Dissolution Testing for Poorly Soluble Drugs: A Continuing Perspective

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ABSTRACT
The development of a meaningful dissolution procedure for drug products with limited water solubility has been a challenge to both the pharmaceutical industry and the agencies that regulate them. These challenges include developing and validating the test methods, ensuring that methods are appropriately discriminatory, and addressing the potential for an in vivo–in vitro correlation (IVIVC). Dissolution test media selection should be justified for pH (recommended pH range is 1.2–7.5) as well as surfactant type (ionic versus non-ionic) and amount. If the drug is not soluble in the in vivo pH range, with or without surfactants, then the use of nonaqueous media can be preferred with proper justifications. Physical modifications of the drug, such as particle size reduction, use of metastable polymorphs, eutectic mixtures, solid dispersions, or complexation, are being widely used in the industry to enhance the drug dissolution characteristics. In recent years, newer physical modifications (e.g., microemulsions and nanocrystals) are giving promising results in enhancement of drug dissolution and bioavailability of poorly soluble drugs. Whatever method is used by the dissolution scientists, it must aim towards the cheaper but most effective approach to enhance the dissolution behavior of poorly soluble drugs.

INTRODUCTION
Drug dissolution testing is an analytical technique used to assess release profiles of drugs from pharmaceutical products, generally solid oral products such as tablets and capsules. For a dosage form to produce its effect, drug must be released and generally should be dissolved in the fluids of the gastrointestinal tract. Drug dissolution testing plays an important role as a routine quality control test, for characterizing the quality of the product, for accepting product sameness under SUPAC (Scale-Up and Post-Approval Changes) related changes, in waiving bioequivalence requirements for lower strengths of a dosage form, and in supporting waivers for other bioequivalence requirements (1). Dissolution from the dosage form involves mainly two steps: liberation of the drug from the formulation matrix (disintegration) followed by the dissolution of the drug (solubilization of the drug particles) in the liquid medium. The overall rate of dissolution depends on the slower of these two steps. In the first step of dissolution, the cohesive properties of the formulated drug play a key role. For solid dosage forms, these properties include disintegration and erosion. If the first step of dissolution is rate-limiting, then the rate of dissolution is considered disintegration controlled. In the second step of dissolution (i.e., solubilization of drug particles), the physicochemical properties of the drug such as its chemical form (e.g., salt, free acid, free base) and physical form (e.g., amorphous or polymorph and primary particle size) play an important role. If this latter step is rate-limiting, then the rate of dissolution is dissolution controlled. This is the case for most poorly soluble compounds in immediate-release (IR) formulations whose solubility is less than 1–2 mg/L in the pH range of 2–8. Recent advanced technologies like combinatorial chemistry and high-throughput screening are effective in the discovery of new drugs with good pharmacological activities (3). About 35–40% of the drugs discovered with these technologies have poor aqueous solubility (4).

Dissolution testing of poorly soluble compounds in immediate-release (IR) solid dosage forms poses many challenges. These challenges include developing and validating the test method, ensuring that the method is appropriately discriminatory, and addressing the potential for an in vivo–in vitro relationship (IVIVR) or correlation (IVIVC). Satisfying all of these challenges and developing a meaningful dissolution method is a large task, because the extent of release is too low (i.e., one cannot get 100% of the dosage form dissolved) and secondly, the rate of release is too slow (i.e., one cannot get dissolution fast enough for a convenient test) (5).

Here, an attempt has been made to highlight the approaches to improve the dissolution of poorly soluble drugs.

To improve the dissolution of poorly soluble drugs, one needs to increase the maximum dissolvable dose in the dissolution media. The maximum dissolvable dose of the drug is given by

Maximum Dissolvable Dose = \( V \times C_s / \text{Sink} \)

where \( V \) is the dissolution medium volume, \( C_s \) is the saturated solubility of the compound in the medium, and

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Sink is sink condition calculated as $C_s/CD$ (where $C_s$ is the concentration of compound in the bulk medium) and should be greater than or equal to 3.

To increase the maximum dissolvable dose, one needs to increase the dissolution medium volume, change the medium to increase the saturation solubility of the compound, or reduce the dissolution sink requirements. There are several methods that are physiologically relevant that will increase the solubility of the drug in the medium. Alternatively, nonaqueous solvents can be used if justified. Therefore, the first step is to select a proper and justified medium for dissolution testing (5).

**Media Selection and Approaches to Improve the Saturation Solubility**

The choice of medium will depend on the purpose of the dissolution test. The dissolution characteristics of oral formulations should first be evaluated using test media within the physiologic pH range of 1.2–6.8 (1.2–7.5 for modified-release formulations) because low solubility drugs include those with adequate aqueous solubility at either acidic (e.g., amines) or neutral (e.g., organic acids) pH levels. During method development, it may be useful to measure the pH of the test medium before and after a run to see if the pH changes during the test (2).

For batch-to-batch quality testing, selection of the dissolution medium is based, in part, on the solubility data and the dose range of the drug product to ensure that sink conditions are met. Usually, USP dissolution tests specify 900 mL of water or buffers as a dissolution medium to provide sink conditions. The term *sink condition* is defined as a volume of medium at least three times the volume required to form a saturated solution of a drug substance. Some sources recommend five times and even ten times (5). However, how much is really needed? This question has yet to be justified. For poorly soluble drugs, finding appropriate sink conditions is challenging, particularly for drugs whose solubility is less than 2 mg/L. With regard to the sink condition, an alternative approach has been made by USP is the designing of flow-through cell apparatus (USP 4). The flow-through apparatus (USP 4) allows flow rates exceeding 50 mL/min (3 L/hr). Although these volumes can provide the theoretical capacity for complete extent of dissolution, for slowly dissolving compounds a limiting dissolution rate can be reached. One then ends up merely diluting the sample concentration to a point at which it becomes difficult to detect analytically. Using reasonable flow rates and long assay times, this apparatus can provide a significant increase in the volume (5).

As we mentioned above, intrinsic solubility of drug depends upon pH of medium, sink conditions as well as nature of the medium. For freely aqueous soluble drugs and their immediate-release dosage forms, the use of water as a dissolution medium is satisfactory. However, for drugs with limited aqueous solubility, the use of water as a dissolution medium is limited.

**Water as a Dissolution Medium**

Dissolution testing is used widely by the pharmaceutical industry and regulatory agencies to assure the continued quality of many oral dosage forms relative to the approved lot tested for bioavailability/bioequivalence (BA/BE). Many USP dissolution tests specify water as the dissolution medium.

Solubilities measured in water are not always indicative of solubilities in the gastrointestinal tract. The use of aqueous solubility to predict oral drug absorption can therefore lead to very pronounced underestimates of the oral bioavailability, particularly for drugs that are poorly soluble and lipophilic. Also, water lacks buffering capacity and thus, in some instances, the pH of the medium may change as the drug dissolves (as for salts). In addition, because water is not representative of the gastrointestinal environment, it is not considered a physiologically relevant medium (6).

But in many USP monographs, water is still frequently used as a better dissolution medium (e.g., Acarbose, Acetaminophen/Butalbital/Caffeine/Codeine Phosphate, Amodiaquine/Clavulanate Potassium, Aspirin/Meprobamate, Busulfan, Capecitabine, Carbamazepine, Cefadroxil, Cephalexin, Cetirizine HCl, Clonazepam, Cyclophosphamide, Dexamethasone HCl, Desmopressin Acetate, Didanosine, Estazolam, Fenofibrate) (7).

In addition, it has long been felt by members of the USP and FDA, probably based upon empirical observations, that water may be a better discriminating medium than the more physiological systems. The argument is that water appears to make it more difficult for some products to release the active ingredient and therefore good dissolution in water indicates that it will release even better in vivo. With regard to the above points, the question, Is the purpose of the medium to make the product look good just to pass a test, or is it to anticipate potential absorption problems? must be justified (8). For example, products formulated with excipients that are insoluble at pH values above 1–2, can release well when 0.1 N HCl is utilized for dissolution. However, in water this product would release much more slowly. Unfortunately, the physiological medium does not indicate what the release will be in achlorhydric subjects or simply when the stomach is not at a pH value of 1 (8).

Therefore, we strongly support Carol Noory and co-workers’ statement (6) that the in vitro dissolution must serve as both a quality control tool and as a potential surrogate marker of drug bioavailability and bioequivalence. Using a dissolution medium that better simulates the environment of the gastrointestinal tract will help make dissolution testing conditions more physiologically relevant to in vivo absorption and useful in evaluating the quality and stability of these drug products.

**Biorelevant Media**

In the last five to ten years, it has been thought that when dissolution testing is used to forecast the in vivo...
Intestinal Fluid (FaSSIF), which also contains sodium whose pH is adjusted to 6.5, and Fasted-State Simulated Intestinal Fluid (FeSSIF), which also contains sodium taurocholate and enzymes (optional) to the acetate buffer whose pH is adjusted to 5.0 (9). The development of biorelevant gastrointestinal media that simulate the fasted and fed states has given a better result when compared to release media as IVIVC is concerned. These media have been used to examine the solubility and dissolution characteristics of several classes of drugs including poorly soluble weak bases and lipophilic drugs to assist in predicting in vivo absorption behavior. Biorelevant in vitro dissolution testing is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs. It has been observed that biorelevant media can provide a more accurate simulation of pharmacokinetic profiles than simulated gastric fluid or simulated intestinal fluid. The use of biorelevant media can have a great impact on the pharmacokinetic studies performed to optimize dosing conditions and product formulation. In addition, biorelevant dissolution testing could be used to assess bioequivalence of post-approval formulation changes in certain kinds of drugs.

Due to their complex composition, availability of costly surfactants (sodium taurocholate and lecithin), and questionable storage stability, these media are expensive, and their use is limited as a regular quality control medium. But a simple test medium can be developed which can work almost like biorelevant media as well as regular QC (quality control) media is the replacement of which can work almost like biorelevant media as well as regular QC (quality control) media is the replacement of natural bile components (Sodium taurocholate and lecithin) with different type and concentrations of surfactants (popularly known as mixed micelles) (9).

Use of Surfactants and Mixed Micelles

Because of the unique characteristics of surfactants, small concentrations added to water will immediately form a stable monolayer. As more surfactant is added, a bilayer is formed. If the concentration of surfactant is increased sufficiently, the bilayer becomes unstable and micelles are formed. The micelle consists of a hydrophilic shell and a hydrophobic core (10).

Two factors that must be considered when evaluating surfactants are cost and concentration needed. If the dissolution assay is to be run in a Quality Control setting, choosing an inexpensive surfactant will be important to keep overall assay costs down. Examples of inexpensive surfactants are sodium dodecyl sulfate or SDS (also referred to as sodium lauryl sulfate or SLS) for an anionic surfactant, Cetyl Trimethyl Ammonium Bromide or CTAB for a cationic surfactant, and the polysorbates or Tweens for a nonionic surfactant.

To get any substantial solubility enhancement, the surfactant concentration must be at least above the critical micelle concentration or CMC. The CMC will depend upon the surfactant itself and the ionic strength of the media. The amount of surfactant needed depends on the CMC and the degree to which the compound partitions into the surfactant micelles. Because of the nature of the compound–molecule interaction, there is typically a linear dependence between solubility and surfactant concentration above the CMC.

For a dissolution method developer, the aim must always be to use the lowest amount of surfactant to solubilize the drug substance in the dosage form to achieve greater than 85% dissolution in a reasonable amount of time. Moreover, there must be a solid justification for using more than 2% (as per FDA). Compared with media containing a single surfactant, the mixture of surfactants seems to be more favorable because it is likely that mixed micelles are formed, which is analogous to the behavior of natural bile components. The use of mixed micelles in the dissolution media is a novel approach.

Mixed micelles are a mixture of the same or different proportions of different types of surfactants. They have a hydrophobic core in which low solubility compounds can dissolve. To reflect the physicochemical parameters of FaSSIF and FeSSIF adequately, only those surfactants resulting in surface tensions of 52–56 mN/m should be used in concentrations above their critical micelle concentration (CMC). Some synthetic surfactants, several of which are prescribed in compendial dissolution test methods, appeared to be unsuitable for the stated purpose since they lower the surface tension too much. In particular, this is the case for sodium dodecyl sulfate (SLS/SDS), which results in surface tensions of about 30 mN/m at concentrations above the CMC. On the other hand, the polysorbates Tween 20, 40, 60, and 80 show promise in the concentration range of 0.05–0.5%, because their surface tensions reflect the surface tensions of FaSSIF and FeSSIF. Zoeller and Klein (9) have reported on the dissolution behavior of ketoconazole under fasted-state, small intestinal conditions using buffers containing simple surfactants like Tween 60 and 80, while for fed-state conditions, Tween 20 and 40 proved useful. They reported that a blank FeSSIF containing a combination of 0.25% Tween 80 and 0.25% triethanolamine resulted in dissolution profiles almost superimposable to those in FaSSIF. Triethanolamine itself has no emulsifying properties. Because it is both a tertiary amine and a tri-alcohol, it possesses hydrophilic and hydrophobic properties. Here, the use of triethanolamine was to simulate some functional domains of the lecithin molecule, thus facilitating the formation of mixed micelles and stabilizing them.

These or similar media can be utilized to develop test methods for the early phases of formulation development and have potential for “biorelevant” quality control (QC).
tests. Additional advantages of their use include much better storage stability, ease of preparation, and—probably the most significant criterion for everyday use—a far lower price. For example, one liter of FeSSIF can cost as much as US$700, whereas the price of one liter of medium containing synthetic surfactants (mixed micelles) is only around US$1 (9).

In rare cases, when drug is practically insoluble in normal buffered aqueous medium (with or without surfactants), then the use of a nonaqueous medium is an alternative approach.

Use of Nonaqueous Media

Nonaqueous solvents can be used with aqueous buffered media as a cosolvent for nonpolar (hydrophobic) drugs. A cosolvent system is one in which a water miscible or practically miscible organic solvent is mixed with water to form a modified aqueous solution. Cosolvents have some regions of hydrogen bond donating or accepting as well as hydrocarbon regions. The resulting solution will have physical properties that are intermediate to that of the pure organic solvent and water through the reduction of water–water interactions. This affords a system that is more favorable for nonpolar solutes.

The use of nonaqueous solvents for dissolution media is unconventional. From a practical point of view, if such a medium is filed with the regulatory authorities, one will probably be expected to show that conventional tactics for getting adequate solubility and dissolution do not work. One also has to deal with the waste disposal problem since nonaqueous media often cannot be merely neutralized and poured down the drain. However, if aqueous-based methods for achieving solubility have been exhausted, use of hydroalcoholic media may be the best alternative. Another solvent that can be used as the dissolution medium is 30:70 isopropanol/0.01 N HCl (5).

Dissolution Enhancement by Physical Modification of the Drug

The solubility of a drug is not only determines the dissolution behavior of an active pharmaceutical ingredient (API) in the formulation, but it also affects the absorption as well as therapeutic efficacy of the drug. In intrinsic dissolution limited absorption (in which disintegration of the dosage form is rapid but dissolution is slow as in poorly soluble drugs), some commonly used physical modifications of the API are reduction of particle size, complexation, and solid dispersions of drug in suitable carriers. In solubility limited absorption (intrinsic solubility controlled), the formulation approach is commonly used to enhance the solubility of the API. This approach includes the use of different salt forms of API, surfactants in the formulation (solid dispersions), and noncrystalline materials.

1. Particle Size Reduction

According to the modified Noyes–Whitney equation, the rate of mass lost from the particle is given by

\[ -dM/dt = DS/h \left( C_s - C_i \right) \]

where \( M \) is the mass of compound dissolved in time \( t \), \( D \) is the diffusion coefficient of the compound in medium, \( S \) is surface area, \( h \) is thickness of the stagnant film layer, \( C_s \) is the saturated solubility of the compound at the particle–media interface, and \( C_i \) is the concentration of compound in the bulk medium.

In evaluating each term in the equation in terms of its role in dissolution, we can recognize that effective changes in two parameters, surface area and solubility, can lead to a significant enhancement in the dissolution rate of the drug. Moreover, both parameters are controlled and easily measurable. On the other hand, any modification in the film thickness \( h \) or the diffusion coefficient \( D \) is either impractical or useless from a bioavailability point of view. The film thickness only can be decreased by increasing the stirring rate dramatically, a condition that is not applicable to the in vivo environment. In addition, the diffusion coefficient is a function of temperature, the radius of the molecule, and the viscosity of the medium, all of which are constant under in vivo conditions.

a) Micronization

Increasing the dissolution rate by reducing the particle size of poorly water-soluble drugs has been the most popular practice for many decades. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Today, micronization of drugs is widely done by milling techniques using a jet mill, rotor stator, colloidal mill, and air attrition. Kornblum and Hirschorn (11) evaluated two specific methods of micronization, spray drying and air attrition, which provided drug forms of different specific surface areas and particle size ranges. With the aforementioned advantages, micronization has some limitations; micronization of sparingly or poorly soluble drugs is by no means a guarantee of better dissolution and absorption. A hydrophobic powder with small particle size leads to aggregation, making it difficult to disperse. The particles float on the dissolution medium because of entrapped air. It is difficult to remove or wet these particles. All these effects, in fact, reduce the rate of dissolution (12).

b) Nanotechnology

Nanotechnology will be used to improve drugs that approaches have poor solubility. Nanotechnology broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less (13). For many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency to agglomerate, which leads to decreased effective surface
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area for dissolution (14), and the next step taken was nanonisation (15).

i) Nanosuspension
Nanosuspensions are submicron colloidal dispersion of pure particles of drug that are stabilized by surfactants (16). The advantages offered by nanosuspension is an increased dissolution rate due to a larger exposed surface area. The recent techniques widely used to form nanosuspensions are homogenization, wet milling, sonocrystallization, super critical fluid technology, and spray drying.

Homogenization
The suspension is forced under pressure through a valve that has a nano aperture. This causes bubbles of water to form, which collapse as they come out of the valves. This mechanism cracks the particles.
Three types of homogenizers are commonly used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high-shear fluid processors (17).

Wet Milling
Active drug in the presence of surfactant is defragmented by milling. Drying of nanosuspensions can be done by lyophilization or spray drying. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel, and bupravaquone.

Sonocrystallization
Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. Most applications use ultrasound in the range of 20 kHz to 5 MHz to reduce the particle size (18).

Supercritical Fluid Process
In the supercritical fluid (SCF) process, micronization is done by the supercritical fluid. Supercritical fluids are fluids whose temperature and pressure are greater than their critical temperature ($T_c$) and critical pressure ($P_c$). An SCF is highly compressible, which allows moderate changes in pressure to greatly alter the density and mass transport characteristics that largely determine its solvent power. The SCF process can create nanoparticulate suspensions of particles 5–2,000 nm in diameter (19, 20).

Spray drying
Spray drying is a commonly used method for drying a liquid feed through a hot gas. Typically, this hot gas is air, but sensitive materials such as pharmaceuticals and solvents like ethanol require oxygen-free drying, and nitrogen gas is used instead. The liquid feed varies depending on the material being dried. This method of drying is a one-step, rapid process (21). Spray drying of the poorly water-soluble salicylic acid dispersed in acacia solutions resulted in as much as a 50% improvement in its solubility (22).

ii) Nanocrystals
A nanocrystal is a crystalline material with dimensions measured in nanometers, a nanoparticle with a structure that is mostly crystalline. Nanocrystallization is defined as a way of diminishing drug particles to the size range of 1–1000 nm. Keck et al. (15) formulated nanocrystals of poorly soluble drugs by high-pressure homogenization to enhance their dissolution and bioavailability.

iii) Nanomorphs
Nanomorph technology converts drug substances with low water solubility from a coarse crystalline state into amorphous nanoparticles to enhance their dissolution. A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth.
Water-redispersable dry powders can be obtained from the nanosized dispersion by conventional methods (e.g., spray drying).
Using this technology, a coarse, crystalline drug substance is transformed into a nanodispersed amorphous state without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticles (23).

2. Use of Metastable Polymorphs
The presence of metastable, polymorphic crystalline forms can exert a great influence on the solubility, dissolution rate, and biological activity of medicaments. The separation and selective use of a specific polymorphic form that possesses the highest solubility is a technique that can be applied, in certain cases, for the increase of dissolution rates. Melting followed by rapid cooling or recrystallization from different solvents can produce metastable forms of a drug. For example, a metastable form of chloramphenicol palmitate is more water-soluble than the A and C forms (24).

3. Drug Dispersion in Carriers
a) Solid Solutions
A solid solution is a binary system comprising a solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogeneous one-phase system, solid solutions are also called molecular dispersions or mixed crystals. They are generally prepared by a fusion method, whereby a physical mixture of solute and solvent are melted together followed by rapid
solidification. The solid solution of griseofulvin–succinic acid dissolves 6–7 times faster than pure griseofulvin (25).

When the resultant solid solution is a homogeneous, transparent, and brittle system, it is called a glass solution. Carriers that form glassy structures are citric acid, urea, polyvinyl pyrrolidone, polyethylene glycol, and sugars such as dextrose, sucrose, inulin, and galactose. When the solid solution, in which solute and solvent molecules are randomly arranged in a crystal lattice, is exposed to the dissolution fluid, the soluble carrier dissolves rapidly leaving the insoluble drug stranded at almost the molecular level.

b) Eutectic Mixtures

These systems are prepared by a fusion method. Eutectic melts differ from solid solutions in that the fused melt of solute and solvent show complete miscibility but negligible solid–solid solubility (i.e., such systems are basically an intimately blended physical mixture of two crystalline components). When the binary mixture is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles. Examples of eutectic mixtures include paracetamol–urea, griseofulvin–urea, and griseofulvin–succinic acid (26).

Sekiguchi and co-workers (26) suggested that submicron particle size reduction could be achieved through eutectic formation between a poorly soluble drug and a rapidly soluble carrier and reported one of the earliest techniques used. As an example, significant improvement in the dissolution rate of chloramphenicol was obtained when incorporated in a eutectic mixture with urea (27). The soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion consisting of extremely fine particles.

The advantage with solid solutions and eutectics is that they are melts, are easy to prepare, and are economical because no solvent is used. Some limitations are that it cannot be applied to drugs that fail to crystallize from the mixed melt, thermolabile drugs, and carriers such as succinic acid that decompose at their melting points.

c) Solute–Solvent Complexation Reactions

Molecular complexation between molecules of dissolving solutes and certain solvents have been known to affect dissolution rates. The major complexation mechanism in these systems is hydrogen bonding. Higuchi et al. (28) studied the dissolution rate of 2-naphthol tablets in cyclohexane (an inert solvent) containing various amounts of additives such as 1-propanol and 1-undecanol. These additives are known to react rapidly and reversibly with the dissolved molecules of 2-naphthol to yield soluble complexes. Here, both the diffusion coefficient of the complexing component in the solvent and the stability constant of the resulting complex are the major factors that control the dissolution kinetics of these systems.

d) Solid Dispersions

In 1965, Tachibana and Nakamura (29) described a new approach utilizing water-soluble polymers for the preparation of aqueous dispersions of β-carotene. Mayersohn and Gibaldi (30) applied the same approach to improve the solubility and dissolution characteristics of griseofulvin. The dispersion method allows the preparation of physically modified forms of the drug that are much more rapidly soluble in water than the pure compound. The most commonly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols, and plasdone-S630. Surfactants may also be used in the formation of solid dispersions. Surfactants like Tween-80, Myrij-52, and Pluronic-F68 and sodium lauryl sulfate are used. Chiuo and Riegelman (31) recommended polyethylene glycol, a water-soluble polymer, as an excellent universal carrier for improving the dissolution rate and oral absorption of water-insoluble drugs. They reported that the dissolution of griseofulvin, as well as its absorption and total availability in both dog (32) and man (33), was significantly higher when the solid was dispersed in polyethylene glycol 4000, 6000, or 20,000, as compared with the traditionally micronized form of the drug. Deshpande and Agrawal (34) reported that the dissolution rates of chlorothiazide, hydrochlorothiazide, flumethiazide, and cyclopentathiazide also were increased when dispersed in polyethylene glycol 6000. Takai et al. (35) studied the quantitative relationship of the dissolution behavior of griseofulvin with the properties of the polyethylene glycol polymer used.

Various newer strategies investigated by several investigators include fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration, extrusion, spray drying, surfactant use, electrostatic spinning, and super critical fluid technology for solid dispersions.

4. Complexation with β-Cyclodextrins

Complexation is the association between two or more molecules to form a nonbonded entity with a well-defined stoichiometry. The two types of complexation that are most useful for increasing the solubility of drugs in aqueous media are stacking and inclusion. Stacking complexes are formed by the overlap of the planar regions of aromatic molecules, while inclusion complexes are formed by the insertion of the nonpolar region of one molecule into the cavity of another molecule (or group of molecules).

The α-, β-, and γ-cyclodextrins are cyclic oligosaccharides consisting of six, seven, and eight glucose units, respectively. One of the important properties of these naturally occurring cyclodextrins is their ability to form inclusion complexes with smaller molecules that fit into the hydrophobic cavity of the cyclodextrin. The formation of inclusion complexes alters a variety of the physicochemical properties of the drug molecule such as its solubility, dissolution rate, membrane permeability, chemical reactivity, and dissociation constant. In some
cases, as the concentration of cyclodextrin increases, the solubility increases initially, levels off, and then decreases. In 1963, Cohen and Lach (36, 37) were the first to report that inclusion complexes with various drugs in solution increase drug solubility and improve the dissolution rate. In 1975, Kurozumi et al. (38) made a simple freeze-dried complex of drug and β-cyclodextrin to improve the solubility and dissolution of drug. Although natural cyclodextrin, especially the β-type, has been utilized extensively to improve the dissolution rate and absorption of insoluble drug molecules, Uekama and others have reported that β-cyclodextrin has some undesirable characteristics, the most important of which are its definite cavity size and its relatively low aqueous solubility (1.8% at 25 °C) (39, 40). Recently, chemically modified cyclodextrins have been introduced to overcome this limitation. Uekama et al. (41) demonstrated that the inclusion complex of the anti-inflammatory drug flurbiprofen with the heptakisdimethyl derivative of β-cyclodextrin was superior to the natural β-cyclodextrin. Zerrouk et al. (42) reported the aqueous solubility of glyburide was improved 40-fold when mixed with hydroxypropyl-β-cyclodextrin and 25-fold when mixed with β-cyclodextrin. Another cyclodextrin chemically modified with epichlorhydrin is extremely soluble in water and interacts with a variety of guest molecules (43, 44) like phenytoin.

Miscellaneous Approaches
Microemulsions
Shulman first used the term microemulsion in 1959. A microemulsion is a four-component system composed of external phase, internal phase, surfactant, and cosurfactant. The addition of surfactant, which unlike the cosurfactant, is predominately soluble in the internal phase, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed a microemulsion because the internal or dispersed phase has a droplet diameter of less than 0.1 µm. Microemulsion formation is spontaneous and does not involve the input of external energy as for coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsion. Lawrence and Rees (45) reported microemulsion-based media as novel drug delivery systems to enhance the dissolution and bioavailability of poorly soluble and poorly bioavailable (Biopharmaceutical Classification System class IV) drugs. Nonionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hydrophilic–lipophilic balances are often used to ensure immediate formation of oil-in-water droplets during production.

Plasma Irradiation
Plasma irradiation has been investigated as a possible technique for increasing the dissolution rate of poorly soluble drugs. A plasma is a partially ionized gas that contains an equal number of positive and negative ions and unionized neutral species such as molecules, atoms, and radicals. It is created by subjecting a gas (e.g., O2) to a radio-frequency potential in a vacuum chamber. This leads to the production of electrons, which are accelerated by an electric field and collide with neutral molecules to produce free radicals, atoms, and ions. In an oxygen plasma, O2 can be excited from the ground state to higher electronic levels to form O2⁻ and O2⁻. Further dissociation reaction leads to the production of oxygen atoms and ions such as O⁻ and O⁺. During plasma treatment, these oxygen radicals then react with the chemical groups on the surface of an exposed sample that leads to the formation of an O2⁻-containing functional group such as hydroxyl, carbonyl, or carboxyl group. The production of these functional groups leads to an increase in wettability and thus increases the effective surface area available for dissolution, which increases the dissolution rate (46).

Liquisolid Compacts
Liquisolid compact formulation is a technique that utilizes hydrophobic drugs dissolved in nonvolatile, nontoxic, hydrophilic solvents like polyethylene glycol, glycerin, propylene glycol, or polysorbate-80 (well known as Liquid Medications) mixed with carriers like microcrystalline cellulose, lactose, or polyvinyl pyrrolidone–K30 using coating materials like silica in optimized proportions and finally compressed into a compact mass. In recent years, this technique was used to enhance the dissolution rate of carbamazepine (47), piroxicam (48), naproxen (49), famotidine (50), and prednisolone (51).

CONCLUSION
Understanding the physicochemical properties of a drug is crucial for determining the most effective strategy for enhancing dissolution. Typically, the greatest enhancement in the dissolution of poorly soluble compounds is made by changing the dissolution medium to increase compound solubility. Surfactants and pH changes are very effective ways to increase solubility. The in vitro dissolution must serve as both a quality control tool and a potential surrogate marker of drug bioavailability and bioequivalence. It is important to note that no matter what new, innovative, and clever dissolution methods will be developed to deal with poorly soluble compounds, they will have to affect one or more of the variables discussed above in a way to affect the extent or rate of dissolution. Some articles suggest helping the dissolution process by increasing the bath temperature, which affects solubility. This has its own set of problems (i.e., regulatory acceptance and perhaps increased drug degradation), but nevertheless is a potential strategy. One might also design a different agitation device or increase sink conditions by using a partitioning phase to remove compound from an aqueous phase. In any case, increasing the dissolution rate or extent will have to change one of the aforementioned variables.
REFERENCES


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