ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEMS

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Managing Director,
Sparsha Pharma

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Agenda

1. Transdermal Drug Delivery System
2. Microneedle Patch
3. Regulatory Aspects
4. Open Q&A

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Context Setting

We are: Young pharma experts to create a research based Pharmaceutical company

We intend to: create a platform for TDDS Technology in India

Our goal is to: be a research based TDDS global pharmaceutical company

Our business model: Develop own products & establish commercial Manufacturing

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Therapy With Touch

SPARSHA USA

TRANSDERMAL DRUG DELIVERY

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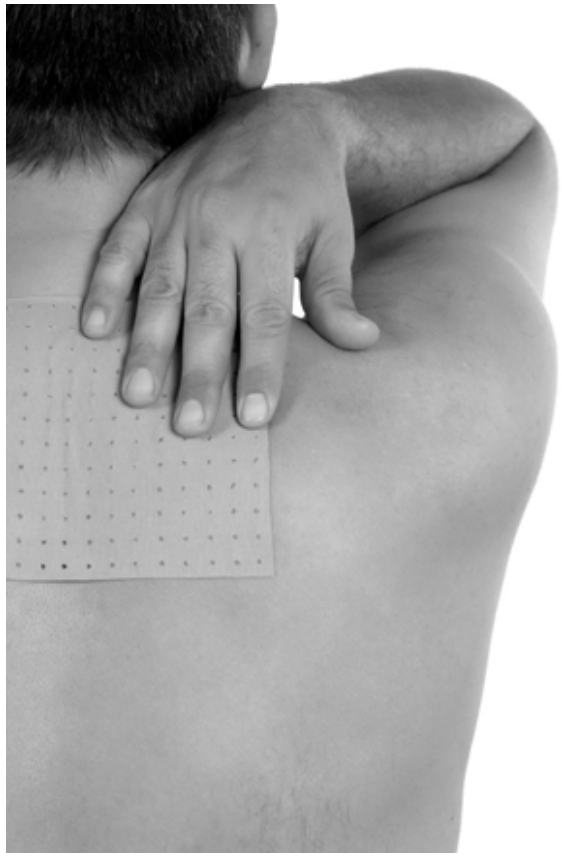
Transdermal Drug Delivery



- Frost and Sullivan – July 2013:

'Among the 15 drug delivery systems surveyed by Frost and Sullivan, Physicians prefer topical delivery, either as a Transdermal Patch or Topical gel/cream, and expressed a willingness to switch their current mode of therapy to one of these available forms'

Major Advantages:

EASE OF USE/APPLICATION

COMPLIANCE

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Transdermal Drug Delivery System (TDDS)

A TDDS comes in patch form and offers an alternative route of administration for drugs that are not ideally suited to oral administration such as:

- First pass metabolism
- Gastrointestinal toxicity or low bioavailability
- Better dose control and less frequent dosing than gels or creams.

Other benefits of TDDS include:

- Thin, flexible, comfortable and moisture-resistant with good adhesion
- Can potentially improve the pharmacokinetics and safety profile of a drug
- Permeation enhancers and other excipients can be included in the formulation to tailor the rate of drug release

Easy Identification
Easy to terminate dosing
Longer duration

Safe administration
Better patient compliance
Patient friendly

Avoid hepatic first pass metabolism
Stable blood level control
Good for narrow therapeutic windows

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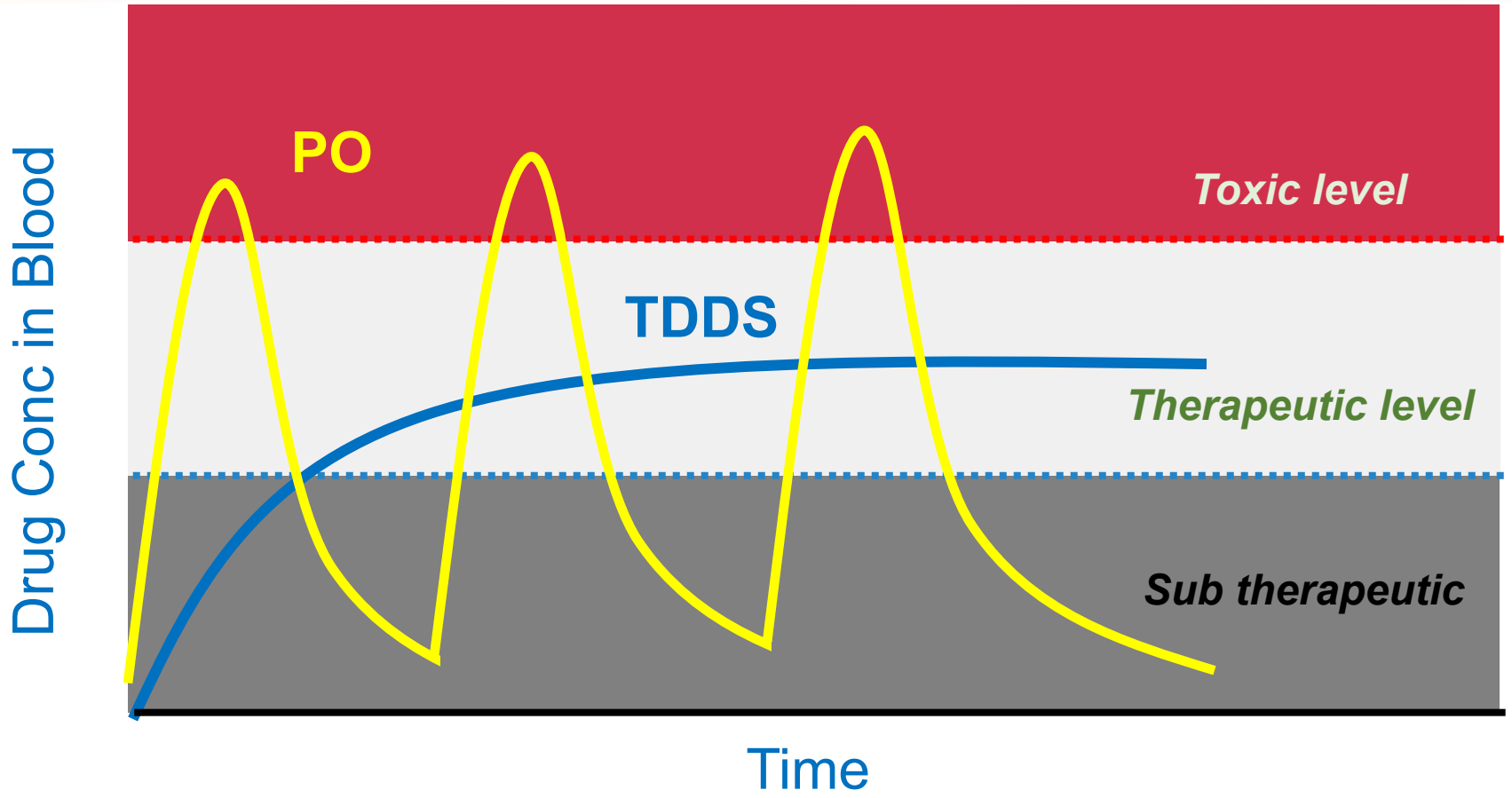
Sustained drug delivery by TDS



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Global Market Has Explored Technologically Advanced Patches

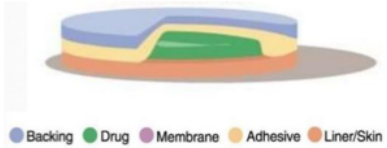
With evolution of technology, the design of patches has improved over the years
Transdermal patches have progressed as follows in terms of technology:

Reservoir technology

- Drug stored in a compartment and released through a permeable membrane
- Disadvantages:
  - Larger in size
  - Challenges with controlled drug release

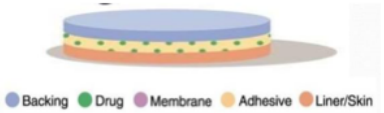
Matrix technology

- The drug is suspended in an internal polymer matrix
- **Improved control of drug delivery**
- **Thinner and more flexible patches with better adherence**



Drug-in-adhesive technology

- The drug is directly included in the adhesive polymer
- **Lighter, thinner and more flexible patches that are more comfortable to wear**



- The research and development efforts have been directed towards improvement in the design of transdermal patches
- **As a result, patches have evolved to provide better control over the drug release and more acceptable products**

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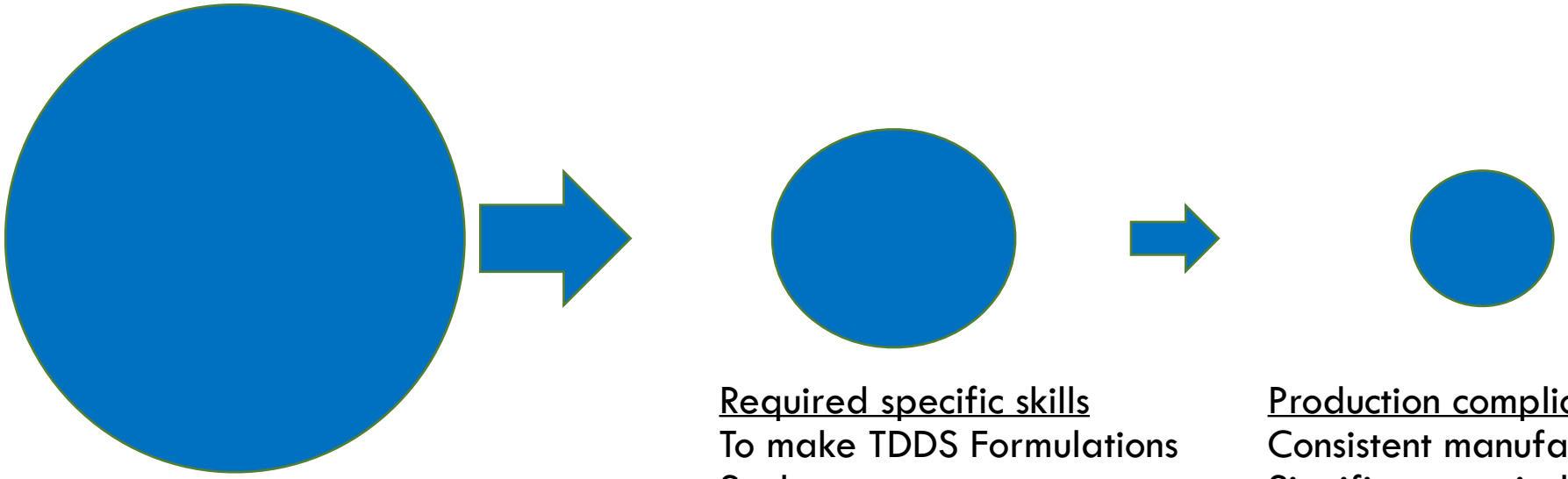
Challenges Facing Transfer of Technology From Bench to Commercial Production

Transdermal patch production is a **niche area** in pharmaceutical industry.

Transdermal Research

Development

Commercial



Required specific skills
To make TDDS Formulations
Scale up
Clinical Studies (Human)
Complicated regulations

Production complications
Consistent manufacturing process
Significant capital investment(Capex)
Product specific manufacturing

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Prominent Players in Global Transdermal Patch Market

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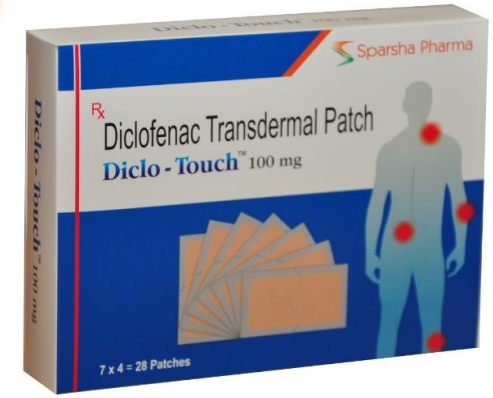
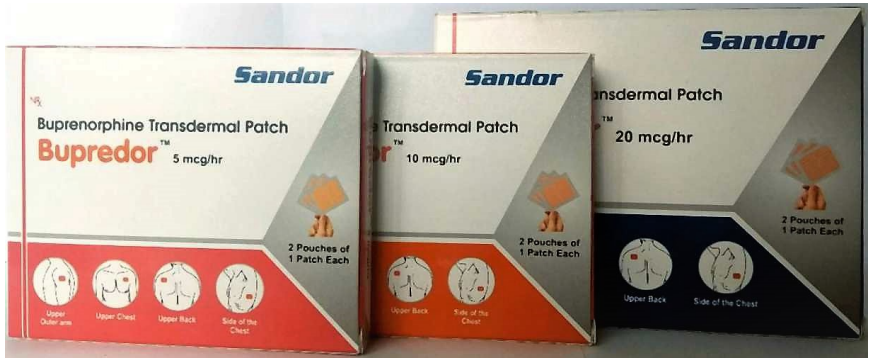
Currently Available Products From Sparsha Pharma, India





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Next Generation Transdermal Drug Delivery

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Structure of the Human Skin

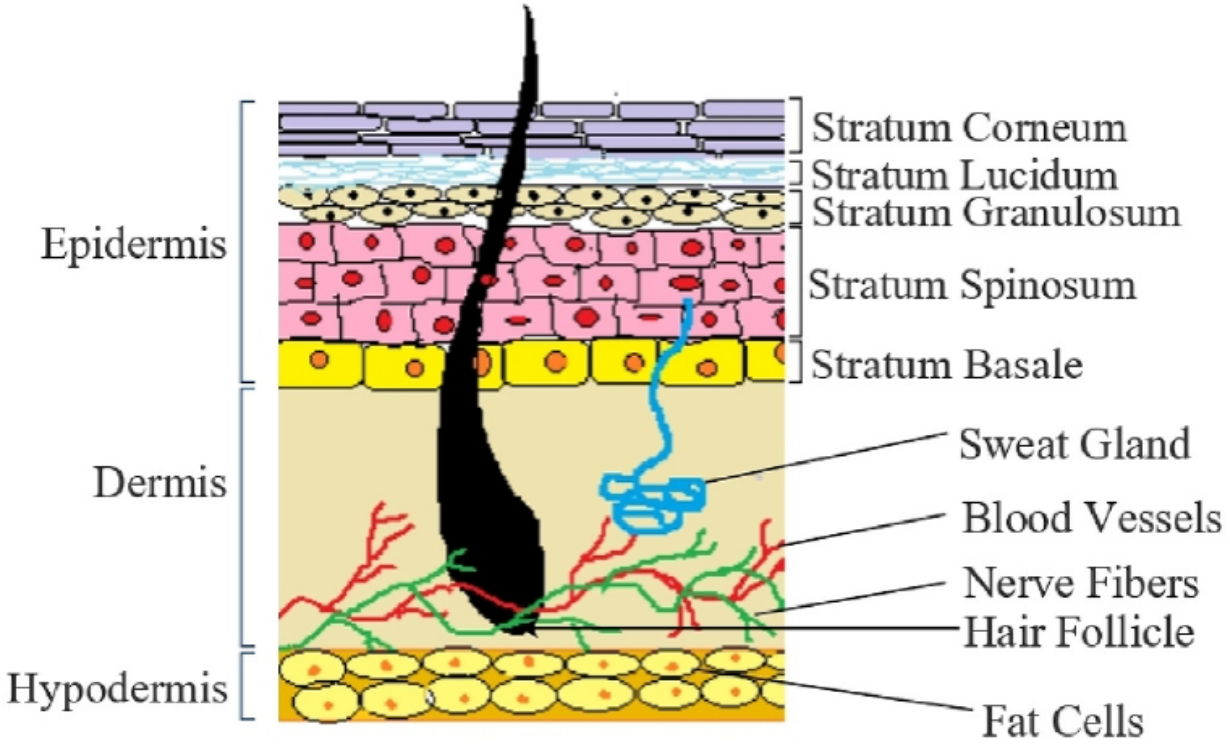

Fig. 1. Human skin structure details.

Azmana, et al, J Drug Deliv Sci Technol, 2020

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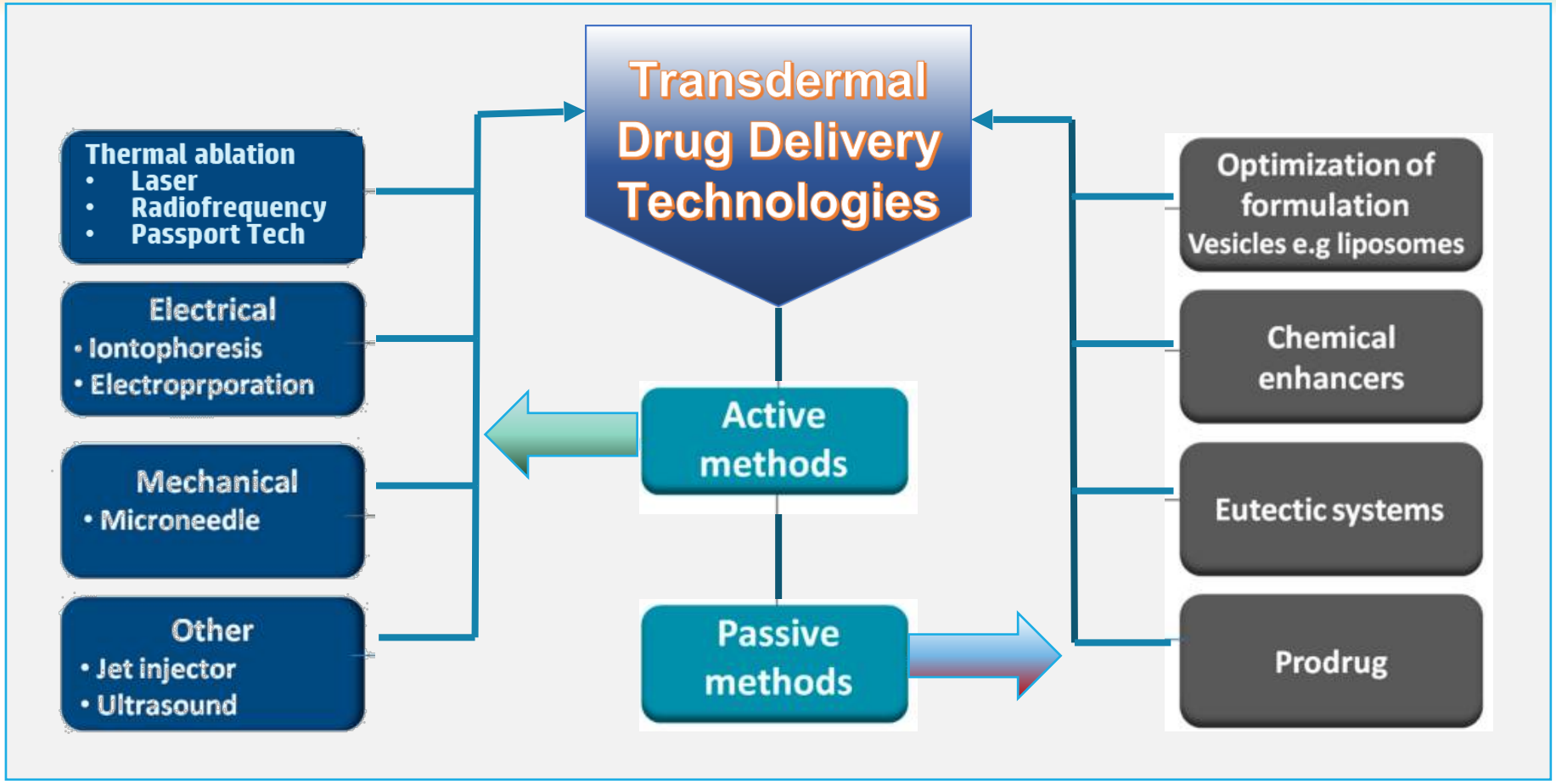
Transdermal Drug Delivery Technologies



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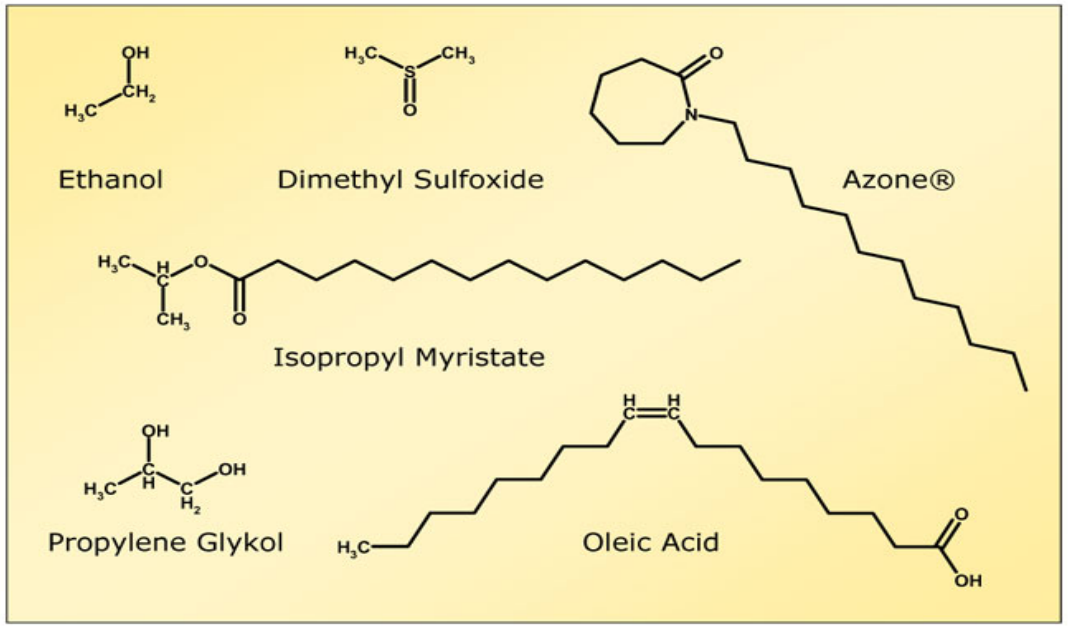
CHEMICAL ENHANCERS

Water
Hydrocarbons
Sulphoxides
Pyrrolidones
Fatty acids
Esters and alcohols
Azone and derivatives
Surfactants
Amides (including urea)
Polyols
Essential oils
Terpenes and derivatives
Oxazolidines
Epidermal enzymes
Polymers
Lipid synthesis inhibitors
Biodegradable enhancers



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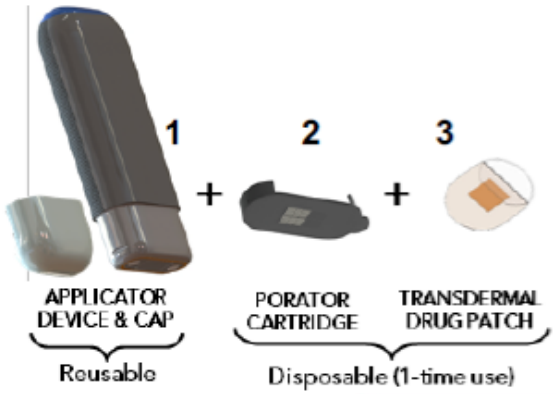
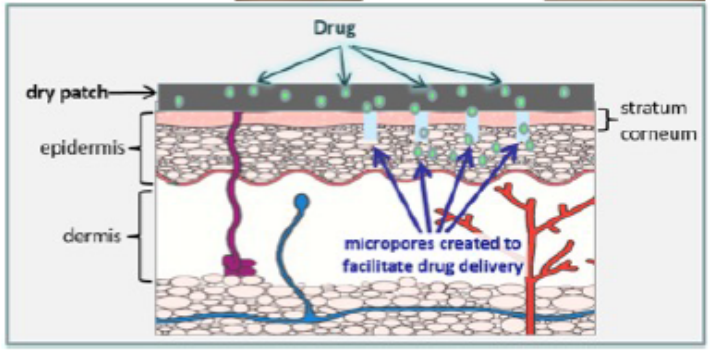
Passport® Transdermal Microporation Technology

PassPort® transdermal platform combines microporation and dry-patch technologies to deliver both small molecule drugs and biologics

- Comprised of a reusable portable device[1] ("Applicator") and a single-use filament array[2] ("Porator") with transdermal drug patch[3]
- Porator **painlessly** creates micropores in the stratum corneum via heat ablation to access the viable epidermis (**no needles**)
- A drug patch is then placed on top of the porated skin and interstitial fluid flows through the pores to dissolve the drug
- Micropores enable dissolved drugs to flow from the transdermal patch, enter the viable epidermis, and then into systemic circulation





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Simple Application and Drug Administration

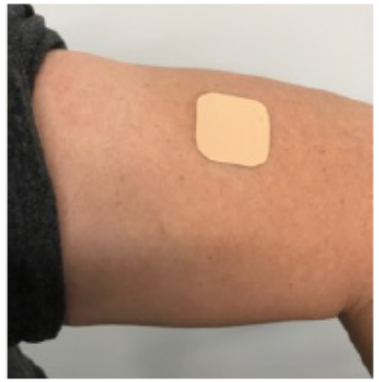
1. A pre-assembled single-use “porator” combined with drug patch is easily attached to the handheld reusable applicator device by the patient or caregiver

2. Pressing the activation button of the applicator releases a pulse of energy to the porator
   - ❖ Stratum corneum is painlessly ablated within milliseconds
   - ❖ Electronic feedback ensures reproducible pores in the skin

3. Drug patch is then applied to “microporated” skin and drug is delivered

① Attach Drug Cartridge

② Apply Device to Skin



③ Drug Delivery Commences

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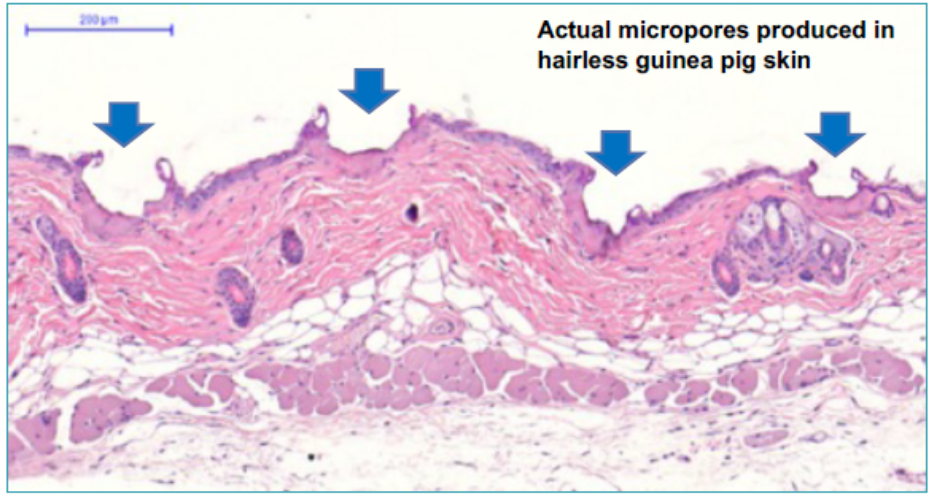
Advantages of Passport Technology

- ✓ Improvement of storage conditions (**room temperature**) using dry patch formulation
- ✓ **At-home therapy**, improved pharmacoeconomics (reduced healthcare costs)
- ✓ Improves therapeutic efficacy with **modified pharmacokinetics**
- ✓ **Reduces systemic side effects** with controlled drug delivery
- ✓ Convenient for patients/consumers (**self-administration**; small discreet patch)
- ✓ **Minimally invasive** (no needle insertion)
- ✓ Reduces needle disposal and **reduces needlestick injuries**
- ✓ Good **patient compliance** (no needle phobia)
- ✓ New feature: **medication adherence control**



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Development of Novel Microneedle Technology

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Advantages of Microneedles

Enhance skin permeability by creating micron-scale pathways

Deliver drugs either as coated material or encapsulated cargo

Primarily target their effects to the stratum corneum

Fabrication methods: sculpting of silicone-based structures or low cost FDA approved metals and polymers.

Microneedles made with water soluble polymers dissolve in the skin and leave no sharp medical waste.

Used to deliver small molecules, proteins, DNA, and viruses

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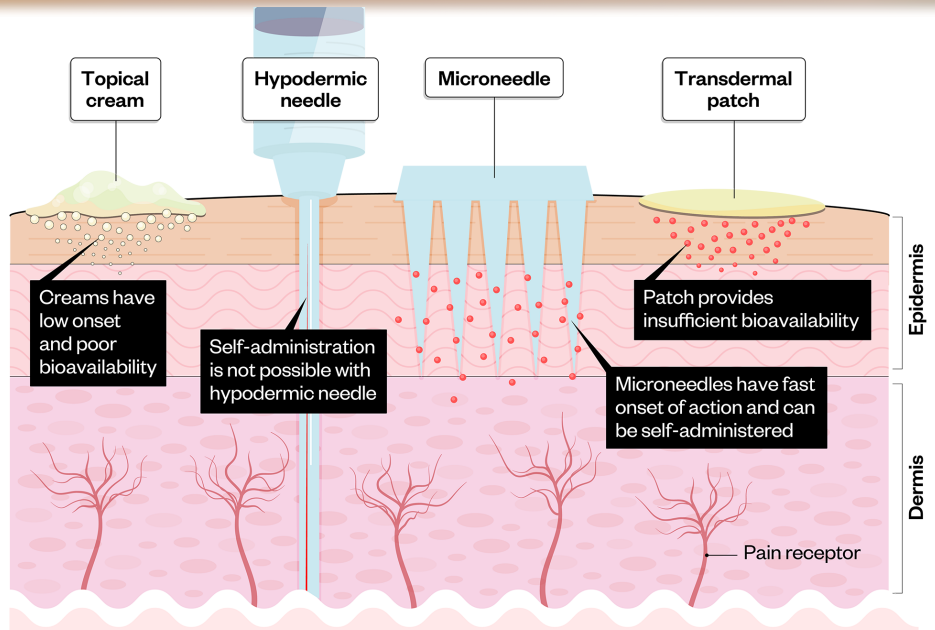
Advantages of Microneedles Over Other Delivery Systems



	Topical cream	Hypodermic needle	Microneedle	Transdermal patch
Onset of action	Slow	Fast	Fast	Slow
Painful	No	Yes	No	No
Bioavailability	Poor	Sufficient	Sufficient	Insufficient
Self-administration	Possible	Not possible	Possible	Possible
Fridge storage	No	Yes	No	No

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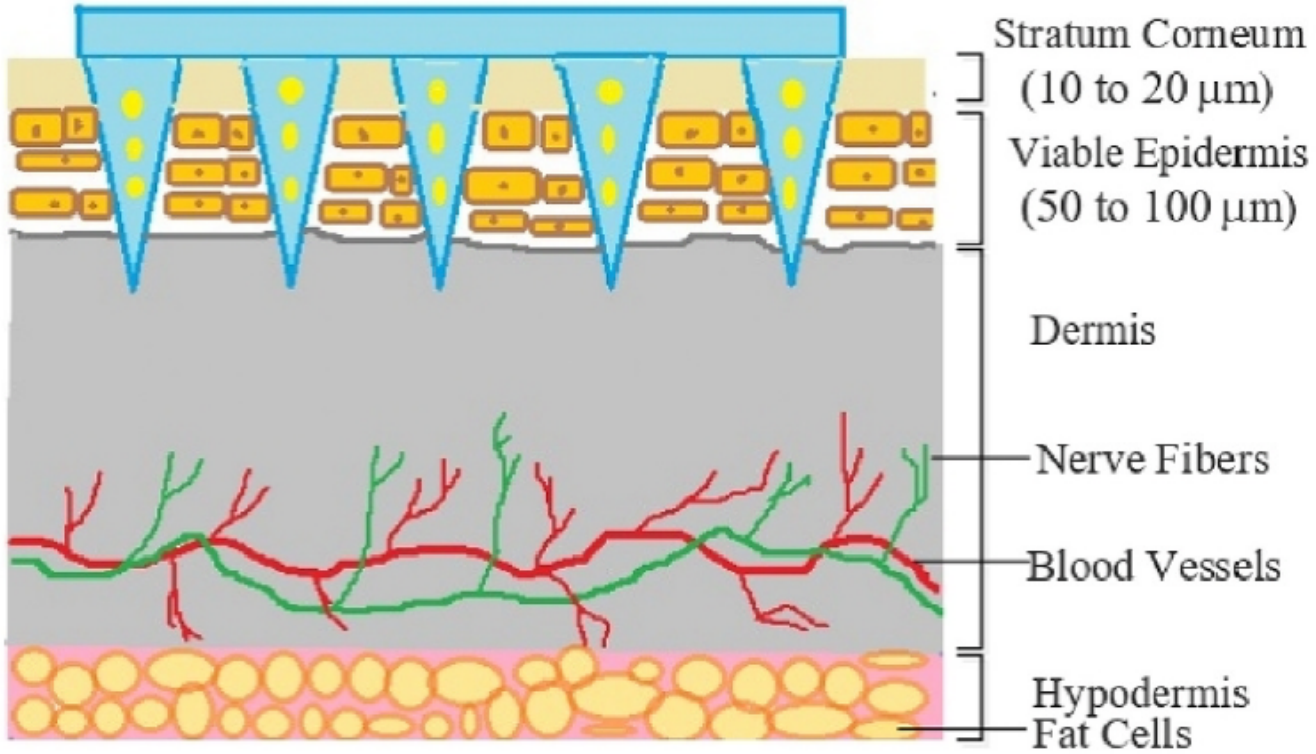
Drug Delivery Across Stratum Corneum By Microneedles



Azmana, et al, J Drug Deliv Sci Technol, 2020

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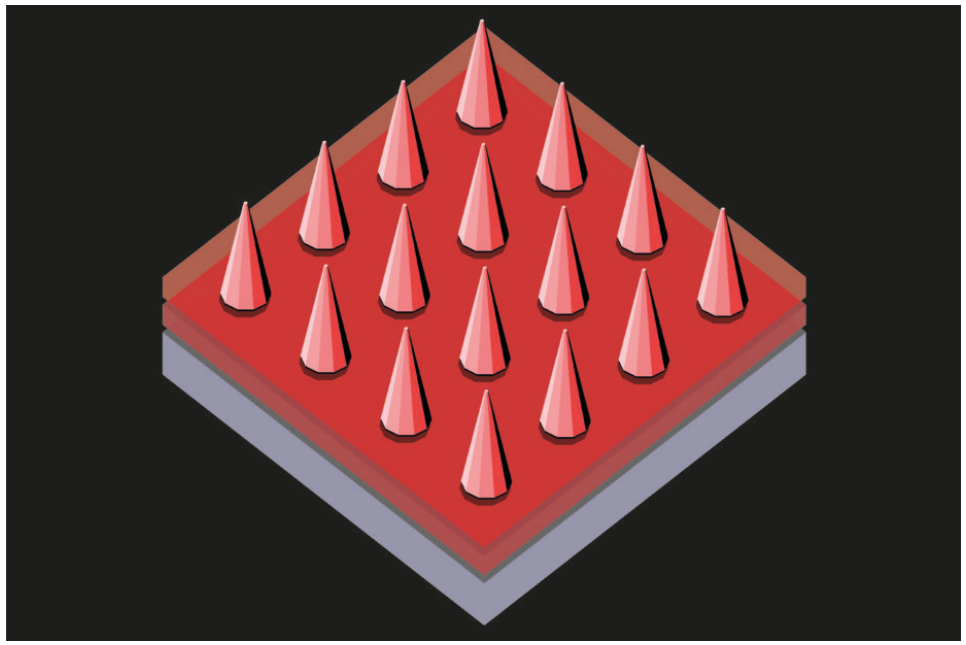
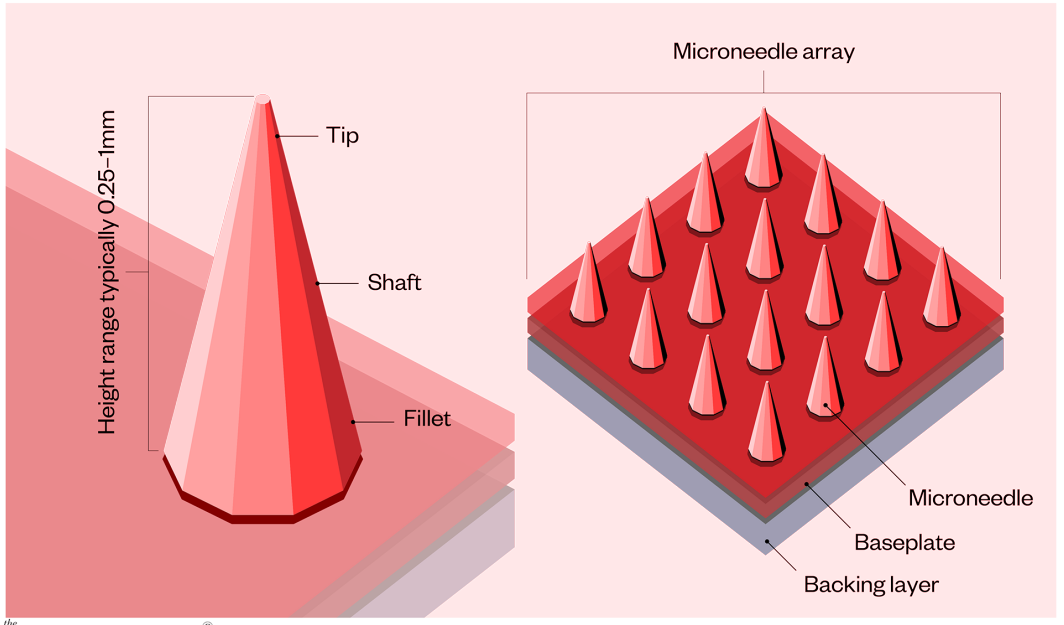
Microneedles are a Hybrid Between a Hypodermic Needle and a Transdermal Patch





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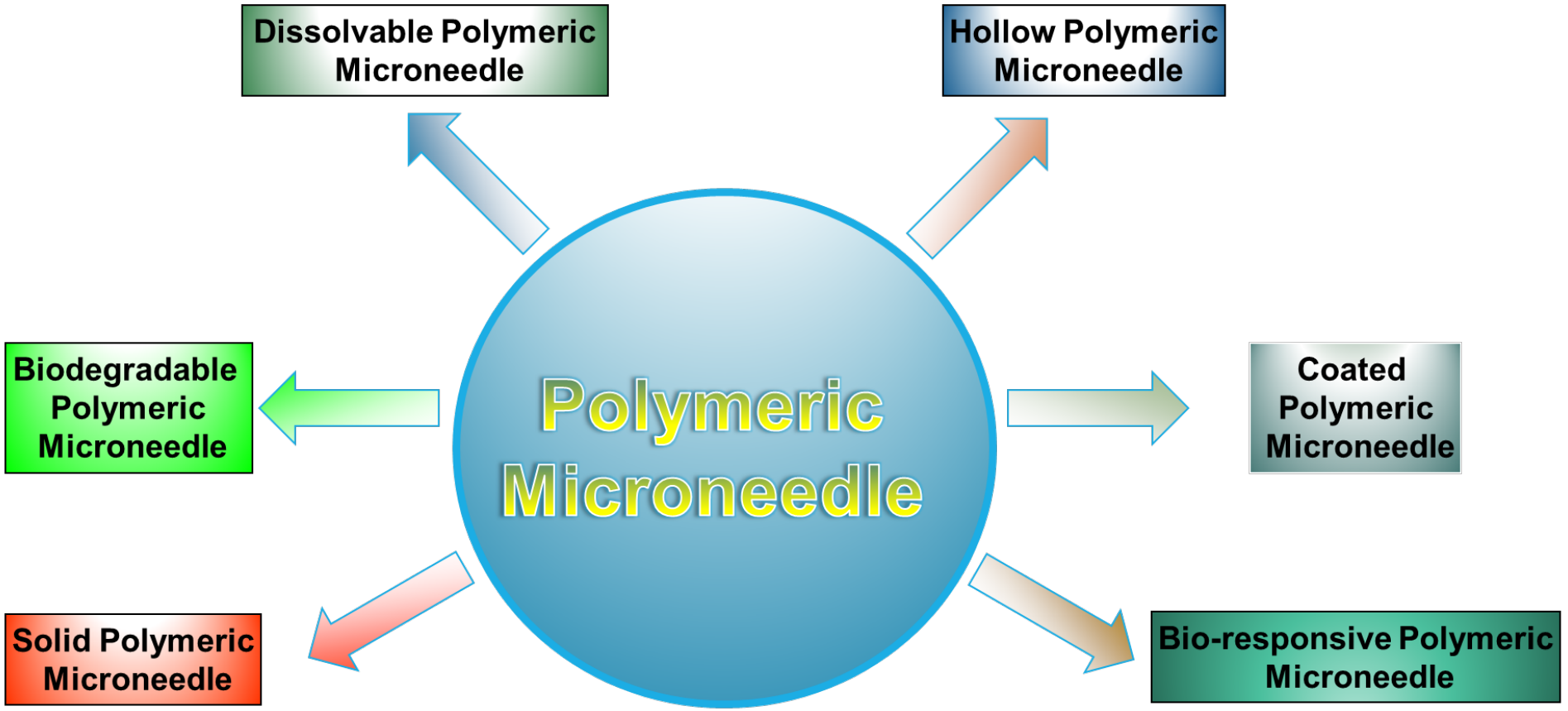
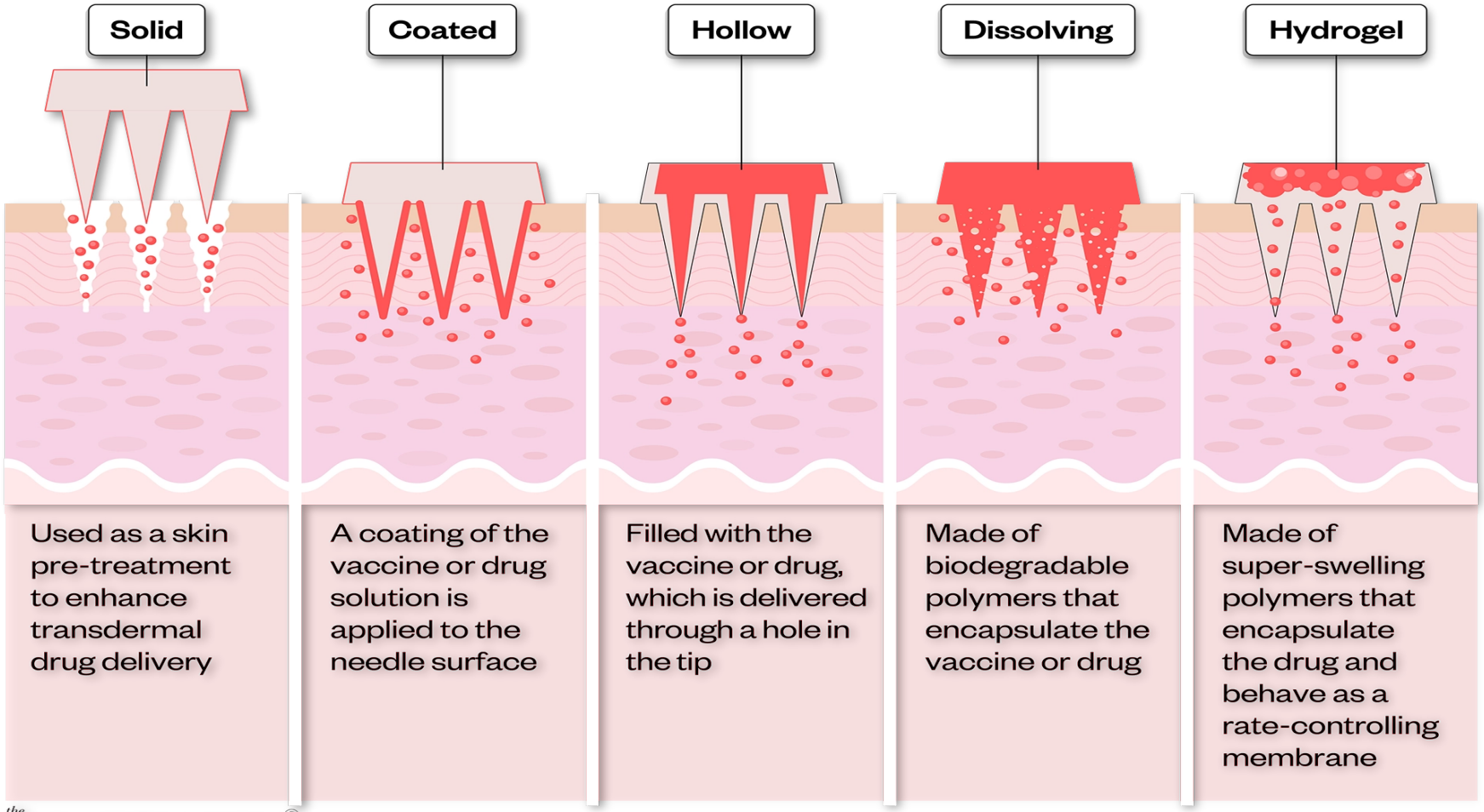
Classification Of Polymeric Microneedles



Classification of Microneedles



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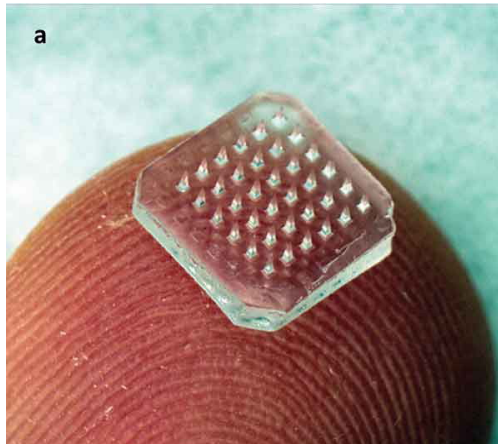
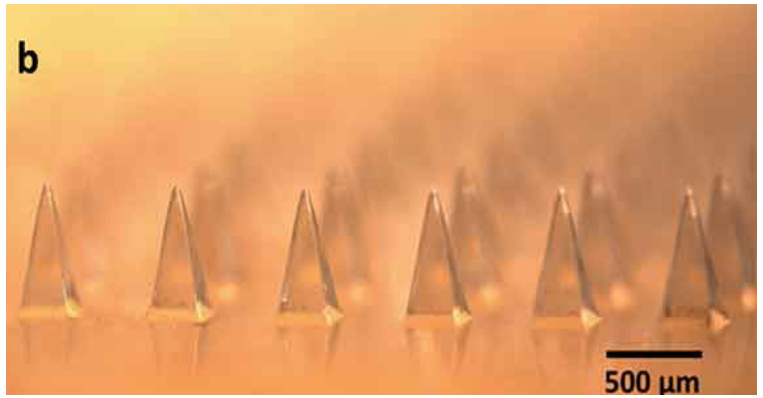
Microneedle Patches

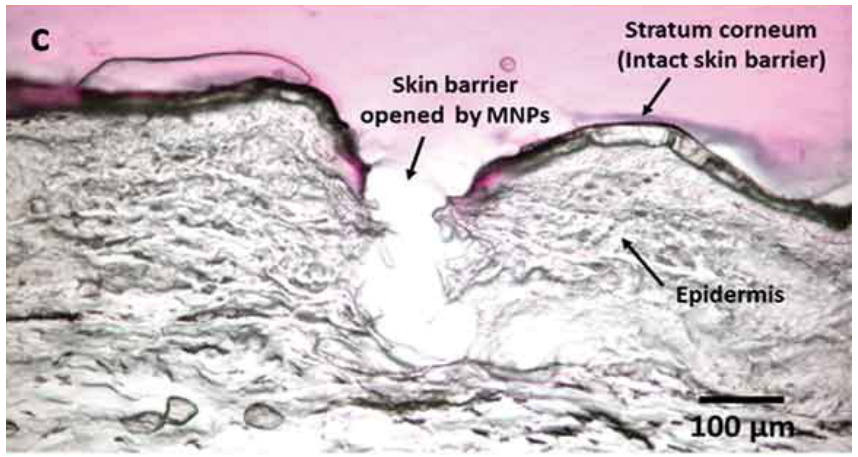
Microneedle Patch



Magnified view



After puncture with a microneedle



(Expert Opin Drug Deliv. 2018;15:541)

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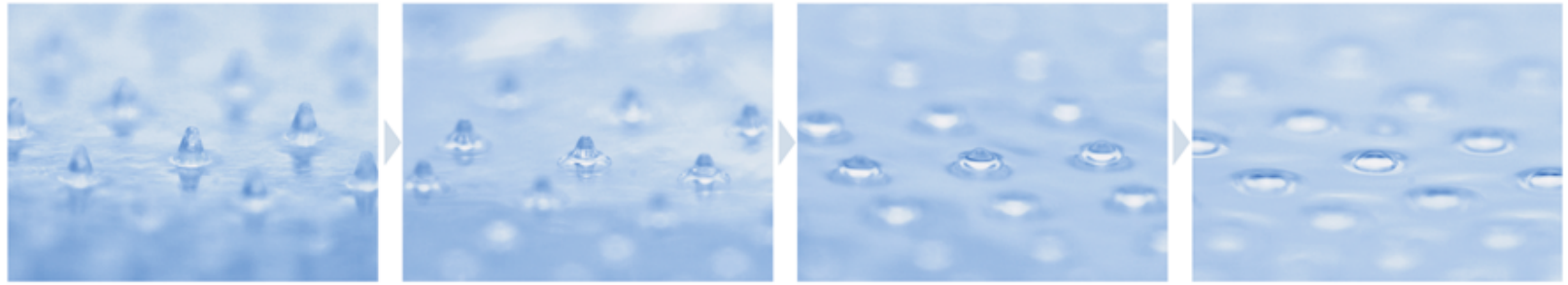
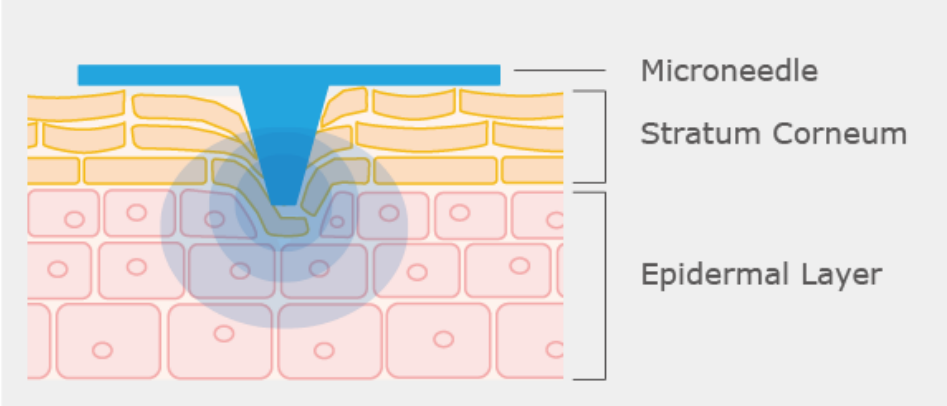
Biodegradable Microneedle Technology



Polymers that dissolve in vivo are blended with APIs and molded into the shape of fine needles. They can be placed directly on the skin.



By Nissha Co., Ltd.

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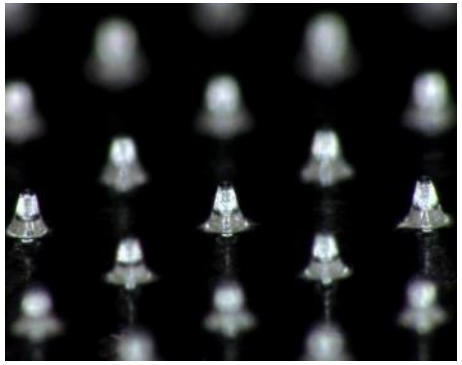
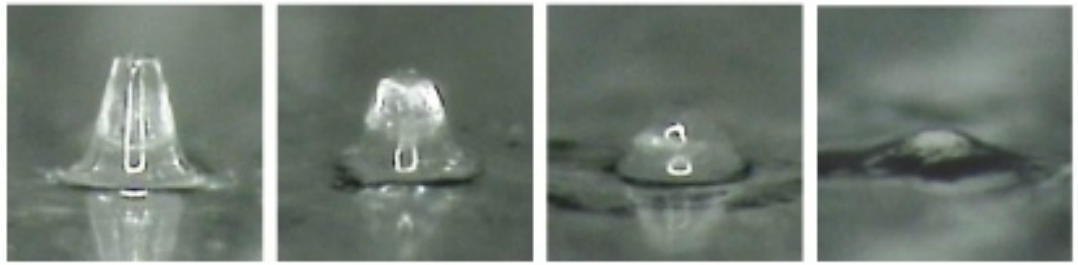
What is a Dissolving Microneedle Patch?

Sheet Consisting of Needles



Enlarged View of the Surface

The dissolving Microneedle patch is a **sheet consisting of fine needles** made with **dissolvable polymers** such as hyaluronic acid. It is an application of cutting-edge Transdermal Drug Delivery System technology developed by Nissha.



Dissolving Change Over Time

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Target Positioning in Beauty Care Methods

"Cutting-Edge Cosmeceutical Item" and "Safer Medical-like Treatment at Home"

Effect HIGH

Medical Cosmetic Treatment

Microneedle Patch

HIGH Safety

Conventional Cosmetic Dosage Forms (eg. Liquid, emulsion or mask)

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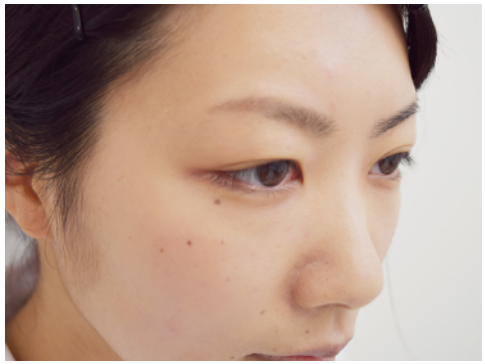
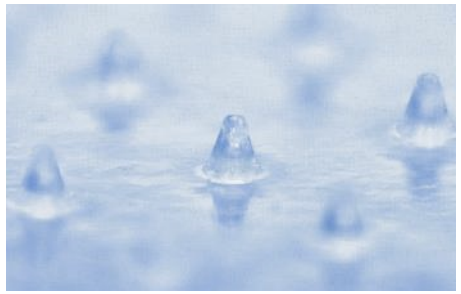
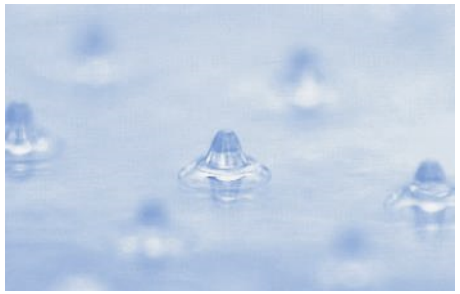
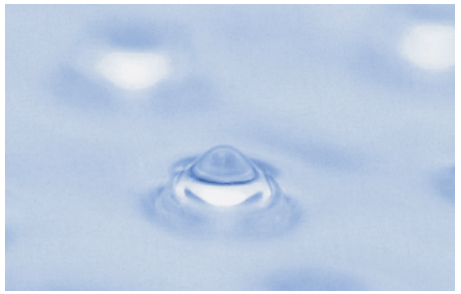
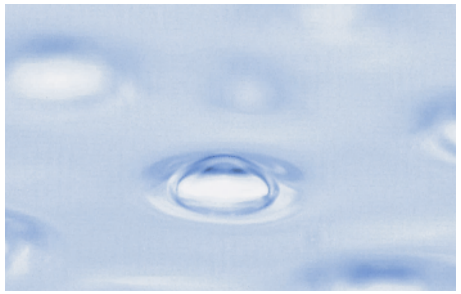
Application of Microneedle patches

Microneedle's are gradually dissolved by moisture inside the skin.
It takes about 5 hours on average to completely dissolve.

Attach **Sleep** **Peel off next morning**





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Efficacy Evaluation of Basic Formulation

Improvement on Wrinkles at the Outer-corner of Eyes

Week 0

Week 4

[Conditions]

Product: Standard MNP Type

Subjects：female / 40's

Period of Use：Twice a week for 4 weeks

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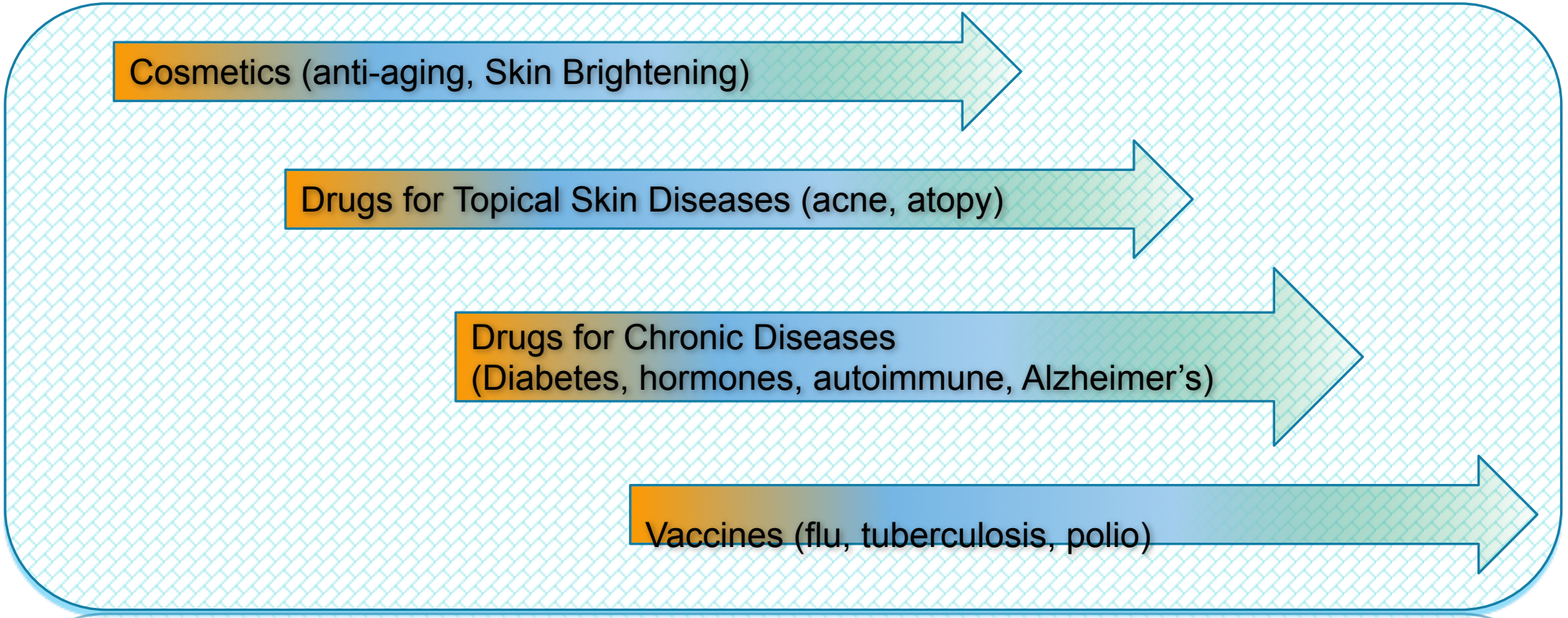
Road Map for Microneedle Technology



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Regulatory Challenges for TDS Development

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FDA Approval Process

New Drug Application (NDA)	Abbreviated New Drug Approval (ANDA)
Safety: Toxicity Studies • Skin Irritation • Cutaneous Toxicity • Contact Sensitivity • Contact Photodermatitis	• • Skin Irritation • Cutaneous Toxicity
Efficacy: Clinical Studies • Bioavailability • Adhesion	Pharmacokinetic Equivalence • Bioequivalence Studies • Adhesion
Manufacturing Controls	Manufacturing Controls
In Vitro Release Studies	*In Vitro* Release Studies

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Requirements for FDA Approval

Clinical Concern	Quality Aspects
Adhesion to skin	• Selection and quality control of raw materials (particularly adhesives)
Irritation / Sensitization of skin	• Selection of raw materials and APIs

Effectiveness / Bioequivalence	• Uniformity (robust manufacturing process)
	• In vitro release testing
	• Stability (comparative clinical endpoint studies typically are performed on fresh batches, not on aged batches)
	  • Adhesive property change and cold flow
	  • Drug crystallization
	  • Delivery profile change
	  • Drug-substance / excipient migration

Safety	• Impurities of toxicological relevance
	  • Adhesive impurities (monomers, catalysts, crosslinkers, etc.)
	  • Extractables and leachable
	• Residual drug (accidental or environmental exposure, abuse)
	• Heat influence (e.g., application of a heat pack)
	• Proper labeling of each system

Patient Use	• Release liner peel • Product design

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Q&A

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