Achieving immediate release dosage forms using DoE and Injection Moulding

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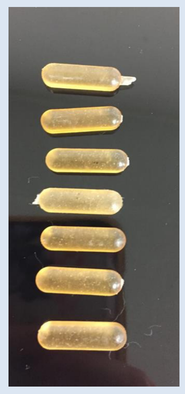
Workflow:

Powder blends

Hot Melt Extrusion

Extrudate

Injection Moulding



Dosage forms

Aim: to produce a solid oral dosage form that is both immediate release and has a homogeneous API dispersion

Polymer problem:

- Dosage forms produced using polymers via 3D printing or Injection Moulding do not behave in the same way as standard compressed powder tablets.
- Compressed powders have the ability to break apart of disintegrate increasing the particle surface area to produce an immediate release of API
- Due to the complex polymer matrix this does not occur but instead either swelling of the polymer where the drug can diffuse out or a slow erosion process
- Both these methods can hinder the release of drug
- To try and increase drug release rates disintegrating agents can be introduced to the formulation which can either produce larger holes within the polymer matrix when the agent dissolves are quicken the erosion process
- This study investigates a variety of disintegrating agents and small molecules to assess their suitability to increase the rate of the erosion process of Polyvinyl Alcohol (PVA)

Hot Stage Microscope:

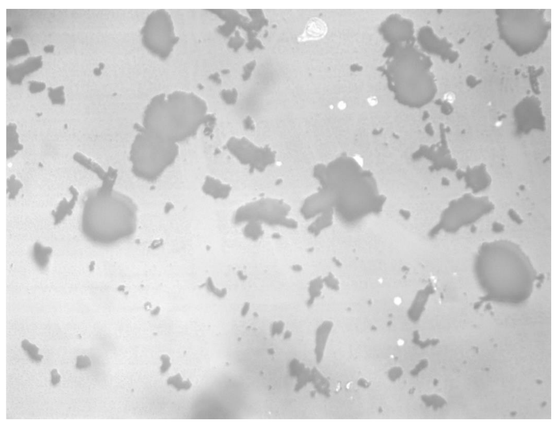


Fig 1a: Cellulose before heating

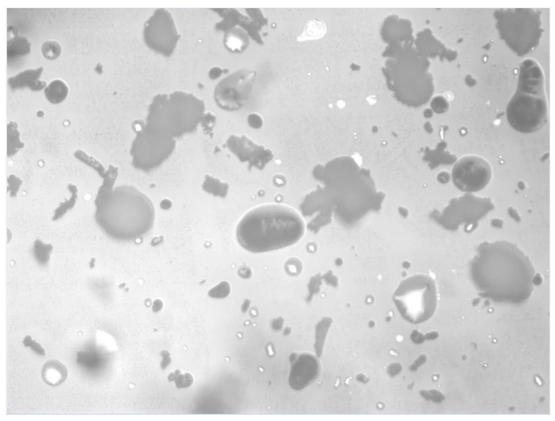


Fig 1b:Cellulose blend showing the melting of carvedilol

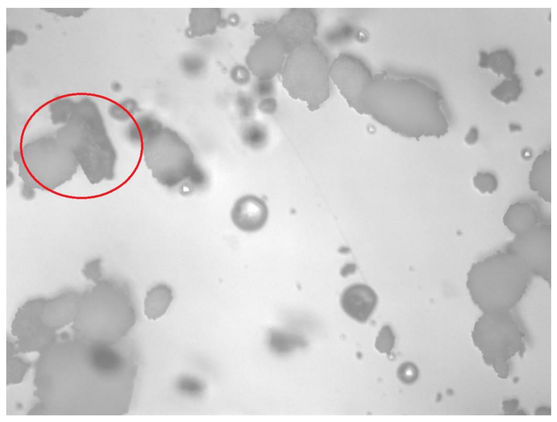


Fig 1c: Glycine at 200°C before hold time

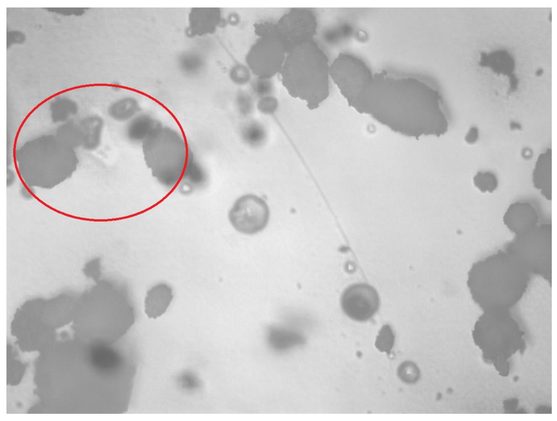


Fig 1d: Glycine at 200°C after hold time

The melting of carvedilol (approx. 117°C) was observed for all powder blends as expected according to the DSC traces (figure 3). However other events could be seen as the temperature reached the maximum 200°C for blends containing Glycine and Klucel HXF. This is assumed to be degradation of the disintegrating agent.

Design of Experiments:

Figure 2: After excluding 3 disintegrating agents from the initial DSC and HSM screen: NaCl, Glycine, Callulose, Klucel ELF and Klucel HXF will be further analysed for their effectiveness as a disintegrant

Exp No	Exp Name	Run Order	Incl/Excl	API (%)	Disintegrting Agents (%)
1	N1	6	Incl	1	0
2	N2	5	Incl	20	0
3	N3	3	Incl	1	10
4	N4	4	Incl	20	10
5	N5	2	Incl	10.5	5
6	N6	1	Incl	10.5	5

DSC:

- The figure on the left (figure 4a) shows the DSC trace for the first heating cycle.
- A small endotherm can be observed at approximately 117°C corresponding to the melting of Carvedilol. The peak is of relatively low intensity due to the small concentration of drug present in the powder blend.
- The second heat cycle on the right (figure 4b) shows no events due to the drug becoming amorphous and dissolving into the polymer.
- There is no degradation occurring for any of the disintegrating agents.
- DSC traces were obtained for raw PVA at different molecular weights (data not shown) to determine which to use in the DoE. From this and solubility data PVA at Mw 13,000 was chosen.

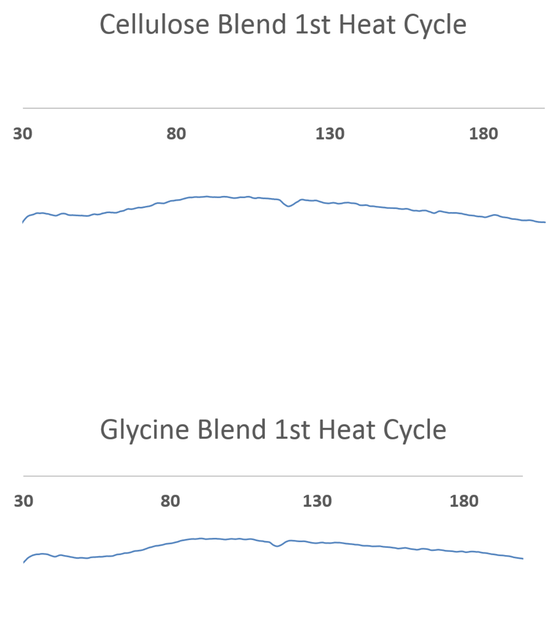


Figure 3a: DSC traces for Cellulose blend (top) and Glycine blend (bottom) obtained from the first heat cycle 20-200°C

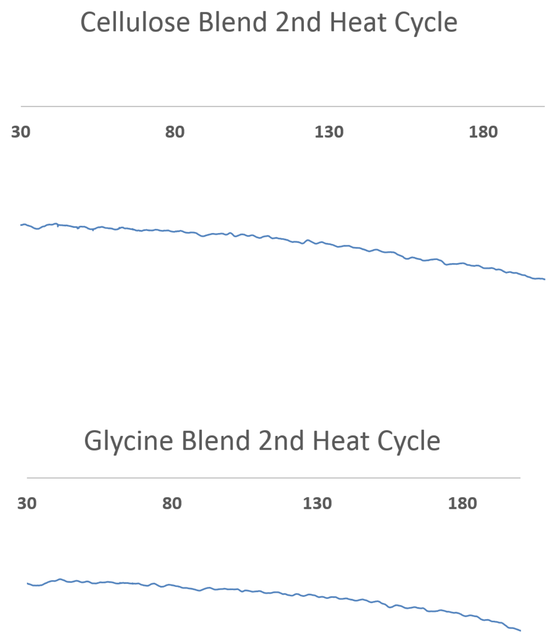


Figure 3b: DSC traces for Cellulose blend (top) and Glycine blend (bottom) obtained from the second heat cycle 20-200°C

Conclusion & Future Work:

- Using the combination of HME and Injection Moulding solid oral dosage forms can be produced however due to compaction pressure and the slowly eroding properties of the polymers-immediate release can be difficult to achieve.
- Introducing disintegrating agents to the formulation is one possible route of increasing the dissolution of the dosages.
- Design of Experiments is a useful statistical tool to obtain the most information from a minimum number of experiments.
- The DSC and Hot Stage Microscope indicated that all agents chosen were compatible at the temperature chosen to extrude at.
- A pharmaceutically irrelevant compound, small molecule, natural polymer and high and low molecular weight synthetic polymers were chosen.
- The next steps is to extrude the formulations mentioned in figure 3 and to measure the disintegrating time of the strand produced.

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