Poster #: W1053

Inkjet Printing Scalable Oral Dosage Forms Capable of Increasing the Solubility of BCS Class II Drugs

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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 ratio 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].

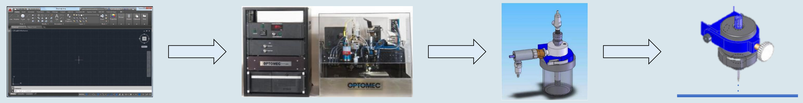

Fig. 1: Inkjet printing using an Optomec AJ200 Inkjet Printer. Images obtained from Optomec Ltd. [2].

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 analysed by HPLC using a validated method of 80:20 acetonitrile: acidified water at 1 ml per minute on a C-18(2) 100Å 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 250 µm nozzle.

Due to the size of the formulations dissolution was analysed using the innovative method of surface dissolution imaging as standard USP methods 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.

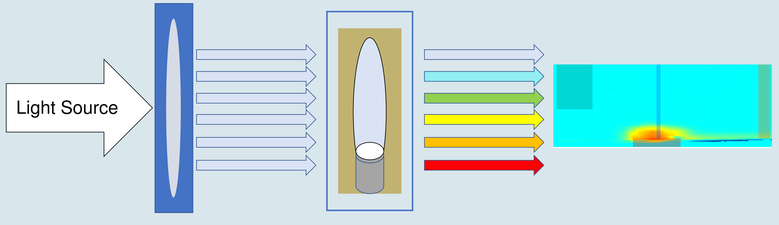

Fig 2: Surface Dissolution Imaging is achieved by shining UV light through a sample chamber within a quartz cell to image the release of the drug from the surface as media is passed over the sample. The image is then collected in real time using computer software.

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).

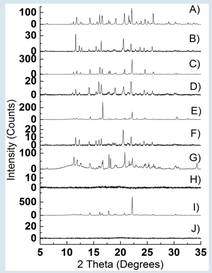

Fig 3: XRD of physical mixtures (A, C, E, G and I) and printed samples (B, D, F, H and J) in the following ratios: A) and B) API alone, C) and D)1:1; E) and F) 1:2, G) and H)1:3 I) and J) 1:4 API:polymer.

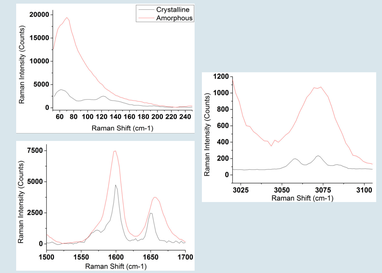

Fig 4: Raman spectroscopy of the terahertz (top) 1500-1650 cm-1 (bottom) and 3050-3100 cm-1 (middle) regions of the drug as its crystalline powder form (black) and as part of a solid dispersion (red)

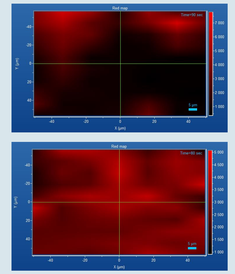

Fig 5: Raman Mapping of API:polymer 1:1 as a physical mixture (top) and printed (bottom)

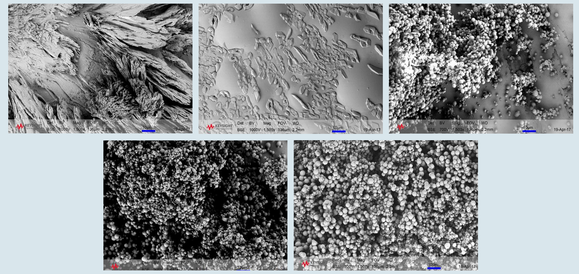

Fig 6: SEM of printed samples: API (top left) and premixed API and polymer 1:1 (top middle), 1:2 (top right), 1:3 (bottom left), 1:4 (bottom right) , 1.5K magnification

Printer capabilities tests on the HPLC (Fig. 7) show a linear, reproducible relationship between mass and deposition size, mass and layer number and mass and nozzle size. Speed was also analysed but was found to be much less linear overall. At the lower speeds, the ink seemed more prone to blocking the printer, while the higher speeds seemed to result in too little time for sufficient deposition to occur.

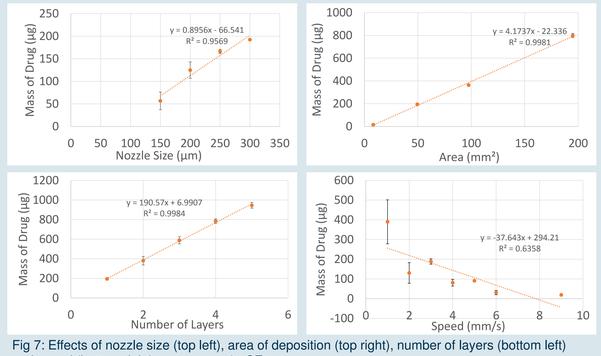

Fig 7: Effects of nozzle size (top left), area of deposition (top right), number of layers (bottom left) and speed (bottom right) on mass, n=6 ±SE

Dissolution testing (Fig. 8) so far shows increased drug release and intrinsic dissolution rates from the printed samples relative to comparable physical mixtures, which is believed to be due to greater control over drug content and distribution, and reduced crystallinity.

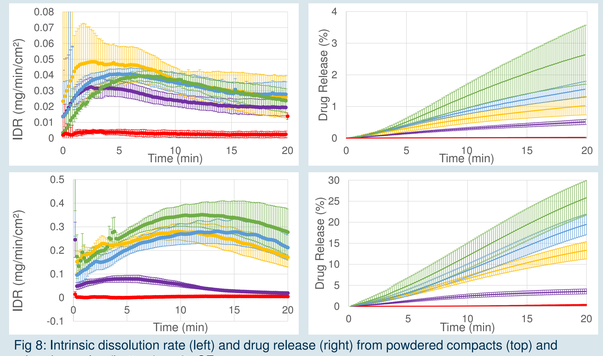

Fig 8: Intrinsic dissolution rate (left) and drug release (right) from powdered compacts (top) and printed samples (bottom), n=3 ±SE

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

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[1] Mahajan, A., Frisbie, C. D., and Francis, L. F., Optimization of aerosol jet printing for high-resolution, high-aspect ratio silver lines. ACS Applied Materials and Interfaces, 5 (11) (2013) 4856–4864.

[2] Optomec Ltd., 3D Printing Electronic Laser Additive Manufacturing Systems [Online], (2013) Available from: http://www.optomec.com/ [Accessed 1st October 2015]

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