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The Benefits of Using Polyplasdone™ crospovidone and Cellulosic Polymers as Processing Aids in Extrusion-Spheronization Process

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Introduction

Extrusion-spheronization is a common process used to develop spherical pellets for formulations containing multiple APIs and in the nutraceutical industry. The pellets can be pressed into a tablet but are commonly inserted into a gelatin or hypromellose (HPMC) capsule. Aesthetic or functional (enteric or controlled) coatings may be applied onto the pellets using a fluidized bed. This process involves the need for robust pellets in order to prevent surface attrition and cracking of the pellets to maintain aesthetics and dose uniformity. This study investigated the use of Polyplasdone™ XL-10 crospovidone, Klucel™ ELF HPC, Benecel™ E5 HPMC, and Benecel K100LV HPMC as extrusion-spheronization processing aids in improving pellet robustness. Vitamin C was used as the model API. Microcrystalline cellulose, a common filler, was used as the base and control.

Methods

Extrusion-Spheronization. Extrusion-spheronization polymer aids tested consisted of Benecel E5 HPMC, Benecel K100LV HPMC, Polyplasdone XL-10 crospovidone, and Klucel ELF HPC. Blends consisting of 50% Vitamin C, 5 or 10% processing aid, and the balance being microcrystalline cellulose (MCC) were produced. The blend was wet granulated in a high shear mixer at 500 rpm chopper and agitator speed. Deionized water was sprayed onto the blend until the wet granules formed a dough of a certain consistency was extruded with the Marumerizer at 35 rpm with a 0.8 mm die. The extruded strands were shaped into spherical pellets using the Marumerizer spheronizer and dried in an industrial oven until they reached a moisture content of < 2%. The dried pellets were screened through 18 and 35 mesh screens to get 0.5 mm to 1.0 mm diameter pellets.

Image Analysis A Morphologi G3 particle size analyzer was used to determine the circularity of the pellets. Each sample was spread on a glass plate and scanned under a microscope objective. Digital images were taken of approximately 1500 particles. The circularity aspect ratio was calculated as the ratio of the width to the length of the particle (0 indicating a rod/oblong shape and 1 a perfect circle).

Pellet Stiffness and Force-Distance Curves. AFM measurements were performed in air on a BioScope Catalyst Atomic Force Microscope (Bruker Corporation) using a high spring force silicon nitride cantilever (200N/m, Tap525; Bruker Corporation). Samples were placed on standard microscope slides and fixed in place with epoxy. The elastic modulus was determined using the Peak Force Quantitative Nano Mechanical (PFQNM) mode of operation and scanning a 5 × 5 m^2 sample area. The PFQNM mode uses the Derjaguin-Muller-Toporov (DMT) model to estimate the elastic modulus (1). The average elastic modulus of each sample was calculated from the histogram of values obtained from approximately 10,000 individual force-separation measurements.

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientist, October 14-18, 2012, Chicago, Illinois

<u>Crushing Force</u>. A pellet was placed between two polished stainless steel platens. A crosshead speed of 0.02 inch/min and a terminal test gap of 0.4 mm were used. The crushing force was reported as the first peak in the load deflection curve.

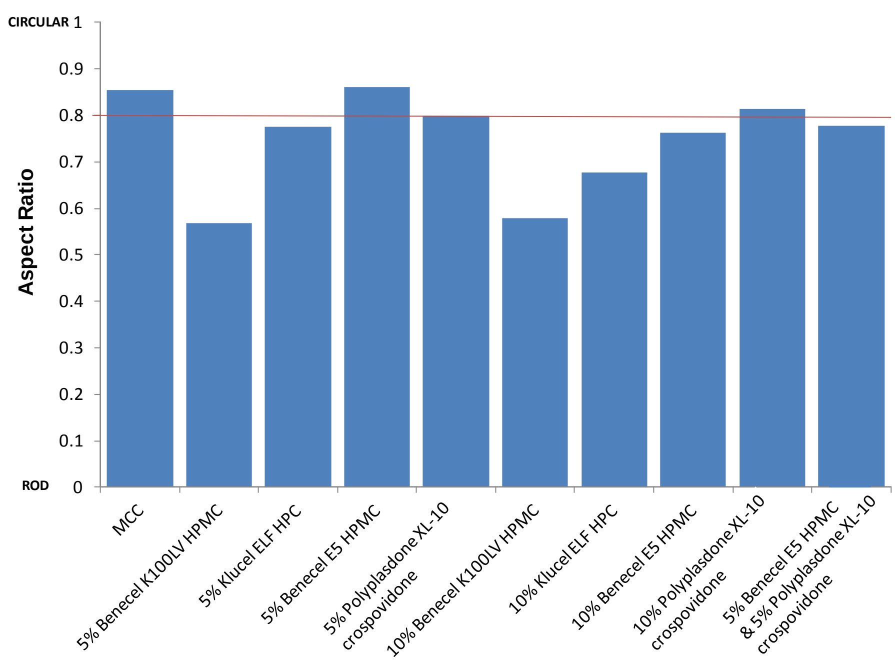
Materials

1. Vitamin C (RIA International, East Hanover, NJ)
2. Benecel™ E5 HPMC and K100LV, (Ashland Inc., Wilmington, DE)
3. Polyplasdone™ XL-10 crospovidone, (Ashland Inc., Wilmington, DE)
4. Klucel™ ELF HPC, (Ashland Inc., Wilmington, DE)
5. Avicel* MCC microcrystalline cellulose PH 102 (FMC BioPolymer, Philadelphia, PA)

Results and Discussion

The Vitamin C pellets made by extrusion-spheronization were all reasonably spherical in shape, as indicated in Figure 1. The pellets made with only MCC as the filler had good spherical shape, as indicated by an aspect ratio above 0.8. The addition of crospovidone or the cellulose ether polymers did not provide a great benefit in improving the shape of the pellet. The formulation containing 5% Benecel E5 HPMC exhibited an aspect ratio of above 0.8. In addition, formulations containing 5% or 10% Polyplasdone XL-10 crospovidone just met the criteria of an acceptable circularity aspect ratio of 0.8. Formulations containing other polymers (Benecel K100LV HPMC and Klucel ELF HPC) produced more oblong or rod-shaped pellets.

Figure 1
Circularity of Extrusion-Spheronization Pellets Made With Different Processing Aids



Benefits of using Polyplasdone™ XL-10 crospovidone and the cellulosic Benecel™ E5 HPMC were observed when investigating the crushing force (Figure 2), stiffness (Figure 3), and plasticity (Figure 4) of the Vitamin C pellets. The addition of Polyplasdone XL-10 crospovidone improved the crushing force of the pellet. A synergistic effect is observed when using both Polyplasdone XL-10 crospovidone and Benecel E5 HPMC further improving the pellet robustness. Benecel E5 HPMC did improve the stiffness of the pellets (Figure 3) due to enhancing the elasticity of the pellets (Figure 4C) as indicated with the approach and retract force aligning with each other. Pellets made with MCC only as the filler had similar elastic behavior with slight plastic deformation. Polyplasdone XL-10 crospovidone produced more flexible pellets (Figure 3) prone to plastic deformation (Figure 4B).

Figure 2
Effect of Processing Aid on the Crushing Force of Pellets

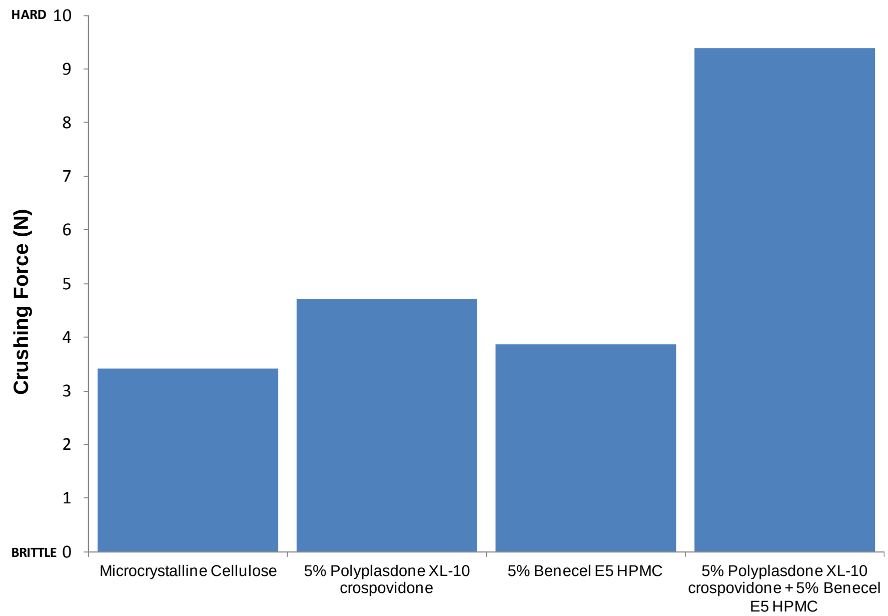


Figure 3
Effect of Processing Aid on the Stiffness of the Extrusion-Spheronization Bead

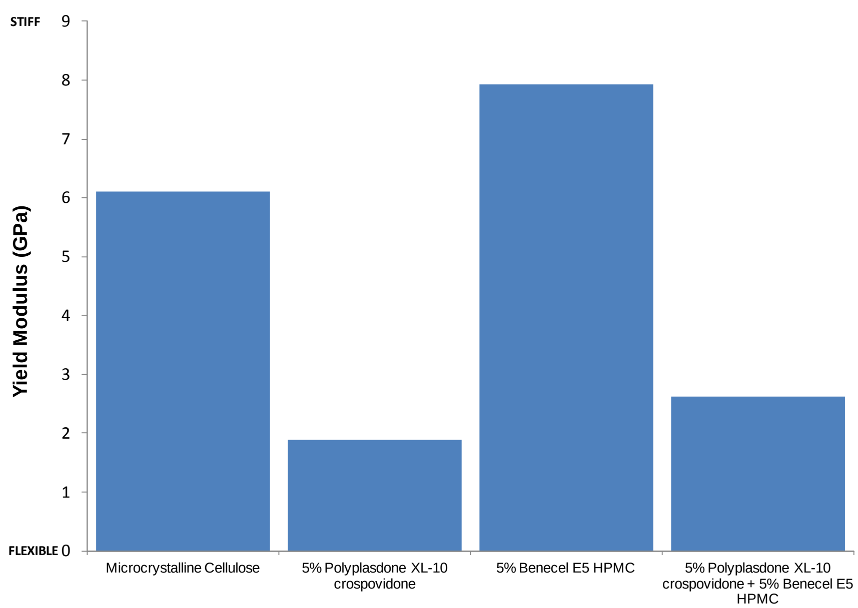
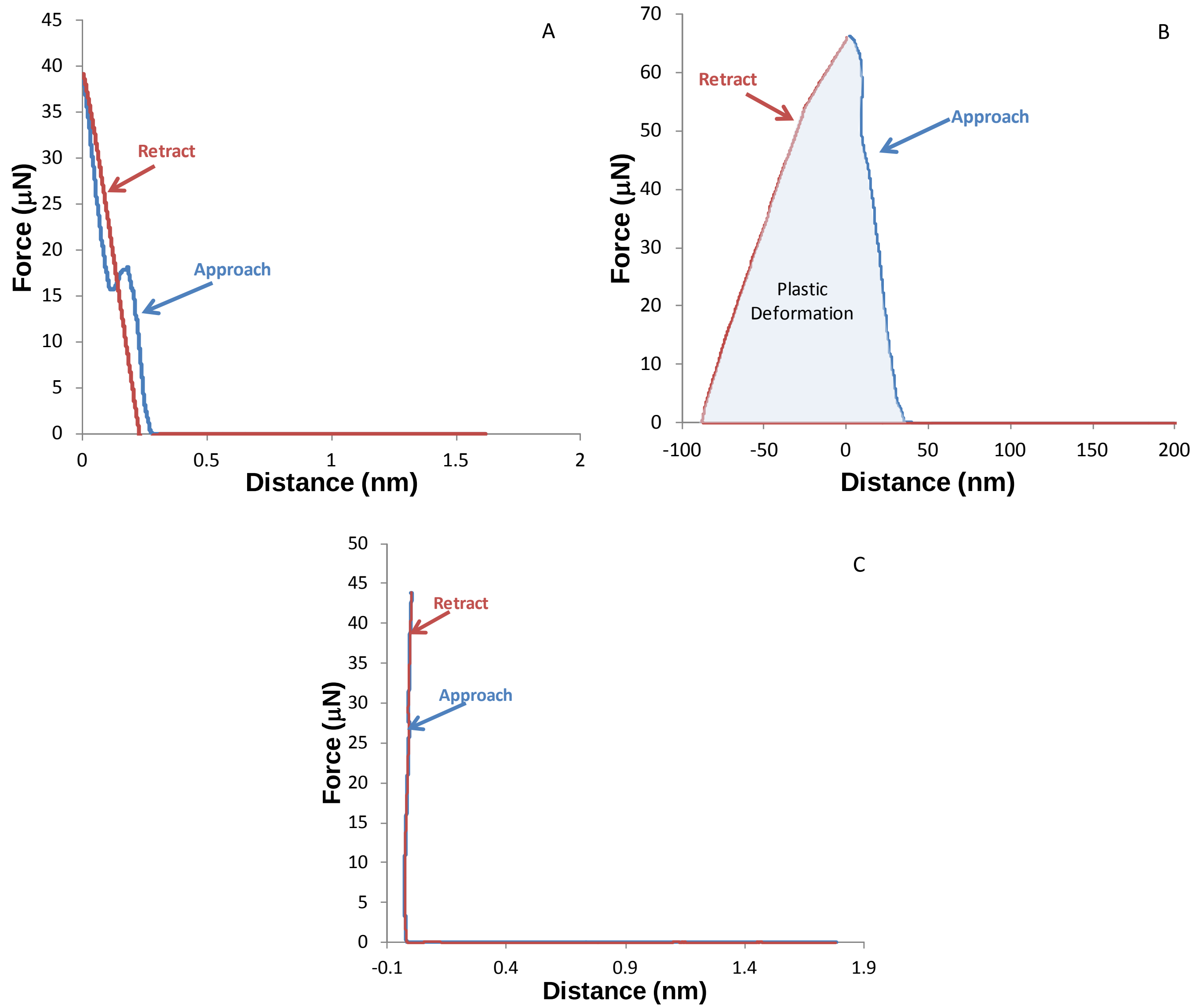


Figure 4
Effect of Using (A) No Processing Aid and (B) The Processing Aid Polyplasdone™ XL-10 crospovidone or (C) The Processing Aid Benecel™ E5 HPMC on the Stiffness and Plasticity of the Extrusion-Spheronization Bead Using Atomic Force Microscopy (AFM)



Conclusions

The effect of excipients on the aesthetics and robustness of pellets made by extrusion-spheronization is an important factor to consider when developing formulations for the purpose of preparing such pellets. While microcrystalline cellulose (MCC) is an universal and cost-effective filler, additives, such as Polyplasdone XL-10 crospovidone and Benecel E5 HPMC assist in improving the robustness of the pellets. Polyplasdone XL-10 crospovidone was observed to enhance the crushing force of the pellets making them less susceptible to fracture during a coating. Benecel E5 HPMC improved the elasticity behavior of the pellets making them less prone to surface deformation.

References

1. Derjaguin, Boris V., Vladimir M. Muller, and Yuri P. Toporov. "Effect of Contact Deformations on the Adhesion of Particles." Journal of Colloidal and Interface Science. 1975; 53: 314.