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An In-vitro Evaluation of Silicone Elastomer Latex for Topical Drug Delivery

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Abstract

A silicone elastomer latex was evaluated as a topical drug-delivery system.

With the addition of a fumed silica and the removal of water, the latex produced elastomeric solid films. The water vapour permeability of the solid film was found to be a function of the film composition. An increase in silica content and the incorporation of a water-soluble component, PEG 3350, rendered the silicone elastomer-free film even more permeable to water vapour. The release of hydrocortisone from the elastomer film can be described by a matrix-diffusion-controlled mechanism. Drug diffusion is thought to occur through the hydrophobic silicone polymer network and the hydrated hydrophilic silica region in the film matrix. Silicone elastomer film with a higher silica content exhibited a faster drug-release rate. The addition of PEG 3350 to the film further enhanced the drug-release rate.

The primary role of a topical drug-delivery system is to present the drug in a form permitting percutaneous absorption. The vehicle of a topical dosage form should provide a balance that partitions the drug between the vehicle and the skin, so that the drug has a significant degree of affinity for the vehicle but still attains adequate delivery from the vehicle to the skin (Higuchi 1960; Barr 1962). Although semisolids such as ointment, cream, and gel are the most commonly used topical dosage forms, film-forming topical formulations also have a long history of application. Polymer films containing no therapeutic agents were initially used for wound healing (Miller et al 1961). Later, film-forming polymer solutions were also proposed for use as topical drug-delivery vehicles (Sciarra & Gidwani 1970; Sciarra & Patel 1976). In comparison with semisolid topical dosage forms, the use of film-forming delivery systems have the advantages of reducing product loss due to normal human body activity and staining of clothing by the product. However, as with the non-medicated polymer dressings, these film-forming systems are often applied as solutions containing an organic solvent which is flammable and irritates injured skin.

Latex and pseudolatex systems are aqueous colloidal dispersions of water-insoluble polymers. Pharmaceutically, a variety of commercial latex and pseudolatex products have been developed mainly for controlled-release film coatings (Chang et al 1987). Because of the film-forming capability and water-based nature of these dispersions, they may offer unique advantages as vehicles for topical drug delivery. The release kinetics of a variety of compounds from films derived from ethylcellulose pseudolatex and latex of acrylate copolymers has been characterized (Jones et al 1987; Ho & Suryakusuma 1988; Jenquin & McGinity 1988; Bodmeier & Paeratakul 1989).

A silicone elastomer latex consisting of a cross-linked hydroxy-end-blocked polydimethylsiloxane was recently evaluated as a controlled-release film coating system for tablets and beads (Li & Peck 1989a,b; Dahl & Sue 1992). With adequate silica reinforcement, silicone elastomer latex produces elastomeric, non-tacky, and water-insoluble films upon the removal of water. The primary goal of this study was to investigate the potential use of silicone elastomer latex as a topical drug-delivery system. The water vapour-transmission properties and drug-release characteristics of silicone elastomer films were evaluated as a function of the film composition.

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Materials and Methods

Materials

The silicone elastomer latex was supplied by the Dow Corning Company, Midland, MI. The elastomer latex has a pH of 8·2 and a total solids content of 53% (w/w). The mean particle size of the latex is 200 nm in diameter. The fumed silica (Cab-O-Sil) was obtained from the Cabot Corporation, Tuscola, IL. The particle size of the primary particles of the fumed silica is 7 nm. Polyethylene glycol (PEG) 3350 and hydrocortisone were purchased from Sigma Chemical Company, St Louis, MO.

Methods

Preparation of drug-containing silicone elastomer dispersions. Six silicone elastomer dispersions containing hydrocortisone and varying amounts of fumed silica were prepared. PEG 3350 was added to three of the six dispersions. The composition of these dispersions is presented in Table 1. A predetermined amount by weight of hydrocortisone powder was dispersed in the silicone elastomer latex using a mortar and pestle. A dispersion of fumed silica was separately prepared by uniformly dispersing a predetermined amount by weight of fumed silica in an adequate quantity of de-ionized water. This silica dispersion was subsequently added to the silicone elastomer-drug

Table 1. Composition of various silicone elastomer-hydrocortisone dispersions.

	Formulation number					
	1	2	3	4	5	6
Silicone/silica ratio	9·0	5·5	4·0	9·0	5·5	4·0
Hydrocortisone (%)*	2·5	2·5	2·5	2·5	2·5	2·5
PEG 3350 (%)*	0	0	0	10	10	10

* Percent by weight of the total solids in the dispersion.

dispersion. The solid content of the combined dispersion was adjusted to 20% w/w by adding an adequate amount of water. For formulations containing PEG 3350, the PEG was dissolved in water and added to the silicone elastomer-drug dispersion before the final mixing with the silica dispersion. The combined dispersion was passed once through a hand homogenizer to ensure uniform dispersion of all solid components in the product. Before application, the dispersion was shaken gently to ensure uniform dispersion of the drug. Vigorous shaking should be avoided because it can result in extensive foaming of the product.

Preparation of free films. A free film was prepared from the silicone elastomer dispersions following a standard casting procedure. Fifteen millilitres of each dispersion was poured into a 9 × 13 × 1 cm Plexiglass rectangular frame mounted on a piece of Teflon plate, and a high vacuum grease was used to produce a tight seal. The dispersion was allowed to dry at room temperature (21°C) on a level surface for 24 h. The film formed on the frame was subsequently transferred to a vacuum oven (37°C) containing anhydrous calcium sulphate as desiccant and stored for 24 h before use. The thickness of the cast films prepared for this study was controlled at 350 ± 10 μm.

Water vapour transmission. Water vapour-transmission cells, 10-dram amber screw-cap bottles with a 1·65 cm^2 circular opening in the cap, were used for this study. Ten millilitres of saturated sodium tartrate solution was placed in each cell to provide a water vapour pressure of 37·9 mmHg at 35°C (Washburn 1928). Film disks, 2·2 cm in diameter, were cut from the cast films using a cork borer. Each film disk was placed between two Teflon gaskets which were then fixed inside the screw cap. The water vapour-transmission cells with the solution and film disks in place were stored in a vacuum desiccator. The desiccator contained anhydrous calcium sulphate, used to produce a virtually zero water-vapour pressure environment outside the cells. The desiccator was placed in a 35°C constant-temperature oven. The transmission of water vapour from the cell to the desiccator is assumed to reach a steady state after 12 h. At this time, the weight of the cells was determined and used as a baseline weight. The cells were then weighed every 12 h for the following 60 h. The weight loss from a cell at each time point represents the amount of water vapour transmitted through the film. The cumulative amount of water transmitted was plotted against time. The slope of the linear plot (amount of moisture transmitted h^{-1}) was determined by the least squares method and was later used in the following equation to calculate the rate of water vapour transmission through the film disk:

$$R_{wvt} = W/(A \times \Delta P) \quad (1)$$

where R_{wvt} is the water vapour-transmission rate (g cm^{-2} h^{-1} $mmHg^{-1}$), W is the amount of moisture transmitted per hour (g h^{-1}), A is the area of film available for vapour transmission (cm^{-2}) and ΔP is the pressure difference across the film. The permeability coefficient (g cm^{-1} h mmHg) for each film was calculated as:

$$P = R_{wvt} \times t \quad (2)$$

where P is the permeability coefficient and t is the film thickness in cm.

Drug release from free films. Franz diffusion cells (15 mL in volume and 2·5 cm i.d.) were used for this study. Film disks, 4·0 cm in diameter, were cut from the cast films and used for the drug-release experiments. Each film disk was clamped between the donor and receptor compartments of a Franz diffusion cell. A 0·9% NaCl solution (saline) was placed in the receptor compartment and served as the receptor medium for the active ingredient being released from the film. The saline was maintained at 37°C by circulating heated water through the cell jacket. The receptor medium was constantly stirred by a magnetic stirring bar rotating at a speed of 600 rev min^{-1}. To ensure that the receptor medium was maintained in a sink condition for the release of hydrocortisone, the entire contents of the receptor compartment was withdrawn and replaced with 37°C fresh medium at each sampling time point. Sampling was done at 15, 30, and 60 min, and then at each hour through 8 h after the experiment was initiated. The absorbance of saline was determined at a wavelength of 248 nm and the concentration of hydrocortisone in each sample was calculated by means of a calibration curve.

Results and Discussion

The drug-containing silicone elastomer latex evaluated in this study produced elastomer-free films upon drying. The mechanical properties of these silicone elastomer-free films vary with their film composition. Free films with a silicone-to-silica ratio of 9·0 are soft and slightly sticky. As the content of silica increases (a lower silicone-to-silica ratio), the films become stronger but more brittle. Free films derived from formulations with a silicone-to-silica ratio lower than 4·0 crack upon drying. The incorporation of PEG 3350 does not significantly change the overall physical properties of the film.

Fig. 1 shows the effect of film composition on the linear regression lines of the water transmission data when plotted as a function of time. A correlation coefficient (r) of 0·995 or higher was calculated for all linear plots presented in Fig. 1. Table 2 presents water-vapour permeability constants for the various free-film formulations. It is apparent that free films containing an increasing percentage of silica are more permeable to water vapour. However, data in the literature indicate that silica significantly reduces the permeability of silicone elastomers to various gases by immobilizing the silicone polymer chains through attachment of them onto

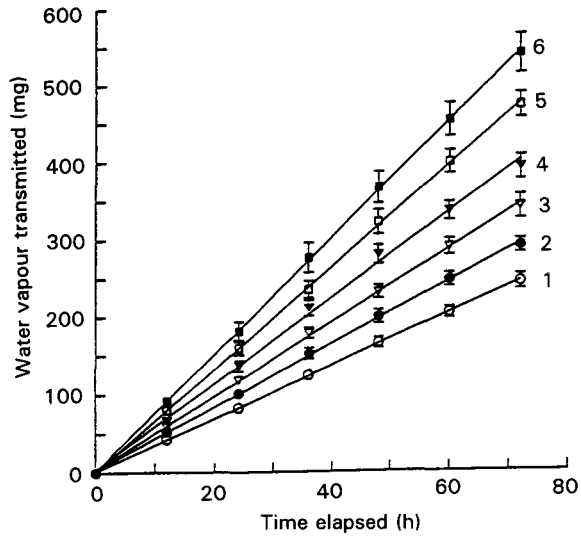

FIG. 1. Water vapour transmission through various silicone elastomer films.

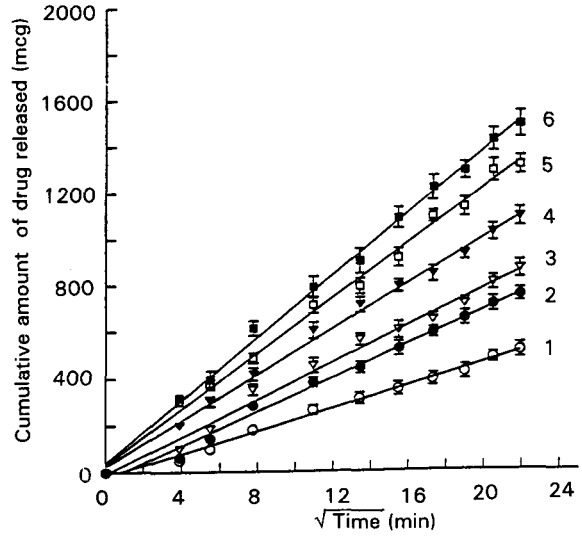

FIG. 2. The square root time plots for the release of hydrocortisone from various silicone elastomer-free films.

the silica surface (Iler 1979). The results of this study can be explained by the difference in the film-formation process for a conventional vulcanized silica-filled silicone elastomer and that for a silicone elastomer-silica aqueous dispersion. In a conventionally vulcanized system, silica is blended with the silicone polymer in a liquid state so that silica particles and the silicone polymer chains are in intimate contact, which allows the maximal filler-to-polymer linkages formation as the system is cured. In such a system, an increase in silica content results in enhanced polymer chain immobilization and the consequent reduction in gas permeability. In an aqueous dispersion of silicone elastomer and silica, the removal of water facilitates the interaction between the silicone elastomer latex particles and the silica particles. Owing to the vast difference in their particle size, the silicone elastomer latex particles (200 nm) are actually coated by the much smaller silica particles (7 nm) during the film-formation process. Unlike the vulcanized elastomer, the filler-polymer interaction between the latex and silica particles is limited to the free silicone polymer chains on the surface of the latex particles and the surface hydroxyl groups of silica particles (Saam et al 1981). As the concentration of silica increases, the silica layers surrounding the silicone particles become thicker and eventually give rise to regions consisting of free solid silica within the elastomer film matrix. Because of the relatively hydrophilic nature of silica, the formation of the silica-rich regions in the hydrophobic silicone elastomer matrix provides additional channels for the transmission of water vapour through the free film. Table 2 shows that the addition of 10% PEG 3350 results in a higher water-vapour permeability coefficient for all three film formulations. The high water solubility of PEG 3350 is probably the major contributory factor in the enhanced water-vapour permeability seen in the free films containing 10% of this compound.

Table 2. Water-vapour permeability coefficient for silicone elastomer-free films.

	Formulation number					
	1	2	3	4	5	6
Permeability coefficient $\times 10^6$ ($g cm^{-1}$ h mmHg)	1·85	2·23	2·63	3·06	3·67	4·19

Fig. 2 depicts the square root-time plots for the cumulative amounts of hydrocortisone released from various silicone elastomer-free films into the aqueous sink. A linear relationship ($r > 0.995$) is shown between the cumulative amounts of hydrocortisone released and the square root of the time elapsed, indicating that the release of hydrocortisone from the silicone elastomer film can be described by a matrix-diffusion controlled mechanism. It was also observed that, upon completion of the drug-release study, the portion of film in direct contact with the receptor medium changed from translucent to transparent and remained transparent when it was dry, evidence for depletion of the solid drug in the film matrix. Hydrocortisone was incorporated into the latex system as a fine powder and most of the drug remained as a solid during the film-formation process and eventually embedded in the silicone-silica matrix as the film formed.

Mechanistically, the release of hydrocortisone from the films may take place through the hydrophobic silicone polymer network as well as through the hydrated hydrophilic silica region in the film matrix. The moderately nonpolar nature of hydrocortisone is likely to affect its dissolution in the silicone polymer and the subsequent diffusion through the polymer network into the aqueous sink. This may be an important pathway for the release of hydrocortisone from films with a high silicone-to-silica ratio. On the other hand, hydrocortisone with a water solubility of 0·28 mg mL^{-1} at 25°C (The Merck Index 1989) is not completely insoluble in water. It is conceivable that the aqueous medium penetrating into the film matrix causes the hydration of the silica-rich regions and also

effects the dissolution of the drug in the hydrated region of the film, giving rise to a saturated solution. The subsequent diffusion of the dissolved hydrocortisone through the hydrated silica regions into the aqueous sink is believed to be an important drug-release mechanism for the film.

The incorporation of 10% PEG 3350 in the silicone elastomer film enhances the hydrophilic nature of the film matrix and leads to a greater degree of film hydration (Li & Peck 1989b). Apparently, the dissolution of PEG 3350 in the penetrating aqueous medium may also increase the concentration of dissolved hydrocortisone in the film because of a higher solubility of hydrocortisone in an aqueous solution containing PEG 3350. Furthermore, voids generated in the film matrix as the result of the leaching of PEG 3350 may also serve as additional water-filled channels for the diffusional transport of the dissolved hydrocortisone within the film. The combined effect of these factors is considered to be responsible for the enhanced drug release in films containing 10% PEG 3350.

In conclusion, the results of this study have shown that the silicone elastomer latex can be used as a topical drug-delivery system. The release of a relatively low water-soluble drug, hydrocortisone, can be described by a matrix-diffusion controlled mechanism. The drug-release rate is enhanced by increasing the hydrophilic component, silica, in the film or by adding a water-soluble ingredient. Because of the high solids content of the silicone elastomer latex and the high water-retention capacity of the fumed silica, topical products with the consistency of a semisolid (cream) or a liquid (lotion) can be readily prepared by controlling the amount of water added to the system. Since the silicone elastomer latex is capable of becoming both an adhesive and a flexible film, the use of a skin-irritating plasticizer can be avoided. The excellent biocompatibility of silicone elastomer, as substantiated by its long history of transdermal application, also complements its use as a topical delivery system.

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