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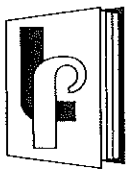

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Most of the drugs used today are potent and, increasingly, specific. However, finding a chemical that selectively binds to an enzyme in the myocardium or inhibits the synthesis of a key element in blood clotting does not constitute drug discovery. Among the requirements for a drug, we must be able to administer it to the whole animal and it must find its way to the site of action. In this sense, the modern dosage form is a *drug delivery system;* its selection may be as important to the clinical outcome of a given course of therapy as is the selection of the drug. With virtually any drug, one can routinely produce a 2- to 5-fold difference in the rate or extent of gastrointestinal absorption, depending on the dosage form or its formulation.[1] In some cases, even greater differences may be observed. A difference of more than 60-fold has been found in the absorption rate of spironolactone from the worst formulation to the best formulation.[2–4] The peak concentration of spironolactone metabolites in the plasma after a single dose of the drug in different dosage forms ranged from 0.06 to 3.75 μg/L per mg of administered drug.

From first principles, one would expect the bioavailability of a drug to decrease in the following order: solution > suspension > capsule > tablet > coated tablet. Although this ranking is not universal, it provides a useful guideline. The results of bioavailability studies with pentobarbital in man are summarized in Figure 5–1. The absorption rate of pentobarbital after administration in various oral dosage forms decreased in the following order: aqueous solution > aqueous suspension of the free acid ≈ capsule of the sodium salt > tablet of the free acid.[5] These findings demonstrate how the dosage form can influence drug absorption.

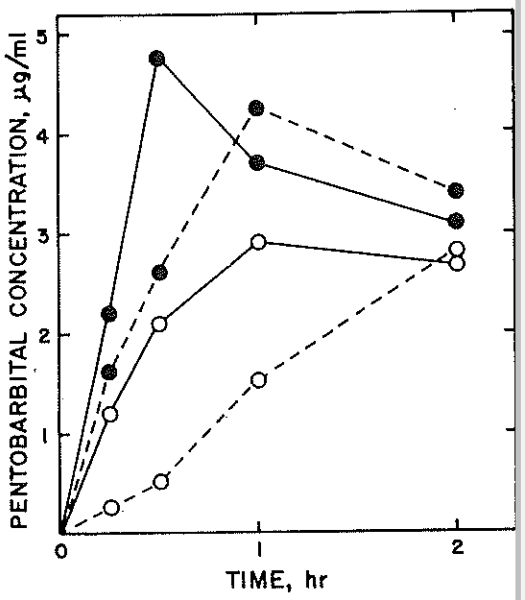

Fig. 5–1. Pentobarbital concentrations in plasma after single 200-mg dose in various oral dosage forms. ●— aqueous solution, ●– – – aqueous suspension, ○— capsule (sodium salt), ○– – – tablet (acid). (Data from Sjögren, J., Sölvell, L., and Karlsson, I.[5])

This chapter deals with the biopharmaceutic characteristics of dosage forms. The first section is an overview of the potential effects on absorption that may be observed with conventional oral dosage forms, including solutions, suspensions, capsules, tablets, and coated tablets. Special enteral dosage forms, like buccal or sublingual tablets and rectal preparations, are discussed in Chapter 6; prolonged-release medication is considered in Chapter 7. The second section deals with the correlation

drugs, particularly in pediatric and geriatric patients. With rare exception, drugs are absorbed more rapidly when given as a solution than in any other oral dosage form. The rate-limiting step in the absorption of a drug from a solution dosage form is likely to be gastric emptying, particularly when the drug is given after a meal.

When an acidic drug is given in solution in the form of a salt, there is the possibility of precipitation in gastric fluid. Experience suggests that these precipitates are usually finely subdivided and easily redissolved. However, with highly water-insoluble drugs, like phenytoin or warfarin, this may not be the case; one may find that the absorption rate or extent of absorption from a well-formulated suspension of the free acid is greater than from a solution of the sodium salt.

Many drugs, unless converted to a water-soluble salt, are poorly soluble. Solutions of these drugs can be prepared by adding cosolvents, such as alcohol, propylene glycol, polyethylene glycol 400, agents that form water-soluble complexes with the drug, or surfactants in sufficient quantity to exceed the critical micelle concentration and to effect solubilization. After administration of such water-miscible preparations, dilution with gastrointestinal fluids may result in precipitation of the drug. Again experience suggests that in most cases rapid redissolution takes place. Reversible interactions that occur between the drug and solubilizing agent or other component of the formulation are unlikely to affect drug absorption if the interaction product is water-soluble.

Serajuddin et al.[6] studied the physical properties and bioavailability of a poorly water-soluble drug dissolved in polyethylene glycol (PEG) 400 or polysorbate 80. On dilution of the water-miscible solutions with simulated gastric fluid, the drug immediately formed saturated solutions and the excess drug separated as finely divided emulsified oily globules with a high surface area. The average globule size of the oily form was 1.6 μm or less,

with water facilitates its dissolution and abs

Certain materials such as sorbitol or hyd
polymers are sometimes added to a solution
form, to improve pourability and palatab
increasing the viscosity of the preparati
higher the viscosity of the formulation, the
are gastric emptying and absorption. Such
however, are unlikely to be clinically imp

There has been some interest in givin
dissolved in oil. Rapid and complete ab
may be observed in some instances, partic
the oil is administered in emulsified form
clinical studies with indoxole, a poorly w
uble, investigational, nonsteroidal anti-in
tory agent, suggested incomplete absorptio
drug from a suspension or capsule dosag
Administration of indoxole dissolved in
phase of Lipomul-Oral, a commercially a
oil-in-water emulsion, resulted in a three
provement in the extent of absorption com
that observed after administration of an
suspension and a ninefold improvement c
to a hard gelatin capsule.[7]

Serajuddin et al.[6] found that a soluti
poorly water-soluble drug in peanut oil gav
75% greater bioavailability than an aque
pension of the drug when both dosage for
studied in the rat. Bioavailability from th
immiscible peanut oil solution, however,
as great as that found when the drug was d
in PEG 400 or polysorbate 80 to form wa
cible solutions.

Certain nontoxic but unpalatable solve
be used for solubilizing drugs if the solu
be encapsulated. This approach can, in som
dramatically improve the absorption of
insoluble drugs. For example, the bioava
of indoxole after administration of a sof
capsule containing the drug dissolved in
bate 80 was comparable to that found afte
istration of the drug dissolved in the oil
an oil-in-water emulsion.[7]

contained in a capsule or tablet may never achieve the state of dispersion in the gastrointestinal tract that is attained with a finely subdivided, well-formulated suspension.

Several studies have demonstrated the superior bioavailability characteristics of suspensions compared to those of solid dosage forms. For example, the blood levels of trimethoprim and sulfamethoxazole were compared in 24 healthy subjects following oral administration of 3 forms (tablet, capsule, and suspension) of the antibacterial combination. The absorption rate of each drug was significantly greater with the suspension than with the tablet or capsule.[8] There were no significant differences between the preparations in the extent of absorption of either drug. Similar results have been found with pentobarbital[5] and penicillin V.[9]

Among the more important factors to consider in formulating suspension dosage forms for maximum bioavailability are particle size, inclusion of wetting agents, formation of insoluble complexes, crystal form, and viscosity. Figure 5–2 compares the serum levels of phenytoin after a single 600-mg dose in the form of an aqueous suspension containing either micronized (Formulation G) or conventional (Formulation F) drug. Based on the total area under the drug concentration in serum versus time curve (AUC), almost twice as much phenytoin is absorbed after the micronized suspension.[10]

The higher the viscosity of a suspension, the slower is the dissolution rate of the drug. The inclusion of methylcellulose in an aqueous suspension of nitrofurantoin has been found to impair its rate and extent of absorption.[11]

Merely shaking some drug powder in an aqueous solution of a gum such as acacia neither constitutes a well-formulated suspension nor guarantees good absorption. This extemporaneous approach to formulation is sometimes used in screening drugs for biologic activity and in the safety assessment of promising compounds in laboratory animals. More sophisticated methods than these are called for to avoid costly mistakes regarding a drug's safety o efficacy.

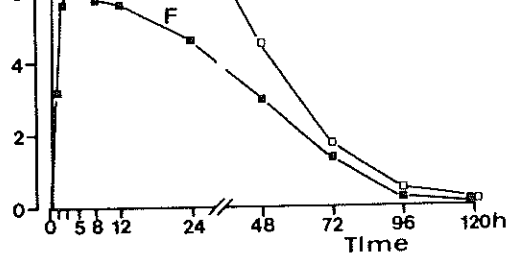

Fig. 5–2. Phenytoin concentrations (mg/L) in serum afte a 600-mg oral dose in aqueous suspensions containin either micronized (G) or conventional (F) drug. The are under the serum level-time curve is noted for each formu lation. (From Neuvonen, P.J., Pentikäinen, P.J., an Elfving, S.M.[10])

Bioavailability studies with drugs suspended i oil-in-water emulsions have yielded some prom ising results. One study compared the absorptio of micronized griseofulvin after its administratio to healthy subjects in a corn oil-in-water emulsio (in which the drug was suspended), an aqueou suspension, and two different commercial tablets. Based on cumulative urinary excretion of grise fulvin metabolites, the extent of absorption of th drug after administration of the emulsion was abo twice that observed after administration of th aqueous suspension or tablets. A mechanism base on the ability of fatty acids, liberated during th digestion of corn oil, to inhibit gastrointestinal m tility (which would increase the residence time the drug in the small intestine) and to stimula gallbladder evacuation and, thereby, elevate th concentrations of surface-active bile constituen in the intestine (which would promote dissoluti of the drug) may explain the results.

Capsules

The capsule dosage form has the potential to an efficient drug delivery system. The hard gela shell encapsulating the formulation should disru quickly, and expose the contents to the gastroi

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