(264 mg of I or 400 mg of II, 2.2 mmol) in anhydrous tetrahydrofuran (20 ml) at −78° under an argon atmosphere. The reaction mixture was stirred at the same temperature for 20 min, then an appropriate electrophile (2.4 mmol, or 1: 1 mmol of ethyl benzoate) was added (*via* a syringe) and the mixture was allowed to warm to room temperature during 1 hr, with stirring. The reaction was quenched by the addition of wet silica gel (10 g, 70—230 mesh), which was removed by filtration. The solvent was evaporated off, and the residue was chromatographed[6] on silica gel, using ethyl acetate as an eluent, to give the α′-substituted β-ketosulfoxide Va or VIa—f.

Independent Syntheses of α′-Benzylated β-Ketosulfoxide Va and VIa——A solution of sodium hydroxide (1.38 g, 35.5 mmol) in water-methanol (15 ml+25 ml) was added to a stirred solution of phenethyl mercaptan (4.14 g, 30 mmol) in methanol (10 ml) at 0°. The reaction mixture was stirred at the same temperature for 30 min, a solution of chloroacetone (2.78 g, 30 mmol) or phenacyl bromide (5.97 g, 30 mmol) in methanol (40 ml) was added dropwise at 0°, and stirring was continued at 50—60° for 1 hr. The reaction mixture was poured into ice-water (100 ml) and extracted with ethyl acetate. The extract was washed with 10% hydrochloric acid and dried ($MgSO_4$). The solvent was removed by evaporation, and the residue was distilled *in vacuo* to give acetonyl phenethyl sulfide (4.72 g, 88%, bp 142°/6 mmHg) or phenacyl phenethyl sulfide (6.68 g, 87%, bp 188°/0.3 mmHg). Oxidation of the resulting β-ketosulfide with an equimolar amount of *m*-chloroperbenzoic acid in methylene chloride followed by usual work-up gave the corresponding β-ketosulfoxide Va (69%, mp 94—95°) or VIa (70%, mp 73—74°), which gave spectral data identical with those of the material obtained by benzylation of the dianion III or IV, respectively.

6) The compound VId was obtained by recrystallization of the residual mass from methylene chloride.

[Chem. Pharm. Bull. 27(12)3188—3192(1979)]

UDC 615.451.23.011.3.014.23 : 615.31.014.23.073

Detoxication Capacity of a Multiple (w/o/w) Emulsion for the Treatment of Drug Overdose: Drug Extraction into the Emulsion in the Gastro-intestinal Tract of Rabbits

YASUNORI MORIMOTO, KENJI SUGIBAYASHI, YUKIYA YAMAGUCHI, and YOSHIO KATO

Faculty of Pharmaceutical Sciences, Josai University[1]

(Received July 23, 1979)

The drug extraction ability of water-in-oil-in-water emulsion was evaluated *in vitro* and *in vivo*. *In vitro* drug extraction into the emulsion was determined using a dialysis system and was significant compared to the control. Blood concentration of salicyclic acid, selected as a model drug, co-administered with the multiple emulsion to rabbits was significantly lower than that in the control. The *in vitro* and *in vivo* experimental results suggest that the emulsion may be useful for the emergency treatment of drug overdose.

Keywords——w/o/w emulsion; detoxication; drug overdose; drug extraction; salicylic acid; emergency treatment for drug overdose; rabbit

Poisoning due to drug overdose is a continuing problem. The present modes of emergency treatment are aimed at removal of the drug from the body by various methods, *e. g.* peritoneal dialysis, ingestion of adsorbants such as activated charcoal, and administration of emetics. However, these methods have limitations.

Water-in-oil-in-water (w/o/w) emulsion represents a potential new drug-carrier system with the ability to facilitate gastro-intestinal absorption.[2] Asher *et al.*[3] also showed the

1) Location: *1-1, Keyakidai, Sakado, Saitama, 350-02 Japan.*

2) R.H. Engel, S.J. Riggi, and M.J. Fahrenbach, *Nature* (London), **219**, 856 (1968).

3) W.J. Asher, K.C. Bovee, J.W. Frankenfeld, R.W. Hamilton, L.W. Henderson, P.G. Holtzapple, and N.N. Li, *Kidney Int.*, **7**, s-409 (1975).

utility of such a multiple emulsion for the removal of uremia toxins. Recently, Frankenfeld *et al.*[4] reported the *in vitro* removal of salicylates and barbiturates by w/o/w emulsion, and they suggested that the emulsion was capable of rapid uptake of the drug *in vitro*.

We therefore selected salicylic acid as a model drug and measured the blood levels following oral administration of water-in-oil-in-water emulsion in rabbits to investigate the feasibility of Frankenfeld's suggested emergency treatment for drug overdose *in vivo*.

Experimental

Materials——Salicylic acid was of J.P. grade, and was used after passage through a No. 150 test sieve. Liquid paraffin was used as an oil phase for the emulsion. A nonionic surfactant, Arlacel C (Tokyo Kasei Kogyo Co.), and a cationic surfactant, cetyltrimethylammonium bromide (CTAB) (Wako Pure Chemical Industries, Ltd.), were selected as the stabilizing agent and dispersing agent for the continuous aqueous phase, respectively.

Preparation of the Multiple Emulsion——Twenty % (v/v) Arlacel C in liquid paraffin as an oil phase and 0.1 N NaOH as a central aqueous phase (1 : 1) were mixed and stirred with a magnetic stirrer for 5 min to prepare the w/o emulsion (1st emulsification). Nine volumes of 0.01 N HCl containing 0.05% CTAB (continuous aqueous phase) were added to the resulting emulsion and mechanical agitation completed the formation of the w/o/w dispersion (2nd emulsification) (Chart 1).

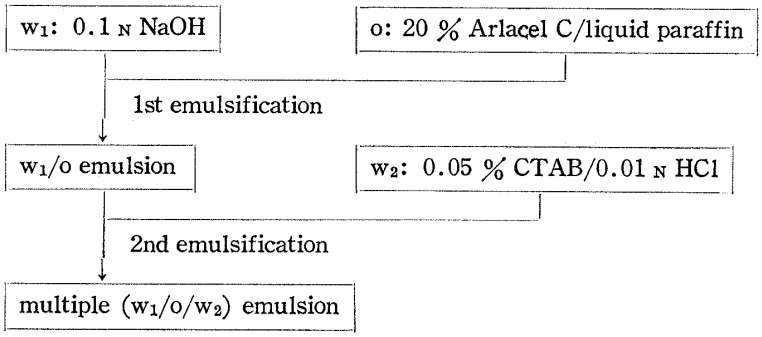

Chart 1. Schematic Diagram of the Preparation of the w/o/w Emulsion

***In Vitro* Experiment**——*In vitro* drug extraction into the emulsion was determined by dynamic dialysis through a cellulose membrane (Visking Co.) (available area=3.80 cm^2). The diffusion cell used in the present experiments is shown in Fig. 1. In cell A, 50 ml of emulsion was mixed with 50 ml of 0.05% CTAB/0.01 N HCl solution at a drug concentration of 100 mg/50 ml or 1000 mg/50 ml, and 100 ml of 0.01 N HCl was placed in cell B. The whole system was maintained at 37±1° using a water bath. At appropriate intervals, aliquots of 1 ml of HCl solution were withdrawn from cell B and determined spectrophotometrically.

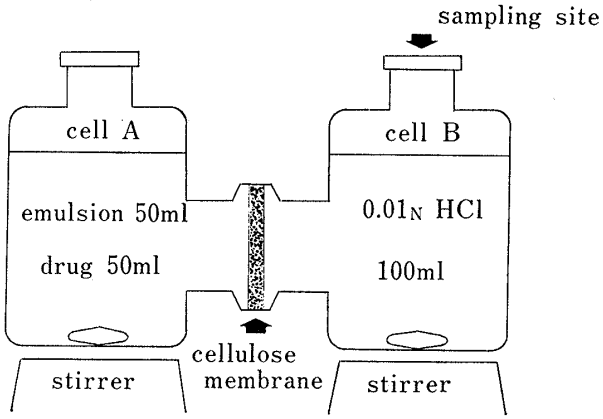

Fig. 1. Apparatus used for the Extraction of Salicylic Acid into w/o/w Emulsion

***In Vivo* Experiment**——Unanesthetized male white rabbits weighing 2 to 3 kg were used. Food was withheld for 24 hr before each experiment. Salicylic acid was suspended in 0.01 N HCl with 0.05% CTAB at a concentration of 20 mg/ml. This suspension was prepared immediately prior to administration and given through a catheter leading into the stomach (16 mg/kg). The emulsion or 0.01 N HCl as a control (9 volumes) was orally administered at the same time. At appropriate times, venous blood samples (0.9 ml each) were collected from an ear vein with a one ml syringe containing 0.1 ml of 3.8% sodium citrate solution and assayed, for drug content.

4) *a*) J.W. Frankenfeld, G.C. Fuller, and C.T. Rhodes, *Drug Dev. Commun.*, **2**, 405 (1976); *b*) C.-W. Chiang, G.C. Fuller, J.W. Frankenfeld, and C.T. Rhodes, *J. Pharm. Sci.*, **67**, 63 (1978).

Analytical Methods——Salicylic acid samples obtained during *in vitro* extraction experiments were determined colorimetrically at 530 nm using a Hitachi 100-20 spectrophotometer after reaction with $FeCl_3$ solution. Blood samples were assayed using a Hitachi 650-10S spectrofluorophotometer by the method of Rowland *et al.*[5]

Results and Discussion

The emulsions prepared as described above are milk-white, and contain spherical oil drops (w/o drops) independently dispersed in the continuous aqueous phase (Fig. 2). The diameter of the oil drops was mostly in the range of 12 to 30 μm, and the average diameter was 19 μm.

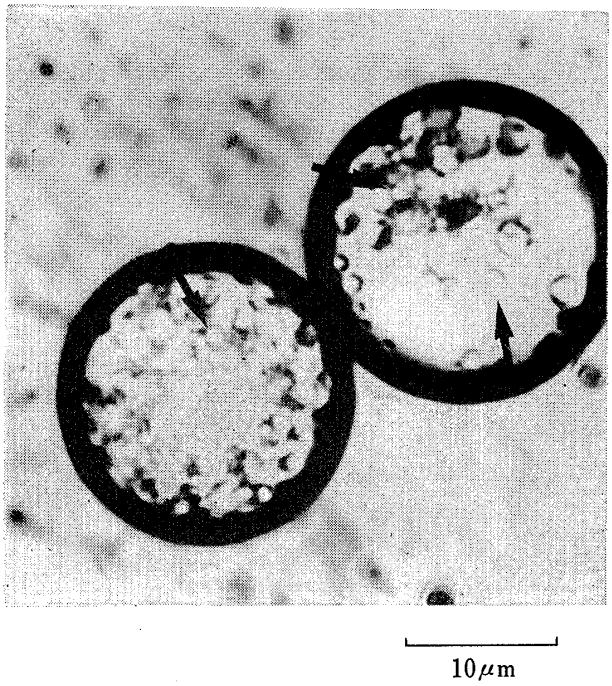

Fig. 2. Photomicrograph of Oil Drops Dispersed in the Continuous Aqueous Phase

Arrows indicate the central aqueous phase.

The emulsion was stable during slow stirring, but if stirring was stopped, it separated into two layers and the oil phase was gradually segregated into the upper layer. Dilute emulsions were more stable than concentrated emulsions. Because salicylic acid is a weak acid, 0.1 N NaOH was selected as a trapping agent for the central aqueous phase (w_1), and this agent did not influence the stability of the emulsion.

In the case of *in vitro* drug extraction experiments into emulsions, Fig. 3 shows the amounts of salicylic acid that passed from cell A to cell B through a cellulose membrane with trapping by the emulsion. The amounts of drug in cell B apparently decreased when emulsion was present in cell A. In Fig. 3a (solution type), the initial amount in cell A was 100 mg (per 100 ml) and all of the drug

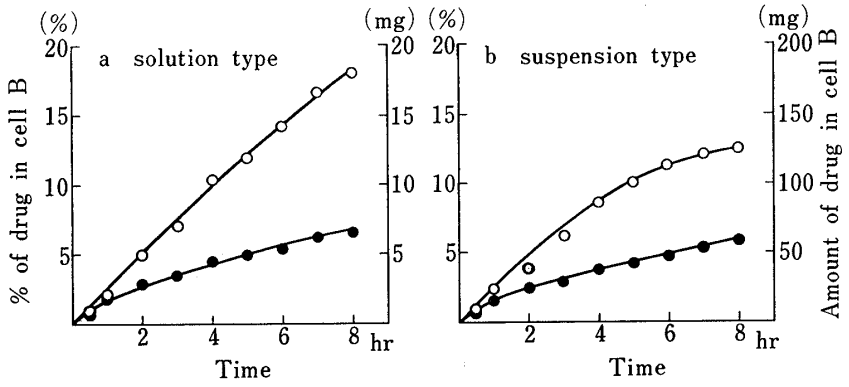

Fig. 3. The Effect of Extraction of Salicylic Acid into the Emulsion on Its Permeability through a Cellulose Membrane

●; with emulsion, ○; control.

5) M. Rowland and S. Riegelman, *J. Pharm. Sci.*, **56**, 717 (1967).

was dissolved in the solution. However, in Fig. 3b (suspension type), the initial amount was 1000 mg; about 22% of the drug was dissolved in solution and 78% was solid particles. These figures confirm the ability of the emulsion to remove salicylic acid.[6]

The time course of blood concentration of salicylic acid following oral administration into rabbits is shown in Fig. 4. The blood concentration in rabbits treated with the emulsions was lower than that in the control. The results suggest that the emulsion may be useful for the emergency treatment of drug overdose. Moreover, the emulsion can be readily prepared using simple equipment, such as an ordinary kichen blender, and thus might be useful as an emergency home treatment for drug overdose. Based on the data obtained in rabbits treated with and without emulsions, we compared the peak concentrations, the times of the peak concentrations, and the areas under the blood concentration-time curves (AUC), as shown in Table I. The peak concentration following co-administration of salicylic acid and emulsion was 40% less than that in the control. The peak concentration is the most important factor in the onset of poisoning. The decrease in the value in rabbits treated with the emulsion is consistent with a process of detoxication. The time at which the peak concentration was established was about 1 hr, and this indicates that the absorption step was completed earlier than in the control, which is consistent with a decrease of absorbable drug content in the stomach due to extraction of the drug into the emulsion. The area under the curve from

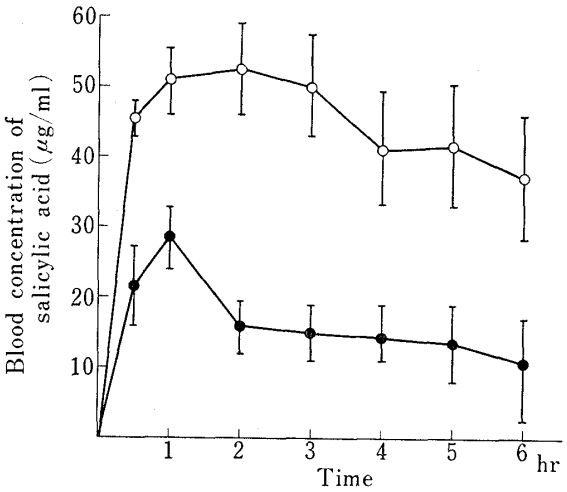

Fig. 4. Time Course of Blood Concentration of Salicylic Acid after Oral Administration

●; with emulsion, ○; control.
Each point represents the mean value of four experiments. Vertical bars indicate ± S. E. M.

Table I. The Peak Concentration, the Time of the Peak Concentration and the Area under the Blood Concentration-time Profiles after Oral Administration of Salicylic Acid

		Peak concentration (μg/ml)	Time of peak concentration (hr)	AUC_{0-6} (μg hr/ml)
Control	1	56.5	2	250.9
	2	40.6	0.5	199.9
	3	64.2	1	356.6
	4	62.8	3	354.0
Mean ± S. E. M.		56.7 ± 5.4		290.4 ± 38.9
Emulsion	1	30.7	1	89.6
	2	22.4	1	116.4
	3	39.6	1	83.7
	4	29.2	2	148.3
Mean ± S. E. M.		30.5 ± 3.5		109.5 ± 14.8
Significance		$p < 0.01$		$p < 0.01$

6) The dissolution of solid drug particles, drug extraction into the emulsion, and dialysis through a Visking membrane all obey first-oder kinetics. An analysis of the data as shown in Fig. 3 could be simulated using the compartment model with an analog computer, *etc.* Thus, the time course of extraction of the drug into the emulsions should be predictable. These results will be reported elsewhere.

0 to 6 hours was measured by the trapezoidal method. The resulting AUC_{0-6} was 46% less than that in the control experiments. The values of the peak concentration and AUC_{0-6} were significantly different from those of the control ($p<0.01$).

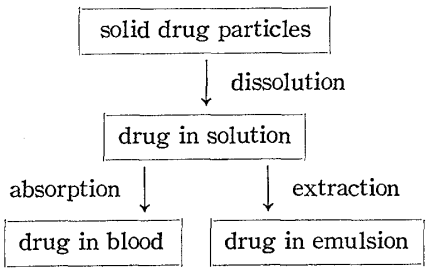

Chart 2. The Processes of Absorption and Extraction into the Emulsion after Ingestion of Salicylic Acid

Upon administration of excess drug, however, a large portion remains as a solid in the stomach, so the dissolution rate of the drug might affect the drug extraction capability of the emulsion (Chart 2). If the extraction potential into the emulsions is saturated, the unextracted portion of the drug will be absorbed into the blood. This might be overcome by continuous infusion of the emulsion.

The amount of drug absorbed into the blood and extracted into the emulsions in the stomach were influenced by the gastric contents. In our experiments, rabbits were fasted during the entire day before oral administration. However, there was some gastric content due to coprophagy by the rabbits, and this might affect the stability of the emulsion in the stomach with resulting changes in the blood level of the drug.

Chiang *et al.*[4b] reported *in vitro* studies showing that the extraction of a drug into the emulsion decreased in the presence of bile salt. We did not observe any effect of bile salts on drug extraction by the emulsion *in vivo* in this study, but further work is planned.

These experimental results suggest that w/o/w emulsions may be useful for the emergency treatment of drug overdose. However, there are still many difficulties facing clinical trials of the emulsion. Studies are presently under way in our laboratory to improve the stability of the w/o/w emulsion and to make it capable of rapid uptake of many weakly acidic drugs. In addition, we plan to investigate the usefulness of the emulsion following ingestion of basic drugs or co-administration of two or three drugs *in vivo*.