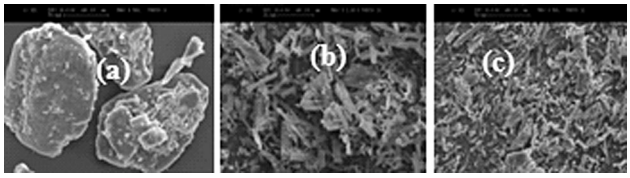

Fig. 1. SEM images for (a) commercial mannitol (b) mannitol crystallised from acetone: water (100 : 0 ml) and (c) from acetone: water (97.5, 2.5).

tap density and higher carrier fines and surface area may be responsible for their enhanced inhalation performance. SEM showed that all engineered mannitol crystals were more elongated than the commercial mannitol (Figure 1). Carriers with higher elongation ratios were proved to produce better drug aerosolisation properties (Table 1).

Crystallised mannitol formulations produced lower content uniformity, but higher recovery, emission, and FPF indicating better performance for crsytallised samples (Table 1).

Table 1. CV (%) and deposition parameters obtained from commercial and crystallised mannitol formulations.

Man.[a]	CV (%)	Recovery (%)	Emission (%)	FPF (%)
Com[b].	1.76	79.3 ± 1.7	96.3 ± 0.2	15.4 ± 1.1
100/0[c]	6.25	88.7 ± 5.3	92.9 ± 1.6	41.5 ± 2.6
97.5/2.5	10.56	91.3 ± 7.1	93.3 ± 0.9	43.2 ± 0.7
95/5	3.39	95.4 ± 15.4	94.5 ± 0.6	44.0 ± 2.6
92.5/7.5	6.43	87.8 ± 14.7	94.7 ± 0.9	42.9 ± 1.3
90/10	7.67	94.7 ± 6.8	94.9 ± 1.1	41.6 ± 7.9
85/15	5.33	82.2 ± 19.8	93.9 ± 3.3	34.0 ± 5.3
80/20	6.39	91.8 ± 4.3	93.9 ± 0.7	41.0 ± 0.5
75/25	17.40	83.2 ± 8.5	93.6 ± 2.7	33.1 ± 3.7

[a]Mannitol; [b]Commercial; [c]Anti-solvent mixture (Acetone/Water)

CONCLUSIONS

All crystallised mannitol samples were in different physicochemical properties and improved deposition behaviour. Carriers with higher ρ_{true}, amounts of fines, S_v produced higher FPF.

ACKNOWLEDGMENTS

Waseem Kaialy thanks University of Damascus.

REFERENCE

[1] Steckel, H., Bolzen, N., 2004. Alternative sugars as potential carriers for dry powder inhalations. Int. J. Pharm. 270,297–306.

Experiences of melt fill production of Fenretinide/Lym-X-Sorb™ hard gelatin capsules for Phase I clinical trial

M.A. Elliott, E. Schmidt, S.J. Ford and G.W. Halbert

Cancer Research UK Formulation Unit, Strathclyde Institute for Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0NR, UK.

Abstract – **Fenretinide is a pro-apoptotic, cytotoxic, synthetic Vitamin A analogue with application in the treatment of Ewing's sarcoma. For paediatric study, a 'cookie dough' formulation had been developed, improving upon an existing corn oil formulation. We report on a simplified capsular formulation of fenretinide with the novel solubility and bioavailability enhancing lipid matrix, Lym-X-Sorb™.**

INTRODUCTION

4-HPR [N-(4-Hydroxyphenyl) retinamide, Fenretinide] in corn oil capsules can give poor dosing consistency and wide patient-to-patient variation. In children's cancer studies, consumption of large numbers of capsules and big capsule size has lead to poor patient compliance. To overcome these issues, a formulation was developed using Lym-X-Sorb™ (LXS), an organised lipid matrix designed to enhance solubility and bioavailability. When blended with sugar and wheat flour, a 'cookie dough' of 4-HPR and LXS was produced for mixing in food or liquids [1].

For UK Phase I trial, a simplified capsular formulation was sought for ease of GMP production, and to regulate and escalate doses given.

MATERIALS AND METHODS

4-HPR was provided by the National Cancer Institute (NCI), Maryland, USA. Avanti Polar Lipids Inc., Alabama and BioMolecular Products Inc., Massachusetts, USA gifted the LXS. Size 0 hard gelatin Licaps® were used on a CFS1000 capsule-filling machine (Capsugel, Belgium). Other materials were of laboratory grade or better from the Sigma-Aldrich Company Limited, Dorset, UK. 'Fed' buffer dissolution was according to the method of Dressman and Reppas [2].

RESULTS AND DISCUSSION

LXS has a 'buttery' consistency at room temperature and can be melted by heating to around 30°C. A maximum of 11% w/w 4-HPR was incorporated into LXS by blending into the molten base. Hand filled size 0 capsules gave 'fed' buffer dissolution profiles indicative of slow release when compared with 11% 4-HPR in corn oil, and with poor release from a 4-HPR powder only capsule (Figure 1).

Using the 11% w/w 4-HPR in LXS formulation on the CFS1000 machine resulted in a 'bridging' phenomenon [3] during the fill. Specifically, the capsule fill was not clean, producing a melt 'trail' over the capsules and dosing stations. This was potentially attributable to melt viscosity and assumed thixotropic behaviour.

Bridging during the fill was overcome with alterations to hopper filling temperature, rate of melt stirring and machine fill speed. Capsules produced were analysed by UV for drug content, and for uniformity of mass.

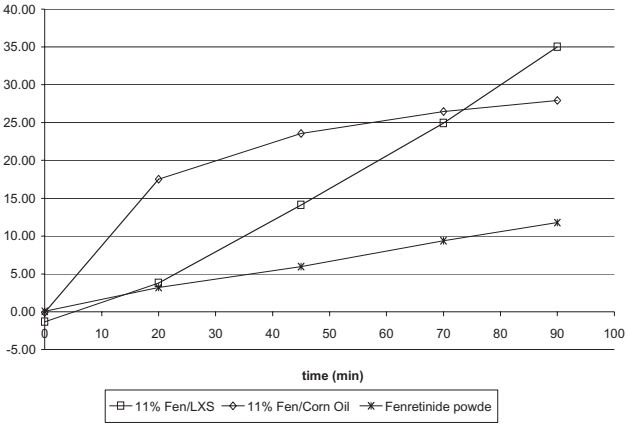

Fig. 1. 'Fed' buffer capsule dissolution for 4-HPR powder only, 11%w/w 4-HPR in LXS and in corn oil.

CONCLUSIONS

4-HPR in LXS capsules for oral dosing can be consistently made. Full-scale analytical and stability studies would be required on the proposed formulation before entering clinical trial.

ACKNOWLEDGMENTS

Cancer Research UK sponsored this work. The authors acknowledge the invaluable assistance of Dr. Rao Vishnuvajjala (NCI), Dr. Walter Shaw (Avanti Polar Lipids) and Dr. Nigel Westwood (Cancer Research UK). Lym-X-Sorb™ was invented by David W. Yesair, is proprietary to BioMolecular Products Inc., and manufactured under license by Avanti Polar Lipids Inc.

REFERENCES

[1] B. J. Maurer, O. Kalous, D. W. Yesair, X. Wu, AV. Maldondo, V. Khankaldyyan *et al*, "Improved oral delivery of *N*-(4-Hydroxyphenyl) Retinamide with a novel LYM-X-SORB organised lipid complex" *Clin. Cancer Res.*, **13(10)** (2007) 3079–3086.

[2] J. B. Dressman and C. Reppas, "In vitro-in vivo correlations for lipophilic, poorly water soluble drugs" *Eur. J. Pharm. Sci.*, **11** Suppl 2 (2000) S73-S80.

[3] A. Kattige and G. Rowley, "Influence of rheological behaviour of particulate/polymer dispersions on liquid-filling characteristics for hard gelatin capsules" *Int. J. Pharm.*, **316** (2006) 74–85

Exploring roll compaction of two commonly used pharmaceutical powders

Shen Yu[1], Bindhu Gururajan[2], Gavin Reynolds[3], Ron Roberts[3], Chuan-Yu Wu[1], Mike Adams[1]

[1]School of Chemical Engineering, University of Birmingham, Edgbaston, Birmingham, B15 2TT
[2]Pharmaceutical Development, AstraZeneca, Charnwood Bakewell Road, Loughborough, LE11 5RH
[3]Pharmaceutical Development, AstraZeneca, Macclesfield, Cheshire, SK10 2NA

Abstract – **The effect of powder flow properties on roll compaction behaviour of microcrystalline cellulose (MCC) and di-calcium phosphate dihydrate (DCPD), which have distinctive flow properties, was experimentally investigated. A robust approach for determining the nip angle that defines the compaction region was also developed. It was found that powder flow properties play a significant role in roll compaction.**

INTRODUCTION

Roll compaction is widely used as a dry granulation process in the pharmaceutical industry. The densification of the feed powder is primarily described by two parameters: the maximum pressure and the nip angle. The process behaviour depends on system layouts, processing conditions and feed powder properties.

MATERIALS AND METHODS

Two commonly used pharmaceutical excipients: MCC (Avicel PH102) and DCPD (Calipharm D) were considered. The flow functions (ff_c) of these powders measured using a ring shear cell indicates that MCC is easy flowing (i.e. $4 < ff_c < 10$) while DCPD is cohesive (i.e. $2 < ff_c < 4$). The powders were roll-compacted using a lab-scale instrumented roll com-