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Research paper

Effect of colloidal silica on rheological properties of common pharmaceutical excipients

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ABSTRACT

In pharmaceutical industry, the use of lubricants is mostly based on historical experiences or trial and error methods even these days. It may be demanding in terms of the material consumption and may result in sub-optimal drug composition. Powder rheology enables more accurate monitoring of the flow properties and because the measurements need only a small sample it is perfectly suitable for the rare or expensive substances. In this work, rheological properties of four common excipients (pregelatinized maize starch, microcrystalline cellulose, croscarmellose sodium and magnesium stearate) were studied by the FT4 Powder Rheometer, which was used for measuring the compressibility index by a piston and flow properties of the powders by a rotational shear cell. After an initial set of measurements, two excipients (pregelatinized maize starch and microcrystalline cellulose) were chosen and mixed, in varying amounts, with anhydrous colloidal silicon dioxide (Aerosil 200) used as a glidant. The bulk (conditioned and compressed densities, compressibility index), dynamic (basic flowability energy) and shear (friction coefficient, flow factor) properties were determined to find an optimum ratio of the glidant. Simultaneously, the particle size data were obtained using a low-angle laser light scattering (LALLS) system and scanning electron microscopy was performed in order to examine the relationship between the rheological properties and the inner structure of the materials. The optimum of flowability for the mixture composition was found, to correspond to empirical findings known from general literature. In addition the mechanism of colloidal silicone dioxide action to improve flowability was suggested and the hypothesis was confirmed by independent test. New findings represent a progress towards future application of determining the optimum concentration of glidant from the basic characteristics of the powder in the pharmaceutical research and development.

1. Introduction

Manufacturing of pharmaceutical solid dosage forms involves several processing steps including flow through hoppers, sieving, pouring, blending, die-filling, and compaction. These steps are highly sensitive to powder properties such as flowability and bulk density, which are to some extent inter-related. The knowledge of flow properties of raw excipients and their mixtures is essential for predicting the behaviour during blending, compression, handling or leaving in storage. These properties are critical for manufacturing since they can affect the final product quality and the efficiency of the processes [1,2].

Most pharmaceutical excipients used these days are fine powders 100 μm or less, which typically have a wide size distribution [3]. The ability of fine powders to flow is complicated due to the action of Van der Waals forces, which become dominant compared with gravitational forces as the particle size decreases [4,5]. The relative magnitude of both types of forces is decisive for the flow properties of powders [6]. Powders are cohesive if the adhesive forces exceed the particle weight. For most organic materials this condition is fulfilled at particle diameters smaller than approximately 30 μm. This means that particles of this size tend to agglomerate and to aggregate. As a direct consequence, such materials tend to show bad flow properties [7].

The flow properties of powders can be improved significantly by the addition of small amounts of substances described as 'glidants' in the area of tableting technology. The primary particles of the glidants exist in the form of agglomerates which are broken

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down into smaller aggregates during the blending process. These smaller aggregates adsorb at the surface of the other solid component grains and thus diminish attractive Van-der-Waals-forces by increasing the roughness of the host surface [8].

Colloidal silicon dioxide (trade name AEROSIL) is widely used as a glidant in the manufacture of powders, capsules, and tablets [8,9]. As its primary particles as well as its agglomerates are very small, they are strongly adsorbed at surfaces of larger particles, e.g., corn starch [7]. However, due to the very fine particles that have a strong tendency to form agglomerates, segregation after simple mixing with other excipients can also occur as a result of differences in the density. Thus, proper dispersion of the glidant is a very important issue for obtaining uniform coating and flowability improvement [10,11].

In previous studies, there are examples of the improvement of the functional characteristics including flowability through 'co-processing' of pharmaceutical excipients with other materials [11]. A material produced by a process of 'silicification' has recently been described [12]. Staniforth and Tobyn [12] demonstrated that mixing of Microcrystalline Cellulose (MCC), usually added to formulations to enhance compactibility, with colloidal silicon dioxide, can significantly increase its relatively low bulk density and improve flow characteristics. This was supported by the works of Sherwood and Becker [13] and Khalaf and Tobyn [14]. In another work, York [15] studied the effect of three types of glidants on the flowability of fine lactose powder. From the data obtained, it was shown that mixing lactose with fine silica produced the largest increase in flowability. The ideal concentration of glidants can significantly affect the behaviour of the powder mixtures [16]. Augsburger and Shangraw have shown an optimum silica-type glidants activity when added to microcrystalline cellulose at a concentration of about 0.5% by weight [17]. Similar values for the ideal silica glidant concentration were also found in the work of Abe et al. [18] and York [19]. The flow-enhancing effect of a new compacted, hydrophilic colloidal silicon dioxide on microcrystalline cellulose and pregelatinized starch was studied in the work of Jonat et al. [9]. It was found that the optimal concentration of glidant was 0.25% under gentle and 0.125% under strong mixing conditions, as measured by the angle of repose.

Many studies have examined the effect of lubricants and glidants on tablet properties [13,20] but only a few have examined the effect on flowability [21,22]. Several methods have been developed to measure the flow properties of powder. These methods commonly include the static angle of repose, flow through a funnel, consolidation test, determination of tapped density (Carr's compressibility index, Hausner Ratio), fluidization test, bed collapse test, uniaxial compression test and shear cell testing [16,23].

Powder rheology is a key approach to assess properties such as flowability and powder cohesion. There are various commercially available instruments for measuring powder flow and fluidization properties. The FT4 Universal Powder Rheometer methodologies are generally based on an empirical approach [24]. It allows the measurement of the powder response to various stress fields, thus simulating the range of processing conditions more closely. In the dynamic mode, the flow properties are measured by the energy (or torque) required to rotate a helical blade at a set speed whilst simultaneously traversing the blade in or out of a powder bed. This energy is called the flow energy and is the product of all the forces acting on the rheometer blade during the displacement of a powder sample. From the observed values of the flow energy, a series of indexes related to the flow properties of powders can be derived. In order to ensure repeatable and comparable data, a conditioning procedure allows the generation of a stable consolidation state that can be reproduced [25,26].

The aim of this study was to investigate the rheological properties of silicified microcrystalline cellulose and pregelatinized starch in comparison with the characteristics of pure excipients. The binary mixtures of these excipients and different concentration of anhydrous colloidal silicon dioxide were blended in a Turbula® mixer for a defined period of time. The Freeman FT4 rheometer was then used to measure flowability and to find the optimum flow-enhancing composition.

2. Materials and methods

2.1. Materials

The following powders have been used: pregelatinized maize starch (Starch 1500, Colorcon, UK), microcrystalline cellulose (Avicel PH102, Mingtai Chemical Ltd., Taiwan), croscarmellose sodium (Ac-Di-Sol, FMC BioPolymer, USA), magnesium stearate (LIGAMED, Peter Greven, Germany) and anhydrous colloidal silicon dioxide (Aerosil 200, Cabot, USA). The function of the powders in pharmaceutical blends, and the size distribution and shape characteristic of pure excipients are listed in Table 1. The particle size data were obtained using a static light scattering system (type Mastersizer X, Malvern Instruments, UK) equipped with a dry powder feeder.

SEM photographs of all materials are shown in Fig. 1. Scanning electron microscopy was performed using InduSEM (Tescan USA Inc., Cranberry Township, USA) equipped with SE and BSE detectors – EDX microprobe Quantax 125 eV (Bruker, Massachusetts, USA).

2.2. Preparation of blends

The raw materials were pre-screened through a 1.0 mm sieve. They were used independently or in binary mixtures. The preparation of the physical mixtures with colloidal silicon dioxide was performed with a Turbula drum blender model T10B (W.A. Bachofen, Basel, Switzerland) at 32 rpm for a period of 10 min and the batch size 600 g. The concentrations of colloidal silicon dioxide were set at 0.25%, 0.5%, 1%, 2%, 5% and 10% by weight based on the total formulation. Samples were stored in sealed containers to avoid the influence of atmospheric moisture.

2.3. Flowability and rheology of the powders and their mixtures

The flowability parameters of pure excipients as well as their binary mixtures were measured by the FT4 Powder Rheometer (Freeman Technology Ltd., UK). The powder rheometer device provides dynamic testing, shear cell testing and bulk properties measurement. Dynamic testing used a 48 mm diameter blade and a 160 ml powder sample contained in a 50 mm bore, borosilicate test vessel. An automated, 18 segment, 48 mm diameter rotational shear cell accessory was used for all shear testing using an 80 ml sample. All samples for dynamic and shear tests

Table 1
Size and morphological properties of used materials.

Excipient type	Material	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Shape
Filler/binder	Pregelatinized Maize Starch (MAP)	0.01	3.5	14.8	Ovoid
Diluent	Microcrystalline Cellulose (MCC)	27.7	117.1	257.4	Needle-like
Disintegrant	Croscarmellose sodium (NC)	0.01	0.2	20.0	Needle-like
Lubricant	Magnesium stearate (MS)	4.92	12.3	41.3	Soft-plates
Glidant	Anhydrous colloidal silicon dioxide (ACSD)	14.2[a]	25.0[a]	43.9[a]	Spherical

[a] Size of primary aggregate measured at wet dispersion without sonication.