**Purpose**

Oral drug delivery remains the preferred method of administration but BCS Class II drugs are not ideally suited to this due to their inherent poor solubility. Although a number of methods to increase solubility already exist, there is a need for manufacturing methods which are more flexible to the requirements of the individual patient. The current work aims to increase the solubility of poorly soluble drugs using the innovative manufacturing technique of inkjet printing with a view to creating formulations which are more easily tailored to the needs of the patient.

**Methods**

Dosage forms were produced using an Optomec AJ200 Inkjet 3D Printer (Fig. 1), which functions by aerosol jet powered by pneumatic atomisation. Pressurised nitrogen is forced through API and/or polymer based solutions causing this "ink" to form a vapour which ultimately transverses a ceramic nozzle tip in a jet stream. The formulation "ink" can be deposited on an appropriate substrate in a similar manner to how ink is applied to paper in a conventional home printer. The printer allows scaling of the formulation at a number of points. This can be achieved firstly at the design stage, in which CAD drawings can be used as a template, secondly by changing the ink ratios or components, thirdly by changing the nozzle diameter utilised and ultimately by building formulations up in layers. This printer has never been used in pharmaceutical manufacture previously and as such anything we can achieve is highly innovative [1-2].

Solid state analysis was carried out by powder x-ray diffraction, scanning electron microscopy. Raman spectroscopy and differential scanning calorimetry. This allowed comparisons to be made between the powdered materials and the printed ones, and also between the API alone and with varying concentrations of a polymer present. Raman spectroscopy also allowed analysis of drug distribution to establish whether printing gives the higher degree of precision reported previously.

Content analysis and printer capabilities were examined by HPLC using a validated method of 80:20 acetonitrile:acified water at 1 ml per minute on a C18(2) 10µA silica reversed phase column. Samples were tested for the effects of speed, deposition size, layering and nozzle size, when compared to a control of a 5 mm diameter circle deposition, created at 3 mm/s using a 25µm nozzle.

Due to the size of the formulations dissolution was analysed using the innovative method of surface dissolution imaging as standard USP method proved inadequate. Samples were subjected to UV light passed through a filter of suitable wavelength as simulated intestinal fluid passed over the surface (Fig. 2). The UV images were detected on a computer and from this drug release and intrinsic dissolution could be ascertained.

**Results**

Solid state analysis (Fig. 3-4) reveals that printing the drug alone results in a fully crystalline product, however on application of a polymer this crystallinity is reduced with a completely amorphous product being achieved by 75% polymer content or higher. Raman mapping suggests drug distribution is significantly improved by printing with physical mixtures showing distinct areas of the drug and polymer, while the printed samples have a more striated appearance (Fig. 5). The morphology noticeably changes on printing with the polymer with the needle crystals of the API gradually forming spherical amorphous particles as the polymer forms a matrix around the drug (Fig. 6).

**Conclusions**

Ultimately it has been established that printing the BCS Class II drug alone results in a crystalline product but on addition of a polymer this crystallinity is reduced and it is possible to print solid dispersions which are fully amorphous. Printing has also allowed greater control over drug distribution, which has allowed improved solubility overall. Additionally, the printer has proved itself capable of producing scalable products with a view to more patient centric dosage form manufacture.

Acknowledgments

The author would like to thank Gavin Halbert, John Robertson, Elke Prasad, Deborah Bowering, Lauren Connor, Kelly Etheran, Laura Harvey, Alan Martin and Monika Wazczega for their help and support. She would also like to thank the EPSRC and the Doctoral Training Centre in Continuous Manufacturing and Crystalisation for funding this work.

## References
