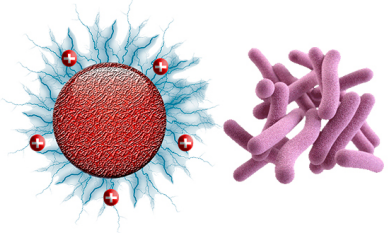
Drug Nanocrystal for the treatment of neglected diseases

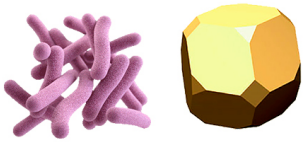
Profa. Assoc. Nádia Bou-Chacra

PATENTES

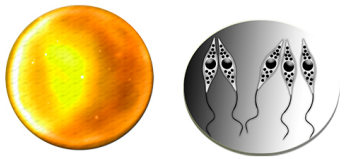
DOENÇAS NEGLIGENCIADAS



Rifampicina:
tuberculose/hanseníase



Rifampicina:
Tuberculose/hanseníase

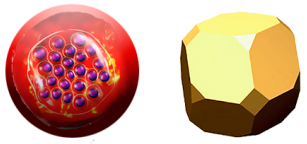


Buparvaquona: leishmaniase

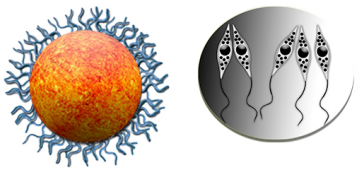
NFOH: leishmaniase

NANOTECH

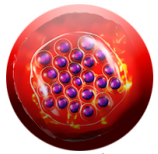
USP

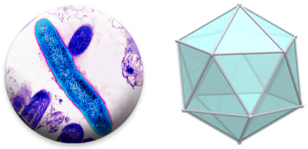


Artemeter:
malária

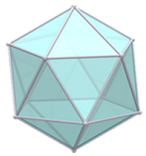


NFOH: leishmaniase





Dapsona:
hanseníase



Ácido orótico:
malária

Outlines

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

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

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

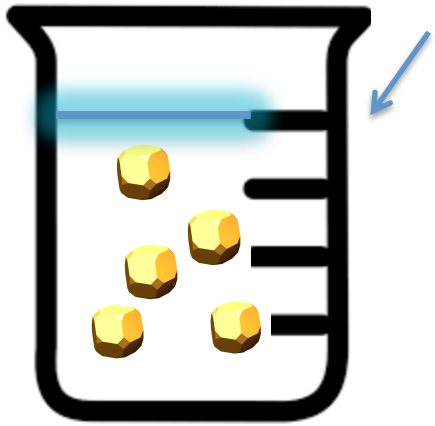
Nearly 90% of molecules in the discovery pipeline

Fonte: Rodriguez-Aller et al., 2015

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

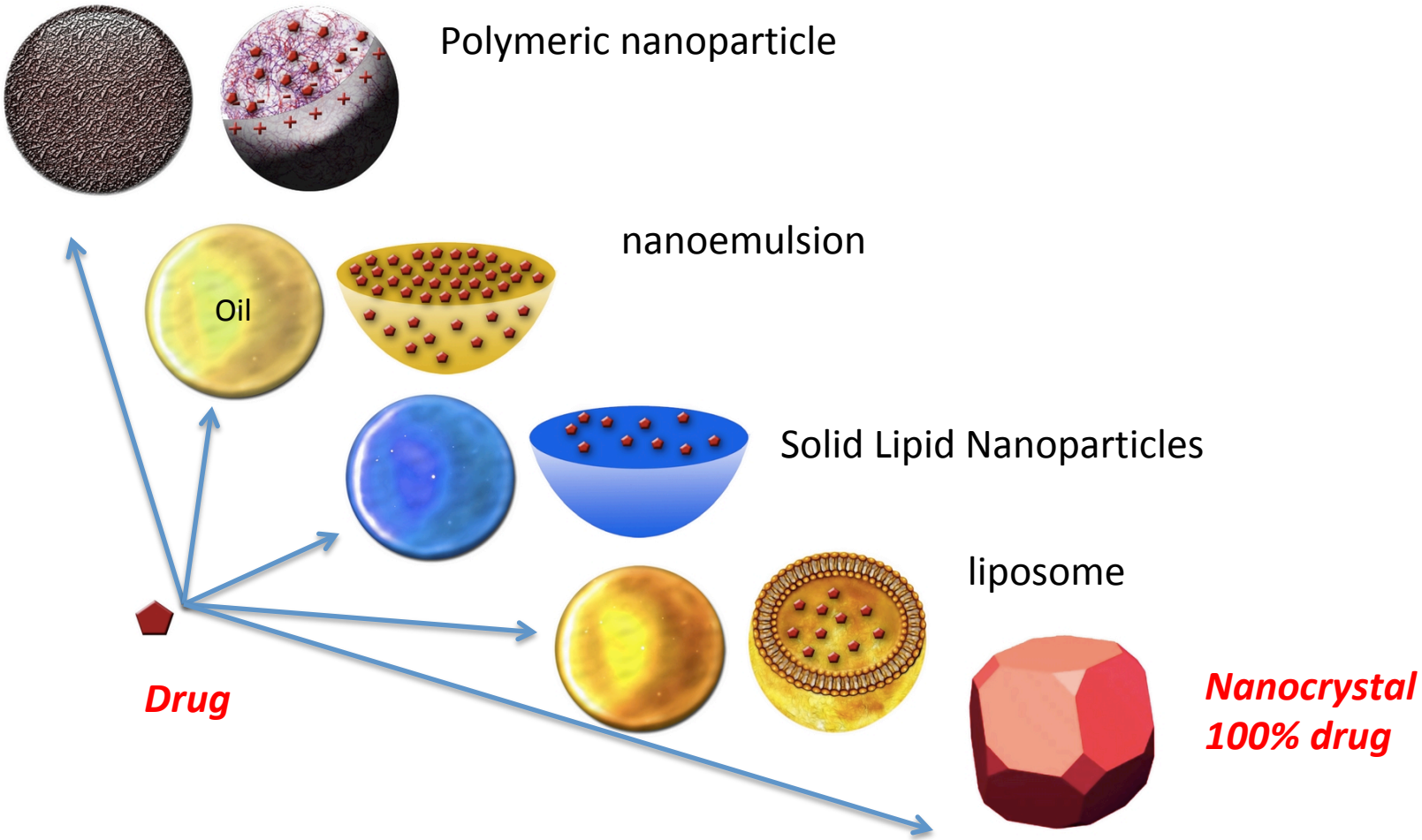
Drug Nanocrystal: definition

- 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

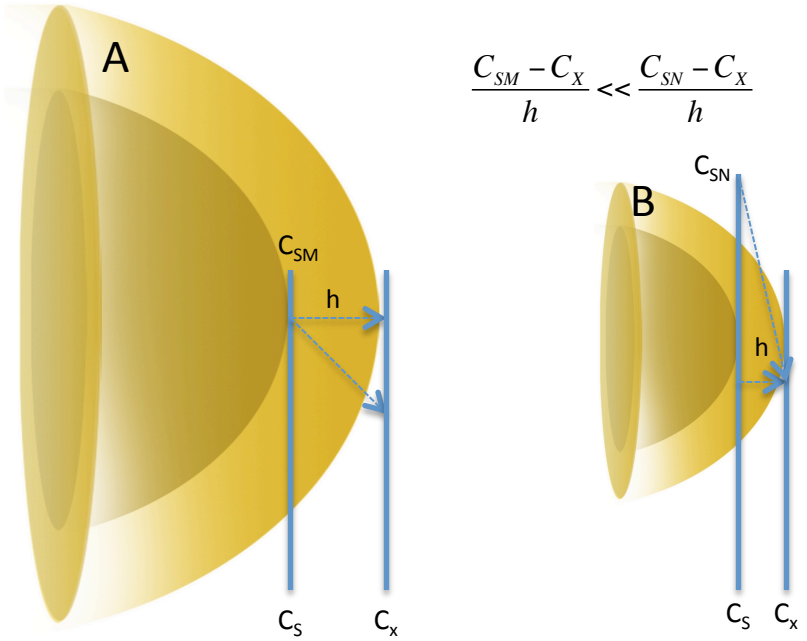


Fundamentals: Noyes-Whitney Equation

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

Eq.(1)

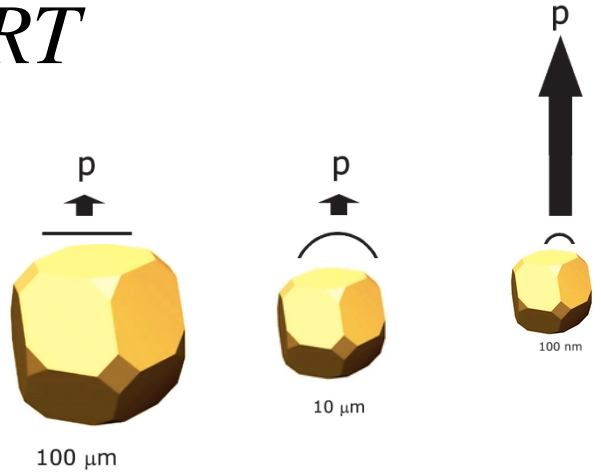
dx/dt : dissolution velocity
D: dissolution coefficient
A: particle surface area
h: diffusion distance
C_s saturation solubility
X: liquid interstitial concentration
V: dissolution medium volume



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

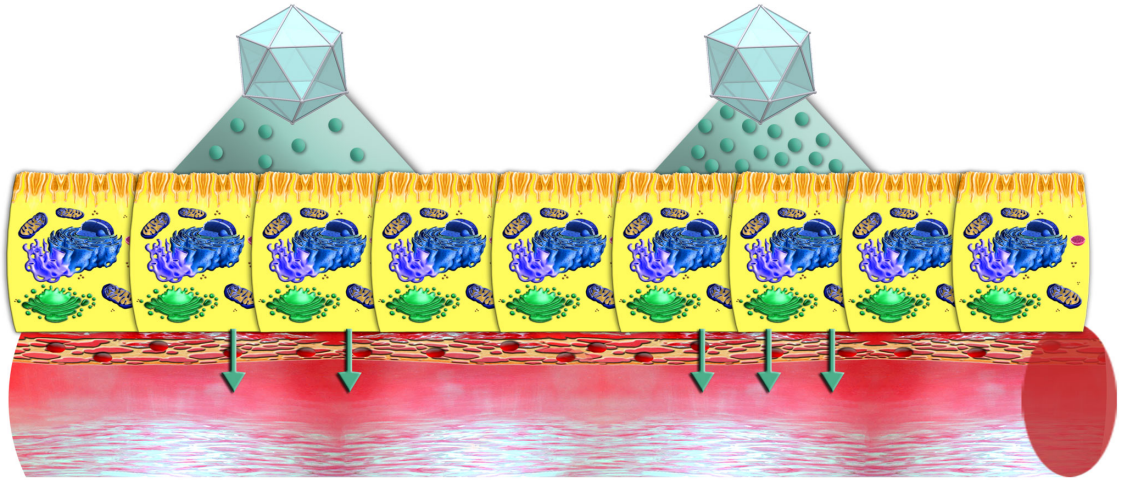


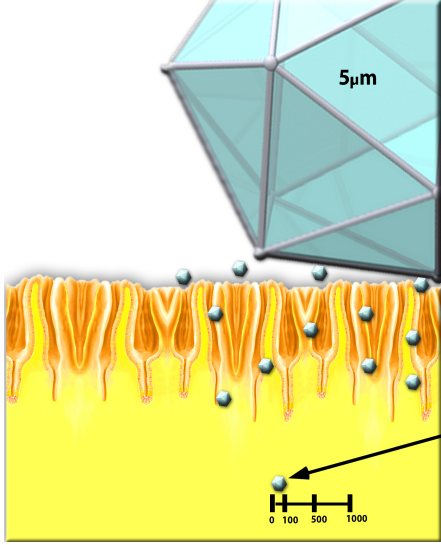
- ✓ due to the increased saturation solubility, the concentration gradient between gut lumen and blood is increased, consequently the absorption by passive diffusion will be improved (JUNGHANNS & MÜLLER, 2008)

Microcrystals

Fasted state

Fed state

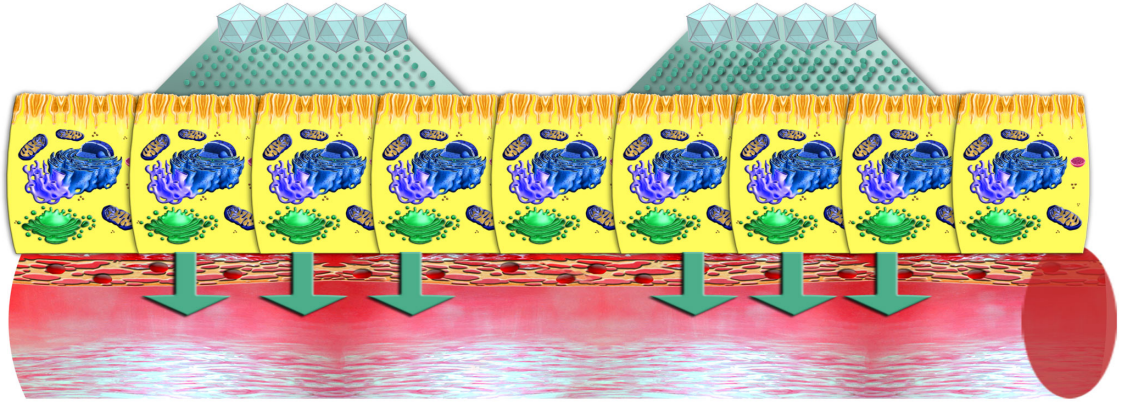




Nanocrystals

Fasted state

Fed state



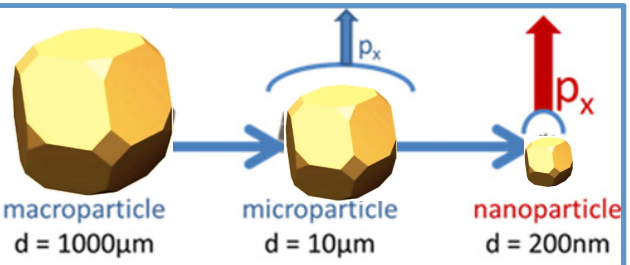
Surface area to volume ratio

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

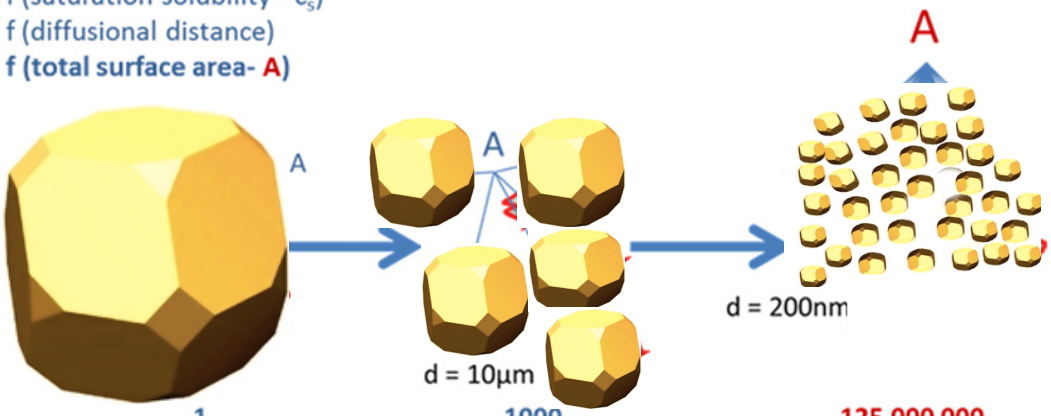
Area = 1 nm x 1 nm x 6 x 1.25 x 10^{23} = 7.5 x 10^{23} nm^2 or 750,000 m^2

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)

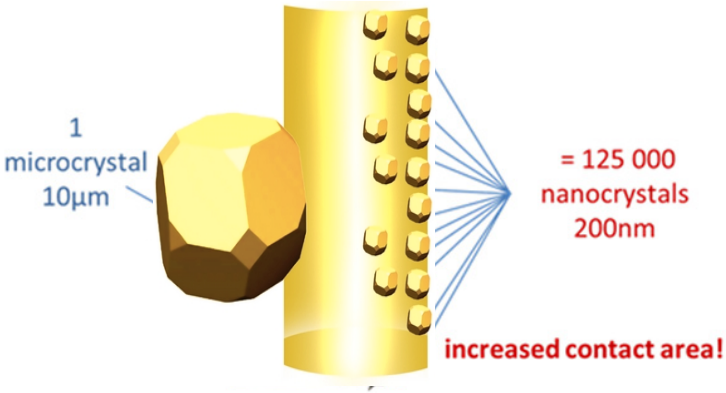


1
macroparticle
d = 100µm
A = 60,000µm²

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

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

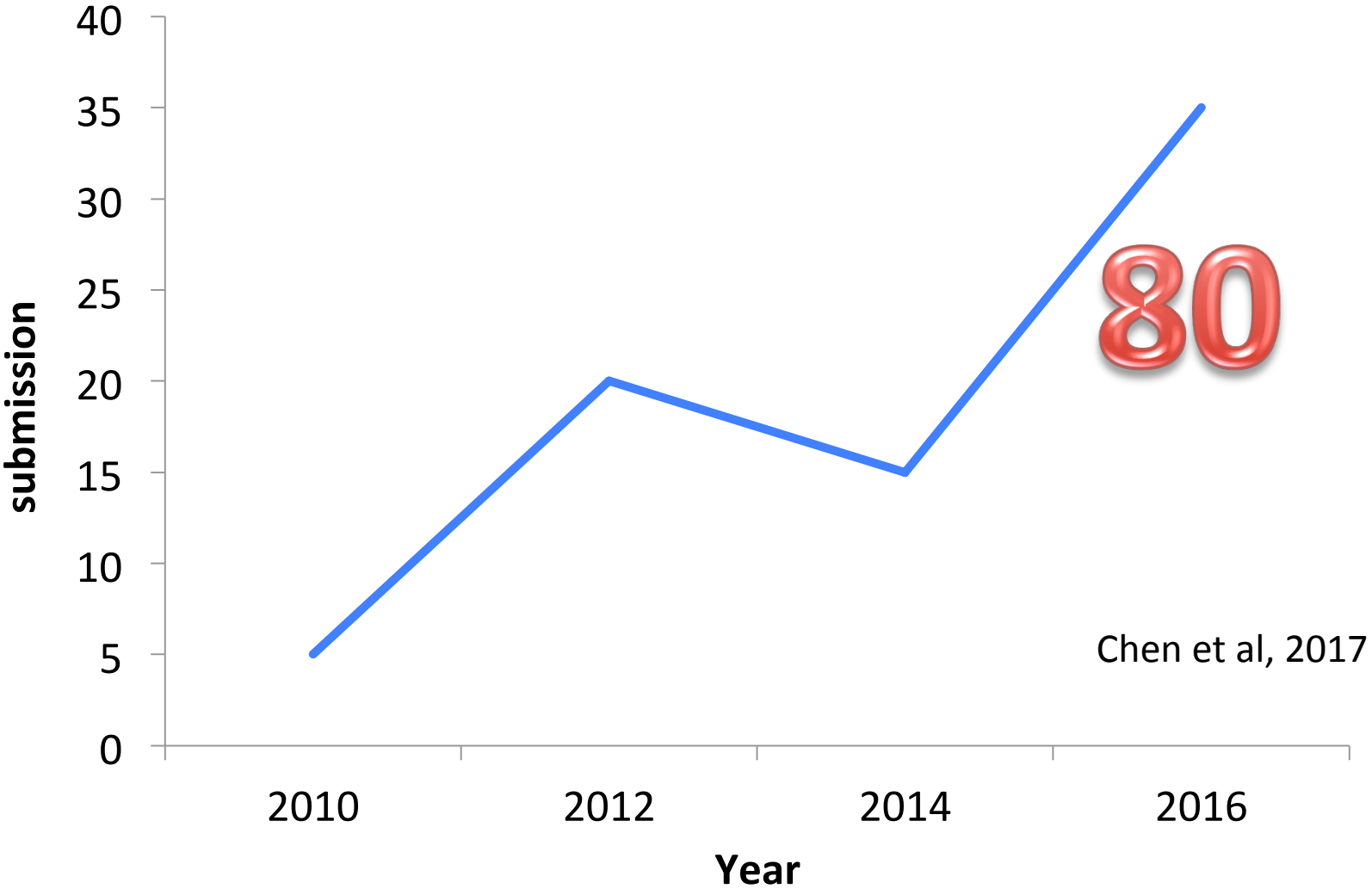
3. adhesiveness:
= f (size)
= f (contact area)



1 contact point versus 125,000 contact points

Nanocrystal: sales 2016

Nanocrystal: FDA submission



ReportLinker

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.

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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

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Rifampicin nanocrystals: Towards an innovative approach to treat tuberculosis

Katherine Jasmine Curo Melo[a], Mirla Anali Bazán Henostroza[a], Raimar Löbenberg[b,*], Nádia Araci Bou-Chacra[a,*]

[a] Faculty of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo, Brazil
[b] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada

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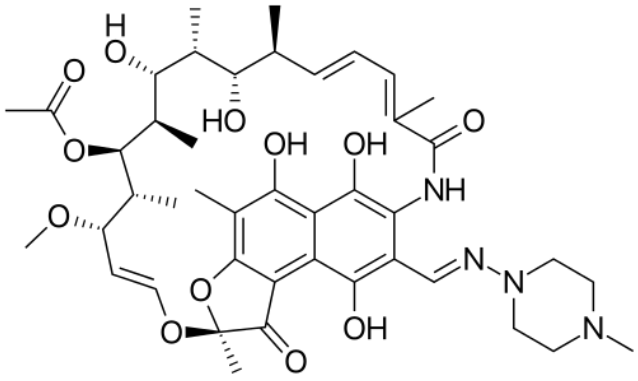
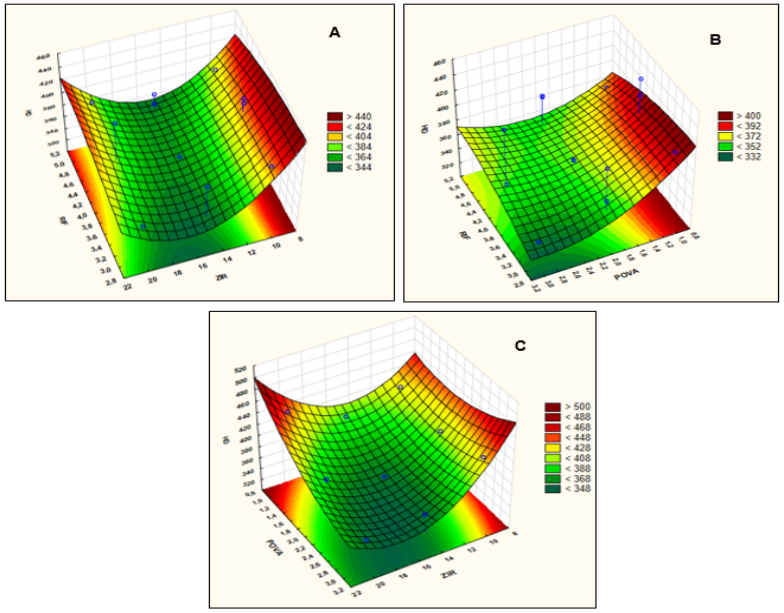
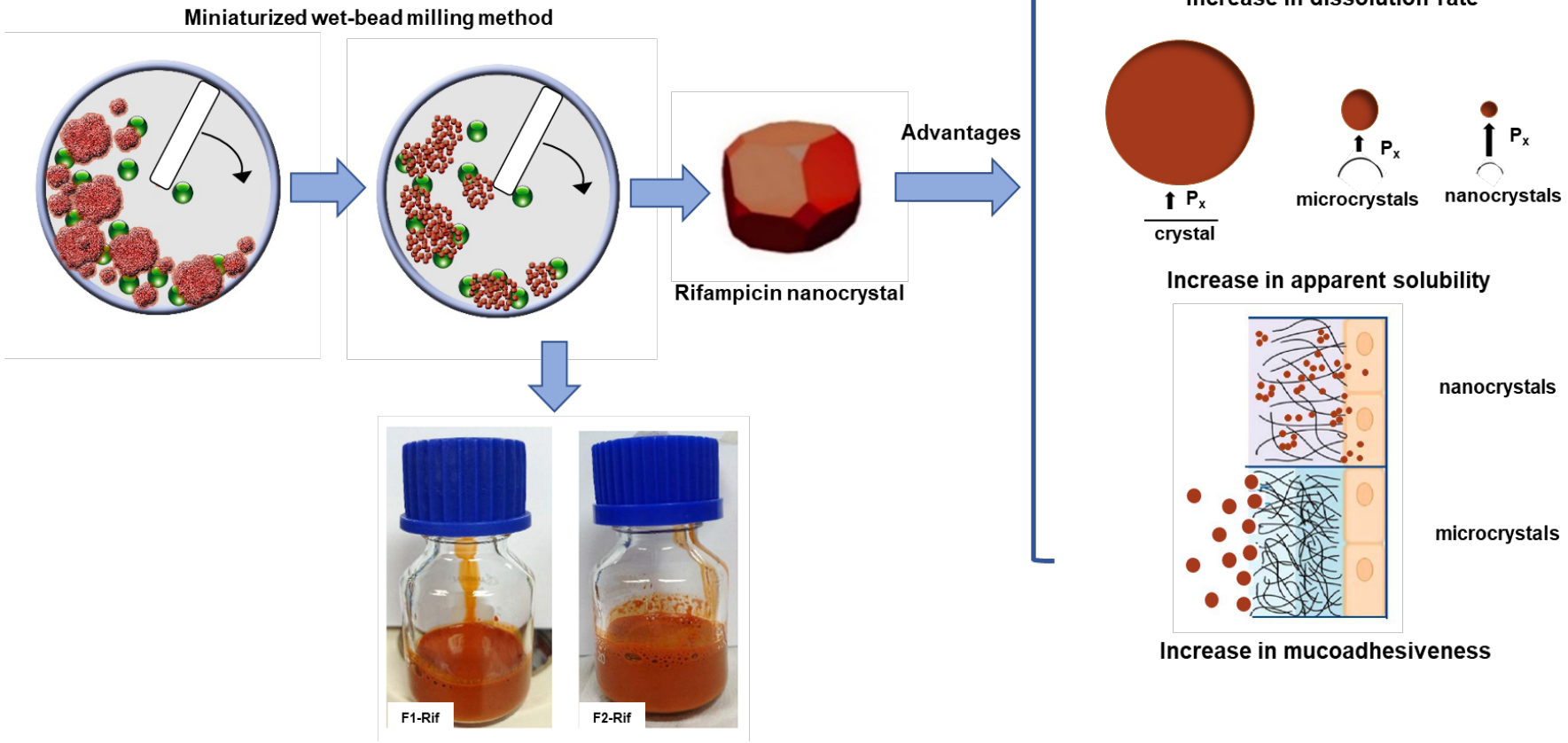
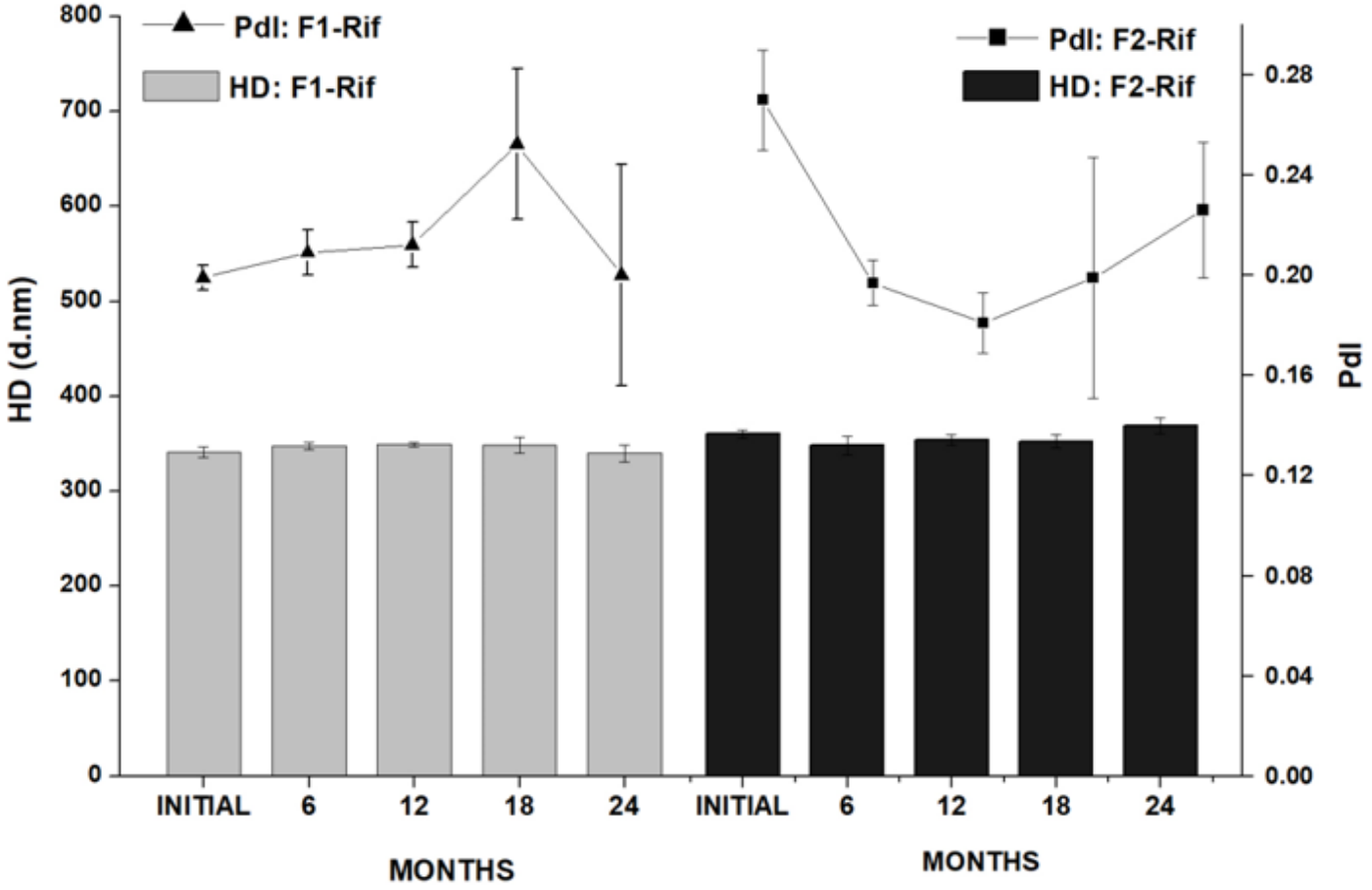





Miniaturized wet-bead milling method
Rifampicin nanocrystal
Advantages
F1-Rif
F2-Rif
crystal
microcrystals
nanocrystals
Increase in dissolution rate
Px
crystal
Px
microcrystals
Px
nanocrystals
Increase in apparent solubility
nanocrystals
microcrystals
Increase in mucoadhesiveness


Pdl: F1-Rif
HD: F1-Rif
Pdl: F2-Rif
HD: F2-Rif
HD (d.nm)
Pdl
800
700
600
500
400
300
200
100
0
0.28
0.24
0.20
0.16
0.12
0.08
0.04
0.00
INITIAL
6
12
18
24
INITIAL
6
12
18
24
MONTHS
MONTHS

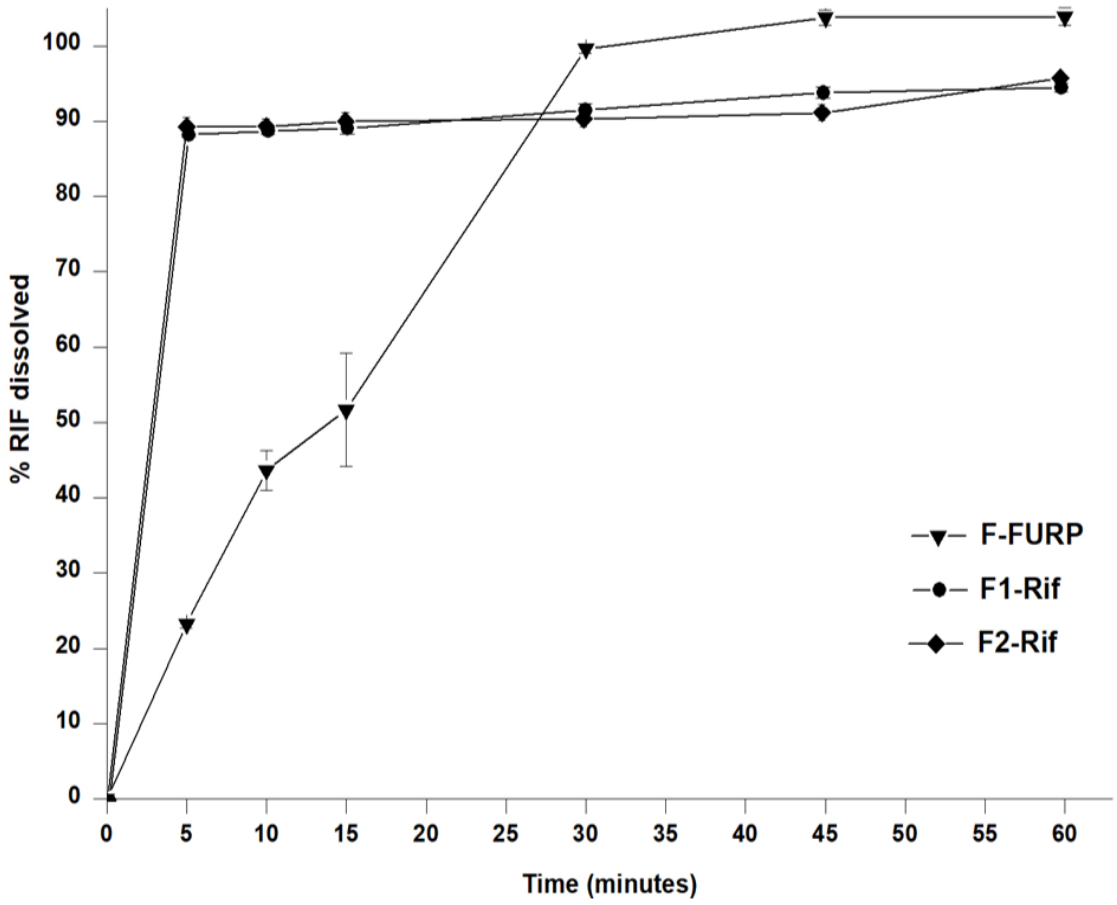


Fig. 11. Dissolution profiles of Rif nanosuspensions (F1-Rif and F2-Rif) and micronized rifampicin commercial suspension (F-FURP) obtained with paddle dissolution test (900mL of phosphate buffer pH 6.8, 50 rpm, 37 °C) (n=3).

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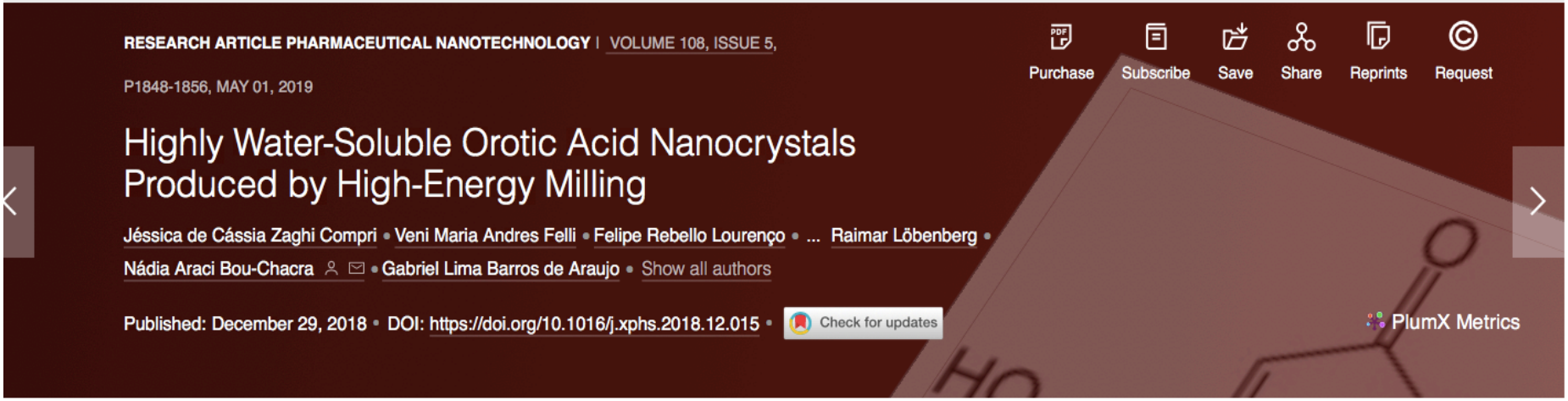

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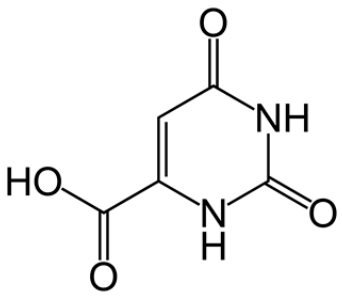


Figure 3. (a) Z-average, (b) zeta potential and (c) polydispersity index of FA, FB and FC for three months.

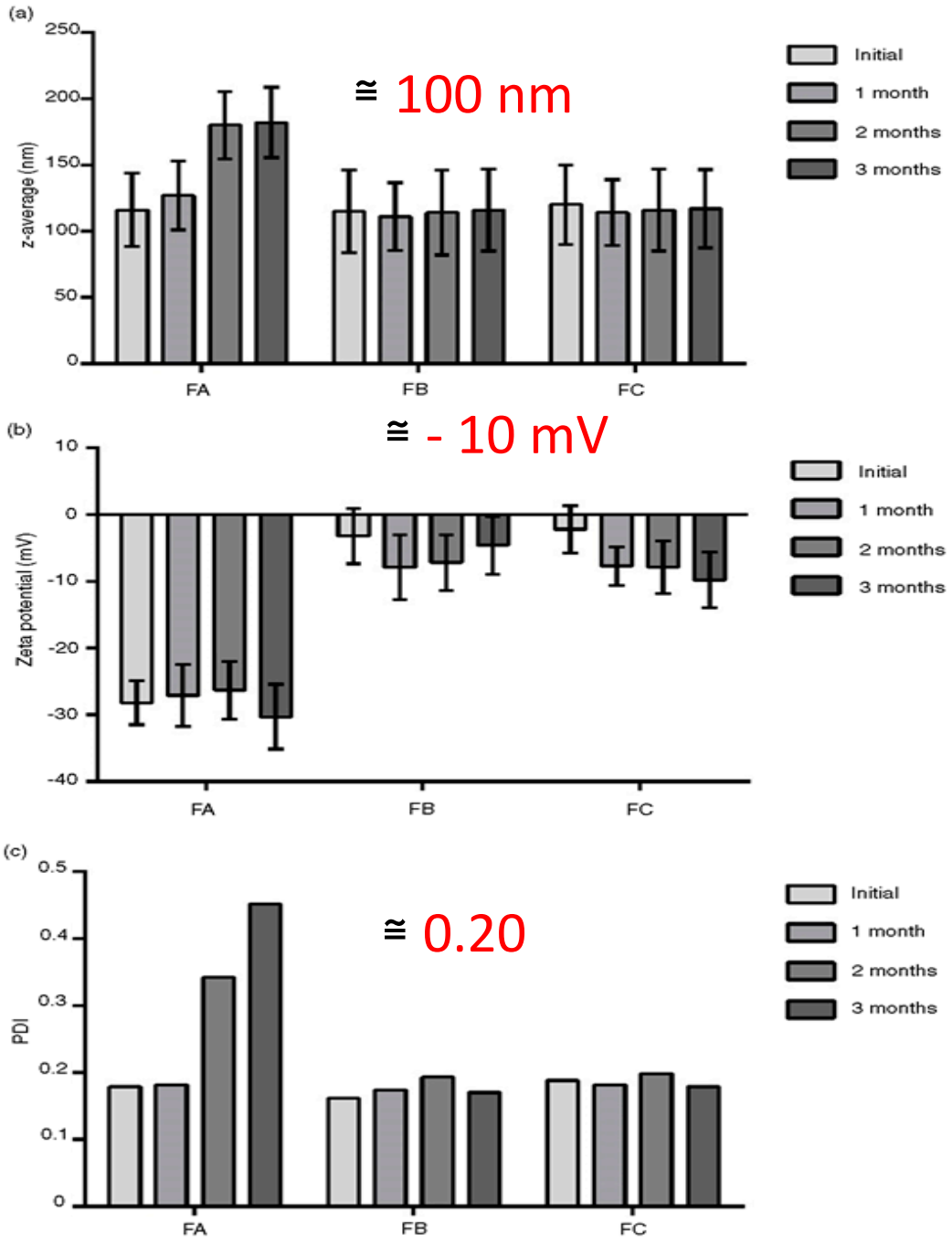


Table 1. Saturation solubility (n=3) of OA raw material, physical mixtures of FA (PM-FA), FB (PM-FB) and FC (PM-FC), nanocrystals formulations (FA, FB and FC) and the increase in solubility.

Formulation	Media (mg/mL)						Increase in solubility (times)	
	Water			Acetate pH 4.5			Water	Acetate pH 4.5
OA	0.10	0.11	0.10	0.20	0.18	0.19	RV	RV
PM- FA	0.09	0.10	0.09	0.21	0.20	0.20	-	-
PM- FB	0.11	0.11	0.10	0.22	0.21	0.21	-	-
PM- FC	0.11	0.10	0.10	0.19	0.20	0.20	-	-
FA	1.35	1.37	1.36	2.20	2.22	2.20	13.6	11.0
FB	0.65	0.66	0.63	1.50	1.48	1.51	6.3	7.5
FC	0.65	0.56	0.56	1.02	1.03	1.04	5.6	5.0

RV: reference value; - : not observed; OA: orotic acid raw material; PM-FA: physical mixtures of orotic acid, methylcellulose, polysorbate 80 and glucose; PM-FB: physical mixture of orotic acid, methylcellulose, polysorbate 80, povacoat® and glucose; PM-FC: physical mixtures of orotic acid, methylcellulose, povacoat® and glucose; FA: nanocrystal formulation FA; FB: nanocrystal formulation FB; FC: nanocrystal formulation FC.

Natureza Patente: 10 - Patente de Invenção (PI)

Título da Invenção ou Modelo de Utilidade (54): NANOCRISTAIS DE ARTEMETER, PROCESSOS DE OBTENÇÃO E USO DOS MESMOS

Resumo: A presente invenção refere-se à obtenção de nanocristais de artemeter com potencial e maior eficácia antimalárica quando comparada aos produtos convencionais. Os referidos nanocristais compreendem de 4,5 a 5,0% p/p de artemeter e de 2,4 a 3,5% p/p de polivinil caprolactama acetato de polivinilo polietilenoglicol copolímero (Soluplus®); e são obtidos empregando três diferentes processos: moagem a alta energia, homogeneização a alta pressão e moagem via úmida em escala reduzida, sendo também esses objetos da presente invenção. Adicionalmente, a presente invenção refere-se ao uso dos referidos nanocristais de artemeter no preparo de medicamentos com formas farmacêuticas orais para tratar a malária.

INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL

13/03/2018 870180020365 22:14

29409161711876312

Pedido nacional de Invenção, Modelo de Utilidade, Certificado de Adição de Invenção e entrada na fase nacional do PCT

Número do Processo: BR 10 2018 005010 9

Dados do Depositante (71)

Depositante 1 de 2

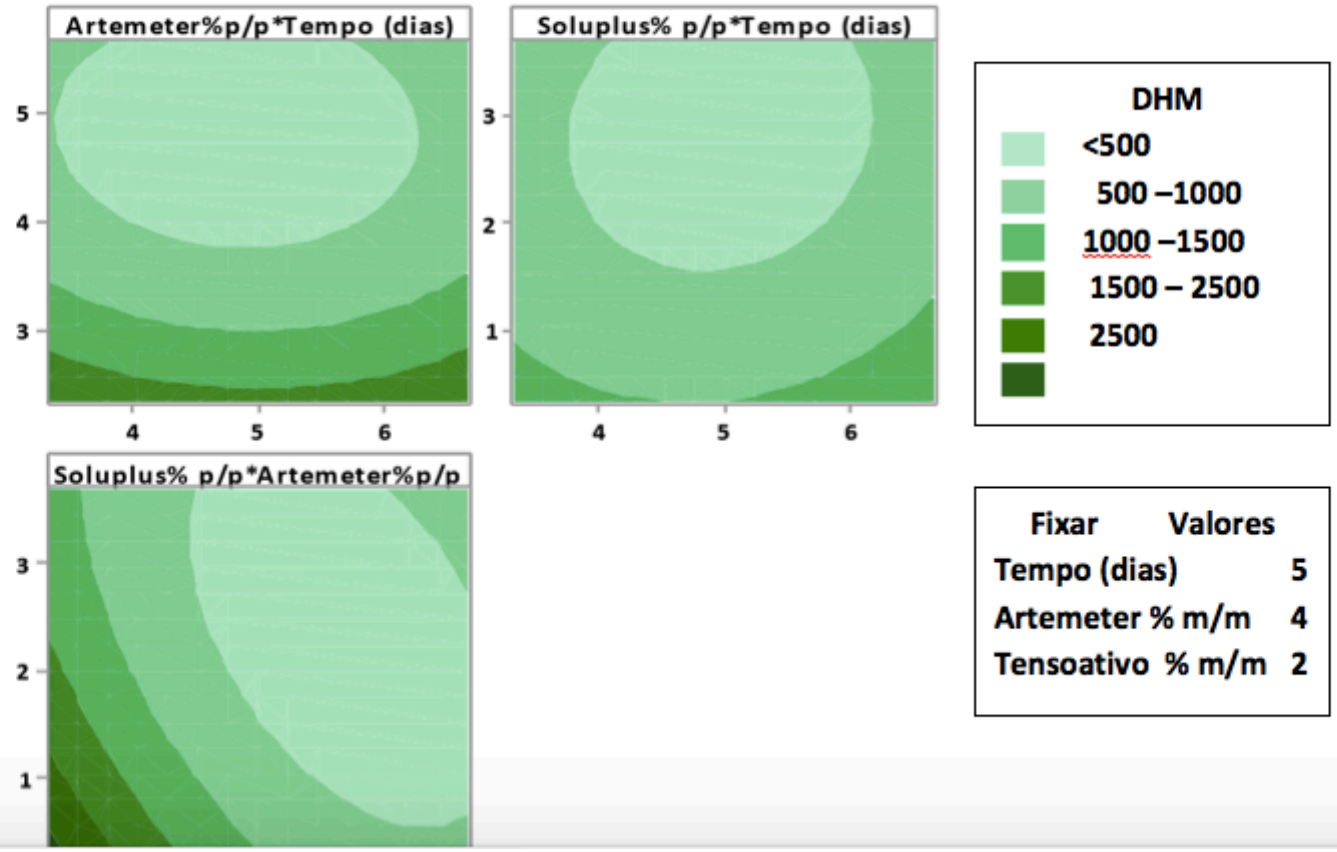
Nome ou Razão Social: UNIVERSIDADE DE SÃO PAULO - USP

Depositante 2 de 2

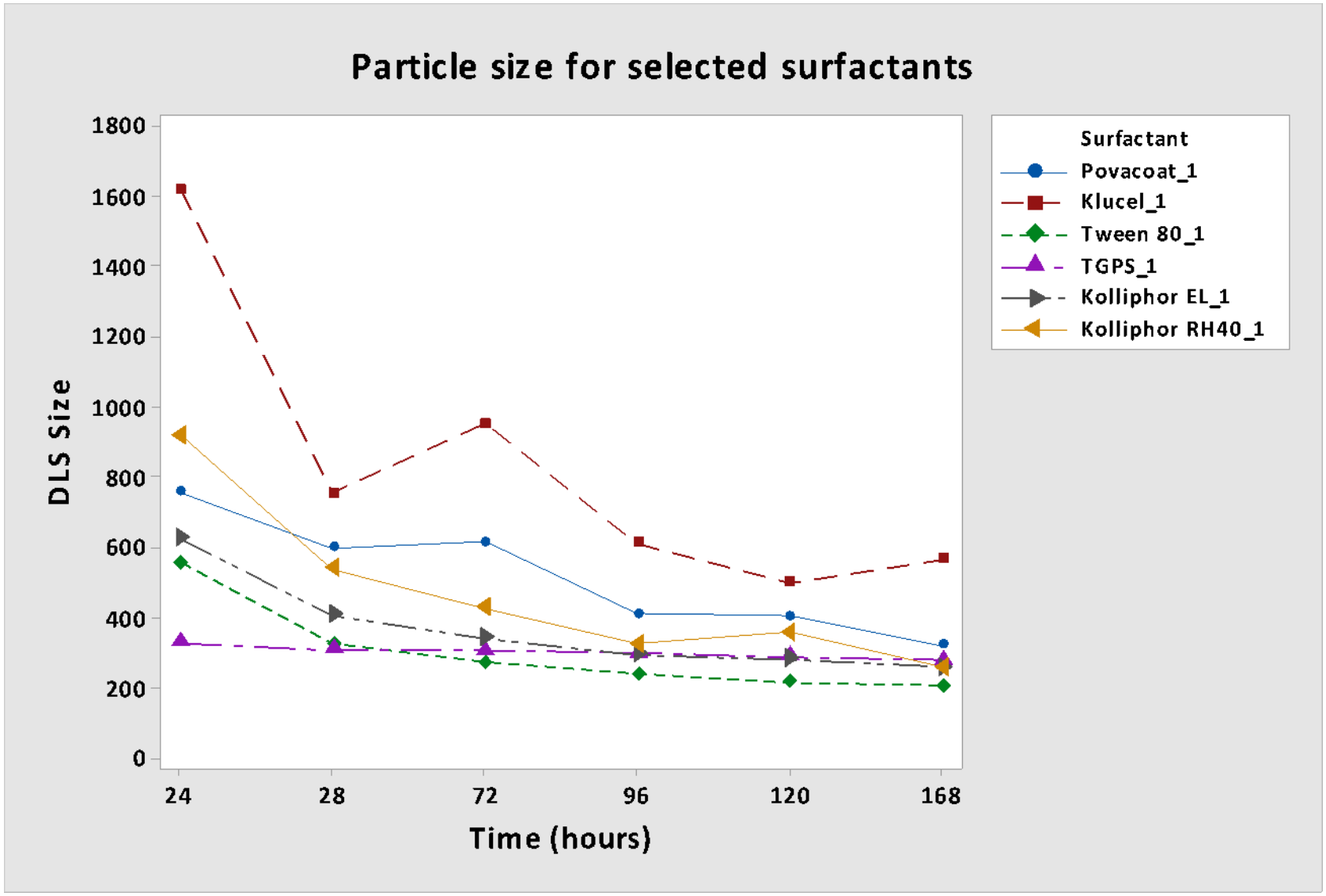
Nome ou Razão Social: FUNDAÇÃO PARA O REMÉDIO POPULAR - FURP

Tipo de Pessoa: Pessoa Jurídica

Figura 15. Gráficos de contorno relativo à da avaliação do diâmetro hidrodinâmico médio de partícula de nanocristais de artemeter contendo as seguintes variáveis: tempo de moagem (dias), concentração de artemeter (%m/m) e concentração do soluplus® (%m/m).



Nanocristais de dapsona para o tratamento de Hanseníase: preparação e caracterização físico-química


Particle size for selected surfactants
DLS Size
1800
1600
1400
1200
1000
800
600
400
200
0
24
28
72
96
120
168
Time (hours)
Surfactant
Povacoat_1
Klucel_1
Tween 80_1
TGPS_1
Kolliphor EL_1
Kolliphor RH40_1

Lipid nanosystem for the treatment of neglected diseases

Profa. Assoc. Nádia Bou-Chacra

Hindawi
BioMed Research International
Volume 2017, Article ID 9781603, 11 pages
https://doi.org/10.1155/2017/9781603

BR 102017021294

PCT 2018050364

Research Article

Buparvaquone Nanostructured Lipid Carrier: Development of an Affordable Delivery System for the Treatment of Leishmaniases

Lis Marie Monteiro,[1] Raimar Löbenberg,[2] Paulo Cesar Cotrim,[3] Gabriel Lima Barros de Araujo,[1] and Nádia Bou-Chacra[1]

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BR1020180762494

ELSEVIER

Colloids and Surfaces A: Physicochemical and Engineering Aspects

Volume 597, 20 July 2020, 124755

Cationic rifampicin nanoemulsion for the treatment of ocular tuberculosis

Mirla Anali Bazán Henostroza [a], Katherine Jasmine Curo Melo [a], Megumi Nishitani Yukuyama [a], Raimar Löbenberg [b], Nádia Araci Bou-Chacra [a]

https://doi.org/10.1016/j.colsurfa.2020.124755

Abstract

Ocular infection caused by *Mycobacterium tuberculosis* affected an estimated 0.1–0.2 million people in the year 2018 worldwide and may result in irreversible loss of vision if not treated properly. Despite this significant figure, the only therapy used to date is the oral administration of anti-tuberculosis drugs substances, mainly rifampicin (Rif), which presents severe adverse effects. Besides, the blood-retinal barrier (BRB) impairs the drug substance bioavailability into the eye. Thus, it is

Colloids and Surfaces B: Biointerfaces
Volume 193, September 2020, 111097

A new medium-throughput screening design approach for the development of hydroxymethylnitrofurazone (NFOH) nanostructured lipid carrier for treating leishmaniasis

Aline de Souza [a] ✉, Megumi Nishitani Yukuyama [a] ✉, Eduardo José Barbosa [a] ✉, Lis Marie Monteiro [a] ✉, Ana Cristina Breithaupt Faloppa [b] ✉, Leandro Augusto Calixto [c] ✉, Gabriel Lima de Barros Araújo [a] ✉, Nikoletta Fotaki [d] ✉, Raimar Löbenberg [e] ✉, Nádia Araci Bou-Chacra [a] ✉

Polymeric nanoparticle for the treatment of neglected diseases

Profa. Assoc. Nádia Bou-Chacra

International Journal of Antimicrobial Agents
Volume 50, Issue 1, July 2017, Pages 88-92

BR1020140079238

Short Communication

Targeting *Leishmania amazonensis* amastigotes through macrophage internalisation of a hydroxymethylnitrofurazone nanostructured polymeric system

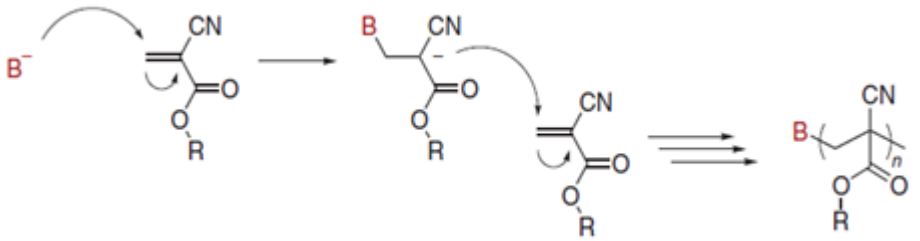
Lis Marie Monteiro [a], Raimar Löbenberg [b], Elizabeth Igne Ferreira [a], Paulo Cesar Cotrim [c], Edite Kanashiro [c], Mussya Rocha [c], Man Chin Chung [d], Nadia Bou-Chacra [a]

Show more

https://doi.org/10.1016/j.ijantimicag.2017.01.033

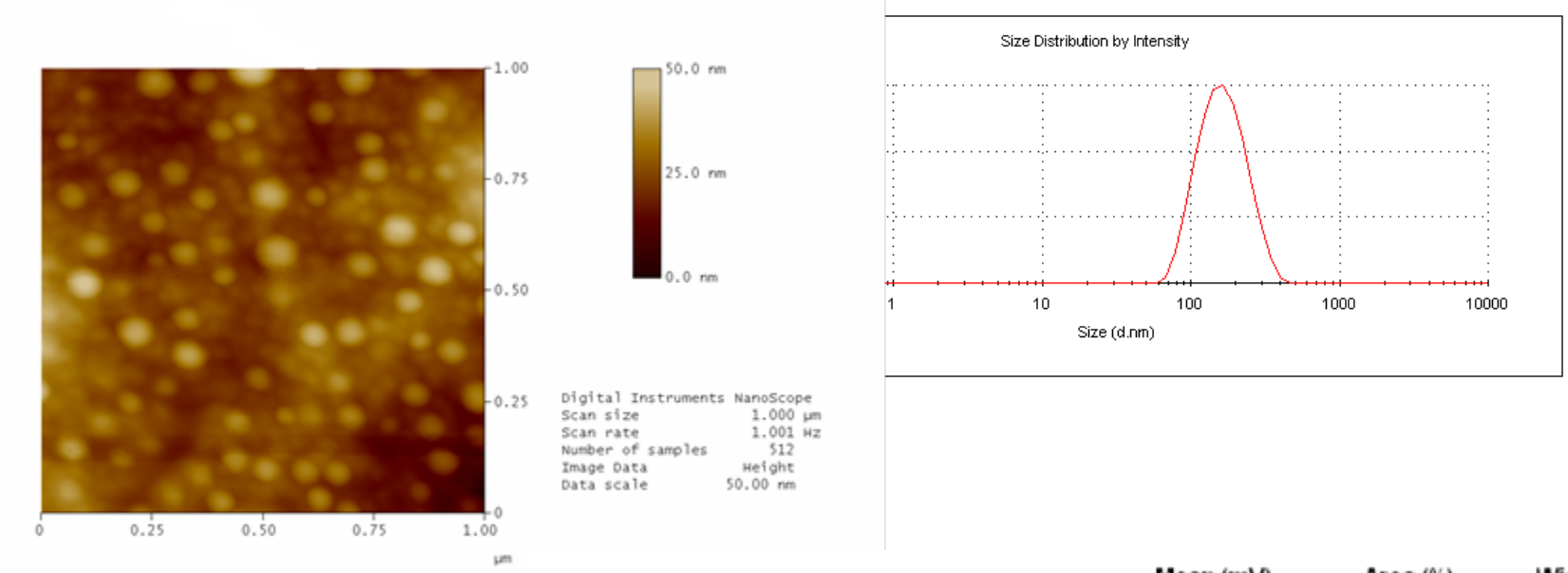
PBCA nanoparticles

- PBCA emulsion polymerization first introduced by Couvreur in 1979;
- Most frequently used method to obtain poly butylcyanoacrilate nanoparticles;
- The polymerization initiated by hydroxyl ions of water and polymer elongation occurs by anionic polymerization mechanism;
- Size usually ranged from 50 to 300 nm;
- Promising method for nanoparticle development for drug targeting to macrophages.



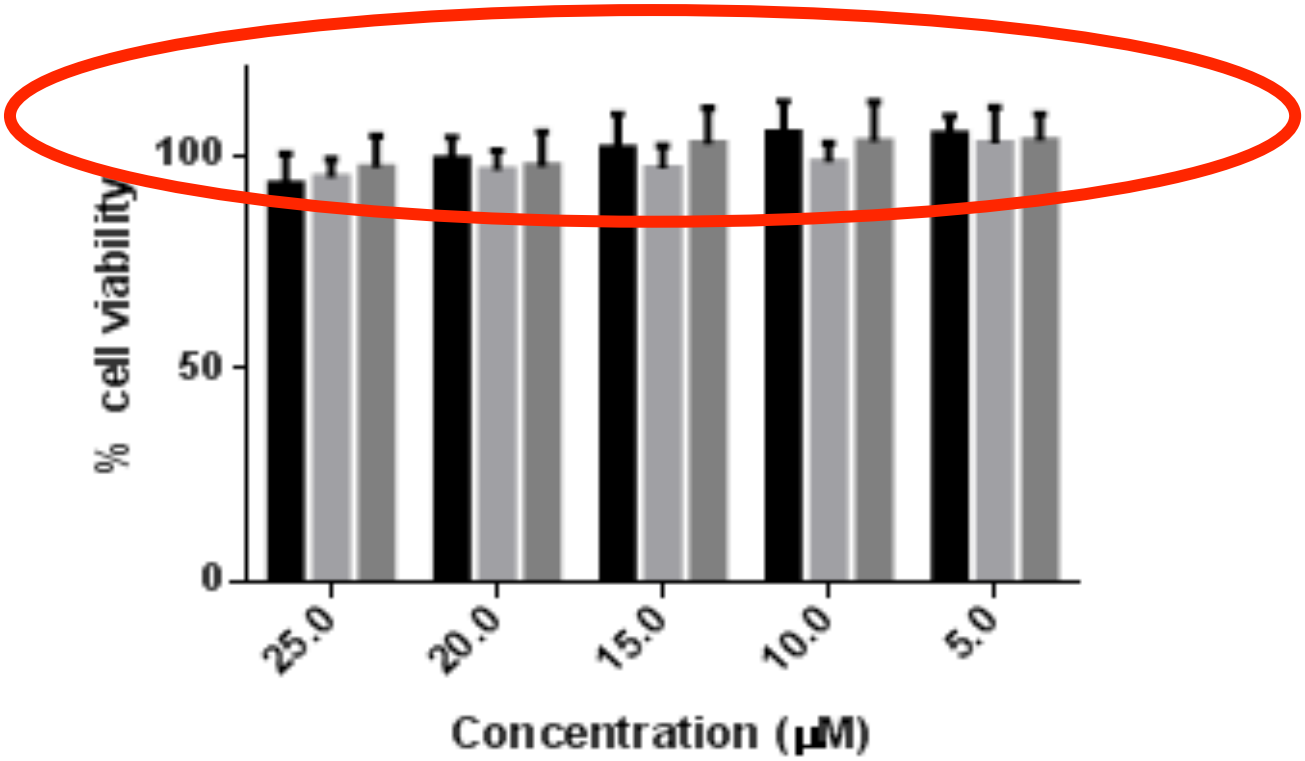
PS, PDI and ZP

		Diam. (nm)	% Intensity	Width (nm)
Z-Average (d.nm):	151,5			
PdI:	0,104	Peak 1:	170,9	100,0	61,97
Intercept:	0,942	Peak 2:	0,000	0,0	0,000
Result quality :	Good	Peak 3:	0,000	0,0	0,000



		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV):	-10,1			
Zeta Deviation (mV):	6,49	Peak 1:	-10,1	100,0	6,49
Conductivity (mS/cm):	0,178	Peak 2:	0,00	0,0	0,00
Result quality :	Good	Peak 3:	0,00	0,0	0,00

Macrophage cytotoxicity assay

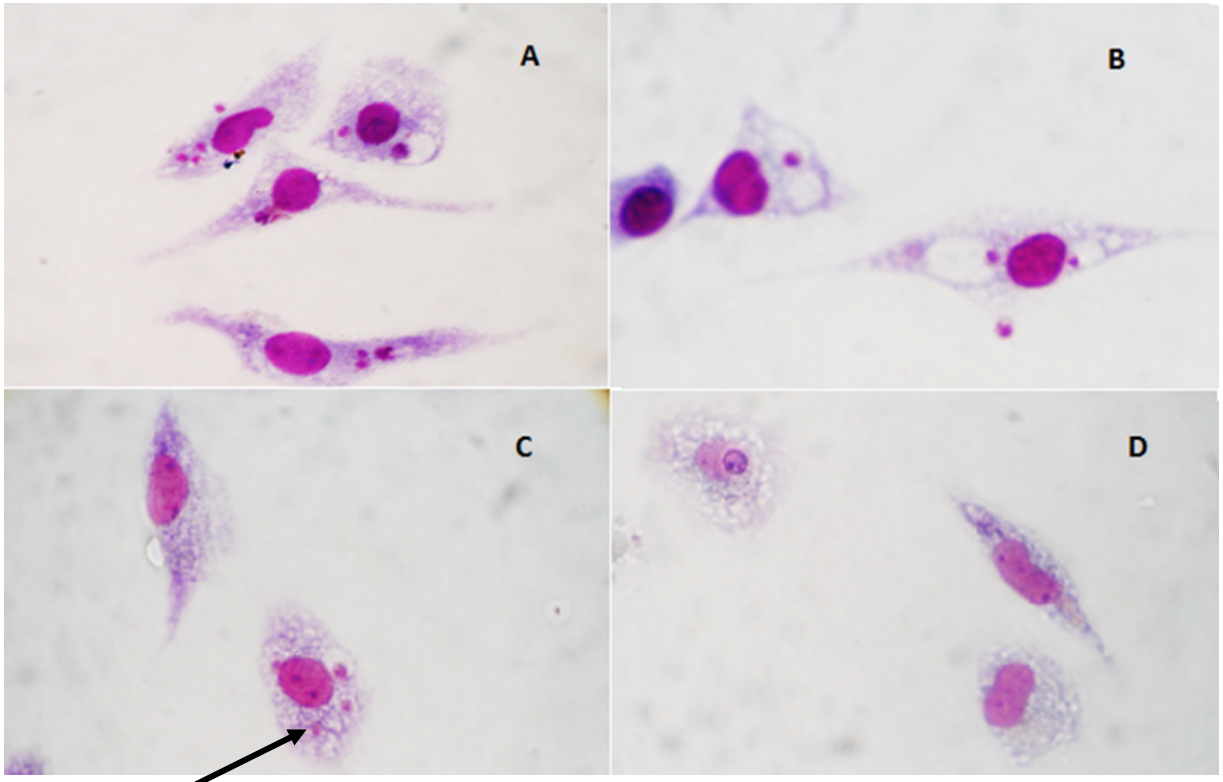


Free hydroxymethylnitrofurazone (NFOH) ( ); Nanostructured NFOH ( ); Unloaded nanoparticles ( ).

No statistically significant difference was observed

Leishmanicidal activity evaluation against *L. amazonensis* amastigotes

Infected macrophage



Free NFOH

Polymeric nanoparticles (blank)

Nanostructured NFOH

Parasite

Concentration: 15 µM

Leishmanicidal Activity

Table 1. Inhibition leishmanicidal concentration (IC_{50}) of blank nanoparticles, nanostructured NFOH and free NFOH.

IC_{50}	Polymeric Nanoparticles (blank)	Nanostructured NFOH	Free NFOH
µM	25.2	0.33	31.2

Nanostructured NFOH activity 94.5-fold higher than the free NFOH

Encapsulation efficiency: 64.4 ± 0.7% (w/w)