Blending in pharmaceutical industry

Importance and challenges

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Nootdorp, 05 April 2016

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Mission Aspen Oss

Aspen Oss supplies complex Active Pharmaceutical Ingredients (APIs) of very high quality worldwide with an excellent customer service. Based on this value proposition our customers are able to build and maintain a sustainable position in the world of the pharmaceutical business.

Our high level technology is developed over many years by our highly motivated and knowledgeable staff and business partners. Teamwork is and has been a key success factor in these developments.

We act in a respectful manner towards society and environment. Safety, compliance and labor satisfaction are essential to support our business.

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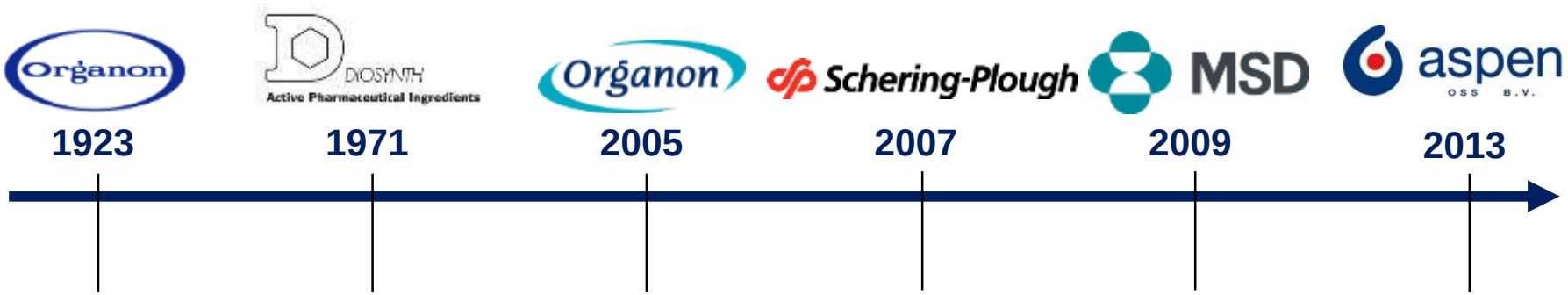
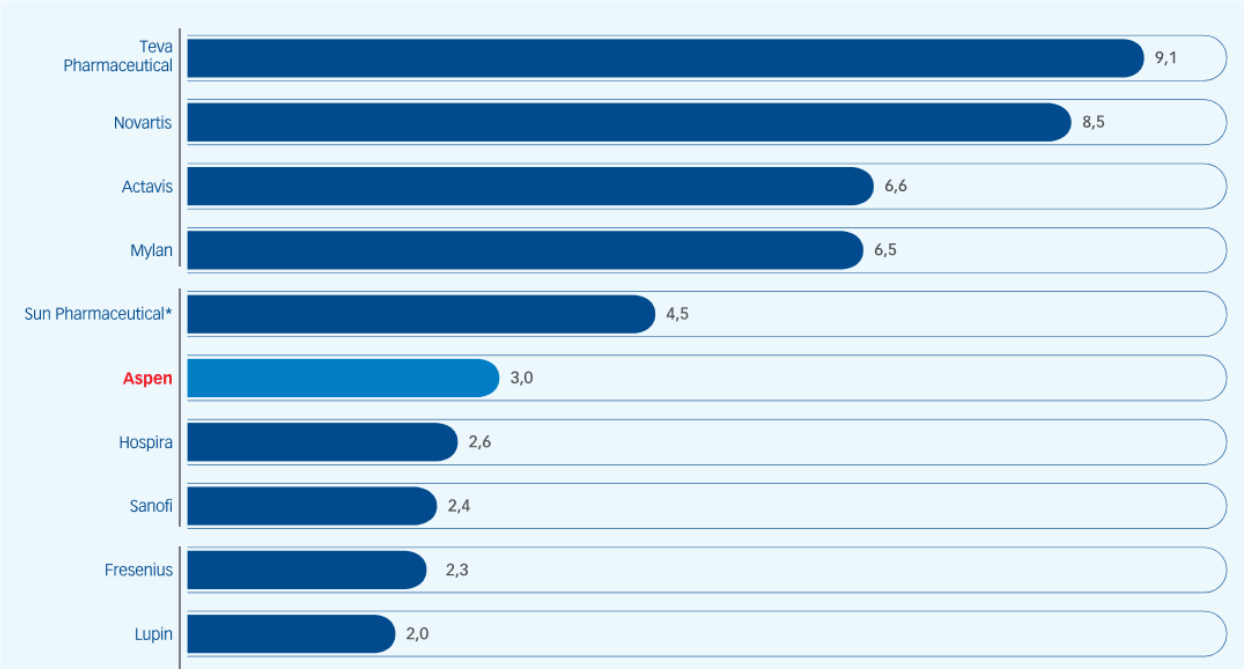
History of Aspen Oss



Aspen Pharma

Top 10 generic pharmaceutical companies based on sales

Global ranking on worldwide generic pharmaceutical sales in 2014 (Sales in USD'billion)



- Aspen stands with ~10 000 employees at the 6th place in the world of the largest generic pharmaceutical companies.
- Aspen has 26 manufacturing facilities in 18 locations on six continents. With a market value of >$ 12 billion.
- Core business: Pharmaceuticals and APIs: >150 countries.

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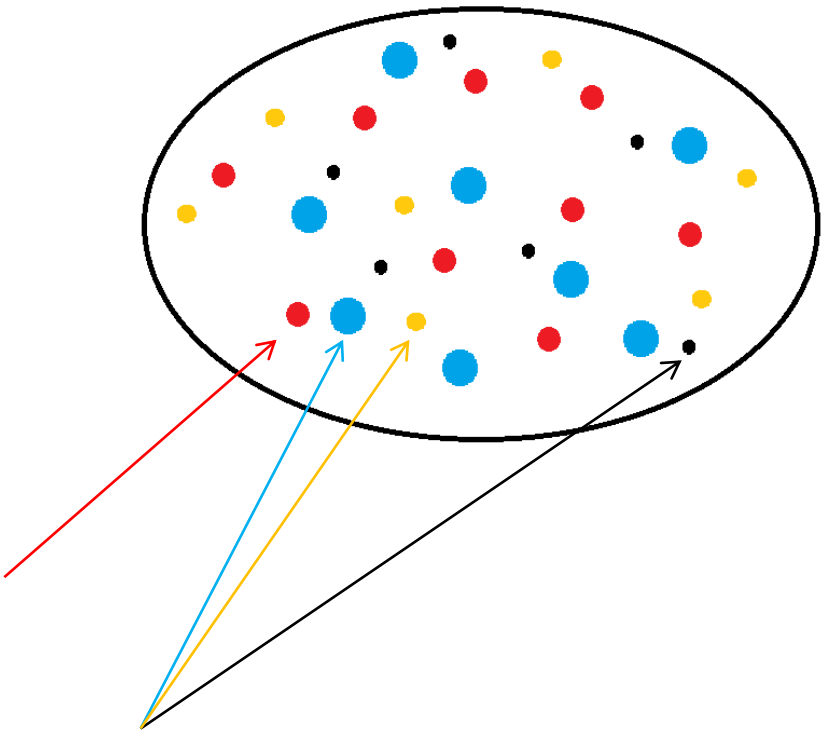
Drug product

Drug product

- Tablets
- Capsules



Drug product = API + Excipients

API = Active Pharmaceutical Ingredient
Ingredient that is biologically active

Excipients = inactive ingredients in drug product

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Drug product (tablet)

Excipients = inactive ingredients in drug product

- **Transport** the active drug to the site in the body where the drug is intended to exert its action, in the right concentration, and at the right rate
- Improve **processability** and **handling**
- Help the drug to **disintegrate** into particles small enough to reach the blood stream more quickly
- Protect the product's **stability** so it will be at maximum effectiveness at time of use
- Make the product **taste** and **look** better

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Drug product

Ingredient	Function	Amount (mg)
Paracetamol	API	**500.0**
Starch, pregelatinized	Diluent (filler), disintegrant, binder	**75.0**
Calcium carbonate	Diluent (filler)	**66.0**
Povidone	Disintegrant, binder	**2.5**
Crospovidone	Disintegrant	**5.9**
Potassium sorbate	Antimicrobial preservative	**0.6**
Granulation from above		**650.0**
Alginic acid	Binder, disintegrant	**15.0**
Colloidal silicon dioxide	Glidant	**0.4**
Magnesium stearate	Lubricant	**0.8**
Total		**666**

Ingredient	Function	Amount (mg)
DRSP (Drospirenone)	API	**3**
EE (Ethinyl estradiol)	API	**0.03**
Lactose monohydrate	Diluent (filler)	
Corn starch	Diluent (filler), disintegrant, binder	
Pregelatinized starch	Diluent (filler), disintegrant, binder	
Povidone	Disintegrant, binder	
Magnesium stearate	Lubricant	
Total		**100-200**

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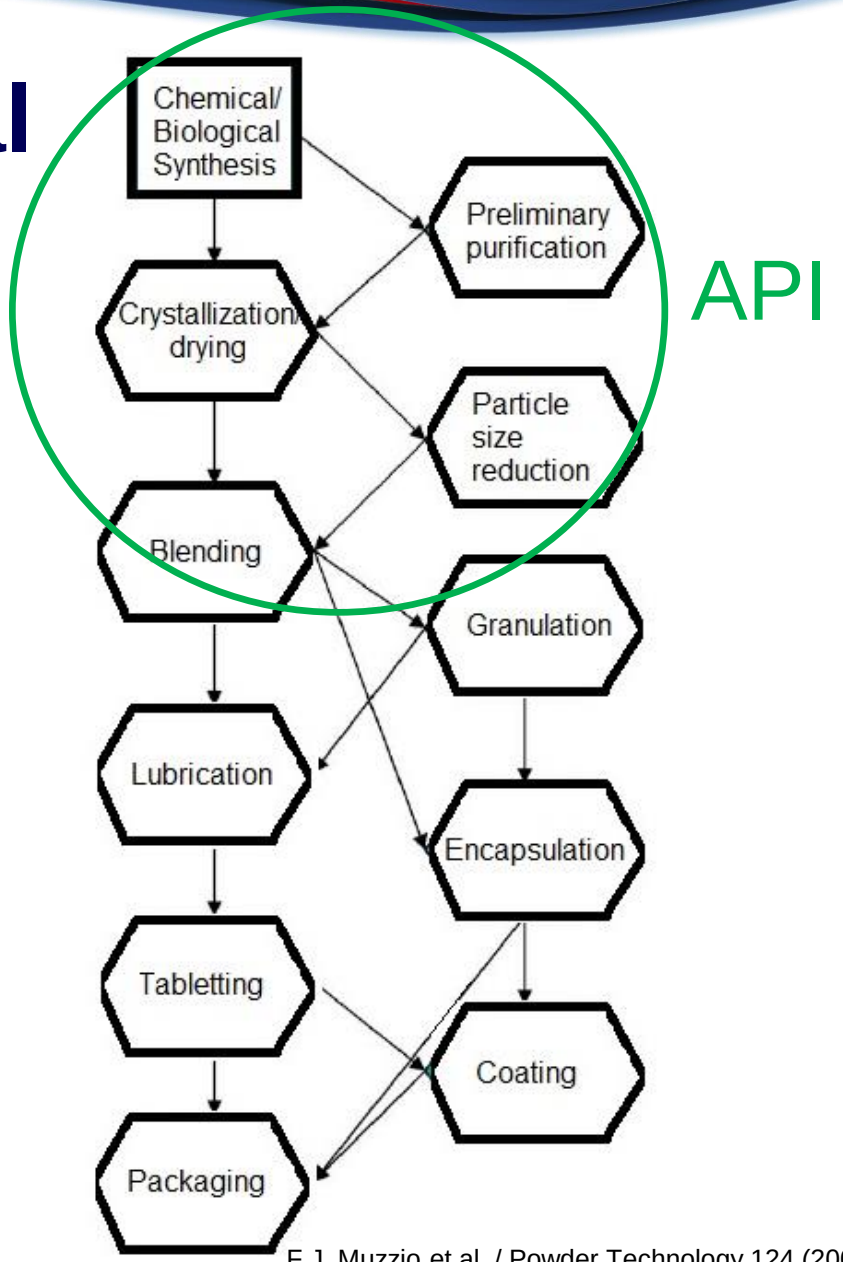
Round tablets of 120 – 700 mg are easy to handle and produce

How pharmaceutical products are made

Typical flowsheet for tablet and capsule manufacturing, which comprise more than 80% of domestic pharmaceutical products.



F.J. Muzzio et al. / Powder Technology 124 (2002) 1–7

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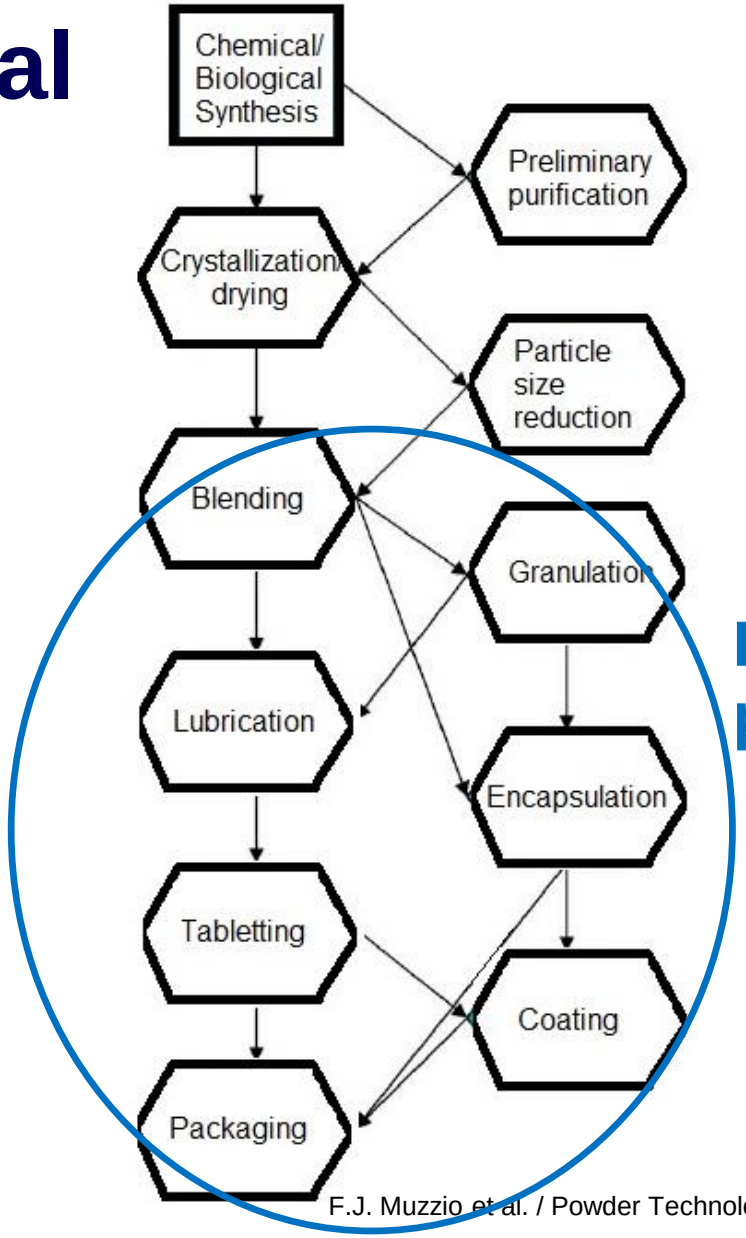

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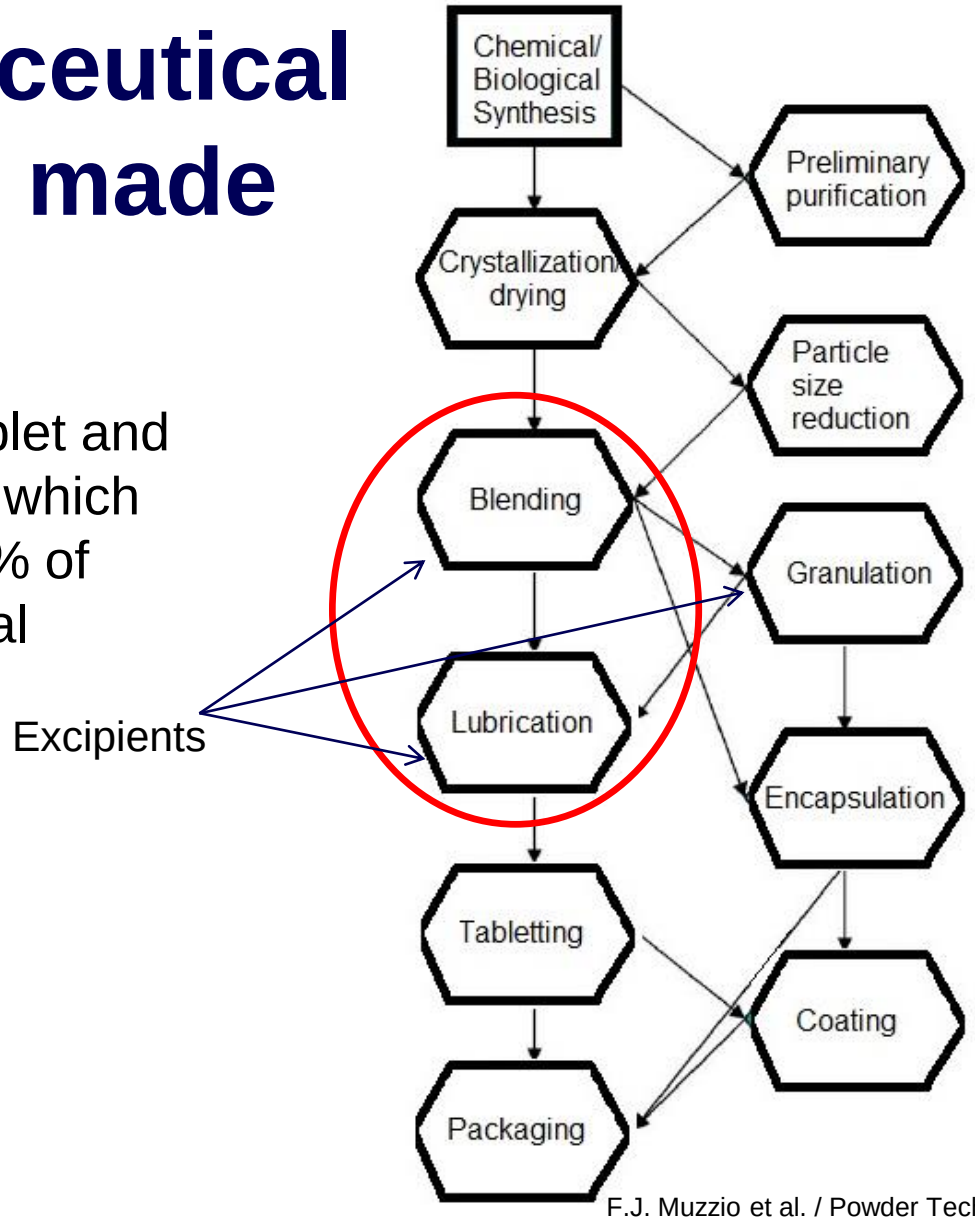

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API

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Homogeneity of API

Last steps of API production process

Final precipitation/crystallization

→ filtration

→ drying

→ particle size reduction

→ homogenization by dry mixing

→ drum filling

One substance, same particle size distribution in each drum!

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Main challenges/issues

- Fine particle size of API (d50 <20 µm) to improve bioavailability
- Poor flowability
- Segregation when particle size distribution is very wide/bimodal
- Difficulty to characterize the quality of mixing using an efficient, precise and non-destructive procedure

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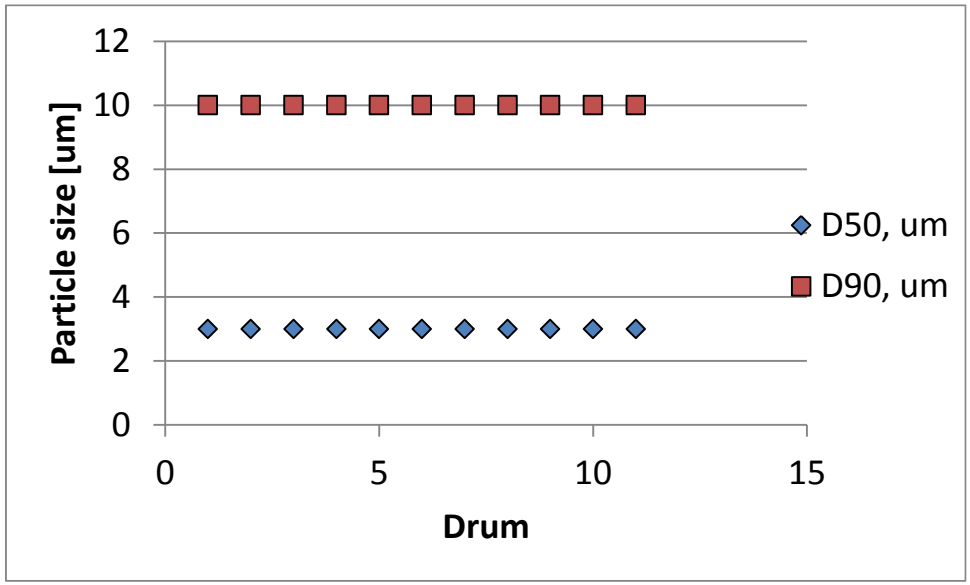
Particle size distribution per drum without homogenization



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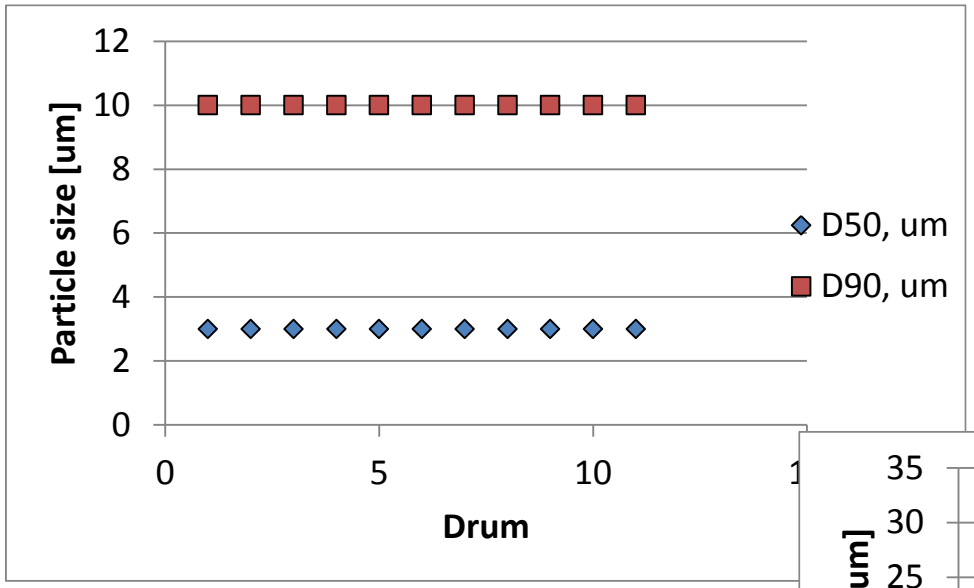
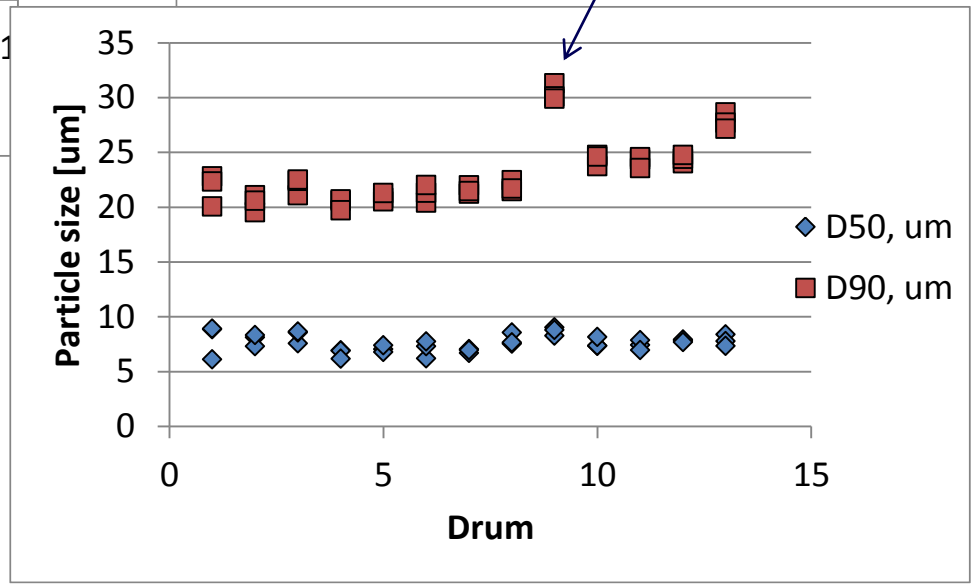
Particle size distribution per drum without homogenization



Production issue during drum 9



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Drug product

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Content uniformity

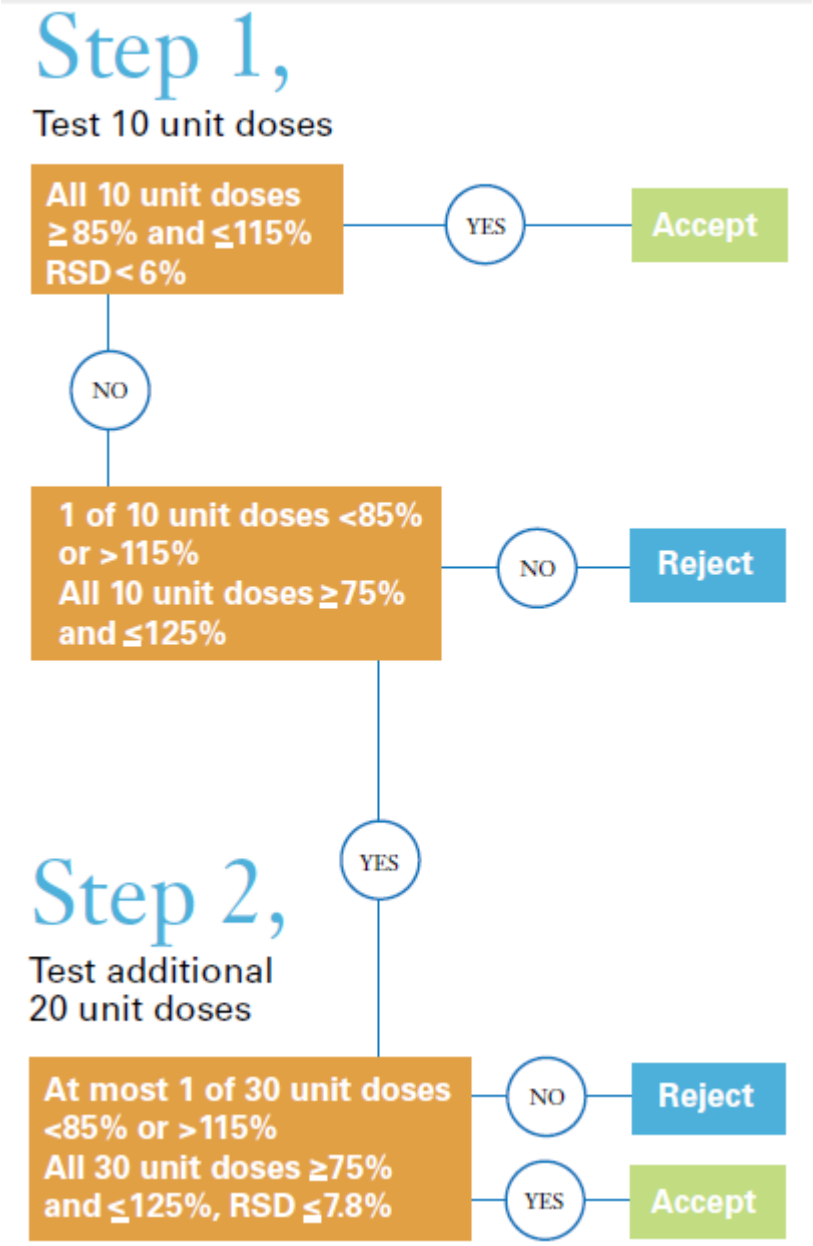
Is this pill OK?

Does every tablet contain the appropriate amount of API?

USP test <905> for content uniformity

=>

ensure that the amount of drug substance in each individual tablet is the same



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Content uniformity challenge

10 million tablets of 100 mg

1 mg API / tablet

1000 kg drug product powder of which

10 kg API

10 million tablets of 100 mg

1 µg API / tablet

1000 kg drug product powder of which

10 g API

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Content uniformity – typical dose

Birth control pills - dose of API per tablet:

- **15 µg** ethinyl estradiol + **60 µg** gestodene
- **20 µg** ethinyl estradiol + **150 µg** desogestrel
- **20 µg** ethinyl estradiol + **3000 µg** drospirenone:
- **50 µg** ethinyl estradiol + **1000 µg** norethindrone
- **1.5 mg** estradiol + **2.5 mg** nomegestrol acetate

Paracetamol 500 mg per tablet

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Particle size – 1 µg API per tablet

1 million API particles for 1 million tablets

=> 1 API particle per tablet with mean particle size of **114 µm**

10 million API particles for 1 million tablets

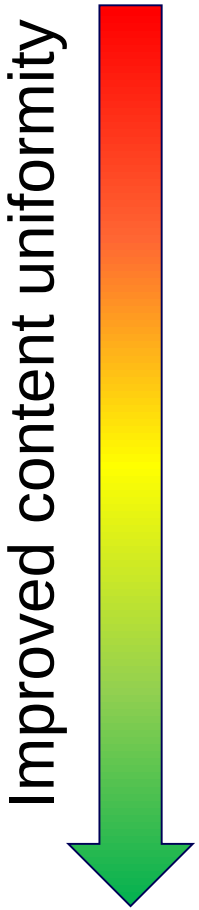
=> 10 API particle per tablet with mean particle size of **53 µm**

100 million API particles for 1 million tablets

=> 100 API particle per tablet with mean particle size of **11 µm**

1000 million API particles for 1 million tablets

=> 1000 API particles per tablet with mean particle size of **1 µm**



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Dose versus number of particles in a tablet

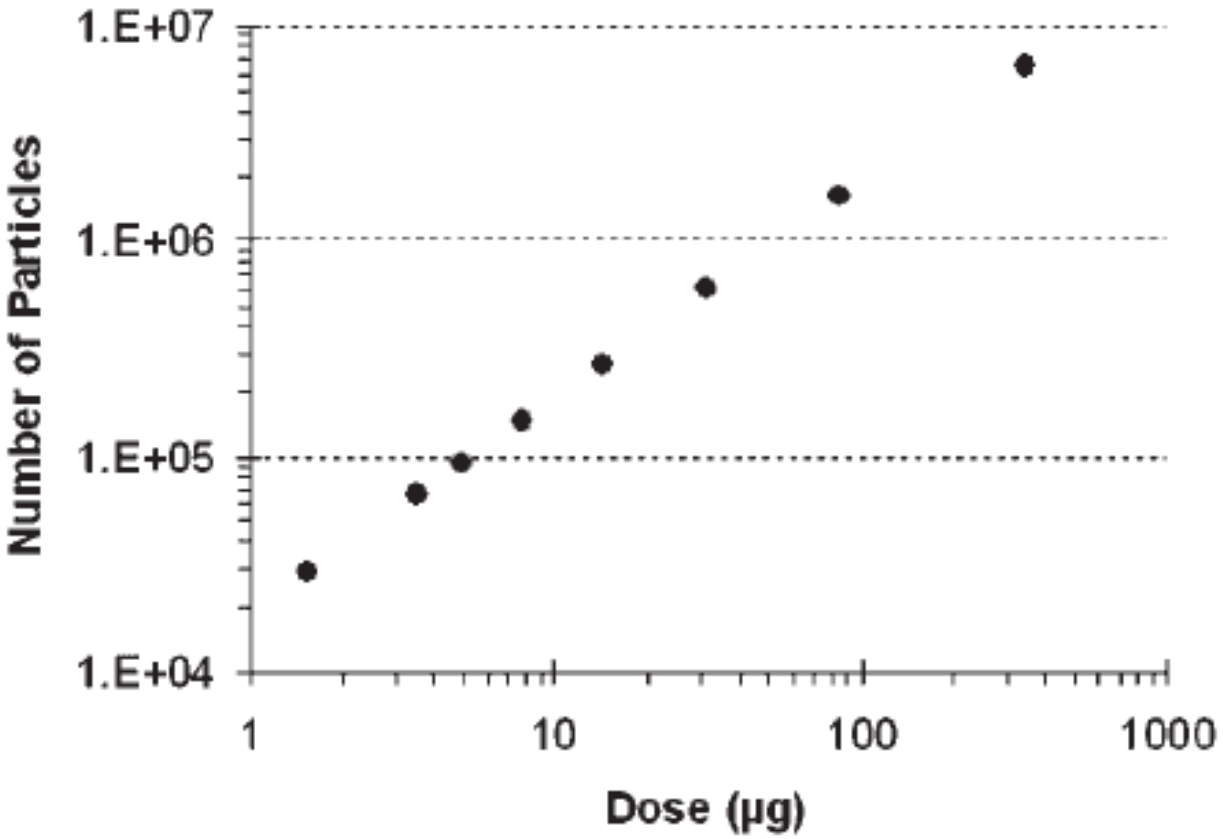

Figure 5. Estimated number of particles in a single tablet versus dose.

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Content uniformity

Maximum mean particle diameter and coefficient of variation which assures 99% probability to pass content uniformity test

Particle diameter coefficient of variation, C (%)	Dose					
	0.1 μg	1 μg	10μg	100 μg	1 mg	10 mg
	Maximum mean diameter (μm)					
0	8.36	18.0	38.8	83.6	180.0	388.0
20	7.15	15.4	33.2	71.5	154.0	332.0
40	4.62	9.95	21.4	46.2	99.5	214.0
60	2.44	5.27	11.3	24.4	52.7	113.0
80	1.16	2.49	5.37	11.6	24.9	53.7
100	0.523	1.13	2.43	5.23	11.3	24.3
120	0.236	0.508	1.10	2.36	5.08	11.0
140	0.109	0.235	0.506	1.09	2.35	5.06
160	0.0521	0.112	0.242	0.521	1.12	2.42
180	0.0259	0.0558	0.120	0.259	0.558	1.20
200	0.0134	0.0288	0.0621	0.134	0.288	0.621

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Yalkowsky, 1990, Pharm. Res., 7(9), 962-966

Main challenges/issues for blend and content uniformity

- Fine particle size of API (d50 <20 µm) to improve bioavailability
- Poor flowability
- How to mix tiny proportions of predominantly minute particles within a matrix of much larger ingredients?
- Multiple ingredients of various particle sizes beyond the active pharmaceutical ingredients
- Particle shape, density, and cohesiveness vary
- Ingredients from different vendors may behave differently due to their particle size and shape and other factors, and their tendency to form aggregates.
- Segregation during tabletting, drum filling, transport, …
- Difficulty to characterize the quality of mixing as it is difficult to accurately measure the mixture composition using an efficient, precise and non-destructive procedure

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Root causes of blend or product content uniformity problems

1) Non-optimum blending
2) Sampling error
3) Segregation
4) Loss of component
5) Analytical error

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Some solutions to content uniformity issues

- Correct choice of API particle size to promote blend uniformity
- Correct choice of excipients to promote blend uniformity
- Active pre-blend (“ordered mixture”)
  - first blend the active with a portion of a suitable “carrier” excipient
  - progressively blend with increasing amounts of the remaining components
- Issues with segregation can be reduced by matching the particle size and density of the active drug substance with excipients

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Correct choice of API particle size to promote blend uniformity

Experimental and simulated percent of intended potency profiles of drug-excipient blends made with either the smaller particle size drug and the larger particle size drug. Geometric means of 6.1 and 18.5 µm. The intended potency was 10µg.

	Number of unit doses within the given percent of intended range			
percent of intended range	Smaller 6.1 µm	simulated	Larger 18.5 µm	simulated
86-90			1	
90-94			5	
94-98	5		13	483,249
98-102	59	1,000,000	20	313,436
102-106			16	145,337
106-110			7	45,337
110-114			1	9,744

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Correct choice of API particle size to promote blend uniformity

$$d_{97.7} = d_{50} \cdot \left(e^{\sqrt{\frac{\ln\left[\frac{\left(\frac{d_{50}}{1000}\right)^3}{\left(\frac{6.D}{\pi.\rho}\right)\left(\frac{C_v}{100}\right)^2}\right]}{-4.5}}} \right)^2$$

d_i	Particle diameter of the API (µm)
D	dose (mg)
C_v	coefficient of variation of the dose
ρ	Density of the drug (g/cm^3)

Rohrs, B.R., G.E. Amidon, , R.h. Meury, , P.J. Secreast, H.M. King and C.J. Skoug (2006), J. Pharm. Sci., **95**, 1049-1059.

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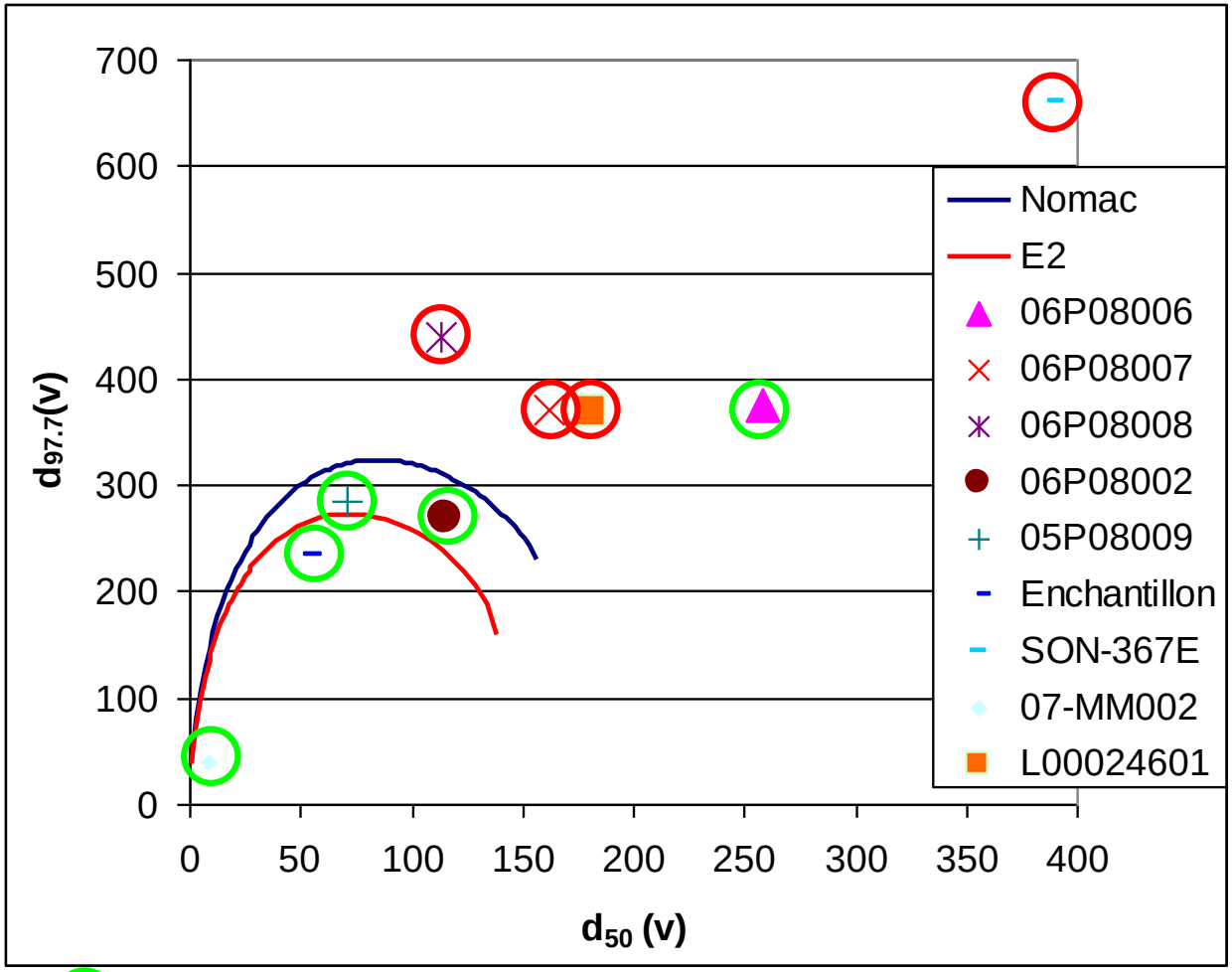
Effect of particle size on content uniformity



Batches with a low variability (actual data)

Batches with a high variability (actual data)

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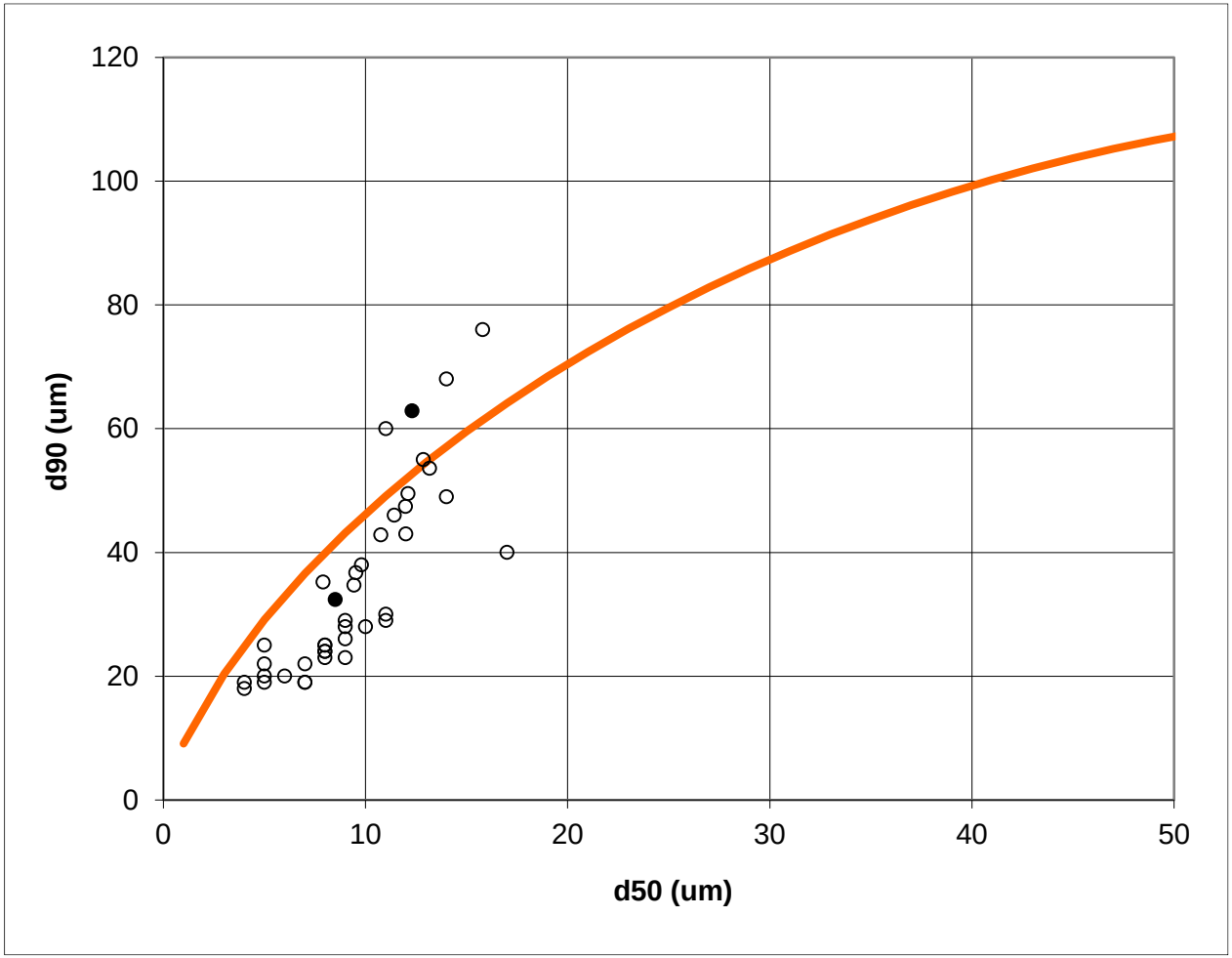
Effect of particle size on content uniformity

99% probability for passing content uniformity criteria

$\rho_g = (d_{90}/d_{50})^{0.78}$



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Blending in pharmaceutical industry – Importance and challenges

- **Every tablet must contain the appropriate amount of API**

- Fine particle size of API (d50 <20 µm) to improve bioavailability
- Choice of excipients to improve blending and drug product performance
- Segregation of powder during processing (tabletting) & transport

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Thank you!

Acknowledgements

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