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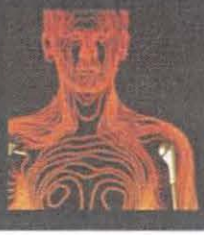


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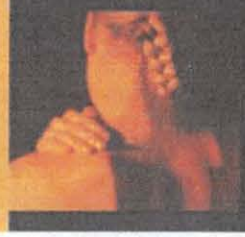

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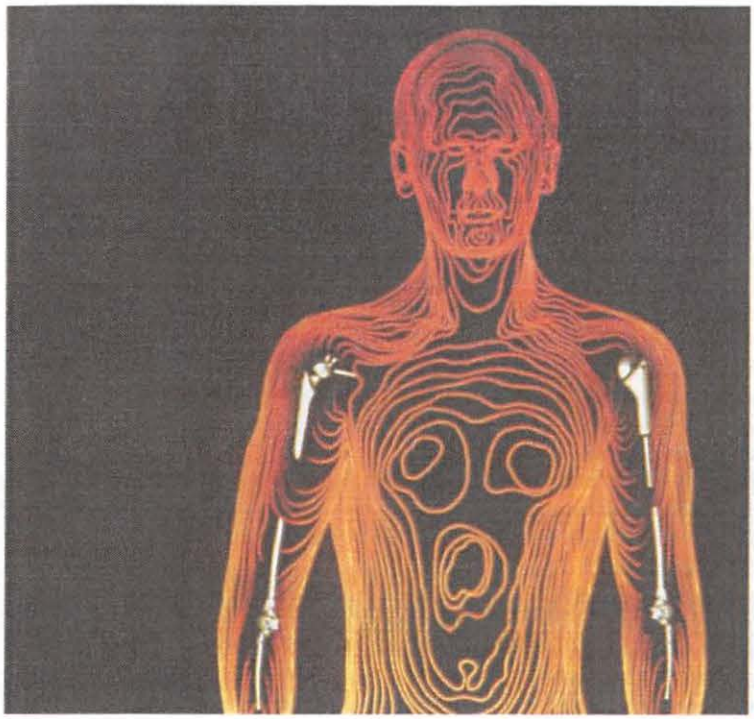

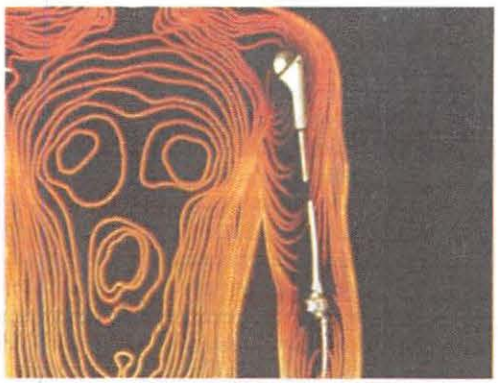

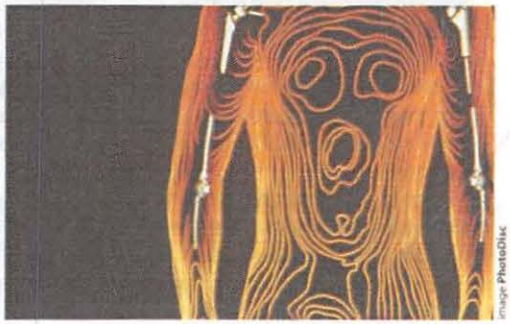

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Physicochemical Approaches to **Enhancing Oral Absorption**

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.

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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 necessary, particularly with novel therapeutic agents being dosed to humans 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

Hence, good understanding of the physicochemical 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,

chemist. Low aqueous solubility (which is usually associated with high lipophilicity) and poor 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 μg/mL.[2] The hydrochloride salt in contrast had solubility of approximately 30 μg/mL whereas a value of 1800 μg/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 RPR127963 afforded significantly improved solubilites compared with the free base (Table II).[3]

Enhanced 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 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 forms. 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 mg/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.

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 tract environment.

Modest improvements in solubility or dissolution rate may be of little benefit *in vivo*. Poole *et al.* claimed that slight differences in solubility and dissolution rate of the anhydrous

Table I Aqueous solubilities of tetracycline and erythromycin derivatives.

Compound	Solubility in water (mg/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 (mg/mL^{-1})
RPR127963 (base)	Below detection limit
Hydrochloride salt	3.9
Mesylate salt	108
Citrate salt	0.8

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 can affect absorption.[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 a morphous 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 is 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. For instance, 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 provides 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.

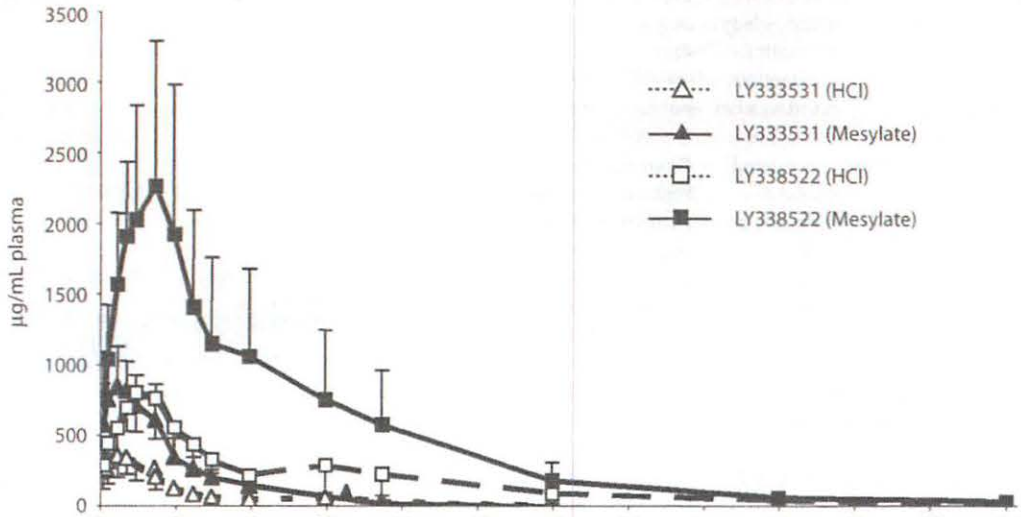
Whereas it may be advantageous from an absorption perspective to select a particular salt, polymorph or material in some other physical state, other selection criteria must not be ignored. With respect to counter ions in salts, the potassium ion can be a GI irritant unless the dose is low. Other cations, such as magnesium or calcium, can influence GI tract motility and 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.

Table III Bioavailability of tolbutamide polymorphs in dogs.*

Polymorphic form	C_{max} (μg/mL^{-1})	t_{max} (h)	AUC (μg/h/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).*



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