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MINIREVIEW

Unconventional Dissolution Methodologies

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Introduction

In line with the key focus of recent publications[1−3] emerging from the labs of Dressman, Amidon, and Shah, and in conjunction with the aims of both the FDA and US Pharmacopoeial Convention to improve and possibly develop alternative dissolution testing procedures as well as techniques for data analysis, this work considers an overview of the constantly changing areas of in vitro dissolution research in the evaluation of novel oral drug delivery systems. Over the years, dissolution testing has been employed as a quality control procedure in pharmaceutical production, in product development to assist in selection of a candidate formulation, in research to detect the influence of critical manufacturing variables such as binder effect,[4] mixing effect,[5,6] granulation procedure,[7] coating parameters,[8,9] excipient type,[10] and/or in comparative studies of different formulations,[11] in in vitro−in vivo correlations,[12−15] and possibly as an in vivo surrogate under strictly defined conditions.[16,17] It therefore becomes apparent that sensitive and reproducible dissolution data derived from physicochemically and hydrodynamically defined conditions are necessary in order to compare various in vitro dissolution data and be able to use such results as a surrogate for possible in vivo bioavailability, bioequivalence testing, and in vitro−in vivo correlations (IVIVC). However, the influence of technological differences and process variables involved during manufacturing on dissolution rate often complicates the decision making process in selection of the appropriate dissolution method and subsequent data interpretation technique. Moreover, Skoug and co-workers[18] stressed that this consequence is the reason dissolution studies and the defined specifications so often generate strong interest during regulatory review of solid oral dosage forms. As a result, the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) has recently released guidelines called Scale-Up and Post Approval Changes, commonly referred to as SUPAC[19] and Extended Release Solid Oral Dosage Forms: Development, Evaluation and Application of In vitro/In vivo Correlations, commonly known as IVIVC,[20] to be used by the pharmaceutical sponsor in quality assurance and specific postapproval changes and to demonstrate that the "dissolution profiles of prechange product and postchange product are similar". The impact of the process and establishment of an in vitro and in vivo performance (IVIVR) as a critical stage in development of oral controlled release products has been further highlighted in the recent work of Devane and Butler.[21]

The current sophistication in formulation of new modified release drug delivery systems and associated diversity in dosage form design necessitates the development of new procedures or appropriate modification to the existing apparatus as an alternative for dissolution measurements.[22,23] More recently, it has been shown that the complex hydrodynamics and three-dimensional fluid flow pattern produced by the USP paddle[24] within different regions of the dissolution vessel varies significantly with a relatively more stagnant region at the bottom portion of the vessel.[25,26] Consequently, to mimic and more closely reflect the possible in vivo dosage form surface exposure, have reliable dissolution data, and be able to discriminate between release behavior of various modified release formulations, it becomes apparent that a better understanding of the role of hydrodynamics in relation to delivery

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system and release mechanisms are necessary for the development of alternative dissolution methods.[22,23]

In general, the design of alternative dissolution methods may be approached in one of two ways or a combination. First, the method might consider the establishment of in vitro testing conditions similar to an actual in vivo setting. This approach may encompass instrumental developments mimicking gastrointestinal peristaltic motion with combination of flow-through methods for ensuring sink condition maintenance. All media used in testing of dosage forms should also be very similar to fluids comprising the gastrointestinal compartment particularly with respect to composition. Furthermore, other technical considerations may incorporate fabrication materials that are in contact with the dosage to possibly behave as pliable, flexible gastrointestinal tissue. Irrespective of the extent to which the ideal testing conditions are achieved, this approach becomes a mammoth task flawed by numerous inconsistencies. The second and more amenable approach is to establish in vitro dissolution conditions that may provide drug release profiles very similar to deconvoluted (i.e., fraction absorbed) blood plasma profiles through different levels of correlation as described in the USP. This entails an establishment of in vitro–in vivo correlation through manipulation of process variables such as selection of appropriate dissolution media systems taking into consideration sink condition maintenance and/or manipulation of fluid flow hydrodynamics by use of additional devices within the standard dissolution vessel. A useful example of the latter suggestion is the reported ring/mesh assembly used for the in vitro enhancement of dosage form positioning and surface area exposure in order to simulate hydrodynamically comparable conditions to that of in vivo.[27,28]

Generally reviews, theoretical papers, and research publications on the subject of dissolution have focused on standardizing, expanding, and developing useful mathematical and physical models principally due to apparent unresolved mechanistic complexities in the thermodynamic sense.[29–34] On the basis of such past in-depth analyses, researchers may presently use those concepts in experimental design of alternative dissolution methods. Therefore, to consolidate the principles governing the dissolution process, this article will attempt to provide a brief theoretical perspective of dissolution theory and associated concepts used in drug release from oral dosage forms. In keeping with the significant research activities with hydrophilic swellable matrixes, priority will be given to the optimization of dissolution studies pertaining to modified/controlled release drug delivery from such systems. A summary of attempts to improve the currently recommended USP, 23 dissolution methodologies for swellable sticking and swellable floatable delivery systems is provided, and the approaches recently used to overcome the associated difficulties are referred to in the text.[27] In addition, aspects relating to the lack of an official in vitro dissolution test method for lipid-filled capsules and the strategy used to solve this dilemma is discussed.[28] A critical review on the advantages and limitations of commonly used mathematical and statistical parameters for comparison of dissolution data, including the newly developed FDA-recommended f_2 similarity factor and f_1 difference factor, also follows. The use of "chemical stabilizers" in dissolution testing of drugs (such as ascorbic acid), normally susceptible to rapid decomposition in solution, is discussed for a gel-based controlled release product. We also briefly examine the problems associated with non-UV responsive drugs and the implications of colorimetric adaptation for the evaluation of release characteristics of both soluble and insoluble active substances.

Fundamental Dissolution Theories

Dissolution of a solute is a multistep process involving heterogeneous reactions/interactions between the phases of the solute–solute, solute–solvent, solvent–solvent, and at the solute–solvent interface. As one of the most commonly known mass transfer rate processes, the component heterogeneous reactions may broadly be categorized into (i) diffusion or convective transport of the solute from the interface to the bulk phase; and (ii) the rate of solute liberation and transport from and across the interfacial boundaries.

Various researchers in the field have developed theories to define the dissolution process and these have been comprehensively reported.[35–37] As three of the pioneering theories in the field, this review will not be complete without a brief description of the diffusion layer model, surface renewal theory, and limited solvation theory.

Table 1 concisely depicts the principal mathematical equations associated with the theories and highlights key points regarding the theory. Selected information is derived from the text of Abdou[35] for diffusion layer and surface renewal theories. The limited solvation theory is presented from the original work of Goldberg and co-workers.[38]

In the diffusion layer theory, the simplest model used to describe dissolution makes use of a single crystal in a nonreactive environment. The initial step in solution of the solid (solute or crystal) at the interface is usually very rapid and results in the formation of a saturated stagnant layer around the particle. This is contrasted by the second diffusion step that is slow and becomes the rate-limiting step in the dissolution process. In particular, the Noyes–Whitney equation (eq 3) illustrates that one of the main factors determining the rate of dissolution is drug solubility.[37] From this it is understood that in vivo the dissolution process may become the rate-limiting step if the rate of solution is much slower than the rate of absorption. This may be the case when the drug in question has a very low solubility at both gastric and intestinal pH.

The surface renewal theory assumes an equilibrium at the solute–solution interface is attained and that the rate-limiting step in the dissolution process is mass transport. The model is thought of as being continually exposed to fresh dissolution medium. The agitating medium consists of numerous eddies or packets into which the solute diffuses and is carried to the bulk medium. Due to the turbulence at the surface of the solute, there is no boundary layer and therefore no stagnant film layer. In other words the surface is continually being replaced with fresh medium.

The limited solvation theory[38] predicts that a crystal undergoes dissolution through an interfacial process in the dissolving medium. The true surface area of the crystal must be considered since each face of the crystal may have a different interfacial barrier. Hence each surface may provide a different contribution to the dissolution process.

Basic Theories of Dissolution Profile Analysis

Table 2 in summary depicts four prominent theories used in dissolution profile analysis, namely Wagner's,[39] Kitazawa's,[40–42] El-Yazigi's,[43] and Carstensen's.[44]

Wagner's theory[39] for the interpretation of percent dissolved–time plots of tablets and capsules relates the apparent first-order kinetics under sink conditions to the fact that a percent dissolved value at a certain time may be equivalent to the percent surface area generated at the same time. Kitazawa's theory[40–42] showed that the biphasic straight lines were obtained from plots of $\ln c_s/(c_s - c)$ vs t. The first segment was due to tablet disintegration or

Table 1—Summary of Fundamental Dissolution Theories[a]

theory[b]	equations		associated characteristics
diffusion layer[35]			
Fick's First Law	$J_{ix} = -D_i (\partial c_i/\partial x)$	(1)	Considers diffusion only under steady-state conditions.
Fick's Second Law	$\partial c/\partial t = D (\partial^2 c/\partial x^2)$	(2)	Used when drug concentration decreases with time; hence, considers non-steady state conditions.
Noyes and Whitney	$dc/dt = K (c_s - c_t)$	(3)	Description of drug dissolution based on constant surface area.
Brunner and Tolloczko	$dc/dt = kS (c_s - c_t)$	(4)	Manipulation of Noyes–Whitney's eq 3 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 into the bulk.
Nernst	-		
Brunner	$dc/dt = kDS/vh (c_s - c_t)$	(5)	Manipulation of Fick's first law and expansion of eq 4 by incorporation of a diffusion coefficient D, stagnant layer thickness h, and volume of dissolution medium v.
	If $c_t \ll c_s$ (i.e. <10%) $\Rightarrow dc/dt = kDS/vhc_s$	(6)	
	If v and S are constant $\Rightarrow dc/dt = K$	(7)	
Hixson and Crowell Cube Root	$w_0^{1/3} - w^{1/3} = (4\pi\rho\eta/3)^{1/3} (Dc_s/h\rho)t$	(8)	Originally developed for single particles but has been extended to use in multiparticulate systems.
	or $w_0^{1/3} - w^{1/3} = Kt$	(9)	
surface renewal[35]	$Vdc/dt = dW/dt = S(\gamma D)^{1/2} (c_s - c_t)$	(10)	Assumes solid–solution equilibrium is achieved at the interface and that mass transport is the rate-limiting step in the dissolution process.
limited solvation[38]	$G = k_i(c_s - c_t)$	(11)	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.

[a] Key to symbols and abbreviations: J_{ix}: flux (mg/cm^2 s^{-1}); D_i: diffusion coefficient; $\partial c_i/\partial x$: concentration gradient; $\partial c/\partial t$ or dc/dt: drug dissolution rate; K: first-order dissolution constant; c_s: equilibrium drug concentration; c_t: drug concentration at time t; k: dissolution constant; S: surface area; v: volume of dissolution medium; h: thickness of stagnant layer; w_0: 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. [b] Superscript numbers in first column denote references.

Table 2—Summary of Basic Theories of Dissolution Profile Analysis[a]

theory[b]	equations		associated characteristics
Wagner[39]	$\log(w^\infty - w) = \log M - k_s/2.303 (t - t^\circ)$	(12)	Relates apparent first-order kinetics under sink conditions to the distribution of available surface area and not dissolution per se. In case of exponential decrease in surface area with time, then first-order kinetics could be related to dissolution data.
	where $M = K/k_sC_sS^\circ$	(13)	
Kitazawa[40−42]	$\ln w^\infty/(w^\infty - w) = K't$	(14)	Assumes constant surface as long as sink is maintained. Under these conditions C^∞ is not always equal to C_s. A plot of $\ln w^\infty/(w^\infty - w)$ vs t yields a straight line with slope as the dissolution rate constant K'.
El-Yazigi[43]	$(100 - f_s) = 100k_d/(k_d - k_s)e^{-k_st} - 100k_s/(k_d - k_s)e^{-k_dt}$	(15)	Disintegration and dissolution are consecutive first-order processes. Because disintegration is usually much faster than dissolution, the semilog plot of $(100 - f_s)$ vs t yields a biexponential curve.
Carstensen[44]	If q is small and $F/q \ll 1$		Considered that the dissolution process in the USP basket proceeds in three steps: some disintegration but particles not dislodged from basket; more disintegration and particles move out of basket; more disintegration and first particles have completely dissolved. These three phases have to be mathematically explained to calculate the mass of solute undissolved at time $t = 0$.
	$\Rightarrow \ln m = -q\theta + \ln m_0$	(16)	
	If q is large		
	$\Rightarrow \ln m = -q\theta + q\theta_2 + \ln m_0\ 6(F/q)^3$	(17)	

[a] Key to symbols and abbreviations: w^∞: amount of drug in solution at infinite time; $(w^\infty - w)$: amount of undissolved drug; K: dissolution constant; k_s: dissolution rate constant; t: time in question; t°: time $t = 0$; C_s: aqueous solubility of drug; S°: surface area at time t°; K': dissolution constant; f_s: cumulative percentage of drug dissolved at time t; k_d: disintegration rate constant; k_s: dissolution rate constant; q: erosion constant; m: mass of undissolved solute; θ: experimentally observed time; F: factor as a function of the intrinsic dissolution rate (either in basket or vessel), drug solubility, and particle density. [b] Superscript numbers in first column denote references.

disruption of the capsule shell, while the second segment was obtained from this point onward to the end of the dissolution. Through multiplication by volume the concentration terms were changed to weight as depicted in eq 14. This theory was seriously criticized because it assumed a sudden increase in surface area rather than a continuous change, as proposed by Wagner. The major difference between the approach of El-Yazigi[43] and Kitazawa is that the former treats disintegration and dissolution as two kinetically distinct processes. The application of the eqs 16 and 17 in Carstensen's approach[44] generated curves that had skewed S shapes and followed Weibull or log-normal distributions when the percent dissolved was plotted against time. This may be attributed to the initial lag phase in the dissolution process (also expected from the proposed theory in terms of the time-dependent phases of disintegration, escape of particles through the basket, and dissolution of initial particles).

Currently Recommended USP 23 Methods

The currently available USP-23 has been one of the most valuable references to pharmaceutical scientists involved in the area of dissolution studies. The available dissolution methods within individual drug monographs with respect to solid oral dosage forms have been divided, where appropriate, into immediate and controlled or extended release products. Irrespective of this division and prominence given to differences in specifications such as tolerance (Q) values between immediate and controlled release products, there are no substantial differences in the methodologies used to test these products. Expected differences in dissolution test methods may include variation in the pH of the buffer medium depending on where the designed controlled release product is to deliver the drug or depending on the drug release rate, drug solubility, and absorption window. In most cases, the monographs are not up to date and the necessary refinements reflecting the recent advances in research findings with respect to both changes in media and methods are not included. With the recent tendencies toward application of hydrophilic floatable and/or sticking materials, new impetus has taken over in drug delivery systems design. Another unspoken reason for this shift in scientific momentum has been due to the "sudden" expiration of drug product patents and concurrent

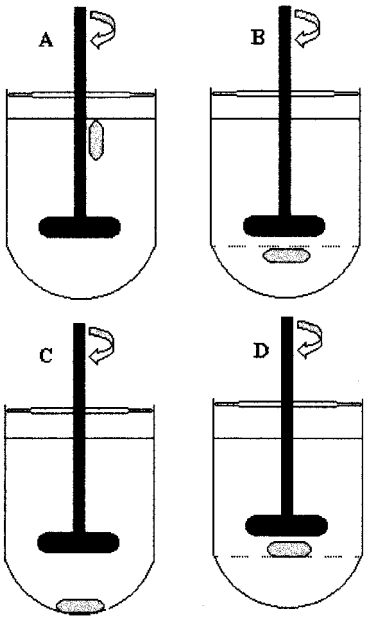

Figure 1—Schematic of drug delivery system positioning within a dissolution vessel: (A) floatable system close to the paddle shaft; (B) floatable system under the ring/mesh assembly; (C) sticking system adhering to bottom of dissolution vessel; (D) sticking system placed over the ring/mesh assembly. (Modified from Pillay and Fassihi[27]).

progress and expansion of "generic" industries. The application of new polymeric materials to enhance drug delivery, particularly in certain aspects of controlled release, has from our experience led to the recognition of limitations in the versatility of the currently recommended USP-23 dissolution methods.[24] This aspect has been adequately demonstrated in the recent publications showing the benefits of alternative dissolution approaches to the currently recommended USP-23 methods applied to swellable sticking and swellable floatable delivery systems, the summary of which is presented in the following sections.

Alternative Dissolution Methods and Examples

(i) Application of Ring/Mesh Assembly for Determination of Release Profiles from Swellable Low- and High-Density Matrices—As pointed out above, new modified release formulation technologies and diversity in dosage form design necessitates the development of new procedures or appropriate modification to the existing apparatus as alternative dissolution measurement methods.[22,23,27,28] For example, in dissolution studies of low-density swellable, floatable controlled release drug delivery systems, often position of the dosage form appears to be close to the paddle shaft and liquid surface as illustrated in Figure 1A (i.e., in schematic). On the other hand, when a sinker such as the USP-recommended[24] "wire helix" is wound around the delivery system, position of the dosage form will vary within the vessel (inconsistent hydrodynamics), and its free three-dimensional swelling process would be adversely affected and difficult to control.[45] Furthermore, and contrary to floatable dosage forms, many drug delivery systems having high density tend to adhere (stick) to the bottom of the dissolution vessel as illustrated in Figure 1C. This problem of sticking is accentuated with the use of swellable polymers such as hydroxypropylmethylcellulose, hydroxypropylcellulose, and poly(ethylene oxide). Under these conditions, the lower surface of the dosage form is not exposed to the dissolution medium, and drug release is limited to the exposed surfaces only. Similar phenomena are unlikely to occur in the human gastrointestinal tract. Furthermore, it may be anticipated that the USP 23 Apparatus 1 (rotating basket method) may be used to surmount this problem by allowing complete immersion of the dosage form and full surface area exposure. However, the early work of Withey and Bowker[46] on fluid flow dynamics clearly show that the rotating basket produces nonreproducible flow patterns with least fluid flow in the axial plane directly above and below the basket as well as within the basket. In addition, our experience has shown that some swellable delivery systems tend to expand greater than the diameter of the basket and often float against the flat base of the rotating shaft. These events will result in restriction of swelling and erosion processes, as well as limited surface exposure to dissolution medium. More recently, it has been shown that the complex hydrodynamics and three-dimensional fluid flow pattern produced by the USP paddle within different regions of the dissolution vessel varies significantly with a relatively more stagnant region at the bottom portion of the vessel.[25,26] Consequently, to mimic and more closely reflect the possible in vivo dosage form surface exposure, have reliable dissolution data, and be able to discriminate between release behavior of various modified release formulations, a better understanding of the role of hydrodynamics, delivery system, and release mechanisms together with the development of alternative dissolution methods is apparent.[22,23]

Recently Pillay and Fassihi[27] have used a new device (ring/mesh assembly) in conjunction with the paddle method to study the influence of the position of various dosage forms on release behavior and evaluated the release profiles obtained with such modification with those derived under standard dissolution conditions including the USP 23- recommended helical wire sinker used for swellable floatable delivery systems (see schematic Figure 1). Model drugs used included theophylline (0.85% water soluble at 25 °C) and diltiazem hydrochloride (>50% water soluble at 25 °C). It was shown that for a low water-soluble drug such as theophylline, full surface exposure was necessary in order to accomplish complete drug release from the delivery system (Figure 2a). This was accomplished by placing the delivery system over the ring/mesh assembly as depicted in Figure 1. This surface area exposure phenomenon was also applicable to a floatable theophylline system. Application of the USP-recommended helical wire sinker to the swellable floatable theophylline delivery system appeared to inhibit the three-dimensional swelling process of the dosage form and consequently suppressed drug release from the formulation (Figure 2b). Such a limitation was alleviated by positioning the delivery system below the ring/mesh assembly (Figure 1). In the case of diltiazem hydrochloride (solubility in water >50% at 25 °C) similar release differences as in the case of theophylline ($p < 0.05$) were also observed when the sticking delivery system was placed either in the vessel as recommended by the USP 23 standard method or when it was positioned over the ring/mesh assembly (Figure 2c). However, in the case of a swellable floatable system containing the highly soluble drug diltiazem hydrochloride, no differences in release were found by employing the helical wire sinker, placing the dosage form in the vessel as such or when the delivery system was fully submerged under the ring/mesh assembly (see Figure 2d). Hence, the nature of drug release behavior from swellable floatable systems depended both on full surface exposure and unhindered swelling as well as drug solubility.

(ii) Evaluation of Drug Release from Lipid-Filled Hardshell or Softgel Capsules—Considerable interest has been shown in the formulation of lipid-filled capsules for the enhancement of either in vivo dissolution rates or

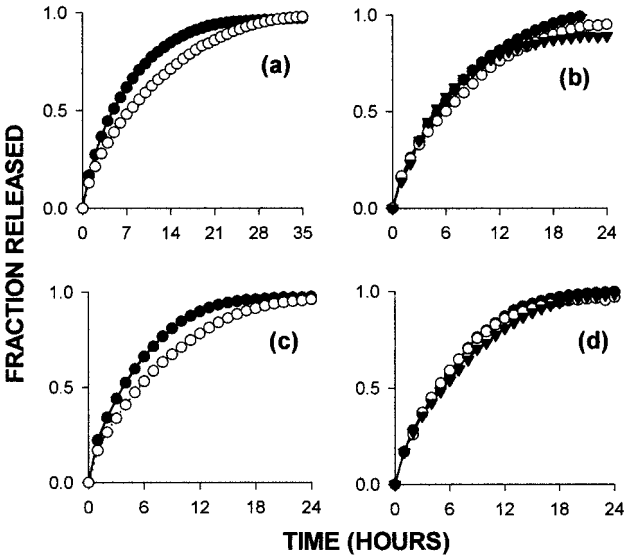

Figure 2—(a) Theophylline release from a swellable sticking drug delivery system. Key: ●, delivery system placed over the ring/mesh assembly for full surface exposure to the dissolution medium; ○, delivery system dropped into the vessel with one surface sticking to the bottom of the vessel. (b) Theophylline release from a swellable floatable drug delivery system. Key: ○, delivery system placed under the ring/mesh assembly to prevent flotation to the surface of the dissolution medium; ●, delivery system dropped into the vessel and allowed to float at the surface of the dissolution medium; ▼, delivery system enclosed within a helical wire sinker to prevent flotation to the surface of the dissolution medium. (c) Diltiazem hydrochloride release from a swellable sticking drug delivery system. Key: ●, delivery system placed over the ring/mesh assembly for full surface exposure to the dissolution medium; ○, delivery system dropped into the vessel with one surface sticking to the bottom of the vessel. (d) Diltiazem hydrochloride release from a swellable floatable drug delivery system. Key: ○, delivery system placed under the ring/mesh assembly to prevent flotation to the surface of the dissolution medium; ●, delivery system dropped into the vessel and allowed to float at the surface of the dissolution medium; ▼, delivery system enclosed within a helical wire sinker to prevent flotation to the surface of the dissolution medium. ($N = 3$ in all of the above cases; standard deviations are not shown because they are smaller than the symbol size; modified from Pillay and Fassihi[27]).

bioavailability of bioactive agents.[28,47,48] To ascertain that drug is completely delivered from its formulation over an appropriate time period and is able to reach and cross the gut wall, an aqueous environment similar to the gut luminal fluid and a sink resembling the lipoidal nature of the gastrointestinal mucosa becomes a necessary condition for the development of a prognostic in vitro test method. Both softgel and hard shell capsules filled with vehicles which are capable of self-emulsification (due to their ability to form fine oil-in-water emulsions) offer great potential for the oral delivery of insoluble hydrophobic and poorly absorbable drugs. However, in vitro evaluation of such dosage forms have thus far been problematic, since no official dissolution method for lipid-based formulations as yet has been established. This may be due to the relative difficulties associated with the evaluation methodology of lipid-based formulations. A greater challenge is presented when poorly soluble drugs in a lipid-based vehicle are presented as lipid-filled capsules for enhancement of solubility. Such matrixes, however, are not soluble in commonly used aqueous dissolution media. With some conventional dissolution methods, the use of surfactants[48–50] or hydro-alcoholic media[47,50] have been recommended. However, it is speculated that exposure of the gelatin shell to such media may induce physical and/or chemical changes, arising either through complex formation or cross-linking reactions. Typically, sodium lauryl sulfate (SLS), an anionic surfactant, is often employed in dissolution media; however, many researchers fail to recognize that SLS will bind to cationic charges of gelatin at pH values equivalent to

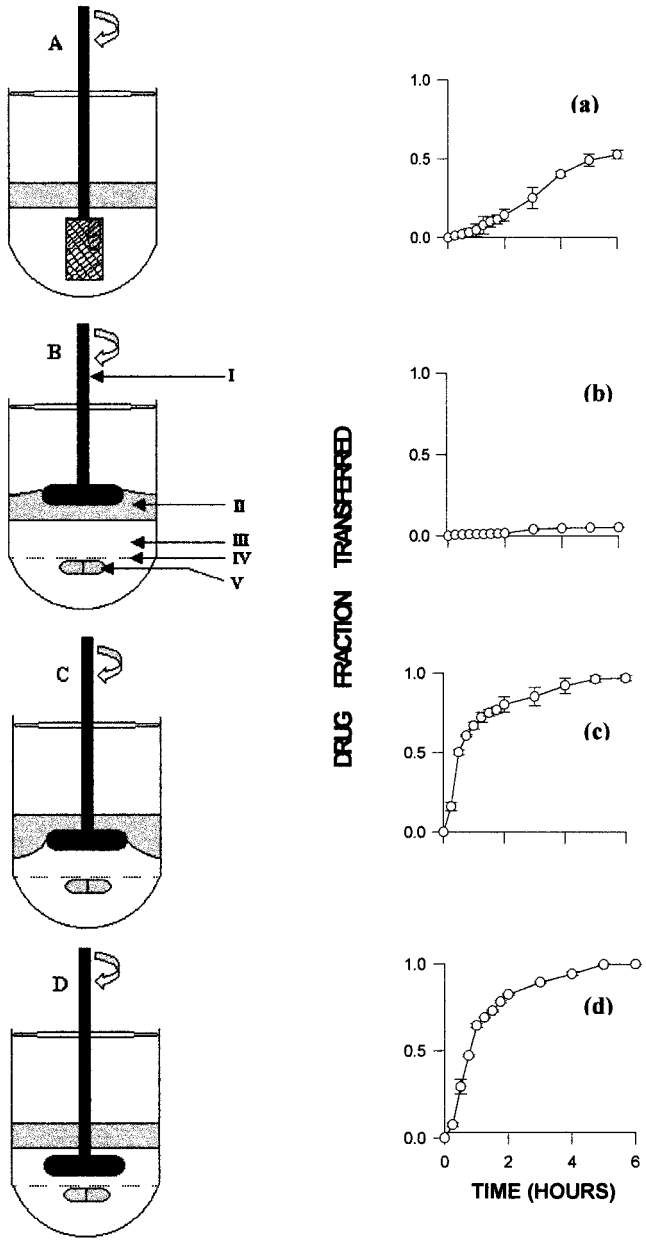

Figure 3—A comparative illustration of the four dissolution designs employed for the induction of different hydrodynamic conditions. Left panel: Key: I = Position of either rotating basket or paddle with hydrodynamic arrangements as follows. Design A: Centrally positioned in aqueous phase between boundaries of organic phase and bottom of vessel. Design B: Halfway at air/organic phase interface. Design C: Halfway at organic/aqueous phase interface. Design D: Centrally positioned in aqueous phase between boundaries of organic phase and ring/mesh assembly. Stirring rate of 75 rpm was used in all designs with exception of design D where in addition 100 rpm was also tested. II = organic phase, i.e., 100 mL 1-octanol. III = aqueous phase i.e., phosphate buffer: 400 mL for design A, 200 mL for designs B and C, 300 mL for design D. Note that 400 and 300 mL of phosphate buffer were employed in designs A and D to ensure that basket and paddle are fully immersed in aqueous phase. IV = ring/mesh assembly. V = Position of capsule either within basket or below ring/mesh assembly. Right panel: Transfer profile of lipid-based nifedipine capsule preparation derived under different hydrodynamic conditions and designs as described above ($N = 3$). (a) Profile obtained using the USP 23 rotating basket method at 75 rpm (dissolution design A). (b) Profile obtained using paddle over ring/mesh assembly halfway at air/organic interface at 75 rpm (dissolution design B). (c) Profile obtained using paddle over ring/mesh assembly halfway at organic/aqueous interface at 75 rpm (dissolution design C). (d) Profile obtained using paddle over ring/mesh assembly in aqueous phase at 100 rpm (dissolution design D). (Modified from Pillay and Fassihi[28]).

gastric pH. These interactions may influence the solubility and disintegration time of the shell and/ or true release potential of the product. Therefore, difficulties that may be experienced include, but are not limited to, exposure of gelatin shell to the organic phase, separation of poorly soluble drugs as metastable liquid crystals, lack of reproducibility in dissolution data, dosage form and lipid flotation in the dissolution vessel, etc.

In a recent report[28,51] a method which encompasses the development, design, and use of a modified two-phase dissolution media system by a novel approach for testing of either soft or hard shell lipid-filled gelatin capsules was proposed. Nifedipine was chosen as the model compound due to its water-insoluble nature (<10 μg/mL at 25 °C) and high octanol–water partition coefficient (10000:1). The experimental design takes advantage of the inherent immiscibility of aqueous phosphate buffer and 1-octanol, as well as the ability to modulate dissolution hydrodynamics and position of the formulation in the aqueous phase within the vessel (see Figure 3, i.e., schematic in left panel). Furthermore, the organic phase will act as a sink for drug removal from the aqueous phase in the dissolution vessels, a concept also recognized and pointed out in the early work of Gibaldi and Feldman[52] on the establishment of in vitro sink conditions in dissolution rate analysis and the merits of using a two-phase dissolution media system.

With USP-23 Apparatus I, it was demonstrated that the standard dissolution basket pores (mesh no. 40) and lack of appropriate hydrodynamic conditions within the basket have a significant limiting effect on drug release from the oleaginous formulation; hence, incomplete release was achieved (maximum of 50% released in 7 h; see profile in Figure 3a in right panel). As depicted in Figure 3, different hydrodynamics and various positionings of the rotating paddle was attempted to afford complete drug transfer to the upper organic 1-octanol phase from the lower aqueous phosphate buffer phase. Note that each design is accompanied by its appropriate release profile as depicted in Figures 3a–d in the right panel. With design C, induction of fluid dilatation at the organic/aqueous interface proved to be effective in encouraging rapid dissolution of the capsule shell and subsequent self-emulsification of the formulation. This essentially enabled complete drug transfer in 6 h (96.84%) (see profile in Figure 3c in right panel). Manipulation of the hydrodynamic conditions in the case of design D proved crucial in determining the rate of drug transfer and reproducibility of such a process (see profile in Figure 3d in right panel).

(iii) Determination of Dissolution Profile under Nitrogen Blanket for Oxidizable or Unstable Substances—A typical example of such substance evaluated in our laboratory will be given below. Ascorbic acid displays very poor stability characteristics in aqueous media in the presence of oxygen. As a result during the release process of ascorbic acid in a typical dissolution study, significant degradation products are simultaneously formed. To suppress the degradation process initially, the dissolution media can be purged with nitrogen gas while the gas flow would continue throughout the dissolution study. To generate a blanket of nitrogen gas over the medium within the vessel, individual vessels were sealed with the exception of allowing enough tolerance for shaft rotation. A typical profile obtained under such conditions is shown in Figure 4. Therefore full stability considerations and utilization of appropriate analytical techniques for determination of degradation and other byproducts is essential.

(iv) Glucosamine Release Study from Swellable Hydrophilic Matrix System—Typically in any dissolution study, UV spectrophotometry measurements are more preferable in terms of simplicity and cost saving. When

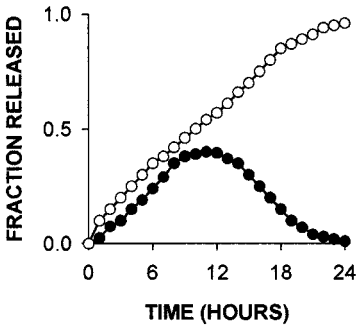

Figure 4—Typical profile for release of ascorbic acid in aqueous medium from a hydrophilic gel-based system ($N = 3$) under standard dissolution conditions showing significant degradation (●) and under modified conditions using a constant nitrogen purge (○). (From Fassihi, unpublished data).

substances do not absorb UV light often derivatization or complexation by addition of specific reagents may be adapted. Glucosamine as such does not absorb UV light. To measure the amount of glucosamine released, sufficient quantity of ninhydrin was added to the dissolution medium and color reduction as a result of glucosamine–ninhydrin complex formation could have been measured. This, however, resulted in the medium penetration into the swellable hydrophilic matrix causing significant peripheral stiffening of the matrix as a result of intragel complexation and suppression of release rate. As a result it was decided to remove samples of glucosamine solution periodically from the medium, adding to standard ninhydrin solution and measuring the color changes spectrophotometrically. Under these conditions, the rate constant of complex formation has to be optimized.

(v) Use of Reverse-Binding Technique for Evaluation of DMP 504, a Water-Insoluble Bile Acid Sequestrant—DMP 504 is a water-insoluble, cross-linked polymeric bile acid used as a nonsystemic cholesterol lowering agent, since it has the ability to bind bile salts with a slow dissociation rate. A film-coated DMP 504 tablet formulation was recently developed.[53] To evaluate the release characteristics of this dosage form, a new dissolution test method was proposed,[53] since direct measurement of drug concentration in the dissolution medium cannot be accomplished due to the water-insoluble nature and the fact that it has a binding function. A sodium cholate–phosphate buffer solution was selected as a dissolution medium. The amount of drug released from the tablet was calculated from the amount of cholate bound by the released drug at various time points using a binding calibration curve. By HPLC analysis, the bound cholate was calculated from the free cholate remaining in the dissolution medium at different time intervals. Through this approach it was determined that DMP 504 was completely released from the film-coated tablets within 15 min. Furthermore, from recovery testing on the bile salt, it was established that the reverse binding technique is robust, and values obtained were representative of complete release/binding.

Elementary and Supac-Based Dissolution Data Analysis

In the past decade many approaches have been proposed for the comparison of dissolution profiles.[54–57] In spite of the development of complicated approaches employing multivariate analysis, time series models, and mathematical models, the main problem persisting in the comparison process was the inability to define an exact measure of quantification, a point strongly acknowledged by Shah et

al. in their recent work on dissolution profile analysis.[2] Over the years, scientists have given much consideration to use of the Weibull function,[58,59] a model-dependent approach, as depicted in eq 18:

$$m = 1 - \exp[-(t - T_1)^{b/a}] \quad (18)$$

where m is the percent dissolved at time t, a is the time scale parameter, b is the shape factor, and T_1 is the location parameter. The shape factor, b, qualitatively defines the curve, i.e., when $b = 1$, the curve becomes a simple first-order exponential. If $b > 1$, the drug release rate is slow initially followed by an increase in release rate. The shape factor also provides qualitative information on diffusion and disintegration processes. The effective surface area for dissolution will be maximum after a certain time at the outset when $b > 1$, while when $b \leq 1$ no disintegration occurs at all, and the rate of dissolution will decrease steadily. The scale factor, a, provides a quantitative evaluation by differentiating the curves along the time axis. As pointed out by Polli and co-workers,[60] the Weibull model becomes fraught with an element of subjectivity because the judgment of the researcher is used in devising criteria for an adequate model fit. This further introduces a lack of metric sensitivity since as with all model-dependent approaches, no acceptance limits have been set as standard. In addition, the success of this approach relies on linearizing the dissolution data. However, a considerable curvature may be found in the upper region of the plot if the accumulated fraction of drug dissolved is not 1.0. In addition, the location parameter, which represents the lag time before the actual onset of the dissolution process, has to be estimated indirectly by a least-squares analysis or a graphical trial and error technique.

Therefore, it may be useful to consider a second category of analyses, i.e., model-independent treatment of dissolution data in order to determine the release profile similarity and concomitant dissimilarity where applicable. In this work we will focus on two classes of model-independency, namely time point or ratio test approaches and pairwise models. Model-independency, previously described by Rescigno,[61] in general would generate results for which the values do not depend on the selection of the specific parameter for fitting the data, but are dependent on the sampling times t_1, t_2,..., t_n and on an appropriate coefficient w_j representing the weight that the sampling time t_j has in the determination of the specific fitted functions.

In the time point/ratio test approach the $t_{50\%}$, $t_{70\%}$, and $t_{90\%}$ values as well as the mean dissolution times ($MDT_{50\%}$, $MDT_{70\%}$, $MDT_{90\%}$) are calculated for each formulation in each of the replicate dissolution measurements. Application of MDT provides more accurate drug release rate as compared to the $t_{x\%}$ approach and is determined as the sum of the individual periods of time during which a specific fraction of the total dose is released.[62]

The following equation (eq 19) may be used to calculate the MDT for each percentage point:

$$\mathrm{MDT} = \sum_{i=1}^{n} \hat{t}_i \frac{M_t}{M\infty} \quad (19)$$

where M_t is the fraction of dose released in time $\hat{t}_i = (t_i + t_{i-1})/2$, and M_∞ corresponds to the loading dose.

In the pairwise approach, determination of a "difference factor, f_1"[63] and "similarity factor, f_2"[19,20,63] (as outlined in the SUPAC and IVIVC guidelines) using the mean percentage released values can be performed by using eqs 20 and 21. To validate the acceptance of the f_1 and f_2 fit factors, calculations should be performed on the individual dissolution data of each formulation, which should reflect no statistical difference ($p > 0.05$) to the mean dissolution values.

The recent guidelines by the CDER at the FDA[20] describes the necessary criteria for granting biowaivers for specific changes in drug product manufacturing such as formulation changes or even changes in manufacturing site. To this end, the guidelines and specific published work[63] on extended release solid oral dosage forms describe the mathematical treatment of dissolution data derived from the pre- and postapproval changes by comparing their release profiles using the "similarity factor, f_2" which may be defined as follows:

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} w_t(R_t - T_i)^2\right]^{-0.5} \times 100\right\} \quad (20)$$

where n is the number of dissolution time points, w_t is an optional weight factor, R_t is the reference assay at time point t, and T_t is the test assay at time point t. Note that the "reference" and "test" products may be identical formulations. Optimization of release profiles may be achieved by the appropriate adoption of standard or alternative dissolution methods. The f_2 value between 50 and 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the test and reference release profiles are identical, and as the value becomes smaller, the dissimilarity between release profiles increases. Equation 20 is a logarithmic transformation of the sum of squared error. It takes the average sums of squares of the difference between test and reference profiles and fits the result between 0 and 100. It is important to note that eq 20 is for the comparison of dissolution curves in which the average difference between R_t and T_t is <100. The use of the weight factor allows some values to be more important than other values, where w_t will be >1. If all values are treated equally, then $w_t = 1.0$.

In addition, Moore and Flanner[63] in their recent work also describe an f_1 fit factor or "difference factor" as follows:

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} \times 100\% \quad (21)$$

where f_1 describes the relative error between two dissolution profiles. "It approximates the percent error between two curves. The percent error is zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the two profiles".

Advantages and Limitations Associated with the Time Point/Ratio Test and Pairwise Approaches Used in Dissolution Data Treatment

The time point approach ($t_{x\%}$) for the interpretation of dissolution data appears to be inadequate for complete characterization of the profiles, since comparison of profiles not following a single path or void of crossover are not uncommon. Consequently, the choice of single data points for the calculation of meaningful dissolution values are questionable in the case of such issues revolving around product bioequivalence. Similarly, the choice of $MDT_{50\%}$, $MDT_{70\%}$, and $MDT_{90\%}$ may not always provide accurate information when profile crossover is too close. In the case of immediate release products such crossover in drug

release profiles may not present a major problem since the time scale of the release event is very short, often in the range of a few minutes to hours. On the contrary, such occurrences with controlled release products may have a significant impact on both quality assurance during product development and establishment of in vitro−in vivo correlations. Therefore, in the characterization of such dissolution profiles, a more in-depth analysis of data could provide a better description of the overall release profile.

Polli and co-workers[60] recently undertook an extensive study to mathematically and statistically evaluate various methods for the comparison of dissolution profiles of conventional metoprolol tartrate dosage forms for the demonstration of IVIVC. One of the selected methods included the application of the "similarity factor, f_2". In this work[60] as well as in studies from our lab,[27,28] it is shown that the similarity factor, f_2" is useful in providing an overall basis for dissolution profile comparisons. In addition, the fit factors evaluate curves that cross without a canceling effect. This effect may be unavoidable when the $t_{x\%}$ and $MDT_{x\%}$ models are used. While the method appears accurate, one of the main difficulties experienced is the "dependence of metric value on length of dissolution profile". When the "similarity−difference factor approach" is employed in data treatment (pairwise procedure), it becomes apparent that the selection and determination of the number of dissolution time points play a critical role in the calculation of the similarity factor value and the subsequent decision as to whether the test and reference profiles resemble each other or not. This observation is in agreement with the latest addition to the CDER document on the dissolution guidance for immediate release products.[64] However, it should be noted that as yet no limit on the selection of the dissolution time points has been released in the case of modified release dosage forms. For example, in the case of the high-density sticking formulation of theophylline (Figure 2a), f_2 values of 49.85 and 51.30 are obtained when time points (i.e., the *n* value) up to 30.5 and 35 h are respectively selected. This is also the case for the high-density sticking system of diltiazem hydrochloride (Figure 2c), i.e., f_2 values of 47.57 and 52.09 are obtained when time points up to 15 and 25 h are selected. Therefore, marginal differences observed in the comparison of dissolution data between the "test" and "reference" products may result in rejection of the test product as it is currently stipulated in the guidelines.

Conclusions

Historically, the theories applied to dissolution have remained unchanged, though to date their application and basic understanding is essential for design and development of sound alternative dissolution methodologies as well as for deriving complementary statistical and mathematical techniques for unbiased dissolution profile comparison. The various approaches described in this review, including intervention with the ring/mesh assembly, application of two-phase dissolution media systems, use of reverse binding technique, chemical stabilization via constant nitrogen gas purge into aqueous dissolution media, and chemical complexation/interaction outside the dissolution vessel as a colorimetric tool for analytical measurements, emphasize the potential of new or alternative methods for both qualitative and quantitative in vitro dissolution analysis. In particular, and as defined by dissolution theories, strict control of sink conditions by possibly mimicking the role played by the lipoidal nature of the gastrointestinal tissue in drug dissolution and absorption is primarily an absolute necessity prior to validating any in vitro−in vivo comparison. Various model-dependent and independent techniques have been used to characterize dissolution profiles for the primary purpose of comparison. With the advent of international harmonization of scientific protocols and implementation of SUPAC guidelines including site-to-site manufacturing conditions, such process comparisons have important regulatory implications. Although not infallible, the most statistically viable approach at this stage appears to be the use of f_2 similarity factor and f_1 difference factor. As outlined earlier, one of the distinct features of these two model-independent statistical measures surpassing all other techniques for profile comparison is their unique ability for complete profile characterization. However, more data on their utility in conjunction with similarity of in vivo drug absorption profiles will provide the ultimate measure of their discerning potential.

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