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Physicochemical Approaches to Enhancing Oral Absorption

This article reviews various physicochemical approaches that may be employed to enhance absorption following oral administration of solid dosage forms in humans. This article also examines strategies based on capitalizing or neutralizing physiological processes.

Oral absorption efficiency can be influenced by several factors, acting independently or in concert. These include the physicochemical properties of the administered agent, human physiology, pathology (including disease state), the way the drug is presented (formulated) and possibly the amount that is administered (dose). Other influences include time of administration, whether the patient is resting or active and body position, for example, recumbent or standing. Optimizing absorption requires knowledge of how these variables affect the drug or formulation. However, it may take many years before such comprehensive knowledge can be gleaned on compound-specific behaviours.

In the absence of such detailed insight it may be necessary, particularly with novel therapeutic agents being dosed to man for the first time, to design a formulation based on generic considerations of factors affecting absorption, the physicochemical properties of the agent being administered and *in vivo* or *ex vivo* findings in animals or animal tissue. Such a strategy can help identify the optimum form of the drug and clarify possibilities and limitations for manipulating its properties to optimize delivery.

Hence, good understanding of the physicochem-

ical properties of the drug, and of the anatomy and physiology of the gastrointestinal (GI) tract provides valuable insight on the possibilities and constraints for optimizing oral absorption.

Solubility enhancement

Some materials are absorbed by active transport across the intestinal barrier, but absorption by passive diffusion is probably far more prevalent.¹

Regardless of the mode of transport, however, it is reasonable to conclude that, in the vast majority of cases the drug must be in the solvated state to diffuse into and across the enterocytes lining the intestinal lumen. Thus, solubility and rate of dissolution of the drug are of major importance and many approaches to absorption enhancement concern the optimization of these properties.

Poorly soluble drugs present a major challenge in dosage form development. In simple terms, a material must be in solution if it is to pass from the intestine to the systemic system. At the same time, lipophilicity is frequently associated with higher activity, or receptor specificity and is invariably incorporated in molecular structures by the medicinal chemist. Low aqueous solubility and poor

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bioavailability are often a consequence of such molecular design. Improving absorption in such cases may mean using a form of the drug with optimum solubility, or employing a vehicle in which the compound is soluble. Optimizing solubility may entail using a more soluble salt or polymorph (if one exists), or even the amorphous form of a compound. Each approach has advantages and complications, and such options may not always be available, depending on the molecular composition and physical behaviours of the material under consideration.

Salt forms. Agharkar found that the solubility of the free base form of the antimalarial, α -(2-piperidyl)- β -3, 6-bis(trifluoromethyl)-9-phenanthrenemethanol was 7 $\mu\text{g/mL}$.² The hydrochloride salt in contrast had solubility in approximately 30 $\mu\text{g/mL}$ whereas a value of 1800 $\mu\text{g/mL}$ was attained for the dl-lactate salt. Tetracycline and erythromycin salts also exhibit differing solubilities (Table I). Bastin *et al* also found that some salts of the cardiovascular compound RPR 127963 afforded significantly improved solubilities compared with the free base (Table II).³

Table I Aqueous solubilities of tetracycline and erythromycin derivatives.

Compound	Solubility in water ($\mu\text{g/mL}^{-1}$)
Tetracycline (base)	1.7
Tetracycline hydrochloride	10.9
Tetracycline phosphate	15.9
Erythromycin	2.1
Erythromycin stearate	0.3
Erythromycin lactobionate	20

Table II Aqueous solubilities of salts of RPR127963.

Compound/form	Solubility in water ($\mu\text{g/mL}^{-1}$)
RPR127963 (base)	Below detection limit
Hydrochloride salt	3.9
Mesylate salt	108
Citrate salt	0.8
Tartrate salt	0.9
Sulfate salt	50

Enhancing solubility does not necessarily translate to better *in vivo* absorption. There are several reports of salts with differing solubilities behaving no differently in bioavailability studies.^{4,5} Better solubility may simply be a pH effect that is neutralized in the gastric or intestinal milieu, with solubility changing to reflect local environmental pH. Conversely, it is also feasible that the pH engendered by a salt in its micro-environment facilitates dissolution. The salt acts as its own buffer so to speak. Once in the solvated state, the dynamics of transport or reprecipitation may be such that there is a net enhancement of amount dissolved and absorbed.

The counter ion can be important for other reasons. Many drug substances are organic bases and hydrochlorides are usually the first (sometimes only) salts considered when seeking a more soluble form. However, the presence of chloride ions in gastric acid may well depress solubility *in vivo* because of common ion effects.^{6,7} Consequently, absorption may not be improved.

The work by Engel *et al* is revealing in this context.⁸ The hydrochloride and mesylate salts of two novel protein kinase inhibitors were more soluble than other salts, but when bioavailability in beagle dogs was evaluated the mesylate salts of both compounds had better bioavailabilities than the hydrochlorides (Figure 1).

This may have been because of better solubility of the mesylate salts (five times more soluble than hydrochloride), but a common ion effect with the hydrochloride salts cannot be ruled out. Interestingly, these authors established (from a review of recently approved compounds) that mesylate salts are now being more widely used. It would be of interest if such increasing popularity was a result of better *in vivo* performance.

The potential for absorption enhancement by salts could be usefully explored in small animal *in vivo* studies, particularly in cases where human studies are not possible or appropriate, for example, at the compound selection stage in drug discovery programmes. Animal studies, while not necessarily predicting

absorption efficiency in humans may provide useful rank order ratings on the effects of different salts.

Crystal form. Medicinal compounds may exist in a variety of crystal forms that can have differing aqueous solubilities. Riboflavin has three polymorphs with solubilities varying from 0.06–1.2 $\mu\text{g/mL}^{-1}$.⁹ Bioavailability of various morphic forms of cimetidine was shown to correlate with dissolution rates suggesting that solubility might be important for oral absorption.¹⁰ Kimura *et al* obtained differing plasma levels in dogs when dosed with different polymorphs of the poorly soluble hypoglycaemic agent tolbutamide (Table III).¹¹ *In vivo* performance reflected *in vitro* differences in dissolution rates and solubilities between the forms.

Polymorphs with the lowest free energy (lowest solubility) are usually most stable in thermodynamic terms; more soluble forms tend to transform to the low energy state. Such transformation can occur during storage, processing or even during dissolution.¹¹ This makes polymorph selection for solubility enhancement an uncertain process. The more soluble form might become less soluble with time because of reversion to the more thermodynamically stable form, with absorption being compromised as a consequence. It is important, therefore, that any promising crystal form is thoroughly assessed to confirm that

- It can be prepared consistently by a realistic and reliable process.
- The preferred form can be readily identified by a technique suitable for routine quality control.
- It does not transform to a less useful form on storage, during processing or after incorporation in the dosage form.
- It does not transform to the less soluble state after ingestion but prior to absorption, that is, in the GI environment.

Modest improvements in solubility or dissolution rate may be of little benefit *in vivo*. Poole *et al* claimed that somewhat slight differences in solubility and dissolution rate of the anhydrous and trihydrate forms of the antibacterial ampicillin lead to differences in oral bioavailability in

dogs and humans.¹² However, a later study using unformulated drug showed that both forms were bioequivalent, suggesting that the results from the Poole study might be ascribable to formulation differences.¹³ The work by Aguiar and Zelmer provides further elucidation on solubility differences. They showed, using polymorphs of mefenamic acid and chloramphenicol, that when free energy differences (reflecting solubility values across a range of temperatures) were modest, bioavailability differences would not be expected. When differences are large they might affect absorption profiles.¹⁴

Amorphous forms. Amorphous materials can be more soluble and have faster dissolution rates than crystalline forms because of lower

solvation energy. Amorphous novobiocin dissolves rapidly and is well absorbed in humans. The crystalline form, by contrast, is less soluble, has slower dissolution rates, and exhibits poor and erratic bioavailability.¹⁵

Amorphous materials have the same potential disadvantages as polymorphs or pseudopolymorphs in that they may transform to the less soluble crystalline state. The molecular mobility (and associated tendency to transform) of an amorphous solid is a function of the differential between storage temperature and its glass transition temperature (T_g). It has been claimed that storage at temperatures of 50 °C below T_g are required to avoid crystallization.¹⁶ Therefore, the T_g for most amorphous solids should be greater than 75–80 °C if they are to remain stable in the morphic sense at

ambient storage. Excipients with a much higher T_g can sometimes be added to stabilize a drug in the amorphous state.

Polyvinylpyrrolidone (PVP) (T_g of 280 °C) inhibits the crystallization of indomethacin.¹⁶

Crystallization is the preferred technique of the organic chemist for isolation in a pure state, and possibly provide a consistent physical form. Isolation may be more difficult if an amorphous form is preferred.

“Upstream” purification, or reprecipitation following original isolation in the crystalline state may be necessary. This will add to cost and complexity.

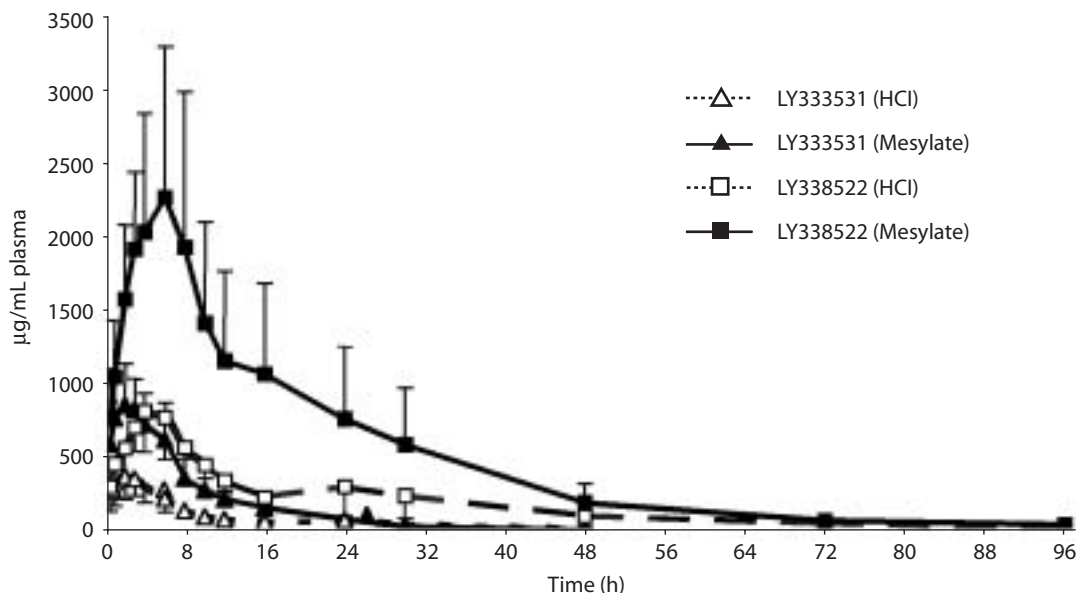
Whereas it may be advantageous from an absorption perspective, to select a particular salt, polymorph or material in some other physical state, other selection criteria must not be

Table III Bioavailability of tolbutamide polymorphs in dogs.*

Polymorphic form	C_{max} ($\mu\text{g}/\text{mL}^{-1}$)	t_{max} (h)	AUC ($\mu\text{g}/\text{h}/\text{mL}^{-1}$)
I	44	3	226
II	85	2	590
IV	80	3	576

*Taken from reference 11.

Figure 1 Mean plasma concentrations of LY333531 and LY338522 in male beagle dogs orally administered with LY333531-HCl and LY333531 mesylate (20 mg LY333531/kg).



*Taken from reference 8.

ignored. With respect to counter ions in salts, the potassium ion can be a GI irritant unless the dose is low. Other cations, such as magnesium or calcium, can affect GI tract motility. Such effects can affect absorption where GI tract residence time is important. However, the dose of counter ions may be too low in most cases to evince undesirable effects.

Different salts might also contain different residual impurities because of solubility, partitioning or crystallization effects during isolation, or different impurities in the reagent providing the desired counter ion. A preferred salt may not be stable or optimal for processing to product because of moisture sorption, flow or

compaction properties, or other such pharmaceutical behaviours. In the examples given in Table II, the sulfate salt was chosen because solubility was adequate and the physical characteristics were better than for the more soluble mesylate salt. The selection of a preferred form has to be a multidisciplinary exercise, ensuring that advantages for one facet of the programme are not negated by introducing other problems.

Cocrystal formation. Use of the crystalline form of a drug can be advantageous from purity, stability and processing perspectives. Thus, methods of retaining crystallinity

whilst enhancing solubility and bioavailability may be worth considering. The recent upsurge of interest in cocrystal formation reflects this. Properties such as solubility can be influenced by crystal packing and this in turn can be influenced by the crystalline alignment of drug molecules with structurally complementary moieties.

Hydrogen bond donors can, therefore, be aligned with hydrogen acceptors. In this context it appears that drug molecules with appropriate amide groups can align, in the crystallographic sense, with 1,4-dicarboxylic acids such as citric and tartaric acids, which are suitable materials, from a safety perspective.¹⁷ The poorly soluble/poorly bioavailable antifungal itraconazole had comparable dissolution profiles with the amorphous, optimally bioenhanced commercial product when presented in cocrystal forms with the L forms of malic and tartaric acids (Figure 2).¹⁸ Such crystal engineering technology is potentially very promising for poorly soluble drugs.

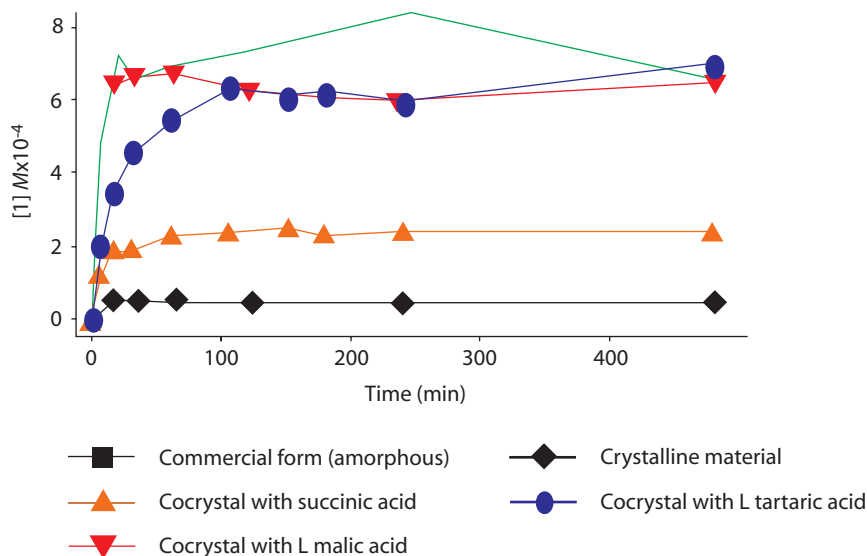
pH adjustment. If a compound is ionizable it may be possible to increase solubility by adjusting pH. Compounds with pKa/b values between 3–11, namely weak acids and bases, may have solubility enhanced in this way.¹⁹ If a drug is poorly soluble at low pH, it is conceivable that co-administration or coformulation with an acid-neutralizing material provides a gastric environment more conducive to better solubility and dissolution rate. Elevation of gastric pH could also reduce presystemic degradation of acid labile compounds, leaving more available for absorption.²⁰

Magnesium and calcium carbonate can be used as compression aids in tablet formulations. It is feasible that their acid-neutralizing effects could be capitalized on to enhance absorption of acid labile compounds or those with poor solubility at normal gastric pH. Some antacids have also been shown to increase the rate of passage from the stomach to the small intestine, consequent to elevating gastric pH.²¹ This can have theoretical benefit, not only for acid-unstable drugs or acid-insoluble

Solvent	Compound solubilized
Cremophor	Miconazole, paclitaxel
Ethanol	Diazepam, phenytoin
Glycerin	Epinephrine, idarubicin
Polyethylene glycol 300 and 400	Lorazepam, etoposide
Propylene glycol	Phenobarbital, hydralazine
Sorbitol	Nicardipine, triamcinolone
Polysorbate 80	Dexamethasone, docetaxel

* Taken from reference 24.

Figure 2 Dissolution profiles of itraconazole forms in 0.1N HCl at 25°C.*



*Reproduced with permission from reference 8.

drugs, but also where increased rate of absorption can have therapeutic benefit.

Such possibilities must be carefully considered, however. Any effect is likely to be related to the amount of material utilized. Inadequate quantities may lead to marginal or no benefit; conversely, excessive amounts might stimulate acid rebound. Physiological effects may also play a part. Magnesium carbonate has laxative properties; by contrast calcium carbonate is a known constipating agent. Such effects on GI tract motility could complicate absorption processes. Antacids may also act as adsorbents, making less drug available for dissolution and adsorption.²²

Absorption enhancement approaches based on altering pH may be difficult to study preclinically in animal models. Differences in gastric volumes, acidity and physiology are likely to complicate responses. There may be no alternative but to explore possibilities in human Phase

I studies.

Solubilizing vehicles. The least complex way to present a material to the GI tract for absorption is to administer in solution, thereby removing any dissolution stage. Occasionally, non-aqueous (organic) solvents are used to solubilize drugs for parenteral use. Use in oral products is constrained and complicated by many factors. They may not exert sufficient solubilizing action to be of practical value unless the dose of drug is low. Otherwise the volume of vehicle required cannot be readily contained in a convenient dose unit. Liquid-filled gelatin capsules offer possibilities for compounds when the drug dose is approximately 40–60 µg, but only a limited number of non-aqueous solvents can be employed for such presentations.

Some synthetic aluminosilicates or silicates can absorb significant amounts (up to and exceeding an equal mass) of certain organic sol-

vents whilst retaining the properties of a solid. Drug dissolved in the organic solvent and then absorbed on the silica provides a form that can be filled into capsules and even compressed to tablets.²³ The drug is thus “in solution,” but can be formulated as a solid dosage form. This approach requires that the drug has high solubility (and good stability) in the chosen organic solvent, and that the silicate in turn has high absorption capability for the solvent. These requirements restrict the applicability to potent medicinal agents (dose not greater than 10–20 µg) that have high solubility in a limited number of organic solvents.

Organic solvents can have long-term effects on GI mucosa if the medication is for chronic use, even if levels employed comply with International Conference on Harmonization (ICH) guidelines. It is also possible that precipitation of drug from solution may follow administration, when the material encounters the aqueous environments in the GI tract. Thus, there may be little or no absorption enhancement. Table IV outlines solvents used in commercial parenteral formulations, which with the above caveats might also be considered for oral delivery.²⁴

Complexation. Cyclodextrins can provide a novel way to get small-molecule drugs in a molecular dispersion. These cyclic glucose polymers have hydrophilic “outer surfaces” and hydrophobic cavities that can accommodate molecules of mass between 400–500 (Figure 3).

If interactions between drug and the pendant groups within the cavity are strong, a stable molar complex is formed. The compound “hides” in the cavity and the complex assumes the solubility of the cyclodextrin. Dissociation of the complex “releases” the drug in the molecular state.

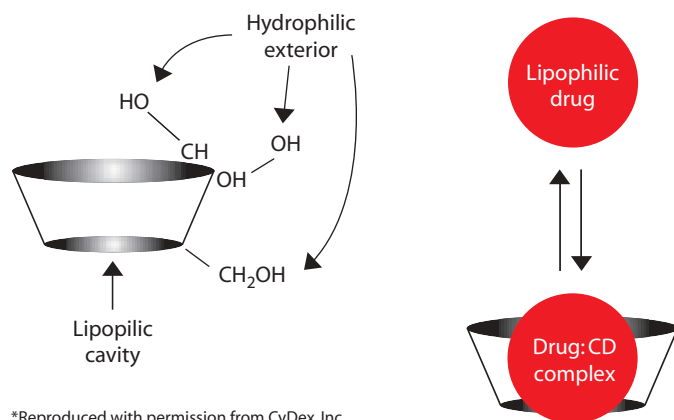
Table V summarizes bioavailability data, expressed as “area under curve” (AUC) for an azole antifungal drug dosed to animals, either parenterally or orally, as a hydroxypropyl cyclodextrin complex or as a dispersion in aqueous methylcellulose.²⁵ The cyclodextrin complex afforded better absorption than the

Table V Bioavailability of SCH 56952 (azole antifungal).*

Species	Bioavailability (AUC; 0-inf, mcg/h/mL)		
	IV	HP-Cyclodextrin complex	Suspension in methylcellulose
Mouse	137.0	143.0	63.7
Rat	89.4	58.6	43.0
Dog	89.4	58.6	43.0
Monkey	115.0	59.4	15.9

*Taken from reference 25.

Figure 3 Cyclodextrins as solubilizers.



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conventional suspension in all cases, but the differentials varied with animal species. Data from mice and monkeys suggest that absorption is significantly enhanced whereas improvement was more modest in the dog and rat. Such findings exemplify the uncertainties of accurately predicting absorption in humans using animal models.

The original (alpha, beta and gamma) cyclodextrins had limited application for solubility enhancement because they themselves were not particularly soluble, thereby limiting the overall dose that could be contained in a conventional unit such as a tablet or capsule. Derivatized cyclodextrins such as the hydroxypropyl or sulphobutyl ether forms are much more soluble. Some have been subjected to comprehensive safety screening and do not seem to have undesirable features such as nephrotoxicity or propensity to cause erythrocyte hemolysis that were associated with earlier cyclodextrins. The sulfobutyl form in particular has excellent solubility; (ca

50 g/100 mL), so can “carry” a lot of drug.²⁶

For a particular cyclodextrin to be suitable for absorption enhancement it must not only accommodate the drug in “molecular dispersion” form to enhance solubility, but must also “release” the drug by complex dissociation in the GI tract. Too stable a complex can be problematical. Trapani showed that when cyclodextrin complexes of the hypnotic zolpidem were dosed to rats the induction period for ataxia was prolonged compared with controls. The effect was ascribed to complex dissociation being rate limiting to absorption.²⁷ Complex formation can, therefore, possibly affect pharmacokinetics and compromise absorption if the complex is too stable. In effect, cyclodextrins, similar to all other approaches do not always provide solutions for solubility-related problems.

In summary, a number of strategies can be considered for solubility enhancement where this is necessary. The conundrum for the pharmaceu-

tical technologist concerns whether such approaches are warranted. There is fairly general agreement that when aqueous solubility at physiologically relevant pH is less than 1–5 µg/mL at 37 °C there is potential for solubility and dissolution-related absorption problems.^{28–30} By inference, steps to improve solubility might seem warranted when solubility is lower than this. However, factors such as site-specific absorption, elimination half-life and even dose may also be important. Additionally, it is likely that modest solubility increases may effect little or no improvement, particularly where solubility is very low. Each case has to be judged on its merits and studied accordingly.

Maximizing dissolution rate

The Noyes-Whitney equation quantitatively describes the factors contributing to dissolution rate

Noyes-Whitney equation

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

where
dW/dt = dissolution rate

A = surface area of the dissolving solid

C = concentration of drug in the bulk dissolution medium

C_s = concentration in the diffusion layer surrounding the dissolving solid (saturated solution)

D = diffusion coefficient

L = diffusion layer thickness

The terms D and L can be considered immutable, being material-specific. In practical terms (*in vivo*) C can pragmatically be considered to be zero if it is assumed that dissolved material is absorbed quickly. Thus C_s (which can be considered to be equal to the saturation solubility) and A (surface area of solid exposed to the dissolution medium) are the prime drivers for dissolution. Increasing either or both increases the rate of passage from solid to solvated state in situations where the rate and extent of absorption can be influenced by the dissolution rate.

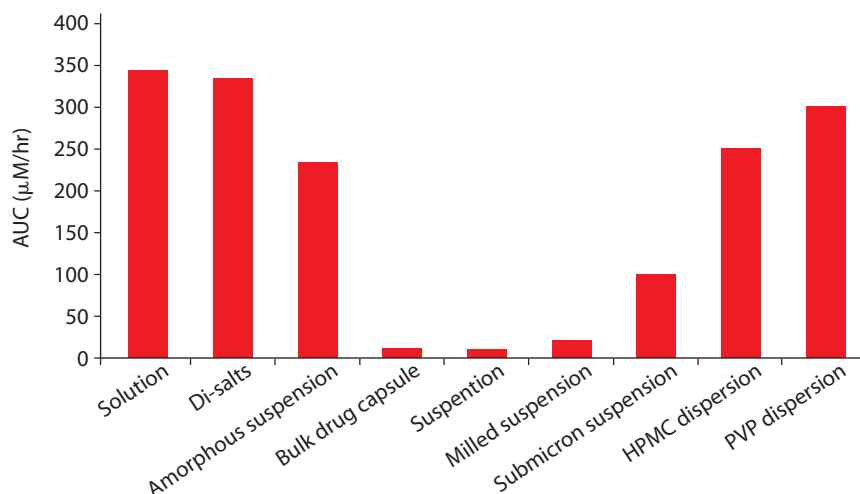
Surface area enhancement is most readily affected by reducing particle size. Reduction to micron-sized particles boosted absorption of the antifungal agent, griseofulvin in humans,

Table VI Pharmacokinetics of unmilled and nanoparticle naproxen in rats.*

Formulation	C _{max} (µg/mL)	t _{max} (min)	AUC (µg h mL ⁻¹)
Unmilled naproxen	126	33.5	15 228
Nanoparticle naproxen	187	23.7	19 062

*Taken from reference 34.

Figure 4 The effects of different solubility and dissolution rate enhancement approaches on absorption.



comparable plasma levels being obtained with half the dose of micronized drug compared with the non-micronized form.³¹ Micronization is a mature, well characterized technology and, arguably, ought to be considered where aqueous solubility is less than approximately 1 µg/mL.³² However, it does not necessarily guarantee improved absorption. Small particles can form aggregates and disperse poorly.³³ It may be necessary, therefore, to add dispersants or other physical stabilizers.

More recently, technologies from the reprographic and photographic industries have been utilized to provide submicron particles of even greater surface area than micronized material. Table VI shows the effect of using such nanoparticles on absorption of naproxen in rats.³⁴ Nanoparticulate material provided higher peak plasma levels and shorter time to peak, although overall absorption enhancement as quantified by AUC was modest.

Physical stability of ultra fine materials can be problematical; small particles can agglomerate, negating surface area enhancement effects. It is usual, therefore, to add small quantities of surfactants such as polyoxyethylene derivatives to prevent such association and provide material that disperses readily on wetting. It may also be that where surfactants are undesirable, techniques such as surface plasma treatment may evince a wetting effect by rendering particle surfaces more hydrophilic and amenable to wetting by the dissolving solvent.³⁵

The study by Wald *et al* dosing the poorly soluble HIV-protease inhibitor, U-103017 to beagle dogs, demonstrates very elegantly the effects of different solubility and dissolution rate enhancement approaches on absorption (Figure 4).³⁶ This type of study is typical of most of the literature on studies to determine the effect of physicochemical manipulation on bioavailability; most report *in vitro* findings, or results from studies in animals. The question “how relevant are these to performance in humans?” must always be posed when considering such findings.

Use of surfactants. Many poorly soluble materials are hydrophobic, do not disperse readily in aqueous systems or agglomerate such that surface area for dissolution is reduced. Absorption can be reduced or be more variable in consequence. Surfactants can reduce the interfacial tension between solid and solvent, aid wetting and facilitate dissolution rate. However, the concentration of the surfactant can be crucial. If it is included at a level that promotes contact between drug and the medium for dissolution (or possibly the intestinal epithelium) absorption may be enhanced. However, if surfactant concentration is such that micelle formation occurs, the drug may partition into the micelle interior with absorption being inhibited.³⁷ Both ionic and non-ionic surfactants have been shown to inhibit absorption because of such behaviour.^{38,39}

Surfactants can disrupt barriers to absorption in the intestinal epithelium, evincing non-specific absorption enhancement. This can lead to overdosage of concomitant medication and so must be considered carefully.

Conclusions and perspectives

Optimizing oral absorption requires appreciation of the physicochemical factors that influence presentation of material to the GI tract in a form suitable for passage across the intestinal epithelium. It is a complex area and doubtless other factors that have not been discussed in this review contribute to the complexity. Patient age, health, dietary habits, whether ambulatory or resting, and many other factors can also contribute to inconsistency. However, awareness of the physicochemical properties of a compound affords opportunities for the selection of the best form, and for formulating for optimal and more consistent delivery.

Special formulations or dosage forms to enhance absorption will only be effective if they incorporate, or capitalize on relevant properties of the drug, companion additives or the *in vivo* environment to optimize dissolution, partitioning, GI tract residence or epithelial transit such that passage to the systemic circulation is

facilitated. When factors that compromise or complicate absorption can be obviated or minimized, the medication and its mode of use is likely to be optimal with respect to safety and efficacy.

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