3-9-2020

Additive manufacturing in pharmaceutical formulation - Development of biodegradable printed dosage forms for oral drug delivery

Matej Novak  
University of Chemistry and Technology Prague, Czech Republic, matej.novak@vscht.cz

Frantisek Stepanek  
University of Chemistry and Technology Prague, Czech Republic

Follow this and additional works at: https://dc.engconfintl.org/imam

Recommended Citation

This Abstract and Presentation is brought to you for free and open access by the Proceedings at ECI Digital Archives. It has been accepted for inclusion in Innovative Materials For Additive Manufacturing (IMAM) by an authorized administrator of ECI Digital Archives. For more information, please contact franco@bepress.com.
ADDITIVE MANUFACTURING IN PHARMACEUTICAL FORMULATION - DEVELOPMENT OF BIODEGRADABLE PRINTED DOSAGE FORMS FOR ORAL DRUG DELIVERY

Ing. Matěj Novák  
Bc. Adam Waněk, Ing. Veronika Lesáková  
(Bc. Luna Cantillo)  
Supervisors:  
Prof. Ing. František Štěpánek, Ph.D. (UCT Prague)  
Ing. Pavel Kovačík, Ph.D. (Zentiva)
Process outline - comparison

Drug + Excipients

Hot-melt extrusion

3D printing (FDM)

Tablets
Motivation + advantages

- Personalized dosing, flexibility
- Multi-drug loading, multilayer tablets (multiple nozzles)
- Adjustable geometry and porosity (=> dissolution rate)
- Potential for scale-up (printhead arrays)
- August 2015 – First commercial application - Spritam (Levetiracetam) approved by FDA
ZipDose Technology

- First approved 3D-printed dosage form
- High dose of the drug Levetiracetam, immediate release
ZipDose Technology

- First approved 3D-printed dosage form
- High dose of the drug Levetiracetam, immediate release
Solid paste extrusion

- Easy formulation (drug can be in a dispersion)
- No thermal processing, but time-consuming paste preparation
- Multitablet – up to 5 different drugs with varying release rates
Solid paste extrusion
Ink-jet 3D printing

- High resolution (30µm)
- Time-consuming process, friability
- Typically involves solvent evaporation
- Example: Heated chamber, Fenofibrate + beeswax
Stereolitography (SLA)

- Excipients – photo-curable resins => UV radiation
- High resolution (10µm), no external heating
- “Applicable” for most drugs, UV-drug interaction poses risk
Selective light sintering (SLS)

- Sintering of excipients + drug in powder form
- Material loss, rinsing step
- Example: Kollicoat IR, Eudragit L100-55 + Paracetamol
Fused deposition modelling
General filament composition

- An approved drug (API)
  - thermal stability of the molecule
- Polymer matrix (Soluplus, Eudragit XX, Kollidon XX, cellulose derivates)
  - biodegradable approved excipients, solubilize/amorphize the drug
  - suitable thermal and rheological properties
- Functional additives – plasticizers (PEG XX, glycerol, …),
  glidants/anticaking agents (Talcum, MgStearate), disintegrants (Ac-Di-Sol, starch), desiccants (citric acid anhydrous)
  - affect mechanical properties of the filaments, process temperature, properties of the powder form, dissolution / disintegration kinetics
Important filament properties & extrusion parameters

- Mechanical properties (Young's modulus, hardness)
- Shape homogeneity (affected by extrusion parameters)
- Heat transfer rate (heating & cooling)
- Surface roughness / stickiness
- Lowest achievable process temperature
- Homogeneity of composition (drug content)
- Drug structure (amorphous / crystalline) and stability
- Dissolution / disintegration rate
Pharma-grade hot-melt extrusion

- Filament cooling
- Filament conveying
- Powder agglomeration
- Cavity formation

=> Anticaking agents (glidants)
Rheology of the powder form

A - Original powder composition
B - with 1% Anticaking Agent 1
C - with 5% Anticaking Agent 1
D - with 1% Anticaking Agent 2
E - with 5% Anticaking Agent 2
Inner structure of the filaments

- Mechanical properties affected by microporosity (in some cases up to 40% v/v)
- Micro-CT, Image analysis and reconstruction
- Porosity lowered by adding dessiccants or glidants
## Important filament properties & extrusion parameters

<table>
<thead>
<tr>
<th>Property</th>
<th>Value and units</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elasticity modulus</td>
<td>$55.65 \pm 3.31 \text{ kN/m}$</td>
<td>Three-point bending test</td>
</tr>
<tr>
<td>Indentation hardness</td>
<td>$62.58 \pm 5.07 \text{ kN/m}$</td>
<td>Needle-probe test</td>
</tr>
<tr>
<td>Normalized viscosity at 145 °C</td>
<td>$10658 \pm 1308 \text{ Pa\cdot s}$</td>
<td>Rotational rheometry</td>
</tr>
<tr>
<td>Thickness uniformity</td>
<td>$2911 \pm 31 \text{ \mu m}$</td>
<td>Digital caliper</td>
</tr>
<tr>
<td>API content uniformity</td>
<td>$9.96 \pm 0.53 \text{ % wt.}$</td>
<td>HPLC + UV spectroscopy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Component</th>
<th>Mass fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>10 - 40</td>
</tr>
<tr>
<td>HPC EF</td>
<td>20 - 80</td>
</tr>
<tr>
<td>Soluplus</td>
<td>0 - 55</td>
</tr>
<tr>
<td>Peg 6000</td>
<td>1 - 8</td>
</tr>
<tr>
<td>Citric acid</td>
<td>0 - 3</td>
</tr>
<tr>
<td>Magnesium St.</td>
<td>0 - 8</td>
</tr>
</tbody>
</table>
Printing parameter adjustment

- Gear speed, inner filling characteristics, nozzle movement speed, filament retraction, perimeter characteristics, …
- Printing temperature, bed temperature, …
- Printing resolution distribution, layer overlap, nozzle distance, …
Drug structure analysis

- Amorphous / crystalline after extrusion?
  => X-ray powder diffractometry, differential scanning calorimetry
Homogeneity of drug content

UV spectroscopy:
- Absorption of excipients
- Light scattering
- Solubility

HPLC:

<table>
<thead>
<tr>
<th>Initial content (%)</th>
<th>Measured content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>29.7 ± 0.9</td>
</tr>
<tr>
<td>10</td>
<td>9.5 ± 2.6</td>
</tr>
<tr>
<td>10</td>
<td>10.3 ± 0.2</td>
</tr>
<tr>
<td>15</td>
<td>14.4 ± 4.0</td>
</tr>
</tbody>
</table>
Disintegration enhancement

=> Effervescent compounds – disintegration due to CO$_2$ production, but leads to increased porosity and brittleness
„Exploding“ effervescent tablet

- Hollow tablet filled with effervescent mixture
Virtual prototyping and parametric design of 3D printed tablets based on the solution of inverse problem

1) Parametric series of tablets with varying internal porosities
   => library of dissolution profiles, superpositions

2) Adjusting parameters of a mathematical model to accurately predict dissolution and intrapolate between measured data

3) Superpositions of different porosities to achieve new release profiles

4) A desired release profile met by iterative programming
   => tablet design and printing, experimental verification
Virtual prototyping and parametric design of 3D printed tablets based on the solution of inverse problem.
Virtual prototyping and parametric design of 3D printed tablets based on the solution of inverse problem.
Dissolution of single-porosity tablets
Model overview, parameter fitting

**Dimension form**    **Dimensionless form**

**Diffusion flux between voxels:**

\[
N_{ij} = D \frac{c_i - c_j}{h^2} \quad \hat{N}_{ij} = \left( \frac{D\tau_0}{h^2} \right) (\hat{c}_i - \hat{c}_j)
\]

**API component balance in pore voxels:**

\[
h^3 \frac{dc_i}{dt} = \sum_j N_{ij} \quad \frac{d\hat{c}_i}{d\hat{t}} = \sum_j \hat{N}_{ij}
\]

**API component balance in tablet voxels:**

\[
\frac{dn_i}{dt} = \sum_j N_{ij} \quad \frac{d\hat{n}_i}{d\hat{t}} = \sum_j \hat{N}_{ij}
\]

**Boundary conditions:**

- at pore/tablet interface
  \[c_i = c^* \quad \hat{c}_i = 1\]
- at pore/external boundary interface
  \[c_i = 0 \quad \hat{c}_i = 0\]

**Initial conditions:**

- in pore voxels
  \[c_i(0) = 0 \quad \hat{c}_i(0) = 0\]
- in tablet voxels
  \[n_i(0) = \alpha c^* h^3 \quad \hat{n}_i(0) = \alpha\]

\[\hat{c} = c/c^*\]

\[\hat{t} = t/\tau_0\]

\[\hat{n} = n/(h^3 c^*)\]

\[\alpha = \frac{\rho}{M c^*}\]
Model overview, parameter fitting
Model overview, parameter fitting

\( D = 1.8 \times 10^{-10} \text{ m}^2/\text{s}; \text{boundary layer} = 3 \)
Conclusion

- Parametric study of composition and process parameters led to achieving FDM printability of 8 drugs
- Products analyzed (homogeneity, drug structure, material porosity, powder rheology, mechanical stability, in vitro dissolution, …)
- Dissolution kinetics predicted through mathematical 3D modelling, linked to tablet structure
- Employing genetic (evolutional) algorithm to find desired tablet structure
- Mapping and predicting “printability” for new drugs

\[ \text{res} = 200 \ \mu\text{m} \quad \text{res} = 100 \ \mu\text{m} \]
Thank you for your attention

The author would like to acknowledge support by the Czech Science Foundation (project GAČR no. 19-26127X), the Technology Agency of the Czech Republic (project no. TJ02000383) and Zentiva, k.s.