Effect of fine particle shape on the stability and performance of adhesive mixtures intended for inhalation

Sohan Sarangi, Kyrre Thalberg, Göran Frenning

Department of Pharmaceutical Biosciences and the Swedish Drug Delivery Centre (SweDeliver), Uppsala University, Uppsala, Sweden
Emmace Consulting AB and Medicon Valley Inhalation Consortium, Lund, Sweden

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1. Introduction

One of the increasingly popular ways for efficient delivery of drugs to the lungs is through dry powder inhalers (DPIs) [1]. A special type of ordered mixture known as adhesive mixture is most commonly used for delivery of the active pharmaceutical ingredient (API) [2,3]. Adhesive mixtures consist of a blend of large carrier particles (~100 μm aerodynamic diameter) and small micronised fine particles (<5 μm aerodynamic diameter) of API. An adhesive unit consists of fine particles adhered onto the surface of the carrier particle. APIs have a high surface to volume ratio and van der Waal’s forces dominate the interaction producing a highly cohesive powder with poor flowability and a tendency to form agglomerates. Adhesive units prevent agglomeration of fine particles, improve flowability, maximise homogeneity and improve dispersibility of API during the process of aerosolisation [4]. Maintaining the integrity of these units during the process of handling is an important step to ensure the delivery of the drug load, and this is gaining increasing importance when dosage forms with higher drug loads are explored [5].

Numerical studies to understand the micro mechanics and dynamics of adhesive units is steadily gaining impetus [6–8], Computational Fluid Dynamics (CFD) [9] and the Discrete Element Method (DEM) are the two most commonly used tools to study the particle dynamics. There have been studies involving particle mixing [10], agglomeration and deagglomeration of fines in DPIs [11], collision with inhaler walls [12–14] and micromechanics of adhesive units during handling [15], to name a few. Recently there has been an increased focus towards understanding the effect of morphology of lactose particles during particle mixing [16] and dispersibility of the APIs from the carrier surface [17]. The focus has mostly been on carrier shape and surface asperities [16,18]. Both numerical and experimental studies [19] have been conducted focusing on the aggregate shape of the fines and its breakage and impact on dispersibility and/or mixing performance [20]. Release of fine particles is important in an inhaler [8] while dispersion should not occur during gentle handling and powder filling. In order to improve the understanding of the stability and integrity of adhesive units, we have in a previous study focused on the behaviour of adhesive units with different surface coverage ratio (SCR, representing different drug load) and different surface energy of interactions, but confined ourselves to the case of adhesive units with monodisperse spherical APIs [15]. In fact, there have not been many studies exploring the effect of API shape on the integrity of adhesive units in the velocity regime that correspond to typical handling [21,22] and this is the first DEM investigation of the effect of API shapes. The purpose of this work is to assess the effects of the fine particle shape on the effective mechanical properties and stability of adhesive units formed from them. To this end, three distinct shapes of fines (tetrahedral, triangular bipyramidal and spherical) are considered, maintaining the maximum diameter of the particle constant, whereas spherical carriers are used. An extension of the methodology described in [15] is used, i.e. numerical studies of binary head on collisions are
performed and from the obtained data, stability ratios and restitution coefficients are extracted. In addition, the redistribution of the fine particles on the surface of the carrier particle is studied in terms mean shift and dispersion. For simplicity carrier particles will henceforth be referred to as carriers and fine (drug) particle as fines in this article.

2. Numerical framework

The DEM was used to simulate the effect of collision of two adhesive units. In DEM, particles are treated as discrete entities and are governed by Newton’s laws of motion. Newton’s law governing translational motion between particles is represented as,

\[ m_i \frac{d^2 x_i}{dt^2} = m_i \mathbf{g} + \sum_j \left( f_{ij}^n + f_{ij}^t \right) + f_{i,\text{fluid}}, \]  

where \( i \) is the target particle and \( j \) is the neighboring particle, \( m_i \) is the mass and \( x_i \) is the position of particle \( i \), \( \mathbf{g} \) is acceleration due to gravity, \( f_{ij}^n \) and \( f_{ij}^t \) are normal and tangential forces acting on particle \( i \) due to contact with particle \( j \) and \( f_{i,\text{fluid}} \) is the force on particle \( i \) resulting from fluid interaction. The system under consideration was studied in the low velocity regime and hence fluid forces could be neglected in Eq. (1). The equation of motion for the rotational degrees of freedom could be expressed as,

\[ \frac{d}{dt} \left( \mathbf{I} \frac{d\omega}{dt} \right) + \mathbf{I} \omega \times (\mathbf{I} \omega) = \mathbf{M}, \]

where \( \mathbf{I} \) is the inertial tensor, \( \mathbf{M} \) is the applied torque and \( \omega \) is the angular velocity about the center of mass of the particle. The interaction between two particles is expressed in terms of contact forces between them which are based on their mutual overlap. In this work, cohesive contact laws similar to the ones stated by Thornton et al. [23,24] are used. Their salient features are the following:

- The effective radius \( R_e \), mass \( M^* \), Young’s Modulus \( E^* \) and shear modulus \( G^* \) of two particles \( i \) and \( j \) in contact are defined as follows [25],

\[ \frac{1}{R_e} = \frac{1}{R_i} + \frac{1}{R_j}, \]

\[ \frac{1}{M^*} = \frac{1}{M_i} + \frac{1}{M_j}, \]

\[ \frac{1}{E^*} = \frac{1−ν_i^2}{E_i} + \frac{1−ν_j^2}{E_j}, \]

\[ \frac{1}{G^*} = \frac{2−ν_i}{G_i} + \frac{2−ν_j}{G_j}. \]

In the above expressions, \( R_i \) is the radius, \( M_i \) the mass, \( G_i \) the shear modulus and \( ν_i \) Poisson’s ratio for particle \( i \) (and analogously for particle \( j \)).

- The Tabor parameter [26] is a dimensionless parameter which provides guidelines for selecting the appropriate contact model for adhesive/cohesive contacts given by,

\[ \mu = \left( \frac{R^2 \Gamma^2}{E^* \epsilon^2} \right). \]

where \( \epsilon \) is the equilibrium distance between two spherical particles and \( \Gamma \) is the surface energy of interaction between the two particles. For the parameters used in this work (see below), \( \mu \) was calculated for interactions between pairs of particles and was found to be greater than 1 which corresponds to the JKR (Johnson–Kendall–Roberts) [27] model.

- The normal \( (F_{ne}) \) and tangential \( (F_{te}) \) elastic forces are obtained from the JKR interaction between two spherical particles. Hence, the normal elastic force is represented as,

\[ F_{ne} = 4 \left( \frac{a_0^3}{a_0} \right) - \left( \frac{a^3}{a_0} \right)^2. \]

where \( a \) is the contact area at a given time, \( a_0 \) is the finite contact area due force of adhesion in absence of external load and \( F_c = 3\pi R \Gamma \) is the pull-off force between the two particles (\( \Gamma \) is the surface energy). Likewise, the tangential elastic force is defined as [28],

\[ F_{te} = S_t \dot{\theta}_t, \]

where \( S_t \) is the tangential stiffness and \( \dot{\theta}_t \) is tangential overlap.

- Normal \( (F_{nd}) \) and tangential \( (F_{td}) \) damping forces are defined as, [28]

\[ F_{nd} = 2 \sqrt{\frac{5}{6}} \delta \sqrt{S_t M^*} v_t, \]

\[ F_{td} = 2 \sqrt{\frac{5}{6}} \delta \sqrt{S_t M^*} v_t, \]

where \( \delta \) is a dimensionless factor dependent of coefficient of restitution, \( S_t (S_n) \) is normal (tangential) stiffness and \( v_t (v_n) \) is the normal (tangential) relative velocity between the particles.

3. Method

3.1. Formation of composite particles and adhesive units

Carriers were modelled as elastic spheres of 100 μm diameter with contact damping. Fines were modelled as spherical (Fig. 1a), tetrahedral (Fig. 1b) or triangular bipyramidal (Fig. 1c) shaped particles of 3 μm maximal Feret diameter. The multispher composite fines were designed so as to ensure conservation of volume between different particle shapes. If \( r_{\text{sph}} \) is the radius of a spherical fine, \( r_{\text{tet}} \) is the radius of the tetrahedral particle, and \( r_{\text{bip}} \) is the radius of the triangular bipyramid, the radius of microspheres could be represented by,

\[ r_{\text{tet}} = \frac{r_{\text{sph}}}{2^2}, \]

and

\[ r_{\text{bip}} = \frac{r_{\text{sph}}}{3^2}. \]

The overlap between the microspheres was fixed so that the maximum length of each side of tetrahedron or triangular bipyramid was 3 μm. The mass of tetrahedral and triangular bipyramidal shaped fines are similar to the spherical fines. The microspheres in the tetrahedral and triangular bipyramidal shaped fines are fixed with respect to each other. The non-spherical shape of the composite particles helps reduce the rolling motion of the particles. The particle shapes were chosen to represent different degrees of contact area with the carrier particle and interlocking between each other. Combinations of these composite particles could be used to computationally design complex irregular particles.
Adhesive units were formed by pseudo-randomizing the distribution of fines on to the surface of the carrier particles to reach the desired surface coverage ratio (SCR), defined as

$$\text{SCR} = \frac{N \times r_{\text{fines}}^2}{4r_{\text{carrier}}^2},$$

where $N$ is the number of fines attached to the carrier, and $r_{\text{fines}}$ and $r_{\text{carrier}}$ are the radii of fines and carriers, respectively. This was achieved by formation of a uniform distribution of fines in a spherical envelope, each of the fines was given a random velocity following a central velocity directed to the centre of the carrier particle. More information can be found in [15].

### 3.2. Simulation setup

Adhesive units with varying SCR were created. Three different SCRs 0.5, 0.7 and 1 accounted for different number density of particles on the surface of the carrier, ranging from traditional dosage loads [29] to high drug loads for potential future applications [5]. The surface energy of interaction between carrier – carrier, carrier – fine and fine – fine was fixed at 0.03 J/m² [7,9,10]. In order to account for the variability of the pseudo randomisation of fines, three initial seed values were considered which represent initial spatial distribution. Fines and carrier properties are mentioned in Table 1. The above described setup was repeated for tetrahedral and triangular bipyramidal shaped fines.

### 3.3. Simulations

Binary head on collisions between the adhesive units as shown in Fig. 2 were studied in a low velocity regime corresponding to typical handling. The relative velocity of collision was varied from 0.04 to 1.7 m/s [21,33] with 15 velocity data points in the range. It is worth noting that dispersion of fines from adhesive units normally occurs in a much higher velocity regime of 5–20 m/s [34]. Based on the above parametric variation more than 400 independent simulations were performed and stability ratios and mechanical properties were extracted.

Specifically, the quantification of the stability of adhesive units was based on three ratios: The Transfer Ratio, defined as the fraction of fines exchanged between the carriers during collision. The Retention Ratio, that represents the fraction of fines which remain adhered to the carriers during collision. The Loss Ratio, that represents the fraction of fines which are lost from the binary system of carriers during collision. The restitution coefficient ($e$) was used as a measure of the effective mechanical properties of the adhesive units. It is defined as,

$$e = \frac{v_{\text{after}}}{v_{\text{before}}}$$

where $v_{\text{after}}$ is the relative velocity between the pair of adhesive units after collision and $v_{\text{before}}$ is the relative velocity between the adhesive units before collision.

Moreover, redistribution of the fines on the surface of the carrier was studied in an attempt to understand the effect of different particle shapes resulting from interlocking, sliding and rolling. Specifically, a thin strip of particles (6 times the diameter of fine particle) around the centre of each carrier particle was identified as shown in Fig. 3. The strip was chosen perpendicular to the direction of impact to capture the maximum displacement of fine particles on the carrier surface. The initial configuration was compared to the configuration after impact, shown in Fig. 3b. The displacement of each particle in the strip was determined and normalised by the diameter of the fine particles. The mean and standard deviation of the normalised displacement were analysed as measures of the collective behaviour of the fines on the carrier.

![Fig. 1. Adhesive units formed from (a) spherical (b) tetrahedral and (c) triangular bipyramidal shaped fines.](image1)

![Fig. 2. Illustration of a binary collision between two adhesive units of SCR 0.7, with tetrahedron shaped fines and surface energy of interaction between them fixed at 0.03 J/m².](image2)

### Table 1

Model parameters typical for lactose carriers and fines [30–32].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coarse Particle (carrier)</th>
<th>Fine Particle (fines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle Size (Diameter, μm)</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>Poisson’s ratio (—)</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>Density (kg/m³)</td>
<td>1540</td>
<td>1540</td>
</tr>
<tr>
<td>Young’s Modulus (GPa)</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Coefficient of Static Friction (—)</td>
<td>0.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Coefficient of Rolling Friction (—)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Surface Energy (J/m²)</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Coefficient of Restitution (—)</td>
<td>0.85</td>
<td>0.65</td>
</tr>
<tr>
<td>Surface Coverage Ratio (—)</td>
<td>0.5, 0.7, 1</td>
<td>—</td>
</tr>
</tbody>
</table>
The collision is analysed based on the following parameters:

- Mechanical Stability: The restitution coefficient ($e$) is used to explain the mechanical stability in terms of the energy conserved in the system after undergoing collision.
- Stability ratios: Retention, transfer and loss ratios are used to investigate the movement of fines from and/or between adhesive units.
- Redistribution: The displacement of fines on the surface of the carrier is used to determine the spread of fines after collision.

DEM simulations and analysis were conducted using Altair EDEM® 2020 bulk material simulation software provided by Altair. A Verlet integration scheme with a timestep of 0.69 ns was used to maintain numerical consistency.

3.4. Statistical analysis

To establish an understanding of the data trends and overall behaviour of the restitution coefficient and loss ratios various statistical tools were applied. As a result of the stochastic uncertainty at low velocity as observed and explained in our previous work [15], relative velocities of 1 m/s or higher were considered and the data for different velocities were averaged for each seed value. The thus derived variable (the average) constitutes a summary measure of the results obtained in the selected velocity range. One way ANOVA (Analysis of Variance) was used to compare the results for the three different particle shapes for the same SCR and Tukey HSD (Honestly Significant Difference) test was used for multiple comparison across the data set. The result was reported in terms of $p$ values and the statistical significance level was taken as 0.05.

4. Results and discussion

Understanding the effect of the shape of fines on the integrity and effective mechanical properties of adhesive units and thus on the flowability of adhesive mixtures is important for particle formulation in order to optimise functional characteristics like particle movement through an hopper and stability inside capsules. In order to address the aforementioned challenges, binary collision between adhesive units with parametric variation of SCR, velocity and shape was studied. The collision is analysed based on the following parameters:

- SCR 0.5. Fig. 4a summarizes the result of binary collision between two adhesive units with an SCR of 0.5. Whereas the restitution coefficient approaches a relatively high and fairly constant value for the spherical fines, considerably more randomness is seen for the more irregular particle shapes. As a result, the restitution coefficient shows statistically no significant difference for the three fine particle shapes for velocities exceeding 1 m/s. Interlocking is highest in case of tetrahedron shaped fines owing to the large angle between the composite microspheres followed by triangular bipyramidal and spherical fines. This results in higher energy loss and may explain the rank order between the results obtained at moderate velocities (around 0.9 m/s), but this effect is not large enough to result in significant changes in the overall mechanical behaviour of the adhesive units at larger velocities.

The behaviour of the stability ratios for the three different fine particle shape cases can be observed in Fig. 4b. The loss is highest and the retention is lowest for spherical shaped fines ($p < 0.05$). This is attributed to the spherical fines having a higher tendency to roll and whereby get detached during collision as they have a higher energy per particle compared to that of the triangular bipyramidal and tetrahedral ones, which have a comparatively larger surface area of contact with the carrier thus leading to higher energy dissipation and higher retention on the surface of the carrier particle. Tetrahedral and triangular bipyramidal fines also have a higher tendency to interlock, leading to higher dissipation of energy and higher retention ratios.

Rearrangement of fines on the surface of the carrier is similar for different fine shapes as seen in Fig. 4c and d. The net movement of fines on the surface of carrier is normalised by fines undergoing multiple collisions with each other.

SCR 0.7. Fig. 5a shows the result of binary collision of adhesive units with an SCR of 0.7. No significant difference was observed between the restitution coefficients for the spherical, tetrahedral and triangular bi-pyramidal shaped fine particles. An increase in SCR leads to the reduction in the movement of the particles on the surface of carrier. The restitution coefficient for an SCR of 0.7 is on average less than that of an SCR of 0.5 as the fines tend to provide a shielding effect with an increase in the number whereby increasing the interaction among the fine particles.

Spherical fines are the least stable ($p < 0.05$) followed by similar stability for triangular bipyramidal and tetrahedral fines as seen in Fig. 5b. For spherical fines, most of the energy is conserved which leads to higher energy per fine particle and higher losses from the carrier.

Rearrangement of particles (Fig. 5c and d) is similar for all the three fine shapes as the packing of particles on the carrier surface increases it reduces the movement of fines.

SCR 1. Fig. 6a shows the binary collision of adhesive units with an SCR of 1. The restitution coefficient was found to be similar for all the three different shapes of particles suggesting that the increase in number density restricts the motion of particles on the surface of carrier so that the restitution coefficient is insensitive to particle shape. The average restitution coefficient is lower compared to SCR 0.5 and SCR 0.7 due to higher energy loss at the collision interface owing to interlocking which is consistent with the increase in SCR.

A similar trend as for the coefficient of restitution was observed for the stability ratios. As a result of an increase number density, the particle movement on the surface of the carrier is reduced resulting in similar stability ratios as seen in Fig. 6b.
As seen in the previous cases and also from Fig. 6c and d rearrangement of particles is similar for different fine shapes. An increase in SCR lead to a decrease in the coefficient of restitution and thus an increase in stability. Higher SCR produces a better shielding effect on the carrier particle resulting in a net interaction between the fine particles leading to higher retention and smaller loss ratios as observed from Figs. 4, 5 and 6. It could be observed that the systems (especially for spherical shaped fine particles) are more stable for a relative impact velocity of 0.8 m/s or lower, which is consistent with the observations in our previous study [15]. This result could possibly serve as a guideline for better handling of adhesive powder mixtures. Transfer ratios during the collision of adhesive units are negligible during the handling phase as seen from Figs. 4b, 5b, and 6; most of the fines are either retained on the carriers or lost from the binary system (but could potentially be picked up by other carrier in a real mixture which is not accounted for in the current simulation setup).

Overall, the shape of fine particle did not have any statistically significant effect on the restitution coefficient of adhesive units and thus on their effective mechanical property. A possible exception is spherical fines at low SCRs, for which the restitution coefficient exhibited a less random trend. As observed from our previous study [15], SCR and surface energy of the interaction thus are the major contributors to the
The shift is normalised by the diameter of the particles analysed based on, a) Restitution coefficient b) Stability ratios c) Mean shift of band of fine particles located at the centre of carrier particles d) Dispersion of band of fine particles on the surface of the carrier. The shift is normalised by the diameter of the fine particles. Each data point is an average of three initial seed values representing initial spatial distribution.

![Graphs showing restitution, stability, mean shift, and dispersion vs velocity for different shapes of particles](image)

**Fig. 6.** Binary collision between two adhesive units with a surface coverage ratio (SCR) of 1 and surface energy, 0.03 J/m² for spherical, triangular bipyramidal and tetrahedral shaped fine particles analysed based on, a) Restitution coefficient b) Stability ratios c) Mean shift of band of fine particles located at the centre of carrier particles d) Dispersion of band of fine particles on the surface of the carrier. The shift is normalised by the diameter of the fine particles. Each data point is an average of three initial seed values representing initial spatial distribution.

![Images of spherical, triangular bipyramidal, and tetrahedral particles with varying surface coverage ratios](image)

**Fig. 7.** Contact/force chains formed by contact between the fine particles with varying surface coverage ratio (SCR) of 0.5, 0.7 and 1 and a spherical, triangular bipyramidal and tetrahedral shaped fine particles.

restitution coefficient of adhesive units. Consistent with the findings in that study, the restitution coefficient tended to decrease with increasing SCR and this decrease was independent on the fine particle shape.

An evident effect of the shape of the fines could be inferred from stability ratios as seen in Figs. 4b and 5b. Tetrahedral shaped fines have a higher tendency to interlock with each other followed by triangular bipyramidal and spherical. In addition, impact and sliding of the fines may lead to higher energy loss for the tetrahedral than for the triangular bipyramidal and spherical fines as a result of their more shape and their higher surface area of contact. On increasing the SCR of adhesive units the effect of fine shape reduces as observed in Fig. 6b. Increasing the SCR leads to formation of larger interlinked chains (contact chains/force chains) of fines as observed in the reconstruction in Fig. 7. The formation of larger interlinked chains of weakly bonded fines increases the stability of these units whereby masking the effect of the shape of fines observed for low SCRs. This corresponds to the flow regime [21,22] of fine cohesive powders which is representative of plastic flow [35]. Plastic flow is characterised by a small spacing between the constituent particles which leads to an effective motion of the particles as a collective rather than as individual units, making the flow independent of the single particle geometry. The tendency of regularly shaped particles to segregate is higher compared to that of irregular particles owing to the ease of movement on the carrier surface. This study could serve as a guideline for establishing lower limits for the handling regime. Further studies into irregular particles and reconstruction using composite sphere models could further strengthen the understanding.

5. Conclusion

A systematic study of different shapes of fines was performed starting with a regular spherical shape followed by adding further complexity to form tetrahedral and triangular bipyramidal fines as composite particles from 4 and 5 primary particles. This increased the contact surface area of the fines for the same diameter of the particle and the angle between the primary particles. Binary interaction with varying SCR of 0.5, 0.7, 1 was studied for a fixed surface energy (0.03 J/m²) in a handling velocity regime with low impact velocities.

It was observed that for low SCR values a distinct effect of fine shapes is observed due to interlocking of particles at the point of collision leading to higher loss during collision for adhesive unit with spherical shaped fines. On the surface of the carrier the tetrahedral shaped particles have a higher surface area of contact which leads to higher energy loss and thus higher stability. With increase in SCR the effect of fines shape is reduced significantly. This is due to formation of large interlinked network of particles which reduces the net motion on the surface of the carrier. It could be inferred that for low SCR, tetrahedron...
or in other words fines with higher contact area and/or larger angle between the microspheres is favourable. For systems with higher SCR the cohesive powder exhibits plastic flow which is independent of fines shape. No statistically significant effect was observed in restitution coefficient with change in fine particle shape.

The understanding of the effect of the fine particle shape could be used to better design fine particles during formulation which would help maximise packing efficiency, flow through a hopper, reduces bridging and clumping. The study provides a further insight into the understanding the micromechanics of adhesive units and provides a stepping stone towards the development of a macroscopic model. Such a model could be further extended to include not only the effect of the fine particle shape but also the effect of the carrier shape on the dispersion of particles inside an inhaler.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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