PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÊUTICAS

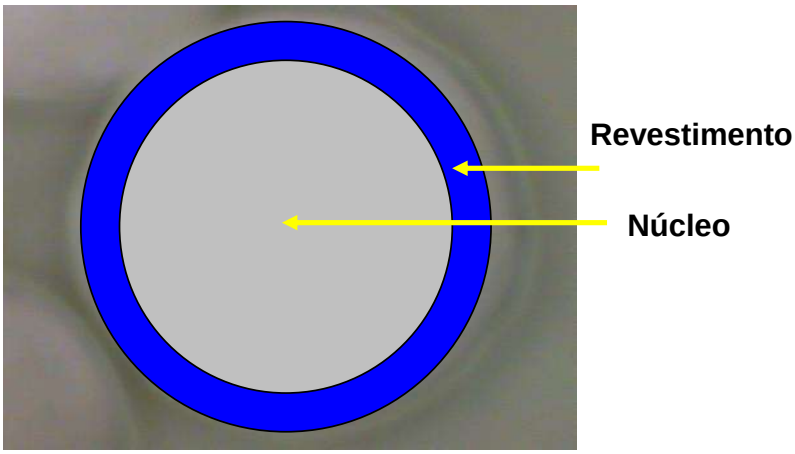
# Encapsulação: Processos e Aplicações

**Prof. Dr. Wanderley Pereira Oliveira**

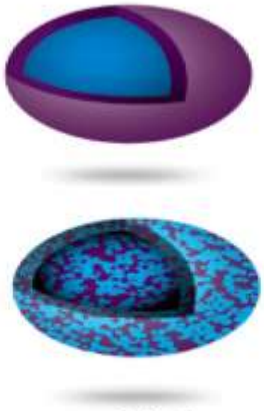
Universidade de São Paulo
Laboratório de P&D em Processos Farmacêuticos

**2020**

# ENCAPSULAÇÃO ?



# MORFOLOGIA

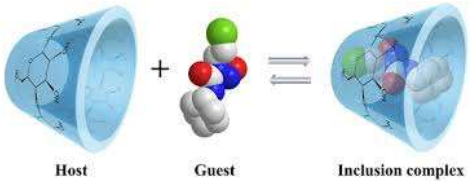


e 3.3. Morphologies of different microer
eft), polynuclear (top right), matrix (botto
ım right) (Jurkowska and Szczygieł, 2016)

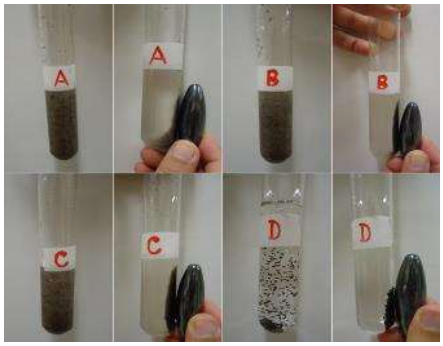
# PROPÓSITOS DA ENCAPSULAÇÃO

- **Encapsular produtos bioativos para:**
  - Imobilização
  - Proteção
  - Controle da velocidade de liberação
  - Estruturação
  - Funcionalização

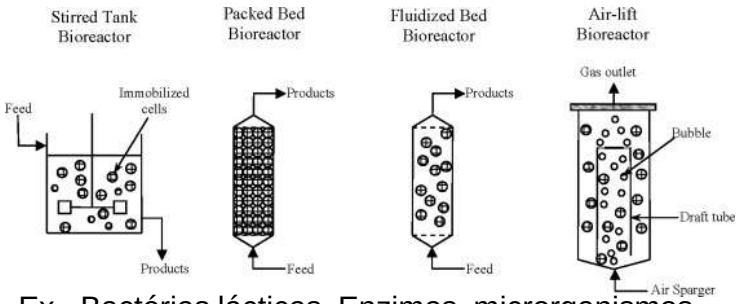
## ➢ Imobilização:




Aromas e óleos essenciais

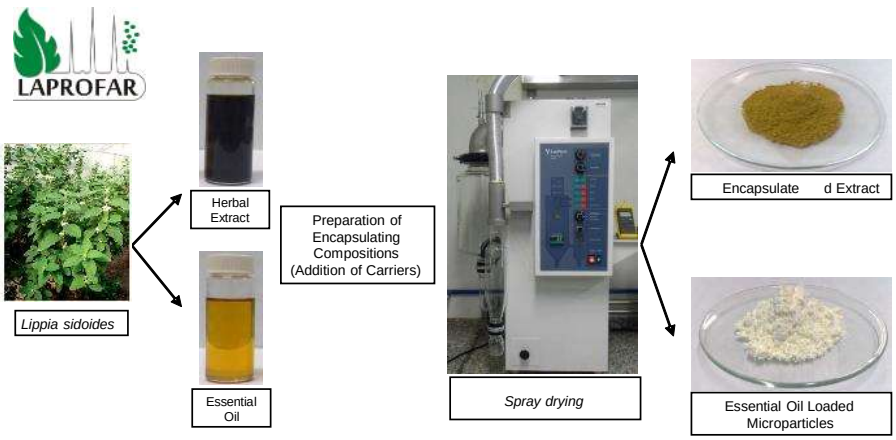



Enzimas



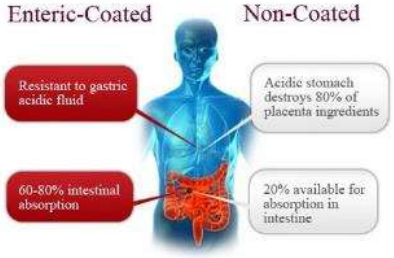

Ex. Bactérias lácticas, Enzimas, microrganismos

## ➢ Transformar líquidos em sólidos:

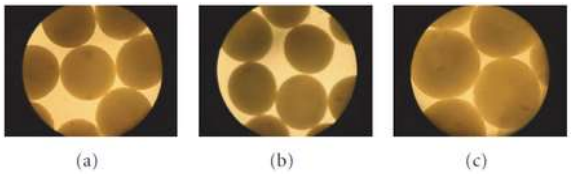


## ➢ Proteção:

Ex. Revestimento entérico



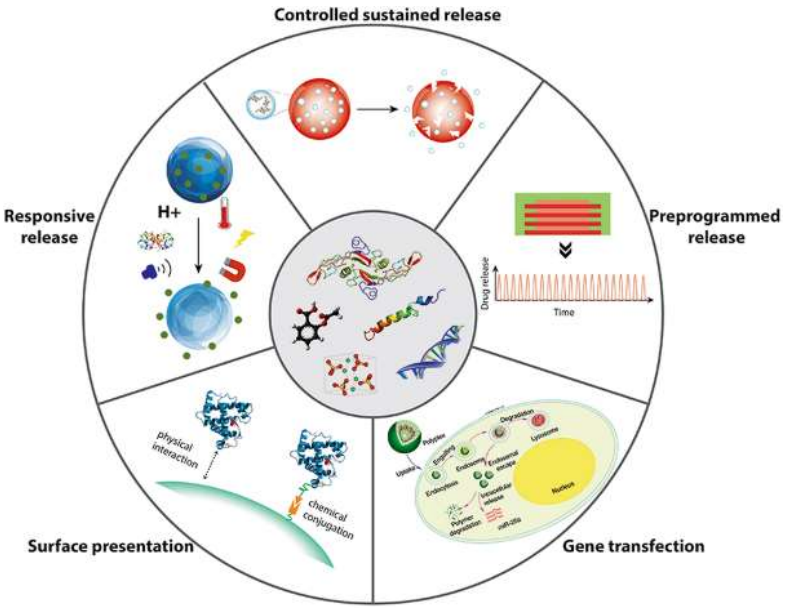

- Vitaminas (T, umidade e calor)
- Sais minerais

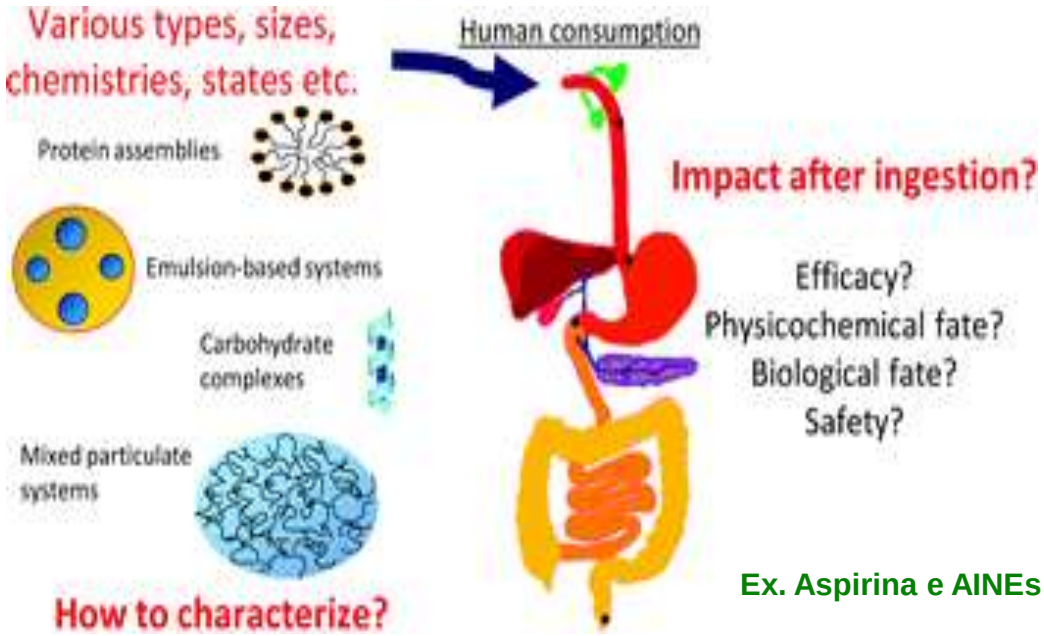



Ex. Encapsulação Ilhotas de Langerhans

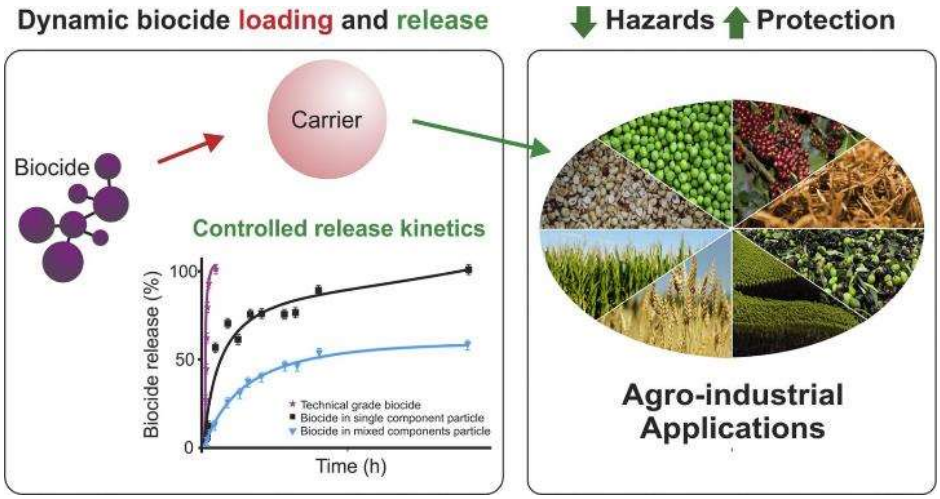
- Mascarar Sabor e Odores

## ➢ Controle velocidade e alvo de liberação:






## ➢ Controle velocidade de liberação:




Ex. Pesticidas, fertilizantes, suplementos animais, etc

## ➢ Proteção e Controle velocidade de liberação:

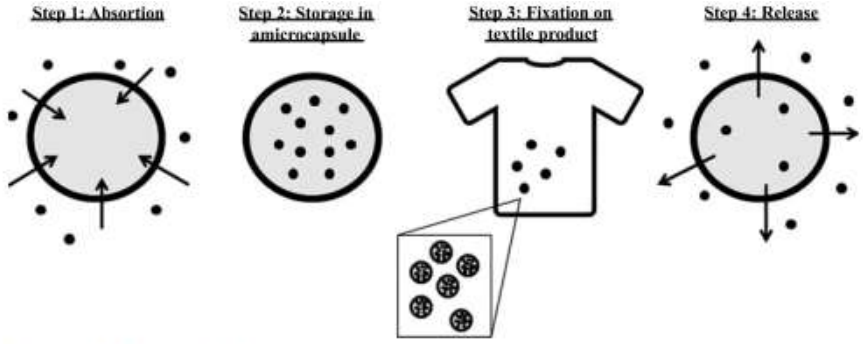



**Fig. (1).** Schematic diagram of microencapsulation process.

## ➢ Proteção e Controle velocidade de liberação:

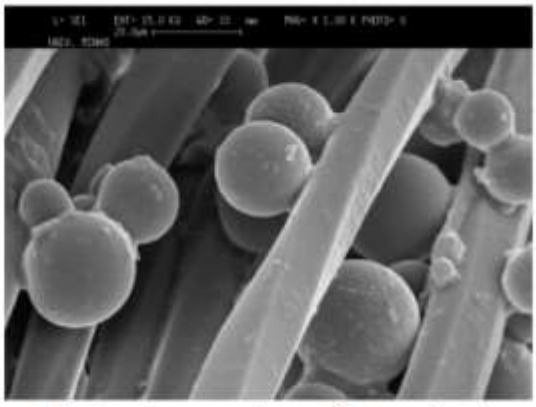


Figure 11.5. Insect repellent microcapsules on fibre surface(source: Devan Chemicals).

## ➢ ENCAPSULAÇÃO NO COTIDIANO



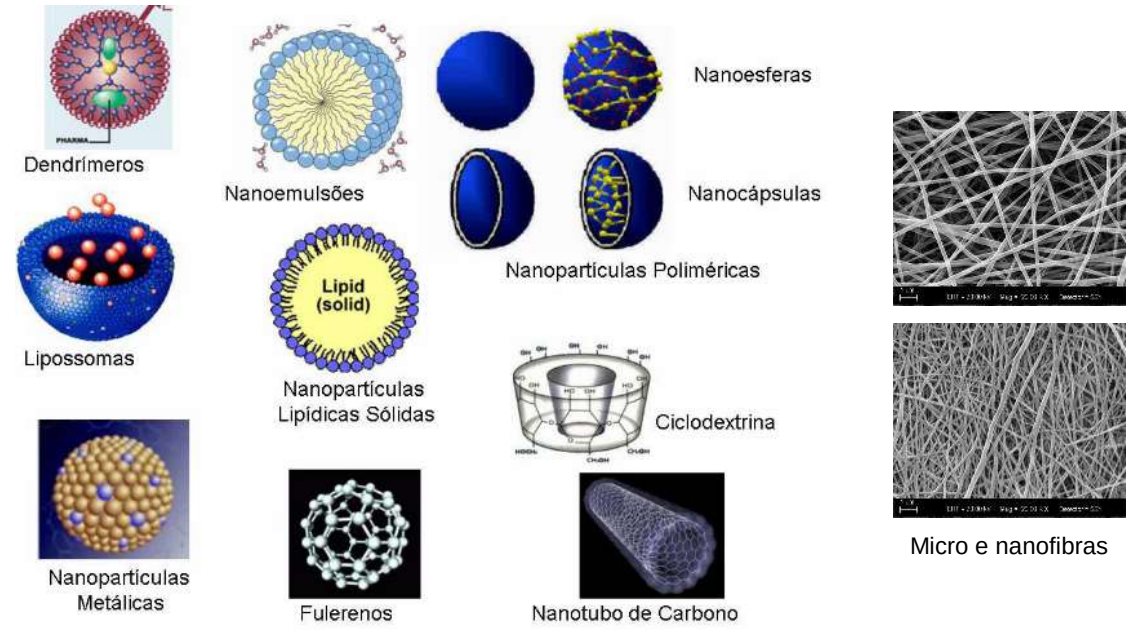




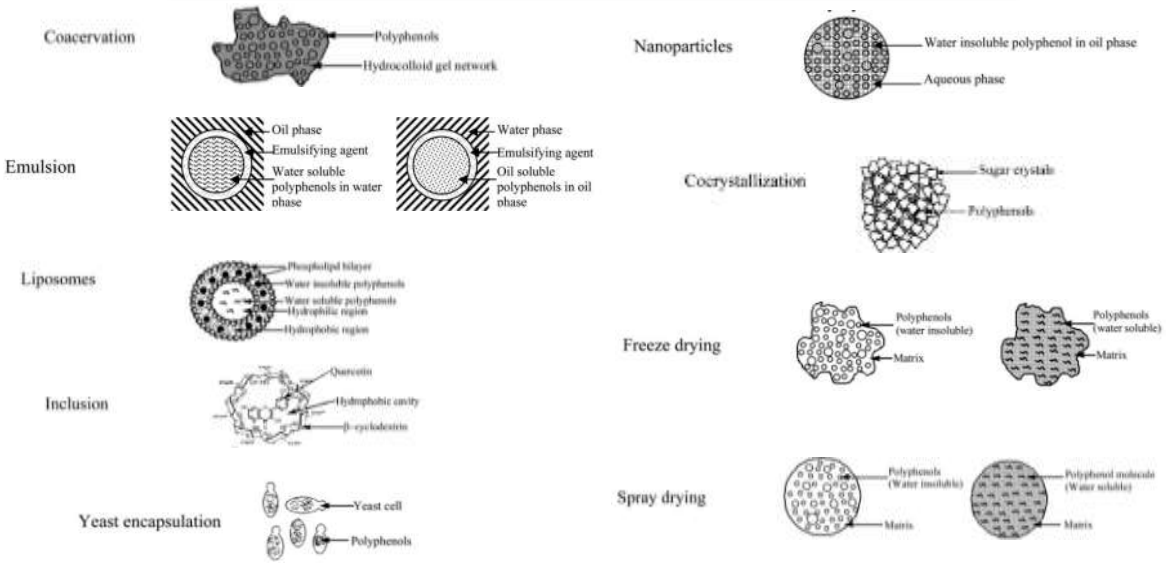
## ➢ Proteção e Controle velocidade de liberação:

# ENCAPSULATION TECHNOLOGIES

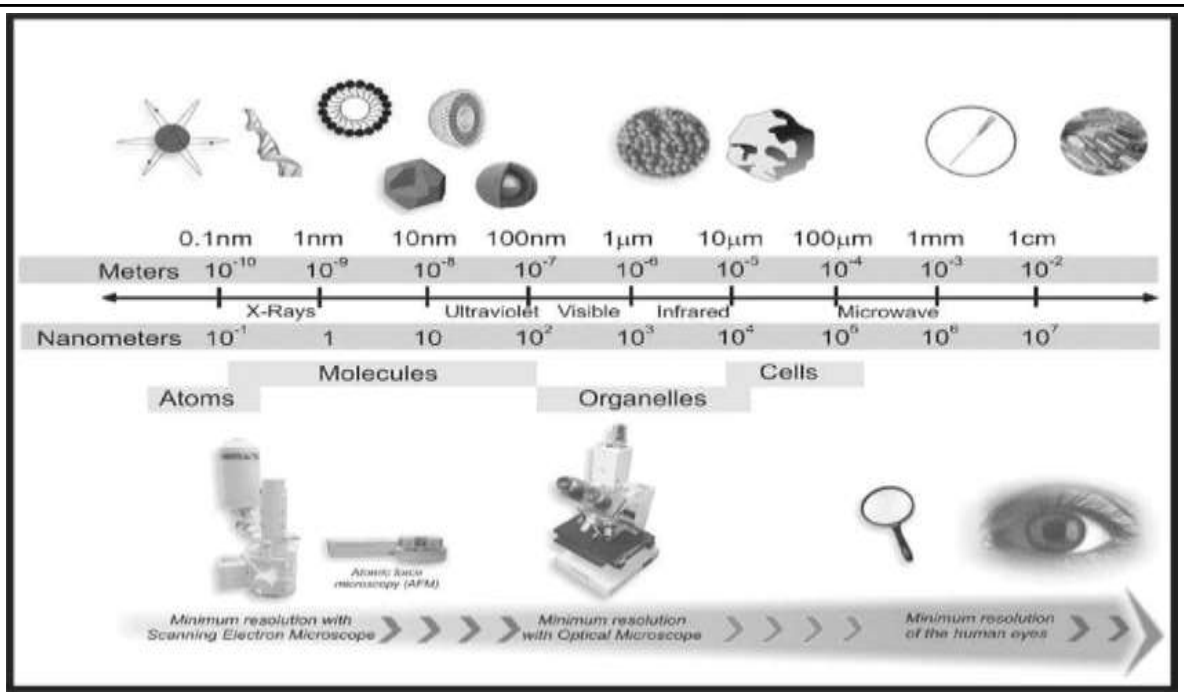
- *Polymeric nanoparticles and nanocapsules*
- *Solid lipid nanoparticles, Nanostructured lipid carriers*
- *Cyclodextrin complexation*
- *Liposomes "phytosomes"*
- *Emulsion, microemulsion,nanoemulsion*
- *Proliposomes*
- *Dried emulsions*
- *Co-crystallization*
- *Ionotropic gelation (e.g. alginate based)*
- *Micro and nanofibers*

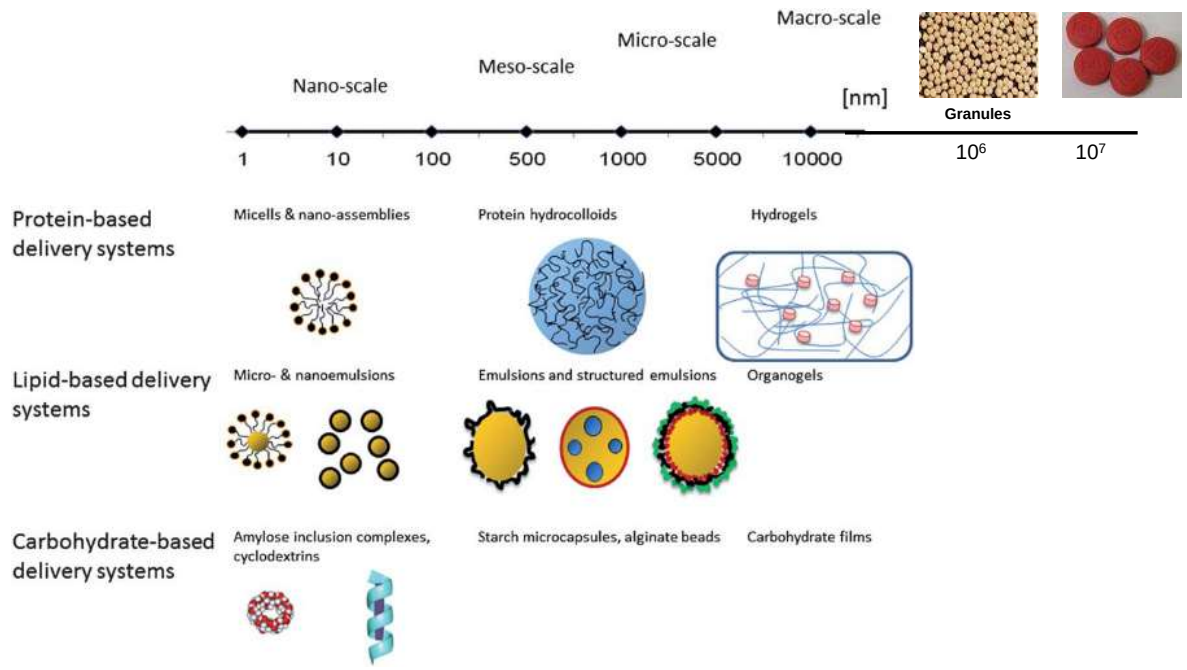


## Encapsulation technologies to delivery polyphenol compounds




Fang, Z. and Bhandari, B. Trends in Food Science & Technology 21 (2010) 510-523






# *PRODUCTION PROCESSES*

## * *Physicochemical processes*

- *Ionotropic gelation*
- *Emulsification methods*
- *Simple and complex coacervation*
- *Solvent evaporation*
- *Interfacial polymerization*
- *Cyclodextrin complexation*
- *Sol-gel process*

# *PRODUCTION PROCESSES*

## * *Physical processes*

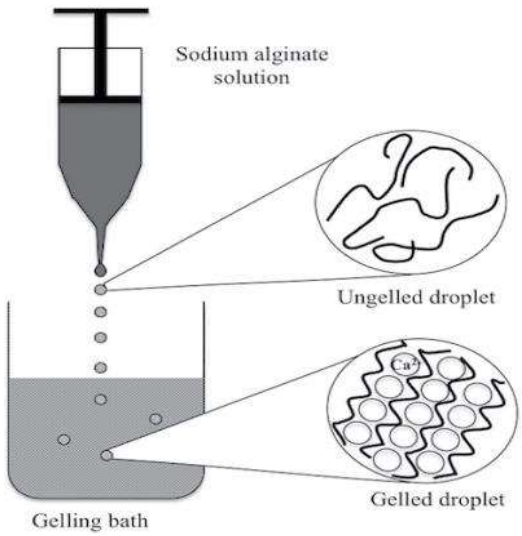
- *- spray drying,*
- *- spray chilling/cooling/congealing*
- *- spray freeze-drying*
- *- suspended state methods (spouted beds, fluidized beds, wurster system, rotary fluidized bed)*
- *milling and micronization*
- *supercritical fluid based process (RESS)*
- *microfluidization and high pressure homogeneization*
- *electrospinning e electrospraying*

| Physico - Chemical Processes | Physico - mechanical Processes |
|---|---|
| Coacervation (2 – 1200 um) | Spray-drying (5 – 5000 um) |
| Polymer-polymer incompatibility (0.5 – 1000 um) | Fluidized- bed technology (20 – 1500 um) |
| Solvent evaporation (0.5 – 1000 um) | Pan coating (600 – 5000 um) |
| Encapsulation by supercritical fluid | Spinning disc (5 – 1500 um) |
| Encapsulation by Polyelectrolyte multilayer (0.02 – 20 um) | Co-extrusion (250 – 2500 um) |

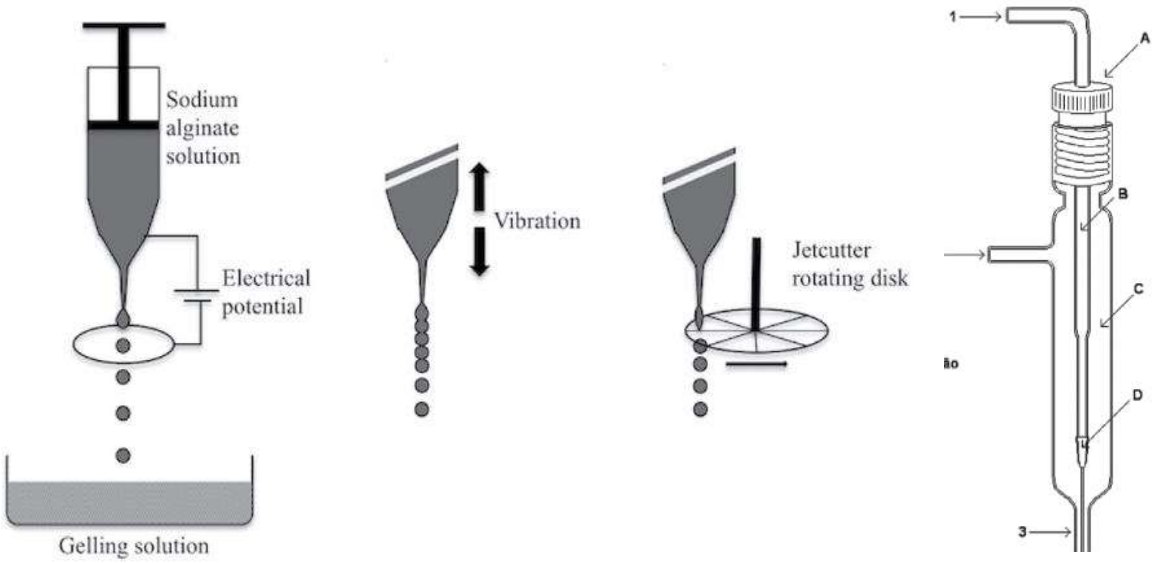
| Physico-Chemical Processes (cont.) | Chemical Processes |
|---|---|
| Hydrogel microsphere | Interfacial polymerization (0.5 – 1000 um) |
| Phase Inversion (0.5—5.0 um) | In situ polymerization (0.5 – 1100 um) |
| Hot Melt (1—1000 um) | |

## PROCESSOS DE FABRICAÇÃO

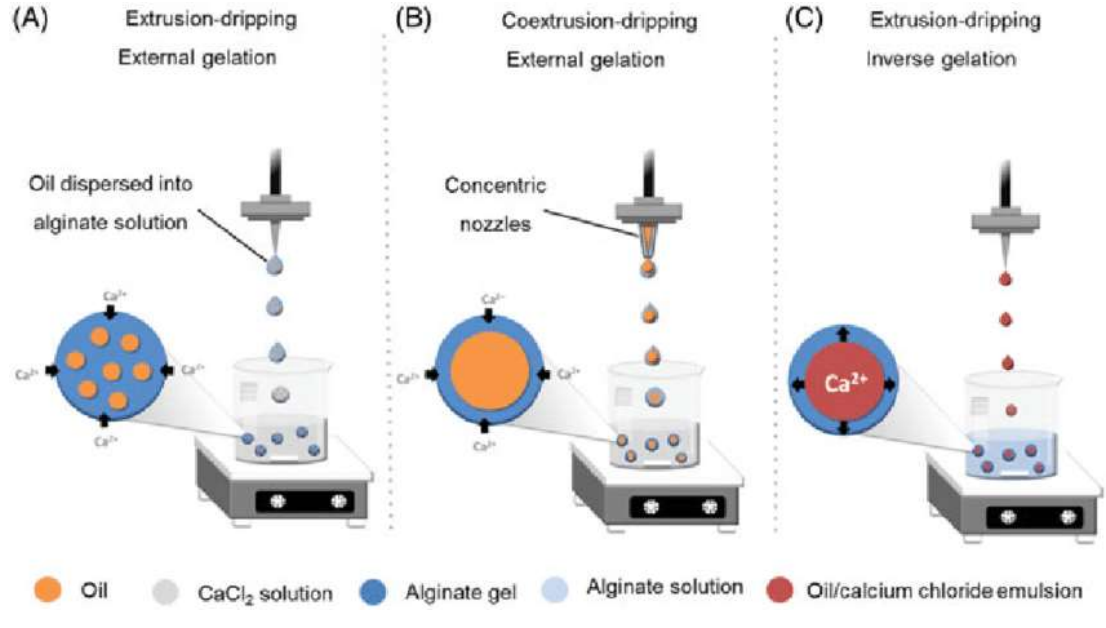
- **Gelificação covalente e ionotrópica**



- **Gelificação covalente e ionotrópica**




- **Gelificação covalente e ionotrópica**



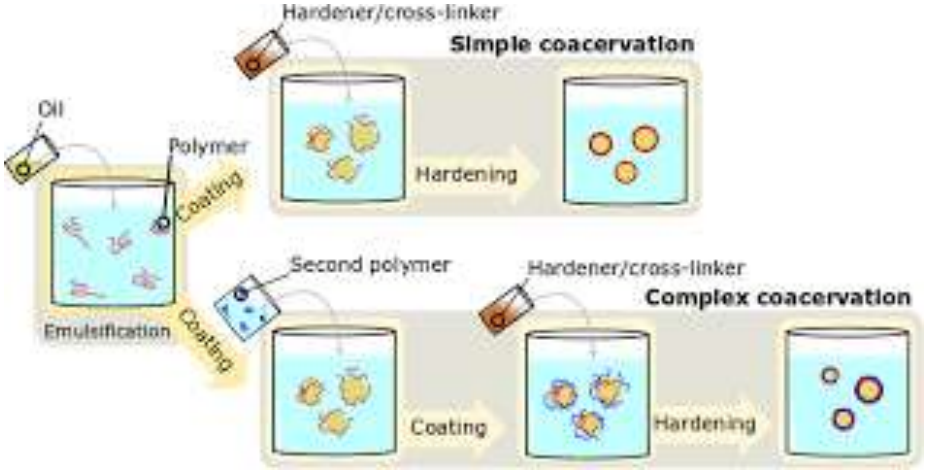
# PROCESSOS DE FABRICAÇÃO

- **Coacervação Simples**


Nanomaterials (Basel). 2017 Jul; 7(7): 179. Published online 2017 Jul 10. doi: 10.3390/nano7070179

# PROCESSOS DE FABRICAÇÃO

- **Coacervação Complexa**

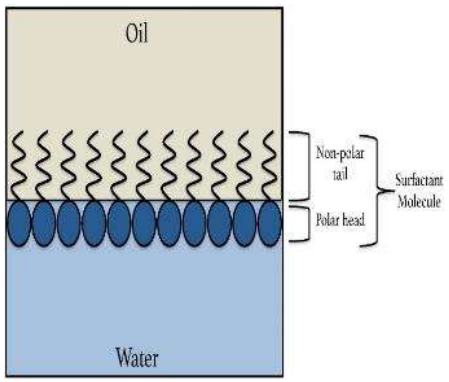


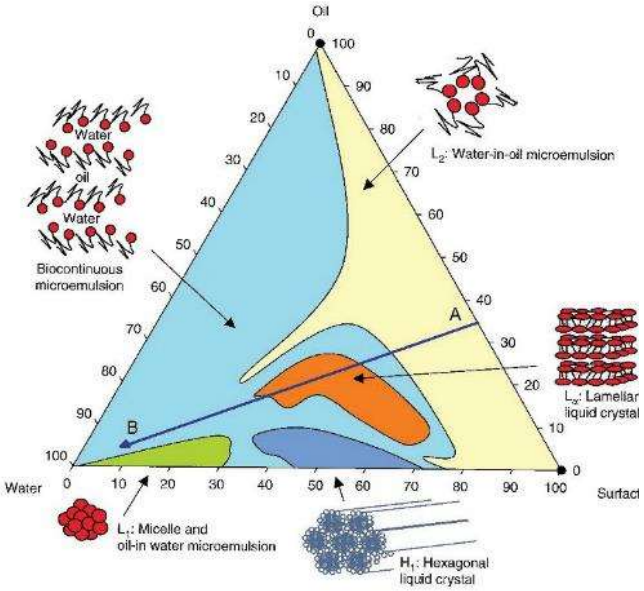
- **Emulsões, microemulsões e nanoemulsões**


Figure 6: Appearance comparison between emulsion, micro emulsion and nano emulsion.

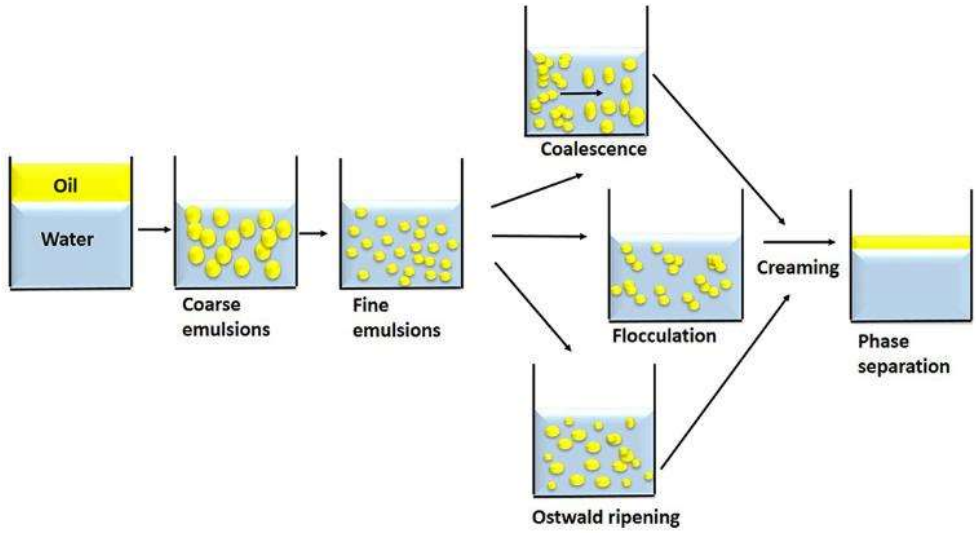
| | | | |
|---|---|---|---|
| Particle size | 1 to 20 mm | 1 and 100 nm | 1 and 100 nm |
| Formation | Mechanical shear | Self assembly | Mechanical shear |
| Stability | Thermodynamically unstable, Kinetically Stable | Thermodynamically Stable<br>Long shelf life | Kinetically stable/ metastable, thermodynamically unstable |
| Phases | Biphasic | Monophasic | Monophasic |
| Viscosity | High | Low | Low (about 1 cP at room temperature) |

- **Emulsões, microemulsões e nanoemulsões**

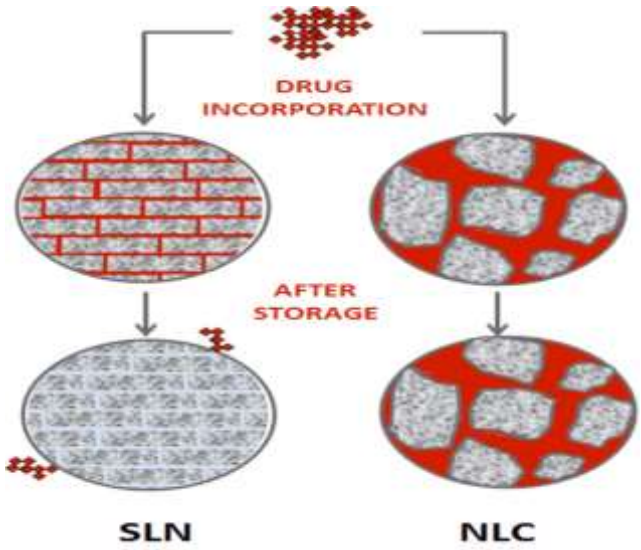


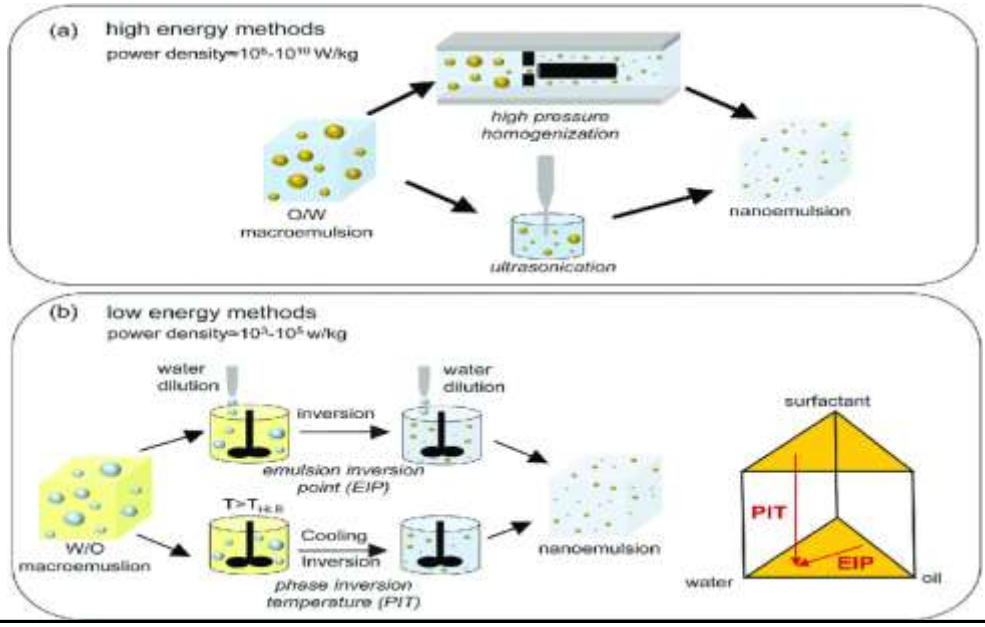
- **Emulsões, microemulsões e nanoemulsões**



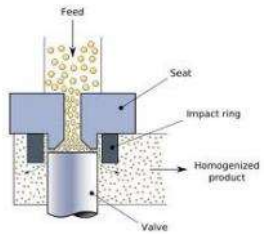

- **Partículas Lipídicas Sólidas (SLN) e Carreadores Lipídicos Nanoestruturados (NLC)**

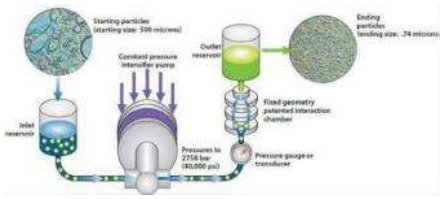


# * Métodos de fabricação




# * Métodos de Alta Energia

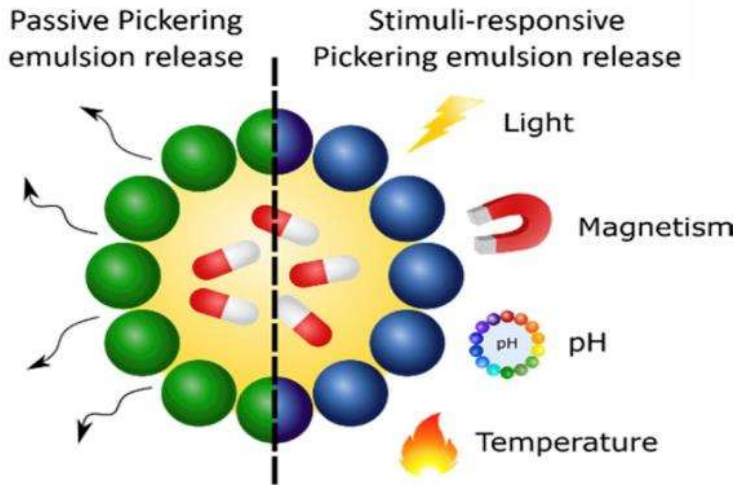


## * Ultrasound processing

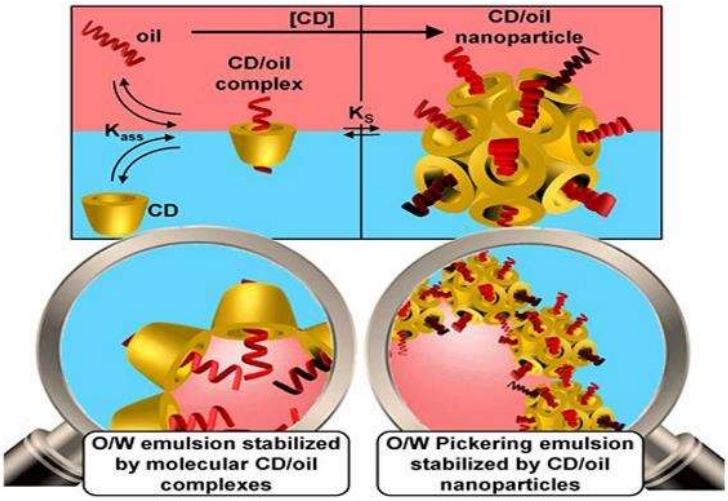
## PROCESSOS DE FABRICAÇÃO

- **Emulsões Pickering**



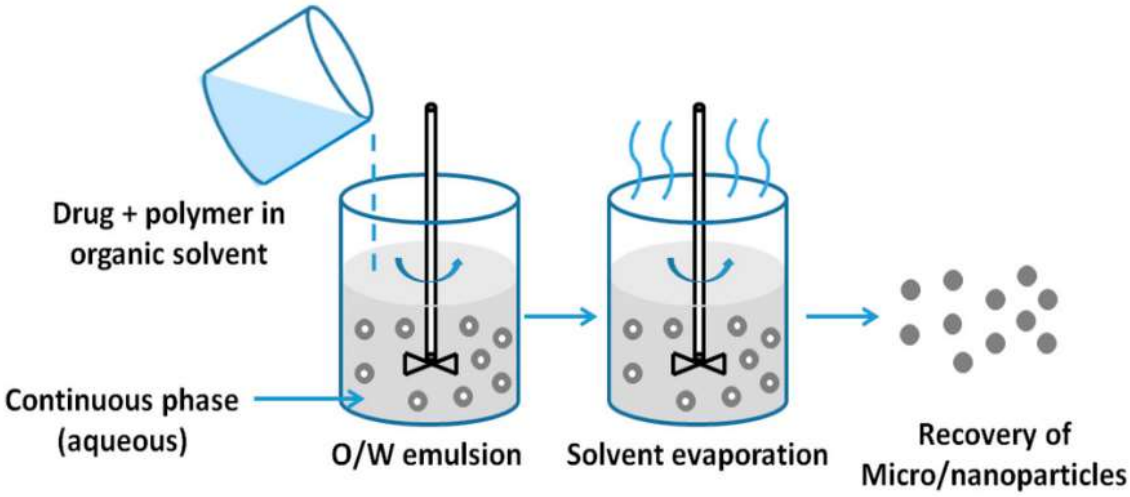
## PROCESSOS DE FABRICAÇÃO

- **Emulsões Pickering**




## PROCESSOS DE FABRICAÇÃO

- **Evaporação do solvente**



# PROCESSOS DE FABRICAÇÃO

- **Polimerização interfacial**

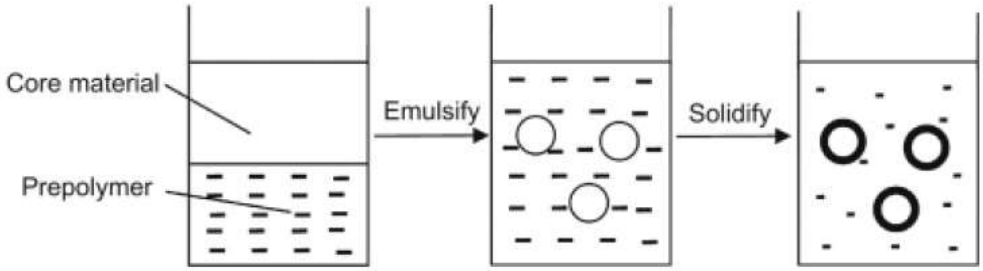



Figure 15.6. Diagram of the in situ polymerization for liquid core materials.

# PROCESSOS DE FABRICAÇÃO

- **Polimerização interfacial**

Ativo + monômero (isocianato) + Surfactante + catalizador (ou agente de cura – trietanolamina)

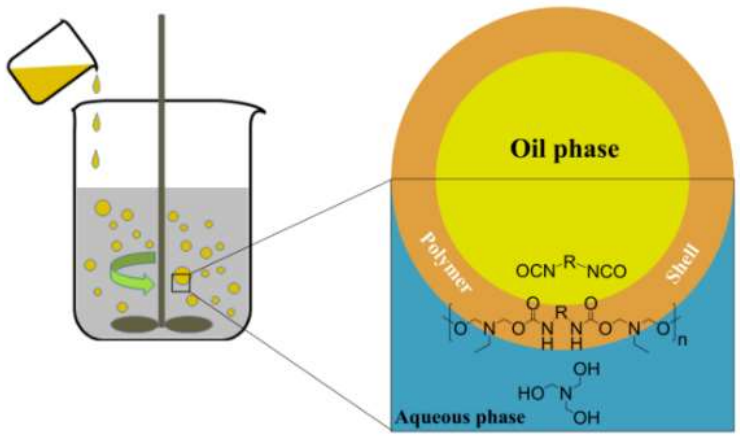
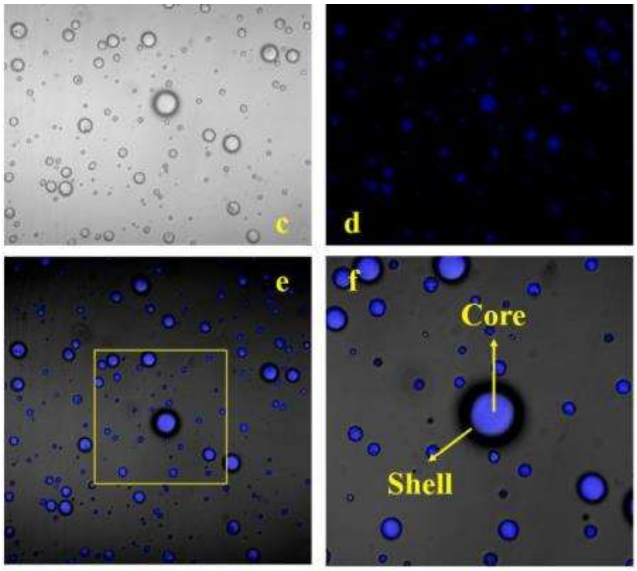



Fig 1. Schematic diagram of the possible formation mechanism of pirimiphos-methyl/polyurethane microcapsules.



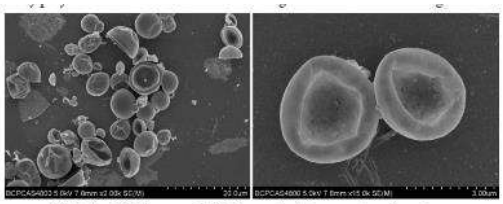
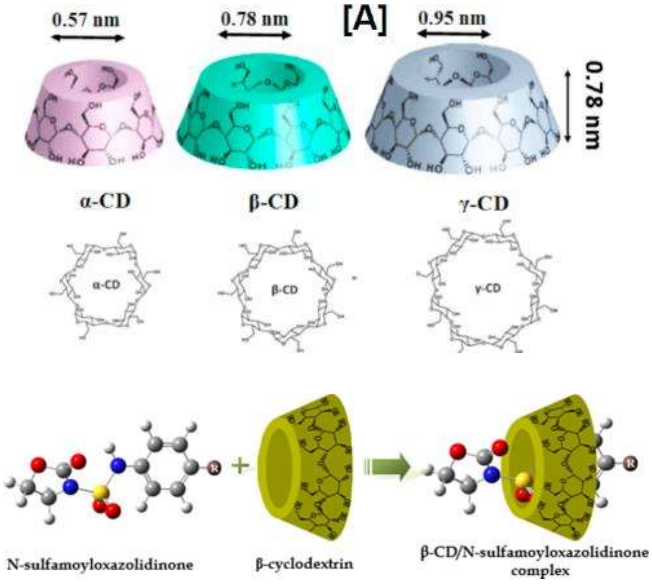



Fig 8. The SEM images of pirimiphos-methyl microcapsules after release.

- **Inclusão molecular**



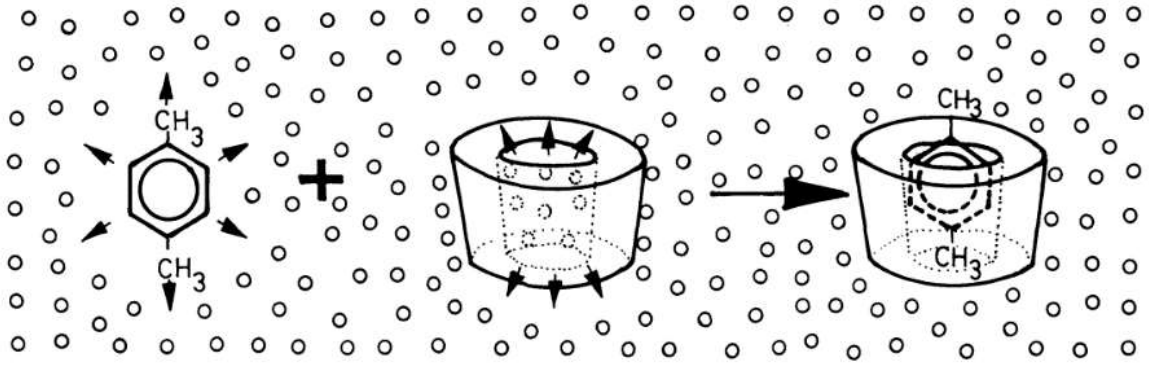
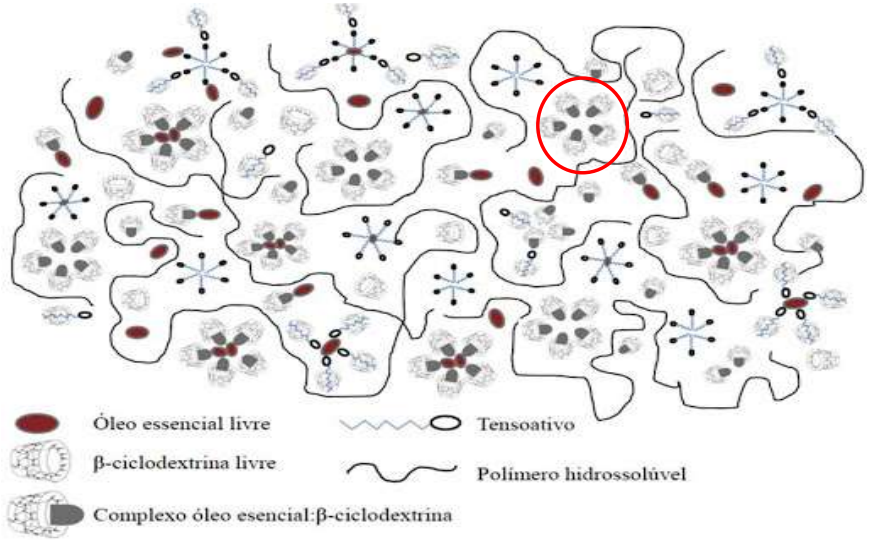



Fig.2-1. *Schematic representation of cyclodextrin inclusion complex formation. p-Xylene is the guest molecule, the small circles represent the water molecules.*

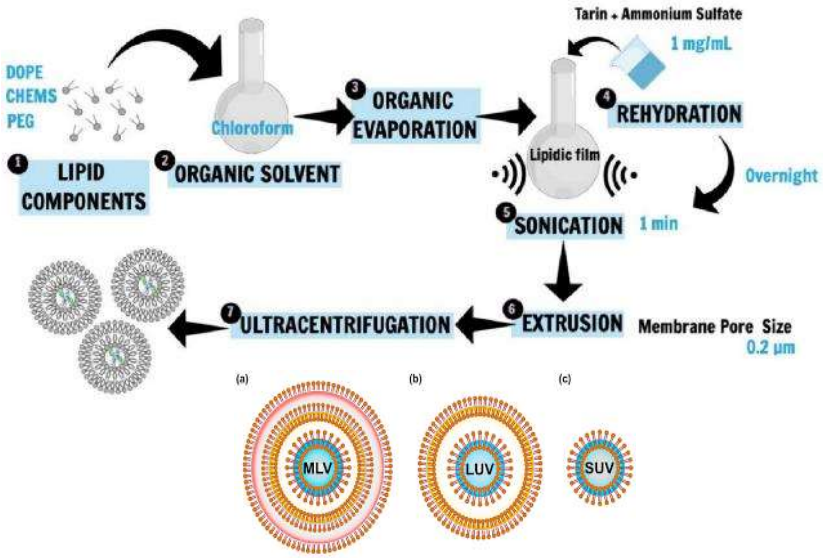
- Podem ser usados para aumentar a solubilidade de compostos insolúveis, estabilizar compostos sensíveis à oxidação, controlar volatilidade e modificar sabores e odores.



# MÉTODOS DE FABRICAÇÃO

- *Método de Co-Precipitação*
- *Malaxagem*
- *"Slurry"*
- *Evaporação do solvente*
- *Secagem em spray-drying*
- *Liofilização*
- *Fluido supercrítico*

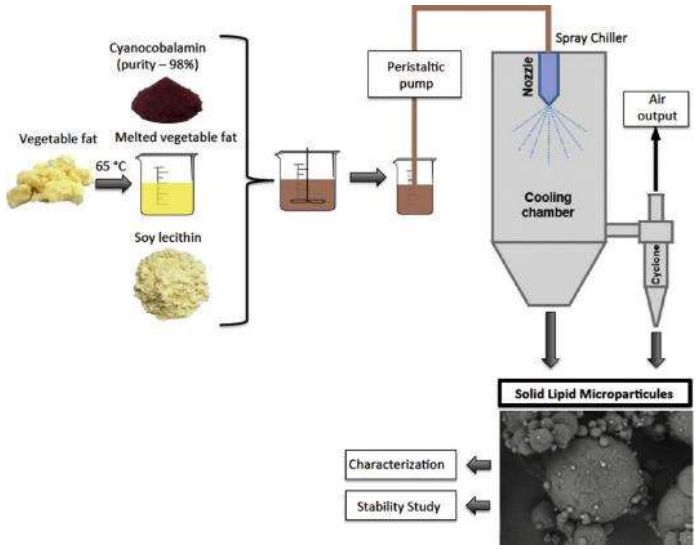
- **Liposomas e proliposomas**




(a) Multilamellar vesicles (MLV) (b) Large unilamellar vesicles (LUV) (c) Small unilamellar vesicles (SUV)

# PROCESSOS DE FABRICAÇÃO

- **Solidificação de material fundido**




## Emulsificação por membranas

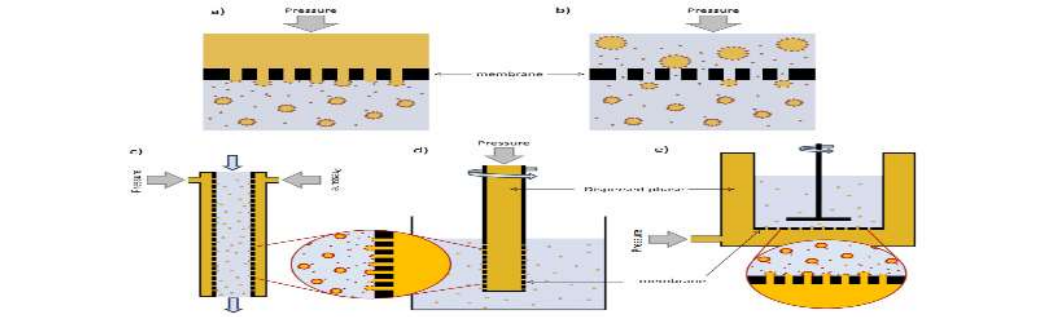



Fig. 3. Schematic representation of the four main types of membrane emulsification techniques: a) direct membrane emulsification (DME), b) premix membrane emulsification, both adapted from Piacentini et al. [134], c) cross-flow membrane emulsification (XME), adapted from Yuan et al. [135], d) rotational membrane emulsification (RME), adapted from Manga et al. [111] and e) stirred-cell membrane emulsification (SCME).

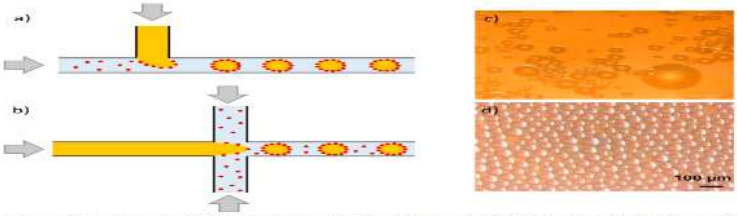



Fig. 4. a) and b) examples of microfluidic devices for Pickering emulsions preparation: a) T-junction, b) flow focusing, c) and d) light micrographs of oil/water dodecane emulsions prepared by c) a homogenizer and d) a microfluidic emulsification. Some scale bar on both (c) and d) from Xu et al. [137].

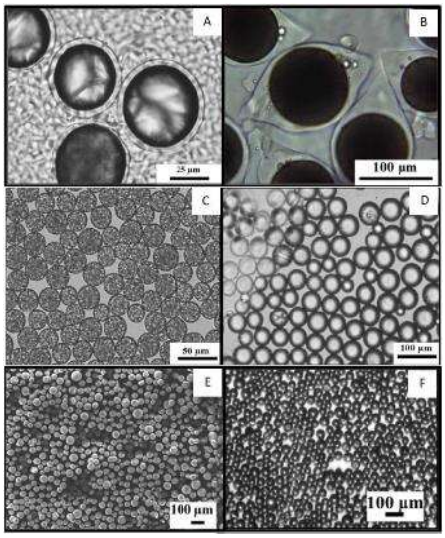
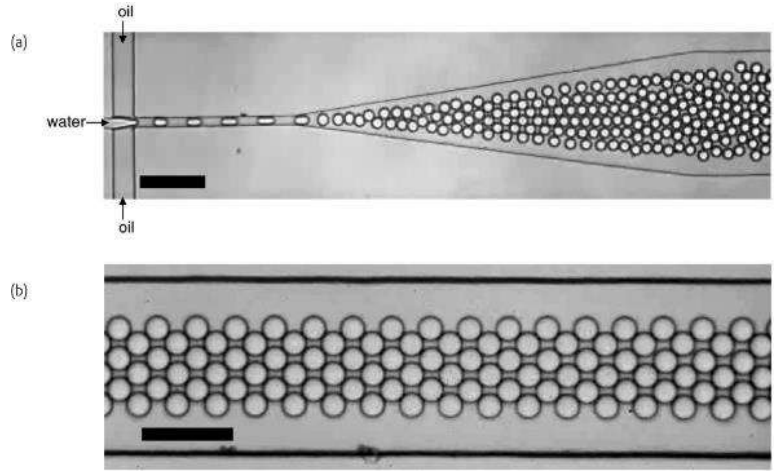



**Fig. (7).** Particles produced by membrane emulsification coupled with; **A-B**) complex coacervation (core-shell particles); **C-D**) solvent diffusion (biodegradable polymer particles) and **E-F**) drying (inorganic particles).

Fonte: Piacentini, E., Dragosavac, M., & Giorno, L. (2017). Pharmaceutical particles design by membrane emulsification: preparation methods and applications in drug delivery. *Current pharmaceutical design*, *23*(2), 302-318.

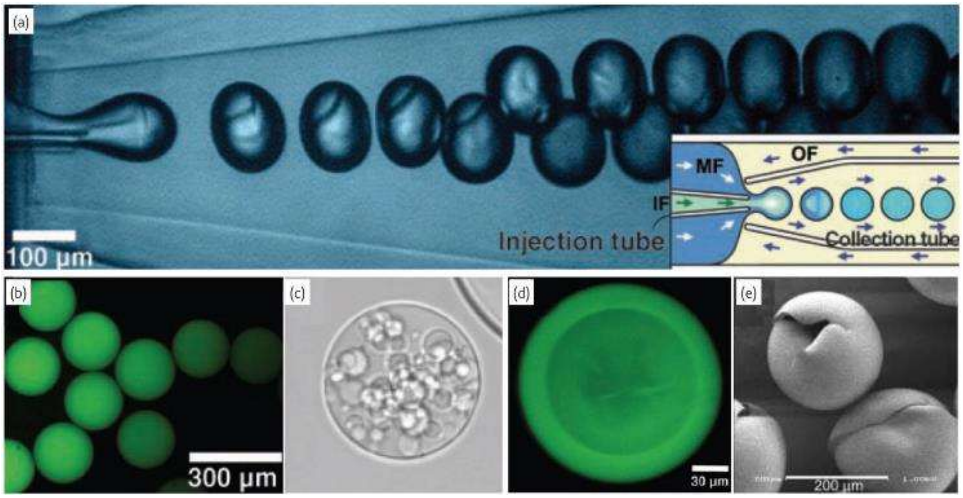
# PROCESSOS DE FABRICAÇÃO

## Microcanais (microfluidics)



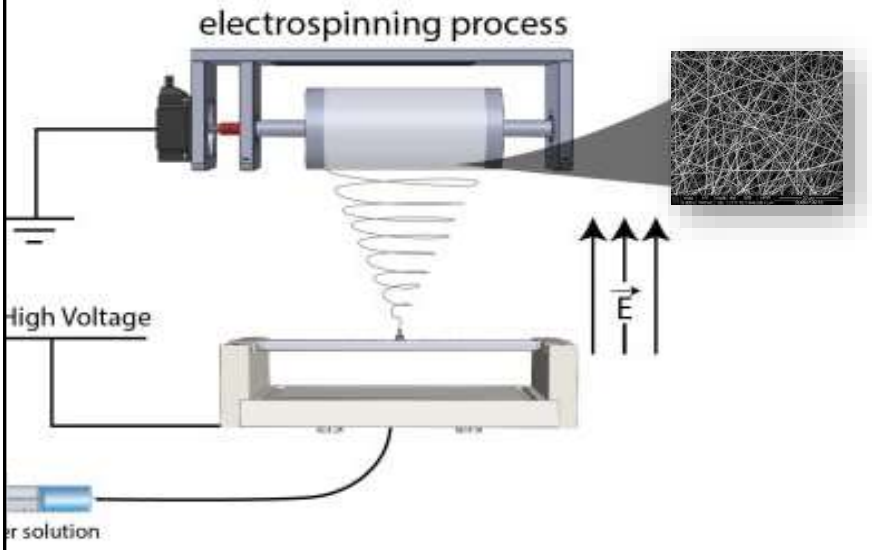
## PROCESSOS DE FABRICAÇÃO

### Microcanais (microfluidics)

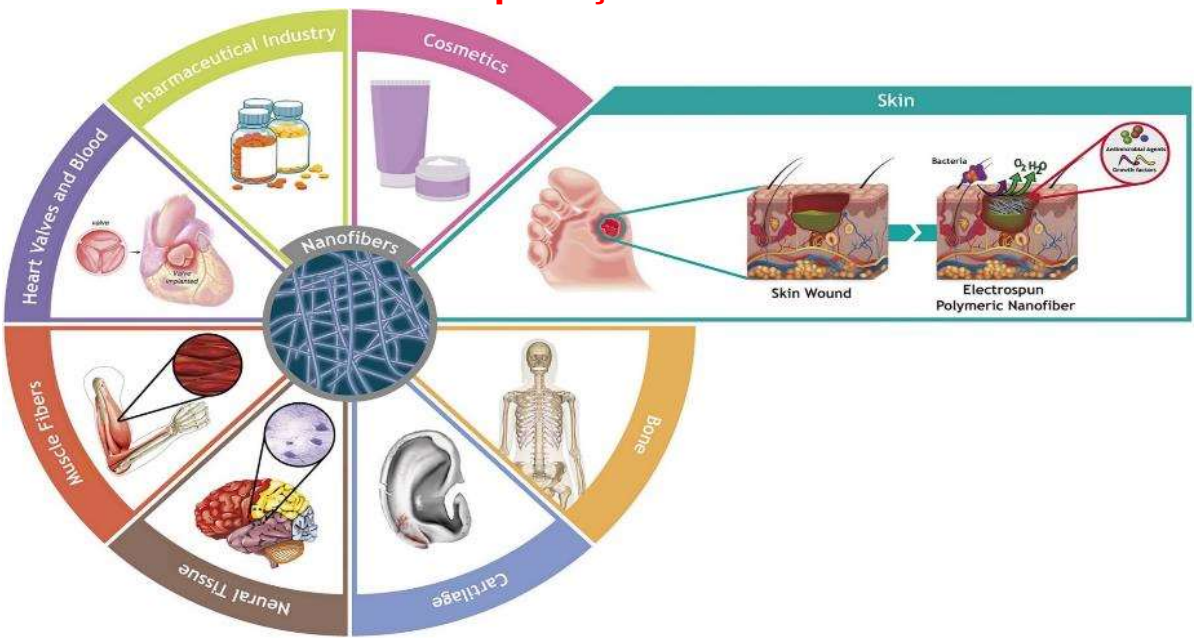



## PROCESSOS DE FABRICAÇÃO

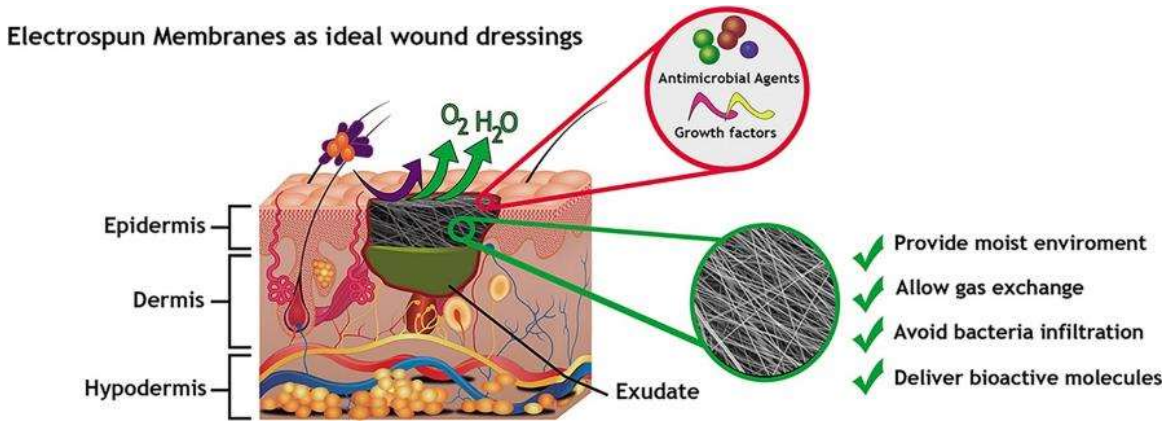
- **Eletrofiação (electrospinning) - Micro e nanofibras**



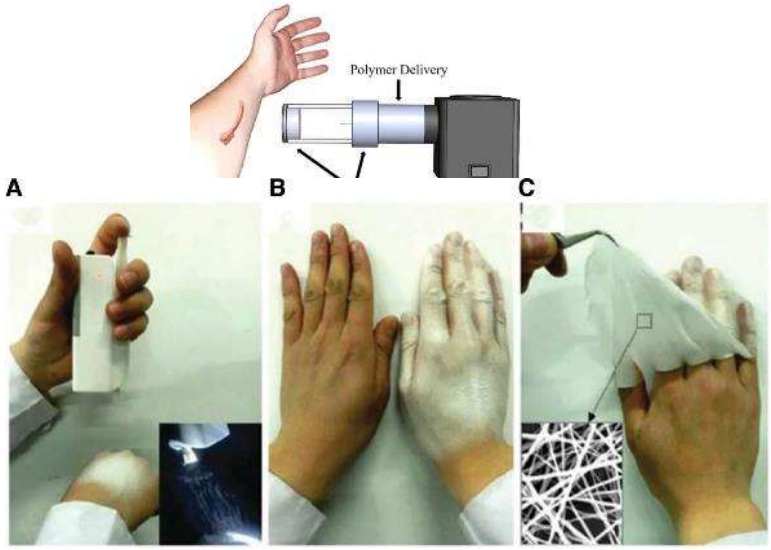

- **Micro e nanofibras - Aplicações**




- **Micro e nanofibras - Curativos de feridas crônicas**

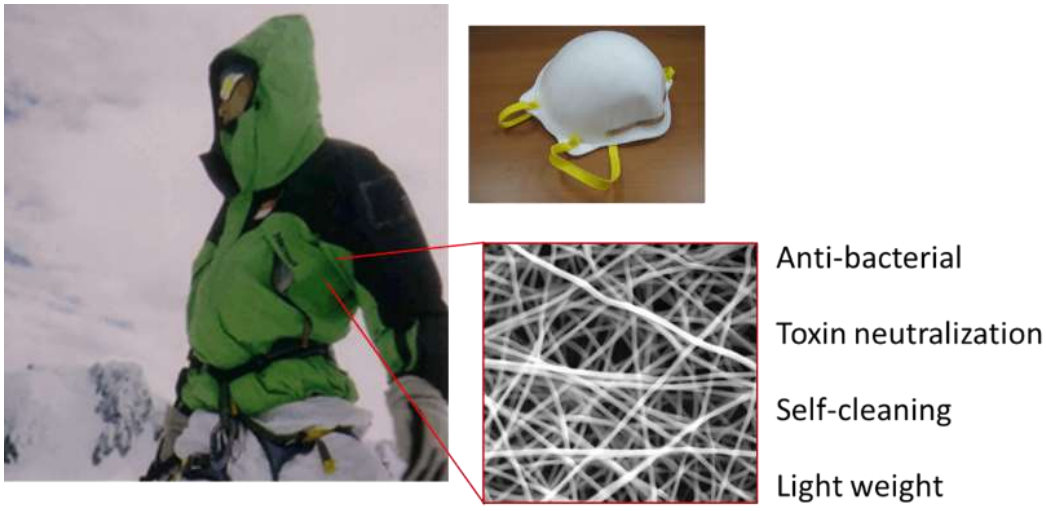


- **Micro e nanofibras - Curativos de feridas crônicas**

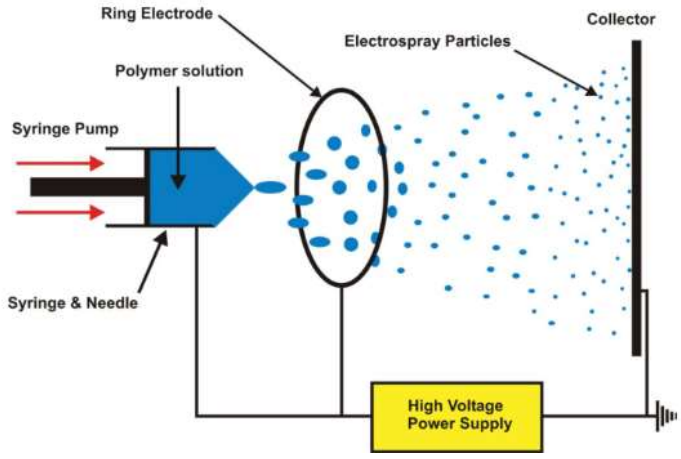



Liu, Y., Zhou, S., Gao, Y., & Zhai, Y. (2019). Electrospun nanofibers as a wound dressing for treating diabetic foot ulcer. *Asian Journal of Pharmaceutical Sciences*, *14*(2), 130-143.

- **Micro e nanofibras - Tecidos inteligentes - EPIs**



- **Eletroatomização (electrospraying)**




Alehosseini, Ali, et al. "Principles of electrospraying: A new approach in protection of bioactive compounds in foods." *Critical reviews in food science and nutrition* 58.14 (2018): 2346-2363.

- **Eletroatomização (electrospraying)**

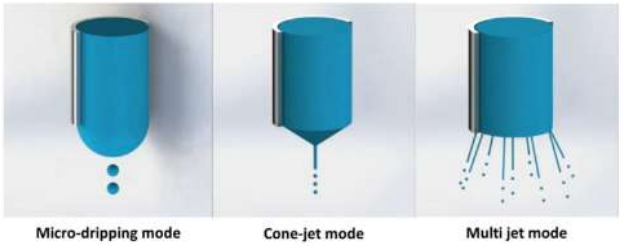
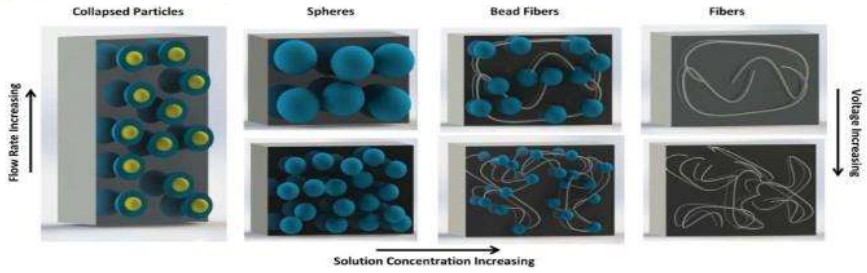



Figure 3. Common modes of electrospraying process.




Alehosseini, Ali, et al. "Principles of electrospraying: A new approach in protection of bioactive compounds in foods." *Critical reviews in food science and nutrition* 58.14 (2018): 2346-2363.

- **Micro e nanofibras - Tecidos repelentes de insetos**

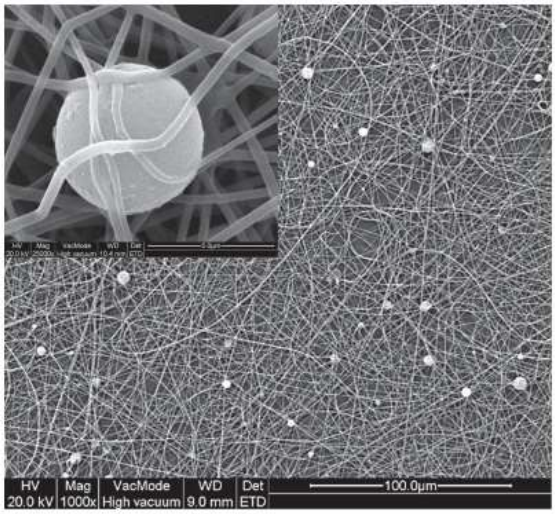
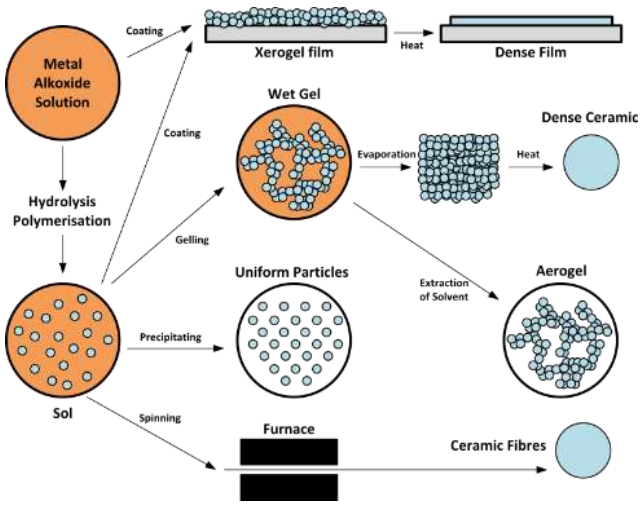



**Figure 11.4** Nanofibres with insect repellent microcapsules (source: Ghent University).

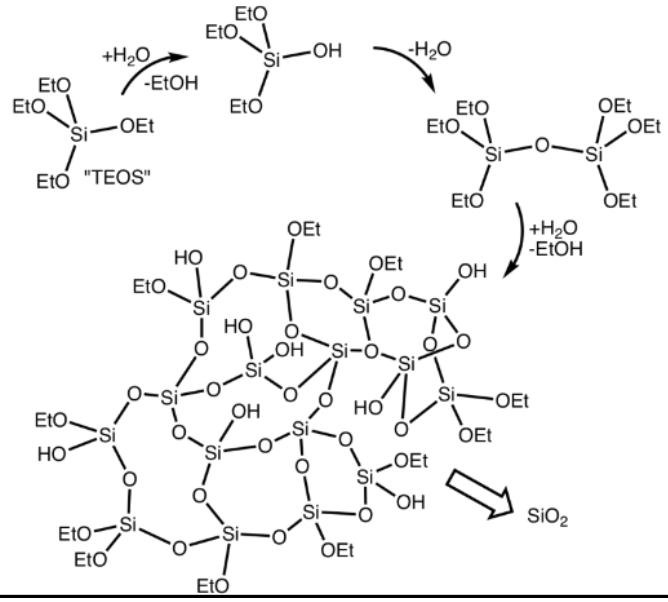
# PROCESSOS DE FABRICAÇÃO

- **Processo Sol-Gel**

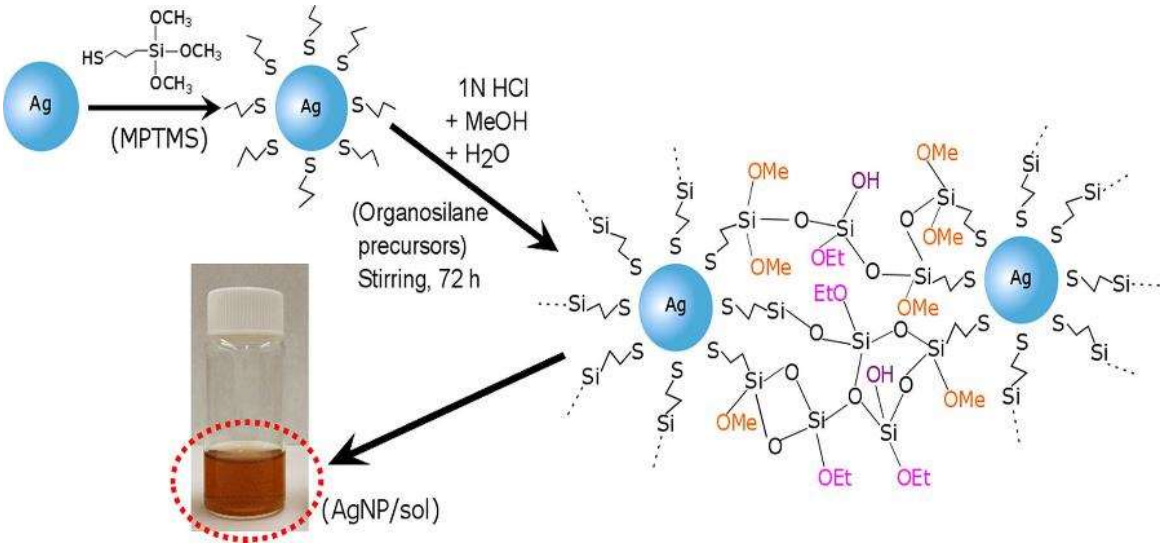


***Processo Sol-Gel : Stöber process***

**Precursor**: Tetraethyl orthosilicate, **TEOS**



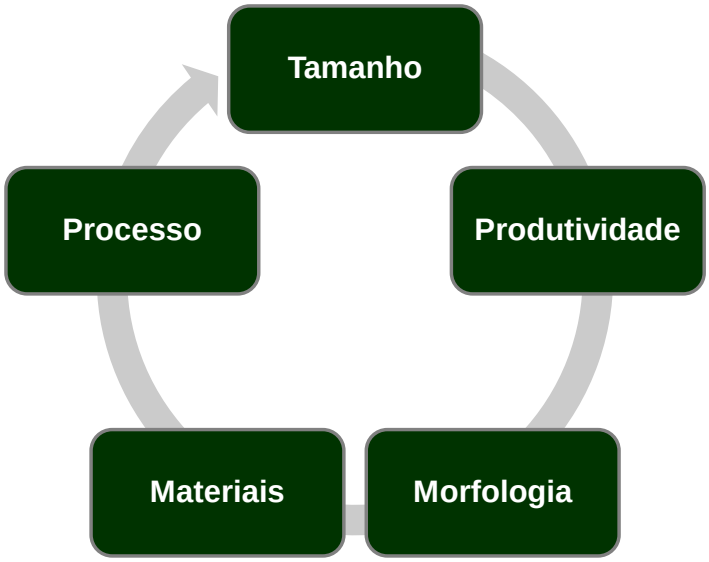

- **Processo Sol-Gel**



# SELEÇÃO DO PROCESSO

**PLANEJAMENTO RACIONAL**

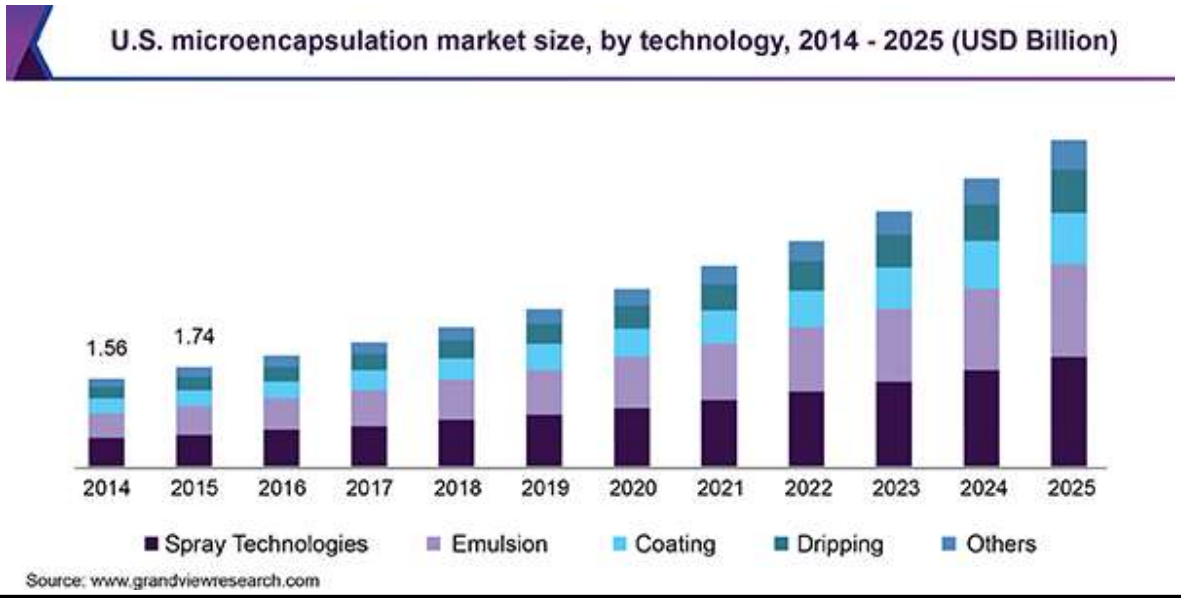
1. ***Decida por um ponto de partida***
2. ***Avalie a viabilidade***
3. ***Analise as expectativas***




# PROJETO DE UM PROCESSO DE ENCAPSULAÇÃO

| | |
|---|---|
| **Quantidade** | **Ativo?** |
| **P&D** | **Propriedades físicas?** |
| **Processo e Scale-up** | **Estado físico?** |
| **Composição** | **Dimensão do produto?** |
| **Processo de encapsulação** | **Estrutura ?** |
| **Secagem** | **Condições de armazenagem?** |
| **Armazenagem** | **Incorporação em produtos?** |
| **Reidratação** | **Processamento Final?** |
| **Liberação** | **Forma física final?** |
| **Absorção** | **Tipo de liberação?** |

## ➢MERCADO



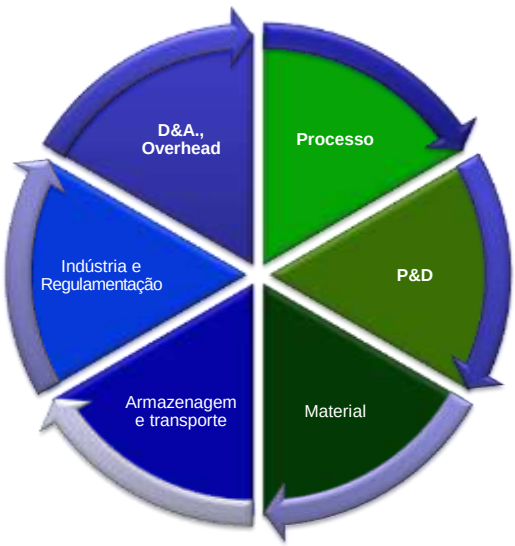

# CUSTOS DA ENCAPSULAÇÃO

**Regulamentações:**

- BPF
- Controle Qualidade
- Normatização

**Indústria:**

- Materiais aprovados
- Qualificação Processo
- Questões Ambientais




- Disponibilidade
- Batelada x Contínuo
- Qtd produzida
- Equipamentos
- Recursos humanos
- Qualidade
- Controle Ambiental
- Utilidades

# CONSIDERAÇÕES FINAIS

*Existem uma grande diversidade de tecnologias, materiais e processos de encapsulação, o que torna bastante complexa a definição do processo ideal para uma determinada aplicação.*

*A definição do processo deve envolver um estudo sistematico e racional, avaliando questões de disponibilidade de equipamentos, materias primas possíveis de serem utilizadas, facilidade de escalonamento, propriedades do produto, custos e questões de aprovação nas Agências Reguladoras.*

*Não há uma receita pronta e o estudo deve ser realizado para cada tipo de produto e aplicação onde o processo é exigido.*

***Thank You !!!***