Enhancing Metal Ion Scavenger Delivery Using Porous Materials

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I. Introduction

The amyloid beta (Aβ) hypothesis associates Alzheimer's Disease (AD) with Aβ aggregation in the brain. Metal ions, such as copper, iron, and zinc, are believed to induce this aggregation and form neurotoxic reactive oxygen species (ROS). As a result, metal chelation therapy has been extensively studied as a treatment option for AD. These possible therapeutic drugs, the metal chelators, would still require efficient delivery systems that can cross the blood-brain barrier and release the drugs appropriately.

To release drugs appropriately means to release them in a slow and steady manner shown in Figure 1 with the sustained release curve as opposed to the conventional profile observed in most of the common drugs. The conventional profile shows a large burst effect immediately after intake which leads to the side effects observed when the concentration is above the ideal therapeutic range. With sustained release, the burst effect is minimized and release is prolonged keeping the concentration in the ideal range.

In order to achieve this sustained release, mesoporous silica ($pSiO_2$) was used as the carrier agent to the brain. Mesoporous silica particles, shown in Figure 2, are nanoscale particles that ideally (if small enough) allow them to cross the blood brain barrier. Their pores are loaded with the chelating agents to be released in the brain.

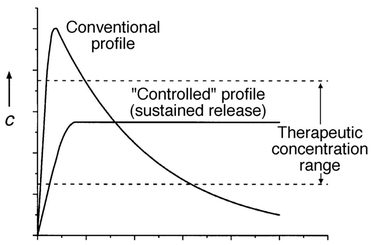


Figure 1. Comparison between a conventional release profile and a controlled release profile.

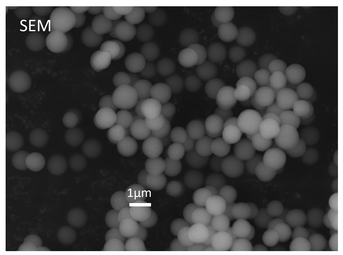
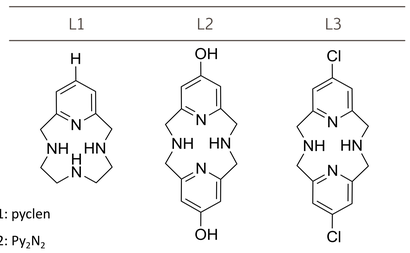


Figure 2. SEM image of 1µm mesoporous silica used as the delivery system.

The candidates for chelating agents tested were systematically chosen to demonstrate different structural characteristics. This would allow the study of the effects of intermolecular interactions on the release profiles. The three agents used are shown in Figure 3. Pyclen, referred to as L1, and its derivatives, L2 and L3, are strong antioxidative agents. After pyclen was tested as the basis, the dimeric OH-substituted L2 molecule was chosen to test whether the larger size would decrease the speed of release because the molecules would be more likely to get stuck in the pores of the silica particles. The OH group would also allow for some hydrogen bonding with the silica further decreasing the rate of release. The Cl-substituted dimer, L3, was then used to test the effects of having a negative charge in the molecule.

All experiments were done in environments that mimicked that of the human body. The temperature was kept at 37 °C and the pH level was controlled by using HEPES buffer at physiological pH 7.4. The structure of HEPES is shown in Figure 4.



L1: pyclen

L2: Py_2N_2

L3: $^{Cl}Py_2N_2$

Figure 3. The structures of L1, L2, and L3 chelating agents.

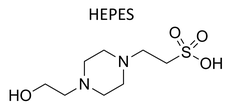
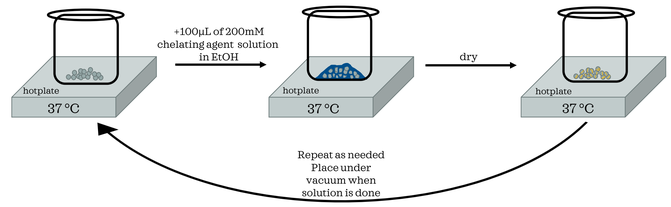


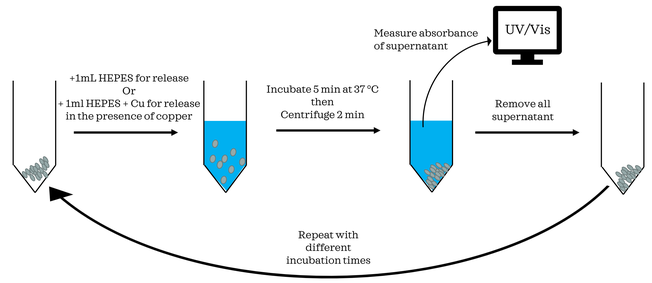
Figure 4. The structure of HEPES, the physiological buffer.

II. Experimental

A. *Incipient Loading of Pyclen Derivatives into Porous Silica*

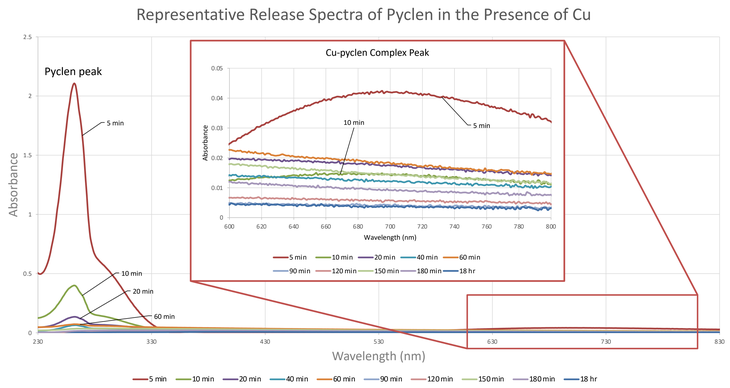


B. *Release into HEPES Buffer and HEPES + Cu(II)*



- The release is done in both HEPES buffer with and without the presence of Cu(II) ions to test whether complex ion formation affects the rate of release.
- A Cu-containing complex ion peak could provide a second source for monitoring the release over time

III. Results



- The pyclen peak at 260nm is the result of the π -> π* transition in the pyridine ring.
- The Cu-pyclen peak at 700 nm is the result of d-d transitions which intrinsically have a much lower intensity than the pyclen peak transition.
- Since the small Cu-pyclen complex peak was overridden with noise, only the pyclen peak was used to plot the release profiles.

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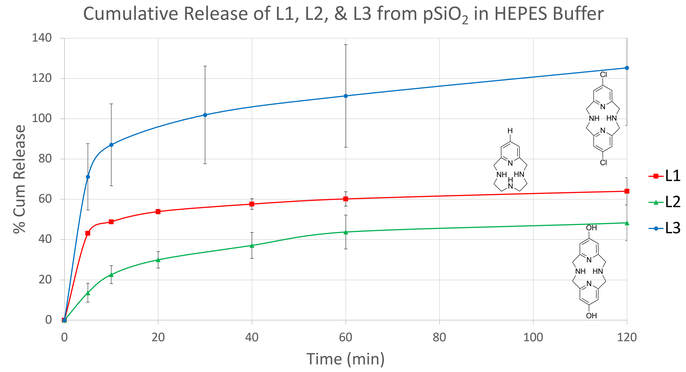
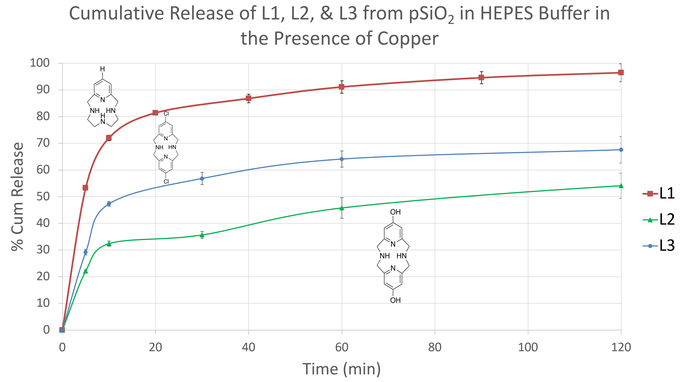
III. Results cont.



- Pyclen, L1, showed a high burst effect relative to its maximum release.
- L2 showed a much slower initial release rate and continued to release steadily over time.
- The maximum loading is difficult to measure since mesoporous silica entraps the loading solvent, EtOH. This results in measurements above 100% release. The curves should be analyzed relative to their individual maximum values comparing their relative speeds of reaching that value.
- L3 showed a relative release rate slower than that of L1 but faster than that of L2.



- The release profiles of both the dimer forms, L2 and L3, showed a slower rate than that of the monomer, L1.
- The release profile of L2 might be artificially slightly slower than the true value because of some precipitates forming when complexed with Cu at physiological pH.

IV. Conclusions

- Larger chelating molecules show a slower rate of release from porous silica.
- The molecule capable of hydrogen bonding showed the slowest release when studied in the absence of copper.
- Ways to accurately measure maximum loading are still under investigation.

V. Future Work

- Continue comparing the release profiles of different chelating agents with various structural differences from porous .
- A trimer form is being synthesized that could be used to further this investigation.
- Perform a soluble protein assay with amyloid beta comparing the effectiveness of the different chelating agents.

VI. References

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