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The Impact of Formulation on Dissolution Coning: Supporting Development of a Classification System and Predictive Tool

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SUMMARY

Coning is a phenomenon that is specific to dissolution tests using USP Apparatus 2 due to the hydrodynamics of the system, resulting in the reduced dissolution of API. Experiments were conducted using design of experiment principles on various tabletted blends to investigate factors impacting coning. It was observed that the brittle filler used impacts the extent of coning present for the APIs studied. Particle size was found to have less of an impact than the brittle filler type. To resolve coning problems, it could be recommended that the brittle filler type is changed rather than the grade. Work with low solubility APIs is required to confirm this. This work has the potential to form the basis for a classification system to provide early warning if a formulation is likely to have coning issues.

INTRODUCTION

The most used apparatus for the dissolution testing of solid oral dosage forms is USP Apparatus 2. Lower shear rates and smaller fluid velocities exist at the centre of the vessels base, directly below the paddle. Due to the relatively low shear rate and velocity under the paddle, material can remain at the bottom of the vessel during dissolution testing and form a cone in this area (referred to as coning). The reduced agitation of this cone of material limits the dissolution of any API within. Dissolution tests in which coning is present will produce abnormal dissolution profiles which can lead to issues with regulatory applications. This study aims to understand the impact of formulation factors on coning.

MATERIALS AND METHODS

Design of experiment (DoE) principles were used to determine the key factors impacting coning. Seven factors, each with two options, were chosen with carbamazepine (CBZ) as the API. These include a ductile filler (DF) of Avicel PH-102 or PROSOLV SMCC90; a brittle filler (BF) of A-TAB or FastFlo316; a disintegrant (DT) of EXPLOTAB or Kollidon CL-SF; a lubricant (LT) of HyQual or PRUV; a buffer system (BS) of pH 1.2 or pH 6.8; a solid fraction (SF) of 0.85 or 0.7; and a drug loading (DL) of 25% or 10%. Sixteen tabletted blends (11mm SRC) each with a different combination of variables were created for the 75 rpm dissolution tests.

A series of six tabletted Acetaminophen (APAP) blends (9mm SRC) were also made, each using a different BF. The BFs chosen were two grades of anhydrous dibasic calcium phosphate with different PSDs (DCP, A-TAB and Calipharm A), two grades of lactose monohydrate with different PSDs (Lactochem Regular and Tablettose 80), precipitated calcium carbonate, and mannitol (Pearlitol 160C). Other variables included the tablet mass and BS (pH1.2 and pH6.8). 50 rpm dissolution testing was conducted for the blends in the different conditions.

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The buffer solution was degassed using the RIGGTEK DissoPrep X8 degasser, 900 mL media was dispensed into apex and standard vessels in the Agilent 708-DS Dissolution Apparatus at 37ºC (± 0.5). Tablets were added and the dissolution test was conducted at the chosen rpm. Fractions were taken automatically through 10-micron filters at 5, 10, 15, 20, 30, 45, and 60 minutes, with a 250 rpm 15-minute infinity spin at the end of a run. The fractions were analysed contemporaneously using the Agilent Cary 60 UV-Vis with Hellma analytics QS high precision cell (light path: 2 mm).

RESULTS AND DISCUSSION

For the CBZ DoE blends the strongest effect impacting dissolution in standard vessels was consistently the BF (see Fig. 1.). In Apex vessels, the BF was only a factor for the first 5 minutes, so it can be assumed that its impact may be specific to coning. The later impact of the BS on dissolution in standard vessels could show some pH dependent partial solubility of the BFs used (A-TAB and FastFlo316).

Time (mins)	Factors Impacting Dissolution
5-10	Brittle filler, disintegrant, drug loading
15-20	Brittle filler
30-60	Brittle filler, buffer system, interaction between brittle filler and buffer system

Fig. 1. *Factors impacting CBZ blend dissolution in standard vessels at different timepoints.*

It was observed that 50% of the CBZ blends aggregated in standard vessels, and a strong correlation with the BF used was found. Blends containing A-TAB aggregated in 7/8 cases, whereas 7/8 blends containing FastFlo316 did not. The aggregation is suggested to have occurred due to the stagnation of material caused by coning.

For the APAP BF blends tablet mass had an impact across all blends and all timepoints, with a 1 g mass having dissolution that is 7-12% slower than a 0.5 g mass. BS was less important but impacted the first 5 minutes of dissolution for Lactochem Regular, and the infinity spin of Lactochem Regular, A-TAB and Pearlitol 160C. In general, it was found that pH 6.8 buffer resulted in faster dissolution than pH 1.2 for A-TAB, Calipharm A, Tablettose 80 and Lactochem Regular, but was slower for precipitated calcium carbonate and Pearlitol 160C. Calcium carbonate behaved uniquely, since it floated in the pH 1.2 BS. This resulted in no coning and equal dissolution rates between the standard and apex vessels. At pH 6.8 coning was present visually, and there was a difference between dissolution rates in standard vs apex vessels.

Particle size appears to have a minimal impact within the first few timepoints, with larger particle size resulting in slightly slower dissolution. The BF itself appears to have the largest impact, with lactose BFs showing the best performance, followed by mannitol and then DCP. Due to the floating tablets calcium carbonate dissolution in pH 1.2 cannot be compared to other BFs, but in pH 6.8 it shows comparable results to DCP. Tablet mass also has an impact on a dosage forms propensity to cone, with lower masses exhibiting reduced coning (likely due to the reduced amount of insoluble excipients).

CONCLUSIONS

Overall, it was found that the BF used in the blend has the potential to impact the extent of coning present for the APIs studied. For the BFs studied, particle size resulted in less of an impact than the type of BF. As such, there is the potential to recommend that for issues with coning, the BF type rather than grade is changed. Further work with a lower solubility API is required to make this recommendation. Tablet mass also has an impact on a dosage forms propensity to cone, with lower masses exhibiting reduced coning. There is an interaction between BS and BF, with each performing better at a specific pH. A further DoE study investigating the impacts of API properties on coning is currently being conducted. This work has the potential to form the basis for a classification system that can provide early warning as to if a formulation is likely to have issues with coning.

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