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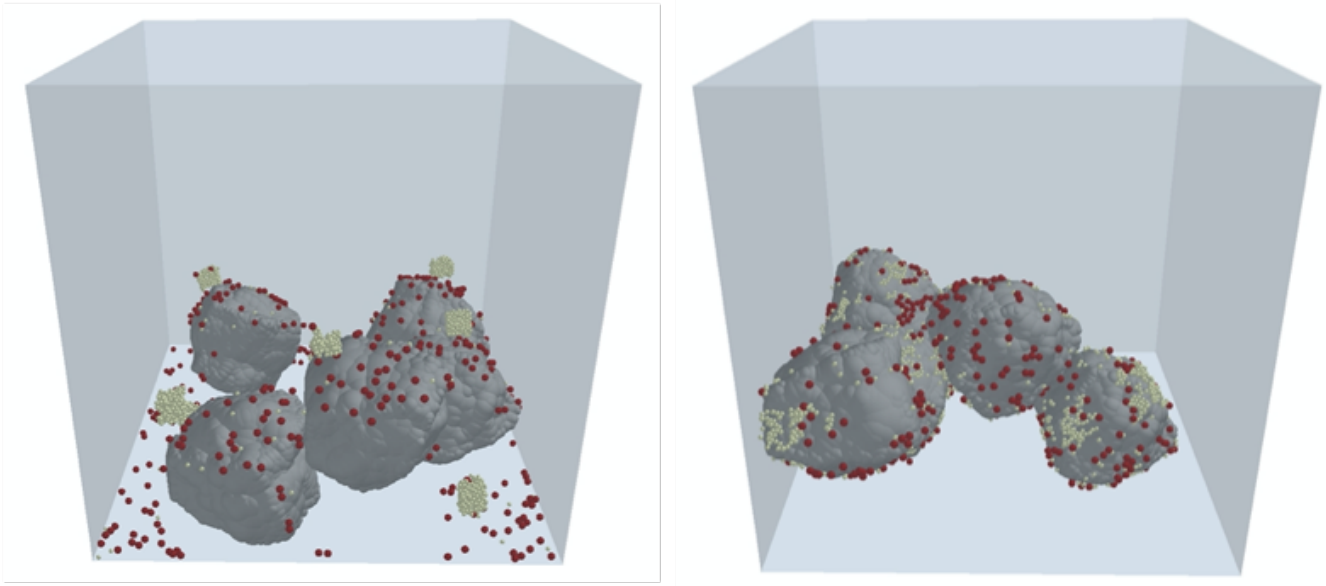

Discrete element modelling (DEM) of adhesive ternary mixture

Effect of critical attributes on the DPI formulation

Master's thesis in Chemical Engineering

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DEPARTMENT OF CHEMISTRY
AND CHEMICAL ENGINEERING

CHALMERS UNIVERSITY OF TECHNOLOGY
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MASTER'S THESIS IN CHEMICAL ENGINEERING

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DEM of a ternary mixture before and after formulation.

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ABSTRACT

The dependency of our lives on pharmaceutical products has been never sensed to a level as today. This is due to significant progress in the development of different treatment techniques to deal with corresponded diseases. Many such advances have taken place in the field of drug delivery, where the main objective is focused on delivery systems of the active pharmaceutical ingredients (APIs). Inhaled drug delivery as one of the main branches of drug delivery, has drawn much attention during the last decades. This is because of the great potential that exists for the enhancement of the common methods as well as the growing number of applications for other disorders [1]. The most common and convenient way of Inhaled drug delivery is via a small device known as a dry powder inhaler (DPI). Dry powders in DPIs are made up of three different components: carrier, drug, and fine excipient particles, each with specific characteristics to cope with the main challenge of DPIs regarding the cohesivity of drug particles. Because of this feature, drug particles tend to stick to each other, and subsequently, they cannot pass through the fine lung cavities, which in turn causes a reduction in the efficiency of DPI devices.

The deliverability of APIs is highly influenced by both the formulation and aerosolization of pharmaceutical components in DPIs [2,3]. In this study, a complex pharmaceutical mixture was modeled to grasp the fundamentals of a ternary formulation. This was done to facilitate further studies regarding the DPI formulation. Moreover, it was attempted to discover the governing mechanisms in the mixing for the purpose of improving DPIs in later studies. These goals were achieved by the simulation of several case studies together with the assessment of key variables. According to the literature study, the mass ratio and particle size corresponded to the fine excipients as well as the drug particle surface energy were chosen as the critical attributes that can affect the mixing performance the most [2,4]. Studying such factors can lead us to have a better understanding of the phenomena occurring during the ternary formulation.

Key words: Ternary formulation, Adhesive mixing, Agglomerate, Discrete Element Method, DPI formulation, Dispersion

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PREFACE

In this study, the effect of the main attributes on the ternary formulation of DPIs has been investigated. The issue was addressed by modeling different case studies with the EDEM, the platform used to track particles via discrete element modelling. This master's thesis was carried out from January 2020 to June 2020 as a part of a research project concerning the adhesive ternary mixing of DPI formulation. The project was conducted and financed through the consulting company, Afry along with collaboration with the Department of Chemistry and Chemical Engineering at Chalmers University of Technology, Gothenburg, Sweden. Additionally, the project benefited from consultation with the pharmaceutical company, Astra Zeneca by their great feedback and input during the entire project.

The idea of the project stems from a Ph.D. work by Mohammadreza Tamadondar and was done as a continuation of his work. The project has been carried out under the supervision of Per Abrahamson as the industrial supervisor and Mohammadreza Tamadondar as the academic supervisor. Also, Professor Anders Rasmuson contributed to the project as the main examiner from the Department of Chemistry and Chemical Engineering at Chalmers.

It should be noted that this work could never have been conducted without the excellent guidance and support of the people mentioned above. Finally, I would like to thank my parents who deserve a particular note of thanks: your wise counsel and kind words have, as always, served me well.

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Kian Salehi

LIST OF NOTATIONS

The following symbols are used in this report.

Roman upper-case letters

$\boldsymbol{A_n}$	Coefficient of magnitude for Fourier harmonic series
$\boldsymbol{B_n}$	Coefficient of phase for Fourier harmonic series
$\boldsymbol{D_n}$	Normalized Fourier descriptor
$\boldsymbol{E}$	Elastic moduli
$\mathbf{F_A}$	Contact force
$\mathbf{F_C}$	Maximum particle adhesive force
$\mathbf{F_n}$	Normal force
$\mathbf{F_{nd}}$	Dissipative part of normal collision/adhesion force
$\mathbf{F_{ne}}$	Elastic part of normal collision/adhesion force
$\mathbf{F_s}$	Sliding resistance
$\boldsymbol{G}$	Shear moduli
$\boldsymbol{K}$	Stiffness coefficient
$\boldsymbol{N}$	Total number of Fourier harmonics
$\mathbf{M_A}$	Contact torque
$\mathbf{M_t}$	Twisting resistance
$\mathbf{M_r}$	Rolling resistance
$\boldsymbol{I}$	Particle momentum of inertia
$\boldsymbol{N}$	Total number of Fourier harmonics
$\boldsymbol{N}$	Total number of Fourier harmonics

Roman lower-case letters

$\boldsymbol{a}$	Radius of contact region
$\boldsymbol{a_0}$	Equilibrium contact radius
$\boldsymbol{e}$	Restitution coefficient
$\boldsymbol{k_N}$	Elastic stiffness
$\boldsymbol{k_S}$	Rolling stiffness
$\boldsymbol{k_T}$	Tangential stiffness coefficient
$\boldsymbol{n}$	Normal vector
$\boldsymbol{m}$	Particle mass
$\boldsymbol{r_i}$	Particle radius

$\boldsymbol{r_0}$	Average radius of Fourier harmonic
$\boldsymbol{R}$	Effective radius of colliding particles
$\boldsymbol{t}$	time
$\boldsymbol{t'}$	Dimensionless time number
$\mathbf{t}_{\boldsymbol{R}}$	Direction of particle rolling velocity (V_L /$\lvert V_L \rvert$)
$\mathbf{t}_{\boldsymbol{S}}$	Direction of particle sliding velocity (V_S /$\lvert V_S \rvert$)
$\boldsymbol{v}$	Particle velocity
$\boldsymbol{v}_{\mathbf{R}}$	Particle relative velocity at contact time
$\boldsymbol{w}$	collision rate (dδ/dt)
$\boldsymbol{w_0}$	measure of particle relative collision velocity
$\boldsymbol{W_S}$	Work of adhesion
$\boldsymbol{x}$	Particle centroid position

Greek letters

$\boldsymbol{\delta'}$	Dimensionless overlap
$\boldsymbol{\delta_C}$	Critical overlap
$\boldsymbol{\delta_N}$	Particle normal overlap
$\boldsymbol{\delta_C}$	Critical overlap
$\boldsymbol{\gamma}$	Surface energy
$\boldsymbol{\eta_N}$	Normal friction coefficient
$\boldsymbol{\mu}$	Tabor number
$\boldsymbol{\sigma}$	Poisson ratios
$\boldsymbol{\Omega}$	Angular rotation rate of particle

Mathematical operators

d/dt	Derivative following particle
$\boldsymbol{\Sigma}$	Summation

Acronyms

AFM	Atomic force microscopy
API	Active pharmaceutical ingredient
CAE	Computational aided engineering
DEM	Discrete element modeling
FPF	Fine particle fraction
FPD	Fine particle dose

GW	Greenwood and Williamson
IGC	Inverse gas chromatography
LPT	Lagrangian particle tracking
MFV	Minimum fluidization velocity
ODEC	Overlapping discrete element cluster
pMDI	Pressurized metered-dose inhaler
SEM	Scanning electron micrograph

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1. INTRODUCTION

During the past few decades, pharmaceutical components have been developed significantly to deal with human disorders. This is done by improving the physicochemical characteristics of drug particles as well as discovering new methods to deliver such components through body cells [1]. All these techniques aim to optimize processability, stability, availability, and delivery of active pharmaceutical ingredients (APIs) in order to have an efficacious pharmaceutical influence with the consideration of economic and technical aspects [2]. APIs are biologically active and can be presented in the form of various shapes and sizes depending on their purposes. Capsule, pill, pod, tablet, cream, drop, spray, liquid, syrup, and inhalation aerosols are some of the common forms of delivering medicines.

1.1 DRUG DELIVERY

To improve the deliverability of APIs, many academic disciplines were engaged in various fields of pharmaceutical science both in academia and industry. One of these fields which has grabbed noticeable attention among engineers is known as drug delivery. Drug delivery is the process of inserting the drug components into humans or animals' bodies in a predetermined manner [3]. APIs in such processes are released with a controlled rate to reach the target site for healing, controlling, and preventing purposes [3]. This can be done through various routes of drug delivery such as buccal, oral, pulmonary, transdermal, ocular, and nasal based on the type of therapy needed. These methods used to be only applied for particular disorders but thanks to the undergoing technology progress, the number of applications for each delivery system expands considerably by discovering and developing new techniques and medicines.

1.2 INHALED DRUG DELIVERY

The administration of APIs can be carried out via different delivery systems to eventually deposit the drug powders into a target organ. One of these methods is based on inhaled drug delivery, where API is transferred through the respiratory system [4]. Due to the unique features that come with delivering drug components through lung cavities, aerosol therapy has recently grabbed much attention for the systematic administration of APIs [5]. Important lung properties are the high permeability, the great surface area, and the extensive blood supply of lung capillaries [5]. Moreover, the level of deliverability of drug particles to a targeting site in the respiratory systems determines the effectiveness of aerosol therapy.

Drug delivery via inhalation can be achieved through three different methods depending on their physical state [2]. The first technique is via Nebulizers, in which API is suspended or dissolved into a liquid container with a polar characteristic. This technique is typically applied in either ambulatory care settings or hospital facilities due to their large volumes and the inconveniency that comes with the usage procedure [2]. The two other types of inhaled drug delivery are pressurized metered-dose inhalers (pMDIs) and Dry powder inhalers (DPIs). By triggering either device the patient inhales an entrained fluid containing the drug particles. The inhaled fluid in pMDIs and DPIs is in the form of either a dried powder mixture or a nonpolar propellant consisting of dissolved or suspended solid drugs [2, 6]. Furthermore, among different categories of inhaled drug delivery systems, DPIs are relatively easy to use from a consumers' perspective and they have less environmental impact compared to pMDIs, which can contain greenhouse gases or ozone-depleting gases [2].

1.3 DRY POWDER INHALER

DPIs are particularly designed to deliver a certain number of APIs into the respiratory system by fluidizing particles, during the inhalation, to deal with a particular disorder [6]. This field of inhaled drug delivery is gaining great significance as a hot topic among researchers due to the development of DPI techniques.

These techniques not only treat respiratory diseases such as asthma, bronchitis, cystic fibrosis, and chronic obstructive pulmonary diseases but also can deal with systematic disorders concerning other organs of the human body including cancer and diabetes [2]. Likewise, DPIs are efficient and stable in comparison with other systems of inhaled drug delivery [2].

In general, DPI technology is divided into three main categories; 1) dose-metering or controlled dose system which gives the detailed information about the drug doze per unit of consumption, 2) drug formulation/mixing which describes the condition in which particles should be mixed, and finally 3) aerosolization as the dispersion process [6, 7]. When it comes to the formulation and aerosolization, most of the pharmaceutical components show poor performance in terms of their physicochemical characteristics, which in turn requires engineering solutions to cope with relevant issues [2].

One of the main challenges within the DPI technology is to effectively deliver the drugs into the peripheral airways, where APIs are transferred into the bloodstream, and subsequently, reach the target organ [2, 6, 8]. To do so, particles need to be in an aerodynamic diameter range of 1 to 5 μm to be deeply absorbed by lung capillaries [2, 6, 4]. Particles with less than 0.5 μm diameter do not settle due to the fluctuations caused by Brownian motion [2]. On the other hand, particles may be deposited in Pharynx (a part of the throat behind the mouth and nasal cavity) or oral cavity if their diameter surpasses the cut-off value of 5 μm [4, 9]. In general, the small size of particles causes an issue concerning the agglomeration of fine drug particles in the DPI formulation, which in turn terminates the efficacy of the drug [4]. In other words, due to the high surface energy of drug particles, there is enough adhesive force among particles to make clusters once fine drugs collide with each other. Because of such a phenomenon, APIs cannot penetrate through the peripheral airways, and in response, the efficacy of the drug would wear off.

1.4 BINARY ADHESIVE MIXING

To avoid aggregation due to the cohesive property of drug powders, particles can be delivered with the help of a larger element known as carriers [4]. By coating drug particles over the carrier surface through the adhesive mixing process, particles cannot aggregate anymore and will remain functional [4]. This formulation process is aimed to make a stabilized homogenous mixture during the mixing followed by an increase in the dispersity of drug particles at the aerosolization stage [4, 10]. The level of dispersion, i.e. the distribution fraction of individual drug particles through the lungs, is extremely important since the therapeutic is directly affected by the deposition of drug particles in the peripheral airways [2]. For instance, polydisperse particles can settle within different regions of the lungs with different concentrations, resulting in the variation of efficacy and quality over the healing process [2].

The presence of many entities in a dense control volume causes a strong interaction among particles, which in turn creates high adhesive force among particles [2, 1, 8]. The resultant adhesive force comes from the inherent Van der Waals forces that exist in dry systems. The Van der Waals force is caused by the intrinsic electromagnetic character of uncharged materials [2, 6]. Broadly speaking, collision impact causes tangential and normal forces over each particle during the contact time. To specify more, forces and torques arising from collision decompose into four main categories of normal force, twisting resistance, sliding resistance, and rolling resistance [8]. These forces and torques in total, establish the collision-induced impacts which are highly dependent on the number of contacts between two particles as well as the curvature radius at each contact point [4].

The drug particles stay on the carrier surface until the user triggers the inhaler, where a turbulent airstream stimulates the particles to fluidize through a filter located at the end of the DPI device [2]. Subsequently, the clash between the triggered bulk powder and the impact grid results in the breakage of the drug-carrier agglomerates. The process of how aerosolization occurs in DPIs is illustrated in Figure 1. It should be mentioned that the size of the filter channels arranged in the device is designed to stop the coarse carriers while drug particles can pass through.

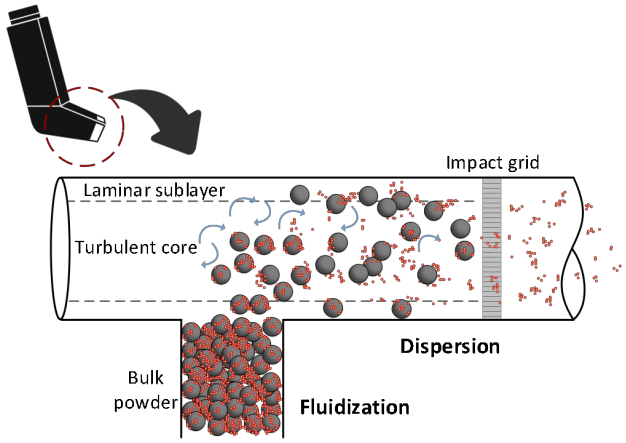


FIGURE 1, THE AEROSOLIZATION PROCESS OF DPIS DURING INHALATION [11]

When aerosolization occurs, the process of drug detachment from carrier particles is not fully efficient. It means that a large portion of drug particles will remain on the carrier surface and cannot pass through the filter placed inside the inhaler [4, 12]. This phenomenon arises from the fact that the adhesive force exceeds the inertial force during the contact time with the grid, causing drug particles to remain attached to the coarse surface. To quantify the overall efficiency of such processes, fine particle fraction (FPF) is defined as the ratio of the delivered API into the respiratory system over the total amount of drugs in the inhaler [4]. The FPF for most of the drugs is, nowadays, limited to only 20 to 30 % approximately [13].

1.5 TERNARY ADHESIVE MIXING

The number of inhalable drugs in DPI is affected by three main factors consisting of the inhaler device shape, the reaction that the body shows during inhalation, and the formulation of the mixture [14]. Concerning the formulation, the performance of carrier-based DPIs can be significantly enhanced by the inclusion of a number of fine excipients into the binary blend of carrier-drug particles. Fine excipients help the delivery of the medication into the blood vessels, and together with APIs constitute the main parts of any pharmaceutical drug [15]. Furthermore, adding fine excipients as the third element into the formulation process makes the system to shift from a binary to a ternary mixture [3]. The schematic of the respective DPI formulation is illustrated in Figure 2.

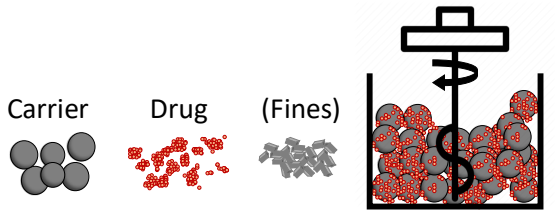


FIGURE 2, THE SCHEMATIC OF THE TERNARY DPI FORMULATION [11]

Fine excipients in any pharmaceutical drug, help the delivery of the medication into the blood vessels. According to a review by M. Jones and R. Price, the characteristics of the fine element play a key role in the performance of DPI formulation [14]. The main objective of adding fine particles is to improve the stability of APIs in terms of the nonpharmacological characteristics including physical, mechanical, and chemical properties [2]. In other words, the performance of drug particles i.e., handling, metering, and dispensing of APIs are dramatically enhanced by the presence of fine excipients since micronized drug particles can liberate more easily [2]. Among different characteristics of fine excipients, particle size, the amount of fine added, and the method by which different elements are mixed are considered as the main factors affecting the mixing behavior [16].

The fine particle can be made up of various materials from either the carrier or any other chemically inert substance such as erythritol, sorbitol, mannitol, glucose, etc. [14]. Studies show that the increase in the number of fines added to the mixing results in a higher number of FPF and fine particle dose (FPD) until the performance of formulation reaches an optimum condition [14]. However, the ideal state is different among various studies due to the diverse implemented methodologies, as well as the number of factors contributing to the mixing behavior such as mixing process, aerosolization, and materials selected [17]. As a result of all these dependencies and variables, the process becomes dramatically difficult in order to draw any overall conclusion. Having said that, different values have been suggested by M. Jones and R. Price for the optimum concentration and the optimum particle size of fine excipients, varying from 9 to 50 % w/w and from 5.5 to 7.9 µm, respectively [14]. These values can be changed for different cases as the outcome is highly dependent on the selected variables; for instance, by changing the drug from one to another the outcome can be thoroughly different.

There are four major hypotheses on how the third element i.e., fine excipient particles can positively affect the formulation. Among those, two hypotheses have drawn more attention, namely the active site and agglomeration theories [6, 14]. In the former hypothesis, fine particles are assumed to partially occupy areas with high surface energy [6, 14, 18, 11]. Therefore, drug particles have less chance to contact areas that have high surface energies as they are already occupied with fine particles. As a result, drug particles can liberate easier from the carrier surface during the inhalation, and thus, a higher number of APIs will penetrate through the filter placed in the DPI.

In the second hypothesis that is called the agglomeration theory, particles can make a cluster in the presence of fine excipients. This phenomenon comes from the high number of elements in the system, which in turn cause multilayer contacts between carriers and other particles in the mixing. Therefore, the created cluster will separate more easily from the carrier surface due to the higher contact force between drug and fine particles. Thereafter, the collision between the cluster and the filter causes the breakage of drug-fine agglomerates.

Besides the mentioned hypotheses, there are two more theories, where the results are compatible with experimental data, namely fluidization reinforcement and buffer hypotheses [11]. In fluidization reinforcement theory, particles behave similarly to what happens in a fluidized bed, i.e. particles can act as a granular flow, and subsequently, by inserting any element regardless of its type into the system, the minimum fluidization velocity (MFV) goes up [11]. Consequently, particles collide harsher with a higher frequency, resulting in an easier breakage of drug-carrier agglomerates. This shift in MVF is due to the increase in the tensile strength of the powder bulk [11].

In the other hypothesis, known as the buffer theory, fine excipients prevent drug particles to be pressed by two colliding carriers in cases where fine excipients have a larger particle size than drug particles [11]. Therefore, drug particles will be less pushed towards carrier areas with relatively high surface energies. Owing to the lower drug-carrier adhesive force as a result of the press-on force over fine excipients rather than drug particles, the corresponding mechanism allows deagglomeration to occur easier during aerosolization. Figure 3 illustrates the schematic of four potential mechanisms that can happen in the ternary formulation.

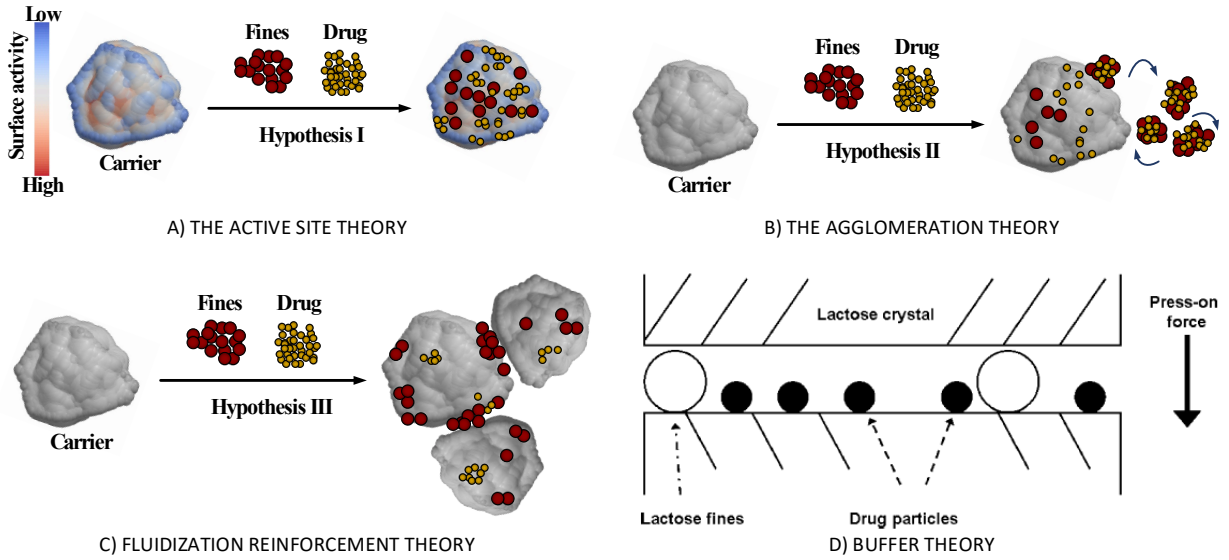


FIGURE 3, POSSIBLE FORMULATION MECHANISMS IN THE MIXING [11]

It should also be mentioned that the various research methods, including simulation and lab works employed within different research studies, may need validation through experimental techniques due to the high number of variables, and some inconsistencies exist among different studies. Atomic force microscopy (AFM), inverse gas chromatography (IGC), and scanning electron micrograph (SEM) are the main approaches to experimentally validate results [2, 14].

1.6 MODELING OF THE MIXING PROCESS

Efficient drug delivery can be achieved by knowing the predominant mechanisms that exist in the mixing phase, as well as the key factors attributing to the overall efficiency of the system. Having a good understanding of the multiphase flow nature is crucial to be able to grasp the fundamentals and the exact physics behind such a ternary mixing process when elements interact with one another. With that said, the highest possible drug delivery efficiency of DPIs can be obtained with the help of computational aided engineering (CAE) as a tool to model the system.

Dispersion and delivery of drug particles into the lungs are affected by both the interaction forces and the aerodynamics of the system [2]. Many parameters including particle shape, particle diameter, level of roughness, surface chemistry, interfacial energy, morphology, contact deformation, and the mass ratio of different elements affect forces and torques that exist among particles [6, 8]. To be able to study the impact of these factors on the system, there is a need to model a range of systems within an appropriate frame.

Modelling of the formulation process can only be achieved by defining the right system characteristics into the simulation. Otherwise, the resultant model cannot be the representative of a real mixing condition, and thus, the corresponding outcome would be unreliable. One of these main characteristics is the shape of inserted particles that can significantly affect the mixing performance. To be able to model such micron-sized particles, there is a need to assign a right level of roughness over the particle surface. Thanks to a recent work by Tamadondar et al., an appropriate mathematical method for generating carrier particles was provided which makes it possible to model the formulation process that represents the system close enough to reality [4].

The discrete element modeling (DEM) or the Lagrangian particle tracking (LPT) was selected as the favorable numerical method in which the equation of motion is solved for each element in the disperse phase. This model

tracks real particles as individual entities via the Lagrangian reference frame, whereas, Eulerian is applied to solve the continuous phase in a fixed coordinate system. Furthermore, DEM is theoretically straightforward and provides a fine temporal and spatial resolution, which results in quite accurate solutions in comparison with results from other numerical models especially when collision effects are taken into account [4].

2 AIMS AND SCOPE OF THE PROJECT

In this study, an attempt is made to model adhesive ternary mixtures consisting of fine, drug, and carrier components in order to eventually understand the underlying formulation mechanisms that govern the mixing stage. To understand these mechanisms and to unravel the effect of critical parameters on the DPI formulation, a series of simulations are required with consideration of the main physics governing the system. So far, most of the studies in the context of DPI formulation and dispersion have primarily focused on either carrier or drug particles in a ternary system, where the physical properties of those elements were analyzed. Having said that, in this project, the impact of fine excipient particles on DPI mixing was evaluated with consideration of different physical characteristics.

After reviewing a number of articles regarding the application of DPI, the following main attributes on the ternary mixing were selected to conduct further investigation in this study: (i) fine particle size, (ii) fine particle mass ratio, and (iii) drug particle surface energy. These factors are considered as the key thermodynamic properties which impose an immense effect on the mixing performance [6, 14]. By modeling the mentioned system within the Lagrangian framework, it is possible to study the impact of the critical contributes to the DPI formulation. This can be achieved by numerical simulation of ternary systems using the discrete element modeling (DEM). To do so, different characteristics for simulation need to be adjusted to deploy suitable settings within the platform (software) for simulation.

2.1 LIMITATIONS AND ASSUMPTIONS

Compared to a binary formulation, a ternary mixture results in a system with a higher level of complexity encompassing more variables that affect the mixing performance in DPIs. To be able to run such a simulation within the DEM framework, there is a need to apply some simplifying assumptions which still represent the system well close to reality. One of these simplifications is to consider the collision impact as the dominant phenomenon throughout the control volume. The validity of this assumption can be checked by Bagnold number which is the ratio of grain collision stresses to viscous fluid stresses in granular flow. As a result of this assumption, the effect of the fluid-induced forces on each particle can be neglected [2, 4, 8]. Furthermore, the optimum mixing condition can be achieved according to the selected variables that undergo sensitivity analysis, and because of that other variables will remain constant. With that said, the level of roughness, the mixing condition, and the particle concentration which is well below the real value, are all kept constant.

Some other assumptions that have been made are as following:

- Fines and drugs are spherical; Theses particles are relatively smaller than the carrier particle.
- Monodisperse particles; All particles from the same category (drug, carrier, or fine) are assumed to have the same size as their peers.
- No moisture and no impurity; All components are completely dry.
- A system with only three carriers; Only a small part of a real mixing is modeled to make it computationally possible.
- Elastic deformation; To make it computationally less expensive.
- One type of carrier particle; The three carriers are identical.

The reason why these statements have been assumed together with the resultant effects on the simulation is discussed in more detail in the next chapters.

2.2 WORKFLOW

The project begins with a literature study to gain good theoretical knowledge as the essential prerequisite of the project. The literature study was focused mainly on three different categories, namely thermodynamics of adhesive particle systems for DPI formulation, Discrete-element modeling of particulate systems, and the role of fine excipient in adhesive mixing in DPIs. Owing to the underlying physics of the system, it is possible to run several simulations based on the selected settings to obtain the project goals i.e., finding the dominant mechanisms governing the ternary mixing, and performing a parameter study for key variables. Post-processing including a comparison of the results with literature data is implemented to be able to rely on the project outcomes. Finally, implications on the energy aspects of the production process are evaluated by analyzing the results coming from simulations.

3 THEORY

In this section, the main physics of a ternary formulation is explained in detail. These physics include the simulation framework, the main forces and torques that govern the mixing, different formulation mechanisms that have been introduced so far, and eventually a brief explanation regarding the aerosolization stage.

3.1 SIMULATION FRAMEWORK

The way that particles interact with each other in the DEM framework is highly influenced by the surface profiles of different elements in the system. The particle surface area can also change the level of dispersity and stability of elements both in the mixing and inhalation stage. This arises from the Van der Waals forces that exist among small particles. The surface profile is characterized by the particle size, particle shape, and the level of roughness for irregularities over the particle surface. Therefore, to have a more realistic outcome, there is a need to incorporate roughness for those elements which have a considerable effect on the mixing.

Naturally, all particles in the system have a level of roughness and irregularities over their surface area. This uneven structure brings more complexity into the simulation, which in turn makes the model computationally expensive. Therefore, it is desired to consider particles as spheres in order to reduce such costs in the simulation. This simplification can be employed as long as the model represents the system close enough to reality. Therefore, with a reasonably good assumption, it is possible to deal with both fine and drug elements as spherical elements. This comes from the fact that both particles have relatively small sizes, and thereby changes due to the simplification can be ignored. This assumption cannot be applied to the coarse carrier as it is too large to neglect the impact of the surface roughness on results coming from the simulations. Figure 4 represents the shape of a simulated carrier particle containing the surface irregularities together with the corresponded level of surface activities.

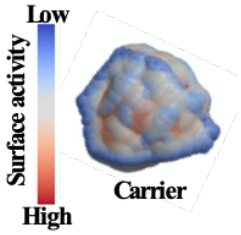


FIGURE 4, SURFACE IRREGULARITIES ON THE CARRIER PARTICLE [11]

It can be understood that surface areas on the carrier asperities have a low surface activity, whereas, deep regions that are presented with red color in the figure are areas that have a high active site. Those active sites are subjected to the relatively higher adhesion force if particles make contact with such regions. Consequently, the shape of the carrier is of great importance and needs to be modeled to have a proper surface profile on particle asperities.

3.1.1 ROUGH SURFACES IN CONTACT

Modelling the contacts needs of great attention as it can change the real contact area between two colliding particles. Using a statistical description of the surface roughness, it is possible to provide a proper contact model between solid particles. Greenwood and Williamson (GW) have introduced a practical approach to employ irregularities into the contact surface [19]. In this method, each particle asperity is considered as a spherical shape with a unique curvature radius, which can be deformed under a certain amount of force. Furthermore, GW is based

on the statistical model and assumes that the height of particle asperities follows the Gaussian distribution. Further methods have also been proposed, where plasticity or elastic-plastic deformation is taken into calculations [20, 21].

Alternatively, in this study, the microscale layout of the surface asperities is obtained using the Fourier transform for the mathematical definition of the particle morphology. Having a proper simulation environment makes it possible to resolve the contact model for each asperity height. This is done by considering the curvature radius of the related contact point for adhesion force calculations. To govern the contact model, initially, the Fourier harmonic is defined as a tool for mathematical definition and then a method for integrating the spherical elements will be introduced.

3.1.2 FOURIER SHAPE DESCRIPTOR

This model was first introduced by Ehrlich and Weinberg [22]. In this algorithm, the rough surface is modeled by a Fourier series, where the outline of a 2D morphology is traced. The series of closed-form discrete Fourier function is defined as the following:

$$\boldsymbol{r_i(\theta) = r_0 + \sum_{n=1}^{N} A_n \cos(n\theta_i) + B_n \sin(n\theta_i)]} \tag{1}$$

In equation (1), r_0 and N denote to the average radius and the total number of Fourier harmonics. N in this case is equal to 64, meaning that there is a need to assign 64 parameters to be able to draw the 2D particle outline. A_n and B_n also give the coefficients for respectively, the magnitude and the phase of each harmonic. Finally, the normalized amplitude $\boldsymbol{D_n}$ for the Fourier spectrum is obtained using the coefficient of the Fourier series, yielding:

$$\boldsymbol{D_n = \frac{\sqrt{A_n^2 + B_n^2}}{r_0}} \tag{2}$$

Each of those 64 parameters for normalized amplitude ($\boldsymbol{D_n}$), also referred to as normalized Fourier descriptor, shows a specific characteristic of the surface morphology. These factors can be achieved using experimental methods such as scanning or imaging the solid particle. However, every parameter of normalized amplitudes can be estimated by knowing the three of those factors (D_2, D_3, and D_8), which in turn leads to the description of the particle shape.

Mollon and Zhao proposed a novel idea by which the particle shape can be generated for any given set of normalized Fourier descriptors, [23, 24]. This is done by using the inverse Fourier transform as an initial step. They inversed the prescribed method according to the theory of random field to adapt a mathematical algorithm for their calculation. Finally, an analogy with the signal processing theory, made it possible to determine all those points on the surface profile by having an initial random point together with the respective Fourier spectrum. The result of such a method is a 2D or 3D convex-hull, containing the faces and vertices that display the particle. Figure 5 illustrates a 3D convex hull of a random particle based on the mentioned algorithm.

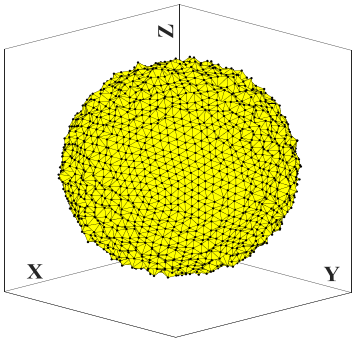


FIGURE 5, THE 3D CONVEX HULL FOR AN ASSUMED PARTICLE

3.1.3 SHAPE REPRESENTATION WITH MULTISPHERE MODEL

In order to convert the 3D convex-hull of the solid particle into a surface profile, and utilize it in the DEM framework, there is a need to apply a suitable method. In 1999, Favier et al. introduced a method commonly known as multisphere model [25, 26, 27]. In this model, the particle is made up of spheres with different radii, making the model more realistic and easier to implement compared with other proposed methods. This can be done by applying the mathematical algorithm referred to as overlapping discrete element cluster (ODEC) [28]. In this algorithm, an arbitrary point is chosen on the surface of the convex-hull. Then from the desired point, one sphere is expanded and grown along its internal normal direction until it touches another point on the particle surface. This procedure is continued until there would be one sphere per each point. The accuracy of the shape modeled can be even more improved by increasing the resolution of the surface discretization together with introducing more spheres to ODEC. Implementing the mentioned algorithm for each single point results in a 3D shape, containing a number of overlapping spheres with different sizes. Eventually, the particle surface profile is generated by considering the shape outline of the created multisphere body and ignoring the internal contact among spherical elements [4]. An example of a rigid particle that is resulted from the multisphere model is presented as the following:

FIGURE 6, THE SHAPE REPRESENTATION OF A MULTISPHERE PARTICLE USING ODEC AS THE MATHEMATICAL ALGORITHM [4]

3.1.4 REAL PARTICLE MORPHOLOGY

The level of interaction among particles in the mixing hinge upon the particle surface profile [4]. Accordingly, to have a reliable outcome from simulations there is a need to apply the correct level of irregularity on particle asperities. Figure 7 shows a picture taken by scanning electron micrograph (SEM) which represents the particulates after the ternary formulation in the mixing box.

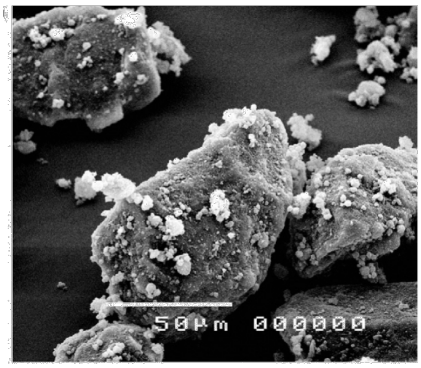


FIGURE 7, REAL PARTICULATES AFTER THE TERNARY MIXING [THALBERG ET AL. 2012]

To accurately assess the surface roughness of particles, different experimental methods have been introduced. Several of those are based on the amount of solid-gas adsorption by the powder surface [2]. This is done by measuring the volume of adsorbed gas on the particle area at a certain pressure. New methods have also been developed in the last decades to measure the level of roughness for nano-scaled particles. Two practical approaches, namely atomic force microscopy and inverse gas chromatography are commonly used for scanning the surface profile of different matters. For more details, it is recommended to refer to [29, 30, 31].

3.2 PARTICLE KINEMATICS (CONTACT MECHANISMS)

The kinematic of the mixing is directly affected by the concentration of the total number of entities in the control volume. In dilute systems, elements are mainly conveyed by fluid-induced forces through translational motion, and thereby, particle interaction can be neglected due to the low probability of binary collisions. This simplification cannot be the case at dense flows where particles are mainly influenced by collision impact. In such cases, forces and torques induced from particle interaction gain significant importance in governing equations.

By increasing the concentration of the dispersed phase in the control volume, the total number of particles becomes so high that collision-induced mechanisms may be considered as the dominant phenomena in low-viscous fluid, while hydrodynamic impact can be neglected. As a result, the system turns from either one-way or two-way couplings to a four-way coupling where particle movement affects themselves as well as the fluid flow. Bagnold number can be used as an index to justify the dominance regime in which particles and the flow interact with each other.

In the mixing control volume, the local concentration of all particles is high enough (around 10% of the volume fraction) to be able to consider the collision as the predominant physics throughout the domain [8]. Also, the calculated Bagnold number is above 450 which turns the flow into a grain-inertia regime i.e., grain collision stresses dominate the system compared to the viscous fluid stresses. Consequently, with a reasonably good approximation, it is possible to neglect the impact of the air flow-induced forces such as drag, lift, buoyancy (pressure gradient), and added mass in the system [4, 8]. With that said, contact mechanisms, together with the body force i.e. gravity are the only forces that are taken into consideration in the system. Under such a simplifying assumption, the complexity of the momentum equation over each particle in the control volume will be considerably reduced, resulting in fewer terms to be closed. This simplification makes the model mathematically robust and easy to implement as well as, it will be less expensive from a computational point of view.

Assume that there is a moving particle with the mass of m, the velocity of v, and the particle diameter of d. Neglecting the impact of the fluid-induced forces over the system, the following equations can be written for the particle translational and rotational motion based on Newton's second law:

$$\boldsymbol{m\frac{dv}{dt}} = \mathbf{F_A}, \tag{3}$$

and

$$\boldsymbol{I\frac{d\Omega}{dt}} = \mathbf{M_A}, \tag{4}$$

where I is the particle momentum of inertia and can be obtained via $I = \left(\frac{1}{10}\right)\mathrm{md}^2$. F_A in equation (3) is the contact force, which in this case refers to the Van der Waals adhesion and elastic collision forces. Similarly, in the angular momentum equation, Van der Waals adhesion and collision torques are together denoted as M_A. At last, $\boldsymbol{\Omega}$ denotes the angular rotation rate of particle.

The inherent Van der Waals force that exists in dry particulates, give rise to an adhesive contact mechanism between colliding particles. The size of adhesive forces among particles is highly dependent on the number of contacts and the curvature radius at the contact interface [4, 11]. This mechanism can be modeled via different adhesive mixing models according to the respective Tabor number (μ) [32]. Tabor is a dimensionless number that determines the level of elastic deformation in the system, and its value depends on the size of the surface forces at the interface [33]. In the application of the discrete element method, JKR which is a model proposed by Johnson, Kendall, and Roberts, complies well with the adhesive mixing process when μ >1 [4, 34]. On the other hand, for Tabor number μ <1, a model by Derjaguin, Muller, and Toporov called the DMT model is recommended to apply for calculations [4, 35]. According to this standard, JKR was used as the contact model in this study to involve the adhesive force and the resultant overlap that is caused by the collision. This contact model was selected due to the similarity between the mixing condition in this study and the one conducted by Tamadondar et al. [11].

In general, contact impact which arises from particle inertia causes different types of forces and torque fields in the system. Regarding the forces that exist in the system, there are two ways in how particles induce forces on each other namely, the normal (F_n) and the sliding resistance (F_s) forces [8]. The total collision force imposed on each particle can be written as:

$$\mathbf{F_A} = \boldsymbol{F_n}\mathbf{n} + \boldsymbol{F_s}\mathbf{t_S}, \tag{5}$$

where n refers to the normal vector passing through the particle centroids and t_S corresponds to the direction of the relative particle motion projected onto the contact plane at the interface.

When it comes to the torques acting on particles, there are three different mechanisms; sliding (F_s), twisting (M_t), and rolling (M_r) resistances, which are discussed in more detail in the next chapters [8]. The total torque induced on each particle is written as the following:

$$\mathbf{M_A} = \boldsymbol{r_i F_s}(\mathbf{n} \times \mathbf{t_S}) + \boldsymbol{M_r}(\mathbf{t_R} \times \mathbf{n}) + \boldsymbol{M_t}\mathbf{n}, \tag{6}$$

where r_i is the radius of particle i, and t_R is the direction of particle rolling velocity.

Having said that, Figure 8 illustrates different modes of particle interaction including the normal force and the resistance from sliding, twisting, and rolling for two colliding particles. However, the corresponded mechanisms can

also happen during a particle-wall collision. The resultant forces and torques are discussed in more detail in the next sections.

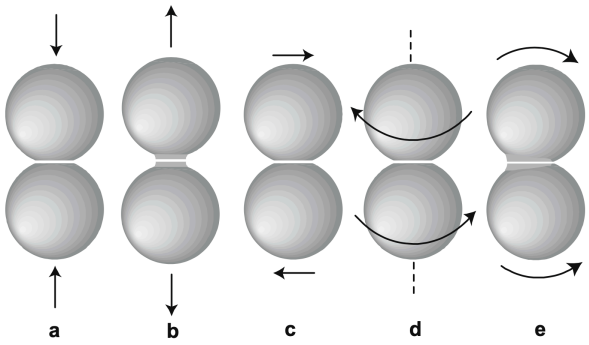


FIGURE 8, THE SCHEMATIC OF ALL CONTACT PHYSICS BETWEEN TWO PARTICLES IN CONTACT [8]

Overall, all forces and torques affecting the system are somehow in balance with other impacts that arise from particle deformations during the contact time. To be able to understand each of these impacts in the system, it is crucial to have a good understanding of deformation mechanisms and also the way in how deformation can be modeled. It is then possible to study the effect of each force and torque in the ternary system. It should be mentioned that the following sections are mainly based on a study by J.S. Marshall [8].

3.2.1 DEFORMATION

Deformation is a physical phenomenon, which causes distortion of the contact region at the interface of any colliding couples. This can be in the form of elastic, plastic, or viscoelastic, each with different physics. Plastic deformation refers to the distortion that would resist after contact time, whereas in elastic, particles show a flexible characteristic, and thus can reform to the original shape after detachment. Viscoelastic substances reveal both characteristics of elastic and plastic materials, meaning that the particle can reform, to some extent, to its primary structure after the collision.

In the mixing, elements show both elastic and viscoelastic behaviors. However, for the sake of simplicity, it is considered that all distortions in the ternary system are elastic deformation in order to make the simulation computationally less expensive. Accordingly, overlap or deformation in this study can be illustrated as a spring-dashpot-slider model for different types of forces and torques acting on each particle in contact. This model is illustrated in Figure 9, where k_N and k_S in the system denote the elastic stiffness and rolling stiffness, respectively.

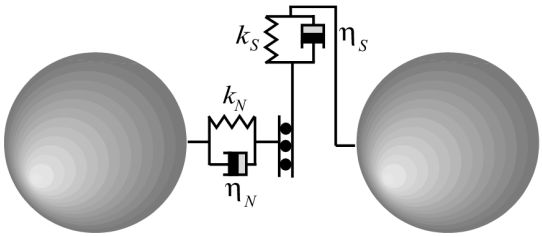


FIGURE 9, THE SPRING-DASHPOT-SLIDER MODEL PROPOSED BY CUNDALL AND STRACK (1979) OF TWO COLLIDING PARTICLES [8]

Imagine that there are two particles in contact, which are distinguished by indexes i and j. Knowing the radii r, elastic moduli E, and Poisson ratios σ, the following equations can be written for the two colliding particles:

$$\frac{\mathbf{1}}{\boldsymbol{R}} \equiv \frac{\mathbf{1}}{\boldsymbol{r_i}} + \frac{\mathbf{1}}{\boldsymbol{r_j}}, \qquad \frac{\mathbf{1}}{\boldsymbol{E}} \equiv \frac{\mathbf{1-\sigma_i^2}}{\boldsymbol{E_i}} + \frac{\mathbf{1-\sigma_j^2}}{\boldsymbol{E_j}}, \qquad \frac{\mathbf{1}}{\boldsymbol{G}} \equiv \frac{\mathbf{2-\sigma_i}}{\boldsymbol{G_i}} + \frac{\mathbf{2-\sigma_j}}{\boldsymbol{G_j}}, \tag{7}$$

where R is the effective particle radius and E and G are the elastic and shear moduli, respectively. The particle normal overlap (δ_N) during a collision can also be defined by the following equation:

$$\boldsymbol{\delta_N = r_i + r_j - |x_i - x_j|}, \tag{8}$$

where x refers to the particle centroid position.

Eventually the elastic stiffness of JKR model can be expressed as a function of flattened contact region radius a(t):

$$\boldsymbol{k_N = \frac{4}{3} E a(t)} \tag{9}$$

where

$$\boldsymbol{a^2 = R\delta_N} \tag{10}$$

The tangential stiffness coefficient k_T can also be written using a contact region radius. The following expression, which is derived from a work by Mindlin is used to calculate the coefficient [36]:

$$\boldsymbol{k_T = 8Ga(t)}. \tag{11}$$

Before going through different forces and torques imposed on particles, it is recommended to study the effect of viscoelastic deformation on the mixing performance for further investigation.

3.2.2 NORMAL IMPACT

The normal force as one of the main forces during collision is derived from both elastic deformation of particles (F_{ne}) and energy losses during particle interactions (F_{nd}). These forces are derived by Hertz as following [37]:

$$\boldsymbol{F_{ne} = -k_N \delta_N} \tag{12}$$

And

$$\boldsymbol{F_{nd} = -\eta_N \mathbf{v_R} \cdot \mathbf{n}} \tag{13}$$

where $\boldsymbol{\eta_N}$ and $\mathbf{v_R}$ denote normal friction coefficient and particle relative velocity at the contact time, respectively. There are some expressions that have been proposed for η_N as a function of $(mk_N)^{0.5}$, where m is the particle mass. For $\mathbf{v_R}$, it can be calculated according to the vectors from particle centroids to the contact point.

3.2.3 EFFECT OF VAN DER WAALS FORCES

Owing to the presence of dry powders in the system, there is an electromagnetic force, which in turn gives rise to the Van der Waals adhesion among particles in contact. As a result, the contact mechanisms including the impact force and the resistance from twisting, sliding, and rolling, are directly influenced by the adhesion force due to the inherent Van der Waals.

According to the JKR model, the Van der Waals adhesion force imposes solely on the flattened surface at the contact region. The magnitude of this force can be calculated using surface energy (γ) [8]:

$$W_S = 2\,\pi\gamma a^2 \tag{14}$$

where W_S refers to the work needed to separate the two particles in contact with consideration of particles as rigid bodies.

NORMAL IMPACT

Assume that the two particles in contact are in an equilibrium state. Under such conditions, the adhesion force yielded from Van der Waals is in balance with elastic repulsion. In this state, the equilibrium contact radius $a_0(t)$ at the particles interface is defined by

$$a_0 = \left(\frac{9\pi\gamma R^2}{E}\right) \tag{15}$$

Subsequently, the elastic rebound force F_{ne} and the radius at contact region in equations (10) and (12) can be written with some modification as following [34, 38]:

$$\frac{F_{ne}}{F_C} = 4\left(\frac{a}{a_0}\right)^3 - 4\left(\frac{a}{a_0}\right)^{1.5} \tag{16}$$

and

$$\frac{\delta_N}{\delta_C} = 6^{1/3}\left[2\left(\frac{a}{a_0}\right)^2 - \frac{4}{3}\left(\frac{a}{a_0}\right)^{0.5}\right] \tag{17}$$

where the critical overlap δ_C and the critical force F_C are defined by

$$\delta_C = \frac{a_0^2}{2(6)^{1/3}R}, \qquad F_C = 3\pi\gamma R \tag{18}$$

If particles in contact start to pull apart from each other by either a collision or a fluid shear, F_{ne} gets a negative value until its magnitude reaches the critical value of F_C. Surpassing the determined threshold results in the detachment of particles from each other.

3.2.4 NORMAL COLLISION

To investigate the collision impact in terms of the size of the length deformed over time, adhesive forces are initially neglected. Assume there are two colliding particles at time t_0 while they are traveling directly towards each other. The two particles, in the beginning, are located at $x = \pm x_0$, where they have linear velocities of $^{dx}/_{dt} = \pm v_0$. These particles are identical and thus have the same radius of r_1 and the elastic modulus of E_1. Knowing the overlap $\delta \equiv \delta_n = 2(r_1 - x)$, the following relation can be written for the particle inertia via elastic and dissipative normal collision forces [8]:

$$\frac{d^2\delta}{dt^2} + 2\alpha\left(\frac{K}{m}\right)^{0.5}\delta^{0.25}\frac{d\delta}{dt} + 2\left(\frac{K}{m}\right)\delta^{1.5} \tag{19}$$

where the stiffness coefficient K is given by

$$\boldsymbol{k_N = \frac{4}{3} E\sqrt{R}} \tag{20}$$

The equation (19) can also be written in the form of the following:

$$\boldsymbol{\frac{d^2\delta'}{dt'^2} + 2\alpha\delta'^{0.25}\frac{d\delta'}{dt'} + 2\delta'^{1.5} = 0} \tag{21}$$

where the dimensionless overlap and time numbers are given by

$$\boldsymbol{\delta' = {\delta}/{r_1}', \quad t' = t\sqrt{\frac{r_1^{0.5}K}{m}}} \tag{22}$$

The parameter α in equations (19) and (21) is the coefficient of dissipation and is dependent on the value of restitution coefficient e via a polynomial relation. The coefficient of restitution determines the ratio of relative velocity before and after the collision. In order to achieve such factors in the system, the rate of collision is introduced by $w \equiv d\delta/dt$. Therefore, the restitution coefficient can be yielded from

$$\boldsymbol{e \equiv |w_f/w_0|} \tag{23}$$

Indexes 0 and f in relation (23) denote the conditions just before and after the collision, respectively.

Finally, the generic term of normal collision for two colliding particles is obtained considering the effect of Van der Waals adhesion into the equation (21):

$$\boldsymbol{\frac{d^2\delta'}{dt'^2} + 2.378\alpha a'^{0.5}\frac{d\delta'}{dt'} + 4.757a'^3\left[1 - \left(\frac{a_0}{a}\right)^{1.5}\right] = 0} \tag{24}$$

and

$$\boldsymbol{\delta' = 2a'^2\left[1 - \frac{2}{3}(a'_0 - a')^{1.5}\right]} \tag{25}$$

where, $a' = {a}/{r_1}$ and $a'_0 = {a_0}/{r_1}$.

Using the relation in (24) it is possible to calculate how much particles have overlap with each other in elastic deformation.

3.3 FORMULATION MECHANISMS

There are several explanations on why adding fine excipient particles to the mixing can improve the deliverability of drugs in DPI devices. Basically, various processes can occur during the ternary mixing, that can result in higher efficiency of DPIs. Depending on the system characteristics, some of those mechanisms are considered more important and need more attention under special conditions. To be able to differentiate between those mechanisms there is a need to grasp mechanistic fundamentals of each possible process. So far, four likely theories have been introduced, each with specific features and interpretation. Theses hypotheses have still remained speculated as some experimental findings show contradictory with the corresponded outcomes, considering the fact that formulation characteristics may change case by case [11].

Moreover, different mechanisms in the system get affected by changing variables such as particle size and the total number of particles. Consequently, this dependency makes the evaluation challenging as it becomes difficult to distinguish the impact of each variable on the related mechanism or mechanisms in the mixing. Or the other way around, it gets tricky to see which mechanism causes a change in the mixing performance.

In addition to the size and the concentration of fine excipients, the order of what fine or drug is primarily mixed with the carrier can have a great impact on results coming from any of those hypotheses. The impact of this factor can increase FDP to about 60 to 70% when the mixing is performed by first blending fine and carrier particles [39, 40]. This effect of blending order needs significant attention especially at times when the aerosolization occurs at low flow rates [40]. On the contrary, during the longer blending time, this effect can be neglected as the mixture reach an equilibrium state in the redistribution of particulates among binding sites [41].

To be able to track the effect of various factors on the formulation mechanism, there is a need to learn the characteristics of each theory by applying suitable analytical methods. With that said, the two major hypotheses, namely, the active site theory and the agglomeration theory are presented first followed by two other theories with less popularity but still promising.

3.3.1 ACTIVE SITE THEORY

In the first hypothesis, known as the active site theory, fine excipients show a high tendency to adhere to the strong binding sites located on the surface of the coarse carrier [6, 14, 18, 11]. These areas are partially occupied by means of fine excipients, giving drug particles less chance to attach to areas of high surface energy. Consequently, the drug particle liberates more readily at the aerosolization stage due to the weaker bond with the carrier surface, which in turn results in a higher dosage of inhalable drugs [6, 14, 18, 11]. The schematic of the first theory is illustrated in Figure 10, a recent work by M. R. Tamadondar [11].

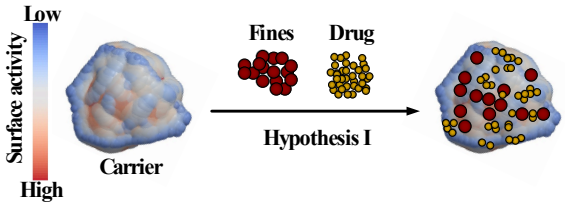


FIGURE 10, THE SCHEMATIC OF THE ACTIVE SITE THEORY [11]

Although the active site theory was thought to be the main mechanism for the ternary formulation, many studies are proving the opposite. This theory claims that adding fine excipients to the mixing would leave fewer areas with high surface energy for drug particles [11]. Accordingly, the more fines added to the mixing the better efficiency in terms of drug delivery must be achieved. This is in contrary to the outcomes coming from recent studies since it has been revealed that adding fine particles above a certain point, can result in lower efficiency of DPI devices [14]. However, it does not necessarily mean that this hypothesis is false as another mechanism may be governing in that condition.

The active site theory can be evaluated using different methods. One promising approach is to analyze the drug-carrier contacts by checking the distribution of non-dimensional adhesion force according to the number of drug particles in contact with the carrier at the end of mixing. This can provide us with useful information regarding how strong drug particles have been attached to a lactose carrier. Having the respective figures for cases with different

numbers of fine excipients, it is possible to see the effect of such a factor (number of fine particles) on this theory and subsequently, on mixing performance.

3.3.2 AGGLOMERATION THEORY

The high number of entities present in the system gives rise to indirect contact between particles and the carrier via one or more units in the middle. These multilayer contacts cause particulates to remain on each other and make drug-particle agglomerations on the carrier surface.

The agglomeration theory claims that the reason why the efficiency improves via the inclusion of fine excipients is because of further binding areas provided by drug-fine multiplets [6, 14, 42, 43, 11]. These agglomerates that are formed during the mixing are subjected to higher inertia and greater aerodynamic forces as they become larger [11]. Therefore, upon aerosolization, the drug-fine multiplets are entrained more intense, leading to a higher rate of deagglomeration.

It is also argued that during the inhalation, drug particles can separate much easier from a multiplet than the surface of a coarse carrier. This is due to the formation of drug-drug and drug-fine bindings with relatively lower adhesion force, as well as fine particles have a smoother surface than that of a carrier, resulting in a reduction of contact and attrition forces [6, 14, 42, 43, 11]. Furthermore, drug powders may get stuck on the carrier surface due to mechanical interlocking. This cannot be the case for drug-fine or drug-drug contacts as they are relatively smooth [44, 45]. The schematic of the agglomeration theory is presented in Figure 11.

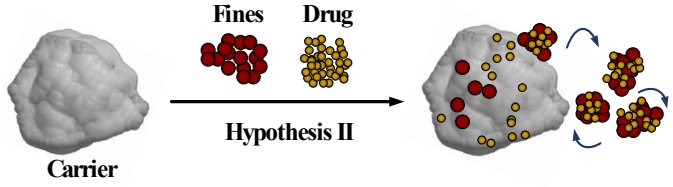


FIGURE 11, THE SCHEMATIC OF THE AGGLOMERATION THEORY [11]

Moreover, this hypothesis brings an explanation for why there is a higher FPF in cases with a certain number of fine excipient particles. Based on the theory, as long as the number of entities in the system goes up, there would be a higher chance for the formation of drug-fine clusters. Also, in cases with less number of fine particles, there is relatively more cohesive contacts among drug powders, which makes the deagglomeration harder as soon as aerosolization occurs [44, 45]. On the other hand, if the total number of particles in the system surpasses a certain level, agglomerates become too large to break during the aerosolization. In such cases, outer layers of agglomerates act as a shield by protecting the drug particles placed in the middle from external forces. Therefore, this theory is compatible with the effect of adding fine particles to the mixing performance.

This hypothesis can be traced by assessing the number of drug-carrier, drug-fine, and fine-fine contacts. This can provide us information regarding the number of monolayer and multilayer bonds that exist at the end of mixing. Assessing the level of fines added to the system can also give valuable information for this mechanism. When it comes to the experimental measurements, this theory has only been proved by SEM pictures of the formulation.

3.3.3 FLUIDIZATION REINFORCEMENT THEORY

The mechanism regarding the fluidization reinforcement theory is very similar to what happens in fluidized beds. In a fluidized bed, particles act as a granular flow due to the high number of entities that coexist in the system. The

high volume density of particulates causes an increase in the tensile strength of bulk materials, and therefore, adding any particle regardless of its type elevates the MFV of the bed-chamber to a higher level [11]. With that said, there is a physical correlation between the minimum fluidization velocity and the number of elements that exist in a fluidized bed.

According to the fluidization reinforcement hypothesis, this mechanism is very similar to what happens in DPIs during aerosolization. The added fines cause a more cohesive powder bulk that results in larger agglomerates – where a larger particle of the same density has a higher MFV. Moreover, a more packed bed should be subjected to a higher MFV than a packed bed of the same material with a lower number of entities. As a result, the fluidization reinforcement theory states that the inclusion of fine excipient particles in the system comes with a growth in the minimum inhalation velocity when the patient triggers the inhaler. Therefore, interparticle collisions occur with higher kinetic energy, leading to an easier separation and breakage of agglomerates that exist in the inhalation chamber, and subsequently, a better rate of dispersion can be achieved. It should be mentioned that the increase in the kinetic energy of particles during the aerosolization attributes to mostly the translational kinetic energy of the whole system.

Furthermore, this theory lacks compatibility with the number of fine particles when the total number of entities in the system is above a certain point. According to the hypothesis, FPF increases by adding any particle in the system but it has been observed that there is an optimum value in terms of the number of particulates in the system.

When it comes to the methodology, the fluidization reinforcement theory is by far the most difficult mechanism to study in comparison with other counterparts. From a simulation point of view, there is no practical method to track the effectiveness of this theory on the mixing performance except by checking the influence of the total number of particles, which can affect other mechanisms as well. Instead, it is relatively straight forward to measure the contribution of this hypothesis according to the experimental data.

3.3.4 BUFFER THEORY

During the mixing, particles are constantly pressed by other components especially when they are placed between two colliding carriers. In the formulation mechanism regarding the buffer theory, particulates with relatively large sizes can prevent carriers to press drug particles in between. Fine particles in the system act as a shelter against the press-on force over drug particles. This phenomenon causes drug particles to contact the carrier surface with less adhesive force, which results in an easier detachment as soon as aerosolization happened. The mechanism corresponded to the buffer theory is illustrated in Figure 12.

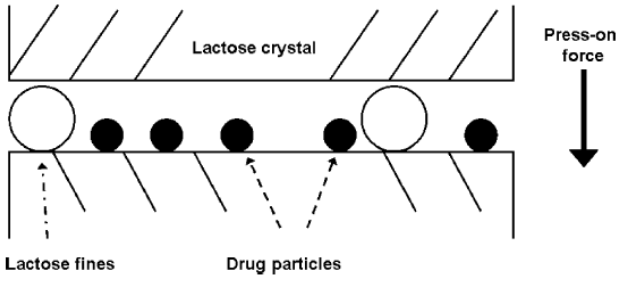


FIGURE 12, THE SCHEMATIC OF THE MECHANISM HAPPENS IN THE BUFFER THEORY [11]

Considering the buffer theory basis, the drug-carrier contact force needs to be directly correlated with the size of fine excipients. However, the majority of the studies worked in DPI mixing suggest that the optimum particle size,

depending on the formulation properties, is in the range of 2 to 15 µm. Therefore, this theory can be true for a limited range of particle sizes until its mechanism become relatively negligible compared to other forces that exist in the system.

Even though the mechanism that takes place in the buffer theory is difficult to screen both in reality and simulation, there are some methods to evaluate the impact of this mechanism. According to this theory, the corresponded mechanism is highly affected by the size of both drug and fine particles in the ternary system. Having said that, it can be a good idea to count the number of drug-carrier collisions as a function of the fine particle size. This could be done to see how the change in the fine excipient size can avoid drug powders to be pressed by two carriers. Besides, this hypothesis can be investigated by observing the number of particles released once the carrier collides to a random wall after the mixing.

3.4 AEROSOLIZATION

To be able to improve the formulation of DPIs, it is good to know the basics of the aerosolization stage including the detachment mechanisms and dependencies that can elevate the rate of dispersion in the inhaler device. Having good dispersion characteristics during the inhalation can result in high overall efficiency of DPIs in terms of the amount of fine particle fraction reaching the pulmonary capillaries, which is the ultimate objective in such studies. With that said, in this section, it was attempted to give an overview of phenomena happens at the aerosolization phase in a conventional DPI device.

However, it should be pointed out that due to the focus of the present study on the formulation mechanisms of DPIs, the mechanisms regarding the detachment of drug particles from the coarse carriers are just briefly explained without mentioning the exact physics. For that reason, it is recommended to refer to [46] for further details, including the corresponding relations during the collision.

3.4.1 AEROSOLIZATION PROCESS

On the contrary to the mixing phase, where fluid forces were considered negligible compared to the collision forces, at aerosolization, the aerodynamic of the system plays an important role. During the inhalation, formulated particles are entrained into a capsule chamber with the help of a triggered fluid entering from the DPI inlet or inlets. The fluid flow coming to the DPI device causes carriers, together with the agglomerates created during the mixing, to enter to a swirling chamber, where particles can collide to the chamber wall.

According to [46], most of the drug particles can detach in the circulating chamber due to the high number of particle-wall collisions. The dispersion rate of such a system is dependent on the flow rate, DPI shape, geometry, and obviously, particle characteristics by which the energy needed to overcome the adhesion/cohesion forces are determined. It should be mentioned that the high rate of separation between drug particles and the carrier surface does not essentially refer to the high efficiency of the DPI device as many of those particles are either stuck on chamber wall or remained in drug-fine clusters.

The entrained fluid flow eventually pushes particles towards a mouthpiece, where a micro-sized grid is placed at the entrance of the mouthpiece. The mouthpiece makes the flow enough turbulent and prevents clusters larger than a certain size to pass through the lattice. Therefore, the shapes of the grid and mouthpiece are of great importance for the level of turbulent kinetic energy in the inhaler, and subsequently the DPI performance. The following figure illustrates two considered swirl-type inhalers as two conventional DPI devices.

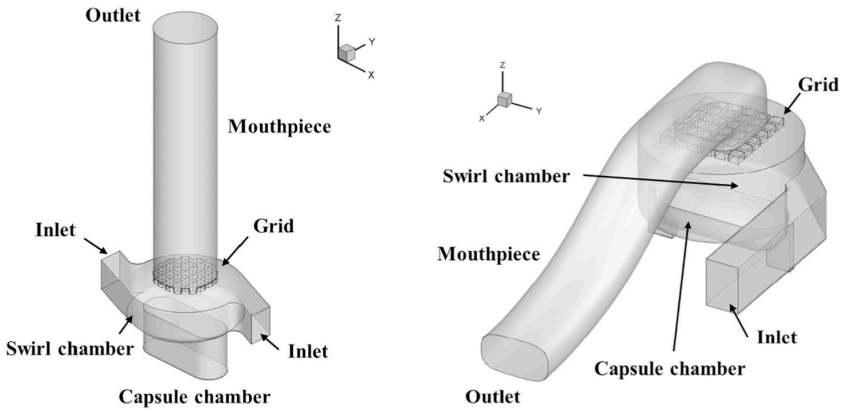


FIGURE 13, THE REPRESENTATION OF TWO TYPICAL GEOMETRIES FOR DPI DEVICES; LEFT) COMMERCIAL CYCLOHALER®, RIGHT) MODULAR INHALER [47]

3.4.2 DETACHMENT MECHANISMS

In general, there are three main mechanisms in which particles and agglomerates can detach from carrier surfaces, namely lift-off, sliding, and rolling [46]. Each force type has a certain contribution to the detachment of particles depending on the location of the corresponding particle once collision happens. According to [46], the lift-off mechanism contributes to nearly half of the detachments per collision if it is assumed that particles are evenly distributed over the carrier surface. After the lift-off mechanism, sliding has the largest contribution, and the remainder is detached by the rolling mechanism [46]. However, it should be mentioned that all mechanisms impose both normal and tangential forces on individual particles and their sizes are dependent on the location of where the particle is attached on the carrier surface.

During the collision of a carrier with the wall or with another carrier two main phenomena occur, the compression phase and the recovery phase. The former is the phase in which the kinetic energy of the carrier turns into the elastic potential energy, while in the recovery phase the opposite happens [46]. This conversion of energy is irreversible since a portion of the energy is always transformed into other types of energy, especially in the form of heat. For example, almost 12% of the tangential velocity, during the collision of a carrier with a wall, is consumed by the friction force on average according to [46]. This irreversibility can be taken into account by introducing a coefficient of restitution into the system for both normal and tangential velocities. Besides, the kinetic energy can be converted from one type to another by exchanging momentum between angular and translational velocities. This is due to the relative velocity that exists between the impact surface and the surface of the carrier, which in turn causes sliding at the interface.

LIFT-OFF

Lift-off as one of the separating mechanisms accounts for the most of detachments of particles from the carrier surface during the aerosolization stage [46]. At the collision time, approximately half of the particles are facing the wall and the rest are on the opposite side. For simplicity, it is assumed that carriers vertically collide to the impact surface. Having such assumptions, the side in which particles are in front of the impact surface is, from now on, known as the southern hemisphere and the other one is called the northern hemisphere.

With that said, it is argued that the particles located at the southern hemisphere are exposed to a higher separating force compared to the other counterpart. This is because of the relative velocity that arises between particles and

the coarse carrier once carriers start to be compressed. In other words, particles' inertia in both hemispheres causes particles to relatively move either towards or against the carrier, which depends on the particle state. If the particle is placed in the northern hemisphere, it moves towards the carrier, otherwise, it starts to move away.

The latter reaction is so-called the lift-off force, which can cause particles to detach from the carrier surface if its magnitude reaches a certain value. This cut-off value depends on the strength of the adhesion force at the contact point which will be discussed in more detail later. Furthermore, the energy that is required to break such contacts is provided by the inertia which comes from the impact force. Accordingly, it can be understood that larger particles or agglomerates are, more likely, pulled off by collision since they are subjected to more inertia force.

Other types of detachments mechanisms including the sliding, rolling and turbulent shear together with their dependencies are beyond the purpose of this study. Therefore, it is recommended to refer to [46, 47, 48] for more details.

4 METHODOLOGY

In this section, the method by which different formulation mechanisms have been studied is discussed. This includes the main characteristics for each case, the analysis method, and the post-processing techniques that were used to study the results obtained from DEM simulations.

4.1 SIMULATION SETUP

To have a reliable outcome from the simulations, there is a need to apply the right physic into the system. This can be done by having a good understanding of the system characteristics as well as the distinction of plausible phenomena that occur during the mixing. The system characteristics are categorized as particle mechanical and physicochemical properties, the condition of where mixing is performed, and the simulator settings including the time step corresponded to each case. Therefore, in this section, it is tried to give an insight into how the simulation setup has been employed for different case studies.

4.1.1 PARTICLES CHARACTERISTICS

For the sake of consistency among different cases, the chosen components need to be identical to have the same physicochemical characteristics regarding the properties which are solely dependent on the material selected. In the present study, salbutamol sulfate is chosen as the drug component due to its vast use and frequent investigations conducted within DPI applications [11]. Moreover, both fine and carrier particles in the adhesive mixing process are made up of lactose as it is a common substance for inhalation purposes, having suitable physicochemical properties for both formulation and aerosolization make it a favorable substance [11]. Table 1 represents particle physical and mechanical properties, which are constant within different case studies.

TABLE 1, CONSTANT PARTICLE CHARACTERISTICS WITHIN DIFFERENT SIMULATIONS

Component	Material	Particle density (kg/m^3)	Poisson ratio	Young modulus (GPa)	Restitution coefficient	Static friction coefficient	Rolling friction coefficient
Drug	salbutamol sulfate	1330	0.3	2	0.5	0.26	0.002
Fine	lactose	1550	0.29	0.1	0.5	0.5	0.002
Carrier	lactose	1550	0.29	0.1	0.5	0.3	0.002

The focus of the present study is on the effect of particle characteristics on the formulation performance. These characteristics are limited to the size and the amount of fine excipient added to the system as well as the effect of drug particle surface energy on the mixing performance.

PARTICLE SIZE

The performance of the ternary formulation can be highly influenced by the size of different particles that exist in the system. However, the impact of this factor is different within different components in the mixing. For example, when it comes to the coarse carrier, the particle size is not that effectual due to the relatively larger size of carriers [14]. On the contrary, the size of the fine excipients has a significant effect on the performance of the formulation according to the studies done so far [14]. For the drug component, this factor can be important depending on the system characteristics and the type of pharmaceutical components under investigation.

Three different cases in addition to a base case are introduced based on the fine particle size to evaluate the influence of such a factor on the mixing performance. The fine excipient is selected as the favorable variable due to its high importance compared to other elements in the system in addition to the fact that the focus of the present study is more on the fine particle. Therefore, the base case is first introduced with the characteristics of different particles followed by three case studies with corresponded changes due to the particle size alteration.

TABLE 2, PARTICLE CHARACTERISTICS OF DIFFERENT COMPONENTS REGARDING THE BASE CASE

Component	Particle size (μm)	Mass loading ratio (% w/w)	Surface energy (J/m^2)	Number of particles
Drug	3	1.32	0.015	900
Fine	5	5.7	0.008	700
Carrier	80	93	0.005	3

The characteristics of the base case are selected based on a recent study by Tamadondar et al., where different properties are chosen in accordance with the conventional ranges in DPI formulation [11]. With that said, particle properties regarding three cases with various sizes of the fine particle are defined as:

TABLE 3, FINE PARTICLE PROPERTIES OF THE BASE CASE IN ADDITION TO THREE CASES WITH DIFFERENT SIZES OF FINE EXCIPIENTS

Case number	Particle size (μm)	Mass loading ratio (% w/w)	Surface energy (mJ/m^2)	Number of particles
Base case	5	5.7	8	700
1	3	5.7	8	3241
2	4	5.7	8	1367
3	7	5.7	8	255

As can be seen, by changing the particle size, the total number of fine excipients is the only parameter that needs to be adjusted in order to have the same amount of this component in the system. Other parameters, including the mass loading ratio and the surface energy corresponded to each particle, would remain constant in those simulations. Care will be taken in the analysis to scale for both the increased number of particles and the increased surface area that comes with lowering the particle size while the mass loading is kept constant.

MASS RATIO

Besides the influence of the particle size, the number of different components added to the system can cause a considerable change in the performance of DPI devices. Similar to the previous section regarding the particle size, fine excipients are the favorable component to be studied in terms of the mass ratio. Changing the mass loading ratio of fine excipients, in general, has a relatively high impact on the mixing performance compared to other counterparts in the system. Consequently, due to the focus of the current study on the fine excipients, this component is again selected for further studies regarding the mass loading ratio.

In all simulations, the total number of elements is in the range of 1065 to 4241 particles depending on the case under investigation. There are three cases wherein the amount of added fine excipients is studied to evaluate the impact of this factor on the formulation performance. The following table shows the details of those cases in terms of fine particle characteristics.

TABLE 4, PROPERTIES OF FINE EXCIPIENTS FOR THREE CASE STUDIES TOGETHER WITH THE BASE CASE WHEN THE NUMBER OF FINE PARTICLES ADDED CHANGES

Case number	Particle size (μm)	Mass loading ratio (% w/w)	Surface energy (mJ/m^2)	Number of particles
Base case	5	5.7	8	700
4	5	1.32	8	162
5	5	3.5	8	430
6	5	8	8	982

It can be pointed from Table 4 that the total number of fine particles changes by changing the fine mass loading ratio. This is done for the purpose of keeping other parameters constant such as the size of fine particles. Parameters regarding other components will also remain the same as the base case.

SURFACE ENERGY

Surface energy is another factor which is of great importance when adhesive forces are taken into consideration. Changing the surface energy comes with substituting the particle substance as it is a function of temperature and the material selected. Consequently, the characteristics of the particle that is subjected to the material replacement will completely change. Therefore, to avoid the involvement of other variables as disturbing factors into the assessment (analogy), other parameters except the drug surface energy will remain constant. The drug particle is considered the main variable in this case since the focus of the present study is on the lactose fine particle as a conventional excipient in DPI applications. However, it shall be mentioned that the corresponded simulations are based on a drug particle that does not exist in reality as it has the same characteristics as the salbutamol sulfate with the exception of the surface energy.

Even though the simulations regarding various surface energies in this section are based on virtual drug components, the results are as useful as other cases. This is because of the purpose of the study which is partially focused on the impact of the surface energy on the DPI performance. This effect can be identified by varying the surface energy of the drug component while other parameters are kept constant. The impact of this alteration is revealed in the coupled surface energy which in turn causes a change in the adhesion force of bonds that are in connection with the drug particle. Table 5 represents the characteristics of drug particle when surface energy changes.

TABLE 5, THE DRUG PARTICLE PROPERTIES OF THE BASE CASE IN ADDITION TO THE THREE CASE STUDIES WHEN THE DRUG SURFACE ENERGY CHANGES

Case number	Particle size (μm)	Mass loading ratio (% w/w)	Surface energy (mJ/m^2)	Number of particles
Base case	3	1.32	15	900
7	3	1.32	9.6	900
8	3	1.32	19.6	900
9	3	1.32	26.7	900

All particle properties will remain constant by changing the surface energy except for those adhesive forces that are subjected to at least one drug particle. Table 6 shows different adhesion and cohesion forces for the cases with different drug particle surface energies.

TABLE 6, THE SIZE OF ADHESION FORCE BETWEEN DIFFERENT COMPONENTS AS A FUNCTION OF VARYING DRUG PARTICLE SURFACE ENERGIES

Case number	Surface energy (J/m2)	Drug-drug cohesive force (μJ/m)	Fine-drug adhesive force (μJ/m)	Carrier-drug adhesive force (μJ/m)
Base case	0.015	0.106	0.097	0.118
7	0.0096	0.068	0.077	0.094
8	0.0196	0.139	0.111	0.135
9	0.0267	0.189	0.129	0.157

It can be seen that decreasing the drug surface energy results in the reduction of different adhesive forces that exist between a drug particle and any other component. Therefore, particles show reluctance to attach during the adhesive ternary mixing in such cases.

PARTICLES SHAPES

When it comes to reality, different components in the ternary mixing have various ranges of sizes and shapes. For the sake of simplicity and thereby less computational costs, it is tried to treat those particles as spheres with mono-sized units. This simplifying assumption can be employed for both drug and fine particles due to their relatively smaller sizes, but this is not the case when considering carriers. In contrast with other elements in the mixing, the carrier surface profile can have a significant impact on particle interactions. Therefore, as previously discussed in the section regarding the simulation framework, carrier particles need to be modeled to incorporate roughness and irregularities on their surfaces via an appropriate method. However, to avoid the possible differences that the collision of an asymmetrical carrier particle may cause, the overall shape of carrier particles was maintained nearly spherical. The carrier shape which has been modeled to use in this study is presented in Figure 14.

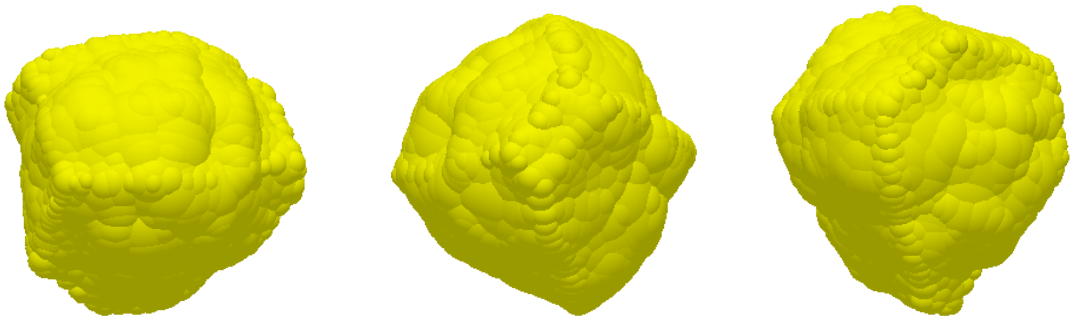


FIGURE 14, THE SURFACE PROFILE CORRESPONDED TO THE CARRIER PARTICLE, VIEWING VIA THREE PERSPECTIVES OF X, Y, AND Z, FROM LEFT TO RIGHT, RESPECTIVELY [11]

This carrier is made up of 579 small spherical elements, with different radii which provide the asperities that exist on the carrier surface. Such a shape could be achieved using the Fourier harmonic to assign particle vertices as well as the multisphere model to generate the surface profile [11].

4.1.2 MIXING CONDITIONS

The large number of particles that exist in a real mixing makes it impossible to model the entire system because of the high computational demand. Therefore, only a portion of the whole mixing vessel is modeled. Having said that, the control volume is selected so that only three carriers together with the proportional number of drug and fine particles remain in the mixing. The designed system will have a volume concentration of around 20% which is well below than that of a real mixing condition, let's say almost half. The lower particle concentration is favorable to reduce the simulation costs in addition to make the rotation easier during the mixing. However, having such an

assumption may change the simulation results to some extent but the effect of the parameter variations should be still valid for denser systems while the main purpose of this study is to have a better understanding of the adhesive ternary mixing. Besides, having a dense system leads to only a higher number of collisions among particles.

The adhesive ternary formulation can be performed either in a container with an impeller or via a vibrating machine. In this study, the latter approach has been applied, and thereby, there is a need to assign the right values for vibration's characteristics including the frequency and amplitude. These values are selected so that the mixing is performed in accordance with the typical blending condition in DPI applications. With that said, the mixing condition is performed with the following characteristics according to a recent work by Tamadondar et al. [11]:

TABLE 7, THE SIMULATION MIXING CONDITION CORRESPONDED TO ALL CASE STUDIES

Process time (s)	Vibration frequency (Hz)	Vibration amplitude (μm)	Box size (μm)
0.5	120	200	180 x 180 x 180

Moreover, the simulation is done starting with the insertion of different particles in the control volume. The three carriers together with the fine particles are initially mixed for 0.015 s. Thereafter, nine clusters of drug powders are released from the top of the vibration box on the mixed particles. Once particles are settled (at around time 0.05 s), a motion will be induced to the system to simulate the vibration condition. The motion is employed via a sinusoidal translation along three different coordinates of X, Y, and Z, respectively to achieve the highest possible blending in a short period. By doing so, we make sure that kinetic energy is well distributed to all elements during the mixing. Eventually, the entire process ends in half a second. In this study, the simulation of the ternary adhesive mixing is done using EDEM®, a commercial software provided by DEM solution Ltd.

4.1.3 EDEM CONFIGURATIONS

The presence of a high number of micro-sized particles with different characteristics in the mixture makes the simulation computationally expensive. Besides, carrier particles in the mixing have irregular shapes to account for the surface roughness in the simulation. This could be done by applying the multisphere model, which gives different curvatures at the particle asperities. From the computational point of view, all these curvatures are treated as an individual spherical rigid body with the respective radius, which in turn makes the system even more complex. As a result, the simulation needs to be run in an appropriate time step to be able to trace the particle movement and to catch the collision impacts.

TIME STEP

Generally, in a discrete-element method where collision impact is taken into account, there are three different time steps in the system, namely fluid, particle, and collision time steps [8]. In the present study, since the impact of the fluid-induced forces has been neglected the corresponding time step can also be ignored. Moreover, the particle time step is related to the movement of individual particles, which are not affected by any external force except gravity. This time step can also be neglected since the collision time step is much lower than that of particle while the collision rate is quite high in a dense system. Therefore, collision is the only time step that is taken into consideration.

There are two practical methods explaining how the system time step shall be defined, namely Rayleigh and Hertz time steps. The former is based on the fact that particles need to be irrespective of any impact from particles, that are not in contact [49]. If the selected time step becomes too large, then the particle under investigation might be

affected by those located far from the local neighboring. That is because of the disturbing particles after a random time step. Those particles can be situated at positions regardless of what can really happen in between, which is not realistic. This phenomenon is called the propagation of disturbance waves and can be solved by choosing a suitable time step [49].

The Rayleigh time step is based on the minimum particle size and the critical time step fraction that exists in the control volume. The Rayleigh critical time step Δt_C can be obtained using the following relation for each particle in the simulation:

$$\Delta t_C = \frac{\pi R_{min}}{v_R} = \frac{\pi R_{min}}{\lambda}\sqrt{\frac{\rho}{G}}, \tag{26}$$

where ρ is the particle density and R_{min} denote the minimum particle radius. G and v_R also refer to the particle shear modulus and Rayleigh wave speed, respectively. λ as a parameter in equation (26) can be approximated by

$$\lambda = 0.8766 + 0.1631\nu, \tag{27}$$

where ν denotes the Poisson's ratio of the particle with the minimum size in the system.

Applying the characteristics of the particle with the shortest radius into the equation (26) and then taking the minimum value, gives the Rayleigh time step within the simulation framework. The value of Rayleigh time step in the mixing for all cases is equal to $6.619 \times 10^{-9}(\mathrm{s})$.

When it comes to the time step according to the Hertz method, its value is calculated based on the maximum relative velocity that is expected during the simulation. To practically obtain such a value, the Hertz time step can be estimated using the maximum collision velocity between two identical particles. The following equation is employed to estimate the Hertz time step while any mesh motion is taken into consideration [50]:

$$\Delta t_{Hertz} = 2.87\left[\frac{\left(\frac{4}{3}\rho\pi r_{sphere}^3\right)^2}{r_{sphere}E^2V_{max}}\right]^{0.2} \tag{28}$$

where E and V_{max} are referred to as particle Young modulus and maximum relative velocity. Inserting all values corresponding to the drug particle into the equation (27), results in the Hertz time step of $2.605 \times 10^{-8}(\mathrm{s})$. The drug characteristics were selected as this component has the smallest size throughout the system. It should also be mentioned that the maximum relative velocity in the calculation was estimated using the results of the base case, which has been simulated through the Rayleigh time step.

Eventually, the overall simulation time step can be achieved by either combination of both time steps or by taking the minimum value, which comes with a higher computational cost. In this case, the time step is appointed by the minimum value, which equals the Rayleigh time step. To make sure if simulations are conducted with an appropriate level of accuracy, a portion of the obtained time step is used. Therefore, 60% of the Rayleigh time step as the safety margin for calculations has been employed in EDEM. It gives the final time step of $4.0 \times 10^{-9}(\mathrm{s})$ within the simulation framework.

4.2 ANALYSIS METHOD

According to the literature study, different formulation hypotheses can be the leading mechanisms under different physicochemical conditions. Owing to the characteristic of each formulation mechanism, it is possible to relate the

effect of changing different variables to the corresponded leading mechanism in each case. This is not an easy task as there are many unknowns when it comes to the formulation mechanisms in the adhesive ternary mixing. Therefore, it is highly important to give a valid interpretation for each case in order to have a reliable outcome from the study. The following approach has been employed to investigate each mechanism based on its characteristics.

Analysis of the mixing mechanisms is conducted depending on the formulation enhancement theory that is under investigation. With that said, various types of analysis are introduced using different particle characteristics. These properties are presented either in terms of the processing time or based on the system characteristics at the completion of the simulation. To do so, there is a need to vary the key parameters to make changes in terms of the governing mechanism. As discussed earlier, these variables are limited to the size and the mass ratio of the fine excipients, as well as the surface energy of the drug particle due to the significant influence that they impose on the mixing performance.

Besides the quantitative analyses via statistical measures, simulation results can be assessed qualitatively using visual observation of mixing state at the end of the process. This technique can be beneficial in many different ways. For instance, when it comes to the agglomeration theory, the quality of drug-fine agglomerates created can be monitored by looking into those clusters that exist at the end of the simulation. This can help us to see how well drug particles have been mixed with fine particles and to see if results are compatible with the ones coming from analysis. Therefore, a combination of different techniques gives a better perception of actual phenomena that happen along the adhesive ternary mixing.

The study begins with the analysis of general trends and phenomena that are common among all cases. To do so, first, the base case is thoroughly investigated to monitor the general patterns that occur during the mixing. This analysis includes: 1) the kinetic energy of carriers, 2) the number of different contacts, 3) the adhesion force and the size of overlap between drug and carrier particles, 4) the quality of drug-fine agglomerates, and eventually, 5) the rate of dispersion in terms of the number of drug particles detached from the carrier surface after the carrier-wall collision. The detailed explanation and the reason why these parameters have been selected for this study will be discussed in the next section.

After the general study, all cases are studied according to the critical attribute that is under investigation, meaning that all the mentioned parameters will be presented for cases corresponding to one main variable before studding another variable.

4.2.1 STUDIED PARAMETERS

Different parameters have been assessed in order to study the effect of main variables on the mixing performance. Having said that, these parameters are explained in more detail in this section.

KINETIC ENERGY

The kinetic energy of the carrier particles is studied by tracking the accumulated rotational and translation kinetic energies along the mixing process. This is done to first make sure that the mixing condition has been correctly implemented within all simulation cases and also to see how changing particle characteristics can affect the mixing behavior. The former can be evaluated by looking at the data regarding the translational kinetic energy and the effect of particle characteristics can be observed via rotational kinetic energy over the mixing time.

NUMBER OF CONTACTS

The total number of bonds for each contact type can help us to see if the mixing process is in accordance with the principles of different formulation mechanisms that play during the ternary mixing. Therefore, together with other results, it is possible to determine whether the studied mechanism is dominant in the adhesive formulation.

The total number of drug-drug contact is one of the most important parameters to study. Tracking this parameter over the simulation time gives us information in terms of the breakage of drug agglomerates before and after mixing which is the main purpose of the adhesive formulation.

Studying drug-carrier contact is another parameter which is of great importance when it comes to the evaluation of active site theory, where it is argued that inserting fine excipients provides fewer areas on the carrier surface that have a high adhesion force. This hypothesis can be investigated by looking at the number of drug-carrier contacts and the size of the adhesion force related to those contacts. Another factor that needs to be taken into consideration is the number of contacts per drug particle rather than the number of contacts itself. This parameter is important too as each drug particle can have multiple contacts with the rough carrier surface.

With the same reasoning, the number of fine-carrier contacts is significant as it tells us to what extent the carrier surface has been occupied by adding fine excipients. Comparing the results of different cases for such parameters can lead us to better understand the principles of the active site theory.

Drug particles can also make contact with fine excipient particles to make drug-fine clusters. The creation of these clusters is the reason why adding fine particles can increase the deliverability of APIs according to the agglomeration theory. Therefore, studying the number of drug-fine contacts gives information regarding the quality of such clusters, meaning how well particles were distributed within those clusters. Finally, the number of fine-fine contacts is evaluated to see how fine particle characteristics can influence the rate of fine agglomerates breakage.

Adhesion force

The average size of the adhesion force between drug and carrier particles is of great importance in the theory of active site. This tensile force needed to detach drug particles alongside the number of drug-carrier bonds per number of drug particles determines whether fine excipient characteristics can affect the strength of those contacts. The size of adhesion is correlated well with the magnitude of the corresponded overlap and accordingly, the results of the adhesion force can be obtained from the data regarding the overlap size. In this study, the size of overlap is considered as an index for the evaluation of drug-fine contacts.

Overlap

Overlap is the translation of the adhesion force on the particle surface and its size, depending on the type of material, can be changed with different components. With that said, knowing the size of overlap between different components after mixing, it is possible to estimate the size of the adhesion force established between those particles. Therefore, the results can reveal if the drug-carrier overlap is affected by fine particle characteristics. However, it should be mentioned that other factors including gravity, meaning the load which is felt by each particle on top of it, can have a minor effect of the overlap size.

Drug-fine agglomerates

The drug-fine clusters are studied both quantitatively and qualitatively. In other words, the number of those clusters is studied according to the minimum number of particles that is assumed, can constitute each drug-fine cluster. Moreover, the quality of such clusters is studied to see how many drug and fine particles are located within those drug-fine clusters. Studying these parameters together with the number of drug-fine contacts can provide us with a better perception of drug-fine clusters created during the ternary formulation.

DISPERSION

The rate of dispersion of drug particles can be considered as the main index to distinguish between different cases in terms of the deliverability of drug powder. The level of dispersity for drug components is defined as the total number of drug particles that individually detach from the carrier surface during the collision with a rigid wall. More clearly, after the mixing, particles collided with an impact wall at different impact velocities. This is done to see how the rate of dispersion is affected by both the magnitudes of the impact velocity and the critical variable under investigation. It should be pointed out that for the sake of consistency between different cases, particles hit the impact wall with a vertical angle. Figure 15 represents the dispersion of particulates when a collision happens. The state of the particles is illustrated before and after the collision with the impact wall.

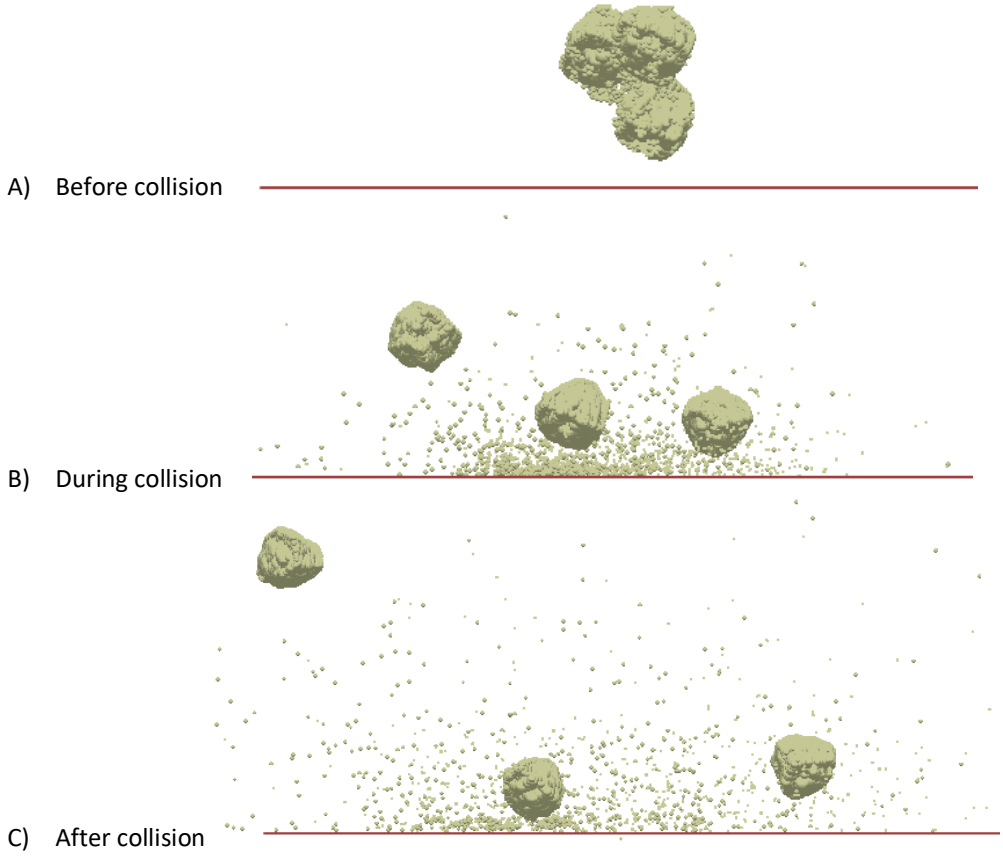


FIGURE 15, PARTICLES REACTION BEFORE, DURING AND AFTER COLLISION WITH THE RIGID WALL

4.2.2 FORMULATION MECHANISMS

To have a better understanding of the adhesive ternary formulation all parameters in the previous section are studied for different cases. These results are summarized in the discussion section and depending on the formulation mechanism under investigation, only the key parameters are shown. This is due to the distinct physical interpretation that is claimed in each theory. With that said, different formulation mechanisms are discussed according to their corresponded parameters as the following:

ACTIVE SITE THEORY

In the theory of active site, fine particles are assumed to make contact with those areas of the carrier surface that have a high potential of adhesion forces. Occupying these areas by fine excipients leaves the weaker spots for drug particles, which eventually facilitates the separation of drug particles from the carrier surface once aerosolization happens.

To study the contribution of this hypothesis on the mixing performance, the strength of drug-carrier contacts can be investigated in terms of both the quality and quantity of those contacts. In other words, the strength of drug-carrier contacts can be determined by the size distribution of the adhesion force after mixing. Also, the number of such contacts over the number of drug particles in contact with carrier results in the average number of contacts per drug particle, which can be used as an index to determine the strength of those contacts. Comparing these results with the number of fine-carrier contacts can give us determining information regarding the active site theory.

For the sake of analogy between different cases, the probability distribution of the non-dimensional adhesion force is preferably used rather than the original adhesion force. This is due to the fact that different cases have different numbers of drug-carrier contacts. Consequently, to analyze the distribution of the adhesive forces, the normalized values are instead used.

Comparing such findings from different cases makes it possible to see the effect of the main variables on this mechanism. It can be predicted that the number of fine excipients as a key variable can have the highest impact on the mixing performance as this factor determines whether or not adding fine excipients into the mixing can occupy sites with high surface activity. Accordingly, changing such a factor should lead to a significant change in the contribution of this mechanism in the system. Therefore, depending on the case under investigation, this theory can be eliminated or signified as a governing mechanism.

AGGLOMERATION THEORY

In brief, the agglomeration hypothesis claims that the efficiency of DPI devices increases by the formation of drug-fine agglomerates during the mixing. This corresponds to an easier detachment of such clusters from the carrier surface once aerosolization occurs. With that said, agglomerates are the constituents that must be scrutinized in this theory.

The primary approach to investigate such drug-fine agglomerates from both qualitative and quantitative points of view is as follows. This method comes with counting the number of contacts that exist between different sets of particles. This is expressed in terms of the drug-carrier contact numbers in order to quantify the portion of drug particles that are directly settled on the carrier surface. The remaining drug particles, if still attached to the carrier particles, are considered to adhere indirectly. This indirect adhesion implies that small multiplets of fine-drug or drug-drug structures that exist on the carrier surface.

With that said, drug-fine agglomerates are studied according to the minimum number of particles that constitute each multiplet. This assessment includes the total number of multiplets and the total number of drug and fine particles within such multiplets. According to the agglomeration theory, if there is a higher number of drug particles within the drug-fine multiplets, the rate of dispersion shall be increased. However, if the agglomerates are large enough the surrounding particles can act as a shelter for particles placed in between. This can be true at low impact velocities where a little impact force is induced on particles during the collision, whereas, the energy needed to detach all particles is adequately provided at high impact velocities.

Moreover, varying the drug particle surface energy and the number of added fine excipients can significantly change the contribution of this theory over the formulation. Therefore, by comparing those cases, it is possible to see if the agglomeration theory can possibly be a dominant mechanism in the ternary formulation or not.

4.2.3 MIXING PERFORMANCE

Mixing performance describes how well different particles in the system have been distributed over the carrier surface. One promising method is to check the number of drug-drug contacts as the main purpose of adding fine excipients into the binary mixing is to avoid the formation of drug agglomerates. Accordingly, a lower number of contacts between drug particles implies a better distribution, and thus a higher mixing performance is obtained via the DPI formulation. However, this reasoning is not always true as, for example, drug particles may just have occupied those areas on the carrier surface that have high surface energies, thereby, no efficient drug delivery will be achieved.

Alternatively, the mixing performance can be evaluated by checking the level of dispersity regarding those carries that have been blended with other particles during the adhesive ternary mixing. The corresponded rate of dispersion can be modeled by throwing particles to an imaginary wall once mixing is finished. The wall must be placed well far away so that carriers could reach a velocity in which drug particles can potentially detach from the carrier surface. In this study, particles are forced by a gravity higher than reality to reach the average velocity of 0.5, 1, 2, 3, and 4 m/s just before they hit the imaginary wall. Comparing different cases in terms of the portion of drug particles separated from the carrier surface provides useful information regarding the quality of formulation performance.

By doing sensitivity analysis on favorable variables, different mechanisms can be potentially determined as the governing process in each case. Changing any setting of the system configuration can result in switching from one leading mechanism to another, and thus, no general conclusion can be drawn in terms of the global formulation mechanism. Instead, there may be some leading mechanisms determined from a local perspective, i.e., the governing mechanism is selected by doing sensitivity analysis for one variable. Therefore, the leading mechanism is only valid for corresponded system characteristics.

5 RESULTS

These results are categorized into particle kinetic energy, number of contacts between different components, adhesion force-overlap, quality of drug-fine agglomerates, and eventually dispersion characteristics. Considering this amount of data for 10 different cases, the results are presented based on the parameter that is studied in each case. But first, the base case is fully reviewed to assess the main trends and phenomena that happened in all cases regardless of the effect of varying parameters on results.

5.1 GENERAL TRENDS AND SPECIFICATIONS

To have a better understanding of phenomena happening during the ternary mixing, the base case has been selected to analyze different particle properties. This assessment is done on the basis of either particle characteristics over time or the system properties after the mixing. Figure 16 illustrates the simulation vessel of the base case before and after the ternary mixing.

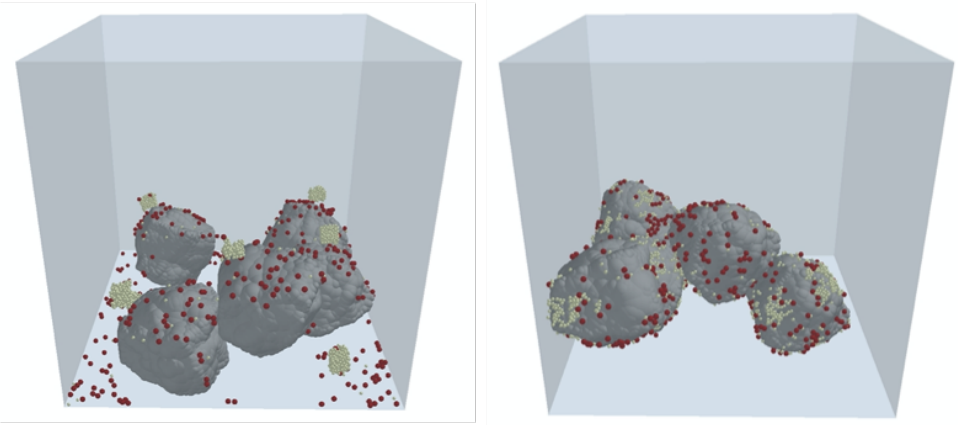


FIGURE 16, THE MIXING BOX BEFORE AND AFTER THE TERNARY FORMULATION; LEFT) BEFORE MIXING, RIGHT) AFTER MIXING

As can be seen, the drug agglomerates which are represented with yellow particles on the left-hand side figure, are partially distributed over carrier particles after the blending. The remainder is either kept within the drug agglomerates or get mixed with fine agglomerates to constitute the drug-fine clusters.

5.1.1 KINETIC ENERGY

The particle kinetic energy is investigated to make sure that the mixing kinetic condition has been correctly implemented in the system by checking the cumulative values over time. The kinetic energy is independently reported based on both the translational and rotational kinetic energies as each gives certain information.

TRANSLATIONAL KINETIC ENERGY

The accumulated translational kinetic energy of carriers is studied to see how particle characteristics can affect the mixing condition. This can be a good measure in the sense that how easy particles can move and displace in the vessel. With that said, the translational kinetic energy regarding the base case is plotted in Figure 17.

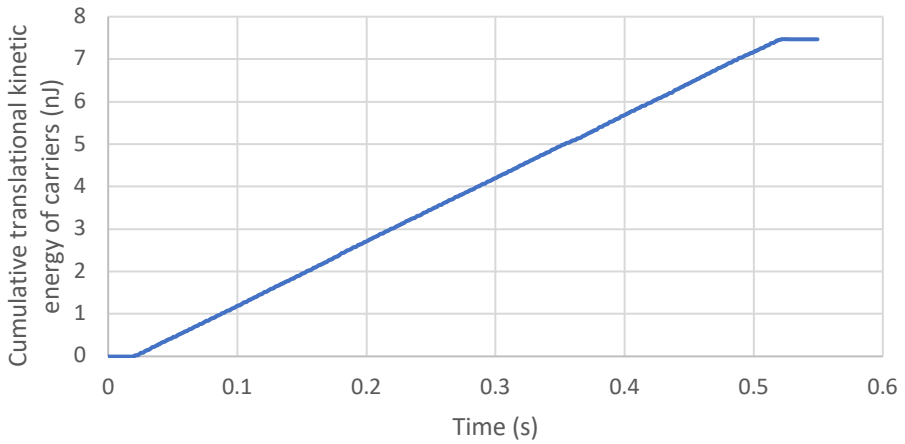


FIGURE 17, THE CUMULATIVE TRANSLATIONAL KINETIC ENERGY OF CARRIER PARTICLES IN THE BASE CASE OVER TIME

As can be seen, the cumulative translational kinetic energy starts to grow at t=0.02 s, where the vibration in the vessel begins and subsequently becomes constant at t=0.52 s, where the mixing is completed after half a second. It can also be understood that the slope of the corresponding figure is almost constant throughout the blending time, while the direction of vibration is the only factor that changes during the mixing. Therefore, the rate of growth in the cumulative translational kinetic energy must be only related to the frequency and amplitude of vibration which specifies the average velocity of all components in the mixing. Consequently, it is expected that all cases show the same tendency as the mixing condition is identical for all of them in addition to the fact that the same amount of coarse carrier is added to each case.

ROTATIONAL KINETIC ENERGY

The rotational kinetic energy is also important to look at as it shows how the rotation is affected by the presence of different particles in the system. This dependency comes from the fact that the rotation of different components is limited by the size of the friction force that is induced by other elements within the simulation box. Studying such a factor can also help us to make sure if the mixing has been correctly simulated. With that said, Figure 18 illustrates the accumulated rotational kinetic energy of carriers in the base case over mixing time.

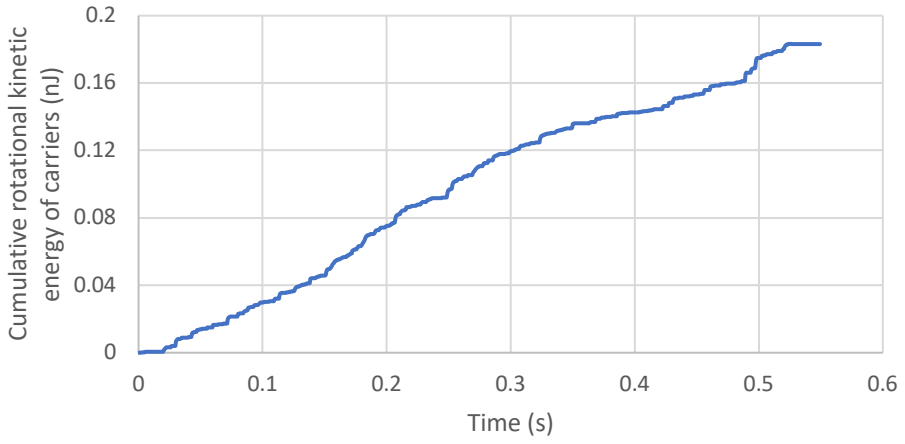


FIGURE 18, THE CUMULATIVE ROTATIONAL KINETIC ENERGY OF CARRIER PARTICLES IN THE BASE CASE OVER TIME

As can be observed from the graph, the rotational kinetic energy changes along the vibration time. On the contrary to the translational kinetic energy, the slope of this figure is not constant and changes over time. This is because of the confined space of the vessel as well as the friction that exists among particles which acts as a resistance against the angular movement of carriers. Therefore, besides the effect of vibration frequency and amplitude, the accumulated rotational kinetic energy is most likely a function of particle characteristics.

5.1.2 NUMBER OF CONTACTS

The number of contacts between different components in the simulation can reveal important information regarding the system characteristics as discussed earlier in the methodology section. In the present section different types of contact are monitored over time to achieve a better understanding of the ternary mixing. The different contacts include drug-drug, drug-carrier, drug- fine, fine-carrier, and fine-fine bonds.

NUMBER OF DRUG-DRUG CONTACTS

Number of contacts between drug particles is of great importance since it can show how well drug particles are mixed with other elements during the blending. In other words, it can be estimated that to what extend the primary drug agglomerates are broken over the vibration time. However, it should be mentioned that the corresponding results are just based on the number of contacts and are regardless of the number of drug particles attached to one another. For example, four spherical particles can have different numbers of contacts from zero to 4 (when particles are placed as a pyramid) depending on the arrangement of particles. Therefore, great care must be taken to draw any conclusion based on the following results. With that said, Figure 19 shows the data regarding the number of drug-drug contacts of the base case over time.

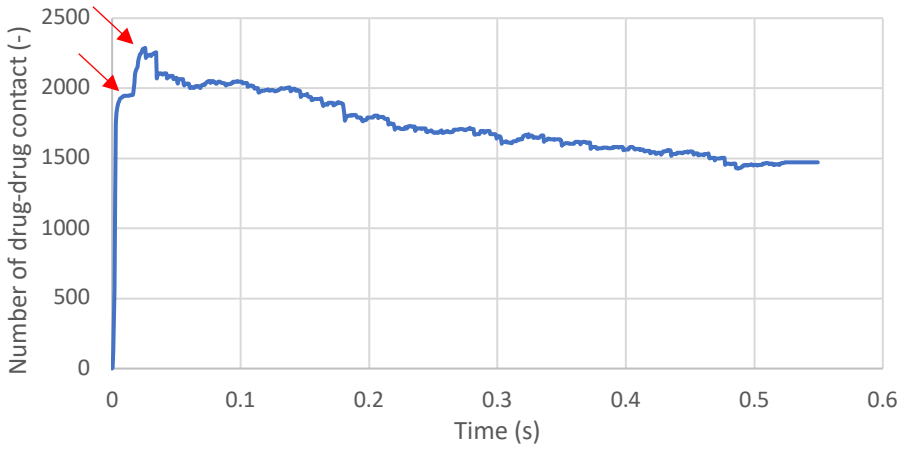


FIGURE 19, THE NUMBER OF DRUG-DRUG CONTACTS OVER TIME FOR THE BASE CASE

As can be seen, the figure shows a dramatic increase at the very beginning of the simulation followed by a gradual reduction in terms of the total number of drug-drug contacts to reach a semi-stable condition at the completion of the simulation. The sudden increase of the contact number since the start of simulation is because of the generation of drug particles at the initial steps. These particles are randomly inserted at 9 different confined spaces to create nine primary drug agglomerates just after insertion to eventually make around 1950 contacts. After a temporary steady-state condition, the graph experiences its peak at t=0.02 s, where mixing is started to reach its global peak of approximately 2250 contacts after a short while. Thereafter, due to the collision between different components in the system, drug particles begin to detach from their clusters to make contact with other particles. Therefore, as long as the mixing proceeds, the number of drug-drug contacts decreases gradually. However, it can be understood

that the graph becomes almost constant at the end of mixing, which implies that simulation has reached a pseudo-steady-state condition in terms of the number of drug-drug contacts.

NUMBER OF DRUG-CARRIER CONTACTS

Another important factor to study is the number of drug-carrier contacts over time. The corresponding information can help us to see how well drug particles are distributed over the carrier surface. However, it is not enough to just make a conclusion based on these data and other results need to be considered as well. Another thing that needs to be mentioned is the correlation between the trend here and the trend in the figure of drug-carrier contacts. In overall, by the reduction in the number of drug-drug contacts, the number of drug-carrier contacts increases. This can make sense since the more the drug agglomerate breaks, there is a higher number of drug particles available to make contact with the carrier surface.

Figure 20 represents the number of drug-carrier contact for the base case over simulation time.

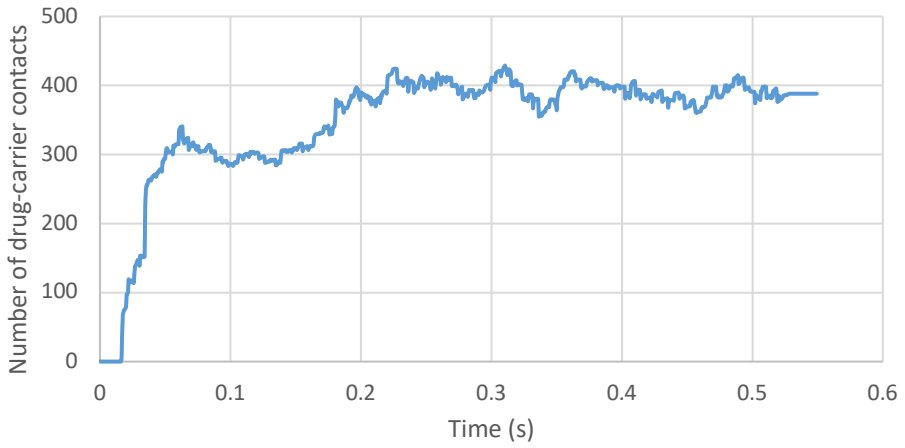


FIGURE 20, THE NUMBER OF DRUG-CARRIER CONTACTS OVER TIME FOR THE BASE CASE

As can be observed, there is not any significant contact number until the mixing starts at t=0.02 s. After that, as it was expected, the number of contacts increases as long as the mixing continues. However, this trend experiences an intensive fluctuation, and even at some points, it decreases substantially. This is mostly due to the presence of fine excipients. In other words, there is a chance for drug particles after detachment to bind with either a coarse carrier or a fine particle, depending on the mixing condition. From a larger perspective, the position of different particles can easily change during the collision and basically, there is a trade-off between numbers of drug-carrier and drug-fine contacts.

Moreover, it can be understood that the number of drug-carrier contacts is limited to a specific range at times close to t=0.5 s, which implies that the system is close to a pseudo-steady state if it has not already reached it.

NUMBER OF DRUG-FINE CONTACTS

Number of drug-fine contacts can give us information regarding the agglomerates created during the mixing. It can be expected that the contact number increases with time as drug and fine particle agglomerates are colliding with each other during the mixing. Figure 21 illustrates the number of drug-fine contacts of the base case over time.

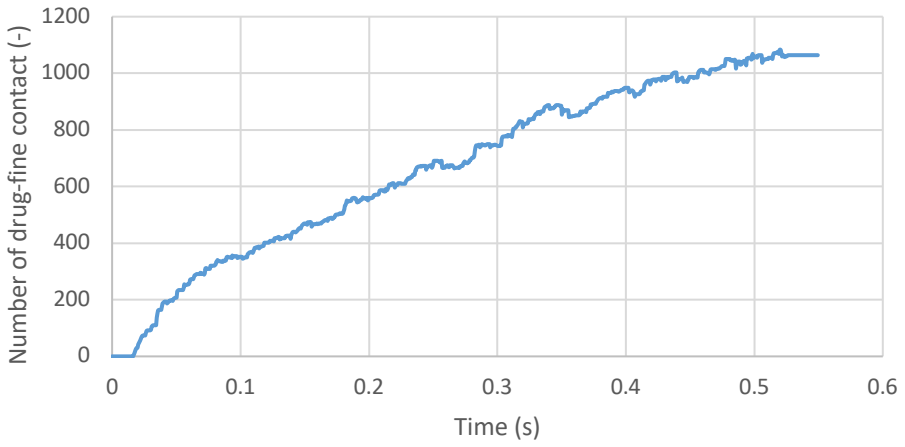


FIGURE 21, THE NUMBER OF DRUG-FINE CONTACTS OVER TIME FOR THE BASE CASE

As discussed above, the number of contacts starts to grow as soon as mixing begins at t=0.02s. The figure shows a gradual increase with a descending growth rate over vibration time. At times close to the completion of simulation the rate of change in drug-fine contacts becomes zero, which means that the number of contacts reaches a saturated value.

NUMBER OF FINE-FINE CONTACTS

Fine particles have been inserted randomly within the mixing box. After all, particles settled in the vessel, the vibration begins, and fine agglomerates are created. Figure 22 shows the base case data in terms of the number of fine-fine contacts over mixing time.

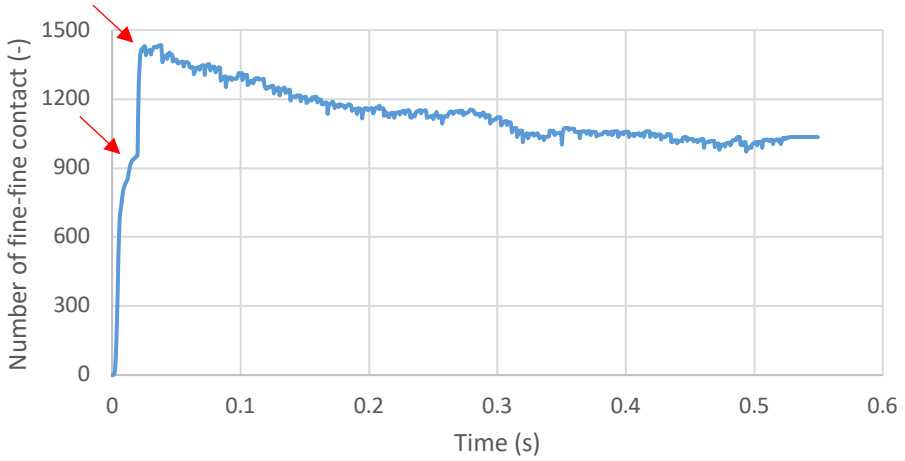


FIGURE 22, THE NUMBER OF FINE-FINE AGGLOMERATES OF THE BASE CASE OVER THE VIBRATION TIME

As can be seen, two sudden growths occur at the beginning of the simulation. The first increase happens once the fine particles are settled in the vessel while making new contacts between themselves. When the vessel starts to vibrate, the graph experiences its peak at t=0.03 s where fine particles start to make small agglomerates. Afterward, these agglomerates together with the individual particles collide to the other particles including drug clusters. As a result, fine agglomerates, with a lower surface energy break to make new contacts with drug particles instead. It should also be mentioned that the number of fine-fine contacts becomes constant at the end of the simulation, which implies that the system reaches a pseudo-steady state condition in terms of the number of related contacts.

NUMBER OF FINE-CARRIER CONTACTS

When it comes to the active site theory, the number of fine-carrier contacts becomes important in the sense that it can help us to understand how fine particles have occupied areas with high surface energy. This can be achieved by knowing the number of fine particles in contact, the number of fine-carrier contacts, and also the size of the adhesion force of those bonds. Figure 23 shows the trend regarding the number of fine-carrier contacts for the base case.

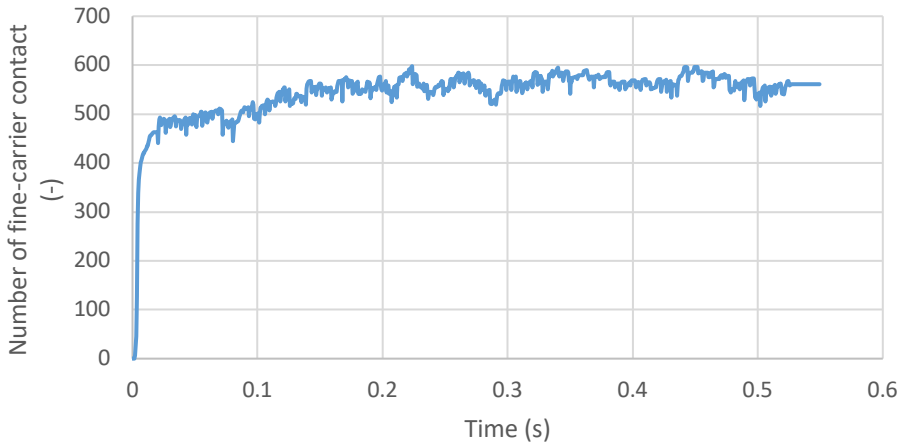


FIGURE 23, THE NUMBER OF FINE-CARRIER CONTACTS OF THE BASE CASE OVER TIME

As can be seen, the number of contacts increases at the beginning of the simulation due to the initial insertion of the fine particles. By starting the mixing, the new contacts are established between carriers and the fine particles remaining at the bottom of the vessel. After a short while, the number of contacts starts to fluctuate between around 550 to 600 contacts until the completion of the simulation. The fluctuation is because of the contacts that are constantly breaking and establishing by collisions with other particles.

5.1.3 ADHESION FORCE AND OVERLAP

Adhesion force and overlap are two distinct concepts that are highly correlated. Basically, the overlap is the translation of the normal force for each particle-particle contact. Therefore, these two parameters are categorized in the same context and presented together. Among different types of adhesion force among various contacts, the drug-carrier and fine-carrier contacts should be paid more attention. Owing to such results, it is possible to analyze the strength of contacts that fine and drug particles have made with carrier surface. This information is of great importance when it comes to the active site theory as it is argued that fine particles occupy the carrier areas that have high surface energies, and thus there is less chance for drug particles to make contact with high active sites. Therefore, only the adhesion force regarding these two types of contact are assessed in this study.

DISTRIBUTION OF DRUG-CARRIER OVERLAP

Overlap is the translation of the adhesion force on the particle surface and having either data would be useful to see how strong drug-carrier contacts are. This gives us a better understanding of the mechanism corresponded to the active site theory. Figure 24 shows the drug-carrier contact number over the overlap size for the base case.

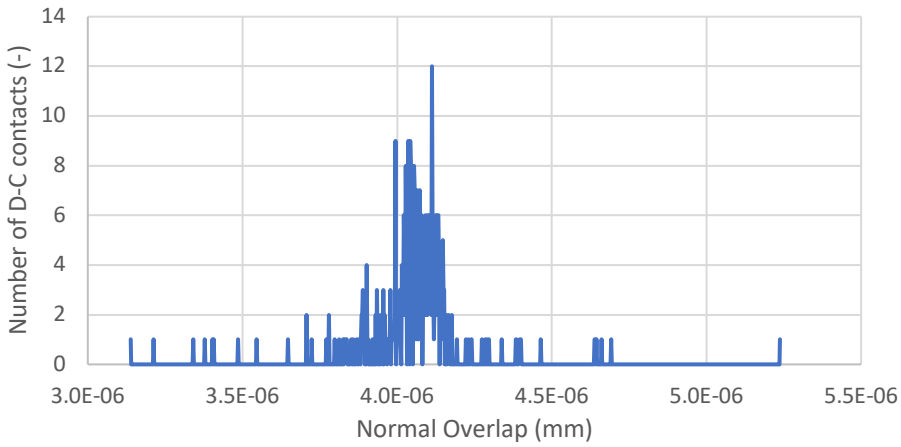


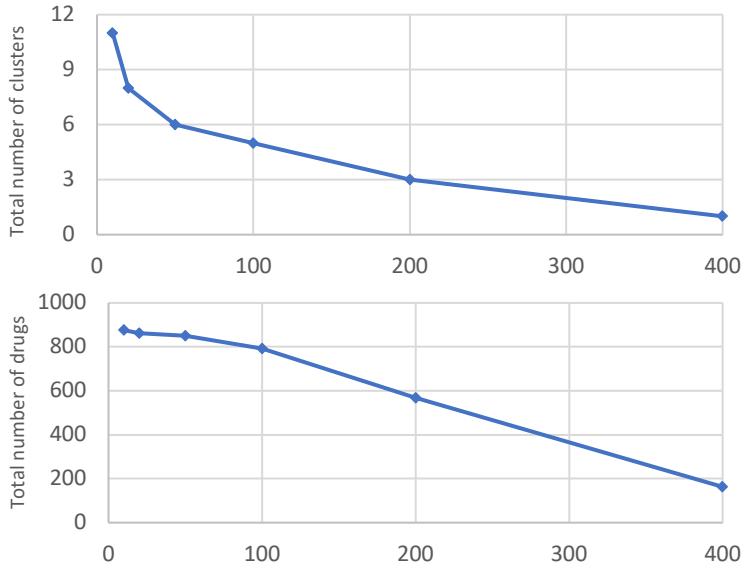
FIGURE 24, THE NUMBER OF DRUG-CARRIER CONTACTS VERSUS THE SIZE OF NORMAL OVERLAP FOR THE BASE CASE

The range of normal overlap varies within less than one order of magnitude. This can be explained by the spring-dashpot-slider model as a proper representative for the adhesion force and overlap; by increasing the size of adhesion force the rate of change in the size of overlap decreases due to the spring constant. In other words, with an increase in the size of the overlap, the amount of force needed for the compression increases exponentially.

Most of the contacts have a normal overlap around 4.1x10-6 mm and there are only a few data at the tails of the overlap range. Moreover, the distribution of drug-carrier overlap is expected to get highly affected by the magnitude of the drug surface energy.

5.1.4 AGGLOMERATES QUALITY

In the agglomeration theory, the formation of drug-fine agglomerates is considered as the reason to increase the efficiency of DPI devices, therefore, studying these components is of great importance. With that said, the drug-fine agglomerates are evaluated in terms of the total number of clusters according to the minimum number of particles that constitute each cluster. Also, the total number of drug and fine particles in such clusters are investigated.



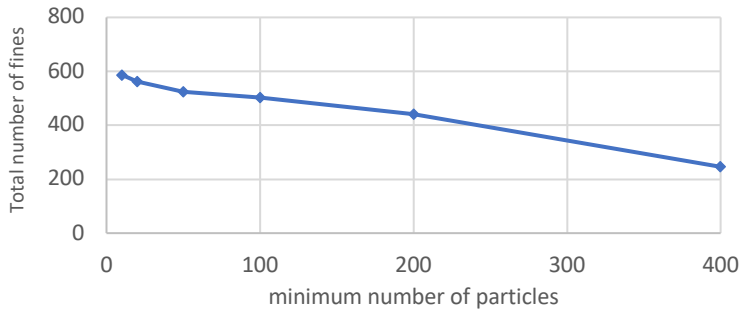


FIGURE 25, THE TOTAL NUMBER OF CLUSTERS AND THEIR CONSTITUENT DRUG AND FINE PARTICLES WITHIN DRUG-FINE AGGLOMERATES

As can be seen in Figure 25, drug-fine clusters up to the minimum number of 50 particles include 6 to 11 agglomerates that contain almost all drug particles. This implies that there are a few particles that individually (or very small agglomerates) left on the carrier surface. The remaining drug particles are either involved within drug-fine agglomerates or constitute the drug clusters. Another thing that should be mentioned is the total number of drug and fine particles which decrease with increasing the minimum number of particles that create each drug-fine agglomerate.

5.1.5 DISPERSION

The rate of drug particle dispersion is the most determining factor among various analyzing tools to see the effect of parameter study on the ternary formulation. Varying the selected parameters in the system results in different rates of dispersion depending on the relative impact velocity. Therefore, it can be understood which mechanism or mechanisms are governing in that mixing condition.

The data for dispersion is presented based on the drug FPF as a function of the velocity in which agglomerates collide to the impact surface. To remind, FPF or fine particle fraction is defined as the portion of drug particles that reach the lung cavities compared to the total amount of drugs inserted to the DPI device. However, in this study, the FPF is used as the number of individual drug particles detached after a collision. With that said, the ratio of separated drug particles is plotted as a function of the impact velocity in Figure 26.

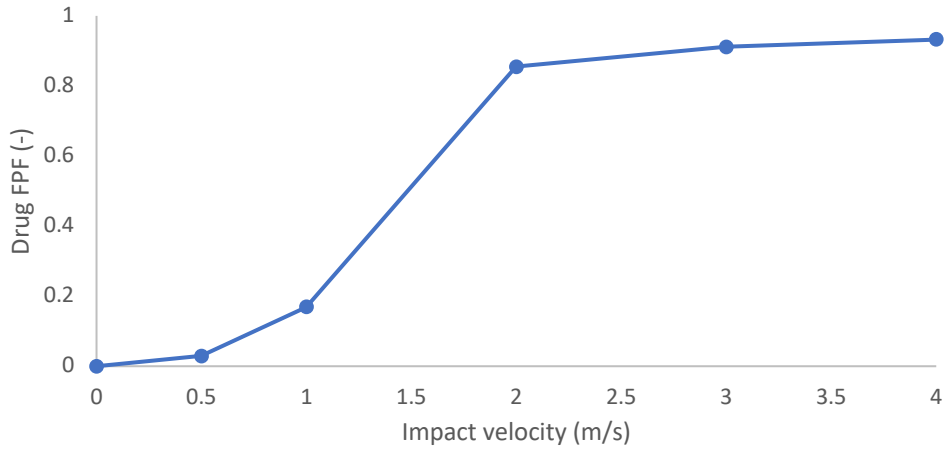


FIGURE 26, THE AMOUNT OF FPF FOR DRUG PARTICLES AS A FUNCTION OF THE IMPACT VELOCITY FOR THE BASE CASE

As can be observed from the graph, the level of drug particles that are individually released from the carrier surface increases with the impact velocity. It was expected because the higher kinetic energy of particles before the collision

must provide adequate energy to overcome the work of adhesion for drug contacts. Also, it can be understood that FPF for drug particles is not significant at low velocities, while with collision speed higher than 2 m/s, the FPF elevates considerably. This sudden change in the amount of FPF could imply that the impact force required for breaking drug particle contacts, is averagely provided at the impact velocity between 1 and 2 m/s. Moreover, the amount of FPF becomes almost constant at high enough impact velocity. This is due to the adequate impact energy that is provided for almost all drug particles to detach from their contact surfaces. In such a case, only drug particles at certain locations or the ones with multiple contacts can still remain on the carrier surface.

5.2 Fine particle size

The size of fine excipient particle affects different mechanisms in the mixing. Therefore, the data in this section can provide us with useful information to be able to discover the governing mechanisms in the system. However, great care must be taken in order to distinguish between the effect of particle number and the particle size as both parameters are changing while the total fine particle mass ratio is kept constant. By looking at the corresponding results it is possible to determine which factor (size or number of fine particles) has a higher effect on the mixing performance.

Similar to the previous section, different cases are investigated based on the following factors: 1) Kinetic energy, 2) Number of different contacts, 3) Overlap, 4) Agglomerates quality, and 5) Dispersion ratio.

5.2.1 Kinetic energy

The data regarding the particle kinetic energy is used to make sure that simulations have been run correctly in terms of the kinetic condition. These data are divided into rotational and translational kinetic energy to also consider the effect of particle characteristics on the mixing performance. With that said, the translational kinetic energy is, first, presented to confirm that the mixing condition has been successfully implemented in the system followed by the rotational kinetic energy to reveal the effect of particle size on the mixing performance.

Translational kinetic energy

The accumulated translational kinetic energy is illustrated for cases with different fine particle sizes in Figure 27.

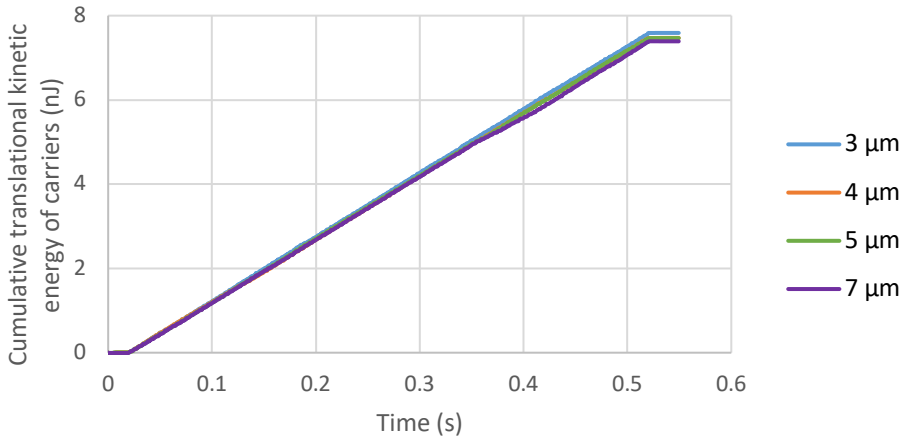


FIGURE 27, THE CUMULATIVE KINETIC ENERGY OF CARRIERS OVER TIME FOR DIFFERENT FINE PARTICLE SIZES

From the graph, it can be seen that different sizes of a fine particle do not affect the translational kinetic energy stored by carrier particles. The results are in line with what was discussed earlier regarding the translational kinetic energy of particles that is only a function of vessel conditions including the vibration amplitude and frequency.

ROTATIONAL KINETIC ENERGY

The rotational kinetic energy of carriers can be affected by particle characteristics as the friction coefficient, which is a function of particle properties and acts as a resistance against the rotational movement of particles. Therefore, the rotational kinetic energy should change with the fine particle size, which determines the size of the adhesion force and thus, the magnitude of friction force. Figure 28 shows the effect of fine particle size on the rotational kinetic energy of carriers over simulation time.

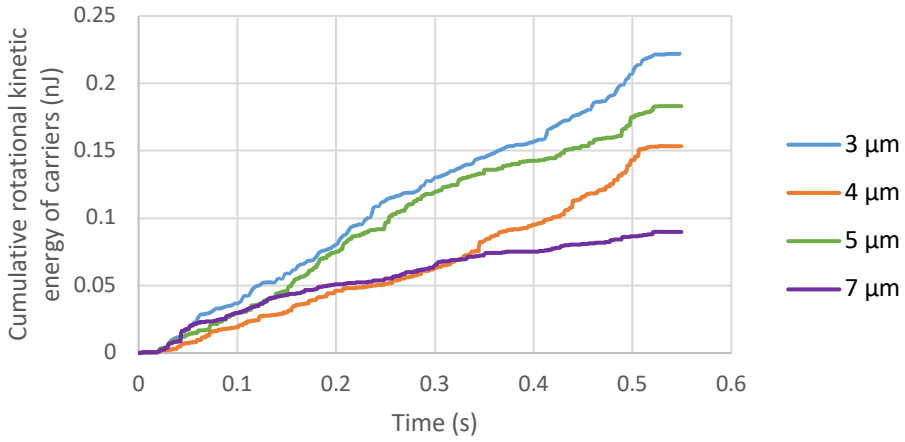


FIGURE 28, THE CUMULATIVE KINETIC ENERGY OF CARRIERS OVER TIME FOR DIFFERENT FINE PARTICLE SIZES

As can be seen, no specific pattern can be observed from the graph if all cases are taken into account. Therefore, there is not any specific advantage between the size and the number of fine particles. On the other hand, if the data regarding the case with 5-micrometer fine particle size is neglected, it can be seen that the rotational kinetic energy goes down with an increase in the size of fine particle size. Thereby, the number of particles has a higher influence on particle rotation in general.

Both reasonings could be true and there is a need to have more data available in order to make a statistically significant conclusion out of these results. Consequently, drawing any general conclusion is avoided at this point.

5.2.2 NUMBER OF CONTACTS

In this section numbers of different contacts are studied based on the size of fine particles at the completion of the simulation. For more clarification, the trend regarding the number of drug-drug contacts is investigated to have a better understanding of the mixing process. Furthermore, for some cases, the number of contacts is divided by the total surface area of fine excipient particles to account for both the size and the number of fine particles in contact.

NUMBER OF DRUG-DRUG CONTACTS

The following results show the effect of fine particle size on the mixing performance over the simulation time.

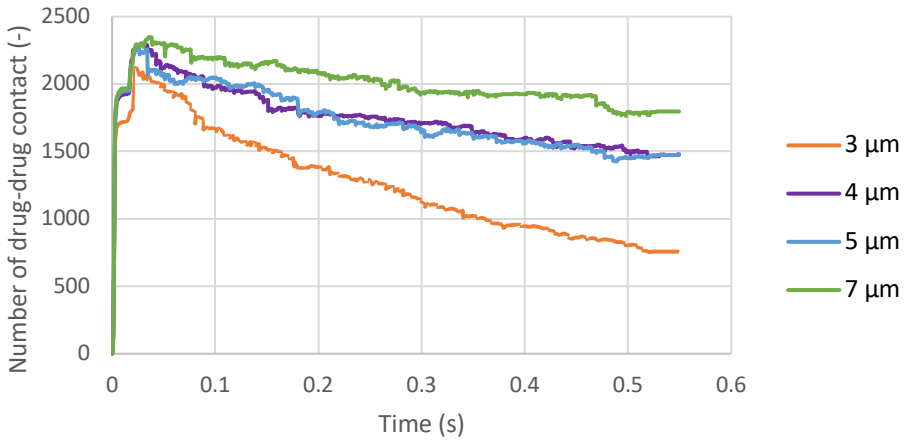


FIGURE 29, THE NUMBER OF DRUG-DRUG CONTACTS OVER TIME AS A FUNCTION FINE PARTICLE SIZE

As can be seen from Figure 29, the number of drug-drug contacts increases with the size of fine particles. Having said that, the number of fine particles is a more determining factor for breaking drug agglomerates compared to the size of fine particles, considering the trade-off that exists between these two parameters. Moreover, it can be understood from the trend of all cases that the rate of drug-drug detachment decreases with time to reach a pseudo-steady state condition at the end of the mixing.

The impact of the fine particle size is also studied based on the number of drug-drug contacts divided by the total surface area of fine particles. This is done to simultaneously account for the effect of both the size and number of fine excipient particles rather than only taking one of these parameters into consideration. Figure 30, shows the data regarding the number of drug-drug contacts as well as the number of drug-drug contacts divided by the total fine particle surface area after mixing. These results are plotted as a function of the fine particle size.

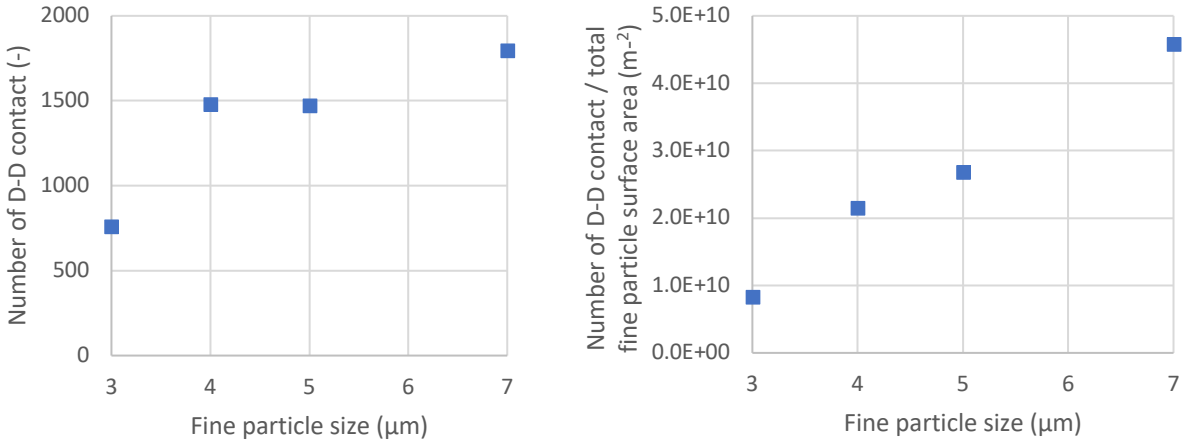


FIGURE 30, THE EFFECT OF THE FINE PARTICLE SIZE ON THE NUMBER OF DRUG-DRUG CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACTS OVER THE TOTAL FINE PARTICLE SURFACE AREA

As can be seen, both graphs show an ascending trend in terms of the number of drug-drug contacts as a function of the fine particle size. However, the rate of change is higher in the right graph ,and therefore, the smaller fine particles play a more effective role during the ternary formulation.

NUMBER OF DRUG-CARRIER CONTACTS

Figure 31 illustrates how the number of drug-carrier contacts as well as the number of drug particles in contact with carriers are affected by changing the size of fine excipient particles.

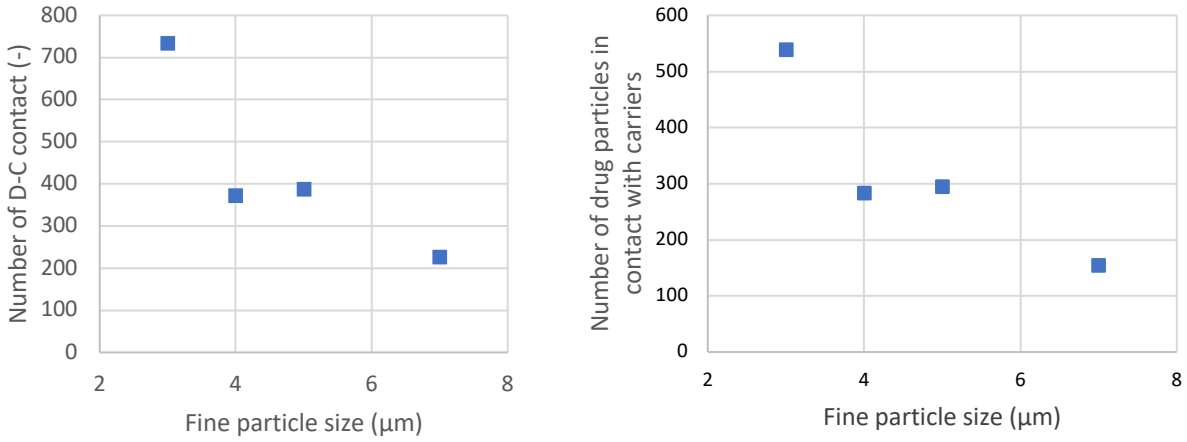


FIGURE 31, THE EFFECT OF THE FINE PARTICLE SIZE ON; LEFT) THE NUMBER OF DRUG-CARRIER CONTACTS, RIGHT) THE NUMBER OF DRUG PARTICLES ON THE CARRIER SURFACE

As can be observed, both figures depict a decreasing trend with almost the same slope. Therefore, similar to the previous section, it is argued that smaller fine particles are more efficient in making drug-fine contacts. Having more particles with a less volume size causes more drug-drug detachment, and subsequently, there are more drug particles available to make contact with the carrier surface. Having said that, the results for drug-carrier contact is in line with the results regarding the drug-drug contact.

As discussed above, each particle can have multiple contacts with the carrier surface. Therefore, knowing the effect of the fine particle size on the average number of bonds per drug particle in contact could be beneficial for studying the active site theory. Figure 32 represents such data for cases with different fine particle sizes.

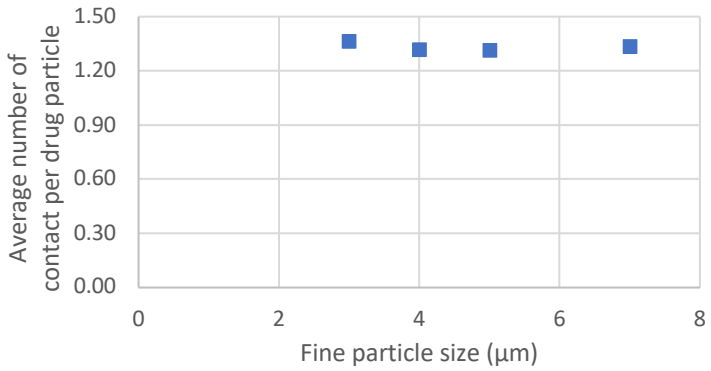


FIGURE 32, THE EFFECT OF THE FINE PARTICLE SIZE ON THE AVERAGE NUMBER OF CONTACTS PER NUMBER OF DRUG PARTICLES

As can be observed, the average number of contacts for drug particles is almost constant regardless of the fine particle size. Moreover, each drug particle in contact has roughly 1.33 bonds with the carrier surface on average.

NUMBER OF DRUG-FINE CONTACTS

In this section, the number of drug-fine contacts is plotted as a function of the fine particle size. To account for both the effect of size and number of fine particles, the contact number is divided by the total surface area of fine particles. With that said, Figure 33 shows how the fine particle size can influence on data regarding the number of drug-fine contacts.

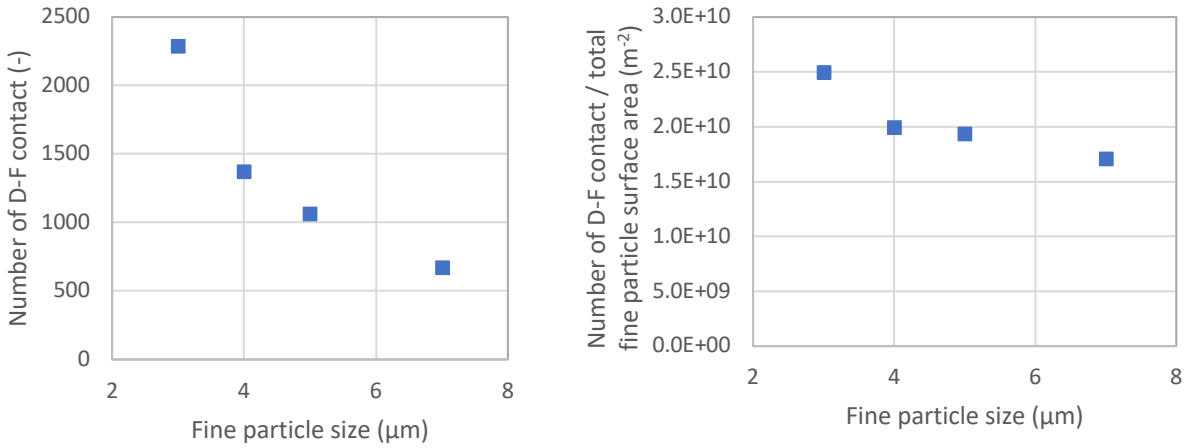


FIGURE 33, THE EFFECT OF THE FINE PARTICLE SIZE ON THE NUMBER OF DRUG-FINE CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACT OVER THE TOTAL FINE PARTICLE SURFACE AREA

Both graphs show a reduction with an increase in the number of fine particle sizes. This corresponds to the fact that fine particles can make more contacts with drug particles that have a higher total surface area. This shows consistency with results from previous sections regarding other types of contacts for drug particles.

NUMBER OF FINE-CARRIER CONTACTS

As discussed earlier, the number of fine-carrier contacts is important when it comes to the active site theory. By looking at the number of contacts in addition to the average size of the adhesion force for such contacts, the effect of fine particle size on the active site theory can be revealed. Figure 34, shows the number of fine-carrier contacts as a function of the fine particle size. Also, the number of contacts is divided by the total fine particle surface area to account for both the number and the size of fine particles.

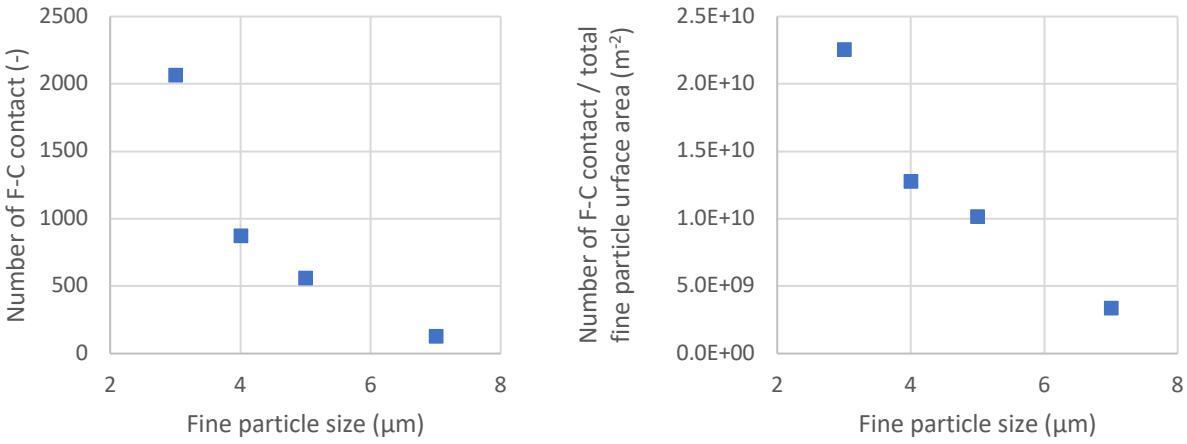


FIGURE 34, THE EFFECT OF THE FINE PARTICLE SIZE ON THE NUMBER OF FINE-CARRIER CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACTS OVER THE TOTAL FINE PARTICLE SURFACE AREA

As can be seen from both graphs, the results show a descending trend with increasing the fine particle size. In other words, smaller fine particles make more contact with carrier particles overall. Accordingly, in those cases, high active sites are more occupied by fine particles, which in turn leaves less space for drug particles to have a strong bond with carriers.

5.2.3 ADHESION FORCE AND OVERLAP

The size of the adhesion force between different particles determines how strong each contact has been established. Such a result for drug-carrier contact is of great importance as it can reveal useful information regarding the mechanism for the active site theory. In other words, by looking at the average data for drug-carrier normal adhesion, it is possible to check how the contribution of the active site theory alters with a change in the size of fine particles. This can later help us to eventually determine the governing mechanism within the studied range. With that said, only results regarding the drug-carrier contacts are studied in this section. The same reasoning is also true for overlap since adhesion force and overlap are two related concepts and thus, only overlap for the drug-carrier contact is studied.

OVERLAP

Overlap is the translation of the adhesion force in the form of particle deformation and thus it represents the size of adhesion force. However, due to the small range of overlap compared to that of adhesion force, the results for overlap are relatively similar but it can still be used to see if there is any specific trend. With that said, the normalized number of drug-carrier is accumulatively plotted against the magnitude of the normal overlap. The corresponding result is shown in Figure 35 for cases with different fine particle sizes.

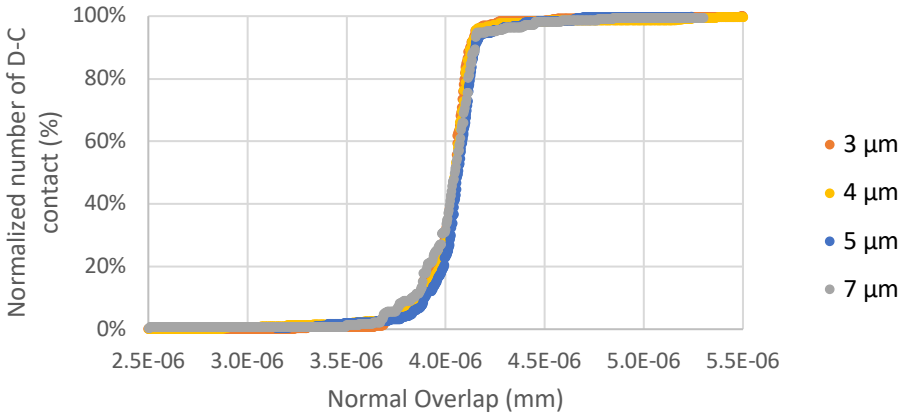


FIGURE 35, THE NORMALIZED-CUMULATIVE NUMBER OF DRUG-CARRIER CONTACTS AS A FUNCTION OF THE NORMAL OVERLAP FOR CASES WITH DIFFERENT FINE PARTICLE SIZES

As can be seen, the graph shows almost the same trend regardless of the size of fine particles, and thereby the distribution of the normal overlap is not affected by the fine particle size in general. However, the range of normal overlap changes with the change in the fine particle size but no particular pattern has been observed.

The average size of normal overlap is studied at the end of the mixing to monitor the effect of fine particle size on the drug-carrier contacts. Figure 36 shows the average drug-carrier normal overlap with varying the size of fine particles.

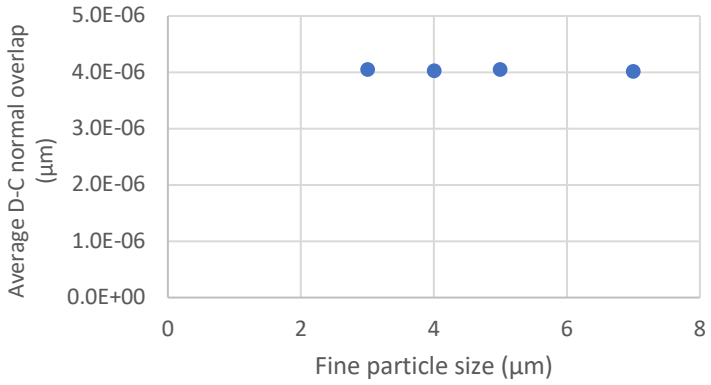


FIGURE 36, THE AVERAGE MAGNITUDE OF THE NORMAL OVERLAP AS A FUNCTION OF THE FINE PARTICLE SIZE

Similar to the previous figure, the average size of overlap is constant regardless of the fine particle size. Therefore, the strength of drug-carrier bonds is not affected by the size of the fine particles.

5.2.4 AGGLOMERATES QUALITY

The drug-fine agglomerates are investigated in order to study the impact of the agglomeration theory on the mixing performance. This investigation is done according to the minimum number of particles that constitute each drug-fine cluster. Having said that, drug-fine clusters are studied in terms of the number of clusters created as well as the number of drug and fine particles that are involved within those clusters. Such results are illustrated in Figure 37.

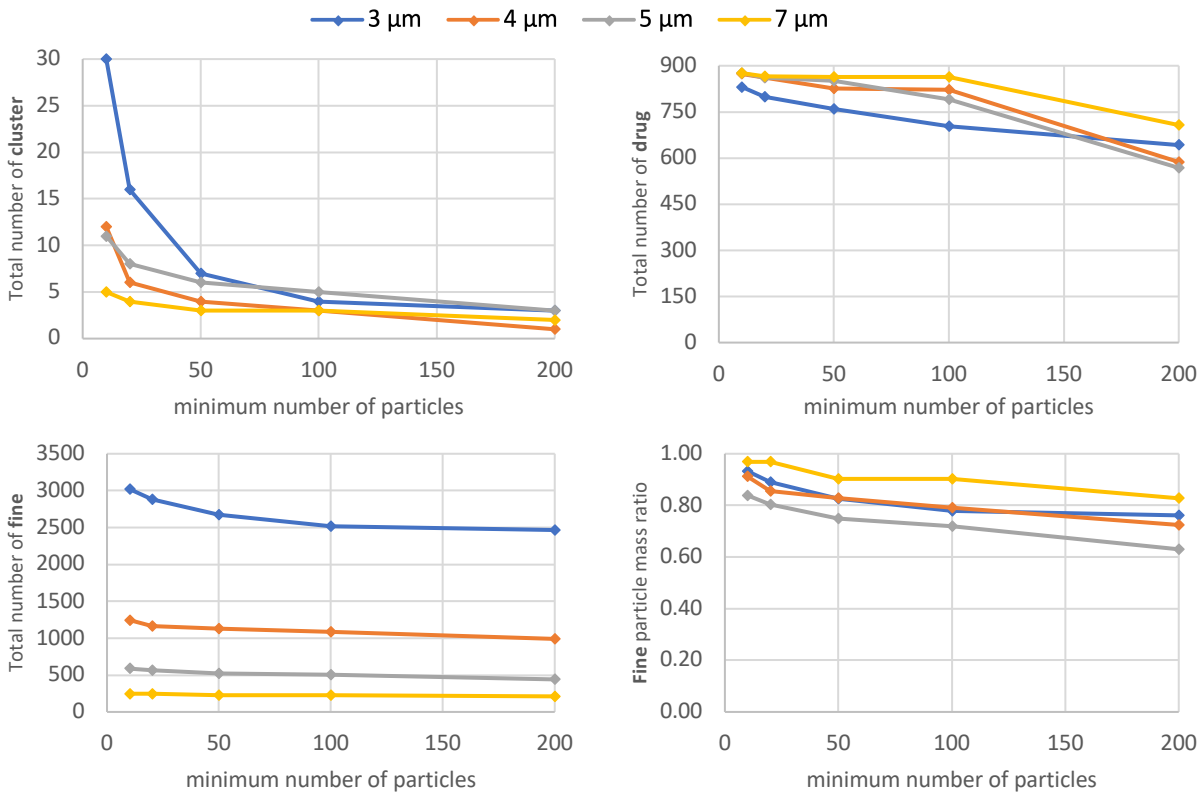


FIGURE 37, THE TOTAL NUMBER OF CLUSTERS AND THEIR CONSTITUENT DRUG AND FINE PARTICLES WITHIN DRUG-FINE AGGLOMERATES

From the graph regarding the number of clusters, it can be understood that smaller fine particles make more agglomerates during the mixing time. However, these agglomerates contain a smaller number of drug particles in total, according to the graph for the number of drug particles. Moreover, there is a higher number of fine particles for cases with a lower fine particle size but no specific trend has been observed in terms of the total fine particle mass ratio in such clusters.

5.2.5 DISPERSION

The dispersion of drug particles is of great importance to discriminate between different mixing mechanisms. This is done by tracking the level of drug dispersity as a result of a particle-wall collision at different impact velocities. Figure 38 shows the corresponded result based on the drug-fine particle fraction for cases with different fine particle sizes.

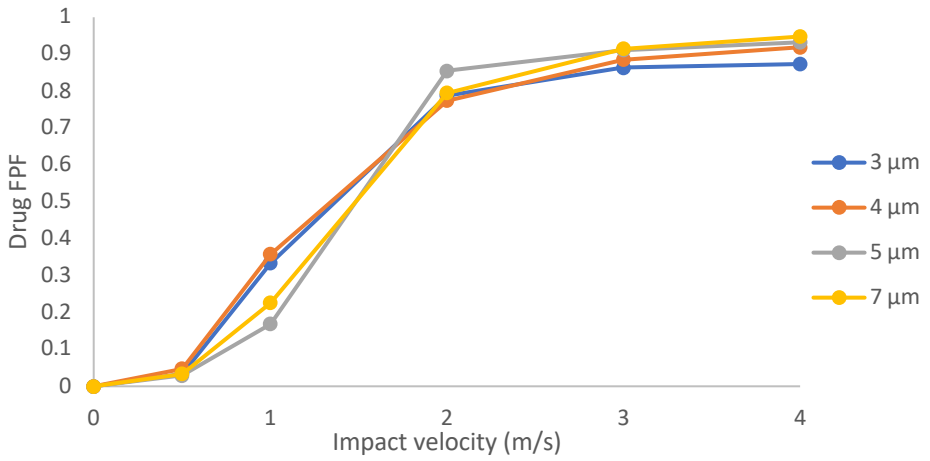


FIGURE 38, THE DISPERSION OF DRUG PARTICLES AS A RESULT OF WALL-COLLISION AT DIFFERENT IMPACT VELOCITIES FOR CASES WITH DIFFERENT SIZES OF FINE PARTICLES

From the graph it can be understood that results show different behavior within different ranges of impact velocities. More clearly, at low impact velocities, (up to 2 m/s) it can be observed that smaller fine particles result in a higher rate of drug dispersion from a general perspective. This is opposite of what happens at high impact velocities where, cases with a higher fine particle size cause more drug particles to individually detach from the carrier surface. No specific order has been observed, whereas, in high velocities, dispersion increases with the size of fine particles. However, the difference between cases is not that significant at very high impact velocities.

5.3 FINE PARTICLE LOADING RATIO

The number of fine excipients added to the system can change the contribution of all formulation mechanisms in the mixing. The process of how such a variable can affect different formulation mechanisms was discussed in section 3.3 and thus no more detailed explanation is brought here. However, it should be mentioned that the fine particle mass ratio has a direct relationship with the effect of different formulation mechanisms. In other words, by adding more fine particles into the system, the formulation mechanisms will change as following: 1) Active site theory, there are more fine particles available to occupy high adhesive areas of carriers. 2) Agglomeration theory, more drug-fine agglomerates with a higher number of drug particles can be created. 3) Buffer theory, more fine particles can act as a shelter for drug particles 4) Fluidization reinforcement theory, the presence of more particles in the system makes the MFV higher. Furthermore, since the effect of all mechanisms will increase by adding more fine particles into the

system, distinguishing different theories becomes challenging, and finding the exact governing mechanism requires considering all results together.

With that said, the effect of fine particle mass ratio is studied on different system characteristics. Similar to the previous section, these characteristics are categorized into kinetic energy, the number of contacts, adhesion force, and overlap, quality of agglomerates and eventually rate of dispersion.

5.3.1 KINETIC ENERGY

The kinetic energy of carriers is studied to make sure that simulations have been run correctly. This is done by looking at the results to check if the corresponding trends are in line with what to be expected.

TRANSLATIONAL KINETIC ENERGY

The translational kinetic energy regarding the carrier particles is plotted to see if the number of fine particles can affect the vibration energy induced on the system. Figure 39 shows such results for cases with different amounts of fine particles inserted into the vessel.

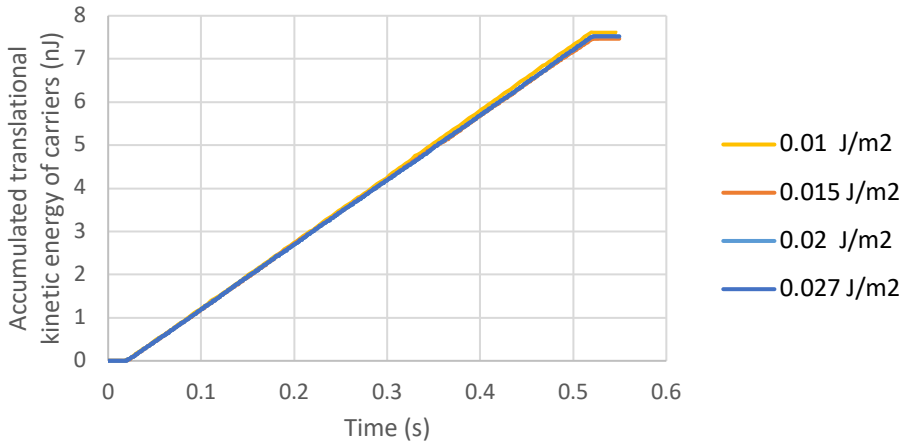


FIGURE 39, THE ACCUMULATED KINETIC ENERGY OF CARRIERS OVER SIMULATION TIME FOR DIFFERENT FINE PARTICLE MASS RATIOS

Similar to the results for different fine particle sizes, the translational kinetic energy induced on carriers is regardless of the number of fine particles. This was expected as the exchange of kinetic energy must be a function of the mixing condition, which is identical in all cases.

ROTATIONAL KINETIC ENERGY

The rotational kinetic energy is studied to see how the fine particle mass ratio can influence the rotation of carrier particles and thus the mixing performance. Figure 40 illustrates the accumulated rotational kinetic energy regarding the carrier particles as a function of the total amount of fine particles added to the system.

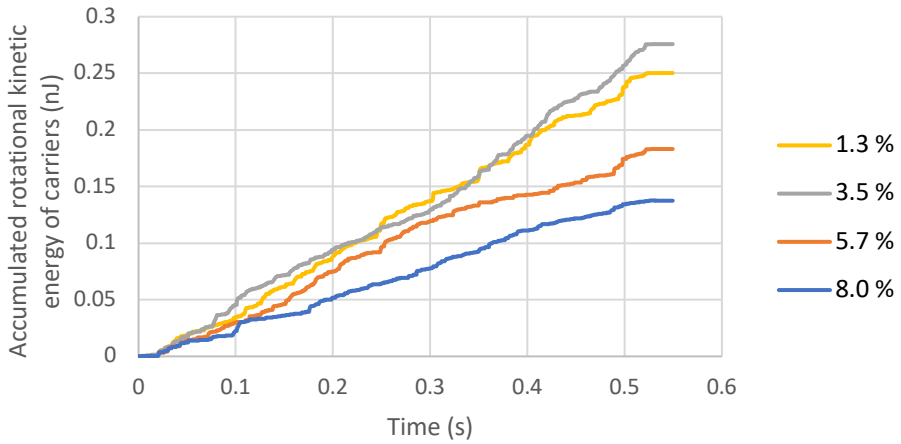


FIGURE 40, THE CUMULATIVE ROTATIONAL KINETIC ENERGY OF CARRIER PARTICLES AS A FUNCTION OF THE FINE PARTICLE MASS RATIO

At the first glance, no specific trend is observed from the graph as two cases with the least fine particle mass ratio show more or less the same pattern. This can happen as the initial carriers' position changes for different cases due to the initialization of simulations. But from a more general perspective, meaning that by considering the main trend among different cases, it can be observed that the kinetic energy increases with a reduction in the number of fine particles. This makes sense as the rotation of carrier particles should be restricted by the presence of more particles since particles prevent the carrier rotation by friction force. Besides, the presence of more particles in the system leaves less space for other particles to move freely within the vessel.

5.3.2 NUMBER OF CONTACTS

Number of contacts between different particles can be used to see how the fine particle mass ratio can influence the simulation progress. With that said, in this part, the number of particle-particle contacts, as well as the number of bonds divided by the number of fine particles are reported as a function of the fine particle mass ratio.

NUMBER OF DRUG-DRUG CONTACTS

Number of drug-drug contacts is important to check how the breakage of drug agglomerates is affected by inserting more fine particles in the system. Figure 41 shows the data regarding the number of drug-drug contacts in terms of the fine particle mass ratio. The corresponding data is presented in terms of both the number of contacts and the number of contacts over the total number of fine particles.

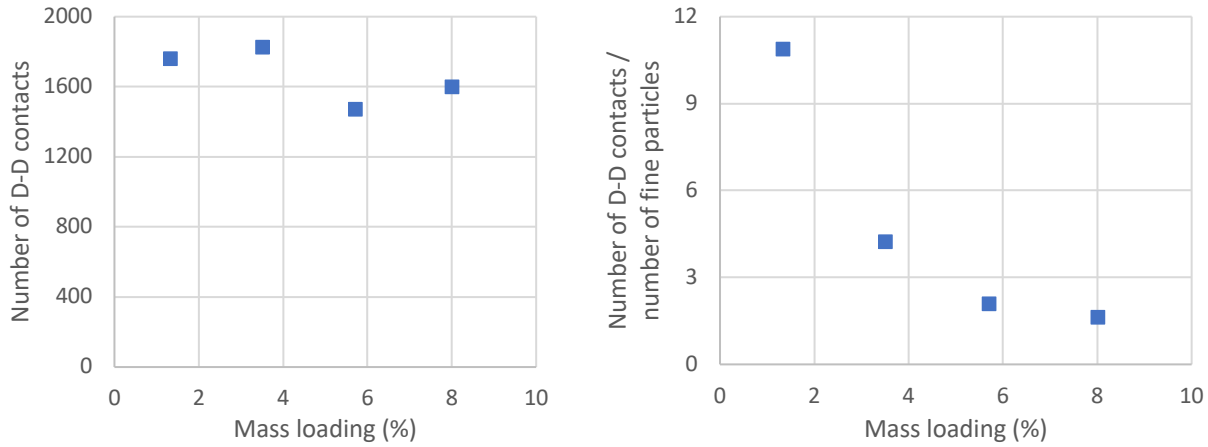


FIGURE 41, THE EFFECT OF THE FINE PARTICLE MASS RATIO ON THE NUMBER OF DRUG-DRUG CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACTS OVER THE NUMBER OF FINE PARTICLES

In the figure on the left side, no significant change has been observed between cases with different numbers of fine particles in such a range. However, the case with 5.7 % fine particle mass loading (the base case) shows the minimum number of drug-drug contacts which may correspond to the optimum condition at that point. Regarding the small changes that occurred in the graph, they can be related to the initialization of the simulation or the random movement of particles during the mixing. Therefore, no general conclusion is drawn from the corresponding graph.

By looking at the data in the right figure, it can be seen that the graph shows a descending trend with an increase in the fine particle mass loading. Therefore, the more fine particles added to the system, the less the fine particles become effective to break drug agglomerates.

NUMBER OF DRUG-CARRIER CONTACTS

By looking at the number of drug-carrier contacts it is possible to estimate what portion of drug particles that have made contact with coarse carriers. Owing to the exact number of drug particles in contact, the strength of those bonds in terms of the number of contacts per drug particle is revealed. This can help us to analyze the quality of the bonds created between the drug and carrier particles, which is something substantial regarding the active site theory.

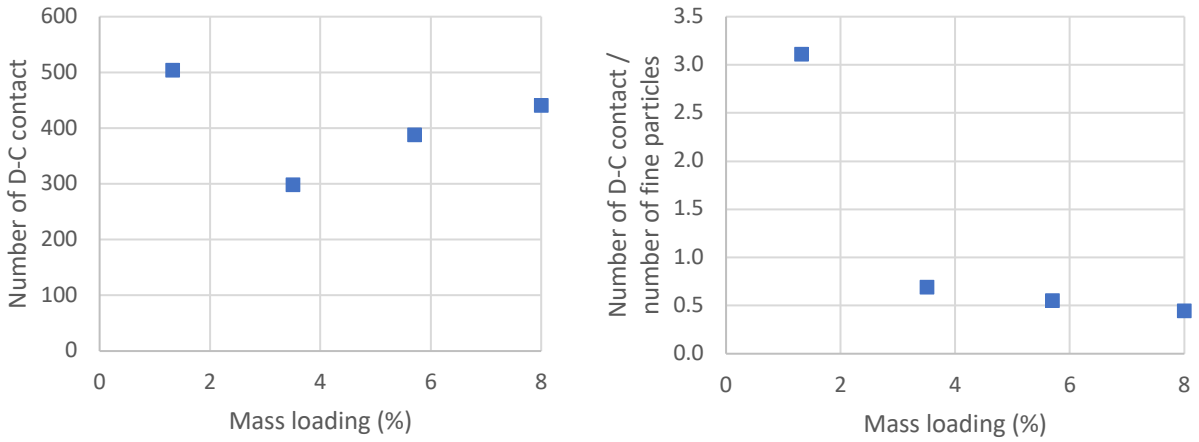


FIGURE 42, THE EFFECT OF THE FINE PARTICLE MASS RATIO ON THE NUMBER OF DRUG-CARRIER CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACTS OVER THE TOTAL NUMBER OF FINE PARTICLES

The graph on the left side experiences a minimum at around 3.5 % fine particle mass ratio. For fine particles with less than 3.5 % mass ratio, the graph shows a descending trend as adding more fine particles in the system includes more drug particles in drug-fine agglomerates. For cases with higher mass loading than 3.5 %, the total number of drug-carrier contacts increases with the fine particle mass ratio. However, it should be mentioned that to be able to make a valid conclusion out of such a figure there is a need to have more data.

Moreover, it can be seen from the figure on the right side that by adding more fine excipients into the system fine particles are individually less effective during the ternary formulation.

Another parameter important is the number of drug-carrier contacts over the number of drug particles in contact since each drug particle can have multiple contacts with the carrier surface. This parameter gives us the average number of contacts for each drug particle which is presented in Figure 43.

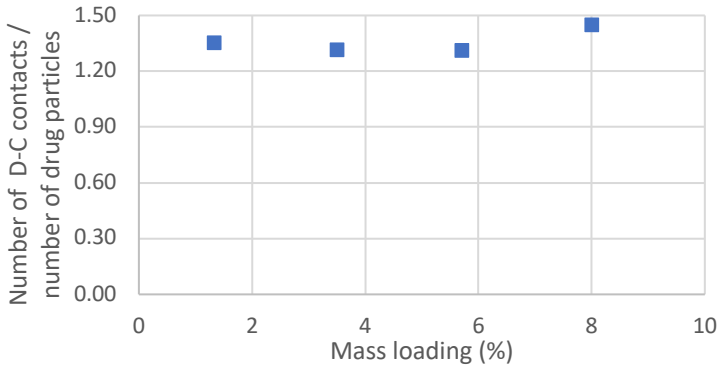


FIGURE 43, THE EFFECT OF THE FINE PARTICLE ON THE AVERAGE NUMBER OF CONTACTS PER NUMBER OF DRUG PARTICLES

According to the figure, changing the fine particle mass ratio in the ternary formulation cannot affect the average number of drug-carrier contacts. Moreover, each drug particle in contact has roughly 1.35 bonds with the carrier surface on average.

NUMBER OF DRUG-FINE CONTACTS

Number of drug-fine contacts at the completion of the simulation can give us an estimation from the number and size of agglomerates created after the mixing. However, for making a valid conclusion, the data regarding the number of particles in contact rather than the number of contacts needs to be taken into consideration too. With that said, the effect of the fine particle mass ratio on the number of drug-fine contacts is investigated in Figure 44. The results correspond to the data after the mixing.

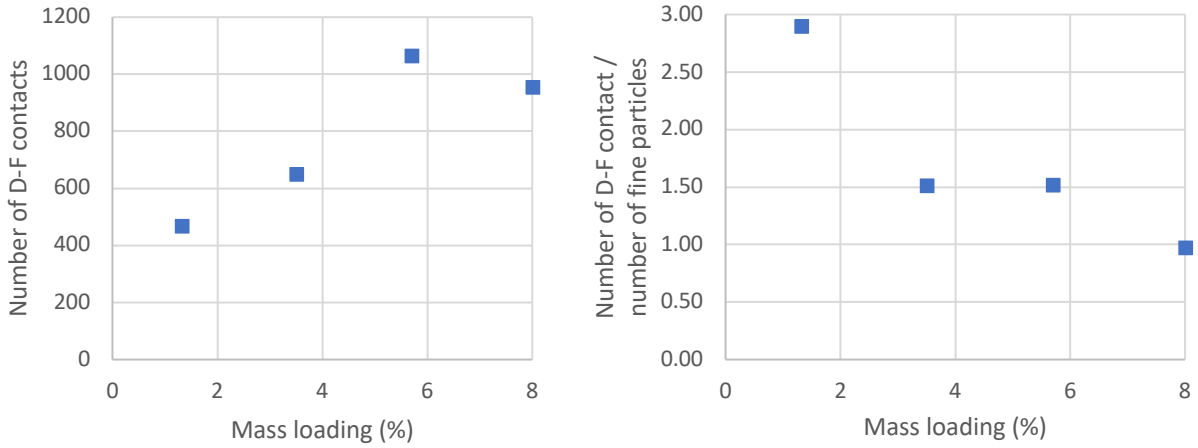


FIGURE 44, THE EFFECT OF THE FINE PARTICLE MASS RATIO ON THE NUMBER OF DRUG-FINE CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACTS OVER THE TOTAL NUMBER OF FINE PARTICLES

From the figure on the left side, the number of contacts, from a general perspective, increases by increasing the mass loading of fine particles. The trend is aligned with what was expected since logically there is a higher probability for drug particles to collide with fine particles if more fine particles are added to the control volume.

In contrast to the first graph, the figure on the right-hand side shows a descending trend if the number of drug-carrier contacts is divided by the number of fine particles. As a result, the effect of each fine excipient particle decreases by adding a larger portion of this additive.

NUMBER OF FINE-CARRIER CONTACTS

Number of fine-carrier contacts is important when it comes to the active site theory. The results will be used to understand to what extend the carrier surface area has been occupied by fine particles. With that said, the number of fine-carrier contacts is plotted against the number of fine particles in Figure 45.

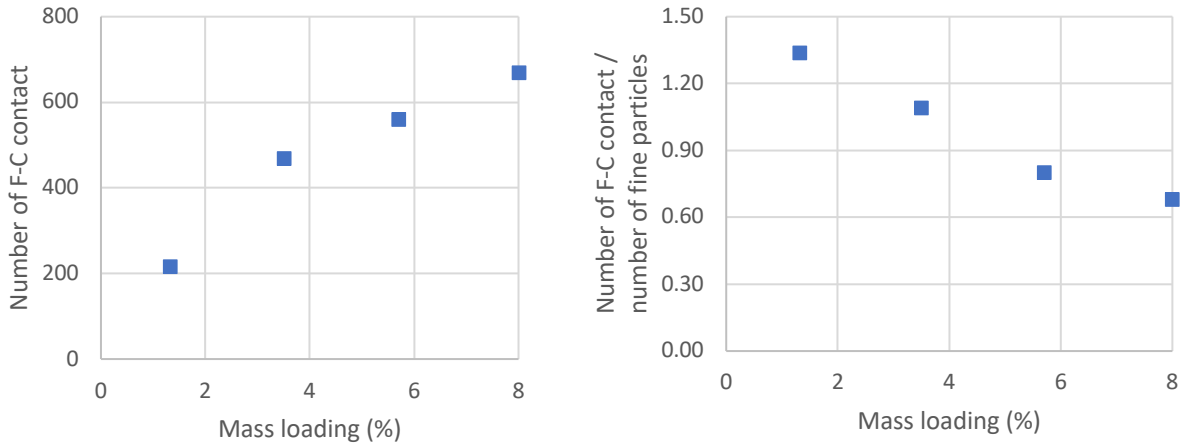


FIGURE 45, THE EFFECT OF THE FINE PARTICLE MASS RATIO ON THE NUMBER OF FINE-CARRIER CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACTS OVER THE TOTAL NUMBER OF FINE PARTICLES

It can be seen that the number of contacts increases with the number of fine particles from the figure on the left side. This completely makes sense as there are more fine excipients available to make contact with any particle in cases with a higher portion of fine particles. On the other hand, there is less chance for each fine particle to establish a bond with the coarse carrier if there exists a larger number of fine particles in the system.

5.3.3 ADHESION FORCE AND OVERLAP

Adhesion force and overlap are studied as a function of fine particle mass ratio to see how the mechanisms regarding the active site theory and buffer theory can affect the simulation output. The latter mechanism is affected since the probability of fine particles for acting as a shelter against drug-carrier collision changes with change in the number of fine particles. Subsequently, the average size of the drug-carrier adhesion force should alter with fine particle mass loading, plus a better shelter must results in a lower size of adhesion force according to the mechanism regarding the buffer theory.

Furthermore, from the active site theory perspective, more fine particles in the system should leave fewer areas for drug particles to attach to carrier surfaces that have high adhesive energy. Therefore, the average size of the drug-carrier adhesion force should be changed as a function of the fine particle mass ratio and thus reveals the effect of the active site theory on the mixing.

Due to the reasons mentioned earlier, the size of the adhesion force cannot be studied directly, and therefore, it is only possible to rely on data regarding the size of overlap, which is the translation of adhesion force to particles deformation.

OVERLAP

As discussed earlier the range of change in the size of overlap is significantly smaller than that of adhesion force. Therefore, similar to the previous section regarding the fine particle size, the change in the amount of fine particle should not make a big difference in terms of the magnitude of overlap, while the drug particle characteristics are the same for all cases. Figure 46 illustrates the normalized number of drug-carrier contacts as a function of normal overlap for cases with different fine particle mass ratios.

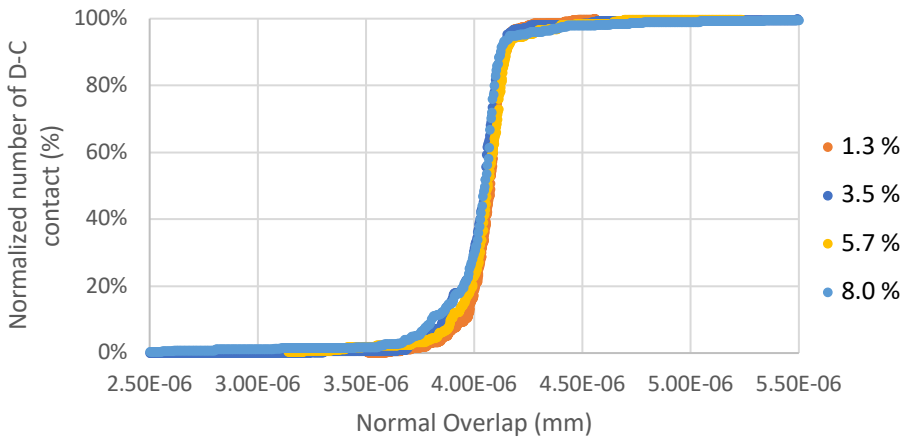


FIGURE 46, THE NORMALIZED-ACCUMULATED NUMBER OF DRUG-CARRIER CONTACTS AS A FUNCTION OF THE NORMAL OVERLAP FOR CASES WITH DIFFERENT FINE PARTICLE MASS RATOS

From the graph, it can be understood that cases with different amounts of fine particle fractions show similar trends in terms of the overlap size. This implies that the size of overlap between drug and carrier particles is independent of the number of fine excipients added to the mixing.

The effect of the fine particle mass loading on the average size of the drug-carrier overlap is also studied. Such results are presented in Figure 47.

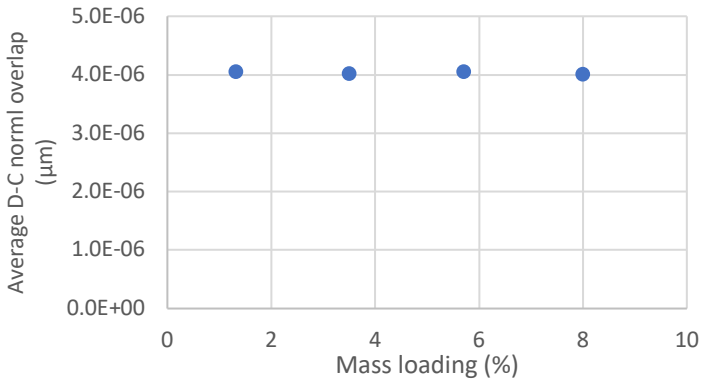


FIGURE 47, THE AVERAGE DRUG-CARRIER NORMAL OVERLAP AS A FUNCTION OF THE FINE PARTICLE CHARACTERISTICS

As can be seen, the average size of normal overlap between drug and carrier particles is independent of the fine particle mass ratio. With that said, the mass loading of the fine particles cannot affect the contribution of the active site theory on the ternary formulation in the studied range of variables.

5.3.4 AGGLOMERATES QUALITY

The quality of agglomerates is important to study the contribution of the agglomeration theory in the ternary formulation. This investigation is conducted according to the number of clusters created in addition to the number of drug and fine particles that exist within drug-fine clusters. Having said that, Figure 48 shows the data regarding the quality of drug-fine agglomerates according to the minimum number of particles that constitute each agglomerate.

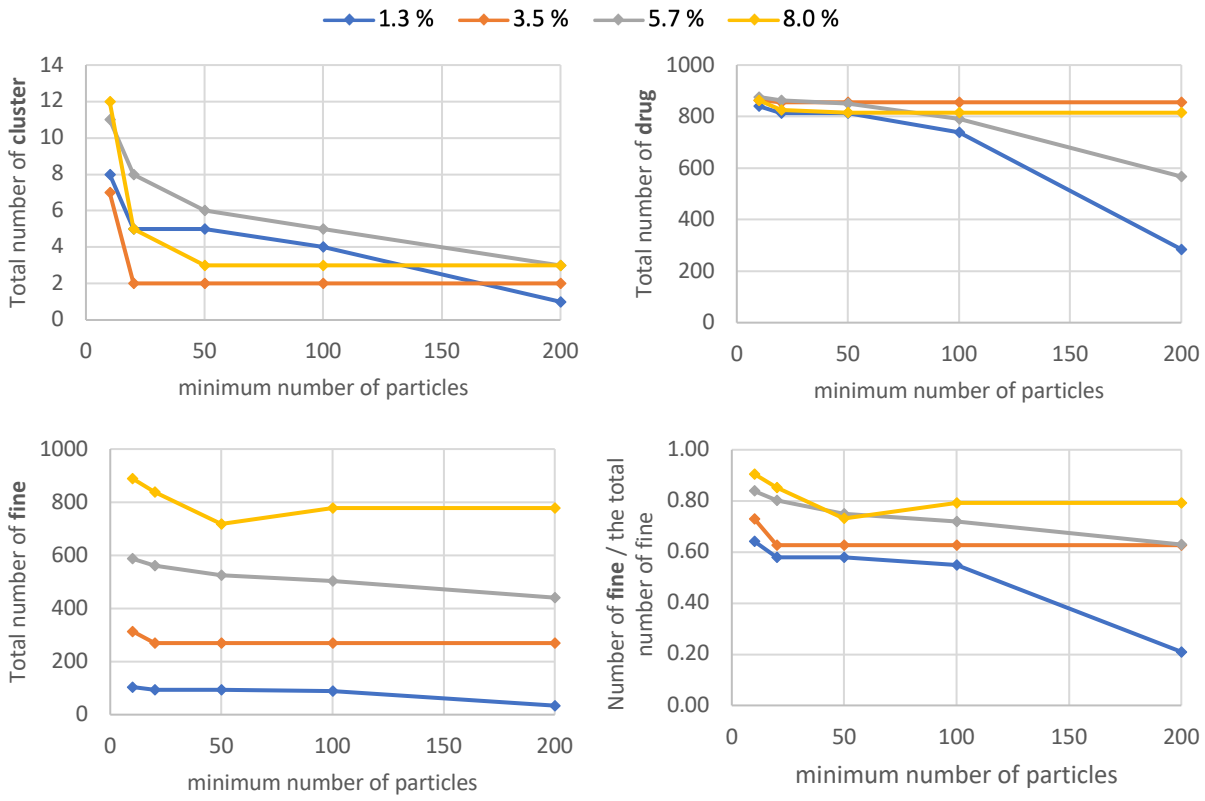


FIGURE 48, THE TOTAL NUMBER OF CLUSTERS AND THEIR CONSTITUENT DRUG AND FINE PARTICLES WITHIN DRUG-FINE AGGLOMERATES

No specific trend has been observed regarding the total number of particles except the fact that the case with the fine particle mass ratio of 5.7% results in a higher number of drug-fine agglomerates. However, the case with the highest number of fine particles creates larger clusters according to the figure regarding the total numbers of particles. Moreover, almost all cases have the same amount of drug particles within drug-fine agglomerates considering the agglomerates with the maximum 100 particles. And finally, cases with more fine particles include a higher ratio of fine particles that exist in the mixing.

5.3.5 DISPERSION

The rate of drug particle dispersion is studied to discriminate between different cases and to see what formulation mechanism has the highest level of contribution in the mixing. Figure 49 shows the ratio of drug particles that have been individually detached after a collision to an impact wall, versus impact velocity.

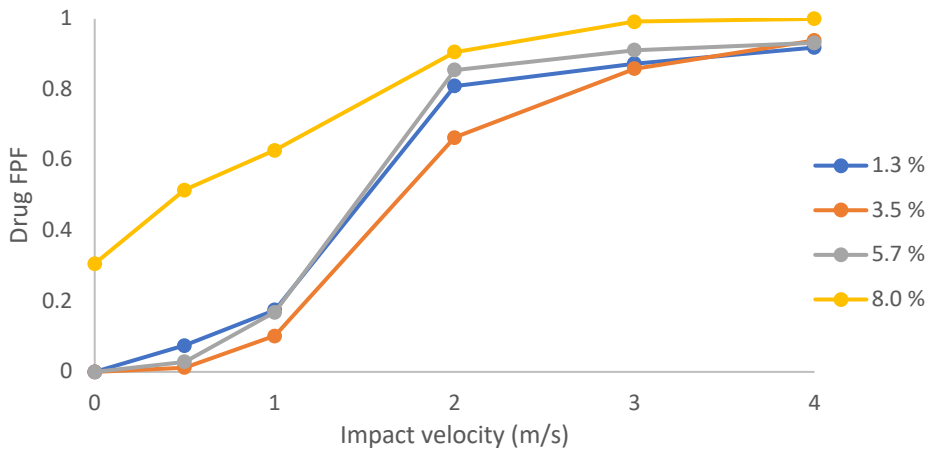


FIGURE 49, THE DISPERSION OF DRUG PARTICLES AS A RESULT OF WALL-COLLISION AT DIFFERENT IMPACT VELOCITIES FOR CASES WITH DIFFERENT AMOUNTS OF FINES ADDED

From a general perspective, it can be observed that cases with more added fine particles result in a higher rate of dispersion. This is regardless of the impact velocity value in which wall collisions occur. It should also be noted that the case with the fine particle mass ratio of 1.3 % shows inconsistency with other results. This could be due to the possible variations that may be caused by the initialization in addition to the fact that the system never reaches the steady-state condition.

5.4 DRUG PARTICLE SURFACE ENERGY

The surface energy of drug particles is studied to see the effect of such a factor on the formulation mechanisms and thus, the performance of the ternary mixing. This parameter mostly influences the first two hypotheses, i.e. the active site and the agglomeration theories. The former hypothesis is affected since drug particles with high surface energy cannot disperse well over carrier particles, and therefore, the impact of occupying active sites by means of adding fine particles will be less determining. Regarding the latter hypothesis, cases with a higher level of surface energy should result in a lower rate of drug breakage. Accordingly, drug particles show a less tendency to be mixed with fine clusters, and subsequently the less drug-fine agglomerates will be created.

One base case plus three different variations have been studied to evaluate how varying drug particle surface energy can impact on the contribution of mixing mechanisms. To do so, different parameters including the kinetic energy, number of different contacts, size of overlap and adhesion force, quality of drug-fine agglomerates, and eventually, the dispersity of system after mixing have been thoroughly analyzed.

5.4.1 KINETIC ENERGY

The kinetic energy is evaluated to first make sure that the mixing is done correctly and to see how much varying drug particle surface energy can influence the movement of particles within the mixing box. The latter gives us the overall mixing performance as a result of the drug particle characterized.

TRANSLATIONAL KINETIC ENERGY

By looking at the data regarding the translational kinetic energy it can be seen if the kinetic condition of the mixing has been correctly implemented during the simulation time. Figure 50 shows the accumulated translational kinetic energy of carrier particles versus the mixing time.

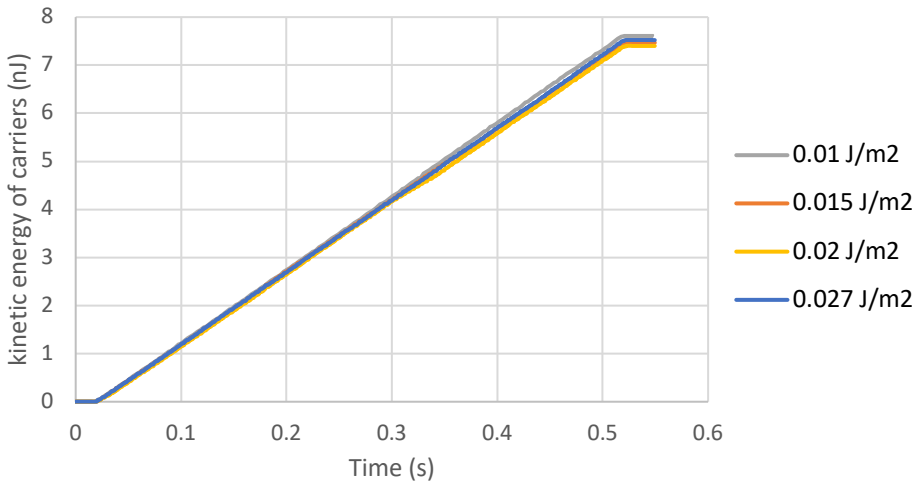


FIGURE 50, THE CUMULATIVE KINETIC ENERGY OF CARRIERS OVER SIMULATION TIME FOR DIFFERENT DRUG PARTICLE SURFACE ENERGIES

It can be seen that the carriers' kinetic energy is constant regardless of the case under investigation. Thus, the kinetic condition has been correctly implemented in all cases.

ROTATIONAL KINETIC ENERGY

The effect of the drug particle surface energy on the overall mixing performance can be studied by looking at the rotational kinetic energy of carrier particles. Figure 51 represents such results for cases with different drug particle surface energies.

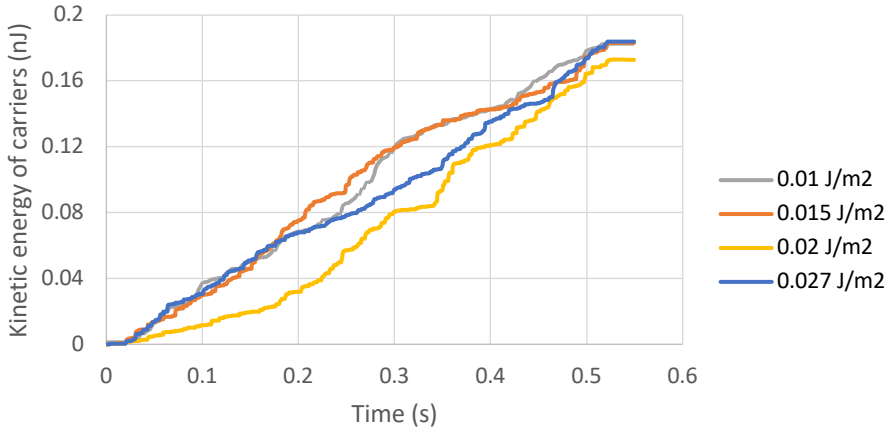


FIGURE 51, THE CUMULATIVE ROTATIONAL KINETIC ENERGY OF CARRIER PARTICLES AS A FUNCTION OF THE FINE PARTICLE MASS RATIO

According to the graph, no specific trend has been observed between different cases. Therefore, the rotation of carrier particles within the mixing box is not affected by the drug particle surface energy selected.

5.4.2 NUMBER OF CONTACTS

Investigating the number of different contacts can help us to better understand the distribution of different components within the mixing box in each case. Therefore, the effect of drug particle surface energy can be revealed for each type of contact according to the number of different bonds that have been established after the mixing.

NUMBER OF DRUG-DRUG CONTACTS

The number of drug-drug contacts after the mixing shows us the rate of drug breakage according to the selected surface energy. Figure 52 presents the number of drug-drug contacts after and during the mixing time.

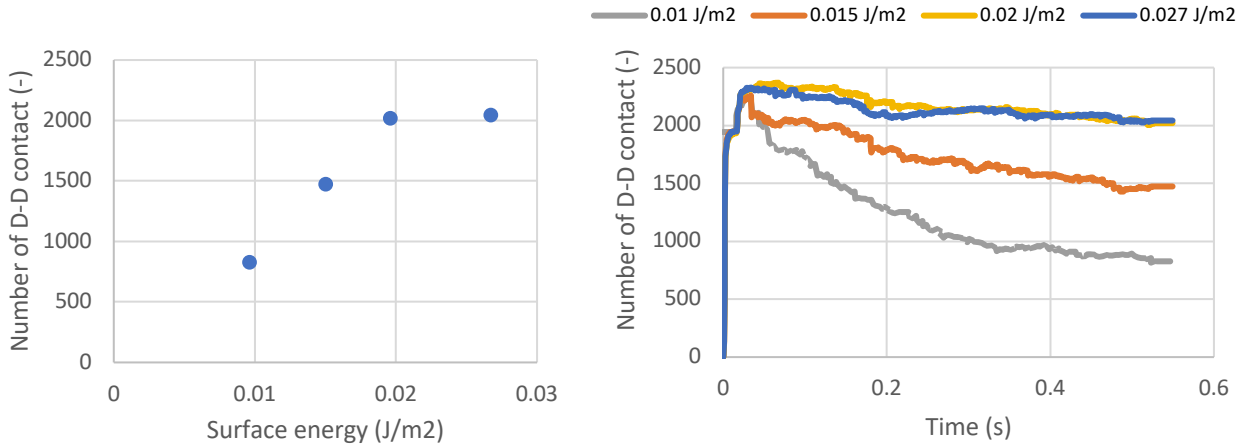


FIGURE 52, THE EFFECT OF THE DRUG PARTICLE SURFACE ENERGY ON THE NUMBER OF DRUG-DRUG CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACTS OVER THE MIXING TIME

As can be seen, the number of drug-drug contacts increases with the drug particle surface energy. This is in line with what was expected, meaning that drug particles with higher surface energy show less tendency to detach from each other. Furthermore, cases with the two highest surface energies behave similarly to each other along the ternary formulation.

NUMBER OF DRUG-CARRIER CONTACTS

By looking at the number of drug-carrier contacts it is possible to estimate what portion of drug particles that made contact with coarse carriers. Owing to the exact number of drug particles in contact, the strength of those bonds in terms of the number of contacts per drug particle is revealed. This can help us to analyze the quality of the bonds created between the drug and carrier particles, which is of high relevance in the active site theory. Figure 53 represents the number of drug-carrier contacts after and during the mixing time.

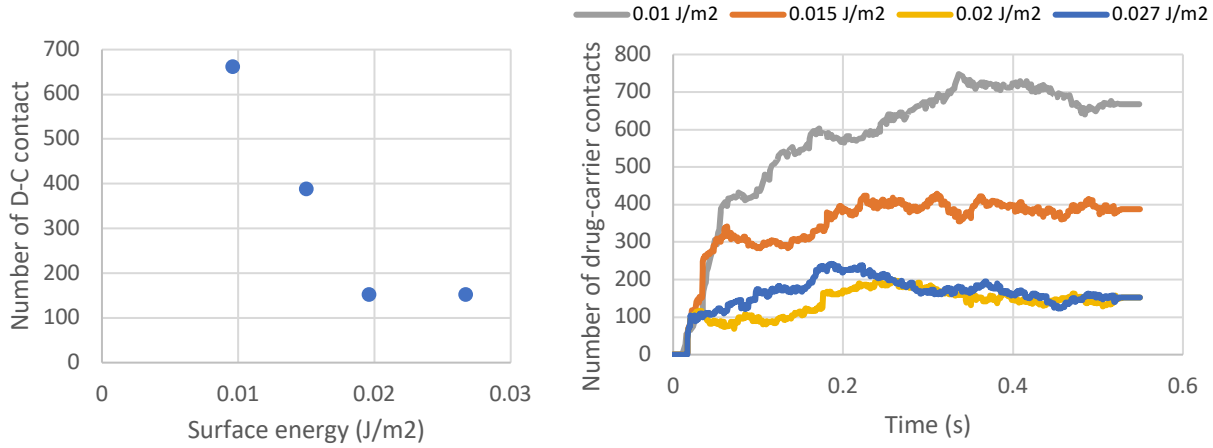


FIGURE 53, THE EFFECT OF THE DRUG PARTICLE SURFACE ENERGY ON THE NUMBER OF DRUG-CARRIER CONTACTS; LEFT) NUMBER OF CONTACTS, RIGHT) NUMBER OF CONTACTS OVER THE MIXING TIME

It can be observed that cases with higher surface energies result in a lower number of drug-carrier contacts after the mixing. This is compatible with results in the previous section, where it was observed that cases that have a higher drug particle surface energy causes lower drug deagglomeration. Therefore, there would be fewer drug particles available to make contact with the carrier surface. Moreover, similar to the previous results, cases with the two highest surface energies show a similar behavior within the mixing vessel.

Another parameter which is of great importance is the average number of contacts per drug particle in contact with the carrier surface. The corresponding result is illustrated in Figure 54, where the average number of contacts is plotted as a function of drug particle surface energy.

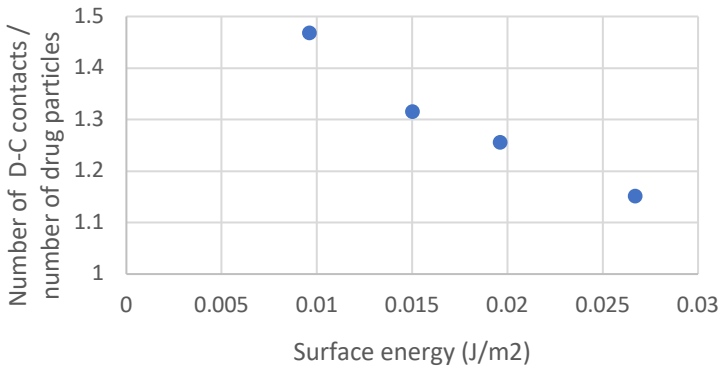


FIGURE 54, THE EFFECT OF THE DRUG PARTICLE SURFACE ENERGY ON THE AVERAGE NUMBER OF CONTACTS PER NUMBER OF DRUG PARTICLES

It can be seen that the higher particle surface energy results in the lower number of bonds on average. Less adhesive drug particles tend to make more contacts with the carrier surface as they are pushed towards local cavities.

NUMBER OF DRUG-FINE CONTACTS

The number of drug-fine contacts is important when it comes to the agglomeration theory as it shows how well drug clusters would be mixed with fine clusters. The number of drug-fine contacts is presented according to the size of drug particle surface energy in Figure 55.

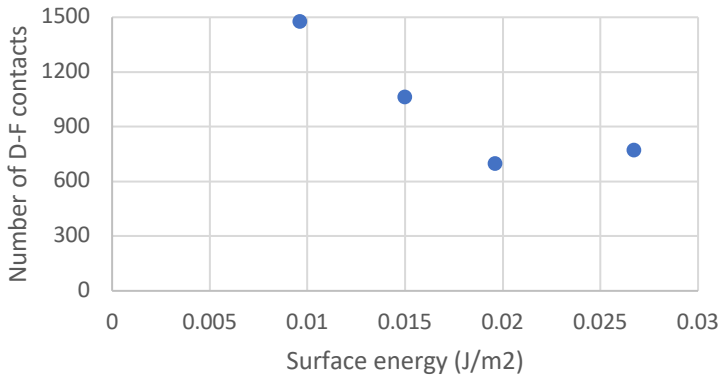


FIGURE 55, THE NUMBER OF DRUG-FINE CONTACTS VERSUS THE SIZE OF THE DRUG PARTICLE SURFACE ENERGY

In general, lower drug surface energy causes a higher number of drug-fine contacts. This shows consistency with other results in this section, meaning that cases with the high surface energies provide fewer drug particles available

to make contact with the carrier surface. Therefore, it can be expected that the contribution of agglomeration theory must be lower in cases with high surface energy.

NUMBER OF FINE-CARRIER CONTACTS

In the active site theory, the number of fine-carrier contacts plays a key role as it is argued that fine particles can occupy areas that have a high adhesion force. The number of drug-fine contacts is plotted against the size of drug particle surface energy in Figure 55.

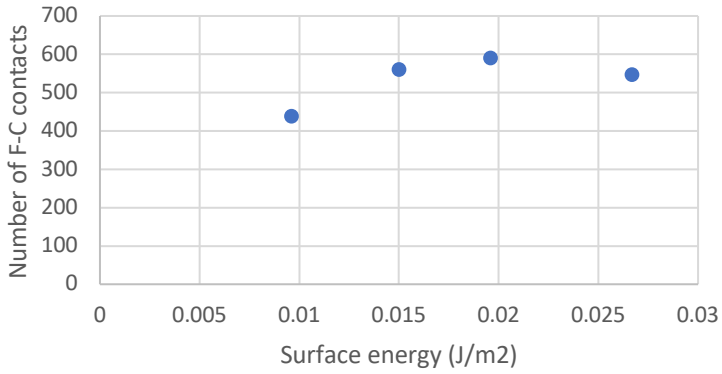


FIGURE 56, THE NUMBER OF DRUG-FINE CONTACTS VERSUS THE SIZE OF THE DRUG PARTICLE SURFACE ENERGY

As can be seen the number of contacts increases with the size of drug surface energy in general. It makes sense since there is a smaller number of fine-carrier contacts established after the mixing and thus there are more fine particles available to make contact with the carrier surface. It should also be noted that the rate of change in terms of the number of contacts decreases at high drug particle surface energies. This is due to the similar behavior that cases with the high surface energies show during the mixing.

5.4.3 ADHESION FORCE AND OVERLAP

The size of adhesion between different particles determines how strong each contact has been established. This parameter is analyzed for drug-carrier contacts in order to study the effect of the active site theory on the ternary formulation. Moreover, the magnitude of adhesion force is a function of the surface energy of particles in contact as well as the curvature radius of the interface where particles make contact with each other. Therefore, changing the drug particle surface energy should result in different sizes of adhesion force that exist between drug and carrier particles.

As discussed earlier, the adhesion force size could not be obtained from the simulation and instead, the magnitude of overlap in drug-carrier contacts needs to be considered.

OVERLAP

Overlap is the translation of adhesion force in terms of the particle deformation. The normalized number of drug-carrier contacts is plotted as a function of overlap size in Figure 57.

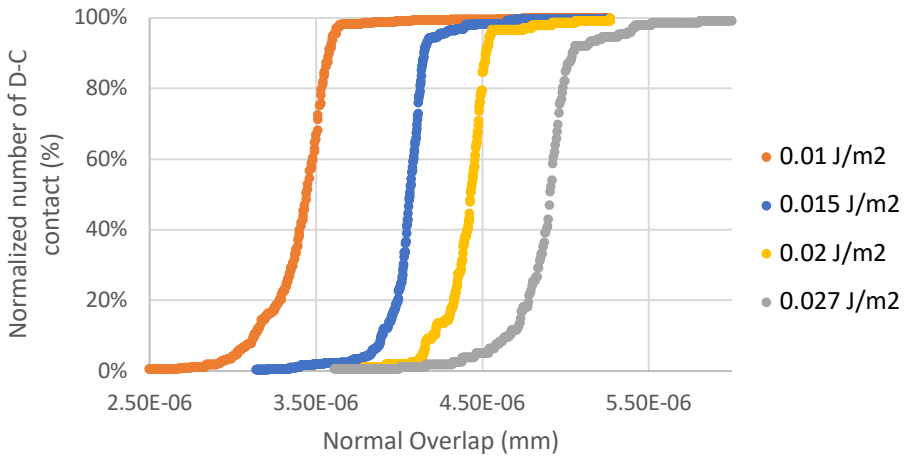


FIGURE 57, THE NORMALIZED-ACCUMULATED NUMBER OF DRUG-CARRIER CONTACTS AS A FUNCTION OF THE NORMAL OVERLAP FOR CASES WITH DIFFERENT DRUG PARTICLE SURFACE ENERGIES

It can be observed that the increase in the drug particle surface energy shifts the graph to a higher normal overlap. This is in line with what was expected since the normal overlap is directly affected by the drug particle surface energy. Moreover, it can be understood that the distribution of normal overlaps regardless of its size is the same for all cases.

The normal overlap is also studied based on the average size of the drug-carrier overlap over different surface energies. Such results are presented in Figure 58.

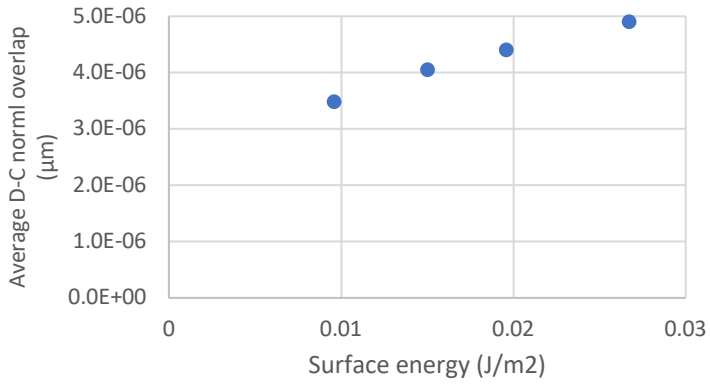


FIGURE 58, THE AVERAGE SIZE OF THE NORMAL OVERLAP VERSUS THE MAGNITUDE OF THE DRUG PARTICLE SURFACE ENERGY

As can be observed, the size of normal overlap increases linearly with the drug particle surface energy. This was expected since the size of adhesion and subsequently, the overlap has a direct correlation with the magnitude of the surface energy of components in contact.

5.4.4 AGGLOMERATE QUALITY

In the agglomeration theory, the formation of drug-fine clusters is considered as the reason for why adding fine particles can increase the deliverability of DPIs. Therefore, investigating the corresponding clusters are crucial to have a better understanding of the contribution of this theory on the ternary formulation. The quality of drug-fine agglomerates is analyzed in terms of the total number of clusters that have been formed after the mixing as well as the total number of drug and fine particles within those agglomerates. Such results can be highly influenced by the drug particle surface energy as it determines the tendency of drug particles for mixing with fine clusters. Figure 59

shows the data regarding the quality of drug-fine agglomerates according to the minimum number of particles that constitute each agglomerate.

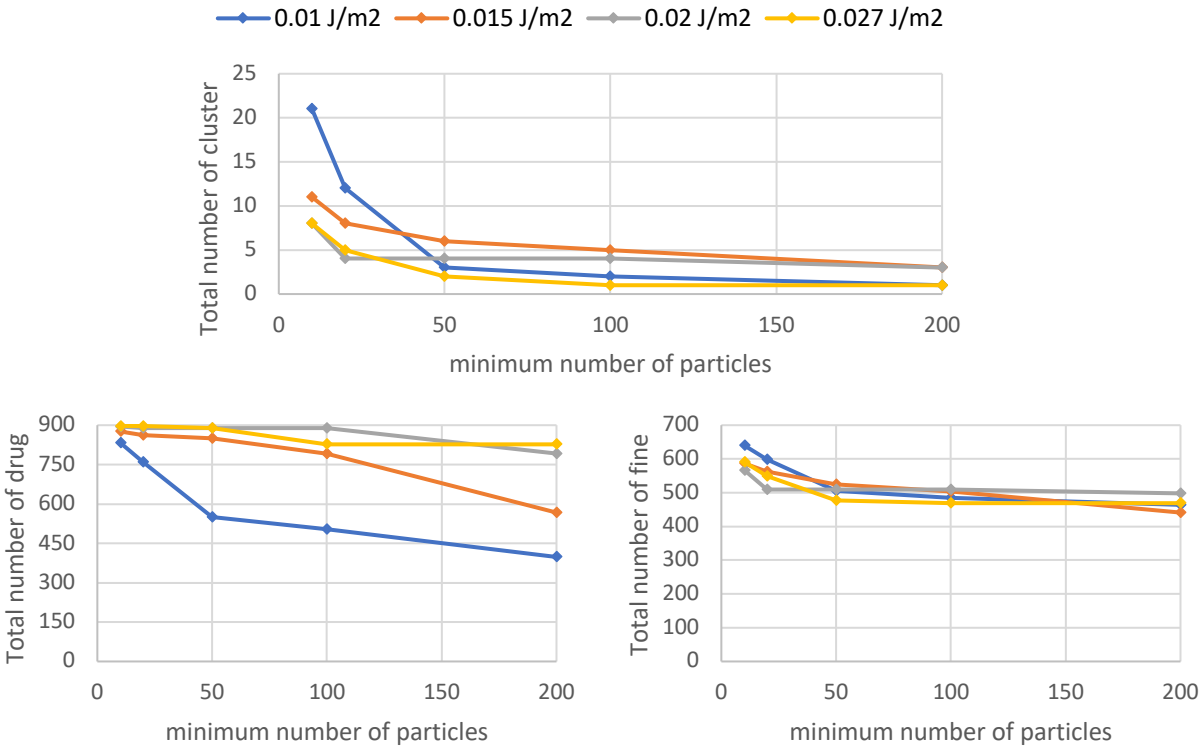


FIGURE 59, THE TOTAL NUMBER OF CLUSTERS AND THEIR CONSTITUENT DRUG AND FINE PARTICLES WITHIN DRUG-FINE AGGLOMERATES

As can be seen from the graph regarding the number of clusters, drug particles with lower surface energies result in a higher number of clusters. This is only true for drug-fine agglomerates with the maximum number of 50 particles in total, and above this point, no specific pattern has been observed. Moreover, cases with the high surface energy include more drug particles within drug-fine agglomerates, whereas, the number of fine particles that are involved within those clusters is almost constant. As a result, drug particles that have higher surface energy constitute the smaller number of drug-fine agglomerates with the larger size.

5.4.5 DISPERSION

The level of dispersity for different cases is studied by means of the ratio of drug particles that are detached individually during the collision with an impact wall. The system is designed so that particles can collide orthogonally to the impact wall with different magnitudes of impact velocities. Figure 60 shows the dispersion data for cases with different drug particle surface energies.

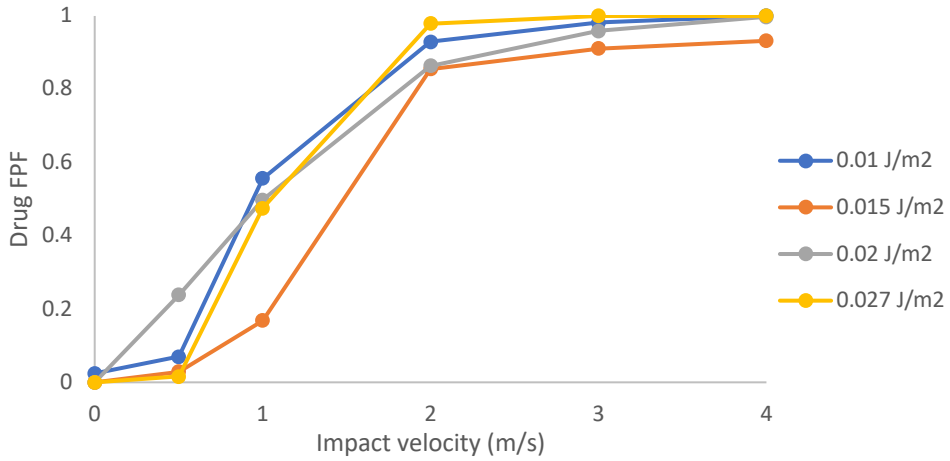


FIGURE 60, THE DISPERSION OF DRUG PARTICLES AS A RESULT OF WALL-COLLISION AT DIFFERENT IMPACT VELOCITIES FOR CASES WITH DIFFERENT DRUG PARTICLE SURFACE ENERGIES

According to the graph, there is no specific trend observed between cases with different sizes of surface energy. However, it should be mentioned that the dispersity of drug particles becomes similar to high impact velocities.

6 DISCUSSION

In this section, all results and the possible conclusions are discussed based on the data that have been obtained from the result section. Although most of the resultant conclusions are valid, there are some conclusions that have been drawn with a level of uncertainty due to the minor inconsistency that was observed in some graphs. In other words, the general pattern is considered rather than the exact trend in some of those figures, considering the possible variations as a consequence of the initialization and the pseudo-steady state nature of the system. According to the obtained results, it is possible to claim that what mechanism or mechanisms can be the governing ternary formulation in the studied range of variables. However, the reliability of such results and the corresponding conclusions will be discussed in more detail in the section regarding the outcome reliability.

6.1 RESULTS ANALYSIS

In this part, results are summarized with the purpose of a better understanding of the system after the mixing. By doing so it is possible to draw solid conclusions regarding the possible leading mechanism during the ternary formulation. Moreover, the results are categorized according to each main attribute except for the overall results that have been made regardless of the variable under investigation. First, general trends are reported and thereafter, the results corresponding to each selected variable are presented.

6.1.1 GENERAL TRENDS

Regardless of the variable that was studied, it was observed that the translational kinetic energy induced on carrier particles is the same for all cases. This can be understood from the corresponding graphs which have the same slope throughout the simulation time. This finding implies that the kinetic condition of the mixing box is a function of the vessel box including the amplitude and frequency of the vibration.

According to this study, it was understood that the fine particle characteristics are irrelevant to the drug-carrier contacts. Put differently, it was observed that the main fine excipient properties have nothing to do with neither the average number of bonds per contact nor the size of adhesion force between drug and carrier particles. The latter comes from the identical size of adhesion for cases that fine particle characteristics were changed. The former finding can be concluded from the constant average number of bonds per drug particle in contact according to the results from the same cases. It was, instead, observed that the strength of the drug-carrier contacts is a function of the drug or carrier particle properties. As a result, inserting fine excipients or changing the characteristics of this component within the studied range cannot affect the drug-carrier contacts. In conclusion, this finding shows contradiction to the principles of the active site theory, where it was discussed that adding fine particles should cause a change in the strength of the contact between drug and carrier particles.

Moreover, the data for the dispersion reveals that the velocity in which particles collide to the impact wall can significantly affect the rate of drug particle detachment. More clearly, in most cases that have been studied the dispersion ratio varies from 3% to 97%. Therefore, the critical impact velocity which determines the dispersity of drug particles is between 0.5 m/s to 4 m/s. Also, it was observed that different cases result in similar rates of dispersion at impact velocities higher than 3 m/s. The rate of dispersion at such speed is roughly above 0.9, i.e. nine out of 10 drug particles can be detached individually after the collision to the impact wall.

6.1.2 FINE PARTICLE SIZE

The results in this section are related to the data that comes from varying fine particle sizes. According to the results it could be observed that cases with smaller fine particles result in better mixing performance. In other words, smaller fine particles are more effective during the ternary formulation. This can be concluded because the smaller the fine particle is, the easier the drug agglomerate breaks considering the higher number of drug-particle contacts at cases with lower fine particle sizes. Furthermore, there is a higher number of contacts established after the mixing among different components including drug-carrier, drug-fine, and fine-carrier contacts. However, it should be mentioned that such a conclusion cannot be drawn for ranges of fine particle sizes other than 3 to 7 micrometers as other factors may considerably affect the mixing performance in those ranges.

To be able to discuss the second conclusion in this section, there is a need to explain two different scenarios that exist in the agglomeration theory. 1) In the first scenario it is argued that in large enough drug-fine agglomerates the surrounding particles can act as a shelter for other particles in between, and therefore, drug particles cannot detach properly during the inhalation. 2) The second scenario just simply argues that involving more drug particles within drug-fine agglomerates should result in more liberation of drug particles and thus a higher rate of dispersion must be achieved. Comparing both scenarios, the former can be the governing factor at low impact velocities where the magnitude of the impact force is not enough to detach all particles within drug-fine agglomerates. On the contrary, the latter scenario will be the leading factor at high impact velocities due to the high enough impact force induced on particles in between. It is now possible to discuss the possible formulation mechanism in the mixing.

According to the dispersion data, it was observed that fine excipients with the smaller particle size result in a higher level of dispersion at low impact velocities. On the one hand, by looking at the system from the active site theory perspective, with smaller fine particles there should be a higher level of dispersion due to the higher number of fine-carrier contacts in those cases. On the other hand, according to the first scenario in the agglomeration theory, since smaller drug particles constitute larger drug-fine agglomerates, the corresponding cases should result in a higher rate of dispersion. As a result, both mechanisms can be dominant within the ternary formulation.

Furthermore, when it comes to the high impact velocities, it was observed that larger fine particles cause a higher level of dispersion. From the active site theory points of view, the smaller fine particles should instead result in a higher dispersion rate. This is because of the higher number of fine-carrier contacts that exist in cases with smaller fine particles. Considering the second scenario in the agglomeration theory, it is expected that larger fine particles cause a higher level of dispersion due to the higher number of drug particles involved within drug-fine agglomerates. Therefore, while results from the high impact velocity are compatible with the agglomeration theory, it shows contradiction to the outcome that was expected from the active site theory. As a conclusion, it can be understood that the active site theory cannot describe the dominant mechanisms in the mixing in such ranges of variables.

6.1.3 Fine particle mass ratio

According to the results from different ratios of fine particle mass loading, cases with more fine particles are more effective within the ternary formulation. This can be concluded from, first, the higher rate of breakage in terms of drug-drug contacts for cases with the high fine mass loadings and, second, the higher number of drug-fine and fine-carrier contacts that have been established after the mixing. However, it should be noted that data regarding the number of drug-drug contacts are not completely consistent and the corresponding conclusion can be made by looking at the results from a general perspective.

Moreover, it can be concluded that fine particles are individually less effective in mixing when more fine particles are added to the system. Such a conclusion comes from the lower breakage of drug agglomerates as well as the lower number of drug-carrier, drug-fine, and fine-carrier contacts that exist after the mixing.

Considering the results regarding the number of drug-carrier contacts, it can be concluded that the active site theory must be more effective in cases with more fine particles. This is because of the higher number of fine-carrier contacts that are established after the mixing and therefore, according to this hypothesis, there must be a lower probability for drug particles to bind to carrier areas that relatively have a high adhesive surface. Comparing such reasoning with the results obtained from the dispersion, it can be understood that the rate of dispersion does not increase with the number of fine particles. In other words, the dispersion data do not show consistency with the active site theory if it is assumed that this mechanism is dominant in the ternary formulation.

6.1.4 Drug particle surface energy

The results in the corresponding section show us that the higher drug particle surface energies make the mixing less effective. This comes from the fact that a smaller number of drug agglomerates have been broken during the ternary mixing. Additionally, fewer numbers of drug-carrier and drug-fine contacts have been established as a result of the lower drug agglomerate breakage.

Another interesting finding is the similar behavior of cases with the two highest surface energies. Such behavior has been observed within different types of results obtained from the simulation. From that, it can be understood that drug particles with surface energy above a certain point behave similarly in the ternary formulation.

Cases with the higher drug particle surface energies include more drug particles within drug-fine agglomerates but no solid conclusion can be made in this regard for the agglomeration theory since the number of drug-fine contacts decreases. As a result, it can be concluded that the drug particles with high surface energy cannot be distributed well over the carrier particles, and instead, they are settled separately on carrier particles. Moreover, there is a smaller number of drug-fine clusters in cases with high surface energy even though the size of those agglomerates is relatively larger compared to cases with the lower drug particle surface energy.

6.2 Obtaining the governing mechanisms

Obtaining the exact mechanism which governs the mixing requires studying the contribution of each possible mechanism in the ternary formulation. To do so, there was a need to model a system that accounts for all formulation theories. As discussed earlier, in this study only mechanisms regarding the agglomeration and the active site theories have been studied. The fluidization reinforcement theory could be investigated since then there was a need to simulate the aerosolization process together with coupling with the CFD. Also, to be able to study the effect of the buffer theory on the mixing, the assumption regarding the elastic nature of all components should have been replaced with the viscoelasticity. These two hypotheses were eventually neglected due to the huge computational cost that comes with modelling of each required system.

It is not possible to make any overall conclusion regarding the exact mechanism that leads to the ternary formulation. However, conducting such a study can reveal a lot of valuable information including the determining factors and their dependencies which result in a better understanding of the mixing process. Furthermore, it might not be possible to find the governing formulation mechanism in such models but instead, it is possible to claim what mechanism or mechanisms are of minor importance within the studied range of variables.

In this study, the main attributes of the ternary mixing have been studied with consideration of the first two theories. According to the results obtained from this study, the active site theory cannot be the dominant mechanism in the ternary formulation. With a more rigorous consideration, the active site theory is neither the dominant mechanism nor even exists in the mixing since the obtained results show contradiction to the principles of this hypothesis. This can be concluded from the strength of the drug-carrier contacts which is not a function of the fine particle

characteristics. Also, the data regarding the rate of dispersion is not compatible with what is expected from the active site theory, i.e. the dispersion ratio does not increase with the number of fine-carrier contacts.

On the contrary to the first hypothesis, the outcome of this study support the existence of the agglomeration theory in ternary mixing. It was also argued that this theory can be the dominant mechanism in the mixing. That can be understood from the results for the dispersity of drug particles as a function of the fine particle size; there, it was observed that the corresponded graph is in line with the agglomeration theory according to two scenarios introduced.

6.3 OUTCOME RELIABILITY

The reliability of this study cannot be validated with experimental data since, at the time of writing this report, there was no similar mixing condition conducted via experiment. Therefore, it is not possible to see if the data resulted from the simulation is in line with the experimental data. Moreover, some cases do not even exist in reality since the surface energy of drug particles in those cases was selected so that the effect of that critical variable is revealed on the mixing. So, basically, there is no way to confirm such cases with experiments.

The outcome of this study can be more reliable if fewer assumptions are considered, even though it comes with a higher computational cost. The elastic assumption could be one of those as it ignores the effect of the permanent deformation on different types of contacts, and therefore, consider the effect of the buffer theory in the mixing. The effect of fluid-induced force is another simplifying assumption which could be accounted for by coupling with CFD.

7 CONCLUSION

Inserting fine excipients into DPI devices can increase the deliverability of APIs through lung cavities and eventually body cells. The mechanism of which adding fine particles into the binary formulation of drug and carrier components can increase the efficiency of such devices remains still unknown and that is the key question that has initiated this study. The answer to this fundamental question is something crucial in order to optimize the efficiency of DPIs to eventually higher amounts of APIs that can be delivered through the respiratory system. Therefore, in this study, it was tried to model a simplified version of a real mixing condition to better understand what is exactly happening during the ternary formulation. It was also argued what theories that have been introduced so far, could be the dominant formulation mechanism and which one cannot. Furthermore, the outcome from this research as well as the method by which the ternary formulation was analyzed can be utilized for further studies in this area.

According to the outcome of this study, it is concluded that the active site theory cannot be the dominant mechanism in the mixing. It is also argued that the mechanisms regarding this theory do not even exist in the ternary formulation as different results show contradiction to the fundamentals of this theory. On the contrary, the results obtained from this study confirm the presence of the agglomeration theory in the ternary formulation. Moreover, while different results reinforce the governorship of the agglomeration theory in the mixing, this hypothesis is not introduced as the dominant formulation mechanism since there is a need to conduct much research to make sure whether this mechanism is indeed the governing one.

Besides the mentioned conclusions, other findings were also discovered which have been explained thoroughly in the discussion section. There it was discussed that smaller fine particles and lower drug particle surface energies can act more effectively in the mixing within studied range of variables. Higher amounts of added fine excipients to the system result in better mixing performance.

8 SUGGESTIONS FOR FURTHER WORK

8.1 VALIDATION OF RESULTS

As discussed earlier, the outcome of the simulation needs to be validated with the experimental data like any scientific research. This is done to make sure that the resultant data are aligned with reality and therefore, the outcome of the study is reliable. In this study, the mixing condition of the simulated cases could not have been validated with experimental work, since no similar mixing condition have been carried out with the experiment at the time of writing this report. Therefore, it is highly recommended to conduct a similar experimental mixing condition as the ones simulated in this study.

8.2 SIMULATION FOR MORE CASES

In this study each main variable has been analyzed with four different cases, one base case and 3 particular cases for each attribute. The studied ranges of those variables were selected so that the dominant formulation mechanism is kept the same in order to make the investigation less challenging and more precise. With that said, some changes could not have been recognized as a trend, or at some figures, the corresponded conclusions have been made from a general perspective with a level of uncertainty. That is because of the minor changes in variables that exist between different cases.

To cope with this issue, one thing that can be done is to run more cases with different values of the parameter that is under investigation. By doing so, solid conclusions can be made from those that have a level of uncertainty. Also, some of those trends that could not be identified with only four cases, can now be distinguished by having more cases.

8.3 EXTENSION OF THE MIXING TIME

As discussed earlier, even in a real mixing condition, the system never reaches a steady-state condition as particles within the mixing vessel constantly make new contacts with other regions and particles. Instead, it can be assumed that the mixing has reached to a pseudo-steady state condition in which the rate of change among different parameters is very low. However, it should be noted that a real ternary mixing can take up to one hour, whereas, the selected mixing time for all cases is only 0.5 seconds. This time interval has been chosen to simultaneously make the model computationally possible and to relatively reach a pseudo-state condition.

The results from those simulations are, of course, different from reality and even from simulations with extended mixing time. Consequently, there is a chance for possible variations and deviations from a case with longer simulation time. Therefore, one thing that can be done to eliminate the impact of the possible variations/deviations on the ternary formulation model is to extend the simulation time to a longer period.

8.4 MODELING OF THE AEROSOLIZATION STAGE

By simulating the aerosolization stage, it is possible to consider the effect of the fluidization reinforcement theory on the mixing performance. The contribution of this hypothesis to the ternary formulation could not be investigated in this study since only the mixing phase was modeled. The inhalation phase needs to be modeled in order to account for fluid-induced forces such as drag, lift, and added mass force in the system. This can be done by simulating the DPI device shape as well as coupling with CFD to account for aerodynamic forces. Then it is possible to study the effect of other dispersion mechanisms such as turbulent shear during the inhalation.

It is highly recommended to model the aerosolization stage to not only account for all forces that play during the inhalation process but also to discover the exact formulation mechanism that governs the mixing. However, it shall be mentioned that the modeling of such a system is highly expensive from a computational point of view since there is a need to combine DEM with CFD.

8.5 CONSIDERING VISCOELASTIC PHYSICS

With the consideration of the viscoelastic deformation rather than the elasticity, it is possible to test the validity of the buffer theory. This is done by considering the effect of the press-on force on drug particles, which in turn leaves a permanent deformation on particles in contact. As a result, the size of the adhesion force needed to detach drug particles from carrier surfaces increases to some extent. The elastic physics was initially chosen due to the high computational cost that comes with the elastic model in addition to the fact that there is no reliable viscoelastic model at the moment which can represent the micron-sized particles precise enough. By having a proper viscoelastic model, it is possible to study the mechanism regarding the buffer theory, which eventually helps us to find the main mechanism in the ternary formulation.

8.6 ADDITIONAL VARIABLES

In this study, only three variables, i.e. particle size and particle mass ratio corresponding to the fine excipients and the drug particle surface energy, were investigated. These variables were selected as the main critical attributes of the mixing performance according to the literature review. However, there are still many more variables that can affect the formulation and thus studying those can help us to better understand the mechanisms that occur during the mixing. Fine particle surface energy, drug particle size, and characteristics of the carrier particle including the size and the material chosen are some of the potential variables that can provide us with more information regarding the main mechanisms.

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10 APPENDICES

10.1 APPENDIX A

Starting Date: 20-Jan-2020					Week number																
Code	**Milestones**	**Period**	**Start date**	**Due Date**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	**Project plan**	**2 weeks**	20-Jan	3-Feb																				
1.1	sketch the draft of project plan	1 week	20-Jan	27-Jan																				
1.2	make the detailed project plan with deliveries and time needed	1 week	27-Jan	3-Feb																				
2	**Literature review**	**5 weeks**	20-Jan	24-Feb																				
2.1	read the existing articles and text book	2.5 weeks	20-Jan	8-Feb																				
2.2	expand the literature sources (DEM modelling & Application theorie	2.5 weeks	3-Feb	10-Feb																				
5	**Initial simulation**	**4 weeks**	10-Feb	9-Mar																				
5.1	evaluate and expand the existing models provided by Masood	2 weeks	10-Feb	24-Feb																				
5.3	model series of simulation with different methods	2 weeks	24-Feb	9-Mar																				
6	**Sensitivity analysis**	**5 weeks**	9-Mar	13-Apr																				
7	**Post-analysis**	**3 weeks**	27-Apr	18-May																				
8	**Report**	**18 weeks**	27-Jan	8-Jun																				
8.1	framework	1 week	27-Jan	3-Feb																				
8.2	introduction	3 weeks	27-Jan	17-Feb																				
8.3	theory	3 weeks	17-Feb	9-Mar																				
8.4	workflow	2 weeks	2-Mar	16-Mar																				
8.5	simulation setup	1 week	16-Mar	23-Mar																				
8.6	result and discussion	5 weeks	23-Mar	4-May																				
8.7	post-processing	3 weeks	4-May	25-May																				
8.8	Overview	1 week	25-May	1-Jun																				
9	**Prepair for project presentation**	**1 week**	1-Jun	8-Jun																				
10	**Close project (safe margin)**	**1 week**	8-Jun	15-Jun																				

FIGURE 61, THE PLANNED SCHEDULE REPRESENTED VIA A GANT-CHART

10.2 APPENDIX B

PARTICLES PHYSICAL PROPERTES													
Case no	Key variable	Component	Particle size (µm)	Mass loading ratio (% w/w)	Surface energy (J/m^2)	Number of particles	Particle density (kg/m^3)	Poission ratio	Young modulus (GPa)	Restitution coefficient	Static friction coefficient	Rolling friction coefficient	D-F adhesive force/ F-F cohesive force
Base case	-	drug	3	1.32	0.015	900	1330	0.3	2	0.5	0.26	0.002	1.027
		fine	5	5.7	0.008	700	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	93	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
1	fine particle size	drug	3	1.32	0.015	900	1330	0.3	2	0.5	0.26	0.002	1.369
		fine	**3**	5.7	0.008	3241	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	93	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
2	fine particle size	drug	3	1.32	0.015	900	1330	0.3	2	0.5	0.26	0.002	1.174
		fine	**4**	5.7	0.008	1367	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	93	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
3	fine particle size	drug	3	1.32	0.015	900	1330	0.3	2	0.5	0.26	0.002	0.822
		fine	**7**	5.7	0.008	255	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	93	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
4	fine mass ratio	drug	3	1.32	0.015	900	1330	0.3	2	0.5	0.26	0.002	1.027
		fine	5	**1.32**	0.008	162	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	97.36	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
5	fine mass ratio	drug	3	1.32	0.015	900	1330	0.3	2	0.5	0.26	0.002	1.027
		fine	5	**3.5**	0.008	430	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	95.18	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
6	fine mass ratio	drug	3	1.32	0.015	900	1330	0.3	2	0.5	0.26	0.002	1.027
		fine	5	**8**	0.008	982	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	90.68	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
7	drug surface energy	drug	3	1.32	**0.0096**	900	1330	0.3	2	0.5	0.26	0.002	0.822
		fine	5	5.7	0.008	700	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	93	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
8	drug surface energy	drug	3	1.32	**0.0196**	900	1330	0.3	2	0.5	0.26	0.002	1.174
		fine	5	5.7	0.008	700	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	93	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	
9	drug surface energy	drug	3	1.32	**0.0267**	900	1330	0.3	2	0.5	0.26	0.002	1.370
		fine	5	5.7	0.008	700	1550	0.3	0.1	0.5	0.5	0.002	
		carrier	80	93	0.005	3	1550	0.3	0.1	0.5	0.3	0.002	

FIGURE 62, PHYSICAL PROPERTIES OF DIFFERENT ELEMENTS IN THE TERNARY FORMULATION

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