A Sustainable Transdermal Alternative to Oral Medications for Iron Deficiency

Anushka Mistry

Abstract:

Anemia, characterized by a deficiency in red blood cells or hemoglobin, poses significant health challenges globally. Traditional solutions, such as iron pills, face limitations in accessibility, side effects, and environmental impact. This research explores an alternative treatment: a sustainable hydrogel patch for transdermal iron delivery. The study compares two patch versions that I engineered, differing in iron concentration, through an iron release experiment. Surprisingly, the patch with double the iron content released less iron than the patch with the standard amount of iron, indicating potential solubility and material interaction complexities at higher concentrations. Therefore, the first version of the patch with the standard amount of iron concentration was more effective and could be used as a sustainable and effective solution for infants and children with anemia. Future research could explore how varied patch characteristics may impact the iron release. Overall, the current hydrogel patch I created is a promising, environmentally sustainable solution for anemia, laying the groundwork for further innovation in transdermal iron delivery methods.

Introduction:

Anemia is a medical condition characterized by a deficiency in the number of red blood cells, or a decreased amount of hemoglobin in the blood. Hemoglobin is a protein found in red blood cells that carries oxygen from the lungs to the rest of the body's tissues. Therefore, anemia leads to a reduced ability of the blood to carry oxygen effectively, resulting in various symptoms and health complications. Symptoms of anemia may include fatigue, weakness, shortness of breath, dizziness, pale skin, and an increased heart rate. The severity of symptoms can vary depending on the type and underlying cause of anemia. Iron is a treatment for anemia as it helps produce red blood cells. According to the American Society of Hematology, anemia affects over 3 million Americans (*Anemia,* 2021). Additionally, anemia is more prevalent in some areas of the world, especially in low- and middle-income countries, where access to adequate nutrition, healthcare, and preventive measures may be limited. There are various types of anemia, but according to the National Institutes of Health, the most common types include iron deficiency, pernicious, aplastic, and hemolytic anemia (*In brief: Your guide to anemia*, 2011). These various types of anemia can be linked to a wide variety of conditions and diseases.

Traditional Solution to Anemia and Its Drawbacks:

Today, the most common treatment of iron-deficiency anemia is through an iron pill. However, taking a pill isn't feasible for everyone due to various reasons, such as patient compliance, accessibility, and the side effects of these pills. Additionally, anemia is more prevalent in some areas of the world, specifically in low- and middle-income countries, where access to adequate nutrition, healthcare, and preventive measures may be limited, and pills may be less accessible to these populations as well (Brody, 2017). In addition to accessibility factors, iron pills have numerous side effects: nausea, fatigue, headaches, stomach pain, and a metallic taste in the mouth. In addition, iron pills generally can degrade in the intestinal tract and must be taken frequently. As a result, some patients may not take the pills regularly due to the

side effects or simply because they do not like taking oral tablets. Even if a patient intends to take their pills, patient error is a concern as a patient may still forget to take them consistently, which may hinder the treatment of their anemia. Additionally, the iron pill is not a viable solution for all ages. According to Johns Hopkins Medicine, children under the age of four cannot safely swallow pills because of the choking hazards associated. Therefore, children with anemia cannot take an iron pill as a solution (*Teaching your child how to swallow a pill,* 2023). However, according to the Boston Children's Hospital, anemia is a common health problem in children, including those under the age of four (Moscheo et al, 2022).

Environmental Impacts of Iron Pills:

Besides the health implications associated with the iron pill, there are also negative environmental impacts to medical solutions like pills. For example, Harvard Medical School found that chemicals from prescription drugs and other medications pollute water sources such as rivers, lakes, and streams. The chemicals contaminate the water and create negative impacts to aquatic life and cause harm to humans. One study done by the U.S Geological Survey found measurable amounts of chemicals from medications in 80% of the water samples drawn from a network of 139 streams in 30 states. Therefore, the iron pill solution to anemia can lead to iron in water sources, which causes negative impacts to the environment long-term (*Drugs in the Water,* 2011). Additionally, iron contamination in water sources is problematic because it can promote the growth of bacteria, such as *E. coli* (*Effects of Iron in Water,* 2023). Additionally, pathogenic bacteria can grow on small particles of iron like those in iron pills, and when ingested by humans can cause illness. Another danger of iron in humans is iron poisoning, which is when iron levels are too high, and can cause damage to internal organs (Edwards, 2023).

Science Behind the Distribution of Iron in Bloodstream:

Drugs don’t accumulate in the human body. This is because the human body is using, absorbing, and displacing that drug over a day, meaning that the drug won’t accumulate in the body. This is also known as ADME, which stands for absorption, distribution, metabolism, and excretion. In other words, the body absorbs the consumed drug, distributes it throughout the body, metabolizes it, then the remains of the drug get excreted. Every drug breaks down in different amounts of time, but generally, the method for the human body breaking down drugs is consistent. One of these delivery systems includes transdermal drug delivery, which uses adhesive patches to deliver drugs through the skin continuously over some time. Other transdermal delivery methods include topical gels and creams.

Another important concept for drug delivery is drug release. The drug release rate refers to how quickly or slowly a drug is released from its original form (i.e., tablet, capsule, patch) into the body. Some types of drug release rates include zero-order release, first-order release, and delayed release.

Zero-order release is a completely linear release. A first-order release is non-linear, such that the system is faster in the beginning but slows down as fewer and fewer drugs are in the system. A delayed release is when the release of the drug is slowed or delayed at the beginning of the system and then over time will release more of the drug into the system. Transdermal delivery methods can be any of these releases. The type of drug release rate determines how the drug, which in this paper is iron, is administered into the human body.

Alternatives to the Iron Pill:

While oral drug delivery is a traditional delivery system, other anemia solutions have advantages. One of these additional anemia solutions outside the traditional iron pill is transdermal delivery methods which is done through a patch. A current alternative to the iron pill for anemia is adhesive patches, which have been shown to be effective and avoid many of the drawbacks of the iron pill. However, the adhesive patch is not environmentally sustainable (*Testimonials - Patchmd, 2023*).

Research Goals:

The goal of this research project was to engineer an alternative method for iron delivery for anemia that is more environmentally sustainable than the iron pill. To do this I created a hydrogel delivery system that delivers the same amount of iron with a patch as you would get within one week of taking iron pills. Additionally, the hydrogel iron patch I created is also novel because it is environmentally sustainable, which other alternatives, such as the iron pill are not. For example, the hydrogel iron patch created in this research project is biodegradable and the hydrogel iron solution is contained in a cotton sleeve, which is waterproof and contains the iron, so it does not seep into water sources; therefore not polluting the water like the iron pills may. I hypothesize that **the sustainable gelatin hydrogel patch loaded with iron that I created will deliver iron at the same dose and concentration as a weeklong oral regime, therefore being equally as effective.**

I formulated a rough draft diagram of how the patch would look with the different components of a patch, shown in Figure 1.

Materials and Methods:

In my experiment, certain materials were required to form a hydrogel patch that would be used to administer the iron through transdermal delivery. Included in these materials were gelatin powder, a kitchen scale, iron powder, glass beakers, and freestyle adhesive patches. I was able to retrieve all of these items from Amazon. I also constructed the molds in which the hydrogels were stored out of aluminum foil, but any mold would be sufficient in the process of creating a hydrogel. While the adhesive patches (also denoted as the sleeves) are not entirely necessary for this experiment, it was beneficial for figuring out the dimensions of my hydrogel.

In order to know how much of each material to put into my hydrogel, I first identified how much iron an anemic person needs daily, and I found that for the correction of anemia 200 mg were needed, not considering the average absorption. I determined that I would need to use 1.8 g of iron powder for 40 mL of water and 9.9 g of gelatin powder. These ingredients are what founded my hydrogel. For the molds, I measured the diameter of a round bottle cap and I molded aluminum foil to the cap multiple times in order to make a circular mold.

For the construction of this project, I started by weighing out the iron and gelatin. Then I measured 40 mL of hot water and put it into the beaker, where I dissolved my gelatin powder into the water until it was completely dissolved. After the gelatin was dissolved, I went on to mix the iron powder into the gelatin mixture. I stirred the iron into the gelatin for 10 minutes. I then poured them into the premade molds, tapped them against the surface to remove any bubbles, and refrigerated them overnight. I then took the molds out and trimmed all the gels to make sure

they were all uniform in size. I put them in an airtight container to store before starting my control release study.

When looking at the iron release experiment, the materials needed were the iron-loaded hydrogel, non-iron-loaded hydrogel, water, an adhesive patch, and a container to submerge the hydrogel in. The hydrogels without iron act as a control to ensure that nothing could alter the results or mess with the data collected. I did this twice as I wanted to create two different measures of iron to test. On the second version (referred to as iron patch 2x) of my patch, I doubled the amount of iron added to determine if doubling the iron would result in more iron released. The hydrogel with double the amount of iron will be referred to as “iron patch 2x”, while the first version of the hydrogel is referred to as “iron patch 1x”.

For the experiment, the additional materials needed are an iron detector (in this case a Hanna Detector), Hanna Instruments Reagents, a vial, the iron-loaded hydrogel, the control non-loaded hydrogel, and water. To prepare the system, I put each of the hydrogels in a small tub and filled it with 50 mL of water. I then labeled the tops of all the tubs with their trial number and if they were iron loaded or not. This experiment went on over the course of 7 days. I collected the water every other day (on days 1, 3, 5, and 7), the water collected was stored in a tub labeled with the day it was collected, if it was iron-loaded, and the trial it belonged to. The measurement of the iron in each water involved emptying the water into the vial, then dissolving the reagent into the vial and mixing the two together. I then opened the Hanna Detector and placed the vial into the detector and I recorded the measurement into a Google spreadsheet. I repeated the measuring process for all of the trials including the controls in order to ensure that the experiment was not compromised. The measurements from the detector were originally in parts per million (PPM), so I converted them into mg to find the total amount of iron.

Results:

Data Collection:

The process of compiling my data involved the creation of a spreadsheet chart with the timepoints, PPM initial measurement of iron, and the total amount of iron in mg. The initial measurement of iron came from the Hanna Detector, and I directly put it into the table. I did this for both versions of the patch. With this data, I calculated the average amount of iron accumulated per day, using all three trials, and the standard deviation. Standard deviation is a measurement that says how dispersed the values in a set of data are from the average of the data.

If the standard deviation is low, that means that the data are closer to the average. If the standard deviation is high, then the data points are more spread out from the average. The standard deviation provides a sense of the typical distance between the data points and the average, which reflects the consistency and variability in a data set. The p-value, which is a statistical measure that helps determine if the observed results are due to chance or if they represent a significant effect. The p-value is often accompanied by stars which corresponds to the level of significance. No stars or 1 star (*) means that the p-value is greater than 0.01 but less than 0.05 ($0.05>p>0.01$), and 2 stars (**) means that the p-value is greater than 0.01 but less than 0.001 ($0.01<p<0.001$). Three stars (***) means that the p-value is less than 0.001 ($p < 0.001$). The purpose of the stars is to provide a quick visual indicator of statistical significance. In summary, the more stars, the lower the p-value, which is typically more favorable. Having

fewer stars associated with a p-value isn't necessarily negative. It is essential to consider the scientific relevance of the findings rather than just focusing on the number of stars, it is common for a result with fewer stars to contribute valuable information, especially in exploratory or preliminary studies like this one.

Deciphering Data:

After gathering and compiling my data, I analyzed the data. I graphed the data points to illustrate the release rates of both patches I created, version 2—with double the iron content—and version 1, compared to the control. The graph below, *Figure 5,* illustrates the cumulative iron released over the days. The graph shows the control, version 1 of the patch, and version 2 of the patch. Also on the graph is the p-value shown through stars and standard deviation.

When comparing the data table from the first version of the patch and the second version of the patch as seen in *Figure 5*, it is evident that iron patch version 2, the one with double the amount of iron, released significantly less iron than version 1.

Discussion:

I examined the results of the amount of iron released, and compared this to medical literature from the Mayo Clinic (*Is Your Child Low on Iron? Prevention Tips for Parents*, 2023). I found the iron hydrogel patch I created in version 1 could be sufficient for an infant or child. However, an adult would require more iron. Therefore, I decided to create the additional second patch, version 2, with double the amount of iron to study if doubling the iron added would double the iron released.

Efficiency of Version 2 of the Hydrogel Patch:

Suprisingly, version 2 released less iron than the first, despite the higher dosage of iron in it. The reason the second hydrogel patch did not release the iron properly may be attributed to a few factors: iron concentration, geometry, material, or density. One theory is that not all of the added iron was solubilized and was unable to solubulize. Therefore, it is likely that there is a certain limit on the amount that can be released from the system. Another possibility is the material, for instance, the gelatin may have internalized large amounts of iron and kept it in.

Additionally, version 2 of the hydrogel patch was darker, which may indicate it was more dense. A denser hydrogel patch could lead to difficulties with the release rate of iron, so it may have been harder for the iron to get out of the patch due the increased density. Another potential reason is due to the iron concentration. The iron may not have fully dissolved or absorbed into the gelatin. Additionally, there is also the possibility that there is a cap on the amount of iron that can be mixed into the gelatin providing a limit on how much iron can be released.

Future Research with Sustainable Transdermal Iron Delivery Methods:

The most interesting part of my research is that both versions of the patches follow a similar trend of a slower release at the start, before switching to a more rapid release over time. This trend follows that of a delayed release, which means that if this experiment time period was extended, it could potentially release even more iron over a longer span of time. This would mean that in future versions of this patch, studying this patch for a longer timespan may be beneficial.

Therefore, if I repeated this study in the future, I would prolong the study to see the longevity of the patch as well as the efficacy over prolonged periods of time. Looking to the future, I'd also like to answer the question on how to get more iron to release since increasing the iron concentration did not work.

Another route I'd like to explore is changing the material from gelatin to alginate as it does not interact strongly with iron. Alginate also originates from seaweed and has been used in drug delivery before. Additionally, alginate is sustainable for the environment, which was one of the research goals I had when creating the transdermal method of iron delivery, which ended up being the hydrogel patch in today's research.

Additionally, I would like to experiment with the concentration of iron in the iron patch created. Specifically, I would like to lower the concentration of iron in the patch as the relationship may be inverse and therefore release more iron. Another possibility to explore is playing with the ratio of gelatin to iron, as well as changing the texture of the hydrogel to see if that has an impact. These are all potential options to better achieve my goal, although I successfully achieved the goal of significantly releasing iron at a higher amount that is physiologically relevant and this iron patch can be used as a baseline. Additional future directions include changing the shape of the patch, making it smaller or bigger, skinnier or thicker, or even changing the shape from a circle to a square to see if that has an impact on the iron released.

Conclusion:

To conclude, hydrogel patches are essential in medical fields, especially as an alternative method to oral medications and their unsustainable effects. **I successfully engineered a patch that can release an amount of iron that is significant to be a solution for anemic patients, and that is environmentally sustainable.** I determined that these patches were both delayed releases. Additionally, I discovered that increasing the iron concentration does not necessarily increase the amount of iron dispersed. Future possible approaches that may increase the amount of iron released include changing the material, lowering the iron concentration, or altering the density. I was able to determine these conclusions by examining my findings from the data I collected, as well as the graphs.

References

1. "Anemia." *Hematology.Org*, 2021, https://www.hematology.org/education/patients/anemia
2. *"In Brief: Your Guide to Anemia" - NHLBI, NIH*, 2011, https://www.nhlbi.nih.gov/files/docs/public/blood/anemia-inbrief_yg.pdf
3. Brody, Jane E. "The Cost of Not Taking Your Medicine." *The New York Times*, The New York Times, 17 Apr. 2017, www.nytimes.com/2017/04/17/well/the-cost-of-not-taking-your-medicine.html#:~:text=%E2%80%9CStudies%20have%20consistently%20shown%20that,in%20Annals%20of%20Internal%20Medicine.
4. "Teaching Your Child How to Swallow a Pill." *Johns Hopkins Medicine*, 20 Dec. 2023, https://www.hopkinsmedicine.org/health/wellness-and-prevention/teaching-your-child-how-to-swallow-a-pill
5. Moscheo, Carla et al. "New Insights into Iron Deficiency Anemia in Children: A Practical Review." *Metabolites* vol. 12,4 289. 25 Mar. 2022, doi:10.3390/metabo12040289
6. Drugs in the Water. *Harvard Health*, 1 June 2011, https://www.health.harvard.edu/newsletter_article/drugs-in-the-water
7. "Effects of Iron in Water?" *Longs Ecowater*, 25 Aug. 2023, https://longsecowater.com/blog/effects-of-iron-in-water#:~:text=However%2C%20research%20has%20shown%20that,become%20contaminated%20with%20harmful%20bacteria.
8. Edwards, Brian. "The Harmful Health Effects of Iron in Your Water." *Hague Quality Water of Maryland*, 1 July 2023, haguewaterofmd.com/the-harmful-health-effects-of-having-iron-in-your-drinking-water/.
9. "Testimonials - Patchmd - Vitamin Patches and Supplements." *PatchMD*, 21 Aug. 2023, www.patchmd.com/testimonials.html.
10. "Is Your Child Low on Iron? Prevention Tips for Parents." *Mayo Clinic*, Mayo Foundation for Medical Education and Research, 2 Dec. 2023, www.mayoclinic.org/healthy-lifestyle/childrens-health/in-depth/iron-deficiency/art-20045634.