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The Use of Compaction Simulation as a Tool to Aid Successful Tablet Formulation

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SUMMARY

Early assessment of compaction properties of both APIs and formulations is an important consideration in early tablet development and can help to de-risk scale up from R&D to production scale. In this work, three model APIs and a tablet formulation were assessed using a compaction simulator. Compaction simulation was shown to be able to differentiate between the compaction properties of APIs and formulations and when combined with additional information on API properties (flowability, solubility) and tablet requirements (size, strength) can guide formulation strategy.

INTRODUCTION

Early assessment of the compaction properties of active pharmaceutical ingredients (APIs) and formulations is an important consideration in drug product development. Consideration of API compaction properties, in combination with preformulation characterisation (API solubility, flowability, particle size, shape etc), allows intelligent formulation design and manufacturing process selection to be achieved despite limited API availability (Leane 2014, 2018). In addition, compaction simulation has been demonstrated to be predictive of production scale (Pitt, 2015), and can help to de-risk the costly and time-consuming process of scaling up from R&D to production scale.

MATERIALS AND METHODS

Metoclopramide hydrochloride (MTH) and Diclofenac sodium (DS) were purchased from Tokyo Chemical Industries. Paracetamol (PAR) was purchased from Sigma-Aldrich, UK. The following excipients were also sourced: Avicel PH102 (DuPont), SuperTab 21AN (DFE Pharma), L-HPC NBD-022 (ShinEtsu) and Ligamed MF-2-V (Peter Greven).

Compaction analysis was carried out using a Gamlen D500 powder compaction analyser, tablet tensile analyser (TTA) and Gamlen Dashboard Software. Three model APIs (MTH, DS and PAR) and a 25% PAR formulation (directly compressed (DC) and dry granulated (DG)) were analysed. Tablets (100 mg) were prepared using the Gamlen D500 powder compaction analyser at a compaction speed of 120 mm/min using 6 mm round flat faced tooling at a range of compression forces (35 MPa to 200 MPa). Tablet weight, diameter, thickness, and hardness were measured using the TTA and graphs were generated using the Gamlen Dashboard software.

RESULTS AND DISCUSSION

A section of the Gamlen Dashboard API compaction analysis is shown in Fig1.

These graphs highlight the significant differences in compaction properties that can occur between APIs. As expected, PAR had the worst tabletting and

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compressibility properties (Keshavarz, 2014), followed by MTH and DS, respectively. This information, along with other API properties (flowability, solubility, melting point etc) and dosage form properties (tablet size and strength) can guide formulation decisions and strategies.

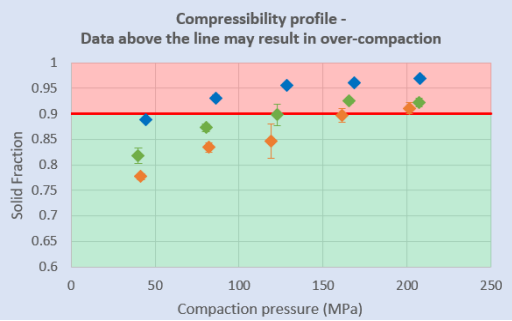

Fig. 1. *Compaction analysis of DS (orange) MTH (green) and PAR (blue).*

Excipients need to be included in formulations to aid manufacturing processes or to improve tablet properties such as dissolution, API stability or bioavailability. A section of the Gamlen compaction analysis dashboard of a direct compression (DC) and dry granulation (DG) formulation is shown in Fig.2.

PAR API results are also shown on these graphs for comparison. By including excipients in the formulation, the poor tableting, and compressibility properties of paracetamol have been improved. In addition, a comparison of the DC and DG formulations can be made. DG carries the inherent risk of reduced compressibility and reduced tablet tensile strength as a result of double compression (Herting, 2008). These graphs show that no significant loss of tablet tensile strength results from roller compaction of this formulation.

CONCLUSIONS

Compaction analysis of APIs and formulations was shown to be a useful tool and allows informed decisions to be made about formulation design and manufacturing process despite minimal API resources expected in early development.

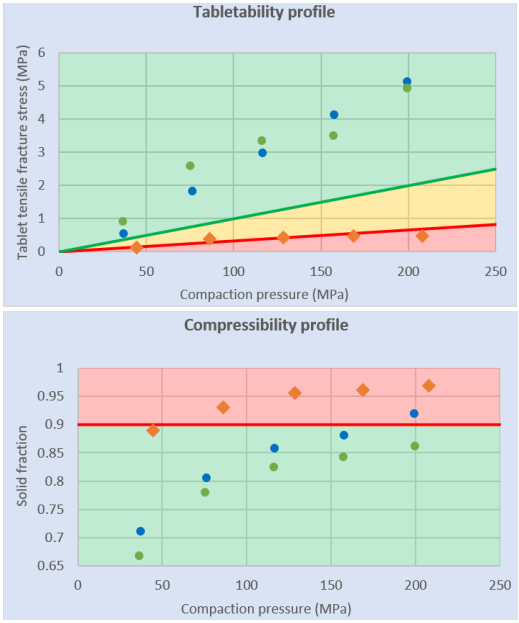

Fig. 2. *Compaction analysis of PAR (orange), PAR 25% direct compression blend (blue) and PAR 25% dry granules (green).*

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