Drug Physicochemical Properties Relevant to Powder Flowability in Pharmaceutical Appliance: A Review

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ABSTRACT

Background: Studies have shown that the powder flowability rate significantly impacts the content uniformity and weight of the active pharmaceutical ingredients in drug tableting procedures.
The aim was studying the physicochemical properties relevant to the powder flowability in some pharmaceutical instruments.
Powders with good flow characteristics are required to ensure a continuous flow through the die and other compartments of the pharmaceutical appliances used for manufacturing. Several factors, such as size, density, adhesiveness, shape, surface conditions, and electrostatic chargeability of the drug ingredients, tend to influence the flowability of a drug.
Conclusion: The study highlights that particle size is one of the major determinants of powder flowability. Large particles are expected to aid better flowability resulting in a clearer feeder during the manufacturing process. The flowability of the powder could be improved by adding a small number of fine particles and granules as excipients.

Keywords: powder porosity, physicochemical properties, flowability, pharmaceutical appliances.

المدخل: أظهرت الدراسات أن معدل تدفق مسحوق الدواء يؤثر بشكل كبير على توحيد المحتوى ووزن المكونات الصيدلانية في معامل التصنيع الدوائي. المساحيق ذات خصائص التدفق الجيدة مطلوبة لضمان تدفق مستمر من خلال القالب ومقصورات أخرى من الأجهزة الصيدلانية المستخدمة في التصنيع.
تهدف الى دراسة الخصائص الفيزيوكيميائية المتعلقة بانسيابية المساحيق في الاجهزة الصيدلانية.
المساحيق ذات الخصائص التدفق الجيد مطلوبة لضمان التدفق المستمر في قوالب والاجزاء الاخرى للاجهزة الصيدلانية المستخدمة في عملية التصنيع. عوامل عديدة تمثل حجم ، كثافة، الالتصاق والشكل وظروف السطح، الشحن الكهروستاتيكي لمكونات الدواء وتمثل تاثير على قابلية دفق الدواء.
الملخص: تم تسليط الضوء على حجم الجسيمات كأحد المحددات الرئيسية لسريان المسحوق. ومن المتوقع ان تساعد الجزئيات الكبيرة على تحسين التدفق مما يؤدي الى وحدة التغذية اثناء عملية التصنيع. يمكن تحسين قابلية تدفق المسحوق بإضافة عدد صغير من الجسيمات الدقيقة والحبيبات كسوا غات.

الكلمات المفتاحية :
مسامية المسحوق، الخصائص الفيزيوكيميائية، قابلية التدفق ، الاجهزة الصدلانية.

INTRODUCTION:

The filling of the die and compaction of the powder is the most crucial processes in the tabletting process for pharmaceutical powders. Powders with good flow characteristics must ensure a continuous flow through the die. Indeed, filling the die is critical for achieving low variability

in tablet mass and ensuring a consistent drug load for the patient[1]. However, the followability of the drug powder is frequently too low to be processed directly, requiring specially designed excipients to improve the followability[2]. This review article aims to look into the effect of a drug load on powders' packing characteristics and followability.

A common example is the silicified microcrystalline cellulose and Acetaminophen (APAP) blends have been made at various APAP drug doses[3]. The GranuPack and the GranuDrum are used to explore the impact of the APAP fraction on the followability and packing dynamics of the blends[2]. The tablets are then made in a rotary press to see how changing the powder behaviour affects the mechanical qualities of the tablets. Finally, illustrate how accurate powder characterization can aid in gathering crucial data for predicting their performance in the tabletting device[1]. Several studies[2,3,4], highlight that powders' flowability in drug tabletting tend to significantly impact the content uniformity and weight of the active pharmaceutical ingredients. While on the other hand, certain studies have highlighted that the physiochemical properties greatly impact the flowability of these drugs. According to the study by Wong (2017), the physical and chemical properties of a substance or compound tend to determine a chemical substance's ability to elicit a pharmacological and therapeutic effect with the surface of the substance with which it comes in contact. The chemical properties allow the drugs to react extracellular, such as ionization. In contrast, the physical properties of the drug are responsible for the action of the drug particles[2].

Powder Followability

A bulk of particles move relatively between nearby particles or along the container wall surface is characterized as powder flow, also known as followability[1,2]. Additionally, powder followability refers to the ability of the powder to flow in a certain piece of apparatus in the desired direction. The flow of powder is thus a multidimensional problem in which powder properties are combined with a geometry's application to predict followability[2].

Factors Affecting Powder Flowability

The flowability of a drug is substantially influenced by factors such as the size, density, adhesiveness, shape, surface conditions and electrostatic chargeability of the drug ingredients[2]. These factors highly depend on the physical and chemical properties of the drug substances, including solubility, partition coefficient, hydrogen bonding, ionization, disassociation constant, surface activity, and protein binding, etc[3]. Nevertheless, powder flowability fundamentally depends on the distribution of the drug formulations' physical properties, including their particle size and shape. Generally, the powder beds, including lactose, microcrystal cellulose and mannitol (granules or spray-dried), are directly affected for their flowability[4]. A research study conducted by Somnache et al. (2016) quantitatively evaluated how the flowability of granulated lactose was affected by the distribution of physical properties of the drug formulations[5]. The sample considered in the study included three types of granulated lactose divided into narrower size fractions. While the tests conducted to determine the flowability of the powder involving lactose included the angle of repose, compressibility, and static and dynamic friction[1,4]. The results show minimal dependence of flow properties on the particle shape. However, the R2 (coefficient of determination) value for the static friction was greater than that for dynamic friction. Based on this evaluated the study suggested that decreased proportion of small particles increased the

flowability of the powder bed (lactose) related to static and dynamic friction[5].

Size Distribution of the Powder Bed

Particle size distribution (PSD) is considered among the most crucial parameters in the pharmaceutical industry. It is used to determine the number of particles present in a tablet by their size[1,5]. Particle size needs to be measured during particle control and while developing new API (Active pharmaceutical ingredients)[2,4]. The porosity and surface area of any particular drug substance or API is greatly influenced by its particle size. As a result, it indirectly impacts the shelf life, bioavailability, and overall effectiveness of a drug[3,5]. While in the drug manufacturing process, particle size is one of the major determinants of powder flowability as it affects the tabletting and granulation process[6,7]. Although small particles facilitate dissolution, over-compression may result in hard tablets that barely disintegrate upon consumption[1,6]. Contrarily, large particles are expected to aid better flowability resulting in a clearer feeder during the manufacturing process. In addition to this, certain research studies have also stressed narrow particle size distribution to achieve a more homogenous distribution[8].

Porosity

Certain previous studies, such as by Kudo et al. (2017), explain that the powder's flowability could be improved by adding a small number of fine particles, which indirectly depends on the mixture's mixing time and intensity within the mixture pharmaceutical appliances[9]. The apparent contact distance between the drug ingredients and the surface is increased when the particles are in fine powdered form. Therefore, the drug adhesion with the surface and the friction between these two is potentially reduced, resulting in an increased flowability[2,9]. As the surface roughness of the pharmaceutical appliances can potentially result in friction with the drug ingredients, spherical particle forms are the most preferred to be used in the manufacturing process as they glide more easily over the surface and lead to enhanced flowability. This relates to another basic property of the powder known as porosity[6,7]. Elongated and flat-shaped particles result in higher porosity, rough surface texture, and eventually lower flowability[1,4]. While on the other hand, more refined or spherical particles demonstrate reduced porosity and increased flowability[2,3]. Although fabricating API into smaller particle diameters is observed to be successful in enhancing drug dissolution during formulation, minimal improvements are only observed in the flowability of the drug. According to several studies, such as Traina et al. (2013), granulated material must be preferred to be used instead of powdered materials. This implies that coarse materials are more efficient in improving the followability instead of using powdered material[10].

Ionization of the Active Drug ingredients

The study by Gupta (2020)[11] highlights some significant conventional methods used to evaluate powder flowability, including measurement of compressibility and the angle of the repose. However, as the direct compaction technique has improved the tablet design, there has emerged the need for alternative methods to determine powder flowability[6,7]. In the direct compaction procedure, also known as the direct compression process, the powdered active drug substance API and a suitable excipient are directly compressed into a firm compact without undergoing the process of granulation. Therefore, forming a tablet design[1,8]. However, certain properties of the API involved interfering with the efficient functioning of the high-speed direct compression tabletting procedure.

According to the study by Gupta et al. (2020), powders must flow well to attain consistent die filling and manufacturing tablets with sufficient tensile strength[11]. Although API with finely powdered form is preferred to attain fast dissolution rates as discussed above, micro-ionization within the drug ingredients often cause cohesion in the powder bed resulting in adhesion and inadequate flow rate[12]. To improve the flow and packing of the powder blend, the pharmacists are formulators who tend to add excipients with large particle sizes (>100 µm) to improve the flow and packing of the powder blend[3,6].

Interparticle Cohesion with the Excipients

Excipients are defined as the substances included in a pharmaceutical dosage form while facilitating the manufacturing process of the medicine and do not contribute to direct therapeutic actions[5]. In addition, pharmaceutical excipients enhance the stability of the drugs in which they are involved and improve the bioavailability of active ingredients and patients' acceptability towards these substances[3,6]. This implies that excipients play an essential role in optimal tablet performance. However, certain studies, such as Takeuchi et al. (2014), have shown that combining inappropriate excipients with API (active pharmaceutical ingredients) can potentially reduce the powder flowability[13]. As a result, the content uniformity of the API and the tablet weight is affected. One of the most significant excipients used in lactose is low hygroscopicity, water-solubility, chemical and physical stability and cost-effectiveness. In addition, several studies such indicated that blending large particle size excipients with fine APIs (Active pharmaceutical ingredients) may eventually lead to segregation issues[6,7,14]. Moreover, despite the benefits of heavy drug loading (>50%), including increased therapeutic response, the limit for drug loading of APIs is typically restricted to 30%. It is because larger percentages of APIs are considered to build more cohesion in the powder blend, causing it to lose the required properties for direct compression[15]. This implies that the more the cohesion will be, it would be difficult for the drug particles to flow easily[6,7]. Therefore, certain previous studies have highlighted the significance of using dry coating in reducing the antiparticle cohesion within the powder bed, thereby increasing the flowability[3,8].

Dry Coating

A study by Kunnath et al. (2021)[16] describes dry coating as the procedure in which the host particle is passed through surface modification by coating them with nano-sized guests. As the nano-sized guest particular particles are relatively finer by orders of magnitude than the host particles, this eventually reduces the surface roughness of the host particles and creates separation among these particles. Therefore, the antiparticle cohesion is reduced, whereas the flowability is improved. Several studies by Alfano et al. (2021)[17] explained that APIs are subjected to dry coating to improve their flow through the pharmaceutical appliances packing in tablet form. Therefore, these dry coated APIs are appropriate for high-speed direct compression tabletting procedures. A study concluded by Kunnath et al. (2021)[16] evaluated the impact of dry coating, guest particle hydrophilicity, and particle size of excipient on the high drug-loaded blend. While on the other hand, three different cohesive APIs, including Acetaminophen (mAPAP), coarse Acetaminophen (cAPAP) and micronized Ibuprofen (mIBU), were used in these drug blends. To improve the flowability and pack properties, these APIs were micro-ionized by dry coating them with either hydrophobic (R972P) or hydrophilic (M5P) nano-silica, which

function as an excipient. The results demonstrated that due to the dry coating procedure, several properties of the pharmaceutical blend were enhancing such as flow (FFC) and blending parking (bulk density). Moreover, another careful observation demonstrated that the API blend used along with fine excipients experienced a more effective impact of the silica coating than coarse excipients. Therefore, dry coating increased drug flowability and made it suitable for direct compression tabletting without disrupting the drug's tensile strength and dissolution rate[1,6,7].

Static Electricity and Powder Flowability

The pharmaceutical powder tends to pass through several compartments during the manufacturing process before reaching its final package destination[1,8]. While passing through these compartments, the powder particles are obliged to collide with one another and along with the walls of the containers or processors[1,3,4]. This eventually produces friction between the two surfaces, increasing electrostatic charges. This phenomenon is also referred to as triboelectrification and is measured as follows[18]:

I= (Ka x M x Vb)/d

Whereas I =tribo electric current

Ka= constant dependant on the material

M= mass flow rate

V= velocity

d= particle diameters

b= constant

These charged particles are expected to adhere to oppositely charged surfaces, thereby minimizing their flowability. A study by Schwindt et al. (2017)[18] highlights that fine particles conveyed at high flow rate and high velocity preferentially generate static electricity among them. Therefore, static electricity generation among powder particles can eventually lead to several consequences such as a change in bulk density of the powder, segregation of the build particles from other fine particles, and bad powder flowability out of the hoppers of pharmaceutical appliances. Although the disturbed flowability due to static electricity where the drugs may get adhered to the hopper surface may not be a major concern for large scale production, it must be considered while working with high precisions. Such as in the volumetric filling process[1,3].

Hydrogen Bonding

Aside from interparticle cohesion, the particles of the pharmaceutical ingredients could also absorb the moisture in the air, changing the physicochemical properties of the powder. This could also impact the flowability of the powder within the pharmaceutical appliances. Interfacial tension and capillary pressure are significant factors that contribute to the formation of liquid bridges. Whereas studies such as Naël-Redolfi, Keita, & Roussel (2018)[19] have identified capillary forces dominating compared to other force components, provided that the substances are given a humid environment. Pharmaceutical blends are passed from various compartments during the manufacturing process, such as storage, grinding, blending and transportation. The pharmaceutical solids can come in contact with water through the atmosphere during storage and from a water-basedwater-based excipient. Nevertheless, the water could be transferred among these particles. The amount of water determines the impact of moisture on the powder flowability of drugs and their distribution, where water could either be absorbed from the surface or could even penetrate it[18,19].

This distribution of the water within the pharmaceutical blend may alter the physicochemical properties of the material, such as in the case of anhydrous theophylline. It is converted into a hydrate upon absorbing moisture. According to the study by Li et al.

(2018)[20], the absorption of the water through the surface occurs through the formation of hydrogen bonds with the hydrophilic sites of the pharmaceutical powder. This absorption generally relies on the hydrophilic properties of the powdered material. Nevertheless, several studies have focused on the humidity-dependent changes in the pharmaceutical powder blend flowability. According to Sandler et al. (2010)[21], a lower amount of water tends to eliminate the micro-irregularities and electrostatic charges within the powdered particles, thereby positively affecting the powder flowability. On the other hand, the presence of a higher amount of water around the powder increases the thickness of the absorbing layer, which ultimately enhances the strength of liquid bridges formed. Therefore, as the hydrogen bonding and cohesion increase, the powder flowability is expected to decrease in such cases substantially[18,20].

CONCLUSION

Powder flowability fundamentally depends on the distribution of the drug formulations' physical properties, including their particle size and shape. The study concludes that if small particles are subjected to over-compression, they may form hard tablets that barely disintegrate upon consumption. Contrarily, large particles are expected to aid better flowability resulting in a clearer feeder during the manufacturing process. Moreover, rather than preferring elongated and flat-shaped particles, spherical particles must be used, demonstrating lower porosity, less rough surface texture, and eventually increasing flowability. The study further concludes that interparticle micro-ionization may alter the powder flowability, which could be regained through the dry coating. And lastly, the humidity environment must be strictly considered while dealing with precise drug measurements and manufacturing as these force the powder to adhere to the surface walls of the pharmaceutical appliances. Therefore, also affecting the powder flowability.

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