DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(7), 1171-1196 (1987)

PHARMACOKINETICS OF SULFISOXAZOLE SOLID DISPERSIONS IN RABBITS

M.A.Kassem[A], M.S. El Ridy[A] and L.M. Khairy[B]

A Laboratory of Pharmaceutical Sciences, National Research Centre, Dokki, Cairo, Egypt.

B El-Nile Co. for Pharmaceuticals, Cairo, Egypt.

ABSTRACT

The approach of solid dispersion was found useful for optimizing the pharmacokinetics of sulfisoxazole in Rabbits. This was illustrated on the example of bicomponent solid dispersions containing water-soluble, urea and pvp 25000 , and water insoluble, DCA and GMS, carriers. The effect of the type and concentration of the inert carrier was investigated and found to influence the pharmacokinetic parameters studied to different extents. The multicomponent (Tri and quaternary) solid dispersions implied different effects on the pharmacokinetics of sulfisoxazole according to the nature and the proportion of the carrier used. Dispersing sulfisoxazole in the solid state in innert carriers such as GMS, DCA, urea and PVP was shown to influence significantly the dissolution rate of the drug to different extents. Dispersion of sulfisoxazole in soluble carriers resulted in significant enhancement of the dissolution rate whatever the equipment used. Correlation of sulfisoxazole in-vitro dissolution rate parameters, D.E. and $t_{75\%}$, to the pharmacokinetic parameters revealed no or very poor correlation. However, the $t_{75\%}$ parameter by the USP disintegration tester may be considered to exhibit the most reasonable correlation to the pharmacokinetic parameter K_e.

INTRODUCTION

Sulfisoxaxole tablets are on the FDA list of drugs presenting actual or potential bioequivalence problems (1). Several comparative bioavailability studies on sulfisoxazole tablets have been published (2-4). More recently, a study of the bioavailability of sulfisoxazole in experimental animals (5,6), was performed and proved excellent correlation to the bioavailability data obtained in human subjects. This was more thoroughly investigated by Reimerdes and Thumin (7), who stated that the metabolism of sulfonamides in animals and humans was the same. Although the metabolism, distribution and elimination of sulfisoxazole, as well as the bioavailability of several sulfisoxazole commercial products have been throughly investigated (8) few investigations have been undertaken to examine drug pharmacokinetics when dispersed in inert carriers (9) . Here, the effect of solid dispersing suflisoxazole, in soluble and insoluble carriers, on the pharmacokinetics of the drug in rabbits was considered.

The dissolution behaviour of the solid dispersions was investigated and an attempt was made to correlate in-vitro parameters to in-vivo ones.

MATERIALS AND METHODS

Materials: Pharmaceutical grades of sulfisoxazole (Roche, France), Dehydrocholic acid (DCA), glyceryl monostearate (GMS) Pure, Emery Industries USA, urea and PVP, Mol.Wt. 25000-30000, (Hoechst, West Germany).

Apparatus: Beckman spectrophotometer model (S_{25}). USP XIX disintegration tester, USP XIX dissolution rate tester (Hanson Research corporation). Sartorius solubility simulator (Sartorius Company).

METHODS

Assessment of the Bioavailability of Sulfisoxaxole in Rabbits:

Bioavailability studies were conducted on randomized groups, 6, each of male Albino rabbits. Particulars of the

animals as well as other experimental conditions are the same as those previously published (10). The colourimetric method of Bratton and Marshall (11) was employed for the determination of the free unmetabolized sulfisoxazole present in the plasma.

Dosage Regimen: for each sulfisoxazole preparation, a group of six animals was used with a fortnight washout period between each use, the animals were fasting overnight. The administration of each sulfisoxazole preparation was based on a crossover sequence designed to minimize the influence of any residual or cumulative effects of preceding doses (12). A single dose of 100 mg sulfisoxazole or its equivalent of solid dispersion/kg body weight was administered orally in capsules. 2 ml blood samples were withdrawn from each rabbit just prior to and 1,2,3,4,5,7,8,9,18,20 and 22 hours after capsule ingestion. The blood level curves were plotted, each, representing the mean of 6 animals. These were the basis for the computation of the pharmacokinetic parameters.

Preparation of Sulfisoxazole Solid Dispersions:

Sulfisoxazole solid dispersions in DCA, G.M.S, and PVP were prepared by the solvent method using absolute ethanol as a solvent. The sieve fraction , <63 µm, of these dispersions was used in the bioavailability studies.

Dissolution Rate measurement:

These measurements were performed using the USP disintegration tester (13), the USP XIX dissolution method (14), and the Sartorius solbuility simulator. In the three methods,sampling of 5 ml portions of thedissolution medium , 1:12.5 HCl kept at 37 ± 0.5° throughout the dissolution run, was carried out at definite time intervals, replacing the volume withdrawn with fresh dissolution medium. Sulfisoxazole was measured spectrophotometrically at 267 nm after suitable dilution.

RESULTS AND DISCUSSION

Pharmacokinetics of sulfisoxazole:

Semilogarithemic plots of the plasma concentration of sulfisoxazole are presented in Figure 1 and the pharmacokinetic

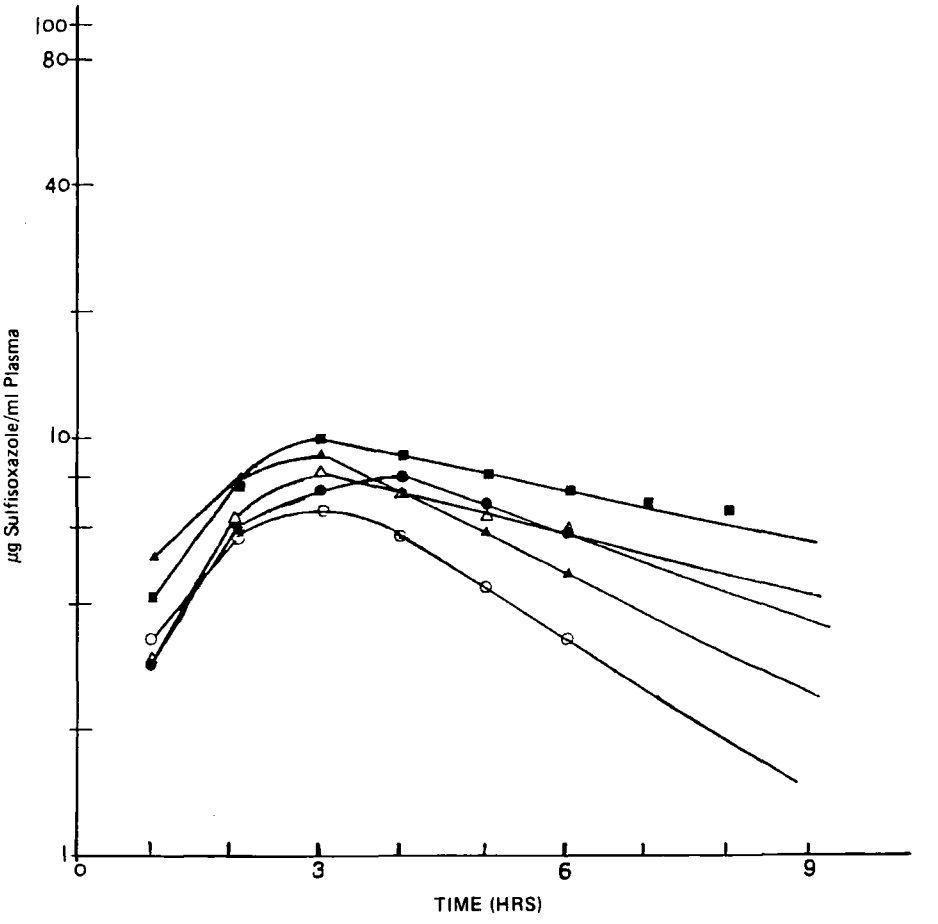

FIGURE 1

Mean plasma Sulfisoxazole Concentration, after Oral Administration of Bicomponent Solid Dispersions (100 mg Equivalent Sulfisoxazole/ kg Rabbit). Key: △ Sulfisoxazole:GMS.(96:4), ▲ Sulfisoxazole:Urea (96:4), ◐ Sulfisoxazole: DCA (96:4), ■ Sulfisoxazole:PVP (96:4), ● Sulfisoxazole Powder.

parameters are summarized in Table 1. The pharmacokinetic data obtained recall the findings of Kaplan et al.,(4) and those of Van Petten et al., (15), both on human subjects, who discovered a delayed peak blood level (observed) for sulfisoxazole at 2-3 hours as compared with that from oral solution (30 minutes).

Table (1)

Pharmacokinetic Parameters for Sulfisoxazole Biocomponent Solid Dispersions.

Parameter	Sulfisoxazole Powder	Bicomponent Solid Dispersions (96:4)			
		Sulfisoxazole/ GMS	Sulfisoxazole/ DCA	Sulfisoxazole/ Urea	Sulfisoxazole/ PVP
ABSORPTION					
K_a (hr^{-1})	0.82	0.92	1.04	1.19	1.12
$t_{1/2}$ (hours)	0.84	0.75	0.67	0.58	0.62
lag time (min)	38.62	33.10	32.30	32.50	35.30
t_{max} (hours)	2.55	2.63	1.90	1.70	2.33
C_{max} (µg/ml)	87.53	83.27	83.36	120.33	103.01
Intercept (µg/ml plasma)	141.14	110.68	125.68	176.75	130.01
ELIMINATION					
K_e (hr^{-1})	0.15	0.11	0.22	0.22	0.09
$t_{1/2}$ (hours)	4.76	6.40	3.22	3.13	7.43
BIOAVAILABILITY					
Auc $\int_0^\infty \cdot Ke$	105.48	94.50	92.50	117.31	114.40
Auc $\int_0^6 \cdot Ke$	49.40	36.70	57.92	70.32	57.73

Pharmacokinetics of sulfisoxazole solid dispersions:

Sulfisoxazole bicomponent solid dispersions were investigated as regards the effects of type of inert carrier and matrix concentration, on drug pharmacokinetics, It is evident, Figure (1), that the pharmacokinetics of sulfisoxazole is affected markedly by the type of the dispersing agent used. Thus, for sulfisoxazole-GMS solid dispersion the absorption rate was enhanced compared to that of the plain drug. The elimination rate and extent of absorption were slightly decreased. Sulfisoxazole-DCA solid dispersion exhibited an enhancing effect on the absorption and elimination rate constants and a suppressing effect on the extent of absorption relative to sulfisoxazole powder (Table 1). On the other hand, dispersion of sulfisoxazole in urea resulted in an increase in the absorption and elimination rate constants and in the extent of absorption of the drug. Sulfisoxazole urea solid dispersion can thus be expected to exhibit the optimum effectiveness compared to the other bicomponent solid dispersions investigated.

Sulfisoxazole-PVP solid dispersions were considered as regards the relevance of the matrix concentration in the dispersion system to the pharmacokinetics of the drug.Mean plasma concentrations for the three systems, containing 2,4 and 8% PVP, were plotted on semi-logarithmic paper, Figure (2). The pharmacokinetic parameters computed are presented in Table (2). The data obtained reveal marked differences in the parameters values with change in the carrier ratio. Thus, the absorption extent, maximum plasma levels, and maintenance of sulfisoxazole ($t_{\frac{1}{2}}$) for PVP solid dispersions were increased proportional to PVP concentration. However, the absorption rate constant and the time of maximum concentration were more favourable for the 4% PVP solid dispersion.

Figure (3) shows,in semi- logarithmic presentation,the mean plasma levels versus time for sulfisoxazole - GMS- DCA tri-component solid dispersions. The ternary solid dispersions investigated, exhibited increased peak concentrations,marked change in elimination rates and improved absorption extent relative to the plain drug powder. The Pharmacokinetic

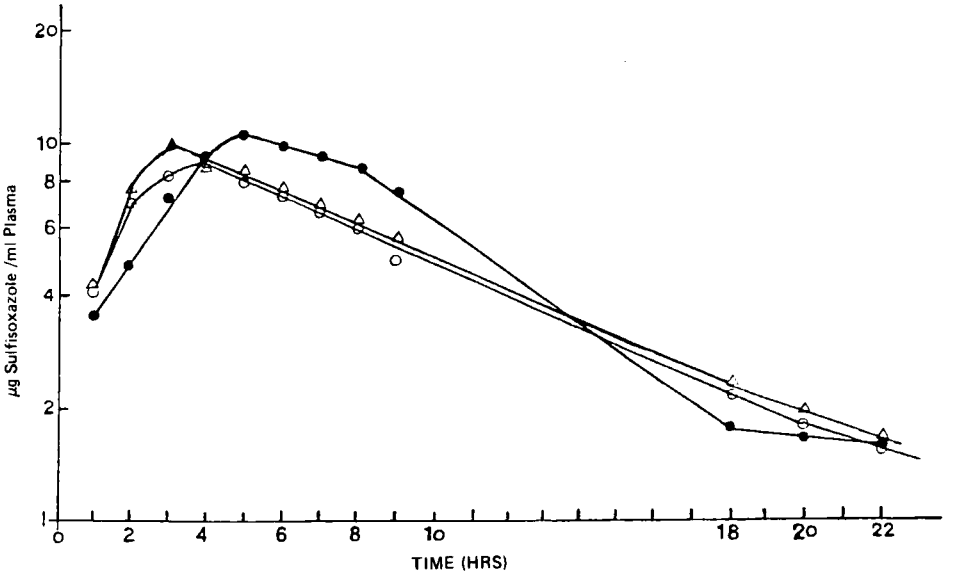

FIGURE 2

Mean Plasma Sulfisoxazole Concentration,after Oral Administration of Sulfisoxazole:PVP Solid Dispersion (100 mg Equivalent Sulfisoxazole/kgRabbit). Key:Sulfisoxazole:PVP ● (98:2), ○ (96:4), ▲ (98:2).

parameters for these solid dispersions indicate that, the composition 80:18:2 exhibited the best absorption characteristics (in terms of absorption rate constant, maximum blood level and extent of drug absorption) and the least elimination half-life. Figure (3) and Table (3) show the mean plasma concentration of sulfisoxazole quarternary solid dispersion (sulfisoxazole: GMS: DCA: PVP, 80:12:3:5) and its pharmacokinetic parameters. The results reveal a suppressed absorption rate constant compared to the drug powder perse, while the absorption extent, and peak concentration were highly increased. However, the elimination half-life of the drug from this solid dispersion was markedly prolonged , resulting in excellent maintenance of the drug in the blood circulation.

Table (2)

Pharmacokinetic Parameters for Sulfisoxazole/PVP Solid Dispersions.

Parameter	Sulfisoxazole powder	Sulfisoxazole : PVP Solid Dispersions		
		(98 : 2)	(96 : 4)	(92 : 8)
ABSORBTION				
K_a (hr^{-1})	0.82	1.00	1.12	0.62
$t_{1/2}$ (hours)	0.84	0.69	0.62	1.11
lag time (mins)	38.62	22.25	25.33	23.50
C_{max} (µg/ml)	87.53	101.91	103.70	111.35
t_{max} (hours)	2.55	3.10	2.33	3.55
Intercept	141.14	131.44	132.00	144.63
ELIMINATION				
K_e (hr^{-1})	0.15	0.10	0.09	0.06
$t_{1/2}$ (hours)	13.75	20.16	21.42	10.75
BIOAVAILABILITY				
Auc ∞ K_e (µg/ml) hr.	105.48	111.90	114.43	123.94
Auc $^{6}_{0}$ K_e	49.40	58.08	57.93	60.53

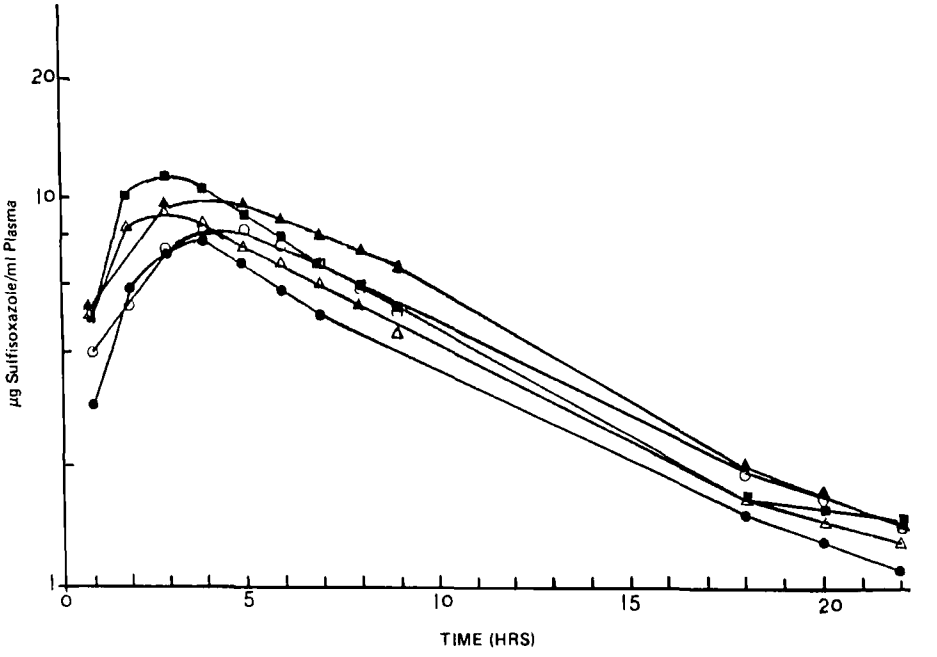

FIGURE 3

Mean Plasma Sulfisoxazole levels,after Oral Administration of Multi-Component Solid Dispersion (100 mg Equivalent Sulfisoxazole/kg Rabbit). Key: ● Sulfisoxazole Powder,Sulfisoxazole:GMS:DCA:PVP Solid Dispersion ○ (90:8:2), △ (90:6:4), ■ (80:18:2), ▲ (80:12:3:5).

In an attempt to select the formula of expected optimum effectiveness, it would be plausible to compare the sulfisoxazole dispersions according to pharmacokinetic parameters. Accordingly, sulfisoxazole: urea (96:4) solid dispersion exhibits the most enhanced absorption rate and ranks second with regard to the absorption extent parameter following the ternary solid dispersion sulfisoxazole: GMS: DCA (80:18:2). The latter solid dispersion exhibited a markedly elevated peak (C_{max}) and at the same time an enhanced t_{max} parameter of two hours. As far as the elimination characteristics of these solid dispersions are concerned, sulfisoxazole: GMS:DCA: PVP (80:12:3:5) exhibited the highest elimination rate constant (K_e).

Table (3)

Pharmacokinetic Parameters for Sulfisoxazole Multicomponent Solid Dispersions

Parameters	Sulfisoxazole powder	Sulfisoxazole Multicomponent Solid Dispersions			
		Sulfisoxazole GMS:DCA (90:8:2)	Sulfisoxazle GMS:DCA (80:18:2)	Sulfisoxazole GMS:DCA (90:6:4)	Sulfisoxazole GMS:DCA:PVP (80:12:3:5)
ABSORPTION					
K_e (hr^{-1})	0.82	0.56	1.15	1.05	0.78
$t_{1/2}$	0.84	1.23	0.60	0.66	0.88
lag time(mins)	38.62	32.93	37.56	21.62	18.70
C_{max} (ug/ml)	87.53	93.77	142.41	104.21	113.39
t_{max} (hours)	2.55	3.85	2.09	2.38	3.17
Intercept	141.14	133.80	186.73	136.63	148.67
ELIMINATION					
K_e (hr^{-1})	0.15	0.09	0.14	0.11	0.08
$t_{1/2}$ (hours)	4.76	7.49	4.98	6.10	8.12
BIOAVAILABILITY					
Auc $\overline{C}_0 \cdot K_e$ (ug/ml) hr	105.48	110.20	218.06	135.39	115.04
Auc $C_0^6 \cdot K_e$	49.40	47.10	98.11	68.44	59.87

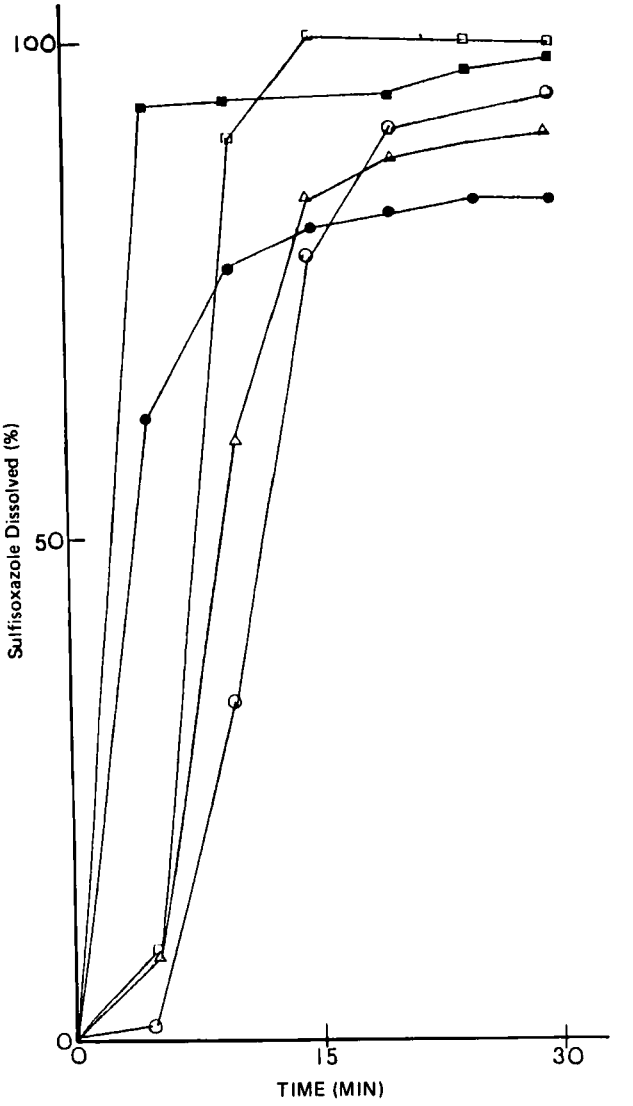

FIGURE 4

Dissolution Rate of Sulfisoxazole Bicomponent Solid Dispersions (USP Dissolution Method).

Key: ● Sulfisoxazole Powder, ◘ Sulfisoxazole:Urea (96:4), ■ Sulfisoxazole: PVP (96:4), ▲ Sulfisoxazole:DCA (96:4), ◘ Sulfisoxazole:GMS (96:4)

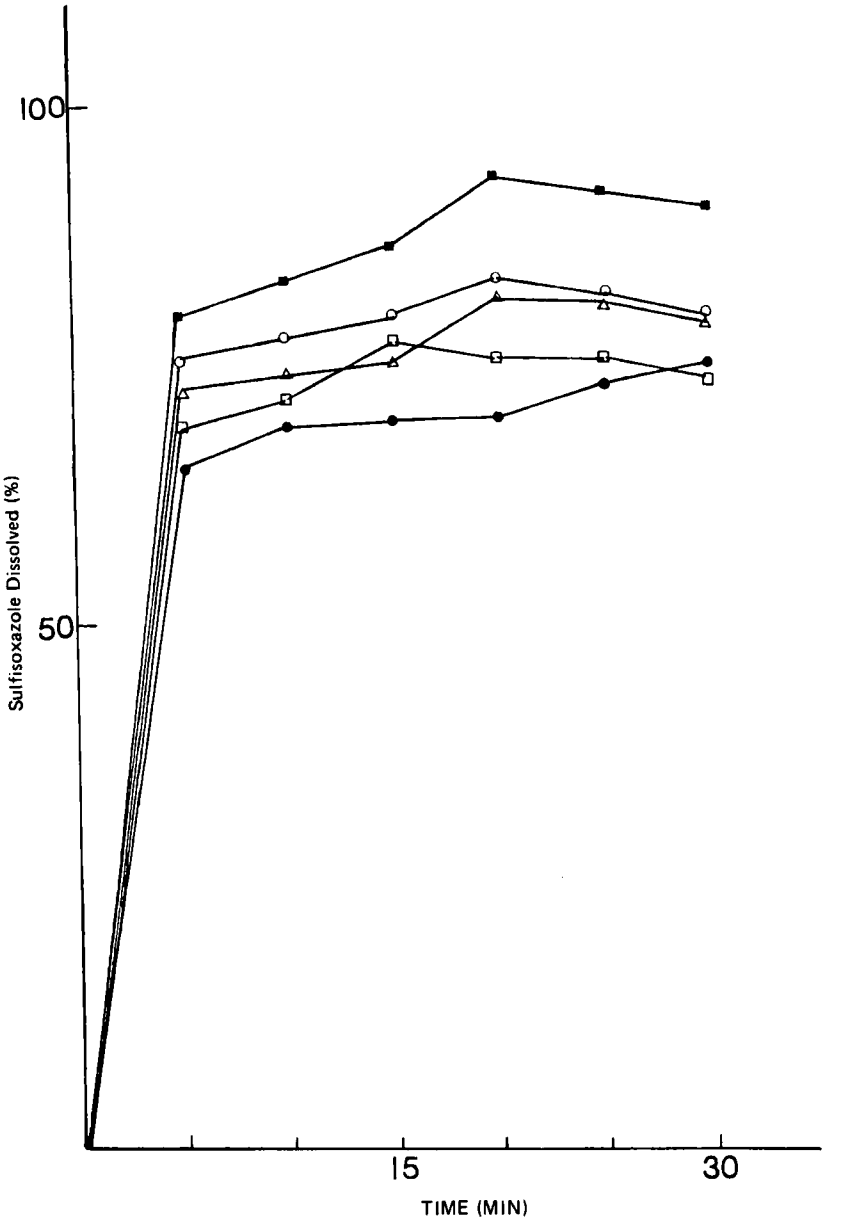

FIGURE 5

Dissolution Rate of Sulfisoxazole Bicomponent Solid Dispersions (USP Disintegration Method).

Key: ● Sulfisoxazole Powder, ◆ Sulfisoxazole:GMS (96:4), ▲ Sulfisoxazole: DCA(96:4), ■ Sulfisoxazole:Urea(96:4), ■ Sulfisoxazole:PVP(96:4).

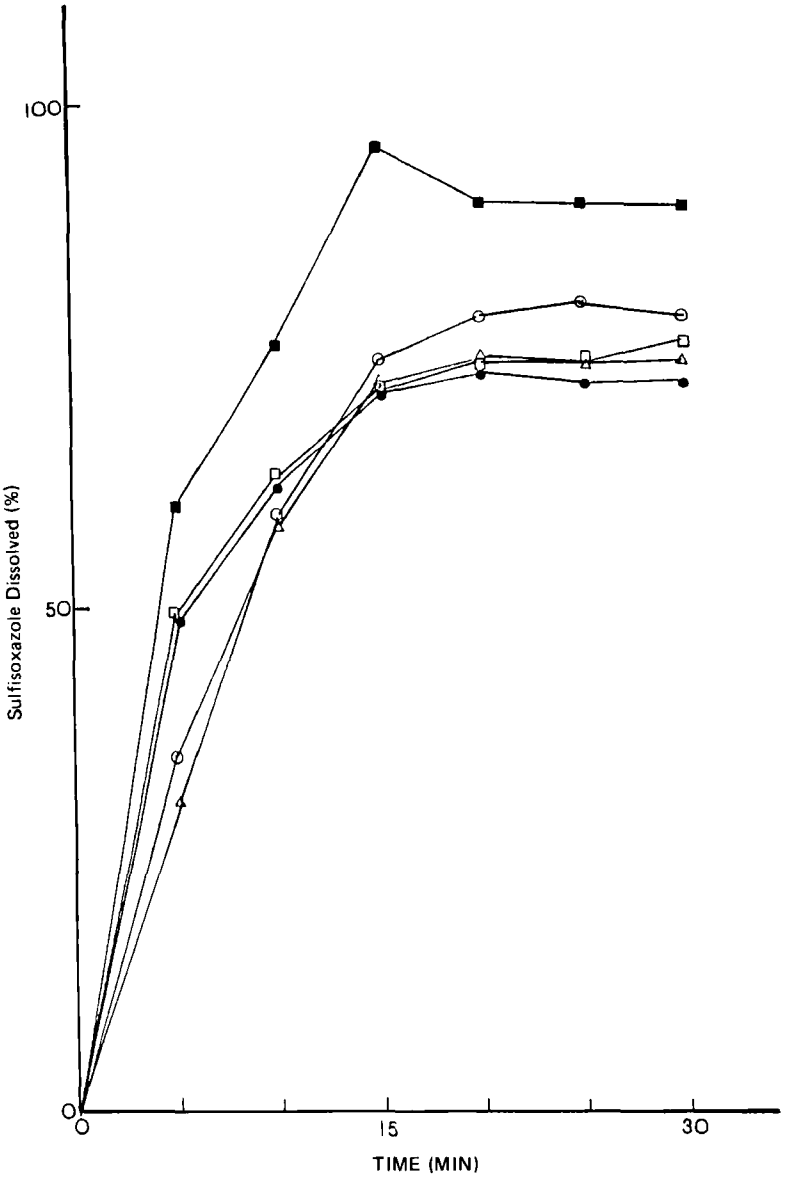

FIGURE 6

Dissolution Rate of Sulfisoxazole Bicomponent Solid Dispersions (Sartorious Solubility Simulator Method).

Key: ● Sulfisoxazole Powder, ◐ Sulfisoxazole:GMS (96:4), ▲ Sulfisoxazole: DCA (96:4), ◘ Sulfisoxazole:Urea (96:4), ■ Sulfisoxazole:PVP (96:4) .

Dissolution of Sulfisoxazole and its solid Dispersions:

The dissolution profiles of sulfisoxazole bicomponent solid dispersions, are presented in Figures 4,5 & 6. The dissolution rate of the drug is found to depend on the dissolution model itself. While the USP basket dissolution assembly revealed suppression of the dissolution for GMS solid dispersion, the other models revealed enhancement to different extents. For DCA solid dispersions a positive or negative influence may be experienced according to the model used. In the case of sulfisoxazole-urea comprecipitates, it is obvious, from the dissolution parameters D.E. and $t_{75\%}$, that the USP XIX method exhibited the best discriminating capability for the moderate enhancing effect of the urea coprecipitates. For PVP coprecipitates the dissolution rate profiles obtained by usingthe USP disintigration device agree with those obtained by the other two methods revealing significantly improved sulfisoxazole dissolution (Table 1).

Ternary solid dispersions of sulfisoxazole with GMS and DCA in the following three ratios 90:8:2, 90:6:4,80:18:2 and a quaternary solid dispersion of the same components plus PVP in the ratio 80:12:3:5, were considered. Figures 7,8 and 9 show the dissolution rate profilesof sulfisoxazole multi-component solid dispersion according to the USP disolution method, the USP disintegration device and the sartorius solubility simulator method. What should be pointed out is that the bicomponent solid dispersion, sulfisoxazole 96:PVP 4, exhibited the best D.E. and $t_{75\%}$ parameters depicted by the use of any of the 3 equipments investigated (Table 4).

The in-vitro-in-vivo correlation was attempted through the examination of the relevance of the dissolution parameters, obtained by the three dissolution methods to the pharmacokinetic parameters of sulfisoxazole assessed for rabbits. The parameters considered in this correlation are the dissolution efficiency (D.E) and $t_{75\%}$ for the in-vitro models and the following pharmacokinetic parameters for the in-vivo method: the absorption rate constant (K_a), the absorption half-time ($t_{a\frac{1}{2}}$), maximum blood level (C_{max}),time

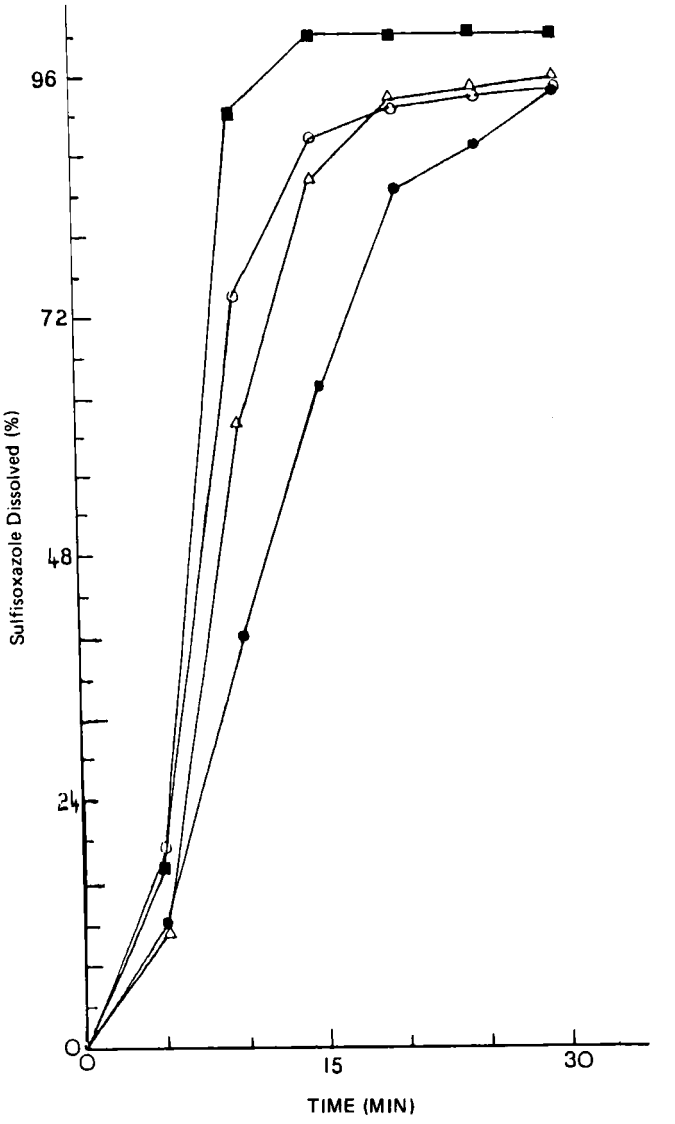

FIGURE 7

Dissolution Rate of Sulfisoxazole Multicomponent Solid Dispersions (USP Dissolution Method).

Key:Sulfisoxazole:GMS:DCA:PVP:- ○(90:8:2), ●(80:18:2), ▲(90:6:4), ■(80:12:3:5).

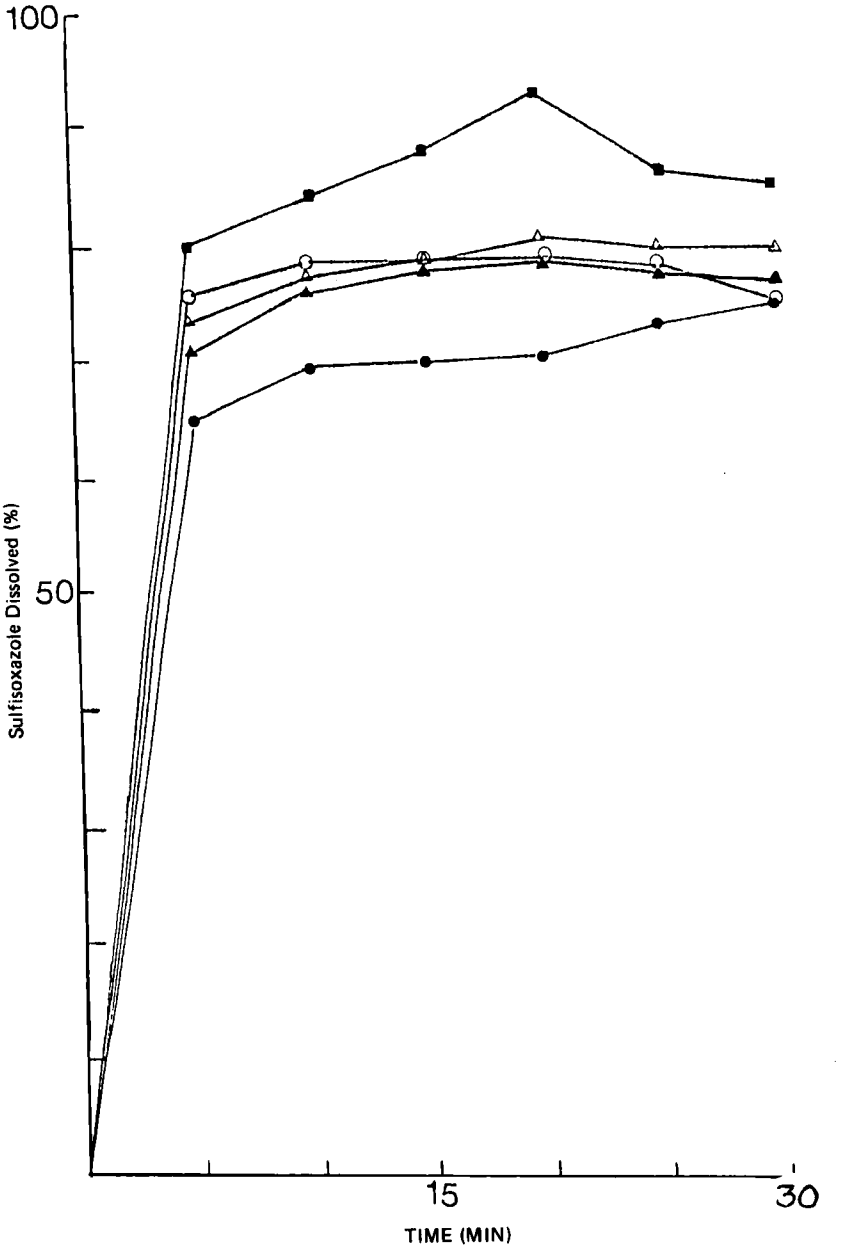

FIGURE 8

Dissolution Rate of Sulfisoxazole Multicomponent Solid Dispersions (USP Disintegration Method)

Key: Sulfisoxazole:GMS:DCA:PVP:- ○ (90:8:2:-), ▲ (80:18:2:-), △ (90:6:4:-), ■ (80:12:3:5), ● Sulfisoxazole Powder.

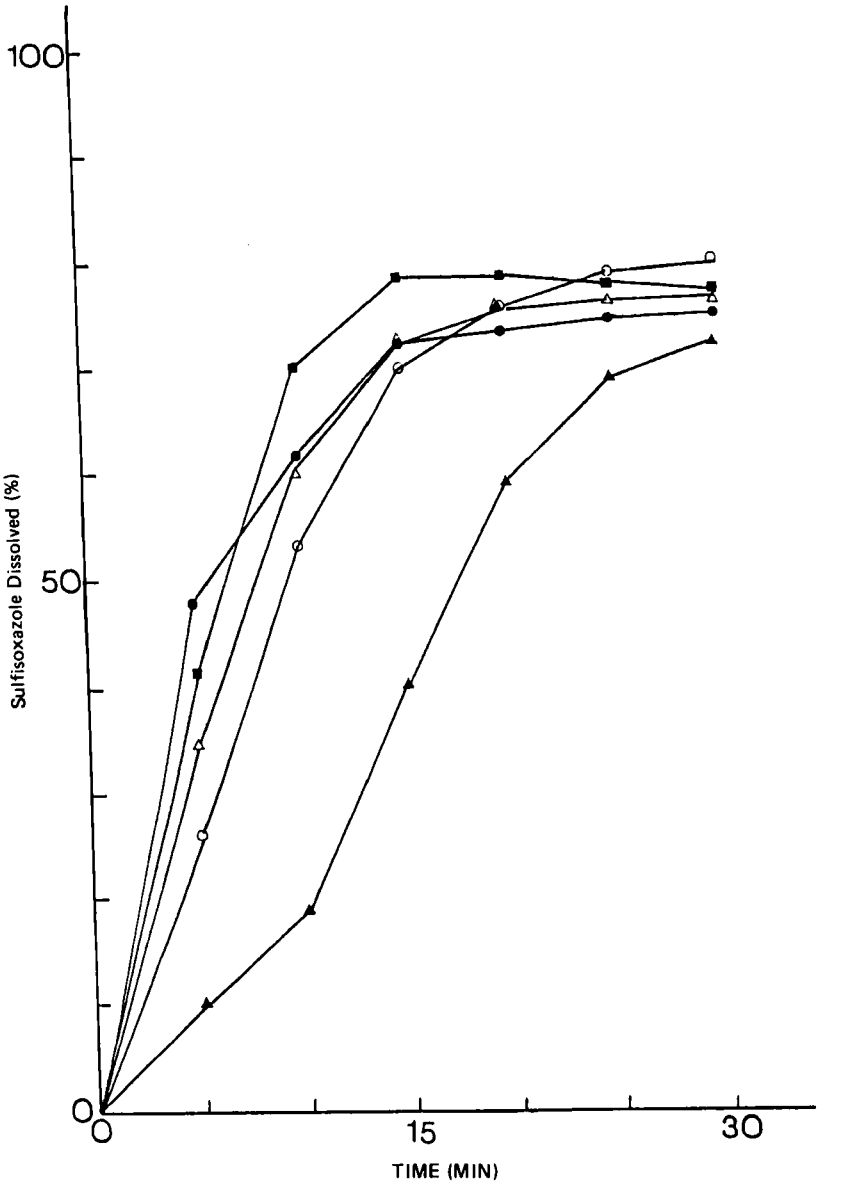

FIGURE 9

Dissolution Rate of Sulfisoxazole Multicomponent Solid Dispersions

(Sartorious Solubility Simulator Method)

Key: ● Sulfisoxazole Powder, Sulfisoxazole:GMS:DCA:PVP: ○ (90:8:2:-), ▲ (80:18:2:-), △ (90:6:4:_), ■ (80:12:3:5).

for the maximum blood level (t_{max}), the corrected area under the curve from zero to infinity (AUC $\int_0^\infty .K_e$) and the elimination rate constant (K_e).

Considering the rank order correlation on the basis of the in-vitro parameters and pharmacokinetics, it is obvious from Tables 5 & 6, that there is no direct rank order correlation between the pharmacokinetic parameters and the in-vitro dissolution ones. In the case of the dispersions with sparingly soluble matrices, the in-vitro parameters are found to give the reverse picture elicited by the pharamacokinetic parameters especially with regards to the absorption rate and extent.

On the basis of the correlation coefficient computed for the different parameters, it is obvious that there is no fair correlation between the pharmacokinetic parameters and the in-vitro parameters D.E. and $t_{75\%}$ for any of the three dissolution models investigated (Tables 7 & 8). The presentation of the same parameters considered in Tables 7 & 8, with the exception of sulfisoxazole powder per se, whichproved to occupy an odd position, gives rise to the correlation presented in Table 9. On the other hand,this table reveals an interesting finding which reflects an excellent correlation with a coefficient 0.98467 between the in-vitro dissolution parameter $t_{75\%}$ obtained by the USP disintigration tester and the pharmacokinetic parameter K_e.

Thus, dissolution, would be an interesting parameter for comparisons within one and the same system, however its value is rather limited in comparisons of different systems especially those containing drug carriers of variable solubility. In-vitro discrimination between different systems on the basis of their dissolution rate may thus lead to the unjustified exclusion of systems having better in-vivo performance though exhibiting lower in-vitro dissolution rate. This is best examplified by the sulfisoxazole multicomponent solid dispersion,sulfisoxazole: GMS: DCA (80:18:2), which performs best in-vivo and worst in-vitro

Table (4)

Values of D.E. and $t_{75\%}$ for sulfisoxazole powder, Bi- and Multicomponent solid Dispersions.

Sulfisoxazole Preparation	Dissolution Method					
	U.S.P. Dissolution		U.S.P. Disintegrator		Saratorius Solubility Simulator	
	D.E. (%)	$t_{75\%}$ (min)	D.E. (%)	$t_{75\%}$ (min)	D.E. (%)	$t_{75\%}$ (min)
Sulfisoxazole powder	73.40	9.50	66.00	30.00	63.30	29.50
Sulfisoxazole:GMS (96:4)	62.50	14.75	74.10	5.00	66.60	15.50
Sulfisoxazole: DCA (96:4)	66.20	13.00	71.70	13.00	60.40	20.00
Sulfisoxazole:Urea (96:4)	78.40	9.25	68.60	13.00	63.90	26.30
Sulfisoxazole:PVP25,000 (96:4)	89.20	4.00	81.00	4.75	79.90	9.75
Sulfisoxazole:GMS:DCA (90:8:2)	73.10	10.50	71.90	5.00	58.70	20.00
Sulfisoxazole:GMS:DCA (90:6:4)	70.20	12.75	72.80	7.50	62.00	19.00
Sulfisoxazole:GMS:DCA (80:18:2)	61.90	17.75	79.80	4.65	66.00	13.00
Sulfisoxazole:GMS:DCA:PVP (80:12:3:5)	80.10	99.00	71.10	9.00	43.60	30.00

Table (5)

Rank Order Correlation of Sulfisoxazole solid Dispersions with regards to the In-Vitro Dissolution Parameter (D.E.).

USP Dissolution Method		USP Disintegrator Method		Sartorius Solubility Simulator Method	
1	Sulfisoxazole : PVP (96:4)	1	Sulfisoxazole:PVP (96:4)	1	Sulfisoxazole:PVP (96:4)
2	Sulfisoxazole:GMS:DCA:PVP (80:12:3:5)	2	Sulfisoxazole:GMS:DCA:PVP (80:12:3:5)	2	Sulfisoxazole:GMS (96:4)
3	Sulfisoxazole:Urea (96:4)	3	Sulfisoxazole:GMS (96:4)	3	Sulfisoxazole:GMS:DCA:PVP (80:12:3:5)
4	Sulfisoxazole Powder	4	Sulfisoxazole:GMS:DCA (90:6:4)	4	Sulfisoxazole:Urea (96:4)
5	Sulfisoxazole:GMS:DCA (90:8:2)	5	Sulfisoxazole:GMS:DCA (90:8:2)	5	Sulfisoxazole Powder
6	Sulfisoxazole:GMS:DCA (90:6:4)	6	Sulfisoxazole:DCA (96:4)	6	Sulfisoxazole:GMS:DCA (90:6:4)
7	Sulfisoxazole:DCA (96:4)	7	Sulfisoxazole:GMS:DCA (80:18:2)	7	Sulfisoxazole:DCA (96:4)
8	Sulfisoxazole:GMS (96:4)	8	Sulfisoxazole:Urea (96:4)	8	Sulfisoxazole:GMS:DCA (90:8:2)
9	Sulfisoxazole:GMS:DCA (80:18:2)	9	Sulfisoxazole Powder	9	Sulfisoxazole:GMS:DCA (80:18:2)

Table (6)

Rank Order Correlation of Sulfisoxazole Solid Dispersions with Regards to Different Pharmacokinetic Parameters.

Ka	$C_{(max)}$	T_{max}	AUC $\int_0^\infty$.Ke	Ke
1. Sulfisoxazole:Urea (96:4)	1. Sulfisoxazole:GMS: DCA (80:18:2)	1. Sulfisoxazole: Urea(96:4)	1. Sulfisoxazole: Urea(60:18:2)	1. Sulfisoxazole: GMS:DCA:PVP (80:12:3:5)
2. Sulfisoxazole:GMS: DCA:(80:18:2)	2. Sulfisoxazole:Urea (96:4)	2. Sulfisoxazole: DCA (96:4)	2. Sulfisoxazole: Urea(96:4)	2. Sulfisoxazole: GMS:DCA (90:8:2)
3. Sulfisoxazole:PVP (96:4)	3. Sulfisoxazole:GMS: DCA:PVP (80:12:3:5)	3. Sulfisoxazole: GMS:DCA (80:18:2)	3. Sulfisoxazole: Urea(96:4)	3. Sulfisoxazole: PVP(96:4)
4. Sulfisoxazole:GMS: DCA (90:6:4)	4. Sulfisoxazole:GMS: DCA (90:6:4)	4. Sulfisoxazole: PVP (96:4)	4. Sulfisoxazole: GMS:DCA:PVP (80:12:3:5)	4. Sulfisoxazole: GMS (96:4)
5. Sulfisoxazole:DCA (96:4)	5. Sulfisoxazole:PVP (96:4)	5. Sulfisoxazole: GMS:DCA (90:6:4)	5. Sulfisoxazole: (96:4)	5. Sulfisoxazole: GMS:DCA (80:18:2)
6. Sulfisoxazole:GMS	6. Sulfisoxazole:GMS: DCA (90:8:2)	6. Sulfisoxazole:	6. Sulfisoxazole: GMS:DCA (90:8:2)	6. Sulfisoxazole: GMS:DCA (80:18:2)
7. Sulfisoxazole: Powder	7. Sulfisoxazole: Powder	7. Sulfisoxazole: GMS(96:4)	7. Sulfisoxazole Powder	7. Sulfisoxazole: Powder
8. Sulfisoxazole:GMS DCA:PVP (80:12:3:5)	8. Sulfisoxazole:DCA (96:4)	8. Sulfisoxazole: GMS:DCA:PVP (80:12:3:5)	8. Sulfisoxazole: (96:4)	8. Sulfisoxazole: DCA (96:4)
9. Sulfisoxazole:GMS: DCA (90:8:2)	9. Sulfisoxazole:GMS (96:4)	9. Sulfisoxazole: GMS:DCA (90:8:2)	9. Sulfisoazole: (96:4)	9. Sulfisoxazole: Urea (96:4)

Table (7)

Correlation of Dissolution Efficiency (Vitro) to the Pharmacokinetics of Different Sulfisoxazole Capsule Preparations.

Parameters	Correlation Coefficient (r)	Parameters	Correlation Coefficient (r)	Parameters	Correlation Coefficient (r)
D.E./k_a (USP Dissolution)	0.01864	D.E./C max (USP Dissolution)	0.11368	D.E./Auc $\int_0^\infty K_e$ (USP Dissolution)	0.22280
D.E./k_a (USP Disintegrator)	0.02814	D.E./C max (USP Disintegrator)	0.09053	D.E./Aux $\int_0^\infty K_e$ (USP Disintegrator)	0.06850
D.E./k_a (Sartorius)	0.02252	D.E./C max (Sartorius)	0.42370	D.E./Auc $\int_0^\infty K_e$ (Sartorius)	0.65570
D.E./$t_{a½}$ (USP Dissolutin)	0.02553	D.E./T max (USP Dissolution)	0.09770	D.E./K_e (USP Dissolution)	0.29431
D.E./$t_{a½}$ (USP Disintegrator)	0.04760	D.E./T max (USP Disintegrator)	0.33000	D.E./K_e (USP Disintegrator)	0.67396
D.E./$t_{a½}$ (Sartorius)	0.04000	D.E./T max (Sartorius)	0.09620	D.E./K_e (Sarotorius)	0.30231

Table (8)

Correlation of Time Required for 75% Dissolution (Vitro) to the Pharmacokinetics of Different Sulfisoxazole Capsule Formulations.

Parameters	Correlation Coefficient (r)	Parameters	Correlation Coefficient (r)	Parameters	Correlation Coefficient (r)
$t_{75\%}/K_a$ (USP Dissolution)	0.11406	$t_{75\%}/C_{max}$ (USP Dissolution)	0.14530	$t_{75\%}/Auc_0^{\infty} K_e$ (USP Dissolution)	0.44090
$t_{75\%}/K_a$ (USP Disintegrator)	0.0 3799	$t_{75\%}/C_{max}$ (USP Disintegrator)	0.23273	$t_{75\%}/Auc_0^{\infty} K_e$ (USP Disintegrator)	0.13097
$t_{75\%}/K_a$ (Sartorius)	0.12587	$t_{75\%}/C_{max}$ (Sartorius)	0.28950	$t_{75\%}/Auc_0^{\infty} K_e$ (Sartorius)	0.44090
$t_{75\%}/t_{a\frac{1}{2}}$ (USP Dissolution)	0.15750	$t_{75\%}/T_{max}$ (USP Dissolution)	0.14580	$t_{75\%}/K_e$ (USP Dissolution)	0.53180
$t_{75\%}/t_{a\frac{1}{2}}$ (USP Disintegrator)	0.10706	$t_{75\%}/T_{max}$ (USP Disintegrator)	0.28040	$t_{75\%}/K_e$ (USP Disintegrator)	0.53180
$t_{75\%}/t_{a\frac{1}{2}}$ (Sartorius)	0.17455	$t_{75\%}/T_{max}$ (Sartorius)	0.36166	$t_{75\%}/K_e$ (Sartorius)	0.5225 0

Table (9)

Correlation of Time required for 75% Dissolution (Vitro) to the Pharmacokinetics of Different Sulfisoxazole Capsule preparations (Sulfisoxazole Powder is Excluded).

Parameters	Correlation Coefficient(r)	Parameters	Correlation Coefficient(r)	Parameters	Correlation Coefficient(r)
$t_{75\%}/Ka$ (USP Dissolution)	0.06744	$t_{75\%}/C_{max}$ (USP Dissolution)	0.10165	$t_{76\%}/AUC_0^{\infty}Ke$ (USP Dissolution)	0.42552
$t_{75\%}/Ka$ (USP Disintegrator)	0.54235	$t_{75\%}/C_{max}$ (USP Disintegrator)	0.14421	$t_{75\%}/AUC_0^{\infty}Ke$ (USP Disintegrator)	0.15823
$t_{75\%}/Ka$ (Sartorius)	0.25884	$t_{75\%}/C_{max}$ (Sartorius)	0.53312	$t_{75\%}/AUC_0^{\infty}Ke$ (Sartorius)	0.60619
$t_{75\%}/t_{a\frac{1}{2}}$ (USP Dissolution)	0.12931	$t_{75\%}/T_{max}$ (USP Dissolution)	0.15593	$t_{75\%}/Ke$ (USP Dissolution)	0.27948
$t_{75\%}/t_{a\frac{1}{2}}$ (USP Disintegrator)	0.48186	$t_{75\%}/T_{max}$ (USP Disintegrator)	0.82368	$t_{75\%}/Ke$ (USP Disintegrator)	0.98467
$t_{75\%}/t_{a\frac{1}{2}}$ (Sartorius)	0.20320	$t_{75\%}/T_{max}$ (Sartorius)	0.44975	$t_{75\%}/Ke$ (Sartorius)	0.63370

CONCLUSIONS :

1. The approach of solid dispersion was found useful for enhancing the pharmacokinetics of sulfisoxazole. Bicomponent solid dispersions, containing water-soluble and sparingly soluble carriers, were found to influence markedly all the pharmacokinetic parameters of the drug.
2. The multicomponent solid dispersions implied different effects on the pharmacokinetics of sulfisoxazole.
3. The USP XIX disintegration tester and the sartorius solubility simulator proved higher in-vitro- in-vivo correlation of sulfisoxazole solid dispersions, than the USP XIX dissolution method.

REFERENCES

1. "Holders of Approved Drug Applications for Drugs presenting Actual or Potential Bioequivalence Problems". New Publication No.76-3009 (FDA) (Jan.,1976).
2. Solomon, H., Drug. Inform.Bull.,3,75 (1969).
3. Martin,C.M.,Ibid, 72.
4. Kaplan, S.A., Weinfold, R.E., Abruzzo, C.W., and Lewis, M., J.Pharm.Sci.61, 773, (1972).
5. Cohen, M., and Pocelinko, R., J.Pharmac.Exp.Ther.,185, 703, (1973).
6. Garrett, E.R., SueverKrup, R.S., Eberst, K.,Yost, R.L., and O'leary,J.P, Biopharm.Drug. Dispos, 2,329,(1981).
7. Reimerdes, E., and Thumin, J.H., Arzneim-Forsch (Drug Res.) 20, 1171, (1970).
8. Oeie S., Int.J.Pharm., 3 , 311, (1979).
9. Shim, Eung-Ki, Lee, H.B., Kim, K.S., Kang, C.S., and Kim H.J., Kungnip Pogon Yon'guwonpo, 15,331,(1978).
10. Kassem , M.A., El Ridy,M.S., Gad, Z., and Khairy, L,M. Bull N.R.C., Cairo, Egypt. Accepted for Publication (1984).
11. Bratton, A.C., and Marshall, E.K., J.Biol.Chem.,128, 537, (1939).

12. Whyatt, P.L., Schyrwka, G.W.A.,Malikian,A.P., and M.C. Meyer,J.Pharm .Sci.,65, 652,(1976).

13. United States Pharmacopeia, XIX,(1975),P.650.

14. Ibid,P.83.

15. Van Petten,G.R., Becking,G.C., Withey, R.J., and Lettau, H.F. J.Clin.Pharmacol., 11, 35,(1971).
