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A methodological approach for determining the effect of moisture content on the compaction properties of powders: Granular hydroxyapatite

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ABSTRACT

The effect of moisture on the compaction properties of hydroxyapatite (HA) was studied. A single lot of commercially available HA was heated at various temperatures to provide samples containing 2.12, 4.02, 4.56, 4.97 and 5.26% moisture content as determined by thermogravimetric analysis (TGA) at 450 °C. Compressibility, compactibility, elastic recovery and Young's modulus of elasticity were determined as a function of moisture content. An increase in moisture content increased the compressibility coefficient of HA facilitating volume reduction at constant compaction pressure. However, increased moisture content also reduced the bonding capacity of HA particles, resulting in reduced tablet tensile strength at constant porosity. Elastic recovery increased and Young's modulus of elasticity decreased, with increasing moisture content, which contributed to reduced tablet tensile strength. The plasticising effect of moisture was outweighed by the reduction in bonding capacity and the increase in elastic behaviour, resulting in a negative effect of moisture on tablet tensile strength over the range studied.

1. Introduction

Hydroxyapatite (HA) is a plastically deforming material [1–3] which has gained prominence in pharmaceutical and dietary supplement formulations due to low toxicity, desirable flow properties, good compaction characteristics, reasonably low cost and high orally available calcium content [3–5]. HA is anhydrous and does not form a hydrate upon exposure to water [4]. Aqueous solubilities between 0.017 and 0.025 mg/L at 20 °C [3,5] and melting points between 1550 °C and 1614 °C [6,7] have been reported. It is worth noting that HA has a Ca/P molar ratio of 1.667 and chemical formula of $Ca_5(PO_4)_3(OH)$ or $Ca_{10}(PO_4)_6(OH)_2$, but has often been erroneously referred to as tricalcium phosphate [8], tricalcium orthophosphate or tribasic calcium phosphate [9] which all have a Ca/P ratio of 1.5 [10] and the chemical formula $Ca_3(PO_4)_2$.

A number of pharmaceutical grade HAs are commercially available for use in direct compression and wet granulation manufacturing processes. TRI-CAL WG™ (Innophos Ltd.), a roller compacted granular form of HA, is specifically designed for use in aqueous wet granulation processes and is the focus of the present study. Wet granulation typically involves the mixing of an aqueous binder liquid with powdered materials to form moist granules, which are subsequently dried to a pre-determined moisture content. The effect of moisture on the compaction properties of these materials is therefore of interest.

The presence of moisture in pharmaceutical powders can have a marked effect on their compaction properties, and the mechanical strength of the resulting tablet [4]. The mechanical strength of a tablet is critical to the success of downstream processes such as film coating, imprinting and packaging, and also plays a role in tablet disintegration and drug dissolution.

The mechanical strength of a tablet is commonly described by its tensile strength and is considered to be primarily determined by two parameters: the bonding force between powder particles and the area over which these bonding forces act [11]. Three types of bonding forces are generally accepted to act between pharmaceutical powder particles: solid bridges, mechanical interlocking and distance forces [12]. Solid bridges describe the continuous solid phase formed between two, or more, particles and contribute markedly to the strength of materials with a simple structure, low melting point, some degree of solubility in adsorbed moisture, or have a glass transition temperature similar to that experienced during compaction [13–15]. Mechanical interlocking is considered possible for some materials with a rough texture and/or irregular shape, which allow for hooking or twisting together of particles [16], however the pharmaceutical relevance of this mechanism has been challenged [17]. Interparticulate distance forces, i.e. van der Waals forces, hydrogen bonds, and electrostatic interactions, are generally considered to be the dominant bonding mechanism for most pharmaceutical powders [18]. Additionally, capillary forces between particles caused by the condensation of moisture have

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also been reported to contribute to interparticulate bonding force of powders particles [19].

An increase in moisture content has been reported to increase the bonding area of plastically deforming materials during compaction due to plasticising and lubricant effects [20,21]. Moisture facilitates particle rearrangement and deformation during compaction resulting in tablets with a lower porosity at constant compaction pressure, and therefore increased area over which interparticulate bonding can take place. This effect has been reported for pharmaceutical powders as a reduction in the mean yield pressure derived from the Heckel equation [22–24] and also by an increase in the compressibility coefficient derived from the Walker equation [25].

Moisture on particle surfaces has been proposed to enhance interparticulate interactions. Moisture adsorption can mediate molecular attraction forces if the layers touch or penetrate each other [26,27]. Surface moisture can also be seen as part of the particle surface thus reducing interparticulate distance, leading to an increase in interparticulate bonding and tensile strength [27–29]. Adsorbed moisture can also function as a surface-restructuring medium, increasing the contribution of solid bridges [30], particularly for salts and soluble materials.

However, moisture has also been reported to have a negative effect by disrupting certain bonding forces. For example dissolution of solid bridges can take place at elevated relative humidity, which acts to reduce tensile strength [31]. Sodium chloride and saccharose tablets stored at 100% RH for 15 days demonstrated complete loss of tensile strength due to this phenomenon [32]. Similarly, for anhydrous dextrose an increase in moisture content from 0.34 to 8.9% w/w resulted in increased tensile strength due to recrystallisation effects, however the tensile strength was significantly reduced at moisture contents of 9.20 and 9.66% w/w as a result of condensation of moisture and dissolution of solid bridges [33]. Adsorbed moisture on the particle surface can also interfere with intermolecular forces, thus reducing the bond strength and resultant tablet tensile strength [11,34,35].

Studies with HPMC polymers suggest that the effect of moisture on tablet tensile strength is a balance between the relative quantities of each physical form of moisture [23]. Tensile strength increased to a maximum at 6% w/w moisture content, but decreased with further increases in moisture content [30]. The first 6% w/w moisture content is suggested to strongly bind by hydrogen bonds to the hydroxyl groups in the cellulose structure, rather than being present as monolayer or multilayer moisture on the surface of the particles. Moisture in the hydrogen bonded state acts as a plasticiser to facilitate plastic deformation and increases the area over which interparticulate bonds can act [36]. Above 6% w/w moisture forms a monolayer at the surface of the particles acting to disrupt intermolecular bonds and facilitate elastic recovery, through a lubrication effect, resulting in decreased tensile strength of tablets at a solid fraction of 0.9 [30]. The interplay between plasticity and the positive or negative effects of moisture on bond strength have also been the topic of study for a number of other researchers [20,30,37–39].

Investigation of the compaction of polymeric materials found that below a critical moisture content (~3.3% w/w) microcrystalline cellulose tablet tensile strength was at a maximum [22]. This is attributed to the plasticising effect of moisture distributed within the relatively porous particles; moisture forms hydrogen bonds with the surfaces of microfibrils and is concentrated in amorphous regions, resulting in a decreased glass transition temperature [40]. Increases above the critical moisture content, postulated to be represented by the monolayer moisture coverage, resulted in decreased tensile strength, despite the decreased tablet porosity that was achieved [41].

Similar findings were reported for pregelatinized starch [39] where an increase in the sample water activity from 0.22 to 0.70 resulted in an increase in tensile strength, but a further increase to 0.95 water activity caused a decrease in tensile strength. When constant tablet porosity was considered, by applying the Ryshkewitch–Duckworth equation, it became evident that increasing moisture content resulted in a steady decrease in bonding capacity and tensile strength at zero porosity. In addition, the observed increase in tensile strength at constant compaction pressure was due to the decreased mean yield pressure and therefore increased bonding area.

Increased moisture content significantly reduced amylodextrin tablet porosity when compressed at a pressure of 250–300 MPa [20]. However, despite the increased bonding area, the tablets of higher moisture content had significantly lower tensile strength, due to a reduction in bond strength caused by multiple water-layers on the particle surfaces. Similar results were obtained for crystalline materials also, since ibuprofen tablets exhibited a maximum tensile strength at ~2.5% w/w moisture content, which decreased as the moisture was increased to 10% w/w [42]. Non-hygroscopic paracetamol tablets yielded maximum tensile strength at 6% w/w moisture, but decreased at 8% w/w [43]. However, both these latter studies only evaluated the effect on tabletability and tablet porosity, therefore the interplay between bonding area and bond strength was not considered.

The quantity and distribution of moisture will depend upon the chemical properties of the powder, various physical properties such as particle size and pore structure, and the ambient relative humidity (RH) in which the material is handled and stored [43]. The relative importance and contribution of bonding area and bond strength to tablet tensile strength varies as a function of moisture content and should be evaluated on a material-by-material basis [22].

Only limited characterisation of HA compaction properties has been reported previously. Published results are restricted to studying the effect of compaction force on tablet breaking strength and Heckel analysis [2,3,44–46], whilst the role of moisture in HA compaction properties has received notably less attention. An aqueous wet granulated formulation comprising 84% HA, 10% starch, 5% naproxen and 1% magnesium stearate has been investigated [47]. As moisture content increased over the range of 1.5–4.9% w/w the mean breaking strength decreased. Nevertheless, these findings can be considered preliminary since the focus of the study was on the effect of relative humidity conditions during storage upon changes in tablet breaking strength. Over the moisture content range studied there was no difference in tablet breaking strength upon storage at 23 °C/44% RH. However, storage of tablets compressed at lower initial moisture contents of 1.5–3.1% at 23 °C/93% RH showed a significant decrease in tablet breaking strength, despite tablets with a higher initial moisture content of 4.0% and 4.9% displaying negligible change in breaking strength under the same storage conditions. Clearly, although moisture is important in the compaction properties of HA and the resultant tablet tensile strength, there is much that remains to be investigated. Specifically the simultaneous relationship between compaction pressure, tablet porosity and tensile strength, and the effect of moisture on this relationship require study.

2. Materials and methods

2.1. Materials

Pharmaceutical grade hydroxyapatite (TRI-CAL WG™) was obtained from Innophos, IL, USA. Moisture content was altered by thermal treatment. A sample was also stored under ambient conditions (20 °C/30% RH) for 72 h to be used as a reference. Samples of 500 g were heated at 60, 100 or 325 °C in a drying oven (Lindberg/Blue, MO1490A-1, Waltham, Massachusetts, USA) for at least 72 h prior to compaction. A 250 g sub-sample of the material heated to 100 °C was re-equilibrated to ambient conditions for at least 72 h. Moisture content was determined using thermogravimetric analysis (Q1000, TA Instruments, New Castle, DE, USA). Samples (~12 mg) were placed in standard aluminium pans and heated to 450 °C at a rate of 10 °C/min to determine the loss on drying for each of the samples.