

Starch Contrasts

Knowing the differences among pregelatinized starches will produce desired formulation release rates.

IN RECENT YEARS, FORMULATORS HAVE BEGUN TO LOOK PAST THE traditional uses of pregelatinized starch as binder, disintegrant and filler. Pregelatinized starch has revealed new applications to enhance drug stability by preferentially binding moisture, and to control release rates for developing modified-delivery dosages.

Pregelatinized starch is defined in USP26/NF21 as, “Starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. Some types of pregelatinized starch may be modified to render them compressible and flowable in character.” The monograph does not specify the level of gelatinization or modification of the starch or differentiate between fully and partially pregelatinized starches. Many commercially available pregelatinized starch products meet monograph requirements, but differ in levels of modification and functionality. Brookfield viscosity testing determines starch variations and provides insight into functional and physical—particle size, density and morphology—differences among starches with varying levels of modification (Fig. 1).

For instance, fully pregelatinized starch is extremely soluble in cold water, eliminating the need to prepare heated starch pastes for wet granulation applications. By eliminating this pre-solubilization step, the starch can be added directly to granulation equipment with other actives and excipients. Water can then be used as the granulation fluid.

Partially pregelatinized starch (PPS) contains soluble (gelatinized) and insoluble fractions. In most cases, the insoluble fraction comprises intact starch grains. The larger particle size of the more granular pregelatinized starch imparts better flow properties than native starch.

PPS contains unmodified and modified starch, so can be used in wet granulation applications as a cold-water binder and still retain high-disintegrant functionality for immediate-release dosage forms. PPS also has been used as a disintegrant and powder flow aid in direct-compression applications, improving content uniformity of low-dose actives. In order to ensure the homogeneity of small amounts of potent actives within a large quantity of excipients or diluents, blending techniques such as geometric dilution are often employed. The primary diluent, or pre-blend carrier, is mixed in equal proportion to the active. Then, twice the volume of excipient is added and the mixing continued. This process is repeated until all the diluent is used. In one direct-compression

application, Ahmed et. al.¹ evaluated various excipients as pre-blend carriers or diluents to enhance uniformity and reduce the segregation potential of a micronized, low-dose (0.7% w/w) active. The researchers mixed the drug substance with either lactose, microcrystalline cellulose or PPS and subjected each blend to vibration at a constant amplitude. The blend containing PPS as the pre-blend excipient yielded the most uniform results and superior content uniformity, with a mean drug content of 99% and relative standard deviation of 2%. Researchers speculated that PPS’ adhesive characteristics, pregelatinized nature and inherent moisture content could have contributed to blend homogeneity.

While the moisture content of starch is higher than other direct-compression excipients, the water activity—or equilibrium relative humidity (ERH)—is lower. Thus, formulations containing starch can equilibrate more slowly when exposed to high humidity. PPS might also enhance drug stability by preferentially binding moisture and decreasing the rate at which the ERH equilibrates with the environment².

The potential of PPS to bind moisture has practical applications in formulating moisture-sensitive actives. Superdisintegrants, while advantageous in some for-

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mulations, have a high propensity for moisture uptake compared to PPS and should not be used at higher than their recommended levels (Fig. 2).

For example, one study examined the effect of PPS on the stability of aspirin 81mg tablets³ combined with microcrystalline cellulose and two hydrophilic superdisintegrants. Aspirin is moisture sensitive and can hydrolyse into acetic and salicylic acids when exposed to elevated humidity and temperatures⁴. The study found that formulations without PPS, containing just

3% of either sodium starch glycolate or croscarmellose sodium, resulted in severe degradation of the aspirin under accelerated storage conditions. The formulations with PPS and aspirin—with or without superdisintegrants—exhibited exceptional stability and minimal degradation.

A more surprising use of PPS is in formulating sustained-release dosages. Leach et. al.⁵ claimed that PPS has a limited obstructive gel layer on the surface of the tablet. This would indicate that PPS is not suitable for sustained-release applications. However, in combination with other polymers, PPS can be a viable excipient.

The cellulose ether derivative, hypromellose, is commonly used in controlled-release tablets. The drug release rate from the HPMC (Hydroxypropyl Methylcellulose) matrix depends on the type and amount of other excipients used in the formulation. Including PPS in HPMC sustained-release tablet formulations can result in slower drug release compared to other commonly used fillers, such as lactose and microcrystalline cellulose (Fig. 3)⁶.

The effect seen with PPS is not just a spatial one resulting from the presence of insoluble or partially soluble fillers, which may change the physical permeability characteristics of the polymer gel. When used in combination with HPMC, PPS actively contributes to drug-release kinetics. This contribution might be imparted via interaction between PPS and HPMC or the filler actively forming an integral structure within the HPMC gel layer.

Note: In the previous examples of new applications for PPS, the specific grade used was Starch 1500®.

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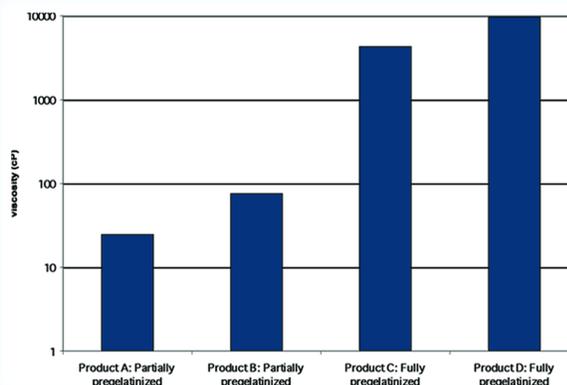


Fig. 1. Viscosity comparison of pregelatinized starch dispersed in water (24°C) at 10% solids concentration

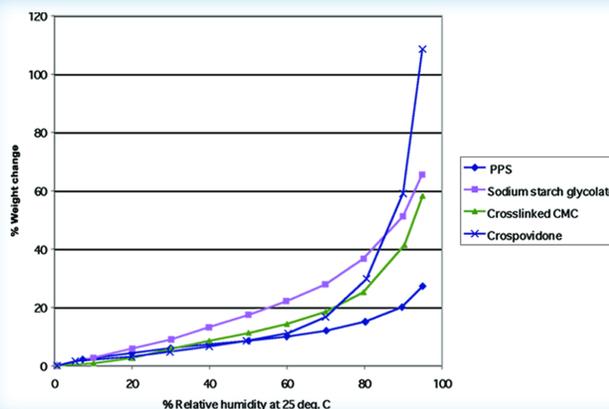


Fig. 2. Moisture uptake comparison between PPS and various superdisintegrants

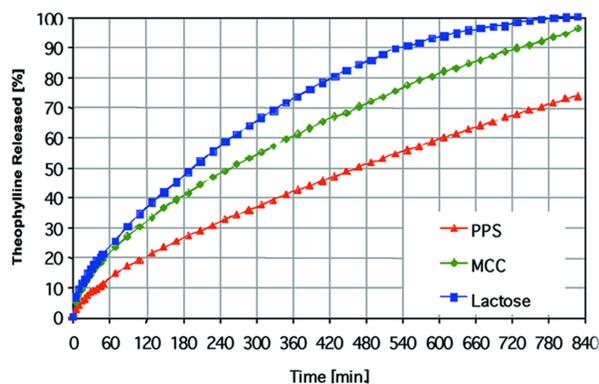


Fig. 3. Effect of three fillers on theophylline 100mg dissolution