Recent research related to Q3 characterization of topical products containing porous microparticles

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Disclaimer

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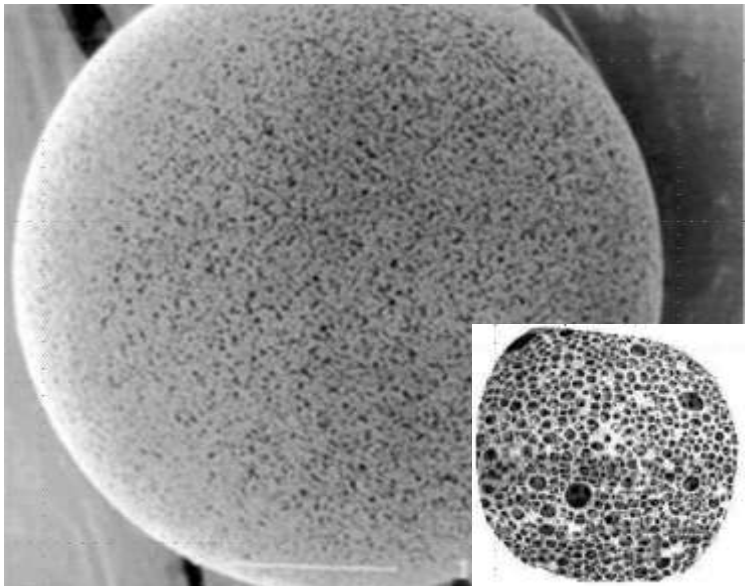
Porous Microparticles

- Microsponges® are spherical solid particles with a network of pores.
- The pore structure provides large surface area and space for inclusion of various active ingredients.
- The porous microparticles vary in diameter size and size distribution.
- The pore dimensions within the microparticles vary considerably.

"Bag of Marbles"



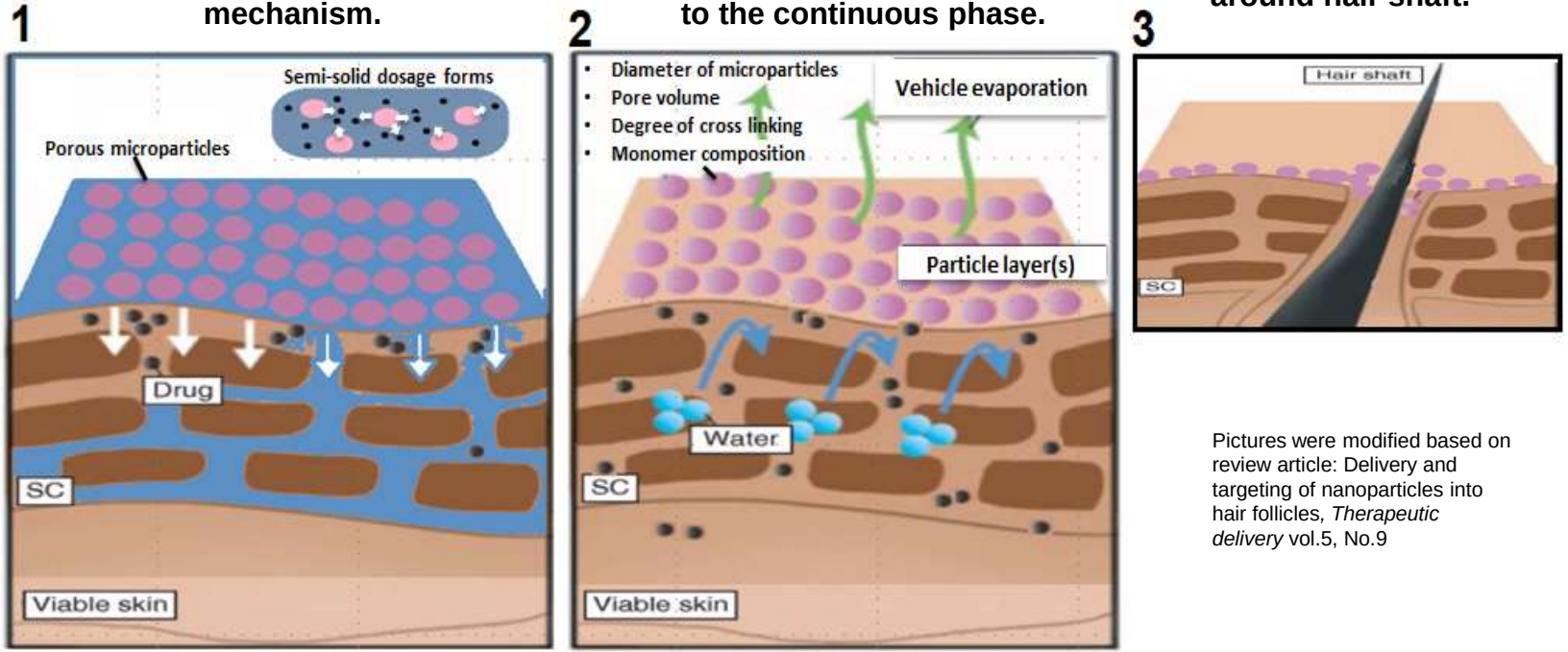
- **Size:** 5-300 um in diameter
- **Pore volume:** 0.1-0.3 cc/gm
- **Surface area:** 20-500 m^2/gm

Skin Transportation of Topical Microparticles

API diffusing from microparticles to the skin through a fusion mechanism.

API diffusing from microparticles within semi-solid dosage forms to the continuous phase.

Deposition of the microparticles around hair shaft.

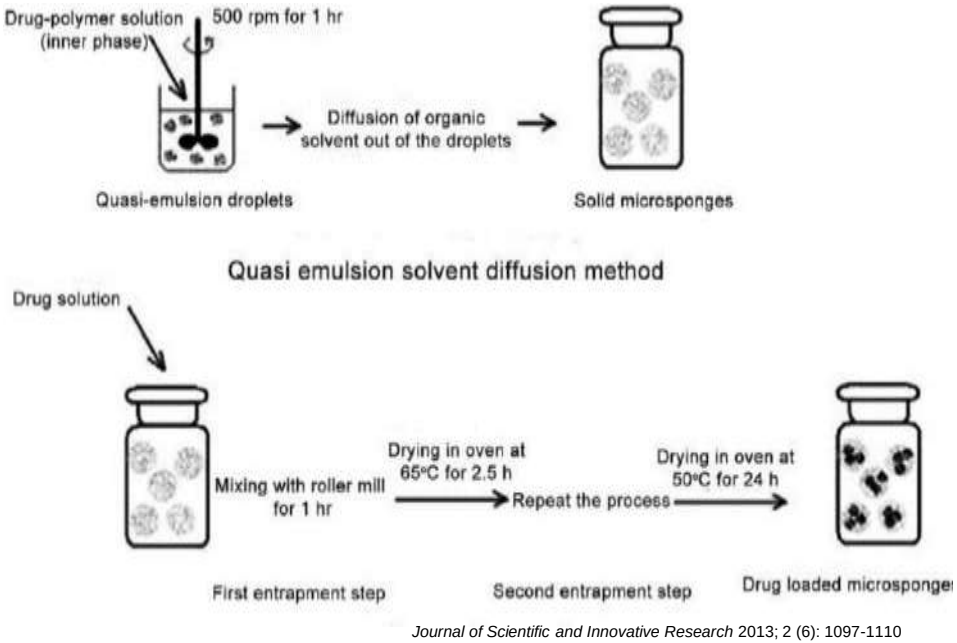


Pictures were modified based on review article: Delivery and targeting of nanoparticles into hair follicles, *Therapeutic delivery* vol.5, No.9

Preparation of Microparticles

Drug loading to microparticles based on physiochemical properties of drug

- **One-step process** → **Liquid-liquid suspension polymerization method** → Passive loading
- **Two-step process** → **Quasi-emulsion solvent diffusion method** → Active loading



Journal of Scientific and Innovative Research 2013; 2 (6): 1097-1110

Advantages of Microparticles in Topical products

Conventional topical products (gels, creams, lotions, ointments, foams)

- Local action and site-specific action, reduced side effects
- Convenient for patients who have difficulty in oral administration.
- Easy to administer and termination of medications when needed
- Irritation to some patients (one potential limitation)

VS

Topical products containing microparticles

- Sustained release
- Improve efficacy and safety
- Prolonged stability
- High internal space for more drug loading capacity
- Undesirable properties (i.e., feel odor) can be considerably reduced
- Liquids can be transformed into free-flowing powder

BE Considerations – Q3/IVRT/IVPT

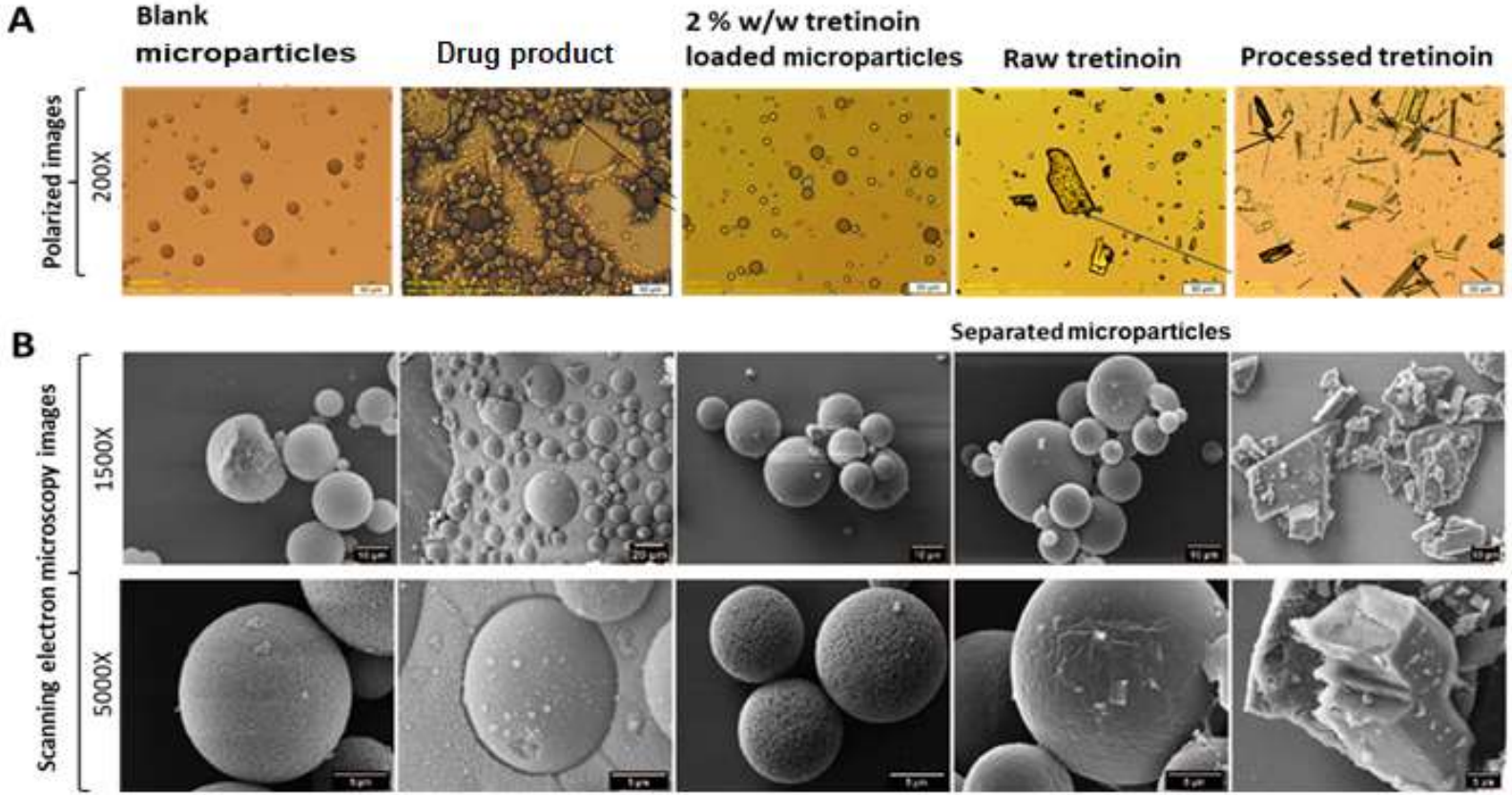
Q3 similarity	IVRT	IVPT
• Drug loading, Rheology, pH, etc. • Drug-polymer ratio • Polymer crosslinking • Particle size distribution (microparticles, dispersed drugs) • Morphological assessment of microparticles (i.e., pore size, pore volume and dimension, surface area) • Spatial distribution of API in microparticle pores • Electrical surface potential • Physical stability and globule size distribution for emulsion • Polymorphic form of API	API release from micro-particles API release from drug product	Drug distribution among various phases of the product API bioavailability from drug product

Case study of tretinoin topical gels containing microparticles

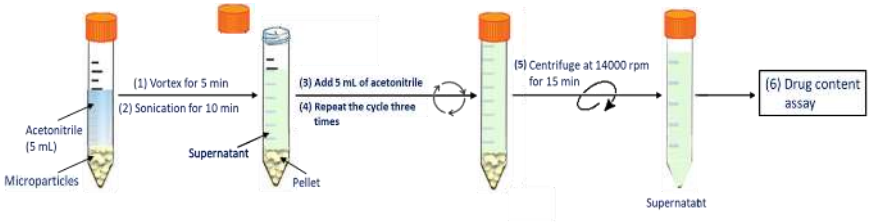
Objectives:

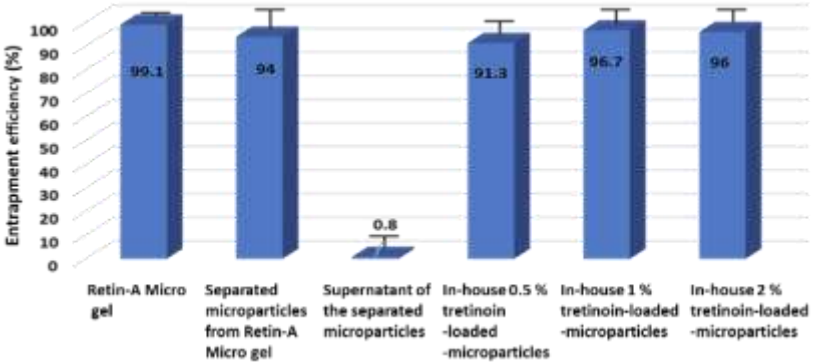
- Identifying the critical physiochemical properties.
- Evaluating the effect of physiochemical properties on the in vitro performance of drug product.
- Understanding the interaction between tretinoin and the microparticles.
- Evaluating the proportionality of tretinoin release rates across four strengths of tretinoin gel.

Surface Morphology of the Microparticles



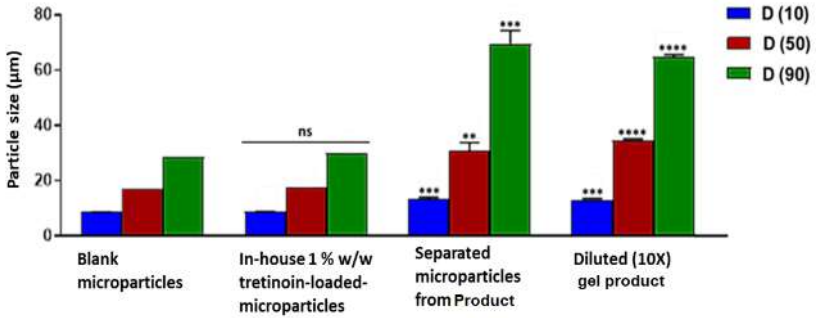
Entrapment Efficiency



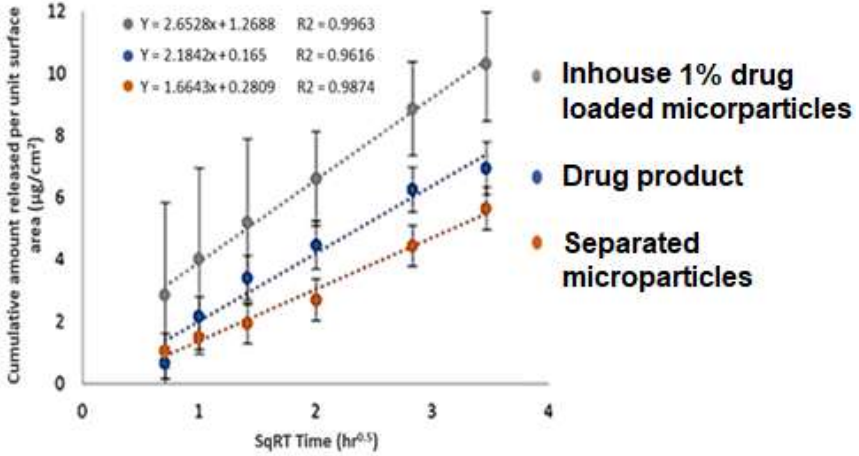


Particle Size Distribution

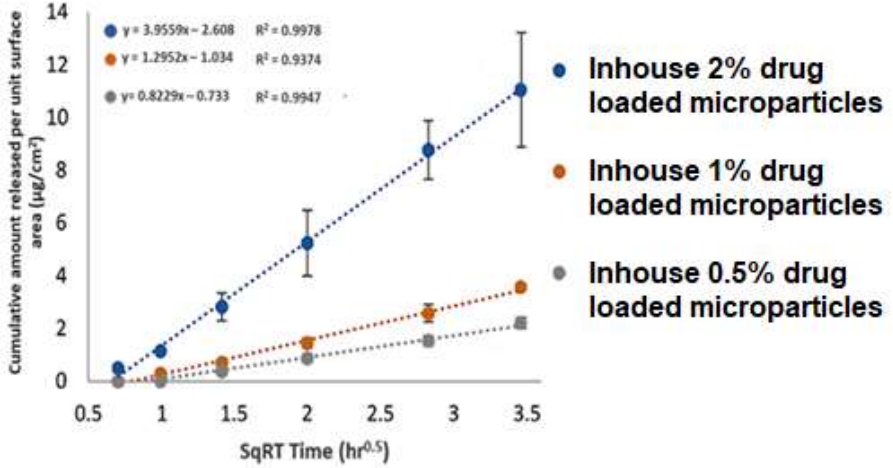
Pharmaceutics 2018, 10(3), 94; https://doi.org/10.3390/pharmaceutics10030094



In Vitro Release Testing (IVRT)

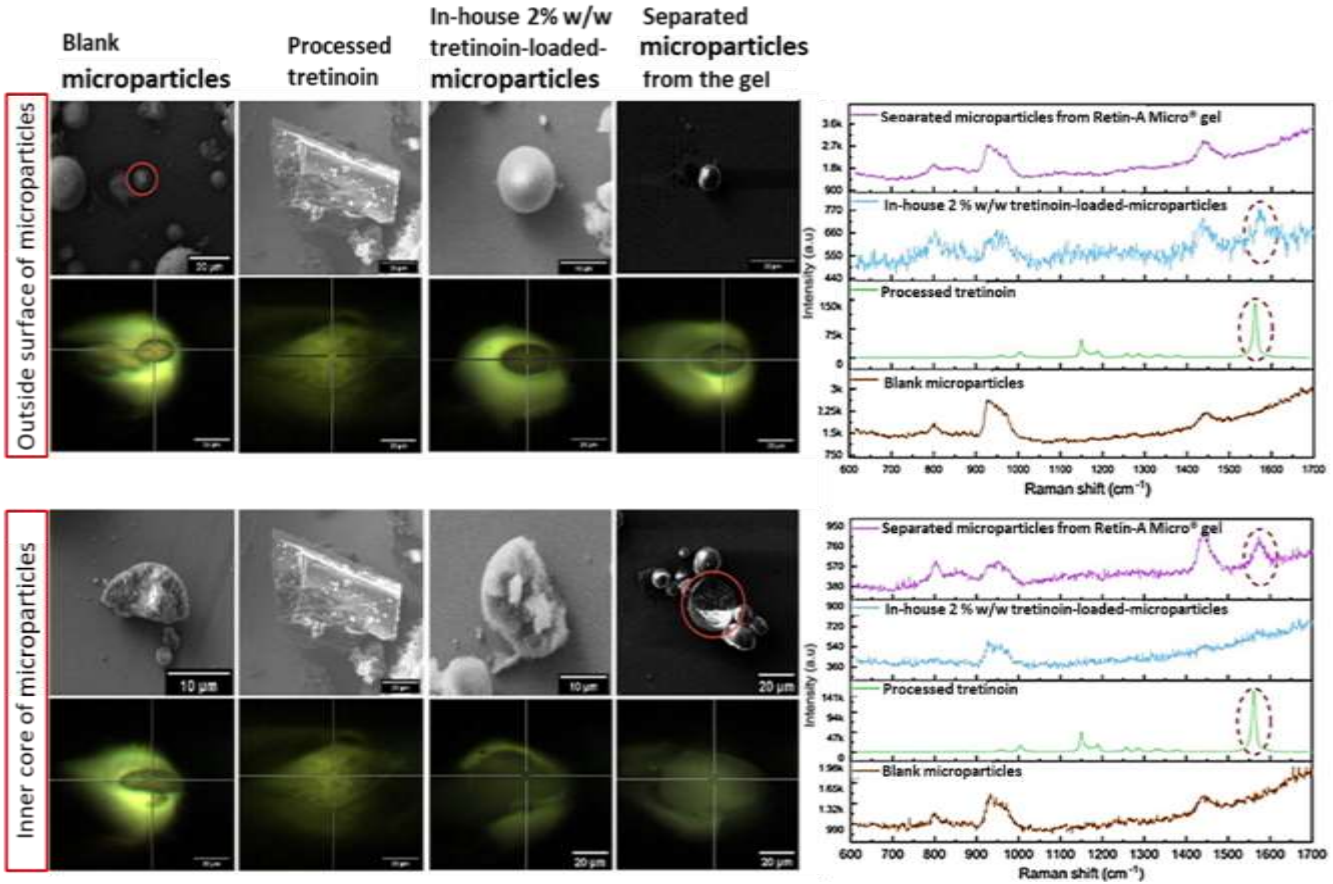


Release of tretinoin from microparticles



Effect of tretinoin loading on the release properties

In-SEM SCA Raman Analysis

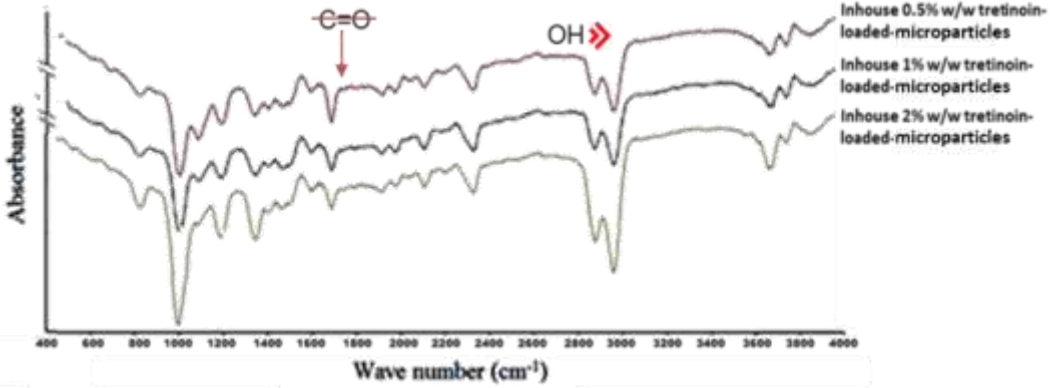


Raman-in-SEM analysis of microparticles at the surface and inside of various microparticles in whole and broken form. The top and bottom spectra show the Raman analysis of whole microparticles and the broken microparticles, respectively. The peak of tretinoin at ~1561-1590 cm^{-1} is shown in red dotted ellipse.

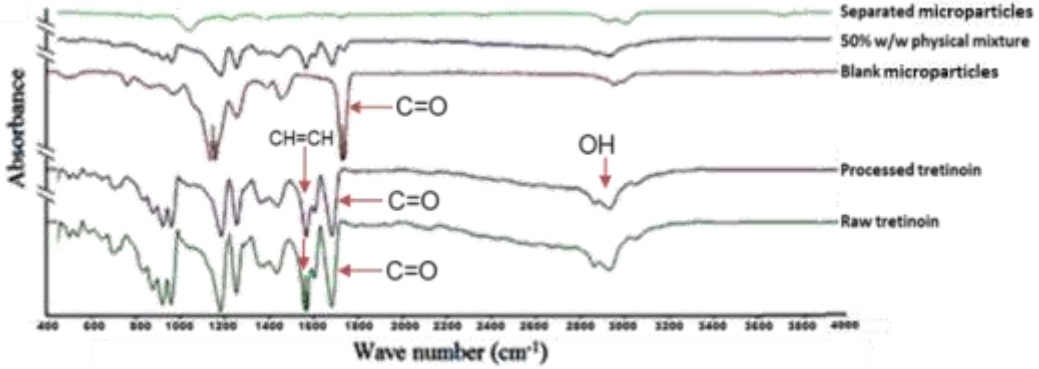
Courtesy of OTR/DCDA, St. Louis, MO

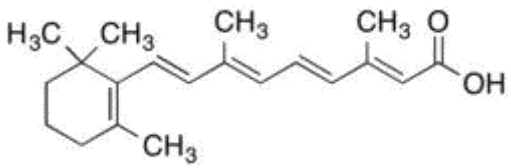
Interaction Studies: (FTIR, DSC, and XRD)

A

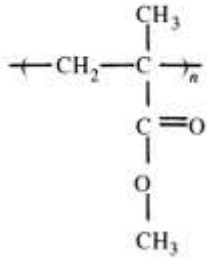


B





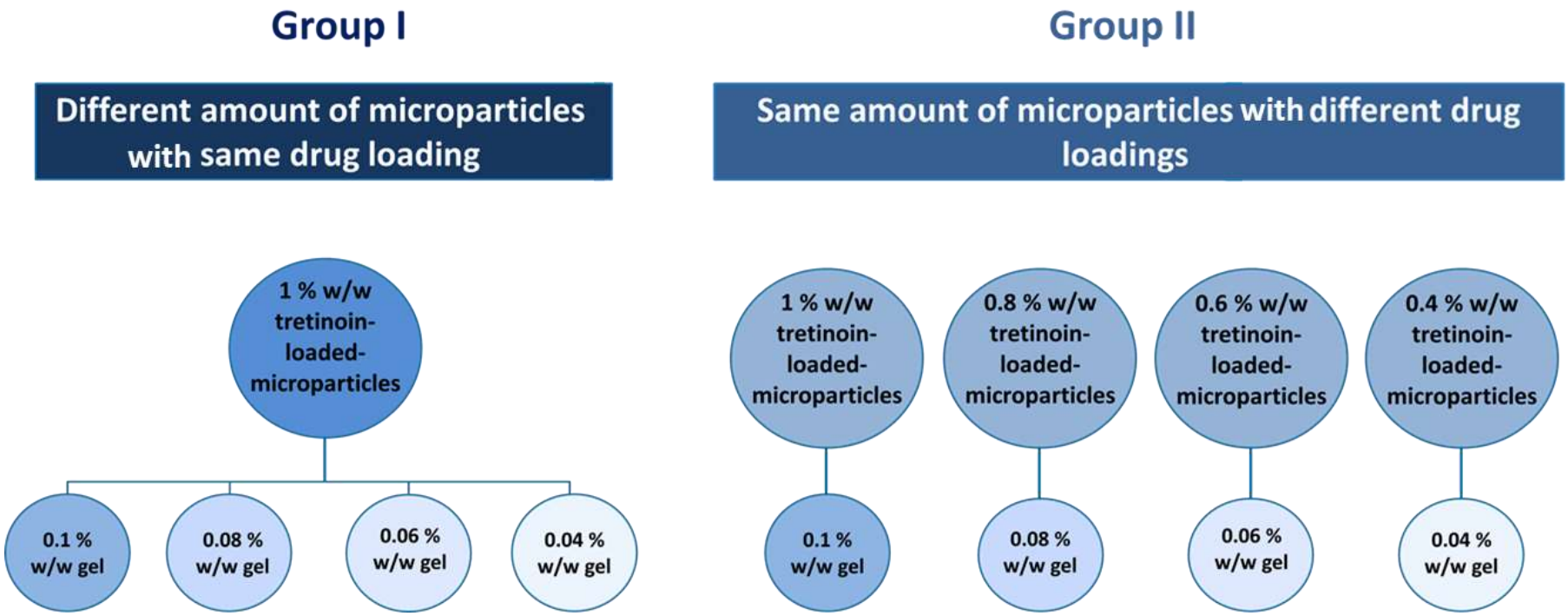
Tretinoin: Structural formula



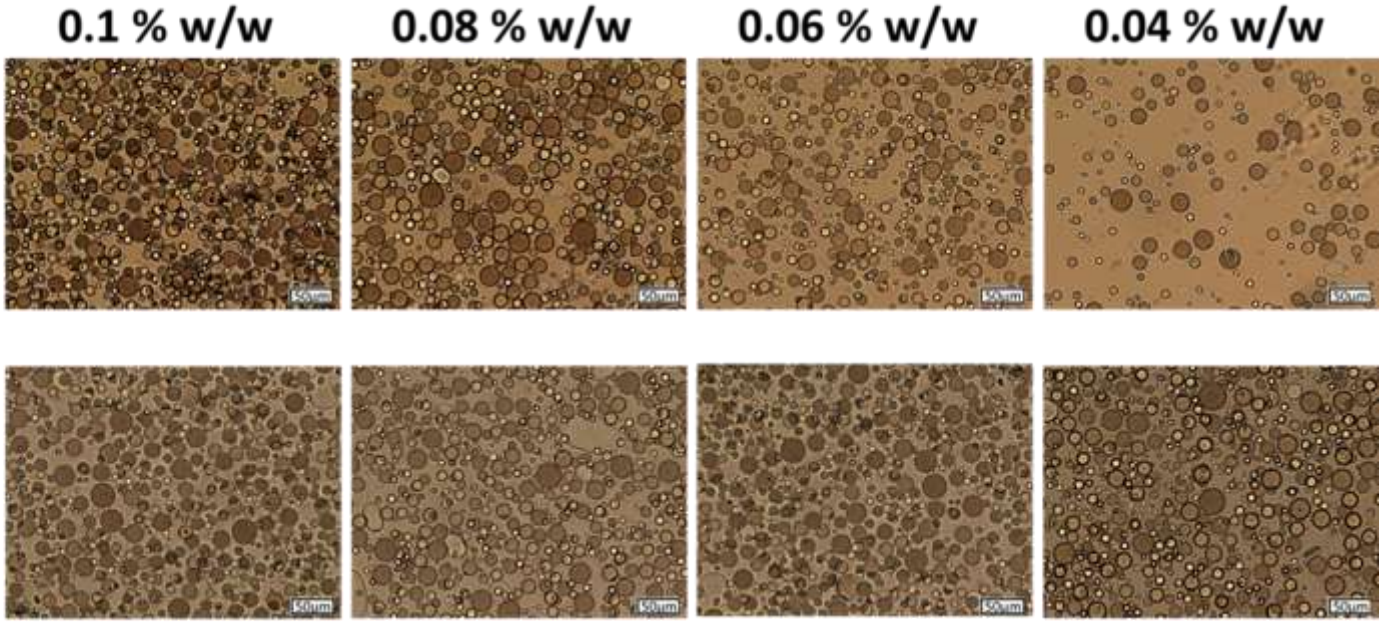
Chemical structure of the repeating unit of Poly(methyl methacrylate) polymer

FTIR spectra of raw and processed tretinoin powder, physical mixtures, and various microparticles samples. The Y-scale ranges are different for spectra of group A and B.

Investigation of Dose Proportionality for Different Strengths of the gels

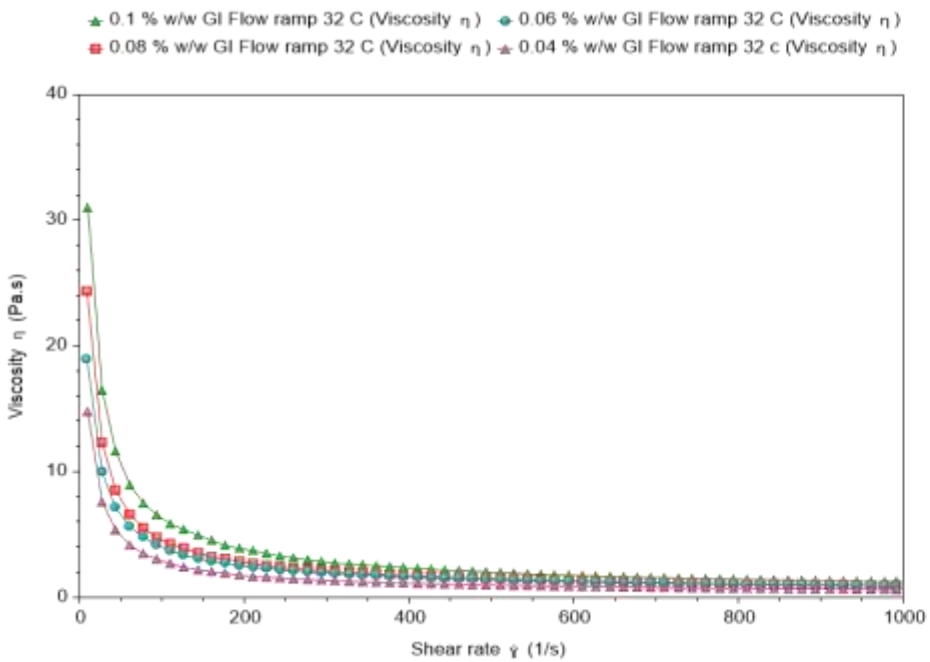


Microscopic Examination

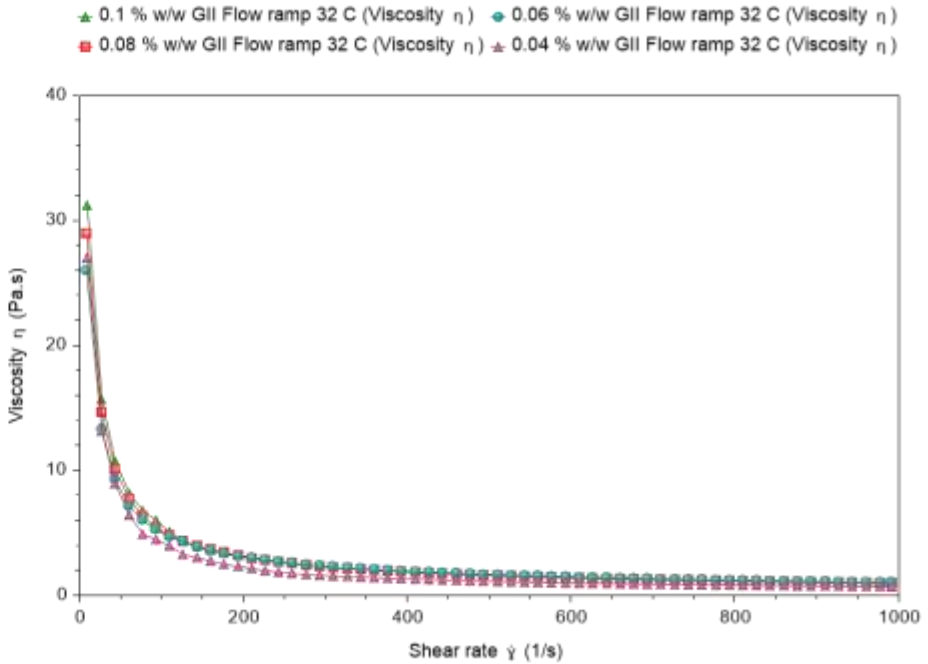


Rheology assessment

Group I

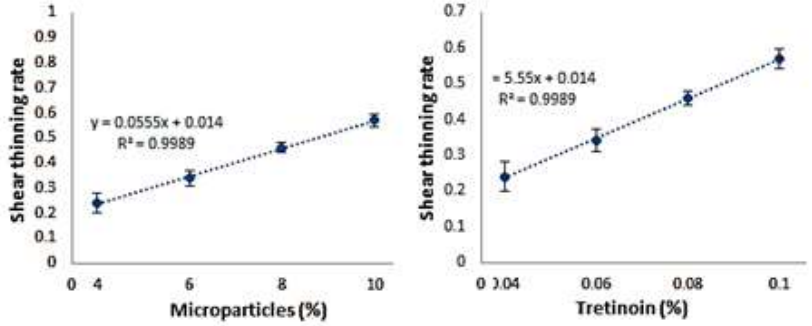


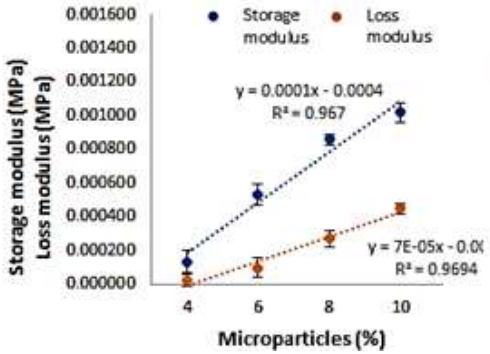
Group II

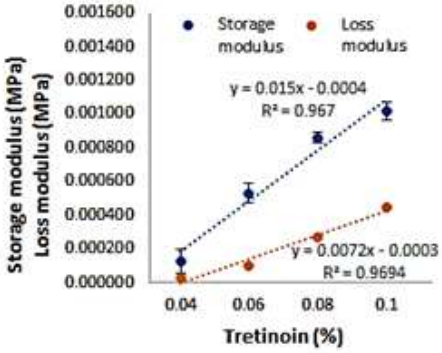


Rheology assessment

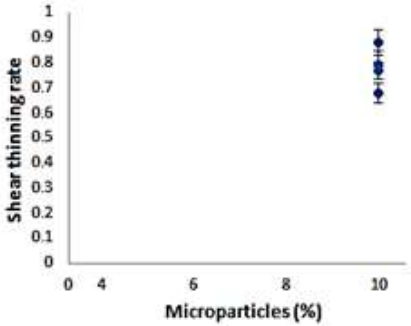
Group I: Different amount of microparticles with same drug loading

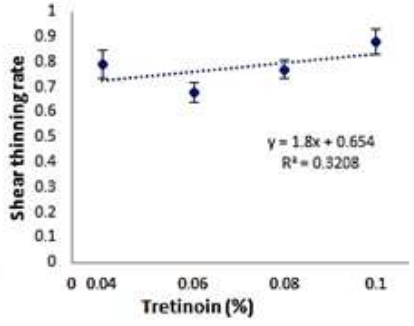


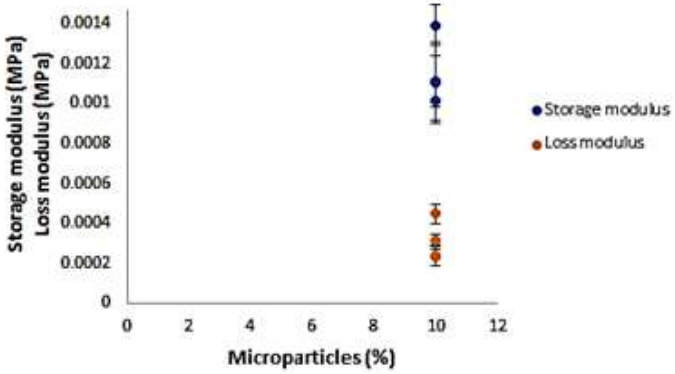




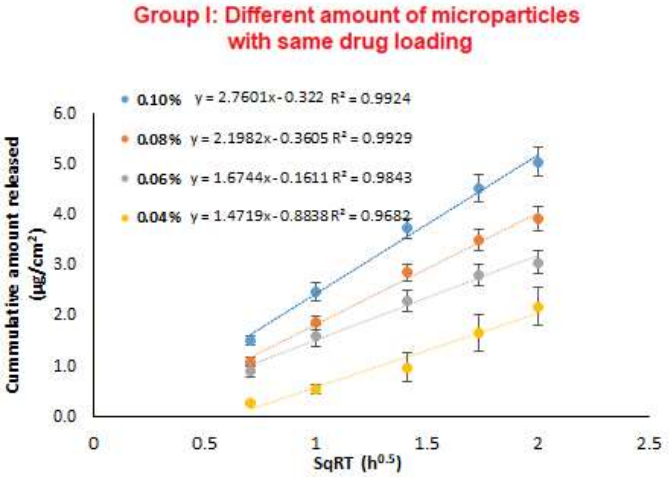
Group II: Same amount of microparticles with different drug loading

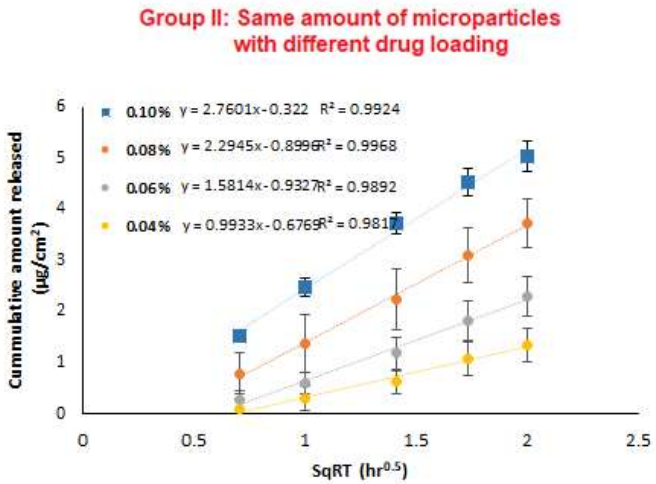


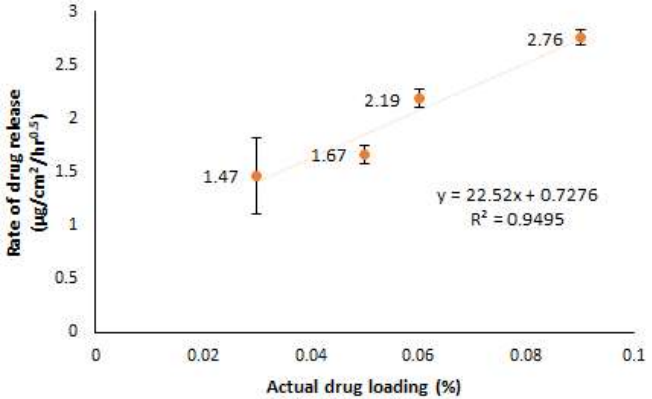


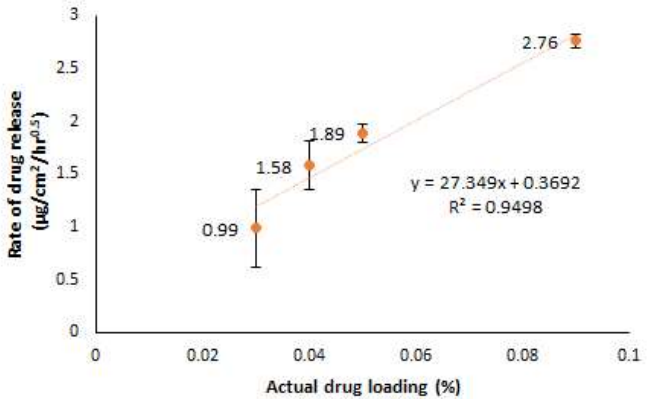


In vitro release rate







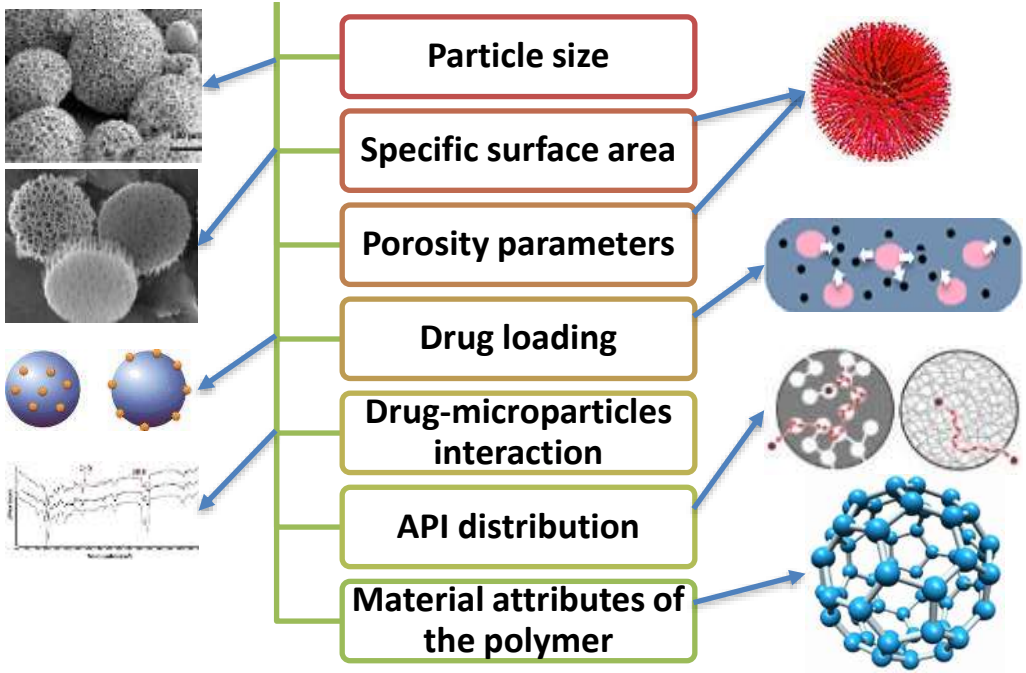


Conclusion

Performance parameters

- Drug release characteristics
- Drug permeation
- Rheology
- Drug delivery to skin
- Drug retention by skin
- Efficacy and safety profiles

Critical physicochemical characteristics of microparticles in topical products



Analysis matrices

- Microscopic evaluation
- Chromatography
- Helium pycnometer
- Solid state characterization
- BET nitrogen adsorption
- IVRT
- Raman mapping

Challenge Question #1

The followings are routes for skin transportation of topical microparticles except:

A. Transcellular transport of microparticles across skin.

B. Paracellular transport of drugs released from microparticles across skin.

C. Accumulation of microparticles in the hair follicle for further release of drugs.

D. Fusion and lysis of microparticles at stratum corneum.

Challenge Question #2

Which of the following statements is NOT true?

A. Amount of microparticles may affect drug release and rheological properties of topical products.

B. Topical microparticles may be used to transform liquid drugs into a free-flowing powder.

C. Chemical interaction of drug with polymeric matrix of the microparticles can be detected by XRD analysis.

D. Spatial distribution of drugs within the topical microparticles is one of Q3 similarity parameters that can affect the drug release properties.

Resources

- Draft Guidance for Industry: Transdermal and Topical Delivery Systems - Product Development and Quality Considerations
- Prescription Drug Labeling Resources
- FDA Label: Full-Text Search of Drug Labeling
- FDA Label: Fluorouracil topical cream
- FDA Label: Retin-A-micro topical gel
- USP general chapter <1724>: Semisolid drug products – performance tests

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Thank you

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