International Journal of Pharmaceutics, 42 (1988) 161–169
Elsevier

IJP 01422

Controlled drug release from silicone coated tablets: preliminary evaluation of coating techniques and characterization of membrane permeation kinetics

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(Received 15 October 1986)
(Modified version received 6 August 1987)
(Accepted 7 September 1987)

Key words: Silicone-coated tablet; Tablet holder; Coating technique; Permeation kinetics

Summary

Investigations were conducted to evaluate the feasibility of using a silicone elastomer as coating material to control the release of drugs from the oral tablet. A two-component silicone elastomer system was utilized to coat tablets fabricated from progesterone and some of its hydroxyl derivatives both with and without a binder. Several coating techniques were explored for application of polymer dispersion onto tablet surfaces on a laboratory scale. The effects of these methods on drug release were found to differ. The effect of tablet binder content on the release of drug was also evaluated. Another goal was to study the effects of drug structure on steroid permeation through the resulting applied silicone coatings.

Introduction

A survey of the pharmaceutical market shows that a significant volume of pharmaceutical solid dosage forms today are coated for reasons ranging from the aesthetic to a desire for controlling the rate of drug delivery. Film coating is routinely used to accomplish these goals.

Among physiologically-active compounds, the steroids are a major focus of development because of their high potency and lipophilic properties as well as the desirability of a sustained chronic effect (Sundaram and Kincl, 1968; Roseman, 1972; Shippy et al., 1973).

Being non-irritating and non-antigenic, polydimethylsiloxane (PDMS) has been evaluated for use in controlling the delivery of therapeutic, prophylactic, and physiologic compounds (Garrett and Chemburkar, 1968; Sciarra and Gidwani, 1972). Aside from its biocompatibility, PDMS makes a good candidate for controlling release because small drug molecules are able to dissolve into and diffuse through the polymer.

The screening and testing of polymers as potential film coatings are the subjects of numerous investigations (Kanig and Goodman, 1982; Munden et al., 1964; Fites et al., 1970; Allen et al., 1972; Swarbrick et al., 1972; Aulton et al., 1961; Kallstrand and Ekman, 1983). When films

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are investigated for use as specialized coatings on dosage forms, the film-forming agents are evaluated on the basis of their performances on coated tablets or as free unsupported films. Free films are prepared by casting or spraying a solution of the polymer in a volatile solvent onto a suitable surface (Banker et al., 1966; Sciarra and Gidwani, 1972; Swarbrick et al., 1972).

Aside from evaluating the characteristics and performance of free, unsupported films, the usual method of evaluating new polymers and their potential involves the direct coating of a polymer onto a solid dosage by spraying, either on an intermittent or continuous manner, in a conventional tablet coating equipment. Since casted polymer free films are structurally quite different from those which have been casted or sprayed onto tablets, three different techniques of film coating utilizing simple laboratory equipment were used in this study. This allowed preparation of small batches of coated tablets with ease while trying to simulate films produced in industrial practice.

The main purpose of our work was to evaluate a silicone polymer ordinarily used to mold medical devices, as a coating material for solid oral dosage forms. A previous paper (Liu et al., 1986) dealt with the design of a tablet holder that would accommodate film coating permeation studies by maintaining a constant tablet surface area to the elution medium. Its calibration and some mechanisms of dissolution studies were presented. This paper will discuss membrane permeation kinetics and effects of drug structure and binder content on it.

Experimental

Materials

Progesterone, desoxycorticosterone, 11α- and 17α-hydroxyprogesterone, hydrocortisone (all Sigma Chemicals, St. Louis, MO), 17α-hydroxydesoxycorticosterone (Upjohn Co., Kalamazoo, MI), Avicel PH 101 (FMC Corp., Philadelphia, PA), FDC Yellow Golden Shade (Leeben Color and Chemical Co., New York, NY) were all used as received. Silicone elastomer Q7-4840 (Dow Corning Corp., Midland, MI) was dispersed in a cosolvent system of 30:70 methylene chloride/cyclohexane (both of Fisher Scientific, Fairlawn, NJ) and used as coating material. 40% aqueous solution of polyethylene glycol 400 (Fisher Scientific, Fairlawn, NJ) was prepared and used as the elution medium to maintain sink condition.

Preparation of tablets

The tablet holder consists of a die and two caps which were machined from 316 stainless steel (Fig. 1). The die measures 11/16 inch in outside diameter, 1 inch in height and has threads on the whole external surface. The upper cap, 3/4 inch, both in height and inner diameter, has threads on the inside rim. To the upper cap, a stainless steel shaft (5/16 inch in diameter) was coupled in place. The lower cap, which measures 3/4 inch in inner diameter and 9/16 inch in height, has a 1/2 inch opening at the bottom.

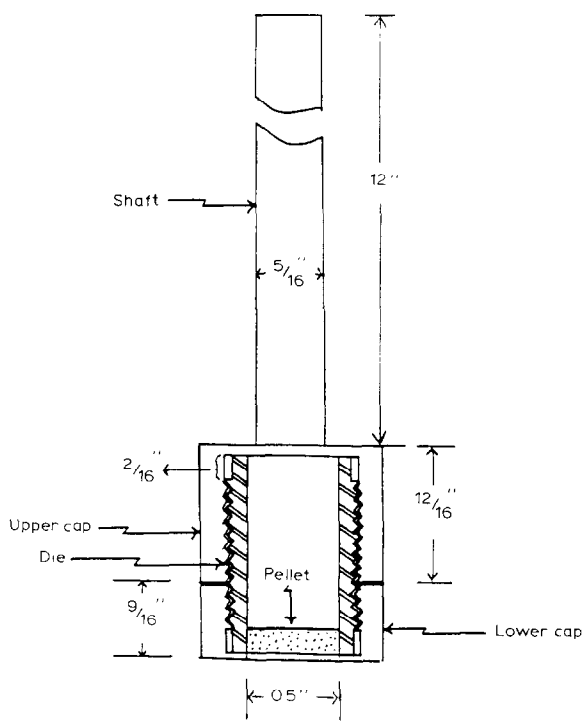


Fig. 1. Cross-sectional view and dimension of the specially-designed tablet holder.

Using a hydraulic (Carver) press, 250 mg of drug was compressed directly in the die, both with and without a binder. For tablets containing Avicel PH 101 as the binder, the required amount of drug was first mixed well with a corresponding proportion of binder before it was compressed.

To detect any potential defects of a coating membrane, a second layer of Avicel PH 101, containing 10% FDC Yellow Golden Shade, a water-soluble dye, was made on top of the formed drug tablet by compression. The dye was added to serve as indicator for any leakage or defects in the applied polymer film.

Tablet coating methods

A binary co-solvent system of methylene chloride/cyclohexane (30 : 70) was used as the solvent medium for the dispersion of equal portions of the A and B components of Q7-4840 silicone elastomer. The dispersion was stirred continuously for 3 h.

(a) Direct pouring method. The die element of the tablet holder containing a compressed tablet in position was turned end-face up and a dispersion of 27% (w/w) polymer was poured directly onto the tablet. Excess liquid was scraped off carefully using a stainless steel spatula to obtain a smooth surface.

(b) K-Bar. The die component of the tablet holder was placed on a flat surface with the compressed tablet facing up. The dispersion was cast onto the tablet surface using a K-bar (Testing

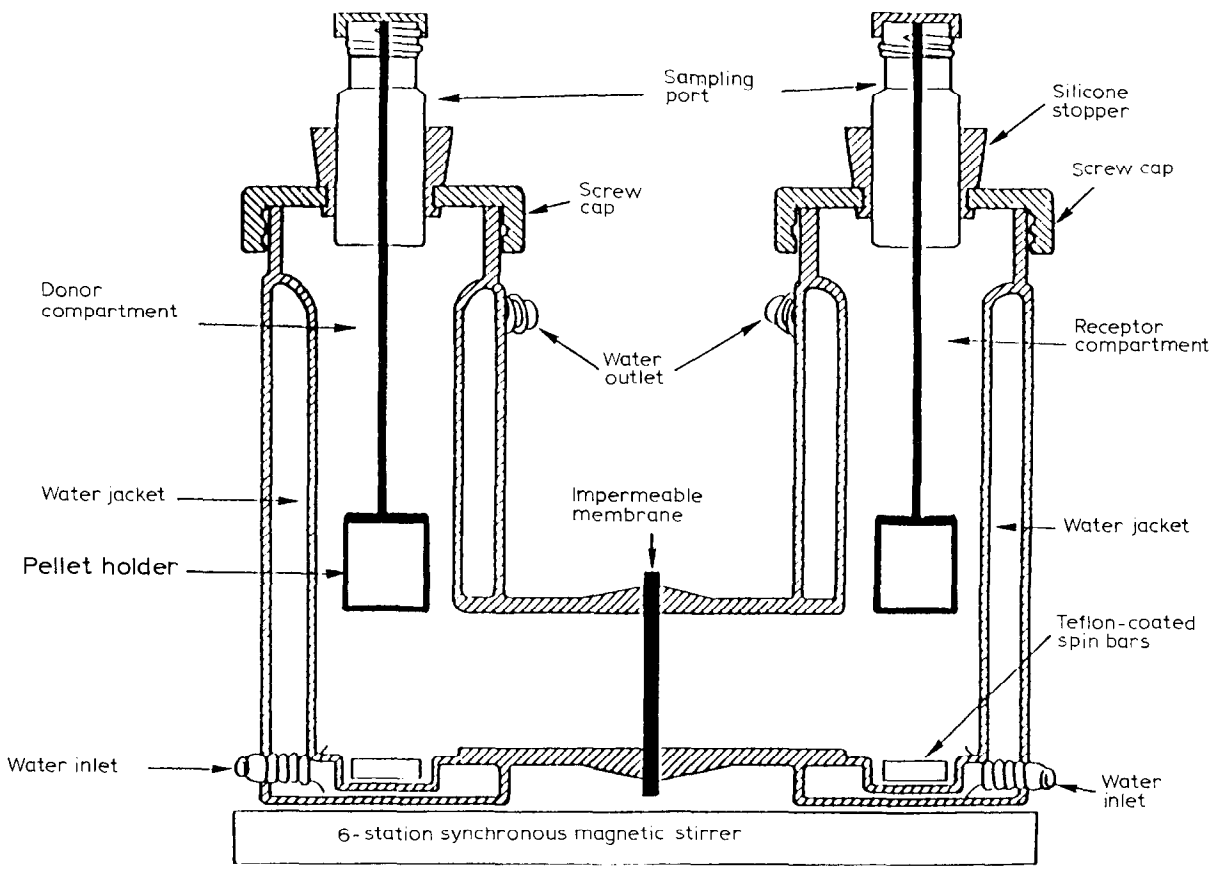


Fig. 2. Diagrammatic illustration of one unit of the in vitro drug release cells used in this investigation.

Machines, Long Island, NY), which is a stainless steel bar wound with stainless steel wire of selected diameter.

(c) Spraying method. Using an atomizer such as those used in chromatogram spraying (Fisher Scientific, Fair Lawn, NJ), a dispersion of 27% (w/w) polymer was delivered onto the tablet surface by dry gas under a pressure of 30 psi. Spraying was from a distance of 5 inches for 2 min while the tablet was held in place at a position perpendicular to the spraying stream.

In all 3 methods of coating applications, the applied polymer films were air-dried for 15 min and cured by hot air at 64°C from a blow-dryer. The upper and lower caps of the holder were screwed on securely afterwards to ensure a liquid-tight seal.

Drug permeation through the film coating

The Ghannam-Chien membrane permeation system (Tojo et al., 1984) was modified and used in the determination of drug release kinetics through the polymer coating. Each pair of half-cells was made to form two dissolution cells for duplicate experiments by placing an impermeable Teflon disc in between the half cells. 170 ml of the elution medium, 40% aqueous solution of PEG 400 preheated to 37°C, was added into each of the cells and the tablet holder assembly was immersed in the center (Fig. 2). Stirring speed was controlled at 425 rpm.

At predetermined intervals, 10 ml samples were withdrawn and quickly replaced with a same volume of the drug-free elution medium to maintain constant total volume. The steroid concentrations were analyzed by UV spectrophotometry (Perkin Elmer, 559A UV/vis Spectrophotometer, Elmwood Park, NJ) from the peak absorbance at 245 nm.

Results and Discussion

Comparison of film coating methods

When a tablet is coated with a water-insoluble silicone polymer, it is expected that a membrane-controlled permeation system results. In membrane-controlled permeation, drug molecules have to partition to and then diffuse through the membrane before they are released into the elution medium surrounding the coated tablet. A linear Q–t zero-order release profile should be obtained. It is therefore interesting to observe that the mechanism of permeation through applied polymer films varies as a function of the method of film coating.

Aside from controlling polymer concentration, weight of polymer dispersion applied, spraying distance and time, the film coatings were peeled off each tablet surface after every run and cleaned of any remaining drug powder as much as possible. Thickness was then measured using a micrometer (Brown & Sharpe Mfg. Co., Prov., RI).

In order to compare the release profile of various film thicknesses, the normalized cumulative amount of drug released, Q_N, was therefore actually used in place of Q in numerous instances.

$$Q_{\text{Normalized}}\ (\mu\text{g/cm}) = Q\ (\mu\text{g/cm}^2) \times \text{film thickness (cm)} \quad (1)$$

Fig. 3 indicates that films obtained by direct pouring and K-bar methods yielded curved plots of normalized cumulative amount of progesterone released, Q_N, versus time, t. Spraying resulted in a linear Q_N–t relationship. Replotting the release data from the 2 former methods according to the square-root model (matrix-controlled)

$$Q = \left[Dt(2A - C_s)C_s \right]^{1/2} \quad (2)$$

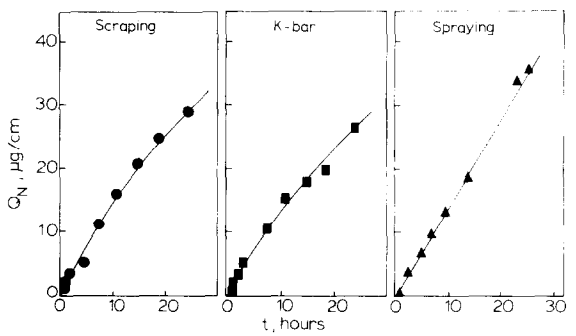


Fig. 3. Normalized permeation profiles of progesterone from the pure drug tablets coated by 3 methods: ●, scraping; ■, K-bar; ▲, spraying ($n = 3$ for each method and S.D.s are enclosed in the symbols).

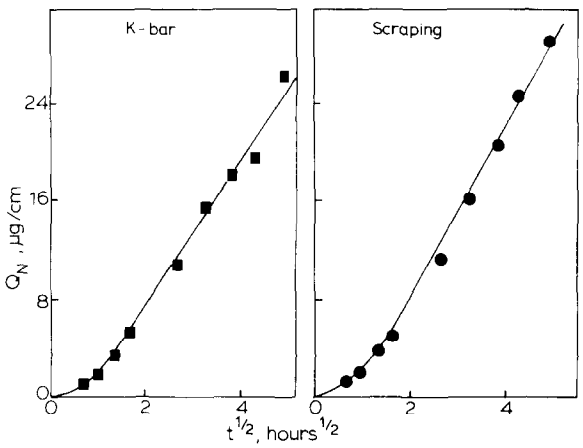


Fig. 4. Linear Q vs $t_{1/2}$ relationship for the normalized permeation profiles of progesterone from the pure drug tablets coated by: ■, K-bar; and ●, scraping methods ($n = 3$ for each method and S.D.s are enclosed in the symbols).

by Higuchi (Higuchi, 1963) gave a linear Q_N vs $t_{1/2}$ profile (Fig. 4). In this equation, D is diffusivity of drug in the homogeneous matrix media; A is the total amount of drug present in the matrix per unit volume and C_s stands for the solubility of the drug in the matrix substance.

The observed non-linear Q vs t release profile may be attributed to the migration of progesterone molecules into the polymer coating and/or the penetration of polymer dispersion into the tablet during the course of coating process. This is highly possible when one considers the fact that progesterone has a very high solubility in the organic solvent used in preparing the polymer dispersion. It was noticed that with the direct pouring and K-bar methods, a thick layer of polymer dispersion stayed on the tablet surface for a length of time before the organic solvent totally evaporated. During this period of close contact, a certain amount of progesterone can dissolve and diffuse into the polymer dispersion and produce a drug-dispersed polymer matrix. In other words, as the organic solvent evaporates, the amount of progesterone dissolved would crystallize out to form a dispersion in the film. This is the rationale for treating tablets coated by the K-bar method as matrix-controlled systems.

On the other hand, a polymer dispersion that is sprayed on would have a relatively fast rate of evaporation. This is due to the deposition of fine droplets of polymer coating which can dry up to form a thin film before the deposition of the next coating. Only a minimal amount of drug has the chance of being dissolved in the applied coating dispersion. As expected, the drug release profile for tablets coated by spraying yielded a linear Q vs t relationship (Fig. 3), indicating that drug release across a sprayed film follows Fickian diffusion.

Fig. 5 analyzes the time dependency of normalized progesterone release rates from tablets coated by the three methods. The results demonstrate that spraying produces a film which gives a practically constant rate of drug release. Both

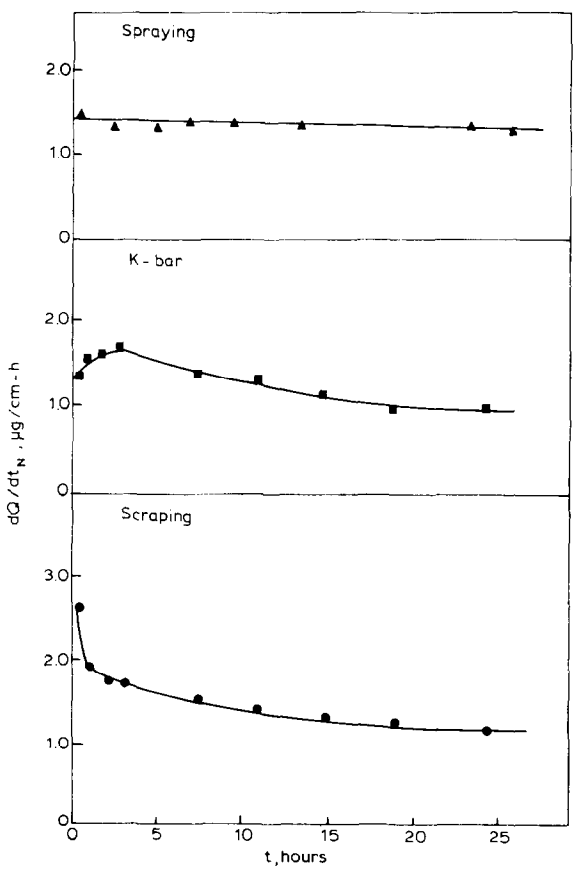


Fig. 5. Normalized release rate profiles of progesterone from the pure drug tablets coated by 3 methods: ▲, spraying; ■, K-bar; ●, scraping ($n = 3$ for each method and S.D.s are enclosed in the symbols).

direct pouring and K-bar techniques resulted in films which gave rates of release which were high initially and then tapered off.

Effect of pharmaceutical excipients

Pharmaceutical excipients are often incorporated into tablet formulations to improve compression and manufacturing processing. To investigate the effect of adding a pharmaceutical excipient, Avicel was used. The effect was studied by varying the ratio of progesterone to Avicel in the tablets and using spraying and the K-bar to apply the polymer coating.

Fig. 6 represents the dissolution profiles of uncoated progesterone tablets containing varying amounts of Avicel and it shows drug release to be a function of the quantity of diluent present.

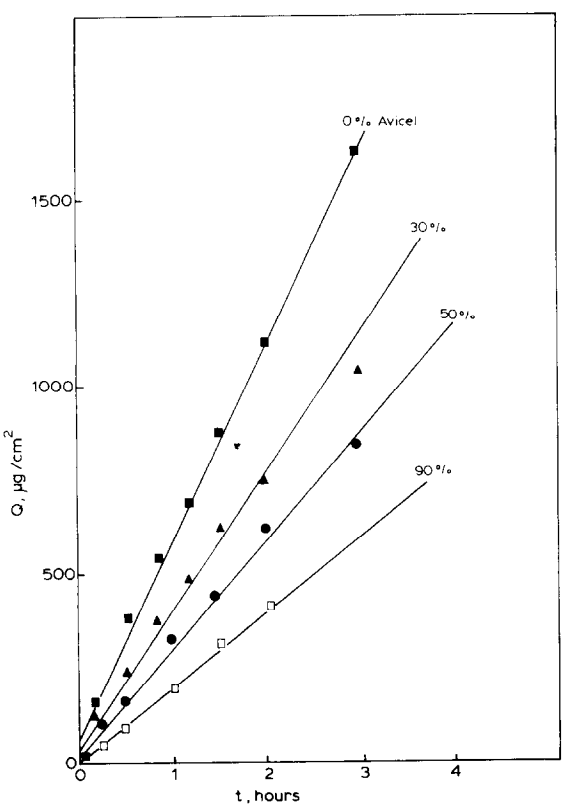


Fig. 6. Dissolution profiles of uncoated progesterone tablets containing varying amounts of Avicel PH 101 as binder: ■, 0% (w/w); ▲, 30% (w/w); ●, 50% (w/w); □, 90% (w/w) ($n = 3$ for each point and S.D.s are enclosed in the symbols).

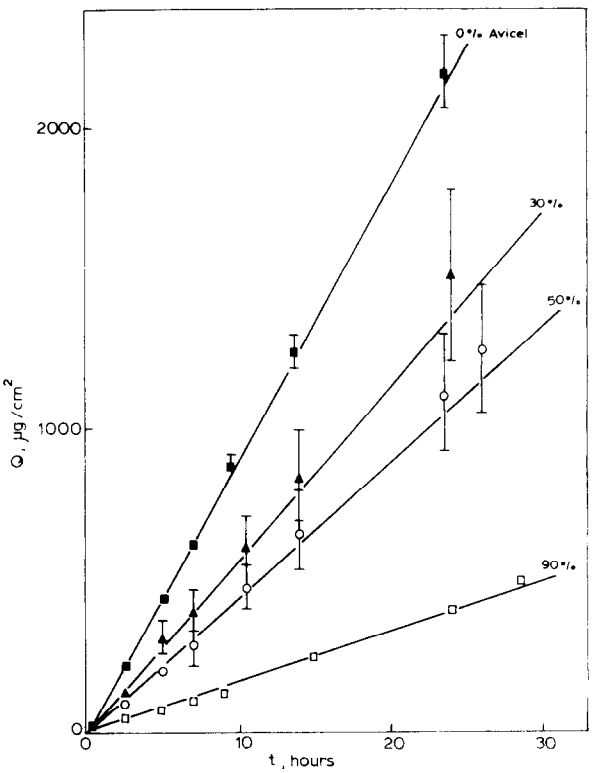


Fig. 7. Permeation profiles of progesterone from the tablets coated by the spraying method which contain various amounts of Avicel PH 101 as the binder; ■, 0% (w/w); ▲, 30% (w/w); ○, 50% (w/w); □, 90% (w/w) ($n = 3$ for each point).

Unfortunately, disintegration of tablets prevented data collection for periods of time greater than 5.5 h in most cases. Tablets containing 90% Avicel did not stay intact beyond 2.5 h.

Coating the progesterone tablets with silicone polymer drastically reduces cumulative amount released per square area as can be noted from the values of the y-axes in Figs. 7 and 8. Table 1 compares the fluxes of the progesterone-Avicel tablets, with and without coating. Drug diffusion through the tablet matrix appears not to be the only rate-controlled step in our coated tablets, indicating that the polymer layer does play a role by acting as an additional resistance barrier through which progesterone must partition into and diffuse through.

Expectedly, the pattern of decreasing slopes of the Q–t and Q–$t_{1/2}$ (Figs. 7 and 8) with increas-

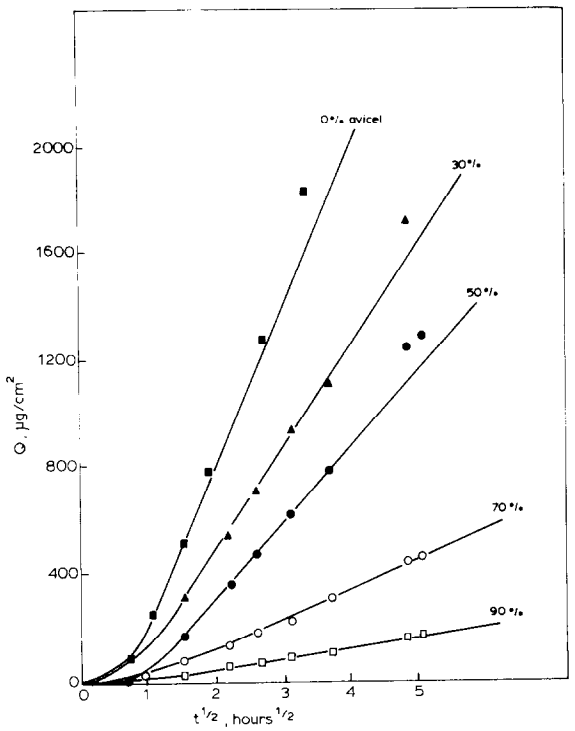


Fig. 8. Permeation profiles of progesterone from the tablets coated by the K-bar casting method which contain various amounts of Avicel PH 101: ■, 0% (w/w); ▲, 30% (w/w); ●, 50% (w/w); ○, 70% (w/w); □, 90% (w/w) ($n = 3$ for each point and S.D.s are enclosed in the symbols).

ing percentage of diluent in the coated tablets persists. As in the case of the uncoated progesterone tablets, the amount of released drug is dependent on diluent content. Furthermore, the

TABLE 1

Fluxes of uncoated and coated progesterone tablets with increasing amount of Avicel PH 101 as binder

Percent binder (%)	Flux ($\mu g/cm^2/h$)	
	Uncoated tablets	Spray-coated tablets
0	548.63 ± 35.04	93.98 ± 2.09
30	365.00 ± 44.67	75.33 ± 1.34
50	282.22 ± 21.18	35.50 ± 3.82
90	208.85 ± 20.66	15.04 ± 2.32

Note: Each data point represents results from triplicate experiments. Flux is an average rate in a time period covering 23 h for coated tablets and 4 h for uncoated tablets.

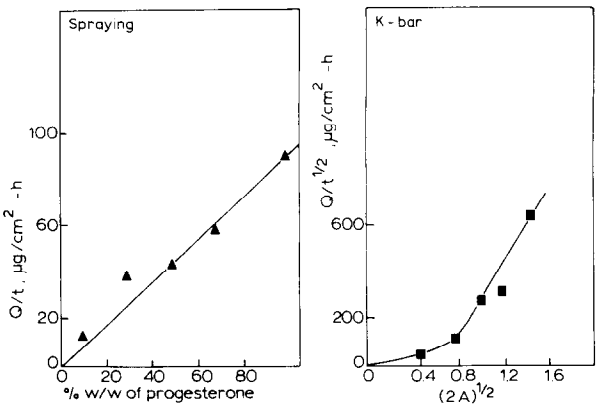


Fig. 9. Effect of drug content on the release rate profiles of progesterone from the tablets coated by (▲) spraying and (■) K-bar casting methods ($n = 3$ for each method and S.D.s are enclosed in the symbols).

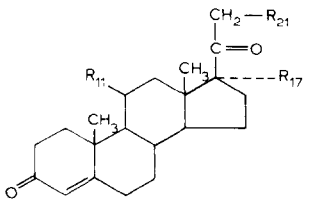
diluting effect of Avicel leads to a reduction in the surface concentration of progesterone in the tablet, thereby minimizing the dissolution of progesterone into the coating membrane which results in a reduction of release rates. Decreasing progesterone release rates with increasing diluent concentration indicates decreased permeation of drug molecules through the coating membrane where partitioning occurs at the tablet–membrane interface.

There does not seem to be any apparent drug–excipient interaction occurring in the tablets because rate of drug release appears to be approximately proportional to the weight fraction of progesterone present (Fig. 9). The results demonstrate that the rate of drug release through the membrane produced by spraying is linearly dependent upon the loading dose of the tablet while a linear $Q/t_{1/2}$ vs $(2A)_{1/2}$ dependency (Higuchi, 1963) is observed with the K-bar casted membrane.

It was noted that for the latter case, greater linearity occurs only after drug loading dose is greater than the 30% level. When the drug loading dose is at 10% (w/w) level, the progesterone concentration present in the coating membrane is too small and may not be homogeneously dispersed so as to have a true matrix system present. It is only when the concentration of available progesterone at the tablet surface is high enough that interdiffu-

TABLE 2

Chemical structure of progesterone derivatives investigated



Drugs	R_{21}	R_{11}	R_{17}
Progesterone	H	H	H
Desoxycorticosterone	OH	H	H
11α-Hydroxyprogesterone	H	OH	H
17α-Hydroxydesoxycorticosterone	OH	H	OH
Hydrocortisone	OH	OH	OH

sion of drug with the applied polymer dispersion can occur to form a drug-dispersed polymer matrix. What is happening then is the transition of drug release pattern from a partition-controlled to a matrix-controlled system as loading dose goes from low to high, thus accounting for the deviation from the expected $Q/t_{1/2}$ vs $(2A)_{1/2}$ linearity.

Effect of drug structure on drug permeation

To study the effects of increasing drug hydrophilicity on the controlled release kinetics across a lipophilic polymeric membrane, the permeation of several hydroxyl derivatives of progesterone through the silicone membrane coating was also investigated. The chemical structure and the position of hydroxyl groups of these progesterone derivatives are illustrated in Table 2. It has been reported that hydroxylation at various positions of the steroidal structure increases the hydrophilicity of progesterone and substantially reduces its rate of permeation across the silicone polymer (Ghannam et al., 1986) and its rate of release through the silicone polymer matrix (Chien et al., 1979).

Similar to the results reported earlier (Ghannam et al., 1986) for drug solution/membrane system (Study B), the data generated in the present solid drug/membrane system (Study A) also demonstrate that rate of permeation across the silicone membrane is dependent upon the number

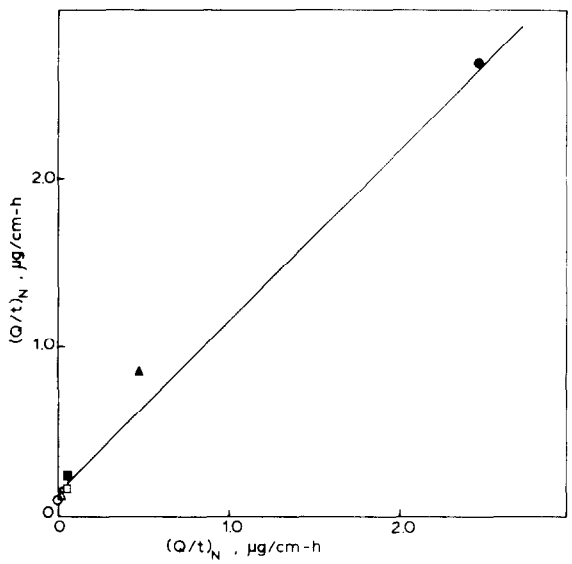


Fig. 10. Relationship between the normalized membrane permeation rates of progesterone derivatives from solid drug/binder tablets (Study A, y-axis) and their normalized membrane permeation rates from aqueous 40% PEG 400 solution (Study B, x-axis). Slope = 1.033 (corr. coeff. = 0.9946).

and position of the hydroxyl groups on the steroidal skeleton (Fig. 10). Decreased rates with increasing number of –OH groups could be attributed to the reduction in drug solubility in the polymer. Apparently, the presence of hydroxyl groups adds hydrophilicity to the progesterone, which in turn, reduces the interfacial partitioning of the drug molecule from the solid tablet or aqueous solution toward the lipophilic polymer membrane, causing a decrease in the rate of drug release through the membrane. The data obtained in this investigation (Study A) correlated well with data generated from Study B, even though the physical state of the donor phases was different between these two studies.

Conclusions

The method of film coating was observed to influence the mechanism and rate of drug release. The various coating methods developed for this investigation appear to be suitable for laboratory evaluation of film coating although refinement of the techniques needs to be done.

The presence of diluent was noted to change the interfacial partitioning of the drug from the tablet toward the polymer coating through the dilution effect on the surface drug concentration. An increase in diluent content appeared to decrease the rate of permeation and release of drug.

The rate of membrane permeation is dependent upon the chemical structure of drug molecule. Addition of hydroxyl group to the lipophilic progesterone molecule was observed to reduce the rate of permeation across the lipophilic silicone membrane.

Lastly, silicone elastomer Q7-4840 shows potential for use in oral controlled release as film coating.

Acknowledgements

The authors wish to thank FMC Foundation for their funding support. They are also grateful to Dow Corning Corporation for their donation of silicone elastomer used in this investigation.

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