Analysis of “Recent advances of controlled drug delivery using microfluidic platforms(Sharma T. Sanjay et al.)”

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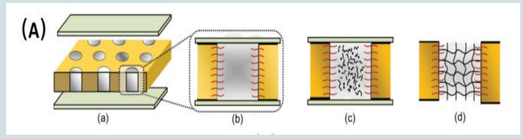
Microreservior systems

Passive Mode (Diffusion depending)

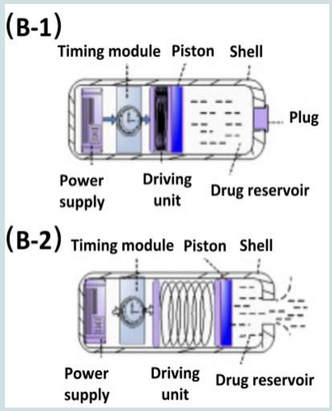
In the passive mode, drugs are released slowly via the osmotic potential, diffusive transport, concentration gradients, or in response to other external environmental stimuli. For instance, a micro-reservoir system to delivery dextrans by using a temperature-responsive poly(PNIPAAm) hydrogel showed a passive mode using a temperature response strategy. The hydrogel was synthesized via photoinitiated in situ copolymerization through grafting of linear PNIPAAm chains When temperature increased up to 32 °C, the flux increased and rejection decreased significantly, resulting in a reversible microfiltration behavior.



Figure(1) passive mode microreservior

Active Mode (In-battery)

MEMS-based controlled drug delivery is activated by a piston and applied for drug release in the alimentary canal. The device comprises four components: 1) a time module 2) a driving unit 3) a microfluidic chamber for drug reservoir 4) a power supply. All components are in a swallowable capsule, which can set up the timing parameter and indicate a signal to monitor the working state. Once the piston activates the system, which releases a desired dose of the drug from the reservoir.

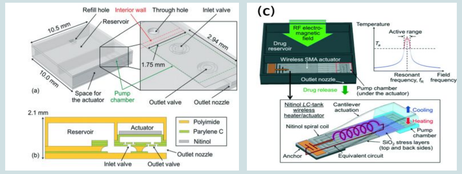


Figure(2) In-battery active mode microreservior

Active Mode (Wireless)

Also, drug can be delivered by wirelessly activating the actuator using external radio-frequency (RF) electromagnetic field. The diaphragm pump of the DDD is a three dimensional (3D) structure with two out-of-plane microvalves, all made up of thin films of Parylene C, a biocompatible polymer. One microfluidic channel is used to carry the drug from the reservoir to the inlet valve of the pump chamber and another channel to carry it from the outlet valve to outside the device.

A self-heat source activated via RF power transfer to enable frequency-selective nitinolcoil actuator’s cantilever motion, which occurs pumping, flow. Pull-up motion causes negative pressure inside the chamber that brings the drug in from the reservoir through the inlet valve. Pull down occurs positive and therefore, repetitive activations of the actuator with these mechanisms lead to full pumping cycles. As can see in the Fig(3), both valve cannot be opened simultaneously due to the structure.

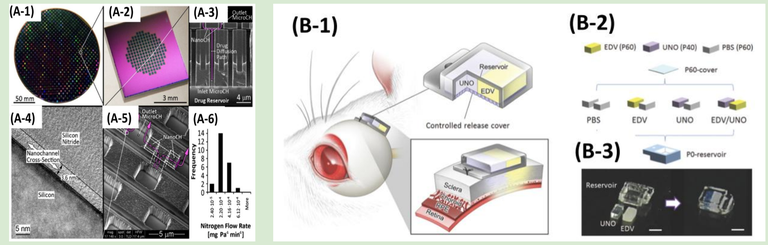


Figure(3) Wireless active mode microreservior .

Carrier-free microfluidic lap-on-chip

Nanochannel

Passively controlled drug delivery on another implantable LOC device with nanochannels as small as 2.5 nm was developed by Ferrati *et al*. These nanochannels controlled the release of drugs by physical-electrostatic confinement, resulting in constant drug diffusion. By varying the size of nanochannels, various drugs such as leuprolide, letrozole, and octreotide were delivered to consistently and clinically appropriate plasma levels.



Figure(4) Carrier free lap-on-cjip: (A) Nanochannel based chip, (B) LOC platform.

LOC platform

The LOC platform is controlled transscleral co-delivery of two drugs to the retina in rats in the active model. The drug formulations and the cover were manufactured based on the photopolymerized tri(ethyleneglycol)dimethacrylate(TEGDM) and poly(ehtyleneglycol)dimethacrylate(PEGDM). Each of drug release rate via the transscleral route are determined by ratio of PEGDM/TEGDM in the formulations and its cover. This system is effective for light injury more than single-drug-loaded devices.

Microneedles

Solid MNs

When SMN is removed from the skin, temporary microchannels are produced in stratum corneum(SC), and then drugs in the form of solutions, gel, cream or transdermal patches are applied. The drug penetrates into the target site through passive diffusion through microchannels, and the drug is transported for the systemic delivery or a localized effect. The use of cylindrical stainless steel MN, which can roll over the skin surface to create micropores, can significantly increase drug delivery efficiency.

Porous MNs

Porous microneedle has porous tips through which drugs diffuse. Liquid drug formulations that pre-loaded in the pores of PMNs are diffused from MN to skin. Dry drug formulations that pre-loaded drugs dried by vacuum, heat or freeze-drying are hydrated first when injected into the skin by interstitial fluid and then spread to the skin from the pore of PMNs drug. Nanoporous materials used to make PMNs, for the delivery of peptides, vaccines and analgesics.

Coated MNs

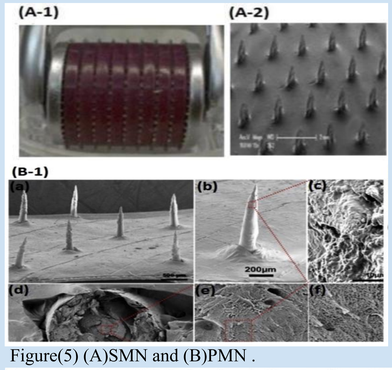
CMN is a microneedle in which SMNs are coated and dried with therapeutic drug formulation. It can be made by various methods such as dip coating, spray-coating, inkjet printing. CMNs may be used for the transfer of various biologics such as nucleic acids, proteins. In particular, CMN can be used as a vaccine delivery tool, and studies have shown that it induces a stronger immune response than conventional intramuscular syringe injection for vaccine delivery. CMNs may be applied to various application, but the disadvantage is that the amount of drugs that may be coated on CMNs is limited.

Dissolvable MNs

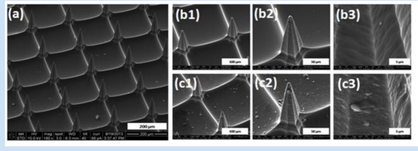
DMNs are micro-sized needles in which a therapeutic agent is encapsulated within a matrix consisting of biodegradable polymers. When DMNs are inserted into the skin, after contact with the interstitial fluid of the skin, the polymer dissolves or get biodegraded at a predetermined rate over time. Unlike SMNs and CMNs, DMNs are completely soluble in the skin, so there is no biological risk after treatment. There have been various efforts to improve drug penetration or induce drug release through DMNs by attempting electric current, ultrasound, and near-infrared light.

Hollow MNs

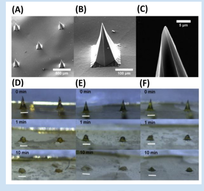
In HMNs, the drug formulation (solution or dispersion) is loaded in the interior of the MN, then the drug is injected and transferred into the skin after insertion of the MN. (Figure(8) Hollow MNs allow greater amounts of drug loading, when compared to solid and coated MN. Similar to solid MN, hollow MN can be manufactured using metals, silicon, glass or polymer. However, the major disadvantage of using hollow MN is the possibility of blockage after the needles are inserted due to the open needle bores. In Figure(8), needle tips of coated MNs are shown.



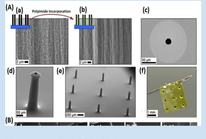
Figure(5) (A)SMN and (B)PMN .



Figure(6) CMN



Figure(7) DMN



Figure(8) HMN

Integration of drug carriers in microfluidic platforms

Microcapsules

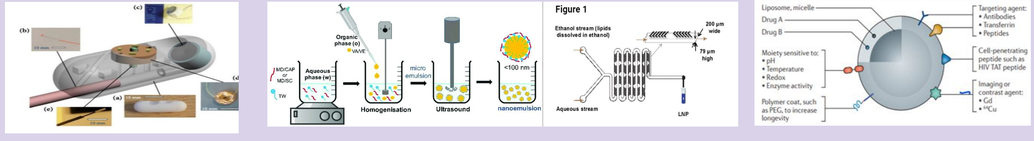
Microcapsules are very attractive drug carrier, which have a pore size of a few micrometers, excellent properties of biocompatibility and biodegradability. Glucose and temperature-responsive microcapsule release drugs and sense biomolecular. It has a challenge of monodispersity for the precise loading control and the release kinetics of encapsulated substances. Controlled drug release of pH-responsive microcapsule using biocompatible pH-responsive polymer shells can dissolve and degrade at a target pH, and release the active drug molecules or chemicals encapsulated in microcapsules at a prescribed rate.

Microcapsules

Nanoemulsion is a multiphase colloidal dispersion, which contains small particles or droplets with the average diameters ranging from 20 to 200 nm (transparent), or up to 500 nm (milky appearance). Emulsion is a system containing two immiscible phases and composed of at least three components: water phase, oil phase and (amphiphillic)surfactant phase. Nanoemulsions have been used to solubilize and protect drugs against harsh environmental factors (oxidation, pH, hydrolysis),, to target specific organs by exploiting enhanced permeability and retention effect of cancer, and to evade reticuloendothelial system. Also these days, nanoemulsion occurred by microfluid mixing is used to load weak base drug in limit size POPC LNP. The process is: (1)Lipid in ethanol is pumped into one inlet and aqueous buffer into the other inlet of the microfluidic mixing device using a syringe pump. (2)Herringbone structures induce chaotic advection of the laminar streams causing rapid mixing of the ethanol and aqueous phases and correspondingly rapid increase in the polarity experienced by the lipid solution. (3) At a critical polarity lipid precipitates form as LNP. Depending on the flow rate, the amount of LNP can be controlled.

*Nanoparticles

Nanoparticles are usually microscopic in size between 1~100nm, so they can be absorbed by cells. NPs target specific tissues without being excluded by the immune system. NPs can load drug molecules, so they have tremendous potential as drug carriers in controlled drug delivery. Microfluidic systems have enabled the new development of NPs as drug carriers. In microfluidic, NPs with the desired size and shape could be uniformly and reproducibly synthesized. Nanoparticles drug carriers created using microfluidic platforms include lipid nanoparticles, polymer nanoparticles, nano-sized polymeric conjugates, and lipid-polymer hybrid nanoparticles.



Figure(9) Theranostic microcapsule / Nanoemulsion’s process and LNP making microfluidic chip / structure of nanoparticle for drug delivery