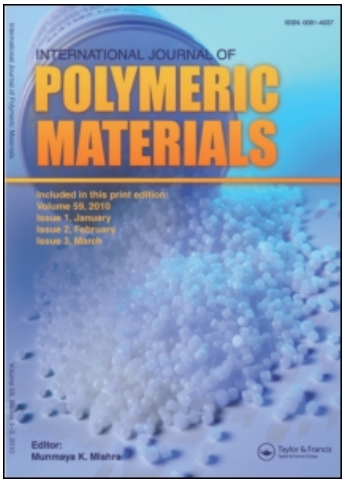


**International Journal of Polymeric Materials**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713647664

# A Model of Controlled Release of Polymer-dispersed Drug Systems Containing Regulatory Particles

Jan-Chan Huang[a]
[a] Plastics Engineering Department, University of Massachusetts Lowell, Lowell, MA, USA

**To cite this Article** Huang, Jan-Chan(2001) 'A Model of Controlled Release of Polymer-dispersed Drug Systems Containing Regulatory Particles', International Journal of Polymeric Materials, 49: 3, 367 — 377
**To link to this Article: DOI:** 10.1080/00914030108039787
**URL:** http://dx.doi.org/10.1080/00914030108039787

*Intern. J. Polymeric Mater.*, 2001, Vol. 49, pp. 367–377
Reprints available directly from the publisher
Photocopying permitted by license only



# A Model of Controlled Release of Polymer-dispersed Drug Systems Containing Regulatory Particles

JAN-CHAN HUANG*

*Plastics Engineering Department, University of Massachusetts Lowell, Lowell, MA 01854, USA*

*(Received 1 September 1999)*

A model of controlled release systems using a polymer matrix with mixtures of dispersed drug particles and regulatory particles is considered. The regulatory particles are fillers that release at a slower rate than the drug and open more paths for the passage of the drug. Mathematical analysis shows that both the drug and regulatory particles have Fickian diffusion behaviors. The use of regulatory particles increases the release rate and can make the system responsive to physiological change.

*Keywords*: Drug delivery; Controlled release; Diffusion; Polymer



## INTRODUCTION

Many therapeutic drugs work best when the drug is maintained at a constant level. In the 1960's, the method of "controlled" drug delivery came into being. By incorporating drugs in polymers or placing a drug solution in a pump, drug release was possible for extended periods of time [1]. In a polymer-drug system, the rate of the release is determined by the properties of the drugs and polymers, and by the mechanisms of releasing. There are several general types of polymeric drug release mechanisms [2]: diffusion, chemical control, solvent activation, magnetism [3] and ultrasound [4].

*e-mail: Jan_Huang@uml.edu

The diffusion process is basically the migration of the drug from its initial position inside the polymer to the polymer's outer surface and into the human body. Diffusion systems can be classified as either membrane-reservoir or matrix systems. The advantage of the membrane-reservoir system is that zero-order release kinetics can be reached. However, there are many disadvantages to the system. It is not useful for the delivery of high molecular weight drugs. The implant must be surgically removed if it is not biodegradable. If a leak occurred the entire incorporated drug would be released quickly. This could be a dangerous situation. Also, this type of system is more expensive than others. Matrix systems consist of uniformly dispersed drug particles in a solid polymer. These systems are prepared by mixing finely powered drug with a polymer solution. The mixture is then placed in a mold and allowed to dry. The advantages of the matrix systems are that they are easy to make and can be made to release high molecular weight polypeptides and other macromolecules.



There are different diffusion mechanisms which exist for matrix systems: dissolved drug diffusing through the polymer, dispersed drug diffusing through the polymer, and dispersed drug diffusing through channels [5]. In the first case, the drug is molecularly dissolved in the polymer matrix, similarly to plasticizer or solvent molecules, and the drug diffusion occurs *via* a solute-diffusion mechanism. This approach is limited to small molecules that are miscible with the polymer and can diffuse through the polymer. In case two, the drug with limited solubility in polymers is dispersed in the polymer matrix and diffusion occurs *via* a solution-diffusion mechanism after contacting water. This approach is also limited to small molecules that can diffuse through the swollen polymer matrix. In case three [5], the drug is dispersed in the polymer matrix as a separate phase and diffusion occurs through water filled pores created by the dissolution of the drug particles. This approach was successfully used for the release of protein molecules using a polymer matrix [2–8].

Ethylene vinyl acetate (EVA) copolymer is the polymer of choice for dispersed drug systems because of its good solubility in organic solvents and because it has been approved by the Food and Drug Administration for use in several human controlled release systems. In the most common procedure, EVA is dissolved in methylene chloride to make a polymer solution. Polypeptide drug powder is suspended in

the polymer solution, and the mixture is poured into a cooled mold. The suspension congeals in the mold, and the solvent is removed in vacuum. In the end a polymer matrix with a high loading of polypeptide filler is prepared.

Since the macromolecular drug particles are insoluble in polymer and separated randomly, at low loading some particles are completely surrounded by the polymer and are trapped and unable to release. At sufficiently high loading the drug particles contact each other and extend from the exterior surface deep into the matrix. These clusters result in connected pore space upon dissolution of the filler particles. Therefore, all particles can be released. Experimental studies on release of macromolecular drugs from polymer matrices were conducted by Langer and coworkers [2–8]. The results showed Fickian diffusion behaviors with an apparent diffusivity which depends on the particle size, nature of the drug, and percentage loading. The characteristic of Fickian behavior is that the diffusion length increases as the release takes place and the cumulative release increases in proportion to $\sqrt{t}$ in the early state of release while the diffusion rate decreases in proportion to $1/\sqrt{t}$.



One way to improve the release is a method to reduce the diffusional resistance as the release takes place. It is proposed in this study to mix drug particles with a different type of particles which release at a slower rate than the drug to open additional paths and reduce the diffusional resistance. As drug particles dissolve and release, the water-drug interface moves into the polymer. A new interface of water-regulatory particle is also created and moves behind the water-drug interface. By opening additional paths through the release of the regulatory particles, the effective diffusional resistance of the drug molecules will be lower than the case without the additional paths.

The preparation of this system requires careful balance of the amount and size of the particles. It has been reported that the release rate increases when the particle size is increased [7]. When the loading of particles was above 50 wt%, nearly complete release was observed [8]. The use of drug particles therefore must be near 50% with proper particle size distribution. Additional regulatory particles can be added into the system without affecting the packing density if the diameter of the new particles differ by a factor of more than 2.42 [9]. In this case, small particles can fill into the voids between the large particles without disrupting the packing order.

## MATHEMATICAL MODEL

### Release of Single Filler

When a polymer-dispersed filler system contacts water the filler particles on the exterior surface dissolve first and the water-filler interface starts to move into the polymer. At the interface, the concentration of the filler molecules in water is constant as a saturated solution at the test temperature. At the exterior surface of the polymer the concentration of the filler molecules in solution is zero because the filler molecules are carried away by body fluids. The diffusion of the filler molecules in the channel created by the dissolution of the filler particles in the polymer can be considered to be the rate-determining step. A quasi-equilibrium process can be used to determine the concentration of filler molecules in the polymer. Using rectangular coordinates the concentration profile is a linear function of depth from the surface, $z$:

$$C = zC_o/z_f \tag{1}$$

where $C_o$ is the saturation concentration of the filler in water and $z_f$ is the depth of the water-filler interface below the exterior surface of the polymer.

The flux is:

$$-J = D_f \frac{\Delta C}{\Delta z} = D_f C_o/z_f \tag{2}$$

where $D_f$ is the apparent diffusion coefficient of the filler molecules through the channels in the polymer. The flux is also related to the rate of advancement of the water-filler interface by:

$$-J = \rho_f \frac{dz_f}{dt} = D_f C_o/z_f \tag{3}$$

where $\rho_f$ is the bulk density of the filler incorporated in the polymer matrix. With the initial condition $z = 0$ when $t = 0$, Eq. (3) can be solved to give:

$$z_f = \sqrt{2\zeta t} \tag{4}$$

where $\zeta = D_f C_o / \rho_f$. This is a Fickian type result. The cumulative amount of release and the erosion length increase in proportion to $\sqrt{t}$ and the flux decreases in proportion to $1/\sqrt{t}$. The decrease of the flux occurs because the length of diffusion increases as the release takes place.

## Release of the Drug and Regulatory Particles

A new system of polymer-drug system is considered in this study, which contains dispersed drug particles and a second filler called regulatory particles. The regulatory particles and drug particles are mixed uniformly in the polymer matrix. The regulatory particles dissolve at a slower rate than the drug. This has the advantage of opening more diffusion paths and reducing the diffusional resistance of the drug molecules from the water-drug interface to the exterior surface. Another advantage that is unique to the use of a regulatory filler is that it can be selected to respond to some physiological changes. For example, diabetic patients in acidosis will have low blood pH. If a calcium salt of a weak acid, such as calcium carbonate, is used as the regulatory particles, it will dissolve more quickly in acid condition and release more drugs into body fluids.

Figure 1 shows the schematic figure of a polymer drug system with regulatory particles. The regulatory particles dissolve at a slower rate than the drug. The distance that the regulatory particles have dissolved is $z_1$ and the similar distance for the drug particles at the same time is $z_2$. Zone I designates the region where both drug particles and regulatory particles have dissolved. Zone II designates the region where the drug particles have dissolved but the regulatory particles have not dissolved. The location of $z_1$ is the boundary between zone I and zone II. Note that in zone I and zone II the concentrations of the drug are both linear but the slope is lower in zone I because diffusivity is higher there. Although the dissolution of drug particles exposes some regulatory particles in zone II, the regulatory particles are not dissolved in zone II because the solution is considered to be a saturated solution of the regulatory particles. In zone I the concentration of dissolved regulatory particles is also linear.

The distance $z_1$ is determined by a relation similar to Eq. (4) with parameter $\zeta$ calculated based on the properties of the regulatory

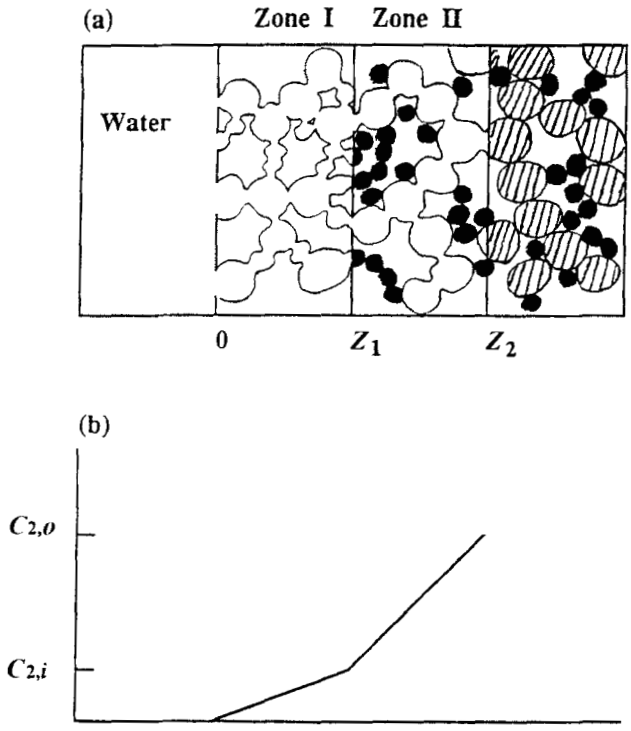


FIGURE 1 Schematic illustration of the system (a) and concentration of the drug (b). In (a) black areas are regulatory particles, shaded areas are drug particles, and the open areas are the channels created by dissolution of particles.

particles in zone I:

$$z_1 = \sqrt{2\alpha t} \tag{5}$$

where

$\alpha = C_{1,o} D_{1,I}/\rho_1$

$C_{1,o}$ = the saturation concentration of the regulatory particles.

$D_{1,I}$ = the diffusivity of the molecules of the regulatory particles in zone I.

$\rho_1$ = the density of the regulatory particles initially incorporated in the polymer matrix.

The concentration of drug in the solution has a break between zone I and zone II. Within each zone the concentration is linear and the flux

is the same:

$$-J_2 = D_{2,\mathrm{II}} \frac{C_{2,o} - C_{2,i}}{z_2 - z_1} = D_{2,\mathrm{I}} \frac{C_{2,i}}{z_1} = \rho_2 \frac{dz_2}{dt} \tag{6}$$

where

$C_{2,i}$ = the concentration of the drug at $z_1$.
$C_{2,o}$ = the saturation concentration of the drug.
$D_{2,\mathrm{I}}$ = the diffusivity of the drug in zone I.
$D_{2,\mathrm{II}}$ = the diffusivity of the drug in zone II.
$\rho_2$ = the density of the drug initially incorporated in the polymer matrix.

The above equations can be combined to give:

$$\frac{dz_2}{dt} = \frac{D_{2,\mathrm{II}} D_{2,\mathrm{I}} C_{2,o}}{\left(D_{2,\mathrm{II}}\sqrt{\alpha t} + D_{2,\mathrm{I}} z_2 - D_{2,\mathrm{I}}\sqrt{\alpha t}\right)\rho_2} \tag{7}$$

Let $\gamma = D_{2,\mathrm{I}}/D_{2,\mathrm{II}}$ and $\beta = C_{2,o} D_{2,\mathrm{I}}/\rho_2$, Eq. (7) can be simplified to:

$$\frac{dz_2}{dt} = \frac{\beta}{(1-\gamma)\sqrt{\alpha t} + \gamma z_2} \tag{8}$$

with the initial condition that $z_2 = 0$ when $t = 0$. The parameter $\beta$ is similar to $\alpha$ but represents the corresponding properties of the drug in zone I. Equation (8) is also Fickian and can be solved by assuming the solution with the expression:

$$z_2 = \sqrt{2st} \tag{9}$$

The parameter $s$ is similar to $\alpha$ in Eq. (5). By substituting Eq. (9) into Eq. (8), the following relation is obtained:

$$\sqrt{\frac{s}{\alpha}} = \frac{\gamma - 1}{2\gamma} + \sqrt{\left(\frac{\gamma - 1}{2\gamma}\right)^2 + \frac{\beta}{\alpha\gamma}} = \frac{z_2}{z_1} \tag{10}$$

From Eqs. (5) and (9) the value $\sqrt{s/\alpha}$ also represents the ratio $z_2/z_1$, which is the ratio of erosion length of the drug particles and the erosion length of the regulatory particles. Figure 2 shows the

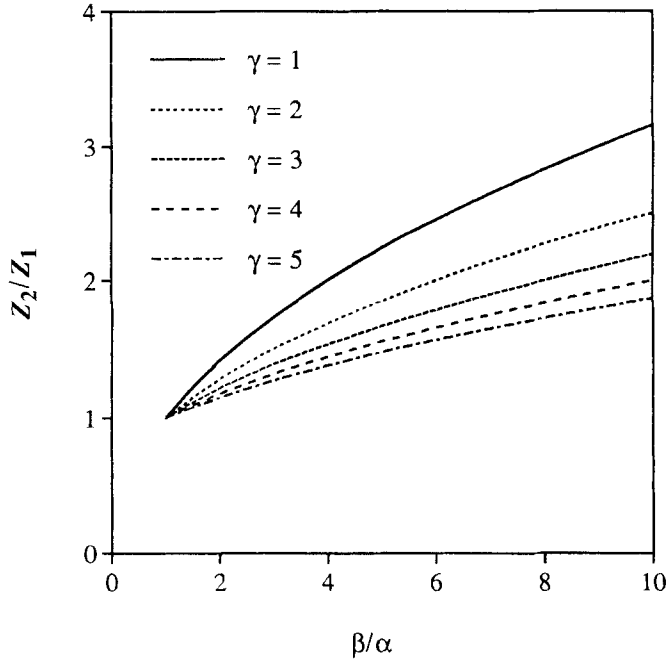


FIGURE 2 The ratio of erosion length of drug and regulatory particles *vs.* $\beta/\alpha$.



relationship between $z_2/z_1$ and $\beta/\alpha$ using $\gamma$ as the parameter. Note that $\gamma$ is the ratio of diffusivity of the drug in zone I *vs.* zone II. The value of $\gamma$ is larger than unity because more passages are available in zone I. It also indicates the relative amount of the regulatory particles in the system. When $\gamma$ is much larger than unity, the amount of drug is less than the regulatory particles. In this case, the release rate of the drug in zone II is slow because of the narrow path, and the thickness of zone II is thin compared to zone I. The ratio $z_2/z_1$ therefore decreases toward unity when $\gamma$ increases as shown in Figure 2. When $\gamma$ decreases toward unity there are few regulatory particles and the ratio $z_2/z_1$ approaches a limit, $\sqrt{\beta/\alpha}$, which depends on the relative release rate of drug and regulatory particles in zone I. When $\beta/\alpha = 1$, Eq. (10) gives $s = \alpha$ and $z_2 = z_1$, which is the case when the drug and the regulatory particles are released at the same rate in zone I. This would make $z_1 = z_2$ and the thickness of zone II equal to zero. It can be seen that in Figure 2 all lines converge at unity when $\beta/\alpha = 1$.

Equation (9) has meaning only when the ratio $s/\alpha$ is greater than unity. If the ratio is less than unity, the drug is released at a rate slower than the regulatory particles. In this case, use of Eq. (4) with appropriate properties is sufficient for the calculation. A value of $s/\alpha$ higher than unity indicates that the drug is released at a higher rate than the rate of the regulatory particles, and $z_2 > z_1$. From Figure 2 it can be seen that when $\beta/\alpha > 1$ and $\gamma > 1$ the value of $\sqrt{s/\alpha}$ is also greater than unity. To obtain a suitable value of $\beta/\alpha$, the best method would be to select a regulatory particle with a proper combination of solubility and diffusivity. The diffusivity of dilute inorganic salt solutions can be estimated from ionic conductance, and does not vary very much [10]. In contrast, a wide selection of solubility is available. Calcium salts generally have low solubility and are safe for implant applications. As mentioned previously the use of calcium carbonate has advantages in that it can also response to acid conditions.

Another way to examine the effect of regulatory particles is to rewrite Eq. (10) as:

$$\sqrt{\frac{s\gamma}{\beta}} = \frac{(\gamma - 1)}{2\gamma}\sqrt{\frac{\alpha\gamma}{\beta}} + \sqrt{\left(\frac{\gamma - 1}{2\gamma}\right)^2 \frac{\alpha\gamma}{\beta} + 1} \tag{11}$$

From Eq. (9) the value $\sqrt{st}$ represents the erosion length of the drug at time $t$ when the regulatory particles are functioning. From the definition of $\gamma$ and $\beta$, $\sqrt{\beta t/\gamma}$ represents the erosion length of the drug if the regulatory particles do not dissolve. Their ratio represents the effect of the regulatory particles in promoting the dissolution of the drug. It can be seen that the values are always higher than unity when $\gamma > 1$ and $\beta/\alpha > 1$, which is the case for practical applications in the system proposed in this study. As mentioned previously, when $\gamma$ is much larger than unity there are more regulatory particles than drug particles and the release is improved. When $\gamma = 1$ the value of $\sqrt{s\gamma/\beta}$ is unity because there is no effect from the regulatory particles. When $\beta/\alpha$ increases above unity, the release rate of the regulatory particles decreases either due to low solubility or due to low diffusivity and the effect of the regulatory particles is also decreased. The maximum value can be obtained at the same $\gamma$ occurs when $\beta/\alpha = 1$. At this case zone I and zone II merge together as previously mentioned. When $\beta/\alpha$ is less than unity the regulatory particles

are released more quickly and will not increase the releasing rate of the drug further. They are shown as the horizontal portion of each curve having $\gamma > 1$. Equations (10) and (11) are not applicable in this case.

The effect of physiological change can also be seen from Figure 3 by a change of the value of $\alpha$. For a polymer matrix system with certain values of $\gamma$ and $\beta/\alpha$ the value of $\sqrt{s\gamma/\beta}$ is determined from Figure 3. If the value of $\alpha$ increases in response to a higher solubility, the ratio of $\beta/\alpha$ will decrease. Following the curve with the same $\gamma$ a new value of $\beta/\alpha$ can be located. Since the slopes of all curves having $\gamma > 1$ decrease continuously, any decrease in $\beta/\alpha$ will increase the value of $\sqrt{s\gamma/\beta}$ and the erosion length of the drug. The drug within this incremental length will release in response to the increase of $\alpha$. This shows the effect of the regulatory particles. The effect, however, is more significant when $\gamma$ is large and $\beta/\alpha$ is not too much higher than unity. These are guidelines for the design of the proposed system.



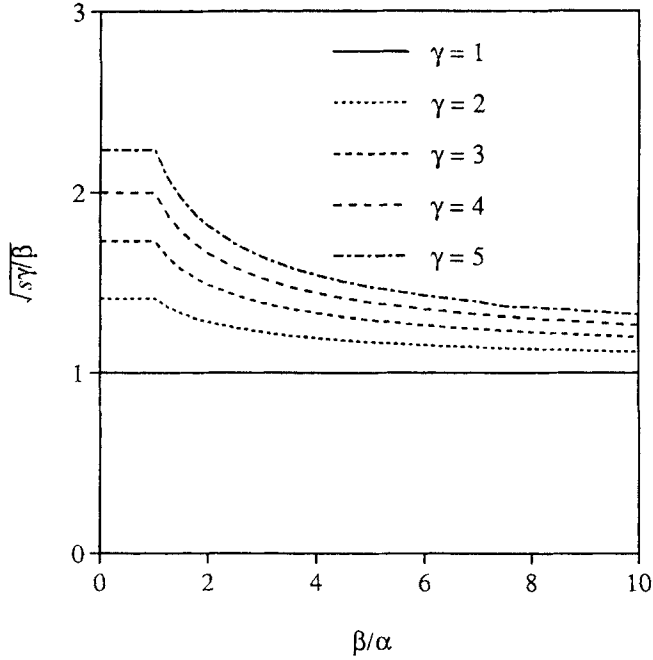


FIGURE 3 The square root of $s\gamma/\beta$ *vs.* $\beta/\alpha$.

## CONCLUSION

A model of controlled release from a polymer filled with drug particles and the regulatory particles is considered. The regulatory particles and drug particles are considered to be distributed randomly in the polymer matrix. During the release process into a solvent, the regulatory particles dissolved more slowly than the drug particles and open more paths to reduce the diffusional resistance of the drug. Mathematical modeling shows that both the drug and the regulatory particles have Fickian type behavior. The use of the regulatory particles increases the rate of release of the drug and offers the opportunity of a system that will react to a physiological change.



### *Acknowledgement*

The author would like to express his special thanks for Dr. R. Deanin for his invaluable help and useful suggestions.

### *References*

[1] Blackshear, P. J., *Scientific American*, December, 1979, p. 66.
[2] Langer, R. (1983). *Pharm. Theraphy*, **21**, 35.
[3] Hsieh, D. W. D. and Langer, R., In: *Controlled Release of Bioactive Materials* (Marcel Dekker, New York, 1983), Mansdroff, Z. and Roseman, T. J. Eds., p. 121.
[4] Kost, J., Leong, K. and Langer, R. (1989). *Proc. Nat. Acad. Sci.*, USA, **86**, 7663.
[5] Langer, R. and Peppas, N. A. (1981). *Biomaterials*, **2**, 201.
[6] Siegal, R. and Langer, R. (1984). *Parm. Res.*, **1**, 2.
[7] Brown, L. R., Wei, C. L. and Langer, R. (1983). *J. Pharmaceutical Sci.*, **72**, 1181.
[8] Langer, R., Hsieh, D. W. D., Rhine, W. and Folkman, J. (1980). *J. Membrane Sci.*, **7**, 333.
[9] Utracki, L. A., *Polymer Alloys and Blends* (Hanser Publishers, New York, 1989), p. 156.
[10] Reid, R. C., Prausnitz, J. M. and Sherwood, T. K., *The Properties of Gases and Liquids* (McGraw-Hill, New York, 1975), 3rd edn., p. 591.