Effect of Dioctyl Sodium Sulfosuccinate and Poloxamer 188 on Dissolution and Intestinal Absorption of Sulfadiazine and Sulfisoxazole in Rats

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Abstract □ The influence of two medicinal surfactants, poloxamer 188 and dioctyl sodium sulfosuccinate, on the dissolution of sulfisoxazole and sulfadiazine was investigated. A dramatic increase in the dissolution rate was observed at all surfactant concentrations. Drug absorption from the rat small intestine was also studied, and a significant but less dramatic increase was noted. Dissolution rate and absorption could be correlated only qualitatively. The two surfactants had no effect on the amount of sulfisoxazole excreted by the rat in 24 hr.

Keyphrases □ Absorption, intestinal—sulfadiazine and sulfisoxazole, effect of dioctyl sodium sulfosuccinate and poloxamer 188, rats □ Dissolution—sulfadiazine and sulfisoxazole, effect of dioctyl sodium sulfosuccinate and poloxamer 188 □ Sulfadiazine—dissolution and intestinal absorption, effect of dioctyl sodium sulfosuccinate and poloxamer 188, rats □ Sulfisoxazole—dissolution and intestinal absorption, effect of dioctyl sodium sulfosuccinate and poloxamer 188, rats □ Dioctyl sodium sulfosuccinate—effect on dissolution and intestinal absorption of sulfadiazine and sulfisoxazole, rats □ Poloxamer 188—effect on dissolution and intestinal absorption of sulfadiazine and sulfisoxazole, rats □ Surfactants—dioctyl sodium sulfosuccinate and poloxamer 188, effect on dissolution and intestinal absorption of sulfadiazine and sulfisoxazole, rats

Surfactants are common adjuvants in many pharmaceutical preparations. Certain surfactants also are used medicinally. Dioctyl sodium sulfosuccinate (I) and poloxamer 188 (II) are two such agents used internally as fecal softeners. The effect of these two surfactants on the absorption of readily absorbable and poorly absorbable drugs, from solution, in animals and humans was reported previously (1–4).

The influence of synthetic as well as physiological surfactants on the solubility of poorly soluble drugs has been widely investigated (5–9). The change in the dissolution rate of solid drugs also has been studied. Until recently, most dissolution studies were carried out in the presence of high concentrations [above the critical micelle concentration (CMC)] of surfactants. The increases in dissolution rates and solubilities were attributed to micellar effects (10–12).

Few investigators have studied the effect of premicellar concentrations of surfactants. Polyoxyethylene lauryl ether and lysolecithin, in premicellar concentrations, increased the dissolution rate of salicylic acid powder (13). The synthetic agent also increased the rate of dissolution of a commercial aspirin tablet dosage form at low concentrations and approached a stable value around its CMC. Low concentrations of polysorbate 80 increased the dissolution rate of phenacetin powder, and this finding was attributed to the lowering of interfacial tension between the drug and the dissolution medium (14). Increasing the concentration of the surfactant above 0.01% had little effect.

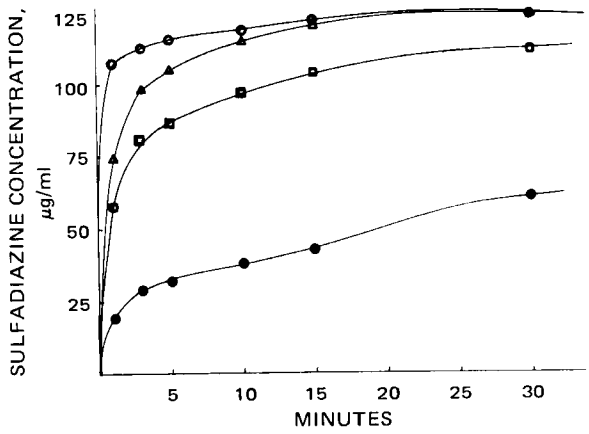

Figure 1—*Effect of poloxamer 188 on sulfadiazine dissolution. Key:* ●, *control;* □, *0.001%;* △, *0.01%, and* ○, *0.1%.*

Since both dioctyl sodium sulfosuccinate and poloxamer 188 are used in medicine primarily for their high wetting ability, the purpose of this study was to examine the influence of low concentrations of these two surfactants on the dissolution rate of drug powders. The effect of the same surfactant concentrations on absorption from the rat intestine was also examined. Sulfadiazine and sulfisoxazole were chosen as models because of their low solubility.

EXPERIMENTAL

Materials—Sulfadiazine[1] and sulfisoxazole[2] were pharmaceutical grade. Dioctyl sodium sulfosuccinate[3] and poloxamer 188[4] were used as received. All other chemicals were either reagent or analytical grade.

Absorption Studies from Rat *In Situ* Intestinal Loops—Male Sprague–Dawley[5] rats, 180–240 g, were fasted for 16–20 hr prior to the experiment, but water was allowed *ad libitum*. The procedure used was similar to the one reported by Nightingale *et al.* (15). Fifty milliliters of normal saline, warmed to 37°, was used to wash the intestinal loop, and a 10-min period was allowed for absorption of any residual solution prior to injection of the drug suspension. The abdominal cavity was closed with sutures, and the anesthetic was removed. At the end of 0.5 hr for sulfisoxazole and of 3 hr for sulfadiazine, the animal was sacrificed by placing it in an ether tank.

Analytical Procedure—After sacrifice of the animal, the intestinal loop was excised and homogenized with 10 ml of 0.1 *N* NaOH in a blender for 2 min. The blender was washed with water to yield 100 ml, and a fraction of the homogenate was centrifuged at 5000

[1] Matheson, Coleman and Bell, Norwood, Ohio.
[2] Supplied by Hoffmann-La Roche Inc., Nutley, N.J.
[3] Aerosol O. T. 100%, Sargent-Welch Scientific Co.
[4] Ethylene oxide–propylene oxide polymer of average molecular weight 8350, supplied as Pluronic F-68, by Wyandotte Chemicals Corp., Wyandotte, Mich.
[5] Horton Laboratories, Oakland, Calif.

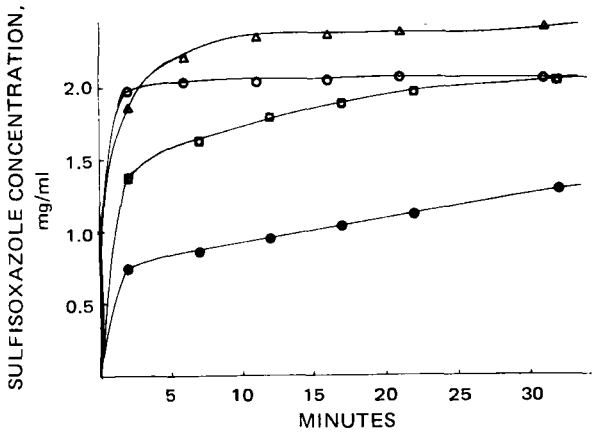

Figure 2—*Effect of poloxamer 188 on sulfisoxazole dissolution. Key: ●, control; □, 0.001%; △, 0.01%; and ○, 0.1%.*

rpm for 10 min. Ten milliliters of the supernate was pipetted into an equal volume of 30% trichloroacetic acid (w/v) and recentrifuged. The supernate was filtered, and an aliquot was assayed by the Bratton–Marshall method (16). All spectrophotometric[6] analyses were carried out at 533 nm for sulfisoxazole and at 530 nm for sulfadiazine. Tissue blanks were similarly analyzed, and no measurable absorbance was detected.

Absorption Studies in Intact Rats—The procedure used was similar to the one reported by Malik *et al.* (2). A 3.5-ml suspension of sulfisoxazole in water or a solution of the surfactants was administered by gastric intubation. Urine was collected for 24 hr, and the total sulfisoxazole was estimated by the Bratton–Marshall method.

Preparation of Drug Suspension—Drug suspensions for both *in situ* and intact rat studies were prepared in the same manner. The dosing volume was held constant at 3.5 ml. Eleven milligrams of the drug was weighed in a syringe, and the 3.5 ml of fluid was used in portions to inject or intubate the drug. The exact amount of drug administered was calculated by analyzing syringe washings and subtracting the amounts from the weighed value.

Drug Recovery—To see if the surfactants affected drug recovery, the following study was performed. After exposing the intestine and making a loop, the animal was sacrificed with ether and the drug suspension in water or surfactant solution was injected. After 0.5 hr (for sulfisoxazole) or 3 hr (for sulfadiazine), the loop was excised and analyzed for drug content. A mean recovery of 100% was obtained in the presence and absence of the surfactants.

Solubility Study—An excess of the drug was placed in 50-ml stoppered erlenmeyer flasks together with 25 ml of different concentrations of surfactant solutions in pH 6 phosphate buffer. The flasks were rotated in a constant-temperature water bath[7] at 37 ± 0.1° until equilibrium was attained (determined by repetitive sampling).

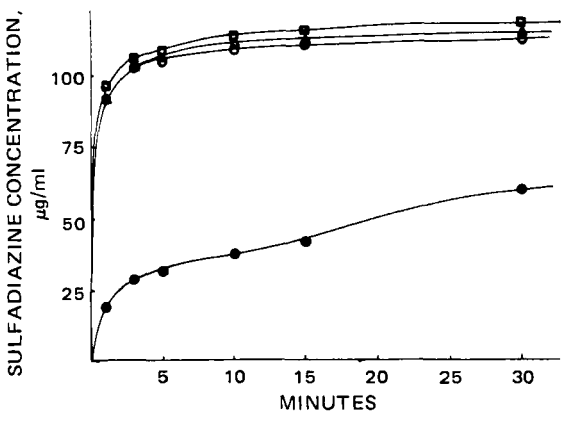

Figure 3—*Effect of dioctyl sodium sulfosuccinate on sulfadiazine dissolution. Key: ●, control; □, 0.001%; △, 0.01%; and ○, 0.1%.*

[6] Beckman ACTA CIII.
[7] Metabolyte water bath shaker, New Brunswick Scientific Co.

Table I—Effect of Poloxamer 188 and Dioctyl Sodium Sulfosuccinate on the Absorption of Sulfisoxazole from Rat Intestinal Loops[a]

Surfactant	Concentration, % w/v	Dose Absorbed, % ± *SD*
Control	—	45.3 ± 6.5
Poloxamer 188	0.01	56.1 ± 3.9
	0.10	57.3 ± 10.1
Dioctyl sodium sulfosuccinate	0.01	53.9 ± 9.4
	0.10	55.0 ± 8.4

[a] Values represent mean of six animals.

Dissolution Rate Studies—The dissolution rate was determined by the beaker method of Levy and Hayes (17) with slight modification. An 80–100-mesh powder was used. The dissolution medium consisted of 500 ml of 0.5 *M* phosphate buffer, pH 6, containing various concentrations of the surfactants. A 1-liter beaker was kept in a constant-temperature water bath at 37 ± 0.1°, and a three-blade, 4.4-cm (1.75-in.) diameter polyethylene stirrer[8] was centered and adjusted so that when the dissolution medium was added it would dip 3.5 cm into the liquid medium.

Sulfisoxazole (5 g) or sulfadiazine (2 g) was added to the beaker, and the fluid was poured along the walls of the beaker. Before the addition of the fluid, the stirrer was set to rotate at 60 rpm by means of a variable speed motor. At frequent time intervals, 2 ml of the dissolution medium was pipetted out and filtered through a membrane filter[9] (0.45-μm pore size) into a flask. The flask was kept at 37° to prevent possible crystallization of the drug. Two milliliters of fresh dissolution medium was immediately added to the beaker.

The amount of drug in solution at various time intervals was determined spectrophotometrically at 252 nm in a pH 7.5 phosphate buffer for sulfisoxazole and at 240 nm in 0.1 *N* HCl for sulfadiazine. Correction was made for the dilution effect (18). All dissolution rate experiments were performed at least in duplicate.

RESULTS AND DISCUSSION

Dissolution and Solubility Studies—Figures 1 and 2 illustrate the effect of poloxamer 188 on the dissolution behavior of sulfadiazine and sulfisoxazole, respectively. The presence of the surfactant in the dissolution medium significantly increased the dissolution rate of the two drugs. Figure 1 shows that increasing the concentration of poloxamer 188 from 0.001 to 0.1% increased the dissolution of the drug both initially and during the entire experiment. With sulfisoxazole (Fig. 2), an increase in the surfactant

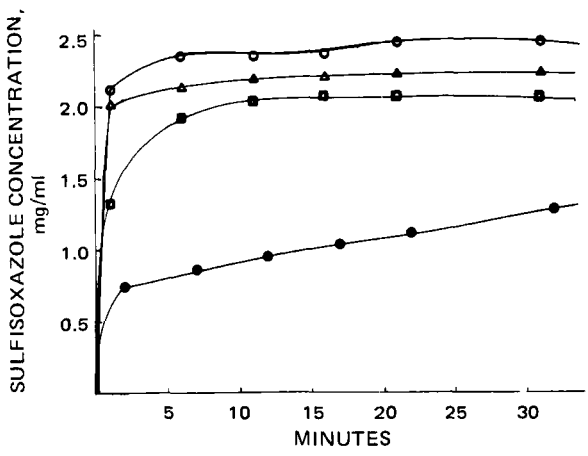

Figure 4—*Effect of dioctyl sodium sulfosuccinate on sulfisoxazole dissolution. Key: ●, control; □, 0.001%; △, 0.01%; and ○, 0.1%.*

[8] No. 6160, Nalge Co., Division of Sybron Corp.
[9] Millipore.

Table II—Effect of Poloxamer 188 and Dioctyl Sodium Sulfosuccinate on the Absorption of Sulfadiazine from Rat Intestinal Loops[a]

Surfactant	Concentration, % w/v	Dose Absorbed, % ± *SD*
Control	—	57.5 ± 5.0
Poloxamer 188	0.01	70.9 ± 4.3
	0.10	70.1 ± 3.2
Dioctyl sodium sulfosuccinate	0.01	66.9 ± 7.2
	0.10	71.3 ± 4.0

[a] Values represent mean of six animals.

concentration from 0.001 to 0.1% resulted in an initial increase in drug dissolution. However, there was less dissolution of sulfisoxazole in 0.1% poloxamer 188 than in 0.01% after 4 min. This slight decrease in dissolution at the higher surfactant concentration could be the result of particle aggregation or flocculation due to this specific concentration of the surfactant.

The dissolution behavior of sulfadiazine in the presence of dioctyl sodium sulfosuccinate is shown in Fig. 3. The dissolution rate of the drug increased in the presence of all surfactant concentrations studied. Increasing the concentration of the surfactant from 0.001 to 0.1% had no significant effect on the dissolution behavior of the drug.

Figure 4 shows the dissolution behavior of sulfisoxazole in the presence of various concentrations of dioctyl sodium sulfosuccinate. A concentration of 0.001% of the surfactant significantly increased the dissolution rate. Higher concentrations caused only a slight increase over that caused by 0.001%.

The solubility of sulfadiazine in the same pH 6 phosphate buffer, containing no surfactant, was 13.0 mg/100 ml. The solubility of the drug in 0.001, 0.01, and 0.1% of both surfactant solutions was 13.5 mg/100 ml. For sulfisoxazole, the solubility in the buffer solution and in all concentrations of the two surfactants was 242.4 mg/100 ml. The solubility studies indicate, in accordance with the reported CMC values of these two surfactants (19, 20), the lack of micellar solubilization. Therefore, the effect of these surfactants on the dissolution rate of the two sulfonamides studied is mainly caused by their ability to decrease the interfacial tension between the drug particles and the dissolution medium. Such lowering of interfacial tension is expected to increase the effective surface area of the drug exposed to the dissolution medium (14, 21, 22).

Absorption Studies—Results of the effect of both surfactants on the absorption of sulfisoxazole from *in situ* intestinal loops of rats are summarized in Table I. Except for 0.01% dioctyl sodium sulfosuccinate, the presence of the surfactants resulted in a small but significant ($p < 0.05$) increase in drug absorption. Table II shows the effect of these two surfactants on the absorption of sulfadiazine. A significant ($p < 0.001$; except for 0.01% of I, $p < 0.05$) increase in drug absorption was caused by all surfactant concentrations. A 10-fold increase in the surfactant concentration, from 0.01 to 0.1%, did not significantly increase drug absorption. This finding correlates well with what was observed in the dissolution studies (Figs. 1–4).

The observed effect of the two surfactants on the absorption of the two sulfonamides seems due primarily to the enhancement of the dissolution rate. Previous studies (2) indicated that poloxamer 188 does not have a direct effect on the permeability of the rat GI membrane. With dioctyl sodium sulfosuccinate, an additional effect on the intestinal membrane may also be operative (1–4). The extent of increase in drug absorption in the presence of the surfactants did not quantitatively correlate with the increase in dissolution rate. This finding could be due to the obvious difference in the intensity of agitation. In addition, the control experiments in the dissolution studies did not contain any surfactant whereas the controls in the absorption studies could have had residual bile and mucin in the intestinal loop. These physiological materials would probably lower the surface tension; therefore, the effect of the surfactants could be in addition to the effect of such materials.

Table III—Effect of Poloxamer 188 on the Total Urinary Excretion of Sulfisoxazole after Oral Administration to Rats[a]

Concentration, % w/v	Dose Absorbed, % ± *SD*
Control	76.7 ± 3.9
0.01	80.0 ± 6.0
Control	78.3 ± 5.5
0.10	80.0 ± 6.0

[a] Values represent mean of six animals.

Table IV—Effect of Dioctyl Sodium Sulfosuccinate on the Total Urinary Excretion of Sulfisoxazole after Oral Administration to Rats[a]

Concentration, % w/v	Dose Absorbed, % ± *SD*
Control	73.2 ± 9.0
0.01	77.9 ± 6.8
Control	75.5 ± 6.2
0.10	83.4 ± 10.4

[a] Values represent mean of six animals.

The amounts of sulfisoxazole excreted in 24 hr after oral administration of suspensions containing dioctyl sodium sulfosuccinate and poloxamer 188 are shown in Tables III and IV. The surfactants had no significant effect on the total drug absorbed in 24 hr. It seems that the effect of the surfactants on drug absorption is primarily on the initial rates—not on the total amount of drug absorbed. Fincher *et al.* (23) found that the same proportion of an oral dose of sulfisoxazole was absorbed when dogs were given suspensions of different particle sizes. Studies in humans indicated a difference in rate, but not in the extent, of urinary excretion of sulfisoxazole (24, 25). Solomon (26) found that although the dissolution rates of three commercial tablet dosage forms of sulfisoxazole were markedly different, the cumulative amount excreted in the urine at various times from 1 to 24 hr after administration did not differ significantly. In summary, the results of this study indicate that the dissolution rate of both sulfadiazine and sulfisoxazole increases dramatically in the presence of the two medicinal surfactants, poloxamer 188 and dioctyl sodium sulfosuccinate. A less dramatic but significant increase in the absorption rate of the two drugs was also observed.

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Polarographic Determination of Isosorbide Dinitrate

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Abstract □ Isosorbide dinitrate and two isomeric isosorbide mononitrates are shown to be polarographically reducible in aqueous sodium perchlorate or potassium chloride solution. The current, measured at −1.6 v, *versus* the saturated calomel electrode is proportional to the concentration of organic nitrate in the 10–100-μg/ml range. Inorganic nitrate produces no interference. However, the mononitrate isomers produce an additive response to isosorbide dinitrate and cannot be determined individually. The polarographic method is applicable to single-tablet assay for content uniformity determination, with precision and accuracy comparable to automated colorimetric analysis. Comparison is made between replicate analyses obtained polarographically and by IR and automated colorimetric analysis for six different commercially available formulations. The polarographic determination is sensitive, specific for nitrate esters, precise, requires little sample preparation, and utilizes relatively inexpensive apparatus.

Keyphrases □ Isosorbide dinitrate—polarographic analysis, compared to IR and automated colorimetric methods, six commercial formulations □ Polarography—analysis, isosorbide dinitrate, compared to IR and automated colorimetric methods, six commercial formulations

Since the discovery that organic nitrate esters are reducible at the dropping mercury electrode, several polarographic methods have been developed for such pharmaceutically important compounds as nitroglycerin and pentaerythritol tetranitrate. Nitrate esters are reduced polarographically in a two-electron, pH-independent process to yield nitrite ion and the corresponding alcohol (1). The polarographic determination of nitroglycerin and other polynitrate esters, including pentaerythritol tetranitrate, was reported (2, 3).

Polarographic procedures have several advantages over other procedures for determining nitrate esters of pharmaceutical interest. The principal advantages are sensitivity, specificity, speed of analysis, and the moderate cost of the apparatus. Samples generally can be analyzed without prior separation or other sample preparation, since excipients usually do not interfere. This procedure results in a considerable saving in time, particularly when large numbers of single tablets must be analyzed to establish content uniformity.

For example, a procedure was developed for determining content uniformity for nitroglycerin sublingual tablets in which single tablets are introduced into the polarographic cell and are analyzed in the presence of tablet excipients such as lactose, mannitol, and corn starch (4). Lactose and mannitol had no effect on the polarographic reduction. Although corn starch produced a slight increase in the current–concentration ratio, this increase was negligible at concentrations normally found in sublingual tablets.

Table I—Current–Concentration Relationships for Isosorbide Dinitrate[a]

Concentration, μg/ml of Dinitrate	Current, μamp
10	0.92
20	1.66
30	2.46
40	3.44
50	4.26
60	4.94
70	5.80
80	6.82
90	7.53
100	8.33

[a] Micrograms per milliliter of dinitrate = 12.0 × μamp −0.41, and r = 0.9995.

There are several procedures for analyzing isosorbide dinitrate (I). A colorimetric procedure was described based on the hydrolysis of the nitrate ester and the determination of the nitrate ion produced using *vic-m*-xylenol (5). In a study of the dissolution rates of isosorbide dinitrate tablets, a UV absorption spectrophotometric method was utilized for assay

Table II—Current–Concentration Relationship for the Two Isosorbide Mononitrates

Micrograms per Milliliter of Mononitrate	Equivalent Concentration of Dinitrate, μg/ml	Current for *exo*-Mononitrate[a], μamp	Current for *endo*-Mononitrate[b], μamp
16.2	10	0.96	0.95
32.4	20	1.78	1.75
48.6	30	2.72	2.64
64.8	40	3.53	3.45
81.0	50	4.37	4.34

[a] Micrograms per milliliter of *exo*-mononitrate = 18.89 × μamp −1.88, and r = 0.9997. [b] Micrograms per milliliter of *endo*-mononitrate = 19.12 × μamp − 1.65, and r = 0.9999.