

# Liposomes and nanotechnology in drug development: focus on ocular targets

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**Abstract:** Poor drug delivery to lesions in patients' eyes is a major obstacle to the treatment of ocular diseases. The accessibility of these areas to drugs is highly restricted by the presence of barriers, including the corneal barrier, aqueous barrier, and the inner and outer blood–retinal barriers. In particular, the posterior segment is difficult to reach for drugs because of its structural peculiarities. This review discusses various barriers to drug delivery and provides comprehensive information for designing nanoparticle-mediated drug delivery systems for the treatment of ocular diseases. Nanoparticles can be designed to improve penetration, controlled release, and drug targeting. As highlighted in this review, the therapeutic efficacy of drugs in ocular diseases has been reported to be enhanced by the use of nanoparticles such as liposomes, micro/nanospheres, microemulsions, and dendrimers. Our recent data show that intravitreal injection of targeted liposomes encapsulating an angiogenesis inhibitor caused significantly greater suppression of choroidal neovascularization than did the injection of free drug. Recent progress in ocular drug delivery systems research has provided new insights into drug development, and the use of nanoparticles for drug delivery is thus a promising approach for advanced therapy of ocular diseases.

**Keywords:** intravitreal injection, drug delivery system, age-related macular degeneration, APRPG-modified PEGylated liposome, DDS

## Introduction

Nanotechnology is a general term used for technologies that use the properties of nanoscale substances to develop new functions for these substances and improve their properties. Many research projects are underway in this domain around the world. Nanotechnology has been used for various applications in the medical field, such as diagnosis, biosensors, and drug delivery, and has thus provided novel nanomedicines and nanodevices.<sup>1</sup>

For the effects of a drug to be maximized, the molecules of the drug need to reach specific locations within the target tissue. Because drug molecules typically cannot selectively reach their site of action, there is a need for carriers that can efficiently deliver the required amount of the drug to its target site. The eye, particularly the posterior segment, is composed of tissues that are difficult for drugs to penetrate because of structural peculiarities such as the barrier function. Thus, many research studies on nano-sized drug carriers have been conducted in the field of ophthalmology.<sup>2,3</sup>

This review provides an overview of recent progress in drug delivery methods for posterior ocular disease and the use of nanotechnology for intravitreal injection as a strategy for overcoming these issues.

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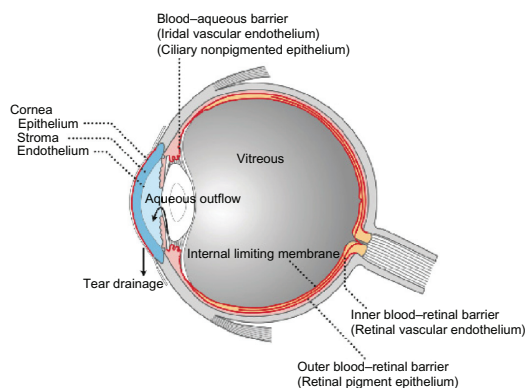
## Eye diseases and structural peculiarities of the eye

Among eye diseases, age-related macular degeneration (AMD) with neovascularization, pathologic myopia, central retinal vein occlusion/diabetic retinopathy, and cytomegalovirus-associated macular edema cause severe blindness.<sup>4</sup>

Structures that function as a barrier to limit the permeability of the eye to pharmacological agents include the sclerocorneal parenchyma, the corneal epithelium and endothelium, the inner and outer blood–retinal barriers, and the retinal inner limiting membrane (Figure 1).<sup>5</sup> Topical administration using eye drops, which is the most commonly used method for administering medications into the eye, results in excretion of the drug through tear drainage and peribulbar and choroidal blood flow. As a result, less than 5% of the drug can cross the corneal barrier and gain access to the inner eye.<sup>6–8</sup> In contrast, although systemically administered drugs can reach the choroid membrane, drug delivery into the retina or the vitreous body is difficult to achieve through conventional methods because of the presence of the blood–aqueous barrier and the inner and outer blood–retinal barriers in those structures.<sup>9</sup> As a result, large doses are often required, which leads to concern over systemic side effects. Based on this background, intravitreal administration of pharmacological agents has been performed for vitreoretinal diseases wherein drug delivery is difficult (Figure 2).<sup>10</sup>

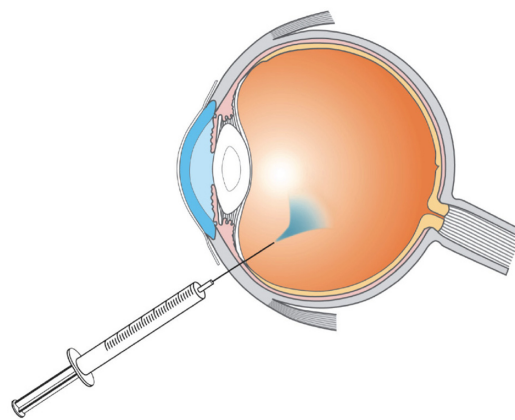
## Overview of the treatment modalities used and barriers encountered in the past

Most current clinical applications of intravitreal injections involve the treatment of AMD. AMD causes neovascularization



**Figure 1** Structural particularities of the eye.

**Notes:** There are many barriers to drug delivery to the retina. Drugs cannot be easily delivered to the retina by topical administration, for example, by using eye drops, because of the presence of tear drainage and peribulbar and choroidal blood flow. In contrast, systemically administered drugs hardly enter the retina because of the presence of the blood–aqueous barrier and the inner and outer blood–retinal barriers.



**Figure 2** Intravitreal injection.

**Note:** Intravitreal injection of drug is recently used for treatment of several ocular diseases.

in the choroid membrane in the macular region, which leads to blindness, and it has a high prevalence in developed countries.<sup>11,12</sup> Vascular endothelial growth factor (VEGF) plays a major role in the development of choroidal neovascularization (CNV), and VEGF is expressed in choroidal neovascularized tissues as well as in the retinal pigment epithelium.<sup>13–15</sup> Therefore, drugs capable of inhibiting VEGF are being developed, and currently in the United States of America, three such drugs have been approved by the Food and Drug Administration (FDA) for use in the treatment of AMD, namely, Macugen® (Eyetechnic Pharmaceuticals, Palm Beach Gardens, FL, USA), Lucentis® (Genentech, San Francisco, CA, USA), and Eylea® (Regeneron, Tarrytown, NY, USA).

Because intravitreal injections allow the administration of small amounts of the drug in each injection, they enable an increase in intraretinal and intravitreal drug concentrations while avoiding the adverse effects caused by systemic administration.<sup>4,16</sup> However, because the drug remains in the eye for only a short duration, it needs to be administered frequently into the vitreous body, and there are concerns about the development of complications such as intravitreal hemorrhage, retinal detachment, cataracts, and endophthalmitis.<sup>17</sup>

## Development of a drug delivery system (DDS) by using nanotechnology

The development of a DDS that can be used for the posterior segment of the eye and that involves nanocarriers to overcome the issue of frequent intravitreal administration has received considerable attention.

DDSs with appropriate spatiotemporal characteristics are designed to allow drugs to affect the target tissue

efficiently, and three classes of techniques are generally used: (1) absorption promotion – promotion of the passage of a drug through the tissue, which functions as a barrier; (2) controlled release – efficient time-controlled sustained release of a locally administered drug; and (3) drug targeting – to allow it to act efficiently and exclusively on the target tissue.<sup>5</sup>

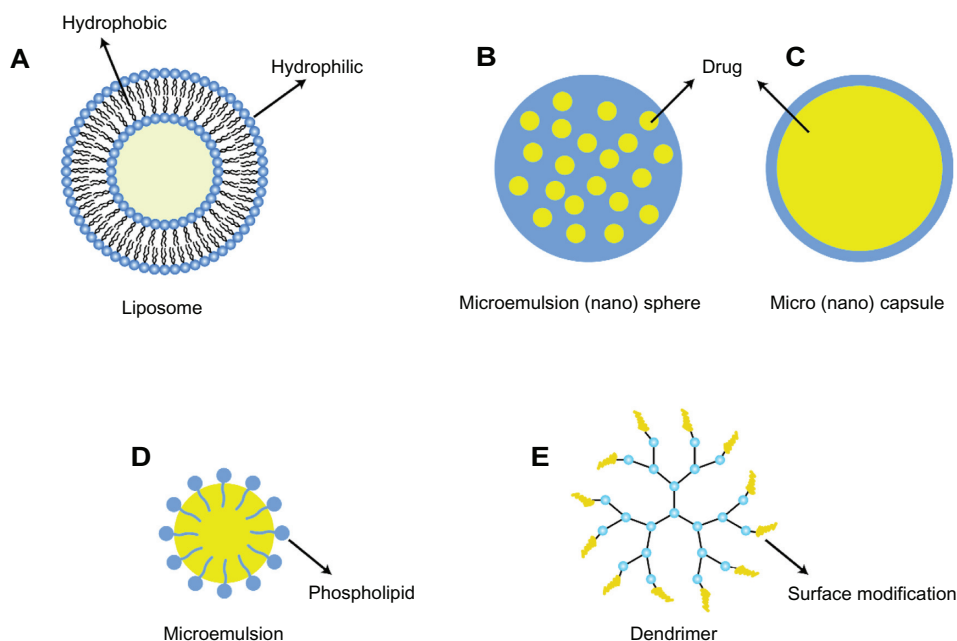
Among ophthalmic drug delivery systems (DDS) that use nanocarriers, liposomes and micro/nanospheres have been studied the most extensively; other systems include emulsions and dendrimers (Figure 3). In this review, we have provided a description of nanocarriers used in the field of ophthalmology, focusing on those that are delivered intravitreally.

## Liposomes

Liposomes are closed vesicles (small lipid vesicles) composed of a phospholipid bilayer, and water-soluble drugs can be incorporated into their aqueous phase, whereas lipid-soluble drugs can be incorporated into their lipid phase.<sup>18</sup> Liposomes have various advantages as drug carriers: (1) Because they are noncovalent aggregates, their lipid composition, size, and electric charge can be easily controlled;<sup>19,20</sup> (2) Their modification, with surface polymers, carbohydrates, and antibodies, can be easily achieved to facilitate targeting;<sup>21</sup> (3) Liposomes have almost no toxicity

and low antigenicity;<sup>22</sup> (4) Liposomes can be biodegradable and metabolized *in vivo*;<sup>22</sup> (5) Properties such as membrane permeability can be controlled to some extent;<sup>23</sup> and (6) Liposomes can hold various types of solutes with different properties and molecular weights, such as fat-soluble molecules,<sup>23</sup> water-soluble molecules,<sup>24</sup> and amphiphilic molecules.<sup>25</sup> Because of these characteristics, studies have been conducted on the intravitreal injection of drug-bearing liposomes and have demonstrated that the release of the drug can be controlled, the half-life of the drug inside the vitreous body can be prolonged, and the toxicity of the drug can be reduced.<sup>26–31</sup>

With the goal of eventually using liposome-encapsulated ganciclovir (GCV) for the treatment of cytomegalovirus retinitis in acquired immune deficiency syndrome (AIDS) patients, liposome-encapsulated GCV and free GCV were injected into the vitreous body of rabbits in a previous study.<sup>32</sup> The intraocular concentration of GCV was determined by an enzyme linked immunosorbent assay (ELISA) assay of the vitreous after a single intravitreal injection of different doses of the free drug (0.2–20 mg) or 1 mg of liposome-encapsulated GCV. At 72 hours after the intravitreal injection, only the vitreous of rabbits injected with a free GCV dose greater than or equal to 5 mg showed therapeutic levels of the drug. In addition, free GCV caused retinopathy at doses



**Figure 3** Various formulations of injectable particles. **(A)** Liposomes: Liposomes are closed vesicles (small lipid vesicles) composed of a phospholipid bilayer, and water-soluble drugs can be incorporated into their aqueous phase, whereas lipid-soluble drugs can be incorporated into their lipid phase; **(B)** Micro/nanocapsule: Drugs are encapsulated in synthetic and natural polymers to permit sustained local release and tissue targeting; **(C)** Micro/nanocapsules are similar to microspheres, and both names are used without a clear distinction; **(D)** Microemulsion: A microemulsion is a type of dispersion system that is composed of two types of liquids. The diameter of the micelles is as low as approximately 100 nm or less. These micelles are thermodynamically stable and can be formed easily without requiring strong agitation; and **(E)** Dendrimer: Dendrimers are repetitive/single molecules with a regularly branched structure, and they are composed of a central molecule known as the “core” and side chain moieties.

of 15 mg or higher. In contrast, no retinopathy was found in the group that received 1 mg of liposome-encapsulated GCV, and the concentration of the drug demonstrated therapeutic levels up to 14 days after injection.<sup>32</sup> Furthermore, compared with the effects of injection of free GCV as a control, intravitreal injection of 0.25 mL (1 mg) of liposome-encapsulated GCV in patients with AIDS-induced cytomegalovirus retinitis prevented the progression of retinal hemorrhages, retinal detachment, and cytomegalovirus (CMV) retinitis. In addition, previous reports have shown that fewer intravitreal injections were required for liposome-encapsulated GCV than for free GCV.<sup>33</sup>

The stability of the drug inside the vitreous body can be improved even further by adding polyethylene glycol (PEG) to the surface of the liposomes, since PEG-modification of liposomes sterically stabilizes them by covering the liposomal surface with a fixed aqueous layer.<sup>31</sup>

Other reports have also demonstrated the usefulness of liposomal formulations after intravitreal injection (Table 1), and the drugs delivered in these studies have included amikacin,<sup>34</sup> amphotericin B,<sup>35</sup> a model anti-sense oligonucleotide,<sup>31,36</sup> bevacizumab,<sup>37</sup> cyclosporine,<sup>38</sup> 5-fluorouridine 5'-monophosphate,<sup>39,40</sup> fluconazole,<sup>41</sup> GCV, gentamicin,<sup>28</sup> tacrolimus,<sup>42</sup> tobramycin,<sup>43</sup> vasoactive intestinal peptide,<sup>44</sup> an angiogenesis inhibitor,<sup>45</sup> tilisolol,<sup>46</sup> and ofloxacin.<sup>47</sup>

The toxicity of various doses of intravitreal amphotericin B deoxycholate, amphotericin B lipid complexes (ABLC),

and liposomal amphotericin B (L-AmB) (AmBisome®; Astellas Pharma Inc, Tokyo, Japan) in rabbits was examined by Cannon et al.<sup>35</sup> Eye examination was performed before and after injection, and at the designated times, the vitreous humor was aspirated, and amphotericin B concentrations were determined, followed by enucleation for histological studies. Vitreous band formation was significantly higher in the ABLC-treated eyes than in those treated with L-AmB. Vitreal inflammation was higher in eyes treated with L-AmB, amphotericin B deoxycholate, and ABLC than in the control eyes. Based on histological data, increased doses of all three agents appeared to be associated with increasing toxicity; however, based on ophthalmic data, L-AmB appeared to be less toxic than amphotericin B deoxycholate and ABLC.<sup>35</sup>

Fishman et al<sup>28</sup> investigated the effect of liposome encapsulation on the pharmacokinetics of gentamicin, after injection in rabbits. The final liposomal suspension contained 10 mg/mL gentamicin with 95% encapsulation.<sup>28</sup> Each rabbit received an intravitreal injection of 100 mg liposome-encapsulated gentamicin or 100 mg gentamicin in 0.1 mL of phosphate-buffered saline. The peak free drug concentration in the vitreous was significantly greater for liposome-encapsulated gentamicin than for gentamicin at 24, 72, 120, and 192 hours. The areas under the drug concentration-time curve for the total drug and for the free drug in the case of liposome-encapsulated gentamicin were twofold and 1.5-fold higher, respectively, than those for gentamicin.

**Table 1** Improvement of drug pharmacokinetics by intravitreal injection of the liposomal drug

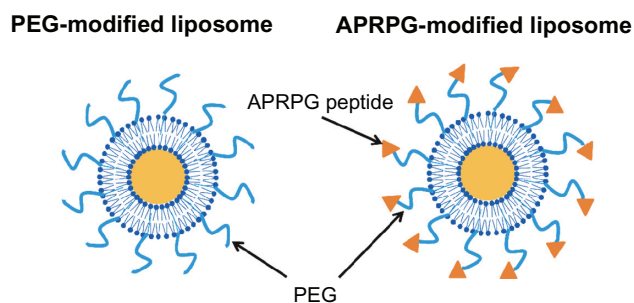
Drug	Observations	Reference(s)
Amikacin	The half-life of the drug in vitreous;	34
Amphotericin B	The toxic intravitreal dose of liposomal amphotericin B The concentration after intravitreal injection of various doses of the drug	35
Bevacizumab	The concentration in the aqueous humor and vitreous	37
Cyclosporine	Retinal toxicity	38
5-fluorouridine 5'-monophosphate	The half-life of the drug	39, 40
Fluconazole	The half-life of the drug	41
Ganciclovir	The concentration of the drug in the vitreous	32
Ganciclovir	The number of intravitreal injections	33
Gentamicin	The pharmacokinetics of the drug	28
Ofloxacin	Retinal toxicity	47
Oligonucleotide	Distribution and clearance of the drug in the vitreous	31, 36
Tacrolimus (FK-506)	The efficacy and safety of the drug on EAU in rats	42
Tisolol	Retention in the vitreous; concentration of the drug	46
Tobramycin	The duration of administration of the drug at therapeutic concentrations	43
Tyrosine kinase inhibitor	Targeting in the CNV and release	45
Vasoactive intestinal peptide	The concentration and safety of the drug on EIU in rats	44

**Abbreviations:** EAU, experimental autoimmune uveoretinitis; CNV, choroidal neovascularization; VIP, vasoactive intestinal peptide; EIU, endotoxin-induced uveitis.

Bevacizumab (Avastin<sup>®</sup>, Genentech/Roche, San Francisco, CA, USA), molecular weight, 149 kDa, is a synthetic monoclonal antibody against VEGF and has been approved by the FDA for colorectal cancer treatment. Intravitreal injection of bevacizumab has also been recently used for the treatment of several ocular diseases. In one study, the liposomal bevacizumab concentration in the aqueous humor and vitreous was investigated after injection.<sup>37</sup> The mean concentration of free bevacizumab in the eyes that received liposomal bevacizumab was onefold and fivefold higher at days 28 and 42, respectively, than that in the eyes injected with soluble bevacizumab. The results of this study showed the beneficial effects of liposomes in prolonging the time that bevacizumab is retained in the vitreous.

The authors of this review encapsulated SU5416 (a VEGF receptor tyrosine kinase inhibitor) into PEGylated liposomes that had been modified to display Ala-Pro-Arg-Pro-Gly (APRPG) (a peptide targeting newly formed blood vessels)<sup>48,49</sup> and injected the liposomes intravitreally into a rat experimental model of CNV to determine whether it was possible for the CNV-targeted drug to be released inside the vitreous body (Figure 4).

First, excessive laser irradiation of the retina of Brown Norway (BN) rats was performed; then, APRPG-liposomal SU5416 and liposomal SU5416 without APRPG (0.1 mL) were each injected once into the vitreous body of the rats. At 4 days and 2 weeks postinjection, reflux staining was performed using fluorescein isothiocyanate (FITC-dextran), after which the rats' eyes were removed, and a flat mount was created. Using fluorescence microscopy, we determined whether CNV targeting occurred. Compared with liposomal SU5416 without APRPG, APRPG-liposomal SU5416 accumulated markedly in CNV, which suggests that APRPG-liposomal SU5416 could be used to target CNV lesions



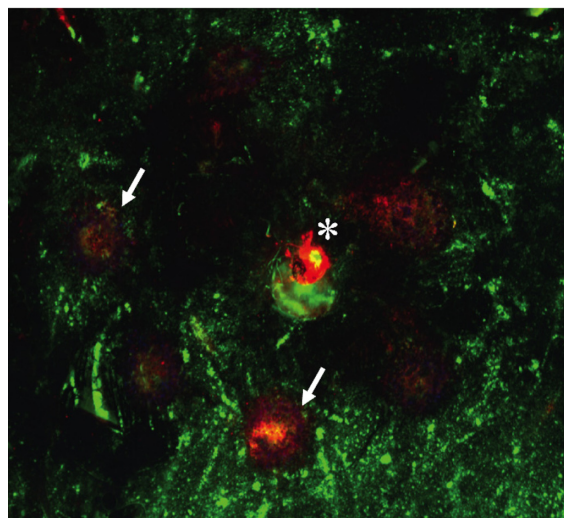
**Figure 4** APRPG-modified PEGylated liposomes for angiogenic vessel targeting.  
**Notes:** APRPG-PEG-Distearoylphosphatidylethanolamine was synthesized and incorporated into liposomes to prepare APRPG-modified PEGylated liposomes. The APRPG peptide was originally identified by in vivo biopanning using a phage-displayed peptide library. PEGylated liposomes were used as nontargeted control liposomes.  
**Abbreviations:** APRPG, Ala-Pro-Arg-Pro-Gly; PEG, polyethylene glycol.

(Figure 5). APRPG-liposomal SU5416 was still found in the choroid membrane of the rats even at 2 weeks after the intravitreal injection.<sup>45</sup>

In addition, the following experiments were performed to examine the inhibitory effect of APRPG-liposomal SU5416 on CNV.<sup>45</sup> APRPG-liposomal SU5416, balanced-salt solution (BSS), APRPG-liposomes, and soluble SU5416 were injected once into the vitreous body of CNV model rats at a dose of 0.1 mL.

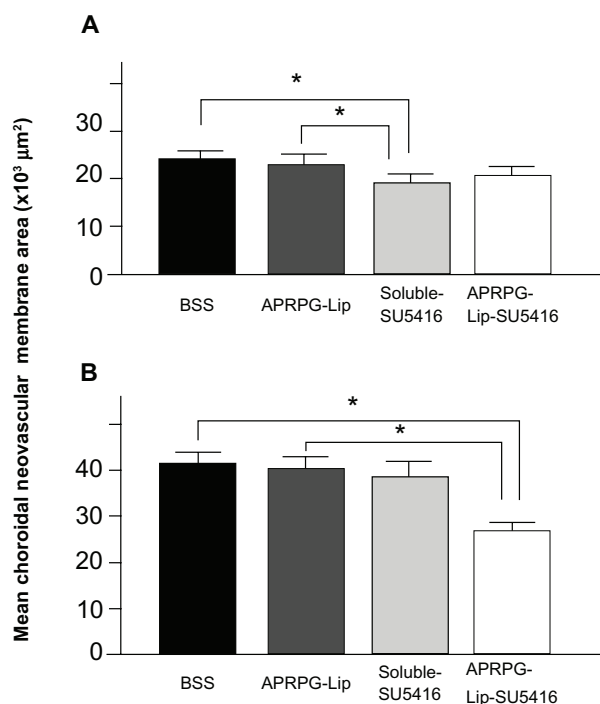
At 1 week and 2 weeks after the injections, flat mounts were created using the method described above, and the inhibitory effect on CNV was examined by using a fluorescence microscope to measure the area occupied by CNV. The inhibitory effect on CNV at 1 week after injection was almost the same as that in the group injected with APRPG-liposomal SU5416 and in the group injected with soluble SU5416. However, at 2 weeks after injection, CNV was only significantly inhibited in the group injected with APRPG-liposomal SU5416 (Figure 6).

Barriers to the use of liposomes include the blurring of vision after injection of the suspension into the vitreous body; the limited storage conditions, depending on the composition of the drug and the liposomes; the poor maintenance of efficiency when a water-soluble substance is encapsulated; the predominant usage of cationic liposomes in gene delivery;<sup>50</sup> and potential proinflammatory effects.



**Figure 5** Double labeling of liposomal SU5416 (red) and choroidal vascularization (green).

**Notes:** Localization of APRPG-liposomal SU5416 at 4 days after intravitreal injection. Asterisks: optic nerve; arrows: CNV region; arrowheads: normal choroidal vessels. Copyright © 2011. American Medical Association. All rights reserved. Honda M, Asai T, Umemoto T, Araki Y, Oku N, Tanaka M. Suppression of choroidal neovascularization by intravitreal injection of liposomal SU5416. *Arch Ophthalmol.* 2011;129(3):317–321.<sup>45</sup>  
**Abbreviations:** APRPG, Ala-Pro-Arg-Pro-Gly; CNV, choroidal neovascularization.



**Figure 6** Quantitative analysis of the CNV area in each experimental group. Data obtained at 1 week (A) and 2 weeks (B) after intravitreal injection.

**Notes:** The results are expressed as simple average CNV area  $\pm$  SE (n = 6). The asterisks show statistically significant differences between the indicated groups ( $P < 0.05$ ). Copyright © 2011. American Medical Association. All rights reserved. Honda M, Asai T, Umemoto T, Araki Y, Oku N, Tanaka M. Suppression of choroidal neovascularization by intravitreal injection of liposomal SU5416. *Arch Ophthalmol.* 2011;129(3):317–321.<sup>45</sup>

**Abbreviations:** CNV, choroidal neovascularization; SE, standard error; BSS, balanced-salt solution; APRPG, Ala-Pro-Arg-Pro-Gly; Lip, liposome.

Visudyne® (Valeant Pharmaceuticals Int, Montreal, Canada; Novartis AG, Basel, Switzerland) (principal agent: verteporfin), which is a liposomal formulation that is used in the treatment of AMD but not administered through intravitreal injection, has already been released on the market. When intravenously administered Visudyne is activated by irradiation of the diseased region (with a nonthermal laser), selective occlusion of newly formed blood vessels occurs, resulting in a decrease in bleeding and exudation. The formulation is a lyophilized product and contains 15 mg of the principal agent per vial; the liposomal membrane is composed of egg yolk phosphatidylglycerol (egg yolk PG) and dimyristoylphosphatidylcholine (DMPC), and other additives include lactose, palmitic acid, ascorbic acid, and dibutyl hydroxytoluene. In this case, liposomes are used to formulate hydrophobic verteporfin in an injectable form for intravenous injection.

## Micro/nanospheres

Microspheres are spherical preparations in which particles have a diameter ranging from 1  $\mu$ m to several hundreds of

micrometers or less. In some cases, particles with a smaller diameter are also considered nanospheres.<sup>4</sup> Drugs are encapsulated in synthetic and natural polymers to permit sustained local release and tissue targeting of the drugs. Micro/nanocapsules are similar to microspheres, and both names are used without a clear distinction. However, in the strict sense of the terms, microspheres are multinuclear microcapsules. The most common substrates are poly(lactic acid) (PLA), polyglycolic acid (PGA), and their copolymer, poly(lactic-co-glycolic acid) (PLGA). These substrates are nonenzymatically hydrolyzed and degraded in vivo. Intravitreally injected PLA and PLGA do not exhibit electrophysiological or histological toxicity in the retina.<sup>51,52</sup>

A GCV intraocular implant is the first FDA-approved sustained-release formulation (Vitrasert®; Bausch and Lomb, Rochester, NY, USA) that is nondegradable in vivo and is being used in the treatment of cytomegalovirus retinitis in AIDS patients. This device, which uses the biodegradable polymers ethylene vinyl acetate (EVA) and polyvinyl alcohol (PVA), is implanted through a 5.5-mm scleral incision generated using a pulse planner and allows the sustained release of 450 mg of GCV for 6 to 8 months.<sup>53</sup>

However, in some cases, if CMV retinitis is not alleviated after the sustained release of the drug, removal of the device followed by insertion of a new device is often considered. In previous reports, the sub-Tenon capsule placement of Vitrasert using a 8-0 nylon suture, followed by removal of the device after sustained release of the drug, did not result in any complications.<sup>54</sup>

The in-vivo biodegradable implant Ozurdex® allows the sustained intravitreal release of 350 mg and/or 700 mg of dexamethasone. Visual acuity and retinal thickness have both been reported to show a marked improvement at 180 days after the intravitreal injection of Ozurdex for the treatment of macular edema associated with retinal vein occlusion.<sup>55</sup> The efficacy of Ozurdex against uveitis<sup>56</sup> and diabetic retinopathy<sup>57</sup> has also been confirmed.

After intravitreal injection, microspheres are likely to be trafficked to retinal pigment epithelial cells.<sup>58,59</sup> The tissue distribution of microspheres after intravitreal injection depends on the diameter of the particles. When fluorescent 2000 nm, 200 nm, and 50 nm nanospheres were injected into the vitreous body of rabbits, the 2000 nm particles were found in the intravitreal cavity and the trabecula, whereas the 200 nm and 50 nm particles were found even inside the retina.<sup>60</sup>

When devices that are non-degradable in vivo are used, drug release is stable for a long period, but surgical removal of the device after sustained drug release is generally difficult

to achieve. When biodegradable implants are used, they do not need to be removed after sustained drug release; however, in comparison with implants that are non-biodegradable *in vivo*, intravitreal drug concentration is unstable, and the sustained-release period is shorter.<sup>61</sup>

## Other nanocarriers

### Microemulsions

A microemulsion is a type of dispersion system composed of two types of liquids. The diameter of the micelles is as low as approximately 100 nm or less. These micelles are thermodynamically stable and can be formed easily without the need for strong agitation. They look transparent or semitransparent because of the limited dispersion of visible light arising from their small size.<sup>62</sup> They comprise three components, including two types of immiscible substances (represented by water [W] and oil [O]) and a surfactant. In some cases, they may contain auxiliary agents. The properties of microemulsions depend on the nature and composition of these components.

Microemulsions have good tissue permeability because of the small size of the micelles and the presence of a surfactant among the components; as a result, studies on DDSs have been conducted mainly in the field of ophthalmic drugs.<sup>63</sup> The instillation of dexamethasone-containing microemulsions in the eyes of rabbits has been shown to result in enhanced intraocular permeability.<sup>64</sup>

Because sterilization is normally performed by autoclaving, microemulsions are unsuitable when the drug is water-soluble or insoluble (does not dissolve in water or oil), thermolabile, or if the drug should appear transparent externally. In comparison with microspheres and liposomes, microemulsions are also unsuitable for long-term sustained drug release.

### Dendrimers

Dendrimers are repetitive/single molecules with a regularly branched structure, and they are composed of a central

molecule known as the “core” and side chain moieties known as “dendrons.” Dendrimers are included in the category of polymer compounds, and they have a spherical structure and homogenous molecular weight. Hydrophobic drugs can be incorporated into the core. In addition, their chemical structure, physical properties, and size can be controlled at the molecular level, and attempts to use them as drug carriers are underway.<sup>65,66</sup>

Lipophilic and cationic dendrimers have been used to mediate the delivery of a sense oligonucleotide, ODN-1, and to inhibit the expression of VEGF (*in vitro*). Furthermore, when fluorescence leakage from the CNV was evaluated in a rat laser model, using fluorescein fundus angiography after intravitreal injection of two types of dendrimers selected from *in vitro* experiments, fluorescence leakage from CNV was prominently inhibited in both cases.<sup>67</sup>

Dendrimers can incorporate a lower amount of drugs than other carriers. In addition, among the dendrimers synthesized so far, few have been proven to be safe *in vivo* when compared with liposomes and microspheres. As described above, advantages and disadvantages of the different types of nanocarriers are listed in Table 2.

## Future prospects

With the introduction of the intravitreal injection of VEGF inhibitors, an improvement in visual acuity has been achieved in many patients. However, discontinuation of the injection of anti-VEGF antibodies often results in recurrence of CNV, and in some cases, the treatment has to be continued for the rest of the patient's life. The frequent and long-term intravitreal injection of drugs poses a heavy burden on the patient, not only in terms of complications but also financially, emotionally, and physically. DDSs are considered to be essential for overcoming the current limitations with regard to drug efficacy, and the currently used method of sustained release of anti-VEGF antibodies is considered to have great potential.

**Table 2** Advantages and disadvantages of different types of nanocarriers

	Advantages	Disadvantages
Liposome	<ul style="list-style-type: none"> <li>• Low toxicity and antigenicity</li> <li>• Biodegradable and metabolized <i>in vivo</i></li> <li>• Can prolong the drug half-life in the vitreous</li> <li>• Reduces drug toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Blurring of vision after intravitreal injection</li> <li>• Limited storage conditions</li> </ul>
Micro/nanosphere	<ul style="list-style-type: none"> <li>• Drug release is stable for a long time (nondegradable)</li> </ul>	<ul style="list-style-type: none"> <li>• Need to be removed surgically (nondegradable)</li> <li>• Sustained release period is short (biodegradable)</li> </ul>
Microemulsion	<ul style="list-style-type: none"> <li>• Good tissue permeability</li> </ul>	<ul style="list-style-type: none"> <li>• Unsuitable for long-term sustained drug release</li> </ul>
Dendrimer	<ul style="list-style-type: none"> <li>• Physical properties and size can be controlled at the molecular level</li> </ul>	<ul style="list-style-type: none"> <li>• Conjugates low amount of drugs</li> <li>• Safety is unclear <i>in vivo</i></li> </ul>

Intraocular implants in the posterior segment of the eye, which are promising for sustained drug action, have already been used for clinical applications. Implants with the same shape as that of Vitrasert and that ensure a sustained release of fluocinolone acetonide are also used in the treatment of uveitis, and recently, clinical trials have been initiated for their use in the treatment of macular edema. Moreover, implants having this shape might be used for sustained release of drug candidates for the treatment of AMD.

More potent drugs might be required for use in the new devices. In the future, there will be a growing demand for DDS formulations using biodegradable implants, particularly for the establishment of standard treatments combining multiple drugs.

## Acknowledgments

This work was supported in part by the “High-Tech Research Center” Project for Private Universities and a matching fund subsidy from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

## Disclosure

The authors have no conflicts of interest to declare.

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