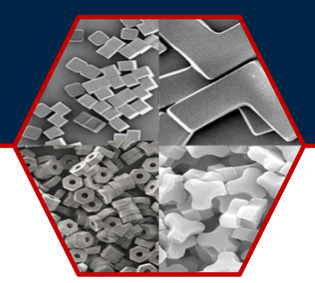
PRINT® Particle Design Improves Skin Penetration in a Topical Formulation

Christina L. Hofmann[1], John R. Savage[1], Drew Folk[1], Jake J. Sprague[1], Priya Kalluri[2], Robert Leming[2], Piyush Jain[2], Alan Colborn[2], Leandro Santos[2], Geoffrey Hird[1]

1. Liquidia Technologies, Inc., P.O. Box 110085, RTP, NC 27709; 2. Dermavant Sciences, Inc., Durham, NC 27701

Corresponding Author: Geoffrey Hird, Geoff.Hird@Liquidia.com



Introduction

Problem Statement:

High throughput drug screening methodologies create topical drug delivery challenges by identifying API candidates with intermediate polarities. These candidates are difficult to formulate in traditional topical vehicles such as creams and gels.

Approach:

Design a PRINT® particle gel suspension which creates a supersaturated solution upon application to drive skin penetration.

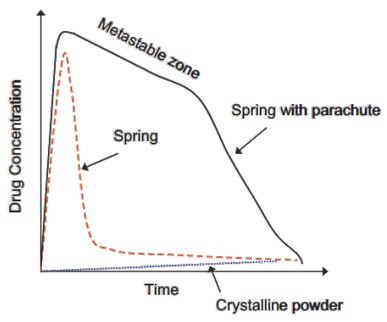


Figure 1. *Supersaturation* is dissolution of a molecule above its equilibrium solubility, which increases the chemical potential. The excipients in the formulation can provide the "parachute" to inhibit precipitation. Figure from ref 1.

PRINT (Particle Replication in Non-wetting Templates) technology is a versatile particle engineering platform that can be used to address topical drug delivery challenges. It offers independent control of particle composition, physical form, size, and shape to enable exploration of a broad formulation design space.

To create a supersaturated solution of drug on the skin, a *triggered release* formulation containing API-loaded PRINT particles suspended in a gel was developed to facilitate rapid dissolution of drug as water evaporates.

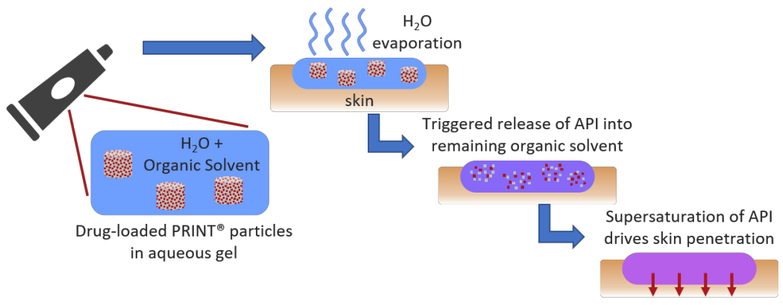
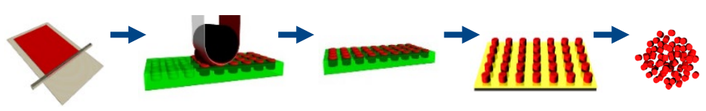


Figure 2. Triggered release mechanism of PRINT gel suspension.

The PRINT® Process



The core technology involves four basic steps:

1. Create a film of the desired drug/excipient composition on a delivery substrate.
2. Laminate the film with a patterned template to fill the cavities.
3. Remove drug-loaded particles from the patterned template.
4. Collect particles to create a particle suspension or dry powder for packaging of drug product.

Gel Solvent System

Kinetic API solubilities in 36 solvents with precedent in topical formulations were screened. The top 3 solvents based on solubility and known penetration enhancing properties were chosen for mixture design studies.

To trigger API release and supersaturation, high solubility in the solvents remaining on the skin after application is desired. However, for physical stability, low solubility is desired in the aqueous gel.

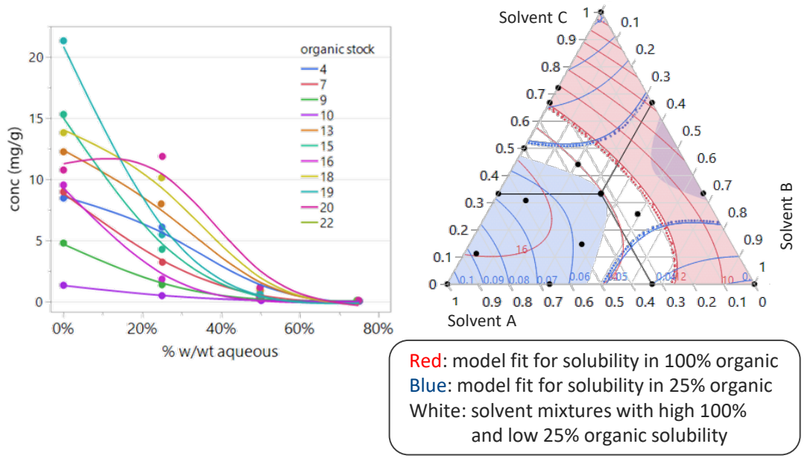


Figure 3. Left: Organic solvent blends were mixed with water and tested for thermodynamic API solubility. Right: The mixture design was modeled to maximize API solubility in 100% organic solvent and minimize solubility in 25% organic solvent.

PRINT® Particle Designs

API and excipient solvent compatibility studies were conducted to identify water-insoluble excipients suitable for incorporation of amorphous API. Compositions capable of rapidly releasing drug in lead solvent systems were fabricated into PRINT particles of varying geometries and drug loadings for evaluation in gel formulations.

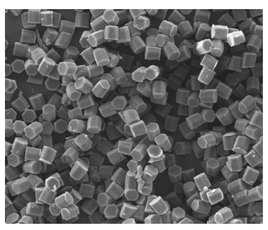


Figure 4. SEM of water-insoluble PRINT particles with uniform size and shape.

PRINT® Particles in Aqueous Gels

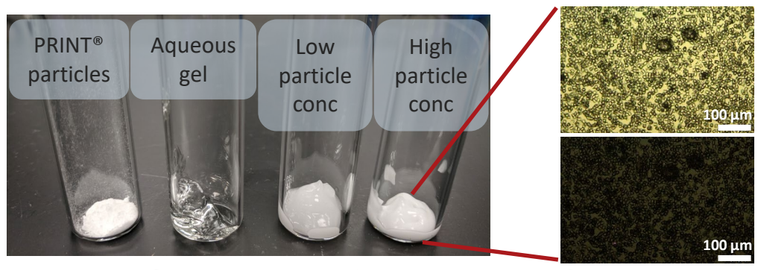


Figure 5. Left: PRINT particles composed of water-insoluble excipients plus API are easily incorporated into aqueous-based gels to create homogeneous suspensions with desirable organoleptic properties. Right: Optical microscopy of an aqueous-based gel containing amorphous PRINT particles. (Top) brightfield of particle morphology, (Bottom) cross-polarized microscopy reveals lack of crystalline material.

The PRINT technology provides a mechanism for incorporating API into a matrix at various *API* concentrations. These particles are suspended within gels at various *particle* concentrations, which allows for easy adjustment of API dose.

PRINT Gel Design Space	
Factor	**Levels**
Particle Excipient	3
API Load in Particles	3
Particle Size	2
Formulation Strength	3
Organic Solvent Blend	2
Organic Solvent Content	3

Results: Supersaturation by Hot Stage Microscopy

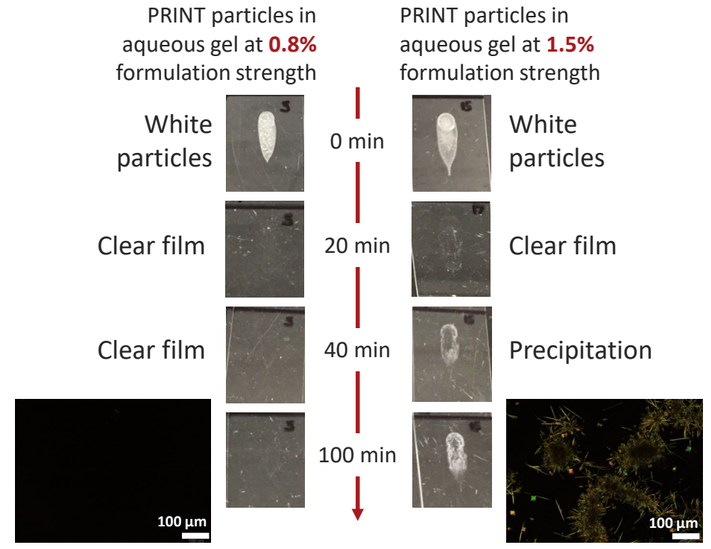
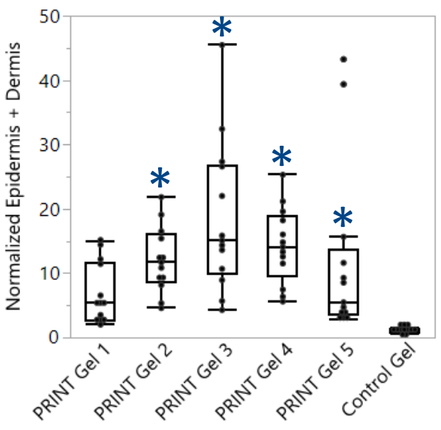


Figure 6. Gels were cast into 250 µm thick films on glass slides and heated to 35°C. Upon water evaporation, the gels became clear. At higher API concentration, the API crystallized within 40 min (right), while the lower concentration remained clear (left). These results support triggered release and supersaturation of the API in the remaining organic formulation.

Results: PRINT® Particle Suspension Improved in vitro Dermal Delivery >18x over Soluble API Gel Formulation

Gels were formulated with a range of organic solvent contents, particle designs, and formulation strengths.

Figure 7. Performance of PRINT gel formulations were studied by an in vitro permeation test (IVPT) with 3 skin donors. API content in the epidermis + dermis was normalized to the content measured after treatment with the soluble API control gel. Mean content for PRINT Gel 3 was >18x the control gel.



* significantly higher than control gel, Tukey HSD α = 0.05

Conclusions

- PRINT particle suspensions improved in vitro dermal delivery up to 18x over a traditionally-formulated gel containing solubilized API.
- Triggered release and supersaturation of API upon water evaporation was demonstrated by optical microscopy studies. This is hypothesized to be the mechanism for higher skin penetration.
- PRINT particles of API dispersed in water-insoluble excipients were easily incorporated into aqueous gels at multiple strengths with desirable organoleptic properties.
- Engineered PRINT suspensions offer an alternative topical formulation strategy for challenging APIs.

References

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3. www.Liquidia.com

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Conflict of interest: CLH, GH, JRS, JJS are employees of Liquidia Technologies Inc. DF was an employee of Liquidia Technologies Inc. at the time the research was conducted. PK, RL, PJ, AC, LS are employees of Dermavant Sciences, Inc.

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