Evaluating various wet binders to gain lactose based agglomerates applicable for orally disintegrating tablet formulations

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INTRODUCTION

In regard to line extensions or improving administration convenience orally disintegrating tablets (ODTs) have become a popular dosage form over the last years [1]. Nowadays, the formulator has some ready-to-use aids on hand, allowing quick and simple drug formulation [2].

However, the application of these ready-to-use aids is (to a certain extend) limited. Highly dosed active pharmaceutical ingredients (APIs) can be formulated with these excipients in direct compressible formulation, yet these tablets might become comparatively large. Furthermore, poor flow characteristics or poor compressibility of the API might become a dominant characteristic. As a result, granulation procedures need to be applied to gain processible blends.

The aim of this work was to investigate the performance of various wet binders onto the properties of ODTs based on agglomerates, deriving from a high shear granulation process. Furthermore, the impact of the formulation on the disintegration characteristics was investigated.

MATERIALS AND METHODS

The following wet binders were used for the investigation: native maize starch (C*PharmGel™, Cargill), poly(vinyl pyrrolidone) (Kollidon® 25 and 90F, BASF), copovidone (Kollidon® VA64, BASF), poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (Kollicoat® IR, BASF). As filling material lactose (GranuLac® 230, Meggle Pharma) was used.

For tabletting 10.0% crospovidone (Kollidon® CL-SF, BASF) and 0.5% magnesium stearate (Bärlocher) were added to the agglomerates.

Wet Granulation

The wet granulation processes were conducted in a high shear mixer (Diosna P 1/6) applying an impeller speed of 200 rpm and a chopper speed of 2,000 rpm. The binder (2.0% w/w final granules) was added as aqueous solution within 120 s, followed by a granulation time of 180 s.

The wetted agglomerates were passed through an oscillating sieving machine (w=1.6 mm, AR400, ERWEKA), dried on a tray (ambient conditions), and finally passed through a sieve (w=0.8 mm).

Tabletting

The compression was done using a single punch press XP 1 (Korsch) equipped with flat faced, faceted punches with a diameter of 8.0 mm. Compression forces of 2 to 8 kN were applied at a tabletting speed of 20 tablets per minute.

Analytical Testing

The friability of the dried agglomerates was tested in an air jet sieve (Rhewum LPS 200), using a sieve of 125 µm mash size. During this test, agglomerated particles are accelerated (fluidised) adjusting an air flow of 70 m^3/h. As a result, the particles hit the lid of the sample chamber with a dedicated impact force. Any losses in mass (sample) represent initial fine particles breaking of the agglomerates herewith indicating a value for friability [3].

The particle size distribution was determined employing a sieve tower (Retsch AS 200), using sieves in the range of 63–1,000 µm (according to the European Pharmacopeia). The results were categorised into three different particle size classes: coarse (>355 µm), mean (125 –355 µm) and fine (<125 µm) particles [4].

Disintegration time of the tablets (n=6) was tested (ERWEKA ZT 74) in demineralised water (37°C ±1 K).

RESULTS AND DISCUSSION

Viscosity of the polymer solution is a crucial and important parameter when selecting a binder for high shear granulation processes. Solutions containing the synthetic polymers used in this investigation led to low or moderate viscosities whereas starch (which was prepared with hot water, 80°C) was applied as paste.

The binders used for this investigation could clearly be distinguished regarding their individual performance. Both particle size distribution and friability of the agglomerates revealed the lowest binding efficiency for Kollidon® VA64, followed by Kollidon® 25, Kollicoat® IR and Kollidon® 90F. The strongest and also largest agglomerates were gained with the binder maize starch (Figure 1, Figure 2).

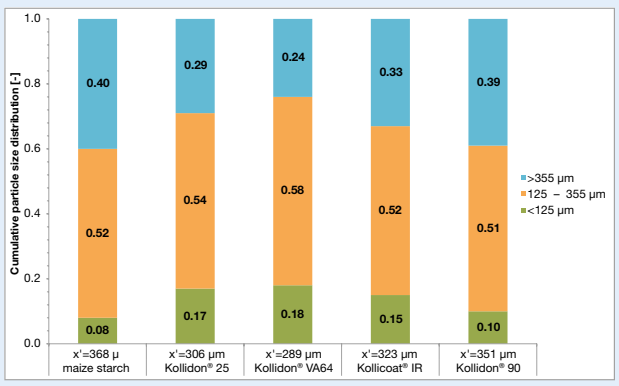

Figure 1. Cumulative particle size distribution and mean particle size of agglomerates containing different binders.

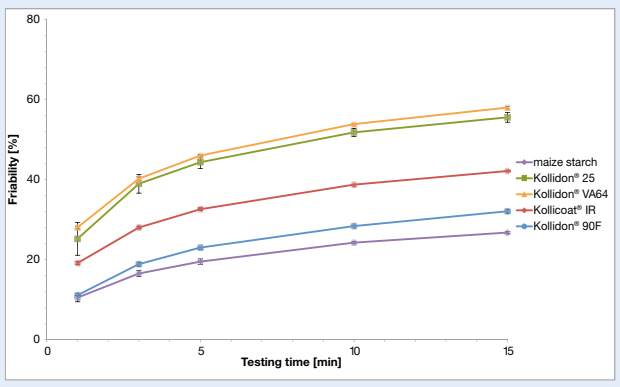

Figure 2. Friability of agglomerates containing different binders as function of testing time.

Interestingly, the results of tablet's disintegration properties showed a varying picture (Figure 3). When comparing tablets of the same tensile strength (0.9– 1.0 N/mm^2) formulations containing a synthetic polymer showed disintegration characteristics which could be correlated with the strength of the granules: stronger granules led to tablets of longer disintegration time. However, agglomerates containing maize starch resulted in tablets offering a disintegration time of merely about 30 seconds without any additional disintegrant added to the formulation (Figure 3).

As soon as a disintegrant was added (10% Kollidon® CL-SF), disintegration times of all tablets containing synthetic polymers were below 30 seconds (Figure 4).

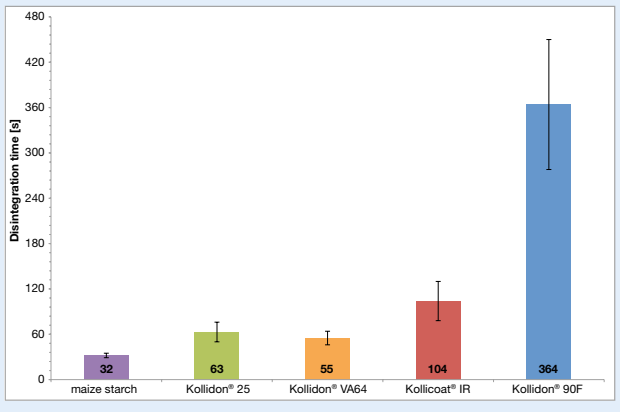

Figure 3. Disintegration time of tablets, containing no disintegrant (mean value (n=6), ±SD).

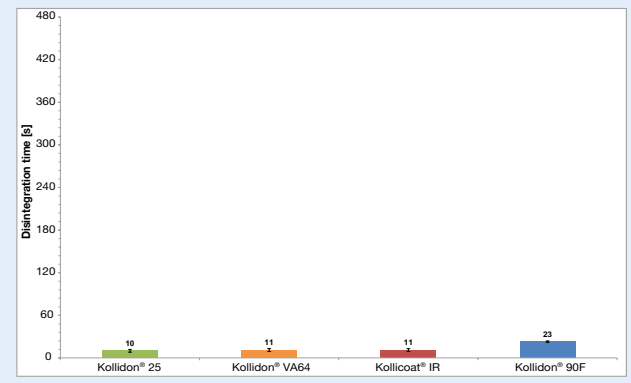

Figure 4. Disintegration time of tablets, containing 10% of disintegrant (mean value (n=6), ±SD).

CONCLUSION

Even though starch paste offered distinct disadvantages in regard to its application, it offered some benefits regarding the resulting agglomerates. Firstly, strength of the formed agglomerates was high (low friability) allowing good blending and processing, and secondly, disintegration time of the tablets was low, even without disintegrant in the formulation.

Solutions of synthetic polymers were easier (and safer) to prepare (no heated water) and easier to process (low viscosities). But, tablet formulations required some disintegrant to allow quick disintegration.

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