Drug Development and Industrial Pharmacy, 23(3), 253-257 (1997)

RESEARCH PAPER

Release of Urea from Semisolid Formulations Using a Multilayer Membrane System*

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ABSTRACT

A method for the determination of in vitro release of urea from semisolid formulations using a multilayer membrane system (MMS) has been developed. The artificial model membranes consisted of collodion as the matrix and glycerol as the hydrophilic acceptor phase. The method can be employed as a tool for comparison of in vitro release profile of semisolid formulations and, thus, can be used as a quality control procedure for assuring lot-to-lot uniformity.

INTRODUCTION

The evaluation of in vitro release of active substances from semisolid formulations has been gaining more and more attention in the last few years. At present, however, there is no official method to evaluate the release of drugs from such dosage forms. Therefore, intensive efforts have been directed by a number of investigators to the development of model systems for characterization of drug release from semisolid formulations (1–4). Recent articles have described a model system with a multilayer membrane system (MMS) serving as an acceptor phase. The acceptor system of the MMS consists of membranes with collodion as a matrix and can be adapted to a broad range of experimental conditions by varying the content and type of the membranes (lipophilic or hydrophilic) (1,2,5). This model system has been used as a penetration model to simulate the penetration profiles of drugs in human excised skin (5–7) and has also been applied as a simple release model system (8–10).

The purpose of this study was to develop a multilayer membrane system for estimating the in vitro release of urea from semisolid formulations and to assure lot-to-lot uniformity.

*Part of this work was presented at the Second European Congress of Pharmaceutical Sciences.

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MATERIALS AND METHODS

Materials

The following commercially available products were used in the study: A_1 and A_2 urea 12% hydrophilic cream, Ureotop® (Stada, Arzneimittel AG, lot no. 02 and lot no. 950503); B_1 and B_2 urea 10% hydrophilic cream, Nubral® (Galderma Laboratorium GmbH, lot no. 14251 and lot no. 023.4); C_1 and C_2 urea 12% lipophilic cream, Carbamid® (Louis Widner GmbH, lot no. 1814 and lot no. 45011); D_1 and D_2 urea 10% lipophilic cream, Laceran® (Beiersdorf AG, lot no. 51340230 and lot no. 51330130).

Collodion 4% (w/w), glycerol 98% (w/w) (Caesar and Loretz GmbH, Hilden, Germany), absolute ethanol, and ether (Merck, Darmstadt, Germany) were used to produce the hydrophilic membranes as the acceptor system for the liberations studies.

Urea reference substance and sulfuric acid were obtained from Merck (Darmstadt, Germany). *p*-Dimethylaminobenzaldehyde was obtained from Sigma Chemie GmbH (Deisenhofen, Germany).

Analytical Assay

A solution (0.5 ml) containing 4% (w/v) of *p*-dimethylaminobenzaldehyde and 4% (v/v) of sulfuric acid in absolute ethanol was added to 2 ml of a solution of urea. After 10 min, the absorbance was measured at the maximum (422 nm) against a reagent blank using a Shimadzu spectrophotometer (Duisburg, Germany). The concentration of urea in the samples was determined by reference to the calibration curve.

Preparation of the Hydrophilic Membranes

The components of the membrane were dissolved in a mixture of absolute ethanol and ether (1.5:8.5). The resulting mixture was placed on a glass surface of a film-forming device (constructed by Mechanische Werkstatt, College of Pharmacy, Martin-Luther University, Halle, Germany). The membrane formed was dried for 4 hr at room temperature and cut into disks of 4 cm diameter (corresponding to the base plate on the model system; see Fig. 1). The membrane disks were stored at room temperature in a vacuum desiccator over silica gel for 24 hr before use. The content of glycerol in the membranes (3.92 mg/4 cm^2 $\pm$ 0.08; $n = 6$) was assayed as described earlier (11,12).

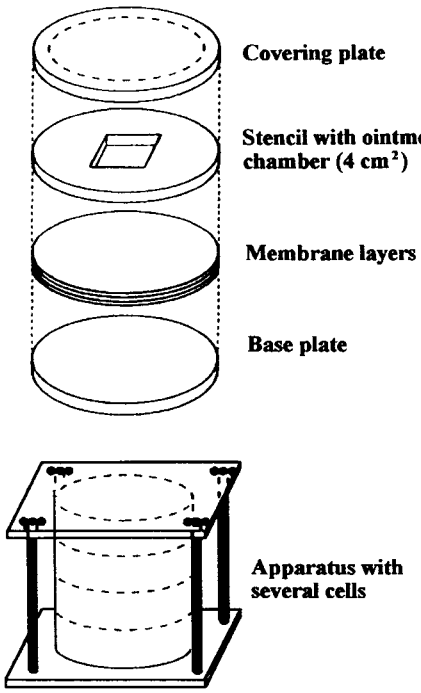


Figure 1. Multilayer membrane system used.

Release Studies

Multilayer Membrane System

The model system has been described previously (1,5). One cell is outlined in Fig. 1. An accurately weighed quantity of the topical formulation (10 mg) was applied to the acceptor system, which was fixed in a penetration cell with an exposed application area of 4.0 cm^2. The penetration cells were fixed in the model construction and placed in a chamber maintained at 32.0°C $\pm$ 0.2°C during the experimental period. The model apparatus was removed from the thermostated chamber at selected time intervals. After removal, the release cells were separated and the amount of applied formulation remaining on the first acceptor layer was removed. Urea was extracted from the separated membranes with 3 ml of absolute ethanol by shaking for 30 min. The content of urea was determined as described above.

RESULTS AND DISCUSSION

A multilayer membrane system (MMS) was used to measure the release of urea from semisolid formulations

(1). Membranes consisting of glycerol were used as hydrophilic acceptor phase, because of the high hydrophilic properties of the model drug urea. The number of acceptor membranes was attached to the solubilities of the urea in glycerol and was increased up to three layers to maintain approximately sink conditions.

The in vitro release of urea from all semisolid products was monitored over a period of 200 min. The area under the concentration–time curve (AUC) was used as a quantitative parameter to characterize the rate and extent of release in vitro according to Brockmeier (13,14). The results were expressed as plot of urea concentration in the acceptor membranes as a function of time (Table 1; Fig. 2).

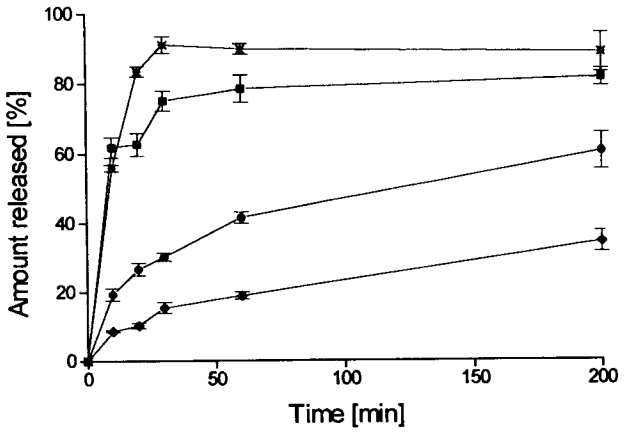


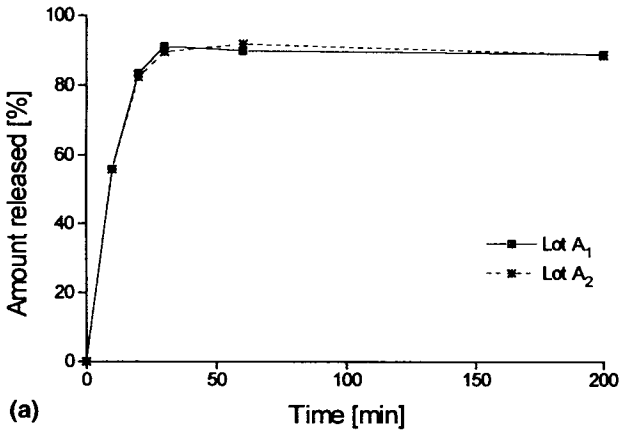
Figure 2. In vitro release profile of urea creams using the multilayer membrane system. Values are means of 6 determinations: *, product A_1; ■, product B_1; ●, product C_1; ◆, product D_1.

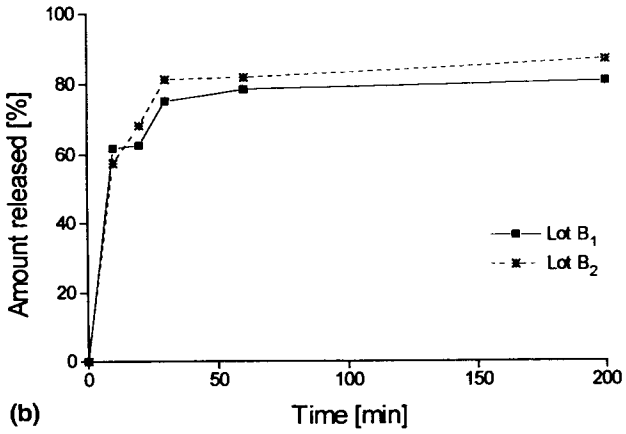
Table 1

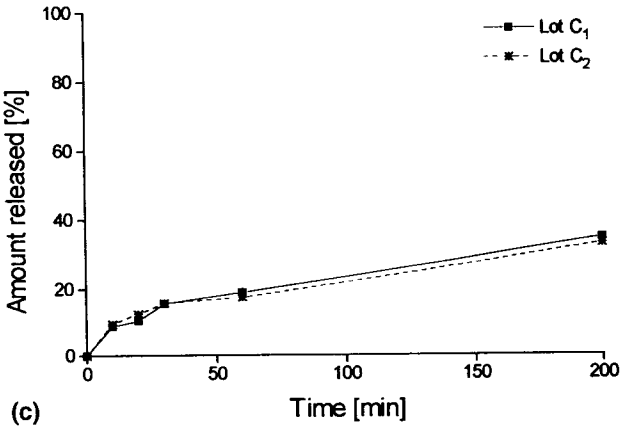
Comparison of the Parameters Amount Release (%) and AUC for Evaluating the In Vitro Release of Urea from Semisolid Formulations

Formulation	Amount Released[a,b] (%)	AUC[b] (% · min)
A_1	89.04 ± 5.44	16978.06 ± 409.07
B_1	81.25 ± 2.82	15138.85 ± 269.26
C_1	34.73 ± 3.02	4547.83 ± 296.21
D_1	10.31 ± 0.33	1790.50 ± 65.61

[a]Using a three-layer membrane system. After 200 min.
[b]Mean ± standard deviation (n = 6).







(*continued*)

Figure 3. In vitro release profile of two lots of urea creams: (a) Ureotop cream; (b) Nubral cream; (c) Carbamid cream; (d), page 256, Laceran cream.

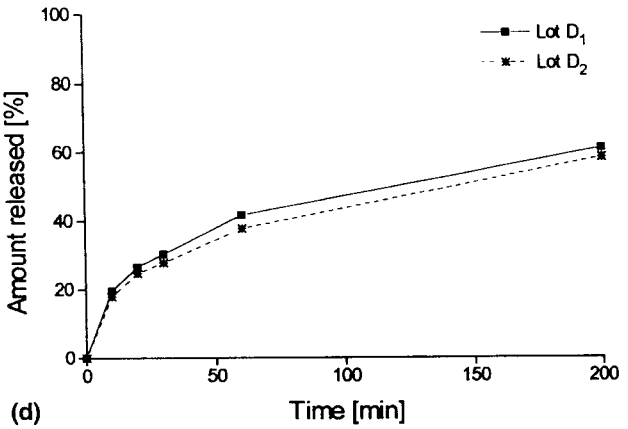


Figure 3. Continued

It was found that the highest quantity of urea was released from product A_1, about 91% in 30 min. The AUCs from the different creams, under these test conditions, were significantly different ($p < 0.05$) and can be ranked as follows: product A_1 > product B_1 > product D_1 > product C_1 (Table 1 and Fig. 2).

These data illustrate the influence of vehicle composition on the liberation–time profiles of urea. The rate as well as the extent of release of urea was higher from the hydrophilic vehicles (O/W creams: products A_1 and B_1) than from the lipophilic creams (products C_1 and D_1) (Fig. 2). Similar order of release was reported by Horsch and coworkers (15) using a release system with water as the acceptor phase. However, in their method water from the acceptor phase can migrate across the dialysis membrane used to separate the semisolid formulation from the acceptor phase and can affect its release characteristics, particularly when O/W emulsions are used (16).

The low release of urea from lipophilic creams (products C_1 and D_1) may be explained as follows. Urea is located in the internal phase of the emulsion when W/O creams are used. Therefore, the release of the hydrophilic drug urea from products C_1 and D_1 is sustained. The release–time profiles from these formulations appear to follow a first-order kinetic. Such release profiles can be useful for formulations that are to be administered overnight.

In the O/W creams, the drug was in the external phase. The presence of urea in the external phase facilitated its diffusion into the acceptor phase because the drug molecules were in direct contact with the glycerol membranes used as the acceptor system.

The release profiles of additional batches were also studied. The results, shown in Fig. 3, demonstrate that the release profiles between the batches from a given manufacturer were not significantly different ($p < 0.05$) and had very reproducible release profiles.

CONCLUSIONS

The MMS developed can be used as a tool for comparison of in vitro release profiles of semisolid urea formulations and can be adopted as a quality control procedure for assuring lot-to-lot uniformity of topical products.

ACKNOWLEDGMENTS

The authors are grateful to the Deutscher Akademischer Austauschdienst (DAAD) for financial assistance.

REFERENCES

1. W. Fürst, R. Neubert, R. Wildner, G. Beyrich, and C. Bendas, Pharmazie, 42, 452 (1987).
2. R. Neubert and W. Wohlrab, Acta Pharm. Technol., 36, 197 (1990).
3. V. P. Shah, J. Elkins, J. Hanus, C. Noorizadeh, and J. P. Skelly, Pharm. Res., 8, 55 (1991).
4. M. Corbo, T. W. Schultz, G. K. Wong, and A. Van Buskirk, Pharm. Tech., 17, 112 (1993).
5. R. Neubert, C. Bendas, W. Wohlrab, B. Gienau, and W. Fürst, Int. J. Pharm., 75, 89 (1991).
6. B. Bendas, U. Schmalfuß, and R. Neubert, Int. J. Pharm., 116, 19 (1995).
7. R. Neubert, W. Wohlrab, and B. Bendas, Skin Pharmacol., 8, 119 (1995).
8. R. Mank, R. Neubert, and I. Kawelke, Pharmazie, 44, 575 (1989).
9. R. Neubert and B. Bendas, in *Proceedings of the 11th Pharmaceutical Technology Conference*, Manchester, U.K., April 6–8, 1992, p. 119.
10. R. Neubert, K. Winter, and B. Bendas, Pharmazie, 48, 54 (1993).
11. K. Hartke and E. Mutschler, *Deutsches Arzneibuch, 9. Ausgabe 1986 Kommentar*, Stuttgart, Govi Verlag GmbH Frankfurt, 1987, Vol. 2, p. 1002; Vol. 4, p. 563.

12. S. Matschiner, Ph.D. thesis, Martin-Luther University, Halle, Germany (1993), p. 91.
13. D. Brockmeier, Arzneim.-Forsch./Drug Res., 31, 1746 (1981).
14. D. Brockmeier, Acta Pharm. Technol., 32, 164 (1986).
15. W. Horsch, J. Kögel, M. Schiefer, and I. Finke, Pharmazie, 29, 720 (1974).
16. W. Horsch, D. Bertram, and B. Wolf, Pharmazie, 39, 281 (1974).