Nanocrystals: a smart strategy for the development of safer and more efficient products

Profa. Dra. Nadia Bou-Chacra
Faculdade de Ciências Farmacêuticas
Universidade de São Paulo

Outlines

- Why nanocrystal is a smart approach…
- How nanocrystal works…
- What can be accomplished using nanocrystal platform?

Global Nanotechnology in Drug Delivery Industry

Nanotechnology in Drug Delivery market worldwide is projected to grow by US$104. 9 Billion, driven by a compounded growth of 20. 4%. Nanocrystals, one of the segments analyzed and sized in this study, displays the potential to grow at over 18.

February 22, 2020 03:51 ET | Source: ReportLinker

New York, Feb. 22, 2020 (GLOBE NEWSWIRE) -- Reportlinker.com announces the release of the report "Global Nanotechnology in Drug Delivery Industry" - https://www.reportlinker.com/p05621749/?utm_source=GNW

3%. The shifting dynamics supporting this growth makes it critical for businesses in this space to keep abreast of the changing pulse of the market. Poised to reach over US$74.6 Billion by the year 2025, Nanocrystals will bring in healthy gains adding significant momentum to global growth.

- Representing the developed world, the United States will maintain a 18.3% growth momentum. Within Europe, which continues to remain an important element in the world economy, Germany will add over US$3.9 Billion to the region's size and clout in the next 5 to 6 years. Over US$3.4 Billion worth of projected demand in the region will come from Rest of Europe markets. In Japan, Nanocrystals will reach a market size of US$3.5 Billion by the close of the analysis period. As the world's second largest economy and the new game changer in global markets, China exhibits the potential to grow at 25.6% over the next couple of years and add approximately US$26 Billion in terms of addressable opportunity for the picking by aspiring businesses and their astute leaders. Presented in visually rich graphics are these and many more need-to-know quantitative data important in ensuring quality of strategy decisions, be it entry into new markets or allocation of resources within a portfolio. Several macroeconomic factors and internal market forces will shape growth and development of demand patterns in emerging countries in Asia-Pacific, Latin America and the Middle East. All research viewpoints presented are based on

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Contact Data

Clare: clare@reportlinker.com
US: (339)-368-6001
Intl: +1 339-368-6001

Poorly water-soluble drug: United States Pharmacopeia

Table 1. Relative terms of solubility

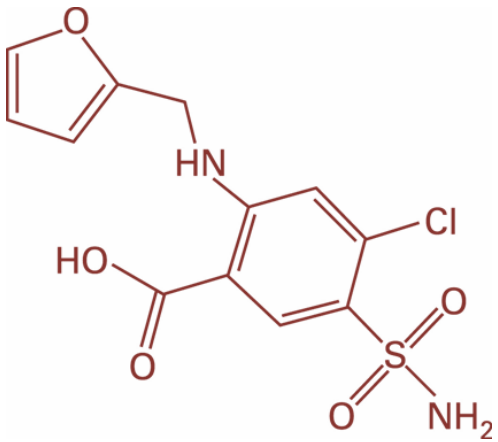
DESCRIPTIVE TERM	PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble or insoluble	>10,000

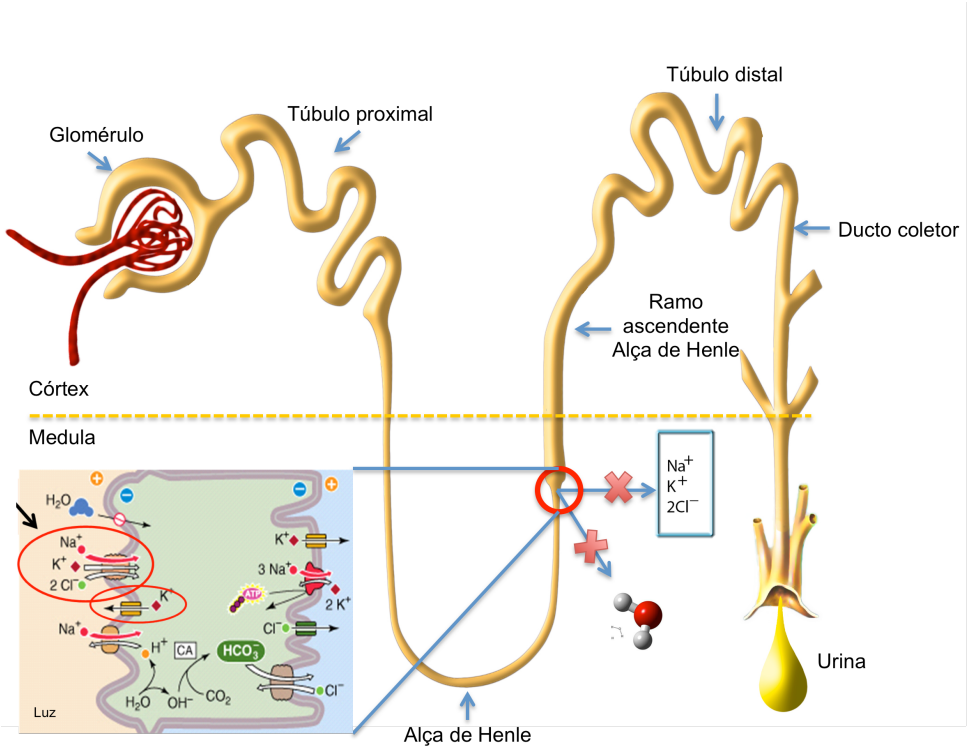
Biopharmaceutical classification System (BCS)

BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/ or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	

Source: Technical Brief 2011 Volume 9
Particle Sciences

Furosemide, a loop **diuretic**, inhibits water reabsorption in the nephron by blocking the sodium-potassium-chloride cotransporter





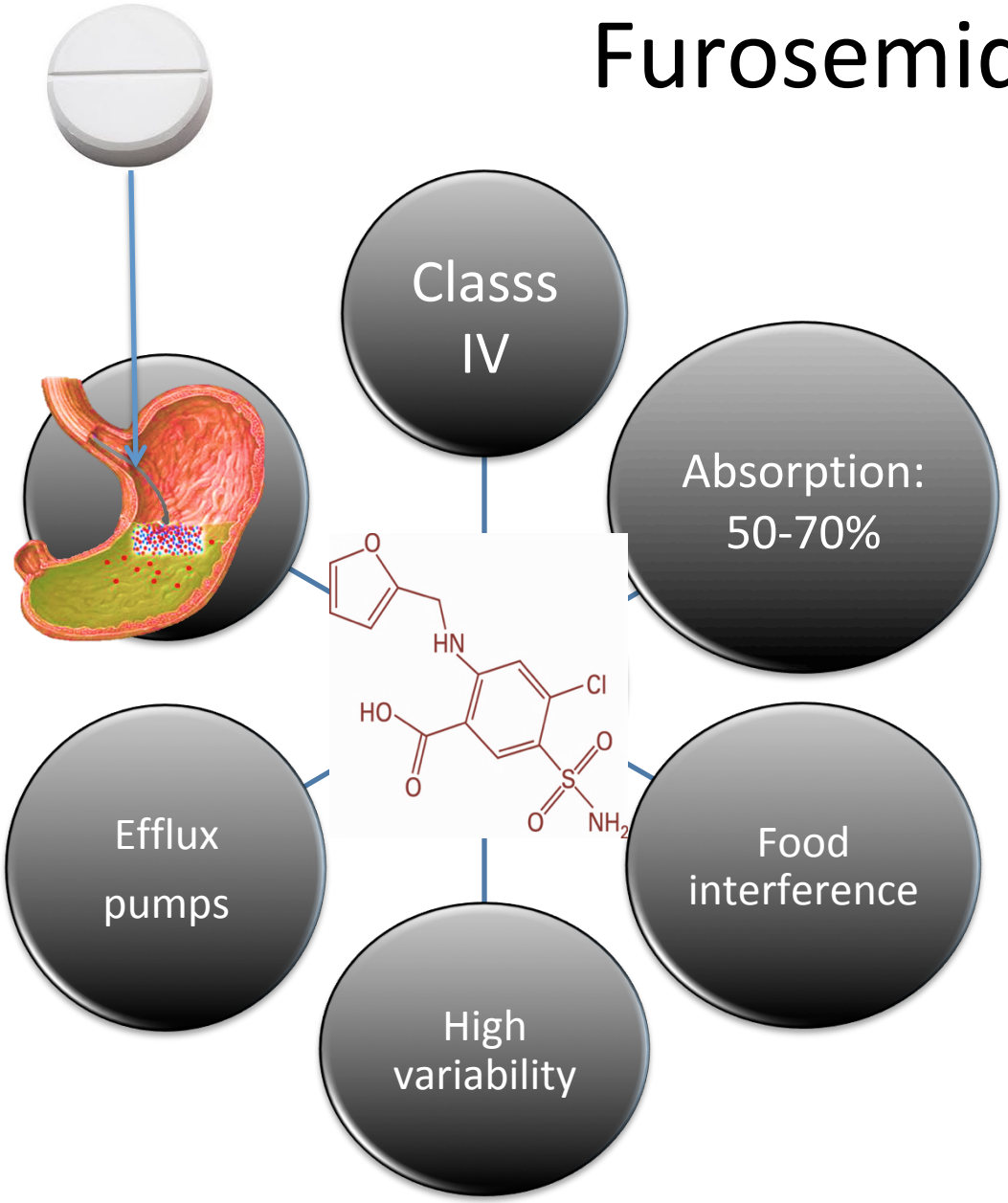
Medicine essential list (WHO, 2013)

oral solution: 20 mg/5 mL

Injection: 10 mg/mL (pH=9,5)

Tablets: 10, 20 e 40 mg

Furosemide



pH=9,5

How big is the problem?

About 40% of of the top 200 oral drugs marketed in the United States

33% of drugs listed in the US Pharmacopeia

75% of compounds under development

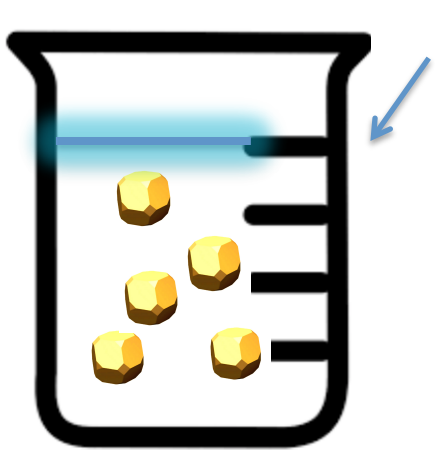
Nearly 90% of molecules in the discovery pipeline

Fonte: Rodriguez-Aller et al., 2015

Ilustração: Orlando Paes Filho® http://www.anguswar.com

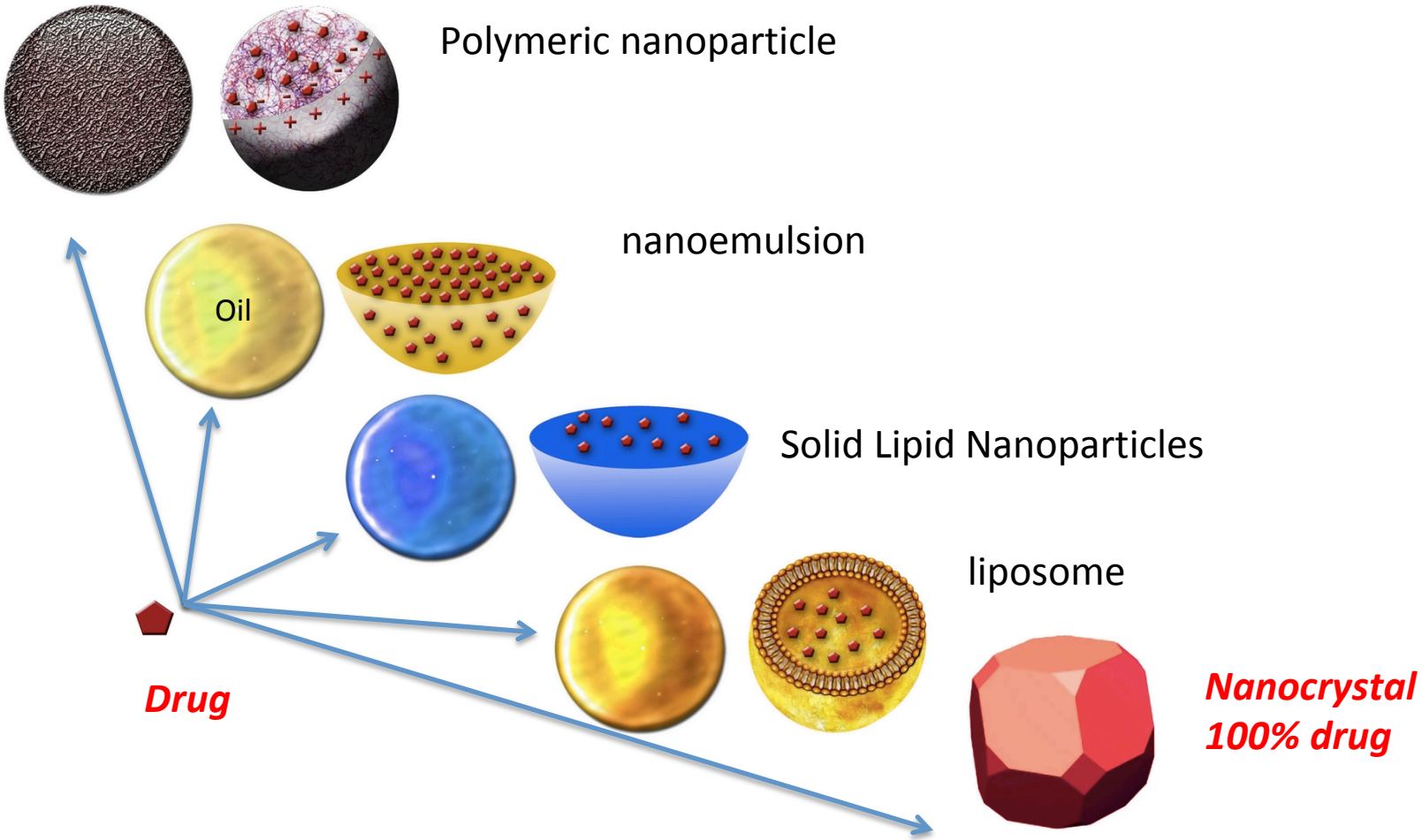
Nanocrystal: definition

- Particle with average size in the sub-micron range, which has no matrix and its structure can have amorphous or crystalline character. Such particles are stabilized in the water through the addition of surfactants or polymers in the formulation.



(MAULUDIN & MULLER, 2013)

Nanotech Strategies: poorly soluble drug substance

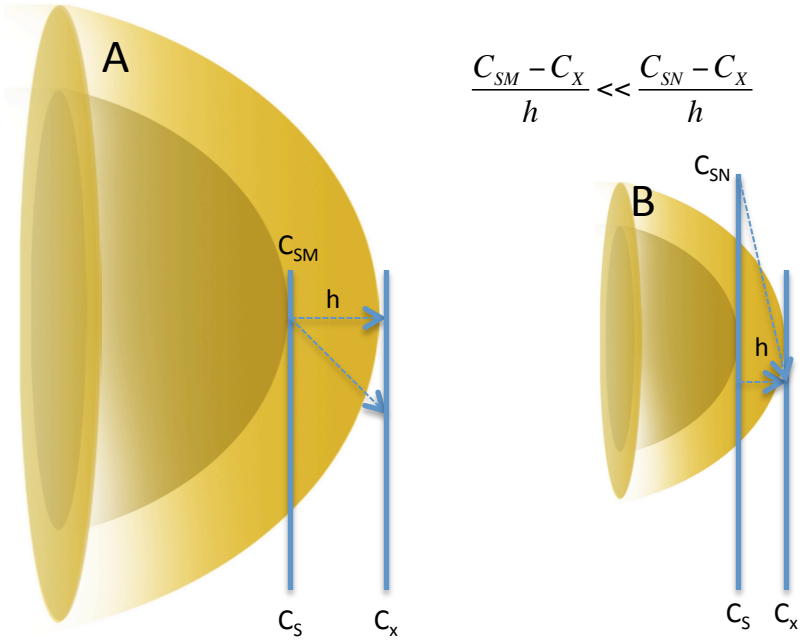


Fundamentals: Noyes-Whitney Equation

$$\frac{dx}{dt} = \left[\left(D \times A\right) \div h\right] \times \left(Cs - \frac{X}{V}\right)$$

Eq.(1)

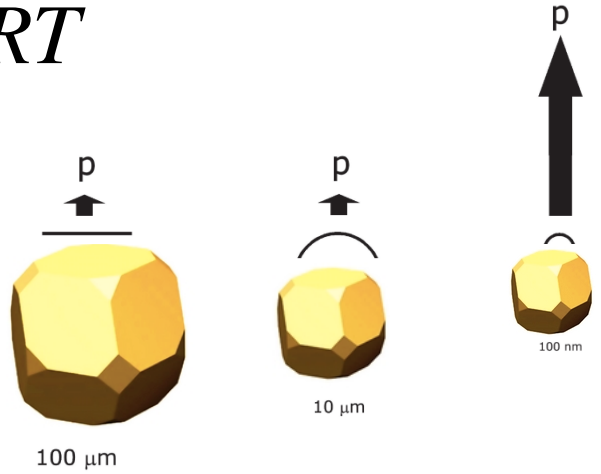
dx/dt : dissolution velocity
D: dissolution coefficient
A: particle surface area
h: diffusion distance
C_s saturation solubility
X: liquid interstitial concentration
V: dissolution medium volume



Fundamentals: Kelvin Equation

$$\ln \frac{p}{p_0} = \frac{-2\gamma V_m}{rRT} \qquad \text{Eq.(2)}$$

p: actual vapor pressure
P_0 : saturated vapor pressure
γ: surface tension
V_m : molar volume
R: constant
r : radius droplets
T: temperature

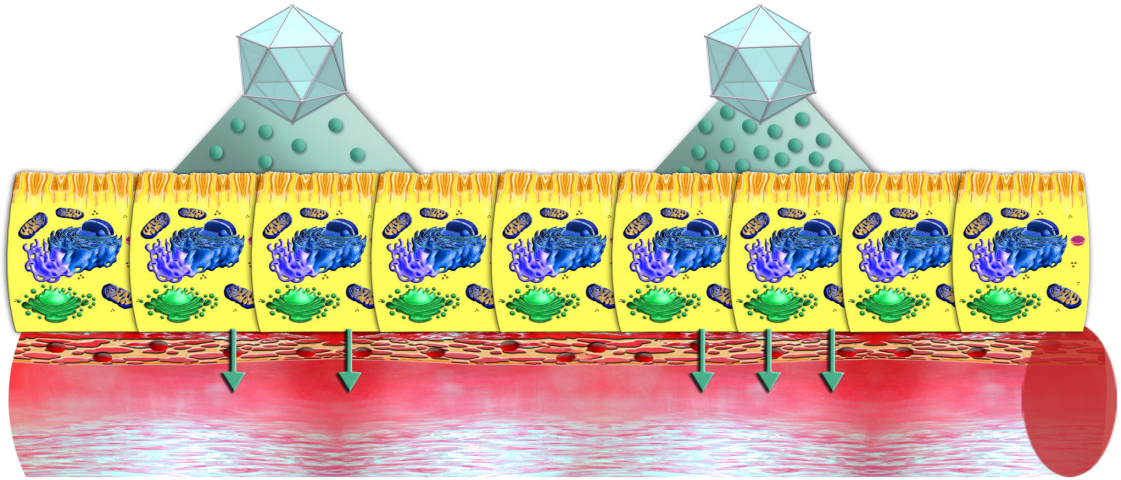


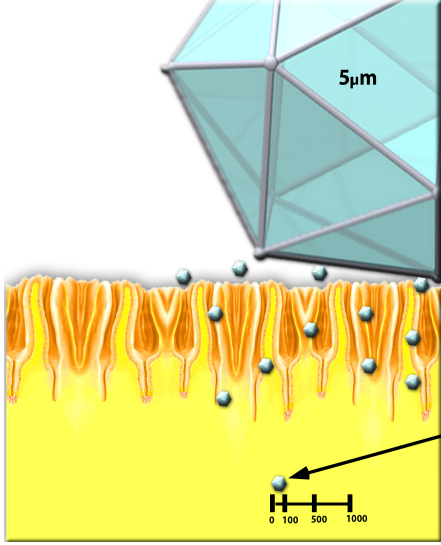
- ✓ due to the increased saturation solubility, the concentration gradient between gut lumen and blood is increased, consequently the absorption by passive diffusion will be improved (JUNGHANNS & MÜLLER, 2008)

Microcrystals

Fasted state

Fed state

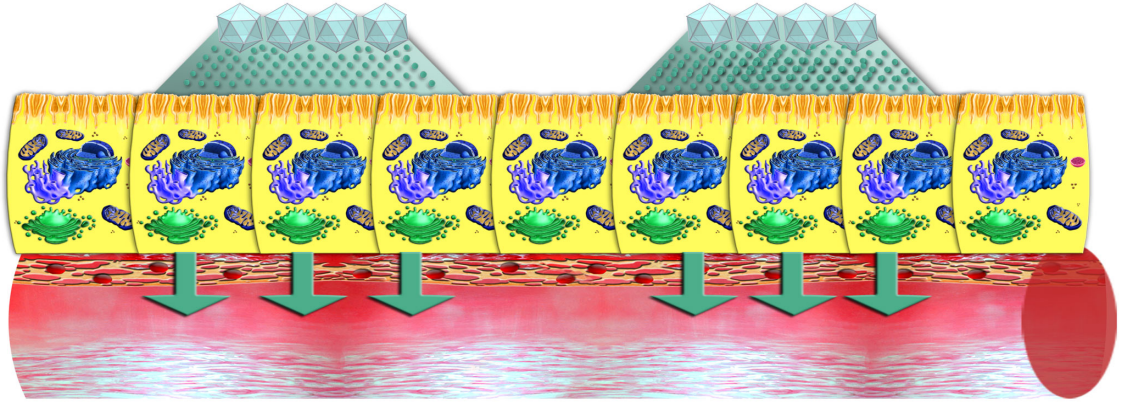




Nanocrystals

Fasted state

Fed state



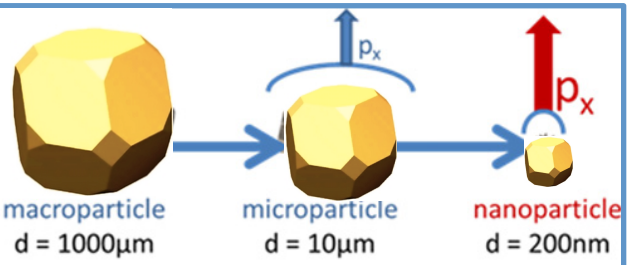
Surface area to volume ratio

Area = 5 cm x 5 cm x 6 = 125 cm^2 (1 cube) or 0.015 m^2

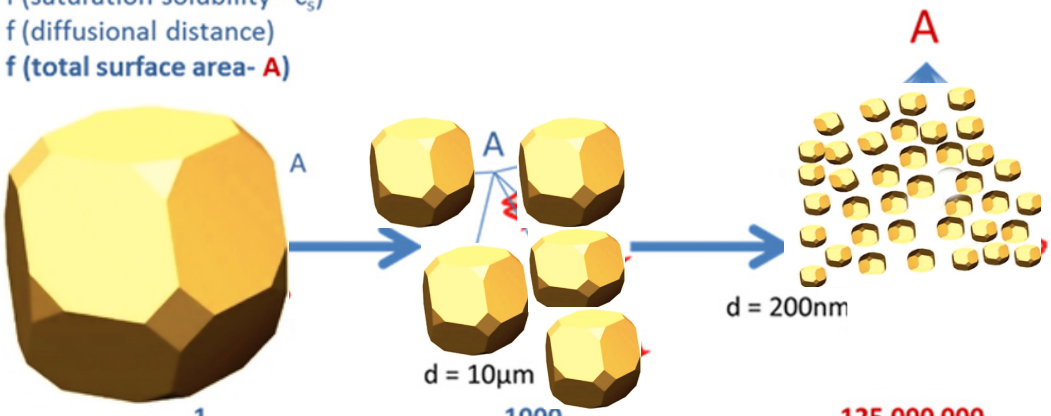
Area = 1 nm x 1 nm x 6 x 1.25 x 10^{23} = 7.5 x 10^{23} nm^2 or 750,000 m^2

Ratio: 750,000 ÷ 0.015 = 50 million

1. saturation solubility c_s:
= f (size - d)
= f (curvature)
= f (dissolution pressure - p_x)



2. dissolution velocity dc/dt:
= f (saturation solubility - c_s)
= f (diffusional distance)
= f (total surface area- A)

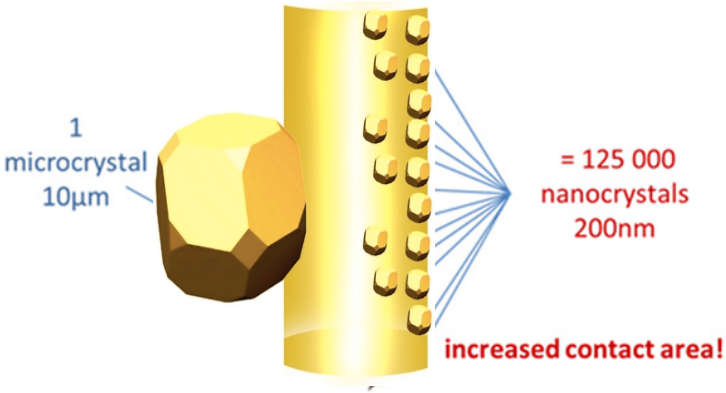


1
macroparticle
d = 100µm
A = 60,000µm²

1000
microparticles
decrease in d: /10
increase in A: • 10

125 000 000
nanoparticles
decrease in d: /500
increase in A: • 5000

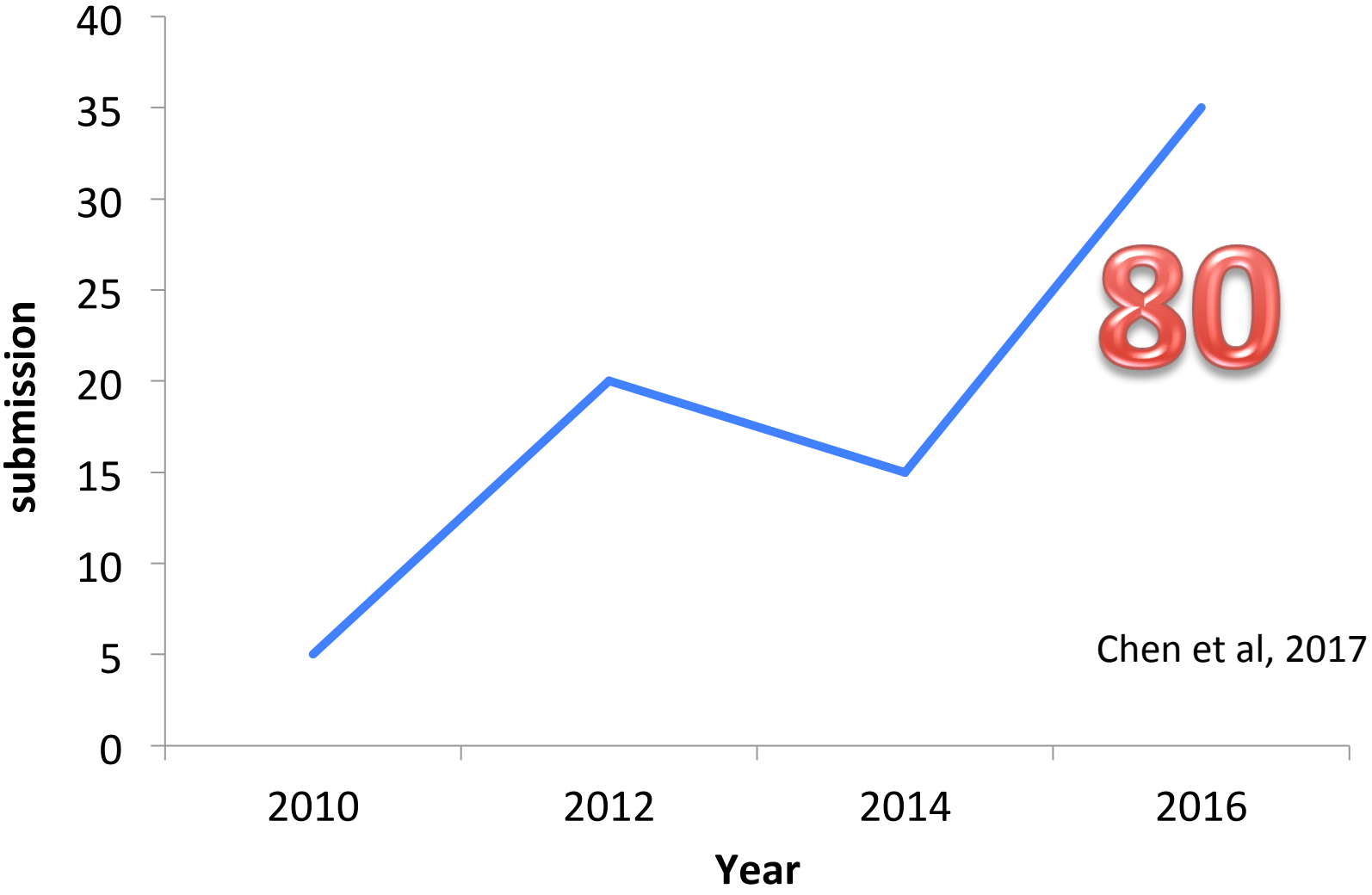
3. adhesiveness:
= f (size)
= f (contact area)



1 contact point versus 125,000 contact points

Nanocrystal: sales 2016

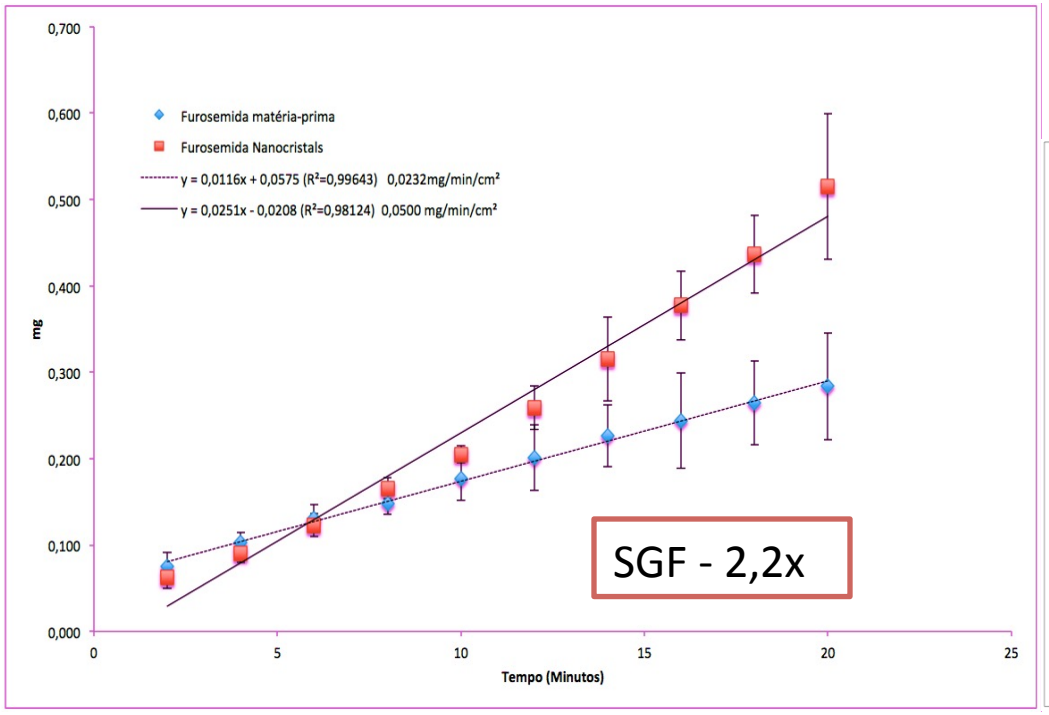
Nanocrystal: FDA submission

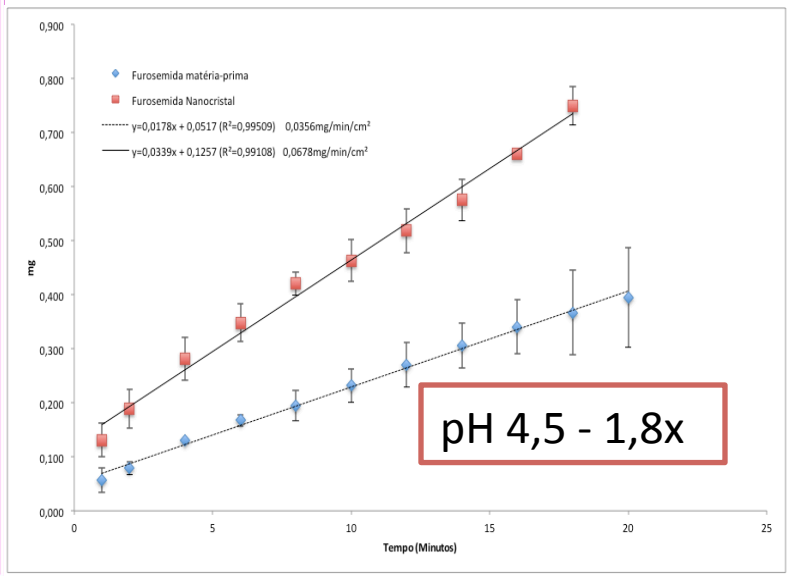


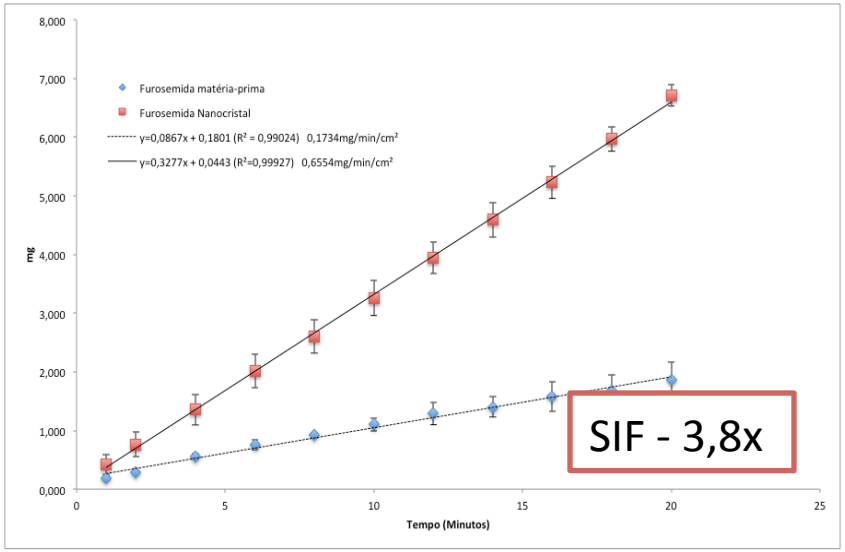
Furosemide Nanocrystals

Pharm Dev Technol. 2016 Nov;21(7):812-822. Physical- chemical properties of **furosemide nanocrystals** developed using rotation revolution mixer

(Barbosa et al., 2015)

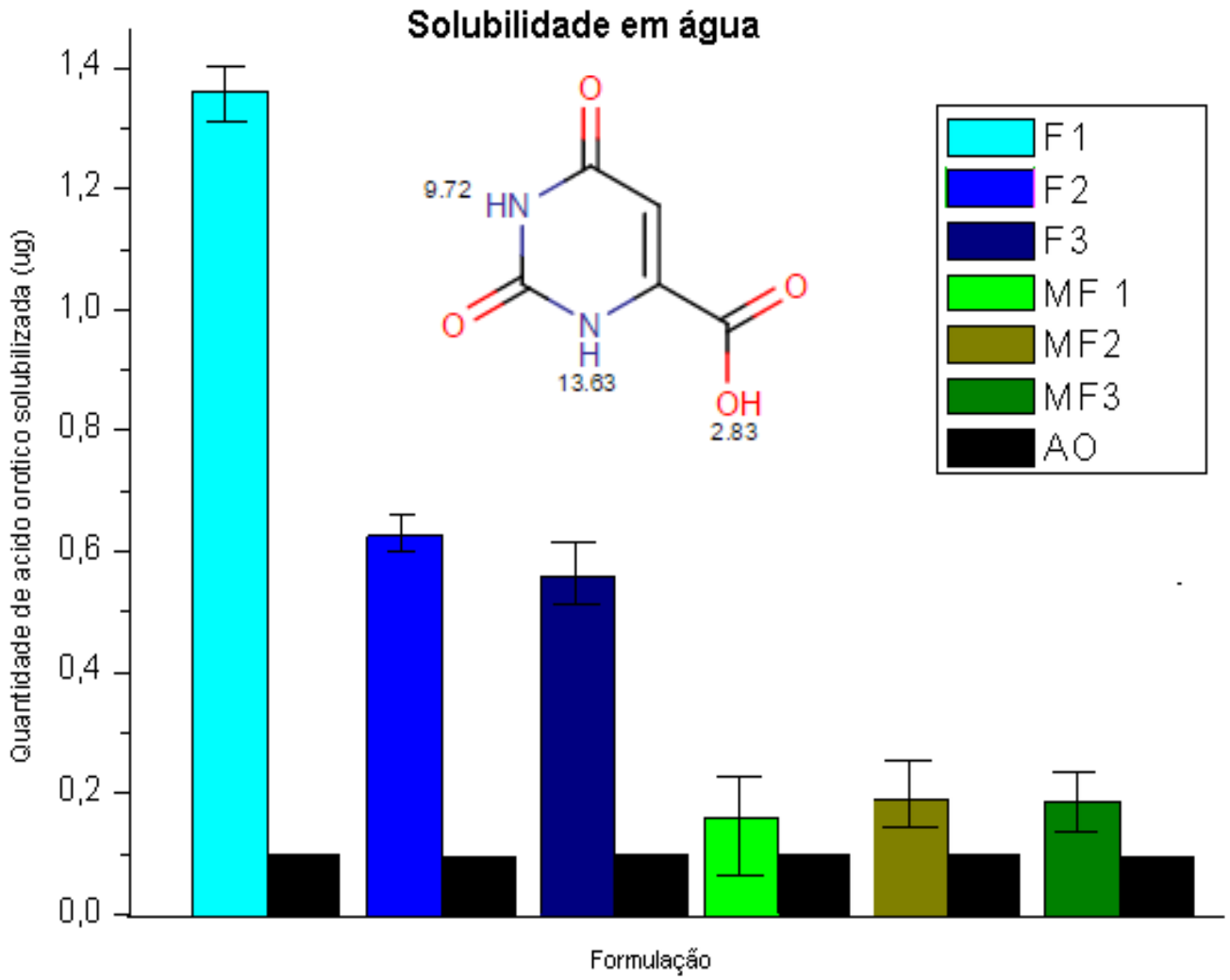

Furosemida matéria-prima
Furosemida Nanocristals
y = 0,0116x + 0,0575 (R²=0,99643) 0,0232mg/min/cm²
y = 0,0251x - 0,0208 (R²=0,98124) 0,0500 mg/min/cm²
mg
Tempo (Minutos)
SGF - 2,2x


Furosemida matéria-prima
Furosemida Nanocristal
y=0,0178x + 0,0517 (R²=0,99509) 0,0356mg/min/cm²
y=0,0339x + 0,1257 (R²=0,99108) 0,0678mg/min/cm²
mg
Tempo (Minutos)
pH 4,5 - 1,8x


Furosemida matéria-prima
Furosemida Nanocristal
y=0,0867x + 0,1801 (R² = 0,99024) 0,1734mg/min/cm²
y=0,3277x + 0,0443 (R²=0,99927) 0,6554mg/min/cm²
mg
Tempo (Minutos)
SIF - 3,8x

Orotic acid nanocrystals

BR1020160202434


Solubilidade em água
Quantidade de acido orotico solubilizada (ug)
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
Formulação
F1
F2
F3
MF 1
MF2
MF3
AO
O
9.72
HN
O
N
H
13.63
O
OH
2.83

Processo de obtenção de nanocristais de rifampicina, nanocristais de rifampicina obtidos e seu uso

BR10201701524

HYDRODYNAMIC MEAN DIAMETER (DHM), POLYDISPERSITY INDEX (PI) AND THE ZETA POTENTIAL (ZP) OF THE NANOCRYSTALS

Table 13 . DHM, PI and ZP of. nanocrystals F1-MU e F2-UM.

Sampler	DHM (d. nm)	PI	ZP (mV)
F1-MU	340.60 ± 5.44	0.20 ± 0,01	-8.80 ± 0.45
F2-MU	364.20 ± 4.50	0.27 ± 0.02	-8.91 ± 0.03

LYOPHILIZATION OF NANOSUSPENSIONS

Table 14 . DHM, PI and ZP of. nanocrystals F1-MU e F2-UM reconstituted after lyophilization.

Sampler	DHM (d. nm)	PI	ZP (mV)
F1-MU	340.60 ± 5.44	0.20 ± 0.01	-8.80 ± 0.45
F1-MU after resuspension	345.70 ± 3.45	0.31 ± 0.04	-8.98 ± 0.36
F2-MU	364.20 ± 4.50	0.27 ± 0.02	-8.91 ± 0.03
F2-MU after resuspension	363.20 ± 2.96	0.24 ± 0.02	-9.01 ± 0.03

CONTENT OF RIFAMPICIN IN NANOSUSPENSIONS

Table 15- Quantification of rifampicin in reference suspension rifampicin 20 mg/mL (FURP) and nanosuspensions F1-MU and F2-MU.

Sampler	Concentration (mg/mL)	Content (%)
F1-P	42.87 ± 0.38	96.27 ± 0.38
F2-P	42.39 ± 0.47	95.97 ± 0.47
F-FURP	17.78 ± 2.02	88.9% ± 2.02

SATURATION SOLUBILITY OF RIFAMPICIN NANOCRYSTALS

Table 16- Rifampicin nanocrystals solubility in different media at 37.0 ° C. n = 3

Media/pH	Rifampicin (mg/mL)	MF F1-MU (mg/mL)	MF F2-MU (mg/mL)	F1-MU (mg/mL)	F2-MU (mg/mL)
Acetate buffer pH 4,5	0,31 ± 0,02	0,92 ± 0,03	0,93 ± 0,24	1,30 ± 0,05 (4,19x)	0,94 ± 0.04 (3,03x)
Water pH 6.0	0,95 ± 0,03	1,21 ± 0,01	1,40 ± 0,03	1,82 ± 0,02 (1,92x)	1,58 ± 0,01 (1,66x)
Phosphate buffer pH 6.8	1,37 ± 0,01	2,13 ± 0,03	2,01 ± 0,04	2,38 ± 0,04 (1,74x)	2,14 ± 0,02 (1,56x)
Phosphate buffer pH 7.2	1,89 ± 0,05	2,67 ± 0.02	2,47 ± 0.03	2,73 ± 0,01 (1,44x)	2,69 ± 0.02 (1,42x)

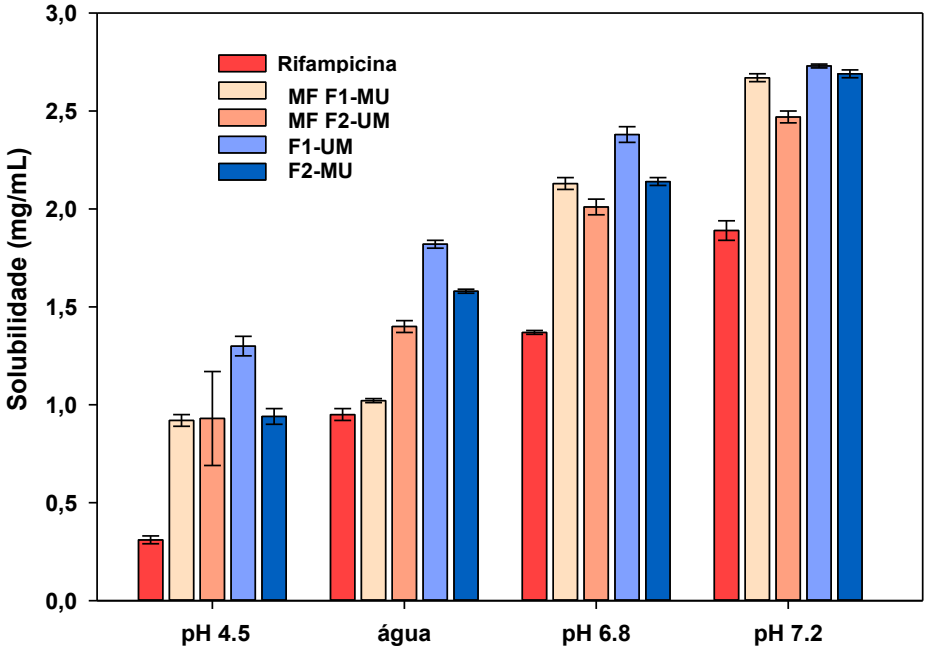


Table 17- Dissolution Efficiency (% DE) of F1-MU and F2-MU rifampicin nanosuspensin and reference rifampicin suspension 20 mg / ml (F-FURP) evaluated in 45 minute test time.

Sampler	DE%
F1-MU	89.3
F2-MU	89.6
F-FURP	78.0

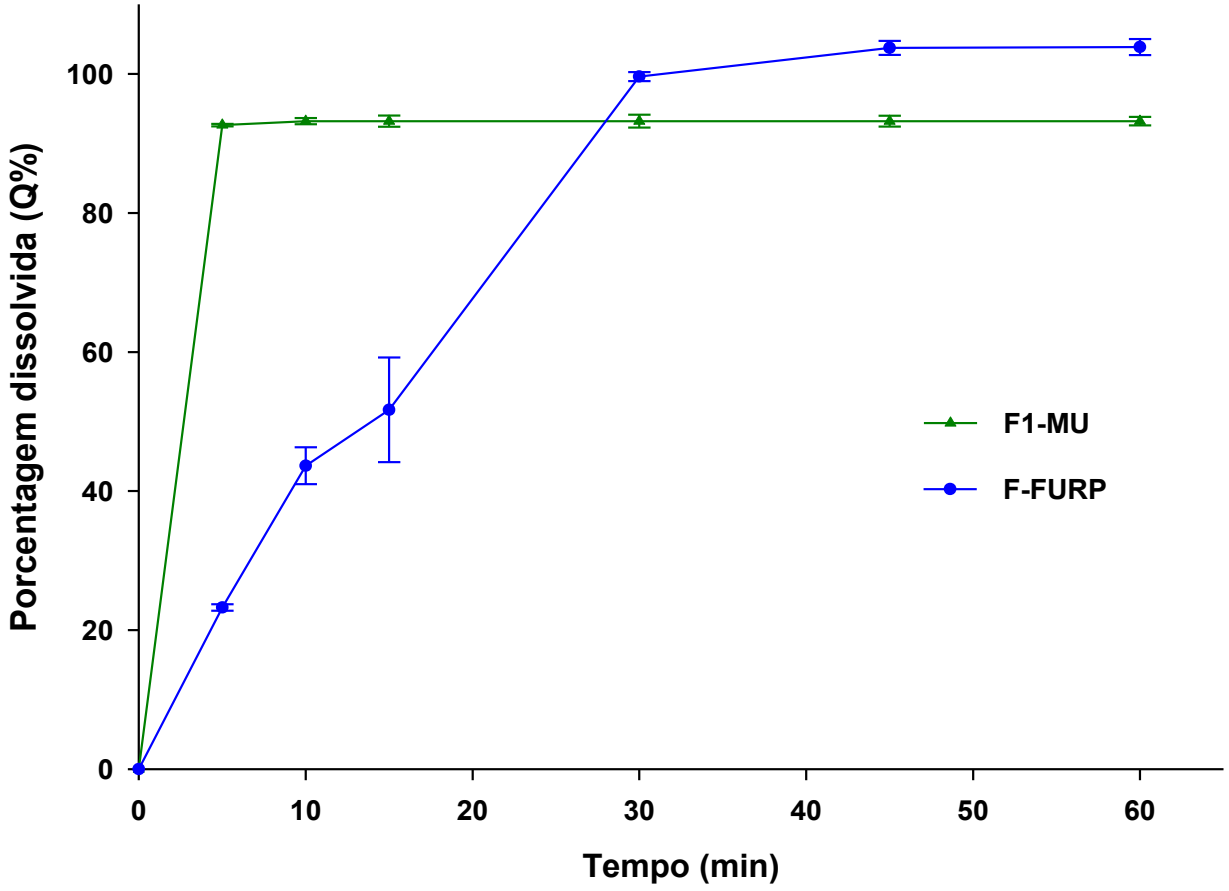
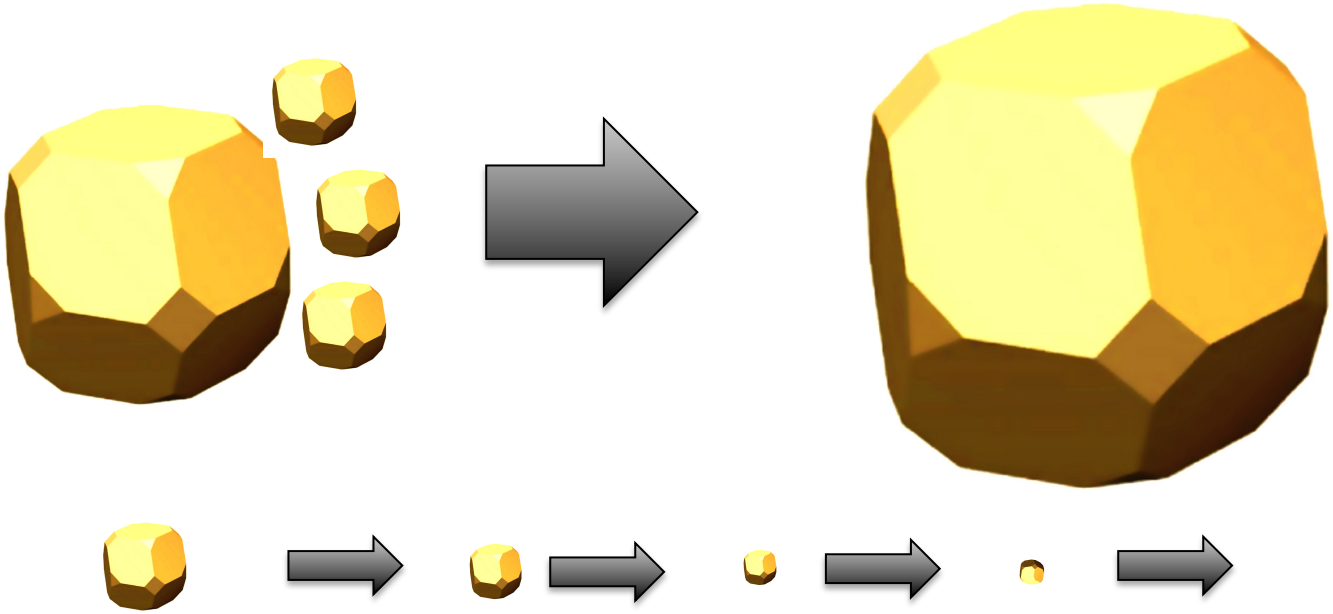


Figura 19- Dissolution profile of F1-UM.

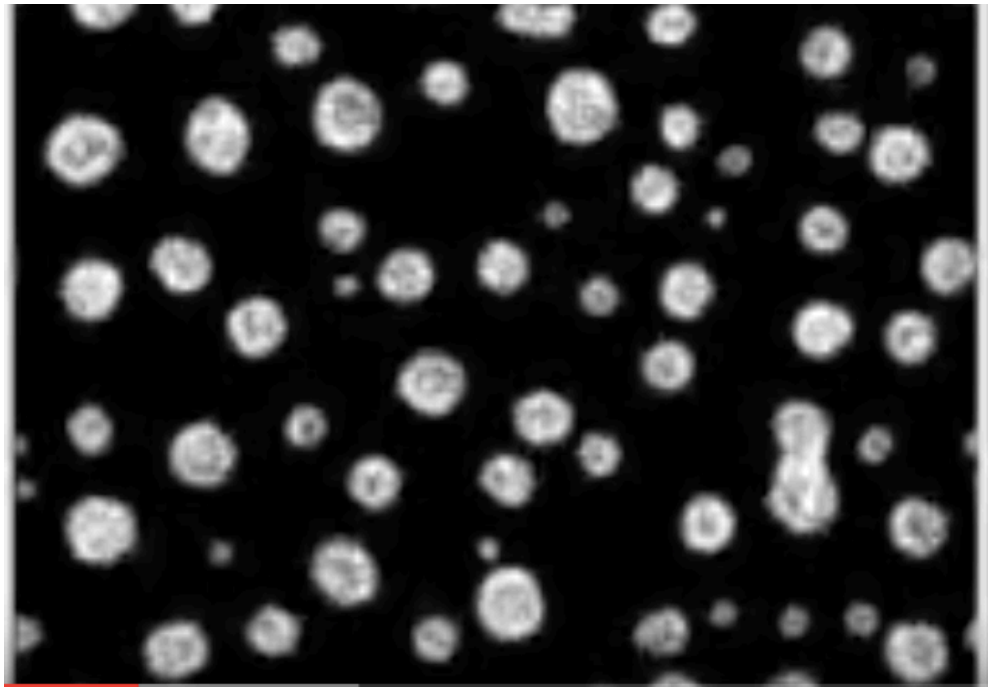
Ostwald ripening

- Due to the different Laplace pressure, a diffusion of molecules of the disperse phase from small droplets to big droplets occurs through the continuous phase. Thus the small droplets dissolve whereas large droplets grow, affecting the long-term stability of the system.



Ostwald ripening phenomenon

- https://www.youtube.com/watch?v=afarOfvrGMU



larger particles are more energetically stable than smaller particles

Obrigada

Thank you

感谢

Breaking time

Source: Orlando Paes Filho® http://www.anguswar.com (my husband)

Saturation solubility

- The thermodynamic solubility constant is defined for large monocrystals. Solubility will increase with decreasing size of solute particle because of the additional surface energy. This effect is generally small unless particles become very small, typically smaller than 1 µm.

Source: Orlando Paes Filho® http://www.anguswar.com