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Applications of Polymers in Intraocular Drug Delivery Systems

Review Article

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Abstract

We are entering a new era of ophthalmic pharmacology where new drugs are rapidly being developed for the treatment of anterior and posterior-segment of the eye disease.

The pharmacokinetics of drug delivery to the eye remains a very active area of ophthalmic research. Intraocular drug delivery systems allow the release of the drug, bypassing the blood-ocular barrier. The main advantage of these preparations is that they can release the drug over a long time with one single administration. These pharmaceutical systems are of great important in the treatment of posterior segment diseases, and they can be prepared from biodegradable or non-biodegradable polymers. Biodegradable polymers have the advantage of disappearing from the site of action after releasing the drug. The majority of intraocular devices are prepared from non-biodegradable polymers, and they can release controlled amounts of drugs for months. Non-biodegradable polymers include silicone, polyvinyl alcohol (PVA) and ethylvinylacetate (EVA). The polymers usually employed to prepare nanoparticles for the topical ophthalmic route are poly (acrylic acid) derivatives (polyalquilcyanocrylates), albumin, poly-ε-caprolactone, and chitosan. Dendrimers are a recent class of polymeric materials with unique nanostructure which has been studied to discover their role in the delivery of therapeutics and imaging agents. Hydrogels are polymers that can swell in aqueous solvent system, and they hold the solvents in a swollen crosslinked gel for delivery. This review exhibits the current literature regarding applications of polymers in ophthalmic drug delivery systems including pharmacokinetics, advantages, disadvantages and indications aimed to obtain successful eye therapy.

Keywords: Polymers; Nanoparticles; Route; Eye; Pharmacokinetic; Hydrogels.

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Introduction

Pilocarpine and mydriatics were the first ophthalmic sustained-release drug which was developed in an acrylate co-polymer-based matrix for insertion into the conjunctival fornix [1]. In the western world in the 1970s, Ocusert (Alza), a sustained-release pilocarpine, was introduced [1]. Different approaches have been proposed to deliver drugs into the eye. One of the main aims is to achieve therapeutic concentrations at the posterior pole. Successful ophthalmic therapy requires therapeutic concentrations of the active substance on the target site. Systemic applications may lead to sufficient concentrations at the retina; however systemic side-effects may develop, especially in the long term use. Physicians and patients accept topical administration as a route for ocular medication. However, only 5% of the administered dose penetrate the eye which limits the therapeutic effect at the posterior pole [2]. A major barrier to drug delivery after eye drop application is diffusion through the cornea [3, 4]. However, a good number of low-molecular-weight substances are able to reach the aqueous humor through the transcorneal route by passive diffusion which follows Fick's law. The diffusion rate is conducted by a concentration gradient, specified by the hydrophilic or lipidic nature of the different layers of the cornea and the nature of the drugs administered (hydrophilic/lipophilic balance) [5]. Conjunctiva is a tissue with an endogenous transport machinery to allow penetration of active substances. It is considered an alternative route for ocular drug delivery with good absorption [6]. The transscleral route consists of the injection of the drug into a periocular space (subconjunctival, sub-Tenon, peribulbar, posterior juxtascleral, and retrobulbar spaces) [7]. Transport barriers in the transscleral route have been classified as static and dynamic barriers [8]. Knowing the permeability of the sclera, periocular may also offer an alternative route to potentiate drug delivery and tissue targeting [9, 10].

To overcome these routes limitations, numerous physicians have

suggested intravitreal drug injections to reach locally therapeutic levels with prolonged effective concentrations.

The eye is an ideal organ for sustained-release drug delivery implants. Posterior segment structures can be easily treated through an intravitreal drug delivery system or surgical implantation. The blood-retina barrier further helps to localize the intraocular concentration of the drug while decreasing the systemic absorption and side-effects. The eye is also an immunologically privileged site, which limits the amount of inflammation related to the sustained-release device [1, 2, 12].

Several different technologies exist for sustained-release drug delivery devices, including (1) biodegradable implants; (2) non-biodegradable implants; (3) Dendrimers; (4) Hydrogels

The major benefits of intraocular implant are reduction of systemic side-effects of the medication, decreased risk of repeated intravitreal injections, decreased total amount of drugs used for treatment, and localized therapeutic drug levels bypassing the blood-retina barrier [13, 14].

Intraocular polymers implants

Biodegradable polymers

Biodegradable polymers are widely used in the production of controlled drug delivery systems. These devices release the drug while the polymer is being degraded in the target site. With time, the device disappears avoiding the need of surgical removal. These materials have been used to prepare implants, liposomes, and injectable particles (nanoparticles and microparticles).

Advantages:

*Do not require removal.
*Designed in various shapes.
*Can be injected.

Disadvantages:

*Shorter duration of action.
*Require surgical implantation or injection.

Clinical examples:

Liposomes (verteporfin & ganciclovir): Liposomes are biodegradable vesicles. They can be prepared with natural lipids as phospholipids. Hydrophilic can be encapsulated in the aqueous zone, and lipophilic active substances can be encapsulated in the lipid walls.

Liposomes have been dispersed in thermo-sensible poloxamers to save the activity of oligonucleotides and enhance their intracellular penetration [15].

a. Prodrug of ganciclovir: The administration of liposomes by the intraocular route has been studied in several studies. Liposomes loaded with a prodrug of ganciclovir was used to treat cytomegalovirus retinitis in rabbits [16]. These vesicles have been loaded with oligonucleotides to protect them from nucleases [16]. A liposomal formulation of verteporfin (Visudyne, Novartis Pharmaceuticals) is accepted for the treatment of age-related macular degeneration (AMD) and choroidal neovascularization (CNV). Liposomes of verteporfin are given to the patient by intravenous infusion, causing an occlusion of the targeted vessels after its activation through a nonthermal red laser applied to the retina [17, 18]. Another example is Photrex (Miravant Medical Technologies) that contains rostaporfin [19].

b. poly(lactic) acid and poly (lactic-co-glycolic) acid (PLGA): They are biodegradable polymers and disappear from the injection site after drug delivery. These polymers have been employed to make implants, scleral plugs, pellets, discs, films, and rods [20]. The implant is introduced into the eye through pars plana insertion [21]. Ocular administration of micro and nanoparticles has been employed by intravitreal [22] and periocular injections [23]. Different drugs have been prepared with PLGA microparticles, such as, dexamethasone for uveitis, aciclovir for herpes infection, ganciclovir for cytomegalovirus retinitis, neurotrophic factors for neuroprotection, 5-fluorouracil (5-FU), adriamycin, and retinoic acid for proliferative retinopathy, and inhibitor of protein kinase C (PKC412) for choroidal neovascularization [24, 25] PLGA microspheres loaded with triamcinolone have also already been used in humans [26].

dexamethasone sustained-release device (Ozurdex®): The dexamethasone implant provides an initial shot of highly concentrated dexamethasone, followed by a gradual release over the following 3 months. Ozurdex is implemented in the treatment of posterior uveitis, diabetic macular edema (DME), and neovascular AMD. The clinical effects of Ozurdex for the treatment of macular edema may last up to 6 months. Several studies demonstrated that there were minimal cataract progression and 2% of study patients versus 1% of controls developed intraocular pressure elevation of 10 mmHg at 3-months follow-up [1, 3, 27]. An important advantage of Ozurdex is immediate effect of inflammation control in uveitis diseases or treatment of other retinal pathologic conditions with a gradual steady-state release without the need to explant the device. The major disadvantage is the shorter duration of action.

fluocinolone acetonide implant (Iluvien): Iluvien (fluocinolone acetonide intravitreal implant) 0.19 mg is a sustained release intravitreal implant approved to treat DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. In analyses of two multinational trials in patients with DME previously treated with macular laser photocoagulation, fluocinolone acetonide intravitreal implant 0.2 µg/day was significantly more efficacious than sham injection in improving visual acuity [28]. The implant is a linear tube 3 mm long and 0.37 mm in diameter that can be injected through a 25-gauge needle. The duration of action is between 18 and 36 months [1]. The advantage of this drug delivery system is that it is a minimally invasive procedure, and it is biodegradable. This device has the same risk of glaucoma and cataract consistent with all intraocular corticosteroid implants.

Non-biodegradable Polymers

Advantages:

*Controlled release for long duration

***Disadvantages*:**

*Require surgical implant and removal.
*Need replacement of new implants.

Clinical examples:

ganciclovir: The ganciclovir implant (Vitrasert) by Bausch & Lomb was the first intraocular sustained-release drug device approved for the treatment of cytomegalovirus (CMV) retinitis [29]. It is useful if patient is intolerant of systemic ganciclovir or if progression continues despite intravenous treatment [30]. Their use was limited by serious side-effects such as myelosuppression and renal toxicity, commonly encountered in acquired immunodeficiency syndrome (AIDS) patients [31]. Intraocular administration of ganciclovir minimized these systemic side-effects. The ganciclovir implant is composed of a non-biodegradable polymer that released ganciclovir roughly 1μg/h over a period of 8 months [1, 32]. Uncommon complications related to the surgical implant of the device included retinal detachment, endophthalmitis, and vitreous hemorrhage [1, 3, 32, 33].

fluocinolone acetonide: A fluocinolone acetonide implant (Retisert) by Bausch & Lomb has been approved by the Food and Drug Administration (FDA) for the treatment of chronic uveitis. This is the second non-biodegradable intraocular polymer implant that needs surgical placement through the pars plana for the treatment of noninfectious posterior uveitis. The FDA-approved implant contains 0.59 mg of Retisert with a burst release of 0.6 μg/day. Over the next 30 days, the drug level gradually decreases to a steady level of 0.3 μg/day [1, 34-36]. In a multicenter, randomized clinical trial of Retisert implants for the treatment of noninfectious posterior uveitis, the rate of recurrence was decreased from 51.4% before implant to 6.1% after implant [34]. Visual acuity remained stable or improved in 87% of the patients studied. More than 50% of patients had pressure-lowering medication, and 5.8% required glaucoma surgery during the 34-week follow-up [34]. At 3-year follow-up, implanted eyes showed significantly lowered the incidence of cystoid macular edema. The side effects included 92% of Phakic patients requiring cataract surgery, increased intraocular pressure in 38% of patients requiring filtering procedure and 2% requiring removal of the implant for glaucoma management [1, 3, 34]. Rofagha et al. reported a spontaneous intraocular dissociation of a (Retisert) could happen years after placement, in the absence of trauma or other risk factors. Surgeons and patients must be aware of this potential complication [37].

Dendrimers

Dendrimers are a new class of polymeric materials. They are "tree-like," nanostructured polymers that have been investigated in terms of ocular drug delivery. They are interesting systems for drug delivery due to their nanosize range, ability to have multiple surface groups that permit for targeting, and easy preparation and a good function [38]. Ocular dendrimeric systems may enhance effective delivery of therapeutic agents to intraocular tissues, such as the retina or choroid, using noninvasive delivery methods. Dendrimers have been investigated for ophthalmic drug delivery since it offers a number of advantages as a carrier system. It has been reported that dendrimers were used for several purposes as a carrier system for ocular drug delivery, antioxidant delivery, peptide delivery, biomedical imaging, gene delivery, and genetic testing in ophthalmology [39].

Advantages:

1. Nanosize ranging from 1 to 100nm
2. Can encapsulate hydrophobic drug molecules into their internal cavities [40].
3. targeting anywhere in the body is possible, due to the multiple functional groups on their surface which makes it potential to attach vector devices [41, 42].
4. Smaller generation dendrimers also have an enhancer effect on permeability since they have a better ability to move between cells [43].

Disadvantages

1. Cytotoxicity is related to the chemistry of dendrimers. The interaction between surface cationic charge of dendrimers and negatively charged biological membranes is the main reason of toxicity [44].
2. It was shown that following repeated intravenous use or topical ocular application, dendrimers with cationic end groups are often toxic, whereas anionic dendrimers are not. For this reason, it is necessary to modify the surface amine groups of these dendrimers with neutral or anionic moieties order to reduce toxicity [45, 46].

Clinical examples:

Pilocarpine nitrate and tropicamide: Several series of polyamidoamine (PAMAM) dendrimers was used to control ocular drug delivery of pilocarpine nitrate and tropicamide. A study of a "miotic activity test" on albino rabbits reported that these PAMAM formulations enhance pilocarpine nitrate bioavailability compared to the control and caused the prolonged reduction of intraocular pressure (IOP), indicating increased precorneal residence time [47].

Gatifloxacin: Durairaj et al. [48] investigated dendrimeric polyguanidilyated translocators (DPTs), which are the potential ophthalmic carriers for gatifloxacin, a "fourth-generation fluoroquinolone". They approved for conjunctivitis treatment. The results have shown that the DPT forms stable gatifloxacin complexes and improves solubility, permeability, anti-MRSA activity, and *in vivo* delivery of gatifloxacin.

VEGF-ODN: Oflipophilic amino-acid (ODN) dendrimers have been created with collagen scaffolds to improve better physical and mechanical properties and adhesion ability. Dendrimers-based approach was used for antivascular endothelial growth factor oligonucleotide (VEGF-ODN) delivery. They were successfully tested in a rat model to treat choroidal neovascularization (CNV). The results concluded that dendrimer/ODN-1 complexes significantly suppressed VEGF expression in cell level studies around 40 to 60%. Examinations of injected rat eyes also showed that the complex injections caused no significant toxicity and damage [48].

Hydrogels

The first appearance of the term 'hydrogel' in the literature was in 1894 [49]. Hydrogels are polymers which have the characteristic to swell in water or aqueous solvent, and they keep the solvents in

a swollen cross-linked gel for drug delivery. They can be nondegradable or degradable in application [50, 51]. A thermo-sensitive hydrogel delivery system can encapsulate and release anti-VEGF agents [52]. Due to its thermo-sensitive feature; the hydrogel can be injected in a liquid form to the vitreous cavity via a small gauge needle. When it is exposed to the body temperature, the solution rapidly becomes a solid gel that releases the encapsulated protein such as anti-VEGF agent. The current investigation showed that the thermosensitive hydrogel can encapsulate bevacizumab at a high rate, is nontoxic, and the characteristics of biodegradability and bioactivity appear to be a promising intravitreal injection carrier for bevacizumab delivery [53].

Advantages: There are several advantages that make hydrogels an interesting drug delivery system the posterior segment [51, 54]. The aqueous environment of hydrogels can protect cells and fragile drugs (such as peptides, proteins, oligonucleotides, and DNA). They serve as a good means of transport of nutrients to cells and products from cells. They can also be modified with cell adhesion ligands, and can change physical state (liquid to solid) in response to pH or temperature changes, and, most importantly, they are highly biocompatible.

Disadvantage: Among all the hydrogel systems investigated over the years are temperature-and pH-responsive hydrogels. Kang Derwent and Mieler examined the potential toxicity of crosslinked thermo-sensitive hydrogels in a cell culture model [55]. Poly (N-isopropylacrylamide) (PNIPAAm) hydrogel was examined. Pure NIPAAM (unpolymerized form), particularly acrylamide, has been shown to be toxic in the nervous system [56]. However, there are some of the studies that have demonstrated that PNIPAAm (polymerized form) is not toxic [57, 58].

Clinical examples:

Poly (N-isopropylacrylamide) (PNIPAAm) hydrogel: It is one of the famous thermo-sensitive materials which has a lower critical solution temperature (LCST) or transition temperature at ~32°C [59, 60]. Below the LCST, the hydrogel is swollen and above the LCST, the hydrogel will shrink. A change in physical state is rapid and reversible, which makes the thermo-sensitive hydrogel an attractive means of drug delivery. Hydrogel exists in a liquid gel-like phase; however, once the temperature is raised beyond its LCST, a solid gel is formed rapidly.

Conclusion

Polymers implants are potential future sustained-release retinal drug delivery systems. Modern sustained-release technology will offer safety and long duration of action, and maintain continued bioactivity. Sustained-release technology may offer treatment for age related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, retinal vascular occlusion, and uveitis.

References

[1]. Del Amo EM, Urtti A (2008) Current and future ophthalmic drug delivery systems: a shift to the posterior segment. Drug Discov Today 13(3-4): 135-143.

[2]. Maurice DM, Mishima S (1984) Ocular pharmacokinetics. In Handbook of Experimental Pharmacology. Springer-Verlag, Berlin. 19-116.

[3]. Urtti A (2006) Challenges and obstacles of ocular pharmacokinetics and drug delivery. Adv Drug Deliv Rev 58(11): 1131-1135.

[4]. Montero JA, Ruiz-Moreno JM, Fernandez-Muñoz M, Rodriguez-Palacios MI (2008) Effect of topical anesthetics on intraocular pressure and pachymetry. Eur J Ophthalmol 18(5): 748-750.

[5]. Shirasaki Y (2008) Molecular sign for enhancement of ocular penetration. J Pharm Sci 97(7): 2462-2496.

[6]. Hosoya K, Lee VH, Kim KJ (2005) Roles of conjunctiva in ocular drug delivery: a review of conjunctival transport mechanism and their regulation. Eur J Pharm Biopharm 60(2): 227-240.

[7]. Ranta VP, Urtti A (2006) Transscleral drug delivery to the posterior eye: prospects of pharmacokinetic modeling. Adv Drug Deliv Rev 58(11): 1164-1118.

[8]. Robinson MR, Lee SS, Kim H, Kim S, Lutz RJ, et al. (2006) A rabbit model for assessing the ocular barriers to the transscleral delivery of triamcinolone acetonide. Exp Eye Res 82: 479-487.

[9]. Dib E, Maia M, Longo-MaugeriI M, Martins MC, Mussalem JS, et al. (2008) Subretinal bevacizumab detection after intravitreous injection in rabbits. Invest Ophthalmol Vis Sci 49(3): 1097-1100.

[10]. Herrero-Vanrel lR, Fernández-Carballido A, Frutos G, Cadórniga R (2000) Enhancement of the mydriatic response to tropicamide by bioadhesive polymers. J Ocular Pharmacol Ther 16(5): 419-428.

[11]. Maurice D (2001) Review: practical issues in intravitreal drug delivery. J Ocul Pharmacol Ther 17(4): 393-401.

[12]. Hsu J (2007) Drug delivery methods for posterior segment disease. Curr Opin Ophthalmol 18(3): 235-239.

[13]. Davis JL, Gilger BC, Robinson MD (2004) Novel approaches to ocular drug delivery. Curr Opin Mol Ther 6(2): 195-205.

[14]. Bourges JL, Bloque C, Thomas A, Froussart F, Bochot A, et al. (2006) Intraocular implants for extended drug delivery: therapeutic applications. Adv Drug Deliv Rev 58(11): 1182-1202.

[15]. Fattal E, DeRosa G, Bochot A (2004) Gel and solid matrix systems for the controlled delivery of drug carrier-associated nucleic acids. Int J Pharm 277(1-2): 25-30.

[16]. Cheng L, Hostetler KY, Lee J, Koh HJ, Beadle JR, et al. (2004) Characterization of a novel intraocular drug-delivery system using crystalline lipid antiviral prodrugs of ganciclovir and cyclic cidofovir. Invest Ophthalmol Vis Sci 45(11): 4138-4144.

[17]. Odergren A, Algvere PV, Seregard S, Kvanta A (2008) A prospective randomized study on low-dose transpupillary thermotherapy versus photodynamic therapy for neovascular age-related macular degeneration. Br J Ophthalmol 92: 757-761.

[18]. Antoszyk AN, Tuomi L, Chung CY, Singh A, FOCUS Study Group (2008) Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. Am J Ophthalmol 145(5): 862-874.

[19]. Chakravarthy U, Soubrane G, Bandello F, Chong V, Creuzot-Garcher C, et al. (2006) Evolving European guidance on the medical management of neovascular age related macular degeneration. Br J Ophthalmol 90(9): 1188-1196.

[20]. Yasukawa T, Ogura Y, Tabata Y, Kimura H, Wiedemann P, et al. (2004) Drug delivery systems for vitreoretinal diseases. Prog Retin Eye Res 23(3): 253-281.

[21]. Gould L, Trope G, Cheng YL, Heathcote JG, Sheardown H et al. (1994) Fifty: fifty poly (DL glycolic acid-lactic acid) copolymer as a drug delivery system for 5-fluorouracil: a histopathological evaluation. Can J Ophthalmol 29(4): 168-171.

[22]. Herrero-Vanrell R, Refojo MF (2001) Biodegradable microspheres for vitreoretinal drug delivery. Adv Drug Deliv Rev 52(1): 5-16.

[23]. Kompella UB, Bandi N, Ayalasomayajula SP (2003) Subconjunctival nano- and microparticles sustain retinal delivery of budesonide, a corticosteroid capable of inhibiting VEGF expression. Invest Ophthalmol Vis Sci 44(3): 1192-1201.

[24]. Jiang C, Moore MJ, Zhang X, Klassen H, Langer R, et al. (2007) Intravitreal injection of GDNF-loaded microspheres are neuroprotective in a rat model of glaucoma. Mol Vis 13: 1783-1792.

[25]. Saishin Y, Silva RL, Saishin Y, Callahan K, Schoch C, et al. (2003) Periocular injection of microspheres containing PKC412 inhibits choroidal neovascularization in a porcine model. Invest Ophthalmol Vis Sci 44(11): 4989-4993.

[26]. Cardillo JA, Souza-Filho AA, Oliveira AG (2006) Intravitreal bioerudivel sustained-release triamcinolone microspheres system (retaac). Preliminary report of its potential usefulnes for the treatment of diabetic macular edema. Arch Soc Esp Oftalmol 81(12): 675-682.

[27]. Kuppermann BD, Williams GA, Blumenkranz MS, Dugel P, Haller JA, et al. (2006) Efficacy and safety of a novel intravitreous dexamethasone drug-delivery system after applicator or incisional placement in patients with macular edema. Invest Ophthalmol Vis Sci 47: 5913.

[28]. Sanford M (2013) Fluocinolone acetonide intravitreal implant (Iluvien®): in diabetic macular oedema. Drugs 73(2): 187-193.

[29]. Sanborn GE, Anand R, Torti RE, Nightingale SD, Cal SX, et al. (1992) Sustained-release ganciclovir therapy for treatment of cytomegalovirus retinitis.

Use of an intravitreal device. Arch Ophthalmol 110(2): 188-195.

[30]. Roth DB, Feuer WJ, Blenke AJ, Davis JL (1999) Treatment of recurrent cytomegalovirus retinitis with the ganciclovir implant. Am J Ophthalmol 127(3): 276-282.

[31]. Martin DF, Dunn JP, Davis JL, Duker JS, Engstrom RE Jr, et al. (1999) Use of the ganciclovir implant for the treatment of cytomegalovirus retinitis in the era of potent antiretroviral therapy: recommendations of the International AIDS Society-USA panel. Am J Ophthalmol 127(3): 329-339.

[32]. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD (1997) Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. N Engl J Med 335(2): 83-90.

[33]. Dunn JP, Van Natta M, Foster G, Kuppermann BD, Martin DF, et al. (2004) Complications of ganciclovir implant surgery in patients with cytomegalovirus retinitis: the Ganciclovir Cidofovir Cytomegalovirus Retinitis Trial. Retina 24(1): 41-50.

[34]. Jaffe GJ, Martin D, Callanan D, Pearson PA, Levy B, et al. (2006) Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter, randomized clinical study. Ophthalmology 113(6): 1020-1027.

[35]. Goldstein DA, Godfrey DG, Hall A, Callanan DG, Jaffe GJ, et al. (2007) Intraocular pressure in patients with uveitis treated with fluocinolone acetonide implants. Arch Ophthalmol 125(11): 1478-1485.

[36]. Jaffe GJ, Yang CH, Guo H, Denny JP, Lima C, et al. (2000) Safety and pharmacokinetics of an intraocular fluocinolone acetonide sustained delivery device. Invest Ophthalmol Vis Sci 41(11): 3569-3575.

[37]. Rofagha S, Prechanond T, Stewart JM (2013) Late spontaneous dissociation of a fluocinolone acetonide implant (Retisert). Ocul Immunol Inflamm 21(1): 77-78.

[38]. Quintana A, Raczka E, Piehler L, Lee I, Myc A, et al. (2002) Design and function of a dendrimer-based therapeutic nanodevice targeted to tumor cells through the folate receptor. Pharm Res 19(9): 1310-1316.

[39]. Marco Zarbin A, James Leary F, Montemagno C, Ritch R, Humayun MS (2013) "Nanomedicine in ophthalmology," in Retina. 689-711.

[40]. Cheng YY, Xu ZH, Ma ML, Xu TW (2008) Dendrimers as drug carriers: applications in different routes of drug administration. J Pharm Sci 97(1): 123-143.

[41]. Bharti JP, Prajapati SK, Jaiswal MK, Yadav RD (2011) Dendrimer multifunctional nano-device: a review. Int J Pharm Sci Res 2(8): 1947-1960.

[42]. Garg T, Singh O, Arora S, Murthy R (2011) Dendrimer: a novel scaffold for drug delivery. Int J Pharm Sci Rev Res 7(2): 211-220.

[43]. Kaminskas LM, Boyd BJ, Porter CJ (2011) Dendrimer pharmacokinetics: the effect of size, structure and surface characteristics on ADME properties. Nanomedicine 6(6): 1063-1084.

[44]. Jevprasesphant R, Penny J, Attwood D, McKeown NB, D'Emanuele A (2003) Engineering of dendrimer surfaces to enhance transepithelial transport and reduce cytotoxicity. Pharm Res 20(10): 1543-1550.

[45]. Chen HT, Neerman MF, Parrish AR, Simanek EE (2004) Cytotoxicity, hemolysis, and acute in vivo toxicity of dendrimers based on melamine, candidate vehicles for drug delivery. J Am Chem Soc 126(32): 10044-10048.

[46]. Jain K, Kesharwani P, Gupta U, Jain NK (2010) Dendrimer toxicity: let's meet the challenge. Int J Pharm 394(1-2): 122-142.

[47]. Vandamme TF, Brobeck L (2005) Poly (amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. J Control Release 102(1): 23-38.

[48]. Marano RJ, Toth I, Wimmer N, Brankov M, Rakoczy PE (2005) Dendrimer delivery of an anti-vegf oligonucleotide into the eye: a long-term study into inhibition of laser-induced CNV, distribution, uptake and toxicity. Gene Ther 12(21): 1544-1550.

[49]. Van Bemmelen JM (1894) Der Hydrogel und das kristallinische Hydrat des Kupferoxydes. Z Anorg Chem 5: 466.

[50]. Hoffman AS (2002) Hydrogels for biomedical applications. Adv Drug Deliv Rev 54(1): 3-12.

[51]. Kim SW, Bae YH, OkanoT (1992) Hydrogels: swelling, drug loading and release. Pharm Res 9(3): 283-290.

[52]. Wang CH, Hwang YS, Chiang PR, Shen CR, Hong WH, et al. (2012) Extended release of bevacizumab by thermosensitive biodegradable and biocompatible hydrogel. Biomacromolecules 13(1): 40-48.

[53]. Hu CC, Chaw JR, Chen CF, Liu HW (2014) Controlled release bevacizumab in thermoresponsive hydrogel found to inhibit angiogenesis. Biomed Mater Eng 24(6): 1941-1950.

[54]. Lee KY, Mooney DJ (2001) Hydrogels for tissue engineering. Chem Rev 101(7): 1869-1879.

[55]. Kang Derwent JJ, Mieler WF (2008) Thermo-responsive hydrogels as a new ocular drug delivery platform to the posterior segment of the eye. Trans Am Ophthalmol Soc 106: 206-213.

[56]. Hashimoto K, SakamotoJ, Tanji H (1981) Neurotoxicity of acrylamide and related compounds and their effects on male gonads in mice. Arch Toxicol 47(3): 179-189.

[57]. Takezawa T, Mori Y, Yoshizato K (1990) Cell culture of a thermo-responsive polymer surface. Biotechnology 8(9): 854-856.

[58]. Malonne H, Eeckman F, Fontaine D, Otto A, Vos LD, et al. (2005) Preparation of poly (N-isopropylacrylamide) copolymers and preliminary assessment of their acute and subacute toxicity in mice. Eur J Pharm Biopharm 61(3): 188-194.

[59]. Heskin M, Guillet JE (1968) Solution properties of poly (N-isopropyl acrylamide). J Macromol Sci 2(8): 1441-1455.

[60]. Dhara D, Chatterji PR (2000) Phase transition in linear and cross-linked poly (N-isopropyl acrylamide) in water: effect of various types of additives. J Macromol Sci Part C: polymer reviews 40(1): 51-68.

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