The Synthesis and Characterization of Gadolinium Alginate Spheres and Potential Uses as a Contrast-Enhancing Anti-Cancer Material

Tyler C. Owens[1,2], Marvin Bernadino[1], Archana Mishra[1], Allan John R. Barcena[1], Isias Workeneh[1], Erin Marie D San Valentin[1], Marites Melancon[1]

[1]The University of Texas MD Anderson Cancer Center, Department of Interventional Radiology

[2]The Warren Alpert Medical School of Brown University

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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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.

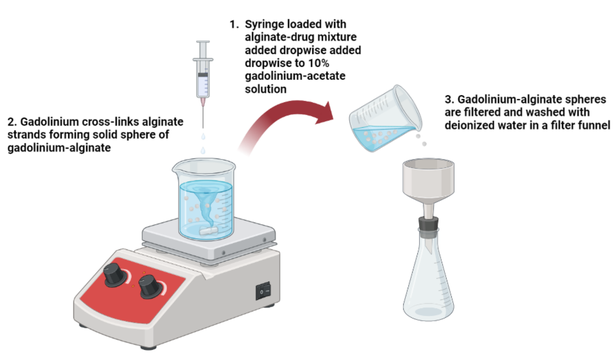

Fig. 1. Visual depiction of the synthesis of gadolinium-alginate spheres

Results

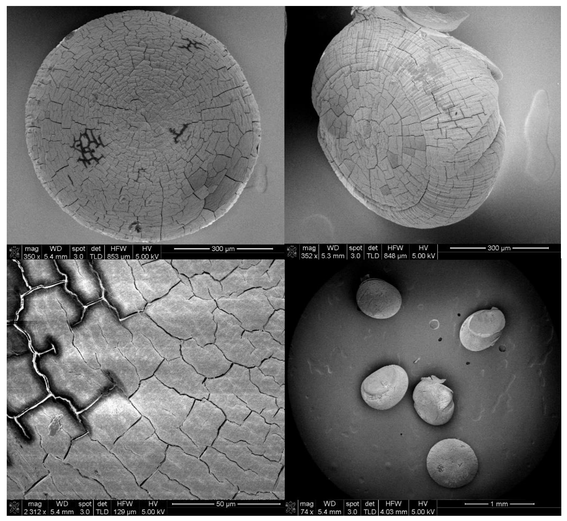

Fig. 2. SEM images of dried gadolinium-alginate spheres at several levels of magnification

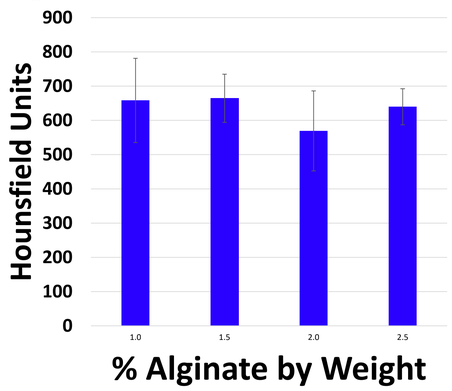

Fig. 3. Radiopacity of gadolinium-alginate spheres is independent of alginate concentration. Mean radiopacity was between 550 and 700 Hounsfield units.

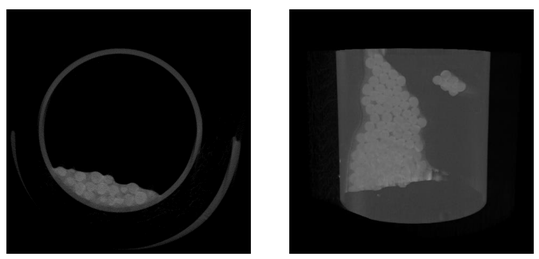

Fig. 4. Micro-CT images. Left: 2D slice of microcentrifuge tube containing gadolinium-alginate spheres. Right: 3D reconstruction of section of microcentrifuge tube containing gadolinium-alginate spheres.

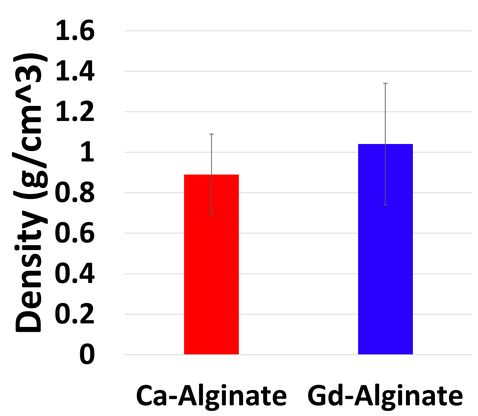

Fig. 5. The density of gadolinium-alginate spheres is similar to calcium-alginate spheres prepared under the same conditions.

Fig. 6. Doxorubicin-loaded gadolinium-alginate exhibiting fluorescence under blue light displays high loading capacity for doxorubicin and viability as a fluorescent agent.

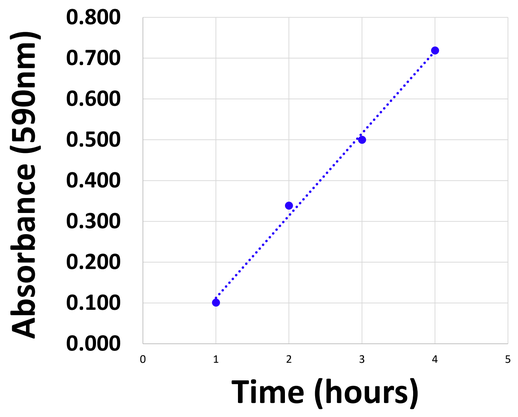

Fig. 7. Absorbance at 590nm of supernatant from wells of a 96-well plate containing crystal-violet loaded spheres in 100uL PBS.

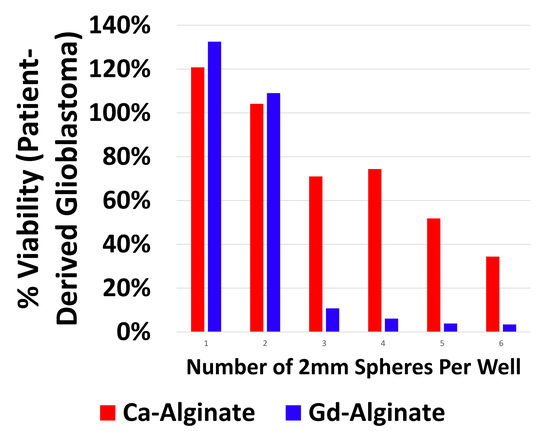

Fig. 8. Viability curves for calcium alginate and gadolinium alginate. Gadolinium alginate decreases the viability of U87 cells significantly more than calcium alginate.

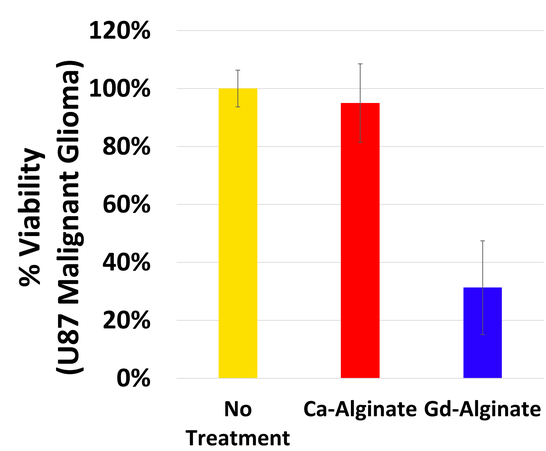

Fig. 9. U87 malignant glioma viability assay. Treatment with 3% gadolinium-alginate showed significant cell killing as compared with 3% calcium alginate and untreated cells.

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 propertied 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.

Acknowledgements

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