Review Article

# Sustained Drug Delivery Systems for Treatment of Age Related Macular Degeneration: A Review

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## Abstract

The number of people with age-related visual problems, such as macular degeneration, has increased in recent decades due to population aging. Currently, many pharmacologic therapies exist for age-related macular degeneration (AMD), however none have satisfactory results. This underlines the need for novel drug delivery systems to improve pharmacological drug concentrations at specific locations, thereby boosting treatment effects. This study includes the current findings on sustained drug delivery systems focused at improving treatment results for patients with AMD.

**Keywords:** Age-Related Macular Degeneration; Drug Delivery System; Review.

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## Introduction

Age-related macular degeneration (AMD) is a retinal disease that can cause vision impairment and even blindness [1]. The clinical symptoms of AMD include distinct drusen deposits, pigmentary alterations, geographic atrophy, and neovascularization [2]. It is a major cause of permanent blindness in persons over 60 years old in the developed world, accounting for 8.7 % of all legal blindness worldwide [3]. The overall prevalence of AMD is projected to grow from 4.2 % in patients aged 45-49 years to 27.2 % in those aged 80-85 years [4]. AMD exists in two primary forms: dry AMD, which accounts for the majority of cases, and neovascular or wet AMD, which is responsible for just 10-20 % of instances [5]. However, it should be emphasized that 90 % of vision loss cases are caused by the neovascular form of the disease despite its lower prevalence [6]. AMD affects the retina in the posterior portion of the eye, producing a considerable impediment for medication delivery due to the presence of several physiological and anatomical barriers, including the sclera, choroid, retinal pigment epithelium, and blood-retinal barriers [7,8]. To increase drug transport and absorption in the treatment of AMD, the physicochemical properties of potential drugs should be adjusted to bypass these obstacles [3,9].

Intravitreal and periocular channels are the two main medication delivery techniques used for the treatment of AMD [3]. The intravitreal method offers direct administration of medications to the target area but may produce consequences such as retinal detachment or endophthalmitis [10]. Periocular delivery offers a decreased risk of problems but is less efficient at reaching the target tissue [3,10].

Currently, there is no approved medication that significantly changes the course of dry AMD, however numerous FDA-approved pharmacologic medicines exist for neovascular AMD [11]. Evidence suggests unsatisfactory outcomes in a considerable majority of patients receiving these medications, underlining the need for novel methods to manage this condition [12]. This review covers the latest data regarding sustained drug delivery systems targeted at improving treatment outcomes for patients with AMD.

## Sustained Drug Delivery Systems for Treatment of AMD

While a reliable treatment for dry AMD has yet to be established, various treatment options such as photodynamic therapy, laser photocoagulation, and vascular endothelial growth factor (VEGF) inhibitors have been suggested to treat neovascular AMD, with VEGF inhibitor injections showing the most promising results [13]. Despite the demonstrated benefits of VEGF inhibitors, they require recurrent intravitreal injections, which are associated with significant consequences, including endophthalmitis, retinal detachment, and elevated intraocular pressure [14]. It is important to note that repeated injections result in a high local concentration of the medication shortly after administration, followed by rapid clearance, which reduces its effectiveness over time. Therefore, improved drug delivery techniques are needed to minimize the risks associated with repeated injections and to maximize therapeutic efficacy by maintaining sustained drug concentrations.

## Sustained Drug Delivery Systems for Treatment of Dry AMD

Ciliary neurotrophic factor (CNTF) is a member of the interleukin (IL)-6 family with protective characteristics against

retinal degeneration in animal models [15]. However, getting CNTF to the retina poses a considerable hurdle due to the blood-retina barrier [15]. To tackle this difficulty, implants have been created employing encapsulated cell technology (ECT) to enable a sustained drug delivery system in the vitreous cavity [16]. In a pilot, phase II trial, Zhang et al., [17] reported promising results for CNTF in the treatment of geographic atrophy. CNTF was administered by an intraocular ECT implant, and they concluded that CNTF delivered by this technique reduces the course of vision loss in geographic atrophy, particularly in eyes with 20/63 or greater vision at baseline [17]. In another trial, Kauper et al., [16] examined the efficacy of CNTF administered over a period of up to two years using an intraocular ECT implant in patients with retinitis pigmentosa and geographic atrophy. They concluded that the intraocular CNTF implant has a favorable pharmacokinetic profile for the treatment of chronic retinal degenerative disorders without systemic exposure [16]. On the other hand in a review by Ghasemi et al., [15] the authors concluded that the therapeutic efficacy of sustained CNTF delivery methods to the retina is still far from attaining predicted outcomes, and future studies should focus on optimizing these delivery methods.

Brimonidine, an alpha2-adrenergic agonist with cyto/neuroprotective action, is another potential treatment for geographic atrophy, given by an intravitreal implant as a sustained drug delivery method. Kuppermann et al., [18] evaluated the safety and efficacy of the brimonidine drug delivery system (Brimo DDS), a biodegradable intravitreal implant, in the treatment of geographic atrophy secondary to age-related macular degeneration. They concluded that Brimo DDS has a positive safety profile and lowers the geographic atrophy lesion area at months 3 and 12 [18]. Freeman et al., [19] examined the safety and efficacy of repeated injections of Brimo DDS containing 400-µg brimonidine among individuals with geographic atrophy secondary to age-related macular degeneration, delivered every three months from day 1 to month 21, and compared the findings with a placebo. The primary endpoint was the change in lesion area from baseline, measured with fundus autofluorescence imaging, at month 24 [19]. They noticed that numerous intravitreal injections of Brimo DDS were well tolerated, and there was a quantitative tendency toward reduced geographic atrophy progression at 24 months compared to the placebo therapy [19].

## Sustained Drug Delivery Systems for Treatment of Neovascular AMD

The port delivery system (PDS) with ranibizumab is an intraocular medicine delivery device designed for the continuous provision of ranibizumab into the vitreous for six months or more [20]. It is a refillable device surgically inserted via a small incision in the sclera near the pars plana, permitting for the sustained release of ranibizumab by passive diffusion into the vitreous cavity [20,21]. Ranibizumab is an intriguing candidate for the PDS due to its unique physicochemical stability and high solubility [22,23].

In a phase 2 clinical research, Campochiaro et al., [20] evaluated the safety and efficacy of the PDS with ranibizumab for the treatment of neovascular AMD. They randomized patients diagnosed with neovascular AMD within nine months who had received two or more prior VEGF inhibitor intravitreal injections and were responsive to treatment, to receive the PDS filled with ranibizumab at 10 mg/mL, 40 mg/mL, or 100 mg/mL, or monthly

intravitreal ranibizumab 0.5-mg injections [20]. They reported that the PDS was usually well-tolerated and had a dose response across several endpoints, with visual and anatomic outcomes equivalent to monthly intravitreal ranibizumab 0.5-mg injections [20].

In a more recent phase 3 trial by Regillo et al., [24] the authors reported the two-year results of the PDS with ranibizumab for the treatment of neovascular AMD. Patients were randomized to receive either PDS with ranibizumab 100 mg/mL with fixed refill-exchanges every 24 weeks or intravitreal ranibizumab 0.5 mg injections every four weeks [24]. They concluded that the PDS regimen demonstrated non-inferior effectiveness to monthly ranibizumab [24].

In another study by Chang et al., [25] the authors investigated the treatment satisfaction for ranibizumab administered via PDS compared to intravitreal ranibizumab injections, as well as patient preference among those patients assigned to PDS. Patients were randomized to receive either PDS with ranibizumab 100 mg/mL with fixed refill exchanges every 24 weeks or intravitreal ranibizumab injections 0.5 mg every four weeks [25]. They reported that PDS treatment was preferred by almost all patients randomized to PDS over previous intravitreal injections [25].

Another possible sustained medication delivery strategy for the treatment of neovascular AMD is glucocorticoid implants. Anecortave acetate, triamcinolone acetonide, and dexamethasone have been explored for this reason [26].

Augustin et al., [27] examined the clinical safety of anecortave acetate delivered as a posterior juxtascleral depot every six months for up to four years and reported it to be clinically safe. This safety profile was also reported in another investigation by Regillo et al., [28]. Lim et al., [29] examined the safety and efficacy of an intravitreal, liquid, sustained drug delivery system prepared with triamcinolone acetonide in combination with ranibizumab for neovascular AMD. They reported that this combination therapy was well-tolerated and resulted in fewer ranibizumab re-treatments [29].

Kuppermann et al., [30] evaluated the efficacy and safety of dexamethasone intravitreal implants as additional therapy to ranibizumab in neovascular AMD They reported a reduced demand for supplementary ranibizumab treatment and acceptable tolerability among their patients. However, in a review report by Geltzer et al., [31] evaluating the effects of steroids with antiangiogenic properties in the treatment of neovascular AMD, the authors concluded that there is no evidence that antiangiogenic steroids diminish vision loss in patients with neovascular AMD. They stated that with the development of VEGF inhibitors, the role of steroids in treating neovascular AMD remained unclear. Similarly, in another review article evaluating the use of intravitreal injection of triamcinolone acetonide in the treatment of AMD, the authors suggested that with the advent of VEGF inhibitors, triamcinolone acetonide has taken a back seat in the treatment of neovascular AMD [32].

## Discussion

The human visual system has several hurdles that limit medicine delivery for AMD treatment, and currently accessible therapeutic approaches, such as intravitreal injections, can produce side effects including retinal detachment or endophthalmitis [4,10,33]. Suboptimal results are reported in a considerable majority of patients receiving conventional medicines, underlining the need for innovative approaches. This study covered the latest findings on sustained drug delivery systems aiming at improving treatment

outcomes for patients with AMD.

Based on the findings discussed in this review, sustained drug delivery systems for the treatment of dry AMD, incorporating CNTF or brimonidine, have shown some promise. However, these systems are still in the early stages, and further studies are needed to enhance delivery to the retina and evaluate the safety and effectiveness of these approaches. Regarding neovascular AMD, the ranibizumab PDS has shown promissing outcomes, but corticoid implants appear to be less beneficial as an optimum therapeutic option.

Although these innovative approaches may greatly enhance the management of patients with AMD and lessen the negative effects associated with existing drug delivery systems, the present body of research remains limited. Future research on sustained drug delivery mechanisms and implant devices for AMD treatment should involve more randomized clinical studies comparing the efficacy and safety of these new modalities with established treatments, such as intravitreal ranibizumab injections.

## Conclusion

The recent findings on sustained drug delivery systems for improving treatment outcomes in patients with AMD are promising. However, further randomized clinical trials are necessary to compare the efficacy and safety of these new methods with traditional treatment modalities.

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## Footnotes and Financial Disclosures

### Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.