9	13.0	12.2	19.6	16.6	25.7
	r^2	0.873	0.854	0.853	0.870	0.822	0.913
Tablet Area	cm^2	3.84	5.06	4.96	4.31	4.30	4.81
Flow Rate	ml/min	5.83	5.6	4.4	5.4	5.7	4.8
Flow Velocity	cm/min	1.86	1.79	1.41	1.73	1.80	1.53
Cell Load	mg/cm^2	141	143	141	140	140	179

TABLE 3. Release and Dissolution Parameters (Rotating Bottle)[a]

Group		I			II			
Formulation No.		11	12	13	21	22	23	24
First Order	k_r	3.72	6.48	8.51	27.9	29.3	51.6	31.5
	r^2	0.944	0.927	0.937	0.892	0.930	0.863	0.934
Zero Order	k_r^o	13.7	20.5	23.5	42.3	43.6	41.7	47.3
	r^2	0.949	0.941	0.953	0.957	0.977	0.971	0.963
Hixson-Crowell	rate	1.48	2.45	3.07	8.04	8.38	11.3	9.00
	r^2	0.946	0.932	0.943	0.922	0.955	0.931	0.953
$Q \rightarrow \sqrt{t}$	slope	1.65	2.54	2.81	5.48	5.59	5.41	5.51
	r^2	0.885	0.870	0.888	0.896	0.939	0.932	0.927
Higuchi Eq.	slope	6.92	18.6	27.9	123	131	194	140
	r^2	0.913	0.886	0.900	0.873	0.919	0.909	0.925
Tablet Area	cm^2	4.04	3.90	4.06	3.76	3.90	3.80	4.30

[a]Nomenclature as in Table 2 .

TABLE 3. continued

Group		II	III				
Formulation No.		25	31[a]	32	33	34	35
First Order	k_r	28.8	21.5	19.2	49.8	56.1	72.8
	r^2	0.935	0.998	0.974	0.939	0.787	0.989
Zero Order	k_r^o	43.8	27.3	33.9	41.1	48.0	46.5
	r^2	0.971	0.987	0.966	0.952	0.923	0.980
Hixson-Crowell	rate	8.31	5.95	5.91	1.13	13.1	15.7
	r^2	0.953	0.999	0.974	0.955	0.833	0.999
$Q \rightarrow \sqrt{t}$	slope	5.75	2.38	3.46	4.52	4.54	3.69
	r^2	0.933	1.00	0.966	0.950	0.862	0.997
Higuchi Eq.	slope	1.30	103	90.0	202	235	275
	r^2	0.923	0.999	0.969	0.939	0.804	0.999
Tablet Area	cm^2	3.81	5.02	4.92	4.31	4.30	4.84

[a]This run was carried out for 5.5 hrs.

TABLE 4. Blood Levels of Subject 2 with Formulation 33.

t[a]	0.43	0.67	1.03	1.52	2.22	3	4.1	6.05	8.09
c[b]	41.8	51.3	32.8	90.6	46.5	52.5	37.6	17.6	34.9

[a]hrs.; [b]μg/ml.

Zero order and first order dissolution rate parameters obtained with formulation 33 were among the highest. The values obtained from the two dissolution systems are quite different. Although some are lower than the target values, the main difficulty here is that, we really dont know how much these in vitro systems mirror the in vivo situation. We concluded that, we might be in the ballpark with formulation No. 33. In order to get a better picture of the in vivo profile, we administered this formulation to subject No. 2[f] orally and obtained the blood levels in Table 4.

It is seen that, the blood level was around the target values for the eight hour period. These results were considered satisfactory for the main purpose of our study and work was directed towards making the final formulation with the initial dose. So, formulation 35 was made by adding the initial dose to No. 33. For this end, the drug was granulated with simple syrup and NaCl was employed as the disintegrant. In this fashion, initial and sustaining granules were compressed together as a double-layered tablet.

[f]This was one of the subjects used in the study for determining the pharmacokinetics of sulfamethizole(3, 7).

DISCUSSION

Formulation Studies : We worked with a fast and slow releasing type of polymethylmethacrylate. In the early part of the work, we employed both of these polymers in the ratio of 1:1. In order to obtain the relatively higher target release rates, we used only the faster releasing type (PMM I) in the last part.

In formulation Group I, the polymer was incorporated into the powder mixture, as well as also being used as a binder in solution. In this fashion, very hard and suitable tablets were obtained. This method however, did not produce the desired high release rates. Insoluble fillers like talc and calcium carbonate adversely affected the dissolution rate.

In formulation Group II, the polymer was used only in solution form as the binder. The incorporation of lactose and sodium chloride into the formulation was carried out in order to increase the release rate. These did not produce a significant improvement.

In the third group of formulations, direct compression was the method employed. Tablets of good quality were produced in this way. In order to increase the release rate, sodium chloride was incorporated into the formulation. It was found that the amount used was critical. Used in the proper amount, sodium chloride increased the porosity of the matrix by fast dissolution, which increased the release rate. As a final experiment, drug powder which was less than 37 μm in size was used. This, however, did not produce a significant change in dissolution.

Release and Dissolution Studies : During the preliminary work for determining the operational parameters of the flow-through cell, distilled water with 0.05 % polysorbate 80 was employed as the dissolution medium. The flow rate was varied from 6 to 20 ml/min. The results obtained with nine formulations were assessed kinetically for first, zero order and Hixson-Crowell kinetics. Highest r^2s were obtained with 6 ml/min. Tingstad et al. suggests using lower flow rates to mimic the in vivo environment(26,27). Since we also got better fit with the lower flow-rate, that value was adopted throughout the study. Actual flow rate obtained was calculated at the end of each run from the volumes of the dissolution media collected and appear in Table 2.

Upon checking the kinetic fits, it is seen that zero-order results are better than the others. First order and Hixson-Crowell fits follow. The fits for inert matrix equations (Eq.s 3-6). are not as good. We believe, this dicsrepancy comes from the fact, that the Higuchi equations are derived either for planar surfaces or for spherical pellets whereas our tablets were cylindirical in shape. In addition to this, we employed dissolution fluids of varying pHs, which resulted in different solubilities. During some runs done with the rotating bottle, we noticed some erosion of the tablets. This necessarily changes the physical parameters of the tablet, which may contribute to the deviations observed.

One of the assumptions made in the simplification of the Hixson-Crowell equation is sink condition. We believe, the flow-through cell is much better in this respect than the rotating

bottle, because in some runs with the latter, we determined that the concentration rose as much as 60 % of the solubility; especially at pH 4.5 where sulfamethizole dissolves least.

When the parameters obtained from the two dissolution systems are compared, it is seen that the rotating bottle apparatus gives higher values in all the kinetics. This is quite understandable, since the agitation rate is much higher in the latter.

The parameters obtained from kinetic fits are obviously apparent rates, since we do not know at this moment what the actual in vivo rates are. However, they are quite suitable for comparison purposes and serve useful guides in formulation studies.

CONCLUSION

We conclude that, polymethylmethacrylate is a suitable polymer for sustained release sulfamethizole inert matrix tablets. In a follow-up article, results of in vivo testing of formulation 35 will be presented.

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