the tablet. Results are also presented which show that an intramuscular dosage form is very well absorbed and excreted readily in the urine.

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Physiologic Surface-Active Agents and Drug Absorption IV: Effect of Pre-Micellar Concentrations of Surfactant on Dissolution Rate

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Abstract ☐ The influence of a nonionic surfactant and certain physiologic surfactants and components of gastric juice on the dissolution rate of drug powders was examined. In addition, the effects of pre-micellar concentrations of surfactant on the dissolution rate of aspirin from commercial dosage forms were determined. Low concentrations of polyoxyethylene (23) lauryl ether (POE lauryl ether), and lysolecithin markedly enhanced the dissolution rate of salicylic acid powder while pepsin and gastric mucin were without effect. Sodium glycocholate was found to increase considerably the dissolution rate of salicylamide powder in pH 6.0 buffer. Both POE lauryl ether and lysolecithin enhanced the dissolution rate of aspirin from a tablet dosage form but were without effect on the dissolution rate of the drug from a capsule dosage form. Good correlation was observed between the surface tensions of the POE lauryl ether solutions and the dissolution rates of aspirin from the tablet dosage form in these media. The relevance of these data to the design of *in vitro* dissolution tests is discussed.

Keyphrases ☐ Surfactants, physiologic—dosage form dissolution ☐ Pre-micellar surfactant concentration—dissolution rates ☐ Dissolution rates—surfactants, gastric mucin ☐ UV spectrophotometry—analysis

There is a strong likelihood that certain components of the gastrointestinal tract facilitate drug dissolution. Biliary secretion results in relatively large concentrations of highly surface-active materials in the proximal intestine. Components of bile such as conjugated bile salts and lysolecithin have been found to markedly increase the solubility and dissolution rate of various poorly water-soluble drugs (1–4). Pekanmaki and Salmi (5) report a marked decrease in the absorption of poorly soluble phenolphthalein when drainage of bile into the rat intestine is prevented. However, the absence of bile had no effect on the absorption of the water-soluble glucuronide conjugate of phenolphthalein. More recently Meli *et al.* (6) note that endogenous bile influences the rate of intestinal absorption of ethynylestradiol-3-cyclopentyl ether in rats. The rate of absorption of the estrogen is considerably lower in bile duct-cannulated rats than in control animals. Since the drug is relatively water-insoluble, it is reasonable to consider that the presence of bile increases the solubility of the drug in the intestinal lumen and thereby enhances the dissolution and absorption rate.

Finholt and Solvang (7) have suggested the presence of physiologic surfactants in human gastric fluid. Samples of gastric juice obtained from patients under examination for diseases of the stomach manifested rather low surface tenson values (35 to 50 dynes/cm.) and marked wetting activity as judged by powder dissolution studies. The rates of dissolution of phenacetin in diluted gastric juice and in dilute HCl at the same pH and adjusted to the same surface tension as gastric juice with polysorbate 80 were similar but markedly faster than the rates observed in dilute HCl alone.

The influence of surface-active agents on the dissolution rates of relatively water-insoluble drugs may involve several mechanisms. For example, a surfactant may decrease the interfacial energy barrier between the drug and the dissolution medium, allowing the drug to be "wet" more completely and thereby effectively increase the available surface area of the solid. Additionally, concentrations of surfactant above the critical micelle concentration (CMC) may markedly increase the apparent solubility of the drug in the medium by means of micellar solubilization and thereby effect an increase in the dissolution rate, which is a function of diffusional parameters and the hydrodynamics of the system (8–10). While the influence of micellar solubilization on dissolution has been studied rather extensively, the effect of low concentrations (below the CMC) of surface-active agents on the dissolution of drugs from

powders and other solid dosage forms has been given limited attention. It was the purpose of the present study to examine the influence of surfactants, physiologic surfactants and certain components of gastric juice on the dissolution rates of drug powders and to determine the possible effects of pre-micellar concentrations of surfactant on the dissolution rate of aspirin from certain commercial dosage forms of the drugs.

EXPERIMENTAL

Powder Dissolution—The dissolution rates of salicylic acid[1] and salicylamide[1] were determined at 37° according to the methods of Finholt and Solvang (7). In each case 100 mg. of salicylic acid or 150 mg. of salicylamide was passed through a 12-mesh standard sieve onto the surface of 200 ml. of dissolution medium contained in a 250-ml. jacketed beaker. The medium was agitated by means of a magnetic stir bar at a rate of about 60 r.p.m. The agitation was of sufficiently low intensity to prevent the formation of a vortex in the system.

The dissolution media for the salicylic acid studies consisted of 0.1 *N* HCl with various concentrations of additives including polyoxyethylene (23) lauryl ether[2] (POE lauryl ether), lysolecithin,[3] gastric mucin,[4] and pepsin NF.[5] The dissolution medium for the salicylamide studies consisted of pH 6.0 phosphate buffer (0.05 *M* total phosphate) containing 10 m*M* sodium glycocholate.[6]

After addition of the drug to the dissolution medium, 1-ml. samples of the medium were taken periodically with a filter pipet, diluted appropriately, and analyzed spectrophotometrically[7] at 302.5 mμ for salicylic acid (in 0.1 *N* HCl) and at 300 mμ for salicylamide (in pH 6.0 buffer) against an appropriate blank.

Dosage Form Studies—The influence of low concentrations of POE lauryl ether and lysolecithin on the dissolution of aspirin at 37° from two commercially available preparations was studied using a modification of the beaker method (11) as described previously (12). The dosage forms consisted of a buffered tablet and hard gelatin capsule each containing 325 mg. (5 grains) of aspirin, and were obtained from retail outlets. The dissolution medium consisted of 400 ml. 0.1 *N* HCl containing various concentrations of surfactant. Agitation was provided by a 7-cm. Teflon blade fitted to a glass stirring rod attached to an overhead motor, and maintained constant at 50 r.p.m. The depth of the stirring blade in the dissolution medium was kept constant with the bottom edge of the blade maintained 4.5 cm. below the surface of the liquid.

A problem was encountered in that the capsule, due to its low bulk density, floated on the surface of the dissolution medium. This was overcome by placing the capsule in a rectangular wire frame with all faces open to the dissolution medium. The frame provided sufficient weight to prevent floating and did not appear to interfere with the flow of fluid about the capsule itself. With either dosage form little material was found at the surface upon disintegration or disruption and undissolved drug and excipients were present in the form of a mound at the bottom of the round-bottom flask.

Preliminary experiments with the tablet dosage form indicated a marked difference in the dissolution rate of aspirin depending upon which face of the tablet is presented to the dissolution medium, i.e., which face is up. When the manufacturer's identifying mark (logogram) was facing up the time required to dissolve 50% of the drug content ($t_{50\%}$) was about twice that observed when the logogram was facing down. The dosage form appears to be a two-layer tablet; one layer contains the buffering ingredients while the other contains the aspirin. The logogram is impressed on the layer containing the buffering ingredients. Arbitrarily it was decided to evaluate the dissolution rates only when the logogram was facing up and all results in this report are based on this experimental condition.

After introduction of the dosage form to the flask, 1-ml. samples were taken at appropriate intervals with a filter pipet. One milliliter of 1 *N* NaOH was added to each sample and the sample was then hydrolyzed for 1 hr. at 100°. The pH of the hydrolyzate was adjusted to pH 1 with HCl and the sample diluted to volume with 0.1 *N* HCl. Total salicylate was determined spectrophotometrically as described above.

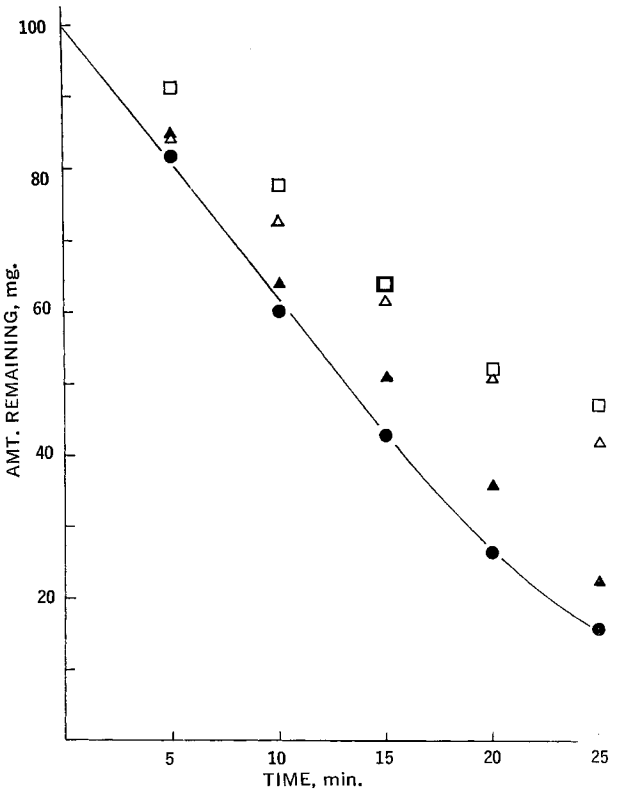

Figure 1—*Effect of pepsin and gastric mucin on the dissolution of salicylic acid powder in 0.1 N HCl. Key:* (●), *control;* (△), *0.32% w/v pepsin;* (▲), *0.05% w/v gastric mucin;* (□), *0.2% w/v gastric mucin. Data represent means of three to five determinations.*

RESULTS

The dissolution rate of salicylic acid from the surface of 0.1 *N* HCl solution is shown in Fig. 1. Approximately 70% of the material dissolves in an apparent zero-order fashion at a constant rate of about 4 mg./min. This indicates that during the initial course of dissolution the effective surface area of the powder is relatively constant and there is little permeation or wetting of the solid phase by the solvent. Dissolution occurs primarily from the liquid-solid interface which is limited in area. Also included in the figure is the dissolution data obtained in 0.1 *N* HCl containing pepsin and gastric mucin. The lower concentration of mucin had little effect on the dissolution of salicylic acid but the higher concentration of mucin as well as 0.32% (w/v) pepsin inhibited dissolution.

The influence of surface-active agents on the dissolution of salicylic acid is shown in Fig. 2. Both POE lauryl ether and lysolecithin markedly enhance the dissolution rate of the drug compared to that observed in 0.1 *N* HCl. The results are essentially a function of enhanced wetting and increased effective surface area in the surfactant systems since based on equilibrium solubility studies these concentrations of surfactant have virtually no effect on drug solubility. When the drug is dusted on the surface of the surfactant solutions, wetting is observed and the powder rapidly leaves the surface and is dispersed in the bulk.

A similar plot of the influence of 10 m*M* sodium glycocholate on the dissolution of salicylamide in pH 6 buffer is shown in Fig. 3. This concentration of glycocholate is comparable to the usual concentration of conjugated bile salts in the proximal intestine (13). Salicylamide is about 12.5% more soluble in the glycocholate solution than in the buffer solution alone. This difference however cannot account for the pronounced increase in dissolution rate. Hence

[1] Eastman Organic Chemicals, Rochester, N. Y.
[2] Polyoxyethylene (23) lauryl ether. Generously supplied by Atlas Chemical Industries Inc., Wilmington, Del.
[3] Nutritional Biochemical Co., Cleveland, Ohio.
[4] K & K Laboratories, Plainview, N. Y.
[5] Fisher Scientific Co.
[6] Mann Research Laboratories, New York, N. Y.
[7] Hitachi-Perkin Elmer spectrophotometer model 139

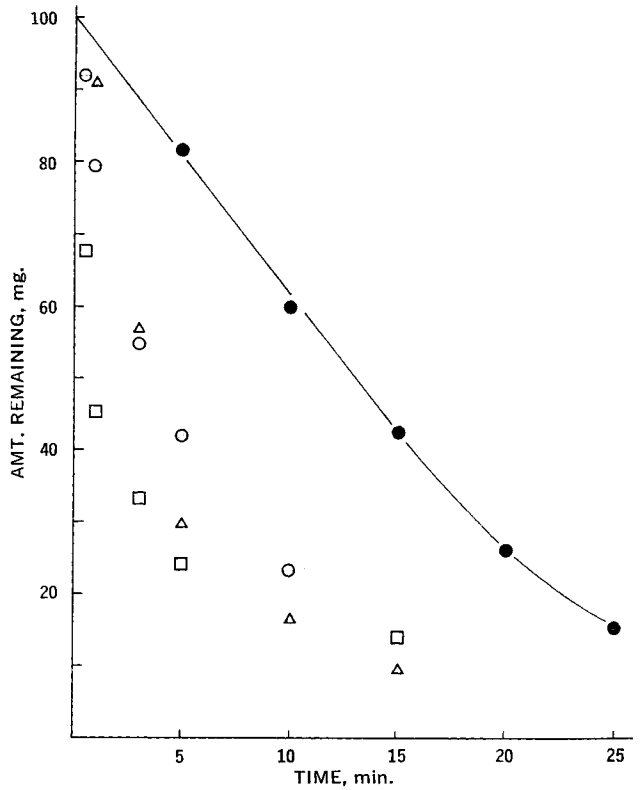

Figure 2—*Effect of pre-micellar concentrations of polyoxyethylene (23) lauryl ether and lysolecithin on the dissolution of salicylic acid powder in 0.1* N *HCl. Key:* (●), *control;* (□), *0.01% w/v POE lauryl ether;* (△), *0.0025% w/v lysolecithin;* (○), *0.005% w/v lysolecithin. Surfactant data represent means of two determinations.*

the results primarily demonstrate the marked wetting activity of physiologic concentrations of conjugated bile salts.

Comparison of the dissolution rates of aspirin from the tablet and capsule dosage forms in 0.1 *N* HCl at 50 r.p.m. is shown in Fig. 4. There is little difference in the initial dissolution rates, and the time required to dissolve about $^1/_3$ of the drug content from each dosage form is identical. However after disintegration or disruption of the dosage form and formation of a mound, the dissolution from the capsule formulation is considerably faster than from the tablet formulation. Consequently there is a marked difference in the $t_{50\%}$ values for each dosage form (see Table I).

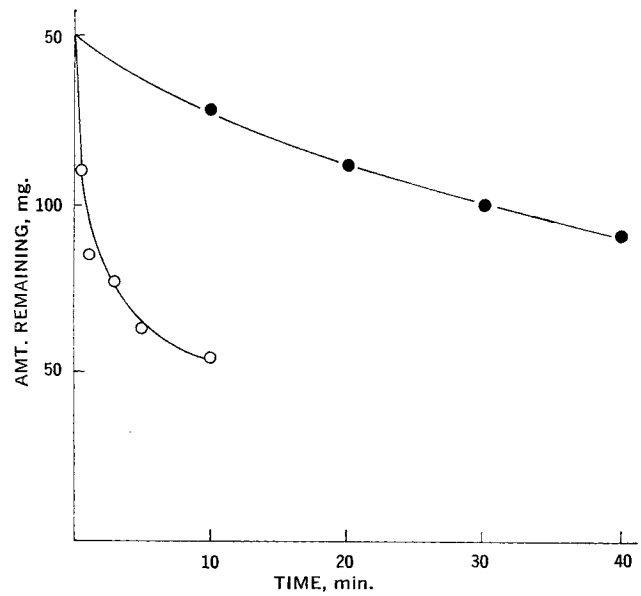

Figure 3—*Effect of physiologic concentrations of conjugated bile salt on the dissolution of salicylamide powder in pH 6.0 phosphate buffer. Key:* (●), *control;* (○), *10 mM sodium glycocholate.*

Table I—Mean Time Required to Dissolve 50% of the Aspirin Content ($t_{50\%}$) from Two Dosage Forms in 0.1 *N* HCl Under Various Experimental Conditions

Dosage Form and Conditions of Expt.	No. of Determinations	Mean $t_{50\%}$ ($\pm SD$), min.
Capsules—0.1 *N* HCl	5	34.7 (10.5)
Capsules—0.01% POE lauryl ether	4	34.3 (11.2)
Capsules—0.0025% Lysolecithin	2	48.5 (51, 46)
Tablets—0.1 *N* HCl	3	52.0 (9.9)
Tablets—0.01% POE lauryl ether	5	14.5 (7.2)
Tablets—0.0025% Lysolecithin	3	8.2 (5.9)

Inclusion of 0.01% w/v POE lauryl ether in the dissolution medium produces rather interesting results, as may be seen in Fig. 4. The surfactant had virtually no effect on the dissolution of aspirin from the capsule but markedly increased the dissolution rate of drug from the tablet. As shown in Table I the $t_{50\%}$ value in the surfactant solution is reduced to about one-third of tablet control levels. Comparison of the dissolution rates of aspirin from the tablet and capsule dosage forms in surfactant solution indicated a statistically significant difference ($p < 0.01$) in favor of the tablet dosage form.

Inclusion of the physiologic surfactant, lysolecithin, in the dissolution medium produced results similar to those observed with POE lauryl ether. As shown in Table I, the $t_{50\%}$ value for the capsule was actually increased somewhat over control values, principally due to a delay in the initial disruption of the gelatin. Lysolecithin markedly decreased the $t_{50\%}$ of the tablet dosage form from a control level of 52 min., to 8 min.

The influence of POE lauryl ether concentration on the dissolution of aspirin from the tablet dosage form is shown in Fig. 5. Initial dissolution rates are found to increase as a function of surfactant concentration. This is evident by considering the mean $t_{50\%}$ values in Table II. However the effect appears to approach a maximum at about 0.01% w/v which corresponds closely to the CMC of 0.011 g./100 ml. at 35° reported by Becher and Arai (14). Also shown in Table II are the surface tension values for the various solutions determined by means of a ring tensiometer[8] at room temperature. Apparently good correlation is observed between surface tension lowering and the change in $t_{50\%}$.

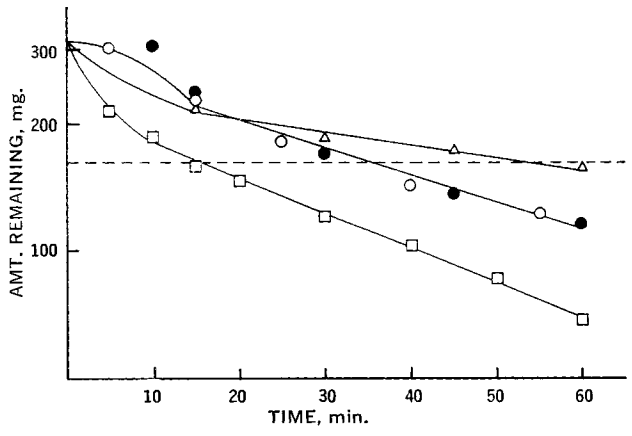

Figure 4—*Effect of 0.01% w/v polyoxyethylene (23) lauryl ether on the dissolution of aspirin from a capsule and tablet dosage form in 0.1* N *HCl. Key: controls:* (○), *capsule;* (△), *tablet; surfactant solution:* (●), *capsule;* (□), *tablet.*

[8] Fisher Surface tensiometer model 20, Fisher Scientific Co.

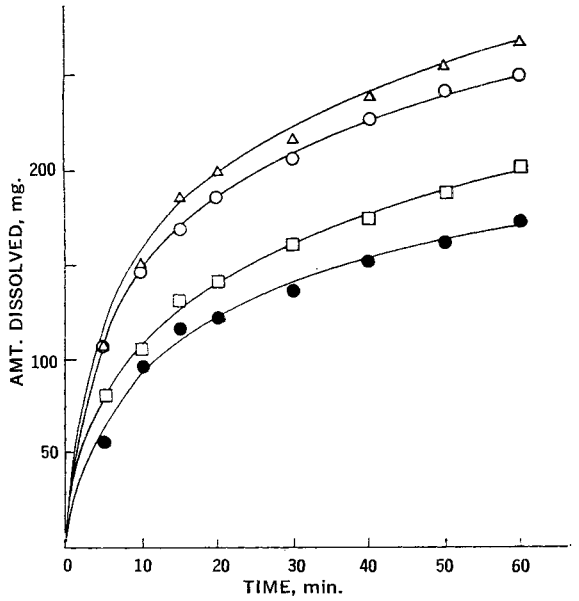

Figure 5—*Dissolution of aspirin from a tablet dosage form as a function of polyoxyethylene (23) lauryl ether concentration in 0.1* N *HCl. Key:* (●), *control;* (□), *0.005% w/v;* (○), *0.01% w/v;* (△), *0.03% w/v.*

DISCUSSION

Although there is a great deal of interest in the development of systems to generate dissolution data which may be related to *in vivo* data on dissolution rate-limited absorption, there has been very limited attention given to a consideration of the inclusion of surface-active agents in such systems. The presence and role of physiologic surfactants in intestinal fluid is well established. The presence of physiologic surfactants in gastric fluid has been suggested (7) but not proven conclusively. Samples of gastric juice obtained from patients under examination for gastric disorders show a great deal of surface activity. The source of this activity is undetermined, however. The present studies indicate that neither gastric mucin nor pepsin possess a high degree of surface activity as judged by powder dissolution studies. On the other hand, conjugated bile salts and lysolecithin, both of which may be present in small amounts in gastric fluid, demonstrate marked wetting activity and their presence may exert a significant influence on dissolution. Several investigators (15, 16) suggest a reflux of duodenal contents into the stomach. Hence normal gastric fluid may frequently be contaminated by intestinal contents which are highly surface-active. Lysolecithin may also be present in gastric fluids by virtue of the normal turnover and breakdown of gastric mucosal cells (16–18).

The possible influence of physiologic surfactants on dissolution has been clearly demonstrated in the powder dissolution rate study reported previously (7) and in the present study. However, the use of systems whereby powder is dusted on the surface of the dissolution medium certainly optimizes the influence of a wetting agent on dissolution rate. Moreover, this type of system has no physiologic relevance with respect to usual dosage forms. Hence it was of interest to examine the influence of low concentrations of surface-active agents on the dissolution rate of a drug from a dosage form using more conventional methodology. The tablet data summarized in Table I clearly support the possibility that physiologic surfactants play a role in dissolution rate-limited absorption. Low concentrations of POE lauryl ether or lysolecithin markedly increase the dissolution rate of aspirin from the tablet presumably by a wetting and/or deaggregation effect, both of which would result in an increased effective surface area. Based on the data in Fig. 5 and Table II it appears that the magnitude of this effect increases as a function of surfactant concentration and approaches a maximum at concentrations in the range of the CMC.

Preston (19) studied certain physical properties of detergent solutions and observed that striking alterations in the various properties occur in the region of the CMC. He finds, for example,

Table II—Relationship Between Surface Tension (γ) of Dissolution Medium and Dissolution Rate ($t_{50\%}$) of Aspirin from Tablet Dosage Form as a Function of Surfactant Concentration in 0.1 *N* HCl

% (w/v) Polyoxyethylene (23) Lauryl Ether in 0.1 *N* HCl	γ, dyne cm.$^{-1}$	Mean $t_{50\%}$, min.
0.00	78	52
0.005	58	30
0.01	41	14.5
0.03	40	11

that the ability of sodium dodecyl sulfate to lower surface and interfacial tension is maximal at the CMC. The term wetting as used in various practical situations tends to be defined in terms of the effect desired. Usually, however, wetting means that the contact angle (θ) between a liquid and a solid approaches zero (20). According to the Dupre equation

$$\cos\theta = (\gamma_S - \gamma_{SL})/\gamma_L \qquad \text{(Eq. 1)}$$

where γ_S and γ_L refer to the surface tensions of the solid and liquid, respectively, and γ_{SL} refers to the solid-liquid interfacial tension. Adamson (20) notes that if good wetting is to be observed, both γ_L and γ_{SL} should be made as small as possible. From a practical standpoint, this is best accomplished by adding a surfactant to the liquid phase, which is adsorbed at the solid-liquid and liquid-air interfaces and therefore lowers these interfacial tensions. If the surfactant is nonvolatile, it may be presumed not to affect γ_S. It follows, therefore, that wetting is maximal at the CMC.

The lack of effect of either surfactant on the dissolution of aspirin from the capsule formulation is quite interesting in contrast to the effects observed with the tablet formulation. Moreover this differential effect may have pertinence in studies attempting to correlate *in vitro* dissolution with *in vivo* absorption. For example let us assume that one desires to predict a rank correlation of absorption rates of the two formulations. The dissolution data obtained in 0.1 *N* HCl using the modified beaker method (Table I) suggest that more rapid dissolution occurs with the capsule formulation. However urinary excretion studies in man (unpublished observations) indicates that the initial absorption rate of aspirin is significantly more rapid from the tablet than from the capsule dosage form. Upon addition of the surfactant to the dissolution media one finds the same rank correlation as observed *in vivo*. This type of crossover phenomenon in *in vitro* correlation studies is not unique. Similar effects have been reported by Levy (21) as a function of pH and agitation rate.

The authors wish to clearly state that it is not the intent of this report to propose the arbitrary inclusion of surfactants in dissolution test systems. They have attempted to point out the physiologic realities, the potential effects of wetting agents, and, equally important, the complexities of the situation. They propose that the presence of physiologic surfactants in the gastrointestinal tract and the observed effects of these surfactants on dissolution warrant serious consideration in the design of dissolution rate tests for predicting drug absorption and availability.

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Intestinal Absorption of Heparin: A Study of the Interactions of Components of Oil-in-Water Emulsions

R. H. ENGEL* and S. J. RIGGI

Abstract □ It was previously reported that intraduodenal administration of heparin in an emulsified form to rats and gerbils results in the intestinal absorption of heparin and appearance of serum clearing factor (lipase) activity. The present studies were undertaken to define the effects of the emulsion components on the absorption of heparin as measured by clearing factor activity and to determine optimum composition of the emulsion. Using a three-component composite design, the effects of varying heparin, surfactant (an anionic phosphate ester), and oil (trioctanoin) concentrations have been studied simultaneously and the characteristics of the interrelationships analyzed. Clearing factor activity was directly related to the concentration of each of the emulsion components. An inverse relationship was evident for heparin and oil such that the loss of activity resulting from a lowered heparin concentration can, within limits, be compensated for by an increase in the oil concentration. The data suggest that heparin absorption is directly related to and may vary with the particle size and total surface area of the oil droplets. The relationships presented may be unique for the particular surfactant and oil chosen.

Keyphrases □ Heparin absorption, effects of emulsion composition □ Emulsions, oil-in-water—interaction of components □ Clearing factor activity, emulsions

It was previously reported (1, 2) that the intestinal absorption of heparin could be effected by its intraduodenal administration in an emulsion containing vegetable oil and a suitable surfactant. A number of possible combinations were described (1). The present studies were undertaken to investigate the effects of emulsion composition on heparin absorption and to determine the concentrations of heparin, oil, and surfactant necessary to achieve maximum absorption of the polysaccharide. Combinations of emulsion components were varied in a factorial manner according to a three-factor composite design (3) to take into account possible interactions between components.

Table I—Concentrations Studied in Composite Design[a]

Heparin, mg./kg.	Trioctanoin, %	Surfactant, % 0.01	0.023	0.10	0.435	1.0
150	3.2					
	5.5					
	12.5			*9*[a]		
	28.6					
	50.5					
100	3.2					
	5.5		*1*		*5*	
	12.5					
	28.6		*6*		*2*	
	50.0					
55	3.2			*10*		
	5.5					
	12.5	*11*		*15*		*12*
	28.6					
	50.0			*13*		
30	3.2					
	5.5		*7*		*3*	
	12.5					
	28.6		*4*		*8*	
	50.0					
	3.2					
20	5.5					
	12.5			*14*		
	28.6					
	50.0					

[a] Numbers in italics correspond to points indicated in Fig. 1.

EXPERIMENTAL

Materials and Methods—Heparin, sodium (Lederle Laboratories), trioctanoin (Eastman), and a phosphate ester surfactant (RE-610, Antara Chemicals) were used. Preparation of the emulsions was carried out in a single step as previously described (1). Heparin in aqueous solution with the surfactant was used as control. Final concentrations of the surfactant and trioctanoin and doses of heparin are presented in Tables I and II. The volume of emulsion or solution administered was 5 ml./kg. body weight.

Animals used were male Wistar rats (175-250 g., obtained from