ELSEVIER

International Journal of Pharmaceutics 122 (1995) 57–67

international journal of pharmaceutics

Solubility characterization of practically insoluble drugs using the Coulter counter principle

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Received 14 October 1994; revised 16 January 1995; accepted 24 January 1995

Abstract

A new method was evaluated to determine the solubility of some sparingly soluble materials, using a Coulter counter TA II. This method was based on characterizing the remaining undissolved amount of the suspended material for different initial amounts added, after a specific agitation time. The amounts remaining were then plotted vs the initial concentration of each respective suspension. After applying linear regression and an extrapolation procedure the aqueous solubility was obtained from the intercept. The most important advantage of this method is, firstly, the possibility to determine the solubility of a compound down to 0.1 ppm (μg/ml) or less and, secondly, its applicability to preformulation studies, which require a quick and accurate estimation of solubility using a minute amount of sample. It could be of especial importance when no conventional assay procedure, such as a photometric method, exists.

Keywords: Solubility; Coulter counter

1. Introduction

For drugs with a low solubility (i.e., less than 100 μg/ml), the determination of solubility can pose many problems. Long equilibration time, heterogeneity in the energy content of the crystalline solid, the presence of impurities (Higuchi et al., 1979) and the existence of a more soluble amorphous layer around the less soluble crystalline core of the particles (Elamin et al., 1994) are some factors which may complicate the interpretation of solubility data.

To determine the solubility of drug compounds, different techniques have been suggested which normally involve analytical methods. In most cases an excess amount of the compound is agitated in a certain volume of a solvent until an equilibrium is reached and the amount dissolved determined analytically. In some cases a method has been suggested whereby a known amount of a substance is agitated while known volumes of solvent are gradually added until the entire quantity is dissolved (Grant and Higuchi, 1990). Another way of determining the solubility of sparingly soluble drugs was suggested by Saad and Higuchi (1965a,b) and was later further developed by Nyström et al. (1985a,b) using a Coulter

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SSDI 0378-5173(95)00035-6

counter technique. This method has been described and is used as a reference method in the present study.

All these methods have their own advantages and disadvantages. Photometric methods, based on the UV absorption technique, for example, are highly dependent on the molecular structure of the compound. The technique based on the use of a Coulter counter has been claimed to be limited to compounds having an aqueous solubility above approx. 5 μg/ml (Nyström and Bisrat, 1986). The accuracy of both these methods can be questioned, especially for extremely sparingly soluble drugs.

The objective of the present study was to improve the Coulter counter technique so it would become applicable for solubility determination of drugs with a solubility even less than 5 μg/ml.

2. Important parameters in using the Coulter counter technique

The following factors can affect the results obtained by a Coulter counter technique.

2.1. The covering size range of a capillary tube

If a material is highly polydisperse, it is possible that the whole particle size range cannot be covered by a single aperture tube. Hence, some information would be lost and a misleading estimation of the particle size distribution would result.

2.2. Background count

A knowledge of the real number of particles in the dissolution medium before adding the sample and starting the experiment is necessary. It is also important to make sure that this amount is as constant as possible during the subsequent experiment. Some of the factors that can affect a background count are described below.

2.2.1. Mechanical factors

The creation of electrical fields between a Coulter counter and other electrical equipment such as a computer screen, or vibrational effects caused by a magnetic stirrer or an ultrasonic bath or passage of people, in the neighbourhood of Coulter counter, are some of the mechanical factors which can affect the results.

2.2.2. Particulate contamination

Working with a Coulter counter requires a clean environment, as free from dust as possible. The operator plays an important role. All the flasks and pipettes using in the experiment must be washed carefully with particle-free water before starting the experiment and the operator should conduct all parts of the experiment to be as particle free as possible.

3. Materials and methods

3.1. Materials

3.1.1. Drug compounds

Griseofulvin (Glaxo, UK), glibenclamide (Hoechst, Germany), Felodipine micronized (Astra Hässle AB, Sweden), ubiquinone, sometimes referred to as 'vitamin Q10' and 4'-demethylpodophyllotoxin-4,6-*O*-benzylidene-β-D-glucopyranoside (DPBG) (Analytecon SA, Switzerland) were used as model substances. The Q10 was size reduced in a pin disc mill (Alpine 63 c, Alpine AG, Germany), but due to its highly cohesive nature, the material was strongly aggregated and caused some practical problems which will be discussed below.

3.1.2. Dissolution medium

To be able to use a Coulter counter the dissolution medium must be an electrolyte. Hence, it was prepared by the addition of 0.9% w/w NaCl to a specific volume of deionized particle-free water. To increase the wettability of the powders, 0.01% w/w polysorbate (Tween 80) was also added to the electrolyte. In the case of felodipine the experiments were carried out at two different concentrations of Tween 80 (i.e., 0.001 and 0.01 w/w).

In all cases except that of griseofulvin, the dissolution process was carried out at a pH of 7.4.

This was achieved by the addition of PBS Tablets (EC Diagnostic AB, Sweden) containing 0.01 M phosphate buffer to the dissolution medium.

The dissolution medium was filtered through a Millipore filter with a pore size of 0.22 μm (Millipore Products Division, USA), before starting the experiment.

3.2. Particle size analysis

Particle size analysis were carried out using a Coulter counter TA II. The choice of capillary tube was dependent on the particle size range of the materials. Hence, a 30 μm aperture tube was used for griseofulvin, felodipine and glibenclamide, 70 μm for DPBG and a 100 μm capillary tube for Q10. All the capillary tubes were calibrated using latex spheres of different specific sizes. The particle size distribution of each sample was then determined as follows:

A stock suspension of each sample was prepared and treated ultrasonically for 10–30 min to break up aggregates. A certain volume of the stock suspension was added to 200 ml particle-free electrolyte and the numbers of particles in 14 different size classes were determined. A mean volume diameter by weight was then calculated for each sample. The results are the mean value of three measurements.

3.3. Density measurement

The apparent particle density of each sample was determined using a gas comparison pycnometer (Beckman Model 930, USA). The results are mean values of three measurements.

3.4. Determination of solubility

The solubility of the materials was determined by two methods, which are described below. The 'subtraction method' refers to a method described in an earlier study (Nyström et al., 1985a,b) and the 'extrapolation method' is a method which is suggested in the present study to be a more sensitive and accurate method of solubility determination, especially for materials having a solubility less than 5 μg/ml. In both methods the Coulter counter TA II was used in order to count the number of particles remaining. Knowing the number of particles in the different size classes, the weight remaining of each sample after specific time intervals was calculated from Eq. 1 (Nyström et al., 1985a,b):

$$W_t = \rho_s \pi / 6 \Sigma \left(n_r \bar{d}_{vr}^3 \right) \quad (1)$$

where W_t is the total weight of undissolved particles at time t, ρ_s denotes the density of the material, n_r is the number of particles in class r and d_{vr} represents the arithmetic mean volume diameter by weight in class r. For this equation to be valid, the particle density has been assumed to remain constant during the experiment. The capillary tubes used for these experiments were the same as for particle size analysis.

3.4.1. Subtraction method

A dissolution medium of 'non-sink'-condition was prepared so that the amount of particles present in the medium would exceed that required for a saturated solution. Then the number of particles in the 14 size classes during the dissolution process was recorded as a function of time, until an equilibrium was reached. The amount remaining of each sample in the suspension was then calculated according to Eq. 1. The equilibrium solubility was obtained by subtracting the measured amount remaining of compound, from the initially monitored amount (Nyström et al., 1985a,b; Nyström and Bisrat, 1986; Anderberg et al., 1988). Fig. 1 shows solubility determination according to this method.

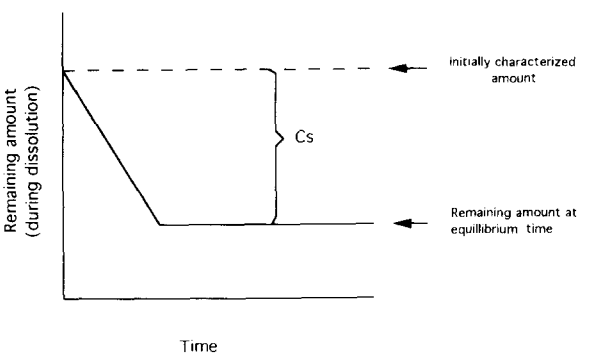

Fig. 1. Solubility determination according to the subtraction method.

A limiting factor in solubility determinations of extremely polydisperse materials by this method is the covering capacity of the capillary tube. Thus, in those cases where the capillary tube is not capable of covering the whole particle size range, an accurate solubility characterization by this method is not possible. This will be discussed below in more detail, concerning the solubility determination of materials with extremely low water solubility such as felodipine and Q10.

3.4.2. Extrapolation method

A stock suspension of each sample was prepared and treated ultrasonically for 10–30 min to break up eventual aggregates. Different concentrations of each sample were prepared by diluting certain volumes of the stock suspension. These suspensions had a volume of 250 ml and concentrations of 0.5–12 μg/ml in the case of griseofulvin, glibenclamide and DPBG and 0.02–1.0 μg/ml in the case of Q10. For felodipine the final concentrations were in the range of 2–15 and 0.4–2.0 μg/ml using 0.01 and 0.001% w/w Tween 80, respectively.

The suspensions were agitated at room temperature (22 ± 1° C) using a magnetic stirrer. The number of particles present in a certain volume of the suspension was measured after 2–24 h, using the Coulter counter TA II. The characterized remaining weight of sample in each suspension after these agitation times was then calculated according to Eq. 1, and plotted against the initially added concentrations. Solubility of materials after an equilibration time of 24 h was then calculated by determining the intercept on the *X*-axis (added amount) by applying linear regression and subsequent extrapolation. Additionally, for most test materials, and especially those with the lowest solubility, it was important to subtract the amount of background particles from the total characterized amount.

Fig. 2 demonstrates the solubility determination according to this method for an ideal case where 100% of the test material is covered by the capillary tube, resulting in a straight line with a slope of unity.

It should be mentioned that a similar method was suggested by Saad and Higuchi (1965a), where

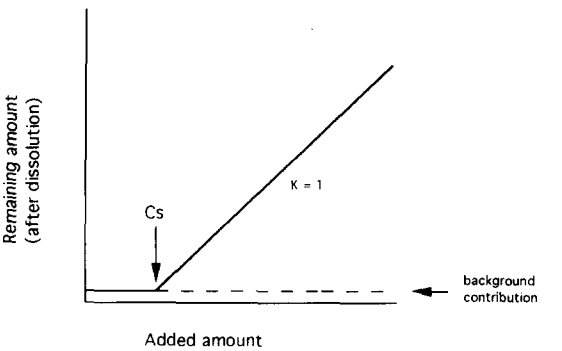

Fig. 2. Solubility determination according to the extrapolation method.

they used a Coulter counter in a more or less similar way to obtain the solubility of cholesterol. However, the details of the experimental procedure are not well described and discussed in their work. They suggested that solubility determination of cortisone was possible from its size distribution data, assuming that the solubility is not greater than the concentration of cortisone in which particle counts were just measurable. They found the solubility of cortisone in water to be about 0.025 μg/ml. However, the use of an extrapolation procedure, from higher additions down to the solubility level, to increase the sensitivity of the method was not utilized in the paper by Saad and Higuchi (1965a).

In the method suggested in the present study, the solubility is obtained by applying linear regression and extrapolating to the *X*-axis as was explained before (Fig. 2). The equilibrium solubility is then equal to the intercept of the straight line on the *X*-axis. Unlike the method suggested by Saad and Higuchi (1965a), this value is not always equal to the lowest concentration of the sample where particles are detectable for the first time. Even slight changes in the amount of background presented in the suspension during the experiment can cause an increase in the number of particles detected, especially in concentrations less than 0.1 μg/ml. Thus, the existence of these particles which may be due to background particles, should not be confused with sample particles. Since it is almost impossible to predict the source of particles which arise in the suspension

in such low concentrations, the extrapolation method seems to be more reliable than assuming that solubility is equal to the lowest concentration in which particles are just detectable.

4. Results and discussion

4.1. Particle size analysis

4.1.1. Size distribution and the mean particle size

As listed in Table 1 the mean particle size of the materials was in the size range of 1–16 μm. In all cases particle size was defined as a geometric mean volume diameter by weight, due to the log-normal size distribution of the materials, except in the case of DPBG whose size distribution was of a normal character and hence its particle size was defined, with the aid of an arithmetic mean volume diameter by weight.

4.1.2. Degree of polydispersity

Considering the standard deviations listed in Table 1, it can be concluded that the degree of polydispersity of Q10 is much greater than for griseofulvin, felodipine and glibenclamide. This can readily be seen in a log-normal size distribution, where the geometric standard deviation by weight is equal to unity, for a monodisperse material. As this value becomes larger, the degree of polydispersity of the material increases. Therefore, according to the geometric standard deviations of particle size distributions listed in Table 1, the degree of polydispersity is much greater for Q10 ($\partial = 2.53$) than glibenclamide ($\partial = 1.84$), griseofulvin ($\partial = 1.76$) and felodipine ($\partial = 1.56$). There was also a greater probability for Q10 not to be covered totally by the capillary tube during the dissolution process.

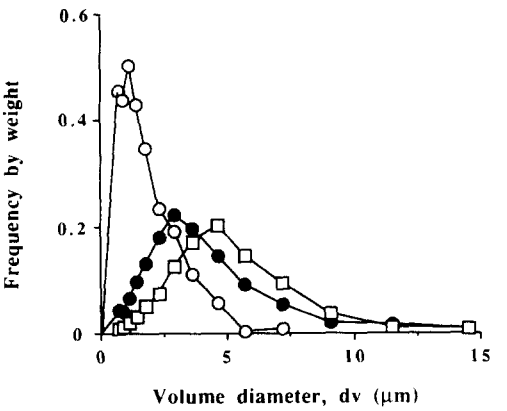

Fig. 3. Particle size distributions of griseofulvin, glibenclamide and felodipine, using a Coulter counter TA II and a capillary tube with a 30 μm orifice. (●) Griseofulvin, (○) glibenclamide, (□) felodipine.

4.1.3. Estimation of the fraction being covered by capillary tube

Considering the size distribution profiles of the drug compounds (Fig. 3), it can be concluded

Table 1
Primary characterization of drug compounds

Material	Particle size distribution [a]		Capillary tube		Density [b] (g/cm³)
	Geometric mean (μm)	Geometric standard deviation (–)	Aperture size (μm)	Covering range (μm)	
Griseofulvin	3.70	1.76	30	0.6–12.0	1.44
Glibenclamide	1.84	1.84	30	0.6–12.0	1.37
DPBG [c]	15.7 [d]	12.1 [e]	70	1.4–28.0	1.87
Q10	11.1	2.53	100	2.0–40.0	1.06
Felodipine	4.96	1.56	30	0.6–12.0	1.45 [f]

[a] Measured with the aid of a Coulter counter assuming a log-normal distribution of the material.
[b] Measured using an air comparison pycnometer (Beckman Model 930, USA).
[c] Denotes 4′-demethylpodophyllotoxin-4,6-*O*-benzylidene-β-D-glucopyranoside.
[d] Arithmetic mean volume diameter by weight, based on a normal distribution of the material.
[e] An arithmetic standard deviation (μm) based on the normal distribution.
[f] Nyström and Bisrat (1986).

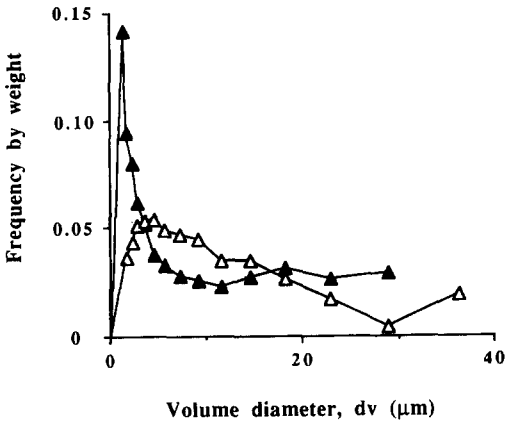

Fig. 4. Particle size distributions of 4′-demethylpodophyllotoxin-4,6-*O*-benzylidene-β-D-glucopyranoside and Q10 using the Coulter counter TA II and capillary tubes with orifices of 70 and 100 μm, respectively. (▲) 4′-Demethylpodophyllotoxin-4,6-*O*-benzylidene-β-D-glucopyranoside, (△) Q10.

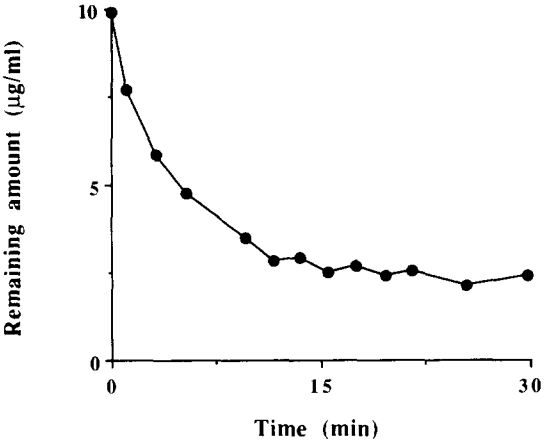

Fig. 5. Solubility determination for griseofulvin according to the subtraction method, using a 30 μm capillary tube.

that in the case of griseofulvin and felodipine almost all the particles are in the capillary size range and therefore have been covered by the 30 μm capillary tube.

In the case of glibenclamide, however, a large number of the particles smaller than 0.6 μm are not covered by the aperture. However, as the contribution of these small particles to the weight of particles characterized is minute, this amount can be neglected in the calculation of the remaining weight characterized during or after the dissolution process.

Considering the size distribution of Q10 (Fig. 4), it can be concluded that a certain fraction of larger particles (> 40.0 μm) and an amount of particles smaller than 2 μm are not covered by the 100 μm aperture tube. Large particles in this context can have a significant effect on the remaining weight of material being characterized and thus lead to an underestimation of the calculated amount of particles remaining.

DPBG with a normal size distribution and an arithmetic mean particle size of 15.7 ± 12.1 shows a broad size distribution. Also here it is concluded, considering the size distribution in Fig. 4, that a large amount of the particles with a signifi-

Table 2
Aqueous solubility characteristics of drug compounds at 22 ± 1° C as measured by the Coulter counter techniques [a]

Material	Subtraction method (μg/ml)	Extrapolation method	
		Solubility (intercept) (μg/ml)	Covering degree (slope) [b] (%)
Griseofulvin	8.10	6.55	100
Glibenclamide	5.90	5.33	100
Q10	–	0.06	98
DPBG [c]	1.41	1.53	87
Felodipine	–	4.53	100
Felodipine	0.66 [d]	0.83 [e]	–

[a] If not stated otherwise, the solvent medium contained 0.01% w/w Tween 80 and presented data obtained after 24 h equilibration.
[b] These values are equal to the slope of the dashed line, as shown in Fig. 7–12.
[c] Denotes 4′-demethylpodophyllotoxin-4,6-*O*-benzylidene-β-D-glucopyranoside.
[d] Value obtained by an extrapolation procedure using decreasing additions of Tween 80 (Nyström and Bisrat, 1986).
[e] Solvent medium contained 0.001% Tween 80.

cant effect on the remaining weight of the material are not covered by the 70 μm capillary tube.

4.2. Solubility determination

4.2.1. General discussion

The solubility results obtained from both methods are compared against each other and against earlier published data in Table 2.

These results indicate that solubility of sparingly soluble drugs such as griseofulvin, glibenclamide or even a quite low solubility drug such as DPBG can be determined by both methods.

In Fig. 5, the determination of solubility according to the subtraction method is illustrated for griseofulvin to exemplify an acceptable solubility determination according to this method, whereby the amount of remaining material is measured during the dissolution process, until a measurable equilibrium is reached. However, as is illustrated in Fig. 6 and Table 2, solubility determination of Q10 was not possible by the subtraction method and in the case of felodipine was just possible in an indirect way using the subtraction method (Nyström and Bisrat, 1986).

4.2.2. Solubility determination of felodipine

According to Nyström and Bisrat (1986) a direct solubility determination of felodipine at low concentration of Tween (< 0.025% w/w) was not possible by a Coulter counter technique, due to the very low water solubility of felodipine. Therefore, in their study the solubility of felodipine was measured indirectly using the solubilization effect of Tween and determining the solubility of felodipine in different concentrations of Tween (from 0.025 up to 1.0% w/v) according to the subtraction method. The solubility of felodipine in the absence of Tween was then obtained by plotting the solubility values against Tween concentrations and extrapolating to the *Y*-axis (Nyström and Bisrat, 1986).

However, according to the results obtained in the present study as is illustrated in Fig. 7 and 8, solubility determination of felodipine was possible even at lower concentrations of Tween than 0.025% w/w utilizing the extrapolation method. The lowest amount of Tween added was 0.001% w/w which is close to the CMC for Tween 80 (Wan and Lee, 1974). However, solubility determination of felodipine by the extrapolation method can probably also be possible at lower concentrations, or even in the total absence of any surfactant, if the powder is wetted sufficiently. Increasing the amount of Tween from 0.001 to 0.01% w/w caused an increase in solu-

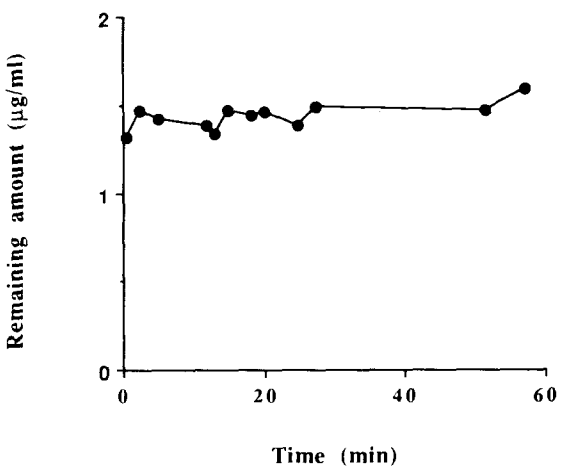

Fig. 6. Solubility determination of Q10, according to the subtraction method, using a 100 μm capillary tube.

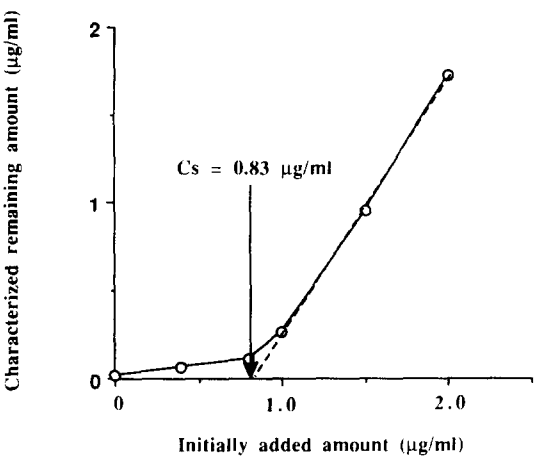

Fig. 7. Solubility curve for felodipine in 0.001% w/w Tween 80 after 22 h agitation at 23° C according to the extrapolation method. The inserted solubility value (C_s), calculated by linear regression, is indicated by the dashed line.

bility from 0.8 to 4.5 μg/ml. This result also demonstrates that even a minute concentration in excess of CMC, could be effective for solubilization of felodipine.

4.2.3. Solubility determination of Q10

As is illustrated in Table 2, the solubility of Q10 could not be measured by the subtraction method. Because of the high degree of polydispersity of the sample (even after a long ultrasonic treatment), some problems due to the inadequate covering size capacity of the capillary tube and a subsequent error in estimation of the amount of sample present in the suspension at different time intervals were experienced.

For an almost insoluble, highly polydisperse material such as Q10, the remaining amount did not decrease with time in any measurable sense as illustrated in Fig. 6. Therefore, it was impossible to achieve a concentration difference between the initial and final amounts, i.e., a solubility determination according to the subtraction method was not successful for Q10. The reason for this may partly be explained by the degree of polydispersity of Q10 and the amount of substance not being covered by the aperture tube.

In order to minimize this problem, the stock suspension was wet sieved (Precision sieve, Veco, Eerbeck, Holland) and the particle size fraction smaller than 15 μm was collected and used to determine the solubility. Unfortunately, the results (not presented), showed that as the amount remaining did not reduced by time (see a similar graph in Fig. 6), it was impossible to determine the solubility of Q10 by this method.

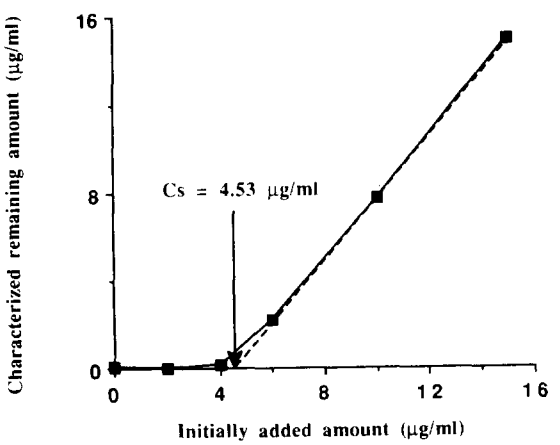

Fig. 8. Solubility curve for felodipine in 0.01% Tween 80 after 22 h agitation at 23° C according to the extrapolation method.

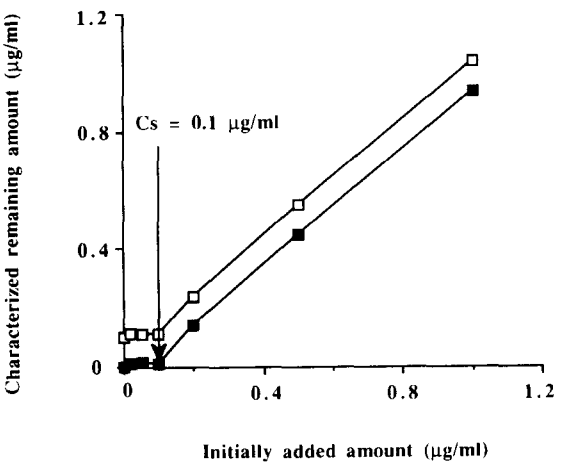

Fig. 9. Solubility curves for Q10 after 20 h agitation at 23° C according to the extrapolation method. (□) Before subtracting the amount of background. (■) After subtracting the amount of background.

The possibility to determine the solubility of Q10 using a different concentration of a surfactant according to Nyström and Bisrat (1986) was also tested. However, an increase in the amount of the surfactant did not cause any further improvement in the solubility determination of Q10 (results are not presented).

By using the extrapolation method, on the other hand, the solubility of Q10 could be determined, and was found to be about 0.06 μg/ml. In solubility determination of Q10 according to this method the experiment was repeated three times. In Fig. 9 one of these experiments is illustrated. The linear regression of each graph was then obtained and the solubility of Q10 was determined in each case. The solubility value of Q10 presented in Table 2 is a mean value obtained from the three experiments.

4.2.4. Material polydispersity and size range covered by the aperture tube

The greater the amount of a material that is outside the range covered by the aperture tube

used, the more difficult and inaccurate the estimation of solubility will be. This problem was especially pronounced in solubility determinations according to the subtraction method, since the calculations are directly based on the absolute measurements of particle weights obtained. For the extrapolation method only relative measurements of amounts remaining are needed. Here even certain size fractions could be used in such procedures.

Another advantage is that all data used in the profile construction are obtained after the same equilibrium time (e.g., 2 or 24 h) and thus eventual changes in particle size polydispersity due to dissolution effects are to some extent corrected.

For the subtraction method, on the other hand, different dissolution times and possible polydispersity values are applied for the different data points in the solubility profile (Fig. 1). This effect for extremely sparingly soluble materials, such as Q10, sometimes resulted in increasing amounts of weights remaining being found in relation to initial weight. This was probably due to the fact that dissolution of larger particles, initially outside the covering range of the aperture tube, after partial dissolution and subsequent size reduction, became 'visible' for the Coulter counter.

Comparing the slope values obtained by linear regression of solubility curves resulted from solubility determinations according to the extrapolation method, it can be concluded that 100% of particles in the case of griseofulvin, felodipine and glibenclamide, 98 and 87% in the case of Q10 and DPBG were covered by the capillary tube at the time of measurement (Table 2). It is believed that the extrapolation method is somewhat more accurate than the subtraction method, as it is not directly related to the absolute amount and polydispersity of the drug compound.

4.2.5. Operator and amount of background particles

The operator plays an important role in both methods. As was mentioned earlier, any electrical disturbance or particulate contamination during the experiment can affect the results.

The latter is especially pronounced for materials of extremely low solubility such as Q10. Determination of their solubility is possible by the extrapolation method but is still sensitive to the number of particles in the background medium. In the case of griseofulvin and glibenclamide the amount of background (0.001 and 0.035 μg/ml, respectively) was not significant in relation to their solubility (6.6 and 6.0 μg/ml, respectively). As illustrated in Fig. 12, 7 and 9, for drugs with lower solubility such as DPBG, felodipine and Q10 with solubility values of 1.5, 0.83 and 0.06 μg/ml, respectively, the importance and influence of background count become more significant. Therefore, in the first two cases linear regression can be applied after or before subtracting the background amount from the characterized remaining amount, without any significant difference in the resulted solubility value. However, in the last three cases the amount of background must be subtracted from the characterized amount before applying any linear regression, otherwise negative values for the solubility will be obtained.

4.2.6. Homogeneity of stock suspension and efficiency of ultrasonic treatment

Another factor which must be considered is the homogeneity of the stock suspension. Sometimes ultrasonic treatment is not sufficiently ef-

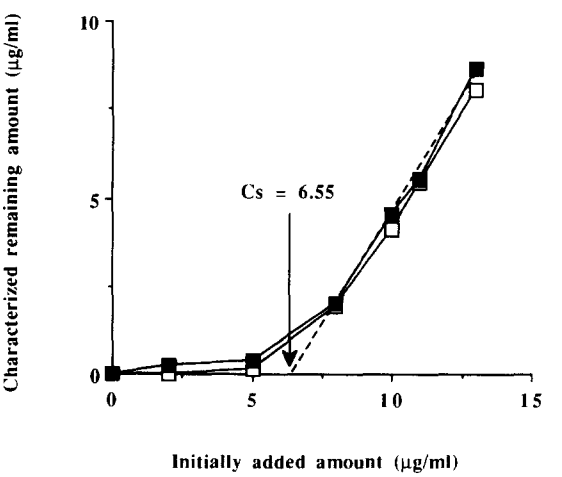

Fig. 10. Solubility curves for griseofulvin after 5 and 24 h agitation at 23° C according to the extrapolation method. (□) After 5 h stirring. (■) After 24 h stirring.

fective in breaking the aggregates to primary particles. This effect was observed for oxazepam (unpublished data) and Q10, where a longer period of treatment (up to 30 min) was required to break up the aggregates. However, even after such a long ultrasonic treatment there were still some aggregates left in the suspension, which caused uncertainty in characterization of the final suspensions. The degree of uncertainty was of course dependent on the fraction of the sample which were not broken up into primary particles. In the case of oxazepam this amount was so large that it was impossible to use the Coulter counter technique for solubility determination.

4.2.7. Dissolution time

For griseofulvin an agitation time of 30 min in the subtraction method was sufficient for determination of solubility. As illustrated in Fig. 10 in the extrapolation method the solubility of griseofulvin was determined both after 5 h and after 24 h. As the results indicate, a longer agitation time did not result in a higher solubility value. This is also correct for glibenclamide (Fig. 11).

On the other hand, as was expected for materials with extremely low solubility such as felodipine or Q10, a longer time is required to reach the equilibrium and any solubility determination before that would not give an accurate value. This

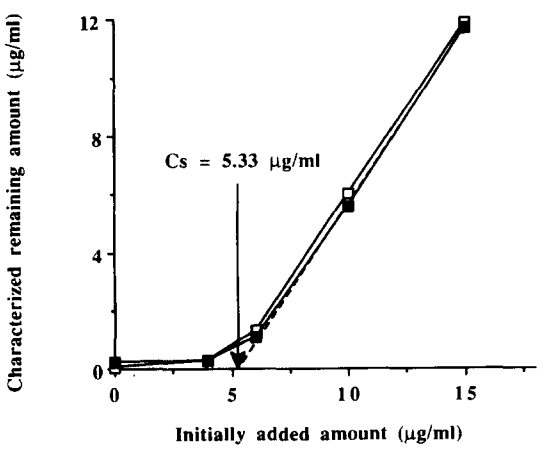

Fig. 11. Solubility curves for glibenclamide after 2 and 24 h agitation at 23° C according to the extrapolation method. (□) After 2 h stirring. (■) After 24 h stirring.

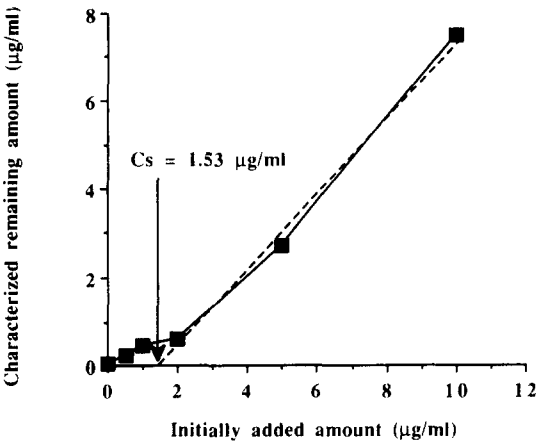

Fig. 12. Solubility curve for 4'-demethylpodophyllotoxin-4,6-*O*-benzylidene-β-D-glucopyranoside after 22 h agitation at 23° C according to the extrapolation method.

may therefore be an advantage for the extrapolation method where in contrast to the subtraction method, the operator does not need to follow the dissolution process during specific time intervals. The extrapolation method just requires one measurement for each suspension after the equilibrium has been reached.

4.3. Comparison between results in this study and earlier reported data

The solubility data obtained in this study for griseofulvin agree reasonably well with those suggested in literature (e.g., Nyström et al., 1985a,b, Sjökvist and Nyström, 1988).

In the case of glibenclamide, the reported data varied so markedly that they could not be used as reliable references.

The only solubility data found in the literature on Q10, describe it as an 'insoluble compound in water' (Reynolds, 1982), without giving any further information.

As DPBG is a quite new compound, there were no data available in the literature on its solubility.

In the case of felodipine the solubility value obtained by the extrapolation method using a dissolution medium containing 0.001% Tween was in fair agreement with those suggested in previ-

ous studies (e.g., Felle et al., 1984; Nyström and Bisrat, 1986).

5. Conclusion

The method described as the extrapolation method in this study is, in contrast to earlier methods based on the Coulter counter (here referred to as the subtraction method), a rapid and convenient means of estimating the solubility of materials with extremely low solubility, especially when no adequate technique for analysing the dissolved fraction exists. The method requires that the material can be suspended in a substantially particle-free solution which is sufficiently electrically conductive for a Coulter counter to be used. It also requires a good knowledge of the amount of background particles.

The method is sensitive and has the advantage of being able to determine the solubility of practically insoluble compounds down to 0.05 μg/ml. It is a simple and rapid method that can be useful in preformulation studies where a quick estimation of solubility using a minute amount of substance is required. It is relatively insensitive to the initial size distribution of the test materials and can therefore be applied to solubility determination of sparingly soluble compounds having a large degree of polydispersity.

Acknowledgements

The authors are very grateful to Astra Hässle AB, Sweden, Glaxo, UK, Hoechst, Germany and Analytecon SA, Switzerland, for supplying the samples of felodipine, griseofulvin, glibenclamide and DPBG respectively. We would also like to thank Mrs Elizabeth Börjeson for milling the Q10 powder.

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