In Vitro Release of Therapeutically Active Ingredients from Polymer Matrixes

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Abstract □ Several therapeutically active ingredients including benzocaine, cyclomethycaine, and methapyrilene hydrochloride were incorporated into ethylcellulose and polyamide films. The effect of cetyl alcohol and tributyl citrate upon the release of these ingredients was studied. The films containing the active ingredient and plasticizer were cast upon a mercury substrate, and the *in vitro* release of these drugs from each film into a desorbing medium of distilled water was measured. The results indicated that the film-forming agent and plasticizer affected the drug release rate and that the release followed first-order kinetics. Benzocaine was slowly released from polyamide–cetyl alcohol films and polyamide–cetyl alcohol–tributyl citrate films. Polyamide–tributyl citrate films showed enhanced release of benzocaine and cyclomethycaine. Ethylcellulose films plasticized with tributyl citrate produced a fast drug release. Based upon these results, a water-soluble, highly polar, noncomplexing additive would tend to increase the drug release from the film. When the amount of benzocaine released from ethylcellulose was plotted as a function of the square root of time, a linear plot was obtained. Since this linear plot passed through the origin, ethylcellulose should be an ideal matrix for benzocaine according to the Higuchi diffusion-controlled model. These studies demonstrated the *in vitro* release of therapeutically active agents from a polymeric film as a function of the solubility of the active agent in both the polymer matrix and the desorbing medium.

Keyphrases □ Polymer matrixes—*in vitro* drug release of benzocaine, cyclomethycaine, and methapyrilene hydrochloride, effect of plasticizers □ Drug release—*in vitro* from polymer matrixes, effect of plasticizers □ Ethylcellulose films—*in vitro* drug release, effect of plasticizers □ Polyamide films—*in vitro* drug release, effect of plasticizers □ Benzocaine—*in vitro* release from polymer matrixes, effect of plasticizers □ Cyclomethycaine—*in vitro* release from polymer matrixes, effect of plasticizers □ Methapyrilene hydrochloride—*in vitro* release from polymer matrixes, effect of plasticizers

Protective films containing therapeutic agents have been used for dermatological, surgical, and cosmetic applications. Several of these preparations have been available in pressurized containers and included the use of cellulose compounds in the management of wounds and general surgical practice (1). A spray-on bandage containing methacrylate resin and thiram dissolved in ethyl acetate has been employed as a dressing for donor sites in skin grafting (2). Ethylcellulose and carboxymethylcellulose sodium with levomycellin and nitrofurazone were employed as bactericidal film-forming liquids in treating cuts and wounds (3). Polymeric films of ethylcellulose and polyamide resins were studied for their potential use as wound dressings and, in particular, their ability to release active ingredients such as gentian violet, benzalkonium chloride, and other antiseptic agents (4, 5).

Films composed of poly(methyl vinyl ether)–maleic anhydride copolymer, cross-linked with polysorbate 20, were reported to be promising for controlling drug release (6). Inert and insoluble matrixes of plastic polymers were shown to exhibit time-dependent release profiles (7). The release rate for sodium salicylate, benzoic acid, caffeine, and benzocaine from a polyethylene matrix was significantly changed when (*a*) different plastics were used, (*b*) the amount of drug in the matrix was changed, (*c*) drug solubility was changed, and (*d*) additives were used. The release rate of gentian violet from various plastic matrixes and different desorbing media was explained by first-order kinetics based on the Whitney–Noyes equation (4–8).

In addition, the mechanism of drug release from an inert insoluble polymeric matrix was described by the Higuchi equation (9, 10). The release of benzoic acid and salicylic acid into an aqueous medium from a wax matrix using both first-order release and the Higuchi diffusion-controlled release model also was investigated (11, 12).

This study concerned the development of a suitable film–plasticizer system containing benzocaine, cyclomethycaine, and methapyrilene hydrochloride that can be applied topically as an aerosol dosage form. Additionally, the release rates of these drugs from the films were determined.

EXPERIMENTAL

Based upon data obtained previously (4), ethylcellulose[1] and a polyamide[2] film were selected for investigation. Their alkali resistance, film hardness, flexibility, water vapor transmission, and insolubility in the desorbing medium were the bases for their selection. Cetyl alcohol and tributyl citrate[3] were used as plasticizers because of their polarity and plasticizing characteristics. Benzocaine[4], cyclomethycaine[5], and methapyrilene hydrochloride[5] were used as the model drugs.

Preparation of Drug–Film Matrix—The films were prepared from a 5% (w/w) solution of the film-forming agents and plasticizers. Ethylcellulose was dissolved in absolute alcohol, and the polyamide resin was dissolved in 2-propanol. A specific amount of drug was added to the plasticized polymer solution (concentration ranging from 150 to 200 mg/5 g of resin solids) so that the resulting solutions formed a good film without any cracks or fissures and contained sufficient drug for the drug release measurements.

The films were cast using the previously developed mercury substrate technique (4), and the drug-containing films were stored in a desiccator overnight. The drug–polymer-pretreated film (4.5 cm in diameter) was mounted onto the flat surface of a glass stopper using an epoxy-bonding cement as previously described (4). The film was then immersed in the drug release apparatus (Fig. 1). The flat head of the glass stopper was suspended in a water-jacketed, 400-ml capacity beaker containing 300 ml of distilled water at 37 ± 0.5°. Two such units were used.

The compositions of the films used for the drug release profile are shown in Table I. Two plasticizers at different concentration levels were used to determine the effect of both the nature and the concentration of the plasticizer on the drug release rate profile.

At selected time intervals over 6–8 hr, samples of the desorbing medium were removed and assayed spectrophotometrically[6] for the released drug at 294, 264, and 244 nm for benzocaine, cyclomethycaine

[1] Hercules, Inc., Wilmington, Del.
[2] Emerez 1155, Emery Industries, Cincinnati, Ohio.
[3] Citroflex-4, Chas. Pfizer and Co., Brooklyn, N.Y.
[4] Mallinckrodt Chemical Works, St. Louis, Mo.
[5] Eli Lilly & Co., Indianapolis, Ind.
[6] Coleman-Hitachi model 124 double-beam spectrophotometer.

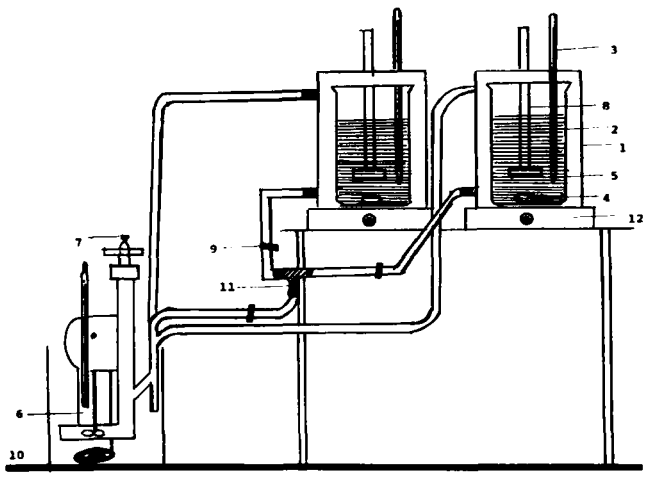

Figure 1—*Schematic diagram for* in vitro *drug release determination. Key: 1, plastic jar; 2, 400-ml beaker; 3, thermometer; 4, magnetic stirrer; 5, model drug film; 6, water circulating pump; 7, temperature variable; 8, plastic rod with a glass stopper; 9, pinch cock; 10, heating element; 11, glass T-tube; and 12, magnetic stirrer control.*

sulfate, and methapyrilene hydrochloride, respectively. The volume of desorbing medium removed (10 ml) from the release cell was replaced by an equal volume of desorbing medium, previously equilibrated at 37°. A cumulative correction was made for the previously removed samples in determining the total amount dissolved according to the following formula:

$$C_n = C_n \text{ meas} + \frac{10}{300} \times \sum_{s=1}^{n-1} C_s \text{ meas} \qquad \text{(Eq. 1)}$$

where C_n meas is the spectrophotometrically measured concentration, C_n is the concentration of the nth sampling expected in the medium if previous samples had not been removed, $n - 1$ is the total volume of all samples removed prior to the sample being measured, and C_s meas is the total of all spectrophotometrically measured concentrations at $n - 1$ samples (13).

Two to four determinations were performed on each sample. When a linear relationship was expected according to first-order kinetics, the data were treated by the least-squares method and the lines of best fit were reported using a multiaccess computer. The initial concentration of benzocaine, cyclomethycaine sulfate, or methapyrilene hydrochloride was determined spectrophotometrically by dissolving a 4.5-cm disk of the film in 1-butanol (Figs. 2–7 and Table II).

DISCUSSION

It is evident from the results that the nature of the film-forming agent affects the rate of drug release. Values of log A (drug remaining in the film) were plotted as a function of time. The linearity of these plots indicated that the drug release apparently followed first-order kinetics (Figs. 2–5). Figures 2 and 3 show the release rate profiles of benzocaine from ethylcellulose and polyamide films plasticized with varying concentrations of either tributyl citrate or cetyl alcohol. Similarly, the amounts of drug released from the polyamide film as a function of time for cyclomethycaine sulfate and methapyrilene

Table I—Film System Selected for Drug Release Studies

Film	Polymer	Plasticizer (parts per hundred)
1	Ethylcellulose	None
2	Ethylcellulose	Tributyl citrate (10)
3	Ethylcellulose	Tributyl citrate (20)
4	Ethylcellulose	Cetyl alcohol (20)
5	Ethylcellulose	Cetyl alcohol (30)
6	Ethylcellulose	Tributyl citrate–cetyl alcohol (10 and 10)
7	Polyamide	Tributyl citrate (20)
8	Polyamide	Cetyl alcohol (20)
9	Polyamide	Tributyl citrate–cetyl alcohol (10 and 10)

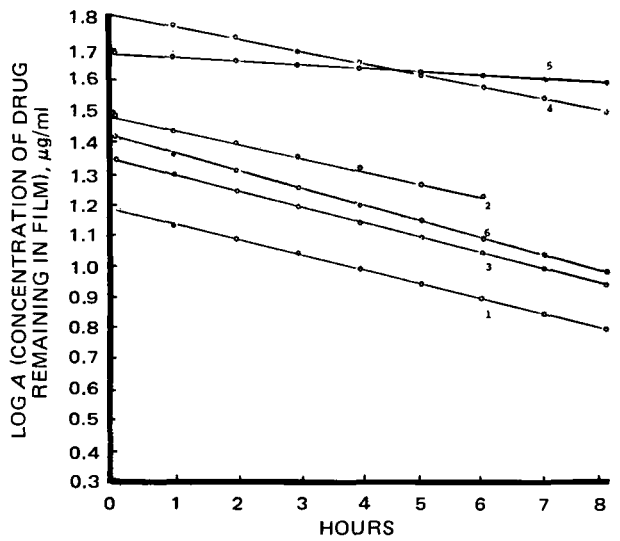

Figure 2—*Release of benzocaine from ethylcellulose films. Key: 1, unplasticized; 2, tributyl citrate (10 parts per hundred); 3, tributyl citrate (20 parts per hundred); 4, cetyl alcohol (20 parts per hundred); 5, cetyl alcohol (30 parts per hundred); and 6, tributyl citrate–cetyl alcohol (10 and 10 parts per hundred).*

hydrochloride are illustrated in Figs. 4 and 5. The incorporation of methapyrilene hydrochloride in the ethylcellulose film resulted in a film that could not be cast due to an incompatibility between ethylcellulose and the drug.

The rate constant and half-life for the release of each drug were calculated from the slope of these lines according to:

$$k = \text{slope} \times 2.303 \qquad \text{(Eq. 2)}$$

$$t_{1/2} = \frac{0.693}{k} \qquad \text{(Eq. 3)}$$

and are shown in Table II. Benzocaine was slowly released from the polyamide films plasticized with cetyl alcohol and a mixture of cetyl alcohol–tributyl citrate. Polyamide film plasticized with tributyl ci-

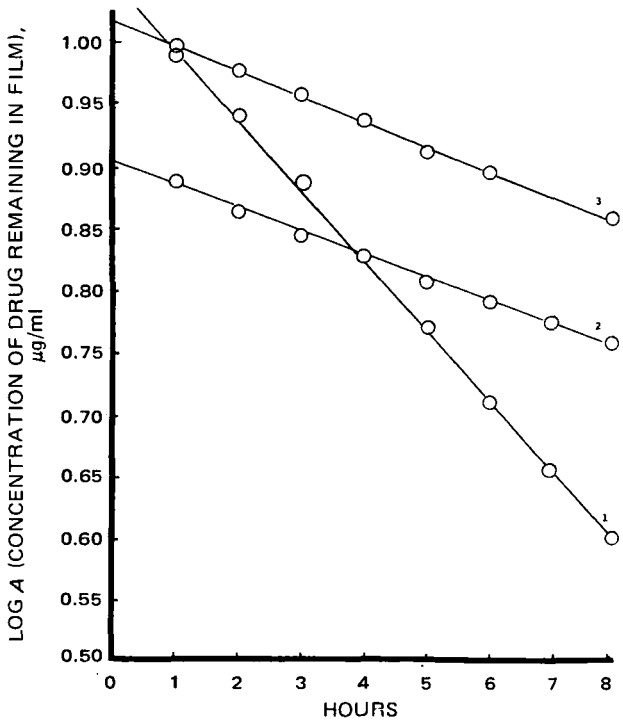

Figure 3—*Release of benzocaine from polyamide resin films. Key: 1, tributyl citrate (20 parts per hundred); 2, cetyl alcohol (20 parts per hundred); and 3, tributyl citrate–cetyl alcohol (10 and 10 parts per hundred).*

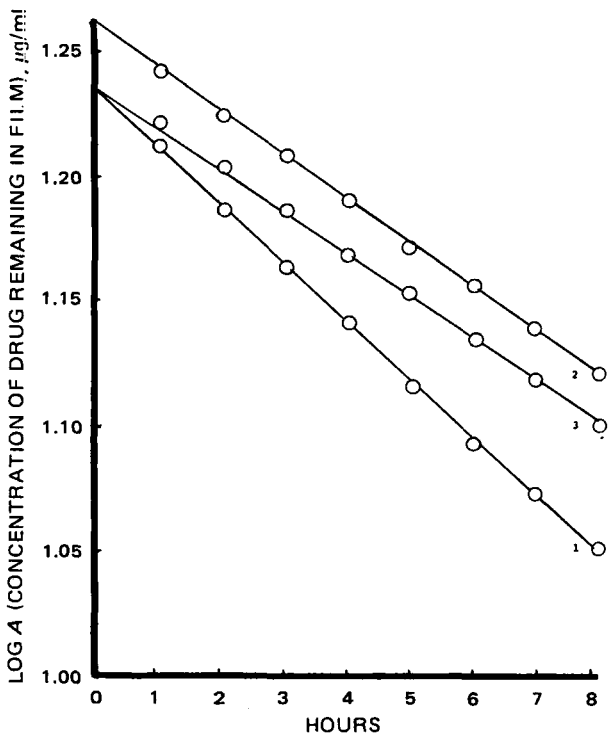

Figure 4—*Release of cyclomethycaine from polyamide resin films. Key: see Fig. 3.*

trate showed enhanced benzocaine and cyclomethycaine release. Ethylcellulose films plasticized with tributyl citrate produced a fast drug release profile. This finding indicated that water-soluble, highly polar, noncomplexing additives (plasticizers or film modifiers) would tend to increase the drug release from the film.

When the amount of drug released was plotted as a function of the square root of time, a linear plot was obtained for benzocaine from an ethylcellulose film (Fig. 6). Since this linear plot passes through the origin, ethylcellulose would be an ideal matrix for benzocaine according to the Higuchi diffusion-controlled model. The diffusion-controlled drug release data were plotted, and the value of the slope obtained from the plot of the logarithm of the amount of drug released per unit surface area *versus* the logarithm of time supports the diffusion-controlled drug release mechanism (Fig. 7).

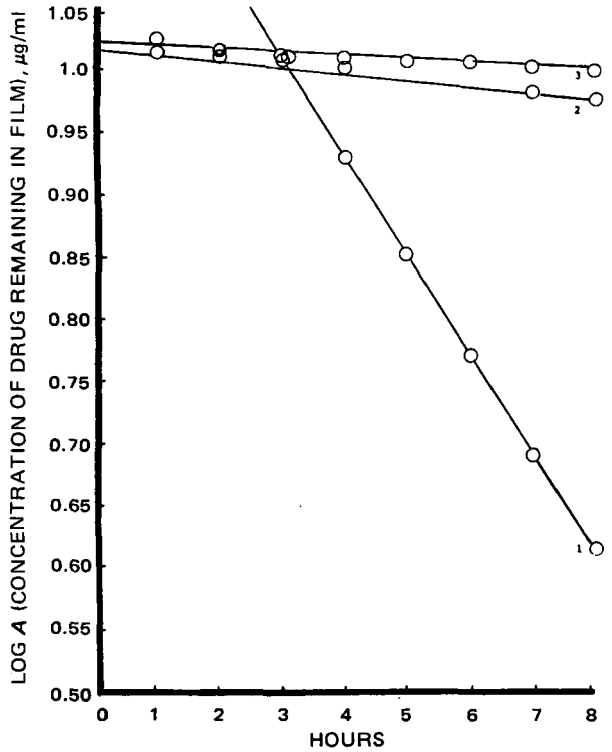

Figure 5—*Release of methapyrilene hydrochloride from polyamide resin films. Key: see Fig. 3.*

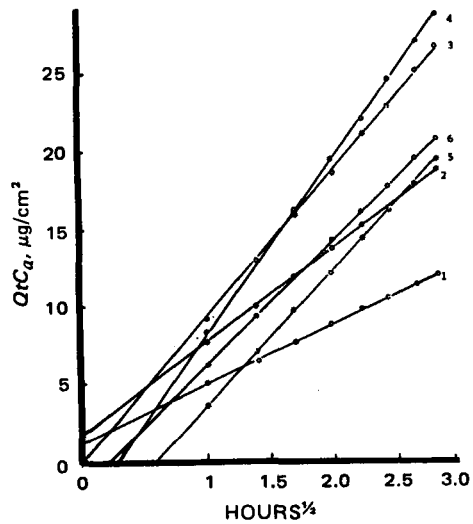

Figure 6—*Release profile of benzocaine plotted according to the diffusion model* (QtC_a = *corrected concentration of the drug released at time* t). *Key: see Fig. 2.*

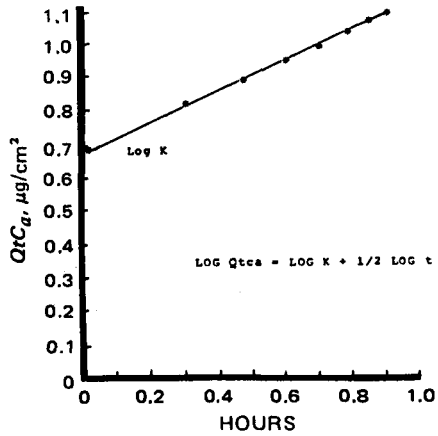

Figure 7—*Confirmation of diffusion-controlled drug release benzocaine–ethylcellulose system.*

Table II—Parameters for Release of Therapeutically Active Ingredients from Polymeric Films in Demineralized Water

Drug	Film	Slope × 10^{-2}	$K \times 10^{-2a}$, hr^{-1}	$t_{1/2}$, hr
Benzocaine	1	3.32	7.65	9.0
	2	3.00	6.90	10.0
	3	4.88	11.23	6.1
	4	2.54	5.84	11.8
	5	9.79	2.26	30.7
	6	5.18	11.94	5.8
	7	5.77	13.28	5.2
	8	1.93	4.44	15.5
	9	1.97	4.53	15.3
Cyclomethycaine sulfate	3	19.06	43.90	1.5
	6	2.40	5.52	12.5
	7	2.28	5.26	13.1
	8	1.69	3.90	17.7
	9	1.73	3.99	17.3
Methapyrilene hydrochloride	7	8.18	18.85	3.6
	8	3.43	7.90	8.7
	9	2.51	5.78	11.9

[a] First-order rate constant.

CONCLUSION

This study demonstrated a simple method that was useful for the determination of the release of certain drugs from a polymer–plasticizer combination. The drug release data indicated the usability of ethylcellulose and polyamide films. An ethylcellulose–tributyl citrate combination proved to be an excellent matrix for benzocaine. Cyclomethycaine could be incorporated into an ethylcellulose and polyamide film while methapyrilene hydrochloride was found to be incompatible with ethylcellulose.

A kinetic study of the release of benzocaine from ethylcellulose showed that the diffusion mechanism was operative according to the Higuchi diffusion-controlled model where the rate of release was inversely proportional to the concentration of drug released. The release rates were changed significantly with cetyl alcohol or tributyl citrate at different concentrations. These studies demonstrated the release of therapeutically active agents from polymeric film into the surrounding medium. The medicinal agent must be sufficiently insoluble in the film to allow for its release into the surrounding medium but not so soluble as to remain preferentially in the film.

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NOTES

Automated Analysis of Warfarin Sodium Tablets

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Abstract □ An automated procedure was developed for the determination of warfarin sodium by following the steps of the manual USP procedure. The automated procedure is applicable to single tablets and composites of 20 tablets at different tablet concentrations. Sensitivity, precision, accuracy, and reproducibility are equivalent to the manual USP procedure. Sensitivity was approximately 15 μg/ml, with a coefficient of variation of 0.711%.

Keyphrases □ Warfarin sodium—automated analysis, commercial dosage forms □ Automated analyses—warfarin sodium, commercial dosage forms □ Anticoagulants—warfarin sodium, commercial dosage forms

The semiautomated method recognized officially by the Association of Official Analytical Chemists (1–3) is an adaptation of the USP compendial assay (4) for warfarin sodium tablets. This semiautomated method uses suspensions of either single tablets or portions of tablet composites equivalent to single tablets. The preparation of these suspensions requires the disintegration of individual tablets or dispersion of weighed composites in an accurately measured volume of 0.01 *N* NaOH to give a drug concentration of 0.1 mg/ml. Homogenization of the sample is achieved by using an ultrasonic generator for at least 10 min with intermittent swirling and letting the suspension stand for 1.5 hr with occasional mixing. An aliquot of the homogenized sample is then transferred to the automatic analyzer.

This report discusses an automated system that follows the manual USP procedure and saves the labor and time consumed in the semiautomated method.

EXPERIMENTAL

Apparatus—The analytical system consisted of the following modules: solid sampler II[1], programmed at 20/hr, homogenizing speed 3, and stir speed 1; proportioning pump III[1]; a continuous filter[1], speed

[1] Technicon Corp., Tarrytown, N.Y.