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Manufacturing process for hydrogel vessel phantoms

Abstract: Phantoms mimicking special physiological processes of the human body are essential for evaluating prototypes of medical devices. Especially for thermometric MRI measurements, the temperature distribution in the brain needs to be simulated. Since this parameter is dependent on the tissue perfusion, a new hydrogel by MAGDASSIS et al. was evaluated in this work for building models with hollow artery structures. This hydrogel can be polymerized through UV-light due to the nanoparticles contained in it. Additionally, thermal parameters were measured and compared to human brain tissue. The indirect manufacturing of hydrogel phantoms showed good qualitative results for vessels with a diameter > 3 mm. In this process a 3D printed wax core was inserted in the hydrogel and the structure was then UV cured after molding. After curing the core was dissolved in an isopropanol bath. The thermal properties, obtained by the transient plane-source-method, showed similar values compared to that of human brain tissue mentioned in literature. Further limitations in the manufacturing process needs to be overcome to use the indirect manufacture approach for smaller vessels of the brain.

Keywords: Hydrogel, nanoparticles, phantom, MRI, human brain tissue.

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1 Introduction

Every year, 500,000 people in Germany suffer from a stroke ¹. Failure to treat the patient in time will damage the brain ². For the research and development of stroke therapy, it is necessary

to first evaluate the respective processes on a suitable phantom before they can be approved for use on the patient ^{3,4}.

In the medical field phantoms are used for evaluation of conventional imaging techniques ⁵. However, due to material property mismatch, current phantom models are incompatible for temperature distribution measurement in the MRI. Either the material cannot be shaped correctly ⁶ or their material properties are too different from those of the brain ⁷, which means that no realistic evaluation is possible.

One solution to this problem could be the use of hydrogels. Due to the high water content, these gels are similar in their properties to those of the brain ⁶. Marketable gels have been existing for a long time, but they are difficult to get into a suitable form. This could be remedied by a hydrogel developed by Casali Center of Applied Chemistry (The Hebrew University of Jerusalem) ⁸. Due to the nanoparticles (NP) it contains, which initiate polymerization when excited by UV light, it could be used in a casting process.

The aim of this work was therefore to reproduce cerebral vessels as well as the tissue in the brain. The material used should have a similar temperature behavior as the brain tissue. This similarity should ultimately provide the opportunity to simulate for example the temperature changes inside a brain during a stroke.

2 Materials and Methods

2.1 Hydrogel

The hydrogel used in this work contains nanoparticles as UV-curable ink. „The extinction coefficient of the new water-dispersible nanoparticles of 2,4,6-trimethylbenzoyldiphenylphosphine oxide (TPO) is more than 300 times higher than the best and most commonly used commercial water-soluble photo initiator. The TPO nanoparticles absorb the light in the range of 385 nm to 420 nm, which allows the hydrogel to be used for light-emitting diode-based curing with digital light processing.” ⁸

The exact contents of the hydrogel used are listed in Table 1.

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All ingredients are mixed and magnetically stirred under a hood for 3 minutes until complete dissolution of the particles.

Table 1: Contents of TPO-NP-Hydrogel.

Contents of TPO-NP-	percent by weight [%]
acrylic acid	23.8
PEG diacrylates 600	2.4
TPO nanoparticles	2.4
isopropanol	23.8
distilled water	47.6

Particularly important parameters are thermal conductivity and heat capacity (Table 2).

Table 2: Thermal properties of Hydrogel compared to brain and gelatin

Material	Thermal conductivity k in $\left[\frac{W}{mK}\right]$	Heat capacity C in $\left[\frac{J}{kgK}\right]$	Geometry
Gelatin ⁹	~0.55	~3900	Simple geometry
TPO-NP-Hydrogel	0.3-0.6	3610 +/-210	Complex geometry (3D printing possible)
Brain ¹⁰	0.528	3676	

The TPS2500s (Hot Disk, Sweden) was used to determine the thermal conductivity k and the heat capacity C of the TPO-NP-Hydrogel. Sensors with 6.4 mm and 9.2 mm diameter were used. The heating power of the sensors was 130 mW and the measuring time up to 640 seconds.

2.2 Manufacturing of the phantom

For manufacturing, a combination of 3D printing and a casting process was used. With a 3Z Pro 3D printer (SolidScape, USA) a negative of the print to be displayed was produced. The wax kernel was then placed in a mold, filled with a liquid hydrogel and polymerized in a UV cabinet for 30 minutes.

In order to remove the wax from the phantom in this work two approaches are pursued. According to the properties of the wax, it becomes liquid at a temperature above 70°C. To prevent dehydration of the phantom, the phantom is placed for 1 h in a 90°C water bath. After the bath, the wax should be liquefied and can then be removed out of the phantom using a syringe.

The manufacturer also states that residues of the wax can be easily cleaned with isopropanol. If the phantom is placed in an ultrasound bath filled with isopropanol for 3 h, the wax contained will dissolve.

Both processes are shown in Figure 1.

Figure 1: Production principle of a TPO-NP-hydrogel phantom by a casting process with a wax core. 1&2: Vessel is printed out of wax. 3: Removing the support structure if necessary. 4: Fix printed vessel in a plastic container. 5: Fill up the plastic container with unpolymerized hydrogel and cure it in a UV-cabinet. 6: Dissolve the wax through a ultrasound isopropanol bath or a hot water bath.

3 Results

3.1 Qualitative evaluation

As seen in Figure 2, there are small cracks on the entrances after loosening the wax core. In addition, the course in both test casts has expanded in the middle (diameter increased by ~60 %). The edge of the course is blue colored, which decreased to the outside. The edges of the phantom cylinder are slightly torn. The wax softened after the water bath but remained in the phantom. The core had to be pushed out of the phantom manually.

Figure 2: Comparison of the hydrogel samples with wax kernel before (a & b) and after dissolving (c & d) the wax through a 90°C hot water bath.

Figure 3 shows the process in which the wax core is dissolved by means of isopropanol ultrasound bath. Unlike Figure 2, the simple course of the vessel can be recognized without any deformation. The bluish color, however, is more pronounced. In addition, it appears that the entire phantom has a blue tint. Like in Figure 2 the phantom cylinder is slightly frayed. The swelling of the phantom returns to its original state after 5 hours drying in air.

Figure 3: Hydrogel sample before (a) and after (b) the three-hour isopropanol ultrasound bath with a dissolved wax core.

Due to the complications with the water bath for removing the wax core, only the isopropanol technique was used for a more complex course of vessels. The exposure time has been increased to 1 h due to the bigger size of the phantom.

Figure 4 shows the wax kernel alone (a) and the finished phantom after the wax kernel has been removed by ultrasound

bath (b). Unlike the previous samples, the phantom was very hot due to the absorbed energy from the UV radiation. Looking more closely at Figure 4 (b), it can be seen that air bubbles have formed within the phantom.

The course contains vessels of diameters between 1.5 mm and 4 mm. Vessels with a diameter larger than 2 mm could be produced without any problems. If the diameter is less than 2 mm, the accuracy and reproducibility of the course decreases.

Figure 4: (a) Wax core of a vessel course in a mold. (b) Phantom of a vessel course after the wax core has been dissolved by ultrasound isopropanol bath.

4 Discussion

The casting process with hydrogel and a wax core shows, that even complex structures like vessels can be manufactured. The hydrogel can cure in time without the wax core being already dissolved by the gel. It can be assumed that exactly the dissolution of the wax core is responsible for the strong bluish coloration on the edge of the vessel.

By removing the wax from the phantom, the method of isopropanol ultrasound bath has been evaluated. Unlike the water bath, the phantom is not exposed to high temperature, which prevents cracks in the phantom by the resulting expansion. Since the wax does not dissolve in the water but is softened, only simple structures could be produced with this method. More complex vascular structures could be damaged during the extraction of the wax structure. In the isopropanol process, the wax kernel dissolves completely in the isopropanol. The stronger bluish discoloration is most likely occurring exactly because of this. The hydrogel absorbs a part of the colored isopropanol in this process.

Blistering on larger phantoms was due to a leak in the plexiglass container. During the curing process, which first

takes place in the upper part of the phantom. Hydrogel has been leaking out at a permeable point between the plexiglass joints. Since the upper area had already hardened and therefore no material could flow, bubbles were formed. No blistering was observed using a small one-piece injection molded plastic box. Since the hydrogel consists in large proportions of isopropanol, it started to dissolve the wax kernel before the hydrogel had fully hardened. This effect is not so strong and still acceptable by vessels with a diameter larger than 2 mm. The smaller the diameter is the more noticeable this process becomes. Vessel diameters of 1 mm or smaller are thus not possible to manufacture, since the core has already dissolved before the hardening of the hydrogel. Capillary vessels are therefore not possible to manufacture with the current state of the technology.

A possible solution could be a coating of the wax. This coating would have to be resistant to isopropanol. After dissolving the wax through the isopropanol bath, the coating would have to be flushed out with another solution which does not damage the hydrogel but dissolves the coating. Another option for capillary vessels to be incorporated into the phantom would be to punch out material through a cannula. It turned out that heating the cannula tube up to 200°C reduces cracks while punching out the capillary vessels. Since isopropanol is easily volatilized, the storage of the phantom in an airtight container is recommended. The toxic surface of the phantom prevents the formation of moldiness and bacteria.

Hydrogel may not be the material with the closest thermal properties of the brain but compared to other materials it is possible to create complex shapes thanks to the nanoparticles.

5 Conclusion

The TPO-NP-Hydrogel casting process with a subsequent removal of the core by isopropanol is perfectly suited to visualize complex vasculature with a diameter of more than 2 mm in a phantom. Due to the polymerized hydrogel, the phantom has a toxic surface and thus does not provide a surface for fungi or bacteria. To prevent dehydration of the phantom while storing, the phantom is sealed airtight. The hydrogel has a comparable thermal conductivity to that of the brain. For a greater precision, the temperature distribution inside the phantom could be compared with the one inside of a real brain. If a material that is not susceptible to isopropanol inside of the phantom can be found, even finer vasculature is possible to be produced. In this case another liquid to dissolve the wax out of the phantom needs to be found.

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6 Reference

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