International Journal of Pharmaceutics, 5 (1980) 101–107

SINK CONDITIONS IN THE FLOW-THROUGH CELL DURING DISSOLUTION

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(Received November 1st, 1979)
(Accepted January 21st, 1980)

SUMMARY

An equation is derived which relates the effective surface area of a powder sample dissolving in a flow-through or column type in vitro cell to the average saturation degree of the flowing solvent due to the dissolution process. Three parameters are needed to define the experimental conditions: the volumetric solvent flow rate, the diffusion layer thickness, and the effective surface area of the sample. The equation indicates that sink conditions in a flow-through cell are independent of the solubility of the dissolving species. As a consequence of the equation there are some theoretical limitations for the range of applicability of the column in vitro dissolution method. Dissolution rates of fine and coarse paracetamol powders in doses of 50 mg and 500 mg demonstrate the validity of the equation.

INTRODUCTION

The flow-through dissolution cell or the column type in vitro dissolution method has found wide acceptance in pharmaceutical research (Baun and Walker, 1969; Langenbucher, 1969; Tingstad and Riegelman, 1970; Kwee and Ulex, 1974; Cakiryildiz et al., 1975; Langenbucher and Rettig, 1977). This method has been compared with the beaker and the USP dissolution method in distinguishing in vitro performance of and formulation differences between solid dosage forms (Bolhuis et al., 1973; and Bathe et al., 1975). Conventionally, sink conditions are thought to exist in the flow-through dissolution cell. It can, however, be shown that depending on the effective surface area of the dissolving sample and on the volumetric and linear flow rate of the solvent, different degrees of saturation up to practically solvent saturation with solute can prevail in the cell during the dissolution process.

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Theory

The equation of Nernst (1904) and Brunner (1904) describes the rate of a diffusion-controlled dissolution process:

$$dm/dt = (D \cdot S/h) \cdot (C_s - C_t) \tag{1}$$

The driving-force concentration difference between the saturation concentration and the average solute concentration in the flowing solvent surrounding the dissolving particles for column-type flow is defined by Eqn. 2. This equation is applicable to the open solvent system with inlet solute concentration zero (Dryden et al., 1953). Eqn. 2 can be approximated by Eqn. 3 which is valid up to a saturation degree of about 0.7 in the dissolution cell effluent (Langenbucher, 1969):

$$\Delta C = \frac{C_e}{\ln(1/(1 - C_e/C_s))} \tag{2}$$

$$\Delta C = C_s - C_e/2 \tag{3}$$

The concentration of the effluent leaving the dissolution cell is determined by the actual dissolution rate, divided by the volumetric flow rate of the dissolution medium (solvent). This concentration can also be defined in terms of the saturation degree of the effluent solution:

$$C_e = (dm/dt)/Q = a \cdot C_s \tag{4}$$

Sink conditions are said to prevail when the concentration of the dissolution medium does not exceed 10–20% of the saturation concentration or solubility of the solute.

Combining Eqns. 1, 2 and 4 yields an equation which defines the maximum 'allowed' effective surface area of the dissolving sample, so that the defined degree of saturation, a, in the effluent will not be exceeded:

$$S_{max} = \frac{Q \cdot h \cdot \ln\left(\frac{1}{1 - a}\right)}{D} = -\frac{Q \cdot h \cdot \ln(1 - a)}{D} \tag{5}$$

Combining Eqns. 1, 3 and 4 results in an approximative equation for S_{max}:

$$S_{max} = \frac{a \cdot Q \cdot h}{D(1 - a/2)} \tag{6}$$

If the effective surface area, S, of the dissolving sample is known, Eqn. 5 can be rewritten in a form to estimate the saturation degree of the effluent:

$$a = 1 - e^{-D \cdot S/Q \cdot h} \tag{7}$$

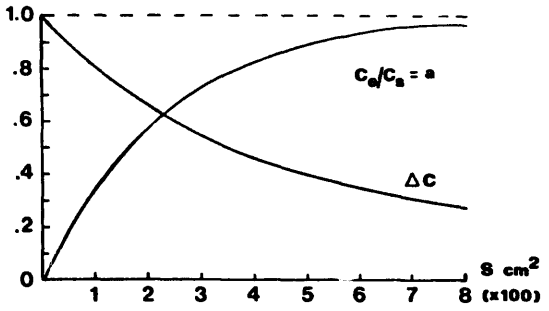

Fig. 1. Dependence of effluent saturation degree, a (C_e/C_s), and driving-force concentration difference, ΔC, (relative to C_s) on the effective surface area, S, of the sample at constant, D ($4.4 \cdot 10^{-4}$ cm^2 min^{-1}), Q (20 ml/min), and h (0.005 cm) in an open flow-through dissolution cell; according to Eqns. 7 and 2.

Fig. 1 gives an example of the dependence of saturation degree of the effleunt and of ΔC on the effective surface area, S, at constant D, Q and h.

EXPERIMENTAL

Apparatus

A flow-through type dissolution apparatus having the same specifications as the commercial apparatus [1] described and discussed by Langenbucher and Rettig (1977), connected with a UV–VIS spectrophotometer [2] equipped with flow-through cuvettes and a recorder [3] for continuous or intermittent monitoring of the effluent concentration from the dissolution cell was used.

Experimental conditions

Solvent: 0.1 N HCl at 37°C. Solvent flow rate: 20 ml/min or 5 cm/min linear in the cylindrical dissolution cell lumen. The effluent drug concentration was automatically measured and recorded every 0.2 min.

Material

Two particle size fractions of paracetamol (acetaminophen) were used, the fine powder [4] having a specific surface area of about 670 cm^2/g and the coarse sieve fraction (500–800 μm) [5] about 66 cm^2/g as determined by the photo-microscopic method [6]. For the dissolution rate studies, dosages of 50 mg and 500 mg paracetamol were used.

Sample preparation

The conical lower part of the dissolution cell was filled with glass beads of 0.5–1 mm

[1] Disotest, Sotax AG, CH-4008 Basle.
[2] Zeiss PMQ II spectrophotometer, West-Germany.
[3] W + W Model 3212, W + W electronic AG, CH-4002 Basle Münchenstein.
[4] N-acetyl-*p*-aminophenol, Siegfried, CH-Zofingen.
[5] A sieve fraction of N-acetamino-phenol purum, Fluka, CH-Buchs SG.
[6] Zeiss particle sizer (Endter Zähler), West-Germany.

TABLE 1

CUMULATIVE AMOUNT PARACETAMOL DISSOLVED (%)

Dissolution time (min)	Dose 50 mg		Dose 500 mg	
	Fine	Coarse	Fine	Coarse
0.2	34.8	5.0	13.0	3.9
0.4	55.0	9.6	23.3	10.5
0.6	66.3	14.3	33.0	16.5
0.8	74.5	19.0	43.0	21.3
1	80.5	23.3	50.5	27.3
2	93.8	43.3	76.3	49.1
3	97.9	59.7	88.9	68.7
5	100.0	83.0	96.7	88.7
8		97.3	100.0	98.5
10		100.0		100.0

diameter. The powder sample which had previously been gently mixed with 2.0 g of glass beads was introduced upon this layer, into the cylindrical cell part. The sample was further covered with a glass bead layer of 2 mm thickness.

RESULTS

The results presented in Table 1 are mean values of 3 experimental runs.

DISCUSSION

To the two essential apparatus parameters, the volumetric solvent flow rate and the dissolution cell diameter, as discussed by Langenbucher (1969), a third parameter has to be added which also has an effect on the sink conditions in a flow-through dissolution cell: the effective surface area of the dissolving sample. Eqns. 5–7 show that the saturation degree of the dissolution cell effluent is a function of the hydrodynamic conditions in the cell and of the effective surface area of the sample. It is interesting to note that the factor solubility of the dissolving sample is not included in these equations and thus solubility has no effect on the actual sink conditions prevailing in the cell, provided that overall sink conditions are maintained. Under constant experimental conditions, the saturation degree of the flowing solvent in the cell is determined by the effective surface area of the sample only. Eqns. 5–7 show another interesting feature: an increase in the volumetric flow rate increases the 'allowed' maximum effective surface area to the same extent. But, at the same time, the increased linear solvent flow rate causes a thinning of the diffusion layer and in this way partly offsets the effect of the increased volumetric flow.

According to Eqn. 3, the concentration of the effluent is twice as high as the average

concentration of the solvent flowing through the powder bed. Consequently, saturation degrees of 20–40% of the effluent, e.g., correspond to average saturation degrees of 10–20% of the solvent in the dissolution cell and in contact with the dissolving sample. When comparing sink conditions in an open flow-through dissolution cell with those in a fixed-volume in vitro method (e.g., the beaker and the USP method), it can be noted that in the latter the driving-force concentration difference, ΔC, is decreasing from the maximum value, C_s, towards an end value ($C_s - C_t$); Eqn. 1. In the flow-through method, on the other hand, ΔC has its minimum value during the initial phase of the dissolution process, at the moment of the maximum effective surface area and maximal dissolution rate of the sample (maximum of C_e); Eqns. 2–4. In most instances this methodological difference is merely a theoretical one without any practical significance.

For practical purposes Eqn. 6 is applicable to the calculation of the effective surface area of the dissolving sample. Effluent saturation will be reached just when the surface area equals 20 h/D, cm^2. If the sample has an effective surface area larger than this limiting value, solvent saturation within the cell prohibits further dissolution, and the dissolution rate will remain constant (apparent zero-order). In reality, total solvent saturation (a = 1) can be reached only if, under defined experimental conditions (Q and h are constant), the effective surface area of the sample becomes infinitely large, or if the solvent flow rate approaches zero; see Eqn. 7.

As an example of the concentration build-up during dissolution, we substitute in Eqn. 6 approximate values describing the in vitro conditions used here: solvent flow rate, Q = 20 ml/min, diffusion layer thickness, h = 0.005 cm, diffusion coefficient of paracetamol, $D = 4.4 \cdot 10^{-4}$ cm^2 min^{-1}, and 'allowed' saturation degree of the effluent, $C_e/C_s = a = 0.2$. As a result we get the limiting value

$$S_{max} = \frac{0.2 \cdot 20 \cdot 0.005}{4.4 \cdot 10^{-4}(1 - 0.2/2)} = 50.5 \text{ cm}^2 .$$

For the same experimental conditions, the calculated limiting value of the effective surface area of the sample just enough to saturate the effluent (a = 1) is 454.5 cm^2. The specific surface area of the fine paracetamol powder was 670 cm^2/g or 335 cm^2/500 mg or 33.5 cm^2/50 mg sample. From the results in Table 1 it can be concluded that the initial dissolution rate corresponding to the maximum available surface area of the 50 mg sample was relatively much higher than that of the 500 mg fine powder sample. This result can be explained as follows: the surface area of 335 cm^2 of the 500 mg sample was 'too high', and sink conditions were not maintained any more during the initial fast dissolution. The corresponding surface areas of the coarse powder samples were 33 cm^2/500 mg and 3.3 cm^2/50 mg sample; i.e. well below the reference value of 50.5 cm^2. There was practically no difference between the dissolution rates of the 50 mg and 500 mg samples of the coarse paracetamol powder.

The results in Table I show further that during the first 0.8 min, the dissolution process of the 500 mg dose of the fine paracetamol powder was apparent zero-order. During this time the constant dissolution rate was about 10% or 50 mg in 0.2 min. Using Eqn. 4, one can calculate the solute concentration or saturation degree of the effluent: C_e = (50 mg/0.2 min)/(20 ml/min) = 12.5 mg/ml which corresponds to 0.57 to 57% of

the solubility of paracetamol in the solvent (C_s = 22 mg/ml; Posti, 1978). This experimental result indicates that even smaller effective surface areas than those theoretically calculated from Eqns. 5 or 6 can in practice saturate the solvent flowing through the powder bed and in this way set a limit for the maximum dissolution rate.

Eqns. 5 and 6 give an idea of the 'allowed' effective surface area of a sample when sink conditions are to be maintained during the dissolution process and when using the flow-through dissolution cell method. This limit value may well be exceeded with unit doses of some antibiotics, anti-inflammatory agents and sulfonamides, for example, administered as fine powders in a tablet or capsule. In these cases the column in vitro method may fail to detect possible initial dissolution rate differences between different drug formulations.

Eqn. 5 presented in this publication can implicitly be found as Eqn. 4 in the ref. Dryden et al. (1953), but until now it has not been discussed in connection with the effective surface area and the in vitro dissolution test methodology. S_{max} as defined in this publication can also be derived from the modified cubed-root law equations, presented as Eqns. 6 and 7 by Langenbucher (1969). But these equations are, as the author states, valid only for sufficiently low effluent concentrations (de facto, for $\Delta C \approx C_s$), and they do not take into account the concentration build-up within the dissolution cell during dissolution.

APPENDIX

Notation used:

a = saturation degree of the effluent = C_e/C_s; $0 \leqslant a < 1$;
ΔA = driving force concentration difference $C_s - C_t$, mg/ml;
C_e = effluent concentration, mg/ml;
C_s = saturation concentration or solubility, mg/ml;
C_t = solute concentration in fixed-volume solution at time t, mg/ml;
D = diffusion coefficient of the solute, $cm^2\ min^{-1}$;
dm/dt = dissolution rate, mg/min;
h = diffusion layer thickness, cm;
Q = volumetric solvent flow rate, ml/min;
S = effective surface area of the sample, cm^2;
S_{max} = maximal effective surface area as defined by Eqns. 5 and 6, cm^2.

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