Nanocosméticos & Absorção Percutânea

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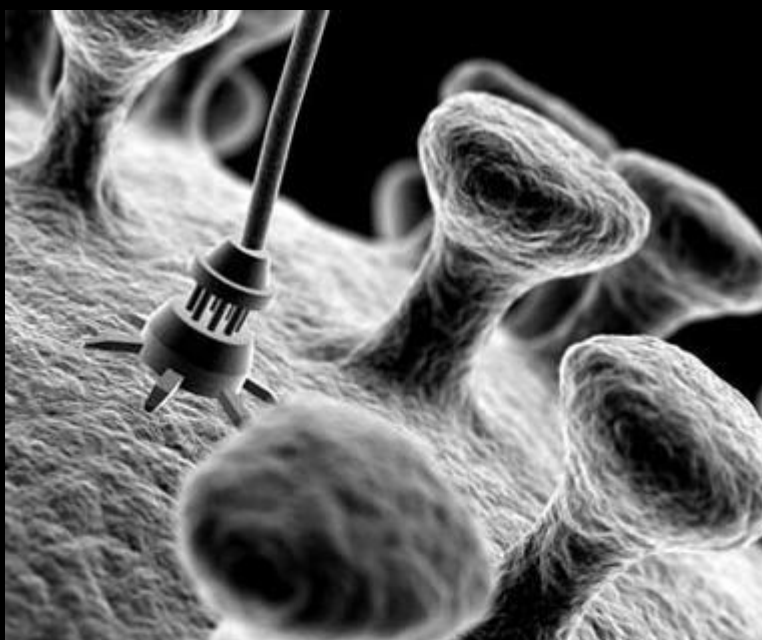
PUCPR

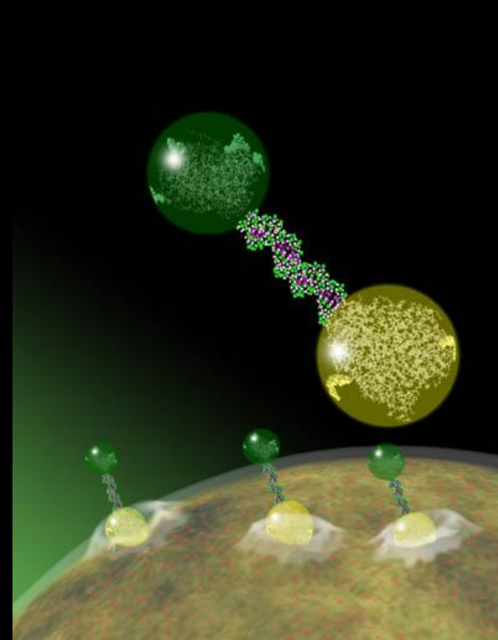
Equilibra&ABC

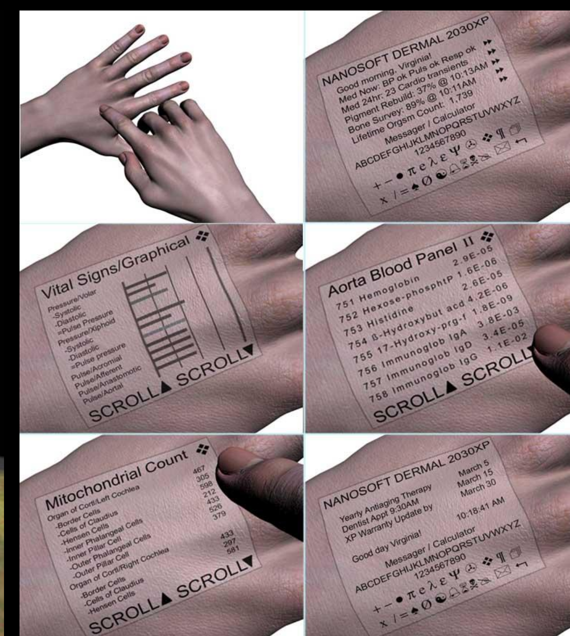
JLJansen Consultoria

Introdução

Nanotecnologia - ciência capaz de integrar engenharia com biologia, química e física.







ESTĒE LAUDER

CHANEL

Dermazone SOLUTIONS

SHISEIDO

REVLON

SKINCEUTICALS

O Boticário®
você pode ser o que quiser

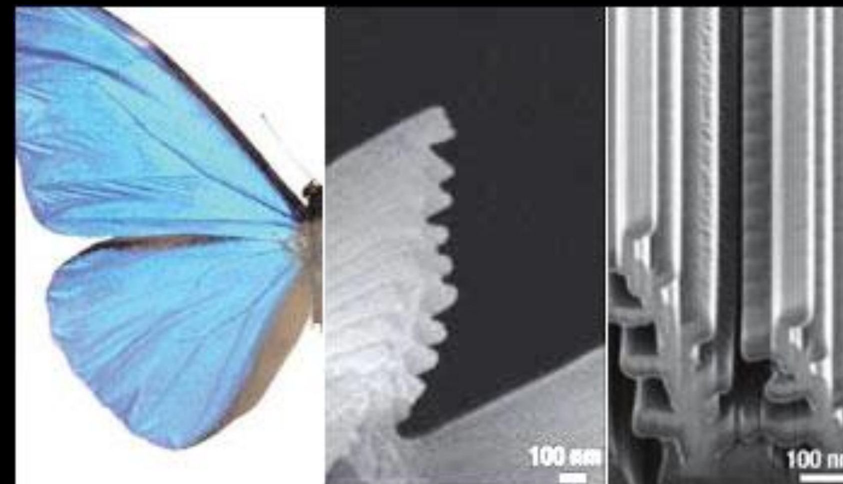
L'ORÉAL PARIS

natura

dr. brandt®

Procter&Gamble

A indústria de produtos cosméticos incorporou esta tecnologia com sucesso há aproximadamente duas décadas.


100 nm


SHISEIDO
Benefiance
NutriPerfect
Night Cream / Crème de Nuit


PreACTIVE
MÁSCARA PURIFICANTE
COM ARGILA BRANCA
O Boticário
O Boticário
VitACTIVE
SISTEMA ANTI-SINAIS AVANÇADO
ADVANCED ANTI-AGING SYSTEM
FPS 25
O Boticário
VitACTIVE
O Boticário


LANCÔME
PRIMORDIALE
OPTIMUM NUIT


LANCÔME
RE-SOURCE


CHANTECAILLE
Crème Energisante aux Nano Particules d'Or
Nano Gold Energizing Cream
Aromacologie


HR
HELENA RUBINSTEIN
30
DEFENSE
HIGH/HAUTE
PROTECTION
GOLDEN BEAUTY
anti-ageing suncare protection
soin solaire protection anti-âge
face - visage

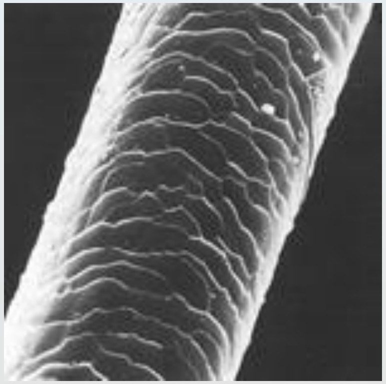

GARNIER
AMBRE
SOLAIRE
men 25
High protection gel-cream
100% non-greasy
with aloe vera + vitamin E
especially designed for sport, sweat resistant
instantly absorbed, non-sticky
photostable UVA/UVB protection
100mL
dermatologically tested

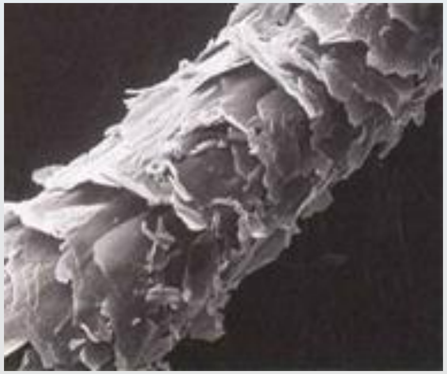

BLOQUEADOR SOLAR
SUNDOWN
EMBALAGEM ECONÔMICA
FPS
50
Johnson & Johnson
Conteúdo 200 ml

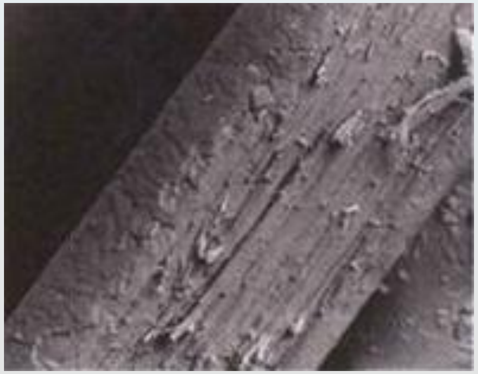
Tintura de Cabelo

- **Tinturas comuns - abertura das cutículas do cabelo → cabelos mais danificados**

- **Tinturas com tecnologia nano - permeação da tintura sem abrir as cutículas → cabelos menos degradados**





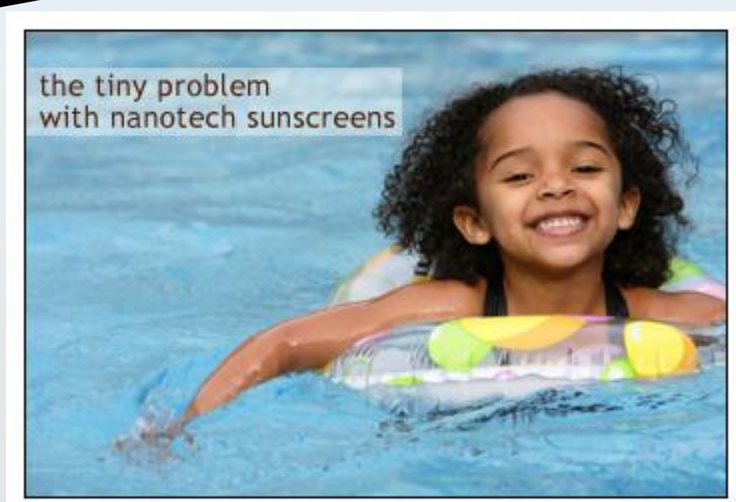


Mídia

The Washington Post

Nanotechnology Precaution Is Urged
Minuscule Particles in Cosmetics May Pose Health Risk, British Scientists Say

Small Ingredients, Big Risks



CERTIFIED BY THE GLYCEMIC RESEARCH INSTITUTE • WASHINGTON, D.C. •
NANO SAFE
NANO INSIDE ®
NANO TECHNOLOGY

Os antigos Egípcios usavam nanotecnologia

Nanotechnology, 2006

Centre de recherche et de restauration des musées de France discovered that the lead-based chemistry invented by the ancient Egyptians over 4,000 years ago could be used to synthesize nanoparticles.

Dr. Philippe Walter and his team used an ancient Egyptian hair-dyeing recipe, dating to the Graeco-Roman period, to dye black hair. The hair was later shown to contain lead-sulphide nanocrystals of 5 nanometers

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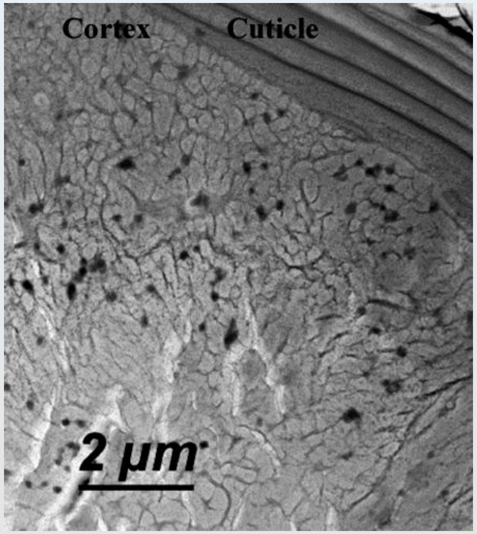
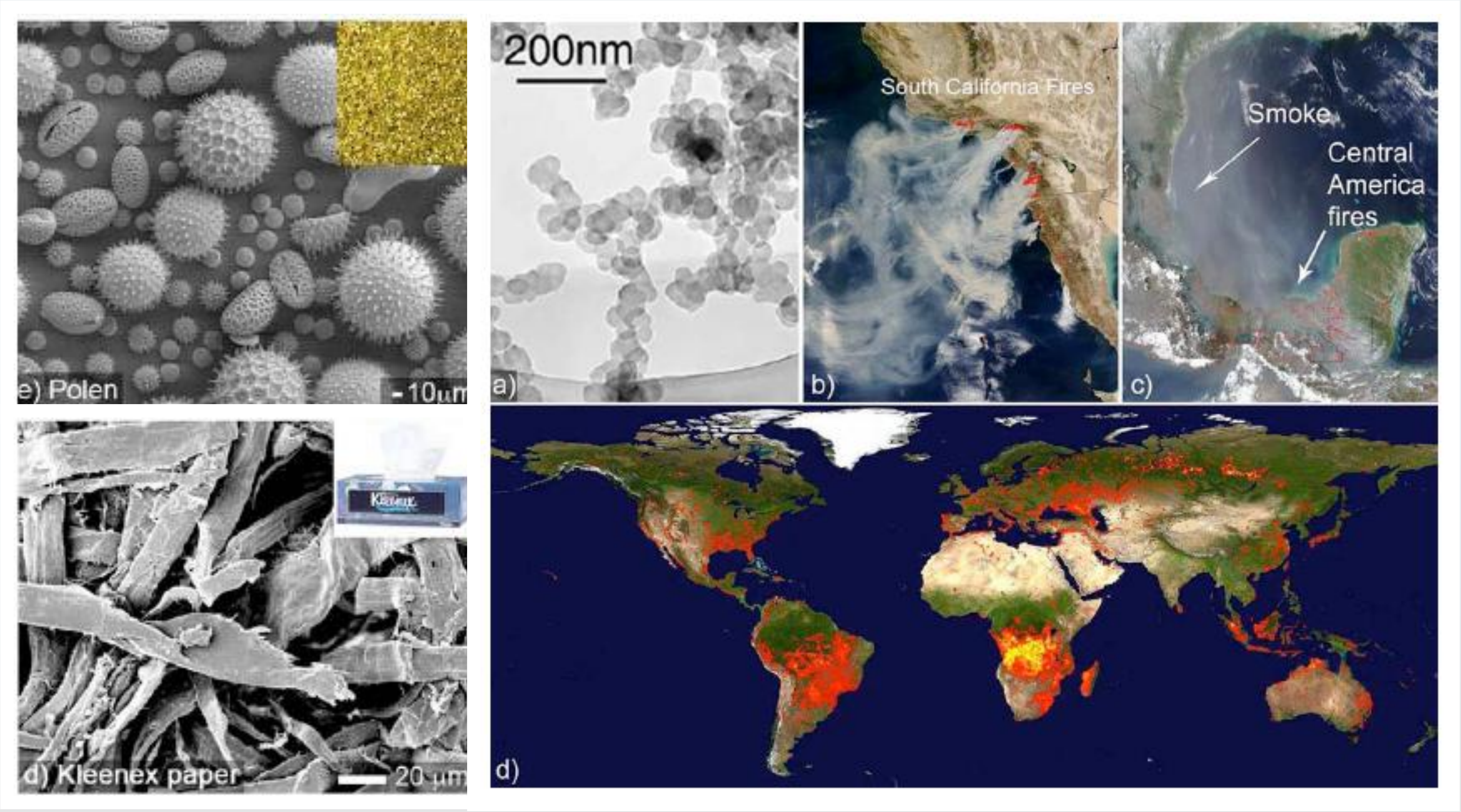
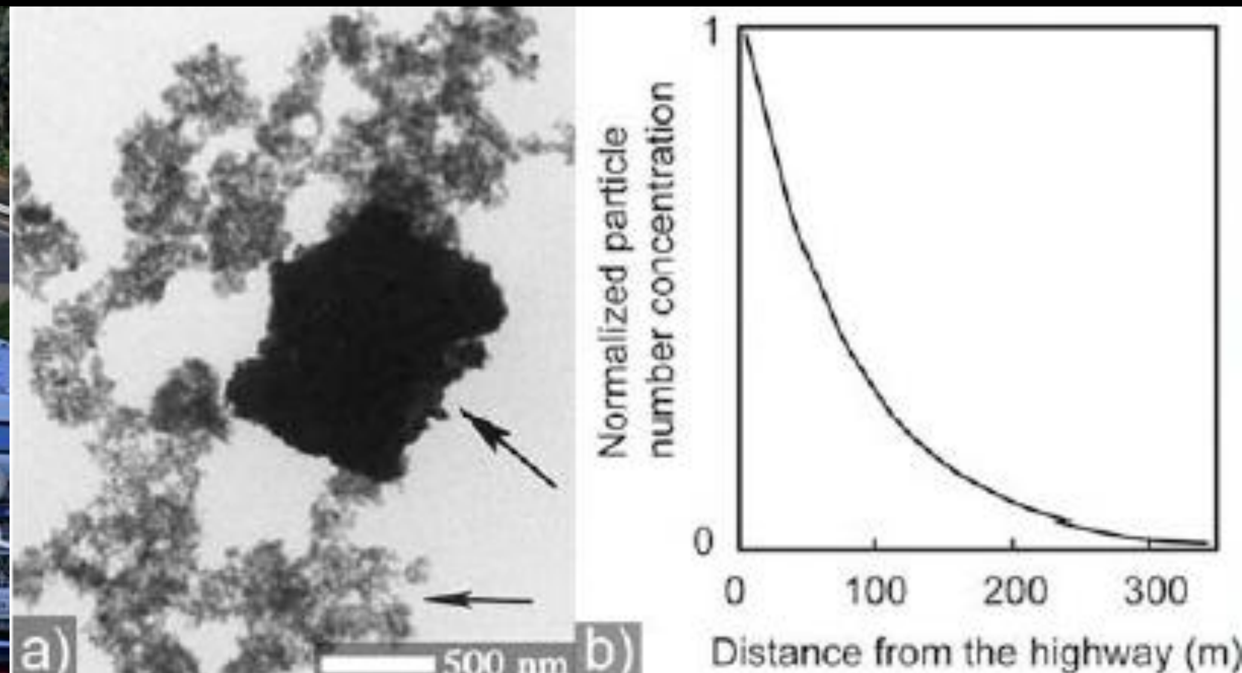
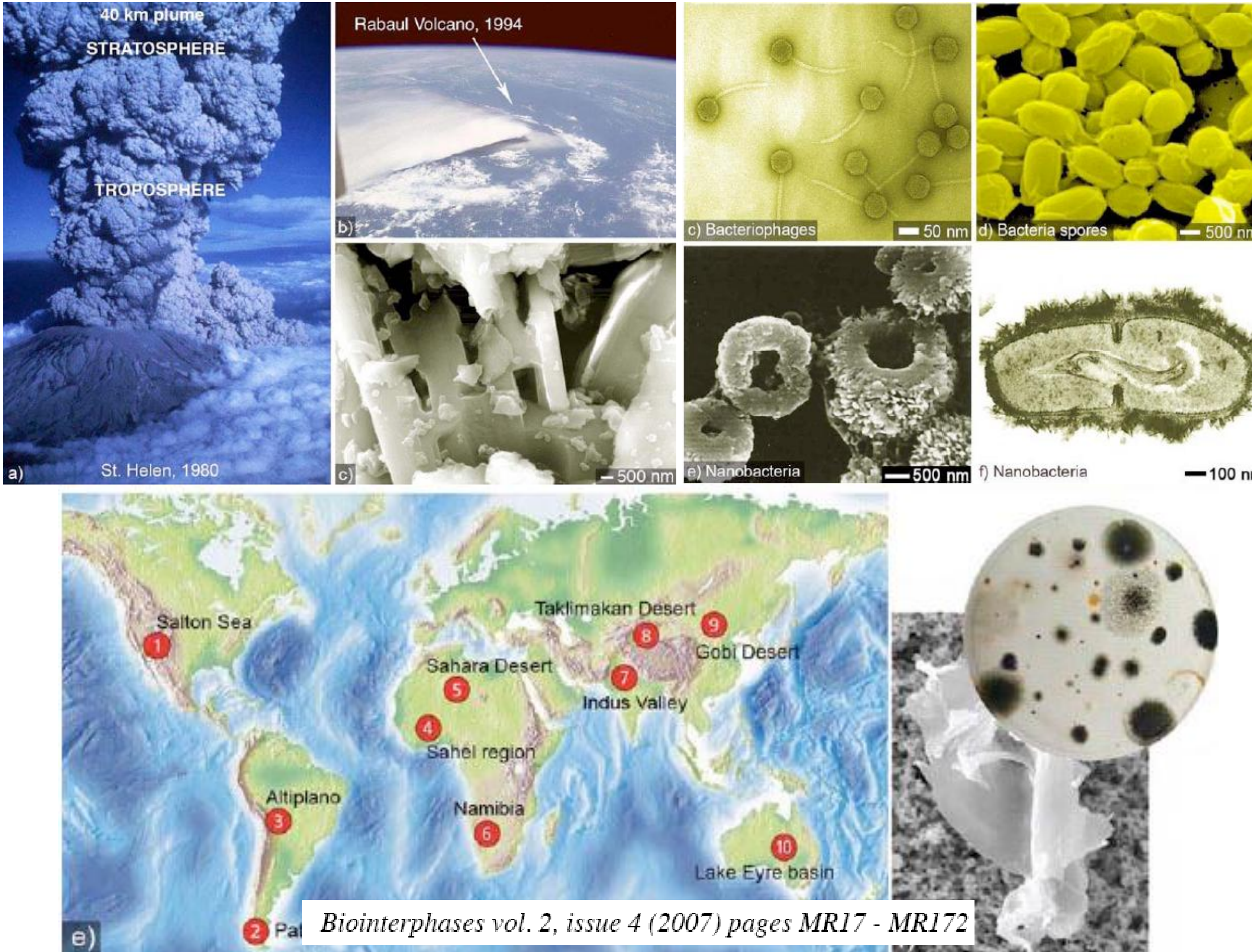


1 cm^3 de ar urbano contêm de 10000 – 50000 nanopartículas





(a) TEM showing typical engine exhaust particles (carbon aggregates)
(b) Particle concentration decreases exponentially with downwind distance from the freeway (diameter 6 – 220 nm)



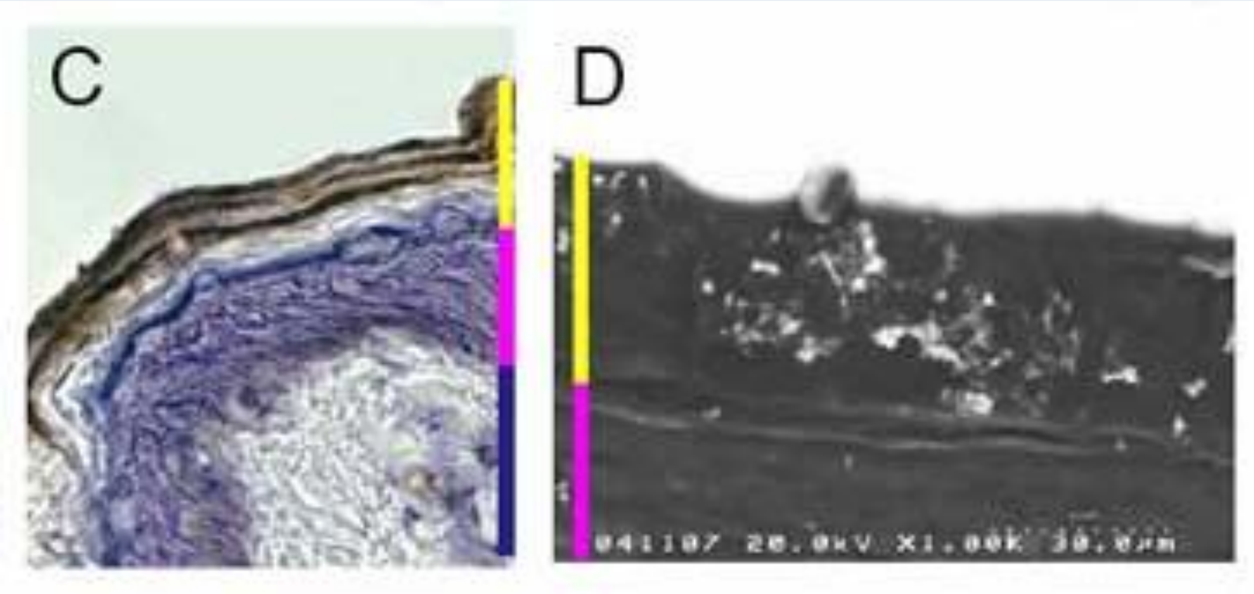
Biointerphases vol. 2, issue 4 (2007) pages MR17 - MR172

Aspectos toxicológicos

Journal of Investigative Dermatology (2007) **127**, 1701–1712;

Penetration of Metallic Nanoparticles in Human Full-Thickness Skin

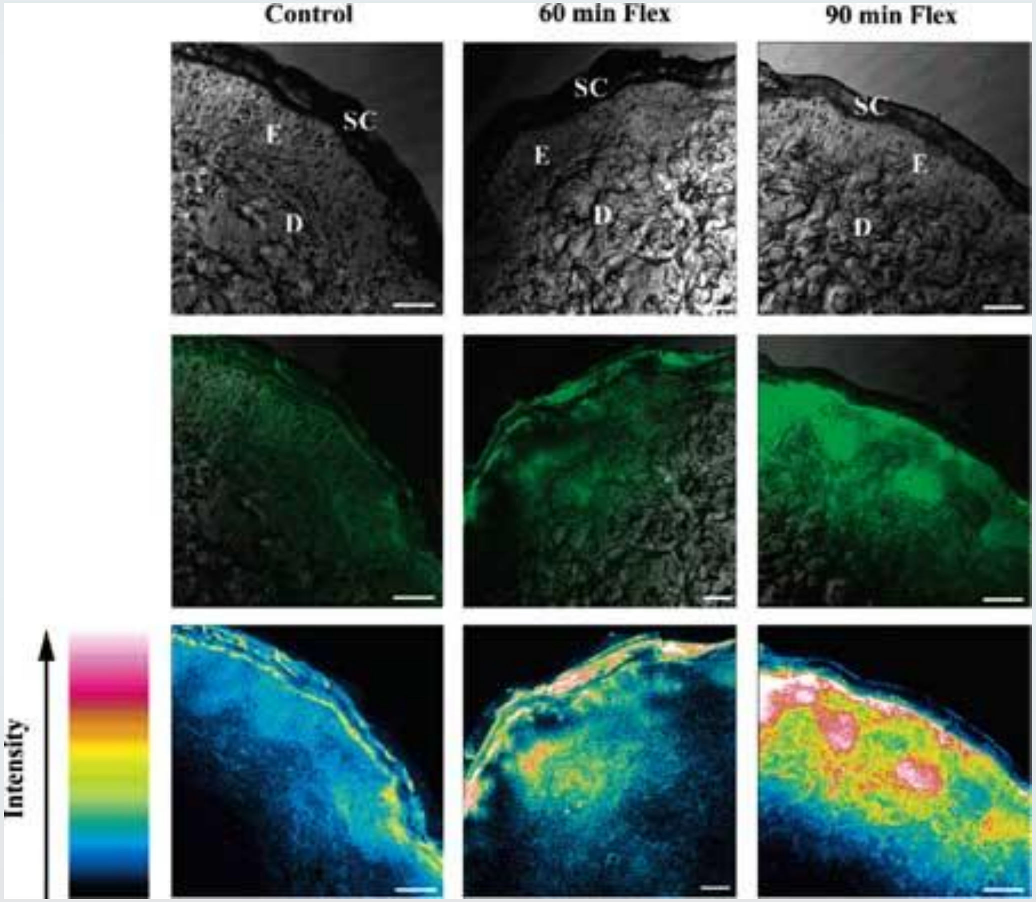
Baroli et al.



< 10 nm

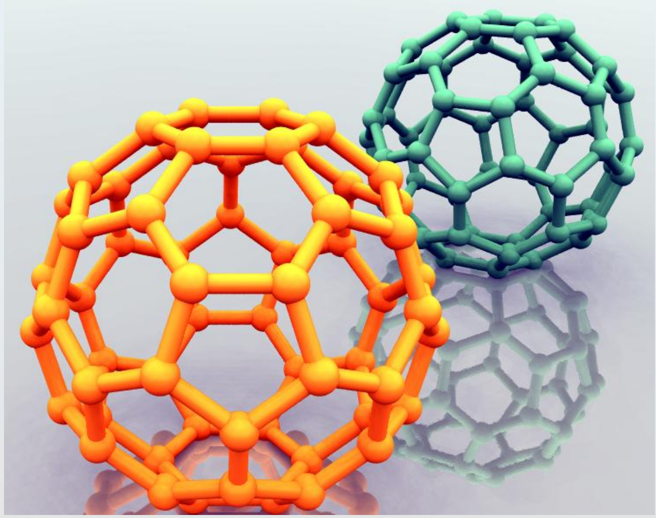
C) Hematoxylin-stained human skin exposed to TMAOH-maghemite nanoparticles.
D) EDS-SEM micrograph showing nanoparticle deposits (white spots) within the stratum corneum, stratum corneum-viable epidermis junction, and a little below the junction.

Aspectos toxicológicos



"Fullerene-based amino acid nanoparticle interactions with human epidermal keratinocytes"

3,5 nm



Jillian G. Rouse [a,b], Jianzhong Yang [c], Andrew R. Barron [c], Nancy A. Monteiro-Riviere [a,b,*]

Toxicology in Vitro 20 (2006) 1313–1320

PRELIMINARY OPINION ON

SAFETY OF NANOMATERIALS IN COSMETIC PRODUCTS

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risk

Approved by the SCCP for public consultation
12th plenary of 19 June 2007

The actual situation for dermal exposure is as follows:

1) There is evidence of some skin penetration into viable tissues (mainly into the *stratum spinosum* in the epidermal layer, but eventually also into the dermis) for very small particles (less than 10 nm), such as functionalised fullerenes and quantum dots.

2) When using accepted skin penetration protocols (intact skin), there is no conclusive evidence for skin penetration into viable tissue for particles of about 20 nm and larger primary particle size as used in sunscreens with physical UV-filters.

3) The above statements apply to healthy skin (human, porcine). There is an absence of appropriate information for skin with impaired barrier function, e.g. atopic skin or sunburned skin. A few data are available on psoriatic skin.

4) There is evidence that some mechanical effects (e.g. flexing) on skin may have an effect on nanoparticle penetration.

5) There is no information on the transadnexal penetration for particles under 20 nm. Nanoparticles of 20 nm and above penetrate deeply into hair follicles, but no penetration into viable tissue has yet been observed.

Análise CEE

Table 2. Examples of nanocosmetic products in the market

After sun products VITAMIN NANOCAPSULES
Anti aging FULLERENES Firming Anti-Oxidant Serum FULLERENES Aging Skin Resuscitating Serum MICRONIZED GLUCONOLACTATE Anti Aging Finishing Powder MICRONIZED INGREDIENTS Vitamin A and C Serum MICRONIZED LIPOSOMES Serum MICRONIZED ZINC OXIDE, MICRONIZED TITANIUM DIOXIDE NANOENCAPSULATED INGREDIENTS RETINOL NANOCAPSULES VITAMIN NANOSOMES OF SODIUM LACTATE, NANOSOMES OF CALENDULA, NANOSOMES OF WITCH HAZEL, NANOSOMES OF GINSENG, NANOSOMES OF UREA, NANOSOMES OF VITAMIN A AND E, NANOSOMES OF PRO-VITAMIN B5, NANOSOMES OF ALPHA-BISABOLOL AND GERMAL II NANOSOMES OF VITAMIN A
Anti-itch / rash cream MICRONIZED ZINC OXIDE NANOENCAPSULATED INGREDIENTS
Around-eye cream FULLERENES LYPHAZOME NANOSPHERES MICROSOME Eye Gel MICRONIZED LIPOSOMES
Blush MICRONIZED INGREDIENTS MICRONIZED POWDER BRUSHES MICRONIZED TITANIUM DIOXIDE (COATED or not WITH DIMETHICONE) MICRONIZED ZINC OXIDE
Body firming lotion NANO_DELIVERY SYSTEM Reduction Anti-Cellulite NANOSOMES OF CENTELLA ASIATICA
Body wash /cleanser NANOSOMES OF VITAMIN A
Bronzer/highlighter MICRONIZED ITALIAN TALC POWDER MICRONIZED ROSE QUARTZ POWDER, MICRONIZED TOPAZ POWDER MICRONIZED ZINC OXIDE NANO-VITAMINS
Camouflage makeup MICRONIZED GLUCONOLACTATE
Concealed MICRONIZED POWDER MICRONIZED TITANIUM DIOXIDE, MICRONIZED ZINC OXIDE NANOSPHERES OF HYALURONIC ACID AND FULVIC ACID
Conditioner MICRONIZED TITANIUM DIOXIDE
Diaper cream MICRONIZED ZINC OXIDE

Nanotecnologia em Cosméticos

Inovação	Produto	Benefício da nanotecnologia
Nanoemulsões	Condicionadores capilares	Textura única, transparência
Nanocápsulas e Vesículas	Skin care	Proteção & Transporte do ingrediente ativo
Nanopigmentos	Filtros solares	Filtro UV, transparência

Nanotecnologia em Cosméticos

Cuidado!

A avaliação de um ingrediente cosmético deve ser efetuada com respeito às suas propriedades físicas, químicas e físico-químicas.

Isto significa que, **independente do processo utilizado para fabricar e da dimensão das partículas** de um determinado ingrediente utilizado em produtos cosméticos, os **requisitos de segurança** devem ser cumpridos antes que esse ingrediente possa ser utilizado em cosméticos.

Nanotecnologia em Cosméticos

Para termos grandes soluções, sem grandes problemas

Recomendação:

Estudos de permeação utilizando modelos *in vitro / in vivo*, que garantam a segurança de uso dos nanocosméticos.

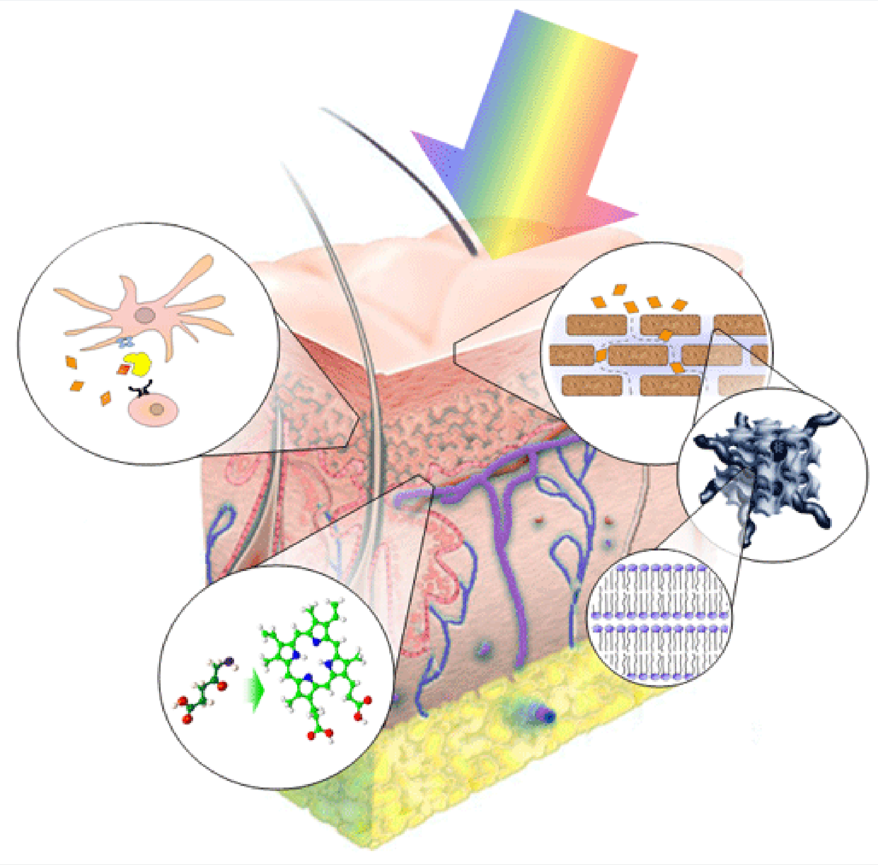
Estudos de Nanotoxicidade que assegurem a inocuidade destes materiais aos trabalhadores das industrias de cosméticos, aos consumidores, e ao meio ambiente.

Absorção Percutânea

Processo biológico complexo

Tecido dinâmico

Parâmetros de absorção



Quando aplicamos um cosmético estamos colocando em contato com a pele ativos no seio de uma formulação, como um creme, um pó, uma loção ...

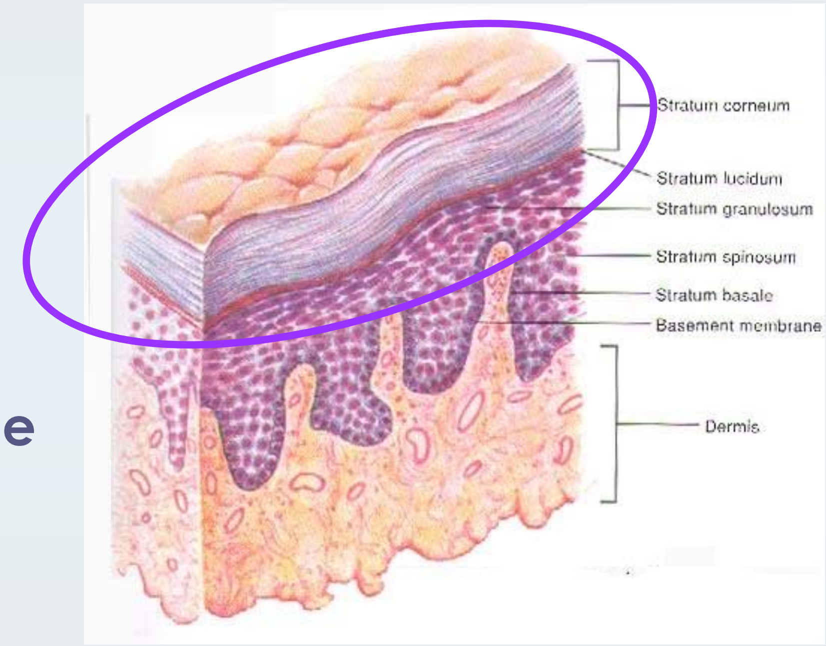
A absorção percutânea depende de como esse conjunto de moléculas interage com o stratum corneum e a pele.

Pele

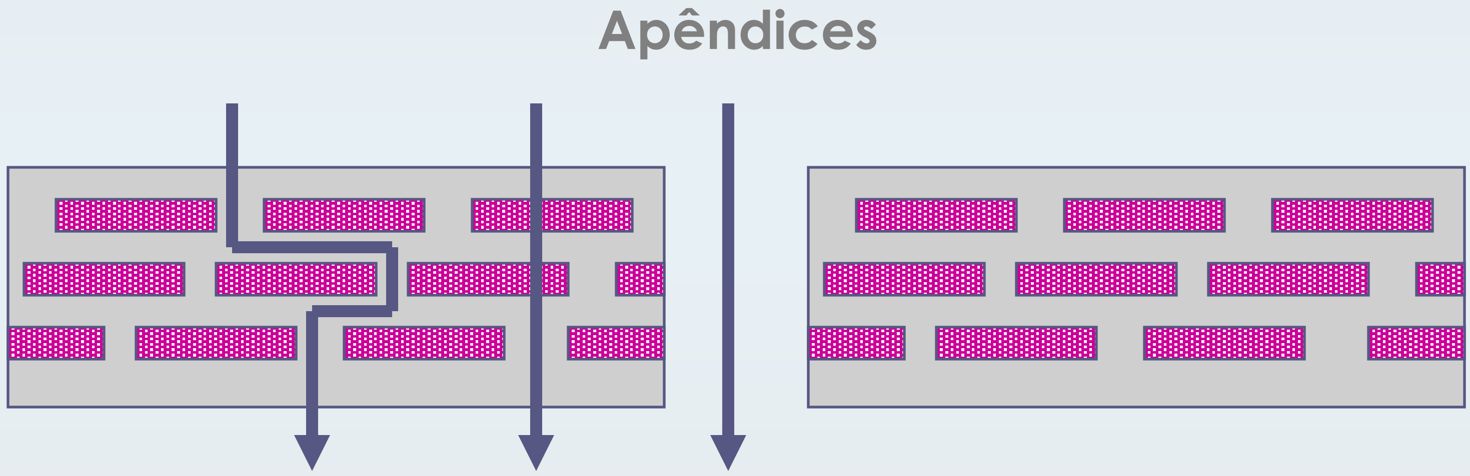
Uma das principais funções da pele é a função barreira.

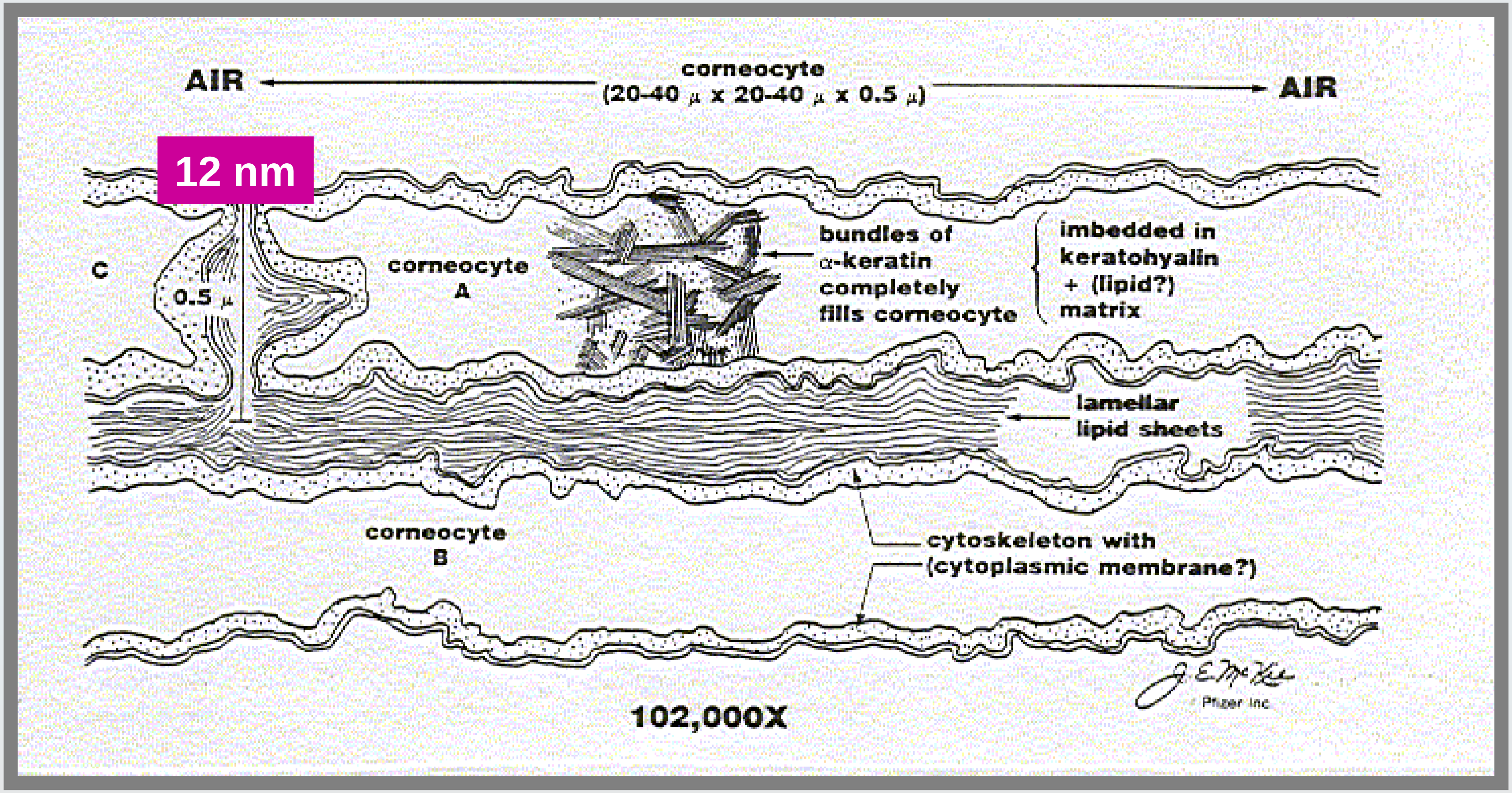
Stratum corneum

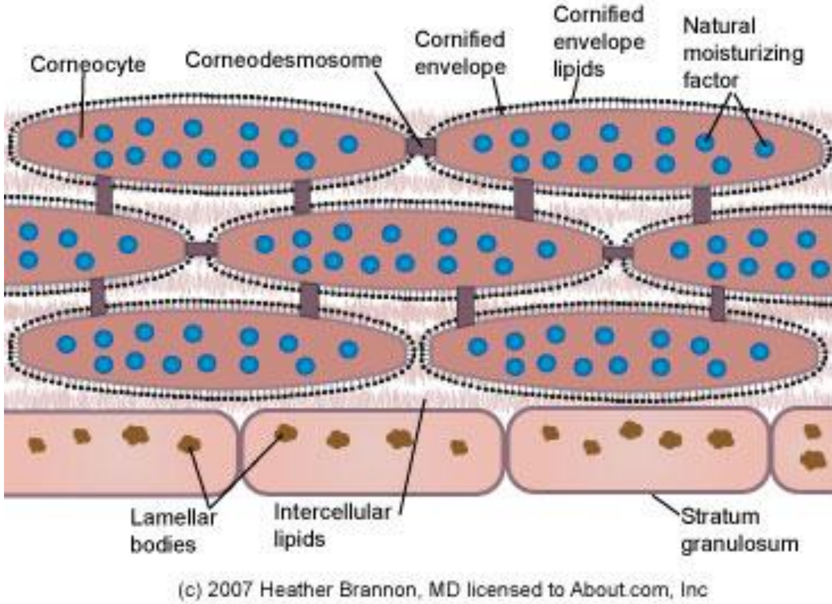
Evita a perda de água, eletrólitos e outros constituintes e "impede"(no seu limite) a penetração de moléculas do meio ambiente.

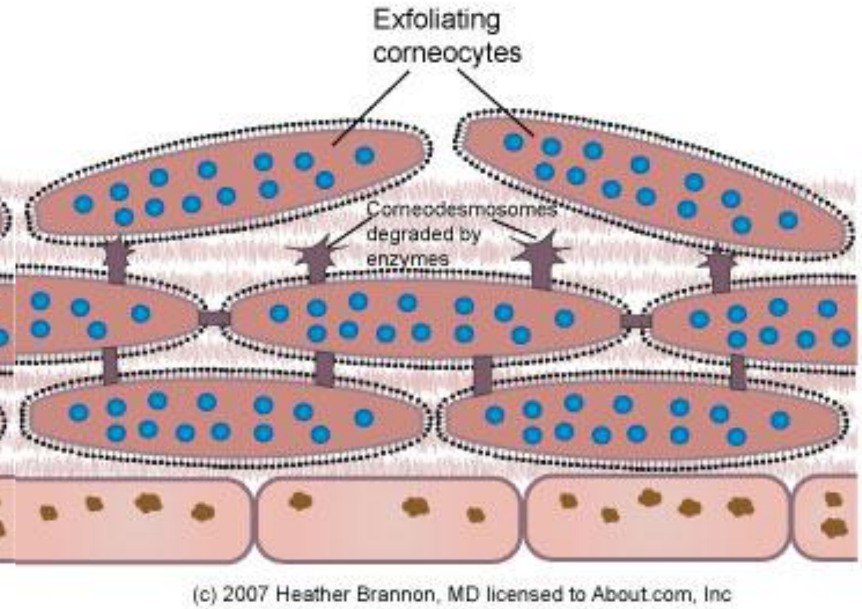


Caminhos da penetração através do Stratum Corneum




AIR
corneocyte
(20-40 μ x 20-40 μ x 0.5 μ)
AIR
12 nm
C
0.5 μ
corneocyte
A
bundles of
α-keratin
completely
fills corneocyte
imbedded in
keratohyalin
+ (lipid?)
matrix
lamellar
lipid sheets
corneocyte
B
cytoskeleton with
(cytoplasmic membrane?)
Pfizer Inc
102,000X





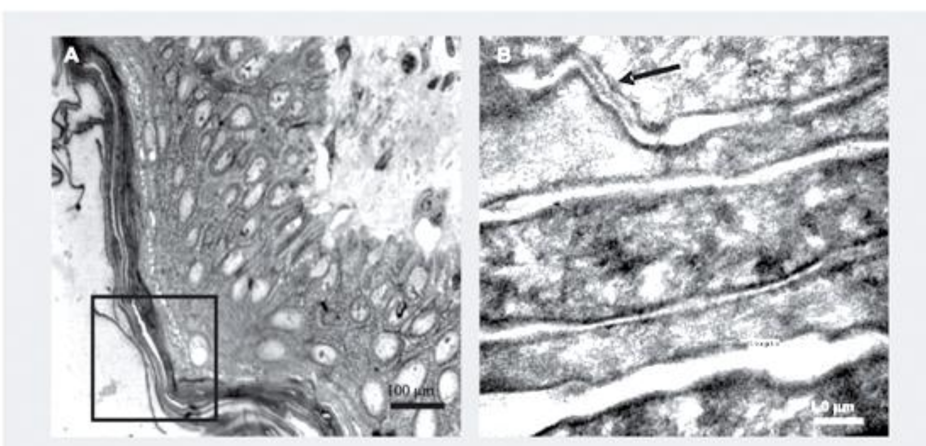
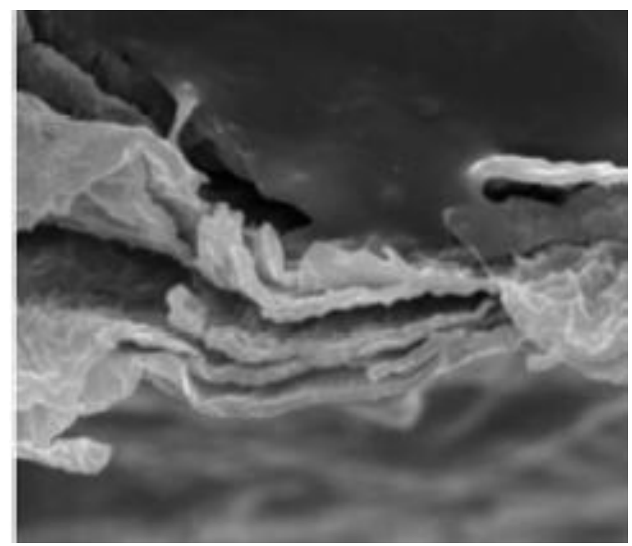


FIGURE 1 - (**A**) Light microscope micrograph of human epidermis. (**B**) Transmission electron micrograph of control, untreated epidermis. The corneosomes are characterized by an extracellular electron dense plug (black arrow).

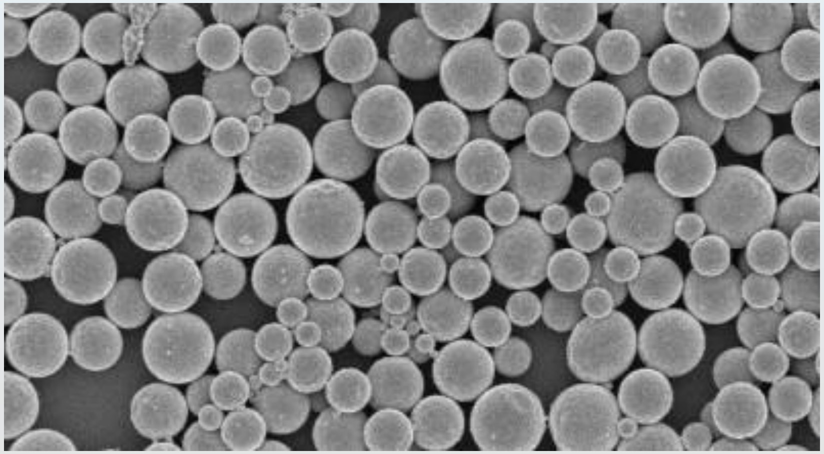


Nanopartículas - sistemas de liberação atraentes

A matriz sólida dá flexibilidade ao formulador para modificar o perfil de liberação do ativo,

O tempo de liberação pode ser rápido ou extremamente lento de acordo com a formulação,

Pode se obter uma proteção eficiente do ativo contra degradações.



Polímeros nanopartículas

Sintéticos

- Poli(ácido lático)
- Poli (ácido lático-coglicólico)
- Poli (e-caprolactona)

Naturais

- Albumina
- Gelatina
- Colágeno
- Quitosana
- Lipídeos e ceras

Nanotecnologia & Absorção

STUDY	MATERIAL	RESULTS
Tan et al., 1996	Microfine TiO_2	
Lademann, 1999	Microfine TiO_2	No penetration into epidermis / dermis in vivo, man
Pflücker et al., 2001	TiO_2, 10 and 100 nm	
Alvarez-Roman et al., 2004	Polystyrene NPs, 20 and 200 nm	No penetration into epidermis / dermis, accumulation in the follicle orifice, but no penetration ibto living skin (pig)
Howard, P, 2005 (SoT Meeting, 2005)	Fluorescent polymeric NPs	No penetration into epidermis / dermis in vivo, man
EU Nanoderm project (Tilmann Butz)	Fluorescent particles	No evidence for penetration into living skin (preliminary data, ECETOC, 11/2005)

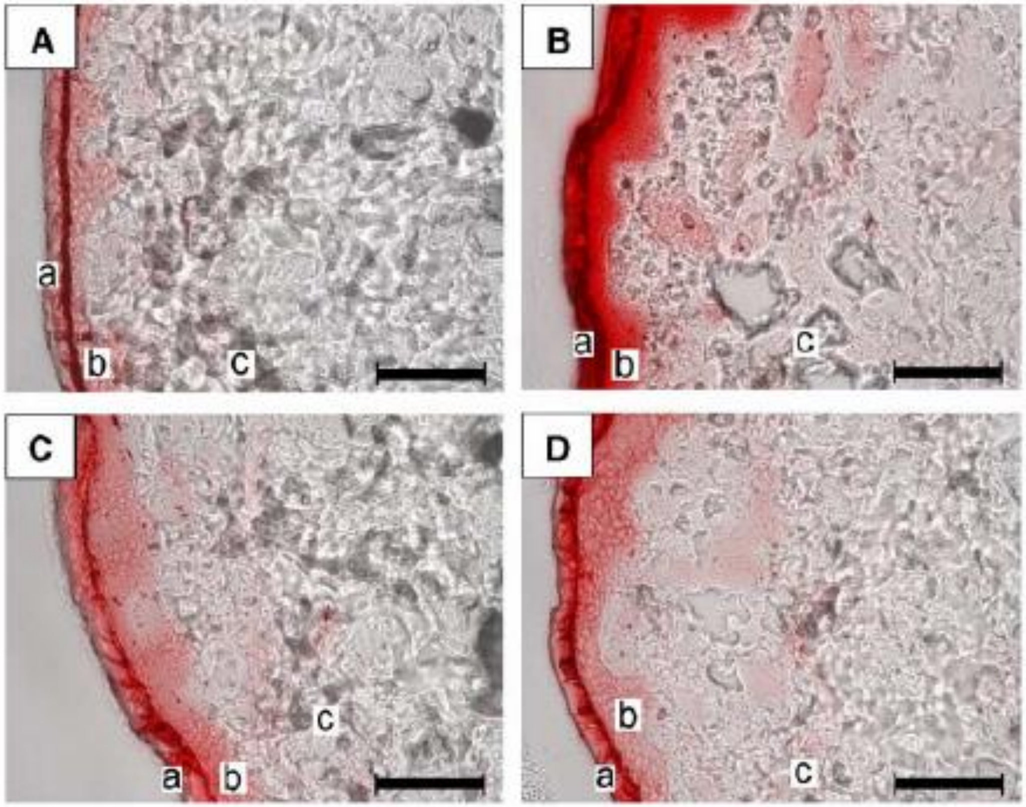
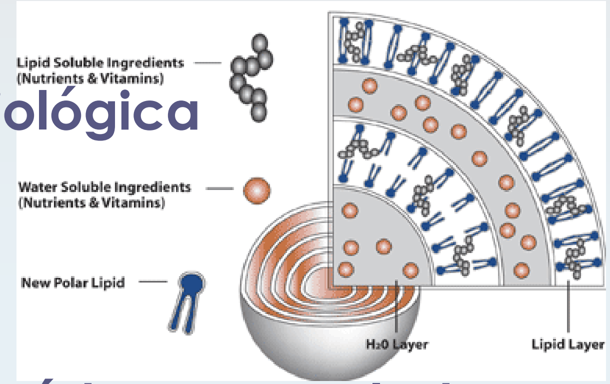


Fig. 4. Penetration of nile red from cream and Precirol-based nano-particles into pig skin after 8 h. (A) Cream. (B) SLN. (C) NLC, oleic acid. (D) NLC, Miglyol. The vertical section depicts the stratum corneum (a), the epidermis (b), and the dermis (c). Pictures are obtained by superposing normal light and fluorescence images of the same area; scale (black bar) is 100 µm.

Schafer-Korting, Journal of Controlled Release 110 (2005) 151– 163

Nanotecnologia & Absorção

Lipossomas - Modelo de membrana biológica



- biocompatibilidade
- fornece meios lipofílicos e hidrofílicos
- proteção e liberação controlada do conteúdo encapsulado
- direcionamento com marcadores específicos

- 85% das publicações - difusão facilitada
- 10% seletividade em pele humana
- 5% efeitos negligenciáveis

Nanotecnologia & Absorção

Várias revisões estão presentes na literatura e na grande maioria mostram que produtos cosméticos contendo nanotecnologia não levam a uma penetração em células vivas.

Uma revisão completa sobre lipossomas em produtos cosméticos elaborada por D.Imbert (1995) conclui que estes não penetram intactos na pele.

Joke Bowstra (University of Leiden) publicou mais de 30 artigos sobre a permeação de lipossomas e formulações similares usando ^{14}C como marcador e conclui que os lipídeos formadores das vesículas penetram nas camadas superficiais do SC, mas estão ausentes nas células vivas.

Effect of vesicles on the permeation of drugs through the skin

Reference	Year	Drug	Type of vesicle	Results
Guénin and Zatz	1995	Retinyl palmitate	NSV	augmentation of the retention of hydrophobic substances in stratum corneum
Paul et al.	1998	Gap junction proteins	Transfersomes	protein transported across the intact murine skin and processed immunologically
Maghraby et al.	1998	Oestradiol	Transfersomes	augmentation of the flux in 8 fold
Simões et al.	1998	Cu, Zn-superoxide dismutase	Transfersomes	reduced local inflammation
Cevc et al.	1998	Insulin	Transfersomes	transported into the body between the intact skin with a bio-efficiency of at least 50% of sub-cutaneous
Hofland et al.	1994	Estradiol	NSV	penetration enhancing effect
van Hal et al.	1996	Lidocaine	NSV	the flux was not influenced by the encapsulation
Vora et al.	1998	Levonorgestrel	Niosomes	penetration enhancing effect

Nanoemulsões

Advances in Colloid and Interface Science 108–109 (2004) 145–149

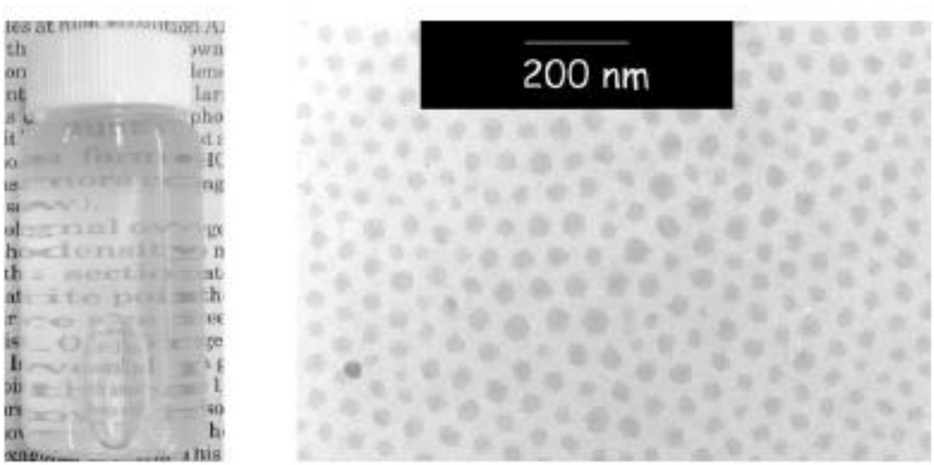


Fig. 1. (a) Visual appearance and (b) a CryoTEM picture of a nanoemulsion.

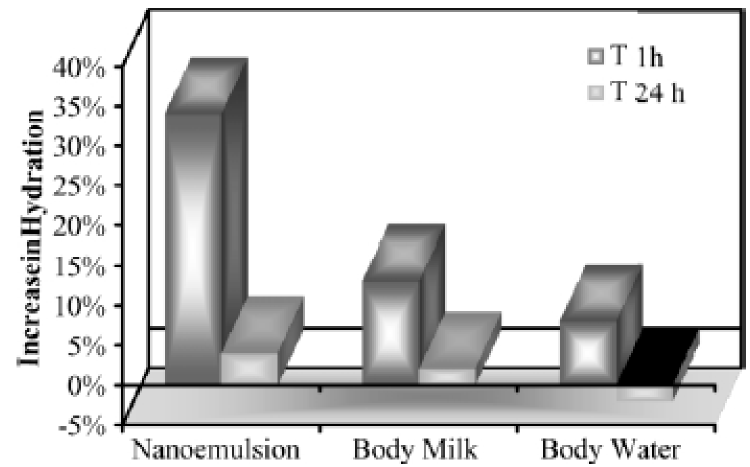
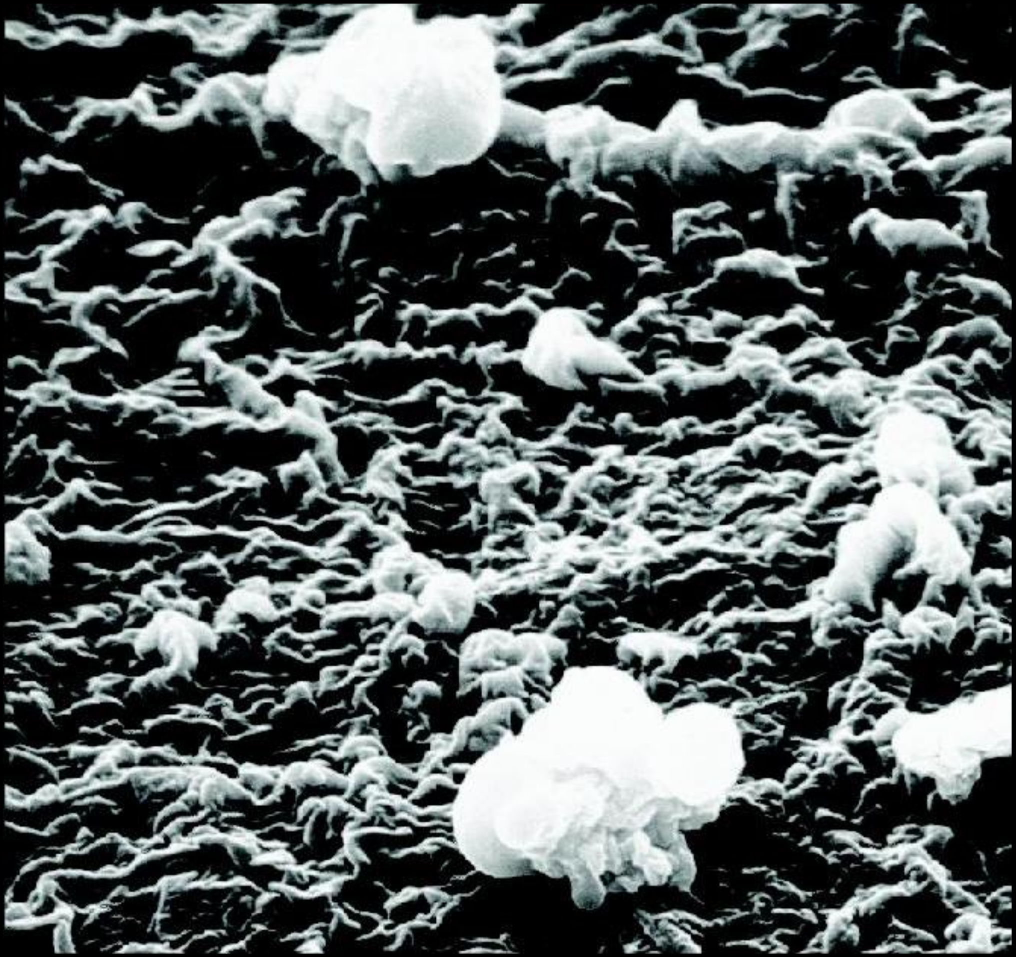


Fig. 9. Increase in Hydration of fore-arm Stratum Corneum 1 and 24 h after treatment with different products.

Nanotecnologia & Aderência



Observation de nanocapsules intactes sous les premières couches cellulaires du stratum cornéum (MEB).

Caminhos da penetração através do Stratum Corneum

- **A penetração através dos apêndices dá uma contribuição pequena no fluxo total através da pele.**

- **O transporte é significante no período inicial da absorção percutânea.**

Hair Follicles – A Long-Term Reservoir for Drug Delivery

J. Lademann[a] H. Richter[a] U.F. Schaefer[b] U. Blume-Peytavi[a]
A. Teichmann[a] N. Otberg[a] W. Sterry[a]

Skin Pharmacol Physiol 2006;19:232–236

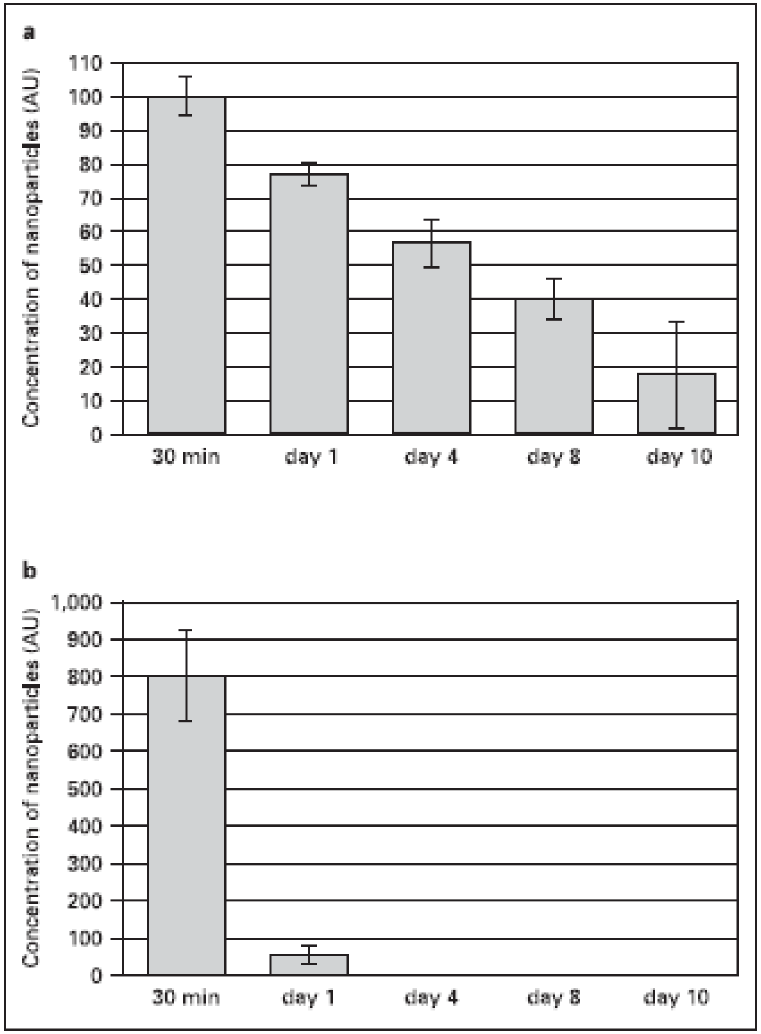
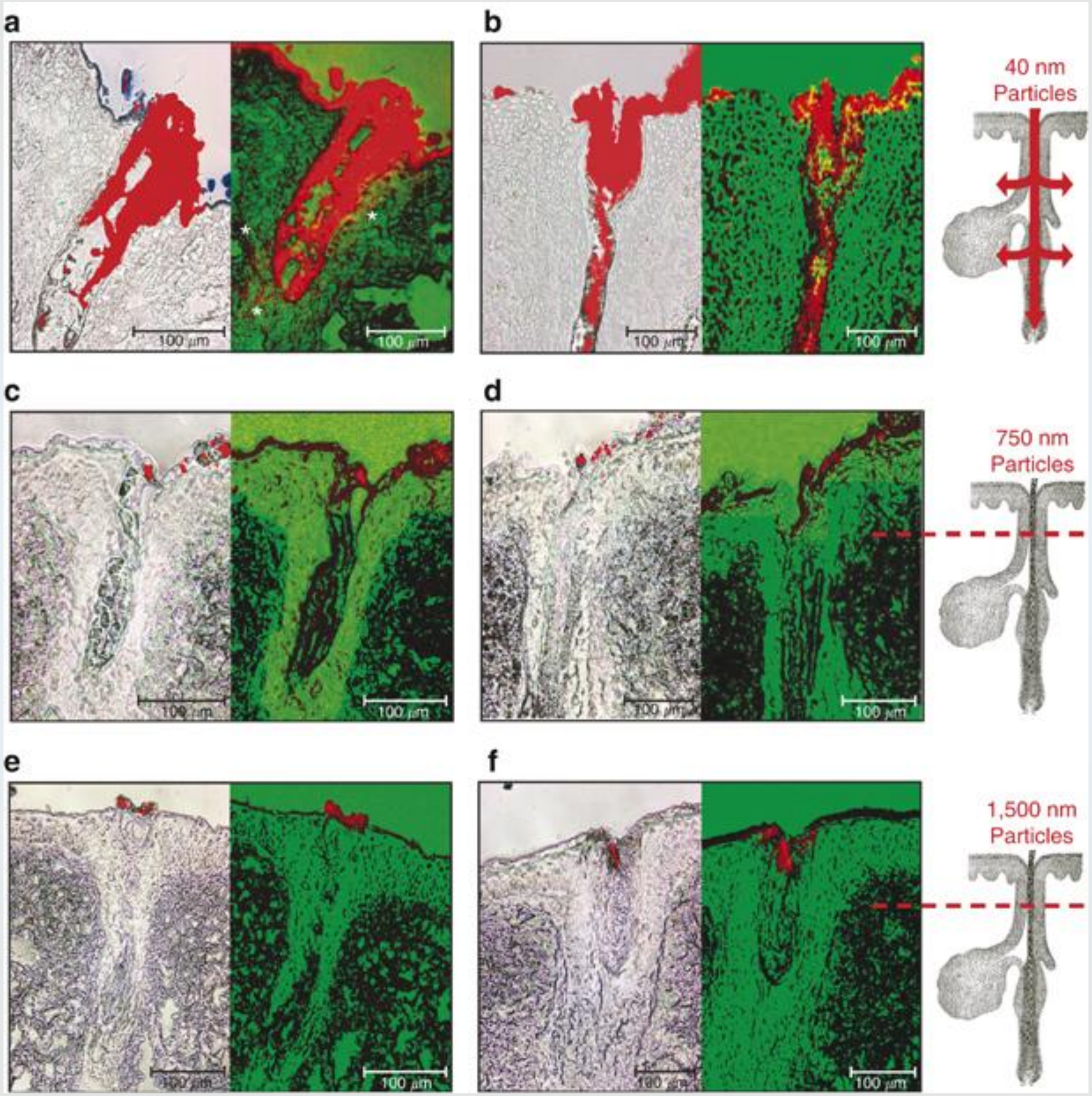
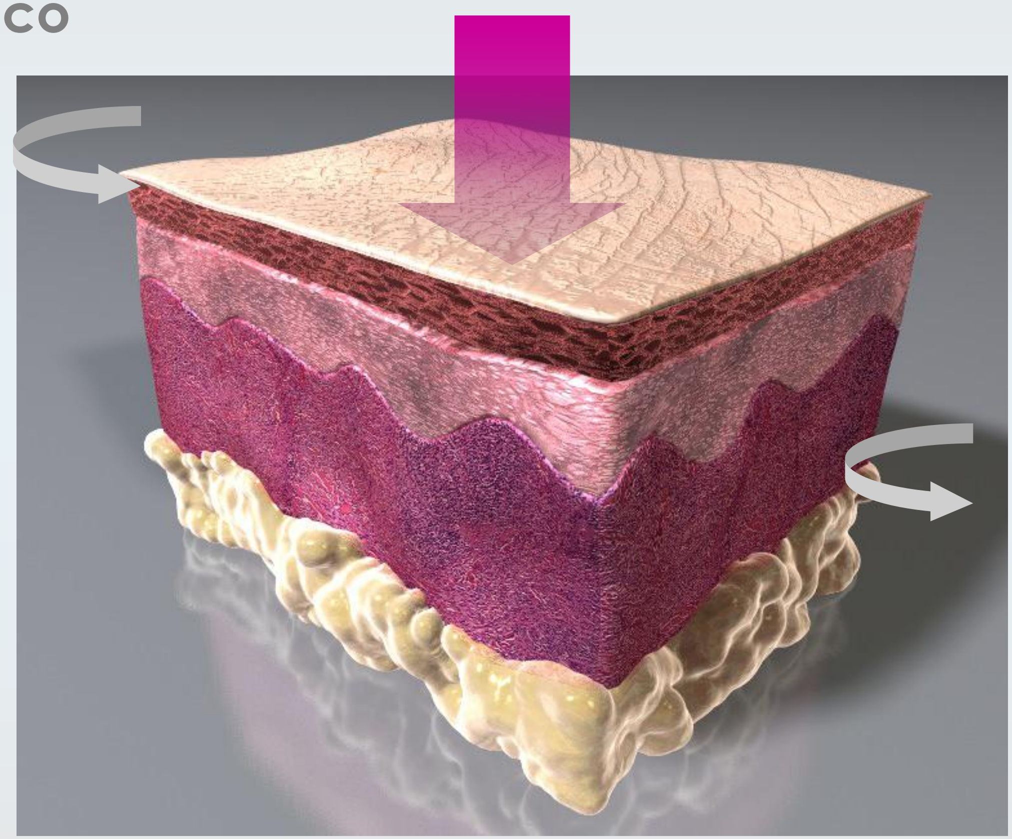


Fig. 4. Kinetics of the storage of nanoparticles in the hair follicles (**a**) and in the stratum corneum (**b**).



Vogt et al. *Journal of Investigative Dermatology* (2006) **126,** 1316–1322.

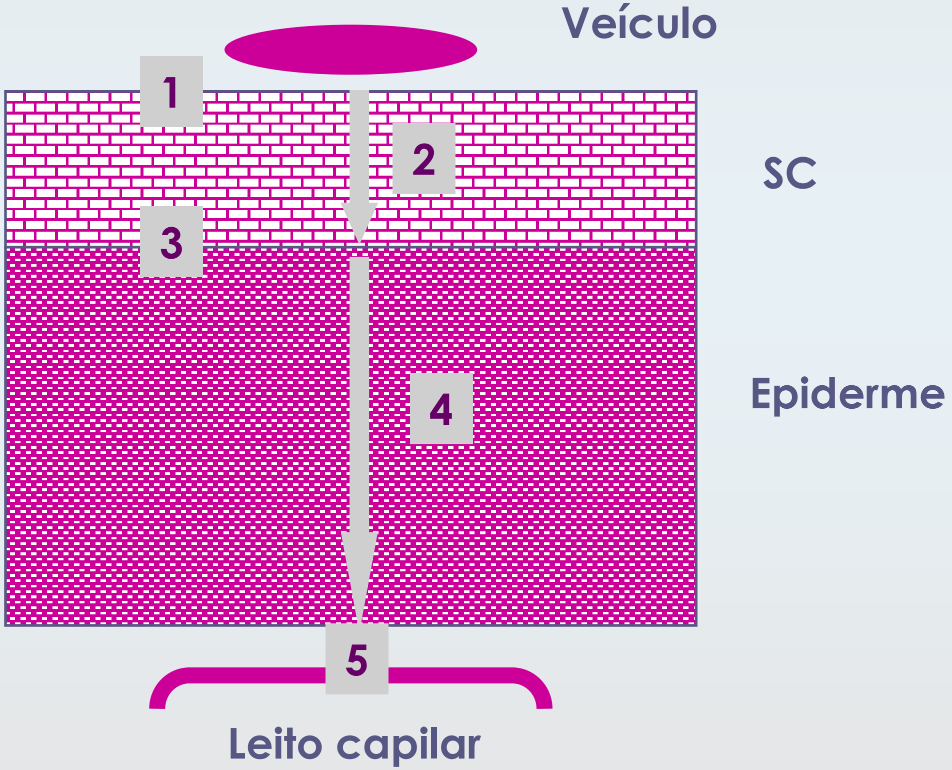
Absorção



A absorção responde as leis físico-químicas da natureza

Passos seqüenciais envolvidos na absorção percutânea

1. Partição
2. Difusão
3. Partição
4. Difusão
5. Rede capilar

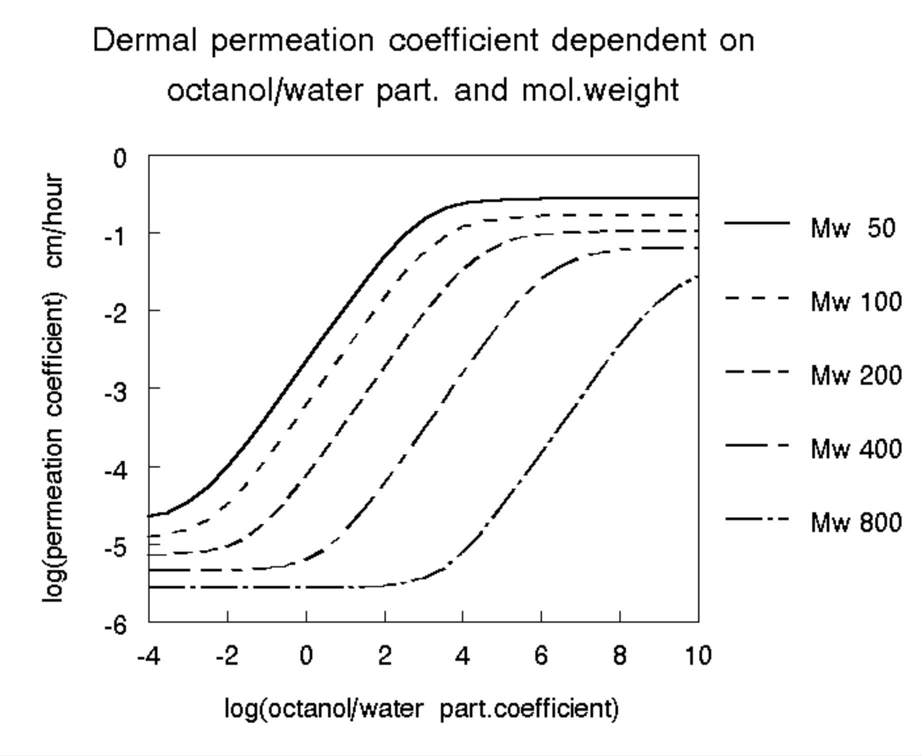


Coeficiente de Partição octanol/água

Substâncias com um **Log $K_{oct/água}$ abaixo de 0**, terão uma penetração limitada pela pele.

Valores **abaixo de** 1 sugerem que a substância não é suficientemente lipofílica para cruzar a camada córnea.

Valores entre 1 e 4 favorecem a absorção.



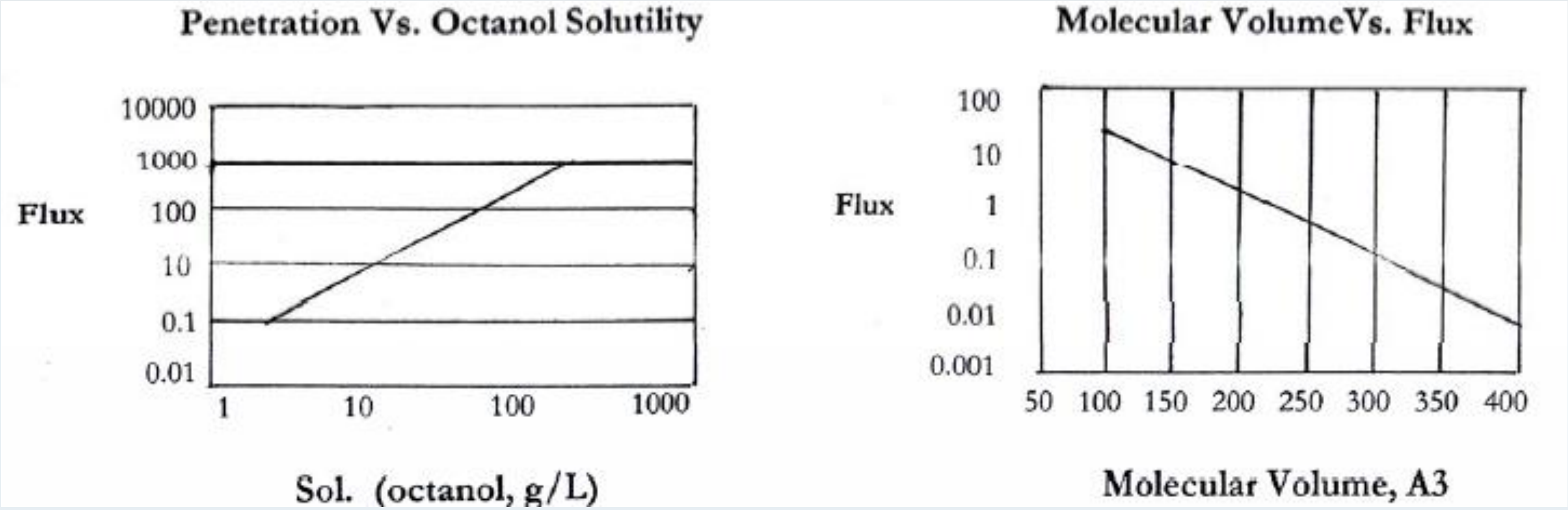
Coeficiente de Partição octanol/água

Acima de 4, o fluxo pode ser limitado pela taxa de transferência entre a camada córnea e a epiderme, com grande acúmulo na camada córnea.

Para substâncias com **Log Koct/água maior que 6**, a taxa de difusão entre as várias camadas da pele se torna realmente limitante, dificultando uma absorção dérmica (EC, 2003).

Para uma substância permear precisa estar no seu estado molecular

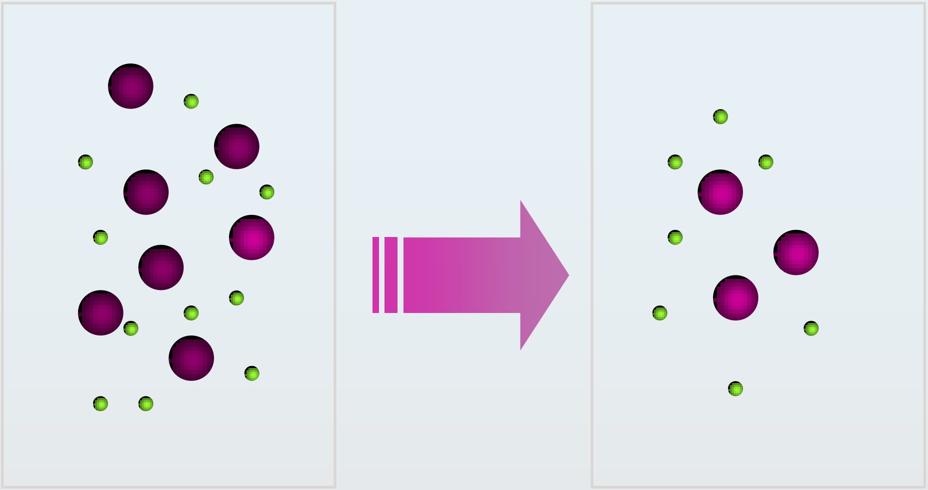
Coeficiente de Partição octanol/água e Peso molecular

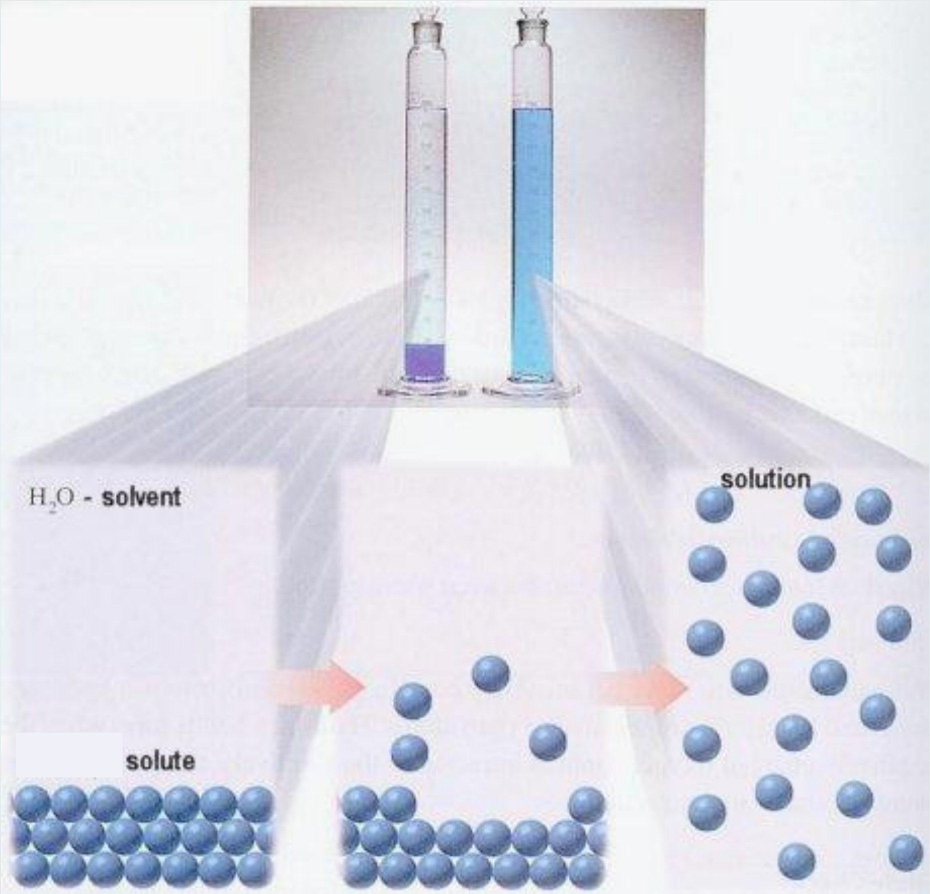


Mantendo a solubilidade constante, químicos com baixo peso molecular (PM 100), penetram de 100x a 1000x mais rápido que moléculas com peso molecular elevado (PM 400 ou +).

Difusão

- **Difusão Passiva**
  - Moléculas se movem do compartimento mais concentrado para o menos concentrado.





Saturação

Atividade termodinâmica = 1

Pouca variação entre veículos.

Liberação máxima.

Supersaturação – AT ↑ 1

EDETOX Website

Chemical	Vehicle	Species	Site	Membrane	Area (cm2)	Cell Type	Exposure Time (h)	Study Length (h)	% Absorbed
Caffeine	Loreal anti-cellulite cream	Human	Abdomen /Breast	Dermatomed to 0.344mm	1.86	Static	16	16	1.22
Caffeine	Petrolatum	Human	Abdomen	Dermatomed to 0.35mm	0.64	Flow-through	36	36	61.8
Caffeine	Petrolatum	Human	Abdomen	Dermatomed to 0.35mm	0.64	Flow-through	36	36	40.6
Caffeine	Ethylene Glycol Gel	Human	Abdomen	Dermatomed to 0.35mm	0.64	Flow-through	36	36	32.2
Caffeine	Water Gel	Human	Abdomen	Dermatomed to 0.35mm	0.64	Flow-through	36	36	4.7
Caffeine	Water Gel	Human	Abdomen	Dermatomed to 0.35mm	0.64	Flow-through	36	36	5.1

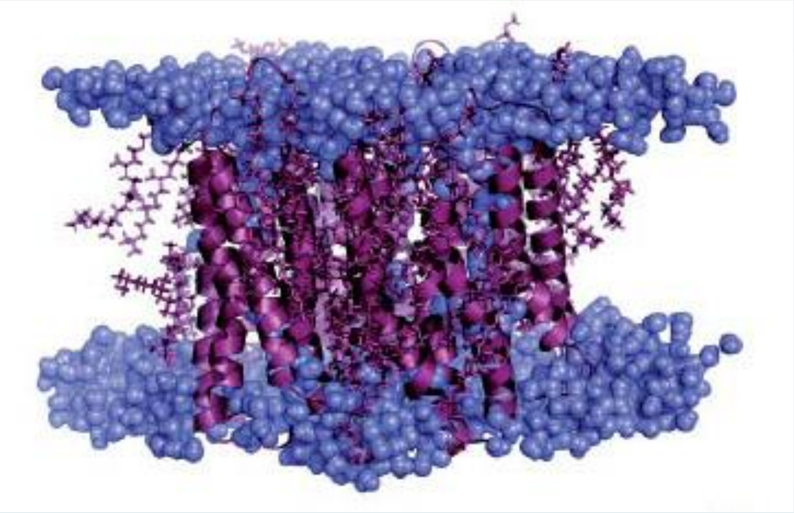
Influência dos Veículos na Permeação

Formulação

Determina a cinética e o nível de absorção; influencia a resposta biológica.

Maximizar a eficácia.

Coeficiente de Partição



Os químicos que apresentam maior coeficiente de partição, tem maior afinidade pela fase orgânica e, portanto, tendem a ultrapassar com maior facilidade as biomembranas hidrofóbicas.

PERCUTANEOUS ABSORPTION OF NANOPARTICULATE SYSTEMS

J.Jansen, H. I. Maibach

The kinetics of compound delivery to deeper compartments of the skin from topical applications are strongly influenced by its reservoir function.

An accumulation of the drugs released from liposomes and nanoparticles in the epidermis was observed. A higher diffusion was obtained in function of time for the encapsulated formulations compared to traditional formulations.

- **nanoparticles of PLA.**
- **pro-liposomes of soya.**

- **Caffeine**
- **Melatonin**
- **Benzoic acid**
- **P-aminobenzoic acid**
- **Hidroquinona**

Melatonin absorption into human stratum corneum: an adhesive tape stripping study in vitro

Log P = 1,2 MW = 232.3

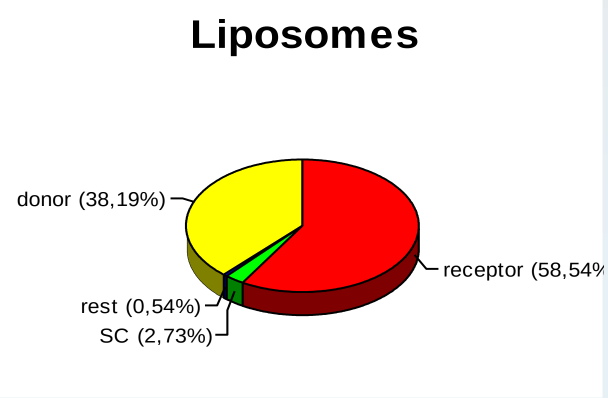
	Solution	Liposomes	Nanospheres
Epidermis	1.36%	27.83%	8.58%
Dermis	0.26%	7.88%	0.39%
Diffusion	4.01%	1.80%	6.61%
Rest	0.11%	0.15%	3.93%
Skin Wash	94.26%	62.34%	80.49%

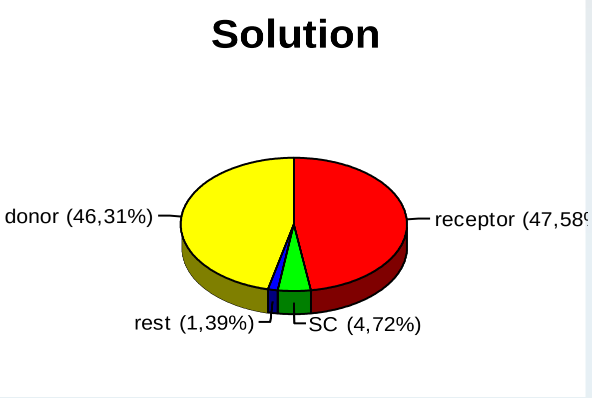
Conclusion

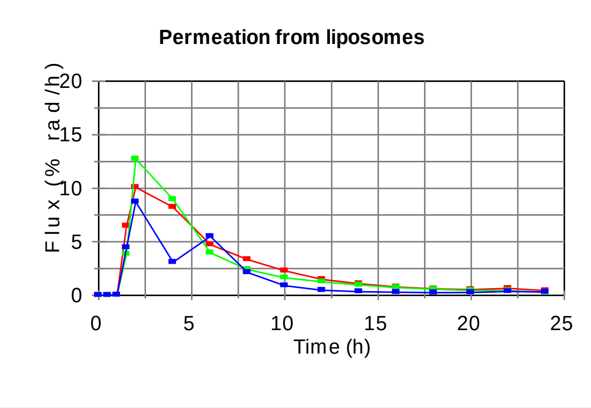
This study has shown the influences of encapsulation for delivering melatonin. The results showed an accumulation of melatonin from liposomes and nanospheres in the epidermis and dermis.

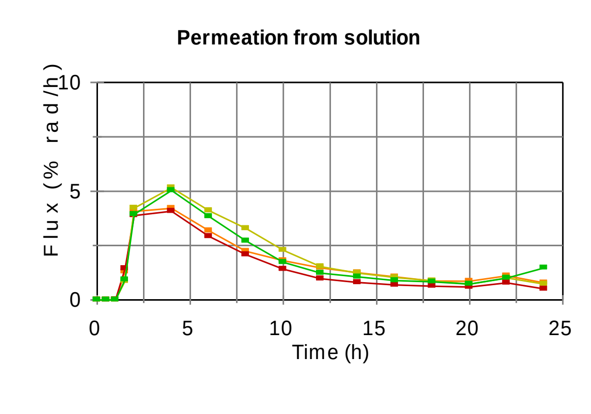
Benzoic acid absorption into human skin: Study *in vitro*

Log P 1,96 M.W. 122.1



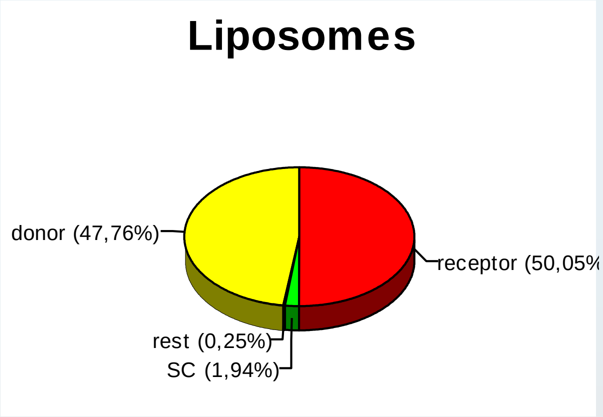


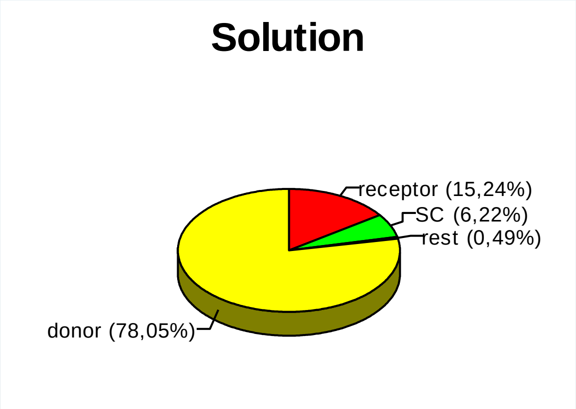




Cafeine absorption into human skin: study *in vitro*

MW 194,19 Log P -0,091





HUMAN SKIN DRUG DELIVERY USING BIODEGRADABLE PLGA – NANOPARTICLES

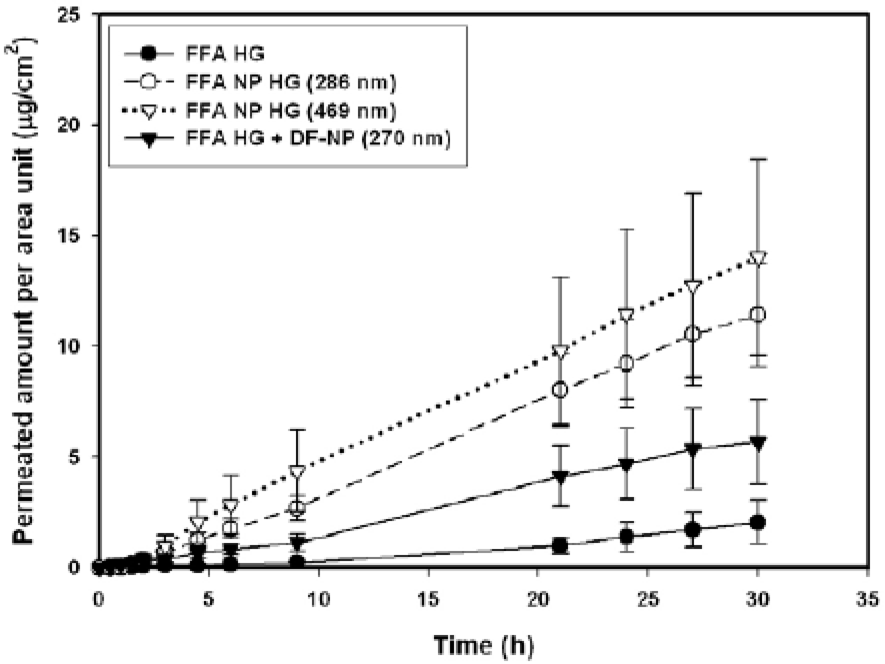


Figure 17: Heat separated human epidermis permeation profiles of flufenamic acid using infinite dose regime of non buffered hydrogels containing: dissolved drug (FFA HG), loaded nanoparticles of different size (FFA NP HG), and dissolved drug with drug-free nanoparticles (FFA HG + DF-NP).

Flufenamic acid – Log P 4,88 – MW 281.24
Doutorado J. Contreras, 2007

Partículas nanométricas

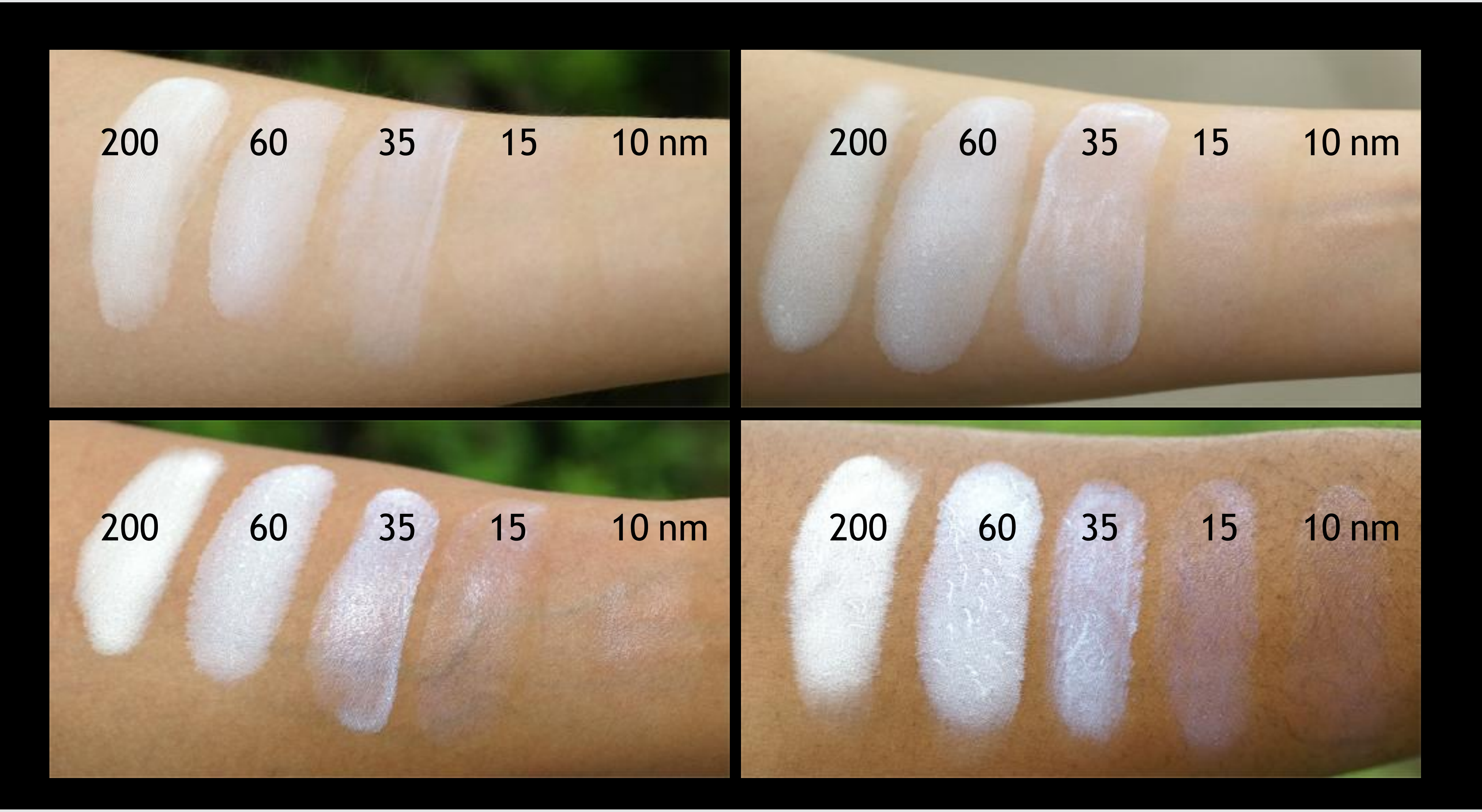
Dióxido de Titânio (TiO_2) e óxido de zinco (ZnO)

Maior uso- maquiagem e filtros solares como agentes protetores contra a radiação UVA e UV B.

Atenuam a luz UV por absorção e dispersão.

Normalmente tem a superfície tratada para amenizar sua atividade fotocatalítica.

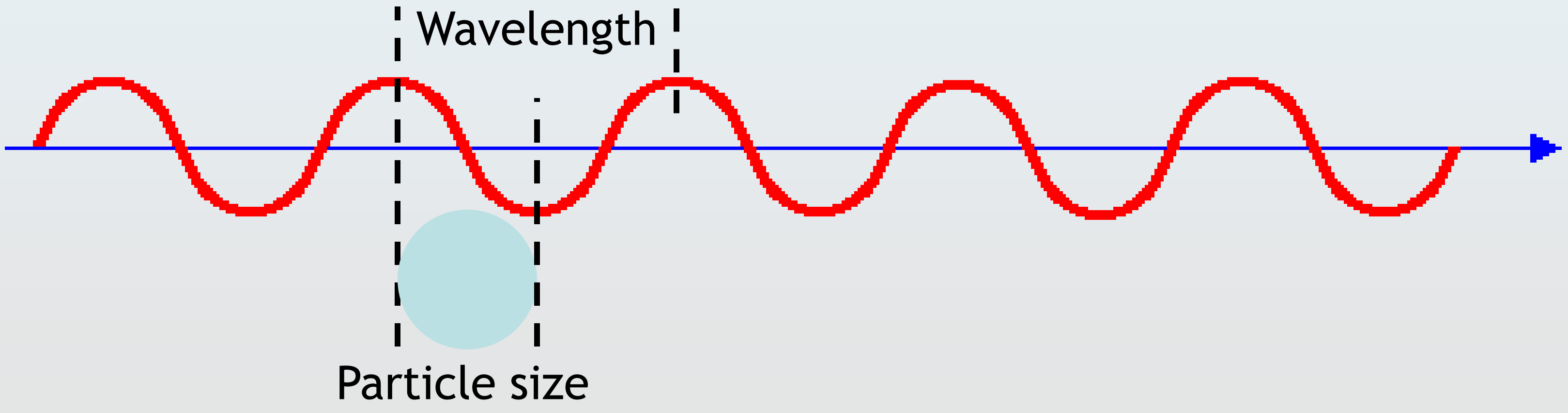
TiO_2 (em Cyclopentasiloxane)

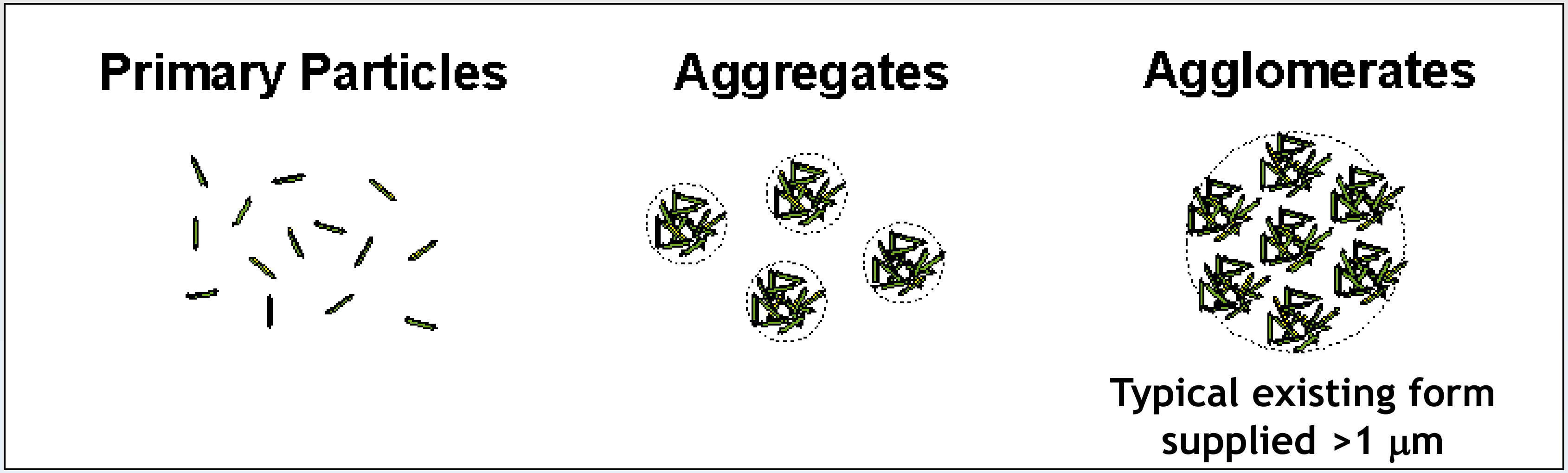


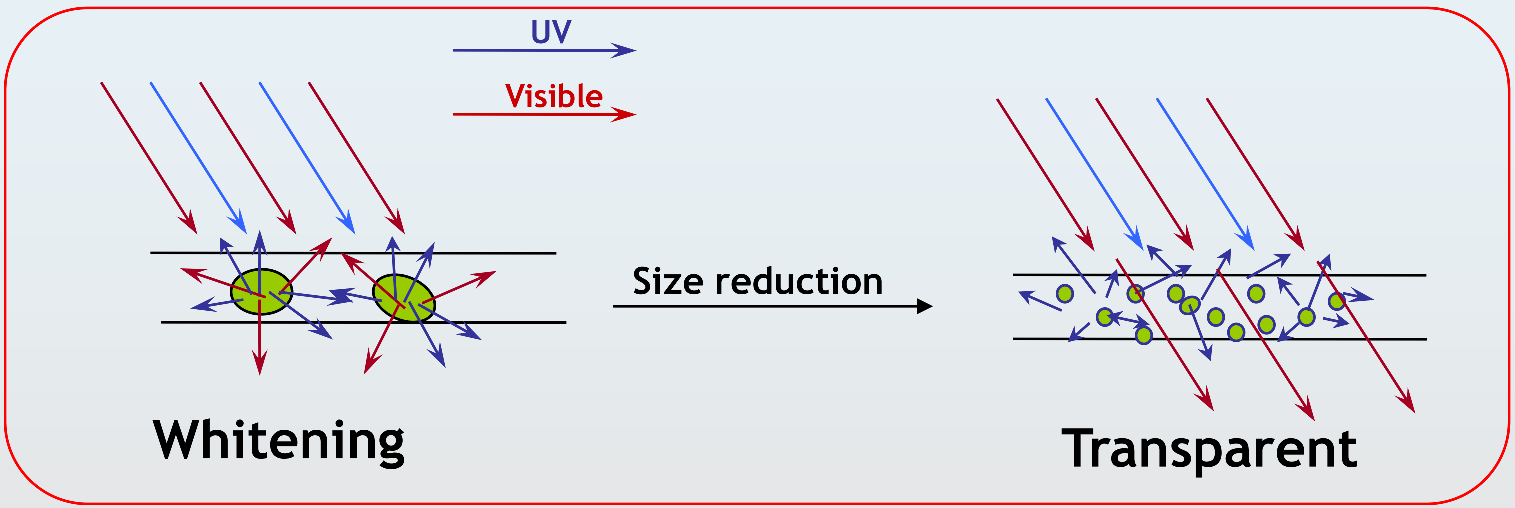
10nm TiO_2 transparente em qualquer tipo de pele

Partículas nanométricas

- **A dispersão da luz visível é influenciada pelo tamanho de partícula e pela diferença entre o índice de refração entre o pigmento e o meio no qual está dispersado.**
- **O máximo de dispersão ocorre quando o tamanho é igual a metade do comprimento de onda e quando as partículas estão uniformemente dispersadas (Mie theory).**

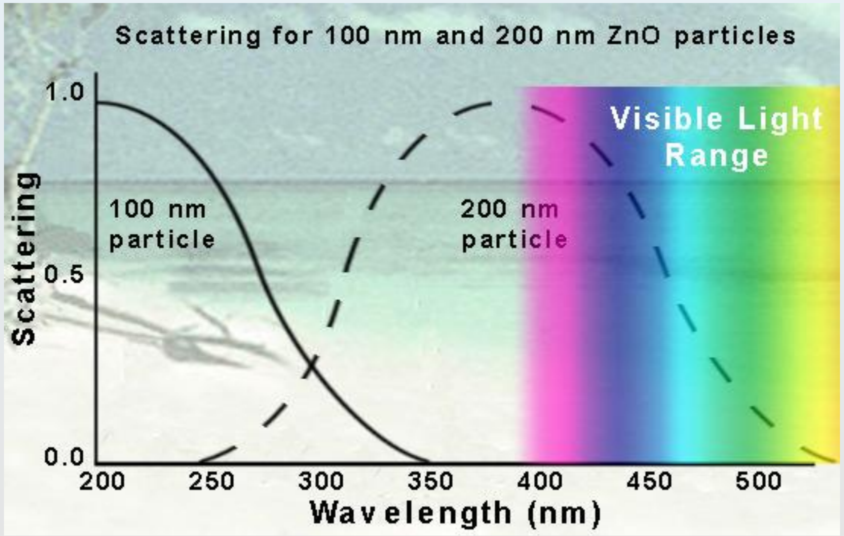



Primary Particles
Aggregates
Agglomerates
Typical existing form
supplied >1 µm


UV
Visible
Size reduction
Whitening
Transparent

Efeito do Tamanho de Partícula

Pigment	ZnO	ZnO	TiO_2	TiO_2
PPS (nm)	25 - 35	15 - 25	35	15
PS in disp. (nm)	228	130	154	125
Active (%)	14.97	13.80	10.29	10.29
SPF**	14	25.4	28.4	50

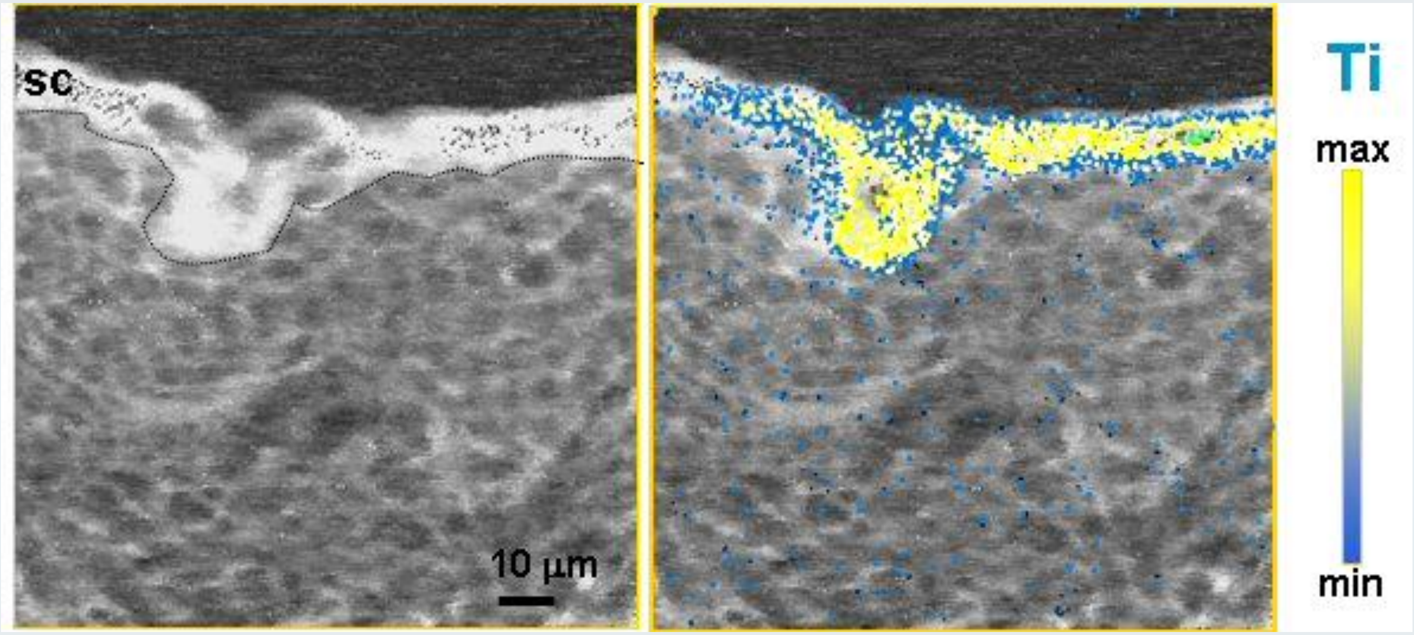


In vitro percutaneous absorption of TiO2 and ZnO in pig skin (4 mg/cm2, 24 hrs)

TEST MATERIAL	SKIN WASH (%)	TAPE STRIPS (%)	SKIN (%)	RECEPT. FLUID (%)	ABSORBED DOSE (%)	RECOV. (%)
TiO_2, 30-60 x 10 nm, silica / methicone-coated O/W emulsion (10%)	97.7 to 100.2	0.1 to 0.2	0.1 to 0.3	0.0	0.0	98.2 to 100.4
TiO_2, 30-60 x 10 nm, methicone-coated O/W emulsion (10%)	85.4 to 92.9	0.0 to 0.3	0.1 to 0.5	0.0	0.0	86.1 to 93.0
ZnO, 80 nm, O/W emulsion (10.3%)	NP	98.6 to 102.3	1.4 to 1.5 **	0.8 to 1.4 **	0.0	102.3 to 106.8

Gamer et al., *Toxicol. In Vitro*, BASF, 2005;

Partículas nanométricas



Imagens da morfologia e da distribuição de Ti (cor) numa secção de pele obtidas com Microssonda Nuclear.
O Ti está confinado ao *stratum corneum* - sc.