Drug Delivery Systems for the Treatment of Cancer - A Review

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***Abstract*: Cancer is uncontrolled growth of abnormal cells. It forms tumors which if untreated grow larger destroying the healthy cells in the body. The advent of MEMS technology has led to the evolution of a new class of drug delivery systems for various cancer types that has in turn improved the efficiency and the consent of patients. To the world of pharmaceutical industry the utmost priority is the efficacy of drug delivery and better administration of drugs with least side effects. The techniques and methods of drug delivery have shown immense potential in such administration of drugs with MEMS having come into the existence. Implantable drug delivery systems, Microneedles, Microvalves and Micropumps are all designed and fabricated on the microscale which makes them perform much better than the convention drug delivery systems, since the prior ones target specifically the affected or disease bearing cells or sites. There are various microdevices that have been designed in such a way that they can release drugs either serially or parallely and at a controlled rate and controlled time as well. This paper basically discusses about the MEMS based drug delivery devices and their features.**

Index Terms: Drug delivery, Microneedles, Microvalves, Micropumps, microfabrication

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I. INTRODUCTION

MEMS are the tiny microscopic devices that are developed by microfabrication techniques to perform electrical or mechanical functions or both. MEMS have a lot of applications in the field of biomedicine and drug delivery devices are the one amongst those. The delivery of drugs is as important as the drug itself and thereby lot of research is being carried out to come up with good drug delivery devices. MEMS technology is used in design and development of drug delivery devices. These MEMS devices can be used for controlled therapeutic delivery and their microscopic sizes help in targeting the site more precisely. These devices enable and enhance controlled drug kinetics thus avoid the wastage of the drugs and also avoid the side effects. The microneedles are almost painless. With the development of these MEMS based drug delivery devices the treatment efficiency has improved and quality of patients' life is also much better.

MEMS based drug delivery systems can deliver more than one type of medicine and precise dosage for each medicine simultaneously. They are smart devices. Micropatches and Microneedles can be used in transdermal drug delivery for targeted drug delivery and painless delivery. This makes the patients more comfortable due to reduced pain unlike in the conventional drug delivery devices. Microvalves and Micropumps are being used in implantable drug delivery systems.

II. ORAL DRUG DELIVERY

Drug administered through the mouth is the Oral drug delivery and this is the most common way of delivering drugs. Tablets, capsules or pills are given to be swallowed through mouth. But this type of drug administration is affected by mucus, PH value of saliva and body fluids present in gastrointestinal tract and hence the curing of ailments may not happen properly. Using MEMS technology the polymers of certain proteins or peptides can be delivered so that the above mentioned barriers can be overcome. Also with the use of MEMS the therapeutics can be controlled in the gastrointestinal tract and the affectivity of the dosage can be improved [1, 2]. Orally delivered particles pass through the gastrointestinal tract, the size of drug material shouldn't be that large else it could get cornered in mucus layer covering up the epithelium, there is a high probability of poison accumulation and also the poor distribution of the drug over the site [3-5].

MICROPATCH

A micropatch is a microfabricated oral drug delivery device that helps better absorption and stability of drugs in the intestinal epithelium. These patch systems are designed with thin, flexible rate controlling membrane, a drug reservoir, an impervious backing and an adhesive. These patches stick to the intestinal villi. They cause the controlled flow of drugs from the drug reservoirs present on these patches. In this way, the movement of drugs is properly regulated into the blood stream, thus, preventing any harsh effects of the drugs on the patient and also there is a lot of improvement in the patient compliance. Microfabricated patches for oral drug delivery helps in precisely controlled release of drugs to improve its effectiveness and prevent any side effects of these drugs, and also, release of drugs in the direction of the intestinal epithelium to improve the efficacy of dosage preventing the wastage of drugs and improving their therapeutic benefits [3].

Micropatches are thin and flat so that the maximum area of it can come in contact with the intestinal villi which definitely enhances the absorption. Unlike the particulate drugs which gets cornered due to mucus layer, these micropatches are very easy to transit and because of their wider structure they are not swallowed by other cells either. Due to their flat structure the probability of these getting in contact with intestinal fluids is very less, rather they quickly flow through and bioadhesion with intestinal villi takes place [6]. Different polymers can be used to make a number of reservoirs on the micropatches that can store different types of drugs. These drugs' release can be controlled from the timing and the dosage perspective. Different polymers would have different solubility and thereby drug release is more precise leading to better therapeutic effects [7, 8].

III. TRANSDERMAL DRUG DELIVERY

The permeability of skin limits the absorption of drugs with heavy molecular weight which is quite common in conventional drug delivery. The epidermal layer obstructs the flow of drug within the skin. The average thickness of this layer is 0.1mm. The advent of MEMS technology and the production of microneedles paved a way for better and precise drug delivery. The Microneedles help addressing a particular cell for the treatment by creating the micropath for it [6, 9]. These microneedles allow localized delivery of drugs that are absolutely painless. This shows that the hit only the targeted cell and thereby reduce the side effects of drug delivery to a greater extent [10]. Types of Microneedles are:

- Solid Durable Microneedles-This is most widely used microneedles array system that micropunctures the skin's epithelial cells making it more permeable

- Solid Degradable Microneedles
  In this type, entire needles are manufactured from drug infused biodegradable and water-soluble polymers. This maximizes the drug volume capacity of microneedles however their fabrication is more difficult [11]

- Hollow Microneedles- In this type of microneedle array system there are bores on the tips of the arrays which are directly connected to the reservoirs where drugs are stored. They function like a typical injection, which basically punctures the skin when pressed and releases the drugs into those punctures. Advantage of these is, they don't limit the capacity of drugs as in comparison with the other two types of microneedles but they pose the risk of getting broken under the skin due to their hollow structures.

IV. IMPLANTABLE DRUG DELIVERY

The technological advancement in MEMS technology has led to the development of various drug delivery devices that can be implanted in the human body. These tiny devices are so fabricated that they consume very less power and in conjunction with the sensors they work independently once implanted. Advantage of these devices is that they release drugs in a controlled fashion and hence are very less prone to the side effects as compared to that of the conventional ones. MEMS devices are ideal for precise and localized delivery. This improves the efficacy of the treatment.

The design parameters include applied voltage, frequency, power and the concerned parameters for model are drug absorption, toxic formation, accuracy of drug release and most importantly biocompatibility. These implantable devices are designed for in vitro and in vivo applications [12, 13]. There are two categories of implantable drug delivery devices:

- Passive Drug Delivery Device
- Active Drug Delivery Device

In passive drug delivery implantable device, the drug release happens due to diffusion [13], whereas in active drug delivery device the drug release happens due to actuation of the actuator associated with it. In active devices the drug reservoirs aren't that big since they are refillable and based on the actuators output the drug is either released or if need be refilled. Since the implantable device remains in the body for longer duration, there would be chances of toxic formation and have an adverse effect on the patients. Hence it is very much necessary that the implanted devices are biocompatible. The immune system can consider these devices an external agent and start acting against them which would hinder the performance of the devices and may lead to malfunctioning as well [14]. Hence the devices should be made of biocompatible materials and also the simulations have to run before the actual implantation so that the results can be predicted and evaluated well. Some of the biocompatible materials used for implantable drug delivery devices in today's era are SU-8, poly-Dimethylsiloxane (PDMS), Poly Methyl Methacrylate (PMMA), and parylene C [15].

MICROPUMPS

Micropumps are the devices that control and manipulate the fluid flow on a micrometer scale. Inkjet printers, blood analyzers, implantable insulin delivery systems are the common examples of the Micropumps. Micropumps have gained a lot of interest in recent years and lot of research is going in the field of biocompatible Micropumps. The developments have led to design and fabrication of various types of biocompatible micropumps. There are two categories of micropumps:

- Mechanical Micropumps

- Non-mechanical Micropumps

Based on various performance parameters such as flow rate, pressure generated, operating voltage and size different micropumps care used for different applications. Electrowetting, electrochemical and ion conductive polymer film (ICPF) actuator micropumps appear to be the most promising ones which provide adequate flow rates at very low applied voltage. Electroosmotic micropumps consume high voltages but exhibit high pressures and are intended for applications where compactness in terms of small size is required along with high-pressure generation. Bimetallic and electrostatic micropumps are smaller in size but exhibit high self-pumping frequency and further research on their design could improve their performance. Micropumps based on piezoelectric actuation require relatively high-applied voltage but exhibit high flow rates and have grown to be the dominant type of micropumps in drug delivery systems and other biomedical applications [19].

1) **Mechanical Micropumps**

These micropumps have an actuator for performing the pumping action [14]. They provide larger flow rate and the flow direction can be regulated using valves. Micropumps can use turbines to deliver constant volume of the fluid in every cycle of the pumping action [16]. Mechanical micropumps are further classified into electrostatic, piezoelectric, thermo-pneumatic, Shape memory alloy (SMA), iconic conductive polymer film (ICPF)

2) Non- Mechanical Micropump

These micropumps do not have any actuator associated for the pumping action to be performed, thus making their design and fabrication much simpler. These micropumps drive the fluid into the microchannels by converting non-mechanical energy into kinetic momentum. But the flow rate of these is not as appreciative as the mechanical micropumps. They can be driven by electrohydrodynamic (EHD), electrowetting, magnetohydrodynamic (MHD), phase transfer or electrochemical [14]. Among these, the electrochemically driven pump has lower power consumption, accurate flow rate and low heat generation [17].

MICROVALVES

Microvalves are the tiny microscopic devices that control the flow of fluids, their timing, separation or mixing and their routing in the microchannels [18]. Based on the requirement the design will be done such that the check valves remain either closed or opened so that there is the control on the fluid movement and this is the time constant. This 'time constant' is evaluated based on the design specifications for particular application. Based on the actuation of the valves they are categorized as, Electrokinetic, Pneumatic, Pinch, Phase change and burst microvalve [18]

Both the Micropumps and Microvalves together form the Implantable Drug Delivery system.

V. CONCLUSION

The controlled drug delivery has gained a lot interest in last few years since the better therapeutic effects do, not only, cure the disease but also give a better life for the patients post treatment. If the drug delivery doesn't happen well then the side effects may cause lot of pain and inconvenience for the patients than the actual disease itself. Much previous work in drug delivery focused on achieving sustained drug release rates over time, while a more recent trend is to make devices that allow the release rate to be varied over time. Advances in microfabrication technology have made an entirely new type of drug delivery device possible. Future scope is the total smart device which releases drugs, refills on its own once over and also deliver apt amount of drugs for only the targeted cells thereby minimizing the risk of side effects.

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