

Overview of Sustained-Release Drug-Delivery Systems

A novel technique may avoid some of the limitations of current preparation methods.

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The number of intravitreal injections performed for the treatment of posterior segment diseases has dramatically escalated as new therapies have become available. Intravitreal injections, however, have limited efficacy. Monthly dosing of a drug would seem to deliver a consistent effect of that drug; however, very high local concentrations immediately after injection are typically followed by rapid clearance of the drug, thus necessitating frequent treatment.

Several approaches described in this article have been approved or are being explored for extended release of drugs for the treatment of retinal diseases. In general, the rationale for these innovative delivery systems is to deliver sustained drug concentrations to the target site so as to decrease the treatment burden associated with repeated injections (Table).¹⁻⁵ Such systems may be combinations of drug and biomaterial and can be classified according to size as implants (> 1 mm), microparticles (1 to 1000 μm), or nanoparticles (1 to 1000 nm). The biomaterial may be biodegradable or nonbiodegradable.

Depending on their size, implants and microparticles may release drug for longer durations compared with nanoparticles. However, drug-releasing implants may require a surgical procedure or special injection devices. It is our belief that a microparticle-based approach administered in the doctor's office can be formulated into an ideal therapy that would reach therapeutic doses in the target tissue with infrequent administration and a positive safety profile.

IMPLANT PREPARATION

Implants act as reservoirs for a drug or drugs so that the therapy can be delivered over a long interval. Commonly used techniques for implant preparation include solvent casting and extrusion.^{6,7}

Solvent Casting and Compression Molding

In this method, polymer and drug are dissolved in a common solvent and cast at a temperature to completely evaporate the solvent. The resultant structure is a composite material of drug together with polymer; the material is then compression-molded into the desired implant geometry. Solvent casting methods are not ideal for industrial scale-up because the process requires large quantities of organic solvent. In addition, solvent casting is not a continuous process and may result in batch-to-batch variability.

Extrusion

The extrusion process mitigates the disadvantages associated with solvent casting. It is a continuous process of drawing a polymer mixture through a die (mold cavity) to manufacture implants of a fixed cross-sectional profile. In this process, the polymer-drug mixture is heated to a semiliquid state by a heating element and by the stress from the extrusion screw. The screw pushes the mixture through a die, and the resulting extrudate is cooled and solidified before being cut into the desired implant lengths. The disadvantage of this technique is that the drug is exposed to high temperatures, and denaturation may occur.

MICROPARTICLE PREPARATION

The commonly used techniques for the manufacture of drug-incorporated microparticles are emulsion methods, phase separation, and spray drying.⁸⁻¹¹

Emulsion Methods

Single emulsion methods have been used to encapsulate hydrophobic drugs through an oil-in-water (o/w) process. In this process, the polymer is dissolved in a water-immiscible volatile organic solvent (eg, dichloromethane), and the drug is dissolved or suspended into the polymer solution. The

TABLE. SELECTED DRUG DELIVERY SYSTEMS FOR RETINAL DISEASES ON THE MARKET OR IN CLINICAL TRIALS

Device	Dosage Form	Active Agent	Disease Target	Approximate Duration
Dexamethasone intravitreal implant (Ozurdex, Allergan)	Biodegradable free-floating implant	Dexamethasone	Uveitis, DME, ME associated with secondary venous occlusion	6 months
Fluocinolone acetonide implant 0.59 mg (Retisert, Bausch + Lomb)	Nonbiodegradable intraocular scleral-fixed implant	Fluocinolone acetonide	Uveitis	3 years
Vitraser (ganciclovir; recently discontinued)	Nonbiodegradable intraocular scleral-fixed implant	Ganciclovir	CMV retinitis	6 months
Fluocinolone acetonide implant 0.19 mg (Iluvien, Alimera Sciences)	Nonbiodegradable free floating implant	Fluocinolone acetonide	DME	3 years
RETAAC System	PLGA microparticles	Triamcinolone acetonide	ME	unknown
DuoCat System	PLGA microparticles	Combination of triamcinolone and ciprofloxacin	Prevention of intraocular inflammation after cataract surgery	unknown

Abbreviations: CMV, cytomegalovirus; DME, diabetic macular edema; PLGA, poly(lactic-co-glycolic acid); ME, macular edema

resulting mixture is emulsified in a large volume of water in the presence of an emulsifier (eg, polyvinyl alcohol). The solvent in the emulsion is removed either by evaporation at elevated temperatures or extraction in large quantities of water. To encapsulate hydrophilic drugs (eg, peptides or proteins), double emulsion methods like water-in-oil-in-water (w/o/w) have been used. The aqueous solution of the water-soluble drug is emulsified with polymer-dissolved organic solvent to form a water-in-oil (w/o) emulsion. The emulsification is carried out using high-speed homogenizers or sonicators. The primary emulsion is transferred into an excess amount of water containing emulsifier under vigorous stirring, thus forming a w/o/w emulsion.

The process parameters that affect the drug-release characteristics of these microparticles include ratio of polymer to drug, particle size distribution, type of solvent, concentration and nature of emulsifier, temperatures, stirring and agitation speed, and affinity between phases of the active ingredient that leads to loss of drug in the antisolvent, which is typically water.

Phase Separation (Coacervation)

In this method, the drug is dissolved or dispersed in a polymer solution; an organic solvent (eg, silicone oil, vegetable oil, liquid paraffin) is added to this mixture while it is stirred continuously. Next, the polymer solvent is gradually extracted, and soft coacervate droplets containing drug are created.

Exposing these droplets into an excess amount of another nonsolvent (eg, hexane or heptane) hardens the coacervate phase. The process parameters that control the release of drug from these microparticles include the rate of nonsolvent addition to extract the polymer solvent and the viscosity of the nonsolvent along with formulation parameters (eg, polymer concentration, type, and molecular weight).

Spray Drying

In this process, the drug is dissolved or dispersed in a polymer solution. The resulting solution or suspension is sprayed through a nozzle in a stream of heated air to produce microparticles. The size of the microparticles is determined by atomizing conditions. In order to minimize aggregation, a double-nozzle spray drying technique was developed, in which polymer drug solution is sprayed from one nozzle and another nozzle sprays a solution of mannitol that coats the surface of the microparticles. This coating technique prevents aggregation. In some cases, the polymer drug solution is sprayed into liquid nitrogen and hardened by -80° C temperatures, at which solvent extraction occurs.

DRAWBACKS OF CURRENT MICROPARTICLE TECHNOLOGIES

The emulsion and spray drying methods for particle formation are random and result in microparticles of variable sizes. Microparticle size is an important factor that affects the

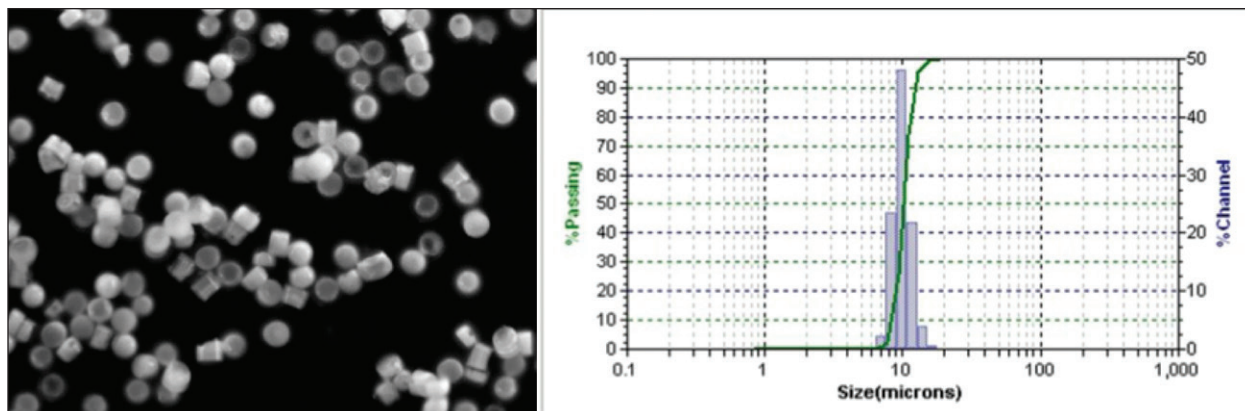


Figure 1. Microfabrication technology produces microparticles of predefined sizes with a homogeneous size distribution.

administration route and drug encapsulation within the microparticle, and, therefore, the drug release profile and duration. Another major problem with these techniques is that the drug loading (content) is often less than 10%. In addition, the spray drying technique may be unsuitable for substances sensitive to heating and the mechanical shear of atomization. Low product yield due to deposition of materials on the interior surface of the chamber is another cause for concern.

For preparation of microparticles using biodegradable polymers, it is important to choose a system that meets the following requirements:

- The process of manufacture should be continuous and avoid harsh environments;
- encapsulation and yield of microparticles should be high for scale-up;
- microparticles should possess a narrow size range distribution that can be administered through a needle and syringe;
- the release profile of the drug should be reproducible without significant initial release (burst); and
- the process should produce free flowing microparticles so that it is easy to prepare a uniform suspension of microparticles.

A NOVEL DRUG DELIVERY PLATFORM

A novel sustained release ocular drug delivery technology developed by Ohr Pharmaceutical Inc. circumvents many of the challenges associated with current drug delivery technologies. This technology allows delivery of any drug, including biologics, for extended durations with programmable, individualized release characteristics.

The Ohr Pharmaceutical Inc. sustained release technology employs a hydrogel template approach to prepare nano- or microparticles of predefined size and shape and with homogeneous size distribution (Figure 1). The size of the particles can be adjusted, providing flexibility in controlling the size and release rate of drug delivery formulations. The

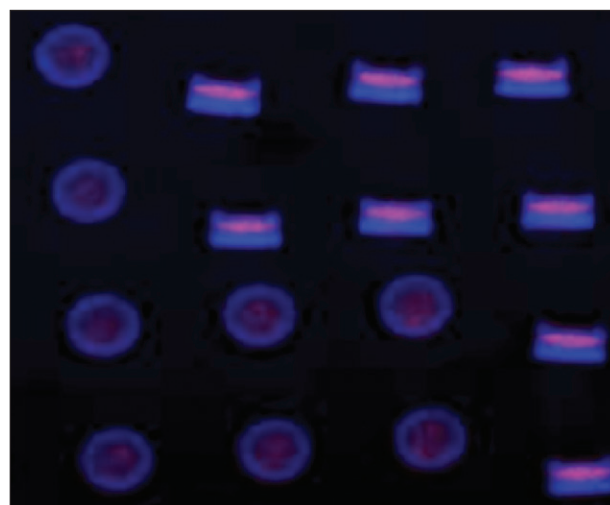


Figure 2. Multilayered microparticles.

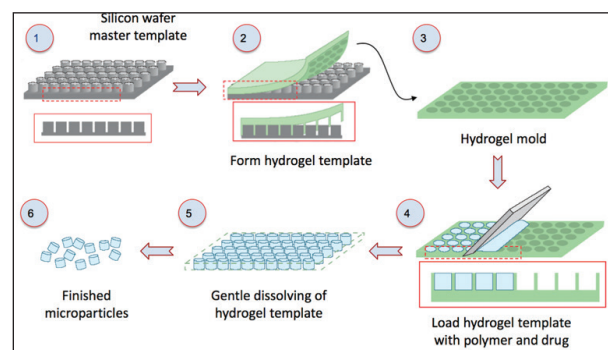


Figure 3. Process flow for creation of microfabricated microparticles using a dissolvable hydrogel template.

drug loading capacity is higher than that achieved by conventional methods (30% or greater), and there is a minimal controlled initial release of drug. A multilayered architecture can be created by incorporating homogeneous distribution of a combination of drugs (Figure 2). Simplicity in process-

ing makes the hydrogel template method useful for scale-up to manufacturing of particles. The major steps in microparticle manufacture are described in Figure 3.

The limits of emulsion technology include low drug loading capacity (usually much less than 10% of the total weight) and often significant initial release of a drug. The Ohr technology has significant advantages over currently available microparticle drug delivery systems prepared by emulsion methods. Moreover, this technology platform is adaptable to multiple routes of ocular delivery.

CONCLUSION

It is becoming increasingly clear that sustained release technologies using biodegradable or nonbiodegradable materials will extend the pharmacotherapy of treatments in the ophthalmic pharmaceutical industry. Several techniques described here are used to manufacture these technologies. The Ohr microfabrication approach offers a novel, scalable, continuous process for manufacture of sustained release therapies with low initial release, high incorporation efficiency or drug content, and multidrug delivery opportunities for small molecules or protein biologics. ■

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1. Lowder CY, Belfort Jr R, Lightman S, et al, for the Ozurdex HURON Study Group. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 10 January 2011. [Epub ahead of print].
2. Jaffe GJ, Martin D, Callanan D, et al; Fluocinolone Acetonide Uveitis Study Group. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter randomized clinical study. *Ophthalmology*. 2006;113(6):1020-1027.
3. Campochiaro P. Sustained Release Corticosteroid for DME. Paper presented at: Angiogenesis, Exudation and Degeneration 2011; February 12, 2011; Miami, FL.
4. Cardillo JA, Paganelli F, Melo LA Jr, et al; Brazilian Ocular Pharmacology and Pharmaceutical Technology Research Group. Subconjunctival delivery of antibiotics in a controlled-release system: a novel anti-infective prophylaxis approach for cataract surgery. *Arch Ophthalmol*. 2010;128(1):81-87.
5. Lavinsky D, Cardillo JA, A. A. S. Lima Filho, et al. Phase I/II Study of Intravitreal Triamcinolone Acetonide Microspheres for Treatment of Diffuse Diabetic Macular Edema Unresponsive to Conventional Laser Photocoagulation Treatment. *Invest Ophthalmol Vis Sci*. 2008;49: E-Abstract 2698.
6. Makadia HK, Siegel SJ. Poly Lactic-co-Glycolic Acid as biodegradable controlled drug delivery carrier. *Polymers*. 2011;3:1377-1397.
7. Widmer, M. Manufacture of porous biodegradable polymer conduits by an extrusion process for guided tissue regeneration. *Biomaterials*. 1998;19:1945-1955.
8. Park JH, Ye M, Park K. Biodegradable polymers for microencapsulation of drugs. *Molecules*. 2005;10:146-161.
9. Jain RA. The manufacturing techniques of various drug loaded biodegradable Poly Lactic-co-Glycolic Acid devices. *Biomaterials*. 2000;21:2475-2490.
10. NV Satheesh Madhav et al. Review on microparticle drug delivery system. *Int J PharmTech Research*. 2011;3(3):1242-1254.
11. Sahil K, Akanksha M, Kapoor B, et al. Microsphere: a review. *Int J Res Pharm and Chem*. 2011;1(4):1184-1198.