EFFECT OF DISEASE STATES ON DRUG ABSORPTION

Drug absorption may be affected by any disease that causes changes in (1) intestinal blood flow, (2) gastrointestinal motility, (3) changes in stomach emptying time, (4) gastric pH that affects drug solubility, (5) intestinal pH that affects the extent of ionization, (6) the permeability of the gut wall, (7) bile secretion, (8) digestive enzyme secretion, or (9) alteration of normal GI flora. Some factors may dominate, while other factors sometimes cancel the effects of each other. Pharmacokinetic studies comparing subjects with and without the disease are generally necessary to establish the effect of the disease on drug absorption. Several clinical examples are given below.

Patients in an advanced stage of *Parkinson's disease* may have difficulty swallowing and greatly diminished gastrointestinal motility. A case was reported in which the patient could not be controlled with regular oral levodopa medication because of poor absorption. Infusion of oral levodopa solution using a j-tube gave adequate control of his symptoms. The patient was subsequently placed on this mode of therapy.

***Patients on tricyclic antidepressants* (imiprimine, amitriptyline, and nortriptyline) and antipsychotic drugs (phenothiazines) with anticholinergic side effects may have reduced gastrointestinal motility or even intestinal obstructions. Delays in drug absorption, especially with slow-release products, have occurred.**

Achlorhydric patients **may not have adequate production of acids in the stomach**; stomach HCl is essential for solubilizing insoluble free bases. Many weak-base drugs that cannot form soluble salts will remain undissolved in the stomach when there is no hydrochloric acid present and are therefore unabsorbed. Salt forms of these drugs cannot be prepared because the free base readily precipitates out due to the weak basicity.

Dapsone, itraconazole, and ketoconazole may also be less well absorbed in the presence of achlorhydria. In patients with acid reflux disorders, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption. **Co-administering orange juice, colas, or other acidic beverages can facilitate the absorption of some medications requiring an acidic environment.**

HIV-AIDS patients are prone to a number of gastrointestinal (GI) disturbances, such as increased gastric transit time, **diarrhoea, and achlorhydria**. Rapid gastric transit time and diarrhoea can alter the absorption of orally administered drugs. Achlorhydria may or may not decrease absorption, depending on the acidity needed for absorption of a specific drug. **Indinavir,** for example, requires a normal acidic environment for absorption. The therapeutic window of indinavir is extremely narrow, so optimal serum concentrations are critical for this drug to be efficacious.

Congestive heart failure **(CHF**) *patients* with persistent edema have reduced splanchnic blood flow and develop edema in the bowel wall. In addition, intestinal motility is slowed. The reduced blood flow to the intestine and reduced intestinal motility results in a decrease in drug absorption. For example, f**urosemide** (Lasix), a commonly used loop diuretic, has erratic and reduced oral absorption in patients with CHF and a delay in the onset of action.

Crohn's disease **is an inflammatory disease** of the distal small intestine and colon. The disease is accompanied by regions of thickening of the bowel wall, overgrowth of anaerobic bacteria, and sometimes obstruction and deterioration of the bowel.

The effect on drug absorption is unpredictable, although impaired absorption may potentially occur because of **reduced surface area and thicker gut wall for diffusion**. For example, higher plasma propranolol concentration has been observed in patients with Crohn's disease after oral administration of propranolol**.**

Alpha-1-acid glycoprotein level is increased in Crohn's disease patients.

Higher alpha-1-acid glycoprotein may affect the **protein binding and distribution of propranolol in the body and result in higher plasma concentration**.

Celiac disease is an inflammatory disease affecting mostly the proximal small intestine. Celiac disease is caused by sensitization to gluten, a viscous protein found in cereals. Patients with celiac disease generally have an increased rate of stomach emptying and increased permeability of the small intestine. Cephalexin absorption appears to be increased in celiac disease, although it is not possible to make general predictions about these patients. Other intestinal conditions that may potentially affect drug absorption include corrective surgery involving peptic ulcer, gastrectomy with gastroduodenostomy, and selective vagotomy.

Drugs that Affect Absorption of Other Drugs

Anticholinergic drugs in general may reduce stomach acid secretion. Propantheline bromide is an anticholinergic drug that may slow stomach emptying and motility of the small intestine. Tricyclic antidepressants and phenothiazines also have anticholinergic side effects that may cause slower peristalsis in the GI tract. Slower stomach emptying may cause delay in drug absorption.

Metoclopramide is a drug that stimulates stomach contraction, relaxes the pyloric sphincter, and, in general, increases intestinal peristalsis, which may reduce the effective time for the absorption of some drugs and thereby reduce the peak drug concentration and the time to reach peak drug concentration. For example, **digoxin** absorption from a tablet is reduced by metoclopramide but increased by an anticholinergic drug, such as propantheline bromide.

Allowing more time in the stomach for the tablet to dissolve generally helps with the dissolution and absorption of a poorly soluble drug, but would not be helpful for a drug that is not soluble in stomach acid.

Antacids should not be given with **cimetidine,** because antacids may reduce drug absorption.

Antacids containing aluminum, calcium, or magnesium may complex with drugs such as, resulting in a decrease in drug absorption. **tetracycline, ciprofloxacin, and indinavir.** To avoid this interaction, antacids should be taken 2 hours before or 6 hours after drug administration. As mentioned, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption.

Cholestyramine is a nonabsorbable ion-exchange resin for the treatment of hyperlipidaemia. **Cholestyramine adsorbs warfarin, thyroxine, and loperamide**, similar to activated charcoal, thereby reducing absorption of these drugs.

Absorption of calcium in the duodenum is an active process facilitated by vitamin D, with calcium absorption as much as four times more than that in vitamin D deficiency states.

It is believed that a calcium-binding protein, which increases after vitamin D administration, binds calcium in the intestinal cell and transfers it out of the base of the cell to the blood circulation.

Nutrients that Interfere with Drug Absorption

Many nutrients substantially interfere with the absorption or metabolism of drugs in the body. The effect of food on bioavailability was discussed earlier. Oral drug nutrient interactions are often drug specific and can result in either an increase or decrease in drug absorption. Absorption of water-soluble vitamins, such as vitamin B-12 and folic acid, are aided by special absorption mechanisms. **Vitamin B-12 absorption is facilitated by intrinsic factors in the stomach, where it forms a complex with the factor and is carried in the intestinal stream to the ileum, where it binds to a specific receptor**. **Vitamin B-12 then ultimately disassociates from the complex and is absorbed.**

Grapefruit juice often increases bioavailability, as observed by an increase in plasma levels of many drugs that are substrates for cytochrome P450 (CYP). Grapefruit juice contains various flavonoids such as naringin that inhibits certain cytochrome P-450 enzymes involved in drug metabolism. In this case, the observed increase in the plasma drug blood levels is due to decreased presystemic elimination in the GI tract and/or liver. Indirectly, the amount of drug absorbed systemically from the drug product is increased. **Grapefruit juice can also block drug efflux by inhibiting P-gp for some drugs.**

MISCELLANEOUS ROUTES OF DRUG ADMINISTRATION

For systemic drug absorption, the oral route is the easiest, safest, and most popular route of drug administration. Increasingly popular nonparenteral alternatives to oral drug delivery for systemic drug absorption include nasal, inhalation, and transdermal drug delivery. Nasal, inhalation, and topical drug delivery may also be used for local drug action.

Nasal Drug Delivery

Nasal drug delivery may be used for either **local or systemic effects**. Because the nasal region **is richly supplied with blood vessels, nasal administration is also useful for systemic drug delivery.**

However, **the total surface area in the nasal cavity is relatively small**, **retention time in the nasal cavity is generally short**, **and some drug may be swallowed.**

These factors may limit the nose's capacity for systemic delivery of drugs requiring large doses.

Surfactants are often used to increase systemic penetration, although the effect of **chronic drug exposure** on **the integrity of nasal membranes must also be considered**.

In general, a drug must be sufficiently **lipophilic** to cross the membranes of the nasal epithelium in order to be absorbed.

Small molecules with balanced lipophilic and hydrophilic properties tend to be absorbed more easily.

This observation poses a challenge for nasal delivery of larger molecules such as proteins and peptides, which would benefit from delivery routes that avoid the degradative environment of the intestine.

Dosage forms intended for nasal drug delivery include nasal drops, nasal sprays, aerosols, and nebulizers.

Depending on the metabolic, absorption, and chemical profile of the drug, some drugs are rapidly absorbed through the nasal membrane and can deliver rapid therapeutic effect. Various hormones and insulin have been tested for intranasal delivery. In some cases **the objective is to improve availability**, and in other cases it is to reduce side effects.

Vasopressin and oxytocin are older examples of drugs marketed as **intranasal products**. In addition, many **opioids are known to be rapidly absorbed from the nasal** passages and can deliver systemic levels of the drug almost as rapidly as **an intravenous injection**.

A common problem with nasal drug delivery is the challenge of developing a formulation with nonirritating ingredients.

Many surfactants that facilitate absorption tend to be moderately or very irritating to the nasal mucosa.

Intranasal corticosteroids for treatment of allergic and perennial rhinitis have become more popular since intranasal delivery is believed to **reduce the total dose of corticosteroid required**.

A lower dose also leads to minimization of side effects such as **growth suppression**.

This logic has led to many second-generation corticosteroids such as beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide that are being considered for intranasal delivery. However, the potential for growth suppression in children varies. In one study, beclomethasone dipropionate reduced growth in children, but mometasone furoate nasal spray used for 1 year showed no signs of growth suppression. Overall, the second-generation corticosteroid by nasal delivery have been concluded to cause minimal systemic side effects.

Inhalation Drug Delivery

Inhalation drug delivery may also be used for **local or systemic** drug effects. The lung has a potential absorption surface of some 70 m^2. When a substance is inhaled, it is exposed to membranes of **the mouth or nose, pharynx, trachea, bronchi, bronchioles, alveolar sacs, and alveoli.**

The lungs and their associated airways are designed to remove foreign matter from the highly absorptive peripheral lung surfaces via mucociliary clearance. However, if compounds such as aerosolized drug can reach the peripheral region of the lung, absorption can be very efficient.

Particle (droplet) size and velocity of application control the extent to which inhaled substances penetrate into airway spaces. Inhalation devices deliver approximately 10% of the administered dose to the lower respiratory tract.

Topical and Transdermal Drug Delivery

Topical drug delivery is generally used for local drug effects. Drug may be applied as an ointment or cream to the skin or various mucous membranes such as intravaginally.

Even though the objective is to obtain a local drug effect, some of the drug may be **absorbed systemically.** For transdermal drug delivery the drug is incorporated into a transdermal therapeutic system or patch, but it may be incorporated into an ointment as well.

Transdermal drug delivery is generally for systemic drug absorption.

The advantages of transdermal delivery include continuous release of drug over a period of time, low presystemic clearance, and good patient compliance.

RATE-LIMITING STEPS IN DRUG ABSORPTION

Systemic drug absorption from a drug product consists of a succession of rate processes . For solid oral, immediate-release drug products (eg, tablets, capsules), the rate processes include

(**1) disintegration of the drug product** and subsequent release of the drug,

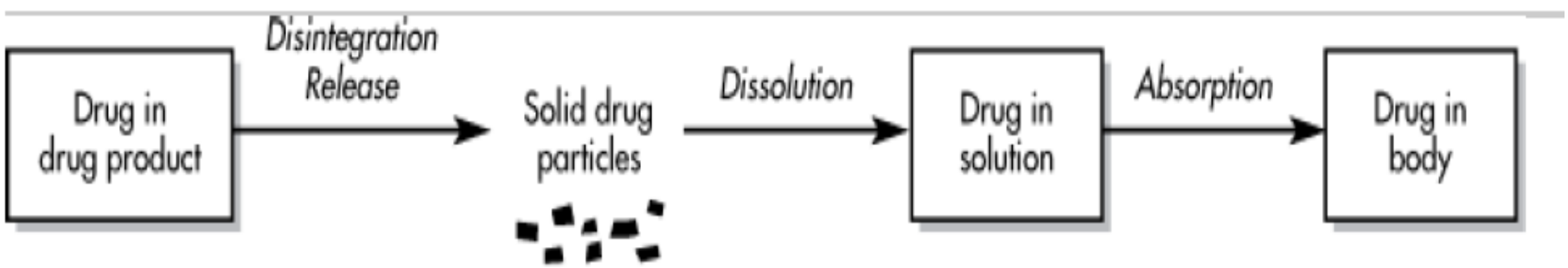
(2) dissolution of the drug in an aqueous environment, and

(3) absorption across cell membranes into the systemic circulation.

In the process of drug **disintegration, dissolution, and absorption**, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence.

The slowest step in a series of kinetic processes is called the *rate-limiting step* .

For drugs that have **very poor aqueous solubility**, **the rate at which the drug dissolves (*dissolution*) is often the slowest step and therefore exerts a rate-limiting effect on drug bioavailability**. In contrast, for a drug that has a **high aqueous solubility**, **the dissolution rate is rapid, and the rate at which the drug crosses or permeates cell membranes is the slowest or rate-limiting step.**



PHARMACEUTIC FACTORS AFFECTING DRUG BIOAVAILABILITY

Considerations in the design of a drug product that will deliver active drug with the desired bioavailability characteristics include (1) the type of drug product (eg, solution, suspension, suppository), (2) the nature of the excipients in the drug product, (3) the physicochemical properties of the drug molecule, and (4) the route of drug administration.

Disintegration

For immediate-release, solid oral dosage forms, the drug product must disintegrate into small particles and release the drug. To monitor uniform tablet disintegration, the *United States Pharmacopeia* (USP) has established an official disintegration test. **Solid drug products exempted from disintegration tests include troches, tablets that are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action.**

The process of disintegration does not imply complete dissolution of the tablet and/or the drug.

Complete disintegration is defined by the USP () as "that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen of the test apparatus in the soft mass have no palpably firm core."

The official apparatus for the disintegration test and procedure is described in the USP. Separate specifications are given for drug products that are designed not to disintegrate. These products include troches, chewable tablets, and modified-release drug products.

Although disintegration tests allow for precise measurement of the formation of fragments, granules, or aggregates from solid dosage forms, **no information is obtained from these tests on the rate of dissolution of the active drug.**

However, there has been some interest in using only the disintegration **test and no dissolution test for drug products that meet the Biopharmaceutical Classification System (BCS) for highly soluble and highly permeable drugs.**

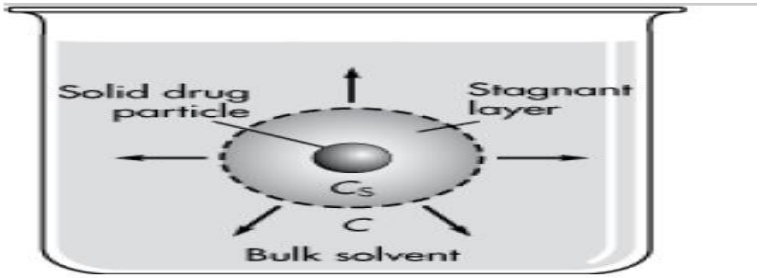
In general, the disintegration test serves as a component in the overall quality control of tablet manufacture.

Dissolution and Solubility

Dissolution is the process by which a **solid drug substance becomes dissolved in a solvent**. ***Solubility* is the mass of solute that dissolves in a specific mass or volume of solvent at a given temperature (eg, 1 g of NaCl dissolves in 2.786 mL of water at 25 °C).** Solubility is a static property; whereas dissolution is a dynamic property. In biologic systems, drug dissolution in an aqueous medium is an important prior condition for systemic absorption. The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the gastrointestinal tract often controls the rate of systemic absorption of the drug. **Thus, dissolution tests may be used to predict bioavailability and may be used to discriminate formulation factors that affect drug bioavailability.**

The dissolution test is required for all U.S. Food and Drug Administration (FDA)-approved solid oral drug products.

Noyes and Whitney (1897) and other investigators studied the rate of dissolution of solid drugs. According to their observations, the steps in dissolution include the process of drug dissolution at the surface of the solid particle, thus forming a saturated solution around the particle. The dissolved drug in the saturated solution, known as **the *stagnant layer*** , **diffuses to the bulk of the solvent from regions of high drug concentration to regions of low drug concentration.**



The overall rate of drug dissolution may be described by the *Noyes Whitney equation* (Eq. 14.1),

$$\frac{dC}{dt} = \frac{DA}{h}(C_S - C)$$

where dC/dt = rate of drug dissolution at time t , D = diffusion rate constant, A = surface area of the particle, C_S = concentration of drug (equal to solubility of drug) in the stagnant layer, C = concentration of drug in the bulk solvent, and h = thickness of the stagnant layer. The rate of dissolution, dC/dt , is the rate of drug dissolved per time expressed as concentration change in the dissolution fluid.

The Noyes Whitney equation shows that dissolution in a flask may be influenced by the physicochemical characteristics of the drug, the formulation, and the solvent. Drug in the body, particularly in the gastrointestinal tract, is considered to be dissolving in an aqueous environment. Permeation of drug across the gut wall (a model lipid membrane) is affected by the ability of the drug to diffuse (D) and to partition between the lipid membrane.

A favorable partition coefficient (K oil/water) will facilitate drug absorption.

In addition to these factors, the **temperature of the medium and the agitation rate** also affect the rate of drug dissolution. *In vivo* , the temperature is maintained at a constant **37°C,** and **the agitation (primarily peristaltic movements in the gastrointestinal tract) is reasonably constant**.

In contrast, *in-vitro* studies of dissolution kinetics require maintenance of constant temperature and agitation. Temperature is generally kept at 37 °C, and the **agitation or stirring rate is held to a specified rpm (revolutions per minute**).

An increase in temperature will increase the kinetic energy of the molecules and increase the diffusion constant, D . Moreover, an increase in agitation of the solvent medium will reduce the thickness, h , of the stagnant layer, allowing for more rapid drug dissolution.

Factors that affect drug dissolution of a solid oral dosage form include (1) the physical and chemical nature of the active drug substance, (2) the nature of the excipients, and (3) the method of manufacture.

PHYSICOCHEMICAL NATURE OF THE DRUG

In addition to their effect on dissolution kinetics, the physical and chemical properties of the drug substance as well as the excipients are important considerations in the design of a drug product. For example, intravenous solutions are difficult to prepare with drugs that have poor aqueous solubility.

Drugs that are physically or chemically unstable may require special excipients, coatings, or manufacturing processes to protect the drug from degradation.

The potent pharmacodynamic activity of drugs such as estrogens and other hormones, penicillin antibiotics, cancer chemotherapeutic agents, and others, may cause adverse reactions to personnel who are exposed to these drugs during manufacture and also presents a problem.

Table 14.1 Physicochemical Properties for Consideration in Drug Product Design

Solubility, pH, and Drug Absorption

The ***solubility-pH profile*** **is a plot of the solubility of the drug at various physiologic pH** values. In designing oral dosage forms, the formulator must consider that the natural pH environment of the gastrointestinal tract varies from acidic in the stomach to slightly alkaline in the small intestine. A basic drug is more soluble in an acidic medium, forming a soluble salt. Conversely, an acid drug is more soluble in the intestine, forming a soluble salt at the more alkaline pH.

The solubility-pH profile gives a rough estimation of the completeness of dissolution for a dose of a drug in the stomach or in the small intestine.

Solubility may be improved with the addition of an acidic or basic excipient. **Solubilization of aspirin, for example, may be increased by the addition of an alkaline buffer.**

In the formulation of controlled-release drugs, buffering agents may be added to slow or modify the release rate of a fast-dissolving drug. To be effective, however, the controlled-release drug product must be a nondisintegrating dosage form. The buffering agent is released slowly rather than rapidly, so that the drug does not dissolve immediately in the surrounding gastrointestinal fluid.

Stability, pH, and Drug Absorption

The *stability pH profile* is a plot of the reaction rate constant for drug degradation versus pH. If drug decomposition occurs by acid or base catalysis, some prediction of degradation of the drug in the gastrointestinal tract may be made. For example, erythromycin has a pH-dependent stability profile. In acidic medium, as in the stomach, erythromycin decomposition occurs rapidly, whereas in neutral or alkaline pH, the drug is relatively stable.

Consequently, erythromycin tablets are enteric coated to protect against acid degradation in the stomach.

This information also led subsequently to the preparation of a less water-soluble erythromycin salt that is more stable in the stomach. The dissolution rate of erythromycin powder varied from 100% dissolved in 1 hour to less than 40% dissolved in 1 hour. The slow-dissolving raw drug material (active pharmaceutical ingredient) also resulted in slow-dissolving drug products. Therefore, the dissolution of powdered raw drug material is a very **useful *in-vitro* method for predicting bioavailability problems of the erythromycin product in the body.**

Particle Size and Drug Absorption

The **effective surface area** of a drug is increased enormously by a reduction in the particle size. Because dissolution takes place at the surface of the solute (drug), the greater the surface area, the more rapid is the rate of drug dissolution. The geometric shape of the particle also affects the surface area, and, during dissolution, the surface is constantly changing. In dissolution calculations, the solute particle is usually assumed to have retained its geometric shape.

Particle size and particle size distribution studies are important for drugs that have low water solubility. Many drugs are very active intravenously but are not very effective when given orally, because of poor oral absorption.

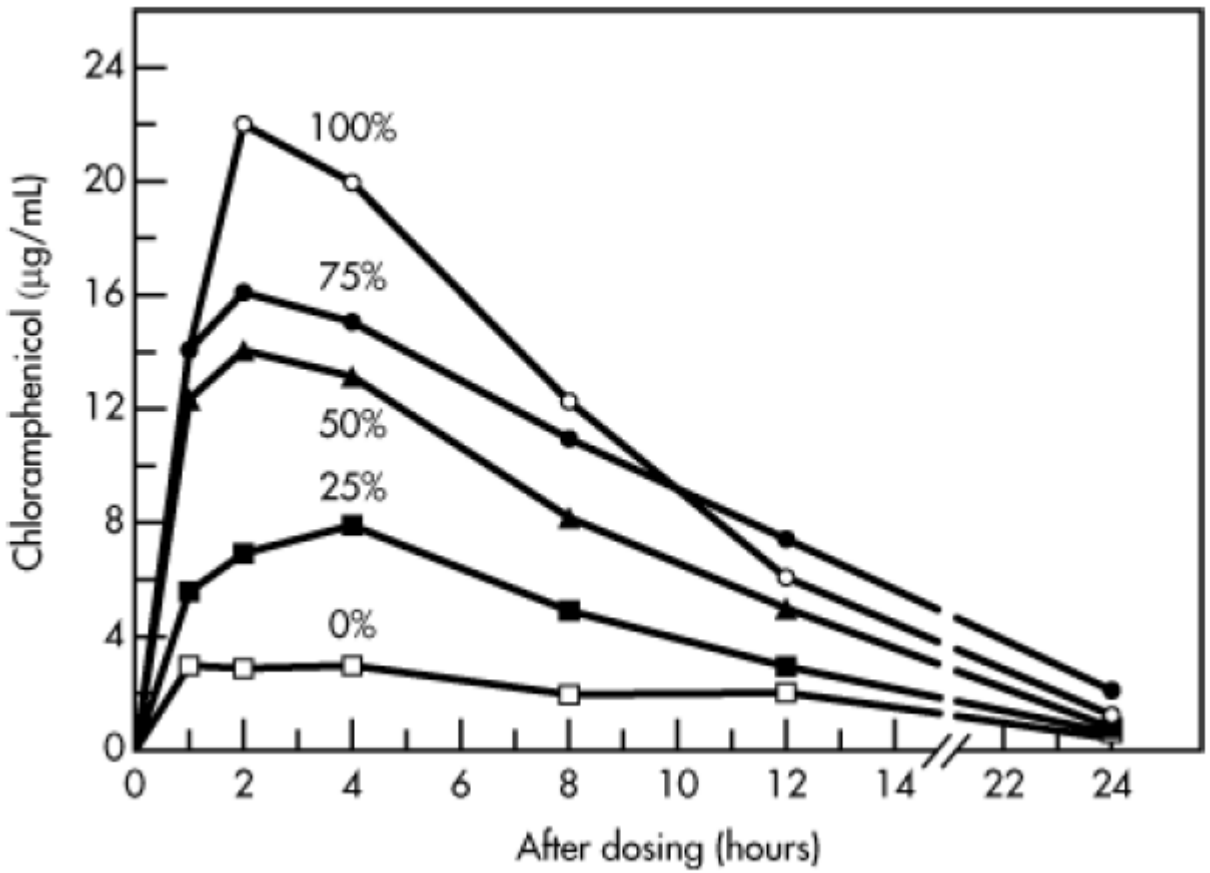
Griseofulvin, nitrofurantoin, and many steroids are drugs with low aqueous solubility; reduction of the particle size by milling to a micronized form has improved the oral absorption of these drugs. **Smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles, and increases the dissolution rate.**

For poorly soluble drugs, a **disintegrant** may be added to the formulation to ensure rapid disintegration of the tablet and release of the particles. The addition of **surface-active agents** may increase wetting as well as solubility of these drugs.

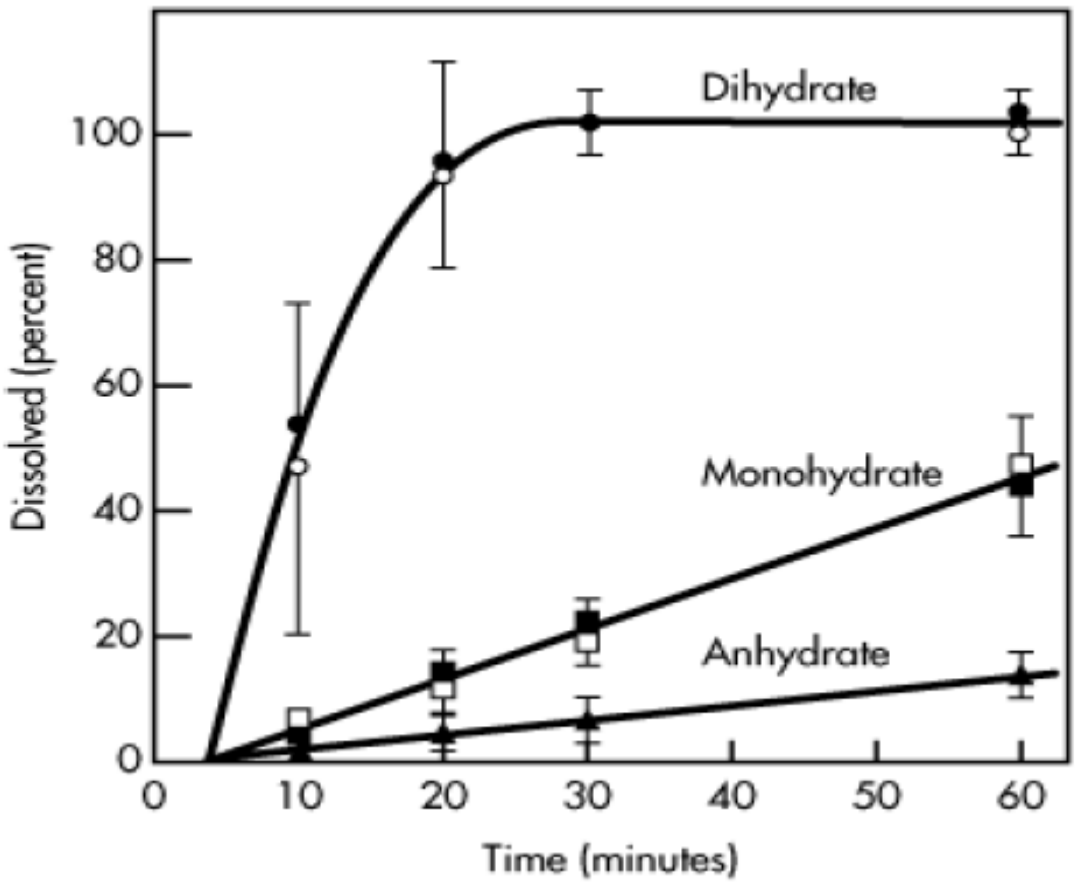
Polymorphism, Solvates, and Drug Absorption

***Polymorphism* refers to the arrangement of a drug substance in various crystal forms or polymorphs.** In recent years the term polymorph has been used frequently to describe polymorphs, solvates, amorphous forms, and desolvated solvates. ***Amorphous forms* are noncrystalline forms**, *solvates* are forms that contain a solvent (solvate) or water (hydrate), and *desolvated* solvates are forms that are made by removing the solvent from the solvate.

Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics. Some polymorphic crystals have much lower aqueous solubility than the amorphous forms, causing a product to be incompletely absorbed. Chloramphenicol, for example, has several crystal forms, and when given orally as a suspension, the drug concentration in the body was found to be **dependent on the percent of -polymorph in the suspension.** The form is more soluble and better absorbed. In general, the crystal form that has the lowest free energy is the most stable polymorph. **A drug that exists as an amorphous form (noncrystalline form) generally dissolves more rapidly than the same drug in a more structurally rigid crystalline form.** Some polymorphs **are *metastable* and may convert to a more stable form over time**. A change in crystal form may cause problems in manufacturing the product. For example, a change in the crystal structure of the drug may cause cracking in a tablet or even prevent a granulation from being compressed into a tablet. Re-formulation of a product may be necessary if a new crystal form of a drug is used. Some drugs interact with solvent during preparation to form a crystal called a *solvate* . Water may form special crystals with drugs called *hydrates;* for example**, erythromycin hydrates have quite different solubility compared to the anhydrous form of the drug . Ampicillin trihydrate, on the other hand, was reported to be less absorbed than the anhydrous form of ampicillin because of faster dissolution of the latter.**



Comparison of mean blood serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of α and β polymorphs, following single oral dose equivalent to 1.5 g chloramphenicol. Percentage polymorph β in the suspension.



Dissolution behaviour of erythromycin dihydrate, monohydrate, and anhydrate in phosphate buffer (pH 7.5) at 37 °C.

FORMULATION FACTORS AFFECTING DRUG DISSOLUTION

***Excipients* are added** to a formulation to provide certain functional properties to the drug and dosage form. Some of these functional properties of the excipients are used to improve the compressibility of the active drug, stabilize the drug against degradation, decrease gastric irritation, control the rate of drug absorption from the absorption site, increase drug bioavailability, etc. Some of the excipients used in the manufacture of solid and liquid drug products are listed in table 14.2 and 14.3.

Excipients in the drug product may also affect the dissolution kinetics of the drug, either by altering the medium in which the drug is dissolving or by reacting with the drug itself. Other excipients include **suspending agents that increase the viscosity of the drug vehicle and thereby diminish the rate of drug dissolution** from suspensions.

Tablet lubricants, such as magnesium stearate, may repel water and reduce dissolution when used in large quantities. **Coatings, particularly shellac, will crosslink upon aging and decrease the dissolution rate.** However, **surfactants may affect drug dissolution in an unpredictable fashion. Low concentrations of surfactants decrease the surface tension and increase the rate of drug dissolution, whereas higher surfactants concentrations tend to form micelles with the drug and thus decrease the dissolution rate**. Large drug particles have a smaller surface area and dissolve more slowly than smaller particles. **High compression of tablets without sufficient disintegrant may cause poor disintegration of a compressed tablet.**

Some excipients, such as **sodium bicarbonate, may change the pH of the medium surrounding the active drug substance.** Aspirin, a weak acid when formulated with sodium bicarbonate, will form a water-soluble salt in an alkaline medium, in which the drug rapidly dissolves. The term for this process is ***dissolution in a reactive medium***. The solid drug dissolves rapidly in the reactive solvent surrounding the solid particle. However, as the dissolved drug molecules diffuse outward into the bulk solvent, the drug may precipitate out of solution with a very fine particle size. These small particles have enormous collective surface area, **dispersing and redissolving** readily for more rapid absorption upon contact with the mucosal surface.

Excipients in a formulation may interact directly with the drug to form a water-soluble or water-insoluble complex. For example, if tetracycline is formulated with calcium carbonate, an insoluble complex of **calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.**

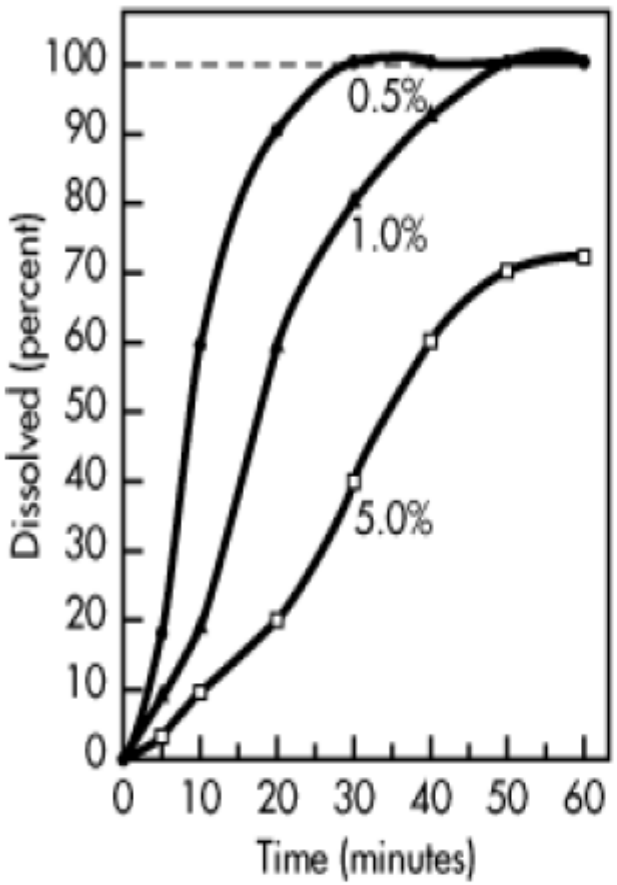
Excipients may be added intentionally to the formulation to enhance the rate and extent of drug absorption or to delay or slow the rate of drug absorption (). For example, excipients that increase the aqueous solubility of the drug generally increase the rate of dissolution and drug absorption. Excipients may increase the retention time of the drug in the gastrointestinal tract and therefore increase the total amount of drug absorbed. Excipients may act as carriers to increase drug diffusion across the intestinal wall. In contrast, many excipients may retard drug dissolution and thus reduce drug absorption.

Common excipients found in oral drug products are listed in tables 14.4 and 14.3. **Excipients should be pharmacodynamically inert.** However, excipients may change the functionality of the drug substance and the bioavailability of the drug from the dosage form. For solid oral dosage forms such as compressed tablets, excipients may include (1) a diluent (eg, lactose), (2) a disintegrant (eg, starch), (3) a lubricant (eg, magnesium stearate), and (4) other components such as binding and stabilizing agents. If used improperly in a formulation, the rate and extent of drug absorption may be affected. For example, shows that an excessive quantity of magnesium stearate (a hydrophobic lubricant) in the formulation may retard drug dissolution and slow the rate of drug absorption.

The total amount of drug absorbed may also be reduced. To prevent this problem, the lubricant level should be decreased or a different lubricant selected. Sometimes, increasing the amount of disintegrant may overcome the retarding effect of lubricants on dissolution.

However, **with some poorly soluble drugs an increase in disintegrant level has little or no effect on drug dissolution because the fine drug particles are not wetted.**

The influence of some common ingredients on drug absorption parameters is summarized in table 14.4. These are general trends for typical preparations.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

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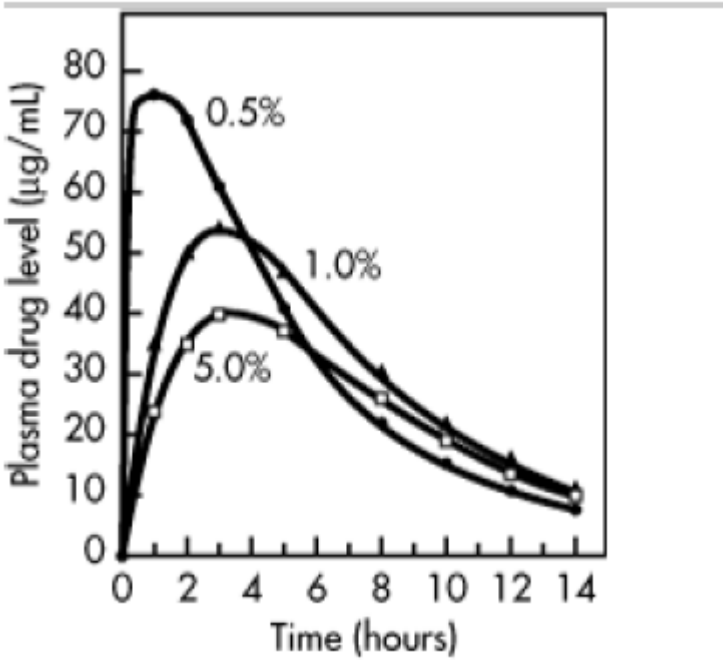
Effect of lubricant on drug dissolution. Percentage of magnesium stearate in formulation.


Plasma drug level (µg/mL)
80
70
60
50
40
30
20
10
0
0.5%
1.0%
5.0%
0
2
4
6
8
10
12
14
Time (hours)