International Journal of Pharmaceutics, 86 (1992) 9–15

IJP 02795

Physical-chemical characterization of semisolid topical dosage form using a new dissolution system

I.A. van Amerongen, H.A.G. de Ronde and N.T.M. Klooster

Brocades Pharma R&D, P.O. Box 5009, 2600 GA Delft (The Netherlands)

(Received 2 October 1991)
(Modified version received 3 January 1992)
(Accepted 3 February 1992)

Key words: In vitro dissolution; Diffusion model; Semisolid topical dosage form; Budesonide; Artificial membrane

Summary

A dissolution model for drugs in semisolid topical dosage forms is presented. In this model diffusion through an artificial membrane is measured. Sampling is performed in an automated manner. Budesonide has been used as test substance. The release of this corticosteroid appears to be dependent on the formulation. It is concluded that this model can be used in formulation development and for measuring batch-to-batch consistency as a tool in quality control.

Introduction

Dissolution testing is the most appropriate method to characterize the physical properties of solid dosage forms. Apart from testing batch-to-batch equivalence, dissolution measurements can also be used to control stability during storage and certainly to optimize a pharmaceutical formulation during development.

Test set-ups for solid oral dosage forms are standardized and accepted by pharmacopoeal committees. However, to date no official method exists for testing dissolution rates from topical semisolid products, although guidelines have been published (Skelly et al., 1987). We believe it is important to test for in vitro release to ensure product equivalence, since a change in production method could, e.g., induce a change in drug particle size or crystal shape, thereby possibly influencing the therapeutic effect.

Test cells that have been developed (Franz, 1975; Barry, 1983; Gummer et al., 1987; Tiemessen et al., 1988; Martin et al., 1989) are normally used for studying percutaneous absorption. In these cells the dosage form is generally applied to one side of a membrane (mostly skin) and the diffusion of drug is measured. For in vitro characterization, it is much better to use artificial membranes (Martin et al., 1989; Shah et al., 1989a) instead of skin.

In order to characterize topical formulations physically and to be able to control batch-to-batch variance, we developed a test model on the basis of a flow-through cell for the dissolution of topi-

Correspondence to: N.T.M. Klooster, Brocades Pharma R&D, P.O. Box 5009, 2600 GA Delft, The Netherlands.

cal dosage forms. We investigated and optimized this model with respect to temperature, stirring rates, amount of drug applied, and composition of acceptor medium. We used three different topical formulations containing the corticosteroid, budesonide, as model substance.

Materials and Methods

Materials

Budesonide (molecular formula: $C_{25}H_{34}O_6$; chemical name: 16*a*,17*a*-(22*R*,*S*)-butylidenedioxy-11-*b*,21-dihydroxy-1,4-pregnadiene-3,20-dione) standard was supplied by Draco. The C22 atom is chiral as a consequence of which the molecule is synthesized as a mixture of two epimers. These epimers can be separated by methods such as HPLC.

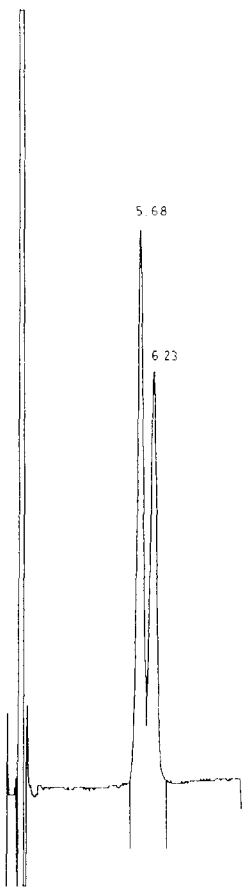

Fig. 1. HPLC chromatogram for budesonide under the experimental conditions described in the text. Total run time was 10 min.

Budesonide-containing formulations were a cream, ointment (both Preferid®, Brocades Pharma) and fatty cream (o/w) (Lipocream®, Brocades Pharma).

Cetomacrogol 1000 (Cremophor-A25) was obtained from BASF. All other chemicals were HPLC or p.a. grade.

HPLC analysis

Budesonide concentrations were determined by means of HPLC. The system used consisted of a Kontron model 420 pump, a Gilson 231 injector, an Applied Biosystems 757 UV detector, a LCD/Milton Roy CI10B integrator and recorder and a Chrompack Chromspher RP C18 10 cm column. Detection was at 242 nm; samples of 50 μl were injected. The mobile phase consisted of acetonitrile/water in a ratio of 35:65. The flow rate was 0.8 ml/min. The detection limit was 10 ppb.

An example of a chromatogram of budesonide is given in Fig. 1. It can be seen that the two epimers of budesonide are clearly separated under the experimental conditions chosen.

Results

Description and validation of the model

Diffusion cell

Figs 2 and 3 are schematic representations of the newly designed diffusion cell. The cell consists of a flow channel plate (part of a modified Amicon diffusion cell) and a perspex upper part. The membrane is placed in between and fastened with butterfly nuts and bolts. Measurements were performed in four identical cells.

Cell temperature was controlled by means of thermostated water flowing through holes in the body part of the cell. Release of drug varied linearly with temperature, thus obeying Fick's laws. Following this, the temperature of the water-bath was maintained at 35 ± 0.5°C.

Underneath the membrane, acceptor medium flowed to and from receptor vessels (KWG isotherm 0.5 l). These vessels were filled with 100 ml of medium, thermostated and stirred with a magnetic stirrer, thus ensuring homogeneity of the sample solution.

Sampling was performed manually at first but was automated at a later stage of the investigation. Subsequently, flow-through vials were placed in the autosampler and connected to the receptor vessel.

Acceptor phase

Due to the very low solubility of budesonide in water (0.023 mg/ml), modification of the composition of the aqueous acceptor phase was required in order to permit measurements under sink conditions. Therefore, experiments were performed in alcoholic media (30% (v/v) ethanol in degassed water) and aqueous media to which surfactants were added (0–1% (w/w) cetomacrogol 1000 in water; sodium dodecyl sulfate 1% in water). Results obtained for the cetomacrogol-containing solutions were in agreement with those of Shah et al. (1989b). A 0.5% cetomacrogol solution was chosen for all further measurements due to the ease of sample treatment. The solubility of budesonide in this medium was of the order of 200 mg/l.

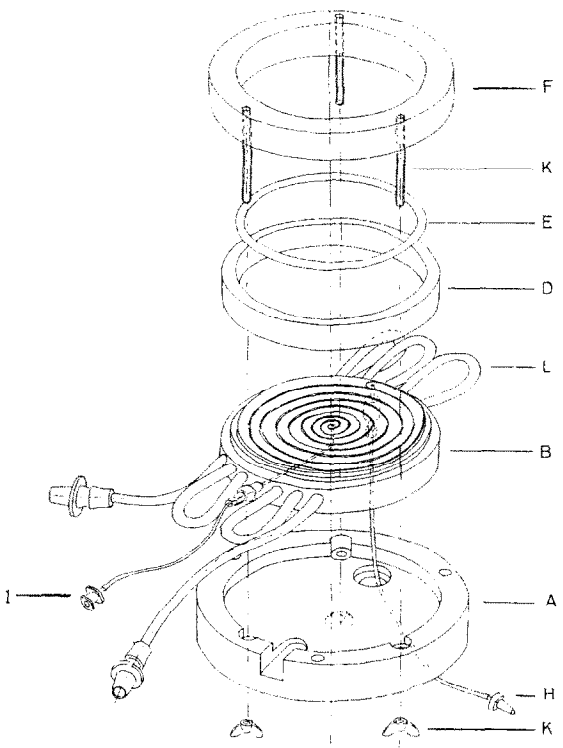

Fig. 2. Schematic representation of the cell. A, base plate; B, flow channel plate, supporting the membrane; D, support ring for the membrane; E, O-ring; F, upper part; H, inlet for acceptor medium; I, outlet for acceptor medium; J, butterfly nut for clamping on thread K; L, thermostat tubing.

Flow rate

The flow rate of the receptor medium was controlled by means of a peristaltic pump (Cenco Instruments). It appeared that release increased with flow rate up to 0.6 ml/min, but thereafter was independent of flow rate for higher values (see Fig. 4). In further experiments the flow rate was arbitrarily fixed at 1.8 ml/min.

Cream applicator

The influence of the amount of cream on the release characteristics was investigated with the help of a 'cream applicator'. The side S of this applicator (see Fig. 3) glide over the upper side of part F of the cell. By adjusting spacers underneath sides S, the distance between the bottom of the applicator and the membrane could be varied. In this way we were able to apply different amounts of cream in a very accurate manner.

The influence of the thickness of the layer of cream on drug release is of minor importance as shown in Fig. 5. Further measurements were performed at a fixed thickness of 1.8 mm.

Membranes

Seven different, more or less hydrophilic membranes (Amicon or Sartorius) were utilized: regenerated cellulose (three different cut-off values), cellulose nitrate, cellulose triacetate, polysulfonic and acrylic. The characteristics of these membranes are listed in Table 1. All membranes appeared to be chemically inert towards the formulations. The results of measurements with these membranes are depicted in Fig. 6. As expected, more budesonide passed the ultrafiltra-

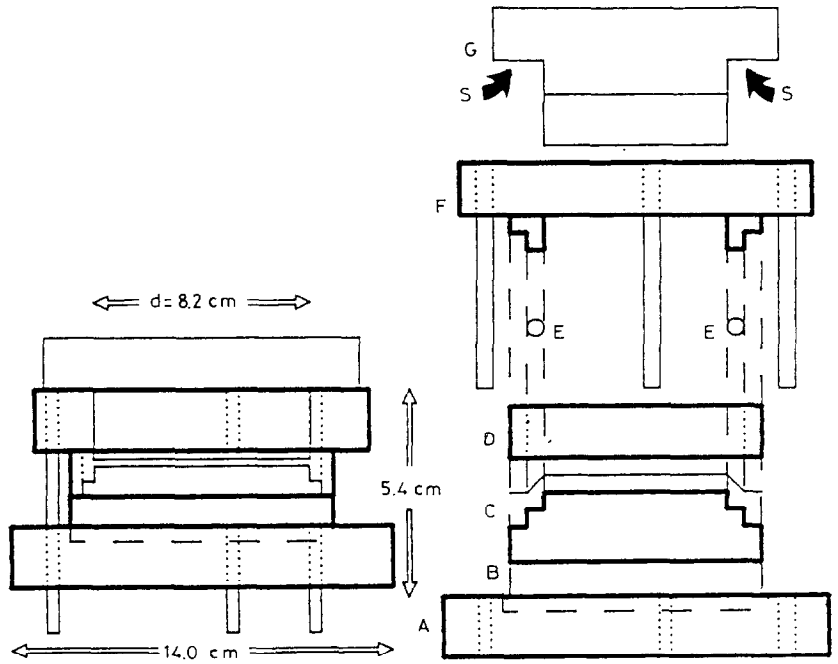

Fig. 3. Diagrammatic crossview of the diffusion cell in the normal and expanded states. Symbols as in Fig. 2; C, membrane; G, cream applicator. Sides S of the applicator are indicated by arrows.

tion membranes with high cut-off values. Since no true lag time was observed, none of the membranes appeared to be rate limiting. For all further measurements type SM 14539 (Sartorius) was chosen.

Correlation coefficients for least-squares fits of the release data in Fig. 6 vs square root of time indicated a linear relationship. This means that the membranes are highly permeable to budesonide and true sink conditions exist. Consequently, in agreement with Crank (1975), T. Higuchi (1960) and W.I. Higuchi (1962), the plots of amount of drug diffused per unit area can be presented vs square root of time (see Fig. 7).

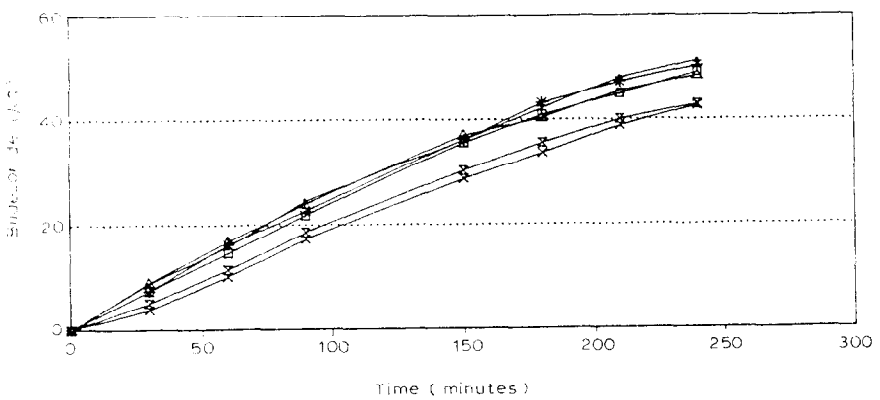

Fig. 4. Influence of flow rate on budesonide release from budesonide cream. Membrane used: YM 100. Flow rates in ml/min: (×) 0.3, (⧖) 0.4, (□) 0.6, (∗) 0.9, (●) 1.8, (△) 3.2.

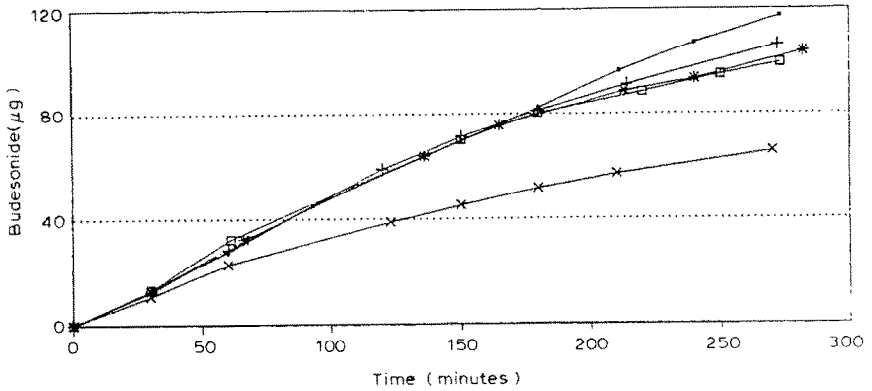

Fig. 5. Influence of thickness of cream layer in donor phase on budesonide release from budesonide fatty cream. Membrane used: SM 14539. Thicknesses in mm ± S.D.: (×) 0.3 ± 0.1, (□) 0.9 ± 0.1, (*) 1.3 ± 0.1, (+) 1.8 ± 0.2, (●) 2.5 ± 0.2

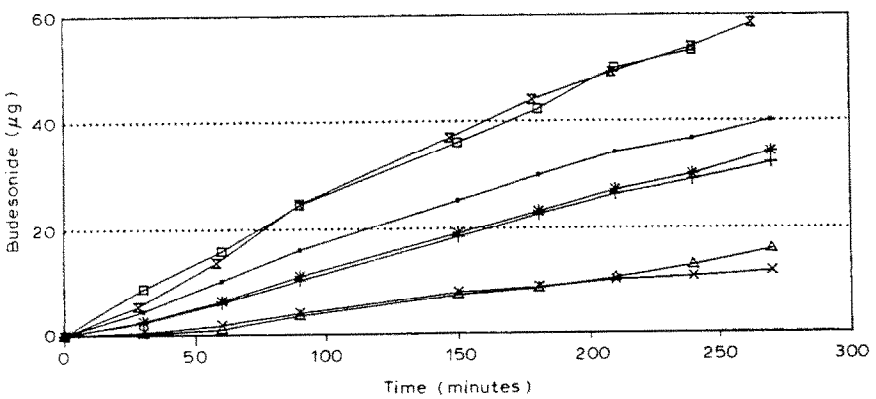

Fig. 6. Release of budesonide from cream for different membranes: Membranes used: (●) YM 30, (+) YM 5, (*) SM 14539, (□) YM 100, (×) SM 11318, (△) XM 50, (⧖) SM 14669.

Budesonide formulations

A series of experiments were carried out in order to investigate the reproducibility and de-

TABLE 1

Data characteristic of the membranes

Code (MW)	Material	Cut-off value
YM 5	regenerated cellulose	5000
YM 30	regenerated cellulose	30000
YM 100	regenerated cellulose	100000
XM 50	acrylic	50000
SM 11318	cellulose nitrate	n.a.
SM 14539	cellulose triacetate	10000
SM 14669	polysulfonic	100000

n.a., not available.

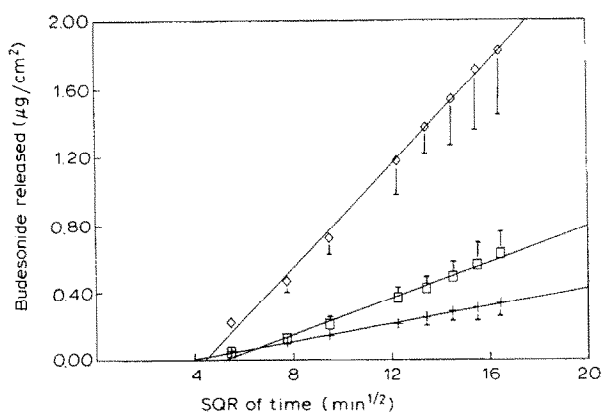

Fig. 7. Budesonide release from different formulations. Curves are means of measurements in triplicate on five different batches. Formulations: (□) cream, (+) ointment, (◇) fatty cream. Error bars represent 3×S.D.

pendence of the release process on the type of formulation. Therefore, five different batches of ointment, cream and fatty cream were measured in different cells on different days in triplicate.

The results are presented in Fig. 7 (each drawn line is the mean of 15 individual release curves). It is clear that large differences in release exist between the different formulations.

Discussion

We believe the dissolution system described in the present work for semisolid topical dosage forms has the following advantages over a Franz cell equipped with synthetic membranes (see, e.g., Shah et al., 1989a):

(1) Great ease of applying the sample in a completely reproducible way; (2) no degassing problems (in a Franz cell all air bubbles tend to collect underneath the membrane); (3) ease of automation of sampling; (4) possibility for measurements during long time intervals due to the large acceptor volume by which sink conditions are guaranteed; and (5) excellent reproducibility.

With reference to this last item, for each formulation the standard deviation within batches was always smaller than that between batches. This indicates that small differences might exist between the batches, meaning that the model can be used for quality control purposes to test batch-to-batch reproducibility. Indeed, it was found in preliminary experiments that batches with the same qualitative and quantitative composition but produced at other conditions such as different temperatures may show different release characteristics. However, this feature needs further investigation.

In line with this argument, it is conceivable that the model will be useful for investigating the dissolution behaviour of topical formulations in stability trials; in this way the ruggedness of the formulation could be ensured physico-chemically. Such studies are planned for budesonide fatty cream (o/w).

Finally, it should be possible to use the model for discriminating competitor products from the innovative product (e.g., differences in solubilization of the drug) and for characterizing new formulations. That large differences can be anticipated clearly follows from Fig. 7 in which various formulations give rise to completely different release profiles.

When our model is compared with that of Martin et al. (1989), a striking difference appears concerning the dependence on the flow rate of the acceptor medium. While we find budesonide release to be independent of flow rate (reflecting true sink conditions), a strong dependence was reported in their investigation. It might be suggested that their result was due to artefacts following the use of octanol as acceptor phase.

We believe the different release characteristics of budesonide from the several topical formulations can be interpreted in the following way: the slow release from the ointment is more or less according to expectation as the donor medium is completely apolar, the membrane hydrophilic and the acceptor phase aqueous. Budesonide is probably released much more rapidly from fatty cream than from cream, since it is not completely dissolved in the latter medium and is considered to be solubilized by micelle formation in the former medium.

References

Barry, B.W., (i) Skin transport. (ii) Methods for studying percutaneous absorption. *Dermatological Formulations, Percutaneous Absorption*, Dekker, New York, 1983, (i) pp. 95–120; (ii) 255–280.

Crank, J.C., *The Mathematics of Diffusion*, Clarendon, Oxford, 1975, pp. 32–38.

Franz, T.J., Percutaneous absorption on the relevance of in vitro data. *J. Invest. Dermatol.*, 64 (1975) 190–195.

Gummer, C.L., Hinz, R.S. and Maibach, H.I., The skin penetration cell: a design update. *Int. J. Pharm.*, 40 (1987) 101–104.

Higuchi, T., Physical chemical analysis of percutaneous absorption process from creams and ointments. *J. Soc. Cosm. Chem.*, 11 (1960) 85–97.

Higuchi, W.I., Analysis of data on the medicament release from ointments. *J. Pharm. Sci.*, 51 (1962) 802–804.

Martin, B., Watts, O., Shroot, B. and Jamoulle, J.C., A new diffusion cell – an automated method for measuring the pharmaceutical availability of topical dosage forms. *Int. J. Pharm.*, 49 (1989) 63–68.

Shah, V.P., Elkins, J., Lam, S.Y. and Skelly, J.P., Determina-

tion of in-vitro drug release from hydrocortisone creams. *Int. J. Pharm.*, 53 (1989a) 53–59.

Shah, V.P., Konecny, J.J., Everett, R.L., McCullough, B., Carol Noorizadeh, A. and Skelly, J.P., In vitro dissolution profile of water-insoluble drug dosage forms in the presence of surfactants. *Pharm. Res.*, 6 (1989b) 612–618.

Skelly, J.P., Shah, V.P., Maibach, H.I., Guy, R.H., Wester, R.C., Flynn, G. and Yacobi, A., FDA and AAPS report of the workshop on principles and practices of in-vitro percutaneous penetration studies: relevance to bioavailability and bioequivalence. *Pharm. Res.*, 4 (1987) 265–267.

Tiemessen, H., Bodde, H.E., Van Koppen, M., Bauer, W.C. and Junginger, H.E., A two-chambered diffusion cell with improved flow-through characteristics for studying the drug permeability of biological membranes. *Acta Pharm. Technol.*, 34 (1988) 99–101.