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A new approach in the prediction of the dissolution behavior of suspended particles by means of their particle size distribution

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Abstract

Though various attempts have been made in literature to model the particle size distribution of an active pharmaceutical ingredient (API) in function of the required release profile of the pharmaceutical product, so far one has not succeeded to develop a universal approach in the correlation of particle size distribution and in vitro dissolution data. In this publication, a new approach is presented on the use of particle size distribution data in the prediction of the in vitro dissolution profile of a suspension formulation. For this purpose, various theoretical experiments were done simply on paper and based on the Noyes–Whitney [A.A. Noyes, W.R. Whitney, J. Am. Chem. Soc. 19 (1897) 930–934] equation, the normalized dissolution profiles of various imaginary size distributions were calculated. For each size distribution, its weighted mean diameters were then calculated. Based on these theoretical data, a model could be developed which scientifically explains the dissolution profile of a suspension in function of its volume-weighted mean particle size (D[4, 3]). The applicability of this correlation model could experimentally be confirmed by evaluation of laser diffraction and in vitro dissolution data as they were obtained for different batches of a suspension formulation. This new approach in the correlation between particle size and dissolution may be an important analytical tool in the engineering of the particle size distribution of drug substance, and more precisely monitoring the D[4, 3] volume-weighted mean diameter may allow one to model the dissolution profile of a suspension formulation and thereby its in vivo release profile.

Keywords: Particle size distribution; Volume-weighted mean diameter; Laser diffraction; Dissolution; Correlation

1. Introduction

In pharmaceutical industry, the development of new drugs is not only related to the discovery of new pharmaceutical active ingredients (API), but also to the (chemical) development of a stable form of the API and the (pharmaceutical) development of an effective pharmaceutical dosage form. The latter should most of all be considered as a dosing device to enable the accurate and repetitive dosing of the API. However, a dosage form is far more than a simple drug carrier, since it may affect the absorption rate of the API, and thereby its effectiveness in the patient. As a result, one can state that the development of a pharmaceutical dosage form is an essential part in the entire drug development process. One of the objectives in the development of a pharmaceutical dosage form is to link what goes in the formulation in terms of ingredients and manufacturing conditions, and what comes out in the patient in terms of bioavailability, therapeutic activity and side effects. Once this relationship is known, the tools are available for the development in a shorter period of time of a better pharmaceutical dosage form with an improved therapeutic activity.

One of the aspects of the pharmaceutical dosage form, which may affect the effectiveness of the drug, is the particle size of the API [1,2]. The latter can readily be understood, since the dissolution rate of the API may highly depend on its particle size (distribution). As a means to mimic the disintegration and dissolution behavior of solid oral dose formulations in the gastro-intestinal tract of a patient, various in vitro dissolution techniques are available. Though in many cases in vitro dissolution testing is used as a quality control

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parameter to monitor the constant manufacturing of a product, it can also be used as a basis for correlation of the in vitro dissolution profile and in vivo pharmacokinetic data (IVIVC). For innovative pharmaceutical R&D organizations IVIVC is regularly applied as an important analytical tool to design effective solid oral dosage forms. Various attempts have been made as well to correlate the particle size of the API with in vitro dissolution data [3–7]. However, so far these attempts did not succeed in a universal approach for the modeling of the in vitro dissolution profile of a pharmaceutical dosage form based on the particle size characteristics of the API.

The correlation between the particle size (distribution) of an API and the dissolution profile of its solid oral dose formulation is generally quite complex, since any relationship may depend not only on the dissolution of the API, but also on the disintegration of the dosage form itself. To keep things simple, the study as described here has initially been limited to particles that are already in suspension. For the correlation between two physical or physiological parameters (e.g. particle size distribution versus in vitro dissolution profile), one may use either a statistical or a scientific model. A statistical approach can be very effective and has the advantage that the chemistry and/or physics not necessarily need to be known. However, unlike a statistical model once the chemistry and physics are known, based on a scientific model analytical data can more readily be interpreted to better understand (or predict) the behavior of the product. As will appear from this publication, the dissolution behavior of particles in function of their particle size distribution can be estimated quite well if some basic fundamentals are taken into account. In the following sections, it is shown in more detail how a theoretical model on the dissolution of suspended particles can be derived by the performance on paper of some theoretical experiments. This theoretical model is at the end empirically verified for a series of suspension formulations by the determination of both the in vitro dissolution and the particle size distribution profile.

Based on the Noyes–Whitney equation, for a product its dissolution profile can exactly be calculated, provided that the solubility of the drug (c_s) and the rate constant of dissolution (k) are known. This publication will however show that the exact values of c_s and k do not need to be known if only the correlation between the dissolution profile and the particle size distribution is aimed for. In Fig. 1, a schematic presentation is given on the stepwise approach, which is followed in the modeling of dissolution profiles based on particle size data. This approach as schematically outlined here can be used as a basis in the correlation of particle size characteristics and other physical or physiological aspects of a drug.

As a first step in the modeling of dissolution and particle size data, its theoretical basis will be discussed by means of a systematic explanation of:

a. the Noyes–Whitney equation;
b. the rate constant of dissolution (k) in function of the diameter (D) of a single particle;
c. the average rate constant of dissolution ($\bar{k}$) for a number of particles not necessarily having the same particle size.

As one can expect, the dissolution profile of a product relates to the cumulative contribution of all individual particles present in the product. For spherical particles, the theory according to Noyes–Whitney implies that if the dissolution behavior is known for a single particle with a certain size, the dissolution profile of other particles with known sizes is automatically known as well.

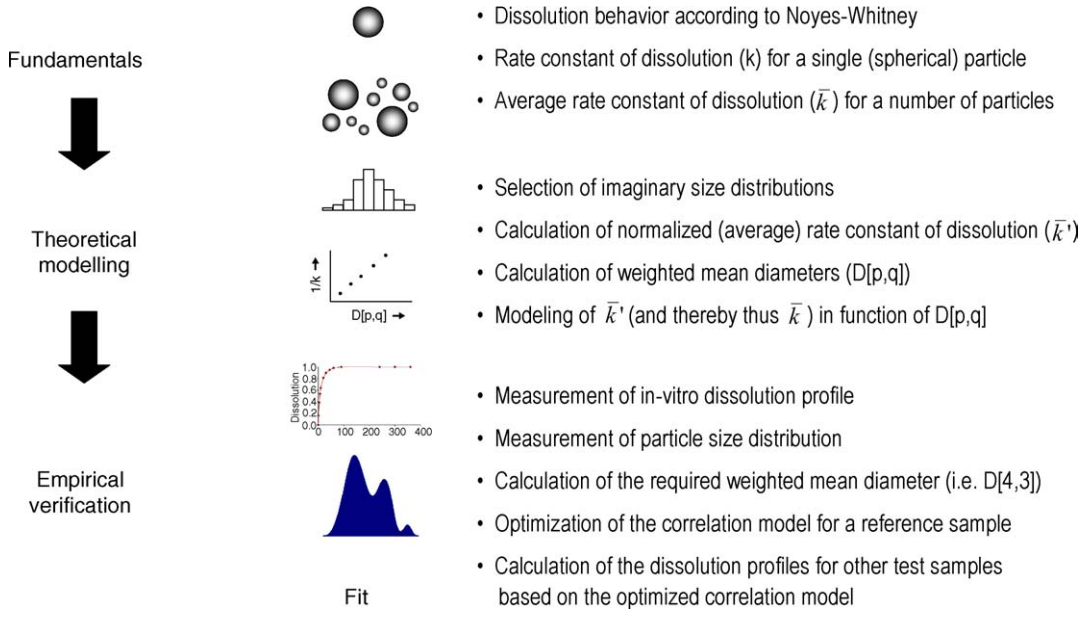

Fig. 1. A schematic presentation of the stepwise approach in the empirical modeling of the in vitro dissolution profile based on the particle size distribution profile of a suspension.