



# Elaborations on the Higuchi model for drug delivery

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## ABSTRACT

The Higuchi model for the rate of drug release from matrix devices where the drug loading exceeds the solubility in the matrix medium, whose 50-year anniversary is celebrated in this issue, has proven to be a robust framework and an invaluable tool in developing a significant part of the modern controlled drug delivery industry. This paper reviews the conceptual and mathematical bases for this model and some consequences of its inherent assumptions. In addition, selected extensions of the model that have proven useful over the years are summarized. These include the effects of external mass transfer resistance and spatial variations of drug loading.

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## 1. Introduction

It is quite common these days to measure the impact of someone's scientific papers by the number of times they are cited in the writings of others. However, the ultimate accolade is when someone's work or result can be mentioned or used without citation. For example, in scientific writings it is considered perfectly acceptable to write  $F=ma$  without citing any writings by Newton or  $E=mc^2$  without explicitly referencing a paper by Einstein. In polymer science, it is common to use the Flory–Huggins or the Mark–Houwink equations without citing any source. In the field of drug delivery, it has become common to mention the Higuchi equation or model or to simply say “Higuchi kinetics” in a similar fashion (Higuchi, 1961, 1963).

This famous equation addresses the rate of release of a solute, typically a drug, from a matrix, usually a polymer, where the loading of solute,  $A$ , exceeds its solubility,  $C_s$ , in the matrix, into a surrounding fluid. The analysis made by Takeru Higuchi while he was at the University of Wisconsin involved two key steps. The first of these was the greatest breakthrough, in my opinion. That is, the physical visualization of dividing the matrix, as illustrated in Fig. 1, into an inner region where undissolved particles exist,  $x > \xi$ , and an outer region,  $x < \xi$ , where all the drug is dissolved (no particles) but there is a gradient of concentration that by Fick's law governs the rate of release of solute to the surrounding fluid. The model further envisions this boundary to move inward as the

undissolved drug is completely converted to dissolved drug and eventually released from the matrix to the surrounding fluid; in other words, this becomes a “moving boundary” problem (Crank, 1984). This picture is so obvious now, but I am pretty sure it was not 50 years ago! To complete the model in explicit form, Higuchi used a “pseudo steady-state” analysis combined with a global mass balance to get the now famous result

$$M_t = \sqrt{DC_s(2A - C_s)t} \quad (1)$$

or

$$J = \frac{dM_t}{dt} = \sqrt{\frac{DC_s(A - 1/2C_s)}{2t}} \quad (2)$$

where  $M_t$  is the accumulative amount of solute released up to time  $t$  from unit area of surface and  $D$  is the diffusion coefficient of the solute in the matrix. This analysis describes a number of other physical problems in addition to drug release from a “matrix” tablet.

Eqs. (1) and (2) were developed for a simple slab geometry using rectangular coordinates; however, some attention has been devoted to cylindrical, spherical, and other shapes (Flynn et al., 1976; Liu and Hsu, 2006; Kosmidis et al., 2003).

At this point it is necessary to explain my interest in this model and my connection to Tak Higuchi (and to his brother Bill). At this writing, I have been involved in polymer science and technology for 50 years with a continuous interest in many aspects of diffusion in polymers starting with Ph.D. research in the Department of Chemical Engineering at the University of Wisconsin during 1961–1965. I first became aware of papers by the Higuchi brothers (Higuchi, 1958; Finger et al., 1960; Higuchi and Higuchi, 1960) on topics not directly related to Eqs. (1) and (2) while guiding the research of my

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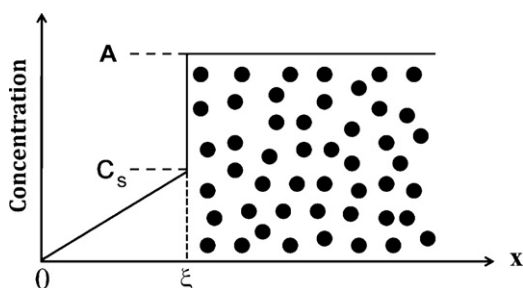


Fig. 1. Schematic illustration of the Higuchi model.

first Ph.D. student at the University of Texas at Austin (Paul and Kemp, 1973; Kemp and Paul, 1974). Eventually I became interested in drug delivery problems as a result of my interest in diffusion of solute molecules in polymers; however, drug delivery never has been more than a small part of my university research. On the other hand, I have been very involved in the field as a consultant to industry for nearly 40 years. It was in the latter capacity that I became aware of “Higuchi kinetics” and very much interested in this problem. A longstanding regret is that I was unaware of Tak Higuchi while I was at the University of Wisconsin although I was there when the famous Eqs. (1) and (2) were first published. Later, I came to understand that many of my classmates in chemistry classes were his graduate students. As time went on I came to know and respect many former students from the Higuchi group. In time, I knew Tak rather well, mainly through consulting activities.

It is a pleasure to add to this issue and to reflect on his many contributions including, but not only, Eqs. (1) and (2). The theme here is to give some examples that illustrate how the physical model conceived by Tak Higuchi formed the basis for mathematical extensions for describing many aspects of drug delivery and to point out some of its assumptions and limitations. Most of these examples come from my own experiences over the years in dealing with drug delivery problems.

## 2. Accuracy of the pseudosteady-state approximation

In developing Eq. (1), Higuchi employed the approximation that the diffusion in the solute depleted zone,  $0 < x < \xi$ , could be described by a steady state version of Fick's first law, i.e.,

$$J = \frac{dM_t}{dt} = \frac{DC_s}{\xi} \quad (3)$$

which includes the additional assumption that  $C = 0$  at  $x = 0$ . For the remaining boundary condition Higuchi used the following global mass balance:

$$\frac{dM_t}{dt} = \left(A - \frac{1}{2}C_s\right) \frac{d\xi}{dt} \quad (4)$$

to complete the pseudosteady-state analysis. Eqs. (3) and (4) can be combined and integrated to get Eqs. (1) or (2).

In the early 1970s I wondered about the accuracy of the assumptions implicit in these approximations. The diffusion problem in the depleted zone is more rigorously defined in terms of Fick's second law

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \quad (5)$$

with the boundary conditions at  $x = \xi$

$$C = C_s \quad (6)$$

$$(A - C_s) \frac{d\xi}{dt} = D \frac{\partial C}{\partial x} \quad (7)$$

assuming again that  $C = 0$  at  $x = 0$ ; more will be said about this later. With a great deal more effort this problem can also be solved, but the solution is rather complex and will not be reproduced here (Paul and McSpadden, 1976).

As it turns out, for  $A \gg C_s$ , Eqs. (1) and (2) involve negligible error relative to this exact solution. There is a small error in Eqs. (1) and (2) when  $A$  is not much higher than  $C_s$  and amounts to an underprediction of only 11.3% when  $A \rightarrow C_s$ . Thus, for most purposes one can use Eqs. (1) or (2) without concern for these approximations. However, the more rigorous analysis is absolutely necessary for some situations (Paul and McSpadden, 1976). Tak Higuchi was always very gracious about my effort to “improve” on his analysis and embraced the possibilities of more rigorous analyses of drug diffusion problems.

## 3. Effects of mass transfer resistance in the surrounding fluid

As noted earlier, an implicit assumption in Eq. (1) is that there is negligible resistance in the surrounding fluid to mass transfer of solute away from the matrix surface. In many situations, this cannot be ignored in spite of attempts to eliminate such effects by stirring or motion of the surrounding fluid. This is especially true for a delivery platform in the intestinal tract. A finite external mass transfer resistance appears mathematically as a finite concentration  $C_o$  at  $x = 0$  inside the matrix. Eq. (1) can be extended to include this effect as follows (Paul and McSpadden, 1976).

Eq. (2) must be replaced by

$$\frac{dM_t}{dt} = D \frac{C_s - C_o}{\xi} \quad (8)$$

and the following surface boundary condition has to be introduced:

$$\frac{dM_t}{dt} = \alpha C_o \quad (9)$$

where  $\alpha$  is a mass transfer coefficient that characterizes the resistance in the external phase. Eqs. (8) and (9) can be combined to get

$$C_o = \frac{C_s}{(1 + \alpha\xi/D)} \quad (10)$$

Combining Eqs. (4), (8) and (10) followed by an integration gives the following simple modified form of Eq. (1) in the limit of long times:

$$M_t = \sqrt{2DC_s \left(A - \frac{1}{2}C_s\right)} [\sqrt{t} - \sqrt{t_o}] \quad (11)$$

where

$$\sqrt{t_o} = \frac{1}{\alpha} \left(\frac{A}{C_s}\right) \sqrt{\frac{D}{2(A/C_s - 1/2)}} \quad (12)$$

In other words, a plot of  $M_t$  vs.  $\sqrt{t}$  remains linear at long enough times but there is an intercept on the  $\sqrt{t}$  axis of  $\sqrt{t_o}$ . This modified form of the Higuchi model can be very useful in data analysis as demonstrated by Paul and McSpadden (1976).

## 4. Dissolution-controlled release kinetics

An implicit assumption in the physical model in Fig. 1 and in the derivation of Eqs. (1) and (2) is that the rate at which the drug dissolves into the matrix from the particles must be much more rapid than the diffusional processes. This condition may not be satisfied when diffusion in the matrix is fast or when the drug dissolves very slowly (Chandrasekaran, 1982). Slow dissolution might be expected for drugs having low solubility in the matrix.

In the limit of very slow drug dissolution, the system cannot be divided into zones like those shown in Fig. 1, and as a result the model embodied in Eqs. (1) and (2) breaks down. In the extreme case where there are undissolved drug particles throughout the matrix, the release process may be described by a form of Fick's second law with a term to represent the local rate of drug dissolution like the following:

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} + K(C_s - C) \quad (13)$$

where  $K$  is a solute dissolution rate constant (Chandrasekaran and Paul, 1982; Kurnik and Potts, 1997; Gurny et al., 1982). This equation has been solved for the semi-infinite geometry with the following boundary and initial conditions (Chandrasekaran and Paul, 1982)

$$C = 0 \quad \text{at} \quad x = 0 \quad \text{for all } t \quad (14)$$

$$C = C_s \quad \text{at} \quad t = 0 \quad \text{for all } x \quad (15)$$

The solution, which is not reproduced here, shows that the amount of drug released is proportional to  $\sqrt{t}$  for early times and to  $t$  for longer times (Chandrasekaran and Paul, 1982). The dissolution rate constant depends on the size of the undissolved drug particles (Chandrasekaran and Paul, 1982).

There are many intermediate cases between the limits of fast dissolution or diffusion control (Eqs. (1) and (2)) and fast diffusion or dissolution (control) that can be addressed by models like the one described above.

## 5. Membrane–matrix composites

The holy grail of controlled release technology has long been to achieve a constant, or zero-order, release rate (Michaels, 1974; Paul, 1976; Stannett et al., 1979; Rhine et al., 1980a; Chandrasekaran et al., 1978). An elegant approach to this goal is to encapsulate a drug reservoir with a rate limiting membrane (Chandrasekaran et al., 1978). The reservoir contains a drug suspension in a fluid or gel phase where the drug loading far exceeds its solubility in this medium. Thus, the dissolved drug concentration remains constant during most of the delivery of drug from the system, i.e., the thermodynamic activity of the drug remains at unity even though the loading continues to decline as delivery proceeds. As a result, the rate of drug delivery or flux,  $J$ , remains at its maximum value  $J_m$  throughout except in the very initial (burst effect) and end (depletion) stages of delivery. Fig. 2(a) schematically illustrates a reservoir system.

This construction assumes drug migration in the reservoir is very fast such that there is no depletion layer adjacent to the membrane. If drug diffusion in the reservoir is not very fast, the drug reservoir may behave according to the Higuchi model in Fig. 1, see Fig. 2(b), allowing a prediction of the decline in flux  $J$  from the maximum value  $J_m$  using the following result:

$$J = J_m \frac{C_0}{C_s} = D \frac{C_s - C_0}{\xi} \quad (16)$$

and a mass balance analogous to Eq. (4) (Paul, 1984). To a good approximation, this result can be simplified to

$$\text{or } J \cong \left[ \frac{1}{J_m^2} + \frac{2t}{DC_s(A - 1/2C_s)} \right]^{-1/2} \quad (17)$$

In the limit where transport in the reservoir is very fast, this reduces to  $J = J_m$ ; while when  $J_m = \infty$ , this reduces to Eq. (2) above. Eq. (17) predicts the situations in between these limits.

The construction in Fig. 2 is also applicable to situations where there is a non-soluble overcoat on a matrix tablet. This will tend to mitigate the inverse  $\sqrt{t}$  dependence of release rate characteristic

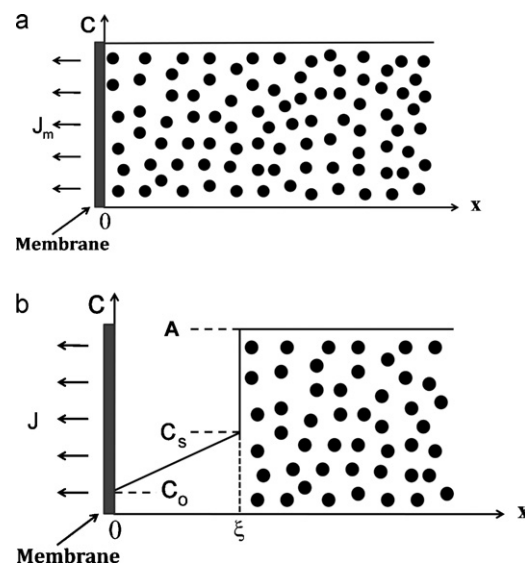


Fig. 2. Illustration of a drug reservoir with a rate limiting membrane attached where drug transport in reservoir or matrix is very fast (a) and where the drug transport is not fast (b).

of true matrix systems. Eq. (17) is useful for analyzing or designing such systems.

## 6. Laminated matrix systems

While typically matrix systems are more economical to manufacture than reservoir-type systems, a clear disadvantage is the declining flux with release time as predicted by Eq. (2). There has been much thought given to how to retain the economical advantage of matrix systems while obtaining a more constant release rate. One approach to this problem is to spatially vary the drug loading in a matrix system (Paul, 1985). One of the simplest ways to implement this concept is to construct a laminate whose layers have different drug loadings as suggested in Fig. 3; clearly, the higher loading needs to be in the center. Other geometries and greater numbers of layers could be envisioned, but Fig. 3 is adequate for illustrating the concept (Paul, 1985). Laminated constructions were well known in this field.

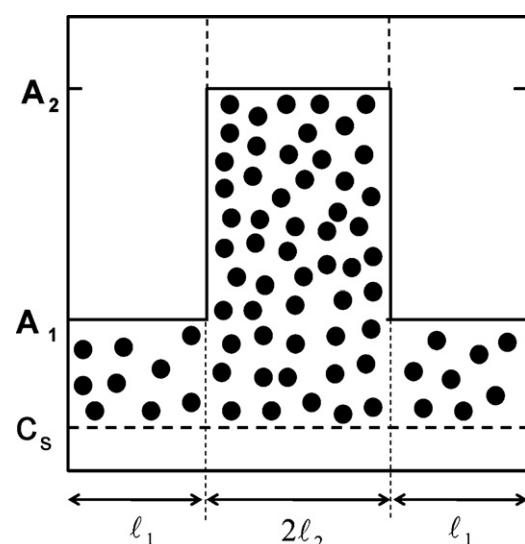


Fig. 3. Illustration of a two-layer laminate with different drug loadings in each layer at  $t=0$  before and during release.

As taught by the Higuchi model, the release rate declines as the front shown in Fig. 1 moves inward, i.e., as  $\xi$  increases the diffusion distance increases and the rate slows. However, Eq. (2) shows that increasing drug loading  $A$  increases the delivery rate. Thus, the concept is to give a boost to the rate as delivery progresses.

Analysis of such a design is tedious but the methodology has been worked out (Paul, 1985). Reproducing such results is beyond the scope of this contribution, but suffice it to say that the release profile can be significantly flattened by this approach as sample calculations have shown (Paul, 1985). Techniques for manufacturing such systems are not overly complicated. As a side note, publication of this concept was delayed by a few years at the request of a consulting client who was concerned this might damage the market position of their established business with reservoir systems. However, eventually it was decided that publication might be a better strategy since it was inevitable that others would come to the same conclusion eventually. This concept has subsequently been extended in more sophisticated ways by others (Lee, 1984a,b; Pywell and Collett, 1988; Lu et al., 1998; Hassan et al., 2000; Charalambopoulou et al., 2001; Watkins et al., 2007; Chandrasekaran and Hillman, 1980).

There have been other interesting approaches to achieving more constant release rate profiles from matrix systems. One of these is an “inwardly releasing hemisphere” (Rhine et al., 1980b). The concept here is that the tendency for the flux to decline with time owing to the increase in diffusion path length can be compensated in part by an increasing area of the front at  $\xi$ . Another concept is to use a glassy polymer as the matrix where, owing to complex relaxation processes, the swelling front caused by immersion in water can move into the polymer linearly in time rather than as the square root, i.e., so-called Case II diffusion (Hopfenberg and Hsu, 1978; Ritger and Peppas, 1987; Grassi and Grassi, 2005). The drug is essentially immobile in the glassy core but diffuses rapidly in the swollen region behind the front.

## 7. Highly loaded matrix systems

The model envisioned in Fig. 1 does not explicitly deal with what happens around a particle as drug molecules dissolve in the matrix in the region just ahead of the front at  $x = \xi$ . Naturally the particle must become smaller as these molecules leave. Does the drug particle lose contact with the matrix as this occurs? Most likely osmotic effects cause water to be imbibed into the space around the shrinking drug particle forming a saturated solution. Thus, the model does not need to address such details in order to arrive at Eqs. (1) and (2). However, in the depleted zone, i.e.,  $x < \xi$ , there will be holes left, in most cases, where drug particles were; these are most likely filled with a drug solution in water at a concentration (less than saturation) at equilibrium with drug dissolved in the surrounding matrix. The solution filled holes may alter the diffusion process in the zone  $0 < x < \xi$ , but this is apparently not a very important effect at low drug loadings. Nevertheless, attempts have been made to deal with matrix “porosity” effects (Flynn et al., 1974).

However, at very high drug loadings, the issues can become much more significant. At high enough loadings, the particles may percolate to form a continuous network resembling a sponge. Such percolated structures lead to pores that provide a new pathway for drugs to permeate from the system. Indeed, high molecular weight proteins, which have effectively no possibility of permeating through a solid matrix polymer, can be released from matrix systems by such a mechanism (Langer and Folkman, 1976; Langer et al., 1980a,b; Rhine et al., 1980b; Hsieh et al., 1983; Balazs et al., 1985).

## 8. Summary and conclusion

The Higuchi model has been an invaluable framework over its 50-year history for developing large parts of modern drug delivery technology. It captures the essence of what governs drug release from a permeable matrix when the drug loading is well in excess of its solubility limit and allows prediction of release rates with good accuracy in most cases. It has endured because of its simplicity. Naturally, it embodies a number of assumptions and approximations, some of which are not so obvious. This paper deals with some of these issues and shows how, in some cases, the model can be extended to incorporate additional complexity when needed.

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## References

- Balazs, A.C., Calef, D.F., Deutch, J.M., Siegel, R.A., Langer, R., 1985. The role of polymer matrix structure and interparticle interactions in diffusion-limited drug release. *Biophys. J.* 47, 97–104.
- Chandrasekaran, S.K., 1982. Dissolution controlled active agent dispenser. US Patent 4,314,557.
- Chandrasekaran, S.K., Capozza, R., Wong, P.S.L., 1978. Therapeutic systems and controlled drug delivery. *J. Membr. Sci.* 3, 271–286.
- Chandrasekaran, S.K., Hillman, R., 1980. Heterogeneous model of drug release from polymeric matrix. *J. Pharm. Sci.* 69, 1311–1313.
- Chandrasekaran, S.K., Paul, D.R., 1982. Dissolution-controlled transport from dispersed matrixes. *J. Pharm. Sci.* 71, 1399–1402.
- Charalambopoulou, G.C., Kikkinides, E.S., Papadokostaki, K.G., Stubos, A.K., Papaioannou, A.T., 2001. Numerical and experimental investigation of the diffusional release of a dispersed solute from polymeric multilaminate matrices. *J. Control. Release* 70, 309–319.
- Crank, J., 1984. *Free and Moving Boundary Problems*. Oxford University Press, Oxford.
- Finger, K.F., Lemberger, A.P., Higuchi, T., Busse, L.W., Wurster, D.E., 1960. Investigation and development of protective ointments. IV. The influence of active fillers on the permeability of semisolid. *J. Am. Pharm. Assoc., Sci. Ed.* 49, 569–573.
- Flynn, G.L., Yalkowsky, S.H., Roseman, T.J., 1974. Mass transport phenomena and models: theoretical concepts. *J. Pharm. Sci.* 63, 479–510.
- Flynn, G.L., Ho, N.F.H., Higuchi, W.I., Kent, J., 1976. Analysis of diffusion through concentric right circular cylinders and concentric spheres. *J. Pharm. Sci.* 65, 154–158.
- Grassi, M., Grassi, G., 2005. Mathematical modeling and controlled drug delivery: matrix systems. *Curr. Drug Deliv.* 2, 97–116.
- Gurny, R., Doelker, E., Peppas, N.A., 1982. Modeling of sustained release of water-soluble drugs from porous, hydrophobic polymers. *Biomaterials* 3, 27–32.
- Hassan, C.M., Stewart, J.E., Peppas, N.A., 2000. Diffusional characteristics of freeze/thawed poly(vinyl alcohol) hydrogels: applications to protein controlled release from multilaminate devices. *Eur. J. Pharm. Biopharm.* 49, 161–165.
- Higuchi, T., 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.* 50, 874–875.
- Higuchi, T., 1963. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* 52, 1145–1149.
- Higuchi, W.I., 1958. A new relationship for the dielectric properties of two-phase mixtures. *J. Phys. Chem.* 62, 649–653.
- Higuchi, W.I., Higuchi, T., 1960. Theoretical analysis of diffusional movement through heterogeneous barriers. *J. Am. Pharm. Assoc., Sci. Ed.* 49, 598–606.
- Hopfenberg, H.B., Hsu, K.C., 1978. Swelling-controlled, constant rate delivery systems. *Polym. Eng. Sci.* 18, 1186–1191.
- Hsieh, D.S.T., Rhine, W.D., Langer, R., 1983. Zero-order controlled-release polymer matrices for micro- and macromolecules. *J. Pharm. Sci.* 72, 17–22.
- Kemp, D.R., Paul, D.R., 1974. Gas sorption in polymer membranes containing adsorptive fillers. *J. Polym. Sci. Polym. Phys. Ed.* 12, 485–500.
- Kosmidis, K., Argyrakakis, P., Macheras, P., 2003. A reappraisal of drug release laws using Monte Carlo simulations: the prevalence of the Weibull function. *Pharm. Res.* 20, 988–995.
- Kurnik, R.T., Potts, R.O., 1997. Modeling of diffusion and crystal dissolution in controlled release systems. *J. Control. Release* 45, 257–264.
- Langer, R., Folkman, J., 1976. Polymers for the sustained release of proteins and other macromolecules. *Nature* 263, 797–800.
- Langer, R., Hsieh, D.S.T., Rhine, W., Folkman, J., 1980a. Control of release kinetics of macromolecules from polymers. *J. Membr. Sci.* 7, 333–350.

- Langer, R.S., Rhine, W.D., Hsieh, D.S.T., Bawa, R.S., 1980b. Polymers for the sustained release of macromolecules: application and control of release kinetics. In: Baker, R.W. (Ed.), *Controlled Release of Bioactive Materials*. Academic Press, New York, pp. 83–98.
- Lee, P.I., 1984a. Effect of non-uniform initial drug concentration distribution on the kinetics of drug release from glassy hydrogel matrices. *Polymer* 25, 973–978.
- Lee, P.I., 1984b. Novel approach to zero-order drug delivery via immobilized nonuniform drug distribution in glassy hydrogels. *J. Pharm. Sci.* 73, 1344–1347.
- Liu, B.-T., Hsu, J.-P., 2006. Theoretical analysis on diffusional release from ellipsoidal drug delivery devices. *Chem. Eng. Sci.* 61, 1748–1752.
- Lu, S., Ramirez, W.F., Anseth, K.S., 1998. Modeling and optimization of drug release from laminated polymer matrix devices. *AIChE J.* 44, 1689–1696.
- Michaels, A.S., 1974. Therapeutic systems for controlled administration of drugs: a new application of membrane science. In: Hopfenberg, H.B. (Ed.), *Permeability of Plastic Films and Coatings to Gases, Vapors and Liquids*. Polymer Science and Technology Series, vol. 6. Plenum Press, New York, pp. 409–421.
- Paul, D.R., 1976. Polymers in controlled release technology. In: Paul, D.R., Harris, F.W. (Eds.), *Controlled Release Polymeric Formulations*. ACS Symposium Series, vol. 33, pp. 1–14.
- Paul, D.R., 1984. Solute release from membrane–matrix composites. *J. Membr. Sci.* 21, 203–207.
- Paul, D.R., 1985. Modeling of solute release from laminated matrices. *J. Membr. Sci.* 23, 221–235.
- Paul, D.R., Kemp, D.R., 1973. The diffusion time lag in polymer membranes containing adsorptive fillers. *J. Polym. Sci. Polym. Symp.* 41, 79–93.
- Paul, D.R., McSpadden, S.K., 1976. Diffusional release of a solute from a polymer matrix. *J. Membr. Sci.* 1, 33–48.
- Pywell, E.J., Collett, J.H., 1988. Drug release from polymeric, multi-perforated, laminated matrices. *Drug Dev. Ind. Pharm.* 14, 2397–2416.
- Rhine, W.D., Sukhatme, V., Hsieh, P.S.T., Langer, R.S., 1980a. A new approach to achieve zero-order release kinetics from diffusion-controlled polymer matrix systems. In: Baker, R.W. (Ed.), *Controlled Release of Bioactive Materials*. Academic Press, New York, pp. 177–187.
- Rhine, W.D., Hsieh, D.S.T., Langer, R., 1980b. Polymers for sustained macromolecule release: procedures to fabricate reproducible delivery systems and control release kinetics. *J. Pharm. Sci.* 69, 265–270.
- Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release. I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J. Control. Release* 5, 23–36.
- Stannett, V.T., Koros, W.J., Paul, D.R., Lonsdale, H.K., Baker, R.W., 1979. Recent advances in membrane science and technology. *Adv. Polym. Sci.* 32, 69–121.
- Watkins, A.W., Southard, S.L., Anseth, K.S., 2007. Characterizing multilaminated hydrogels with spatially varying network structure and solute loading using confocal laser scanning microscopy. *Acta Biomater.* 3, 439–448.