European Journal of Pharmaceutical Sciences 91 (2016) 265–277

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Dissolution and coarsening of polydisperse, polymorph drug particles liberated from a disintegrating finished dosage form: Theoretical considerations

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ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form 30 April 2016
Accepted 3 May 2016
Available online 4 May 2016

Keywords:
Dissolution kinetics
Nanoparticles
Solubility
Polymorphic forms
Particle size-independent diffusion layer thickness
Effective diffusion layer thickness
Ostwald-Freundlich equation

ABSTRACT

In order to improve the bioavailability of substances with limited water-solubility, they are often formulated as nanoparticles. Nanoparticles show enhanced dissolution properties when compared to large particles. In this paper a dissolution theory is presented that comprehensively describes the dissolution properties of both large- and nanoparticles. It comprises non-sink conditions and arbitrary shaped isometrically dissolving particles, considering particle-size-independent dissolution layer thickness and several polymorphic drug forms. The known root-laws of dissolution kinetics happen to be special cases that depend on particle-size in relation to the diffusion layer thickness i.e. whether the particles are much larger, comparable, or much smaller than the diffusion layer thickness. The presented theory explains the improved dissolution properties of nanoparticles, such as their increased solubility, almost immediate dissolution, and the dissolution kinetics which is independent from hydrodynamic conditions. For polydisperse, polymorphic particles of arbitrary shapes that are liberated from a disintegrating finished dosage form, the Ostwald ripening (coarsening of particles and transition of metastable polymorphic forms into a more stable crystalline form) is described as water mediated mass transport. The presented theory points to certain limitations of the Ostwald-Freundlich equation for nanoparticles and provides their better characterization. This way it may contribute to a more specifically targeted development of finished dosage forms and may help to reduce the bias of toxicological and environmental assessments especially for drugs that are formed as nanoparticles.

1. Introduction

The dissolution of the active pharmaceutical ingredient (API) liberated from the finished dosage form (FDF) is a prerequisite for drug absorption and hence has impact on the bioavailability. Understanding the role of API characteristics, such as particle size, shape, specific density and polymorphic form in process of dissolution, is important for targeted development of FDF and for the assessment of drug safety and efficacy. Such understanding may be achieved by analysis of dissolution time profiles using various dissolution theories, such as: diffusion layer model, surface renewal theory, and limited solvation theory (Pillay and Fassihi, 1999). The commonly used diffusion-controlled dissolution theories analyze predominantly spherical particles under sink conditions and result in equations that depend on the size of dissolving particles, such as: the "cube-root law" (Hixon and Crowell, 1931), the semi-empirical square root law expression (Niebergall et al., 1963), or the two-third root law dependency on weight (Higuchi and Hiestand, 1963).

To increase the bioavailability of poorly water-soluble compounds, they are often used in the form of nanoparticles (Junyaprasert and Morakul, 2015; Merisko-Liversidge and Liversidge, 2008). Nanoparticles, besides increased solubility, show rapid dissolution (Jinno et al., 2006) and changed dissolution properties when compared to large particles, like the hydrodynamic condition independent dissolution kinetics (Bisrat and Nyström, 1988; Liu et al., 2013; Nyström et al., 1985).

Based on the description of the dissolution of an individual particle, dissolution theories of increasing complexity were built for models such as: characterization of API powder consisting of homomorphic heterogeneous particles by their dissolution properties (Horkovics-Kovats, 2004), for determination of the disintegration rate of an FDF and properties of homomorphic, polydisperse API particles from continuous dissolution time profiles (Horkovics-Kovats, 2014), and finally for determination of the tableting-pressure-dependent disintegration kinetics and the physiochemical properties of polymorphic, polydisperse API particles from discretely measured dissolution time profiles considering additionally chemical instability of dissolved API (Horkovics-Kovats et al., 2015). The solubility of the drug in all mentioned investigations was assumed to be independent on the actual size of dissolving particles.

In the current work the influence of particle size relative to a constant diffusion layer thickness (Wang and Flanagan, 1999) on the

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http://dx.doi.org/10.1016/j.ejps.2016.05.003
0928-0987/

dissolution rate was implemented into the dissolution theory. This implementation led to the dependence of drug solubility on the actual particle size in accordance to (Lifshitz and Slyozov, 1961). The theory was developed in detail for one particle, however, equations for more complex dissolving systems are also provided in this paper.

Based on the analysis of the dissolution of uniform particles under sink conditions the various root-laws (Higuchi and Hiestand, 1963; Hixon and Crowell, 1931; Niebergall et al., 1963) were derived as special cases, in which the characteristic particle dimensions were much larger, comparable or much smaller than the diffusion layer thickness. The theory also provides explanation for the observed agitation-speed-independent dissolution kinetics of nanoparticles (Liu et al., 2013) and immediate dissolution of nanoparticles as was observed e.g. in case of cilostazol suspension (Jinno et al., 2006).

When expanding the theory for non-sink and supersaturated conditions assuming polydisperse, polymorphic particles of arbitrary shape liberated from a disintegrating FDF, it was possible to conjecture the coarsening of particles (increase in size observed in some subpopulations of particles) and the transition of metastable polymorphic form into a more stable crystalline form indicated by its lower solubility (Shefter and Higuchi, 1963), describing thus the effect of Ostwald ripening (Ostwald, 1897) as water mediated mass transfer caused by size dependent solubility of particles.

Using the derived equations, the dissolution profiles of samples containing a wide range in particle size measured by Jinno et al. (2006) could be successfully described. Based on those results limitations of the Ostwald-Freundlich equation for nanoparticles are discussed.

2. Theory

The presented theory is based on following assumptions/simplifications:

- A particle in the medium is accompanied with a cloud of dissolved drug created by its dissolution.
- The thickness of that cloud depends on the hydrodynamic conditions as the agitated medium deducts a part of dissolved drug from the cloud, reducing thus its thickness and facilitating its distribution in the medium. The thickness of the cloud is supposed to be equal to the diffusion layer thickness and is assumed to be particle-size independent (Wang and Flanagan, 1999).
- At the outer border of the cloud, the drug concentration is equal to the concentration of the bulk medium.
- The shape of the particle does not change during dissolution, i.e. the particles dissolve in an isometric fashion (Carstensen, 1980).
- The specific density of the particle does not change during its dissolution.

2.1. Diffusion controlled dissolution of one particle

The dissolution of one particle of mass m and the total amount of dissolved drug M are described by a system of equations (Horkovics-Kovats, 2004) indicating two processes.

$$\frac{dm}{dt} = -k_1 A + k_2 A \frac{M}{V} \tag{1}$$

$$\frac{dM}{dt} = +k_1 A - k_2 A \frac{M}{V} \tag{2}$$

The dissolution of the solid particle on its surface A leading to a decreased mass, m, and to a process of crystallization or precipitation acting against the particle mass loss caused by drug dissolution. The two processes are characterized by their rates: k_1 as the drug amount dissolved from unit surface area per unit of time and k_2 as the drug amount crystallized or precipitated from a solution of unit concentration to a unit surface area per unit of time.

Using the assumptions of constant form and specific density, the particle surface A and its mass m can be expressed by particle shape dependent factors f_A and f_V as:

$$A = f_A a^2 \tag{3}$$

$$m = f_V \rho a^3. \tag{4}$$

In these equations a represents the characteristic dimension of the particle and ρ its specific density. Using equations Eqs. (3) and (4) from equation Eq. (2) yields

$$\frac{dM}{dt} = k_1 \frac{f_A}{(f_V \rho)^{2/3}} m^{2/3} \left[1 - \frac{k_2}{k_1}\frac{M}{V}\right]. \tag{5}$$

The net amount of drug dissolved from the particle per unit of time expressed from Eq. (5) is

$$\frac{dM}{dt} = k_1 \frac{f_A}{(f_V \rho)^{2/3}} m^{2/3}. \tag{6}$$

This amount of drug is distributed into the space around the particle by diffusion. The distribution of the dissolved amount of drug is governed by Fick's first law:

$$\frac{dM}{dt} = -DA \left.\frac{\partial c}{\partial r}\right|_{r=a}, \tag{7}$$

where D is the diffusion rate constant, A is the surface of the particle, and a is the radius or characteristic dimension of the particle. We assign the concentration gradient in the cloud at a distance R from surface of the particle having a radius, a, as

$$G(a,R) \equiv \left.\frac{\partial c}{\partial r}\right|_{r=a+R} \tag{8}$$

and assume that at the outer border of the cloud the drug concentration is equal to the concentration of the bulk. For the pseudo steady-state (Wang and Flanagan, 1999) of the overall mass transport rates across the inner and outer spherical surfaces (at $r = a$ and $a + \delta$), where δ is the thickness of the diffusion layer (or cloud), yields:

$$4\pi a^2 G(a,0) = 4\pi (a+R)^2 G(a,R), \tag{9}$$

for $0 \le R \le \delta$, is thus

$$G(a,R) = \frac{a^2}{(a+R)^2} G(a,0). \tag{10}$$

The concentration gradient in front of a planar surface ($a \to \infty$) is then

$$G(\infty,R) = G(\infty,0), \tag{11}$$

which is constant up to the distance δ.

For the concentration difference between the distance 0 and δ from the surface of the particle having a characteristic dimension a, one obtains

$$\int_0^{\delta} -G(a,R)dR = -a^2 G(a,0) \int_a^{a+\delta} \frac{dr}{r^2} = -\frac{a\delta}{a+\delta} G(a,0) = \Delta c. \tag{12}$$