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INJECTABLE RECONSTITUTED COLLAGEN FLUID ADJUVANT FOR VACCINES AND OTHER DRUGS

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8 Claims

ABSTRACT OF THE DISCLOSURE

An injectable medicinal composition and method of preparing the same comprising a fluid adjuvant characterized by the property of undergoing an in vivo increase in viscosity in the body of a host upon injection thereof and thereafter substantially complete dissociation and absorption in the host's body at a relatively slow rate, combined with a medicinal agent. The carrier comprises reconstituted collagen prepared by the mild acid extraction of precursor material obtained from the connective members of vertebrate animals, a partially repolymerized, reconstituted collagen as defined above, mixtures of these two types of reconstituted collagen, or mixtures of procollagen with either or both of the types of reconstituted collagen.

This invention relates to an injectable adjuvant, methods for preparing and utilizing the same, and to novel medicinal compositions including such adjuvant as a part thereof. More particularly, this invention relates to utilization of such adjuvant as a carrier to increase the effectiveness of an agent incorporated therewith.

It has been found that the effectiveness of some medicinal agents may be increased when the agent is incorporated into an injectable vehicle which includes an adjuvant to effect slow release of the medicinal material into the host. The term adjuvant, in this context, refers to a substance that operates as a binder, carrier, or suspending vehicle, for vaccines and medicinal agents alone or in combination, the function of which is to retard dispersion of such vaccines and medicinal agents, to allow for slow absorption thereof within the host's system and thus attain greater prophylactic or therapeutic activity. In the selection of such an adjuvant, many factors must be taken into consideration to insure a reduced rate of release of the medicinal agent with minimum toxic, allergenic, and antigenic effects imposed upon the host. Thus, the adjuvant carrier should not only be capable of slow dispersion in the host but also should be able to bind the vaccine or medicinal agent and release the active material to the host over a desired period as the carrier is itself dispersed within the host. The carrier may, thus, be used to introduce various types of medicaments into the host's body. In this sense the terms medicament and medicinal agent are used as synonyms and are employed in their broad sense as defining an agent useful in the prevention, cure, or alleviation of disease or the prevention of some physiological condition or occurrence, such as pregnancy.

A number of carriers for the general purposes outlined have been proposed in the past, and have included, e.g., metallic oxides (i.e., aluminum hydroxide), inorganic chelates of salts, gelatins, various paraffin-type oils, synthesized resins, alginates, mucoid and polysaccharide compounds, caseinates, and blood-derived substances such as fibrin clots. None of these materials have been found entirely satisfactory primarily because of their adverse effects on the host.

The metallic oxides and chelates of salts have been associated with the production of sterile abscesses. In addition, these chemicals are rapidly dispersed within the body, thereby decreasing their effectiveness as an

adjuvant. Other researchers have claimed that it is doubtful if such chemicals are ever completely removed from the body through the host's natural processes, thus leaving an inorganic debris as a residuum. Moreover, while these salts and oxides appear to be low in toxicity, there exists the possibility that they may be phagocytized by the cells of the reticuloendothelial system (littoral cells and sinusoidal cells of the liver and spleen) as part of the insoluble debris residuum. There is evidenced that such debris may be physically harmful to the various filter mechanisms of the body, e.g., the liver, spleen and kidneys.

The synthesized oils and petroleum derivatives may be particularly undesirable, in spite of relatively slow dispersion thereof in the body, inasmuch as they frequently are broken down into aromatic hydrocarbons, which may, in fact, be carcinogenic. Furthermore, these substances have been found to be capable of producing sterile abscesses and also may never be completely eliminated by the body.

With respect to fully denatured animal-derived substances, such as gelatin, the primary objection thereto is not the deleterious effect of the substance on its host, but rather that dispersion of the gelatin from the site of injection throughout the body of the host may be too rapid to qualify as an efficient absorption retarding vehicle; hence a poor adjuvant. Thus, whenever gelatin is used as a carrier, the gelatin is usually pre-treated with tanning agents or other inorganic compounds to retard rapid dispersion of the material throughout the body. These supplements may prove deleterious. The fate of such materials in the body of the host is not completely understood but the possibility exists that the formation of residual debris can result. Finally, with substances such as gelatin, which have a tendency to swell when introduced parenterally, under in vivo conditions, unpleasant mechanical side effects including discomfort and swelling may be produced.

Because blood derived fibrin substances have been found to elicit immune responses in the body of the host, use of such substances as adjuvants is undesirable because of immunogenic dangers. It is common knowledge that certain similarities exist in the fibrins, fibrinogens and thrombins derived from various species of animals thereby increasing the likelihood of immune or allergenic response when such materials are used. Although a few of the above described vehicles have been previously used or suggested as adjuvants, in part at least because of their attributes of relatively slow dispersion from the site of injection, they possess characteristics which make for poor control of their rate of intra-host dispersion.

It is, therefore, the primary objective of this invention to provide an injectable composition of the type described, wherein the adjuvant is operable to control the release of a vaccine or medicament to the host without the attendant detrimental effects associated with previously known adjuvants.

As a corollary to the foregoing object, it is a primary aim of this invention to provide as a part of an injectable composition an adjuvant of natural protein origin that has been derived by processing in a manner to extract and permit discarding of undesirable material to the end that a vehicle is produced which has attributes of unaltered collagen and thus may be used in combination with a medicinal agent, for slow release of the active material without attendant undesirable side effects.

A very important object of this invention is to provide an injectable composition of the type described, wherein the adjuvant is capable of slow dispersion in the body of the host so that the medicinal agent combined therewith is disseminated at a controlled rate over a predetermined period of time.