Drug Release from Semisolids: Effect of Membrane Permeability on Sensitivity to Product Parameters

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Received September 13, 1994; accepted November 29, 1994
KEY WORDS: drug release; release from semisolids; effect of membrane resistance.

INTRODUCTION

Measurement of drug release from semisolids in vitro has been proposed as a universal regulatory tool to monitor batch-to-batch uniformity in manufacturing. Citing parallels with dissolution testing. Shah and coworkers explored the feasibility of measuring hydrocortisone release from two marketed creams (1). These investigators utilized vertical diffusion cells and aqueous receptors; the sample size was approximately 1 g, so that diffusion occurred under infinite dose conditions. Comparable results were obtained using several commercially available membranes to separate the cream from the receptor. Further work with other hydrocortisone formulations using an automated procedure was later reported (2). The amount released plotted against the square root of time was linear in accordance with theoretical diffusion models. Release data for other corticosteroid creams have also been reported (3). Development and validation of release testing methodology for terconazole creams were recently described (4). Among the variables investigated were drug particle size, drug concentration and manufacturing technique. The suggestion made in all of these studies is that the slope of a plot of amount released against the square root of time can serve as an index of important product parameters. Batch-to-batch constancy of the release slope would then imply that these parameters have remained constant.

The first theoretical description of release from dispersions in ointment bases was published by T. Higuchi in 1961 (5). A key assumption in the derivation is that the drug diffuses into a perfect sink. The matrix-boundary layer model was later developed to account for the resistance of a diffusion layer at the surface of a matrix (6). Tojo described a graphical method for determining the intrinsic release, which is independent of the contribution of a diffusion layer, from real data which may include such a contribution (7). The matrix-boundary layer model was applied by Bottari et al. to the analysis of benzocaine release from a gel through an inert membrane into a receptor fluid (8).

Drug release measurements in connection with research on topical delivery systems have appeared in the literature for many years. In much of the early work, the semisolid was placed in direct contact with a receptor liquid (9,10). A variation of this technique utilized an apparatus in which a screen loaded with semisolid was lowered into the receptor fluid (11). With these methods, it is important to guard against dissolution or dispersion of the semisolid into the receptor. There may be physical disturbance of the semisolid surface by the agitation needed to maintain homogeneity within the receptor. Utilization of a membrane between the semisolid and the receptor is designed to prevent these artifacts but may introduce other problems. Since the release test is designed to measure properties of the drug and formulation, it is essential that drug diffusion within the semisolid be rate limiting (12). Clearly, if diffusion either through the membrane or within the receptor is rate limiting, the measured release slope will not reflect conditions within the semisolid. Since the receptor is chosen to give high drug solubility and is stirred, excessive diffusional resistance within the membrane appears to be the major concern.

Membranes used in release testing tend to be porous rather than continuous. The pores of the membrane are filled with receptor medium, so that drug transfer to the membrane from the semisolid really involves partitioning into the liquid within the pores. Drug molecules then diffuse through the pores, finally reaching the bulk of the receptor. Physical factors influencing the kinetics of this process include the thickness, porosity and tortuosity of the membrane, the viscosity of the receptor fluid and the receptor/semisolid partition coefficient. Optimally, transport through the membrane is much more rapid than through the semisolid, but situations may arise in which this is not the case and the membrane resistance contributes to the overall diffusional resistance. This may occur, for example, when viscous receptors are used or when the receptor/semisolid partition coefficient is not high. A key question is to what degree the membrane's contribution might affect the ability of the release test to perform its purported function, that is, as a monitor of batch-to-batch uniformity. To address this question, simulated data were generated and the effect of deliberate changes in membrane and vehicle properties on net release were determined.

SIMULATION PROCEDURE

The equations in reference 7 were used to generate simulated release data using Excel software. Model parameters were the diffusion coefficient within the semisolid, D_v, drug solubility, C_v, drug loading, A, and the permeability coefficient of the membrane, P. These parameters were assigned realistic values and a number of simulated data sets obtained.

RESULTS

Figure 1 shows the effect of changing the membrane permeability coefficient on net release for a hypothetical semisolid product containing suspended drug in which the total drug concentration is 1%. The curve for intrinsic release corresponds to the situation in which the membrane offers no resistance. With a membrane whose permeability coefficient is 3×10^{-4} cm/s, the release curve parallels that

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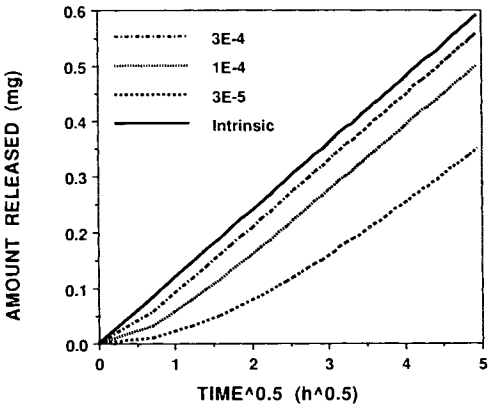

Figure 1. Plots of simulated release data. $D_v = 1 \times 10^{-6}$ cm²/s; A = 10 mg/ml; C_v = 0.2 mg/ml. Permeability coefficient values are shown in the figure.

for intrinsic release but exhibits a small intercept with the abscissa. The same is true for a membrane with a permeability coefficient of 1×10^{-4} cm/s, although the intercept is considerably longer. With a permeability coefficient of 3×10^{-5} cm/s, the release data follows a curved line which gradually increases in slope. The time required for the slope of this curve to approach that of intrinsic release is considerable, beyond the scale of the figure. The curvature in some of the lines at early times is obvious in Figure 1, although it would not necessarily be apparent when working with real, discrete data (see the next paragraph).

Since a 6-hour time period is convenient for conducting release comparisons, the times for data collection were selected to match those of a published 6-hour protocol (1) and the data replotted in Fig. 2. Plotted in this manner, all of the curves appear to be linear and have reasonably high correlation coefficients when fit to the equation for a straight line. However, with a membrane permeability coefficient of 1×10^{-4} cm/s, the slope differs from that of the intrinsic case by about 13% (Table 1). For data obtained assuming a permeability coefficient value of 3×10^{-5} cm/s, the slope deviates further from the intrinsic value (Fig. 2, Table 1). The intercept with the abscissa is larger the smaller the value of the membrane permeability coefficient (Table 1).

Additional simulations were run in which certain parameters were altered by a predetermined percentage. In some, the membrane permeability coefficient was reduced by 50%. This represents a change in experimental conditions that is unrelated to the characteristics of the formulation or product under evaluation. In another series, the diffusion coefficient was increased by 50%. This represents a change in the product characteristics that the release test should pick up. Finally, both of these changes were made simultaneously. The data were generated for the same 6-hour protocol as in Figure 2. Amount released was plotted against the square root of time and the slopes were obtained. The slopes are tabulated in Tables 2 and 3. Table 2 summarizes the results for the situation where the release data represent intrinsic release. A change in permeability coefficient has no effect on release slope in this case. A change in diffusion coefficient of 50% causes a corresponding change in release slope of 22.5%. When both parameters are changed, the release slope is again altered by 22.5%.

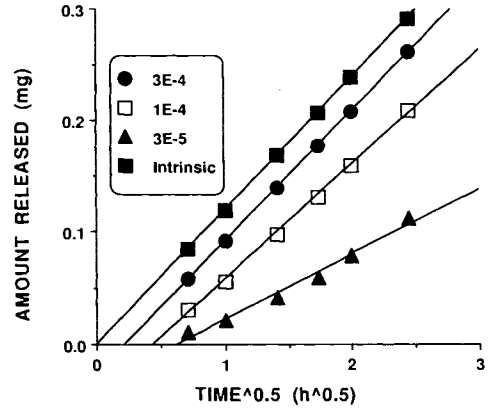

Figure 2. Plots of simulated release data based on a published protocol (see text). Parameters as for Figure 1.

Table I. Results of Least Squares Fit for Data in Fig. 2.

Permeability coefficient (cm/s)	Slope (mg/h$^{0.5}$)	Intercept with abscissa (h$^{0.5}$)	r
—	0.119	0	1.000
3×10^{-4}	0.117	0.23	1.000
1×10^{-4}	0.103	0.44	0.999
3×10^{-5}	0.060	0.64	0.992

With a P value of 3×10^{-4} cm/s, the release slope is almost identical to that for intrinsic release. Lowering P by 50% results in a 5.1% reduction of the slope (Table 3). Raising D_v by 50% results in a 21.4% increase in the slope, nearly the same as for intrinsic release (22.5%). Thus with this relatively high membrane permeability coefficient, changes in individual parameters cause the release values to change as anticipated for vehicle-controlled release. However, when both parameters are shifted, the effect on release slope (+12%) is considerably less than that for intrinsic release under the same circumstances (+22.5%).

When the permeability coefficient is 1×10^{-4} cm/s, a reduction in P of 50% results in a 22.6% decrease in release slope (Table 3). An increase in D_v occasions an increase in slope, but the increase is only about 2/3 that for intrinsic release. When both parameter changes are made, the alteration in P has the greatest significance. The result is a significant decrease in release slope despite the fact that the product has changed in such a way that the slope should

Table II. Effect of Changing Model Parameters on Intrinsic Release Slope (Reference $D_v = 10^{-6}$ cm²/s; A = 10 mg/ml; C_v = 0.2 mg/ml)

	Reference	Lower P 50%	Raise D_v 50%	Change Both
Slope (mg/h$^{0.5}$)	0.119	0.119	0.146	0.146
r	1.000	1.000	1.000	1.000
% change in slope	—	0.0	+22.5	+22.5

Table III. Effect of Changing Model Parameters on Release Slope (Reference $D_V = 10^{-6}$ cm²/s; A = 10 mg/ml; C_V = 0.2 mg/ml)

Permeability coefficient (cm/s)	Parameter(s) assigned	Slope (mg/h$^{0.5}$)	r	% Change in slope
3×10^{-4}	Reference	0.117	1.000	
	Lower P 50%	0.111	1.000	−5.1
	Raise D_V 50%	0.142	1.000	+21.4
	Lower P 50% and raise D_V 50%	0.131	0.999	+12.0
1×10^{-4}	Reference	0.103	0.999	—
	Lower P 50%	0.0797	0.996	−22.6
	Raise D_V 50%	0.119	0.998	+15.5
	Lower P 50% and raise D_V 50%	0.0870	0.994	−15.5
3×10^{-5}	Reference	0.058	0.992	—
	Lower P 50%	0.0325	0.988	−44.0
	Raise D_V 50%	0.0607	0.991	+4.6
	Lower P 50% and raise D_v 50%	0.0330	0.988	−43.1

increase. The release data reflect the artifactual change in experimental conditions more strongly than the physical environment within the semisolid.

This effect is amplified with further reduction in the permeability coefficient to 3×10^{-5} cm/s. The influence of a change in diffusion coefficient is all but lost (Table 3); when both P and D_v are altered, only P has any significant effect on the slope.

Figure 3 shows the relationship between the deviation from intrinsic release and the sensitivity of release slope to alterations in P and D_v, individually and in combination. For these simulations, the value of D_v was either 1×10^{-6} or 1×10^{-7} cm²/s and the membrane permeability coefficient was assigned various values. The trends are independent of the particular values of the parameters. Other changes, in A or C_v, produced data that fell on the same lines. The response to changes in diffusion coefficient within the semisolid becomes more muted as the deviation from intrinsic release conditions is more pronounced. Simultaneous changes in the permeability coefficient tend to overpower any effect of D_v on the release slope, particularly at higher

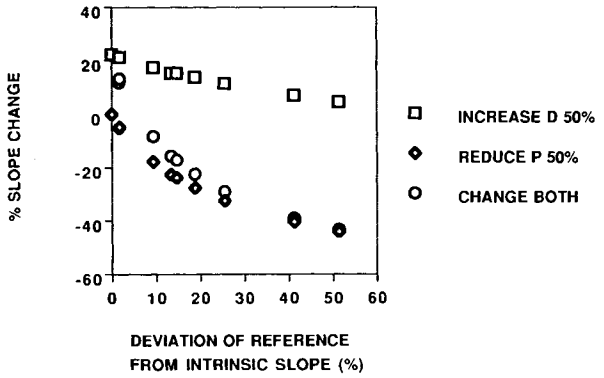

Figure 3. The influence of parameter changes on alteration in release slope. See text for details.

deviations from intrinsic conditions. Note however, that even when the difference between the reference slope and the intrinsic slope is only 10%, the effect of increasing D_v is not discernible when both P and D_v are changed to the same extent.

DISCUSSION

The data and comparisons presented raise the question of sensitivity of in vitro release methodology to detect alterations in product characteristics. When the intrinsic release rate is measured, the technique is capable of discerning differences in physical characteristics within the semisolid that reflect changes in the details of manufacture. However, the technique loses sensitivity when the membrane permeability is such that it affects the release profile. Even relatively small deviations from intrinsic release make the results unduly sensitive to differences in membrane characteristics and blunt the response to physical changes within the product. It is therefore important to designing release experiments to choose the membrane and receptor fluid (which fills the pores of the membrane) to minimize resistance to drug transport. It is not sufficient merely to control experimental conditions to yield reproducible values in a series of repetitive experiments.

To offer the lowest diffusional resistance, the membrane should have high porosity, minimal thickness and exhibit no drug binding. To maximize partitioning from the semisolid and transport through the pores of the membrane, the receptor should be a nonviscous liquid of high solvency for the drug.

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