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

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Abstract - **The rheological properties of pharmaceutical formulations intended for liquid fill hard gelatin capsules are fundamental for their filling performance. Here we used the rheological characteristics of particulate drug formulations to develop formulations suitable for automated capsule filling.**

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 and dripping. For a dispersion of solid drug particles in the excipient, the rheology is affected by the properties of the disperse 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 50µm. 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 (5 wt% API) and high (30wt%) strength formulations were required to cover the expected dose range for a clinical trial, both showing their own limitations.

Initial experiments with Kollisolv P124 showed that high apparent viscosities (>610mPa.s) showed good flow and dosing in the capsule filling machine. High viscosity formulations were also preferable because of their improved ability to keep drug particles in suspension for longer. For the high strength formulation, PEG300 was added to adjust the viscosity of Kollisolv/API to the working range of the capsule filling machine.

Table 1. Apparent viscosities (at a shear rate of 140 s^{-1}) of excipients in absence/presence of particulate API. Low strength and high strength formulations are compared. Highlighted areas indicate suitability within the viscosity working range (10 - 1000 mPa.s [1]) of the capsule filling machine. Green (red) framed results indicate good (unsatisfactory) filling in the capsule filling machine.

Formulation	T (deg C)	Apparent viscosity (mPa.s)		
		no API	5 wt% API	30 wt% API
Kollisolv P124	20	897	1111	6626
	35	289	422	-
	40	245	295	2243
Kollisolv P124/	20	459	493	3713
PEG300	40	167	201	1537
(70:30)	50	-	-	1170
	60	81	-	726
Labrasol	20	89	-	1048
Gelucire 44/14	40	139	-	1310
	50	91	107	-
	60	69	-	710
	65	55	73	-
Miglyol 812 N	20	29	-	302

Good filling with the capsule filling machine was achieved with Kollisolv P124 based formulations, for both low and high strength API formulations. Capsule filling of low viscosity particulate formulations (5wt% API in Gelucire) was possible at 50°C, however the API content uniformity was limited.

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.

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