Manufacturing Classification System: (MCS) Recent Developments & Publications

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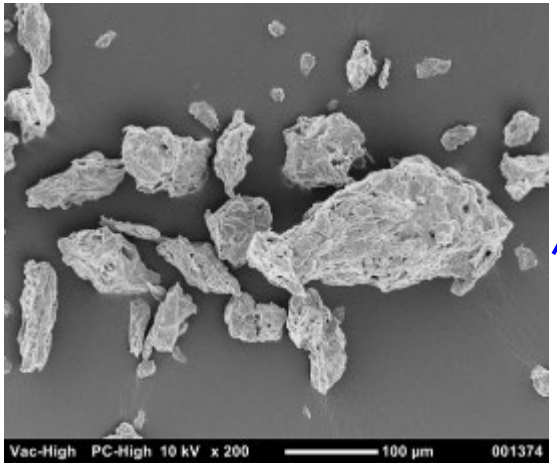
MCS Working Group

13 Sept 2019

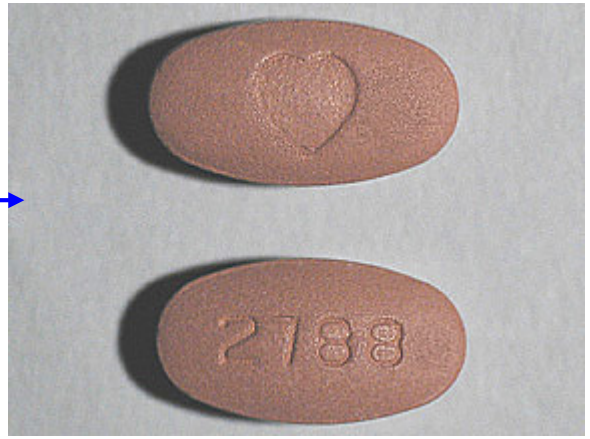
The Tableting Process

Drug

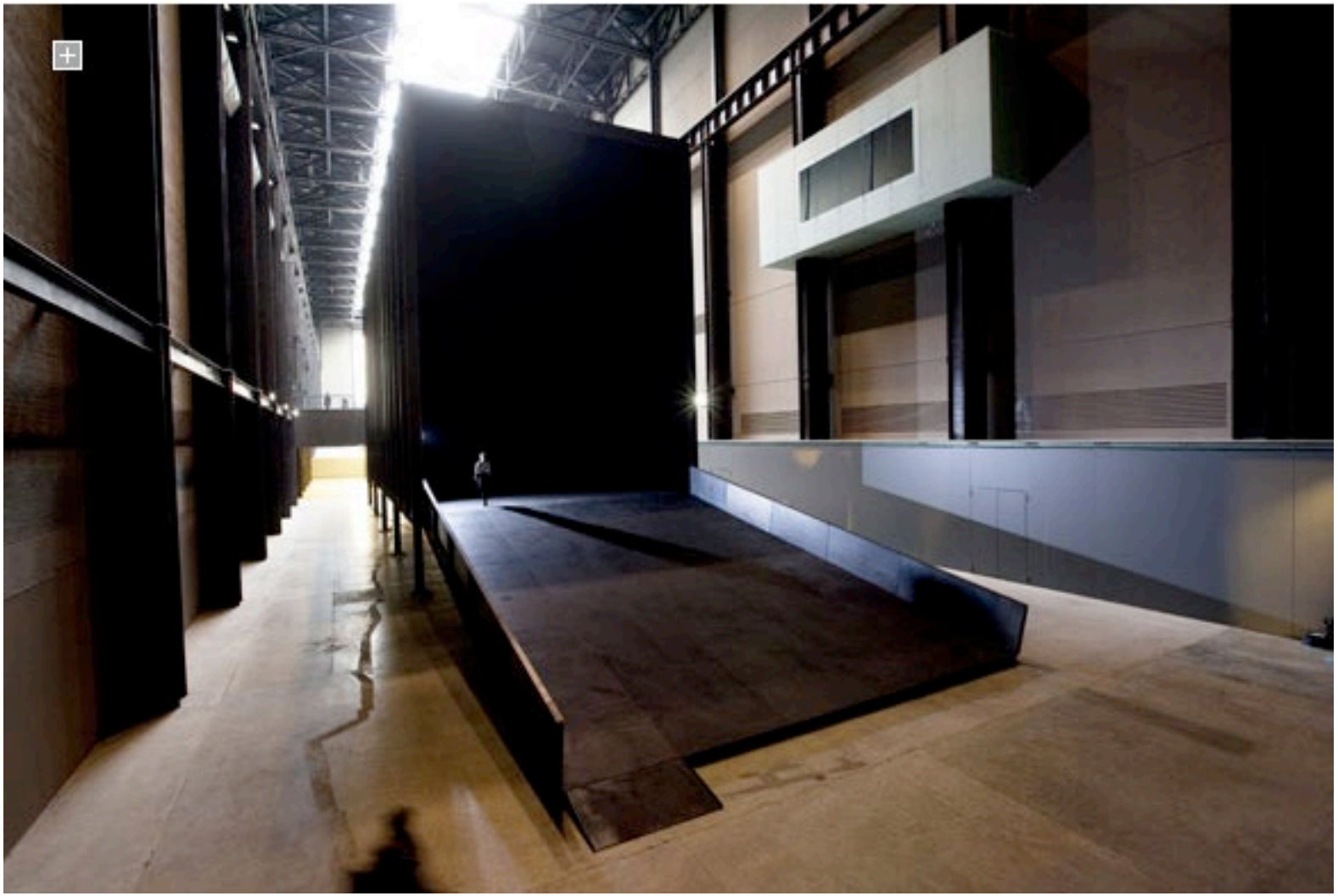


Excipient

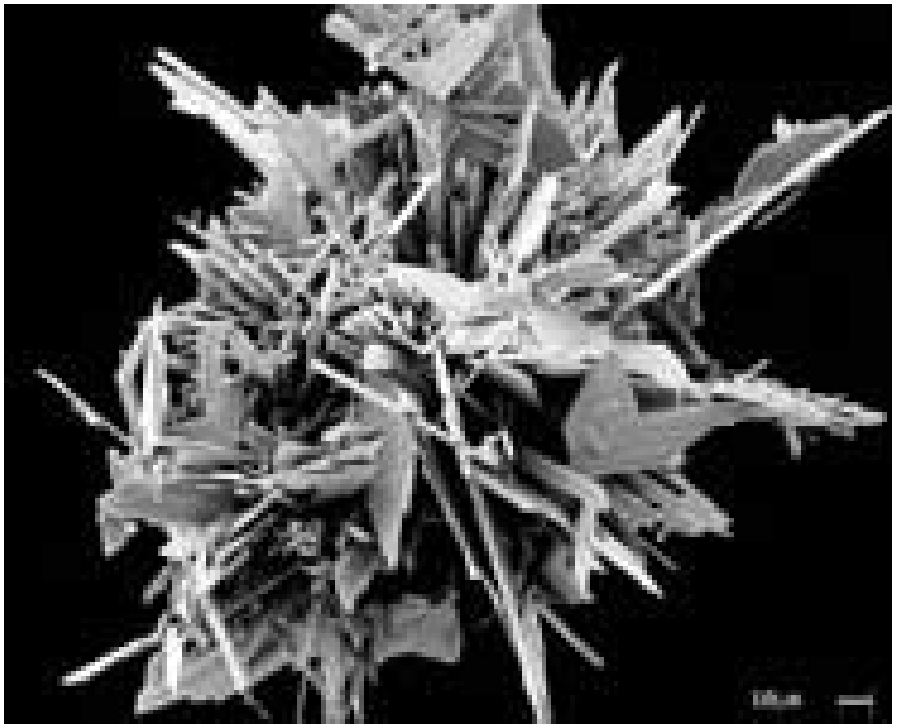
Black box



Inside the black box



Same form – Different tableting characteristics?



APIs or excipients?
determinants of performance

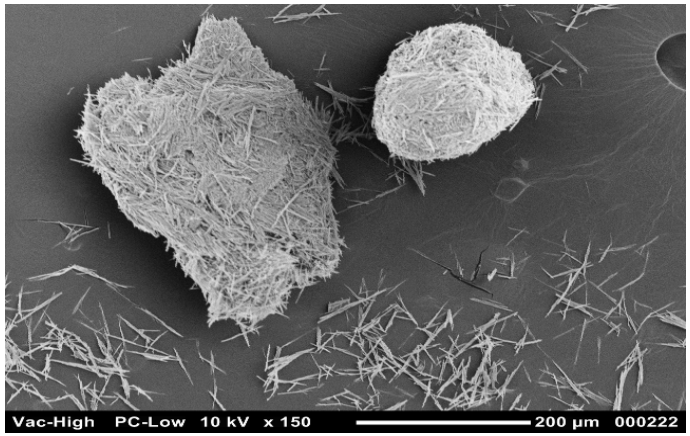
	API	Common excipient
Size, properties	Small, Hydrophobic	Large, Hydrophilic
Invented for	Curing maladies	Facilitating tableting
Commercial experience	'Never seen in nature'	40+ years

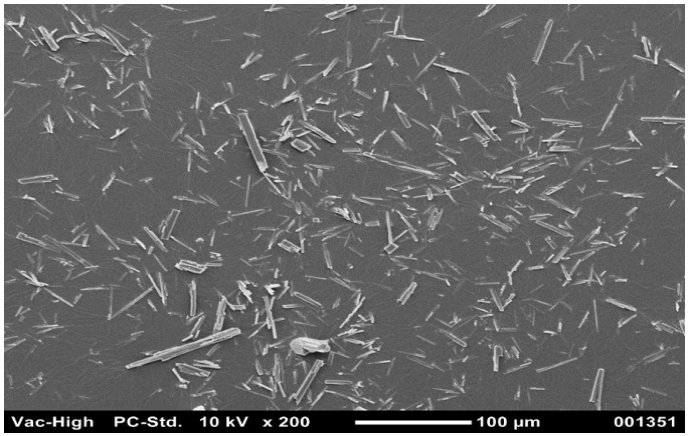
Tabletting Issues

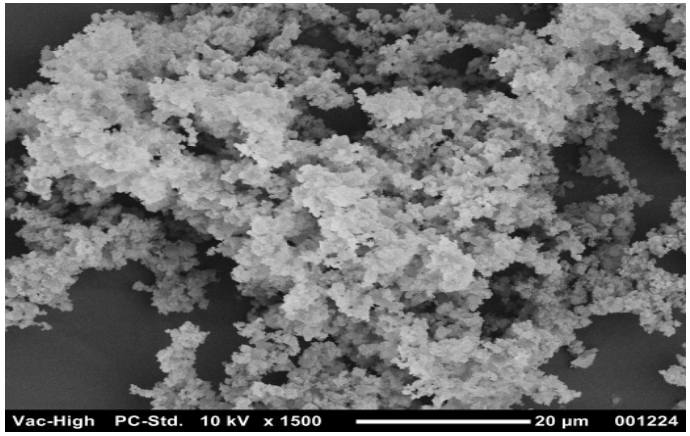
Tablet Size

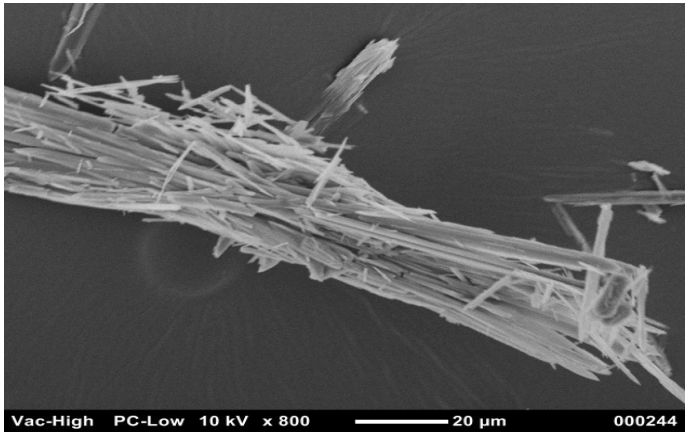
Drug Product	Dose Regimen	Trade Dress	Core Tablet Weight	Tablet Dimension
Truvada®	FTC 200 mg TDF 300 mg		1000 mg	L: 19.3 mm W: 8.7 mm T: 7.3 mm
Sustiva®	EFV 600 mg		1200 mg	L: 19.2 mm W: 9.7 mm T: 7.2 mm
Atripla	EFV 600 mg FTC 200 mg TDF 300 mg		1550 mg	L: 20.2 mm W: 10.6 mm T: 8.8 mm

‘Difficult’ API

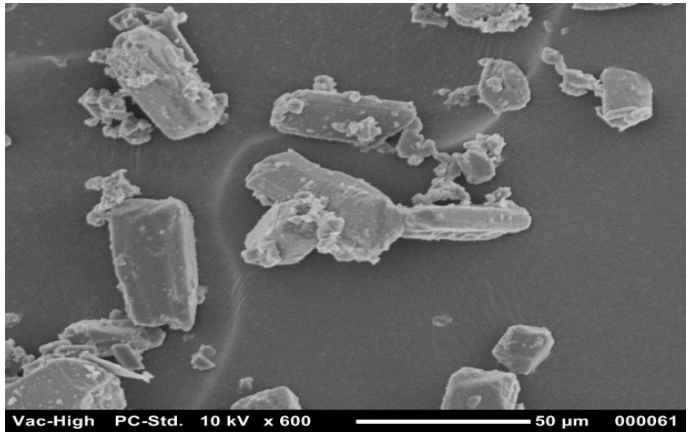


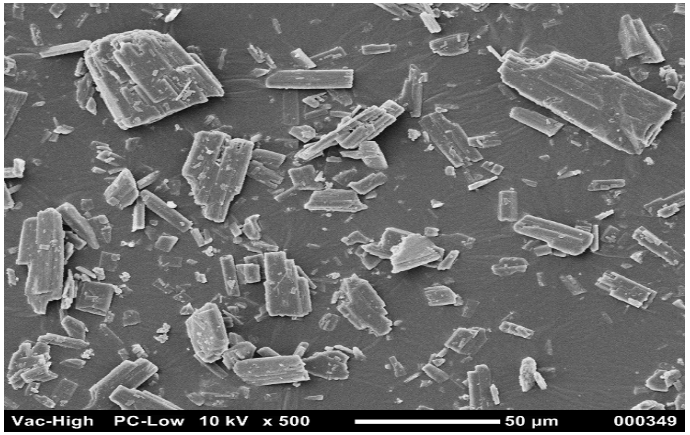


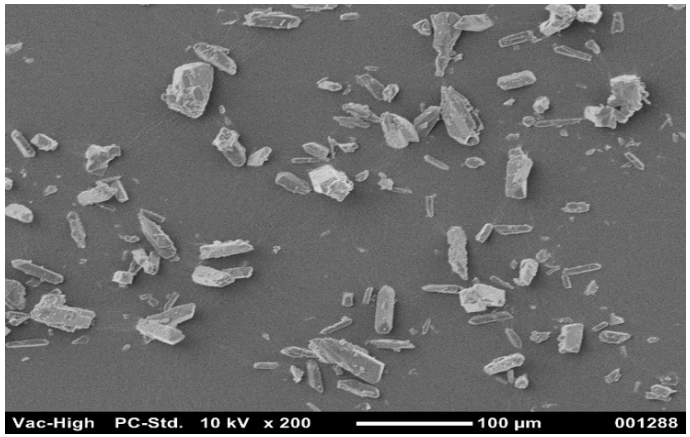


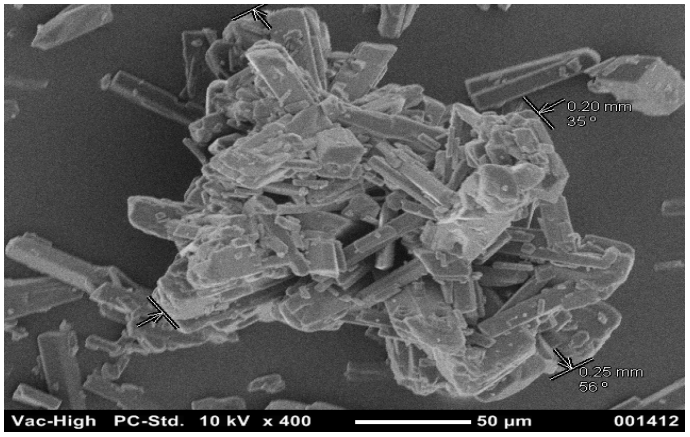


“Good” API

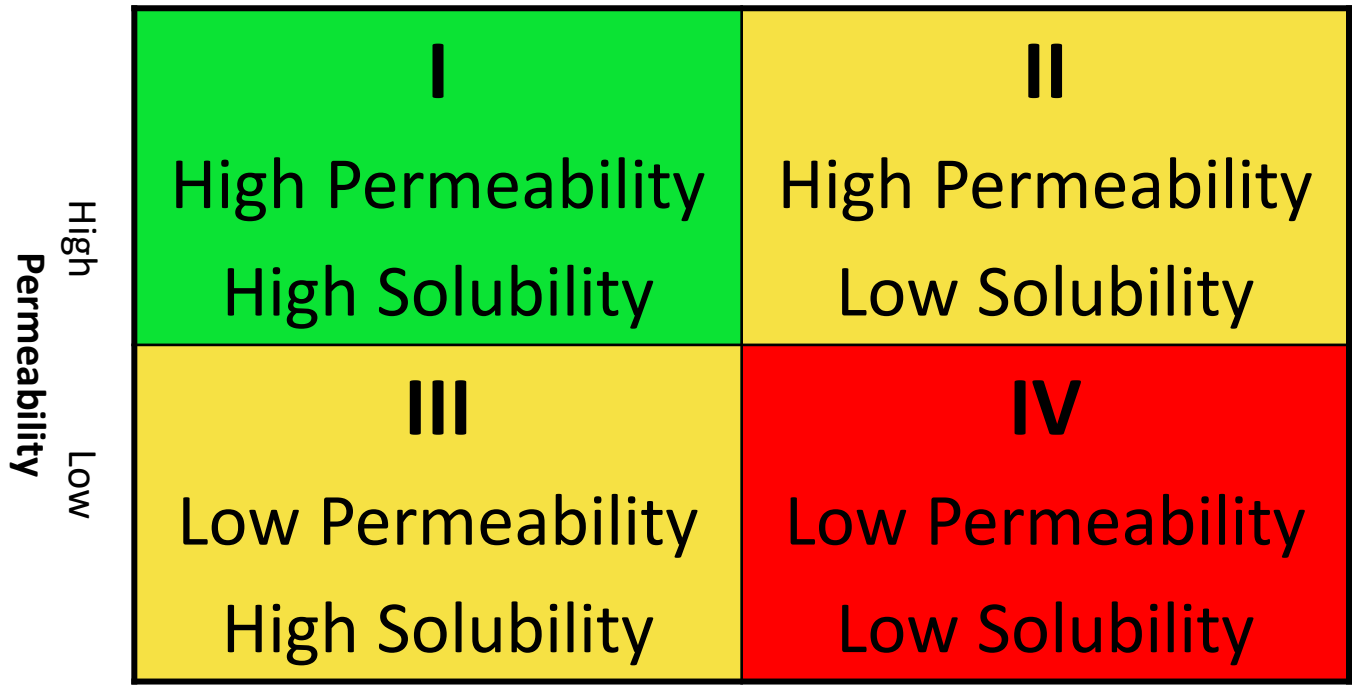

Vac-High PC-Std. 10 kV x 600 50 µm 000061


Vac-High PC-Low 10 kV x 500 50 µm 000349


Vac-High PC-Std. 10 kV x 200 100 µm 001288


0.20 mm
35 °
0.25 mm
56 °
Vac-High PC-Std. 10 kV x 400 50 µm 001412

Biopharmaceutics Classification System (BCS)



Development Classification System (DCS) Butler & Dressman (2010) provided an important advance on this as it discriminates particle size and dissolution rate

Amidon GL, Pharm. Res., 12 (3), 1995. - Guidance for industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. August 2000, CDER/FDA.

JAMES M. BUTLER, and JENNIFER B. DRESSMAN Journal of Pharmaceutical Sciences, Vol. 99, 4940–4954 (2010) The Developability Classification System: Application of Biopharmaceutics Concepts to Formulation Development

MCS: Why have one?

- Borrowing from BCS, use properties of particles to form a new classification to aid drug product manufacturing.

- Defines the "right particles" and "best process".
- Assist in particle engineering to provide targets for API properties.
- Aid development and subsequent transfer to manufacturing.
- Provide a common understanding of risk.
- Fits with QbD principles. Potential of obtaining regulatory relief by demonstrating that the properties of the ingoing API and excipients are within established ranges for the process.

MCS: Initial discussions

APS Joint Focus Group Meeting

BCS to MCS: From the particle to drug product: Predictions from Material Science through to manufacturing

May 13th and 14th 2013, East Midlands Conference Centre, University of Nottingham, UK.

- Mat Sci and PEFDM focus groups

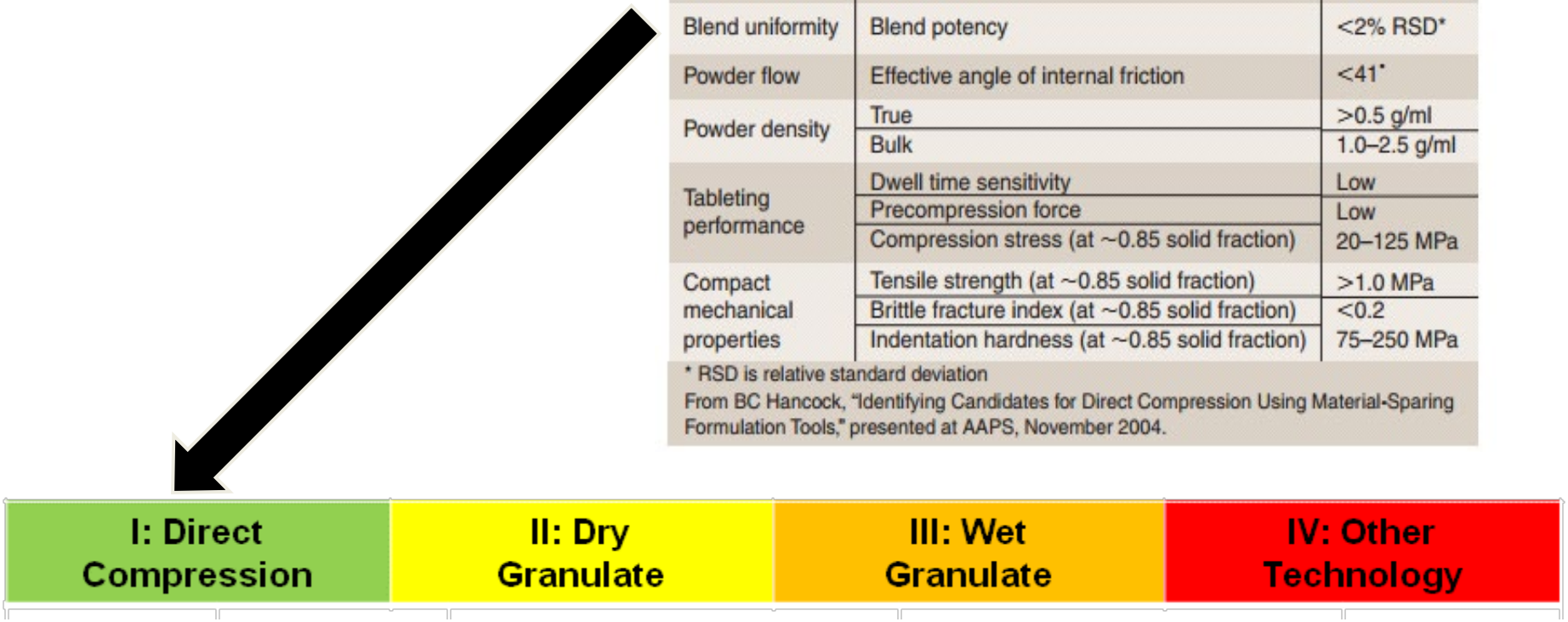
MCS Based on Processing Route

Table II: Properties of an ideal direct-compression material.

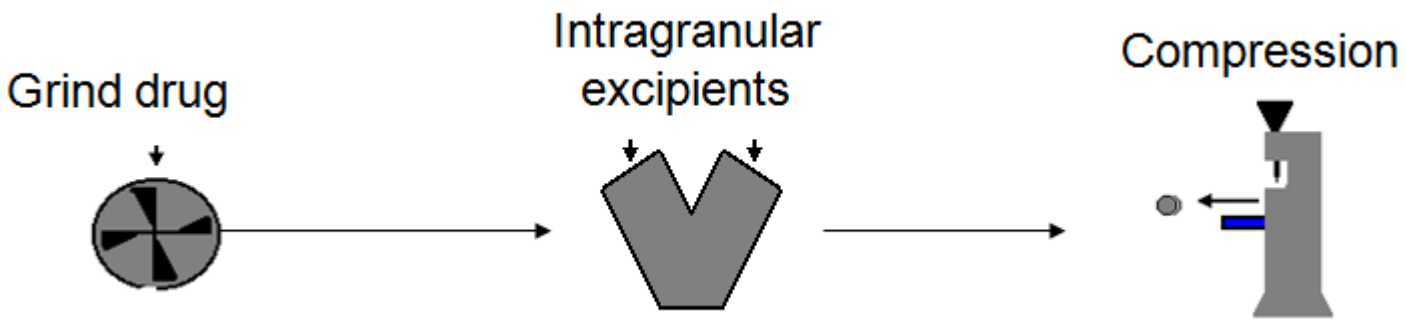
Property	Parameter	Target value
Particle size and shape	D 4,3 (mean volume diameter)	>80 μm
	D 10 (10th percentile diameter)	>30 μm
	D 90 (90th percentile diameter)	<1000 μm
	Aspect ratio	<1.5
Blend uniformity	Blend potency	<2% RSD*
Powder flow	Effective angle of internal friction	<41°
Powder density	True	>0.5 g/ml
	Bulk	1.0–2.5 g/ml
Tableting performance	Dwell time sensitivity	Low
	Precompression force	Low
	Compression stress (at ~0.85 solid fraction)	20–125 MPa
Compact mechanical properties	Tensile strength (at ~0.85 solid fraction)	>1.0 MPa
	Brittle fracture index (at ~0.85 solid fraction)	<0.2
	Indentation hardness (at ~0.85 solid fraction)	75–250 MPa

* RSD is relative standard deviation

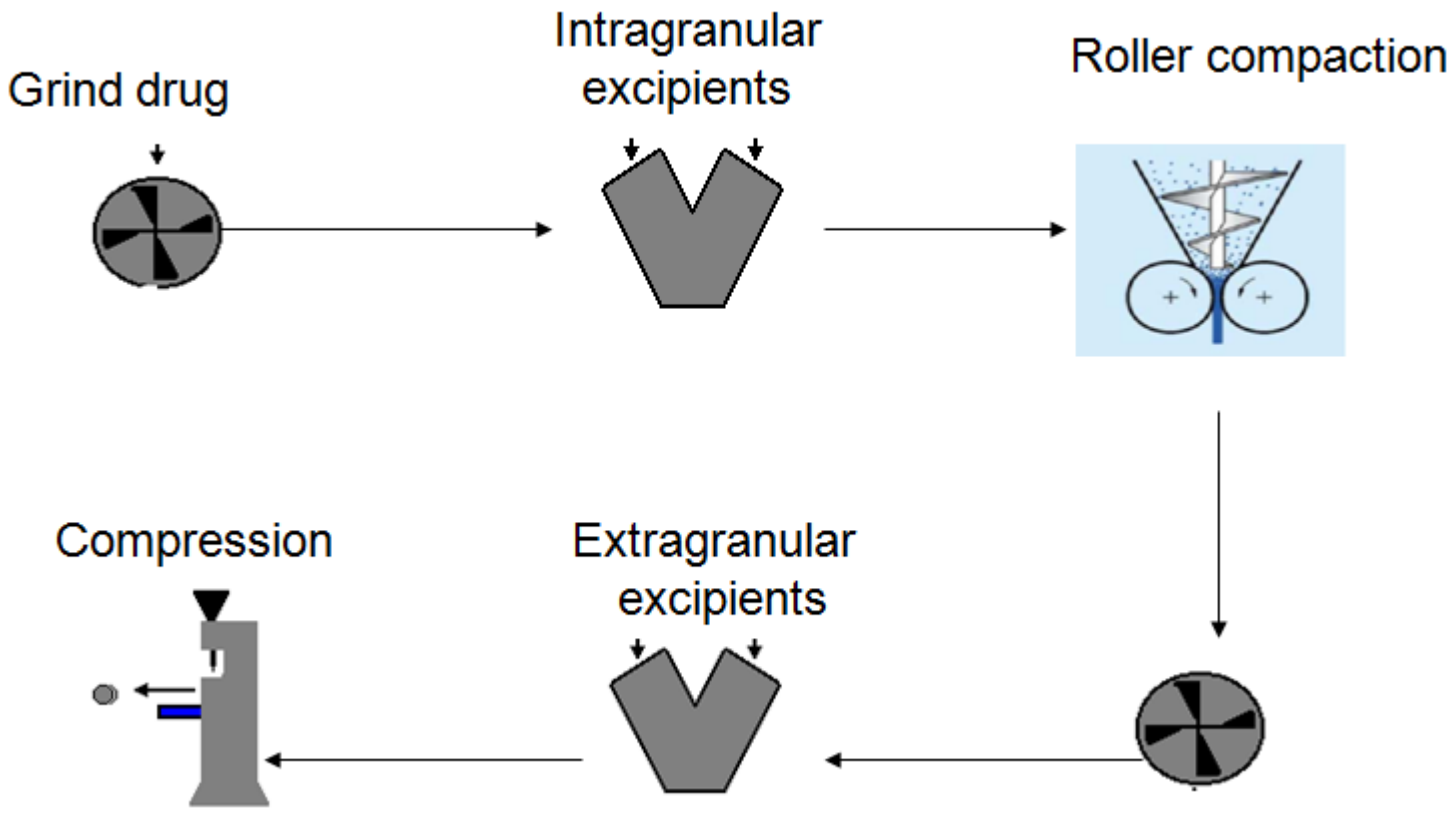
From BC Hancock, "Identifying Candidates for Direct Compression Using Material-Sparing Formulation Tools," presented at AAPS, November 2004.



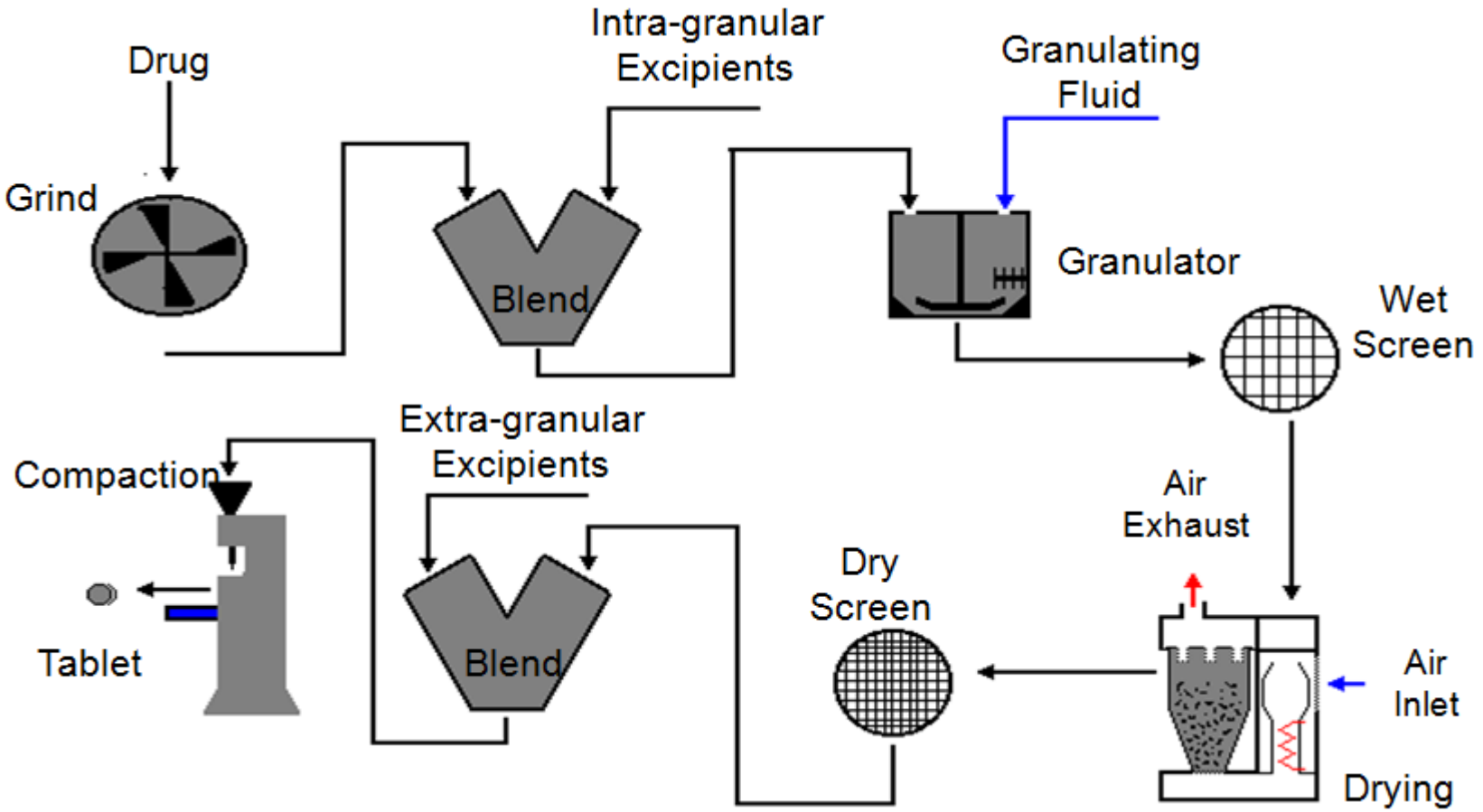
Direct compression



Dry Granulation



Wet granulation



White Paper

Pharmaceutical Development and Technology

http://informahealthcare.com/phd
ISSN: 1083-7450 (print), 1097-9867 (electronic)

Pharm Dev Technol, 2015; 20(1): 12–21
 DOI: 10.3109/10837450.2014.954728

informa healthcare

REVIEW ARTICLE

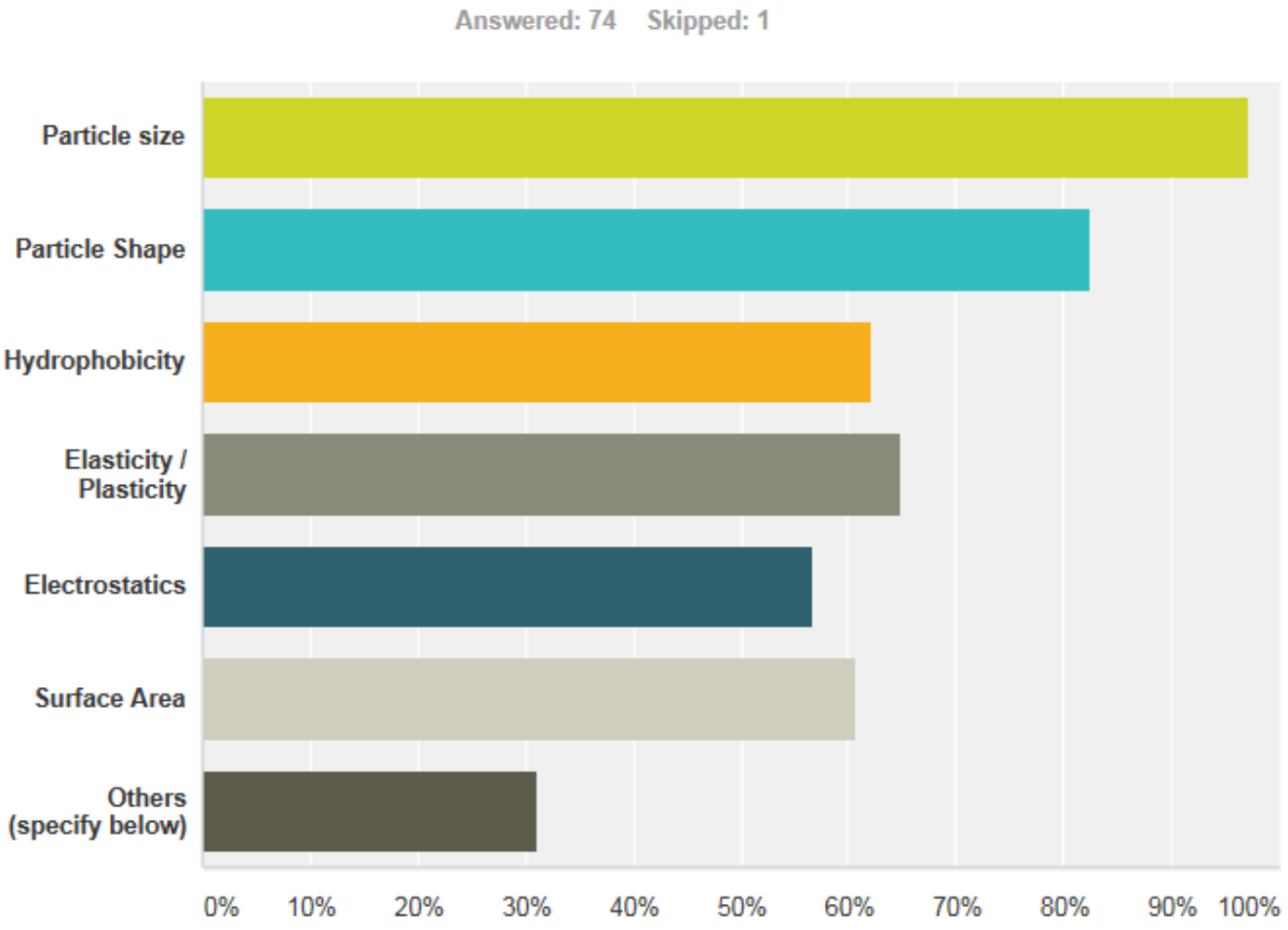
A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms

Michael Leane[1], Kendal Pitt[2], Gavin Reynolds[3], and The Manufacturing Classification System (MCS) Working Group*

[1]*Bristol-Myers Squibb, Moreton, UK,* [2]*GlaxoSmithKline, Ware, UK, and* [3]*AstraZeneca, Macclesfield, UK*

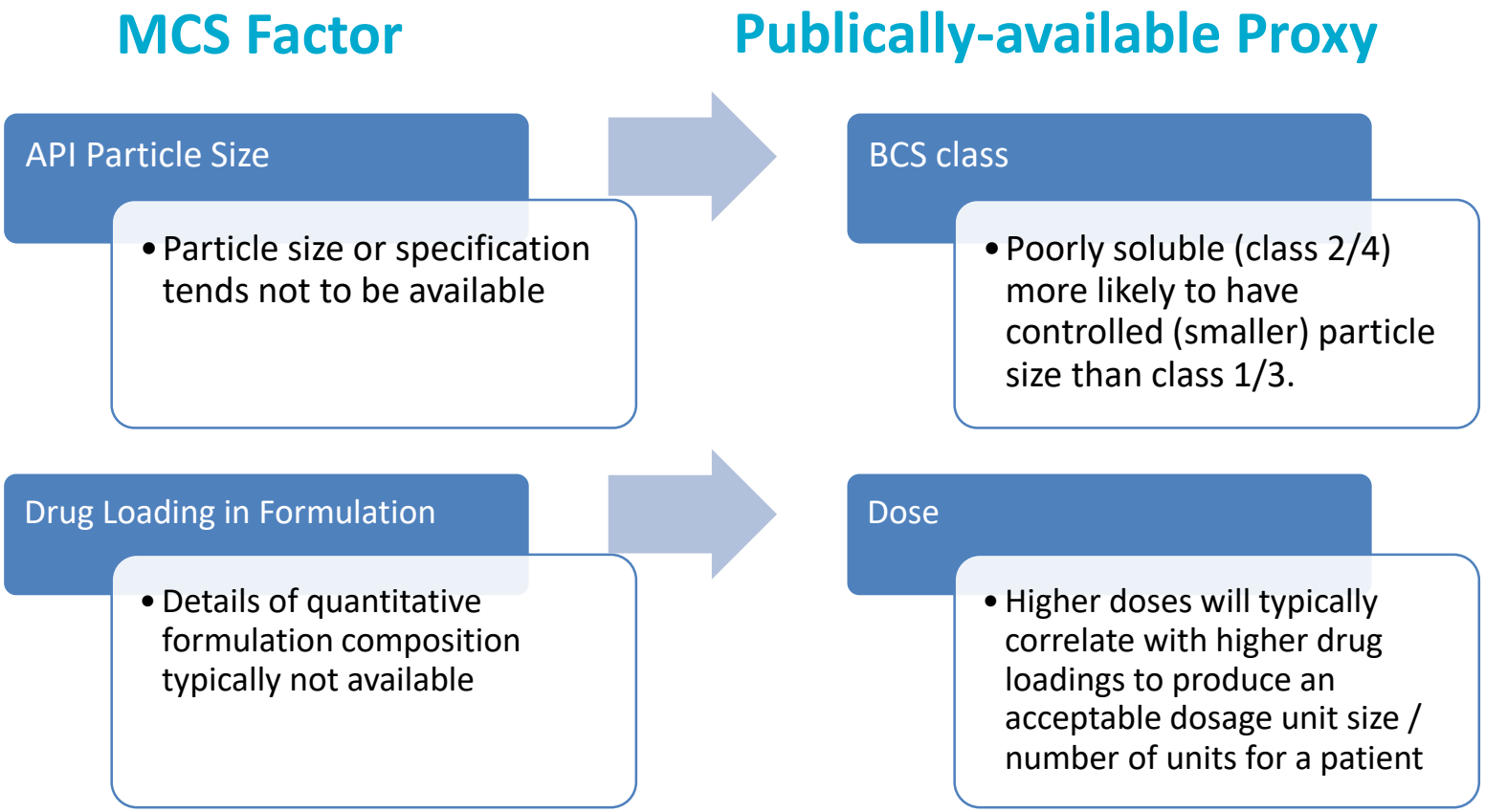
- Industry and academic collaboration
- International contributions
- Feedback questionnaire rolled out

What API properties are important when selecting or modifying materials to enable an efficient and robust pharmaceutical manufacturing process?



Data Mining

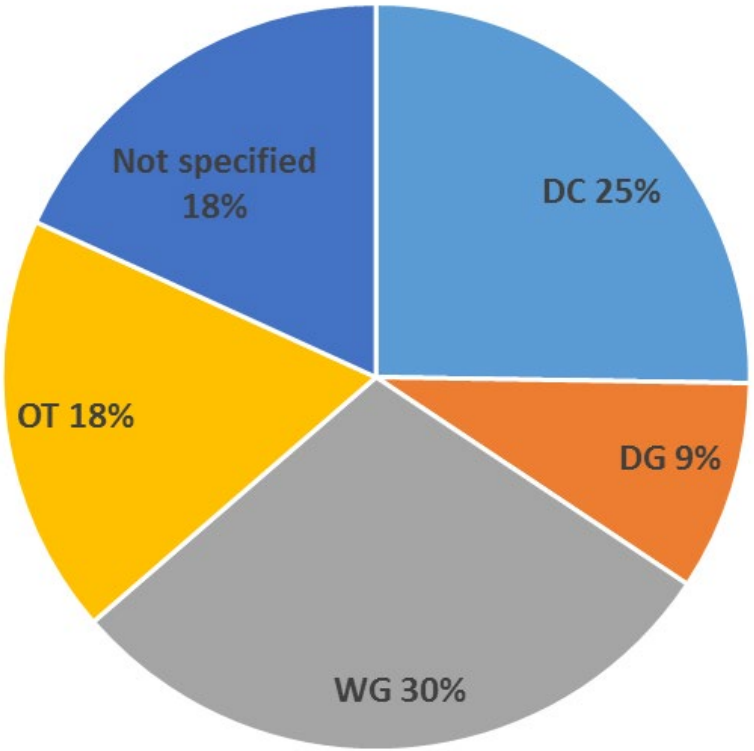
- Data generally proprietary and difficult to access in the public domain

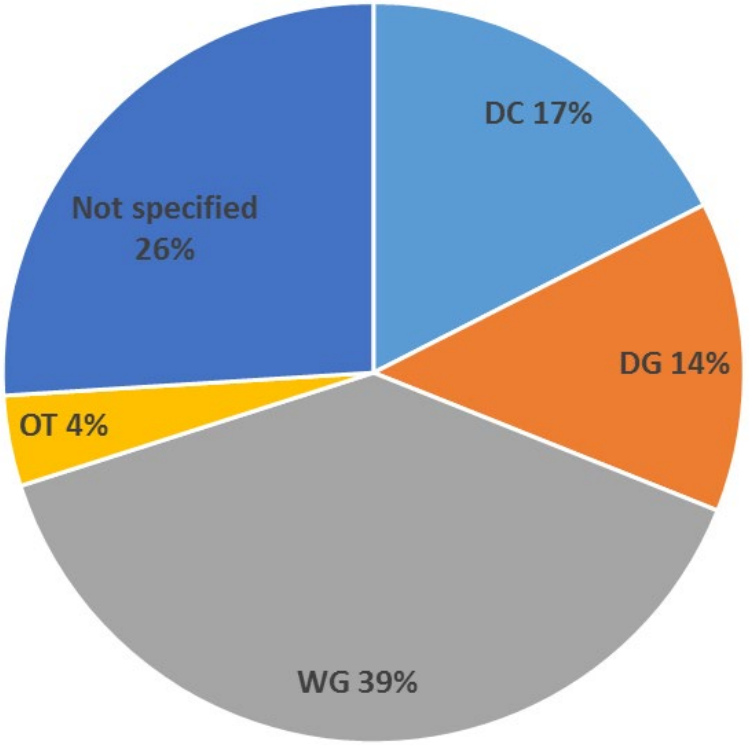


Methodology for Data Mining

- Data collated from EPAR regulatory filings
  - European public assessment reports
  - EMA (European Medicines Agency)
  - Full scientific assessment reports of authorised medicines 1996 – 2017
  - 99 Capsule formulations
  - 354 Tablet formulations
- Data
  - Therapeutic class
  - Commercial name
  - Active pharmaceutical ingredient (API)
  - Range of dose and dosage strengths
  - Dosage form description
  - Manufacturing process description
  - Company responsible for batch release and Marketing Authorisation Holder
  - Date of issue of marketing authorisation valid in European Union

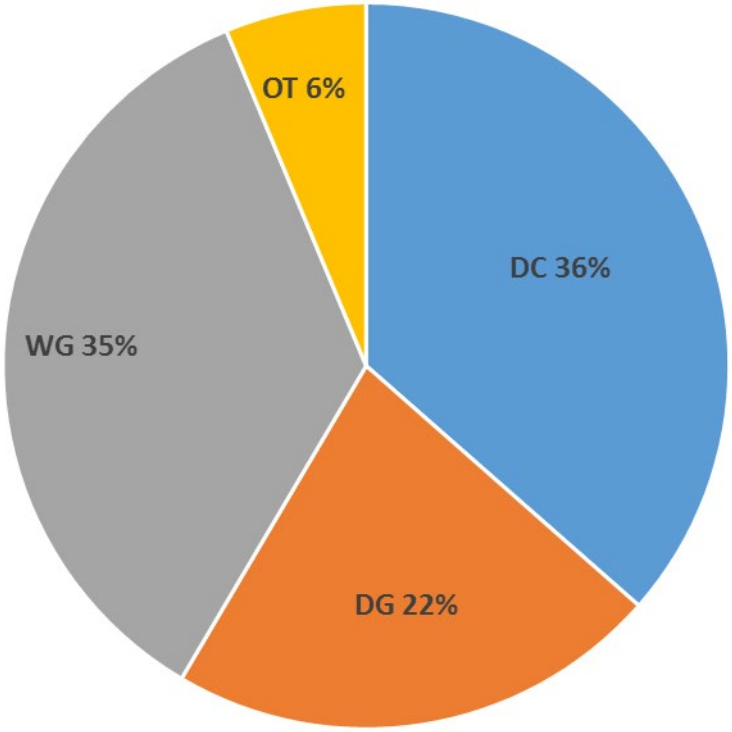
Process Choices for Tablet / Capsule Formulations



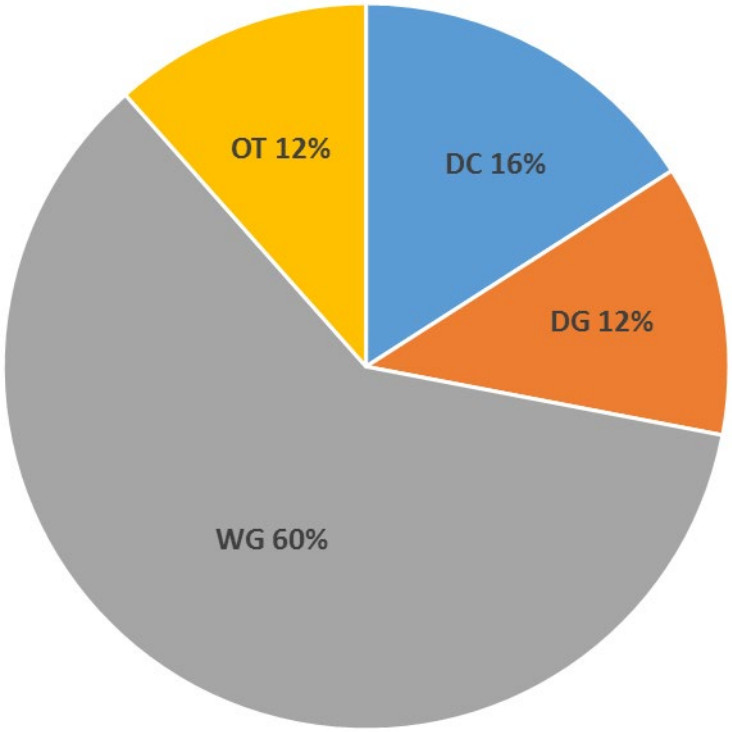


- Capsules (n=99)
  - Roughly equal split between WG and DC
  - Large number of 'OT' formulations
- Tablets (n=354)
  - WG most popular process choice
  - DC only slightly ahead of DG
  - Few 'OT' formulations

Process Choices for Tablet / Capsule Formulations



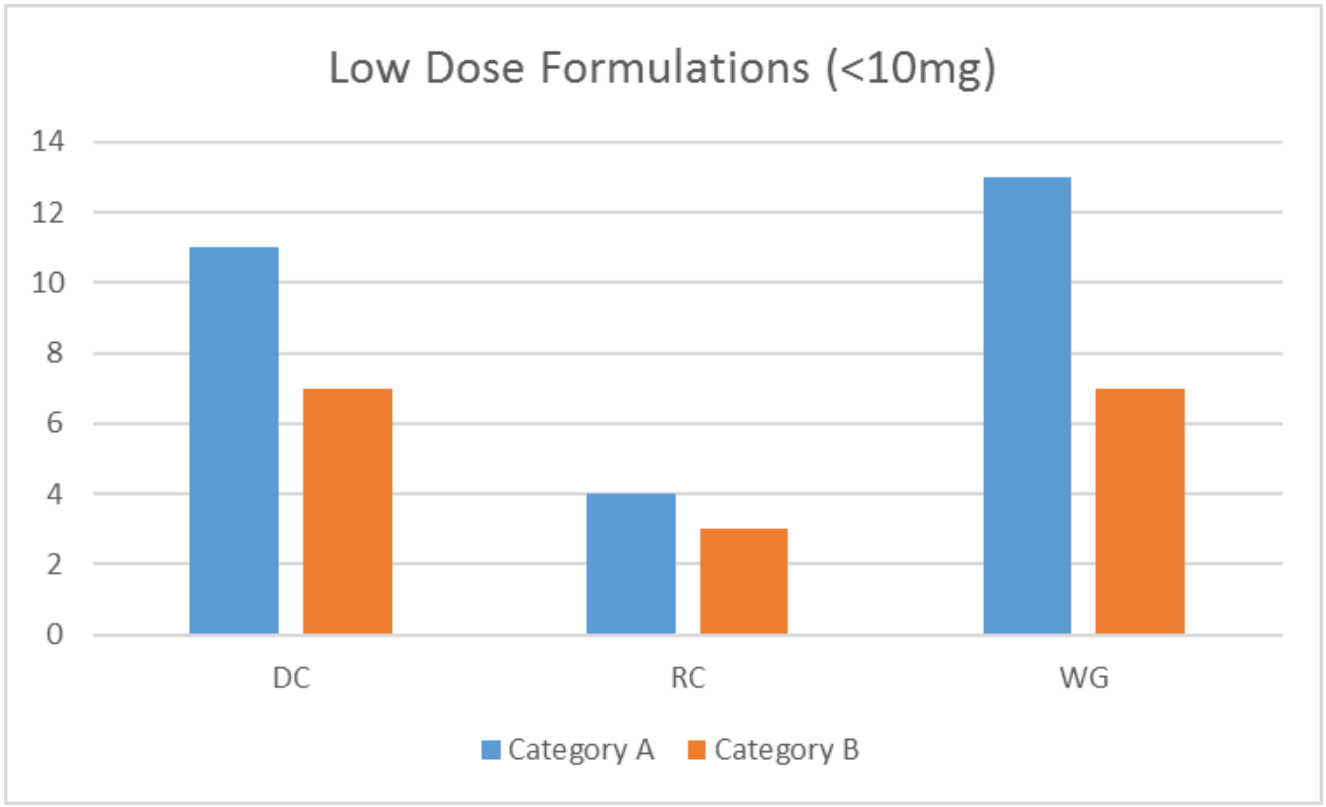
A: Soluble Category A (n=159)



Category B (n=182) **B: Poorly Soluble**

- DC/DE and DG almost 2x as likely for Category A than Category B
- WG and OT almost 2x as likely to be chosen for Category B compounds

Process Choices for Tablet / Capsule Formulations

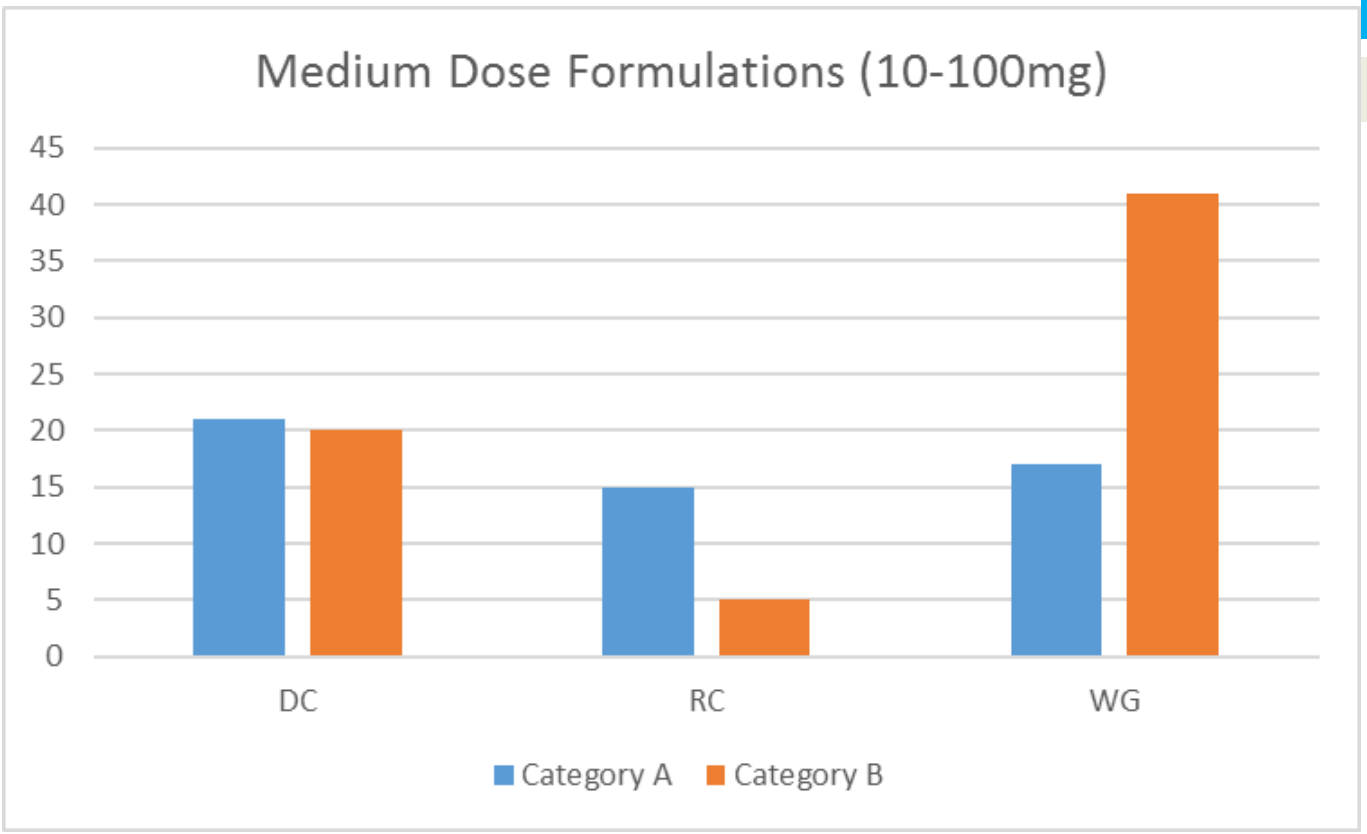


A: Soluble

B: Poorly Soluble

- Higher proportion of DC at lower doses
- RC more likely for Category A
- Category A outnumbers Category B
- WG significant across all doses

Process Choices for Tablet / Capsule Formulations

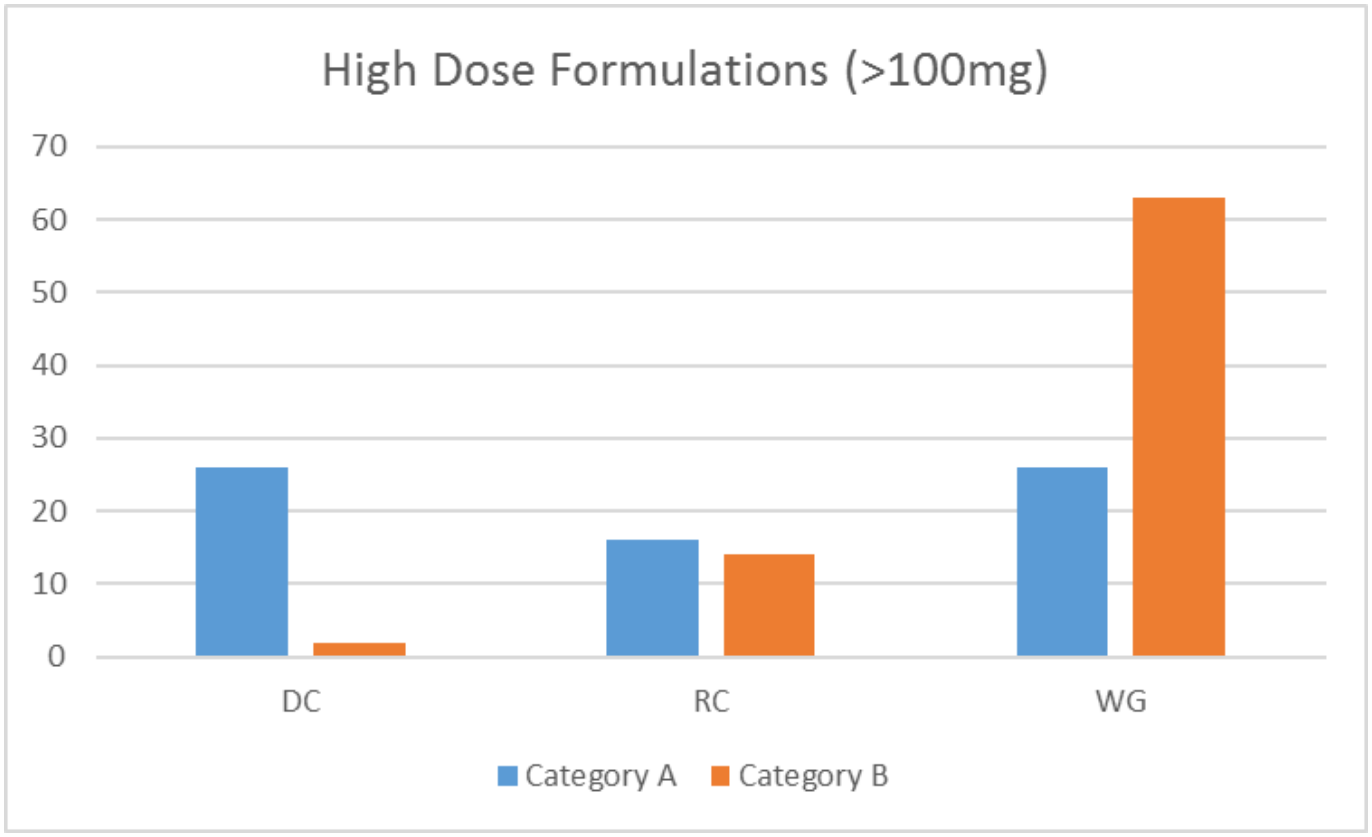


A: Soluble

B: Poorly Soluble

- Higher proportion of DC at lower doses
- RC more likely for Category A
- Category B outnumbers Category A
- WG significant across all doses

Process Choices for Tablet / Capsule Formulations

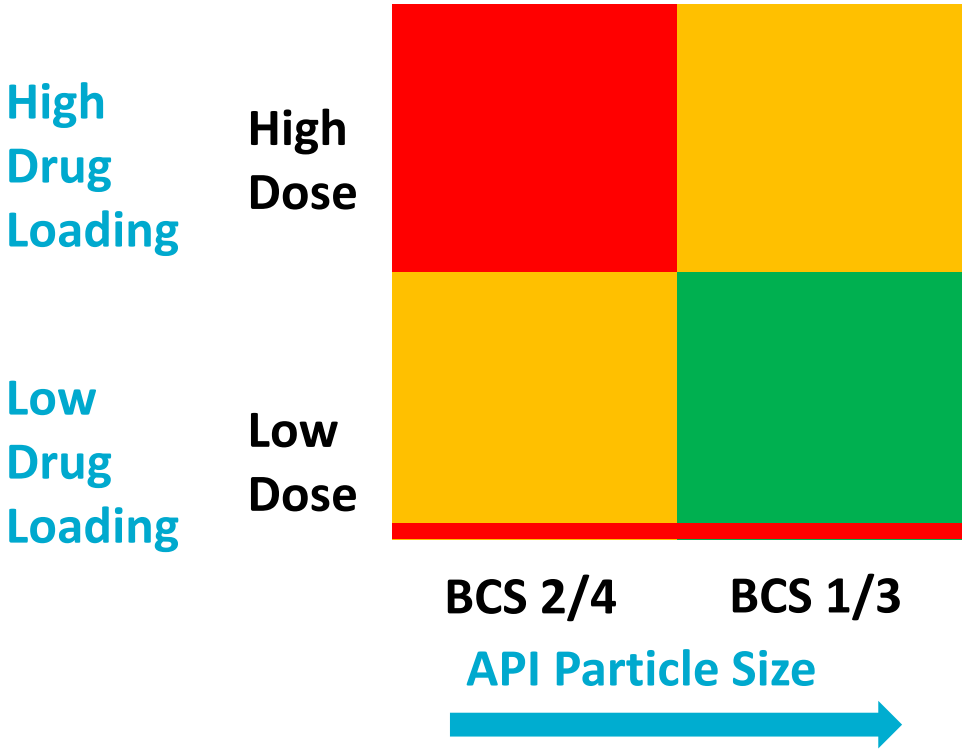


A: Soluble

B: Poorly Soluble

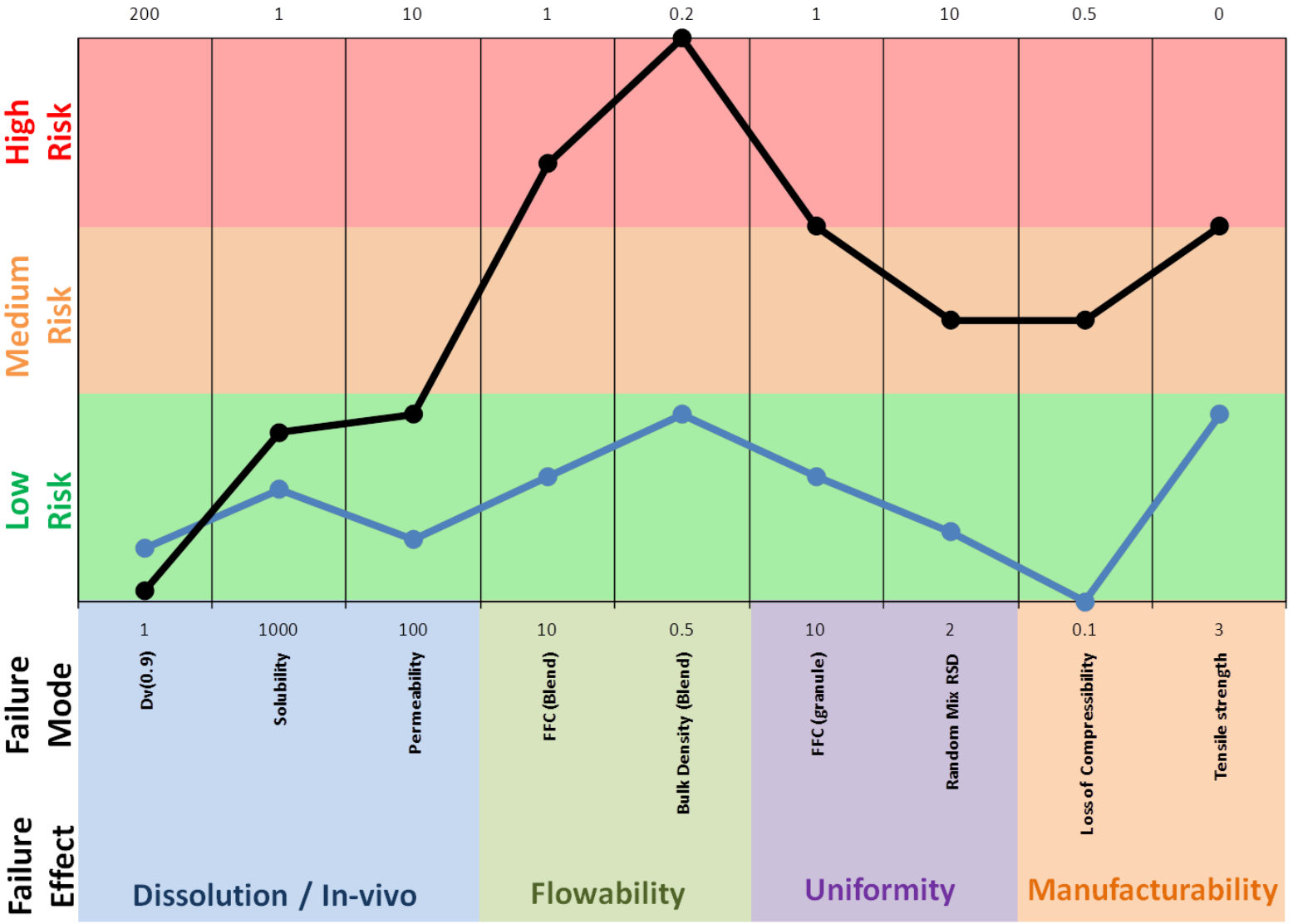
- DC preferred for Category A and WG preferred for Category B
- RC more likely for Category A
- Category B outnumbers Category A
- WG chosen in 80% cases where dose > 100mg & Category B

A ‘High level’ MCS



- Building on the concepts of drug loading and API particle size
- Supported with data analysis of ‘publically-available proxies’
- ‘High level’
  - Clearly exceptions
  - However this may provide a useful first step in assessing potential manufacturing risk

Parallel Co-ordinates Charts



Acknowledgements

PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY
https://doi.org/10.1080/10837450.2018.1534863

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REVIEW ARTICLE

Check for updates

Manufacturing classification system in the real world: factors influencing manufacturing process choices for filed commercial oral solid dosage formulations, case studies from industry and considerations for continuous processing

Michael Leane[a], Kendal Pitt[b], Gavin K. Reynolds[c], Neil Dawson[d], Iris Ziegler[e], Aniko Szepes[f], Abina M. Crean[g,h], Rafaela Dall Agnol[i] and The Manufacturing Classification System (MCS) Working Group*

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