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PSEUDO-SYNOVIAL PLASTIC BODY FLUIDS AND METHOD OF PREPARING SAME

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ABSTRACT OF THE DISCLOSURE

A fluid having the rheological properties of synovial fluid or other body fluids exhibiting pseudo-plasticity which fluids are found in human bodies and consisting essentially of a water solution of sodium carboxymethylcellulose, an anti-microbial preservative and certain inorganic salts in the approximate concentrations found in human synovial fluid. The fluid is prepared by adding the salts and preservative to water being stirred at high speed and thereafter the sodium carboxymethylcellulose is slowly added and stirred into the liquid. This abstract is neither intended to define the invention of the application which, of course, is measured by the claims, nor is it intended to be limiting as to the scope of the invention in any way.

BACKGROUND OF THE INVENTION

Synovial fluid is normally present in human bodies in the cavities of the freely movable joints, in the bursae and within tendon sheaths, particularly where the tendons change their direction and pass under or through the fibrous slings or bony prominences. Such fluid appears to function as a lubricant and a shock absorbing medium. It is believed that the visco-elastic or pseudo-plasticity of the synovial fluid contributes crucially to optimum joint function. The synovial fluid has the property of having an apparent viscosity increase as the rate of shear applied is decreased.

Studies of saline solutions of hyaluronic acid at pH 7 and 25° C. show a sharp transition from viscous to elastic behavior at strain frequencies above about 30 cycles per second. At higher temperatures (body temperature) this transition would move to a higher frequency. Those frequencies are well above the frequency of loading and unloading of joints in the natural movements of walking and running. Thus, it can be concluded that the in vivo rheological behavior of synovial fluid is that of a viscous liquid and not elastic.

The viscosity and pseudo-plasticity of synovial fluid is sharply impaired as a result of pathological conditions such as rheumatoid arthritis, osteoarthritis and trauma. The resulting impairment of lubrication ability would predispose the articulating surfaces of the joint to premature wear trauma.

SUMMARY

The present invention relates to an improved fluid having substantially the same rheological properties as human synovial fluid.

An object of the present invention is to provide a pseudo-synovial fluid suitable for injection into a joint to replace or augment synovial fluid to prevent additional wear trauma of the joint.

Another object is to provide an improved fluid which has properties closely resembling human synovial fluid and is useful as a lubricant between articulating surfaces.

A further object is to provide an improved pseudo-synovial fluid which may be injected into joints to replace impaired synovial fluid and which provides adequate lubrication without creating an inflammatory response.

Another object is to provide an improved pseudo-synovial fluid which is stable for storing at room temperatures and which can be sterilized by boiling or autoclaving.

A still further object is to provide a pseudo-plastic fluid having properties close to body fluids exhibiting pseudo-plasticity.

These and other objects and advantages of the present invention are hereinafter set forth and explained.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Synovial fluid may be considered to be a dialysate of blood plasma with the addition of hyaluronic acid. Hyaluronic acid is an anionic polyelectrolyte formed by alternating molecules of D-glucoronic acid and acetylated glucosamine. In a physiological salt solution this anionic polymer would characteristically interact with cations and water within the solution with concomitant formation of ionic double layers. These interactions would magnify the effect of volume of the hyaluronic acid molecule giving rise to the observed pseudo-plastic behavior. Direct chain to chain interaction at least in concentrated hyaluronic acid solutions appears to play a relatively minor role in the overall viscoelastic behavior of such solutions.

Although there have been many theories on the mechanism of physiological joint lubrication laying varying emphasis on hydrodynamic considerations, liquid-solid interfacial effects, cartilage permeability and more recently cartilage deformability and surface morphology, it is increasingly accepted that the pseudo-plastic properties of synovial fluid contribute crucially to optimum joint function.

It has been discovered that the pseudo-synovial fluid of the present invention does not create an inflammatory response and closely approximates the properties of human synovial fluid. This pseudo-synovial fluid is prepared as hereinafter set forth from a premium refined grade of sodium carboxymethylcellulose which is widely used in the preparation of foods and is commonly known as cellulose gum. Sodium carboxymethylcellulose has been found to have a close structural resemblance to hyaluronic acid. The sodium carboxymethylcellulose is prepared from natural cellulose and therefore reflects a molecular weight range according to the cellulose source. It is characterized by an average degree of polymerization derived from the range of molecular weight fractions within the raw cellulose. The molecular weight is a major factor controlling the viscosity of aqueous solutions of sodium carboxymethylcellulose.

Sodium carboxymethylcellulose is prepared by reacting cellulose swelled with alkali with sodium monochloroacetate. Since each anhydroglucose unit in the cellulose structure has three reactive hydroxyl sites which can react with sodium monochloroacetate, a fully substituted product would have a degree of substitution of three. The degree of substitution is the prime factor effecting water solubility of sodium carboxymethylcellulose. Optimum solubility for most applications occurs at a degree of substitution of about 0.7 which is far below the theoretical maximum. The crystalline regions of cellulose increase the possibility of non-uniform substitution because these regions are not as readily accessible to the reactants as the amorphous regions. Non-uniform substitution causes degrees of thixotropicity of sodium carboxymethylcellulose solutions.

The target pseudo-plastic behavior selected for modeling was that reported by Dintenfass, L. in his article "A Theoretical Approach to the Problem of Joint Movements and Joint Lubricantion" in J. Bone J. Surg. 45A: 1241, 1963. Attempts were made to confirm such data but since

non-pathological fluid could not be obtained such confirmation was not made. However, certain tests were run with fluid from human knee joints with no gross clinical pathology and such fluid exhibited the same trend as the Dintenfass data and showed increased pseudo-plasticity.

The sodium carboxymethylcellulose used was a premium refined grade P–75–XH obtained from the Explosive Department of E. I. du Pont de Nemours & Company (Inc.). The sodium salt of this grade material constitutes not less than 99.5% of the total product on a dry weight basis.

In order to simulate the human synovial fluid the salts normally occurring in the body were added. Such salts were sodium chloride, sodium hydrogen carbonate, potassium chloride and potassium orthophosphate-mono-H. In order to prevent bacteria attack an anti-microbial agent such as methyl parahydroxybenzoate was added. The amounts of the salts used were adjusted to be close to those occurring in blood plasma.

The following formulation when mixed with 500 milliliters of distilled water as hereinafter described provides a preferred composition:

	Grams
Sodium carboxymethylcellulose, Grade P–75–XH	5
Analytical grade sodium chloride	2.47
Analytical grade sodium hydrogen carbonate ($NaHCO_3$)	1.26
Analytical grade potassium chloride	0.11
Analytical grade potassium orthophosphate-mono-H (K_2HPO_4)	0.09
Methyl parahydroxybenzoate (food grade)	0.05

The pseudo-synovial fluid is prepared by adding the 500 ml. of distilled water to a mixer, or other suitable stirring device having sufficient liquid capacity such as 1,000 ml. With the mixer operating at high speed the salt ingredients and anti-microbial ingredient were sprinkled into the water and mixing continued for approximately three minutes to assure complete solution. The sodium carboxymethylcellulose was then added by sprinkling slowly into the vortex of the salt solution over a period of three minutes with the mixer still at high speed. A uniform dispersal and solution of the ingredients was thereby obtained. This method produced the most pronounced pseudo-plastic behavior of the prepared fluid. It should be noted that in the same formulation prepared by adding the sodium carboxymethylcellulose to the water and thereafter adding the anti-microbial and salt ingredients, the fluid produced thereby consistently yielded a product of reduced pseudo-plasticity as compared to the fluid prepared in the preferred manner.

In the preferred formulation, the sodium carboxymethylcellulose is used in the range from 0.8 to 1.2 percent (preferably 1.0 percent) by weight and has a Brookfield viscosity in a one percent aqueous solution of at least 2,500 cps. at 25° C. The sodium carboxymethylcellulose is selected to have a distribution of anions along its chain and a molecular weight distribution to provide the desired pseudo-plasticity or viscosity/shear characteristics of the fluid which is being simulated.

In testing procedures established to determine the viscosimetric data for various sodium carboxymethylcellulose solutions it was determined that the best approximation of the human synovial fluid behavior could be obtained using sodium carboxymethylcellulose of a molecular weight of 350,000, a degree of substitution of 0.8 and a weight percent equal to 1.

The viscosity and shear rate characteristics for human synovial fluid as published in the aforementioned Dintenfass article illustrate that the logarithm of the viscosity and the logarithm of the shear rate for human synovial fluid are linearly related with the viscosity being 0.17 newtons seconds per square meter when the shear rate is 200 $sec.^{-1}$ and 1.0 newtons seconds per square meter when the shear rate is 10 $sec.^{-1}$.

Also solutions of 0.8 weight percent of sodium carboxymethylcellulose showed a pronounced decrease in viscosity as total anionic concentration decreased from about 150 milli-equivalents per liter to about 130 milli-equivalents per liter. Solutions of 0.9 and 1.0 weight percent sodium carboxymethylcellulose did not exhibit analogous decrease until levels were well below 130 milli-equivalents per liter. Thus, total anionic concentration appears to be the governing variable controlling effective polymer volume (psuedo-plasticity).

Actual tests showed that the pseudo-synovial fluid of the present invention efficiently simulates the pseudo-plastic behavior of synovial fluid. It has been subjected to animal tests and was found non-irritating in the anterior chamber of the animal's eyes and to knee joint tissue.

It has also been discovered that a similar fluid may be prepared which approximates the aqueous and vitreous humour by increasing the concentration of the sodium carboxymethylcellulose to a concentration within the range from 2 to 4 weight percent. The aqueous humour from animals such as canines and rabbits is approximated by the lower end of such range and then vitreous humour is approximated by the higher end of such range. The simulated human vitreous humour would fall within the range from 2½ to 3½ weight percent.

With the advent of higher molecular weight versions of sodium carboxmethylcellulose such materials have applications to the desired formulations of the present invention but they should be used in lower concentrations to balance for their increased molecular weight. Such materials should not be substituted for the preferred material of the present invention unless they meet all of the purity and quality standards and have the same general characteristics as the preferred sodium carboxymethylcellulose which has been set forth above.

From the foregoing it can be seen that the present invention has provided an improved pseudo-synovial fluid which closely simulates human synovial fluid and does not have an inflammatory response. The preferred method of preparing such pseudo-synovial fluid has also been clearly disclosed.

What is claimed is:

1. The method of preparing a synthetic body solution, including the steps of

mechanically stirring distilled water,

slowly adding inorganic salts to said water while continuing the stirring until all of said inorganic salts are dissolved,

said inorganic salts being those salts normally present in blood plasma and being in relatively the same proportion in the resulting synthetic body solutions as in blood plasma, and

thereafter slowly adding sodium carboxymethylcellulose to said water solution while continuing stirring until all of said sodium carboxymethylcellulose is dissolved,

said sodium carboxymethylcellulose having a Brookfield viscosity in an aqueous solution of one percent by weight of at least 2,500 cps. at 25° C.,

the resultant concentration of said sodium carboxymethylcellulose being sufficient to provide approximately the physical characteristics of the body solution being simulated.

2. The method of preparing a synthetic body solution, including the steps of

mechanically stirring distilled water,

slowly adding inorganic salts to said water while continuing the stirring until all of said inorganic salts are dissolved,

said inorganic salts being those salts normally present in blood plasma and being in relatively the same proportion in the resulting synthetic body solution as in blood plasma, and

thereafter while continuing the stirring, slowly adding sodium carboxymethylcellulose to said water solu-

tion while continuing stirring until all of said sodium carboxymethylcellulose is dissolved,

said sodium carboxymethylcellulose having a Brookfield viscosity in an aqueous solution of one percent by weight of at least 2,500 cps. at 25° C.,

the concentration of said sodium carboxymethylcellulose being in one of the ranges from 0.8 to 1.2 and 2 to 4 weight percent.

3. The method according to claim **2**, including the step of

slowly adding an anti-microbial agent while adding said inorganic salts.

4. A synthetic body solution, comprising

a water solution of sodium carboxymethylcellulose and inorganic salts,

said inorganic salts being those salts normally present in blood plasma and being in relatively the same proportion as in blood plasma,

the resultant concentration of said sodium carboxymethylcellulose being sufficient to provide approximately the physical characteristics of the body solution being simulated and not greater than four percent by weight.

5. A synthetic body fluid having properties similar to aqueous and vitreous humour according to claim **4** wherein

said concentration of sodium carboxymethylcellulose falls in the range from 2 to 4 weight percent.

6. A synthetic body solution according to claim **4**, including an anti-microbial agent, and said inorganic salts including, sodium chloride, sodium hydrogen carbonate, potassium chloride, and potassium ortho-phosphate mono-H.

7. A pseudo-synovial fluid, comprising

a water solution of sodium carboxymethylcellulose and inorganic salts,

said inorganic salts being those salts normally present in blood plasma and being in relatively the same proportion as in blood plasma,

said sodium carboxymethylcellulose having a Brookfield viscosity in an aqueous solution of one percent by weight of at least 2,500 cps. at 25° C.,

the resultant concentration of said sodium carboxymethylcellulose being sufficient so that the resultant solution has viscosity and shear rate characteristics

whose logarithms are linearly related and approximate the viscosity, shear rate relationship of human synovial fluid.

8. A synthetic body solution, comprising

a water solution of inorganic salts and sodium carboxymethylcellulose,

said inorganic salts being those salts normally present in blood plasma and being in relatively the same proportion as in blood plasma,

said sodium carboxymethylcellulose having a Brookfield viscosity in an aqueous solution of one percent by weight of at least 2,500 cps. at 25° C.,

the resultant concentration of said sodium carboxymethylcellulose being sufficient to provide the approximate characteristics of the body solution being simulated and being in one of the ranges from 0.8 to 1.2 and 2 to 4 weight percent.

9. A pseudo-synovial fluid according to claim **8**, wherein

said sodium carboxymethylcellulose has a molecular weight of at least 350,000 and a degree of substitution of 0.8.

10. A pseudo-synovial fluid, comprising a solution which is the equivalent of the following dissolved in 500 milliliters of distilled water,

5 grams of premium refined grade sodium carboxymethylcellulose having a molecular weight of 350,000 and a degree of substitution of 0.8,

2.47 grams of analytical grade sodium chloride,

1.26 grams of analytical grade sodium hydrogen carbonate,

0.11 grams of analytical grade potassium chloride,

0.09 grams of analytical grade potassium orthophosphate-mono-H, and

0.5 grams of methyl parahydroxybenzoate.

References Cited

Rozenberg et al., Chem. Abst., vol. 53 (1959), p. 13402h.

SAM ROSEN, Primary Examiner

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