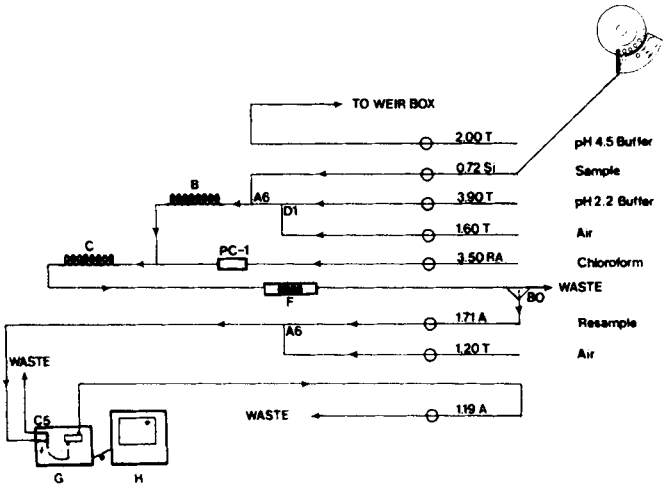

Figure 1—*Flow of automated system for aspirin dissolution. Key: Si, silicon pump tube; T, Tygon tube; A, Acidflex pump tube; RA, red Acidflex pump tube; B, 28-turn × 2.4-mm i.d. mixing coil; C, 28-turn × 2.4-mm i.d. mixing coil with one double end; F, 5.5-turn settling coil; G, UV spectrophotometer; and H, recorder. Pump tube sizes are in milliliters per minute.*

water, air can be introduced into the solution. A test was performed to determine if boiling the pH 4.5 buffer solution affects the pH of the solution. The pH of the freshly prepared solution and the boiled solution was the same.

Survey Results—The automated method was employed to analyze 59 tablet formulations representing 37 manufacturers using both the basket and the paddle techniques (Table I). Of the total samples tested, 22% failed the proposed USP XX dissolution requirement using the basket method and 75% failed using the paddle technique.

Of the 59 formulations tested, 49 were plain aspirin tablets and 10 were buffered tablets. None of the buffered tablets and 26.5% of the plain tablets failed the proposed USP XX requirements by the basket method. Eighty-six percent of the plain tablets and 20% of the buffered tablets failed the proposed USP XX requirements by the paddle method.

During this survey, the basket method gave higher results than the paddle method for ~75% of the samples. For some samples, the basket method results were twice as high as those for the paddle method. Therefore, if the basket method is used as the USP XX requirement, all buffered and most plain tablets would pass the test; but if the paddle method is used, some buffered tablets and most plain tablets would fail the proposed requirement. These results pose the question of which method will predict bioavailability more accurately.

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NOTES

Poloxamer 188 as Vehicle for Injectable Diazepam

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Abstract □ The significant occurrence of thrombophlebitis in patients administered diazepam intravenously was described recently. This side effect has been attributed to the crystallization of diazepam and its subsequent precipitation upon contact with blood or intravenous fluids. The current study was designed to reveal whether the solubilizing capability of poloxamer 188 reduces the incidence of thrombotic and inflammatory effects of diazepam in rabbits. The incidence of early (3-hr) ear vein necrosis was 72% in the diazepam-treated ears, while the incidence of necrosis in the ears that received poloxamer 188 as a vehicle for diazepam was 25%. The occurrence of thrombosis and loss of vessel integrity also was higher in diazepam-treated ears than in those treated with diazepam plus poloxamer 188. Solubilization of diazepam with poloxamer 188 may decrease the incidence of the tested side effects.

Keyphrases □ Diazepam—reduction of thrombosis and inflammation using poloxamer 188 as vehicle, rabbits □ Poloxamer 188—use as vehicle for reduction of thrombosis and inflammation induced by injectable diazepam, rabbits □ Sedatives—diazepam, reduction of thrombosis and inflammation using poloxamer 188 as vehicle, rabbits

Diazepam[1] is generally accepted as an intravenous sedative/anesthetic with usefulness in dentistry and medicine (1–6). Its increased use over the past decade has resulted in support for its benefits in various procedures, but the literature also contains references to side effects.

Pain upon injection is a frequent side effect of diazepam use (3, 7–9), and there have been many reports of thrombophlebitis following diazepam injection (1–3, 9). These side effects have been associated with precipitation of di-

[1] Valium Injectable, Hoffmann-La Roche, Nutley, N.J.

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Table I—Effect of Poloxamer 188 on the Incidence of Diazepam-Related Rabbit Ear Vein Alterations [a]

	Thrombosis			Necrosis			Loss of Vascular Integrity		
	I[b]	II	III	I	II	III	I	II	III
Morrhuate sodium[c]	0	0	5	1	4	2	4	0	0
Saline	0	0	0	0	0	0	0	0	0
Diazepam	0	0	3	4	1	1	4	0	1
Diazepam plus poloxamer 188	0	0	1	2	0	0	0	0	0

[a] The values are the number of ears, within each group of eight ears injected, that showed the side effect. [b] Key: I = mild, II = moderate, and III = severe. [c] Known inflammatory agent.

azepam from the injectable solution in the presence of an aqueous medium, including blood (10).

The present study was designed to reveal whether the solubilizing capability of poloxamer 188[2] reduces the incidence of thrombotic and inflammatory effects of diazepam in rabbit ear veins.

EXPERIMENTAL

Sixteen male, adult, albino New Zealand rabbits[3], 2–3 kg, received an injection of a control or test solution in the marginal ear vein. After 180 min, the animals were sacrificed with ether. Vein cross-section samples, beginning 2 cm proximal to the injection site, were taken for pathological evaluation of vasculitis, necrosis, hemorrhage, thrombosis, edema, and vessel integrity. Standard staining and tissue handling techniques were used.

The animals were divided into two test groups. Group A (n = 8) animals received 0.9% saline (0.6 ml/kg) in one ear and morrhuate sodium (10 mg/kg), a known inflammatory agent, in the opposite ear. Group B (n = 8) animals received injectable diazepam[4] diluted (2×) with vehicle (diazepam, 1.5 mg/kg) in one ear and injectable diazepam diluted with water containing 5% poloxamer 188[5] (diazepam, 1.5 mg/kg) in the opposite ear. The diazepam vehicle contained 40% propylene glycol, 10% ethanol, 5% sodium benzoate, and 1.5% benzyl alcohol.

RESULTS AND DISCUSSION

Necrosis was more prevalent in diazepam-treated ear veins than in ear veins treated with diazepam plus poloxamer 188 (Table I). Necrosis also was closely associated with diazepam injection in other studies. Schneider and Mace (11) described an episode of necrosis associated with thrombosis that was related to a diazepam injection in a patient. Knill and Evans (12) injected diazepam into the central artery of rabbit ears and observed consistent necrosis and gangrene.

Antemortem thrombosis was observed in three of eight ear veins biopsied 3 hr after diazepam injection, while one ear vein contained a thrombus following diazepam plus poloxamer 188 (Table I). In ears treated with diazepam, two demonstrated hemorrhage and five showed a loss of vessel integrity. These changes were not seen in the ears treated with diazepam plus poloxamer 188.

Thrombosis after diazepam injection also was a frequent finding in previous studies. Graham *et al.* (13) found that thrombosis developed in the vein used for drug infusion within 48 hr in rats that received at least 0.25 mg of diazepam. Baker (1) reported a 15% incidence of superficial venous thrombosis in 400 patients receiving diazepam anesthesia. Three patient case reports of thrombosis following injection of diazepam also were described (14). Brown (15) observed a 15% incidence of thrombophlebitis or thrombosis following intravenous injection of 35 mg of diazepam and a 30% incidence with 50 mg of diazepam administered intravenously to patients. A 39% incidence of thrombosis was reported in patients 7–10 days after intravenous administration of 10 mg of diazepam (16).

The occurrence of thrombophlebitis probably is related to the insolubility of diazepam in aqueous media. Langdon (17) decreased the incidence of phlebitis from 7 to 2% by using 150–250 ml of saline flush. Jusko *et al.* (10) concluded that the thrombophlebitis associated with diazepam injection probably is due to precipitation of diazepam from solution when injected into a slow intravenous drip or a slow venous stream. Their calculations indicate that only a high flow rate allows the diazepam to stay in solution in an aqueous medium, where it is relatively insoluble.

This flow-related factor may be the reason that some investigators experienced fewer problems with diazepam when it was injected into a large vein (2) and may explain the lower incidence of thrombophlebitis when diazepam was followed by a large volume of saline flush (17). Graham *et al.* (7) reduced the incidence of thrombophlebitis after injection of 10 mg of diazepam in patients from 16 to 3% by diluting the drug in 20 ml of 5% dextrose–Ringer's lactate solution.

Ecanow and coworkers[6] found that a milky precipitate appeared upon introduction of injectable diazepam into whole blood and serum samples *in vitro*. The mixtures were centrifuged, and the precipitate was collected and observed under a light microscope; amorphous and needle-shaped crystalline particles were seen. A similar type of precipitate was obtained by adding the injectable diazepam to distilled water. Reformulation of the injectable diazepam was accomplished by adding poloxamer 188 (5% and more) to the commercial formulation. When the reformulated diazepam was introduced to the *in vitro* serum and whole blood solutions, no precipitation was apparent.

Poloxamer 188[7] [poly(oxypropylene) poly(oxyethylene) condensate], a surface-active agent with low toxicity, is used intravenously in humans. The present data indicate that poloxamer 188-solubilized diazepam causes fewer thrombotic and inflammatory effects in rabbit ear veins than does the injectable form of diazepam. Further studies are indicated to determine if this compound will effectively reduce diazepam side effects in patients.

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[7] Poloxelene, Instant Microsphere Kit, Minnesota Mining and Manufacturing Corp., St. Paul, Minn.