Tablet Disintegration Studied by High-Resolution Real-Time Magnetic Resonance Imaging

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Received 19 September 2013; revised 22 October 2013; accepted 25 October 2013

Published online 25 November 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23789

ABSTRACT: The present work employs recent advances in high-resolution real-time magnetic resonance imaging (MRI) to investigate the disintegration process of tablets containing disintegrants. A temporal resolution of 75 ms and a spatial resolution of 80 × 80 μm with a section thickness of only 600 μm were achieved. The histograms of MRI videos were quantitatively analyzed with MATLAB. The mechanisms of action of six commercially available disintegrants, the influence of relative tablet density, and the impact of disintegrant concentration were examined. Crospovidone seems to be the only disintegrant acting by a shape memory effect, whereas the others mainly swell. A higher relative density of tablets containing croscarmellose sodium leads to a more even distribution of water within the tablet matrix but hardly impacts the disintegration kinetics. Increasing the polacrilin potassium disintegrant concentration leads to a quicker and more thorough disintegration process. Real-time MRI emerges as valuable tool to visualize and investigate the process of tablet disintegration. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:249–255, 2014
Keywords: excipients; tableting; polymers; solid dosage form; materials science; MRI; tablet disintegration; superdisintegrants; disintegration mechanism; shape recovery

INTRODUCTION

The role of disintegrants in promoting the disintegration of tablets and thereby enhancing the dissolution rate of a drug is widely acknowledged. Their general purpose is to generate the smallest possible particles of a tablet in the least amount of time to maximize the exposed surface area of the incorporated drug substance, which in turn accelerates its release from the particles. Nevertheless, the underlying mechanisms of action and the physicochemical characteristics that influence the dissolution kinetics are not yet fully understood.

Tablet disintegrants mainly comprise modified starch and cellulose as well as synthetic polymers. The natural polymers are cross-linked to achieve insolubility, whereas carboxylic functions are introduced to improve the hydrophilic properties. The most widely used synthetic polymers are cross-linked polyvinylpyrrolidone (crospovidone) and a copolymer of cross-linked methacrylic acid and divinyl benzene (polacrilin potassium).[1–3]

The forces required to overcome the cohesion in a tablet are mostly thought to be generated by swelling, shape recovery, and wicking.[4] Swelling particles expand omni-directionally and push the surrounding tablet matrix apart until the bonding forces are too weak and the tablet breaks into pieces. In contrast to swelling, shape recovery is a two-step process.[5] During tableting, the shape of the disintegrant particles is permanently altered. The corresponding high-energy state of the polymers is stabilized by entangled polymer chains or localized crystallization. When water and the deformed particles come into contact, water molecules enhance the mobility of the polymer chains and the particles regain their original shape. Unlike the omni-directional swelling, shape recovery acts as a uni-directional process, that is, in the opposite direction of compression. Thirdly, if a disintegrant acts by wicking, the hydrophilic properties of the disintegrant suck water into the tablet. This water is supposed to annihilate the bonds within the matrix and therefore causes disintegration. Nevertheless, wicking is not able to explain the observable disintegration process during which particles actively detach from the tablet core. Presumably, it supports swelling and shape recovery of the disintegrating particles by absorbing more water into the tablet.

Although extensive work has been devoted to factors influencing the disintegration process,[6–8] only few authors investigated the mechanisms of different disintegrants. One of the earliest systematic studies was performed by Patel and Hopponen,[9] who found that starch particles swell. Since then, swelling has been perceived as the major mechanism of action for most disintegrants and the swelling pressure has been taken as a suitable determinant for the disintegration ability of an excipient as proposed by List and Muazzam.[10,11] Shape recovery was also discovered in starches[12] and discussed as disintegration mechanism,[4] but only recently described for crospovidones.[13] Similarly, Bele and Derle[14] recently concluded that the polacrilin potassium disintegrant Kyron T-314 mainly acts by wicking.[14]

Obviously, the outer appearance of a disintegrating tablet reveals only limited information about the underlying mechanism. On the other hand, this situation may change if it were possible to adequately visualize the process of disintegration

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This article contains supplementary material available from the authors upon request or via the Internet at http://onlinelibrary.wiley.com/.

Journal of Pharmaceutical Sciences, Vol. 103, 249–255 (2014)

Table 1. Abbreviations of Used Excipients

Brand Name	Substance	Abbreviation
Explotab	Sodium starch glycolate	SSG I
Primojel	Sodium starch glycolate	SSG II
Amberlite IRP88	Polacrilin potassium	PP I
Kyron T-314	Polacrilin potassium	PP II
Polyplasdone XL	Crospovidone	XPVP
Ac-Di-Sol	Croscarmellose sodium	CCS

from within a tablet, for example by magnetic resonance imaging (MRI). Advanced MRI techniques nowadays allow for dynamic investigations of a thin cross-sectional slice through a tablet using movie recordings at high spatial and temporal resolution. An early version of dynamic MRI at 425 ms temporal resolution was applied by Tritt-Goc and Kowalczuk[15] to investigate acetaminophen tablets in acidic water, which resulted in an erosion rather than a true disintegration. While the in-plane resolution of the images was 117 × 117 μm, the use of a large section thickness of 2000 μm prevented a more detailed analysis because of extensive partial volume effects merging multiple excipient particles and water. In general, however, MRI has hitherto mainly been used to investigate the relatively slow kinetics of swelling over a time scale of hours, for example, see Refs. 16–21 and not for the description of rapid disintegration processes.

The primary aim of this study is the development and introduction of a new method for the nondestructive visualization and quantitative evaluation of rapidly disintegrating tablets by exploiting recent technical advances in high-resolution real-time MRI.[22,23] The approach is applied to the investigation of tablets containing different disintegrants at variable concentration and density to further detail the mechanisms of action and spatiotemporal characteristics of the respective disintegration processes.

MATERIALS AND METHODS

Materials

The following disintegrants were used in the tablet formulation: croscarmellose sodium (Ac-Di-Sol; FMC BioPolymer, Wallingstown, Ireland), sodium starch glycolate (Explotab; JRS Pharma, Rosenberg, Germany, and Primojel; DMV-Fronterra Excipients, Goch, Germany), crospovidone (Polyplasdone XL; ISP, Waalwijk, Netherlands), and polacrilin potassium (Amberlite IRP88; Rohm and Haas France SAS, Chauny, France; Kyron T-314; Corel Pharma Chem, Ahmedabad, India). Dibasic calcium phosphate (Di-Cafos C92-14; Chemische Fabrik Budenheim, Budenheim, Germany) was used as filler, and magnesium stearate (Parteck LUB MST; Merck, Darmstadt, Germany) as lubricant. Dibasic calcium phosphate was chosen as filler for its insolubility but easy wettability in water. Hence, solubility effects of the matrix on the disintegration process were minimized. The disintegrants and their abbreviations are summarized in Table 1.

Blend and Tablet Preparation

Mixtures contained 97.5% filler, 2% disintegrant, and 0.5% lubricant. Mixtures of 20 g were prepared and blended for 10 min in a Turbula-Mixer (T2C; W.A. Bachofen AG, Basel, Switzerland). After addition of the lubricant, mixing continued for another 2 min. To investigate the influence of different PP I concentrations, mixtures containing 0.5%–16% PP I and 0.5% of magnesium stearate were prepared likewise.

Tablets were prepared on a rotary die press (Pressima MX Eu-B/D; IMA Kilian, Cologne, Germany) using 10 mm flat-faced punches. Seven hundred milligrams of powder were weighed and filled into the die manually. The tablet height was adjusted to compress tablets to a porosity of either 15% (comparisons of all disintegrants and varying concentrations of PP I) or to porosities ranging from 15% to 35% in 5% steps (for tablets containing CCS). The true density of the excipients was determined with a helium pycnometer (AccuPyc 1330; Micromeritics, Norcross, Georgia) and the height for the chosen relative density calculated. Six tablets of each batch were analyzed 5 days after production. For simplification, tablets containing a certain disintegrant will be referred to with their abbreviation.

Real-Time MRI

All measurements were performed on a 9.4 T 30 cm-bore MRI system (Bruker Biospin, Ettlingen, Germany) with a Bruker BGA12S gradient system yielding a maximum gradient strength of 660 mT/m and slew rate of 4570 T/(m s). Mildly T1-weighted real-time MRI was based on a radial FLASH sequence with pronounced data undersampling.[24] Dynamic acquisitions were performed with a repetition time TR = 3.0 ms, echo time TE = 1.8 ms, and flip angle = 5°. The images covered a field of view of 25.6 × 25.6 mm with an in-plane resolution of 80 × 80 μm and a section thickness of 600 μm. The temporal resolution was 75 ms using only 25 radial spokes per frame.

The images were reconstructed by regularized nonlinear inversion (NLINV)[22,23] as recently described for human real-time MRI of cardiac function and flow.[25–27] However, the present use of much stronger magnetic field gradients for spatial encoding than applicable for human studies required special eddy current corrections[28,29] to properly sample the radial data sets. Offline reconstructions of serial images employed a parallelized algorithm of the NLINV method implemented on a computer equipped with 8 graphical processing units (GPU) and a specially designed library of newly developed basis functions for the efficient computing on multiple GPUs.[30] The current version achieves a reconstruction speed of about 20 frames per second.

Real-time MRI data sets were acquired over a period of 28 s to cover the entire disintegration process. Acquisitions were started at least 1 s before releasing the tablet into a water-filled cavity (see below). While preliminary tests were performed with tap water, subsequent recordings achieved a twofold higher signal-to-noise ratio by using a 4 mM solution of $CuSO_4 \times 5 H_2O$, which shortens the proton T1 relaxation time, but has no influence on tablet disintegration.

MRI-Compatible Reaction Cavity

Standardized manipulation of all tablets was assured by a custom-made device tailored to the Bruker gradient system BGA12S (inner diameter 118 mm) and the phased-array head coil for rats (coil elements pointing upward). The reaction cavity was positioned on top of the coil array, precisely fitting the hollow curvature of the coil body to ensure the nearest coil-to-tablet distance and highest MRI sensitivity possible. The tablet-launching device was loaded by placing a single tablet

 DOI 10.1002/jps.23789