PLGA Nanoparticulate System for Idealization of Drug Carrier

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PLGA nanoparticles (NP) have been extensively studied for many years. Nowadays poor solubility drug and peptide-like drug can be well encapsulated in nanoparticles by controlling different conditions such as formulation, preparation parameters and preparation method, and drug delivery systems be widely applied for various kinds of drugs. The aim of this review is to introduce the history of PLGA nanoparticles, the preparation method of PLGA nanoparticles and application of PLGA nanoparticles. Many examples including our own groups' are cited to provide the readers with an extensive knowledge about PLGA nanoparticles

Keywords: PLGA; Nanoparticles; Preparation; Oral; Ocular; Pulmonary; Gene

1.Introduction

1.1 Nanoparticles (NP)

NP have been studied extensively as particulate carriers in several pharmaceutical and medical fields. The research was historically initiated by the group of Speiser in the 1970s [1,2,3].In recent years, significant effort has been done to develop nanoparticles for drug delivery systems in order to solve the challenges of drug delivery. The NP systems offer a suitable means for delivering low molecular weight drugs, as well as macromolecules such as proteins, peptides or genes by either localized or targeted delivery to the tissue of interest. They can be administered via different routes of administration, such as parenteral, oral, intraocular, transdermal or pulmonary inhalation. The size range of these delivery systems is typically less than 1000 nm in diameter. Due to the sub-cellular and submicron size, thereby increased surface area and quantum effects, the system can offer certain distinct advantages for drug delivery compared to the larger size, which was with the same material. Generally, the aims of these systems can be classified as follows:

- to improve the bioavailability of drugs with poor absorption characteristics. With the smaller size, NP have in general relatively higher intracellular uptake [4] compared to microparticles, therefore allows an increasing bioavailability. It was demonstrated that when the formulations of nano- and microparticles were tested in a rat in situ intestinal loop model, the efficiency of uptake of 100 nm size particles was 15-250 fold greater than larger size (1 and 10 μm) microparticles [5].
- to provide targeted delivery of drugs to the very specific sites of action, organ or tissue.
- to solubilize drugs for intravascular delivery.
- to control the release of drugs, and even maintain them in the targeted regions.
- to reduce the GI mucosa irritation caused by drugs.
- to improve the stability of therapeutic agents against enzymatic degradation [6,7].
- Furthermore, these nanoparticle-drug formulation reduces the patient expenses, and risks of toxicity [8].

Nanomedicines of the dreadful diseases like cancer, AIDS, diabetes, malaria, prion disease and tuberculosis are in different trial phase for the testing and some of them are commercialized[9,10]. The targeting capabilities of NP

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are influenced by particle size, surface charge, surface modification, and hydrophobicity.

1.2 PLGA

Materials used for nanoparticle drug delivery must fulfill several requirements, such as biocompatibility, drug compatibility, suitable biodegradation kinetics and mechanical properties, as well as ease processing. Synthetic polymers and natural macromolecules have been extensively researched as colloidal materials for nanoparticle production designed for drug delivery because synthetic polymers have the advantage of high purity and reproducibility over natural polymers. Polylactide, polyglycolide, and their copolymers poly(lactide-co-glycolide), polycaprolactones, polyacrylates, polyacrylics, poly(vinyl chloride- co-acetate) and polystyrene were usually used for preparation of NP.

Among them, the copolymer poly (lactic-co-glycolic acid) (PLGA), has a long history and vast extent of use as biomaterials due to their excellent biocompatibility and biodegradability. It is synthesized by means of random ring-opening copolymerization of two different monomers, the cylic dimmers (1,4-dioxane-2,5-diones) of glycolic acid and lactic acid. During polymerization, successive monomeric units (of glycolic or lactic acid) are linked together in PLGA by ester linkages, thus yielding a linear, amorphous aliphatic polyester product. They exhibit a wide range of physicochemical properties by varying the ratio of lactic acid moiety to glycolic acid moiety in the copolymer. Solvation in organic solvent is also dependent on the lactide:glycolide ratio because the lactide is hydrophobic while glycolide is hydrophilic [11]; a 50:50 ratio is commonly used in NP fabrication. The amphipathic properties of PLGA could be changed by varying their composition [12,13] and the selection of PLGA with desired composition becomes critical in the research and formulation of protein drug delivery systems [14]. On exposure of PLGA NP to an aqueous environment, degradation of PLGA occurs through hydrolysis of the ester linkages [15]. Lactic acid and glycolic acid are freed and eliminated from the body solely by metabolism and exhalation as carbon dioxide and water in the case of lactic acid or in combination with direct excretion via the kidneys in the case of glycolic acid [16,17], and there is very minimal systemic toxicity associated by using PLGA for drug delivery or biomaterial applications. Therefore, PLGA has been approved by US Food and Drug Administration (USFDA) for human use over 30 years. In this review, we will summarize the preparation methods of some types of PLGA NP based on chemical reactions as drug carriers. Furthermore, we will describe some of the applications of PLGA-based nanomedicines.

2. Preparation of NP

2.1 Methods of PLGA NP preparation

Usually, bottom-up and top-down techniques are the most classic methods for PLGA NP synthesis. The bottom-up techniques, such as emulsion or microemulsion polymerization, interfacial polymerization and precipitation polymerization, which employ a monomer as a starting point. But there are several drawbacks such as the probable presence of the residual, the potentially toxic monomers or oligomers. In addition, the polymer aggregation is often observed at high polymer concentration or low organic solvent/water ratio. From previously published papers, NP are most often synthesized from the top-down techniques, such as emulsion solvent diffusion method, emulsion solvent evaporation, and salting out, by using pre-formed polymer. So, the top-down methods are reviewed in this paper.

2.1.1 Emulsion solvent diffusion method

Emulsion solvent diffusion (ESD) is one of the most commonly used techniques for preparing PLGA NP. It can be classified into two categories: the “in water” method, the “in oil” method and emulsion phase separation method in oil.

Generally, in the “in water” method, the PLGA and lipophilic drugs are dissolved in an organic solvent (EtAc, MEK,PC,BA,etc.), which must be partially miscible in water, then poured into aqueous phase with or without emulsifier/stabilizer (mostly water), subsequently emulsified, and finally, the PLGA polymers are separated as particles mostly by centrifugation. Finally, the NP is powdered by lyophilization. The powdered NP can be readily dispersed to form a colloidal suspension just by rehydrating.

The principle is that when the polymer solution is poured into aqueous solution, a o/w emulsion is spontaneously formed due to immediate reduction of the interfacial tension with rapid diffusion of organic solvent into the aqueous phase (the Marangoni effect) [18]. After the diffusion, the NP is obtained by coprecipitation of polymer and drug because of the reduction in solubility. For the formulation of PLGA NP, polyvinyl alcohol (PVA) has been the

most commonly used as emulsifier [19], because the particles formed using this emulsifier are relatively uniform and smaller in size, and are easy to be redispersed in aqueous medium. It is reported that a fraction of PVA remains on the nanoparticle surface and prevents the aggregation and fusion of emulsion droplets, furthermore it also can affect the physical and cellular uptake properties of NP [20]. By using this method, PLGA NP with narrow distribution and ready dispersibility can be obtained (Fig.1).

The typical "in water" method of PLGA nanoparticles was previously reported by Kawashima et al [21]. PLGA (100 mg) and the weighed drug (TRH, 5 mg or elcatonin, 1 mg) were dissolved completely in a mixture of acetone (2 ml) and methanol (1 ml). The resultant organic solution was poured into 25 ml of an aqueous PVA solution (1.0%, w/v) and stirred at 400 rpm using a propeller type agitator with three blades for 5 min. The entire dispersed system was then centrifuged (43, 400 g for 10 min; Kubota 7800, Kubota, Japan) and resuspended in distilled water. This process was duplicated. The resultant dispersion was dried using a freeze drying method. However, when using this method, water-soluble drugs tend to leak from the emulsion droplets during the solvent diffusion process, resulting in a low degree of entrapment of drug. To improve the encapsulation efficiency of water soluble drugs, two strategies were made. One is to enhance the liposolubility of the hydrophilic molecules. In our study, we modified insulin with sodium oleate to form a more hydrophobic complex, and the encapsulation efficiency of insulin increased from 42.5% to 93.2%. Due to the formation of the hydrophobic complex, insulin was much easier to be dissolved in organic phase, and the affinity to PLGA was evidently increased. The other way is to change the dispersing medium from an aqueous solution to a medium chain triglyceride (MCT, caprylate and caprate triglyceride), which called "in oil method". PLGA-drug NP can be prepared by pouring the organic solution containing PLGA and drug into an oily medium. The difference between the two methods, ESD in water and in oil, involves the submicronized emulsion formation process. In the "in water" method, the emulsion is spontaneously submicronized due to the rapid solvent diffusion at the surface of droplets. In the "oil" method, however, such rapid diffusion does not occur.

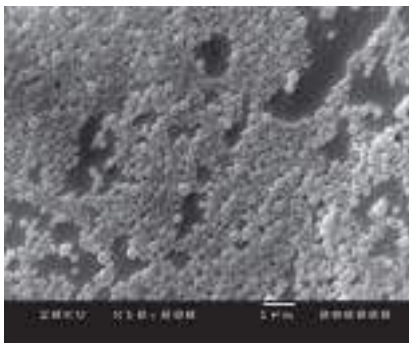

Fig.1 The scanning electron microphotograph of PLGA nanospheres with insulin prepared by the emulsion solvent diffusion method in water

The typical preparation method of NP by using "in oil" method was illustrated as follows [21]: The PLGA (100 mg) and the weighed drug (TRH, 5 mg or elcatonin, 1 mg) were dissolved in a mixture of acetone (2 ml), methanol (1 ml) and Span 80 (100 mg). The resultant polymer-drug solution was emulsified into Triester F-810 containing 2% (w:w) HGCR (50 ml) using a high shearing homogenizer, (Pyscotoron®, Nition, Japan) for 5 min. Decomposition of the drug under high shear homogenization was not detected. The entire dispersed system was then centrifuged (43, 400 g for 10 min). The sediment was dispersed with hexane and centrifuged under the same running condition as above. The sediment was dispersed in an adequate volume of PVA solution (ca. 5 ml). An additional dispersing in distilled water (ca. 5 ml) was carried out. The resultant dispersion was then freeze dried.

In addition to the "in water" and "in oil" methods, emulsion phase separation method in oil was also studied by our group. The typical preparation method was also reviewed before [21]. Specifically, the drug (TRH, 5 mg or elcatonin, 1 mg) was dissolved in distilled water (0.5 ml) and then emulsified into the dichloromethane (15 ml)-acetone (0.5 ml) mixture containing the dissolved PLGA (100 mg) and Span 80 (100 mg), using a homogenizer (15 000 rpm) (Physcotoron). The addition of the triester oil dissolved 2% (w/w) of HGCR (30 ml) into the resultant water-in-oil (w/o) emulsion, induced the phase separation of PLGA when stirred with a magnetic stirrer. During evaporation of the dichloromethane under reduced pressure (for 3 h), the coacervated droplets enclosing the drug were transformed into nanospheres in the oily medium. The entire dispersed system was filtered through a 400 mesh sieve (opening, 37 μm) and a poly(tetrafluoroethylene) membrane filter (pore size, 1.0 μm, PTFE; T100A047A, Toyo Roshi, Japan) to remove the aggregates and oil. The

nanospheres remaining on the membrane filter were washed with n-hexane and water to remove the oil and unencapsulated free drug crystals, respectively, and then dried. The schematic procedures of Emulsion solvent diffusion methods are shown in Fig.2, Fig.3 and Fig4.

2.1.2 Solvent emulsion evaporation

The significant difference between emulsion solvent diffusion method and solvent emulsion evaporation method lies in whether the organic solvent is volatile. In the solvent evaporation method, the organic solvent is volatile (such as DCM, acetone, $CHCl_3$, EtAc, etc.), and finally was evaporated. Furthermore, PVA is also used as emulsifier. A variety of therapeutic agents including low molecular weight lipophilic or hydrophilic drugs and high molecular weight DNA or antisense can be encapsulated in NP using emulsion solvent evaporation technique [22].

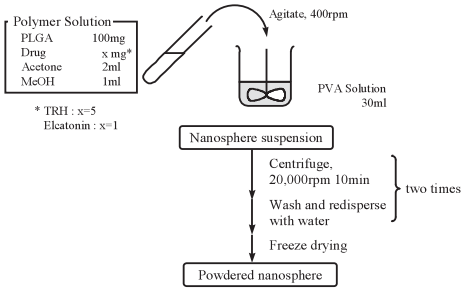

Fig.2 Schematic procedure for the preparation of PLGA nanospheres with emulsion solvent diffusion method in aqueous PVA solution (solvent diffusion method in water)

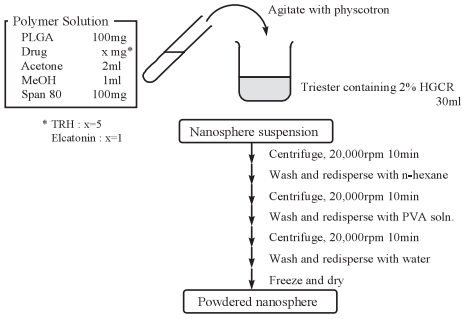

Fig.3 Schematic procedure for the preparation of PLGA nanospheres with emulsion solvent diffusion method in triester (solvent diffusion method in oil)

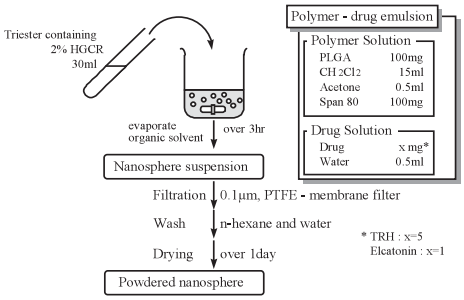

Fig.4 Schematic procedure for the preparation of PLGA nanospheres in triester oil system (phase separation method)

2.1.3 Salting out method

In this preparation method, the polymer is dissolved in water-miscible the organic phase such as acetone or tetrahydrofuran (THF). Under strong shear stress, the organic phase can be emulsified in an aqueous phase containing the emulsifier and a high concentration of salts, which are not soluble in the organic phase. Then, pure water was fast added to the o/w emulsion, under mild stirring. The reduction of the ionic strength leads to the migration of the water-soluble organic solvent to the aqueous phase, inducing NP formation. Different from the emulsion diffusion method, there is no diffusion of the solvent due to the presence of salts. Then, the salting out agent is purification by cross-flow filtration or centrifugation. Common salting out agents are electrolytes (sodium chloride, magnesium acetate or magnesium chloride) or non-electrolytes, such as sucrose.

2.2 Modifications of traditional methods

The methods mentioned above are the main methods extensively employed in the synthesis of PLGA NP for different purposes. In order to improve the nanoparticle size and size distribution, to better entrap the active components and to reduce the potential toxicity of the different components involved, continuous efforts were made. Therefore so many new methods, based on slight modifications of traditional methods and the application of new synthesis steps in the PLGA NP formation were discovered. Such as membrane emulsion evaporation method, spray dry method, double emulsion with emulsion diffusion method and so on.

2.3 Parameters affecting PLGA NP

Generally, surface modification of PLGA, drug encapsulation methods and particle size, additives added during formulation, molecular weight of drug, ratio of lactide to glycolide moieties has strong influence on the release and effective response of formulated nanomedicines [23]. Knowledge of the fundamental relationships between

physicochemical parameters and their quantitative effects on the features of PLGA NPs would allow NPs to be designed with defined size and surface characteristics for delivery to specific cells or organs without requiring exhaustive experimental procedures. Rodriguez et al. [24] studied the influence of certain physicochemical properties of the aqueous and organic phases used during NPs preparation and the effects on the characteristics of NPs produced and concluded that the mean size of the NPs could be narrowed, using different methods.

3 Application of PLGA NP

3.1 Application of PLGA NP to protein and peptide orally delivery

Macromolecules such as proteins and peptides play an increasingly important role in our therapeutic field. Traditionally, they are delivered parenterally via solutions that are injected subcutaneously, intramuscularly, and intravenously. Although such injections benefit from high bioavailability, they fail to provide sustained plasma concentrations and suffer from poor patient compliance due to the required frequency of injections. Therefore, more and more effort has been devoted to the oral administration of proteins and peptides.

It is well known that the bioavailability of peptide and protein drugs after oral administration is very low, because they are too large and hydrophilic to readily cross the intestinal mucosa. In addition, extensive enzymatic degradation by proteases is unavoidable before they reach their site of absorption. PLGA NP are good candidates for particulate carriers to deliver peptide and protein drugs. Such particles are expected to be adsorbed in an intact form in the gastrointestinal tract after oral administration.

A study reported by Bilati et al. [25] discussed the processing and formulation issues related to PLGA protein-loaded NP. They evaluated the effect of some typical formulation factors and processing conditions on the mean size and the drug entrapment efficiency of PLGA NP. They found that the parameters that generally increase the entrapment efficiency are high molecular weight of the polymer, the presence of uncapped carboxylic end groups when PLGA is used, the use of methylene chloride instead of ethyl acetate, and the increased nominal drug loading. In some study, it has been shown that the translocation through the intestinal barrier by the paracellular pathway, or via M-cells, which are located on the surface of Peyer's patches, are the possible pathways for transporting the NP through the epithelium of the gut [26,27 ,28].

Yoo and Park [29] formulated salmon calcitonin (sCT) into biodegradable PLGA NPs using sCT oleate complexes. They found that SCT NPs were readily taken up by Caco-2 cells and sCT was transported across the Caco-2 monolayer in vitro. In vivo experiments, it is showed sCT was orally absorbed.

Moreover, we have studied a series of orally administrated PLGA NP. In one of the researches, a novel oral delivery system of PLGA-Hp55 NP encapsulating insulin was successfully prepared in water by the modified emulsion solvent diffusion method [30]. The NP exhibited an excellent insulin entrapment ability and the initial release in simulated gastric fluid was reduced. Comparing with insulin solution used as a control, the oral administration of PLGA-Hp55 NP reduced significantly the serum glucose level over 24 h.

Recently, by combination of hydrophobic ion pairing method and emulsion solvent diffusion method, PLGA NP loaded insulin-sodium oleate complex was prepared by our group[31]. The insulin encapsulation efficiency reached up to 91.2% and mean diameter of the NP was sized about 160 nm under optimal conditions. In order to evaluate hyperglycemic effect of the NP for oral administration, Ins-S.O complex loaded PLGA NP (20 IU/Kg) were administered orally by force-feeding to diabetic rats. In the case of the NP, the plasma glucose level reduced to 23.85% from the initial one 12 h post administration and this continued for 24 h. The results showed that the use of Ins-S.O complex loaded PLGA NP is an effective method of reducing plasma glucose levels (Fig.5). The insulin NP also improved the glycemic response to an oral glucose challenge.

3.2 Application of PLGA NP to pulmonary route

Pulmonary drug delivery using particulate drug carrier systems is becoming a popular method to deliver therapeutic compounds either locally or systemically [32] as shown by the development of inhalable insulin [33]. It has many advantages over other delivery routes because the lungs have a large surface area (43-102 m^2), extensive vascularization, relatively low enzymatic activity, and the absence of the first-pass metabolism [34,35,36,37]. In addition, the alveoli of the lungs have a slower mucociliary clearance than the airways, and the lung epithelia are thinner and more permeable. In general, nanoparticle delivery to the lungs is an attractive concept because it can cause

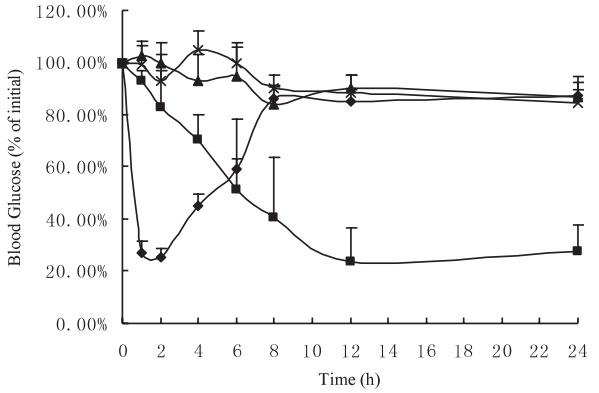

Fig.5 Plasma glucose level after administration of various insulin samples: Data represents the mean ± S.D., n=6 per group (◆) S.C. injection of 1 IU/kg insulin solution; oral administration of (■) Ins-S.O complex loaded PLGA nanoparticles (20 IU/kg), (×) free insulin (20 IU/kg) and (▲) saline

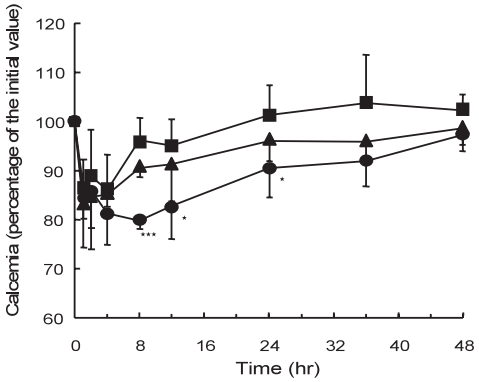

Fig.6 Profiles of the blood calcium level after pulmonary administration of the elcatonin -loaded nanosphere suspension (100 IU/kg) to male guinea pigs (6 weeks). (■) elcatonin solution; (▲) non-coated PLGA nanospheres; (●) chitosan-coated PLGA nanospheres. Data are presented as the means ± SD (n=5). ***p<0.001, *p<0.05 compared with elcatonin solution

retention of the particles in the lungs accompanied with a prolonged drug release if large porous nanoparticle matrices are used [38]. Several studies have exhibited the absorption of high-molecular-weight drugs such as insulin, heparin, and GCSF (recombinant human granulocyte colony stimulating factor) through pulmonary DDSs [39,40]. As these peptides have a short life, the development of delivery systems with sustained pharmacological action would be very useful.

Kawashima et al. [41] incorporated insulin into PLGA NPs and administered them using a sieve type ultrasonic nebulizer into the trachea of guinea pigs. They showed that the insulin loaded NPs were able to reduce the blood glucose significantly and the hypoglycemic effect was prolonged over 48 h compared to a nebulized aqueous solution of insulin as a reference. They linked their results to the sustained release of insulin from the NPs deposited widely throughout the lung.

As reported in our previous literature [39], we used chitosan to modify the surface of PLGA NPs and demonstrated that the modified NPs had enhanced mucoadhesiveness and enabled pulmonary delivery of peptide elcatonin. We administered the NP into the trachea of guinea pigs using a nebulizer. After pulmonary administration, CS-modified PLGA NP loaded with elcatonin reduced blood calcium levels to 80% of the initial calcium concentration and prolonged the pharmacological action to 24 h (Fig.6). These results were attributed to the retention of NP adhered to the bronchial mucus and lung tissue and sustained drug release at the adherence site. Furthermore, a new mechanism of the drug absorption-enhancing effect of CS by opening the intercellular tight junction of the lung epitherium was proposed. These findings demonstrated that the CS-modified PLGA NP is useful for improving peptide delivery via a pulmonary route due to prolonged mucoadhesion for sustained drug release at the absorption site.

Dailey et al. [42] studied the potential of biodegradable polymeric NP of PLGA and a novel PLGA derivative, diethylaminopropylamine polyvinyl alcoholgrafted- poly (lactic-co-glycolic acid), to provoke inflammatory reactions in mice lungs after intratracheal instillation. As control, they used two sizes of polystyrene NPs (75 and 220 nm) in their study. They instilled NP and then evaluated the inflammatory parameters such as lactate dehydrogenase release, protein concentration, macrophage inflammatory protein-2 mRNA induction and polymorphonucleocyte recruitment in the bronchial alveolar lavaged fluid. Their results suggest that biodegradable polymeric NP designed for pulmonary delivery may not induce the same inflammatory response as nonbiodegradable polystyrene particles of comparable size.

3.3 Application of PLGA NP to ocular route

Most ocular diseases are treated by topical application of ophthalmic drugs. A low bioavailability is observed due to the cornea's low permeability, rapid and extensive precorneal loss [43,44,45], and systemic absorption; consequently, application of highly concentrated solutions or frequent administration is required, which results in poor patient compliance. Therefore, numbers of noninvasive

approaches for enhancing ocular drug absorption have been studied, involving the use of prodrugs, the use of viscosity agents designed to prolong the drug residence time, and colloidal systems. Amongst them, the PLGA NP are considered nowadays as a strategy that can enhance the ocular bioavailability of topically administered drugs. Treatment with this system reduces administration frequency and provides as well as maintains an adequate concentration of the therapeutic agent in the precorneal area.

In Mohamed G's paper [46], it is demonstrated that uptake of PLGA particles in rabbit conjunctival epithelial cells is dependent on the particle size, with smaller, 100-nm particles exhibiting the highest uptake compared to larger 800 nm and 10 μm particles. In addition, it is suggest that endocytosis is the main internalization mechanism of PLGA NP in rabbit conjunctival epithelial cells. Endocytosis through the corneal epithelium depends on the particle size and size distribution of the particles: NP have been found in corneal cells, but no presence of microspheres was reported [47,48]. Furthermore, the size dependency and efficiency of uptake along with the facilitated uptake of bovine serum albumin indicate that PLGA NP can be used for the enhancement of drug absorption to the eye.

In another study, E. VEGA et al. evaluated the suitability and feasibility of PLGA NPs as an ocular flurbiprofen delivery system [49]. In this study, PLGA NP incorporating flurbiprofen were prepared. The resulting NP were on average 200-300 nm in size and bore a negative charge (ξ-potential around -25 mV). Furthermore, the entrapped flurbiprofen was released in vitro from the polymer system by dissolution and diffusion in high drug loaded NP, whereas those with a lesser load showed only diffusion. The ex vivo corneal permeation study demonstrated that flurbiprofen-loaded PLGA NP showed a significantly higher capability of making the drug permeate compared with the commercial eye drops.

3.4 Application of PLGA NP to Gene delivery

The encapsulation into PLGA is recently being investigated as a novel way to control the release of gene. It is clear that these carriers need to be conveniently optimized in order to preserve the biological activity of the encapsulated DNA and also in terms of improving their interaction with the biological environment [50,51]. Furthermore, new trials for gene delivery are extensively carried out. S. Prabha1[52] has reported that NP formulated using PLGA polymer demonstrated greater gene transfection, and it was attributed to the higher DNA release from PLGA NP. NPs formulated with higher molecular weight PLGA polymer showed enhanced gene transfection. This was attributed to the relatively higher DNA loading and its release from NPs prepared with high molecular weight polymer [53]. In addition, the NP with lower amount of surface-associated PVA demonstrated higher gene transfection. Higher gene transfection with these NP was attributed to their higher intracellular uptake and cytoplasmic levels. Further study demonstrated that the molecular weight and the degree of hydrolyzation of PVA also affect the gene expression of NP. They also have previously studied the nanoparticle-mediated gene transfection both *in vitro* [54] and *in vivo* [55] and determined the influence of particle size of NP on gene transfection *in vitro* It is also reported that cellular internalization of NPs depends on their particle size and has been shown to affect the gene transfection efficiency of plasmid DNA-loaded NPs. The smaller size (less than 100 nm) NPs showed 27-fold higher gene transfection than the larger size (more than 100 nm) NPs [56].

Furthermore, H. Cohen's group has also investigated the transfection efficiency of gene-loaded PLGA NP in comparison to the naked DNA and liposomal formulations both *in vitro* and *in vivo* [57]. It was reported that despite the lower transfection levels observed in vitro with NPs as compared to liposomal formulations, the in vivo gene transfection with NPs was 1-2 orders of magnitude greater than the liposomes, 7 days after an intramuscular injection in rats. Such sustained gene expression is advantageous especially if the half-life of the expressed protein is very short and/ or a chronic gene delivery is required for better therapeutic efficacy.

We also successfully prepared mucoadhesive PLGA NP by modifying the nanoparticulate surface with chitosan to improve mucosal peptide absorption after oral and pulmonary administration. Furthermore, we found that nucleic acid, which was not dispersed in organic solvent, could be dispersed by forming a complex with cationic acid lipid [58]. Using this phenomenon, polynucleic acid for gene therapy (plasmid DNA, antisense oligonucleotide, small interfering RNA, etc.) can be encapsulated into the matrix of the polymer particles with the emulsion solvent diffusion method. The resultant NP show better cellular uptake and different gene therapeutic effects compared with conventional vectors due to their improved adherence to the

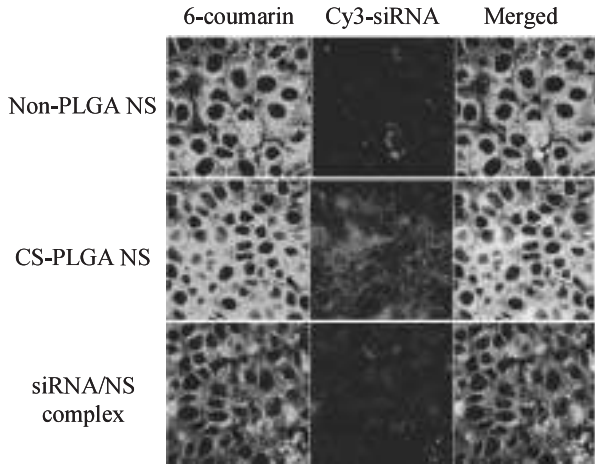

Fig.7 CLSM Images of A549 Cells (magnification 100×) following 4 h uptake of 50 um siRNA preparations (Green fluorescence; 6-coumarin, Red fluorescence; Cy3 labeled siRNA)

cells and sustained release of polynucleic acid in the cells (Fig.7).

One of the key features of PLGA NP-mediated gene delivery is the ability to achieve sustained gene expression. Prabha and Labhasetwar have shown a slower intracellular release of plasmid DNA from the PLGA-NPs, while sustained intracellular release of DNA with NPs resulted in a prolonged gene expression [59].

Conclusions:

There are tremendous opportunities exist for applications of NP for delivering macromolecular drugs and poor solubility drugs through PLGA polymers. This review outlines the history and research on PLGA-based nanoparticles as drug carrier, and their application by various routes. The PLGA nanoparticulate system is also bright in the field of food, cosmestic, nanomedicine and medical device. All in all, PLGA nanoparticulate system is attractive for more scientists to do further research.

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