THE MECHANISM OF DRUG RELEASE FROM SOLID DISPERSION IN WATER-SOLUBLE POLYMER

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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.
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, 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 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 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 (has led to a broadening of these definitions to include water insoluble matrices such as that may yield either slow or rapid release and absorption. Numerous reviews have appeared in the literature, attempting to bring together the various publications and ideas associated with these dosage forms. The latest of these 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 bioavailability 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, 2)

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 as 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.

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 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 it 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. 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.

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. 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. (34)
Fig. 1

(a) Liquidus
(b) Liquidus
(c) Liquidus

α - Solid solution of Y in X
β - Solid solution of X in Y

Solidus

Solid

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. 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 are a specific objective. In this, 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.

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 and applied to solid dispersions by Corrigan (1985) provides a satisfactory explanation. The dual observations for low drug loadings regarding drug controlled, carrier-controlled dissolution. We believe that both may be facets of essentially the same process.

![Graph](image)

Fig.2. Relationship between initial intrinsic dissolution rate and concentration of para-aminobenzoic acid (PABA) in PEG4000 solid dispersions. (-) Methyl PABA; (-) ethyl PABA; (-) propyl PABA; (-) butyl PABA. Same process and propose a model 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. 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.

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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