Disintegration Rate and Properties of Active Pharmaceutical Ingredient Particles as Determined from the Dissolution Time Profile of a Pharmaceutical Formulation: An Inverse Problem

STEFAN HORKOVICS-KOVATS

Stefan Horkovics-Kovats, Sandoz GmbH, Kundl, Austria

Received 13 June 2013; revised 8 October 2013; accepted 10 October 2013

Published online 11 December 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23767

ABSTRACT: Dissolution profile of a finished dosage form (FDF) contains hidden information regarding the disintegration of the form and the particle properties of the active pharmaceutical ingredient. Here, an extraction of this information from the dissolution profile without limitation to sink conditions is provided. In the article, mathematical relationships between the continuously measured dissolution profile of an FDF containing uniform or heterogeneous particles and its disintegration rate are developed. Further, the determinability of the disintegration kinetics and particle properties released from an FDF using the derived recurrent procedure was analyzed. On the basis of the theoretical data sets, it was demonstrated that the introduced analysis of dissolution profiles correctly identifies the disintegration rate of FDF containing multiple particle types. Furthermore, for known disintegration rates, the intrinsic lifetime of particles (time needed for total particle dissolution in infinite volume) released from the FDF and their relative amount can be determined. The extractable information from FDF dissolution time profiles can be utilized in designing of the formulation process, resulting in improved understanding of FDF properties, contributing thus to the implementation of quality by design in the FDF development. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:456–464, 2014

Keywords: quality by design; disintegration; dissolution; physicochemical properties; particle size; solubility; mathematical model; Volterra integral equations; inverse problem

INTRODUCTION

Quality by design (QbD) requires that the pharmaceutical quality for generic drugs has to be assured by understanding and controlling formulation and manufacturing variables.[1] Because dissolution is a common characterization test used by the pharmaceutical industry to guide formulation design and to control product quality,[2] a deep understanding of the dissolution time curves measured from finish dosage forms (FDFs) would facilitate the implementation of QbD into FDF development process.

The release of an active pharmaceutical ingredient (API) from an immediate release FDF involves two distinct processes: disintegration of the formulation and dissolution of the API from the released particles.[3] Consequently, a measured dissolution curve of an FDF includes information about both processes. Nelson and Wang[3,4] suggested an extraction of the disintegration information from the dissolution curve by a numerical calculation of the time course of tablet disintegration. They described the dissolution of the powder using the Hixon–Crowell cube-root equation[5] considering strictly sink conditions, neglecting thus any influence of the dissolved API on the kinetics of dissolving powder. When, however, taking into account the increasing amount of APIs belonging into class II and class IV of the biopharmaceutical drug classification[6] in the development pipeline of pharmaceutical companies,[7] the analysis of dissolution profiles of substances of low solubility, considering strictly sink conditions, may not be applicable for the suggested calculation of the disintegration curves of the FDFs.

The dissolution kinetics of powder formulation is sensitive to the particle shape, size, and particle size distribution of dissolving particles.[8] These parameters may further change during the process of compaction and tableting, for example, due to brittle fracture of the primary particles or their plastic deformations leading to permanent particle–particle contact regions.[9] Therefore, the properties of the API particles released from an FDF may differ significantly from the properties of the particles entering the process of FDF formation making an analysis and interpretation of dissolution curves even more challenging.

In the following pages, a relationship between the dissolution profile of an FDF and its disintegration rate will be established. It will be shown that this relationship, having a form of a Volterra integral equation of the first kind, can be for this particular case regularized to a Volterra equation of the second kind, which based on the properties of its kernel and function has a unique and continuous solution. Further, equations converting the dissolution time profile expressed as saturation state function into the disintegration rate of the FDF while taking into account the intrinsic lifetime distribution of particles (related to the particle size distribution) of the API particles released from the FDF will be derived.

Finally, the determined FDF disintegration rate will be compared with its theoretical target and analyzed the determinability of particle properties from the dissolution curves, when the disintegration of the FDF is known.

THEORETICAL DEVELOPMENT

The theory, developed in more details in Appendixes 1 to 3, is based on the following three basic assumptions:

Correspondence to: Stefan Horkovics-Kovats (Telephone: +43-5338-200-5517; Fax: +43-5338-200-3130; E-mail: stefan.horkovics-kovats@sandoz.com)

Journal of Pharmaceutical Sciences, Vol. 103, 456–464 (2014)

1. A particle entering the dissolution media is fully characterized by its initial mass, m_0 and a particle-shape-dependent dissolution rate, α,
2. Only particles, which have been released from the disintegrating FDF into the dissolution media, contribute to the dissolved amount of drug, M,
3. The disintegration process is described as the release of API particles from FDF into the dissolution media, which immediately start to dissolve after release.

Two time variables will be introduced to describe the time courses of disintegration and dissolution processes, ξ and t, respectively. The dissolution profile of an FDF will be analyzed from the point of view of an individual particle.[8]

When assuming that a particle is released from the FDF at time ξ, then its mass m will change during an infinitesimal time interval $(t,\ t + \mathrm{d}t)$ according to Eq. (1):

$$\frac{\partial m(t,\xi)}{\partial t} = -\alpha m^{2/3}(t,\xi)\left[1 - \frac{M(t)}{c_s V}\right] \tag{1}$$

where α is a particle-shape-dependent dissolution rate, M is the total amount of drug already dissolved in the medium at time t, c_s is the maximal solubility of the API, V is the volume, in which the dissolution takes place, and the exponent 2/3 reflects that the dissolution process takes place on the surface of the particle.

The change in the amount of dissolved drug $\dot{M}(t)$ results from the contribution of all particles in the dissolution medium available for dissolution at time t, therefore, it can be expressed as:

$$\dot{M}(t) = -\int_0^t N_0 \frac{\partial m(t,\xi)}{\partial t} \nu(\xi)\, d\xi \tag{2}$$

where N_0 is the total number of uniform, homogeneously distributed particles in FDF and $\nu(\xi)$ is the rate of FDF disintegration. Equation (2) represents a nonhomogeneous Volterra integral equation of first kind, which does not always have classic solutions.[10] In Appendixes 1 and 2, the disintegration rate $\nu(t)$ will be expressed from Eq. (2) for FDFs containing uniform particles, further Eq. (2) will be expanded for the case that an FDF contains $p = 1, 2, \ldots, L$ different kinds of particles with initial mass m_{0p} and relative weights w_p, having intrinsic dissolution times $t_{0p} = \frac{3m_{0p}^{1/3}}{\alpha_p}$ and released from the FDF into the dissolution medium at time $j\Delta t$. The disintegration rate $\nu(i\Delta t)$ will be expressed in Appendix 3 using a recurrent formula as:

$$\nu(i\Delta t) = \frac{g(i\Delta t)\sum_{p=1}^{L}\frac{w_p}{t_{0p}}}{\sum_{p=1}^{L}\frac{w_p}{t_{0p}} - \sum_{p=1}^{L}\frac{w_p}{t_{0p}^2}\left[1-S(i\Delta t)\right]\Theta_p(i\Delta t, j\Delta t)\Delta t} + 2\frac{\left[1-S(i\Delta t)\right]\sum_{j=0}^{i-1}\sum_{p=1}^{L}\frac{w_p}{t_{0p}^2}\left[1-\frac{i\Delta t - j\Delta t - \sum_{k=j}^{i} S(k\Delta t)\Delta t}{t_{0p}}\right]}{\sum_{p=1}^{L}\frac{w_p}{t_{0p}} - \sum_{p=1}^{L}\frac{w_p}{t_{0p}^2}\left[1-S(i\Delta t)\right]\Theta_p(i\Delta t, j\Delta t)\Delta t} \times \Theta_p(i\Delta t, j\Delta t)\, v(j\Delta t)\,\Delta t \tag{3}$$

where $S(i\Delta t)$ is the value of the saturation state function defined as $S(t) = \frac{M(t)}{c_s V}$ at time $t = i\Delta t$ and $g(i\Delta t) = \frac{\dot{f}(i\Delta t)}{\sum_{p=1}^{L}\frac{3w_p}{t_{0p}}}$, $f(t) = \frac{c_s V}{\mathrm{Dose}}\frac{\dot{S}(t)}{1-S(t)}$. Appendix 1 further shows that the function $\nu(t)$ is a unique and continuous solution of the Volterra integral equation of second kind describing the disintegration and dissolution of particles released from a formulation.

NUMERICAL EXPERIMENTS

Determination of the Disintegration Rate

To test the determination of the disintegration rate of an FDF containing three types of particles, a step-wise changing disintegration rate was assumed:

$$\nu(\xi) = \begin{cases} \dfrac{16\xi}{3\xi^{*2}}, & 0 \le \xi \le \dfrac{\xi^*}{4} \\ \dfrac{4}{3\xi^*}, & \dfrac{\xi^*}{4} \le \xi \le \dfrac{3\xi^*}{4} \\ \dfrac{16}{3\xi^{*2}}(\xi^* - \xi), & \dfrac{3\xi^*}{4} \le \xi \le \xi^* \\ 0, & \xi > \xi^* \end{cases},$$

where ξ^* is the time of complete disintegration of the formulation.

For this function, a theoretical dissolution profile was numerically calculated for $L = 3$ types of particles using Microsoft Visual Basic by solving the following system of differential equations: $\frac{\partial m_p(t,\xi)}{\partial t} = -\alpha m_p^{2/3}(t,\xi)\left[1 - \frac{M(t)}{c_s V}\right]$ and $\dot{M}(t) = \int_0^t \sum_{p=1}^{L} N_{p_0}\alpha m_p^{2/3}(t,\xi)\left[1 - \frac{M(t)}{c_s V}\right]\nu(\xi)\, d\xi$ with initial conditions $m_1(t,t) = m_1(0)$, $m_2(t,t) = m_2(0)$, $m_3(t,t) = m_3(0)$, and $M(0) = 0$. These equations represent Eqs. (1) and (2) expressed for the case when the FDF contains L particle types.

The obtained theoretical dissolution curve (theoretical data set) was used for analysis of conditions, under which the numerical calculation of the disintegration function (Eq. (3) derived in Appendix 3) resulted in acceptable determination of the disintegration rate.

Evaluation of the Determinability of Particle Properties

To answer the question whether particle properties (expressed in terms of the relative amount and their intrinsic lifetimes) can be determined out of the dissolution time profile of an FDF a disintegration rate function deliberating the particles in four discrete steps was considered. This function described the disintegration of an FDF containing three particle types with relative amounts of 1/6, 1/3, and 1/2 of the dose in the FDF, with intrinsic lifetimes of particles equaling to 2.5, 5, and 10 arbitrary time units, respectively. The FDF was assumed to disintegrate in discrete steps (at 0, 10, 20, and 30 arbitrary time units) releasing 1/4 of total amount of API during each step. Theoretical dissolution curves were calculated for doses resulting final drug concentrations of 1%, 30%, 50%, 80%, and 99% of the drug solubility, c_s. The numerically calculated theoretical dissolution profiles according to Eqs. (1) and (2) were used as theoretical data sets.