An investigation of magnesium stearate mixing in a V-blender through gamma-ray detection

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A R T I C L E   I N F O
Article history:
Received 10 July 2009
Received in revised form 21 February 2010
Accepted 22 February 2010
Available online 26 February 2010

Keywords:
Magnesium stearate
V-blender
Cohesive powder
Powder mixing
Core sampling
Radioactivity measurement

A B S T R A C T
Magnesium stearate (MgSt) is a widely used powder lubricant in the pharmaceutical industry whose mixing dynamics remain poorly understood. In this work, MgSt was used as a radioactive tracer to investigate its mixing behaviour in a V-blender. MgSt was mixed with a microcrystalline cellulose and spray-dried lactose pre-blend, and a number of samples were then extracted from the powder bed with a core sampler. The amount of lubricant measured in each sample allowed the investigation of the effect of the blender fill volume and rotational speed, the pre-blend composition and the lubricant loading profile on mixing performance. Results indicate that, of these 4 parameters, the rotational speed and the pre-blend composition had the most significant effect on mixing behaviour. Contrary to our expectations, the MgSt loading profile had little effect on mixing performance. Both results indicate the overriding importance of the shear force applied on the powder bed on mixing performance. In a final experiment, the mixing performance of MgSt was compared to that of Sodium Lauryl Sulfate (SLS) at identical fill volumes and rotational speeds. Results show that, in spite of its larger particle size, SLS is more difficult to mix to the other excipients than MgSt.

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1. Introduction

Lubricants such as magnesium stearate (MgSt) play a crucial role in tablet formulation, namely to prevent the adhesion of the final powder blend to the punches and dies during compression, which would result in damaged tablets and punch fouling. It is generally acknowledged that MgSt acts as a lubricant by forming a semi-continuous film on larger excipient particles due to its very small particle size [1]. MgSt is the preferred lubricant in the pharmaceutical industry because of its low cost and high lubrication potential, melting point and chemical stability. However, because of its highly apolar molecular structure, it is insoluble in water and can thus delay the dissolution of the API in the GI tract [2–4]. Furthermore, the physical bonds between MgSt-lubricated particles are weaker than those between un lubricated ones; over-lubrication of the powder blend can thus lead to tablets with unacceptably low hardness [5–8].

1.1. Cohesive forces

When the particles of an excipient or API have an average size of approximately 40 μm, their flow properties can be affected by three main cohesive forces: capillary forces, electrostatic forces and van der Waals forces. These forces as well as their relevance to MgSt will be briefly described, although none of them were measured directly in the scope of this work. A more thorough description of each can be found in [9].

1.1.1. Capillary forces

In particulate systems, capillary forces arise when the interstitial liquid concentration, most often water, is not negligible. This force can present itself in two ways depending on the relative humidity of the environment: if the relative humidity is below a critical value generally close to 60%, particles will adhere to one another through surface-adsorbed humidity; otherwise, liquid bridges will form between them. In the context of this research project, it can be assumed that the surface-adsorbed humidity is the main source of the capillary force between two neighbouring particles.

1.1.2. Electrostatic forces

The friction between two moving particles creates an electrostatic charge between them and this potential difference will then lead to a transfer of electrons from one to the other. The force of this interaction can be described by Coulomb’s law,

\[ F_{elec} = \frac{k_e q_1 q_2}{Z^2} \]

where \( q \) corresponds to the electrostatic charge of a particle, \( Z \) to the distance between the two particles and \( k_e \) Coulomb’s constant based on vacuum permittivity. The charge that a particle can build up...
depends not only on its physical properties, but also sometimes on the
substance with which it comes into contact. In this manner, certain
cipients, such as MgSt, can build up charges of identical magnitude,
but opposed signs [10]. Even though it has not been measured, MgSt
seems to have a rather high electrical resistance due to its apolar
chemical structure.

1.1.3. Van der Waals forces

Van der Waals forces result from the induction of a dipole in the
atomic nucleus, which leads two particles to bind themselves under
the effect of the electronic attraction. Within the context of powders,
the van der Waals attraction force between two spherical particles can
be determined by the following equation,

\[ F_{vdw} = \frac{\hbar w}{8\pi Z_0^2} \left( \frac{R_1 R_2}{R_1 + R_2} \right) \]

where \( Z_0 \) corresponds to the distance between particles of respective
radii \( R_1 \) and \( R_2 \), and \( \hbar w \) designates the energy of a photon of angular
frequency \( w \). Eq. (2) shows that, in the same manner as electrostatic
forces, van der Waals forces decrease with the square of the distance
between particles. However, the distance for which van der Waals
forces are significant is much smaller than that of electrostatic forces,
which is of a few tens of microns in scale. Within a distance between
particles of 1 to 10 \( \mu \)m, van der Waals forces are more important than
electrostatic forces by several orders of magnitude.

1.1.4. Effect of MgSt on cohesiveness

The cohesive forces described in the previous section are all
dependent to a greater or lesser degree on the surface properties of
the particles involved. Since MgSt lubricates particles by forming a
film around them, it no doubt has a definitive influence on the
cohesive forces between these particles. This manifests itself as an
improvement in the flow properties of the blend after the mixing of
MgSt.

It has been hypothesized that this film can take three forms: a
monomolecular film, a monoparticulate film or a film of varying depth
which fills the cavities on the surface of the lubricated particles [1].
These films are described in Fig. 1.

The monomolecular film consists of a single layer of MgSt
molecules bound to lubricated particles by their apolar heads. This
hypothetical film is based on the comparison between the theoretical
amount of MgSt required to completely cover a single excipient, as
determined by the surface area of both substances, and the measurement
of this quantity, which corresponds to the amount of MgSt
required to obtain tablets of null hardness [5]. However, the
surface area of MgSt is very difficult to measure accurately [11], which
in turn makes it almost impossible to determine the amount of MgSt
needed to form a single layer of lubricant around every particle.

The latter two films described in Fig. 1 are the most plausible,
particularly the third one [1]. Indeed, SEM observations have shown
that a uniform distribution of MgSt on excipient particles is impossible
to achieve. Instead, these observations indicate that the first MgSt
particles lodge themselves in the cavities of other excipient particles
and form a film of variable thickness after these cavities have been
filled [12]. This type of film implies that MgSt improves the flow
properties of a powder blend mainly by diminishing the surface
roughness of the particles.

1.2. MgSt mixing and detection

MgSt mixing has been studied in the Bohle bin-blender [13,14]
and very recently in the ribbon blender [15]. To the best of our
knowledge, no study of the mixing performance of the V-blender in
the case of MgSt has been reported, apart from one study on the
impact of V-blender size on tablet crushing strength at constant fill
level [16].

Because of the drawbacks inherent to the use of MgSt, the link
between the amount of MgSt added to a formulation, the mixing
parameters and the final tablet properties, such as those mentioned
above, have been extensively studied over the past three decades
[6,17,12]. However, in nearly every study, the MgSt was assumed to be
homogeneously mixed, which is a dubious assumption given the low
amount of MgSt usually added to a formulation and its cohesiveness. If
the impact of MgSt on a formulation is easy to determine by
examining the tablet physical properties, the detection of MgSt in a
powder blend, let alone the measurement of its concentration, is far
from simple. The latter is mainly due to the amphiphilic nature of the
MgSt molecule, which makes it insoluble in most solvents and
impossible to quantify by methods such as HPLC or vacuum filtration.

Since the chemical properties of MgSt make it difficult to measure
its amount in a powder blend, most techniques used to detect it are
based on the physical properties of the Mg atom. MgSt can be
observed under an SEM [5,18,4], and the amount present in the
observed samples can be quantified if the SEM is linked to an energy-
dispersive X-ray (EDX) analyzer [19,20]. It can also be tracked and
quantified using NIR spectroscopy, whether in an on-line [21,22] or
off-line mode [13,14]. EDX analysis and NIR spectroscopy can both
measure very low amounts of MgSt in a sample. However, the former
is a very laborious method that does not easily lend itself to the
analysis of the many samples required to obtain an accurate picture of
the degree of mixing, even though it can quantify every chemical
element present in the observed sample. There is currently a growing
interest in on-line NIR spectroscopy as a Process Analytical Technol-
ogy (PAT), the use of which is encouraged by the FDA [23]. However,
this method suffers from severe technical limitations [24]. These
include its very low depth of perception within the blender or the
sample, and its reliance on assumed homogeneous blends to
determine the end-point of mixing [25].

For these reasons, we believe that there is a need for a more robust,
efficient and specific method to quantify MgSt in a powder blend.
This method should combine the specificity of EDX analysis and the
relatively high throughput capability of off-line NIR spectroscopy.
Furthermore, this method should not rely on a reference sample to
assess the homogeneity of the studied sample. These three advantages
are found in certain characterization methods based on radioactivity,
such as Positron Emitting Particle Tracking (PEPT) [26] and Radioac-
tive Particle Tracking (RPT) [27,28]. These two methods can
determine in real-time the position of a radioactive particle in a
blender according to the gamma-ray flux it emits. This flux is
measured by two cameras on either side of the blender in the case
of PEPT [29], and by a number of strategically-placed scintillation
detectors in the case of RPT. The use of RPT has allowed the
measurement of the chaotic parameters of mixing in a V-blender
[30] and has led to the definition of a new mixing index [31]. In spite
of the fact that the Mg atom can form a relatively stable radio-isotope
(\(^{24}\)Na), MgSt particles are too small to be tracked by RPT. Note
however that RPT is currently being adapted to track many
radioactive particles in a blender, in which case it is referred to as
BRPT [32].

The objective of this paper is to study the mixing of MgSt to
microcrystalline cellulose (MCC) and lactose, two excipients

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**Fig. 1.** Schematic representation of the three possible films that MgSt can form around
other excipient particles: monomolecular film (left), monoparticulate (center),
monomolecular or monoparticulate filling of cavities (right) [1].
commonly used in the pharmaceutical industry as diluents in the production of tablets, in a V-blender through the use of a method based on the detection of a gamma-ray flux. The methodology used in this work will first be described, followed by the presentation of preliminary experiments performed to validate it. Afterwards, the influence on MgSt mixing performance of the blender fill volume, the excipient loading profile, the composition of the pre-blend and the rotational speed will be investigated. Finally, a mixing experiment was performed in which Sodium Lauryl Sulfate (SLS), a lubricant made of larger and less cohesive particles, was substituted for MgSt. The results obtained will be discussed to shed light on the influence of the lubricant physical properties on mixing performance although no direct measurement of interparticle forces were made since the current state of the art makes it very difficult to obtain reliable data on these forces.

2. Materials and methods

The methodology used for this research project can be divided into three steps, beginning with the activation of inert MgSt in a SLOWPOKE nuclear reactor. Afterwards, the radioactive MgSt is mixed with the inert excipients and a number of samples are collected from the powder bed using a core sampler. Finally, the gamma-ray flux of each sample is measured and correlated to the mass of MgSt present in these samples.

2.1. Materials

3 g of radioactive, vegetable-grade MgSt monohydrate (Peter-Greven Fett-Chemie GmbH, Germany) was mixed with blends of MCC PH101 (JRS Vivapur, Germany) and Spray-dried (SD) lactose (Meggle GmbH, Germany). The flowability of an excipient, which increases as the cohesive forces between particles decrease, reflects itself in the ratio of the tapped density to the bulk density or Hausner ratio. The difference between the bulk density and the tapped density of an excipient is related to its particle size distribution (PSD) in the sense that an excipient with a smaller average particle size can be compacted into a smaller volume. As such, the gap between its tapped density and bulk density is higher, which translates into a higher Hausner ratio and a lower flowability. The Hausner ratio for of MCC and lactose are given in Table 1 and the PSD of each excipient and lubricant are presented in Fig. 2 and Table 2. As Fig. 2 indicates, the MCC PH101 particles are much smaller than the lactose SD particles, which explains the higher Hausner ratio and poorer flow properties of the former excipient. The fact that the PSD of both excipients are rather wide is due to the fact that neither of them was sieved prior to the mixing experiments.

2.2. MgSt activation

The MgSt particles to be mixed were put in the SLOWPOKE nuclear reactor of École Polytechnique de Montréal for 4 h. During that time, it underwent a neutron bombardment that converted some of the ground-state $^{24}\text{Mg}$ atoms into radioactive $^{24}\text{Na}$:

$$^{24}\text{Mg} + n^0 \rightarrow ^{24}\text{Na} + p^+ \quad (3)$$

This reaction is not the only one taking place in the nuclear reactor, nor is it the main reaction. Other reactions include the absorption of neutrons by the Mg atom, leading to the formation of heavier Mg radio-isotopes, as well as the formation of other radio-isotopes due to the presence of chemical substances used during the synthesis of MgSt. However, $^{24}\text{Na}$ is by far the most stable radio-isotope produced, with a half-life of 14.5 h. To allow the more unstable radio-isotopes to return to a ground state, the radioactive MgSt was kept at rest for approximately 18 h before being used in the mixing experiments. At the beginning of these mixing experiments, the MgSt showed an activity of approximately 730 kBq.

The gamma-ray flux emitted by $^{24}\text{Na}$ was measured by (NaI)Tl scintillation detectors (EG&G Ortec Inc., USA) linked to a data acquisition system. Since the intensity of such a flux is proportional to the mass of radio-isotopes present, the calibration curve shown in Fig. 3 was generated and used to determine the mass of MgSt in the samples collected during the mixing experiments. The gamma-ray flux plotted in Fig. 3 is normalized to 100% to a flux emitted by $^{24}\text{Na}$.

Fig. 4(a) and (b) are SEM images of MgSt that were taken before and after the neutron bombardment to assess that it does not affect the morphology of the particles. These figures show that, even after

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Hausner ratio</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC PH101</td>
<td>1.47</td>
<td>Very poor</td>
</tr>
<tr>
<td>Lactose SD</td>
<td>1.24</td>
<td>Average</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Lubricant</th>
<th>$d_{10}$ (μm)</th>
<th>$d_{50}$ (μm)</th>
<th>$d_{90}$ (μm)</th>
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<tr>
<td>MgSt</td>
<td>3</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>SLS</td>
<td>56</td>
<td>258</td>
<td>512</td>
</tr>
</tbody>
</table>
being submitted to a neutron bombardment, MgSt still presents itself as flaky particles with clearly defined edges; the neutron bombardment does not significantly affect the morphology of the lubricant particles.

2.3. Mixing experiments

All mixing experiments were performed in the 8-qt acrylic V-blender shown in Fig. 5. The inside of the blender was covered with tin foil and grounded to prevent cohesive particles from adhering to the blender walls due to electrostatic forces.

Previous research on the mixing of non-cohesive powders in tumbling blenders has revealed that the most important parameters affecting mixing performance are the fill volume, the loading profile and the rotational speed. Raising the fill volume of a tumbling blender above 70–80\% will result in a significant degradation of mixing performance [33–35], as will loading the excipients along the axis of rotation since axial mixing is generally much slower than radial mixing in such blenders [36]. Cohesive mixing involves not only distributing one or more substances homogeneously within the powder bed, but also preventing the formation of agglomerates by applying sufficient shear force [37]. This is thought to be the rate-limiting mechanism in cohesive powder mixing [38]. Therefore, the blender rotational speed plays a much broader role in the mixing of cohesive powders than it does in the mixing of non-cohesive ones. It has also been observed that the composition of the powder bed can have a determining influence on mixing performance [37].

Based on these considerations, it was decided for our work on MgSt to study not only general blending parameters such as fill volume, rotational speed and lubricant loading profile, but also the composition of the powder bed. The values of each parameter studied in this work are summarized in Table 3. As previously mentioned, the amount of MgSt added to the V-blender in every mixing experiment was 3 g.

Two types of pre-blends were considered, one composed entirely of MCC and another composed of equal parts by weight of MCC and lactose, in order to determine whether or not the cohesiveness of the excipients being lubricated had an impact on MgSt mixing performance. The blend consisting of equal amounts of MCC and lactose SD is less cohesive because the lactose particles are bigger than those of MCC, as already discussed. The sampling approach used will be described in the following section. The MCC-lactose pre-blends were prepared by mixing these excipients in the V-blender for 5 min at

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Fill volume</td>
<td>30, 50, 70%</td>
</tr>
<tr>
<td>Rotational speed</td>
<td>26, 41 rpm</td>
</tr>
<tr>
<td>Loading profile</td>
<td>Top-bottom, left-right</td>
</tr>
<tr>
<td>Pre-blend MCC concentration</td>
<td>50, 100 wt.%</td>
</tr>
</tbody>
</table>
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26 rpm prior to the addition of MgSt. To determine the adequacy of the pre-blend mixing time, 20 samples were extracted from the powder bed, dissolved in warm water and vacuum-filtered. Since lactose is soluble in water while MCC is not, one phase of the pre-blend can be completely recovered and the other completely removed, which allows a precise assessment of the sample composition. The relative standard deviation (RSD) of the recovered fraction of MCC reflects the homogeneity of the pre-blend: the pre-blend was deemed homogeneous if the RSD value was inferior to 1%.

The fill volumes used correspond to MCC amounts varying between 704 and 1680 g. A fill volume of 70% was used in most experiments because it reflects typical industrial settings. Because of the higher density of lactose, a pre-blend composed of equal parts of MCC and lactose weighs approximately 2216 g for a fill volume of 70%. Since the amount of MgSt added was set at 3 g, this translates into an MgSt target concentration varying between approximately 0.17 and 0.41% for the pure MCC pre-blends and approximately 0.13% for the MCC-lactose pre-blends. The amount of MgSt added was limited by the capacity of the SLOWPOKE reactor.

In a “top–bottom” (T–B) loading profile, the lubricant was loaded first into the blender, beneath the pre-blended excipients, whereas in a “left–right” (L–R) profile, it was placed on top of them in one of the branches, as shown in Fig. 6(a) and (b). In all experiments, the MgSt was first sieved through a 70-mesh (210 μm) screen prior to mixing. This was performed to enhance the mixing performance of MgSt, as will be discussed further in Section 3.

The rotational speeds that were chosen are typical of those used in production-scale mixing equipment.

Table 4 gives the characteristics of the mixing experiments performed. Note that experiments 7 and 8 are repetitions of experiments 6 and 5 respectively, and were performed to assess the reproducibility of the experiments. In experiment 10, Sodium Lauryl Sulfate (SLS) was substituted to MgSt as the lubricant. Experiment 11 was performed to determine whether the amount of MgSt added to the blender could influence the results.

![Fig. 6. Description of the two MgSt loading profiles in the V-blender (MgSt shown in black): (a) Left–right, (b) Top–bottom.](image)

![Fig. 7. Core sampler used in the mixing experiments.](image)

### Table 4

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Fill volume (%)</th>
<th>Rotational speed (rpm)</th>
<th>Loading profile</th>
<th>Pre-blend concentration (wt.% MCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>26</td>
<td>T–B</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>26</td>
<td>T–B</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>26</td>
<td>L–R</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>26</td>
<td>L–R</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>26</td>
<td>L–R</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>26</td>
<td>T–B</td>
<td>100</td>
</tr>
<tr>
<td>7*</td>
<td>70</td>
<td>26</td>
<td>T–B</td>
<td>100</td>
</tr>
<tr>
<td>8*</td>
<td>70</td>
<td>26</td>
<td>L–R</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>26</td>
<td>L–R</td>
<td>50</td>
</tr>
<tr>
<td>10*</td>
<td>70</td>
<td>26</td>
<td>L–R</td>
<td>100</td>
</tr>
<tr>
<td>11*</td>
<td>70</td>
<td>26</td>
<td>L–R</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>41</td>
<td>L–R</td>
<td>100</td>
</tr>
</tbody>
</table>

*Experiments with an additional objective besides the study of a blending parameter.

2.4. Sampling

Because it is a non-intrusive method with unlimited perception depth [32], BRPT would have been an ideal method to study MgSt mixing, but it is not yet suited to the complex geometry of the V-blender. Because of this limitation, it was decided to rely on thief probe sampling instead. The occurrence of sampling bias when a thief probe is used to extract samples from a powder bed is well documented in the literature [39,40]. The so-called core sampler was used in this work because this design has proven to minimize the disturbance of the powder bed as well as the sampling bias [40].

The extraction of the samples was performed with the core sampler shown in Fig. 7, which has an outside diameter of 12.7 mm and an inner diameter of 9.5 mm. Different sampling depths were used for the different sampling locations, as shown in Fig. 8, in order to avoid the transfer of material from one branch of the blender to the other during the extraction operation. In all cases, the sampling depth was determined in order to collect the highest mass of powder in a given sampling location without transferring material between branches. A smaller sample size allows the study of the mixing performance at a finer scale of scrutiny, although more samples may then be needed to detect broader mixing trends within the blender. In this work, it was decided to collect samples as large as possible since MgSt is present in very small amounts in the V-blender.

For each mixing experiment, samples were extracted from each branch of the V-blender at 7 regular intervals. The number of samples collected from each arm of the V-blender during each sampling varied from 6 for a fill volume of 30% to 10 for a fill volume of 70%. As such,
the total number of samples extracted during an experiment varied between 84 \((7 \times 2 \times 6)\) and 140 \((7 \times 2 \times 10)\). Note that the sampling locations used in each experiment were selected so as to maintain symmetry along the plane shown in Fig. 8.

Each sample was transferred directly from the core sampler to a 20-mL vial (Fisher Scientific, USA) for the gamma-ray flux measurements. The vial was then placed directly on the scintillation detector and the flux was measured over 1 min with a 0.01 s acquisition period. The calibration curve shown in Fig. 3 was used to convert the radioactivity measured by the scintillation detector to the amount of MgSt in the sample, which was converted to a concentration by dividing it by the sample mass. The relative standard deviation (RSD) of every sample collected at one point in time was then calculated to describe the state of the blend at that time.

The sampling error associated with a thief probe is usually evaluated by sampling at different depths a powder blend whose composition is known and by comparing, for a given depth, the composition of the samples to those of the powder bed. This method was used by Lemieux et al. [35] in their comparative study of V-blenders and Tote bin-blenders using \(500 \mu m\) spheronized granules. They concluded that a minimum distance of 2 cm between sampling positions was necessary to avoid disturbing one by the sampling of the other. Since the same core sampler was used for the current work in the case of cohesive and therefore more mechanically stable excipients, it can be assumed that this sampler probe does not significantly disturb the powder bed.

3. Results and discussion

In this section, the reproducibility of the experiments and a validation of the sampling scheme are first discussed. Afterwards, the effect on mixing performance of each parameter listed in Table 3, namely the fill volume, blender rotational speed, MgSt loading profile and pre-blend composition is investigated. Finally, results of an experiment involving SLS are presented.

3.1. Reproducibility of experiments

As previously mentioned, experiment 5 of Table 4, which involved a 70% fill volume, 26 rpm rotational speed and a pre-blend comprised exclusively of MCC, was performed a second time as experiment 7 in order to assess the reproducibility of the experiments.

As shown in Fig. 9, the two mixing curves are very close to each other, which shows that our methodology based on gamma-ray detection is adequate.

3.2. Influence of operating parameters on mixing time

3.2.1. Blender fill volume

The effect of the blender fill volume on MgSt mixing performance was investigated for a rotational speed of 26 rpm, a L–R loading profile and a 100% MCC pre-blend. This effect was investigated from experiments 3, 4 and 5, with respective fill volumes of 30, 50 and 70%, as described in Table 4. Fig. 10 indicates that blending performance, as characterized by the asymptotic RSD value, decreases as the fill volume increases, which complies with what is generally observed in the case of free-flowing and cohesive powders in tumbling blenders. The deleterious effect of fill volume on mixing performance can be explained here by the decrease in shear stress per unit volume \([14]\). At 30% fill volume, mixing of MgSt stabilizes after approximately 4.5 min, whereas with a fill volume of 50% or higher, mixing requires more than 7 min.

The final point of the mixing curve of experiment 3 is slightly elevated; this is due to the fact that three of the samples taken during the final sampling showed above-average MgSt concentrations. As mentioned in Section 3, the fill volume affects the MgSt target overall concentration, since the amount of MgSt added to the blender remains constant. In order to assess the impact of the MgSt concentration on mixing performance, experiment 9 was performed.
with 7.35 g of MgSt at a fill volume of 70% and a rotational speed of 26 rpm. A higher mass of MgSt at a constant fill volume should translate into an MgSt concentration higher than in experiments 3, 4 and 5. Fig. 11 compares the mixing curves obtained from experiments 5 and 11. The higher RSD value obtained at the beginning of experiment 11 is due to the very high MgSt concentrations measured in the left arm of the blender during the first sampling. Since the two mixing curves are nearly superimposed for the other six samplings, Fig. 11 indicates that the MgSt concentration has little impact on mixing performance. Therefore, the impact of the fill volume on MgSt mixing performance is related to the shear stress per unit volume alone.

3.2.2. MgSt loading profile

The effect of the loading profile on mixing performance was investigated for a rotational speed of 26 rpm, a fill volume of 70% and a 100% MCC pre-blend. Two loading profiles were considered: L–R in experiment 5 and T–B in experiment 6, as described in Table 4. The mixing curves shown in Fig. 12 indicate that the MgSt loading profile has little impact on the mixing time at similar fill levels. Note that previous results from the literature have shown that the difference between axial (diffusive) and radial (convective) mixing rates in tumbling blenders, which can be as high as an order of magnitude for free-flowing powders, is much less important in the case of cohesive powders [41]. The results obtained here are therefore not entirely unexpected.

The relative lack of influence of the loading profile on mixing performance in the case of cohesive powders may be caused by three factors: relatively slow radial mixing, relatively fast axial mixing, or the overriding importance of shear mixing with respect to the previous two mechanisms. The relative performance of axial and radial mixing can be assessed by examining the evolution of the concentration of MgSt in both branches of the V-blender when MgSt is added according to a left–right loading profile, as shown in Fig. 13. In this situation, one would expect axial mixing to be the limiting mixing mechanism. In every experiment in which a left–right MgSt loading profile was used, MgSt was initially positioned in the left arm of the blender. Fig. 13 indicates that convective and diffusive mixing occur simultaneously. If free-flowing excipients were mixed, axial mixing would be the rate-limiting step and there would be a certain time lapse between the beginning of the experiment and the rise in MgSt concentration in the right arm, during which a certain amount of MgSt would diffuse from the left arm to the junction of both arms. This is not observed here, since the MgSt concentration in the right arm begins to increase immediately, indicating a relatively rapid transfer of MgSt particles from the left arm to the right one. This phenomenon indicates that the axial mixing rate is accelerated in comparison to what is normally observed with free-flowing excipients, to a point...
where it is comparable to the radial mixing rate. A possible explanation for the relative ease with which lubricated particles migrate from the left arm to the right one lies in the fact that such particles become less cohesive and therefore more mobile. This elucidates the steep rise in the MgSt average concentration in the right arm during the first 5 min of mixing. The increase in the axial mixing rate indicates that MgSt transfer to the other excipient particles and not the particle mobility is the limiting factor in MgSt mixing performance and this reflects the importance of shear on MgSt mixing. Shear in this case allows the transfer of MgSt from more lubricated particles to less lubricated ones. Over time, more and more particles have a certain amount of MgSt adsorbed on them, which increases their mobility and facilitates the dissemination of MgSt throughout the powder bed.

In order to confirm that mixing an excipient with MgSt does in fact increase its mobility, the flowability of lubricated and unlubricated MCC PH101 particles was measured (Sotax FT300 Flow Tester, Switzerland). This instrument performs six tests in which the mass flow of powder is measured under certain conditions, and returns an index reflecting the average flowability of the powder. Table 5 confirms that mixing MgSt to MCC PH101 increases its flowability and that this increase is mostly felt at low concentrations (<0.50%).

3.2.3. Blender rotational speed

The effect of the blender rotational speed on MgSt mixing performance was investigated for a L–R loading profile and a 100% MCC pre-blend. Two different rotational speeds were considered: 26 rpm in experiment 5 and 41 rpm in experiment 12, as described in Table 4. Fig. 14 reveals the importance of the rotational speed on mixing performance, both in terms of the RSD value at a given time and the asymptotic RSD value. Not only does the RSD value decrease more quickly at 41 rpm, but the final RSD value is also lower than that obtained at 26 rpm, as expected.

A comparison of Fig. 15(a) and (b) indicates that an increase in rotational speed by approximately 50% from 26 to 41 rpm only accelerates the transfer of lubricated particles to the right arm without affecting the quality of the blend since in both cases the concentration levels off to approximately 0.14%. Because it becomes very difficult to stop the blender in a vertical position at high speeds, no attempt was made to raise the rotational speed beyond 41 rpm.

3.2.4. Pre-blend composition

The influence of the pre-blend composition on MgSt mixing performance was investigated for the L–R loading profile and a rotational speed of 26 rpm. Two different pre-blends were considered, one that consisted exclusively of MCC PH101 (experiment 5) and one that consisted of equal parts of MCC PH101 and lactose SD (experiment 9). Fig. 16 indicates that the dilution of a cohesive excipient like MCC PH101 with an equal part of a non-cohesive one such as lactose SD slightly improves the mixing performance of MgSt, since the RSD values obtained in experiment 9 decrease more quickly and reach a lower final value than in experiment 5. A comparison of Figs. 14 and 16 reveals that, for an identical number of rotations of the blender, the influence of the composition of the pre-blend on mixing performance is comparable to that of the rotational speed.

The evolution of the concentration of MgSt in both arms of the V-blender is shown in Fig. 17(a) and (b) for experiments 5 and 9, respectively. The different asymptotic values of the concentration that can be observed are due to the higher density of lactose. As previously mentioned, the increased axial mixing rate is due to the fact that lubrication increases particle mobility. This also explains why the

<table>
<thead>
<tr>
<th>MgSt added (%)</th>
<th>Flowability measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.21</td>
</tr>
<tr>
<td>0.5</td>
<td>0.39</td>
</tr>
<tr>
<td>1</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Fig. 14. Mixing curves obtained from experiments 5 and 12, corresponding to rotational speeds of 26 and 41 rpm respectively (see Table 4).

Fig. 15. Average concentrations in both arms of the V-blender at 2 rotational speeds: a) 26 rpm (experiment 5) and b) 41 rpm (experiment 12).
transfer of lubricated particles from the left arm to the right one seems slightly faster in the case of a lactose-MCC pre-blend than when pure MCC is used, since lactose has better flow properties than MCC.

However, in both cases, the average concentrations in both arms converge to the same value after approximately 10 min, which suggests that MgSt mixing performance is not significantly affected by a pre-blend with better flow properties. Fig. 17(b) shows that the initial average concentration of MgSt in the left arm is significantly lower than expected. Since the mass of the samples collected during that experiment are nearly constant despite the fact that MCC and lactose have different densities, segregation of the components of the pre-blend was ruled out as a possible explanation. One possible cause would be that a certain amount of MgSt was located outside the sampling locations at that time.

### 3.3. Shear and MgSt agglomeration

With the exception of the loading profile, the operating parameters studied in the previous section are all related to the amount of shear stress developed in the V-blender, and this explains their influence on MgSt mixing performance. In order for a transfer of MgSt to take place between two particles, a minimum level of shear stress is needed to dislodge the MgSt from the host particles. A lower fill volume implies a smaller number of particles and a higher average speed on impact, which translates into a higher shear stress and an enhanced transfer of MgSt. In the same manner, a higher rotational speed leads to more energetic collisions between particles as a result of a higher shear stress. When lactose particles are added to the pre-blend, their larger size and better flow properties give them a higher acceleration at a given rotational speed, which also leads to a higher shear stress. The loading profile is the only parameter with no link to the amount of shear developed in the V-blender, which explains its lack of influence on MgSt mixing performance.

As already mentioned, the performance of cohesive mixing depends not only on the homogeneous distribution of particles throughout the powder bed, but also on the pulverization of agglomerates of cohesive particles. By their nature, the particles of cohesive excipients such as MgSt will bind themselves together or to other excipient particles, thereby forming agglomerates. In the context of MgSt mixing, the increased mobility of the excipient particles after being lubricated implies that mixing performance is not linked so much to a homogeneous distribution of the lubricant as it is to the control of the size of the agglomerates.

Previous studies have shown that MgSt can form relatively strong agglomerates that will not be broken in a V-blender [21]. Increasing shear within the blender, for instance through the use of an intensifier bar, can reduce the size of these agglomerates but, at higher MgSt concentrations (≈2%), there is a risk of over-lubrication of the larger excipient particles [42]. These factors imply that a proper lubrication involves a lower amount of lubricant as well as an adequate control of agglomerate size. In this case, sieving of MgSt particles was substituted to the use of an intensifier bar as a means to control agglomerate size.

Fig. 18 shows the importance of MgSt sieving prior to mixing. Indeed, it can be seen that the RSD curve for the unsieved case is not monotonically decreasing and that there is a significant increase at the beginning of the mixing experiment. This increase is due to the fact that the MgSt concentration in three out of the twelve samples collected after 45 s is much higher than the target concentration. The fact that this behaviour is not observed in experiments for which the MgSt was sieved prior to mixing indicates the presence of MgSt agglomerates. The higher asymptotic RSD value in the case of unsieved MgSt indicates that the final mixing quality is poorer. In fact, one can observe that sieving the MgSt particles through a 70-mesh screen leads to a more than four-fold reduction in RSD after 3 min. The sieve size was chosen as a compromise to obtain MgSt particles as small as possible while limiting the time needed to sieve the MgSt powder.

Fig. 16. Mixing curves obtained from experiments 5 and 9, corresponding to pre-blends containing 100% MCC PH101 and 50% MCC PH101/50% lactose SD (see Table 4).

Fig. 17. Average concentrations in both arms of the V-blender for two different pre-blends: a) 100% MCC PH101 (experiment 5), and b) 50% MCC PH101/50% lactose SD (experiment 9).
3.4. Dynamics of Sodium Lauryl Sulfate mixing

As mentioned in the introduction, the mechanism of lubrication of MgSt is well understood. Its small particle size allows it to form a film on larger excipient particles. The results presented in the previous two sections reflect the importance of shear forces on mixing performance when using film-forming lubricants such as MgSt. Other lubricants, however, may present themselves as particles too big to bind themselves to other excipient particles. This is the case with Sodium Lauryl Sulfate (SLS). As indicated in Table 2, one of the main differences between SLS and MgSt is the much larger particle size of the former, which translates into a better flowability. SLS is most commonly used as a surfactant, but can also serve as a lubricant [43,44]. The difference in particle size between SLS and MgSt suggests that both substances have different lubrication mechanisms. The particle size distribution of SLS summarized in Table 2 indicates that less than 10% of the SLS particles are small enough to adsorb themselves onto bigger excipient particles in the same manner as MgSt, which implies that the most plausible lubrication mechanism for the remaining SLS particles would be the deformation of loose particles under shear. This deformation can be elastic or plastic in nature and may even take the form of a fragile fracture.

Since SLS is a hydrophilic molecule, it does not decrease the dissolution rate of an API and can even counter the drawbacks of hydrophobic MgSt when both are present in a formulation [45]. To our knowledge, no study exists on the mixing dynamics of SLS when it is used as a lubricant. Because the SLS molecule contains a sodium atom, it can be made radioactive in the same manner as MgSt, and the same methodology used to investigate MgSt mixing can be applied to SLS. These two factors have incited us to briefly look into the mixing dynamics of SLS to pure MCC. Radioactive SLS was produced in the SLOWPOKE reactor according to the following reaction:

\[
{}^{23}_{11}\text{Na} + {}^{0}_{0}\text{n} \rightarrow {}^{24}_{11}\text{Na} \quad (4)
\]

Just as in the case of radioactive MgSt, the radioactive SLS was kept at rest for 18 h in order to allow the more unstable radio-isotopes to return to a ground state.

The mixing dynamics of SLS were investigated for a 100% MCC pre-blend, a 70% fill volume, a L–R loading profile and a rotational speed of 26 RPM, as shown in Table 4. Approximately 1.88 g of SLS was added to the left arm of the blender, yielding an overall concentration of approximately 0.11%. As previously mentioned, the overall concentration of MgSt in these conditions was approximately 0.18%. The amount of SLS added to the blender was limited by the volume that could be made radioactive in the SLOWPOKE nuclear reactor. Since the density of SLS is approximately 0.15 g/ml compared to 0.37 for MgSt, the amount that can be added to the blender is significantly lower.

The mixing curve obtained is compared to that of MgSt obtained under similar conditions in Fig. 19. It shows that SLS mixing performance is poorer than that of MgSt, the early RSD values being higher. This may be due to slower axial mixing as a consequence of the larger size of SLS particles. Indeed, because most of them are too big to adsorb themselves on MCC particles and be “carried” by them in the same manner as MgSt particles, they must diffuse by themselves across the blender, which is a slower process. Fig. 20(b) shows that the average SLS concentration in the right arm increases with the decrease of concentration in the left arm, revealing that convective and diffusive mixing occur simultaneously, just as in the case of MgSt.

An examination of all samples taken during the final sampling has indicated that every measured SLS concentration is above the overall concentration and that, in both branches of the V-blender, the concentration decreases as the samples are taken at a higher depth. This may imply that SLS particles tend to segregate during mixing. Considering the sampling positions as shown in Fig. 8, this would mean that the concentration of SLS is highest in the line where positions 1, 2, 4 and 5. Since these samples were taken at a low depth, this may also imply that SLS is mostly found near the top of the
powder bed. Particle segregation at the center of the V-blender and along the axis of each arm has been observed when non-cohesive particles of different sizes are mixed [46,34]. However, to the best of our knowledge, it has never been observed when a small amount of a non-cohesive excipient, such as SLS, is mixed in a tumbling blender to a large amount of a cohesive one, like MCC PH101.

The poorer mixing performance of SLS relative to MgSt is significant, since it contradicts the common idea that larger, and therefore less cohesive, particles are easier to mix than cohesive ones. In the present case, both types of lubricants reach a similar average concentration in both arms of the V-blender after 10 min, as shown in Fig. 20. This shows that factors other than size play a role in the mixing dynamics, such as the fact that lubricant particles small enough to adsorb onto larger ones can only move from a more lubricated particle to a less lubricated one, which ensures that the blend quickly homogenizes as more and more particles become lubricated. In the case of MgSt, the mixing dynamics are enhanced by its chemical structure, since lubricated particles become more mobile, which facilitates their contact with less lubricated particles. The main effect of this mechanism is that the diffusion of MgSt throughout the blender proceeds at an increased speed. By contrast, even though the size of SLS particles makes them more mobile by themselves, it also hinders their diffusion across the junction of the arms of the blender, which explains the poorer mixing performance of non-cohesive particles when a left–right loading profile is used [25]. Since their size also prevents them from adsorbing onto excipient particles, it can lead to segregation as well.

4. Conclusion

In this work, a method by which MgSt can be detected in samples extracted from an excipient blend was validated and used to study the effect of different blending conditions on the mixing performance of this lubricant in a V-blender. It was observed that the mixing of cohesive MgSt particles is governed by shear, as well as by dispersive and convective mechanisms. Blender rotational speed and fill volume were shown to be the two parameters that influence mixing performance the most, which indicates that shear mixing is more important than the other two mechanisms. Contrary to what is observed with non-cohesive excipients, the loading profile did not significantly affect mixing performance.

The mixing dynamics of MgSt were also compared with that of SLS, a lubricant presenting itself as bigger particles that cannot adsorb on excipient particles. The poorer mixing performance of SLS under conditions similar to those for MgSt indicates that their larger size actually hinders their mixing to the other excipients.

Related work in the context of this research project will involve the production of tablets made from MCC and lactose lubricated with MgSt and SLS, using information gathered from the mixing experiments described here. The physical properties of these tablets will be related to the amount of lubricant, which should help optimize the amount to be added to the formulation. It is also planned to resort to Bulk Radioactive Particle Tracking (BRPT) when it is available to gain more insight into the mixing dynamics of MgSt and SLS in the V-blender used in this work.

Acknowledgements

The financial and technical support of ratiopharm operations, and the financial support of NSERC are gratefully acknowledged. We would also like to thank Mr. Jean St-Pierre and Mr. Greg Kennedy for the preparation of radioactive MgSt and SLS.

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