International Journal of Pharmaceutics, 6 (1980) 155–166

COMPARISON OF IN VIVO DISSOLUTION OF SULFA DRUGS CALCULATED BY DECONVOLUTION TO ABSORPTION RATES CALCULATED BY MULTICOMPARTMENT MODEL METHOD *

NOBUTOSHI WATARI, NOBUYOSHI KANENIWA and MANABU HANANO **

*The School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku and ** The Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo (Japan)*

(Received May 6th, 1980)
(Accepted June 9th, 1980)

SUMMARY

A comparative study between in vivo drug dissolution calculated by deconvolution and absorption rate calculated by the multicompartment model method was made in rabbits, using 5 powder sulfa drugs with a solubility ranging from 0.001 to 0.1%. The semilogarithmic plots of undissolved vs time for the in vivo dissolution process, and of unabsorbed vs time for the absorption process were biphasic with convex-descending time course curves for the large particle sizes of low-solubility drugs of SDM, SD and SIX. On the other hand, for high-solubility drugs of ST and SMT, the undissolved-time course was a single line and the unabsorbed-time course was biphasic with a concave-descending curve. The rate constants of in vivo dissolution correlated well with those of absorption at a constant ratio for each drug during the initial linear portions (2–5 h), thereafter, this correlation disappeared.

There was a good particle-size dependent correlation between in vitro and in vivo dissolution rates for SDM and SD; it ceased with increasing drug solubility.

INTRODUCTION

Many reports have been published on the effect of particle size on blood level (Fincher, 1968). Particle size appreciably affected bioavailability when the solubility of sulfa drug (in distilled water at 37°C) was less than 0.1% (Kaneniwa and Watari, 1978a). In the present work, we investigated the relationship between in vivo drug dissolutions calculated by deconvolution and overall absorption rates calculated by the multicompartment model method, using powder sulfa drugs with a solubility ranging from 0.001 to 0.1%. Then we intended to elucidate what extent in vivo dissolution rate depends on the absorption rate and to elucidate the absorption process for these sulfa drugs. Further-

* This paper forms Part VII of a series entitled 'Dissolution of Slightly Soluble Drugs'.

more, we also report on the particle-size-dependent correlation between in vitro and in vivo dissolution rates.

MATERIALS AND METHODS

Materials

Powder sulfa drugs; sulfadimethoxine (SDM), sulfadiazine (SD), sulfisoxazole (SIX), sulfathiazole (ST) and sulfamethizole (SMT) used were JP grade (Table 1). The different particle sizes were obtained by sieving through a Ro-Tap testing sieve shaker, using Japan Industrial Standard (JIS) sieves. The mean diameter of the sieved particles is given as the arithmetic mean diameter of sieve opening.

Animal studies and drug administration

Male Japanese White rabbits, weighing approximately 2.5 kg were fasted for 48 h and divided at random into 5 groups of 3 or 4 animals each. Group 1 was used for SDM, group 2 for SD, group 3 for SIX, group 4 for ST and group 5 for SMT. At 1-week intervals, each group orally received 4 particle sizes of 200 mg of the sulfa drug in suspension form with 20 ml water and two administrations of aqueous solution orally and intravenously. The aqueous solution was prepared by dissolving sulfonamide sodium salt in distilled water.

Sulfa drug assay

Blood specimens (0.5 ml) were assayed as described previously (Kaneniwa and Watari, 1978a).

In vitro dissolution rate and solubility

The same apparatus and procedure (Kaneniwa and Watari, 1974) were used for the determination of the amount of sulfa drugs dissolved in the medium and of the dissolution rate.

Kinetic studies

The computer programs used were CMNLR2 (OS7 Hitachi Statistical Analysis Pro-

TABLE 1

ACID DISSOCIATION CONSTANT, MOLECULAR WEIGHT, DENSITY AND SOLUBILITY OF SULFA DRUGS

Sulfonamide	pka_1	pka_2	Mol. wt.	Density	Solubility * (mg/100 ml)
Sulfadimethoxine	2.02	6.05	310.3	1.56	4.63
Sulfdiazine	2.00	6.48	250.3	1.59	12.8
Sulfisoxazole	1.55	5.10	267.3	1.61	29.2
Sulfathiazole	2.36	7.12	255.3	1.71	87.9
Sulfamethizole	2.00	5.45	270.3	1.53	88.4

* Measured in distilled water at 37°C.

gram, 8700-7-004-02, Tokyo, Japan 1973) for non-linear regression analysis and the deconvolution program (Kiwada et al., 1977), in which the anterior phenomenon was approximated by the appropriate exponential polynomial and the deconvolution calculation was made from the posterior phenomenon by the point–area method. The absorption rate for SDM was calculated by the modified method of Loo-Riegelman (Boxenbaum and Kaplan, 1975), for SIX by the method of Loo-Riegelman (1968) due to the large distribution phase, respectively, and for SD, ST and SMT by the method of Wagner-Nelson (1963). The computation was carried out by a HITAC 8800/8700 digital computer, University of Tokyo.

RESULTS AND DISCUSSION

Comparison of in vivo dissolution to absorption rate

The effect of particle size on rabbit blood levels was appreciable, indicating that the dissolution is rate-limiting in the absorption (Kaneniwa and Watari, 1978a). In vivo drug dissolution was calculated from the deconvolution between blood levels after the administration of aqueous solution and the administration of each powder sample. The blood level after oral administration of aqueous solution was standardized as the anterior phenomenon.

Fig. 1 shows a typical integrated weight function time course of in vivo dissolution for the lowest, middle and highest solubility drug of SDM, SIX and SMT, respectively (Table 1). As seen in Fig. 1, the effect of particle size on the plateau level of integrated weight function was minimal except for SDM. The data of plateau level for the integrated weight function value correlated with the data of the area under the blood concentration–time curve (AUC) and of the urinary excretion ratio (parent plus acetylated sulfonamide) reported previously (Kaneniwa and Watari, 1978a). For SDM, the amount excreted in the feces significantly increased with increasing particle size (Watari et al., submitted). Furthermore, Fig. 1 shows that drug dissolution estimated by integrated weight function was particle-size-dependent and that the time required for reaching 50% of the plateau level for the dissolution decreased greatly with increasing drug solubility (Table 1).

Fig. 2A shows the undissolved-time plots calculated from the data of integrated weight function for low-solubility drugs of SDM, SD and SIX. For SD, a typical example is shown for the examined powder sample sizes because of its large deviation. The unabsorbed-time plots calculated by the multicompartment model method are shown in Fig. 2B. Both undissolved-time and unabsorbed-time courses were biphasic with convex-descending curves for the large particle sizes. These times courses of the mean value of SDM and SIX were fitted to two lines by the least-squares method. Table 2 illustrates the approximated equations. The plot of the slope of the initial linear portion for the dissolution (Fig. 2A) vs that for the absorption (Fig. 2B) revealed a good linear relationship ($y = 0.45x + 0.01$, $r = 0.995$ for SDM; $y = 0.58x + 0.007$, $r = 0.999$ for SIX). However, in the second linear portion, the slopes of the absorption were almost constant, irrespective of the slopes of the dissolution; the effect of particle size on the absorption rate constant disappeared (Fig. 3).

The unabsorbed-time courses of aqueous solution (Fig. 2B) were biphasic with concave-descending curves. These time courses were approximated by bi-exponential equa-

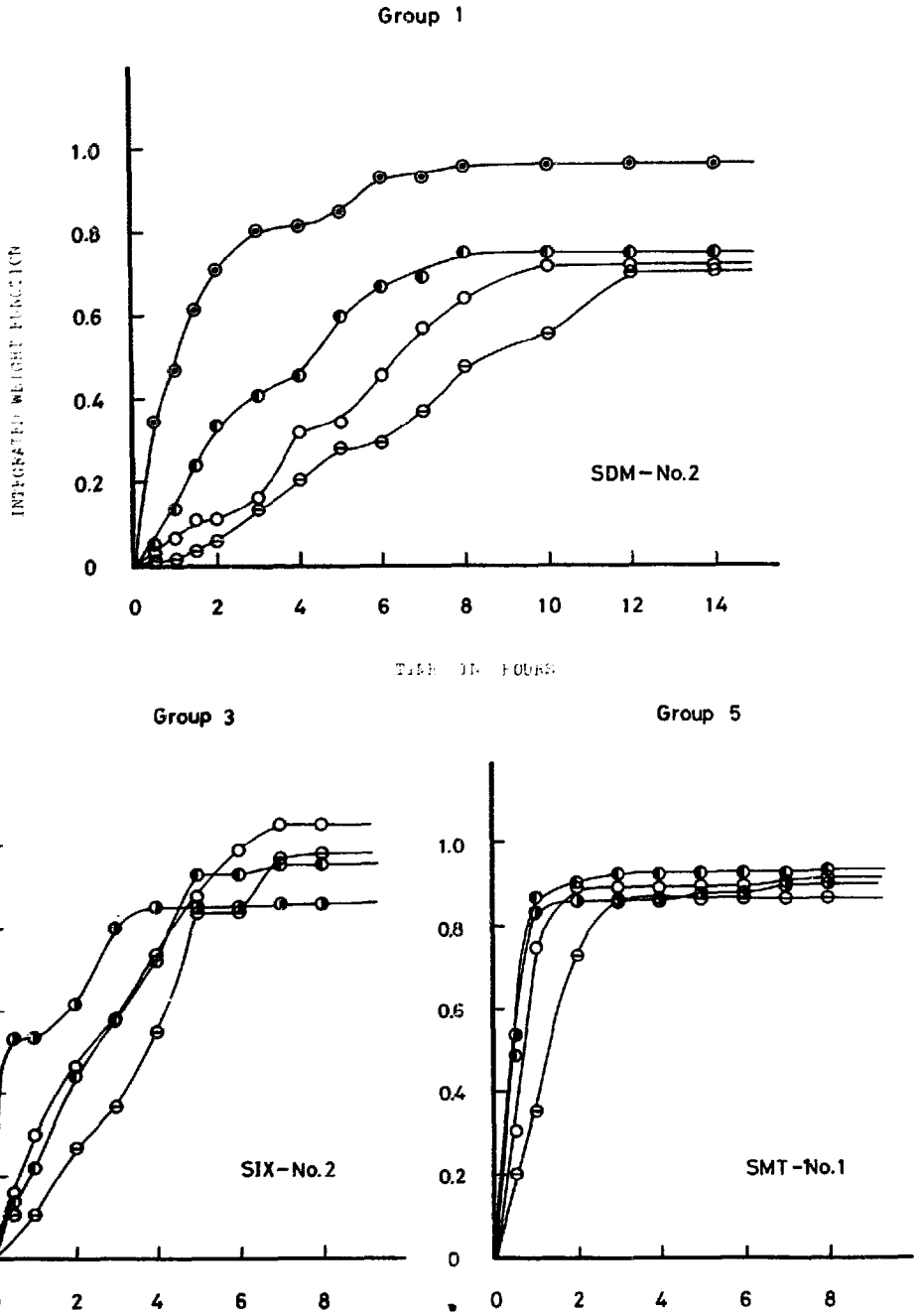

Fig. 1. Time course of the integrated weight function of sulfonamide for in vivo dissolution. Particle size (μm) ⊙, 33; ●, 81; ◐, 163; ○, 324; ⊖, 650.

tions ($y = 40.8\, e^{-2.67t} + 59.1\, e^{-0.298t}$ for SDM; $y = 50.4\, e^{-2.50t} + 49.6\, e^{-0.440t}$ for SIX). In fitting to appropriate bi-exponential equation, at initial time, the percentage unabsorbed was fixed to 100 because the AUC of aqueous solution between oral and intravenous administration was almost the same for each drug. The initial absorption rate

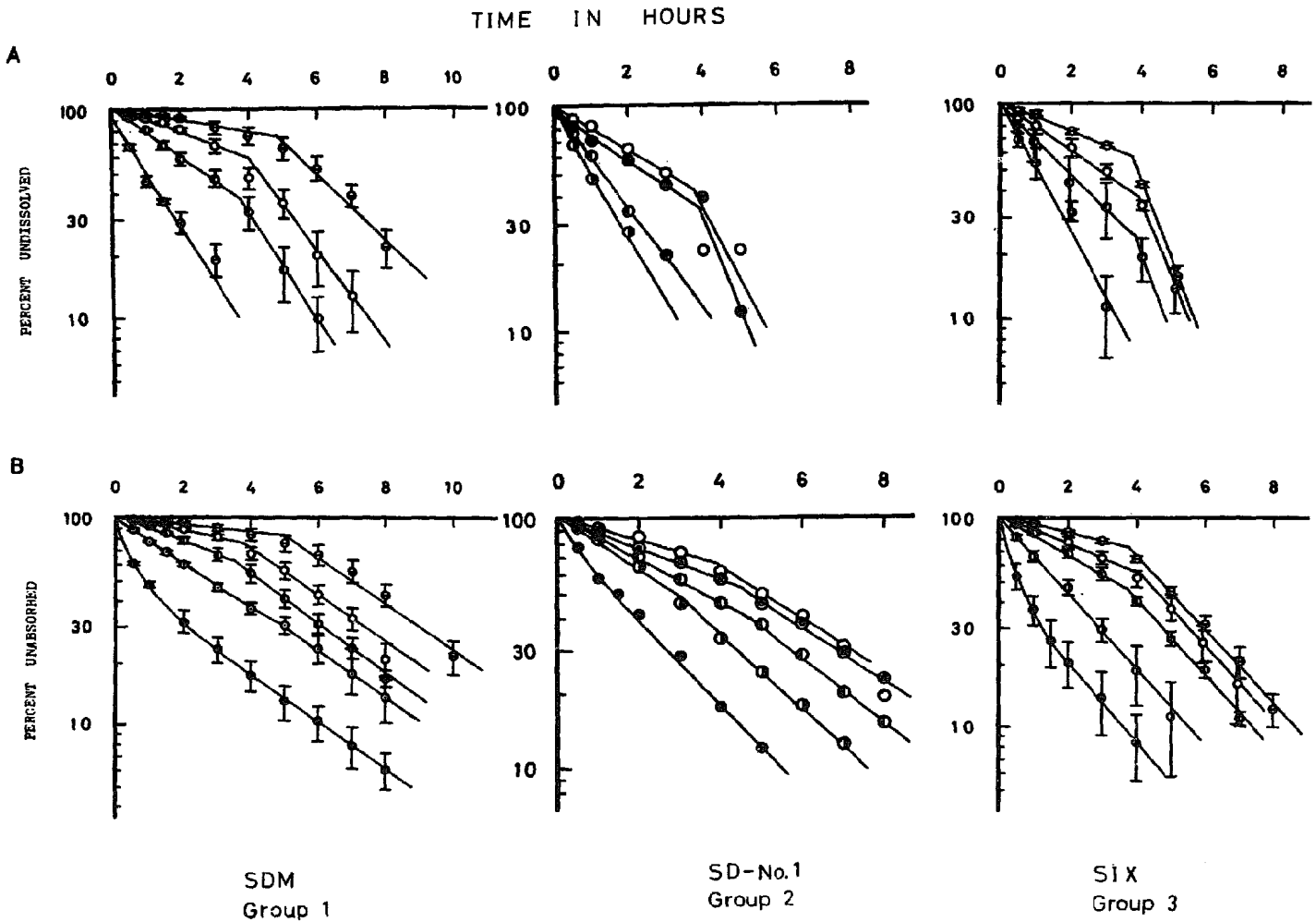

Fig. 2. Semilogarithmic plot of per cent undissolved or unabsorbed vs time ●, solution. Particle size (μm) ⊙, 33; ◍, 81; ◐, 163; ●, 230; ○, 324; ⊖, 650; ——— calculated lines. Each point for SDM and SIX represents the mean of 4 (SDM) or 3 (SIX) rabbits. For SD, a typical example is shown. The vertical bar is S.E.

TABLE 2

EQUATIONS APPROXIMATED BY THE LEAST-SQUARES METHOD

Initial linear portion ($0 < t < T$). Second linear portion ($t > T$).
In vivo dissolution process $y = D_1e^{-kd_1t}$. $y = D_2e^{-kd_2(t-Td)}$.
Absorption process $y = A_1e^{-ka_1t}$. $y = A_2e^{-ka_2(t-Ta)}$ where T is the time for the intersection of two lines.

	SDM Sample size (μm)				SIX Sample size (μm)			
	33	163	324	650	81	163	324	650
D_1, %	92	106	105	102	108	94	103	103
kd_1, h^{-1}	0.553	0.277	0.140	0.060	0.719	0.358	0.265	0.154
A_1, %	101	107	104	102	104	106	106	104
ka_1, h^{-1}	0.258	0.153	0.075	0.035	0.420	0.220	0.160	0.093
D_2, %	–	38	60	76	–	24	36	58
kd_2, h^{-1}	–	0.601	0.532	0.364	–	1.048	0.910	1.004
Td, h	–	3.7	4.0	4.8	–	3.8	3.9	3.7
A_2, %	34	62	78	85	–	47	55	73
ka_2, h^{-1}	0.272	0.279	0.269	0.257	–	0.426	0.424	0.414
Ta, h	4.5	3.5	3.8	5.0	–	3.7	4.1	3.8

constant in these equations is very large. Crouthamel et al. (1971) and Koizumi et al. (1964) reported that the transfer of sulfa drug from the stomach to the body is one-tenth (or more) less than that from the small intestine. Based on these considerations, we suggest that the aqueous solution did not remain in the stomach for long, but quickly moved to the small intestine and was transferred to the body. A similar phenomenon was also observed with water-soluble sulfa drug of sulfanilamide (Kaneniwa et al., 1978b).

The rate constants of absorption of SDM and SIX obtained from the initial linear portions of Fig. 2B were about one-half of those of dissolution (Fig. 2A). This may be explained in part by the difference of the gastric emptying rate; an aqueous solution produced by the dissolution of powder drugs moves relatively faster to the small intestine than the suspension and is rapidly transferred to the body. This hypothesis is further supported by the fact that the difference between the initial dissolution and absorption rate constants decreased with increasing drug solubility.

The ratio of the second slope of large particle sizes to their initial slope increased remarkably in both undissolved- and unabsorbed-time plots. Higuchi et al. (1953) and Kaplan et al. (1972) reported that the solubility of sulfa drugs increased remarkably with an increase in pH. Therefore, this phenomenon may be explained by the change of the dissolving environment as the powder drugs move along the GI tract (Crouthamel et al., 1975).

For SDM, the effect of particle size on the slopes of the second linear portion for the dissolution was noted. On the other hand, the slopes of the second linear portion for the absorption were almost constant, irrespective of particle size, and approximately corresponded to those of the aqueous solution, indicating that absorption is rate-limiting in the

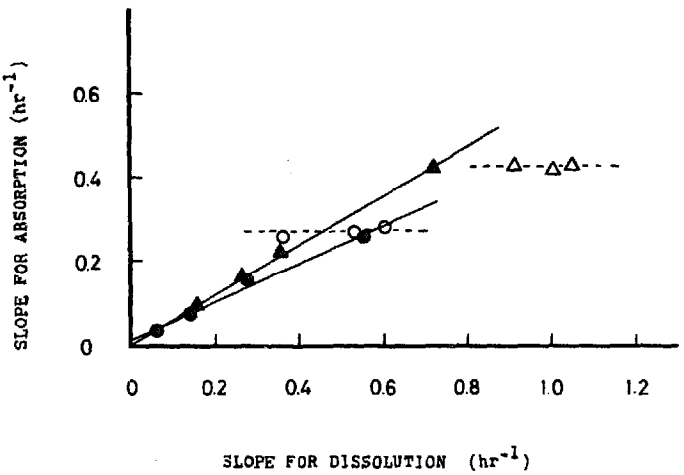

Fig. 3. Comparative plot of slopes in Fig. 2. •, SDM, initial linear portion; ○, SDM, second linear portion; ▲, SIX, initial linear portion; △, SIX, second linear portion.

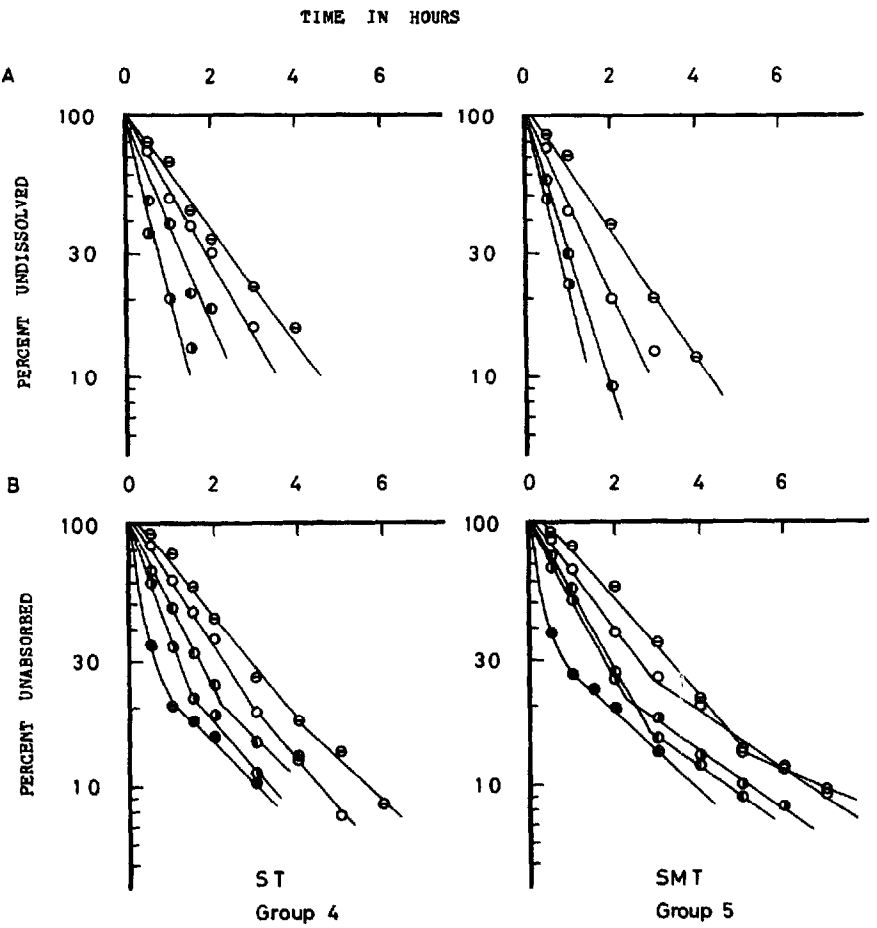

Fig. 4. Semilogarithmic plot of percent undissolved or unabsorbed vs time. The symbols are the same as in Fig. 2 and each plot represents the mean of 3 rabbits.

second linear portion for the absorption (Fig. 3). This result suggests that the aqueous solution (or an aqueous solution produced by the dissolution of the solid drug in the upper small intestine) moved quickly to the lower small intestine (e.g. ileum) or the large intestine and that the absorbability of the drug decreased (Creamer, 1974). The phenomenon that the slopes of the second linear portion for the absorption became constant, independent of the sample, was also observed with the other sulfa drugs used (Fig. 4B) and sulfanilamide. Furthermore, it was apparent that in such SDM drugs, the dissolution estimated by the deconvolution method is very useful to elucidate the behavior of in vivo drug dissolution.

In high-solubility drugs of ST and SMT, the undissolved-time course (Fig. 4A) was a single line and the unabsorbed–time course for powder drug was biphasic with a concave-descending curve (Fig. 4B). This was different from the convex-descending curves of SDM, SD and SIX. This difference may be due to the increase in solubility of ST and SMT. Furthermore, the slope of the second linear portion for the absorption was almost

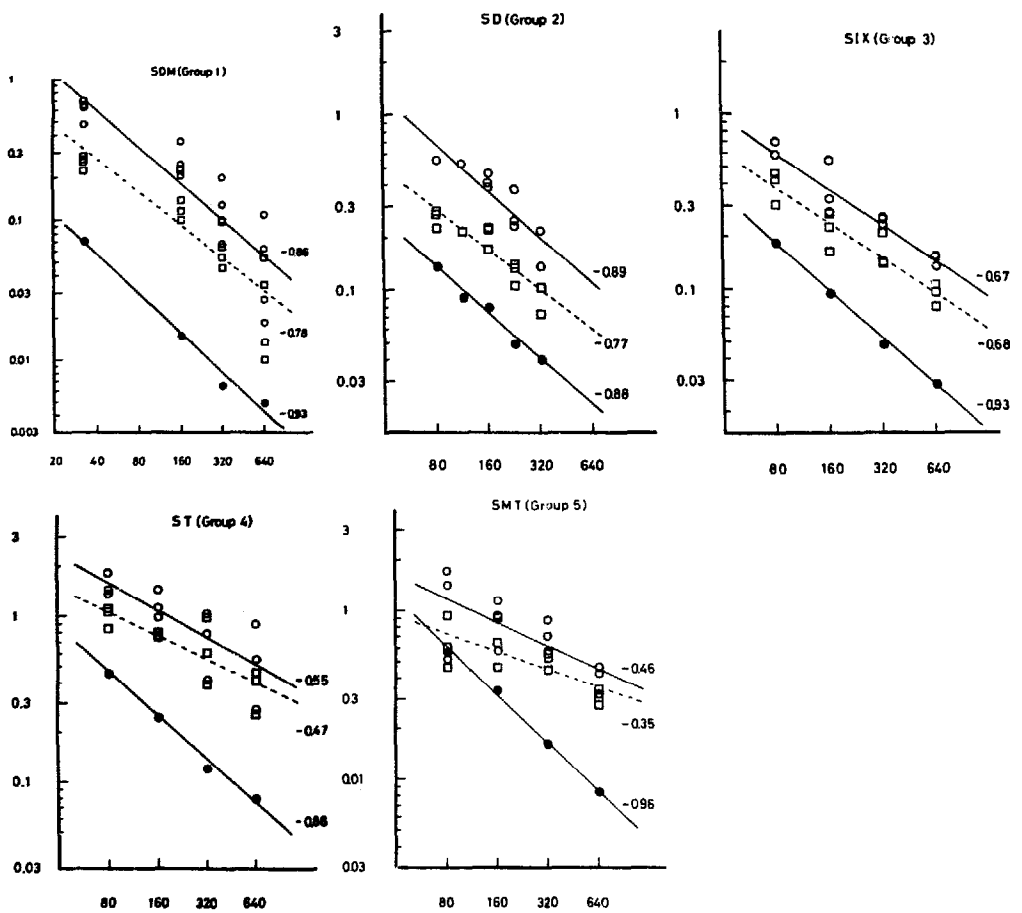

Fig. 5. Logarithmic plot of rate constants vs particle size. Ordinates show the apparent rate constant and abscissas the particle size (μm). ○, in vivo dissolution rate constant (h^{-1}); □, absorption rate constant (h^{-1}); ●, in vitro dissolution rate constant ($mg^{1/3}$ min^{-1}). In vivo rate constants were obtained from the initial linear portions of Figs. 2 and 4 for each rabbit.

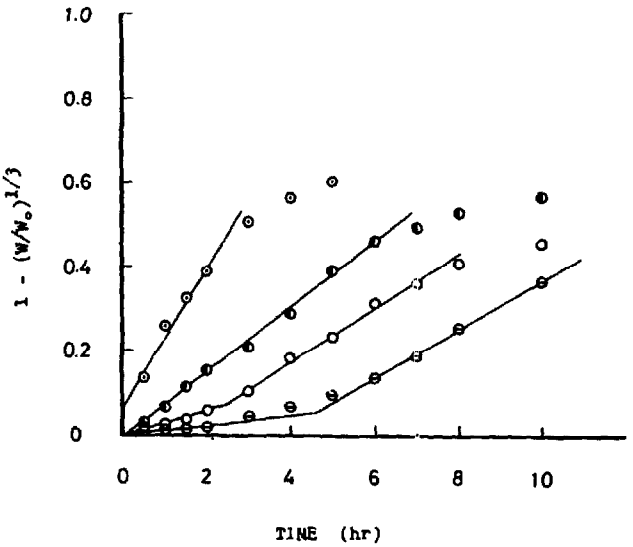

Fig. 6. Plot of the Hixson-Crowell cube-root law vs time for in vivo dissolution of SDM (Group 1). The symbols are the same as in Fig. 2.

the same and approximately corresponded to that of the aqueous solution.

The ratio of the rate constant of dissolution to that of absorption in the initial linear portions was 2.01 ± 0.34 (mean of all samples ± S.D.) for SDM, 2.15 ± 0.41 for SD, 1.61 ± 0.19 for SIX, 1.42 ± 0.35 for ST and 1.47 ± 0.48 for SMT. This ratio decreased obviously with increasing drug solubility (Fig. 5).

As described above, in vivo dissolution calculated by deconvolution correlated well with absorption rates calculated by the multicompartment model method at a constant ratio for each drug during 2–5 h for the initial linear portions, and thereafter, this correlation disappeared.

Application of the Hixson-Crowell cube-root law (1931) to the mean value of the integrated weight function data of SDM resulted in good linearity until 80% dissolved, indicating that drug dissolution proceeds under the sink condition (Fig. 6). Similar results were obtained with the other sulfa drugs used.

In vitro–in vivo correlations

The in vitro dissolution test was performed at 700 rpm in distilled water so as to obtain thoroughly wet and completely dispersed powder particles because we were interested in the relative value or ratio of the dissolution rate constant. To facilitate the particle-size-dependent correlation between in vitro and in vivo, the in vivo dissolution rate constant was adopted from the initial portions of Figs. 2A and 4A. These periods can be expected to correspond to the dissolving period of powder drugs in the stomach.

The amount of SDM excreted in the feces significantly increased with increasing particle size. Significantly reduced availability was noted, possibly due to the simultaneous occurrence of drug dissolution and movement down the GI tract. Goto et al. (1973) reported this movement to be according to a first-order process. Therefore, the in vivo

dissolution rate constants of powder samples of SDM were obtained by multiplying the apparent rate constant by the fraction (F) of orally administered dose absorbed (Notari et al., 1972).

Fig. 5 shows the logarithmic plot of the dissolution rate constants for in vitro and in vivo vs particle size. The slope of the line in Fig. 5, i.e. the effect of particle size on these rate constants, was calculated for each drug. The slopes of the lines in Fig. 5 were almost the same between in vitro and in vivo for SDM and SD. The absolute values of the slopes of ST and SMT for in vivo were smaller than those for in vitro; the effect of particle size on the in vivo dissolution rate constants decreased. The dissolution rate of a solid is described by the Noyes-Whitney equation:

$$\frac{dC}{dt} = KS\,(Cs - C) \qquad (1)$$

where dC/dt is the dissolution rate, K, the dissolution rate constant, S, the surface area of the solid, Cs, the saturated concentration and C, the solute concentration of the bulk medium. The constant K has been shown to be equal to D/hV where D is the diffusion coefficient of the dissolving material, h, the thickness of the diffusion layer and V, the volume of the medium. In the present study, the surface area (S) is replaced with total surface area of the particles assuming that powder particles are all spherical: $S = 6W/\rho d$ where W is the weight of the particles, ρ, the density of the particles and d, the mean diameter of the particles. This decreased particle-size effect on the in vivo dissolution rate constants for ST and SMT may partly be explained as follows; with increasing drug solubility, the dissolution rate increased compared with the absorption rate of the drug. Consequently, the solute concentration of the bulk medium in Eqn. 1 was not negligible in the GI tract according to decreasing particle size, i.e. the sink condition would fail under such circumstances and thereby the dependence of particle size on the in vivo dissolution rate constants would decrease.

To correlate in vitro and in vivo dissolution rates among the sulfa drugs used, a particle size of 324 μm was adopted. The plot of the rate constant of in vivo dissolution vs that of in vitro dissolution is shown in Fig. 7. There was a good linear relationship with a slope

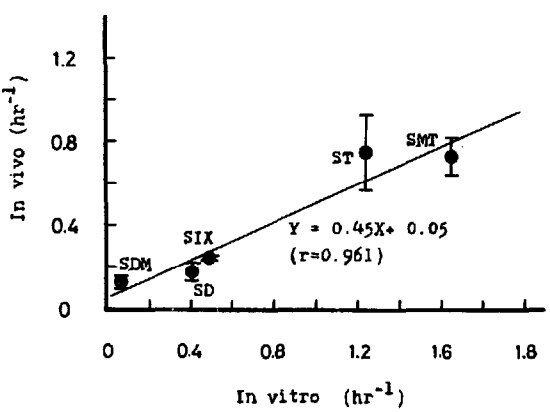

Fig. 7. In vitro–in vivo correlation of dissolution rate constant for a particle size of 324 μm. Vertical bars indicate S.E.. The points indicate the mean for 2 (SD), 3 (SIX, ST, SMT) and 4 (SDM) rabbits.

of 0.45, indicating that in vivo drug dissolution was very slow. Although in the present study, the in vitro dissolution test was made in distilled water, the in vitro dissolution rate may increase appreciably at pH such as exists in the stomach. Watari et al. (submitted) found that the dissolution rate of SDM in 0.1 N HCl solution was about 4 times that in distilled water. As the pka_1 value of sulfa drugs used was around 2 (Table 1), the ratio of solubility in 0.1 N HCl solution to that in distilled water may be almost the same among these sulfa drugs. This difference between in vitro and in vivo dissolution rates may be primarily ascribable to the agitation intensity because a high agitation speed of 700 rpm was used in the in vitro dissolution test, although Levy et al. (1965) had proposed a speed of 50 rpm.

REFERENCES

Boxenbaum, H.G. and Kaplan, S.A., Potential source of error in absorption rate calculations. J. Pharmacokin. Biopharm., 4 (1975) 257–264.

Creamer, B., Biomembranes, Vol. 4A D.H. Smyth, (Ed.) Plenum Press, London, New York, 1974, pp. 1–42.

Crouthamel, W.G., Abolin, C.R., Hsieh, J. and Lim, J.K., Intestinal pH as a factor in selection of animal models for bioavailability testing. J. Pharm. Sci., 64 (1975) 1726–1727.

Crouthamel, W.G., Tan, G.H., Dittert, L.W. and Doluisio, J.T., Drug absorption. IV. Influence of pH on absorption kinetics of weakly acidic drugs. J. Pharm. Sci., 60 (1971) 1160–1163.

Fincher, J.H., Particle size of drugs and its relationship to absorption and activity. J. Pharm. Sci., 57 (1968) 1825–1835.

Goto, S., Yamagata, T., Tsuzuki, O. and Iguchi, S., Rate of gastric emptying of phenol red in a rabbit. Chem. Pharm. Bull., 21 (1973) 2495–2499.

Higuchi, T., Gupta, M. and Busse, L.W., Influence of electrolytes, pH, and alcohol concentration on the solubilities of acidic drugs. J. Am. Pharm. Ass., Sci. Edn., 42 (1953) 157–161.

Hixson, A.W. and Crowell, J.H., Dependence of reaction velocity upon surface and agitation. Ind. Eng. Chem., 23 (1931) 923–931.

Kaneniwa, N. and Watari, N., Dissolution of slightly soluble drugs. I. Influence of particle size on dissolution behavior. Chem. Pharm. Bull., 22 (1974) 1699–1705.

Kaneniwa, N. and Watari, N., Dissolution of slightly soluble drugs. IV. Effect of particle size of sulfonamides on in vitro dissolution rate and in vivo absorption rate, and their relation to solubility. Chem. Pharm. Bull., 26 (1978a) 813–826.

Kaneniwa, N., Watari, N. and Iijima, H., Dissolution of slightly soluble drugs. V. Effect of particle size on gastroinestinal drug absorption and its relation to solubility. Chem. Pharm. Bull., 26 (1978b) 2603–2614.

Kaplan, S.A., Weinfeld, R.E., Abruzzo, C.W. and Lewis, M., Pharmacokinetic profile of sulfisoxazole following intravenous, intramuscular, and oral administration to man. J. Pharm. Sci., 61 (1972) 773–778.

Kiwada, H., Morita, K., Hayashi, M., Awazu, S. and Hanano, M., A new numerical calculation method for deconvolution in linear compartment analysis of pharmacokinetics. Chem. Pharm. Bull., 25 (1977) 1312–1318.

Koizumi, T., Arita, T. and Kakemi, K., Absorption and excretion of drugs. XIX. Some pharmacokinetic aspects of absorption and excretion of sulfonamides. (1). Absorption from rat stomach. Chem. Pharm. Bull., 12 (1964) 413–420.

Koizumi, T., Arita, T. and Kakemi, K., Absorption and excretion of drugs. XX. Some pharmacokinetic aspects of absorption and excretion of sulfonamides. (2). Absorption from rat small intestine. Chem. Pharm. Bull., 12 (1964) 421–427.

Levy, G., Leonards, J.R. and Procknal, J.A., Development of in vitro dissolution tests which correlate quantitatively with dissolution rate-limited drug absorption in man. J. Pharm. Sci., 54 (1965) 1719–1722.

Loo, J.C.K. and Riegelman, S., New method for calculating the intrinsic absorption rate of drugs. J. Pharm. Sci., 57 (1968) 918–928.

Notari, R.E., DeYoung, J.L. and Reuning, R.H., Effect of parallel first-order drug loss from site of administration on calculated values for absorption rate constants. J. Pharm. Sci., 61 (1972) 135–138.

Wagner, J.G. and Nelson, E., Per cent absorbed time plots derived from blood level and/or urinary excretion data. J. Pharm. Sci., 52 (1963) 610–611.

Watari, N., Hanano, M. and Kaneniwa, N., Dissolution of slightly soluble drugs. VI. Effect of particle size of sulfadimethoxine on the oral bioavailability. Chem. Pharm. Bull., 28 (1980) 2221–2225.