Hydraulic Permeability of 25/75 HEMA/TBM Particles

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Table of Contents

Abstract

In order to remove the benzalkonium chloride preservative present in ophthalmic solution, filter tips are packed with HEMA/TBM particles. In this paper, the hydraulic permeability of 25 % HEMA and 75 % TBM particles was experimentally determined for four size fractions (63-125 µm, 125-250 µm, 250-500 µm, and >500 µm). The hydraulic permeability was determined by measuring volumetric flow under a pressure drop of 40,530 Pa. The results showed that the hydraulic permeability ranged from 1.87 to 5.41 Darcy for the 63-125 µm and >500 µm size fractions respectively. Additionally, the hydraulic permeability was evaluated for three mixtures of the smallest and largest particle size. The three mixtures were mass ratios of 25/75, 50/50, and 75/25. Results from these trials showed a heavier dependence on the smaller size fraction. Overall, the hydraulic permeability increased with larger particle sizes.

Introduction

In modern ophthalmic medicine, the easiest way to treat many ocular diseases is through the use of self-administered eye drops. Many topical eye drop bottles utilize a preservative to prevent the formation of microbial growth and improve shelf life, specifically benzalkonium chloride (BAK). Despite its benefits as a preservative, BAK has been associated with several damaging effects on eye health. These include inflammation, tear film instability, and corneal damage [4].

As a solution to the damaging effects of BAK, research was conducted into the applications of a particle bed that could absorb the preservative prior to dispersion out of the eye drop bottle. Particles composed of 2-hydroxyethyl methacrylate (HEMA) and tert-butyl methacrylate (TBM) have shown a high affinity for BAK removal with limited disruption to drug dosage [4].

2-hydroxyethyl methacrylate is made from methacrylic acid or methyl methacrylate [3]. The synthesis of the HEMA monomer can be performed via a reaction with methyl methacrylate and ethylene glycol or methacrylic acid and ethylene oxide [3]. However, both these reaction schemes result in the unwanted byproduct of ethylene glycol dimethacrylate [3]. In order to purify the HEMA monomer, the reaction products are exposed to hexane and water [3]. The ethylene glycol dimethacrylate is soluble in hexane, while HEMA is not [3]. This allows the two products to be separated with the HEMA monomer being extracted in diethyl ether [3]. The commercially available HEMA used in these trials was acquired from Sigma-Aldrich Chemicals. Tert-butyl methacrylate is an ester utilized in polymer synthesis [5]. TBM provides hydrophobicity and high reactivity as a result of its methacrylate designation [5]. Due to its ability to rapidly form copolymers and homopolymers, the TBM requires a stabilizer or inhibitor to prevent polymerization [5]. The TBM used in these trials was purchased from Sigma Aldrich at larger than 98% concentration.

Particles in this experiment were created via free radical polymerization. 2-hydroxyethyl methacrylate (HEMA) monomer is combined with tert-butyl methacrylate (TBM) in a 25 % to 75 % ratio. The HEMA monomer and TBM were combined with the ethoxylated trimethylolpropane tri acrylate (SR9035) cross linker as well as a photo initiator and deionized water [4]. Upon being stirred thoroughly and purged with nitrogen, the particles were UV cured within a petri dish covered with Parafilm M [4]. Once polymerization occurred, the gel was recovered from solution via vacuum filtration [4]. The vacuum filtered product was a gel that was then soaked in ethanol overnight [4]. The gel was vacuum filtered once more and subsequently soaked in deionized (DI) water for several days [4]. These procedures all served to purify the HEMA gel. The final product was dried in an oven at 80 ^{o}C [4]. Once dried the particles were crushed using a mortar and pestle and then sieved in order to separate particles into four size fractions. The size fractions were 63-125 microns, 125-250 microns, 250-500 microns, and >500 microns.

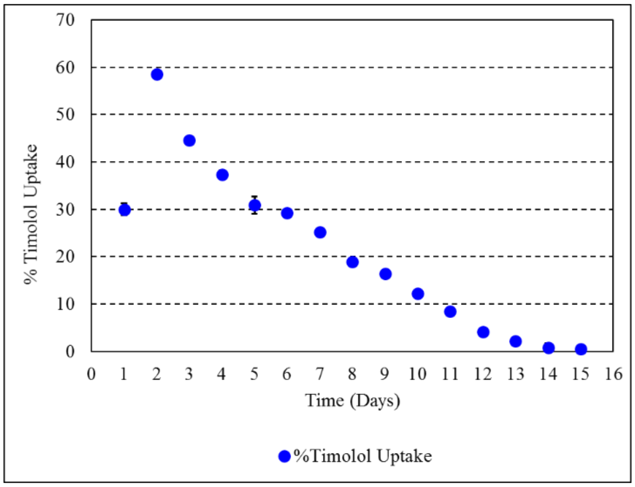


Figure 1. Drug uptake of p-HEMA only particles

Conducted research showed the effectiveness of these developed particles in achieving over 95% BAK removal [4]. Although initially the particles were only composed of HEMA, those trials showed a high drug uptake, which would invalidate the particle bed [4]. This high drug uptake in purely HEMA particles can be seen in Figure 1 [4]. As a solution to the high drug uptake from HEMA particles, the TBM was introduced, yielding the 25 % HEMA and 75 % TBM formulation. The BAK removal in these particles was still higher than 95%, with minimal drug uptake [4]. This can be seen in Figure 2 [4].

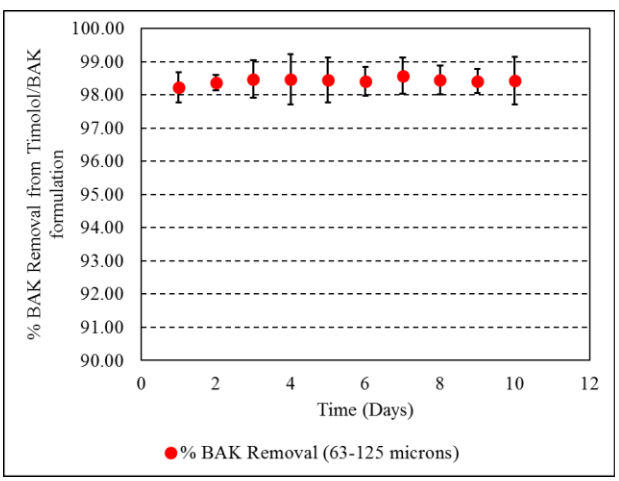


Figure 2. BAK removal of 25% HEMA 75% TBM 63-125 µm particles

Now that we know the ideal particle formulation to provide optimal BAK removal, we can evaluate the properties of these packed beds. In order to apply these packed bed particles in industry, the particles must allow for sufficient flow without a significant increase in the pressure necessary to propagate flow. This is directly related to the hydraulic permeability of these packed beds. Hydraulic permeability defines the ability of water to flow through a porous medium. The hydraulic permeability is a function of flow rate, pressure drop, filter bed length, and fluid viscosity. The research conducted here explores the hydraulic permeability of these particles under constant pressure drop. All four size fractions were tested in order to determine a range of hydraulic permeability.

Relevant Equations and Calculations

The calculations conducted throughout these experiments are dependent on Darcy's law, which defines the velocity of a laminar flow based on the pressure drop across a packed bed. As shown in the equation below, the velocity through the packed bed is dependent on the hydraulic permeability (κ), viscosity (μ), pressure drop (ΔP), and length (L) [2].

$$u = -\frac{\kappa \Delta P}{\mu L}$$

The viscosity used in these trials was the viscosity of water, which is .00089 Pa s. L is the length of the filter bed, which was measured as 5.92 mm with a micro caliper. Because trials in this experiment determine the volumetric flow rate, the above equation can be rearranged in terms of volumetric flow rate and area.

$$Q = -\frac{A\kappa \Delta P}{\mu L}$$

The cross-sectional area, *A*, of the filter bed is 12.1 mm^2 or 1.21×10^{-5} m^2. This was calculated by determining the circular area with a diameter of 3.93 mm, which was measured with a micro caliper.

In order to determine the pressure gradient, the ideal gas law was utilized. The temperature (T), number of moles (N), and gas constant (R) were all assumed to be held constant, which provided an equation relating two pressures and two volumes. In these trials, P_1 was the pressure of the air in the filter bottle once a volume of 3 mL had been dosed out. Because the bottle was exposed to the atmosphere, it was assumed the 3 mL of air reached atmospheric pressure. An additional 2 mL were dosed out, bringing the volume within the bottle to 5 mL, while the moles of air within the bottle remained constant. Therefore, we can solve for the pressure within the bottle, P_2.

$$PV = NRT$$

$$P_1 V_1 = P_2 V_2$$

$$P_2 = P_1 \frac{V_1}{V_2}$$

Assuming P_1 is atmospheric pressure at 101325 Pa, P_2 was determined to be 60,795 Pa. Once P_2 was known, it could be used to determine ΔP. As shown in the diagram below, the pressure drop is P_b minus P_a. In this case, P_b is equivalent to P_2 because P_b indicates the downstream pressure in the direction of flow. In this case P_a is the atmospheric pressure, or 101325 Pa, since the other end of the bottle is exposed to the atmosphere.

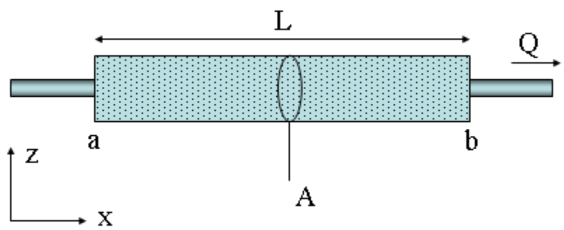


Figure 3. Pressure versus direction of flow diagram [1]

Now that all the values are known, they can be plugged into the equation above. After solving for the hydraulic permeability in units of m^2, it could be converted to Darcy.

Upon conducting this research and obtaining valid hydraulic permeability data, we attempted to utilize the Ergun Equation in order to calculate the theoretical hydraulic permeability after assuming (or determining) porosity. The Kozney-Carman equation, presented below, is closely related to the Ergun Equation and related pressure drop through a packed bed for laminar flow.

$$\frac{\Delta P}{L} = -\frac{150\mu}{\varphi_s^2 D_p^2}\frac{(1-\varepsilon)^2}{\varepsilon^3} v_s$$

In this case, φ_s is the sphericity of the particles and D_p is the particle diameter. Based on Darcy's law, we know that the superficial velocity, v_s, is a function of hydraulic permeability, as shown below. By combining the equation below with the one above, we can determine the hydraulic permeability as a function of porosity, particle diameter, and sphericity.

$$v_s = -\frac{\kappa \Delta P}{\mu L}$$

$$\kappa = \frac{\varphi_s^2 D_p^2}{150}\frac{\varepsilon^3}{(1-\varepsilon)^2}$$

Another opportunity to determine the theoretical hydraulic permeability is to determine the effective hydraulic permeability, which accounts for any resistance from the base. By rearranging Darcy's law, we can say hydraulic permeability is as follows.

$$\kappa = -\frac{Q\mu L}{A\Delta P}$$

For flow through two consecutive packed beds, we can assume that the pressure drop is additive. The length can also be assumed as additive. The pressure drop terms can then be replaced in terms of the individual hydraulic permeabilities. Some simplification leads to the following equation. This allows the calculation of the effective hydraulic permeability from two unique beds.

$$\kappa_{eff} = -\frac{Q\mu(L_1 + L_2)}{A(\Delta P_1 + \Delta P_2)}$$

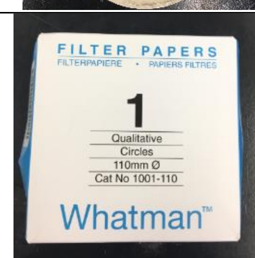
$$\kappa_{eff} = -\frac{Q\mu(L_1 + L_2)}{-A(\frac{Q\mu L_1}{A\kappa_1} + \frac{Q\mu L_2}{A\kappa_2})}$$

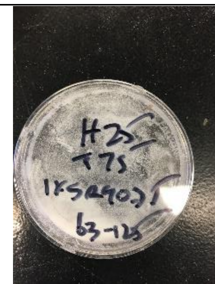
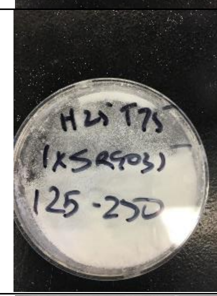
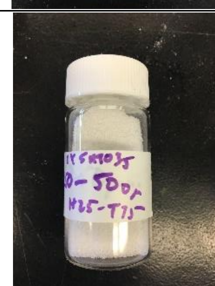
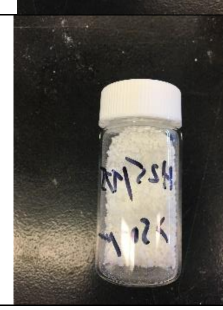
$$\kappa_{eff} = \frac{L_1 + L_2}{\frac{L_1}{\kappa_1} + \frac{L_2}{\kappa_2}}$$

Materials

The materials necessary for this experiment are as follows:

Material	Description	Image
A plastic filter tip	The tip was attached to the filter bottle and packed with particles.	

A plastic filter bottle	The bottle was filled with DI water and secured with the filter tip. It was used to dose out the required amount of water.	
Graduated cylinder	5 mL glass graduated cylinder was used to keep track of all volume of liquid dosed.	
1 mL pipet stem	Pipet stem was sliced off of the pipet in order to create an easy method of determining volume flow. The pipet stem was attached to the filter plug with tape.	
Marking tape	3M Comply Indicator Tape was used to attach the pipet stem to the filter tip.	
Filter paper	Standard Whatman 110 mm filter paper circles were cut into squares to plug the filter tip.	
Filter cloth	Standard fibrous filter cloth was used to keep the bed stabilized and prevent dispersion.	

3-D printed base	A small base was 3-D printed to fit the upper base of the filter tip without falling into the lower base of the tip. The 3-D printed base was made out of PLA.	
25/75 HEMA/TBM particles 63 - 125 µm	Particles were crushed and sieved. The particles within this size fraction were collected in their respective mesh.	
25/75 HEMA/TBM particles 125 - 250 µm	Particles were crushed and sieved. The particles within this size fraction were collected in their respective mesh.	
25/75 HEMA/TBM particles 250 - 500 µm	Particles were crushed and sieved. The particles within this size fraction were collected in their respective mesh.	
25/75 HEMA/TBM particles >500 µm	Particles were crushed and sieved. The particles within this size fraction were collected in their respective mesh.	

Method

Trials were conducted by packing particles of four different size fractions into a filter tip to a precise length. As shown in Figure 4, the filter tip used has two sections of differing diameters.

In order to ensure consistency, only the bottom section of the tip was packed with particles. Any tapering of the tip was considered relatively minute, and therefore negligible. The tip was first packed with two small squares of filter paper in order to keep the particles within the bed. Then, the particles were added to fill the lower base of the tip. The tip was subsequently packed with a piece of filter cloth to keep the bed stable during trials.

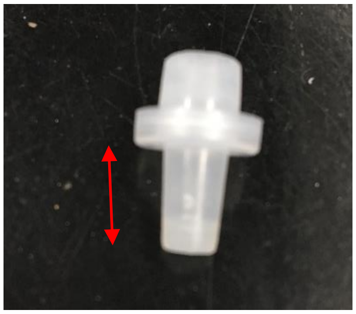


Figure 4. Image of filter tip

In the second round of trials, the filter cloth was eliminated and replaced with a 3-D printed base that fit into the upper section of the tip (the larger diameter section) as shown in Figure 5. Due to the diameter of the base being too large to fit into the lower section, it prevents an over-filling of particles as well. The 3-D printed base contained grating that had to be blocked with two additional squares of filter paper.

Figure 5. Green 3-D printed base within filter tip

Once a bed was packed, a filter bottle filled with deionized water to the maximum capacity. At this point the tip was secured onto the bottle and the stem of a pipet was attached to the tip using tape. The stem of a 1 mL standard pipet was cut in order to be able to view the flow of the water more efficiently. The filter bottle setup can be seen in Figure 6 below.

Figure 6. Filter bottle with attached pipet stem

Once the bottle was secured with the packed tip, 3 mL of DI water was dosed out into a graduated cylinder. The pressure within the bottle was then allowed to equalize with atmospheric pressure. Soon after, an additional 2 mL was dosed out into the graduated cylinder. The final 2 mL dosage was recorded so it could be replayed and timed to determine volumetric flow. Figure 7 shows a screenshot of one of the videos utilized. In this image, the blue arrow indicates the water line, while the two black arrows indicate the volumetric markings on the pipet stem. The volume in between these two markings is .25 mL.

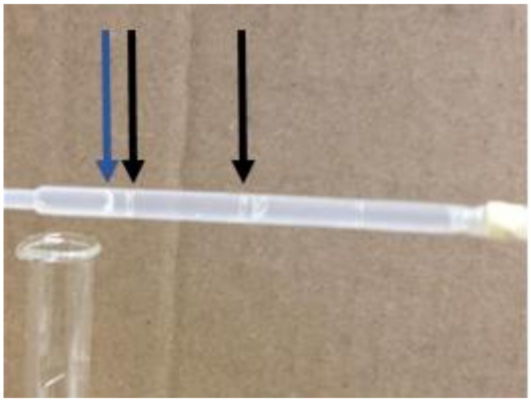


Figure 7. Example of videos used to determine volumetric flow rate

The designated volume markings on the pipet stem were used as approximations of volume. The amount of time for the water to pass through that region was determined by re-inspecting each video and determining the duration of flow. The video was paused when the water line reached the first marking. It is then restarted and paused again when the water line reaches the second marking. The elapsed time between these two moments was recorded. Once the time was determined, the volume of water was divided by the time taken for the water to move that volume. This yielded the volumetric flow rate. This process can be seen in Figure 8 below. As we can see on the left, the water line is at the first volumetric marking, which indicates the start time, and on the right, it is at the second volumetric marking, which would be the stop time.

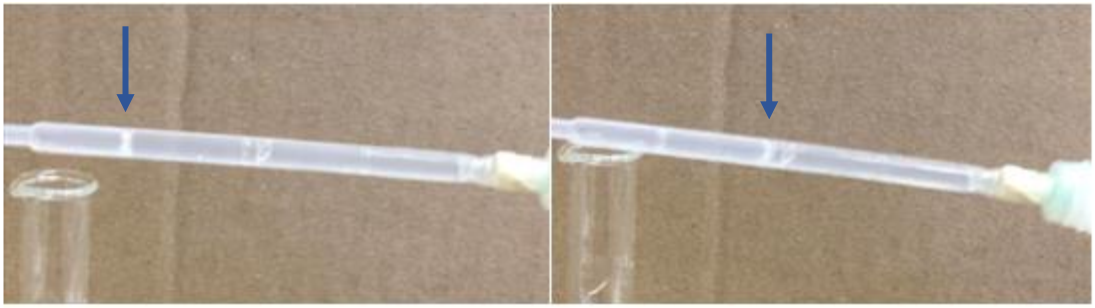


Figure 8. Water line at first volume indicator line (left) and at second volume indicator line (right)

Upon conducting these trials with all four size fractions, the largest and smallest size fractions were mixed in order to evaluate the dependence of hydraulic permeability on size. The procedure to measure hydraulic permeability was identical to that described above. However, prior to filling the particle tip, the particles, 63-125 micron and >500 micron, were weighed and combined in accordance with the fractions listed in Table 1 below. In order to ensure even dispersion of both size fractions throughout the tip, the particles were combined in a weigh boat and mixed. The mixed batch of particles was then packed into a tip with the procedure described above.

Ratio by mass (smallest size fraction/largest size fraction)	Weight of 63-125 μm particles (g)	Weight of >500 μm particles (g)
25/75	.02	.06
50/50	.04	.04
75/25	.06	.02

Table 1. Mass distributions for 63-125 and >500 micron particles

Results and Discussion

Overall, the data showed an increase in experimental hydraulic permeability as particle size increased. This is representative of the increased porosity in a bed packed with particles of higher size fractions. The increase in gaps allows more water to pass through. This trend can be seen in Figure 9. Table 2 also provides the hydraulic permeability values in Darcy.

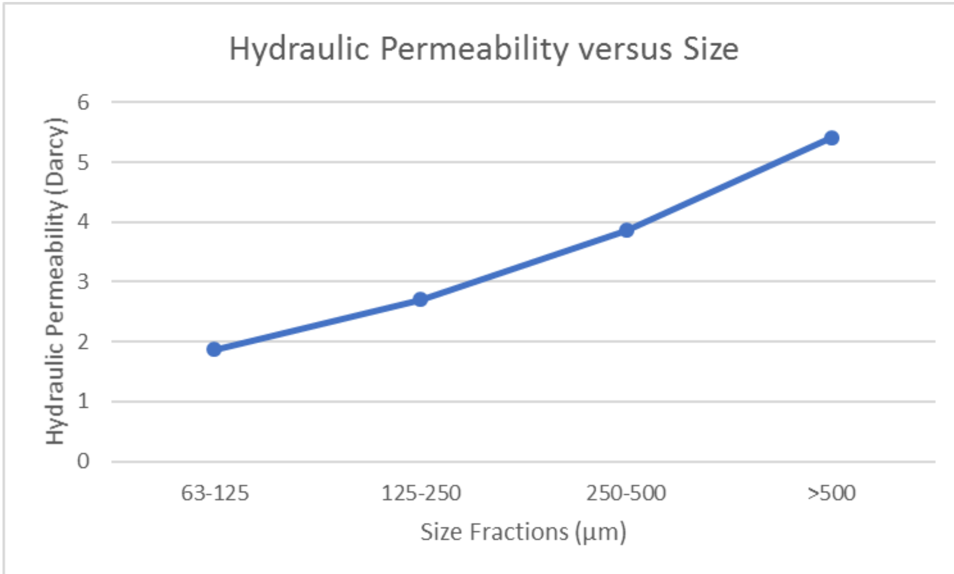


Figure 9. Hydraulic permeability versus various size fractions (without filter cloth)

Size Fraction (µm)	**Hydraulic Permeability without filter cloth (Darcy)**	**Hydraulic Permeability with filter cloth (Darcy)**
63-125	1.87	1.04
125-250	2.71	1.57
250-500	3.87	1.95
>500	5.41	3.85

Table 2. Hydraulic permeability of each size fraction of tested particles

In Figure 10, there is a clear difference between the trials conducted with the use of a filter cloth and those without a filter cloth. The trend across all four size fractions suggests that the filter cloth was providing significant resistance to flow through the filter tip. The filter cloth could also cause excessive packing of the filter bed because it could be forced into the lower section of the tip. Additionally, it appeared the filter cloth was absorbing excess water, which could lead to the resistance. These results show that industrial applications for a packed bed should not be performed with a filter cloth due to the increased pressure required to propagate flow.

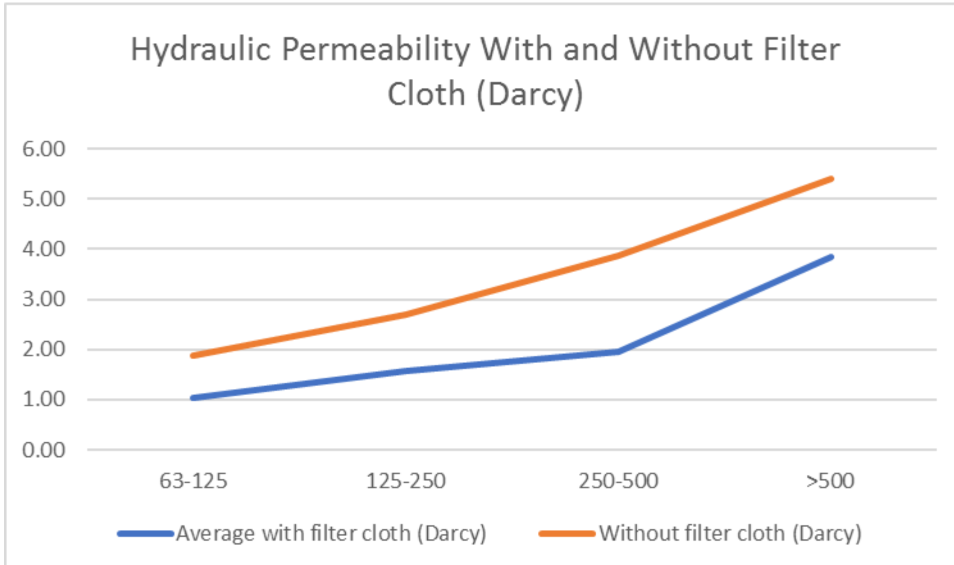


Figure 10. Hydraulic permeability determined with the use of filter cloth and without

Upon evaluating the effect of mixing particle size fractions, there was a larger dependence on smaller size fractions than larger size fractions. As we can see in Figure 11, hydraulic permeability increased as the ratio of larger size fractions increased. Figure 11 also depicts the hydraulic permeability of the two pure size fractions. This shows how the hydraulic permeability of the mixed ratios compares to the original pure size fractions.

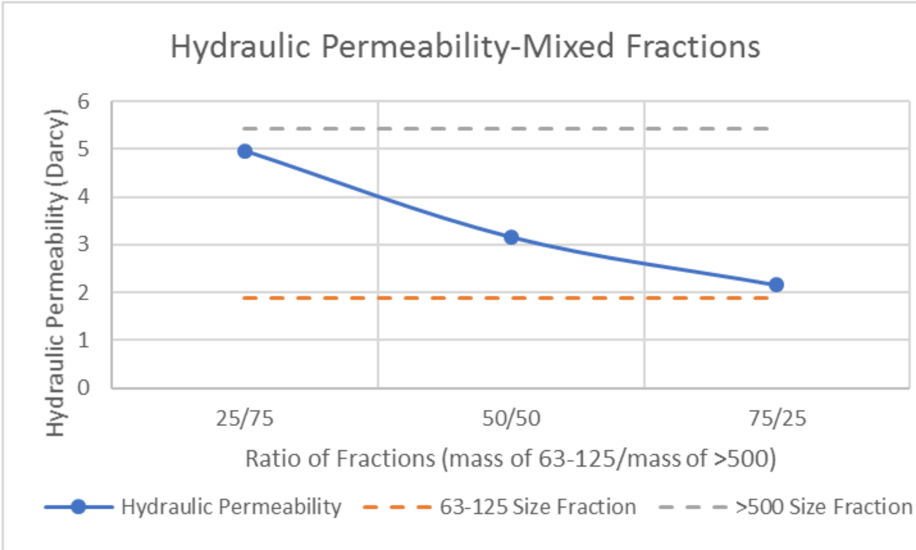


Figure 11. Hydraulic permeability of mixed fraction trials

When the particle bed is 50 % 63-125 µm by mass and 50 % larger than 500 µm by mass, the hydraulic permeability is more similar to that of the 63-125 µm size fraction. This can also be demonstrated by the percent proximity in hydraulic permeability from the pure size fractions to each of the mixed fraction trials. This can be seen in Figure 12, where the percentage proximity is shown on the hydraulic permeability graph shown above.

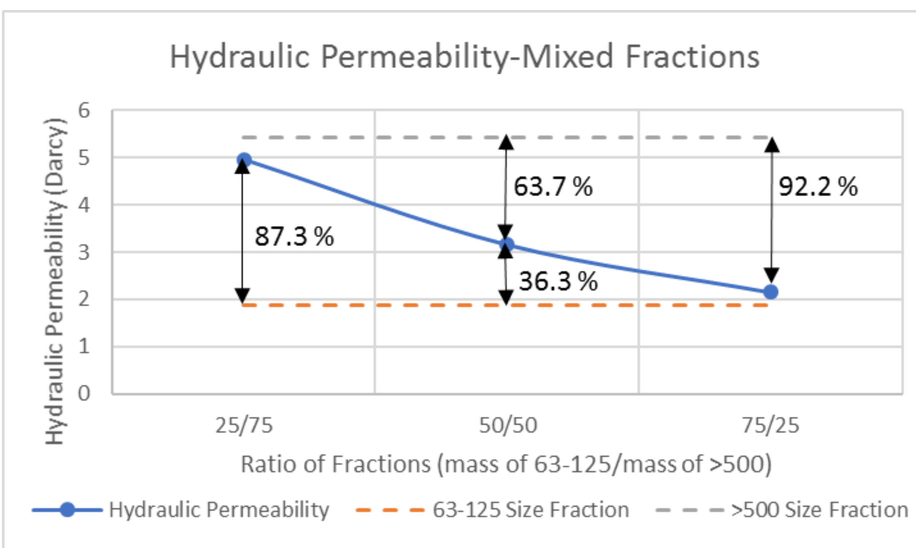


Figure 12. Hydraulic permeability of mixed size fractions with percent proximities

As indicated by the percent proximity, the difference between the 50/50 mixed fraction trial and the pure 63-125 μm is only 36.3 % compared to the 63.7 % difference between the mixed fraction and the > 500 μm particles. This demonstrates the greater dependence on the smaller size fraction, as predicted. This is likely due to the ability of the smaller particles to fill the gaps created by the porosity of the larger particles.

When attempting to confirm the theoretical hydraulic permeability by using the Kozney-Carman equation, a sphericity of 1 could not be used. It is fairly clear that these particles are not entirely spherical. Upon a closer examination of the particles, it is evident that the sphericity is fairly low. Assuming a sphericity comparable to that of sand, which is .75, and a porosity of .4, we see the values shown in Table 3 below [2]. In the same table, we can see the calculated hydraulic permeability with an assumed porosity of .4 but a sphericity of .5. Although the latter yields hydraulic permeability values more similar to experimental results, there were still significant differences, particularly when the larger size fractions are concerned.

Size Fraction (μm)	**Hydraulic Permeability (sphericity of .75)**	**Hydraulic Permeability (sphericity of .5)**
63-125	2.67	1.19
125-250	10.52	4.68
250-500	42.09	18.71
>500	168.35	74.82

Table 3. Hydraulic permebility based on an assumed porosity of .4 with two different sphericities

The next attempt to confirm the theoretical hydraulic permeability was to determine the effective hydraulic permeability. It was possible that the green 3-D printed base was still providing significant resistance to flow. By measuring the hydraulic permeability of the base by itself and equating it to κ_1, we can determine the effective hydraulic permeability using the equation above. In this case, the theoretical hydraulic permeability is κ_2. The results of these calculations can be seen in Table 4.

Size Fraction (µm)	K_{eff}	K_1	K_2
63-125	1.33	4.57	1.19
125-250	4.66	4.57	4.68
250-500	12.93	4.57	18.71
>500	23.23	4.57	74.82

Table 4. Effective hydraulic permeability based off of theoretical calculations

Even with these calculations, there is a clear misalignment between the experimentally determined hydraulic permeability and the theoretical hydraulic permeability. These deviations affirm that there is a clear need for more extensive research into the theoretical hydraulic permeability in order to verify experimental results.

Conclusion

Overall, these experiments have shown reasonable hydraulic permeability, indicating that the packed bed could be applied in industry. These results indicate some resistance from the particle bed. The smallest size fraction could produce significant resistance, although it could be optimal for BAK removal.

An evaluation of the hydraulic permeability of these packed particle beds shows that they would provide a useful BAK removal mechanism without requiring excessive pressure to propagate flow. This is crucial to the ability of these packed beds to be implemented in commercial products. The packed filter tip cannot detract from the convenience and applicability of eye drop bottles.

Future Work

There is an opportunity for future experimentation to achieve greater agreement to theoretical calculations. One possibility could be to expand the length of the packed bed. The largest discrepancy between theoretical and experimental hydraulic permeability occurs at the largest size fraction. This could indicate that as the resistance from the packed bed itself decreases, the resistance of the base becomes overpowering. With a much larger packed bed, this issue could be avoided.

Another possible experiment is to alter the method by placing a weight atop a syringe packed with particles and water to force flow through the packed bed. This differs from the method used previously in that it does not generate a vacuum to create a pressure drop. The syringe would also allow for a longer packed bed with no base needed since dispersion into a filter bottle is not a possibility. However, this method might not be realistic to industrial applications since it does not reflect the flow from a filter bottle.

Overall, the largest opportunity for improvement is an exploration into the theoretical hydraulic permeability. An understanding of why experimental values and theoretical values differ so sharply is crucial to the application of these particles for BAK removal.

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