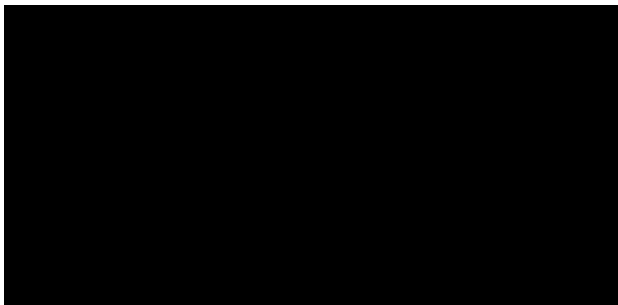


Submission 14

Engineering World Health Design Competition 2014

ZnDermal: A Transdermal Zinc Delivery System



1. Problem Definition

Every year, 2 million people--a number equal to the entire population of New Mexico--die from diarrheal diseases. Accounting for 1.5 million of these deaths, Diarrheal disease is the second-leading cause of death in children under the age of five¹. Diarrheal diseases are both preventable and completely treatable, causing only minor annoyances to those living in developed countries with access to clean water and health care. But in underdeveloped countries diarrhea is a common and deadly side effect of many infectious diseases that are spread through contaminated drinking water, food, and interpersonal contact.

Developing countries do not have access to food that is rich in nutrients, which leaves one third of the world's population zinc deficient and kills over 450,000 children each year.² Zinc deficiency weakens the immune system and increases vulnerability to infectious diseases.³ These infectious diseases cause diarrhea which in turn secretes fluid and nutrients further declining the child's state of malnutrition and dehydration, and not only putting them at risk for future infections but also stunting their growth both cognitively and physically⁴. The average child in developing countries gets diarrhea 3.2 times each year, and with each diarrheal episode their malnutrition worsens, thus continuing the vicious cycle until their bodies can no longer survive.

The current treatment for diarrheal diseases, as recommended by the World Health Organization, involves daily intake of water with oral rehydration salts (ORS) and suggests zinc supplementation. ORS, a salt/sugar/water slurry, is intended solely to combat dehydration and has not been strongly correlated with reducing the duration or severity of diarrhea itself. However, administering 20 mg of zinc to children for 10-14 days after the first diarrheal episode has shown to reduce the duration by 25%, stool volume by 30%, and rate of death by 42%, in addition to preventing recurring diarrheal episodes for over two months.⁵

Despite the promise that zinc provides in both the developing and developed worlds, oral zinc treatment is of mediocre value to consumers. The human gastrointestinal tract is relatively inefficient at absorbing zinc, with a 20-30% absorption rate in healthy adults. Of note, this rate is drastically lower in those suffering from diarrheal diseases. As a result, most zinc simply passes through the digestive system without making it to the bloodstream, thus being of no use. In addition, if the child is vomiting--a common side-effect of diarrheal disease--the zinc will not have had time to reach the intestines and the dose is therefore useless.

2. Impact in developing world

Haiti has been chosen as a test model for our product because of its need for the treatment as well as its known relationship with NGO's from the United States. We also chose Haiti because of the concerning number of cholera cases. Cholera is a diarrheal disease caused by an infection in the small intestine. Since October 2010, there have been 694,843 cases of cholera resulting in 8,494 deaths.

Even before this outbreak, diarrheal disease was the leading cause of child mortality, and the second leading cause of death overall in Haiti⁸. The Red Cross, one of the first respondents to the Haitian cholera outbreak, has spent \$19 million fighting cholera by distributing water, vaccinations, and OR and continue to have a strong presence in the country promoting public health⁶. For this reason, we have identified the Red Cross as our first hopeful partnership, once ZnDermal has been proven and tested.

In the case of Haiti, where a long-term solution to end cholera and diarrheal disease will take decades to achieve, the need for emergency care and response medical supplies such as ORS, vaccinations, and zinc treatment is paramount. ZnDermal has the potential to sustain Haitians and many other countries in similar circumstances as they experience epidemics and work to produce long-term solutions to eradicate diarrheal disease. While the Red Cross has been identified as our first hopeful partner, ZnDermal's ultimate goal is to be partners with many more Non-Government Agencies and Government Health Agencies in order for the largest amount of people to be reached.

3. Required Performance specifications

Our goal to end unnecessary death due to diarrheal disease is an admirable one, but to ensure that this goal will come into fruition we must also make it economically feasible. Because our main venture is not a profitable one, we looked into ZnDermal application in the United States. Unlike in third world countries, death due to diarrheal diseases is quite rare in developed countries. However, there is still a need for zinc as an essential micronutrient. Nutrients and micronutrients such as calcium, vitamins, minerals and zinc are all excluded from mandatory FDA approval. This is advantageous in that we will be able to bypass the years of human trials required for drug administration. The FDA only requires the label on our product contain a disclaimer that our product has not been evaluated by the FDA and that our product is not intended to diagnose, treat, cure or prevent any disease. Although ZnDermal will in fact treat diarrheal disease in the third world, in developed countries it is not a replacement for proper health care treatment of an infectious disease.

Unlike in first world countries, the performance specifications for the developing world are not well defined and vary for different geographic areas. However, there are a few key criteria that apply for all regions and are based upon the physical limitations of third world. Because the product must be transported from the U.S. during the initial manufacturing stages, the product must be easily transported. The current treatment is a 14 pill regimen of over-the-counter zinc tablets, sold in bulky plastic bottles. Our product must be of small or similar size and also be able to be transported without refrigeration. The product must be able to be manufactured at a similar cost with greater efficacy. If the product is not a substantial improvement over the current treatment then it will not be implemented.

The more difficult product specifications are detailed in the World Health Organization's guide to informative research titled, "Introducing Zinc into a Diarrheal Disease Control Programme." The guide allows for the proper identification of the local symbols, terms, and social views that will allow for proper usage and understanding of a zinc treatment for diarrheal disease. This document identifies issues mothers in developing countries have with the current zinc treatment. Even though the tablet form of zinc is low-compliance, mothers fear that too much of the responsibility of the treatment lies with them.

Because current treatment is in supplement form and most of the patients suffering from these diseases are children under the age of 5, administration involves force-feeding a sick child a tablet or grinding up and dissolving a tablet into a solution for the child to drink. In order to rectify this, our technology must fit the compliance of our target user-- children under age 5. vomiting is another common side-effect of diarrheal diseases, oral zinc administration can only occur once the stomach has settled enough to allow digestion. This small window of opportunity worries mothers and usually leads to lack of use. In order to prevent this delay in treatment, our system must not be dependent on the digestion system.

An important regulation of transdermal patches relates to skin safety. The substance must be delivered at an appropriate rate through the skin, and cannot irritate or have any negative reactions with it¹². Our team made sure to focus upon this regulation in our product development by incorporating Hydrogel, a skin perforation enhancer, to help transport zinc through the dermis. Hydrogel is also used on open wounds to promote healing; it is actually beneficial to skin. In developing country, a child's skin is often dry from dehydration and sun, to the Hydrogel in ZnDermal is a large benefit.

4. Implementation of prototype

ZnDermal is a zinc containing transdermal delivery system composed of three layers (see attached figure). The first layer is a film backing that provides the gel matrix with occlusivity and physical integrity protecting the zinc. The second layer is the zinc-containing adhesive composed of Zinc oxide in a hydrogel purchased from Alliqua Biomedical. The final layer is a release liner, two overlapped strips, that protect the adhesive layer until they are peeled off and discarded allowing the zinc to diffuse through the skin.

ZnDermal is designed to deliver 4 mg of zinc oxide per day over a 7-10 day interval once applied to the skin. Zinc nanoparticles have been chosen to facilitate transdermal diffusion of the lipophilic zinc molecule due to their microscopic size, which is beneficial to cross the skin barrier. The duration of administration is lower than the current recommended dose because, in addition to zinc being absorbed 100% through the bloodstream in IV application, zinc has a 94% retention rate in the blood after 5 days. In contrast, the zinc from tablets becomes inactive after only two days. The absorption and retention of zinc through IV eliminates the cost and manufacture of excess zinc while avoiding the already aggravated GI tract.

5. Proof of performance

ZnDermal has been engineered in compliance with FDA regulations on dietary supplements. Because zinc already exists as a dietary supplement the product does not need go into further in addition to being conscientious of the limitations of healthcare in third world countries, specifically of the difficulty of adequate refrigeration. ZnDermal patches are durable and do not need to be kept within a

specific temperature range to remain functional; the current patch materials we are constructing the patch with can be kept anywhere between 32-86 degrees Fahrenheit.

The uniqueness of our system, the diffusion of ZnO nanoparticles, is being overseen by the [REDACTED] Research Facility at [REDACTED]. The [REDACTED] is a NNIN nodal facility supported by the National Science Foundation.¹ The [REDACTED] is providing various sizes of zinc nanoparticles for our testing diffusion rates, allowing for the optimal dosage. The [REDACTED] will also be manufacturing the zinc particles used in early prototyping and trials. Initial diffusion testing on both synthetic stratM millipore and porcine skin have shown promising results (Table 2). Our data shows diffusion rates of 4mg of ZnO over a 24 hour period, proving that our system is capable of reaching our target dose. Further diffusion testing of zinc nanoparticles and various diffusion enhancers will allow us to optimally control the dosage and release of the particles.

In terms of unit cost, we would eventually be able to deliver a week of transdermal zinc treatment at a lower price point than one week of oral tablets (\$0.49-0.66). Much of these savings come from the reduced daily dosage of zinc required, down to 4 mg from 20 mg. Our projected cost for a one-week transdermal patch is shown in the attached table. Not only is ZnDermal more effective at administering zinc, but also requires less patient compliance.

The patch is not dependent on the state of the digestive tract and can be applied at any time during the diarrheal episode. It can even be applied as a preventative as zinc has been shown to prevent diarrheal episodes for up to 2 months after a 14 day dosage regimen. In addition our patch will only require compliance for the initial administration, similar to putting a bandage on a child's cut. Only this bandage might save the child's life.

6. Business plan for manufacture and distribution of the technology

While our primary goal is to treat diarrheal disease in the third world, creating a U.S. market for the product will help fuel this pursuit. In developing countries our customers will be NGOs--such as the Red Cross, Plan International, and Defeat DD--whose goal is to alleviate the suffering of people from diarrheal diseases. These large NGOs have already integrated health care clinics and on-site staff who not only distribute current zinc treatment but also educate the consumers about the treatment. The patches will be distributed along with ORS packets to health care clinics, leaving pricing and further distribution up to each NGO. Because the current treatment, zinc tablets, are not being profited from, these NGOs will want the most effective product to distribute. In multiple studies, the use of zinc in supplementation to the regular Oral Rehydration Salt (ORS) therapy greatly increased the cost effectiveness of the standard treatment of diarrhea. By comparing treatment with just ORS versus ORS and zinc, using no treatment as a base case, it was found that the cost-effective-ratio of just ORS treatment was \$3200 per death averted, versus just \$1200 when zinc treatment was included¹³. Therefore ZnDermal would not only save lives but be a more cost effective way to do so; there is a large need for our product. The market for ZnDermal in developing countries is clearly evident and

¹ National Nanotechnology Infrastructure Network

calculable given the extensive data on diarrheal diseases, however, the first world market is not as easily estimated because of the numerous uses for zinc as a dietary supplement. The first world market is comprised of two sectors: the healthcare sector, primarily comprised of patients with Gastrointestinal Disorders receiving total parenteral nutrition, and the over-the-counter sector.

Inflammatory bowel disease encompasses both Crohn's disease (CD) and ulcerative colitis (UC); approximately 1.4 million people in the U.S. are affected annually. These autoimmune diseases cause the immune system to attack the digestive tract, inducing high volume defecation and severe fluid loss prevention. The body is left incapable of absorbing nutrients from ingested food, so patients must receive Total Parenteral Nutrition (TPN). Dr. [REDACTED], a contact of ours at the [REDACTED] School of Medicine, specializes in Inflammatory Bowel Syndrome. She administers zinc parenterally to her patients daily, and stressed the importance of intravenous delivery because of the inefficiency of the GI tract in both her patients and others with diarrheal diseases.

GI tract disorders and TPN are not the only uses for zinc administration. Dr. [REDACTED] has a colleague, [REDACTED], who is a pharmacist with [REDACTED] home care services and personally administers TPN to patients. He brought our attention to the current micronutrient shortage in the United States. This shortage causes their patients to go without zinc *for months*. Recently the shortage was further exacerbated when a generic manufacturer quit making injectable zinc, leaving the US market supported by a single manufacturer. Both Dr. [REDACTED] and Mr. [REDACTED] were excited at the prospect of our product being able to treat their patients zinc deficiency in place of the current IV zinc treatment, and that we have the capability to bring zinc back to the market and fill the micronutrient shortage.

However, zinc deficiency in developed countries is relatively low with the exception of these specific medical problems, therefore, we would need a larger consumer population to ensure our product is profitable. Luckily, there are many uses of zinc treatment that ZnDermal can target.

Zinc is most widely known for its immune enhancing properties and has been marketed in the past for cold remedies like Zicam®. However, these intranasal applications of zinc have caused anosmia, loss of smell, and consumers have been urged by the FDA to stop using them. Our zinc patch fits perfectly into this market as a safer alternative for the common cold, which affects millions of Americans every year.

ZnDermal can also be marketed as a preventative against traveler's diarrhea. As people travel to third world countries, 30-70% experience diarrheal attacks¹¹. This amounts in over 10 million cases per year. Current treatment options include antimicrobial drugs and Pepto-Bismol, which are expensive, inconvenient, and non preventative. To be effective, an individual needs to take 8 Pepto-Bismol tablets per day amounting to \$8.29. With ZnDermal, we can administer dose in only one patch and would prevent diarrheal episodes for up to two months. With the low cost of one ZnDermal patch, not only would consumers spend less money, we could also make a considerable profit from the millions of people going abroad. Traveler's Diarrhea is realist concern in travelers and one that can easily be solved with ZnDermal.

The initial funding for the startup of ZnDermal technology will, in hopes, be provided through grants and competition winnings. Thus far, we have received funding from the [REDACTED] Discovery Competition and the Engineering Peer Review Board, we are finalists in for the Skandalaris Global Impact award, and the Dean of Engineering [REDACTED], has expressed interest in helping fund our endeavour as well. These funds will help cover the cost of patch materials, testing equipment, early advertising, and an initial outsourcing fund for the manufacturing of patches. We are continually searching for new sources of funding as well. After the initial setup, we anticipate that the U.S. sales alone will sustain the manufacturing, processing and distribution of patches within the U.S.; any additional income made through sales will be used to reduce the cost for the patch in third world countries.

Since sales will likely be slow in the beginning, we will look to outside funding sources such as the Bill and Melinda Gates foundation as well as the World Health Organization, Unicef, and other non-profit organizations to further support our venture. However, due to the considerable number of people in the US that we have identified earlier who are in need of an effective treatment for zinc we expect sales to eventually more than cover the cost of production.

As the popularity of transdermal technology grows worldwide, many of the countries in need of our patch have already developed the means for its production. The most notable of these is India, which is hit particularly hard by diarrheal disease. In 2008, Sparsha Pharma became India's first transdermal patch manufacturer to focus solely on global health issues, including chronic pain, asthma, and neurodegenerative disease. Its fentanyl patch for pain management was India's first WHO-certified fentanyl patch. Other Indian transdermal manufacturers have also focused on global health issues, including Dr. Reddy's. Ultimately, the success of pharmaceutical manufacturers in countries such as India has shown it is possible to produce transdermal patches in the areas we are targeting. Hence, we would want to take advantage of these developments and manufacture in these developing nations.

However, since our patch is made from commercially available components, we would not need to worry about manufacturing individual components in the developing country at first. Instead, we would purchase the patch parts from a certified supplier and assemble the product in the developing country using local labor. This would contribute to the local economy by providing employment and eliminate the need to ship the final product from a developed country. Furthermore, our product has the potential to increase local productivity by reducing the number of lost work hours caused by diarrheal diseases. In the long run, we can further reduce our variable costs by producing the patch components locally as well. This would reduce the patch cost by eliminating the profit margin of the components purchased from suppliers.

While all of our variable manufacturing cost (patch supplies and labor) would be spent locally, it would be wisest to spend our fixed cost, namely assembly equipment, abroad. For example, Sparsha Pharma purchases its crucial production equipment from countries such as the US and Japan, in order

to improve quality control and conform to the standards of more developed countries as well. We would likely do the same, purchasing assembly equipment such as heat sealers from abroad.

As previously mentioned, our primary method of distribution will be through NGO groups. NGOs such as the Red Cross, Plan International, and Defeat DD have been aggressively working to reduce deaths from diarrheal disease globally. Many other groups, particularly the Bill Gates Foundation, have been searching for innovative new ways to treat the issue of diarrheal disease. We have recently begun contacting these groups, and look forward to partnering with at least one of them in the future. Our patch also makes distribution for NGOs easier. Since our patch contains less zinc mass per week of treatment when compared to zinc tablets, our product will be less bulky and lighter, making transport easier.

We believe that we can design a zinc delivery device that is more portable and exponentially more effective than the current treatment. We want our technology to be simple to use and affordable, with the goal of increasing accessibility to the children and adults suffering from diarrheal diseases. Because there is such a dire need for this product we have decided not to patent our technology, allowing for maximum distribution and treatment. Moreover, this project contributes as a model of innovation-methodology and provides a basis for future use of transdermal technology. Our initiative for a non-profit health solution keeps our goals unclouded in the pursuit of improving the health condition of children in the developing world.

Appendix A

Table 1: Itemized manufacturing cost for a single ZnDermal system.

Material	Material Cost	Material per Patch	Cost per Patch
3M 9733 Backing	\$3.10 per square yard	4 square inches	\$.01
Nanoparticles	\$30.30/100g	25 mg	\$.08
Diffusion Enhancing Hydrogel	\$1.00 per 16 square inches	4 square inches	\$.25
Total			\$0.37 per patch

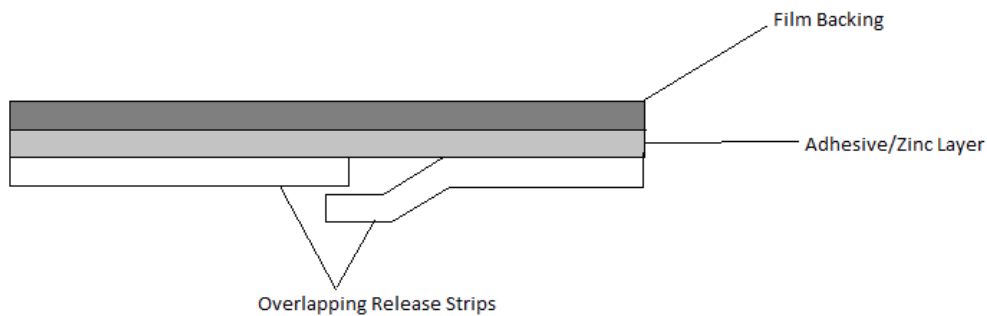


Figure 1: Three layer transdermal zinc delivery system.

Table 2: Amount diffused in initial trial with four different sizes of nanoparticles.

	<u>15-20nm</u>	<u>25-30nm</u>	<u>50-80nm</u>	<u>Tetrapods</u>
Amount Diffused (mg)	1.89	5.43	4.35	1.85
Percent Diffusion	18.8	54.3	43.5	18.5

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