The Effect of the Physical States of Binders on High-Shear Wet Granulation and Granule Properties: A Mechanistic Approach Toward Understanding High-Shear Wet Granulation Process. Part II. Granulation and Granule Properties

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ABSTRACT: The objective is to provide mechanistic understanding of a preferred wet granulation process that a binder is added in a dry state. Blends of $CaCO_3$ and binders were prepared and used as model systems, and they were exposed to either 96% RH (rubbery/solution state) or 60% RH (glassy state) at room temperature to control the physical state of the binders, followed by high-shear granulation and particle size measurement. The blends of PVP K12, PVP K29/32, and HPC showed a significant increase in particle size after exposure to 96% RH. An increase of aspect ratio was also observed for the blend of HPC. In contrast, the blends being exposed to 60% RH did not exhibit any increase in particle size or aspect ratio. Regarding the effect of binder molecular weight on the mechanical strength of granules, granules of PVP K29/32 had higher strength than granules of PVP K12. This can be explained using polymer entanglement theory, in which the degree of polymerization (DP) of ($N \sim 440$–540) of PVP K29/32 is above the critical value ($N_c \sim 300$–600) for entanglement; while DP of PVP K12 ($N \sim 20$–30) is below it. Finally, a water sorption-phase transition-diffusion induced granule growth model for granulation has been suggested. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:294–310, 2011

Keywords: wet granulation; binder; phase change; glassy state; rubbery/gel/solution state; granule strength; compactibility; entanglement; polymer adhesion; diffusion; mechanism

INTRODUCTION

High-shear, wet granulation processes, in which powder particles are agglomerated to increase their size and density, as well as to alter their shape through the addition of a granulating liquid such as a binder solution to the powder bed with the aid of mixing, is a key unit operation in the pharmaceutical industry and other industries such as those pertaining to food and fertilizer production.[1–3] Wet granulation is a flexible and versatile process compared to other particle agglomeration technologies such as dry granulation. In addition, granules prepared by wet granulation generally have better particle size distribution than those prepared by dry granulation,[4] a normal particle size distribution. The binder is a key component in wet granulation formulations and plays a critical role in the formation of granules.[5–8] Polymers, including synthetic, semi-synthetic and natural, are commonly used as wet granulation binders in the pharmaceutical industry.[9,10] It has been long recognized in the pharmaceutical industry that the method of binder incorporation is an important factor influencing granulation processes.[11] The polymeric binders are incorporated into a granulation process either in a dry state or in a solution state. In the former process, binders are first dry-mixed with API and other excipients, and then activated by spraying water onto powder particles.[12] In particular, addition of binder in a dry state has the advantage of being simple and easy to operate from a manufacturing point of view, as compared to adding polymer solution to a powder bed.

The agglomeration mechanisms involved in the wet granulation process, in which binder is added in a

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solution state, have been extensively investigated. The results were summarized by Lister and Ennis.[13] According to Lister and Ennis, the wet granulation process can be divided into three different phases: (1) wetting and nucleation, (2) consolidation and granule growth, and (3) breakage and attrition.[13,14] It is commonly regarded that the distribution of granulation liquid (binder solution) is a critical factor to control wetting and nucleation; while mixing dynamics affect consolidation and granule growth, as well as breakage and attrition.[15–17] Lately, Hapgood and coworkers, introduced the nucleation regime map, in which the liquid penetration time correlated with the spray flux of the granulation liquid.[15,17] By doing this, the region, which is controlled by either the droplets or the mechanical dispersion, was identified.

In the pharmaceutical industry, it is becoming increasingly popular to incorporate binder in a dry state. Therefore, there is a need to study the mechanisms involved. The hypothesis of this article is that the physical state of binders is the major factor affecting the granulation processes and the resulting granule properties. The physical state (G to R–S) change of binders after exposure to 95% RH or liquid water has been reported in Part I.[18] The focus of Part II is to investigate the effect of the physical state and other properties of a binder on the granulation process as well as the mechanical properties of the resulting granules. For this purpose, $CaCO_3$ is selected as filler because $CaCO_3$ is inert and it has less or no interaction with water so that the interaction between water and a binder can be focused on. Research on a complex and more realistic system including an API and lactose monohydrate is ongoing and the results will be reported as Part III. The binary blends of $CaCO_3$ and each binder were made at binder concentrations of 5% (w/w), 10% (w/w), and 20% (w/w) and after exposing to either 60% RH or 96% RH at room temperature the equilibrated blends were mixed in a Diosna high-shear granulator for 2 min. The particle size distribution, as well as the aspect ratio distribution of the resulting granules was then measured using a Sympatec dynamic microscope with image analysis capability. Granule friability (as a surrogate test for granule strength) and the compaction properties of granules were evaluated using a sonic sifter and a compaction simulator, respectively. A mechanistic model for particle agglomeration, based on the effect of the physical state of binders, is proposed. Finally, the effect of the molecular weight of the binders on the mechanical properties of the granules has been evaluated from a polymer dynamic point of view, in which the formation of chain entanglement only occurs at or above the critical values of the degree of polymerization (N_c). Entanglement is also proportional to the molecular weight of a polymer. Although a high-shear granulation process was used in this study, the conclusions from this study should be applicable to fluid bed processing as well, given that the binder is added in a dry state. This is because the current study has taken an equilibrium approach to investigate the effect of phase transition on granulation, and the kinetics of phase change involved in granulation processes, which can vary from one process to another, is not considered.

EXPERIMENTAL

Materials

Four commonly used polymeric binders (simply referred to as binder in the following text), including polyvinylpyrrolidone (PVP) K12 and K29/32, hydroxypropylcellulose (HPC EXF), and hydroxypropylmethylcellulose (HPMC E5), were used in this study. PVP K12 was obtained from BASF Chemicals, Inc. (Florham Park, NJ) and PVP K 29/32 was purchased from ISP Technologies, Inc. (Wayne, NJ), separately. HPC EXE was purchased from Hercules Chemicals, Inc. (Wilmington, DE), and HPMC E5 was obtained from Univar Chemicals, Inc. (Redmond, WA), respectively. Calcium carbonate ($CaCO_3$) from Konoshima Chemicals Co. (Osaka, Japan) was used as filler in this study. Potassium sulfate (K_2SO_4) and sodium bromide (NaBr), were both purchased from Sigma–Aldrich Chemicals, Inc. (St. Louis, MO). They were used to control the relative humidity (RH) (K_2SO_4 for 96% RH and NaBr for 60% RH) for preparing granulation samples. Ziplock plastic bags (4 mil, 12 in. × 18 in.) purchased from VWR International (Wester Chester, PA), were used as humidity chambers.

Sample Preparation

Preparation of Dry Blends

Binary blends of $CaCO_3$ with each binder at binder concentrations of 5% (w/w), 10% (w/w), and 20% (w/w) were prepared as follows. To prepare a 400 g batch of a binary blend of $CaCO_3$ with PVP K12 at a binder concentration of 5% (w/w), $CaCO_3$ and PVP K12 were weighed out in a ratio of 95% (w/w) to 5% (w/w), transferred into a P 1/6 Diosna high shear granulator (Diosna, Dieerks and Sohne Gmbn, Osnabruck, Germany), and then mixed for 2 min with an impeller speed of 700 rpm and a chopper speed of 1200 rpm. For preparing the binary blends (400-g batches) of $CaCO_3$ with PVP K12 at binder concentrations of 10% (w/w) and 20% (w/w), $CaCO_3$ and PVP K12 were weighed out in ratios of 90% (w/w) to 10% (w/w) and 80% (w/w) to 20% (w/w), respectively. The same mixing parameters used to prepare the blend with 5%