Introduction

Many chemotherapeutic agents suffer from poor aqueous solubility and thus necessitate the use of stabilizing agents that are often toxic and lead to decreases in bioavailability or maximum dose. Hydrogels have the ability to stabilize insoluble compounds, facilitate controlled release and allow dose optimization.

Here we describe the first macro-scale synthesis of gadolinium-alginate hydrogels and the high-capacity loading of multiple chemotherapeutic agents within these gels. Furthermore, we show that this material is highly radiopaque and is directly toxic to patient-derived glioblastoma, U87 malignant glioma, and U251 glioblastoma cell lines.

This material may be suitable as a radio sensitizing, contrast-enhancing, drug delivery system for treating a wide variety of neoplasms including gliomas.

Methods

Gadolinium-alginate hydrogel beads were synthesized by the dropwise addition of 1-3% sodium alginate into flask of 10% by weight gadolinium-acetate under magnetic stirring at 200 RPM. (Figure 1)

HU values were obtained by micro-CT of the beads immediately following synthesis. 5 beads were chosen at random for each group.

Bead morphology was examined using scanning electron microscopy of dried beads.

In vitro assays were conducted by incubating glioblastoma cell lines with gadolinium alginate spheres for 24 hours followed by a resazurin-based viability assay and fluorescence measurement.

Results

Fig. 2. SEM images of dried gadolinium-alginate spheres at several levels of magnification

Fig. 3. Radiopacity of gadolinium-alginate spheres is independent of alginate concentration. Mean radiopacity was between 550 and 700 Hounsfield units.

Fig. 4. Micro-CT images. Left: 2D slice of microcentrifuge tube containing gadolinium-alginate spheres. Right: 3D reconstruction of section of microcentrifuge tube containing gadolinium-alginate spheres.

Discussion

Gadolinium alginate is a material with physical properties highly similar to the calcium-alginate hydrogels already under widespread investigation. The chemical properties of gadolinium-alginate have distinct advantages over other existing hydrogels in that the substance is radiopaque without the addition of any other agents such as iodinated contrast media. Furthermore, the presence of gadolinium ions within the gels allow for MRI contrast enhancement that is highly desirable in the context of direct administration within the CNS.

To our knowledge, this work represents the first description of gadolinium-hydrogels loaded with multiple chemotherapeutic agents, including temozolomide, methotrexate, and doxorubicin.

Further work is necessary to determine variables that affect the pharmacokinetics of loaded substances and in-vivo biocompatibility. While the majority of gadolinium present in the gels is expected to be chelated to alginate, we could not rule out the presence of free gadolinium ions which may be toxic in animals.

The synthesis described here represents low-cost, simple, method which is suitable for widespread and economical production of gadolinium-alginate spheres.

Conclusions

This work describes the synthesis and characterization of gadolinium alginate hydrogels that may serve as a versatile theranostic agent with high drug loading capacity and contrast enhancing properties. Physical properties of gadolinium alginate are similar to calcium alginate. Future applications for this material include intratumoral injection or placement at the site of resection. In-vivo testing for safety is warranted. Limitations of the current study include lack of safety profile data and long-term storage stability.

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