UPI Journal of Pharmaceutical Medical, and Health Sciences
Content Available at www.uniquepubinternational.com ISSN: 2581-4532

Open Access **Review Article**

MICRONEEDLES & MICROFLUIDICS EMPLOYING IN DRUG DELIVERY

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DOI: https://doi.org/10.37022/jpmhs.v7i4.118

Article History
Received: 05-11-2024
Revised: 23-11-2024
Accepted: 09-12-2024

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Keywords: Microneedles, microfluidics, wound healing, biosensing.

Abstract
Microneedles and microfluidics are technologies that can be combined to create devices for biomedical applications such as drug delivery, wound healing, biosensing, body fluid sampling, and health monitoring. In vitro microfluidic drug delivery is closely linked to the emerging concept of lab-on-a-chip systems for cell culture studies. These systems can be used to administer drugs at the cellular or tissue level, assess the therapeutic index, and potentially be applied in personalized medicine.

Introduction

Microfluidics refers to a system that manipulates a small amount of fluids (10−9 to 10−18 liters) using small channels with sizes of ten to hundreds of micrometres. It is a multidisciplinary field that involves molecular analysis, molecular biology, and microelectronics. It has practical applications in the design of systems that process low volumes of fluids to achieve multiplexing, automation, and high-throughput screening.

Active microfluidics refers to the defined manipulation of the working fluid by active (micro) components such as micropumps or microvalves. Micro pumps supply fluids in a continuous manner or are used for dosing. Microvalves determine the flow direction or the mode of movement of pumped liquids. The processes normally carried out in a lab are miniturised on a single chip, which enhances efficiency and mobility, and reduces sample and reagent volumes.

History of Microfluidics

In the 1950s, principally in inkjet printer manufacturing. The mechanism behind these printers is based on microfluidics, and involves the use of very small tubes carrying the ink for printing. In the 1970s, a miniaturized gas chromatograph was constructed on a silicon wafer. By the end of the 1980s, the first microvalves and micropumps based on silicon micro-machining had also been presented.

In the following years, several silicon-based analysis systems were presented. All of these examples represent microfluidic systems, since they enable the precise control of decreasing fluid volumes on one hand, and involve miniturization of fluid handling systems on the other.

A major contribution in this field has been the development of soft lithography in a fast prototyping polymer, polydimethylsiloxane (PDMS), as a method for fabricating prototype devices and testing new ideas.

In the 1990s, advancements in microfabrication technologies expanded the possibilities of microfluidic systems. Researchers began designing lab-on-a-chip devices for applications ranging from chemical analysis to medical diagnostics. This era saw the emergence of the first microfluidic devices with integrated sensors and valves.

In the 21st century unfolded, microfluidics experienced a surge in popularity. The technology found applications in genomics, proteomics, drug discovery, and point-of-care diagnostics. Researchers explored the potential of organ-on-chip models, replicating human physiological conditions for more accurate testing

Types of Microfluidic Flows

Micro fluidic flows need only be constrained by geometrical length scale – the modalities and methods used to achieve such a geometrical constraint are highly dependent on the targeted application. Traditionally, micro fluidic flows have been generated inside closed channels with the channel cross section being in the order of 10 µm x 10 µm. Each of these methods has its own associated techniques to maintain robust fluid flow have matured over several years.

Digital Microfluidics

The analogy of digital microelectronics, this approach is referred to as digital micro fluidics. Le Pesant et al. pioneered the use of electro capillary forces to move droplets on a digital track. The "fluid transistor" pioneered by Cytonix also played a role.. By using discrete unit-volume droplets, a micro fluidic function can be reduced to a set of repeated basic operations, i.e., moving one unit of fluid over one unit of distance. This "digitisation" method facilitates the use of a hierarchical and cell-based approach for micro fluidic biochip design.

Therefore, digital micro fluidics offers a flexible and scalable system architecture as well as high fault-tolerance capability. Moreover, because each droplet can be controlled independently, these systems also have dynamic reconfigurability, whereby groups of unit cells in a micro fluidic array can be reconfigured to change their functionality during the concurrent execution.

Although droplets are manipulated in confined micro fluidic channels, since the control on droplets is not independent, it should not be confused as "digital micro fluidics". One common actuation method for digital micro fluidics is electro wetting-on-dielectric (EWOD).

Many lab-on-a-chip applications have been demonstrated within the digital micro fluidics paradigm using electro wetting. However, recently other techniques for droplet manipulation have also been demonstrated using magnetic force, surface acoustic waves, opto electrowetting, mechanical actuation, etc.

Open Microfluidics

The behavior of fluids and their control in open micro channels was pioneered around 2005 and applied in air-to-liquid sample collection and chromatography. In open micro fluidics, at least one boundary of the system is removed, exposing the fluid to air or another interface (i.e. liquid). Advantages of open micro fluidics include accessibility to the flowing liquid for intervention, larger liquid-gas surface area, and minimized bubble formation

. Another advantage of open microfluidics is the ability to integrate open systems with surface-tension driven fluid flow, which eliminates the need for external pumping methods such as peristaltic or syringe pumps. Open micro fluidic devices are also easy and inexpensive to fabricate by milling, thermoforming, and hot embossing.

In addition, open micro fluidics eliminates the need to glue or bond a cover for devices, which could be detrimental to capillary flows. Examples of open micro fluidics include open-channel micro fluidics, rail-based micro fluidics, paper-based, and thread-based micro fluidics. Disadvantages to open systems include susceptibility to evaporation,] contamination, and limited flow rate.

Continuous- Flow Microfluidics

Continuous flow micro fluidics rely on the control of a steady state liquid flow through narrow channels or porous media predominantly by accelerating or hindering fluid flow in capillary elements. In paper based micro fluidics, capillary elements can be achieved through the simple variation of section geometry and Continuous-flow micro fluidic operation is the mainstream approach because it is easy to implement and less sensitive to protein fouling problems.

These are adequate for many well-defined and simple biochemical applications, and for certain tasks such as chemical separation, but they are less suitable for tasks requiring a high degree of flexibility or fluid manipulations.

Droplet Based Microfluidics

Droplet-based micro fluidics is a subcategory of micro fluidics in contrast with continuous micro fluidics; droplet-based micro fluidics manipulates discrete volumes of fluids in immiscible phases with low Reynolds number and laminar flow regimes. Interest in droplet-based micro fluidics systems has been growing substantially in past decades. Micro droplets allow for handling minute volumes (µL to fL) of fluids conveniently, provide better mixing, encapsulation, sorting, and sensing, and suit high throughput experiments.

Exploiting the benefits of droplet-based micro fluidics efficiently requires a deep understanding of droplet generation to perform various logical operations such as droplet manipulation, droplet sorting, droplet merging, and droplet breakup.

Paper-Based Microfluidics

Paper-based micro fluidic devices fill a growing niche for portable, cheap, and user-friendly medical diagnostic systems. Paper based micro fluidics phenomenon of capillary penetration in porous media. To tune fluid penetration in porous substrates such as paper in two and three dimensions, the pore structure, wettability and geometry of the micro fluidic devices can be controlled while the viscosity and evaporation rate of the liquid play a further significant role. Many such devices feature hydrophobic barriers on hydrophilic paper that passively transport aqueous solutions to outlets where biological reactions take place.

Particle-Deetection Microfludics

One application area that has seen significant academic effort and some commercial effort is in the area of particle detection in fluids. Particle detection of small fluid-borne particles down to about 1 µm in diameter is typically done using a Coulter counter, in which electrical signals are generated when a weakly-conducting fluid such as in saline water is passed through a small (~100 µm diameter) pore, so that an electrical signal is generated that is directly proportional to the ratio of the particle volume to the pore volume.

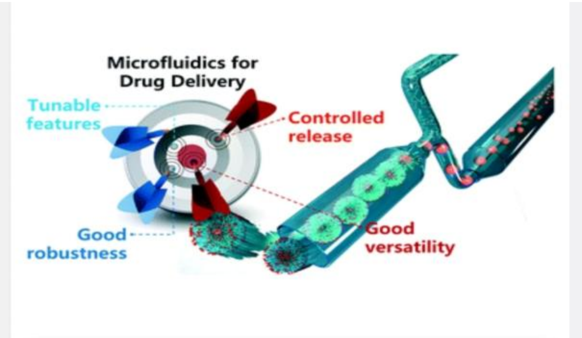
The limit on the pore size in traditional RPS Coulter counters is set by the method used to make the pores, which while a trade secret, most likely uses traditional mechanical methods. This is where micro fluidics can have an impact: The lithography-based production of micro fluidic devices, or more likely the production of reusable molds for making micro fluidic devices using a molding process.

Microfluidic Assisted Magnetophoresis

The major application for micro fluidic devices is the separation and sorting of different fluids or cell types. Recent developments in the micro fluidics field have seen the integration of micro fluidic devices with magnetophoresis: the migration of particles by a magnetic field.

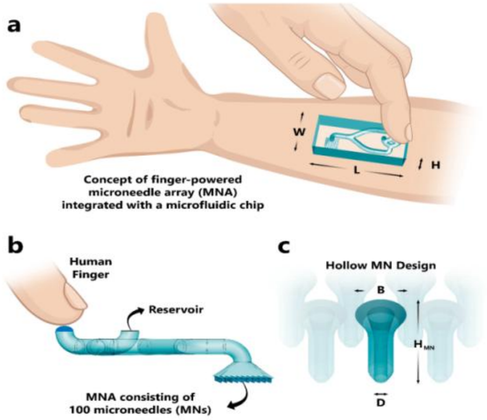
This can be accomplished by sending a fluid containing at least one magnetic component through a micro fluidic channel that has a magnet positioned along the length of the channel. This creates a magnetic field inside the micro fluidic channel which draws magnetically active substances towards it.

Effectively separating the magnetic and non-magnetic components of the fluid. This technique can be readily utilized in industrial settings where the fluid at hand already contains magnetically active material. These are necessary for traditional, channel-based droplet mixing.



Advantages of Microfluidics:

- **Miniaturization:** Microfluidic systems use fluids in extremely small volumes, resulting in significantly lower reagent and sample consumption. This saves costs and reduces waste. The small sizes enable the development of portable applications such as point-of-care diagnostics and field research in agriculture and marine biotechnology.
- **Rapid Analysis:** The small scale ensures rapid heat and mass transport, leading to shorter reaction times and higher analysis throughput. Microfluidics allows parallelization and automation, enabling researchers to conduct experiments faster.
- **Precision and Reproducibility:** With precise control over fluid flows, experiments can be conducted with high precision and reproducibility. This is crucial for processes like cell isolation, cell culture, and enzymatic assays.
- **Integration and Automation:** Microfluidic systems can be easily integrated with optical detection or sensors, enabling automated sample preparation and analysis. Lab-on-a-chip systems offer research teams the opportunity to fully automate processes.
- **Improved Reaction Speed and Efficiency:** The increased heat and mass transfer in microfluidic channels enables faster reactions, resulting in higher productivity. In enzymatic applications, biocatalysts can be used more efficiently in continuous-flow reactors.
- **Energy and Material Efficiency:** Due to miniaturization, microfluidic devices use significantly less energy and chemicals compared to traditional laboratory equipment



Disadvantages of Microfluidics

- **Complexity:** Microfluidic devices can be complex to design and fabricate, requiring specialized knowledge and equipment.
- **Scale-up:** While microfluidic devices are effective for small-scale experiments, scaling up to larger production volumes can be challenging.
- **Interfacial effects:** Fluid behavior at the microscale can be influenced by interfacial effects, such as surface tension and wetting, which can be difficult to control.
- **Clogging:** Microchannels in microfluidic devices can easily become clogged by particulate matter, which can affect the accuracy of experiments.Limited

- **viscosity range:** Microfluidics is most effective for fluids with low to moderate viscosity, and working with highly viscous fluids can be challenging

Applications of Microfluidics

- Drug screening
- Polymerase chain reaction
- Single cell manipulation
- Cell culture studies
- Screens for protein crystallization studies
- DNA sequencing
- Analysis of unpurified blood samples

Introduction of Microneedles

Microneedles are medical tools used for microneedling, firstly in drug delivery, disease diagnosis, and collagen induction therapy such as minimally invasive and precise nature. Microneedles consist of arrays of micro-sized needles ranging from 25µm to 2000µm. Microneedles was first introduced in the 1970s, its popularity has surged due to its effectiveness in drug delivery and its cosmetic benefits.

Microneedles are 350µm in depth to standard hollow-bore needle.Since the 2000s, there has been discoveries on new fabrication materials of Microneedles are like silicon, metal and polymer. Microneedles are four different types solid, hollow, coated, hydrogel has also been developed to possess different functions. The research on Microneedles has led to improvements in different aspects, including instruments and techniques.

Microneedle patches or Microarray patches are micron-scaled medical devices used to administer vaccines, drugs, and other therapeutic agents. Microneedles were initially explored for transdermal drug delivery applications, their use has been extended for the intraocular, vaginal, cardiac, vascular, gastrointestinal, and intracochlear delivery of drugs.

Microneedles are made from a variety of material ranging from silicon, titanium, stainless steel, and polymers. Some microneedles are made of a drug to be delivered to the body but are shaped into a needle so they will penetrate through the skin.

The microneedles range in size, shape, and function but all are used as an alternative to other delivery methods like the conventional hypodermic needle or other injection apparatus. Microneedles are advanced devices that respond to environmental triggers such as temperature, pH, or light to release therapeutic agent

History of Microneedles

Microneedles was first derived from the use of large hypodermic needles in the 1970s, but it only became prominent in the 1990s as microfabrication manufacturing technology developed Microneedles are finally came into experimentation in 1994. When "Orentreich" discovered the insertion of tri-beveled needles to the skin could possibly stimulates the release of fibrous strand. The investigation on Microneedles potential to improve transdermal drug delivery.

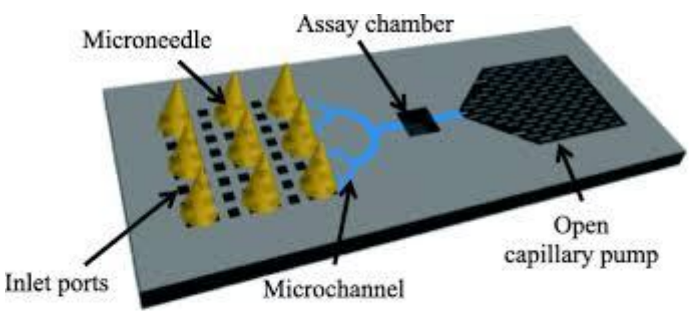
In the 2000s, clinical trials on Microneedles use in drug delivery. Microneedles were first mentioned in a 1998 paper by the research group headed by "Mark Prausnitz" at the "Georgia Institute of Technology" that demonstrated that microneedles could penetrate the uppermost layer (stratum corneum) of the human skin and were therefore suitable for the transdermal delivery of therapeutic agents.

Microneedle drug delivery has explored the medical and cosmetic applications of this technology through its design. The major goal of "any microneedle design is to penetrate the skin's outermost layer, the stratum corneum (10- 15µm)".Microneedles are long enough to cross the stratum corneum but not so long that they stimulate nerves which are located deeper in the tissues and therefore cause little to no pain.

Research has shown that there is a limit on the type of drugs that can be delivered through intact skin. Only compounds with a relatively low molecular weight, like the common allergen nickel 130 Daltons can penetrate the skin. Compounds that weigh more than 500 Daltons cannot penetrate the skin

Various Kinds of Microneedles

- **Solid micro needles:** These micro needles are used to create pores in the skin to allow drugs to penetrate. They are often made from metals like stainless steel, titanium, or gold.
- **Coated micro needles:** These micro needles have a drug solution applied to their surface.
- **Dissolving micro needles:** These micro needles are made from biodegradable polymers that dissolve in the skin.
- **Hollow micro needles:** These micro needles are filled with a drug solution and deposit the drug in the dermis.
- **Hydrogel-forming micro needles:** These micro needles are another type of micro needle.



Microneedling is a minimally invasive procedure for your skin. Your healthcare provider uses thin needles to make tiny holes in the top layer of your skin. The damage helps stimulate your skin's healing process, so it produces more collagen and elastin. These proteins keep your skin firm and smooth.

Polymers Used In Microneedles

Dissolving microneedles are made from several bio-absorbable polymers like maltose60, sugar61, salmon sperm DNA (SDNA)62, poly(methylvinylether maleic anhydride) (PMVE/MA)63, carboxymethyl cellulose (CMC)43,64 and polyvinylpyrrolidone

Benefits for Microneedling:

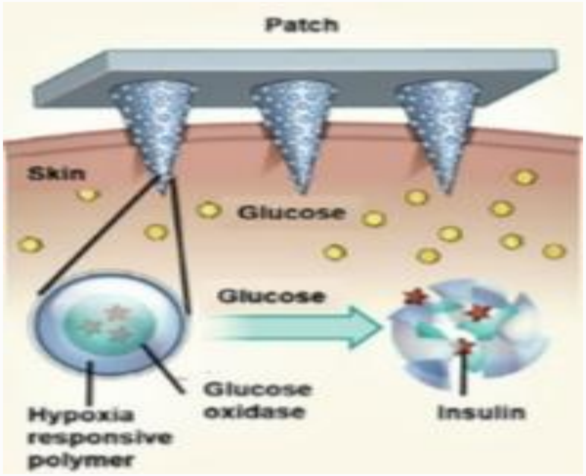
1. Microneedling Stimulates Collagen Production

The reason this is important is that collagen is the primary protein responsible for maintaining skin elasticity and firmness. Microneedling stimulates collagen fibres. People generally find that, after a microneedling treatment, they see ongoing improvements to their skin health and texture for at least six to eight weeks. This is because of the cumulative effect of new collagen production.

2. Skin Needling Reduces the Appearance of Fine Lines and Wrinkles

By adding elasticity and firmness to the skin, microneedling can help to smooth out and minimise the appearance of fine lines and wrinkles.

In addition, this is a treatment that can help to reduce deeper furrows and wrinkles on the face, including around the mouth and eyes (if carried out by an experienced professional). This is because it strengthens the underlying structures of your skin.



3. Microneedling Improves Skin Tone And Texture

The benefits of boosting your collagen and elastin production extend beyond addressing lines and wrinkles. This is a popular treatment because it also visibly improves your skin tone and texture

Again, this happens because healthy, collagen-rich tissue is undamaged and has an even tone.

4. Skin Needling Can Help To Improve Acne Scars

If you have deep, pitted scarring because of acne, then it's worth exploring skin needling as a treatment option.

By creating micro-injuries where your skin is scarred, we can stimulate collagen production and new skin cell growth, which acts like a filler and breaks down scar tissue. This should leave your acne scars looking far less visible. For the best results, you will probably need a series of treatments rather than one appointment.

This treatment may not be suitable for raised scars, however. This is because raised scars are usually caused by an overproduction of collagen when and even after the skin is healing.

5. Microneedling Can Shrink Enlarged Pores

Enlarged pores (openings on the surface of the skin that allow the secretion of sweat and oils) can be caused by a range of factors, both environmental and genetic. Frustratingly, once you have enlarged pores, your skin is more vulnerable to dirt and debris from outside, which can damage your skin health further.

Microneedling offers one of the most effective ways to shrink enlarged pores. Again, this is due to increased collagen production, as it narrows the pores by strengthening them with healthy skin cells.

6. Skin Needling Can Treat Hyperpigmentation

Melanin doesn't always spread evenly, so you may find you have areas of skin that are darker than others (hyperpigmentation). In addition, hyperpigmentation can be caused by sun damage, acne, cuts, bites and other causes of skin trauma.

By triggering the skin's natural healing response, skin needling encourages the treated area to make new, healthy skin cells and to reduce the amount of melanin concentrated in that area.

If the hyperpigmentation resides in the epidermis (the outer most layer of the skin), then skin needling can deliver fantastic results. It's not a cure-all for everyone, but it some people see clear improvements to their skin tone, while others benefit from coupling skin needling with other treatments designed to tackle hyperpigmentation.

7. Microneedling Boosts Your Skin's Ability to Absorb Skincare Products

It's often appropriate to use high-quality topical skincare products and serums during a microneedling treatment. This is because microneedling opens up microscopic channels into yosur skin, allowing for better absorption of skincare products within and below the epidermis.

We offer RadaraMicro-Channelling Patches, an at-home treatment that works on the same principle, creating tiny channels into the skin to enable the absorption of a serum packed with hyaluronic acid, another building block of healthy, smooth and hydrated skin.

8. Skin Needling Promotes Overall Skin Health

As the points above have hopefully shown, skin needling is a non-invasive and minimally painful procedure that promotes overall skin health. By tackling an array of issues such as scarring, hyperpigmentation, skin tone and texture, hydration and more, it's a great all-round treatment that delivers ongoing improvements as a cumulative effect of fresh collagen production.

9. Microneedling Is Safe For All Skin Types

Medical skin needling is widely recognised as a safe procedure for all skin types, including sensitive skin. That being said, it may not be suitable if you have a chronic skin condition, or you take blood thinning tablets.

The eDermastamp uses a disposable single-use tip with each new treatment to ensure that there are no risks of cross-contamination.

Another benefit of this treatment is that it can be used on the face, neck, décolleté and hands, helping you tackle areas of your skin that are vulnerable to damage.

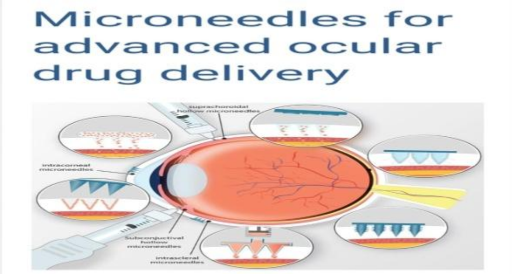
Advantages of Microneedles

These micro needles have many advantages, such as

- **Lower dosage:** Micro needle patches often require a lower dosage than oral ingestion to achieve the same therapeutic effect.
- **Stability:** Microneedles can be manufactured at room temperature without heating, which can help retain the stability of medications.
- **Immune therapies:** Microneedles can be used to stimulate cellular immune responses.
- **Diabetes management:** Microneedles can be used to detect glucose levels.
- **Transdermal drug delivery:** Microneedles can deliver a variety of therapeutics directly to the skin, including small molecular drugs, proteins, vaccines, and more.
- **Minimal invasiveness:** Microneedles are minimally invasive and can be easily operated.
- **Wound healing:** Microneedles can pass through physical barriers at wound sites, such as clots and scars, to release drugs.
- **Precise delivery:** Microneedles can deliver drugs with a high degree of precision.

Disadvantages of Microneedles

- **Skin irritation:** Microneedles can cause skin irritation or allergic reactions in some patients.
- **Microneedle tips breaking:** Microneedle tips can break and remain in the skin, which can cause problems.
- **Mechanical strength:** Microneedles made from certain materials, like silicon, can fracture during insertion into the skin.



Microneedles for advanced ocular drug delivery

- **Drug delivery rate:** Microneedle patches can take a long time to wear because the drug delivery rate is slow.
- **Clogging and infection:** Repeated use of microneedles can lead to clogging and infections

Applications of Microneedles

- Avoids pain and bleedingOffers better medication adherencez
- potentally alitering Allows self-applications by patients
- Improves patient compliance due to the absence of needle phobiaEnchances the stability of encapsulated drugs molecules, avoiding the use of cold chain (eg: insulin pen)
- Provides the option of delivering drugs immediately as well as in a controlled manner external conditions like skin hydration can impact the effectiveness of microneedles drug absorption

Conclusion

Microneedles and microfluidics are innovative technologies for drug delivery, diagnostics, and biomedical applications. Microfluidics enables precise manipulation of small fluid volumes, supporting automation and high-throughput analysis. Microneedles offer minimally invasive drug delivery methods, improving patient compliance and reducing dosage requirements.Both technologies are adaptable for personalized medicine and point-of-care diagnostics.Various types of microfluidics and microneedles cater to specific applications, enhancing flexibility and precision. They minimize reagent usage, lower costs, and allow for rapid analysis and integration with sensors. Challenges include fabrication complexity, clogging, scale-up issues, and potential skin irritation. Microneedles support painless drug delivery, collagen induction, and wound healing. Microfluidics improves efficiency in drug screening, cell culture studies, and DNA sequencing. These technologies are promising for future advancements in healthcare and research, requiring ongoing development for scalability and optimization.

Author contributions

All authors are contributed equally.

Financial support

None

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

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