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Review

The mechanisms of drug release from solid dispersions in water-soluble polymers

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Abstract

Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability, of a range of hydrophobic drugs. However, despite the publication of numerous original papers and reviews on the subject, the mechanisms underpinning the observed improvements in dissolution rate are not yet understood. In this review the current consensus with regard to the solid-state structure and dissolution properties of solid dispersions is critically assessed. In particular the theories of carrier- and drug-controlled dissolution are highlighted. A model is proposed whereby the release behaviour from the dispersions may be understood in terms of the dissolution or otherwise of the drug into the concentrated aqueous polymer layer adjacent to the solid surface, including a derivation of an expression to describe the release of intact particles from the dispersions. The implications of a deeper understanding of the dissolution mechanisms are discussed, with particular emphasis on optimising the choice of carrier and manufacturing method and the prediction of stability problems.

Keywords: Dissolution; Eutectic; Particle size; Polyethylene glycol; Solid dispersion; Stability

1. Introduction

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. More specifically, Chiou and Riegelman (1971), in their classic review, defined these systems as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method', while Corrigan (1985) suggested the definition as being a 'product formed by converting a fluid drug-carrier combination to the solid state'. In practice, these dosage forms have been traditionally regarded as being synonymous with systems whereby the in vitro release of the drug is enhanced compared to conventional dosage forms, with concomitant implications for

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in vivo release. Furthermore, the carrier used has, again traditionally, been a water-soluble or water-miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as sugars. However, the proliferation of publications in the area since the first solid dispersions were described (Sekiguchi and Obi, 1961) has led to a broadening of these definitions to include water insoluble matrices such as Gelucires and Eudragits that may yield either slow or rapid release and absorption. Numerous reviews have appeared in the literature (Chiou and Riegelman, 1971; Ford, 1986; Craig, 1990; Serajuddin, 1999), attempting to bring together the various publications and ideas associated with these dosage forms. The latest of these (Serajuddin, 1999) gives details of some more recent approaches such as the use of surface active carriers and the use of melt-extrusion of PVP dispersions as a means of manufacturing viable dosage forms using this technology.

One aspect of solid dispersion technology on which most workers in the field would agree is that the number of marketed products arising from this approach has been disappointing. Indeed, the sheer simplicity of the manufacturing method, the fact that in general only the drug and carrier are required and the frequently reported improvements in both the dissolution rate and bioavailabilty would lead one to expect that the transfer to the market place would be rapid and widespread. This has not been the case, despite approximately 500 papers having been published on the subject. While this is to a large extent associated with manufacturing and stability considerations, it is also arguable that a primary reason is poor predictability of solid dispersion behaviour due to the lack of a basic understanding of their properties. In particular we believe there are four key problem areas in this respect:

1. *The solid state structure*. It is still not clear how the drug is dispersed within the matrix in the majority of cases. Methods such as DSC, XRD and hot stage microscopy have been widely employed but the question as to whether the drug is present as a molecular, a crystalline particulate or an amorphous particulate dispersion is far from clear in the majority of cases. Fortunately, this issue has been studied in more detail in recent years, with techniques such FTIR, Raman spectroscopy and solid state NMR being employed in addition to the aforementioned methods, particularly to study the nature of the molecular interactions between the drug and the carrier in amorphous systems (e.g. Matsumoto and Zografi, 1999; Forster et al., 2001).
2. *The mechanism by which dissolution enhancement occurs*. While a number of theories have been proposed (outlined below) the mechanism by which the dissolution rate is improved in relation to conventional dosage forms is again not fully understood.
3. *The stability of the dispersions on storage*. Numerous studies have observed changes to the dissolution rate on storage. However, again the mechanism responsible is not yet clear. This is arguably a direct result of the poor understanding of the dissolution rate mechanism or mechanisms; it is by definition difficult to understand why a dissolution profile changes with time if the factors determining the initial dissolution behaviour are not known. Clearly, such instability, though not universal, renders the dispersions unsuitable as products when it does occur.
4. *Poor understanding of the in vitro/in vivo correlation*. While numerous studies have reported enhanced dissolution rates and absorption rates from solid dispersions the correlation between the two is not straightforward. It should also be born in mind that the literature tends to be success led, hence examples of poor absorption improvement are less likely to be brought to the scientific community's attention.

The above difficulties are all functions of the fundamental understanding of the behaviour of the systems, with the first three being related to the physical behaviour of the dispersions. Consequently, while developments in manufacturing methods and the use of alternative carriers are undoubtedly welcome there remains a need to consider what has been learned over the past forty years in terms of the mechanisms by which dissolution enhancement occurs. The function of the

current discussion is therefore not to review the field of solid dispersions as a whole but instead to examine the current state of knowledge with regard to the dissolution mechanisms.

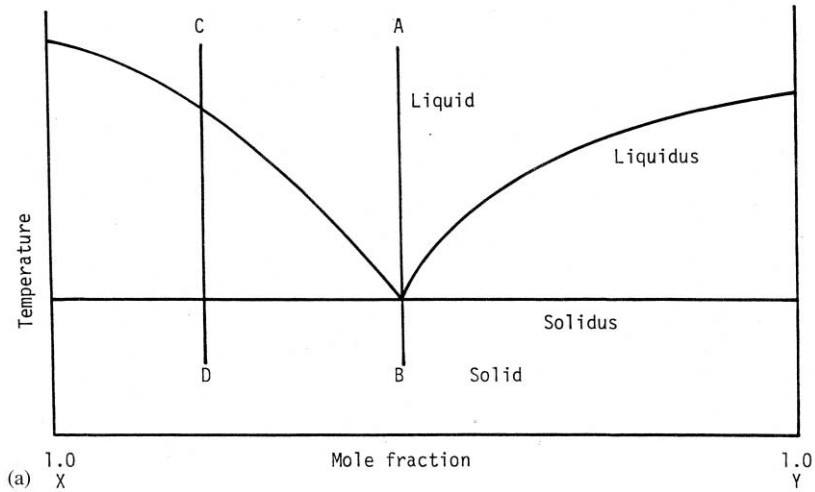
2. Proposed structures of solid dispersions

Before discussing the dissolution properties of the dispersions, it is clearly essential to have some consideration of the solid-state properties of these systems. The dispersions have traditionally been formed by heating mixes of the drug and carrier to the molten state (although whether this molten mix is a suspension or solution is usually not defined) followed by resolidification via cooling. Alternative methods involve dissolving the components in a mutual volatile solvent followed by evaporation or dissolving the drug in a solvent such as propylene glycol and adding that to the molten carrier. Other approaches include melt-extrusion methods (Sprokel et al., 1997; Zhang and McGinity, 2000; Forster et al., 2001) that appear to offer a number of interesting opportunities.

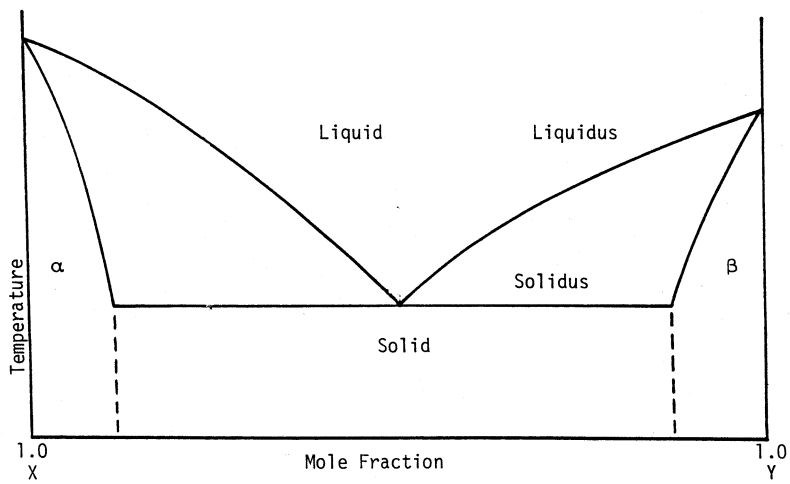
Irrespective of the methodology used, the question as to the physical nature of the dispersion remains unanswered in many cases. Classically, Chiou and Riegelman (1971) defined a number of possibilities. These include eutectic systems, whereby on cooling the molten mix the system forms a microfine dispersion of the two components with a concomitant decrease in melting point. This has been a favoured explanation for several systems, particularly in the light of DSC studies that have frequently been reported to show a eutectic melting point and a lowering of the melting points of the principle components. However, some caution is required in this interpretation for a number of reasons. In the first instance, it is essential to bear in mind that unless one is exactly at the eutectic composition, the system will contain a mixture of the microfine dispersion and one or other component as a separate phase, as indicated in Fig. 1a. Indeed, as one cools from the melt of any composition other than that corresponding to the eutectic, one component will progressively solidify, thereby rendering the remaining liquor richer in the other component until the eutectic composition is reached, at which point the remaining liquid will solidify as a fine dispersion. Consequently, if the reported systems are indeed eutectics it is necessary to appreciate the complex nature of the mixes used in practice. The second issue is that the polyethylene glycols used for the majority of solid dispersion studies (molecular weight 4000–20,000) may exist in more than one crystal form, exhibiting multiple melting points in the region of 55–65 °C (Beech et al., 1972; Buckley and Kovacs, 1976). It has been suggested that many of the dual melting points described in the literature ascribed to eutectic behaviour may in fact be chain folded forms of the PEG itself (Craig, 1990). Thirdly, it is arguably essential to compare the melting behaviour of the solid dispersion to that of a physical mix of the drug and carrier, as many studies have indicated that the phase diagrams of the two systems may be extremely similar (Sekiguchi et al., 1963; Chiou and Niazi, 1971, 1973). Indeed, the presence of the carrier in the molten state may itself lower the melting point of the drug. Consequently, the detection of melting point lowering and, in the case of PEGs, the appearance of a lower temperature melting peak, does not necessarily indicate the presence of a eutectic. While some systems must inevitably form eutectics, the number of studies that have demonstrated unequivocally that a eutectic is present is in fact very limited.

The second common explanation is that of a solid solution, whereby the drug is present as a molecular dispersion within the carrier. This is a fully feasible explanation but again caution is required in terms of the detection of such systems.

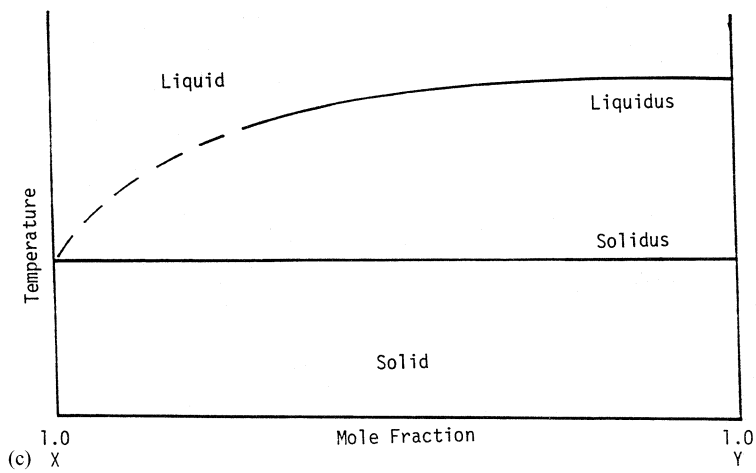
Fig. 1. (a) Schematic eutectic phase diagram, showing effect of cooling at the eutectic point (A to B) whereby only the eutectic solidifies. This is compared to cooling at an alternative composition (C to D) whereby component X solidifies during cooling, leaving the remaining liquor richer in Y until the eutectic temperature/composition is reached. (b) Schematic solid solution phase diagram (partial miscibility), showing regions of solid solubility at the extremes of composition. (c) Schematic monotectic phase diagram, showing convergence of the liquidus with the melting point of one component.



(a)



α - Solid solution of Y in X
(b) β - Solid solution of X in Y



(c)

Fig. 1.

In practice the majority of such systems are likely to show only partial miscibility, hence the drug may only be in 'solution' at low concentrations (Fig. 1b), although it is appreciated that partial miscibility could in theory involve quite extensive drug incorporation at a molecular level. Nevertheless unequivocal demonstration of solid solubility is not as simple as one may imagine. For the reasons outlined above the melting point of a drug may be lowered and broadened so as to make it undetectable using DSC (Lloyd et al., 1997a). Similarly, XRD analysis needs to be conducted in comparison to physical mixes of identical composition to ascertain whether the lack of appearance of drug peaks is due to solid solution formation or is simply a function of the sensitivity of the instrument.

Thirdly, the drug may be present as a dispersion in a glassy matrix. This is certainly the case with amorphous polymers such as PVP and is probably also of relevance in many cases to semicrystalline materials such as PEGs (e.g. Anguiano-Igea et al., 1995; Tantoshaiyakul et al., 1996). Again, questions still remain as to whether the drug is dispersed on a molecular basis, is present as a separate amorphous phase or is present as a separate crystalline phase (or some combination of these). In some respects this is perhaps the area in which the most progress has been made, as the work by the group of Zografi (e.g. Matsumoto and Zografi, 1999) and others over the last decade has provided a more thorough basis by which to study and understand amorphous systems. This is arguably ironic as such systems may be expected to be more complex than crystalline dispersions. Finally, complex formation has been suggested as a further possibility. Clearly this is applicable to materials such as cyclodextrins and may also be of relevance to PVP and other carriers.

A further category that has been suggested since the review of Chiou and Riegelman (1971) has been that of monotectic systems (e.g. Kaur and Grant, 1979; Najib and Suleiman, 1989). These systems were suggested on the basis of the frequent observation that many reported eutectics had eutectic points that appeared to be convergent with the melting point of the pure material, as indicated in Fig. 1c. Such systems have been reported in the alloy literature but later studies have indicated that, rather than indicating specific equilibrium phase behaviour, such diagrams may be simply a reflection of a completely non-interacting system, whereby the drug is simply present as a separate phase within the carrier. This was exemplified by a study by Lloyd et al. (1997b) whereby the model drug (paracetamol) was found to simply crystallise as a separate phase on cooling, as demonstrated by hot stage microscopy, the lowering of drug melting point being a simple reflection of the presence of molten carrier.

Overall, therefore, there still remain numerous questions regarding the physical nature of solid dispersions, despite the chemical simplicity of these systems. There is an argument that, at least in the case of PEGs and other largely crystalline carriers, the system may be simpler than has been assumed, with the two components simply existing as separate phases (Craig, 1990; Lloyd et al., 1997a,b). Similarly it could also be argued that hot stage microscopy observations during cooling is one of the most reliable methods for ascertaining the solid state structure, especially given the propensity of DSC to demonstrate effects that are a function of the temperature programme rather than being a direct reflection of the solid state structure at room temperature.

3. Drug release from solid dispersions

While a number of potential and realised advantages of solid dispersions have been described in the literature, the single most widely cited consideration is the improvement in dissolution rate, with concomitant implications for improving the bioavailability of poorly water-soluble drugs. Such improvements in dissolution rate are often considerable, with increases of up to four hundred fold having been reported (Said et al., 1974). It is therefore all the more remarkable that the mechanism underpinning these increases is so poorly understood. This may be largely because there are comparatively few papers available whereby elucidation of the mechanism (or mechanisms) involved is a specific objective. In this article,

therefore, emphasis is placed on discussing some of the ideas associated with the release process with a view to developing the argument that a more fundamental understanding of the process will facilitate rational design of the associated dosage forms.

The currently accepted range of possible mechanisms of enhanced dissolution effectively stems from the seminal review by Chiou and Riegelman (1971). These include the following:

3.1. Particle size reduction and reduced agglomeration

These may be usefully considered together as both are related to increases in the exposed surface area of the drug. Size reduction has been classically considered to be a result of eutectic or solid solution formation; it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties, hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area.

3.2. Increased solubility or dissolution rate of the drug

Again, many of the carriers used may increase the solubility of the drug. There has been some debate over this mechanism as solubility studies have indicated that at the concentrations used for in vitro experiments the carriers often elicit minimal solubility increases. This does, however, work on the assumption that the concentration of the carrier after complete dissolution in the water bath (e.g. 0.5 g/l) may be used as a model of the behaviour at the dissolving surface. Similarly, the carrier and drug may form a soluble complex, as is well established for cyclodextrins, although the evidence for this occurring with other carriers is weaker. Finally, changes to the physical properties of the drug such as degree of crystallinity and polymorphic form may also be considered under this category.

In parallel with these considerations, there has also been an alternative line of thinking that has attempted to consider the processes that may be involved during dissolution in more detail. It may be argued that this type of approach has arisen as a result of seminal papers by the groups of Corrigan, Ford and Nystrom in the 1980s but has not yet been fully incorporated into the common parlance within the field, despite the possibilities for dissolution prediction that it appears to offer. However, the strands of these arguments have not yet been weaved together in a single article and it is this deficiency that the present communication is attempting to address.

There have been two apparently conflicting lines of research along these lines. In the first instance, Corrigan (1985, 1986) provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case PEG. The author found that the dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by that of the inert carrier. This finding was supported by the work of Dubois and Ford (1985) who noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most cases. This again implies that it is the dissolution rate of the carrier and not the drug that may dominate the process. Similarly, a study by Craig and Newton (1992) indicated that a log-linear relationship existed between the (measured as opposed to nominal) molecular weight of the PEG carrier and the dissolution rate, again implying that the properties of the polymer were dominating the dissolution process.

Corrigan (1985) has suggested that carrier-controlled dissolution may be modelled in terms of the approach outlined by Higuchi et al. (1965) and Higuchi (1967), whereby the dissolution of two-component systems is considered. Upon exposure to the solvent both components dissolve at rates proportional to their solubilities (C_s) and

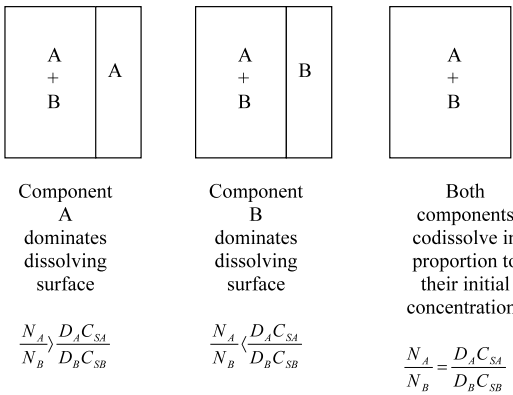


Fig. 2. Schematic representation of the dissolution model for a two component system (after Higuchi et al., 1965). See text for explanation of symbols.

diffusion coefficients (D) in the dissolving medium, as predicted for single component systems by the well-known Noyes–Whitney equation. However this model predicts that the interfacial layer between the dissolving front and the solvent will become depleted in the more rapidly dissolving component, leading to the creation of a surface layer rich in one component through which the other must diffuse prior to release into the bulk phase (Fig. 2). More specifically the model predicts that one component (for example A) will form such a surface layer when

$$\frac{N_A}{N_B} > \frac{D_A C_{SA}}{D_B C_{SB}} \quad (1)$$

where N is the proportion of each component and the subscripts A and B refer to the two components, respectively. Under these circumstances the dissolution rates will be given by

$$G_A = \frac{D_A C_{SA}}{h} \quad (2)$$

and

$$G_B = \frac{N_B}{N_A} G_A \quad (3)$$

where G is the dissolution rate/unit area and h is the diffusion layer thickness. In other words the model predicts that the dissolution rate of the minor component will be determined by that of the component in excess (although it should be noted that 'minor' is more precisely defined in terms of Eq. (1) rather than simply the weight fraction present). This may in turn be applied to solid disperse systems by arguing that when the drug is present as a 'minor' component (which is almost invariably the case) the dissolution of that drug will be dominated by the dissolution behaviour of the carrier, as is indeed seen in practice (Corrigan, 1986). Interestingly, the predicted component ratio at which dominance changes between the two components is given by

$$\frac{N_A}{N_B} = \frac{D_A C_{SA}}{D_B C_{SB}} \quad (4)$$

This therefore predicts that if a drug (B) has a very low solubility in relation to that of the polymer (A) then the drug loading up to which carrier-controlled dissolution will apply will be similarly low, while a more soluble drug will show carrier-controlled dissolution up to a higher drug loading (assuming similar diffusion coefficients). This would appear to contradict the observations of Dubois and Ford (1985), who noted that phenacetin (0.77 mg/ml solubility) showed a more limited range of carrier-controlled dissolution (up to 5% loading) than did the less soluble (0.04 mg/ml) indomethacin (up to 10% drug loading). This could be due to diffusion coefficient effects or else to differences in the dispersion profiles of the two drugs within the polymer.

Leading on from these studies, Lloyd et al. (1999) argued that if dissolution was dominated by the properties of the carrier and not the drug (at least in some cases) then the physical form of the drug should be irrelevant to the release rate. These authors examined the release of paracetamol from PEG 6000 dispersions, using different drug size fractions in the initial preparation process and different manufacturing methods which were known to alter the physical properties of the drug (Lloyd et al., 1997b). First inspection of the dissolution data indicated a higher release from the larger size fraction systems. However, these authors also measured the concentration of drug at the dissolving surface, finding that settling had occurred during the solidification process on cooling from the melt. Once this had been corrected for (see Eq. (3)), the dissolution rates were found

to be independent of manufacturing conditions or initial particle size. This therefore confirmed that for these systems the physical form of the drug was unimportant as far as the release rate was concerned but also highlighted the danger of settling leading to higher effective concentrations of drug being present at the dissolving surface than may be anticipated from the total drug content.

However, while these studies, described together, give the impression of there being a common unifying mechanism underpinning release, there have been a number of papers suggesting that other mechanisms may be of relevance. For example, Sjökvist and Nyström (1991) measured the particle size of the griseofulvin particles released from the dispersions and produced strong evidence that dissolution rate enhancement was a direct function of the size of the released particles. In an attempt to reconcile these contradictions Sjökvist-Saers and Craig (1992) used an homologous series of drugs (*para*-aminobenzoates) in PEG 6000 in an attempt to interrelate the solid state structure, drug solubility and dissolution rate. These authors noted that there was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility, clearly linking the properties of the drug (and not the polymer) to the dissolution rate; it may be helpful at this stage to refer to such behaviour as drug-controlled dissolution as opposed to carrier-controlled dissolution. It was also noted that as the concentration of the drug increased the dissolution rate became effectively independent of composition and very similar to the drug alone (Fig. 3); in this respect therefore the behaviour corresponds to the Higuchi model when the drug is the dominant component. However the interrelationship between the dissolution rate and the solubilities of the drugs at high polymer contents runs contrary to what one would expect from the Higuchi model; if the dissolution was carrier controlled the drug properties should make no difference to the dissolution rate.

Overall, therefore, there appear to be two sets of observations with regard to the mechanism of drug release from solid dispersions. In the first instance, some systems appear to show carrier-controlled release whereby, at least at low drug loadings, the rate of release is controlled by that of the carrier and is independent of drug properties. Secondly some systems show release behaviour that is dependent on the properties of the drug rather the polymer, even at low drug loadings. The following questions therefore arise; what is happening to the drug during either of these processes, which factors determine whether the dissolution is carrier- or drug- controlled and what are the implications of understanding the mechanism for dosage form design?

4. Possible mechanism of dissolution from solid dispersions and implications for manufacture

Given the above considerations, there does appear to be more than one mechanism by which drugs may be released from solid dispersions. Probably the simplest scenario is that found at high drug loadings, where authors appear to agree that the formation of the drug-rich layer suggested by Higuchi et al. (1965) and applied to solid dispersions by Corrigan (1985) provides a satisfactory explanation. This leaves the dual observations for low drug loadings regarding drug-controlled and carrier-controlled dissolution. We believe that both may be facets of essentially the

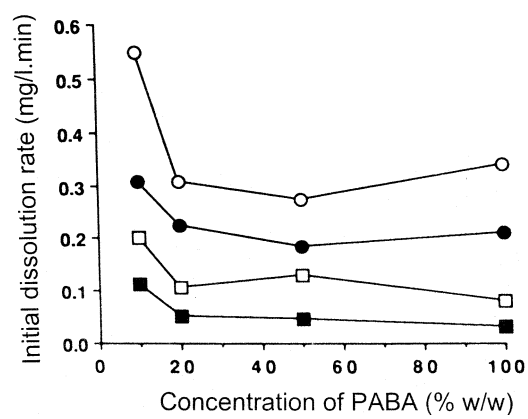


Fig. 3. Relationship between initial intrinsic dissolution rate and concentration of *para*-aminobenzoic acid (PABA) in PEG 4000 solid dispersions. (○) Methyl PABA; (●) ethyl PABA; (□) propyl PABA; (■) butyl PABA (reproduced with permission from Sjökvist-Saers and Craig, 1992).

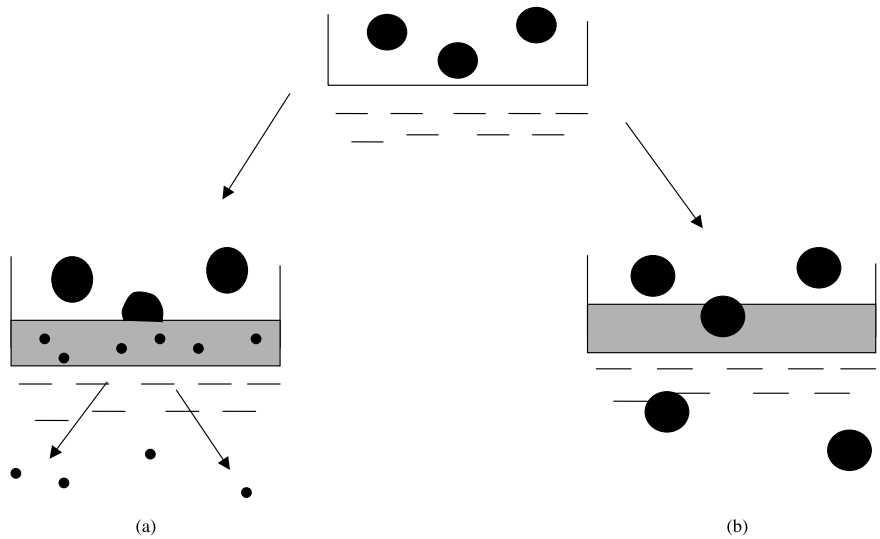


Fig. 4. Schematic diagram showing the fate of drug particles during the dissolution process. (a) Carrier-controlled dissolution, whereby the drug dissolves into the concentrated carrier layer prior to release and (b) drug-controlled dissolution whereby the drug is released effectively intact into the dissolution medium. Large spheres represent undissolved drug particles, small spheres partially dissolved drug particles, shaded regions correspond to hydrated material.

same process and propose a model, outlined in Fig. 4, that attempts to explain how the drug particles may be behaving during the dissolution process. The model works on the premise of there being a highly concentrated polymer layer at the dissolving surface (at least at low drug loadings) through which the drug must pass prior to release into the bulk phase.

In Fig. 4a, the process associated with carrier-controlled dissolution is described. In this instance the particles dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate that there is insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer. However, the viscosity of the layer is such that drug diffusion is very slow as predicted by the well-known Stokes–Einstein equation

$$D = \frac{kT}{6\pi\eta r} \tag{5}$$

where k is Boltzmann's constant, η is the viscosity and r is the radius of the diffusing molecule. Consequently the rate-limiting step to dissolution of the drug becomes the release of the polymer itself and hence Eq. (3) becomes applicable to describe the release of the drug. It should be noted that the dissolution of a water soluble polymer may not be modelled by simple diffusion equations with complete confidence as such polymers do not show saturation solubility as such but rather will swell and sorb water to produce a continuum of concentrations between the solid surface and the bulk medium; these and related issues have been addressed in communications by Ueberreiter (1968). However, the principle outlined above is nevertheless still applicable.

The second scenario, that of drug-controlled dissolution, is outlined in Fig. 4b. In this case dissolution into the polymer diffusion layer is comparatively slow and the drug is released as solid particles. Consequently the dissolution will not be associated with the polymer but will instead be dominated by the properties (size, physical form, etc.) of the drug itself. This may still lead to considerable improvements in dissolution compared to conventional dosage forms due to the higher surface area associated the particles and the possibility of improved wetting and decreased agglomeration.

The question therefore arises as to why some drugs will follow the scenario shown in Fig. 4a and others 4b. The most likely explanation must be the tendency of the drug to dissolve into the concentrated polymer diffusion layer. As stated previously, the solubility of drugs in low concentrations of carrier solutions does not tend to be significantly enhanced compared to that in water alone. However, several studies have demonstrated that the drug solubility increases disproportionately in higher concentration solutions. More specifically, a log-linear relationship has been described for several systems as predicted by the expression given by Yalkowsky et al. (1972) for cosolvent systems

$$\log S = \log S_W + \sigma f \quad (6)$$

where S is the solubility of the solvent under investigations, S_W is the solubility in water, σ is a constant and f is the proportion of cosolvent present in the system. It is therefore feasible that for many drug-carrier combinations the drug solubility in the concentrated layer is sufficiently high so as to allow dissolution to occur prior to the dissolving front of the composite solid reaching the particles. Once in solution in the diffusion layer, the viscosity is sufficiently high so as to render diffusion through the concentrated layer slow and the rate-limiting step to release becomes the diffusion of the carrier molecules into the bulk phase, as predicted by the Higuchi model. In the case of drugs whereby the solubilisation is low, however, the particles may be simply released partially or completely intact from the matrix, whereupon dissolution occurs from the free particle surface.

Overall, therefore, the release mechanism will depend on whether the drug dissolves in the polymer diffusion layer rapidly or not which will in turn be dependent largely on the solubility of the drug in this layer. However, other considerations must also be borne in mind. For example, the hydrodynamics of the dissolution process may also play a role in determining the mechanism in that more rapid stirring speeds may favour drug-controlled dissolution by enhancing the rate of polymer dissolution into the bulk in relation to drug dissolution into the diffusion layer. Similarly by changing the physical form of the drug (e.g. size reduction), one could conceivably change the mechanism by altering the dissolution kinetics into the diffusion layer. Furthermore, while the process has been described above as one of two extremes it is possible that in many cases elements of both are present, e.g. the particles may partially dissolve in the diffusion layer before being released intact, thereby providing two simultaneous mechanisms of dissolution. However, the model does serve to provide an explanation for the differences in behaviour of various drugs and also suggests that the measurement of drug solubility in carrier solutions may, with refinement, provide a means of predicting the dissolution mechanism.

5. Mathematical modelling of drug-controlled dissolution

As there are already effective expressions available to model carrier-controlled drug dissolution (Eqs. (1)–(4)), it would clearly be desirable to derive an expression whereby the intact particle release mechanism could be described. Outlined below is a suggested basis for such an analysis. This approach has been developed on the idea of the solid polymer receding to a distance such that a single particle is released, as indicated in Fig. 5. Two of the main assumptions of the model become immediately apparent. Firstly it is assumed that the drug is released only when the solid front has receded a distance equivalent to the diameter of that particle and secondly that the particle does not undergo significant dissolution prior to release. A third assumption concerns the equivalence of the densities of the drug and polymer; this may be easily corrected for but it is felt that the error arising from this assumption will be small in relation to the other approximations involved. Fig. 5 presents a representation of the salient features of the solid dispersion structure relevant to the proposed model.

The overall dissolution rate at time t ($G_T(t)$) may be considered to be essentially a function of the mean dissolution rate from each individual particle ($G_P(t)$) and the number of particles available $N(t)$, i.e.

$$G_T(t) = \sum^{N} G'_P(t) \approx G_P(t)N(t) \quad (7)$$

where G'_P is the dissolution rate at time t of the individual particles. In the first instance it is necessary to calculate the time dependence of the particle release process by considering the time required for sufficient polymer to dissolve in order to release a particle. This is achieved by considering the intrinsic polymer dissolution rate P_A (wt/$A \cdot t$ where A is area of dissolving surface). The dissolution rate (P_T) may also be expressed in terms of the volume of polymer dissolved in unit time from a disk of diameter $2R$

$$P_T = \frac{P_A}{\rho}\pi R^2 \quad (8)$$

where ρ is the density of the polymer. The volume of dispersion (V_P) that needs to dissolve for a particle of diameter r to be released is given by

$$V_P = 2\pi r R^2 \quad (9)$$

hence the time (t_P) required to release such a particle is given by

$$t_P = \frac{V_P}{P_T} = \frac{2r\rho}{P_A} \quad (10)$$

Note that equivalence of matrix dissolution and polymer dissolution can be reasonably assumed from the Higuchi model (Higuchi et al., 1965) if the polymer is present in large excess. The above may be modified for situations where this does not apply but for the present purposes this assumption is satisfactory.

To calculate the number of particles released in time t_P (N_P) it is merely necessary to calculate the number of particles present in V_P by multiplying by the weight fraction x (here we assume density equivalence of the two components) and dividing by the volume of a single particle

$$N_P = \frac{3R^2x}{2r^2} \quad (11)$$

Consequently from Eqs. (10) and (11)

$$\frac{\partial N}{\partial t} = \frac{3R^2xP_A}{4r^3\rho} \quad (12)$$

Integrating between $t = 0$ and $t = t$ gives

$$N(t) = \frac{3R^2xt}{4r^3\rho} \cdot \int_{t=0}^{t=t} P_A \, dt \quad (13)$$

It is then possible to combine the above with an expression describing the dissolution of a single particle. Numerous such models are available with varying degrees of sophistication but for the present purposes one may use the simple expression derived by Goyan (1965)

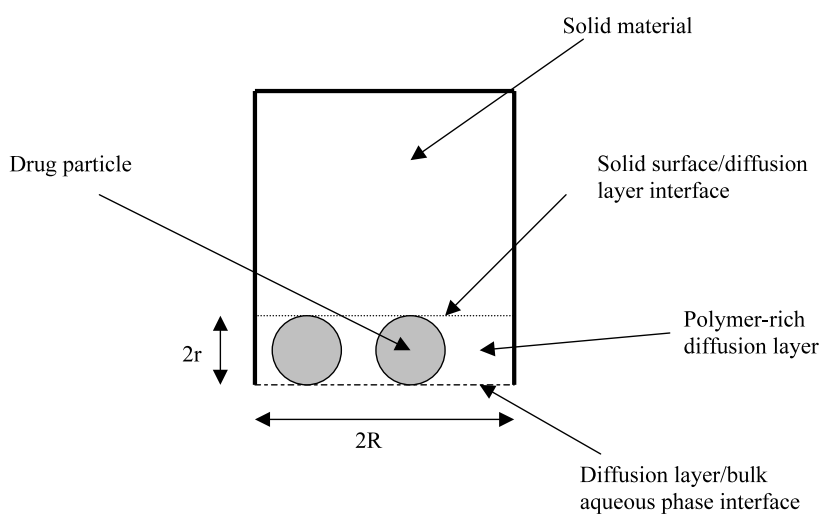


Fig. 5. Schematic representation of the structure of solid dispersions with reference to the model derived for drug-controlled dissolution.

$$G_P = \frac{D}{r}(C_S - C) \quad (14)$$

where C_S and C represent the solubility and bulk concentration. Overall therefore the dissolution rate of the system is given by

$$G_T = \frac{3D(C_S - C)R^2xt}{r^4\rho} \cdot \int_{t=0}^{t=t} P_A \, dt \quad (15)$$

The integral term is simply the intrinsic dissolution rate constant of the polymer. Clearly this model may be further refined and many of the assumptions accounted for. However, it does provide a basis for further work and also, interestingly, predicts that the dissolution rate will be highly dependent on the initial particle size. It also predicts non-linearity of the dissolution profiles, even from a constant surface area disk. This was indeed observed in the study by Sjökvist-Saers and Craig (1992) for systems showing drug-controlled dissolution.

6. Implications of understanding the dissolution mechanism for the practical use of solid dispersions

The obvious question to arise at this stage is what are the implications of such knowledge for dosage form design? The primary issue must be the prediction and control of dissolution rate. If a system is undergoing carrier-controlled dissolution then the physical properties of the drug should be largely irrelevant (given the proviso stated above regarding changing the mechanism). This then means that the initial particle size and the physical form of the drug are of minimal importance. This in turn implies that, provided the physical form of the carrier is not greatly changed, the manufacturing process variables such as maximum temperature used is irrelevant. This specific factor is an interesting case in point as it has not yet been fully established whether the drug needs to be dissolved in the molten polymer during preparation or not; indeed it has been largely assumed that both components need to be fully liquefied during manufacture. Studies by Lloyd et al. (1999) for a carrier-controlled system have shown this not to be the case, with the manufacturing temperature used having no effect on paracetamol release. In fact the drug recrystallizes as a separate phase anyway on cooling hence the maximum fusion temperature, with concomitant costs and safety issues, may not need to be as high as has been assumed. If, on the other hand, the dissolution process is drug-controlled then the properties of the drug become crucial.

This distinction also has implications for the choice of carrier. If the system is carrier controlled, then changing the molecular weight of the carrier, incorporating a proportion of lower molecular weight material or adding surfactants may all have a beneficial effect. Indeed, if a carrier-controlled system is desirable then screening could be performed to determine which carriers or mixtures of carriers provide ample solubilisation of the drug prior to extensive experimentation. However, perhaps the most important implication of such knowledge concerns the understanding of a perennial problem associated with these systems, namely stability issues. Despite the plethora of reports describing changes in dissolution rate on storage, a universal explanation for this phenomenon has not yet been established. In the light of the above, one can see why this has been the case, simply because the mechanism of ageing must be intimately linked to the mechanism of dissolution. More specifically, if the system is carrier-controlled then, in the absence of a change of mechanism, the ageing effects must be due to changes in the properties of the polymer. This is a large and well studied field within the polymer sciences, particularly for amorphous or semicrystalline polymers, and it is likely that means of predicting and preventing such effects may be found in this literature. If, on the other hand, the system is drug controlled then it is the properties of the drug itself that must be considered such as slow recrystallisation from unstable solid solutions, changes in polymorphic form, particle size increases or recrystallisation from the amorphous state. However, the key issue is that unless the basic mechanism of release is understood it does seem unlikely that prediction of ageing effects will be possible.

7. Conclusions

This article has outlined some of the current thinking with regard to the mechanisms by which drugs may be released from solid dispersions, focussing on the solid state properties of the dispersions and the possible fates of drug particles within a solid disperse matrix. It is proposed that two mechanisms may be of relevance, involving either carrier or drug controlled release, the predominance depending on the solubility of the drug in concentrated solutions of the carrier. The implications for this model have been outlined, with particular emphasis on understanding stability issues. Overall, solid dispersions present the industry with some extremely exciting possibilities with regard to the formulation of poorly soluble drugs, yet until the fundamental behaviour of these systems is understood the utility of this approach will inevitably remain limited or at best empirical.

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