Drug Delivery System Using Polymers (Lactide–Co-Glycolide)

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Abstract — **For last decade, we are developing the novel local drug delivery devices using biodegradable polymers, especially polylactide (PLA) and poly(D,L-lactide-co-glycolide) (PLGA) have been developed in our labaortory due to its relatively good biocompatibility, asily controlled biodegradability, good processability and only FDA approved synthetic degradable polymers. The relationship between various kinds of drug and different types of geometrical devices and pharmacological activity are proposed and discussed for the application of pharmaceutics formulations. Also, local drug delivery devices proposed in these works are introduced in view of preparation method, drug release behavior, biocompatibility, pharmacological effect, and animal studies. In conclusion, we can control the drug release profiles varying with the preparation, formulation and geometrical parameters. It is very important to design a suitable formulation for the wanted period of bioactive molecules loaded in biodegradable polymers for the local delivery of drug. The drug release is affected by many factors such as hydrophilicity of drug, electric charge of drug, drug loading amount, polymer molecular weight, the monomer composition, the size of implants, the applied fabrication techniques, and so on.**

Keywords — **local drug delivery system, delivery devices, biodegradable polymers, pharmaceutics.**

I. Introduction

It has been recognized that biodegradable polymers have become increasingly important in the development of drug delivery system (DDS) during the past two decades. Massive researches have been done to designed appropriate devices like microspheres (MSs) and nanospheres, injectable form, wafer, tablet, and so on using synthetic and natural biodegradable polymers.[1] In the 1970s, simply and mainly long term controlled release devices of contraceptive steroids, local anesthetic, narcotic antagonist, anticancer and antimalarials drugs were developed to test the possibility of the pharmacological activities and elimination of the inconvenience of the repeated injection. Beginning of1980s, rapid and innovative progress in the area of biotechonolgy, especially cell and cloning technology, made possible the successive and massive production of therapeutic peptides and proteins like cytokine, monoclonal antibody, hormone and growth factors. So, DDS using biodegradable polymers were extensively studied and commercialized for these peptides and proteins to achieve efficiency and to increase patient compliance. It can be avoided the difficulties associated with parental and oral delivery and patient compliance problems. Above DDS method would deliver the drug at a continuous rate, and reduce the dose-dependent toxicity by minimizing the fluctuation in plasma concentration.

Biodegradable polymers for local delivery system for DDS have been applied. Among of these biodegradable polymers, one of the most significant candidates for the development of the biodegradable polymeric controlled release system is the poly(a-hydroxy acid)s family such as poly(glycolide) (PGA), poly(L-lactide) (PLA) and its copolymers as poly(L-lactide-co-glycolide) (PLGA; chemical structure) which is only approved by the Food and Drug Administration (FDA) due to its controllable biodegradability and relatively good biocompatibility.[2] It provides many advantages such as regulating varying degradation period according to the molecular weight and mole fraction of lactide and glycolide in the copolymer, especially PLGA, producing toxicologically safe by-products that are further eliminated by the normal metabolic pathways.

Typical and successful commercial product is Lupron Depot® (leuprorelin acetate) and Decapeptil® (tryptorelin) composed of LH-RH agonist in biodegradable PLGA for the treatment of advanced prostatic cancer and endometriosis. Another successful commercial product is Gliadel® wafer which composed of polyanhyride polymer and BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) for the treatment of malignant brain tumor. This localized and controlled delivery device of anticancer agent using biodegradable polymeric implant provides to solve the problem of low penetration of blood brain barrier (BBB).[3]

This presentation will be discussed for recent our works on the development of various drug delivery applications with like MSs, microcapsule, nanoparticle, wafers, pellet, beads, multiple-layered beads, implants, fiber, scaffolds, and films applied using PLGA, PLA and PHVB biodegradable polymers during last 5 years.[4] Water soluble small molecule drugs [gentamicin sulfate (GS), fentanyl citrate (FC), BCNU, pamidronate (ADP), 5-fluorouracil (5-FU), azidothymidine (AZT), 1,25$(OH)_2$ vitamin D_3], water insoluble small molecule drugs [fent-anyl, ipriflavone (IP)

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and nifedipine], and water soluble large molecule drug[nerve growth factor (NGF),[5] vascular endothelial growth factor,[6] brain derived neurotrophic factor and Japanese encephalitis virus (JEV)] were applied for the development of local DDS devices.

Table 1 Typical Biodegradable Polymers Used In DDS.

Natural Biodegradable Polymers	Synthetic BiodegradablePolymers
- Polypeptides and proteins: Albumin, fibrinogen, gelatin, Collagen, etc - Polysaccharides: Hyaluronic acid, starch, chitosan - Virus and living cells: Erythrocytes, fibroblast, Myoblasts, etc.	- Aliphatic polyesters of hydroxy acids:PLA, PGA, PLGA,poly(hydroxybutyric acid),poly(e-caprolactone) - Polyorthoester - Poly(alkylcarbonate) - Polyaminoacids - Polyanhydrides - Polyacrylamides - Poly(alkyl-a-cyanoacrylate)s - Etc.

II. Applications

A. *JEV Vaccine Loaded PLGA MSs for the Oral Immunization*

The extensive studies for biodegradable MSs with incorporated antigens as oral vaccine are of particular interests in making currently available vaccines more effective and in developing new vaccines against infections for which no currently exist.

The control of some fabrication parameters for the preparation for JEV vaccine as a model vaccine loaded PLGA MSs have been investigated such as the types of emulsifier (polyvinylalcohol (PVA) and sodium dodecyl sulfate (SDS)), the concentrations of emulsifier, agitation speed, and the concentration of PLGA in W/O/W method. Also, the effect of surface morphology on biodegradation of PLGA has been observed. For the oral vaccination of JEV/PLGA MSs via the across the gastrointestinal tract as Peyers patches, the size of MSs must be below around 15.0 mm. For the satisfaction of this size, the rate of agitation of 2000 rpm could be minimum stirring speed in this study with 5.0 w/v% of PLGA concentration, and 100 mL of 1.0 wt% PVA. To investigate the effect of emulsifier types on the surface morphology of JEV vaccine loaded PLGA MSs, two kinds of emulsifiers as PVA and SDS were applied. In conclusion, the formulation and the process variables play important roles in morphology of PLGA MSs, biodegradation of PLGA MSs and resulting the release pattern of drug.[7]

B. *GS Loaded PLGA MSs*

Controlled GS releasing MSs manufactured from biodegradable PLGA (75:25 by mole ratio) were prepared with an oil/oil solvent evaporation method. The MSs of different size (30~350 mm) were obtained with varying the experiment conditions, and the shape of MSs was smooth and spherical. The efficiency of encapsulation was over 81%. The effects of the preparation conditions on the size of MSs have been investigated. In vitro release studies showed that different release patterns and release rates could be achieved by simply modifying factors in the preparation conditions such as polymer concentration, surfactant concentration, molecular weight of PLGA and initial amount of drug. PLGA MSs with 20% of initial drug loading, 0.2% (w/w) of surfactant concentration and 50% (w/v) of PLGA concentration, were free from initial burst effect and a near-zero order sustained release was observed for over 60 days. The release of GS loaded MSs with larger size like over 300 mm was more prolonged over 2 month, whereas small size batch like below 100 mm was observed burst effect. This study demonstrated that the release pattern of drug from MSs could be improved by optimizing the preparation conditions of MSs.[8]

C. *Glycolide Monomer Containing GA-Loaded PLGA Microparticles by Melt Extrusion*

For the achievement of more precise release pattern of GS, we developed GS-loaded PLGA microparticle (GSMP) containing glycolide monomer (GM) prepared by melt-extrusion method. After the preparation of polymer blend by melt extrusion, the powders of different sizes (90~1000 mm) were obtained by freezer mill as shown in Figure 8. In vitro drug delivery release study was performed in pH 7.4 phosphate buffered saline (PBS). GSMP released from 2 days to 7 days in case of the highest loading amount of GM (10%) and showed a near-zero-order with initial burst. GM affected to increase of GS release during the in vitro release test, which was the positive result of what would be expected based upon decrease of pH of medium. The morphological evaluations of samples were characterized by SEM. GM did not distinctive influence to change of morphology by the analysis of GPC and DSC, respectively. Bacterial inhibition zone test was established to identify antibiotic activity of GS.

From these results, we expected that containing GM would be a good dosage form with the sustained release pattern to deliver the antibiotic for the prevention of infections after surgery for 1 week or more. This locally sustained delivery form of scattering powders at infection site will be may be decreasing the side effects comparison to oral dosage forms with high dosage and frequent

administration. Moreover, this delivery system has an advantage which does not need to remove the any materials after surgery due to its spontaneous degradation property by human body fluid.[9]

D. Preparation of Fentanyl-Loaded PLGA MSs

Fentanyl loaded biodegradable PLGA MSs were prepared to study the possibility for long acting local anesthesia. We developed the fentanyl base (FB, slightly water soluble)-loaded PLGA MSs by means of conventional O/W solvent evaporation method. The size of MSs was in the range of 10~150 mm. The lowest porous cross-sectional morphology and the highest encapsulation efficiency were obtained by using gelatin as an emulsifier. The influences of several preparation parameters, such as solvent types (MC and ethyl acetate), emulsifier types (gelatin and PVA), molecular weights and the concentrations of PLGA, and initial drug loading amount, etc, have been observed in the release pattern of fentanyl. The release of fentanyl in in vitro was more prolonged over 25 days, with close to zero order patterns by controlling the preparation parameters. We also investigated the physicochemical properties of fentanyl-loaded PLGA MSs by XRD and DSC.

From the results of preparation conditions, the encapsulation efficiencies of fentanyl were between 61.5 and 99.8%, depending on the particular formulation. The total MSs recovered amount varied between 52.8 and 87.6%. It was observed that the encapsulation efficiency and the yield decreased as a function of the increase in initial drug loading amount. As increasing of PLGA concentration from 3 to 20%, encapsulation efficiency was increased from 62.7 to 99.8%. Similar results were also obtained when decreasing the solvent volume. We assumed that the dominating loss of fentanyl must be due to transport of droplets of the O phase to the W phase. The increased viscosity in the O phase caused by the increased PLGA concentration or decreased solvent volume will decrease the loss transport of fentanyl and contribute to the enhanced entrapment efficiencies. Moreover, the O droplets containing fentanyl formed from the W phase were very small and the diffusion amount of fentanyl to the external phase during the solvent evaporation was relatively small, explaining the high encapsulation efficiency obtained. The pattern of drug release depends on various factors, such as initial drug loading ratio, polymer concentration, and solvent volume in W phase. Generally, small size and fast drug release are attributed to more water uptake, swelling ratio, and polymer degradation. In contrast, in our case, fentanyl release rate from the all batches decreased with decreasing MSs size. It might be suggested that the drug release profiles would be affected by the morphology of the MSs increased concentration of O phase made porous stable MSs and resulted in denser MSs. In conclusion, this sustained, besides, constant localized release system can potentially provide anesthesia for a longer period than injection or topical administration.[10]

E. Characteristic of Nifedipine Loaded PLGA Wafer

Nifedipine also was chosen as the model drug for the PLGA wafer for the local delivery device due to practically insoluble drug in water with solubility less than 10mg/ml, a well known and most widely used coronary vasodilator from the group of dehydropyrine derivatives. Biodegradable wafers were prepared with PLGA oligomer (50: 50 mole ratio, molecular weight 5000 g/mole) by direct compression method for the sustained release of nifedipine to investigate the possibility of the treatment of hypertension. PLGA wafers were prepared by altering initial drug/polymer loading ratio, wafer thickness, and HPMC content, and their morphology and release pattern have been investigated. These wafers showed steady static release pattern for 11 days, and various biphasic release patterns could be obtained by altering the composition of wafers such as addition of matrix binder as HPMC to the PLGA wafer to reduce release rate of initial phase. The onset of polymer mass only occurred after 4 days and about 40% of mass loss was observed after 11 days nifedipine release. This system had advantage in terms of simplicity in design and controling of drug release rate and may be useful as an implantable dosage form.[11,12]

F. Treatment of Aural Cholestoma Using ADP-Loaded PLGA Wafer as Local Delivery System.

Implantable biodegradable wafers were prepared with ADP-loaded PLGA (75:25 mole ration by lactide to glycolide, molecular weight: 20000 g/mole) by direct compression method for the sustained release of ADP to investigate the possibility for the treatment of bone resorption.[92-94] The release pattern of ADP/PLGA wafers were observed by HPLC and the wafers were implanted the Mongolian gerbils mastoid. The release rate of APD increased with increase of its initial loading amount as shown in Figure 19. We also measured the osteoclast index (Figure 20), i.e, number of osteoclast cell per total bone length and the surface area of osteoclast cell per total bone surface in experimental cholestoma, in which APD/PLGA wafers were implanted. The result indicated these wafers could reduce the osteoclast activities in experimental aural cholestoma. It may suggest the possibility for the treatment of bone resorption by implantable dosage form.[13]

III. Conclusions

Until recently, many biodegradable polymers come from natural and synthetic have been tested and applied for the development for drug carrier of DDS based on the following three mechanisms: mucosal absorption, controlled release and targeting. Among of these polymers, PLGA and PLA seems to be most desirable for the drug delivery device as many different types. Also, we can relatively and easily control the drug release profiles varying with the preparation, formulation and geometrical parameters. Moreover, any types of drug such as water-soluble, water-insoluble, small, large molecule, negatively or positively charged, and so on were successfully applicable to achieve linear sustained release from short period (1~3 days) to long period (over 2 months), in other words, it is very important to design a suitable formulation for the predetermined releasing period of bioactive molecules loaded biodegradable devices. The form of device can be MSs, microcapsule, nanoparticle, wafers, pellet, beads, multiple-layered beads, implants, fiber, scaffolds, and films for the purpose of local delivery in the research area of drug delivery and tissue engineering. It is also considered the drug release is affected by many factors such as hydrophilicity of drug, electric charge of drug, drug loading amount, polymer molecular weight, the monomer composition, the size of implants, the applied fabrication techniques, and so on.

It is well known that the development of new drug needs lots of money (average: over 10 million US dollar per one drug) and long time (average: above 9 years) whereas the development of DDS for potent generic drug might be need relatively small investment and short time. Also, one core technology can be applicable to many drugs to meet the market within time frame. From these reasons, the research on DDS for potent generic drug has less risk and high return than new drug development. For the next DDS generation, DDS will provide more complex release control such as a stimulus control, sensor control, and targeting using "intelligent" PLGA or PLA biodegradable materials responsive to external stimuli and more complex devices mimicking viruses or living cells such as drug self-producing system without need for a periodic drug supply must be necessary.

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