UCSF
UC San Francisco Electronic Theses and Dissertations

Title
Homogenization and Stabilization of Novel Enteric Dual-Energy CT Contrast Material

Permalink
https://escholarship.org/uc/item/24p9321k

Author
Sun, Yuxin

Publication Date
2014

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

Homogenization and Stabilization of Novel Enteric Dual-Energy CT Contrast Material

by

Yuxin Sun

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Biomedical Imaging

in the

GRADUATE DIVISION

ACKNOWLEDGEMENT

First and foremost, I would like to thank Dr. Benjamin M. Yeh, M.D. for his continued support and mentorship through this this thesis research, and for always being so enthusiastic about my occasionally unorthodox ideas. I would also like to thank Dr. Yanjun Fu, Ph.D. for his expertise, wisdom, and guidance in the laboratory.

Thank you to my thesis committee members, Dr. Youngho Seo, Ph.D. and Dr. Henry VanBrocklin, Ph.D., for generously donating their time and efforts to provide constructive feedback and discussions on my research.

I would like to thank the all the faculty and students of the UCSF Biomedical Imaging Master's Program, Class of 2014 for the fruitful discussions, endless laughter, and genuine friendship that flourished in this past year.

Lastly, I would like to dedicate this work to my family. I am forever grateful for their unwavering support and words of encouragement.

Homogenization and Stabilization of Novel Enteric Dual-Energy CT Contrast Material

Yuxin Sun

ABSTRACT

Computed tomography (CT) is a one of the essential imaging modalities widely used in clinical diagnosis. To further increase the diagnostic value of CT, contrast agents, based on iodine or barium, are routinely administered to patients for enhancement blood vessels and organ parenchyma for various clinical indications. Over the course of the last four decades, there have been dramatic improvements in CT technology, including the more recent introduction of dual-energy CT (DECT) technology that enables the simultaneous image acquisition at two different x-ray tube potentials (ie. 80 kVp and 140 kVp), such that materials can be differentiated based on characteristic x-ray attenuation properties. However, a major limitation with the currently available contrast agents is that the elements iodine and barium cannot be readily distinguished due to their near-identical 80:140 kVp CT number ratios.

The objective of my thesis work is to explore viable formulations of a novel CT contrast material, based on silica microparticles. Four common excipients were tested to formulate a suspension of silica microparticles such that the solution is 1) stable, 2) homogenous, and 3) sufficiently nonviscous for translation towards potential clinical applications as an oral enteric contrast agent. Formulations were evaluated for stability at 30°C and 4°C over a period of 10 days; homogeneity was assessed by CT scanning and analysis of attenuation; viscosity measurements were obtained via a falling-ball viscometer method. One of the four excipients achieved all three criteria as stated above, and allows for further in-depth development towards pre-clinical testing and future clinical use.

TABLE OF CONTENTS

Page

LIST OF FIGURES

Disclosure: For proprietary reasons, the exact details of the materials used, and the numerical values of the experimental formulations cannot be disclosed.

1. INTRODUCTION

1.1. Computed Tomography

Computed tomography (CT) is able to provide high-resolution anatomical images for the clinical diagnoses of a broad range of diseases. Even with the use of ionizing radiation, the clinical value of CT is profound, and over 70 million CT scans are performed each year in the United States [1]. To further enhance the diagnostic power of CT, contrast materials are routinely administered to patients. These contrast materials, when scanned with CT, serve to highlight vascular anatomy, bowel lumen, tumors, active bleeds, and many other clinical indications. All currently used CT contrast materials are either iodine based (intravascular and enteric) or barium based (enteric). The major limitation of the presently available contrast materials is that the two elements cannot be adequately distinguished during imaging, even with the recent advances in CT technology [2].

1.2. Dual-Energy CT Technology

Dual-energy computed tomography (DECT), while first introduced in 1976 with promising clinical applications [3], was not widely used for CT indications due to hardware limitations because each energy acquisition required a separate CT gantry rotation. The basic principle of dual-energy technology is the acquisition of two datasets from the same anatomic location with different x-ray peak kilovoltages (kVp), usually at low 80 kVp and high 140 kVp, with the low kVp images providing higher contrast [3]. These dual-energy data allow for material decomposition between the two image series at different kVp to improve the ability of

CT to distinguish between materials, even when they have the same CT attenuation properties. Fig. 1 is a comparison of images from conventional CT and DECT where the latter clearly shows three distinct materials, which cannot be readily distinguished except by context on the conventional CT image. The theory is that elemental compositions of the human body vary in their K-shell binding energies in consideration with the photoelectric effect and therefore exhibit fixed ratios of attenuation coefficients between low and high tube potentials [4]. The rapid acquisition of both low and high kVp data sets largely eliminates image misregistration artifacts that may be seen with serial conventional CT scans.

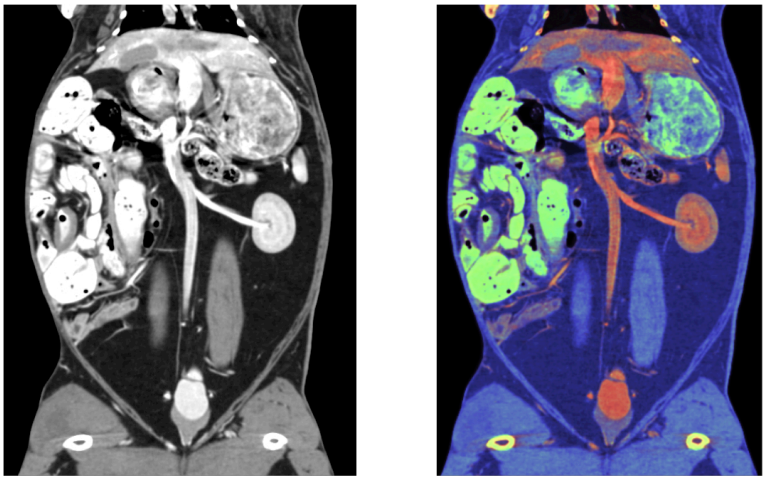


Figure 1. Conventional CT (left) versus. Dual-energy CT (right). Color enhanced three-material (blue = soft tissue) decomposition of complementary silicon oral (green) and iodinated IV (red) contrast enhanced DECT. Images courtesy of Margaret Wong, UCSF.

Currently, assessment of enhancement characteristics of a lesion or tissue requires acquisition of true unenhanced images as part of a multiphase CT protocol so that the amount of enhancement can be measured after the administration of contrast material [5]. The use of DECT can circumvent the need for non-contrast enhanced images with the near simultaneous acquisition of the two kVp datasets, followed by reformatting of virtual unenhanced images

using dual-energy workstation software [4]. The two kVp datasets can be used to obtain virtual non-contrast, iodine map, and mixed kVp images, as well as virtual monochromatic images [6].

1.3. Contrast Material for CT

An extension from the growing advancements in dual-energy technology is improved clarity with the use of two or more simultaneously administered contrast media that can then be digitally separated with DECT. The potential clinical applications of such combined method are numerous—the goal of this research is to investigate a novel enteric contrast material for future use with DECT.

The ability of dual-energy CT to digitally differentiate between two different contrast materials depends heavily on the difference between their 80:140 kVp CT number ratios. As earlier stated, current clinically available CT contrast material is based on iodine or barium, but the two are poorly differentiated with dual-energy scanners because their 80:140 kVp ratios are highly similar to each other [2]. Previous studies have highlighted the *in vivo* use and efficacy of two simultaneously administered contrast media with complementary x-ray attenuation ratios [7]. For instance, separate intravascular (iodine) and intraluminal (bismuth) material density maps could be obtained with clear delineation of the lumen from bowel wall [8]. The combined use of DECT with dual-contrast administration permits distinctive positive bowel contrast without the sacrifice of vasculature enhancement, and holds exciting clinical potential.

1.4. Development of Novel Contrast Material for DECT

A novel oral contrast material for enteric imaging has recently been identified with promising future applications with DECT and eventual clinical use. The basis of this agent is silica (silicon dioxide) microparticles, which are ideal for dual-energy considerations for a variety of reasons. Firstly, of the available types of silica, fumed silica is a form of amorphous

silica that is less toxic and non-carcinogenic than crystalline silica. Also, these silica microparticles are much less toxic and reactive than their nanoparticle counterparts [9]. Most importantly, the silica microparticles exhibit an 80:140 kVp ratio of 1.26, which is substantially different from that of barium or iodine contrast agents (1.76), calcium (1.48), and soft tissue (1.00) [10].

Despite the aforementioned advantages of silica microparticles as a suitable contrast material, there are several challenges that need to be addressed. First, a stable and non-separable suspension of the microparticles is required for oral administration. Second, a relatively high concentration of microparticles is required for adequate x-ray attenuation and contrast in imaging. For effective translation into clinical use as an oral enteric CT contrast material, the final product should be safe, relatively low viscosity, stable across various pHs, and homogeneously mixed. Ideally, the material should remain homogenously in suspension for long periods of time, on the order of months or years, and require no additional mixing before oral administration. Furthermore, the material should not sediment or separate over time to allow for optimal biodistribution and enhancement during imaging. Lastly, in consideration for use in dual-energy scans with multiple complimentary contrast agents, the material should allow for simultaneous suspension with traditional barium or iodine-based contrast agents.

The following work seeks to determine and optimize viable formulations of a novel contrast material, characterized by silica microparticles, through experimental testing using various common pharmaceutical excipients. An excipient is defined as an inactive substance that serves as a vehicle for an active drug (in this case, silica microparticles). There are four main requirements to take into consideration for the formulation and evaluation of this silica contrast material.

1) Homogeneity – contrast material remain well suspended and evenly distributed in solution, and the solution achieves acceptable enhancement properties for CT imaging.

2) Stability – contrast material exhibit minimal separation and sedimentation over time in solution.

3) Viscosity – solution displays optimal viscosity and flowability suitable for oral administration and passage through the gastrointestinal tract.

4) Biocompatibility – solution is safe, non-toxic, and biophysically compatible for oral administration.

The specific aims for this work only address the first three criteria mentioned above, with the goal of formulating a contrast material solution that can be utilized for future pre-clinical testing and development towards use with DECT.

2. MATERIALS AND METHODS

2.1. Materials and Experimental Formulations

The silica microparticles were purchased online directly from the manufacturer. The microparticles are available in a variety of diameters ranging from 5 μm to 35 μm, and have a specific gravity of 2.4. A total of four pharmaceutical excipients, all of which are listed as common excipients in the US Pharmacopeia [11] were tested. The four excipients were chosen based on extensive literature and patent review of previous and currently approved formulations of CT contrast agents, an example of which is the barium sulfate suspensions, Readi-Cat 2, made by Bracco Inc. Henceforth, the four excipients will be individually referred to as “A”, “B”, “C”, or “D”.

Each excipient was individually tested for effectiveness as a thickening and/or stabilizing agent in combination with the silica microparticles. The formulations were prepared in combinations of "low", "medium", or "high" excipient concentrations along with "low", "medium", or "high" concentrations of the silica microparticles. The appropriate range of concentrations for each excipient was individually determined as they varied depending on their respective properties, such as viscosity and thickness, when added to distilled water. The "low", "medium", and "high" concentrations of silica microparticles were kept consistent for all batches of formulations.

The formulations were made in Falcon 50 mL conical tubes. For each excipient, every formulation combination (ie. low excipient [A] + low silica, low excipient [A] + medium silica, etc.) was made in triplicate and the concentrations were determined on a % weight-by-weight (% w/w) basis, with a final solution net weight of 25 g (height of tube = 11.5 cm, orifice diameter = 3.0 cm, mean height of final mixtures in tube = 8.0 ± 0.5 cm). If an excipient exhibited overall positive results in the suspension of silica microparticles in terms of homogeneity, stability, and viscosity, the solutions were re-formulated with the addition of barium (barium sulfate powder, 98% w/w, Bracco Inc.), or iodine (Iohexol 350 mgI/mL, Omnipaque 350). The addition of barium or iodine serves to provide improved enhancement during imaging and is important for future considerations and use with DECT.

2.2. Homogeneity Assessment

For each batch of formulations, all samples were vigorously shaken, vortexed, and inverted to ensure even mixing, and allowed to settle for a few hours such that minimal contrast material remained on the inner sides of the Falcon tubes. Then, each batch of samples was imaged with a multi-detector CT scanner (LightSpeed VCT 64 slice scanner; GE Medical

Systems, Milwaukee, WI) at both 80 kVp and 140 kVp tube potentials. The scan parameters were kept consistent at FOV = 40 mm FOV; slice thickness = 2.5 mm; mA = 200.

Homogeneity was subjectively assessed based on overall visual appearance and distribution of contrast material in the physical tubes, and also based on CT images by the presence of bubbles, layering, poorly suspended specks or blotches. CT images were viewed using OsiriX software (free 32-bit version online download). Homogeneity was objectively assessed based on CT images using OsiriX to measure standard deviation within a region-of-interest (ROI) (Fig. 2). An ROI of area = 2.5 cm^2 was drawn on each individual tube to record the mean and standard deviation of CT number in Hounsfield (HU) units. Hounsfield units are a measure of the extent of X-ray attenuation at CT. Since each formulation was made in triplicate, the values for mean and standard deviation were averaged. The 80:140 kVp ratios were also calculated and used as an indicator of overall enhancement capabilities, with a desired value of 2.7, which is needed for adequate contrast during imaging

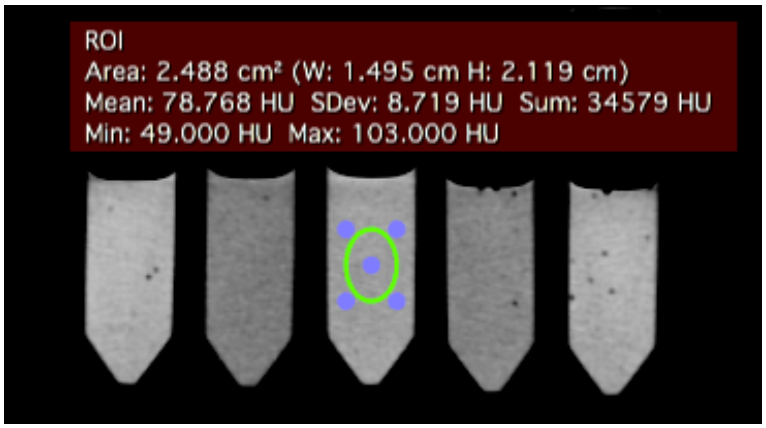


Figure 2. Representative CT image with ROI showing mean and standard deviation in HU.

2.3. Stability Monitoring

The amount of phase separation over time was monitored and measured (in cm) daily at conditions of 30°C and 4°C, over a period of 10 days. At time t = 0 days, all samples were

vigorously shaken and mixed, and then placed in the respective incubators to be left undisturbed. Measurements were taken daily at the same time of day, and the temperature of the incubators was recorded.

2.4. Viscosity Measurements

A custom-designed setup, based on the falling-ball viscometer method, was used to measure viscosity. This method is based on Stokes' Law in which a solid sphere of known diameter (d) and density (ρ_{sphere}) is dropped into the contrast material solution of known volume (25 mL) and mass, which can be used to calculate the solution density (ρ_{fluid}). The time it takes for the sphere to fall a certain length of a 25 mL fixed diameter glass graduated cylinder can then be used to calculate the velocity of the falling sphere, which is related to fluid viscosity (η) by the following equation [12]:

$$v_{sphere} = \frac{d^2(\rho_{sphere} - \rho_{fluid})g}{18\eta}$$

In order to most accurately and precisely obtain the time measurements, a slow-motion video camera (SloPro iPhone application, Sand Mountain Studios) was used to record the falling-ball trial for each formulation, and then the video was further slowed down by 50% using video processing software (VLC Media Player). A stopwatch was used to measure the time from when the sphere first touches the meniscus till either a sound was heard that indicated the sphere had dropped to the bottom of the graduated cylinder, or by visual confirmation of the sphere reaching the bottom of the cylinder. Each trial was viewed three times, and the final time was determined as an average of the three, to minimize human error. The appropriate back-calculations were performed to determine the actual time of fall (in seconds).

Due to the small diameter (D) of the graduated cylinder, some interaction between the fluid and the internal cylinder wall is expected, and thus, the viscosity (η) must be corrected (η_{corr}) for such interaction using the following equation [12]:

$$\eta_{corr} = \eta\left[1 - 2.104\left(\frac{d}{D}\right) + 2.09\left(\frac{d}{D}\right)^3 - 0.95\left(\frac{d}{D}\right)^5\right]$$

3. RESULTS AND DISCUSSION

3.1. Excipient A

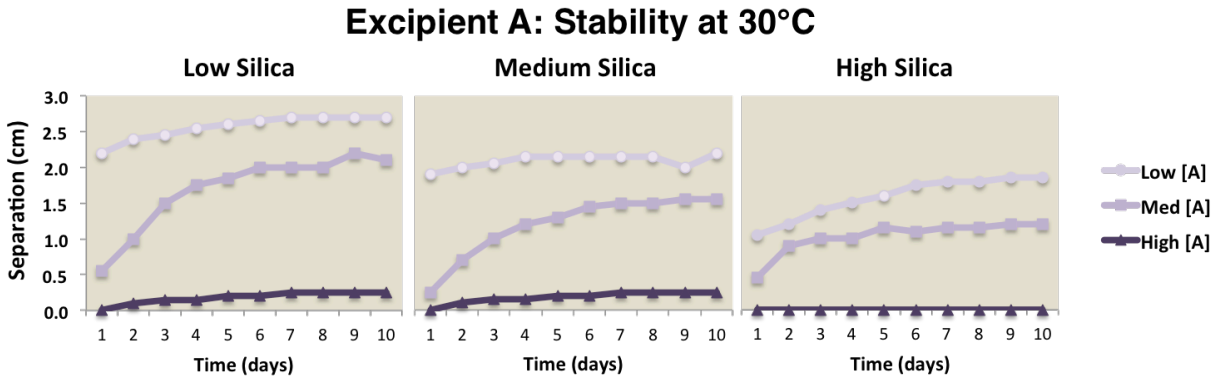


Figure 3. Excipient A stability monitoring at 30°C over a period of 10 days.

Excipient A exhibited poor stability at 30°C, at both low and medium excipient concentrations, as see in Fig. 3. The combination of low excipient [A] + low silica resulted in > 2.0 cm of distinct phase separation just after one day. At the highest excipient concentration, the solutions remained stably mixed and exhibited minimal separation, if any, across all three concentrations of silica.

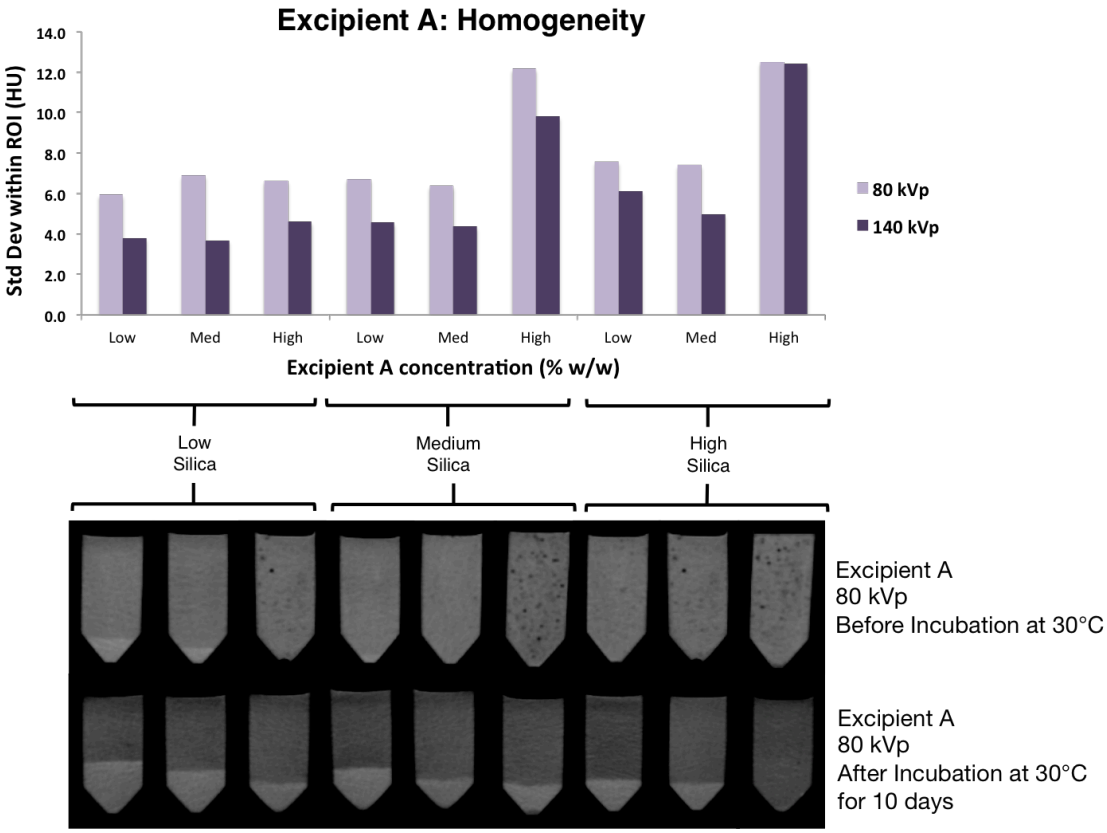


Figure 4. Top: Excipient A homogeneity assessment. Bottom: CT images of Excipient A scanned at 80 kVp before and after 10 day incubation at 30°C.

Excipient A showed best homogeneity at low excipient + low silica concentrations, as seen in Fig. 4 at both 80 and 140 kVps. The distinct amount of phase separation can also be seen in Fig. 4 above, both before and after incubation. Excipient A at low concentrations was not sufficient as a suspension medium; however, at higher concentrations there was a negative effect on the viscosity such that the solutions became thick and non-flowable. There was no feasible combination of Excipient A and silica combination that exhibited optimal tradeoff between stability and viscosity, and thus, the viscosities of the formulations were not measured.

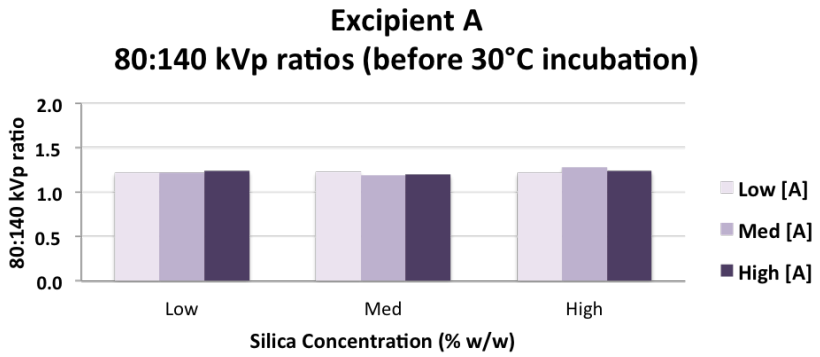


Figure 5. Excipient A 80:140 kVp ratios, calculated from CT images taken before 10 day incubation at 30°C

According to the data shown in Fig. 5, the enhancement properties of Excipient A did not vary significantly across either excipient or silica concentrations.

3.2. Excipient B

Excipient B exhibited similar physical characteristics as Excipient A yet showed much worse homogeneity, as seen in Fig. 6. The main difference between these two excipients was that Excipient B did not mix well with the silica microparticles, as indicated in the CT images by the high presence of air bubbles, seen as black blotches. In particular, at medium and high excipient concentrations, it was very difficult to achieve homogeneity and the standard deviation of HU was significantly higher than that of Excipient A. Upon visual inspection of the Excipient B formulations, it was clear that this excipient was not a suitable medium for adequate suspension of the silica, and thus, no further evaluation of stability or viscosity was conducted.

Fig. 7 shows the 80:140 kVp ratios for Excipient B, slightly higher than the corresponding formulations for Excipient A. However, the presence of bubbles in Excipient B must be taken into account as the dark bubbles serve to decrease the measured HU values, thus resulting in a larger 80:140 kVp ratio.

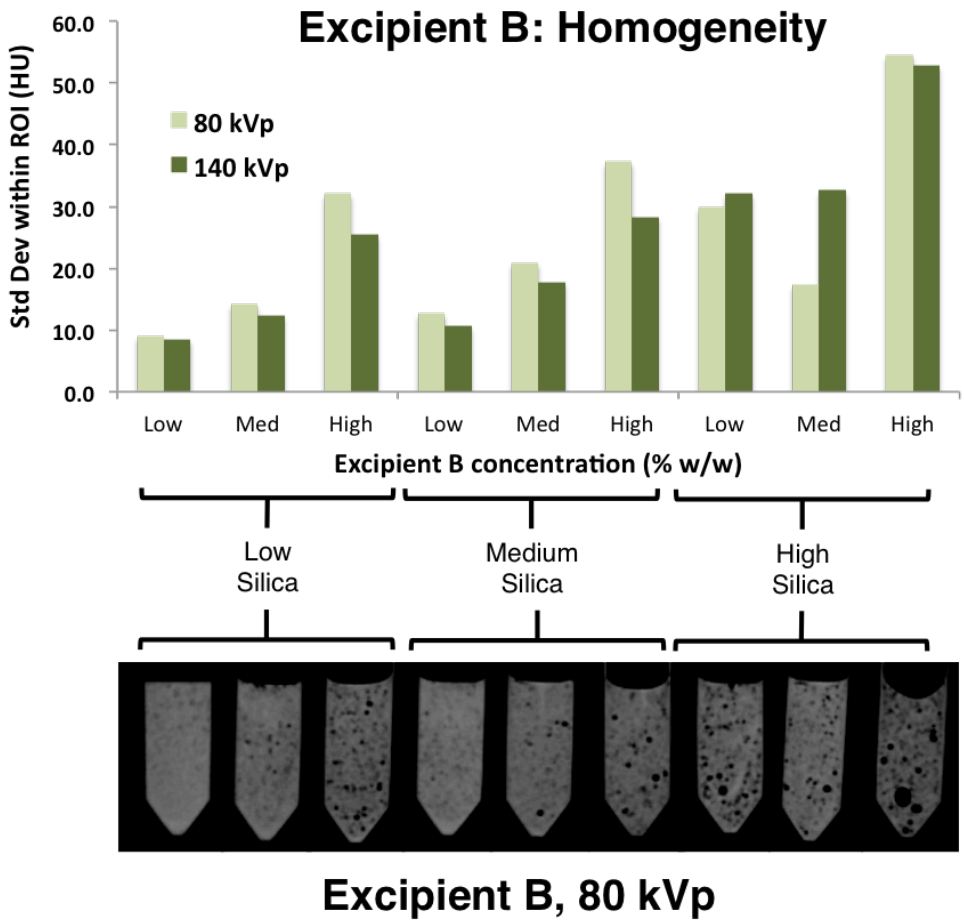


Figure 6. Top: Excipient B homogeneity assessment. Bottom: CT images of Excipient B scanned at 80 kVp.

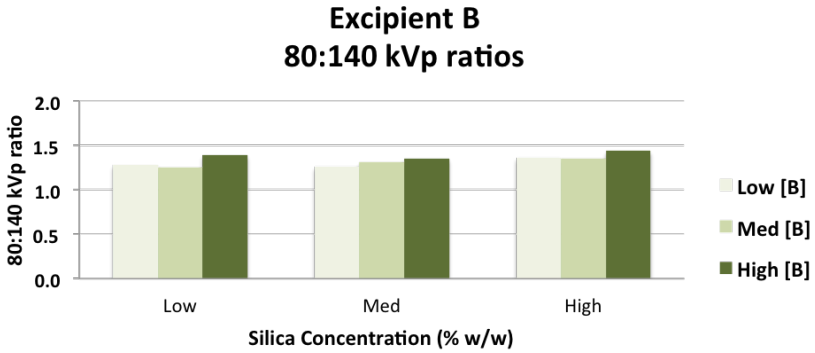


Figure 7. Excipient B 80:140 kVp ratios, calculated from CT images.

3.3. Excipient C

Use of excipient C resulted in the poorest silica suspensions of the four excipients tested. At the time of experimental formulations, excipient C did not mix readily with the silica when

added, and the solutions remained relatively clumped and inhomogeneous despite vigorous shaking ,vortexing, and stirring. Fig. 8 displays the homogeneity and CT images of Excipient C, and the presence of nonsuspended excipient specks can be seen as a contributing factor of such varied homogeneity, particularly in the high silica concentration formulations.

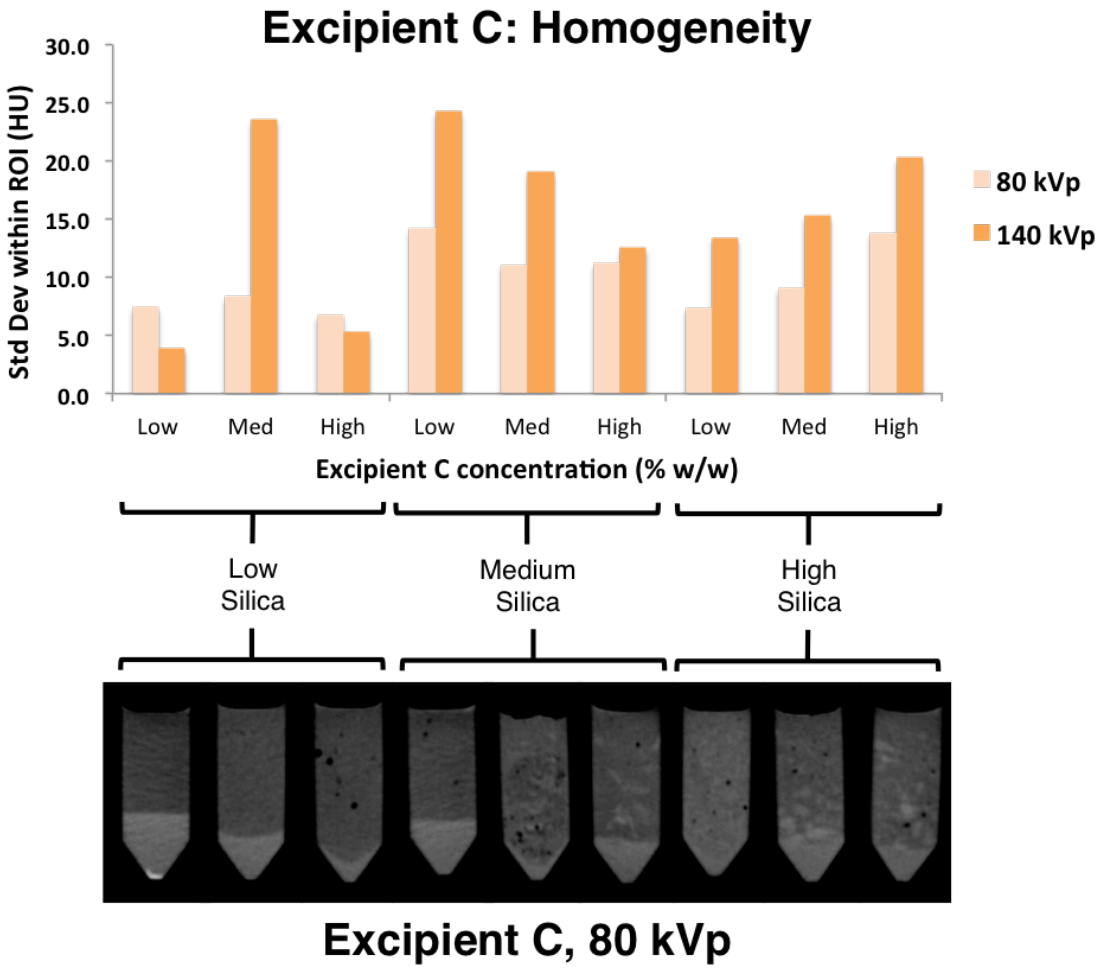


Figure 8. Top: Excipient C homogeneity assessment. Bottom: CT images of Excipient C scanned at 80 kVp.

Fig. 9 shows the 80:140 kVp ratios of Excipient C, and the ratios generally decrease as the excipient concentration is increased, as expected due to the bright blotches of non-suspended excipients that artificially increase the HU values. Similar to Excipient B, no further stability or viscosity tests were performed, as Excipient C was clearly not suitable as a suspension vehicle for the silica microparticles.

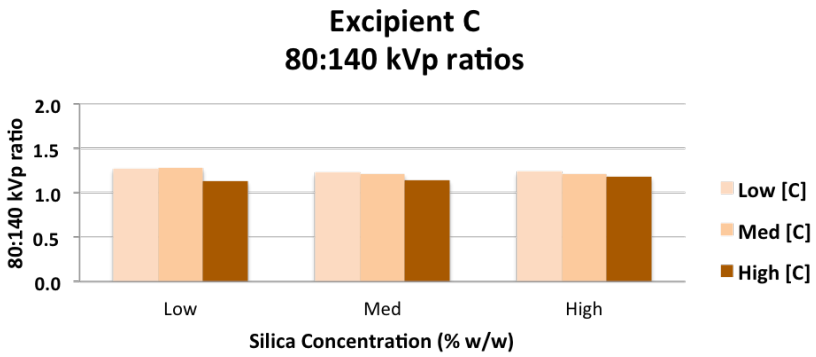


Figure 9. Excipient C 80:140 kVp ratios, calculated from CT images.

3.4. Excipient D

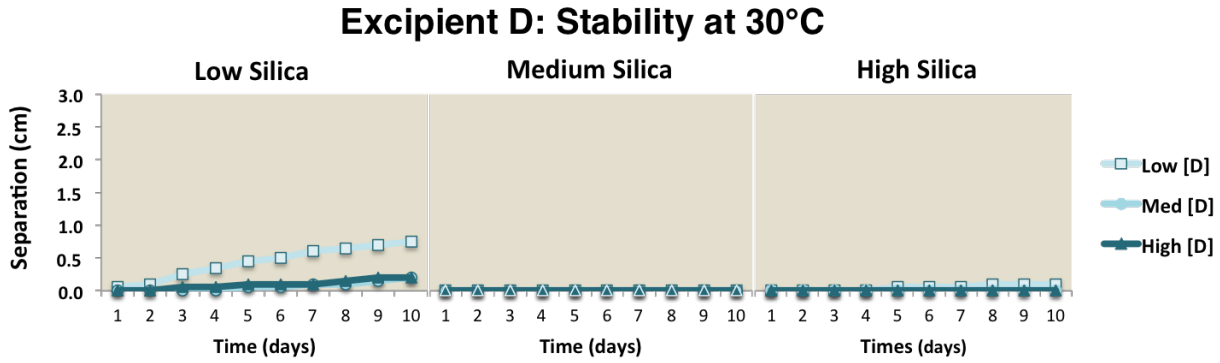


Figure 10. Excipient D stability monitoring at 30°C over a period of 10 days.

Excipient D formulations showed the most uniform suspension of silica of the four tested excipients. Suspensions with excipient D showed substantially less particle separation than observed with Excipient A. Fig. 10 shows that at low silica concentrations, there was only moderate separation observed in combination with low excipient concentration. At medium and high silica concentrations, there was very minimal separation over time, indicating an optimal excipient concentration for a stable suspension medium.

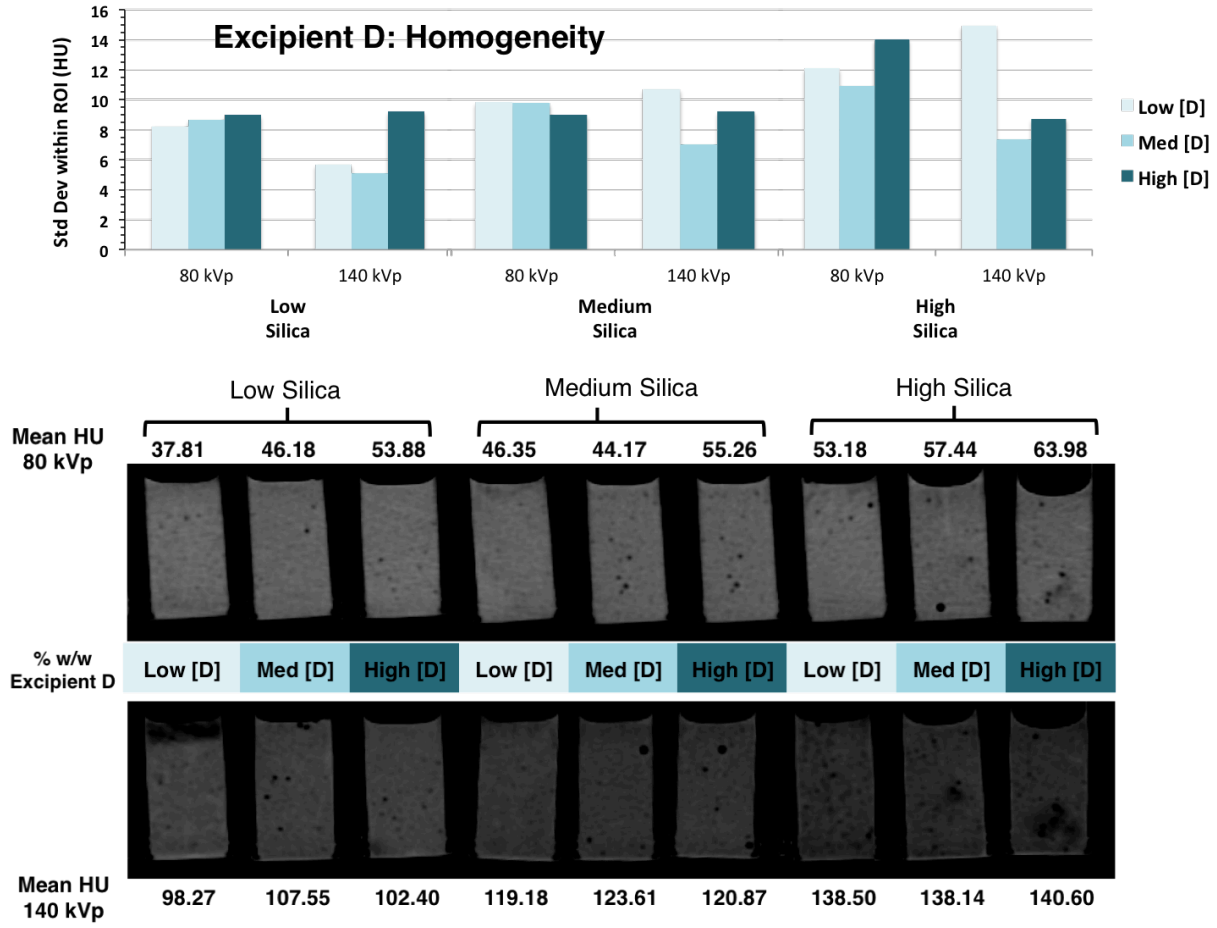


Figure 11. Top: Excipient D homogeneity assessment. Bottom: CT images of Excipient D scanned at 80 and 140 kVps.

The homogeneity data of Excipient D is shown in Fig. 11 and the variation in homogeneity is best seen in the 140 kVp CT images, noticeably in the high silica formulations, there appears some unevenly distributed blotches of the excipient. Nonetheless, Excipient D exhibited significantly improved homogeneity (particularly at low silica concentrations) compared to B and C, and was more consistent in comparison to Excipient A. Similarly, the 80:140 kVp ratios (Fig. 12) for Excipient D were more ideal than the other 3 excipients, with improved enhancement as both excipient and silica concentrations increased.

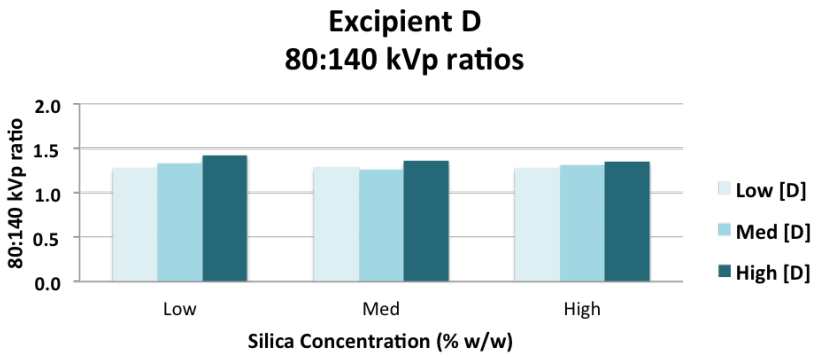


Figure 12. Excipient D 80:140 kVp ratios, calculated from CT images.

3.4.1. Excipient D with Barium and Iodine

The stability and homogeneity evaluation of Excipient D deemed it suitable for further formulations and testing with the addition of barium and iodine. Barium at "low" and "medium" concentrations were tested in combination with various Excipient D and silica concentrations. The results from previous Excipient D formulations were used to fine-tune the excipient and silica concentrations used for formulations containing barium and iodine. Thus, lower concentrations of both Excipient D and silica were used.

The 80:140 kVp ratios and CT images are shown in Fig. 13. The significant increase in enhancement properties due to the added barium is clearly seen in the bright CT images, as well as the large improvement in 80:140 kVp ratios, so much that many of the formulations achieved higher than the targeted ratio of 2.7. One notable distinction seen in the barium-containing formulations is the presence of poorly suspended barium, appearing as white specs in the images. This observation is common with barium and may cause artificial increases in the mean HU values, resulting in a greater 80:140 kVp ratios than expected, as apparent in the high silica formulations containing low and medum barium.

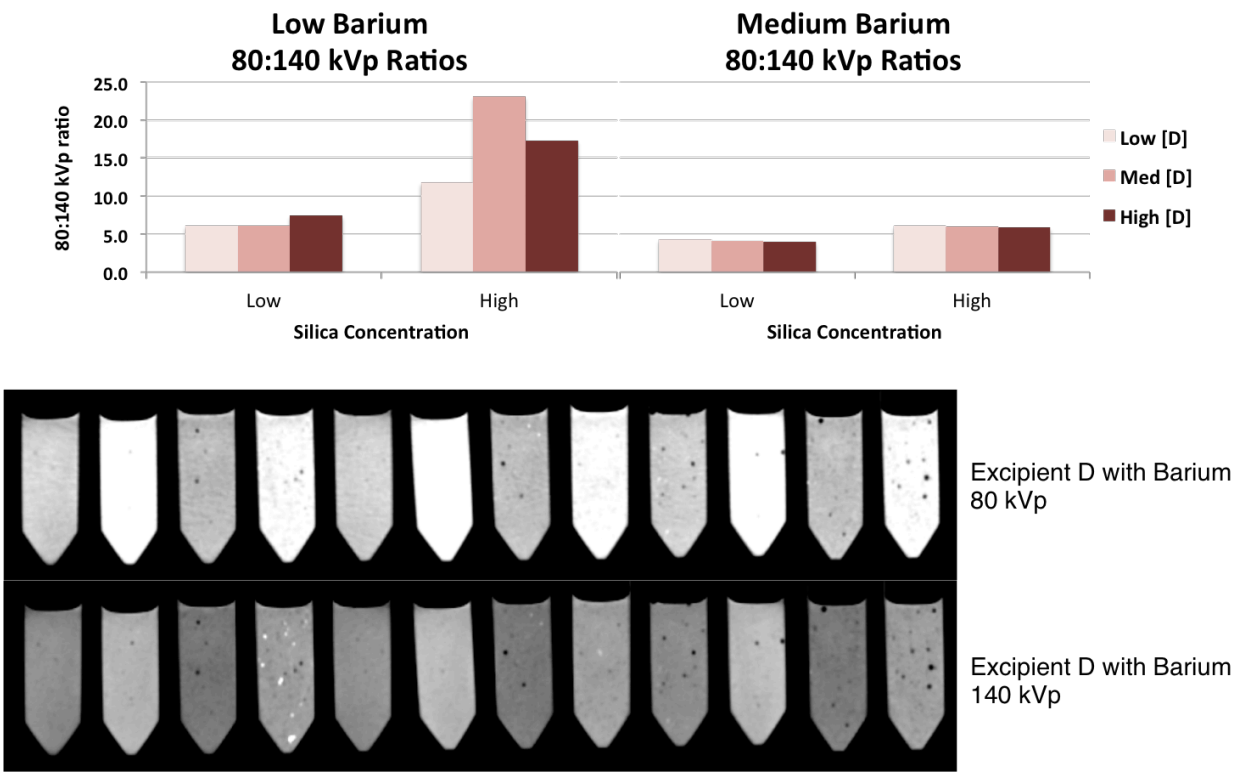


Figure 13. Top: Excipient D with barium, 80:140 kVp ratios calculated from CT images. Bottom: CT images of Excipient D with barium scanned at 80 and 140 kVps.

Iodine at "low" and "medium" concentrations were also evaluated with Excipient D, and the 80:140 kVp CT number and homogeneity results are shown in Fig. 13. While iodine produced somewhat lower enhancement properties than barium at the concentrations tested, the 80:140 kVp ratios for both were still within range of the desired value of 2.0 to 6.0 and would be suitable for clinical imaging. Also, since iodine was added in the form of water-soluble iohexol, the homogeneity of the resultant suspensions was excellent without on the CT images compared with what was seen with solid barium sulfate particles, which required aggressive mixing to achieve relative homogeneity in distilled water.

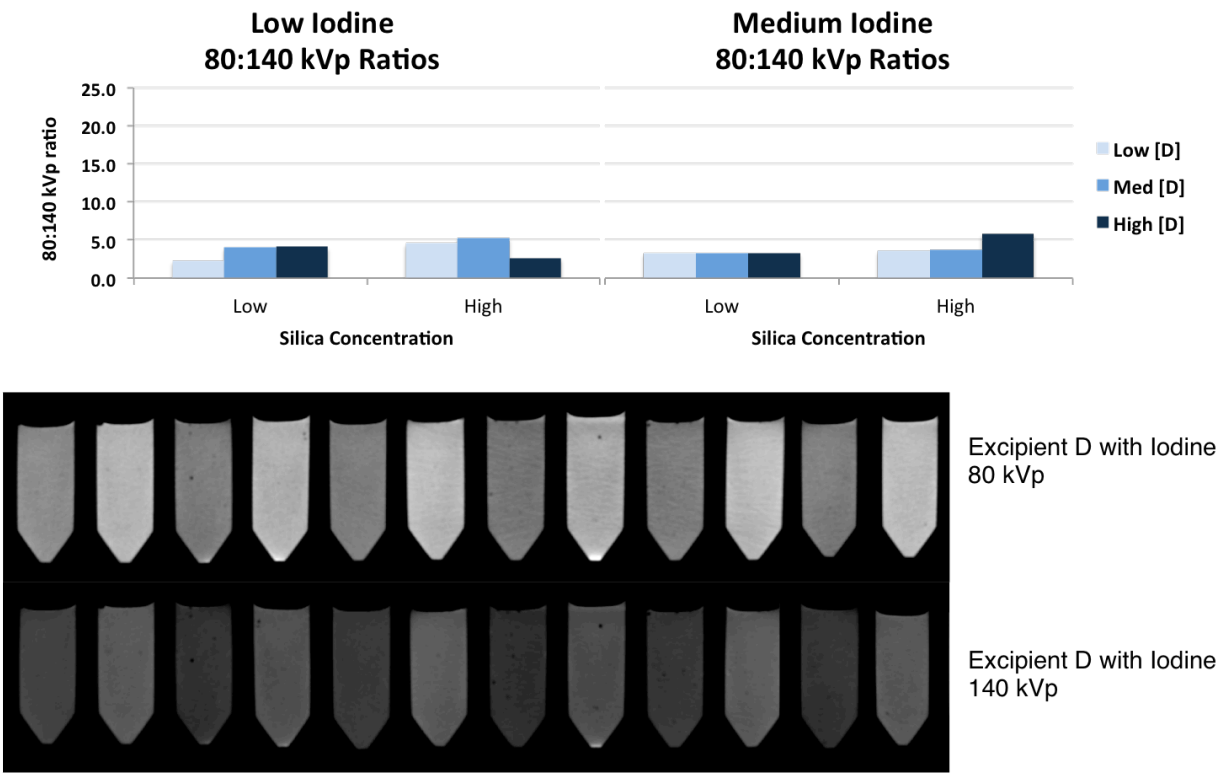


Figure 14. Top: Excipient D with iodine, 80:140 kVp ratios calculated from CT images. Bottom: CT images of Excipient D with iodine scanned at 80 and 140 kVps.

Interestingly, the stability testing of all batches of Excipient D formulations (with and without the addition of barium or iodine) at 4°C showed no visible phase separation, even after 10 days. Furthermore, subjective assessment of the formulations indicated that the viscosity and flowability characteristics were preserved at low temperatures, possibly even improved upon after incubation. This phenomenon is likely the effect of the low temperature on the texture and stability of Excipient D, which contributes to stronger suspension medium interactions with the silica microparticles. This observation has critical importance for future considerations and development of this silica contrast material and requires further testing.

3.4.2. Excipient D Viscosity Measurements

All Excipient D formulations, including ones with barium and iodine, were subjected to viscosity measurements using the falling-ball viscometer method. The data is shown in Fig. 15.

The viscosity for Readi-Cat 2, a barium sulfate suspension commonly used in clinical practice, was measured to be 140.4 g/cm-sec, and was designated as the preferred viscosity for subsequent measurements and comparison. With Excipient D, the lowest and most ideal viscosities were observed at low excipient and low silica concentrations, as expected, with trending increases in viscosity as the concentrations increased.

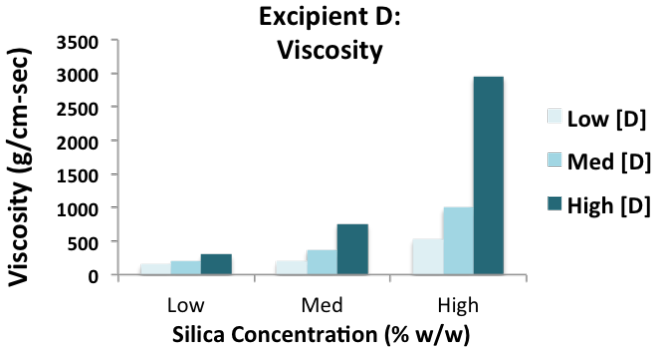


Figure 15. Viscosity measurements of Excipient D (without any added barium or iodine).

Due to the adjustments in excipient and silica concentrations for Excipient D formulations containing barium and iodine (Fig. 16), the viscosity measurements of these two batches cannot be directly compared to the viscosities of Excipient D only batch o formulations. Between barium and iodine, the barium exhibited overall higher viscosities, however, there is no clear explanation as to why this is the case. The general trend of increasing viscosity correlated with increasing excipient and silica concentrations still seen. In comparison with the Readi-Cat 2 suspension, the barium and iodine formulations containing low Excipient D concentrations exhibited the most ideal viscosities that would be appropriate for potential use as an orally administered contrast agent.

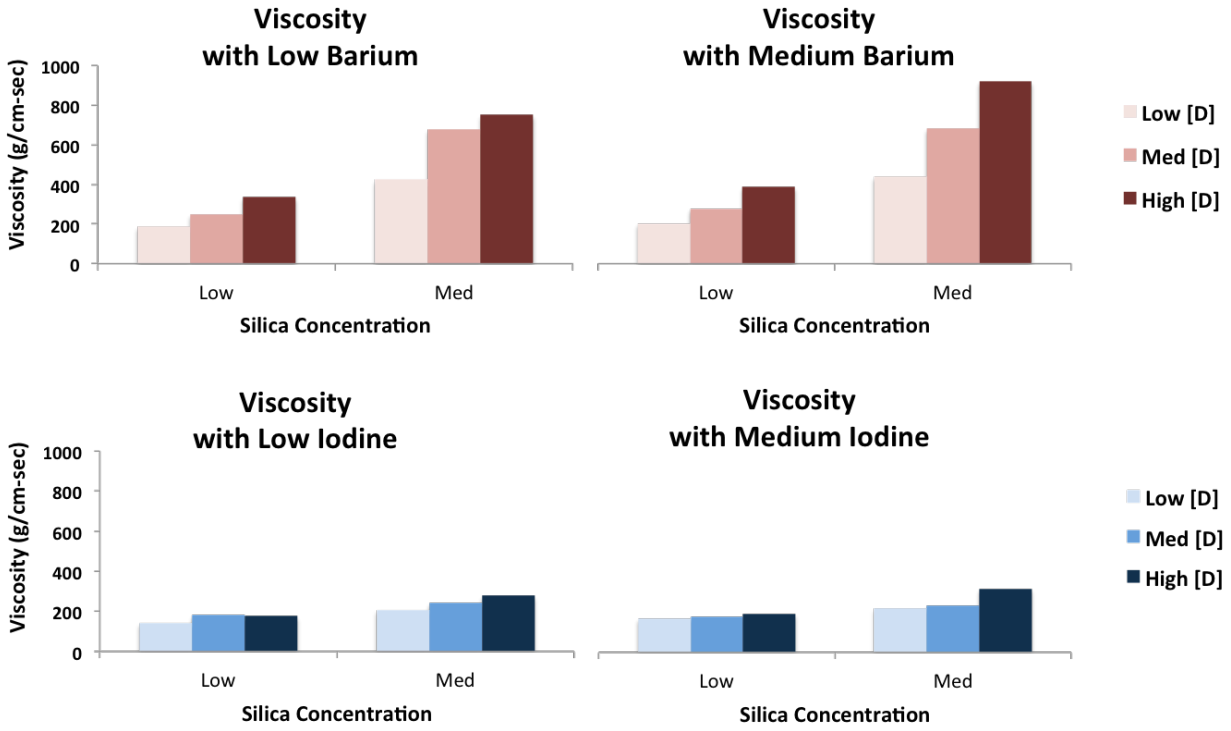


Figure 16. Top: Viscosity measurements of Excipient D with barium. Bottom: Viscosity measurements of Excipient D with iodine.

The viscosity measurements of this study are limited to relative comparisons due to unavailability of appropriate instrumentation. A digital viscometer or rheometer should be used to most accurately determine fluid viscosities as they take into account other factors such as shear stress and flow conditions.

4. CONCLUSION

A total of four pharmaceutical excipients were evaluated for the purposes of formulating viable solutions of a novel silica-based CT contrast agent for oral administration. Of the excipients tested, compounds A, B, and C were determined to be unsuitable as a suspension medium based on experiments that assessed solution stability, homogeneity, and viscosity

properties. Excipient D was the most favorable and an optimal range of concentrations was determined such that all three criteria were adequately satisfied.

Future work towards the development of this silica contrast material would involve *in vivo* pre-clinical imaging studies using animal models to evaluate toxicity and biocompatibility. Also, the capabilities of this contrast material for sufficient material decomposition when imaged with DECT should be examined in detail. Further accelerated stability testing under conditions such as UV light, varied humidity, extreme temperatures, pH, and more is needed for a more comprehensive assessment of this silica contrast material, and for effective translation towards potential clinical use. Other lesser important considerations for oral contrast agents include palatability and shelf life, and these aspects should also be addressed in future experiment.

REFERENCES

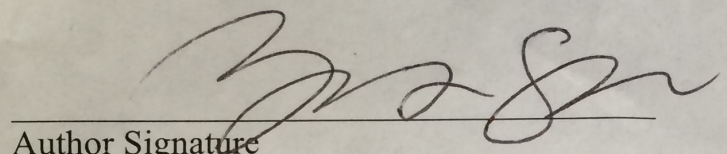
1. Fuchs VRS, H.C.Fuchs, V.R., Sox HC. Physicians' Views of the Relative Importance of Thirty Medical Innovations. Health Affairs. 2001;20:30-42.
2. Anderson NG, Butler AP, Scott NJ, et al. Spectroscopic (multi-energy) CT distinguishes iodine and barium contrast material in mice. Eur Radiol. 2010; 20(9):2126–2134.
3. Flohr TG, McCollough CH, Bruder H, et al. First performance evaluation of a du- al-source CT (DSCT) system. Eur Radiol. 2006; 16:256–268.
4. Johnson TR, Krauss B, Sedlmair M, et al. Material differentiation by dual energy CT: initial experience. Eur Radiol. 2007; 17:1510–1517.
5. Fletcher JG, Takahashi N, Hartman R, et al. Dual-energy and dual-source CT: is there a role in the abdomen and pelvis? Radiol Clin North Am. 2009; 47(1):41–57.
6. Karçaaltıncaba M, Aktaş A. Dual-energy CT revisited with multidetector CT: review of principles and clinical applications. Diagn Interv Radiol. 2011; 17(3):181-94.
7. Mongan J, Rathnayake S, Fu Y, et al. In vivo differentiation of complementary contrast media at dual-energy CT. Radiology. 2012; 265(1):267–272.
8. Mongan J, Rathnayake S, Fu Y, et al. Extravasated contrast material in penetrating abdominopelvic trauma: dual-contrast dual-energy CT for improved diagnosis—preliminary results in an animal model. Radiology. 2013; 268(3):738-742.
9. Zhang HY, Dunphy DR, Jiang XM, Meng H, Sun BB, Tarn D. et al. Processing Pathway Dependence of Amorphous Silica Nanoparticle Toxicity: Colloidal vs Pyrolytic. J Am Chem Soc. 2012;134:15790–15804.
10. Coursey CA, Nelson RC, Boll DT, et al. Dual-energy multidetector CT: How does it work, what can it tell us, and when can we use it in abdominopelvic imaging? Radiographics. 2010; 30:1037-1051.
11. United States Pharmacopeia and National Formulary (USP 37-NF 32). Rockville, MD: United States Pharmacopeia Convention; 2014.
12. Shearer S. A., Hudson J. R., Fluid Mechanics: Stokes Law and Viscosity, Measurement Laboratory Investigation No. 3, Kentucky, EGR 101.

Publishing Agreement

It is the policy of the University to encourage the distribution of all theses, dissertations, and manuscripts. Copies of all UCSF theses, dissertations, and manuscripts will be routed to the library via the Graduate Division. The library will make all theses, dissertations, and manuscripts accessible to the public and will preserve these to the best of their abilities, in perpetuity.

Please sign the following statement:

I hereby grant permission to the Graduate Division of the University of California, San Francisco to release copies of my thesis, dissertation, or manuscript to the Campus Library to provide access and preservation, in whole or in part, in perpetuity.



Author Signature

9/10/14

Date