MICROFLUIDICS DEVICE IN PHARMA INDUSTRY

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Abstract:

In pharmacy field many type of test carried for the new drug or formulation .Small amount of sample of drug are required for this new technique named microfluidics is developed. This technique used in sample preparation and formulation, clinical trial, preclinical test, chemical synthesis, combinatorial synthesis, lead identification, lead optimization and formulation study. It is application for the drug discovery and development.

Keyword:

Elastomeric material (polydimethyl siloxane); lab-on-achip;pharmaceuitical industry; drug discovery.

Introduction:

In 2006, only 18 new molecular entities and 4 new biologic license applications were approved by the US Food and Drug Administration (FDA). Recent developments, such as combinatorial chemistry, have greatly enhanced our ability to generate drug candidates .Microfluidics is a field with physics, chemistry, engerning, micro technique and biotechnology. Microfluidics is system, device and method used very small fluid flow like micro, Pico, Nano. This scale is very small than human hair. This technique, differences include faster thermal diffusion, predominantly laminar flow, electric double layer, surface force for capillary phenomenon. In this technique, minute quantities of media, reagents and nanoparticles are guided to move through narrow channels on the device where they are delivered, manipulated, and analyzed by such techniques as fluorescence detection. The processes are generating two stages-drug discovery and drug development. Drug discovery stages include target selection, preclinical studies, lead identification while drug development stage include clinical trials, manufacturing and product management. Drug discovery stage is to identify and select a ‘target’, such as a gene or protein, which can potentially be affected by a drug .The target is established, a promising molecule or a ‘lead’ is identified that can interact with the target. The lead is optimized by screening many similar compounds and assessed based on its strategic portfolio fit, preliminary safety, technical issues and commercial opportunity. The drug candidate will be tested for safety and efficacy in animal studies. After

starting with thousands of compounds, only a few drug candidates continue into the development stage for trials clinical and manufacturing.

The microfluidic devices of drug discovery for both the R and D chemists involved in target identification, compound generation, lead identification and optimization, and for the R and D biologists involved in life science technologies such as genomics, proteomics, high throughput screening and molecular diagnostics. The concept of encapsulating a drug within a polymeric particle use micro- and nanoparticles as drug delivery vehicles. Drug encapsulation within polymer spheres offers a number of benefits over conventional dosage forms. It can protect the API from enzymatic or acidic degradation. It also leads to a more uniform absorption rate, as the particles are distributed over a greater area of the gastrointestinal tract. In addition, dividing a dose across multiple particles improves safety and reduces the risk of toxicity in the event of defective delivery. Microencapsulation also provides a solution to an ongoing problem that plagues pharma companies; many promising small molecule drug candidates are hydrophobic and poorly soluble in water, which makes them unusable. Encapsulation overcomes this barrier, helping a candidate drug's transition from discovery to development. Typically in microfluidic systems fluids are transported, mixed, separated or otherwise processed. The various applications of such systems rely on passive fluid control using capillary forces, in the form of capillary flow modifying elements, akin to flow resistors and flow accelerators. In some applications, external actuation means are additionally used for a directed transport of the media. Examples are rotary drives applying centrifugal forces for the fluid transport on the passive chips. Active microfluidics refers to the defined manipulation of the working fluid by active (micro) components such as micro pumps or micro valves. Micro pumps supply fluids in a continuous manner or are used for dosing. Micro valves determine the flow direction or the mode of movement of pumped liquids. Often processes which are normally carried out in a lab are miniaturized on a single chip in order to enhance efficiency and mobility as well as reducing sample and reagent volumes.

Keys of Application Area of Microfluidics:

The basic idea of microfluidics chips is to integrate an assay operation that is detection, sample pre-treatment and sample preparation on a chip. Advances in this technology are revolutionizing molecular biology procedure for enzymatic analysis (glucose and lactase assay), DNA analysis (polymerase chain reaction and high throughput sequencing) and proteomics.

Many diverse advantages of this technology for microbiology are listed below:

- single cell studies including growth
- Cellular aging: microfluidic devices such as the "mother machine" allow tracking of thousands of individual cells for many generations until they die.
- Micro environmental control: ranging from mechanical environment to chemical environment
- Confining cells and exerting controlled forces by coupling with external force-generation methods such as Stokes flow, optical tweezer, or controlled deformation of the PDMS (Polydimethylsiloxane) device

- Electric field integration .
- Plant on a chip and plant tissue culture.
- Antibiotic resistance: microfluidic devices can be used as heterogeneous environments for microorganisms. This can be useful for testing the acceleration of evolution of a microorganism / for testing the development of antibiotic resistance.

Some of these areas are elaborated in below:

- Open Microfluidics
- Paper-Based Microfluidics
- Droplet-Based Microfluidics
- Continuous-Flow Microfluidics
- DNA Chips (Microarrays)
- Molecular Biology
- Evolutionary Biology
- Cell Behavior
- Cellular Biophysics
- Acoustic Droplet Ejection (ADE)
- Fuel Cells

❖ Open Microfluidics:

In this system, at least one boundary of the system is removed, exposing the fluid to air or another interface (i.e. liquid). Open microfluidics eliminates the need to glue or bond a cover for devices which could be detrimental for capillary flows.

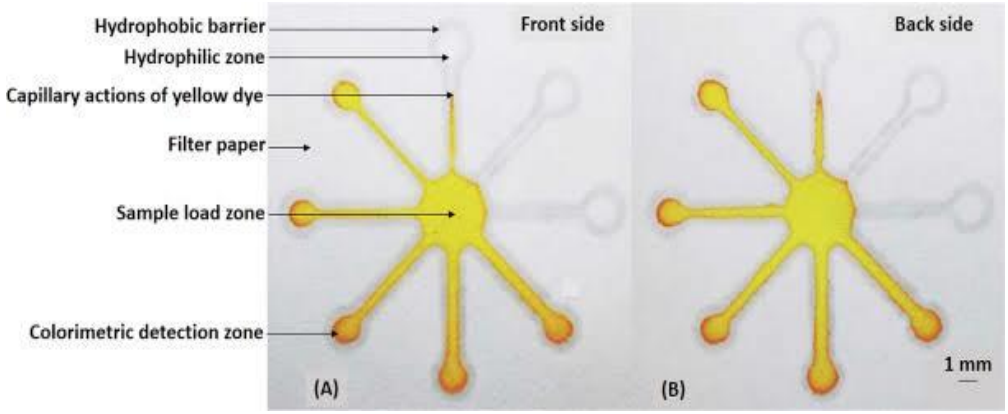
Advantages:

- 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.
- Easy and inexpensive to fabricate by milling, thermoforming and hot embossing.

Disadvantage:

- Evaporation, contamination, and limited flow rate.

❖ Paper-Based Microfluidics:



This device fill a growing niche for portable cheap. In phenomenon of capillary penetration in porous media. Fluid penetration in porous substrates i.e. Paper, in two and three dimensions. Pore structure, wettability and geometry of the microfluidic devices can be controlled while the viscosity and evaporation rate of the liquid play a further significant role. It include portable glucose detection, environmental testing and medical diagnostic tools.

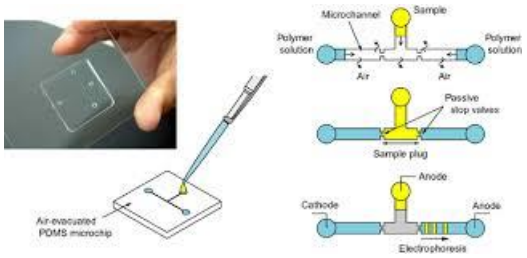
❖ Droplet-Based Microfluidics:

It is manipulates discrete volumes of fluids in immiscible phases with low Reynolds number and laminar flow regimes.Microdroplets allow for handling miniature 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 microfluidics efficiently requires a deep understanding of droplet generation to perform various logical operations such as droplet motion, droplet sorting, droplet merging, and droplet breakup.

❖ Continuous-flow Microfluidics:

In this device liquid flow is control of a steady state liquid flow through narrow channels or porous media predominantly by accelerating or hindering fluid flow in capillary elements. Continuous-flow microfluidic operation is the mainstream approach because it is easy to implement and less sensitive to protein fouling problems. Continuous-flow devices 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.

❖ DNA Chips (Microarrays):



DNA microarray and protein array is a miniature array where a multitude of different capture agents, most frequently monoclonal antibodies, are deposited on a chip surface. They are used to determine the presence and/or amount of proteins in biological samples, e.g., blood.

Drawback:

DNA and protein arrays is that they are neither reconfigurable nor scalable after manufacture.

❖ Molecular Biology:

Biochips have been designed for two-dimensional electrophoresis, transcriptome analysis and PCR amplification. It include various electrophoresis and liquid chromatography applications for proteins and DNA, cell separation, in particular, blood cell separation, protein analysis, cell manipulation and analysis including cell viability analysis and microorganism capturing.

❖ Evolutionary Biology

Landscape ecology and Nano fluidics, a Nano/micro fabricated fluidic landscape can be constructed by building local patches of bacterial habitat and connecting them by dispersal corridors. Landscapes can be used as physical implementations of an adaptive landscape, by generating a spatial mosaic of patches of opportunity distributed in space and time. Fluidic landscapes allows for the study of adapting bacterial cells in a Meta population system. The evolutionary ecology of these bacterial systems in these synthetic ecosystems allows for using biophysics to address questions in evolutionary biology.

❖ Cell Behavior

The ability to create precise and carefully controlled chemoattractant gradients makes microfluidics the ideal tool to study motility, chemotaxis and the ability to evolve / develop resistance to antibiotics in small populations of microorganisms and in a short period of time. These microorganisms including bacteria and the broad range of organisms. Microfluidics has also greatly aided the study of durotaxis by facilitating the creation of durotactic (stiffness) gradients.

❖ Acoustic Droplet Ejection (ADE)

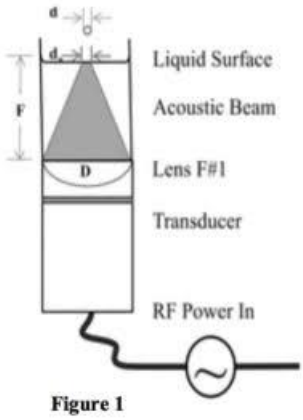
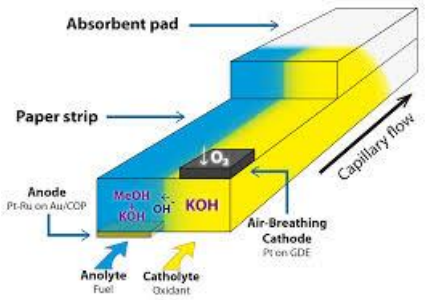


Figure 1

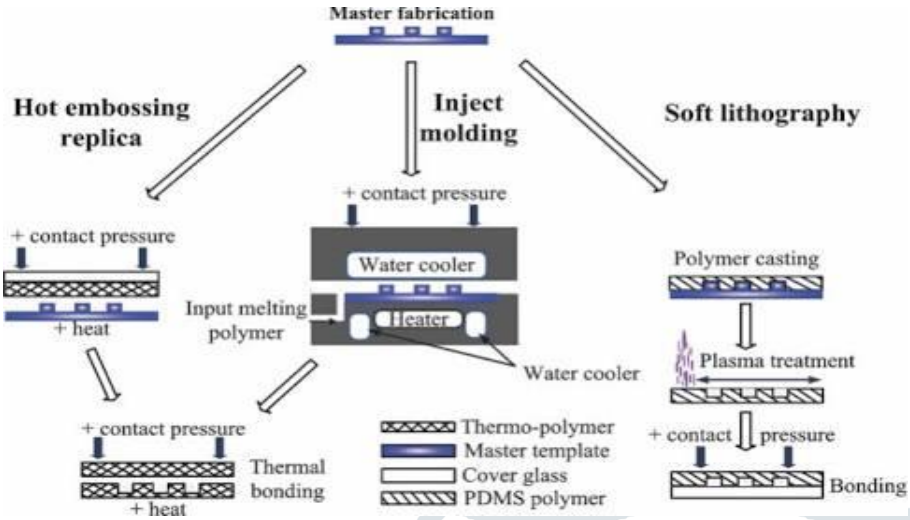
Acoustic droplet ejection uses a pulse of ultrasound to move low volumes of fluids (Nano liters or Pico liters) without any physical contact. This technology focuses acoustic energy into a fluid sample in order to eject droplets as small as a millionth of a millionth of a litre (picoliter = 10^{-12} litre). ADE technology is used to transfer proteins, high molecular weight DNA and live cells without damage or loss of viability.

❖ Fuel Cells



Microfluidic fuel cells can use laminar flow to separate the fuel and its oxidant to control the interaction of the two fluids without a physical barrier as would be required in conventional fuel cells.

Fabrication of Microfluidic Devices



The development in the fields of microfluidics can be attributed to the adoption of the micro fabrication technologies enabled the creation of complex miniaturized systems in materials such as silicon, glass and metals. Microfluidic devices initially composed of silicon or glass. This development of fabrication technologies and materials for microfluidic systems, such as injection molding, hot embossing and laser ablation of polymeric materials, such as polycarbonate and poly-methyl methacrylate, and casting techniques, such as rapid prototyping in silicone elastomers or epoxies. Fabrication of microfluidics device include wet etching, reactive ion etching, conventional machining, photolithography, hot embossing, injection molding, laser ablation, in situ construction and plasma etching.

Advantages:

- surface stability
- solvent compatibility
- optical properties

Disadvantage:

- high cost of device
- cost of the material

Micro Replication Techniques

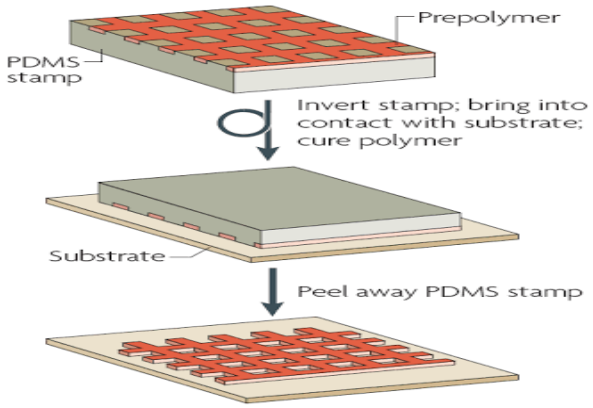
Replication of microfluidic devices used polymeric materials. Injection molding is used to fabricate macroscopic and microscopic objects in thermoplastic materials and has of late been employed for the production of microfluidic devices. The principle of operation is that a melted polymeric material is injected into a mold cavity under high pressure. The temperature is then decreased. Microfluidics is a potentially powerful method of performing high throughput experiments that encompass a series of techniques used for controlling the flow and reaction of minute amounts of liquids or gases. Microfluidic systems have a number of benefits, which include reduced waste, improved sensitivity/precision, reduced cost, reduced energy consumption, miniaturized experiments and an increase in the speed of the reactions by reducing diffusion times. With typical channel a dimension of 5–100 μm devices comprised of

complex networks of fluidic micro channels and interconnects can be generated around the size of postage stamps. Many companies have been developing microfluidic technology for various high through put applications such as immunoassays, diagnostic devices, single molecule DNA and protein detect as cell separation. Research is also being performed in many academic laboratories on novel applications of microfluidic
Technology. For example, researchers from the University of Chicago, USA, and other laboratories have demonstrated the use of two-phase droplet systems to generate droplets within microfluidic channels that could be used as microreactors.

Micro-Construction Techniques

There are many different ways to manufacture microfluidic devices. Kovacs provides a good review of following some techniques,
1. Soft lithography technique
2. Traditional lithographic techniques
3. Laminate fabrication technologies

1. Soft Lithography Technique:



This technique use soft elastomer material (PDMS) to transfer patterns to substrate material. It consist of building elastomeric microchannel.Microchannel are designated in specific program and printed on the high resolution transparency mask or remodeled into conventional chrome mask to produce a mold for soft material. Fluid flow depending on the pH of the fluid. Two imprinting techniques were used to fabricate microfluidic devices on poly methyl methacrylate (PMMA) substrates: creating an impression with a wire in heated substrate and imprinting with a mold micro machined on silicon waver. Reproducible electrophoretic injections and an immunoassay were demonstrated. Analysis of DNA fragments by another wire imprinted PMMA device was described for fabrication of free standing, non-cylindrical three-dimensional micro structures from two-dimensional patterns. Microelectrode position adds strength to the thin metal designs. Another method described as the ‘‘membrane sandwich’’ was developed to produce topologically complex three-dimensional microfluidic channel systems in PDMS. It can divided into three different subcategories which are replica molding,microcontact printing and embossing.

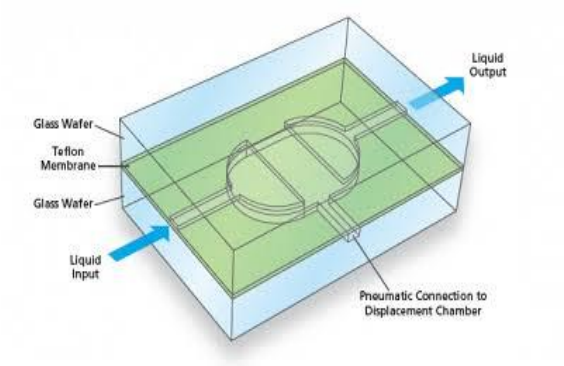
Advantage:

- low cost
- easy fabrication process
- Rapidit

2. Traditional Lithographic Techniques:

It is used hard substrates, commonly silicon, are used as the primary construction material. This techniques involves the use of electromagnetic radiation, typically ultraviolet (UV) light, to transfer a pattern to a surface, such as silicon, covered with photoresist. The ‘‘mask’’ that contains the pattern can be as simple as an overhead with the desired design printed on it or more elaborate, such as a chrome mask. The pattern is transferred to the photoresist-covered surface by shining electromagnetic radiation through the mask onto the surface. Typically ultra-violet (UV) light is used, although electromagnetic waves with narrower wavelengths, such as X-rays, have been used to achieve a finer resolution. The photoresist is developed such that the areas exposed to the electromagnetic radiation behave in an opposite manner to unexposed areas; one set of areas polymerizes and remains on the surface while the other set is washed away.

3. Laminate Fabrication Technologies



It is based on a different paradigm than either of the two methodologies described above. Laminate fabrication the device consists of layers of material, lamina that have been laser-cut or stamp-cut into the desired shape and then held together with some form of adhesive, most commonly pressure-sensitive or thermally-activated adhesive. Mylar is presently the most commonly used materials such as glass and PDMS have also been successfully incorporated into laminate devices. Laminate fabrication has been used to perform hematology analyses. Micronics microfluidic circuits comprise laminates built of several layers of individually cut or stamped fluidic circuits. Each layer can be manufactured very easily and inexpensively, the lamination process yields complex 3-dimensional microfluidic structures. This allows the design, for example, of 3D hydrodynamic focusing channels for cell analysis, or of multiple separate circuits with crossing channels on a single card. While other processes such as hot embossing, micro-injection molding and silicon or glass lithographic techniques yield significantly better dimensional tolerances, the plastic laminate method has its major advantages in turn-around time, cost, and the ease of generating 3-dimensional structures, as

well as incorporating hybrid elements into the design (such as electrodes, filter membranes, sensors, etc.).

Application:

- Microfluidic technologies are powerful tools for the drug discovery and development processes. Microfluidics has incredible potential in a variety of areas 20-22.
- A microfluidics application include DNA analysis methods and have been linked to mass spectrometry and thus enables picomole amounts of peptide to be analyzed within a controlled micro-environment.
- In pharmaceutical industry; its applications are found in the areas of diagnostics and drug research.
- Drug discovery and development and highlighted their applications in different stages of the process, including target selection, lead identification, optimization and preclinical tests, clinical trials, chemical synthesis, formulations studies and product management process.
- It is used to enable High Throughput Screening studies such as multiplexed systems, microwell arrays, plugbased methods and gradient-generating devices.
- Elastomeric materials such as PDMS have emerged recently as excellent alternatives to the silicon and glass used in early devices fabricated by microelectromechanical systems processes.
- Microfluidic devices provided cheaper and easier screening process than in traditional *in vivo* approaches.
- PDMS technology can be successfully used for integrating complex preparation protocols of protein samples.
- Microfluidic-based applications in neurobiology, with emphasis on neuron culture, neuron manipulation, neural stem cell differentiation, neuropharmacology, neuroelectrophysiology.
- Researchers have designed a microfluidic device that mimics the microenvironment gradients present in tumors.
- Microfluidics find applications in drug discovery, drug delivery, *in-vitro* diagnostics, chemical analysis, highthroughput screening, Researchers are of the opinion that microfluidics will enable efficient screening of more drugs in less time and drastically cut down the costs of drug development.
- Micro fluidizer processors are used to create products for numerous applications such as improved bioavailability, stability, uniform particle size reduction, sterile-filtration (< 200 nm) of Nano emulsions.
- It is useful for observing and analyzing the effect of a drug compound on normal and diseased cells as well as determining optimal dosing.
- Study of the nervous system, including architecture for isolation of axons, integrated electrophysiology, patterned physical and chemical substrate cues, and devices for the precisely controlled delivery of possible therapeutic agents such as trophic factors and drugs.
- Microfluidics-based biochips find applications in clinical diagnosis, deoxyribonucleic acid (DNA) sequencing, and other laboratory procedures involving molecular biology.
- Drug evaluation is also an important aspect of drug analysis. Study of drug-cell interactions can provide valuable drug evaluation information. evaluate the effectiveness, toxicity and safety of the drug.

Conclusion

Microfluidic technologies are powerful tools for various applications for the drug discovery and development process. Microfluidic based approaches have already made a significant impact in the area of chemical synthesis, protein crystallization, high throughput drug screening and drug delivery, because they address a number of limitations imposed by conventional macroscale methods including low throughput, expensive processes and large volume of reagents. Microfluidic technologies have great potential in high-throughput studies involving target

Selection, lead compound generation, identification and dosage design. Pharmaceutical industry can greatly benefit from applying new microfluidic assays in various drug development stages, from target screening, lead optimization to absorption distribution metabolism elimination, toxicity studies in preclinical evaluations, diagnostics in clinical trials, drug formulation and manufacturing process optimization. The new detection technology and unique design allow researchers to easily detect trace amounts of drugs in biological samples, as well as to detect metabolic processes and metabolites of drugs Moreover, microfluidics offers innovative technological opportunities for obtaining new information about biological systems. The ability to miniaturize assays, increase experimental throughput, and utilization of microfluidic systems to achieve results closer to those expected in *in-vivo* studies will continue to generate a significant amount of interest in drug discovery companies. The implementation of extended time imaging along with microfluidics by drug discovery and development companies is a key step on the road to personalized medicine and thus microfluidics has a bright future.

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