2021

Interfacial Dynamics and Ionic Transport of Radiologic Contrast Media in Carbohydrate Matrix: Utility and Limits of X-Ray Imaging

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Interfacial Dynamics and Ionic Transport of Radiologic Contrast Media in Carbohydrate Matrix: Utility and Limits of X-Ray Imaging

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Abstract

Carbohydrate matrix in model fruits and vegetables like apples and sweet potatoes that are also mineral rich were mildly treated with a microwave heat source and radiologic contrast media (Gadolinium based Gadovist, K-edge 50 keV and Iodine based Omnipaque , k-edge 33 keV) that are strong absorbers of x-rays. Soft x-rays from a clinical radiographic system were used at mid keV range to identify diffusing patterns of contrast nano-complexes in the heat treated and untreated carbohydrate matrix and test for transmetallation (exchange of biometals, particularly alkaline earth Ca^{2+}, Mg^{2+} and transition metals Cu^{2+}, $Fe^{2+/3+}$, Mn^{2+} from biochemical pools with Gd^{3+} of the infused media). X-ray attenuation surrounding the infusion points using regions of interests (ROI) analysis showed the diffusion of contrast media away from infusion points stopped after 24-48 hours while build up of x-ray absorbing material continued in the nearby regions demonstrating recruitment of native biometals from the bulk regions of the mineral rich fruit and vegetable, hence transmetallation (commonly observed by ion mass spectrometry). This effect seems to be more prominent in the heat shock matrix. Our work seems to be the first demonstration of such metal exchange in carbohydrate matrix using direct imaging technique and may add biomedical insight for metal toxicity and effects of heat waves during climate change in plants and vegetables.

Materials and Methods

This project involved the injection of fruits with varying contrasts and the imaging of the diffusion and interactions of the contrast within the fruits with X-rays. The technical parameters were: low kvp range of 55 kVp and the constant mAs of 4.8. Images were taken with identical setups at an hourly rate for several days.

Samples: Store-bought apples and sweet potatoes were obtained. The contrasts that were injected in the fruits are Eovist (Gd), Dotarem/Gd, Gadavist, Iodine, Omnipaque 240 and 360, and Saline.

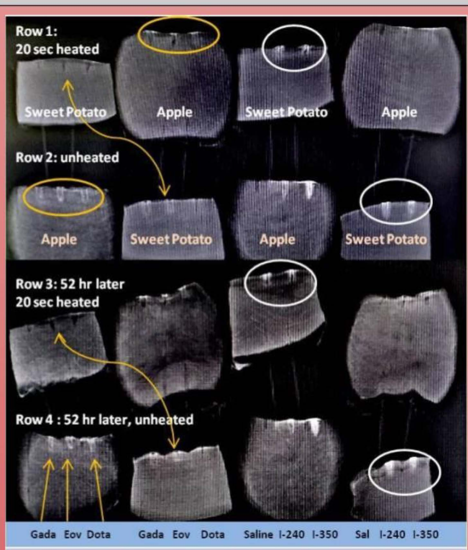
The apple and sweet potato were cut into wedge-like shapes and little holes were created uniformly at the top for the contrast to be injected in them through syringes. The top row was heated in the microwave then wrapped in seran wrap.

Table 1. Estimated amounts of added Gadolinium (Z=64) and Iodine (Z= 53) from various radiologic contrast media in 0.2 mL wells and bulk minerals (in µg) in the same volume adjacent to wells in apple and sweet potato.

Metal (in µg) & Iodine (in mg) / Model System	pH at 25C	Gd from Gadavist	Gd from Dotarem	Gd from Eovist	I (Z=53) Omnipaque 240	I(Z=53) Omnipaque 350	Na (Z=11)	K (Z=19)	Mg (Z=12)	Ca (Z=20)	Mn (Z=25)	Cu (Z=29)	Fe (Z=26)
Red Delicious Apple	3.9	3.2	1.6	0.8	48	70	2	208	10	12	0.06	0.06	0.22
Sweet potato (Beauregard, USA)	5.3-5.6	3.2	1.6	0.8	48	70	110	498	42	98	0.6	0.4	1.6
K-edges (keV)		50	50	50	33		1	3.3	1.3	3.7	5.9	8.0	6.4

Cell color blue indicates x-ray attenuation is expected either due to high density (ρ) or due to high atomic number Z) or the K-edge close to effective x-ray energy (approx 1/3xkVp or 18 keV for the 55 kVp used) per equation: $\mu \approx \rho Z^4/AE_{eff}^3$; high Z and low kVp offer most attenuation.

Contrasts used:
Gadavist: 0.1 mmol/kg $C_{18}H_{31}GdN_4O_9$ (MW 605) supplied 3.2 µg of Gd in 0.2 mL size wells in apple and sweet potato that diffused into bulk.
Dotarem: 0.05 mmol/kg $C_{23}H_{42}GdN_5O_{13}$ (MW 754) supplied 1.6 µg of Gd in 0.2 mL size wells that subsequently diffused into bulk.
Eovist: 0.025 mmol/kg $C_{23}H_{28}GdN_3Na_2O_{11}$ (MW 726) supplied 0.8 µg of Gd in 0.2 mL size wells that also subsequently diffused into bulk.
Omnipaque 240 and 350: $C_{19}H_{26}I_3N_3O_9$ containing 240 and 350mg iodine/mL respectively supplied 48 and 70mg of Iodine in 0.2 mL size wells.



None of the Gd contrasts stay localized in both heated samples (yellow arrows) while Iodine contrast stay on heated sweet potato only (elliptical markers) but not on apples, contrast mechanisms are different , Iodine is chelating more metal ions in sweet potato.

Results

Two types of changes were assessed:
(1) changes in attenuation due to heat treatment
(2) diffusivity and breakdown potential of native structure by contrast nanomaterials.

For pre-contrast samples heat treated and untreated the ROI based X ray attenuation magnitudes were very similar (within 2-3%) for each model system (apple or sweet potato) after adjusting for the Anode heel effect (that was approx 3%).

The standard deviation (x-ray attenuation fluctuations) were also very similar, i.e. mild heat treatment did not drastically alter attenuating carbohydrate or mineral distribution.
Post infusion of control solution (normal saline, 0.9% physiological) didn't affect the ROI based assessment and remained the same as the pre-contrast values.

Discussion

To asses the breakdown potential of bulk structures by contrast agents the following were observed:

1. Post contrast ROIs within the contrast filled wells showed decreasing attenuation values over time presumably due to contrast diffusing out of the wells while the attenuation values in bulk matrix outside the wells close to the edges steadily increased during six days of data collection (3/16-3/22/21, 12 noon-12 noon)
2. Attenuation values for Omnipaque 350 were higher than Omnipaque 240 indicative of attenuation dominated by Iodine in all samples. However, the rate of attenuation values were higher in Omnipaque 240 indicative of lower viscosity and greater diffusivity of lower iodine contrast medium.
3. Similarly rate of change with time of attenuation for Gadolinium based agents were from highest to lowest: Eovist>Dotarem>Gadavist indicative of higher complexation with matrix macromolecules by the macrocyclic agent Gadavist thereby reducing diffusivity of such Carbohydrate/Gadavist moieties.

Conclusion

Overall the time rate of changes in all Gadolinium based nanomaterials were higher than those from iodinated media, perhaps indicating greater mineral breakdown by Gadolinium agents. Among Gadolinium based agents the high concentration of Gadolinium in Gadavist seems to indicate attenuation was caused primarily by Gadolinium atoms while lowest diffusivity may indicate minimal breakdown of mactocyclic complex Gadavist compard to linear Dotarem or loosely bound Eovist. The final results also indicated that compared to iodine Gadolinium destroyed the safe structure and water structure of substances therefore making it significantly more toxic than iodine. This research is important to understand as the usage of these contrast agents and their toxic levels must be understood.

Acknowledgments

We would like to acknowledge the priceless help from Seanetta Humpherys, at Maimonides medical center, and Jodi-ann Douglas, at NYCCT radiology department, for providing us with the necessary items such as the contrast and the use of the college equipment to make this project possible. This work was made possible with student stipends to the student researchers of this project under CRSP.

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