CHAPTER

9

Dissolution Profile Consideration in Pharmaceutical Product Development

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OUTLINE

Dosage Form Design Considerations
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9.1 INTRODUCTION: DRUG DISSOLUTION CONCEPT

Dissolution involves the interaction of solid drug with the dissolution medium resulting in the movement of drug molecules into the bulk solution (Qiu et al., 2016). It is fundamentally dependent on relative molecular affinities between the drug and dissolution media. Under specific experimental conditions, dissolution is also known as solubility. The maximum quantity of the solute dissolved in a pure solvent under fixed environmental conditions (temperature, pressure, and pH) is called absolute solubility (Khadka et al., 2014). The process of dissolution may thus be understood as the relocation of solute and solvent molecules involving intermolecular attraction forces as shown in Fig. 9.1.

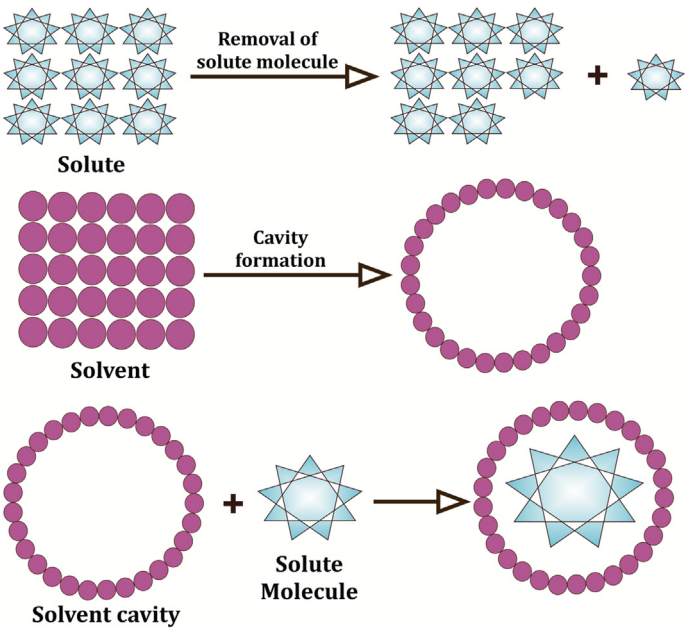

FIGURE 9.1 Diagrammatic representations of the processes involved in dissolution of a crystalline solute. Firstly, solute molecules are disintegrated; solvent molecules dispersed to form cavity; the cavity is filled with disintegrated solute molecules one by one to complete the process of dissolution.

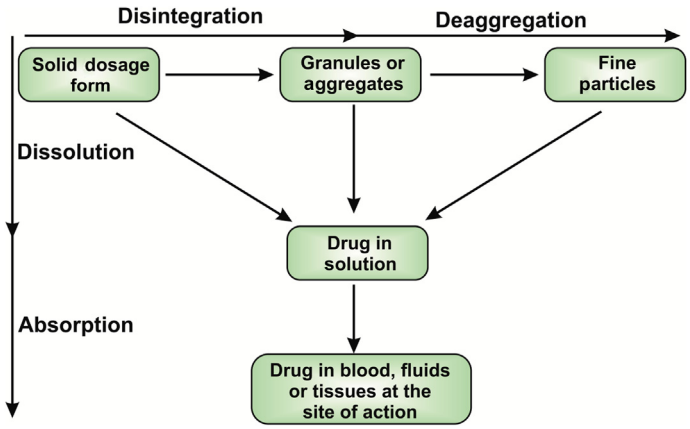

FIGURE 9.2 Schematic representation of dissolution of a solid dosage form. There are two pathways for solid dosage forms to get absorbed into the blood. (1) It can be disintegrated into granules or aggregates and further deaggregates to form fine particles, which further go into solution and subsequently gets absorbed. (2) Solid dosage form can be directly gets dissolved into the solution and gets absorbed.

The dissolution process gets initiated by the general movement of solid solute from the largest form to fine particles before becoming molecularly dispersed (dissolved). It is a multistep process involving wetting of the solid phase, followed by sequential penetration of solvent into the solid formulation. The dissolution of the solid formulations like tablet initially involves its breakdown into granular or fine particulate form followed by de-aggregation, leading to a considerable increase in the total solute surface area (Rahul et al., 2017). The last step involves the dissolution of the drug to be available for systemic circulation. However, dissolution can take place anytime during these steps as illustrated in Fig. 9.2.

In the case of liquid formulations like suspension, dissolution can occur directly or involves a lesser number of steps as the solid present in the formulation is already in a fine particulate form. The site of these events can be stomach or intestine or both. The slowest step in the overall dissolution process is considered to be the rate determining step. For the drugs with poor solubility, solubilization is found to be slower in comparison to the disintegration or de-aggregation of the formulation, thus making it dissolution controlled. Conversely, if the disintegration is slower than solubilization, then the rate-limiting step is considered to be disintegration (Bourlieu et al., 2015).

9.2 THEORIES OF DISSOLUTION

Each of the events of the drug dissolution process has its own rate. Various physical models have been drafted to explore the theoretical concepts, study these rates, and to get the deeper insight of dissolution mechanism (Babu et al., 2015). These models can precisely explain the parameters of the dissolution and highlight the corresponding factors that affect these parameters. This could act as a foundation of a dissolution method development. Dissolution mechanism can be explained by utilizing any of these models.

9.2.1 Diffusion Layer Model

Nernst and Brunner initially proposed this model which is also called film theory. This model explains the dissolution of a single particle (sphere). It is the simplest and most useful theory in the estimation of the dissolution rate of pharmaceutical particles. According to this theory, the process comprises of two steps: first, the formation of the diffusion layer (stagnant liquid layer) around the solid particle by dissolution of the solid particle (drug) at the solid/liquid interface. Later this layer gets saturated by the drug (Wurster and Taylor, 1965). This is an instantaneous step, and the equilibrium is attained at the solid/liquid interface. The concentration of the drug in this stagnant layer is denoted as C_s. In the second step, the drug molecule diffuses through the stagnant layer to the interface and ultimately moves towards the bulk solvent. In this model, diffusion of the drug via a film layer is considered as the rate determining step (Siepmann and Siepmann, 2013). Noyes and Whitney coined the equation for dissolution rate concerning the difference in concentrations of the drug at stagnant layer C_s and in bulk at time C_t. The Noyes-Whitney equation assumes that during the dissolution process, the surface area of the solute remains constant, which is practically not possible for dissolving particles. In accounting for the change in the surface area concerning the decreasing particle size during dissolution, Hixon and Crowell's cube root law of dissolution is used (Berthelsen et al., 2016).

9.2.2 Interfacial Barrier Model

In contrast to the diffusion layer model, the interfacial barrier model suggests that the activity at the solute surface along with its subsequent diffusion across the interface is comparatively slower than the diffusion across the stagnant layer. Surface activity in this model is not considered to be instantaneous as in the case of the previous model. This is because of the presence of an obstruction of high activation energy that has to be overcome before the dissolution of the solid. Thus the rate of solubilization of the solute (drug) in the static layer is the rate determining step, instead of the diffusion of the solubilized drug towards the bulk solvent (Higuchi, 1967). This model also suggests that due to the solvation, an intermediate concentration is present at the interface as a function of solubility instead of diffusion.

9.2.3 The Danckwerts Model

Similar to the diffusion layer model, Danckwerts model also postulates that the activity on the solute surface is instantaneous (Danckwerts, 1951). However, the mechanism of mass transfer of a solute from solid surface to bulk liquid varies. This model suggests that the macroscopic solvent packets or eddies in the fluid randomly approach to the characteristic solid−liquid interface owing to agitation. Diffusion of the solute particles takes place into these solvent packets that deliver them to the bulk solvent. Due to penetration of these solvent packets into the solid−liquid interface, this is called the Penetration theory. This is also known as the Surface Renewal theory because of the continuous replacement of solvent packets with fresh supplies of solvent which then interact with the new solid surface at each instance (Zhang and Chatterjee, 2015).

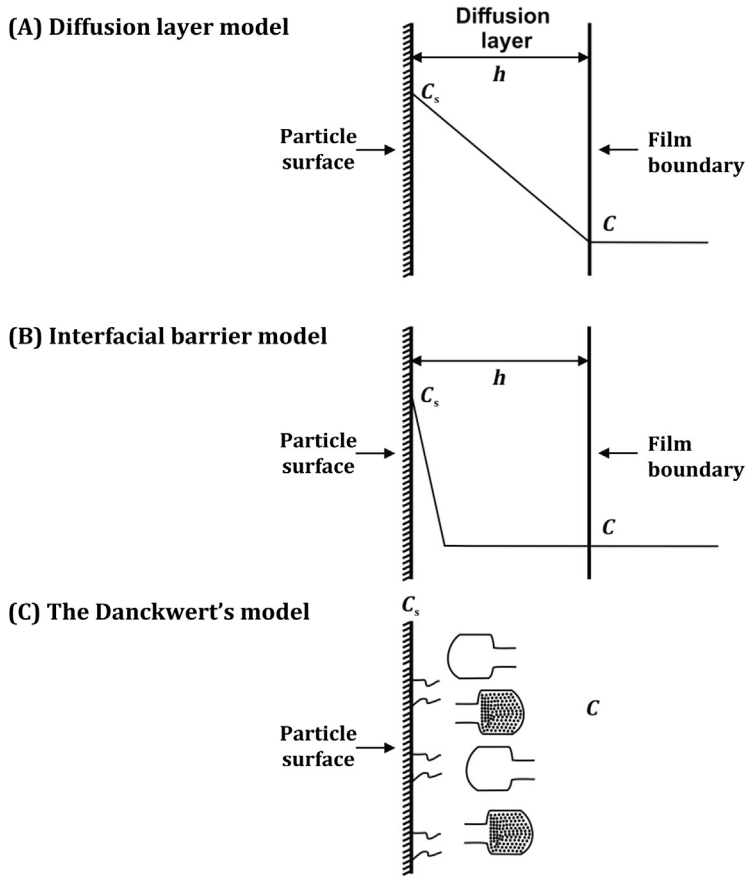

FIGURE 9.3 Schematic illustrations of (A) the Diffusion Layer Model, (B) the Interfacial Barrier Model, and (C) the Danckwerts Model. C_s = concentration of the drug in this stagnant layer$_s$; C = Concentration of the drug in the bulk at time t; h = Thickness of the stagnant layer.

The transport phenomenon as per the three models is illustrated in Fig. 9.3 and the dissolution rate equations for the three theories are mentioned in Table 9.1. This section shed light on several theories of dissolution. However, there are many factors which may affect the rate of dissolution from the dosage form. The next section deals with the various factors affecting the rate of dissolution.

TABLE 9.1 Representing Fundamental Dissolution Theories

Fundamental Dissolution Theories	Equations	Equation Characteristics
Diffusion Layer Theory		
Fick's First Law	$J_{ix} = D_i\ (\lambda C_i/\lambda x)$	Diffusion depends on steady state conditions
Fick's Second Law	$\lambda C/\lambda t = D\ (\lambda^2 c/\lambda x^2)$	Governs by nonsteady state conditions
Noyes and Whitney	$dc/dt = K\ (J_s - J_t)$	Constant surface area based description of dissolution of drug molecules
Brunner and Tolloczko	$dc/dt = kdS\ (J_s - J_t)$	Manipulation of Noyes–Whitney's equation by incorporation of surface area term S. Proposed the formation of a stagnant layer around the dissolving particle, a layer through which solute diffuses through the bulk
Nernst Brunner	$dc/dt = kdDS/vh\ (J_s - J_t)$ *if* $J_t \ll J_s$ (*i.e.* $< 10\%$ $\rightarrow$ $dc/dt = kDS/vhc_s$ *if v and S are constant* $\rightarrow$ $dc/dt = K$	Manipulation of Fick's first law and expansion of equation by incorporation of a diffusion coefficient D, stagnant layer thickness h, and volume of dissolution medium v
Hixson and Crowell Cube Root	$w_o^{1/3} - w^{1/3} = (4\pi\rho\eta/3)^{1/3}\ (DJs/h_\rho)t$ *Or* $w_o^{1/3} - w^{1/3} = Kt$	Originally developed for single particles but has been extended to use in multiparticulate systems
Higuchi equation	$ft = Q = A\sqrt{\ }$	Description of drug dissolution
Surface Renewal Theory	$Vdc/dt = dW/dt = S(\gamma D)^{1/2}\ (J_s - J_t)$	Assumes solid-solution equilibrium is achieved at the interface and that mass transport is the rate-limiting step in the dissolution process
Theory Limited Solvation	$G = kd_i(J_s - J_t)$	An intermediate drug concentration less than saturation may exist at the interfacial barrier between the solid surface and solvent. Different faces of a crystal may have different interfacial barriers and therefore make different contributions to the dissolution process
Surface energy Theory	$\gamma = dG/dA$	Increasing the surface by a length

Key to symbols and abbreviations: J_{ix}: flux (mg/cm^2s^{-1}); D_i: diffusion coefficient; $\lambda C_i/\lambda x$: concentration gradient; $\lambda C/\lambda t$ or dc/dt: drug dissolution rate; K: first-order dissolution constant; J_s: equilibrium drug concentration; J_t: drug concentration at time t; kd: dissolution constant; S: surface area; v: volume of dissolution medium; h: thickness of stagnant layer; w_o: initial powder weight; w: powder weight at time t; ρ: particle density; η: viscosity; h: thickness of diffusion layer; γ: interfacial tension; G: dissolution rate per unit area; k_i: effective interfacial transport constant; Q is the amount of drug release per unit time area A.

9.3 FACTORS AFFECTING DISSOLUTION RATE (*IN VITRO*)

9.3.1 Drug-Related Factors

9.3.1.1 Solubility

The solubility of a drug substance is known to affect its intrinsic dissolution rate. Highly soluble drugs usually show faster dissolution rates. Thus, to predict the influence of solubility on drug dissolution, the solubility of the drug must be measured at different physiological pH (Hall, 2015). There are numerous techniques described for complex formation to increase the solubility, dissolution rate, and absorption of the drugs with low water solubility, e.g., conjugates of cyclodextrin with poorly soluble drugs (Gidwani and Vyas, 2014).

9.3.1.2 Drug Ionization: pH Effects, Salt Form of Drug

A drug that exists in the ionized form in the gastrointestinal (GI) fluids tend to be more soluble as compare to its nonionized form. In general, the acidic drug ionizes at basic pH, and the basic drug ionizes at acidic pH. The drug in salt form also exhibits higher rates of dissolution as compared to a nonionized form of the drug (Qiu et al., 2016).

9.3.1.3 Particle Size

Particle size reduction of a drug (micronization) increases its surface area and enhances its dissolution which ultimately increases the absorption of drug (Sharma et al., 2015; Maheshwari et al., 2012). An increase in effective surface area by particle size reduction also improves the wetting properties of the drug. However, this correlation is not applicable in the case of hydrophobic drugs where the augmentation in surface area decreases the rate of dissolution (Javadzadeh et al., 2015).

9.3.1.4 Solid State Characteristics

9.3.1.4.1 POLYMORPHISM

A drug might exist in more than one crystalline form (polymorphs), which differ in their lattice energies, leading to the different solubility profiles. Metastable (high activation energy) polymorphs exhibit better dissolution profiles as compared to the other stable polymorphic forms (Brittain, 2016). A significant variation between dissolution rates of different polymorphic forms of carbamazepine was reported. The tablets of α-form exhibit higher dissolution rates as compared to β-form. In another experiment, it was demonstrated that two different polymorphic forms of oxytetracycline hydrochloride exhibit dissimilar dissolution rates from the conventional tablets (Reischl et al., 2015).

9.3.1.4.2 CRYSTALLINE/AMORPHOUS FORM

The crystal lattice in the drug molecule may either be of particular conformations (crystalline phases) or be indistinguishable (amorphous phases). In general, amorphous drugs show better solubility and dissolution than that of a crystalline form. However, exceptions are also observed as in the case of erythromycin estolate whose crystalline form is more soluble than the amorphous form (Grohganz et al., 2014).

9.3.1.4.3 SOLVATE FORMATION

A drug may exist in various forms as hydrates and solvates containing a stoichiometric or nonstoichiometric amount of solvent. The anhydrous forms of the drug may dissolve faster than the hydrated form, being thermodynamically more active (Reutzel-Edens and Stephenson, 2016). Toluene and pentanol solvates of glibenclamide have been reported to exhibit high dissolution rates when compared to its nonsolvated polymorphic forms (Censi and Di Martino, 2015).

9.3.1.4.4 COMPLEXATION

Drugs may complex with the excipients that can affect the dissolution rate and thereby the therapeutic efficacy. Complex formation may result in alteration of biopharmaceutical or physicochemical properties of the drug (Panakanti and Narang, 2015). The solubility and diffusion coefficient of the complex thus formed may be more or less as compared to the parent drug (Dizaj et al., 2015). The precise use and understanding of complex formation techniques have been explored to increase the solubility, dissolution rate, and absorption of the drugs with poor aqueous solubility, for instance, the conjugates of cyclodextrin with poorly soluble drugs (Gidwani and Vyas, 2014).

9.3.2 Drug Product Formulation Related Factors

Excipients have been reported to significantly affect the rate of drug dissolution. Both the nature as well as the proportion of excipients influences the rate of dissolution. Several excipients have been reported to increase the dissolution characteristics of the drug. This holds true for those excipients that tend to enhance the hydrophilic nature of the drug substance. However, the excipients which are hydrophobic in nature may adversely affect (decrease) the dissolution rate (Parr et al., 2016).

The diluent like starch imparts hydrophilic properties to the exterior surface of the hydrophobic drug by forming a layer around it; thereby increasing the effective surface area and the drug dissolution rate. The disintegrants are generally observed to improve the dissolution process by various mechanisms. Starch, also being a disintegrant, swells with wetting, facilitates breaking up of tablet and deaggregation into a granule. Sodium starch glycolate also has the strong swelling capacity (Van Nguyen et al., 2016).

The influence of binders on the dissolution rate is varied. The hydrophilic binders like gelatin impart hydrophilicity to the hydrophobic poorly wettable drug substance and improve their dissolution rate as in the case of phenobarbital tablet granulated with gelatin. On the other side, some factors may lead to slowing down of the dissolution process like a large amount of binders increases the hardness of tablets (Bandari et al., 2014).

Lubricants that are mostly hydrophobic in nature (e.g., metallic stearates like magnesium stearate, stearic acid, and talc)form water repellant coats around the granules resulting in the reduced effective surface area, reduced wettability, and thereby decreased dissolution rate, e.g., as observed in the case of magnesium stearate used in salicylic acid tablets. When sodium lauryl sulfateis used in the salicylic acid tablet as lubricant, the surface activity of sodium lauryl sulfate increases wetting, promotes solvent penetration into the tablet, and thus enhances the dissolution rate (Li and Wu, 2014).

The surfactants incorporated in various dosage forms (especially poorly soluble drugs) by virtue of micelle formation, improve the wetting of the particles resulting in increased dissolution rates (Sharma, 2016). Some dyes are also observed to affect the dissolution, e.g., FD & C Blue No. 1 decreased the dissolution rate of sulphathiazole by inhibiting the surfactant-like properties of bile salts on the drug (Zishan et al., 2017). The decrease in dissolution rate of capsules prepared by using Polysorbate 80 as an excipient was observed (Dannenfelser et al., 2004). This is because of formation of an additional film due to the denaturation of the capsule's inner surface. This denaturation occurs due to the formation of formaldehyde by autooxidation of Polysorbate 80. This results in reduced dissolution (Khadka et al., 2014).

The polymers used in several formulations considerably impact the drug dissolution rate (Maheshwari et al., 2015; Tekade et al., 2017). They are generally incorporated to control the release of the drug from the dosage form. The nature and amount of these substances play a major role. The majority either form a coat over the drug particles or the formulation, delaying or slowing down the dissolution process. Also, they can form a matrix in which the drug is embedded and gets dissolved and released at a particular desired rate (Ma et al., 2014). In an investigation, it was found that the dissolution of indomethacin from cocrystals of indomethacin − saccharin increases in the presence of polyvinylpyrrolidone (Alhalaweh et al., 2013).

In another experiment, it was revealed that the increase in the concentration of a polymer (Methocel K4M) decreases the release of carbamazepine from matrix tablet containing cocrystals of carbamazepine-succinic acid. However, it was also reported that the increase in concentrations of Soluplus and Kollidon VA/64 increases the release of carbamazepine from the same formulation (Ullah et al., 2015).

9.3.3 Manufacturing/Processing Related Factors

9.3.3.1 Methods Involve in Manufacturing

Wet granulation, in general, is observed to enhance the rate of dissolution of poorly soluble drugs by imparting hydrophilic characteristics and improving the wetting properties of the drug (Wren et al., 2017). On the other hand, a sodium salicylate tablet prepared by direct compression method using spray-dried lactose revealed comparatively higher dissolution rate than those formulated by the wet granulation method (Singh and Van den Mooter, 2016).

9.3.3.2 Compression Force

The force applied by the tablet compression machines affects the hardness of the tablet. There exists a linear relationship between the hardness of the tablet and the compression force as suggested by Higuchi et al. (Higuchi et al., 1953; Higuchi et al., 1954). The higher tablet compression may enhance the particle bonding, increase the hardness and density, alter its porosity, and thus inhibits solvent penetration inside the tablet. This ultimately results in lowering the dissolution rate (Ferrero and Jiménez-Castellanos, 2014).

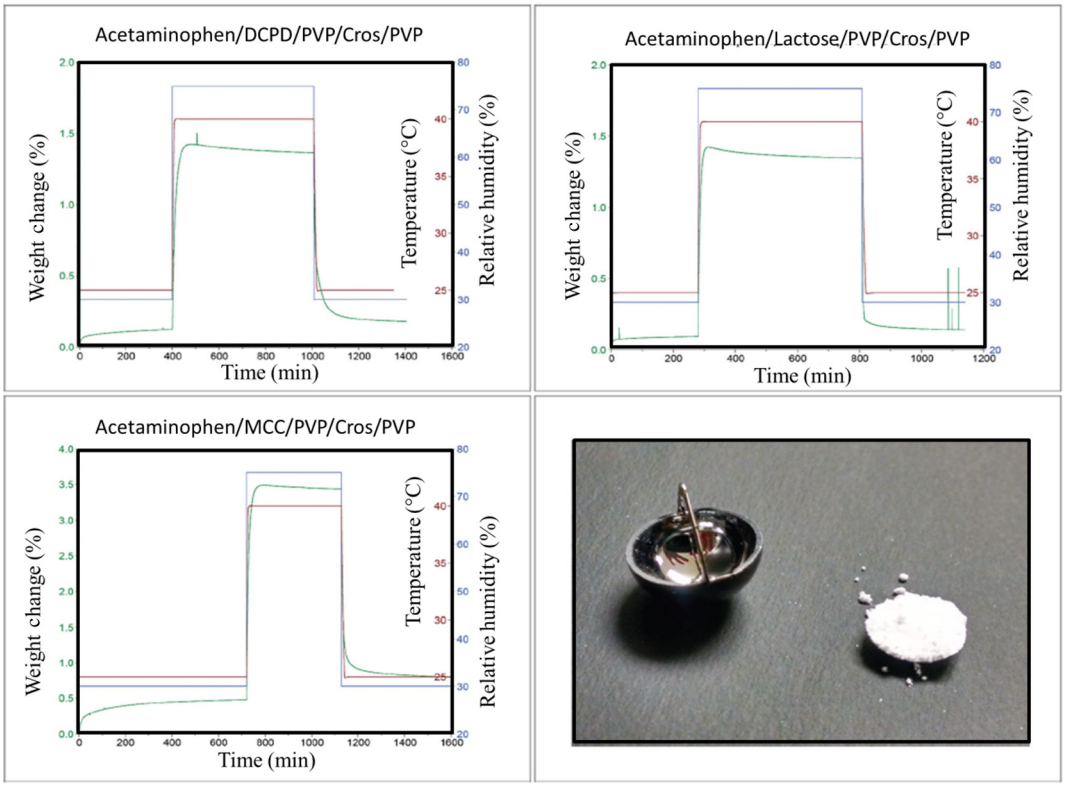

FIGURE 9.4 Water sorption uptake of selected acetaminophen tablets. When exposed to 25°C/30% RH then 40°C/75% RH then 25°C/30% RH, and photo of the DCPD/PVP/CrosPVP precompression blend after completion of the water sorption experiment. *Adapted with permission from Sacchetti, M., Teerakapibal, R., Kim, K., Elder, E., 2017. Role of water sorption in tablet crushing strength, disintegration, and dissolution. AAPS PharmSciTech 1–13.*

9.3.3.3 Moisture Content

Chowhan et al. established the relationship between drug dissolution and crushing strength (Chowhan and Chow, 1981) and found different varying levels of moisture content present in the granules during compression. In another study, it was found that the rate of dissolution of benazepril hydrochloride tablets decreases with an increase in moisture content. This study was performed by storing the tablets under varying conditions of temperature and humidity. Fig. 9.4 shows a photomicrograph of the acetaminophen/polyvinyl pyrrolidone (PVP)/dibasic calcium phosphate dihydrate/Cross PVP formulation after exposing it to 40°C/75% RH in the water sorption experiment.

The outcomes displayed a great enhancement in tablet crushing strength, where it was found that a solid mass was made after exposure to 40°C/75% RH. This mass was readily collapsed to a powder with slight pressure from a spatula. Formulations that did not strengthen remained a powder postexposure to 40°C/75% RH. It was also found that the increased moisture induces structural changes in benazepril hydrochloride tablet due to

preactivation of disintegrating agent that causes reduction in dissolution rate (Sacchetti et al., 2017). The same type of results were obtained in another experiment in which the exposure of delavirdine mesylate tablets to increased humidity conditions resulted in significant reduction in the extent of dissolution (Nie et al., 2017). These studies suggest the control of processing conditions during the manufacturing process and the use of advanced packaging technology should be used to avoid the exposure of moisture in the formulations.

9.3.3.4 Machine

The equipment used in various unit operations of drug product manufacturing sometimes markedly influence formulation properties. It was evident by the study which compared the preparation of granules with low porosity by high speed shear mixer to those made by planetary mixer with high porosity. More porous granules may show improved dissolution by facilitating solvent penetration (Reddy et al., 2017).

9.3.4 Dissolution Testing Conditions Related Factors

9.3.4.1 Dissolution Apparatus

9.3.4.1.1 AGITATION

Agitation forces prevailing in the dissolution apparatus affects the stationary diffusion layer and can markedly affect diffusion-controlled dissolution. The shear forces applied by the dissolution medium affect the thickness of the stagnant layer, thereby influencing the dissolution. High agitation rates can possibly increase the drug dissolution (Jug et al., 2017). In a study, the effect of agitation has been investigated on FDA approved drugs (USP specifies 100 rpm paddle speed). The results of the dissolution test conducted at variable paddle speeds of 50, 75, and 100 rpm indicate that, an increase in the rate of agitation from 50 to 75 rpm enhances the rate of dissolution. However, with the augmentation of agitation rate from 75 to 100 rpm no considerable changes in dissolution rate has been observed (Seeger et al., 2015). In another research, it was demonstrated that the effect of agitation also depends upon the position of the tablet in the dissolution vessel, owing to variation in the agitation force intensity at distinct locations inside the dissolution vessel (Todaro et al., 2017).

9.3.4.1.2 VIBRATION

Vibration may influence the dissolution process by altering the hydrodynamics of the dissolution media around the solute. Vibrational forces may be produced and transferred by several sources like walls, partitions, motors, other laboratory machines, operators, etc. High intensity vibrations may alter the diffusion layer and considerably influence the dissolution outcomes. Effects of vibration on the dissolution rate of Prednisone tablets have been reported in an investigation. It was also observed that the influence of vibration on drug dissolution depends upon multiple factors like properties of the drug, formulation factors, and type of dissolution method selected (Seeger et al., 2015). Marked influence of vibration induced by the laboratory scale mixer on the dissolution of disintegrating prednisone tablets was observed on USP basket as well as paddle-type apparatus.

9.3.4.1.3 FLOW PATTERN NONUNIFORMITIES

Variable flow rates of the dissolution medium have been observed at different sites inside the dissolution vessel. The difference in flow rates in the center of the vessel and near the wall and bottom of the vessel can possibly modify the dissolution profile of the formulation. Experimental findings have revealed variable flow patterns in the USP dissolution apparatus II, particularly at the bottom of the dissolution vessel where the tablet is mostly positioned during dissolution test (Wlodarski et al., 2015).

9.3.4.1.4 ECCENTRICITY OF AGITATING (STIRRING) ELEMENT

Any minute deviation in the circularity of rotation of the central shaft in the dissolution vessel may affect the dissolution rates. As per the standard and officially documented procedures the rotation of the shaft in the dissolution apparatus must be smooth and devoid of any considerable wobble. As per USP XX/NF XV the permissible limit of eccentricity is not more than ± 2 mm from the axis of dissolution vessel, with a condition that it does not considerably influence the dissolution rate (Ameur, 2016).

9.3.4.1.5 SAMPLING PROBE POSITION AND FILTER

Probes used for sampling in the dissolution process may alter the flow system of the dissolution medium and possibly cause considerable changes in dissolution rate. Experimental findings also revealed the differences in results obtained using automatic probe samplers and those acquired from manual sampling. USP/NF specifies that the sampling from the vessel must be done from the region halfway between the dissolution medium surface and the top of the rotating basket or paddle and minimum 1 cm from the vessel wall. Results of an investigation reveal the impact of size of the sample probe as well as location on the rate of dissolution of prednisone tablets. It was found that the large probe induces hydrodynamic variation which results in considerable changes in location-specific dissolution rates as compared to manual sampling (Bredael et al., 2015).

9.3.4.2 Dissolution Test Parameters

Parameters like pH, viscosity, temperature, components, volume, and nature of the dissolution medium may have considerable effects on the dissolution profile of a drug. These parameters might influence the diffusion coefficient of the solute (Miller, 1924). Stokes describes the effect of temperature and viscosity on the diffusion coefficient by the following equation (9.1):

$$D = kT/6\pi\eta r \tag{9.1}$$

where k is the Boltzmann constant, T is the temperature, η is the viscosity of the solution, and r is the radius of a molecule in solution. It is clearly indicated from the equation that the diffusion is directly proportional to the temperature and inversely proportional to the viscosity. The specification for the temperature of dissolution medium as per USP/NF is $37 \pm 0.5^{\circ}$C which must be maintained in dissolution testing of oral dosage forms and suppositories.

An important parameter, i.e., pH, of the medium also significantly influences the dissolution kinetics of the drug. For weak acids, the rate of dissolution enhances with a rise in pH. However, in the case of weak bases, the rate of dissolution increases with a drop in

pH. For the maintenance of sink conditions, around 1 L of dissolution medium is generally taken in a single vessel. Some additional factors that possibly influence the results of the dissolution include adsorption, water sorption (of drug or excipients), humidity, and detection errors in the analytical method (Dressman and Reppas, 2016).

9.4 PHYSIOLOGICAL FACTORS AFFECTING *IN VIVO* DRUG DISSOLUTION RATE

Dissolution of pharmaceutical formulations is of paramount importance, as it is a prerequisite for a dosage form to get dissolved in the GI fluids before being absorbed. Several physiological factors are known to affect dissolution as well as absorption of the drugs. The most common physiological factor includes the composition, pH, temperature buffer capacity, viscosity, osmolality, and hydrodynamics of GI fluid. Apart from the nature of GI fluid, some other factors that may affect the drug dissolution include mean residence time, gastric emptying, the presence of luminal enzymes, intestinal motility, hydrodynamics, and shear rates, etc.

9.4.1 Composition of GI Fluid

GI fluid is composed of liquid as well as solid materials. The liquids like water, gastric acid, electrolytes, and ingested fluids are commonly present along with viscous materials like mucus and swallowed saliva. Ingested solid food materials are also present in the GI fluid (Fuchs and Dressman, 2014). Hydrogen ion concentration of the gastric fluid influences the pH and ultimately affects the dissolution of ionizable drugs. Pepsin present in the gastric fluid can affect the stability of peptide and protein. Presence of lipase may interfere with the release of drug from lipid-based formulations. Bile salts are another important component of gastric fluid that can act as a surfactant. Bile salts along with lipids tend to form micelles that may increase the wetting and solubility of drugs. Fluids present in the small intestine contain pancreatic secretions like bicarbonate, amylases, proteases,and lipases (Ashford, 2017).

Food is a variable component of the composition of GI fluid which results in varied values of the other physiological factors in the fed and the fasted condition. Variation in bioavailability of some drugs in the fed and fasted condition reveals the importance of food as an important component of GI fluids.

9.4.2 pH

Variable pH values were reported throughout the entire length of the GI tract. Degradation of drugs owing to the pH-dependent hydrolysis may be possible in the GI tract. In the lumen also, the pH may affect the dissolution and absorption of some drugs if they are weak electrolytes. The marked effect of the pH on the solubility of weak electrolytes was also reported (Qiu et al., 2016). Influence of pH in dissolution profile of ketoconazole tablets was studied. It was found that the increase in pH decreases the dissolution rate as well as the extent.

TABLE 9.2 Compositions of Various Types of Gastric and Intestinal Fluids

S. No.	Type of Fluid	Compositions
1.	FaSSGF	Sodium taurocholate. . .80 μM
		Lecithin. . .. . .20 μM
		Pepsin. . .. . .0.1 mg/mL
		Sodium chloride. . .. . .34.2 mM
		Hydrochloric acid. . .. .. .q.s. *ad* pH 1.6
2.	FeSSGF	Sodium chloride. . .. . .237.06 mM
		Acetic acid. . .. . .17.12 mM
		Sodium acetate. . .. . .29.75 mM
		Milk/buffer. 1:1
		Hydrochloric acid. . .. .. .q.s. *ad* pH 5
3.	FaSSIF	Sodium taurocholate. . .. .. .3 mM
		Lecithin. . .. . 0.75 mM
		NaH_2PO_4. . .. . .3.9 g
		KCl. . .. . .7.7 g
		NaOH. . .. . .q.s. *ad* pH 6.5
		Deionized water. . .. . .q.s. *ad* 1 L
4.	FeSSIF	Sodium taurocholate. . .15 mM
		Lecithin. . .. . .3.75 mM
		Acetic acid. . .. . .8.65 g
		KCl. . .. . .15.2 g
		NaOH. . .. . .q.s. *ad* pH 5.0
		Deionized water. . .. . .q.s. *ad* 1 L

FaSSGF, fasted-state simulated gastric fluid; *FeSSGF*, + fed-state simulated gastric fluid; *FaSSIF*, fasted state simulated intestinal fluid; *FeSSIF*, fed state simulated intestinal fluid.

9.4.3 Buffer Capacity

The rate of dissolution of the ionizable drugs can be affected considerably owing to the buffer capacity of the fluids present in the GI tract. High buffer capacity may account for the resistance in pH change at the interface between drug and fluid. This may ultimately influence the rate of dissolution of the ionizable drugs (Augustijns et al., 2014).

9.4.4 Osmolality

A number of electrolytes present in the lumen explains the osmolality of gastric fluids (Cl^-, Na^+, K^+, Ca^{2+}; Table 9.2). Osmolality may influence the release profile as well as the dissolution of the drug. Various studies on osmolality were reported to have a significant influence on the dissolution profile (Walsh et al., 2016; Ali et al., 2017).

9.4.5 Surface Tension

Surface tension can affect dissolution by influencing wetting of the dosage form, with a higher surface tension leading to decreased wetting (Yuan and Lee, 2013). Gastric surface tension values in the fasted and fed states range from about 41−46 and 30−31 mN/m, respectively (Xie et al., 2014). In the upper small intestine, surface tension values range from 28−46 mN/m in the fasted state, and 27−37 mN/m in the fed state (Verwei et al., 2016).

9.4.6 Viscosity

The viscosity of the GI fluids depends upon the type and amount of food ingested. Generally the viscosity of the fluids in the GI tract increases in the fed state. Prolonged gastric emptying and GI transit time has been reported with the enhanced viscosity of GI fluids (Van Den Abeele et al., 2017).

9.4.7 Temperature

The temperature of the GI fluids may influence the rate of dissolution. The solubility and diffusion coefficient of the drug may be affected by the variation in the temperature. The GI tract temperature at resting state was reported to be 37°C. This temperature may increase after a physical workout or in the disease condition (Savjani et al., 2012).

9.4.8 Volume

The rate and extent of dissolution of the drug as well as absorption depends on the volume of water in the GI fluids especially in the stomach and small intestine (Mudie et al., 2014). The dissolved drug concentration mainly depends upon the volume of the GI fluids.

9.4.9 Hydrodynamics

Marked effects of GI motility on the hydrodynamics of GI contents, intestinal transit, and gastric emptying time have been reported (Guerra et al., 2012). These contractile motions exert forces on the GI content in which the drug is present and thereby may affect its dissolution rate in multiple ways. These forces may break the drug aggregates and lead to an increase in the effective surface area, an increase in the agitation forces so as to enhance the solubility of the drug in the GI contents, resulting in increased drug dissolution rates. These motility forces may also reduce the thickness of the static diffusion layer. In an investigation, hydrodynamics of the dissolution medium was reported to affect the mass transfer and

dissolution rate of theophylline and naproxen conventional release tablets. Also, variations in hydrodynamics of the dissolution medium have been observed in an experiment which is affected by the surface and location of the cylindrical tablet. The change in fluid velocity at specific regions thus influences the dissolution rate (Shekunov and Montgomery, 2016).

9.4.10 Gastric-Emptying Rate and Forces

Gastric emptying generally refers to the rate at which the contents of the stomach exits into the small intestine. The rate-determining step in the absorption of fast dissolving drugs from immediate release dosage forms can possibly be gastric emptying. Several factors influencing the gastric emptying rate include the quantity of ingested food, the nature of ingested food, and the contraction phase at which the food was taken. The gastric emptying time also influences the contact time of the drug with GI fluids at specific pH, and thus may affect the dissolution of drugs which get preferentially dissolved in the stomach (Koziolek et al., 2015).

9.4.11 Concomitant Use of Antisecretory Therapy

Dissolution and absorption profile of the different formulations of levothyroxine have been investigated on the patients taking proton pump inhibitors. The experimental results suggest that the dissolution rate of the tablet formulation was reduced and the intestinal absorption of levothyroxine was altered owing to the increase in pH by PPI as compared to control. However, the effect of increased pH on drug dissolution and absorption has not been observed in the case of the oral solution of levothyroxine (Vita et al., 2014; Brancato et al., 2014).

9.5 DISSOLUTION TESTING

Dissolution testing is a tool used to measure the release of drug from the dosage form. It is the most important method used in all phases of drug development.

9.5.1 Approaches for Dissolution Test Method Design

Dissolution test method is either discriminatory for QC purposes or biorelevant for IVIVC purpose. A balance is needed to be maintained between the two approaches. If the method is over discriminatory, the result is wasted and delays in development of new products to meet unmet needs, and if it is under discriminatory, it results in a lack of meaningful product quality control (Lawrence et al., 2014).

9.5.2 Design of Dissolution Method

When developing a dissolution method, it is important to take a logical, systematic approach to the process, and ensure that all the scientifically and regulatory guidelines

given are borne in mind. A robust methodology should be free of significant interferences (e.g., matrix effects due to excipients), give low variability (precision), and produce a good profile shape. The methodology must also be challenged to distinguish amongst batches of material with varied quality attributes. Once the process of identifying suitable medium and apparatus are complete, further optimization of the method would be required to evaluate ionic strength of the medium, agitation rate, and, if required, surfactant concentration. The final developed method should have the ability to discriminate between different formulations/batches, but still maintain acceptable precision and robustness. With regards to precision, typical limits for early and later time-points would be <20% and <10% RSD, respectively. In special cases, like modified release or fixed-dose combination products, the relevant variations are done to the basic design of the method (Ashokraj et al., 2016).

9.5.2.1 Choice of Dissolution Equipment

Different designs of dissolution apparatus are important requirements due to variable physicochemical properties of different drug products (Mann et al., 2017). Various types of USP apparatus are available in pharmacopoeias, the most common amongst them are Basket type (USP apparatus I), paddle type (USP apparatus II), reciprocating cylinder type (USP apparatus III), and flow through cell type (USP apparatus IV). If we need to use different types of dissolution medium simultaneously then a reciprocating cylinder type apparatus should be used. Flow through cell type (USP IV) is beneficial in overcoming the nonsink conditions. This apparatus IV is also advantageous in providing better IVIVC due to comparable hydrodynamic flow patterns of dissolution medium (Forrest et al., 2017).

USP Dissolution Apparatus

USP 1: This is a small basket attached to the shaft that contains the sample. The shaft and basket spin inside the test media.
USP 2: This is the most common form of dissolution testing, where a flat paddle is attached to the shaft and spins in the test media.
USP 3: This where the use of a reciprocating cylinder is employed. A sample is placed inside a glass tube with a mesh base and moved up and down in the media vessel.
USP 4: This is where the sample is placed inside a static cell, called a flow-cell, and the test media is pumped through the cell in a continuous flowing motion, often referred to as flow-through. You can have different cells for different sample types.
USP 5: This is the paddle-over-disk method. A USP 2 paddle is attached to the shaft, and a mesh disk is fixed beneath the media vessel. The sample is placed beneath the disk, holding it in place.
USP 6: This is the use of a rotating cylinder. Often a patch is stuck to the outside of the cylinder, which is attached to the shaft and spins.
USP 7: This is the reciprocating disk method. A disk is attached to the shaft which is raised and lowered in the test media. The sample placed above the disk (Vaghela et al., 2011).

9.5.2.2 Selection of Agitation Rate

The rotational speed is also an important parameter that needs to be appropriately controlled. Very low agitation speed may cause coning and lead to very slow dissolution (Higuchi et al., 2015). To avoid this issue, a faster rotation speed can be used. The high rate of agitation speed may also be problematic due to inability to distinguish amongst acceptable and nonacceptable batches. Rotational speeds in the range 50−100 rpm are validated to be appropriate for the paddle method. If the basket method is to be used, a rotational speed of up to 150 rpm may be appropriate, as the linear velocity generated in the vessel is considerably lower for a given rotational speed for the basket than for the paddle. Rotational speeds in these ranges should also be appropriate for quality control tests (Shohin et al., 2016).

9.5.2.3 Dissolution Medium

For selecting the dissolution medium, the most important factor to be considered is the solubility data of the product and dosage regimen to maintain the sink conditions. Oral formulations should be analyzed firstly at the physiological pH range. The selection of medium also depends upon the stability of drug product in the medium and relevance of *in vivo* performance. For poorly aqueous soluble compounds, surfactants can be used to maintain the sink condition and improve the aqueous solubility of those drug products (Shohin et al., 2016; Lawrence, 2012).

9.5.2.4 Analytical Methods Associated With the Dissolutions

UV and HPLC are the most commonly employed methods used to analyze the results of dissolution. With the advancement of analytical equipment, those techniques nowadays are replaced with UPLC or RR LC methods. HPLC is the method of choice in most cases as it is also beneficial in separating and detecting the degradation products. The equipment and methods employed for analyzing the results should be qualified and validated by following the standard guidelines.

9.5.2.5 Automation

Automation of the dissolution methods not only helps in increasing the efficiency of methods but is also beneficial in reducing the manual errors. The fully automated system can free the dissolution scientist from 90% of the protocol steps in the laboratory as it is equipped with functional and mechanical automation (Al-Gousous and Langguth, 2015).

9.5.2.6 Data Simulation

Various simulation tools like DDD plus are used as surrogates for dissolution testing. It enhances product understanding to help with risk assessment process and offer some mitigation options to increase speed in product development to allow for developing a clinically relevant dissolution specification strategy. This technique can be used in dissolution modeling and surrogate testing to achieve real-time release testing for dissolution. GastroPlus is also one of the most commonly used software for analyzing the dissolution data (Khurana et al., 2017).

9.6 DISSOLUTION PROFILE: ANALYSIS AND COMPARISON

Dissolution testing for immediate release drug products could be a single point or two point/multipoint analysis. The quality of drug product is ensured by performing the multipoint dissolution analysis, especially for poorly water-soluble products (Wang et al., 2016).

9.6.1 Dissolution Profile

The percentage of drug dissolved against various sampling time points are plotted. This plot can be termed as dissolution profile and gives a complete understanding of *in vivo* release characteristics.

9.6.2 Analysis of Cumulative Dissolution Profiles

Various theories are proposed for dissolution profile analysis. Wagner's theory interprets the results of plots because drug products follow first-order kinetics under sink conditions (Wagner, 1969). Kitazawa's theory interpreted the results in the form of a straight line with two phases. The first phase suggests the disintegration or disruption of the drug product, while the second phase suggests the initiation of dissolution process (Kitazawa et al., 1977). Another approach is of Carstensen, which generated the skewed S-shaped curves followed by log-normal distributions. This curve gives the idea about the initial lag phase of the dissolution process (Carstensen et al., 1978).

9.7 *IN VITRO-IN VIVO* CORRELATION (IVIVC)

9.7.1 Definition

The Food and Drug Administration (FDA) defines IVIVC as "a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and an *in vivo* response."

Various models have been proposed to predict the data observed by *in vitro* investigation to *in vivo* performance (Rohn, 2014). The IVIVC studies aimed to employ drug release kinetics from two or more formulations to correlate anticipated drug-plasma profile (Somnath, 2016). More exhaustive details have provided in the following subsections dealing with the significance and purpose of IVIVC.

9.7.2 Significance and Purpose of IVIVC

Pharmaceutical product development required IVIVC to establish the release characteristics. IVIVC is also employed as an alternative for *in vivo* experiments in similar conditions (Kesisoglou et al., 2015b). However, even minor changes done in any process variable, demands the establishment of IVIVC making the process highly time consuming as well as expensive (Masaad et al., 2016).

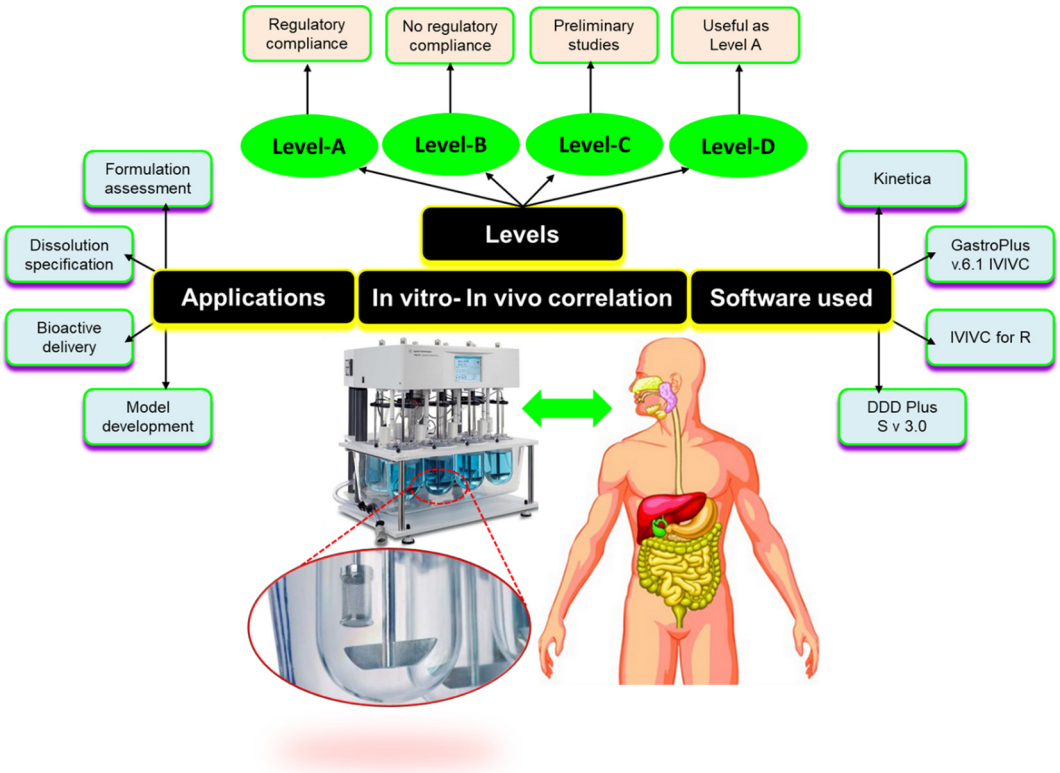

FIGURE 9.5 Schematic representation of various aspects of IVIVC. IVIVC works in various levels of correlation from Level A to Level D. Level A correlation represents maximum degree of correlation and most preferred type of correlation; Level B correlation compares *in vitro* dissolution rates within vivo residence period and does not gives information about *in vivo* plasma profile; Level C correlation is the weakest level of correlation as it involves only a partial relationship between absorption and dissolution and does not represent the complete plasma drug profile; Level D correlation is a qualitative type of correlation and not beneficial for regulatory purposes.

The formulation optimization may need to alter the percentage of compositional materials, formulation processing strategy, machines used to manufacture, and batch sizes. This leads to putting extra efforts for bioequivalence testing with an optimized formulation. IVIVC serves as an index to justify the therapeutic effectiveness of the formulation (Somayaji et al., 2016). A schematic presentation of IVIVC including classification, levels, software used, and applications is depicted in Fig. 9.5.

9.7.3 Levels of IVIVC Correlation

With IVIVC of global dissolution time characteristics we are faced with a situation in which each of several different formulations must be tested, not only in an *in vitro* dissolution system but also, and even more importantly regarding effort and expense, in humans (Margolskee et al., 2016).

9.7.3.1 Level A Correlation

It involves correlation amongst complete *in vitro* and *in vivo* profiles. Level A correlation is most preferred in pharmaceutical industries due to its regulatory relevance. Due to its industrial applicability and regulatory significance, this type of correlation represents a maximum degree of correlation. It involves point-to-point relation amongst *in vitro–in vivo* dissolution data and drug release kinetic data from the pharmaceutical product. Another aspect of Level A correlation is that it permits a biowaiver to alter a manufacturing site, raw product vendors, and minute modifications in the formulation (Mittapalli et al., 2017).

9.7.3.2 Level B Correlation: The Statistical Moment Theory

This correlation follows the principles of statistical moment analysis. It involves the comparison between *in vitro* dissolution rates of the formulation with an *in vivo* residence period. In contrast to Level A IVIVC, it does not give information about the *in vivo* plasma profile. Moreover, this type of correlation does not attribute to the quality standards as per the regulatory guidelines (Gelman et al., 2014).

9.7.3.3 Level C Correlation

This is the weakest level of correlation as it involves the only partial relationship between absorption and dissolution and does not represent the complete plasma drug profile, which is very important to define the behavior of a drug product. This type of correlation shows the relation between dissolution and pharmacokinetics, but it is limited to one pharmacokinetic parameter only.

9.7.3.4 Multiple Level C Correlations

This multiple correlation is important in justifying the biowaiver. This correlation establishes the relationship between one or more parameters related to pharmacokinetics with the dissolution. This correlation shows the relationship by multiple dissolution time points (more than three) such as in early, mid, and late stages of the product development (Kesisoglou et al., 2015a; Shen and Burgess, 2015).

9.7.3.5 Level D Correlation

It is a qualitative type of correlation and not beneficial for regulatory purposes. This type of correlation is helpful only in assisting the product development of a formulation.

9.7.4 Applications of IVIVC

9.7.4.1 Application in Drug Delivery System

Most of the literature available suggest that IVIVC is extensively used for the product development of oral dosage forms. IVIVC is an excellent tool for the prediction of the drug release rate from numerous systems such as modified release system, controlled, sustained, extended, and delayed release systems (Dressman and Reppas, 2016; Andhariya and Burgess, 2016).

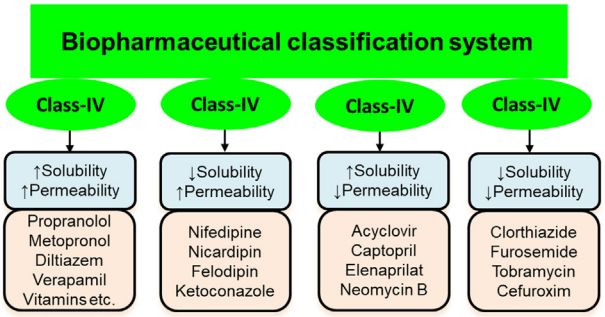

FIGURE 9.6 Illustration of various classes of biopharmaceutical classification system. Class I represents the maximum solubility and maximum permeability class; Class II—maximum permeability but minimum solubility; Class III—maximum solubility but minimum permeability and; Class IV—minimum solubility and minimum permeability.

9.7.4.2 Pharmaceutical Product Development

One of the important requirement for product development is the selection of an appropriate drug molecule, and this selection depends on the drug "developability," involving understanding its physicochemical characteristics.

9.8 BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS) AND BIOPHARMACEUTICAL DRUG DISPOSITION CLASSIFICATION SYSTEM (BDDCS)

The biopharmaceutical classification system (BCS) is a scientific tool to classify drugs and depends on the solubility and intestinal permeability of drug molecules. The principle of the BCS says that if two products produce the similar concentration data along the GIT, they will exhibit the same plasma profile after oral administration. In context to bioequivalence, it assumed that drugs with high permeability, high solubility prepared as fast dissolving products will be bioequivalent. Unless significant alterations are made to the formulation, dissolution data can be employed as a surrogate for pharmacokinetic data to show the bioequivalence of two drug products (Mitra et al., 2015).

9.8.1 BCS Classes and Parameters

According to the BCS, drug candidates are classified as follows (Fig. 9.6).

Class 1: High Solubility—High Permeability
Class 2: Low Solubility—High Permeability
Class 3: High Solubility—Low Permeability
Class 4: Low Solubility—Low Permeability

The reason behind the difference in *in vivo* profiles of two dissimilar products resides in the differences in drug dissolution *in vivo*. However, when the *in vivo* dissolution of an IR solid oral dosage form is rapid or very rapid in relation to gastric emptying and the drug has high solubility, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or GI transit time (Khan et al., 2016). In these

conditions, the performance of *in vivo* bioavailability or bioequivalence may not be necessary for drug products containing class 1 and class 3 drugs, as long as the inactive ingredients employed in the dosage form do not significantly affect absorption of the active ingredients (Kubbinga et al., 2014).

Dose number (Do) may be defined as the mass divided by the product of uptake volume and solubility of the drug or it may be regarded as the volume required for solubility of the maximum dose strength of a drug (Eq. 9.2).

$$DO = \frac{M}{V \cdot Cs} \tag{9.2}$$

where, M = highest dose strength (milligrams), Cs = Solubility (milligrams/milliliter), V = 250 mL (Qiu et al., 2016).

Dissolution number (D_n) can be defined as the ratio of the mean residence time to mean absorption time and can be evaluated concerning the time required for drug dissolution, which is the ratio of the intestinal residence time and dissolution time (Eqs. 9.3 and 9.4).

$$D_n = T_{sit}/T_{diss} \tag{9.3}$$

$$D_n = 3DC_s(T_{sit})/r^2 d \tag{9.4}$$

where D = diffusivity, d = density, r = initial particle radius, T_{sit} = intestinal residence time, T_{diss} = dissolution time (Klutz et al., 2015).

Absorption number (A_n) may be defined as the time required for absorption of the dose administered which is a ratio of mean residence time to mean absorption time of drug (Eq. 9.5).

$$A_n = T_{sit}/T_{diss} = P_{eff}(T_{sit})/r \tag{9.5}$$

where, P_{eff} = permeability, r = gut radius.

BCS Class I compounds (e.g., metoprolol) shows high absorption number (A_n) and a high dissolution number (D_n), signifying that the rate-determining step for drug absorption is possibly dissolution. Class I compounds are generally well absorbed if they are stable or are not affected by the first-pass effect. For immediate-release products of Class I compounds, the absorption rate is likely to be dominated by the gastric emptying time, and no direct correlation between *in vivo* data and *in vitro* dissolution data is expected. Therefore, dissolution analysis for such drug products should be designed chiefly to predict that the drug is released quickly from the dosage form under the particular test conditions. A dissolution specification for which 85% of drug contained in the IR dosage form is dissolved in less than 15 min may be sufficient to ensure bioavailability since the mean gastric half-emptying time is 15–20 min (Papich and Martinez, 2015).

A Class II drug, for example, phenytoin, possesses a high absorption number (A_n) and a low dissolution number (D_n). Dissolution is the rate-limiting step for drug absorption. The influence of dissolution on the absorption of BCS Class II drugs can be classified into two scenarios: solubility-limited absorption or dissolution-limited absorption. These two scenarios are best illustrated by griseofulvin and digoxin. In the case of solubility-limited absorption, griseofulvin exhibits a high dose number (D_o) and a low dissolution number (D_n). Although in theory, absorption of griseofulvin can be

improved by taking more water with the administered dose (decreasing D_o), this approach is impractical due to the limitation in the physiological and anatomical capacity of the stomach for water.

Therefore, the only practical way to improve the absorption of griseofulvin is to decrease D_o and increase D_n by enhancing its solubility through appropriate formulation approaches such as solid dispersion (Stiehler et al., 2015). On the other hand, in the case of dissolution-limited absorption, digoxin has a low dose number (D_o) and a low dissolution number (D_n). Despite the small volume (21 mL) of fluids required to dissolve a typical dose of digoxin (0.5 mg), this drug dissolves too slowly for the absorption to take place at the site(s) of uptake. However, its dissolution rate can be improved simply by increasing D_n through the reduction in particle size. Thus, for BCS Class II drugs, a strong correlation between *in vitro* dissolution data and *in vivo* performance (e.g., Level A) is likely to be established. When a BCS Class II drug is formulated as an extended-release product, an IVIVC may also be expected.

For BCS Class III drugs (e.g., cimetidine), permeability is likely to be a dominant factor in determining the rate and extent of drug absorption. Hence, developing a dissolution test that can predict the *in vivo* performance of products containing these compounds is generally not possible. Since BCS Class IV drugs, which are low in both solubility and permeability, present significant problems for effective oral delivery, this class of drugs is generally more difficult to develop in comparison to BCS Class I, II, and III drugs (Sandri et al., 2014).

9.8.2 Biopharmaceutical Drug Disposition Classification System (BDDCS)

It divides compounds into four classes based on their permeability and solubility. This classification system is useful in predicting effects of efflux and uptake transporters on oral absorption as well as on post absorption systemic levels following oral and intravenous dosing. Wu and Benet recognized that for drugs exhibiting high intestinal permeability rates, the major route of elimination in humans was via metabolism, (e.g. the BCS/BDDCS Class 1 drug letrozole) whereas drugs exhibiting a poor intestinal permeability rate were primarily eliminated in humans as unchanged drug in urine and bile, and they termed this as Biopharmaceutics Drug Disposition Classification System (BDDCS) (Camenisch, 2016).

9.9 ROLE OF DISSOLUTION TESTING IN PHARMACEUTICAL PRODUCT DEVELOPMENT

Product development is a prolonged, arduous, and expensive task with high risk of failure. The pharmaceutical companies spend hundreds of millions of US dollars on research and development, and it takes around 12 to 14 years for the processes of “discovery” and clinical trials from the laboratory to end consumers (patients). Only one-tenth of the drugs entering the preclinical phase could actually reach the clinical phase. Further, regulatory approval is the utmost requirement to bring a drug to market. Regulatory requirements

have definitely up scaled the cost of pharmaceutical research and development. So, there is always a need to reduce the regulatory burden and minimize the time and cost involved in drug development (Pocock, 2013).

Dissolution testing vexes the scientific, technical, and regulatory challenges related to drug development complexities. The major contribution of dissolution testing in Pharmaceutical Product Development includes making the product development process cost-effective and less time-consuming in two ways: reducing the regulatory burden at drug approval and postapproval stages and minimizing the probability of end product failure. Dissolution testing helps to reduce the regulatory burden by acting as a surrogate for *in vivo* product performance, by developing *in vivo* predictive *in vitro* dissolution methods, developing IVIVC, by using BCS, IVIVC as a criterion to waive the bioequivalence studies, predicting drug bioavailability and drug metabolism. The latter is achieved by routine use in QC to ensure batch to batch uniformity and product quality, in research and development, to develop, optimize, and assess the new drug product by QbD, monitoring critical manufacturing variables, and examining the stability of the formulation (Allen and Ansel, 2013).

9.9.1 Pharmaceutical Product Development Phases

As depicted in Fig. 9.7 (Scheubel, 2010), dissolution testing is a necessary part at each stage of the drug development process from nonclinical to postmarketing, performing essential functions like drug selection, formulation selection, method optimization, IVIVC prediction, biowaiver assessment, quality, and stability checks.

9.9.1.1 Drug Product Approval

Pharmaceutical product development cycle includes various stages, and at each stage, dissolution testing performs significant functions.

Investigational New Drug Application (IND)—The application requires data of experiments done on laboratory animals and how clinical trials are planned. Dissolution testing enhances lead formulation quality by salt selection as per BCS and screens out poor-performing prototypes and saves animal resources (Guarino and Guarino, 2016).

Institutional Review Board (IRB) drafts the clinical trial protocols comprising of four phases.

Phase I trials test for safety. Dissolution testing performs various functions at phase 1 level, like designing phase I formulation, salt selection of drug substance, examining excipient compatibility, choosing toxicology formulations, and maintaining quality standards for the first clinical drug administration. This helps to identify formulations with improved dissolution characteristics (He et al., 2017).

Phase II trials test for effectiveness in addition to further safety monitoring. The final dosage form to be tested in phase III studies is ascertained at this level. Dissolution testing can be carried out to serve many important roles at this stage, which include process and product development, a link establishment between design space and the target product profile, elucidation of the drug-release mechanism, regulation of the

FIGURE 9.7 Various applications of dissolution testing in various phases of product development. Blue color showing initial phase and orange color showing late phase development; black color is for market; red arrows show interplay of dissolution and black arrows show the interaction between the different development phases.

variations in drug product stability testing, and maintenance of batch release quality, as well as batch-to-batch uniformity (Blessy et al., 2014).

Phase III includes joint working of the FDA and the drug's sponsor to set the phase III study protocol and determine risk–benefit data. The phase III drug development stage has the main purpose to develop in-depth expertise and robust data regarding the drug product and the manufacturing process for filing drug approval dossiers, to commence the stability studies, and to prepare for effective and profitable product launch. Dissolution testing at this stage serves as a surrogate for *in vivo* bioavailability or bioequivalence, as a tool to project the drug product's clinical

performance, and is used for process development and optimization, as well as quality control testing.

Further, the application review is at the discretion of the FDA under New Drug Application.

Phase IV trials are conducted to analyze the outcomes evolving after the drug approval and its large-scale use. Dissolution testing at this stage contributes to SUPAC or biowaiver dossier filling.

Dissolution testing also plays an important role in FDA's attempts to decrease the regulatory load and unneeded clinical studies in developing consistently high-quality, safe, and effective generic drugs without compromising the drug product quality. Similarity factor data for test drug and reference listed drug can be employed for this purpose.

9.9.2 Determining Drug Developability at Preformulation Stage

Besides being a quality control tool at the formulation stage, dissolution testing also performs some crucial roles at the preformulation level.

Drug candidate selection: drug developability

The complete journey of a drug molecule from thought to the market involves various steps. These are recognizing the target, selecting hit, optimizing hit, choosing lead and further optimizing it, recognizing candidate, and performing clinical trials. In this process, the number of compounds entering the clinical phase are very much fewer than the number of targets identified, almost one-tenth as mentioned earlier in the text. Further, the new screening technologies and automation quicken the process of lead identification and drug discovery. So, the concept of ensuring developability is used for drug candidate selection which focuses on all functional aspects (commercial, marketing, and medical) influencing the efficiency, success rate, and itinerary of a drug product development. This concept helps to set a target product profile with an aim to decrease the cost and time involved in the process (Aungst, 2017).

The examination of the physicochemical properties of a new chemical entity (NCE) is also important along with pharmacokinetic properties such as the half-life and oral bioavailability. This must begin early in the research and development phase. One of the most significant physicochemical properties is the aqueous solubility of a drug substance that governs dissolution rate and ultimately developability. The dissolution characteristics of the candidates are determined so as to ensure their intended performance and bioavailability potential. For this criterion, the solid-state form or the salt with the best solubility, dissolution rate, and stability characteristics should be preferred to enter the full development cycle (Han and Wang, 2016).

9.9.3 Simulation of Food Effects

The gastrointestinal tract exhibits changes in the environmental conditions with and without meals. Food intake is observed to have considerable impact on *in vivo* drug release

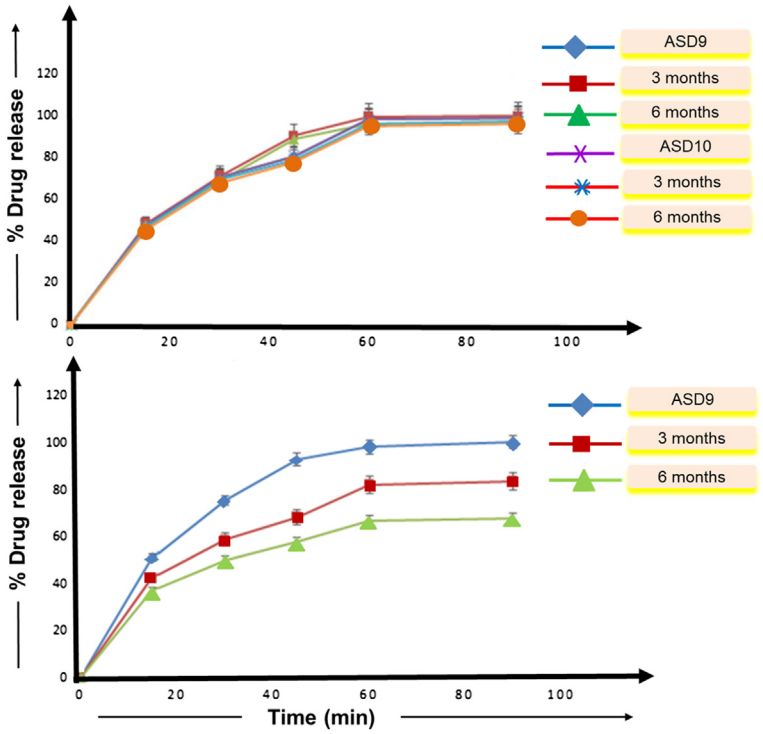

FIGURE 9.8 *In vitro* release profiles of optimized ASDs (top) and prototype ASDs (bottom) stored at 40°C and 75% RH on fresh extrudates and 3, 6 months stability. *Adapted with permission from Pawar, J., Tayade, A., Gangurde, A., Moravkar, K., Amin, P., 2016. Solubility and dissolution enhancement of efavirenz hot melt extruded amorphous solid dispersions using combination of polymeric blends: a QbD approach. Eur. J. Pharm. Sci. 88 (Supplement C), 37–49.*

and absorption and thus affecting drug performance *in vivo*. This necessitates the measurement of food-induced effects on the *in vitro* drug dissolution with an aim to minimize the potential risks during therapy. The physiological differences between fasted and fed state are particularly kept under consideration. Several attempts have been made to model the food-induced effects on drug dissolution by making use of bile salt and lecithin, pH changes, fat emulsions, such as intralipid or milk, well-defined nutritional drinks, enzymes, dynamic lipolytic models, presoaking in oil, viscosity enhancement. For example, an assessment could be performed in connection with an *in vivo* food interaction study to improve the interpretation of the bioavailability data obtained or be used more proactively to select the least-affected candidate formulation for further development. Thus, *in vitro* dissolution tests could clearly play an important role in predicting the influence of food on drug dissolution *in vivo* (Sjögren et al., 2014).

9.9.4 Determination of the Impact of Concomitant Use of Other Substances With Drug Product

The dissolution tests can be modified to determine the impact of other substances administered with a drug product. One of such tests is *in vitro* dose dumping in alcohol test as requested by NDA and for generic MR drug products with respect to RLD using differing amounts of ethanol (0%, 5%, 20%, and 40%) representative of liquor consumption

in 0.1 N HCl media. The purpose of this test is to monitor the potential of dose dumping of modified release drug products occurring due to being coadministered with alcohol. The polymers used for coating or matrix modified release drug products may solubilize in alcohol to varying extents undesirably which may raise serious safety concerns. Since the major portion of ethanol is absorbed through the gastric mucosa, 0.1 N HCl is selected as a baseline medium to proximate the gastric environment conditions. Dissolution data expressed as percentage dissolved is calculated for all strengths of the test product and the reference product using 12 units each (Paixão et al., 2017).

9.9.5 Dissolution as a Key Feature for Biopharmaceutical Approach in QbD

The goal of QbD is to use the recent pharmaceutical knowledge more efficiently throughout the lifecycle of a product to develop meaningful specifications. QbD contributes in establishing the relationships among raw material properties, formulation variables, and process parameters. The concept of integrating such criteria in the drug approval process is quite recent. QbD provides in-depth knowledge of the product properties. This aids in selecting a more justified dissolution method that may achieve the required IVIVR for drug release. In QbD, *in vitro* dissolution testing helps to associate the manufacturing/product design variables with clinical safety/efficacy (Sangshetti et al., 2017). QbD provides a high level of understanding of dissolution mechanisms and influence of pharmaceutical factors. It is a sequential process in which: quality target product profile (QTPP) (Design space) is described; accordingly, the product and method are designed with respect to all aspects affecting drug dissolution results; the appropriate risks to clinical quality are determined by performing Quality Risk Assessment (QRA); dissolution methods with relevance are developed; the correlation between alterations in manufacturing variables and the clinical quality is studied depending on dissolution data (inclusive of bioavailability/IVIVC, BCS data); and the dissolution characteristics ensuring clinical quality (as per design space) are established (Singh and Sharma, 2015; Bhoop, 2014).

Pawar et al. developed a Qbd-based approach to increase the dissolution profile of efavirenz, a BCS class II drug (Pawar et al., 2016). They utilized Soluplus and (Hydroxypropyl methylcellulose acetate succinate (HPMCAS-HF)) polymers to form anamorphous solid dispersion of efavirenz. The investigation revealed that the maximum dissolution rate when Soluplus and HPMCAS-HF were used was in a ratio of 60:20 as optimized by QbD. Also, the authors found that the optimized amorphous solid dispersion was stable at 40°C, 75% RH over a period of 6 months without any dissolution rate alteration, and remained in anamorphous state (Fig. 9.8).

QbD is an evolving process. The integration of QbD to the drug development process has been a little slow as it needs a good amount of time and work to collect enough data, especially in early development stages (Soans et al., 2016).

9.9.6 Prediction of *In Vivo* Dissolution: Biorelevant Dissolution Testing

9.9.6.1 Need of Bio-Relevant Dissolution Testing

Human gastrointestinal physiology is complex and dynamic, inclusive of various physiological factors that impact *in vivo* drug dissolution to a great extent. Conventional pharmacopoeial dissolution tests are mainly used for QC purpose, and their design primarily depends on drug substance's physicochemical properties and drug product characteristics. These methods utilize simple, nonphysiologic buffers and unrealistic hydrodynamic conditions (at times variable with extremely high fluid velocities). These shortcomings of the conventional methods need to be resolved if the results of these methods are to be used for the prediction of *in vivo* drug dissolution and absorption. The new innovative biorelevant dissolution methodologies shall thus be employed to bring close resemblance to the physiological environment in the gastrointestinal tract including major parameters like *in vivo* hydrodynamics, fluid content, etc.

The main purpose of employing biorelevant dissolution techniques is to develop more appropriate *in vivo–in vitro* correlation (IVIVC). This helps to improve the prediction accuracy of bioavailability from *in vitro* dissolution data. This provides more realistic assessment of licensed-in compounds, prevents potential development compounds from being falsely discarded, determines the potential for dosage forms with the modified release, renders QC tests more clinically relevant, and reduces the risk of failure in late-stage pivotal BE studies (Mann et al., 2017).

9.9.6.2 Development of Relevant Dissolution Test

The BCS class of the drug, depending on its solubility and permeability, indicates the site of residence and absorption of the drug in GIT (Beig et al., 2016). This further can help to interpret the time for which drug resides in a specific part of GIT, i.e., how the drug movement is across the stomach, intestine, and colon and what are the major and minor sites of drug dissolution *in vivo*. This can subsequently help to decide the composition and volume of the biorelevant media as well as agitation conditions of the biorelevant dissolution apparatus needed for the intended purpose. For example, the gastrointestinal environment pH and pH-dependent solubility of ibuprofen and ketoprofen (BCS Class II drugs; $pK_a \leq 5$ weak acid) lead to their absorption in higher amounts in the distal small intestine than in the proximal small intestine (Tsume et al., 2014).

Biorelevant dissolution test design is a systematic method to select dissolution conditions taking into consideration all the important physiological parameters like the composition of the gastrointestinal fluid, buffer capacity, pH, surface tension, osmolality, temperature, viscosity, hydrodynamics, gastrointestinal residence time, and gastric emptying rates and forces. It can be utilized to simulate gastric conditions, intestinal conditions, or colonic conditions (Koziolek et al., 2014).

Biorelevant dissolution test design (especially for immediate release drug products) can thus be understoodas

1. Classify the compound according to BCS.
2. Choose an appropriate medium.

Various dissolution media employed for QC and biorelevance purpose include simulated Gastric Fluid (SGF) (with and without pepsin), simulated intestinal fluid (SIF) (with and without pancreatin), fasted-state simulated gastric fluid (FaSSGF), fed-state simulated gastric fluid (FeSSGF), fasted state simulated intestinal fluid (FaSSIF), fed state simulated intestinal fluid (FeSSIF), blank fasted and fed (GF) and (IF), and others (such as Ensure Plus for forecasting food-effect). Compositions of various fluids are given in Table 9.2 (Riethorst et al., 2016). Many drugs are observed to have varied solubilities in all these media, e.g., ketoconazole, danazol, etc.

Class 1 drugs: The suitable media for class 1 drugs could be simulated gastric fluid without enzymes because of their good aqueous solubility and permeability through the gut membranes. More complex, biorelevant media (e.g., FaSSIF and FeSSIF) are unnecessary for dissolution of class 1 drugs.

Class 2 drugs: Class 2 drugs have poor aqueous solubility but are readily permeable through the gut membranes. The appropriate biorelevant media for class 2 drugs could be SGF plus surfactant, to mimic the gastric fasted state, Ensure or milk (3.5% fat) to mimic the gastric fed state, and the two newly developed media, FaSSIF and FeSSIF, to mimic fasted and fed state in the small intestine, respectively. Sometimes use of synthetic surfactants (tweens etc.) in dissolution media is observed in research as using the bile components (lecithin and bile salts) is practically inconvenient on a routine basis. Use of hydroalcoholic mixtures as dissolution media is also reported but less preferred due to physiological insignificance.

Class 3 drugs: A satisfactory IVIVC (level A, B, or C) is unlikely to be obtainable, and the membrane permeability is also a limiting factor to the absorption. So a simple aqueous medium can be used for quality assurance dissolution testing similar to class 1 drugs.

Class 4 drugs: Class 4 drugs have both poor solubility as well as poor permeability. Hence unlike class 3 drugs, they may not achieve complete bioavailability in most cases. Further, IVIVC is unlikely for class 4 drugs, so recommendations can be limited to quality assurance media. Those are the two-basic media SGF and SIF with the use of a surfactant to ensure total drug release in the stipulated media volumes.

Thus, for Class 1, 3 drugs use the most simple yet reliable media possible and addition of surfactants is unnecessary and for Class 2, 4 drugs biorelevant media are warranted for IVIVC SGFsp plus surfactant, FaSSIF (fasted state), Ensure, milk, FeSSIF (fed state), and for QC SGFsp/SIFsp plus suitable surfactant.

3. Choose an appropriate medium volume. In general, volumes for the fasted state will be lower than volumes for the fed state.
4. Choose an appropriate test duration and sampling times. Duration of the dissolution test should also be physiologically relevant based on BCS class of drug, transit times, prandial status and absorption site. Class 1, 3: short test (up to 30 min) with one-point sampling to verify that an appropriate amount (e.g., 90%) has dissolved. Class 2, 4: test duration depends on the region of gut permeable to the drug and whether the drug is to be administered in a fasted or fed state. Multiple sampling required to define the dissolution profile.

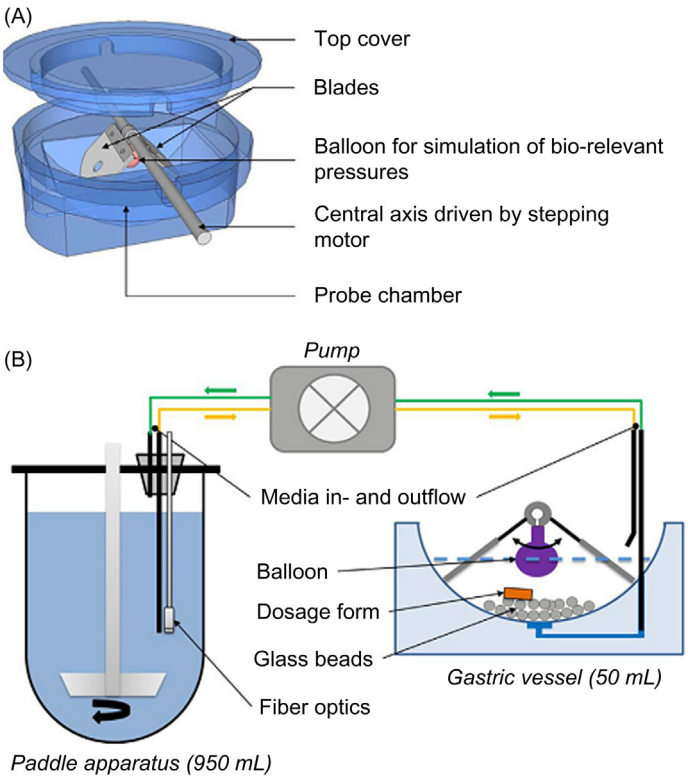

FIGURE 9.9 Fed stomach model: (A) FSM gastric vessel, and (B) closed loop test configuration. *Adapted with permission from Koziolek, M., Görke, K., Neumann, M., Garbacz, G., Weitschies, W., 2014. Development of a bio-relevant dissolution test device simulating mechanical aspects present in the fed stomach. Eur. J. Pharm. Sci. 57, 250–256.*

5. Apparatus: USP II for IR products unless there is a strong reason for another tester type.
6. RPM: 50 or 75 rpm is usually suitable.

9.9.6.3 Biorelevant Dissolution Apparatus

This section presents some examples to suggest how conventional apparatus is modified to develop biorelevant dissolution apparatus.

9.9.6.3.1 FED STOMACH MODEL

The Fed Stomach Model is a modified paddle apparatus, simulating different mechanical aspects present during intragastrical transit. The pendular movement of the two blades placed at 90 degrees at certain driving velocities induces movement in small glass beads at the base of the apparatus. In this way, the dosage form movement is primarily caused by the motion of the glass beads. Pressures of biorelevant dimensions (100–500 mbar) can be exerted by inflation and deflation of a balloon attached to the apparatus (Fig. 9.9) (Koziolek et al., 2014).

9.9.6.3.2 ARTIFICIAL STOMACH DUODENAL MODEL

This two-compartment model comprises a gastric compartment linked to a second intestinal compartment intended to simulate the duodenal area. After dispersion of the drug or formulation in the gastric compartment, contents (liquids) are pumped at a controlled rate to the duodenal compartment with simulated intestinal fluid (SIF).

9.9.6.3.3 DYNAMIC GASTRIC MODEL (DGM)

DGM is claimed to exhibit a precise *in vitro* imitation of gastric mixing (including digestive addition around the gastric bolus), shear rates and forces, peristalsis, and gastric emptying.

9.9.6.3.4 TNO GASTRO-INTESTINAL MODEL (TIM)

The TIM-1 system is a computer governed model of the human upper gastrointestinal tract with numerous dynamic compartments. The water forces exerted on the flexible membranes (that contain luminal contents) are monitored to govern the hydrodynamics related aspects. *In vivo*, muscular peristaltic contractions are simulated by the movements induced by the alternating rhythms of compression and relaxation of the flexible membranes. The passage of liquid and food/drug particles is controlled by regulating the closure (or opening) operation of the peristaltic valves connecting all the compartments. Whereas the TIM-1 system provides information on the bioaccessibility of a compound during passage through the upper GI tract, a combination with TNO's TIM-2 system (that simulates the physiological conditions in the large intestine) enables an investigation of the release of a compound through the entire GI tract.

9.9.6.3.5 GASTRIC DIGESTION MODEL (GDM)

Fernandez et al. developed a gastric digestion model for measuring gastric lipolysis using gastric lipase from dogs (Fernández-García et al., 2009).

9.9.6.4 Limitations of Biorelevant Dissolution Testing

Despite several advantages, biorelevant dissolution testing has some challenges in its practical applications. The major one includes absence of historical database especially when new method is to be established, developing a per run quality check, unestablished standards, handling regulatory aspects and most important unavailability of universal biorelevant methods. As a result, obtaining an IVIVC may involve the development of a different *in vitro* dissolution method each time, for even a small variation in the formulation of the same drug (Mann et al., 2017).

9.9.7 Biowaiver Application: Role of BCS, IVIVC, and Similarity–Dissimilarity Factor

9.9.7.1 Definition and Purpose of Biowaiver

Large numbers of bioequivalence studies are carried out by various industries for abbreviated new drug application (ANDA) for generic drugs or in the supplemental NDA for new indication. Biowaiver refers to a regulatory procedure where the application is

approved for drug approval, by proof of equivalence apart from the actual *in vivo* equivalence testing. It aims at getting the *in vivo* bioavailability, and bioequivalence testing waived as these are both costly as well as time-consuming. So, biowaiver helps to lower the cost involved in drug approval and postapproval changes. Biowaivers find their applications in filling ANDA for generics, NDA supplements, and dossiers for various levels of SUPAC (Licht et al., 2016; Duggal et al., 2014).

9.9.7.2 Criteria for Biowaiver Recommended by USFDA BCS Guidance on Biowaivers

The biowaiver criteria for class I drug products include high solubility, high permeability, rapid dissolution of the drug product (both test and reference), and absence of excipients affecting drug bioavailability. Those for class III drug products include high solubility, very rapid dissolution of the drug product (both test and reference), and qualitative sameness as well as the quantitative similarity between the test product and the reference product (Benet, 2013).

As per the guidance specifications, a drug product is said to have (1) high solubility, when the maximum dose strength gets solubilized in $\leq$250 mL of the aqueous medium in pH 1 to 6.8; (2) high pemeability, when the absorption extent is $\geq$85% (applicable for class Idrugs but not for low permeability class III drugs); (3) rapid dissolution (for class Idrugs), when 85% or more drug dissolution is measured within 30 min in 500 mL or less of the dissolution medium of pH 1.2, 4.5, and 6.8 using basket apparatus (100 rpm) or paddle apparatus (50 rpm or 75 rpm); (4) Very rapid dissolution (for class III drugs), when 85% or more drug dissolution is measured within 15 min using the described dissolution conditions (Shah and Amidon, 2014).

The BCS-Biowaiver guidance for immediate release drug products by USFDA requires few more criteria to be taken into consideration. Some of them are drug substance stability in gastrointestinal tract and the products, excipients should be previously approved by FDA (Burdick et al., 2017), and the similarity factor (f_2:50−100) should be employed to analyze the similarity between the two dissolution profiles (Stevens et al., 2015).

9.9.7.2.1 ADDITIONAL CRITERIA FOR BIOWAIVER APPLICATION

Excipients: (1) For BCS class I drug products, the biowaiver application must contain the data supporting no effect of the new excipients or the higher amounts of known/approved excipients on the bioavailability of the drug. Moreover, the excipient amount should be for the intended purpose (García-Arieta, 2014).

(2) The absorption of low permeability drugs can be affected to a greater extent by the use of excipients. So, for BCS class III drug products, the excipients employed in the test drug product should be the same as those in the reference product (unlike class I drug product) (Niazi, 2014).

Prodrugs: The biowaiver application for IR products containing prodrugs requires the dissolution and pH-solubility data to be documented for both prodrug and drug. However, the decision of whether permeability measurement is to be done on prodrug or drug depends on the mode and site of prodrug conversion to drug substance.

Fixed Dose Combinations: These can be divided into two categories concerning BCS (1) all active ingredients in the combination are class I drugs, (2) all active ingredients in the combination are class III drugs or a combination of class I and class III drugs. The

excipients considerations outlined previously, and the study of pK interactions between the components decides the need for *in vivo* bioequivalence testing.

Dissolution data play a very important role in the approval of new generic drug products as well. BCS-based biowaiver for IR generic products with high solubility, high permeability, and rapid dissolution can be requested if similarity can be proved between the test drug product and the rapidly dissolving reference listed drug (RLD) product (Tampal et al., 2015; Verbeeck et al., 2017).

9.9.7.2.2 EXCEPTIONS

BCS-based biowaivers are not applicable for the drug substance of a narrow therapeutic index and drug products intended to be absorbed in the oral cavity (Saluja et al., 2016).

9.9.7.3 Biowaiver Extension Potential

1. Biowaivers for class II drug products could be considered if permeability criterion is met and rapid dissolution is exhibited at pH of the small intestine.
2. However, biowaivers for class III drug products could be considered if rapid dissolution is observed under all physiological pH conditions.
3. The extension of BCS-based biowaiver concept to oral modified release drug products requires the role of intestinal metabolism to be identified (Parr et al., 2016; Bergström et al., 2014).

9.9.7.4 Data Required for Requesting Biowaiver

1. Data supporting Rapid and Similar Dissolution: drug products dissolution testing, a graph representing the mean dissolution profiles for 12 individual units (the test and the reference products) in the three-stipulated media, data at specified testing interval, and similarity data.
2. Data supporting High Permeability: pharmacokinetic data, permeability study method selection data, permeability data of drug substance, and absorption data for model drugs.
3. Data supporting High Solubility: description of test methods, drug physiochemical information data, detailed solubility data, and pH solubility profile (Davit et al., 2016).

9.9.8 Prognosis of Drug Disposition

Drug bioavailability has two crucial components: dissolution and permeability. Dissolution testing has always been a predictor of drug bioavailability. IVIVC is a major tool to measure the degree of the flaws in anticipating the *in vivo* bioavailability outcomes from *in vitro* dissolution study compilations. This can be done by using the convolution method that refers to transforming *in vitro* dissolution data into plasma concentration data (input to output) (Poongothai et al., 2014).

BCS and the advanced Biopharmaceutical Drug Disposition Classification System (BDDCS) and the Extended Clearance Classification System (ECCS) collectively connect the *in vitro* dissolution data to the pharmacokinetic parameters and could serve as the basis of predicting drug disposition. BDDCS divides the drugs into four categories by their permeability and solubility.

As per BDDCS, the main path of elimination for drugs having high intestinal permeability is via metabolism, whereas those with poor intestinal permeability chiefly eliminate as unchanged drug in the urine and bile. The knowledge of the BDDCS class can help in predicting the main route of elimination. It also helps to measure drug–drug interactions by assessing the effect of transporters and anticipating the development of drug-associated adverse drug reactions (ADRs) (e.g., idiosyncratic cutaneous ADRs with antiepileptic drugs) (Tekade et al., 2018; Camenisch, 2016).

9.9.9 Identification of Critical Manufacturing Variables (CMVs)

Mapping is a tool to determine the correlation between critical manufacturing variables, *in vitro* dissolution data and *in vivo* bioavailability data. It describes the limits for *in vitro* dissolution profiles based on the acceptable bioequivalency standard. This correlation helps in recognizing critical manufacturing variables that majorly impact drug release from the product including method, machine, material, and formulation variables (Patil and Burgess, 2016). The aim is to set the product standards that will assure bioequivalence of forthcoming batches, manufactured within the boundary of acceptable dissolution criteria. The monitoring of the identified CMVs will constantly help in achieving conviction and prognosis of the drug product performance. Mapping-based dissolution criteria will enhance the reliability of an *in vitro* dissolution test as a surrogate for *in vivo* bioequivalence testing.

9.9.10 Surrogate of Bioequivalence Study at Postapproval Changes of Drug Product (SUPAC)

The SUPAC-IR guidance explains the postapproval change levels (1, 2, and 3), stipulated tests involved, and supported data required to assure drug product quality, safety, and efficacy. The comparison of dissolution testing profiles of change batch (reference) to postchange batch (test) performs a crucial role in getting the scale-up and postapproval changes (SUPAC) approved (Van Buskirk et al., 2014).

The USFDA guidelines for an immediate release oral drug product suggest that to get the SUPAC approved for any level 1 or level 2 change, a bioequivalence study is not required and dissolution testing may be sufficient. The difference being that for most level 2 changes, comparative dissolution testing of prechange and postchange products is required along with developing multipoint dissolution profiles in the different stipulated dissolution media (water, 0.1 N HCl, 4.5 pH and 6.8 pH USP buffer). No *in vivo* bioequivalence study is required, if the prechange and the postchange product dissolution profiles are found similar by employing the similarity factor (f_2) (Stevens et al., 2015).

For most level 3 changes, both *in vivo* bioequivalence study and dissolution testing are needed to support SUPAC approval except for "site change" level 3 changes (where dissolution testing may be sufficient, and no bioequivalence study is required). Further, developing a validated and relevant IVIVC may help getting *in vivo* bioequivalence study waived in most level 3 changes and the comparative dissolution testing between prechange and postchange product may be sufficient. As a result, the decreased number of *in vivo* bioequivalence studies required and reduced regulatory load renders the SUPAC

approval process more cost-effective and less time-consuming, especially when IVIVC is established at early stages of drug development. For example, a level "A" IVIVC was obtained for metoprolol succinate in the membrane-coated multiple-unit formulation. After regulatory approval of the original product, the formulation was altered to avoid organic solvents in the manufacturing process and to make the process more efficient. The application of an *in vitro* dissolution test as a surrogate for human bioequivalence studies was confirmed when a strong *in vitro–in vivo* correlation was demonstrated (Mitra et al., 2015).

9.9.11 Quality Control Tool

The dissolution testing is a valuable quality control tool for maintaining batch-to-batch uniformity and for discerning the influence of formulation or manufacturing process changes on drug product outcomes. It is used for batch quality study as well as batch quality control. The dissolution test for quality control purpose for a productis developed with respect to its dosage form. Dissolution testing measures the drug product quality aspects that are susceptible to formulation as well as process changes (Lawrence et al., 2016). For QC purposes, dissolution tests aim at the rate and extent to which the drug release occurs from the formulation. This depends on the physicochemical properties (solubility, particle size, polymorphic form) of a drug substance and its formulation (excipients) (Qiu et al., 2016).

Dissolution acts as a quality control tool for the end product as well as in the process quality control. It brings many advantages to the drug development process, along with improved end product quality, which include savings as it reduces drug rejection rates, promotes faster troubleshooting, at line application as it cuts lead time in any trouble concerning a batch, and investigates the performance of new formulations by studying drug release. The dissolution test as a QC tool tends to maintain both manufacturing as well as product consistency (McCormick and McVay, 2016).

For QC, dissolution must involve selection of media of proper discriminatory power; or else it will lead to variations in the dissolution test results, e.g., mebendazole showed non-discriminating test results in 0.1 N HCl with 1% SLS and metoprolol showed overly discriminating test results (Prasanthi et al., 2014).

The QC dissolution tests should provide the environmental settings under which more than 90% drug release can occur, and routine use can be conveniently possible. So, dissolution media (pH and volume), duration, time points, apparatus, and the other parameters should be selected likewise for both immediate release and modified release dosage forms.

9.9.12 Determination of Product Storage Stability

Throughout the development lifecycle for product release, dissolution tests for all solid oral dosage forms are not only used for release testing but also can be used as an indicator of drug stability on aging, termed as storage stability studies. It can also be extrapolated to product degradation studies. It is a pivotal analytical test and can detect physical and chemical changes in a drug substance as well as a drug product (Aulton and Taylor, 2017).

9.9.13 Investigation of Drug Release Mechanisms

There are some dissolution kinetic models (zero order, Linear, Quadratic, Logistic, Probit & Weibull) that describe the overall drug release from the dosage form. Model fitting is done, and the regression coefficient values determine the best suitable model for that system, indicating the mechanism of drug release based on different mathematical functions (Ahmad et al., 2015; LeBlond, 2016).

9.10 DISSOLUTION MECHANISM: ROLE OF DENSITY FUNCTIONAL THEORY (DFT)

9.10.1 Basics of Density Functional Theory

Density functional theory is based on computational quantum mechanics and makes use of the spatially dependent electron density as functional (that is functions of other functions) which in this case is for determining the properties of many-electron systems (Liu et al., 2016). The Hohenberg and Kohn theorem for DFT asserts that this electron density functional is a simple function of three coordinates (unlike the Schrödinger equation whose function has 126 coordinates and 42 electronic spin components), and can help to understand the total energetics of multibody system in a relatively simple manner (Medvedev et al., 2017). These energies include various potential energies like ion−electron potential energy, ion−ion potential energy, along with kinetic energy, exchange-correlation energy, and electron−electron energy. It is used to examine the structure based, magnetic, and electronic properties of molecules. Although this theory produces accurate results, it faces difficulty in properly describing strongly correlated systems (Koch and Holthausen, 2015; Lejaeghere et al., 2016).

9.10.2 DFT Application to Predict Dissolution Mechanisms

This concept has been exhaustively used in physics, chemistry, and material science but its application to pharmaceutical mass transfer process (like dissolution) is quite recent. Dissolution is a thermodynamic process involving a solute−solvent interaction process at the molecular level. Moreover, the net Gibbs free energy should be negative for dissolution to take place. So, during the dissolution process, this theory helps to determine the nature of molecular interactions (bond formations and bond breakages) occurring by virtue of measuring changes in system energetics. This, in turn, helps to predict the mechanism of dissolution process (Jiang et al., 2015). This was first studied for dissolution of acetaminophen crystal into the aqueous solution. Some research findings on dissolution mechanisms studies undertaken by density functional theory are mentioned below.

NaCl dissolution involves multiple steps, initiating with the initial discharge of Cl ions from the lattice and later followed by the subsequent release of Na ions calculated by free energy barriers. Cellulose triacetate (CTA) II crystal dissolution in dimethyl sulfoxide (DMSO) revealed that the major resistance to solvation was offered by the two stronger H-bonds. The three types of H-bonds with different bond strengths that were the basis of crystal formation vanished during the course of dissolution process (Hayakawa et al., 2011).

The dissolution of silicate as proposed by Kubicki et al. takes place by protonation and hydrolysis of bridging oxygen atoms interceded by intrasurface H-bonding (Kubicki et al., 2012). The dissolution mechanism of SiO_2 in ionic solutions as investigated by Stritto et al. majorly involved proton transfer occurring due to ion-induced stronger H-bonding between terminal hydroxyl groups and bridging oxygen atoms (DelloStritto et al., 2016). The dissolution mechanism of α-cyclodextrin and chitobiose in 1-ethyl-3-methyl-imidazolium acetate was examined using DFT (Cao et al., 2017). Major interactions involved were noncovalent interactions in which hydrogen bonding interactions were predominant. Payal et al. carried out the dissolution of cellobiose and xylan representing cellulose and hemicellulose, correspondingly, in the gas phase, implicit and explicit solvent. The major contribution in the dissolution process was observed to be inter- and intramolecular hydrogen bonding (Payal et al., 2012).

DFT can also be used to investigate the pattern of drug release or the order in which drug molecules release from the crystal surface and the site involved upon the crystal surface and if molecules were observed to leave the crystal surface in an organized fashion. The effect of NaCl on drug dissolution was also analyzed by DFT. DFT was employed successfully for structural elucidation of phosphatidylcholine based on the energetics of the dissolution system. Dissolution mechanism studies using DFT can also help to select the most stable drug form amongst all polymorphs, such as in the case of platinum nanoparticles where a truncated octahedral polymorph was found to be most stable to dissolution (Sanz-Navarro et al., 2008).

9.11 DISSOLUTION CONTROLLED DRUG DELIVERY SYSTEMS

The need for a drug product is not only restricted to faster/improved drug dissolution (mainly for poorly soluble drugs) but the slowing down/delaying of drug dissolution may also be equally important in many cases to get the drug released at the desired rate and site to provide a long-term therapeutic effect. This becomes the basis for dissolution controlled drug delivery systems. Dissolution has emerged as an important tool in controlling the drug release and designing the drug delivery systems on three principles (Khadka et al., 2014; Pundir et al., 2017).

9.11.1 Dissolution of Solid Particles

It follows the basic mechanism of Noyes–Whitney principle (two key steps of solvation followed by diffusion).

9.11.2 Dissolution of Coated Systems

It involves applying the coat of retardant (slowly dissolving) polymer material at drug-dissolution medium interface and is majorly governed by the dissolution of the coat in the targeted release medium, such as in the case of enteric coated systems.

9.11.3 Dissolution of Matrix Systems

It involves the homogenous distribution of the drug in the polymer matrix. It is governed by the selection of the polymer as well as the design and geometry of the matrix. The matrix systems can be surface erodible matrix systems (dissolving type), nonerodible systems (diffusion type), or soluble matrix systems (swelling type).

9.11.4 Examples of Dissolution Controlled Drug Delivery Systems

The low-aqueous-solubility penicillin G salts like penicillin G benzathine suspension can maintain the therapeutic plasma levels for almost a day or more (Rajadhyaksha et al., 2016). Zydis and DuraSolv are quick-dissolve formulations which show spontaneous dissolution in the oral cavity due to the higher values of surface area and solubility of excipients (AdchitreVaishali et al., 2016). NanoCrystals and DissoCubes utilize micronization or nanosizing concepts to improve dissolution for an immediate release dosage form (Lu et al., 2016). Enteric coating polymers like cellulose acetate phthalate exhibit delayed drug release by virtue of its dissolution at higher intestinal pH values and showing no solubility at low gastric pH values (Caillard et al., 2016). Precise demonstrates a zero-order drug release by keeping the dissolving surface area constant. The drug-containing tablet core experiences a decrease in its diameter while there is an increase in its thickness during the drug dissolution process. COSRx (a guar-gum-based tablet) shows improved controlled release rates making use of both aqueous soluble and aqueous insoluble polymers (Pundir et al., 2017). Smartrix tablet exhibits drug release by erosion of the outer layers leading to the increased drug release surface area (Pundir et al., 2017). TIMERx is based on slowly eroding matrix platform technology and consists of two polysaccharides, xanthan gum and locust bean gum (Silas et al., 2017). RingCap is a patented capsular matrix tablet whose rim is provided with the rings of insoluble material which control the surface area and thus the drug release (Tiwari and Batra, 2014). OROS tablets cause the drug release to occur through an orifice, initiated by the water inflow through a semipermeable membrane enforced by osmosis (Mendez et al., 2014).

Other such technologies include Spheroidal oral drug absorption system (SODAS), Intestinal protective drug absorption system (IPDAS), Chronotherapeuticoral drug absorption system (CODAS), and Programmable oral drug absorption system (PRODAS) (Allen and Ansel, 2013; Park, 2014).

9.12 CONCLUSION AND PROSPECTS

Dissolution testing has widened its contributions since its outset in early 1960s. Dissolution testing adds value to the overall drug development sequence right from the selection of phase 1 drug products to the criteria for being surrogate for bioequivalence studies in later stages of drug development and postapproval changes by using BCS and IVIVC attempts. It enable the process to be less time-consuming and more cost-effective due to reduced regulatory burden and increased potential of *in vivo* predictions.

Dissolution testing has several significant applications as a quality control tool for ensuring batch to batch uniformity and in research and development to examine the performance and stability of new formulations.

However, a major limitation is the need to develop a single dissolution test that is efficient to serve both the purpose of QC and biorelevance as both are governed by separate factors. Although success has been achieved in designing biorelevant dissolution media, the *in vivo* prediction results are still not found to be sufficiently precise. This may be due to inability to control the many variables affecting the dissolution *in vivo*. Further, these media are very complex and costly to be used on a regular basis. The dissolution data parameters vary at each phase of drug development based on the intended purpose. Secondly there are insufficient efforts being made in dissolution method development due to time pressure, leading to the lack of profound knowledge of the dissolution testing potential. The new techniques of QbD can thus help in generating detailed expertise of "causes and consequences" and lead to a science-based approach to improving the dissolution method. However, attaining this goal has always been a major challenge for pharmaceutical formulation development.

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ABBREVIATIONS

ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
AUC	area under the curve
BCS	biopharmaceutical classification system
BDDCS	biopharmaceutical drug disposition classification system
CMV	critical manufacturing variables
CODAS	chronotherapeutic oral drug absorption system
CTA	cellulose triacetate
DDD Plus	dose disintegration and dissolution plus
DFT	density functional theory
DMSO	dimethyl sulfoxide
DoE	design of experiment
ECCS	extended clearance classification system
EP	European pharmacopoeia

FaSSGF	fasted state simulated gastric fluid
FaSSIF	fasted state simulated intestinal fluid
FDA	Food & Drug Administration
FeSSGF	fed state simulated gastric fluid
FeSSIF	fed state simulated intestinal fluid
GDM	gastric digestion model
GI	gastrointestinal
GIT	gastrointestinal tract
GMPs	good manufacturing practices
HPLC	high performance liquid chromatography
ICH	International Council for Harmonization
IND	investigational new drug application
IPDAS	intestinal protective drug absorption system
IQ	installation qualification
IRB	Institutional Review Board
IVIVC	*in vitro–in vivo* correlation
IVIVE	*In vitro–in vivo* extrapolation
JP	Japanese Pharmacopoeia
mOsm kg^{-1}	milliosmole per kilogram
MR	modified release
NCE	new chemical entity
NDA	new drug application
NF	national formulary
OQ	operational qualification
PPI	proton pump inhibitors
PQ	performance qualification
PRODAS	programmable oral drug absorption system
PVT	performance verification test
QbD	quality by design
QC	quality control
QRA	quality risk assessment
QTPP	quality target product profile
R&D	research & development
RLD	reference listed drug
RSD	relative standard deviation
SGF	simulated gastric fluid
SIF	simulated intestinal fluid
SODAS	spheroidal oral drug absorption system
SUPAC	scale-up and postapproval changes
TIM	TNO gastro-intestinal model
UPLC	ultra performance liquid chromatography
USP	United States Pharmacopoeia

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