Printing technologies in fabrication of drug-delivery systems

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1. Perspectives of printing technologies in
   • personalization of products & individualized dosing,
   • fabrication of delivery-systems & medical devices

2. Case studies:
   • Accurate dosing of drug substances
   • 3D printing of medical devices
   • Quality control of printed systems

3. Conclusions and perspectives
Why printing in manufacturing?

1. **Customisation** - printing processes allow mass customisation

2. **Flexibility and on-demand** - products are produced where they are needed

3. **Allowing complexity** - digital design > new levels of complexity

4. **Sustainable / Environmentally Friendly** - energy/raw material efficient technology
3D printing is changing the way we manufacture things


http://hansencojewelry.com/create/perspective-new.jpg

http://static4.businessinsider.com/image/52ceb68469beddfe0f1c32cc/researchers-are-making-a-3d-printer-that-can-build-a-house-in-24-hours.jpg


Shift in manufacturing strategies of the future to meet the need of more individualized medicines

How will companies cope with the changing environment? Future manufacturing strategies

What will be the Future Challenges?
- Increase operating efficiency
- Increase flexibility
- Reduce product costs / achieve competitive pricing
- Produce individual products / address niche markets
- Accelerate time-to-market

What is the Strategic Response?
What will be the implications on the way we manufacture in future?

PAT / QbD will be a key enabling technology for future manufacturing scenarios.

Manufacturing strategic leaps to the medium and longer term:

Scenario 1: Modernize within existing facility
But, essentially same approach & scale

Scenario 2: Continuous processing, RTPR, JIT production

Scenario 3 = Speciality Niche products:
Small scale pilot centers, Integration of R&D and production: Small batches 24/7 running

Scenario 4 = Gross / mass market:
Large-scale highly flexible plants, with high throughput

Move to personalized medicines
Clinical and patient feedback loops
Continuous optimization and improvement

(Source: Rebecca Vangenechten, SIEMENS: MIT perspective to Pharma manufacturing, 2011)
NEED FOR PERSONALIZED DOSING
Because no two patients are alike

1. Age appropriate formulations
   - Pediatric and elderly patients

2. Gender differences

3. Life style differences

4. Metabolic capacity
   - Ethnic differences
   - Diseases compromising metabolic activity
Personalised solutions using printing technologies

2D

Medical devices

Individualised dosing

Multidrug systems

3D

3D

2D

2D
This game-changing technology just took a giant leap forward in the pharmaceutical industry. On August 3, 2015, Aprecia Pharmaceueticals, announced that the U.S. Food and Drug Administration (FDA) approved its SPRITAM drug for the treatment of epilepsy. The company claims that SPRITAM is the first drug ever approved by the FDA that is manufactured using 3-D printing technologies.
Schematic picture of the 3D printing process (Billiet et al. 2012).
Medical 3D printing prospects

Medical 3D printing to reach US$965.5 million by 2019

21 October 2014

A report by Transparency Market Research suggests that the global 3D printing in medical applications market will reach US$965.5 million by 2019, growing at a CAGR of 15.4% from 2013 to 2019.

The market was valued at US$354.5 million in 2012.

According to analysts, North America held the largest market share for 3D printing in medical applications in 2012. However, in the forecasted period between 2013 and 2019, Europe is expected to the highest growth rate of 15%. This growth will be attributable to funding by the government, various mergers and acquisitions of companies that have better technology, and conducive reimbursement policies.

Global 3D printing in medical applications market has seen a rise in the recent
Many printing technologies exist

- Piezoelectric inkjet printing
- Thermal inkjet printing
- Flexographic printing
- 3D printing/ additive manufacturing
Comparison of printing technologies

Advantages IJP:
- Additive process
- Digital patterning
- Low viscosity inks
- Thin homogenous layers/patterns
- Contact free
- Low material consumption
- Low preproduction cost

Ref: Roth and Rau
Why inkjet printing?

**Drop-on-demand (DoD) technology:**
- Drops of ink are only ejected when required
- Uniformly spaced and sized droplets
- Precision patterns of the ink
- Accurate deposition
- Flexible dosing

![Graph showing drug delivery vs. number of passes with equation: y = 7.8936x - 2.7920, R² = 0.9996]
INKJET PRINTING

- Inkjet dispensing technology has started to be a widely applied methodology in many fields incl. drug discovery (miniaturised assays, drug screening etc.)

- Inkjet and other printing technologies have recently emerged as possibility in the production of dosage forms and delivery systems

- Great potential for low dose treatments with a narrow therapeutic window due to the accurate deposition capabilities

- On-demand individualized dosing and tailored manufacture of medicines
INKJET PRINTING OF DRUG-DELIVERY SYSTEMS

- **Ink formulation**
  - Drug substance
  - Ink formulation
  - Solvent + Viscosity modifier

- **Substrate**
  - The ink is printed on e.g. edible films (sugar, cellulose, starch), a buccal delivery system, implant etc.

- **Digital design**
  - Pattern, geometry, drop spacing, layering etc.

- **Printing**

- **Drug-delivery systems**
  - Janßen et al. 2013
  - Genina et al. 2012
  - Sandler et al. 2011
Inkjet-printing (Dimatix DMP-2800)

Dimatix DMP-2800 piezoelectric inkjet

- Piezo inkjet cartridges
- Pattern editor
- Cartridge has 16 nozzles linearly spaced
- Drop sizes of 1 and 10 picoliter (1 picoliter = 1 x 10^{-9} milliliter)
- Ink requirements: viscosity 1-40 mPa, surface tension 25-50 mN/m
Inkjet-printing (PixDro LP50)

- Overall system pattern resolution 5μm
- Print Head Assemblies for numerous types of industrial print heads
- Integrated vision system for drop view, print view and accurate alignment, including analysis and calibration software

**Inkjet specifications**
Viscosity range 1 - 10 Centipoise
Nozzle range 1 - 1,000 nozzles
4 - 200 picoliter drop volume range
Inkjet-printing with the LP50 (Roth&Rau)
Inkjet printing process optimisation and quality control

Optimising drop formation

Firing voltage 20 V, drop speed: 8 m/s (400 um/50 μs)
Paracetamol
A Step Toward Development of Printable Dosage Forms for Poorly Soluble Drugs

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Preliminary Roadmap for development of Printable Dosage Forms

**DRUG**
- Water soluble?
  - Yes
  - Water-based / cosolvents
  - No
  - Soluble in organic solvents?
    - Yes
    - Org. solvent based / Cosolvents
    - No
    - Soluble in oils?
      - Yes
      - Emulsions
      - No
      - Nanosuspensions with suspension stabilizing agent
    - Not soluble enough in any of the above?
      - Yes
      - Viscosity modifiers + Moisturizer + surfactants
      - No

**FORMULATION**
- Formulation should not dissolve/disintegrate substrate

**SUBSTRATE**
- Edible
  - Critical for Mechanical strength
  - Porous
- Non-edible
  - Non-porous

**ANALYSIS**
- Chiral
  - Yes
  - SONICC
  - No
  - SEM-EDX
- Distinct element
  - Yes
  - AFM/SEM
  - No
  - Optical microscopy
  - Spectroscopy/XRD

**PRINTING**
- Flexography
- TIJ
- PIJ

- Physical
- Chemical
- HPLC
- LC-MS/TOF-SIMS
- Added functionality Film/coating
- Uniformity/dose accuracy

D. Raijada et. al., J Pharm Sci, 2013

SONICC-second order nonlinear optical imaging
SEM-scanning electron microscopy, EDX-energy dispersive X-ray spectroscopy
AFM-atomic force microscopy
PIJ-piezoelectric inkjet, TIJ-thermal inkjet
Inkjet-printing example – microparticle fabrication

Fig. 1. Schematic representation of the piezoelectric inkjet printing system for fabrication of PTX-loaded PLGA microparticles.

Fig. 2. Fluorescence micrographs of PTX-loaded PLGA microparticles with different geometries: (a) circle, (b) grid, (c) honeycomb, (d) ring. Scale bar represents 500 μm.

Fig. 3. Cumulative release (%) of PTX from PTX-loaded PLGA microparticles with different geometries over time.

Research paper

Evaluation of different substrates for inkjet printing of rasageline mesylate

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**Fig. 1.** A picture of the inkjet-printed rasageline mesylate onto the transparency film with multiple passes.

**Fig. 3.** Drop shape analysis of the ink on the different substrates: (a) copy paper; (b) transparency film; and (c) orodispersible film.

**Table 1**
The content of rasageline mesylate with increasing in the amount of printed layers (passes). Data are presented as mean (mg) ± standard deviation (mg) (n = 5).

<table>
<thead>
<tr>
<th>No. of layers</th>
<th>Orodispersible film</th>
<th>Transparency film</th>
<th>Copy paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.11 ± 0.02</td>
<td>0.20 ± 0.01</td>
<td>0.24 ± 0.07</td>
</tr>
<tr>
<td>2</td>
<td>0.21 ± 0.02</td>
<td>0.50 ± 0.03</td>
<td>0.34 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.29 ± 0.02</td>
<td>0.61 ± 0.28</td>
<td>0.52 ± 0.05</td>
</tr>
<tr>
<td>4</td>
<td>0.41 ± 0.15</td>
<td>0.94 ± 0.04</td>
<td>0.71 ± 0.04</td>
</tr>
<tr>
<td>5</td>
<td>0.60 ± 0.12</td>
<td>1.18 ± 0.05</td>
<td>1.02 ± 0.06</td>
</tr>
<tr>
<td>6</td>
<td>0.87 ± 0.28</td>
<td>1.15 ± 0.28</td>
<td>1.27 ± 0.15</td>
</tr>
<tr>
<td>7</td>
<td>0.86 ± 0.35</td>
<td>1.36 ± 0.06</td>
<td>1.37 ± 0.08</td>
</tr>
<tr>
<td>8</td>
<td>1.31 ± 0.23</td>
<td>1.57 ± 0.10</td>
<td>1.90 ± 0.09</td>
</tr>
<tr>
<td>9</td>
<td>1.03 ± 0.36</td>
<td>1.56 ± 0.18</td>
<td>2.11 ± 0.07</td>
</tr>
</tbody>
</table>
Schematic representation of the combining of inkjet and flexographic printing techniques for fabrication of drug-delivery systems

Tailoring controlled-release oral dosage forms by combining inkjet and flexographic printing techniques

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Each flexographic deposition cycle applies approx. a 100 nm layer of ethylcellulose

Tailoring drug release properties
Printability – substrate properties

Microscopic and digital camera images of riboflavin sodium phosphate printed on the different substrate: a) Substrate A, matt side; b) Substrate A, glossy side; c) Substrate B; d) Substrate C. Top row: cross-section images; middle row: top view images; bottom row – digital camera images of printed areas.

The quality of a printed pattern of API onto a porous substrates depend on the characteristics of the substrates; particularly its wettability, surface roughness and homogeneity of substrate surface.
Example: Flexible dosing of loperamide and caffeine

Dimatix DMP-2800 piezoelectric inkjet

- 16 nozzles (d~23 µm, V~10 pl)

- Two model APIs – caffeine and loperamide hydrochloride
- Ink base – propylene glycol/water (caffeine) and propylene glycol/ethanol (loperamide)
- Substrates – commercial sugar icing sheets, HPC films, PET films
- Droplet spacing – from 10 µm (highest dose) to 50 µm (lowest dose)
- Surface area of a single dose 4 cm²
RESULTS Content analysis

- Accurate dosing
- Very small standard deviations – important for dosing of potent APIs
EDIBLE INKS AND RICE & SUGAR-BASED SUBSTRATES: Accurate dosing of propranolol

Printing of the propranolol formulation

Drug release

Drug content

QC by colorimetry
Quality control: Data visualisation using principal component analysis (PCA)
Flexible dosing of a theophylline formulation

Contour plot of the spectral data from the image
NIR spectra from the region of interest
Score plot to cluster data with similar spectral features
Loadings plot to indicate which spectral regions are contributing to the variability in the data

Vakili et. al., Int J Pharm. 2015 10;483(1-2):244-9
Building a quantitative PLS model to for drug substance content measurement – Flexible dosing of a theophylline formulation

Accurate dose escalation of 7.8 micrograms of theophylline per printing pass (per square)

Vakili et. al., Int J Pharm. 2015 10;483(1-2):244-9
Exploring 3D printing for contraceptive devices

Intra uterine system, IUS
Extrusion/Injection molding
PDMS
Mirena®, Bayer

Intra vaginal ring, IVR
Extrusion/Injection molding
EVA
Nuvaring®, Merck

Implant, rod, cylinder
Extrusion/Injection molding
EVA, PDMS
Jadelle®, Bayer
Implanon®, Merck

Example: 3D Printing of Medical Devices (IUS)

Flexibility of design and manufacture – future opportunities:
- Tailored devices based on the patient’s need > size and shape
- Tailored functionality > controlled drug release properties > tailor-made treatments and devices

3D printing of drug-loaded EVA 5 filaments:

- **Hot-melt extrusion:**
  - 0%, 5% & 15% drug-loading
  - Extrusion at 105-110 °C

- **3D printing** at 165 °C

In vitro release studies (30 days)
Perspectives: On-demand manufacture

Perspectives: Dose flexibility

Printing concepts:
- Complete surface
- Central
- Point by point
- Lines
  - symmetric
  - asymmetric

Fixed dose combinations

Anti-counterfeiting and identification
- Batch: xyz
  - Serialization
- Barcode
- Batch
  - Identification

Hospital Pharmacy

Diagnosis, Treatment & Therapy plan

Individual patient supply

Hospital Pharmacy

Drug-loaded filaments

3D Printer

Edible substrate

Printer (e.g., Inkjet)

Preparation & Printing of individual dosage forms and doses
Continuous manufacturing line would allow fabrication of tailored dosage forms in an industrial setting.
Printing line for large scale manufacture

The FunMat (Functional Materials) printer at Åbo Akademi University which is used as a lab-scale modular prototype printer that can be operated in a continuous manner and can use sequentially up to six different printing units (gravure, flexo, coating, ink-jet, lamination).
Future challenges

- Technological development of printers and production lines
- Development of printable formulations and carrier substrates
- Quality control and characterization
- Regulatory aspects regarding bringing manufacturing closer to the patient/the pharmacies
- Regulatory perspectives regarding flexible dosing/fabrication and manufacture of patient adapted dosage forms
Conclusions

- Closer to the patient
- Lean production based on demand
- Faster availability
- Personalised therapies
- Modular and mobile manufacturing
- Safety maximisation through better quality control
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