The Role of Microparticles and Other Excipients in the Complexity of Certain Topical Drug Products

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This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- Understanding the landscape and unique complexities associated with topical products containing microparticles
- Understanding the impact of excipients on the microstructure, and thereby, drug release and bioavailability from such products
- Understanding the potential challenges associated with developing efficient bioequivalence (BE) approaches for topical products containing microparticles

Topical Products Containing Microparticles

- Topical products containing microparticles are widely used in cosmetics
- FDA approved topical drug products

  Examples

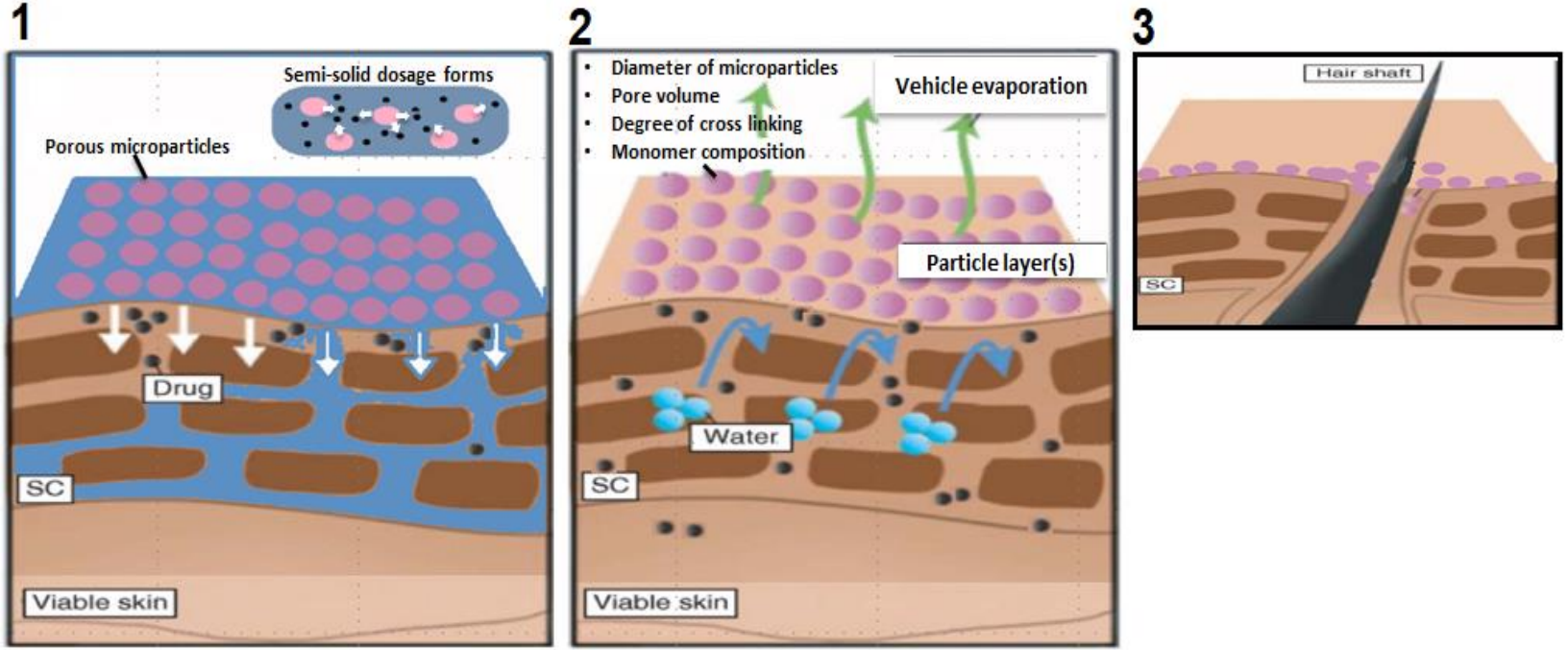
  - Retin-A Micro® (Tretinoin) Topical Gel, 0.04%; 0.06%; 0.08%, 0.1%
  - Carac® (Fluorouracil) Topical Cream, 0.5%
  - Twyneo® (Tretinoin; Benzoyl Peroxide) Topical Cream, 0.1%; 3%

Skin Transport of Topical Microparticles

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

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

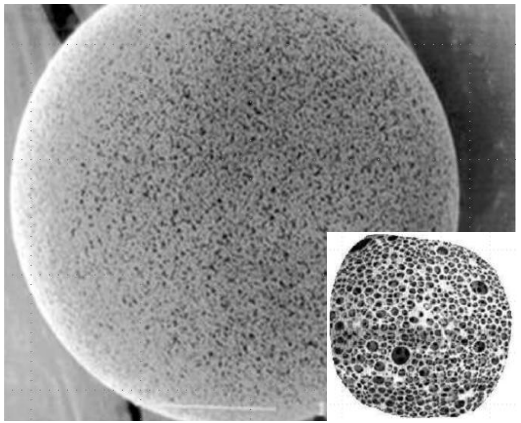
Deposition of the microparticles around hair shaft.



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

Porous Microparticles

- Microsponge® technology
- Microsponge® are spherical solid particles with a network of pores
- Polymers in fabrication of Microsponge
  - Polymethacrylates or Eudragit© polymers (Eudragit RS100, Eudragit RSPO, Eudragit S100)
  - Polylactide -co-glycolic acid
  - Polylactic acid
  - Polydivinyl benzene
  - Polyhydroxy butyrate
  - Ethyl cellulose



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

Microsponges for dermatological applications: Perspectives and challenges. *Asian Journal of Pharmaceutical Sciences 2020; 15: 273-291*

Complexity – Retin-A® vs Retin-A micro®

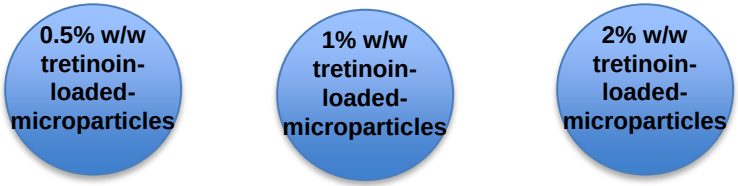
	Retin-A® Topical Gel	Retin-A Micro® Topical Gel
Dosage form	Gel	Gel containing microparticles
Drug state	Drug is dissolved and/or dispersed in gel	Drug is incorporated in microparticles
Physiochemical and structural (Q3) properties	Color, clarity/opaqueness, texture, non-Newtonian flow behavior, pH, etc.	Color, clarity/opaqueness, texture, non-Newtonian flow behavior, pH, etc. Characterization of microparticles
Release mechanism	Release of drug from gel	Release of drug from microparticles and gel
Skin permeation	Drug permeation from gel to skin	Drug permeation includes multiple steps

Complexity increases →

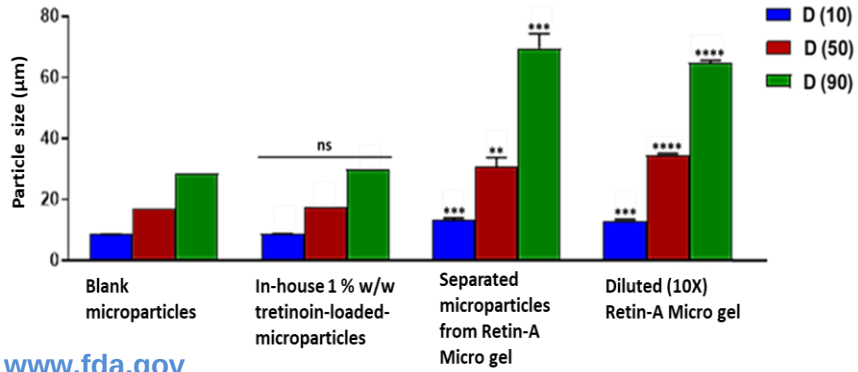
Drug Loading and Particle Size

Drug loading

Particles are loaded using the same manufacturing process

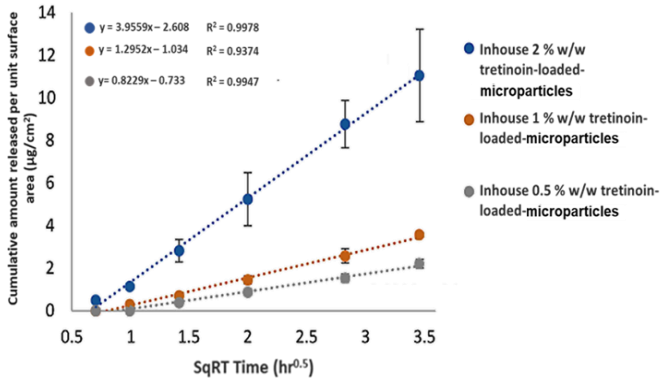


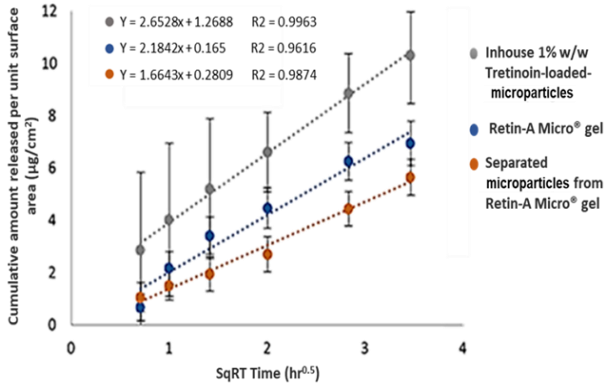
Particles size



www.fda.gov

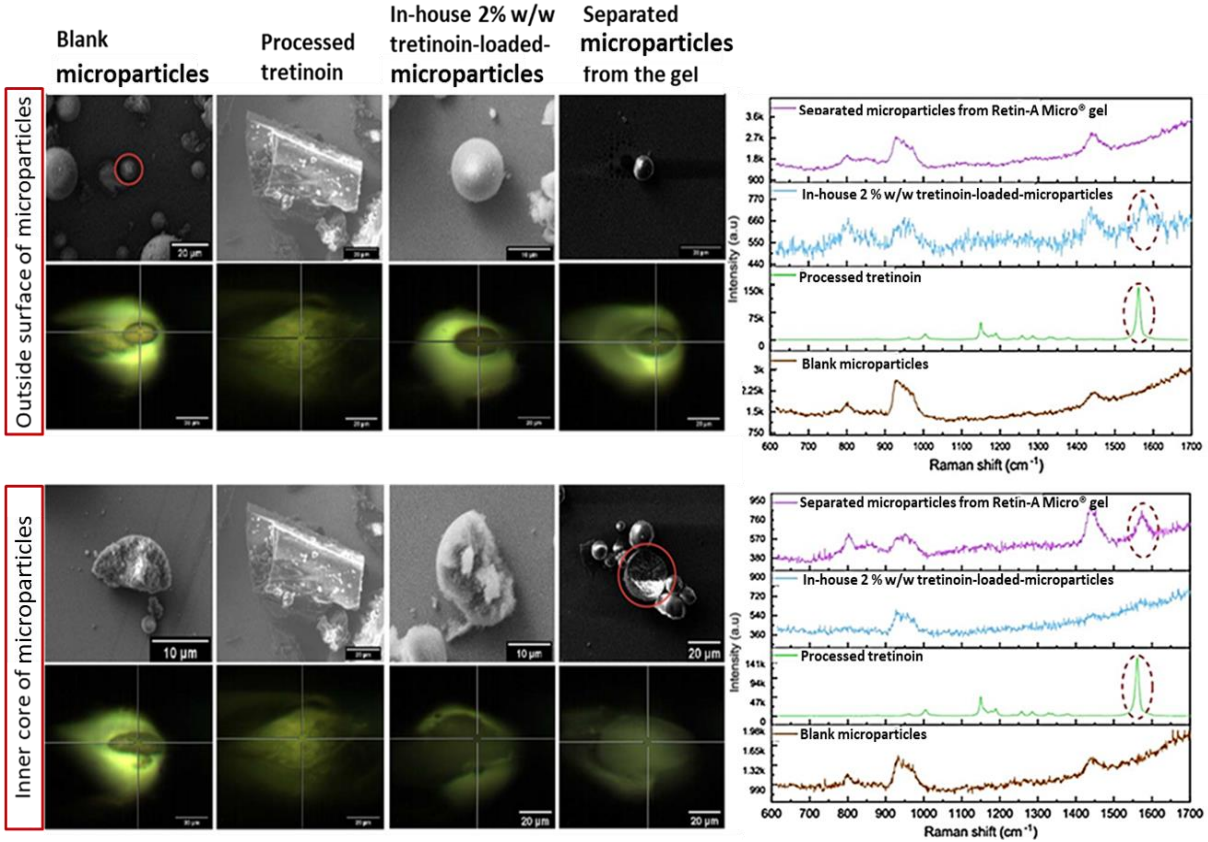
Drug release from microparticles and gel





AAPS 2021 Poster: Drug Release from Porous Microparticle-Based Tretinoin Topical Gels: Proportionality of Release Across Various Strengths

Drug Distribution in Microparticles



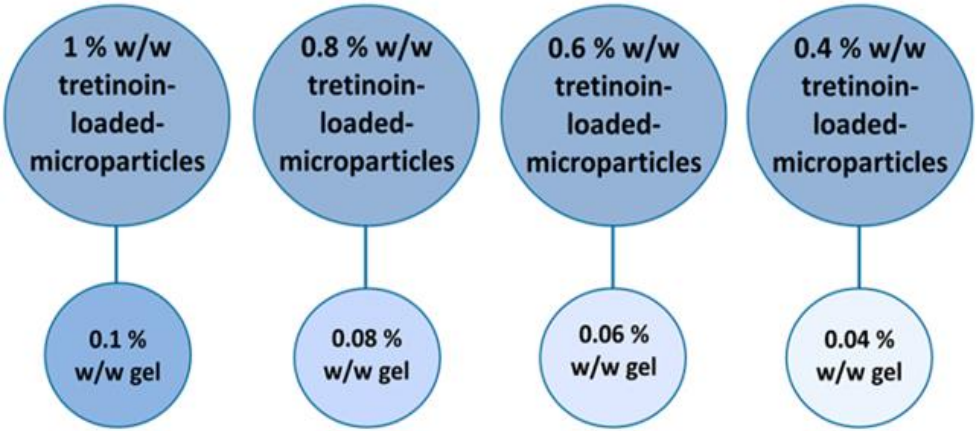
Tretinoin is present mostly on the outside surface of in-house prepared microparticles;

Tretinoin was found in the inner core of the microparticles of Retin-A Micro® Gel

FY2021 GDUFA Science and Research Report Ch6 Dermatological available at https://www.fda.gov/drugs/generic-drugs/fy-2021-gdufa-science-and-research-report

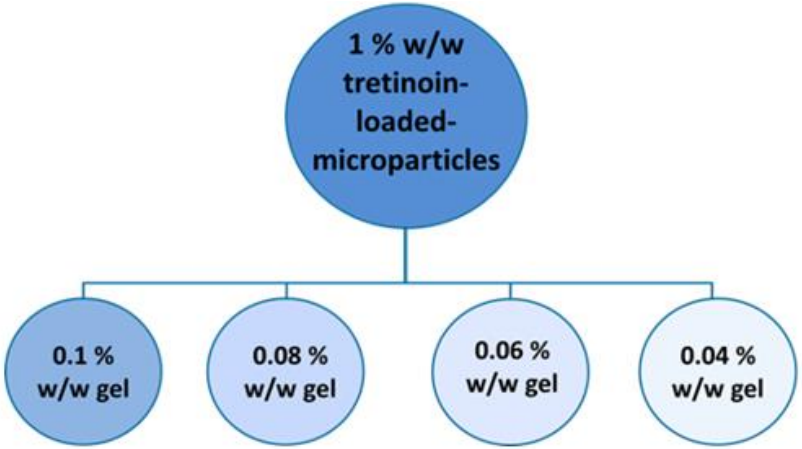
Manufacturing Variables

Same concentration of microparticles with different drug loading



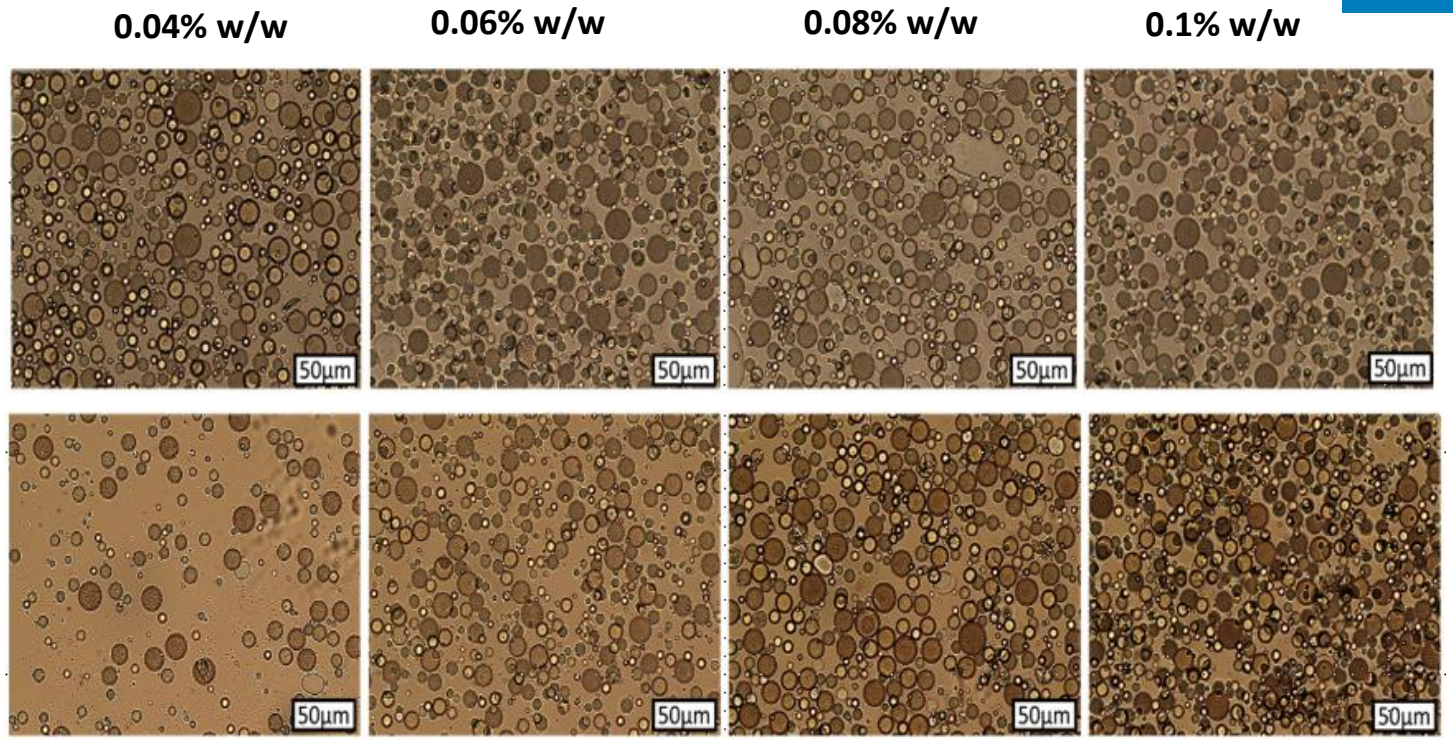
VS

Different concentration of microparticles with same drug loading



Content was adapted from Dr. Ahmed Zidan's slides in SBIA 2021 available at https://sbiaevents.com/advancing-generics-2021/#files

Manufacturing Variables & Q3 attributes/IVRT

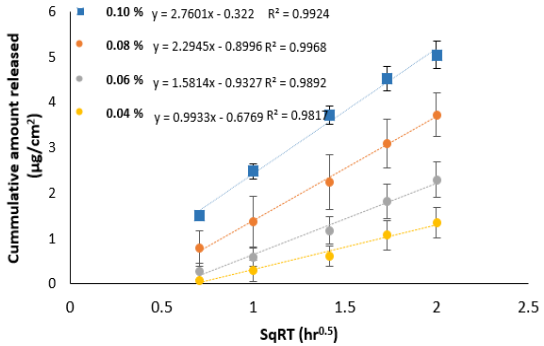


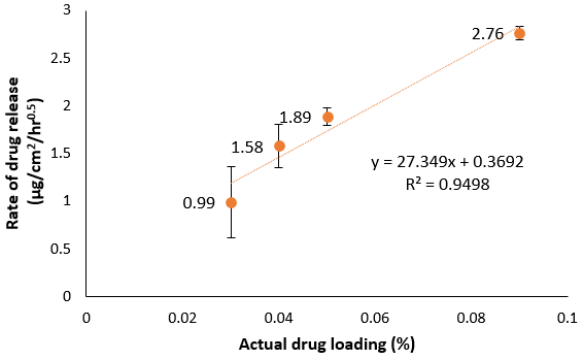
Manufacturing Variables & IVRT

IVRT

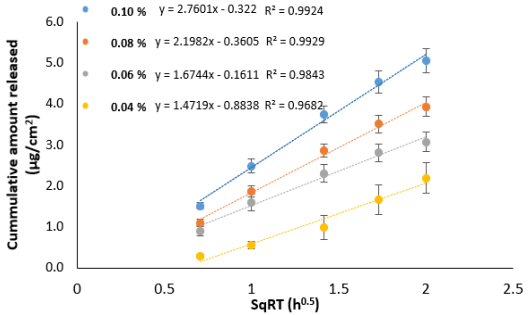
Release proportionality

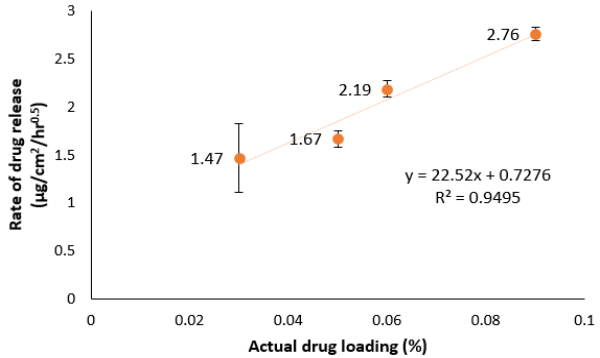
Same concentration of microparticles





Different concentration of microparticles





Complexity – Retin-A micro® vs Carac®

	Retin-A Micro® Topical Gel		Carac® Topical Cream
Dosage form	Gel containing microparticles		Cream (multiple phases) containing microparticles
Drug state	Drug is incorporated in microparticles	*Complexity increases*	70% of drug is incorporated in microparticles, 30% in cream
Q3 properties	Color, clarity/opaqueness, texture, non-Newtonian flow behavior, pH etc. Characterization of microparticles		Color, clarity/opaqueness, texture, non-Newtonian flow behavior, Globule size distribution pH etc. Characterization of microparticles
Release mechanism	Release of drug from microparticles and gel		Release of drug from microparticles and multiple phases of the cream
Skin permeation	Drug permeation includes multiple steps		Drug permeation includes multiple steps, additional complexity

NDA020985 Product labeling available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20985slr004_carac_lbl.pdf

Monomer Concentration and Crosslinking Agent

Encapsulation efficiency and particle size

Sample code	AAm:MMA (wt./wt.)	% NNMBA	% 5-FU	% Encapsulation efficiency	Mean particle diameter (μm)
AAm-1	1:1	1	5	69.6	30.4
AAm-2	1:1	1	10	75.2	31.8
AAm-3	1:1	1	15	79.2	32.6
AAm-4	1:1	2	5	71.5	29.6
AAm-5	1:1	2	10	72.8	30.4
AAm-6	1:1	2	15	76.9	31.6
AAm-7	1:1	3	5	72.5	24.1
AAm-8	1:1	3	10	73.4	26.8
AAm-9	1:1	3	15	75.6	28.4

5-Fu = 5-fluorouracil; AAm = acrylamide; MMA = methylmethacrylate; NNMBA = *N,N* methylene bisacrylamide.

Drug release

Formulation code	*k*	*n*
AAm-1	0.0257	0.624
AAm-2	0.0269	0.617
AAm-3	0.0298	0.597
AAm-4	0.0269	0.602
AAm-5	0.0284	0.612
AAm-6	0.0309	0.593
AAm-7	0.0346	0.568
AAm-8	0.0346	0.546
AAm-9	0.0347	0.493

Development of 5-fluorouracil loaded poly(acrylamide-co-methylmethacrylate) novel core-shell microspheres: in vitro release studies. *International Journal of Pharmaceutics 325 (2006) 55–62*

Complexity – Retin-A micro® vs Carac® vs Twyneo®

Retin-A Micro® Topical Gel	Carac® Topical Cream	Twyneo® Topical Cream
Gel containing microparticles	Cream (multiple phases) containing microparticles	Cream containing "Silica" particles
Drug is incorporated in microparticles	70% drug is incorporated in microparticles, 30% in cream	Tretinoin silica particles and benzoyl peroxide silica particles
Color, clarity/opaqueness, texture, non-Newtonian flow behavior, pH, etc. Characterization of microparticles	Color, clarity/opaqueness, texture, non-Newtonian flow behavior, globule size distribution, pH etc. Characterization of microparticles	Color, clarity/opaqueness, texture, non-Newtonian flow behavior, globule size distribution, pH etc. Characterization of microparticles
Release of drug from microparticles and gel	Release of drug from microparticles and multiple phases of the cream	Release mechanism is not fully understood
Drug permeation includes multiple steps	Drug permeation includes multiple steps, additional complexity	Drug permeation includes multiple steps, additional complexity

NDA214902 Product labeling available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214902s000lbl.pdf

PSGs for Topical Dermatological Products

Potential ways for establishing BE for complex topicals:

- *Efficient* characterization-based BE approaches
  - In vitro characterization-based studies (e.g., formulation sameness, Q3 tests, in vitro release test (IVRT) with/without in vitro permeation test (IVPT))
  - A combination of in vitro characterization-based studies and in vivo pharmacokinetic studies
- In vivo BE approaches
  - Comparative clinical endpoint study
  - Pharmacodynamic endpoint study (e.g., vasoconstrictor studies)

Q3 Tests for Topical Products

1. Characterization of appearance and texture
2. Characterization of phase states
3. Characterization of structural organization of matter
4. Characterization of polymorphic form of the active ingredient
5. Characterization of rheological behavior
6. Characterization of water activity and/or drying rate
7. Characterization of pH and buffering
8. Characterization of oleaginous components
9. Characterization of specific gravity
10. Characterization of metamorphosis-related changes

Topical Products Containing Microparticles

Additional tests to consider for topical products containing microparticles:

- Characterization of constituent material in microparticles (e.g., polymers)
- Characterization of particle size distribution of microparticles
- Characterization of morphology including the surface area and porosity
- Characterization of drug loading
- Characterization of drug distribution, localization and physical state, etc.
- Evaluation of drug release
- Cutaneous pharmacokinetic studies (e.g., IVPT, non-invasive techniques, modeling and simulation, etc.)

Content was adapted from Dr. Ahmed Zidan's slides in SBIA 2021 available at https://sbiaevents.com/advancing-generics-2021/#files

Conclusion

- Topical semi-solid products containing microparticles are potentially more complex in structure compared to conventional semi-solid products
- The microparticles can be manufactured with different excipients
- Based on the complexity of the drug product, additional Q3 tests, as well as release and cutaneous pharmacokinetic studies may be necessary for assessing the bioavailability and establishing BE for such products
- Utilization of advanced in vitro, in vivo and/or in silico technology may also be able to assist with understanding the complexities associated with topical products containing microparticles

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