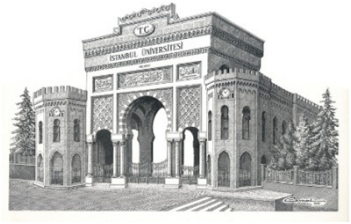

MICELLES AS NANOSIZED CARRIERS FOR SKIN DELIVERY OF DRUGS

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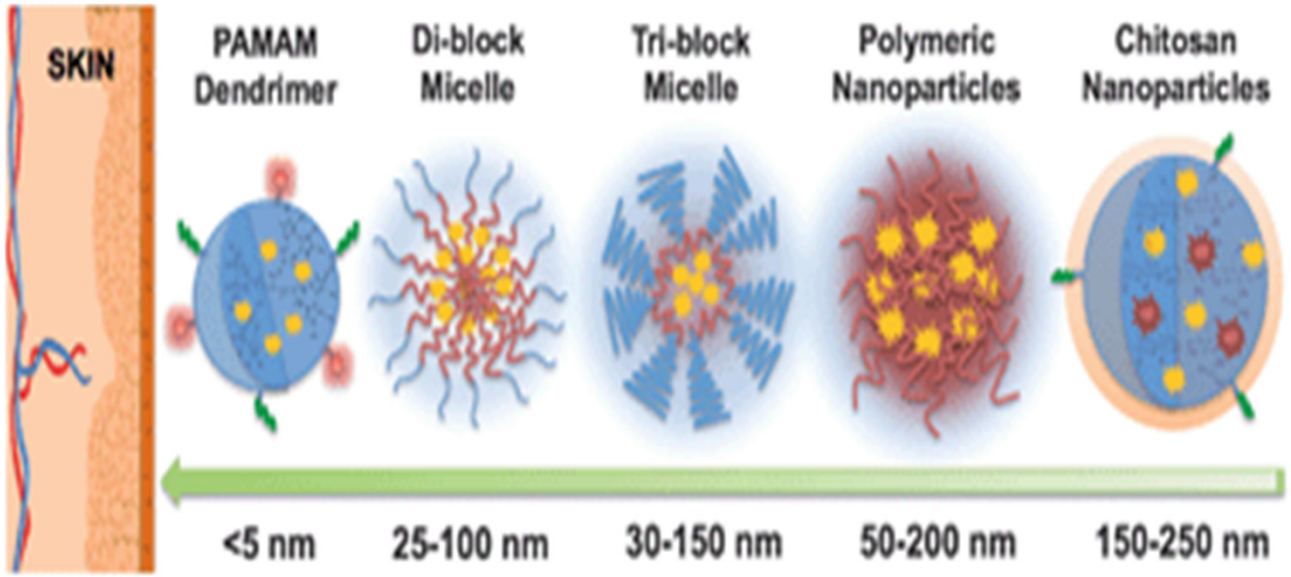
4th International Conference on Nanotek&Expo ,01-03 December 2014, San Francisco, USA

Polymeric Micelles

Polymeric micelles have potential applications in drug delivery as nanocarriers.

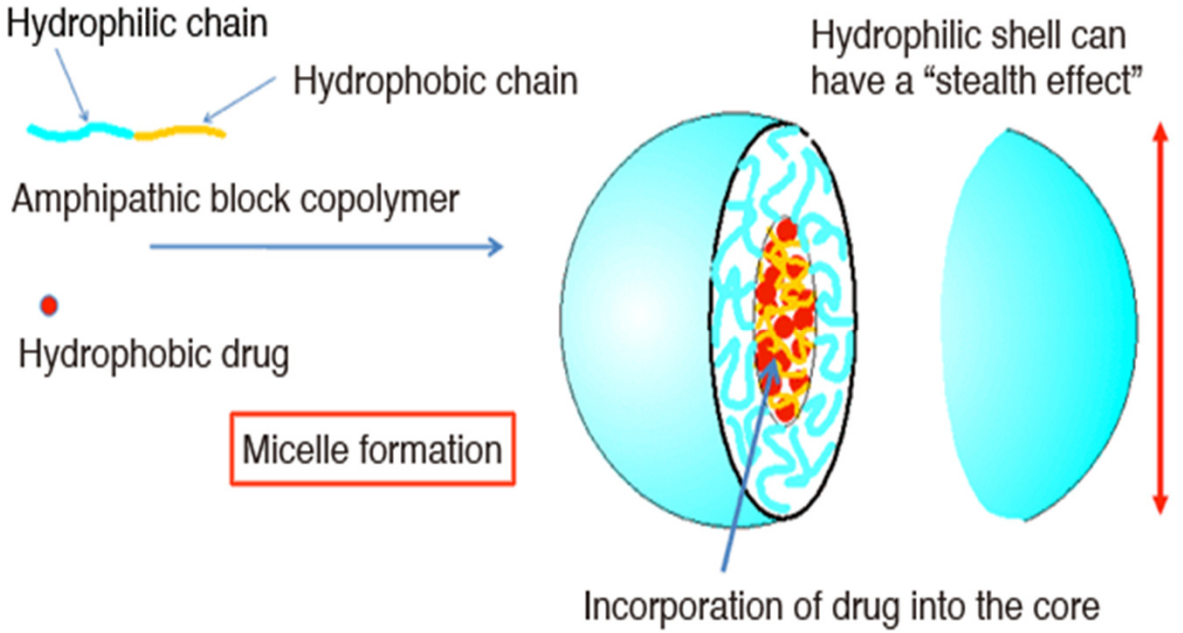
Micelles are assemblies of nanoscale size (**25 to 150 nm in diameter**) from amphiphilic block polymers.



Polymeric Micelles

The polymer micelles characterize by core-shell morphology.

- The hydrophobic internal core is capable of incorporating hydrophobic molecules, making it a candidate for «Drug Delivery System» applications for taking in drugs with **poor water-solubility.**



*J. American Chem. Soc.**135**, 2574–2582, 2013.*

Advantageous of polymeric micelles in topical drug delivery

- The localization of drugs in the skin due to nano-size of micelles
  especially in hair follicules and inflammed areas

- Decreased the skin irritation
  because of encapsulated BPO in micelle cores

- Increased aqueous solubility of hydrophobic drugs

- Enhanced efficacy from prolonged release of drugs and less application frequency.

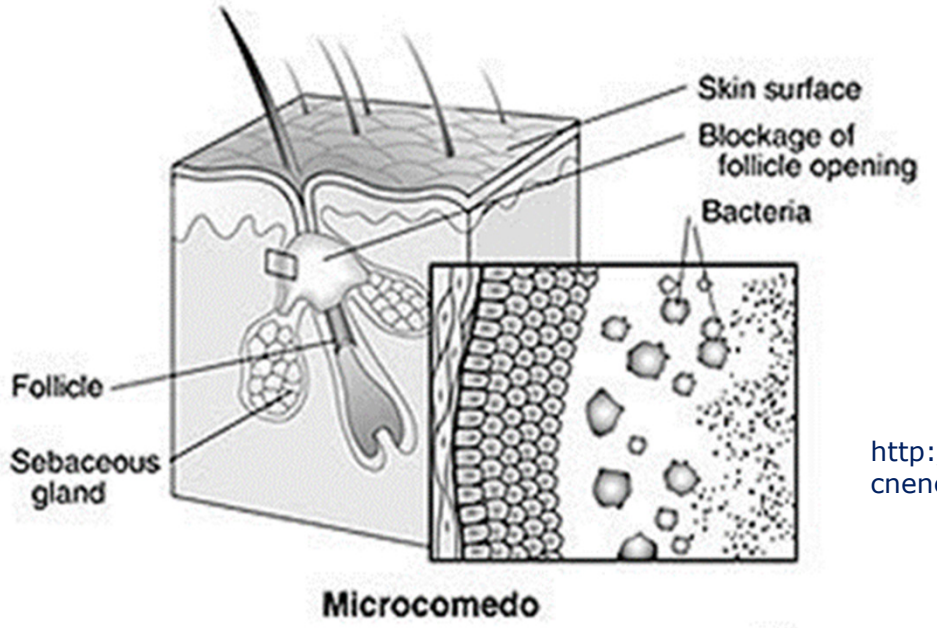
  Conventional dermatological products typically provide active ingredients in relatively high concentrations but with a short duration of action.

- Improved chemical stability of drugs
  Particularly, when the drugs combined with other compounds.

Acne

Acne is the most common cutaneous disorder of multifactorial origin.

- It is a disease of the pilosebaceous unit-hair follicles in the skin that are associated with an oil gland.



http://www.skincarephysicians.com/acnenet/acne.html

Topical Therapy

Topical therapy plays a crucial role in the treatment of acne.

- to targeting the site of infection
- to reduce the risk of sytemic side effects

Topical therapy include;

- **Benzoyl peroxide, retinoids and antibiotics, ….**

	Sebum excretion	Keratinisation	Follicular *Proprionibacterium acnes*	Inflammation
Benzoyl peroxide	–	(+)	+++	(+)
Retinoids	–	++	(+)	+
Clindamycin	–	(+)	++	–
Antiandrogens	++	+	–	–
Azelaic acid	–	++	++	+
Tetracyclines	–	–	++	+
Erythromycin	–	–	++	–
Isotretinoin	+++	++	(++)	++

+++=very strong effect. ++=strong effect. +=moderate effect. (+)=indirect/weak effect. –=no effect.

Table: **Targets of acne treatments**

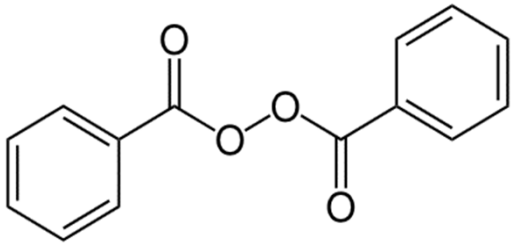
H.C. Williams, R.P. Dellavalle and S. Garner, Acne Vulgaris, Lancet 2012, 379: 361-372.

Benzoyl Peroxide (BPO)

BPO is one of the effective topical agent used in the treatment of acne.

- It has been widely used since 1960s.
- It is one of comedolitics
- The main mode of action of BPO in acne is related to its antimicrobial activity against *P. acnes* in *sebaceous* follicle.
- BPO is a moderately lipophilic molecule and it has low aqueous solubility.
- It has major side effects such as local irritation and burning effect.
- It has also chemical stability problem.

- ***Physicochemical properties***
  - **MW: 242.23**
  - **Log P: 3.43**



Chemical structure

Combination Therapy

The multifactorial nature of acne often requires a combination of topical compounds for successful management.

- The addition of a topical antibiotic into BPO can increase efficacy of acne therapy.

Clindamycin (CLN) is one of the most commonly used antibiotics in the treatment of acne.

- Combined use of BPO+a topical antibiotic can reduce bacterial resistance.

It is useful combination of comedolitic and topical antibiotic

- But it has some stability problems. Particularly, BPO is not stabil chemically in the presence of nucleophilic agents.

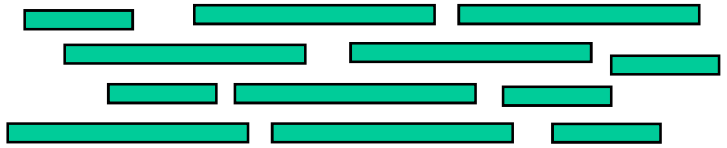
Once opened, these combination products have a short shelf-life due to chemical degradation problem.

- İt requires cold chain transport and storage.

Limitations of Topical Treatment

- **the main barrier of skin: *stratum corneum***
  - *Stratum corneum* (horny layer) has **«brick and mortar»** model (***Elias,*** *1981*)
    - It is a rate limiting barrier to deliver drugs to target layers of skin

Corneocytes: the „bricks"
Intercellular Lipids: the „mortar"



- **side effects of drugs on skin**

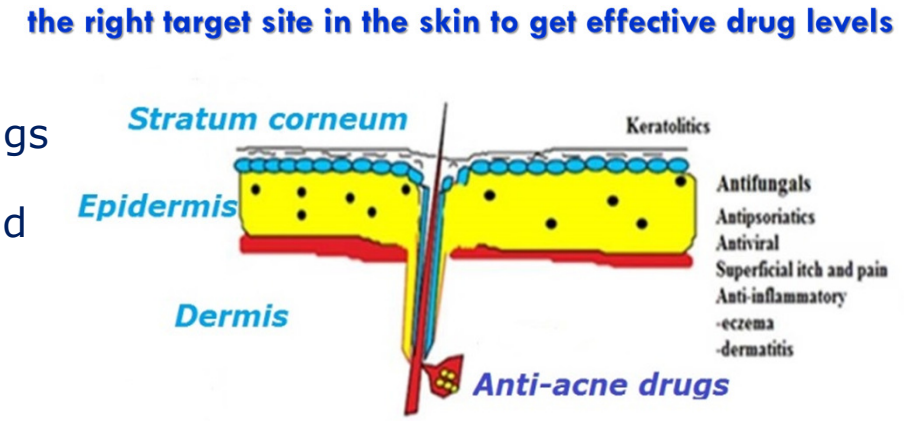
Common Topical Acne Treatments	**Cutaneous Side-effects**
Retinoids (e.g., adapalene, tazarotene, tretinoin)	Burning, peeling, erythema, dryness, photosensitivity
Benzoyl peroxide	Dryness, erythema, peeling, hair and clothing discoloration
Clindamycin phosphate	Erythema, dryness, allergic contact dermatitis
Erythromycin	Dryness, erythema, peeling, allergic contact dermatitis
Salicylic acid	Dryness, erythema, peeling

Challenges for the optimization of a topical product to deliver acne drugs

* Skin Penetration

- to achieve adequate skin deposition of drugs

- to get drugs into the hair follicles and pilosabaceous units



* Stability

- to provide a stable chemical environment in in vehicle for drugs intended to be delivered vehicle for drugs intended to be delivered

* Cosmetic Acceptability

- to overcome the additional physical effects on the skin, such as drying, occluding, or moisturizing

- to optimize the ideal vehicle which would leave minimal residue or oiliness.

Dermatopharmaceutical Research

Novel drug delivery strategies can play an important role in improving the topical delivery of drugs by

- modulating its physicochemical&biopharmaceutical properties.

LIPOSOMES

NANOPARTICLES

MICROSPHERES/
MICROSPONGES

MICELLES

- Biocompatibility
- Nano-sized
- Non-toxic, polymeric drug delivery systems

Background and Aim of the Study

BPO is a highly lipophilic compound, it can easily partition into the lipid–rich intercellular layer of *stratum corneum*.

- the challenge is to develop a stable formulation that facilitates drug release into skin.

In acne therapy, aqueous formulations are desired.

- due to the lipophilic character and poor water solubility of BPO, polymeric micelles could be considered as carrier system.

BPO has some side effects such as dryness, erhythema on skin

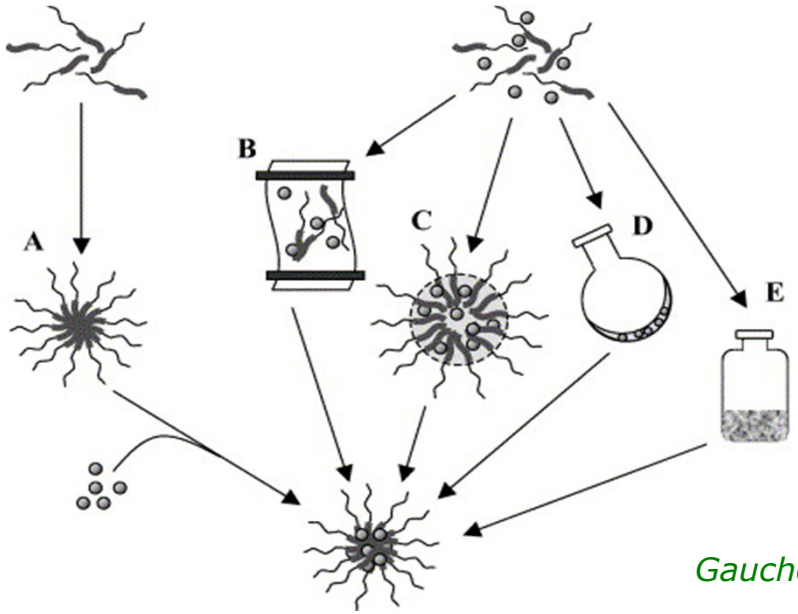
- its side effects would be decreased or minimized by incorporating of drugs into micelles .

and chemical degradation problem

- chemical degradation would be prevented by encapsulation of BPO in micellar nano-carriers

Preparation Methods of Polymeric Micelles

The common procedures for drug-loading into micelles



(A) simple equilibrium,

(B) dialysis,

(C) o/w emulsion,

(D) solution casting, and

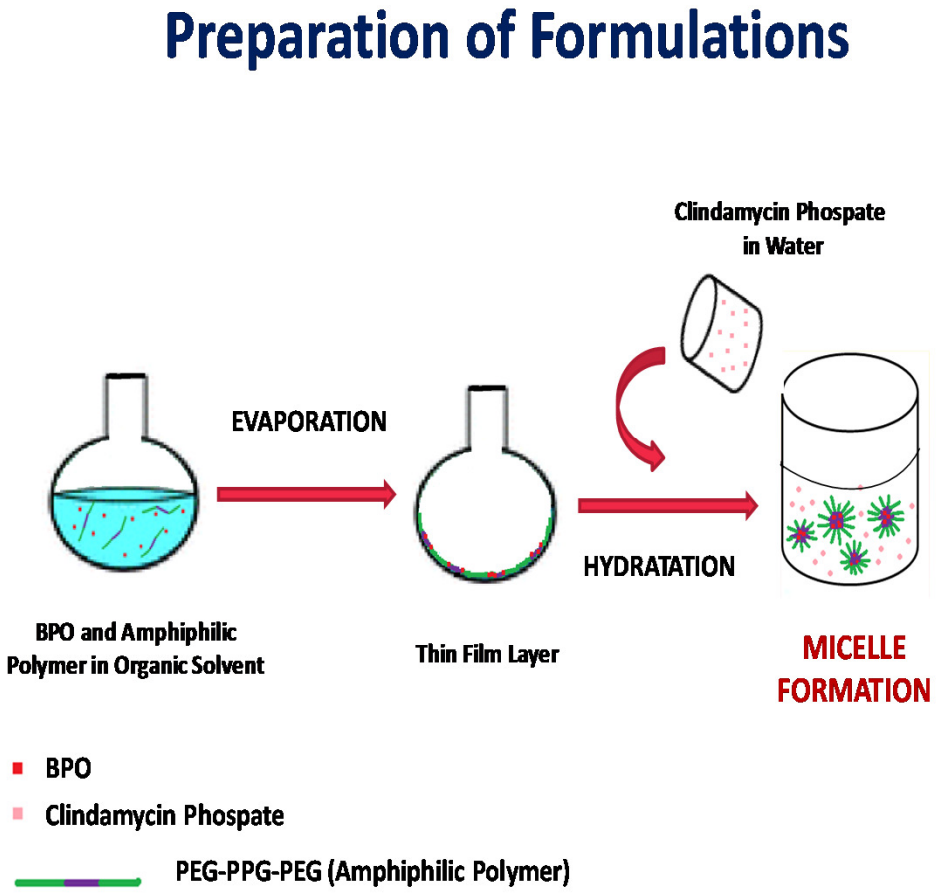
(E) freeze-drying.

Gaucher et al. J. Control Rel., 109, 169-188, 2005.

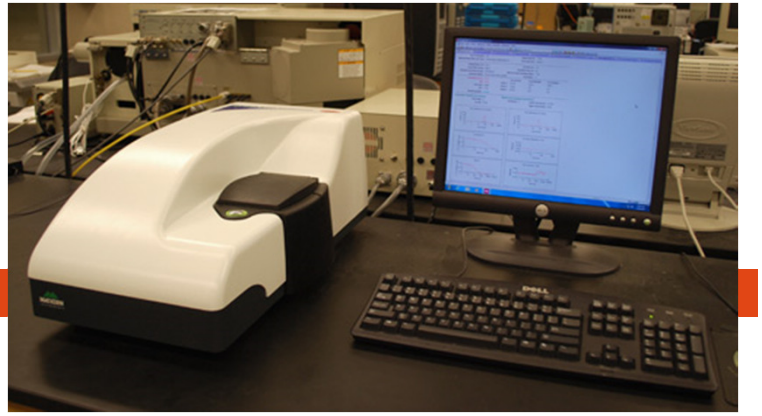
Among these methods, we used solution casting method for preparation of BPO-loaded polymeric micelles.

Preparation of BPO loaded Polymeric Micelles

- Firstly, Pluronic F127 and BPO were solved organic solvent.
- It was evaporated at rotary evaporator until occuring a thin film layer.
- Then, the thin film layer hydrated with clindamycin solution (1 %, w/w).
- It was filtrated (*0.45 µm*).
-
- For the storage, it was lyophilisated by adding trehalose solution (10 %, w/h) after 72 hours.



Characterization of BPO loaded Polymeric Micelles

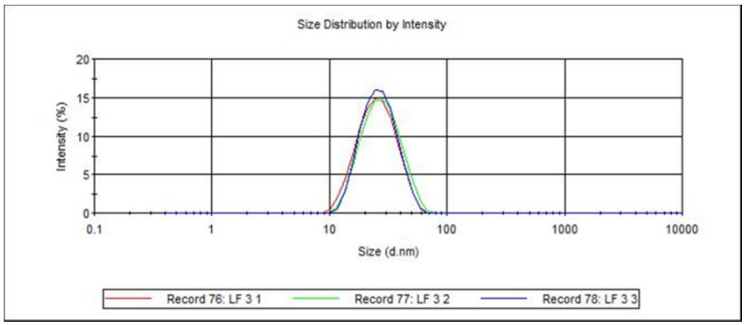


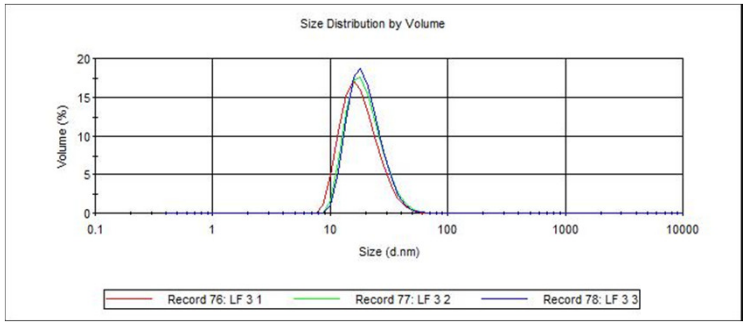
1. Size and Size Distribution

Organic Solvent	Size-0. hour (d.nm)	PDI-0. hour (d.nm)	Size-48. hours (d.nm)	PDI-48. hours (d.nm)
Aceton	25.89±0.11	0.216±0.010	30.44±2.38	0.324±0.042
Dicloromethan	29.46±0.15	0.345±0.006	31.72±0.85	0.778±0.056
Tetrahydrofuran	25.89±0.68	0.210±0.021	31.52±1.88	0.384±0.031
Acetonitril	24.77±0.31	0.176±0.009	25.49±0.31*	0.300±0.026*

*after 72 hours

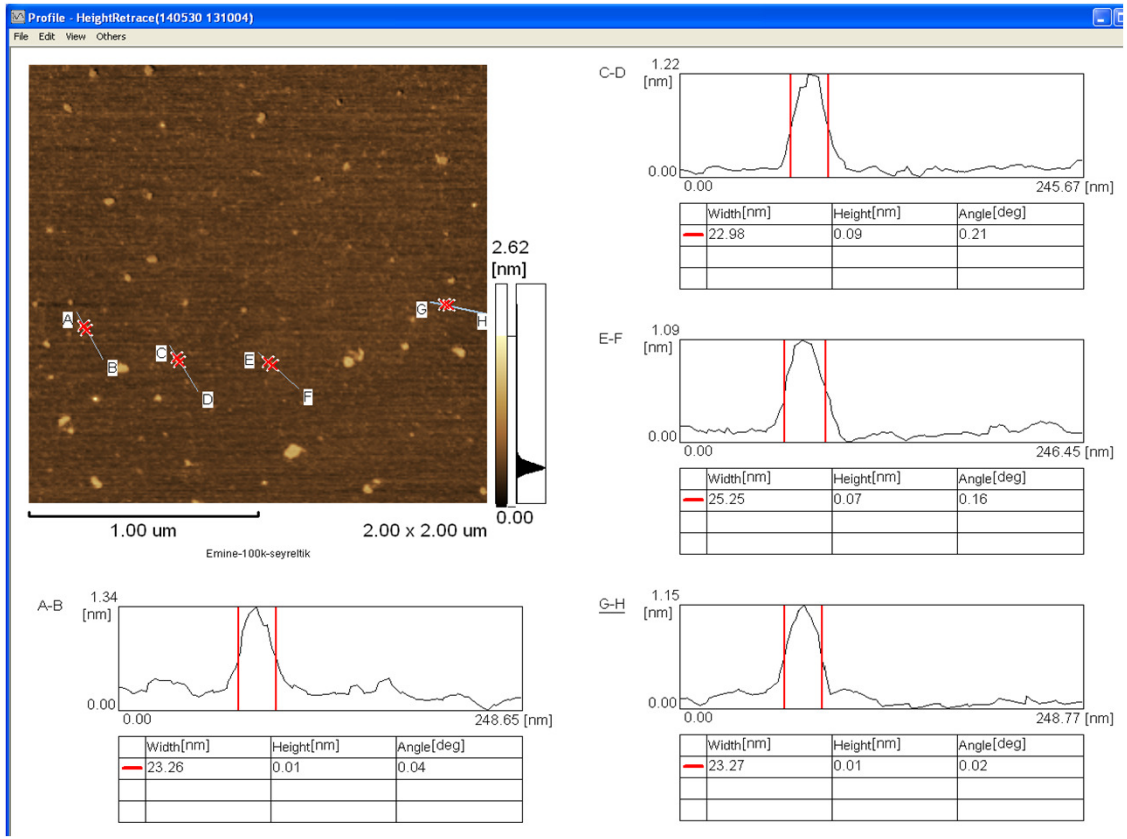
After 48 hours, we decided that acetonitril was the most proper organic solvent for our study due to its higher stabilty than the other solvents.

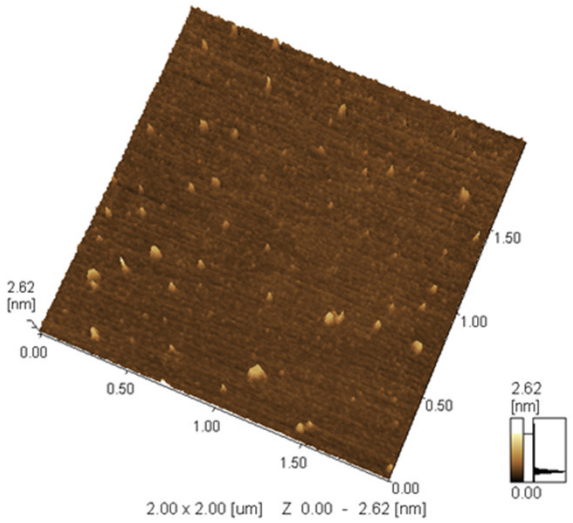




Characterization of Polymeric Micelles

2. Atomic Force Microscopy





Morphology of polymeric micelles should be spherical shape because of kinetic stability.
AFM data correlated to ZetaSizer size measurements.

Characterization of Polymeric Micelles

3. Zeta Potential

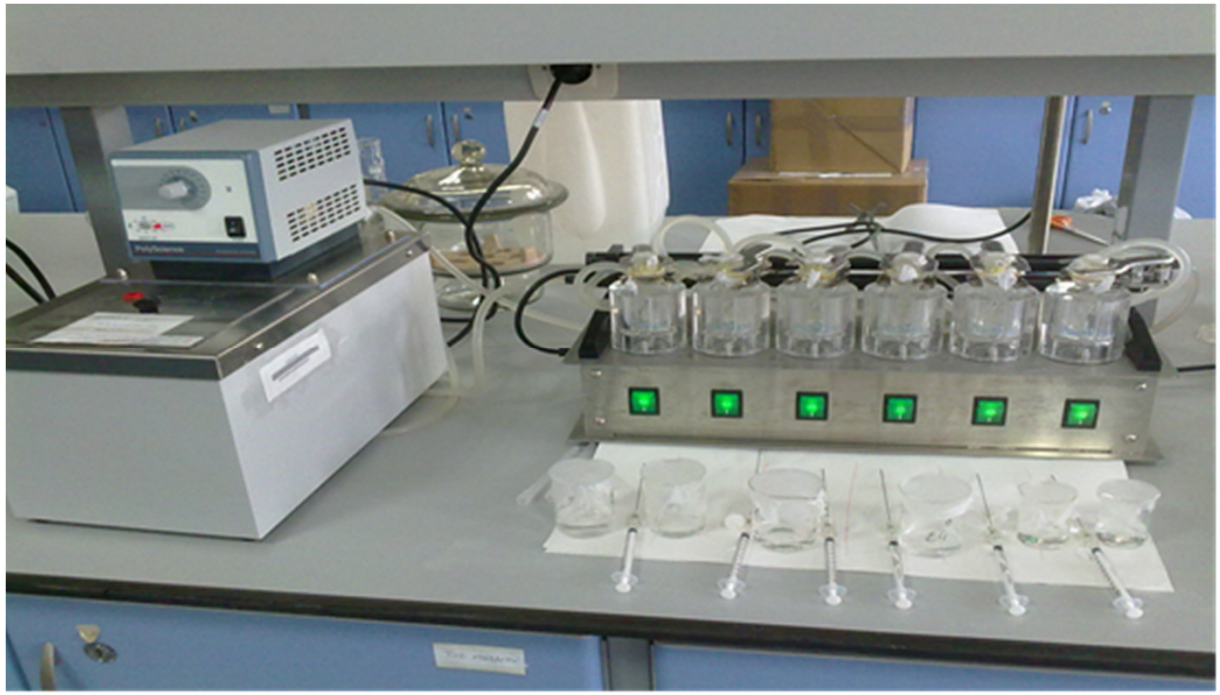
Organic Solvent	Zeta Potantial (mV)
Aceton	-15.01±1.23
Tetrahyrofuran	-7.36±2.01
Acetonitril	-7.63±0.68

4.% Encapsulation Efficiency

Polymer:Drug Ratio (w/w)	% Encapsulation Efficiency
1:0.015	81.937±3.816
1:0.030	18. 570±2.654
1:0.050	4.342±0.982

After % EE measurements, micelles composed of polymer:drug ratio (1:0.015) was selected further studies due to the higher EE (%) than the others.

In vitro evaluation of BPO&CLN in deposition in skin



Stirred at 250 rpm at 37°C

Pig skin (dermatomed to a thickness of 750 µm)

Effective diffusion area:1.77 cm²

Donor phase:

BPO&CLN micelle-gel formulation

MC I: Micelle: water: propylene glycol; (5:5:5, w/w)

MC I: Micelle: water: propylene glycol; (5:7:3, w/w)

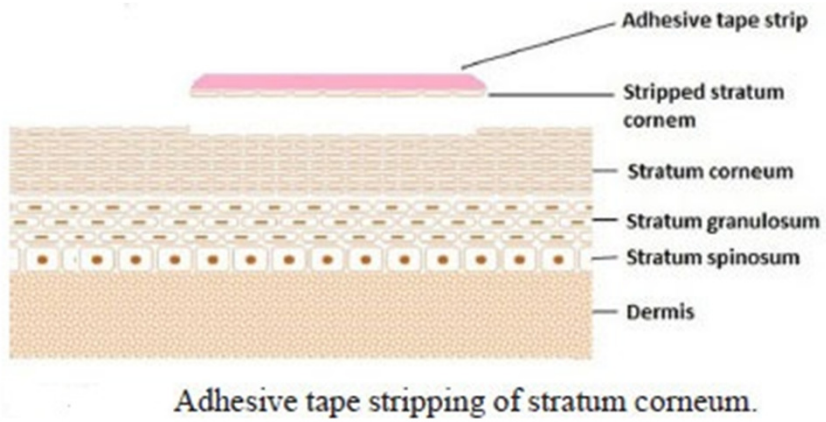
Effective diffusion area:1.77 cm²

Receptor phase:

(PBS, pH 7.4, 12 mL)

Evaluation of BPO/CLN Deposition in Skin

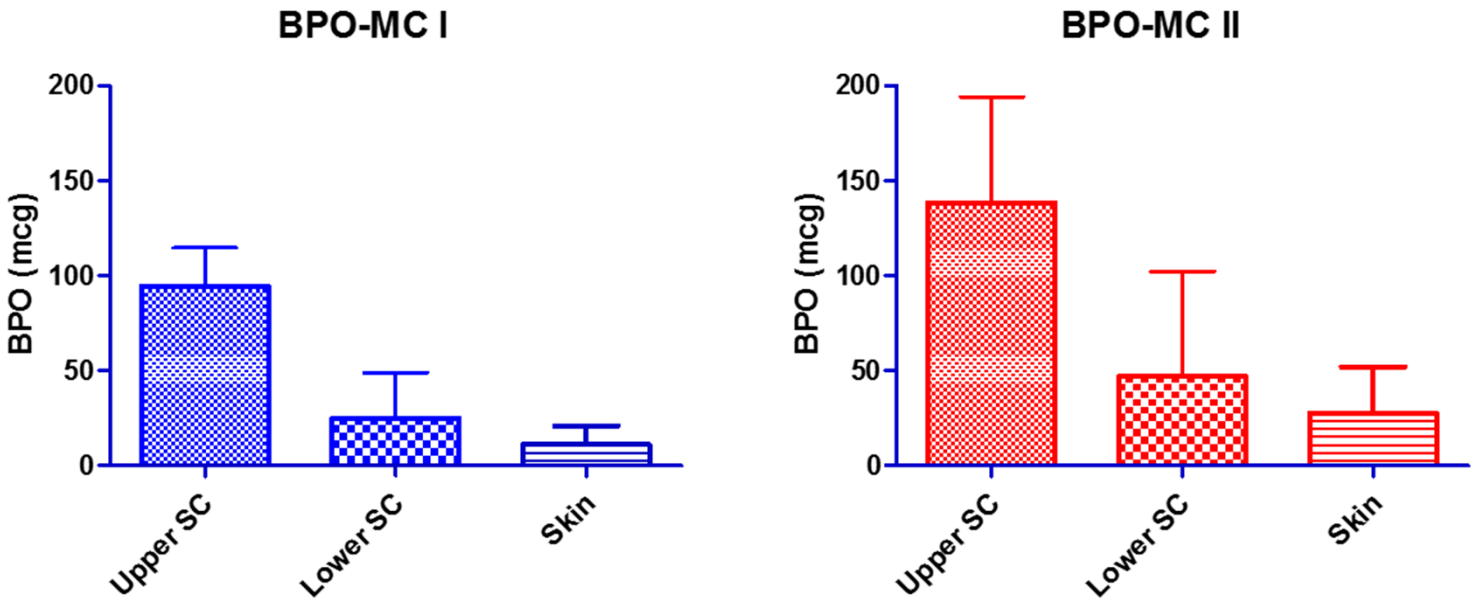
After skin was blotted dry, the **cutaneous penetration** of BPO&CLN was investigated using sequential tape stripping in the SC.



Adhesive tape stripping of stratum corneum.

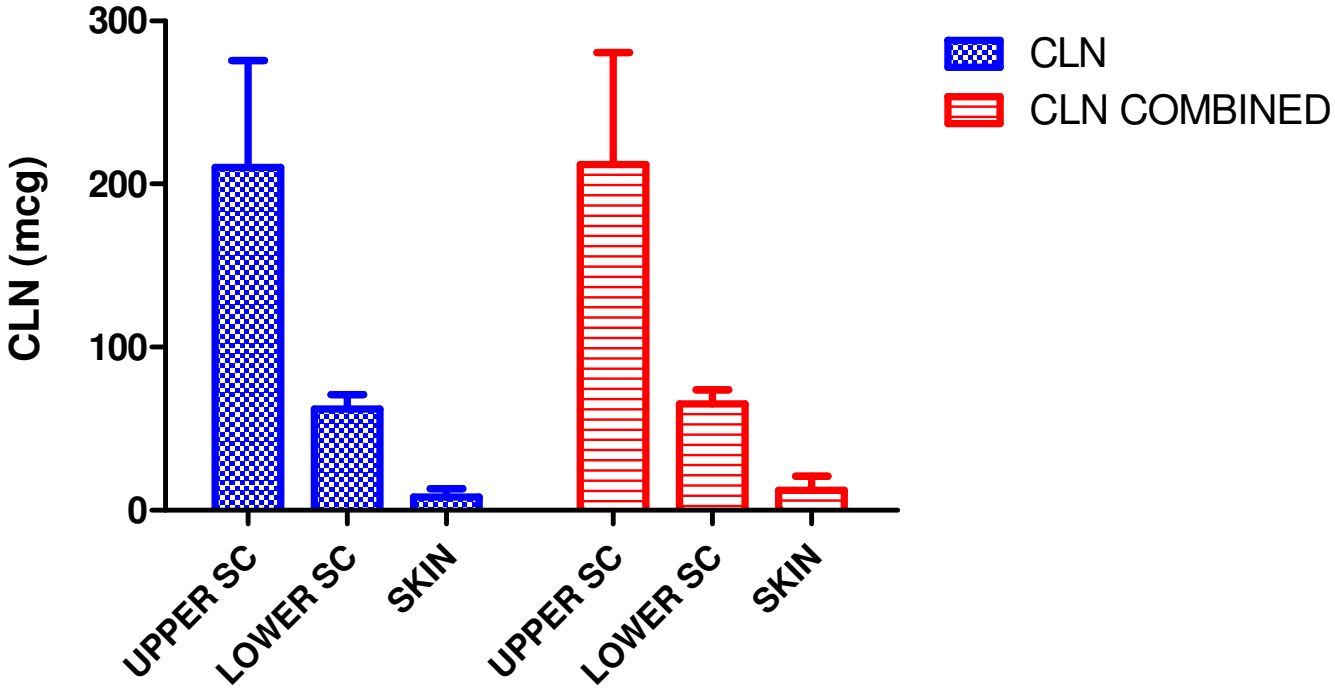
- The treated area on each skin was tape stripped 20 times using Scotch® Book Tape 845 (3M, USA) strips.
- The tapes were extracted (overnight), and samples were analyzed using HPLC.

Skin deposition of BPO after 24 hours



The data showed that BPO was in the lower layers of the skin.

Skin deposition of CLN after 24 hours

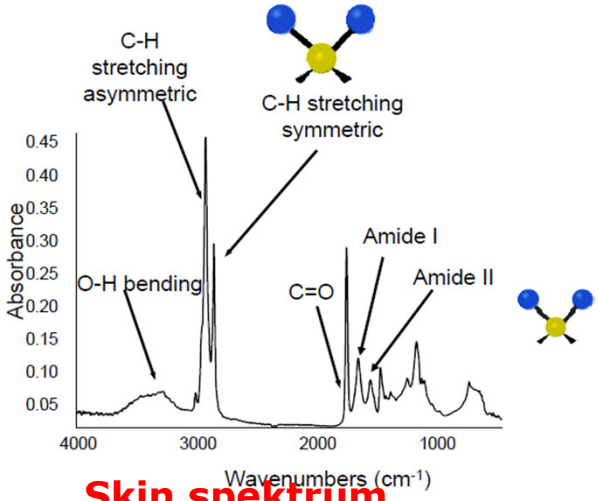


The data showed that CLN was in the lower layers of the skin.

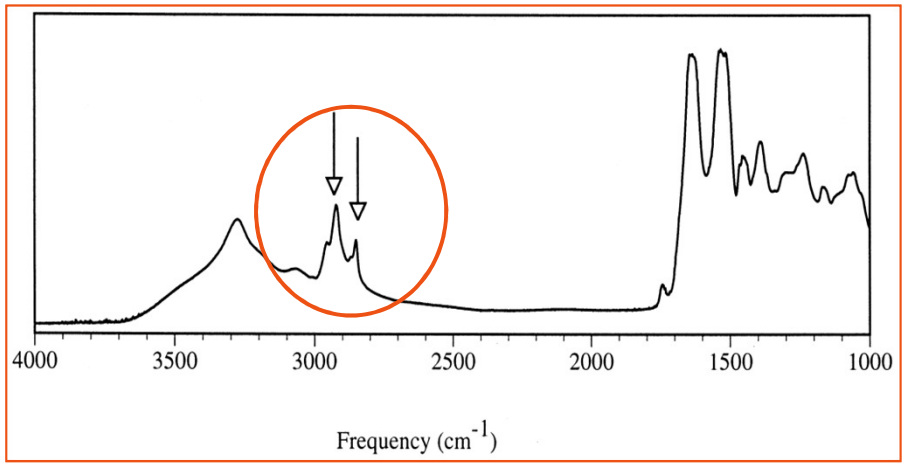
ATR-FTIR Spectroscopy

Biophysical techniques: Fourier Transform Infra Red

ATR-FTIR Spectroscopy is a powerful tool to study biophysical properties of the SC.

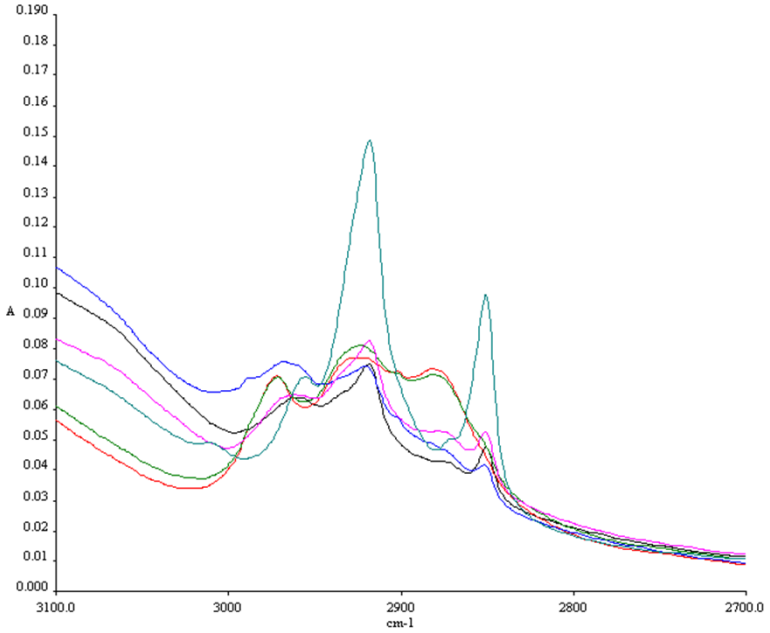


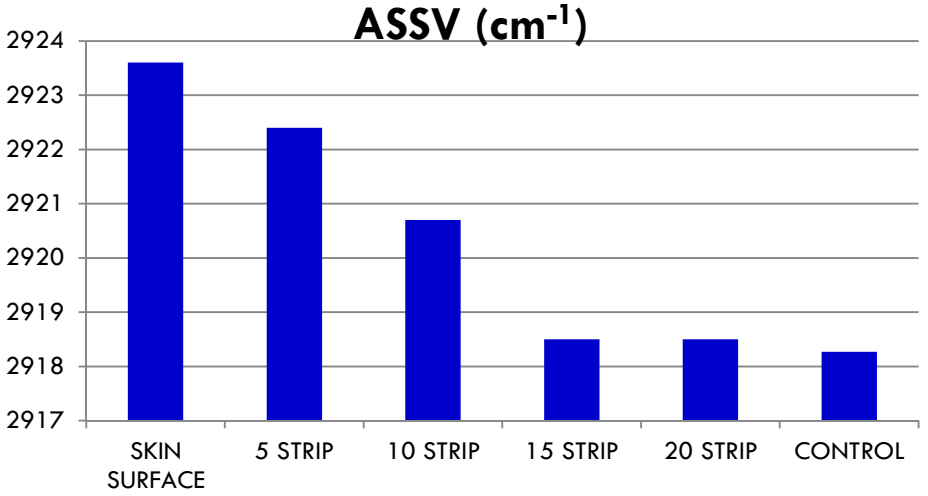
Skin spektrum

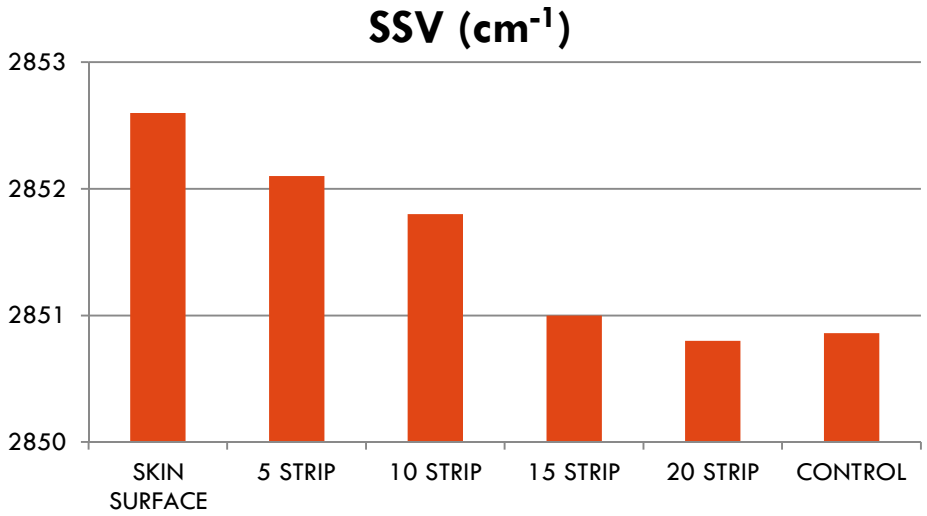


The peaks near 2850 and 2920 cm^{-1} due to the symmetric and asymmetric C-H stretching vibrations (ASSV & SSV), respectively, are sensitive to perturbations in the amount and the conformational order of the SC intercellular lipids.

ASSV & SSV CH2 Peak Positions Following Permeation Study: BPO-MC I

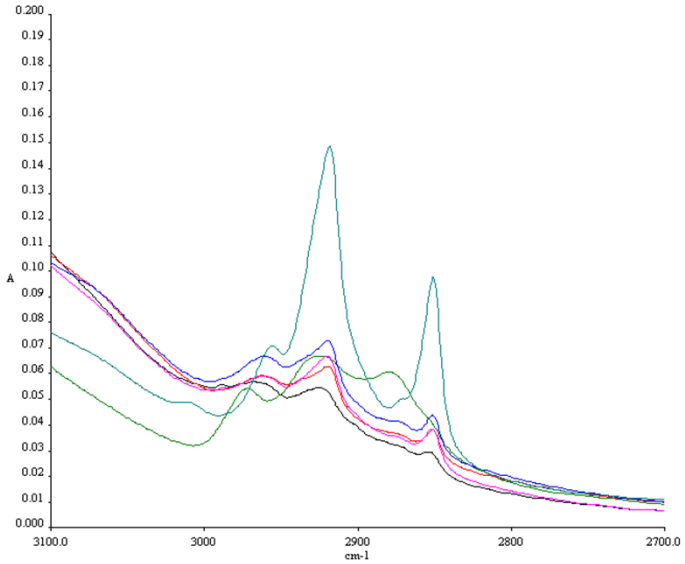


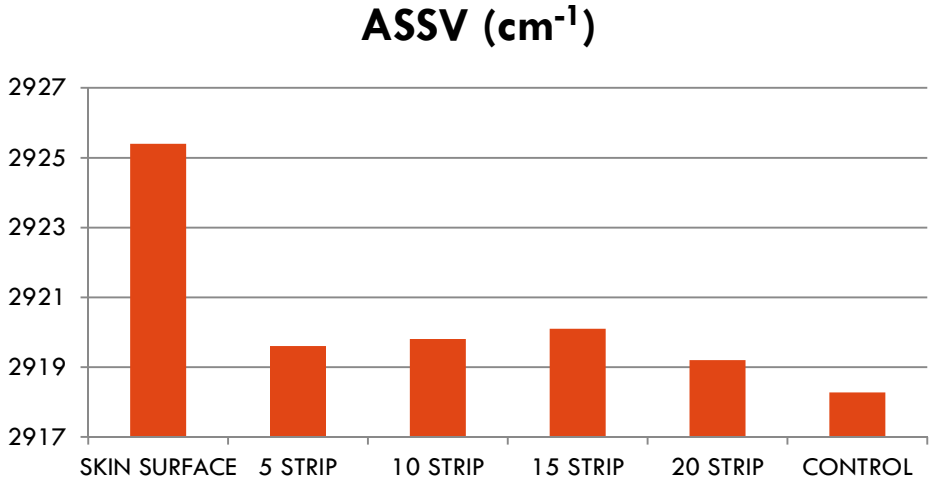


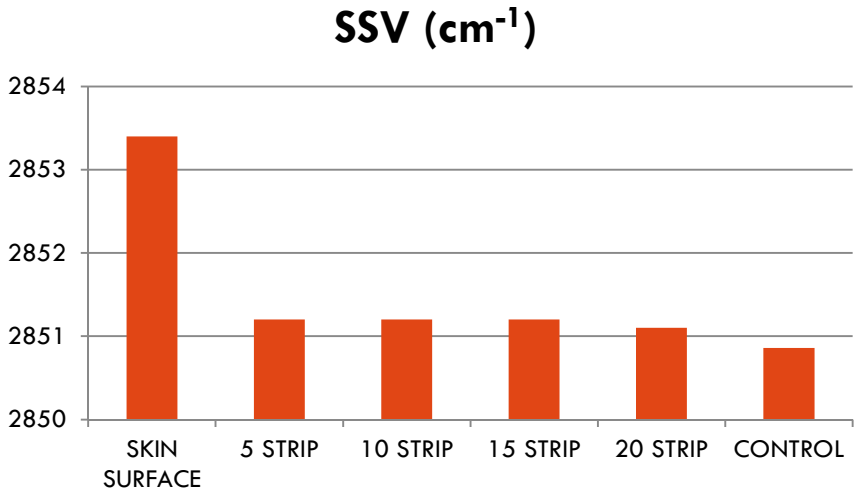


cause a blue shift of +4 cm^{-1} in the ASSV and SSV CH_2 stretching peaks

ASSV & SSV CH2 Peak Positions Following Permeation Study: BPO-MC II







cause a blue shift of +4 cm^{-1} in the ASSV and SSV CH_2 stretching peaks

ASSV & SSV CH_2 Peak Positions Following Permeation Study

- BPO-loaded micellar carriers led to a blue shift shifts to higher frequency for the ASSV and SSV CH_2 peaks especially on the upper skin surface.
- This effect was evident in the lower layers of *stratum corneum* when compared with non-treated control skin.
- The decrease in peak areas of the CH2 stretching absorbances after treatment with formulation suggest that it also affect the lipid extraction from the stratum corneum to some extent.

Conclusion

- The results demonstrate that polymeric micelles optimized had relatively small particle size (~25 µm), and high encapsulation efficiency (>80%).
- The encapsulation of BPO in micellar nanocarriers has overcomed its chemical degradation problem, when it is combined with CLN.
- The shelf-life of the product has been increased without cold-chain transportation and storage.
- BPO delivery with micellar carriers resulted in significantly high drug deposition in skin.
- ATR-FTIR data indicated that micellar formulation affect the lipid extraction from SC to some extent.
- That data supported that BPO passes across lipid domain of SC and both drugs can reach lower layers of skin.
- The micellar nanocarriers can be considered as an appropriate carriers for topical delivery of BPO.

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Embil
PHARMACEUTICAL
www.embil.net

- Topical&Transdermal Drug Delivery Group

Prof. Yıldız Özsoy
MSc.Pharm. Emine Kahraman

Thank you for your attention!