chromatographically identical to methadone (80.5%), morphine (95.5%), and naloxone (100%). Total extracted plasma radioactivity represented methadone (76.9%), morphine (75.5%), or naloxone (91.8%). Parent drug extraction selectivity in each case was acceptable.

Timesaving is the greatest advantage of this method. Extraction of 20 tissue samples required 10–15 min; 1.5–2 hr was required with standard liquid–liquid extraction. Since brain and plasma drug concentrations are routinely required in pharmacological studies, the utility of the present method is obvious. Theoretically, the present procedure could be substituted for any organic base or acid solvent extraction from biological fluids and tissues.

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Effect of Water-Soluble Carriers on Morphine Sulfate Release from a Silicone Polymer

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Received August 14, 1978, from the *Drug Dynamics Institute, College of Pharmacy, University of Texas, Austin, TX 78712.* Accepted for publication November 2, 1978.

Abstract □ The influence of gelatin, sodium lauryl sulfate, lactose, and sodium alginate on morphine sulfate diffusion from cylindrical silicone polymer pellets was examined in isotonic pH 7.4 phosphate buffer. These water-soluble carriers caused the pellets to swell in aqueous media. Sodium alginate exerted the greatest influence on drug release. The morphine sulfate diffusion rate from the cylindrical pellets increased as the matrix alginate content increased up to 20%. Water-soluble carrier incorporation into silicone polymeric matrixes permits controlled release of water-soluble drugs that otherwise would be released extremely slowly from the polymer. Drug diffusion from the silicone matrix containing sodium alginate followed second-order kinetics. The release mechanism probably involves the creation of pores or pathways through the matrix secondary to the swelling.

Keyphrases □ Morphine sulfate—release from silicone polymer, effect of water-soluble carriers □ Drug delivery systems—morphine sulfate, release from silicone polymer, effect of water-soluble carriers □ Silicone polymers—release of morphine sulfate, effect of water-soluble carriers □ Dosage forms, controlled release—morphine sulfate, release from silicone polymer, effect of water-soluble carriers

The drug release rate from an inert matrix is dependent on solute solubility in the matrix and diffusivity as well as on parameters independent of the particular drug (1). Previous silicone polymer work has been concerned largely with developing long acting steroidal delivery systems and investigating factors controlling drug release from silicone devices (2–9).

The divergent *in vitro* silicone polymer release patterns of four progesterone-type steroids with similar diffusion coefficients were attributed to differences in the polymer steroid solubilities (5). The release of salts and water-soluble drugs from silicone polymers has received little attention. Since polymer drug solubility is an important drug release determinant, water-soluble drug diffusion from a silicone polymer would be expected to be extremely slow.

The present study examined the influence of water-soluble carriers on the *in vitro* morphine sulfate release from a polysiloxane polymer. Recent studies (10, 11) demonstrated that polysiloxane rubber implants containing morphine sulfate and a water-soluble carrier are excellent drug delivery systems for inducing morphine dependence in rats.

EXPERIMENTAL

The following items were used: simethicone liquid[1], polydimethylsiloxane polymer and silica filler[2], stannous octoate[3], morphine sulfate, polysorbate 80[4], sodium alginate[5], sodium chloride, 0.1 *N* HCl, lactose, sodium lauryl sulfate, monobasic sodium phosphate, dibasic sodium phosphate, and microcrystalline cellulose[6].

Pellets were prepared by the addition of simethicone fluid to polydimethylsiloxane elastomer (1:1), followed by homogeneous mixing with the powders to be added. The pellets contained 25% (w/w) morphine sulfate. The drug and water-soluble carrier (lactose, sodium lauryl sulfate, gelatin, or sodium alginate) were passed through a 100-mesh screen prior to mixing with the silicone polymer. To polymerize the mixture, stannous octoate catalyst, 25 mg/g of mixture, was added and dispersed uniformly. Next, the mixture was added rapidly to a plastic tablet mold, and the pellets were allowed to cure for 24 hr.

The cylindrical pellets were 5.5 mm in diameter and 3.5 mm in thickness. The mean weights varied from 78 to 88 mg, depending on the amount of powder embedded in the pellet. Surface area measurements were made with a micrometer. Homogeneity studies were carried out by cutting individual pellets into small pieces and extracting them in 100 ml of purified water for 48 hr. Recoveries of 99 ± 2% were obtained (n = 6).

Drug release from the pellets was studied in screw-capped vials, 1.5 cm diameter × 10.5 cm length, containing 15 ml of phosphate buffer (0.13 *N*, pH 7.4). These vials were maintained at 37° and rotated end-over-end at 15 rpm. Aliquots of 5 ml were withdrawn from the vials at various times and assayed by UV spectrophotometry for morphine. To maintain sink conditions, 5-ml volumes of fresh medium were added to each vial after

[1] Medical fluid 360, 200 cps, Dow Corning Corp., Midland, Mich.
[2] Silastic 382 medical grade elastomer, Dow Corning Corp., Midland, Mich.
[3] Catalyst M, Dow Corning Corp., Midland, Mich.
[4] Tween 80, City Chemical Corp., New York, N.Y.
[5] Kelco Gell LV, Kelco Co., Clark, N.J.
[6] Avicel, FMC Corp., Marcus Hook, Pa.

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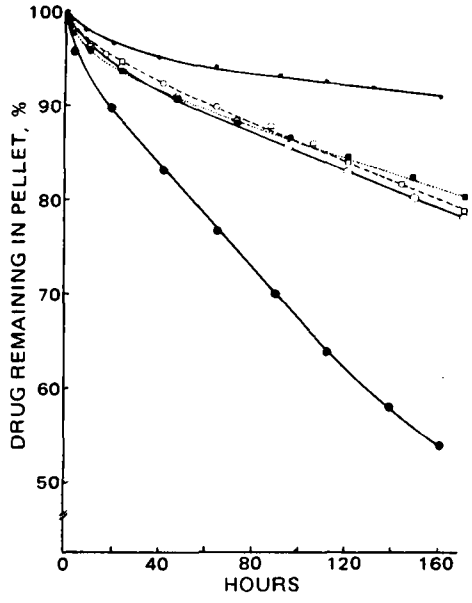

Figure 1—*Influence of various carriers (10% each) on 25% morphine sulfate release from silicone pellets. Key: •, drug alone; ■, gelatin; □, sodium lauryl sulfate; ○, lactose; and ●, sodium alginate.*

sample withdrawal. The reported data represent the means of three or more runs.

RESULTS AND DISCUSSION

The influence of water-soluble carriers on morphine sulfate release from silicone pellets is shown in Fig. 1. As expected, the release of the water-soluble salt from the polymer in the absence of any carrier was very slow; after 1 week, only 9% of the drug was removed from the pellet. This result confirmed the expectation that water-soluble drugs are released slowly from lipophilic silicone matrixes.

The presence of 10% gelatin, sodium lauryl sulfate, or lactose in the silicone matrix all produced similar effects on drug release: approximately 20% of the morphine had diffused from the pellet after 1 week. This value increased to 50% when sodium alginate was incorporated into the matrix.

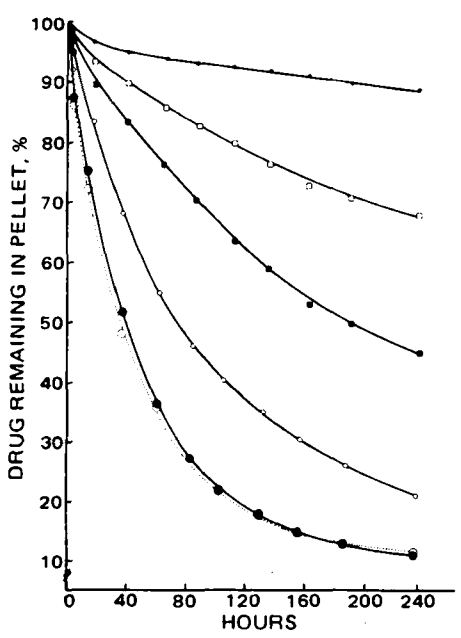

Figure 2—*Influence of sodium alginate concentration formulated within the silicone matrix on 25% morphine sulfate release. Key: •, 0%; □, 5%; ■, 10%; ○, 15%; ●, 20%; and ○, 25%.*

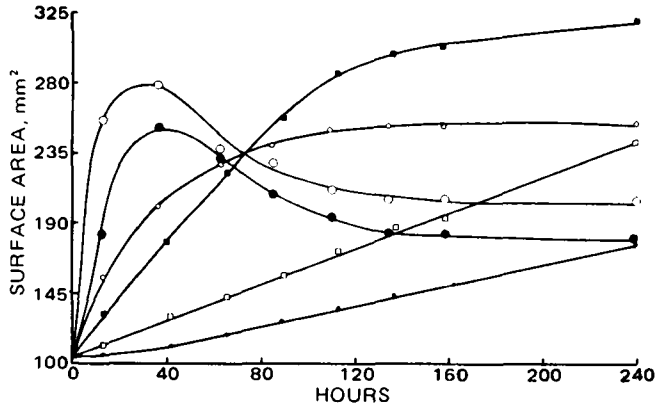

Figure 3—*Plots of Surface area as a function of time for the pellet formulations in Fig. 2.*

With all systems, an initial burst of drug from the pellet lasted for 10–15 hr.

As the sodium alginate content in the matrix was increased, so did the morphine diffusion rate from the polymer (Fig. 2). This influence appeared to be maximal at 20% alginate. One prominent action of each carrier was to swell the pellet. The influence of alginate content on silicone matrix swelling is shown in Fig. 3. Morphine sulfate dissolution from the matrix is probably facilitated by this swelling, which creates microscopic pores or channels from carrier hydration. In the absence of the swelling agent, pellets containing morphine sulfate alone increased in surface area at a uniform rate over the 10-day period studied. This increase was the smallest of the pellets studied, however.

Swelling rates increased during the first 30 hr as the level of sodium alginate in the pellet increased. Pellets containing 20 and 25% alginate achieved maximal surface area at approximately 40 and 30 hr, respectively. The matrix then began to shrink as both the drug and carrier were removed from it (Fig. 3). This phenomenon can be monitored by taking transverse sections of the pellet and measuring the core and the translucent depletion zone.

Morphine diffusion from the silicone matrix (Fig. 4) appeared to follow second-order kinetics with respect to morphine sulfate concentration. The second-order profile correlation coefficients (Fig. 4) for morphine sulfate release from silicone matrixes containing 10, 15, and 20% sodium

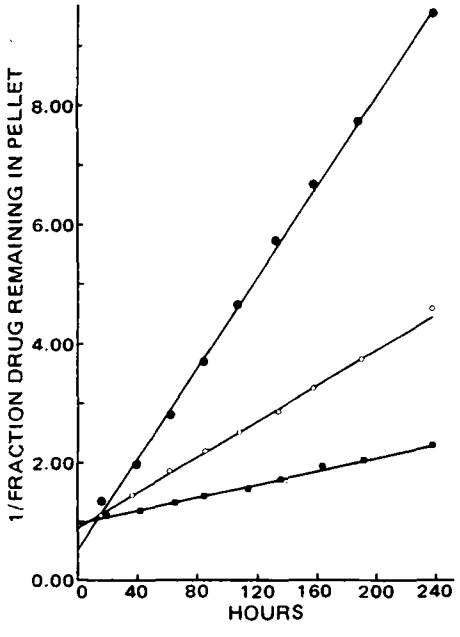

Figure 4—*Second-order profiles for silicone matrixes containing 25% morphine sulfate and three sodium alginate concentrations. Key: ■, 10% sodium alginate; ○, 15% sodium alginate; and ●, 20% sodium alginate.*

alginate were 0.9982, 0.9987, and 0.9983, respectively. The processes giving rise to the second-order elimination from the matrix are not apparent immediately since a shrinking core phenomenon with decreasing core surface area is occurring.

This technique of controlling the diffusion rate from silicone polymers was recently applied by the authors to salts of amphetamine and the barbiturates, and preliminary *in vitro* and *in vivo* results are encouraging. This simple method of drug delivery may find use also in chronic toxicity studies in small animals.

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Wikstromol, Antitumor Lignan from *Wikstroemia foetida* var. *oahuensis* Gray and *Wikstroemia uva-ursi* Gray (Thymelaeaceae)

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Received September 11, 1978, from the *Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, AZ 85721.* Accepted for publication November 1, 1978.

Abstract □ The ethanol extracts of *Wikstroemia foetida* var. *oahuensis* and *Wikstroemia uva-ursi* showed antitumor activity against the P-388 lymphocytic leukemia (3PS) test system. One PS-active constituent of both plants was the lignan wikstromol. Several inactive compounds were identified as daphnoretin, pinoresinol, and syringaresinol.

Keyphrases □ Wikstromol—isolation from plant material, antineoplastic activity □ Antineoplastic agents—wikstromol, isolated from plant material

In the continuing search for plants having antitumor constituents, it was found that the chloroform fractions of *Wikstroemia foetida* var. *oahuensis* Gray and *Wikstroemia uva-ursi* Gray[1] (Thymelaeaceae) ethanol extracts were active against the P-388 lymphocytic leukemia (3PS) test system[2].

DISCUSSION

The lignan wikstromol (I) was isolated from both *Wikstroemia* species. This compound was isolated recently from *Wikstroemia viridiflora* (1) and *Daphne odora* (Thymelaeaceae) (2). Wikstromol is the enantiomer of nortrachelogenin (II, also called pinopalustrin), isolated from *Trachelospermum asiaticum* var. *intermedium* (Apocynaceae) (3) and *Pinus palustris* (Pinaceae) (4).

Comparison of the sample spectra (IR, PMR, and mass) with literature values (1, 3) for wikstromol and nortrachelogenin and comparison of the sample's physical constants with those of these two lignans (Table I) suggested that it was wikstromol. Confirmation was by direct comparison of authentic spectra[3] (IR and PMR) and of the sample[3] of the nortrachelogenin dimethyl ether with the study sample dimethyl ether. The spectra were identical, and TLC behaviors were indistinguishable. Unfortunately, the study sample could not be made to crystallize, and an authentic sample of wikstromol, or its dimethyl ether, was unobtainable.

In addition to the PS-active wikstromol, three inactive compounds were isolated from both *W. foetida* var. *oahuensis* and *W. uva-ursi*. These compounds were daphnoretin (III), pinoresinol (IV), and syringaresinol (V). In each case, identity was confirmed by comparison with authentic specimens[4].

Wikstromol (I) demonstrated activities of 154, 146, 137, 141, and 130% test/control (T/C) at does of 16, 10, 4, 2, and 1 mg/kg, respectively. Activity in the PS test system is defined as an increase in the survival of treated animals over that of control animals resulting in a T/C ≥ 130%[5].

EXPERIMENTAL[6]

Wikstromol was isolated similarly from *W. foetida* var. *oahuensis* and *W. uva-ursi*. The procedure for isolation from the former follows.

Whole *W. foetida* var. *oahuensis* plants were ground in a Wiley mill and stored at −10° prior to extraction. The ground material (9 kg) was exhaustively extracted in a Lloyd-type extractor with petroleum ether

[1] *W. foetida* var. *oahuensis* and *W. uva-ursi* were collected in Hawaii in September 1975 and March 1973, respectively. Identification was confirmed by Dr. Robert E. Perdue, Jr., Medicinal Plant Resources Laboratory, U.S. Department of Agriculture, Bethesda, Md. Reference specimens are maintained by the Department of Agriculture.

[2] Of the Drug Evaluation Branch, Drug Research and Development, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Md.

[3] The authors are indebted to Prof. Dr. Sansei Nishibe, Department of Pharmacognosy, Higashi Nippon Gakuen University, Ishikari-Tobetsu, Hokkaido, Japan, for spectra and sample of nortrachelogenin dimethyl ether.

[4] The authors thank Prof. Dr. G. Legler, Institute für Biochemie der Universität Köln, Germany, for sample of daphnoretin. They are grateful also to Dr. Cornelius Steelink, Department of Chemistry, University of Arizona, Tucson, Ariz., for specimens of pinoresinol and syringaresinol.

[5] John D. Douros, Natural Products Branch, National Cancer Institute, Bethesda, Md., personal communication, Sept. 1977.

[6] Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR and mass spectra were recorded on a Beckman IR-33 and Hewlett-Packard quadrupole spectrometer (model 4930), respectively. PMR spectra were recorded on Varian T-60 and EM-360L spectrometers, and optical rotations were taken on a Perkin-Elmer model 241 MC polarimeter.

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