[Chem. Pharm. Bull. 21(7)1440—1445(1973)]

UDC 547.269.3'233.03

Studies on Absorption of Suppositories. IV.[1] Effect of Buffer Reagents on Absorption of Sulfonamides

Takao Takubo, Hideo Matsumaru, Seishi Tsuchiya, and Mitsuru Hiura

Tokyo College of Pharmacy[2]

(Received January 6, 1973)

Solubility and dissolution rate of four kinds of sulfonamides (sulfanilamide, sulfisoxazole, sulfadiazine, and sulfisomidine) were determined in various pH solutions. The *in vivo* absorption patterns of four sulfonamides after administration to rabbits as a suppository with or without buffer reagents were compared by estimating the blood concentration of sulfonamide as a function of time.

Higher alkalinity of the buffer solution increases the solubility and dissolution rate. The results of blood concentration studies demonstrated that both the rate and extent of absorption of sulfonamides were considerably enhanced by the rectal administration of the buffered suppository. The *in vitro* dissolution charactristics of the four sulfonamides at 37°±1 correlated well with the *in vivo* absorption data; the logarithm of the absorption rate constant is proportional to the dissolution rate.

From the results obtained, it would be expected that a buffered suppository of sparingly soluble sulfonamides was more effective than that of unbuffered suppository with respect to their absorption from the rectum.

Many investigators[3] demonstrated that an enhancement in the dissolution rate of a sparingly soluble drug should facilitate its absorption rate if the absorption process is dependent on dissolution rate. The *in vitro* dissolution properties of some physicochemical states of drugs have been characterized in some detail, and pH of the solution is one of the important factors which regulates the solubility and dissolution rate of sparingly soluble drugs.

Paul,[4] Truitt,[5] and Cotty, *et al.*[6] observed that absorption of aspirin is faster in buffered-type tablet than that of normal-type. In comparative studies on the absorption of aspirin from normal and buffered tablet including buffer reagents, Tebrock[7] reported that the buffered-type decreased the irritation and disease of the stomach which are caused by normal-type aspirin. These desirable observations were due to the increase the dissolution rate of aspirin, because gastric pH becomes high by the buffer reagents.

However, few accurate studies have been reported on the relationship between dissolution rate and absorption rate of drugs containing buffer reagents, and still fewer reports are available on the absorption of sulfonamides from suppositories containing buffer reagents.

Some drugs which do not dissolved in their suppository base are sometimes dispersed throughout the base. In such a suppository, the drug must dissolve in the rectal fluid after the base has been melted or has dissolved. It seems that the addition of buffer reagents to a suppository brings some convenient effect on the solubility of the drug in it. In the present work, therefore, solubilities and dissolution rates of four kinds of sulfonamides were determined

1) The 92 nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, Apr. 1972. Part III: T. Takubo, S. Tsuchiya, and M. Hiura, *Yakuzaigaku*, **31**, 298 (1971).
2) Location: *3-20-1, Kitashinjuku, Shinjuku-ku, Tokyo,160 , Japan.*
3) G. Levy, *J. Pharm. Sci.*, **50**, 388 (1961); E.I. Stupak and T.R. Bate, *ibid.*, **61**, 400 (1972); M. Gibaldi, "Introduction to Biopharmaceutics," Lea & Febiger, Philadelphia, 1971, p. 21.
4) W.D. Paul, R.L. Dryer, and J.I. Routh, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 21 (1950).
5) E.B. Truitt and A.M. Morgan, *J. Pharm. Sci.*, **53**, 129 (1964).
6) V. Cotty, F. Zurzola, T. Beezly, and A. Rodgers, *J. Pharm. Sci.*, **54**, 868 (1965).
7) H.E. Tebrock, *Ind. Med. Sug.*, **20**, 480 (1951).

in various pH solutions. On the basis of these *in vitro* findings, it was decided to characterize and compare the *in vivo* absorption patterns of sulfonamides from suppositories containing buffer reagents in rabbits.

Experimental

Determination of Solubility and Dissolution Rate——Desired pH (2.1—11.3) solutions were obtained by dissolving the buffer reagents, listed in Table I, in 100 ml of distilled water. Aliquots of the buffer solution were placed in a glass-stoppered flask with excess of each sulfonamide. The flask was allowed to stand at 37°±1 and shaken vigorously for 4 hr by which equilibrium was established. One ml of the supernatant was removed with the aid of a filter pipet and its solubility was determined according to the method described in the preceding report.[1]

Table I. Salt Components of Buffer Solution

pH	Citric acid (g)	Na_2HPO_4 (g)	$NaHCO_3$ (g)	Na_2CO_3 (g)
2.1	2.100	—	—	—
3.1	1.680	0.572	—	—
4.2	1.260	1.144	—	—
5.0[a)]	0.990	1.500	—	—
5.8	0.840	1.716	—	—
6.5[a)]	0.630	2.000	—	—
6.8[a)]	0.420	2.228	—	—
7.0[a)]	0.320	2.430	—	—
8.4	—	—	1.680	—
9.1[a)]	—	—	1.512	0.212
9.8	—	—	1.008	0.848
10.7[a)]	—	—	0.168	1.908
11.3[a)]	—	—	—	2.120

a) used for preparation of buffered suppository

To determine the dissolution rate in various pH solutions, 200 ml of appropriate buffer solution was transferred to a 500-ml three-necked round-bottomed flask maintained in a thermostat. The propeller-type stirrer was immersed in the dissolution medium to a depth of 20 mm and rotated at 600 rpm. After the temperature attained 37°±1, 1 ml of the solution was removed at frequent time intervals after the introduction of 500 mg of each sulfonamide (through 200 mesh) into the dissolution medium. The amount of sulfonamide in the solution at each time interval was determined by spectrophotometry.

Test Preparations——The sulfanilamide, sulfisoxazole, sulfadiazine, and sulfisomidine (through 200 mesh) employed in this study were pharmaceutical grade. The suppositories were prepared by hot-melting method using metal molds. Each sulfonamide and buffer reagent were dispersed throughout the melted cacao butter base and poured into molds. Buffered suppository contained one-tenth of buffer reagent listed in Table I. Cacao butter were used as the suppository base in this study because the sulfonamides do not dissolve in this base.

Absorption Experiments——In all *in vivo* experiments, adult male rabbits, weighing from 2.0 to 3.0 kg, were used as the test animal. The rabbits were fasted (with water allowed freely) for 12 hr before start of the absorption experiments. A suppository of the test preparation, at a sulfonamide dosage level of 100 mg/kg body weight, was administered into the rectum and the anal end was pinched with a clip for 4 hr to prevent expulsion of the suppository. Blood specimens were withdrawn at 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 24 hr from the congested aural vain. The concentration of sulfonamides was assayed by spectrophotometry using the same procedure as described in the previous report.[8] Apparent elimination rate constant was obtained from terminal slope of logarithmic plot of the blood concentration, and apparent absorption rate constant was calculated from the gradient of the straight line which plotted the differences between extrapolated values of the terminal data and real data on semi-logarithmic paper.[8,9] Three animals were used for each absorption experiment.

8) T. Takubo, S. Tsuchiya, and M. Hiura, *Yakuzaigaku*, **31**, 292 (1971).
9) E.R. Garrett, *Acta Pharmacologica. et Toxicologica.*, **29**, *suppl.* 3 (1971).

Result

1) Solubility of Sulfonamides

The solubility of sulfonamides in various pH (2.1—11.3) buffer solutions at 37°±1 is shown in Fig. 1. Increasing alkalinity of the buffer solution increased the solubility of sulfisoxazole, sulfadiazine, and sulfisomidine, but the solubility of sulfanilamide was not so affected by the alteration in pH, but the solubility tended to increase at pH 11.3 compared to that at pH 6.5 or 9.1. Therefore, all of these sulfonamides show higher solubility at higher pH region.

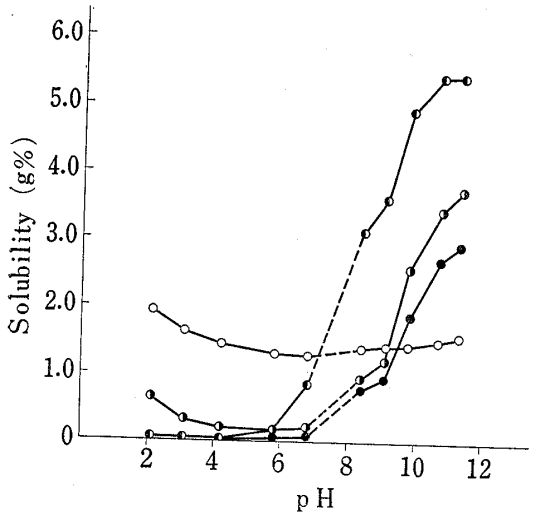

Fig. 1. Relationship between Solubility and pH

key: ○: sulfanilamide
◐: sulfisoxazole
●: sulfadiazine
◑: sulfisomidine
pH 2.1— 7.0 citric acid–Na_2HPO_4
pH 8.4—11.3 $NaHCO_3$–Na_2CO_3

2) Dissolution Rate of Sulfonamides

The amount of sulfonamide which dissolved into various buffer solutions, having the same pH value as buffer suppository, was determined as a function of time. The initial dissolution rate is expressed as the slope of the tangent to the dissolution curve, and these results are listed in Table II. In various pH solutions the order of initial dissolution rate of each sulfonamide runs parallel to the order of its solubility (Fig. 1). The initial dissolution rate becomes larger in the area of higher pH region, and the dissolution rate of higher pH is 3 to 7 times larger than that in lower pH in this experiment.

Table II. Initial Dissolution Rate (Rd) of Sulfonamides in Various pH Solutions

Drug	Sulfanilamide			Sulfisomidine		
pH	6.5	9.1	11.3	6.8	9.1	10.7
Rd (mg/sec)	26.2	30.5	87.0	9.1	18.4	66.0

Drug	Sulfisoxazole			Sulfadiazine		
pH	5.0	7.0	9.1	6.8	9.1	10.7
Rd (mg/sec)	1.8	4.1	6.4	1.6	2.6	7.4

3) Effect of pH on Rectal Absorption

Blood concentration patterns of four sulfonamides were compared after administration to rabbits as a buffered suppository (Fig. 2). For each sulfonamide, the maximum blood concentration is obtained by the buffered suppository of higher pH, and the peak appears in 1 or 2 hr after administration. The maximum blood concentration of sulfadiazine and sulfisomidine was attained 4 times faster from suppository of pH 10.7 than from lower pH suppositories.

The initial blood concentration of sulfisoxazole, sulfadiazine, and sulfisomidine also increased when pH of the buffered suppository tended toward the alkaline side. However, there was almost no difference in the initial blood concentration of sulfanilamide at pH 7.0 or 9.1 but the concentration at pH 11.3 was certainly enhanced. From these blood concent-

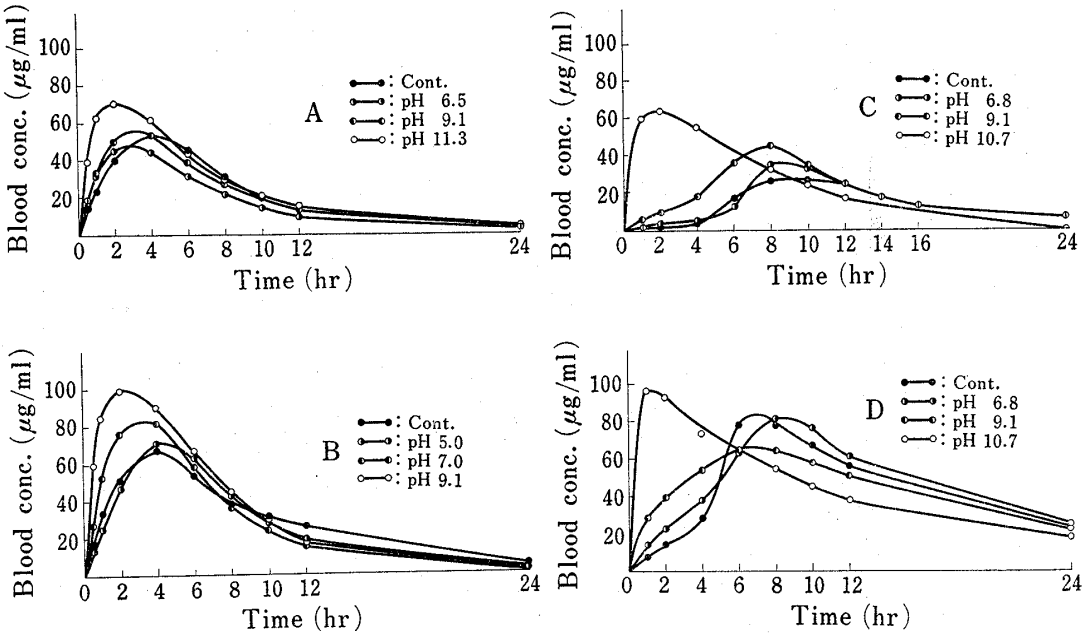

Fig. 2. Blood Concentration of Sulfonamides after Rectal Administration of Suppositories of Various pH
A: sulfanilamide B: sulfisoxazole C: sulfadiazine D: sulfisomidine

ration values, absorption and elimination rate constants were calculated and the values are listed in Table III. Absorption rate of these sulfonamides was accelerated when the pH of buffered suppository was increased, while elimination rate of these sulfonamides was little affected by the pH of buffered suppositories.

Table III. Absorption Rate Constant (Ka) and Elimination Rate Constant (Kel) after Rectal Administration of Buffered Suppository

Drug	Sulfanilamide				Sulfisomidine			
pH	—	6.5	9.1	11.3	—	6.8	9.1	10.7
Ka	0.443	0.752	0.724	0.966	0.124	0.226	0.313	2.881
Kel	0.214	0.196	0.170	0.182	0.084	0.099	0.063	0.091
Drug	Sulfisoxazole				Sulfadiazine			
pH	—	5.0	7.0	9.1	—	6.8	9.1	10.7
Ka	0.584	0.556	0.664	0.826	0.174	0.172	0.201	0.955
Kel	0.124	0.200	0.214	0.205	0.168	0.157	0.156	0.154

Discussion

It was found that when cacao butter suppository containing sulfonamides was applied to the rectum, the vehicle melts at the body temparature and the drug is dissolved into the rectal fluid, then absorbed from the mucous membrane. It is recognized that the absorbability of sparingly soluble drugs is often restricted by the dissolution rate, and pH of the solution regulates the solubility of weak electrolytes. So, it will be considered that the pH of biological fluids is one of the important factors which regulates the solubility and dissolution rate of sparingly soluble drugs.

Therefore, investigations were made on the solubility and dissolution rate of sulfonamides in various pH solutions, and difference in the absorbability of these sulfonamides from suppositories containing buffer reagents.

Solubility (Fig. 1) and dissolution rate (Table II) of sulfonamides are also increased when pH of the solution tends to an alkaline region. These dissolution characteristics of *in vitro* experiments agree with the physicochemical behavior of weakly acid drugs in various pH solutions.

Sulfonamide molecule possesses two ionizing groups and, if the absorption from rectum depends only on pH-partition hypothesis,[10] the maximum absorption will be at the pH of isoelectric point. Kakemi, *et al.*[11] reported that the absorption of sulfonamides depends on its degree of ionization in solution, and the nonionized form is preferentially absorbed. However, they also suggested that the ionized moiety is not completely absorbed, but the ionized moiety of these drugs is also able to be absorbed to a certain extent. As shown in Fig. 2 and Table III, the initial blood concentration and absorption rate constant of sulfonamides increase according as the pH of the buffered suppository getting high. The maximum pH value of the buffered suppository used in this investigation is higher than the isoelectric point of sulfonamides, but the absorption rate constant of sulfonamides increased two to twenty times compared with that of unbuffered suppository.

These are interesting results as to the pH-partition theory. It is considered that this is due to the difference in experimental conditions, the main factor would be the type of drugs in the vehicle. In this experiment, drugs are not dissolved in the suppository base, while in most of *in situ* experiments drugs are dissolved in the vehicle solution. In these suppositories, sulfonamides must be released from the suppository base, and then the absorption must be preceded by dissolution of the drugs. Kakemi[11] and Nogami[12] reported that the ionized form of sulfonamide penetrates through the intestinal barrier. So in this experiment, the ionized form is increased with increasing pH of rectal fluid, then the enhanced dissolution rate will bring about rapid absorption. On the other hand, it can be assumed that the enhancement of the absorbability of sulfonamide in alkaline region is due to the difference of buffer reagents between acid and alkaline region. As shown in Table III, however, the absorption rate constant of sulfanilamide failed to show a marked difference between pH 6.5 (citric acid–Na_2HPO_4 buffer) and pH 9.1 ($NaHCO_3$–Na_2CO_3 buffer). If the solubility and dissolution rate show a similar value at different pH's, it would be expected that the absorption rate closely similar at each pH even though the buffer reagents in the suppository are changed. So the constituents of buffers does not alter the absorbability of sulfonamides.

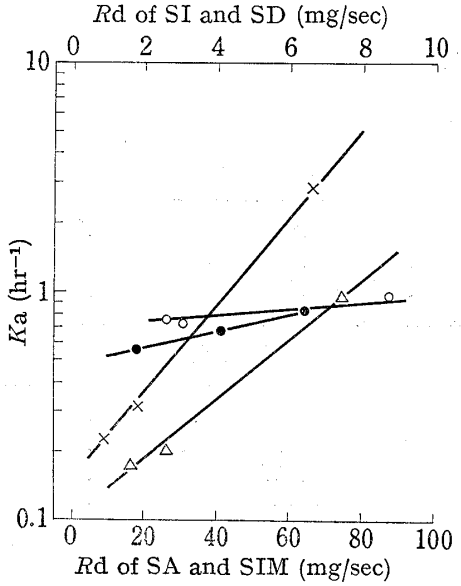

Fig. 3. Relationship between Initial Dissolution Rate (*R*d) and Absorption Rate Constant (*K*a)

key: ○: sulfanilamide (SA)
●: sulfisoxazole (SI)
△: sulfadiazine (SD)
×: sulfisomidine (SIM)

From these results, it would be considered that the dissolved suppository may bufferise the enviromental rectal fluid and then increases the solubility and dissolution rate of sulfonamides.

From the data obtained in these experiments, the *in vitro* dissolution characteristics

10) L.S. Schanker, P.A. Shore, B.B. Brodie, and C.A.M. Hogben, *J. Pharmacol. Exp. Therap.*, **120**, 528 (1957).
11) K. Kakemi, T. Arita, and S. Muranishi, *Chem. Pharm. Bull.* (Tokyo), **13**, 861 (1965).
12) H. Nogami, M. Hanano, and J. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **10**, 1161 (1962).

of these drugs in various pH solutions at 37°±1 correlated well with *in vivo* absorption data (Fig. 3). The relationship between dissolution rate and absorption rate constant can be expressed by following equation:

$$\log Ka = \alpha \cdot Rd + \beta$$

where Ka is the absorption rate constant, Rd is the initial dissolution rate, and α and β are constants. This equation indicates that the logarithm of absorption rate constant is proportional to the initial dissolution rate.

In the present investigation, it was not possible to determine whether the rectal fluid shows the same pH value as the administered buffered suppository or not. However, as shown in the Result, it is evident that the buffer reagents make the dissolution rate of sulfonamides greater because absorption rate constant increased when pH of the buffered suppository tended toward the alkaline side. Accordingly, it is assumed that the buffer reagent exhibits sufficient buffer action as to change the pH of rectal fluid.

In the sparingly soluble drugs which are not dissolved but dispersed through the oleagenous base such as cacao butter, absorption rate of these drugs from a suppository may be influenced by the initial dissolution rate.

Examination of the absorption data reveals that the areas under each curve become greater with increasing pH of the buffered suppository, and the apparent bioavailability of sulfonamides may be increased compared to the unbuffered suppository. From the results obtained, it would be considered that the addition of buffer reagents to the suppository is one of excellent procedures for enhancing the dissolution rate and absorption rate of sulfonamides and possibly other sparingly soluble drugs.