CHARACTERISATION OF A LIQUID-CAPSULE-FILL-FORMULATION-PERFORMANCE ON AN AUTOMATED CAPSULE FILLING MACHINE (CFS1000)

E. Prasad, M. A. Elliott, G. W. Halbert
Cancer Research UK Formulation Unit, Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK.

Abstract – **Automated manufacture of liquid filled hard gelatine capsules is dependant on the physical properties of a pharmaceutical formulation. Here, we investigated the performance of a novel formulation (phase I clinical trial) for automated capsule filling.**

INTRODUCTION

Liquid filled hard gelatine capsules can increase oral absorption of active pharmaceutical ingredients (API) due to poor aqueous solubility [1]. Formulation development requires a balancing act of accommodating many factors such as the compatibility of excipients with the API as well as the hard gelatine capsule, target dose or dose range, capsule size and suitable physical properties of the formulation for automated capsule filling. Formulation development for oral dosing of a novel cytotoxic API in a phase I clinical trial setting was based on covering a dosing range from 5 to 60mg in single dose units using two formulations. Due to containment issues associated with cytotoxic drug powder and poor aqueous solubility of the API, a liquid or semisolid formulation was sought, with the scope to scale-up to batch sizes of up to 1000 capsules. The performance of two formulations, 2.5% w/w API in PEG300 (covering the dose range of 5-30mg) and 10% w/w API in PEG300 (covering the dose range from 30-60mg), was characterised in relation to their physical properties and the uniformity of capsule weights.

MATERIALS AND METHODS

Kinematic viscosity of formulations and PEG 300 only (for comparison only) was measured using a BS/U Tube Viscometer Size E and F, respectively. Measurements were performed at 21°C (n = 7). Formulation density was measured using an Anton PAAR DMA 48 density meter. Measurements were performed at 20°C. Dynamic viscosity was calculated using the kinematic viscosity value and the formulation density. Size 0 hard gelatine Licaps were filled using the CFS1000 (Capsugel) with batch sizes of 900 capsules. QC samples of 20 capsules were taken after 100, 250, 500 and 800 filled capsules and weighed subsequently.

RESULTS AND DISCUSSION

Density and Kinematic viscosity values are tabulated below (Table 1), with the dynamic viscosity of PEG300 only and 2.5% formulation showing similar low values and the 10% formulation showing a 4.4 fold increase in viscosity.

Uniformity of capsule weights of the high strength formulation was very good. QC sample 1-3 showed deviations of only 0.63-1.2% from the average capsule mass. The maximum deviation was recorded in the last QC sample with only one capsule mass deviating by 5.78%. The capsule masses filled with the low strength formulation deviated between 9.2-17.8% for all four QC samples. However, this deviation still meets the EP requirement for immediate release oral dosage forms since no more than 2 capsules deviated by more than 7.5%.

The observed relationship of dosing accuracy and rheological properties has previously been described in the literature [2].

Table 1. Physical properties of PEG300 only and 2.5% w/w AT13148 - P300 and 10% w/w AT13148 - P300.

	P300	2.5% w/w API, P300	10% w/w API, P300
Density (g/cm^3)	1.1266	1.1327	1.1522
Kinematic viscosity (mm^2/s)	60.71±0.33	74.89±0.55	261.16±3.55
Dynamic viscosity (cP, g/(s*cm))	69	85	301

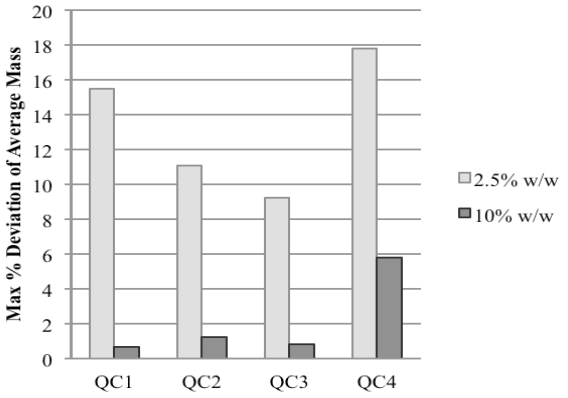

Fig. 1. Deviations from average capsule mass for low and high strength formulations throughout small scale batch manufacture.

CONCLUSIONS

Both formulations performed well on the CFS1000 and meet EP requirements for uniformity of capsule mass. The dosing accuracy of the low viscosity (85cP, 21°C) formulation is high and can cause dosing inaccuracies. However, the low strength formulation still meets EP specification. Higher viscosity formulations (10% w/w formulation, 300cP, 21°C) are related to high dosing accuracy.

ACKNOWLEDGMENTS

Cancer Research UK, Formulation Unit technical staff and Dr Nigel Westwood, Cancer Research UK Drug Development Office.

REFERENCES

[1] E.T. Cole, D. Cadé, H. Benameur "Challenges and Opportunities in The Encapsulation of Liquid and Semi-Solid Formulations into Capsules for Oral Administration" *Advanced Drug Delivery Reviews*, **60** (2008) 747-756.
[2] E. Cole, "Liquid filled and sealed hard gelatin capsules" *Gattefossé Bulletin nr* **92** (1999).
[3] European Pharmacopeia 7.0.