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Manufacturing in Miniature: Drug Delivery via Microneedle Array Patches (MAPs)

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Introduction

- Microneedle array patches (MAPs) are a rapidly emerging platform for intradermal delivery of drugs and vaccines
- MAPs have potential advantages over the needle and syringe in that they:
  - Provide a simple and consistent means to deliver drugs and or vaccines intradermally
  - Provide a non-threatening and minimally invasive format with good patient acceptance
  - May be a dose sparing route for some drugs and vaccines
  - Enable targeting of dendritic cells and Langerhans cells within the skin to trigger a more robust immune response to some vaccines
  - May provide better stability than standard liquid formulations, potentially reducing or eliminating cold chain storage requirements
- However, the significant advantages of MAPs have been difficult to fully realize because of the challenges in developing scalable manufacturing processes
- Kindeva has developed phase appropriate manufacturing processes for solid coated MAPs that extend from lab scale through pilot scale and on to a commercial scale. The first commercial line has the capability to manufacture 14 million units per year. In this work, we will describe this scale-up process, the critical quality attributes for solid coated microneedles, and describe some methods and data on dose uniformity from batches made at scale.

Discussion

- MAPs can be categorized into four major groups:
  - Solid coated MAPs which contain droplets of drug or vaccine formulation on the tips of solid (e.g., polymer) microneedles
  - Hollow MAPs which enable fluid delivery through microneedles containing a lumen
  - Dissolvable MAPs which enable drug release by dissolution after insertion into the skin
  - Hydrogel MAPs, a newer category, which may enable sustained release from swellable hydrogel microneedles
- Solid coated MAPs (see Figure 1) will be the focus of this poster

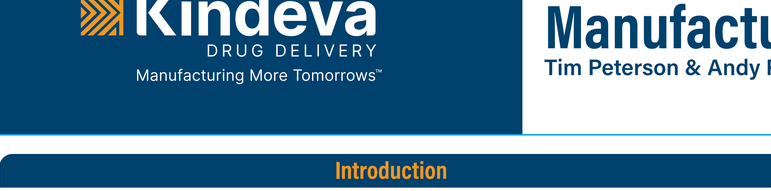


Figure 1: Solid Coated MAP Array, Patch and Applicators

- Processes were developed for the manufacture of solid coated MAPs utilizing a phase appropriate approach to scale-up (see Figure 2)

	Lab Bench	Pilot Scale	Commercial
Methodology	Manual Assembly, 3D Printing	Prototype Tooling, Fixtures and Minimal Automation	Commercial Tooling, Automation, In Process Testing
Drug/Device Product Lot Size	10-100	1,000-15,000	15,000-150,000+
Clinical Phase	Preclinical	Preclinical and Phase I/II Clinical	Phase III Clinical

Figure 2: Typical Scale-Up Pathway for Microneedle Products

- During scale-up, Quality by Design (QbD) principles are used to ensure that the process can repeatably produce the desired quality attributes in the product
- The quality target product profile (QTPP) is a prospective summary of the quality characteristics that will ideally be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product[1]

- For microneedle products, the typical elements of a QTTP are shown in Table 1

Drug product type	Therapeutic indication	Target population	Intended use case
Target dosage and dosing frequency	Dose presentation	Desired site of application and duration of wear	Target PK profile
Packaging requirements	Stability requirements	Target market(s) and cost	

Table 1: Typical Elements of a QTPP for a Solid Coated Microneedle Product

- The critical quality attributes (CQAs) are the physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality[1]
- For solid coated microneedle products, the typical CQAs are shown in Table 2

Physical	Microbiological	Biological	Chemical
Needle Dimensions/Morphology	Microbial Limits/Sterility	Bio-compatibility	Identity
Mechanical Strength	Particulates		Assay
Puncture Performance			Dissolution
Package Integrity			Disintegration
Patch Adhesion			Content Uniformity
			Excipient Content
			Impurities

Table 2: Typical CQAs for a Solid Coated Microneedle Product[2]

- Development of a process that reproducibly generates finished product that meets the desired CQAs is dependent on identifying, understanding, and controlling the Critical Process Parameters (CPPs) impacting the CQAs. Examples of CPPs for solid coated microneedle products include decontamination cycle parameters, filtration pressure, coating parameters, and sealing parameters to name a few.

Results

- By modifying the coating parameters, the coated mass (content) can be adjusted to meet the desired target. Larger droplets are formed by dipping the microneedles deeper into the coating solution, resulting in higher content. Microneedle height and spacing also affect the array content.
- Arrays with a diameter of 1.27 cm containing microneedles of 250-, 500-, or 700-micron in length containing 1,288, 316, or 196 microneedles, respectively, were precision coated with PVP formulation to produce various droplet sizes. The results are shown in Figure 3 as droplet size in terms of droplet length and width (x-axis) and mean (blue circles) PVP formulation content.

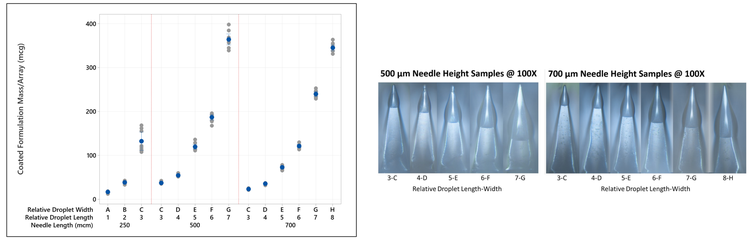


Figure 3: Impact of Droplet Size and Array Configuration on Array Content (images of coated needles shown on the right)

- In a further example, a microneedle product containing abaloparatide was scaled-up for treatment of osteoporosis. Batch sizes up to 15,000 units were produced under low bioburden conditions for clinical studies using Kindeva's pilot scale coating equipment. An image of the coating isolator and through batch content uniformity data is shown in Figure 4.

GMP Pilot Coating Isolator

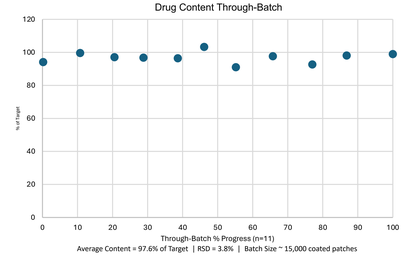
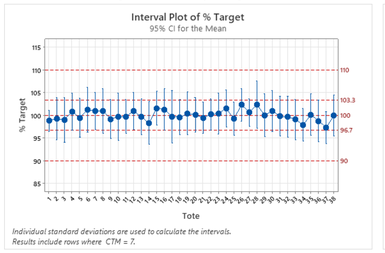


Figure 4: Pilot Scale Coating Process – Through Batch Uniformity

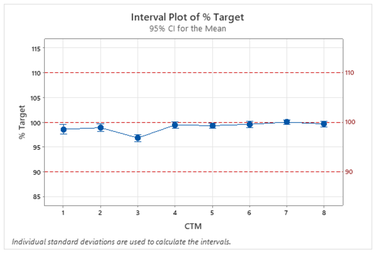
- The same product was then scaled-up and transferred to a commercial facility. Eight more batches were produced at the commercial site with a sterile claim. In total, >200,000 patches were produced to support Phase III studies. Figure 5 shows the through batch and batch-to-batch content uniformity achieved at the commercial site.

Drug Content Uniformity Through-Batch



Individual standard deviations are used to calculate the intervals.
Results include rows where CTM = 7.

Drug Content Uniformity Batch-to-Batch



Individual standard deviations are used to calculate the intervals.

Figure 5: Commercial Scale Coating Process – Content Uniformity Data

- In preparation for commercial launch, the process was further scaled to an aseptic coating isolator capable of simultaneous coating of nine patches at a time, and with an annual capacity of 14 million patches; Figure 6 shows two images from the fully automated line

Trays Containing Sterile Array Patches Placed on Conveyor

Patches Removed From Tray for Coating

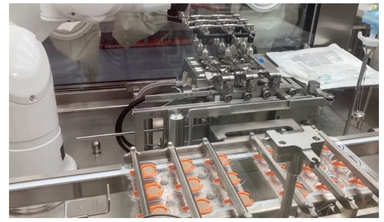


Figure 6: Images of Commercial Scale 9-Up Coater

Conclusions

- QbD principles have been used to develop and scale-up a process for the manufacture of solid coated microneedle patches
- Phase appropriate processes have been developed at the lab, pilot, and commercial scale. The commercial scale process is highly automated and is designed to manufacture sterile microneedle arrays. Multiple lines can be implemented to increase capacity, as necessary.
- Solid-coated MAPs are an exciting new dosage for intradermal delivery and now also have a demonstrated pathway to commercial manufacturing.

References

[1] ICH Q8
[2] MAP Regulatory Working Group