BIOCOMPATIBLE VISCOELASTIC GEL SLURRIES, THEIR PREPARATION AND USE

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BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to biocompatible viscoelastic polymeric gel slurries, methods for their preparation, formulations containing them, and medical uses thereof.

2. The Prior Art

Hereinafter, the term "polymeric gel" is used to define a system which consists of at least two components, one being solvent and the other being polymer, which is not soluble in the solvent, and which exhibits no steady-state flow. The insolubility of the polymer is provided by, or results from crosslinking which may be due to chemical bonds or crystallites or some other kind of junction (J. D. Ferry, Viscoelastic properties of polymers. John Wiley & Sons, Inc., 1961, p. 391). The solvent component usually constitutes a predominant portion of the gel. When the solvent in a gel is water, such a gel is called a hydrogel. The most widespread practical use of a hydrogel is the use of collagen gels for tissue augmentation. In such instances, a hydrogel per se is not used; rather, it is used as a viscous solution injected into the dermal or subcutaneous tissue where the collagen immediately forms a gel and forms an artificial intercellular matrix (T. R. Knapp, et al, Injectable Collagen for Soft Tissue Augmentation. Plastic and Reconstructive Surgery, Vol. 60, 1977, pp. 398–405). Another use of a hydrogel is outside the body, on the surface of the eye as contact corneal lenses (M. F. Refojo, Ophthalmic Hydrogels, in Synthetic Biomedical Polymers, Ed. M. Szycher and W. J. Robinson, Technomics, 1980, p. 171). It has also been suggested to use hydrogels for drug delivery (B. E. McCarey, et al, Current Eye Research, Vol. 3, No. 8, 1984, p. 977), for wound treatment (P. Y. Wang, Infected Skin Wounds in Rodents, Polymeric Materials and Artificial Organs. Ed. C. G. Gebelin, ACS Symposium Series 256, ACS, Washington, D.C., 1984, p. 181). The noted applications of hydrogels are based on their three major properties: (1) the ability to hold large amounts of water, (2) to create and occupy space in the intercellular matrix, and (3) to form well defined solid shapes to refract light. However, there is another property which becomes extremely important when a hydrogel is used for augmentation of the intercellular matrix as for drug delivery, namely a high level of biocompatibility which is expressed as the absence of cytotoxicity and immunogenicity and the lack of causation of inflammation and foreign body reaction.

Recently, hydrogels with exceptionally good biocompatibility have been developed. These gels are based on hyaluronan (hyaluronic acid) crosslinked with vinyl sulfone (Balazs and Leshchiner, U.S. Pat. No. 4,605,691) or on cross-linked mixtures of hyaluronan with other polymers or low molecular weight substances (Balazs and Leshchiner, U.S. Pat. No. 4,582,865). Similar gels prepared from the chemically modified hyaluronan known as hylan are also described in the prior art (Balazs, et al, U.S. Pat. No. 4,713,448). These gels are used for drug delivery (Balazs and Leshchiner, U.S. Pat. No. 4,636,524) and other purposes in the medical field (E. A. Balazs and E. A. Leshchiner (1989). Hyaluronan, its crosslinked derivative—hylan—and their medical applications, In: *Cellulosics Utilization: Research and Rewards in Cellulosics. Proceedings of the Nisshinbo International Conference on Cellulosics Utilization in the Near Future.* (Eds. Inagaki, H. and Phillips, G. O.) Elsevier, Applied Science, New York pp. 233–241.

SUMMARY OF THE INVENTION

In one aspect thereof, the present invention provides biocompatible viscoelastic gel slurries consisting of two phases; the first being a polymeric gel swollen in an aqueous medium, and the second being a fluid phase in which the said gel phase is uniformly dispersed.

In another aspect, the invention provides biocompatible viscoelastic gel slurries in which the fluid phase is an elastoviscous aqueous solution of a polymer.

In yet another aspect, the invention provides biocompatible viscoelastic gel slurries in which the gel phase comprises insoluble hyaluronan and its derivatives.

In still another aspect, the invention provides biocompatible viscoelastic gel slurries in which fluid phase comprises aqueous solutions of hyaluronan and its derivatives.

In still yet another aspect the invention provides biocompatible viscoelastic gel slurries in which the aqueous media of the gel and the fluid phase are physiologically acceptable substances, typically, water or saline.

In still yet another aspect, the invention provides viscoelastic gel slurries having varying degrees of biocompatibility specifically tailored or "engineered" to fit different medical uses.

The invention further provides methods of making these gel slurries.

Finally, the invention provides methods to control the rheological and diffusion characteristics of the instant biocompatible gel slurries.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph showing the kinetics of compression of two viscoelastic hylan gel slurries (Example 6).

FIG. **2** is a graph showing the kinetics of solvent removal from different elastoviscous hylan gel slurries under centrifugal force (Example 9).

FIGS. **3***a* and **3***b* are two graphs illustrating respectively, the diffusion of fibrinogen (**3***a*) and albumin (**3***b*) into two different elastoviscous hylan gel slurries (Example 14).

FIGS. **4***a* and **4***b* are two graphs illustrating respectively, the dependence of the amount of water-soluble dye eosin diffused into the total volume (**4***a*) and the middle portion (**4***b*) of various viscoelastic hylan gel slurries on their concentration (Example 17).

FIG. **5** is a graph showing the diffusion of eosin into a viscoelastic mixed hylan gel slurry (amount of dye diffused vs distance of diffusion (Example 18).

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery that products having very unusual and extremely useful properties can be prepared in the form of two-phase gel slurries in which the first phase comprises swollen polymeric gel particles uniformly distributed in the second phase which is, preferably, a viscoelastic solution of a polymer.