Study of dissolution process and its modelling

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Abstract. The use of mathematical concepts and language aiming to describe and represent the interactions and dynamics of a system is known as a mathematical model. Mathematical modelling finds a huge number of successful applications in a vast amount of science, social and engineering fields, including biology, chemistry, physics, computer sciences, artificial intelligence, bioengineering, finance, economy and others. In this research, we aim to propose a mathematical model that predicts the dissolution of a solid material immersed in a fluid. The developed model can be used to evaluate the rate of mass transfer and the mass transfer coefficient. Further research is expected to be carried out to use the model as a base to develop useful models for the pharmaceutical industry to gain information about the dissolution of medicaments in the body stream and this could play a key role in formulation of medicaments.

1 Introduction

Dissolution is a process in which a solute forms a solution in a solvent. In the study of dissolution we normally come across with several factors that affects this process, namely surface area, agitation, temperature, enthalpy and entropy which affects dissolvability of salts as well as the nature of solvent and solute.[1], [2]

Understanding the dissolution processes of any compound considers the study of kinetic rates, controlling factors, products of dissolution, kinetics of precipitation, chemical equilibrium, mechanism of crystallization among other factors [3], [4]. During the formation of dissolutions, homogenous materials are formed with the combination of more than one chemical species that achieve equilibrium. The components of dissolution (solute and dissolvent) form a homogenous mixture and have a regular distribution of their physicochemical properties. As a result, every portion has the same chemical and psychical characteristics but the quantity of solute and dissolvent are in proportions that varied within some limits. This can be exemplified by the capacity of solubilization that every compound has in a specific solvent. The physical properties are given by the concentration of the components, which can be separated by changes of phases such as evaporation, condensation, or fusion, however, they are not able to be separated by sedimentation or centrifugation. This is normally caused due to the size of the particles, which is normally lower than 10 Angstroms. The stability of materials can be influenced by several factors such as transport process. Additionally, the presence of elements like oxygen or other oxidants (i.e. Fe_2O_3, MnO_2, nitrogen compounds) and proper characteristics of the materials such as structure, surface, reactive area, presence of ligands, temperature affect their dissolution rate. [5]–[7]

The formation of dissolution is strongly related to the attraction between the solute and the solvent. A solution is formed when attractive forces between different particles are bigger than the attractive forces between particles that are similar. Therefore, the amount of solute solubilised depends on the strength of attraction. The attractive intermolecular forces between particles keep the particles together; as a result, these intermolecular forces have to be broken in order to form a solution. [8], [9]

Dissolution process is important in several fields. In the pharmaceutical industry gives information about the disposition of a pharmaceutical compound within an organism or drug release (adsorption, distribution, metabolism and excretion). This is extremely important in cases where drug release should be controlled in time or gradual after specific time of administration. Several systems aimed to control drug delivery try to minimize degradation of compounds prevention of side effects and increment of drug bioavailability. Research in this field has been carried out by the application of micelles as drug carriers, soluble polymers and liposomes. Bioavailability is the fraction of a drug dose in its active form or some of the metabolites absorbed from the site of administration that reaches the systemic circulation or a particular place where it performs the main function. This property can be increased using micellar systems which have the potential to solubilise drugs with low solubility. It also depends on the properties of the pharmaceutical form and its formulation. Drugs can be administrated by various routes, such as oral, rectal, parenteral, topical, inhalational, etc.). They require being in solution to be adsorbed after crossing several semipermeable cell membranes before reaching the systemic circulation. There exists several alternatives to cross cell membranes, among the most important are passive diffusion, facilitated passive diffusion, active

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transport and pinocytosis. Low bioavailability can be present in cases where metabolism of the drug occurs before reaching the required plasmid concentration. This is frequent in oral administration of low hydrosoluble drugs with low adsorption. [10]

2. General model of dissolution process

The general model of dissolution is a first order model, described by the differential equation given in (1)

$$\frac{dC(t)}{dt} = a(C_S - C(t)), \quad C(0) = 0 \qquad (1)$$

where $a > 0$ is constant and C_S is the limit concentration achieved after the solvent is dissolved or the solute is saturated.

When a liquid is flowing through the inner tube formed with crystals of a solute, a gradient of concentrations exist in the solid surface. The solute starts to dissolve slowly and gradually according to the solubility of the material in the respective solution (Fig. 1). For the analysis of the system, we consider a plug flow model with perfect radial mixing, isothermal conditions and constant fluid physical properties. The concentration of the solid varies along the tube (axial coordinate) with absence of radial diffusion and resistance to mass transfer due to liquid phase contribution. The diameter of the cylindrical tube remains constant.
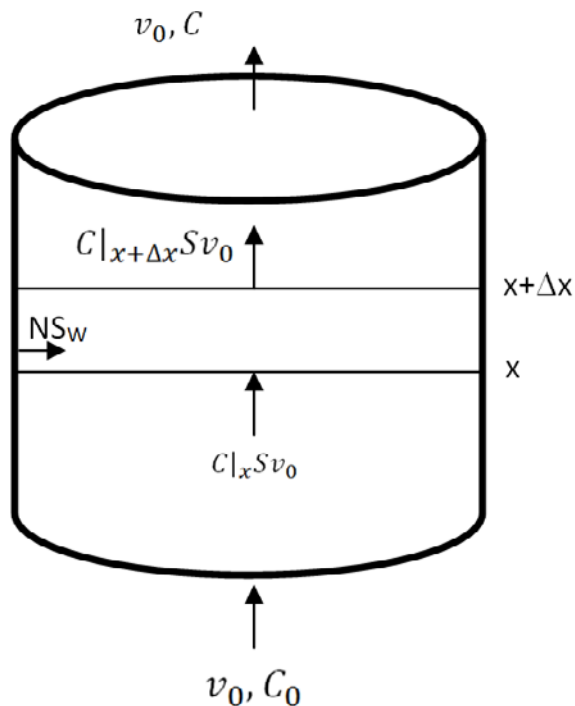

Fig. 1. General representation of the system under study

To describe the process, we consider a differential element (shell) of thickness Δx, with constant cross section area and derive the macroscopic mass balance around the elemental volume. If the process is in steady state, there is no accumulation of mass. There is no chemical reaction but there is transfer of mass between the surface of the solid and the fluid. Additionally, we assume that the system remains infinitesimally close to an equilibrium state at all times. This implies that the process is slow enough to allow the system to adjust itself internally and the properties in one part of the system do not change any faster than those at other parts[11]. As a result, the general conservation law is as expressed in (2):

$$C_x S\vartheta_0 - C_L S\vartheta_0 + \Delta R = 0 \qquad (2)$$

where C is the concentration of the solid, with a distance (x) and a thickness (L), ϑ represents the superficial fluid velocity, S the surface area of the solid, ΔR express the incremental rate expression given by the mass flux [product of the mass transfer coefficient (k), the composition linear driving force $(C*-C)$] and the surface area of the tube (A_W).

Equation (2) takes the form of (3)

$$C|_x \left(\frac{\pi D^2}{4}\right)\vartheta_0 - C|_L \left(\frac{\pi D^2}{4}\right)\vartheta_0 + k[C_S - C(x)]A_W = 0 \qquad (3)$$

Where D is the diameter of the tube, k the mass transfer coefficient, C and C_S are the concentration of the substance and solubility respectively.

Dividing equation (3) by $\pi D \Delta x$ gives

$$C|_x \left(\frac{D}{4\Delta x}\right)\vartheta_0 - C|_L \left(\frac{D}{4\Delta x}\right)\vartheta_0 + k[C_S - C(x)] = 0 \qquad (4)$$

$$\left(\frac{-D\vartheta_0}{4}\right)\frac{[C|_L - C|_x]}{\Delta x} + k[C_S - C(x)] = 0 \qquad (5)$$

Taking the limit when Δx→0 gives the concentration profile with distance, as expressed in equation (6)

$$\left(\frac{-D\vartheta_0}{4}\right)\frac{dC}{dx} + k[C_S - C(x)] = 0 \qquad (6)$$

The system is described by the previous ordinary differential equation, which can be integrated with the following initial condition: $x = 0, C = 0$

The solution can be performed by separation of variables

$$\frac{dC}{C_S - C(x)} = \frac{4k}{D\vartheta_0}dx \qquad (7)$$

$$\int \frac{dC}{C_S - C(x)} = \frac{4k}{D\vartheta_0}\int dx \qquad (8)$$

$$-\ln|C_S - C(x)| = \frac{4k}{D\vartheta_0}x + B \qquad (9)$$

$$e^{\ln|C_S - C(x)|} = e^{-\frac{4k}{D\vartheta_0}x + B} \qquad (10)$$

$$C_S - C(x) = B' e^{-\frac{4k}{D\vartheta_0}x} \qquad (11)$$

$$C(x) = C_S - B' e^{-\frac{4k}{D\vartheta_0}x} \qquad (12)$$

At the boundary, when $x=0$, the concentration corresponds to zero $(C=0)$, therefore the value of the constant B' is equal to C_S. Substituting the value of the constant gives

$$C(x) = C_S \left(1 - e^{-\frac{4k}{D\vartheta_0}x}\right) \qquad (13)$$

Equation (13) can be used to evaluate the concentration at the boundary, when X=L

$$C(L) = C_S \left(1 - e^{-\frac{4k}{D\vartheta_0}L}\right) \qquad (14)$$

The variation of weight (ΔW) according to time ($\Delta \tau$) can be calculated by determining the rate at which the compound is being dissolved (υ), as expressed in (15)

$$\Delta W = \upsilon \Delta \tau \qquad (15)$$

Accordingly, the rate of dissolution [g/s] is determined by multiplying the volumetric flow rate through the cylinder [m^3/s], the concentration at the boundary $C(L)$[mol/m^3] and the molecular weight of the substance [g/mol] as expressed in (16)

$$\upsilon = \frac{\pi D^2}{4} \vartheta_0 C(L) M_W \qquad (16)$$

Substituting (16) in (15) and using equation (14) leads to equation (17)

$$\Delta W = \frac{\pi D^2}{4} \vartheta_0 C_S \left(1 - e^{-\frac{4k}{D\vartheta_0}L}\right) M_W \Delta \tau \quad (17)$$

Equation (17) can be rearranged to have

$$\frac{4\Delta W}{\pi D^2 \vartheta_0 C_S M_W \Delta \tau} = 1 - e^{-\frac{4k}{D\vartheta_0}L} \qquad (18)$$

For any value of x, the exponential function can be represented as a power series as indicated in (19)

$$e^x = \sum_{n=0}^{\infty} \frac{x^n}{n!} = 1 + x + \frac{x^2}{2} + \cdots \qquad (19)$$

Using the approximation of equation (19) gives (20)

$$e^{-\frac{4k}{D\vartheta_0}L} \approx 1 - \frac{4k}{D\vartheta_0}L \qquad (20)$$

From (20) we can obtain (21)

$$1 - e^{-\frac{4k}{D\vartheta_0}L} \approx \frac{4k}{D\vartheta_0}L \qquad (21)$$

Substituting equation (21) into (18)

$$\frac{4\Delta W}{\pi D^2 \vartheta_0 C_S M_W \Delta \tau} \approx \frac{4k}{D\vartheta_0}L \qquad (22)$$

Finally, obtaining for k gives (23)

$$k \approx \frac{\Delta W}{\pi D \, C_S M_W \Delta \tau L} \qquad (23)$$

Since equation 23 is an approximation, the maximum error can be estimated according to equation (24)

$$\varepsilon_k = \left|\frac{\partial k}{\partial \Delta W}\right| \varepsilon_{\Delta W} + \left|\frac{\partial k}{\partial \Delta \tau}\right| \varepsilon_{\Delta \tau} + \left|\frac{\partial k}{\partial D}\right| \varepsilon_D \quad (24)$$

where

$$\left|\frac{\partial k}{\partial \Delta W}\right| = \frac{1}{\pi D \, C_S M_W \Delta \tau L} \qquad (25)$$

$$\left|\frac{\partial k}{\partial \Delta \tau}\right| = -\frac{\Delta W}{\pi D \, C_S M_W \Delta \tau^2 L} \qquad (26)$$

$$\left|\frac{\partial k}{\partial D}\right| = -\frac{\Delta W}{\pi D^2 \, C_S M_W \Delta \tau L} \qquad (27)$$

The substitution of the values of the partial derivatives using equations (25-26), the experimental errors $\varepsilon_{\Delta W}$, $\varepsilon_{\Delta t}$, ε_D and simplifying we obtain equation (28)

$$\varepsilon_k = \frac{\Delta W}{\pi D \, C_S M_W \Delta \tau L} \left(\frac{\varepsilon_{\Delta W}}{\Delta W} + \frac{\varepsilon_{\Delta \tau}}{\Delta \tau} + \frac{\varepsilon_D}{D}\right) + \left|\frac{\partial k}{\partial \Delta \tau}\right| \varepsilon_{\Delta \tau} +$$
$$\left|\frac{\partial k}{\partial D}\right| \varepsilon_D \qquad (28)$$

2 Discussion

Initially, pure water is passed through a tube constructed of a solid. Considering that the solid is slightly soluble in water (C^* moles solid/cm^3 solution), the inner walls of the tube will dissolve very slowly. By weighing the dried tube before and after exposure, it is possible to calculate the rate of mass transfer. As an example to this process, if a crystal of barium hydroxide is dipped into a rapidly stirred solution of dilute acid containing phenolphthalein, a thin layer of solution at the surface of the crystal becomes pink. The thickness of the alkaline layer varies with the stirring speed, and, if the latter is very low, irregular streamers of alkaline solution may extend one or two centimeters out into the solution. With a very soluble base, as sodium hydroxide, even a high stirring speed cannot confine the alkaline solution to a thin, even layer.

Considering that a monomolecular film of liquid next its surface is saturated by the base rapidly, as expressed in the Nernst diffusion layer theory of dissolution rates, a layer is formed in which concentration gradients of both acid and base exist. This type of system has been discussed by other researchers but no systematic study of such cases has been made.

If solid benzoic acid is immersed in an alkaline solution a similar gradient of acid and base concentrations should exist near the surface.

3 Conclusions

We analyzed the dissolution process of solids in a fluid by determining the quasi steady state material balance for velocity profile, the profile of compound concentration through the space dimension and time. We discussed the assumptions implied in the analysis and deduced a method of estimating the maximum possible experimental error in calculating kc

Using mathematical modeling allows evaluating equations based on this assumption that account satisfactorily for the dissolution rate of solid benzoic acid in dilute sodium and potassium hydroxide solutions. Many investigators believe that the outer surface of the diffusion layer is diffuse and ragged and that the average concentration gradient is not linear over a considerable fraction of the total layer thickness. The experiment described with barium and sodium hydroxides indicates that the lower the concentration differences and the better the stirring, the sharper the boundary of the diffusion layer. It is possible to consider two cases: the zone in which solutes are transported both by convection and diffusion may be negligibly thin compared to the entire layer in which concentration gradients exist; or that the distance from the surface at which neutralization occurs may be considered as "effective thicknesses" without destroying the validity of the relation to be derived

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