Beverly Nickerson
Editor

Sample Preparation of Pharmaceutical Dosage Forms

Challenges and Strategies for Sample Preparation and Extraction

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Editor
Beverly Nickerson
Analytical Development
Pfizer Global Research and Development
Pfizer Inc., Groton, CT
USA
beverly.nickerson@pfizer.com

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To my wonderful husband Tom
and my terrific children Haley and Ashley
for their love, encouragement, and support

Preface

Analytical Chemistry is a corner stone of the drug development process. Analytical measurements and data underpin assessments and decisions that are made throughout the drug development process. Development and use of appropriate and robust analytical methods is critical to the ability to generate accurate and reliable analytical data. Sample preparation is an integral part of the analytical method and is often the most time-consuming portion of the method to perform. Developing appropriate and robust extraction and sample preparation methods can be challenging for pharmaceutical dosage forms due to the nature of the sample. Oftentimes method robustness and method transfer problems are the result of issues with the sample preparation portion of the method rather than the analysis portion of the method (e.g., HPLC chromatographic conditions).

This book is intended to serve as a resource for analysts in developing and troubleshooting sample preparation methods. These are critical activities in providing accurate and reliable data throughout the lifecycle of a drug product. This guide is divided into four sections. The first section, Chaps. 1 and 2, is an introductory section that discusses dosage form and diluent properties that impact sample preparation of pharmaceutical dosage forms and the importance of sampling considerations in generating data representative of the drug product batch. The second section of this book, Chaps. 3–5, discusses specific sample preparation techniques typically used with pharmaceutical dosage forms. The third section, Chaps. 6–9, discusses sample preparation method development for different types of dosage forms and includes information on addressing drug excipient interactions and post-extraction considerations (e.g., clarification, derivatization). It also includes discussions on method validation in Chap. 10, and applying Quality by Design (QbD) principles to sample preparation methods in Chap. 11. The last section, Chaps. 12–15, covers additional topics in sample preparation including automation, investigating aberrant potency results, and green chemistry considerations for sample preparation. The last chapter of this section discusses the ideal case where no sample preparation is required for sample analysis.

I would like to acknowledge my friends and colleagues in the pharmaceutical industry that I have worked with in supporting drug development candidates. Many of the issues we have dealt with involved various challenges with sample preparation and extraction of dosage forms. The prevalence of these issues, combined with the limited literature resources available on sample preparation of pharmaceutical dosage forms, prompted me to organize and co-teach a short course on "Sample Preparation/Extraction for Solid Oral Dosage Forms" at the 2006 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting. The next step was the writing and editing of *Sample Preparation of Pharmaceutical Dosage Forms* to provide a comprehensive guide.

I sincerely acknowledge all the authors for their dedication, efforts, and valuable contributions to this work, which I trust readers will find to be a useful resource in developing and troubleshooting sample preparation methods for pharmaceutical dosage forms. I would also like to thank David De Antonis and Ling Zhang for their support and encouragement of my work on this volume and Thomas Bush for his review and proofreading of the manuscript. Last, but not least, I would like to thank my husband Tom and my children, Haley and Ashley, for their patience, understanding, and support during the time I have spent working on *Sample Preparation of Pharmaceutical Dosage Forms*.

Groton, CT Beverly Nickerson, Ph.D.

About the Editor

Dr. Beverly Nickerson received her Ph.D. in Analytical Chemistry at the University of North Carolina at Chapel Hill. After graduate school she worked in the Analytical Research and Development Department at Hoffmann-La Roche in Nutley, NJ. She later joined the Analytical Development Department at Pfizer in Groton, CT where she is currently an Associate Research Fellow. Her primary responsibilities include working as a member of cross-functional teams to develop drug candidates, supporting formulation development efforts, developing and validating methods, problem-solving and addressing analytical issues encountered during drug development, and writing reports and sections for regulatory submissions. Dr. Nickerson has worked on early stage and late stage development compounds as well as product enhancement projects. She served on the Executive Committee of the Analysis and Pharmaceutical Quality (APQ) Section of the American Association of Pharmaceutical Scientists (AAPS) during 2001 through 2005, including Chair of the APQ Section in 2004. Dr. Nickerson has published numerous articles in peer-reviewed journals, is author of several book chapters, and has presented at various scientific meetings.

Contents

Contributors

Edmund J. Bishop, Ph.D. Quality Laboratory Operations, Celgene Corporation, Summit, NJ, USA

Daniel Brannegan, M.S. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

Xin Bu, Ph.D. Analytical Research and Development, Bristol-Myers Squibb Company, New Brunswick, NJ, USA

Sachin Chandran, Ph.D. Biopharmaceutics, Bristol-Myers Squibb Company, New Brunswick, NJ, USA

Hitesh P. Chokshi, Ph.D. Pharmaceutical and Analytical R&D, Hoffmann-La Roche Inc., Nutley, NJ, USA

Ivelisse Colón, Ph.D. Quality: CMC & QbD, Vertex Pharmaceuticals Inc., Cambridge, MA, USA

Eddie Ebrahimi, B.S. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

Paul Ferguson, Ph.D. Research Analytics, Pfizer Global Research and Development, Pfizer Inc., Sandwich, UK

Mark Harding, Ph.D. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Sandwich, Kent, UK

Dawen Kou, Ph.D. Pharmaceutical and Analytical R&D, Hoffmann-La Roche Inc., Nutley, NJ, USA

Carlos Lee, Ph.D. Research Analytical, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

Yang (Angela) Liu, Ph.D. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

K. Rick Lung, Ph.D. Global Technical Services, Operations, AstraZeneca Pharmaceuticals LP, Newark, DE, USA

Hua Ma, Ph.D. Pharmaceutical and Analytical R&D, Hoffmann-La Roche Inc., Nutley, NJ, USA

Gerald Manius, B.S. Pharmaceutical and Analytical R&D, Hoffmann-La Roche Inc., Nutley, NJ, USA

Beverly Nickerson, Ph.D. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

Jackson D. Pellett, Ph.D. Small Molecule Pharmaceutical Sciences, Genentech, Inc., South San Francisco, CA, USA

George L. Reid, Ph.D. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

Garry Scrivens, Ph.D. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Sandwich, UK

John Spirig, Ph.D. Analytical Research and Development, Bristol-Myers Squibb Company, New Brunswick, NJ, USA

Larry Taylor, Ph.D. Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA

Jian Wang, Ph.D. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

Qinggang Wang, Ph.D. Analytical Research and Development, Bristol-Myers Squibb Company, New Brunswick, NJ, USA

Gang Xue, Ph.D. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

Shangdong Zhan, Ph.D. Pharmaceutical and Analytical R&D, Hoffmann-La Roche Inc., Nutley, NJ, USA

Lin Zhang, Ph.D. Department of Engineering, Thermo Scientific Portable Optical Analysis, Wilmington, MA, USA

Zhongli Zhang, Ph.D. Analytical Development, Pfizer Global Research and Development, Pfizer Inc., Groton, CT, USA

Section A
Introduction

Chapter 1
Properties That Impact Sample Preparation and Extraction of Pharmaceutical Dosage Forms

Beverly Nickerson

Abstract A significant portion of the time spent in testing and analyzing samples is spent on the sample preparation portion of the method. Developing appropriate extraction and sample preparation methods can be challenging for pharmaceutical dosage forms. An understanding of the steps involved in sample preparation and extraction as well as an understanding of the drug, dosage form, and diluent properties that impact sample preparation is critical in developing an adequate method. These steps and properties are discussed in detail.

1.1 Introduction

Accurate analytical data are critical in the pharmaceutical industry to ensure the quality and safety of the product. During drug development, this information is used to evaluate and select formulations for use in toxicology and clinical studies, to assess manufacturing processes and to assess the suitability and stability of clinical supplies. For marketed products, analytical data are used to evaluate the suitability and stability of the commercial product.

Development and use of robust analytical methods is critical in the ability to generate accurate analytical data. Sample preparation is an integral part of the analytical method. In a survey conducted by LC-GC (Majors 1991), responses indicated that approximately two-thirds of the time spent testing and analyzing samples was spent on the sample preparation portion of the method. In addition, issues related to sample preparation accounted for one-third of the errors generated while performing an analytical method.

B. Nickerson (✉)
Analytical Development, Pfizer Global Research and Development,
Pfizer Inc., 558 Eastern Point Road, Groton, CT 06340, USA
e-mail: beverly.nickerson@pfizer.com

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Some resources are available that discuss sample preparation and extraction by specific technique (Pawliszyn 1997; Thurman and Mills 1998) or for specific fields of application (Handley 1999; Mitra 2003). This work focuses on aspects of sample preparation for assay, content uniformity, and purity testing of pharmaceutical dosage forms. Sample preparation and extraction challenges and requirements for dosage forms include (1) achieving complete extraction of the drug and impurities without causing degradation; (2) using reasonable sample preparation methods and conditions (e.g., reasonable in terms of time, effort, and solvents); (3) final prepared samples must be compatible with the analysis method; (4) method must be rugged and robust enough to meet its intended purpose; and (5) meeting the time and resource constraints in developing the sample preparation method.

The key steps in the extraction and sample preparation of drug from the dosage form as well as the properties of the drug, dosage form, and solvent that affect extraction and sample preparation are discussed in this first chapter. Specific extraction techniques and sample preparation approaches used for various types of dosage forms are discussed in subsequent chapters of this book.

1.2 Sample Preparation of Pharmaceutical Dosage Forms

The general steps of sample analysis of a drug product are outlined in Fig. 1.1. The drug product batch may consist of hundreds to thousands or millions of individual dosage units. A representative sample of the batch must be taken for use in testing. Sampling and sampling considerations are discussed in detail in Chap. 2. Dosage units from the analytical sample are then selected and prepared for analysis as dosage forms typically cannot be introduced into the analysis equipment as is, although developments in the area of sample testing with no sample preparation are discussed in Chap. 15. Sample preparation can involve a number of steps including dispersion, particle size reduction (e.g., milling, grinding, homogenization), solubilization of the analytes of interest, derivatization, concentration, sample clean-up (e.g., removing interferences), and clarification (e.g., removing insoluble materials). The sample preparation steps required depend on the dosage form type and the end analysis technique. Once the sample preparation has been completed, the sample is then analyzed by the appropriate technique (e.g., chromatography, spectroscopy, titration) and data are available for analysis, interpretation, and decision making with respect to the drug product batch.

As illustrated in Fig. 1.2, the sample preparation steps required in a given method depend on the dosage form type being tested and the end analysis technique. For solution dosage forms (Fig. 1.2a), such as oral solutions and syrups, the drug is already dissolved in solution and uniformly distributed. In these cases, sample preparation is straight forward and typically requires only dilution of the formulation in a diluent (e.g., water or mobile phase) to make it compatible with the analysis method. In some cases, sample concentration, derivatization, or clean-up may be required. For dosage forms that are powders (e.g., powders for oral suspensions or

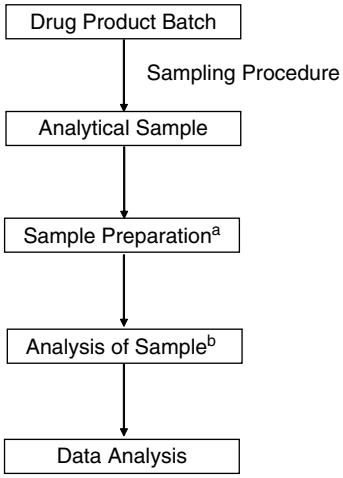

Fig. 1.1 General steps for sample preparation and analysis. (**a**) Sample preparation may include any of the following steps: disintegration/dispersion, particle size reduction (e.g., milling, grinding, homogenization), extraction and solubilization of the analytes of interest, derivatization, concentration, clean-up (e.g., remove interferences) and clarification (e.g., filtration to remove insoluble materials). (**b**) Analysis methods include chromatography, spectroscopy, titration, etc

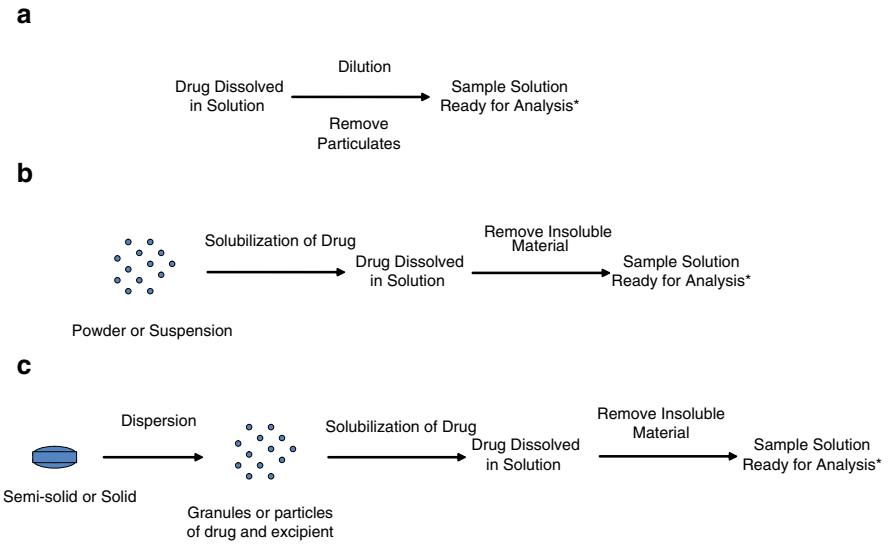

Fig. 1.2 General processes involved in sample preparation of dosage forms such as (**a**) solutions, (**b**) powders or suspensions, and (**c**) solid dosage forms. *Additional steps such as derivatization, sample concentration or sample clean-up may also be required prior to analysis

Table 1.1 Key API, diluent and dosage form properties that impact the (a) dosage form dispersion and (b) drug solubilization steps in sample preparation. The dispersion and solubilization steps are depicted schematically in Figure 1.2. Important components of the solubilization of drug step with respect to sample preparation include the extent of drug solubilization (e.g., total drug dissolved in solution) and the rate of drug solubilization

	(a) Parameters impacting dispersion of dosage forms	(b) Parameters impacting solubilization of drug	
		Extent of drug solubilization	Rate of drug solubilization
API Properties Impacting (a) and (b)		Solubility of API in diluent	Surface area/particle size Diffusion coefficient
Diluent Properties Impacting (a) and (b)	Ability of diluent to wet (solid-liquid contact angles, surface tension) and disperse dosage form Viscosity	Ability of diluent to solubilize API (solvent polarity) Ability of diluent to minimize drug-excipient interactions Volume of diluent	Volume of diluent Amount of API already dissolved
Dosage Form Properties Impacting (a) and (b)	Dosage form type (e.g., disintegrating or non-disintegrating) Excipients Manufacturing process Hardness/porosity	Drug-excipient interactions	Porosity
Other Factors Impacting (a) and (b)	Temperature (e.g., to liquefy semi-solid dosage forms) Particle size reduction techniques	Temperature	Agitation Temperature Time

lyophiles) or suspensions (Fig. 1.2b), the drug must be dissolved into solution and the final solution must be compatible with the end analysis technique. For semi-solid (e.g., creams, ointments), solid oral (e.g., tablets, capsules), and solid non-oral dosage forms (e.g., suppositories) (Fig. 1.2c), the dosage form must first be dispersed to allow efficient dissolution of the drug.

For all dosage form types except solutions, identification of an appropriate diluent is critical to ensuring dissolution and recovery of the drug from the dosage form. In addition, dispersion is important for all non-solution dosage forms. As shown in Table 1.1, the steps of solubilizing the drug and dispersing the dosage form depend on several properties of the API, dosage form, and diluent. Not all the parameters in Table 1.1 can be adjusted in sample preparation method development. For instance, dosage form type (e.g., non-disintegrating controlled release tablet) is selected based on the intended route of administration and dosing regime required to achieve efficacy. Excipients and manufacturing process are set in order to

Table 1.2 Key parameters in sample preparation method develop that impact (a) solubilization of drug from dosage forms (e.g., non-solution dosage forms) and (b) dispersion of dosage forms (e.g., solid oral dosage forms)

(a) Parameters impacting solubilization of drug		(b) Parameters impacting dispersion of dosage forms
Extent of drug solubilization	Rate of drug solubilization	
Diluent selection	Diluent selection	Diluent selection
Diluent volume	Particle size reduction techniques	Particle size reduction techniques
Time	Agitation	Agitation
	Temperature	Temperature
		Time

manufacture a stable and robust dosage form, not to make sample preparation easier. The analytical chemist is left with a subset of the parameters in Table 1.1 to use in method development and these are shown in Table 1.2. It is important, however, to understand how all the parameters in Table 1.1 affect sample preparation. If there is a change in the formulation or the manufacturing process, the impact on the sample preparation method will need to be evaluated and the method adjusted if necessary.

The key parameters to leverage in sample preparation method development are selection of the diluent, agitation conditions (e.g., shaking, sonication) including time, temperature and use of any mechanical particle size reduction techniques (e.g., grinding or homogenization). Selection of the diluent is critical to ensuring complete recovery of the drug. The solubility of the drug in the diluent must be high enough to ensure complete recovery. If not, no amount of agitation or particle size reduction can increase the recovery above this solubility limit. For non-solution dosage forms, not only is diluent selection critical but so is the means chosen to disperse the dosage form. If the dosage form remains intact, recovery of the drug may be slow or incomplete because the drug is not adequately exposed to the diluent. Dispersion of the dosage form may be performed using an appropriate diluent (e.g., water for immediate release tablets) or particle size reduction techniques (e.g., grinding). Agitation (e.g., shaking or sonication) is typically used to facilitate dispersion of the dosage form and to mix the sample solution to speed up the extraction process for all types of dosage forms. Heating may also be used to disperse semi-solid dosage forms (e.g., to melt the sample and form a solution).

The next sections of this chapter discuss details of the dissolution and dispersion steps and factors that influence these processes. Subsequent chapters of this book discuss specific extraction techniques and sample preparation approaches for specific types of dosage forms.

1.3 Properties That Impact Dispersion of Dosage Forms

As noted previously, extraction and sample preparation of drug from a semi-solid or solid dosage form typically involves two processes – dispersion of the dosage form and dissolution of the drug. Dispersion or disintegration can be defined as the breakup

of the dosage form into smaller particles or granules when in contact with a liquid. If disintegration or dispersion does not occur, the drug will not be efficiently or completely extracted from the dosage form. The disintegration and dispersion process is influenced by properties of the dosage form and the extraction diluent. Disintegration mechanisms and the factors that influence dispersion are described below.

1.3.1 Disintegration Mechanisms

Dosage form factors that impact disintegration or dispersion include dosage form type, excipients used in the formulation, manufacturing process, and other factors (e.g., hardness/porosity for tablets). For immediate release and orally dispersive tablet formulations, disintegration occurs when the tablet is exposed to water due to the properties of the disintegrant in the formulation. Several different theories have been proposed to explain the mechanism of tablet disintegration and these have been summarized in a number of publications (Lowenthal 1972; Kanig and Rudnic 1984; Melia and Davis 1989; Guyot-Herman 1992). Most immediate release tablet formulations contain disintegrants, which play a critical role in the tablet disintegration process. Disintegrants appear to function by several different mechanisms, with each disintegrant type having a dominant mechanism or a combination of mechanisms. The two most commonly referenced mechanisms are wicking/capillary action and swelling. Wicking or capillary action is the ability of the disintegrant to draw water up into the porous network of the tablet. This leads to breakup of the intermolecular hydrogen bonding forces between the particles/granules in the formulation and results in tablet disintegration. The extent as well as the rate of wicking are important factors for disintegration. The swelling mechanism involves the swelling of the disintegrant after water uptake. This causes a build up in force and subsequent breakup of the dosage form. The extent and rate of swelling are important factors leading to disintegration.

In both the wicking/capillary action and swelling mechanisms of disintegration, water or solvent uptake is critical. Water or solvent uptake by a porous structure depends on the balance between several factors including capillary forces and viscous forces and is described by the Washburn equation in (1.1) (Washburn 1921):

$$l^2 = \left(\frac{\gamma}{\eta}\frac{\cos\theta}{2}\right) rt, \tag{1.1}$$

where

l = length of liquid penetration at time t,
γ = surface tension of the penetrating liquid,
η = viscosity of the penetrating liquid,
r = radius of capillary or pore size,
θ = solid–liquid contact angle, and
t = time.

1.3.2 Factors That Impact Disintegration and Dispersion

1.3.2.1 Solvent Properties

From (1.1), it is apparent that the water or solvent uptake is dependent on factors related to the dosage form (e.g., pore size) and factors related to the water or solvent as well (e.g., surface tension, viscosity, solid–liquid contact angle). Pore size is set by the formulation and manufacturing process. Therefore, during development of the extraction and sample preparation procedure, selection of the diluent is the key parameter to ensure wicking/solvent uptake since solvent selection impacts surface tension, liquid viscosity, and wettability of the solid by the liquid. Solvent selection is also critical to ensuring tablet disintegration after solvent update by disruption of forces holding the tablet together or by swelling of an excipient.

Before tablet disintegration can occur, the solvent must wet the surface of the dosage form. The degree of wetting is dependent on the contact angle, θ, the liquid makes with the solid surface. When θ is 0°, wetting is complete, while values of θ greater than or equal to 90° are indicative of poor wetting characteristics. A value of θ equal to 180° is indicative of non-wetting (the liquid is a spherical drop on the surface). In general, the lower the surface tension of a liquid, the smaller the contact angle on a given solid. In addition, the more polar the solid, the smaller the contact angle with the same solvent (Bummer 2000). The surface tension of a liquid can be reduced by adding a surfactant or wetting agent or by increasing temperature (Banakar 1992).

After the surface of the tablet is wetted, capillarity may occur in the tablet pores. Capillarity is the spontaneous movement of a liquid into a capillary or narrow tube due to surface forces. The greater the surface tension and the finer the capillary radius that exists, the higher the liquid will rise in the capillary. Capillarity will occur spontaneously in a cylindrical pore even if the contact angle is greater than 0°, but it will not occur at all if the contact angle becomes 90° or more (Bummer 2000).

For sample preparation and extraction considerations, unless a mechanical dispersion technique is used, a solvent that will wet the tablet surface, enter the pores of the tablet, and facilitate tablet dispersion is required.

1.3.2.2 Dosage Form Properties

Dosage form factors that impact tablet disintegration and dispersion include dosage form type, excipients used in the formulation, and the manufacturing process. Dosage form type obviously impacts dispersion as some types are disintegrating dosage forms (e.g., immediate release tablets, orally dispersive tablets) which are designed to disintegrate when exposed to water while others are non-disintegrating dosage forms (e.g., sustained release tablets).

Excipients are ingredients added to the API to enable manufacture of the dosage form. For immediate release tablets, disintegration occurs due to the properties of the disintegrant and therefore the disintegrant impacts tablet disintegration. Other types of excipients can also impact drug recovery. For example, excipients such as polymers that are used to optimize or modify drug release can impact drug extraction by making it difficult to disperse the dosage form or by trapping the drug. In addition, lubricants (may hinder tablet wetting), glidants (may hinder dissolution), diluents (may impact disintegration and dissolution), and binders (may have drug–excipient interactions) may also have an impact. Drug–excipient interactions are discussed in detail in Chap. 6.

During the manufacturing process, disintegrants may be added prior to granulation (intragranular – inside the granules) or during the lubrication step prior to compression (extragranular – outside the granules) or during both of these steps. It has been shown that extragranular formulations disintegrate more rapidly while intragranular formulations disintegrate into finer particles (Peck et al. 1990; Guyot-Herman 1992). The manufacturing process used for immediate release tablets will impact the disintegration process of the tablet and subsequent dissolution of the drug. Direct compression tablets will disintegrate into primary drug particles, while wet granulation tablets will disintegrate into granules consisting of drug and excipients (Carstensen 1977).

Additional dosage form properties may impact disintegration and dispersion. For example, tablet hardness is an important factor. As tablet hardness increases, the porosity or pore diameter throughout the tablet decreases. If the pore size is too small, a longer time will be required for water or solvent to penetrate the pores and disintegration times will therefore increase. On the other hand, if the pore size is too large and allows the tablet matrix to elastically yield as the disintegrant swells, there will be no generation of force to disintegrate the tablet (Guyot-Herman 1992). Thus, if there is a significant change in tablet hardness during the course of development, there could be an impact on the ability of the sample preparation method to adequately disperse and extract the active.

As discussed in detail in Chap. 7, solid oral dosage forms can be dispersed by finding a suitable diluent (e.g., water for immediate release tablets, other diluents for controlled release tablets). For capsule formulations, the capsule shell can be removed or conditions can be found to dissolve or rupture the capsule. For non-disintegrating solid oral dosage forms such as sustained or controlled release tablets, an appropriate solvent needs to be identified to disperse the tablet. Alternatively, mechanical means such as grinding or milling can be used to disperse tablet dosage forms. As discussed in Chap. 8, for solid, non-oral dosage forms (e.g., suppositories or patches), and semi-solid dosage forms (e.g., creams, ointments), appropriate diluents may be used to dissolve excipients and disperse the dosage form. Transdermal patches may also be cut into smaller pieces and heat can be used to liquefy suppositories. Agitation is typically used to facilitate dispersion and mixing of the sample solutions for all types of dosage forms.

1.4 Factors That Impact Dissolution and Solubilization of Drug in Dosage Forms

Dissolution or solubilization of API and components of interest is required during sample preparation of non-solution–type dosage forms. Dissolution models and the factors that influence dissolution are discussed below.

1.4.1 Dissolution Models

1.4.1.1 Pharmaceutical Solids

The diffusion layer theory is the best known model for transport-controlled dissolution (i.e., dissolution rate is controlled by the rate of diffusion of solute molecules across a diffusion layer). The diffusion layer theory accounts for the dissolution rates of most pharmaceutical solids and has been used to predict dissolution rates of drugs in powder form (Higuchi 1967; Stavchansky and McGinity 1990; Grant and Brittain 1995). In the diffusion layer model, which is graphically depicted in Fig. 1.3, interaction of the solvent with the surface of a drug particle produces an infinitesimally thin layer of saturated solution of drug (concentration = C_S) around the drug particle. At the solid–liquid interface, solid–solution equilibrium exits. With increasing distance, x, from the surface of the solid, the concentration of dissolved drug decreases from C_S (at $x = 0$) to that in the bulk solution C (at $x = h$). The rate at which the drug diffuses across this layer, the diffusion layer, controls the dissolution rate. In addition, in a stirred solution, the flow velocity of the liquid dissolution medium increases from 0 at $x = 0$ to the bulk value at $x = h$.

Dokoumetzidis and Macheras reviewed various equations that have been derived and proposed to describe dissolution based on the diffusion layer model (Dokoumetzidis and Macheras 2006). In 1897, Noyes and Whitney developed an equation to describe dissolution, or "The rate of solution of solid substances in their own solutions" (Noyes and Whitney 1897). The Noyes–Whitney equation is shown in (1.2). Bruner and von Tolloczko modified (1.2) to take into account the surface area of the substance and this equation is shown in (1.3) (Bruner and Tolloczko 1900; Dokoumetzidis and Macheras 2006). Nernst and Brunner later derived the Nernst–Brunner equation, (1.4) based on the diffusion layer model and Fick's second law (Nernst 1904; Brunner 1904; Dokoumetzidis and Macheras 2006):

$$\frac{dC}{dt} = k(C_S - C), \tag{1.2}$$

$$\frac{dC}{dt} = k_1 S(C_S - C), \tag{1.3}$$

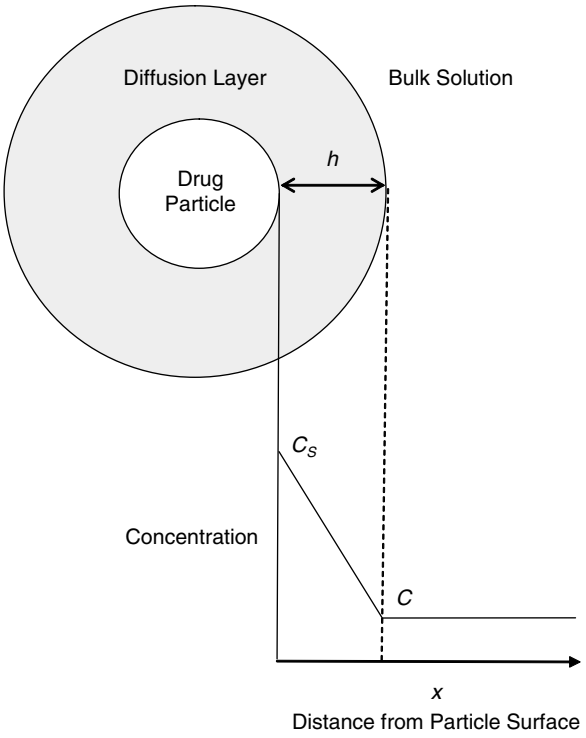

Fig. 1.3 Diffusion layer model describing the mechanism of dissolution of a solid into a solvent

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{DS}{Vh}(C_\mathrm{S} - C), \tag{1.4}$$

where

C_S = saturation concentration or saturation solubility,
C = concentration of drug in the bulk solution at time t,
k = a constant,
k_1 = a constant,
S = surface area,
D = diffusion coefficient,
V = volume of medium, and
h = thickness of the diffusion layer.

In 1931, Hixson and Crowell modified (1.3) to derive (1.5), the Hixson–Crowell cube root law, which relates time to the cube root of weight under sink conditions and accounts for the change in a particle's surface area during dissolution (Hixson and Crowell 1931; Dokoumetzidis and Macheras 2006):

$$w_0^{1/3} - w^{1/3} = k_2 t, \tag{1.5}$$

where

w_0 = initial weight of drug particle,
w = weight of the remaining undissolved drug particle at time t, and
k_2 = a constant.

1.4.1.2 Tablet Dosage Forms

Carstensen described dissolution of disintegrating direct compression tablets and wet-granulated tablets (Carstensen 1977). For disintegrating tablet dosage forms, disintegration is typically rapid and occurs first followed by drug dissolution. As the particles dissolve, the surface area of the drug decreases. The Hixson–Crowell cube root law as written in (1.6) describes the dissolution of primary drug particles after disintegration of direct compression tablets. This equation assumes that the drug is soluble in the dissolving solvent, that sink conditions exist, and that the solvent will cause disintegration of the tablet (Carstensen 1977):

$$m_0^{1/3} - m^{1/3} = K\left[t - t_1\right], \tag{1.6}$$

where

m_0 = original mass of drug in the tablet,
m = amount of drug not dissolved at time t,
$K = kSm_0^{1/3}/(\rho r_0)$,
t_1 = disintegration time,
k = intrinsic dissolution-rate constant,
S = drug solubility,
ρ = true density, and
r_0 = original radius of the particles.

For wet-granulated tablets exposed to a liquid, such as a dissolving solvent, tablets disintegrate into granules containing drug and excipient. These granules may be either porous or non-porous. For porous granules, drug diffusion into the bulk solution takes longer than penetration of the dissolving solvent into the granules. Tablet disintegration and drug diffusion into the bulk solution is therefore rate controlling. For wet-granulation tablets, the following equations by Carstensen describe the dissolution process for (a) granule → drug in solution (1.7) and (b) tablet → drug in solution (1.8) (Carstensen 1977):

$$\ln[(M/V) - C] = -k^*(t - t_{ii}) + \ln(M/V), \tag{1.7}$$

$$\ln[(M/V) - C] = -k''(t - t_i - t_{ii}) + \ln(M/V), \tag{1.8}$$

where

M = amount of drug in the tablet being dissolved,
V = volume of dissolving solvent,

C = concentration at time t,
t_i = disintegration time (tablet into granules),
t_{ii} = time required for solvent penetration into the granule,
k^* *and* k'' = apparent dissolution constants, which depend on the diffusion coefficient of the drug through the granule matrix and the radius of the granule (k^*/k'' is a function of surface area and porosity).

Carstensen notes that for poorly permeable granules, penetration of dissolving solvent into the granules is rate limiting and drug is dissolved from the granules according to the Higuchi square root law, which is shown below in (1.9) (Higuchi 1963; Carstensen 1977). In these cases, particle reduction techniques may speed up the extraction and sample preparation process:

$$Q = [KA\varepsilon t]^{1/2}, \tag{1.9}$$

where

Q = amount of drug dissolved per unit surface area (cm^2),
A = the fraction of drug in the tablet or granule,
ε = the porosity of the granules or dosage form mass,
t = time,
K = a proportionality constant and equals $2DS$, where D is the diffusion coefficient of the drug in the dissolving medium and S is the solubility of drug in the medium.

Carstensen notes that for an erosion tablet that does not disintegrate, and where the matrix erodes and releases drug, the erosion of the tablet is analogous to dissolution of a spherical particle. The disappearance rate of the tablet will follow the Hixson–Crowell cube root law, where m_0 is the amount of drug present in the dosage form at time 0 and m is the amount of drug still undissolved at time t (Hixson and Crowell 1931; Carstensen 1977). Some sustained release products are formulated by suspending drug in a film and grinding up the material, and in these cases, dissolution follows the Higuchi square root law (Carstensen 1977). For extraction and sample preparation of drug from erosion-based tablets and other types of sustained release formulations, mechanical means can be used to disperse the material and speed up drug recovery.

1.4.2 Leveraging Key Factors to Impact Dissolution During Sample Preparation

Mechanisms for dissolution of drug and drug particles are discussed above. Two aspects of dissolution are important for extraction and sample preparation – the extent and the rate of analyte dissolution. The extent of drug dissolution translates into drug recovery and is dependent on the properties of the API, dissolving or extraction solvent (e.g., diluent), and dosage form. Temperature and agitation also affect the rate of drug dissolution. All these factors are discussed below.

1.4.2.1 Extent of Dissolution

API Properties

The key limiting factor for drug dissolution from a dosage form is the solubility of the drug in the diluent. The equations in Sect. 1.4.1 show a dependence of dissolution on drug solubility in the solvent. Solubility is defined as the maximum amount of solute that can dissolve in a specific amount of solvent at a specific temperature. The solubility of a solid is dependent on the nature of both the solute (e.g., molecular size, functional groups/polarity, pK_a) and the selected dissolving solvent (e.g., polarity, pH, and buffer concentration) and the intermolecular interactions between the solute and the solvent.

Analyte functional groups and their interactions with a given solvent contribute to the overall solubility of the analyte and hence play a significant role in sample preparation/extraction. Functional groups can be classified as non-polar (hydrophobic), polar (hydrophilic), or ionic. In order for a solute to be solubilized by a solvent, the solvent must overcome the intermolecular interactions of the solute–solute molecules. In addition, the solvent molecules must be separated from each other by the solute molecules. This is likely to occur when the attractions between solute molecules and between solvent molecules are similar. If the attractions are different, then solute molecules will not separate from each other and the solvent molecules will not separate from each other and hence the solute will not dissolve (Burke 1984). In general, non-polar or hydrophobic dissolving/extraction solvents should be selected for non-polar/hydrophobic analytes and non-ionized analytes. Polar or hydrophilic dissolving/extraction solvents should be selected for polar/hydrophilic analytes and ionized analytes.

For drugs with ionizable functional groups, the pH of the solvent can be adjusted to effect ionization of the analyte (and hence polarity) and affect its solubility in the solvent as ionized groups are more soluble in aqueous and polar solvents, while non-ionized groups are soluble in non-polar solvents. Thus, when choosing a dissolving/extraction solvent for a compound with ionizable functional groups, the pK_a is important in that one can increase the solubility of the drug in polar dissolving/extraction solvents by having the pH of the dissolving solvent be at least two pH units above or below the pK_a on the side of the ionized form of the molecule, while solubility of the compound in non-polar solvents would be increased if the compound is maintained in a non-ionized form.

Solvent Properties

As discussed above, non-polar or hydrophobic solvents tend to dissolve non-polar/hydrophobic analytes and non-ionized analytes. Polar or hydrophilic solvents tend to dissolve polar/hydrophilic analytes and ionized analytes. A number of different solvent polarity classification schemes (e.g., Hildebrand Solubility Parameters, Hansen Solubility Parameters, Solvent-Selectivity Triangle) have been developed

and have been discussed in various reviews (Snyder 1978; Burke 1984). In addition, there are programs (e.g., COSMOtherm, aspenONE) available that will give theoretically calculated estimates of solubility for analytes in different solvents (Klamt 1998). These classification schemes and programs provide a means to rank solvents with respect to their polarity and to identify solvents to maximize solubility for a given solute.

Dosage Form Properties

A significant dosage form factor that impacts the extent of drug dissolution is potential drug–excipient interactions. These interactions can affect the stability of the API and the performance of the formulation. In addition, drug–excipient interactions can affect the development of analytical methodology by impacting the conditions needed to achieve complete drug recovery in assay methods or by effecting dissolution tests. Physical interactions between a drug and an excipient include such interactions as adsorption and physical trapping or inclusion of drug by a nonsoluble or gelling polymer excipient. These physical interactions can result in low recovery of the active during sample analysis and/or delayed drug release during dissolution testing. For sample preparation/extraction of drug from dosage forms with a potential for API to adsorb to excipients or become trapped by polymeric excipients, judicious selection of extraction solvent and sample preparation conditions is needed to minimize or eliminate these interactions. Otherwise, low drug recoveries may be obtained leading to inaccurate results. Drug–excipient interactions are discussed in detail in Chap. 6.

1.4.2.2 Rate of Dissolution

API Properties

As shown in the equations in Sect. 1.4.1, API-related factors that impact the rate of drug dissolution are API surface area (particle size) and diffusion coefficient. The dissolution rate will increase as the surface area of the solid increases. Therefore, solvation or dissolution rate can be increased by decreasing the particle size of the sample through crushing, grinding, milling, etc. to create increased surface area. In addition, smaller particles have a small diffusion boundary layer, resulting in faster transport of dissolved material from the particle surface (Randall 1995). Sample preparation strategies utilizing particle size reduction (e.g., grinding, ball mill) are discussed in Chap. 3. In some cases, however, particle size reduction may decrease (or fail to increase) the dissolution rate. This is caused by incomplete wetting of the solid as a result of increased adsorption of air to the particle surface and results in reduced effective surface area and decreased dissolution. The use of a surfactant in these cases may improve dissolution (Lantz 1990).