The enhancement of the aqueous solubility of Albendazole employing polymeric amorphous solid dispersion (ASD) as an approach

J. Yang[1], V. Mohylyuk[1,2], S. Li[1,2], D. S. Jones[1], G. P. Andrews[1,2]

[1] Pharmaceutical Engineering Group, School of Pharmacy, Queen's University Belfast, BT9 7BL, Northern Ireland

[2] China Medical University - Queen's University Belfast joint College (CQC), Queen's University Belfast.

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PURPOSE

- **Poor aqueous solubility** is a significant issue in the current pharmaceutical industry with approximately 90% of new chemical entities in the development pipeline characterised as poorly water-soluble.
- Amongst various means to address the solubility issue, the amorphous solid dispersion (**ASD) approach is highly attractive but associated with high risks**, due to the inherent instability of the amorphous drug forms. ASDs often contain the drugs in a high energy form but offer increased stability due to significant interaction with the polymeric carrier in which they are embedded.
- **Hot melt extrusion** has been extensively researched to show significant promise in continuous manufacturing of ASDs [1].
- In this study, we examine a **model BCS class II drug Albendazole (ABZ)**, which has been initially utilized as an anti-parasite drug to act in the intestinal lumen, but recently shown anti-cancer effects [2].

METHODS

- ✓ **ABZ** (Kemprotech Limited, UK); **Soluplus®** (Tg 75℃), **Kollidon® VA64** (Tg 107 ℃), and **PEG-6000** (Tm 60℃) provided by BASF, (Germany).
- ✓ **Hansen solubility parameters** (△δ) of ABZ and polymeric excipients were calculated according to **group contribution method** [3] as an initial pre-screening tool to gather basic information on drug-polymer miscibility.
- ✓ **Hot-melt extruded formulations** with ABZ loading (10, 20, 30 and 40% w/w) were manufactured on a HAAKE® MiniLab extruder (Thermo Fisher Scientific, Germany) at 150℃-barrel temperature and at 10rpm screw speed. Extrudates were collected at RT and ground with mortar and pestle.
- ✓ For **characterisation** were used powder X-ray diffraction (**PXRD**) and differential scanning calorimetry (**DSC**) methods.
- ✓ **Dissolution test** has been carried out using USP Apparatus II (paddle) in 900ml of HCl solution pH 1.2 at 100 rpm. ABZ concentration was quantified by UV-spectroscopy. Each profile is representing the average and standard deviation of six repetitions.
- ✓ **To investigation of precipitation inhibition** were used the same conditions as for the dissolution test except the following. The polymer (800mg) was added into the dissolution medium 30 min prior the drug introducing. ABZ (200mg) was dissolved in 5ml of solvent (1ml of 32% w/w HCl in 1000ml of methanol), sonicated for 30 min and then added into the dissolution medium.

OBJECTIVES

- Adopting a range of pre-screening tools as a means of identifying polymers suitable for the formulation of ASDs
- to manufacture those polymeric ASDs using HME
- to examine the potential of this process to produce suitable drug formulation to enable the performance of ABZ

RESULTS

- A range of **polymeric excipients was screened** and ABZ was found to be highly miscible (△δ ≤ 2MPa$^{0.5}$) with three pharmaceutically relevant polymers which predicted **miscibility decreased in the following order**: Kollidon® VA64 > Soluplus® > PEG-6000 with △δ 0.59, 0.82 and 1.61, respectively.
- DSC and PXRD confirmed that ABZ substance had a defined **melting point at 210℃** and **distinct X-ray diffraction bands** (**Fig.1**) that could be used to further characterize the presence of residual crystal content in HME amorphous solid dispersions.
- **ASDs manufactured** using Soluplus® and Kollidon® VA64 were amorphous (DSC and PXRD confirmed) at drug loadings up to 20% w/w, whereas PEG-6000 showed residual crystalline content.
- Despite good **drug-polymer miscibility predicted based on solubility parameters** there was significant differences in the ABZ solubility in each of the polymers **based on DSC-experiment**.
- Kollidon® VA64 was significantly better than Soluplus® and PEG-6000 in its **ability to inhibit ABZ precipitation from a supersaturated solution** (**Fig.2**).
- **Drug release** properties varied as a function of drug content and polymer loading. Comparing with crystalline ABZ, all hot-melt extruded formulations provided oversaturated drug concentrations.
- **Kollidon® VA64 released ABZ** at a faster rate and to a greater extent than PEG-6000 and Soluplus® (**Fig.3**).
- **Interestingly**, this study demonstrated the rank order of miscibility of ABZ with polymeric excipients matched inhibition of crystallisation (precipitation) during supersaturation drug dissolution studies.

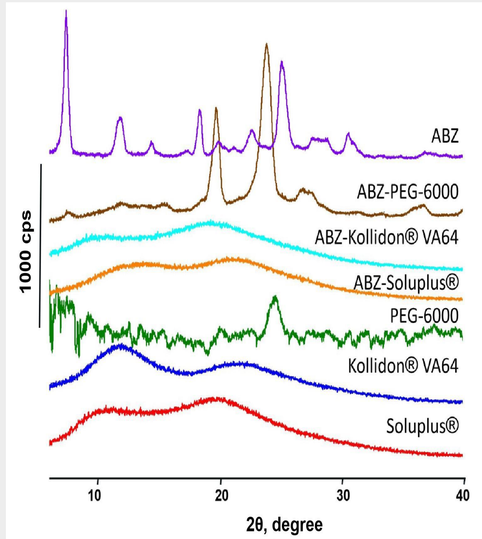

Fig. 1. *The X-ray diffractogram of extruded formulation containing drug (20%, w/w) and polymer in comparison with raw ABZ and excipients.*

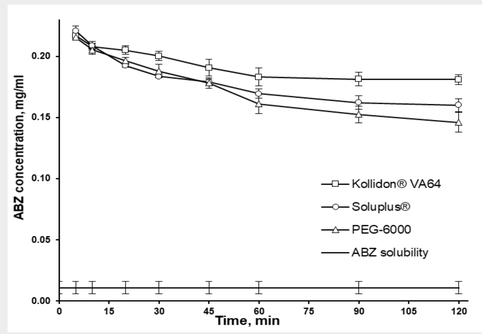

Fig. 2. *Effect of polymer type (800 mg) on the ABZ (200 mg) precipitation from the supersaturated solution.*

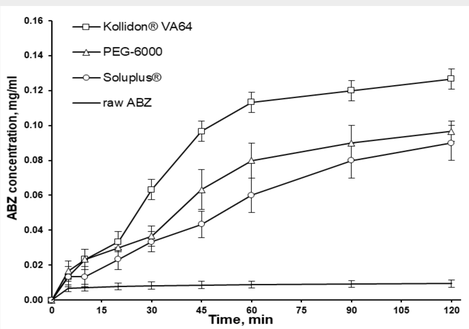

Fig. 3. *The effect of polymer type on the ABZ release from ASD (20% w/w of ABZ). Samples were eq. of 200mg of ABZ.*

CONCLUSIONS

- In this study, we have manufactured amorphous solid dispersions of ABZ and shown that the drug release performance can be improved.
- A range of pre-screening tools was investigated, and it was shown that a combination of methods can be employed to help identify appropriate polymer systems and drug loadings and this a formulation design space for effective manufacture of drug enabled formulations.

REFERENCE

[1] Hengsawas Surasarang, S., Keen, J., Huang, S., Zhang, F., McGinty, J. and Williams, R., 2016. Hot melt extrusion versus spray drying: hot melt extrusion degrades albendazole. Drug Devt Ind Pharm, 43(5), pp.797-811.
[2] Movahedi, F., Li, L., Gu, W. and Xu, Z., 2017. Nano formulations of albendazole as effective anticancer and antiparasitic agents. Nanomedicine, 12(20), pp.2555-2574.
[3] Van Krevelen D.W. et al. Elsevier. Properties of polymers. Their correlation with chemical structure; their numerical estimation and prediction from additive group contributions. 4th edn. Amsterdam, 2009.

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