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Rapid Communication

On the determination of drug release rates from topical dosage forms

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In a recent paper, Shah et al. (1989) described a method to determine the in vitro release of hydrocortisone (HC) from topical formulations using a simple diffusion cell (Franz, 1975) in conjunction with a synthetic membrane. A sample set of data from this work is plotted in Fig. 1, which shows the cumulative release of HC from Synacort cream (Syntex, Palo Alto, CA), across a cellulose acetate membrane, into an aqueous receptor phase buffered to pH 5. The drug release process was then characterized by the slope of linear regression (units: $\mu g/cm^2$ per h) through the last three data points (Shah et al., 1989). While this approach may yield information that can distinguish between formulations, it lacks scientific foundation and ignores a straightforward, and physically precise, analytical manipulation (Higuchi, 1960, 1962), which permits all the data to be productively used. Provided that the synthetic membrane employed is highly permeable to the drug concerned (an obvious prerequisite given the objectives of the original communication (Shah et al., 1989)), and that the amount of drug released during the experiment is less than approx. 30% of the total drug content in the formulation, then the cumulative amount of drug release should vary in direct proportion with the square root of time (t) (Crank, 1975). This dependence exists for formulations both in which the drug is fully dissolved (Higuchi, 1962) and in which the drug is present as a suspension (Higuchi, 1960). Although the physical state of HC in the two creams examined is not disclosed (Shah et al., 1989), it is clear from the results (exemplified by Fig. 1) that considerably less than the total amount of HC available is released during the 6 h duration of the experiment (1 g of a 1.5% cream was administered to 1.77 cm^2 of skin; the maximum cumulative amount liberated was 247 mg/cm^2). In Fig. 2, (all) the release data in Fig. 1 are re-plotted against $\sqrt{t}$. The relationship is linear with $r^2 = 0.991$. Performing the identical procedure to this and the other 19 data sets reported by Shah et al. (1989) gives the results presented in Table 1.

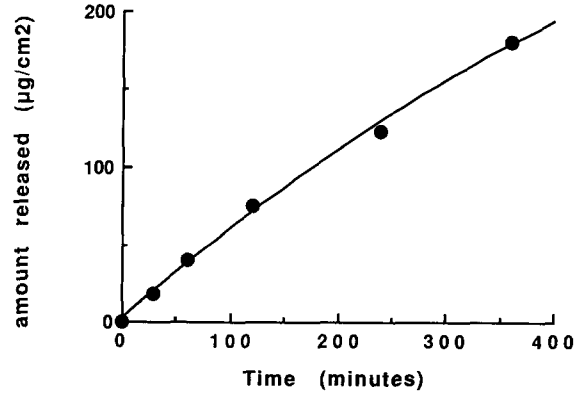

Fig. 1. The cumulative release (as a function of time) of hydrocortisone from Synacort cream, across a cellulose acetate membrane, into an aqueous receptor phase buffered at pH 5 (data taken from Shah et al., 1989).

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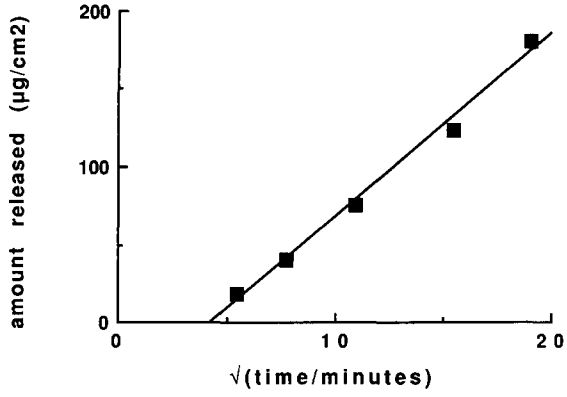

Fig. 2. The cumulative release data, presented in Fig. 1, replotted as a function of the square root of time. The line of linear regression ($r^2 = 0.991$) is drawn through the points.

Consistently, linearity is observed and, for membranes I–IV at least, drug appearance rate in the receptor phase is controlled by the formulation (as shown by the constant values of the measured slopes). Theoretically, the x-axis intercepts should be zero (Crank, 1975). However, the interposition of a membrane (albeit a relatively permeable one) between the formulation and the receptor fluid causes a finite time delay before HC molecules begin to appear 'downstream' of the barrier. If the membranes were rate-limiting in the experiments described, then one would observe a true lag time in the plots of cumulative HC amount in the receptor phase vs time (Crank, 1975). The results in the paper of Shah et al. (1989) (Figs. 2–5) show this to be not the case. As reported in the original paper, and clearly apparent from the raw data, HC release from Hytone cream is faster than that from Synacort. With knowledge of the physical state of HC in the formulations (solution or suspension), it is possible to calculate the apparent drug diffusion coefficient within the cream using standard procedures (Higuchi, 1960, 1962). For the purpose of a batch-to-batch test, or a

TABLE 1

HC release data of Shah et al. (1989): characteristics of the plots of cumulative drug release vs the square root of time

Formulation [a]	Membrane [b]	Receptor phase [c]	Gradient [d] ($\mu g/cm^2$ per $min^{0.5}$)	Intercept [e] on abscissa ($min^{0.5}$)	r^2
S	I	A	11.8	4.4	0.991
S	I	B	10.8	4.0	0.999
S	II	B	11.0	2.9	0.999
S	II	A	11.3	2.8	1.000
S	III	B	10.7	2.3	0.995
S	III	A	10.0	2.3	0.999
S	IV	B	11.3	2.6	0.999
S	IV	A	9.9	2.5	1.000
S	V	B	8.0	2.2	1.000
S	V	A	7.6	1.7	1.000
H	I	B	14.8	4.7	0.997
H	I	A	15.6	4.6	0.998
H	II	B	14.1	3.5	0.996
H	II	A	15.8	3.5	0.999
H	III	B	14.0	3.0	0.999
H	III	A	14.7	3.3	0.998
H	IV	B	15.1	3.2	0.998
H	IV	A	14.3	3.2	0.999
H	V	B	12.2	3.2	0.998
H	V	A	11.9	2.9	0.999

[a] S, Synacort cream; H, Hytone cream.
[b] I, cellulose acetate; II, polysulfone; III, Triton-free cellulose; IV, cellulose with wetting agent; V, glass fiber.
[c] A, pH 5.0 buffer; B, 0.09% NaCl.
[d] Gradient (determined by linear regression) of a plot of cumulative HC released vs the square root of time.
[e] Intercept on the x-axis (abscissa) of the above graph.

comparison between innovator and generic products, the slopes reported in Table 1 would be meaningful and accurate, and would make efficient use of all the experimentally collected data.

Finally, we believe that the paper of Shah et al. (1989) raises the following issues which should be carefully considered by pharmaceutical scientists involved in developing topical formulations:

(1) The stated use of such a system as described in Shah et al. (1989), namely "as a quality control procedure for assuring batch-to-batch uniformity", is not unreasonable. Indeed, if a further goal was to define an in vitro test to compare innovator and competitor products, then the procedure may be equally applicable. However, to do so, it is essential to establish, beyond doubt, that drug appearance in the receptor phase is controlled by the properties of the formulation, not by the properties of the membrane or the receptor phase. Otherwise, the method serves only as a quality control procedure for the membrane, not for the product!

(2) Comparison of data from a test such as this to subsequently measured in vivo bioavailability (e.g., using the vasoconstrictor assay (Barry, 1983)) is inappropriate. In vivo, the rate-limiting process for topical drug effect (at least, for those drugs whose site of action is in the viable epidermis or the dermis) is generally diffusion across the stratum corneum (Barry, 1983). The purpose of the Shah et al. (1989) experiment is not to define a membrane model for the stratum corneum. In that case, a transport-resistant barrier is necessary that will discriminate (in a physicochemical sense) the permeability differences between different drugs (Houk and Guy, 1988). Thus, any correlation between relative release rates in the Shah model and measurements of in vivo bioavailability will be fortuitous.

(3) It must be recognized that a single membrane-receptor phase combination is unlikely to be suitable for all drugs and for all formulations. The ranges of aqueous solubilities and relative lipophilicities covered by existing drug species are enormous. As an example, for a compound of very low aqueous solubility and extremely high octanol-water partition coefficient, the experimental configuration of Shah et al. (1989) will be unable to distinguish formulation differences. Drug diffusion in the vehicle may now become much faster than (e.g.) dissolution into the aqueous receptor phase. Alternatively, a particular structural feature may lead to very strong adsorption or binding of the drug to the chosen membrane: desorption could then assume control of the rate of drug appearance in the receptor phase, again obscuring the behavior of the formulation.

In conclusion, the type of system proposed by Shah et al. (1989) has an important place in the armory of a topical drug formulator. However, the interpretation of data from the approach must be carefully performed, and the over-interpretation and extrapolation of results (particularly to the in vivo situation) avoided. Finally, there should be flexibility in the configuration of the technique to allow drugs of 'extreme' physical chemical characteristics to be accommodated and usefully studied.

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