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Nanocrystallization - Case Study: Nanosizing by Wet Ball-Milling Technique

Dr. Leena Peltonen
Division of Pharmaceutical Technology
University of Helsinki
Finland


Contents of the presentation

- Backgrounds: reasoning behind the nanosizing
- Different techniques and products
- Case study
 - Nanosizing of indomethacin and ibuprofen by wet ball-milling technique
- Concluding remarks

Poor solubility

- About 40% of drugs in the pipeline and 60% of drugs coming directly from synthesis or high throughput screening are classified as poorly soluble, meaning that they have bioavailability and/or delivery problems
- Nanosizing is one way to avoid problems caused by poor solubility

Noyes-Whitney equation



$$\frac{dm}{dt} = \frac{DA}{h}(C_s - C)$$

dm/dt = Mass transfer per time/dissolution rate

D = Diffusion coefficient

A = Surface area

h = Thickness of the diffusion layer

C_s = Saturation concentration

C = Concentration of the solution

Improved solubility with the aid of nanotechnology

Decreased particle size means increased surface area => increased dissolution rate

Below a size of approximately few micrometers, the saturation solubility is a function of the particle size

$$\frac{dm}{dt} = \frac{DA}{h} (C_s - C)$$

Particle size versus solubility

1 nm – 100 nm **Fundamental material properties remain** the same but size, shape and surface area alter some certain properties, like solubility, chemical potential and surface energy.

One very interesting example for size dependency of material properties is solubility: chemists have known for decades that very small crystals (in the nano size range) are more soluble than macroscopic crystals of the same material.

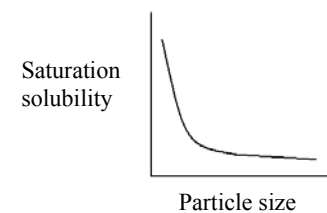
This solubility dependence on crystal size is described by a modified version of the Kelvin equation

Modified Kelvin equation

$$\frac{S}{S_0} = \exp\left(\frac{\gamma V}{RTd}\right)$$

S	solubility
S_0	solubility of the bulk material
γ	surface free energy
V	molar volume
R	gas constant
T	temperature
d	particle size

Solubility as a function of particle size



The exponential increase in solubility starts only somewhere below the 100 nm

Effect of particle size on saturation concentration

Normal drug powder
20-50 μm



Micronized
2-5 μm



Nanonized



$\frac{dm}{dt} \ll \frac{dm}{dt} \ll \frac{dm}{dt}$
 $c_s \sim c_s \ll c_s$

Improved solubility with the aid of nanotechnology

Increase in saturation solubility has two effects:

- Based on the Noyes–Whitney equation an increase in saturation solubility leads to an **increase in dissolution velocity**
- An increased saturation solubility in the lumen of the gut increases the concentration gradient between lumen and the blood, thus **accelerating drug-diffusion, promoting absorption**

Nanocrystallization

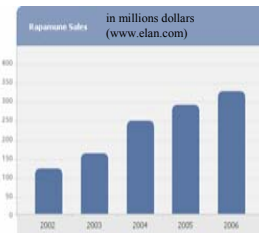
Formulation approach for poorly soluble material

- Drugs
- Cosmetics

Invented at the beginning of the 1990s

In 2000, Elan Pharmaceuticals received FDA approval for its NanoCrystal® technology, by reformulating Rapamune®, a Wyeth drug (sirolimus)

NanoCrystal® Technology involves reducing crystalline drug to particles, the size of which is under 400 nm.



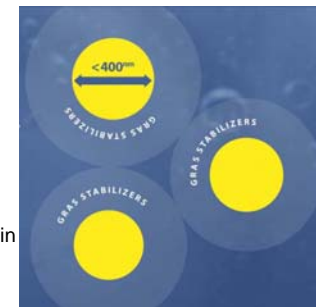
Nanocrystallization

Case Rapamune®, benefits of NanoCrystal® technique:

Improved dissolution and oral bioavailability

Enabled preparation of a tablet (has earlier been available as a once per day in oral liquid form)

Eliminated complicated reconstitution and storage procedure associated with original form => improved patient compliance



Drug core is stabilized by surrounding polymeric or surface active covering



Nanocrystal formulations

Drug	Indication	Drug delivery company	Pharma company	Route	Status
Paclitaxel	Anticancer	American BioScience	American Pharmaceutical Partners	Intravenous	Phase III
Undisclosed multiple	Anti-infective	Baxter NANOEDGE	Undisclosed	Oral Intravenous	Preclinical to Phase II
Undisclosed	Anticancer	Baxter NANOEDGE	Undisclosed	Intravenous Oral	Preclinical to Phase I
Rapamune	Immuno-suppressant	Elan Nanosystems	Wyeth	Oral	Marketed
Emend	Anti-emetic	Elan Nanosystems	Merk	Oral	Marketed
Cytokine inhibitor	Crohn's disease	Elan Nanosystems	Cytokine PharmaSciences	Oral	Phase II
Diagnostic agent	Imaging agent	Elan Nanosystems	Photogen	Intravenous	Phase III
Thymoctacin	Anticancer	Elan Nanosystems	NEwBiotics/flex Oncology	Intravenous	Phase III
Fenofibrate	Lipid lowering	SkyePharma	Undisclosed	Oral	Phase I
Busulfan	Anticancer	SkyePharma	Supergen	Intrathecal	Phase I
Budesonide	Asthma	Elan Nanosystems	Sheffield Pharmaceuticals	Pulmonary	Phase I
Silver	Eczema atopic dermatitis	NUCRYST	Self-developed	Topical	Phase I
Calcium phosphate	Mucosal vaccine adjuvant for herpes	BioSante	Self-developed	Oral	Phase I
Insulin	Diabetes	BioSante	Self-developed	Oral	Phase I

Tricor (fenofibrate)/ Elan Drug Delivery, MegaceES (megesterol acetate)/ Elan Drug Delivery
Both tablets and also suspension forms formulated



Two possible approaches for nanocrystallization

- **Top-down:** production of nanoscale structures by taking a bulk material and forming it into a desired structure e.g. by machining and etching
- **Bottom-up:** building organic and inorganic structures atom-by-atom or molecule-by-molecule; difficult to control

However, so far, all the marketed products are produced by top-down techniques



Nanocrystallization techniques

There are three basic technologies currently in use:

Pearl milling (NanoCrystal® – Élan)

Homogenisation in water (Dissocubes - SkyePharma; Nanoedge - Baxter)

Homogenization in nonaqueous media or in water with water miscible liquids (Nanopure – PharmaSol Berlin)

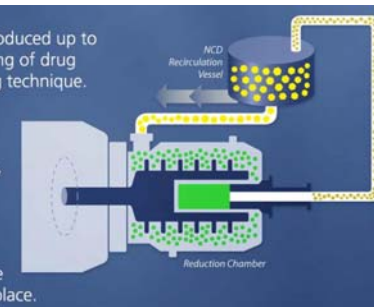


NanoCrystal® technique

NanoCrystal® particles are produced up to commercial scale by the milling of drug substance using a wet milling technique.

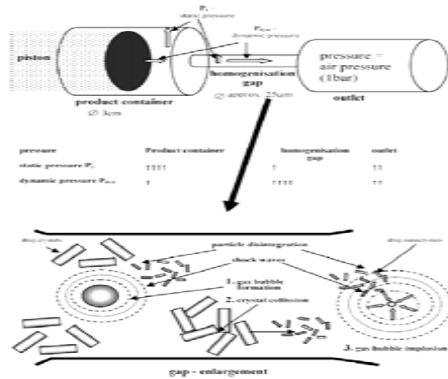
Insoluble drug particles are placed in the mill with purified water and stabilizers, forming a slurry.

This slurry is passed through the recirculation pump into the reduction chamber where particle size reduction takes place.



www.elan.com

Nanocrystallization by high pressure homogenization



J. Biotech. 113, 2004, 151

Nanocrystallization techniques

Ball milling and homogenization in water lead to aqueous nanosuspensions; the water needs to be removed to formulate tablets and capsules, e.g. by using the aqueous nanosuspension as granulation fluid in the tablet production process or by drying.

By nanopure technology it is possible to produce drug nanocrystals dispersed in liquid PEG or in oils.

Nanocrystallization in formulations

- Against solubility problems; it has been claimed that most of the solubility problems of poorly soluble drug substances may be avoided with the aid of nanotechnology
- Minimum size appr. 40 nm for efficient dissolution
- Tablets containing upto 30 % of nanocrystals has been formulated; with higher concentrations the nanocrystals tend to aggregate

Improved solubility with the aid of nanotechnology

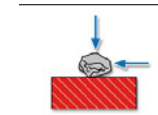
- Especially beneficial for poorly soluble drug materials
- Often even very small changes in particle size can be enough for improved dissolution
- Most simple to achieve by using so called Top-down-techniques:
 - production of nanoscale structures by taking a bulk material and forming it into a desired structure e.g. by machining and etching



Nanocrystallization by wet ball-milling: Case studies ibuprofen and indomethacin



Wet ball-milling



Drug suspension
(solid drug,
surfactant, water)
and balls in the
milling bowl



Nanocrystallization process

- Planetary ball mill
- Aqueous Tween 80 as a media
- Batch size: 4 g pure drug material
- Ibuprofen and indomethacin as a model drug substances
- Milling and pausing cycles were repeated
- Total process time appr. 30-40 min, also longer process times were tested



Characterization methods

- **Size** measurements
 - Photon correlation spectroscopy (nanosized particles)
 - Optical microscopy (micron sized particles)
 - Before particle size analysis by PCS, particle suspensions were filtered
- **Physicochemical** characterization
 - X-ray powder diffractometry
 - DSC (differential scanning calorimetry)

Characterization

- **Solubility** testing
 - Aqueous phosphate buffer solution (pH 7.0 for ibuprofen and pH 7.2 for indomethacin)
 - Shake flask -method
- **Dissolution** testing
 - Dried nanocrystals were packed into gelatin capsules
 - USP paddle method, same media as in solubility testing

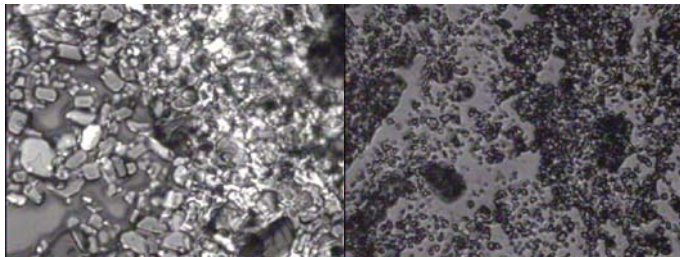
In all the solubility and dissolution testing the relative amount of Tween was kept constant in order to eliminate the effect of surfactant



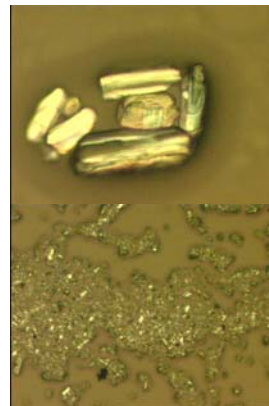
Results

Indomethacin

- Optical microscope images from raw (left) and milled (right) indomethacin (magnification 50x)



Ibuprofen



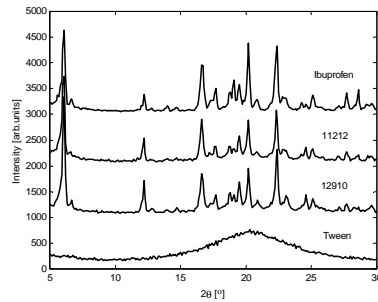
Optical microscopy pictures of raw material and wet milled ibuprofen (magnification 20x). Milling has been performed in aqueous Tween 80 solution.



	Milling media 0.5 % Tween 80		Milling media 1 % Tween 80	
	Raw material	Milled	Raw material	Milled
Solubility/ mg/ml	3.7	7.3	3.8	11.1
Mean particle size (smallest fraction)/nm		77.2		20.0



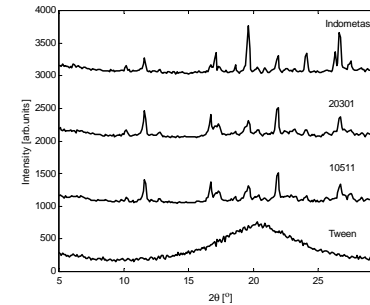
Physicochemical characterization of nanocrystals



XRPD diffraction patterns of ibuprofen (top), ibuprofen nanocrystals (two in the middle) and Tween 80 (down)



Physicochemical characterization of nanocrystals



XRPD diffraction patterns of indomethacin (top), indomethacin nanocrystals (two in the middle) and Tween 80 (down)



Physicochemical characterization

- Both the ibuprofen and indomethacin did remain the crystalline form of the raw material
- Crystallinity of the nanocrystals was almost in the same level as it was with the raw material (notice: amorphous Tween)
- The improvement in the solubility **was not** caused by the crystalline changes



Size vs. solubility and dissolution

	Ibuprofen		Indomethacin	
	Raw material	Milled	Raw material	Milled
Solubility/ mg/ml	4.1	6.8	4.5	92.2
Mean particle size (smallest fraction)/nm		46 (After drying 54)		11 (After drying 43)

Ibuprofen abrasive and more difficult to mill

Milling much more efficient for indomethacin

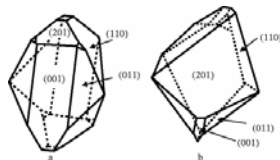
Process time and other process optimization very important

Preliminary dissolution tests with capsulated dried nanocrystals have been made => faster dissolution as compared to raw material

• Powder surfaces

As an example: case study – milling of paracetamol:

The unmilled single crystals exhibited properties reflective of the native external facets of crystal and the effect of milling on a form I crystal exposes a hydrophobic surface with increasing contribution as particle size is reduced



Heng et al. Pharm. Res. (23)2006, 1918

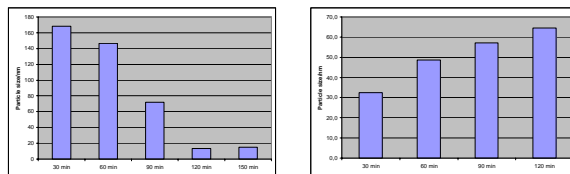
• Particle surfaces

In common: variations in the surface energy of fine pharmaceutical powders can depend upon:

- intrinsic anisotropic surface energetics of crystalline solids
- presence of surface amorphous zones and their surface energy
- effect of processing operations on the prevalence of amorphous zones
- surface area population or distribution for specific crystalline facets, as determined by the processing history of the solid.

=> Effectivity of milling on different kind of raw materials?

• Smallest particle size fractions after wet ball-milling with different process times



Indomethacin on the left and ibuprofen on right hand side.

It is very crucial to select optimal process time.

Material properties (surface energy) do effect very much.

Selection and amount of stabilizer is important.

• Concluding remarks

By nanonization the solubility properties of poorly soluble drug materials can be improved markedly

Nanocrystals produced by wet ball-milling from both the model substances did remain stable during the process

Material properties play a crucial role on the efficacy of the nanosizing process on solubility properties

How small particles are really needed?



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Thank You for Your Attention!