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MEMBRANES IN DISSOLUTION TESTING:

A GOOD CHOICE?

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INTRODUCTION

An in vitro dissolution test for determining the rate at which a drug is released from a dosage form can be a helpful tool in the early stages of dosage form design. Furthermore, the in vitro release can give valuable information about the effects of storage time and storage temperature.

Many different types of apparatus have been designed for the determination of the in vitro availability of a drug from a suppository. A recent survey has been published (1). Five general types can be distinguished (2); in two of these a membrane separates the compartment containing the drug delivery form from the sampling compartment. In the case of fatty suppositories, the main purpose of the membrane is to prevent fatty compounds from entering the samples or the on-line flow-through cell.

Very few authors seem to realize that the introduction of a additional process such as membrane transport can mask the actual release of the drug from the delivery form (2, 3). Since in the development of a drug formulation it are only the actual release characteristics of the delivery form that are of importance and not the apparent release rate (after diffusion), a comparison of apparent rates might give misleading results.

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If a delivery form (A) is placed in a membrane-envelopped compartment (B) and the drug concentration is measured in the adjacent sampling compartment (C), then the release model might be depicted schematically as in fig. 1. If the release of the drug from the delivery form (A→B) is fast compared to the net membrane transport (B⇄C), the latter will become the rate determining step in the overall process and the release rate measured in the sampling compartment will become diffusion controlled. Then the release rate measured in compartment C is not identical to the actual release rate. It is only if the membrane transport is much faster than the release rate that the membrane does not act as a limiting step.
However, since most types of dissolution apparatus for suppositories are provided with membranes having a relatively small surface area and most membranes usually have rather slow diffusion properties, the membrane diffusion might often be a substantial rate determining step.

Moreover, if the same delivery form is tested in two different types of dissolution apparatus, one or both of which are provided with a membrane, one cannot draw any definite conclusions about the release characteristics observed. For instance, a difference in the area of the membrane surface, i.e. the diffusion area, and in the membrane thickness, can create a marked difference in the apparent release rate. On the other hand, comparing formulations tested in different apparatus, which might happen in interlab tests, could mask differences in the actual release rate.

In our opinion it is essential that the actual release be estimated, to give a good comparison between the release characteristics of the dosage forms, even if the latter are tested in different types of apparatus. The aim of this paper is to demonstrate, both theorethically and experimentally, the discrepancy between actual and apparent release rates and to find out whether it is possible to eliminate the disadvantages caused by the use of membranes in release testing. Since the most recently developed

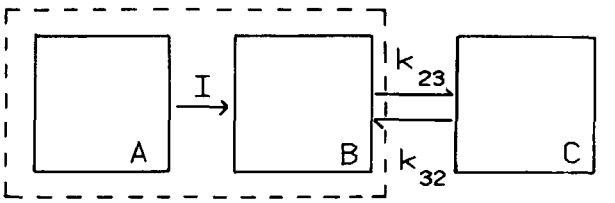

Figure 1: Schematical description of a release apparatus with a membrane envelopped release compartment. For explanation see text.

types of apparatus for the determining of the in vitro availability are provided with a semi-permeable membrane, only this type of membrane will be considered in this paper.

THEORETICAL APPROACH

The release of a drug from a suppository, or any other drug delivery form, enclosed in a small membrane-envelopped compartment, is shown schematically in fig. 1, in which A denotes the delivery form and B is the solvent phase within the membrane compartment with volume V_b. The drug is exchanged between compartment B and the, generally large, sampling compartment C with volume V_c. The rate of exchange is determined by the microconstants k_{23} and k_{32}. The kinetics of the release and the diffusion are represented by the following set of equations:

$$\frac{dM_a}{dt} = -I \qquad \text{(eq. 1)}$$

$$\frac{dM_b}{d_t} = I - K_m (C_b - C_c) \qquad \text{(eq. 2)}$$

$$\frac{dM_c}{dt} = K_m (C_b - C_c) \qquad \text{(eq. 3)}$$

in which M stands for mass and C for the concentration, the subscript refering to a particular compartment, I stands for the

drug release - with undefined kinetics - from the suppository and K_m (unit: volume x time^{-1}) characterizes the membrane transport. In non-equivalent compartments (when $V_b \neq V_c$) eq. 3 can be rewritten as:

$$\frac{dM_c}{dt} = K_m \left(\frac{M_b}{V_b} - \frac{M_c}{V_c} \right) \qquad \text{(eq. 4)}$$

Substituting k_{23} for K_m/V_b and k_{32} for K_m/V_c yields after rearrangement:

$$M_b = \frac{1}{k_{23}} \cdot \frac{dM_c}{dt} + \frac{k_{32}}{k_{23}} M_c \qquad \text{or} \qquad \text{(eq. 5)}$$

$$M_b = \frac{1}{k_{23}} \cdot \frac{dM_c}{dt} + \frac{V_b}{V_c} M_c \qquad \text{(eq. 5a)}$$

Now the total amount of drug released at any time can be estimated using eq. 6:

$$M_t = M_b + M_c = \frac{1}{k_{23}} \cdot \frac{dM_c}{dt} + \left(1 + \frac{V_b}{V_c}\right) M_c \qquad \text{(eq. 6)}$$

If the volume ratio V_b/V_c is very small (i.e. if $V_b \ll V_c$) eq. 6 may be rewritten as:

$$M_t = \frac{1}{k_{23}} \cdot \frac{dM_c}{dt} + M_c \qquad \text{(eq. 6a)}$$

This equation is analogous to the one proposed for the calculation of the in vivo absorption of drugs based on the urinary excretion data of the unchanged drug (4).

In order to solve eq. 5 and eq. 6 the membrane transport rate constant k_{23} must be known. Two approaches are possible. According to eq. 3 K_m can be obtained as the slope of the linear plot of the increase in mass in compartment C per unit time versus the difference in concentration of drug between compartments B and C resp., when a known amount of drug in a fixed volume is put into

compartment B. Since $k_{23} = K_m/V_b$, the membrane transport rate constant k_{23} can now be calculated. But more elegantly, the rate constant k_{23} can be calculated directly in each experiment by means of the time vs. concentration curve (fig. 2). When the release of the drug from the delivery form is finished, it holds that $M_b = M_t - M_c$. Substituting in eq. 3 and rearrangement gives:

$$\frac{dM_c}{d_t} = k_{23} M_t - (k_{23} + k_{32}) M_c \qquad \text{(eq. 7)}$$

Separating the variables and integrating yields:

$$\ln \left(\frac{k_{23}}{k_{23} + k_{32}} M_t - M_c\right) = - (k_{23} + k_{32}) t +$$

$$\ln \left(\frac{k_{23}}{k_{23} + k_{32}} M_t - M_{c_o}\right) \qquad \text{(eq. 8)}$$

In this equation M_{c_o} represents the mass in compartment C at the time that the integration starts, i.e. when $M_t = M_b + M_c$. Since $k_{23}/(k_{23}+k_{32})$ equals $V_c/(V_c+V_b)$, the left-hand side of eq.8 represents the natural logarithm of the transferable mass. When this parameter is plotted versus time one obtains a linear plot with a slope $- (k_{23} + k_{32})$. Since $k_{23}/k_{32} = V_c/V_b$, substituting $k_{23}.V_b/V_c$ for k_{32} shows that the slope equals $- k_{23} (1 + V_b/V_c)$. Again, if the volume ratio is very low, the slope will equal $- k_{23}$ (fig. 2a). The correctness of this approach will be proven both theoretically and experimentally.

When the rate of release of a drug from a delivery form follows first order kinetics with a rate constant k_{12}, and sink conditions in the sampling compartment are obeyed, integration of eq.1 and eq.2, in which now C_c becomes negligible small, and substitution in the mass balance $M_c = M_\infty - M_b - M_a$ gives

$$M_c = \frac{M_\infty}{k_{23} - k_{12}} \left[k_{23} (1 - e^{-k_{12}t}) - k_{12} (1 - e^{-k_{23}t}) \right] \qquad \text{(eq. 9)}$$

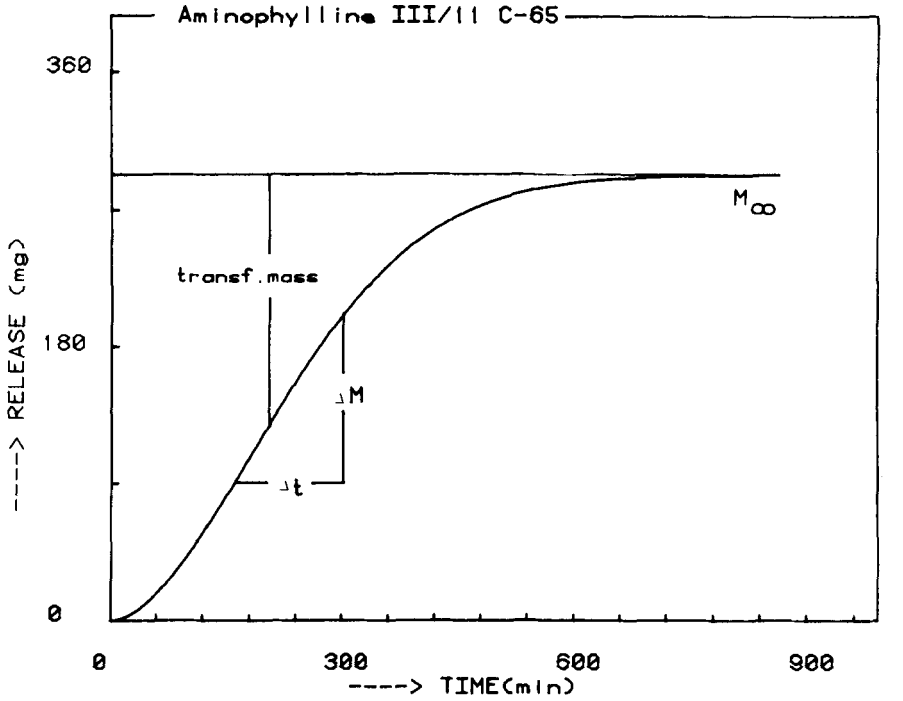

Figure 2: Appearance of the drug in measuring compartment C, using a membrane.

This function describes the mass of the drug in the sampling compartment C as a function of time under sink conditions in C -later we can see that $C_b >> C_c$ in the first part of an experiment.

With the aid of a computer and a non-linear regression program it moight be possible to find the first order release rate constant k_{12} from the concentration data in compartment C, if the amount released and the membrane transport rate constant k_{23} are known.

However, most first order rate-controlled delivery forms will (especially in the first part of the release) deviate from the correct first order kinetics, and the mathematical approach, as distinct from the described numerical approach, will give less correct parameters.

Simulation of the actual and apparent drug release with the aid of a plotting computer shows that there will be no important

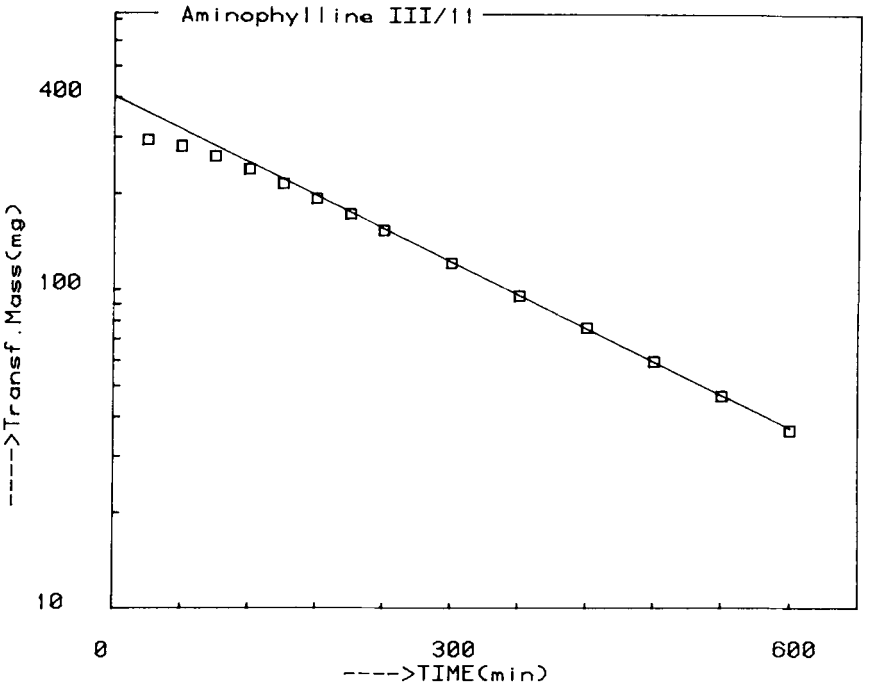

Figure 2a: Ln (transferable mass) vs time curve from the same experiment. For explanation see text.

difference between the actual and apparent release curves if $k_{12} << k_{23}$, e.g. where k_{23} is 13 or 26 times larger than k_{12} resp. (fig. 3). This may be the case when the release rate from the delivery form is very low compared to the diffusion, as a result of a rather slow release or fast membrane transport (due to membrane properties like membrane thickness and/or surface area). In this particular case the last part of the time vs. concentration curve cannot be used for the calculation of the membrane transport rate constant. For the correction of the apparent release curve, one has to calculate the rate constant according to the method described earlier and use a drug solution to calculate K_m. Or, when the difference between apparent and actual release curves is very small, as depicted in fig. 3, one can safely ignore the correction.

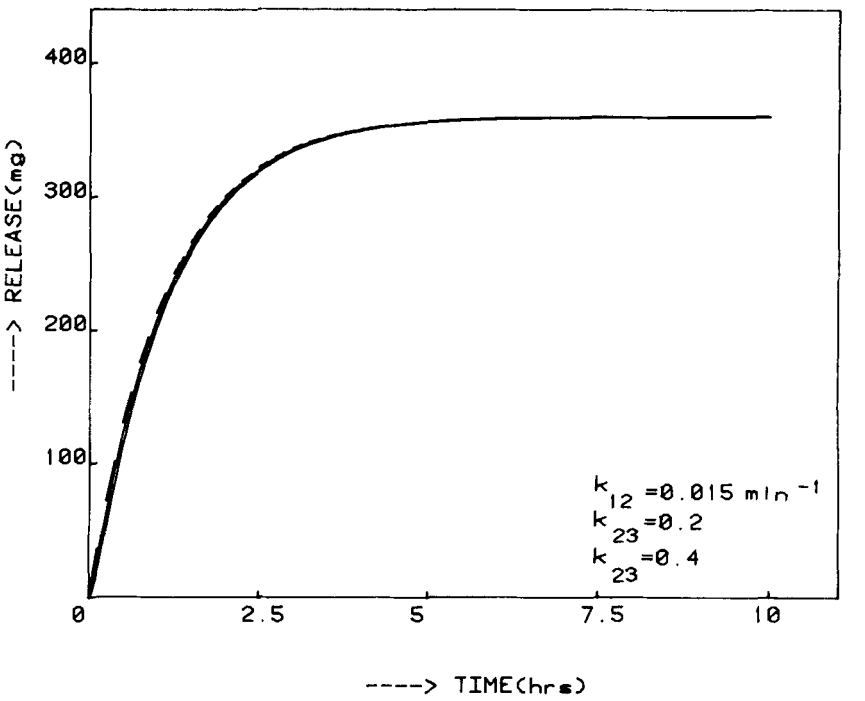

Figure 3: Simulated actual and apparent release curves (see text).

EXPERIMENTAL

I. Suppository preparation. Two batches of suppositories were prepared by the fusion method. Each suppository contained approx. 360 mg of aminophylline in a fatty suppository base (Witepsol H15 or Estarinum B). After preparation the content uniformity was determined and found to be within acceptable limits for all batches (c.v. <1%).

II. Release apparatus. The release apparatus used was essentially the same as described earlier (5) and is depicted schematically in fig. 4. A semi-permeable membrane is attached to one end of the glass tube (int. diam. 36 mm) with the help of a rubber O-ring. Inside the release chamber the solute was mixed by means of a small stirrer to ensure a uniform concentration of drug throughout the central compartment, and reproducible diffusion circumstances without disturbing the suppository. The concentration of the drug

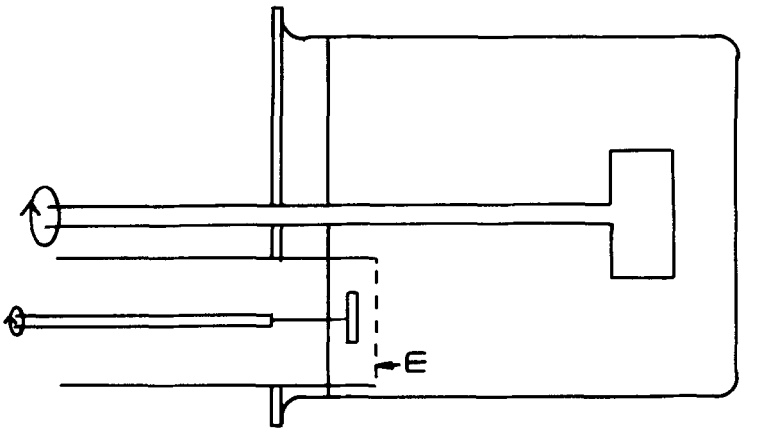

Figure 4: Diagram of the release apparatus used.

in the sampling compartment was measured continuously spectrophotometrically. The temperature in the release compartment was kept constant at 37.0 ± 0.2°C. The release medium was demineralized water and the volume of compartment B was 10.0 or 25.0 ml (accurately known in each experiment) and 2000 ml in compartment C.

III. Membranes. Four different membranes were used: Visking regenerated cellulose dialysis tubing, types 20 and C-65, and Diachema cellulose hydrate dialysis membrane, molecular weight cut-off 5000 and 10000 resp. After the membranes have been attached to the glass tube, they were soaked overnight in demineralized water and rinsed well before use. The release apparatus described was provided with one of these four types of membranes. Suppositories from each batch were tested. Other suppositories from the same batches were tested in the same set up without a membrane.

When the concentration in compartment C reached a constant level, i.e. when the net influx equalled zero, the experiment was terminated. No correction was made for the relatively small amount of drug remaining in solution in compartment B when a membrane was used, since $M_b/M_c = V_b/V_c = 10/2000$. The diffusion rate constant k_{23} was calculated after each experiment by plotting the ln

(transferable mass) vs. time and calculating the slope of the straight line (fig. 2a). Since $k_{32} = k_{23} \times V_b/V_c$ and is therefore very small compared to k_{23} (depending on the volume of water, i.e. 10 or 25 ml in compartment B, k_{23} was 200 and 80 times larger than k_{32} resp.), the slope was taken as $- k_{23}$.

RESULTS AND DISCUSSION

Simulation of the actual and apparent drug release with the aid of a computer, using eq. 9 and microconstants $k_{12} = 0.015\ min^{-1}$ and $k_{23} = 0.002\ min^{-1}$ resp., gave an apparent release curve as shown in fig. 5. Using eq. 6a, the amount in B and thus the total amount released could be calculated, on the basis of the concentration data in compartment C: the total amount calculated is also depicted in fig. 5 by the continuous line. The calculated

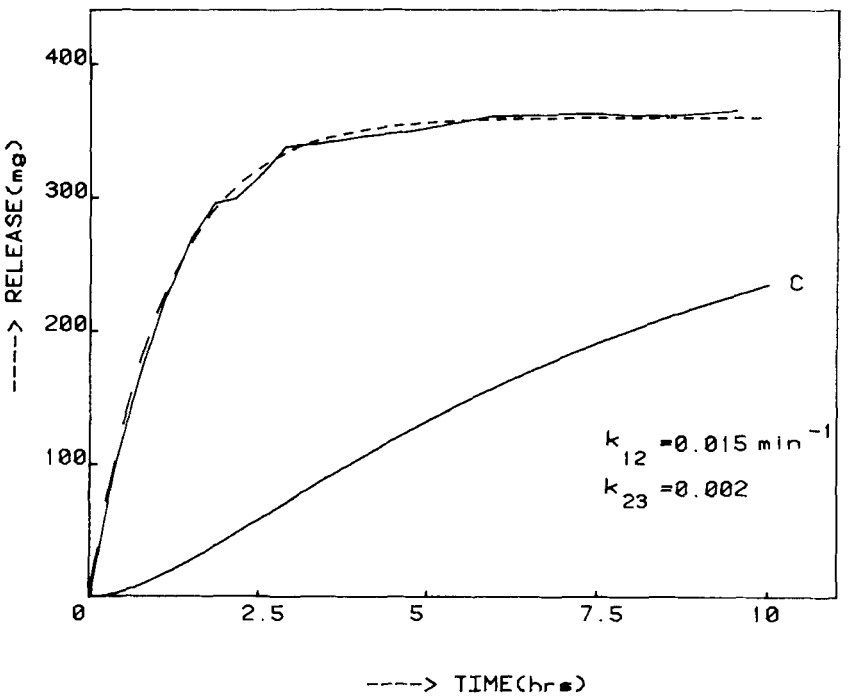

Figure 5: Actual (---) and apparent (C) release curves after simulation. The continuous upper line indicates the calculated release.

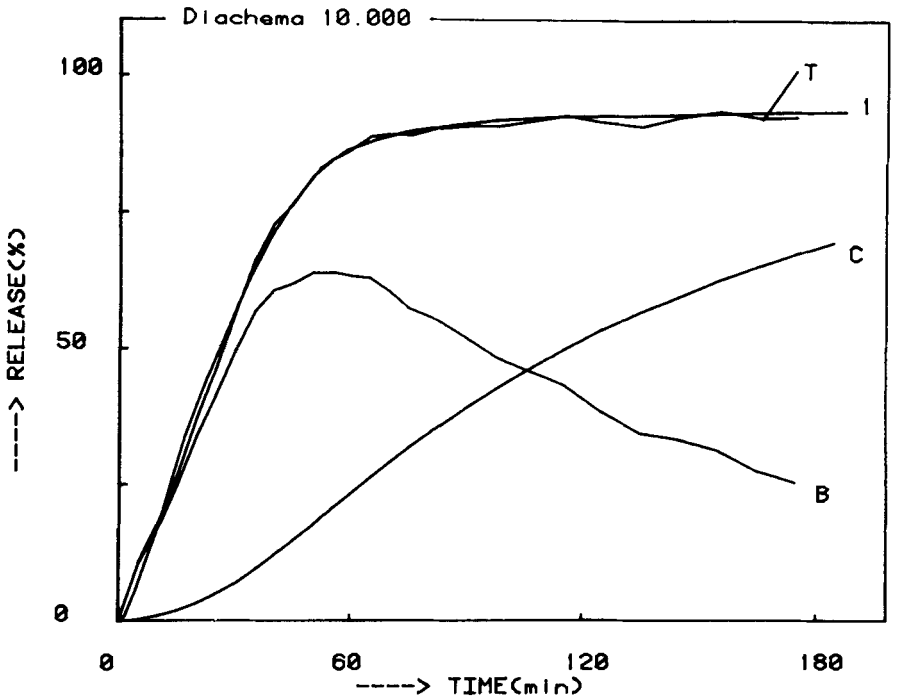

Figure 6: Actual (I) and apparent (C) release curves using a "rapid diffusion" membrane (k_{23}= 9.$10^{-3}$$min^{-1}$). T= calculated release, B= drug in compartment B.

release curve is not essentially different from the simulated curve that is based on first order kinetics, and this indicates that this approach is justified.

In curve C an inflexion can be seen at t = 2.5 hours approx. The time at which this inflexion occurs can be calculated using the second derivative of eq. 9, which gives:

$$t = \ln \left(\frac{k_{23}}{k_{12}}\right) \frac{1}{k_{23} - k_{12}} \qquad \text{(eq. 10)}$$

This inflexion indicates that at the corresponding time the input per unit time in B is equal to the net output; this suggests that the release from the dosage form is almost finished, or has become negligibly small compared to the diffusion.

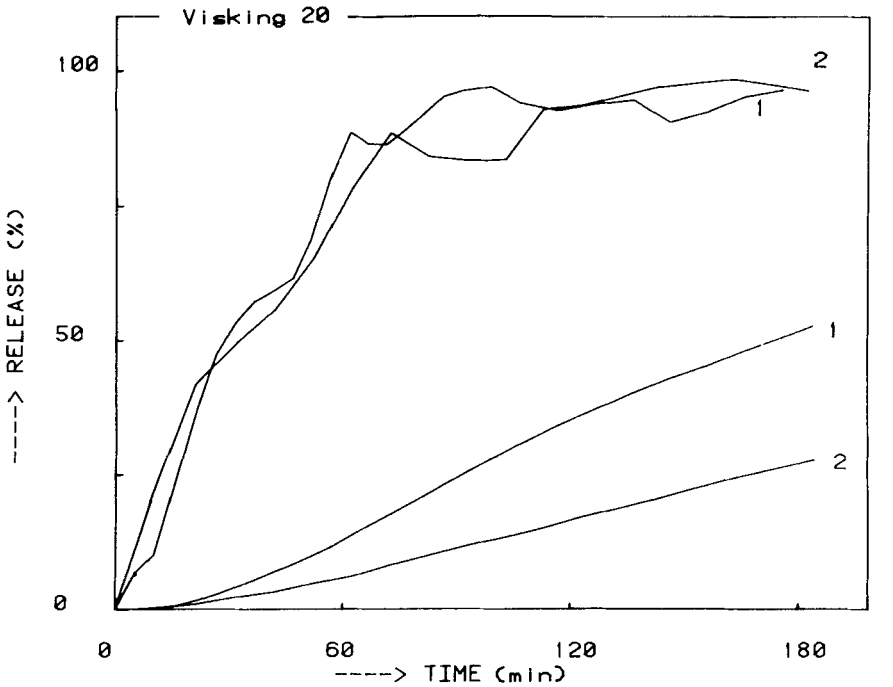

Figure 7: Calculated and apparent release using different volumes of water in compartment B (see text). Curve 1:volume B=10 ml; curve 2:25 ml.

The same numerical method was applied to suppositories tested in the described release apparatus. When a suppository was tested without a membrane, a release of 70% was found to occur within 45 min. (fig. 6, curve 1). When a "rapid diffusion" Diachema 10000 membrane with a transport rate constant $k_{23} = 9.10^{-3}$ min^{-1} was used, the drug was much slower in appearing in the measuring compartment,as expected. Only after 3 hours 70% was found in C (fig. 6, curve C). By calculating the increase in mass in C and using eq. 6a, we could calculate the actual release from the suppository (fig. 6, curve T). It is shown in fig. 6 that this calculated curve, T, is essentially the same as the curve measured without a membrane. The calculated curve shows a slight oscillation, due to the fact that in the calculation of ΔM_c small errors are enlarged because of the division by k_{23} (eq. 6 and 6a). In the

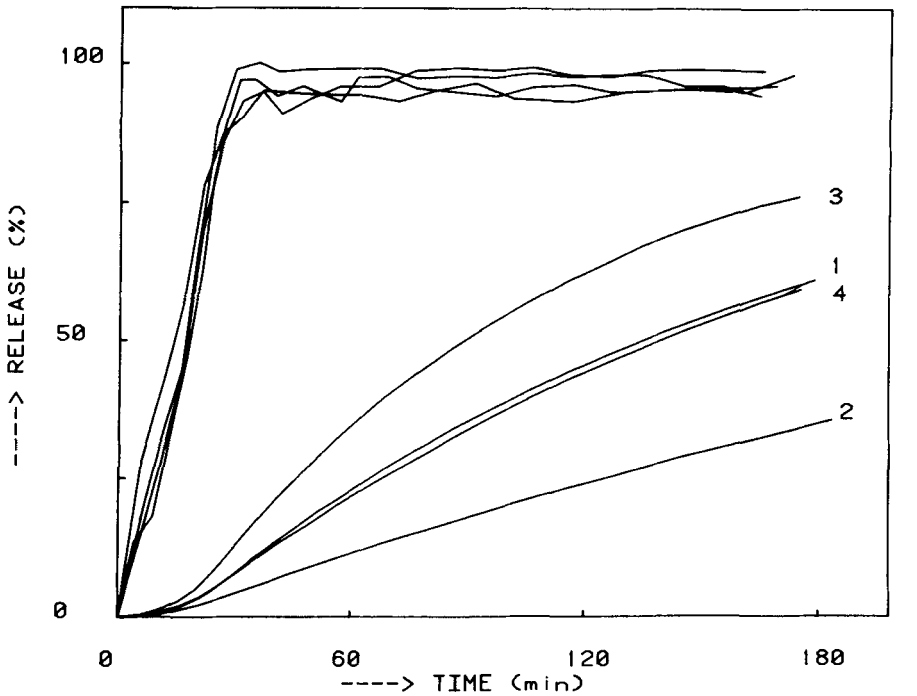

Figure 8: Apparent and calculated release using different membranes.

Key 1 = Visking 20 ; $k_{23} = 6.3 \cdot 10^{-3} min^{-1}$

2 = Visking C-65 ; $k_{23} = 3.5 \cdot 10^{-3}$

3 = Diachema 10000 ; $k_{23} = 9 \cdot 10^{-3}$

4 = Diachema 5000 ; $k_{23} = 5.7 \cdot 10^{-3}$

same figure the mass in B is plotted as a percentage of the total content of the suppository (fig. 6, curve B). It can be seen from this figure that during the first hour of the experiment a substantial amount of drug is present in the central compartment. This curve also shows that the concentration in the central compartment reaches a maximum at the same time as an inflexion appears in curve C. At this moment approx. 90% of the total in vitro availability was reached.

Increasing the amount of water inside the release compartment B from 10 to 25 ml caused a marked decrease in the rate at which the drug appeared in compartment C (fig. 7, curve 1).

In the same figure the mass of the active compound is depicted when the same membrane is used but the amount of water in B was 10 ml (curve 2).
This result shows clearly the pronounced influence of the volume of the central compartment. Since k_{23} equals K_m/V_b, the membrane transport rate constant will decrease in proportion to the volume increase in B (for a 10 ml volume: $k_{23} = 5.29 \times 10^{-3}$ min^{-1}; 25 ml: $k_{23} = 2.36 \times 10^{-3}$ min^{-1}). Calculation of the actual release however, on the basis of these rate constants, shows that in reality the increase in volume of the release compartment has no effect on the release rate of the drug.

When membranes with different membrane tranport rate constants were used, the rate of appearance in the sampling compartment C varied accordingly (fig. 8). In the same figure we give the release curves calculated with the help of eq. 6a. Despite the fact that the drug in the sample compartment was much slower in appearing when e.g. a Visking C-65 membrane was used (curve 2), the calculated release rate was equivalent to the other calculated release rates (within the experimental limits).

CONCLUSIONS

This paper indicates that it might be possible to calculate the actual release rate of a drug from a first order rate-controlled dosage form by means of non-linear regression analysis of the apparent release data, if this release rate is measured in well designed release apparatus provided with a membrane.

However, since most delivery forms do not follow first order kinetics from the very beginning of the release, the described numerical calculation of the release will give more satisfactory results. Although we have shown that it is possible to calculate the actual drug release rate experimentally, it should be pointed out that this technique may only be applied if certain strict conditions are observed: the membrane transport rate constant, necessary for the calculation of the mass in the central compartment, must really be a constant throughout the experiment.

This will only be the case when the area of the membrane surface remains constant, the solute in the release compartment is well stirred and the volume in this compartment remains constant. When there is no mixing in the central compartment, the concentration of the drug in this compartment will not be equal in all its parts. For example due to convection during the release of the drug a certain degree of mixing will occur but when the release deminishes, the flux of the drug towards the membrane will ultimately only occur as a result of diffusion.

If there is too little water in the central compartment the concentrations of the drug inside the membrane envelopped compartment might become too high and thus cause an osmotic influx of water. This influx of water will cause an increase in volume and accordingly a decrease in the rate"constant"k_{23}, which is no longer a constant. In most types of release apparatus the last two conditions relating to mixing and constant central volume are not observed, and thus in most cases it will not be possible to calculate the actual release rate.

Moreover, since the ratio between the membrane transport rate constant and the release rate from the dosage form will have a considerable influence on the difference between apparent and actual release (and thus on the total amount of the drug in the release compartment), it should be clear that a relatively low membrane transport rate might cause a high concentration of the drug in the central compartment, thus causing non-sink conditions. Then the membrane used might have an additional influence on the release rate of the drug. This influence may be considerable in the case of drugs with slow diffusion or membranes with low permeabilities, e.g. due to a small surface area.

In our opinion it is not only useful but it is essential to calculate the actual release rate of any drug from a dosage form if using a dissolution apparatus provided with a membrane. This will only be possible if the release apparatus has been properly designed.

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