Drug Absorption

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Principles of drug absorption as well as the practical, clinical factors that influence drug absorption are important because the vast majority of drug dosage forms are designed for nonvascular administration. Primary among these forms are products intended for oral ingestion, although other routes must also be considered (e.g., transdermal, rectal, pulmonary, intramuscular, etc.). The impression is sometimes given that our understanding of the absorption process was made complete by the development of the pH-partition hypothesis; although an important concept, this is not the case. Furthermore, the implications of this hypothesis have been generalized and incorrectly applied to the clinical situation. In contrast to the tenets of the pH-partition hypothesis, all drugs are best absorbed from the small intestine because of the large absorbing surface area of that region and dissolution rate considerations governed by pH conditions along the tract, regardless of the degree of ionization.

Interest in drug absorption and the absorption efficiency of pharmaceutical dosage forms has been generated in recent years by several factors. The most immediate and forceful, at least from an industrial perspective, have been government regulations pertaining to bioequivalency considerations of commercial products. The second, especially apparent in recent years, has been the development of new delivery systems and alternative routes of administration (e.g., intranasal, buccal, and transdermal). Finally, there are major new efforts to discover and develop drug entities that are unlike those in current use and that have unique problems associated with their efficient administration (e.g., peptides and proteins, including antibodies and their Fab fragments). One can gain an appreciation of the above points from a cursory examination of the recent medical and pharmaceutical literature. Each of these considerations has created new challenges to optimize drug therapy, and our success will depend to a large degree on a better understanding of absorption processes and the factors that influence them. The purpose of this presentation is to highlight some of the newer developments in the area of drug absorption.

Regardless of the mode of nonvascular administration, the drug must penetrate at least one biologic membrane to gain access to the blood stream and produce a systemic effect. The resulting plasma drug concentration–time and response–time curves will be a function of the input process (absorption) and the output processes (disposition). Plasma concentrations will initially rise, reach a maximum, and then decline. The relative magnitudes of the rates of those processes, as well as the dose and completeness of absorption, will determine such factors as the maximum plasma concentration and the time to achieve that maximum, the onset of response, and its duration. The overall efficiency of the absorption process is determined in mathematical terms as the integral of the equation describing the curve, i.e., the area under the curve. For a given subject and for a specific drug, the values of the disposition parameters; e.g., clearance and half-life will generally be reasonably constant from time to time and, therefore, the relative concentration–time profiles will be governed by the input process. For the most part, factors influencing absorption may be divided into two categories: physicochemical characteristics of the drug/dosage form and physiologic factors associated with the route of administration. We have little control over factors such as gastric and intestinal transit rates, blood flow to and pH at the site of absorption. However, considerable latitude exists to alter the efficiency of the absorption process to improve the concentration–time and, therefore, response–time profiles through dosage form modification.

Considerable time is being devoted to exploring theoretical models to describe and predict membrane transport. Depending on the extravascular site of administration and the dosage formulation, absorption kinetics can range from a single apparent first-order process to serial apparent first-order processes to an apparent zero-order process. Although it is likely that the overall kinetic scheme may be a more complex mathematical function that could involve disintegration and dissolution and/or transport through one or more membranes, absorption

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from most sites of administration appears to be reasonably well described by a first-order kinetic process. Absorption may also be best described as a constant or slow first-order rate process that is likely to occur with drugs that have low aqueous solubility or drugs that are formulated to achieve this goal. During early times, the concentration–time profile for the latter process will be similar to that seen after a short intravenous infusion.

Most extravascular doses are administered by the oral route. Therefore, a major focus of this commentary will be variables that can influence oral absorption: food, drug–drug interactions, disease states, and dosage forms. Also discussed are additional other physiologic variables that can influence absorption from other extravascular sites (e.g., transdermal, ocular, and intramuscular–subcutaneous). Finally, there will be a brief discussion of some of the current methods being used to evaluate drug absorption, regardless of the site of administration.

The influence of food on drug absorption has been reasonably well studied. The nature of the effect of food on absorption depends on several factors related to the compound including its chemical stability in gut fluids, site and mechanism of absorption, the characteristics of the dosage form, and aqueous solubility of the drug. These factors tend to interact in a complex fashion so that it is difficult to give general rules without having the information about a specific drug. The presence of food tends to increase the absorption efficiency of poorly water-soluble drugs and those that are absorbed by a specialized process in the proximal small intestine. The latter compounds tend to fall into the nutrient rather than the drug category (e.g., certain vitamins); however, L-DOPA and certain anticancer agents that are structurally related to amino acids or retinoids may also be absorbed by a specialized process. Water-soluble drugs and dosage forms that dissolve rapidly tend not to be influenced by the presence of food, although the rate of absorption may be reduced. Compounds that are unstable in gut fluids (e.g., L-DOPA and some antibiotics) are generally less well absorbed in the presence of food. More recently, several investigators have shown that food increases the systemic availability of compounds having a high hepatic extraction ratio. This effect is partially explained by altered hepatic blood flow, but other factors, as yet unidentified, appear to be involved. Compounds that have high hepatic extraction ratios (or high hepatic clearances) tend to have greater variability in absorption efficiency among subjects, probably reflecting large intersubject differences in intrinsic hepatic clearance.

One important reason for the success in recent years and for the advancements made in transplantation surgery has been the introduction of the drug cyclosporin. There are several issues concerning absorption of this drug that have not as yet been resolved. First, oral absorption is low, highly variable, and apparently time dependent. The drug appears to be inherently poorly absorbed, but there are suggestions that bile flow may increase absorption as is the case for the water-insoluble drug griseofulvin. In addition, the influence of food on absorption may also reflect the increase in bile flow in response to the presence of food as is the case with grisiofulvin isotretinoin and etretinate. This mechanism may lead to several strategies to improve the intestinal absorption of this as well as other aqueous-insoluble drugs.

Drug–drug interactions including food–drug interactions can influence drug absorption. For example, digoxin absorption from conventional tablets is decreased whereas absorption from an oral solution or a polyethylene glycol (PEG) solution in a soft elastic capsule is unaffected by total body x-irradiation and oral anticancer agents. These studies raise two points. First, to what extent does x-irradiation and oral anticancer agents influence drug absorption in general? This question has *not* been addressed. Second, the dosage form used may influence the outcome of the study. It is likely that an optimal dosage form that contains drug in solution or one which rapidly dissolves will be less affected by such factors than a form that dissolves slowly. This is further supported for digoxin dosage forms in studies that have examined the influence of altered gut motility on the completeness of absorption. Absorption from a solution or solution in a capsule is minimally influenced by altered gut motility, whereas poorly dissolving dosage forms have increased absorption when motility is reduced by propantheline and decreased absorption when motility is increased by metoclopramide. One can anticipate similar trends for other drugs and their dosage forms. Drugs that influence absorption include cimetidine and narcotic analgesics.

There is limited information concerning the influence of disease states, including gastrointestinal disease, on drug absorption. Decreased cardiac output and, therefore, altered blood flow to the intestinal tract associated with congestive heart failure may influence the rate but probably not the completeness of absorption. Combined intravenous and oral dose studies are needed to dissociate altered absorption and disposition processes. Similarly, malnutrition states will require IV/PO studies to separate altered absorption from disposition. This is a problem that deserves considerable attention as it may

impact substantially on the success of therapy in Third World countries.

The influence of aging in adults on drug disposition and absorption has received attention in recent years. General and unqualified statements that gastrointestinal absorption in the elderly is impaired in comparison with absorption in young adults have been made and repeated over the years. The issue has been complicated further by errors in experimental design and data analysis, which has, in general, resulted in incorrect or at least questionable conclusions. Although gastric emptying rate, gastric pH, gut blood flow, and surface area change with age, data indicate that while the rate of absorption may be reduced, the extent of absorption is not altered. In contrast, the extent of systemic availability may increase with age due to reduced first-pass clearance of high-hepatic clearance drugs.

There is far less quantitative information about the efficiency of absorption for the other end of the age spectrum, pediatric subjects. There is clearly a need for such data, but the required studies may be hindered by ethical considerations for experimentation in that population. Novel study designs in pediatrics will need to evolve to address this topic.

There have been important recent developments with regard to dosage forms and new drug entities. In the former regard, there is an almost unlimited ingenuity being applied to the creation of new or "novel" forms for oral as well as nonoral administration of drugs. One oral form that has been popular for some time is sustained-release (SR) products. This is especially apparent for theophylline products as is obvious from the large body of literature in recent years. SR forms have an advantage over conventional dosage forms by maintaining relatively constant plasma concentrations and the potential for increased compliance. However, there have been suggestions of dose "dumping" with one product in the presence of food. This is a potentially serious problem because toxic concentrations can result, especially from a once-a-day product that contains a relatively large total dose. Similarly, if a daily dose is missed, it can have a greater impact on the therapeutic profile than missing one tid dose. Food also impairs the absorption of another form, which is intended to be mixed with food and given to children. New technologies (e.g., polymer chemistry) are being applied to the development of sustained-release products that have the potential of improving on existing formulations, and it is likely that at least some of these newer forms will be marketed during this decade. All in all, scientific/medical considerations must be balanced with marketing interests for these dosage forms to offer advantages.

As mentioned earlier, formulation of a digoxin solution in a soft elastic capsule improves the extent of absorption and appears to provide more consistent absorption than does a tablet. One reason for this appears to be avoidance of degradation in gastric fluids. The general premise here is that a drug that is incompletely absorbed will, by definition, be erratically absorbed. Reduction of both intra- and intersubject variability should result in more predictable and consistent therapy. Although this is a relatively expensive dosage form, this approach may have more general applicability for other drugs but there should be a reasonable balance of the benefit-to-cost ratio.

Physiologic factors can also influence absorption from alternate routes of administration. For example, there have been several studies that have examined the influence of numerous factors on ocular drug absorption. This is useful information for the treatment of local eye problems with conventional drops and ointment ocular dosage forms, but it is also important for the potential use of ocular inserts containing drugs intended for both local and systemic effects.

The transdermal route has used both ointments and patches for delivery of drug (e.g., nitroglycerin). While several investigators have proposed theoretical models for describing percutaneous or transdermal drug absorption, there remains need for more experimental data to test the predictions of those models to better understand the factors that influence absorption. These would include such factors as the site of application, the use of absorption enhancers, the state of the skin with regard to hydration and age, and the potential for drug metabolism within the several layers of the skin.

Although the nasal route offers advantages for certain drugs, the factors affecting absorption and the limitations to this route have not been thoroughly explored. Nasal delivery allows rapid absorption due to high vascularization and it bypasses the hepatic first-pass effect. Therefore, this route may be useful for some new drugs such as peptides and proteins that undergo substantial presystemic metabolism.

Possibly one of the major challenges to dosage form design during the coming decade will be with regard to the efficient delivery of new nontraditional drug entities. The potential therapeutic gains from these new drug categories such as peptides and proteins including antibodies and their Fab fragments, is almost unlimited. Nontraditional entities have been tested and are now awaiting approval from the Food and Drug Administration. Biotechnology will unquestionably have a major impact on the drug

field in the coming years. The difficulties associated with the efficient oral administration of these compounds is immense. Two major factors limit the efficient oral absorption of those compounds: instability in gut fluids and the inherent low absorption. Perhaps oral absorption enhancers can be used or appropriate prodrugs can be synthesized. Only one alternative exists if those problems cannot be solved, and that is the use of another route of administration. Whereas the intravenous route would be acceptable for certain drugs in the hospital environment, alternate routes and modes of administration would be required for chronic outpatient dosing. IM and SC routes are used for peptides (including insulin), but degradation at the site of injection leads to dosing error. At this point, these are unanswered questions that will undoubtedly receive considerable attention in the coming years, and perhaps tansdermal or intranasal delivery will find its niche.

There has been considerable interest in experimental design and data analysis techniques to support inquiries into the drug absorption process. Although it is implicitly assumed that clearance is constant in the same subject from experiment to experiment, it is now clear that there are some drugs for which this assumption is not correct. Violation of that assumption results in incorrect estimates of bioavailability. One technique to avoid this problem, and one that has received considerable attention in recent years is the use in a single experiment of a stable labeled and unlabeled form of a drug. This design has been made possible by the use of mass spectrometry in conjunction with gas or liquid chromatography or more recently by tandem mass spectrometry. However, reduction in costs by virtue of one rather than two experiments (a cross-over study) is usually not realized because of the additional costs associated with the assay and in the synthesis of the labeled compound. Nonetheless, this is an elegant design that may be considered for certain compounds.

Traditional data analysis methods that include nonlinear regression fitting of oral data, simple exponential curve stripping, and other model-specific techniques for determining the absorption rate constant are certainly useful. Assuming linear disposition kinetics, there are at least two problems with these analyses. First, if there are competitive pathways (e.g., drug degradation in the gut) for absorption, the rate constant determined represents the sum of all pathways. Second, it is possible that the rate constant determined is confounded by, or represents a hybrid of, other dispositional processes, and this depends on the relative magnitude of the rate constants.

Two interesting approaches fall into the noncompartmental model category (often called "model independent"). They are noncompartmental in the sense that one does not need to use a specific compartmental or structured model, but they do require a statistical or mathematical model and are therefore not truly model independent. The disadvantage of the two methods to be mentioned is that they both require intravenous administration. The first method involves the idea of deconvolution; which means an "uncurling." Disposition processes from intravenous dosing are being uncurled from the combined absorption and disposition processes following nonvascular routes of administration. The resulting curve, which describes the fraction of drug absorbed as a function of time, may be fit by an appropriate equation that is usually in the form of a sum of exponential terms.

The second method makes use of statistical moment theory to calculate mean times for different processes. For example, following intravenous bolus or infusion administration one can calculate the mean residence time of the drug in the body. This idea is very similar to terms used in the physiologic and biochemical literature and is related to the time constant or turnover time. Mean absorption time requires knowledge of the mean residence time obtained after vascular administration. The calculation involves determination of two areas: the area under the plasma concentration–time curve (AUC = the zeroth moment) and the area under the concentration $\times$ time versus time curve (AUMC = the first moment). The ratio of AUMC to AUC is the mean residence time (MRT) following intravenous bolus dosing. After oral or other nonvascular administration the ratio of those areas minus MRT from the IV bolus dose will represent the mean absorption time (MAT). Assuming a one compartment model, the latter is the reciprocal of the absorption rate constant. There is a simple relationship between the more conventional time term used in pharmacokinetics, "half-life," and the MRT; MRT is 1.44 $\times$ half-life. These methods offer the investigator different ways of interpreting the resulting data and will likely lead to a more thorough analysis of the absorption process.

The next decade will unquestionably be an exciting and challenging time for those investigators who are involved in formulation research as attempts are made to provide efficient delivery of new drugs to the body. There will continue to be efforts made to better understand and model the absorption process at different levels of experimental preparation, including isolated tissues, perfusion systems, animal model, and the ultimate model, humans. We will be

better able to describe and understand such complicated processes as enterohepatic recirculation and absorption under conditions of nonfirst-order drug disposition as newer, more powerful methods of data analysis develop. Optimum drug delivery for all drugs is at hand.

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