Release Rate Characteristics of Microencapsulated 2,3,5,6-Tetrachloro-4-methylsulfonylpyridine

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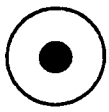
Synopsis

The rate at which 2,3,5,6-tetrachloro-4-methylsulfonylpyridine (TMP) is released from a microcapsular controlled delivery device was determined using aqueous methanol as an extraction medium. The microcapsules were prepared by *in situ* polymerization of a urea–formaldehyde resin. Release rate studies demonstrated that the amount of 2,3,5,6-tetrachloro-4-methylsulfonylpyridine released is proportional to $t^{-1/2}$ and the solubility of 2,3,5,6-tetrachloro-4-methylsulfonylpyridine in the extraction medium. These relationships are characteristic of a porous, monolithic delivery system.

INTRODUCTION

Controlling the release of chemicals such as pheromones, therapeutic drugs, and pesticides is an increasingly fruitful area for research. The two mechanisms which can be employed for continuous release of contained materials are (1) physical control, where the release is controlled by diffusion, desorption, or osmotic pumping; and (2) chemical control, where release is controlled by photochemical, biological, or hydrolytic processes. Slow-release devices such as strips,[1] hollow fibers,[2] and microcapsules[3] are based on physical release methods and are being evaluated as commercial products. A major consideration in the design of prolonged-release devices based on physical control is the rate at which active ingredients are lost through leaching or evaporation. A means to improve the efficiency of controlled chemical release devices is to learn enough about the device's release kinetics to be able to alter release characteristics to obtain a desirable change in performance. Although the kinetics of controlled release has been the subject of considerable research, few studies based on microcapsules have appeared.

Theoretically, two different structures of microcapsules can be formed each with its own characteristic release kinetics. The first device is one having a constant rate of release, $dQ/dt = k$, and consists of a solid core of the material to be released (internal phase) centered exactly in a spherical polymer shell and is known as a depot device.[4] The second[4] has the material to be released dispersed in a polymeric matrix, is known as a monolithic controlled delivery device, and a release rate dQ/dt proportional to $t^{-1/2}$:



Depot Device

Monolithic Device

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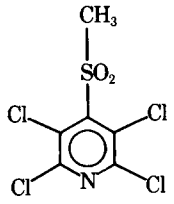
To design a controlled-release device based on microencapsulation for a given application, it is necessary to determine the release kinetics for the microencapsulation product, then correlate the release kinetics with field test experience. Adjustments in the manufacturing procedure can alter the kinetics.

We have investigated a model controlled-release delivery system consisting of an internal phase (IP) of 2,3,5,6-tetrachloro-4-methylsulfonylpyridine (TMP) encapsulated with a urea–formaldehyde resin:



TMP

EXPERIMENTAL

Microcapsules containing TMP were prepared by a known procedure.[5] The percent TMP included in the microcapsules was 63.8% based on chloride analysis. TMP release rate from the microcapsules was determined by solvent extraction using an apparatus which consisted of a 500-ml three-necked flask having two chambers separated by a medium-pore fritted filter, a Turner 350 spectrophotometer set at 315 (λ_{max} for TMP), a constant-flow cell with a flow rate of 40 ml/min, and a Heller (model GT-21) stirrer. The flask was charged with 330 ml of a desired solvent mixture, stirrer and solvent flow (40 ml/min) were started, and about 25 mg microcapsules were added. The absorption at 315 nm was monitored as a function of time on a Texas Instruments Marksman model PS01W6A strip chart recorder.

RESULTS AND DISCUSSION

Linear Beer's law plots were determined at 315 nm using solvents having various water-to-methanol ratios. Some deviation from Beer's law was noted in that a nonzero intercept was obtained at four methanol levels. However, a test for linearity was acceptable in that correlation coefficients greater than 0.99 were obtained in each case. Deviations from Beer's law are known to occur with more complex molecules such as TMP.

Ideally, depot device-type microcapsules should have a constant rate of release or zero-order kinetics due to the presence of a reservoir of solid TMP within a membrane.[4] However, the graphic results of solvent (70% methanol–30% water) extraction studies of microencapsulated TMP (Fig. 1) did not show this theoretical zero-order kinetics over short time periods of ~20 min, and an analysis of the data obtained on extraction of these microcapsules over a 4-hr period shows a gradually declining release rate. This behavior is indicative of a monolithic system[4] and should be observed if TMP is dissolved or dispersed in the polymer matrix. Theory predicts that for a dissolved system the rate would fall exponentially with time or be directly proportional to the reciprocal square root of

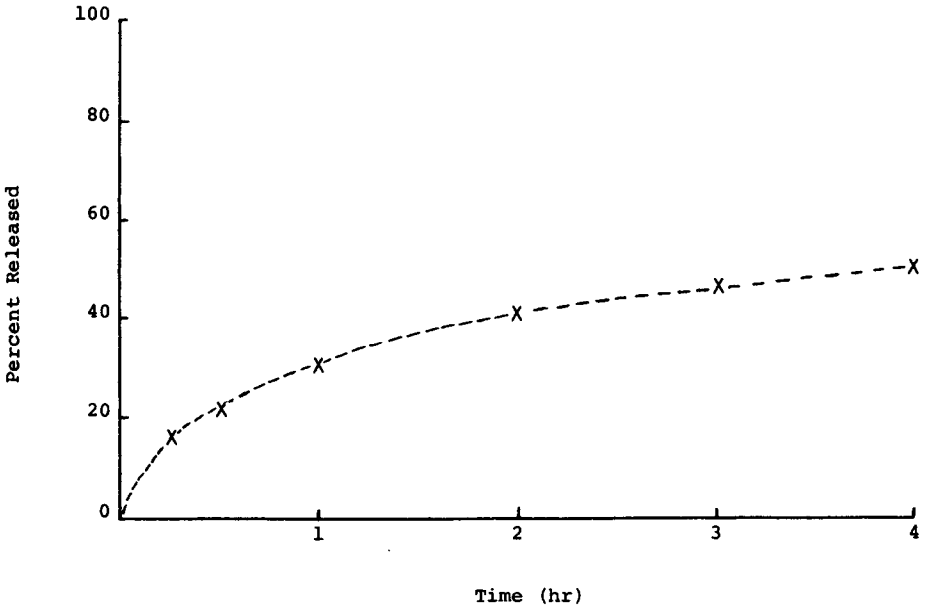


Fig. 1. Extraction of microencapsulated TMP with 70% aqueous methanol.

time ($t^{-1/2}$) for a dispersed system. Due to the large amounts of TMP in the microcapsule (63.8%), it is very likely that the internal phase is dispersed and not dissolved. Indeed, computer analysis of the release data gave eq. (1) as the best fit for the data with a correlation coefficient of 0.986,

$$\text{rate} = \frac{d(\text{TMP})}{dt} = 0.0945 \exp(-0.0121t) \tag{1}$$

while a plot of the rate versus $t^{-1/2}$ (Fig. 2) gave a straight line (least squares)

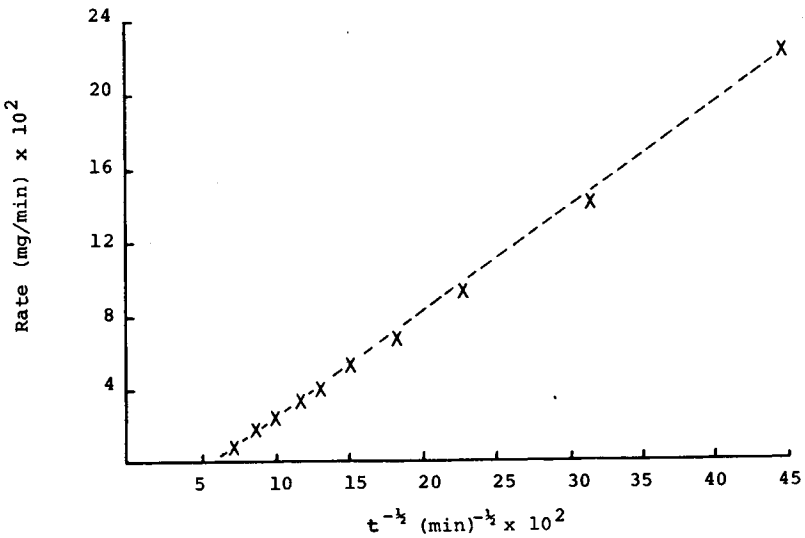


Fig. 2. Plot of microcapsule release rate vs. reciprocal square root of time: $y = 0.559x - 3.08$; correlation coefficient 0.999, 70% methanol:30% water.

with a correlation coefficient of 0.999. According to these data, the initial (4 hr) release kinetics are consistent with a dispersed monolithic-type controlled release system.

Higuchi[6] derived theoretical equations which describe the chemical release characteristics of monolithic delivery systems for several shapes, including planar, cylindrical, and spherical. For each controlled-release device shape, the membrane may be either nonporous, in which case the rate is controlled by the diffusion of the active component through the polymer membrane, or porous, in which case the rate is controlled by the solubility of the active component in the extracting fluid. Higuchi derived eqs. (2) and (3) for a planar controlled-release device:

Nonporous:

$$Q = [D_m t C_p (2A - C_p)]^{1/2} \tag{2}$$

where Q = total release of the internal phase after time t per unit area, D_m = diffusivity of the saturated solution of the internal phase in the polymer phase, A = concentration of internal phase per unit volume in polymer matrix, and C_p = solubility of the internal phase in the polymer phase.

Porous:

$$Q = \left[\frac{D_f e C_s t}{\tau}(2A - eC_s)\right]^{1/2} \tag{3}$$

where D_f = diffusivity of the internal phase in the solvent system, e and τ = porosity and tortuosity factors for the polymer matrix, and c_s = solubility of the internal phase in the solvent system.

The equations for a spherical controlled-release device are extremely complex and have no unequivical solution. Fortunately, a plane of the same surface area as the sphere is a good first approximation, and either eq. (2) or eq. (3) should provide a fit for the initial release data. Thus, a plot of percent released versus the square root of the time ($t^{1/2}$) should be, and is, linear in the initial stages of extraction (Fig. 3). The linear correlation coefficient is 0.998 up to 35% release and then falls off to 0.986 at 50% release. Significant deviation from the release behavior of a planar surface is expected at about the 35–40% release level.[6] The slope of the line should be a constant (k_H) depending on various physical parameters which will be determined by the porosity of the capsule wall. Using the relationship between initial release rate and $t^{1/2}$, the solvent strength on the release characteristics of microencapsulated TMP has been established.

Microcapsules containing TMP were extracted with solvents consisting of various methanol-to-water ratios. Absorption data obtained form multiple runs in each solvent were computer fitted to a linear least-squares formula. The resulting equations are shown in Table I, which compares the Higuchi constant with the solubility of TMP in the solvents used. From these results it is apparent that an increase in the methanol concentration in extraction solvent results in an increase in the amount of TMP released. This relationship is due, at least in part, to the increased solubility of TMP in solvent systems with high concentration of methanol. These data were analyzed by the least-squares technique to yield eq. (4) with a correlation coefficient of 0.98:

$$k_H = 24.4(\text{solubility}) - 1.7 \tag{4}$$

Dependence of release rate on solvent occurs only in eq. (3) and indicates that the microcapsules produced in our work have a porous structure.

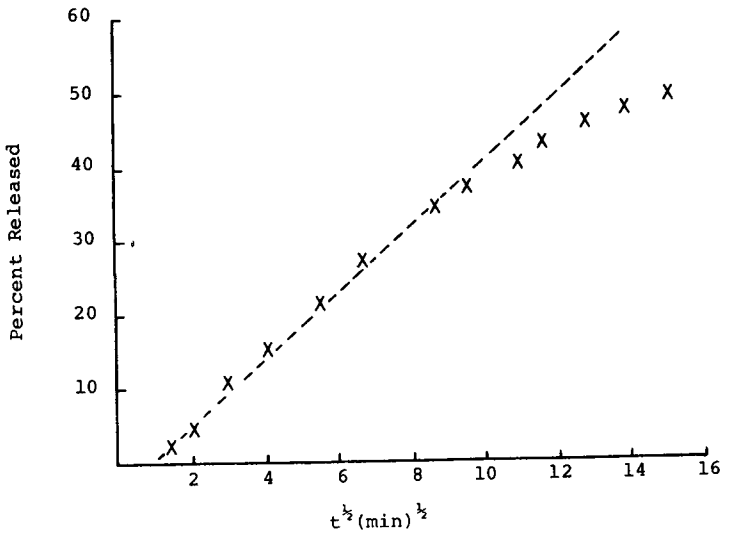


Fig. 3. Typical Higuchi plot of microcapsule release data: $y = 5.45x - 3.81$; correlation coefficient 0.9976; 70% methanol:30% water.

CONCLUSIONS

This research has utilized the release rate theory developed by T. Higuchi to characterize a controlled-release delivery system consisting of microcapsules formed by the *in situ* polymerization of urea–formaldehyde resins. The microcapsules were found to have a monolithic-type structure. Higuchi equations for planar controlled-release devices were found to be useful in analyzing data for the extraction of up to 35% of TMP from the spherical microcapsules. A relationship established between release rate and the solubility of the internal phase indicated a porous structure for the microcapsules.

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TABLE I
Comparison of Higuchi Constants (k_H) With the Solubility of TMP in Aqueous Methanol Solvent Systems

Percent methanol	Linear least-squares equations (correlation coefficient) Run 1	Run 2	Run 3	Ave. k_H	Solubility of TMP, g/l.
100	$y = 28.9x - 13.7$ (0.993)	$y = 27.2x - 11.2$ (0.997)	$y = 33.5x - 15.5$	29.9	1.24
90	$y = 15.2x - 8.0$ (0.996)	$y = 14.6x - 9.1$ (0.999)	$y = 14.1x - 8.5$	14.6	0.70
70	$y = 5.4x - 4.2$ (0.998)	$y = 5.2x - 5.6$ (0.999)	—	5.3	0.41
50	$y = 1.9x - 2.0$ (0.998)	$y = 1.8x - 1.9$ (0.997)	$y = 2.6x - 2.2$ (0.999)	2.1	0.15
25	$y = 0.6x - 0.8$ (0.986)	$y = 0.7x - 1.2$ (0.994)	$y = 0.7x - 1.3$ (0.989)	0.7	0.053
0	$y = 0.4x - 0.6$ (0.999)	—	—	0.4	0.039

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