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Screening of several excipients for direct compression of tablets: A new perspective based on functional properties

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ABSTRACT

Excipients are widely used to formulate solid drug forms by direct compression. However, the powder-forming and tableting properties of these excipients are affected by the presence of lubricants and active ingredients. In this study, a screening methodology was employed to test the performance of an excipient for direct compression. The effects of three lubricants (magnesium stearate, stearic acid and talc) on the compressibility and compaction of these excipients were assessed by the compressibility index and lubricant sensitivity ratio, respectively. Likewise, the dilution potential in blends with a poorly compactible drug such as acetaminophen was also assessed. Finally, the elastic recovery of tablets was evaluated five days after production. All lubricants increased the compressibility of these excipients and improved their flowability. However, hydrophobic lubricants such as magnesium stearate had a marked negative effect on compactibility, especially in plastic-deforming and more regularly-shaped materials with a smooth surface such as Starch 1500. Alginic acid, rice and cassava starches had the largest elastic recovery (>5%), indicating a tendency to cap. Moreover, highly plastic deforming materials such as sorbitol and polyvinylpyrrolidone (PVP-K30) exhibited the best dilution potential (~10%), whereas alginic acid showed a very high value (~70%). In terms of performance, sorbitol, PVP-K30, Avicel PH-101, sodium alginate and pregelatinized starch were the most appropriate excipients for the direct compression of drugs.

Keywords: Filler. Binder. Direct compression. Lubricants. Elastic recovery, Dilution Potential.

INTRODUCTION

The choice of the right combination of excipients during the pharmaceutical tablet development stage is a critical decision and a good knowledge and understanding of the behavior of these materials is very important, to avoid potential problems during manufacturing (Pingali et al., 2011). Currently, about 80% of all tablets are manufactured by wet granulation even though this technique involves a great number of processing steps, the addition and removal of water and stability problems for thermolabile drugs and those that are degraded by hydrolysis. Furthermore, the equipment used, material handling and energy consumption are also problems to consider. One recent trend is to use the direct compression technique (Gohel & Jogani, 2005). However, only a few excipients can be directly compressed into tablets, owing to their poor physical properties such as compactibility, flowability and compressibility. Therefore, it is important to understand how excipients and processing conditions affect product quality (Haware et al., 2010). In order to determine the suitability of an excipient for direct compression its functional properties must be assessed. The most important functional property is compactibility, which is related to the deformation mechanism that occurs when a pressure is applied to bind particles together to form a compact. For example, brittle-deforming materials fragment during compaction, easing the formation of a large bonding area. On the other hand, ductile materials show plastic deformation and deform by dislocation of the crystals along slip-planes, forming hard compacts (Bolhuis et al., 2003).

Powder flow is another important factor to assess in a directly compressible agent. In order to enhance flow, lubricating excipients are employed. Currently, magnesium stearate is the most widely used lubricant. It eases the compaction process by reducing wall friction during tablet ejection, improves flowability, bulk and tap densities, compressibility and reduces the adhesion of the powder to metal surfaces (Riepma et al., 1993). Since it is hydrophobic, the formation of an external film on the blended particles could reduce surface wettability, decreasing dissolution rates and prolonging disintegration times (Çelik & Mollan, 1996). Magnesium stearate could also weaken the bonding of the powder mixture by creating an interface on the surface which could reduce particle binding (Kushner & Moore, 2010). These effects could be aggravated by increasing the amount of magnesium stearate and mixing time and by using mainly plastic-deforming materials. Therefore, the sensitivity to magnesium stearate

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has been used to characterize the consolidation properties of excipients. Fragmenting materials could be less sensitive to magnesium stearate because of the creation of lubricant-free surfaces during compression. In contrast, plastically deforming materials suffer from a high lubricant sensitivity, since the lubricant film is not destroyed during consolidation, because crystal-plane slipping maintains a continuous lubricant matrix over the particles (Bolhuis et al., 1999).

The dilution potential is another crucial property in a direct compression excipient. It is defined as the minimum amount of excipient needed in the blend with an active ingredient to form tablets of adequate compactibility and friability (<1%). The dilution potential varies with the active pharmaceutical ingredient (API) and allows the researchers to select the right combination of API and excipient in a formulation (Wells & Landridge, 1981). For this reason, the selection of appropriate excipients with a low dilution potential has generated great interest among formulation scientists.

Elasticity is another important property to test in an excipient and it is assessed by measuring the increase in tablet thickness due to elastic recovery during ejection (Odeku et al., 2008). This axial elastic recovery (ER) assesses the elasticity of the compact particles and a high value is associated with a decrease in tablet strength due to the reduction in bonding surface area (Viseras et al., 2000). The ER has also been associated with a tendency of tablets to undergo capping and lamination (Asano et al., 1997). It can be divided into two parts, the fast in-die and the slow out-of-die time-dependent measurements (Picker-Freyer, 2004). ER implies the release of potential energy stored in the material by tableting (Hein et al., 2008; Kim et al., 1998). Moreover, interaction between particles affects the relaxation behavior of tablets. For instance, compacts produced from materials with weak interparticle attraction experience more relaxation than tablets made of materials with strong particle attraction (Bolhuis & Zuurman, 1995). Thus, the ability of the tablet to withstand ER due to the release of stored elastic energy is a significant factor in determining the success of a compaction process (Haware et al., 2010). The goal of this study is to compare the performance of several potential direct compression starches with that of conventional excipients, by analyzing elastic recovery, sensitivity to lubricants (magnesium stearate, talc and stearic acid) and dilution potential.

MATERIALS AND METHODS

Materials

Cassava, corn and rice pregelatinized starches were obtained from Corn Industries (lots CS1102, CS1101, and RS1101, respectively; Cali, Colombia), Starch 1500 from Colorcon (lot IN504089, Harleysville, PA, USA), acetaminophen from Sigma-Aldrich (lot GOH0A01, St. Louis, MO), lactose monohydrate from Fonterra Limited (lot 8596021361, Kapuni, New Zealand), alginic acid, sodium alginate, polyvinyl pyrrolidone K-30 (lot 0911106, MW 40,000), sorbitol and dicalcium phosphate ($CaHPO_4$) from Bell Chem Corp. (lot 024M0118, Longwood, FL, USA), Avicel PH-101 from FMC Biopolymers (lot 6N608C, Philadelphia, PA, USA) and calcium carbonate, talc, stearic acid and sodium stearate from ProtoKimica (lot 2256KXDS, Medellin, Colombia).

Lubricant sensitivity (LSR)

Binary blends of excipient:lubricant (99:1) were made in a V-blender (Riddhi Pharma Machinery, Gulabnagar, Gujarat, India) for 15 min. Round flat-faced compacts of ~13 mm in diameter were compressed with a single-punch tablet press (Compac 060804, Indemec Ltda, Itagui, Colombia). The pressure was controlled such as the resulting tablets had a solid fraction (SF) of ~0.8. This was calculated by the equation:

$$SF = \frac{m}{\rho_t h \pi r^2} \quad (1)$$

where m, ρ_t, h and r are the compact mass, true density, height and radius, respectively. Compact breaking strength was determined with a hardness tester (UK200, Vankel, Manasquan, NJ, USA). The sensitivity to lubricant was measured as the breaking strength ratio of ~500 mg compacts, defined as follows (Bolhuis & Holzer, 1996):

$$LSR = \frac{(T_0 - T_l)}{T_0} \quad (2),$$

where T_0 and T_l are the breaking strengths of unlubricated and lubricated compacts, respectively.

Powder properties

Materials were dried on a mechanical convection oven (STM 80; Precision Scientific Inc., Chicago, IL, USA) at 105 °C for 3 h until a moisture content of less than 5% was obtained. True density (ρ_{true}) was measured on approximately 2 g of sample employing a helium pycnometer (AccupycII 1340, Micromeritics, USA) on three independent samples. Powder porosity (ε) was determined by the equation:

$$\varepsilon = [1 - (\rho_{bulk} / \rho_{true})] * 100\% \quad (3),$$

where ρ_{bulk} and ρ_{true} are the bulk and true densities, respectively. Bulk density was determined by dividing the weight of ~20 g of the excipient:lubricant (99:1) blend by its volume measured in a 100-mL graduated cylinder. Tap density was determined directly from the weight and final volume of the tapped sample measured in the Auto-Tap analyzer (AT2, Quantachrome instruments, USA) after 700 taps, when a stable volume was attained. The frequency employed was 3 taps/sec. The compressibility index (Carr's index) was obtained as a percentage from the bulk and tap densities, as follows:

$$CI = \frac{(\rho_{tap} - \rho_{bulk})}{\rho_{tap}} * 100\% \quad (4)$$

Flow rate was determined on ~5 g of powder by recording the time taken to pass freely through a glass funnel (13.09 mm diameter). Flow rate was calculated as the mass divided by the flow time. Photomicrographs at 700x magnification were taken on an optical microscope

(BM-180, Boeco, Germany) coupled with a digital camera (DCR-SX45, Sony, Tokyo, Japan), using ImageJ software (v. 1.37, National Institutes of Health, Bethesda, MD).

Compact friability test and dilution potential

Binary mixtures of excipient:acetaminophen were made up in the ratios 30:70, 50:50, 75:25 and 100:0. These mixtures were prepared in the Riddi Pharma V-blender (see above) for 15 minutes. Compacts of ~500 mg were made at pressures of 40, 75, 110 and 150 MPa, with a dwell time of 1 sec. The friability test was performed in a friabilator (FAB-25; Logan Instruments Corp., NJ, USA). Briefly, 13 compacts, each weighing ~500 mg, were placed in the friabilator drum, which was rotated at 25 rpm for 4min. Compacts were then dedusted and reweighed. The percentage weight loss was taken as friability. Only those materials that passed the friability test were selected for the determination of dilution potential, for which the modified method of Minchom and Armstrong was employed (Minchom & Armstrong, 1987). Compact hardness was measured on a hardness tester (UK200, Vankel, Manasquan, NJ, USA). The area under the curve (AUC) of the strength-pressure diagram for the compact was read, to measure the compactibility of the materials. Individual AUC values were normalized by the total AUC of the pure excipients. The dilution potential was then obtained by extrapolating, to zero compactibility, the curve formed by the area ratios of the excipient:acetaminophen mixtures.

Elastic recovery (ER)

Tablets of ~500 mg were made with the Indemec single-punch tablet press (see above) equipped with flat-faced 13 mm diameter tooling. Heights of tablets were measured immediately after they were ejected (Digital Caliper Titex Gold, Impofer, 0.01 mm sensitivity) and after 5 days of storage. The ER was calculated from the equation of Armstrong and Haines-Nutt (Armstrong & Haines-Nutt, 1972):

$$ER = \frac{(H_5 - H_0)}{H_5} \quad (5)$$

where H_5 and H_0 are the height measured after 5 days of storage and immediately after ejection.

RESULTS

Lubricant effect on flowability, compressibility and porosity of the excipients

Figures 1 and 2 show, respectively, the compressibility index (Carr's index) and powder porosity of materials with various lubricants, together with those of the unlubricated blends. In most cases, the compressibility index remained between 20-30%, indicating a moderate volume reduction and excellent flowability. However, calcium carbonate was the only material that showed a considerable increase in the compressibility index, from 37% to ~45%, indicating a large volume reduction and a poor initial flow, which improved remarkably upon lubrication. Figure 2 shows the effect of the lubricant on the powder porosity of the excipients. In most cases, porosity was reduced from 2 to 5% by addition of the lubricant. Avicel PH-101, calcium carbonate, sorbitol, PVP-K30 and corn starch were the excipients with the largest powder porosity, whereas sodium alginate, starch 1500 and cassava starch showed the lowest powder porosity. Figure 3 depicts the percent flow increase upon excipient lubrication. In terms of flowability, magnesium stearate and stearic acid were more efficient than talc. Materials such as sodium alginate, alginic acid, dicalcium phosphate, sorbitol, cassava, corn and rice starches had a flowability increase of less than 50%. The diverse morphology of the excipients also plays a major role in this effect (Figure 4). On the other hand, Avicel PH-101, lactose monohydrate, PVP-K30, Starch 1500 and calcium carbonate showed a flow increase from 50 to 300%, especially when magnesium stearate and stearic acid were used as lubricants. It is important to highlight calcium carbonate as the material with the highest flowability and volume reduction capacity. Figure 5 shows the lubricant sensitivity of the excipients. Starch 1500, rice starch, PVP-K30 and alginic acid were the materials with the highest lubricant sensitivity, especially with magnesium stearate.

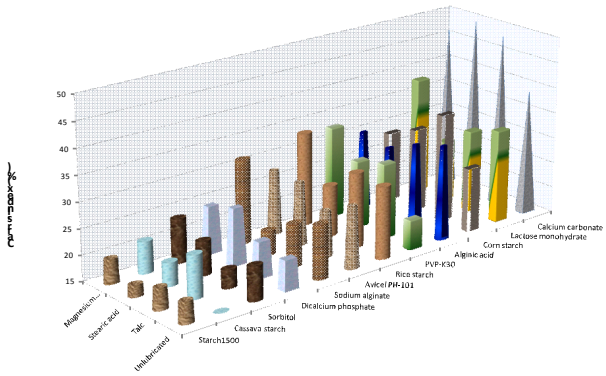

Figure 1- Effect of lubricant on the compressibility index (Carr's index).

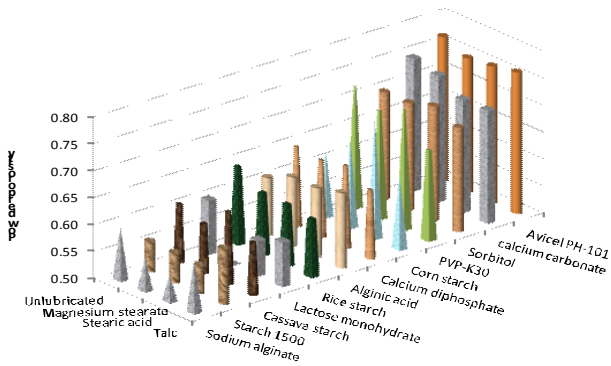

Figure 2- Effect of lubricant on powder porosity.

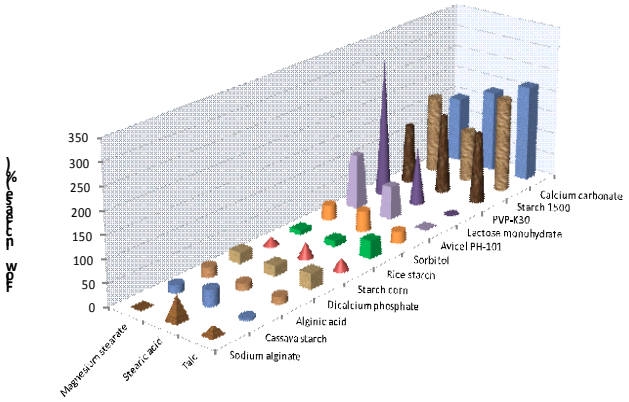

Figure 3-Percentage of flow increase upon lubrication.

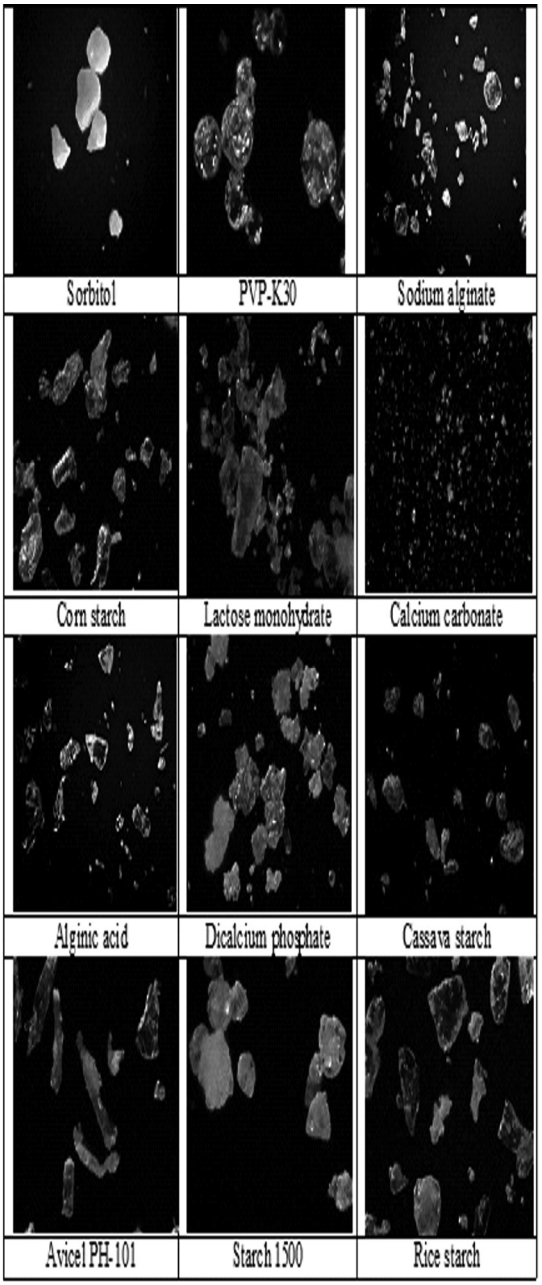

Figure 4-Optical microphotographs of the excipients at a 700X magnification.

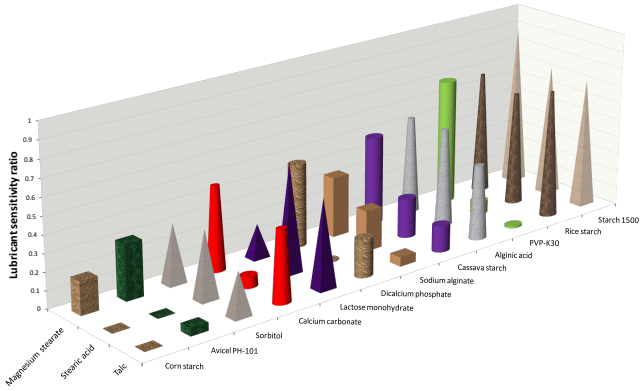

Figure 5-Lubricant sensitivity ratio of conventional excipients.

Dilution potential

Figure 6 illustrates the dilution potential of the excipients studied. Formulations with cassava and rice starches, dicalcium phosphate, lactose and calcium carbonate did not pass the friability test at acetaminophen levels >30% and, thus, their dilution potential for tablets made by direct compression could not be determined.

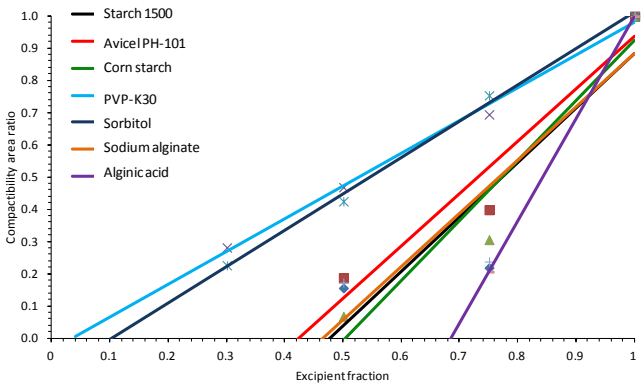

Figure 6 - Dilution potential of the best excipients for direct compression.

Elastic recovery (ER) of tablets

The ER results are depicted in Figure 7. Except for cassava and rice starches, the ER values decreased slightly with increasing compression pressure. Further, Avicel PH-101 showed higher ER (4%) than PVP-K30 (3%). Conversely, the ER value for lactose was ~1%.

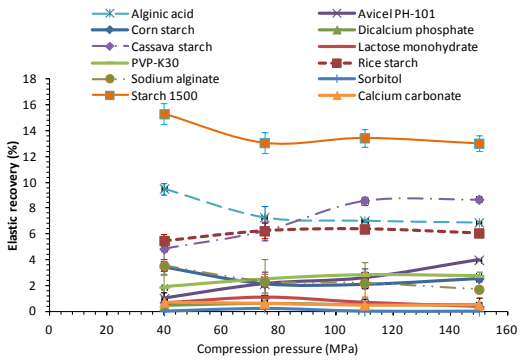

Figure 7. Elastic recovery of the compacts measured five days after ejection.

DISCUSSION

Lubricant effect on compressibility, porosity and flowability

Figure 1 shows the change in percent volume reduction capacity and, indirectly, the flowability of the excipients, as a result of the addition of the lubricant. As expected, most lubricants improved the volume reduction capacity and flow of the excipients when they were added. This means that once the lubricant and the respective excipient were blended, a lubricant film was formed around the excipient particles, easing their rearrangement, sliding and packing in the powder bed. As a consequence, the powder bulk and tap densities increased and porosity decreased, as compared to the unlubricated materials (Figure 2). Other authors have found similar results, especially when lubricants such as talc and stearic acid are employed (Wang et al., 2010). In terms of efficiency, highly hydrophobic lubricants such as magnesium stearate induced the largest volume reduction in most excipients.

Figure 3 shows the increase in flowability due to the presence of lubricant. In most cases, powder flowability was improved by the decrease in friction and adhesion among powder particles. Lubricants, especially magnesium stearate, increased the excipient bulk density. This improvement in bulk density due to the lubricants is an indication of good flowability, a small contribution to particle rearrangement and less friction during powder consolidation, as reported previously (Bolhuis et al., 1988). The small size (<10 μm) and smoothness of calcium carbonate particles promoted good surface coating by the lubricant, resulting in good flow. Likewise, large (>50 μm) and smooth particles, such as Starch 1500, PVP-K30, and lactose monohydrate, showed similar behavior. These results also suggest that a decrease in particle roughness due to lubrication could be associated with an increase in powder flowability (Figure 4). Conversely, the rough surface of corn, rice and cassava starches, dicalcium phosphate, alginic acid, sodium alginate and sorbitol and the fibrous shape of Avicel PH-101 particles allowed them to trap most of the lubricant in their cavities and pores, so that the formation of a lubricant film on these porous materials is expected to be irregular. Similar observations have been reported previously (Rashid et al., 2011).

Some lubricants affected negatively the binding properties of these excipients, as reflected by their high lubricant sensitivity (LSR) ratios (Figure 5). The high magnesium stearate sensitivity (>0.3) of starch 1500, rice starch, cassava starch, alginic acid and PVP-K30 could be attributed to their plastic-deforming character, combined with their regularity in morphology and less porous structure, easing the formation of a continuous lubricant film. It is known that highly plastic-deforming materials are more susceptible to hydrophobic lubricants such as magnesium stearate (Mužíková & Eimerová, 2011). On the other hand, the low LSR of lactose monohydrate, corn starch, Avicel PH-101, sodium alginate and dicalcium phosphate is explained by their partial lubricant coating, which is caused by their irregular shape, rough surface and rearranging tendency during consolidation. The same result has also been observed previously for dicalcium phosphate (Otsuka et al., 2004). In general, the effect of highly hydrophobic lubricants such as magnesium stearate on LSR was stronger than that observed for stearic acid and talc, especially for corn starch, PVP-K30, Avicel PH-101, dicalcium phosphate, sodium alginate and cassava starch.

Further, materials with higher porosity (lower bulk density) have more void space to accommodate lubricant, resulting in a low LSR. For instance, Avicel PH-101, sorbitol and calcium carbonate exhibited the highest porosity (0.7-0.75) and, at the same time, a very low lubricant sensitivity. Moreover, Starch 1500 and rice starch had smoother surfaces than corn starch, which showed an irregular surface, and hence Starch 1500 and rice starch were more prone to film formation, as reflected in their high sensitivity to lubricant.

Sensitivity to magnesium stearate followed the rank (most to least sensitive): Starch 1500 > rice starch > PVP-K30 > alginic acid > cassava starch > calcium carbonate > sorbitol > sodium alginate > dicalcium phosphate > Avicel PH-101 > lactose > corn starch. Since calcium carbonate, lactose and dicalcium phosphate are known to be brittle deforming materials, these results indicate that lubricant sensitivity depended not only on particle characteristics (morphology, packing and surface roughness), but also on the deformation mechanism of these materials.

Dilution potential

An excipient for direct compression should have the ability to incorporate a certain amount of drug and form a tablet of sufficient strength. For this reason, the dilution potential (DP) was only determined for excipients that had friability values less than 1%. These materials were starch 1500, Avicel PH-101, corn starch, PVP-K30, sorbitol, sodium alginate and alginic acid (Figure 6). Surprisingly, all these materials are known to show plastic deformation upon consolidation. This means that in order to form a drug compact of adequate strength, it is important to select materials that form binding points by sliding and dislocation of the crystal planes. In this case, sorbitol, PVP-K30 and Avicel PH-101 were best plastic-deforming materials, affording a perfect combination with acetaminofen for powder consolidation and rendering compacts of good compactibility. Acetaminophen is known to be a drug with a brittle and elastic behavior upon consolidation, making it poorly compressible (Roberts & Rowe, 1985). Thus, its combination with highly plastic-deforming material is needed to counteract this effect. In the excipient:acetaminophen blend, acetaminophen is assumed to have practically no bonding strength, owing to its highly elasticity, and thus, only the excipient contribution is considered relevant to the tablet strength. These results indicate that PVP-K30, sorbitol and Avicel PH-101 are the most desirable excipients when formulating poorly compactible drugs such as acetaminophen.

Elastic recovery of tablets

The percent axial expansion of the compact upon decompression is depicted in Figure 7. As mentioned previously, PVP-K30 and sorbitol had the best dilution

potentials and, thus, excellent binding properties, due to their strongly cohesive and plastic-deforming character, easing the formation of good compacts in blends with acetaminophen. Further, Starch 1500, alginic acid, rice and cassava starches are good examples of plastic-deforming materials which, at the same time, exhibited high elastic recovery (>4%). For this reason, it is possible that these materials are in a rubbery state at room temperature and, as a result, their high elasticity might cause lamination and capping problems, as suggested previously (Schmid & Picker-Freyer, 2009). Conversely, PVP-K30, corn starch, lactose, dicalcium phosphate, calcium carbonate, Avicel PH-101 and sorbitol exhibited virtually no change in elastic recovery with applied compression force. This behavior could be due to the possible low free energy stored upon compression due to the formation of new particles behaving less elastically. Moreover, the starch source clearly affected the elastic relaxation of this material. For example, Starch 1500, cassava and rice starches showed higher ER than corn starch. The above results suggest that sorbitol, Avicel PH-101, PVP-K30, sodium alginate and Starch 1500 could serve as excipients for direct compression, owing to their low elastic recovery and excellent dilution potential.

Concluding remarks

Lubricants increased the powder packing and flowability of the excipients. Surface roughness, irregularity in morphology of the particles and a high tendency to fragment resulted in partial lubricant coating, especially with magnesium stearate, leading to low lubricant sensitivity. Hydrophobic lubricants such as magnesium stearate had a major effect on compactibility, especially of plastic-deforming materials. Lubricant sensitivity alone cannot be used to determine the deformation mechanism of an excipient, since other factors such as powder packing properties and morphology should also be taken into account. Strongly binding excipients, such as PVP-K30, sorbitol, Avicel PH-101, corn starch and sodium alginate, had the best dilution potential, low elastic recovery and good flow, making them suitable as direct compression agents.

ACKNOWLEDGEMENTS

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RESUMO

Triagem de vários excipientes para compressão direta: Uma nova perspectiva com base nas propriedades funcionais

Os excipientes são materiais amplamente utilizados para formular fármacos através de compressão direta. No entanto, as propriedades do pó e compressão desses materiais são afetadas pela presença de lubrificantes e ingredientes ativos. Este estudo utilizou uma metodologia para avaliar a eficácia destes materiais como agentes de compressão direta. O efeito de três lubrificantes (estearato de magnésio, ácido esteárico e talco) na compressibilidade e compactação dos materiais foi avaliado pelo índice de compressibilidade e sensibilidade do lubrificante, respectivamente. Da mesma forma, a capacidade da diluição foi avaliada com um fármaco pouco compressível como o acetaminofeno. Finalmente, a recuperação elástica dos comprimidos foi avaliada aos cinco dias após a produção. Todos os lubrificantes aumentaram a compressibilidade destes materiais e a sua fluidez. No entanto, os lubrificantes hidrofóbicos, tais como o estearato de magnésio tem um efeito negativo sobre a compactação, em especial em materiais plásticos com uma superfície lisa, como o amido 1500. O amido de arroz e de mandioca e ácido algínico apresentaram a maior recuperação elástica (> 5%), indicando uma elevada tendência para a laminação. Além disso, os materiais plásticos com alta deformação, tais como o sorbitol, e polivinilpirrolidona (PVP-K30), exibiram a melhor potencial de diluição (~10%), enquanto que o ácido algínico mostrou um valor muito elevado (~ 70%). Em termos de desempenho, o sorbitol, o PVP-K30, alginato de sódio, Avicel PH-101, e de amido pré-gelatinizado são os materiais mais adequados para a compressão direta de fármacos.

Palavras-chave: Diluente. Ligante. Compressão direta. Lubrificantes. Recuperação elástica. Potencial de diluição.

REFERENCES

Armstrong NA, Haines-Nutt RF. Elastic recovery and surface-area changes in compacted powder systems. J Pharm Pharmacol. 1972; 24(Suppl.):135-36.

Asano T, Kanaya Y, MiyajimaI M, Sato H, Sugawara S, Tsubuku S, Yuasa H. Changes in volume and compression energy upon compression of calcium silicate tablets. Drug Dev Ind Pharm. 1997;23(7):679-85.

Bolhuis GK, Eissens AC, Frijlink HW, Hinrichs LJ. Inulin as excipient for tablets prepared by direct compaction. Eur J Pharm Sci. 2003;15:31-38.

Bolhuis GK, Holzer AW. Lubricant sensitivity. In: Alderborn G, Nystrom C, editors. Pharmaceutical powder compaction technology. New York, NY, USA: Marcel Dekker; 1996. p. 517-60.

Bolhuis GK, Lerk CF, Vromans H. Magnesium stearate susceptibility of directly compressible materials as an indication of fragmentation properties. Adv Powder Techol. 1988;54(1):39-44.

Bolhuis GK, Van Der Voort, MK, Zuurman K. Effect of magnesium stearate on bonding and porosity expansion of tablets produced from materials with different consolidation properties. Int J Pharm. 1999;179(1):107-15.

Bolhuis GK, Zuurman K. Tableting properties of experimental and commercially available lactose granulations for direct compression. Drug Dev Ind Pharm. 1995;21(18):2057-071.

Çelik M, Mollan MJ. The effects of lubrication on the compaction and post-compaction properties of directly compressible maltodextrins. Int J Pharm. 1996;144(1):1-9.

Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. J Pharm Pharm Sci. 2005;8(1):76-93.

Haware RV, Tho I, Bauer-Brandl A. Evaluation of a rapid approximation method for the elastic recovery of tablets. Adv Powder Techol. 2010;202(1-3):71-7.

Hein S, Picker-Freyer KM, Langridge J. Simulation of roller compaction with subsequent tableting and characterization of lactose and microcrystalline cellulose. Pharm Dev Technol. 2008;13(6):523-32.

Kim H, Fasshihi R, Venkatesh G. Compactibility characterization of granular pectin for tableting operation using a compaction simulator. Int J Pharm. 1998;161(2):149-59.

Kushner J, Moore F. Scale-up model describing the impact of lubrication on tablet tensile strength. Int J Pharm. 2010;399(1-2):19-30.

Minchom CM, Armstrong NA. A proposed technique for expressing the capacity of direct compressible tablet diluents. In: 124. British Pharmaceutical Conference; 1987 Sep 14-17; Manchester. 1987:69-72.

Mužíková J, Eimerová I. A study of the compaction process and the properties of tablets made of a new co-processed starch excipient. Drug Dev Ind Pharm. 2011;37(5):576-82.

Odeku OA, Schmid W, Picker-Freyer KM. Material and tablet properties of pregelatinized (thermally modified) Dioscorea starches. Eur J Pharm Biopharm. 2008;70(1):357-371.

Otsuka M, Matsuda Y, YamaneA I. Effects of lubricant mixing on compression properties of various kinds of direct compression excipients and physical properties of the tablets. Adv. Powder Technol. 2004;15(4):477-93.

Picker-Freyer KM. “Soft tableting”: a new concept to tablet pressure-sensitive materials. Pharm Dev Technol. 2004;9(1):107-21.

Pingali K, Mendez R, Lewis D, Michniak-Kohn B, Cuitino A, Muzzio F. Mixing order of glidant and lubrication–Influence on powder and tablet properties. Int J Pharm. 2011;409(1-2):269-277.

Rashid I, Al-Remawi M, Leharne SA, Chowdhry BZ, Badwan A. A novel multifunctional pharmaceutical excipient: Modification of the permeability of starch by processing with magnesium silicate. Int J Pharm. 2011;411(1-2):18-26.

Riepma KA, Lerk CF, Vromans H. A coherent matrix model for the consolidation and compaction of an excipient with magnesium stearate. Int J Pharm. 1993;97(1-3):195-203.

Roberts RJ, Rowe RC. The effect of punch velocity on the compaction of a variety of materials. J Pharm Pharmacol. 1985;37(6):377-384. DOI: 10.1111/j.2042-7158.1985.tb03019.x.

Schmid W, Picker-Freyer KM. Tableting and tablet properties of alginates: characterization and potential for soft tableting. Eur J Pharm Biopharm. 2009;72(1):165-72. DOI: 10.1016/j.ejpb.2008.10.006.

Viseras C, Lopez-Galindo A, Yebra A. Characteristics of pharmaceutical grade phyllosilicate compacts. Pharm Dev Technol. 2000;5(1):53-58.

Wang J, Desai D, Wen H. Lubrication in tablet formulations. Eur J Pharm Biopharm. 2010;75(1):1-15. DOI: 10.1016/j.ejpb.2010.01.007.

Wells J, Landridge J. Dicalcium phosphate dihydrate-microcrystalline cellulose systems in direct compression tableting. Int J Pharm Techol Prod Manf. 1981;2:1-8.

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