Innovaciones en Nanotecnología Farmacéutica:

Estudios de Liberación y Permeación de Sistemas Nanoestructurados para Piel Humana y modelos de piel alternativos

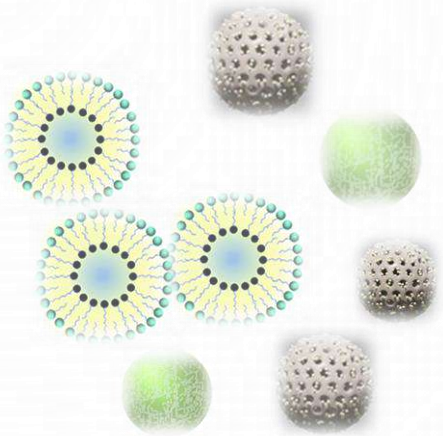
DR. MIREIA MALLANDRICH (mireia.mallandrich@ub.edu)

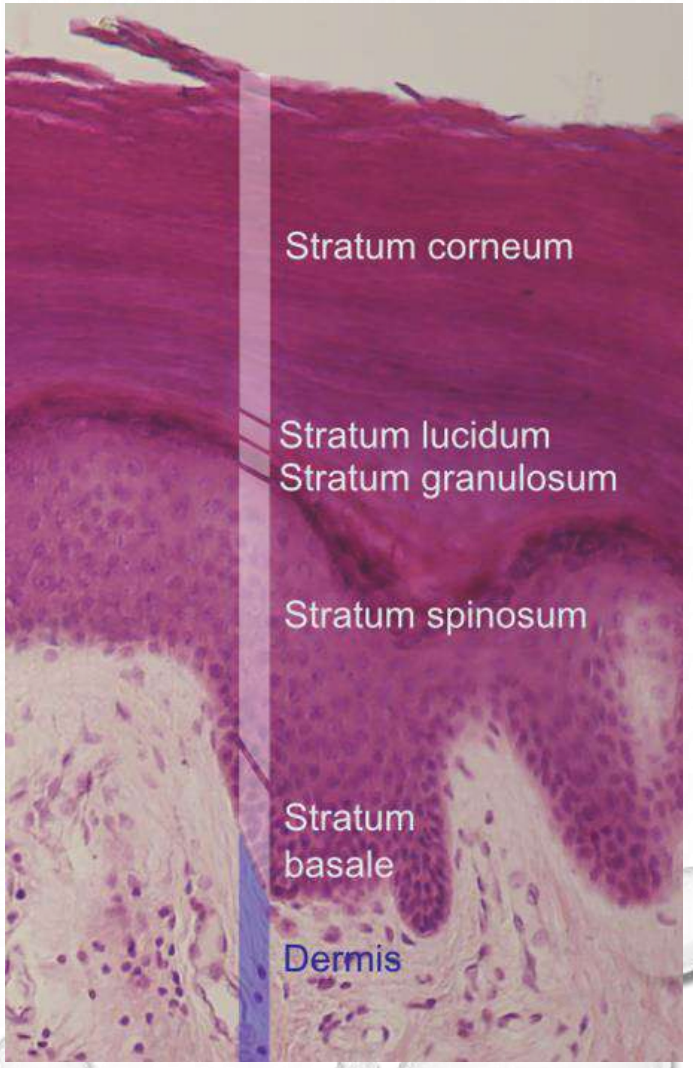
UNITAT DE BIOFÀRMACIA I FARMACOCINÈTICA

SEMINARI DE RECERCA. 14 MARÇ 2024

UNIVERSITAT DE BARCELONA

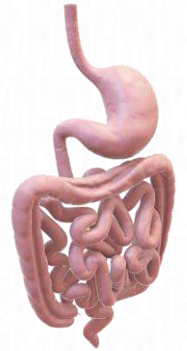
Contenido

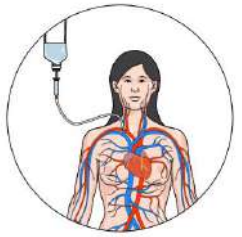


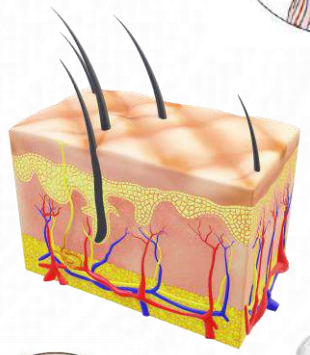


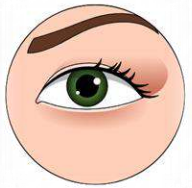
1. ¿Mejor solo que mal acompañado?
2. El interés de las nanopartículas
3. Estudios de liberación y permeación de fármacos
4. Piel, ¿y algo más? Tendencias y futuro

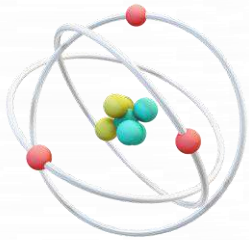
1.NI SOLO NI MAL ACOMPAÑADO. MULTIDISCIPLINAR



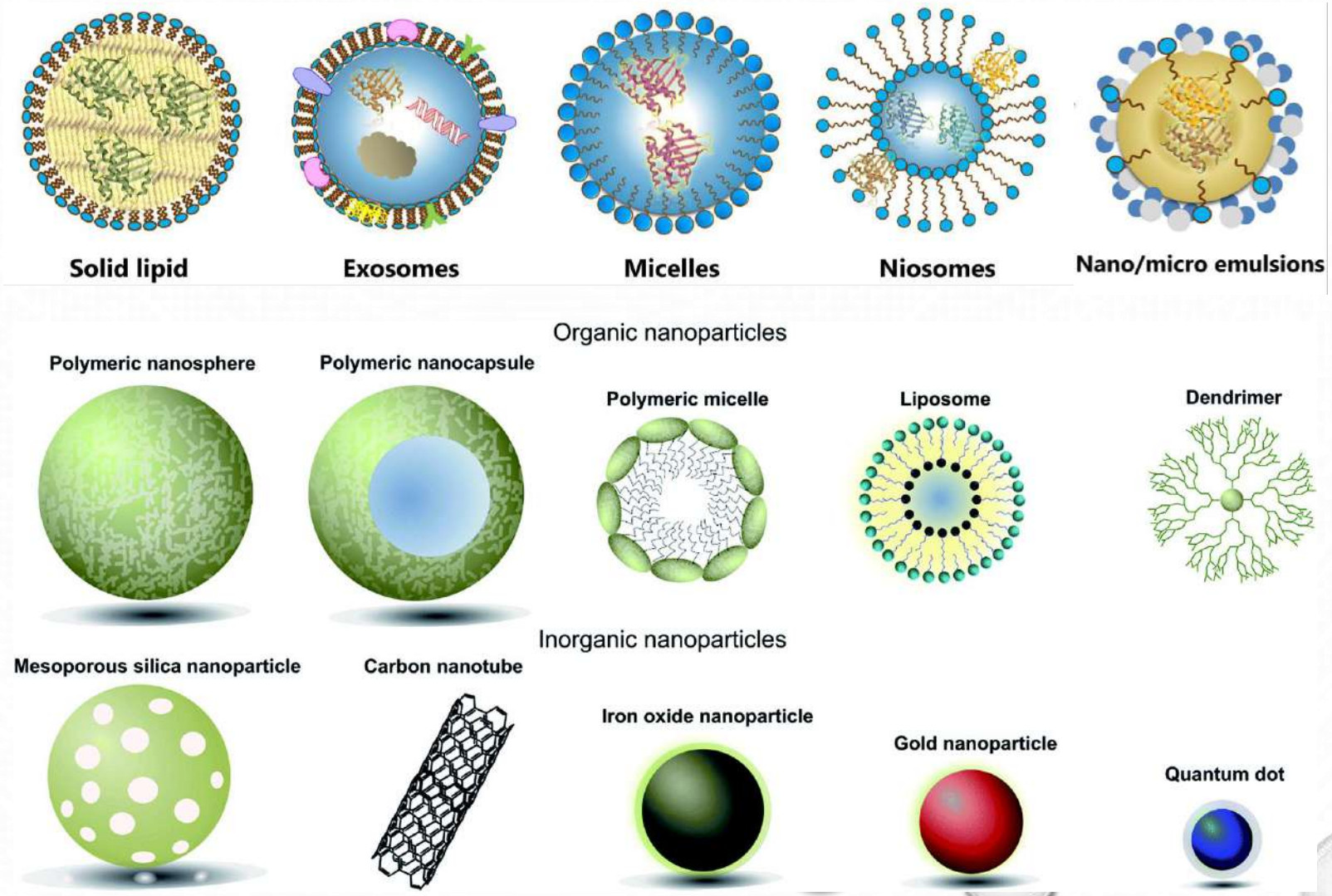








2. EL INTERÉS DE LAS NANOPARTÍCULAS. TIPOS DE SISTEMAS NANOESTRUCTURADOS



NANOPARTÍCULAS POLIMÉRICAS DE TIMOL

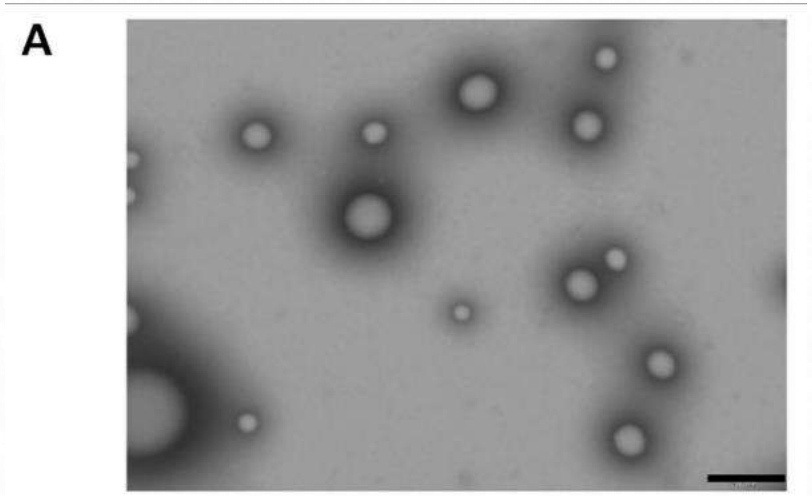


Figure. A Transmission electron microscopy image of TH-NP. Scale bar: 200 nm (Folle et al.)

NANOPARTÍCULAS LIPÍDICAS DE PRANOPROFENO

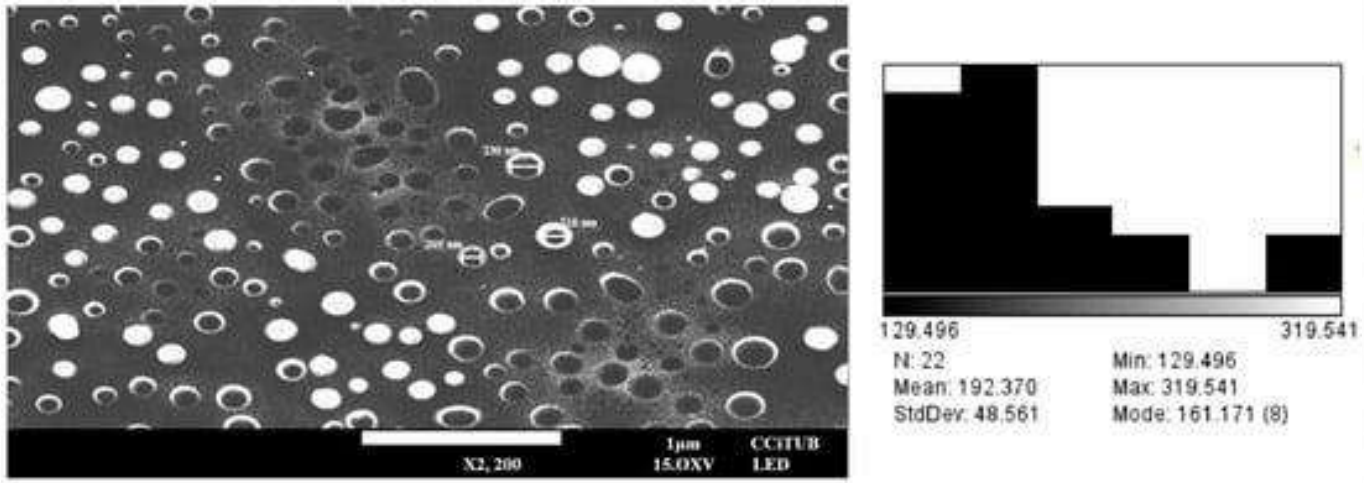
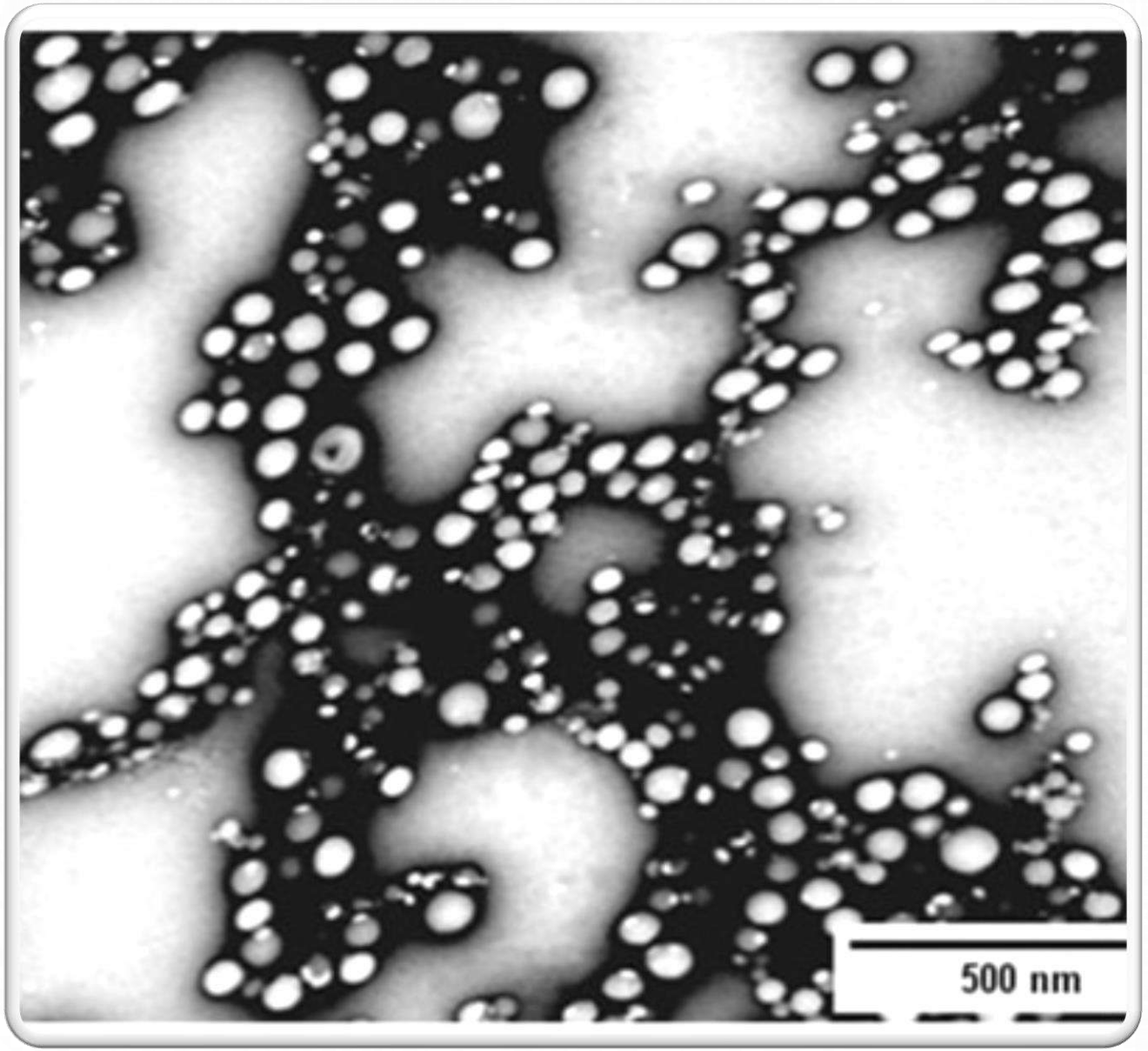


Figure. Scanning Electron Microscopy image of PF-NLCs-N6 and the related histogram. (Rincón et al.)



(Fuente: Mallandrich et al.)

INTERÉS DE LAS NANOPARTÍCULAS

- BCS
- ESTABILIDAD
- ENHANCER

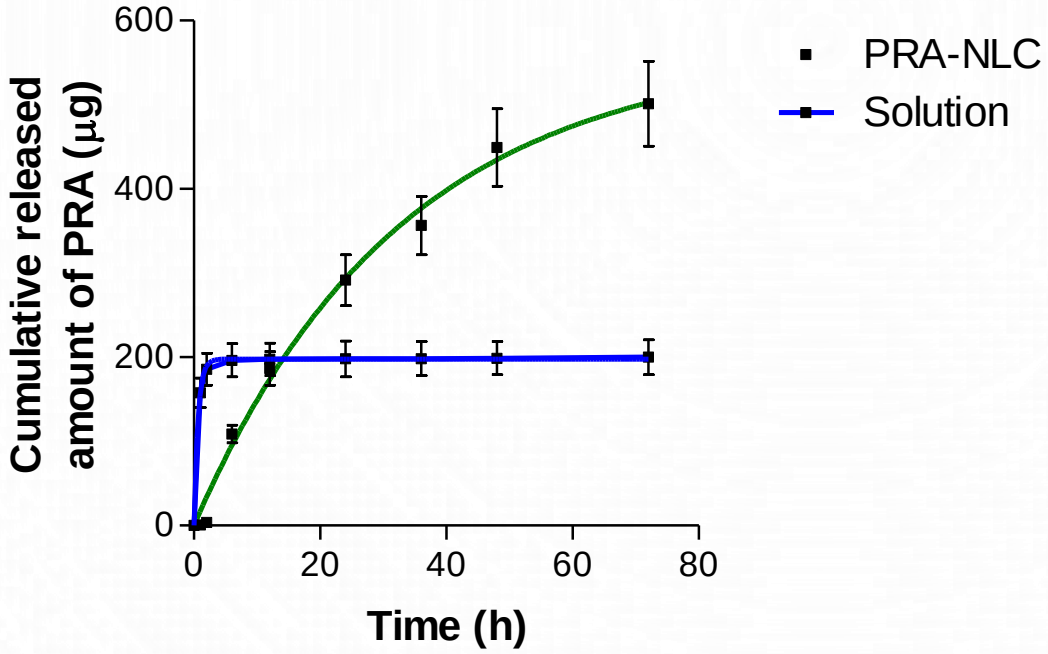


Figure. Release profile of PRA from aNLC and a plain solution. (unpublished material)

Comparación: de la liberación de pranoprofeno des de un sistema lipídico nanoestructurado vs. una solución del fármaco:

- Liberacion sostenida
- Solubilidad

pharmaceutics

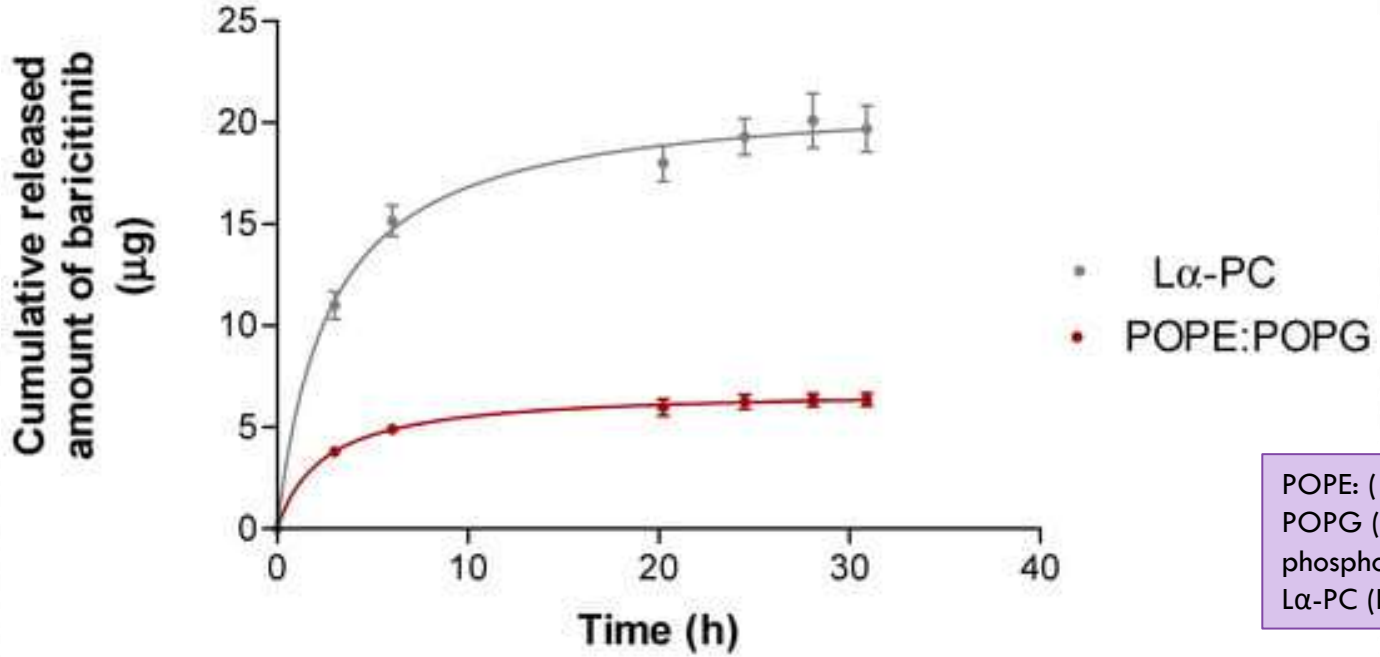
MDPI

Article

Baricitinib Liposomes as a New Approach for the Treatment of Sjögren's Syndrome

Núria Garrós [1], Mireia Mallandrich [1,2,*], Negar Beirampour [1], Roya Mohammadi [1,2], Òscar Domènech [1,2], Maria José Rodríguez-Lagunas [3], Beatriz Clares [2,4] and Helena Colom [1]

1 Department of Pharmacy, Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, 08028 Barcelona, Spain
2 Institute of Nanoscience and nanotechnology, University of Barcelona, 645 Diagonal Avenue, 08028 Barcelona, Spain
3 Department of Physiology, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII, 08028 Barcelona, Spain
4 Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain
* Correspondence: mireia.mallandrich@ub.edu

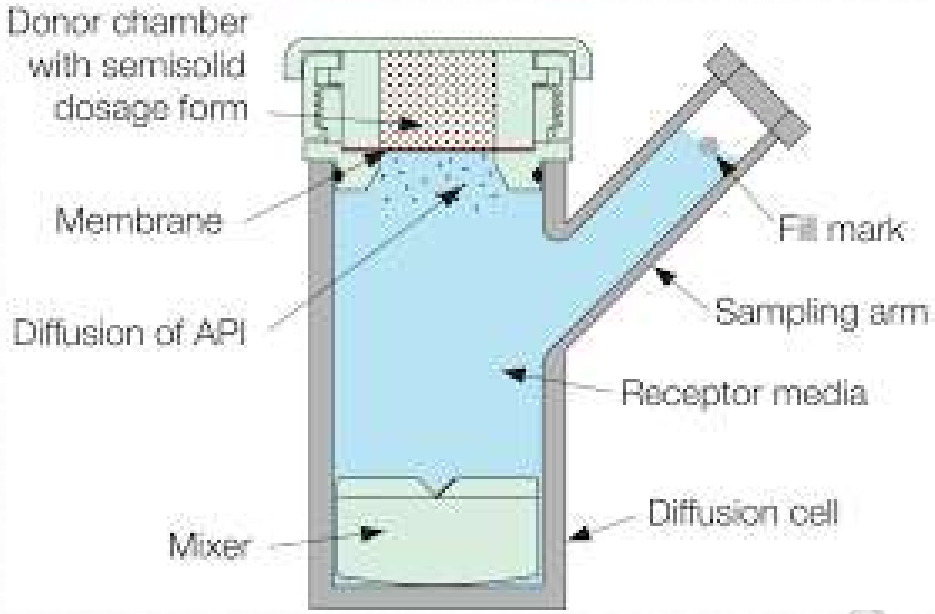


POPE: (1-palmitoyl-2-oleoyl-phosphatidylethanolamine)
POPG (1-Palmitoyl-2-oleoyl-sn-glycerol-3-phosphoglycerol)
Lα-PC (L-α-phosphatidylcholine)

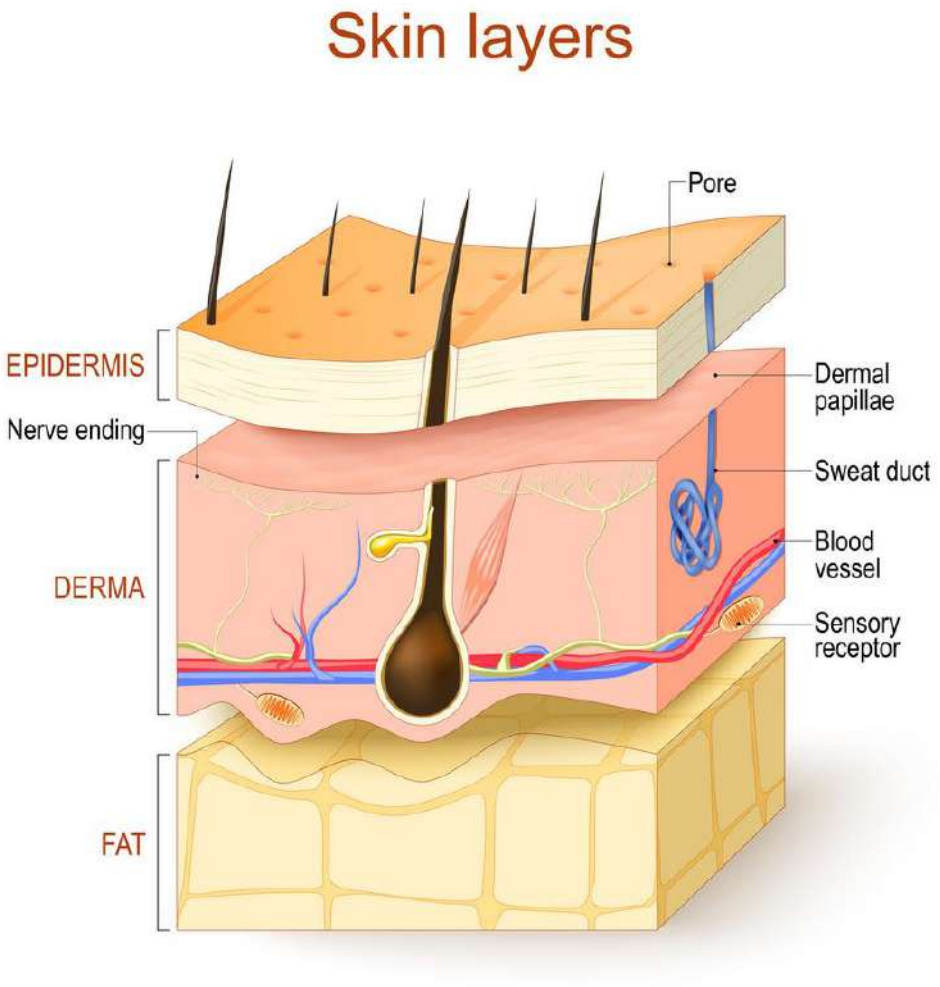
Figure. Release profiles of baricitinib from the liposomes POPE:POPG (3:1, mol/mol), and Lα-PC: baricitinib cumulative released (µg) vs. time (h). Results are expressed by mean ± SD (n = 5). (Garrós et al.)

3. ESTUDIOS DE LIBERACIÓN Y PERMEACIÓN DE FÁRMACOS

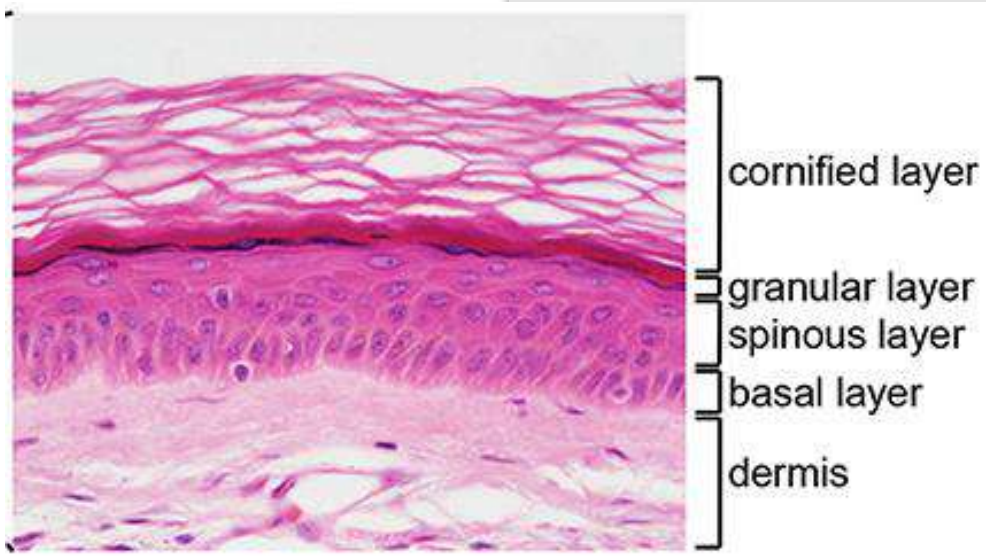
Fuente: Hanson Teledyne



LA PIEL

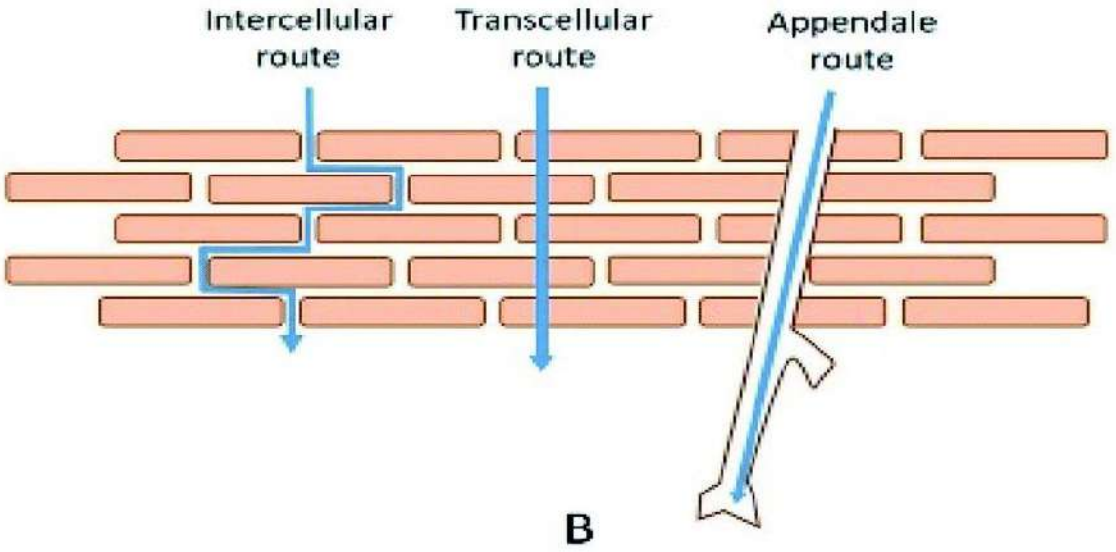


1. Órgano más grande: $2m^2$
2. Protector: **Función barrera**
3. Termoreguladora
4. Sensorial



VÍAS DE PENETRACIÓN (TRANS)-DÉRMICA

1. Vía transcelular
2. Vía intercelular
3. Vía transapendicular:
   - Folículo piloso
   - Glándulas sudoríparas y sebáceas



Fuente: Genoskin

pharmaceuticals

MDPI

Article

Baricitinib Lipid-Based Nanosystems as a Topical Alternative for Atopic Dermatitis Treatment

Núria Garrós [1,2], Paola Bustos-Salgados [1], Òscar Domènech [1,2], María José Rodríguez-Lagunas [3], Negar Beirampour [1], Roya Mohammadi-Meyabadi [1,2], Mireia Mallandrich [1,2,*], Ana C. Calpena [1,2] and Helena Colom [1]

1 Departament de Farmàcia i Tecnologia Farmacèutica, i Fisicoquímica, Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona (UB), 08028 Barcelona, Spain; ngarroar50@alumnes.ub.edu (N.G.)
2 Institut de Nanociència i Nanotecnologia, Universitat de Barcelona (UB), 645 Diagonal Avenue, 08028 Barcelona, Spain
3 Departament de Bioquímica i Fisiologia, Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona (UB), Av. Joan XXIII, 08028 Barcelona, Spain
* Correspondence: mireia.mallandrich@ub.edu

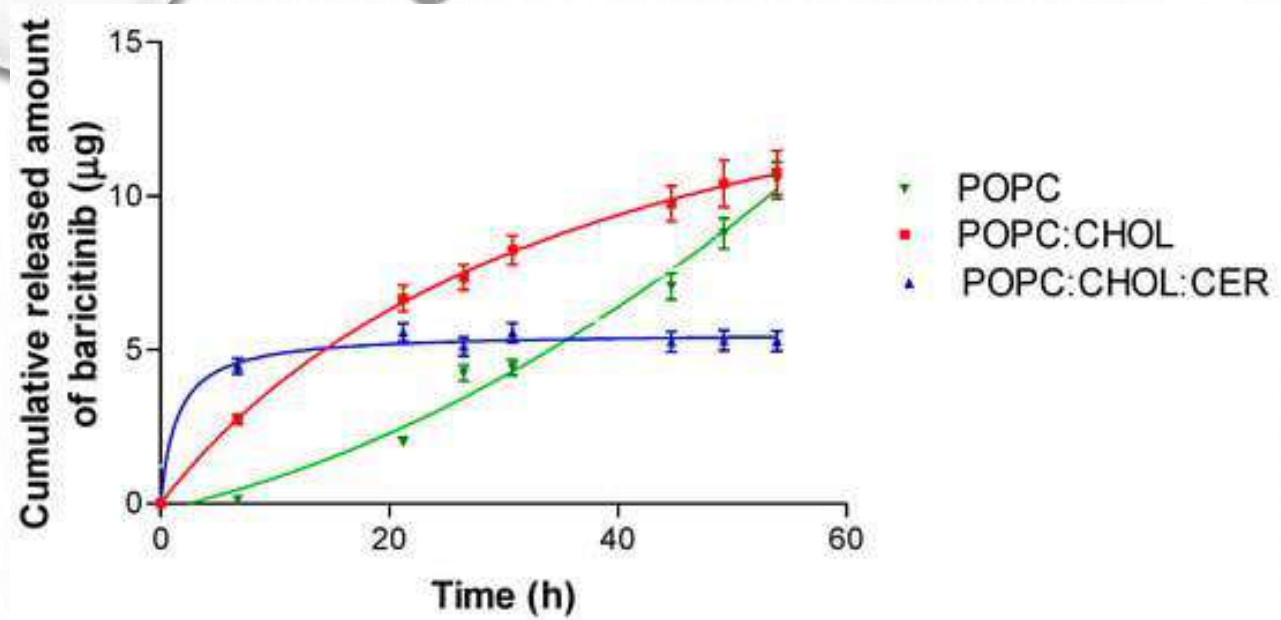


Figure. The baricitinib release profiles from liposomes POPC, POPC:CHOL and POPC:CHOL:CER. Cumulative released amount (µg) vs. time (h). The results are presented as mean ± SD (n = 5). (Garrós et al.)

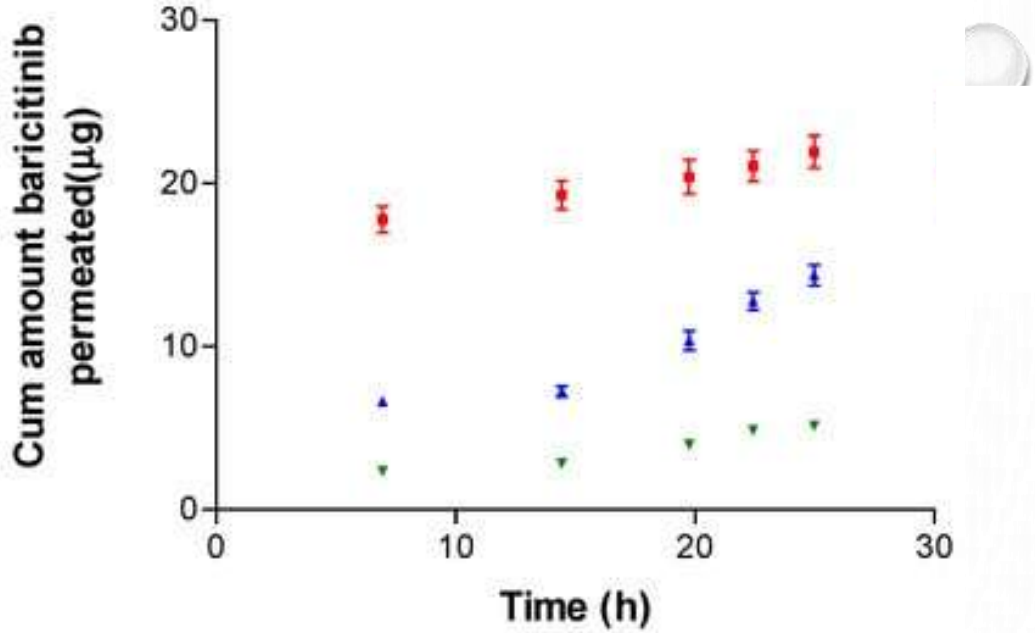


Figure. The baricitinib permeation profiles from liposomes POPC, POPC:CHOL and POPC:CHOL:CER. The results are presented as mean ± SD (n = 5). (Garrós et al.)

POPC (1-palmitoyl-2-oleoyl-glycero-3-phosphocholine), CHOL (Cholesterol) and CER (Ceramide)

pharmaceutics

MDPI

Article

Polymeric Nanoparticles and Chitosan Gel Loading Ketorolac Tromethamine to Alleviate Pain Associated with Condyloma Acuminata during the Pre- and Post-Ablation

Salima El Moussaoui [1,†], Ismael Abo-Horan [1,†], Lyda Halbaut [1], Cristina Alonso [2], Lluïsa Coderch [2], María Luisa Garduño-Ramírez [3], Beatriz Clares [4,5,*], José Luis Soriano [4], Ana Cristina Calpena [1,5], Francisco Fernández-Campos [6,‡] and Mireia Mallandrich [1,5,‡]

1 Department of Pharmacy, Pharmaceutical Technology and Physical-Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII 27-31, 08028 Barcelona, Spain; selmouel9@alumnes.ub.edu (S.E.M.); iabohora7@alumnes.ub.edu (I.A.-H.); halbaut@ub.edu (L.H.); anacalpena@ub.edu (A.C.C.); mireia.mallandrich@ub.edu (M.M.)
2 Institute of Advanced Chemistry of Catalonia-CSIC (IQAC-CSIC), 18-26 Jordi Girona St., 08034 Barcelona, Spain; cristina.alonso@iqac.csic.es (C.A.); luisa.coderch@iqac.csic.es (L.C.)
3 Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Avenida Universidad 1001, Cuernavaca 62209, Mexico; lgarduno@uaem.mx
4 Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Granada, 18071 Granada, Spain; jlsoriano@correo.ugr.es
5 Institut de Nanociència i Nanotecnologia IN2UB, Universitat de Barcelona, 08028 Barcelona, Spain
6 Reig-Jofre Laboratories, Av. de les Flors s/n, 08970 Sant Joan Despí, Spain; ffernandez@reigjofre.com
* Correspondence: beatrizclares@ugr.es
† These authors contribute equally to this work.
‡ These authors contribute equally to this work.

Citation: El Moussaoui, S.; Abo-Horan, I.; Halbaut, L.; Alonso, C.; Coderch, L.; Garduño-Ramírez, M.L.; Clares, B.; Soriano, J.L.; Calpena, A.C.; Fernández-Campos, F.; et al.

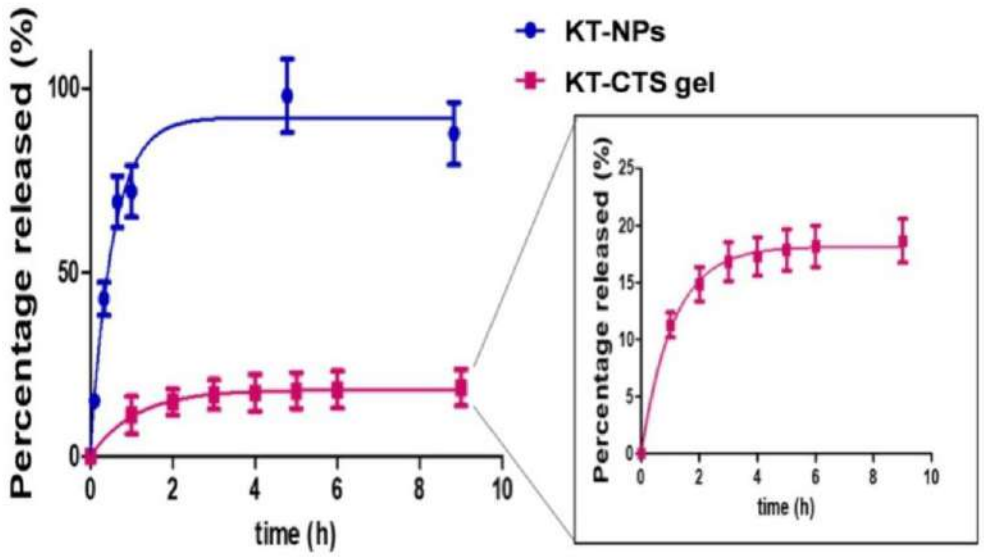


Figure. In vitro release profile of the formulations, KT-NPs and KT-CTS gel ($p < 0.001$). Each value represents mean ± SD ($n = 6$). (Moussaoui et al.)

Table 4. Skin distribution of KT (expressed as μg/cm^2) contained in the formulations with an in vitro test after an exposure time of 24 h. Values are expressed as mean ± SD ($n = 6$).

Biodistribution	KT-NPs (μg/cm^2)	KT-CTS Gel (μg/cm^2)	*p*-Value
Total applied	14.61	26.91	-
Skin surface	12.14 ± 1.31	26.51 ± 0.84	-
Stratum corneum	0.08 ± 0.02	0.04 ± 0.01	0.03 *
Epidermis	0.71 ± 0.32	0.32 ± 0.17	0.13
Dermis	0.001 ± 0.001	0.002 ± 0.001	0.57
Receptor Fluid	0.02 ± 0.01	0.49 ± 0.09	<0.01 *
Total recovery	12.95 ± 0.84	27.36 ± 0.85	-
Percutaneous Absorption	0.73 ± 0.32	0.81 ± 0.19	0.71

* Statistical differences between formulations ($p < 0.05$).

Folle *et al. J Nanobiotechnol* (2021) 19:359
https://doi.org/10.1186/s12951-021-01092-z

Journal of Nanobiotechnology

RESEARCH Open Access

Thymol-loaded PLGA nanoparticles: an efficient approach for acne treatment

Camila Folle[1], Ana M. Marqués[2], Natalia Díaz-Garrido[3,4,5], Marta Espina[1,6], Elena Sánchez-López[1,6*], Josefa Badia[3,4,5], Laura Baldoma[3,4,5], Ana Cristina Calpena[1,6] and Maria Luisa García[1,6*]

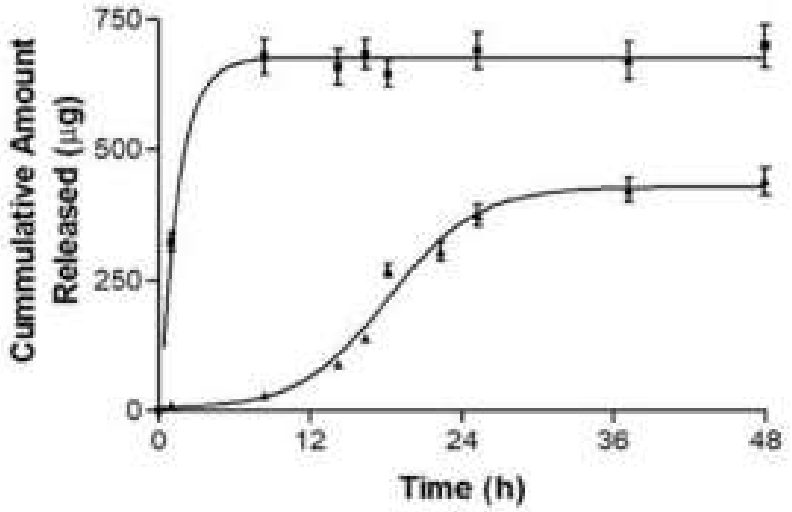


Figure. In vitro release profile of thymol solution and thymol encapsulated in polymeric nanoparticles.

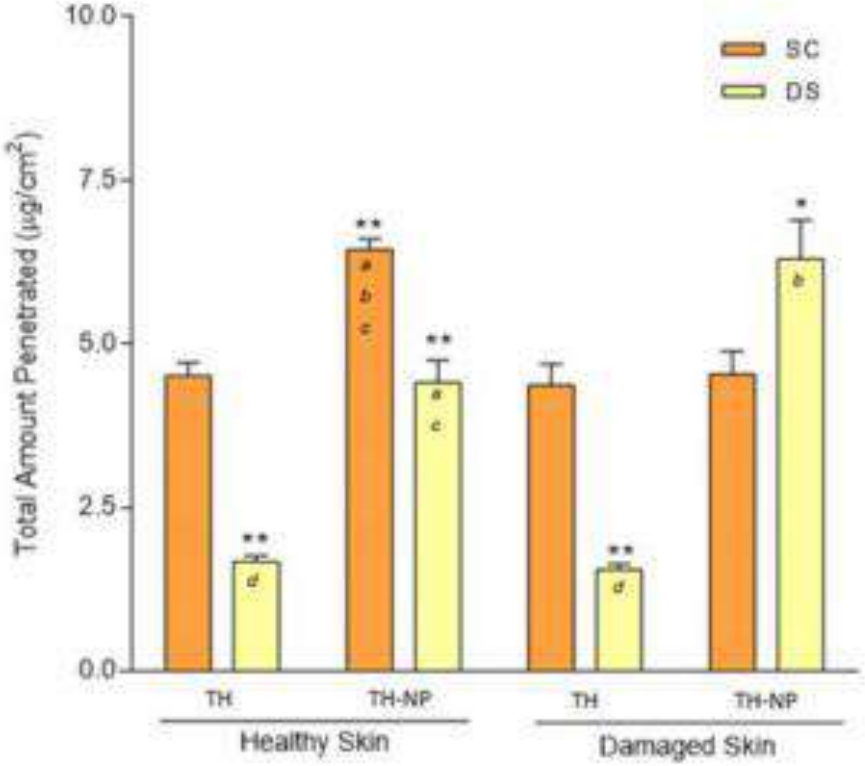


Figure. Total amount of TH and TH-NP penetrated in 24 h in healthy and damaged skin. SC: stratum corneum (tape stripping), DS: deep skin (extraction). (Folle et al.)

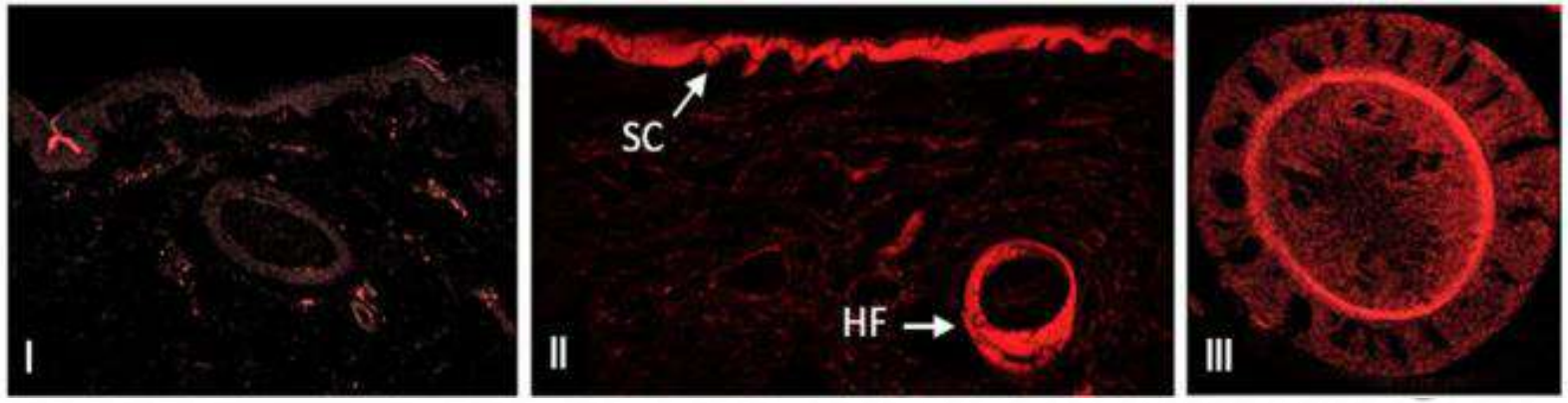


Figure. Confocal microscopy images of pig skin R-TH-NP penetration after 24 h: I untreated skin control, II Stratum corneum (SC) and hair follicle (HF), III hair follicle cross-section. (Folle et al.)

International Journal of Nanomedicine

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ORIGINAL RESEARCH

Gel-Dispersed Nanostructured Lipid Carriers Loading Thymol Designed for Dermal Pathologies

Camila Folle[1], Ana M Marqués[2], Natalia Díaz-Garrido[3–5], Paulina Carvajal-Vidal[1], Elena Sánchez López[1,6], Joaquim Suñer-Carbó[1,6], Lyda Halbaut[1,6], Mireia Mallandrich[1,6], Marta Espina[1,6], Josefa Badia[3–5], Laura Baldoma[3–5], Maria Luisa García[1,6], Ana Cristina Calpena[1,6]

[1]Department of Pharmacy and Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain; [2]Department of Biology, Healthcare and Environment, Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain; [3]Department of Biochemistry and Physiology, Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain; [4]Institute of Biomedicine of the University of Barcelona (IBUB), Barcelona, Spain; [5]Research Institute Sant Joan De Déu (IR-SJD), Barcelona, Spain; [6]Institute of Nanoscience and Nanotechnology (IN2UB), University of Barcelona, Barcelona, Spain

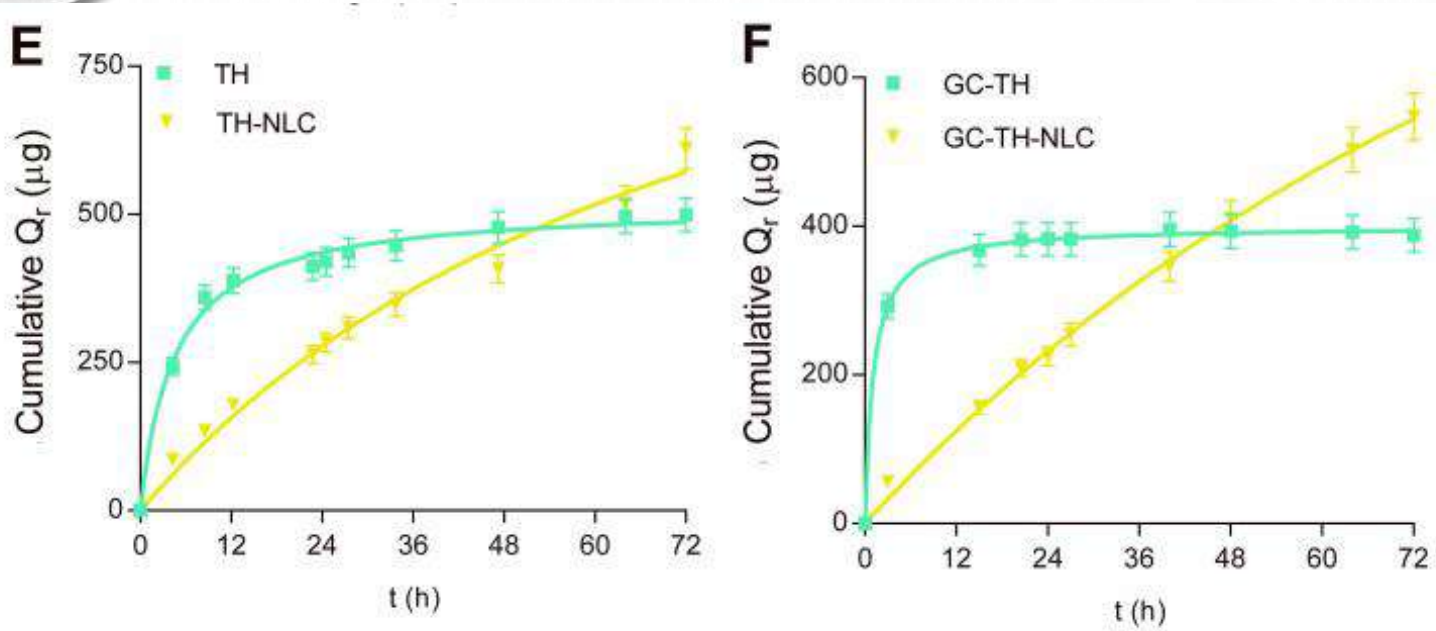


Figure. Drug release profile, E: Thymol solution (TH) and Thymol encapsulated in nanostructured lipid carrier (TH-NLC), F: Thymol gel (GC-TH) and gel loading thymol nanoparticles (GC-TH-NLC). (Folle et al.)

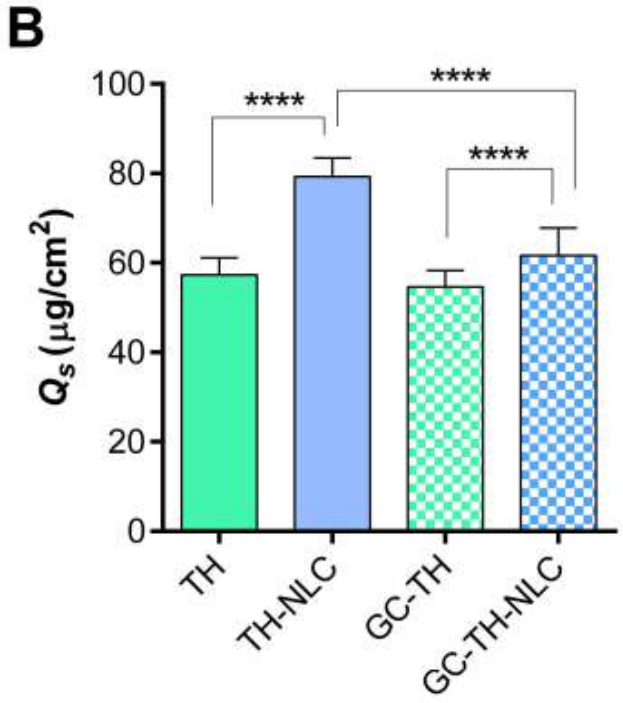
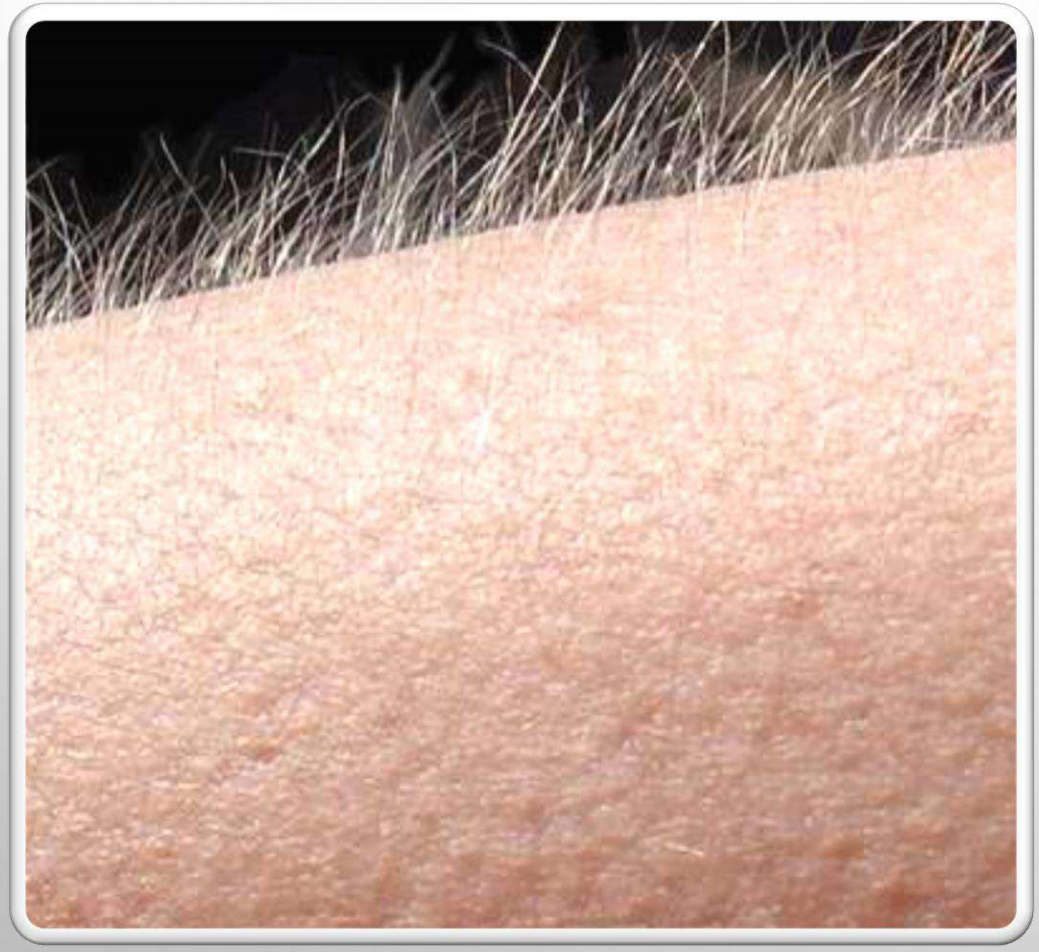


Figure. Amount of Thymol retained in the skin after the ex vivo permeation study from the plain solution, the drug encapsulated in NLC and both formulations incorporated in Carbopol gels. (Folle et al.)

4. ¿ALGO MÁS QUE PIEL?
ALTERNATIVAS A PIEL HUMANA. MODELOS DE PIEL



- De animales
- Membranas biomiméticas
- Piel bioimpresa

Toxicology testing	Skin absorption	Skin corrosion	Skin irritation	Skin sensitization
Test guidelines	OECD TG 428	OECD TG 431	OECD TG 439	OECD TG 442D
Definition	Absorption of chemical through passive diffusion when in direct contact	Irreversible skin damage following application of a test chemical	Reversible skin damage following application of a test chemical	Allergic response to a chemical following application of a test chemical
Validated *in vitro* testing models	Excised human or animal (pig or rat) skin in the range of 200-400 µm thickness	Epiderm™ EpiSkin™ SkinEthicTM RHE epiCS®	Epiderm™ EpiSkin™ LabCyte EPI-Model SkinEthic™ RHE	KeratinoSens™ (immortalized HaCaT stably transfected with a selectable plasmid)
Principle	A radiolabeled test chemical is applied to the skin sample separating the two chambers of a diffusion cell to check for passive diffusion at different time points throughout the experiment	A corrosive chemical can penetrate the stratum corneum of 3D RHE model by diffusion or corrosion and are toxic to underlying cells	An irritant can penetrate the stratum corneum of 3D RHE model by diffusion and cause the underlying damaged cells to release inflammatory mediators or induce an inflammatory cascade	A sensitizer can upregulate the luciferase activity and allows quantitative measurement of luciferase gene induction

Table. Validated in vitro skin models (Ng et al.)

PIEL ANIMAL

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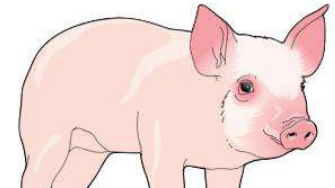


Pharmaceutical nanotechnology

Ex vivo permeation of carprofen from nanoparticles: A comprehensive study through human, porcine and bovine skin as anti-inflammatory agent

Alexander Parra[a,b], Beatriz Clares[c,*], Ana Rosselló[b], María L. Garduño-Ramírez[d], Guadalupe Abrego[d], María L. García[b], Ana C. Calpena[a]

[a] Department of Pharmacy and Pharmaceutical Technology, Biopharmaceutics and Pharmacokinetics Unit, Faculty of Pharmacy, University of Barcelona, Joan XXIII Avenue, 08028 Barcelona, Spain
[b] Department of Physical Chemistry, Faculty of Pharmacy, University of Barcelona, Joan XXIII Avenue, 08028 Barcelona, Spain
[c] Department of Pharmacy and Pharmaceutical Technology, University of Granada, Campus de la Cartuja Street, 18071 Granada, Spain
[d] Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad No. 1001, Col Chamilpa, Cuernavaca, Morelos, Mexico, Mexico

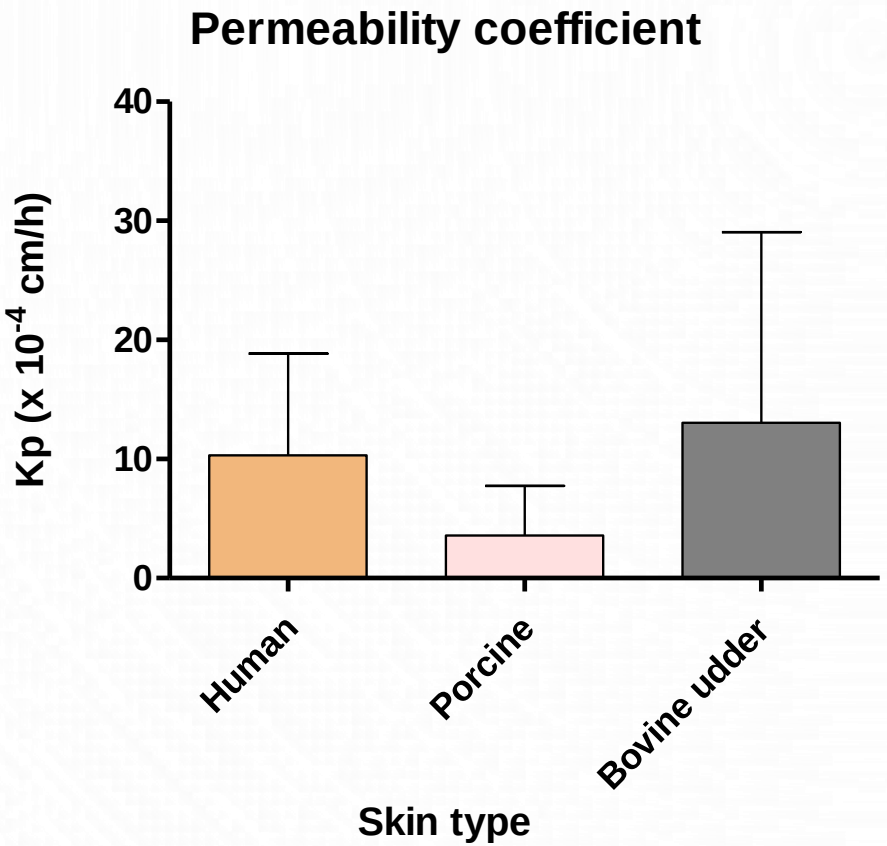


Figure. Permeability coefficient of carprofen from polymeric nanoparticles tested on skin from different species. (Parra et al.)

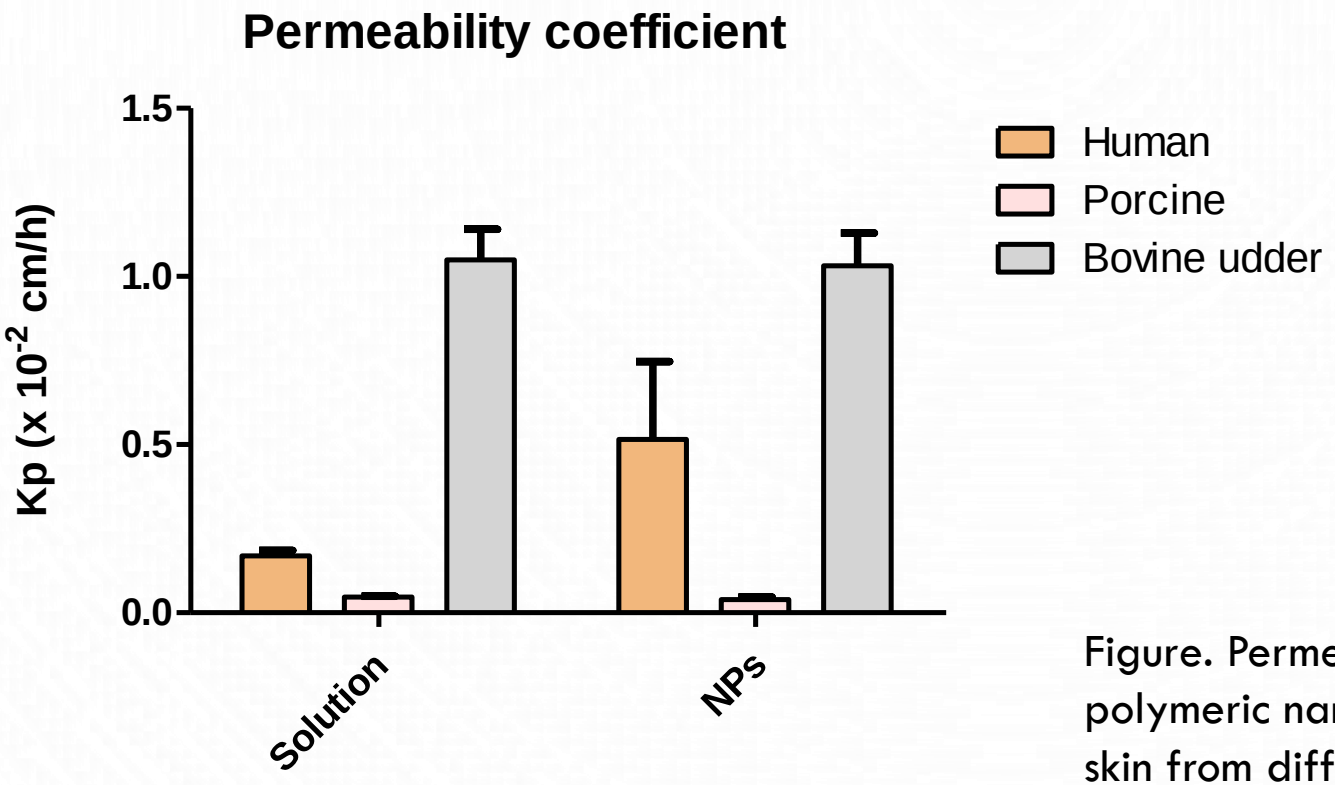
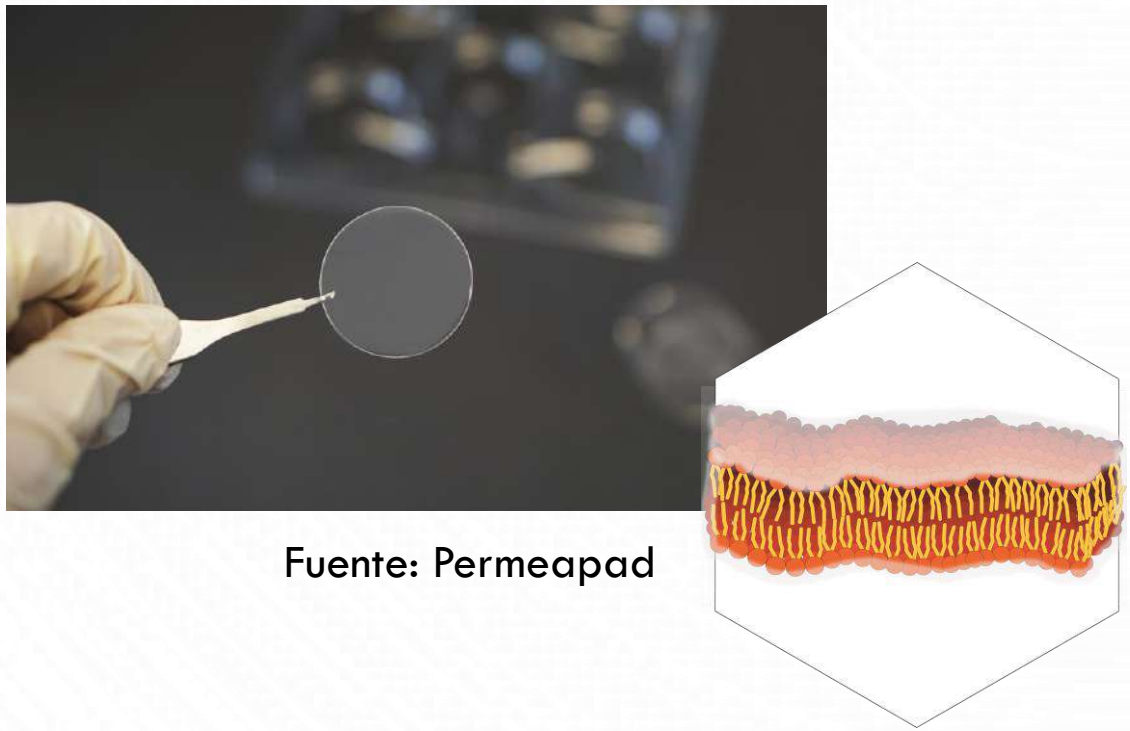


Figure. Permeability coefficient of flurbiprofen from polymeric nanoparticles and plain solution tested on skin from different species. (Unpublished data)

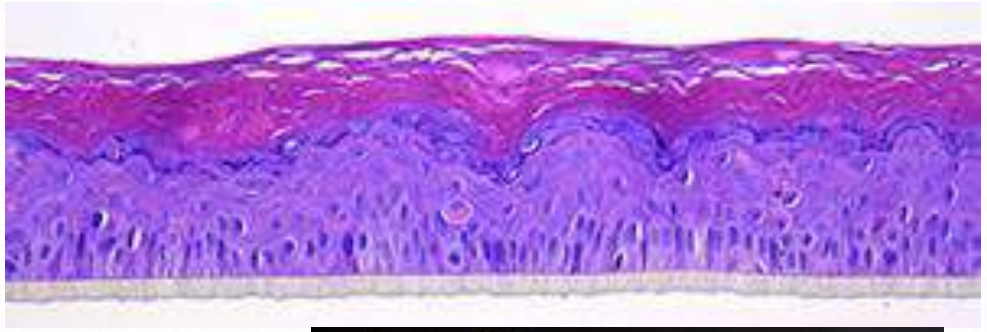
MEMBRANAS BIOMIMÉTICAS Y RHE

Resistente, lista para usar, sin condiciones especiales de almacenamiento ni de manejo.



Fuente: Permeapad

Cultivos celulares, require medios y condiciones específicas de manejo y conservación.



Fuente: EpiSkin

RECONSTRUCTED HUMAN EPIDERMIS

NAME

SkinEthic™ RHE / Reconstructed Human Epidermis

DESCRIPTION

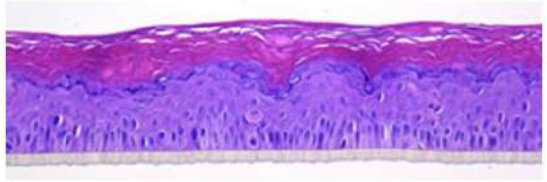
SkinEthic™ RHE is an *in vitro* reconstructed human epidermis from normal human keratinocytes cultured on an inert polycarbonate filter at the air-liquid interface. It is histologically similar to the *in vivo* human epidermis.

Our strong believe in Science and our continuous improvement with ISO 9001 certification push us to keep improving the production process of our model: From cell extraction to reconstruction with chemically defined biocomponents and medium.

Every single biocomponent of each step of our production is clearly defined and their traceability is guaranteed. The process is then more secured, allowing to deliver a SkinEthic™ RHE model more reproducible, robust and reliable than ever.

Different maturities and surfaces are available.

SPECIFIC MARKERS



in vitro

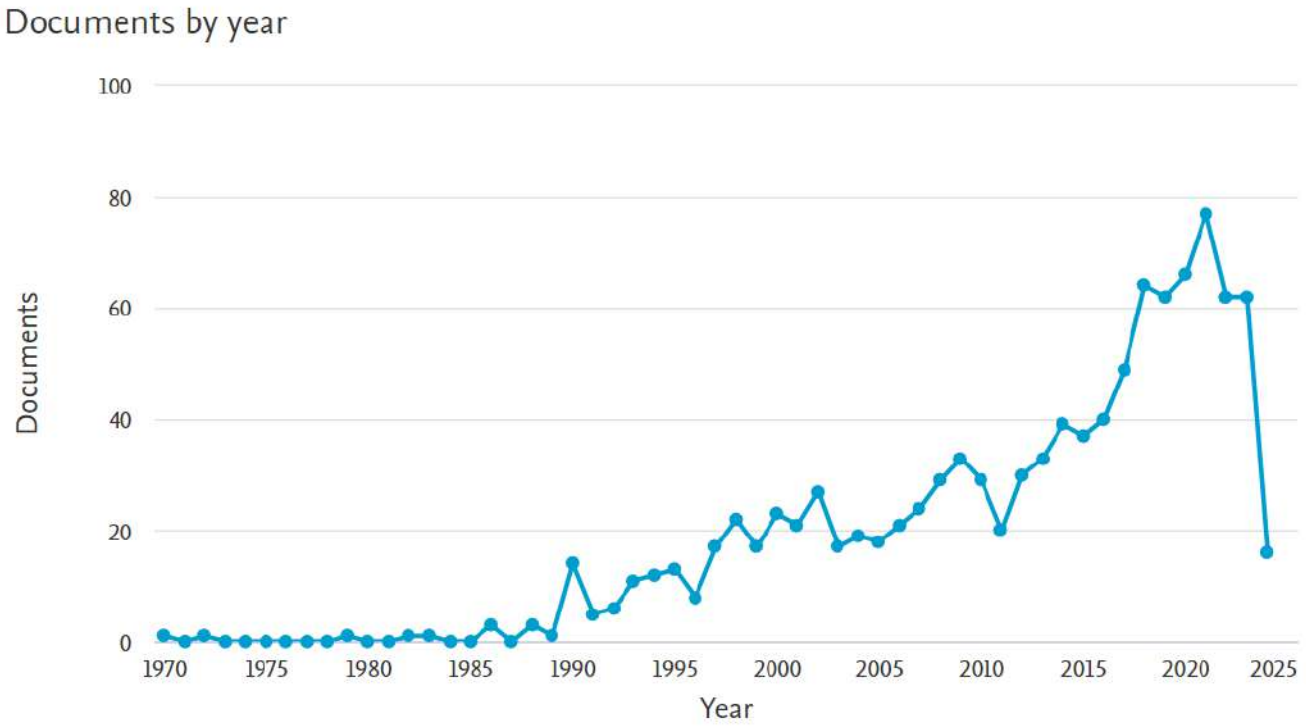
APPLICATIONS

- Skin irritation
- Skin corrosion
- Medical devices
- UV Exposure
- DNA Damage
- Bacterial adhesion
- Omics
- Permeability

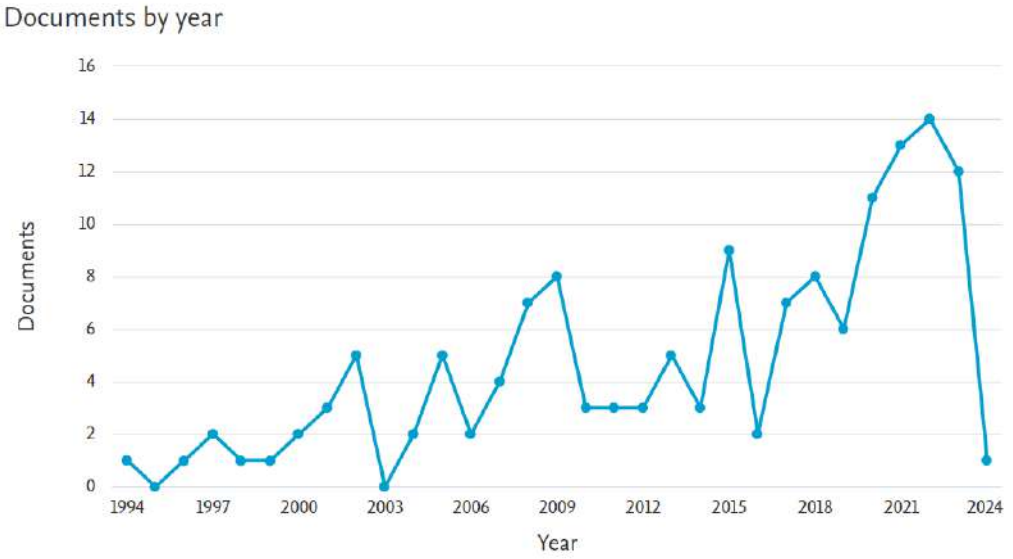
FORMAT

- 0.5 cm² (See picture)
- 4 cm² (See picture)
- HTS 24-well plate 0.33 cm² (See picture)
- HTS 96-well plate 0.11 cm² (See picture)

Fuente: Episkin



(Scopus: Analyze search results of reconstructed human epidermis; 1055 documents)



(Scopus: Analyze search results of reconstructed human epidermis AND permeation; 144 documents)

MEMBRANAS BIOMIMÉTICAS

International Journal of
Molecular Sciences

MDPI

Article

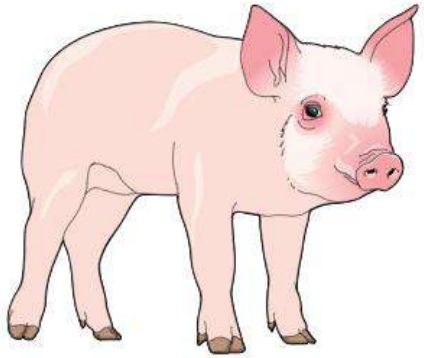
HPV Lesions and Other Issues in the Oral Cavity Treatment and Removal without Pain

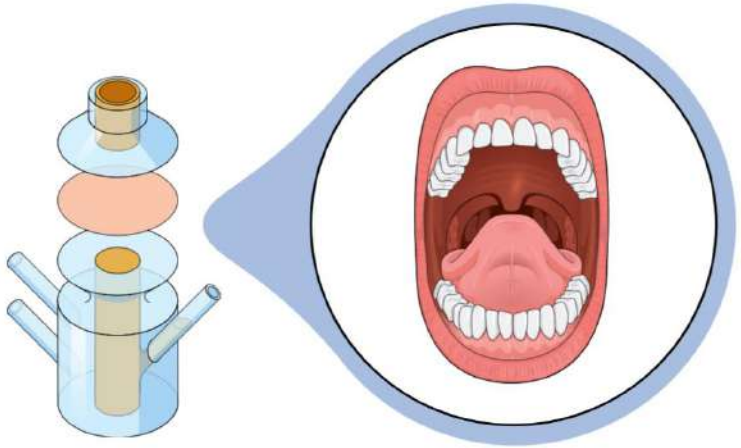
Salima El Moussaoui [1], Mireia Mallandrich [1,2,*], Núria Garrós [1], Ana Cristina Calpena [1,2], Maria José Rodríguez Lagunas [3] and Francisco Fernández-Campos [4]

1 Departament de Farmàcia, Tecnologia Farmacèutica i Fisicoquímica, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII 27-31, 08028 Barcelona, Spain; selmouel9@alumnes.ub.edu (S.E.M.); nuriagarros98@gmail.com (N.G.); anacalpena@ub.edu (A.C.C.)
2 Institut de Nanociència i Nanotecnologia IN2UB, Universitat de Barcelona, 08028 Barcelona, Spain
3 Departament de Bioquímica i Fisiologia, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII 27-31, 08028 Barcelona, Spain; mjrodriguez@ub.edu
4 Reig-Jofre Laboratories, Av. de les Flors s/n, 08970 Sant Joan Despí, Spain; ffernandez@reigjofre.com
* Correspondence: mireia.mallandrich@ub.edu; Tel.: +34-93-4024-560

ESTUDIO DE PEREMACIÓN EN MUCOSA BUCAL Y SUBLINGUAL PORCINA VS. MEMBRANA BIOMIMÉTICA PERMEAPAD

Fuente: Permeapad





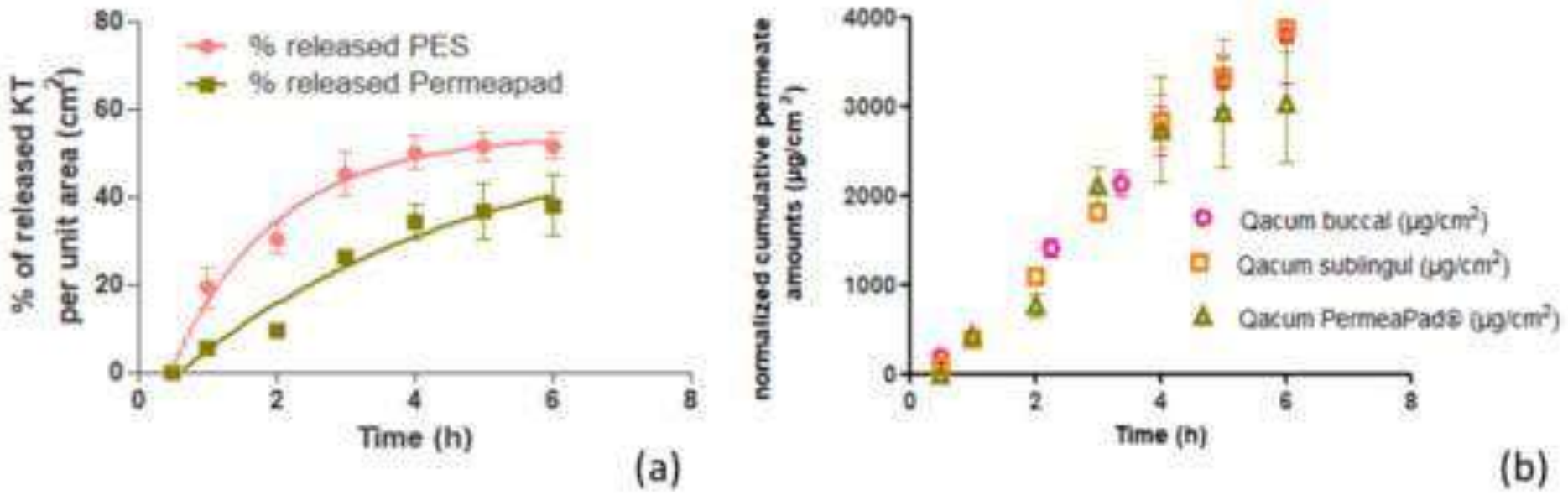
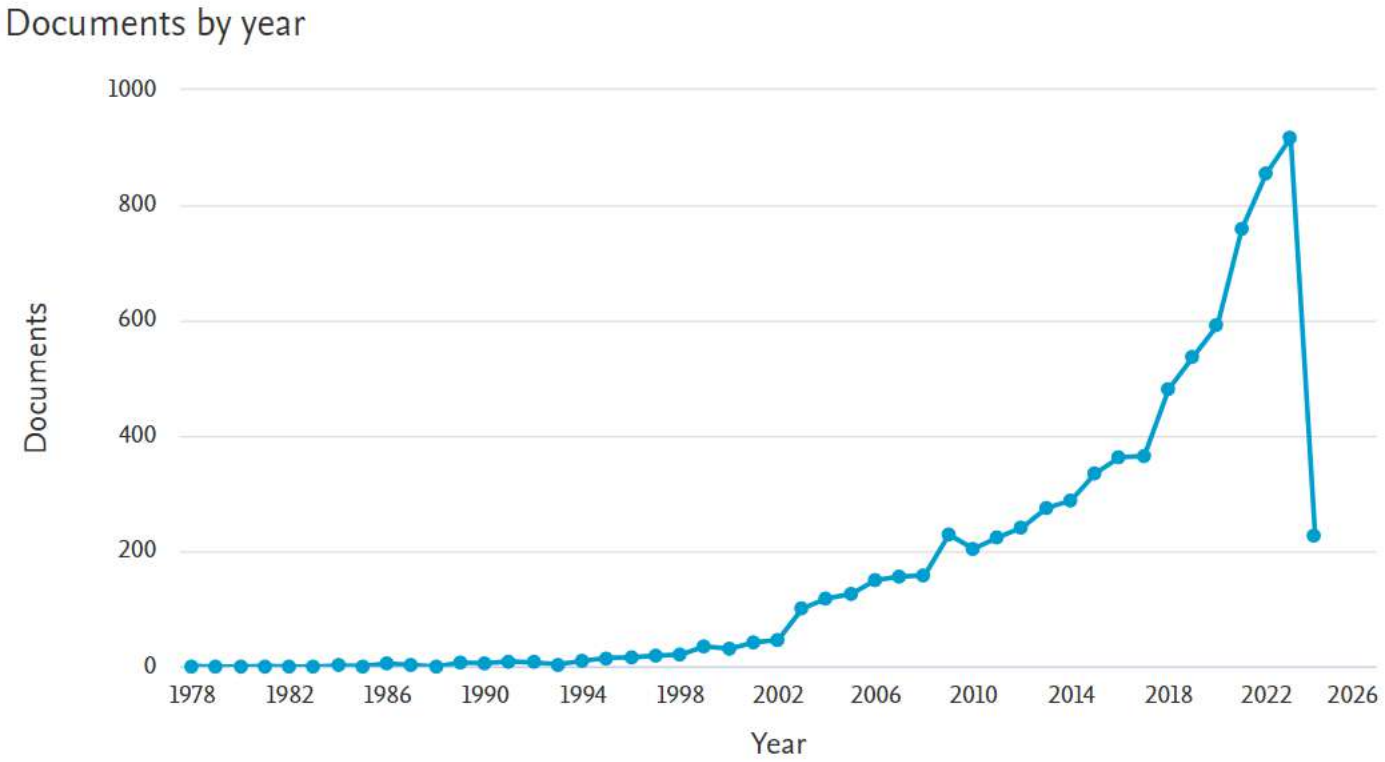
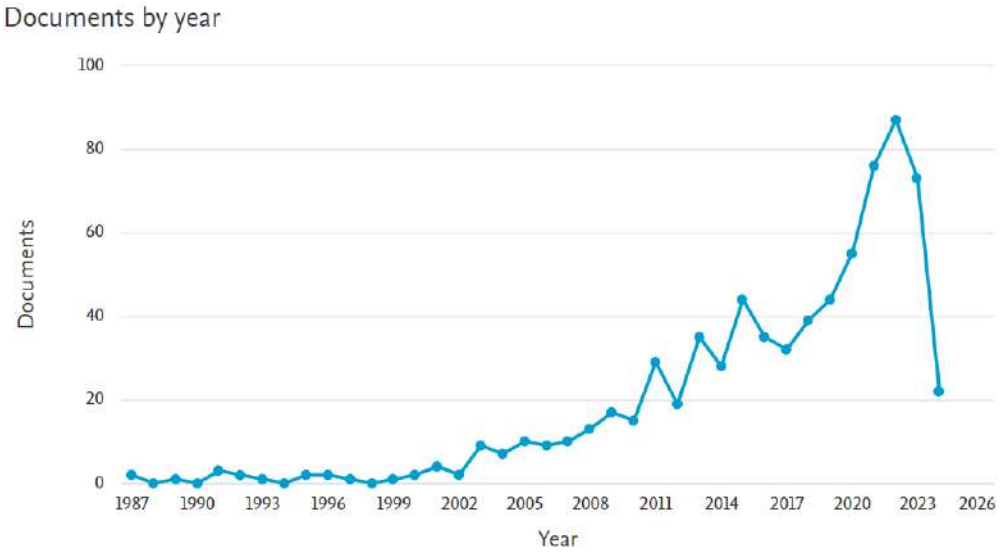


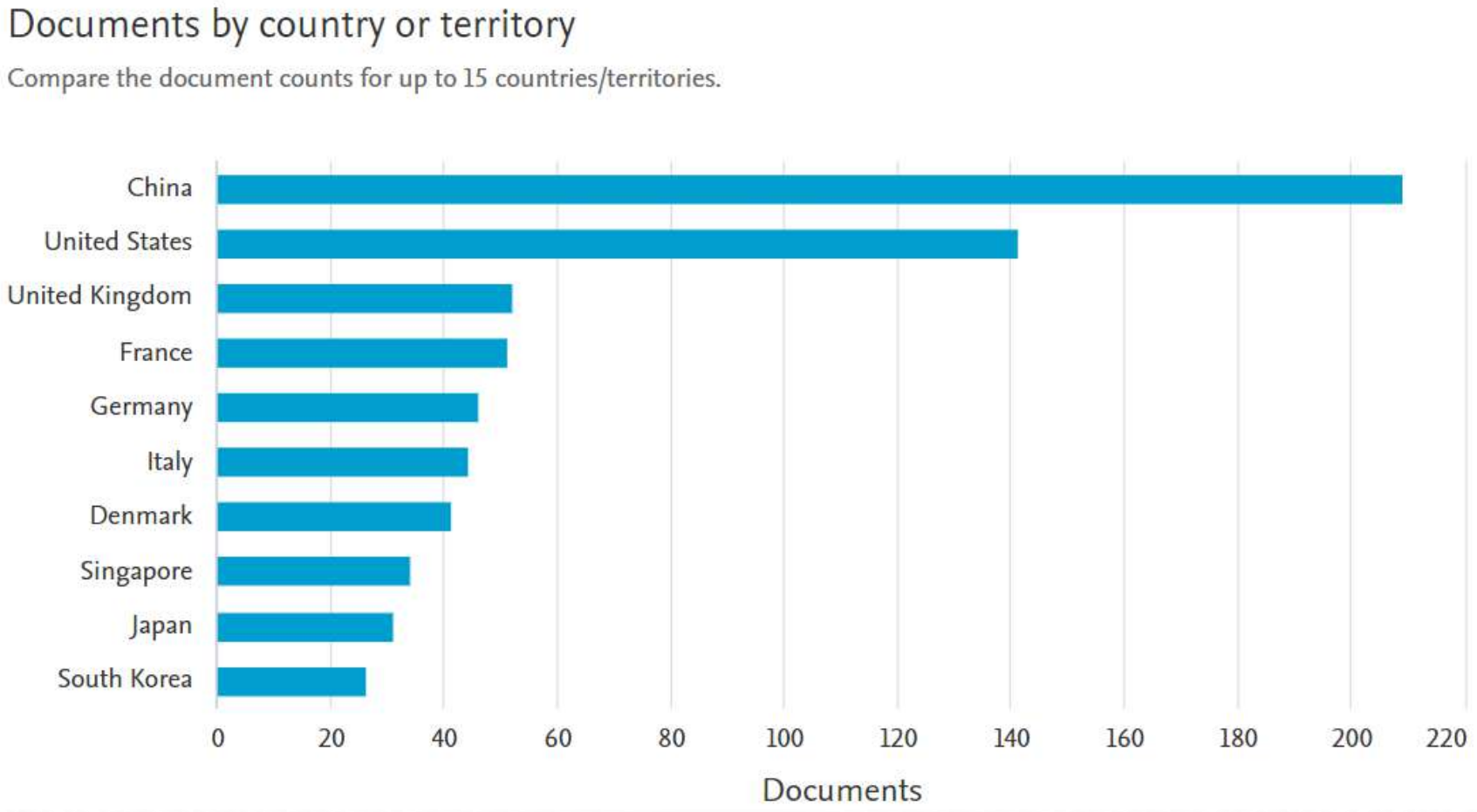
Figure 3. In vitro and ex vivo assays. (a) Representation of the percentage of released KT per unit area (cm2) from the PES membrane (pink curve) and the PermeaPad® biomimetic membrane (green curve). (b) Cumulative amount of KT permeated (µg/cm2) under an infinite dose regimen through buccal and sublingual mucosae and biomimetic membrane upon application of KT hydrogel. Values represent means ± SD (n = 3). (Moussaoui et al.)



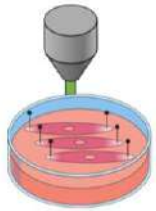
(Scopus: Analyze search results of biomimetic membranes; 7982 documents)

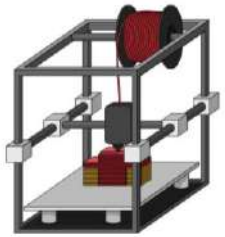


(Scopus: Analyze search results of biomimetic membranes AND permeation; 731 documents)



(Scopus: Analyze search results of biomimetic membranes)

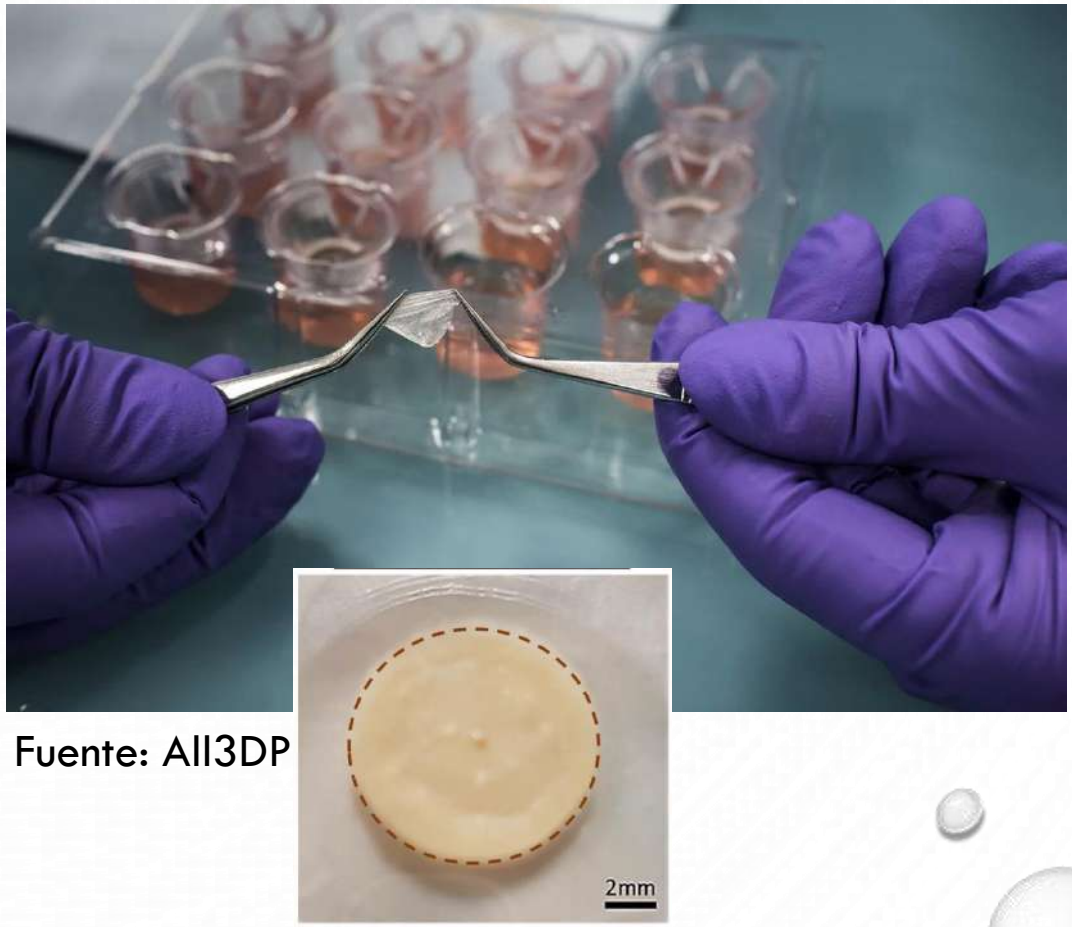




BIOPRINTED SKIN

- Tecnología de impresión 3D, capa a capa, para obtener tejido cutáneo artificial
- Biotinta: distintos tipos de células (fibroblastos, keratinocitos…) combinadas con biomateriales
- Retos: integración adecuada de las células, viabilidad celular, vascularización

Escasez de donantes de piel



Fuente: All3DP

BIOPRINTED SKIN

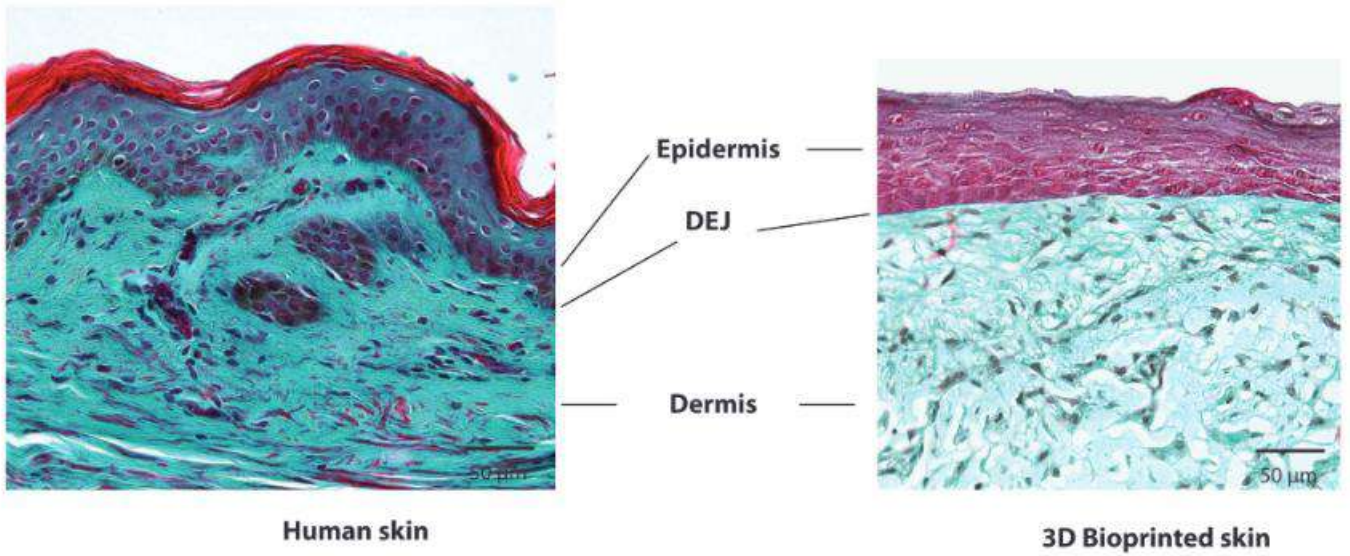


Figure. Histological and morphological characterization of the bioprinted skin. Optical microscopy images of normal human skin and bioprintedskin after 26 d of culture. Tissues were stained with Masson's Trichrome. (Pourchet at al.)

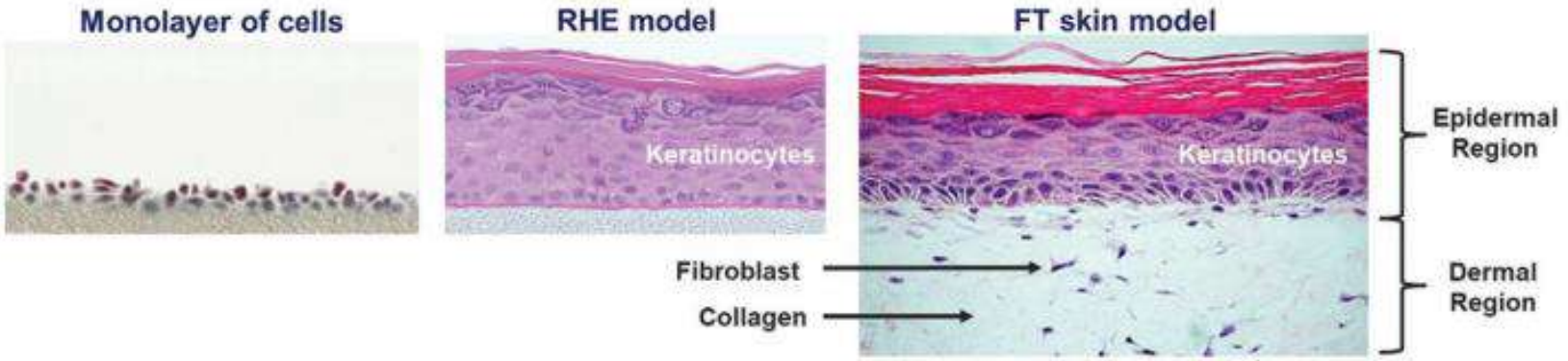
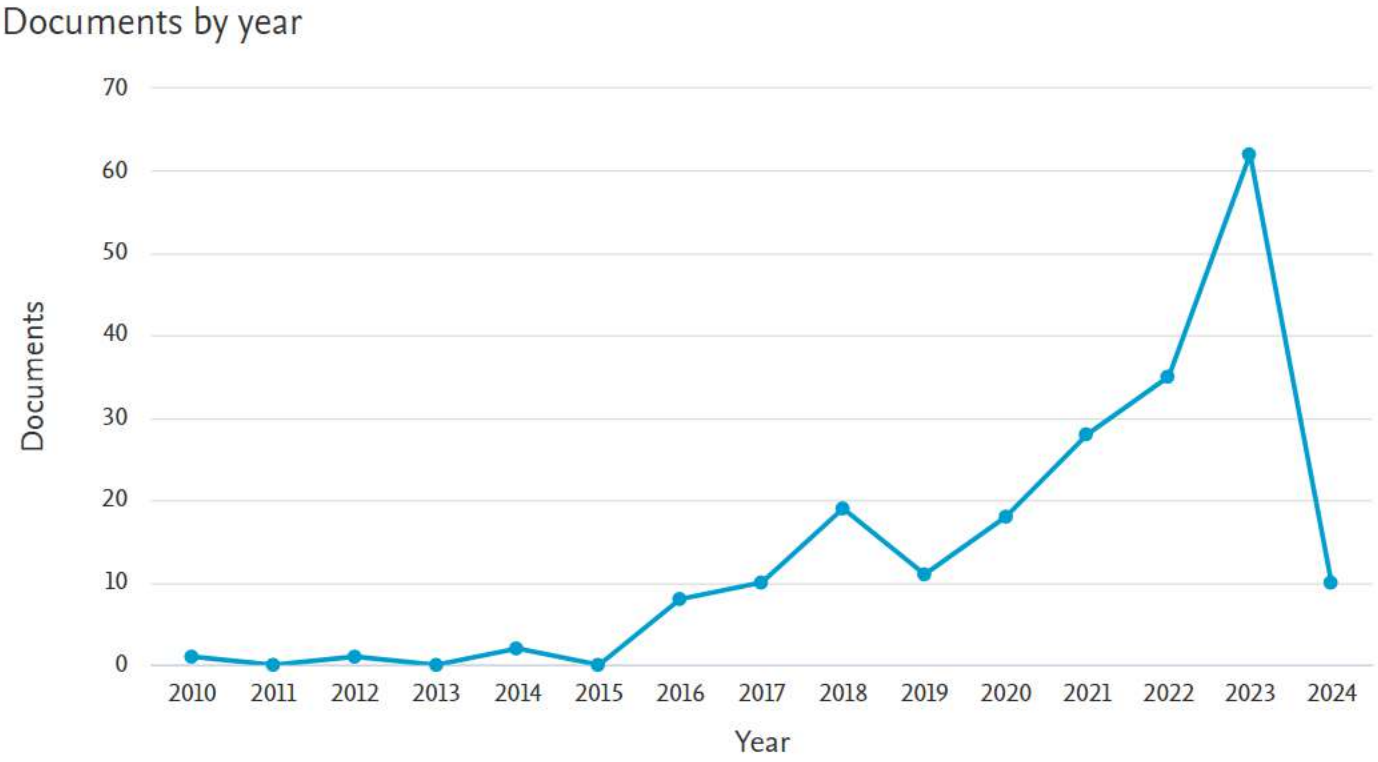


Figure. Bioprinting facilitates the deposition of a monolayer of cells with homogeneous cell distribution[23]; the bioprinting technique can be used to fabricate reconstructed human epidermis or full-thickness skin models. (Ng et al.)

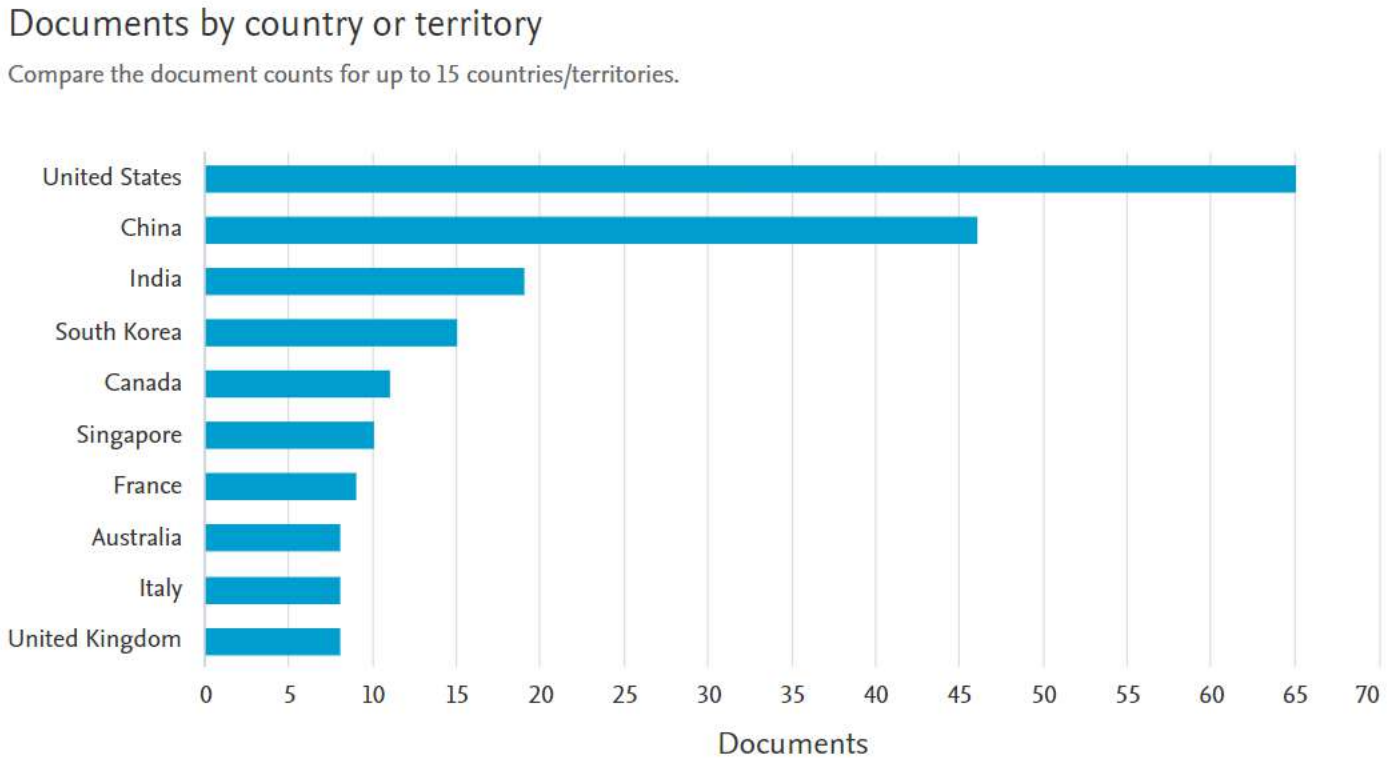
BIOPRINTED SKIN

Year ↓	Documents ↑
2024	10
2023	62
2022	35
2021	28
2020	18
2019	11
2018	19
2017	10
2016	8
2015	0



(Scopus: Analyze search results of bioprinted skin)

BIOPRINTED SKIN



(Scopus: Analyze search results of bioprinted skin)

AGRADECIMIENTOS

Seminari de Recerca 14 març 2024