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Can 3D Printers Create Viable Personalized Therapy in the Treatment of Diabetes?

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Abstract

This study aimed to use 3D printing techniques to create a drug tablet containing two commonly used active ingredients (metformin and glyburide) for treating diabetes in a single pill. The hypothesis was that both drugs can be given in doses not available commercially and that these pills will have appropriate hardness, and extended-release dissolution. I was able to create 48 tablets that contained evenly dispersed active ingredient powder and met the weight requirements with consistency between tablets. Unfortunately, we had to substitute the usual bulk excipient for another because it was incompatible with the metformin and the replacement (mannitol) may have swelled when exposed to the liquid binder. The tablets produced were tilted at the top, were softer than normal, broke more easily, and dissolved too quickly. In future studies, we need to adjust the formulation to enhance hardness and maintain the tablet structure.

Introduction

The 34 million patients with type II diabetes require combination therapy to control their blood glucose and prevent diseases such as strokes, blindness, and kidney failure. Metformin and glyburide are antidiabetic prescription drugs made in bulk in factories. Madsen *et al.* tried to evaluate the effectiveness of this combination treatment and found inconclusive results in addition to an increased risk for hypoglycemia with these two drugs.[1] Why might that be? For

metformin, available pills come in 500mg or 850mg pills while glyburide is available in 5mg or 10mg pills. If a patient requires 8.5mg of glyburide and 760mg of metformin for the maximal benefits with minimal adverse events, they are out of luck. Glyburide pills can be cut in half, but that means the patient must take 1½ tablets to approximate the optimal dose. Metformin pills cannot be cut, so the prescriber must choose between a higher dose with better benefits but more adverse events or a lower dose with inadequate benefits but fewer adverse events. Taking 2 ½ pills a day to treat one disease would reduce patients' willingness to take the drugs over the long term. When faced with the decision, people often choose a higher dose to avoid the strokes, blindness, and kidney failure that come with not adequately treating their diabetes. This puts them at risk of hypoglycemia, as the aforementioned study found, and other adverse events. What if a patient could receive a tablet, created by a 3D printer right in a pharmacy, that has the active ingredients from both drugs in one tablet at exactly the dose that patient needs?

Up to this point, different researchers have used 3D printing to achieve goals like creating a pill with six different drugs that each have unique drug release profiles[2], adding a customized extended release coating around a commercially produced pill[3], and making pills with tailored dosages of an anticoagulant *in vivo*[4]. Many techniques have been used, from mixing the active ingredient into a base powder[5], crystallizing the active ingredient and melting it with a laser onto the building pad[2], and dissolving the active ingredient in the liquid binder[6]. The lab I will be working in has an Inkjet 3D printer, so active ingredients can be added in either the base powder or with the liquid binder. Metformin is soluble in water[7] but comes in a high dose commercially, so putting enough metformin in the binder would create an unfavorable dripping pattern. Glyburide is only soluble in water at a high pH[8], which could harm the print head. As such, I added both drugs into the base powder. I also combined the previously established goals of

having multiple drugs in one pill, using non-commercially available dosages, and having an extended release dissolution time. My finished product used this technology to improve upon the specific combination drug therapy for type II diabetes of metformin and a sulfonylurea (glyburide).

Materials and Methods

UV-Vis spectroscopy was used to create calibration curves (shown in figure 1) for each of my active ingredients by finding the absorbance readings of their known concentrations. This allowed me to analyze the concentration of the active ingredients at various steps. Next, I developed a powder formulation that had a water-soluble excipient (mannitol), an extended-release excipient (Hypromellose), a water soluble binder (Kollidon), and my two active ingredients (metformin and glyburide). My formulation was 72% mannitol, 10% metformin, 9% Hypromellose, 8% Kollidon, and 1% glyburide. For my liquid binder, I used a 5% Kollidon solution. To blend the powder, I used a V-blender at 29 rotations per minute for 18 minutes at 40% fill volume. I analyzed the blended powder with UV-Vs spectroscopy to ensure that it was fully incorporated. Then, I loaded the blended powder mixture and the liquid binder solution into the HuskyJet 3D printer and printed my tablets.

The HuskyJet is a custom built InkJet 3D printer that creates pharmaceutical tablets. As shown in figure 2, it works by spraying a layer of powder from the powder reservoir onto the building platform, dropping the liquid binder from the ink reservoir onto this layer using the print head, and then rolling the binder into the powder to combine them.

I analyzed my printed tablets for inter-tablet weight variation using an electronic scale, friability using a friability tester at 25 rotations per minute for 4 minutes, hardness using an Okey hardness tester, and dissolution behavior using a United States Pharmacopeia (USP) dissolution

apparatus II. I will analyze these tablets again after three months and six months to assess the long-term stability.

Results

Upon visual inspection, I found that the tablets were slanted instead of straight like a commercial tablet. This is shown in figure 3. The average deviation of tablet weight was 3.25%. This passed the United States Pharmacopeia (USP) standards of having less a than 15% average weight deviation. In the friability tester, the tablets lost 27% of their weight. This failed the USP standard of having less than 1% weight loss. I found that the average hardness was 1.1 kg/force from the Okey hardness tester. Most tablets tend to be between 4 and 8 kg/force, and I was aiming for the high end of this range, since it was meant to be extended release. The dissolution time was between 1 and 3 hours. The dissolution behavior is shown in figure 4. The peak in the data is a misreading because any reading over an absorbance of 2 is inaccurate. When the absorbance reading declines, that means the tablet has fully dissolved.

Discussion and Conclusion

The inter-tablet weight variation passing USP standards means that the HuskyJet 3D printer successfully created tablets of similar size. However, the tablets were not the correct shape and were too soft. Since the problem is not the 3D printer, I believe the problem is the formulation. I think the tablets were slanted because when the liquid binder was jetted onto the powder, the powder absorbed it and expanded. So, when the roller reached the powder, it shifted the tablets, making them slant instead of compress. Because of this problem, we had to increase the layer thickness, which means the liquid binder was not able to seep through the entire layer, and it didn’t bind as well. This made my tablets soft. To solve this problem, I will change the formulation. My lab has never tried to use mannitol as the main excipient before. Previous

experiments have determined that lactose monohydrate is the best water soluble bulk excipient for 3D printing. However, lactose monohydrate undergoes the Maillard reaction when in presence of metformin, which could inactivate it. That is why I substituted lactose monohydrate for mannitol. Therefore, I will have to experiment with mannitol in the formulation, like changing the percentage of mannitol or adding another bulk ingredient that will not swell. In addition to changing the formulation, I will also use a film coater to put a coating on the tablets that could improve their friability, hardness, and dissolution behavior.

If I succeed in making this tablet, there could be further studies of the 3D printed drugs *in vitro*. The next step will be to assure that the tablets, and the active ingredients inside them, are stable for 90 days, the time a person would use a personalized tablet for. After this step, there is work *in vivo* to show whether this process works the same inside a living being. Later, there could be large clinical studies of these 3D printed tablets with exact dosages used to treat diabetes in comparison to taking separate commercial metformin and glyburide. Since type II diabetes is a long-term disease, an easier treatment can make a big change for people living with it. Furthermore, if I can make a single pill that is more effective for treating diabetes, then eventually, custom pills can be made to treat multiple diseases. Pill burden decreases quality of life, particularly for the elderly population, so consolidating multiple medications into a single dose can improve the lives of countless patients. 3D printing technology is revolutionary for personalized medicine. Eventually, there could be a 3D printer in every pharmacy to make a particular pill for each person who needs one.

In conclusion, we were able to create tablets with the appropriate amount of active ingredients and with consistent weight. However, we need to further refine our formulation to overcome our excessively soft tablets in the next experiment.

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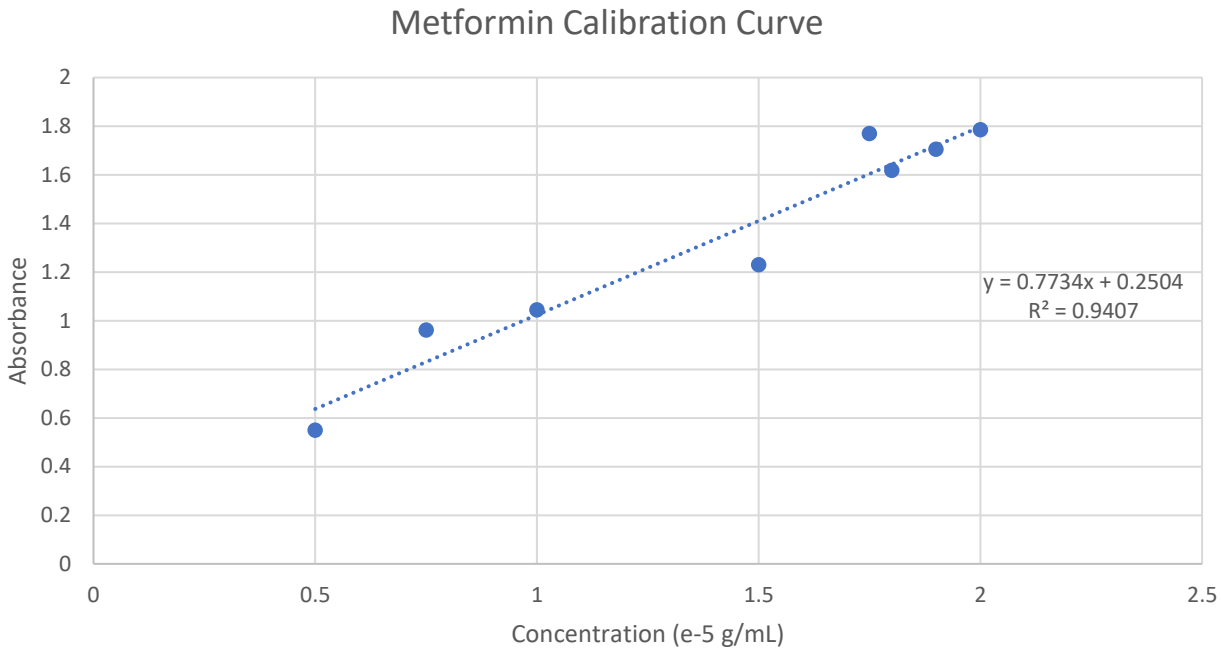
Figure 1: UV-Vis spectroscopy calibration curves of active ingredients



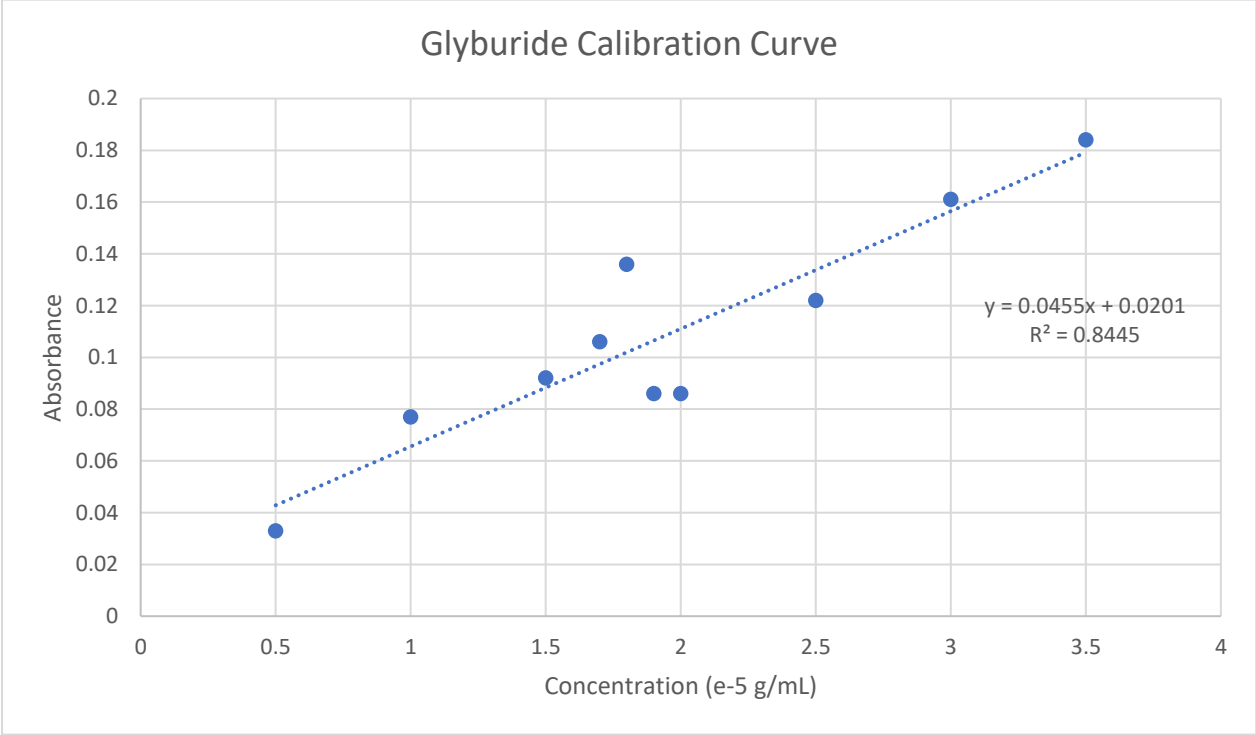


Figure 2: Process of 3D printing drugs[9]

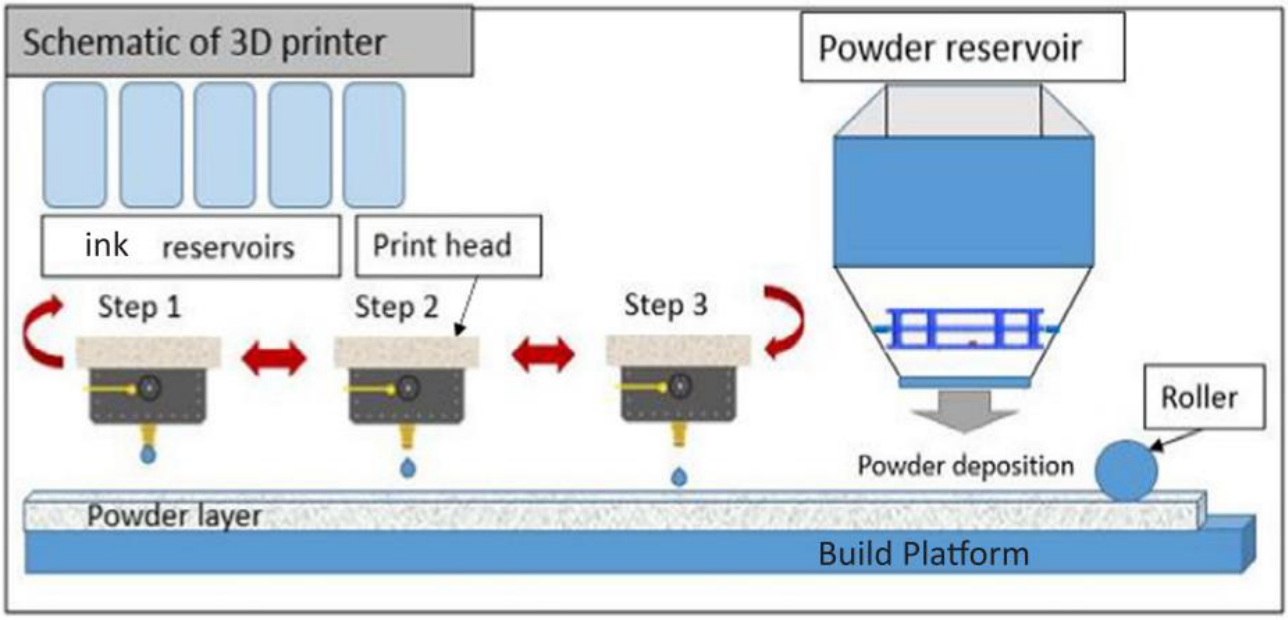
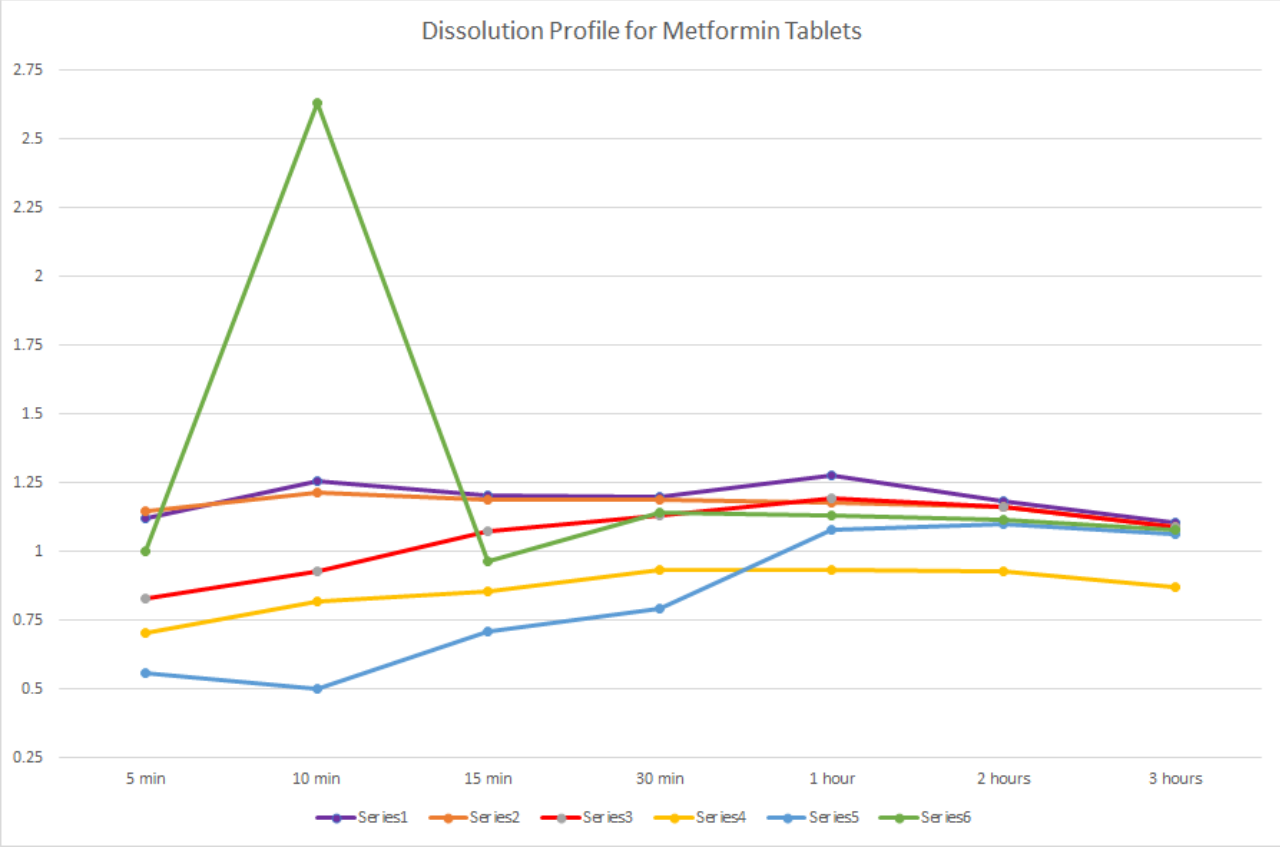


Figure 3: 3D printed tablets

3a

3b

Figure 4: Dissolution behavior of metformin



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