Hydrogel Biotechnologies stand between a healthy heart and a maglev transplant.

Controlling pharmacokinetics /dissolution using Hydrogel delivery systems.

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Abstract

The purpose of this project was to test the ability of hydrogels to control medication dissolution.

The hydrogel-saturated material from a sanitary pad was used to cover a coated Aspirin to mimic the behavior of a hydrogel, to observe and register the dissolution of the Aspirin with a PH environment similar to the human intestine (pH 8). Aspirin has anti-inflammatory properties and is used as an antiplatelet agent to prevent cardiac arrest and stroke and its short half-life makes it an ideal candidate for this experiment as it represents a vast number of medications that get absorbed by the body really fast, hence they have to be taken in multiple doses at a specific time or with a specific diet. This project aims to overcome all these and more restrictions by the suggested hydrogel delivery system.

The five trials in sets of two indicated that hydrogels can delay the dissolution of a medication with a short half-life like Aspirin by as much as 53 times or 46.79 times on average, and therefore supported the hypothesis.

A T-Test value of 0.004% indicated that the difference between the averages of the two sets of times (Aspirin dissolution time without hydrogel encapsulation vs. time within hydrogel encapsulation) collected in the 5 trials is significant.

The physical similarities of hydrogels to human tissue, their elasticity, the ability to shape them and the hardness variety potential, allows for a wide range of applications related to the administration of advanced medication prescriptions, or even ingestible electronics that could monitor certain bacteria or viruses or even image the progress of tumors or ulcers, over the course of several weeks.

Background Research

This project was initiated from last year's project on Maglev technologies that can be used to create maglev hearts for human transplants. The latter is undergoing clinical trials, further research on which, revealed the preparation process prior to the transplant procedure that required treatments with blood thinners to avoid blood clots in the body of the patient. The latter prompted further research on dealing with heart problems and maintaining a good heart health/condition either to prepare for a **successful heart transplant or to avoid one (if possible) altogether**.

Blood thinners are commonly used to prevent **blood clots** from forming and potentially causing a stroke once they have traveled to the brain from the heart. Even more so, such clots are the reason for deep vein thromboses which in turn can lead to pulmonary embolism, once they travel to the lungs.

But not all **blood thinners** (scientifically known as anticoagulants) are created the same. Besides the old-fashioned coagulants, there is a new development of direct oral anticoagulants (DOACs) (1).

In comparison to the traditional blood thinners out there which basically block vitamin K used by the body to form clots, require a specific diet, and frequent monitoring of the speed at which the body creates clots, the DOAC s (1) do not require any of that. They can be administered in fixed dosages without measurements and risks that relate to diet. Hence they lower the number one risk of blood thinners, which is bleeding.

However, they do have two major drawbacks: a) the high cost of about $300 for a 30-day supply (1), compared to the traditional medications that have a respective $4 cost for the same quantity, and b) they have **a short half-life.** Meaning they do not remain for long in the human body active or more scientifically, the length of time required for the concentration of the drug to decrease to half of its starting dose in the body is very short.

Although DOACs anticoagulants specifically are extremely valuable because they can act fast within the human body and deliver immediate results (due to their short half-life), their effects wear off very quickly and that is the very reason they have to be taken several times in short time intervals to have the same effect. In other words, "*if you miss a dose of the newer drugs, especially those taken once a day, you could leave yourself unprotected, Dr. Bartholomew - Head of Vascular Medicine/ MD-cautions.*" *(1)*

At the same time, the half-life of a medication is relevant to the age, size, and overall health of the patient. In other words, the same medication has a different half-life within the body of a child compared to an older person and even a thin compared to an obese individual. (1)

The better knowledge and control we can have over the half-life of a medication, the better treatments we can offer to patients especially when it comes to dealing with life-threatening conditions like the ones of the human heart. The path of a drug in the human body, from digestion to absorption, distribution, and finally excretion, or in scientific terms the **pharmacokinetics** of that medication, is what determines the fine line between an overdose or even worse in some cases, not enough dose to save someone's life.

The starting point of this experiment was the idea of affecting/controlling pharmacokinetics through new biotechnologies that can provide delivery systems that aid and control the release of a medication. Such technologies are the hydrogels that are consumed widely in everyday items within our households.

These systems can "easily encapsulate hydrophilic drugs" (5) because they are mostly water (70% to 90%) while they have "excellent biocompatibility" (not harmful to living tissue) due to their similarities to human tissues. That is why they are so appealing as a drug delivery system to many branches of medicine, from oncology, immunology, and wound healing to pain management and of course cardiology. The **use of hydrogels as a medication delivery system** has many **advantages** due to their small size and solid form originally (prior to digestion), which makes them so convenient for administration orally. They are covered with a mesh which depending on its size (bigger or smaller holes), determines the release of the medication. At the same time, they provide a safe environment for mixing enzymes with the actual medication they carry, to protect and/or facilitate safe absorption. For example, mAB s are developed proteins that break down immediately in the stomach, which is why they have to be injected. But thanks to hydrogels, they can be mixed up with enzymes within the hydrogel so that they may be protected and safely but slowly released into the human body. (5)

Hydrogels are found in abundance in everyday household products like personal hygiene pads as they have the impressive ability to absorb large amounts of bodily fluids, while they swell up. "Cellulose is the most abundant biocompatible matter on this earth which basically originated from plants." (2)

The focus of this project is to test the ability of hydrogels to control medication dissolution. The experiment was carried out using a deconstructed sanitary pad and a fast-releasing common household medication called Aspirin. The hydrogel-saturated material from the sanitary pad was used to cover the coated Aspirin to mimic the behavior of a hydrogel, to observe and register the dissolution of the Aspirin in a PH environment similar to the human intestine (PH 8)

The choice of Aspirin in this experiment was intentional because apart from its use as a fever reducer and pain suppressor, **Aspirin has anti-inflammatory properties and is used as an antiplatelet agent to prevent cardiac arrest and stroke.** At the same time, it is a perfect example of a medication with a **short half-life which makes it a perfect candidate for this experiment**. In fact, according to an article in Harvard Health Publishing, in the event of a heart attack, after calling 911 chewing an aspirin is the immediate next step(3). "Chewing the pills gets the anti-clotting chemicals into your bloodstream much faster than if you swallow it. In one study, platelet activity dropped by 50% within five minutes" (3) in people who chewed an aspirin.

To prove the causality between the Hydrogel casing and the dissolution time of Aspirin, a t-Test will be used for the data derived from the 5 trial sets, to compare the means of the two groups (with and without hydrogel encapsulation). This statistical test will help prove the significance of the difference between the means/average dissolution times.

There are many drugs in use today that have short half-lives, and/or get absorbed /broken down by the human body really fast, hence they have to be taken in multiple doses at a specific time or with a specific diet, etc. All these and more restrictions can easily be overcome by a hydrogel delivery system.

In fact, MIT engineers (4) recently developed an ingestible pill that expands into the stomach inspired by the defense mechanism of a puffer fish. Once it enters the stomach, it swells to the size of approximately a ping pong ball but is soft and squishable. Currently, a number of clinical trials have been performed successfully on pigs, whose gut resembles that of humans, with sensors that measure temperature and there are more scheduled in the future.(4)

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Problem Statement

Can hydrogels help control medication dissolution in the human body?

Hypothesis

If a coated Aspirin, encapsulated in the middle layers of a sanitary pad, is immersed in a liquid solution of PH 8 that mimics that of the human intestines, then it will take longer to dissolve and pass to the solution through the sanitary pad layers, because the latter will swell up from the hydrogels they carry and act as a barrier for the Aspirin. Therefore, proving that hydrogels can help control medication dissolution.

Variables

Independent variable: The **hydrogels (coating** of the sanitary pad layers).

Dependent variable: The **time** it takes for the Aspirin to pass to the solution and dissolve.

Constants: a) Aspirin type, b) sanitary pad layers used for encapsulation (pad brand, type, and size, c) Solution PH 8, ½ cup and temperature 22 C .

Control group: The **time** it takes for Aspirin (without encapsulation in a hydrogel) in a PH 8 solution to dissolve.

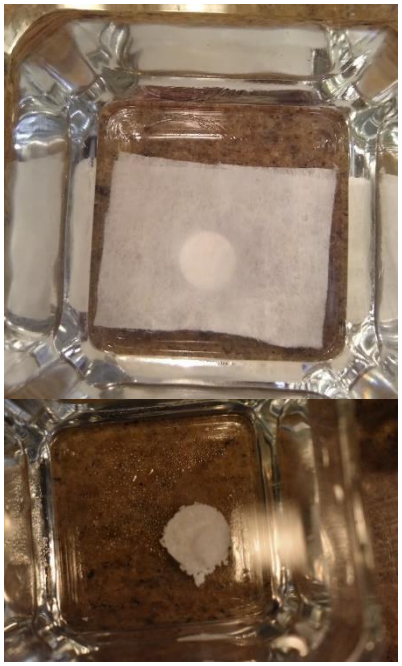
Material

- Ten coated Aspirin tablets of 325 mg each, and two extra for replacement if needed.
- Ten glass containers filled with a solution of PH 8 at 20 C temperature. Big enough to hold I cup of water each.
- One deconstructed sanitary pad (containing hydrogels/alldays was used in this experiment) with the top layer and the bottom adhesive layer removed.
- Hot glue gun to adhere and seal the Aspirin tablet within the sanitary pad layers.
- A stop watch.
- Scissors.
- A camera for the footage. (phone or anything that can capture images)
- A digital thermometer and a digital PH indicator.
- **Gloves, sanitizing bottle and sanitizing wipes for keeping the working surfaces sanitized and clean throughout the experiment as per the Covid-19 safety guidelines and regulations. A surgical face mask worn throughout the experiment.**

Procedures

1. Gather the necessary materials and **follow the Covid-19 protocol/ guidelines for currying out experiments in a lab within enclosed areas (sanitize and disinfect all surfaces to ensure Covid-19 guidelines/regulations are met at all times, with facial mask, gloves and social distancing throughout the experiment).**
2. Prepare the ten glass containers: fill each container with ½ cup of tap running water. Measure the PH of 8 with the PH indicator and the temperature to be at 22 C using a digital thermometer for liquids.
3. Take the deconstructed sanitary pad (with the top layer and the bottom adhesive layer removed). Take scissors and cut around the pad, creating a long strip with dimensions 3" by 10". Divide this strip into five equal size strips with dimensions 3" by 2" each and cut them out. Label them 1, 2, 3,4,5. These strips will be used for each one of the three trials that will follow.

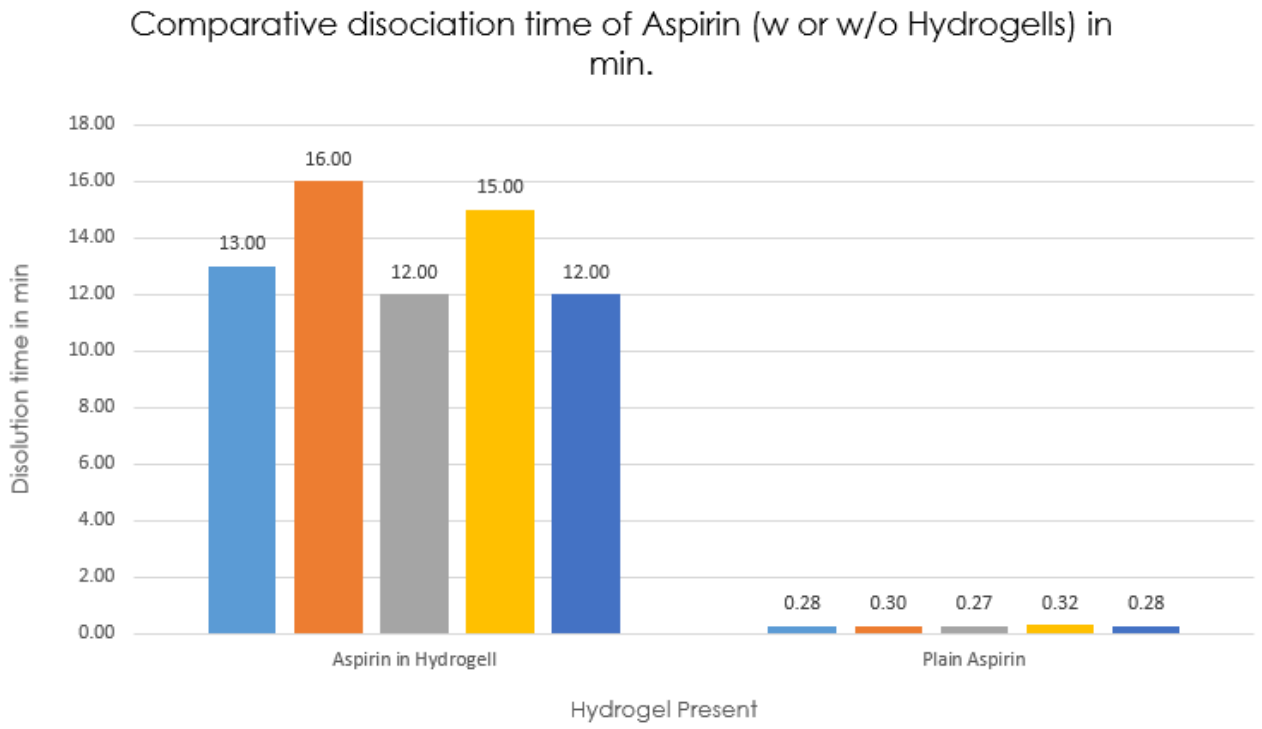
4. Take the first strip fold it in half and place the Aspirin (one of the 10) in the middle (in the side crease of the fold). (first top picture to the right)
5. With the hot glue gun seal around the Aspirin to enclose it within the folded strip.
6. Repeat steps 4 and 5 for the rest of the Aspirins. There should be 5 separately encapsulated Aspirins all together.
7. Take one Aspirin that is not encapsulated in hydrogels and the first of the encapsulated Aspirins (from steps 4 and 5). Hold them on top of the two glass containers filled with the solutions and release them at the same time and start the stopwatch (second from top picture to the right).
8. Using the stopwatch mark the time the Aspirins break down and dissolve/leak into the solution.
9. Repeat steps 7 through 8, for the remaining trials and a total of 5 paired trials.

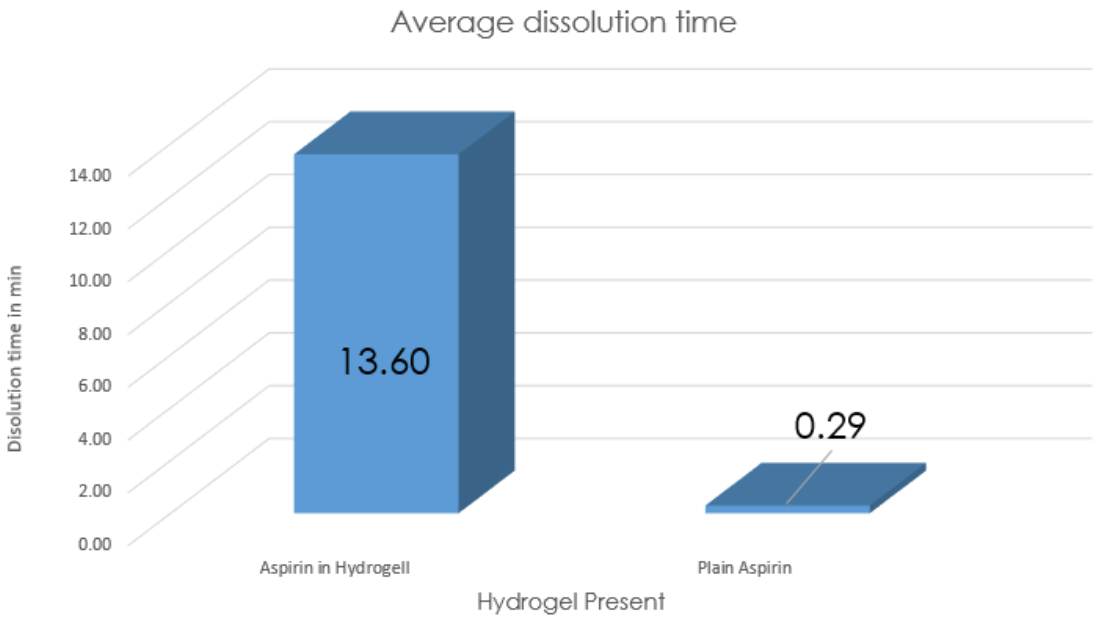


Data

Comparative disociation time of Aspirin (w or w/o Hydrogells) in min.					
	Aspirin in Hydrogell	Plain Aspirin	delay in times (X)	Abs.diff	(in min)
1st trial	13.00	0.28	45.88		12.72
2nd trial	16.00	0.30	53.33		15.70
3rd trial	12.00	0.27	45.00		11.73
4th trial	15.00	0.32	47.37		14.68
5th trial	12.00	0.28	42.35		11.72
Average	**13.60**	**0.29**	**46.79**		**13.31**
		St.Deviation	**3.66**		
		T test	**0.004%**	it is < 0.5 therefore the difference in the Averages of the two columns is important (or statistically significant)	

Figure D1





Aspirin dissolution without Hydrogels

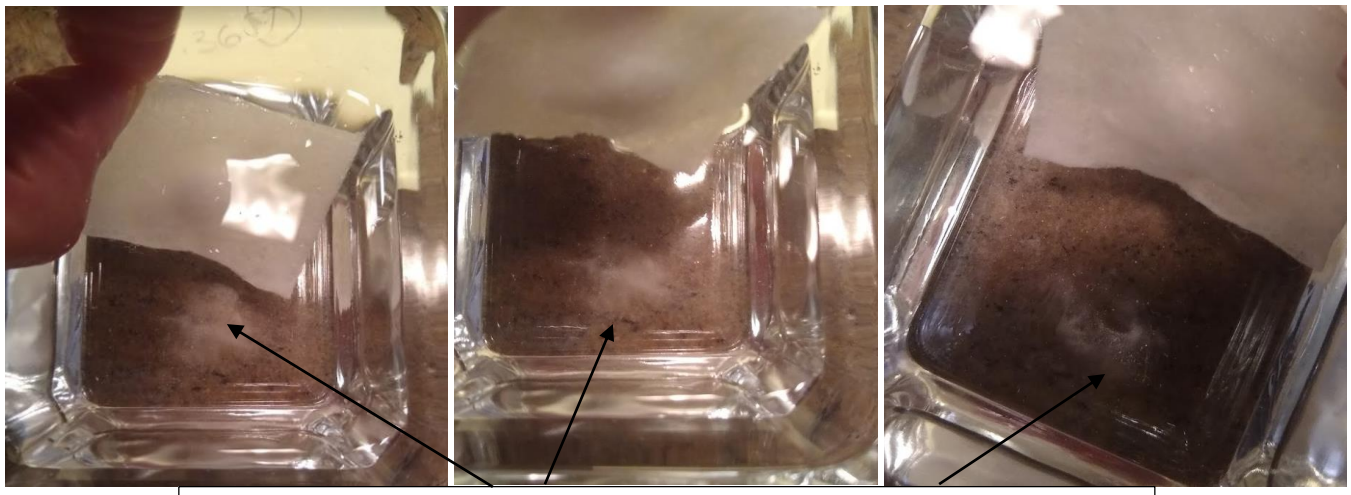
Aspirin inside hydrogel casing

Aspirin inside hydrogel casing

Swollen Hydrogels holding the encased Aspirin.

Swollen Hydrogels after they were removed from the liquid solution

Traces of cloud from Aspirin dissolution inside the hydrogel casing that are visible in the solution as they passed from the hydrogel net.



Particles of dissolved Aspirin that are visible in the solution as they passed through the hydrogel net

Dissolved Aspirin in Hydrogel pouches after removed from the solution

Results

The purpose of this experiment was to test the ability of hydrogels to control medication dissolution. The experiment was carried out using a deconstructed sanitary pad and a fast-releasing Aspirin. The hydrogel saturated material from the sanitary pad was used to cover the coated aspirin to mimic the behavior of a hydrogel, to observe and register the dissolution of the Aspirin with a PH environment similar to the human intestine (pH 8).

In all five paired trials, the **hydrogel-encapsulated Aspirin** started clouding the solution with visual white pieces of the Aspirin within **13.6 min on Average**. Compared to the **exposed Aspirin** that broke down in **0.29 min on Average.** (figure D1)

In all five trials, when the Aspirin was encapsulated within the **hydrogels (coating of the sanitary pad layers -i*ndependent variable)*** the **dissolution time (it takes for the Aspirin to pass to the solution and dissolve - dependent variable)** was longer than that of the **exposed Aspirin (uncoated Aspirin – control group),** by 13.31 min on Average or 46.79 times (or 4,590%).

A T-Test that was conducted to determine if there is a statistical difference between the two groups, revealed a value of 0.004%.

The assumptions for the T-Test were that: a)the **distribution is one-tailed (**because we predict that hydrogel encapsulation of the Aspirin delays dissolution time), b)the **sample data are paired** (the trials are performed in pairs as the Aspirin with and without the hydrogel are released at the same time), c) the **dependent variable (dissolution time) is normally distributed, and measured in a continuous scale (seconds)** and d) a **critical value of 0.05 (confidence interval)** which means that if we were to run the test 100times, then 5% of the times we will be able to reject the null hypothesis (that the means of the two groups of times we are comparing are equal) and 95% we will not.

Conclusion

The data collected from all the trials, supported the hypothesis that If a coated Aspirin, encapsulated in the middle layers of a sanitary pad, is immersed in a liquid solution of PH 8 that mimics that of the human intestines, then it will take longer to dissolve and pass to the solution through the sanitary pad layers, because the latter will swell up from the hydrogels they carry and act as a barrier for the Aspirin. Therefore, proving that hydrogels can control medication dissolution.

Therefore, hydrogels can be used to control medication dissolution.

The **major findings** were that hydrogels can delay the dissolution of a medication with a short half-life like Aspirin by as much as 46.79 times and therefore hydrogels can be used effectively in pharmacokinetics as a medication delivery system. By using a hydrogel infused cover, removed from a sanitary pad to encapsulate a coated Aspirin tablet, the broken down tablet within the hydrogel remained entrapped and away from the solution until the time when they started leaking due to the width of the mesh from the specific hydrogel pads. At the same time, the encapsulation of the Aspirin worked as a barrier for the medication that is well known for causing stomach bleeding in some cases and irritating more often the gut.

A comparison of the T-Test value of 0.004%, with the critical value of 0.05 revealed a very big difference, therefore proving that there is very strong evidence that the two means of the compared groups: the dissolution time of the Aspirin inside the hydrogel and the dissolution time of the Aspirin without the hydrogel, are significantly different.

In this testing the t-Test indicates that there is more than 95% probability (in fact 100 - 0.004% probable), that the difference between the averages of the two dissolution times is significant, therefore proving the causality between the hydrogel encapsulation and the delay in the Aspirin dissolution time.

Further development of this experiment could include:

- Experimentation in different PH levels to understand and test behavior of hydrogels across different PH levels like those of the Human body as well as temperature.
- Use/try other (instead of Aspirin) substance or formulation, perhaps even liquid from, to test effect on potency.
- Use a coloring aid to witness the dissolution easier and faster.
- Try doubling the tablets within the same hydrogel covering to test dissolution/release.
- Try combined formulations to witness interaction and effect on dissolution times. Test the effectiveness of the encapsulated medication before and after the hydrogel submersion into the solution to ensure active ingredient stability.

In **conclusion**, through this experiment, it was evident that hydrogels offer innovative solutions to traditional medicine formulation barriers. Their hydrophilic nature allows room for experimentation and at the same time creates a viable environment for medication delivery within the human body. The natural barrier hydrogels create between the medication and human tissue works both ways to protect the body as well as the medication from immediate degradation. The better knowledge and control we can have over the half-life of a medication, the better treatments we can offer to patients especially when it comes to dealing with life-threatening conditions like the ones of the human heart. The path of a drug in the human body, from digestion to absorption, distribution, and finally excretion, or in scientific terms the pharmacokinetics of that medication, is what determines the fine line between an overdose or even worse in some cases, not enough dose to save someone's life. This hydrogel experiment has shown that short half-life medications like Aspirin which is extremely valuable in the event of a stroke because it acts fast, combined with a hydrogel delivery system can become more reliable preventive alternative against a stroke.

When new anticoagulants called DOACS that act extremely fast have to be taken daily in order to properly shield the human body against a potential heart attack due to their short-lived effects, hydrogel delivery systems seem like a feasible solution.

Application:

Hydrogels, are very formidable and have high water content (typically 70–99%), which gives them physical similarities to human tissue. Their elasticity and the ability to form them in different shapes and sizes not to mention hardness allows for a wide range of mechanical properties that can be very useful when considering different drug formulations/administration alternatives. The potential to encapsulate active ingredients and protect them from early

degradation when combined with specific enzymes paves the way for sensitive therapeutics to be administered in ways other than the traditional injectable formats.

A very tangible application of this potential is a pill that expands into the stomach, developed by MIT engineers, inspired by the defense mechanism of a puffer fish. Once it enters the stomach, it swells to the size of approximately a ping-pong ball but is soft and squishable.

From then it can either be used to monitor the stomach for up to a month through an embedded camera, or it can be used to administer and control the absorption of a medication through the human body. Although it resembles the consistency of Jell-O, it has been coated with a "second, protective hydrogel layer to encapsulate the fast-swelling particles" (8) to withstand a thousand times stronger than regular stomach contractions. When it is time for the pill to be removed from the human body, the consumption of a Milk like calcium concentration but much stronger can shrink it back for excretion.

Currently, a number of clinical trials have been performed successfully on pigs, whose gut resembles that of humans, with sensors that measure temperature and there are more scheduled in the future.

Although this innovative formulation is examined for more applications in the area of "ingestible electronics", the idea of monitoring certain bacteria or viruses or even "image the progress of tumors or ulcers, over the course of several weeks", in combination with the administration of advanced therapeutic prescriptions, paves the way to more customized and reliable treatment solutions that defy existing formulation barriers and hinder pharmacokinetics.