The Ability of Molecularly Imprinted Hydrogels for Drug Reabsorption

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Abstract

Ibuprofen is a nonsteroidal anti-inflammatory drug that is used for many health conditions but causes gastrointestinal damage that could be mitigated by an alternative method of drug delivery. A delivery device can be made from hydrogels, which are biocompatible[8] and can be made to have a specific stimuli-response[9] utilized through molecular printing. This study tested the ability of hydrogels to reabsorb drug after molecular imprinting based on the molecular size of the drug using ATR FT-IR on the samples. The FT-IR spectrums obtained of the samples showed that no drugs were reabsorbed. There had been an error made in the hydrogel rinsing process, deionized water was used instead of distilled, so a conclusion of the ability of hydrogels in drug reabsorption could not be reached.

Introduction

Ibuprofen has been used as a convenient over-the-counter drug in the United States since 1974 and is prescribed by many physicians for rheumatoid arthritis, osteoarthritis, gout, and Barter's syndrome; as well as proving to be an effective analgesic for dysmenorrhea, postpartum pain, and dental extraction.[1, 2] Ibuprofen works by effecting prostaglandins, kinin, and histamine without effecting the production of corticosteroids giving it the classification of a nonsteroidal anti-inflammatory drug (NSAID). [1, 2] The time sensitive action of ibuprofen on prostaglandins is related to pharmacokinetics instead of, such as in the case of aspirin, the replacement rate of enzymes.[1]

The pain relief options of NSAIDs are advantageous for long-term pain because the drugs aren't addictive; the main hindrance of using NSAIDs is that the drugs cause gastrointestinal

damage, leading to damage to the duodenal, gastritis, and ulcers.[3,3] Out of all the other used NSAIDs, aspirin, naproxen, etc., Ibuprofen causes the least amount of gastrointestinal damage.[4] The wide spread use of Ibuprofen along with other attributes of the drug, such as time optimal dosing[1, 2], would make it an ideal candidate for a new drug delivery device. Hydrogels can potentially be used as an alternative delivery option to mitigate the upper gastrointestinal damage done by Ibuprofen because they can be designed for specific uses and dosing,[5,6] like a polymer film that becomes buoyant in the stomach for slow release medication, [7] polymer systems have already been used in treatments for antineoplastic activity, bacterial infections and inflammatory processes.[5] Hydrogels are biocompatible[8] and can be made to have a specific stimuli-response[9], like to pH or the presence of a certain chemical[10], to alter the structure and prompt drug release.[11] Molecular imprinting hydrogels creates spots in the polymer matrix for drug molecules, like a template, and allows more selective binding.[12] The monomer 2-hydroxyethyl methacrylate (HEMA) is especially apt for molecular imprinting, [13] biocompatibility, and physiochemical compatibility when polymerized [8,12] and will act as a backbone monomer for this study.

This study will be looking at the ability, based on the molecular size of ibuprofen (206.28 g/mol), of a hydrogel to reabsorb a drug into the template net of the created polymer. To test whether the drug is reabsorbed into the matrix[14] the samples will be tested with ATR (Attenuated Total Reflectance) FT-IR. As points of comparison the experiment will be repeated with Leucine, of a smaller molecular size (131.17 g/mol), and tetrahydrozoline HCl, of a larger molecular size (236.74 g/mol). As another point of data each drug will be tested at two different concentrations.

Materials and Methods

All chemicals were used as received from Sigma Aldrich. For the polymer: 2-hydroxyethyl methacrylate (HEMA) was used as the backbone monomer, 2-(dimethylamino)ethyl methacrylate (DMA) acted as a pH reactant, tetraethylene glycol dimethacrylate (TEGDMA) was used for crosslinking, 2,2-Dimethoxy-2-phenylacetophenone (DMPAP) acted as a photo initiator, and ethylene glycol acted as a solvent.[15]

Ibuprofen 1	molar ratio	mole percent
Ibuprofen	0.006	0.6
HEMA (back-bone)	0.868	86.8
2,2-Dimethoxy-2-phenylacetophenone	0.001	0.1
TEGDMA (cross linker)	0.009	0.9
ethylene glycol	0.099	9.9
2-(dimethylamino)ethyl methacrylate	0.016	1.6

Ibuprofen 2	molar ratio	mole percent
Ibuprofen	0.003	0.3
HEMA (back-bone)	0.870	87.0
2,2-Dimethoxy-2-phenylacetophenone	0.001	0.1
TEGDMA (cross linker)	0.009	0.9
ethylene glycol	0.100	10.0
2-(dimethylamino)ethyl methacrylate	0.016	1.6

Leucine 1	molar ratio	mole percent
leucine	0.009	0.9
HEMA (back-bone)	0.865	86.5
2,2-Dimethoxy-2-phenylacetophenone	0.001	0.1
TEGDMA (cross linker)	0.009	0.9
ethylene glycol	0.099	9.9
2-(dimethylamino)ethyl methacrylate	0.016	1.6

Leucine 2	molar ratio	mole percent
leucine	0.005	0.5
HEMA (back-bone)	0.869	86.9
2,2-Dimethoxy-2-phenylacetophenone	0.001	0.1
TEGDMA (cross linker)	0.009	0.9
ethylene glycol	0.099	9.9
2-(dimethylamino)ethyl methacrylate	0.016	1.6

tetrahydrozoline HCl 1	molar ratio	mole percent
tetrahydrozoline HCl	0.005	0.5
HEMA (back-bone)	0.868	86.8
2,2-Dimethoxy-2-phenylacetophenone	0.001	0.1
TEGDMA (cross linker)	0.009	0.9
ethylene glycol	0.099	9.9
2-(dimethylamino)ethyl methacrylate	0.016	1.6

tetrahydrozoline HCl 2	molar ratio	mole percent
tetrahydrozoline HCl	0.003	0.3
HEMA (back-bone)	0.871	87.1
2,2-Dimethoxy-2-phenylacetophenone	0.001	0.1
TEGDMA (cross linker)	0.009	0.9
ethylene glycol	0.100	10.0
2-(dimethylamino)ethyl methacrylate	0.017	1.7

Each sample was measured with the amounts listed in the tables using a micropipette and mixed in separate containers before being agitated for 20 seconds on a vortex at half speed. The samples were then left to cool in a refrigerator at 4 °C for 20 minutes to encourage hydrogen bonding. At the end of the 20 minutes each sample was poured individually into a silicone mold (Figure 1) and cured with ultraviolet light via free radical polymerization for two minutes. The samples were then left soaking separately in de-ionized water for two days to

Figure 1: Silicone mold used to shape the hydrogel while curing with UV light.

remove the drugs from the newly formed polymers. After two days, a Control and Tetrahydrozoline HCL sample were tested using FT-IR to confirm that the drug had left the matrix when using deionized water to soak.

To reintroduce the drug to the polymer matrix the samples were “re-doped” for five minutes with 200 µL of the same higher concentration, a solution of 500 µL of .1% molarity NaOH to 20 mg of drug, for both samples of each drug category before being pat dry and set aside for FT-IR testing. Each sample was tested using a Varian 3100 (Excalibur series) ATR FT-IR to test if the drugs were successfully reabsorbed into the polymer matrix.

Results

Figure 2: Hydrogels after soaking in deionized water are rigid and different sizes

Visual examination after the two days soak in deionized water revealed the hydrogels to have shrunk, become rigid, and un-uniformly sized, shown in Figure 2. An ATR FT-IR was done on a control and a tetrahydrozoline HCL sample to ensure that the correct process was used and that the drug

had left the polymer, this is shown in figure 3, the peaks match up enough that it was determined that the drug was absent from the polymer.

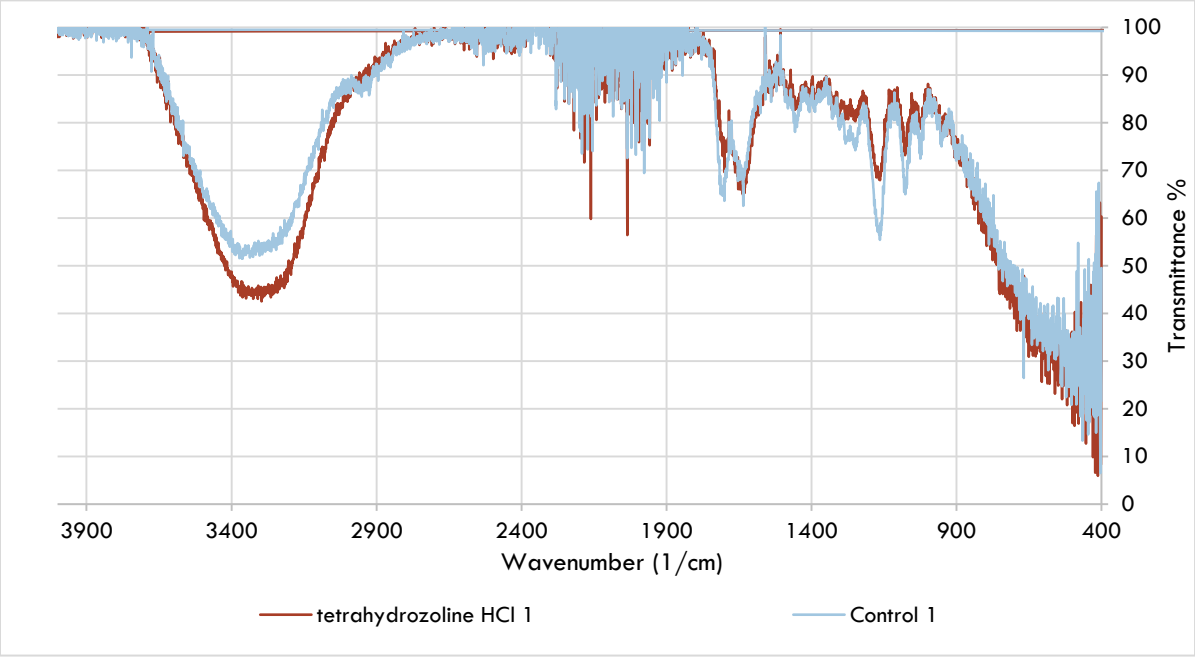

Figure 3: Testing a control and tetrahydrozoline HCL sample after rinse to check that the drug was dispersed. The peaks match indicating no drug.

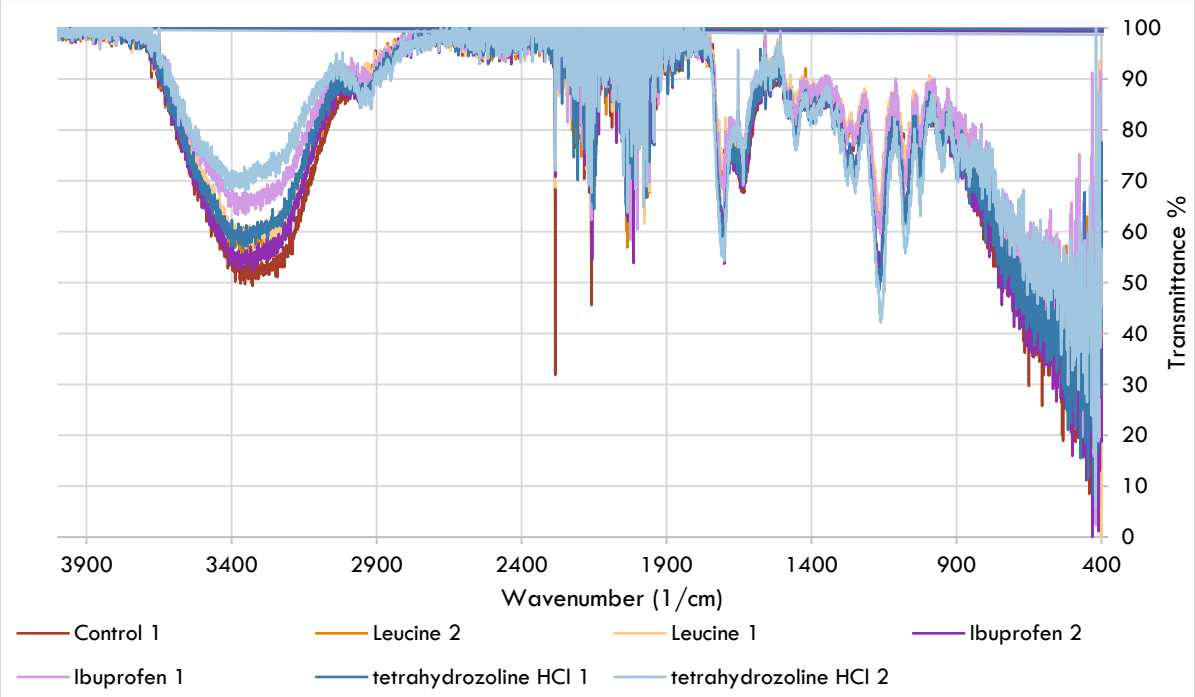

Figure 4: All the FT-IR spectrums for the samples have very similar peaks to the Control.

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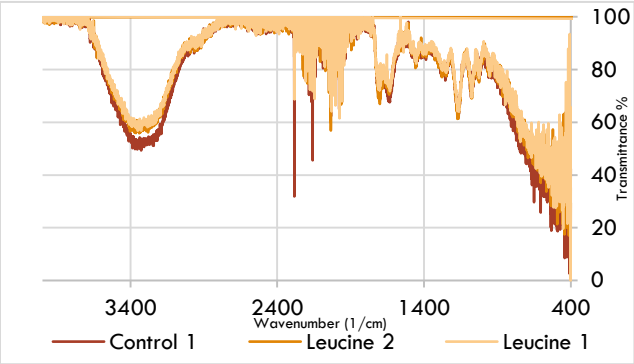

Figure 5: Leucine samples match Control.

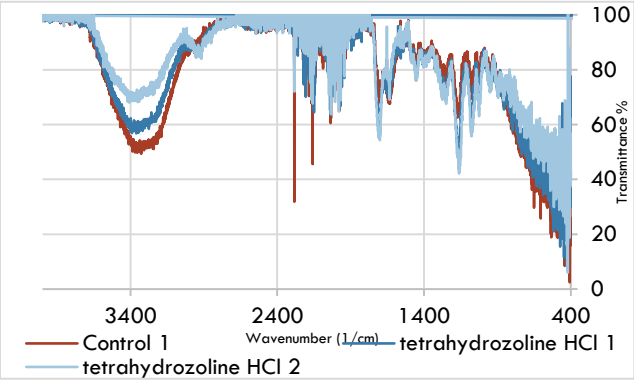

Figure 6: No expected absorption at 3500 cm^{-1} to indicate amines in the tetrahydrozoline HCL sample

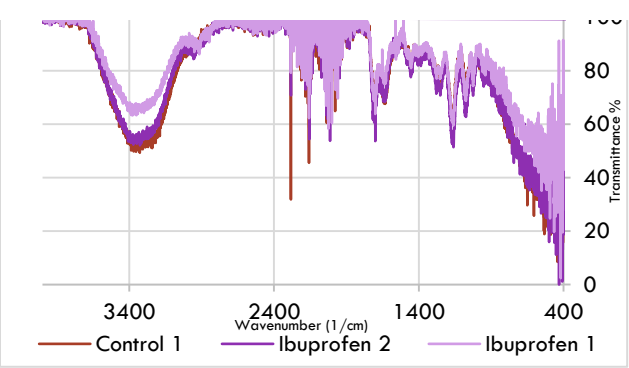

Figure 7: No indication of the drug ibuprofen.

When overlaid the FT-IR spectrums for all the samples are similar, see Figure 4, but when broken down slight differences from the control can be seen. The Control is the only sample that has an abnormal absorption at 2283 cm^{-1}, also on the Control is a broad -OH stretch from 3500-3200 cm^{-1}, this with a corresponding peak at 1700 cm^{-1}, a sign of C=O a carbonyl, would indicate the presence of carboxylic acids. The control also has absorption peaks at 1162 cm^{-1} an indication of an ester C-O, a peak at 1634 cm^{-1} could indicate C=C, and a sharp peak at 2158 that could be C≡C. The Leucine samples match the control, shown in Figure 5, except for the abnormal absorption that was on the Control at 2283 cm^{-1}. The Ibuprofen and Tetrahydrozoline HCL samples match the Control sample for the most part, other for the abnormal absorption that was on the Control at 2283 cm^{-1}, except they show a slight bump from 3000-2900 cm^{-1} which could indicate C-H alkyl groups. Importantly the

Tetrahydrozoline HCL samples, as seen in Figure 6, are absent of any indication of amines in the 3500 cm^{-1} area which was expected for that drug.

Discussion

The FT-IR provided valuable if somewhat disappointing insights for this project. When looking at the results of the attempt to "re-dope" the hydrogels, the missing amine spike in the Tetrahydrozoline HCL samples, Figure 6, is the most telling because that was an expected peak for that drug. The missing amine added with how similar the spectrums all look to the Control, although the Ibuprofen and Tetrahydrozoline HCL samples were slightly different in the 3000-2900 cm^{-1} area, the results of the FT-IR indicate that none of the drug samples were reabsorbed into the hydrogels. When we break down this experiment to clarify the results, whether these results are from error or that these certain drugs cannot be used in molecular imprinting, there are certain very specific points in which this experiment veered away from published literature.

We didn't use the exact measured amounts of monomer as previous studies, but the ratios[15] seemed to have been similar enough not to have caused the hydrogels to be defective. The hydrogels in this experiment were much thicker and used much less solvent, ethylene glycol, than any of the literature reviewed[15, 13,12] but that should have still allowed for reabsorption in at least the surface of the samples. During the process of "re-doping" a base and high concentration of drug was used, 500 µL of .1% molarity NaOH to 20 mg of drug, to ensure successful swelling since the visual inspection after soaking in the deionized water was worrisome because they were supposed to swell in that process, not shrink. This step was not one that was guided by previous literature.

Which leads to one of the bigger overlooked problems, there was a misunderstanding of whether deionized water was supposed to be used to rinse and store the hydrogels or distilled. Upon further review the hydrogels were supposed to be rinsed and stored in distilled water.[15] Distilled water has ions in it which would have stimulated the hydrogel to swell and empty itself of drug. Storing the hydrogel in deionized water seemed to have altered the ability of the hydrogel to respond to stimulus.

The result is believed to be that the hydrogels did not reabsorb the drug at all because the deionized water altered the ability to do so and not that any of the drugs used were incompatible with the "re-doping" process. Were this experiment to be repeated the clarification of using distilled water is one of import.

Conclusion

Ibuprofen is a nonsteroidal anti-inflammatory drug that is used for many health conditions but causes gastrointestinal damage. Those who rely on taking Ibuprofen daily for chronic health conditions would benefit from an alternative method of drug delivery to mitigate that damage. Hydrogels are biocompatible[8] and can be made to have a specific stimuli-response[9] that can be utilized through molecular printing; making it a good candidate for such a device. This study was testing the ability for hydrogels to reabsorb drug after molecular imprinting based on the molecular size of the drug and used two other drugs with different molecular sizes for a comparison.

In conclusion, based on FT-IR results showing little to no difference from the control to the "re-doped" hydrogels, we could not determine the ability of hydrogels to reabsorb the drug after molecular imprinting because of an error in our lab work. It was deduced that distilled

water should be used in this process instead of deionized water. Ibuprofen could still utilize a hydrogel delivery device, but this study would have to be altered and repeated to answer the question of the ability of the hydrogel to "re-doped" with Ibuprofen.

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