Zero-Order or First-Order Release Kinetics of Water-in-Oil-in-Water (W/O/W) Multiple Emulsions of Lipiodol Dependent on the Types of Surfactants

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The mechanism of dye release from the water-in-oil-in-water (W/O/W) multiple emulsions of lipiodol was investigated through dialysis. The oily phase containing hydrophilic HCO-60 exhibited bi-phasic zero-order release kinetics, but the oily phase containing both HCO-60 and lecithin indicated one-phasic zero-order release kinetics. Moreover, the higher the concentration of HCO-60, the slower the release rate of dye. When the oily phase contained other hydrophilic surfactants (Tween 80, Brij 35 and Pluronic F-88) or hydrophobic surfactants (Span 80 and lecithin), these multiple emulsions showed a first-order release kinetic. We also found that the release rate of multiple emulsions with hydrophobic surfactants was slower than that of the multiple emulsions with hydrophilic surfactants. The release kinetic of multiple emulsion was a complicated system.

Keywords release kinetic; multiple emulsion; zero-order; first-order; lipiodol; HCO-60

Introduction

The potential use of water-in-oil-in-water (W/O/W) multiple emulsions for special pharmaceutical needs such as prolonged drug release, drug over-dose treatment, drug taste masking and cancer chemotherapy has been investigated.[1-5] Multiple emulsion is a thermodynamically unstable system, so the formation of long-term stabilized multiple emulsions is difficult.

In general, internal and external aqueous phases of multiple emulsions are separated by an oil layer and require at least two stabilizing surfactants for their formation and stability. To form the primary W/O emulsion a surfactant with a low hydrophilic lipophilic balance (HLB) is used, and for the second emulsification a surfactant with higher HLB is needed.[6] However, we have found that lipophilic Span 80 (HLB: 4.3) in the oily phase is the optimal surfactant for olive oil-type multiple emulsion according to the above rule (olive oil is a light oil, specific gravity: 0.912); but hydrophilic HCO-60 (HLB: 14) in the oily phase is more suitable for lipiodol-type multiple emulsions which contradicts the above rule (lipiodol oil is a heavy oil, specific gravity: 1.28).[7,8] We have also found that the hydrophilic HCO-60 can influence the pharmacokinetics and targeting properties of the lipiodol-type multiple emulsions containing an anticancer drug.[9] A phase inversion from W/O emulsion to O/W emulsion may occur when a hydrophilic surfactant is initially introduced into the oil phase.[10] However, we did not find this inversion in our experiments even though HCO-60 was incorporated into the lipiodol phase. The reason for this behavior is unclear.

Many studies have focused on the formation and practical aspects of emulsions, but little work has been done on the release mechanism of a drug from W/O/W multiple emulsions, particularly on the drug release from multiple emulsions of the sinking (heavy oil) type. Based on our previous investigations,[7-9] several hydrophilic and hydrophobic surfactants were used in the heavy oil phase, and their release kinetics were investigated.

Materials and Methods

Materials Food dye (Red No. 2, Amaranth) as a marker was purchased from Kiriya Chem. Co., Japan. Lipiodol was obtained from Guerbert Lab., France. Surfactants such as HCO-60 (polyoxyethylene hydrogenated castor oil, HLB: 14), Span 80 (sorbitan monooleate, HLB: 4.3), Tween 80 (polyoxyethylene (20) sorbitan monooleate, HLB: 15), Brij 35 (polyoxyethylene (23) lauryl ether, HLB: 16.9), Pluronic F-68 and 88 (polyoxyethylene–polyoxypropylene block copolymer, HLB: 29 and 28, respectively), and lecithin (type X—E from dried egg yolk,

TABLE I. Formulas of the W/O/W Multiple Emulsions with Lipiodol and Different Types of Surfactants

Formulations		Oily phase						External aqueous phase F-68 (100 mg)
		Lecithin	Span 80	Tween 80	Brij 35	F-88	HCO-60	
I	(○)	+(50 mg)						+
II	(■)		+(30 mg)					+
III	(●)		+(100 mg)					+
IV	(●)			+(30 mg)				+
V	(▲)			+(100 mg)				+
VI	(◐)				+(30 mg)			+
VII	(◭)				+(100 mg)			+
VIII	(◧)					+(30 mg)		+
IX	(◐)					+(100 mg)		+
X	(◑)						+(30 mg)	+
XI	(◭)						+(50 mg)	+
XII	(◑)						+(100 mg)	+
XIII	(◨)						+(100 mg)	−
XIV	(△)	+(50 mg)	+(50 mg)					+
XV	(□)	+(50 mg)					+(50 mg)	+

phosphatidylcholine content: 60%) were obtained from Nikkol Chem. Co., Japan and Sigma Chem. Co., U.S.A. All the other chemicals are of reagent grade.

Preparation of the W/O/W Multiple Emulsions of Lipiodol with Various Surfactants An aqueous solution (0.6 ml) containing the dye of Food Red No. 2 (31.67 mg/ml) was introduced into 2 ml of lipiodol solution containing various amounts of surfactant, as listed in Table I, and was emulsified by a homogenizer in a 75 °C water bath for 1 min to prepare a W/O emulsion. An outer aqueous solution (5 ml) with Pluronic F-68 (100 mg) was then introduced into the W/O emulsion and the whole mixture was vibrated with a vibrator mixer for 20 s to prepare the W/O/W multiple emulsions. All the formulations are tabulated in Table I.

Release Rate Studies by Dialysis Two milliliters of the W/O/W multiple emulsions were pipetted into the dialyzer tubing (2 × 3.7 cm, A. H. Thomas Co., U.S.A.) and dialyzed in 200 ml of 0.9% NaCl solution at 37±0.5 °C. The dialyzed solution was stirred with a magnetic stirrer. Ten milliliters of the dialyzed solution was withdrawn at prescribed intervals (0.083, 0.167, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 22.0, 23.0, 24.0 h), and 10 ml of the fresh 0.9% NaCl solution was added immediately to maintain the original volume. The concentrations of the dye dialyzed were analyzed spectrophotometrically at 510 nm (UV-320, Jasco, Japan). All the experiments were carried out by triplicate determinations, then the mean and standard deviation were calculated.

Results and Discussion

Drug release from W/O/W multiple emulsions by dialysis may be simply divided into two steps: first, the drug is released into the external aqueous medium inside the dialysis bag; second, the drug inside the dialysis bag is transported across a dialysis membrane, as illustrated in Chart 1. In the first step, drug release is a complicated mass transfer process across interfaces.[11] If the multiple emulsions could be maintained in a stable for a sufficient length of time, the drug transfer across the oily dispersed droplets into the external aqueous phase was rate-determining in the overall release processes.[12]

Figure 1 shows the profile of dye released from the W/O/W multiple emulsions of lipiodol with different types of surfactants in the oily phase. Three release patterns were clearly demonstrated. The first release pattern showed a rapid release behavior with first-order release kinetics. The scond pattern consisted of an initially rapid release followed by a steady release rate according to the zero-order release kinetics but with a bi-phasic release profile. The third release pattern showed one-phasic zero-order release kinetics. Formulations containing HCO-60 as an emulsifier in the oily phase were zero-order release models, but other formulations were first-order release models. Since the multiple emulsions of Lipiodol could be kept stable for at least 8 h, the theory of drug release kinetic from microspheres might be applied to a multiple emulsion.[13] The release patterns of dye from formulations X—XIII showed a biphasic model with zero-order release kinetics. Thus, a release rate constant could be obtained in each phase. The rate constant of the terminal phase (k_{m_2}) was obtained from the following equation.[13]

$$C_1 = \frac{k_{m_2}}{V_T}\left[t - \frac{1}{K_{cv}}(1 - e^{-K_{cv}t})\right] + \frac{C_2^0 V_2}{V_T}(1 - e^{-K_{cv}t}) \quad (1)$$

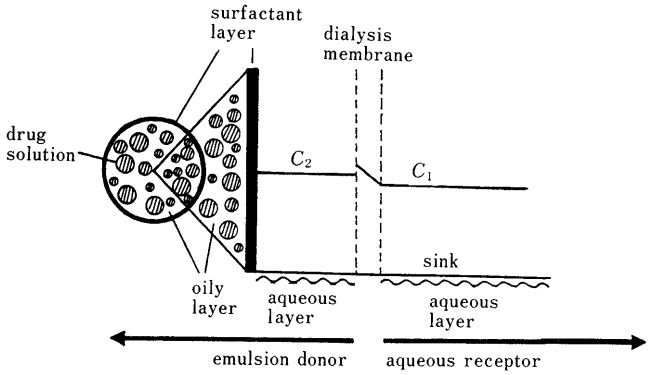

Chart 1. Schematic Presentation of Release Process of Dye from W/O/W Multiple Emulsions

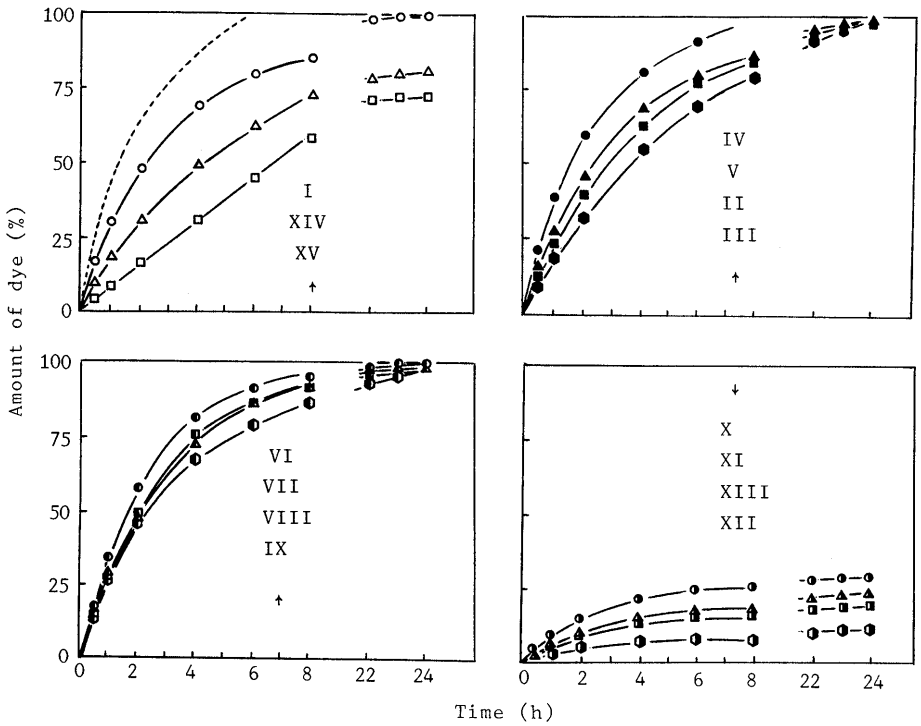

Fig. 1. Release Profiles of Dye from Multiple Emulsions of Lipiodol with Different Surfactants

Key: see Table I. Broken line: unemulsified dye solution. Each point represents the mean of three determinations.

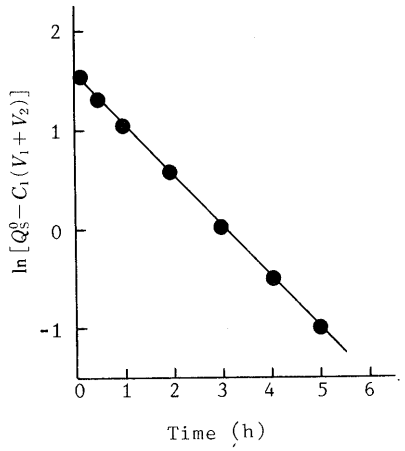

Fig. 2. Plot of $\ln[Q_s^0 - C_1(V_1+V_2)]$ *versus* Dialysis Time

TABLE II. Release Rate Constants of Dye from Multiple Emulsions Determined by Dialysis

Formulations	k_{m_2} (mg/h)	r	k_{m_1} (mg/h)	r
(A) Zero-order release kinetics				
X	0.339	0.896	0.008876	0.997
XI	0.309	0.917	0.007434	0.904
XII	0.189	0.954	0.006626	0.967
XIII	0.349	0.902	0.007619	0.999
XV	—	—	0.366	0.985
(B) First-order release kinetics (k'_m)				
I	0.257	0.996		
II	0.209	0.995		
III	0.166	0.995		
IV	0.396	0.999		
V	0.271	0.998		
VI	0.356	0.996		
VII	0.326	0.999		
VIII	0.337	0.996		
IX	0.244	0.997		
XIV	0.146	0.997		

r, relation coefficient.

where C_1 is the dye concentration outside the dialysis bag at time t. V_T is the total volume of dissolution medium outside (V_1) and inside (V_2) the dialysis bag, $V_T = V_1 + V_2$. K_{cv} is the constant obtained from the dialysis of an aqueous solution of the dye by plotting the $\ln [Q_s^0 - C_1(V_1+V_2)]$ *versus* time, as shown in Fig. 2. The value of K_{cv} is $0.51527\ h^{-1}$ ($r = 0.999$). Q_s^0 is the total amount of dye present in the system. C_2^0 is the concentration of dye inside the dialysis bag at zero time.

If the dialysis time is long enough and K_{cv} is independent of the dye concentration, Eq. 1 will be reduced to Eq. 2.

$$C_1 = \frac{k_{m_2} t}{V_T} - \left(\frac{k_{m_2}}{V_T K_{cv}} - \frac{C_2^0 V_2}{V_T} \right) \tag{2}$$

The terminal release rate constant (k_{m_2}) could be determined from the terminal slope of a plot of C_1 *versus* time, and the result is listed in Table II. The initial release rate constant (k_{m_1}) was estimated from the methods of residuals,[14] *i.e.*, the initial slope of a plot of Q_m *versus* time; where $Q_m = Q_s^0 - C_2 V_2 - C_1 V_1$, and Q_m is the amount of dye remaining inside the multiple emulsions at a certain time. The resulting rate constant (k_{m_1}) is also indicated in Table II. Clearly, the release rate constant was reduced with an increase in HCO-60 concentration. The higher the concentration of HCO-60, the slower the release rate of the dye. This suggests that HCO-60 is a special emulsifier controling dye release. The external aqueous phase of multiple emulsions with or without Pluronic F-68 also plays a key role. The release rate of formulation XIII (100 ml HCO-60/—) was similar to that of formulation X (30 mg HCO-60/100 mg F-68), but was two-fold higher than that of formulation XII (100 mg HCO-60/100 mg F-68). This implies that the surfactant contained in the external aqueous phase also plays an important role in prolonging the release of dye from a multiple emulsion.

When lecithin was added into the oily phase as a cosurfactant which previously contained 50 mg of HCO-60 (formulation XV), the release pattern became apparently different from that of formulations X—XIII. Formulation XV showed an one-phasic zero-order release behavior. When the release rate at the initial stage of formulation XV was comparable to that of formulation XIII, there was no burst effect found in the release profile of formulation XV when lecithin was added into the oily phase. The initially delayed action might be due to the formation of a complex interfacial film between Pluronic F-68 and phospholipid molecules at oil–water interfaces,[15] making C_2^0 equal to zero. When C_2^0 is equal to zero, Eq. 1 can be reduced to Eq. 3.

$$C_1 = \frac{k_{m_2}}{V_T}\left[t - \frac{1}{K_{cv}}(1 - e^{-K_{cv}t}) \right] \tag{3}$$

where k_{m_2} is determined from the plot of C_1 *versus* $(1/V_T[t-(1/K_{cv})(1-e^{-K_{cv}t})]$, and the result is tabulated in Table II. Figure 1 apparently indicates that the release rate of formulation XV was faster than that of formulations X—XIII, but slower than in formulation I, which suggests that HCO-60 could be used as a release control.

Other formulations without HCO-60 showed release profiles with first-order release kinetics (Fig. 1). For first-order release kinetics of W/O/W emulsions,[13] the concentration of dye outside the dialysis bag (C_1) may be calculated according to the following equation.

$$C_1 = \frac{C_2^0 V_2}{V_T} + \frac{Q_m^0}{V_T} + \frac{k_c Q_m^0 e^{-k'_m t}}{(k'_m - K_{cv}) V_1 V_2} \tag{4}$$

where Q_m^0 is the total amount of dye associated with the multiple emulsions at time zero; k_c is the apparent permeability constant of the dialysis bag obtained from $k_c = (K_{cv}) V_1 V_2 / V_T$; and k'_m is the first-order release rate constant. If $K_{cv} > k'_m$ and dialysis time is long, Eq. 4 can be reduced to Eq. 5.

$$\ln\left[\frac{C_2^0 V_2}{V_T} + \frac{Q_m^0}{V_T} - C_1 \right] = -k'_m t + \ln \frac{k_c Q_m^0}{(K_{cv} - k'_m) V_1 V_2} \tag{5}$$

Since $Q_s^0 = C_2^0 V_2 + Q_m^0$, Eq. 5 is changed into Eq 6.

$$\ln\left[\frac{Q_s^0}{V_T} - C_1 \right] = -k'_m t + \ln\left[\frac{k_c Q_m^0}{(K_{cv} - k'_m) V_1 V_2} \right] \tag{6}$$

The values of the first-order release rate constant are listed in Table II. The data suggests that the release rate was slower in multiple emulsions with hydrophobic surfactants (formulations I—III and XIV) than in multiple emulsions with hydrophilic surfactants (formulations IV—IX). Moreover, it was also slower in multiple emulsions with

cosurfactants than in multiple emulsions with a single surfactant. Multiple emulsions obviously are a much more complicated system than microspheres, since the types of surfactant and different oily phases play an important role in these systems.

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