Seminars in Cutaneous Medicine and Surgery

Biocompatibility of Microparticles into Soft Tissue Fillers

Klaus Laeschke, DDS

The increasing need for long-lasting injectable soft tissue fillers for the treatment of wrinkles and folds requires a critical discussion of the biocompatibility on a scientific background. Since biological fillers made of collagen and hyaluronic acid will be resorbed over time, copolymer biomaterials with microparticles have been developed in recent years. The microparticles followed special and essential demands because of the interaction with the tissue. In search of an ideal soft tissue filler substance, a variety of biomaterials with microparticles suspended have been created for injecting into dermal defects, into the urethra of patients with urinary incontinence, and in patients with vocal cord insufficiency. The particles differ in chemical composition, surface structure, surface charge, and particle size and evoke different host reactions, accordingly.
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The ideal injectable material for wrinkle treatment should not only offer esthetic results and a long-lasting effect, it should be safe and biodegradable, with minimal complications and no risk of migration.

For that reason, there are some requirements (Table 1) and essential demands (Table 2) for microparticles into soft tissue fillers.

Chemical Composition

The chemical composition of the microparticles is important because of the possibility to biodegrade. If they are made from a synthetic process like metal, ceramic, polymethyl methacrylate, or other polymers, they cannot degrade after the implantation time into the soft tissue. Biomaterial copolymers, made by a process of fermentation, can have a wide variety of composition and properties. In addition, their surface may be modified physically and biochemically.

Water sorption in biomaterials is very important to the function of the polymers, such as hydrogels or dextranomere particles.[3,4] Water content may also lead to absorption of ions and other molecules, as enzymes, which cause the biodegradation of the microparticles.

The chemical composition of the microparticles is important for biodegradation: biomaterials degraded after time without any adverse reaction and synthetic hard microparticles are not degradable and do not stay permanent in the tissue.

Institut for Skin Care Concept, Friedenstr. 29, 56427 Siershahn, Germany. Address reprint requests to Klaus Laeschke, DDS, Institut for Skin Care Concept, Friedenstr. 29, 56427 Siershahn, Germany.E-mail: matridex@aol.com.

Depending on their chemical structure and surface characteristics, most resorbable biological materials and synthetics such as polymethyl acrylate, polylactic acid, or dextranomere initiate a temporary foreign body reaction which may last up to several months.[9,10]

Nonresorbable or permanent materials tend to chronic inflammation and granuloma formation[37] (Table 3).

Migration of particles in the dermal compartment

• Implanted particles of biomaterials cannot migrate actively	• They have to be phagocytosed by macrophages and migrated to lymph nodes or liver

Migration of particles in the dermal compartment

• The critical particle size to avoid this phenomenon is 80 to 120 μm	Extracellular "migration" by mechanical forces (muscle movement, gravity) is correctly called "dislocation"

Biocompatibility I

- Microparticles with smooth surfaces and regular shape create the best tissue augmentation in the form of fibroblast and collagen fibers surrounding the microspheres
- A monolayer of macrophages surrounded the surface of this type of microparticles
- This is a sign of optimal biocompatibility

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Table 1 Requirements for Injectable Soft Tissue Fillers Containing Microparticles

Biocompatibility
• Chemical composition
• Surface structure
• Surface charge
• Particle size

Biocompatibility II
• Microparticles with rough surface and irregular shape create a foreign body granuloma as a dominant characteristic of the long-term biological response.

Conclusion
• The biocompatibility of implant materials is based upon the "fibrous capsule" that envelops the implant
• No chronic inflammation
• The microparticles are well embedded in "new" collagen
• No long-term biological response

Surface Structure

Although the chemical composition of the implant microparticle would seem to be of primary importance, its physical form is equally critical in determining biocompatibility (Tables 3 and 4). A variety of physicochemical factors affect phagocytosis, including particle size, shape, contact angles, and surface charge.[38]

A simple experiment with rods of 1 mm in diameter, but different shapes, implanted into rats showed that triangular implants with sharp edges caused significantly higher cellular response (chronic inflammation) than square or round implants.

There is also a statistically significant difference between rough and smooth surfaces of the microparticles and the interaction of the tissue with the microparticles.

Table 2 Essential Demands for Particulate Material

• Spherical microspheres or microbeads
• Minimum diameter 40 μm
• Smooth, homogeneous surface
• Liquid medium with excellent biocompatibility

Surface Charge

The presence of an implant grossly changed the local dielectric environment, thus affecting local intermolecular interactions.[10,13,18] This influences the cell attachment to the implanted materials (Tables 5 and 6). Eppley and colleagues demonstrated that different charged surfaces stimulate different cell regeneration. They used dextranomeres as a microparticle due to the chemical possibility to get charged surfaces.[3,4] Microparticles made from dextranomeres have two different charged surfaces: negatively charged, such as the cation exchanger CM Sephadex, which induces new bone formation by stimulating osreogenesis; and positively charged, such as the anion exchanger DEAE Sephadex, which induces new collagen fibers by stimulating collagenesis.

It is not clear why positive charges preferentially attract macrophages nor why and how macrophages are activated by positively charged DEAE Sephadex microparticles.

In tissue culture, macrophages migrate toward positively charged particles and this positively charged material invokes a favorable wound-healing response in rat incisional wounds.

Also, in humans, positively charged DEAE Sephadex microparticles stimulate collagenesis. The microparticles were embedded in new collagen fibers without chronic inflammation after the implantation.[20-22,36]

Phagocytosis of Particles

Phagocytosis, the process by which macrophages recognize and try to destroy injected biomaterial, is an essential

Table 3 Injectable Microparticles

Chemical Name	Trademark	Particle Size	Particle Form	Carrier
Polytetrafluoroethylene Permanent	Polytef	1-100	Spherical	Glycerine
Polydimethysiloxane	Bioplastique	16-409	Spherical	PVP
Polymethylmethacrylate	Artecoll	36	Spherical	Collagen
Polyvinylhydroxide	Evolution	n.n.	n.n.	Acrylamide
Polyethylmethacrylate	Dermalive*	55	Fragments	xHA
Resorbable				
Polylactic acid	New fill*	46	Fragments	Cellulose
Dextranomere uncharged	Reviderm	50	Spherical	HA
Dextranomere charged	Deflux	80-120	Spherical	xHA
	Matridex	80-120	Spherical	xHA

xHA = crosslinked hyaluronic acid; fragments = particles with sharp edges and irregular.
*Resorption time of the particles more than 24 months.

Table 4 Shape and Surface Structure of Microparticles

Irregular shape + rough surface structure resulted in:	Regular/spherical shape + smooth surface resulted in:
foreign body reaction	Fibrous tissue with collagenesis

Table 6 Surface Charge

- All living cells and most biomaterials possess a surface charge (zeta-potential)
- This influences cell attachment to implanted materials
- The presence of an implant changes the local dielectric environment

part of host defense. According to their chemical composition and surface charge, the body reacts either with protein attachment and consequent encapsulation with fibrous tissue or with an attempt to phagocytose the particles.[34,35]

Macrophage activity is affected by the physiochemical state, such as particle size, chemical structure, and surface charge[22,23,24] (Table 7).

Migration of Particles

Migration of particles is a main issue of artificial joint replacement surgery as well as of injectable bulking agents in urology. In this context, however, migration appears to be a misnomer. Particles of biomaterials cannot actively migrate within the body, but have to be phagocytosed by macrophages migrating to lymph nodes or liver, respectively. When trapped in the lung, they have to be injected accidentally into a venous plexus at the injection site.

Of course, extracellular "migration" of particles by mechanical forces such as muscle movement, skin folding, and gravity is a well-known phenomenon, but should be correctly called "dislocation."[25,26,32]

Microspheres from irregular particles between 4 and 40 μm in diameter were detected in the lungs and other organs. The main particle size to avoid this phenomenon is 80 to 120 μm, or so-called "critical particle size" (Table 8).

The usual migration of macrophages with phagocytosed particles is toward the lymph nodes or liver.[39]

Henly stated that particles smaller than 80 μm have a tendency to migrate.[40] Dewan injected silicon particles (Macroplastique) into rats, but found no foreign material at distant sites after 3 months; however, a marked local foreign body granuloma reaction was noted.[41]

Stenberg and colleagues show a lack of distant migration after injection of a 125-iodine-labeled positively charged dextranomer-based implant into the rabbit bladder.[26]

Table 5 Surface Structure

• Particles with rough surface induce:	• Particles with smooth surface induce:
1. Foreign body reaction/giant cells	1. Fibroblast adhesion
2. Rapid attachment of macrophages	2. Collagen synthesis

Discussion

The biocompatibility of implant materials is based on the "fibrous capsule" that envelops the implant.

The types of cells present or absent from the interface characterize the nature of the reaction. For example, the absence of lymphocytes at the material interface and from the perivascular region of nearby capillaries implies that the polymer does not elicit an immune response.

Macrophages and multinucleated giant cells are the dominant characteristics of the long-term biological response to rough surfaces and particles with irregular shape and surface. Both cell types eliminate foreign body material from the tissue. Since most of the injected irregular particles are too big for phagocytosis and subsequent transport, a chronic rejection process is set in motion, which lasts until the implant is removed.

In contrast to the rough and irregular surface, a monolayer of macrophages surrounded by a zone of fibrous tissue is found at the surface of a smooth and charged walled implant or an absolute smooth microsphere. This is the sign of optimal biocompatibility. These microspheres are enveloped with fibrocytes, which remain in a steady state with the implant.

It seems as if substances with positively charged microspheres are able to create the best tissue augmentation in the form of fibroblast and collagen fibers surrounding the microspheres.

Uncited References

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Table 7 Surface Charge When Injected

• Neutral beads	Only foreign body reaction without new tissue formation
• Negatively CM beads	Stimulating osteogenesis, new bone formation, craniofacial repair
• Positively DEAE beads	Stimulating collagenesis, new collagen-rich connective tissue, no migration of the beads

Table 8 Particle Size

- **Particle size is important for migration and phagocytosis**
- **The phagocytosable size of particles is 15 to 20 μm**
- **Particles with a greater diameter than 20 μm are covered by giant cells, a so-called "frustrated macrophage"**
- **For biomaterial implants, the size of particles has to be 40 to 150 μm**

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