Journal of Applied Pharmaceutical Science

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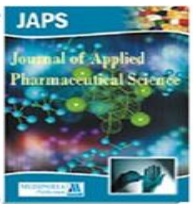

ISSN: 2231-3354
Received on: 12-05-2011
Revised on: 19-05-2011
Accepted on: 25-05-2011

Microchip for Drug Delivery System: A Review

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ABSTRACT

Much Research has been going to find ideal system for drug delivey within body.It is great advantage to find drug delivery device that is capable of controlled or continous release of wide variety of drug.Microchip are provided, which control both the rate and the time release of molecule.This allows release of wide variety of molecule in either continous or pulsatile manner. The device consist of substrate containing multiple reservoir is capped with conductive membrane (gold) and wired with final circuitry controlled by microprocessor.Reservoir are etched into substrate using either chemical etching or ion beam etching techniques. Hundreds to thousands reservoirs can be fabricated on a single microchip using microfabrication.The molecule to be delivered are inserted into reservoir by injection. The reservoir can contain multiple drug or other molecule in variable dosages. The filled reservoirs can be capped with material that degrade or allow the molecule to diffuse out of reservoir over time or materials that oxidize and dissolve upon application of electric current.Release from an active device can be controlled by a preprogrammed microprocessor.It is used in diabetes, Parkinson's disease, congestive heart failure, anti coagulation.

Key words: Microchip, Microfabrication, Controlled release.

INTRODUCTION

Some drug delivery systems already exist that attempt to control the release rate of drugs. One such system includes polymeric devices that have been designed to provide drug release over a period of time via diffusion of the drug out of the polymer and/or degradation of the polymer. This system, however, is too simple to have the ability to precisely control the amount or rate of drug released. In some cases, the polymer degrades too fast because of unexpected environmental conditions within the body (i.e. in the presence of enzymes that increase the degradation rates of biodegradable polymers) It is therefore necessary to design a drug delivery device that has the following characteristics:

1.) One that is simple to use and manufacture,
2.) One that is multi-welled so that drugs and other molecules can be delivered for weeks or years at a time,
3.) One that can hold many different drugs or other molecules of varying dosages and can release these substances in a controlled dependable manner, and
4.) One that is biocompatible and small enough to be implantable in the human body (i.e. a microchip). (Ramille et al, 2000)

Microchip Device Design

The microchip delivery system consists of a substrate containing multiple reservoirs capable of holding chemicals in the solid, liquid, or gel form. Each reservoir is capped (i.e. with a conductive membrane) and wired with the final circuitry controlled by a microprocessor. This central processor should be able to actively control electrically the exact time of release and the amounts of drugs dispersed by controlling the dissolution of the gold membrane. The system should be reasonable to manufacture by standard micro fabrication techniques and still be cost-effective.

The Design Approach—an Overview

The Substrate

According to system design, the reservoirs will be patterned into the substrate. This can easily be done by standard etching techniques of microfabrication. Any material that can serve as a support, is suitable for etching,and is impermeable to the molecules to be delivered and to the surrounding fluids may be used as a substrate. For this in vivo application, biocompatibility should be considered. Non-biocompatible materials, however, can also be enclosed within biocompatible materials like poly (ethlene gylcol). One example of a strong, nondegradable,easily etched substrate that is impermeable to the delivered chemicals and non-degradable to the surrounding environment within the body is silicon. It should be noted that for some applications a material degradable over time might be preferred. For example, brain implants make the removal of a device difficult or too endangering to the patient and therefore this device would not be applicable. (Ramille et al, 2000)

Release System

The design of a release system depends on the treatment required by the patient whether it is a continuous or pulsed release. Drug delivery can be achieved by a passive or active release system. In the passive system, the drugs diffuse through a membrane or enter the body by the degradation of the substrate. Active systems are triggered by a microprocessor and are preferred due to a more predictable release profile. The exact time release and amounts of drugs can then be controlled.The chip can be placed strategically as well for drugs that are too potent for acontinuous release. The device being described will be employing an active system. (Ramille et al, 2000)

Reservoir Caps

In the active timed-release devices, the reservoir caps consist of thin films of conductive material patterned in the shape of anodes surrounded by cathodes. Any conductive material that can oxidize and dissolve in solution upon application of an electric potential can be used for the fabrication of the anodes and cathodes. The anode is defined as the electrode where oxidation occurs. The portion of the anode directly above the reservoir oxidizes and dissolves into solution upon the application of a potential between the cathode and anode. This exposes the release system to the surrounding fluids and results in the release of the molecules or drugs. Gold ischosen as the model membrane material because it is easily deposited and patterned, has a low reactivity with other substances and resists spontaneous corrosion in many solutions over the entire pH range2. However, the presence of a small amount of chloride ion creates an electric potential region which favors the formation of soluble gold chloride complexes (Frankenthal et al, 1982). Holding the anode potential in this corrosion region enables reproducible gold dissolution. Potentials below this region are too low to cause appreciable corrosion, whereas potentials above this region result in gas evolution and formation of a passivating gold oxide layer that causes corrosion to slow or stop (Santini et al, 1999). Gold has also been shown to be a biocompatible material. (Ramille et al, 2000).

Control Circuitry and Power Source

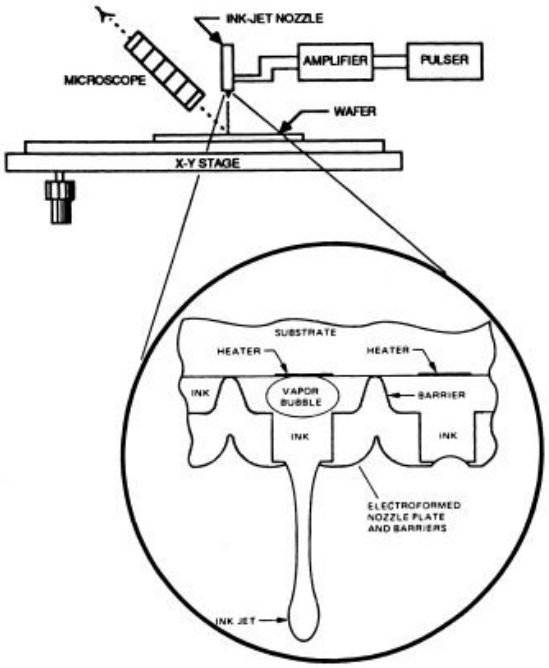
The control circuitry consists of a timer, demultiplexer, microprocessor or an input source. The microprocessor will control the desired reservoir to be activated so that a variety of drugs may be contained in each specific reservoir. The input source can either be a memory source, remote control device or a biosensor. A thin-film microbattery can be used as a power source. All of these can be patterned directly onto the device. (Ramille et al, 2000)

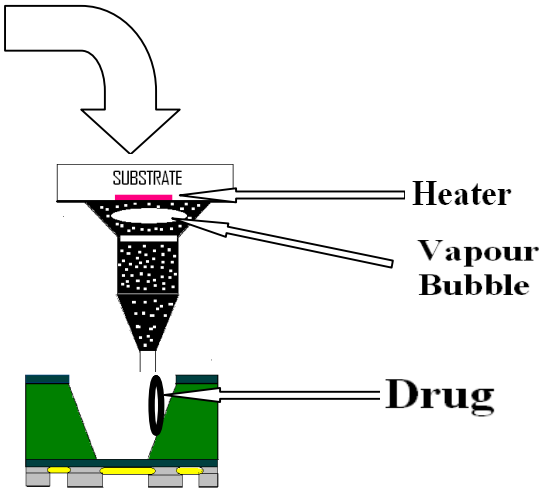
Reservoir filling

Three-dimensional printing is capable of fabricating complex structures by ink-jet printing liquid binder onto loose, fine powder (Wu et al, 1999). The printing pattern can be obtained from a computer-aided-design model (CAD). Inkjet printing in combination with a computer-controlled alignment apparatus is capable of depositing as little as 0.2 nl of a liquid or gel solution of known concentration into each reservoir (Santini et al, 1999).The volume of the reservoirs can be controlled by specifying the appropriate print head to deposit a pre-determined amount of binder. The drug is pushed out of the nozzle as the vapor bubble within the nozzle expands upon heating. The relationship between the amounts expanded by the vapor bubble to the heat added follows the ideal gas law relationship (Fig. 1).

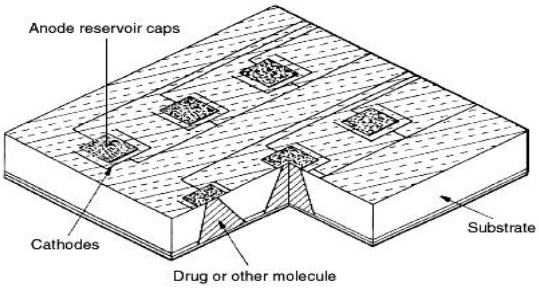
Microfabrication

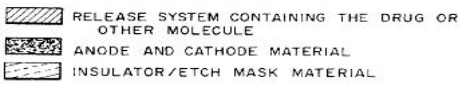
Microfabrication can be generally defined as the production of microscale features in or on a material by techniques such as diposition,etching,micromolding along with patterning techniques such as photolithography or microcontact printing(Jonh et al, 2000).Fabrication of these microchips begins by depositing ~0.12 mm of low stress,silicon-rich nitride on both sides of prime grade, silicon wafers using a vertical tube reactor(Santini et al, 1999). The silicon nitride layer on one side of the wafer is patterned by photolithography and electron cyclotron resonance (ECR) enhanced reactive ion etching (RIE) to give a square device containing square reservoirs. The silicon nitride serves as an etch mask for potassium hydroxide solution at 85°C, which anisotropically etches square pyramidal reservoirs into the silicon along the crystal planes until the silicon nitride film on the opposite side of the wafer is reached.





The newly fabricated silicon nitride membranes completely cover the square openings of the reservoir. Gold electrodes (0.3-0.5 mm thick) are deposited and patterned over the silicon nitride membranes by electron beam evaporation and lift-off. Some portions of the electrodes must be protected from unwanted corrosion by an adherent, non-porous coating that isolates the electrode materials from the surrounding electrolyte. Silicon dioxide is used as a model protective coating because its physical properties can be tailored to a particular application by selecting the appropriate processing conditions2. A layer of plasma enhanced chemical vapor deposition silicon dioxide is deposited over the entire electrodecontaining surface.



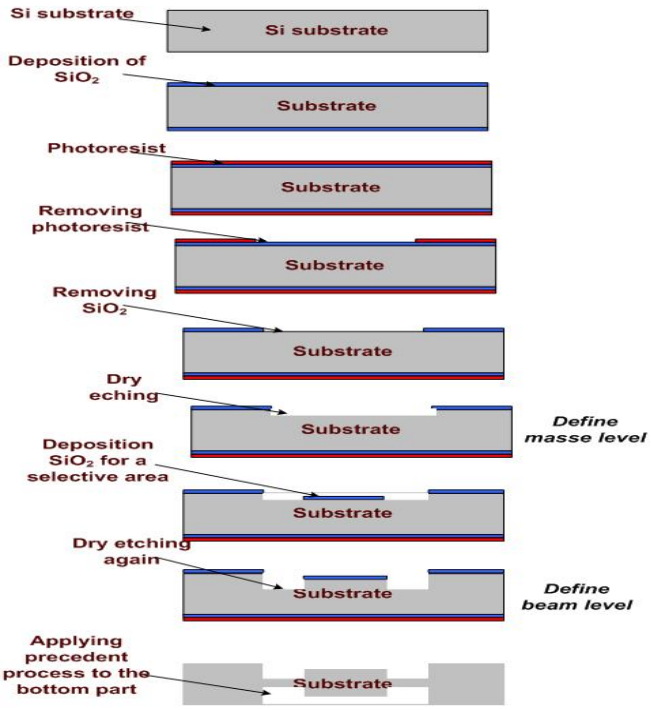


Device Dimensions:
17mm x 17mm x 315mm
Reservoirs: 400 total
.05 mm spacing (bottom side)
25 nl volume
Square pyramid side wall slope: 54°
Fill opening:500m:m x 500mm

Release end:
30mm x 30m:m
Gold caps:
50mm x 50mm x .3mm

The silicon dioxide located over portions of the anode, cathode,and bonding pads are etched with ECR-enhanced RIE to expose the underlying gold film. This technique is also used to remove the thin silicon nitride and chromium membranes located in the reservoir underneath the gold anode. The reservoirs are then filled with the molecules or drugs to be delivered by the aforementioned reservoir filling methods and subsequently sealed. (Mark et al, 2006)

Schematic Representation of Microfabrication Process



1.) Deposit layer of insulating material,silicon nitride (0.12 mm), onto the substrate by PECVD
2.) Pattern by photolithography and square reservoirs are etched by ECR-enhanced RIE
3.) With potassium hydroxide solution at 85°C, anisotropically etch square pyramida reservoirs into the silicon along the (111) crystal
4.) Invert and deposit gold electrodes (0.3-0.5 mm thick). Pattern by E-beam evaporation and liftoff.
5.)Deposit electrode protective coating,silicon dioxide, by PECVD. Silicon dioxide over anode, cathode and bonding pads are etched with ECR-enhanced RIE to expose gold film.
6.) Remove SiN layer in the inside of reservoir by RIE to expose gold membrane.
7.) Fill reservoirs by inkjet printing through opening (500 mm x 500 mm)
8.) Bottom of reservoirs capped with a silicon nitride coating
9.) Device can now be patterned with IC control circuitry and thin-film battery.

APPLICATION

Chemicals to be released

Multiple chemicals can be stored inside and released from the microchip. Each reservoir can be filled with different chemicals or combination of chemicals. Chemicals in any form (solid, liquid, gel) can be delivered by microchip. Micro fluidic device such as pumps are limited to delivering liquids. The controlled release microchip consists of reservoir covered by a thin membrane of material that can be dissolved on demand. The form of the chemical or drug in the reservoir and the presence or absence of other materials such as polymer matrices or excipient has little or no effect on the electrochemical behavior of the membrane. Therefore, controlled release microchip has the potential for a high degree of flexibility in the type of chemicals they can store and release. (Jonh et al, 2000)

Simplicity of release mechanism

The microchip has no moving parts .A thin barrier membrane covers the each reservoir filled with one or more chemicals. The release of chemicals from the microchip is initiated by disintegration of the membrane. The membrane is removed by the application of an electric potential, which cause the membrane to dissolve by simple electrochemical reaction. The absence of moving parts potentially increases device reliability by decreasing the possibility of mechanical breakdown. (Jonh et al, 2000)

Accuracy

A Variety of highly potent drug can potentially be delivered from the microchip in a safe manner. It is important that the amount of drug delivered to a patient matches the amount prescribed, especially for highly potent compounds. Each reservoir of microchip can be accurately filled with a small amount of the drug by using microinjection or ink-jet printing techniques (J.Yoo et al 1997).The amount of the drug administered from a microchip filled by this printing methods can be tightly controlled, and accidental overdose id unlikely because release from active devices can only occur when an electric potential is applied to an anode. Larger doses can be administered by simply opening several reservoirs simultaneously. (Jonh et al, 2000)

Complex release patterns

Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchip. Any complex chemical or drug release pattern can be broken down into a combination of two parameters: Release time and Release rate. A unique feature of the controlled release microchip is the potential to control both of these parameters. The time at which release begins from any reservoir is determined by the time at which the anode membrane covering that reservoir is removed. Spontaneous release from reservoir will not occur if the anode membrane material is stable in the electrolyte solution. Therefore, an anode membrane material is selected that will not dissolve and open until the correct electric potential is applied (Jonh et al, 2000)

Potential for local delivery

The microchip can be made small enough to make local chemical delivery possible. An advantage of local drug delivery is that high concentration of drug ca be achieved at the site where it is needed, while keeping the systemic concentration of the drug at a low level. This technique is particularly useful if the drug has adverse side effect if administered systemically in high doses. (Jonh et al, 2000)

Stability enhancement

Some new protein based drugs have limited stability (i.e., shelf life).Water penetration into this protein drug formulationis one of the most frequent causes of their instability(Cleland et al, 1994).The membrane covering the filled reservoir of a microchip will prevent penetration of water into these reservoirs.Thus,the stability of protein drug is theoretically enhanced first, because the drug can be isolated from the outside environment (hermetically sealed) and second, because they can be stored in the microchip in their most stable form (solid, liquid, gel). (Jonh et al, 2000)

In cancer therapy

Measuring proteins in the blood can help doctors determine patients' cancer risk and monitor the health of the elderly and people with chronic diseases. But current methods for testing these proteins are too expensive and require too much blood to be performed regularly. A micro fluidic chip in clinical trials does on a single chip in 10 minutes what normally takes multiple technicians' hours to do and with just a single drop of blood. Researchers hope to make bedside diagnostics based on blood proteins a reality by bringing down the cost of such tests by at least an order of magnitude. The diagnostic chip is being developed by Caltech chemistry professor James Heath and by Leroy Hood, the president and founder of the Institute for Systems Biology, in Seattle. Heath and Hood have founded a company called Integrated Diagnostics to commercialize the blood chip. (Haruyama et al, 2002).

Microfluidic cell treatment

The testing of compounds on living cells is an important part of the drug discovery process, but optimal drug testing requires conditions that are as close to the physiological context as possible (Haruyama et al, 2002). In micro fluidics, the micro scale dimensions generated are approaching reaction volumes that are typically found in biological systems. Micro fluidic devices therefore make it possible to manipulate single objects of cellular size, and so analysis under controlled yet physiologically relevant environments can be achieved (Petra et al, 2006). Moreover, by parallelization of applied methods large numbers of cells can be observed simultaneously —that is, under comparable conditions. (Haruyama et al, 2002).

CURRENT DEVELOPMENTS

Microchip technology

Electronic identification or radio frequency identification technology has been tested for identification purposes for over twenty-five years. Three types of devices can be categorized, as follows:

- Implantable microchips for permanent application, which are injected or surgically implanted.
- Microchips deposited in body cavities or orally ingested for temporary application.
- Electronic devices that can be attached to the exterior of an animal.

A well-known company with the name Microchips has done research on microchip based drug delivery which is as following. (Santini et al, 1999)

- MicroCHIPS' development of a long-term implant designed to provide 100% compliant delivery of parathyroid hormone for people who suffer from severe osteoporosis. Parathyroid hormone (PTH) is the only drug therapy available in the US that has an anabolic effect on bone, resulting in marked bone growth.
- In November, MicroCHIPS' was awarded the 2008 AAPS Drug Delivery Technology Award for its osteoporosis research. The award is given by the American Association of Pharmaceutical Scientists to recognize outstanding research pertaining to novel drug delivery technologies.MicroCHIPS' device is being developed to conveniently deliver human parathyroid hormone (hPTH 1-34) to help build bone, prevent new fractures, and improve the quality of life for patients with osteoporosis.

CONCLUSION

The development and success of drug discovery is crucially dependent on available technologies. In key areas of drug discovery, such as chemical syntheses, screening of compounds and preclinical testing of drugs in living cells, microfluidic tools can make a useful contribution, and indeed represent an improvement on existing technologies. The designed microchip for drug delivery allows for storage and dependable controlled release of multiple drugs. This device is less complex and much more dependable than the aforementioned devices that attempt to control drug release rate (i.e. electro-mechanical or polymer systems). The microchip can be created by general microfabrication techniques and can also be self-contained, which eliminates the need for patient or doctor intervention. The proposed device described (assuming one dose per day) can last over a year; however, the delivery abilities do depend on patient need.

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