Modifying Drug Release and Tablet Properties of Starch Acetate Tablets by Dry Powder Agglomeration

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Received 30 March 2006; revised 7 July 2006; accepted 25 August 2006

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20784

ABSTRACT: In this study three model drugs (*N*-acetyl-D-glucosamine (NAG), anhydrous caffeine, and propranolol hydrochloride) were agglomerated with starch acetate (SA) by mixing the binary powders on a stainless steel (SS) plate. Agglomeration was induced by triboelectrification of the particles during mixing, and it was evaluated as a method to achieve controlled drug release rate. These agglomerates, mixed with different amounts of a disintegrant, were compressed into tablets whose dissolution characteristics were determined. Triboelectric measurements showed that when the drugs were in contact with SS, charges of the opposite polarity were generated to SA (+) and caffeine and NAG (−) promoting adhesion. Instead, propranolol HCl was charged with the same polarity as SA. SEM micrographs showed that smaller caffeine particles, in spite of their larger negative charge, agglomerated less efficiently with SA than larger NAG particles. This emphasizes the importance of particle size in the agglomeration process. Propranolol HCl did not form agglomerates with SA since their particle sizes and charges were identical. As a result, agglomeration of powders prior to tablet compression allows for modification and control of the release rate of the drugs from the SA matrix tablets as well as the tensile strength of the tablets. J Pharm Sci 96:438–447, 2007

Keywords: agglomeration; triboelectrification; tabletting; controlled release; starch acetate; dissolution

INTRODUCTION

During powder handling, for example, mixing and transferring, pharmaceutical powders are brought into contact with different materials. This leads to contact charging, for example, triboelectrification that occurs when charges are transferred between the contacting surfaces.[1] Electrostatic charge accumulates with increasing number of contacts and collisions between surfaces.[2] This might lead to unwanted agglomeration of powders, since electrostatic forces play a significant role in particle cohesion and adhesion processes.[3,4] In addition, particles of different materials have different particle sizes, surface morphologies, surface impurities, and different amounts of adhered moisture which also affect particle distribution in the mixture.[5]

In spite of the disadvantages of particle adhesion, one can also consider it as an opportunity. Ordered mixtures can be stabilized by charging the particles with opposite polarity by triboelectrification.[6] It is known that the adhesion force between two particles of different materials reaches a maximum if the particles have opposite polarity and have very different particle sizes.[7]

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Journal of Pharmaceutical Sciences, Vol. 96, 438–447 (2007)

This means that small particles will adhere to the surface of a larger particle, forming agglomerates. For example, when small excipient particles coat the crystals of an unpleasantly tasting drug, the taste can be masked.[8] Also, the efficacy of a coloring agent can be optimized by layering it around the other particles in a formulation.[9] The organization of a mixture also affects the powder compactibility. Without changing the composition of a powder mixture, the compactibility of a formulation with a poorly compactible drug can be improved by reducing the size of the used excipient with a good compactibility. Thus, the compactibility characteristics of a powder mixture are mainly dominated by the adhering excipient.[10] In the case of uncompacted, hand filled capsules, it has been observed that the formation of drug-excipient agglomerates decreases the drug release rate.[11] However, the effect of agglomeration on the drug release from direct compression tablets has not been studied before.

In this study, powder agglomeration was evaluated as a method to control drug release rate from direct compression tablets. Dry powder agglomerates were prepared of three model drugs (NAG, caffeine, and propranolol hydrochloride) with an excipient (starch acetate (SA)), these agglomerates being held together by adhesive electrostatic forces. Charging of the powders in contact with different materials was studied with triboelectric measurements in order to evaluate their agglomeration behavior in the powder mixtures. SEM imaging was used for visual inspection of the prepared agglomerates. The agglomerated mixtures were then compressed into tablets in order to study the effect of agglomeration on drug dissolution from compressed tablets. Addition of a disintegrant (crospovidone (CP)) into the agglomerated powder mixture, was tested to determine whether a controlled disintegration of the tablet could be achieved. Thus, the drug release would occur at a more constant rate than from ordinary direct compression SA matrix tablets, which release the drug generally following square root of time kinetics.[12,13]

MATERIALS AND METHODS

Materials

N-acetyl-D-glucosamine (NAG, min. 99%), caffeine anhydrous (Ph Eur), and propranolol hydrochloride (min. 99%) were purchased from Sigma-Aldrich (Sigma-Aldrich Chemie, Steinheim, Germany) and were used as received. Starch acetate with a degree of substitution (ds) of 2.7 was used as a matrix former (Polymer Corex Kuopio Ltd, Kuopio, Finland). A sieve fraction of <53 μm was used in this study. Crospovidone (CP) was used as received as a tablet disintegrant (Polyplasdone XL-10, ISP Technologies, Inc., Calvert City, KY).

Triboelectric Measurements

The extent of powder charging in contact with different materials and the effect of this charging on the agglomeration process was studied by performing triboelectric measurements for SA and model drugs. Prior to the measurements, the powders were neutralized by keeping them in relative humidity of 50% on a conducting bed for 24 h. The measurements were made by sliding the powders through pipes of 50 cm in length into a Faraday's cup where the generated charge was measured using an electrometer (Keithley 6517A, Keithley Instruments, Inc., Cleveland, OH). The pipe materials were stainless steel (SS), glass, polyvinyl chloride (PVC), acrylic, polyethylene (PE), and polypropylene (PP). After measuring the charge, the samples were weighed and the total charge per unit mass, that is, the specific charge, was calculated. The measurements were repeated five times per each powder/pipe material pair. The measurement method has been described in more detail by Murtomaa et al.[14] The SA sieve fraction <53 μm is very cohesive due to its small particle size. This complicates the triboelectric measurement, because the powder sticks to the pipe walls. Therefore, a larger particle size fraction of SA (53–149 μm) was used in these measurements. The generated charge of the larger fraction is probably smaller than that of the fraction <53 μm because of smaller number of possible particle/material collisions.[15]

Powder Properties

The particle size distributions of the materials used were measured by laser diffraction (Mastersizer 2000, Malvern Instruments, Inc., Malvern, Worcestershire, UK). The particle in air method was used. Material densities were measured in five parallel determinations with a Multi Pycnometer (Quanta Chrome Instruments, Boynton Beach, FL) using helium as the measuring gas. Scanning electron microscopy was used for visual observation of the agglomerated