Evaluation of the Types of Emission Systems Observed in Aqueous Media with Controlled-Release Formulations

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Synopsis

Three types of release systems have been observed for controlled release formulations (CRF) of biocides in aqueous media. A type I system, which is concentration dependent, can be divided into a IA system whose concentration maximum is dependent upon sample size and degradation, and a IB system whose concentration is dependent upon the solubility of the biocide in the solvent. A type II system, which is time dependent, can be divided into a IIA system whose release rate is dependent upon $t^{1/2}$ and a IIB system whose emission is zero order or dependent only upon time. A type III system, which is a failure system, can be divided into a IIIA system whose concentration decreases to a nondetectable range as a function of $t^{1/2}$ and a IIIB system whose decreasing concentration is first order. Equations relating the theoretical life of the CRF to its bioactive life are also presented.

INTRODUCTION

Although a number of controlled released formulations (CRF) have been developed for aqueous systems,[1-5] little effort has been made to systematically relate the types of release of the bioactive material from one CRF to another. Baker and Lonsdale[6] postulated the type of release systems which would be encountered with erodible polymers but did not have any experimental data to support their postulations. McCormick and Fooladi[1] presented experimental data on the types of emissions they observed with herbicides but did not attempt to categorize the systems. This paper is an attempt to systematize the different types of emission systems to help relate data obtained by different investigators.

EXPERIMENTAL

Since the interpretation of a CRF release system can be dependent upon the sample, the solution, sampling method, and analytical procedures, several investigators have attempted to standardize the experimental method to reduce these variables.[1,7] The experimental method described below is a modification of these methods.

Analytical sensivity is the usual criteria for determining the sample size used in a CRF study. Because a type I release system is effected by sample size, three different weight samples are usually used in any study; the weight ratios are usually 1:2:5 and may vary from a few milligrams (organotin formulations) to several grams (Dursban formulations).

All samples are weighed to the nearest milligram and a blank containing only

polymer and additives is treated as an unknown sample. The samples are dispersed in 1.000 L of distilled water.

All samples are tightly stoppered and vigorously shaken. They are allowed to quiescently set at ambient laboratory conditions (20 ± 3°C at 750 ± 10 torr). Since the pH of the solvent can seriously effect the release of the bioactive material, the pH is recorded at the time each sample is analyzed. Any significant change is an indication that the release mechanism might have changed and leads to suspicion of data.

After shaking the sample, an aliquot of the solvent is withdrawn for analysis at 24 ± 5 h, 3 and 7 ± 1 day, 10, 14, 21, 29, and 60 ± 3 days. The volume of the aliquot is selected to yield maximum analytical sensitivity (i.e., 200 mL Temephos, 25 mL for an organotin compound, and 10 mL for 2,4-D acid). The aliquot is transferred to a separatory funnel and the time recorded; this is the exposure time used in the calculations.

The remainder of the solvent is withdrawn and discarded. The CRF and container are allowed to drain for 5 min, and the CRF is resubmerged in 1.000 L of solvent, shaken, and replaced on the storage shelf until the time for the next analysis. The analytical methods for the various bioactive materials have been described in the literature.[5,8-10]

Five different aqueous systems have been successfully used for these studies: distilled water, pH 3.5 acetate buffer, pH 4.5 citrate buffer, pH 6.8 phosphate buffer, and pH 9.3 ammonia buffer.[7]

Three dependent calculations were performed on the data: (a) quantity of released bioactive material per mL (g/mL), (b) accumulative percent of bioactive material obtained for each time frame, and (c) accumulative percent of bioactive material obtained for time$^{1/2}$. All three values are plotted to determine the type of release.

RESULTS

Three types of CRF release systems have been observed in aqueous media: (1) a concentration-dependent release system, (2) a time-dependent release system, and (3) a failure system. The emission rate of the bioactive material is primarily dependent upon the polymer matrix, porosigen, coleachant, and water quality and to a much less degree upon the properties of the bioactive material.

Concentration-Dependent Release System

Two types of concentration dependent release rates were observed: type IA (Fig. 1) and type IB (Fig. 2). In both, a plot of concentration vs. time for a concentration-dependent release system indicates a steady state condition within the time frame of the study. In this release system, the concentration of the bioactive material reaches a limiting value and remains at or near that value even though the solvent change rate varies. A type IA release system yields a series of parallel release curves[1] (Fig. 1) when the sample size is changed whereas a type IB system yields the same concentration limitation regardless of the
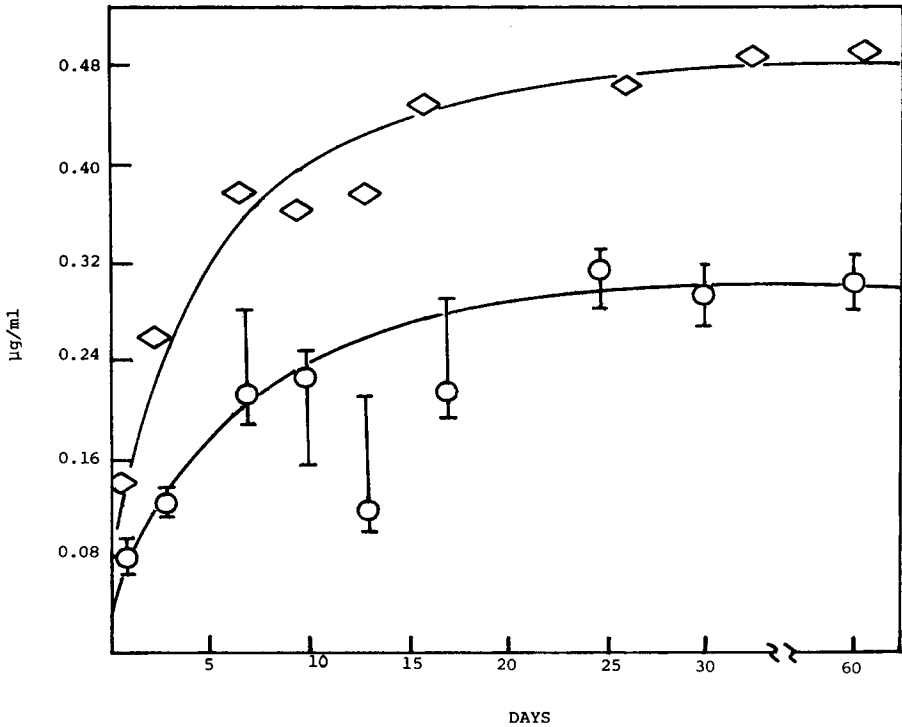
Fig. 1. Type IA release system. 0.149 g (O) and 0.309 (◇) of 20% TBTF in low-density polyethylene; theoretical Life = 735 days; TBTF = tri-n-butyltin fluoride.

sample size.

The type IA emission system may exhibit an unusually large value at the first day analysis. In many CRF, the bioactive material diffuses to the surface during storage and is "washed" off when dispersed in the solvent. Since the solvent is removed after the aliquot is withdrawn on the first day, the excess bioactive material is removed from the solution, and the system becomes diffusion controlled for the next analysis. In many cases where no concentration occurs on the surface, the initial value may be low and gradually increases as the sample reaches equilibrium with its environment (Fig. 1). The type IA system reaches a steady state when the emission rate of the bioactive material is equal to the degradation rate or equal to the removal rate of the material by the solvent. When different size samples are used, different steady states are achieved.

A type IB release system is less common than a IA. In this case, the emission curve appears to be the same as observed for a IA system; however, the mechanism is different. In a IB system the release rate of the bioactive material is much greater than the degradation rate or the solvent change rate, and a concentration-dependent curve occurs because the solvent becomes saturated with the bioactive material. At saturation the CRF achieves a dynamic equilbrium with the solvent and the concentration of bioactive material in the solvent does not change (Fig. 2). A type IB system yields the same saturation concentration when different size CRF samples are studied. The life of a type IB CRF is almost entirely dependent upon the frequency of the solvent change.
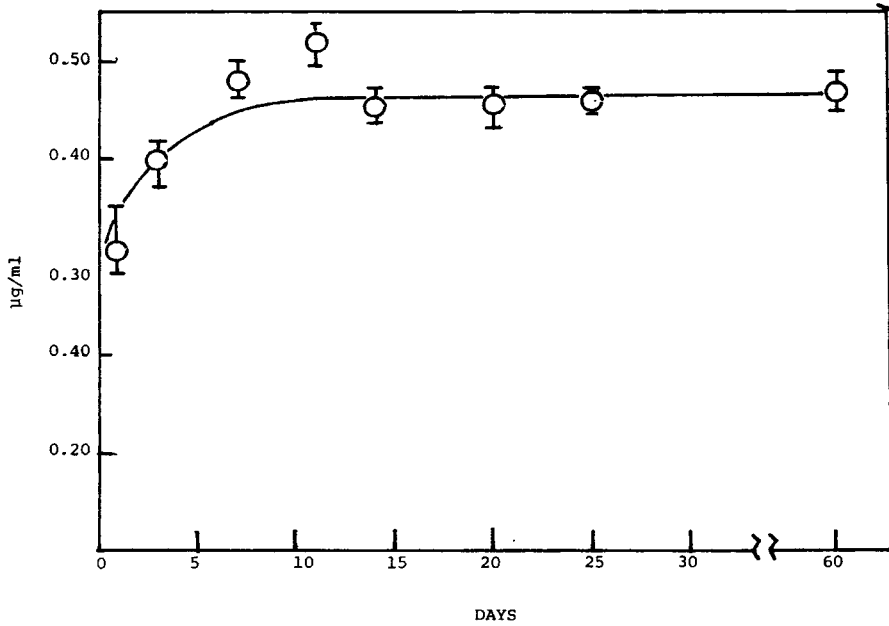
Fig. 2. Type IB release system. 0.458 g of 10% TBTO in a silicone polymer; theoretical Life = 916 days; TBTO = bis(tri-n-butyltin) oxide.

Time-Dependent Release System

Two time-dependent release systems have been observed: type IIA (Fig. 3) and type IIB (Fig. 4). When concentration is plotted vs. time in a time-dependent release system, each subsequent concentration is greater than that obtained for the previous analytical result. The CRF may exhibit "wash off" as described
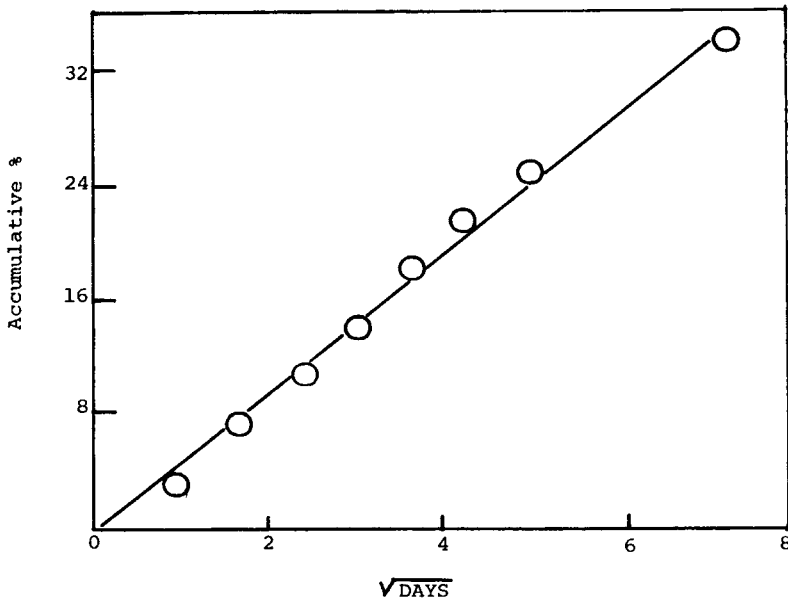

Fig. 3. Type IIA release system. 1.01 g of 25% 2,4-D acid in low-density polyethylene + iron oxide; theoretical Life = 325 days.
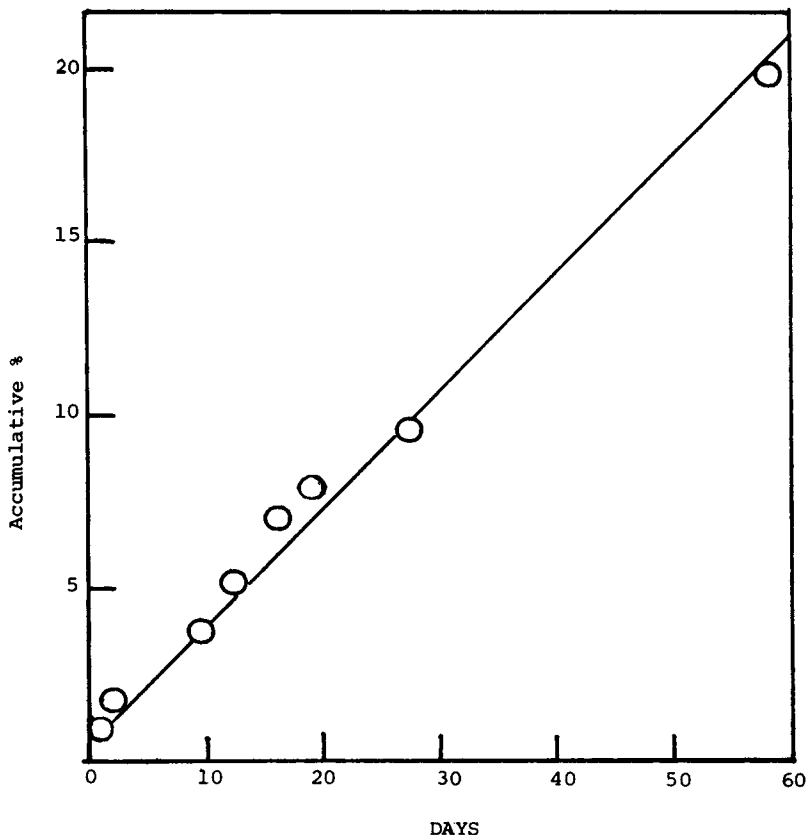
Fig. 4. Type IIB release system. 0.205 g of 20% TBTF in ethylene vinyl acetate; theoretical Life = 290 days; TBTF = tri-n-butyltin fluoride.

above or low values[11] when little or no concentration occurs on the surface of the CRF. A time-dependent release system occurs when the bioactive material diffuses into the solvent at a faster rate than it either degrades or the solvent is exchanged. When accumulative percent of bioactive material is plotted against time, a straight line is obtained for a zero-order release system (Fig. 4). This is referred to as a type IIB system and occurs when the release of the bioactive material is constant at all times and the degradation is negligible between analytical sampling.

A more frequent occurrence is a type IIA system which yields a straight line when the accumulative percent is plotted against $t^{1/2}$. Since most controlled release systems can be explained by classical diffusion equations,[12–15] where the rate of release is proportional to the complimentary error function, the type of release would be expected to be the most prevalent.

Failure Systems

There are two types of failure release systems: type IIIA (Fig. 5) and type IIIB (Fig. 6). The term failure is used because of the lack of a better term.

A failure system is characterized by a release curve whose subsequent analysis was less than the previous analysis. The concentration of bioactive material
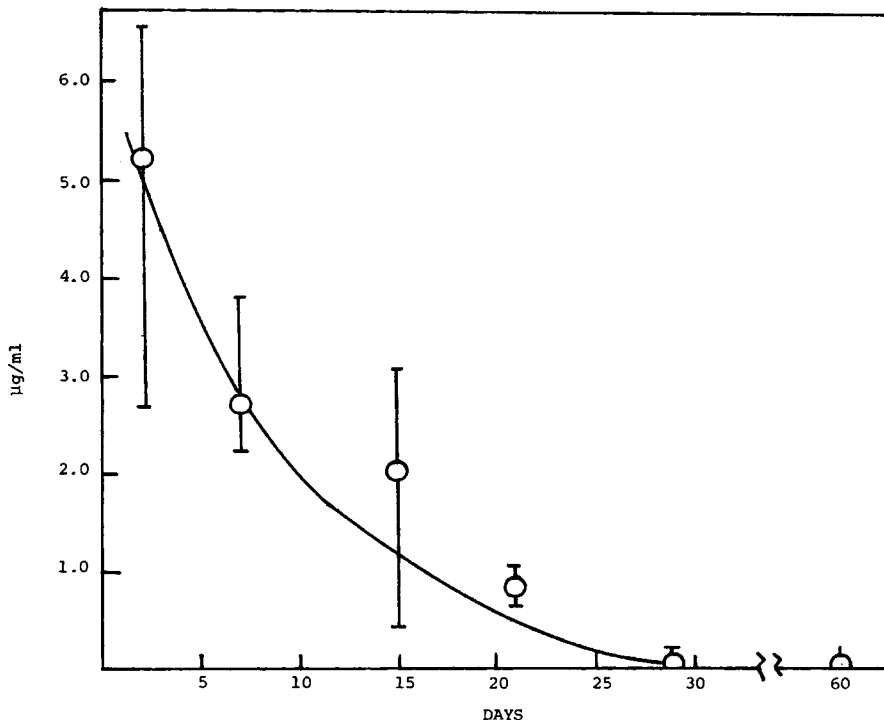
Fig. 5. Type IIIA release system. 2.86 g of 3.5% Dursban in silicone polymer; theoretical Life = 27 days.

usually becomes less than analytically detectable within the time of the study (Fig. 5). A type III release system occurs when the migration of bioactive material into the solvent is less than its degradation or loss through solvent exchanged. A failure system may occur because of incompatibility of the bioactive material and polymer, surface inhibition due to reaction with the porosigen, or lack of mobility of the bioactive material in the CRF.[6,12]

A type IIIA exhibits a smooth decreasing curve. Often, as in the case exhibited in Fig. 5, a plot of concentration vs. $t^{1/2}$ will yield a straight line. The latter plot has little or no advantage over the former since in most cases the CRF has little practical use. A type IIIB release system exhibits first-order degradation kinetics and is characterized by a plot of log concentration vs. time (Fig. 6). A type IIIB system is rarely observed and is probably due to concentrating of the bioactive material about the porosigen and lack of diffusion in the polymer matrix.

DISCUSSION

All CRF eventually fail. From a practical point, they are usually designed for a specific life, but since the life of many CRF are quite long (i.e., 5 months for a flea collar or one season, 6 months, for a mosquito larvicide), some rather simple method is needed to identify the life of the CRF and its effectiveness in the environment. The current classification of release systems is an attempt to do this, and from the classification a theoretical life can be predicted.
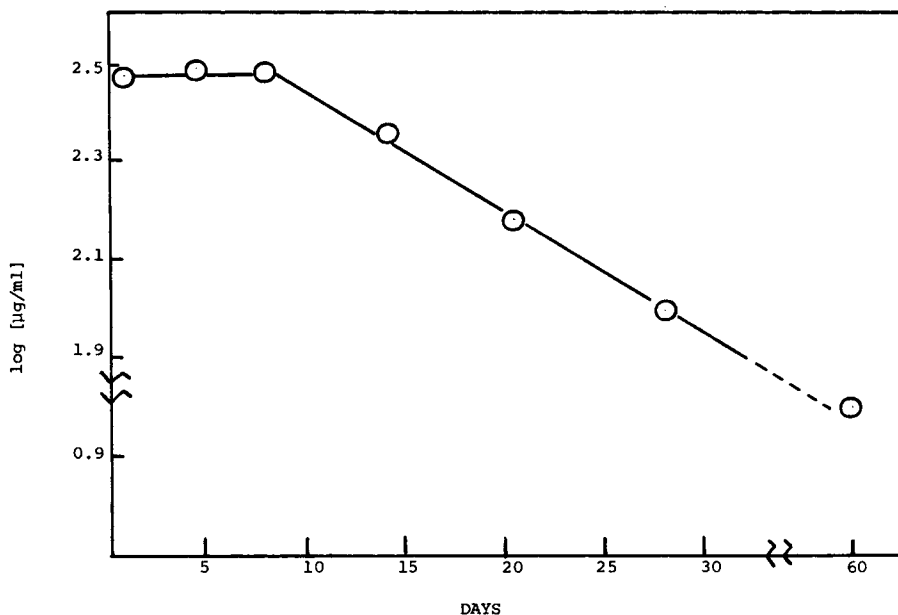
Fig. 6. Type IIIB release system. 1.37 g of 7.2% temphos in polyethylene; theoretical life = 147 days.

Theoretical Life

The theoretical life of a CRF is the life expectancy of the formulation under ideal conditions and is based on the assumption that the bioactive material will migrate from the formulation into the solvent by the same mechanism over its entire life. The real life of a CRF can only be determined by repeat challenge bioassay in the field and may be significantly different than the theoretical life. However, it is hoped that calculating the theoretical life from the laboratory data will give formulators some guide to the usefulness of their creation.

In many systems the analysis of the bioactive material on day 1 is nonrepresentative of the system. As such the data for day 1 is normally deleted before calculating the theoretical life. Furthermore, the theoretical life is dependent upon the type of release system, and the release system must be determined before a theoretical life can be determined.

In a concentration dependent system (either type IA or IB), the emission rate attains a steady state in 3–20 days and the life of the CRF can be calculated from eq. (1). Since the life of a type I CRF is dependent upon the sample size, this equation is written for 1.000 g of CRF:

$$\text{theoretical life} = \frac{\% * (n - 1)}{\sum\limits_{3}^{n} \lambda g_i} \qquad (1)$$

where % is the amount of bioactive material in the CRF, n is the number of days in the study, and λg_i is the quantity of bioactive material in μg/mL found for each analysis.

Since type II release systems yield straight lines, the theoretical life can be determined from the slope of the line as expressed in eq. (2) for type IIA and eq. (3) for type IIB:

$$\text{theoretical life} = \left(\frac{3.56 - 3.56\,y_3}{Y_{28} - Y_3}\right)^2 \tag{2}$$

$$\text{theoretical life} = \frac{2500 - 25\,y_3}{Y_{28} - Y_3} \tag{3}$$

where Y_3 and Y_{28} are the accumulated percents of bioactive material released by days 3 and 28, respectively.

The theoretical life for a type III system can be determined from the curve as indicated in Figure 5 or from eq. (4) for a type IIIA system if straight line is obtained for a concentration versus $t^{1/2}$ and from the first-order rate equation [eq. (5)] for a type IIIB if it is assumed that effective release of bioactive material ceases when the concentration is 0.1% of the initial emission concentration:

$$\text{theoretical life} = \left(\frac{2.16\,Y_1}{Y_{10} - Y_1} + 1\right)^2 \tag{4}$$

where Y_1 and Y_{10} are the concentrations of bioactive material on days 1 and 10, respectively.

$$\text{theoretical life} = 1 - \frac{3\,(D_1 - D_2)}{\log\,(Y_1/Y_2)} \tag{5}$$

where D_1 and D_2 are convenient times from the curve and Y_1 and Y_2 are the corresponding concentrations.

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