3D powder bed printing with lactose: a showcase

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February, 2021

A century of shaping the excipients industry

1900
HMS (Dutch Milk Sugar) founded, NL

1926
Six Dutch dairy producers form DMV

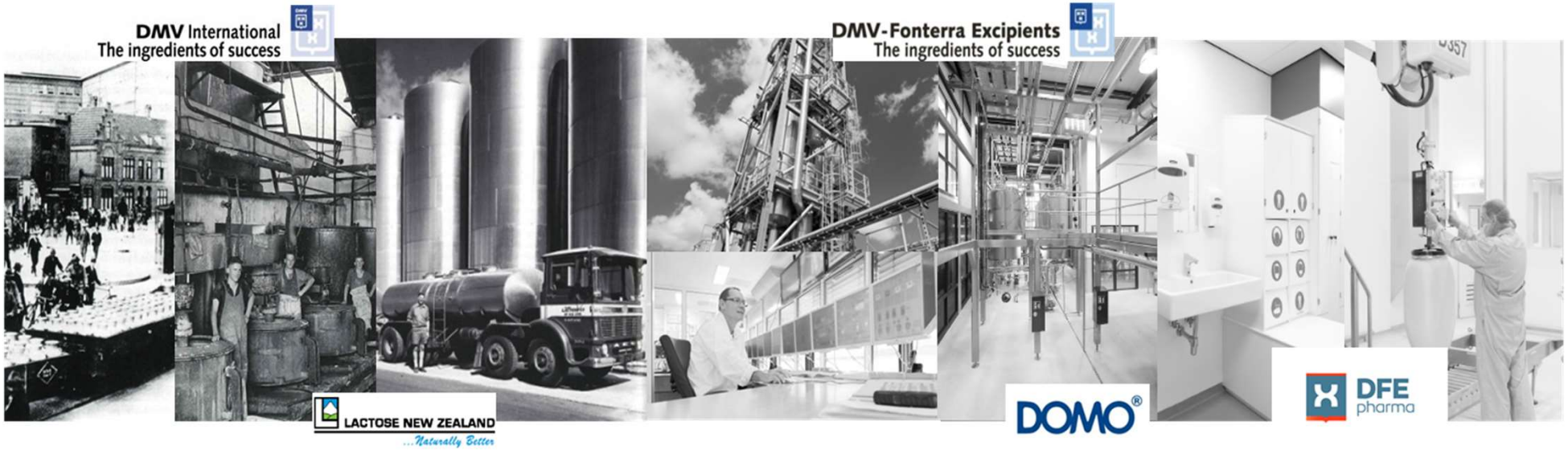
1960
DOMO starts pharma grade lactose

2003
Superdisintegrants acquired from Avebe

2006
DMV-Fonterra Excipients created

2011
Acquisition Brahmar Cellulose, India

2013
Global launch MCC



1913
First lactose plant, NZ

1946
First lactose plant Kapuni, NZ

1985
Inhalation-grade lactose DOMO, NL

2005
Inhalation grade lactose plant, NZ

2010
DOMO-pharma integrated

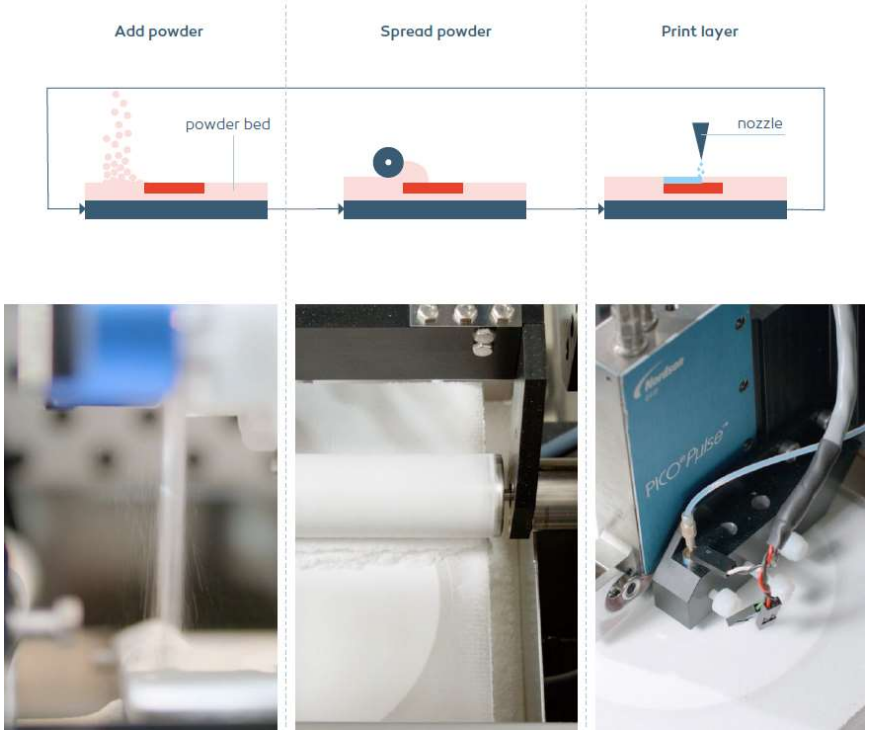
2011
New brandname DFE Pharma

2016
10 years JV anniversary

Why is the pharmaceutical industry interested in 3D printing?

- Very suitable for orphan drugs and personalized medicine (groups or individuals).
- Easy fabrication of tablets with multiple APIs
- Fast disintegration tablets
- Accelerate FIH (first in human trials) → **3DP is an excellent fit with clinical trials, because**
  - High dose flexibility (dose escalation studies)
  - Adequate bioavailability
  - Easy to administer
  - No issues around drug solubility and stability (e.g. for liquid formulations)
  - Easily to blind products
  - On-demand printing could enable the production of several product iterations for testing, could reduce the length of storage and transportation and prevent the need for stability-improving measures

3D printing techniques: powder bed printing



Powder bed printing can create tablets with a quick and complete release of the API, but

Limited information available on powder bed printing in literature:

- Which excipients to select in order to formulate a tablet with appropriate hardness, tablet mass variation, disintegration time and dissolution profile?
- Which print setting to vary in order to have a robust product which meets the specifications?

And limited GMP powder bed printers available

Photographs courtesy of Netherlands Organisation for applied Scientific Research (TNO)

Winning in 3D printing

Currently

- Possibility to produce excipients specific for API and printing equipment needs
- API properties & formulation knowledge
- Printing equipment mainly used in other industries

Future

- Customized pre-blend
- API & tablet require-ments
- GMP Printing equipment

Case study with hydrophilic and hydrophobic model drug compound as starting point formulation

Study set-up

Materials:

- Pre-blend lactose A -fully pregelatinized starch (90-10% w/w %)
- Pre-blend lactose B -fully pregelatinized starch (90-10% w/w %)
- Primojel® (sodium starch glycolate)
- Primellose® (croscarmellose sodium)
- Diclofenac-Sodium as hydrophobic model compound
- Acetominophen as hydrophilic model compound

The three critical parameters for 3D powder bed printing are determined via:

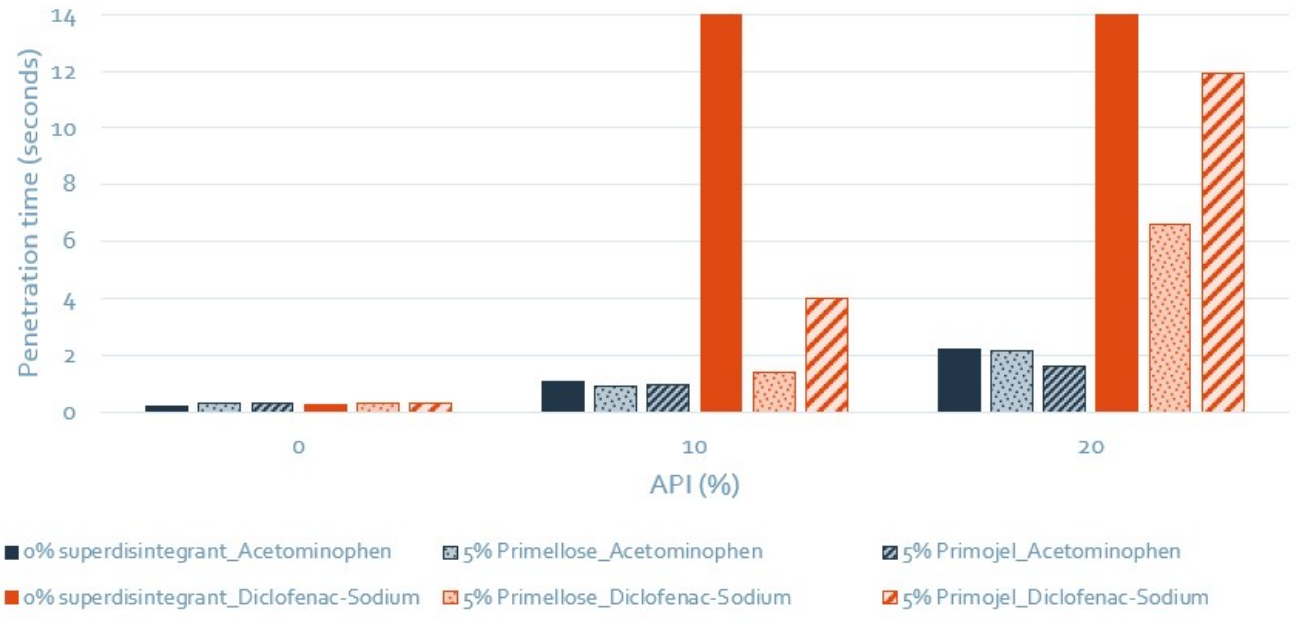
Flow via shear cell

Consolidation via simple wetting test

Wetting via DSA

Pre-blends with 10% model compound and 5% superdisintegrant had a suitable flow and wettability

Primojel® and Primellose® decreased the liquid penetration time for API powder blends

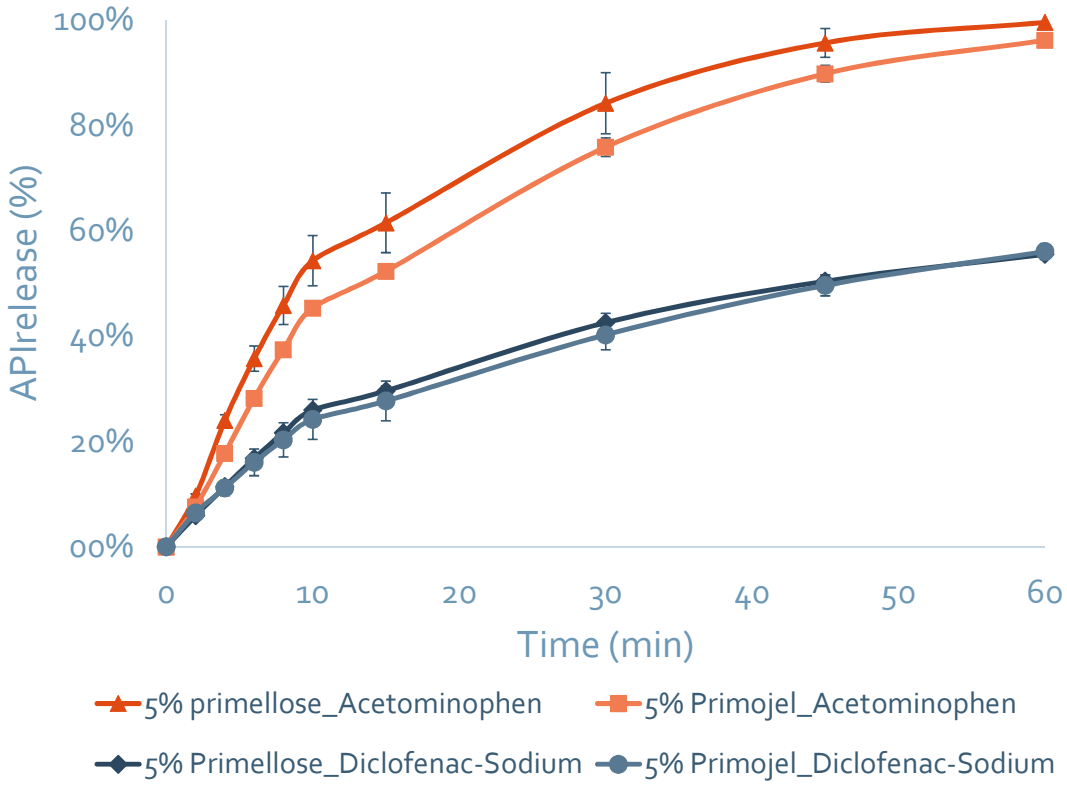


All blends were easy flowing and therefore suitable for powder bed printing:

- FFC pre-blends with 10% model compound and 5% disintegrant: 5.1-8.2
- Bulk density pre-blends with 10% model compound and 5% disintegrant: 0,57- 0,69 g/ml

Penetration time measurement was stopped after 14 seconds, Lactose morphology B was used the for penetration test, FFC= flow functioncoefiicient, PBD= poured bulk density, FFC measured at a pre-shear of 4 kPa

Primojel® was selected as superdisintegrant based on its shorter disintegration time



Formulation	Hardness (N)	Disintegration time (sec)
5% Primellose_ Acetominophen	61 ± 19	122 ± 4
5% Primojel_ Acetominophen	57 ± 7	49 ± 25
5% Primellose_ Diclofenac-Sodium	42 ± 8	265 ± 47
5% Primojel_ Diclofenac- Sodium	57 ± 20	195 ± 7

Pre-screening was performed with n=2, discs were used for disintegration time measurements, target tablet diameter is 9 mm, target height is 2,8 mm, tablet mass around 135 mg

Tablets were successfully printed with lactose based pre-blend

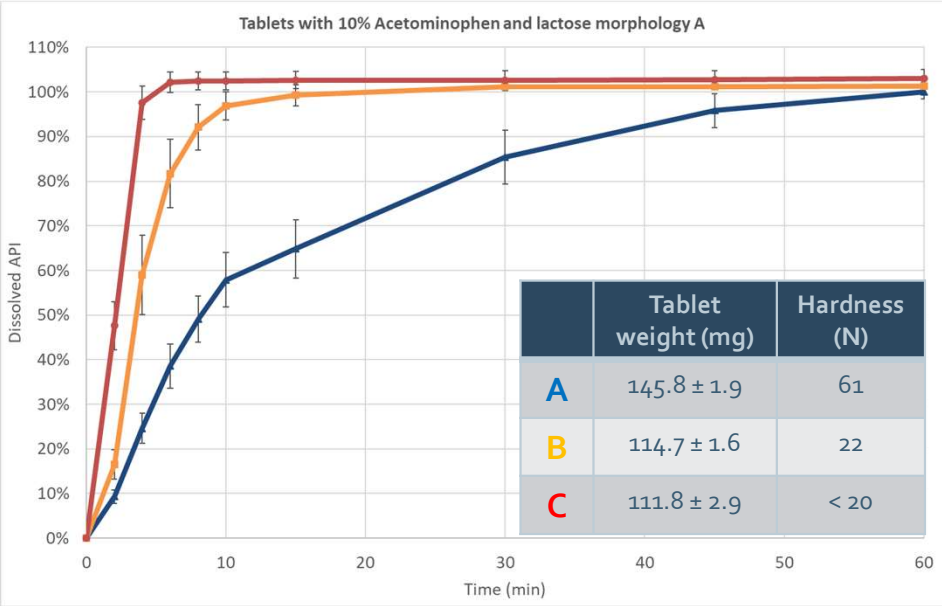
Acetominophen

Diclofenac-Sodium

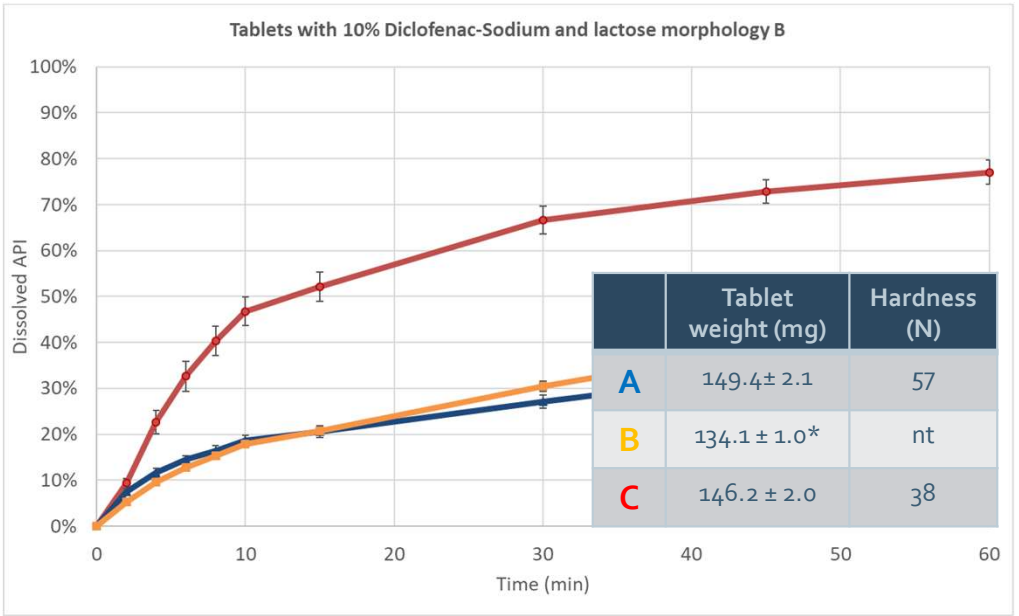
Formulation:
- 10% model compound
- 5% primojel®
- 85% pre-blend (90% lactose-10% fully pregelatinized starch)

Photographs courtesy of Netherlands Organisation for applied Scientific Research (TNO), values in % w/w

The effect of superdisintegrant on dissolution, tablet mass and hardness is depending on hydrophilicity API



	Tablet weight (mg)	Hardness (N)
A	145.8 ± 1.9	61
B	114.7 ± 1.6	22
C	111.8 ± 2.9	< 20



	Tablet weight (mg)	Hardness (N)
A	149.4± 2.1	57
B	134.1 ± 1.0*	nt
C	146.2 ± 2.0	38

Hydrophilic compound: Addition of Primojel® (B) to a formulation with 10% fully pregelatinized (A) increased the API release during dissolution testing, but reduced tablet hardness and mass. Reducing the starch level to 5% (C) increased the API release further.

Hydrophobic compound: Addition of Primoje®l (B) to a formulation with 10% fully pregelatinized (A) had no impact on the API release and limited impact on the tablet mass. Reducing the starch level to 5% (C) did result in an increase in API release.

Further formulation optimization can be obtained via fine-tuning of the print settings or binder selection

A= 10 % Fully pregelatinized starch_0% Primojel®, B= 10 % Fully pregelatinized starch_5% Primojel®, C= 5 % Fully pregelatinized starch_5% Primojel®

Concluding remarks

- Our study with Primellose® and Primojel® shows that adding a disintegrant to a 3D formulation (with model drugs) does not have any impact on flow while it does improve the wettability of the blend
- First screening indicates that Primellose® has more impact on the wettability and Primojel® more on the disintegration time.
- This study shows that disintegrants can well be used in 3D formulations as a means to impact the tablet mass and hardness-dissolution balance of a tablet with a hydrophilic API.
- Further optimization can most likely be obtained by fine-tuning the print settings (amount of print liquid, print pattern, etc) and will therefore be topic of further research.

Summary: DFE offers customized products for 3D printing

Powder bed printing (DOS) is one of the most promising 3D printing techniques

Lactose is a preferred filler for powder bed printing once formulated with a binder.

DOS

FDM

SLS

SSE

lactose/pregelatinized starch

Please feel free to contact us for formulation advise or customized samples for 3D powder bed printing

Please consider the following when discussing opportunities: type of powder bed printer, API size, hydrophilicity, drug load, etc.

DOS: Drop on solid/powder bed, FDM: fused deposit modeling, SLS: selective laser sintering, SSE: semi solid extrusion

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