Optimizing Acetaminophen Release Profiles from Silicas through Surface Functionalization

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Why Silicas?

- Mesoporous silicas (pores 2-50 nm) have a uniform size and morphology, and their pore structure is what is ordered. They have a silanol rich surface that allows for numerous opportunities for functionalization and are bioinert
- There have been a limited number of release studies on these materials, and have been over shorter release times, so there is an opportunity to extend those release studies longer
- SBA-15 has hexagonally ordered straight channel pores and possess micropores within the pore walls. It is a material of interest due to its high surface area, as well as this straight pore structure to allow for easy drug loading
- KCC-1 is a spherical silica with a pom-pom like appearance. It is a material of interest due to this unique morphology which can allow greater surface area access, and the potential to prevent pore blocking

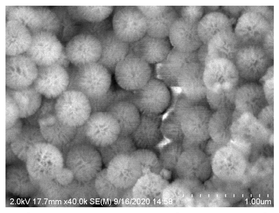

Figure 1. SEM image of KCC-1. The unique particle morphology of KCC-1 can be seen through SEM imaging.

Our Design

- Silica materials modified with various functional groups to decrease burst release percentage and increase the burst release time and controlled diffusional release percentage
- Functional groups are chosen based off their potential interactions with the target molecule, acetaminophen, to tailor the delivery vehicle and exploit the properties of the drug

Synthesis & Characterization

- Acetaminophen, a common analgesic, is an effective model drug
- 3-mercaptopropyltrimethoxysilane (MPTMS), oxidizable to sulfonic acid (SO_3H), serves as an acidic group
- Octyltrimethyloxysilane (C8) serves as a hydrophobic group

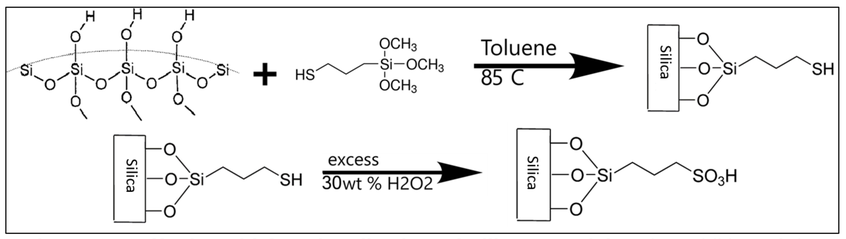

Figure 2: Sulfonic acid functionalization of silica materials. The addition of the sulfonic acid group allows for hydrogen bonding with acetaminophen, thereby providing a drug delivery vehicle tailored towards exploiting the properties of the drug for loading

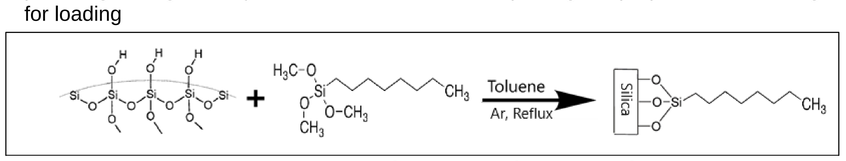

Figure 3. Organic (C8) chain functionalization of silica materials. The addition of the C8 group allows for a more hydrophobic material interaction with acetaminophen and provides a further distance for the drug from the silica material, thus allowing for less drug-silica surface interaction.

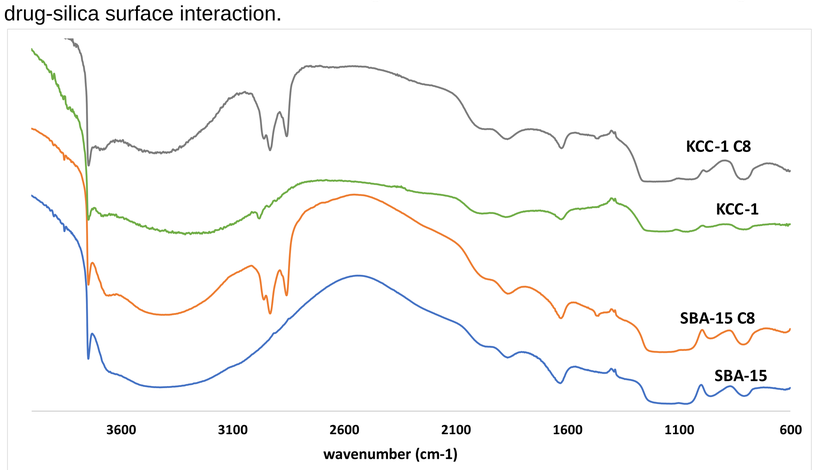

Figure 4. Fourier Transform Infrared Spectroscopy. FT-IR confirmed the functionalization of both SBA-15 and KCC-1 with C8. These CH_2 and CH_3 stretches can be seen from the peaks in the 2960-2860 cm^{-1} range

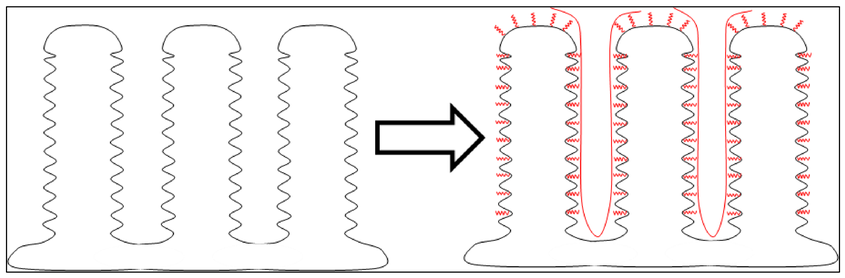

Figure 5. SBA-15 possess mesopores with micropores within the material. Through functionalization, surface area and pore volume decreases (from 985 m^2/g to 615 m^2/g and from 1.10 cc/g to 0.79 cc/g respectively) due to functional groups blocking the micropores and creating a smoother surface.

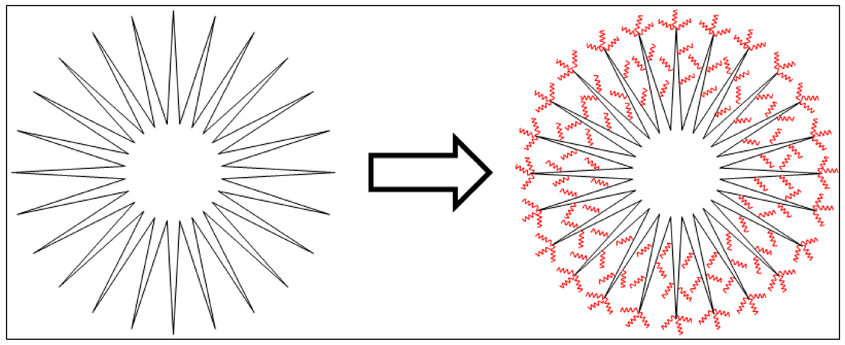

Figure 6. KCC-1 possess an open fiber pore structure. Through functionalization, surface area and pore volume increases (from 675 m^2/g to 840m^2/g and from 1.14 cc/g to 1.57 cc/g respectively) due to better access to material surface area and no pore blocking. Functional groups project out on the ends of each material fiber, allowing for overall increase in pore volume and surface area.

Based on the increase in surface area and pore volume in KCC-1 with functionalization with C8, KCC-1 was chosen as the primary silica material to use in further study.

Drug Release Modeling

Drug Loading Methods

- Direct Loading (-D) involves 200 mg of silica being stirred in acetaminophen solution for 3 days
- Incipient Wetness Impregnation (-I) involves 100 µL of acetaminophen solution being repeatedly added to 200 mg of silica and mixed until material is saturated

Release Studies

- Conducted in PBS based dissolution system, where each drug loading method was run in triplicate per release study
- Unfunctionalized materials released for a total of 24 hours (1 day) and functionalized materials released for a total of 144 hours (6 days)

Mathematical modeling of acetaminophen release from functionalized and unfunctionalized KCC-1, and the impact functionalization has on their release parameters.

$$\frac{M_t}{M_\infty} = \phi_b[1-\exp(-k_b t)] + \phi_d\left[1-\frac{32}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{q_n^2}\exp\left(-\frac{q_n^2}{R^2}D(t-t_b)\right)\sum_{p=0}^{\infty}\frac{1}{(2p+1)^2}\exp\left(\frac{(2p+1)^2\pi^2}{H^2}D(t-t_b)\right)\right]$$

Figure 7. Mathematical model used for acetaminophen release from a silica cylinder that takes into consideration two phases of release. Burst release (ϕ_b) follows a first order kinetics model and controlled diffusional release (ϕ_d) considers bulk matrix morphology and diffusivity, and assumes the drug is dispersed throughout the matrix, and the drug is rapidly dissolved upon water penetration into the matrix.

KD	k_b (min^{-1})	D (cm^2/s) (10-6)	t_b (min)	ϕ_{burst}	ϕ_{diff}	ϕ_{total}
SO_3H	0.0216	2.13	277	.9322	.0984	1.0307
C8	0.0223	1.40	268	.8437	.0433	0.8870

KI	k_b (min^{-1})	D (cm^2/s) (10-6)	t_b (min)	ϕ_{burst}	ϕ_{diff}	ϕ_{total}
SO_3H	0.0243	9.63	247	.7647	.0246	0.7893
C8	0.0234	1.83	256	.8804	.0238	0.9043

KFD	k_b (min^{-1})	D (cm^2/s) (10-6)	t_b (min)	ϕ_{burst}	ϕ_{diff}	ϕ_{total}
SO_3H	0.0180	34.9	333	.6378	.0004	0.6381
C8	0.0205	35.2	293	.7064	.0003	0.7067

KFI	k_b (min^{-1})	D (cm^2/s) (10-6)	t_b (min)	ϕ_{burst}	ϕ_{diff}	ϕ_{total}
SO_3H	0.0225	34.7	266	.7043	.0002	0.7045
C8	0.0205	12.5	293	.8238	.0028	0.8266

Figure 8. Mathematical model release parameters for acetaminophen from KCC-1. KCC-1 functionalized diffusion (KD) and incipient wetness (KI) show higher percent burst release (ϕ_{burst}) and diffusional release (ϕ_{diff}) than their unfunctionalized counterparts for both SO_3H and C8 functionalization.

KCC-1 unfunctionalized diffusion (KFD) and incipient wetness (KFI) display very little diffusional release, indicating that burst release is the primary force without any functional groups and there are little to no surface interactions with the silica material to control longer term release.

Acetaminophen release studies with mathematical model curves fit to experimental data

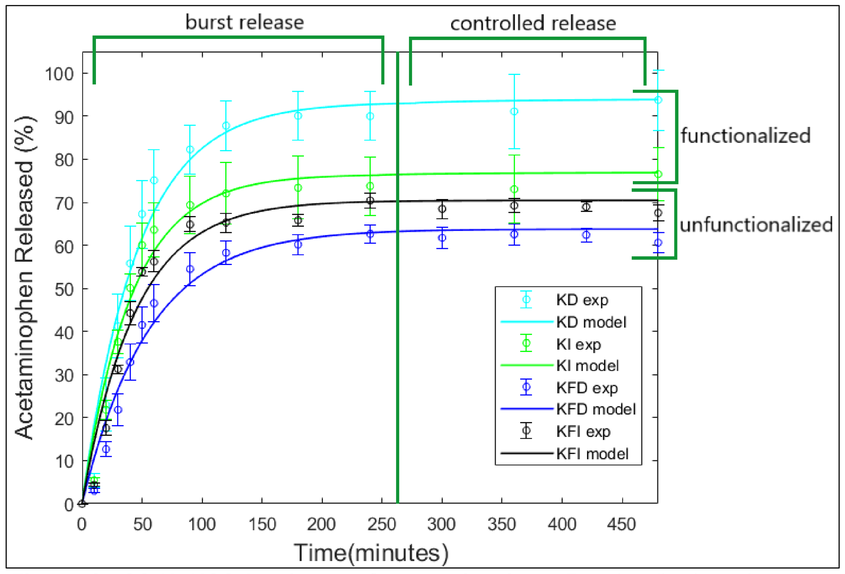

Figure 9. SO_3H KCC-1 release of acetaminophen. Functionalization shows an increase in percent drug released compared to unfunctionalized materials, due to the presence of SO_3H preventing the drug from sticking to the silica. Direct loading also shows the greatest improvement in release due to functionalization (from KFD to KD), indicating that loading method helps improve accessibility to all drug. (n=6, functionalized; n=3, unfunctionalized)

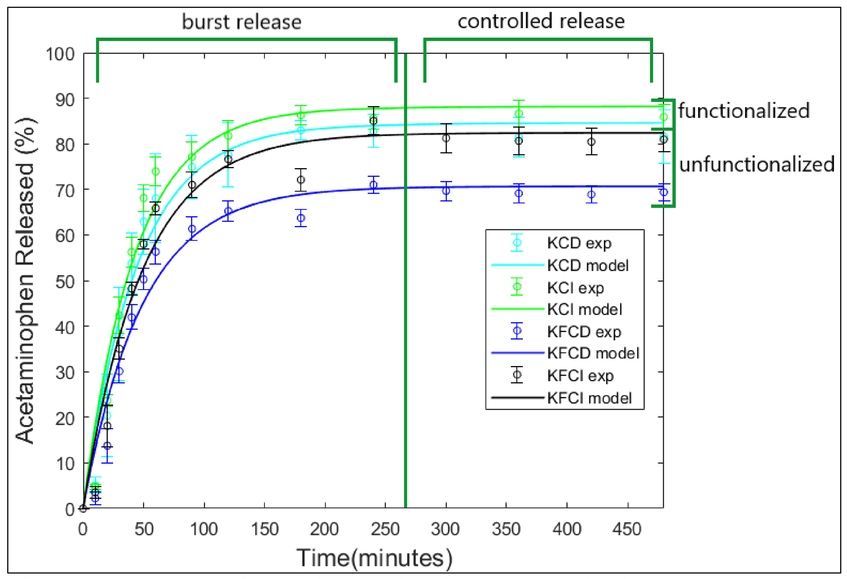

Figure 10. KCC-1 C8 release of acetaminophen. Functionalization shows an increase in percent drug released compared to unfunctionalized materials, due to the presence of C8 preventing the drug from sticking to the silica. Direct loading again shows the greatest improvement in percent release due to functionalization (from KFD to KD), indicating the loading method helps improve accessibility to the drug. (n=3)

Conclusions and Future Work

- The addition of functional groups such as C8 and SO_3H to KCC-1 does not slow down burst release rate, nor does it have a significant impact on controlled diffusional release.
- The addition of functional groups does decrease the loss of drug in the matrix, as there is an increase in total percent of drug released from the system
- Direct loading of acetaminophen shows the greatest improvement in drug release due to functionalization, so only this loading method will be studied going forward
- Additional functional groups will be explored to see their impact on release, such as [Hydroxy(polyethyleneoxy)propyl] triethoxysilane, a short chain PEG functionalized silica

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