



Oral Delivery of Poorly Soluble Drugs, Part 2: Formulation Strategies for Solid Dosage Forms and Novel Delivery Systems for Controlled Release



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The preferred route of oral administration is limited to those drug molecules that are permeable across the gastric mucosa and are at least sparingly soluble. A large majority of the new chemical entities and many existing drug molecules are poorly soluble, thereby limiting their potential uses and increasing the difficulty of formulating bioavailable drug products. There are numerous methods that may facilitate solubility to further enhance performance of poorly soluble drugs for oral administration – several of the techniques available to formulators aimed at facilitating solubility were generally discussed in Part 1 of this article (1). This review focuses on formulation components and novel controlled release technologies, employed to produce a solid oral dosage form which can increase or enhance *in vivo* solubility of poorly soluble molecules.

While this review focuses on solid oral systems, a number of other systems are available for the oral delivery of low solubility drugs, including lipid-based soft-gel systems and self-emulsifying formulations comprising a lipid component and one or more surfactants. Such lipid-based systems are effective in their pursuit of solubilising low solubility drugs, but often require unique production processes and may be difficult to incorporate into controlled release formulations. Osmotic pumps also offer a highly effective method of delivery and are capable of linear release for even nearly insoluble drugs, but are limited in formation flexibility and are complex to manufacture. Solid dosage forms remain the most economic method of delivering any compound precisely due to the large range of technologies available and their familiarity to both the formulator and the manufacturer.

SOLID ORAL DOSAGE FORMULATION STRATEGIES FOR POORLY SOLUBLE DRUGS

Many readily permeable, low solubility compounds (BCS Class II) are ideal candidates for solid oral controlled release formulation. Such compounds include danazol, ketoconazole, mefenamic acid, nisoldipine, nifedipine, nicardipine, felodipine,

atovaquone, griseofulvin, troglitazone glibenclamide and carbamazepine. The incorporation of such compounds into solid oral dosage forms often requires accelerating agents, such as surfactants, wetting agents and dispersants to achieve the desired release profile or complete release. Many of these agents are well-known to the pharmaceutical sciences and have been extensively investigated, making sure their mechanisms of aiding solubilisation are well-understood.

The incorporation of a surfactant or suspending agent into a formulation can enhance solubility but may have detrimental impact on regulatory approval or overall stability of the formulation. By incorporating a small amount of a surfactant (often less than 0.2 per cent) in a formulation, it may be possible to enhance the solubility by increasing the exposure of poorly soluble drugs' physical surfaces to gastrointestinal fluid and facilitate dissolution or dispersion. There is a threshold of usability for surfactants – *in vivo* side effects notwithstanding – above which they begin to depress solubility and complete release often becomes problematic for the formulation, especially within matrix-based systems. Determination of this threshold has been the focus of several studies and may be molecule and formulation specific.

Dispersants may also be useful during formulation, especially when employed in conjunction with matrix-style systems. The dispersant will increase the rate at which the particles separate, enhancing the available surface area so that wetting and dissolution can occur more rapidly, shortening the time needed for some poorly soluble drugs to go into solution. Some examples of common dispersants and disintegrants are carboxymethylcellulose (CMC) of calcium or sodium salts, croscarmellose sodium, crospovidone, povidone, sodium alginate, magnesium aluminium silicate and colloidal silicon dioxide.

Polyethylene glycol (PEG) has traditionally been used as a solubilising agent in several fashions. Liquid PEG is often incorporated as a co-solvent in liquid-based dosage forms to help prevent the precipitation of poorly aqueous soluble materials before administration, and it has been used in higher concentrations as the vehicle for topical or parenteral administration. Its utility in solid dosage forms is as a dispersion-enhancing or wetting agent, often incorporated through solvent evaporation or freeze-drying techniques prior to the formation of a final dosage form. PEG may also be useful in combination with other surfactants and wetting agents such as sodium lauryl sulfate and sodium lauryl sulfate/stearic acid. One example in which PEG has been successfully employed is accelerating the release of carbamazepine from hydrophilic matrix systems through both solubilisation of the drug itself, and enhancement of the physical amorphism of the carbamazepine, which is also known to possess increased bioavailability.

Other formulation strategies incorporate such polar materials as gelatine and lecithin. Gelatine is a naturally derived collagen extract and carries both positive and negative charges. When used as a granulating aid, gelatine can potentially improve the wettability of hydrophobic compounds through polar interaction. Polar compounds such as lecithin are also commonly used as emulsifying agents. When allowed to interact with water or gastric fluids, these compounds may form micelles or other lipid bilayers that can entrap hydrophobic materials and, because the exterior is essentially hydrophilic, these complexes may be used to enhance solubility. These lipid bilayer complexes are often the basis for more complex liposomal delivery systems that are intended specifically for insoluble drugs and macromolecules of very low solubility. One particular advantage of these unique structures is that they may allow access to alternate absorption pathways such as the lymphatic system or the renal portal vein, which could potentially offer significant improvements in bioavailability for those compounds that are highly susceptible to first pass metabolism.

NOVEL CONTROLLED-RELEASE TECHNOLOGIES FOR POORLY SOLUBLE DRUGS

Whilst release-accelerating excipients continue to be relied upon to aid the delivery of poorly soluble drugs from traditional tablet and capsule technologies, the ability to

deliver low solubility drugs orally without excessive reliance upon a wetting agent or dispersant is also desirable in order to develop more robust and distinctive delivery systems capable of both controlled-release and solubilisation. Two novel matrix technologies recently developed address the need to deliver BCS Class II drugs, such as nifedipine and glipizide, in a controlled manner over prolonged duration. One delivery technology employs electrolytes which act as both release-controlling and solubilising excipients within a hydrophilic matrix; a second technology relies upon hydrophobic associations and hydrostatic interactions to facilitate the diffusion of low solubility drugs from a hydrophilic matrix.

The use of alkalisng agents to preserve internal dosage form pH through the acidic regions of the upper gastrointestinal tract is well-established in the pharmaceutical field. One advantage of maintaining a constant internal pH is that a poorly soluble drug may be made more soluble if the environmental pH is at or above the drug's pKa. Through the application of colloidal chemistry principles, it is possible to provide pH control via a formulation component that is also active as a release-controlling excipient within a hydrophilic matrix. In its most basic form, a hydrophilic matrix may be composed of a low solubility drug, hydrophilic swellable polymer (such as hydroxypropylmethyl cellulose or polyethylene oxide) and an hydrophilic electrolyte capable of inducing a given pH (for example sodium, magnesium or calcium carbonate salts) dry-blended to homogeneity and directly compressed into a tablet. Upon ingestion, gastric fluid ingresses into the dosage form, causing it to hydrate and activating the pH and release-controlling characteristics of the delivery system.

The electrolyte's greater hydrophilicity than the other formulation components allows it to hydrate preferentially in comparison to the surrounding polymers and the drug molecules, contributing to the formation of a periphery region of increased polymeric rigidity that is resistant to erosion and the further ingress of water. This peripheral matrix hardening creates a controllable microenvironment within the hydrated gel region, allowing the solubilised electrolyte to induce a pH amenable to the improved solubilisation of the drug. As dissolution and erosion occur during the transit through the gastrointestinal tract, the region of increased matrix rigidity recedes toward the core of the dosage form, allowing the drug to diffuse from the hydrated gel region in a controlled manner over an extended period of time.

One example of such an electrolyte-based formulation strategy is a matrix formulation of the drug glipizide, which has limited solubility due to pH effect and displays a significant increase in solubility in basic media. Previous methods of oral delivery for glipizide have relied on technologies which are capable of pH-independent release, such as osmotic tablets (Glucotrol XL®) rather than technologies devoted to increasing the solubility of glipizide itself. By incorporating one or more alkalisng agents into a hydrophilic matrix formulation, it is

Figure 1: Glipizide in a Hydrophilic Matrix Formulation and Reference Product (V Pillay and R Fassihi, 2001)

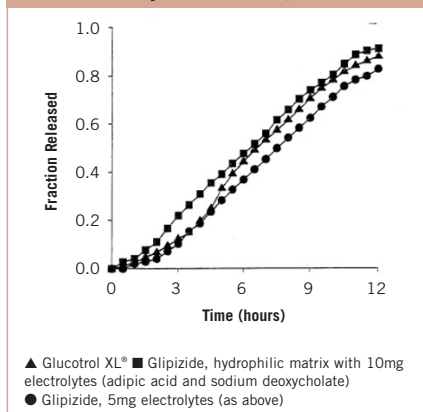


Figure 2: Nifedipine Hydrophilic Matrix Formulation and Reference Product (V Pillay and R Fassihi, 2001)

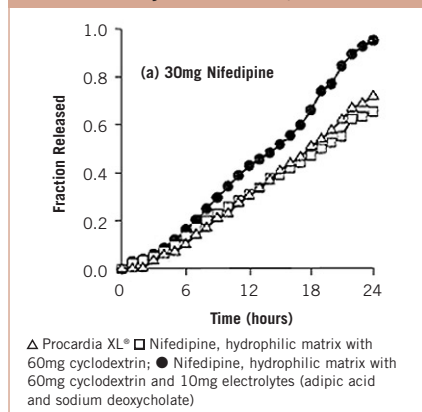
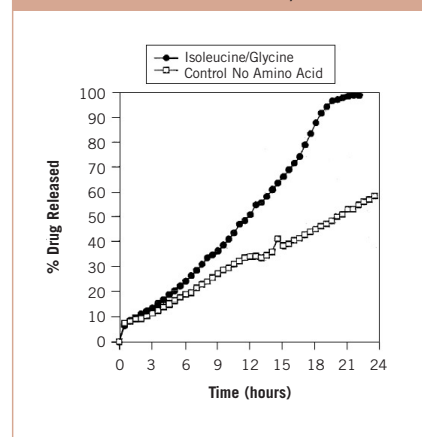


Figure 3: Nifedipine Amino Acid Matrix Formulation (R Fassihi, 2002)



possible to effectively control the pH within the matrix surrounding the glipizide molecules and thereby enhance the drug's solubility in the body. This has been accomplished by incorporating electrolyte's adipic acid and sodium with a hydroxypropylmethyl cellulose gel matrix, so that as the dosage form hydrates, a pH is induced that allows glipizide to solubilise within the hydrated gel region prior to release (see Figure 1).

Another example of a very low-solubility drug, deliverable by an electrolyte-based system, is nifedipine (less than 0.001 per cent water-soluble at 25°C), which is traditionally made available orally in an extended release form through an osmotic pump system. As is common with osmotic pump systems, the release of the reference drug product (Procardia XL®) is near-zero order, yet is incomplete at only 75-80 per cent of drug load. With the incorporation of cyclodextrins, a hydrophilic system is capable of replicating the performance of a more complex osmotic pump system, and when electrolytic excipients are employed in combination with cyclodextrin, complete release is possible without substantially compromising the near-linear nature of the profile (see Figure 2).

An alternative to electrolyte-based solubilisation is an emerging technology involving the use of polar or amphoteric excipients. This novel method incorporates amino acids into a hydrophilic matrix for their ability to facilitate the diffusion of low solubility drugs. The matrix is composed of a low solubility drug granulated with a hydrophilic polymer and two amino acids, whose side chains are of significantly differing hydrophobic character. The granulated mixture is then blended with additional polymer and tableted; this additional polymer facilitates controlled swelling over time and allows for the delayed *in situ* hydration of the granules in the dosage form once introduced into the gastrointestinal tract. The granulation process and homogeneous distribution throughout the dosage form allows for a sufficiently close association to occur between all granulated components, so that during hydration Van der Waals and hydrostatic interactions may occur in a controlled manner sufficient to aid drug solubilisation. The *in situ* hydration of the dosage form facilitates hydrophobic interaction

between the amphoteric amino acids and the drug, allowing them to reorient according to polar and non-polar groups – the side chains of the amino acids form weak complexes with the surrounding molecules of similar hydrophobic character. As the more hydrophilic amino acids solubilise and diffuse from the matrix, these weak hydrophobic interaction complexes remain and aid the diffusion of the low solubility drug itself.

One such example increases the solubility of nifedipine by employing guar gum of differing viscosity, the hydrophobically neutral amino acid glycine and the strongly hydrophobic amino acid isoleucine. As the dosage form hydrates, the hydrophobic side chain of isoleucine associates with the strongly hydrophobic nifedipine molecules, and the hydrophobically neutral side chain of glycine associates with the polar groups of the isoleucine molecule. As the glycine molecules wet preferentially to the other less soluble components, they diffuse from the matrix weakly complexed to the isoleucine molecules which are themselves weakly complexed to nifedipine molecules. This series of weak complexes is sufficient to increase the solubilisation of nifedipine such that complete release is achievable even within a near-zero order extended release matrix (see Figure 3).

The oral delivery of poorly soluble drugs such as nifedipine and glipizide from solid oral dosage forms continues to be confronted with significant formulation obstacles: decreased bioavailability, increased chance of food effect, incomplete release and higher inter-patient variability. By incorporating traditional methods such as surfactants, suspending agents and dispersion agents, or more novel solubilisation technologies such as electrolyte- or amphoteric-based hydrophilic matrices, many of the difficulties encountered during formulation may be addressed. ♦

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Reference

1. Hite M, Turner S and Federici C, Part 1: Oral Delivery of Poorly Soluble Drugs, *PMPS Summer*, pp38-40, 2003