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Determination of Coating Thickness of Microcapsules and Influence upon Diffusion

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Abstract □ Experiments in this study appear to show that the diffusion rate of the encapsulated drug is a function of microcapsule size. The object of this paper is to report the influence of the coating upon diffusion and the determination of the thickness of the coating. An equation was established, which was verified by microscopic measurement of microspheres previously sliced with a microtome.

Keyphrases □ Microcapsules—determination of coating thickness, effect on diffusion rate □ Coating thickness, microcapsules—determination, effect on diffusion rate □ Diffusion rate, encapsulated drugs—influence of nature and thickness of coating

The microencapsulation process is comparatively new (1–7). It consists of coating crystals or microdroplets of liquid with a polymer film. It has been applied successfully to a number of products, from gasoline to tetracycline. Its pharmaceutical use enables one to mix substances incompatible with each other, to mask an unpalatable taste, or to induce a prolonged action. Of course, the nature and thickness of the coating determine the diffusion rate.

THEORETICAL

Influence of Coating upon Diffusion—Studying the dissolution in water of cylinders of benzoic acid and lead chloride, Noyes and Whitney (8) gave the following dissolution equation:

$$\frac{dc}{dt} = K(C_\infty - c) \qquad \text{(Eq. 1)}$$

where K is a constant, C_∞ is the solubility of the substance, and c is the concentration at the expiration of the time t.

According to Brunner (9):

$$K = \frac{DS}{V\delta} \qquad \text{(Eq. 2)}$$

where K is the same constant as in the Noyes–Whitney equation, D is the solute molecule diffusion coefficient, V is the volume of solution, δ is the effective diffusion layer thickness, and S is the surface of the solid–solution interface.

The equation:

$$\frac{dc}{dt} = \frac{DS}{V\delta}(C_\infty - c) \qquad \text{(Eq. 3)}$$

allowed the computation of δ.

As reported by Wurster and Taylor (10): "the idealized film layer is not well defined, but it allows the correlation of experimental data with the physical properties of both the solute and solvent."

Dissolution of Microencapsulated Solute—In this experiment, the material to be encapsulated was viscous and sticky; however, the dry microcapsules did not aggregate. Thus one may disregard the possibility of a spontaneous diffusion of this material through the coating wall, and the phenomenon may be considered as follows: when the microcapsules were suspended in a liquid, the penetration of the solvent into the microspheres occurred first, followed by the dissolution of the encapsulated solute and the diffusion of the solution. The phenomena taking place during this exchange were dependent on osmotic pressure and diffusion.

In the event of the encapsulated substance being only slightly soluble in the liquid, one may disregard the effect of osmotic pressure and consider only diffusion. Thus, Eq. 3 may be expressed as:

$$\left[\frac{dc}{dt}\right]_{\text{coating}} = \frac{DS'\epsilon}{Vh}(C_\infty - c) \qquad \text{(Eq. 4)}$$

where S' is the external surface of a microcapsule, ϵ is a coefficient expressing the porosity and tortuosity of the coating, and h is the thickness of the coating. Other symbols are the same as already defined.

If it is assumed that microcapsules with the same radius have the same coating thickness, and that this thickness as well as that of Brunner's (9) layer are small and negligible with respect to the radius of microcapsules, one may write:

$$S = S' = n4\pi\bar{r}^2 \qquad \text{(Eq. 5)}$$

where $\bar{r}$ is the mean radius of the microcapsules and n is the number of microcapsules. The volume V_1 of the microcapsules is expressed as:

$$V_1 = \frac{4}{3}n\pi\bar{r}^3 = \frac{m}{d} \qquad \text{(Eq. 6)}$$

where m is the mass of n microcapsules, and d is the density of the microcapsules.

From Eq. 6, one may compute n and, reporting its value in Eq. 5, one has:

$$S = S' = \frac{3m}{\bar{r}d} \qquad \text{(Eq. 7)}$$

$$\left[\frac{dc}{dt}\right]_{\text{coating}} = \frac{3Dm\epsilon}{Vh\bar{r}d}(C_\infty - c) \qquad \text{(Eq. 8)}$$

On the other hand, the diffusion that takes place at the Brunner's (9) layer may also be expressed as:

$$\left[\frac{dc}{dt}\right]_{\text{layer}} = \frac{3Dm}{V\delta\bar{r}d}(C_\infty - c) \qquad \text{(Eq. 9)}$$

And the results of both phenomena are:

$$\left[\frac{dc}{dt}\right]_{\text{layer}} + \left[\frac{dc}{dt}\right]_{\text{coating}} = \left[\frac{dc}{dt}\right]_{\text{total}} \qquad \text{(Eq. 10}a\text{)}$$

$$\left[\frac{dc}{dt}\right]_{\text{total}} = \frac{3Dm}{V\bar{r}d}\left[\frac{1}{\delta} + \frac{\epsilon}{h}\right](C_\infty - c) \qquad \text{(Eq. 10}b\text{)}$$

Thus, diffusion is expressed as the sum of a constant and a variable, the latter being a function of the stirring rate.

One may write the empirical relationship:

$$\delta = \frac{a}{(N)^b} \qquad \text{(Eq. 11)}$$

where N is the agitation rate, and a and b are constants. Substituting this into Eq. 10 gives:

$$\left[\frac{dc}{dt}\right]_{\text{total}} = \frac{3Dm}{V\bar{r}d}\left[\frac{(N)^b}{a} + \frac{\epsilon}{h}\right](C_\infty - c) \qquad \text{(Eq. 12)}$$

$$\frac{dc}{C_\infty - c} = \frac{3Dm}{V\bar{r}d}\left[\frac{(N)^b}{a} + \frac{\epsilon}{h}\right]dt \qquad \text{(Eq. 13)}$$

Integrating this equation gives:

$$\ln(C_\infty - c) = -\frac{3Dm}{V\bar{r}d}\left[\frac{(N)^b}{a} + \frac{\epsilon}{h}\right]t + \text{constant} \qquad \text{(Eq. 14)}$$

If it is assumed that for $t = 0, c = 0$, then constant $= \ln C_\infty$:

$$\ln\left[1 - \frac{C}{C_\infty}\right] = -\frac{3Dm}{V\bar{r}d}\left[\frac{(N)^b}{a} + \frac{\epsilon}{h}\right]t \qquad \text{(Eq. 15)}$$

When C is very inferior to C_∞ (generally $C \leqslant 0.1\ C_\infty$), (C/C_∞) is small with respect to 1 and Eq. 15 reduces to:

$$C = \frac{3Dm}{V\bar{r}d}C_\infty\left[\frac{(N)^b}{a} + \frac{\epsilon}{h}\right]t \qquad \text{(Eq. 16)}$$

The curve $C = f(t)$ where N is a constant is interesting because it expresses the diffusion of the solute; the curve $C = f(N)$ where t is a constant is interesting when extrapolated at $N = 0$.

Thus, beyond the area A where the solution is heterogeneous, the equation of this curve is:

$$C = Co + kN^b \qquad \text{(Eq. 17)}$$

where:

$$Co = \frac{3Dm\epsilon C_\infty}{V\bar{r}dh}t$$

and:

$$k = \frac{3DmC_\infty}{V\bar{r}da}t$$

Co is the coating contribution to diffusion; it is representative of ϵ/h and, therefore, of the nature and thickness of the coating. It affords a global view of the coating's rate of diffusion. Thus, it is possible to compare two batches of microcapsules of the same drug by equalizing all of the other parameters.

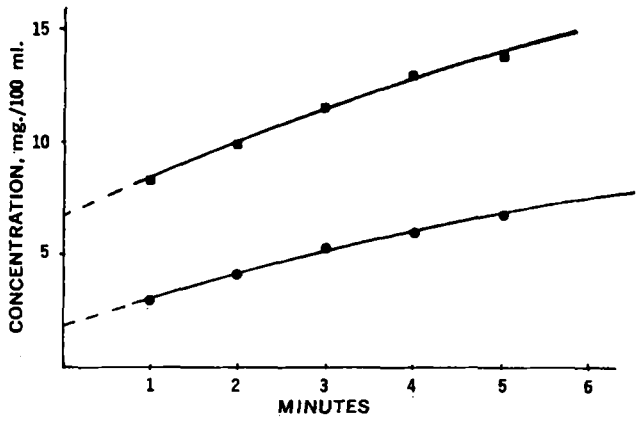

Figure 1—*Liberation rate of microcapsules with* r *different. Key:* ■, r = *140 μ; and* ●, r = *300 μ.*

Determination of Coating Thickness—It follows from Eq. 15 that, for obtaining a prolonged action with microcapsules, it will be advantageous to increase $\bar{r}$ and decrease ϵ/h. Other parameters are determined either by solute and coating (D, d) or by posology (m, V). The formulator is free to work on $\bar{r}$ and h. The mean radius is more easily measured than the coating thickness. The following two methods were used.

Measuring Density and Active Drug Amount—Let us consider a batch of n microcapsules weighing m g. with a mean radius $\bar{r}$. Solute density is d_1, and coating density is d_2.

The solute mass is:

$$m_1 = n\frac{4}{3}\pi(\bar{r} - h)^3 d_1 \qquad \text{(Eq. 18)}$$

The coating mass is:

$$m_2 = n\left[\frac{4}{3}\pi\bar{r}^3 - \frac{4}{3}\pi(\bar{r} - h)^3\right]d_2 \qquad \text{(Eq. 19)}$$

Calling P the relation:

$$P = \frac{\text{solute mass}}{\text{total mass of microcapsules}} \qquad \text{(Eq. 20)}$$

one has:

$$P = \frac{n\frac{4}{3}\pi(\bar{r} - h)^3 d_1}{n\frac{4}{3}\pi(\bar{r} - h)^3 d_1 + n\left[\frac{4}{3}\pi\bar{r}^3 - \frac{4}{3}\pi(\bar{r} - h)^3\right]d_2} \qquad \text{(Eq. 21}a\text{)}$$

$$P = \frac{(\bar{r} - h)^3}{(\bar{r} - h)^3 d_1 + [\bar{r}^3 - (\bar{r} - h)^3]d_2} \qquad \text{(Eq. 21}b\text{)}$$

$$P = \frac{\left[1 - \frac{h}{\bar{r}}\right]^3 d_1}{\left[1 - \frac{h}{\bar{r}}\right]^3 d_1 + \left[1 - \left(1 - \frac{h}{\bar{r}}\right)^3\right]d_2} \qquad \text{(Eq. 21}c\text{)}$$

Assuming that $(h/\bar{r}) \ll 1$, the previous equations reduce to:

$$P = \frac{\left[1 - \frac{3h}{\bar{r}}\right]d_1}{\left[1 - \frac{3h}{\bar{r}}\right]d_1 + \frac{3h}{\bar{r}}d_2} \qquad \text{(Eq. 22}a\text{)}$$

$$1 - P = \frac{\frac{3h}{\bar{r}}d_2}{\left[1 - \frac{3h}{\bar{r}}\right]d_1 + \frac{3h}{\bar{r}}d_2} \qquad \text{(Eq. 22}b\text{)}$$

$$\frac{P}{1 - P} = \frac{\left[1 - \frac{3h}{\bar{r}}\right]d_1}{\frac{3h}{\bar{r}}d_2} \qquad \text{(Eq. 22}c\text{)}$$

Table I—Computation of Coating Thickness from Density and Active Drug Amount Determinations

Mean Radius, μ	Percent of Core Material	Percent of Coating Material	Thickness h, μ
375	0.93	0.07	5.86
300	0.90	0.10	0.80
200	0.89	0.11	5.00
140	0.805	0.195	6.40
87.5	0.755	0.245	5.10

Table II—Computing of Coating Thickness: Number of Observations of Thickness h for the Radius $\bar{r}$

Mean Thickness, μ	Mean Radius, μ 140	200	300	375
3.80	0	1	1	4
4.75	5	6	1	4
5.70	13	10	6	13
6.65	11	8	12	7
7.60	7	10	9	9
8.55	2	4	4	3
9.50	4	5	2	5
Total number	42	44	35	45

$$\frac{3h}{\bar{r}}d_2P = (1 - P)\left[1 - \frac{3h}{\bar{r}}\right]d_1 \qquad \text{(Eq. 22}d\text{)}$$

$$\frac{3h}{\bar{r}}[d_2P + (1 - P)d_1] = (1 - P)d_1 \qquad \text{(Eq. 22}e\text{)}$$

$$h = \frac{\bar{r}}{3}\frac{(1 - P)d_1}{Pd_2 + (1 - P)d_1} \qquad \text{(Eq. 22}f\text{)}$$

d_1 and P are easily measured, and d_2 is computed after measuring of total density and P, from which h is computed.

Direct Measure after Microtome Slicing—Wall thickness is measured with a microscope fitted with a micrometer after slicing with a microtome (slice thickness about 10 μ).

EXPERIMENTAL[1]

This work was carried out using microcapsules containing the liquid organic base, eprazinone, a mucolytic drug, encapsulated by a mixture of gelatin and gum arabic. Eprazinone is 3-[4-(2-methoxy-2-phenylethyl)-1-piperazinyl]-2-methyl-1-phenyl-1-propanone.

The process is carried out in an open top vessel at 40°, and the pH is maintained constant at 6.5 with acetic acid. The core material is dispersed as minute droplets in the solution of the mixture of gelatin and gum arabic; the capsule walls are hardened with glutaraldehyde as a crosslinking agent.

The batch studied was sieve separated into groups with average radii of 375, 300, 200, 140, and 87 μ.

Apparatus—The following were used: a constant-temperature bath kept at 23 ± 0.5°, a mechanical stirrer, a spectrophotometer[2], a chronometer, a pycnometer, a microscope, and a microtome.

Measurement of Diffusion—A volume of 300 ml. of distilled water is stirred until a temperature of 23° is reached. With continuous stirring, 1.5 g. microcapsules is added with the starting of the chronometer. Samplings are made by way of a pipet fitted at its lower end with a small plastic tube filled with glass wool. Each sampling is 3 ml., *i.e.*, 1% of the total volume. After a correct dilution of the sampling, the amount of diffused drug is determined by spectrophotometry at the absorption maximum of 250 nm.

Determination of Thickness—*Calculation*—Densities are determined by way of a pycnometer. Wall density is found by calculation after determination of the total volume of microcapsules and the volume of microencapsulated eprazinone.

[1] The microcapsules were obtained from I.B.F., Paris, France.
[2] Beckman DBG.

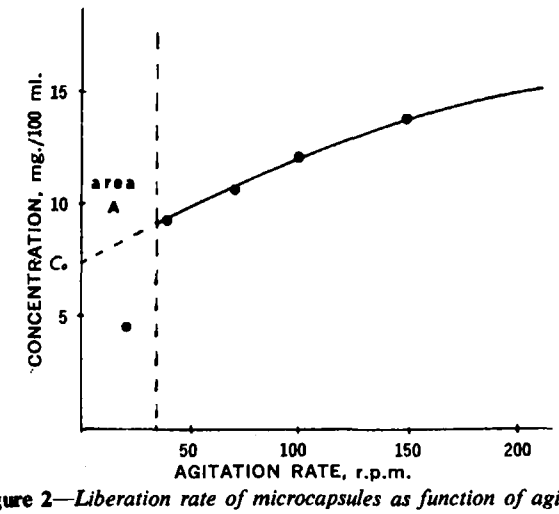

Figure 2—*Liberation rate of microcapsules as function of agitation rate.*

Direct Measure after Microtome Slicing—Microcapsules are imbedded in a gelatin mass according to Baker (11). Paraffin inclusion is unsatisfactory because of the solvent effect of alcohol and toluene and because of the low melting point of the paraffin, which also causes the coating material to melt.

Gelatin is mixed with distilled water in a 1:5 ratio. This mixture is kept 2 hr. at 37° in an incubator. Microcapsules are subsequently added. A separate gelatin bath is used for each size of microcapsules. Cubes of gelatin obtained after hardening are kept at 4°.

The gelatin cubes are subsequently sliced with a congelation microtome. Slice thickness should be about 10 μ. Each slice is placed on an object slide and mounted with levulose syrup, which is water miscible and does not require slice dehydration.

Slides are studied without staining on a microscope fitted with a micrometer and an immersion objective. One can perform a direct measure of coating thickness which appears as a darker zone with respect to the preparation as a whole.

RESULTS AND DISCUSSION

Curves $C = f(t)$ for N = Constant (Fig. 1)—There is good agreement between the experimental curves and the theoretical predictions. The origin of the ordinate is not zero; as a matter of fact, the method for preparing microcapsules requires the pH to be kept constant by adding acetic acid. Thus, some acetate is formed, part of which mixes with the coating. This soluble fraction diffuses at once.

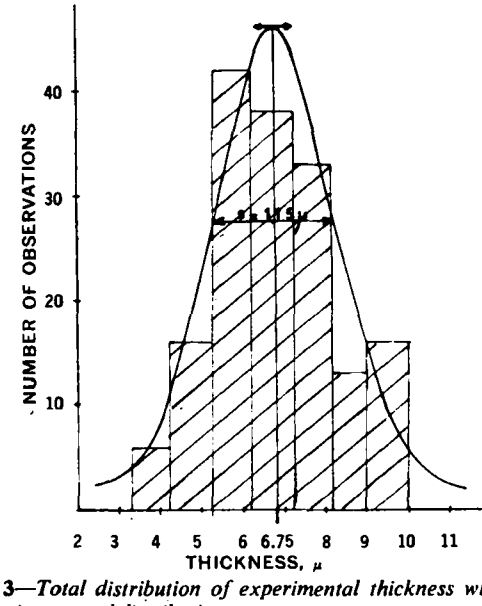

Figure 3—*Total distribution of experimental thickness with an approximating normal distribution.*

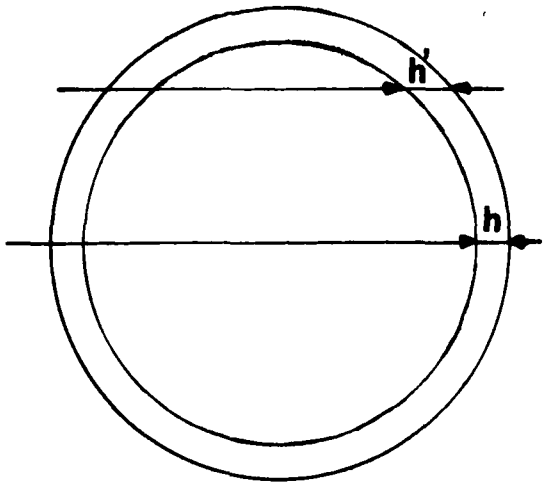

Figure 4—*Section of a microcapsule showing the different values of* h.

Curve $C = f(N)$ for t = Constant (Fig. 2)—Good agreement was found between the experimental curves and the theoretical predictions. The $C0$ value is higher than the ordinate at the origin of the curve $C = f(t)$ for N = constant; acetate dissolution is, therefore, to be disregarded.

Computing Thickness h—*From Densities and Amount of Active Drug*—One finds $d_1 = 1.05$ and $d_2 = 1.60$. The results are given in Table I. The mean value obtained by this method is 5.85 μ.

From Direct Measure—Table II gives the number of observations of thickness h and the total number of measured samples n and $\bar{h}$. The mean value obtained by this method is 6.75 μ.

The coating thickness distribution curve is given with a good degree of precision by microscopic measures (Fig. 3). This curve includes values from 10 to 4 μ. Upper values can be explained by the difficulty in cutting a microcapsule through the center with a microtome (Fig. 4); thus, the resulting coating thickness is larger for one slice than for the other ($h' > h$).

Lower values are not easily explained if thickness is taken as constant. On the other hand, microscopic examination showed that microcapsules are not spherical but rather present a knob at each pole. These knobs appeared only in the smallest microcapsules with a radius between 87 and 140 μ.

For the purpose of simplifying calculation, the microcapsules were assumed to be spherical. The results obtained indicate that this assumption can be made.

In spite of extensive radius differences (×4), the mean coating thickness remains constant, whichever method is used. Differences found with both methods for the mean coating thickness are not significantly different.

CONCLUSIONS

The experiments with microencapsulation seem to demonstrate that, when gelatin and gum arabic are used, the obtained coating is a constant thickness whatever the microcapsule size. Thus, the diffusion rate of the microcapsules will be in direct ratio to the coating material (ϵ) and in inverse ratio to the mean radius ($\bar{r}$).

The proposed equation for determining the coating thickness allows a quick estimation of this thickness, whereas direct microscopic measurement is lengthy and tedious. Knowing the coating thickness would allow the microcapsule manufacturer to determine the best conditions of encapsulation with respect to the objective, and this knowledge would permit the user to verify the constancy of quality of the product.

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