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Research paper

Dissolution and disintegration kinetics of high-active pharmaceutical granules produced at laboratory and manufacturing scale

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ABSTRACT

The effect of process scale-up from 4 to 400-L high-shear granulator on the release kinetics of the active ingredient from pharmaceutical granules has been investigated. The dissolution and disintegration rates of the granules were measured simultaneously by the combination of UV/vis spectroscopy and static light scattering. The granule batches were found to consist of sub-populations with qualitatively different dissolution behavior: "weaker" granules that disintegrated during dissolution, and "stronger" granules that retained their size and from which the active ingredient was gradually leached. The existence of these sub-populations was attributed to non-uniform distribution of normal and shear forces that prevail in granulators of different size. This hypothesis was confirmed by preparing granules at increasing values of the Froude number at the 4-L scale, and observing a transition from the break-up dissolution mode to the leaching dissolution mode with increasing granule densification. The simultaneous observation of solute concentration and particle size distribution during granules dissolution proved to be a useful tool for the understanding of dissolution mechanisms and for identifying non-uniformities of process conditions that can occur during scale-up.

1. Introduction

The release rate of an Active Pharmaceutical Ingredient (API) is one of the most important quality attributes of pharmaceutical solid dosage forms since the shape of the dissolution curve directly affects the *in vivo* absorption and ultimately the bioavailability of the drug [1]. The manufacture of solid dosage forms such as tablets typically consists of a series of processing steps, starting from the crystallization of the API primary particles, through dry or wet granulation, to blending, tablet compression and coating [2,3]. The dissolution process can then be thought of as an inverse sequence: dissolution of the coating layer is the first step, followed by wetting and disintegration of the tablet cores, dissolution and break-up of granules, and finally dissolution of individual particles of the API and excipients. Thus, the entire processing history can to some extent be reflected in the dissolution curve. However, typically only the final product tends to be subjected to dissolution testing [4,5] while the contribution of the intermediate steps to the API release rate is not quantified. Parameters such as the size distribution and bulk density of granules after the granulation step are often measured as an indication of batch-to-batch processing consistency, but it is generally unknown to what extent any variation in these parameters affects the API release from the final product. At the same time, there can be other parameters that are not routinely measured – such as the internal microstructure of granules [6] or their wetting and disintegration rate [7] – which could be far more indicative of the final product performance and its variability. The measurement of granule dissolution and its comparison with the dissolution/release kinetics of the final tablet can reveal the relative contribution of each processing step (granulation, tableting) to the final product performance.

The relationship between the internal structure of granules and their dissolution rate has been subject to a few experimental and theoretical studies in the past. However, only simplified model formulations produced at the laboratory scale were typically considered. For example, Ansari and Štěpánek [8,9] have systematically varied the porosity of granules, the size of primary particles and their spatial location within granules produced by fluid-bed granulation and related these parameters to the release kinetics of the formulation components. Computational models enabling the simulation of granule and tablet dissolution while considering their microstructure have also been developed [10–12]. The solution of convection–diffusion equations in the fluid phase, along with tracking the solid–liquid interface of the dissolving granules made it possible to relate granule microstructure and formulation

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component properties to the overall dissolution rate and the evolution of particle size.

In theory, three elementary mechanisms could be identified during granule dissolution [13]: (i) *leaching*, during which the API would be gradually depleted from the granule by diffusion, resulting in an increase in the granule internal porosity but not affecting the granule external size; (ii) *surface erosion*, during which individual primary particles would be gradually detached from the granule surface due to dissolution of solid bridges, and the granule size would decrease in time; and (iii) *break-up*, during which the granule size would also decrease, but this would happen in a more abrupt manner and the daughter fragments would have various sizes (Fig. 1). It can be expected that in a real sample, all three mechanisms may be present simultaneously to a varying extent during different stages of the dissolution process, and there can be sub-populations of granules that are more prone to one or the other mechanism. The overall observed dissolution curve would then be a superposition of dissolution curves from individual particles that form the population [14].

The measurement of particle size during the dissolution of single-component particles has been reported in the literature for both individual particles [15,16] and for particle populations [17]. The size distributions of particles that emerge from disintegrating tablets have also been measured [18,19]. The measurement of particle size and structure during dissolution can reveal not only the dissolution mechanism, but also provide some information about the process by which the particles were originally formed (inverse problem). The simultaneous observation of granule microstructure and release kinetics from model pharmaceutical formulations by the coupling of X-ray microtomography and UV/vis spectrophotometry has been recently demonstrated by Kašpar et al. [20] and used for explaining the effect of process parameters on the shape of the release curve via diffusion limitations. In a similar spirit, van Kampen et al. [21] have used the measurement of dissolution kinetics for the evaluation of coating thickness uniformity and for the assessment of the quality of the coating process.

The aim of the present work was to relate the dissolution kinetics of pharmaceutical granules to their manufacturing process parameters, addressing specifically the problem of scale-up [22]. A new methodology for the simultaneous measurement of particle size distribution and the amount of dissolved API has been applied for the first time to investigate the effect of process scale-up on the dissolution mechanism of pharmaceutical granules, which were produced in a laboratory-scale 4-L granulator and a production-scale 400-L granulator using a formulation characterized by a high content of the active ingredient. The simultaneous measurement of particle size distribution and release rate made it possible to identify the relative contribution of granule disintegration and intrinsic dissolution kinetics of the API to the overall dissolution process. It has been found that although the bulk properties of the granules produced at different scales were comparable and their composition was identical, their dissolution behavior was different due to the presence of granule sub-populations with different internal microstructure and therefore different disintegration and drug release mechanisms.

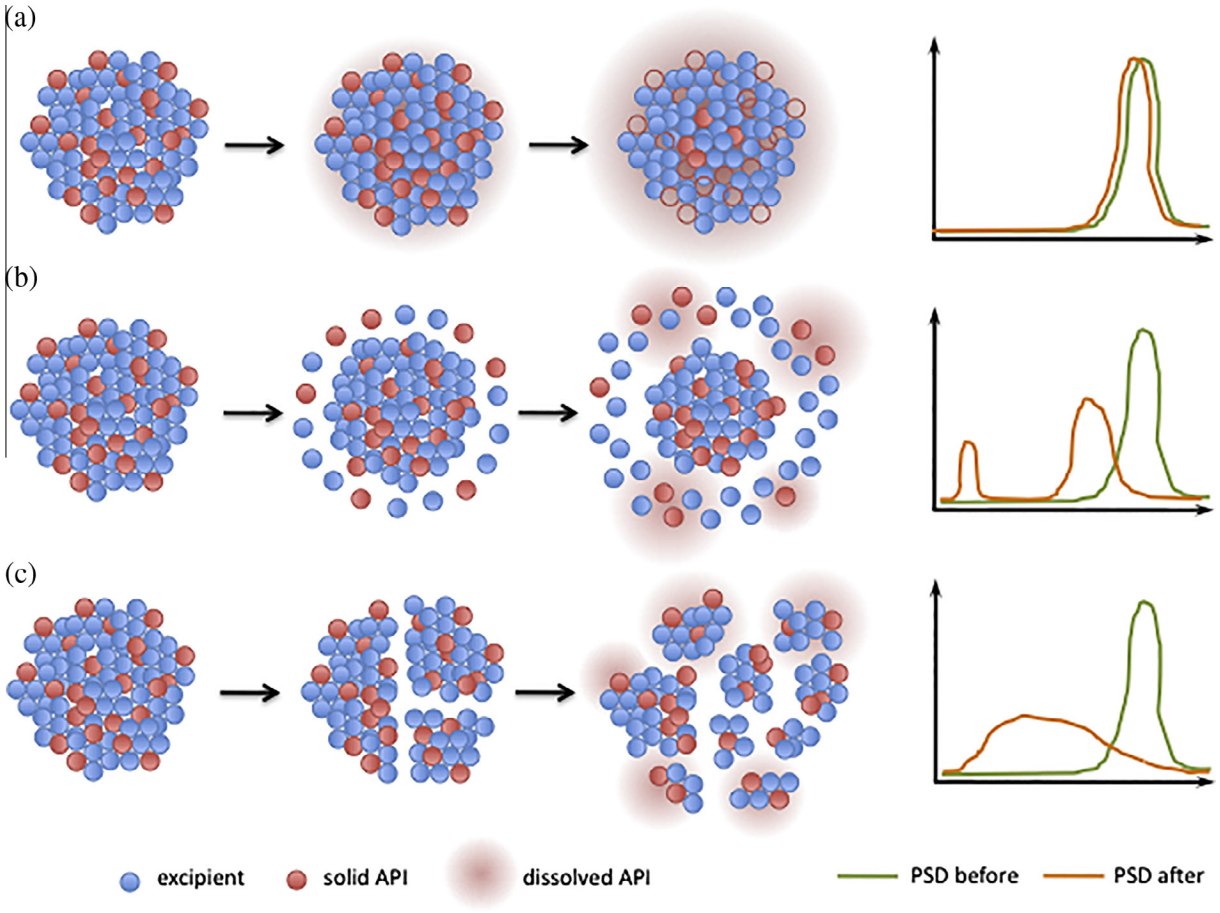

Fig. 1. Schematic illustration of theoretical elementary disintegration mechanisms and the accompanying change of particle size distribution. (a) Leaching; (b) surface erosion; (c) breakup.