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Evaluation of propylene glycol monostearate-ethoxylated stearyl alcohol films and kinetics of cortisol release

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Introduction

The role of film-forming polymers in controlled-release applications is well known (Grass et al., 1984; Shaw et al., 1977; Heilmann, 1978). However, the controlled-released potential of film-forming non-polymeric substances has not received as much attention. Previous investigations from our laboratory (Iyer and Vasavada, 1979; Khan and Vasavada, 1984) have demonstrated film-forming and controlled-release potential of non-polymeric substances such as lanolin alcohols for pharmaceutical applications.

In this study, propylene glycol monostearate (PGM) and ethoxylated stearyl alcohol (ESA) and combinations thereof have been examined for their film-forming ability. The results of film evaluations for wettability, strength, and elastic properties are presented. The release of cortisol (CO) from selected film compositions has been studied in order to explore the controlled-release potential of such films.

Experimental

Materials

Propylene glycol monostearate (PGM), NF (Ruger Chemicals, Irvington, NY). Ethoxylated stearyl alcohol (ESA), (Volpo S.20, Croda, New York, NY). Cortisol

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(CO), USP (Lot no. 0712833, Amend Drug and Chemicals, Irvington, NJ). Ethyl alcohol, USP (Commercial Solvents, Agnew, CA). Isopropyl alcohol, NF (Mallincrodt, St. Louis, MO).

Solubility studies

The solubilities of the film-forming materials were determined in water, isopropyl alcohol and ethyl alcohol at 22 ± 0.5°C. About 6–7 g of the film-former was added to 20 ml of each solvent in 50 ml flasks with screw caps. A teflon-coated magnetic bar was placed in each flask prior to capping it tightly. The flasks were supported by holders at a distance of 1.5 cm from the stirring motors in a constant temperature room. The stirring was stopped at the end of 48 h and the undissolved portion was allowed to settle. An aliquot was filtered using a glass funnel with filter paper. Two milliliters of filtrate was pipetted into a preweighed petri dish and dried in an oven at 50°C for 1 h. The petri dish was then left in a dessicator for at least 24 h at room temperature to attain constant weight. The solubility was calculated from the difference in weight of the petri dish. All studies were conducted in duplicate.

Preparation of films for initial screening

All films were prepared in a controlled environment at 25°C and 40% relative humidity from a 5% (w/v) solution (or suspension in the case of PGM). The films were cast using the mercury substrate technique (Iyer and Vasavada, 1979). Three milliliters of solution or suspension was poured on the surface of mercury contained in a 50 × 10 mm [1] glass petri dish, which was then partially covered with its lid to control the solvent evaporation rate and reduce the blistering of the film surface. The resulting films were carefully removed from the mercury substrate and were individually stored between sheets of weighing paper inside a dessicator over anhydrous calcium chloride. Minimum isolatable film thicknesses were determined by conducting thickness measurements on films prepared with decreasing amounts (2.5, 2, 1.5 and 1 ml) of solution or suspension.

Contact angle measurements

Films for contact angle measurements were cast on glass slides (25 × 75 mm) which were then placed on an adjustable platform of a Reflective Goniometer [2] fitted with a protractor scale. A water drop of 1 μl was applied on the film using a microburette and was allowed to stand for 60 s to reach equilibrium before reading the contact angle. The contact angle measurements were made at 5 points on each test film and mean value based upon 5 drops was calculated and reported.

Determination of hardness and modulus of elasticity

The films were cast on a polished aluminum plate (20 × 20 cm) using a multiple clearance applicator [3] producing a wet film thickness of about 1 mm. The plate was dried in a controlled environment at 25°C and 40% relative humidity. The dry film

[1] 50 mm in diameter and 10 mm in depth.
[2] Kernco Instruments, El Paso, TX.

thickness was then determined using a Minitector thickness measuring gauge (Model-N) [3].

Film hardness was determined using an automatic Sward Hardness Rocker [3] at room temperature. The number of rocks was measured by the average of three determinations rounded off to the nearest whole number. The modulus of elasticity, E, was calculated from the Sward Hardness by the method of Cass (1966).

Determination of drug release kinetics

The film was cast from a freshly prepared vehicle containing 6.6% w/v solids (drug plus film formers), using ethyl alcohol as the solvent. ESA and CO were added in required quantities to ethyl alcohol and were dissolved completely by stirring. PGM was then added and stirring continued for another 24 h to obtain a uniform dispersion. Three milliliters of this suspension was pipetted [4] into a preweighed, glass petri dish (60 mm in diameter), partially covered and kept on a level surface for at least 24 h to ensure slow and uniform evaporation of the solvent. Complete evaporation was confirmed by weighing the petri dish to a constant weight. The film-coated petri dish was stored in a dessicator for at least 24h prior to the release study. Various film compositions prepared and investigated during the course of this study are listed in Table 1. The release studies were conducted using a modified dissolution apparatus [5] described previously (Iyer and Vasavada, 1979). The study was conducted in 300 ml of distilled water at 25 ± 0.5°C. Three ml samples were drawn [4] at appropriate time intervals over a 12-h period and analyzed spectrophotometrically at 242 nm [6]. The samples withdrawn were replaced with an equal volume of water at 25°C The unidirectional release of the drug was assured by good adhesion of the film to the petri dish. No evidence of peeling or breaking of the film was observed during and at the termination of the experiments. The amount released was calculated with the aid of a standard curve. All release studies were conducted in duplicate.

Results and discussion

The solubility of PGM in water, isopropyl alcohol and ethyl alcohol at 22 ± 0.5°C was found to be 0.2, 58.9 and 57.5 mg/ml, respectively, while the solubility of ESA was greater than 150 mg/ml in all three solvents. The solubility of cortisol in water was found to be 0.298 mg/ml at 25°C. The drug content of the films No. 7–17 ranged from 7.69 to 8.39 mg.

Film characteristics

Both PGM and ESA were found to form thin films individually and together as mixed compositions. All films, regardless of composition, were transluscent and

[3] Gardner Laboratory, Bethesda, MD.
[4] Pipetman, Model p-5000D, Woburn, MA.
[5] Hanson Research, Northridge, CA.
[6] Bausch and Lomb, Spectronic 710.

TABLE 1

COMPOSITIONS OF THE FILMS STUDIED [a]

Film No.	Propylene glycol monostearate (PGM)	Ethoxylated stearyl alcohol (ESA)	Cortisol (CO)
1	0	96	4
2	96	0	4
3	94	2	4
4	92	4	4
5	90	6	4
6	88	8	4
7	86	10	4
8	85	11	4
9	84	12	4
10	83	13	4
11	82	14	4
12	81	15	4
13	80	16	4
14	79	17	4
15	78	18	4
16	77	19	4
17	76	20	4
18	82.85	14.15	3
19	83.71	14.29	2
20	84.56	14.44	1
21	81.84	15.16	3
22	82.69	15.31	2
23	83.53	15.47	1

[a] Percent w/w based upon weight of the dry films.

flexible with smooth but slightly tacky surfaces. Film characteristics of selected film compositions are described in Table 2.

(a) Contact angle. The contact angles of PGM-ESA films were found to be

TABLE 2

PHYSICAL PROPERTIES OF SELECTED PROPYLENE GLYCOL MONOSTEARATE-ETHOXYLATED STEARYL ALCOHOL FILMS

Film composition [a]	Contact angle [b]	Isolatable thickness [c] (μm)
100:0	28.7 ± 1.7	48.0 ± 3.2
0:100	58.3 ± 1.5	59.8 ± 2.7
90:10	20.0 ± 1.6	28.2 ± 2.4
85:15	19.8 ± 1.8	28.0 ± 2.2
80:20	19.4 ± 2.9	28.4 ± 2.1

[a] Expressed as propylene glycol monostearate: ethoxylated stearyl alcohol ratio, % w/w.
[b] Expressed as mean $\pm$ standard deviation of 5 readings.
[c] Expressed as mean $\pm$ standard deviation of 5 measurements.

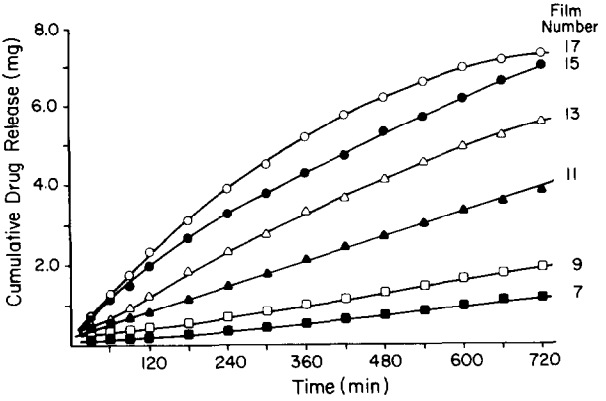

Fig. 1. Cumulative drug release from various propylene glycol monostearate-ethoxylated stearyl alcohol films.

smaller than those of either PGM films or ESA films suggesting that together PGM and ESA provide more efficient wetting of the film surface than either alone. The observed decrease in the contact angle was possibly due to lowering of surface tension at the film–water interface (Martin et al., 1973). A complete and uniform wetting of the film surface would be expected to contribute to a more consistent and predictable release of drugs.

(b) Film thickness. The minimum isolatable film thickness of PGM-ESA films was considerably smaller than that of either PGM or ESA films (Table 2).

(c) Modulus of elasticity. The PGM and ESA films had modulus of elasticity of 5.72 and 2.76 (psi) while films containing 10 and 20% w/w ESA had modulus of elasticity values of 5.41 and 4.06, respectively. Relatively low values of moduli of elasticity obtained for all films might be attributed to slight tackiness of the films.

Release kinetics

Effect of film composition

The films containing only PGM as the film-former were found to release less than 2% of their drug content in the dissolution medium over a 12-h period. On the other hand, films of ESA were found to release their entire cortisol content within about 30 min. The films of mixed composition containing the two film-formers showed drug release profiles somewhere between the two aforementioned extremes (Fig. 1). Since interest was mainly focussed on a potential delivery system capable of releasing the drug over a 10–12-h duration, the effect of film composition on release behavior was closely examined by varying ESA concentration from 10 to 20% w/w in increments of 1%. The initial cortisol concentration in all films was held at 4% w/w. The films No. 7–11 containing 10, 11, 12, 13 and 14% w/w ESA, respectively, had a nearly constant drug release rate over a 10-h period. This suggested that various time-dependent factors such as declining ESA content of the films, changing surface area of contact between the drug and the dissolution medium, and the

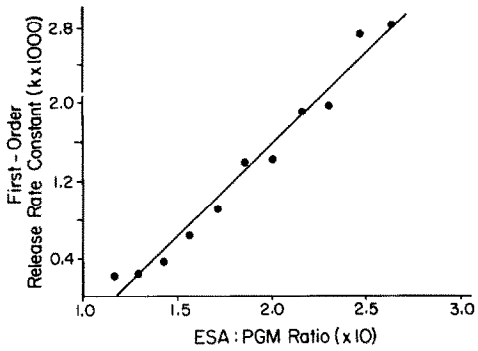

Fig. 2. First-order release rate constant as a function of film composition.

declining content of the drug in the film balanced each other over the 10-h duration of the release period. The effect of drug depletion became quite pronounced when the ESA content of the films was increased beyond 14% w/w, while keeping the cortisol content at 4% w/w, due to increased release rates. This was revealed by the drug release profiles for films No. 12–17.

When log-amounts of cortisol remaining were plotted against time, films No. 7–11 demonstrated linear dependence over the duration of the study (12 h) but the remaining films (No. 12–17) showed linearity only over initial 5-h period. A plot of first-order release rate constants against ESA : PGM ratio (Fig. 2) revealed apparent deviations from linearity especially for films with high ESA content probably due to rapid and variable erosion of the film matrix. Such films may not lend themselves to a predictable release of their contents. The drug release from film No. 7 appeared to be predominantly controlled by its high content of essentially water-insoluble PGM. It was found to follow the Higuchi model more than the other films. Higuchi's model (Eqn. 1) predicts a linear relationship between amount of drug released per unit area (Q) and square-root of time (t) for either homogeneous or granular film matrix (Higuchi, T., 1963). The model, however, does not account for complications arising from erosion of the film matrix as was the case in the system investigated. Deviation from the Higuchi model over the release period became more pronounced as the ESA content of the films increased.

$$Q = Kt^{1/2} \tag{1}$$

Effect of drug concentration

Film No. 11 (PGM : ESA : CO = 82 : 14 : 4) and No. 12 (PGM : ESA : CO = 81 : 15 : 4) were selected for evaluating the effects of changes in drug concentration on release behavior. The drug concentration was varied from 1 to 4% w/w with corresponding adjustment of PGM and ESA content such that PGM : ESA ratio remained constant at a value of 5.86 for variants of film No. 11 and at 5.4 for variations of film No. 12. The release data for film No. 11 and its variants (films No.

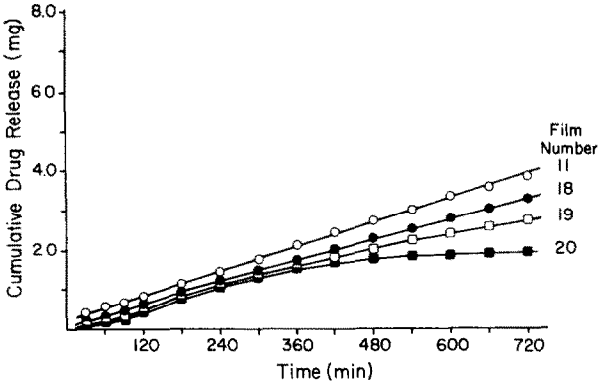

Fig. 3. Cumulative drug release versus time: effect of change in drug concentration.

18, 19 and 20) are presented in Fig. 3. From the inspection of the release profiles of Fig. 3 it is apparent that 3% w/w cortisol represents a limiting concentration for films with PGM : ESA ratio of 5.86 in order to maintain constant release rate over the 12-h release period. The films containing greater than 4% w/w cortisol at a PGM : ESA ratio of 5.86 could conceivably provide faster and constant release rates over periods greater than 12 h. The results of drug release study with film No. 12 and its congeners (films No. 21, 22 and 23) were similar.

Conclusion

The PGM-ESA system has been shown to form thin films with potential pharmaceutical and cosmetic applications. This study has demonstrated that film-forming system composed of PGM and ESA could be suitably manipulated to attain desired and constant release rates over several hours for cortisol. The PGM-ESA films might be useful for constant, slow release of other drugs as well.

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References

Cass, R.A., The Sward Rocker for measuring the modulus of elasticity of paint films. J. Paint Technol., 38 (1966) 281–284.

Grass, G.M., Cobby, J. and Makoid, M.C., Ocular delivery of pilocarpine from erodible matrices. J. Pharm. Sci., 73 (1984) 618–620.

Heilmann, K., Therapeutic Systems: Pattern-Specific Delivery: Concept and Development, PSG Press, MA, 1978.

Higuchi, T., Mechanism of sustained-action medication. J. Pharm. Sci., 52 (1963) 1145–1149.

Iyer, B.V. and Vasavada, R.C., Evaluation of films of lanolin alcohol and kinetics of triamcinolone acetonide release. J. Pharm. Sci., 68 (1979) 782–787.

Khan, A.R., Iyer, B.V. and Vasavada, R.C., In vitro release of salicylic acid from lanolin alcohols-ethyl cellulose films. J. Pharm. Sci., 73 (1984) 302–305.

Martin, N.A., Swarbrick, J. and Cammarata, A., Physical Pharmacy, Lea and Febiger, Philadelphia, 1973, Ch. 15.

Shaw, J.E., Chandrasekaran, S.K., Campbell, P.S. and Schmitt, L.G., New procedures for evaluating cutaneous toxicity. In Cutaneous Toxicity, Academic Press, New York, 1977, pp. 83–94.