Microsystems in Bioscience

1) Abstract

Drug delivery had been an issue in medical science. Conventional methods are not very effective and not successful. Due to their ineffective nature micro systems have been developed. Various substances like micro needles, nano particles have been used for drug delivery in organs of our body. Besides drug delivery, various techniques have been used for gene delivery. Experiments have been done using micro substances on animals and plants .In this paper; we will review many types of Microsystems in biomedical and its recent development.

2) Introduction

In past decades, drug delivery and gene delivery was unsuccessful using conventional techniques. Reasons for its failure were their structures, causing pain in patients and they were not reaching specific target organs. Conventional methods also make blood blockages in body. Applications of micro systems in medical came in recent times leaving behind conventional method.

These technologies allows drug to be delivered at specific target and it doesn't allow blockage of blood in skin .Microsystems had received various application due to low toxicity and high effectiveness in patients...

In this paper we will first discuss micro needles. Different types of micro needles have been developed and they are formed using various fabrication methods [1], [2].They have been used for drug delivery to specific organs. Secondly we will review drug delivery to sensitive organs like heart and inner ear using micro systems [3] .Finally, we will discuss about gene delivery using cell bombardment and nano particles [4]

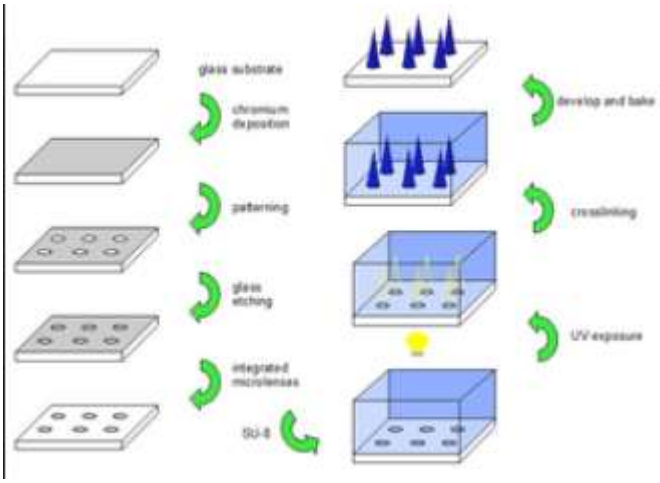
3) Microneedles

Microneedles are made up of materials like silicon, glass and metal. It is micro system technology which is use to enter drug into blood cells. They can also be use to extract blood by reversing direction. [5] In below discussion we will discuss about various developments in fabrication of micro needles.

a) In Plane microneedles

It is structure in which shaft and lumen are parallel to patient surface. It is a straight forward process .Drug delivery was made possible using fabrication in 1 d array of in plane metal micro needles [6]-[8]. Different types of fabrication techniques took place over years.

Micro molding process was used for fabrication. [9]The fabrication process is shown in below figure. The process starts with phosphorous (+) forming initial layer. KOH is making thin layer by etching process on backside of needle while lower layer is of metal. The metal layer is covered with thick toping, made up of positive photoresist materials.



This layered microneedle was able to work through skin ranging between 10 to 100 um and length of needle is 50 um to 150 millimeters. These dimensions can work for epidermis of live cells but without entering into blood vessels and other nerve endings into dermis .Dermis is place where blood vessels reside and it contains maximum nerves. So, by decreasing length of needle, which is inserted in skin can slow down the amount of pain associated with patient.

Silicon based fabrication technique was also used for fluid delivery [10].Top layer of needle is of silicon and rest area is made up of boron, which is doped in silicon using ethylene demine pyrocatechol. The layer is of 50 um to 12 um whereas length of needle is 1 to 6 mm .It also contains integrated poly crystalline silicon at end of needle .These are heated strips which allows in forming bubbles that helps in pumping of more fluids. For extra pumping, electrodes can be attached to them. Due to its advanced structures, many authors claims that drug delivery was successful

Different approach using silicon was developed [11].In this process flow was done with silicon using phosphorous (+) mask. This process uses different etching rates which allow tight control of needle. Etching is done by EDP. These process needles can be used to work for 10 to 100 um. Below 10 um, channel process blocks the passage. Needles are of 58 to 75 um and 4 mm long. The lumen is 42 um deep.

Another fabrication method which a cost efficient method [12].In this method polysilicon molding process took place. The needle consists of two halves, which are produced by micromachining of silicon wafers. The wafers are deposited by phosphosilicate glass on layer. The two halves are made to join each other by nitrogen pressure. After joining halves are covered with thin layer of amorphorous silicon by LPCVD (which is passed through holes). The resulted mold is kept inside nitrogen at 1000 celious. The above process is repeated again and again until desired mould is gained. Mould achieved can be used several times, which make this process cheaper. The resulted needle is of 7mm long.

Another process which is same as above process[12].The only difference in this process is that instead of two waffles one waffles Is used for fabrication technique[13]-[15].The waffle used Is of double polished silicon. This method helps in eliminating method of nitrogen bonding. This method is flexible in structure and cost efficient in nature.
An advanced device is formed which is in shape of mosquito [16]. Its advance shape allows this device to drag blood from body and store inside needle.

b) Out of plane microneedle

These types of needle have their lumen and needle length perpendicular to wafer substance and are controlled by working with each other. Whereas in in plane needles lumen and length are controlled by thick layer which covers the upper area of needle.

Out of plane are flexible in structure .They also have high tendency to store blood, that why it's volumetric strength is high. Its fabrication is possible by two dimensional arrays. The basic disadvantage of these needles is that structure of needles is long and doesn't require high process work. Also, its removal process is very much time consuming and very costly.

Fluid storage in these needles is through backside of needles. The manufacturing method of these needles are not done with electronic processes. Some methods of fabrications will be discussed below.

Fabrication method in which structures of array are turned into micro fabricated syringe [17] [18].Initial step for this process includes oxidization of double sided polished silicon wafers. Lumen is made to react with deep ion mask on the back side of wafers and silicon nitride film is made to cover the backside of lumen. Silicon nitrate layer is made to protect lumen. Position for needle is done through lithographically. These needles are 200 um in length and lumen is of 40 um .Authors claims that this system has reservoir of about 20ul on its back and it was successful for fluid injection on chicken thigh.

Solid silicon microneedle with no lumen has been developed for drug delivery [19] [20].Due to lack of lumens these needles can only be use for drug delivery which increases skin permeability. Process includes chrome mask reacting with deep reactive ion for etching process. The process is made to produce scanning of microscopic tips [21].Etching process is done until mask falls of. Length of needle is about 150um .Due to its robust structure, they are rarely broken during its process.

A method in which micro mashing process is used for fabrication[22].In this process upper and lower part of needle are made to react ion. A hole on top will become lumen while slot will become position of needle. Due to its sharp ends it is very successful for cutting delivery area. The length of needle is 400 um.

c) Solid Micro needles

These needles are widely used for drug delivery. They are easier to fabricate and have sharper end tips. Sharper ends increase its mechanical strength [23]. Silicon is a material which is used for its manufacturing [24] [25]. Silicon's carries various disadvantages like expensive, not compatible to skin and brittle i.e. it gets broken easily when gets connected to skin. [26] Due to silicon weakness, polymer is used instead. Polymer is cheap and strong material i.e. it avoids damaging of skin while working. Weak mechanical strength is polymer's weakness. [27]The best material of all is metal .Metal is strong mechanically and physically. Metal requires cheap manufacturing cost.

d) Hollow Micro needles

These needles are used to deliver drug through bore at needle. But these method weeks the sharpness of needle and doesn't allow proper delivery through skin. This issue was solved when drug was made to enter through opening side of needle than bottom of it. In this method, needle was closed initially but after entering inside skin tips get opened and allow full insertion of drug into skin. [28]

4) Drug delivery in Heart and Inner ear.

Various experiments have been done for drug delivery to target organs. In this section we will conclude drug delivery in heart and inner ear.

Heart diseases are major problem across world. In earlier times balloon angioplasty was used to restore blood flow. It was successful for short period of time. As patents after six months again suffer through same problem. The reason behind failure was this method was not able to reach desired target. The unsuccessful travelling of drug to target was its slow diffusion process. Rest enosis also occurs due to response of angioplasty.in this response a mass material is formed on wall of vessel.

A microfabrication chip called drug eluting stents have been developed. These stents works on drug diffusion process and have been successful to deliver to target organ. Drug is made to attach with stents and slowly drug gets diffused or delivered to vessel. [29].The The efficacy of stents depends upon tissues and cellular composition of vessel.

Earlier stents developed carries some errors and causes restenosis. Stents which have been developed recently are more technical and compact in size. These features allow delivery to vasculature of body and allow entering of drug to even in small diameters area. These stents devices are made of stainless steel and have microneedle in them. Micro electro discharge method is used for fabrication of these stents. [30]

Another organ, Inner ear was challenging for medical sciences for drug delivery. As in conventional methods, devices which used to deliver drug actually blocks blood in inner ear and doesn't allow drug to flow through it. Also, these devices reaches wrong target and make them toxic for body. Recently various approaches have been done which are based on micro systems technologies. These devices use injections which reaches inner ear directly. These devices are safe and quick as compare to conventional techniques.

We will discuss four types of approaches of microsystem for drug delivery.

a) Micro pump based system

Pump based on osmosis process are used to deliver drug in inner and middle ear of animals. Drugs are made to enter and quantity of drug depends upon the perilymph (fluid in ear) in cochlea. Osmosis occurs in outer section of pump .The outer section gives force to enter drug inside ear. The rate at which drug flow take place is 0.1 to 10 ul/hr. The rate of flow can neither be changed nor can it be stopped during injection process. These pumps have been used to control disease like NIHL, ototoxicity and vertigo and have been reviewed in paper [31]

b) Reciprocating microfluidic delivery system

The principle working of such devices are that drugs are made to enter into cochlear perilymph by single hole on tube. [32]The tube situated on devices work for extraction of fluid and also for injection of fluid.[33].Drug delivery take place when high concentration of drug is made to enter inner ear and in return low concentration of fluid is extracted out. During process and after process no change in volume takes place.

c) Directed Cochlear perfusion

In this method drug is delivered through cochlear of ear. In this method drug is allowed to enter directly to cochlear but with basal having strong gradient force. [34][35].The gradient is very useful for process as it acts as protection to cochlear and also allows regeneration of it.

d) Cochlear Prosthesis mediated delivery

It is also known as cochlear implants. It is an advanced technique which comprises of microphone, transmitter, speech processor and electrode. This device is specially designed for patients suffering from profound hearing loss. Device allows direct flow of drug into ear and it can also act as a reservoir [36].200ul drug can be delivered at very slow rate.

5) Gene delivery through microstructures.

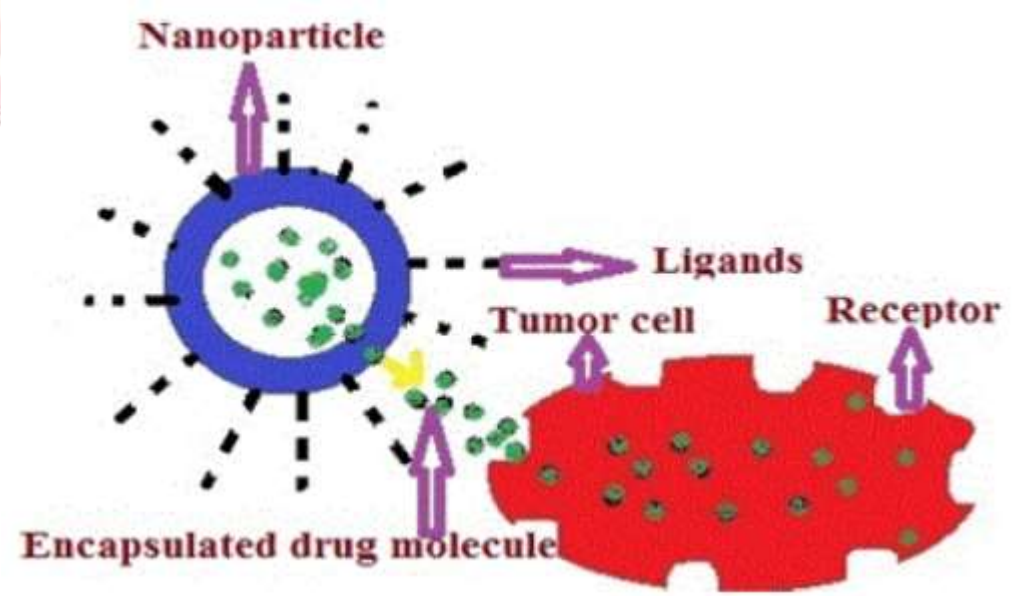
Foreign genes are made to enter plants and animals. Through various methods. Conventionally electroporation technique was used to deliver gene by using electrical field method [37].It was neglected as it consumes time and require skilled labor. But its revisable method is still used in food industry. [38].

A microstructure method which was known as micro chemical piercing [39].In this method, gene was coated on microprobes and is made to inject at target tissue. The sharp tips of probe are made to reach target cell and tissue. It was successfully demonstrated on leaf tissues [40] and mammals [41].

Nanotechnology, another method which is used for gene delivery. This technology widely used in biomedical works. It has replaced conventional method successfully. There are various nanoparticles which are used in this technology for gene delivery. Some we will be discussing.

a) Polymer nano particles

It delivers DNA to target cell by trapping target cell into its spherical structure. The targeted cell act as a gene in patent body. These particles have successfully treated various diseases which were incurable earlier [42].Sometimes for better results two particles are joined together. There best advantages are its high biocompatibility, high encapsulation capacity and its good control on release of drug to targeted cell.



b) Dendrimes

They are synthetic macromolecules which are used for gene delivery. They are highly branched structures. They can interact with both DNA and RNA using nucleic acid. There are mainly three types of dendrimes which are mentioned in table below.

Polyamidoamine (PAMAM)	Polypropylenimine(PPI)	Polyethylenimine(PEI)
These dendrimes have structures that contain amines in it. Also ,amines blocks the escape of endosomal .[43]	These dendrimes have structure which consists of protanable nitrogen [45].	These dendrimes are highly soluble in water.
It is sixth generation of dendrimes .Acc to Braun [44]; dendrimes with high generation shows high transformation and efficacy (leaving behind fact that high generation show high toxicity).	Researcher Kim examined that PPI with arigine shows high efficiency and low toxicity [46].	These dendrimes carries positively charged particles.[47]
It can be use in vitro transfection of liver9hep G2) and colon (CT26) cells. Delivery of siRNA in vivo.	It is used for gene delivery in liver widely .It is also used to deliver siRNA delivery in body.	In vivo transfection in different Cells.

6) Summary

In conclusion, micro systems have been useful for gene and drug delivery. These technologies have showed there results successfully and removed mostly all conventional methods behind.

Micro needles using various fabrications have been used for delivery and extraction of liquids in body. These needles have saved time duration and reduced pain given to patents. Stunts showed great results for delivery of drug in heart. With time and by use of latest technologies problem related to restores (which arrives during drug delivery in heart) had been reduced .Researchers are working more to completely remove this problem during process. Inner ear is always a sensitive organ due to its size. Various pumps technology like osmotic pumps has been developed to deliver drug in ear. These pumps technique doesn't make ear toxic .Various ear related disease such as hearing loss have been resolved.

Gene delivery is done through nano particles and micro piercing .Nano particles have received most successful results. Researchers have shown gene delivery using nano particles to plants and animals. Due to nano particles extremely small size, they had been use to deliver DNA and siRNA in various organs.

7) References

[1]Michael L. Reed and WHYE Kei Lye, micro systems for drug and gene delivery, IEEE January 2004

[2]Jose Juan Escobar, Isabel Marlen Rodriguez Cruz and Clara Luisa Dominguez Delgado, chemicals and physical enhancers for transdermal drug delivery, chapter-19 Intech, march 2012

[3]Erin E Leary Pararas ,David A. Borkholder and Jeffrey T. Borenstein ,Microsystems technologies for drug delivery to the inner ear ,manuscript online, published online 2012 Feb. 21 doi:10.1016/j.addr.2012.02.004

[4]Salam Massadeh, Manal Al-Amery, Shahad Bawazeer, Othman Al Ahmad, Suzan Barker and Duncan Craig, Nano materials for Gene therapy: An efficient way in overcoming challenges of gene delivery, Journal of biosensors and bioelectronics, 2016

[5] D.V Mc Allister, M.G Allen and M.R praunsnitz, Micro fabricated micro needles for gene and drug delivery', Annu Biomedical Eng, vol 2 pp-289-313, 2000

[6] J D Brazzle, I.Papautsky and AB Frazier "Micro machined needle array for drug delivery or fluid extraction", IEEE eng Med Biol, Mag, vol18 Nov dec-1999

[7] J D Brazzle, I.Papautsky and AB Frazier, "Fluid coupled hollow metallic micro machined needle aray"vol 3515.

[8] J D Brazzle, S.Mohanty and AB Frazier, "Hollow metallic micro machined needles with multiple output ports 'in Proc SPIE, Micro fluidic devices and systems 2, vol 3877, 1999

[9] J D Brazzle, I.Papautsky, H Swerdlow, R Weiss and AB Frazier "micro machined pipette array, IEEE trans Biomed Eng vol 47,2000.

[10]L.Lin and A.P Pisano "Silicon processes microneedles"J.Micro electromech syst, vol 8 March 1999

[11]J .Chen, K.D wise, J .F Hetke and S.C Bledsoe Jr."A multichannel neural probe for selective chemical delivery at cellular level" IEEE Trans. Biomed Eng Vol 44, Aug 1997.

[12]N.H Talbot and AP Pisano,"Polymolding: Two wafer polysilicon micromoulding of closed flow passages for micro needles and micro fluidic method" in Tech Dig. Solid State sensor and actuator workshop, 1998.

[13] J.D Zahn, N.H Talbot, D.Liepemann and AP Pisano,"Microfabricated polysilicpon micro needles for minimally invasive biomedical devices." Biomed vol 2, no-4.

[14] J.D Zahn, D. Trebotich and D.Liepemann,"Microfabricated micro dialysis micro needles for continuous medical monitoring" in Proc. 1st Annu Int IEEE special Topic Conf Micro technologies Medicine and Biology, 2000.

[15]] J.D Zahn, A.A Deshmukh, D.Liepemann and AP Pisano,"Continous on chip micro pumping through a micro needle" in Tech Dig 14 Th IEEE Int Conf Micro Electro systems, 2001.

[16]K.Oka, S.Aoyagi Y.Arai, Y.Isono, G. Hashiguchi and H.Fujita "fabrication of a micro needle for trace blood test" Sens.Actuators A, Phy ,2002.

[17]B.Stoeber and D. Liepmann"Two Dimensional array of out of plane needles "in Proc ASME int. Mechanical Engineering Congr. And Exposition, 2000.

[18] B.Stoeber and D. Liepmann "Fluid injection through out of plane micro needles" In Proc 1st Annu Int IEEE EMBS Special topic Conf. Micro technologies medicine and Biology,2000.

[19]S.Henry, D.V Mc Allister, M.G Allen and M.R Prausnitz "Micro fabricated micro needles: A novel approach to transmittal drug delivery" J. Pharm Sci, Vol 87, 1998.

[20] S.Henry, D.V Mc Allister, M.G Allen and M.R Prausnitz " Micro machined needles for transmittal delivery of drugs" in Proc IEEE 11th Annual Int workshop Micro electro mechanical systems,1998

[21]H.Jansen, M.de Boer, B.outer and M. Elwenpoek "The black silicon method IV: the fabrication of three dimensional structures in silicon with high aspect ratio for scanning probe microscopy and other application.

[22]J.G.E Gardeneirs ,J.W Berenshot, M.J de Boer ,Y.Yeshurun M.Hefetrz, R.vant Oever and A.Van den berg "Silicon micro machined hollow micro needles for liquid transformation "in Proc IEEE conf,2002

[23]Roxhed N, Samel B,Nordquist L,Griss P& Stemme G(2008),Painless drug delivery through micro needle based transdermal patches featuring active infusion ,IEEE ,Transactions in Biomedical Engineering, Vol 55 No-3

[24] Donnelly RF, Morrow DI, McCarron PA, Woolfson AD, Morrissey A, Juzenas P, Juzeniene A, Lani, V, McCarthy HO & Moan J," Micro needle arrays permit enhanced intradermal delivery of a preformed photosensitizer. Photochemistry and Photobiology. Vol. 85, pp. 195-204, ISSN 1751-1097, 2009

[25] Haq MI, Smith E, John DN, Kalavala M, Edwards C, Anstey A, Morrissey A & Birchall JC,"Clinical administration of micro needles: skin puncture, pain and sensation", Biomedical Micro devices. Vol. 11, pp 35–47, ISSN: 1387-2176, 2009

[26] Chen B, Wei J, Tay FE, Wong YT & Iliescu C,"Silicon micro needle array with biodegradable tips for transdermal drug delivery. Micro system Technologies" Vol. 14, No. 7, pp. 1015-19, ISSN: 0946-7076, 2008

[27] Park JH," Polymeric micro needles for transdermal drug delivery. PhD Thesis. Georgia Institute of Technology", 2004

[28] Roxhed N, Samel B, Nordquist L, Griss P & Stemme G," Painless drug delivery through micro needle-based transdermal patches featuring active infusion" IEEE Transactions in Biomedical Engineering. Vol. 55 No.3, pp. 1063-71. ISSN: 0018-9294, 2008

[29]C, W.Hwang, D.Wu and E.R Edelman, "Physiological transport forces governs drug distribution for stent based delivery", Circulattion vol.104, 2001.

[30]K.Takahata and Y.B Gianchandani "coronary artery stents micro fabricated from planar metal foil: Design fabrication and mechanical testing" Proc 16 th IEEE int conf Micro electro mechanical systems, 2003.

[31]Swan EEL, Escher MJ ,Sewell WF ,Tao SL ,Borenstein JT, "Inner ear drug delivery for auditory application", Drug Del Rev.2008,PMC free article ,Pub med.

[32]Sewell WF,Borenstein JT,Chen Z,Fiering J,Handzel O,Holmboe M,Kim ES,Kujawa SG,McKenna MJ,Mescher MM,Murphy B,Swan EE,Peppi M,Tao S.Development of a microfluidics based intracochlear drug delivery devices" Audio Neurootol,2009.

[33]Chen Z, Kujawa SG, McKenna MJ, Fiering JO, Mescher MJ, Swan EEL, Sewell WF,"Inner ear delivery via a reciprocating perfusion system in the guinea pig J controls Release, 2005.

[34]Plontke SK, Biegner T, Kammerer B, Delabar U, Salt AN,"Dexamethasone concentration gradients along scala tympani after application to the round window membrance", Neutrol, PMCfree article, 2008

[35]Chen Z,Mikulec AA,Mc Kenna MJ,Sewell WF,Kujawa SG,"A method for intracochlear drug delivery in mouse",J Neuroci method,2006

[36]Shepherd R,Xu J,"A multichannel scala tympani electrode array incorporating drug delivery system for chronic intracochlear infusion", 2002,172 92-98.

[37] H.Potter, L.Weir and P.Leder,"Enchancer dependent expression of human k immune globin genes introduced into mouse pre-b lymphocytes by electroporation", 1984

[38] Ball C, Thomson KR, Kavnoudias H.irreversible electroporation: A new challenge in "out of operating theater", Anesthesia. Anesthesia Analgesia, Vol110, 2010.

[39]R.Dizon,H.Han,A.G Russell and M.L Reed, "An Ion milling pattern transfer technique for fabrication of three dimensional micromechanical structures",J. Microelectromech sys vol 2 ,1993.

[40]W.Trimmer,P.Ling C.K Chin P.Orton,R.Gaugler,S.Hashmi,G.Hashmi,B.Brunett and M.L Reed "Injection of DNA into plant and animal tissues with micromechanical piercing structutres"in Proc 8 int workshop micro electro mechanical systems,1995.

[41]M.D Feldman,B.Sun,B.J Koci,C.C Wu,J.R Kneller,H.S Borovetz ,S.Watkins,A.Nadeem,L.E Weiss M.L Reed,A.J.C Smith and W.Rosenblum"Stent-based gene therapy" JLong term effects Med Implants,vol 10,2000.

[42]Choi K, Jang M, Kim J, Ahn HJ,"tumor specific delivery of siRNA using supramolecular assembly of hyaluronic acid nanoparticles and 2b RNA binding proteins/si RNA, Biomaterials 35:7121-7132, 2014

[43] Tang Y,Li YB,Wang B,Lin RY,van Dongen M,et al,"efficient in vitro siRNA delivery and intramuscular gene silencing using PEG-modified PAMAM dendrimers ",Mol Pharma 9 1812-1813,2012

[44]Shah V,Taratula O,Garbuzenko OB,Patil ML,Savla R,"Genotoxicity of different nanocarriers:possible modifications for the delivery of nucleic acid",Curr Drug Discov Technol 10,2013

[45]Taratula O, Garbuzenko OB, Kirkpatrick P, Pandya I, Savla R,"Surface engineered targeted PPI dendrimer for efficient intracellular and intratumoral siRNA delivery", J control release 140:284-293, 2009.

[46]Intra J,Salem Ak,"characterization of the transgene expression generated by branched and linear polyethylenimine-plasmid DNA nanoparticles in vitro and after intraperitoneal injection in vivo", Fifth int,Nanomedicine Drug Deliv, sym,130,2008.

[47]Arima H, Motoyama K, Higashi T,"Sugar appended polyamidoamine dendrimer conjucates with cyclodextrins as cell specific non viral vectors", Adv Drug delv rev 65:1204-1214, 2013