5

Gastrointestinal Absorption—Role of the Dosage Form

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.

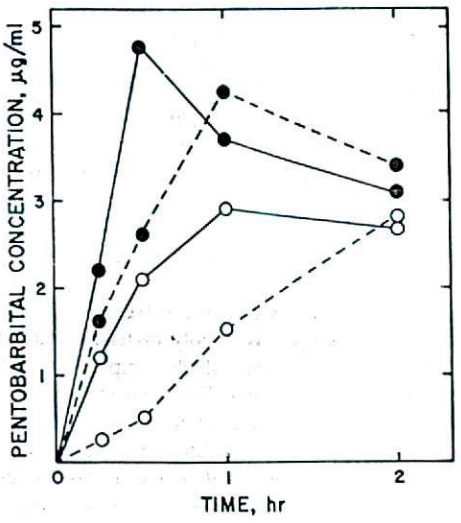

Fig. 5–1. Pentobarbital concentrations in plasma after a single 200-mg dose in various oral dosage forms. ●— aqueous solution, ●- - - aqueous suspension, ○— capsule (sodium salt), ○- - - tablet (acid). (Data from Sjögren, J., Sölvell, L., and Karlsson, I.[5])

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 of

drug absorption in man with in vitro parameters such as the disintegration time of the dosage form or the dissolution rate of the drug from the dosage form.

DOSAGE FORMS

Solutions

The solution dosage form is widely used for cough and cold preparations and for many other 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, as compared with a particle size of 5 to 10 μm for the solid drug.

Absorption studies in the rat using labeled drug resulted in 54% of the radioactivity excreted in the urine when the PEG solution was given and 41% when the polysorbate 80 solution was used, but only 19% of the radioactivity was found in the urine when an aqueous suspension of the drug was administered. The large surface area of drug separating from water-miscible solvents on dilution with water facilitates its dissolution and absorption.

Certain materials such as sorbitol or hydrophilic polymers are sometimes added to a solution dosage form, to improve pourability and palatability by increasing the viscosity of the preparation. The higher the viscosity of the formulation, the slower are gastric emptying and absorption. Such effects, however, are unlikely to be clinically important.

There has been some interest in giving drugs dissolved in oil. Rapid and complete absorption may be observed in some instances, particularly if the oil is administered in emulsified form. Early clinical studies with indoxole, a poorly water-soluble, investigational, nonsteroidal anti-inflammatory agent, suggested incomplete absorption of the drug from a suspension or capsule dosage form. Administration of indoxole dissolved in the oil phase of Lipomul-Oral, a commercially available oil-in-water emulsion, resulted in a threefold improvement in the extent of absorption compared to that observed after administration of an aqueous suspension and a ninefold improvement compared to a hard gelatin capsule.[7]

Serajuddin et al.[6] found that a solution of a poorly water-soluble drug in peanut oil gave nearly 75% greater bioavailability than an aqueous suspension of the drug when both dosage forms were studied in the rat. Bioavailability from the water-immiscible peanut oil solution, however, was not as great as that found when the drug was dissolved in PEG 400 or polysorbate 80 to form water-miscible solutions.

Certain nontoxic but unpalatable solvents may be used for solubilizing drugs if the solution can be encapsulated. This approach can, in some cases, dramatically improve the absorption of water-insoluble drugs. For example, the bioavailability of indoxole after administration of a soft elastic capsule containing the drug dissolved in polysorbate 80 was comparable to that found after administration of the drug dissolved in the oil phase of an oil-in-water emulsion.[7]

Suspensions

As a drug delivery system, the well-formulated aqueous suspension is second in efficiency only to the solution dosage form. Usually, the absorption rate of a drug from a suspension is dissolution-rate limited; however, drug dissolution from a suspension is often rapid because a large surface area is presented to the fluids at the absorption site. Drug 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 or efficacy.

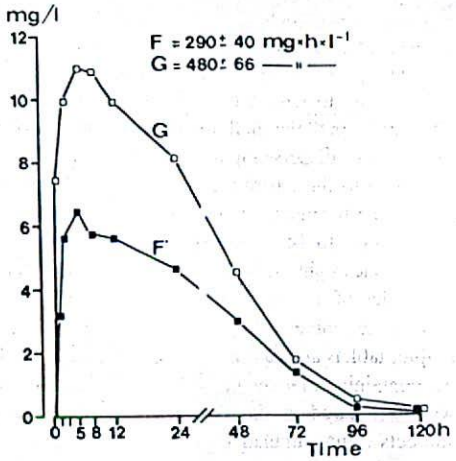

Fig. 5–2. Phenytoin concentrations (mg/L) in serum after a 600-mg oral dose in aqueous suspensions containing either micronized (G) or conventional (F) drug. The area under the serum level-time curve is noted for each formulation. (From Neuvonen, P.J., Pentikäinen, P.J., and Elfving, S.M.[10])

Bioavailability studies with drugs suspended in oil-in-water emulsions have yielded some promising results. One study compared the absorption of micronized griseofulvin after its administration to healthy subjects in a corn oil-in-water emulsion (in which the drug was suspended), an aqueous suspension, and two different commercial tablets.[12] Based on cumulative urinary excretion of griseofulvin metabolites, the extent of absorption of the drug after administration of the emulsion was about twice that observed after administration of the aqueous suspension or tablets. A mechanism based on the ability of fatty acids, liberated during the digestion of corn oil, to inhibit gastrointestinal motility (which would increase the residence time of the drug in the small intestine) and to stimulate gallbladder evacuation and, thereby, elevate the concentrations of surface-active bile constituents in the intestine (which would promote dissolution of the drug) may explain the results.

Capsules

The capsule dosage form has the potential to be an efficient drug delivery system. The hard gelatin shell encapsulating the formulation should disrupt quickly, and expose the contents to the gastroin-

testinal fluids. However, this will not be the case if the formulation or the method of manufacture imparts a hydrophobic nature to the shell.

Drug particles in a capsule are not subjected to high compression forces that tend to compact the powder and to reduce the effective surface area. On disruption of the shell, the encapsulated powder mass should disperse rapidly to expose a large surface area to the gastrointestinal fluids. However, with some formulations the rate of dispersion has been found to be unacceptably slow. Thus, although one might expect better bioavailability characteristics of a drug from a capsule than from a compressed tablet, this is not always so. For example, tablets and capsules of a combination product containing triamterene and hydrochlorothiazide were compared in single-dose studies in normal subjects using cumulative urinary excretion of apparent drug as an index of the extent of absorption.[13] The capsule was a simple formulation containing the drugs, lactose, and a small amount of magnesium stearate. The tablet was a more complex formulation that included a large amount of glycine, used as a water-soluble diluent. The excretion of hydrochlorothiazide after the tablet was twice as much as that found after the capsule. A 3-fold difference in the cumulative excretion of triamterene was observed. The tablets also consistently produced an earlier and a greater peak increase in sodium excretion.

It is usually necessary to have a suitable diluent in a capsule dosage form, particularly when the drug is hydrophobic. Figure 5–3 shows the change in dissolution rate that can be effected by the incorporation of hydrophilic diluents.[14] The diluent serves to disperse the drug particles, minimize aggregation, and maximize the effective surface area and dissolution rate. The incorporation of a wetting agent in the formulation may also be advantageous.

Other attempts to modify the wetting characteristics of poorly water-soluble drugs have included treating the drug with a solution of a hydrophilic polymer such as methylcellulose. Phenytoin was found to dissolve and be absorbed considerably faster from capsules containing drug treated with methylcellulose compared to capsules containing untreated drug.[15]

Many pharmacologic and toxicologic studies with investigational drugs in dogs and monkeys use hand-packed, hard gelatin capsules of the drug alone as the delivery system. This practice may

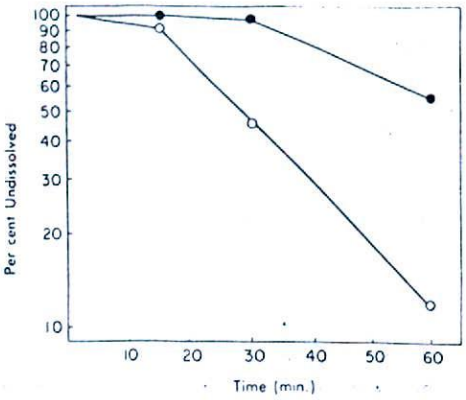

Fig. 5–3. Dissolution from hard gelatin capsules containing drug alone (●) or drug plus diluents (○). The diluents serve to disperse the drug and enhance wetting and dissolution. (Data from Palkoff, M., and Drumm, G.[14])

lead to erratic and incomplete drug absorption, and should be strongly discouraged.

The diluents of a capsule dosage form should have little tendency to adsorb or otherwise interact with the drug. The use of dicalcium phosphate as a diluent in tetracycline capsules has been found to significantly impair absorption, presumably because a poorly soluble calcium-tetracycline complex is formed in the powder mass or during dissolution.[16]

Factors that influence drug absorption from capsule dosage forms include particle size and crystal form of the drug, and selection of diluents and fillers.

Attempts to improve the oral absorption of digoxin has led to renewed interest in the use of soft elastic capsules as a solid oral dosage form. The soft elastic capsule has a gelatin shell somewhat thicker than that of hard gelatin capsules, but the shell is plasticized by the addition of glycerin, sorbitol, or a similar material. Unlike the hard gelatin capsule, the soft elastic capsule may contain nonaqueous solutions of a drug, or drugs that are liquids (e.g., the antitussive drug, benzonatate) or semisolids (e.g., certain vitamins).

A formulation consisting of digoxin dissolved in a mixture of polyethylene glycol, ethanol, and propylene glycol, prepared as a liquid concentrate in soft elastic capsules, has been developed and found to have good bioavailability characteristics. The encapsulated liquid concentrate of digoxin is con-

sistently better absorbed than the standard commercial tablet of the drug.[17-22]

A soft elastic capsule containing 0.4 mg of digoxin is about equivalent to a tablet containing 0.5 mg of the drug. In one study, mean absorption was 75% of the dose from the tablet and 97% from the capsule.[18] Surprisingly, some studies[18,21] but not all[22] suggest that the bioavailability of digoxin from the soft elastic capsule is greater than from an aqueous solution of the drug. The superior bioavailability of the encapsulated liquid concentrate over an aqueous solution may result from less chemical breakdown in the stomach when the capsule is given. Whatever the mechanism, we can conclude that the absorption of digoxin from soft elastic capsules is clearly better than from conventional tablets and at least comparable to an aqueous solution of the drug.

Tablets

Compressed tablets are the most widely used dosage form. They are usually produced by either wet granulation or direct compression. Wet granulation consists of mixing the drug with other powdered materials and wetting the mixture with an aqueous solution of a suitable binder such as gelatin or starch. The damp mass is forced through a 6- or 8-mesh screen and dried to produce cohesive granules. These granules usually flow easily through the tablet press and are easily compressed.

Increasing attention is being given to manufacturing tablets by direct compression. As its name implies, direct compression consists of compressing tablets directly from powdered material without modifying the physical characteristics of the material itself. For tablets in which the drug constitutes a major portion of the total tablet weight, the drug itself must have the physical attributes (crystallinity and cohesiveness) needed for the formulation to be compressed directly. Direct compression can almost always be used for tablets containing 25% or less of the total weight as drug, by formulating with suitable diluents which act as a carrier or vehicle for the drug. These diluents include processed forms of common tablet materials such as dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, anhydrous lactose, and mannitol, as well as spray-dried lactose, pregelatinized starch, compressible sugar, and microcrystalline cellulose.

Most bioavailability problems with compressed tablets are related to the large reduction in effective surface area that results from the tablet manufacturing process, as well as to the difficulty in regenerating well-dispersed primary drug particles in the gastrointestinal tract. After ingestion, the tablet first breaks down to granules and then to primary drug particles. Granules resulting from directly compressed tablets may be softer and more easily wetted than those produced by tablets prepared with the wet-granulation process, but it is difficult to generalize. The disintegration and dissolution processes that take place in the gastrointestinal fluids after oral administration of a tablet are presented in schematic form in Figure 5–4.

The effective surface area of drug in an intact tablet is so limited that k_1, the dissolution rate constant, is usually negligible, except for drugs that

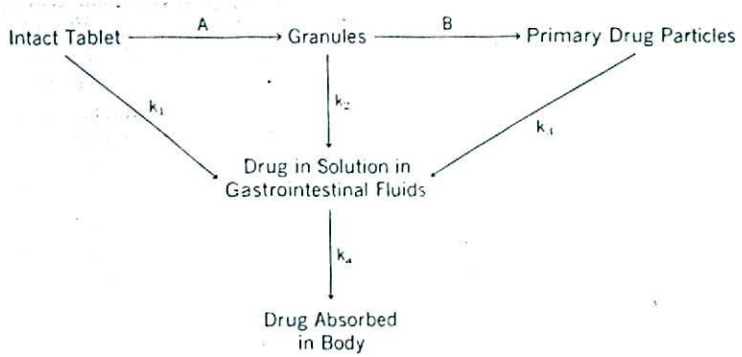

Fig. 5–4. Schematic representation of disintegration (A, B) and dissolution (k_1, k_2, k_3) processes that precede drug absorption after administration of a tablet dosage form. The term k, is a first-order rate constant characterizing drug absorption from solution in the fluids of the gastrointestinal tract.

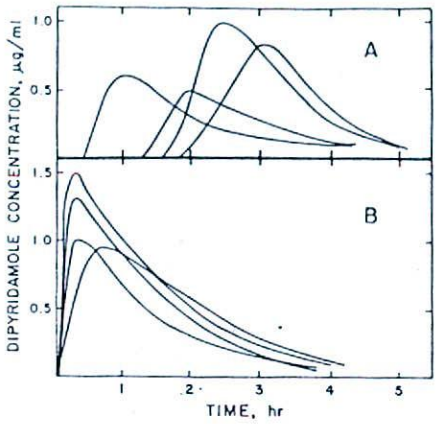

Fig. 5–5. Dipyridamole concentrations in serum of individual subjects after a 25-mg oral dose as intact tablets (A) or crushed tablets (B). When the tablets are chewed before swallowing, the peak concentration tends to be higher and the peak time tends to be earlier. (Data from Mellinger, T.J., and Bohorfoush, J.G.[23])

are extremely water-soluble. Tablet disintegration (step A) greatly increases the effective surface area of the drug. A further increase in surface area is attained upon granule disintegration; accordingly, $k_3 >> k_2 >> k_1$. The dissolution rate from the granules may be likened to that observed with a coarse, aggregated drug suspension, whereas the dissolution rate from the primary particles is probably comparable to that observed with a fine, well-dispersed drug suspension. Poorly water-soluble drugs are likely to dissolve mainly after granule disintegration.

Tablet disintegration and granule disintegration are important steps in the absorption process. A tablet that fails to disintegrate or disintegrates slowly may result in incomplete absorption or an undue delay in the onset of clinical response. The importance of disintegration in drug absorption is evident from the results of clinical studies with dipyridamole.[23] Curves of serum concentrations of dipyridamole versus time after administration are shown in Figure 5–5. When the tablets were taken intact, the appearance of drug in blood was delayed and variable. When the tablets were chewed before swallowing, the drug appeared in the blood within 5 or 6 min. In every patient; the peak drug concentration was higher after the crushed tablet than after swallowing the intact tablet. Similar results have been observed with thioridazine tablets.[24] Studies in the United Kingdom have shown that when commercial digoxin tablets, from which the drug is incompletely absorbed, are crushed and given in a capsule, much higher digoxin levels are obtained.[25]

Tablet disintegration, although important, is unlikely to be the rate-limiting step in the absorption of drugs administered as conventional tablets. In most instances, granule disintegration and drug dissolution occur at a slower rate than tablet disintegration.

Many factors related to the formulation or production of tablets may affect drug dissolution and absorption. Most formulations require the incorporation of hydrophobic lubricants, such as magnesium stearate, to produce an acceptable tablet. In general, the larger the quantity of lubricant in a formulation, the slower is the dissolution rate.[26]

Even seemingly modest changes in formulation may lead to significant effects on dissolution and availability. A classic example has been reported with tolbutamide.[27] Two formulations of the drug were compared in healthy subjects with respect to bioavailability (serum tolbutamide levels) and therapeutic efficacy (hypoglycemic response). One tablet was the commercial product and the other was identical in all respects except for a halving of the amount of a disintegrant. Both tablets met United States Pharmacopeia (USP) specifications. Both tablets disintegrated in vitro within 10 min.

Despite the similar specifications, the experimental formulation was inferior to the commercial product. The area under the average serum tolbutamide curve over an 8-hr observation period was more than 3 times greater with the commercial product than with the experimental formulation. The average cumulative reduction of serum glucose over the 8-hr period after administration of the commercial tablet was twice that after administration of the experimental tablet (Fig. 5–6).

Compression force may also be an important factor in drug bioavailability from compressed tablets. The in vitro disintegration time of tablets has been shown to be directly proportional to compression force and tablet hardness.[28] High compression forces may also increase the strength of the internal structure of the granules and retard dissolution of drug from the granules and disintegration of the granules.

The effect of particle size reduction on dissolution and absorption may be reduced by compression.[29] Studies in man showed that a 3.8-fold

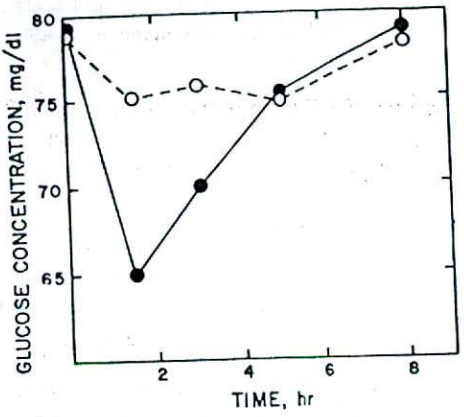

Fig. 5–6. Serum glucose levels after 0.5-g tolbutamide in a commercial tablet (●) or an experimental tablet containing less disintegrating agent (○). (Data from Varley, A.B.[27])

increase in the specific surface area of griseofulvin led to a 2.3-fold increase in blood concentration after administration of a suspension, but only a 1.5-fold increase after administration of a tablet.

A novel approach to enhance the availability of poorly water-soluble drugs from tablets has been used in a marketed griseofulvin product.[30] A molecular dispersion of the drug in polyethylene glycol 6000, a water-soluble, waxy polymer that congeals at about 60°C, is prepared and suitably modified for incorporation into a tablet dosage form. The absorption of griseofulvin from this product appears to be complete and about twice that observed from commercial tablets containing micronized drug.

Coated Tablets

Tablet coatings are used to mask unpleasant tastes and odors, to protect an ingredient from decomposition during storage, or simply to improve the appearance of a tablet. The most common coated medications are sugar-coated and film-coated tablets. Not only do these dosage forms present all the potential problems discussed earlier with respect to compressed tablets, but they also impose an additional barrier between the gastrointestinal fluid and the drug. The coating must dissolve or disrupt before tablet disintegration and drug dissolution can occur. The disintegration of certain coated tablets appears to be the rate-limiting process in drug absorption, since correlations have been found between bioavailability and in vitro disintegration time.

The venerable sugar-coated tablet is still used today. The sugar coating formulation is complex; the coating process is time consuming and requires skill. The first step of the process is the application of a nonaqueous, sealing solution to protect the tablet and its ingredients from the aqueous solutions used in subsequent steps. A special grade shellac dissolved in alcohol is commonly used to seal tablets. Other materials that have been used include fatty glycerides, beeswax, and silicone resins. The other steps of the coating process add bulk and modify the shape of the tablets. Other ingredients of the coating formulation may include talc, acacia, flour, starch, and calcium carbonate, in addition to sucrose.

The application of the sealing coat and the development of a relatively dense crystalline barrier around the tablet retard the release of drug in the gastrointestinal tract. In general, we must assume that a sugar coating may affect the bioavailability of a drug. This dosage form should not be used when a prompt clinical response is desired.

The basic disadvantages of sugar coating have stimulated a search for alternatives. These alternatives include the film-coated tablet and the press-coated tablet. Film-coated tablets are compressed tablets that are coated with a thin layer or film of a material that is usually water soluble or dispersible. A number of polymeric substances with film-forming properties may be used including hydroxypropyl methylcellulose and carboxymethylcellulose. Aqueous vehicles are preferred but a nonaqueous vehicle may be used when moisture is detrimental to the product being coated. A mixture of cellulose acetate phthalate and polyethylene glycol can be applied from aqueous or nonaqueous solvents. Care should be taken when selecting coating materials. Methylcellulose, for example, has been reported to retard drug dissolution.[31]

The film coat masks objectionable tastes and protects, to some degree, tablet ingredients from moisture during storage. The film coat should disrupt quickly in the fluids of the gastrointestinal tract, independent of pH. A well-formulated product should show little difference in bioavailability compared with that of an uncoated tablet.

Press-coated or dry-coated tablets are prepared by feeding previously compressed tablets into a special tableting machine and compressing another

granulation layer around the preformed tablet. Press-coated tablets appear to retain all the attributes of compressed tablets but provide the advantages of sugar-coated tablets. Ideally, there should be little difference in disintegration time between press-coated and uncoated tablets.

Enteric-Coated Tablets

An enteric coat is usually a special film coat designed to resist gastric fluids and to disrupt or dissolve in the small intestine. The enteric coat is used to protect a drug from degrading in the stomach (e.g., erythromycin), or to minimize gastric distress caused by some drugs (e.g., aspirin). Enteric-coated tablets must empty from the stomach before drug absorption can begin. The rate of appearance of drug in the blood after giving an enteric-coated tablet is, therefore, a function of gastric emptying. Differences in gastric emptying from one patient to another or in the same patient from one administration to another contribute to the large variability in drug absorption commonly found with this dosage form.

The time course of an enteric coated aspirin tablet from the stomach to the small intestine was monitored in dogs using radiotelemetry.[32] A 500-mg enteric coated tablet was attached to a Heidelberg capsule calibrated to pH 1 and pH 7. Gastric pH was about 1.5. As the tablet was emptied into the small intestine, the monitored pH rose to about 7. This time interval was termed the gastric emptying time. The pH in the small intestine remained relatively constant until the enteric coating dissolved and aspirin was released. At this time, the monitored pH dropped to about 3.8, close to the pK_a of aspirin. This time interval was defined as the coating dissolution time.

As a result of carrying out four replicates in each of 4 dogs both inter- and intrasubject variability could be evaluated. In 1 dog the gastric emptying time ranged from 7 to 40 min and in another from 8 to 115 min. Mean gastric emptying times varied from 24 to 63 min. Coating dissolution time seemed to be less variable. In 1 dog the dissolution times ranged from 23 to 49 min and in another from 26 to 77 min. Mean coating dissolution times varied from 34 to 57 min. The variable onset of aspirin appearance in the plasma is the result of variance in both gastric emptying time and coating dissolution time, with the variance in gastric emptying time being significantly larger.

The modern approach to enteric-coating makes use of polymers like cellulose acetate phthalate that are "insoluble" at pH 1 to 3 but "soluble" at pH 5 to 7. These materials are polymeric acids with ionizable carboxyl groups. The apparent pKa of these polymers is important. If the pKa is too low, appreciable ionization takes place at low pH, and the coating will dissolve in the stomach. A high pKa may prevent release of drug in the small intestine. In practice, polymers with pKa values ranging from 4 to 7 have been found useful.

In one investigation, a series of half-esters of the copolymer poly (vinyl methyl ether-maleic anhydride) was prepared. The in vitro dissolution pH (i.e., the pH of complete solubility) of films of these polymers varied from 4.25, for the ethyl derivative, to 6.25, for the cyclopentyl half-ester. The bioavailability of aspirin was studied in normal subjects following administration of tablets coated with these copolymers. An inverse correlation was observed between absorption rate and the in vitro dissolution pH. Twelve hr after administration of tablets coated with the ethyl half-ester, 87% of the dose was recovered in the urine, compared to a urinary recovery of 53% after administration of tablets coated with the cyclopentyl half-ester.[33]

The thickness of the coating may also affect bioavailability. Studies with quinine tablets coated with cellulose acetate phthalate show a decrease in both rate and extent of absorption with increasing thickness of the coating.[34] A particular problem with shellac as an enteric coating is that the water solubility of the film decreases with age; an enteric-coated tablet with acceptable bioavailability characteristics at the time of manufacture may perform poorly some time later.

A considerable delay may be observed between the administration of an enteric-coated tablet and the appearance of drug in the bloodstream. This is evident from bioavailability studies with prednisolone and aspirin. Enteric-coated prednisolone has been available for many years because some believe that chronic steroid therapy predisposes to gastric ulceration. Studies comparing blood levels after a single dose of prednisolone in the form of ordinary or enteric-coated tablets show that although the extent of absorption (AUC) and maximum blood levels are comparable, there is, on the average, a 3-hr difference in the time required to attain the peak concentration of the drug (Table 5–1).[35]

Aspirin has maintained an important place in the treatment of rheumatic diseases despite the intro-

Table 5–1. Peak Concentration of Prednisolone in Plasma, Time to Peak, and Total Area Under the Plasma Level-Time Curve (AUC) After an Oral Dose*

Formulation	Peak concentration	AUC	Time (min)
Tablet	1383	347	84
Enteric-coated tablet	1267	311	260
Significance	NS	NS	$p < 0.001$

*Data from Lee, D.A.H., et al.[35]

duction of many other nonsteroidal anti-inflammatory drugs (NSAIDs). However, gastric intolerance and injury are commonly observed with the high doses required for optimal effects. One of the traditional methods of overcoming the gastric side effects of aspirin has been to formulate the drug as an enteric-coated tablet. A well-formulated enteric-coated tablet of aspirin has been compared with uncoated tablets with respect to time of appearance of salicylate in the plasma after a single dose.[36] The results in a representative subject are shown in Figure 5–7. Salicylate was detected in the plasma of all 18 subjects within 1 hr after giving the uncoated tablet but not until 3 hr, on the average, after the enteric-coated tablet. Two subjects showed no salicylate in the plasma for 8 hr after the coated tablets.

Fenoprofen is another NSAID available as an enteric coated tablet. The effects of plain and enteric coated fenoprofen calcium on gastrointestinal microbleeding were studied in healthy male subjects.[37] A one-week baseline (placebo) period preceded two weeks of fenoprofen therapy (enteric coated or plain tablets, 600 mg 4 times a day). Fecal blood loss was estimated by a ^{51}Cr-tagged erythrocyte assay and was averaged over days 4 to 7 (baseline) and days 18 to 21 (active treatment). At the end of the active drug period, mean daily fecal blood loss was lower with enteric coated fenoprofen than with plain tablets, 1.1 ml/day *versus* 1.7 ml/day. Gastric and duodenal mucosal damage, however, as evaluated by endoscopy, was similar for both dosage forms.

The delay in drug absorption typically found after administration of enteric-coated tablets could be the result of prolonged gastric emptying or, alternatively, slow dissolution of the coating after the tablet reaches the small intestine. In most cases, slow gastric emptying appears to be the principal reason for the delay because coadministration of metoclopramide, a drug that accelerates gastric emptying, can dramatically decrease the lag time.[36,38]

Since gastric emptying of the enteric-coated dosage unit plays an important role in the onset of drug absorption, it is to be expected that administration of this dosage form after a meal will further delay absorption. Paull and associates report that giving an enteric-coated aspirin tablet immediately after a heavy breakfast markedly delays the appearance of salicylate in saliva, compared to that observed after giving the tablet 2 hr after a light breakfast.[38]

The Heidelberg capsule, a radiotelemetric indicator of gastrointestinal pH, has also been used in human subjects to evaluate the relationship between gastric residence time (GRT) and variability in aspirin absorption from enteric coated tablets.[39] In a crossover study, subjects received enteric coated aspirin together with the Heidelberg capsule while fasting or with food (breakfast, followed 4 hr later by lunch).

The mean time to peak salicylate concentration was 8.3 hr when the subjects were fasted and 13.8 hr when fed. This shift was related to gastric emptying. Mean GRT was markedly delayed by food,

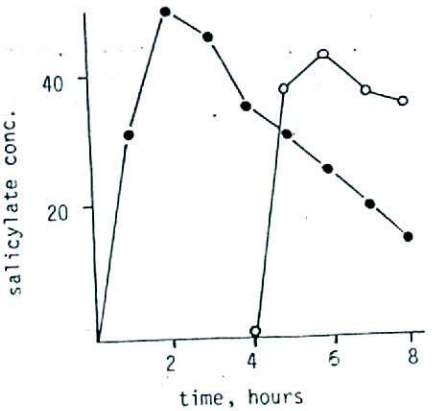

Fig. 5–7. Salicylate concentrations in plasma (μg/ml) after a 650-mg dose of aspirin in conventional tablets (●) or enteric-coated tablets (○). (Data from Day, R.D., et al.[36])

going from about 1 hr to about 6 hr. Time to appearance of salicylate in plasma (lag time) was also delayed when enteric coated aspirin was given with food, from about 3 to 9 hr. There was an excellent correlation ($r = 0.94$) between the lag time for appearance of salicylate in plasma and GRT.

The effect of food on the absorption of quinidine from an enteric-coated tablet has also been studied.[40] In fasting subjects, the delay in the start of absorption after a single dose ranged from 2 to 8 hr (mean = 4.8 hr); in nonfasting subjects the delay ranged from 3 to 10 hr (mean = 6.1 hr). Whether or not the dosage form was given with food, intersubject variability in the length of the delay before the onset of absorption was substantial; in some subjects the delay was longer than the usual dosing interval for the drug. Other studies with this enteric-coated quinidine product suggested that absorption began later and was slower at night, consistent with the fact that gastric emptying is slower when the patient is in the prone position.[40]

The enteric-coated tablet dosage form has been the object of well-deserved criticism in recent years. Many reports of clinical failure because of erratic and incomplete absorption can be found in the literature. Far fewer problems are found with newer products, but variability remains a substantial concern. One approach that appears to minimize variability is the use of individually enteric-coated granules.[41] These granules may be compressed into rapidly disintegrating tablets or administered in capsules. After disintegration of the dosage form in the stomach, gradual but continual emptying of the granules into the intestine is anticipated.

A theoretical analysis of blood level profiles resulting from enteric-coated granules has been published.[42] It concludes that:

> an enteric-coated tablet may take from approximately 0.5 to more than 8 hr. to pass from the stomach to the duodenum. On the other hand, enteric-coated pellets are subjected to dispersion in the stomach and they pass through the pyloric sphincter after a mean residence time in the stomach that would not be different from that exhibited by a suspension dosage form.

Investigators in Sweden have compared the absorption of aspirin from two different enteric-coated dosage forms, tablets and granules, in healthy subjects under fasting and nonfasting conditions.[43] Under fasting conditions, the absorption of aspirin from both preparations was complete. When the dosage forms were taken after a meal, the enteric-coated tablets gave much lower concentrations of salicylate in plasma than under fasting conditions, and absorption was incomplete in some subjects. Neither the rate nor extent of aspirin absorption from the enteric-coated granules was affected by food.

Drug absorption from enteric-coated granules appears to be more consistent than from enteric-coated tablets. Do the granules protect the GI mucosa as well as the tablets? A placebo-controlled study has been reported comparing the effects of aspirin formulated as enteric-coated granules or as buffered tablets on gastric mucosa, as determined by endoscopic examination 2 hours after a single 975-mg dose in fasted subjects.[44] A grading scale of 0 (no damage) to 4 (severe damage) was used.

The granules produced a much lower severity and incidence of gastric lesions than the buffered aspirin formulation. The mean severity score was 0.4 for the granules and 3.0 for the buffered tablet. All subjects receiving the buffered tablet showed one or more sites of submucosal hemorrhage or erosion, compared with 36% of those given the enteric-coated granules. None of the lesions produced by the granules or the placebo was considered clinically significant, whereas nearly two-thirds of the subjects given buffered aspirin had clinically important stomach damage.

Although incomplete and variable absorption has been the most common problem found with enteric-coated tablets, a far more serious problem brought national attention to this dosage form. This problem was the life-threatening toxicity associated with enteric-coated potassium chloride tablets. Enteric-coated KCl was developed to minimize gastric irritation and to enhance palatability and compliance. However, from 1964 to 1974 numerous cases of small bowel ulceration associated with the administration of enteric-coated potassium chloride, alone or in combination with thiazide diuretics, were reported.[45] This serious adverse effect was not found with liquid or effervescent tablet forms of potassium chloride.

The cause of the problem can be found in the crystalline nature and compression characteristics of KCl itself. Tablets of this salt are easily made but do not disintegrate easily. When the enteric-coated tablet empties from the stomach and the film coating dissolves, what remains is a poorly disintegrating tablet of almost pure potassium chloride resting on the mucosa of the small intestine. The limited surface area of the intact tablet results in

slow dissolution and prolonged and corrosive contact. Of the dozens of enteric-coated KCl products that were on the market in the United States, none remains. Today, the need for a solid dosage form of potassium chloride is met by slow-release tablets in which the KCl is embedded in a wax matrix and by tablets or capsules containing small microencapsulated particles of KCl. These preparations are marked improvements over enteric-coated tablets.

Sulfasalazine is used in the treatment of ulcerative colitis. It is poorly absorbed in the small intestine, allowing essentially all of an oral dose to reach the large intestine where bacteria split the diazo bond, forming sulfapyridine and 5-aminosalicylic acid (5-ASA).

There is controversy as to which drug(s) is the active species. Sulfapyridine appears to contribute little or nothing to the effectiveness of sulfasalazine and may be responsible for most of its side effects. Many believe that 5-ASA is the active drug and that sulfasalazine is simply a prodrug for delivery of 5-ASA to the colon. Supporting this idea is the observation that topical (rectal) administration of 5-ASA is in fact effective in ulcerative colitis restricted to the distal large intestine.

There is interest in the development of an oral preparation that retains the activity of 5-ASA, while eliminating sulfapyridine as a source of unwanted effects. One product contains 5-ASA particles coated with an acrylic resin that disintegrates at pH 7 or above. These pH conditions ordinarily occur only in the distal ileum and colon.

Riley et al.[46] studied the ileostomy excretion of this dosage form in human subjects who previously had undergone a colectomy. Following a single dose given after an overnight fast, 5-ASA first appeared in the effluent between 4 and 6 hours in 6 subjects and between 6 and 8 hours in the other two. Within 12 hr of taking the tablet, an average of 88% (range 69 to 114%) of the 400-mg dose was recovered in the effluent as unchanged 5-ASA, indicating that little absorption of resin-coated 5-ASA takes place in the small intestine.

An in vitro dissolution study[46] indicated that at pH values above 7.0, dissolution of the protective coat was rapid. Between pH 6.0 and 7.0, dissolution was considerably delayed. At pH 2.0 and 4.0, the coat remained intact for more than three days.

The results of open-label studies have suggested that the preparation of coated 5-ASA is tolerated actions to sulfasalazine.[47] Other investigators found that administration of 4.8 g per day of coated 5-ASA to patients with mildly or moderately active ulcerative colitis resulted in a complete response in 24% of the patients and a partial response in 50%. This dose is equivalent in terms of 5-ASA content to a 12 g dose of sulfasalazine, "a dosage that could not be tolerated by most patients."[48]

The use of acid-resistant coatings to deliver drugs to the colon has also been applied to cholestyramine.[49] Ileal resection causes malabsorption of bile acid; the increased load of bile acids in the colon induces increased secretion of salt and water and leads to diarrhea. A double blind crossover trial was carried out with placebo and cholestyramine coated with cellulose acetate phthalate. During treatment with cholestyramine, the daily fecal output and the number of defecations each week decreased, and patient acceptance of the preparation was high.

A somewhat different approach to drug delivery has been proposed for peptides.[50] The oral administration of peptide drugs is precluded because they are digested in the stomach and small intestine. As a new approach to oral delivery, vasopressin and insulin were coated with polymers cross-linked with azoaromatic groups to protect them from digestion. When the azopolymer-coated drug reached the large intestine, the indigenous microflora reduced the azo bonds, broke the cross-links, and degraded the polymer film, thereby releasing the drug into the lumen of the colon for local action or for absorption. The feasibility of delivering insulin to lower blood glucose was demonstrated in rats made diabetic with streptozotocin.

IN VITRO CORRELATES OF DRUG ABSORPTION

The advantages to be gained in developing in vitro tests that are predictive of drug absorption in man are considerable and have stimulated an overwhelming number of investigations by pharmaceutical scientists throughout the world. These efforts have focused largely on disintegration and dissolution tests.

Disintegration Tests

The first official method for tablet disintegration was described in a Swiss pharmacopeia in 1934. The United States Pharmacopeia (U.S.P.) has recognized one test or another for tablet disintegration since 1950. The latest revision of the U.S.P.

(U.S.P. XXI) published in 1985 also includes a disintegration test for hard gelatin capsules.

The following is taken directly from U.S.P. XXI.

(701) DISINTEGRATION

This test is provided to determine compliance with the limits on *Disintegration* stated in the individual monographs except for soft gelatin capsules and where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed to liberate the drug content gradually over a period of time or to release the drug over two or more separate periods with a distinct time interval between such release periods. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that stage in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

Apparatus

The apparatus[1] consists of a basket-rack assembly, a 1000-mL, low-form beaker for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-rack Assembly—The basket-rack assembly consists of six open-ended glass tubes, each 7.75 ± 0.25 cm long and having an inside diameter of approximately 21.5 mm and a wall approximately 2 mm thick; the tubes are held in a vertical position by two plastic plates, each about 9 cm in diameter and 6 mm in thickness, with six holes, each about 24 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is 10-mesh No. 23 (0.025-inch) W. and M. gauge woven stainless-steel wire cloth having a plain square weave. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks—Each tube is provided with a slotted and perforated cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five 2-mm holes extend between the ends of the cylinder, one of the holes being through the cylinder axis and the others parallel with it equally spaced on a 6-mm radius from it. Equally spaced on the sides of the cylinder are four notches that form V-shaped planes that are perpendicular to the ends of the cylinder. The dimensions of each notch are such that the openings on the bottom of the cylinder are 1.60 mm square and those on the top are 9.5 mm wide and 2.55 mm deep. All surfaces of the disk are smooth.

Procedure

Uncoated Tablets—Place 1 tablet in each of the six tubes of the basket, add a disk to each tube, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid unless another fluid is specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then add a disk to each tube, and operate the apparatus, using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 30 minutes of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets. If the tablets have not disintegrated completely, substitute simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, and continue the test for a total period of time, including previous exposure to water and simulated gastric fluid TS, equal to the time limit specified in the individual monograph plus 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Enteric-coated Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus, without adding the disks, using simulated gastric fluid

[1] A suitable apparatus, meeting these specifications, is avail-

TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Then add a disk to each tube, and operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for a period of time equal to 2 hours plus the time limit specified in the individual monograph, or, where only an enteric-coated tablet is recognized, for only the time limit specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets*, but omit the use of the disks. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets*, but omit the use of the disks. Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*, but omit the use of disks. In place of disks attach a removable 10-mesh wire cloth,[3] as described under *Basket-rack Assembly*, to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not less than 16 of the total of 18 capsules tested disintegrate completely.

The testing fluid for uncoated tablets and hard gelatin capsules is usually water at 37°C, but in some cases (e.g., alumina and magnesia tablets, benzthiazide tablets) the monograph directs that simulated gastric fluid be used. Tests for enteric-coated tablets call for initial immersion for a specific period of time in simulated gastric fluid, followed by immersion in simulated intestinal fluid. Maximum disintegration times are included in some of the individual tablet monographs but in many cases, a dissolution test has replaced the disintegration test. For most uncoated tablets and capsules, the specified disintegration time is 30 min or less. Exceptions include erythromycin tablets (60 min) and griseofulvin tablets (60 min). For coated tablets, up to 2 hr may be permitted. These specifications are based largely on the disintegration properties of commonly available products of the drug, rather than on bioavailability considerations.

One should expect the disintegration of a tablet in the gastrointestinal tract to take longer than that observed in the U.S.P. apparatus. The disintegration test subjects the tablet to a great deal of abrasion and turbulence, which facilitate disintegration. This is not encountered in the gastrointestinal tract. Since it is unlikely that disintegration would be the rate limiting step in the absorption of drugs from tablets, it is not surprising that the results of in vitro disintegration tests have been found to be of limited value in predicting drug absorption.

Successful correlations between parameters of drug absorption and disintegration times have been reviewed by Wagner.[51] The few quantitative correlations that have been reported involve only sugar-coated or enteric-coated tablets. Results with uncoated tablets have been disappointing. For example, studies with different commercial aspirin tablets showed that their disintegration times had no relation to the rate of absorption of aspirin in human subjects.[52]

There are also reports indicating that although certain enteric-coated products conform to compendial standards for disintegration, they may in fact be poorly absorbed. Bioavailability studies with a marketed enteric-coated aspirin tablet showed incomplete absorption, ranging from 0 to 25% of the dose in 3 of 4 subjects. The fourth subject absorbed the entire dose. Tablet disintegration times, determined by the U.S.P. XVI procedure for enteric-coated tablets, which represents the disintegration time in simulated intestinal fluid after 1-hr exposure to simulated gastric fluid, ranged from 18 to 25 min, well within the 125-min requirement extant at the time.[53] Still another example is a brand of enteric-coated tablets of aminosalicylic acid that met all U.S.P. specifications, including disintegration, but failed to yield detectable blood levels of the drug in 8 normal adults.[54]

The test for tablet disintegration is useful for quality control purposes in manufacturing; however, it is generally recognized that the in vitro disintegration test is a poor index of bioavailability. Conformance of a tablet or capsule product to compendial standards for disintegration does not guarantee adequate drug absorption. On the other hand, failure to conform to a standard for disintegration

[3] A suitable wire cloth cover is available as Van-Kel Industries Part TT-1030.

time surely signals a potential bioavailability problem.

Dissolution Tests

The documented inability of disintegration tests to provide an index of bioavailability intensified interest in the development of dissolution tests that might better serve as predictors of drug absorption. The results of these efforts have been more encouraging. From first principles, one would expect a closer relationship between drug absorption and dissolution rather than disintegration, particularly for poorly water-soluble drugs.

The United States Pharmacopeia has played an important role in the development of dissolution standards. For many tablets recognized in U.S.P. XXI, the monographs direct compliance with specifications for dissolution rather than disintegration. Although these specifications are primarily for the purpose of quality control, they represent a first step in the assurance of bioavailability.

The following is taken from U.S.P. XXI as amended in its fifth Supplement.

(711) DISSOLUTION

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form, except where the label states that the tablets are to be chewed. Requirements for *Dissolution* do not apply to liquid-filled soft gelatin capsules. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. Of the types of apparatus described herein, use the one specified in the individual monograph.

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1], a motor, a metallic drive shaft, and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at 37±0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 mm to 175 mm high, its inside diameter is 98 mm to 106 mm,

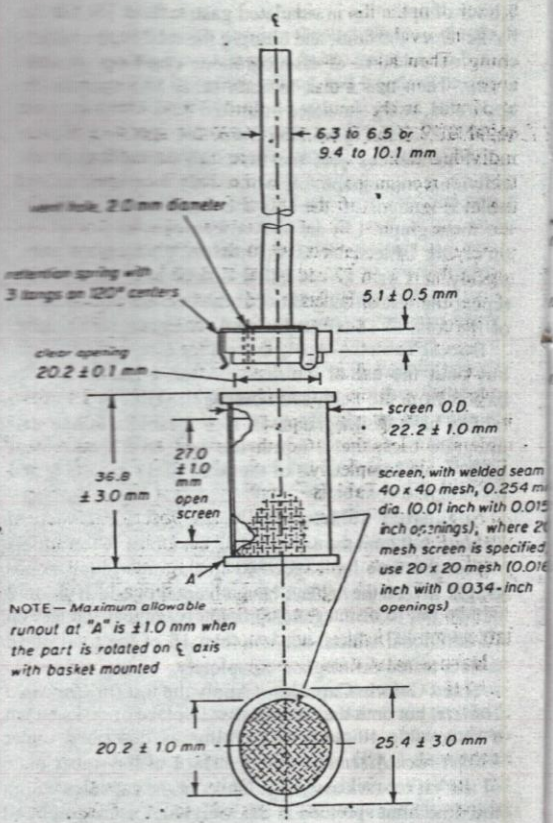

Fig. 1. Basket Stirring Element.

and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 μm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25±2 mm during the test.

Apparatus 2—Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so

[1] If a cover is used, it provides sufficient openings to allow

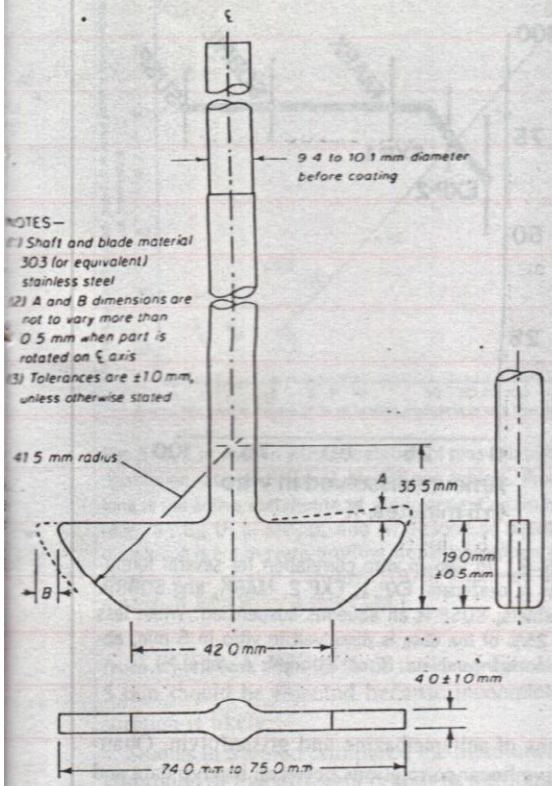

Fig. 2. Paddle Stirring Element.

that its axis is not more than 2 mm at any point from the vertical axis of the vessel, and rotates smoothly without significant wobble. The blade passes through the diameter of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic blade and shaft comprise a single entity that may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float.

Apparatus Suitability Test—Individually test 1 tablet of the *USP Dissolution Calibrator, Disintegrating Type*[3] and 1 tablet of *USP Dissolution Calibrator, Nondisintegrating Type*,[3] according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.

Dissolution Medium—Use the solvent specified in the individual monograph. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph. [NOTE—Dissolved gases can cause bubbles to form which may change the results of the test. In such cases, dissolved gases should be removed prior to testing.]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. If two or more times are specified, specimens are to be withdrawn only at the stated times, within a tolerance of $\pm 2\%$.

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the *Dissolution Medium* to $37 \pm 0.5°$, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying acceptance table. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; both the 5% and 15% values in the acceptance table are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

[3] Available from USP-NF Reference Standards, 12601 Twin-

Two types of dissolution apparatus are officially recognized: Apparatus 1 (basket method), and Apparatus 2 (paddle method). For Apparatus 1, the basket containing the tablet or capsule is immersed in the dissolution fluid and rotated. For Apparatus 2, the dosage form is placed directly in the dissolution medium and the paddle is rotated. The dissolution fluid may be water, buffer solution, or dilute hydrochloric acid, maintained at 37°C. Samples of the fluid are removed at designated intervals and analyzed for drug content.

The U.S.P. monograph for aspirin tablets contains a dissolution test requiring the use of Apparatus 1 at 50 rpm with 500 ml of 0.05M acetate buffer (pH 4.5). Not less than 80% of the aspirin in each tablet must dissolve in 30 min. The dissolution test for digoxin tablets also calls for Apparatus 1, but the basket is rotated at 120 rpm and the dissolution fluid is dilute hydrochloric acid. Not less than 65% of the labeled amount of digoxin must dissolve in 60 min.

The tests described in the U.S.P. are but a few of the large number of dissolution methods proposed to reflect bioavailability. The type and intensity of agitation as well as the dissolution medium usually vary from method to method. There is general agreement that the dissolution medium should be aqueous and, where possible, should be of sufficient volume to easily dissolve the entire dose. It has been proposed that dissolution be studied at more than one pH, and at pH 1 and pH 7 to simulate the usual extremes of pH in the gastrointestinal tract. Others have suggested that small quantities of surface-active agents be added to the dissolution medium to facilitate wetting of the drug, for it is believed that bile salts and other constituents of bile act in this way in the small intestine. There is little agreement regarding the appropriate intensity of agitation and there is difficulty in equating intensities between methods. Many investigators believe that the tablet should be subjected to a minimum degree of abrasion and turbulence and that the agitation intensity of the dissolution test should be fixed accordingly.

Since 1960, there have been many examples of satisfactory correlations between absorption parameters and the results of in vitro dissolution tests. Rank order correlations of absorption data in man with in vitro dissolution data have been reported for different salts of tetracycline and tolbutamide, various commercial aspirin tablets, marketed tablets of spironolactone, and various tablet formulations of sulfamethazine and griseofulvin. Quantitative linear correlations between in vivo data and dissolution data have been found with different brands of prolonged-release amphetamine, aspirin tablets, different salts of penicillin V, different esters of erythromycin, and different dosage forms of salicylamide. These studies have been reviewed in detail by Wagner.[55]

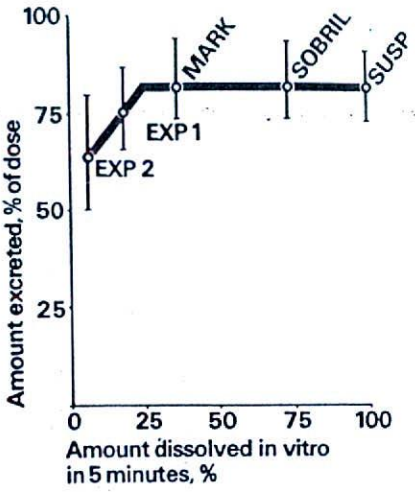

Fig. 5–8. In vivo–in vitro correlation for several formulations of oxazepam. EXP 1, EXP 2, MARK, and SOBRIL are tablets; SUSP is an aqueous suspension. When less than 25% of the dose is dissolved in vitro in 5 min, absorption is incomplete. (From Pilbrant, A., et al.[56])

Investigators in Sweden have studied the dissolution and bioavailability of oxazepam from different tablet formulations and an aqueous suspension.[56] Dissolution rates were determined by means of a paddle method using simulated gastric fluid. Absorption studies were carried out in healthy, fasting subjects. Absorption rate was assessed by determining the peak concentration of oxazepam in serum. The extent of absorption was evaluated from the sum of oxazepam and its conjugates excreted in the urine over 72 hr. An excellent linear correlation was observed between dissolution rate and peak concentration. When the amount excreted is plotted as a function of dissolution rate, a critical point is found for incomplete absorption corresponding to 25% dissolution in 5 min (Fig. 5–8).

These kinds of data are useful for establishing meaningful dissolution standards for quality control of tablet batches. Clearly, oxazepam tablets

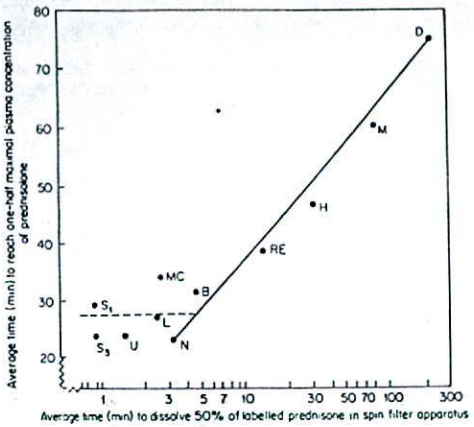

Fig. 5–9. In vivo–in vitro correlation of bioavailability and dissolution rate of different prednisone tablets. Prednisolone is the active metabolite of prednisone. Certain tablets (e.g., S_1, S_3, U, L, MC, B, and N) dissolve so rapidly that dissolution is not the rate-limiting step in absorption. (From Milsap, R.L., et al.[59] Copyright 1979. Reprinted by permission of John Wiley & Sons Ltd.)

from which less than 25% of the drug dissolves in 5 min should be rejected because incomplete absorption is likely.

Studies in Mexico compared the dissolution and absorption of five different brands of nitrofurantoin tablets.[57] A linear correlation ($r = 0.91$) was found between the cumulative amount excreted up to 10 hr after a single dose to healthy fasting subjects and the natural logarithm of the amount dissolved at 60 min using the USP dissolution test. Three of the products showed significantly lower bioavailability than the innovator's product.

Some investigators have proposed that in vitro–in vivo correlations should be based on a comparison of the log of the time required to dissolve 50% of the dose with the time required to reach one-half peak drug concentration in the plasma.[58,59] This type of plot, correlating the dissolution of prednisone from various commercial tablets with the plasma levels of prednisolone, its active metabolite, after a single dose of these tablets, is shown in Figure 5–9. Tablets S, U, L, B, MC, and N differed with respect to dissolution but gave similar in vivo (absorption) values. On the other hand, a linear relationship between plasma concentration and dissolution is found with the more slowly dissolving tablets.

These data indicate that there is some range of in vitro dissolution rates where in vivo measurements will not differ significantly. For these rapidly dissolving tablets, the rate of absorption is independent of the in vitro dissolution rate, perhaps because dissolution is not rate limiting in the absorption of the drug. However, there is a critical value of the dissolution parameter; at this point, further decreases in dissolution will cause a progressive change in the absorption parameter. According to Figure 5–9, the critical time for 50% dissolution of prednisone in the particular apparatus is about 10 to 15 min. Whether this particular correlation applies to all tablet formulations of prednisone is unknown, but the development of a tablet from which at least 50% of the dose dissolves within 15 min would seem to be a desirable goal for a manufacturer wishing to minimize bioavailability problems.

Table 5–2. Influence of Dissolution Time on the Correlation Between Bioavailability and in vitro Dissolution of Digitoxin from Tablets*

Dissolution time (min)	Correlation coefficient
30	0.63
60	0.74
120	0.82

*Data from Cabana, B.E., and Prasad, V.K.[60]

There is some data to support the need for following the dissolution of more than 50% of the dose. Bioavailability and dissolution studies with digitoxin from different tablets have provided the correlations shown in Table 5–2.[60] The longer the dissolution time, the better is the correlation between dissolution and bioavailability. The investigators concluded that, under the stated conditions, 90% dissolution of digitoxin in 2 hr would give at least 90% of the bioavailability of a solution of the drug.[60]

The dissolution test has become an integral part of the control process for the manufacture of tablets, capsules, and other solid dosage forms, but it has also been imbued, by many, with a biologic significance or relevance. Whether or not this conclusion is justified is controversial. The U.S.P. tests and other dissolution methods have been criticized often on technical grounds. There are examples of drug products that failed to meet compendial standards for dissolution but provided adequate bioavailability.[61] On the other hand, there are no examples of a drug product that has met U.S.P. dissolution requirements but showed poor bioavailability characteristics.

Bioavailability studies are by definition clinical studies. Even if the in vitro test faithfully reflects the dissolution process in the gastrointestinal tract, dissolution is but one of several factors determining the bioavailability of a drug. Moreover, there is the reality of intra- and intersubject variability.[62] Nevertheless, dissolution is usually the most important factor in drug absorption, particularly for poorly water-soluble drugs, and carefully correlated in vitro dissolution tests can provide useful guidelines for bioavailability decisions.

REFERENCES

1. Wagner, J.G.: Design and data analysis of biopharmaceutical studies in man. Paper presented to the American Pharmaceutical Association National Meeting, Dallas, Texas, 1966.
2. Gantt, C.L., Gochman, N., and Dyniewicz, J.M.: Effect of a detergent on gastrointestinal absorption of a steroid. Lancet, *1*:486, 1961.
3. Gantt, C.L., Gochman, N. and Dyniewicz, J.M.: Gastrointestinal absorption of spironolactone. Lancet, *1*:1130, 1962.
4. Bauer, G., Rieckmann, P., and Schaumann, W.: Influence of particle size and dissolution rate on the gastrointestinal absorption of spironolactone. Arzneimittelforsch., *12*:487, 1962.
5. Sjögren, J., Sölvell, L., and Karlsson, I.: Studies on the absorption rate of barbiturates in man. Acta Med. Scand., *178*:553, 1965.
6. Serajuddin, A.T.M., et al.: Physicochemical basis of increased bioavailability of a poorly water-soluble drug following oral administration as organic solutions. J. Pharm. Sci., *77*:325, 1988.
7. Wagner, J.G., Gerard, E.S., and Kaiser, D.G.: Effect of dosage form on serum levels of indoxole. Clin. Pharmacol. Ther., *7*:610, 1966.
8. Langlois, Y., Gagnon, M.A., and Tétreault, L.: A bioavailability study on three oral preparations of the combination trimethoprim-sulfamethoxazole. J. Clin. Pharmacol., *12*:196, 1972.
9. Putnam, L.E., et al.: Penicillin blood concentrations following oral administration of various dosage forms of penicillin V and comparison with penicillin G. Antibiot. Annu., 1965–1966, p. 483.
10. Neuvonen, P.J., Pentikäinen, P.J., and Elfving, S.M.: Factors affecting the bioavailability of phenytoin. Int. J. Clin. Pharmacol. Biopharm., *15*:84, 1977.
11. Seager, H.: The effect of methylcellulose on the absorption of nitrofurantoin from the gastrointestinal tract. J. Pharm. Pharmacol., *20*:968, 1968.
12. Bates, T.R., and Sequeira, J.A.: Bioavailability of micronized griseofulvin from corn oil-in-water emulsion, aqueous suspension, and commercial tablet dosage forms in humans. J. Pharm. Sci., *64*:793, 1975.
13. Tannenbaum, P.J., et al.: The influence of dosage form on the activity of a diuretic agent. Clin. Pharmacol. Ther., *9*:598, 1968.
14. Paikoff, M., and Drumm, G.: Method for evaluating dissolution characteristics of capsules. J. Pharm. Sci., *54*:1693, 1965.
15. Lerk, C.F., et al.: In vitro and in vivo availability of hydrophilized phenytoin from capsules. J. Pharm. Sci., *68*:634, 1979.
16. Boger, W.P., and Gavin, J.J.: Evaluation of tetracycline preparations. N. Engl. J. Med., *261*:827, 1959.
17. Mallis, G.I., Schmidt, D.H., and Lindenbaum, J.: Superior bioavailability of digoxin solution in capsules. Clin. Pharmacol. Ther., *18*:761, 1975.
18. Johnson, B.F., et al.: A completely absorbed oral preparation of digoxin. Clin. Pharmacol. Ther., *19*:746, 1976.
19. Johnson, B.F., Smith, G., and French, J.: The comparability of dosage regimens of Lanoxin tablets and Lanoxicaps. Br. J. Clin. Pharmacol., *4*:209, 1977.
20. O'Grady, J., et al.: Influence of soft gelatin on digoxin absorption. Br. J. Clin. Pharmacol., *5*:461, 1978.
21. Lindenbaum, J.: Greater bioavailability of digoxin solution in capsules. Studies in the postprandial state. Clin. Pharmacol. Ther., *21*:278, 1977.
22. Lloyd, B.L., et al.: Pharmacokinetics and bioavailability of digoxin capsules, solution and tablets after single and multiple doses. Am. J. Cardiol., *42*:129, 1978.
23. Mellinger, T.J., and Bohorfoush, J.G.: Blood levels of dipyridamole (Persantin) in humans. Arch. Int. Pharmacodyn. Ther., *163*:471, 1966.
24. Mellinger, T.J.: Serum concentrations of thioridazine after different oral medication forms. Am. J. Psychol., *121*:1119, 1965.
25. Shaw, T.R.D., Howard, M.R., and Hamer, J.: Variation in the biological availability of digoxin. Lancet, *2*:303, 1972.
26. Levy, G., and Gumtow, R.H.: Effects of certain tablet formulation factors on dissolution rate of the active ingredient. III. Tablet lubricants. J. Pharm. Sci., *52*:1139, 1963.
27. Varley, A.B.: The generic inequivalence of drugs. JAMA, *206*:1745, 1968.
28. Higuchi, T., Elowe, L.N., and Busse, L.W.: Physics of tablet compression. V. Studies on aspirin, lactose, lactose-aspirin, and sulfadiazine tablets. J. Am. Pharm. Assoc. (Sci. Ed.), *43*:685, 1954.
29. Atkinson, R.M., et al.: Effect of particle size on blood griseofulvin levels in man. Nature, *193*:588, 1962.
30. Barrett, W.E., and Bianchine, J.R.: The bioavailability of ultramicrosize griseofulvin (GRIS-PEG) tablets in man. Curr. Ther. Res., *18*:501, 1975.
31. Schwartz, J.B., and Alvino, T.P.: Effect of thermal gelation on dissolution from coated tablets. J. Pharm. Sci., *65*:572, 1976.
32. Lui, C.Y., et al.: Application of a radiotelemetric system to evaluate the performance of enteric coated and plain aspirin tablets. J. Pharm. Sci., *75*:469, 1986.
33. Lappas, L.C., and McKeehan, W.: Polymeric pharmaceutical coating materials, II. In vivo evaluation as enteric coating. J. Pharm. Sci., *56*:1257, 1967.
34. Rasmussen, S.: Intestinal absorption of quinine from enteric coated tablets. Acta Pharmacol. Toxicol., *24*:331, 1956.
35. Lee, D.A.H., et al.: The effect of food and tablet formulation on plasma prednisolone levels following administration of enteric-coated tablets. Br. J. Clin. Pharmacol., *7*:523, 1979
36. Day, R.O., et al.: Evaluation of an enteric coated aspirin preparation. Aust. N.Z. J. Med., *6*:45, 1976.
37. Ryan, J.R., et al.: Enteric coating of fenoprofen calcium reduces gastrointestinal microbleeding. Clin. Pharmacol. Ther., *42*:28, 1987.
38. Paull, P., et al.: Single-dose evaluation of a new enteric-coated aspirin preparation. Med. J. Aust., *1*:617, 1976.
39. Mojaverian P., et al.: Effect of food on the absorption of enteric-coated aspirin: correlation with gastric residence time. Clin. Pharmacol. Ther., *41*:11, 1987.
40. Fremstad, D., et al.: Absorption of quinidine from an en-

teric coated preparation. Eur. J. Clin. Pharmacol., *16*:107, 1979.
41. Green, D.M.: Tablets of coated aspirin microspherules—a new dosage form. J. New Drugs, *6*:294, 1966.
42. Story, M.J.: Enteric-coated pellets: Theoretical analysis of effect of dispersion in the stomach on blood level profiles. J. Pharm. Sci., *66*:1495, 1977.
43. Bogentoft, C., et al.: Influence of food on the absorption of acetylsalicylic acid from enteric-coated dosage forms. Eur. J. Clin. Pharmacol., *14*:351, 1978.
44. Anslow, J.A., et al.: Minimization of gastric damage with enteric-coated aspirin granules compared to buffered aspirin. Pharmacol., *30*:40, 1985.
45. Rosenstein, G., and Belton, E.D.: The relation of potassium therapy to small-bowel lesions. Med. Ann. D.C., *38*:539, 1969.
46. Riley, S.A., et al.: Delayed-release mesalazine (5-aminosalicylic acid): coat dissolution and excretion in ileostomy subjects. Br. J. Clin. Pharmacol., *26*:173, 1988.
47. Asacol: mesalazine for ulcerative colitis. Drug Ther. Bull., *24*:38, 1986.
48. Schroeder, K.W., Tremaine, W.J., Ilstrup, D.M.: Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N. Engl. J. Med., *317*:1625, 1987.
49. Jacobsen, O., et al.: Effect of enterocoated cholestyramine on bowel habit after ileal resection: a double blind crossover study. Br. Med. J., *290*:1315, 1985.
50. Saffran, M., et al.: A new approach to the oral administration of insulin and other peptide drugs. Science, *233*:1081, 1986.
51. Wagner, J.G.: Biopharmaceutics and Relevant Pharmacokinetics. Hamilton, Ill., Drug Intelligence Publications, 1971, pp. 82–88.
52. Levy, G.: Comparison of dissolution and absorption rates of different commercial aspirin tablets. J. Pharm. Sci., *50*:388, 1961.
53. Levy, G., and Hollister, L.E.: Failure of U.S.P. disintegration test to assess physiologic availability of enteric coated tablets. N.Y. State J. Med., *64*:3002, 1964.
54. Wagner, J.G., et al.: Failure of U.S.P. tablet disintegration test to predict performance in man. J. Pharm. Sci., *62*:859, 1973.
55. Wagner, J.G.: Biopharmaceutics and Relevant Pharmacokinetics. Hamilton, Ill., Drug Intelligence Publications, 1971, pp. 125–147.
56. Pilbrant, A., et al.: Comparative bioavailability of oral dosage forms of oxazepam—correlation with in vitro dissolution rate. Acta Pharmacol. Toxicol., *40*:7, 1977.
57. Lopez, A.A., et al.: Bioequivalence study of nitrofurantoin tablets: in vitro-in vivo correlation. Int. J. Pharmaceutics, *28*:167, 1986.
58. Sullivan, T.J., Sakmar, E., and Wagner, J.G.: Comparative bioavailability: a new type of in vitro-in vivo correlation exemplified by prednisone. J. Pharmacokinet. Biopharm., *4*:173, 1976.
59. Milsap, R.L., et al.: Comparison of two dissolution apparatuses with correlation of in vitro-in vivo data for prednisone and prednisolone tablets. Biopharm. Drug Dispos., *1*:3, 1979.
60. Cabana, B.E., and Prasad, V.K.: Presentation at the APhA Academy of Pharm. Sci., 21st Nat. Meeting, Orlando, Fla., Nov. 16, 1976.
61. Ylitalo, P., Wilen, G., and Lundell, S.: Bioavailability of digoxin tablets in relation to their dissolution in vitro. J. Pharm. Sci., *64*:1264, 1975.
62. Huttenrauch, R., Speiser, P.: *In vitro-in vivo* correlation: an unrealistic problem. Pharmaceutical Research, 2:97, 1985.