

ADVANCED DELIVERY DEVICES

The AdminPen™ Microneedle Device for Painless & Convenient Drug Delivery

By: Vadim V. Yuzhakov, PhD

AdminMed is developing an innovative line of novel microneedle-based transdermal drug delivery devices. The current pipeline comprises an advanced microneedle array-based pen-injector device (the AdminPen™) that painlessly and conveniently injects therapeutic levels of standard liquid pharmaceutical drugs or cosmetic actives through the skin. This breakthrough technology revolutionizes the way in which medicines can be administered, increasing efficacy, safety, and compliance.¹⁻³

Previous studies have demonstrated that a wide range of pharmaceutical compounds can be delivered using microneedle arrays, including small molecules, peptides, and proteins.⁴⁻¹⁶ Studies with many subjects have shown that the microneedle arrays are essentially painless and have no adverse side effects.^{4,6,17} Nevertheless, the earlier developed microneedle technologies are not well suited for commercialization because of very high manufacturing costs due to use of exotic fabrication techniques, need for significant changes in drug formulations due to their inability to deliver standard liquid drug formulations, and therefore unclear and lengthy regulatory approval processes.

AdminPen is expected to be classified as a Class II medical device with a 510(k) regulatory approval route and can be economically produced to scale using mature high-volume low-cost processes. The injection of vaccines (influenza, HIV, cancer, smallpox, and anthrax), hormones (PTH and hGH), insulin, obesity-management drugs (leptin, liraglutide), and cosmetic dermal fillers (hyaluronic acid and PMMA micro-spheres) would be excellent initial indications for this device.

The system substantially mimics a conventional liquid-reservoir microneedle transdermal patch that can be attached to a standard syringe. One substantial difference from a standard transdermal patch is that this innovative AdminPen drug delivery device will have the ability to deliver large amounts of a drug in a short period of time similar to a standard injection with a hypodermic needle. By comparison, conventional transdermal patches deliver only a small fraction of the pharmaceutical ingredient incorporated in a transdermal patch. In addition, the technology can deliver therapeutic levels of pharmaceutical drugs in 10 to 60 seconds versus the 1 to 2 hours needed for the currently marketed transdermal patches. Existing transdermal patches are limited to using only a very few (less than 10 compounds are currently being delivered in drug patches), small molecule (< 500 Daltons), lipophilic drug formulations that can cross intact skin at a flux sufficient to be clinically useful.

BACKGROUND - MICRONEEDLE ARRAYS

Several methods have been recently proposed for making small pores in the stratum corneum to overcome its barrier properties. In particular, several companies, including 3M, NanoPass, Zosano, TheraJect, and Corium, as well as academic groups at the University of California and at the Georgia Institute of Technology, have been working on the development of microneedle arrays that would make a large number of tiny holes in the stratum corneum.

These known microneedle arrays generally fall into one of three design categories: (1) microneedles with a central hollow bore that are similar in shape to conventional hypodermic needles but much smaller (3M and NanoPass); (2) solid microneedles coated with a special pharmaceutical drug formulation (Zosano); and (3) solid biodegradable microneedle arrays that have a drug encapsulated in the dissolvable microneedle material (TheraJect, Corium).

Hollow microneedles with a central

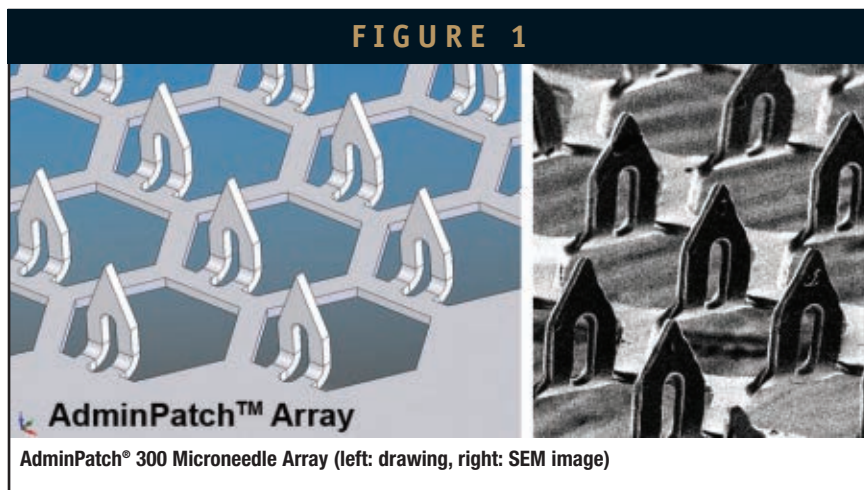
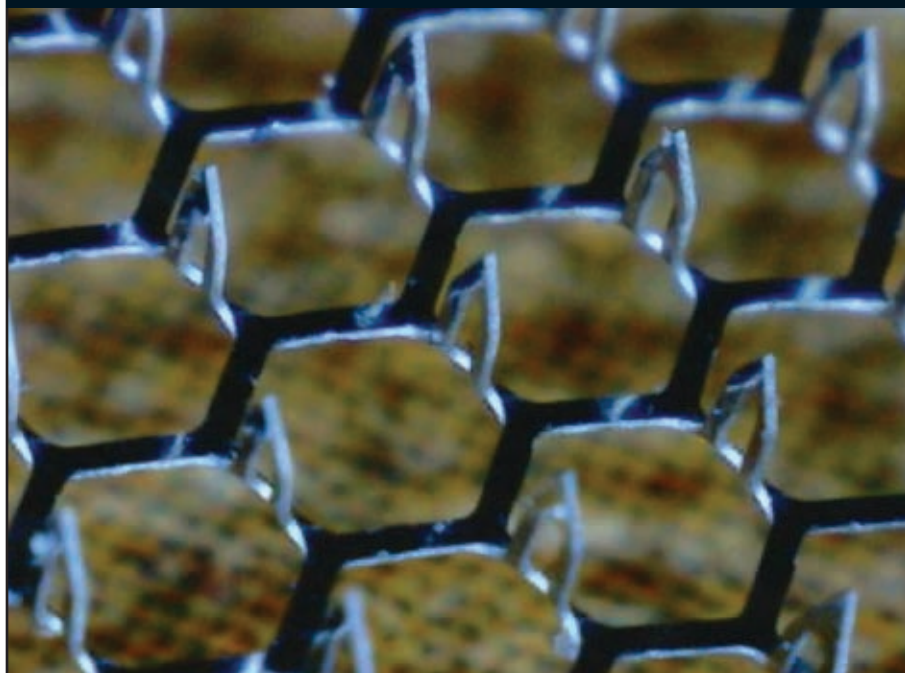


FIGURE 2



AdminPatch® Microneedle Array

bore are expensive to make and require exotic and expensive microfabrication methods. In particular, it is difficult to make sharp tips on hollow microneedles. Consequently, insertion of the microneedles into a patient's skin can be difficult and often painful. In addition, the central bore of the microneedle is quite small and may be easily plugged by skin tissue during the insertion process, thereby blocking the drug delivery conduit. Furthermore, because the length of microneedle central bore is much greater than its diameter, the diffusional transport of the drug through the central bore may be unacceptably slow. It may be even slower than the diffusion of the drug through the stratum corneum in the absence of the microneedle. To our knowledge, only two companies were able to fabricate hollow microneedle arrays. NanoPass fabricated silicon micro-pyramids with internal lumen using an exotic microfabrication technology, and 3M made samples of plastic microneedle arrays using its proprietary technology.

Solid microneedle arrays are essentially

arrays of projections that are used to make holes in the stratum corneum. Since 1996, Zosano (previously a part of Alza Corporation) has developed a method of depositing a drug directly on the surface of these solid microneedles. However, the deposition process is unreliable, and the thin layer of drug formulation on the microneedle could be easily chipped off during storage, transport, or administration (insertion) of the microneedles. Although demonstrated on a laboratory scale, the high-volume microneedle coating process itself is very complex, unreliable, and expensive. Application of a thicker and stronger layer of drug formulation was found to be undesirable because it reduced the sharpness of the microneedles and therefore made insertion more difficult and painful. Zosano even disclosed a special insertion device because patients were unable to insert the microneedle array by themselves without it. Most importantly, the drug-coated microneedles require completely reformulating the drug that leads to long

product development timelines; very expensive and long-term clinical efficacy, drug toxicity, and stability studies; as well as an unclear regulatory approval pathway.

Biodegradable microneedle arrays are made of a material that encapsulates the drug and dissolves when inserted into skin. This approach also requires completely reformulating the drug. In addition, there exist significant technical difficulties and risks in designing a biodegradable material that would be strong enough for inserting into the skin without breakage and would be compatible with a specific drug. And of course, a completely new microfabrication method should be developed for making such arrays in high volumes. Moreover, such biodegradable microneedles arrays would be subject to even more intense scrutiny from the FDA that would lead to even longer product development process.

Also, the skin of a patient is quite flexible. Thus, it may be difficult for other microneedle arrays having a rigid, planar substrate to be inserted uniformly into skin during the application step when the microneedles in the central area of the array may not have sufficient engagement with deformed concave skin tissues. For example, a microneedle array having a base made of silicon is flat and inflexible, and even though a polymeric or metal microneedle base can be slightly bent in one direction, such arrays of microneedles cannot readily be applied to concave skin surfaces formed during the insertion step. The microneedle array may need to have a convex shape to ensure uniform insertion of all microneedles into the skin during the application step.

It therefore would be desirable to provide a microneedle array for drug delivery that avoids the disadvantages associated with known solid and hollow microneedle array designs as well as can be flexed and stretched to better conform to a convex, contoured, or moving surface. In summary, there is an unmet need for a painless, effective, user-

ADVANCED DELIVERY DEVICES

friendly, simple, and inexpensive technology for transdermal delivery of a variety of already approved standard liquid pharmaceutical drugs to a patient.

ADMINPATCH® MICRONEEDLE ARRAY IS REFINED MICRONEEDLE TECHNOLOGY

AdminMed has developed the patented Advanced micro-needle array (AdminPatch® Array), which painlessly and instantaneously forms hundreds of tiny micropores through the stratum corneum and epidermis. Numerous drugs, including proteins and water-soluble molecules, can enter the body through these micropores for local effect or by entering the circulation for systemic effect. The created aqueous channels stay constantly open while the AdminPatch array is applied on the skin, and therefore enables the rapid, sustained, and efficient delivery of drugs through these aqueous channels formed in the skin surface. When the microneedle array is removed from the skin, the micropores simply collapse, and the skin barrier is quickly restored.

The human skin has three distinct layers: the outer layer (stratum corneum), having a reported thickness of between 10 to 30 microns; the viable epidermis, containing sentinel cells of the immune system; and the dermis, within which are capillaries and various trauma-sensing receptors.

The aqueous channels formed by the microneedles in the stratum corneum using the AdminPatch system have a depth of about 100 to 1000 microns, sufficient to extend through the viable epidermis into the dermis to reach blood capillaries but shallow enough to avoid most pain receptors.

AdminMed has completed studies that show that while the AdminPen microneedle devices are kept applied on the skin, the micropores formed by microneedles allows injection of drug or any other liquid from an attached syringe into the underlying tissues.

FIGURE 3

AdminPen™ Microneedle Pen-Injector Device



MICRONEEDLE-BASED ADMINPEN™ PEN-INJECTOR DEVICE

AdminPen™ pen-injector device is based on our own patented proprietary microneedle

array technology called AdminPatch microneedle array (covered by US Patent No. 7,658,728 and Patents pending in the US and other countries). A simple low-cost molded plastic part is simply attached on the back

TABLE 1

Addresses Unmet Patient Needs	AdminPen
Painless	YES
Simple, intuitive operation	YES
Compatible with a standard syringe	YES
Eliminates sharps hazards	YES
Attractive to Pharma Partners	AdminPen
510(k) regulatory approval strategy	YES
Existing drug formulation	YES
Low-cost high-speed manufacturing	YES
Uniformly inserted into flexible skin	YES

AdminPen™ Competitive Advantage

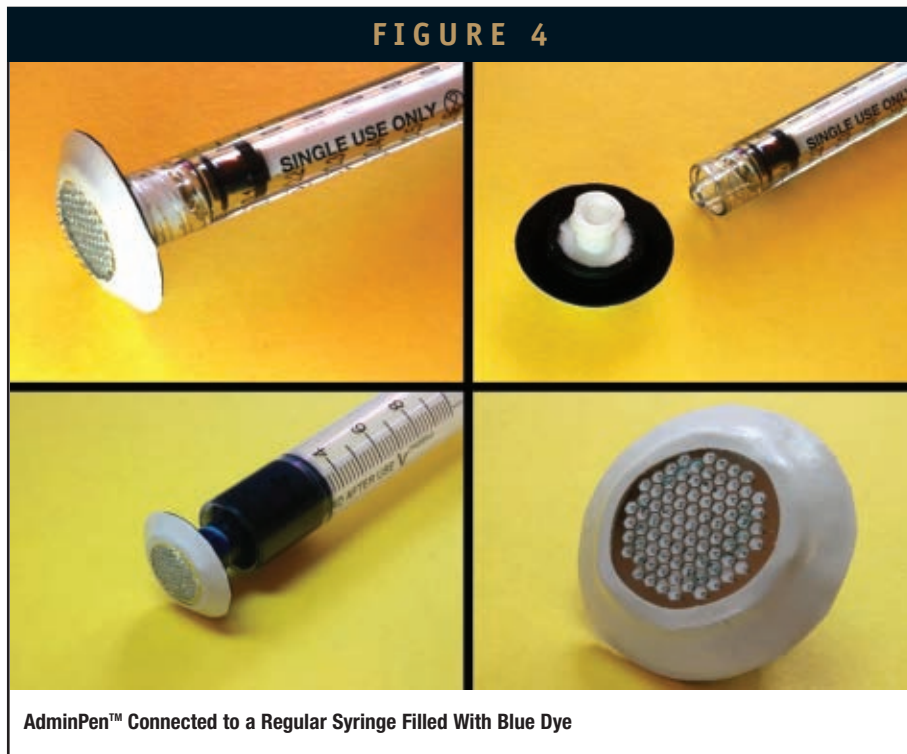
ADVANCED DELIVERY DEVICES

surface of the AdminPatch microneedle array to provide a fluidic connection of AdminPen device to an externally connected liquid drug reservoir. The AdminPen pen-injector device can be mounted on any commercially available standard syringes or injector pens with a prefilled drug cartridge. The AdminPen needle substitute should be an excellent fit for user-friendly and painless delivery of vaccines (influenza, smallpox, anthrax); cosmetics (hyaluronic acid, Botox); or pharmaceutical drugs requiring frequent injections, such as parathyroid hormone, human growth hormone, obesity-management drugs (leptin, liraglutide), anemia drugs (epoetin alfa), and pre-meal insulin. The device is expected to be classified as a Class II 510(k) medical device. During each injection, the drug is uniformly injected into a 1-cm² area of the skin.

Clinical benefits of the AdminPen pen-injector device includes the following:

- Promotes patient compliance through eliminating the use of painful regular needle injections.
- Improves drug efficacy and safety by ensuring proper injections through simple, intuitive operation and by using a standard prefilled glass cartridge or a standard syringe.
- Enhances product safety by eliminating sharps hazards and offering safe, easy disposal of consumables as well as by eliminating electrical and high-pressure parts.

The painless AdminPen device combines effective delivery of drugs through the skin with excellent skin sensation and cosmetics, is easy and intuitive to use by patients and medical personnel alike, and can be economically produced to scale using mature high-volume low-cost processes. The strategy of applying the AdminPen device to the existing already-approved liquid drugs avoids both the costs and time spent on drug

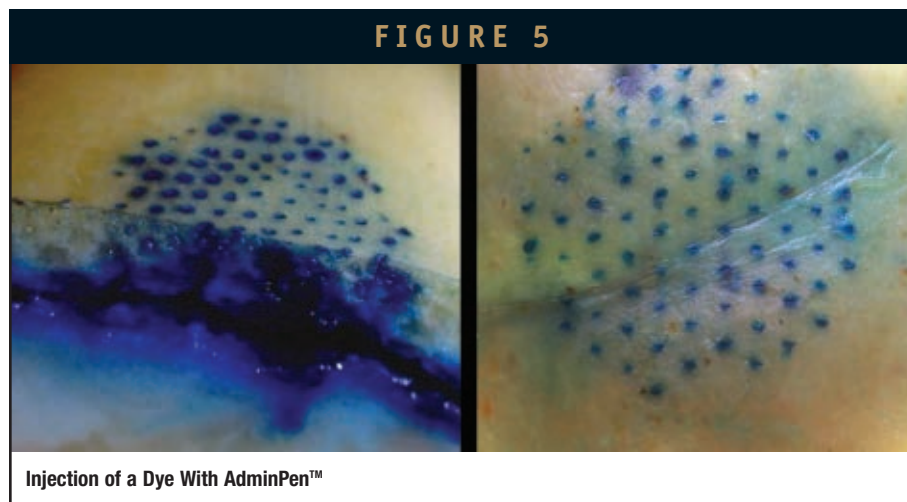


discovery and the risks of bringing a new compound to the market, as well as provides a significant pipeline of potential products based on existing already-approved drugs.

This painless microneedle injection device could potentially address the limited appeal of injections and avoid the first-pass metabolism issues presented by oral delivery. To demonstrate the feasibility of using the AdminPen device for subcutaneous drug

delivery, a study is underway to obtain a pharmacokinetic profile comparable to that observed by subcutaneous injection with a standard needle.

The AdminPen device is expected to have attractive profit margins because the microneedle array and the injection-molded support/syringe connector can be manufactured at low cost using mature, large-scale processes. The device does not use any



ADVANCED DELIVERY DEVICES

electronic components and can be entirely outsourced to low-cost precision stamping and plastic molding vendors.

A patient simply connects the AdminPen to a standard syringe and applies it to the skin. The microneedles penetrate the upper layers of the skin, thereby painlessly and instantaneously cutting the stratum corneum and epidermis to create hundreds of micro-channels near each microneedle. Each microneedle also keeps these channels open to allow injection of pharmaceutical drugs from the syringe through the microporated skin. When the AdminPen microneedle device is removed from the skin, the micropores simply collapse, and the skin barrier is quickly restored.

CURRENT ADMINPEN™ DESIGN

The current design of the AdminPen is composed of a “button” with a convex front-end and a back-end having a luer connector for connection to a standard syringe. The AdminPatch microneedle array is applied on the front convex surface of the button, which also has microfluidic channels that direct the injected drug from the syringe into the microchannels on each microneedle.

The initial testing of the AdminPen microneedle device prototypes has shown the successful insertion of the microneedle array and delivery of a dye through the skin as can be seen in Figure 5. The cross-sectional view demonstrates the successful delivery of dye under the skin using the device.

The results of the initial tests are very encouraging and a more rigorous design optimization and more extensive in vitro testing of the device is being undertaken. Several approaches to fully optimize and improve the design of AdminPen are currently being evaluated. Meanwhile, a web store has been established to quickly provide samples of microneedle arrays and AdminPen microneedle devices to our partners for evaluation. Several AdminPen products based on microneedle arrays of different lengths from 600 to 1500 microns are available.

COMMERCIAL POTENTIAL

There is an unmet need for a user-friendly, painless, simple, effective, and inexpensive technology for delivery of a variety of already approved liquid drug types to a patient. AdminMed estimates the AdminPen transdermal pen-injector device to have an annual worldwide market potential of approximately \$2 billion. ♦

REFERENCES

1. Yuzhakov VV. Microneedle array, patch, and applicator for transdermal drug delivery. US Patent No. 20070161964, WO Patent No. 2007081430;2007.
2. Yuzhakov VV. Advanced micro-needle Patch (AdminPatch™) for minimally invasive transdermal drug delivery. Invited presentation at First Annual Skin Summit: Transdermal Drug Delivery & Development & Beyond, Philadelphia, PA, February 22-23, 2007.
3. Yuzhakov VV. Tissue conforming microneedle array and patch for transdermal drug delivery or biological fluid collection. US Patent No. 20080125743, WO Patent No. 2008067290;2008.
4. Sivamani RK, Stoeber B, Wu GC, Zhai H, Liepmann D, Maibach HI. Clinical microneedle injection of methyl nicotinate: stratum corneum penetration. *Skin Res Technol.* 2005;11(2):152-156.
5. Sivamani RK, Liepmann D, Maibach HI. Microneedles and transdermal applications. *Expert Opin Drug Deliv.* 2007;4(1):19-25. Review.
6. Sivamani RK, Stoeber B, Liepmann D, Maibach HI. Microneedle penetration and injection past the stratum corneum in humans. *J Dermatol Treat.* 2009;20(3):156-159.
7. Henry S, McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles: a novel approach to transdermal drug delivery. *J Pharm Sci.* 1998;87:922-925.
8. McAllister DV, Wang PM, Davis SP, Park J-H, Canatella PJ, Allen MG, Prausnitz MR. Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: fabrication methods and transport studies. *Proc Natl Acad Sci USA.* 2003;100:13755-13760.
9. Chabri F, Bouris K, Jones T, Barrow D, Hann A, Allender C, Brain K, Birchall J. Microfabricated silicon microneedles for noninvasive cutaneous gene delivery. *Br J Dermatol.* 2004;150:869-877.
10. Martanto SP, Davis NR, Holiday JW, Gill HS, Prausnitz MR. Transdermal delivery of insulin using microneedles in vivo. *Pharm Res.* 2004;21:947-952.
11. Lin W, Cormier M, Samiee A, Griffin A, Johnson B, Teng CL, Hardee GE, Daddona PE. Transdermal delivery of antisense oligonucleotides with microprojection patch (Macroflux) technology. *Pharm Res.* 2001;18:1789-1793.
12. Cormier M, Johnson B, Ameri M, Nyam K, Libiran L, Zhang DD, Daddona PE. Transdermal delivery of desmopressin using a coated microneedle array patch system. *J Control Release.* 2004;97:503-511.
13. Matriano JA, Cormier M, Johnson J, Young WA, Buttery M, Nyam K, Daddona PE. Macroflux microprojection array patch technology: a new and efficient approach for intracutaneous immunization. *Pharm Res.* 2002;19:63-70.
14. Mikszta JA, Alarcon JB, Brittingham JM, Sutter DE, Pettis RJ, Harvey NG. Improved genetic immunization via micromechanical disruption of skin-barrier function and targeted epidermal delivery. *Nat Med.* 2002;8:415-419.
15. Roy CJ, Ulrich RG, Harvey NG. Protective immunization against inhalational anthrax: a comparison of minimally invasive delivery platforms. *J Infect Dis.* 2005;191:278-288.
16. Martanto W, Moore JS, Kashlan O, Kamath R, Wang PM, O'Neal JM, Prausnitz MR. Microinfusion using hollow microneedles. *Pharmaceut Res.* 2005;23:104-113.
17. Gill HS, Denson DD, Burris BA, Prausnitz MR. Effect of microneedle design on pain in human volunteers. *Clin J Pain.* 2008;24:585-594.

BIOGRAPHY



Dr. Vadim Yuzhakov is an inventor on 12 granted and numerous pending patents related to microneedle technologies. His career includes

significant experience in the research and development of medical devices and pharmaceutical drug delivery systems. He established and coordinated several research and development projects. As a Program Manager IV, he managed a development program at Abbott Diabetes Care. Previously, as a Principal Engineer at Altea Therapeutics, a specialty pharmaceutical company, he actively participated in the development a new advanced transdermal insulin patch based on a thermal microporation method. As a Senior Scientist at LifeScan, a Johnson & Johnson company, he significantly contributed to the development of an “all-in-one” system for convenient glucose monitoring; and as a Scientist at Procter and Gamble, he led the development of microneedle patches for drug and cosmetics delivery. He is a Certified Project Management Professional (PMP) and earned his MS in Mechanical Engineering from Lomonosov Moscow University and his PhD in Chemical Engineering from the University of Notre Dame. Dr. Yuzhakov can be contacted at Vadim@AdminMed.com.