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Original Research Paper

Nanosmearing due to process shear – Influence on powder and tablet properties

Kalyana C. Pingali [a,*], Rafael Mendez [b]

[a] Department of Chemical and Paper Engineering, Western Michigan University, Kalamazoo, MI 49008, United States
[b] Department of Chemical Engineering, University of Puerto Rico, PO Box 9046, Mayaguez, PR 00681, United States

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ABSTRACT

The objective of the study was to investigate the influence of process shear, blend composition and mixing order on thin film nanosmearing of lubricant and glidant on particle surfaces as a function of powder and tablet properties. Multiple pharmaceutical blends containing avicel 200 and micronized acetaminophen were prepared at three different mixing orders at a shear rate of 80 rpm and a shear strain of 640 rev. Chemical analysis such as inductively coupled plasma mass spectroscopy (ICPMS), scanning electron microscopy with X-ray microanalysis/energy dispersive spectroscopy (FESEM/EDS) and focused ion beam (FIB) were done for sheared powder samples. Powder hydrophobicity and tablet dissolution were carried out to test for powder and finished product properties. Experimental techniques were developed to interpret the general aspects of % area nanosmearing distribution obtained from EDS mapping combined with cameo imaging. Their % area distributions on particle surfaces were quantified for the first time. Applied process shear on powder particles had a significant effect on powder and tablet properties. The nanoscale investigation measured in terms of extent of nanosmearing (% area), amount and thickness of nanosmearing clearly showed that nanosmeared structures influenced the powder hydrophobicity and drug release rate.

1. Introduction

The shear effects on structural factors during the mixing process of pharmaceutical formulations involve a wide range of phenomena related to phase transformations of powder components, formation of smeared layers and changes in tribological behavior. Blending process in pharmaceutical formulations is known to affect tablet properties such as hardness and dissolution which results in product failures [1]. Changes in surface characteristics during mixing in heterogeneous systems can alter the primary function of the components in the powder blend [1]. Characteristics and behavior of the finished product was known to be affected by the surface properties of the constituent particles [1]. Hence there is a technological need to understand what causes the characteristic changes in powder properties at high shear mixing which in turn affects finished product properties.

A systematic investigation of electronic and microscopic structures of thin coatings formed on particle surfaces during high shear mixing is a promising area of scientific investigation. It is believed that the anamolous behavior of physical and mechanical properties of nano and submicrocrystals is caused by the excitation of grain boundaries [2]. Moreover, distribution of coatings on particle surfaces has been widely debated. Non-uniform distributions of thin layers of coatings can result in clusters and particle precipitates at certain localized areas. Although, smearing effect was found to scale linearly with cluster volume, width of the smearing was known to be inversely proportional to the average size of the precipitates [3]. In particular, the thermodynamic and kinetic aspect of transformation is sensitive to the structural and size factors [4].

It is clear that the adhesion properties between the components in a powder mixture can play a critical role in influencing the tablet thickness and drug dissolution. Careful choice of the components and their mixing order during formulation is therefore essential. Previous works have shown that the adhesion tendency between contact surfaces depended on the properties of coating materials [5] and mechanical engagement of particles on rough surfaces [6]. In addition, forces between magnesium stearate and silica gel interactions [7], relative humidity, and electrostatic charging efficiency tend to affect the surface adhesion and coating efficiency [8]. Variations in the tablet properties due to the changes in surface adhesion caused by the possible formation of smeared nanolayers

* Corresponding author. Tel.: +1 269 276 3519.
E-mail address: kalyana.pingali@wmich.edu (K.C. Pingali).

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are relatively unknown. Although, additives were known to modify the surface parameters [9], there exists little evidence on the extent of film coating on the surfaces that alter the particle adhesions. However, distributions of bulk stresses and surface roughness tend to influence the aggregation of particles and adhesion force distribution [9,10].

Surface properties are critical to understand the overall functional properties of powders on a macroscopic scale. Such properties on active pharmaceutical ingredients (API) were found to improve with a thin coating on particle surfaces [11]. However, it is not clear to what extent such coating uniformity affects the bulk material behavior. The primary problem of the extent of coating uniformity is with the phase transitions which are dependent on temperature [12–14]. Surface characteristics are considerably restricted by these temperature variations [14]. Therefore a reliable investigation of surface structures based on the percentage content of coating is a necessary primary step to understand the interactions. It has been previously demonstrated that there is a direct link between surface phenomena, friction and adhesion [15]. Further evidence of surface friction and particle rolling behavior affecting the API can be found in previous research studies [16]. Unique properties of nanostructural materials, their physicochemical characteristics influencing adhesion forces and structural variations were studied [17–20]. Nevertheless, there have been less research works on the precise quantification of nanocoatings on API surfaces that can influence the particle adhesions.

Although the surface chemistry of powder particles has been widely studied relative to coatings, adhesion, friction and their interactions, much basic knowledge about the formation of nanosmeared thin layers on particle surfaces that can alter the functional properties of powders is still lacking in theory and practice. In our previous work, we observed changes at nanoscale level during blending of pharmaceutical powders [21]. In this paper, we introduced a term "nanosmearing" in order to understand the formation of thin nanolayers at component particle level. In the first step, we systematically investigated these nanosmears formed at component particle level. In the second step, we studied the influence of nanodeposits on blend properties or macroscopic powder properties. In the third stage, effect of blend properties on tablet properties and finished product performance is explored. We present a detail investigation of nanosmearing by systematically investigating the electronic and microscopic structures of the nanodeposits on excipient particle surfaces. Extent of nanosmear in terms of% area distribution on excipient particle surfaces, amount of nanosmear and thickness of nanosmear with respect to mixing order of blends were investigated in order to understand the effects on powder and tablet properties under shear environment.

2. Materials and methods

2.1. Materials and sample preparation

Preblend consists of a mixture of microcrystalline cellulose (MCC – Avicel 200, particle size – 190μ) and 9% (w/w) micronized acetaminophen [N-Acetyl-Para-Amino-Phenol (APAP) particle size – 14μ]. Flowing agent such as magnesium stearate (MS) (Mallenkrodtt) was used as a lubricant and colloidal silica (Cab-O-Sil, grade M5-P, particle size – 0.2–0.3μ) was used as a glidant. Three sets of blends were prepared by varying the mixing order (M.O) of the components. Each set again consist of four formulations where the concentration of MS varied between 0.5% and 1% and concentration of colloidal silica (CS) was varied between 0.25% and 0.5%. In the first M.O, four blends (B1–B4) were prepared by changing the concentrations of CS and MS as mentioned above and by adding the CS and MS together (M.O-1). Similarly, second set of four blends (B5–B8) were prepared by adding CS first to the blend and later mixed with MS (M.O-2). Third set of blends (B9–B12) were prepared by adding MS first to the blend (M.O-3). A total of 12 blends thus prepared were gently mixed in the v-blender for with a blender speed of 15 rpm. A fourth (B13–B14) and fifth (B16–B16) of blends were also prepared by mixing CS and MS only with the excipients. A blend without any additives (B17) was prepared as a base reference. Overall, a total of 17 blends were prepared for further analysis. Intensifier bar was not operated during the mixing process in the v-blender in order to minimize the effect of shear on the powder. The blender was operated for 10 min. For the blends consisting of both MS and CS, the blender was operated for 5 min each after adding each of the flowing agents. The blends were collected from the v-blender in a bin and again sheared in a couette shear cell rheometer. All the powder blends were subjected to a shear rate of 80 rpm and a shear strain of 160 rev. In the next stage, the sheared samples collected from the couette cell were evaluated for their hydrophobicity and chemical analysis of microstructures. Experimental design of the formulation can be seen in Table 1 and the percentage composition by weight in Table 2.

2.2. Methods

2.2.1. Powder hydrophobicity

Powder hydrophobicity was measured for sheared samples. The apparatus consists of a column of packed powder dipped in the saturated solution that is prepared by dissolving one of the components of the formulation (active ingredient). Penetration rate of solvent (saturated solution of acetaminophen) through a column of powder by capillarity or the ability of a solution to move by capillarity in a column packed with powder was measured as hydrophobicity in the Washburn technique. The dynamics of capillary rise determines the over-lubrication effect on powder hydrophobicity. A detailed discussion of the method was mentioned in our previous work [21]. Variations in the hydrophobicity

Table 1
Experimental design of the formulations and compositions of powder blends.

MgSt (%)	Cab-O-Sil (%)	
	0.25	0.5
Preblend + (Cab-O-Sil + MgSt) (Together)		
0.5	B1	B2
1	B3	B4
Preblend + Cab-O-Sil (First) + MgSt		
MgSt (%)	Cab-O-Sil (%)	
	0.25	0.5
0.5	B5	B6
1	B7	B8
Preblend + MgSt (First) + Cab-O-Sil		
MgSt (%)	Cab-O-Sil (%)	
	0.25	0.5
0.5	B9	B10
1	B11	B12
Preblend + Cab-O-Sil		
Cab-O-Sil (%)	0.25	0.5
	B13	B14
Preblend + MgSt		
MgSt (%)	0.5	1
	B15	B16
Preblend Only		
	B17	