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A Simple and Inexpensive Image Analysis Technique to Study the Effect of Disintegrants Concentration and Diluents Type on Disintegration

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ABSTRACT

Tablets disintegration is often the result of a size expansion of the tablets. In this study, we quantified the extent and direction of size expansion of tablets during disintegration, using readily available techniques, that is, a digital camera and public domain image analysis software. After validating the method, the influence of disintegrants concentration and diluents type on kinetics and mechanisms of disintegration were studied. Tablets containing diluent, disintegrant (sodium starch glycolate, crospovidone, or croscarmellose sodium), and lubricant were prepared by direct compression. Projected area and aspect ratio of the tablets were monitored using image analysis techniques. The developed method could describe the kinetics and mechanisms of disintegration qualitatively and quantitatively. Sodium starch glycolate and crospovidone acted purely by swelling and shape recovery mechanisms. Instead, croscarmellose sodium worked by a combination of both mechanisms, the extent of which changed depending on its concentration and the diluent type. We anticipate that the method described here could provide a framework for the routine screening of tablets disintegration using readily available equipment.

Introduction

Disintegrants are excipients incorporated into tablets formulations to promote disintegration. Disintegration is the process by which oral solid dosage forms break up into smaller particles on exposure to an aqueous medium, resulting in a net increase in the surface area of contact between the dosage form and the wetting liquid. This is expected to accelerate the drug release into the medium, which potentially enables a prompt therapeutic effect. Despite that disintegration is an essential prerequisite for obtaining immediate drug release from tablets, a deep understanding of this phenomenon has remained elusive for long. Only very recently, with the advent of new analytical techniques, the disintegration process has been investigated more systematically. Three recent reviews have started to shade light on relevant aspects of tablet disintegration.[1-3] Two are thought to be the main mechanisms of tablets disintegration, that is, swelling and shape recovery: swelling is an omnidirectional size enlargement of the disintegrant particles, resulting from the disentanglement of polymer chains, which is driven by the plasticizing effect of water on the polymer. By contrast, shape recovery (or strain recovery) is not an omnidirectional, but a unidirectional expansion of the disintegrant: it is believed that compressed polymer particles within the tablets remain deformed in a metastable, high energy state conformation. On contact with water, the stored energy is released and the particles regain their original shape, expanding in the opposite direction to that of the compression.[1,2] This preferential polymer expansion in the axial direction, as a result of relaxation from the directional stresses imposed by the previous compression, has also been described and studied for hydroxypropyl methylcellulose tablets.[4] The volume enlargement generated by either the swelling or the strain recovery of the disintegrant transforms tablets defects into microcracks, which results in further ingress of water between the pores, thus leading to disintegration.[3] Wicking, which is the liquid penetration between the pores of the tablets by capillary action, does not seem to promote active tablet disintegration because it does not directly generate the pressure required to break bonds between

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particles. Wicking is rather responsible for providing the water necessary for the actual disintegration by swelling and shape recovery to occur.[2,3,5]

Imaging techniques have become a powerful tool in the armoury of formulation scientists. Imaging-based methods have been used to qualitatively and quantitatively describe swelling and erosion of modified-release dosage forms.[4,6-9] In the context of immediate-release tablets, several techniques based on image analysis have been used to study the disintegration of tablets.[10-14] Moreover, Quodbach et al.[15] have used real-time magnetic resonance imaging (MRI) to visualize cross-sections of tablets during disintegration, providing information about the mechanisms of action of different superdisintegrants. Their work was based on the assumption that swelling and shape recovery are the 2 main mechanisms of action of disintegrants. Tablets containing crospovidone (PVPP) disintegrated mainly by shape recovery, while other superdisintegrants, including sodium starch glycolate (SSG) and croscarmellose sodium (CCS), acted mainly by swelling.[15] These results were in agreement with the findings of other authors[16] and were confirmed by further studies of the same research group.[17,18] The main limitation of real-time MRI is that this technique is not yet commercially available.[15] Thus, it would be highly desirable to develop a readily usable imaging method to study the mechanism of tablets disintegration. In this study, we have addressed this need.

This study was designed based on the assumption that superdisintegrants work mainly by swelling (omnidirectional expansion) or shape recovery (unidirectional expansion) mechanism.[15-18] We hypothesized that swelling and shape recovery of given tablet formulations could be measured by quantifying changes in projected area and aspect ratio (AR) (radial dimension/axial dimension) of tablets. For instance, an expansion of the tablet accompanied by a negligible change in AR would signify that disintegration occurred by omnidirectional swelling, whereas a tablet expansion with a major reduction in AR would explain a unidirectional shape recovery mechanism. In this work, changes in both projected area and AR of tablets during disintegration were monitored by taking images of the disintegration using a digital camera. Quantitative data were extrapolated from the image sequences using ImageJ, a public domain image processing program. Thus, the one developed here could be a readily available and simple-to-adopt method to study disintegration.

The aims of this study are as follows: (1) to develop and validate a readily accessible method to study mechanisms and kinetics of tablets disintegration; (2) to use this technique to understand the effect of the disintegrants concentration on disintegration; and (3) to use this technique to study the effect of diluents on disintegration.

Materials and Methods

Materials

The following disintegrants were used: SSG (Explotab-JRS Pharma), and CCS (Vivasol-JRS Pharma); these disintegrants were kindly donated by Rimon Chemical Co. (Amman, Jordan). The third disintegrant, PVPP (Kollidon CL-SF) was kindly donated by BASF, Jordan. The following diluents were used: dibasic calcium phosphate anhydrous (DCP, Emcompress-JRS Pharma) was gifted by Rimon Chemical Co.; α-lactose monohydrate (Foremost #316 Fast Flo NF) was received from Foremost Farms; and ethyl cellulose (EC, Ethocel 7 Premium-Dow Chemical Company) was donated by Colorcon Limited (Dartford, UK). Magnesium stearate was used as a lubricant and was purchased from Laboratory Rasayan (Gujarat, India).

Methods

Preparation of Tablets

Diluents and disintegrants were weighed and manually mixed in a glass vial for 8 min. After addition of the lubricant, the mixing was continued for further 2 min. Composition of the formulations and their abbreviations are summarized in Table 1. Tablets of 1200 mg were prepared by compression at a pressure of 148 kg/cm^2 for 30 s using a manual press (Riken Seiki, Ojiya, Japan), equipped with 13-mm flat-faced punches.

Tablets containing only disintegrants (Table 1) were also prepared by compressing 600 mg of each of the disintegrants under the same compression settings.

Tablet Tensile Strength

The hardness of each tablet formulation ($n = 3$) was measured using a hardness tester (TBH325; Erweka, Heusenstamm, Germany). The obtained values of crushing force (H) were converted into tensile strength (TS) based on the following equation:

$$TS = \frac{2 \cdot H}{\pi \cdot D \cdot t} \quad (1)$$

where t is the tablet thickness, measured by a caliper (Absolute Digimatic; Mitutoyo, Kawasaki, Japan) and D is the tablet diameter. The tensile strengths of all tablets formulation are reported in Table SI1.

Image Acquisition

Tablet disintegration was recorded using a digital camera (Canon 700D; Canon, Tokyo, Japan) fitted with an 18-55 mm lens (Canon). A PYREX™ crystallizing dish (14 cm × 7 cm) was placed in front of the camera, and a light source (tungsten light) was positioned right behind the dish. The dish was filled with 600 mL of distilled water. A custom-made stainless steel mesh was placed inside the dish with the concave side facing up (Fig. SI1A). The tablet to test was rapidly laid flat on the mesh using tweezers (Fig. SI1B and C). During the disintegration process, photographs of the tablet were taken using the "continuous shooting" mode at an average speed of 105 frames per minute. Acquisition of images was initiated at least 1 s before the tablet was placed on the mesh. A stopwatch was placed in the image area to record the exact time at which each image was taken; this was done to obviate the fact that time intervals between frames were not exactly constant. All tablets formulations were tested in quintuplicate, except disintegrant-only tablets (Table 1) that were assessed in triplicate.

Image Analysis

Image analysis was carried out on 10 to 16 images from each sequence. The images were opened in ImageJ (1.49v; National Institutes of Health) as a single sequence of images, that is, "stack" of frames, each stack covering the whole disintegration process for the tablet and each frame corresponding to a single time point. Images of the stack were converted to black and white using the binary threshold algorithm of ImageJ: the "Default" thresholding method was applied for all images, except tablets containing 100% disintegrant, which were binarized using the "Triangle" thresholding method. The black object corresponding to the tablet was then selected as region of interest; "area" and "shape descriptors" of the regions of interest of each frame of the stack were measured. Results were recorded as area (i.e., projected area of the tablet) and AR (i.e., radial/axial dimensions). Values of the projected area measured at different time points during disintegration were used to plot the change in tablet size (%) over time. Values of AR of the tablet at time 0 (t_0) and at the time of maximum size expansion during disintegration (t_{smax}) were also presented.