parent permeability coefficient. The ratio of the surface area to the volume of solution is 0.66.

Absorption experiments were carried out with three rabbits (Tables II–IV). For Rabbits 1 and 3, the experiments were carried out and continued up to the 5th day with two successive runs each day. For Rabbit 2, there were some difficulties with the anesthesia on the 3rd and the 4th days so that experiments on these days were not performed. The data show overall good reproducibility of the method. Both the animal-to-animal and the day-to-day variations were statistically insignificant. Consequently, the method should be useful in carrying out quantitative experiments on a single rabbit as well as with a set of animals.

Effects of pH and Buffer Species on Permeability of Vaginal Membrane—For studies on the vaginal absorption of weak electrolytes, knowledge of the possible adverse effects of pH and buffer species on the integrity and permeability characteristics of the membrane is required. These effects were quantitatively assessed by absorption experiments utilizing *n*-butanol as the reference. The buffer systems employed are listed in Table V.

As can be seen in Table VI, the apparent permeability coefficient of *n*-butanol was the same at pH 3.0 with the phthalate buffer and at pH 6.0 and 8.0 with the phosphate buffers. In comparison, the average P_{app} values for the citrate buffer systems tended to be greater and those for the borate buffers were consistently lower. Although there were wider variations in the experimental results with the tromethamine buffer as compared to the variations with the other buffers at various pH, the average P_{app} was higher than the P_{app} for the phthalate and phosphate buffers. The pH of all buffer solutions changed no more than 0.1 unit in 1 hr.

Although it is not explicit in Table VI, the tabulations of the permeability coefficients are the overall results of crossover experiments involving pH and buffer systems. The crossover experiments gave reproducible and consistent results. As one example, an absorption experiment carried out at pH 6.0 with the phosphate buffer gave a higher P_{app} than that of an immediate followup experiment at pH 9.8 with the borate buffer on the same rabbit (Table VII). The result was the same when the order of the experiments was reversed.

These results show that the membrane is affected by both pH and buffer as adjudged by its permeability to *n*-butanol. There appears to be little effect on the membrane when phthalate and phosphate buffers are used. The citrate and borate buffers and, perhaps, the tromethamine buffer do affect membrane permeability. However, these effects upon the membrane appear to be reversible and not related to the integrity of the membrane.

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Timed Release from Polymeric Films Containing Drugs and Kinetics of Drug Release

M. DONBROW [x] and M. FRIEDMAN

Abstract □ The preparation of cast films of ethylcellulose containing caffeine and salicylic acid is described. These films exhibit timed release of drugs. Release rates were found to agree with both the classical first-order equation (log drug retained against time) and diffusion-controlled release models, as exemplified by Higuchi's equations (drug release linearly related to square root of time). Mathematical analysis of the data shows that the release behavior actually conforms with the diffusion-controlled model. Literature results, reported as first order, for the release of cetylpyridinium chloride and benzalkonium chloride from polyamide films were analyzed similarly and shown to be diffusion controlled. Recommendations are made for presentation and routine treatment of drug release data to avoid ambiguity and provide useful biopharmaceutical information.

Keyphrases □ Ethylcellulose films containing caffeine or salicylic acid—timed release, first-order and diffusion-controlled models discussed □ Timed release of caffeine or salicylic acid from ethylcellulose films—first-order and diffusion-controlled models discussed □ Drug release from polymeric films—first-order and diffusion-controlled mechanisms discussed □ Polymer films containing drugs—kinetics of drug release, first-order and diffusion-controlled models discussed

The methods previously used in achieving timed-release formulations of drugs may be related to four types of processes: *(a)* coating the drug or preparation, *(b)* embedding the drug in fatty, plastic, or hydrophilic matrixes, *(c)* binding the drug to an ion-exchange resin, or *(d)* forming a complex or other chemical derivative of the drug (1). The possibility exists that incorporation of the drug into a polymer

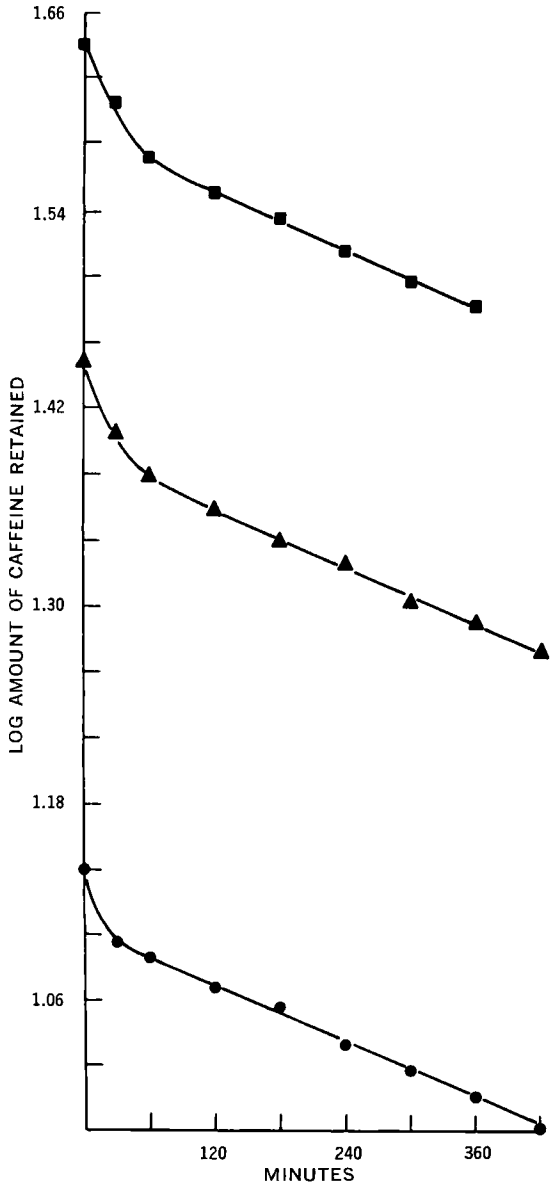

Figure 1—*Apparent first-order release profile for caffeine. Key (caffeine content of film): ●, 5%; ▲, 10%; and ■, 15%.*

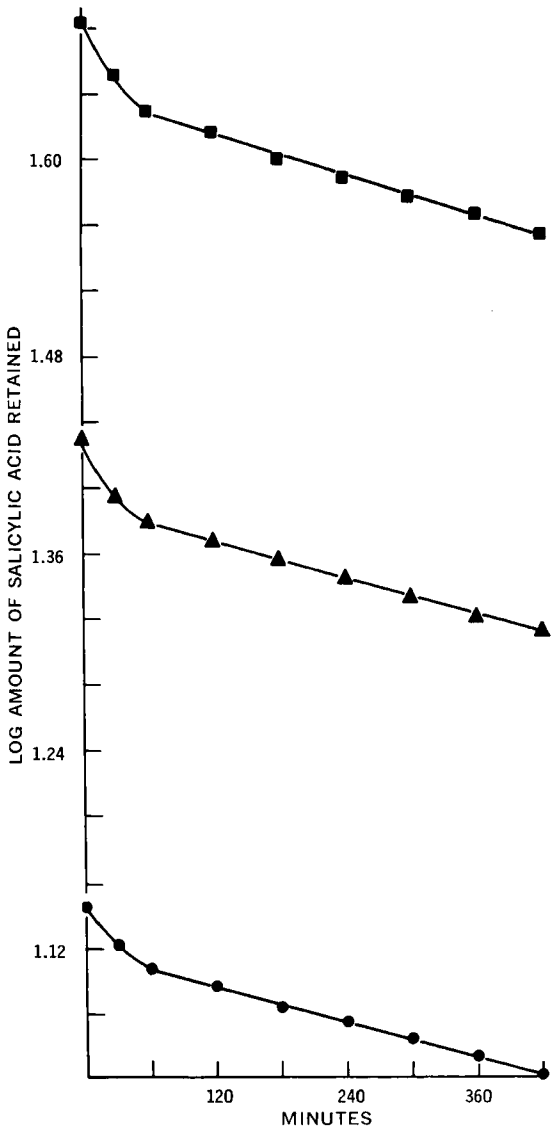

Figure 2—*Apparent first-order release profile for salicylic acid. Key (salicylic acid content of film): ●, 5%; ▲, 10%; and ■, 15%.*

film during its production might yield a useful new class of timed-release preparation. Such films have not been described for peroral use, but Sciarra and Gidwani (2, 3) investigated the preparation of such films for aerosol application to the skin and proposed kinetics for the release of gentian violet, cetylpyridinium chloride, and benzalkonium chloride, which were used as model drugs.

The present authors investigated the permeability of mixed films of ethylcellulose to caffeine (4) and salicylic acid. This report describes the preparation of cast films containing these drugs and the release patterns of these drugs from the films investigated. The applicability of the models of Higuchi (5) and Sciarra and Gidwani (2, 3) to the kinetics of release is examined.

THEORETICAL

The factors determining drug release rates are of particular importance in the formulation and production of timed-release preparations. To control these factors, it is necessary to determine the correct equation for the release patterns observed and to investigate the effects of changing the parameters in the equations upon the kinetics of release.

For film-incorporated drug, classical diffusion models would seem to be applicable (6). Higuchi (5) developed equations for linear and spherical diffusion-controlled release of drugs from insoluble solid wax or plastic matrixes. Where the drug is removed from a slab of matrix by a leaching process, the amount of drug, Q, liberated per unit surface area of matrix into the external medium in time t is given by the equation:

$$Q = \sqrt{\frac{\epsilon}{\tau} D(2A - \epsilon C_s) C_s t} \qquad \text{(Eq. 1)}$$

where A = initial drug concentration in the matrix; C_s = the solubility and D = the diffusion coefficient of the drug in the leaching medium, respectively; ϵ = porosity; and τ = tortuosity of the matrix. Higuchi's equation was found to be applicable in several studies (7–10) on wax-embedded and similar products and would appear to be a possible model for the behavior of film-incorporated drugs.

However, Sciarra and Gidwani (2, 3) based their treatment on the Noyes–Whitney law and reported that the release pattern from

Table I—Film Preparation and Composition

Composition of Film-Forming Solution[a]		Drug Concentration in Films, % w/w	Method of Film Preparation (12)
Ethylcellulose, % w/v	Drug[b], % w/v		
9.5	0.5	5	Glass substrate
9.0	1.0	10	Glass substrate
8.5	1.5	15	Glass substrate

[a] The solvent was chloroform. [b] Salicylic acid or caffeine.

their polymer films agreed with the now classical, first-order release equation:

$$\log A = \log A_0 - \frac{kt}{2.303} \qquad \text{(Eq. 2)}$$

in which A = quantity of drug remaining in the film at time t, and A_0 = initial quantity of the drug in the film. This form of release has been found applicable to many other kinds of timed-release preparations (11).

Although it is conceivable that release may be diffusion controlled in some systems and dissolution controlled in others, depending on parameters such as the permeability of the polymer to water, the solubility of the drug in the polymer and in water, and the particle size of the drug, dissolution control would not be expected to be a normal feature of timed release at low fluxes of drug and water. In this study, the applicability of the two models is investigated for two drugs having similar molecular weights and solubilities in water but vastly different affinities toward organic substances and solvents.

EXPERIMENTAL

Preparation of Films—The films were prepared by the techniques of Kanig and Goodman (12). Their composition and the method of preparation are given in Table I; 10% solutions of mixed solids were used.

Determination of Drug Concentration in Films—The initial drug concentrations in the films were determined spectrophotometrically using samples of the films dissolved in chloroform. Reference standard solutions of the drugs were prepared using the same solvent. No interferences due to the ethylcellulose occurred at the wavelengths of measurement: 273 nm for caffeine and 296 nm for salicylic acid.

Determination of Release Rate—Membranes were attached using an adhesive[1] to the rim of a cylindrical sintered-glass funnel (diameter 3.29 cm), which gave a film area of 33.98 cm^2. The inverted funnel was immersed in water at 37°, the water being mixed and circulated through a 1-cm flowcell in the spectrophotometer[2] using a polystaltic pump[3] operated at a flow rate of 20 ml/min. The film thickness was within 72–76 μm and film weight was 276–296 mg. The total volume of water used was 400 ml. Each experiment was performed in triplicate, and the mean calculated results were reproducible to within 1.5% of the mean.

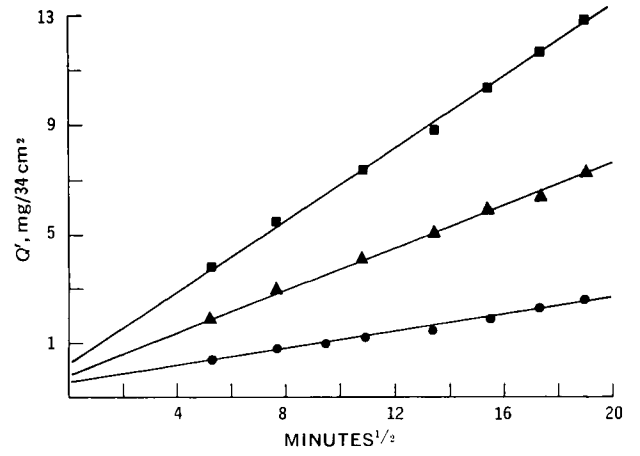

Figure 3—*Apparent diffusion-controlled release profiles, according to Higuchi's model (Eq. 1), for caffeine. Key (caffeine in film): ●, 5%; ▲, 10%; and ■, 15%.*

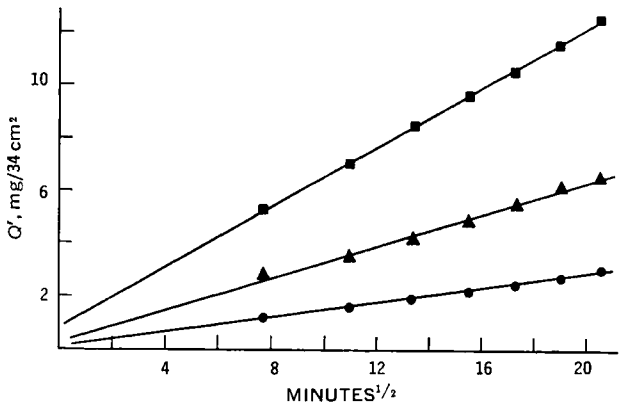

Figure 4—*Apparent diffusion-controlled release profiles, according to Higuchi's model (Eq. 1), for salicylic acid. Key (salicylic acid in film): ●, 5%; ▲, 10%; and ■, 15%.*

RESULTS AND DISCUSSION

Figures 1 and 2 show that both caffeine and salicylic acid appear to give first-order release patterns. The initial curvature can be attributed to the presence of surface drug and can be ignored.

From these figures it is also seen that the rate constant remains relatively constant with change in concentration of the drug in the film; this fact is in agreement with a first-order release model. However, when the amounts of drug released were plotted against the square root of time, straight lines were also obtained (Figs. 3 and 4). These linear plots appear to indicate that drug release in these systems is diffusion controlled, in accordance with Higuchi's equation. Furthermore, the increase in the release rate as the quantity of drug in the film is increased also agrees with this model.

Since both first-order and square root of time plots are acceptably linear, a more stringent test was needed to distinguish be-

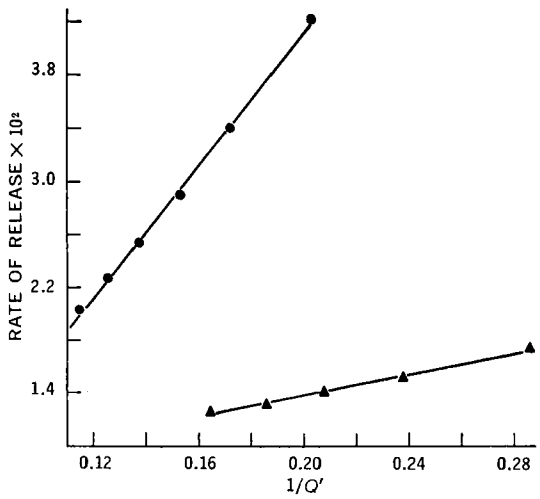

Figure 5—*Plot of release rate against reciprocal of amount of drug released, Q'. Key: ●, 10% caffeine in film; and ▲, 10% salicylic acid in film.*

[1] Silicone pressure-sensitive adhesive, Dow Corning Corp., Midland, Mich.

[2] Unicam SP 1800, Pye Unicam Ltd., Cambridge, England.

[3] Buchler Instruments, Inc., Fort Lee, N.J.

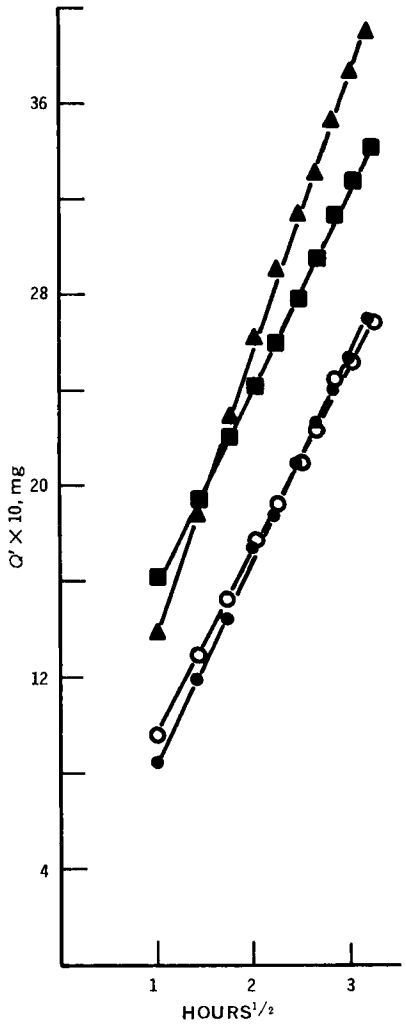

Figure 6—*Apparent diffusion-controlled release profiles, according to Higuchi's model (Eq. 1). Key (for cetylpyridinium chloride): ■, Fig. 7C of Ref. 3; and ○, Fig. 7B of Ref. 3. Key (for benzalkonium chloride): ●, Fig. 9B of Ref. 3; and ▲, Fig. 9D of Ref. 3.*

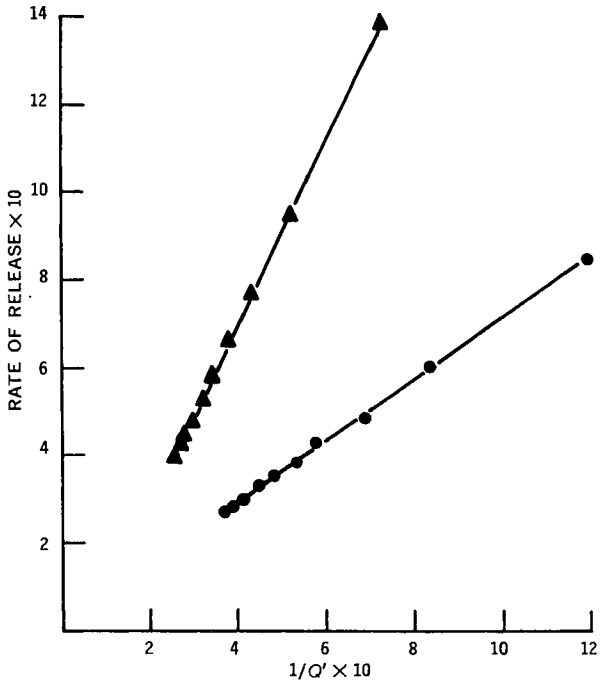

Figure 7—*Plot of release rate of benzalkonium chloride from polyamide films against reciprocals of amount released, Q'. Key (for benzalkonium chloride): ▲, Fig. 9D of Ref. 3; and ●, Fig. 9B of Ref. 3.*

tween the mechanisms. A suitable treatment was developed based upon use of predicted rate equations corresponding to Eqs. 1 and 2 (13). For the diffusion-controlled mechanism, the rate will be inversely proportional to the total amount of drug released, Q', in accordance with Eq. 3:

$$\frac{dQ'}{dt} = \frac{K^2S^2}{2Q'} \qquad \text{(Eq. 3)}$$

where $Q' = QS$ (S = surface area of film). Then:

$$K = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s\right]^{1/2} \qquad \text{(Eq. 4)}$$

The rate predicted by first-order kinetics, however, is given by:

$$\frac{dQ'}{dt} = kA_0 - kQ' \qquad \text{(Eq. 5)}$$

where $A = A_0 - Q'$. This indicates that the rate is proportional to Q' rather than inversely proportional as predicted by the diffusion model.

The rates of release were determined by measurement of the slopes of Q' *versus* time curves. The two mechanisms were clearly differentiated by plots of rates as functions of Q' and of $1/Q'$, because the plots of rate *versus* $1/Q'$ proved to be linear (Fig. 5) and those of rate *versus* Q' curved throughout the whole of the release period, indicating that the process is diffusion controlled. This conclusion was substantiated by the use of Eq. 6, the logarithmic form of Eq. 1:

$$\log Q' = \log K' + 1/2 \log t \qquad \text{(Eq. 6)}$$

where $K' = (K)(S)$.

Plots of log Q' against log t were linear and the slope was 0.5 for both drugs, confirming the diffusion model.

It is a matter of some interest to know whether the mechanism of release from polymer films varies according to the type of drug incorporated. Since Sciarra and Gidwani's (2, 3) results were obtained using the salts cetylpyridinium chloride and benzalkonium chloride, which are considerably more water soluble than caffeine and salicylic acid and form micelles, it seemed possible that a different mechanism might indeed be operative.

However, a replot of their results (Ref. 3, Figs. 7B, 7C, 9B, and 9D) showed linearity in the relationship between the quantity of drug released from the film and the square root of time (Fig. 6), so that the diffusion model also describes their results. That this model is the correct one for the release of cetylpyridinium chloride and benzalkonium chloride from the films was demonstrated by rate plots, which showed unequivocally that the rate was inversely and not directly proportional to Q' (Fig. 7), and by log–log plots, which gave slopes of 0.5, showing that the release mechanism was the same as for caffeine and salicylic acid.

The apparent first-order pattern observed probably reflects the use of a medicinally reasonable period for the study rather than a period sufficiently long to produce significant exhaustion of the film contents, which would be necessary for testing the physical mechanism of release. It is recommended that in all partial drug release studies, the rate plots against Q' and $1/Q'$ and the log–log plots used in the present work should be applied routinely where the mechanism of release is of interest. Moreover, Q *versus* t or $t^{1/2}$ plots or data should always be given to indicate the actual release pattern, since first-order plots showing log of drug retained in the product, even when linear, do not give the requisite information for predicting accurately the drug release over the full range of the dosage present.

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Chemical Constituents of Gentianaceae XIV: Tetraoxygenated and Pentaoxygenated Xanthones of *Swertia purpurascens* Wall.

S. GHOSAL [x], P. V. SHARMA, R. K. CHAUDHURI, and S. K. BHATTACHARYA *

Abstract □ The whole plant of *Swertia purpurascens* Wall. (Gentianaceae) has been shown to contain five tetraoxygenated and three pentaoxygenated xanthones. These are identified as 1,5,8-trihydroxy-3-methoxyxanthone, 1,3,8-trihydroxy-5-methoxyxanthone, 1-hydroxy-3,7,8-trimethoxyxanthone, 1,3,7,8-tetrahydroxyxanthone, 1,3,5,8-tetrahydroxyxanthone, and 1-hydroxy-3,4,7,8-tetramethoxyxanthone by chemical and spectral evidence. Additionally, the crude mixture of natural xanthones has been shown to include two partially methylated pentaoxygenated xanthones as minor entities, which yield 1-hydroxy-3,4,7,8-tetramethoxyxanthone and 1-hydroxy-3,4,5,8-tetramethoxyxanthone on methylation. This is the first time that pentaoxygenated xanthones have been found in a member of the genus *Swertia*. 1-Hydroxy-3,4,7,8-tetramethoxyxanthone was previously known only as a synthetic compound. The total xanthones of *S. purpurascens* produce significant CNS stimulant actions, consistent with some therapeutic uses of the plant extract in the Indian system of medicine. The chemotaxonomic significance of the cooccurrence of various biogenetically related chemical characters in a single plant species is appraised.

Keyphrases □ *Swertia purpurascens* Wall. (Gentianaceae)—five tetraoxygenated and three pentaoxygenated xanthones isolated and identified, screened for pharmacological activity □ Gentianaceae—chemical constituents, five tetraoxygenated and three pentaoxygenated xanthones isolated and identified from *S. purpurascens*, screened for pharmacological activity □ Xanthones, tetraoxygenated and pentaoxygenated—isolated and identified from *S. purpurascens*, screened for pharmacological activity □ Medicinal plants—isolation and identification of tetraoxygenated and pentaoxygenated xanthones from *S. purpurascens*, screened for pharmacological activity

Swertia purpurascens Wall. (Gentianaceae) is widely distributed in India in the temperate North Western Himalayas, 1524–3658 m (5000–12,000 ft), from Kashmir to Kumaon. The plant is used in the Indian system of medicine as a substitute for *Swertia chirata* Buch.-Ham. (1).

In a recent paper (2), isolation and characterization of three tetraoxygenated xanthone *O*-glucosides from the water-soluble xanthone fraction of this plant were reported. Since xanthone-bearing plants generally elaborate multiple xanthones (3), the earlier investigation has now been complemented by examination of the less polar xanthone fractions of this plant. This study has resulted in the isolation and identification of seven tetra- and pentaoxygenated xanthones, three of which are new naturally occurring compounds.

Another reason for the present investigation was to determine the pharmacological profile of activity of the free xanthones on the central nervous system (CNS) of laboratory animals. It was earlier demonstrated (2–6) that, while polyoxygenated xanthones and a xanthone C-glucoside, mangiferin, produced central stimulant action (mediated *via* monoamine oxidase inhibition) (4–6), the corresponding xanthone *O*-glucosides and related compounds showed definite signs of CNS depressant action (antipsycho-

Table I—Glucoxanthone and Glycoflavones Occurring in the Genera *Swertia* and *Gentiana*[a]

Species	Compound	Reference
S. swertopsis	Mangiferin (VIII), isovitexin (IX), homoorientin (X)	15
S. japonica	Orientin (XI), swertiajaponin (XII), swertisin (XIII)	16
S. purpuracens	Swertisin (XIII)	7
S. chirata	Mangiferin (VIII)	3
G. lutea	Mangiferin (VIII), isovitexin (IX), isoorientin (XIV)	17

[a] *Note added in proof: G. verna* was recently shown to contain mangiferin and isoorientin. [K. Hostettmann and A. Jacotguillarmod, *Helv. Chim. Acta*, **57**, 1155(1974).]