

# NANO-BASED DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF LEISHMANIASIS AND MALARIA

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# Outline

- WHO: the most recent official figures
- Therapeutic choices
- Advantages of nano-based drug delivery over conventional systems
- Nano-strategies
- Research topic: targeted drug delivery to macrophages for the treatment of leishmaniasis

# Both vector-borne protozoan diseases: neglected but not lost in oblivion

## • Malaria

- 97 countries
- 3.4 billion people at risk
- 627,000 deaths in 2012
- 90% of deaths: children and pregnant women
- Killed 1,300 children a day, almost **one child every minute**



## • Leishmaniasis:

- 1.3 million new cases and 20 000 to 30 000 deaths occur annually
- 200 000 to 400 000 new cases of VL occur worldwide each year.
- Over two-third of cutaneous leishmaniasis new cases occur in six countries including Brazil

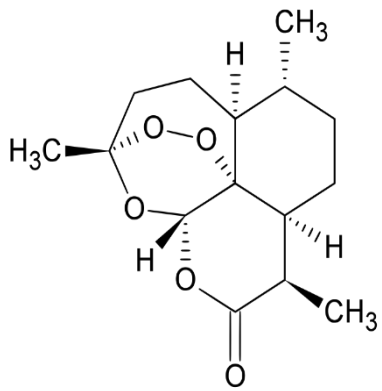
Source:  
[http://www.who.int/malaria/media/world\\_malaria\\_report\\_2013/en/](http://www.who.int/malaria/media/world_malaria_report_2013/en/)

Source:  
<http://www.who.int/mediacentre/factsheets/fs375/en/>

# Therapeutic choices: first and second line

## • Malaria

- Chloroquine
- Artemether

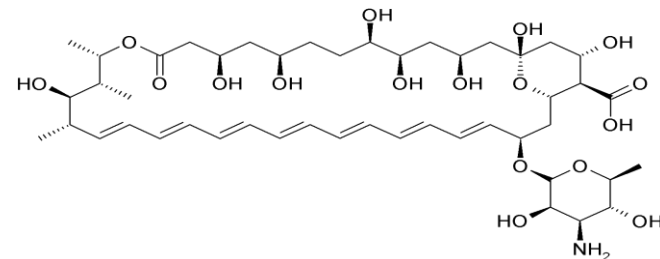


efficacy: parasite resistance

toxicity: severe side effects

## • Leishmaniasis

- Pentavalent antimonials
- Miltefosine
- Liposomal Amphotericin B



# Therapeutic choices: first and second line

- Liposomal amphotericin B injectable (LAmB) AmBisome®
- WHO Essential Medicines List
- AmBisome® remains protected by two patents (US5874104, US5965156) in the US until 2016 and by one patent (CA1339008) in Canada until 2014
- US pharmaceutical company Gilead Sciences



Source: <https://www.ambisome.com>

**Ambisome injetável**  
de: R\$ 17136,9  
**Por: R\$ 16.046,37**

**6 vezes SEM JUROS**

**Débito e Boleto 3% de desconto**

**Parcelamento no cartão SEM JUROS**

1x	R\$ 16046,37
2x	R\$ 8023,19
3x	R\$ 5348,79
4x	R\$ 4011,59
5x	R\$ 3209,27
6x	R\$ 2674,40

**Frete Grátis**

Quantidade:

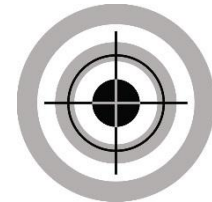
**COLOCAR NO CARRINHO**

# Conventional versus Nano-based drug delivery

## ✧ Conventional

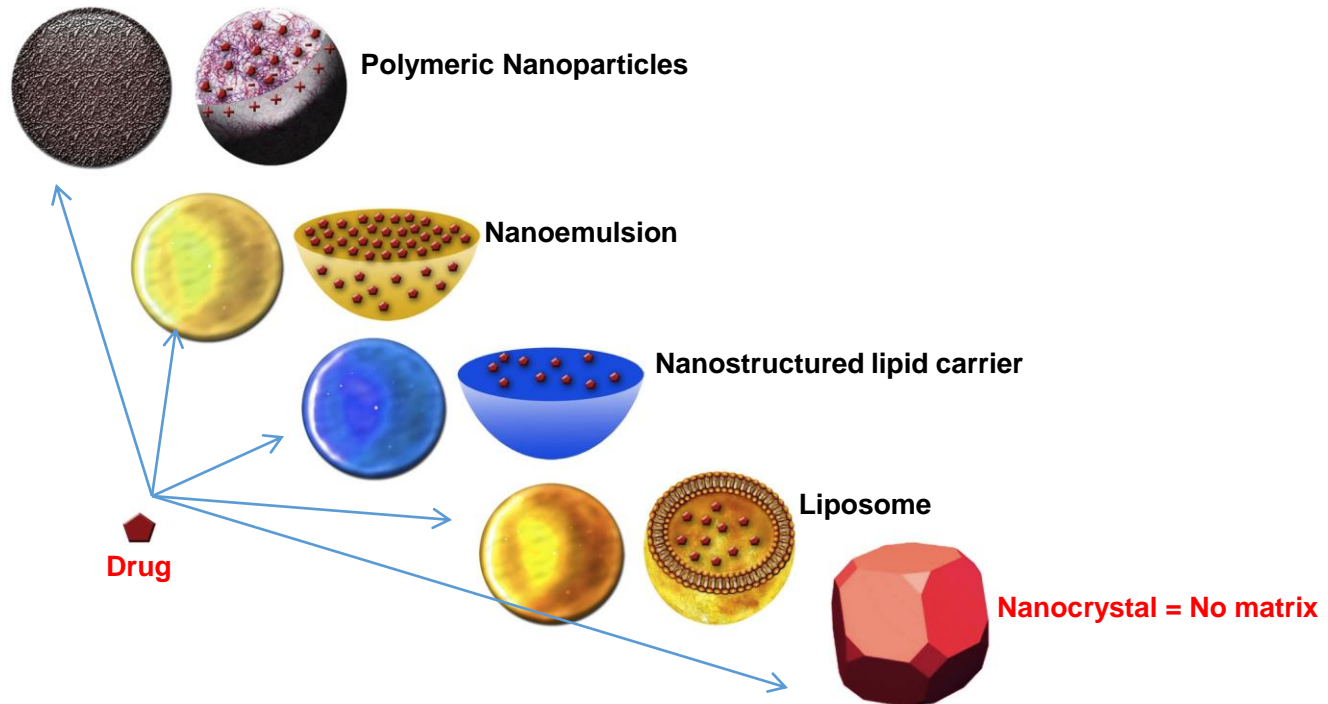
- short half-life usually between 3 h and 5 h
- poor aqueous solubility, and thus low oral bioavailability (40%)
- risk of degradation in acidic conditions
- associated risk of toxicity

## ✧ Nano-based drug delivery



- Targeted
- extended duration of action
- reduced therapeutic dose
- improved patient compliance
- reduced adverse effects of highly toxic, potent drugs

# Nano-based drug delivery system strategies



# Polymeric nanostructured system: targeted NFOH delivery to macrophages for the treatment of leishmaniasis

Lis Marie Monteiro, MSc

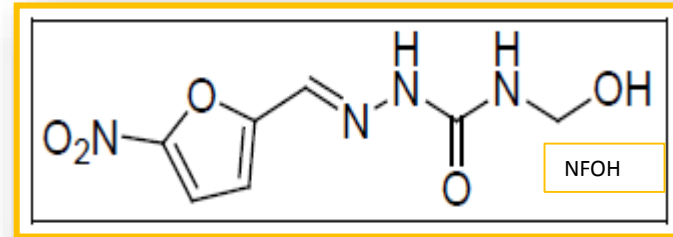
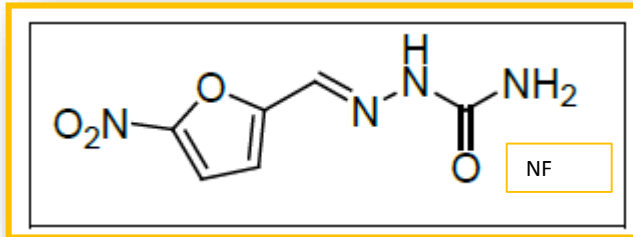
Supervisor: Prof. Dr. Nadia Bou-Chacra

Co-supervisor: Prof. Dr. Paulo Cotrim



# Nitrofurazone (NF)

## Hydroxymethylnitrofurazone (NFOH)



**NF and NFOH:** inhibition of trypanothione reductase/peroxidase – NADPH synthesis and ROS metabolism.



activity when compared to other derivatives

4 X less toxicity when compared to NF



stability at physiological pH

Better tissue distribution

# PS, PDI and ZP

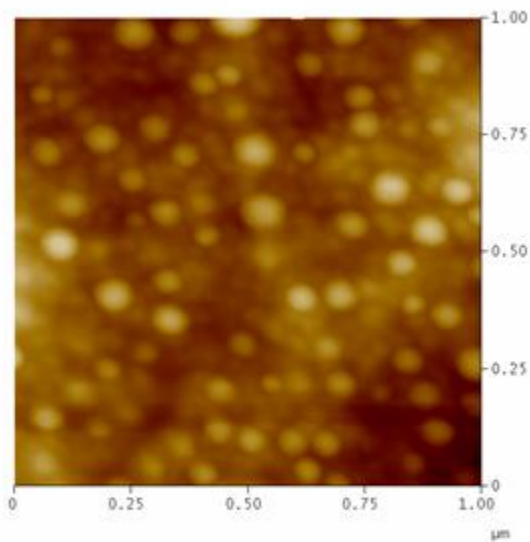
Z-Average (d.nm): 151,5

PDI: 0,104

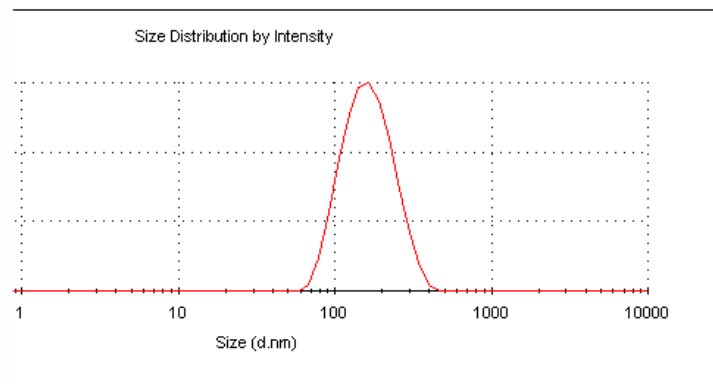
Intercept: 0,942

Result quality : Good

	Diam. (nm)	% Intensity	Width (nm)
Peak 1:	170,9	100,0	61,97
Peak 2:	0,000	0,0	0,000
Peak 3:	0,000	0,0	0,000



Digital Instruments NanoScope  
Scan size 1.000  $\mu\text{m}$   
Scan rate 1.001 Hz  
Number of samples 512  
Image Data Height  
Data scale 50.00 nm



12011218.001

Zeta Potential (mV): -10,1

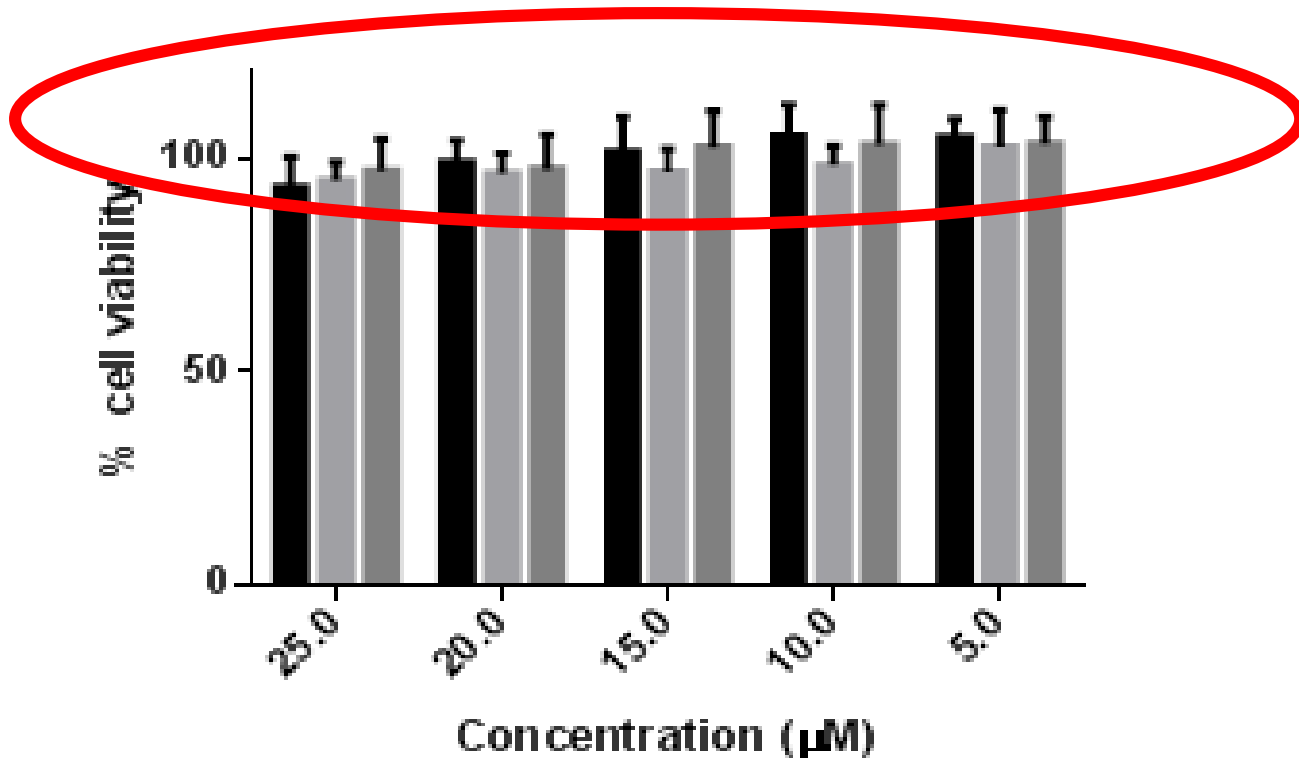
Zeta Deviation (mV): 6,49

Conductivity (mS/cm): 0,178

Result quality : Good

	Mean (mV)	Area (%)	Width (mV)
Peak 1:	-10,1	100,0	6,49
Peak 2:	0,00	0,0	0,00
Peak 3:	0,00	0,0	0,00

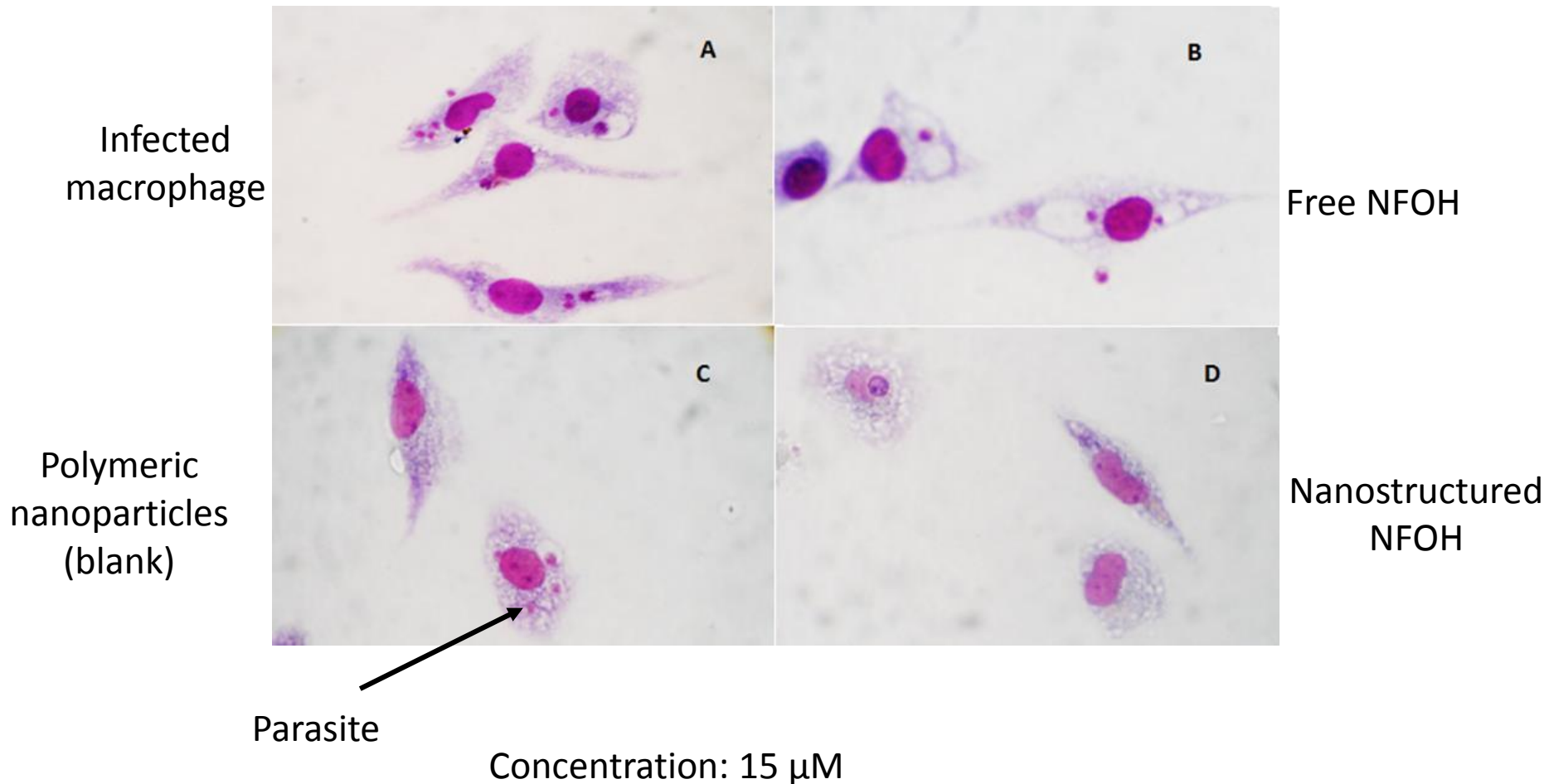
# Macrophage cytotoxicity assay



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

No statistically significant difference was observed

# Leishmanicidal activity evaluation against *L. amazonensis* amastigotes



# Leishmanicidal Activity

Table 1. Effective leishmanicidal concentration ( $EC_{50}$ ) of blank nanoparticles, nanostructured NFOH and free NFOH.

$EC_{50}$	Polymeric Nanoparticles (blank)	Nanostructured NFOH	Free NFOH
$\mu\text{M}$	25.2	0.33	31.2

Nanostructured NFOH activity **94.5-fold** higher than the free NFOH  
Encapsulation efficiency:  $64.4 \pm 0.7\%$  (w/w)

# Conclusion

## Suitable physical and chemical characteristics

- Average PS of 151.5 nm, PDI 0.104, monomodal distribution, ZP equal to -10.1 mV and EE of  $64.4 \pm 0.7\%$  (w/w);

## Low cytotoxicity

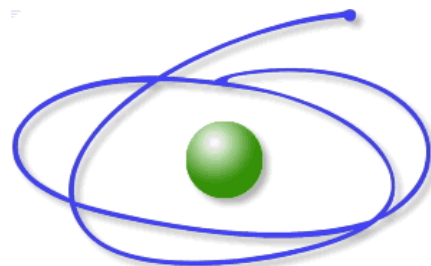
- Cell viability of nanostructured NFOH was approximately 100%;

## Improved leishmanicidal activity

- Nanostructured NFOH activity 94.5-fold higher than the free NFOH against *L. amazonensis* amastigotes.

Patent of invention: Monteiro, L.M., Cotrim P., Ferreira I., E. Bou-Chacra, N. BR 1020140079238,  
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# RESEARCH GROUP



C A P E S



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