DelSiTech

NEW SOLUTIONS FOR OPHTHALMIC DRUG DELIVERY USING BIODEGRADABLE SILICA MATRIX

DelSiTech, a Finnish drug delivery company, has developed a proprietary non-mesoporous, biodegradable silica matrix technology where release of the active pharmaceutical ingredient (API) is based on the dissolution of silica in tissue. Here, Mika Jokinen, DSc, Research Director, Cora Griffin, PhD, Business Development Director, and Lasse Leino, PhD, President and Chief Executive Officer, all of DelSiTech, describe the novel opportunities that biodegradable silica matrix technology offers to ophthalmic drug delivery, and the different silica dosage forms for various types of APIs, ranging from large biological agents, such as proteins and viruses, to small molecules, covering injectable silica hydrogels, silica microsphere-silica hydrogel composites and silica implants.

Due to the aging population, chronic ocular diseases are becoming more common, and the number of patients suffering from conditions such as age-related macular degeneration (AMD), glaucoma, dry eye and diabetic retinopathies is increasing steadily. Drug treatment for ocular diseases is challenging due to the complex and protected structure of the eye, which prevents the penetration of active compounds at the site of action, e.g. the retina, after systemic administration. Although topical administration of eye drops is an easy and non-invasive method of ocular drug therapy, it suffers from low and easily saturated dose, poor bioavailability (less than 5% even in the front part of the eye) due to rapid drainage, and low patient compliance, especially in elderly patients.

> "The injectable silica hydrogel composites can be used both in IVT and subconjunctival delivery where at least one month's sustained release of the API is needed. It is also possible to develop much longer acting composite formulations with 3-6 months' controlled release of API ... With a very potent molecule, it would be possible to design products with more than 12 months release profile."

Invasive systems such as intravitreal (IVT) injections are used to treat the back of the eye. However, IVT injections cannot be given repeatedly in a short period of time because they are associated with potential severe side effects, such as increased pressure in the eye or infection, and they would generate a significant burden in ophthalmology clinics. For small molecules, which are typically rapidly eliminated within hours in the vitreous, immediate-release IVT formulations are not a realistic option because of the need for frequent injections. It is clear that there are unmet medical needs in ophthalmic drug treatment and these needs are not well served by current drug delivery systems. New concepts, tools and approaches should be generated and tested for the development of novel ocular therapies.

Amorphous silica matrix prepared by the sol-gel method is a well-known biomaterial for controlled drug delivery. Silica can be processed into several dosage forms, addressing a number of challenges in

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the development of sustained release parenteral products.

DelSiTech, a Finnish drug delivery company, has developed a proprietary non-mesoporous, biodegradable silica matrix technology where release of the active pharmaceutical ingredient (API) is based on the dissolution of silica in tissue, i.e. it is controlled by bulk matrix erosion rather than API diffusion. The properties of the sol-gel derived silica can be adjusted to ensure proper encapsulation of APIs and the desired degradation rate (dissolution of silica *in vivo*) from days to months, even up to years.1-3 In addition, silica is an inert material that is compatible with different types of APIs, including biologics and advanced-therapy medicinal products. Even compounds with either very low or very high water-solubility can be successfully encapsulated inside the silica matrix.

INJECTABLE SILICA DOSAGE FORMS IN PREFILLED SYRINGES

DelSiTech has developed several types of injectable, silica matrix-based formulation platforms that can be used in ophthalmic drug delivery. In all cases, the flowing (liquid) form of silica, a silica sol, is used to mix different components and API with silica before the system turns into a hydrogel. The silica sol-gel processing is a flexible, low-temperature method allowing the adjustment of the silica sol properties, such as pH to ensure the optimum pH environment on different types of APIs.

The first dosage form is a silica-silica composite material consisting of silica microspheres embedded in a silica hydrogel. The API, either a small molecule or a biologic, is encapsulated in the silica microspheres, which act as the API eluting reservoir and control the drug release by matrix dissolution. By controlling the silica microsphere (bio)degradation rate, it is possible to obtain an accurate control of API release.

Silica matrix itself is water-soluble and when placed in the body it dissolves in aqueous tissue fluids. Water-solubility of silica microspheres is a tuneable property that mainly depends on the number and density of OH-groups on the surface of silica matrix. By simply adjusting and varying the silica sol-gel composition and reaction parameters, such as concentrations of the main precursors (water and tetraethyl orthosilicate (TEOS), the source of silica), it is possible to produce silica microspheres that have different surface characteristics.

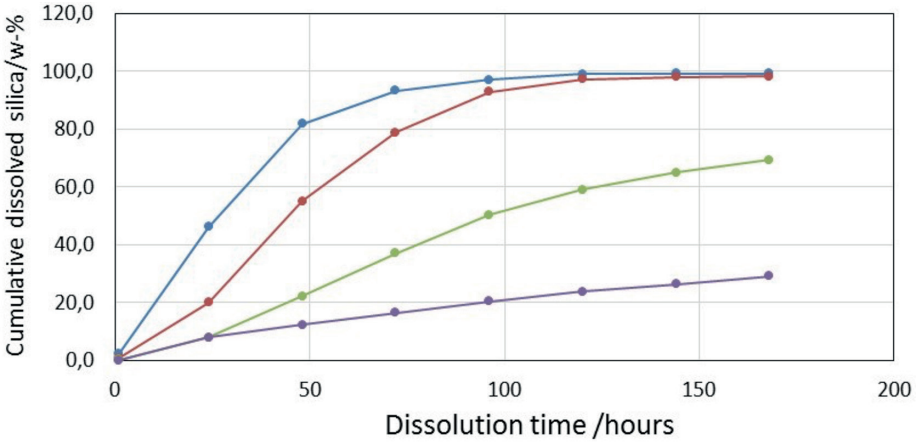

Figure 1: Cumulative in vitro silica dissolution rates in Tris buffer pH 7.4 (in sink) of four silica microsphere formulations which differ only in the water-to-TEOS ratio in the sol-gel reaction. The ratio is (from up to down) 3:1, 5:1, 10:1 and 15:1.

Figure 1 shows an example of how a simple change in water-to-TEOS ratio in the sol-gel process affects the dissolution rate of silica microspheres in aqueous buffer, i.e. the biodegradation time. The other manufacture and microsphere parameters were kept constant (sol pH, spray-drying parameters, and particle size distribution which was 1.5-10 µm, D50=3-4 µm).

Spray-drying is the main form-giving method to produce API-containing silica microspheres. It is inexpensive, fast and an easily scaleable manufacturing method that can be operated in a GMP environment, even in aseptic conditions. The spray-drying parameters are optimised for each API and formulation. Spray-drying is also gentle enough to preserve the biological activity and therapeutic effect of the encapsulated proteins and peptides. The temperatures in the process are kept low and the presence of silica protects sensitive molecules.

After spray-drying, the API-silica microspheres are mixed with a flowing aqueous silica sol and the mixture is transferred into a syringe before the sol turns into a hydrogel. The filling of the syringes is controlled by careful rheological measurements to ensure homogeneous product, long-term stability and good injectability. Shear rate-dependent viscosity is measured to study the shear-thinning behaviour, to ensure easy injectability, and oscillation measurements (for elastic and viscous modulus and their ratio, loss factor that describes the stiffness of the hydrogel) are conducted to ensure a non-flowing, gel-like structure at rest in the syringe.

The goal of the rheological optimisation is to form a non-flowing composite hydrogel structure, which remains stable for prolonged times, but at the same time, the structure has to be loose enough to be injectable through thin needles when shear stress is applied by pushing the plunger of the syringe. The resulting unique silica-silica composite hydrogel is easily injectable with needle sizes of 27-30G as illustrated in Figure 2. Although the hydrogel part of the silica-silica composite most often controls the injectability and homogeneity, it may also fine-tune the release of API from microspheres by controlling/removing the burst, the initial fast phase of the release.

Figure 2: Injectable silica-silica hydrogel composite depot.

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The injectable silica hydrogel composites can be used both in IVT and subconjunctival delivery where at least one month's sustained release of the API is needed. It is also possible to develop much longer acting composite formulations with 3-6 months' controlled release of API. As with all drug delivery systems, the development of an ultra-long acting dosage form with silica matrix technology is limited by the required daily dose of the active compound, which directly impacts the volume of the IVT injection material (typically maximum 0.1 ml). With a very potent molecule, it would be possible to design products with a release profile of more than 12 months.

Topical application of the silica-silica hydrogel composite formulation in the conjunctival cul-de-sac represents another drug delivery opportunity in the treatment of the front part of the eye. The silica composite material is sticky enough to stay in the conjunctiva where it releases API in a controlled fashion. Prototype formulations have been produced where fluorescein as a surrogate molecule is encapsulated into silica microspheres that are further embedded in the silica hydrogel. When these "eye drops" are administered in the rabbit eye, they release fluorescein steadily for 24 hours without any signs of local irritation.

SILICA OCULAR MICRO-IMPLANTS

Traditionally, drug-eluting implants have been the first type of controlled-release dosage forms used in ocular drug delivery. Most implant technologies are based on non-biodegradable materials that have their limitations especially in repeated administration, as they should be removed after use. DelSiTech has developed micro-implant technology for IVT delivery of drugs that is based on biodegradable silica matrix (Figure 3).

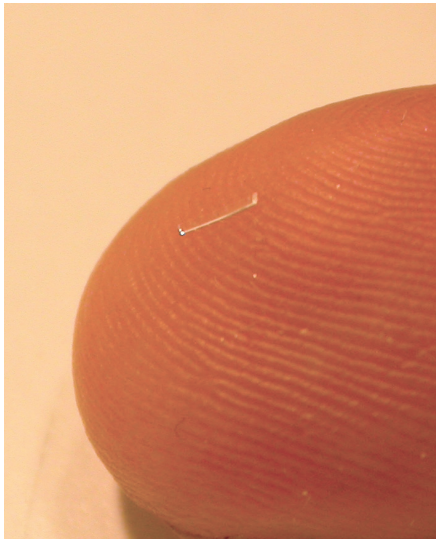

Figure 3: Intravitreal biodegradable silica micro-implant (diameter 0.4 mm) on top of a finger.

Silica implants are typically transparent, especially when in contact with water. The biological activity of biopharmaceuticals and viral vectors can be maintained because the water content inside the implant can easily be controlled.

The silica microimplants are prepared by casting the API-containing silica sol into a mould before the silica sol turns into a gel. The gel is formed in the mould followed by a controlled drying. Silica microimplants offer an attractive alternative to injectable dosage forms in cases where the API is not suitable for spray-drying form-giving.

CONCLUSION

Different biodegradable silica matrix based dosage forms can be used for ophthalmic drug delivery. The technology provides potential formulation solutions both for the anterior and posterior parts of the eye in the form of eye drops, injectable silica-silica composite hydrogels, and micro-implants. Also, the technology is mature enough to fulfil the pharma industry requirements such as GMP manufacture and sterilisation. Currently, DelSiTech is actively working on several projects developing novel drug formulations for ocular delivery.

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