Journal of Pharmaceutical Sciences xxx (2016) 1-11

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Development of a Rational Design Space for Optimizing Mixing Conditions for Formation of Adhesive Mixtures for Dry-Powder Inhaler Formulations

Saurabh Sarkar [1], Bruna Minatovicz [1], Kyrre Thalberg [3], Bodhisattwa Chaudhuri [1, 2, *]

[1] Department of Pharmaceutical Sciences, University of Connecticut, Storrs, Connecticut 06269
[2] Institute of Material Sciences, University of Connecticut, Storrs, Connecticut 06269
[3] Research & Development, Astra Zeneca, Mölndal, Sweden

ARTICLE INFO

Article history:
Received 12 March 2016
Revised 26 June 2016
Accepted 15 July 2016

Keywords:
adhesive mixtures
dry-powder inhalers
press-on forces
abrasion
mixing
pulmonary drug delivery

ABSTRACT

The purpose of the present study was to develop guidance toward rational choice of blenders and processing conditions to make robust and high performing adhesive mixtures for dry-powder inhalers and to develop quantitative experimental approaches for optimizing the process. Mixing behavior of carrier (LH100) and AstraZeneca fine lactose in high-shear and low-shear double cone blenders was systematically investigated. Process variables impacting the mixing performance were evaluated for both blenders. The performance of the blenders with respect to the mixing time, press-on forces, static charging, and abrasion of carrier fines was monitored, and for some of the parameters, distinct differences could be detected. A comparison table is presented, which can be used as a guidance to enable rational choice of blender and process parameters based on the user requirements. Segregation of adhesive mixtures during hopper discharge was also investigated.

Introduction

The concept of ordered mixtures, wherein fine particles coat the surface of a coarse particle held together by adhesive and electrostatic forces,[1] has been used to produce homogenous pharmaceutical formulations containing potent drugs.[2] Strictly speaking, the term “ordered mixture” denotes a high degree of order in excess of that for a random mixture, which may not be realistically achieved. Therefore, an alternate term “adhesive mixture” has been used in more recent literature.[3] Adhesive mixtures are frequently used for dry-powder inhaler (DPI) formulations owing to several distinct advantages: (a) pulmonary delivery of fine active pharmaceutical ingredient (API) is made possible by controlling the carrier-API adhesive forces, without compromising the API release on patient inspiration[3,4]; (b) greater lift forces, which scale to square of the particle diameter (or slightly higher), are generated which is important considering the limited inspiratory force of a target asthmatic patient[4]; and (c) improvement of the powder flow of the formulation so it is possible to scale up, handle, and fill the formulation into the DPI devices.[5]

Translation of these advantages into a commercially viable formulation requires robust manufacturability and performance. Unfortunately however, the manufacture of adhesive mixtures for inhalation is not straight forward. On account of the very small doses inhaled, typically in the range of 10-20 mg, the requirements for dose content uniformity are extremely high. The general property of fine particles to attach to everything, including blender and container walls, impeller wings, sieves, and so forth, does not make the task easier. In addition to being a cause for inhomogeneities, fine particle adhesion to the blender entails loss of content, with the risk to fail achievement of target drug content. The aspect of performance is judged by the fine particle fraction (FPF) of the drug released from the formulation. FPF generally considers particle sizes below 5 μm and is dictated by the

Abbreviations used: API, active pharmaceutical ingredient; AZFL, AstraZeneca fine lactose; d10, diameter at which 10% of the sample's mass is comprised of smaller particles; d50, diameter at which 50% of the sample's mass is comprised of smaller particles; d90, diameter at which 90% of the sample's mass is comprised of smaller particles; DCN, double cone; DPI, dry-powder inhaler; FPA, fine particle aggregate; FPC, fine particulate content; HSM, high-shear mixer; PSD, particle size distribution; rpm, revolutions per minute; RH, relative humidity; RSD, relative standard deviation; SEM, scanning electron microscope; SGI, segregation index; TL, top loading.

* *Correspondence to:* Bodhisattwa Chaudhuri (Telephone: +1-860-486-4861; Fax: +1-860-486-2076).
E-mail address: bodhi.chaudhuri@uconn.edu (B. Chaudhuri).

http://dx.doi.org/10.1016/j.xphs.2016.07.012
0022-3549/

distribution of fines over the carrier surface, which is in turn impacted by the surface and bulk properties of both the carrier and the fines, the mixing process, device design, and the inhalation process itself.[3]

A closer examination of the dual demands of manufacturability and performance reveals that a good mixing process is critical for balancing content homogeneity and dispersibility, which at the particle level implies a balance of cohesive and adhesive forces. This is not easy given the dynamic interplay of process and material variables. The mixing process for producing adhesive mixtures can be summarized to consist of 4 mechanistic processes,[6] which are envisaged to be sequential but often occur with significant overlap during dynamic mixing. These rate processes are as follows: (1) random mixing of agglomerated fines and the carrier, (2) deagglomeration of fines under shearing, collisions, and inertial forces in a mixer wherein the mechanical energy input overcomes drug cohesion, (3) adhesion of the fines to the carrier, and (4) redistribution of fine particles within carrier particles along with compression of fines due to press-on forces. The 2 main types of mixers commonly used in the manufacture are (1) low-shear blenders operating by tumbling the powder and (2) high-shear blenders which mix the powder by the rotational movement of an impeller. Bohle blenders, Turbula blenders, and double cone (DCN) blenders belong to the first type, whereas popular marks for high-shear blenders are Fielder, Diosna, and Collette. Blend properties and performance heavily depend on the type of blender used. For tumbling blenders, good homogeneity may be challenging to reach. Segregation within low-shear drum blenders has been demonstrated to be a function of rotation speed and size difference of the mixture components.[7] On the other hand, mixing conditions are mild, and changes in particle size distribution during mixing are unlikely to occur. For high-shear mixers (HSMs), short mixing times are normally sufficient, and prolonged mixing should be avoided, on account of the risk of powder buildup. In addition to the type of blender, mixing time and speed can be critical parameters, known to influence the performance of the dry-powder blends.[8-10] Thus, both low-shear and high-shear blenders offer their unique advantages and disadvantages, and a careful choice must be made during drug product development. However, research on the influence of processing parameters on powder performance is limited, often leading to empirical processing strategies by formulators.

The first conceivable impact of mixing is particle (drug, coarse carrier, carrier fines) distribution. As drug cohesion is overcome by inertial and frictional forces during mixing, drug aggregates deagglomerate and primary particles are distributed to carrier surface and are held by adhesive forces, or alternatively find shelter in surface discontinuities. The relative importance of residence times at these locations is dependent on the carrier payload.[11-13] Below the concentration of surface saturation, drug particles can shield themselves from the inertial and frictional forces. Above concentrations of surface saturation, agglomerates adhering to the carrier surface are likely to dominate. Performance evaluation by dispersion efficiency was found to be inversely related to the agglomerate size,[14] which in turn was strongly influenced by the porosity of the carrier size bed[15,16] and fundamentally linked to the mixing parameters. Generally, assessment of dispersion performance is done at low flow rates, where fine particle detachment from the carrier will be strongly dependent on agglomerate size and in turn mixing efficiency.

Material properties of the drug and carrier may also change during mixing. In theory, larger carrier particles exert greater press-on forces, which could lead to solid-state disorder as shown by amorphization of salmeterol and fragmentation of fluticasone during high-shear mixing.[17] If the mixing intensity is strong enough, even a typical carrier, like α-lactose monohydrate can undergo changes, as demonstrated by changes in moisture sorption after high-shear blending.[18] This study also showed that energy input and impeller design had significant impact on carrier particle size distribution. This can lead to modification of the energetics of surface interactions which impact the net adhesion and general processability.[19]

Besides direct solid-state physical changes impacting effective adhesion, aggressive mixing can also cause abrasion thereby changing shape, surface roughness, and even the static charge. Direct correlation of these properties with mixing intensity for adhesive mixtures is not readily found in literature, although the impact of these parameters is appreciated. The aerodynamic advantage (aligning with air flow, greater suspendability) provided by elongated carrier particles has been documented.[20] Littringer et al. (2012)[21] found that carrier shape and roughness significantly impacted the FPF for mannitol carrier particles. It has also been demonstrated that surface roughness could modify apparent adhesion depending on the relative strength of electrostatic to adhesive interactions.[22]

Although the role of material properties and particle morphology has been studied with great academic interest and metrics like Cohesive Adhesive Balance[23,24] and Cohesive Index[25] based on material properties have been coined for formulation assistance, similar guidelines for choice of process parameters do not exist. There are several areas of concern where fundamental understanding is not available.[3,25,26] For example, systematic studies on direct quantification of press-on forces during mixing and of abrasion of carrier fines during a mixing process are lacking. The aim of the current article was to reduce this knowledge gap by systematic investigations of the mixing of a binary powder mixture consisting of model drug and carrier lactose. The studies are undertaken in 2 different mixing regimes; a laboratory scale high-shear blender and a low-shear DCN blender. For both, the impact of mixing intensity time, fill, and loading configuration can be assessed. The segregation of the adhesive mixtures is studied in bench-scale hoppers during mass and funnel flow. Finally, the impact of the mixing process and blender with respect to the press-on forces, tribocharging, and abrasion of carrier fines are elucidated to provide the formulator with a tool for rational guidance in choosing the blender and process parameters for optimal DPI performance.

Materials and Methods

Materials

Fine lactose (AstraZeneca fine lactose, d50 = 3.52 μm) was provided by AstraZeneca Inc. which has physical characteristics representative of an API. Lactohale® 100 (LH100, d50 = 119.61 μm) provided from DFE Pharma is used as the carrier lactose. Both AZFL and LH100 are chemically α-lactose monohydrate. The physical characteristics of the fines and lactose carrier are listed in Table 1. It can be seen that the AZFL, referred as “drug” for the purposes of this article, is distinctly finer and more cohesive than the carrier.

Procedure

Particle Size–Based Methods for Quantitative Analysis

In the absence of any chemical or crystallographic difference between the drug and the carrier fines, particle size difference between the carrier and fines was used to characterize the quality of the blend as well as changes induced during the processing. Particle sizing was used to (a) characterize the mixing homogeneity and segregation from the hoppers, (b) characterize the adhesion between the carrier and the drug by means of pressure-titration