Nanosized Smeared Particles Formed During Mixing Affecting Microscopic Behavior of Pharmaceutical Formulations

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Abstract

Nanosmeared in pharmaceutical formulations was studied with respect to powder flow and structural properties. Interaction of flowing agents such as magnesium stearate (MgSt) and colloidal silica (Cab-O-Sil (CS)) among each other as well as with the shear history of the blend was investigated. Flow properties of formulations mixed with various mixing orders at high shear rate in the v-blender with 20 rpm of the shell speed and 500 rpm of intensifier bar speed, were tested for flow properties. Tablets were compacted from the powder formulations and their structural changes were captured. It was found that the nanosmeared particles of MgSt and CS on neighboring particles affected the overall flow property of the blend. The results showed that the best flow property under the selected operating conditions can be achieved by maintaining 1% MgSt and 0.5% CS in the blend. Nanosmeared particles also were found to affect the density of powder. Compared to uncoated particles, coated particles had exhibited higher powder density. A correlation between flow properties existed irrespective of nanosmeared particles affected powder blends. In addition, powders exposed to high shear rates have shown structural changes in relation to the mixing order. The structural properties changed from crystalline to amorphous for the blends exposed to high shear. Interestingly, only certain mixing orders, in which both MgSt and CS were present, showed such structural transformations.

INTRODUCTION

Surface coating of active ingredients as a means for modifying powder properties in the pharmaceutical mixing process is well known for many years [1,2]. A thorough understanding of particle interactions, surface chemistry including their adhesion and bonding configuration is a technological need for many pharmaceutical processes. In this context, it is clear that adhesion properties between flowing agents, active substances and excipients can play a critical role in influencing the tablet thickness and drug release behavior. Studies showed that the tabletting properties of pharmaceutical excipients were influenced not only by the distribution of magnesium stearate (MS) and colloidal silica (CS) on particle surfaces, but also by their concentration [3,4]. Adhesion force microscopy (AFM) measurements of drug-carrier interactions of tertiary systems revealed that the inter-particle and particle-surface contacts reduced the internal friction in presence of magnesium stearate [5].

A thorough understanding of surface chemistry and nanoscale interactions is needed to understand the flow properties of pharmaceutical dosage forms and their spatial variations. Distributions of bulk stresses and surface roughness tend to influence the aggregation of particles and adhesion force distribution [6,7]. Flow properties of ibuprofen powder particles were found to improve with a thin coating of hydroxypropyl methylcellulose onto particle surfaces [1]. Nevertheless, it is uncertain that the coating thickness should be uniform. A reliable estimation of coating or extent of smearing relative to surface interactions is, therefore, a fundamental step to understand the adhesion forces between powder particles. Another problem lies with the introduction of spatial constraints due to quantum phase transitions that are dependent on temperature [8-10]. A direct link between surface chemistry and nanoscale friction was demonstrated by the reductions in nanoscale adhesion and friction by the exposure of surface to atomic hydrogen [11]. Furthermore, surface properties such as friction behavior and sliding speed influence the characteristics of various pharmaceutical dosage forms [12].
Composition and bonding of materials at surfaces is particularly important to understand the adhesion, friction and tribochemical reactions that lead to structural reorganization in the deposited or smeared nanolayers. In addition to surface chemistry, a further investigation of the spatial variations leading to reorganization of organic structures at nanoscale is therefore needed to understand the self-organizing properties and their control at nanoscale level. Spatial variation of adhesion across the surface was found to be dictated by the physicochemical nature of the surface [13]. Thickness of smeared layer, their electron density distributions of local regions can be used to predict the structural variations [14-16]. In particular, atomic scale visualization of surfaces can reveal the atomic pattern and electronic structure [17,18]. Furthermore, molecular weight and the orientation phenomena of the organic groups were found to induce the molecular reorganization of phases [19-21]. A further improvement in the available methodologies is needed to interpret the particle interaction systems in a physically reasonable way. While very little attention has been drawn to understand the adhesion force distributions of organic structures due to smeared nanolayers, structural interpretation underlying the drug release behavior is essential. Reorientation of nanostructures due to the changes in ordered mixing which is vital in controlling the surface properties is not yet fully understood.

Shear history of the sample, in particular, is a factor often ignored in powder characterization, even though there is an awareness of its potential effects. Interactions of the multiple flowing agents, both among each other and with shear history of the blend, potentially affect both processing performance and finish product quality in terms of powder flowability, content uniformity, tableting performance and drug release. Moreover, surface coating of the active material caused by the smearing of the flowing agents at the nanoscale under the influence of shear, has been poorly understood in recent years. The purpose of this paper is to investigate the nanostructural formations caused during shearing of pharmaceutical mixing and its consequent effect on macroscopic powder properties. An attempt was made to study the micromechanical properties of excipient and nanoparticle interactions in a physically reasonable way by gaining generic and valuable insight into the sophisticated heterogeneities associated with the nanosmeared layers.

**EXPERIMENTAL**

**Materials and methods**

Preblend in the formulations consists of fast flow lactose and microcrystalline cellulose (MCC – also known as avicel 102) in the ratio of 50% - 50%. Additives consist of magnesium stearate (MgSt) (Mallenkrodt) and colloidal silica (Cab-O-Sil, grade MS-P, particle size – 0.2 – 0.3µ). Micronized acetaminophen (APAP) was used as an active pharmaceutical ingredient (API) in the formulations. Various blends with additive concentrations ranging from 0.25 to 1% were mixed with APAP, FFL and Avicel 102. The samples were mixed under high shear in a v-blender running at 20 rpm and intensifier bar at 500 rpm. Multiple formulations thus prepared were tested for their powder flow properties in a rheometer. A methodology of this measurement technique was discussed in detail in our earlier works [13]. The concentration of API in all the blends was maintained at 9% by weight.

Various mixing orders of the additives were used during high shear mixing process. Some powders were mixed with both MgSt and CS added together while other blends were mixed by either adding MgSt or CS first to the blend. However, the shear condition was maintained to be constant for all the formulations. In other words, mixing orders of blends were varied by blending the powders at high shear rate and shear strain in the v-blender. Approximately 5 lbs of samples were prepared from all the mixing combinations in order to meet the sample size requirement in the powder flow rheometer (4 lbs) and tablet press (500 g each).

Methods such as flow index and dilation were already discussed elaborately in our previous works [22-24] and will not be mentioned here. All the blends were tested for their flow properties in the rheometer. From the blends prepared, tablets were compacted in a rotary tablet press. X-ray diffraction (XRD) was done on tablets to check for the possible structural changes in powder particles during compaction. An auto-tap density meter was used to measure density of formulation under compacted or tapped condition of the bed. The cylinder that was used to test flow properties was also used on tap density meter. The powders were poured in the cylinder and the cylinder was tapped for 1500 tappings. The volume of powder in the cylinder was measured before and after tapping the cylinder. Change in volume of the powder bed was recorded. A cylinder with the compacted tapped bed of powder was used to measure dilation on powder flow rheometer.

**RESULTS AND DISCUSSION**

Nanostructural distributions affecting blend and tablet properties

Attempts to correlate the formulation composition and shear environment to the parameters of structural transformations (Figure 1) have shown that the applied shear is a critical factor...
that cannot be ignored. A reliable estimation of smearing at high shear condition in the mixing process was, therefore, the first step investigated to understand the structural changes. Secondly, we estimated the distribution of lubricant coating. It is evident from (Figure 1) that the changes in composition alone cannot account for phase alterations. Consequently, the rate of formation of nanolayers with respect to various mixing orders showed a pattern of interrelation between flow properties. The results shown in (Figure 2) reflect that irrespective of the mixing order, the flow correlation between flow index and dilation was linear. Though such relation was established in our previous studies [24] on micronized powders, a repetitive of such correlation on nanocoated formulations shows that the parametric correlation hold true not only for micronized powders, but also in presence of nanosmeared layers on excipients. In this context, we experimentally demonstrated the structural changes as a function of extent of smearing, mixing order and flow rate (flow index and dilation). Figures 1 and 2 together showed that the XRD patterns depend not only on the nanosmeared patterns but also on mixing orders of formulations. However, we found few intrinsic deformations within the tablet compact possibly due to non-uniformity of the coated particle surfaces. The indirect interference of the deformation caused by the non-uniform coatings within various mixing order blends resulted in variations in compaction of powders during tapping of powders as well as tablet pressing process.

One such evidence can be seen in (Figure 3) where coated active pharmaceutical ingredient (API) compacted more than the uncoated API. Several formulations were compacted by tapping in a cylinder for a series of tappings ranging from 500 to 2000 tappings on a tap density meter. The results show that uncoated API particles occupy more volume due to increased interstitial porosity whereas coated powder particles compact tightly reducing the porosity and decreasing the volume. Such phenomenon can be attributed to the variations in the orientations of particles depending upon the coated and uncoated particle surfaces at nanoscale. It is reasonable to attribute the orientation effects of particles to the extent of uniformity or nanosmeared variations. The results show that the extent of thin nanolayers on particle surfaces is a sensitive parameter for the quantification of phase changes. Overall, the findings show that the nanoscale phenomena on particle surfaces alter the macroscopic properties of powders.

**Influence of additive concentration on reducing cohesion**

In an attempt to identify the limitations on additive concentrations in formulations, a series of conditions were studied by varying their concentrations. The intrinsic behavior associated with the cohesion of these materials due to the changes in composition, was determined in relation to the macroscopic blend flow properties. Limitations of the particle size on structural changes are an important aspect leading to the continuous size dependent variations. Partially, this also addresses an important issue of the contribution of localized confinements as a possible cause for inhomogeneities. This condition is due, in large part, to the presence of clusters because of particle size variations arising from the changes in composition. As might be expected, when one considers the surface interactions in pharmaceutical powders, it seems more appropriate to evaluate size and shape factors in terms of spatial confinement. It will be relevant to understand the interrelation of two factors, additive concentration and powder flow, which are both again partially dependent on content uniformity. Therefore, an interrelation between these parameters was evaluated by controlling the additive concentration.

Concentration of lubricant [magnesium stearate (MgSt)] and glidant [colloidal silica – Cab-O-Sil (CS)] in the formulations was varied between 0.25% to 1% and their net effect on cohesion in terms of dilation and flow index was found for multiple blends. It was found that the flow properties of blends improved with an increase in the concentration of additives from 0.5% to 1% for MgSt and 0.25 to 0.5% for CS. It is evident from (Figure 4) that cohesion decreased when the additive concentration is slightly increased. At this stage, either coating uniformity or amount of coating is expected to be the governing factor for particle cohesion. Overall, from the above results, it can be suggested that the typical optimum concentration of 1% MgSt
and 0.5% CS can be maintained in pharmaceutical formulations for their enhanced powder flow, irrespective of their mixing orders. Though nanosmeared particle loading on excipients was non-homogenous, the above mentioned additive concentration was found to reduce the particle attrition which was evident through enhanced flow properties. During high shear mixing, this condition is expected to influence the shear strength of the particle’s surface. The variations in surface characteristics are believed to be dependent on nanosmeasuring inhomogeneity on excipient particle surface. The results demonstrated that the clean critical point of surface parameters affecting the powder flow characteristics precisely depended on additive concentration. Overall, it is interesting to see that the above mentioned concentration of additives not only improved powder flow properties, but also altered material properties at nanoscale thereby affecting the macroscopic performance of blends and formulations.

CONCLUSION

Pharmaceutical powders coated with nanosmeared particles under high shear conditions alter the flow properties of blends compared to uncoated particles. A more uniform surface distribution can be achieved by increasing the concentration of colloidal silica and magnesium stearate. Distribution or presence of one flowing agent enhances the distribution of the other. Nanosmeared particles increased the packing density of powder particles with a corresponding increase in powder density. It was found that powder flow of pharmaceutical formulations depends to a great extent on density of packing. Flow properties of the blends improved with the concentration of coatings between 0.5 and 1%. Structural changes during compaction of tablets occur with respect to mixing order of blends. The structural properties change from crystalline to amorphous during compaction of powders processed under high shear. In summary, nanosmeared under high shear and mixing order are two critical parameters which alter both powder flow and tablet properties.

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REFERENCES


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