Institute of Chemistry

האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

Incorporation of liquid nanodomains into films for dermal applications

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Skin structure and function

Epidermis – outer layer

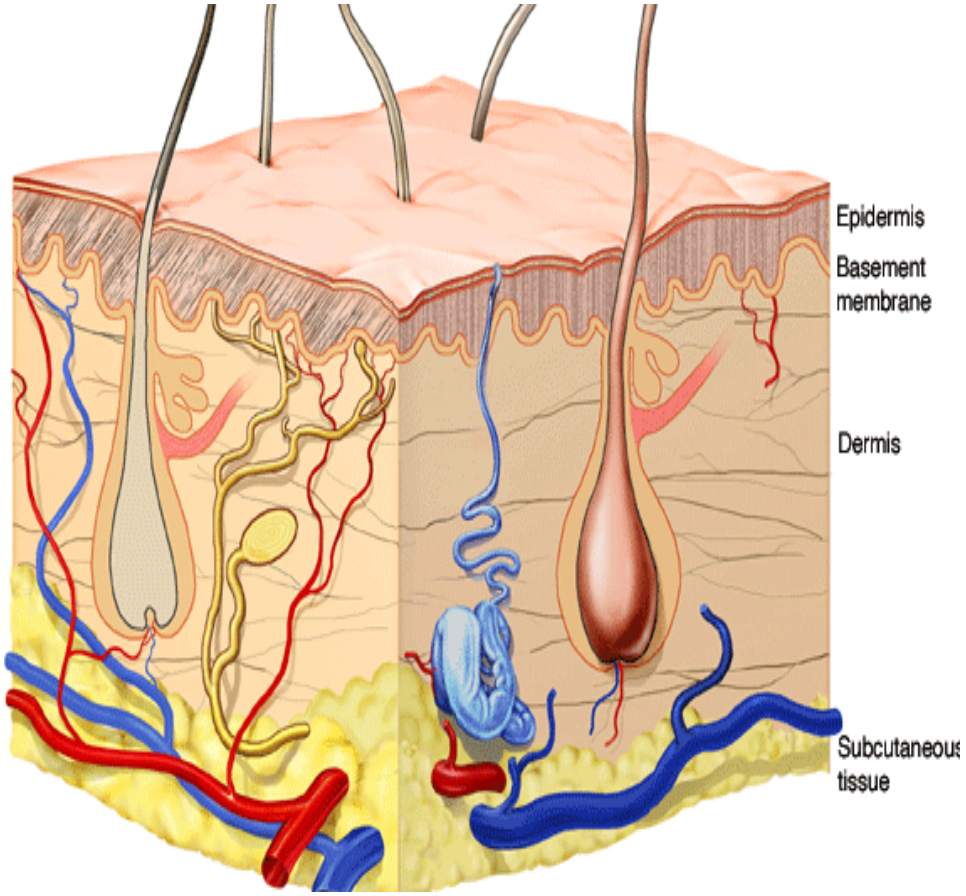
- Stratum corneum provides protective function
- inhibits and limits compounds from crossing through the skin
- non-vascularized

Dermis – inner layer

- composed of connective tissue
- good supply of blood

Hypodermis – subcutaneous layer

- fat storage
- blood vessel passage

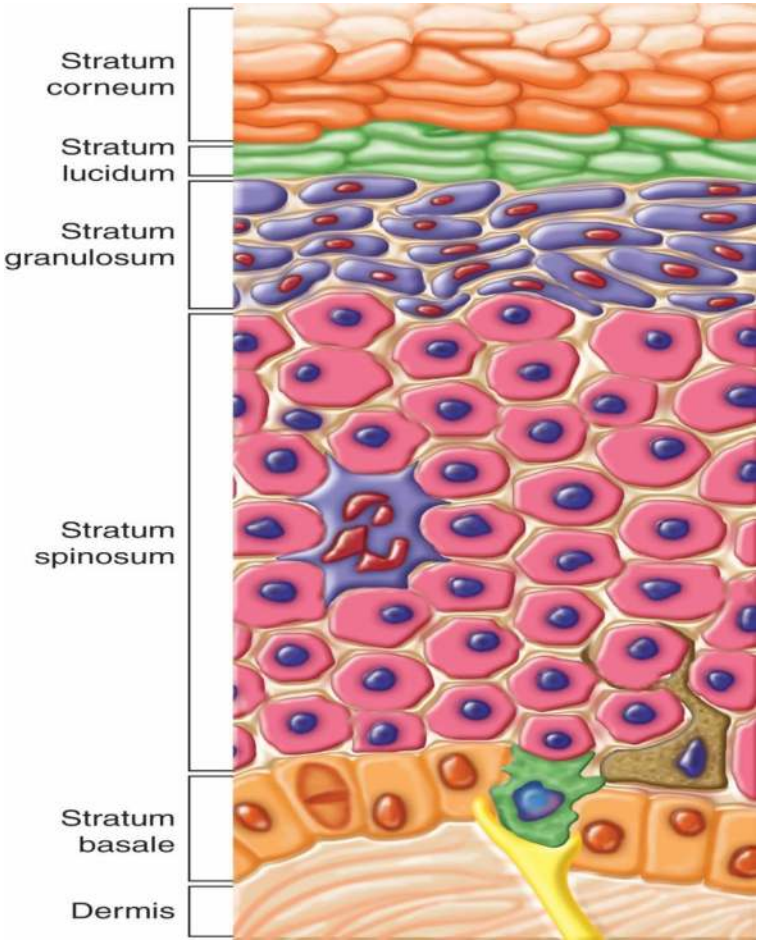


McLafferty E et al (2012), The integumentary system: anatomy, physiology and function of skin. Nursing Standard.

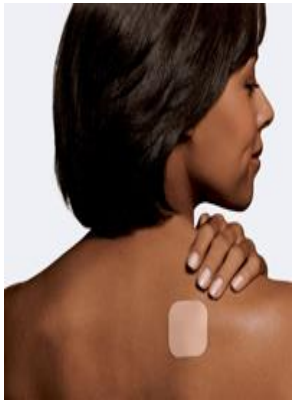
Skin structure and function

Stratum corneum

- Outer layer of epidermis, 25 to 30 flat dead cells filled with keratin
- Dead keratinized cells average thickness of 15-20 μm
- Provide protective function which inhibits and limits compounds from crossing through the skin

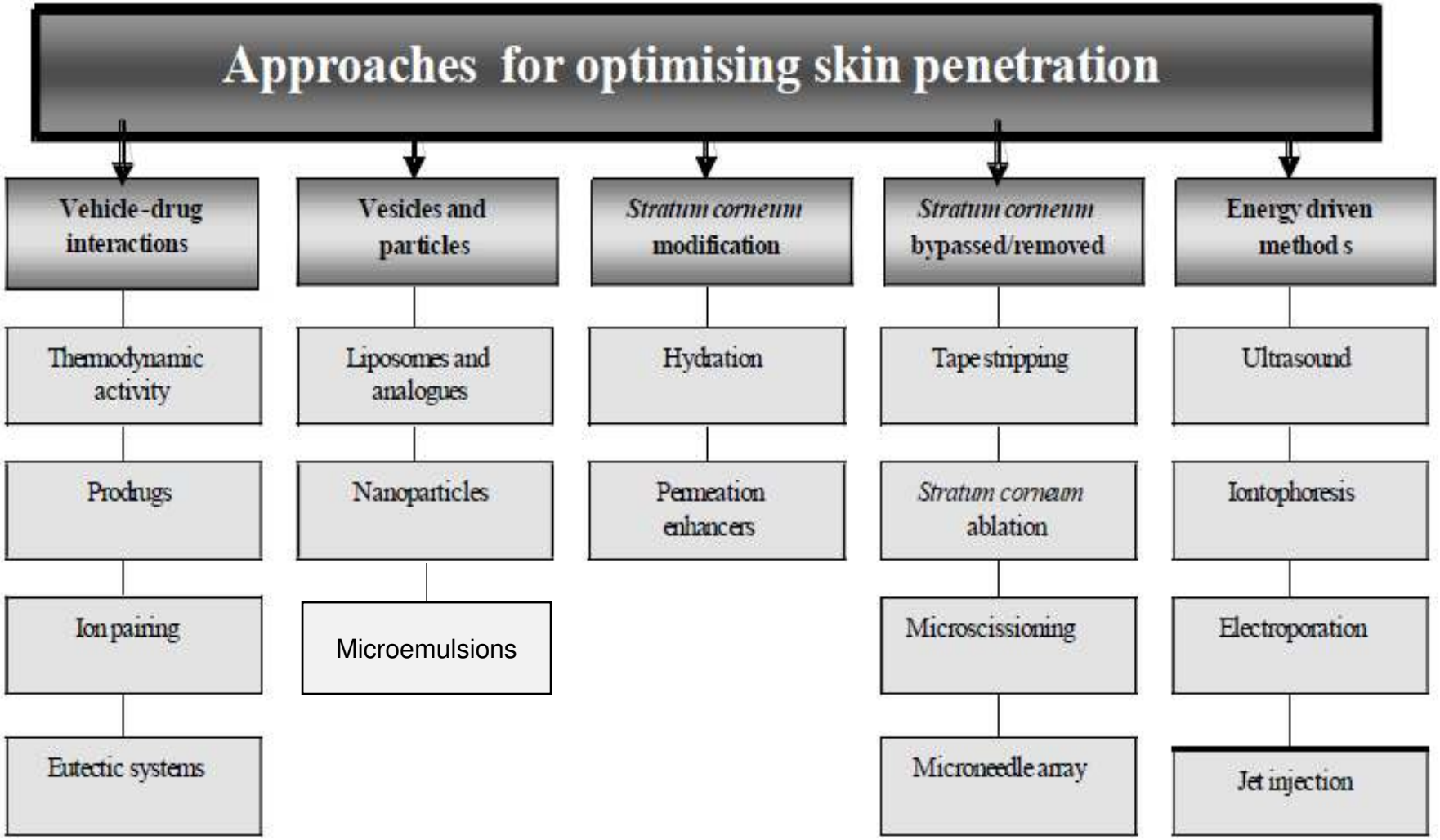


Dermal drug delivery



- Drug products topically administered via the skin fall into two general categories, those applied for local action and those for systemic effects.
- The use of topical medications does not result in significant drug concentrations in the blood and other tissues, and causes fewer adverse reactions.
- Transdermal drug delivery systems are designed to deliver therapeutically effective amount of drug through intact skin to the systemic circulation.

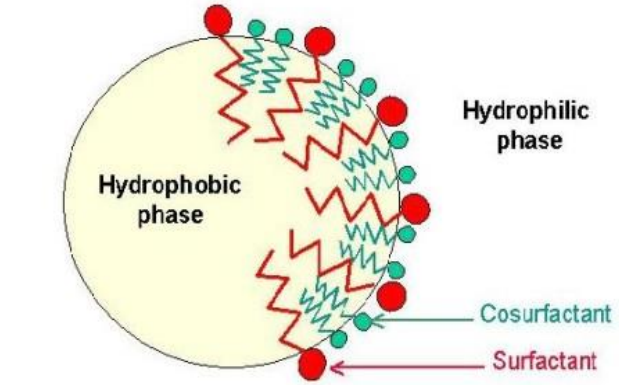
Strategies for penetration enhancing

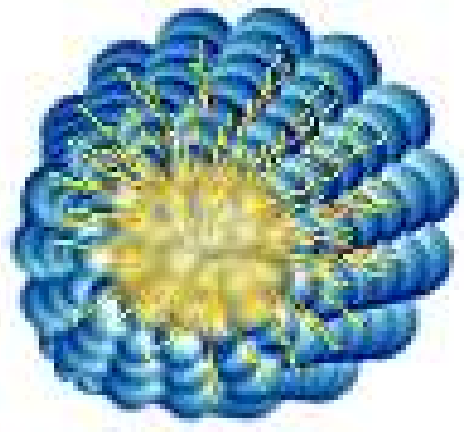


D.I.J. Morrow et al, The Open Drug Delivery Journal, 2007, 1, 36-59

Modified Microemulsions - Nanodomains (NDs)

- Mixture of water, oil, surfactants, cosurfactants, solvents and cosolvents
- Isotropic transparent nanostructured fluid
- Self-assembled, Newtonian and thermodynamically stable
- Monodispersed with structures size below 50 nm





N.Lidich et al, Journal of Colloid and Interface Science, 463 (2016) 342–348

Why NDs as dermal delivery?

Advantages:

- High permeability to the membrane due to nano size and flexibility of the droplets
- High solubilization potential for both lipophilic and hydrophilic drugs
- Increase partitioning and diffusion into the stratum corneum

Limitation:

- Absence of proper controlled drug delivery system for dermal application

P. Santos et al, Skin Pharmacol Physiol 2008;21:246–259

Research rationale

Motivation:

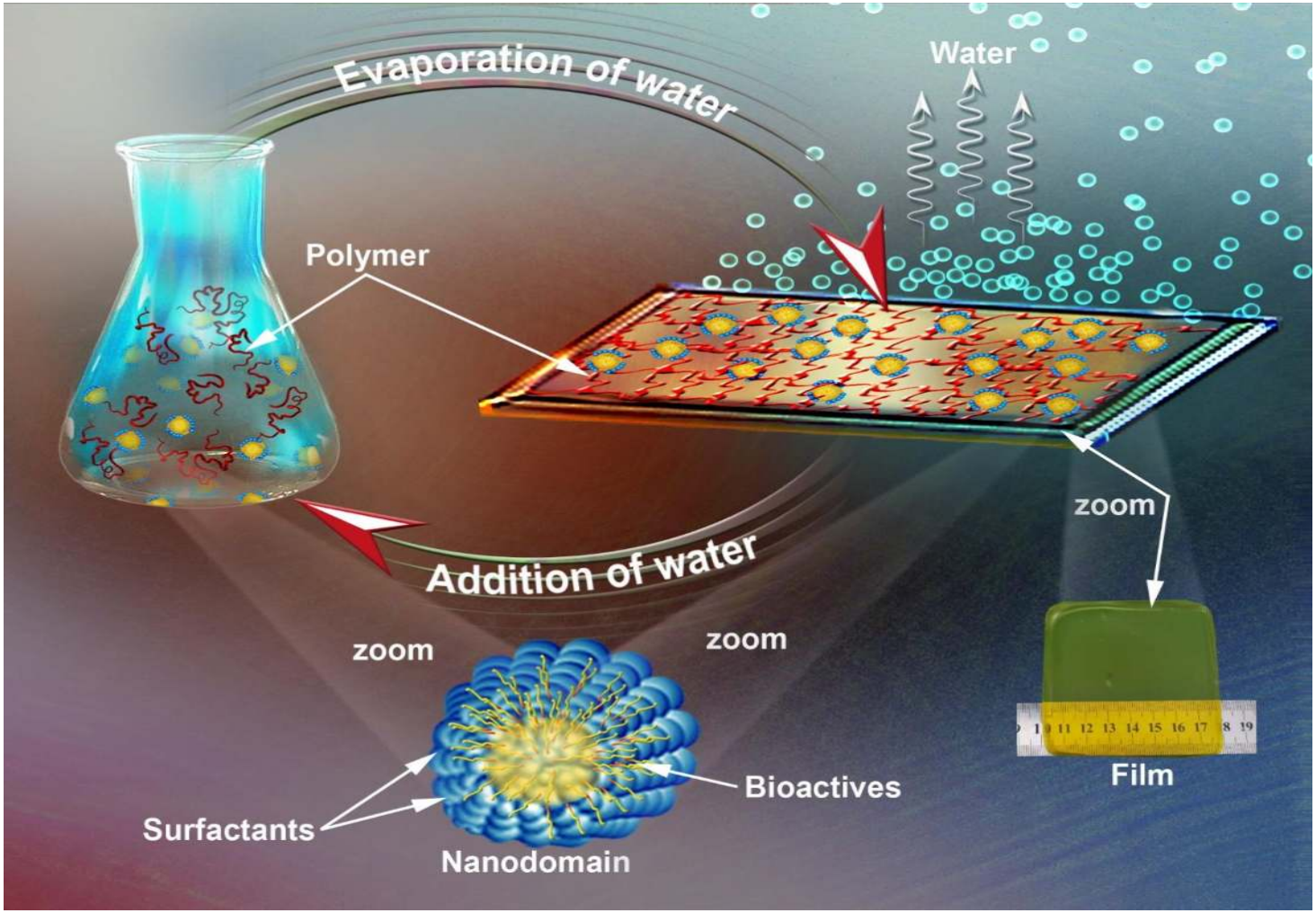
Liquid nanodomais for controlled release are limited to liquids and gels.

Aim of this study is to develop dermal controlled release drug delivery system based on nanodomains embedding into polymeric films.

Significance:

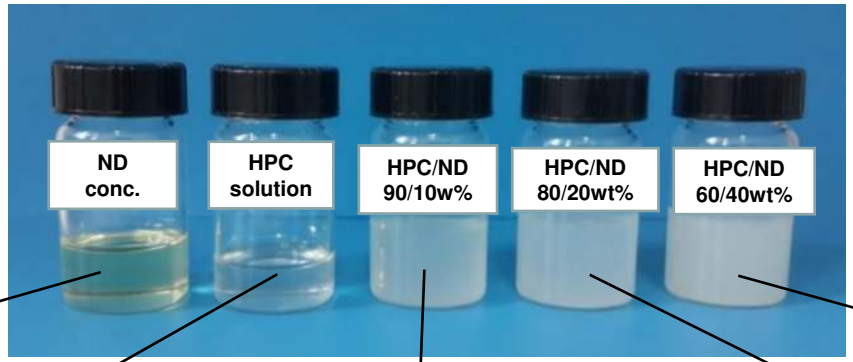
Nanodomains embedded into a polymeric film can offer a novel efficient approach for skin application therapy.

Cartoon illustrating the embedding of nanodomains in a polymeric film

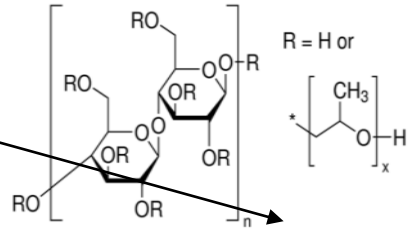


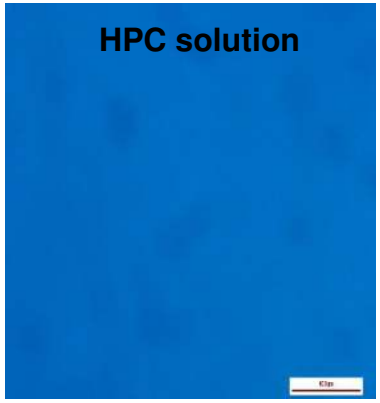
E.Abramov et al, Langmuir 2019, 35, 7879−7886

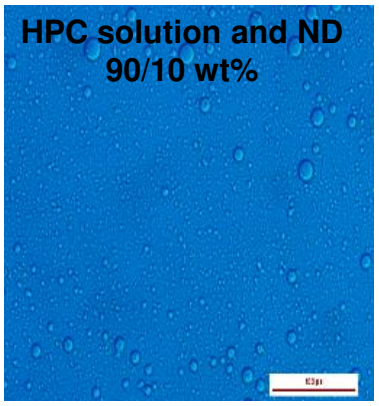
Effect of the destructive NDs-polymer interactions

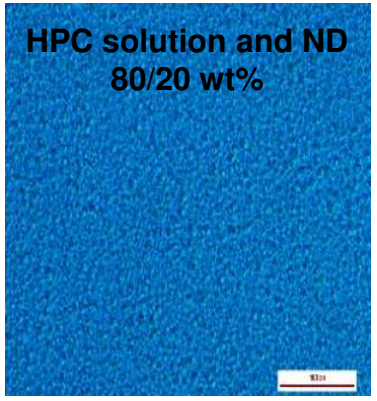


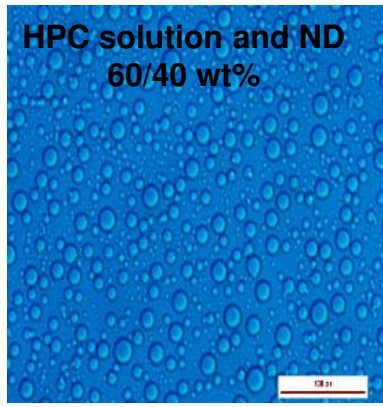
Hydroxypropyl Cellulose (HPC)

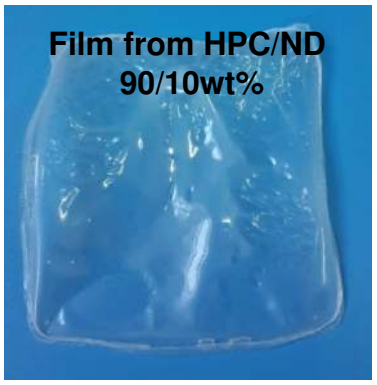


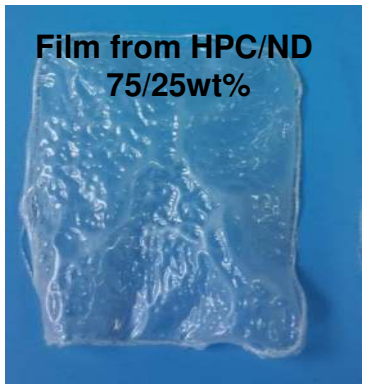


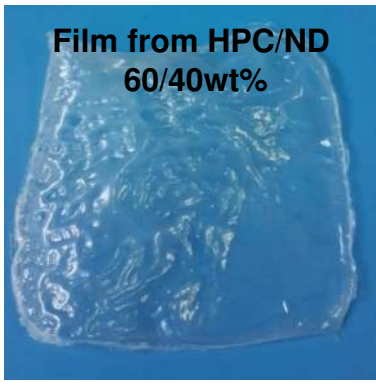








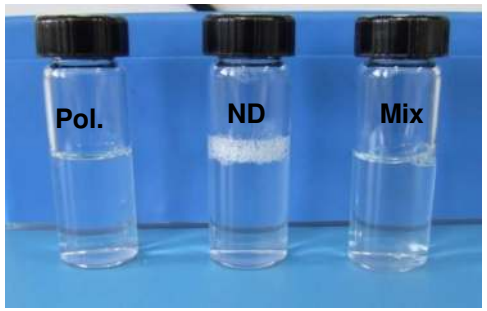


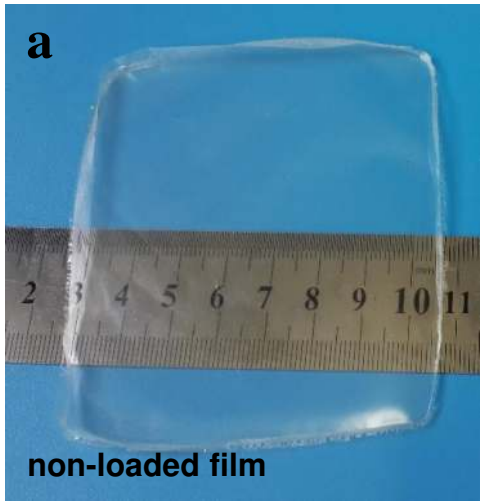


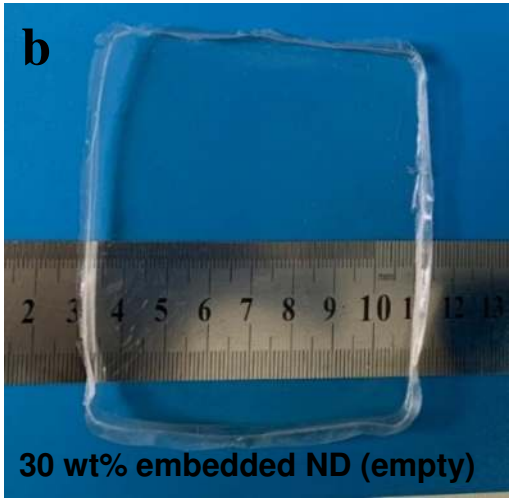
- The HPC solution caused coalescence of the NDs droplets. The drops size increased to ca.20 μm.

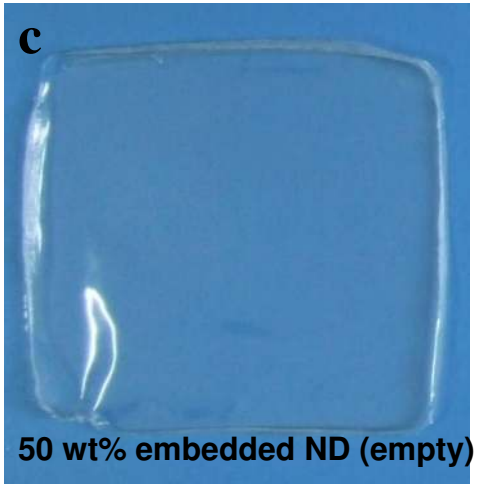
Nanodomains constructive films

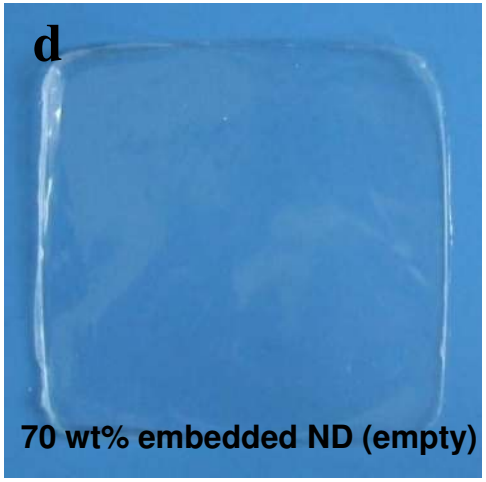
Biopolymer polysaccharide gum

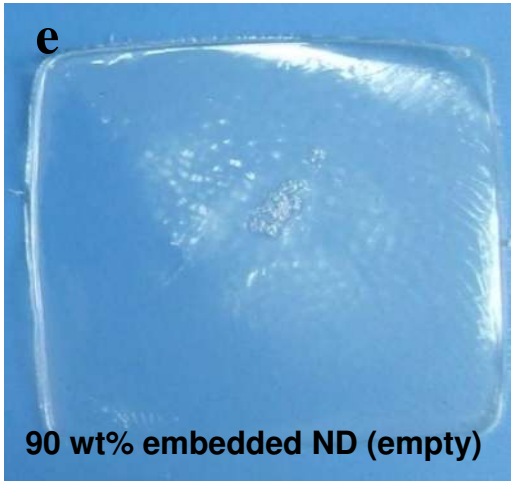








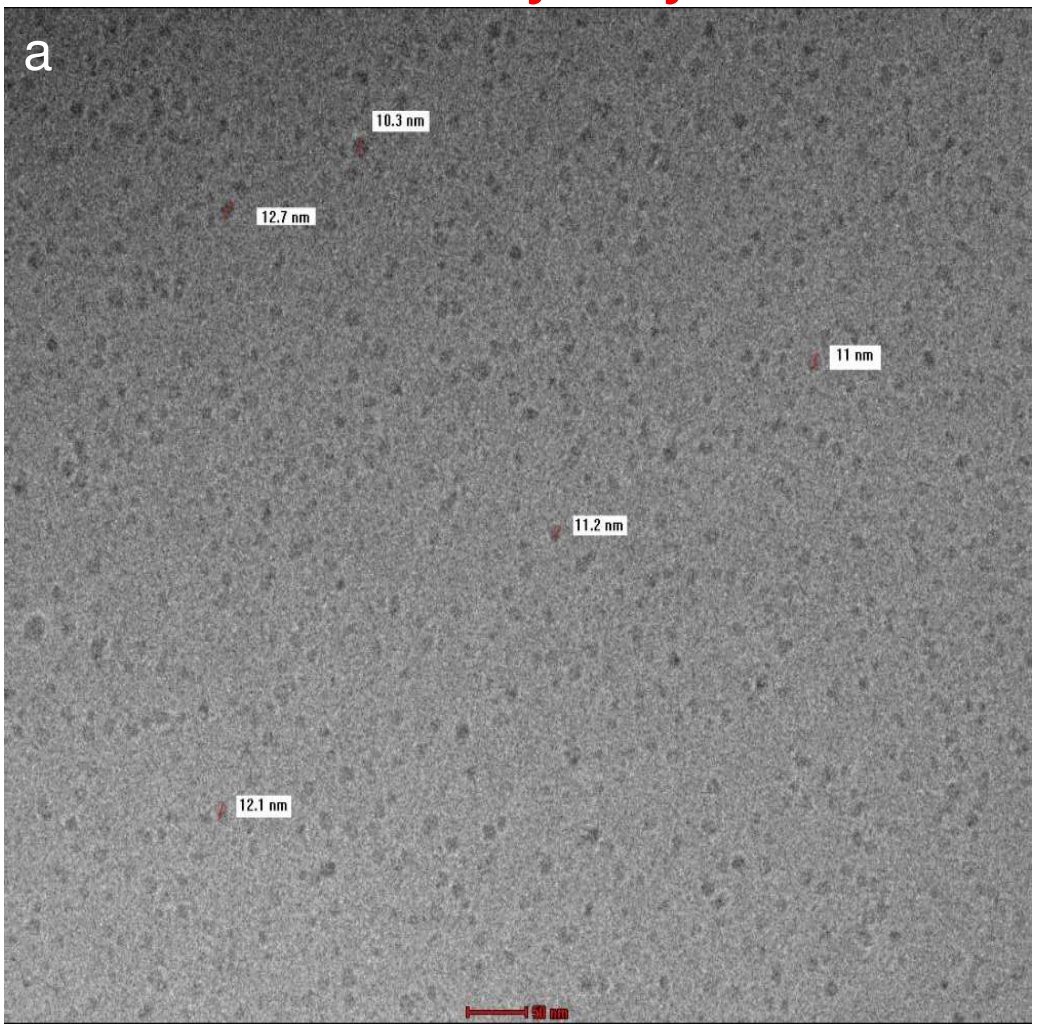




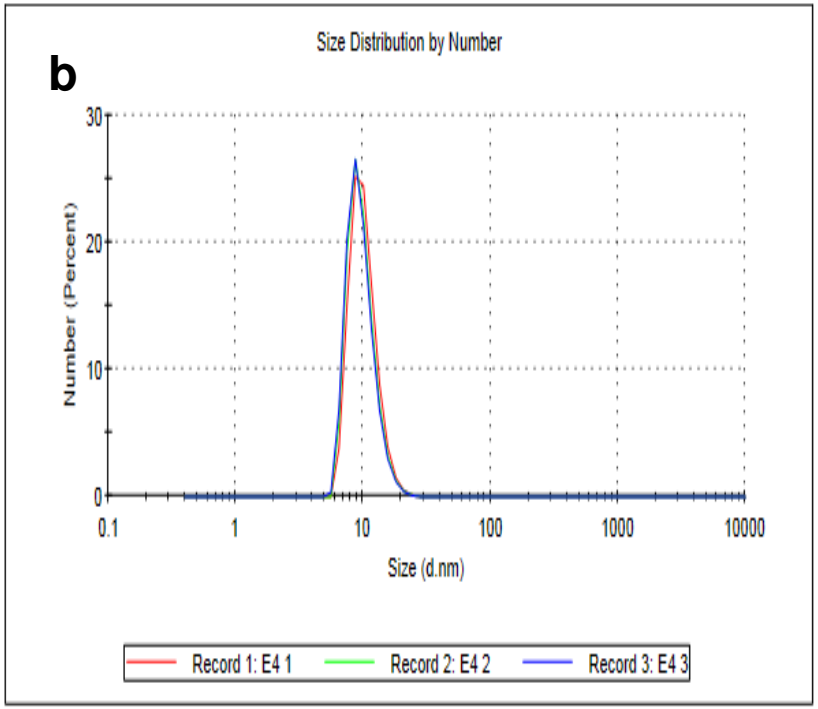
- The films are transparent, homogeneous with high loading capacity (up to 90% of ND).

Droplet size characterizations of the NDs in aqueous solution

by Cryo-TEM images and DLS



$$d(H) = \frac{kT}{3\pi\eta D}$$

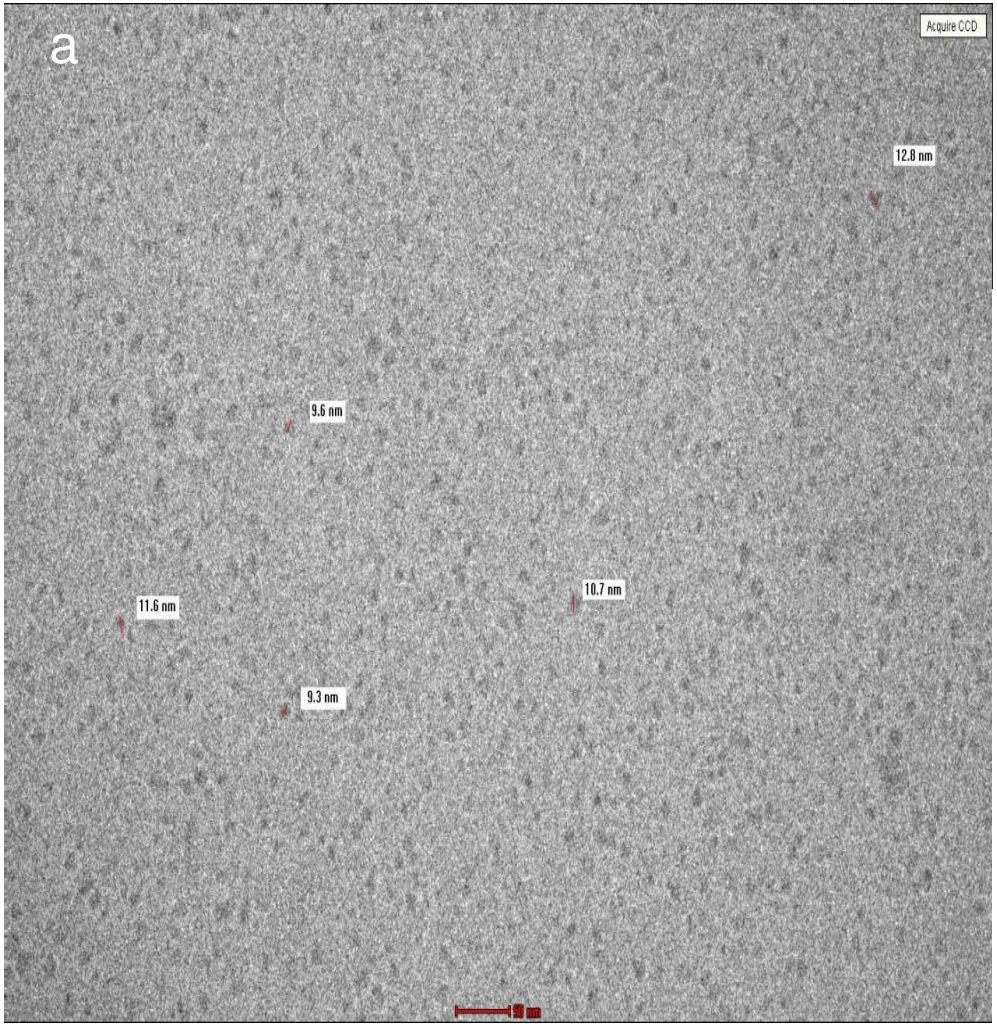


Average size of 20 droplets -11.5 nm

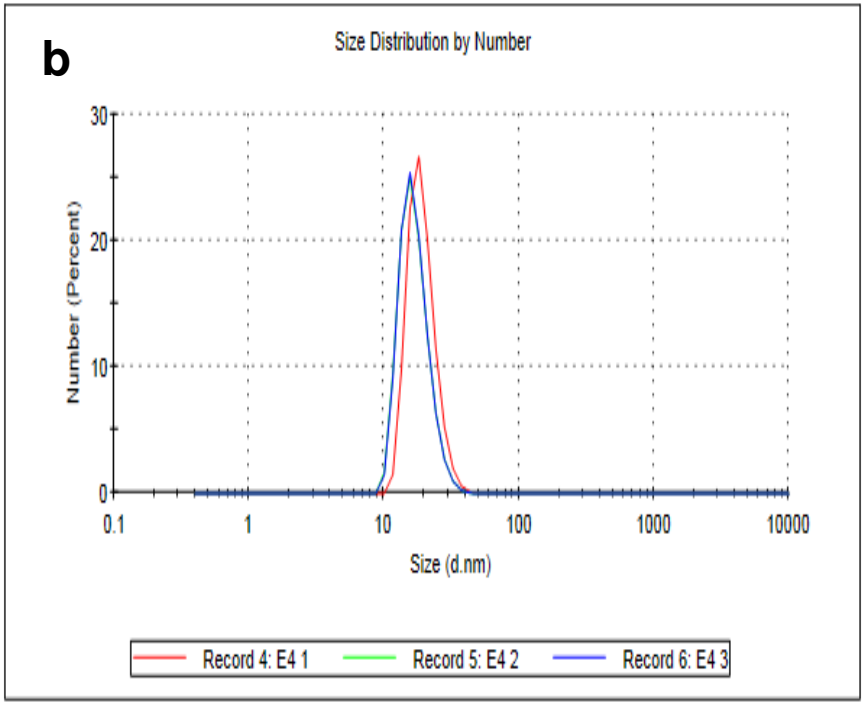
Average size of droplets-9.7 nm

Droplet size characterizations of the NDs in ND-polymer mixture

by Cryo-TEM images and DLS



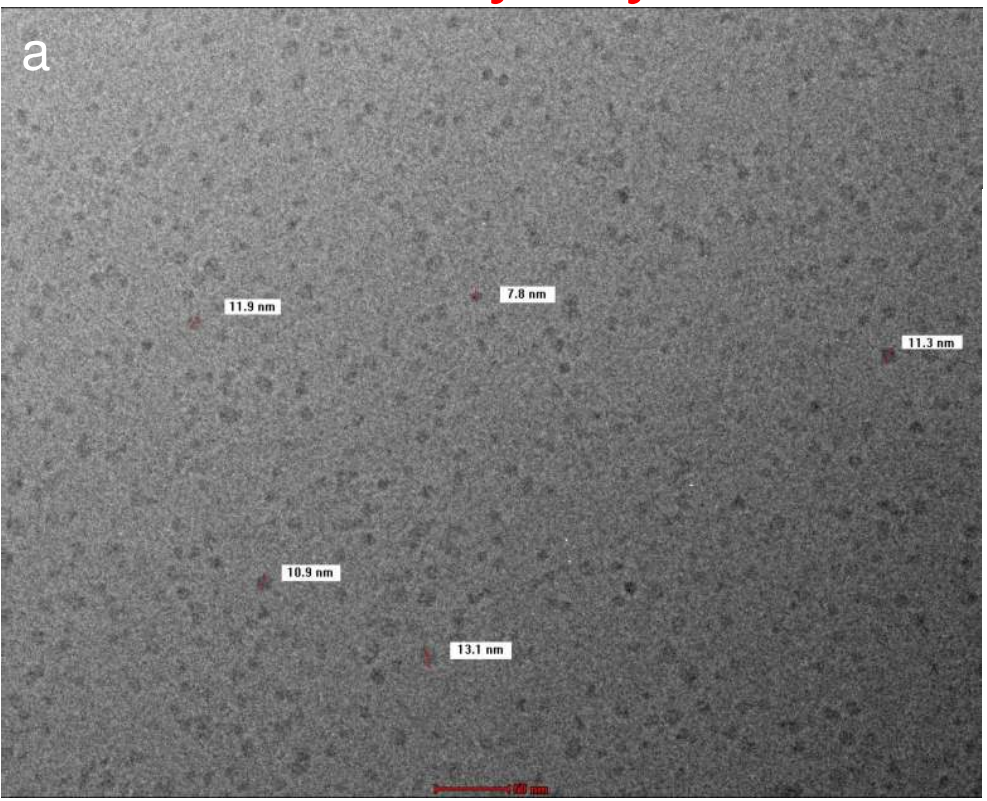
Average size of 20 droplets-10.8 nm



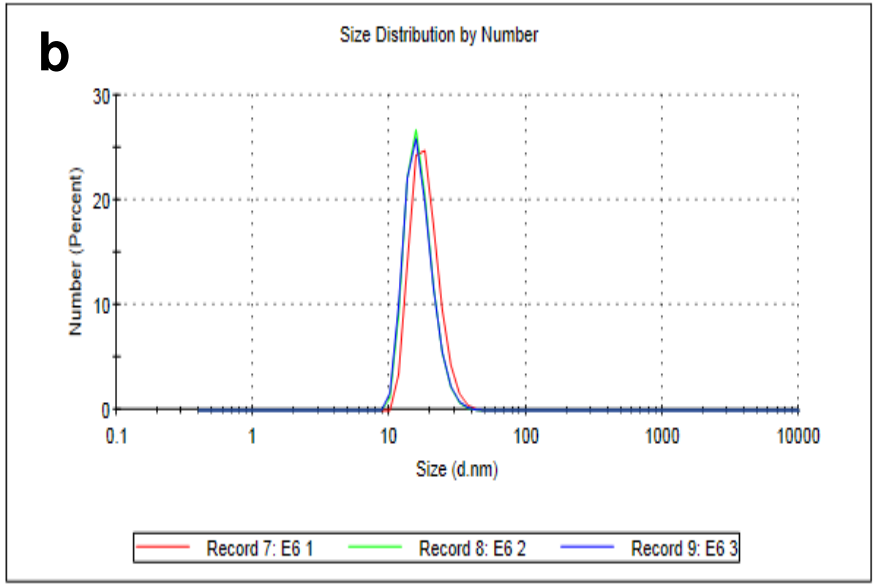
Average size of droplets-17.1nm

Droplet size characterizations of NDs in mixture from reconstituted film

by Cryo-TEM images and DLS



Average size of 20 droplets -11.0 nm

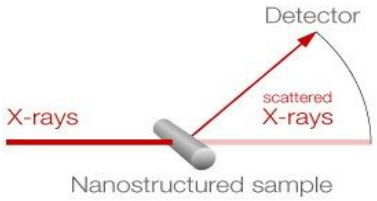


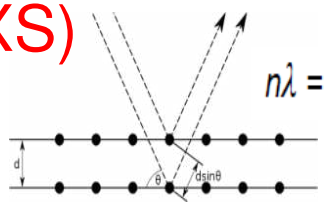
Average size of droplets-16.8 nm

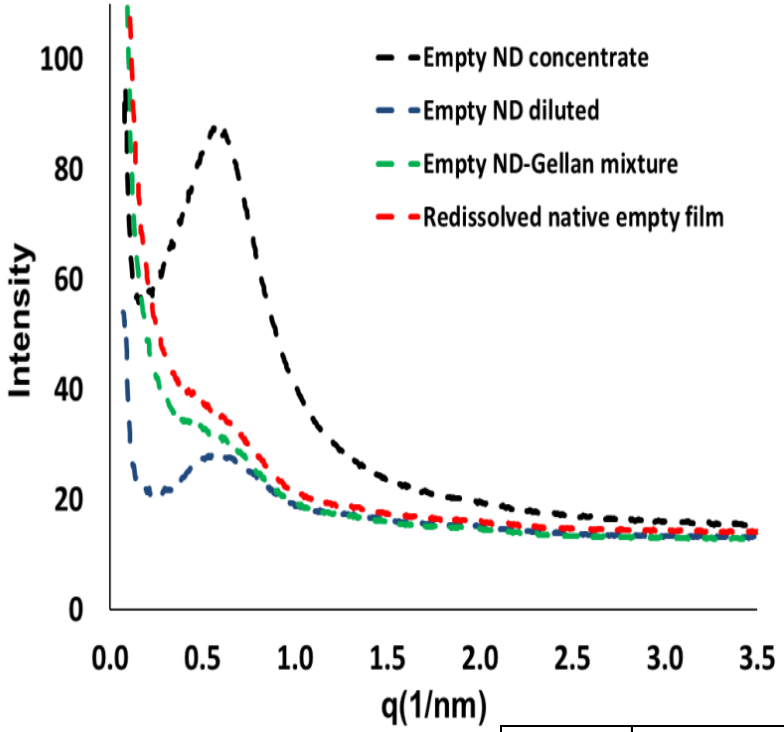
- Cryo-TEM observation of diluted ND structure o/w 90%, ND-polymer mixture and after film redissolution suggests droplet reconstruction with similar droplet size. DLS measurements strengthen the suggestions.

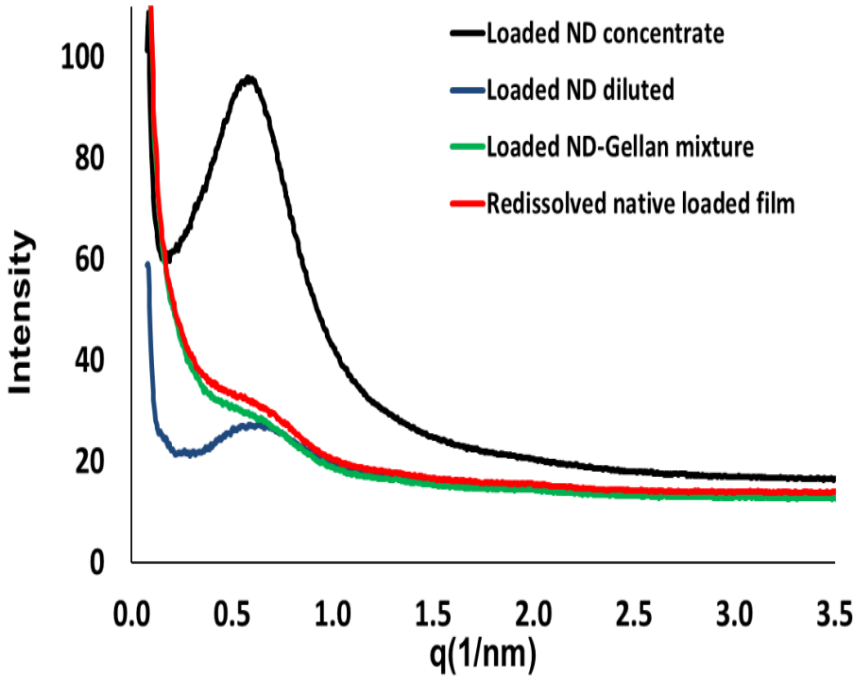
Structural considerations - existence of nanostructures in liquid NDs

by Small angle X-ray scattering (SAXS)





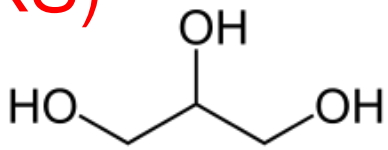


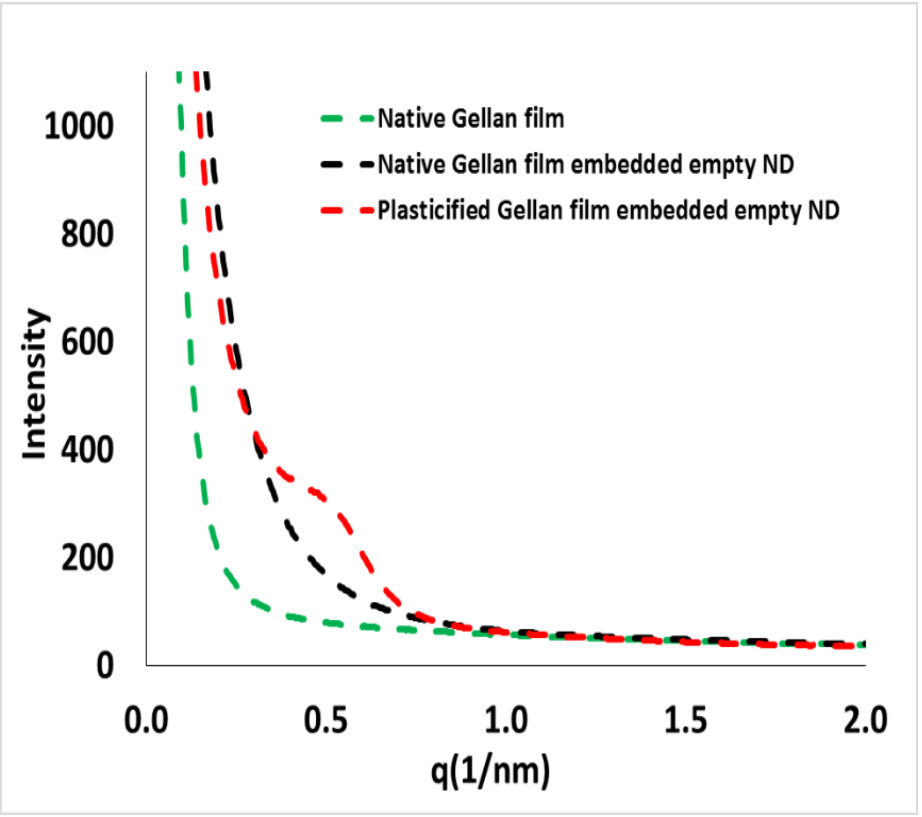


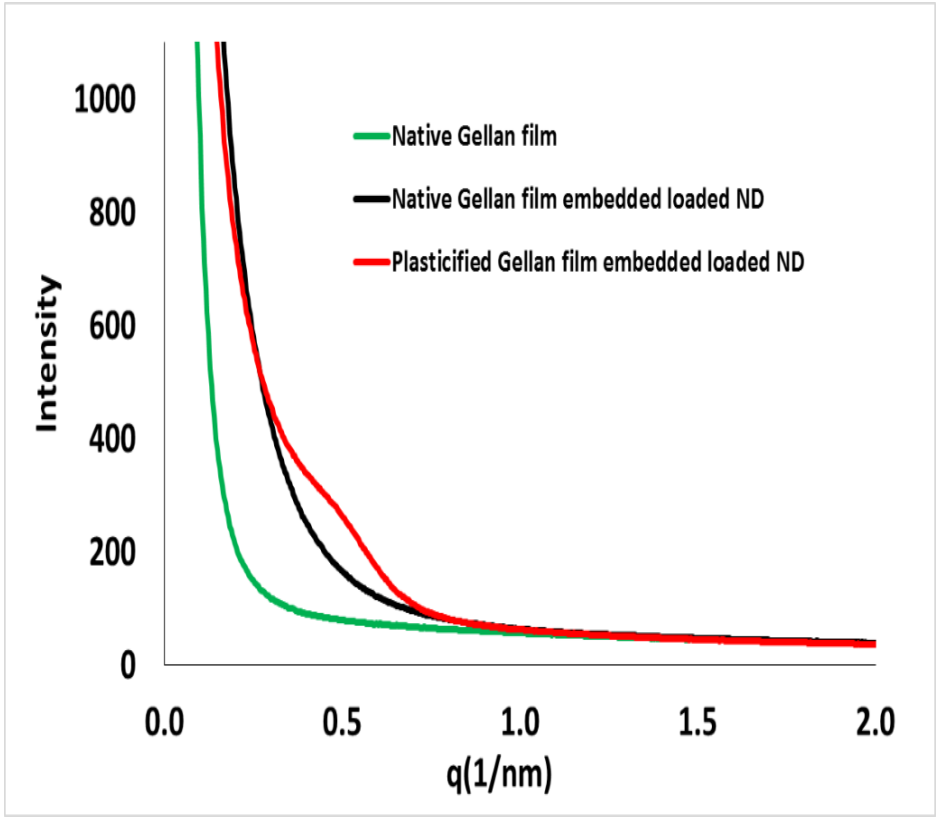
	ND concentrate	ND diluted	ND-Gellan mixture	Redissolved native film
empty	11.02	10.23	9.59	9.73
loaded	10.83	9.73	9.62	9.12

Structural considerations

by Small angle X-ray scattering (SAXS)



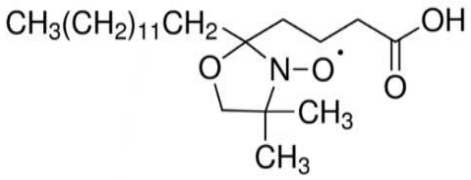




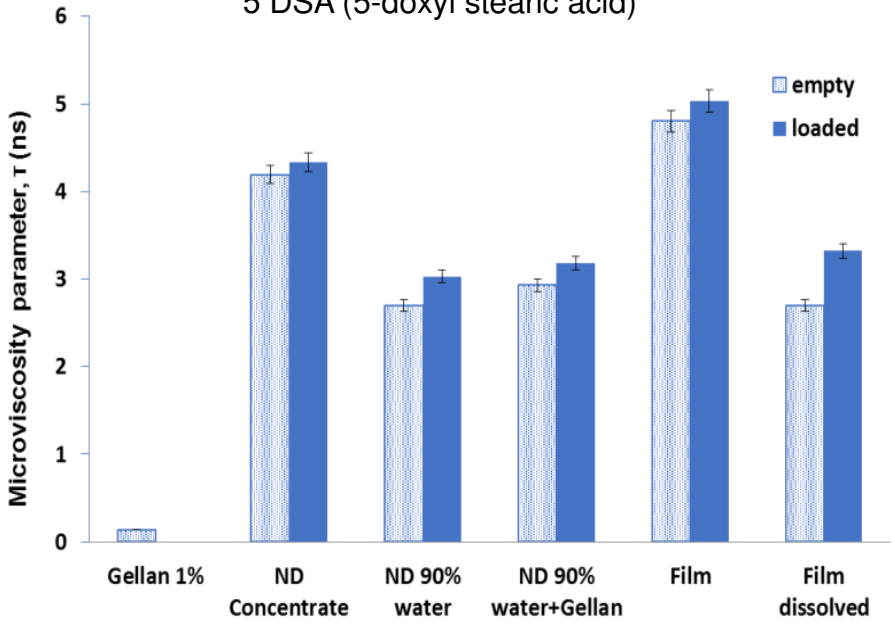
Lack of microstructure in native film (embedded NDs) and existence of microstructure in pre-plasticified film by glycerol (embedded NDs)

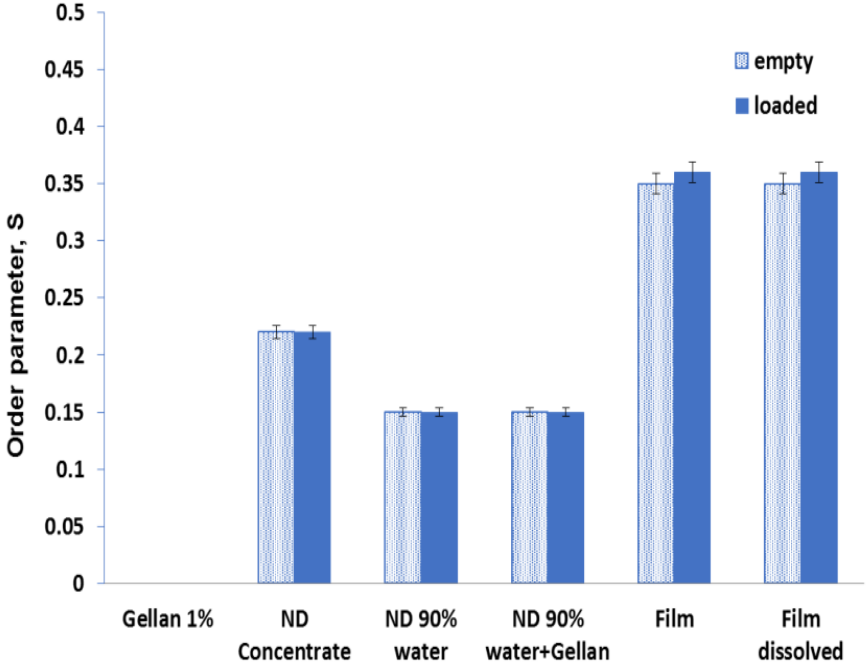
Microviscosity and order parameters of NDs

by Electron Paramagnetic Resonance (EPR)



5 DSA (5-doxyl stearic acid)

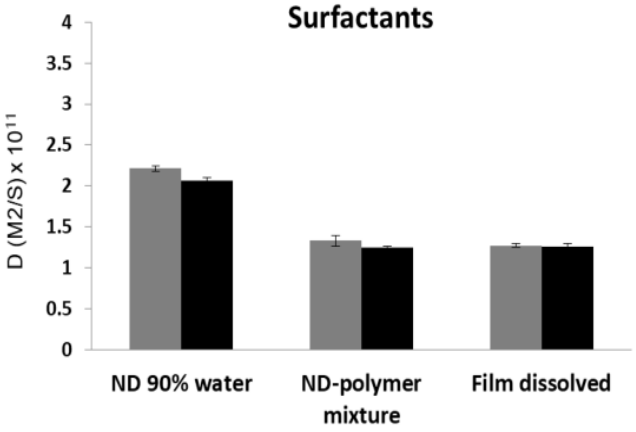


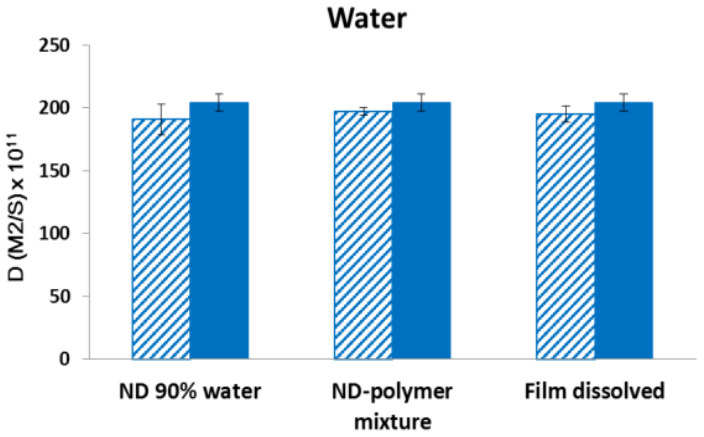


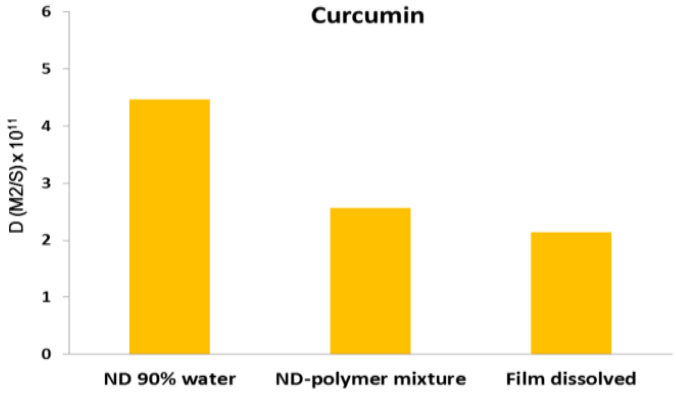
- After redissolution of the film, the microviscosity values decreased returning back to the values of the originally formed ND droplets (τ = 2.80 ns for the ND solution before and after film redissolution, instead of τ = 4.80 ns for the film). This suggests that the ND structure was reconstructed.

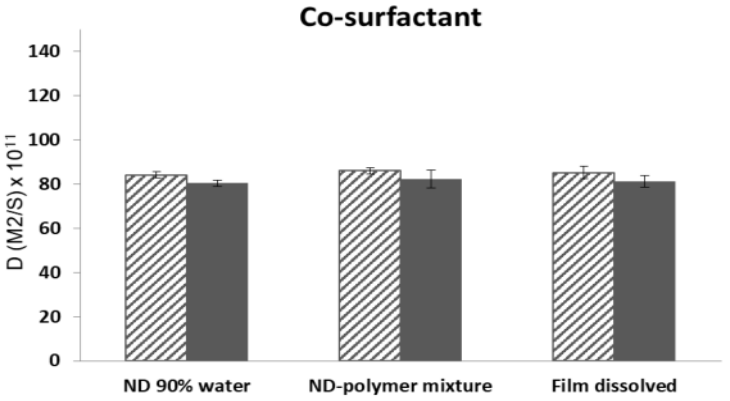
Determination of diffusivity of the ingredients

by Self-diffusion Nuclear Magnetic Resonance (SD-NMR)



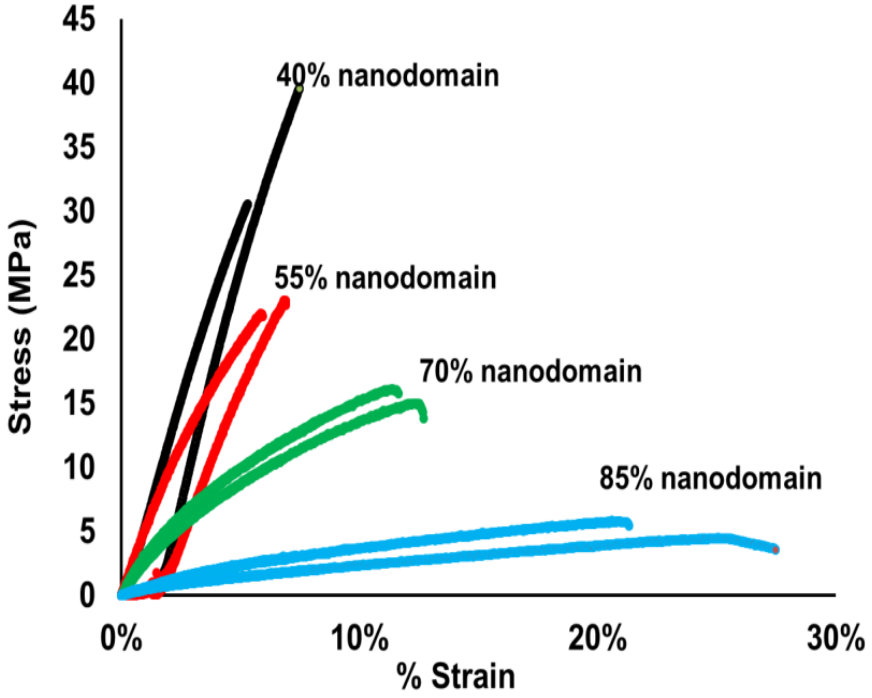


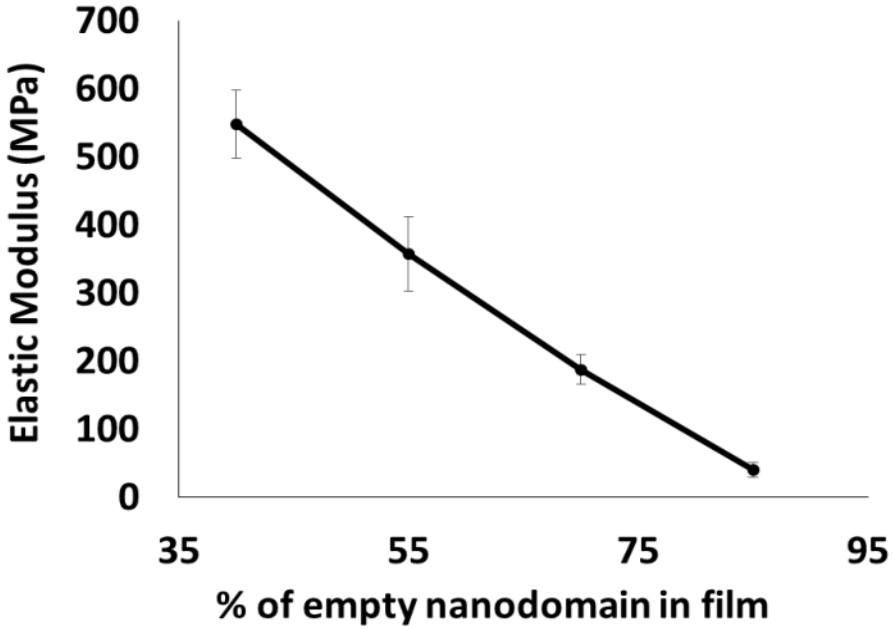




- The diffusivity parameters of ND components before film forming and after its redissolution suggest that ND structure after film redissolution was reversible, and film forming process was reconstructive by allowing the intactness of nanodomain structure.

The effect of empty NDs embedding on mechanical properties of films

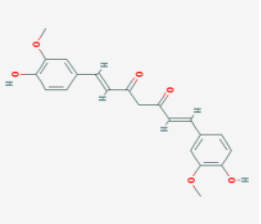


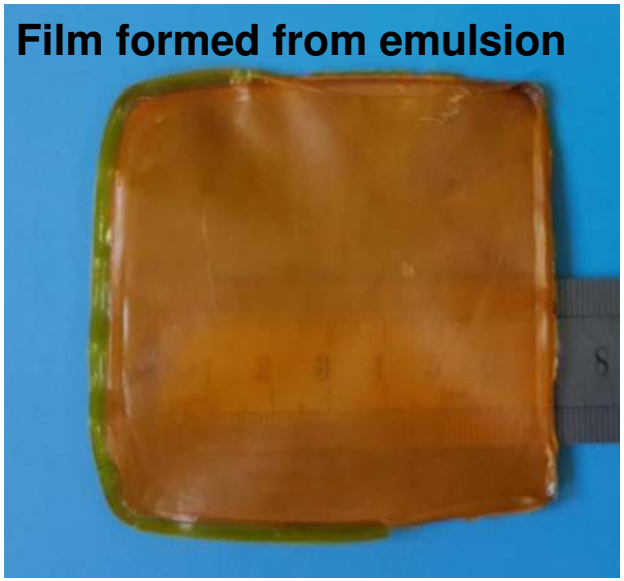


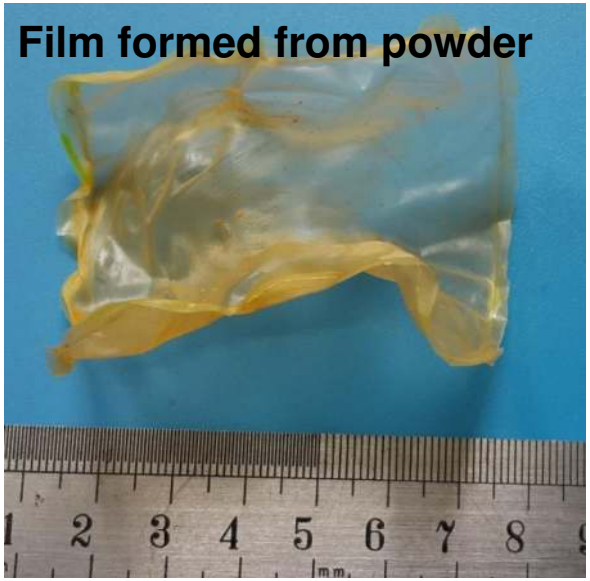
- Embedding of nanodomains decreases the brittleness and increases the plasticity of the films (similar to plasticizers effect) suggesting homogenous incorporation of nanodomains between the polymer's chains inside the film.

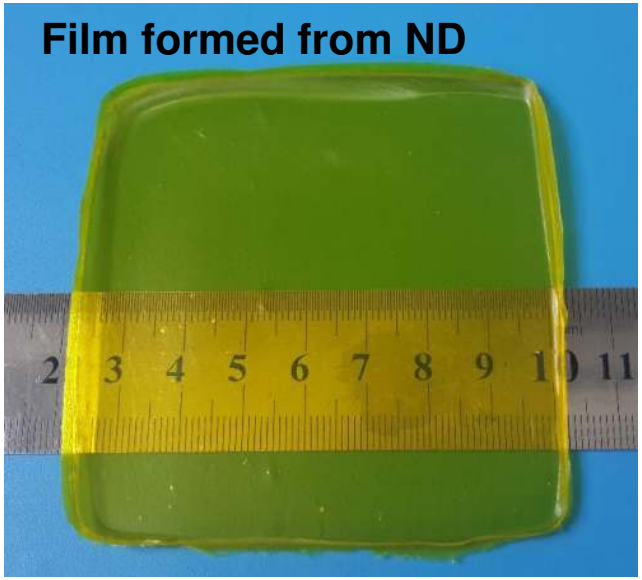
Comparison of gellan film formation from emulsion, powder, NDs

Curcumin is a hydrophobic polyphenol with a variety of biological activities, extracted from the plant of the Curcuma longa.





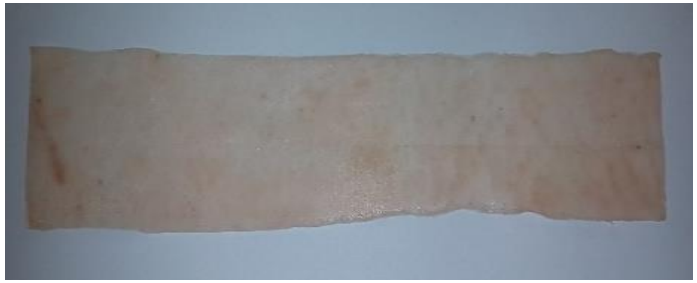


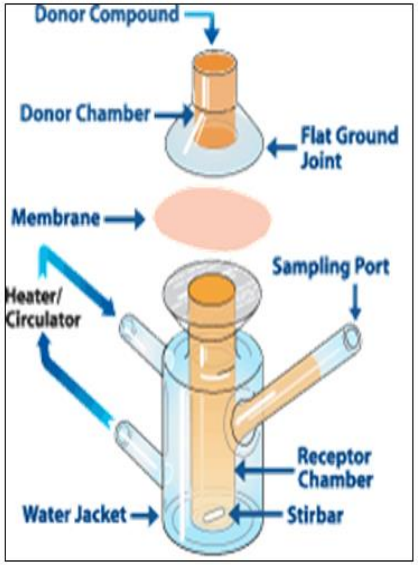


- Film formed from emulsion-gellan mixture is opaque which indicates on dispersion or crystallization of Cucumin. Film formed from curcumin powder dispersion in gellan is defective, non homogeniuos and brittle with inclusions of curcumin powder.
- In contrast, film which formed from ND-gellan mixture is transparent which indicates on solubilization of curcumin in components which composed ND concentrate or solubilization of Curcumin at ND droplets.

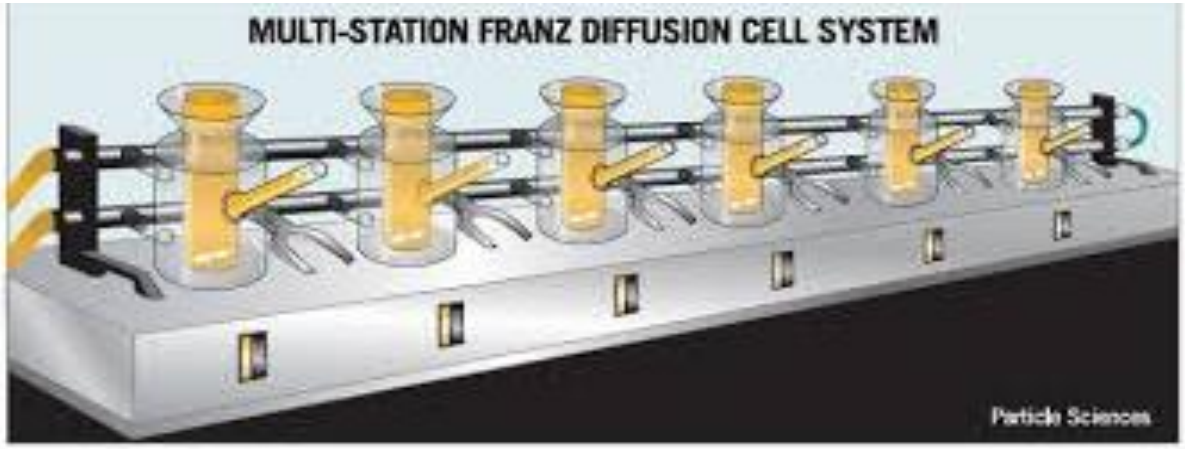
Ex-vivo Franz cell diffusion method for skin penetration study

500-700 µm





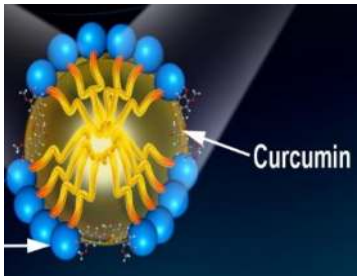
HPLC detection and quantification

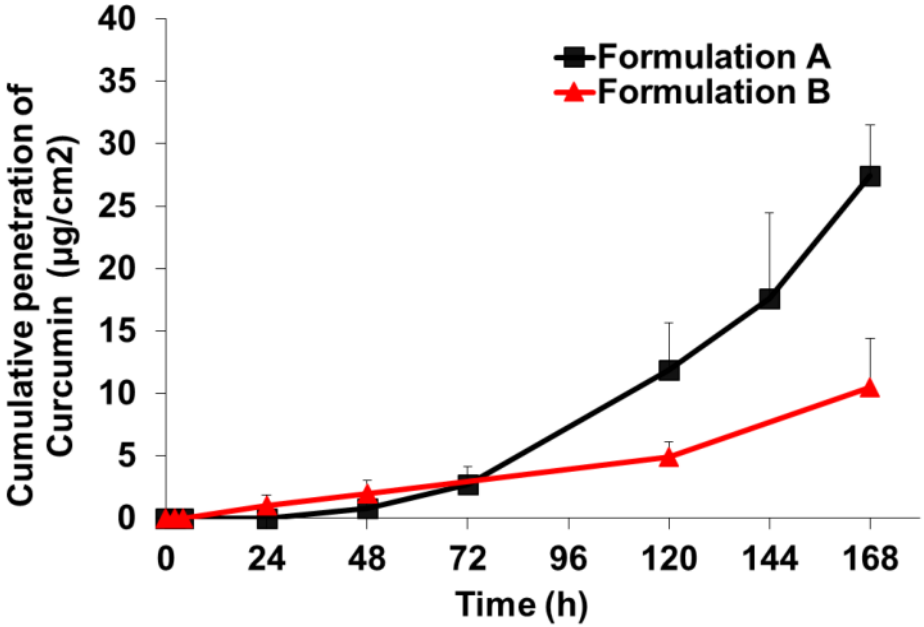


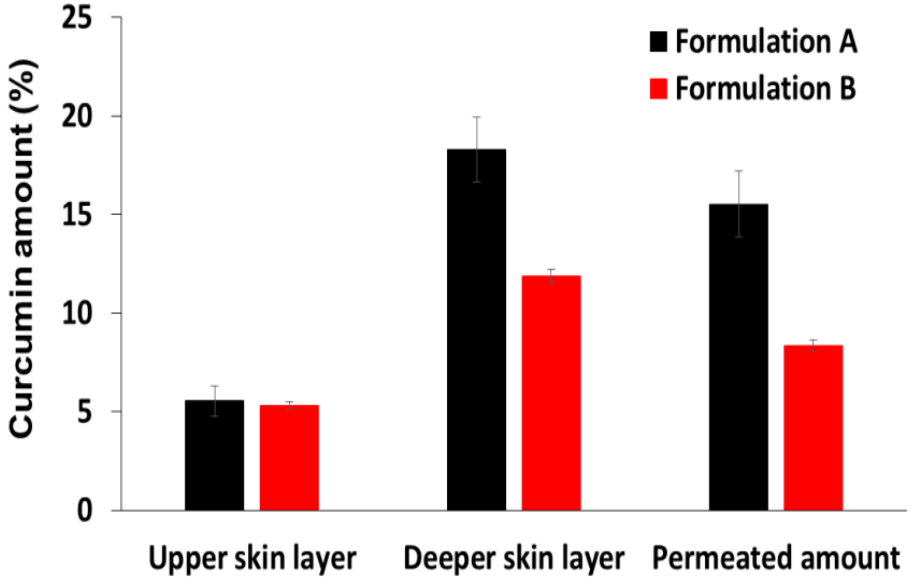
UV – Visible spectrophotometer

Ex-vivo permeation study from Curcumin-loaded nanodomains films

by Ex vivo Franz cell diffusion method



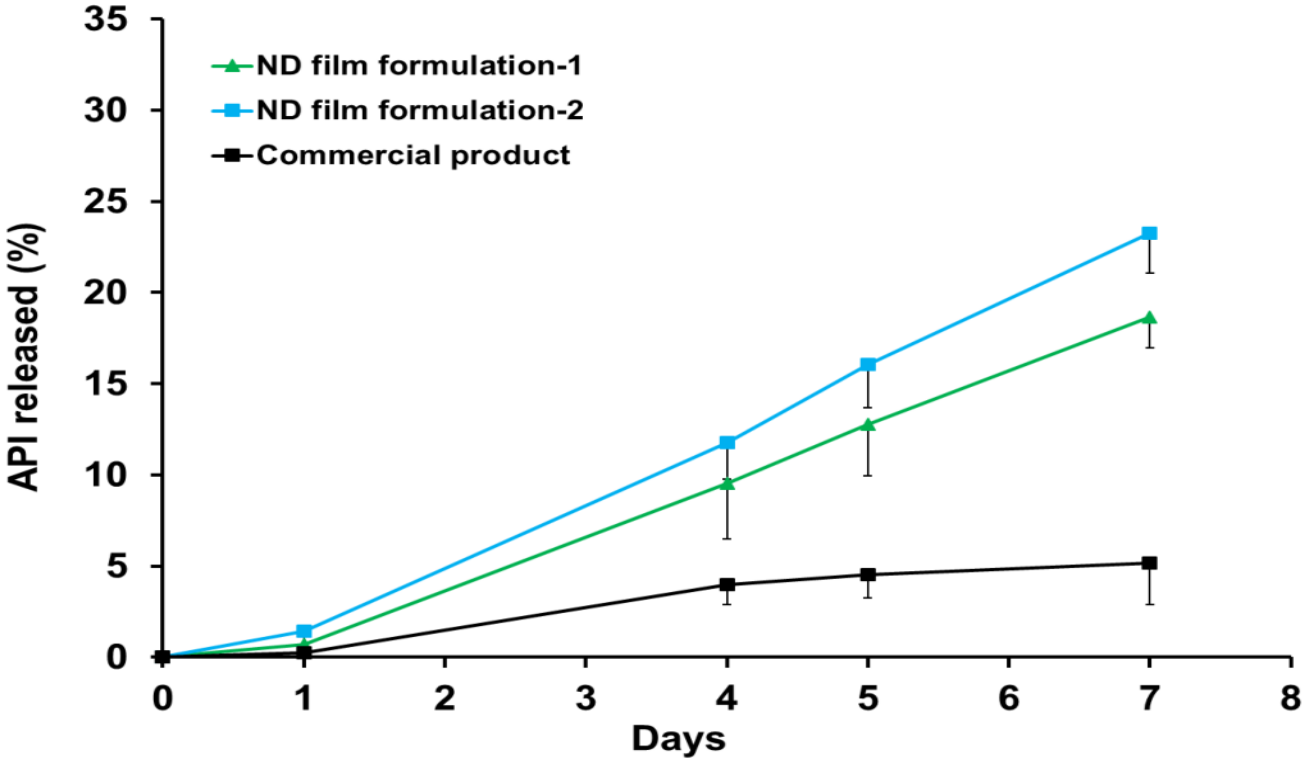


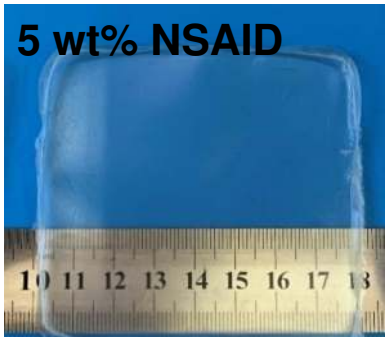


- Conclusion: The permeation of curcumin through the pig skin can be controlled by different ingredients of nanodomains formulations.

Ex-vivo permeation study:

Comparison to commercial product





- Permeation amount of drug from ND embedded films (green line) and (blue line) through the pig skin is significantly higher than from commercial product (black line).

Summary and Conclusions

1. The incorporation of empty and loaded nanodomains into a polymeric film was obtained by formation of homogeneous and transparent films.

2. The nanodomains are reconstituted and self-assembled in contact with moisture on skin surface.

3. The reconstitution process allows enhanced permeation. The release and permeation can be controlled by composition of nanodomains formulations.

4. Nanodomains embedded films may be used as a “solid” platform reservoir for liquid nanodomains which enables controlled release of drug-loaded nanodomains.

Thank you!

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