

**BIODEGRADABLE IN-SITU FORMING  
IMPLANTS AND METHODS OF  
PRODUCING THE SAME**

This application is a Continuation of application Ser. No. 08/532,540, filed Sep. 25, 1995, now U.S. Pat. No. 5,733,950 which is a continuation of U.S. patent application Ser. No. 08/210,891, filed Mar. 18, 1994, now U.S. Pat. No. 5,739,176 which is a continuation of U.S. patent application Ser. No. 07/788,032, filed Dec. 23, 1991, now U.S. Pat. No. 5,340,849 (issued Aug. 23, 1994), which is a division of U.S. patent application Ser. No. 07/513,782, filed Apr. 24, 1990, now U.S. Pat. No. 5,278,201 (issued Jan. 11, 1994), which is a division of U.S. patent application Ser. No. 07/252,645, filed Oct. 3, 1988, now U.S. Pat. No. B1-4,938,763 (issued Jul. 3, 1990; certificate issued Jul. 4, 1995), incorporated herein by reference.

**BACKGROUND OF THE INVENTION**

The present invention relates to a method and composition for producing biodegradable polymers, and more particularly to the use of such polymers for providing syringeable, in-situ forming, solid, biodegradable implants.

Biodegradable polymers have been used for many years in medical applications. These include sutures, surgical clips, staples, implants, and drug delivery systems. The majority of these biodegradable polymers have been thermoplastic materials based upon glycolide, lactide,  $\epsilon$ -caprolactone, and copolymers thereof. Typical examples are the polyglycolide sutures described in U.S. Pat. No. 3,297,033 to Schmitt, the poly(L-lactide-co-glycolide) sutures described in U.S. Pat. No. 3,636,956 to Schneider, the poly(L-lactide-co-glycolide) surgical clips and staples described in U.S. Pat. No. 4,523,591 to Kaplan et al., and the drug-delivery systems described in U.S. Pat. No. 3,773,919 to Boswell et al., U.S. Pat. No. 3,887,699 to Yolles, U.S. Pat. No. 4,155,992 to Schmitt, U.S. Pat. No. 4,379,138 to Pitt et al., and U.S. Pat. Nos. 4,130,639 and 4,186,189 to Shalaby et al.

All of the biodegradable polymers described in these patents are thermoplastic materials. Consequently, they can be heated and formed into various shapes such as fibers, clips, staples, pins, films, etc. Only when heated above their melting point do these polymers become liquid. During their normal use, they are solids.

Thermoset biodegradable polymers have also been previously described for use in medical applications. These polymers have been formed by crosslinking reactions which lead to high-molecular-weight materials that do not melt or form flowable liquids at high temperatures. Typical examples of these materials are the crosslinked polyurethanes described in U.S. Pat. No. 2,933,477 to Hostettler and U.S. Pat. No. 3,186,971 to Hostettler et al. Copolymers based on  $\epsilon$ -caprolactone and L-lactide or DL-lactide crosslinked via peroxide initiators were described in U.S. Pat. Nos. 4,045,418 and 4,057,537, both to Sinclair. Crosslinked caprolactone copolymers have been prepared by incorporation of a bislactone into a monomer feed, as described in U.S. Pat. No. 4,379,138 to Pitt et al. Trihydroxy-functional copolymers of  $\epsilon$ -caprolactone and  $\epsilon$ -valerolactone have been crosslinked with diisocyanates, thereby affording biodegradable polymers, as described in Pitt et al., *J. Polym. Sci.: Part A: Polym. Chem.* 25:955-966; 1987. These polymers are also solids when crosslinked or cured.

Although these two classes of biodegradable polymers have many useful biomedical applications, there are several

important limitations to their use in the body where body is defined as that of humans, animals, birds, fish, and reptiles. Because these polymers are solids, all instances involving their use have required initially forming the polymeric structures outside the body, followed by insertion of the solid structure into the body. For example, sutures, clips, and staples are all formed from thermoplastic biodegradable polymers prior to use. When inserted into the body, they retain their original shape rather than flow to fill voids or cavities where they may be most needed.

Similarly, drug-delivery systems using these biodegradable polymers have to be formed outside the body. In such instances, the drug is incorporated into the polymer and the mixture shaped into a certain form such as a cylinder, disc, or fiber for implantation. With such solid implants, the drug-delivery system has to be inserted into the body through an incision. These incisions are often larger than desired by the medical profession and lead to a reluctance of the patients to accept such an implant or drug-delivery system.

The only way to avoid the incision with these polymers is to inject them as small particles, microspheres, or microcapsules. These may or may not contain a drug which can be released into the body. Although these small particles can be injected into the body with a syringe, they do not always satisfy the demand for a biodegradable implant. Because they are particles, they do not form a continuous film or solid implant with the structural integrity needed for certain prostheses. When inserted into certain body cavities such as the mouth, a periodontal pocket, the eye, or the vagina where there is considerable fluid flow, these small particles, microspheres, or microcapsules are poorly retained because of their small size and discontinuous nature. In addition, microspheres or microcapsules prepared from these polymers and containing drugs for release into the body are sometimes difficult to produce on a large scale, and their storage and injection characteristics present problems. Furthermore, one other major limitation of the microcapsule or small-particle system is their lack of reversibility without extensive surgical intervention. That is, if there are complications after they have been injected, it is considerably more difficult to remove them from the body than with solid implants.

Therefore, there exists a need for a method and composition which provides a biodegradable, polymeric structure useful in overcoming the above-described limitations.

There exists a further need for a method and composition for providing syringeable, in-situ forming, solid, biodegradable implants which can be used as prosthetic devices and/or controlled delivery systems.

Moreover, there exists a need for such a method and composition which can provide implants having a range of properties from soft to rigid, so as to be usable with both soft and hard tissue.

**SUMMARY OF THE PRESENT INVENTION**

The present invention relates to the production and use of biodegradable polymers as prosthetic implants and controlled-release, drug-delivery systems which can be administered as liquids via, for example, a syringe and needle, but which coagulate or cure ("set") shortly after dosing to form a solid. The implants are biodegradable because they are made from biodegradable polymers and copolymers comprising two types of polymer systems: thermoplastic and thermosetting.

A thermoplastic system is provided in which a solid, linear-chain, biodegradable polymer or copolymer is dis-