Proceedings of EQUADIFF 2017
pp. 341–348

MATHEMATICALLY MODELLING THE DISSOLUTION OF SOLID DISPERSIONS

MARTIN MEERE*, SEAN MCGINTY †, AND GIUSEPPE PONTRELLI ‡

Abstract. A solid dispersion is a dosage form in which an active ingredient (a drug) is mixed with at least one inert solid component. The purpose of the inert component is usually to improve the bioavailability of the drug. In particular, the inert component is frequently chosen to improve the dissolution rate of a drug that is poorly soluble in water. The construction of reliable mathematical models that accurately describe the dissolution of solid dispersions would clearly assist with their rational design. However, the development of such models is challenging since a dissolving solid dispersion constitutes a non-ideal mixture, and the selection of appropriate forms for the activity coefficients that describe the interaction between the drug, the inert matrix, and the dissolution medium is delicate. In this paper, we present some preliminary ideas for modelling the dissolution of solid dispersions.

Key words. Solid Dispersion, Mathematical Model, Partial Differential Equations, Activity Coefficients

AMS subject classifications. 74N25, 82C70, 82D60

1. Introduction.

1.1. Motivation: poorly soluble drugs. Drugs that are delivered orally via a tablet should ideally be readily soluble in water. Drugs that are poorly water-soluble tend to pass through the gastrointestinal tract before they can fully dissolve, and this typically leads to poor bioavailability of the drug. Unfortunately, many drugs currently on the market or in development are poorly water-soluble, and this presents a serious challenge to the pharmaceutical industry. Many strategies have been developed to improve the solubility of drugs, such as the use of surfactants, cocrystals, lipid-based formulations, and particle size reduction. The literature on this topic is extensive, and recent reviews can be found in [1] and [2].

One particularly effective strategy to improve drug solubility is to use a *solid dispersion*. A solid dispersion typically consists of a hydrophobic drug embedded in a hydrophilic polymer matrix, where the matrix can be either in the amorphous or crystalline state. The drug is preferably in a molecularly dispersed state, but may also be present in amorphous particles or even in the crystalline form (though this is usually undesirable); see Figure 1.1.

1.2. Storage, stability and phase separation of solid dispersions. Drug loading in most dispersions greatly exceeds the equilibrium solubility in the polymer matrix for typical storage temperatures. Hence these systems are usually unstable, with phase separation eventually occurring ([7]). In such cases, the drug will eventually crystallise out or form an amorphous phase separation. However, if the dispersion is stored well below the glass transition temperature ([3]) for the polymer, and is kept dry, this can happen extremely slowly. The system is then for all

*School of Mathematics, National University of Ireland Galway, University Road, Galway, Ireland (martin.meere@nuigalway.ie).

†Division of Biomedical Engineering, University of Glasgow, Glasgow, G12 8QQ, UK (sean.mcginty@glasgow.ac.uk).

‡Istituto per le Applicazioni del Calcolo, CNR, Rome, Italy (giuseppe.pontrelli@gmail.com).

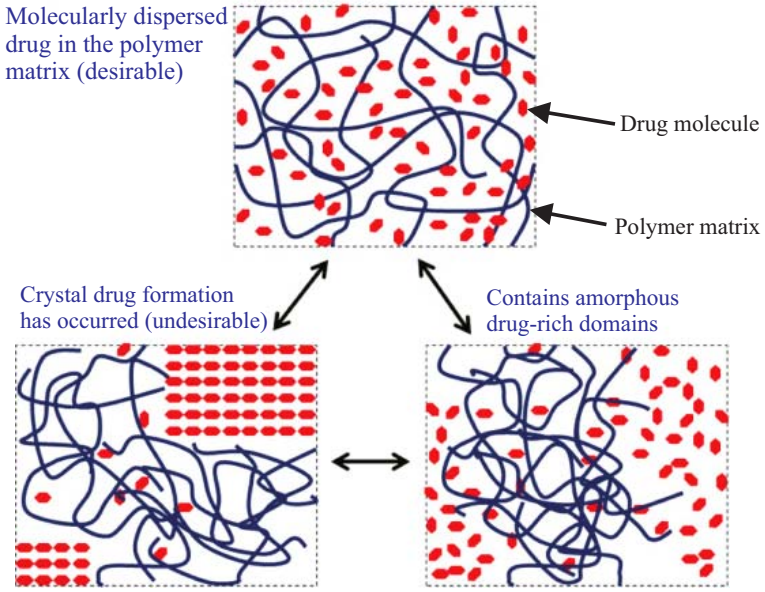

FIG. 1.1. *Adapted from [7]. In this figure, we show three possible structures for a polymer/drug dispersion. Top: Here the drug is in the molecularly dispersed state, which is usually desirable for a solid dispersion. Bottom left: Here the dispersion contains drug in the crystalline form. Bottom right: Here the dispersion contains amorphous drug-rich domains.*

practical purposes stable, and is said to be metastable. The humidity of the storage environment can be an issue because even small amounts of moisture can significantly affect the glass transition temperature. Hence polymers that have high glass transition temperatures and that are resistant to water absorption have become popular. An example of one such polymer is Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS).

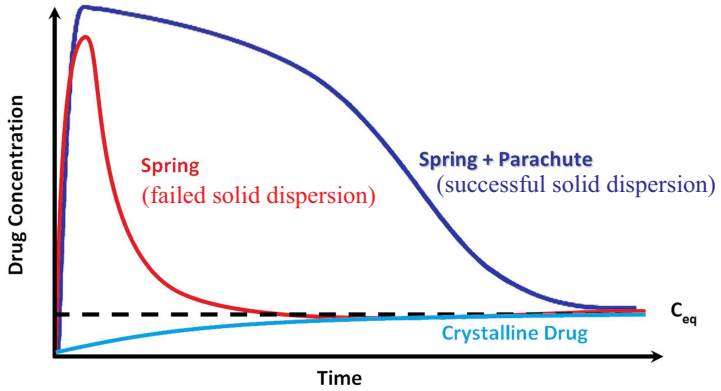

FIG. 1.2. *Adapted from [8]. The drug first dissolves along with the soluble polymer matrix to generate a supersaturated solution (spring) followed by a decline in the drug concentration in the media due to either absorption or precipitation (parachute).*

1.3. Drug release from solid dispersions. The *spring and parachute* concept is the usual strategy associated with drug release from solid dispersions. When the dispersion absorbs fluid, the dispersed drug dissolves along with the soluble polymer to create a solution with a drug concentration that is well above the drug solubility in the fluid (this is the spring). The dispersion then maintains the drug concentration at supersaturated levels for a period of hours while it is being absorbed (this is the parachute); see Figure 1.2.

Unfortunately, despite extensive research, the dissolution behaviour of solid dispersions is only partially understood. In particular, the precise mechanisms via which the polymer prolongs the supersaturation of the drug have not been fully resolved. This makes the design of successful solid dispersions a somewhat *hit and miss* affair. Clearly, the construction of reliable mathematical models that capture the key interactions between drug, polymer and solvent molecules in a dissolving solid dispersion would greatly assist with their rational design. The ultimate goal of such modelling is to identify the regions of the parameter space governing the system that lead to the desired dissolution behaviour for a given pharmaceutical product. Some previous modelling studies for solid solutions can be found in [9], [10], [11] and [12].

2. Mathematical modelling.

2.1. A multicomponent diffusion model for solid dispersions. We develop a multicomponent diffusion model for the evolution of the concentrations of the three components constituting a dissolving solid dispersion. These are the drug molecules (label 1), the polymer molecules (label 2), and the solvent molecules (label 3). For simplicity, we shall restrict our attention here to the one-dimensional form of the equations; that is, the concentrations of the species only depend on a single spatial variable x.

The chemical potential μ_i (J/mole) of species i ($i = 1, 2, 3$) gives the Gibbs free energy per mole of species i, and is given here by ([4])

$$\mu_i = \mu_{i0} + RT \ln(a_i) - \epsilon_i^2 \frac{\partial^2 N_i}{\partial x^2} \tag{2.1}$$

where μ_{i0} is the chemical potential of species i in the pure state, R (J/[K·mole]) is the gas constant, T (K) is the temperature, a_i is the activity of species i, and the term involving $\epsilon_i^2 > 0$ (m^2J/mole) penalises the formation of phase boundaries (see [5] and [6] for some discussion of this issue). Here N_i is the molar fraction of species i ($i = 1, 2, 3$), and the activities can depend on these molar fractions, so that

$$a_i = a_i(N_1, N_2, N_3).$$

The flux of species i (molar·m/s) is given by

$$J_i = c_i v_i \tag{2.2}$$

where c_i (molar), v_i (m/s) give the molar concentration and drift velocity, respectively, of species i. The drift velocity v_i gives the average velocity a particle of species i attains due to the diffusion force acting on it, and is given here by

$$v_i = M_i \mathcal{F}_i = -M_i \frac{\partial \mu_i}{\partial x} \tag{2.3}$$

where M_i (mole·s/kg), $\mathcal{F}_i$ (J/[m·mole]) give the mobility and diffusion force, respectively, for species i. Substituting (2.3) in (2.2) and using (2.1) gives

$$J_i = -M_i c_i \frac{\partial \mu_i}{\partial x} = -M_i c_i \left(\frac{RT}{a_i} \frac{\partial a_i}{\partial x} - \epsilon_i^2 \frac{\partial^3 N_i}{\partial x^3} \right)$$

and then using the fact that the activities depend on the molar fractions gives

$$J_i = -M_i c_i \left(\frac{RT}{a_i} \sum_{j=1}^{3} \frac{\partial a_i}{\partial N_j} \frac{\partial N_j}{\partial x} - \epsilon_i^2 \frac{\partial^3 N_i}{\partial x^3} \right). \tag{2.4}$$

The molar fraction is related to the molar concentration via

$$N_i = V_i c_i \tag{2.5}$$

where V_i (molar^{-1}) is the molar volume of species i. Using (2.5), we can now write (2.4) as

$$J_i = -\sum_{j=1}^{3} D_{ij} \frac{\partial c_j}{\partial x} + D_i \varepsilon_i^2 c_i \frac{\partial^3 c_i}{\partial x^3} \tag{2.6}$$

where the D_{ij} (m^2/s) are given by

$$D_{ij} = D_i \frac{V_j}{V_i} \frac{N_i}{a_i} \frac{\partial a_i}{\partial N_j} \qquad (i, j = 1, 2, 3) \tag{2.7}$$

and where

$$D_i = M_i RT \qquad \text{(Einstein relation)}$$

is the diffusion coefficient for species i. Finally, $\varepsilon_i^2 = M_i V_i \epsilon_i^2 / D_i > 0$ (m^2/molar).

Conservation of mass for species i implies that

$$\frac{\partial c_i}{\partial t} + \frac{\partial J_i}{\partial x} = 0$$

and using (2.6) now gives

$$\frac{\partial c_i}{\partial t} = \frac{\partial}{\partial x} \left(\sum_{j=1}^{3} D_{ij}(c_1, c_2, c_3) \frac{\partial c_j}{\partial x} - D_i \varepsilon_i^2 c_i \frac{\partial^3 c_i}{\partial x^3} \right) \qquad (i = 1, 2, 3) \tag{2.8}$$

where we have included the concentration dependence of the diffusion coefficients D_{ij} here to emphasise that this system is in general a coupled system of nonlinear diffusion equations. It should be noted that the equations (2.8) are not independent since $V_1 c_1 + V_2 c_2 + V_3 c_3 = 1$, and so it is sufficient to solve for two concentrationns only.

2.2. Activity coefficients. The activities a_i are usually written as

$$a_i = \gamma_i N_i$$

where the $\gamma_i = \gamma_i(N_1, N_2, N_3)$ are referred to as *activity coefficients*. Equations (2.7) now give

$$D_{ij} = D_i \frac{V_j}{V_i}\left(\delta_{ij} + \frac{N_i}{\gamma_i}\frac{\partial \gamma_i}{\partial N_j}\right) \qquad (i,j = 1,2,3) \tag{2.9}$$

where δ_{ij} is the Kronecker delta. Notice that if $\gamma_i \equiv$ constant, then the (2.9) reduce to $D_{ij} = D_i$ and the governing equations decouple to give

$$\frac{\partial c_i}{\partial t} = D_i \frac{\partial}{\partial x}\left(\frac{\partial c_i}{\partial x} - \varepsilon_i^2 c_i \frac{\partial^3 c_i}{\partial x^3}\right). \qquad (i = 1,2,3)$$

If we further have $\varepsilon_i = 0$, the governing equations reduce to a set of classical linear diffusion equations.

The details of the interactions between the species in solution are captured in the modelling by choosing appropriate forms for the activity coefficients $\gamma_i = \gamma_i(N_1, N_2, N_3)$. The construction of appropriate forms for the γ_i for various solutions is a large subject with a large literature; see, for example, the books [13] and [14].

2.3. Activity coefficients for polymer solutions.

2.3.1. Flory-Huggins Model. The Flory-Huggins model is a lattice-based model commonly used to describe the thermodynamics of polymer solutions. For a binary solution in which the subscripts 1 and 2 refer to drug and polymer molecules, respectively, this model has ([13])

$$\ln(\gamma_1) = \ln\left(\frac{\Phi_1}{N_1}\right) + 1 - \frac{\Phi_1}{N_1} + \chi_{12}\Phi_2^2$$

where

$$\Phi_1 = \frac{V_1 N_1}{V_1 N_1 + V_2 N_2}, \quad \Phi_2 = \frac{V_2 N_2}{V_1 N_1 + V_2 N_2}.$$

Here χ_{12} is the Flory-Huggins interaction parameter that quantifies the balance between polymer-polymer and polymer-solvent interactions. Note that we need only specify γ_1 here since $N_2 = 1 - N_1$.

For a ternary solution, consisting of drug molecules, polymer molecules, and solvent molecules (molar fraction N_3, molar volume V_3), we have ([13])

$$\ln(\gamma_i) = \ln\left(\frac{\Phi_i}{N_i}\right) + 1 - \frac{\Phi_i}{N_i} + 2V_i \sum_{j=1}^{3} \Phi_i b_{ij} - V_i \sum_{j,k=1}^{3} \Phi_j \Phi_k b_{jk}$$

where

$$\Phi_i = \frac{V_i N_i}{\sum_{j=1}^{3} V_j N_j} \quad \text{for} \quad i = 1,2,3,$$

and where the interaction parameters b_{ij} (molar) are such that $b_{ii} = 0$ and $b_{ij} = b_{ji}$.

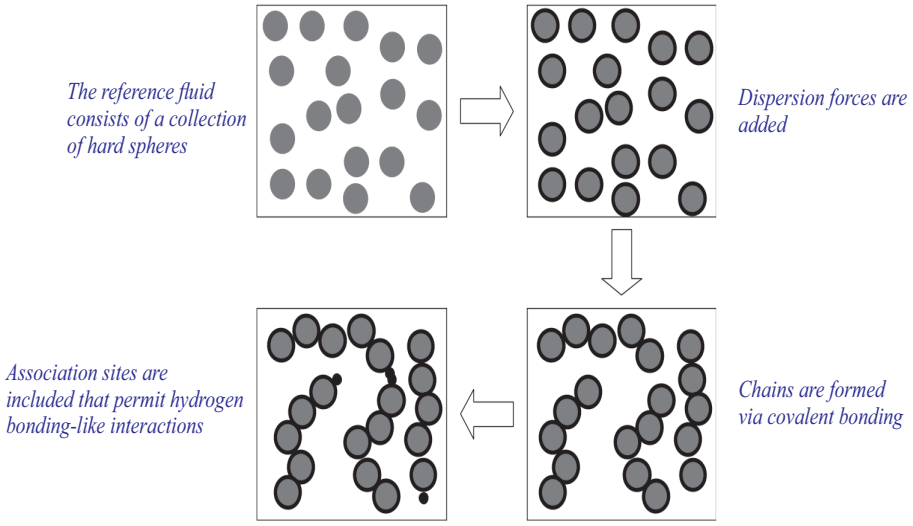

FIG. 2.1. *Adapted from [16]. In the SAFT framework, the reference fluid consists of a collection of hard spheres to which dispersion forces are added. These spheres can form chains via covalent bonding. Association sites are added to the chains that allow for the inclusion of hydrogen bonding type interactions.*

2.3.2. Statistical Associating Fluid Theory. Statistical Associating Fluid Theory (SAFT) is a sophisticated tool for developing realistic thermodynamic models for polymer solutions ([15, 16]). The theory allows for the development of tailored models for specific polymer/drug systems constituting solid dispersions. For a single component fluid system, the physical basis of the SAFT approach is illustrated in Figure 2.1. The reference fluid consists of a system of hard spheres to which weak dispersion forces are added. These spheres can form chains of a given length via covalent bonding. Finally, association sites are added to the chains to allow for hydrogen bonding-type interactions.

The Helmholtz free energy $\mathcal{A}$ (J) of the fluid in SAFT is then calculated as follows

$$\mathcal{A} = \mathcal{A}^{ideal} + \mathcal{A}^{hs} + \mathcal{A}^{disp} + \mathcal{A}^{chain} + \mathcal{A}^{assoc}$$

where

$\mathcal{A}^{ideal}$ = contribution from the ideal fluid,
$\mathcal{A}^{hs}$ = contribution from the hard sphere assumption,
$\mathcal{A}^{disp}$ = contribution from the dispersion force interactions,
$\mathcal{A}^{chain}$ = contribution from the covalent bonding,
$\mathcal{A}^{assoc}$ = contribution from the association interactions.

Expressions for each of these quantities have been calculated by the applied statistical thermodynamics community, and can be found in [16]. A full listing and explanation of these equations would occupy a number pages, and so for brevity we have omitted these details here. Once the free energies for the individual components have been calculated, the free energy for the *mixture* can then be calculated using mixing rules.

With the free energy of the mixture in hand, the activity coefficients can be calculated as follows ([12, 13, 14]). We first define the residual Helmholtz free energy

via

$$\mathcal{A}^{res} = \mathcal{A} - \mathcal{A}^{ideal} = \mathcal{A}^{hs} + \mathcal{A}^{disp} + \mathcal{A}^{chain} + \mathcal{A}^{assoc},$$

and the residual chemical potentials are then given by

$$\mu_i^{res} = \mathcal{A}^{res} + RT(\mathcal{Z} - 1) + \frac{\partial \mathcal{A}^{res}}{\partial N_i} - \sum_{j=1}^{3} N_j \frac{\partial \mathcal{A}^{res}}{\partial N_j},$$

for $i = 1, 2, 3$ as before, and where

$$\mathcal{Z} = 1 + \rho \frac{\partial(\mathcal{A}^{res}/RT)}{\partial \rho}$$

is the incompressibility factor, with ρ the density of the system. The fugacity of component i in the mixture is then given by

$$\varphi_i = \frac{1}{\mathcal{Z}} \exp\left(-\frac{\mu_i^{res}}{RT}\right).$$

Finally, the activity coefficient for component i is now given by

$$\gamma_i = \frac{\varphi_i}{\varphi_{i0}},$$

where φ_{i0} is the fugacity of the pure component i.

3. Future work. The following briefly summarises our future research plan for investigating the behaviour of solid dispersions.

- We shall begin by considering Flory-Huggins type models for polymer solutions. It is envisaged that the consideration of these simpler systems will yield mechanistic insights. Once this work has been completed, we shall use the SAFT framework to develop more realistic models for specific polymer/drug systems.
- We shall address two main problems. The first of these is the storage stability problem. For this problem, we shall develop a representative initial boundary value problem to describe the behaviour of the solid dispersion in storage. Initially, we shall consider a two component model (polymer/drug) and identify those parameter regimes that lead to stable, metastable, and unstable behaviour. It is also worth noting that because we shall be considering the full non-equilibrium problem, we should also be able to obtain information concerning the timescales over which phase separation and drug crystallization occurs. By introducing a third component for water molecules, the effect of air humidity on storage stability will also be investigated.
- The second problem we shall consider is the dissolution problem. In this case, we shall develop a representative initial boundary value problem to describe the dissolution of a solid dispersion. Particular attention will be paid to identifying the underlying mechanisms and parameter regimes that lead to the spring and parachute effect.

Acknowledgments. M. Meere thanks NUI Galway for the award of a travel grant. We thank the referee for their helpful suggestions to improve the paper.

REFERENCES

[1] H. D. Williams and N. L. Trevaskis and S. A. Charman and R. M. Shanker and W. N. Charman and C. W. Pouton and C. J. H. Porter, *Strategies to address low drug solubility in discovery and development*, Pharmacological Reviews, 65 (2013), pp. 315–499.

[2] K. T. Savjani and A. K. Gajjar and J. K. Savjani, *Drug solubility: importance and enhancement techniques*, ISRN Pharmaceutics, 2012 (2012), pp. 1–10.

[3] M. Doi, *Introduction to polymer physics*, Oxford University Press, Oxford, UK, 1996.

[4] E. B. Smith, *Basic chemical thermodynamics*, Sixth Ed., Imperial College Press, London, UK, 2014.

[5] J. W. Cahn and J. E. Hilliard, *Free energy of a nonuniform system. I. Interfacial free energy*, The Journal of Chemical Physics, 28 (1958), pp. 258–267.

[6] N. Provatas & K. Elder, *Phase-field methods in material science and engineering*, John Wiley & Sons, 2010.

[7] Y. Huang and W. Daib, *Fundamental aspects of solid dispersion technology for poorly soluble drugs*, Acta Pharmaceutica Sinica B, 4(1) (2014), pp. 18–25.

[8] C. Brough and R. O. Williams III, *Amorphous solid dispersions and nano-crystal technologies for poorly water-soluble drug delivery*, International Journal of Pharmaceutics, 453 (2013), pp. 157–166.

[9] D. Q. M. Craig, *The mechanisms of drug release from solid dispersions in water-soluble polymers*, International Journal of Pharmaceutics, 231 (2002), pp. 131–144.

[10] N. Ahuja and O. P. Katare and B. Singh, *Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers*, European Journal of Pharmaceutics and Biopharmaceutics, 65 (2007), pp. 26–38.

[11] Z. A. Langham and J. Booth and L. P. Hughes and G. K. Reynolds and S. A. C. Wren, *Mechanistic insights into the dissolution of spray-dried amorphous solid dispersions*, Journal of Pharmaceutical Sciences, 101(8) (2012), pp. 2798–2810.

[12] Y. Ji and R. Paus and A. Prudic and C. Lubbert and G. Sadowski, *A novel approach for analyzing the dissolution mechanism of solid dispersions*, Pharmaceutical Research, 32 (2015), pp. 2559–2578.

[13] G. M. Kontogeorgis and G. K. Folas, *Thermodynamic models for industrial applications*, First ed., John Wiley & Sons, Chichester, West Sussex, UK, 2010.

[14] J. M. Prausnitz and R. N. Lichtenthaler and E. G. de Azevedo, *Molecular thermodynamics of fluid-phase equilibria*, Third ed., Prentice Hall, New Jersey, 1999.

[15] I. G. Economou, *Statistical associating fluid theory: a successful model for the calculation of thermodynamic and phase equilibrium properties of complex fluid mixtures*, Industrial & Engineering Chemistry Research, 41 (2002), pp. 953–962.

[16] C. McCabe and A. Galindo, *SAFT associating fluids and fluid mixtures*, Applied Thermodynamics of Fluids, Chapter 8, Royal Society of Chemistry, pp. 215–279, 2010.