



US005149543A

United States Patent [19][11] **Patent Number:** **5,149,543**

Cohen et al.

[45] **Date of Patent:** **Sep. 22, 1992**[54] **IONICALLY CROSS-LINKED POLYMERIC MICROCAPSULES**

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[21] Appl. No.: **593,684**

[22] Filed: **Oct. 5, 1990**

[51] Int. Cl.⁵ **A61K 9/50**

[52] U.S. Cl. **424/499; 424/489**

[58] Field of Search **424/489, 499, 78; 428/402.22, 402.21, 402.2**

[56] **References Cited****U.S. PATENT DOCUMENTS**

4,016,078 4/1977 Saeki et al. 428/402.22
 4,021,364 5/1977 Speiser et al. 428/402.22
 4,352,883 10/1982 Lim 435/178
 4,880,622 12/1989 Allcock et al. 424/78
 4,908,233 3/1990 Takizawa et al. 424/501

FOREIGN PATENT DOCUMENTS

60-34731 2/1985 Japan 428/402.22

OTHER PUBLICATIONS

Allcock, et al., *Macromolecules*, vol. 10, No. 4, pp. 824-830 (1977).

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[57] **ABSTRACT**

A method for encapsulating biologically-labile materials such as proteins, liposomes, bacteria and eucaryotic cells within a synthetic polymeric capsule, and the product thereof, are disclosed. The method is based on the use of a water-soluble polymer with charged side chains that are crosslinked with multivalent ions of the opposite charge to form a gel encapsulating biological material, that is optionally further stabilized by interactions with multivalent polyions of the same charge as those used to form the gel. In the preferred embodiment, hydrolytically stable polyphosphazenes are formed of monomers having carboxylic acid side groups that are crosslinked with divalent or trivalent cations such as Ca²⁺ or Al³⁺, then stabilized with a polycation such as poly-L-lysine. A variety of different compositions can be formed from the crosslinked polymer. In a preferred embodiment, microcapsules are made by spraying an aqueous solution of polyphosphazene and material to be encapsulated into a calcium chloride solution. A semipermeable membrane is formed on the microspheres by complexation of the surface carboxylate groups with poly(L-lysine).

7 Claims, 3 Drawing Sheets

Scheme 1

