Rheology to guide formulation development of particulate dispersions for automated capsule filling

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Introduction
Encapsulation of pharmaceutical formulations as liquids or semisolids, within hard gelatin capsules, allows for the oral delivery of poorly water-soluble active pharmaceutical ingredients (API), resulting in good bioavailability and reproducible absorption of the drug [1]. For automated capsule filling, rheological characteristics are critical and the working range is limited by the setup of the machine. Rheology-related problems encountered during capsule filling can include spatter (Fig. 1) and dripping. For a dispersion of solid drug particles in the excipient, the rheology is affected by the properties of the dispersed phase (particle size, concentration) and the continuous phase (viscosity), leading to filling limitations. The aim of this work was to investigate the rheological characteristics of particulate formulations to guide formulation development for an oral drug product for use in clinical trial.

Materials and Methods
Rheological analysis was performed using a Haake Mars rheometer (Thermo Scientific) in conjunction with a 2.0 cm stainless steel parallel plate test geometry. The rheological flow behaviour was analysed using flow runs from 0 to 240 s⁻¹ over 30 s and the apparent viscosity was measured (in triplicate) at 140 s⁻¹. API particle diameter was microscopically estimated as less than 50 µm. Automated capsule filling was performed with a Capsugel CFS1000 capsule filling machine.

Results and Discussion
Excipients compatible with hard gelatin capsules and particulate drug formulations thereof were rheologically characterised. Apparent viscosity was markedly increased in presence of particulate API (Table 1). Low (5wt% API) and high (30wt% API) strength formulations were required to cover the expected dose range for a clinical trial, both showing their own limitations.

Results and Discussion (continued)
Initial experiments with Kollisolv P124 showed that high apparent viscosities showed good flow and dosing in the capsule filling machine (Fig. 1). High viscosity formulations were also preferable because of their ability to keep drug particles in suspension for longer which improves formulation homogeneity and increases the robustness of the filling process. For the high strength formulation (30wt% API), PEG 300 was added to adjust the viscosity of Kollisolv/API to the working range of the capsule filling machine. Clean filling with the capsule filling machine and good fill weight uniformity were achieved with Kollisolv P124 based formulations, for both low and high strength API formulations. However, content uniformity was better with the 30wt% API formulation. Capsule filling of low viscosity particulate formulations (5wt% API in Gelucrlec 44/14) was possible at 50°C, however the API content uniformity was limited. At 65°C the viscosity of this formulation was too low leading to severe dripping.

Conclusions
- Rheology is a critical parameter for automated capsule filling of particulate formulations.
- High viscosity formulations (but within the working range of the machine) show good dosing and filling performance.
- Particulate formulations may require a higher apparent viscosity than non-particulate formulations to achieve good filling.

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References