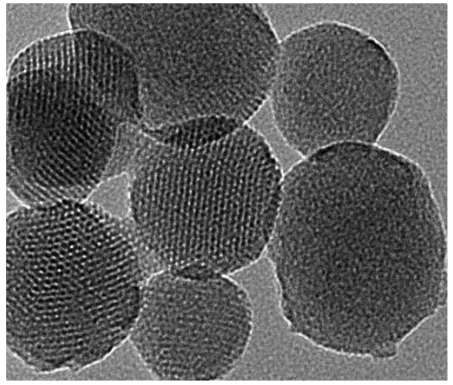
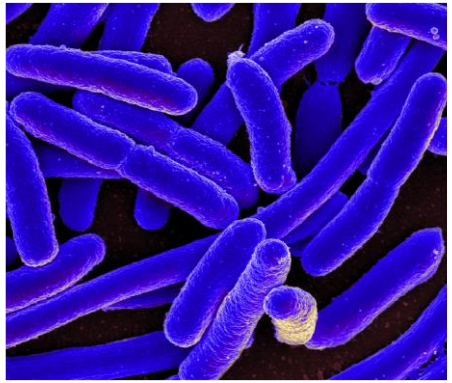
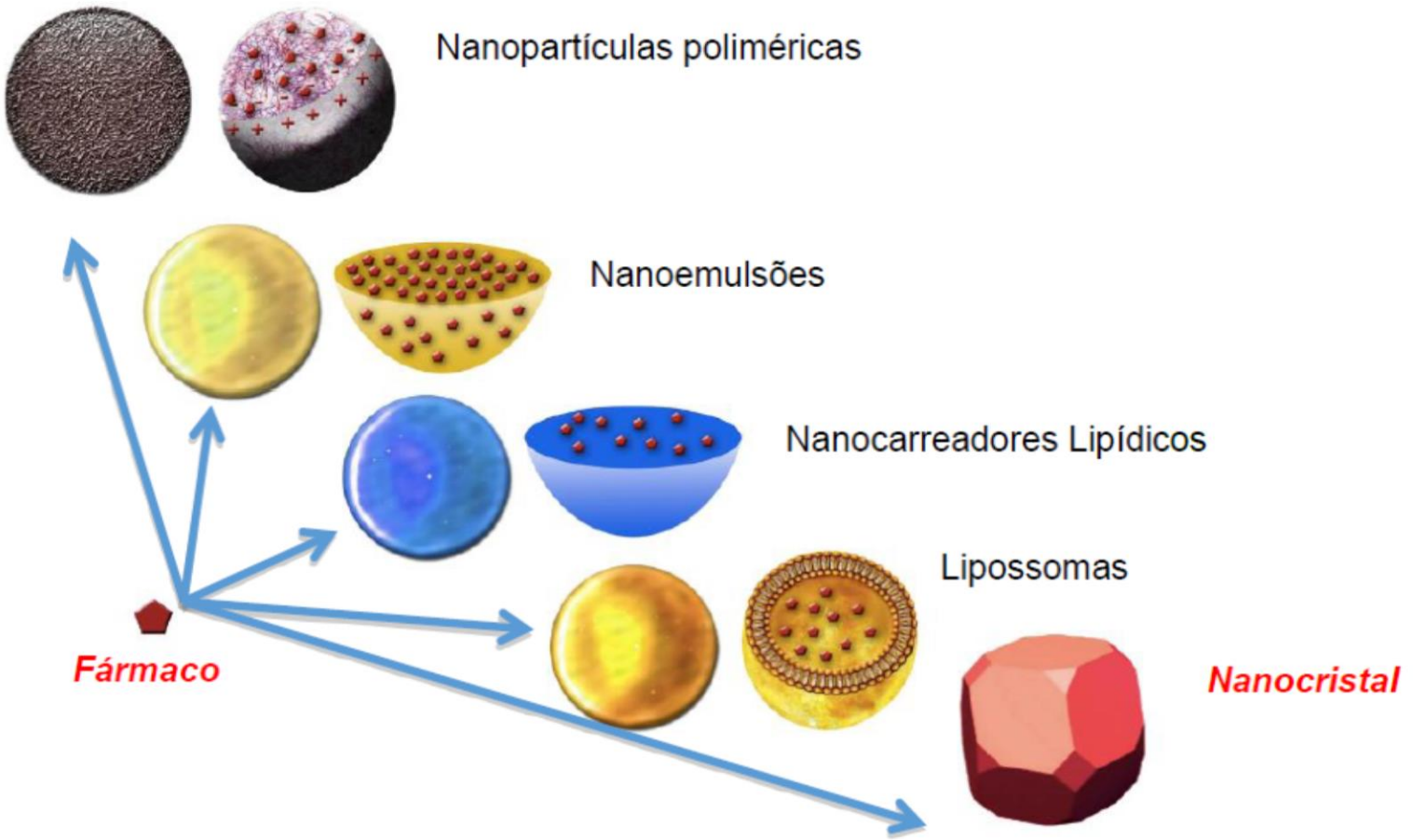
Ferramentas Analíticas do Desenvolvimento de Sistemas Nano-Estruturados

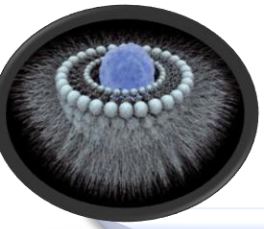
Prof. Dr. Gabriel Lima Barros de Araujo
Faculdade de Ciências Farmacêuticas - USP

Nano	Micro	Macro
		
1-100 nm	2000 nm (E.coli)	5 milhões nm
Nanotecnologia		

Nanotecnologia Farmacêutica (< 1000 nm)



Fonte: Compri, Jéssica de Cássia Zaghi. Nanocristais de ácido orótico: preparação e caracterização físico-química [dissertação]. São Paulo: Universidade de São Paulo, Faculdade de Ciências Farmacêuticas; 2015 [citado 2019-09-05]. doi:10.11606/D.9.2016.tde-30032016-143022.



1995

Doxil®

Cloridrato de Doxirrubicina

Lipossomo Metoxipeguilado

FDA-AIDS-related KS, multiple myeloma, ovarian cancer (IV)

2002

Rapamune®

Immunosuppressant (oral)

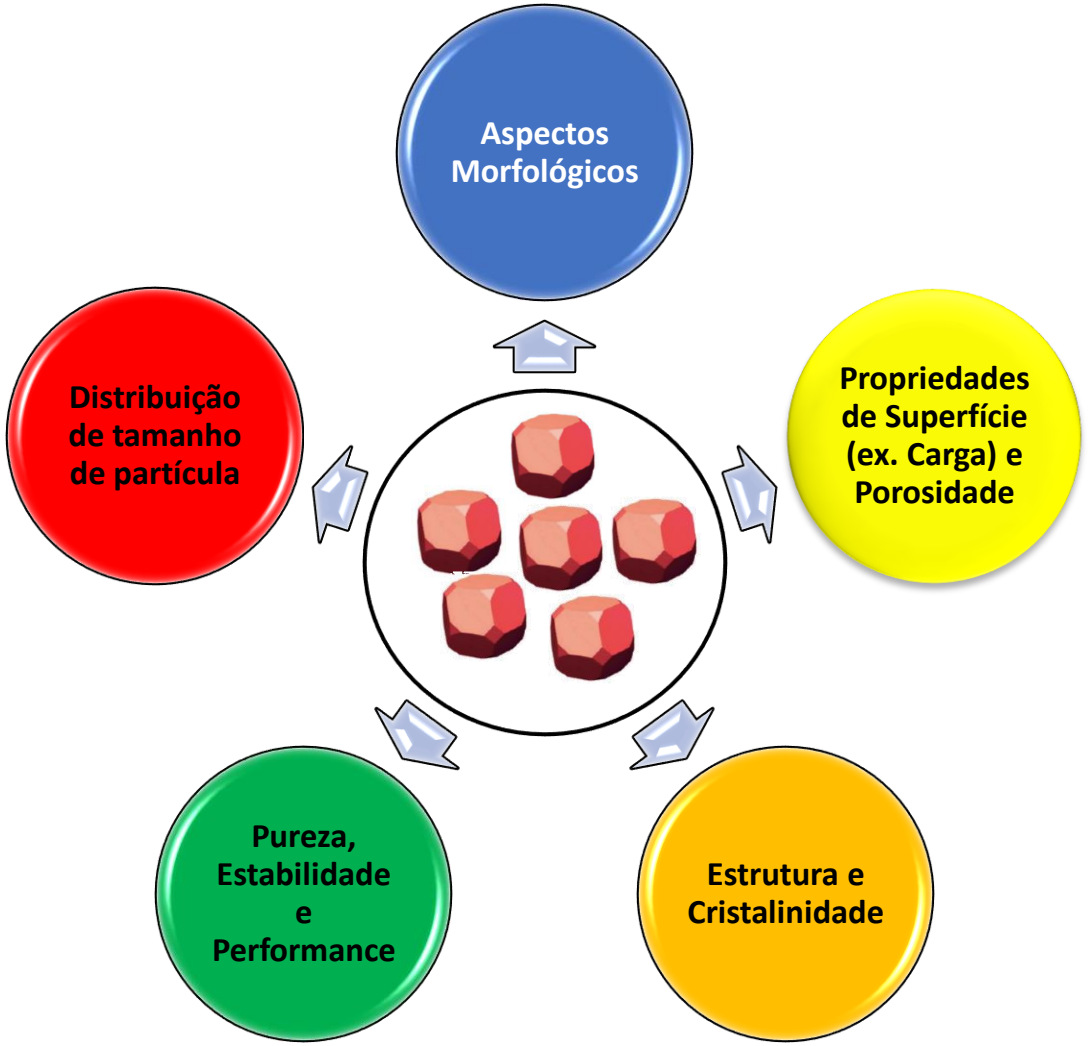
Rapamycin (sirolimus) as nanocrystals formulated in tablets

2013 **NanoTherm®**

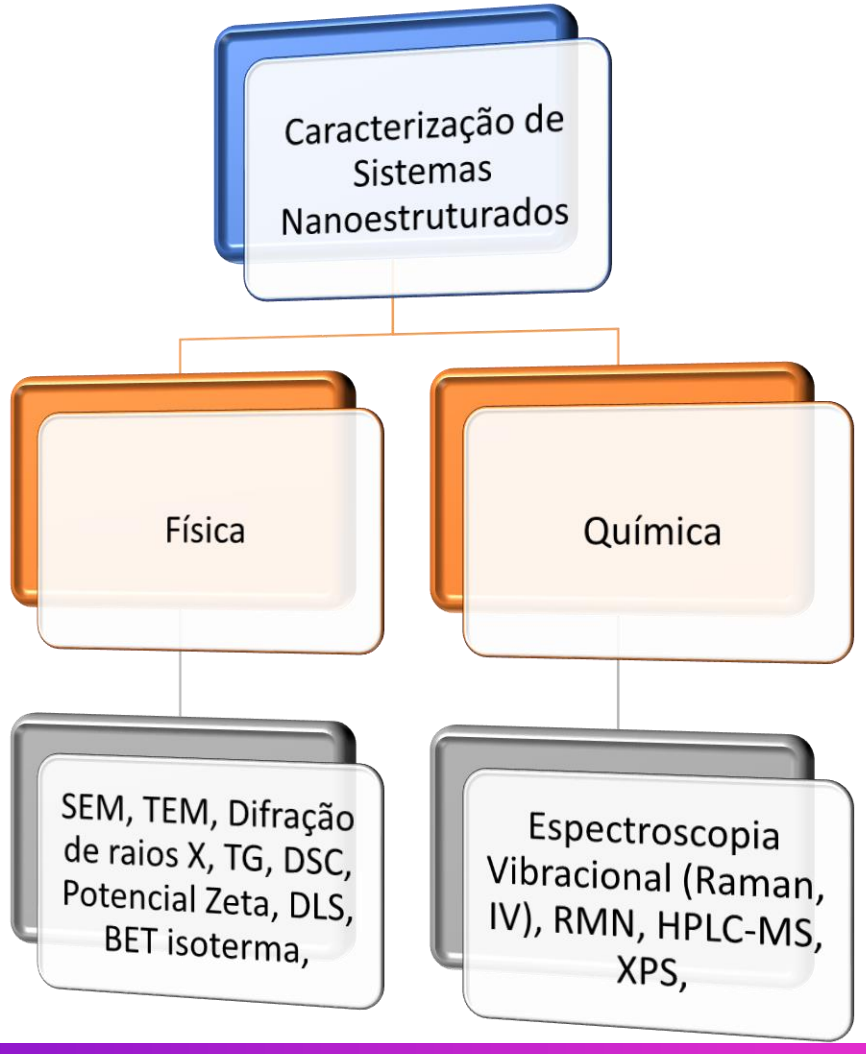
Aminosilane-coated superparamagnetic iron oxide 15 nm nanoparticles

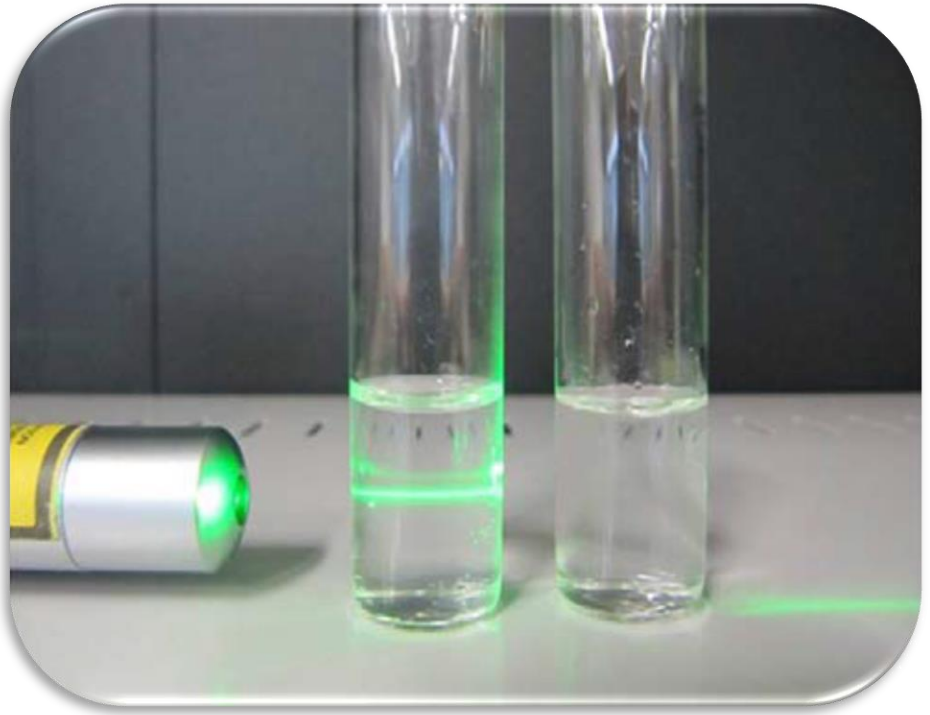
Product	Comments
Abraxane®	Nanoparticles (130 nm) formed by albumin with conjugated paclitaxel (2005)
Gendicine®	Recombinant adenovirus expressing wildtype-p53 (rAd-p53) 2003
Opaxio®	Paclitaxel covalently linked to solid nanoparticles composed of polyglutamate (Glioblastoma, 2012)

Ferramentas Analíticas do Desenvolvimento de Sistemas Nano-Estruturados



Ferramentas Analíticas do Desenvolvimento de Sistemas Nano-Estruturados





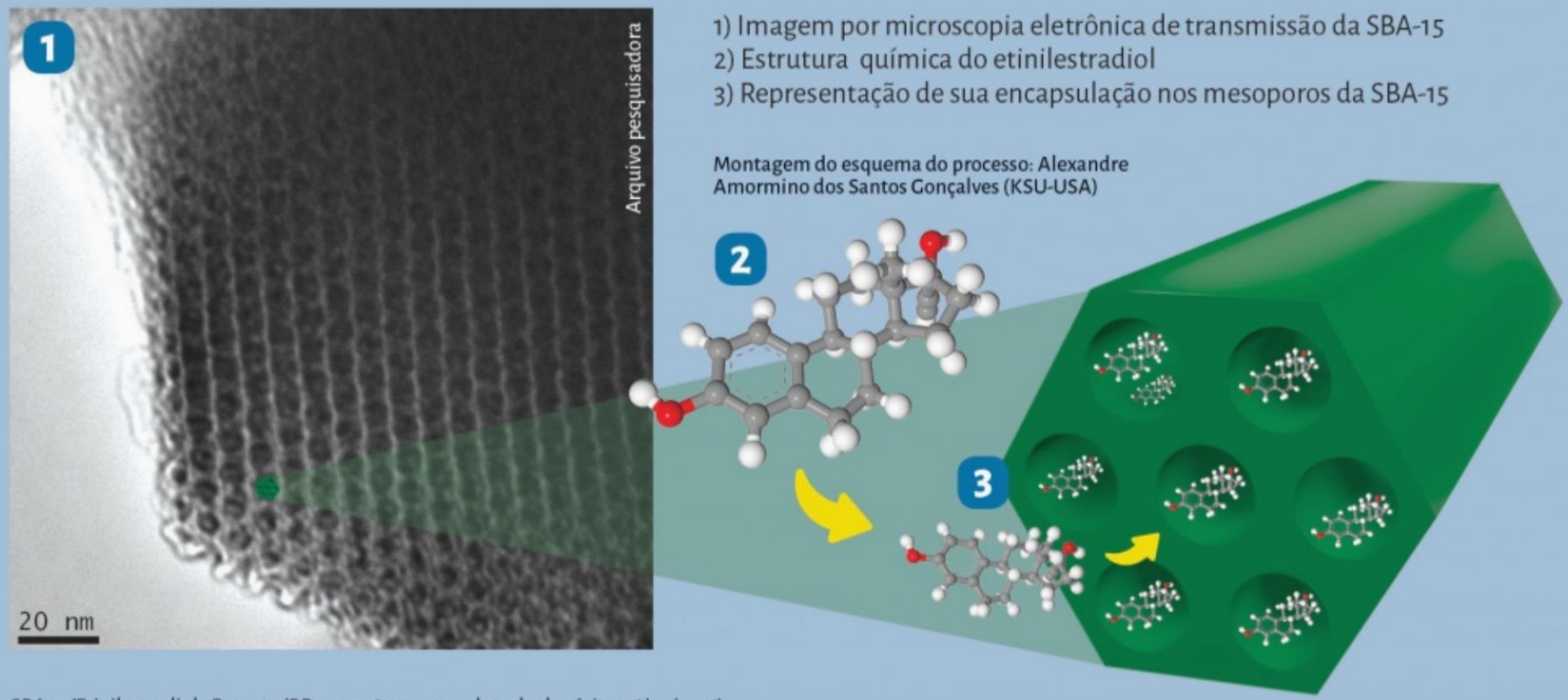
Micelas poliméricas 20 e 50 nm
= > 30% fármaco w/w

Fonte: Annales Pharmaceutiques Françaises (2011) ***69, 116—123***

Tyndall effect

Fonte: http://www.epicphysics.com/wp-content/uploads/2012/01/the-tyndall-effect.jpg

Esquema do processo de encapsulação

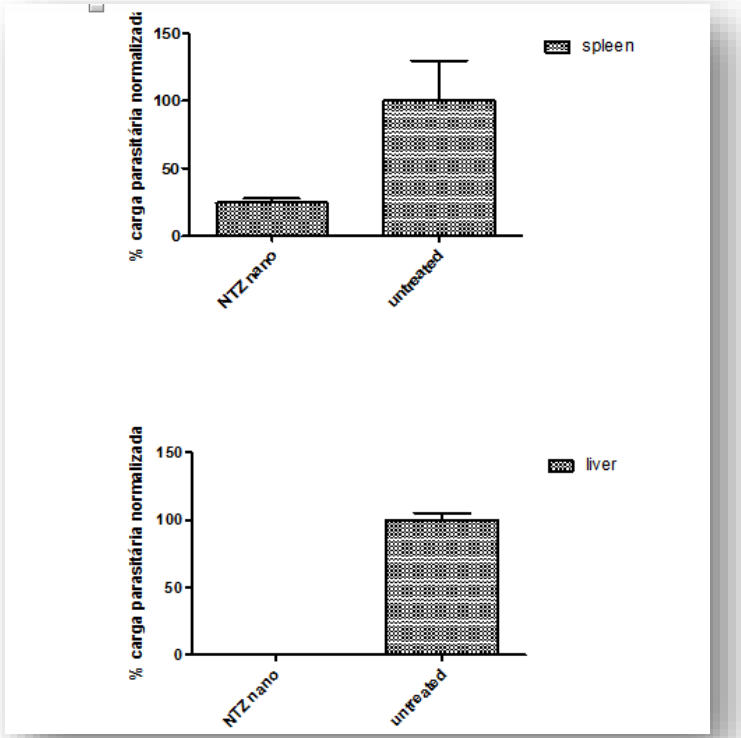


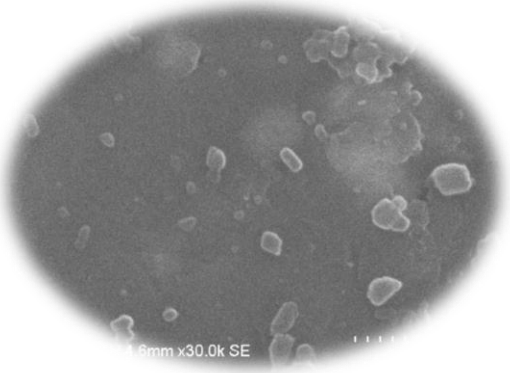
SBA-15/Etinilestradiol - Patente (BR 10 2016 0214459 - data do depósito: 16/09/2016)

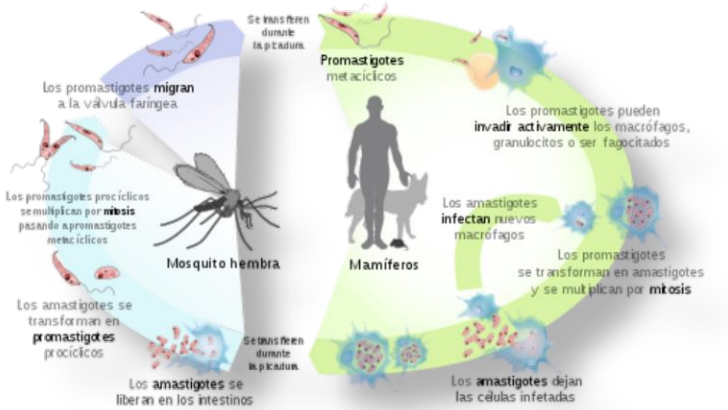
Fonte: https://www.unifesp.br/reitoria/dci/edicao-atual-entreteses/item/3159-silica-mesoporosa-suporte-promissor-para-liberacao-de-compostos

MERCURI, Lucildes P.; CARVALHO, Luciana V.; LIMA, Flávia A.; QUAYLE, Carolina; FANTINI, Márcia C. A.; TANAKA, Gabriela S.; CABRERA, Wafa H.; FURTADO, Maria F. D.; TAMBOURGI, Denise V.; MATOS, Jivaldo do R.; JARONIEC, Mietek; SANT'ANNA, Osvaldo A. Ordered mesoporous silica SBA-15: a new effective adjuvant to induce antibody response. Small, [s.l.]: John Wiley & Sons, Inc., v. 2, n. 2, p. 254-256, fev. 2006. Disponível em: <http://onlinelibrary.wiley.com/doi/10.1002/smll.200500274/epdf>. Acesso em: 4 maio 2017.

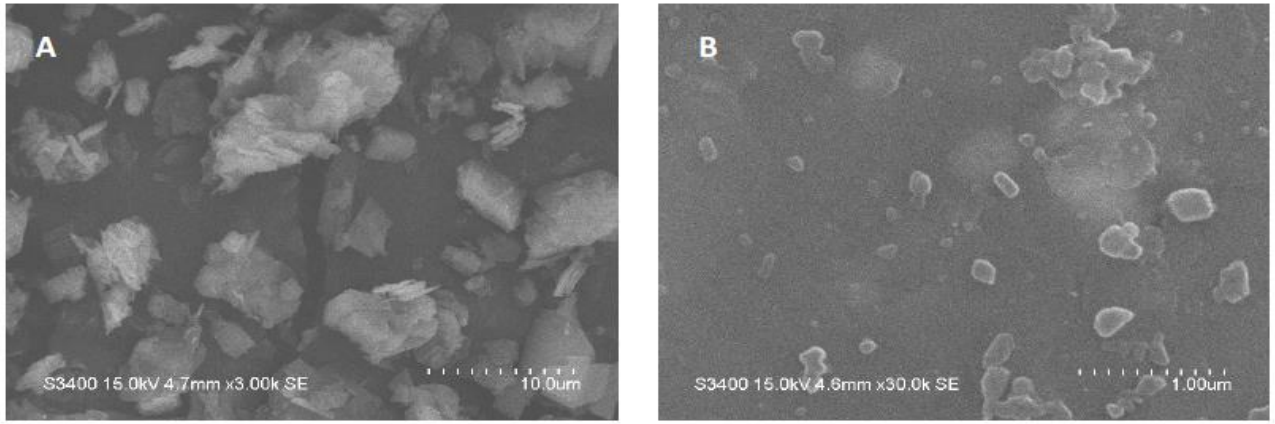
Formulações para doenças negligenciadas



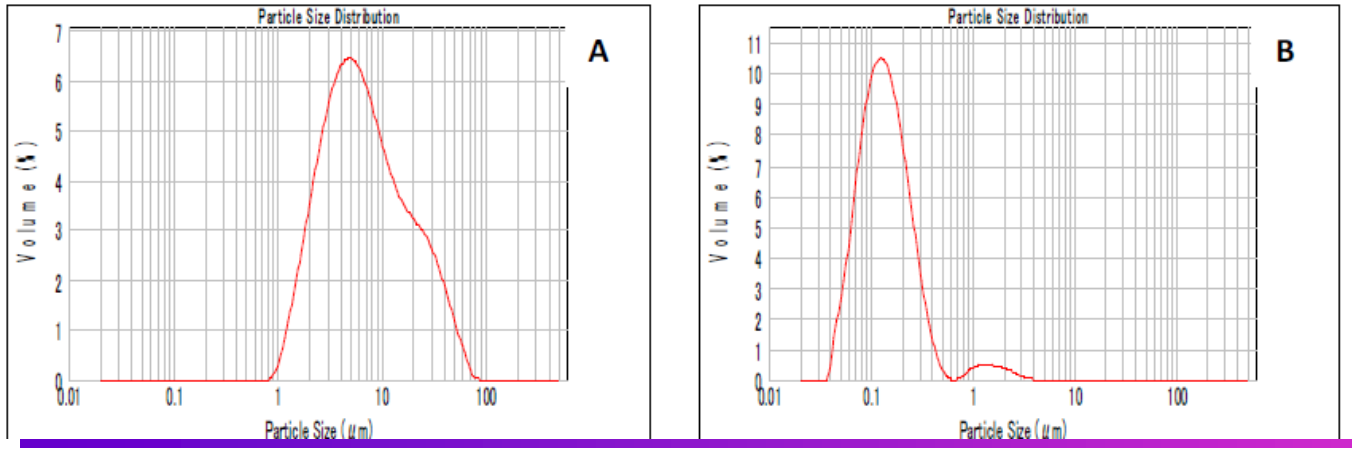




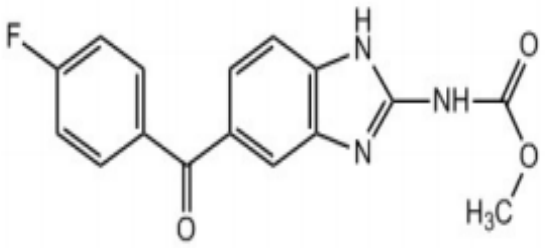
Estudo pré-clínico de hamsteres infectados com *L. infantum* e tratados oralmente com a NTZ-nano a 50 mg/kg por 10 dias consecutivos. A carga parasitária foi avaliada por PCR em tempo real.



Fotomicrograficas de microscopia eletrônica de varredura das partículas de nitazoxanida antes (a) e após a nanopulverização (b).

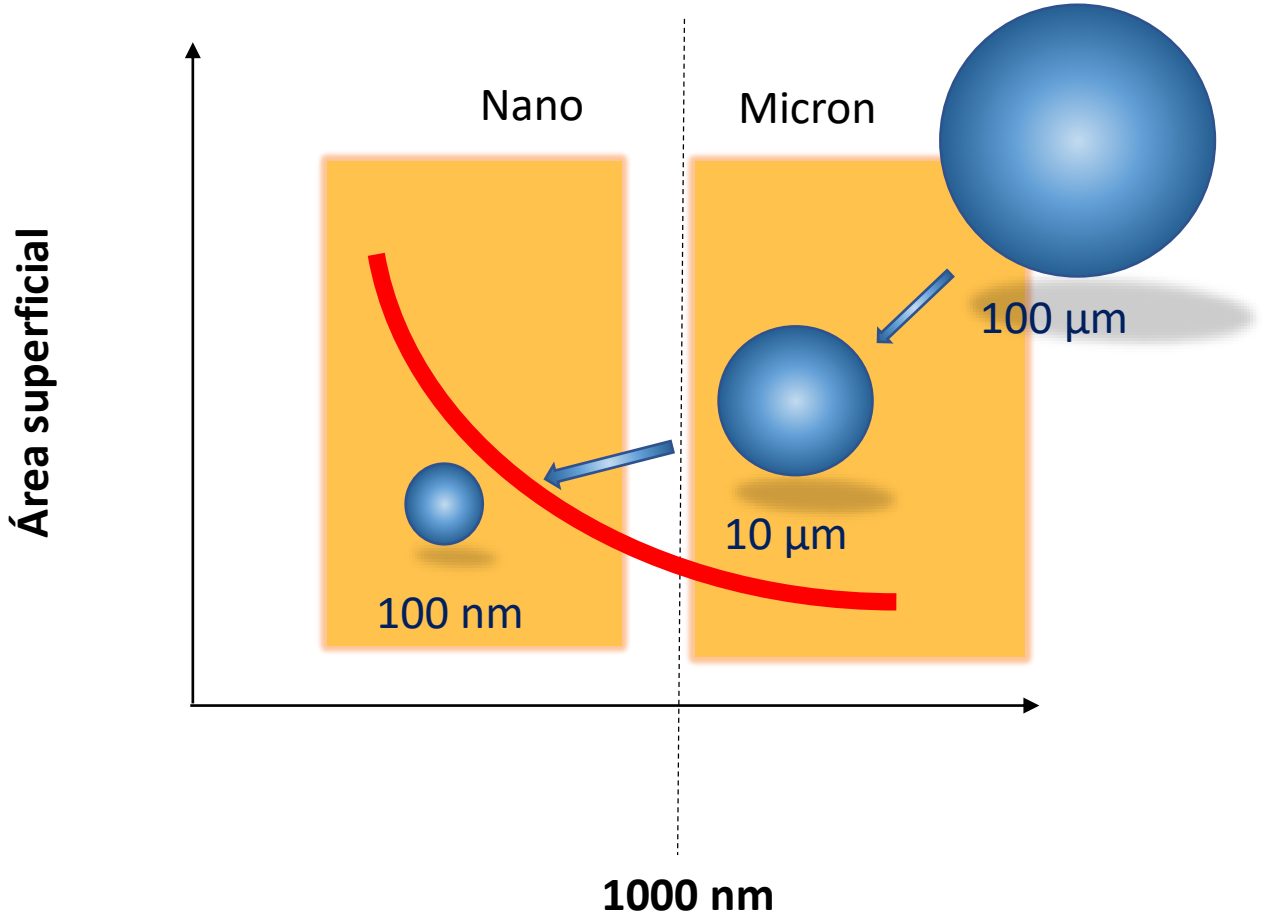


Preparation and Physicochemical Characterization of Flubendazole Nanocrystals



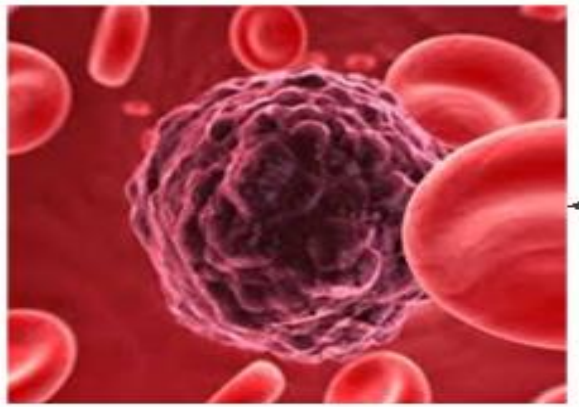
DE ARAUJO, G. L. B.; BOU-CHACRA, NÁDIA A. ; GONÇALVES, DÉBORA S. . Processo de obtenção de formulações nanocristalinas de flubendazol, formulações nanocristalinas de flubendazol e uso. 2018, Brasil.
Patente: Privilégio de Inovação. Número do registro: BR1020180170546, título: "Processo de obtenção de formulações nanocristalinas de flubendazol, formulações nanocristalinas de flubendazol e uso" , Instituição de registro: INPI - Instituto Nacional da Propriedade Industrial. Depósito: 20/08/2018

- Maior área superficial;
- Maior velocidade de saturação;
- Maior velocidade de dissolução;
- ~ 100% ativo.



1. SHEGOKAR, Ranjita; MÜLLER, Rainer H., Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives, International Journal of Pharmaceutics, v. 399, n. 1–2, p. 129–139, 2010.

Propriedades especiais dos nanocristais em células tumorais

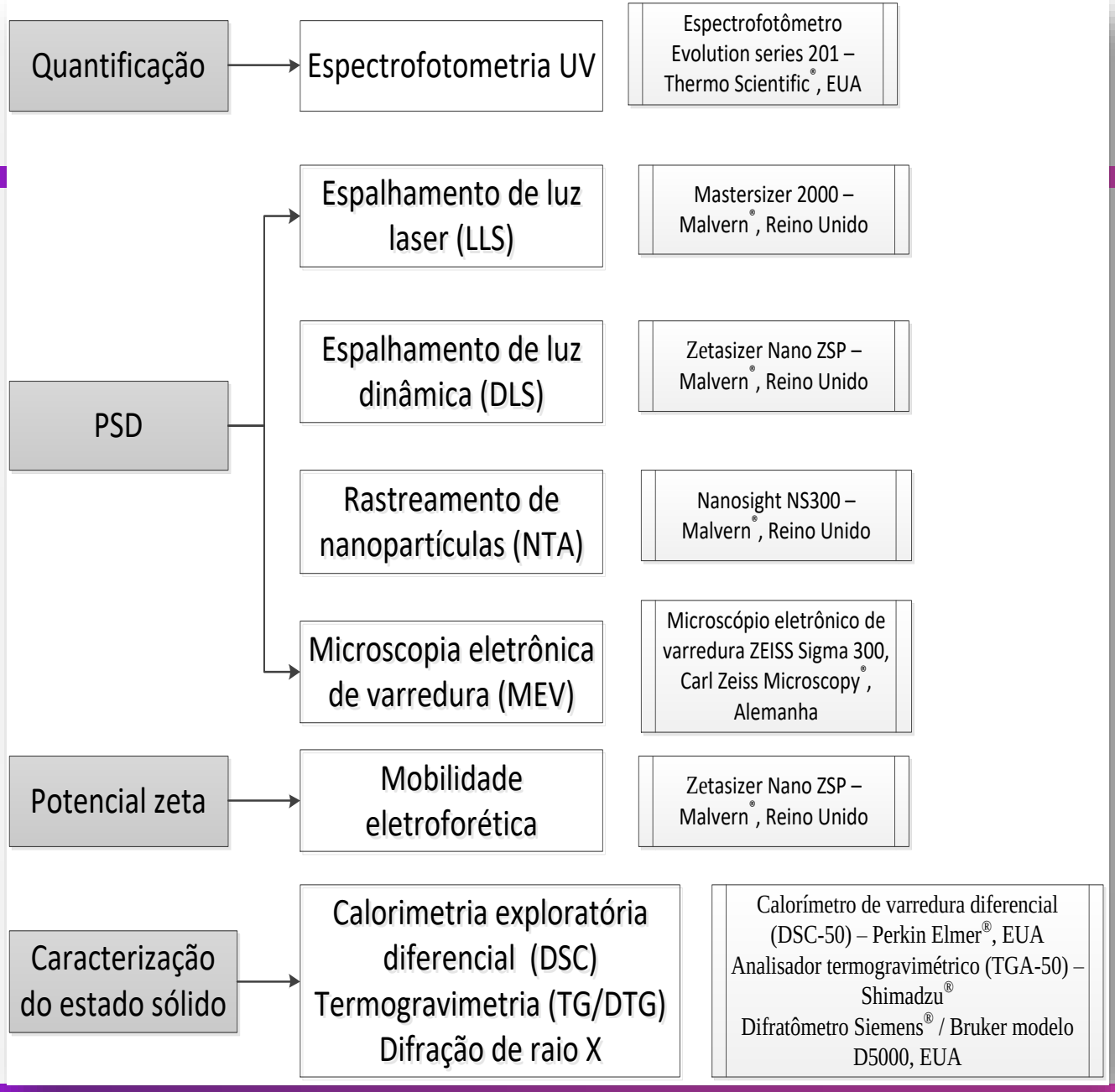


- Maior efetividade
- Melhora na entrega de fármacos
- Retenção/ acúmulo nas células tumorais
- Maior especificidade
- Menor toxicidade

Tamanho reduzido
Geometria partícula
Carga
Característica da superfície

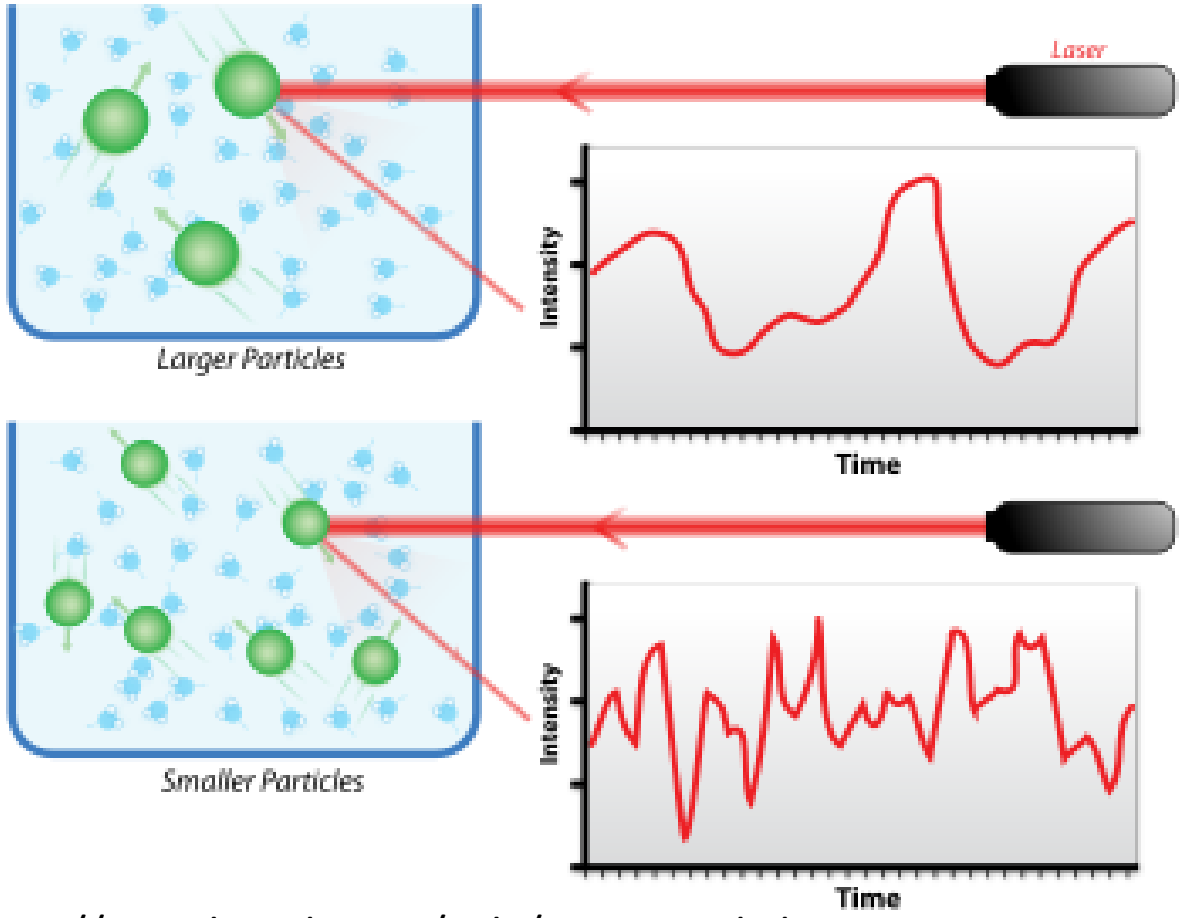
Fonte: Elaborado pelo autor

Caraterização físico-química



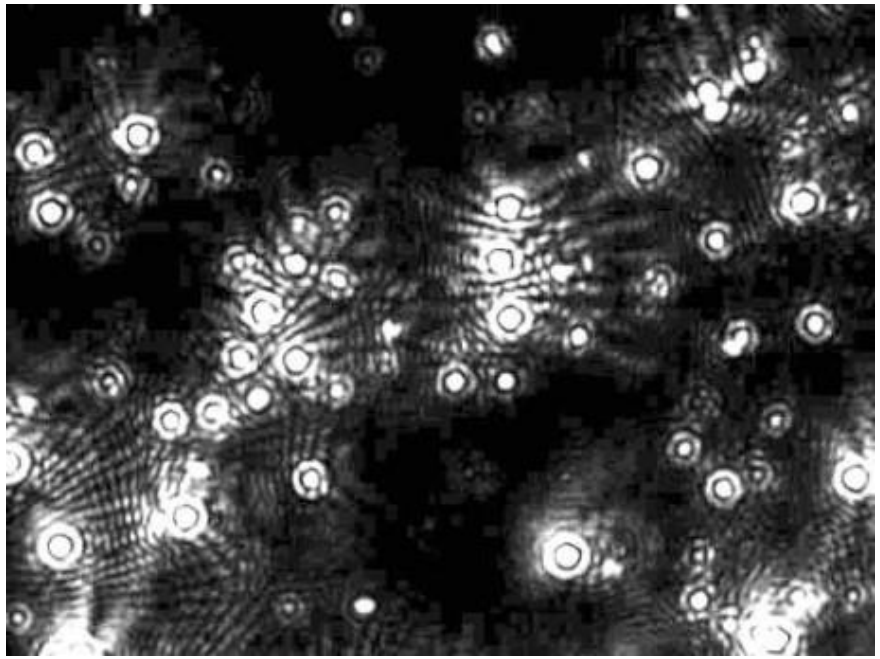
Fonte: Elaborado pelo autor

Dynamic light scattering (Photon correlation spectroscopy)



https://en.wikipedia.org/wiki/Dynamic_light_scattering

Análise de Rastreamento de Nanopartículas (NTA)



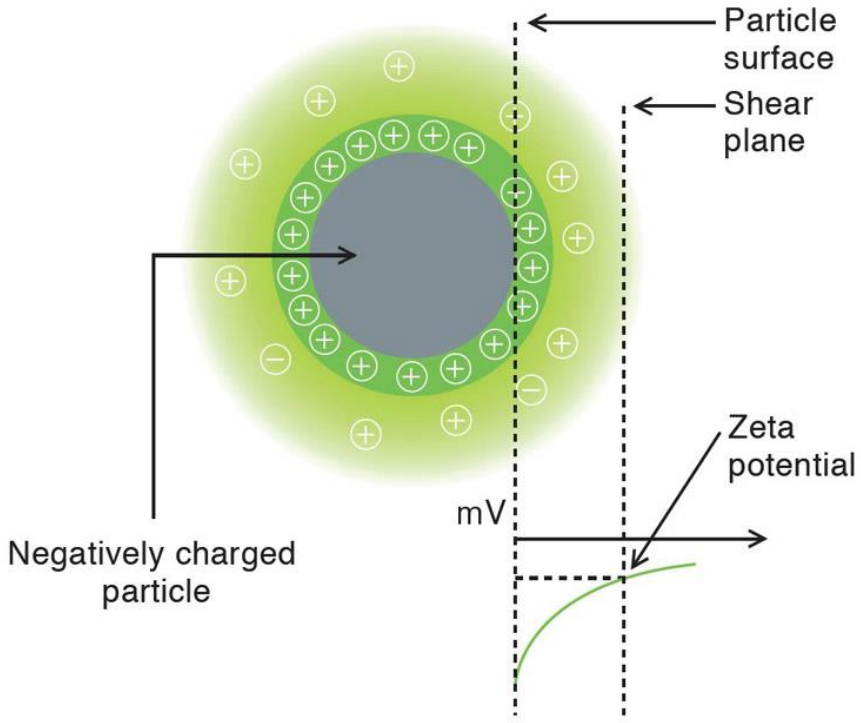
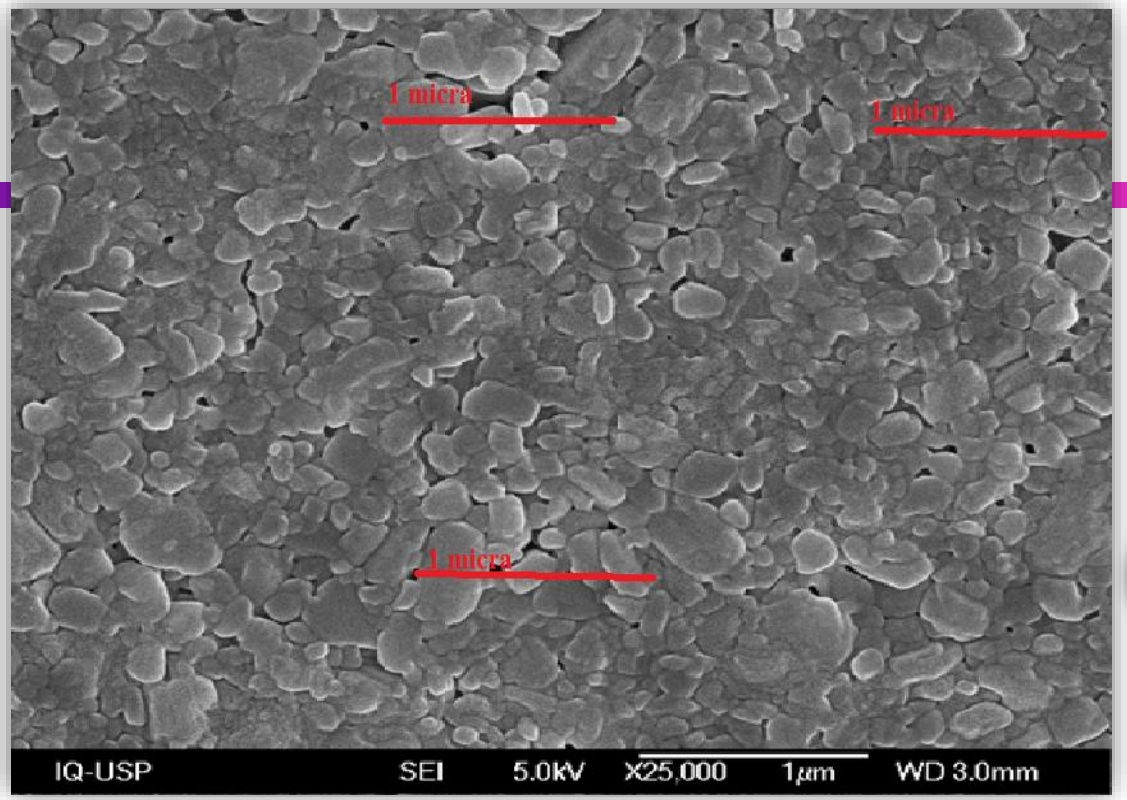
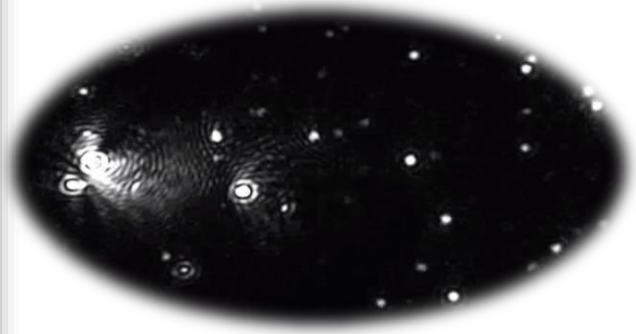


Imagem fonte: http://laser.spbu.ru/images/photos/dzetae1.jpg

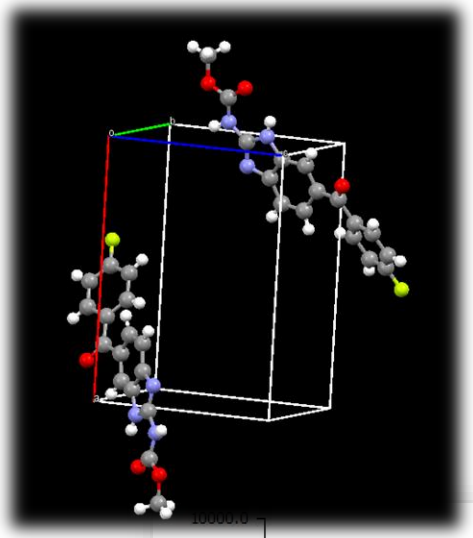
O potencial zeta é uma medida da magnitude da repulsão / atração eletrostática ou de carga entre as partículas e é um dos parâmetros fundamentais conhecidos por afetar a estabilidade.

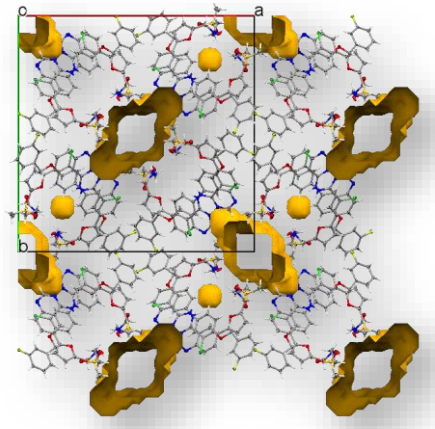
Medida pela relação entre a mobilidade elétrica calculada e o potencial zeta



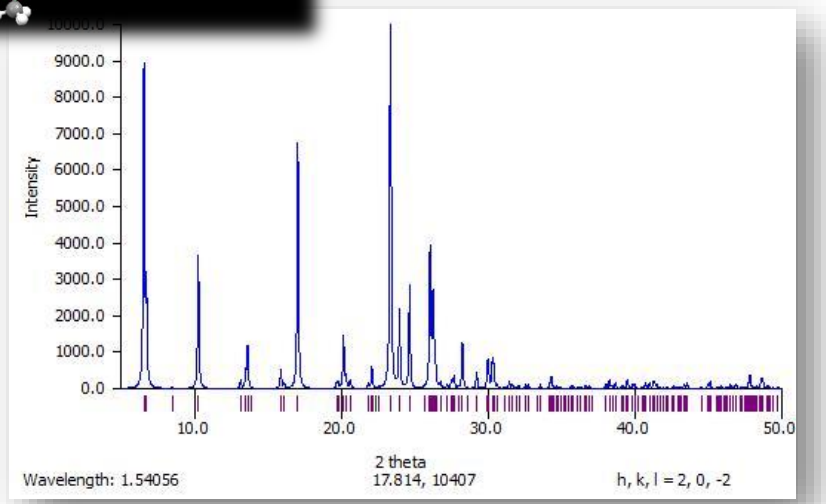


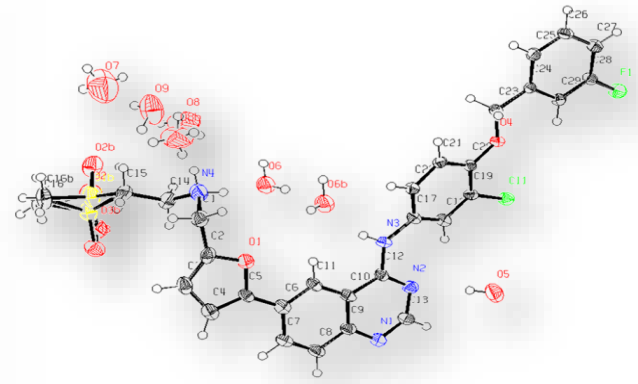
Fórmula	DHM (nm)	IP	PZ (mV)
Nanossuspensão antes da liofilização	253,9 ± 3,0	0,363 ± 0,004	-30,57
Nanossuspensão após a liofilização	278,8 ± 5,6	0,358 ± 0,027	-30,45



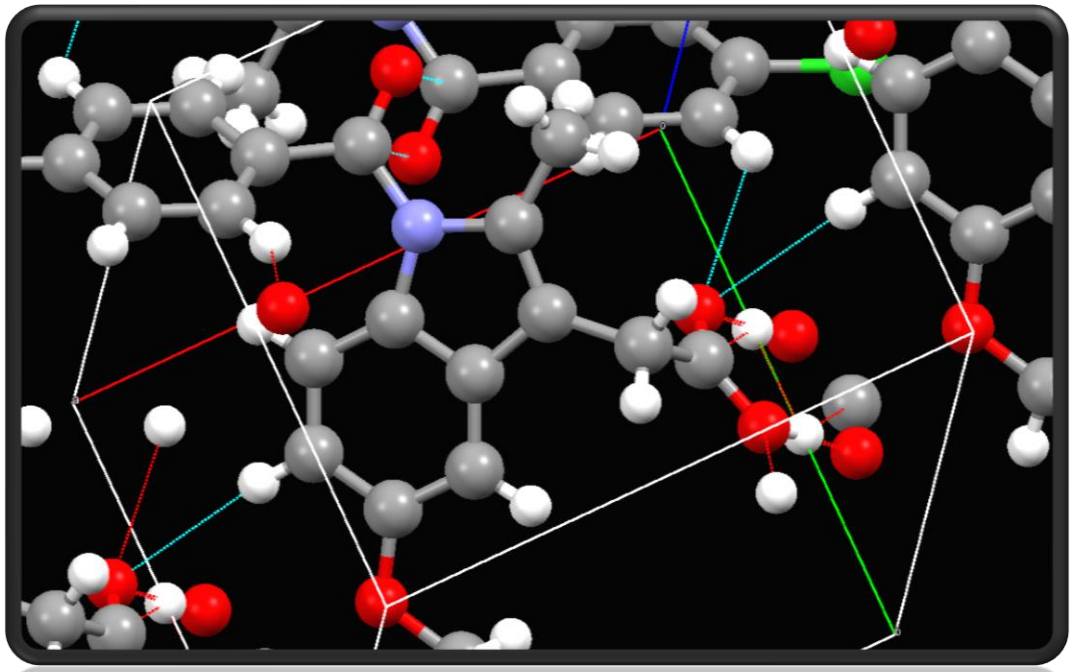


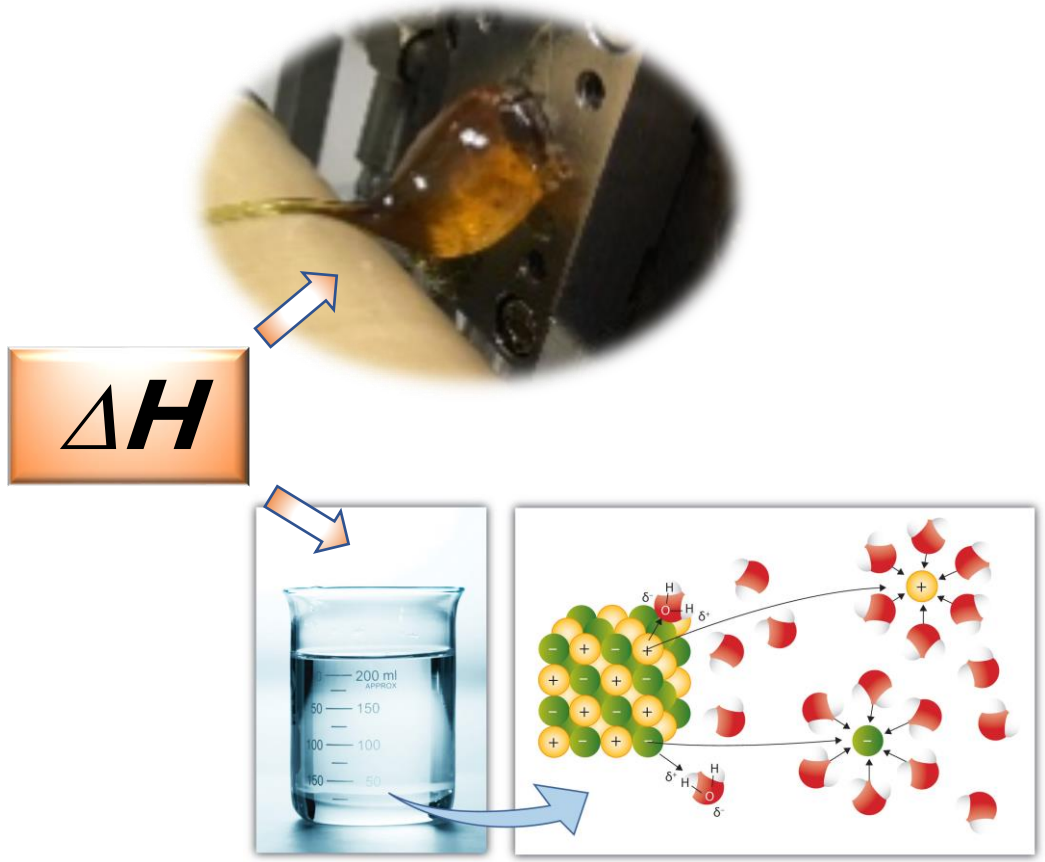
Aspectos estruturais



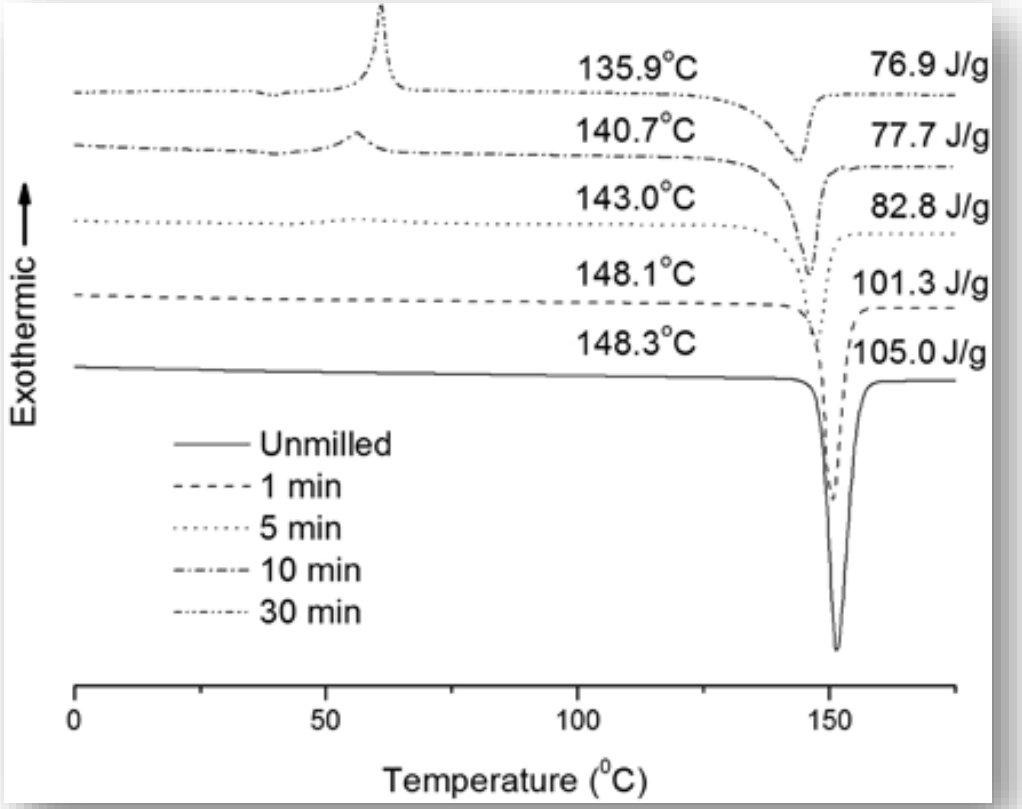


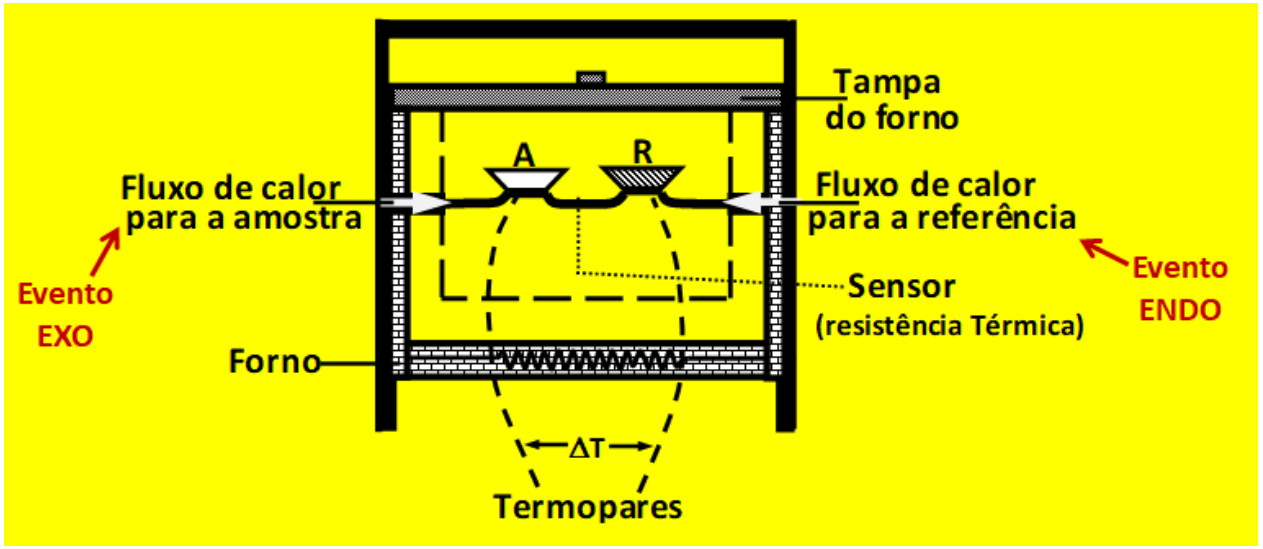
Calorimetria Exploratória Diferencial (DSC): Temperatura de Fusão, Transições de fase, Solubilização





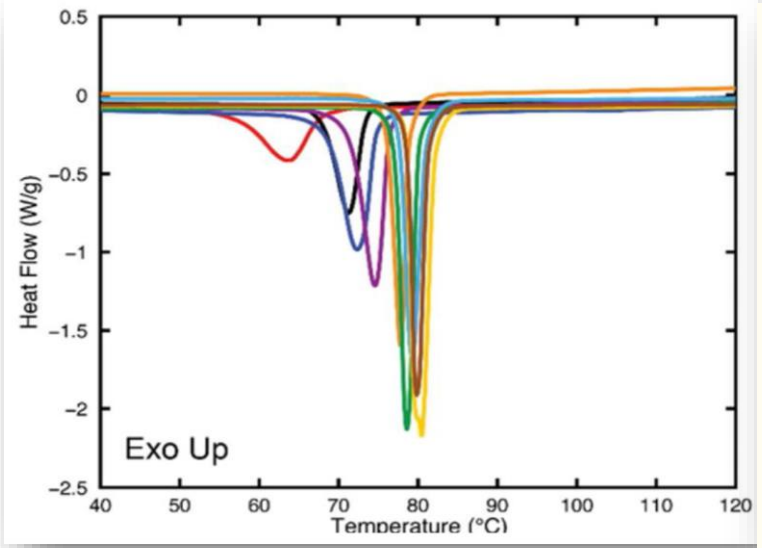
Assessment of milling-induced disorder of two pharmaceutical compounds

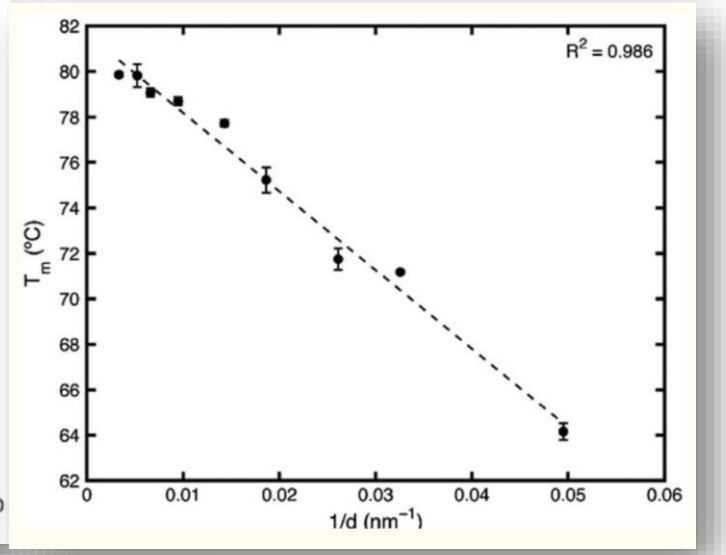




Differential scanning calorimetry results for ketoconazole unmilled and milled with respective *T*m and Δ*H*f.

Assessment of milling-induced disorder of two pharmaceutical compounds, Volume: 100, Issue: 5, Pages: 1793-1804, First published: 16 December 2010, DOI: (10.1002/jps.22415)

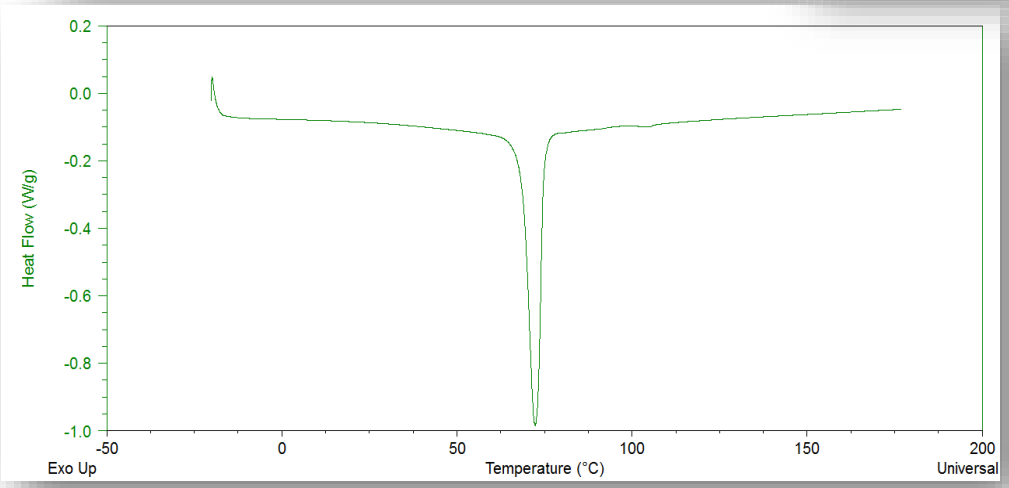




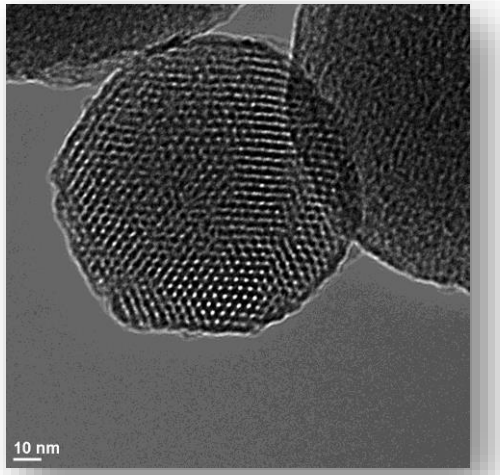
Constant enthalpy-constant surface interaction energy Gibbs-Thomson equation fit to melting points of nanocrystals confined to porous sílica

$$\Delta T_m = T_m - T_m(d) = \frac{4\gamma_{solid-liquid} M T_m}{d\Delta H_{fus}\rho_{solid}} \cos(\theta)$$

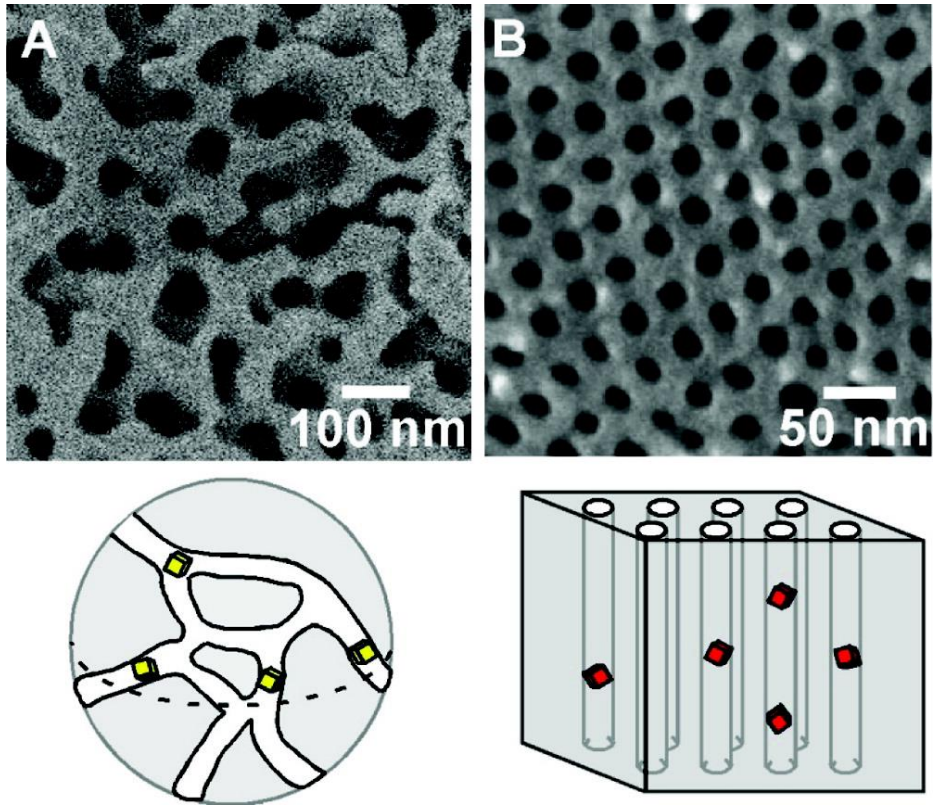
Depression in the melting point that is inversely proportional to the size



Nanocrystals



Dwyer, L. M., et al. "Confined crystallization of fenofibrate in nanoporous silica." *CrystEngComm* 17.41 (2015): 7922-7929.



Nanocrystals

Published in: Jeong-Myeong Ha; Benjamin D. Hamilton; Marc A. Hillmyer; Michael D. Ward; *Crystal Growth & Design* **2009,** 9, 4766-4777.
DOI: 10.1021/cg9006185

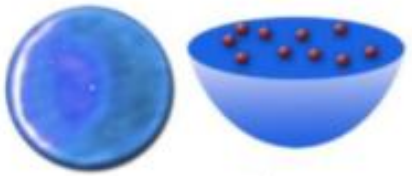
Hindawi
BioMed Research International
Volume 2017, Article ID 9781603, 11 pages
https://doi.org/10.1155/2017/9781603

Hindawi

Nanostructured Lipid Carrier

Research Article

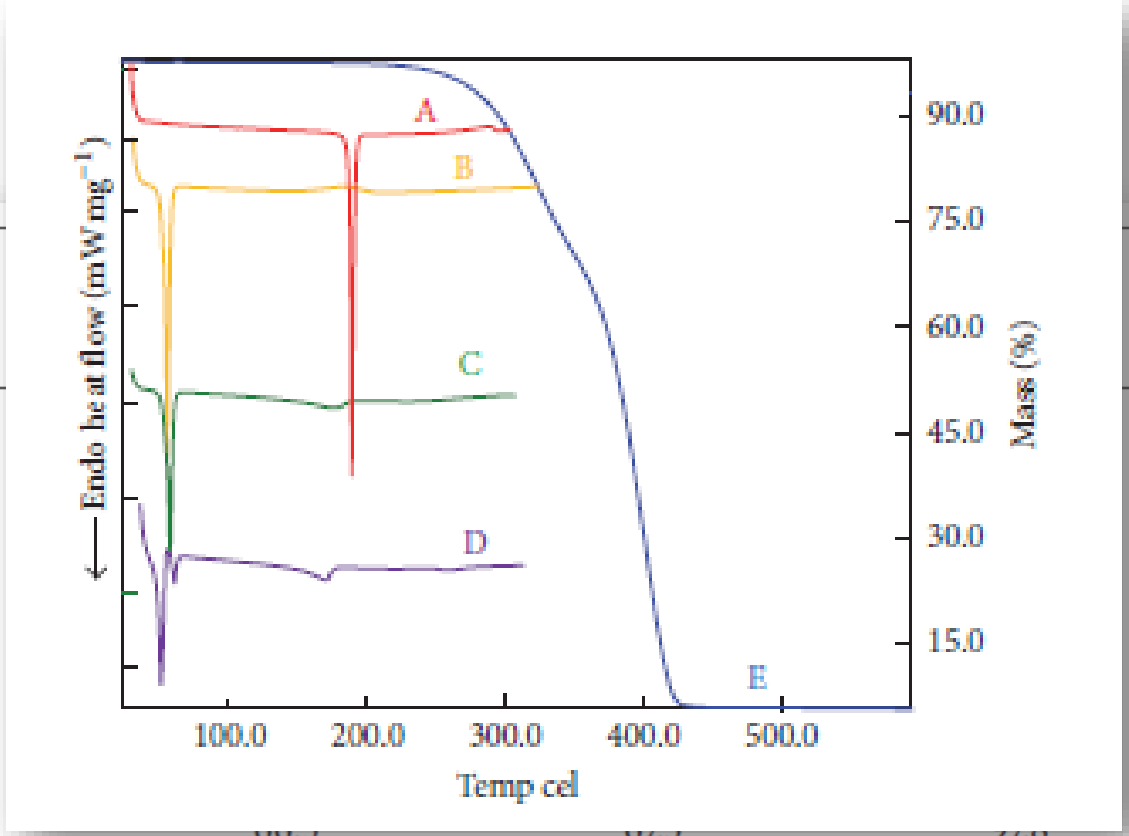
Buparvaquone Nanostructured Lipid Carrier: Development of an Affordable Delivery System for the Treatment of Leishmaniases



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

[1]*Department of Pharmacy, Faculty of Pharmaceutical Sciences, University of São Paulo, Professor Lineu Prestes Av 580, Cidade Universitária, 05508-000 São Paulo, SP, Brazil*
[2]*Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 8613 114th St NW, Edmonton, AB, Canada T6G 2H7*
[3]*Seroepidemiology, Cellular and Molecular Immunology Laboratory, Institute of Tropical Medicine, University of São Paulo, Dr. Enéas de Carvalho Aguiar 470, Jardim América, 05403-000 São Paulo, SP, Brazil*

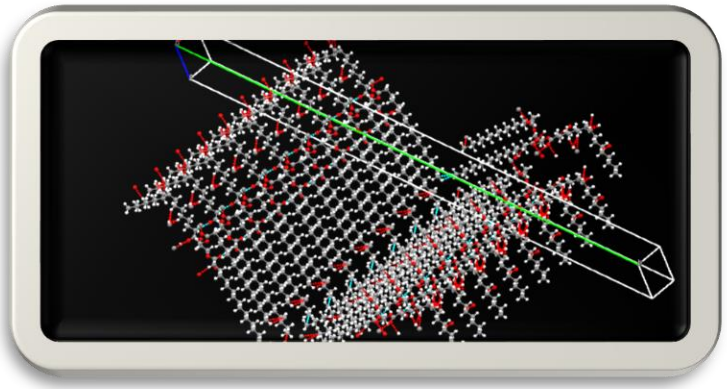
$$\text{CI}\ (\%) = \frac{\Delta H\ \text{BPQ PM} * D}{\Delta H\ \text{BPQ 100\%}} * 100$$



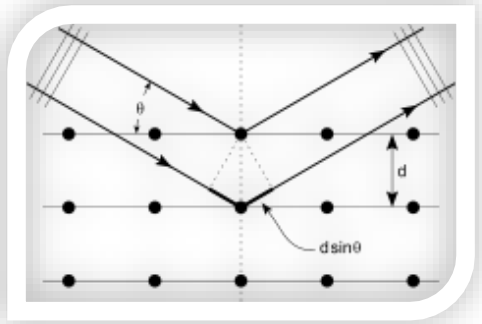
Lipid	ΔH_{BPQ} (J·mg^{-1})	CI (%) 2nd
Witepsol E85	136.0	49.0
Softisan 154	136.0	49.1
Gelucire 50/13	136.0	50.6
Gelucire 44/14	136.0	52.2
Precirol ATO 5	136.0	55.4
Sterotex HM	136.0	64.7
Dynsan P60	136.0	85.1
Compritol 888	136.0	99.0

BPQ: buparvaquone; BPQ-PM: BPQ and lipid physical mixture; CI: crystallinity index = (BPQ enthalpy in lipid mixture (J·mg^{-1}) * D (proportion of BPQ and lipid)/BPQ enthalpy of fusion (J·mg^{-1})) × 100; 1st and 2nd heating cycles.

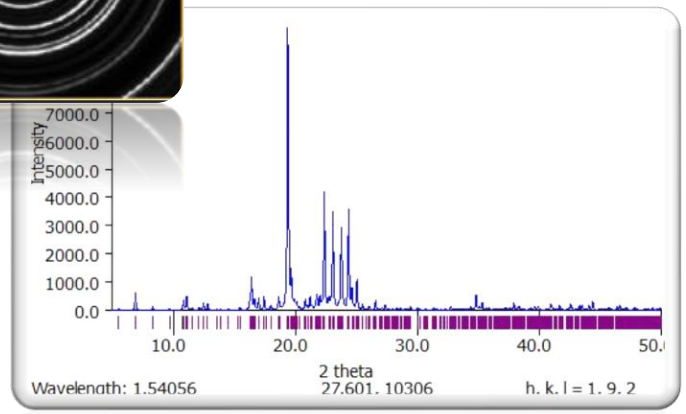
Difração de raios X



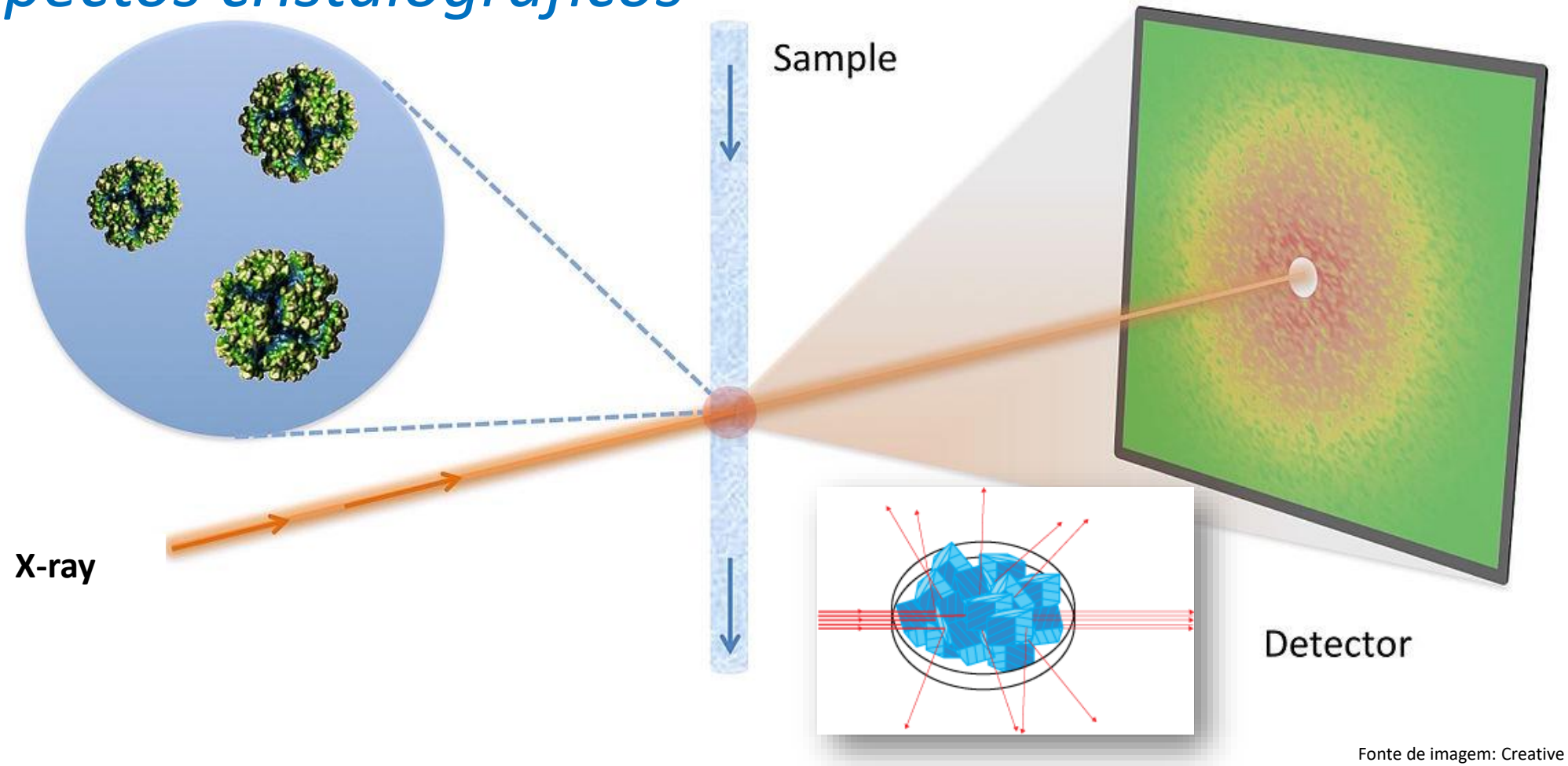
$$n\lambda = 2d\sin\theta$$ Bragg's Law

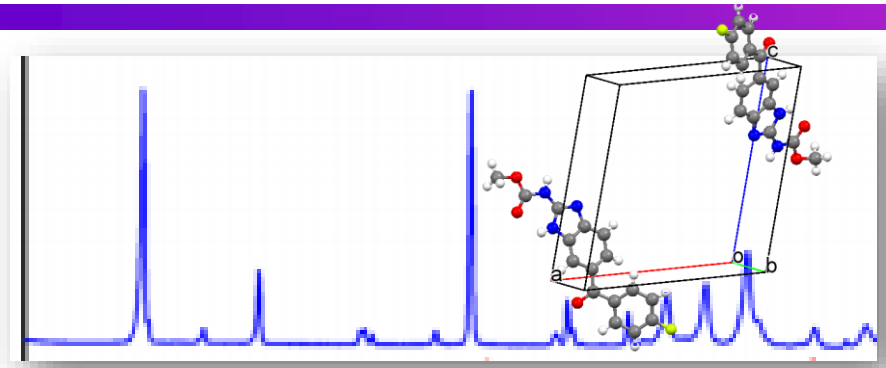


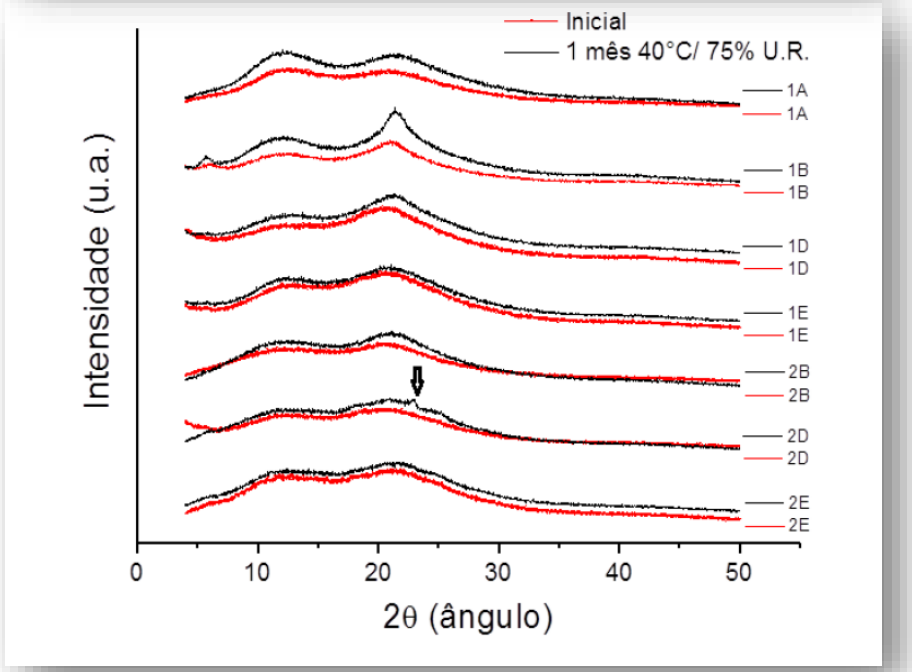
X-ray diffraction



aspectos cristalográficos







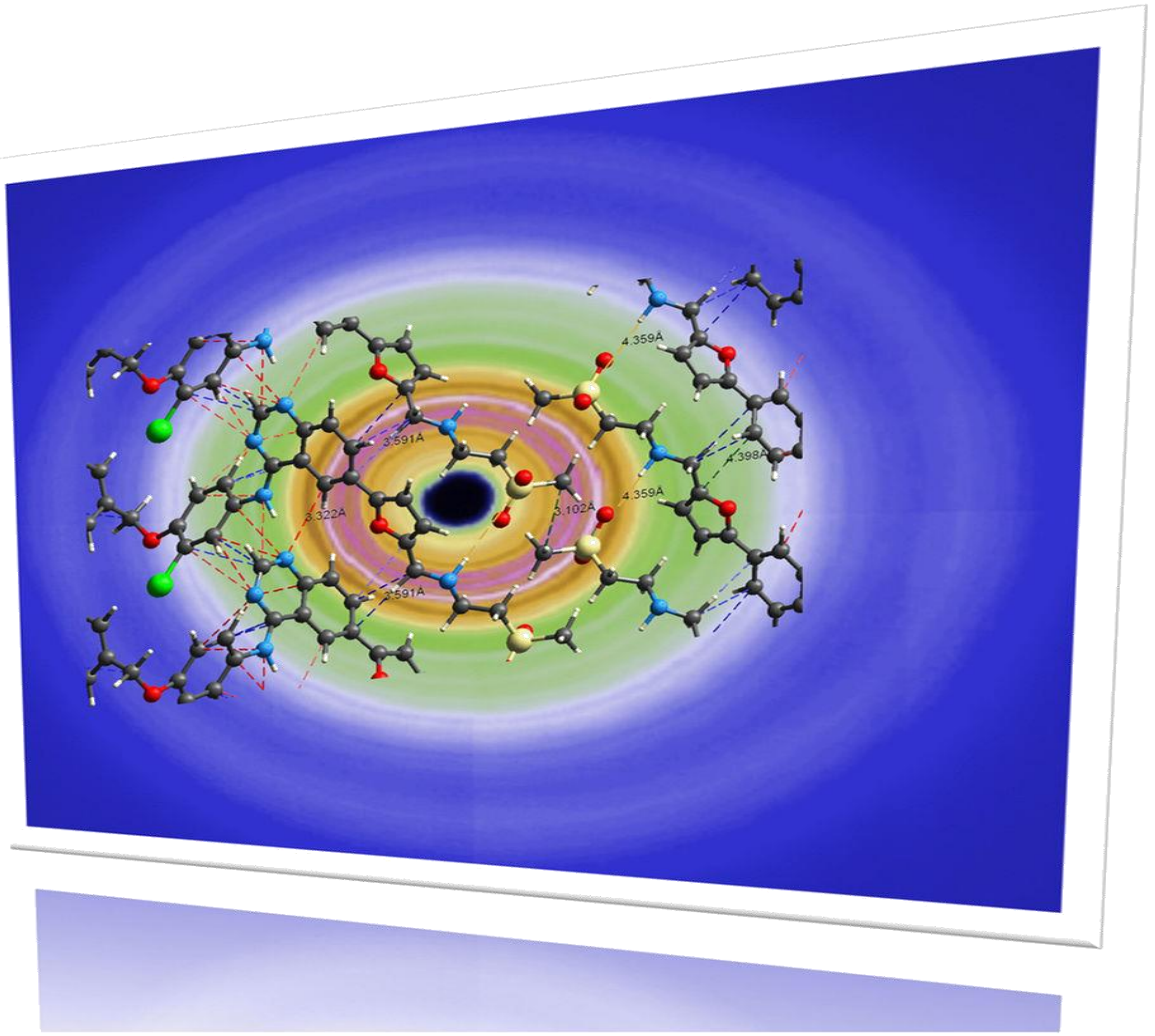
Long-range structure ≥ 20 Å

Is it amorphous or nanocrystaline?

Is it a single phase?

Pair Distribution Function Analysis

High-Energy X-Ray

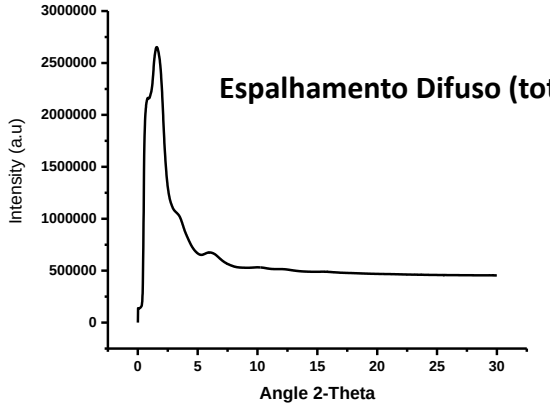


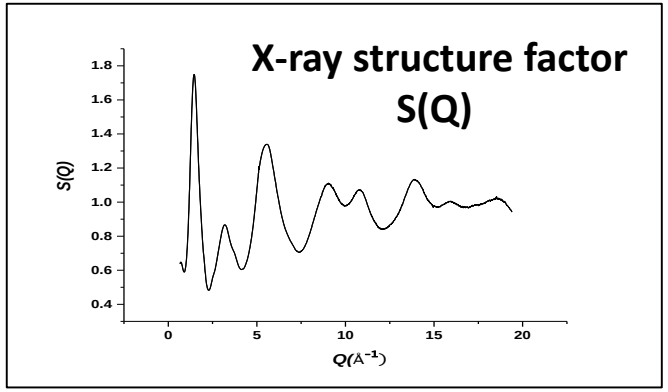
In amorphous systems the atoms are ordered primarily at short (2–5 Å) and medium-range (5–20 Å).

Argonne NATIONAL LABORATORY

Argonne: beam of energy 100.315 keV (1.1 Km)

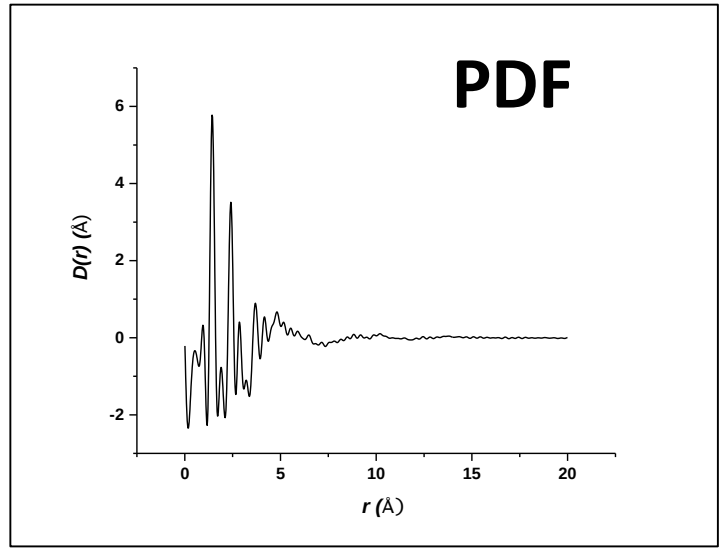
Ferramentas Analíticas do Desenvolvimento de Sistemas Nano-Estruturados





Sine Fourier transformation

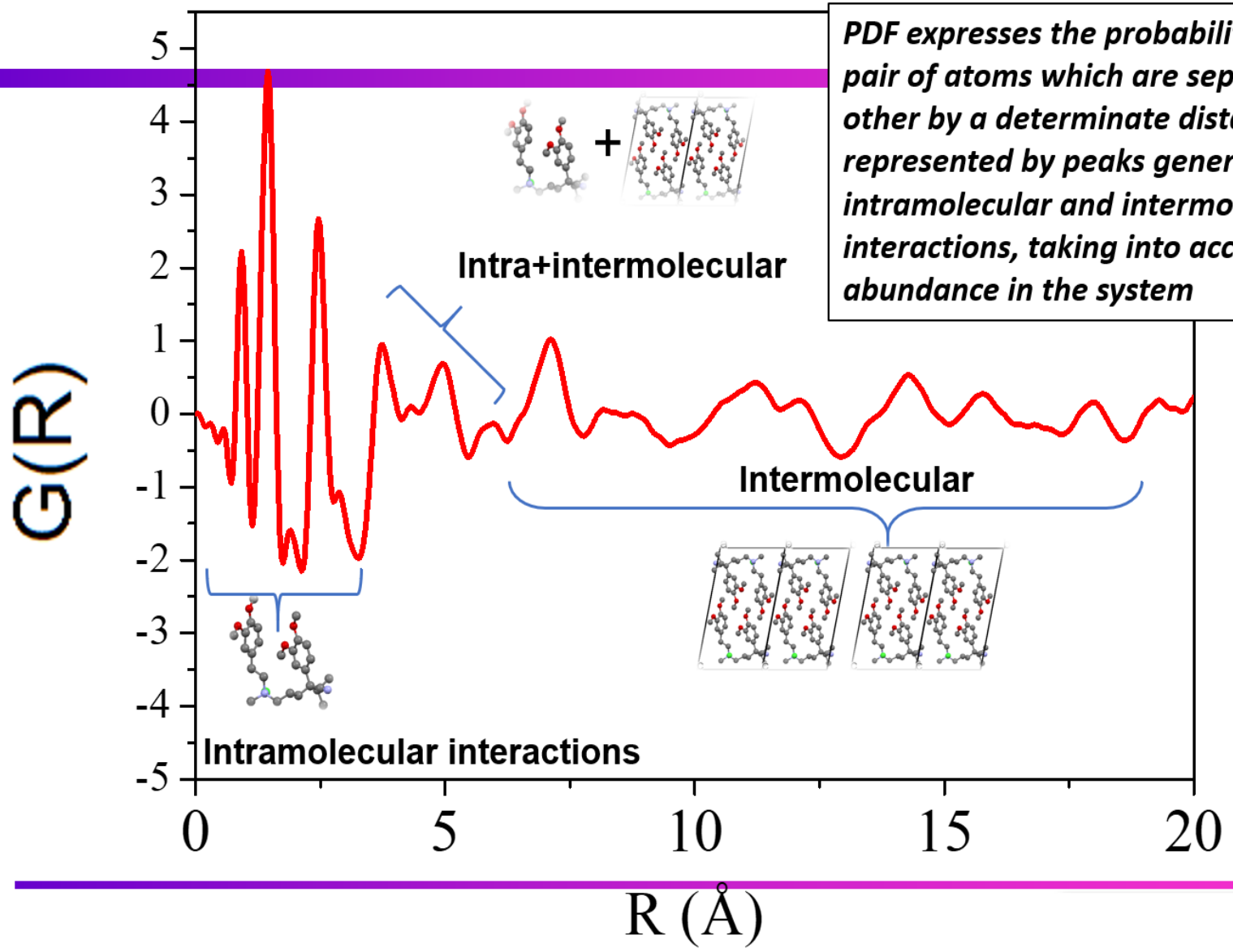
$$D(r) = \frac{2r}{\pi} \int_0^{Qmax} Q^2 [S(Q) - 1] \frac{\sin Qr}{Qr} dQ$$



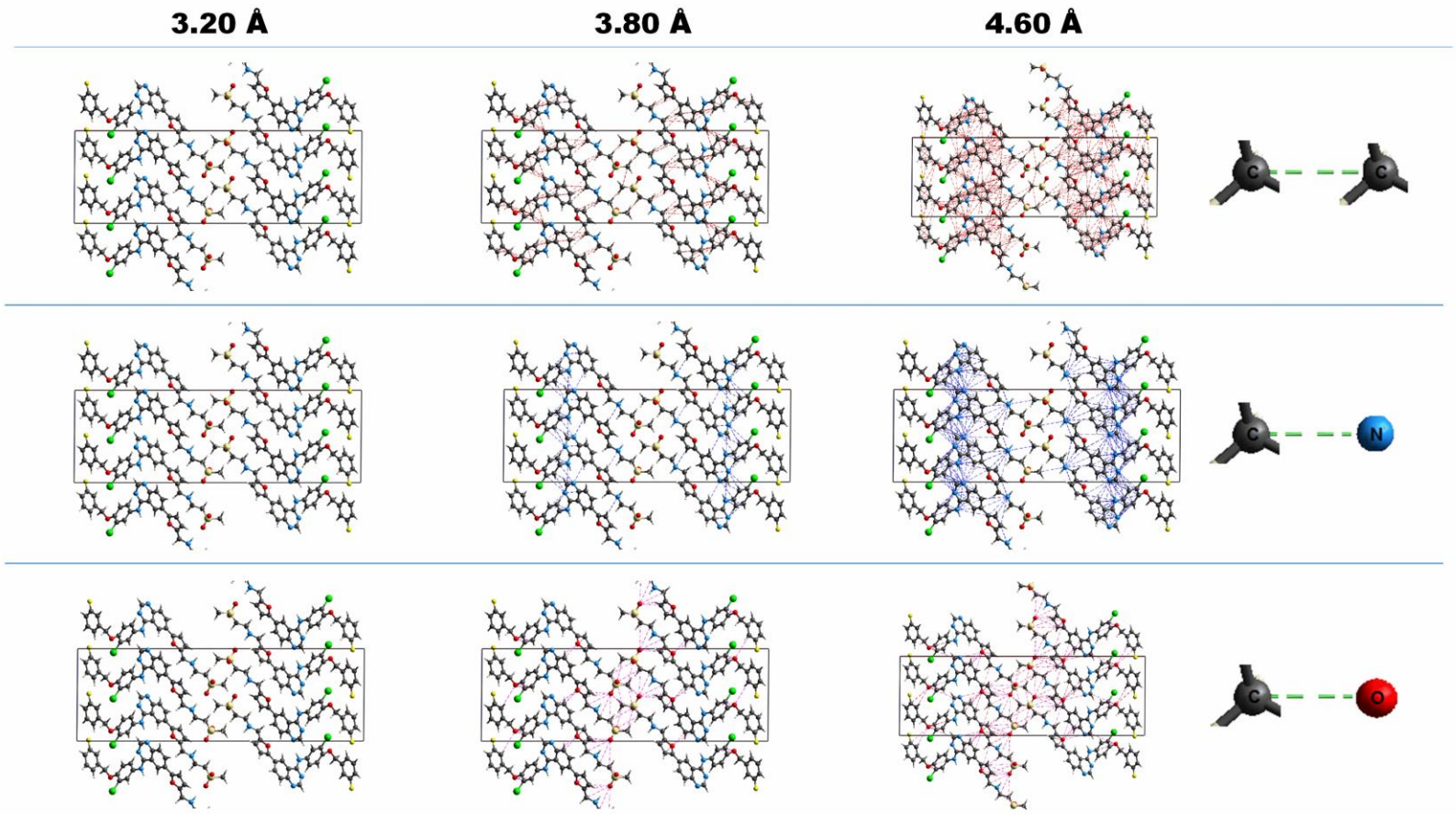
[3] Keen, D. A. A comparison of various commonly used correlation functions for describing total scattering. *J. Appl. Crystallogr.* **34**, 172–177 (2001)

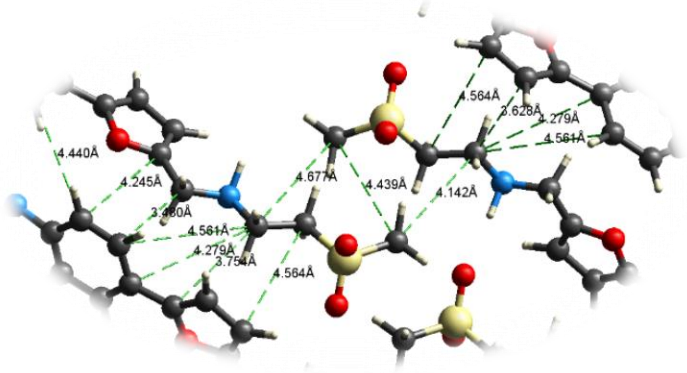
[4] Susman, S., Volin, K. J., Montague, D. G. & Price, D. L. The structure of vitreous and liquid GeSe2: a neutron diffraction study. *J. Non-Cryst. Solids* **125**, 168–180 (1990)

Pair Distribution Function (PDF)



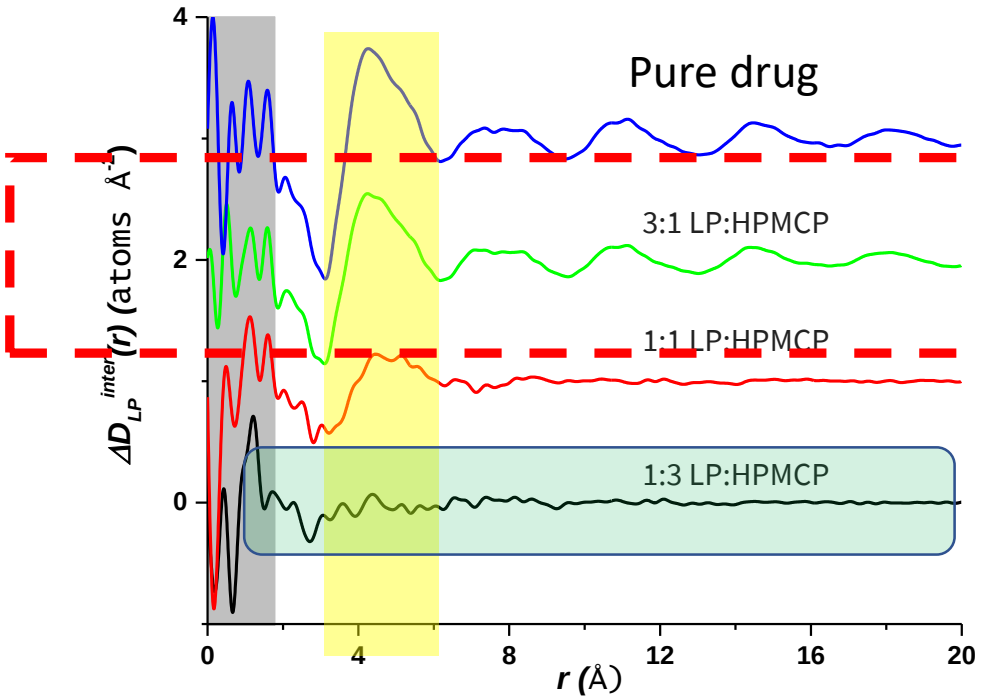
PDF expresses the probability of finding a pair of atoms which are separated from each other by a determinate distance (r), represented by peaks generated by intramolecular and intermolecular interactions, taking into account their abundance in the system





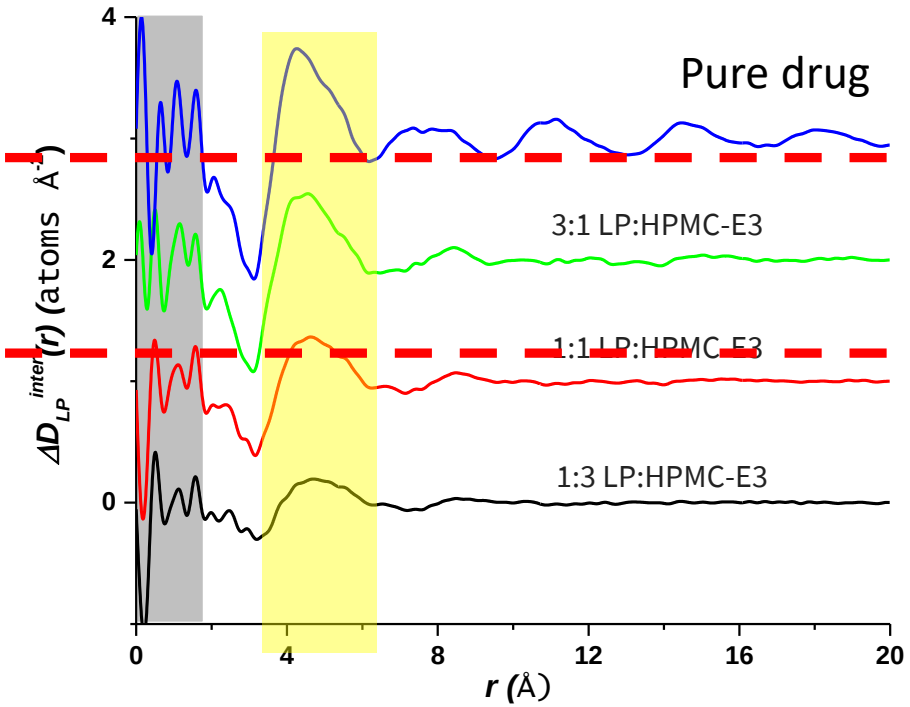
The distances and the number of nearest neighbor contacts related to C-C, C-N and C-O in drug-drug interactions in the crystal

HPMCP

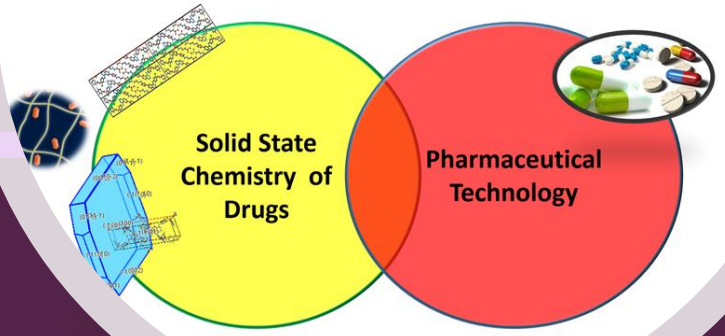


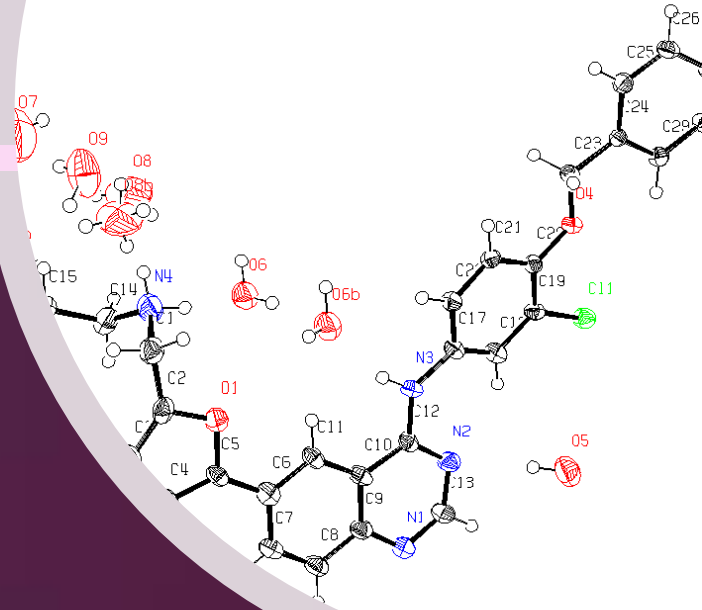
Total absence of those peaks in 1:3 LP:HPMCP preparations suggest that a complete reaction with the polymer has taken place.

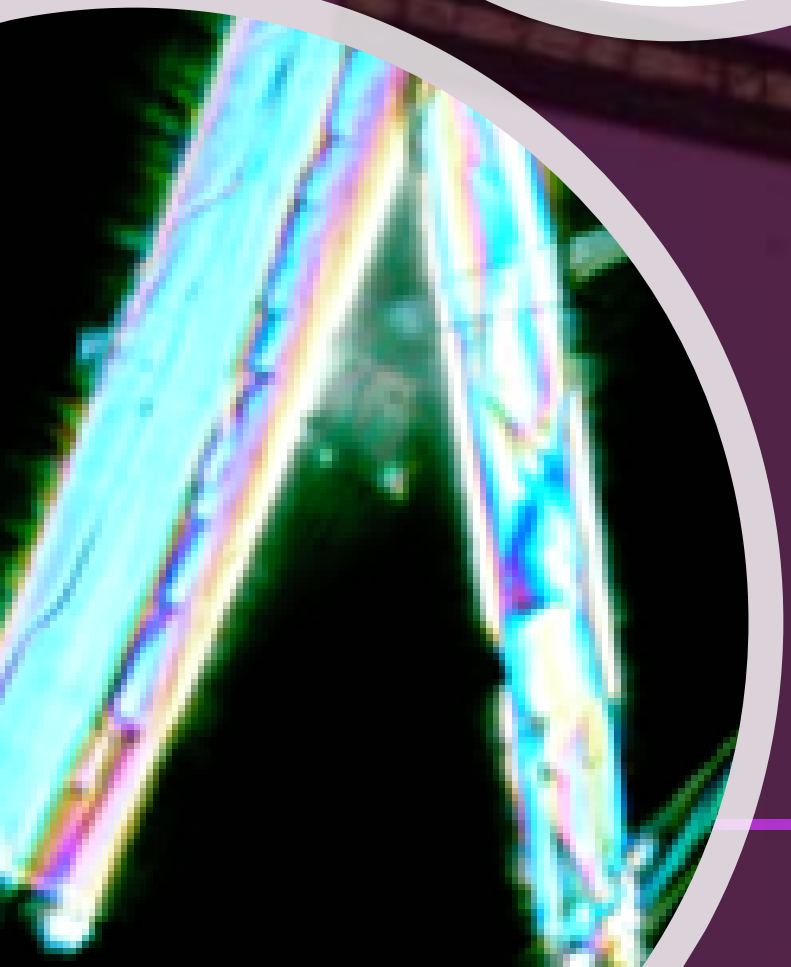
HPMC-E3



When acid-base interaction occurs the local structure is disrupted and drug molecules are dislocated by the acidic groups of the polymer, increasing the disorder of the system.







Pharmaceutical Technology & Solid State Research Group

Prof. Gabriel Lima Barros de Araujo
Faculdade de Ciências Farmacêuticas, USP
gabriel.araujo@usp.br

Website: https://gabriellbaraujo.wixsite.com/thegabalab