Effect of Polysorbate 80 on the Solubility and *In Vivo* Availability of 2-Butyl-3-benzofuranyl 4-[2-(Diethylamino)ethoxy]-3,5-diiodophenyl Ketone Hydrochloride (SK&F 33134-A)

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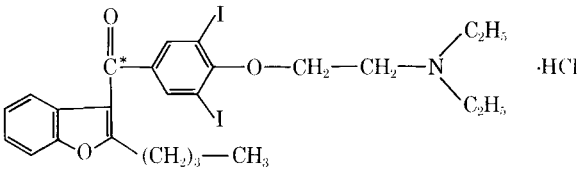
Abstract □ Polysorbate 80 has been shown to have a significant effect on the solubility of 2-butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride (SK&F 33134-A). Subsequent *in vivo* studies in bile-cannulated rats with SK&F 33134-A-^{14}C indicated that the drug was better absorbed when it was solubilized with polysorbate 80. Biliary excretion served as an index of absorption of orally administered drug in the rat. A twofold increase in the amount of drug excreted through the bile was observed for the solubilized form. The data also suggest that urinary excretion measurements should not be used to indicate the degree of absorption of this drug in the rat.

Keyphrases □ 2-Butyl-3-benzofuranyl 4-[2-(diethylamino) ethoxy]-3,5-diiodophenyl ketone hydrochloride (SK&F 33134-A), ^{14}C-labeled—solubility, availability □ Polysorbate 80 effect—SK&F 33134-A-^{14}C solubility, *in vivo* availability □ Biliary, urinary excretion—SK&F 33134-A-^{14}C □ Scintillometry—analysis

It is generally accepted that the type of pharmaceutical dosage form utilized during the preliminary evaluation of a potentially active compound may have some effect on its activity or availability. During the early testing with 2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride (SK&F 33134-A)[1] (1), which has potential antianginal activity, it was found that the compound was almost completely excreted in the feces after oral administration of a tragacanth suspension (1).



* = radioactive carbon

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This observation suggests that the compound was either poorly absorbed from this dosage form or was absorbed and recycled back into the intestines *via* the bile. Therefore the biliary excretion of SK&F 33134-A-^{14}C was measured in rats after oral administration of the drug in solution and suspension.

Because of the poor aqueous solubility of SK&F 33134-A, attempts were made to increase its solubility. Historically, surface-active agents have been used to increase the aqueous solubility of medicinal agents (3,4). In many instances, the apparent increase in aqueous solubility has some effect on the availability of the drug.

[1] Marketed as Cordarone by Labaz Laboratories in several European countries.

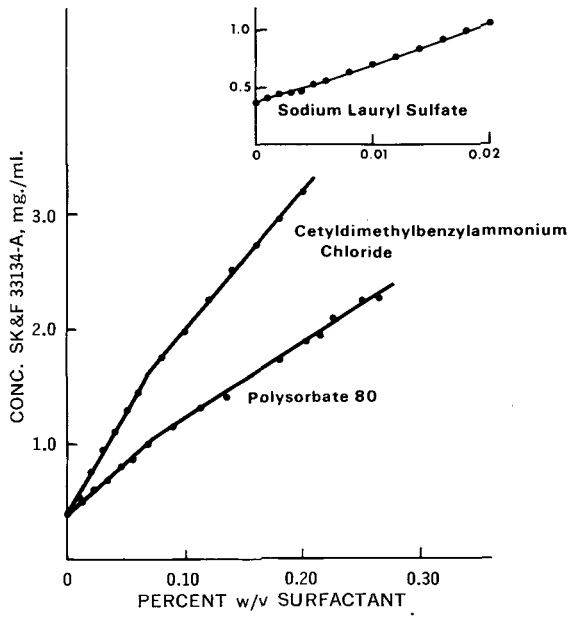

Figure 1—*Effect of surfactant concentration on the solubility of SK&F 33134-A.*

The results are sometimes anomalous. For example, Levy and Reuning (5) reported that the solubilization of salicylic acid with polysorbate 60 led to a decrease in the absorption of the drug. In another study, Kakemi *et al.* (6) demonstrated that the rectal absorption of sulfisoxazole was increased when the compound was solubilized with polysorbate 80. The present study deals with the solubilization of SK&F 33134-A, utilizing surface-active agents, and the subsequent evaluation of the compound following oral administration of both a solubilized form and a suspension to rats.

EXPERIMENTAL

Materials—SK&F 33134-A; SK&F 33134-A-^{14}C; its chemical purity was established by melting point, elemental analysis, IR spectroscopy, and TLC, specific activity 7.7 μc./mg.; polysorbate 80 USP; cetyldimethylbenzylammonium chloride (Winthrop Chemical Co.); sodium lauryl sulfate USP; Ultra Pure water (Harleco); sodium chloride (Baker Reagent Grade); methanol (anhydrous, Merck).

Solubility Determinations—Approximately 200 mg. of SK&F 33134-A was added to screw-cap vials containing 10 ml. of surfactant or sodium chloride solutions of known concentrations. The vials were rotated in a water bath at 30° ± 0.2° for 24 hr. The contents of the vials were filtered through a syringe fitted with a filter adapter (Swinney) containing a 0.45-μ filter disk (Millipore). The resulting clear solutions were diluted with anhydrous methanol and assayed spectrophotometrically at 242 mμ, using a recording

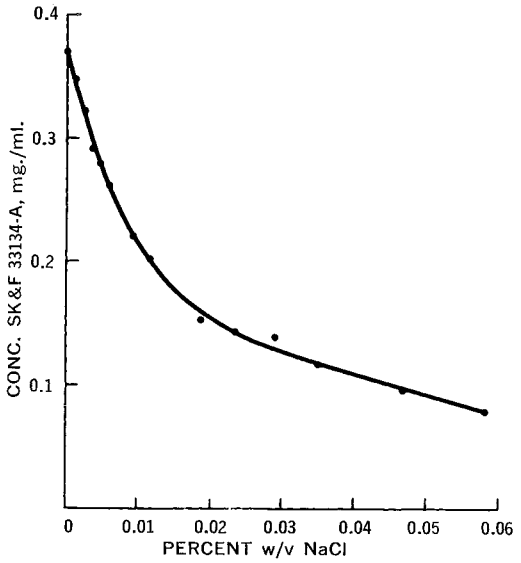

Figure 2—*Effect of sodium chloride on the solubility of SK&F 33134-A.*

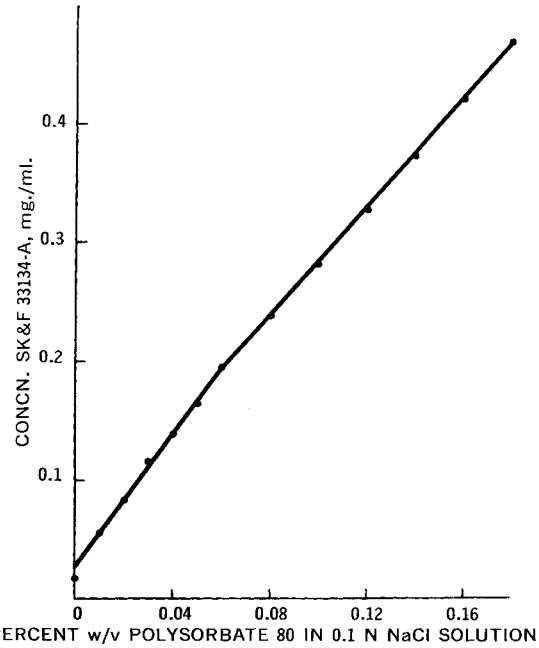

Figure 3—*Effect of polysorbate 80 concentration on the solubility of SK&F 33134-A in 0.1* N *sodium chloride solution.*

spectrophotometer (Cary model 15), to determine the concentrations of SK&F 33134-A.

Preparation of Dosage Forms—*Suspension*—A portion of SK&F 33134-A-^{14}C was ground in a mortar and 20.2 mg. of the finely divided drug was added to 10 ml. of a 1% tragacanth vehicle in a tissue homogenizer. Three drops of a 5% polysorbate 80 solution was added, and the resulting mixture was further ground in the homogenizer. The volume was adjusted to 20 ml. with 1% tragacanth vehicle. A finely dispersed suspension of SK&F 33134-A-^{14}C resulted.

Solution—Twenty milligrams of SK&F 33134-A-^{14}C was added to 20 ml. of a 1% solution of polysorbate 80. The compound was completely dissolved by swirling the container under a stream of hot water for 15 min. The resulting clear solution was filtered prior to use.

Rat Studies—Charles River rats, weighing 240–395 g., were used in these studies. The rats were anesthetized with ether, opened in the midline, and the bile duct was cannulated. Following incision closure, the animals were given SK&F 33134-A-^{14}C by stomach tube so that each rat received a single oral dose equivalent to 10 mg./kg. of the salt.

The rats were then placed in restraining cages, and bile was collected at 1, 2, 3, 4, 5, 6, 6–24, and 24–48-hr. intervals following administration of the drug. In addition, all 24 and 48-hr. urine and feces samples were collected. After 48 hr. the rats were sacrificed, and the gastrointestinal tract was removed. The remaining carcass and the GI tract were prepared for radioactive content determination. Radioactivity was determined in all samples by counting on a liquid scintillation spectrometer (Packard Tri-Carb), with appropriate corrections made for sample quench and counter efficiency. An aqueous phosphor and a suspension-counting-phosphor were used for radioactive counting.[2]

Preparation of Samples for Radioactive Determination—*Gastrointestinal Tract*—The organ was placed into a beaker containing a 25% solution of tetramethylammonium hydroxide (10 ml./g.). The beaker was covered with Saran wrap and allowed to stand at room temperature until the tissues were completely dissolved; usually 24 to 48 hr. were sufficient. The tissue solutions were brought to a convenient volume, mixed thoroughly, and 0.1-ml. aliquots were removed and counted in the suspension-counting-phosphor.

Carcass—The carcass was placed in a plastic jar containing 800 ml. of alcoholic KOH (12% KOH in 85% ethanol) and allowed to stand for 3 or 4 days until dissolved. After this time any intact bones were broken and dissolved. The volume was recorded, and a 0.1-ml. aliquot was removed for counting in the suspension-counting-phosphor.

Feces—Samples were lyophilized, weighed, and ground in a mortar and 75-mg. samples were oxidized in a combustion apparatus (Schöninger) to $^{14}CO_2$ and water. The $^{14}CO_2$ was trapped in 10 ml. of redistilled phenethylamine. One-milliliter aliquots were counted in the aqueous phosphor.

Urine—The volume of urine was measured, then 0.1-ml. aliquots were counted in the aqueous phosphor.

Bile—Samples were diluted to 10 ml. with water, then 0.1-ml. aliquots were counted in the suspension-counting-phosphor.

RESULTS AND DISCUSSION

Solubility Determinations—The effect of various surface-active agents on the aqueous solubility of SK&F 33134-A is shown in Fig. 1. All surfactants studied showed a solubilizing effect on the compound. Based on weight per volume, the greatest effect is exhibited by the anionic surfactant, sodium lauryl sulfate. However, above a surfactant concentration of 0.02% a colloidal solution resulted. Solubility data above this concentration were not obtained. Cetyldimethylbenzylammonium chloride, a cationic surfactant, solubilizes SK&F 33134-A better than the nonionic surfactant, polysorbate 80. The plots indicate that the solubility of the drug is directly proportional to the surfactant concentration in all cases. However, the slopes of the line showed a distinct change which may

Table I—Fecal Excretion of Radioactivity in Bile-Cannulated Rats Following a Single Oral Dose of SK&F 33134-A-^{14}C (10 mg./kg. as the salt)

	Tragacanth Suspension			Polysorbate 80 Solution		
	% Dose in Feces, hr.			% Dose in Feces, hr.		
Rat No.	24	48	Total, 0–48	24	48	Total, 0–48
1	—	73.760[a]	73.760	0.085	11.410	11.495
2	0.948	70.430	71.378	0.216	18.610	18.828
3	29.880	16.700	46.580	0.037	5.420	5.457
4	17.560	58.420	75.980			
Mean % dose	16.129	48.516	66.925	0.113	11.813	11.926

[a] Not included in mean percent dose.

[2] Aqueous phosphor contains 80 g. of naphthalene, 8 g. of BBOT, added to 400 ml. of toluene and 400 ml. of dioxane and subsequently diluted to 1 l. with ethanol. The suspension-counting-phosphor contains the above ingredients plus 50 g. of Cab-O-Sil.

Table II—Biliary Excretion of Radioactivity in Bile-Cannulated Rats Following a Single Oral Dose of SK&F 33134-A-^{14}C (10 mg./kg.)

Rat No.	Bile % Dose, hr. 1	2	3	4	5	6	6–24	24–48	Total, 0–48
					Tragacanth Suspension				
1	—	0.004	0.046	0.185	0.139	0.092	5.814	7.768	14.048
2	—	0.213	0.760	0.863	1.188	1.188	12.068	5.213	21.493
3	0.085	1.042	4.188	2.179	1.837	2.658	17.709	7.367	37.065
4	0.004	0.200	0.350	0.508	0.300	0.300	5.500	11.816	18.978
Mean % dose	0.045	0.365	1.336	0.934	0.866	1.059	10.273	8.041	22.919
					Polysorbate 80 Solution				
1	0.004	0.042	0.170	0.766	2.043	1.618	31.041	14.519	50.203
2	0.002	0.324	0.378	1.136	0.757	1.244	18.668	19.209	41.718
3	0.046	0.463	1.855	1.437	2.922	3.246	39.420	10.899	60.288
Mean % dose	0.017	0.276	0.801	1.113	1.907	2.036	29.709	14.876	50.735

Table III—Urinary Excretion of Radioactivity in Bile Cannulated Rats Following a Single Oral Dose of SK&F 33134-A-^{14}C (10 mg./kg. as the salt)

Rat No.	Tragacanth Suspension —% Dose in Urine, hr.— 24	48	Total, 0–48	Polysorbate 80 Solution —% Dose in Urine, hr.— 24	48	Total, 0–48
1	0.834	0.417	1.251	0.383	0.425	0.808
2	0.358	1.520	1.878	1.082	0.595	1.677
3	0.435	0.170	0.605	0.463	0.510	0.973
4	0.158	0.400	0.558			
Mean % dose	0.446	0.626	1.073	0.643	0.510	1.153

be attributed to the formation of mixed micelles due to an affinity between the surfactant and the solubilizate. This phenomenon has been previously observed by other workers (2, 7).

During the preliminary dissolution rate studies, the observed solubility of SK&F 33134-A decreased in artificial gastric fluid; the decrease was attributed to the presence of chloride ions. Figure 2 illustrates a plot of solubility of SK&F 33134-A as a function of sodium chloride concentration. A concentration of 0.01% sodium chloride reduces the aqueous solubility from 0.37 mg./ml. to 0.215 mg./ml. However, when polysorbate 80 is added to a system containing sodium chloride and SK&F 33134-A, the aqueous solubility increases. These data are shown in Fig. 3, where the solubility of SK&F 33134-A was studied at varying concentrations of polysorbate 80 in 0.1 *N* sodium chloride solutions. Again the curve is linear with an abrupt change in slope. On the basis of these solubility data, a 1% polysorbate 80 solution was used as a vehicle for preparing the solution of SK&F 33134-A for *in vivo* testing in rats.

Absorption Study in Bile Cannulated Rats—The fecal excretion of radioactivity following the administration of an oral dose of SK&F 33134-A-^{14}C in tragacanth suspension and polysorbate 80 solution is shown in Table I. The data indicate that approximately 67% of the administered radioactive dose is found in the feces in 48 hr. when a suspension is used compared to 12% for the solution. It is apparent that the compound is more efficiently absorbed when administered in solution.

The biliary excretion of radioactivity for both dosage forms are listed in Table II. These data suggest that the compound is absorbed and excreted through the bile. After oral administration of the tragacanth suspension and the polysorbate 80 solution, 23 and 51%, respectively, of the total amount of drug absorbed was excreted by the bile. Thus when the compound is administered in solution, the amount of radioactivity excreted through the bile is more than doubled; these results suggest that the compound is more readily available for absorption in solution than in suspension.

The amount of radioactivity excreted in the urine after oral administration of SK&F 33134-A-^{14}C in tragacanth suspension or polysorbate 80 solution was relatively constant. These data, shown in Table III, indicate that approximately 1% of the administered dose is eliminated in the urine for both dosage forms. Since such a small fraction of the compound is excreted in the urine, these measurements should not be used to determine the degree of absorption of this drug. Intravenous administration of SK&F 33134-A-^{14}C to dogs substantiated these data. Approximately 1% of the administered compound was excreted in the urine following a single intravenous dose (1).

Table IV summarizes and compares the data obtained after administration of a single oral dose of 10 mg./kg. of SK&F 33134-A-^{14}C to rats in tragacanth suspension and polysorbate 80 solution. The total amount of radioactivity absorbed was 30.7% for the suspension and 59.3% for the solution. These figures were determined by combining the total amount excreted in the urine and in the bile with that found in the carcass, less the amount in the GI tract. From 93 to 100% of the radioactivity administered was accounted for in each case. The data in Table IV illustrate that the selection of the proper pharmaceutical form is essential during the

Table IV—Comparison of Absorption Parameters in Bile-Cannulated Rats Following Oral Administration of SK&F 33134-A-^{14}C (10 mg./kg. as the salt) in Tragacanth Suspension and Polysorbate 80 Solution

	Mean % Radioactive Dose Bile	Urine	Carcass Less GI Tract	GI Tract, Feces	Total Recovery	Dose Absorbed, %
Tragacanth suspension	22.9	1.1	6.7	4.2 + 64.6 = 68.8	99.5	30.7
Polysorbate 80 solution	50.7	1.2	7.4	21.6 + 11.9 = 33.5	92.8	59.3

preliminary testing of potentially active compounds. In this case a twofold increase in absorption was observed by administering a polysorbate 80 solution rather than a tragacanth suspension of SK&F 33134-A.

SUMMARY

The aqueous solubility of SK&F 33134-A is increased in the presence of sodium lauryl sulfate, cetyldimethylbenzylammonium chloride, and polysorbate 80, the effect being proportional with concentration.

Sodium chloride depresses the solubility of SK&F 33134-A. However, when polysorbate 80 is present in solutions containing chloride ions the solubility of SK&F 33134-A increases.

SK&F 33134-A is excreted mainly by the biliary route.

Urinary excretion is very low and remains relatively constant regardless of the dosage form used. The data suggest that urinary excretion measurements should not be used to indicate the degree of absorption of this compound.

The selection of the proper dosage form is essential during the evaluation of potentially active compounds. A twofold increase in availability was observed for SK&F 33134-A when the compound was administered in polysorbate 80 solution compared to a tragacanth suspension.

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Effect of Colorants on the Solubility of Modified Cellulose Polymers

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Abstract □ The effect of colorants on the solubility characteristics of cellulose polymers was studied. The work was conducted because of earlier findings that FD & C Red No. 3 dye altered the solubility of hydroxypropyl methylcellulose to the extent that dried films were insoluble in media below approximately pH 5.5. A total of 28 dyes was screened in combination with hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium ethylcellulose sulfate. Free film solubility disclosed that six dyes significantly altered the solubility of the polymers tested. Coatings containing FD & C Red No. 3, FD & C Red No. 4, D & C Red No. 17, D & C Red No. 18, D & C Red No. 21, and D & C Red No. 22 dyes were shown to have a retardation effect on tablet disintegration and riboflavin dissolution rate. Riboflavin urine excretion studies confirmed that these dyes may adversely affect *in vivo* product performance. The effects of the insoluble films on *in vitro* and *in vivo* product performance will depend upon the thickness and strength of the film as well as the disintegrating characteristics of the tablet.

Keyphrases □ Cellulose polymers, solubility—colorant effect □ Film coated tablets—colorant effect on dissolution □ Colorant effect—tablet dissolution, absorption □ Polymer film dissolution viscosity—colorant effect

The use of modified cellulose polymers in pharmaceutical products is extensive. These materials are of considerable value in gels, suspensions, tablet core formulations, and tablet coatings. Within the last few years, particular attention has been focused on interaction studies of drug-adjuvant and adjuvant-adjuvant combinations with concern for stability, toxicity, and *in vivo* performance of the dosage form. The literature cites numerous examples of interactions between cellulose polymers and drugs or adjuvants. Tillman and Kuramoto (1) concluded that methylcellulose forms complexes with a number of preservatives including methylparaben and related compounds, *p*-aminobenzoic acid and *p*-hydroxybenzoic acid. Other investigators (2) confirmed and established the extent of such interactions with regard to the effect on solubility of the preservatives in the presence of some cellulose derivatives. Deluca and Kostenbauder (3) established the degree of binding of several quaternary ammonium compounds by methylcellulose. Kabadi and Hammarlund (4) recognized the interaction effects of phenols on the solubilizing and stabilizing properties of some nonionic hydrophilic polymers. Likewise, dyes have been implicated with interaction and stability problems (5, 6). Bornstein *et al.* (7) discussed dye-adjuvant interactions as they apply to color fading. However, little data have been presented on dye-polymer combinations and the effects which some dyes have on the solubility characteristics of cellulose polymers. This study was conducted because of findings that FD & C Red No. 3 dye altered the solubility of hydroxypropyl methylcellulose to the extent that dried films were insoluble in media below approximately pH 5.5. It was therefore desirable to establish if such effects could be expected with other cellulose derivatives and commonly used