

HYDROGEL COMPOSITIONS AND METHODS OF USE

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BACKGROUND OF THE INVENTION

This invention relates to biocompatible and biodegradable hydrogel compositions, and to methods of use of such hydrogels for imaging during interventional procedures of a patient.

A variety of radiologic imaging techniques are available that allow the operator to diagnose disease and monitor therapeutic interventional procedures such as embolizations or abscess drainages. Whereas many imaging techniques are useful for the diagnosis of disease, e.g., ultrasound, scintigraphy, positron emission tomography ("PET"), single photon emission computed tomography ("SPECT"), X-ray, computed tomography ("CT"), and magnetic resonance imaging ("MRI"), only X-ray (fluoroscopy, computed tomography) and MRI are frequently used to monitor therapeutic interventions.

Therapeutic interventional imaging procedures are performed primarily in the fields of interventional radiology ("IR") and minimal invasive therapy ("MIT"). Both fields have become important adjuncts to traditional surgical techniques and have even replaced some classical surgical techniques because of their lower invasiveness, shorter convalescence, and similar or equal effectiveness. Well established IR procedures include abscess drainage, tumor embolizations, and biopsies. IR procedures are always performed in conjunction with radiological imaging, whereas MIT procedures are more surgical in nature and use imaging only when it is necessary to visualize the interventional devices used during the procedure.

Therapeutic drugs are often used in conjunction with procedures such as MIT and IR, and the concentration of these drugs in a patient is indicative of the efficiency of treatment. Therefore, it is important to accurately monitor the delivery, concentrations, and release, of these drugs in vivo, particularly after MIT, IR, and surgery. However, such drugs are typically not detectable by conventional CT or MR imaging techniques, because they do not contain radiopaque or magnetically active labels ("contrast agents").

Contrast agents were originally developed for use with diagnostic imaging techniques to further improve the diagnosis of disease. However, these agents have no therapeutic effect in interventional imaging procedures. For example, CT and MR contrast agents designed for intravascular use are water-soluble and are usually small molecules containing radiopaque, paramagnetic, or superparamagnetic elements. Such contrast agents are primarily administered intravascularly to facilitate diagnosis by selectively altering the signal arising in normal or abnormal tissues. Certain contrast agents also include particulate materials for gastrointestinal (oral or rectal) use. However, these gastrointestinal agents are undesirable for interventional use, because they are hyper-osmolar and/or toxic if administered intravascularly or intracorporally.

Known diagnostic agents for human use, e.g., contrast agents for X-ray imaging, contain labels, e.g., iodine or barium, which are covalently or non-covalently bonded to other atoms to make them biocompatible. Diagnostic MR

contrast agents usually contain a paramagnetic label, e.g., gadolinium ("Gd"), dysprosium, iron, or manganese, or a superparamagnetic label, e.g., iron oxide. These otherwise toxic labels are made biocompatible by chelating the ions, e.g., with diethylenetriamine-pentaacetic acid ("DTPA") to form Gd-DTPA, or by coating particulates with a polymer, e.g., with dextran or arabinogalactan, to form iron oxides.

For example, Hall, PCT patent application 89/11874 (1990), describes contrast preparations containing a biodegradable, porous particulate substrate, e.g., Sepharose™ or polystyrene, with surface bound paramagnetic labels, e.g., Gd-DTPA, with no significant release of the label when administered. The substrate may be a hydrogel, polyglycolic acid, cross-linked protein, and the like. These water-insoluble preparations may be used as MR contrast agents, e.g., for the gastrointestinal tract or the vascular system.

Bligh et al., *Magn. Reson. Med.*, 17:516-532 (1991), describes the use of soluble (e.g., dextran) and insoluble (e.g., starch or cellulose) polysaccharide-linked Gd-DTPA contrast agents for MR imaging. The insoluble polysaccharides are not covalently linked to each other by a cross-linking reagent. Soluble agents were administered intravenously and insoluble agents were fed orally without injections into the blood stream.

Unger, PCT patent application 91/15713 (1991), describes aqueous solutions of polymers as contrast media for MRI. These media comprise biocompatible polymers, e.g., polyethylene glycols, polyoxyethylene glycols, or polymers of galacturonic or mannuronic acid, in admixture (not covalently bound) with, e.g., paramagnetic or superparamagnetic agents. If cross-linked, these contrast media may be water-insoluble.

In addition, Gd-DTPA labeled gel "tissue phantoms," i.e., artificial in vitro models of tissues, made of polyacrylamide, agarose, glutaraldehyde cross-linked albumin gels, or styrenes, have been described for experimental MR imaging or other uses such as magnetic separations. However, these agents are not desirable or suitable for human use because of their local or systemic toxicity.

Inada et al., U.S. Pat. No. 4,814,098, describes the use of a ferromagnetic material bound to a physiologically active substance, e.g., an enzyme, through a PEG derivative linker. These water-soluble colloidal solutions are used for magnetic separation of physiologically active substances.

Some radiopaque particulate materials have also been proposed for embolization purposes. These materials exhibit a strong local toxic reaction, and may elicit an immunogenic response upon repeated administration or may not be biodegradable. Furthermore, these agents do not contain paramagnetic labels and are unlikely to be useful for drug delivery estimation because of the large quantities of radiopaque materials required for CT, e.g., 10 to 40 percent of the particulate is iodine.

For example, radiopaque hylan for embolization contains a combination of hylan, e.g., hyaluronan or hyaluronate (cross-linked with vinyl-sulfone), tantalum, microcrystalline cellulose, hexamethonium chloride, and thrombin. Additional embolization materials include radiopaque non-biodegradable hydrogel microspheres based on poly (2-hydroxyethyl) methacrylate ("PHEMA")/iothalamate or iopanoic acid as described by Jayakrishnan et al., *J. Biomed. Mat. Res.*, 25:993-1004 (1990). These microspheres were non-biodegradable over 6 month interval when implanted into rats.

Other embolization materials include Sephadex™ and Sepharose™, which are polysaccharides cross-linked with