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Direct measurements on individual microcapsule dissolution as a tool for determination of release mechanism

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A method is described for simultaneous microscopic observation of individual microcapsule core material dissolution together with quantitative measurement of the individual kinetics of release of the contents. These may be conductimetric in the case of ionized materials or spectrophotometric otherwise. This enables correlation of changes in core surface area during dissolution with kinetics. Surprisingly, both ethyl cellulose- and polymethacrylate-coated cores of potassium dichromate crystals, used as a model, showed localized internal dissolution universally, providing evidence of the exit of the salt via pores in the membrane, in spite of the kinetics being invariably zero order, as expected for individual microcapsules. The advantages of the method are presented.

In microparticulate sustained release systems such as microcapsules or microspheres, release mechanisms are commonly deduced from kinetic measurements on populations, aided by indirect methods based on probing the effects of solvents, buffers, agitation rate or other variants (e.g. Benita & Donbrow 1982a; Vidmar & Jalsenjak 1983; Si-Nang et al 1973). Since the release profile of any population is a function of the distribution of certain parameters in the individuals (Hoffman et al 1986; Gross et al 1986) such as payload and rate constant, the underlying release mechanism can be established only by studies on the individual microparticles. Some suitable micro methods for studying individual kinetics were recently developed in connection with evaluation of the distribution of parameters in heterogeneous populations of microcapsules (Hoffman et al 1985).

It would be anticipated that direct microscopic observation of single particles simultaneously with kinetic measurements on the same particle might provide valuable information helping to distinguish between alternative possible mechanisms. In the present communication, a method is reported for doing this.

Method

Single microcapsules, sampled from a batch, were immersed in 10 ml release medium in small, glass petri dishes and observed microscopically or photomicrographed during release of contents. Release was monitored conductometrically in the case of microencapsulated salts as model core materials, using microplatinum electrodes (Radiometer Type CDC 314). The medium was circulated continuously at 5 ml min^{-1} through the optical cell and electrode by means of a peristaltic pump.

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This optical microscopic technique is particularly convenient with coloured core materials but is adaptable for dark field phase contrast or fluorescent microscopy, though unsuited to highly opaque wall materials. Since the observed image of three-dimensional processes is two-dimensional, care must be taken over interpretation, especially when the sample orientation fails to give the best-angle of vision, but the rapidity and ease of the method allows many samples to be studied. Where appropriate, release kinetics may alternatively be monitored by circulation through continuous flow microcells in a UV spectrophotometer or more simply by running analogous parallel microscopic and microspectrophotometric studies on different microcapsules from the same batch.

Results and discussion

Fig. 1a shows microscopic changes typical of microencapsulated potassium dichromate in an acrylate-derived coating (Eudragit Retard RS, Röhm Pharm, Darmstadt, W.G.) deposited by means of a two-solvent phase separation process (Benita et al 1985b). Surprisingly, dissolution of the core material occurs at two specific points, about which the dissolved diameter grows progressively while the 'hole' maintains its general shape, the advancing front tending towards spherical. The volume vacated by solution of the crystal was filled with dissolution fluid. Since the dissolution takes place only around the 'hole' it can be seen that, initially, the surface area exposed to dissolution increases gradually, at later stages the separate holes join together (at 4–5 h in the sample) and subsequently the exposed surface becomes constant and then decreases. The number of such centres of dissolution varies in the different microcapsule samples. Potassium dichromate has the advantage as a model of allowing sharp definition of the distinct regions, the solution being yellow and the crystal dark orange, while the walls are white and transparent. Thus not only were the interior 'solution' lacunae clearly revealed but there was no sign whatsoever of uniform dissolution over the exterior surface of the crystals, as would be expected of a homogeneous diffusion process through the whole wall area. This points to the presence of pores or sites of increased permeability having a critical role in governing the dissolution rate. The phenomenon was general for all batches and samples of these microcapsules and was supported by other measurements based upon common indirect methods.

The conductometrically-measured release for the

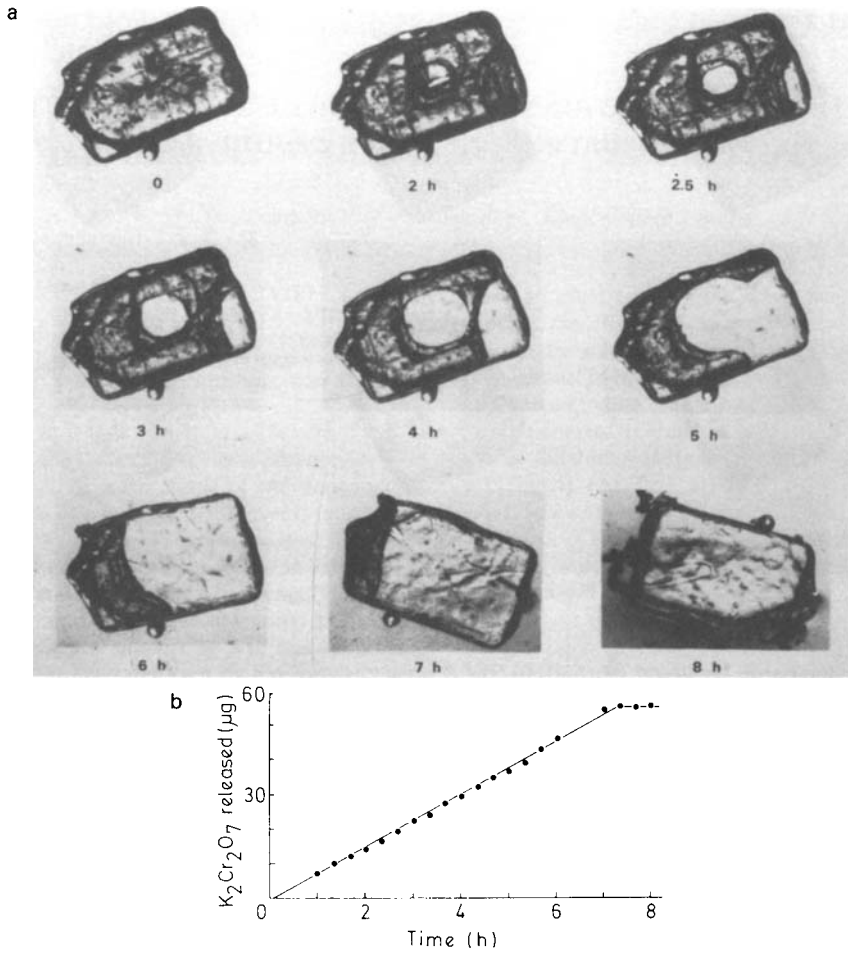

FIG. 1. a. Photomicrographs showing progress of core dissolution in single potassium dichromate-Eudragit RS-coated microcapsules. Microcapsules, prepared by standard process as in Benita et al (1985b), contained 75% core material. The crystal shown weighed 55 μg and measured 400 × 260 μm. b. Release profiles of the microcapsule.

microcapsule shown in Fig. 1a is presented in Fig. 1b. Release is zero order, as expected theoretically for a system having a constant concentration gradient in the interior viz. a saturated solution (Hoffman et al 1986) with diffusion-controlled exit. The plateau represents complete removal of the contents, its onset coinciding with the disappearance of the last trace of the core crystal in every microcapsule examined. The excellent linearity has been confirmed on hundreds of microcapsules, including different core materials and types. The wall evidently remains intact, the release constant being determined by the 'pore' dimensions, a result which would account for the heterogeneity of this parameter within a batch.

On the other hand, the kinetics of surface area change (Fig. 1a) are clearly incompatible with dissolution control (in which release rate is directly related to surface area exposed) since the rate would increase during the surface expansion phase, and, likewise, it is inappropriate to first order or matrix release from individuals. The photomicrographic observations thus provide additional evidence that there is no direct relationship between the cumulative kinetics of a batch (first order, in all the examples tested) and the kinetic profiles of the individuals.

The dissolution in ethyl cellulose-walled microcapsules containing potassium dichromate cores is shown in Fig. 2a. These microcapsules were prepared by a different phase separation method—gradual temperature reduction in a single solvent (Benita & Donbrow 1982b) but display the same type of locally developing sites of dissolution. Individual kinetic release profiles are again heterogeneous and zero order (Fig. 2b) whereas overall release followed first order kinetics (Benita & Donbrow, unpublished data).

Such localized dissolution is thus not restricted to the first example, nor is the divergence between single and population kinetics; in fact both phenomena are pro-

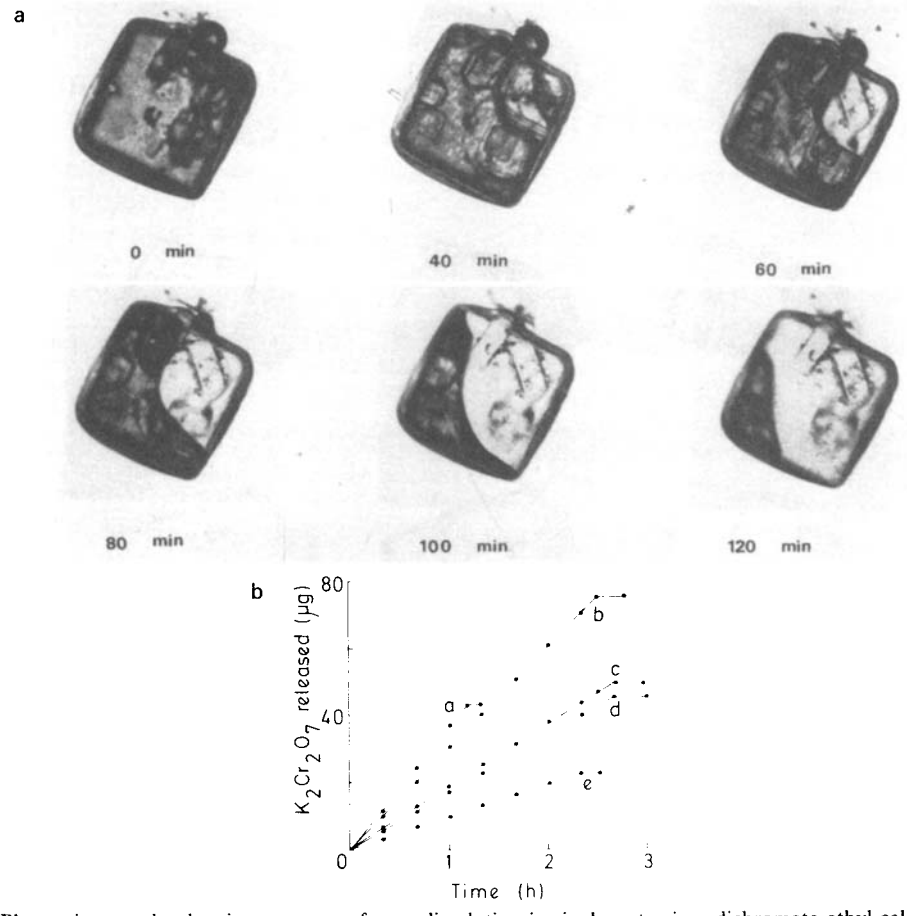

Fig. 2 a. Photomicrographs showing progress of core dissolution in single potassium dichromate-ethyl cellulose-coated microcapsule. Microcapsules prepared as in Benita & Donbow (1982b), contained about 70% core material. The crystal shown weighed 44 µg and measured 340 × 340 µm. b. Release profiles of typical single potassium dichromate–ethyl cellulose-coated microcapsules, line d shows the release from the microcapsule.

bably widespread and justify routine microscopic study of individual dissolution in all such kinetic work.

Finally, it may be recalled that overall release constants are generally reproducible for microcapsules where process parameters are under full control and furthermore, the degree of controlled release achieved may be graded by change of certain formulation and process parameters (e.g Donbrow et al 1984; Benita & Donbrow 1982b; Benita et al 1985a). This indicates that localized dissolution in the individuals is not disadvantageous and that the statical mean dimensions of the rate-controlling pores (or sites of penetration) are reproducible and gradable in process control.

Direct microscopic examination of microparticles offers a useful tool for detection of phenomenological processes involved in the mechanism of release and is particularly valuable in conjunction with simultaneous measurement of individual particle release kinetics.

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