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Research Article

Functionality enhancement of sorbitol and anhydrous calcium diphosphate composites for direct compression applications

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ABSTRACT

Sorbitol and calcium diphosphate have been used as diluents for making solid dosage forms. However, due to their intrinsic properties these two materials cannot be used for direct compression applications. In order to improve their functional properties, coprocessing of sorbitol with anhydrous calcium diphosphate was conducted by spray drying, agglomeration, hot melt granulation and cocrystallization. The resulting powder and tableting properties and the selection of the best technology were evaluated by the principal component analysis. Bulk and tap densities increased with increasing calcium diphosphate levels. Spray drying rendered highly porous materials with the lowest yield, whereas agglomeration rendered a product yield of ~90%. Hot melt rendered materials with the best compactibility. The bulk and tap densities, product yield and porosity of the composites depended on the technology employed. On the contrary, properties such as true density, compact tensile strength and tablet disintegration times were more dependent on the level of calcium diphosphate rather than on the technology used. Further, processing time was independent of the technology and level of calcium diphosphate. Coprocessing proved to be useful tool to modify the powder properties of sorbitol. The agglomeration was selected as the most practical technology for the production of sorbitol:calcium diphosphate composites for direct compression applications.

Keywords: Coprocessed excipient; direct compression; sorbitol; anhydrous calcium diphosphate

INTRODUCTION

For many years, not a single new chemical excipient has been introduced into the market since excipients are developed in response to market demands. This is explained by the high cost involved with discovery, development and toxicology tests required for new chemical entities. However, there is a growing pressure on formulators to search for new multifunctional excipients quickly, with no scaling up, manufacturing and environmental costs to achieve the desired set of functionality. The growing popularity of the direct compression process demands for an ideal excipient, which can substitute two or more ingredients in a tablet formulation (Marwaha et al., 2010).

Nowadays, coprocessing is the most widely used technology to develop new grades of excipients. In this technology excipients interact at the particle level providing a synergy of functionality as well as masking the undesirable properties of the individual components (Block et al., 2009). A coprocessing excipient has superior properties compared to the simple physical

blending of their components (Reimerdes, 1999; Nachaegari and Bansal, 2004).

Currently, sorbitol (SOR) and anhydrous calcium diphosphate (ACD) are excipients used as diluents for the preparation of solid dosage forms. Particularly, sorbitol is used for making lozenges, chewable, and orally disintegrating tablets. It exists in the α , β , and γ forms (Guyot-Hermann, 1985). The γ form is the most stable and presents the best compaction, disintegration and dissolution characteristics. It is lubricant insensitive (Reiff, 1986). However, if stored at RH > 65% induces liquefaction, whereas if stored at a low RH causes recrystallization, causing tablet hardening and instability of moisture sensitive drugs. It also clumps in the feed of the hopper and sticks to the surface of the die during tableting at RH > 50% (Lachman, 1986).

On the other hand, anhydrous calcium diphosphate (ACD) is inexpensive. The anhydrous and hydrated forms can be used for wet granulation (Miyazaki et al., 2009). It is relatively insensitive to alkaline lubricants. It requires the addition of lubricants and disintegrants and its tablets possess high porosity. On storage, compacts become hard delaying dissolution times, specifically when stored at low RH (Doldan et al., 1995).

One way to solve the above mentioned problems and improves their functionality is by coprocessing. Thus, sorbitol is a plastic deforming material and calcium diphosphate is brittle material (Saha and Shahiwala,

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2009). This combination prevents storage of too much elastic energy during powder compression, which is associated to the formation of weak compacts and the tendency for capping and lamination (Bolhuis and Chowhan, 1996). In this study, for the first time coprocessing of sorbitol and calcium diphosphate by spray drying, agglomeration, hot melt granulation and cocrystallization was undertaken and the resulting changes of the functional properties were revealed by principal component analysis. The study of calcium diphosphate with enhanced physicochemical and mechanical properties through coprocessing represents not only an alternative but also an attractive research area. The increasing market is continuously demanding for new, improved or less expensive excipients (Rojas, 2014).

MATERIALS AND METHODS

Sorbitol was obtained from Bell Chem international (Longwood, FL). Anhydrous calcium diphosphate was obtained from Innophos (Cranbury, NJ).

Preparation of SOR:ACD composites by spray drying

Appropriate amounts of sorbitol and calcium diphosphate, equivalent to give 50:50 and 80:20, w/w ratios, were mixed and diluted with distilled water to obtain a 50% dispersion using a homogenizer (JK-T18, Ultraturrax, Taquara, Brazil) for 10 min. A Buchi spray-drier (B290, Zurich, Switzerland) was employed at the previously optimized spraying conditions of inlet air temperature (IT) 150 °C; atomizing air pressure (AA) 180 kPa; drying air rate (DA) 35m³/h; feed flow rate (FR) 5.0 ml/min and nozzle diameter (ND) 0.8 mm.

Preparation of SOR:ACD composites by agglomeration

Appropriate amounts of sorbitol and calcium diphosphate at a 5:95, 10:90, 20:80, 50:50, 80:20 and 90:10 w/w ratios, were mixed and wetted with distilled water. The resulting mass was passed through a # 14 mesh. The resulting homogeneous mixture was agglomerated for 5 min at 30 degrees tilt and dried at 60°C for 24 h and passed through a # 60 mesh sieve.

Preparation of SOR:ACD Composites by hot-melt granulation

Appropriate amounts of sorbitol and calcium diphosphate at a 5:95, 10:90, 20:80, 50:50, 80:20 and 90:10 w/w ratios were prepared and heated until melting with stirring. The melt was poured on a granulator equipped with # 8 mesh screen. The granules obtained were dried, either in air or in a convection oven at 60°C until the moisture content was less than 5%. Then, the material was submitted to ball milling and passed through a # 60 mesh sieve.

Preparation of SOR:ACD CII-SiO₂ composites by cocrystallization

Appropriate amounts of sorbitol slurry and calcium diphosphate, equivalent to give at a 5:95, 10:90, 20:80,

50:50, 80:20 and 90:10 w/w ratios, were mixed and diluted with distilled water to obtain a 10% dispersion using a homogenizer (JK-T18, Ultraturrax, Taquara, Brazil) for 10 min. The resulting dispersion was submitted to heating at 95°C and evaporated slowly with stirring until crystals were obtained. These crystals were dried in a convection oven at 60°C for 24h. Crystals were then ball milled and passed through a # 60 mesh sieve.

Powder and tableting properties

Approximately 20 g of SOR:ACD composites were fractionated for 10 min on a Ro-Tap sieve shaker (RX29, W.S. Tyler Company, Mentor, OH) using stainless steel 250, 177, 150, 125, 105, 75, 45, and 38 µm size sieves, stacked together in the order mentioned. The mean particle size was determined from the log-normal distribution plot constructed between sieve mean diameters versus cumulative percent frequency using the Minitab software (v.16, Minitab, Inc, State College PA). A Helium displacement micropycnometer (Accupyc 1340, Micromeritics Corp, USA) was employed to obtain the materials true density (ρ_{true}). Bulk density (ρ_{bulk}) was obtained directly from ratio of 20 g powder and its volume measured in 50 cm³ graduate cylinder. Tap density (ρ_{tap}) was determined using a tap density analyzer (AT-2, Quantachrome instruments, USA) measuring the volume after 400 taps. Porosity (ϵ) of the powder was determined from the equation: $\epsilon = (1 - \rho_{bulk}/\rho_{true}) * 100\%$. Moisture content was obtained using an infrared moisture scale (MB200, Ohaus, NJ, USA) at 105°C for 5 min. Flowability was determined by filling a glass funnel with ~20 g of the powder and measuring the flow time through a funnel having a 13 mm diameter.

Cylindrical compacts of 1 g each were produced on a single station tablet press (Compac 060804, Indemec, Colombia) equipped with 13 mm flat-faced punches and die tooling at ~150 MPa and a dwelling time of 1 s. The compact tensile strength was determined on a Vankel hardness tester (UK 2000, Manasquan, NJ, USA) and the compact disintegration was determined on a disintegration apparatus (39-133-115, Hanson Research Corp., Northridge, USA).

Statistical analysis

The principal component analysis (PCA) was the type of multivariate analysis used to identify patterns and relationship among data. PCA will be employed to transform the original data on terms or two eigenvectors or axes which are perpendicular to each other. The software Minitab (v. 16, Minitab, Inc, State College, PA) was used for data processing.

RESULTS AND DISCUSSION

The application of spray drying for the production of SOR:ACD composites resulted in large sticking and adhesion problems into the drying chamber when

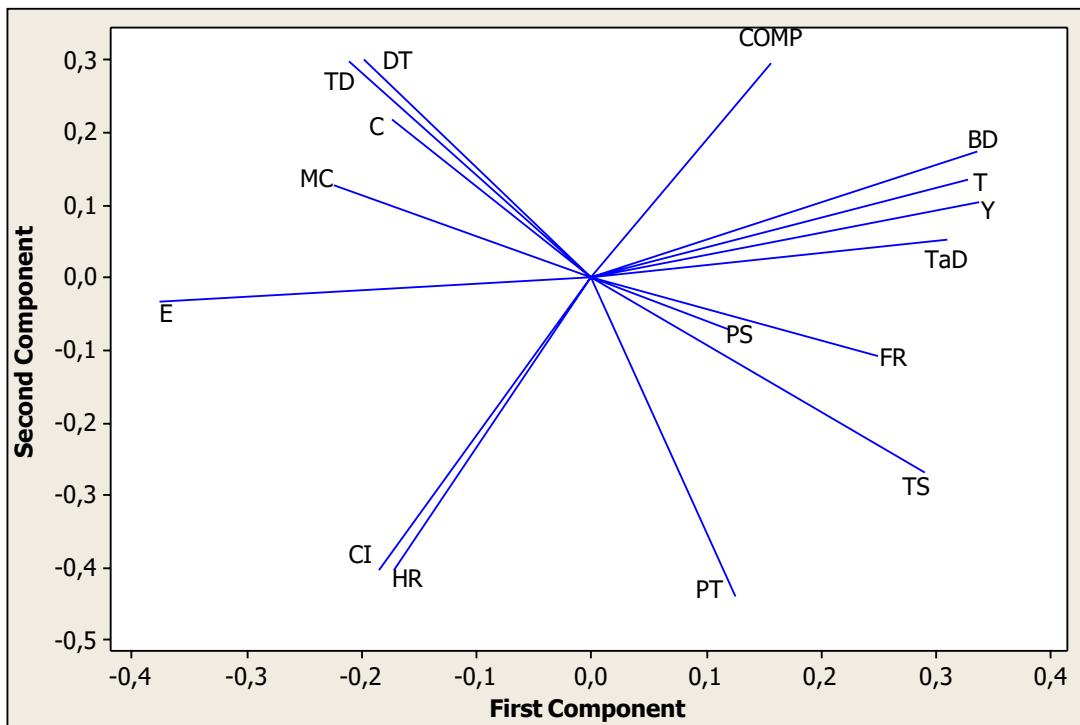


Figure 1: Loading plot of measured properties of SOR:ACD composites

DT: disintegration time, TD: true density, MC: moisture content, E: porosity, CI: Carr index, HR: Hausner ratio, PT: processing time, PS: particle size, TS: tensile strength, FR: flow rate, TaD: tap density, Y: yield, T: technology, BD: bulk density

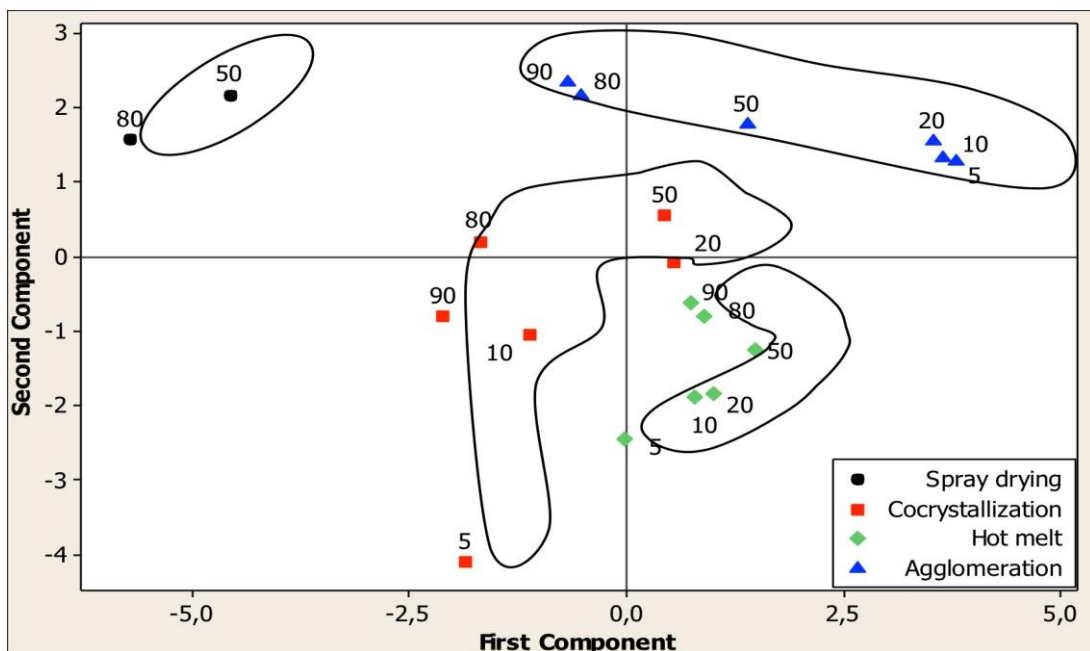


Figure 2: PCA score plot of measured properties for SOR:ACD composites

amounts or sorbitol larger than 50% were employed. As a consequence, the worse product yields of lower than 1% were obtained. For this reason, only the 50:50 and 75:25 (ACD:SOR) ratios were successfully produced and evaluated in this study. On the other hand, agglomeration of these composites was the fastest and more practical technology rendering yields of ~90%.

In general, most composites presented a positively skewed distribution and particle size did not depend on the technology employed. On the other hand, true density of the composites increased with increasing amounts of ACD independent of the technology employed. ACD itself possesses a higher true density and thus, the resulting composite materials have an in-

creased true density. The moisture content for all materials was <5.0 % w/w indicating that sorbitol, which is the only hygroscopic material, did not contribute to moisture of the composites.

Compared to SOR alone, increasing levels of ACD increased the bulk and tap densities of samples. ACD was able to pack more decreasing voids spaces in the composites. Thus, composites having low levels of ACD exhibited low bulk and tap densities, and these composites can be used in the production of high dose tablets, in which bulky compacts are not desirable. On the other hand, the degree of cohesiveness given by the Hausner ratio increased as the level of ACD in the composite was larger than 80%. This suggests that cohesiveness increased with a decrease in particle size. The highly cohesive materials have a high interparticulate friction and thus, they are not recommended for tableting. Further, the technology employed did not vary porosity, except for spray drying which rendered highly porous materials due to a large coating effect on sorbitol. Conversely, all other technologies mostly incorporated sorbitol in the core of the particles. The way in which gravity overcomes the cohesive forces and the interlocking structure of the materials is reflected in their flow. In general, hot melt, rendered materials with slightly largest flow and produced the strongest compacts due to the formation of solid bridges in the compacts attributed to the fused composite particles.

In order to understand the overall relationship among all the functional composites properties a principal component analysis (PCA) was conducted. In this scenario, a loading plot of measured properties depicted in Figure 1 shows projections of these properties onto the PC1 and PC2 in a plot. The loadings can be understood as weights for each original property when calculating the principal component. This plot is the result of the linear combination of original data that maximizes data variance. Further, each point in the graph indicates the contribution of this property in defining these components. Factors contributing very little to the components such as particle size, showed a small loading value and appear plotted near the center. This factor had virtually no effect on the overall behavior of the functional properties, whereas, most of the other factors had a largest influence on all properties. Further, the technologies employed had a large influence on product yield and particle densification and densification and in turn, was most directly opposite to the porosity vector indicating an inverse correlation.

On the other hand, the level of ACD was directly related with the true density of composites and compact disintegration, whereas, it was inversely correlated to particle size, flow rate and compact tensile strength. This is explained by the increasing contribution of ACD particles in the composite formed which made the brittle deforming character more dominant and thus forming weaker compacts with faster disintegration times.

Further, ACD produced composite particles of a more cohesive behavior, hindering flowability and at the same time increased the true density due to the dense crystalline nature which favored densification of the resulting composite particles. Moreover, the Hausner ratio and Carr index were related with densification and inversely related to compressibility. This means that the already highly densified materials had a very low ability for volume reduction.

In this study, the PC1, and PC2 coordinates had a variance of 6.0, and 3.2, respectively, and accounted for ~57.4% of the total variance, indicating that most data structure was captured into these two underlying dimensions.

The PC1 vector was mainly influenced to the technology and densification properties, whereas PC2 was mostly related to the ACD level factor and tablet properties.

The resulting scores for PC1 and PC2 can be expressed as:

$$PC1 = 0.33T+0.29TS+0.34BD+0.31TaD-0.38E+0.34Y$$

$$PC2 = 0.30TD+0.30COMP+0.30DT-0.44PT-0.4HR-0.4CI$$

The score plot of the properties studied is shown in Figure 2. It separated and classified all technologies based on the collective resulting material properties. For instance, spray drying is depicted at the upper left side of the PC. This technology was important for producing materials with the largest porosity, lowest flow and densities and had the lowest yield and processing time. Likewise, in the upper right coordinate the collective data due to the agglomeration technology. They also had a low processing time and the best product yield making it most practical easing its industrial scale-up. On the other hand, the cocrystallization technology is shown as a cluster in the center of the plot, whereas, the hot melt technology is depicted as a cluster in the lower right coordinate. The overall data of these technologies are closed since the resulting properties were very alike.

The label in each data point indicates the level of ACD in the composite. It increased from the right to the left and from bottom to top. This indicates that properties such as densification were highly dependent on the level of ACD and moves in this way since in the loading plot are located in the right side and the level factor is located at the left of the plot.

CONCLUSION

The bulk and tap densities, product yield and porosity of the composites depended on the technology employed. On the contrary, properties such as true density, compact tensile strength and disintegration times were more dependent on the level of ACD rather than on the technology used. Further, processing time was independent of the technology and level of ACD. The agglomeration was selected as the most practical tech-

nology for the production of SOR:ACD composites for direct compression applications.

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REFERENCES

- Block, L.H., Moreton, R.C., Apte, S.P., Wendt, R.H., Munson, E.J., Creekmore, J.R., Persaud, I.V., Sheehan, C. Co-processed Excipients. *Pharm forum*, 35, 2009 pp. 1026-1028.
- Bolhuis, G.K., Chowhan, Z.T. Materials for direct compression. In: Alderborn, G., Nystrom, C., editors. *Pharmaceutical Powder Compaction Technology*, New York, Dekker, 1996 pp. 419-500.
- Doldan, C., Souto, C., Concheiro, A., Martinez-Pacheco, R., Gomez-Amoza, J. Dicalcium phosphate dihydrate and anhydrous dicalcium phosphate for direct compression: a comparative study. *Int J Pharm*, 124, 1995 pp. 69-74.
- Guyot-Hermann, A. and Draguet-Brughmans, M. Gamma sorbitol as a diluent in tablets. *Drug Dev Ind Pharm*, 11, 1985 pp. 551-564.
- Lachman, L., Lieberman, HA., Kanig, J.L. *The Theory and Practice of Industrial Pharmacy*. 3rd ed. Philadelphia: Lea and Febiger, 1986 pp. 1317-1318.
- Marwaha, M., Sandhu, D., Marwaha, R. Coprocessing of excipients: A review on excipient development for improved tableting performance. *Int J Appl Pharm*, 2, 2010 pp. 41-47.
- Miyazaki, T., Sivaprakasam, K., Tantry, J., Suryanarayanan, R. Physical characterization of dibasic calcium phosphate dihydrate and anhydrate. *J Pharm Sci*, 98, 2009 pp. 905-916.
- Nachaegari, S.K., Bansal, A.K. Coprocessed excipients for solid dosage forms. *Pharm Technol*, 28, 2004 pp. 52-65.
- Narang and Boddu. Excipient Applications in Formula-tion Design and Drug Delivery. In *Coprocessed excipients for direct compression application*. 1st ed. Springer, 2015 pp. 220-230.
- Reiff, F., Hartner, H., Basedow, A., Hugenbusch, H.W., Schmidt, P.C., Bardonner, H., inventors; Sorbitol, process for its preparation, and use thereof. US Pat 4,605,794. 1986.
- Reimerdes, D. The near future of tablet excipients. *Manuf Chem*, 64, 1993 pp. 14-15.
- Saha, S., Shahiwala, A.F. Multifunctional coprocessed excipients for improved tableting performance. *Expert Opin Drug Deliv*, 6, 2009 pp. 197-208.