Acoustic Materials for Wearable Ultrasound patches

Developing an ultrasound skin mimicking phantom

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Holst Centre
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TNO

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Developing an ultrasound skin mimicking phantom

Thesis report

by

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An electronic version of this thesis is available at `http://repository.tudelft.nl/`.

Biomedical Engineering · Delft University of Technology

Preface

Hereby, I present my MSc. thesis. This is the final chapter of my time as a student at the TU Delft in the master's program in Biomedical Engineering.

My thesis research was conducted at TNO Holst Centre in Eindhoven. There I received great guidance through the last nine months. Thank you to all the people at TNO Holst Centre for your time, feedback, and advice. Your support helped me get my research to the next level! I especially want to thank Shin Kawasaki for all the guidance in my project, the serious but also fun meetings, advice, support and for giving me confidence in my work. Whenever I needed your help you were available and gave me great advice!

I would like to express my deepest gratitude to my thesis chair, prof.dr.ir. Ronald Dekker, whose guidance and expertise have been invaluable throughout this process. Whenever I called, I would always get an answer straight away. Thank you for your insightful feedback, and support and for helping me contact the right people for questions. This all has significantly contributed to the development and refinement of this work. Also, thank you for staying patient with my spelling and grammar mistakes and continuously taking the time to check them!

I would also like to extend my thanks to the members of my thesis committee for their time and constructive input. Their perspectives have enriched the content and strengthened the overall quality of this thesis.

Special appreciation goes to my friends and family for their encouragement and understanding during this intense phase of my life. Their support through rough times always gave me a constant source of motivation. A special thanks goes out to my parents and my family in Canada for pre-reading my thesis report and for their insightful feedback.

This thesis represents not only an academic achievement but also a personal milestone. It is my hope that this work contributes meaningfully to the research of wearable ultrasound acoustic interface materials. I invite readers to explore the findings and insights presented.

Contents

Nomenclature

List of Abbreviations

AI	Artificial Intelligence
CAD	computer-Aided Design
CT	Computed tomography
ECG	Electrocardiogram
MEMS	Micro-Electro-Mechanical Systems
POCUS	Point of Care Ultrasound
SoS	Speed of sound
US	Ultrasound

List of Symbols

α	Attenuation coefficient
$\varnothing$	diameter
λ	Wavelength
ρ	Density of medium
T	Temperature
t	Time-step
Z	Impedance
$\overline{\alpha}$	mean attenuation coefficient

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Abstract

With today's aging population and the prevalence of chronic illnesses, healthcare systems worldwide are struggling to accommodate the increasing number of patients. This projected growth and rising demand underscore the importance of advancing wearable devices. In the realm of diagnostic healthcare, the pursuit of non-invasive and safe techniques is paramount. Until now, body patches have predominantly focused on monitoring surface-level body parameters such as temperature, humidity, pH, oxygen saturation, and electric potentials. The introduction of ultrasound patches extends the realm of possibilities, enabling a deeper exploration of physiological processes within the body. Additionally, ultrasound serves as a non-invasive diagnostic technique.

To facilitate medical ultrasound imaging, an acoustic interface is indispensable for the unimpeded transmission of waves through the skin and tissue. This interface must maintain proper hydration and adhere to the skin to ensure a conforming acoustic connection.

Goal: Develop an ultrasound phantom for testing acoustic interface materials by answering the following questions:

1. Can an ultrasound phantom be developed which mimics skin properties and can this be used for a prolonged period of time?
2. How do the promising acoustic materials perform over a time period of 5 days?
3. What are the acoustic properties of the promising interface materials and the materials used in the phantom?
4. How can the interface materials be evaluated for skin biocompatibility?

Initially, this MSc. thesis research aimed to conduct lifetime performance tests on promising ultrasound acoustic interface materials. These tests were conducted by placing wearable ultrasound patches with the acoustic interface materials in place on an ultrasound phantom. With the Philips Lumify ultrasound transducer, ultrasound images were made over a fixed period. This experiment was done to see to which extent the image quality would degrade over time for the different interface materials. However, this approach proved to be more complex than initially anticipated. The available ultrasound phantoms did not meet the requirements of skin-mimicking properties, on which the lifetime of the acoustic materials would be tested. Consequently, this research opted to simulate specific skin conditions: temperature, moisture, and acoustic properties like human tissue. Different iterations were made and evaluated during the development of the final ultrasound phantom model. In this thesis, five different models were evaluated, and eventually, the final model was presented: A three-layer model. The phantom model consists of a gel wax filled with scattering objects, visible with ultrasound, at specific depths inside the filling. To mimic the water loss rate of the skin, a hydrating layer of agar was placed on top of the gel wax filling. A PET foil was deployed with a specific number of holes to let water through from the agar layer to regulate the amount of water evaporation over time. To mimic skin temperature, the phantom model was placed in an oven at T = 34 °C. With this final model, the lifetime experiments were conducted with six potential interface materials: AquaFlex (solid hydrogel), HydroAid (solid hydrogel), Ecoflex (silicone), Axelgaard (ECG solid hydrogel), HH5023 (ECG solid hydrogel), and HH5450 (ECG solid hydrogel). The duration of this experiment was eight days, after which the agar layer started to degrade and shrink. The filling and scattering objects of the phantom model are reusable, while the hydration layer has to be replaced or disposed of after five days.

Further, acoustic properties, like materials-specific attenuation coefficient, of potential acoustic interface materials and materials used in the phantom were measured using a though-transmission setup. Also, a validation assessment of skin compatibility of the potential interface materials for a long duration of time was conducted. This was done with the consultation of experts in medical devices, medical professionals and literature.

With these three different subjects of this MSc. the attenuation coefficient of six different acoustic interface materials are characterized and validated to be compatible with human skin for longer periods. The

phantom model developed satisfies the requirements set and, most importantly, mimics skin temperature and water loss rate. One round lifetime (eight days) performance experiments of acoustic interface materials using the phantom model. It is difficult to conclude to which extend the image quality degraded over time for the different interface materials due to the agar layer dehydration after eight days and that the experiment was only conducted once. For future recommendations, it is suggested that the lifetime experiments be repeated using the phantom model for these six different interface materials. It could also be an option to renew the hydration layer every seven days to prevent the agar layer from dehydrating over the acceptable limit if the experiment requires longer periods.

Descriptions

Acoustic Impedance: The resistance to the propagation of ultrasound waves through tissues. Each tissue type has an unique acoustic impedance. Acoustic impedance is the product of the density and speed of sound in the tissue [1].

Attenuation: The loss of energy of transmitted and reflected sound waves owing to scattering, reflection, refraction, and thermal absorption. Attenuation and frequency are directly related (i.e., higher-frequency sound waves attenuate in the body faster than waves of lower frequency). Attenuation limits the maximum depth of penetration and imaging [1].

Beam Pattern: The 3-dimensional shape and size of the acoustic energy field applied by the ultrasound probe. The beam pattern varies by probe; each pattern is designed for specific imaging goals [1].

Frequency: The rate, expressed in cycles per second (unit Hertz [Hz]), at which the patterns of compression and rarefaction pass by a certain reference point. Typical frequencies for medical ultrasound are 2 MHz to 20 MHz, depending on the application. Echocardiography uses frequencies of 2.5 to 7.5 MHz [1].

Piezoelectric Crystals: These crystals can be used to generate or detect ultrasound waves. A voltage is applied across the crystals will produce a pressure field (a stress) on the atoms in their lattice with an accompanying overall contraction or expansion (a strain) in 1 or more dimensions of the material, generating ultrasound waves that emanate from the probe [1].

Probe: Another name for a transducer (see definition below).

Resolution: A measure of the ability of an imaging system to resolve and display 2 closely spaced reflecting tissue boundaries. Snell's Law: A formula describing the relationship between the angle of incidence of a sound wave on a tissue interface and the resultant reflection and refraction of the wave [1].

Transducer: An array of piezoelectric ceramic crystals and electrical connections with support materials housed in a durable enclosure. The shape, operating frequency, and geometric focus of the transducer are intrinsic and fixed. The transducer emits a pattern of ultrasonic waves and interprets the resultant echoes [1].

Ultrasound waves: Regular patterns of mechanical compression and rarefaction traveling in a longitudinal direction in tissue, the frequency of which, by definition, is higher than the human audible range of 20kHz to 20kHz [1].

1

Background: reasons for wearable medical devices

1.0.1. Clinical and Economical

Recently, interest has increased in developing and utilising wearable medical devices. According to a Yole report (2020), the global wearables market will reach $97.9 billion by 2025, as Yole illustrated in Fig. 1.1.

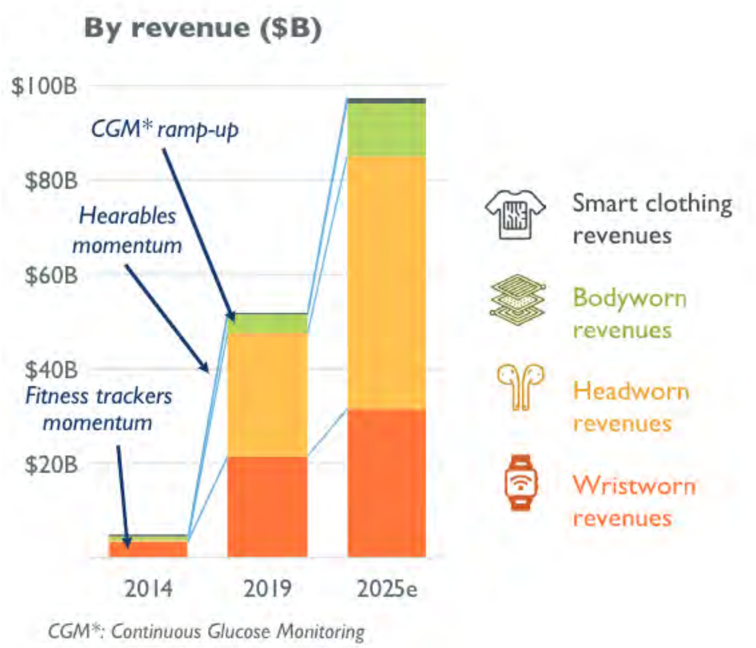

Figure 1.1: Yole report (2020): wearable market evolution 2014-2025 [2]. This report does not take the potential impact of the covid-pandemic into account

This predicted increase is largely the result of an ageing population worldwide and the increase in chronic diseases [3]. In most countries, the current healthcare systems will not be able to deal with this increase in patients. A shift from in-hospital (critical) care to more preventative and diagnostic healthcare will be essential. The further development of wearable devices will play a vital role in dealing with this essential shift. For diagnostic healthcare, non-invasive and safe techniques are required, as well as being cost-efficient. So far, wearable body patches have had moderate application, as monitoring capability has been limited to surface-level body parameters like temperature, humidity, pH, oxygen saturation, and electric potentials. The ultrasound patch, the subject of this thesis, will extend the possibilities and further delve into the physiological processes occurring deeper within the body [4]. In addition, ultrasound imaging does not expose the patient to ionising radiation, making it safer than X-ray and CT [5]. Besides, ultrasound can be used as a non-invasive technique for diagnostics. On top of that, it is less cumbersome and more affordable than techniques such as MRI. Therefore, ultrasound is an up-and-coming imaging, monitoring, and diagnostics technique. But it requires significant research and development attention to have the impact on the medical healthcare as desired. The subject of this MSc. thesis hopefully makes a valuable contribution to the development of wearable ultrasound patches.

1.0.2. TNO Holst Centre

The Holst Centre, where the research of this MSc. thesis took place, is an 'innovation center' where expertise in wearable sensor technology and flexible electronics are combined. The Holst Centre helps partners develop proof-of-concept prototypes and demonstration models. The sharing of knowledge enables a unique collaboration that enhances the strength of the partner companies. TNO connects the latest technologies and innovations with companies that can further develop them and bring them to life. One of the focus areas of TNO Holst Centre is 'Health & Vitality' with subjects like 'Smart Patches' and 'Ultrasound Imaging'; this niche workspace greatly contributes to the relevance of this master thesis topic. Additionally, TNO Holst Centre is a partner in various other relevant consortium projects, e.g. the ULIMPIA bladder monitoring patch [4], the New Life fetal monitoring patch [6] and the PatchUS long sliding patch [7]

1.1. Ultrasound

Ultrasound is an acoustic sound wave mainly used for in-hospital imaging of soft tissues like the abdomen or uterus. To make this image, sound waves are emitted from an ultrasound probe (see Fig. 1.3a). These waves travel through different tissues and get reflected to the probe. These ultrasound echoes return to the transducer from different tissues and depths. When ultrasound waves travel through a body, the waves are reflected at the interfaces between tissues with different acoustic impedances. An ultrasound image is made of the reflected waves. In Fig. 1.2, a schematic view of this process is depicted.

Acoustic sound waves with frequencies greater than 20kHz are named ultrasound waves. For medical ultrasound imaging, frequencies between 2 MHz and 20 MHz are typically used. As S. Suzuki et al. (2018) Elsevier, defined: "Ultrasound waves are regular patterns of mechanical compression and rarefaction travelling in a longitudinal direction in tissue, the frequency of which, by definition, is higher than the human audible range of 20 Hz to 20 kHz" [1].

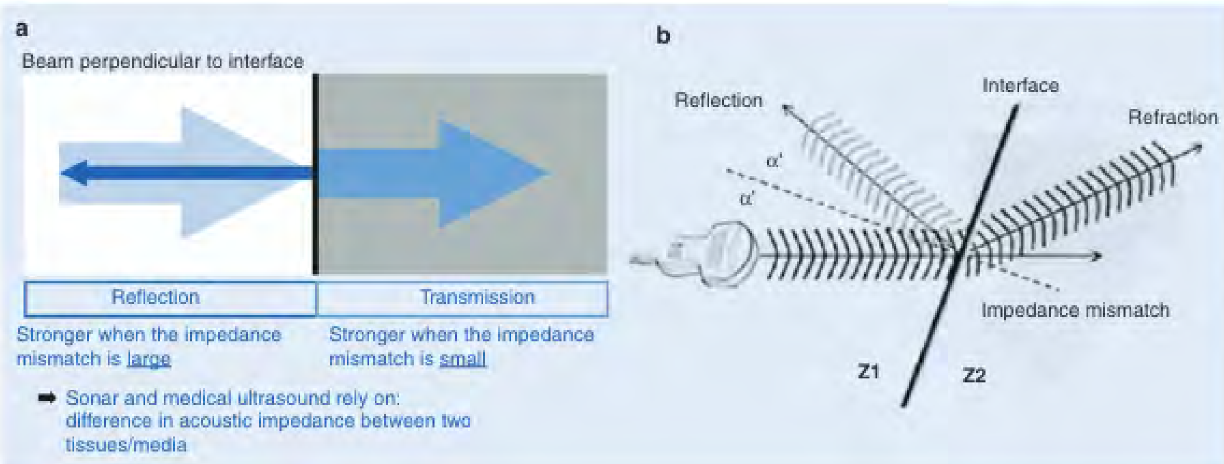

Figure 1.2: Schematic view of reflection, transmission, and refraction. **a)** ultrasound images generation from reflection and transmission of the beam through another medium. **b)** Interaction of ultrasound beam with a tissue interface. The waves that pass through the medium change direction and are described as refracted waves. Figure and caption from Jinlei Li et al. 2021 Springer [8].

PZT Transducers

The waves are generated by a transducer, which commonly has piezoelectric elements oscillating, producing an ultrasound wave [8]. Piezoelectric materials are those capable of generating electricity in response to mechanical stress and, conversely, converting electricity into mechanical stress [9]; For ultrasound generation and receiving the material lead zirconate titanate (PZT) is generally used. In ultrasound probes, PZT crystals vibrate when an electrical current is applied, generating ultrasound waves. Vice versa, when ultrasound waves are reflected to the PZT crystals, it causes them to vibrate, generating an electrical current. This current is then analysed, and the ultrasound machine can form an image [10]. This is illustrated in Fig. 1.3.

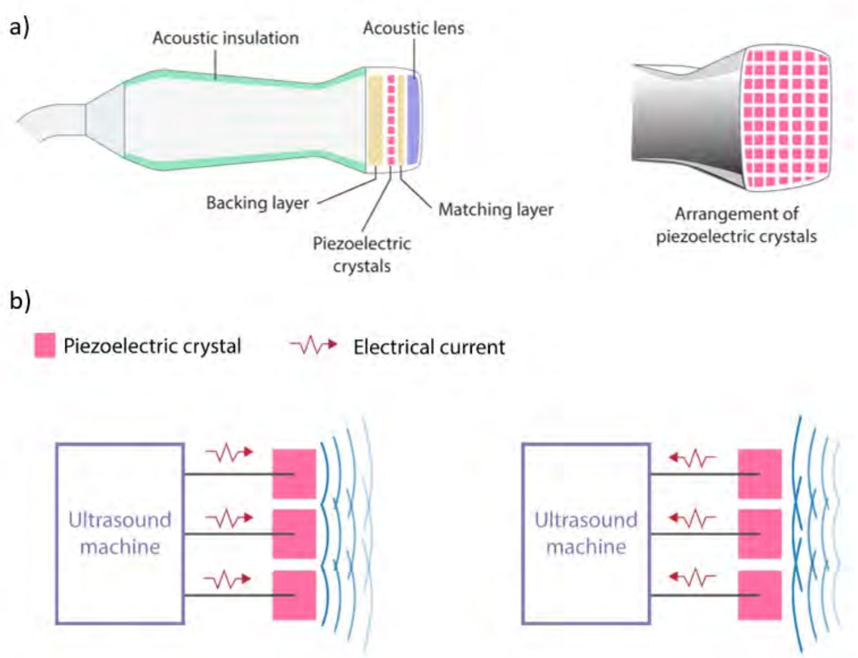

Figure 1.3: a) Schematic side and front view of an ultrasound transducer probe. b) Working principle behind ultrasound transducers with piezoelectric elements. Figures from site: [10].
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Capacitive Micro-machined Ultrasound Transducers (CMUT)
In recent years, instead of using PZT materials for transducers, MEMS (micro-electro-mechanical systems) transducers like CMUT (Capacitive Micro-machined Ultrasonic Transducer) have been developed for ultrasound. The working principle is based on the same concept as PZT crystals; see Fig. 1.4. CMUTs use micro-fabrication techniques to create a thin membrane that vibrates and produces ultrasound waves. Replacing PZT transducers with CMUT reduces the manufacturing costs of the transducers considerably. This is due to integrated circuit technologies and the lower costs of materials like silicon wafers [11], [12]. The image resolution of PZT transducers and CMUTs were compared by imaging a human carotid artery and thyroid gland, according to Mills D.M., in the General Electric Global Research. They found that the image quality acquired by the CMUTs is slightly better than the PZT transducers. However, the CMUTs shows limitations in imaging depth [13], [14]. CMUTs seem to be a very promising technology for wearable ultrasound devices in the future.

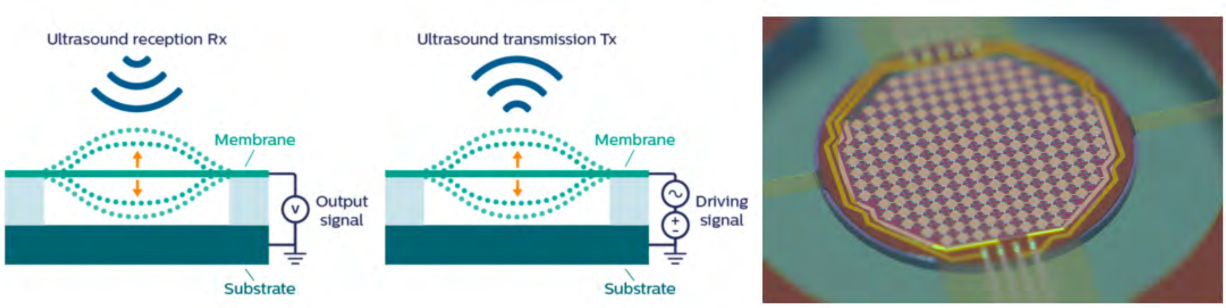

Figure 1.4: CMUT- MEMS devices that transmit and receive ultrasound waves. *Left*: Working principle of CMUT. The membrane vibrates due to ultrasound generating an electrical current and vice versa. *Right*: Image of a silicon wafer with CMUT drums. Figure acquired from Philips Engineering Solutions [12].

1.2. Ultrasound Devices

1.2.1. In-hospital ultrasound machine

Ultrasound is deployed in different medical fields, for instance, imaging and monitoring, but also non-invasive deep brain stimulation and as acoustic medicine for musculoskeletal injuries [15], [16]. To date, this has mostly been done in-hospital care with large machines, such as in Fig. 1.5. Due to the required shift from in-hospital care to diagnostic and monitoring out-of-hospital healthcare, these large devices like the one in Fig. 1.5, have to become more mobile and less expensive. Moreover, these techniques must be moved to general practitioners, also known as first-line healthcare workers.

Figure 1.5: Radiology ultrasound machine: Resona by Mindray. With price point between €$10,000$ - €$20,000$.

With innovations like POCUS and wearable ultrasound devices (see below), remote patient health monitoring is on the horizon. Patients could be monitored at home and without having to go to the hospitals for checkups, making the patient's life much easier, but also taking some workload away from caregivers and unburdening the healthcare system.

1.2.2. Point of care ultrasound

Point of Care Ultrasound (POCUS) has been established as an important imaging technique for first-line healthcare workers. POCUS devices like Butterfly IQ by Butterfly, TE Air by Mindray, Vscan by GE, and Lumify by Philips (Fig. 1.6) have been upcoming in the ultrasound market since 2018. They are called the first 'bedside' ultrasound imaging devices. They are more affordable instruments compared to the sonography machines (Fig. 1.5, €$10,000$ - €$20,000$), decreasing the costs by an order of magnitude, with prices ranging from €$3,500$ - €$6,500$ [17].

Figure 1.6: Lumify by Philips connected to an iPad. Image acquired from: www.philips.nl/healthcare

These tools have since been further developed with the prospect of becoming fully wireless, as seen in the road map of Fig. 1.7 in the Butterfly IQ.

Figure 1.7: Road map of Butterfly showing the Butterfly iQ POCUS to wearable ultrasound device development. This figure was acquired from an investor presentation from Butterfly [18].

1.2.3. Wearable ultrasound patches

Currently, there are only a few wearable ultrasound patches on the market. Wearable devices like SENS-U by Novioscan, Dfree by Triple W, the ULIMPIA project, and Flopatch by Flosonics. In the ULIMPIA project, the first MEMS-based wearable wireless scanning ultrasound patch was developed [7]. These wearable patches can be seen in Fig. 1.8 and 1.9.

Figure 1.8: Different wearable ultrasound patches for bladder monitoring. From left to right: SENS-U by Novioscan [19], DFree by Triple W [20], and ULIMPIA project by Penta [4].

The most common commercial wearable ultrasound patches are for bladder monitoring, Fig. 1.8. The bladder is located in the abdominal area, generally a round surface. The device uses ultrasound to monitor how much urine is in the bladder. The Dfree and SENS-U use a one-element transducer to monitor the fullness of the bladder. When the bladder is full, it sends an alert to a tablet/phone, indicating the patient to go to the restroom [20].

The SENS-U from Novioscan (left in Fig. 1.8) is specially designed for children with incontinence problems [19]. The SENS-U uses a double-sided plaster, which sticks to the device and the skin. Inside the bandage is an opening into which the gel is placed. The SENS-U is used for a maximum of 12 hours during the day or night, depending on the user's type of urinary incontinence.

While the SENS-U and the Dfee are designed in a more simple way (one PZT element which indicates the amount of liquid in the bladder), the ULIMPIA patch developed in the ULIMPIA project was set up to create an open-source technology platform to bring together innovations involving wearable device technology and MEMS ultrasound [4]. The European consortium established the world's first wearable, wireless, CMUT-based ultrasound patch [7].

The SENS-U, Dfree, and the ULIMPIA patch use the standard ultrasound gel (e.g. SONOGEL®) as an acoustic interface between skin and transducer. The SENS-U is designed with a double-sided patch that fixes the device to the skin and keeps the gel enclosed for the intended wearing time [19]

The FloPatch from FloSonics Medical, Fig. 1.9, was the world's first wearable Doppler ultrasound device on the market [21][22]. By measuring the Doppler effect with ultrasound, the patch can receive data on hemodynamic changes of blood flow in arteries [23]. Thereby, clinicians in the hospital can follow ICU patients' orthostatic vital signs in real-time as a response to an intervention [21], [23]. The adhesive sleeves are made out of silicone, seen on each side of the device in Fig. 1.9. As a coupling interface between the transducer and skin (or phantom surface), ultrasound gel is used [22]. This ultrasound patch can be worn for up to 24 hours, while the battery-powered devices can only run measurements for 3 hours [22].

Figure 1.9: Wearable Doppler ultrasound device, the FloPatch developed by FloSonics Medical. It is a Functional Hemodynamic Monitoring patch that can follow the live arterial Doppler trace and display it live on a monitor. Figure made from images of the FloSonics website: [21].

Collaborations projects
Currently, in 2023, a European project is in the process of being launched: PatchUS consortium [7]. This project brings together industry, academia, and clinic experts to work on wearable ultrasound technology. Their objective is to create an open-access platform of technologies from multiple manufacturers that enable the realization of many different wearable ultrasound applications. The main partners are Philips, DEMCON, Mepy, Artritech, BSCI, B-Braun, and Pulsify. The development of wearable ultrasound patches faces many challenges, such as flexible or rigid US transducers, CMUT or PZT, and the optimum trade-off for the amount of data collection for correct interpretation of the images. But also making a device with a stable connection to the skin for continuous prolonged ultrasound monitoring and a conform acoustic interface layer for accurate ultrasound wave propagation through the skin. Likewise, another European collaboration project, NewLife, is developing a fetal monitoring patch for high-risk pregnancies. The patch will be able to continuously image the fetus during pregnancy in both hospital and home environments.

2
Literature Review

The full literature review was conducted in preparation for this thesis, the full review is available in a separate document. The conclusions of the review are stated below.

2.1. Conclusion Literature Review

This literature review aims to be a guiding framework for my MSc. thesis project. Initially, the project aimed to identify and evaluate promising materials for wearable ultrasound devices. However, the project's focus has shifted towards developing a phantom for testing these materials. This review has revealed a gap in existing literature, as no guidance or reference is available for creating an experimental setup for conducting such lifetime performance tests.

2.1.1. Life-time performance

A phantom must be developed to evaluate the lifetime performance of the acoustic materials. An ultrasound phantom must be 'ultrasound transparent', which indicates that ultrasound waves can easily pass through without too much energy loss. An ultrasound phantom also has scattering objects at specific depths and with specific sizes. The phantom must mimic skin features like temperature and water loss to accurately test how the interface materials will perform on the skin.

Promising interface materials

Since the materials found in research papers are still very experimental and not broadly available, it was concluded that currently, the most promising interface materials are the appropriate commercially available materials.

Solid Hydrogel	**Silicon**	**Hydrogels for ECG**
AquaFlex	Envision Civco	AG600 hydrogel
HydroAid	Siblione	ECG gel with nonwoven
		ECG gel without nonwoven

2.1.2. Acoustic performance

Measure the acoustic properties impedance (Z) and attenuation coefficient (α) for f between 1MHz-7MHzm. The through-transmission or pulse-echo experiment can be utilized to measure these properties. In recent literature, the through-transmission experiment is used more often [24]. In addition, a through-transmission setup was available at TNO Holst Centre. Hence, the through-transmission setup is employed to measure the attenuation characteristics of the materials.

2.1.3. Skin compatibility

The material implemented as an acoustic interface must validate ISO10993 (cytotoxicity, irritation, sensitivity). It would be desirable if the materials have been utilized in previous medical devices and to be assessed by medical professionals and experts on medical devices.

3
Problem Statement

This thesis primarily focusses on the interface between the skin and an ultrasound transducer. The importance of this interface is highlighted by its essential role during medical ultrasound monitoring in ensuring that ultrasound gets propagated through the skin and reaches the tissue to form an accurate image of the underlying tissue. In Fig. 3.1, it is illustrated that without an acoustic interface, even the finest ultrasound probes are unable to transmit ultrasound waves through the skin and tissue effectively.

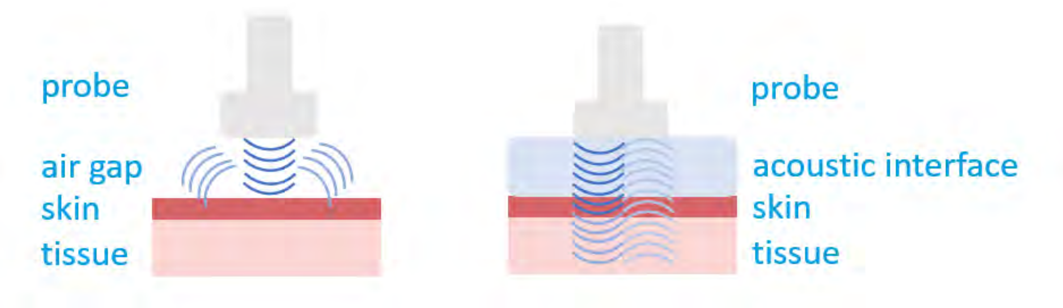

Figure 3.1: Schematic illustration of acoustic interface problem.

Several crucial elements must be carefully considered for the proper functioning of an ultrasound device. These elements include the selection of the appropriate ultrasound transducer, precisely calibrating technical settings, accurately targeting the desired body location and establishing a conformal contact between the transducer and the skin.

This importance is amplified when employing wearable ultrasound devices for extended monitoring periods. The patch must be correctly attached to the skin at the right location to maintain a conform connection. Without this conform interface, meaningful data cannot be received. The acoustic coupling interface plays a crucial role in ultrasound imaging and facilitates precise image formation. To ensure optimal image quality, the interface material must maintain conformal contact with the transducer (probe), avoid deforming the skin surface, and have good acoustic performance. For most medical ultrasound applications, ultrasound gel (liquid hydrogel) is used as the acoustic interface material between the probe and the skin. However, using this material has its downsides for wearable patches. The wearable ultrasound patches being developed focus on prolonged monitoring and attachment to the skin. This implies continuous monitoring for days or even months. The conventionally used liquid gels exhibit high liquidity and rapid dehydration. In addition, they cannot withstand external compressive forces due to their liquid substance. This is why it is essential to find new acoustic interface materials for wearable ultrasound patches which have reduced dehydration rates, can withstand compressive force, form a conformable connection with skin and are acoustically transparent.

This all makes finding the appropriate material a complex issue to be solved. For example, materials like solid hydrogels perform better in respect to anti-dehydration and tolerance to external forces but are less able to maintain conformal contact between the skin and transducer on curved body parts [25].

3.1. Problem Analysis

This problem is significant for the final wearability of the patch and will be further elaborated on in this section. Deciding on what material should be used in different situations forms a complex dilemma. To evaluate the suitability of candidate acoustic interface materials for wearable ultrasound patches, the problem statement was divided into three main topics of interest that will be further analysed:

- Life-time performance:
  - Develop an ultrasound phantom to mimic skin moisture, temperature, tissue transparency and some scattering objects.
  - Evaluate the lifetime performance of acoustic interface materials.
- Acoustic performance:
  - Measure the attenuation coefficient (α) for f between [1MHz-7MHz];
  - Calculate the acoustic impedance (Z_{material}) of the materials.
- Skin compatibility:
  - The acoustic material must validate against ISO10993 (cytotoxicity, irritation, sensitivity);
  - The acoustic material must be biocompatible with the skin;
  - must not cause itchiness, irritation or redness;
  - Assessment of materials used in medical devices by medical professionals and experts.

3.2. Objective

This MSc. project aims to develop an experimental setup to conduct lifetime performance experiments of wearable ultrasound devices coupling materials. Research questions for this thesis are listed below:
Goal: Develop an ultrasound phantom for testing acoustic interface materials through answering the following questions:

1. *Can an ultrasound phantom be developed which mimics skin properties and can be used for a prolonged period of time?*
2. *How do the promising acoustic materials perform over a time period of 5 days?*
3. *What are the acoustic properties of the promising interface materials and the materials used in the phantom?*
4. *How can the interface materials be evaluated for skin biocompatibility?*

3.2.1. Mimicing skin properties

To develop an ultrasound phantom that mimics skin properties, these values and conditions noted below must be simulated.

Human skin water evaporation
The human skin evaporates water via two different pathways:

- Sweat;
  - water loss through the sweat glands [26];
  - normal sweat flowrates: 10 - 250 nL/min*cm² [27].
- Transepidermal water loss (TEWL);[28].
  - water evaporating through the different layers of the epidermis [29];
  - TEWL rates range a lot: 1,9 g/(h*m²) - 2,7 g/(h*m²) [30] and 7,3 g/(h*m²) - 11 g/(h*m²) [31]

The average of these values was taken, which gave a water evaporation rate of $139,5\ nL/(min * cm^2)$;

Temperature
The human skin temperature is generally in the range of $T_{\text{skin}} = 33°C - 36°C$.

Transparantcy to ultrasound
Human skin has a $Z_{\text{human tissue}} = 1,54$-$1,99\ MRayl/m^2$ and $\alpha_{\text{human tissue}} = 0,44$-$0,75\ dB/cm$ @ 1MHZ [32]

4 Introduction

4.1. Acoustic materials

For medical ultrasound imaging to work, an acoustic interface is essential for the continuation of the waves through the skin and to the tissue and back.

To maintain this conform acoustic connection, the interface must stay hydrated with water or other suitable materials and adhere to the skin. Finding suitable materials for this application has proven to be challenging. Ultrasound transmission gels, called liquid hydrogels, are commonly used for medical imaging procedures. This gel has a viscous and gelatinous substance. In recent years, solid hydrogels like AquaFlex, HydroAid and Bioadhesive Ultrasound (BAUS) have been developed and also used as an acoustic interface for ultrasound imaging. These materials are less viscous and are more solid than liquid hydrogels, some call them ’dry gels’. Solid hydrogels contain less water but are still ’acoustically transparent’ and manage to create a conform interface with the skin. Other materials like silicone are also used as acoustic materials, for instance, the Envision Ultrasound Scanning Pad from Civco. All these materials, among others, are listed in Table 4.1.

Ideally, as stated previously, the interface material should fully conform to the skin, filling all the air gaps between the skin and the probe. The impedance of the acoustic material is approximately the same as the impedance of the skin. As for the attenuation, the optimal situation would be to aim for minimum energy loss due to scattering, reflection, refraction, or thermal absorption. Therefore, an attenuation coefficient of $\alpha \approx 0$ [dB/mm] is desired.

Table 4.1: Acoustic impedance values and attenuation coefficients of the materials listed, found in the literature.

Material	Type	Impedance $MRayl/m^2$	Attenuation $dB/cm/MHz$	Ref
Water	liquid	1,48	0,0054	[24], [33]
Breast tissue	human tissue	1,54	0,75 (1-6MHz)	[24]
Muscle	human tissue	1,67	0,52 (1-6MHz)	[24]
Skin	human tissue	1,99	0,44 @ 1MHZ	[32]
Bone	human tissue	5,3	13,3	[34], [35]
AquaSonic Clear	liquid hydrogel	0,07	0,095	[36]
AquaFlex	solid hydrogel	0,117	0,1455 @ 5MHz	[36]
HydroAid	solid hydrogel	1,54-1,99	0,52-0,75	
EcoFlex	silicon	1,03	0,2 (@ 1MHz)	[36]
Envision Civco	silicon	1,43-1,56		[37]
BAUS	hydrogel with elastomer	1,59	0,0835	[36]
Aqualene	elastomer couplant	1,46	0,28	[33]
Gelatin 15%	protein product	1,58-1,59	0,4-0,9 (@ 1-6 MHz)	[24]
Agar 5%	protein product	1,54-1,59	0,2 -0,8 (@ 1-6 MHz)	[24]
PVA	synthetic polymer	1,55-1,56	0,4-1,1 (@ 1-6 MHz)	[24]
PAA (peracetic acid)	acetic acid	1,69-1,71	0,2-0,9 (@ 1-6 MHz)	[24]
Gelwax	candel wax	1,55	0,63 at 7.5MHz	[38]
Nylon	synthetic polymer	3,00	0,39	[39]
PMMA	synthetic polymer	3,25		[40]
polyurethane	synthetic rubber	1,42		[41]
Stainless steel	metal	45.7		[39]
UHMWP	thermoplastic polyethyleen	2,33	8 (@ 5MHz)	[33]
Plexiglas	acrylic clear	1,61	1,13 (@ 5MHz)	[33]

4.1.1. Available interface materials

As previously stated, other materials instead of liquid gels are being developed as interfaces for ultrasound imaging. For instance, solid hydrogels like AquaFlex, HydroAid and Envision. In addition, other materials currently used for other medical devices are being considered as potential interface layers. These materials were evaluated by their intended use and material properties. For instance, interface materials have been developed for making electrocardiograms (ECG) and heart monitoring. Heart patients sometimes undergo a Holter test [42]. This involves a patient having their heart monitored for several days. Patients must keep the ECG electrodes connected to their body for this time. Requiring ECG materials to be approved for prolonged skin contact. There are also other materials, like silicon, which is used in cushioning prostheses for humans. This means these silicones, EcoFlex and Siblione, are required to be biocompatible. An overview of the materials, manufacturers, and intended use are given in Table 4.2.

Table 4.2: * = Electrocardiogram, ** = Electromyogram

name	intended use	make
Aquaflex	ultrasound hydrogel pad	Parker [43]
HydroAid	hydrogel dressing for ultrasound scanning	Kikgel [44]
Envision Civco	silicon adhesive, ultrasound probe scanning pad	Civco [37]
AG600 Hydrogel	hydrogel for ECG* and EMG**	Axelgaard [45]
ECG with nonwoven	hydrogel for ECG and EMG	Hydrogel Healthcare Limited [46]
ECG without nonwoven	hydrogel for ECG and EMG	Hydrogel Healthcare Limited [46]
EcoFlex	silicon for prosthesis and cushioning in orthotics	Smooth-On [47]
Siblione	silicon for cushioning in prostheses	Elkem [48]

4.2. Acoustic Interface

An acoustic interface between an ultrasound transducer probe and the skin is needed to transfer the ultrasound waves through the skin correctly. Three main parameters drive the applicability of this interface;

1. Conformability of the material;
2. Acoustic performance of the material;
3. Biocompatibility with the skin.

4.2.1. Conformablility

The human skin is covered with bumps, gaps, and tears. Because of this 'rough' terrain, the probe cannot make conforming contact with the skin, as shown in the left image of Fig. 4.1. The gaps are filled with air, rendering it impossible for ultrasound waves to reach the tissue, which results in a black image. A material that can function as a conforming layer, filling all the holes and gaps, is needed as an interface. Hence, a gel is often used to serve as an intermediary medium. This gel effectively bridges gaps thanks to its liquid nature, establishing a seamless connection between the ultrasound probe and the skin. This interaction is illustrated in Fig. 4.1c. This acoustic interface facilitates the unhindered transmission of ultrasound waves through the skin, allowing interaction with underlying tissues and the subsequent formation of diagnostic images.

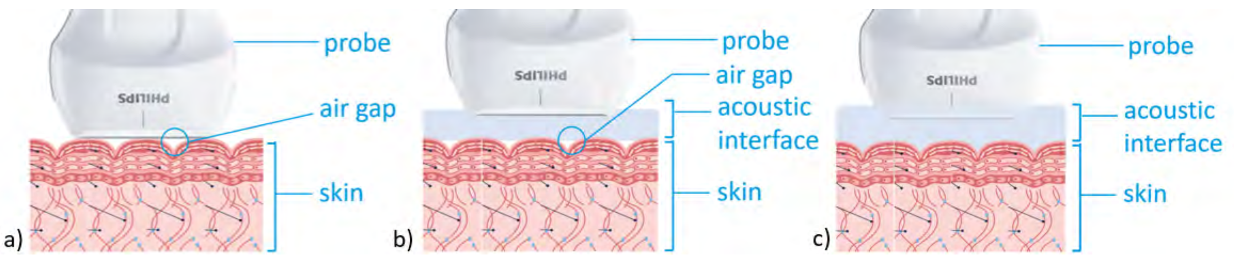

Figure 4.1: Schematic illustration of the interface between ultrasound transducer probe and the skin. a) without acoustic interface material. b) interface without conforming contact. c): with acoustic interface material and conform contact.

4.2.2. Acoustic performance

The acoustic impedance of a material plays a crucial role in determining the acoustic performance of a material. Acoustic impedance is the resistance that an ultrasound beam experiences when passing through a medium. The higher the resistance, the more power the ultrasound wave needs to have to propagate through. The acoustic impedance is the product of the density (ρ) and speed of sound (SoS) in the medium. It depends on frequency, $SoS = f * \lambda = [s/m]$, where SoS is the medium's sound speed.
Acoustic impedance (Z):

$$Z = \rho * SoS = [MPa * s/m^3] = [MRayl/m^2] \tag{4.1}$$

Each tissue (medium) has a unique acoustic impedance, according to Eq. 4.1. In Table 4.1 the acoustic impedances of typically used materials and tissues in medical ultrasound are listed.

Reflection gradient (R) where I0 and I1 are the initial and reflected intensity, respectively. Z1 and Z2 are the acoustic impedances of respective tissues at an interface [8].

$$R = \frac{Ir}{I0} = (\frac{Z1 - Z2}{Z1 + Z2})^2 \tag{4.2}$$

According to Eq. 4.2, the more significant the difference between $Z1$ and $Z2$, the larger the reflection intensity Ir, meaning that most of the ultrasound wave is reflected. Hence, when $Z1 \approx Z2$, approximately no reflection occurs. During ultrasound imaging, the ideal situation would be $R \approx 0$ at the interface between skin and transducer. Human tissue comprises 45% - 75% water, therefore the $Z_{\text{tissue}} \approx Z_{\text{water}}$. To minimize the reflection between the skin and an interface material, generally, an acoustic gel is employed. Gel-like materials consist of approximatly 80% - 90% water, hence $Z_{\text{gel}} \approx Z_{\text{water}}$. As a result, $Z_{\text{tissue}} \approx Z_{\text{gel}}$ typically exists for this interface.

Also, the attenuation coefficient (α) is important when determining acoustic performance. Attenuation is the energy loss, in this case of an ultrasound beam. Attenuation is mainly due to heat generation and increases with frequency. The attenuation coefficient is a parameter unique to each material. A higher attenuation coefficient implies more energy loss, resulting in lower acoustic penetration of the ultrasound beam. The attenuation coefficient can be calculated with the following equations 4.3.

$$A_1 = \alpha * d * f = [\frac{dB}{MHz * cm}] * [cm] * [MHz] = [MRayl/m^2] = [dB] \tag{4.3}$$

$$A_1 = A_0 e^{-\alpha(f)d)}, \text{ in } [dB] \tag{4.4}$$

The A_0 is the acoustic signal measured as a reference for instance, in the water without material in between the transducer and hydrophone, the A_1 is the acoustic signal measured after the ultrasound traveled through the material, and d is the thickness of the material. The attenuation coefficient (α), is given by rewriting Eq. 4.4:

$$\alpha(f) = \frac{1}{d1} ln(\frac{A_0}{A_1}), \text{ in } [\frac{dB}{cm * MHz}] \tag{4.5}$$

The attenuation coefficient is material-specific and indicates how much the signal is attenuated by this material for a specific thickness and frequency.

4.2.3. Skin compatibility

There are different types of regulations researchers and medical device developers follow to validate the biocompatibility of the materials used.

Patch tests

In literature, Wang C. et al. performed a 'wearing comfort test' in their clinical trial and results can be found in Wang C. et al. (2022) Supplementary Materials [49] Fig. S13. This was done to evaluate different coupling materials for their bioadhesive wearable ultrasound device. The coupling materials are situated between the skin and the transducer [49]. The evaluation criteria for the different coupling materials followed the patch test criteria of the International Contact Dermatitis Research Group (ICDRG) [50].

ISO standards

Most acoustic interface materials are already medically approved for temporary use on patients. However, more experimental data is needed to evaluate these materials for long-term use. At present, there are no regulations for long-term continuous ultrasound monitoring, and there are also no regulations for sticking a material on the skin for a prolonged time.

There are standards formulated by the International Organisation for Standardisation (ISO). These standards could help validate materials for other important issues when approving materials for biocompatibility, cytotoxicity and irritation. The ISO standard most important for medical devices is ISO 10993: bio-compatibility evaluation of medical devices [51]. Three parts are most important for evaluating a medical patch or device attached to intact skin for a prolonged time (24 hours to 30 days). These parts are listed below. Materials used in medical devices need to be approved according to these ISO standards.

	ISO 10993
part 5	Tests for in vitro cytotoxicity
part 10	Tests for skin sensitisation
part 23	Tests for irritation

Cosmetic regulations
Some materials have not yet been used in medical patches and, therefore, have not been tested against the above ISO standards. Companies like Novioscan, from the SENS-U bladder monitor seen in 1.8, turned to EU Cosmetic Regulations [19], [52]. These regulations contain a list of cosmetic products approved by the EU for cosmetics. Although cosmetic regulations are less strict than medical device regulations, it is a clear guideline; if a product is on the 'list of substances prohibited in cosmetic products, it cannot be used for medical patches.

Intended use
In the literature review for this thesis, materials intended for ultrasound acoustic interface were evaluated among other materials that are promising for long-term skin connection. Electrocardiogram materials are a potential interface material for wearable ultrasound devices, also called ECG hydrogels. For instance, ECG hydrogels are used to stick electrodes for heart monitoring to a patient's skin. Heart examining procedures use ECG stickers for 7-day heart monitoring, e.g., Holter test [42]. Also, materials intended as wound dressings, such as HydroAid, could be promising for wearable ultrasound interface materials. It can be assumed that materials meant to protect open wounds are appropriate for long-term skin contact.

4.3. Experimental Setup for measuring Attenuation

There are two different techniques for measuring the acoustic properties of a material: the through-transmission technique and the echo-pulse technique (Fig. 4.2). Both techniques are described in section 2 of the literature review.

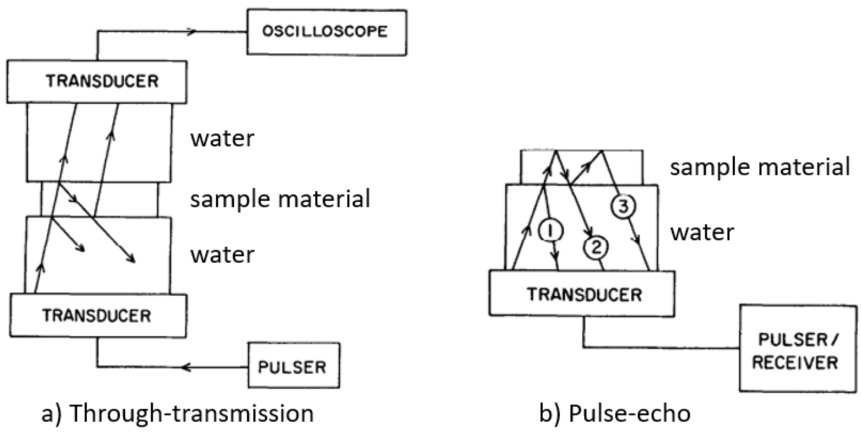

Figure 4.2: Acoustic ultrasound measurements. **a)**: Through-transmission. **b)**: Pulse-echo. Image acquired from Lakes R. et al. (1985) [53].

4.3.1. Through-transmission experiment

A popular measurement scheme to measure the acoustic properties of a material is the through-transmission technique, shown in Fig. 4.2a and in Fig. 4.3. The setup uses two transducers; one transmits ultrasound, and the other receives ultrasound waves. Chen P. et al. (2022) used the through-transmission technique to measure the speed of sound (SoS), acoustic impedance (Z), and the attenuation coefficient (α) of the material between the two transducers [24].

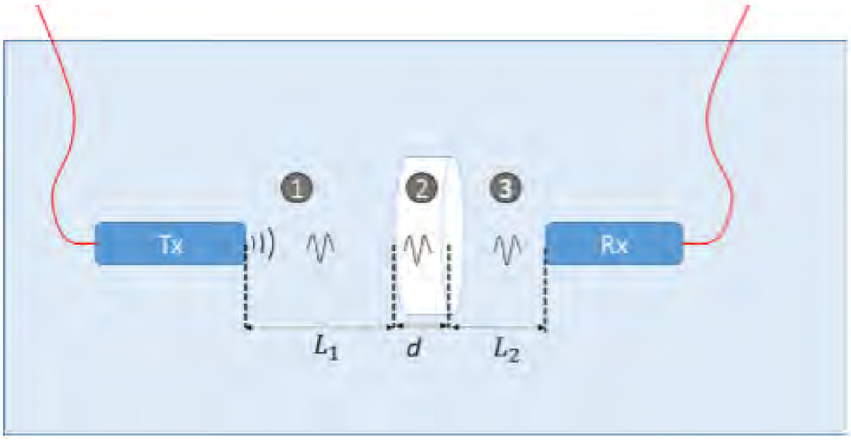

Figure 4.3: Through-transmission experimental scheme: ultrasound transducer (Tx), hydrophone (ultrasound receiver Rx). **1)**: first water interval with length L1. **2)**: material with thickness d. **3)**: last interval with length L2. Image acquired from Chen P. et al. (2022) [24].

The thickness of the investigated material and the propagation time between Tx and Rx have to be measured to calculate the speed of sound.

$$SoS = \frac{d}{\Delta t + \frac{d}{SoS_w}} \text{ with speed of sound in water } SoS_w = 1497\ m/s \tag{4.6}$$

As previously stated in (4.1), the acoustic impedance (Z):

$$Z = \rho * SoS = [MPa * s/m^3] = [MRayl/m^2] \tag{4.7}$$

The acoustic impedance of a material can be calculated from the speed of sound and the material's density (ρ).

4.4. Placing system for ultrasound patches

One of the challenges wearable ultrasound faces is finding the correct position and/or repositioning of the ultrasound pod. A previous MSc student designed a placing system to tackle this problem. The placing system was designed for the Philips Lumify L12-4 probe in the case study of measuring the respiratory condition via monitoring lung sliding for mechanical ventilation patients [54]. The placing system and the components are shown in the infographic Fig. 4.4. This design was utilized for this thesis. The wearable patches and pod designs were modified to fit the requirements. The patch design was customized for thinner acoustic layers between the skin and the Lumify probe and the gel pad 'tub' was designed to be less deep to fit the thinner acoustic materials. The pods were adjusted with a grip for easier pod disassembly from the patch (gel pad holder).

Figure 4.4: Infographic of the placing system with a Lumify probe for wearable ultrasound pod by Annemijn Hintzen [54].

4.5. Ultrasound Phantoms

Phantoms are objects designed to replicate the properties of human tissue. Phantoms play a big role in medical practice, skill training and diagnostic training [24]. The phantoms have sizes, stiffness, shapes, and/or acoustic properties similar to biological tissue [38]. Ultrasound phantoms are phantoms designed for testing and practising with ultrasound. These phantoms are commonly used in radiology for conducting practice ultrasound imaging studies and are also utilized in developing new imaging and treatment techniques [55]. It is especially important for ultrasound phantoms to use materials with well-known acoustic properties. Due to this, certain biological tissue can be precisely mimicked using the appropriate material with similar acoustic properties. For testing the quality or characterizing parameters of newly developed ultrasound transducers, phantoms are also used. To correctly test the transducers, the acoustic properties, such as attenuation coefficient and impedance, must be known.

General Purpose Ultrasound Phantom

The ultrasound phantom available was the CIRS General Purpose Ultrasound Phantom model 054GS, depicted in Fig. 4.5 [56]. This phantom has different scattering objects inside at specific depths, the ultrasound image of the inside of the phantom is shown in Fig. 4.6. The inside of the phantom is made to have an attenuation range between $A = 0.05 - 1.5\ dB/cm\text{-}MHz$ and speed of sound in the range $SoS = 1510 - 1700\ m/s$. The attenuation is slightly higher than the attenuation values of human tissues (Table 4.1). The speed of sound of the phantom matches with the values of human tissue (Table 4.1). The top of the phantom was made of non-transparent rubber material, this layer is meant to represent the skin.

Philips uses this phantom to test newly developed ultrasound transducers. As shown in the Fig. 4.5 on the right, an acoustic interface is applied on the 'skin layer' of the phantom to generate an image with the ultrasound probe. An example of an ultrasound-generated image in this phantom is shown in Fig. 4.6 on the right.

Figure 4.5: Images of CIRS General Purpose Ultrasound Phantom. *Left:* image acquired from: datasheet [56]. *Middle:* ultrasound phantom with 3D printed wearable ultrasound patch and pod on top. *Right:* ultrasound phantom with 3D printed wearable ultrasound patch with Philips Lumify clicked in.

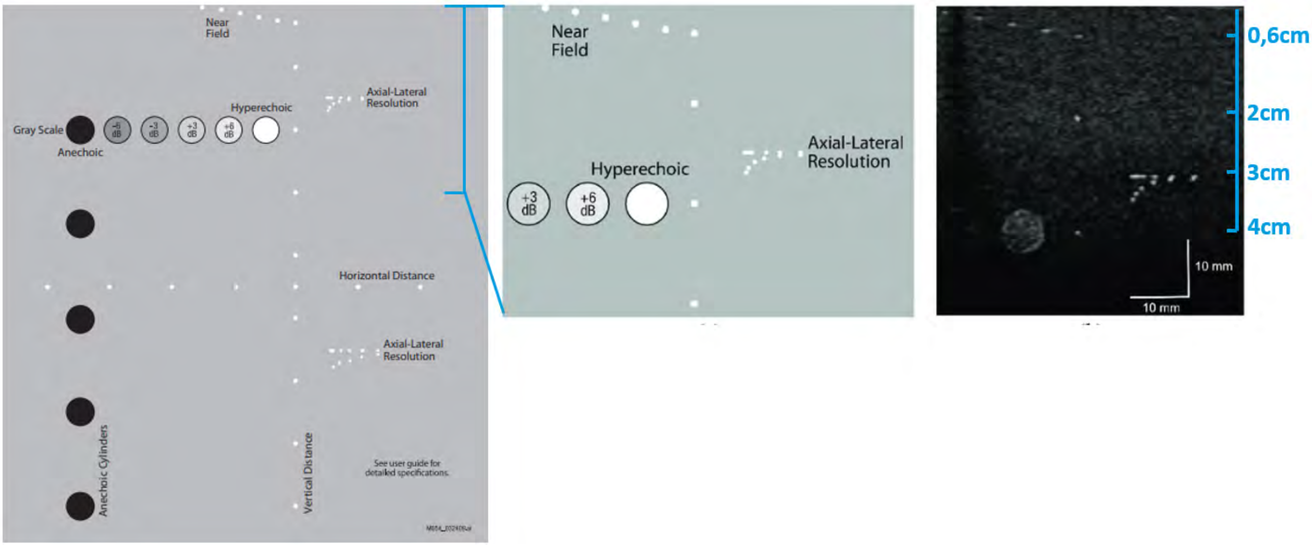

Figure 4.6: Schematic view of the inside of the phantom. Right: images of the near field with ultrasound and related depths.[56]

Other ultrasound phantoms

There is a wide range of ultrasound phantoms and even more materials that can be utilized for such phantoms. In a recent paper by Chen P. et al (2022), the researchers characterized tissue-mimicking materials for ultrasound perfusion imaging research [24]. The materials were ranked according to a scoring system. In this scoring system, the parameters: speed of sound (SoS), acoustic impedance (Z), attenuation (α), nonlinearity (B/A), transparency, lifetime, stiffness and preparation protocol were evaluated.

Table 4.3: Scoring system for ranking materials for an ultrasound phantom. The system was developed by Chen P. et al. (2022) [24].

Parameter	Scoring criteria
Speed ofsound (phantom and case)	$1510 - 1595\ m/s$: 10 points (soft hydrogel) $1400 - 2000\ m/s$: 10 points (stiff case material) Deviation: 1 point less per $10\ m/s$
Acoustic impedance (phantom and case)	$1.54 - 1.69 * 10^6\ kg/m^2s$: 10 points (soft hydrogel) $1.40 - 2.00 * 10^6\ kg/m^2s$: 10 points (stiff case material) Deviation: 1 point less per $1 * 10^4\ kg/m^2s$
Attenuation (phantom and case)	Deviation: 1 point less per $1 * 104\ kg/m^2s$ $0.5 - 0.75\ dB/cm/MHz$: 10 points Deviation: 1 point less per $0.8\ dB/cm$ averaged over the frequency range
B/A (phantom only)	$5.0 - 12.0$: 10 points Deviation: 1 point less per 1
Transparency (phantom and case)	Transparent: 10 points Half-transparent: 5 points Non-transparent: 0 point
Life time (phantom and case)	Stable and long: 10 points Long but has storage requirements: 5 points Short: 0 point
Stiffness (phantom and case)	Stiff: 10 points Soft: 5 points
Preparation protocol (phantom only)	Typical material: 10 points Less common material: 5 points Require extra processing: 3 points less

Phantom material	Score
Agarose 2%	47.0
Agarose 3%	60.6
Agarose 5%	62.3
Alginate 1%	40.6
Alginate 3%	45.3
Gelatin 7.5%	56.2
Gelatin 10%	58.0
Gelatin 15%	63.5
PAA 5%	49.5
PAA 7.5%	55.8
PAA 10%	61.3
PAA 15%	63.4
PAA 20%	68.6
PVA 10%	60.5
PVA 15%	65.6
PVA 20%	63.9
PEGDA 15%	58.6
PEGDA 20%	63.7
PDMS 10:1	[illegible]

Case material	Score
TPX	54.2
PEBAX clear 1200	[illegible]
PEBAX 3533 SA01	50.0
COC	33.8
PMMA	33.1
PC	40.0

Figure 4.7: Images of the ranked materials according to the scoring system of Chen P. et al. (2022) [24].

The phantom and case materials were rated according to the scoring system of Fig. 4.7. The results of the rankings are listed in Fig. 4.7. The yellow boxed show the highest-ranked materials and the red boxed values show the lowest-ranked materials.

5

Materials

In this thesis project, ultrasound phantoms were developed, and experiments were conducted. The equipment and materials for developing these phantom models and the software used for the experiments are listed in this chapter. The acoustic materials with their make are also listed below.

Acoustic Materials:

- AquaFlex® Ultrasound Gel Pad from Parker Laboratories;
- HydroAid® Ultrasound Hydrogel Pad from Kikgel;
- AMGEL® 625 Hydrogel for electrocardiogram (ECG) and electromyogram (EMG) monitoring from Axelgaard Pals®;
- HH5023 ECG hydrogel with and without mesh from © Hydrogel Healthcare Limited;
- HH5458 ECG hydrogel with and without mesh from © Hydrogel Healthcare Limited;
- HH5459 ECG hydrogel with and without mesh from © Hydrogel Healthcare Limited;
- HH5450 ECG hydrogel with mesh from © Hydrogel Healthcare Limited;
- EcoFlex™00-30 liquid rubber from Smooth-On;
- EcoFlex™00-50 liquid rubber from Smooth-On;
- VytaFlex™30 urethane rubber rubber from Smooth-On;
- Envision™Ultrasound Scanning Pad form Civco.

Equipment:

- Philips Lumify L12-4 broadband linear-array Ultrasound transducer [57];
- Future Pad;
- Depex oven set on 33 °C -36 °C;
- Ultimaker 2, Fused Deposition Modeling (FDM) 3D printer [58];
- Formlabs 3+, Stereolithography (SLA) 3D printer [59];
- Temperatuur sensor from Sensirion SEK SensorBridge;
- Double-sided tape;
- CIRS General Purpose Ultrasound Phantom Model 054GS [56];
- trotec CO_2 laser - Speedy300 [60].

Software:

- SolidWorks 2022- Computer-Aided Design (CAD);
- Python 3.11: data analysis;
- Ultimaker Cura: FDM printing;
- FormLabs - Preform: SLA printing;
- Sensirion Control Center: a temperature sensor;

- Siemens Solid Edge: laser cutting.

Ultrasound phantom:

- Glass container with $V = 1.0\ L$ and dimensions (X x Y x Z): $21\ cm$ x $15\ cm$ x $6cm$;
- 3D printed wire holder printed with Rigid 10k by a Formlabs 3+ [59];
- $150\ cm$ nylon wire with $\varnothing = 0,35\ mm$;
- $14\ cm$ stainless steel wires $\varnothing = 0,80\ mm$
- Three 3D-printed wearable patches printed with white thermoplastic (PLA) by Ultimaker 2 [58].

Gelatin phantom:

- Gelatin from Dr. Oetker Professional [61];
- Sheet of teflon $10\ cm$ x $13\ cm$ with thickness $d = 0,25\ \mu m$ with 410 pores with diameter $\varnothing = 0,5\ mm$.

Gelwax phantom:

- Gelwax from Creotime [62];
- Sheet of plastic foil $10cm$ x $13cm$ with thickness $d = 0,25\ \mu m$ with 410 pores with diameter $\varnothing = 0,4\ mm$.

PVA phantom:

- Poly(vinyl alcohol) (PVA) Mw 85,000-124,000, 99+% hydrolyzed from Sigma Aldrich [63];
- Ethylene glycol from EMSURE® [64];
- Sheet of plastic foil $10cm$ x $13cm$ with thickness $d = 0,25\mu m$ with 410 pores with diameter $\varnothing = 0,4\ mm$.

6
Methods

This thesis initially aimed to test acoustic interface materials for wearable ultrasound patches and evaluate the acoustic interface materials on their lifetime performance, acoustic performance and skin compatibility.

The experimental plan regarding the lifetime performance initially involved using an ultrasound phantom. The idea was to attach patches with various acoustic materials to the top layer of the phantom, employ a Philips Lumify probe for imaging, and evaluate image quality over time.

However, this approach proved to be more complex than initially anticipated. The available ultrasound phantoms did not meet the requirements on which the lifetime of the acoustic materials would be tested. It became evident that the appropriate conditions should be properly simulated to test the acoustic materials' lifetime.

The General Ultrasound Phantom from CIRS (Fig. 4.5), initially used, cannot be heated up to normal skin temperature ($T = 34^{\circ}C \pm 1^{\circ}C$) and does not perspire any moisture mimicking human skin, only the acoustic properties (Z and α) are similar to that of human skin (Table 4.1) [56]. This makes it not appropriate to test the lifetime performance of interface materials. Therefore, it was decided to develop a new ultrasound phantom model. Which became the new main subject of this thesis.

Consequently, this research opted to simulate specific skin conditions: temperature and moisture. These parameters were chosen because, for wearable patches, dehydration poses a significant challenge for the acoustic interface. Dehydration can result in a less conformal and poor acoustic transparent interface, potentially losing image clarity as ultrasound waves struggle to penetrate the tissue.

With this newly found knowledge, testing the lifetime performance experimental plan was modified to developing an ultrasound phantom that mimics skin properties.

Therefore, the three main topics of interest are:

- Developing an ultrasound phantom section 6.1;
- Measuring acoustic performance section 6.5;
- Evaluating skin compatibility section 6.6.

For each of these topics, an experimental plan was developed. The following section will further explain these three topics and their analysis methodology.

6.1. Ultrasound Phantoms

The development of the ultrasound phantom was a process. Different iterations were made and evaluated during the development of the final ultrasound phantom model. During this thesis, five different models were evaluated. In this section 6, the material choices and the methods for making these phantoms are explained. Also, the shortcomings that led to different design decisions in further phantom models are briefly noted. To evaluate the shortcomings of a model, the phantom was assessed to see if it met the established requirements. In the Results section 7, the performance and shortcomings of each model are being fully assessed. Tools like the Philips Lumify L12-4 probe and an oven are utilized to check if the phantom model is adequate for the lifetime performance test of acoustic interface materials for wearable patches. The objective was to create a phantom that mimics human skin for at least 5 days.

The requirements for a phantom for lifetime experiments:

- Transparent to ultrasound $Z_{phantom} \approx Z_{water} = 1,48\ MRayl/m^2$;
- Lifetime $t > 5$ days;
- Includes scattering objects, which are visible with ultrasound;
- The phantom must mimic human skin conditions:
  - human skin water evaportation= $139,5\ nL/(min * cm^2)$;
  - human skin temperature: $33°C - 36°C$;
  - acoustic impedance (Z) and attenuation coefficient (α) similar to those of human tissue, $Z_{\text{human tissue}} = 1,54$ - $1,99\ MRayl$ and $\alpha_{\text{human tissue}} = 0,44$ - $0,75 dB/cm/MHz$.

Further wishes for a phantom for lifetime experiments:

- The phantom is reusable;
- The phantom is made in 1-2 hours;

6.1.1. Assessing the ultrasound phantom models

To assess the models, the scheme in Table 6.1 was used. For each requirement and wish, a score between 1-9 was given. All these scores were then summed up, resulting in the final score of the model. In the Results 7, this assessment table is further filled in, and a score per requirement is given.

Table 6.1: Assesment scheme for the ultrasound models

	Assement scheme	1–3	4–6	7–9
1-9	preperation time	2-4 hours	1-2 hours	0-1 hour
1-9	resuable	no	yes	
1-9	transparent to ultrasound	α		
1-9	lifetime t>5 days	no		yes
1-9	withstand temperatures	no		yes
1-9	mimics human skin water evaportation= 133, 8 [nL/min*cm^2)]	too little	too much	enough
1-9	scattering	0	too much	enough
7-63	total score			

Lifetime and temperature
To test the lifetime and if the model could withstand these temperatures, the phantom was placed in an oven (or heating platform) to mimic the conditions at skin temperature. Observations and photos evaluated the lifetime of the phantom model. The phantom models were observed in the composition of the filling, i.e., stiffness, liquidity, and the degradation of the layers.

Transparency to ultrasound and scattering objects
To assess the transparency and scatting objects in the phantom models, ultrasound images were made using the Philips Lumify L12-4 ultrasound transducer. To evaluate the scatting objects, the size, amount of scattering, and reflection in the ultrasound images were compared.

Water evaporation rate
The rate of water evaporation from the phantom models was measured by weighing a container with 15 wt. %, measuring the gelatin area, and placing it in a vacuum oven T= 33°C - 35 °C for an amount of time (t>1 hour). After a fixed time in the oven, the container was weighed again. The volume of water was calculated with: $V_{\text{water evaporated}} = \frac{\Delta m}{\rho_{\text{water}}}$ in nanoliter (nL).

$$\text{water evaporation rate} = \frac{V_{\text{water evaporated}}}{\Delta t * A} \text{ in } [\frac{nL}{min * cm^2}] \tag{6.1}$$

To mimic the amount of water evaporation of skin, the amount of water loss through the skin was estimated. Water evaporates from the skin in two different pathways:

- Sweat;
  - water loss through the sweat glands [26];
  - normal sweat flowrates: 10 - 250 nL/min*cm² [27].
- Transepidermal water loss (TEWL);[28].
  - water evaporating through the different layers of the epidermis [29];
  - TEWL rates range a lot: 1,9 g/(h*m²) - 2,7 g/(h*m²) [30] and 7,3 g/(h*m²) - 11 g/(h*m²) [31]

Table 6.2: Average water evaporation rate from the skin.

average sweat flow rate	130	nL/(min*cm²)
average TEWL	5,73	nL/(min*cm²)
average water loss rate	135,73	nL/(min*cm²)

water evaporation	from	hydrating layer
water loss hydrating layer	1040,50	nl/(min*cm²)
ratio skin/material	7,46	
diameter pore	0,8	mm
area pore	0,00503	cm²
A phantom	19x13	
water area	33,13	cm²
number of pores	6590,14	
pores per cm²	26	

The area of the hydrating layer from which water has to evaporate was calculated with the following equation. The water evaporation rate from the skin is from [26],[27], [28].

$$\text{water area} = \frac{\text{area phantom}}{\text{ratio}} \text{ in } cm^2 \tag{6.2}$$

$$\text{number of pores} = \frac{\text{water area}}{\text{area pores}} \tag{6.3}$$

6.1.2. General phantom model

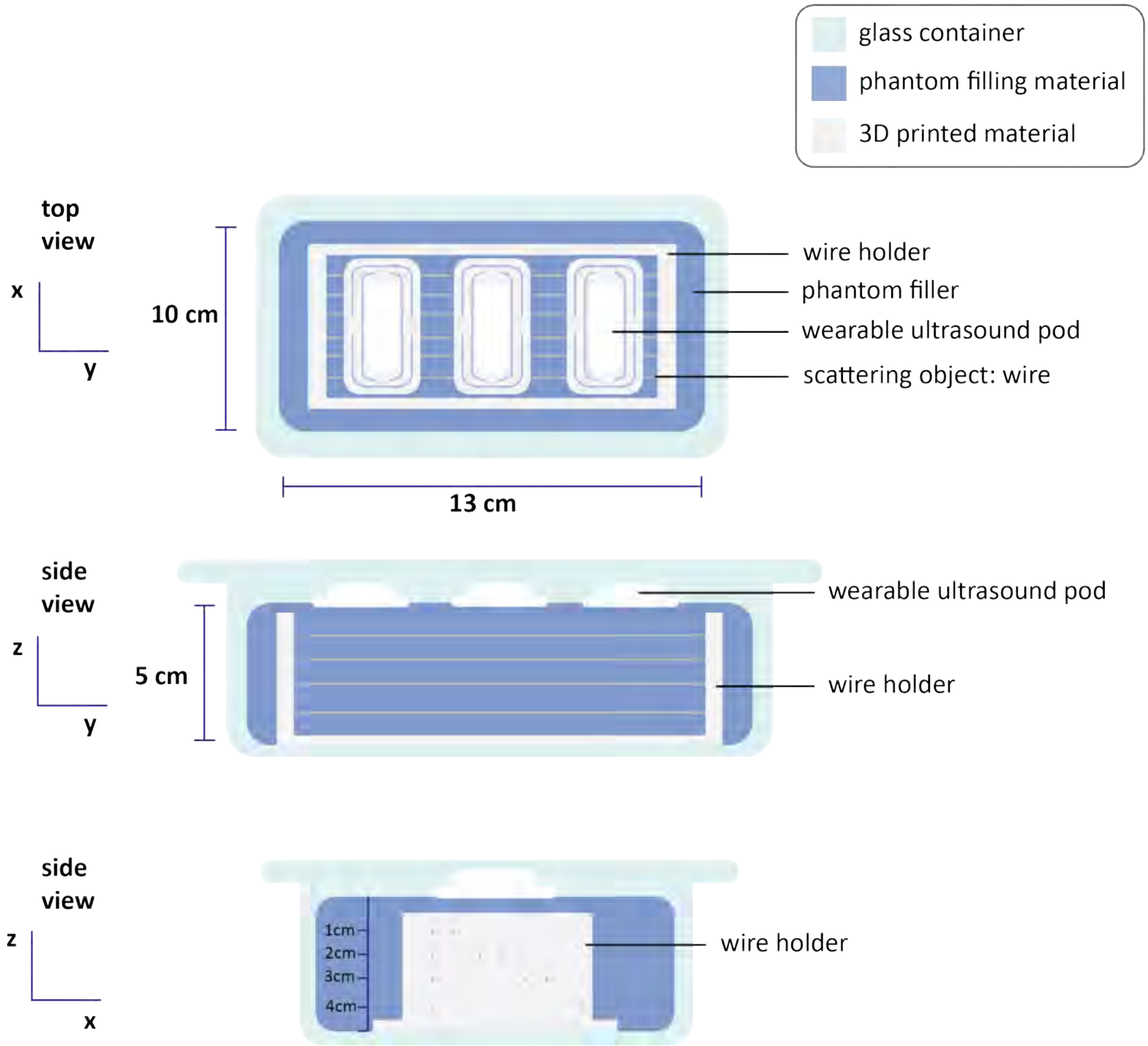

Figure 6.1: Schematatic illustration of the phantom.

The complete phantom consists of the following:

- glass container;
- wire holder;
- wires;
- three wearable patches and pods;
- phantom filling - tissue mimicking material.

The wire holder was 3D printed with a resin (10k Rigid) by a Formlabs 3D printer. The 3D drawing was made with Solidworks. During the phantom developing process, two types of wires were tried out: stainless steel and nylon. The stainless steel wires were cut into 14 cm lengths and placed into the wire holder holes at the right height. The nylon wire was strung tightly through the wire holder holes at the corresponding hols.

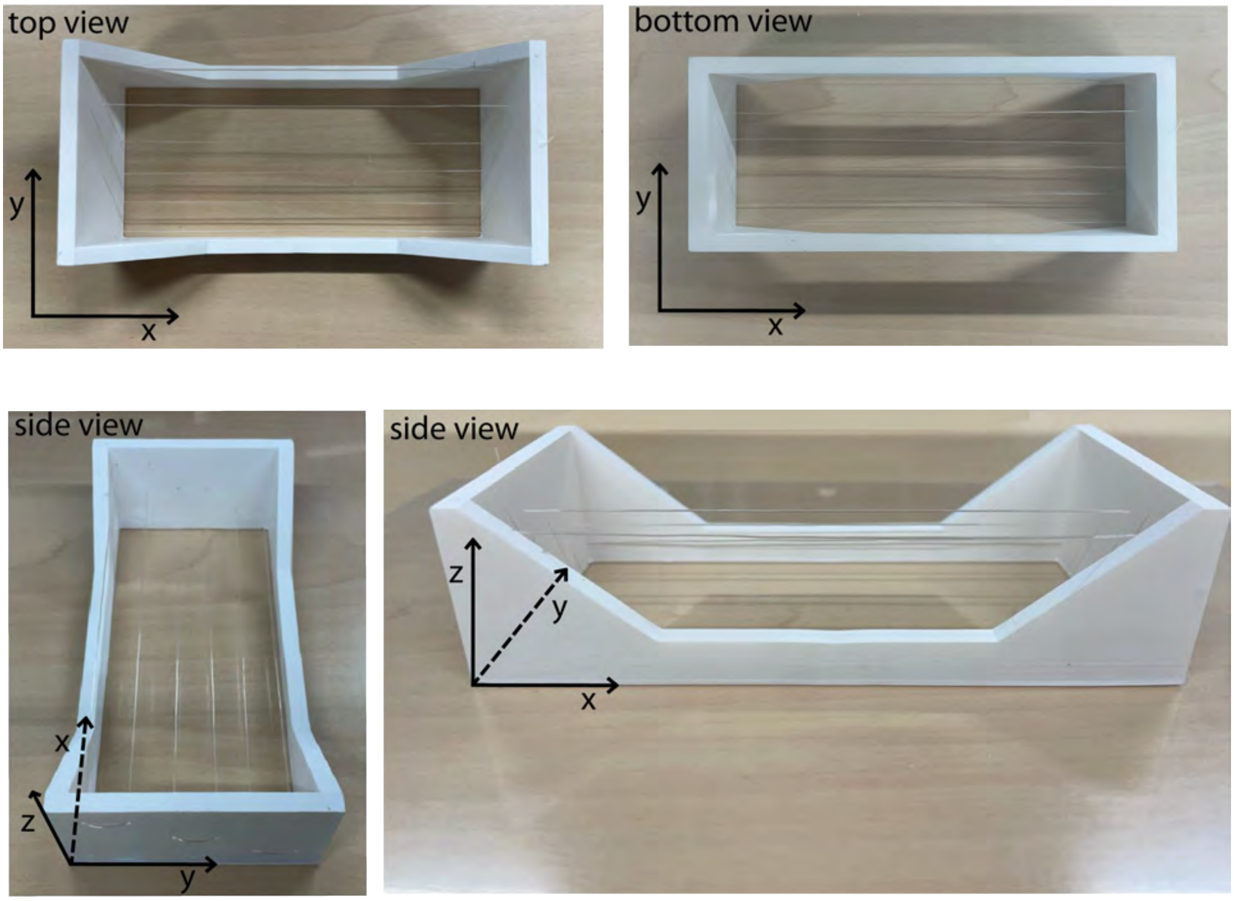

Figure 6.2: 3D wire holder with nylon wires laced through. Starting from upper left to bottom right: top view, bottom view, side view short side, and side view long side.

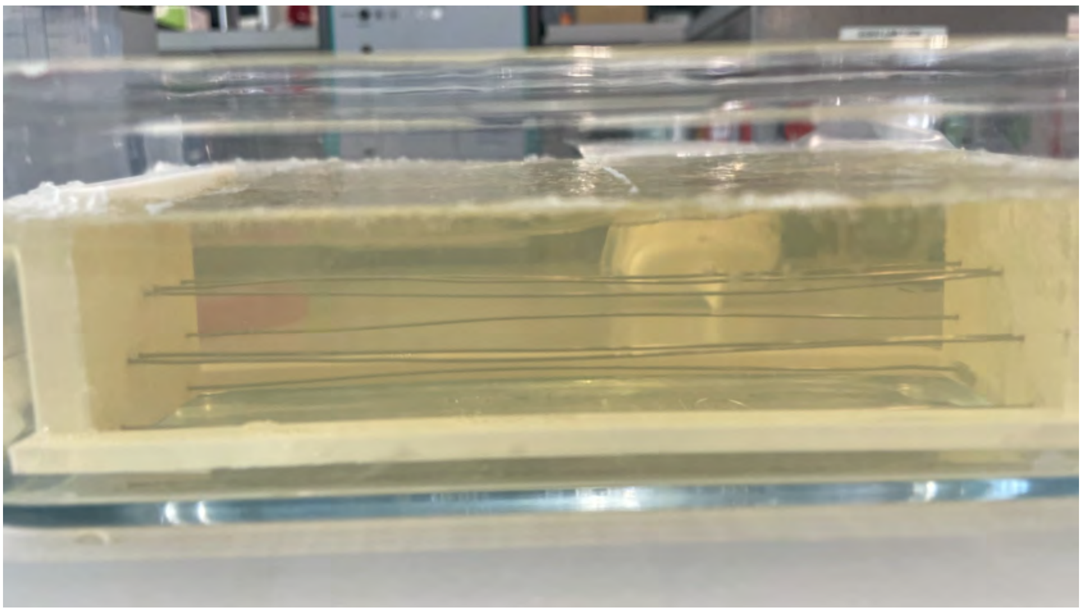

Figure 6.3: Stainless steel wires in gelatin phantom.

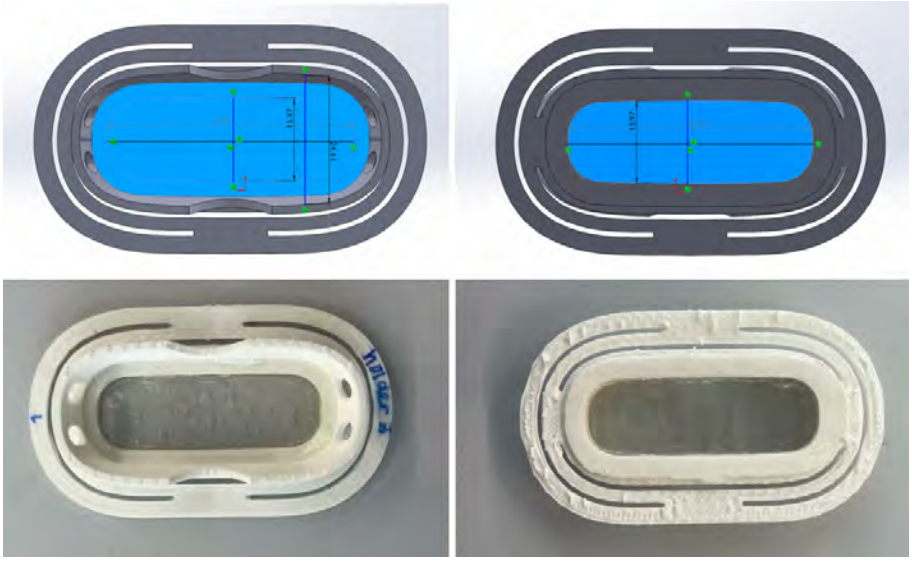

Figure 6.4: CAD design wearable patches with acoustic material illustrated in blue inside and pictures of wearable patches with acoustic material placed inside. *Left:* top of the patch, faced to ultrasound transducer and wearable pod. *Right:* bottom of the patch, faced to the surface of the phantom. The patches were modified from the original design of a previous student. They were 3D printed with PLA by an Ultimaker 2.

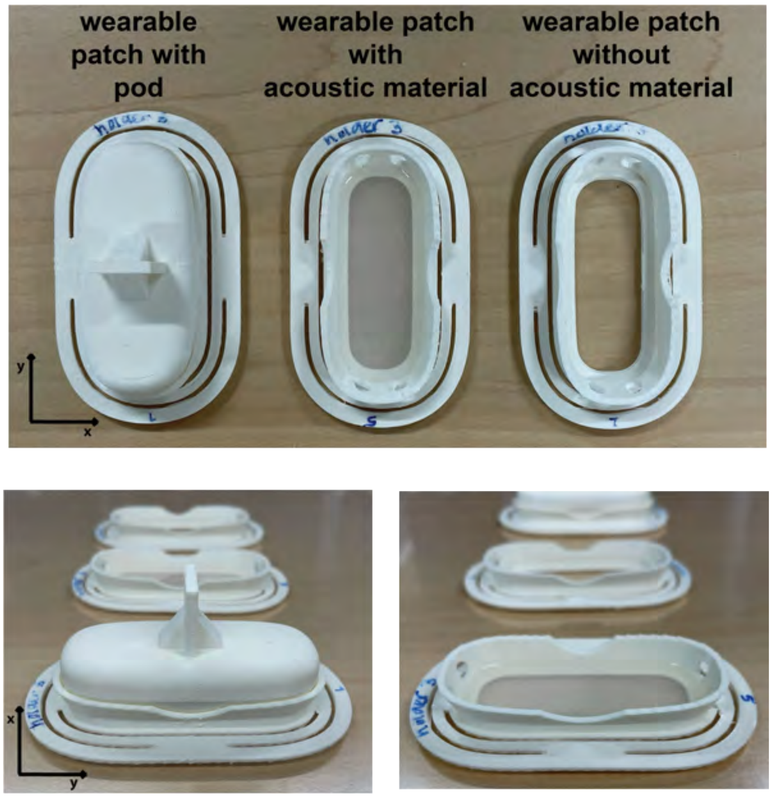

Figure 6.5: Images of wearable patch assembly. *Top:* from left to right, fully assembled wearable patch with acoustic interface material and pod. The upper middle image shows the patch with the interface assembled. The upper right image shows the patch without interface material. *Bottom:* Show the side view of the patches. Left is the fully assembled patch with pod and the right shows the side view of the patch with assembled interface material.

To make the phantom, the following stepwise process was developed.

1. Assemble the wire holder with wires in place.
2. Clean the glass container with alcohol and wait for it to dry.
3. Stick the assembled wire holder in the middle of the glass container with double-sided tape.
4. Make the phantom (filler) material according to the Methods preparing filling materials **??**.
5. Fill the container slowly till the phantom surface is the same height as the top of the wire holder.
6. Follow instructions in Methods 6 to stiffen phantom.
7. Place extra hydration layer according to the instructions.
8. Make a water regulation layer with the appropriate amount of holes according to instructions.
9. Stick three patches to the surface of the phantom as shown in Fig. 6.1.
10. Place acoustic interface material in the patch.
11. Write the name of the acoustic material on the container in the dedicated place.
12. Follow the instructions of the experimental plan.

6.2. Materials for filling of the ultrasound phantoms

Materials for the ultrasound phantoms were chosen using to the scoring system (Fig. 4.7) established by Chen P. et al. and the expertise from Philips and TNO Holst Centre [24].

Gelatin
Gelatin is a colloid gel, well-known in the kitchen and widely used as tissue-mimicking material [61]. It is easily prepared, has good acoustic properties and is low in cost. Gelatin's disadvantages are its short lifetime, instability and weak texture at various temperatures [24]. According to the scoring system, a phantom made of gelatin with 15 wt.% was given a score of 63.5, see Fig. 4.7 [24].

Polyvinyl alcohol
Poly(vinyl alcohol), or PVA, is used as tissue-mimicking material. It is a non-toxic and biocompatible material. A former employee of Philips specialized in creating ultrasound phantoms and usually made these phantoms with PVA. PVA is stiff and resistant to deformation of bending [24]. It can be used for years when stored in a -40 °C fridge. The longevity decreases when the PVA is kept at higher temperatures. The 15 wt.% PVA scored the highest among the other wt.% PVAs, with a score of 65.6 (Fig. 4.7).

Agar-agar
Agar, or Agar-agar, is a mixture of polysaccharides and agaropectin derived from red algae. It is mostly used for medical research, for instance, in petri dishes for bacteria growth. But also used in the kitchen as a vegetarian alternative to gelatin in the paper of Chen et al. Agarose was evaluated instead of Agar-agar. Agarose are polysaccharide linear chains derived from agar. Agaraose is mostly utilized in DNA and protein separation techniques, e.g., Western blots [65]. Agarose- and Agar-based materials have also been widely used for tissue-mimicking, for instance, breast tissue phantoms [66]. Agarose has a similar attenuation coefficient to gelatin and PVA and is cheap and easy to use. The shortcomings of Agarose are their low optical transparency and short lifetime [24]. Both agar and agarose are suitable materials for ultrasound phantoms. The choice for agar is due to the cheaper price and the less complex production process [67]. According to the scoring system (Fig. 4.7), the 5 wt.% Agarose scored 62.2, the highest of the three weight percentages of Agarose ranked. In this thesis, it is assumed that 5 wt.% Agarose and 5 wt.% Agar-agar will perform similarly when used as an ultrasound phantom.

Gel wax
Candle gel wax is a mineral-oil-based material [68]. In previous studies, Shin Kawasaki and Marta Saccher used this gel wax to make phantoms for testing ultrasound transducers. Gel wax as an ultrasound phantom material was studied by Vieira S. et al. (2013) and Maneas E. et al (2018) [38], [68]. In both papers, the researchers tuned the acoustic attenuation and speed of sound (SoS) of the gel wax by adding Parafinn wax or glass spheres. The reasoning was to increase the attenuation and decrease the speed of sound to simulate the biological tissue better. In this thesis, the phantom's aim is not to mimic a specific type of biological tissue precisely. One of the requirements, however, is for the phantom to be transparent to ultrasound. Therefore, there is no need to change the acoustic properties of the gel to correspond with those of specific biological tissues in this particular ultrasound phantom.

6.2.1. Prepairing filling materials

Gelatin
The gelatin phantom was made with Dr Oetker gelatin powder [61] and tap water. The weight percentage was determined during the literature review of Chen P. et al. [24]. The highest-scoring phantom made of gelatin in Fig. 4.7 is gelatin with 15% with a score of 63.5.

The amount of gelatin powder for the phantom container can be calculated with the following equation:

$$gelatin\ [g] = \frac{0,15 * V_{water}[g]}{1 - 0,15} \tag{6.4}$$

For a container with a volume of 1 L, weigh 174 g of powder and add it to the beaker. Add 250 mL of tap water to the beaker. Follow the instructions on the pack, and leave the mixture to set for ~10 minutes. After, heat up the solution to 80 °C while continuously stirring, and slowly add water (740 mL) until the total amount of water added is 1 L. Continue heating and stirring till the gelatin is fully dissolved, with no suspended particles in the solution. When the solution is fully liquid, remove bubbles as much as possible by scooping them out.

PVA
The phantom made of poly(vinyl alcohol) is made according to the recipe of Ed Berber from Philips. Ed Berber was responsible for making ultrasound phantoms for Philips research. The stiffness is also defined by Ed at 12.5%.

Desired amount of PVA solution	(1000)	mL
12,5% PVA	125	gram
non-PVA solution	(875)	gram
60% Demi-water	525	gram
40% Ethylene glycol	350	gram

The steps of the recipe are listed below:

- Measure and add the required amount of PVA to the beaker.
- Measure the ethylene glycol and introduce it into the beaker.
- Measure the deionized water and combine it with the other components in the beaker.
- Cover the beaker with aluminum foil, heat it gradually to approximately 90 °C, and stir continuously.
- Cease heating once the PVA solution becomes completely clear, with no suspended particles.
- Continue stirring and allow the solution to cool to a temperature of 60- 70 °C.

Gel wax
For the correct amount of gelwax for the phantom, 650 gram was weighed out and placed into the assembled container with wire holder, wires. For model 4.2, the attenuator was added on the bottom of the container. The container was placed in a vacuum oven at T $\approx$90 °C voor 3 hours. When all the wax had melted, the oven was turned off, and the container was left in the oven for another 1 hour to let as many bubbles as possible escape the gel wax.

Agar-agar
Agar is prepared following the instructions of Chen P. et al. [24]. The table in Fig. 4.7 also determined the weight percentage of the agar. Agarose is a derived form of Agar [69]. Therefore, the same weight percentage has been applied to make the Agar material as Agarose in Fig. 4.7: 5 % with a score of 62.2.

$$agar\ [g] = \frac{0,05 * V_{water}[g]}{1 - 0,05} \tag{6.5}$$

First, the agar powder was added to a beaker; then, the beaker was filled with distilled water. The beaker was heated to 100 °C, and with a stirrer, the solution was continuously stirred. After the agar powder was completely dissolved, the heater was turned off.

6.3. Phantom models

Phantom	number of layers	filling	scattering objects	hydrating layer	pores layer
model 1	1	gelatin	stainless steel wires	-	-
model 2	2	gelatin	nylon wires	gelatin	Teflon
model 3.1	3	gel wax	nylon wires	gelatin	PET
model 3.2 (+ absorption)	4	gel wax	nylon wires	gelatin	PET
model 4	2	PVA	nylon wires	PVA	PET
model 5	3	gel wax	nylon wires	agar	PET

Table 6.3: Overview of all the models of phantoms made, with corresponding fillings, hydrating layers, and pores

6.3.1. Phantom model 1: one-layer model

For the first phantom model, the decisions for materials and designs were mostly made with information gathered from the literature. It was decided to start with gelatin as a phantom filling. Gelatin is a well-known tissue-mimicking material that is easy to prepare and cheap. According to Chen P. et al. (2022), gelatin with a weight percentage of 15% was rewarded a score of 63.5, see Fig. 4.7 [24]. All the 3D prints were made with an Ultimaker printing with PLA.

Gelatin filling

The gelatin filling was made according to the instructions found in paragraph 6.2.1. After the gelatin was made, it was carefully poured into the glass container with the wire set up. It was left to harden for 15 minutes, then stored in a fridge for ~1 hour. When the gelatin had fully stiffened, the phantom was ready for use.

Scatterings objects

The scattering objects used in this model are stainless steel, as seen in the Fig. 6.3. They are placed in the wire holder, which was printed with an Ultimaker 2 with white polylactic acid (PLA) (Fig. 6.2).

Wearable patches

The wearable patches are also made in an Ultimaker 2 with white PLA (Fig. 6.4).

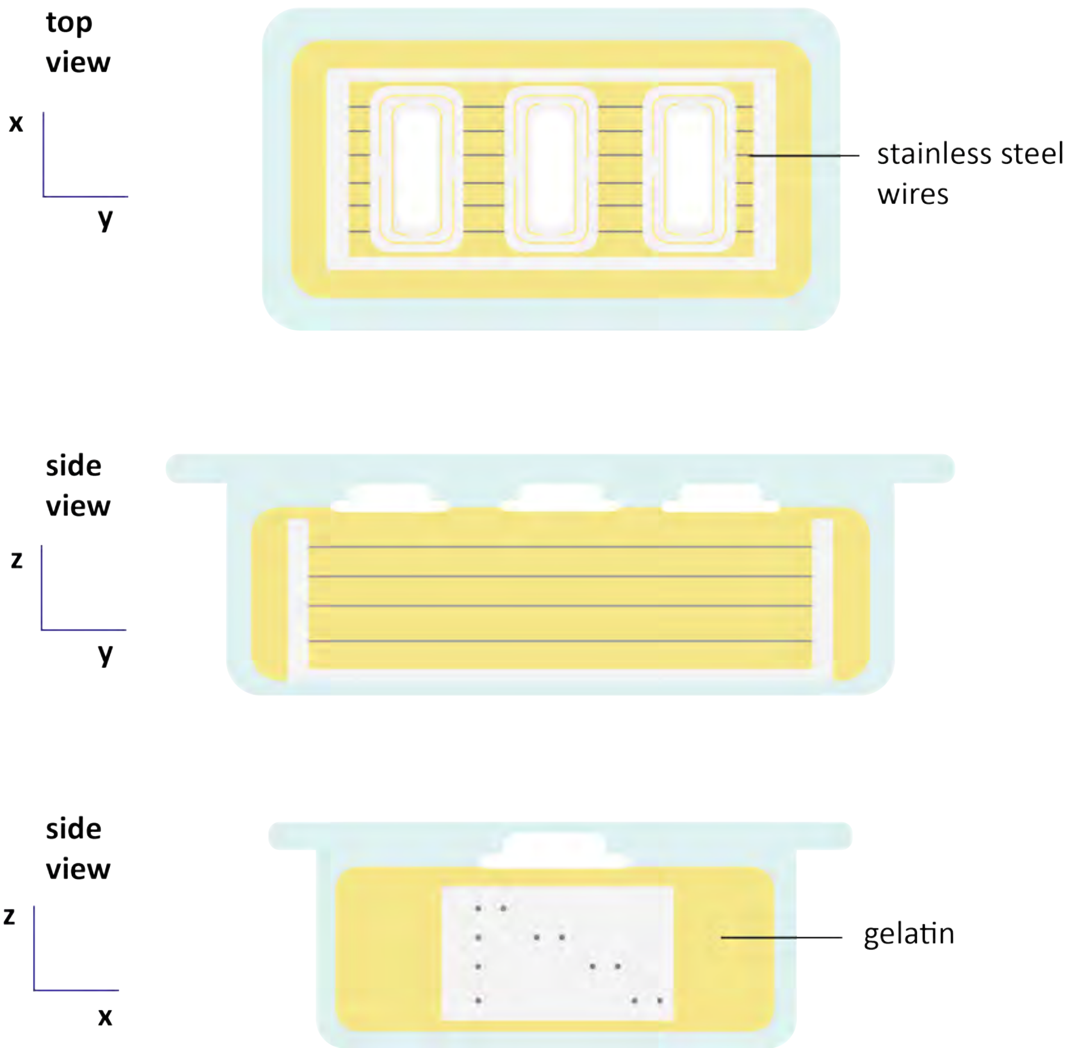

Figure 6.6: model 1 schematic illustration: gelatin filling, wire holder with stainless steel wires.

Shortcomings: Phantom model 1
Phantom Model 1 had a lot of shortcomings. Further explanations of these observations are noted in section 7.1.1. The shortcomings of this model include too short a lifetime, water loss, incapability to mimic skin temperatures, and scattering objects. The phantom model only reached day 3 when it started to degrade, which is shorter than the desired lifetime of the phantom. The amount of water evaporation of gelatin was 7,46 larger than that of human skin. The acoustic materials in the patches stuck on the surface of the gelatin were able to soak up too much water from the gelatin. The abundant excess of water extended the lifetime and improved the acoustic performance of the materials. This situation is not equivalent to the desired situation; therefore, it is a shortcoming of the phantom model. For this model, the maximum temperature that was reached in the setup was 26.1 C as the phantom was placed on a heating platform and no oven was used. For the next models, it was decided that for heating the phantom to the desired temperatures, an oven was always used. Also, the design choice to use stainless steel wires was considered a shortcoming; these gave large reflection spots of the cross sections and notable 'stripe patterns' under the reflection sports in the ultrasound images. After this finding, nylon wires were considered to be used instead of stainless steel wires in future phantom model designs.

6.3.2. Phantom model 2: two-layer model

For the second phantom model, it was aimed to improve the model shortcomings of model 1. An extra layer is deployed on top of the surface to refine the gelatin's water evaporation. The material choice for this layer was made by comparing the ultrasound images made with different materials as the top layer. In this research, it is assumed that the brighter the image, the less attenuation is caused by the interface layer. As shown in Fig. 6.7, Teflon performed the best in regard to making the brightest image.

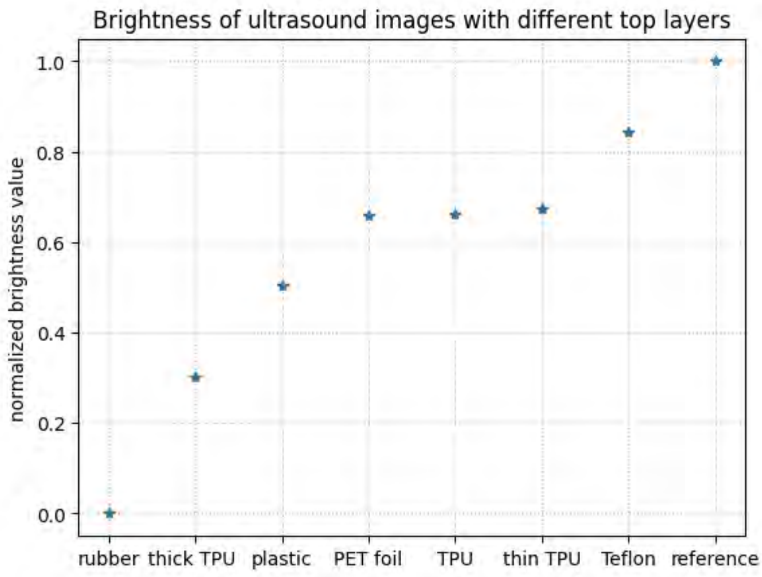

Figure 6.7: Normalized brightness values measured from images made Philips Lumify L12-4 with different top layers between general phantom surface and acoustic interface.

Using an oven with $T_{average} = 34°C$ for testing the phantom model. The stainless steel wires were replaced by nylon wire.

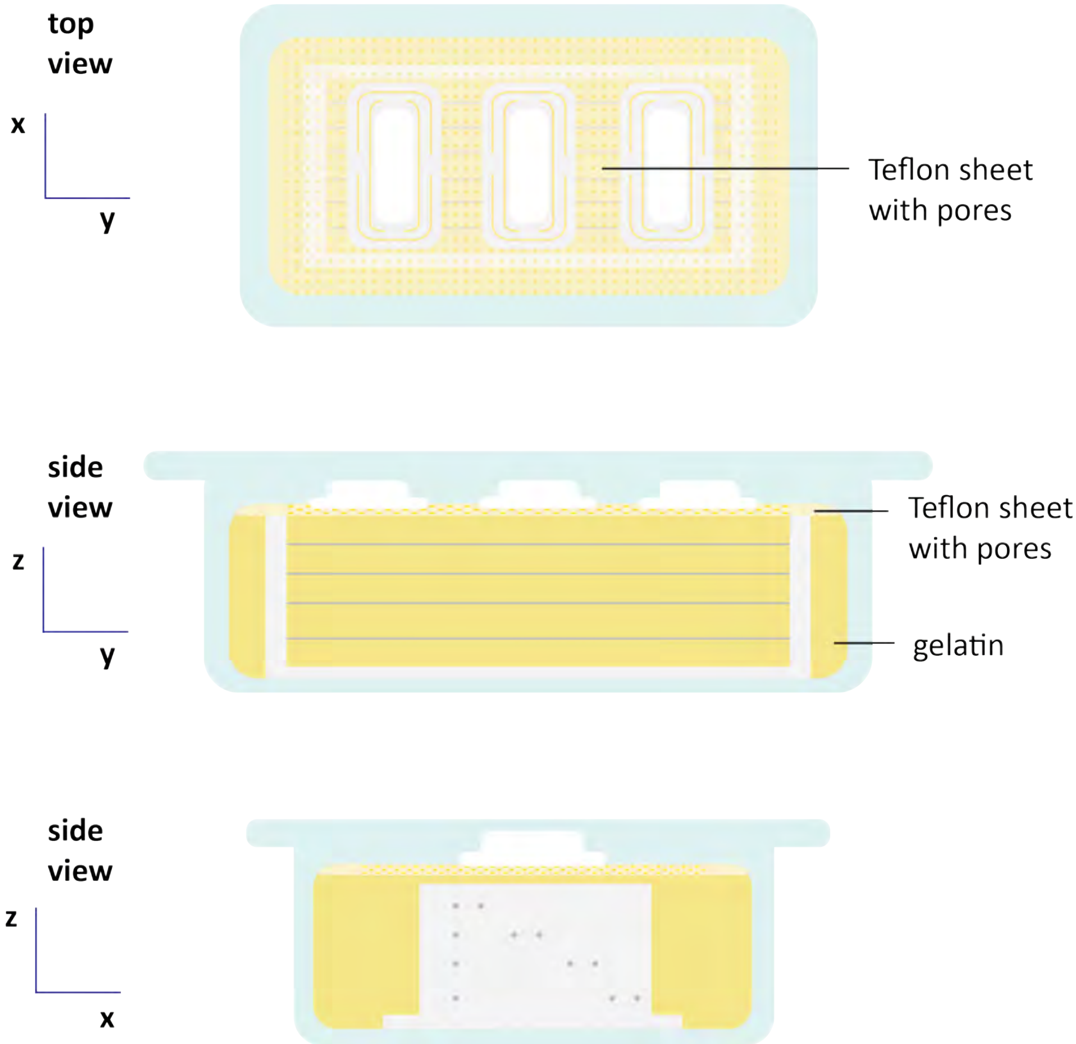

Figure 6.8: model 2 schematic illustration: gelatin phantom with Teflon top layer.

Gelatin filling
The gelatin is prepared following the instructions in (6.2.1). After letting the gelatin harden for 15 minutes, store the phantom in the fridge for another 15 minutes. Wet the surface with lukewarm water when the gelatin is stiffer, and gently lay the Teflon layer. If bubbles form, carefully push them out of the image area. Then put it in the fridge for 2 hours. The phantom is ready for use.

Scatterings objects
The scattering objects used in this model are nylon, as seen in the Fig. 6.3. They are placed in the wire holder, printed with an Ultimaker 2 with white polylactic acid (PLA), a previous version of the wire holder shown in Fig. 6.2.

Wearable patches
The wearable patches are also made in an Ultimaker 2 with white PLA (Fig. 6.4).

Teflon sheet
A Teflon layer was used to mimic the top layer of the skin, the epidermis. The epidermis serves as a protective barrier of the body for UV, pathogens, chemicals, and mechanical injury. It also releases water into the environment, which helps regulate body temperature [70]. There are two main ways for water to evaporate from the body through the skin [71].

To know how many pores are needed to mimic the water loss of an average human skin, gelatin's water evaporation rate must be measured. To measure this, a container with gelatin was weighed and noted. The evaporation area of the gelatin was 140 cm². The container with 15% wt. gelatin was put in a vacuum oven at T= 33°C - 35 °C for 1 hour.

water evaporation	from	gelatin
water loss gelatin	1040,50	nl/(min*cm²)
ratio skin/gelatin	7,46	
diameter pore	0,8	mm
area pore	0,00503	cm²
A phantom	19x13	
water area	33,13	cm²
number of pores	6590,14	
pores per cm²	26	

The area of gelatin from which water has to evaporate is calculated with the following equation. The water evaporation rate from the skin is from [26],[27] [28].

$$\text{water area} = \frac{\text{area phantom}}{\text{ratio}} = \frac{247\ [cm^2]}{7,46} = 33,13\ [cm^2] \tag{6.6}$$

$$\text{number of pores} = \frac{\text{water area}}{\text{area pores}} = \frac{33,21[cm^2]}{0,00503[cm^2]} = 6590 \text{ pores} \tag{6.7}$$

The Teflon layer was utilized to help regulate the water evaporation of the phantom to the acoustic materials on top and the environment. Teflon is a fluoroplastic material, also called polytetrafluoroethylene (PTFE). A Teflon sheet is optically transparent, waterproof, and has a thickness of 0,25 µm. The pores were made manually with a needle with a diameter of 0,8 mm. Per squared centimeter, there were about 14-15 pores poked. For model 2, only pores were poked in 25 cm² around the patches.

Shortcomings phantom model 2
Model 2 was an improved version of phantom model 1, though there were still shortcomings in this model when assessing it for the requirements. Further explanations of these observations from phantom model 2 are noted in section 7.1.2. In this case, the incapability to reach the desired lifetime of the phantom is associated with the inability to withstand the temperatures. The stiff consistency of the gelatin filling turned more liquid when left in an oven at $T = 34°C$. Phantom model 2 was degraded after four days in the oven at 34 °C. The desired lifetime of 5 days was not reached. The gelatin filling can only be used once for four days and must be disposed of afterward.

6.3.3. Phantom model 3.1: three-layer model

The development from model 3.1 to phantom model 3 was dictated to improve the lifetime and reusability of the phantom model. Therefore, 'gel wax' was used as filling for the following models. The gel wax filling was easy to make, cheap, and used as ultrasound phantoms. Gel wax is a hydrophilic material. For this reason, an extra layer was deployed to meet the mimicking skin water loss requirement. This layer was named the hydrating layer. In phantom model 3.1, gelatin was chosen for this layer. A thin sheet with holes (pores) is laid on top of the gelatin surface to passively regulate the water evaporation through the gelatin. For model 3.1, the material used for this layer is PET foil. From the graph in Fig. 6.7 best performing after Teflon would be TPU, though after experimenting with this material it was decided to use PET foil instead. TPU did not stick to the gelatin layer, as PET foil clung more steadily onto the gelatin and agar.

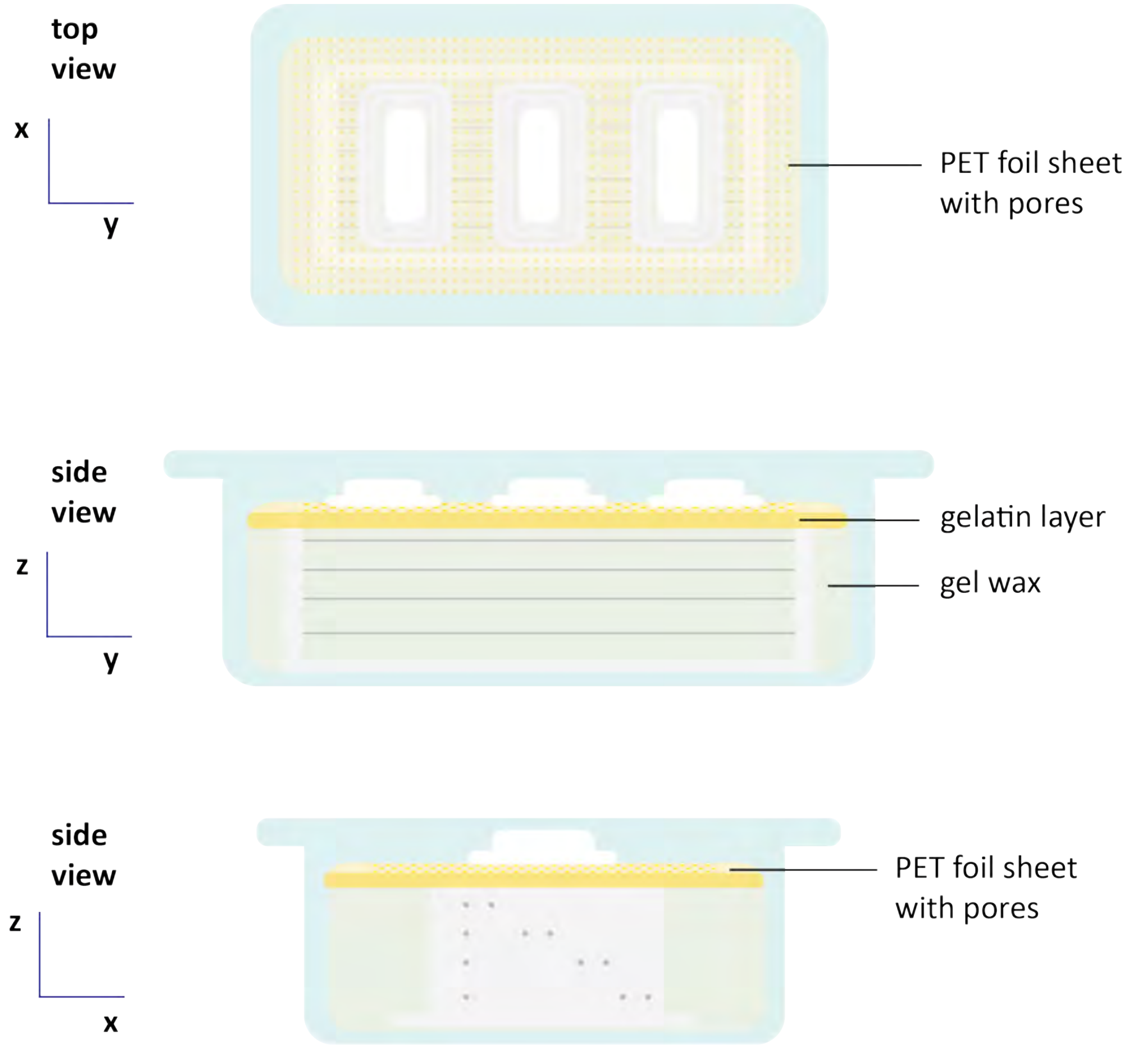

Figure 6.9: model 4.2 schematic illustration: gel wax phantom with gelatin layer and PET foil top layer.

Gel wax filling
Model 4.1 and 4.2 phantom have gel wax as filling. This filling was made following the instructions of 6.2.1. After the gel wax and the glass container had stiffened and cooled off, the rest of the layers could be placed on top.

Gelatin layer
The gelatin layer was made following the instructions for gelatin 15% wt. When the gelatin powder was fully dissolved, it was poured over the gel wax until the height of the surface was 1 cm above the gel wax surface.

Scatterings objects
The scattering objects used in this model are nylon, as seen in the Fig. 6.3. They are placed in the wire holder, printed with a stereolithographic (SLA) printer with rigid 10k resin. The wire holder is shown in Fig. 6.2.

Wearable patches
The wearable patches are also made in an Ultimaker 2 with white PLA (Fig. 6.4).

PET foil sheet
The PET foil sheet was utilized as the top layer and can be laser cut by a Trotec CO2 laser [50]. Therefore, smaller pores can be made more easily (i.e. 0,6 versus 0,8 mm in the previous model). The drawing for

the cut path was made with Siemens Solid Edge.

water evaporation	from	gelatin
water loss gelatin	1040,50	nl/(min*cm²)
ratio skin/gelatin	7,46	
diameter pore	0,6	mm
area pore	0,002827	cm²
A phantom	19x13	
water area	33,13	cm²
number of pores	11716	
pores per cm²	47	

$$\text{water area} = \frac{\text{area phantom}}{\text{ratio}} = \frac{247\ [cm^2]}{7,46} = 33,13\ [cm^2] \tag{6.8}$$

$$\text{number of pores} = \frac{\text{water area}}{\text{area pores}} = \frac{33,13[cm^2]}{0,00283[cm^2]} = 111716 \text{ pores} \tag{6.9}$$

An area of 140 cm² and 5198 pores with a diameter of 0,6 mm gives 37 pores per cm². Due to convenience for the cut path drawing, it was chosen to cut 36 pores per cm².

The shortcomings of this phantom model are covered later in phantom model 3.2.

6.3.4. Phantom model 3.2: four-layer model

This model was identical to phantom model 3.1, apart from placing an ultrasound absorption layer on the bottom of the container. This layer was used to absorb ultrasound waves reflected from the sides of the container and reduce some of the reflection of the nylon wires.

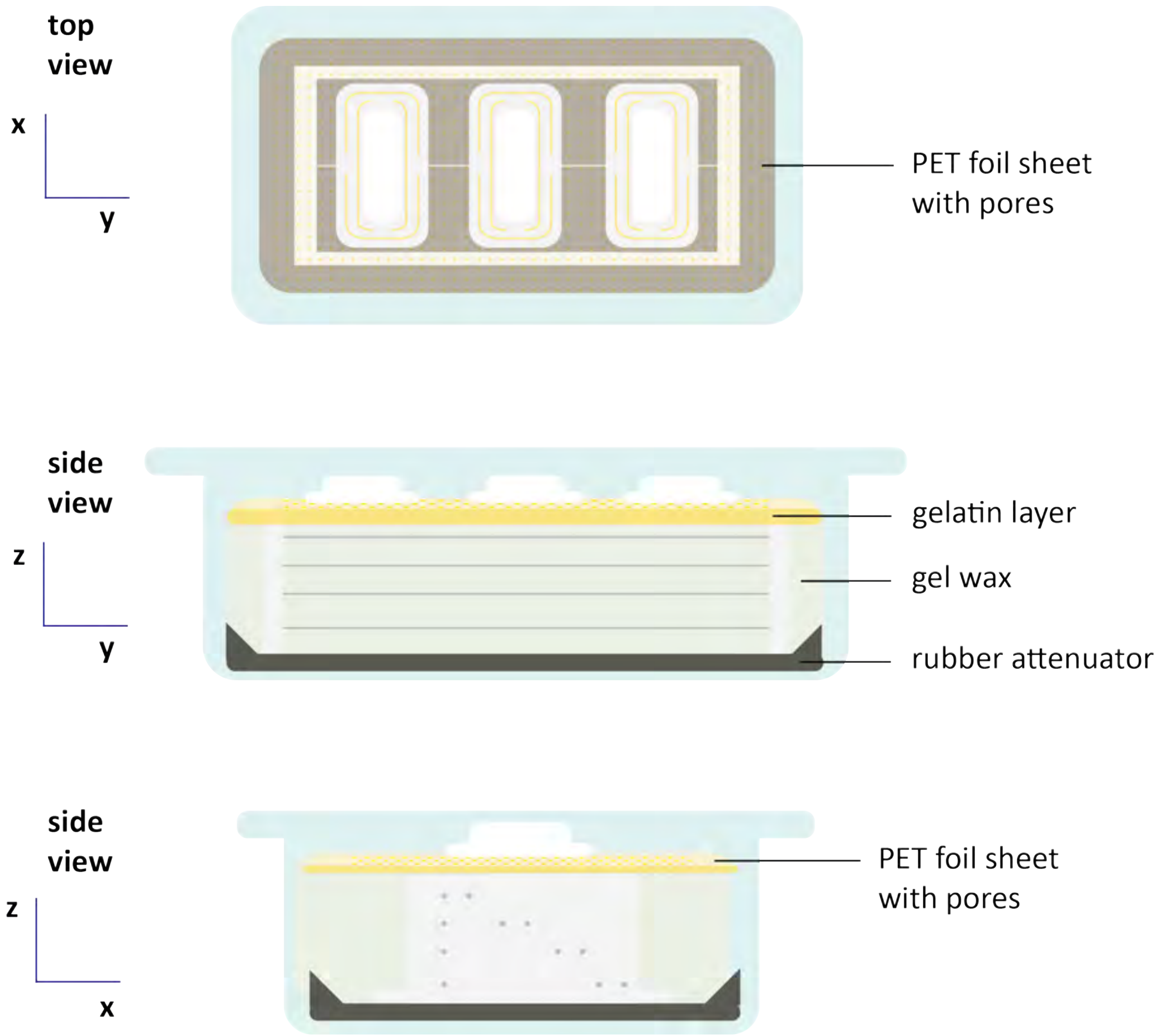

Figure 6.10: model 4.2 schematic illustration: gel wax phantom with rubber attenuation bottom layer, gelatin layer, and PET foil top layer.

Gel wax filling

The gel wax filling was made according to 6.2.1 in the assembled glass container with a wire holder and rubber absorber.

Gelatin layer

The gelatin layer was made following the instructions for gelatin 15% wt. When the gelatin powder was fully dissolved, it was poured over the gel wax till the height of the surface was 1 cm above the gel wax surface.

Rubber absorber

A model of the phantom with an attenuator on the bottom was made. This was done by placing a fitted rubber sheet on the bottom of the glass container. The rest of the phantom's components were assembled following the standard instructions.

Shortcomings phantom model 3.1 and 3.2
Additional explanations of the observations from developing and testing phantom models 3.1 and 3.2 are noted in section **??**. Both phantom models were made with gel wax filling, gelatin as a hydration layer, and PET foil as the top layer with the appropriate number of pores. These two models were made to compare using an absorbing layer on the bottom to not using it. The models needed improvement on the lifetime and temperature issues with the gelatin layer. Both models fell short in the required lifetime, as well as the liquifying of the gelatin layer due to the temperature. Model 3.2, with the ultrasound absorbing layer, turned brown and smelt; The gel wax filling absorbed some of the rubber colorings. In addition, the rubber did not stay tightly adhered to the bottom of the container, resulting in an uneven phantom bottom. This is not desired for a phantom. The nylon wire spots in the ultrasound images became more accurate and lest reflections were visible. It was concluded that the rubber absorber on the bottom of the phantom model resulted in more deficiencies than improvements.

6.3.5. Phantom model 4: two-layer model

Due to the shortcomings of gelatin as a material for this phantom, other materials were looked into. According to literature, polyvinyl alcohol (PVA) is often used as an ultrasound phantom [24]. PVA is made with three ingredients and is more expensive than gelatin, gelwax, and agar. The PVA materials listed in 4.7 were highly ranked by Chen P. et al. [24]. For this phantom model, PVA with a weight percentage of 15%, which scored 63.9, was made.

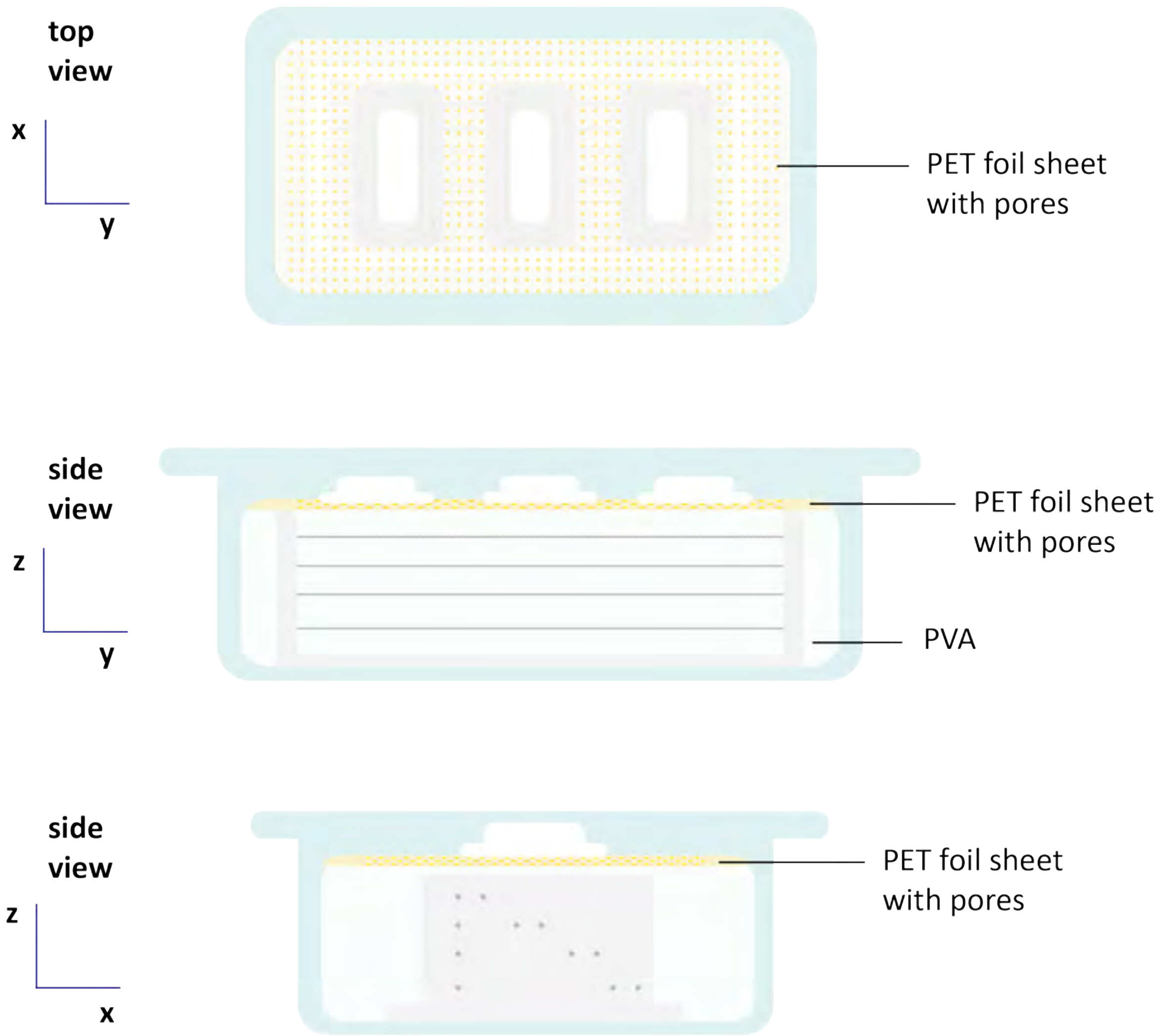

Figure 6.11: model 3 schematic illustration: PVA phantom with PET foil top layer.

PVA filling

The PVA was made according to the instructions in 6.2.1. The liquid PVA was carefully poured into the container. The container was then covered with aluminum foil to cool down further. It was then placed in a freezer at a temperature of -40 °C. By repeating the freezing cycles, a higher stiffness of the PVA can be attained.

PET foil sheet

To know how many pores are needed to mimic the water loss of an average human skin, PVA's water evaporation rate must be measured. To measure this, a container with PVA was weighed and noted. The evaporation area of the PVA was 140 cm². The container with 15% wt. gelatin was put in a vacuum oven at T= 33°C - 35 °C for 1 hour.

water evaporation	**from**	**PVA**
water loss PVA	318,83	nl/(min*cm²)
ratio skin/gelatin	2,28	
diameter pore	0,8	mm
area pore	0,00503	cm²
A phantom	19x13	
water area	108,11	cm²
number of pores	21507	
pores per cm²	88	

$$\text{water area} = \text{ratio} * \text{area phantom} = \frac{247\ [cm^2]}{2,28} = 108,10\ [cm^2] \tag{6.10}$$

$$\text{number of pores} = \frac{\text{water area}}{\text{area pores}} = \frac{108,10[cm^2]}{0,005026[cm^2]} = 21507 \text{ pores} \tag{6.11}$$

PET foil can be laser cut by a Trotec CO_2 laser [60]. The drawing for the laser cut path was made with Siemens Solid Edge. An area of 140 cm² and 12379 pores with a diameter of 0,8 mm gives 88 pores per cm². It was difficult to cut 88 pores with 0,8 mm. Therefore, it was decided to cut pores 88 with a diameter of 0,7 mm per cm².

Shortcomings phantom model 4

Using Polyvinyl alcohol in this type of phantom proved not to be the right choice. The amount of water evaporation from the PVA was insufficient to regulate with a top sheet and an appropriate number of pores. It was impossible to make enough holes in the top layer to mimic the amount of skin water evaporation. Also, the manner in which the water 'evaporated' from PVA was undesired. The PVA seemed to 'melt' like an ice cube would. The PVA phantom would shrink slightly and leave a pool of water around it.

6.3.6. Phantom model 5: three-layer model

Agar-agar was used for the last phantom model developed instead of gelatin and PVA. Agar is widely used in medical research. In literature, Agarose, a purer form of Agar, was considered a phantom material [24]. In Fig. 4.7, Agarose with a weight percentage 5% received a score of 62.3 from Chen P. For phantom model 5, it was assumed that Agarose 5% corresponded to Agar 5%. Due to the success of the three-layer model in phantom model 3.1, this was repeated. Agar retains its stiffness at higher temperatures, is cheap, and is easy to make; therefore, this material was chosen as a hydration layer on top of the gel wax filling. The gel wax filling with the wire holder can be reused after disabling the disposable hydration layer.

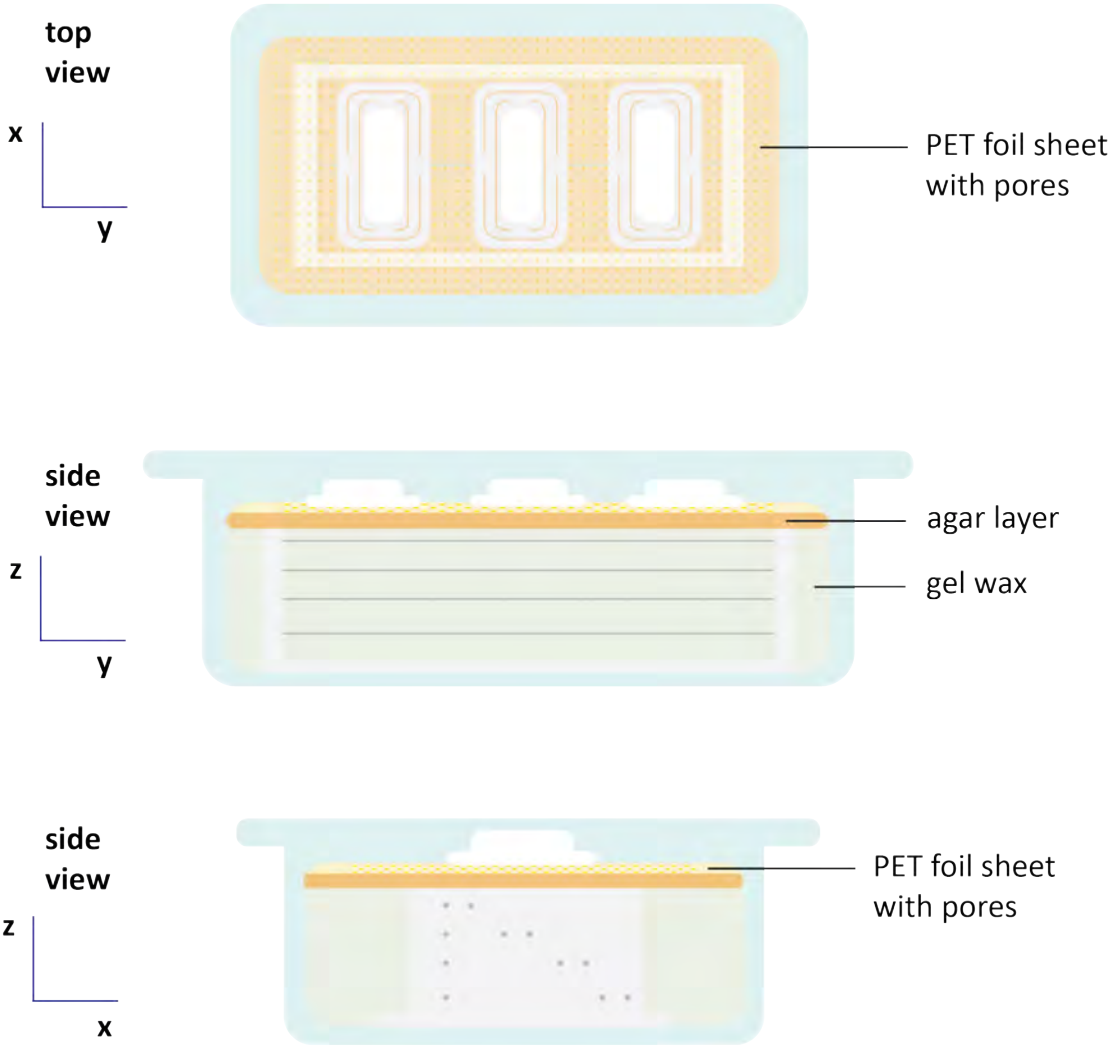

Figure 6.12: model 5 schematic illustration: gel wax phantom with agar layer and PET foil top layer.

Gel wax filling

The gel wax was made following the instructions stated in 6.2.1.

Agar layer

The Agar-agar was prepared according to the instructions in 6.2.1. When the solution was 90 °C, the agar solution was poured over the surface of the gel wax. The thickness of the layer was 1cm. The phantom with agar layer on top was then cooled to room temp to solidify fully.

PET foil top layer

water evaporation	from	agar
water loss agar	474,42	nl/(min*cm²)
ratio skin/gelatin	3,40	
diameter pore	0,7	mm
area pore	0,00385	cm²
A phantom	19x13	
water area	72,65	cm²
number of pores	18878	
pores per cm²	76	

$$\text{water area} = \frac{\text{area phantom}}{\text{ratio}} = \frac{247\ [cm^2]}{3,40} = 72,65\ [cm^2] \tag{6.12}$$

$$\text{number of pores} = \frac{\text{water area}}{\text{area pores}} = \frac{72,65[cm^2]}{0,00385[cm^2]} = 18878 \text{ pores} \tag{6.13}$$

6.4. Lifetime experiments of acoustic interface materials using the phantom

During the lifetime experiments, the acoustic performance of different acoustic interface materials was tested over five days. The acoustic interface materials are listed in Materials 5 under Acoustic Materials. This experiment was done to see to which extent the image quality would degrade over time for the different interface materials. The Philips Lumify probe and the placing system shown in Fig. 4.4 were utilized to make these ultrasound images. The interface materials were placed in the patches on the phantom. Twice a day, an image with the Lumify probe was taken. This was done by assembling the Lumify probe in the adapter and disassembling the pod from the gel pad holder (Fig. 6.13). Then, the Lumify probe with adapter was clicked in the patch, so the transducer was in contact with the acoustic interface, and an image with 'soft tissue' mode and 'vascular mode' was taken (Fig. 6.14). Afterward, the Lumify was clicked out, and the pod was assembled on the patch again. These images were assessed during data analysis by calculating the brightness and image scatter. From this data, an evaluation was done on the acoustic decay and the lifetime assessment of the materials.

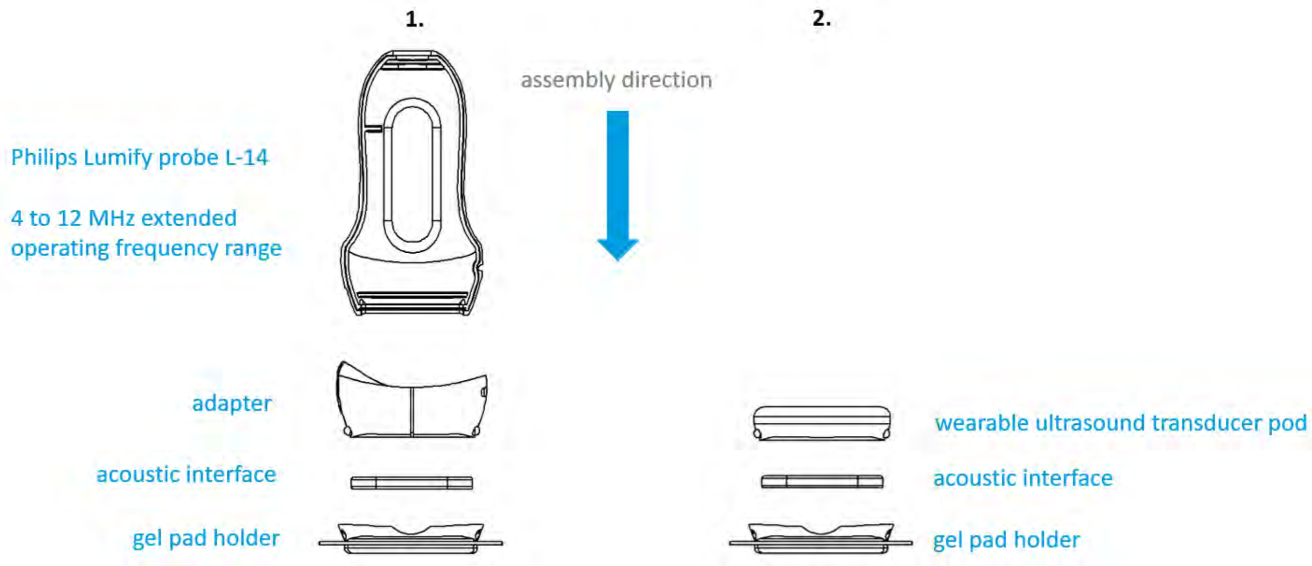

Figure 6.13: Schematic illustration of placing assembly. *1:* assembly path for imaging. *2:* assembly path for a closed wearable patch.

Figure 6.14: Schematic illustration of an ultrasound transducer on a phantom model. It illustrates how the ultrasound images were made during the lifetime experiments for testing performances of acoustic interface materials

6.5. Acoustic performance

For a material to be suitable for an ultrasound acoustic interface, it must satisfy the requirements listed below.
Acoustic properties:

- $Zmaterial \approx Z$human tissue $= 1,48 - 1,99$ $[MRayl/m^2]$;
- Minimise energy loss: low attenuation $\alpha \approx 0$ $[dB/cm/MHz]$;

A through-transmission setup was developed to measure the materials' acoustic properties.

6.5.1. Through-transmission setup

The through-transmission setup is shown in Fig. 6.15. With this setup, the speed of sound (SoS) and attenuation coefficient (α) of interface materials and the materials used for the phantom can be measured. With through-transmission measurements, an ultrasound signal is transmitted from a transducer. These waves go through the sample and are received by a hydrophone. This is typically done in a water tank, SoS_{water} = 1500 m/s.

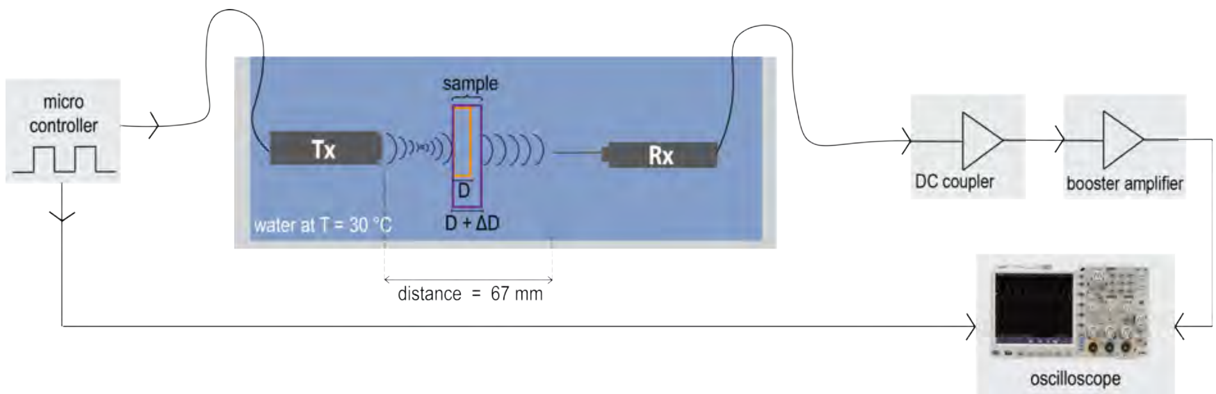

Figure 6.15: Schematic layout of the through-transmission setup. The sample is illustrated with two different thicknesses: D and D + ΔD, orange and purple, respectively. For the reference measurement, the signal delay between the transmitter and receiver was 44,6 μs. The distance can be calculated with the $SoS_{water} = 1500$ m/s. Distance = 44,6 μs x 1500 m/s = 67 mm.

The through-transmission schematic of the setup is shown in Fig. 6.15. The ultrasound wave is generated by a microcontroller and transmitted by the transducer (Tx). It travels through the water (T= 30 °C), through the sample, and eventually reaches the hydrophone (Rx). The ultrasound signal received by the hydrophone is transmitted to a DC amplifier and boost amplifier to be read out on an oscilloscope. The transmitted ultrasound signal is also visible on the scope.

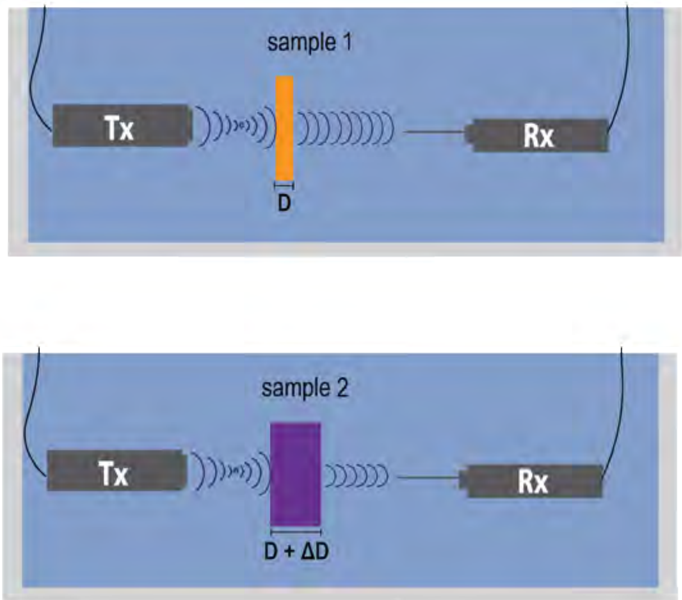

Figure 6.16: Zoomed in on the water tank in the through-transmission setup where the difference between sample 1 and sample 2 is shown. When measuring the signal through a thicker sample (sample 2) it is expected there is more attenuation of the signal than a signal going through a thinner sample (sample 1).

In Fig. 6.16, the expected attenuation of the ultrasound signals going through a thinner and thicker material is schematically shown. The bottom figure shows a weaker received signal than in the top figure. The ultrasound waves are more attenuated when having to travel longer through the same material compared to a shorter distance.

6.5.2. Sample preparation

To do these measurements correctly, the material samples with the correct thicknesses had to be prepared beforehand. Most materials that underwent the attenuation measurements were hydrophilic materials. When these materials were exposed to the water in the tank, they soaked up a lot of water, leaving a misformed sample and inaccurate measurements. For this reason, most samples were put in small plastic bags and vacuumed. Others, AquaFlex, agar, PVA, and gelwax, were melted and poured into the molds with a front and back opening. Once the samples were prepared, the measurement could start. The materials and their corresponding thicknesses are listed in Table 6.4.

Table 6.4: List of materials with corresponding thicknesses for attenuation through-transmission measurements

material	sample 1 thickness [cm]	sample 2 thickness [cm]
Gelatin	1 cm	2 cm
Gelwax	1 cm	2 cm
Poly(vinyl)alcohol (PVA)	1 cm	2 cm
Agar	1 cm	2 cm
polymethyl methacrylate (PMMA)	1 cm	2 cm
solid hydrogel (AquaFlex)	1 cm	2 cm
solid hydrogel (HydroAid)	0,3 cm	0,6 cm
silicone (Ecoflex)	0,74 cm	1,7 cm
ECG (Axelgaard)	0,2 cm	0,8 cm
ECG (HH5023)	0,2 cm	0,8 cm
ECG (HH5450)	0,8 cm	1,8 cm

6.5.3. Measurements

When the setup and the samples are fully prepared the measurements can be conducted. This is done by placing the sample between the transducer and the hydrophone. Then, the measurement can be started, and the transducer will generate the ultrasound signal. The measurements consisted of a sweep through 16 different frequencies in the range of [5 MHz - 12.5 MHz]. A burst of 10 cycles was transmitted for every frequency with a peak-to-peak voltage of 50 volts (Vpp = 50 V). For every sample, two reference measurements were conducted. The reference measurement was done in water with no material between the transducer and the hydrophone.

Settings:
cycles = 10;
Vpp = 50 V;
transmitted frequencies = [5. 0MHz, 5.21 MHz, 5.43 MHz, 5.68 MHz, 5.95 MHz, 6.25 MHz, 6.58 MHz, 6.94 MHz, 7.35 MHz, 7.81 MHz, 8.33 MHz, 8.93 MHz, 9.62 MHz, 10.42 MHz, 11.36 MHz, 12.5 MHz].

To calculate a material's attenuation coefficient α, the attenuation of two samples with different thicknesses were measured with the setup. A measurement was done with sample 'material X' with thickness 1. Then, a measurement for sample 'material X' with thickness 2 was conducted. Due to disturbances in the setup, two measurements were done for every sample. This gave six data sets per material, two references, and four attenuated datasets.

6.5.4. Data Analysis

The raw data of these experiments were given in a data set of 16 different frequencies, per transmitted frequencies a set of [voltage input, voltage output, time]. The output voltage values were converted to pressure values with the hydrophone's datasheet with sensitivity values [mV/MPa]. From the 16 transmitted frequencies, the pressure signal was plotted for each sample and reference. In Fig. 6.17, an example of a plotted pressure signal of a reference measurement is shown. The dataset consists of the ultrasound signal with ten cycles for 16 frequencies.

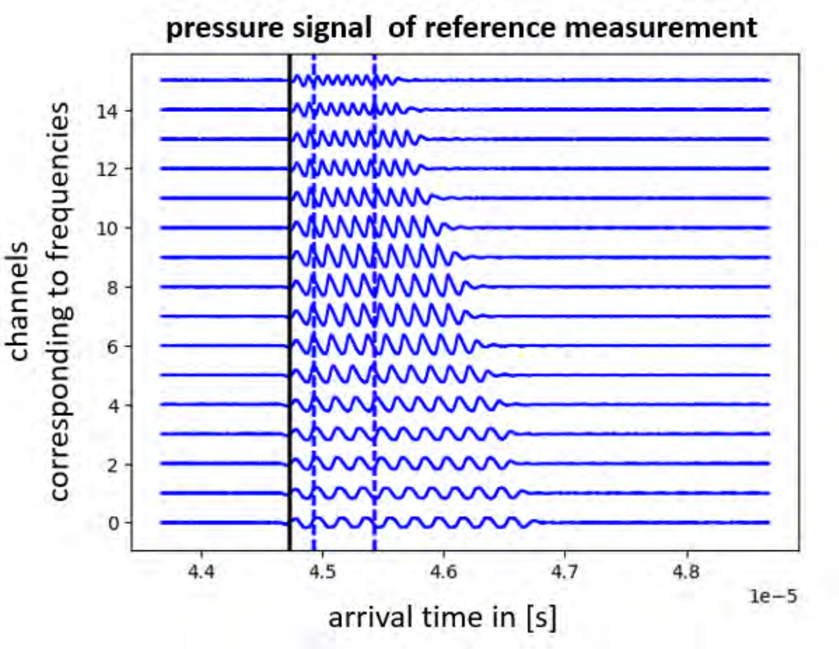

Figure 6.17: Pressure signal of reference measurement. *y-axis:* The 16 different channels correspond to the 16 different frequencies. All signals have ten cycles. *x-axis:* arrival time of the signal from the transducer to the hydrophone.

From each frequency signal, the peak-to-peak pressure was measured and plotted. After that, the attenuation coefficient could be calculated. For these calculations, it is presumed that the reflection of the ultrasound wave at the sample interfaces is neglectable. The P_0 is the attenuation measured in the water without material in between the transducer and hydrophone. P_1 corresponds to the pressure of sample with thickness 1 (D) and P_1 corresponds to the pressure of the sample with thickness 2 ($D + \Delta D$); these are the attenuated signals of the material.

$P_1 = P_0 e^{-\alpha(D)}$, in [dB]
$P_2 = P_0 e^{-\alpha(D+\Delta D)}$, in [dB]
For the attenuation coefficient calculation, the difference between the attenuation of samples 1 and 2 is taken. Below, the explanation of this calculation is given:
$\frac{P_2}{P_1} = \frac{P_0 e^{-\alpha(D+\Delta D)}}{P_0 e^{-\alpha(D)}}$
$\frac{P_2}{P_1} = e^{-\alpha \Delta D}$
$ln[\frac{P_2}{P_1}] = e^{-\alpha \Delta D}$
$ln[\frac{P_1}{P_2}] = \alpha \Delta D$

Gives this equation 6.14 for attenuation coefficient:

$$\alpha = \frac{1}{\Delta D} ln[\frac{P_1}{P_2}] \text{ in [dB/cm]} \tag{6.14}$$

With Eq. 6.14, the attenuation coefficient of each material can be calculated and plotted. These plots can be found in the Results 7.

6.6. Skin Compatibility

Validating biocompatibility of acoustic materials
For a material to be suitable for an ultrasound acoustic interface, the material must satisfy the requirements listed below.
Requirements of the acoustic material for the interface between the ultrasound transducer and skin:
Material properties:

- Conformable to the body: flexible and creating an airtight seal with the skin;
- Biocompatible with human skin;
- Prolonged duration of functional use, $t \geq 5$ days;
  - Hydration;
  - Adherence to skin;

The acoustic interface materials were validated on biocompatibility via ISO 10993. From this ISO standard, the most relevant parts for acoustic interface materials were tested for vitro cytotoxicity, skin sensitization, and irritation. The evaluations of the acoustic interface materials for these tests were all found in the technical datasheets.

Interviews
The topic of wearable ultrasound devices and different potential acoustic interface materials is extremely new. As mentioned in section 4, there are no regulations for long-term continuous ultrasound monitoring and prolonged placement of interface materials on the skin. Therefore, interviews were conducted to explore this topic in the medical and industrial fields. Experts in companies developing wearable ultrasound devices were interviewed on their thought processes behind validating and approving certain aspects of such devices. In addition, medical professionals were interviewed and asked about their experience with wearable (ultrasound) devices, the long-term use of materials like ECG stickers on the skin, and possible other applications of these devices.

Interviews were conducted with medical professionals to assess acoustic interface materials for ultrasound wearables, being:

experts on medical devices	
CEO	NovioScan
General manager	Mepy
Senior product manager	Philips

medical profesionals	
Cardiologist-electrophysiologist	Haga Ziekenhuis
Plastic surgeon	Erasmus MC
Dermatologist	Erasmus MC

The following questions were asked during the interviews with the experts on medical devices:

- What type of wearable device does *(name company)* make?
- What type of ultrasound monitoring does it use?
  - Are there regulations or guidelines for long-term use (t > 48 hours) of wearable ultrasound devices?
  - What regulations do you turn to for guidance?
  - Have you experienced skin irritation difficulties during long-term ultrasound use?
- For how long is it placed on the skin?

  - Have you experienced difficulties with skin irritation during the long-term use of acoustic interface materials on the skin?
- What type of acoustic interface material is used?
  - Have you experienced difficulties with the dehydration of this material?
  - Have you experienced other difficulties with this material?

The following questions were asked during the interviews with medical professionals:

- Do you have experience with ECG patches on the skin for an extended period?
  - What skin irritations would you expect/have you observed with ECG materials?
  - Do you have advice for other materials?
- Do you think ECG-like adhesive patches can be used long-term (>5 days) on a patient's skin without causing too many skin problems?
  - Could this also be done at home?
  - Can the skin stay moist for such a long time?
  - Can the skin endure prolonged tension?
- Do you have ideas for possible applications of wearable ultrasound devices in your medical field?
- What are your thoughts on using a skin-mimicking phantom for testing these materials?
  - What is your opinion on the phantom, especially the 'skin' layer?

Validating biocompatibility of materials
To validate the biocompatibility of the potential acoustic materials, the ISO standards, cosmetic regulations, and intended use of the materials were looked into and noted in a table. To validate the material, it had to be tested against ISO 10993, listed in the approved cosmetic products or had an intended use in medical applications.

7
Results

In this chapter, the results will again be divided into three main parts:

1. Results of all the versions of the developed phantoms 7.1;
2. Through-transmission acoustics properties results 7.3;
3. Skin-compatibility validations and interviews 7.4.

From these three subjects, the main focus was on developing an ultrasound skin-mimicking phantom. This process is thoroughly described in the following sections. While developing this phantom, several different setups and iterations of the phantom model were made. When the final phantom was created, 'lifetime experiments' were carried out using this phantom.

7.1. Ultrasound Phantoms

The ultrasound phantom models are assessed according to the assessment scheme in 6.1 in Methods 6.1.1.

7.1.1. Phantom model 1: one-layer model

The first phantom model was made in two different containers, square and rectangular. Both phantoms were put on the heating platform ($T = 35°C$) for a couple of days. Both phantoms started to show signs of mold growth in the gelatin filling. The pictures of the phantoms over time are shown in Fig. 7.1.

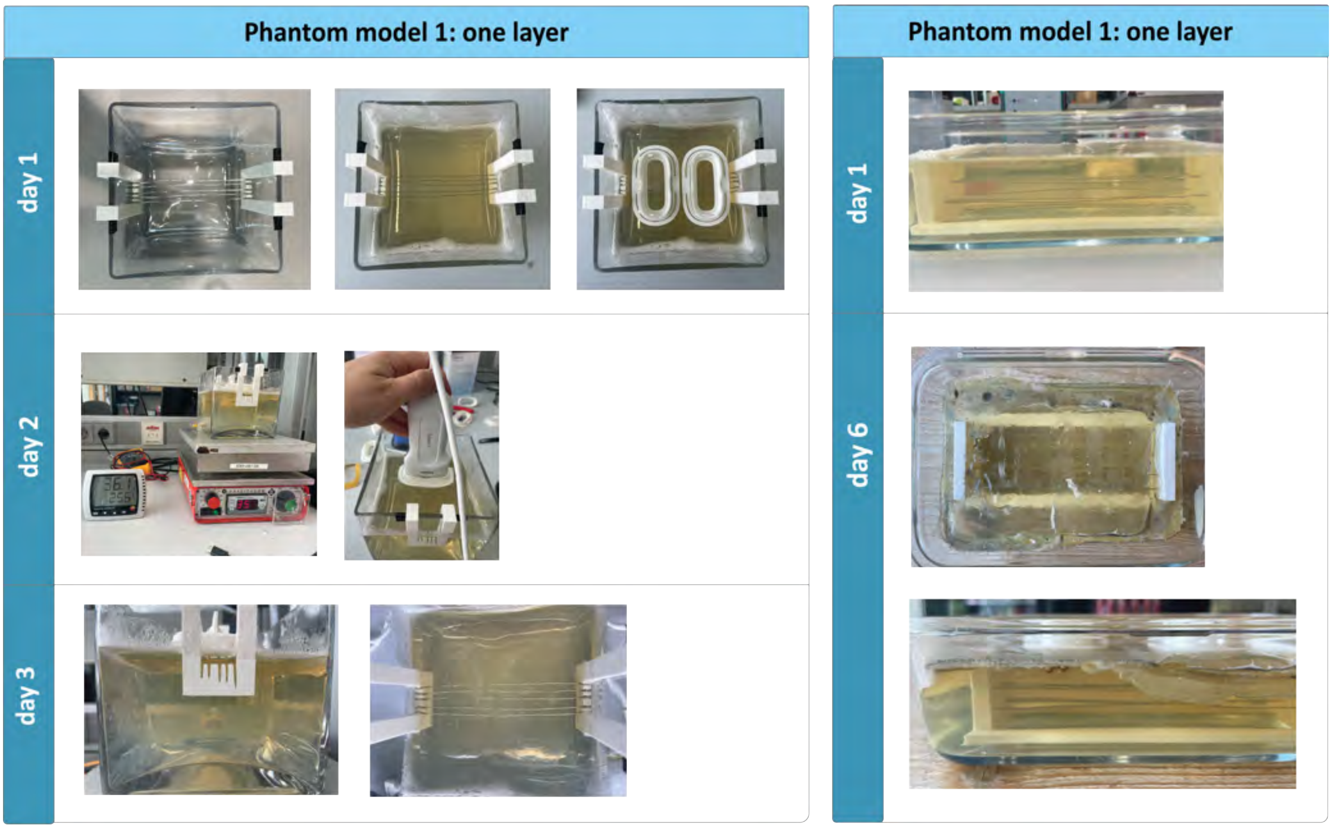

Figure 7.1: Phantom model 1: one-layer. *Left:* model 1 in a square container with as scattering object, stainless steel wires. Two patches were placed on the phantom and heated up ($T = 36°C$) by a heating platform. On day 3, the gelatin would degrade and show signs of mold growth. *Right:* model 1 in a rectangular container with stainless steel wires. This phantom was placed on the heating platform, and after 6 days, the gelatin filling had a lot of mold growth.

	Assement model 1	1–3	4–6	7–9
9	preperation time	2-4 hours	1-2 hours	**0-1 hour**
1	resuable	**no**		yes
8	transparent to ultrasound	α> 5 dB/cm/MHz	α= 1- 5 dB/cm/MHz	α**< 1 dB/cm/MHz**
2	lifetime t>5 days	**no**		yes
1	withstand temperatures	**no**		yes
6	mimics human skin water evaporation	<139,5 nL/(min*cm²)	**> 139,5 nL/(min*cm²)**	139,5 nL/(min*cm²)
4	scattering objects	nothing visible	**to much reflection**	enough
31	total score			

The phantom model 1 was assessed with Table 6.1 and graded with a 31 out of 63 (the maximum score).

Water evaporation
In the section Methods 6.3.1, the explanations of the calculations for water evaporation rates are given. In Table 6.2, the values of the estimated 'average sweat flow rate' and 'average transepidermal water loss' are noted; this gave an average water loss rate of = 139,5 nL/(min*cm²). The water evaporation rate of 15 wt. % gelatin, which was 1040,50 nL/(min*cm²). For the phantom model to mimic the amount of moisture perspiration, an extra layer was employed on top of the gelatin. This layer was meant to act as an epidermis layer by inherently regulating the water evaporation per area. Pores were made in this layer to try and reduce the [skin:gelatin] ratio from [1:7,46] to [1:1].

Temperature
To mimic a temperature of Tskin= 33 °C - 35 °C, phantom model 1 was placed on a heating platform as seen in Fig. 7.1 at T= 35 °C. The surface temperature of the phantom was measured using a thermal imaging camera. This indicated a temperature of 26,1 °C, which was just half a degree warmer than the room temperature at that moment, $T_{room} = 25,6°C$. This resulted in a change of plan regarding the heating. For the following models, 2, 3, 4, and 5, an oven was used to reach the temperature needed.

Scattering objects: Stainless steel wires
This model had stainless steel wires, with a ⌀= 0,8 cm, acting as the scattering objects. The stainless steel wires caused large reflections in the ultrasound image. The cross-section of the wire can be seen in the ultrasound image as a bright spot, indicated by the blue circle in Fig. 7.2.

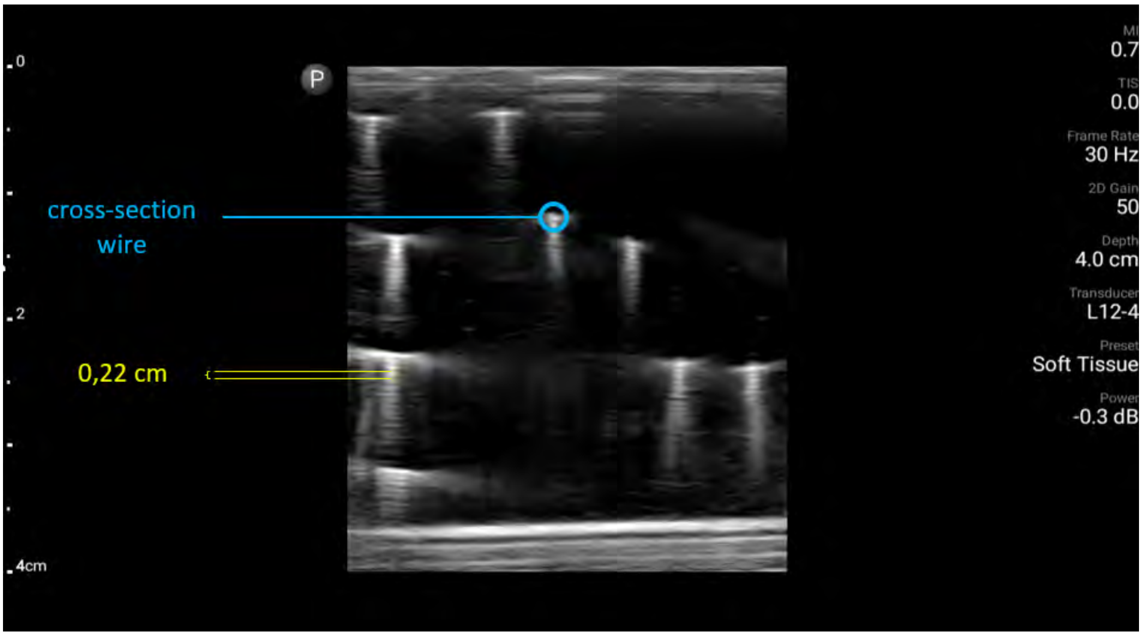

Figure 7.2: Ultrasound image inside phantom model 1 with scattering objects: stainless steel wires, d= 0,8 cm. The image shows the wires, bright spots in the image, and a 'tail' below the spot. Image taken with the Philips Lumify L12-4.

The spots have large 'tails' which consist of bright stripes. It was theorized that these stripes are caused by the ultrasound waves 'bouncing' back and forth in the stainless steel wire.

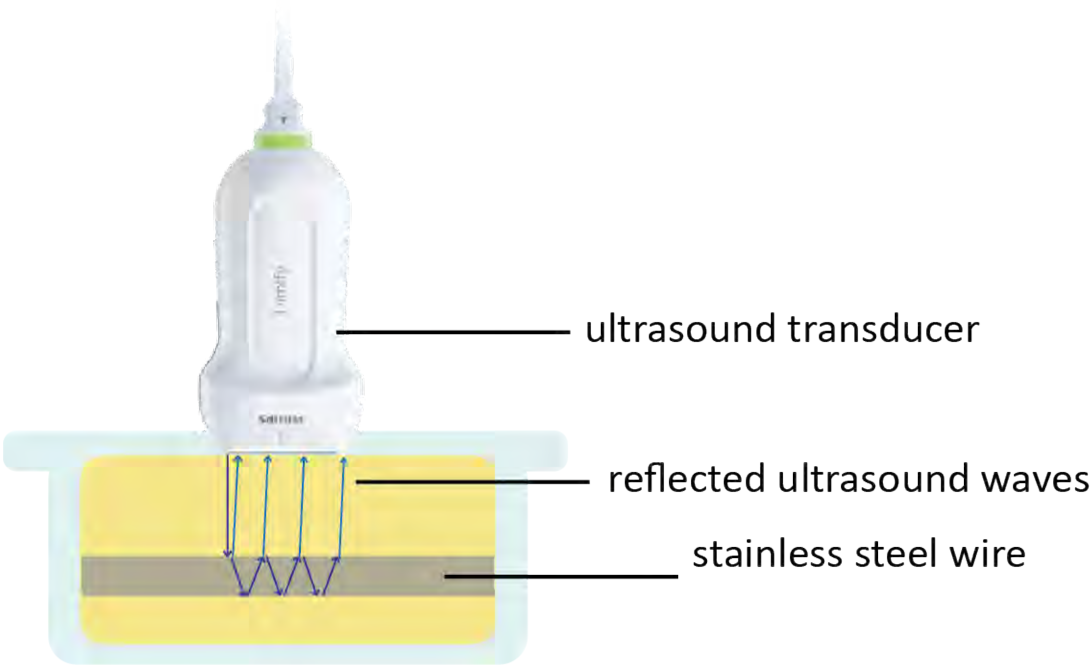

Figure 7.3: Schematic of theory on the 'tails' underneath the stainless steel wires spots in the ultrasound images.

To validate this, the thickness of the stripes was measured, as seen in Fig. 7.2 in yellow, indicating a thickness of 0,22 cm. The speed of sound in steel is 3,4 times faster than in water. This would mean that the thickness of a stripe on the ultrasound image would be 3,4 times smaller than the actual thickness of the wire.

$$x_{stripe} * \frac{SoS_{steel}}{SoS_{water}} = 0,22 \text{ cm} * \frac{5100\text{m/s}}{1500\text{m/s}} = 0,75 \text{ cm} \approx 0,8 \text{ cm} = d_{wire} \tag{7.1}$$

From the above Eq. 7.1 and calculation, the theory of Fig. 7.3 could be a feasible explanation.

Due to the large amount of reflection in the ultrasound images of the stainless steel wires, a different scattering object was chosen for phantom model 2.

Scattering objects: stainless steel wires versus nylon wires

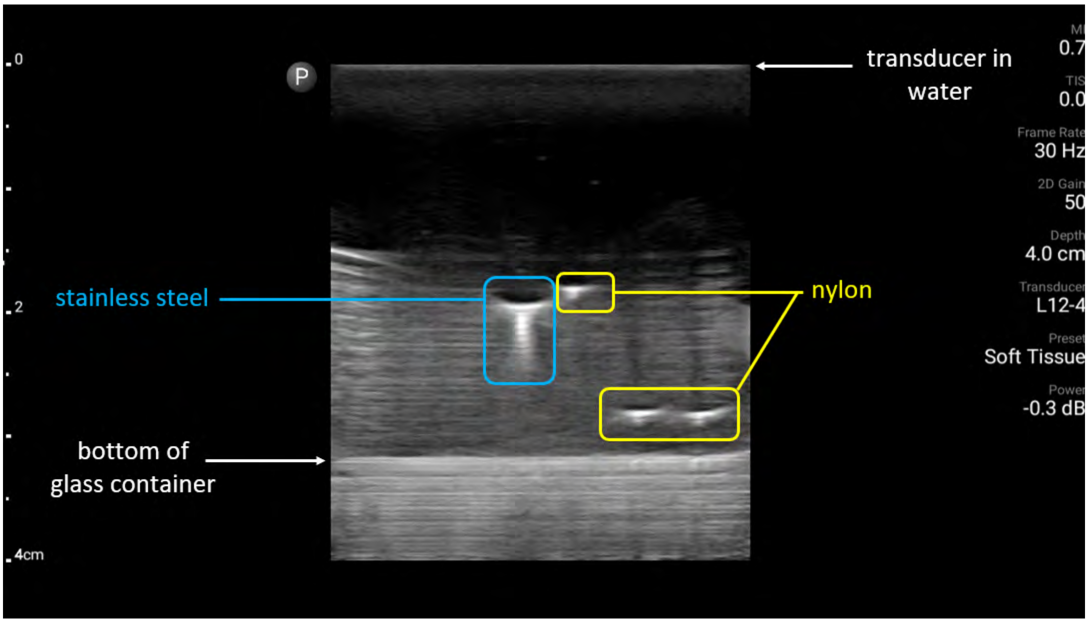

Figure 7.4: Ultrasound image of stainless steel wire and nylon wire in water in a glass container. The grey lines in the image are due to the reflection of ultrasound waves by the glass bottom. Image taken with the Philips Lumify L12-4.

	stainless steel wire $\varnothing$= 0,80 mm	nylon wire $\varnothing$= 0,35 mm
lateral resolution	+/-	+/-
'tail forming'	- -	+
preparation time	- -	+
assembly difficulty	- -	++

Both the stainless steel wires and the nylon wires were imaged in water at approximately the same depth, the stainless steel wire was located 2 mm deeper in the water than the nylon wire. The nylon lateral scattering is 25% shorter than stainless steel lateral scatting. Although the lateral resolution is almost similar, the 'tail', which forms due to the ultrasound bouncing in the wire, is neglectable in the nylon wires. In addition, assembling the wire holder with nylon wires took less time and was easier than assembling the stainless steel wires. Overall, this resulted in the decision to use nylon wires with $\varnothing$= 0, 35 mm as scattering objects for the phantom models 2, 3, 4, and 5.

7.1.2. Phantom model 2: two-layer

The figure below shows images of the two assembled phantoms with a time indication on the left. Day 1 shows the stiff gelatin. Below day 1 are the pictures of day 2; here, the phantoms are shown after 1 day in an oven at $T = 34°C$. The top pictures capture the fully assembled phantoms, the bottom pictures, the pods are taken out and the interface materials are shown. These pictures show that the gelatin filling had become more liquified than on day 1. On day 3, the patches (without pods) on the phantoms are shown. Container 1 shows gelatin 'leaking' through the pores of the pores teflon sheet to the interface materials in the patches. In container 2, bubbles form under the interface materials in the optical area, which could cause problems with ultrasound imaging. After day 3, the gelatin filling in container 1 was too degraded to proceed with the experiment. On day 4, only container 2 was intact; in the picture, more bubbles are formed in the patches and under the rest of the Teflon sheet.

The images taken after the experiment, which was day 3 for container 1 and day 4 for container 2, are shown on the right of the figure. These show 'murky' gelatin, container 2 had more clear gelatin filling after the experiment than container 1.

Figure 7.5: Phantom model 2: two-layer.

	Assement model 2	1–3	4–6	7–9
9	preperation time	2-4 hours	1-2 hours	**0-1 hour**
1	resuable	**no**		yes
8	transparent to ultrasound	α> 5 dB/cm/MHz	α= 1- 5 dB/cm/MHz	α**< 1 dB/cm/MHz**
4	lifetime t>5 days	**no**		yes
1	withstand temperatures	**no**		yes
7	mimics human skin water evaporation	< 139,5 nL/(min*cm²)	**> 139,5 nL/(min*cm²)**	139,5 nL/(min*cm²)
8	scattering objects	nothing visible	to much reflection	**enough**
38	total score			

Temperatures
In the oven, the temperatures varied between $T_{oven} = 32,5°C - 34,02°C$. In this oven, the temperature was controlled by an accurate turn nob, a temperature sensor was hung in the oven to measure the temperature. Below in Fig. 7.6, an example of the output was plotted against the time. The $T_{average} = 33,41°C$, which complies with skin temperature ($T_{skin} = 33 - 35°C$).

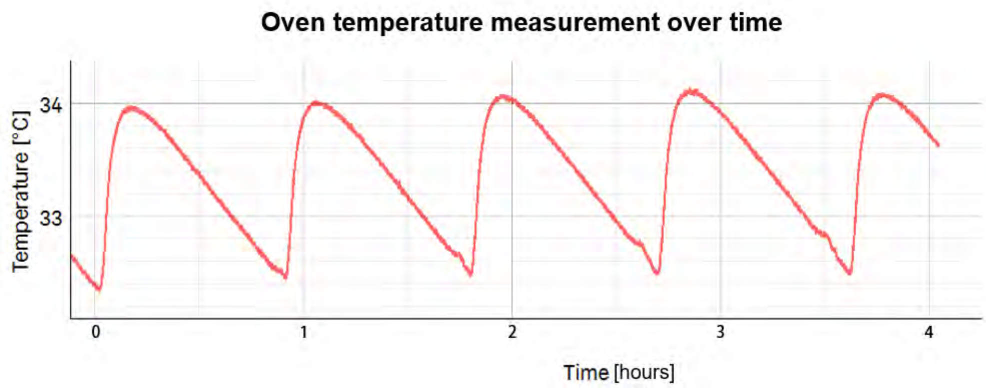

Figure 7.6: Temperature measurement when phantom model 2 was in the oven. $T_{max} = 34,05°C$, $T_{min} = 32,5°C$, over $\Delta = 30$ min, gives $T_{average} = 33,42°C$)

The gelatin filling was liquified at a temperature of 33 °C; the medium became a thickened liquid on day 1, and this liquid became thinner as the days passed. After day 3, both contained a liquid with viscous properties close to water. For a phantom, a stiff and firm medium is desired when placing an ultrasound probe on top for consistent imaging. Therefore, 15 wt% gelatin cannot withstand temperatures of 33 °C - 35 °C.

Lifetime
Phantom model 2 had a lifetime of 3-4 days, where after the gelatin filling was 8 thoroughly degraded and had abundant mold growth.

7.1.3. Phantom model 3.1 and 3.2: Three-layer and four-layer model

The pictures from Phantom Model 3.1 were lost. Only the images taken of phantom model 3.2 are presented below. The comparison of the absorbing layer to that of no absorbing layer in the ultrasound images is also shown in Fig. 7.8.

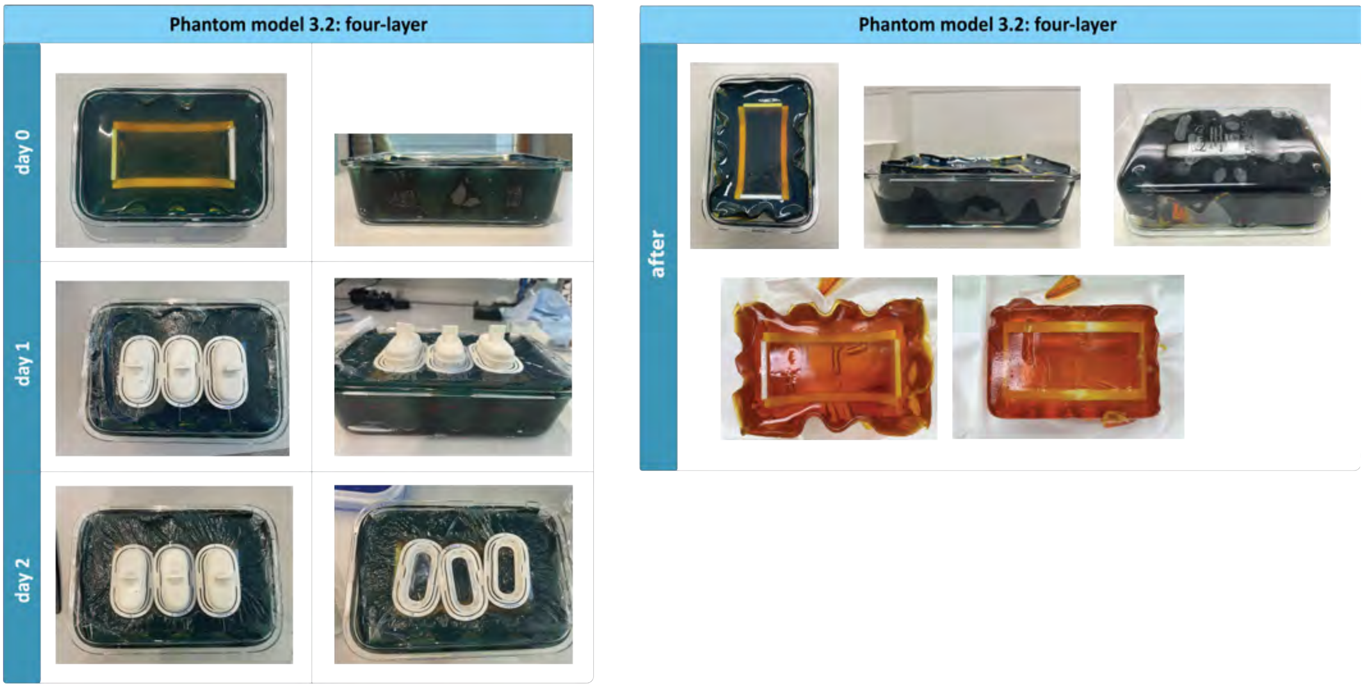

Figure 7.7: Phantom model 3.2: four-layer.

	Assesment model 3.1	1–3	4–6	7–9
2	preperation time	**2-4 hours**	1-2 hours	0-1 hour
8	resuable	no		**yes**
8	transparent to ultrasound	α> 5 dB/cm/MHz	α= 1- 5 dB/cm/MHz	**α< 1 dB/cm/MHz**
5	lifetime t>5 days	**no**		yes
5	withstand temperatures	**no**		yes
7	mimics human skin water evaporation	< 139,5 nL/(min*cm^2)	**> 139,5 nL/(min*cm^2)**	139,5 nL/(min*cm^2)
8	scattering objects	nothing visible	to much reflection	**enough**
43	total score			

	Assesment model 3.2	1–3	4–6	7–9
2	preperation time	2-4 hours	1-2 hours	0-1 hour
6	resuable	no		yes
8	transparent to ultrasound	α> 5 dB/cm/MHz	α= 1- 5 dB/cm/MHz	**α< 1 dB/cm/MHz**
4	lifetime t>5 days	**no**		yes
4	withstand temperatures	**no**		yes
7	mimics human skin water evaporation	< 139,5 nL/(min*cm^2)	**>139,5 nL/(min*cm^2)**	139,5 nL/(min*cm^2)
10	scattering objects	nothing visible	to much reflection	**enough**
41	total score			

Lifetime and temperatures
In the figure below (Fig. 7.7), the pictures of the top and side view of phantom model 3.2 are shown. In the left part of the figure, a difference in gelatin stiffness can be observed while comparing day 1 and day 2. The gelatin was liquified in the oven, resulting in changes in the location of the patches on the phantom. In the right images, the phantom, after three days, the gelatin layer and PET foil were removed. At the top,

the pictures show the detachment from the glass of the rubber layer. On the bottom, air bubbles between the glass and rubber layer are clearly visible. Also, the change of color of the gel wax from no coloring to brown color is shown in Fig. 7.7. In both phantom models 3.1 and 3.2, the gelatin was liquidized, which caused problems for stable ultrasound imaging.

Evaluation of rubber ultrasound absorbing layer
The difference between phantom model 3.1 and 3.2 was using a rubber absorbing layer, to minimize the ultrasound bouncing of the walls and bottom of the glass container. A comparison was done between the two models to evaluate what design choice to make. This evaluation considers the practical use of rubber in the ultrasound phantom and the results of the ultrasound images.

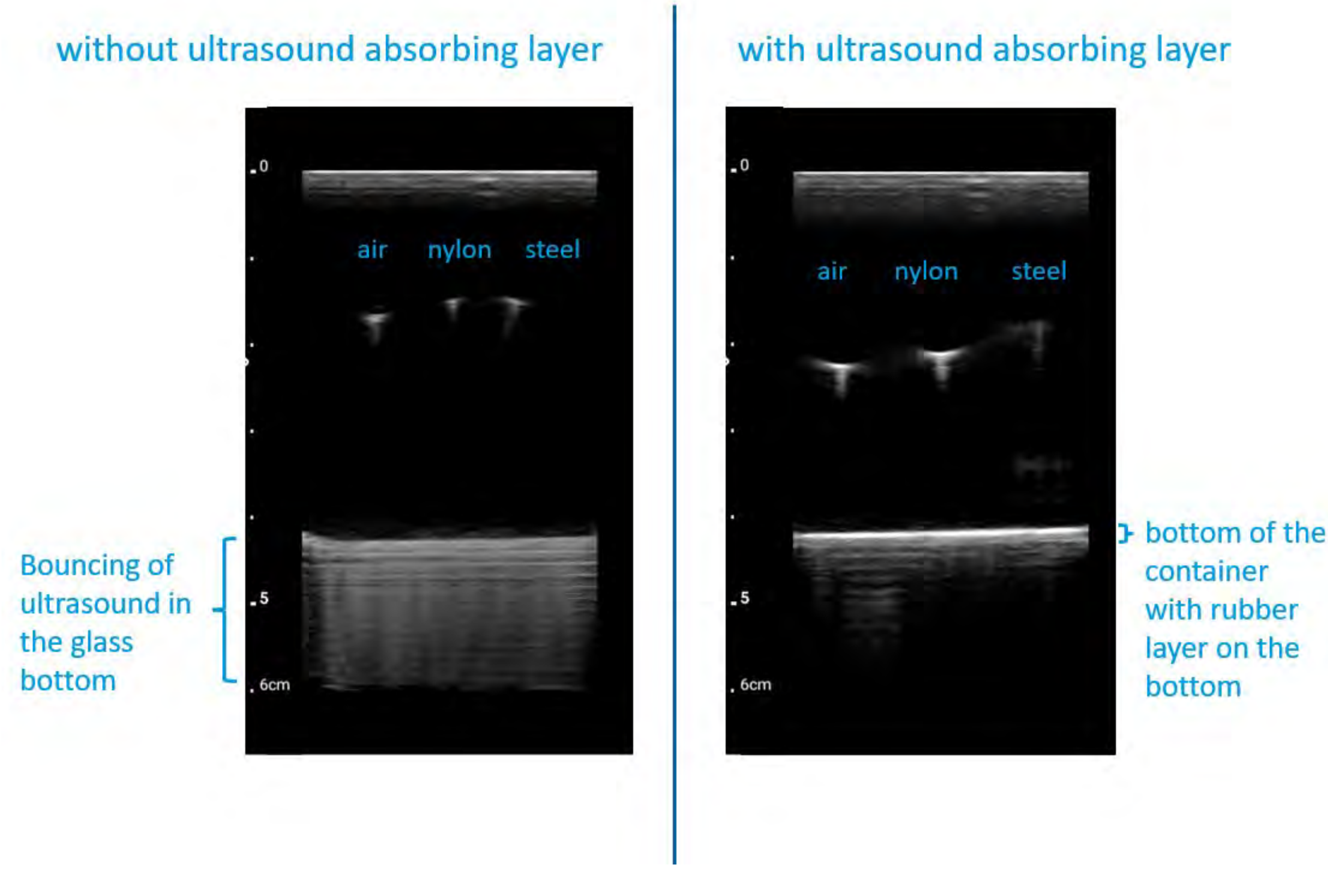

Figure 7.8: The ultrasound images were made with a Philips Lumify L12-4 probe. The depth is indicated on the left side of the ultrasound images. A side-by-side of images made of *left:* phantom model 3.1 without rubber layer and *right:* phantom model 3.2 with rubber layer.

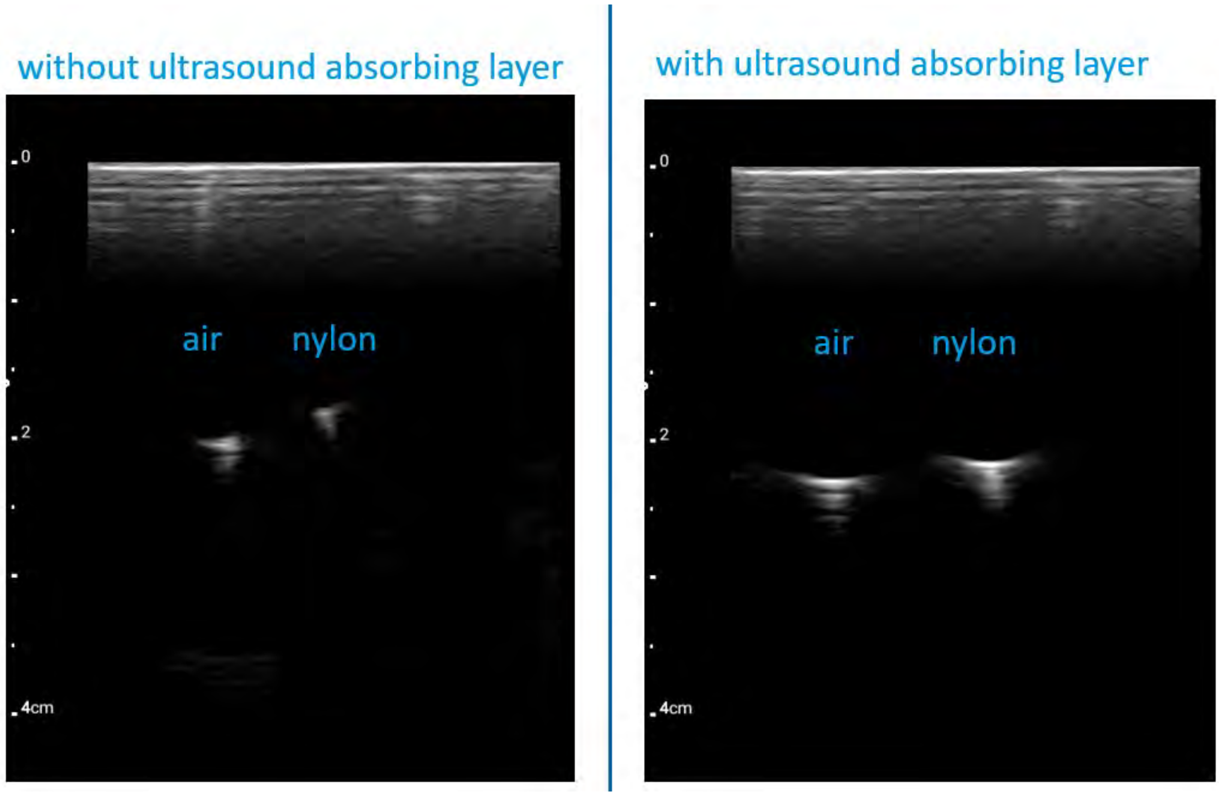

Figure 7.9: The ultrasound images were made with a Philips Lumify L12-4 probe. The depth is indicated on the left side of the ultrasound images. A side-by-side of images made of *left:* phantom model 3.1 without rubber layer and *right:* phantom model 3.2 with rubber layer.

From the above images, a difference in the scatting objects can be observed. The bright spots in the ultrasound images indicate the cross-section of the scattering objects. The type of the scattering object is noted in Fig. 7.8. On the left, these spots are less bright. The top images show ultrasound images capturing the whole phantom until the bottom. The two different phantom models end at a depth of 4,5 cm though the images indicate deeper layers. The images in Fig. 7.9 are shown inside the different phantom models to a depth of 4 cm.

The deeper layers seen in the Phantom model 3.1 images shown in Fig. 7.8 are caused by the bouncing of ultrasound waves in the glass container. This is the same phenomenon as the bouncing of ultrasound in the stainless steel wires Fig. 7.3. Phantom model 3.2 with the absorbing layer on the bottom is shown in the image on the right of Fig. 7.8 and Fig. 7.9. The cross-sections of the scattering objects seem brighter and more concentrated in a precise location. The rubber layer helps create clearer ultrasound images and less bouncing of the ultrasound in the glass bottom. However, in other ultrasound images made on phantom models without a rubber layer, the brightness of the scattering objects in the images never caused problems. Also, as mentioned above, the rubber layer caused deformation, odor, and coloring of the gel wax filling. For these reasons, it was decided not to use a rubber ultrasound absorbing layer in the other models.

7.1.4. Phantom model 4: two-layer

The images of the full phantom model 4 were also lost. The only available pictures are those of a container filled with PVA; see Fig. 7.10.

Figure 7.10: Pictures of PVA filling in a container.

In preparation for phantom model 4, the poly(vinyl) alcohol mixture was tested for water evaporation, temperature, and lifetime performance. From these tests, explained and shown in section Methods 6.3.5, the results indicate that from PVA 2,28 more water evaporates from the surface. It was impossible to make enough holes (pores) in the top layer to regulate the amount of water evaporation to mimic the required amount.

$$\text{water area} = \text{ratio} * \text{area phantom} = \frac{247\ [cm^2]}{2,28} = 108,10\ [cm^2] \tag{7.2}$$

From the equations, it was found that with this ratio of [2,28: 1], a pore diameter of 0,8 mm, and an area of 228 cm², it yielded approximately 87 pores per cm². It is not feasible to have nine pores with diameters of 0,8 mm along the x and y direction per cm². It was also not even workable to have pores with a diameter of 0,7 mm, yielding 114 pores, requiring 12x12 pores along the axis. It was, therefore, infeasible to make a phantom model with PVA for this thesis project.

	Assement model 4	1–3	4–6	7–9
3	preperation time	**2-4 hours**	1-2 hours	0-1 hour
4	resuable	no		**yes**
9	transparent to ultrasound	α> 5 dB/cm/MHz	α= 1- 5 dB/cm/MHz	α**< 1 dB/cm/MHz**
5	lifetime t>5 days	no	**	yes
7	withstand temperatures	no		**yes**
7	mimics human skin water evaporation	< 139,5 nL/(min*cm²)	**> 139,5 nL/(min*cm²)**	139,5 nL/(min*cm²)
8	scattering objects	nothing visible	to much reflection	**enough**
43	total score			

** = a phantom model made of PVA material heated up to at T = 34 °C, performs satisfactory for 3 days.

7.1.5. Phantom model 5: three-layer

The final model was a three-layer model with a gel wax filling, agar hydration layer, and PET foil with pores to regulate the water evaporation. In Fig. 7.11, pictures of the phantom model with assembled wearable patches and acoustic interface materials are shown over a period of five days. The phantom model after eight days is also shown in Fig. 7.12.

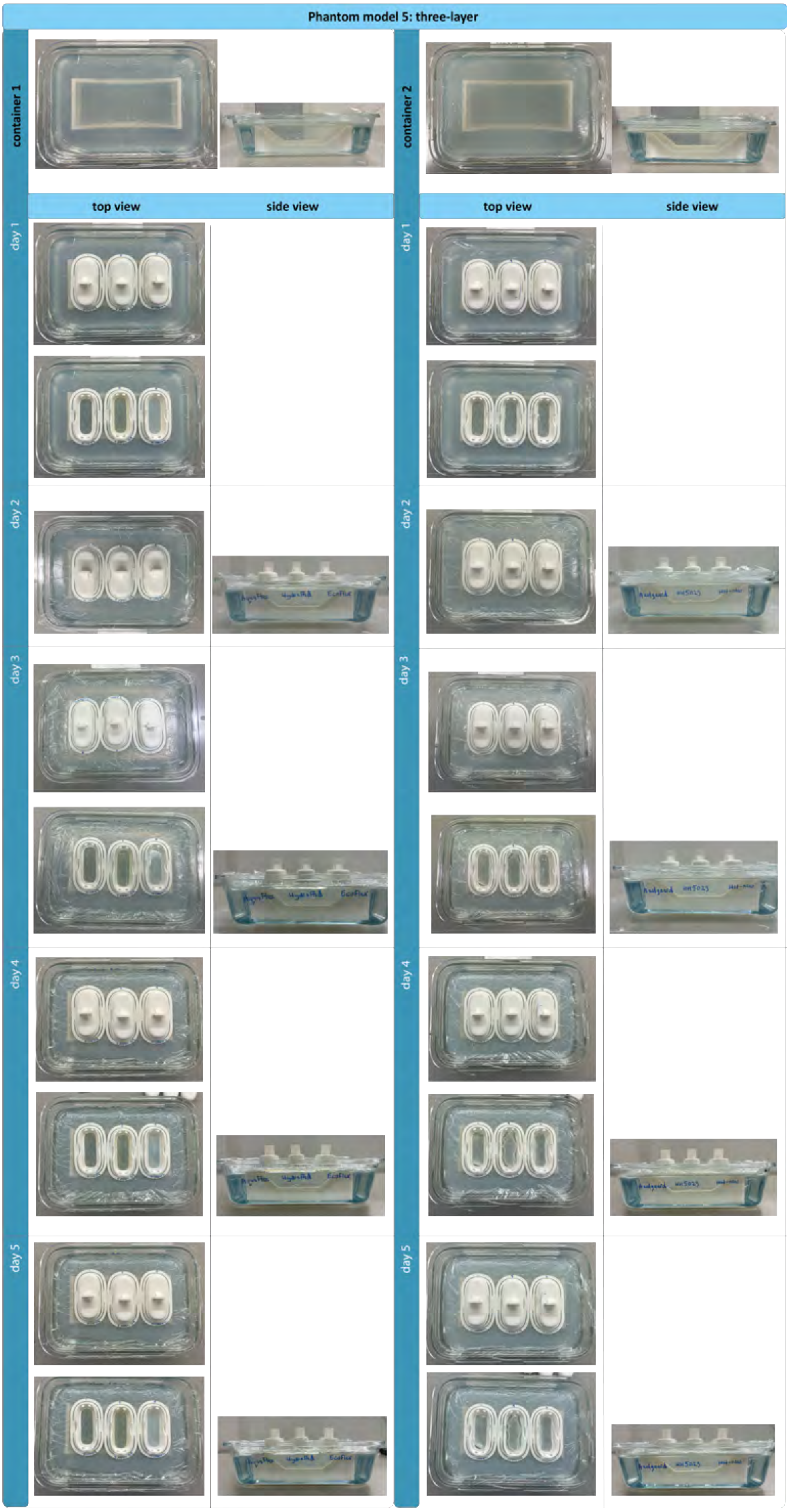

Figure 7.11: Phantom model 5: three-layer.

Figure 7.12: Phantom model 5: three-layer after a period of 8 days. Also the model is shown after the disposable layers were removed, leaving the reusable parts.

	Assement model 5	1–3	4–6	7–9
6	preperation time	2-4 hours	**1-2 hours**	0-1 hour
7	resuable	no		**yes**
8	transparent to ultrasound	α> 5 dB/cm/MHz	α= 1- 5 dB/cm/MHz	α**< 1 dB/cm/MHz**
7	lifetime t>5 days	no		**yes**
8	withstand temperatures	no		**yes**
8	mimics human skin water evaporation	< 139,5 nL/(min*cm²)	> 139,5 nL/(min*cm²)	**139,5 nL/(min*cm²)**
8	scattering objects	nothing visible	to much reflection	**enough**
52	total score			

Lifetime
The lifetime requirement of 5 days was met with phantom model 5. As shown in figures Fig. 7.11 and Fig. 7.12, model 5 was still sufficient to continue the wearable acoustic interface materials lifetime test. There are clear indications that the Agar layer is dehydrating and, hence is reducing in size. Accordingly, the top layer of PET foil started to wrinkle as the phantom was longer in the oven. The gel wax filling and the wire holder stayed in place and did not misform for the entire eight days. Afterward, the agar layer could be disassembled, making the rest of the phantom model reusable.

Temperature
The agar layer stayed stiff in consistency while being in an oven at T= 34 °C. The gel wax filling kept its stiff and bouncy consistency throughout the experiment.

Water evaporation
As mentioned above, the hydration layer made with agar was evaporating water from its surface through the holes in the PET foil. The amount of water evaporation at T= 34 °C for agar with the PET foil layer placed on top was measured. The water evaporation rate of agar without the top layer was 250,8 nL/(min*cm²) while the evaporation rate with a top layer placed on top was 92,90 nL/(min*cm²). Comparing the agar with PET foil water evaporation rate to that of skin resulted in a ratio [agar: skin] of [0,67: 1]. There was 1,5 times less water evaporation from the agar than skin would have.

7.2. Lifetime experiments of acoustic interface materials using the phantom

The final phantom, model 5, was used for the lifetime experiments of the acoustic interface materials. This experiment lasted eight days, on which six of the eight days ultrasound images were made for all the acoustic material in the wearable patches on the phantom.

During this experiment, ultrasound images were made with a Philips Lumify L12-4 probe, which could be placed in the same position as the wearable patches and placement system. The following images were taken and analyzed. In Fig. 7.13, two bright spots can be seen in the middle of the image are the cross-section of the nylon wires in the phantom. Also, one spot on the top left and bottom right in the images made through AquaFlex, HydroAid, and Ecoflex are the nylon wires at 1 cm and 3 cm depths in the phantom, respectively. For images made through Axelgaard, HH5023, and HH5450, the top right and the bottom left are the nylon wires at 1 cm and 3 cm depth, respectively. In all the rows on day 8, the images are distorted or noticeably changed from the previous on day 5. The image through AquaFlex had less bright spots and a 'greyer' background. The image made through Axelgaard also shows slight bright spots. The image made through HH5023 shows a deformed hydrating layer at the top right corner. This also causes some distortion in the rest of the ultrasound image. In the last image made through the HH5450, the scattering objects are not visible anymore due to a distortion in the image.

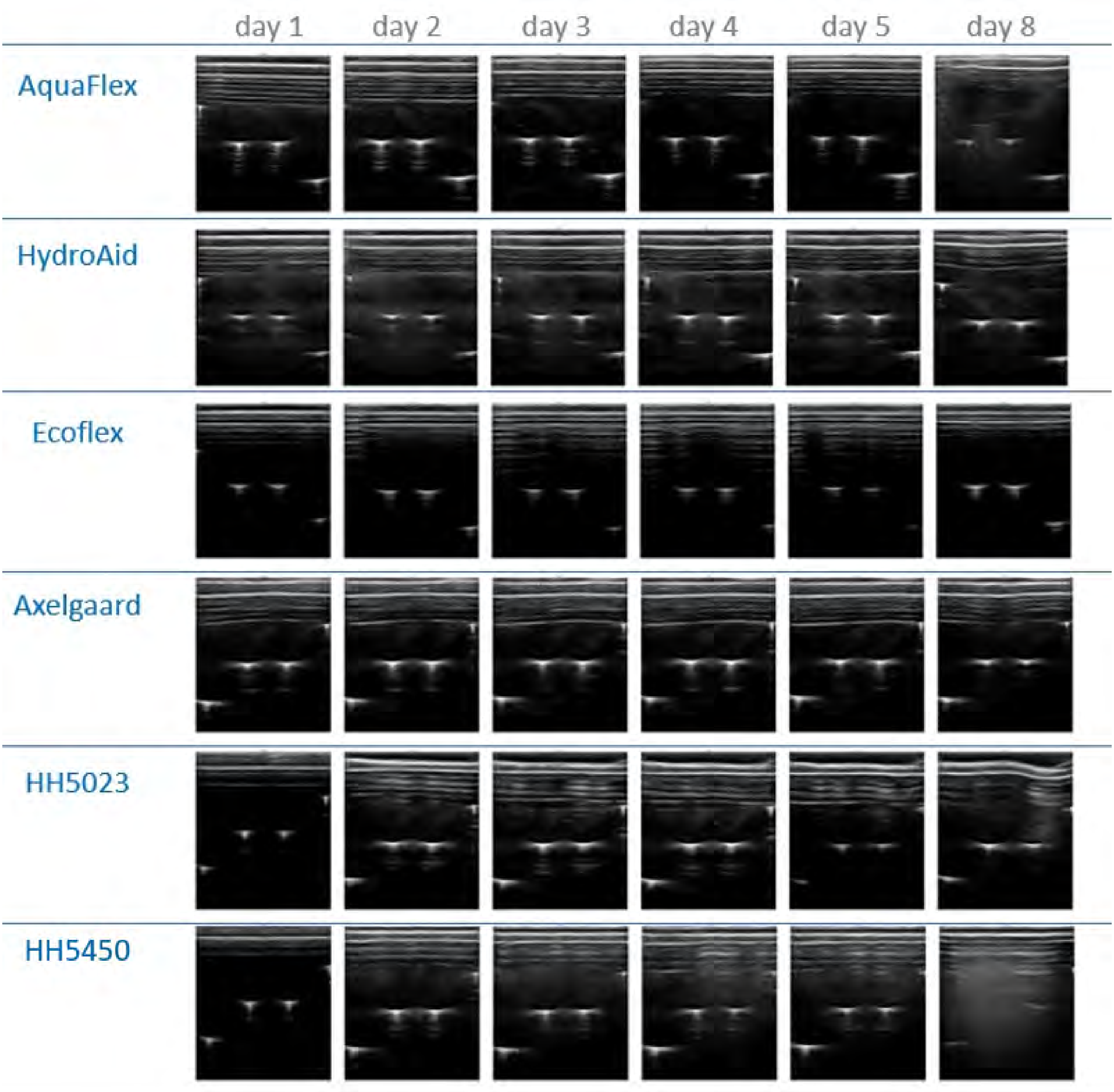

Figure 7.13: Ultrasound images of the lifetime experiments with different acoustic interface materials.

In the Fig. 7.14, the agar layer of 0,5 cm on top of the 'gel wax' is clearly visible. This layer is indicated by the orange line in Fig. 7.14. The agar layer boundaries (from top to bottom) are shown in the ultrasound as the two thick, bright horizontal stripes. This is due to the mismatch in acoustic impedance values. The slightly less bright lines beneath the agar layer, are most likely a result of the bouncing of ultrasound waves in the agar layer. PET foil layer is not visible in the ultrasound images because it is too thin to see with ultrasound. On top of the agar layer in the images, another layer is visible. In some images, this is more prominent than others, for instance, in the image with HH5023 on day 3 (Fig. 7.14). The black layer seen in the image is the ECG solid hydrogel interface material. In other images, this layer is thinner, like AquaFlex, indicating a thinner interface material.

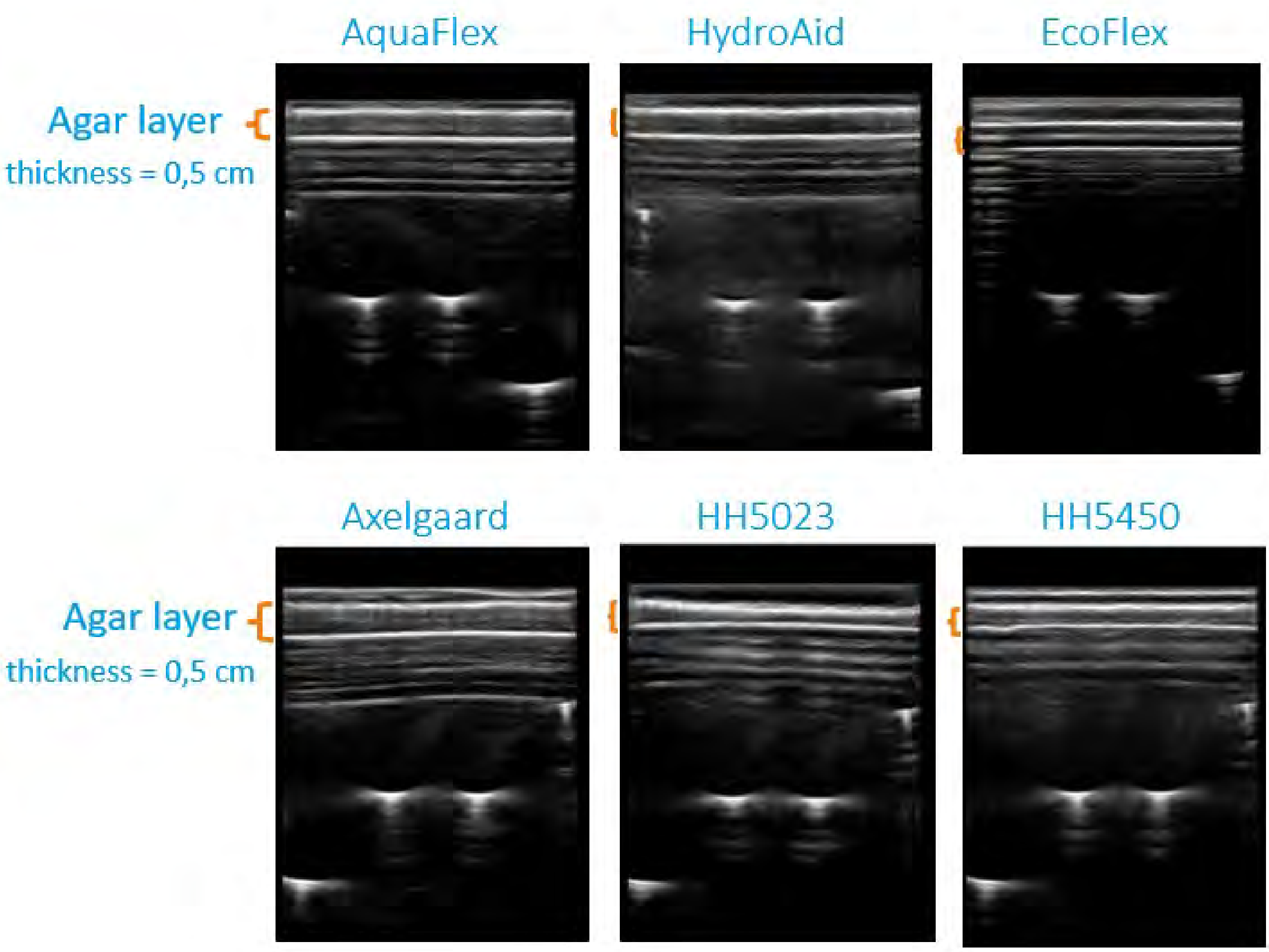

Figure 7.14: Ultrasound images made through the six different interface materials on day three of the lifetime experiments.

From the images taken on specific time stamps per day, the average brightness values were taken at two depths in the phantom. In the following graphs, the average brightness values are plotted. These specifically are the wires at a depth of 3 cm. The brightness values taken from the images were in between these spots at 2,5 cm and 3,5 cm depth. The brightness values measured through the six different wearable patches are plotted over a period of eight days in Fig. 7.15 below. The red graphs indicate the interface materials in container 1, and the blue graphs indicate the ECG interface materials in container 2.

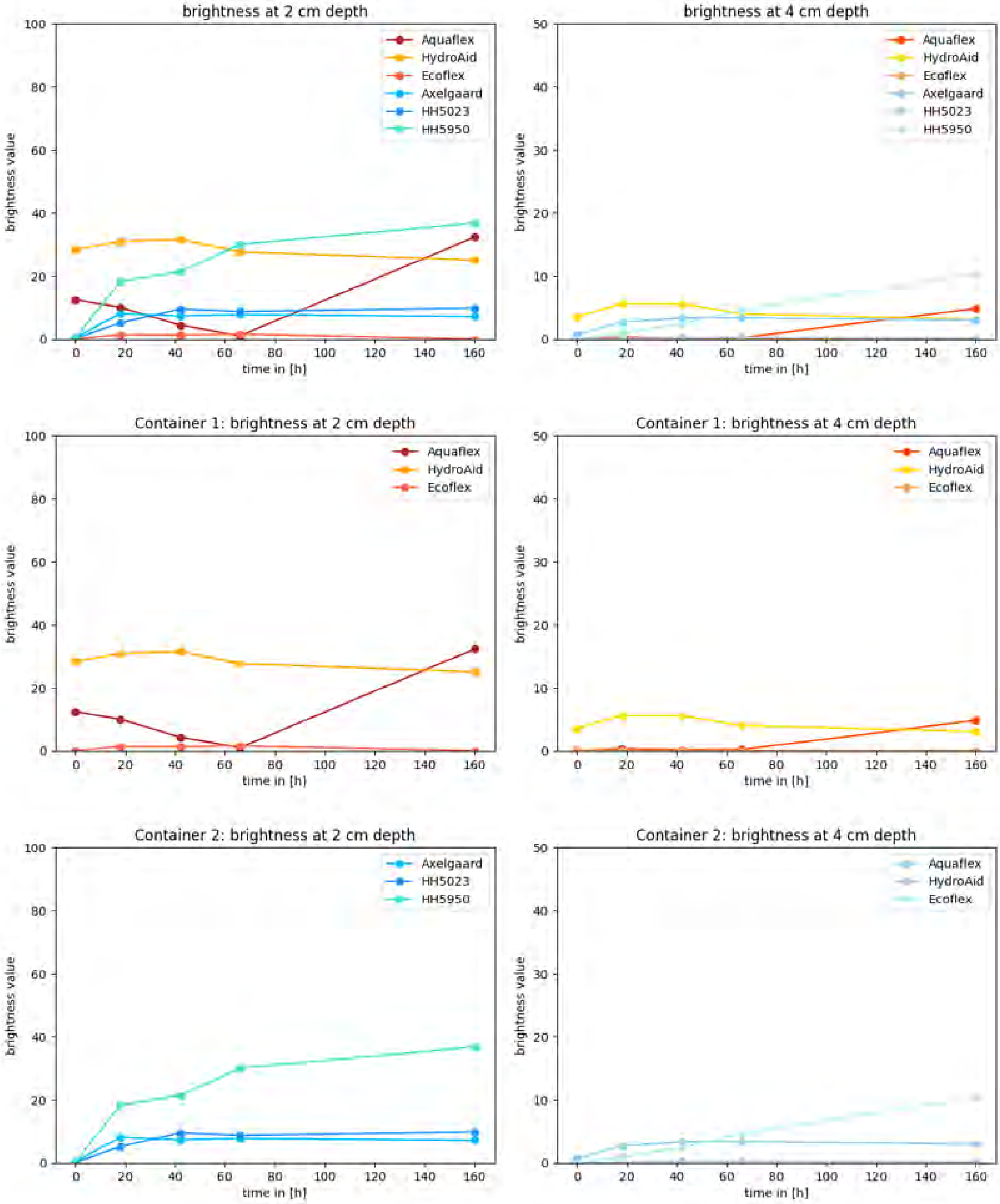

Figure 7.15: Graphs of brightness values of the ultrasound images made during the lifetime experiments with different acoustic interface materials.

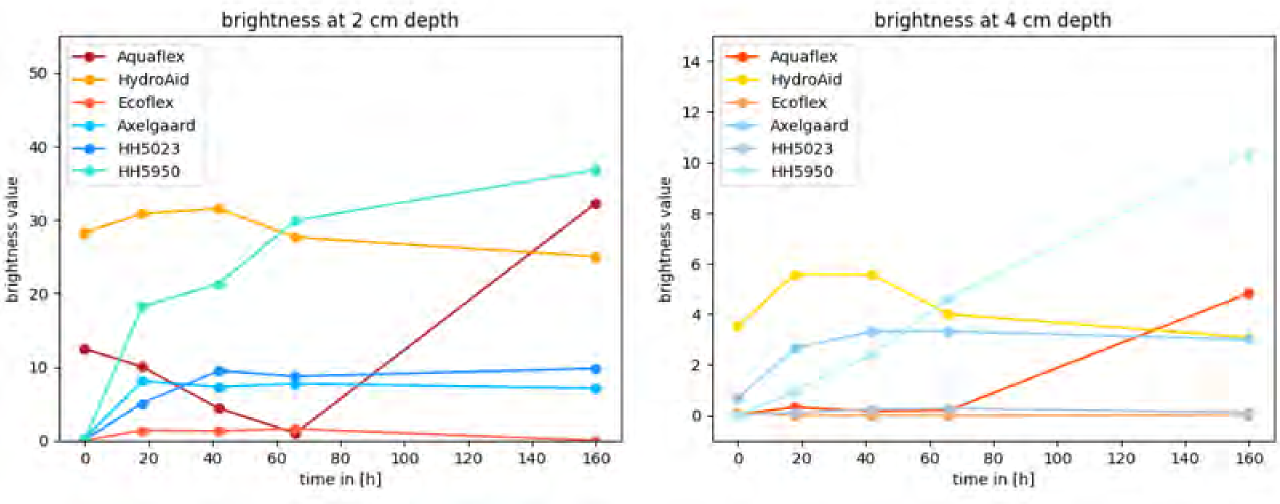

Figure 7.16: In zoomed graphs of brightness values of the ultrasound images made during the lifetime experiments with different acoustic interface materials.

7.3. Acoustic performance

Measurements were carried out on different materials with the through-transmission setup, shown in Fig. 6.15. These materials can be found in Table 6.4 in chapter Methods 6. After the measurements were conducted, the data was collected, analyzed, and plotted. Below in Fig. 7.18, the pressure peak-to-peak pressure values of the signal going through water as a reference, sample with thickness 1 and thickness 2. With these pressure values and the equation for calculating the attenuation coefficient (Eq. 6.14), the attenuation coefficient of the materials at transmission frequencies 5-12 MHz was calculated. The peak-to-peak pressure values indicate a decrease in signal when the ultrasound waves are going through a thicker material. The mean attenuation coefficient values were calculated from measured attenuation coefficients for a 5-12 MHz transmission frequency range. This was done for 11 different materials and noted in the Table 7.1 below. Further in this section, the plots per material are shown in more detail.

Table 7.1: Mean attenuation coefficient values ($\langle\alpha\rangle$)

material	$\langle\alpha\rangle$ in $[dB/cm/MHz]$ over a frequency range of 5-12 MHz
Gelatin	0,2
Agar	0,2
AquaFlex	0,2
HydroAid	0,2
PVA	0,3
Gel wax	0,7
EcoFlex	1,6
HH5459	1,7
PMMA	1,9
HH5023	4,2
Axelgaard	5,0

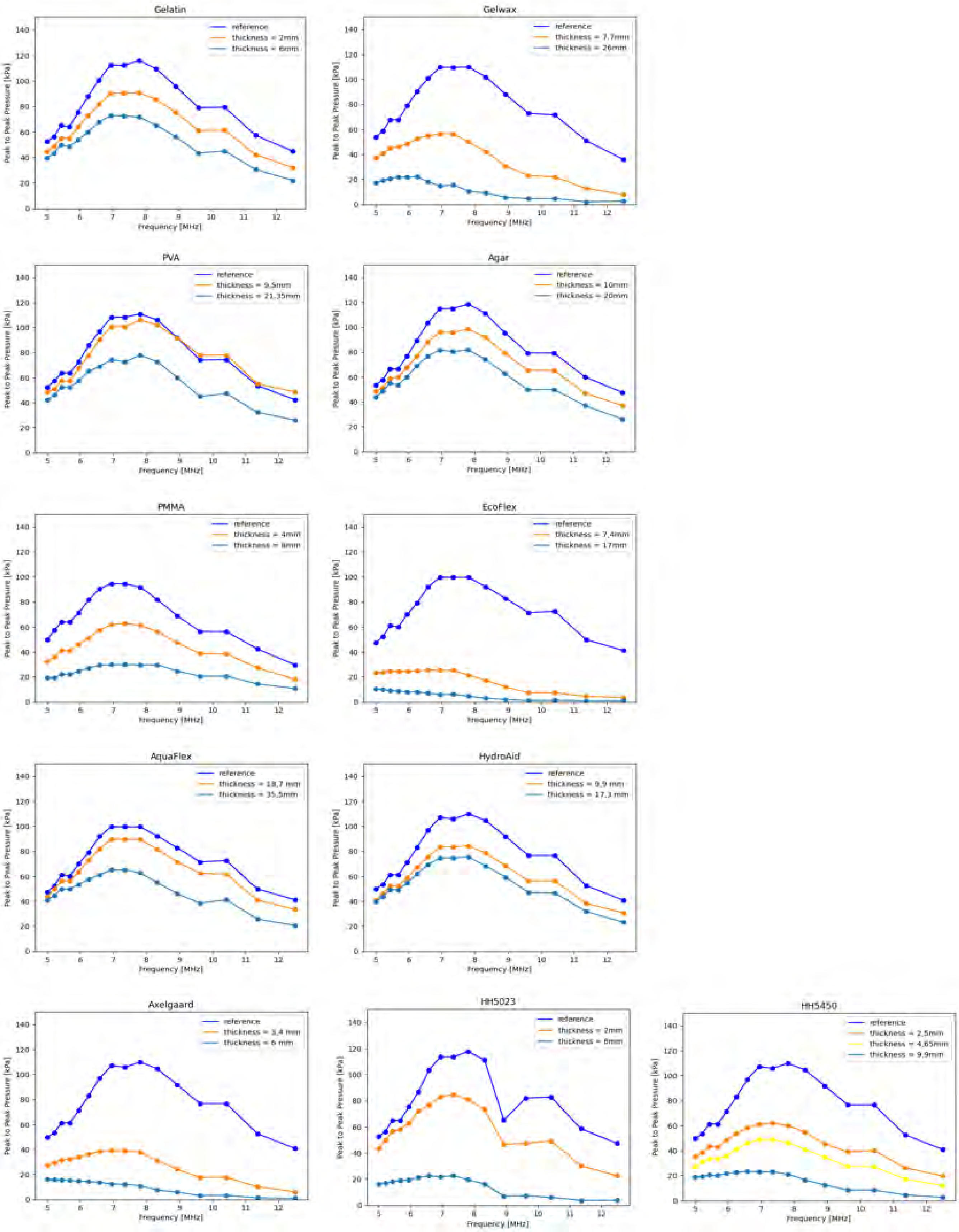

Figure 7.17: Peak-to-peak pressure against frequency plots for all the materials measured.

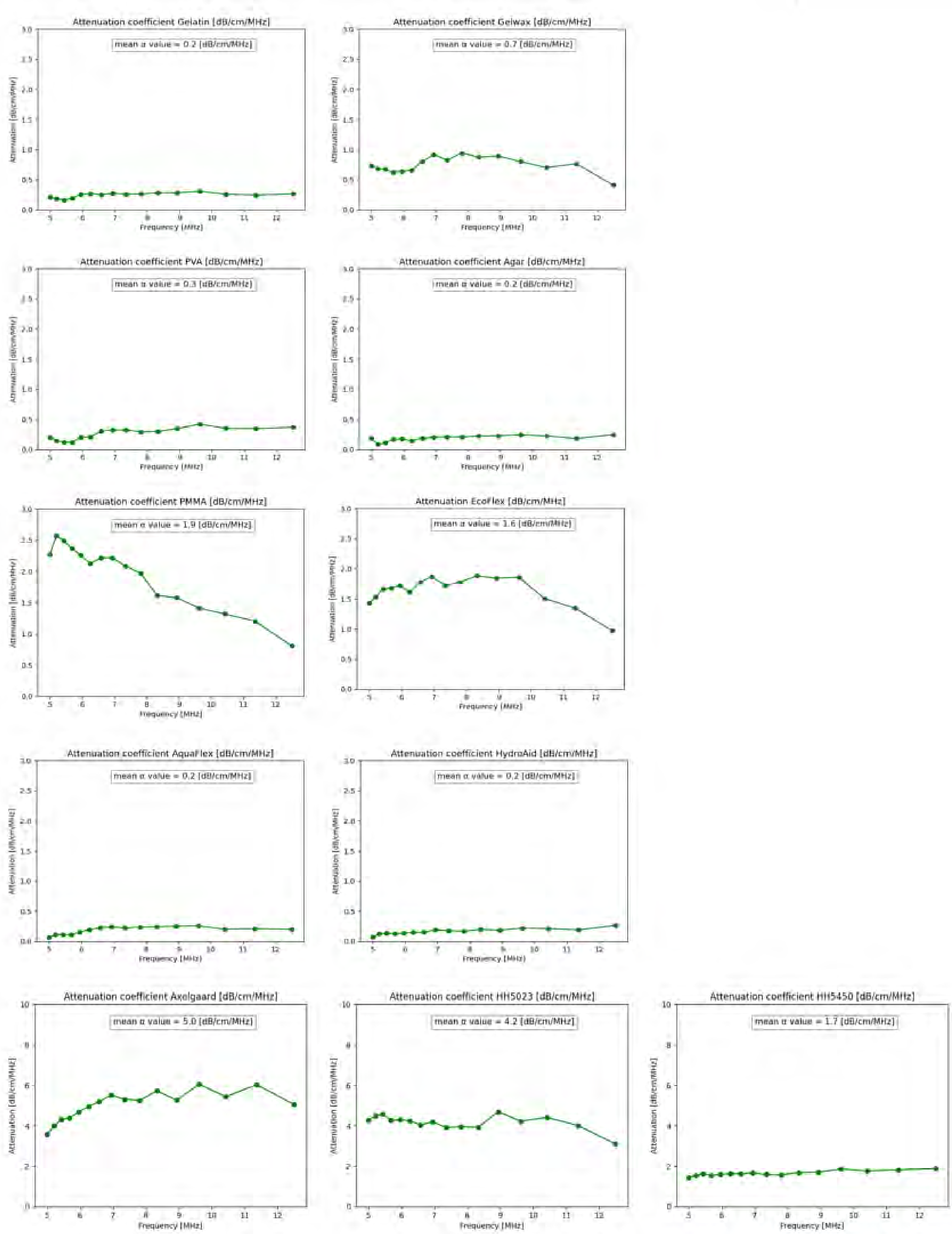

Figure 7.18: Attenuation against frequency plots for all the materials measured.

Plastic bag versus reference measurements

As explained in the Methods 6.5.2. In Fig. 7.19 and Fig. 7.20, the attenuation due to a plastic bag is plotted.

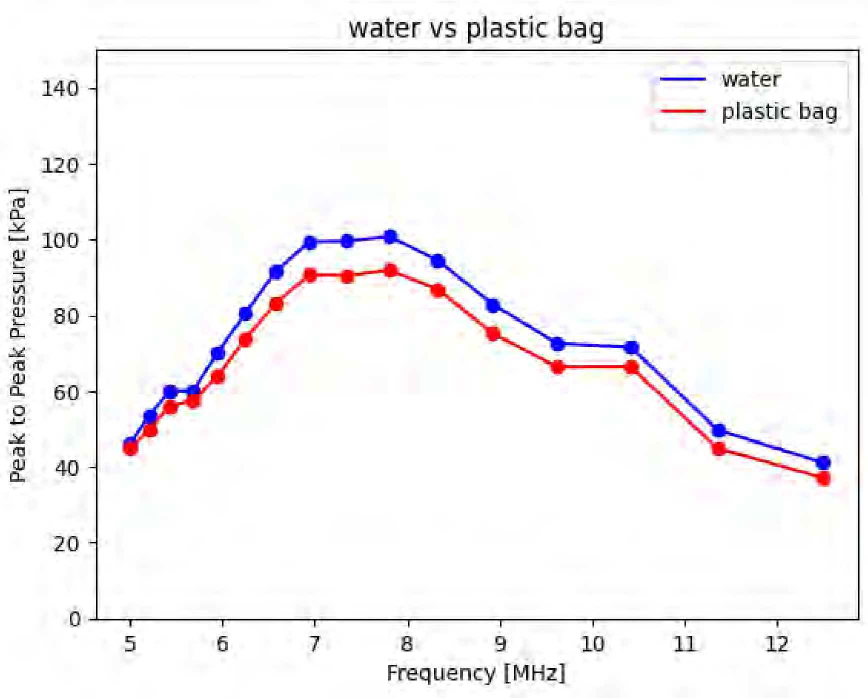

Figure 7.19: Peak-to-peak pressure signal of a plastic bag compared to the signal through water (reference).

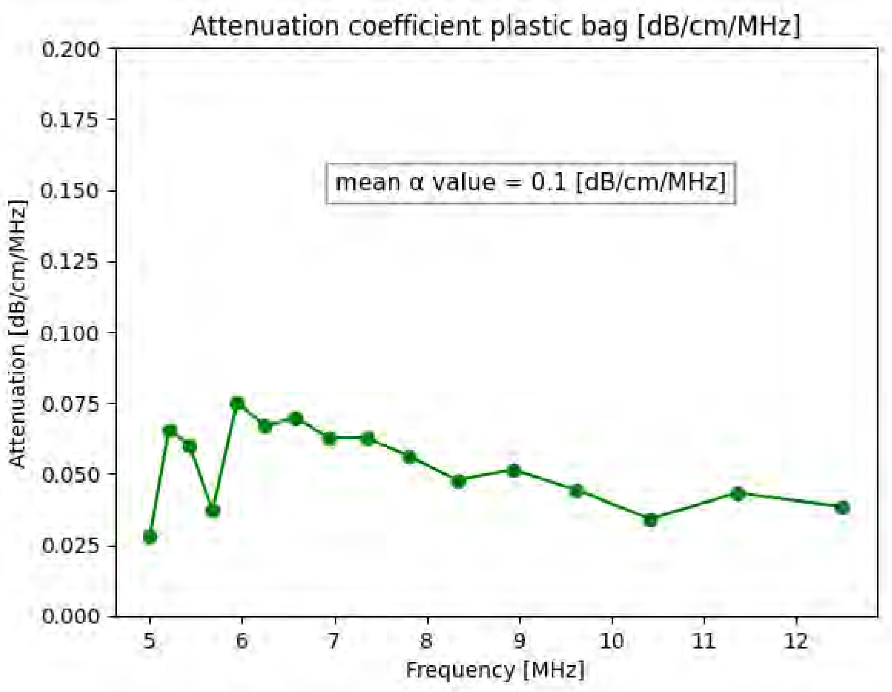

Figure 7.20: Attenuation graph of plastic bag. The plastic bag $\langle \alpha \rangle = 0,1$ dB/cm/MHz.

Gelatin

Results of through-transmission measurements for two gelatin samples with 10 mm and 20 mm thicknesses.

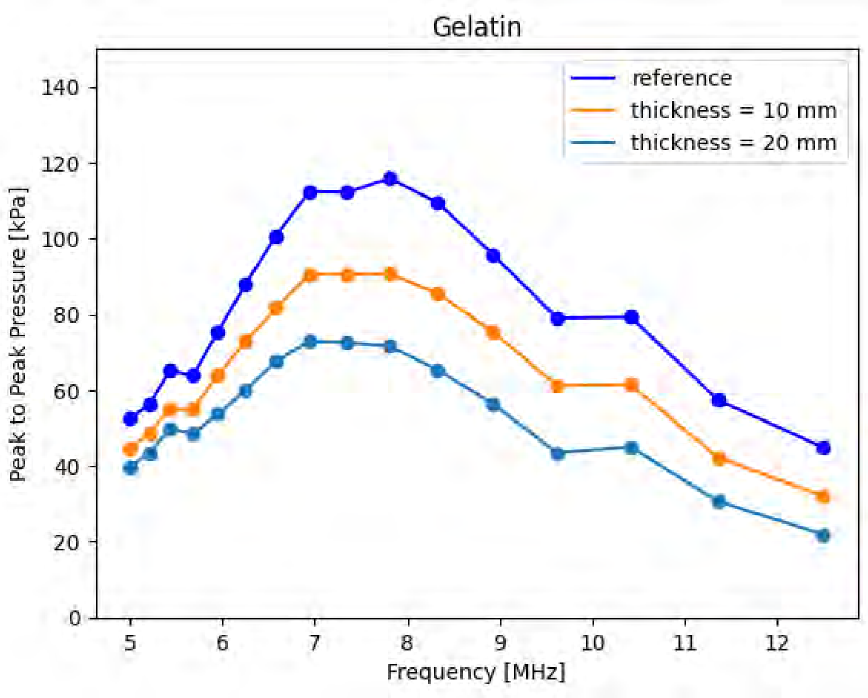

Figure 7.21: Peak-to-peak pressure signal of the two gelatin samples with different thicknesses and reference measurement.

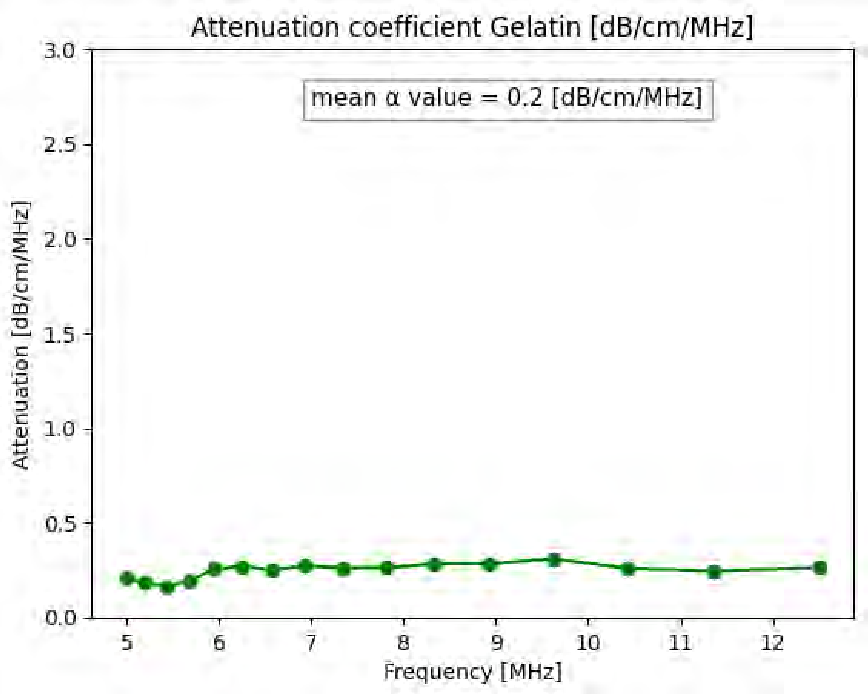

Figure 7.22: Attenuation values of gelatin in decibel per centimeter per MHz. The gelatin $\langle\alpha\rangle = 0,2$ dB/cm/MHz.

Gelwax

Results of through-transmission measurements for two samples of gelwax with thicknesses of 7,7 mm and 26 mm.

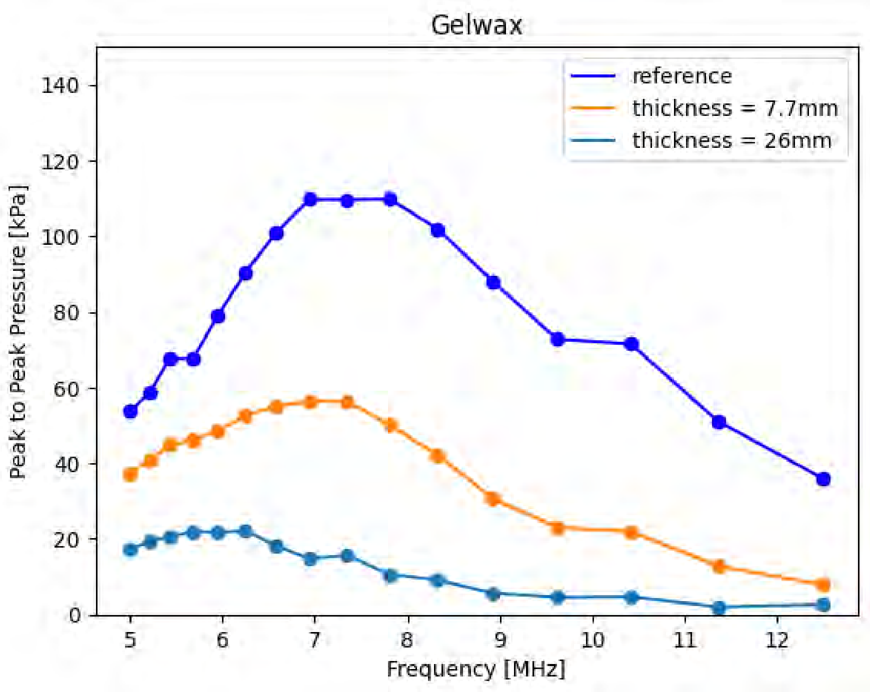

Figure 7.23: Peak-to-peak pressure signal of the gelwax samples with different thicknesses and reference measurement.

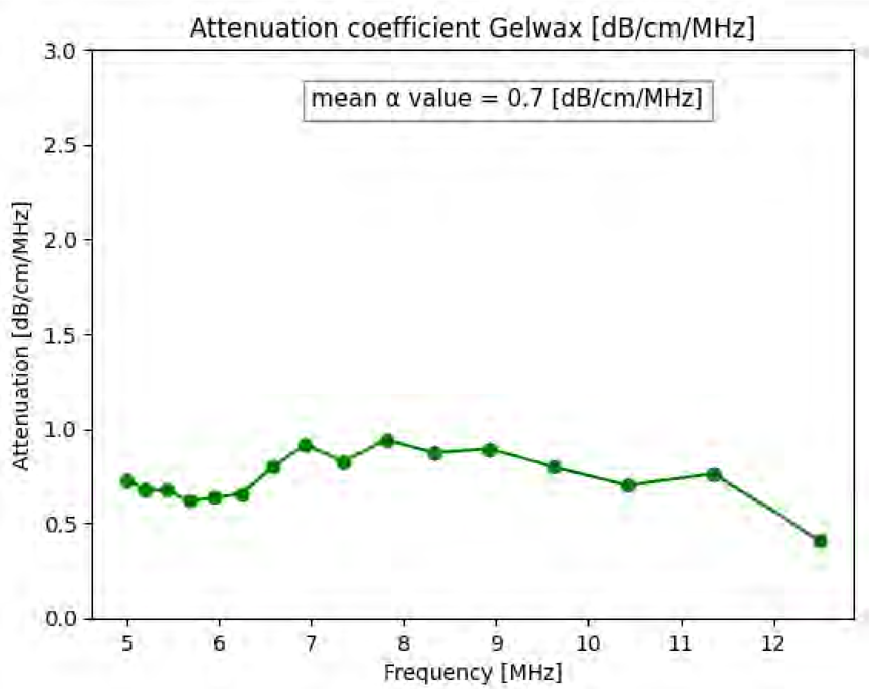

Figure 7.24: Attenuation values of gelwax in decibel per centimeter per MHz. The gelwax $\langle \alpha \rangle = 0,7$ dB/cm/MHz.

Poly(vinyl)alcohol (PVA)
Results of through-transmission measurements for two samples of PVA with thicknesses of 9,5 mm and 21,35 mm.

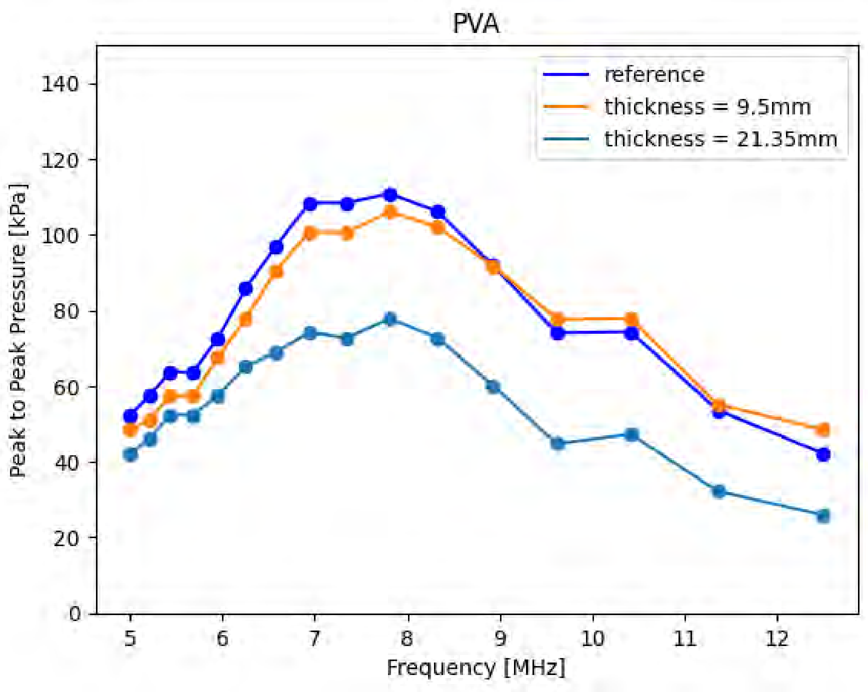

Figure 7.25: Peak-to-peak pressure signal of the two PVA samples with different thicknesses and reference measurement.

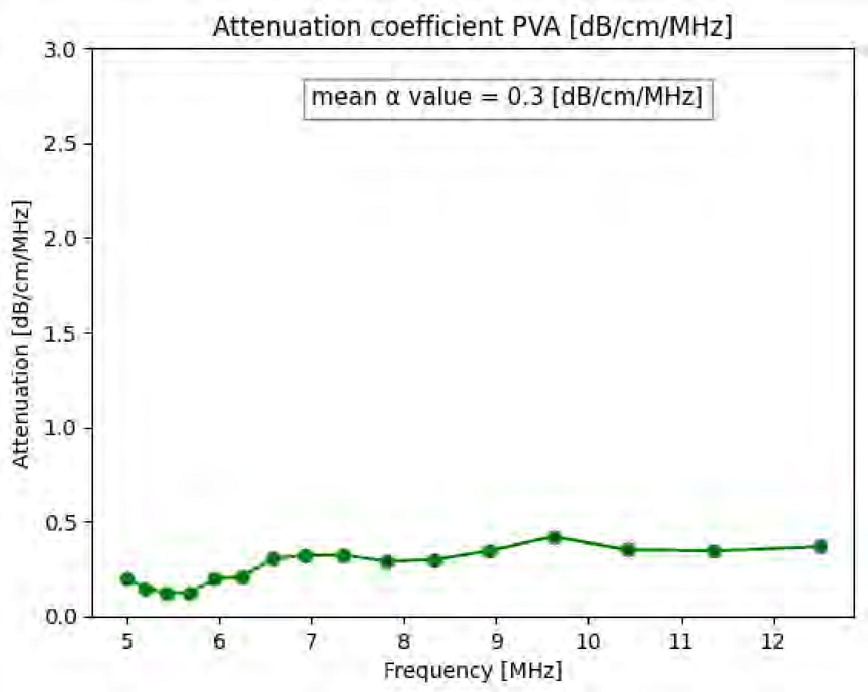

Figure 7.26: Attenuation values of PVA in decibel per centimeter per MHz. The PVA $\langle \alpha \rangle = 0,3$ dB/cm/MHz.

Agar

Results of through-transmission measurements for two agar samples with 10 mm and 20 mm thicknesses.

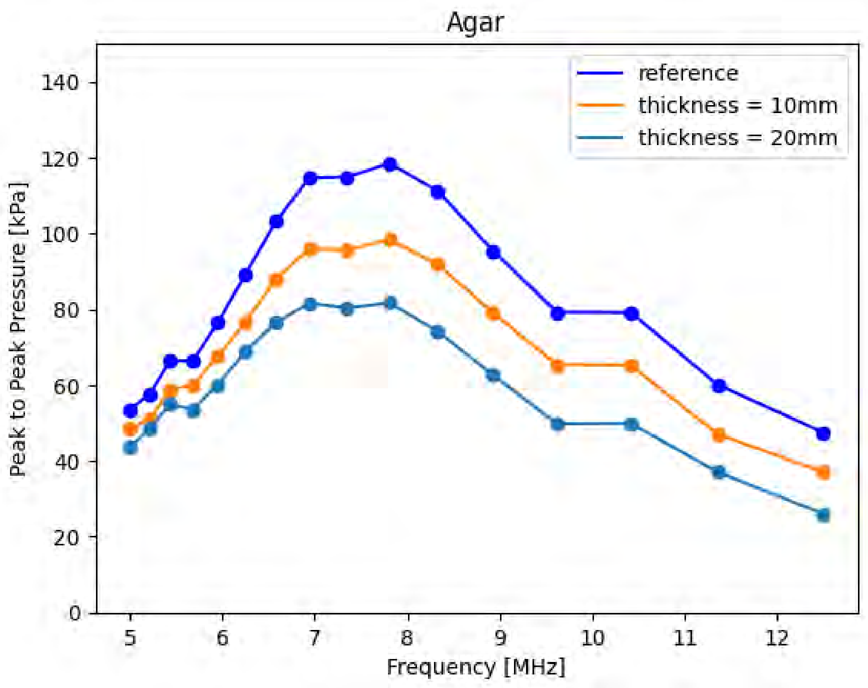

Figure 7.27: Peak-to-peak pressure signal of the two agar samples with different thicknesses and reference measurement.

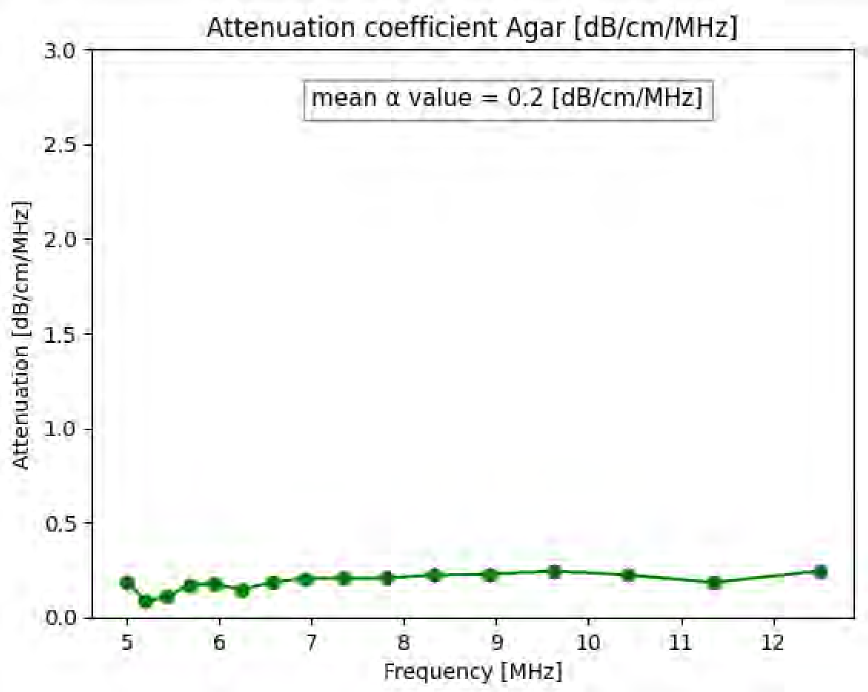

Figure 7.28: Attenuation values of agar in decibel per centimeter per MHz. The agar $\langle\alpha\rangle = 0,2$ dB/cm/MHz.

Polymethyl methacrylate (PMMA)

Results of through-transmission measurements for two samples of PMMA with 4 mm and 8 mm thicknesses.

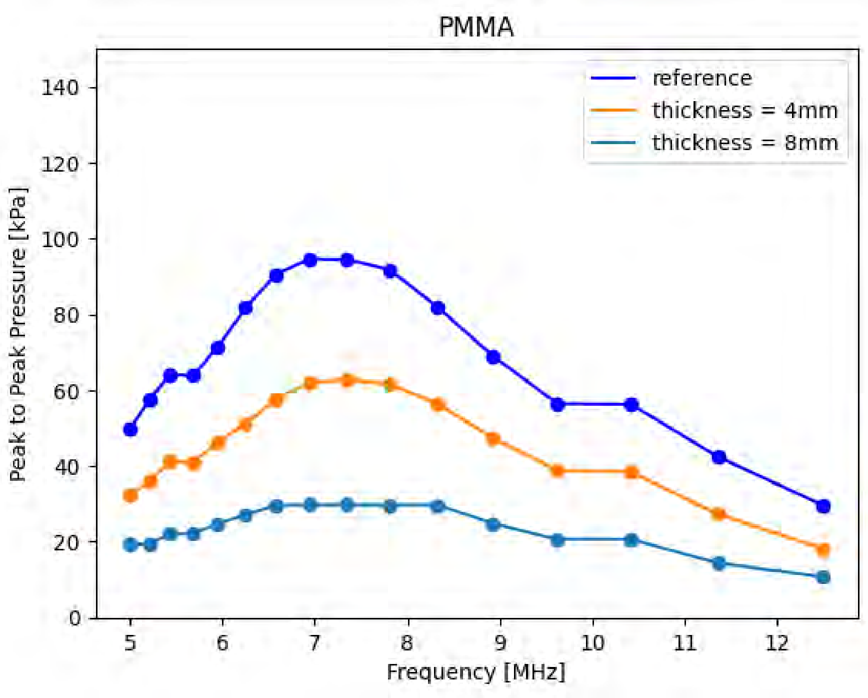

Figure 7.29: Peak-to-peak pressure signal of the two PMMA samples with different thicknesses and reference measurement.

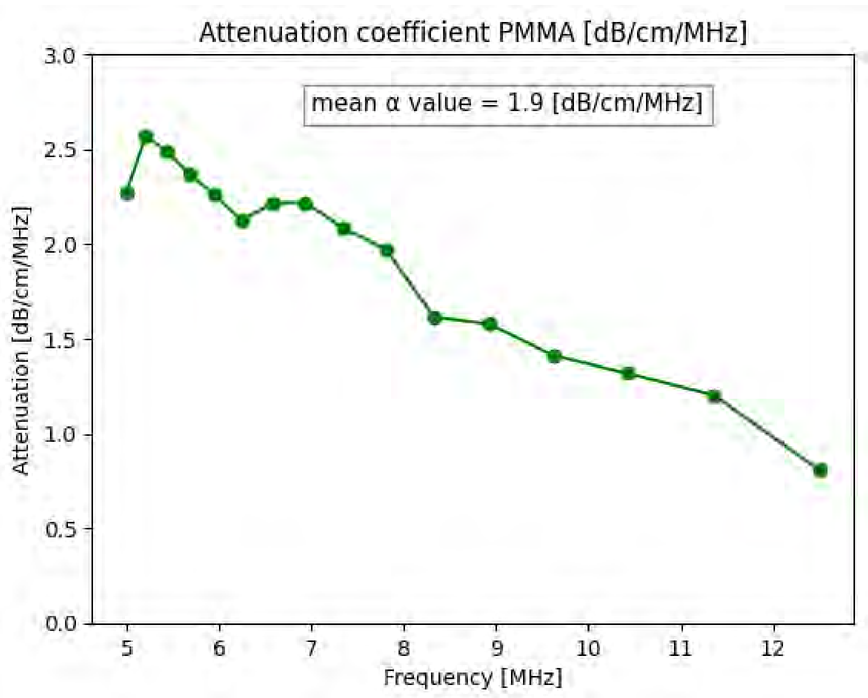

Figure 7.30: Attenuation values of PMMA in decibel per centimeter per MHz. The PMMA $\langle\alpha\rangle = 1,9$ dB/cm/MHz.

Aquaflex (solid hydrogel material)
Results of through-transmission measurements for two samples of Aquaflex with thicknesses of 18,7 mm and 35,5 mm.

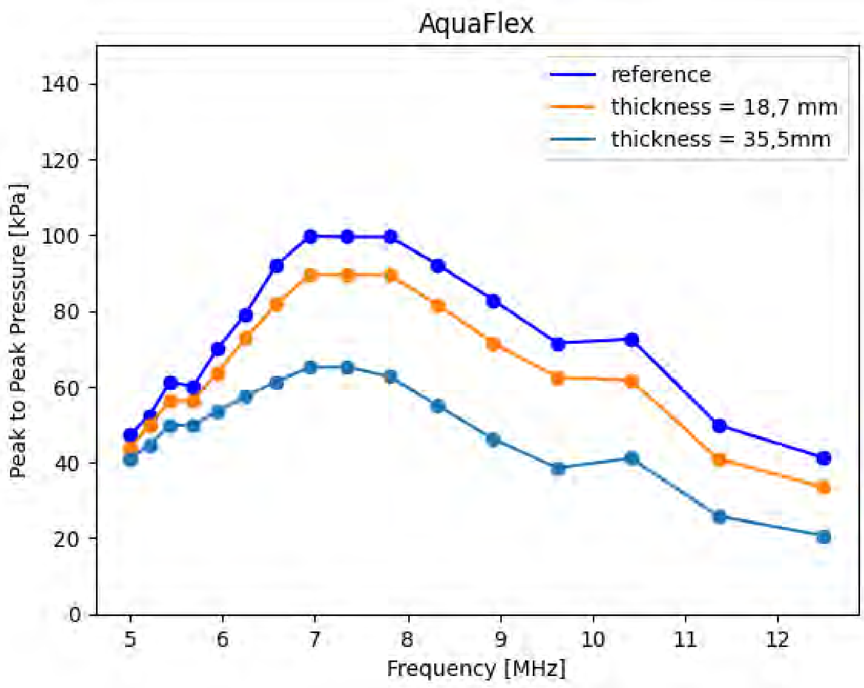

Figure 7.31: Peak-to-peak pressure signal of the two Aquaflex samples with different thicknesses and reference measurement.

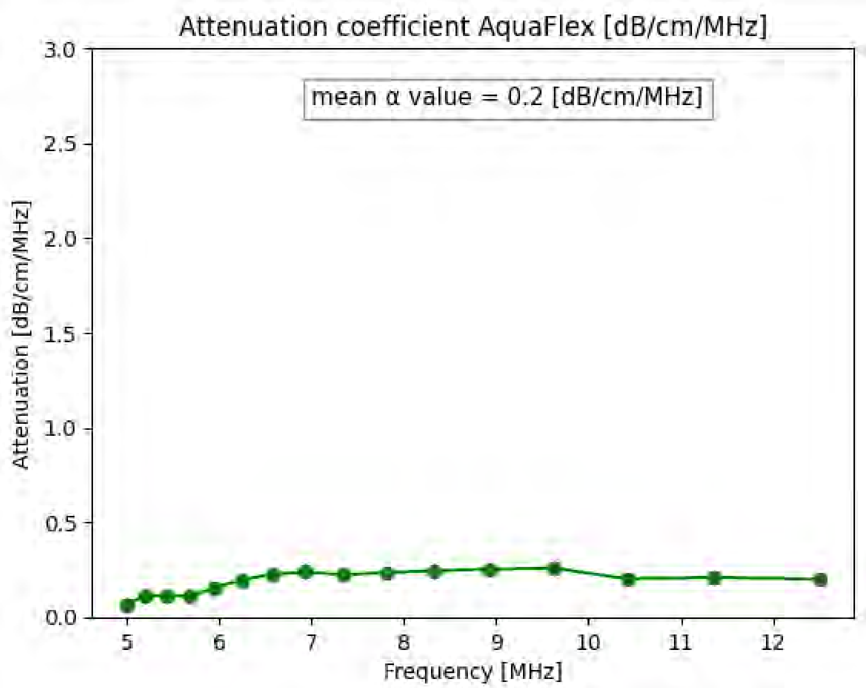

Figure 7.32: Attenuation values of Aquaflex in decibel per centimeter per MHz. The Aquaflex $\langle\alpha\rangle = 0,2$ dB/cm/MHz.

HydroAid (solid hydrogel material)
Results of through-transmission measurements for two samples of HydroAid with thicknesses 9,9 mm and 17,3 mm.

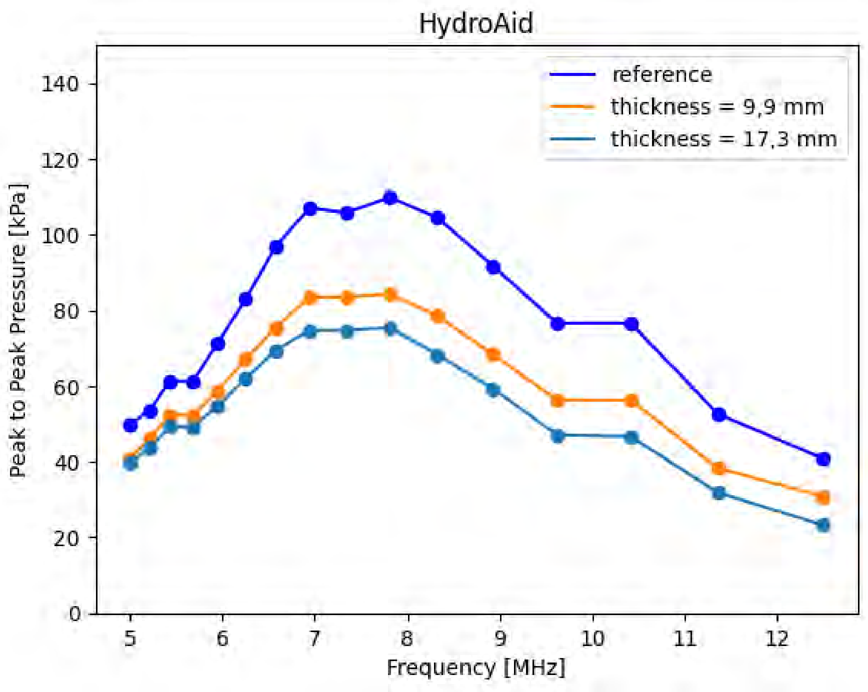

Figure 7.33: Peak-to-peak pressure signal of the two HydroAid samples with different thicknesses and reference measurement.

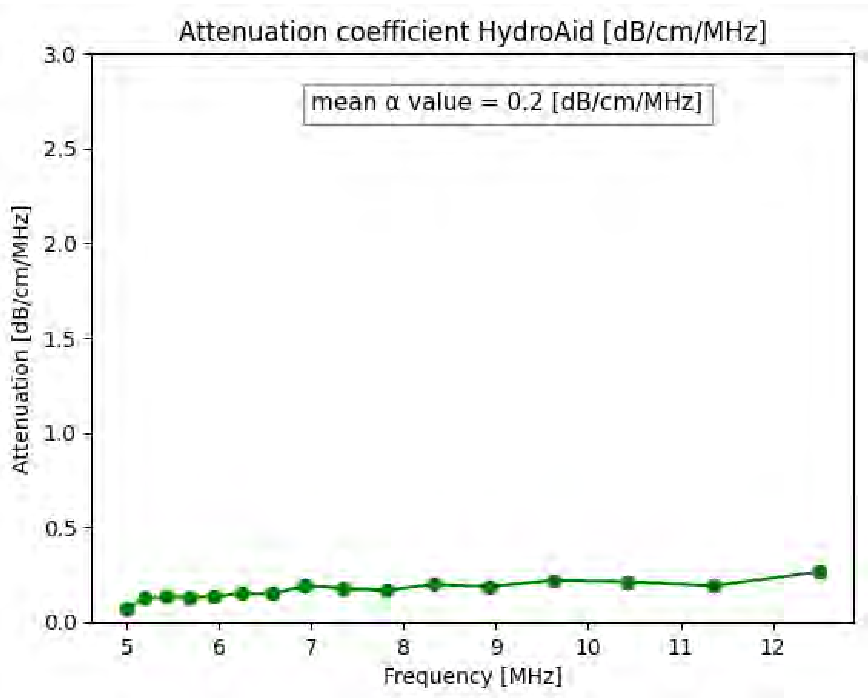

Figure 7.34: Attenuation values of HydroAid in decibel per centimeter per MHz. The HydroAid $\langle\alpha\rangle = 0,2$ dB/cm/MHz.

Ecoflex (Silicon)
Results of through-transmission measurements for two samples of Ecoflex with thicknesses 7,4 mm and 17 mm.

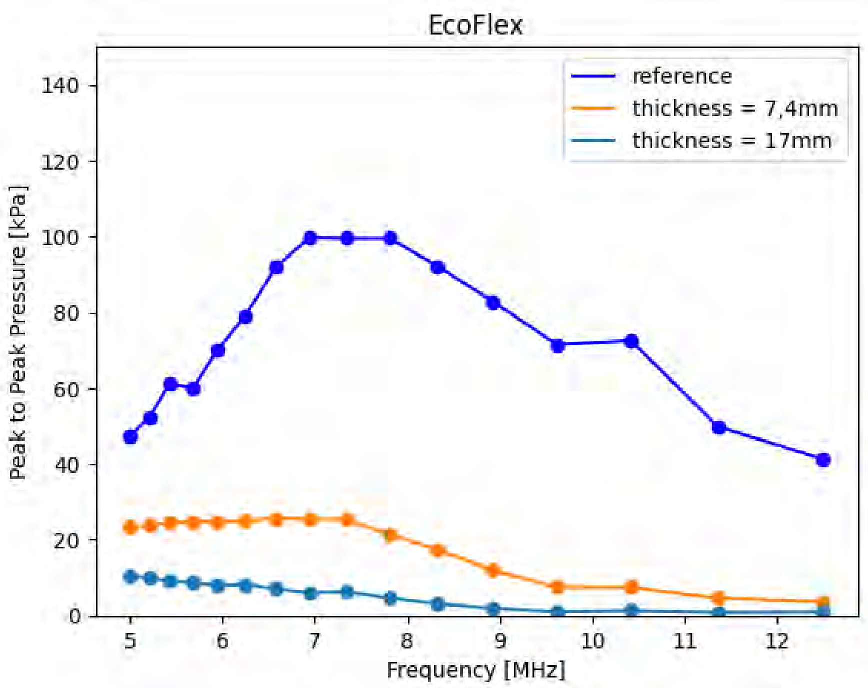

Figure 7.35: Peak-to-peak pressure signal of the two Ecoflex samples with different thicknesses and reference measurement.

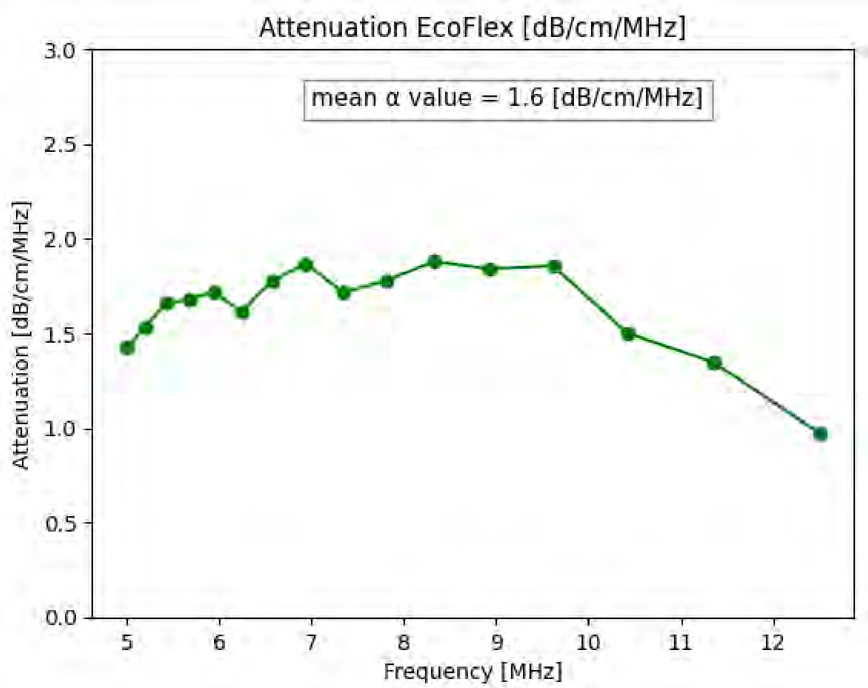

Figure 7.36: Attenuation values of Ecoflex in decibel per centimeter per MHz. The Ecoflex $\langle\alpha\rangle = 1,6$ dB/cm/MHz.

Axelgaard (ECG material)
Results of through-transmission measurements for two samples of Axelgaard with thicknesses 3,4 mm and 6 mm.

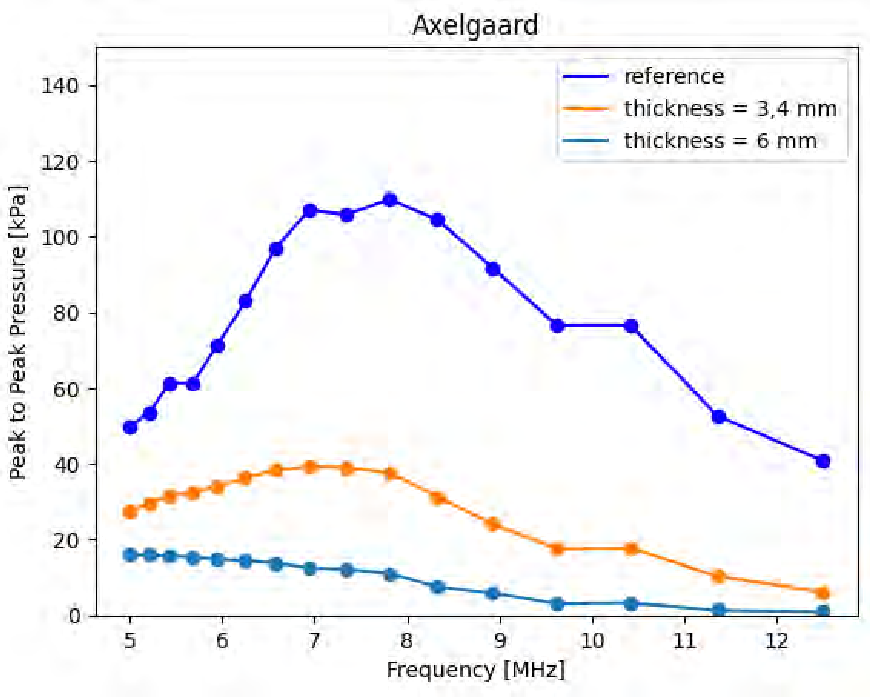

Figure 7.37: Peak-to-peak pressure signal of the two Axelgaard samples with different thicknesses and reference measurement.

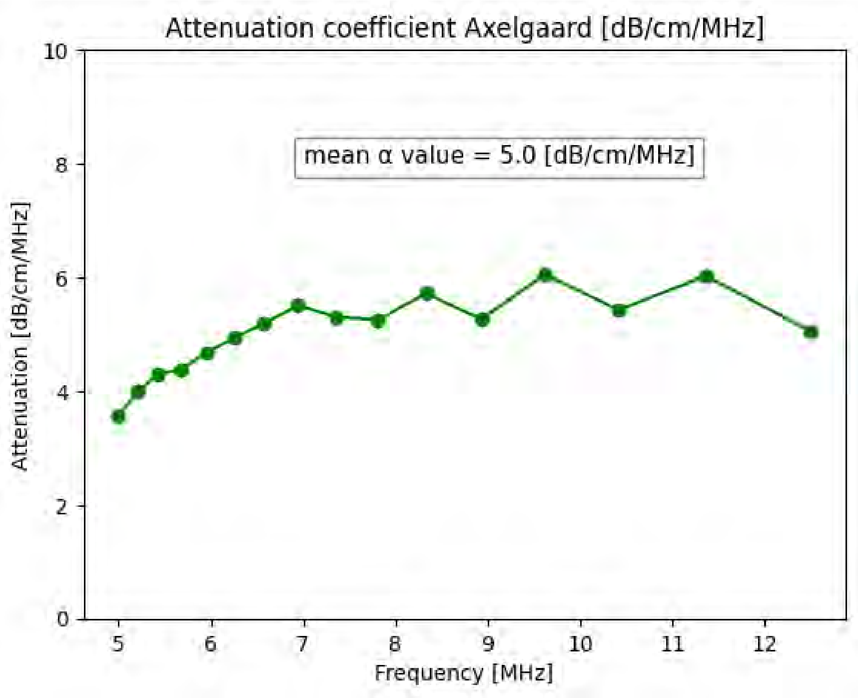

Figure 7.38: Attenuation values of Axelgaard in decibel per centimeter per MHz. The Axelgaard $\langle\alpha\rangle = 5,0$ dB/cm/MHz.

Hydrogel Healthcare 5023 (ECG material)
Results of through-transmission measurements for two samples of HH5023 with thicknesses 2 mm and 6 mm.

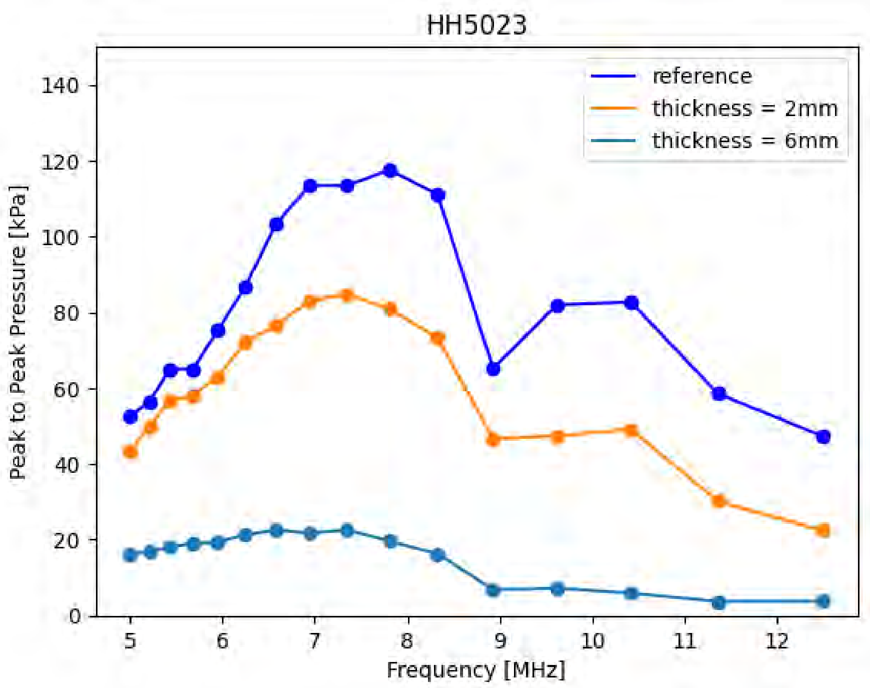

Figure 7.39: Peak-to-peak pressure signal of the three HH5023 samples with different thicknesses and reference measurement.

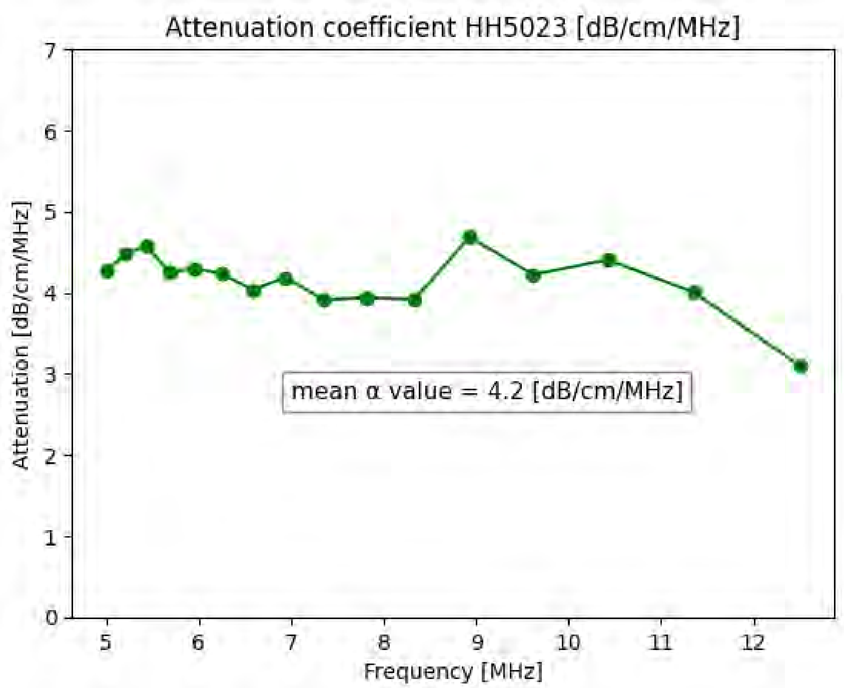

Figure 7.40: Attenuation values of HH5023 in decibel per centimeter per MHz. The HH5023 $\langle \alpha \rangle = 4,2$ dB/cm/MHz.

Hydrogel Healthcare 5450 (ECG material)
Results of through-transmission measurements for three samples of HH5450 with thicknesses 2,5 mm, 4,65 mm, and 9,9 mm. The attenuation values plotted in Fig. 7.42 are calculated with the peak-to-peak pressure signals of the sample with thicknesses 2,5 mm and 9,9 mm.

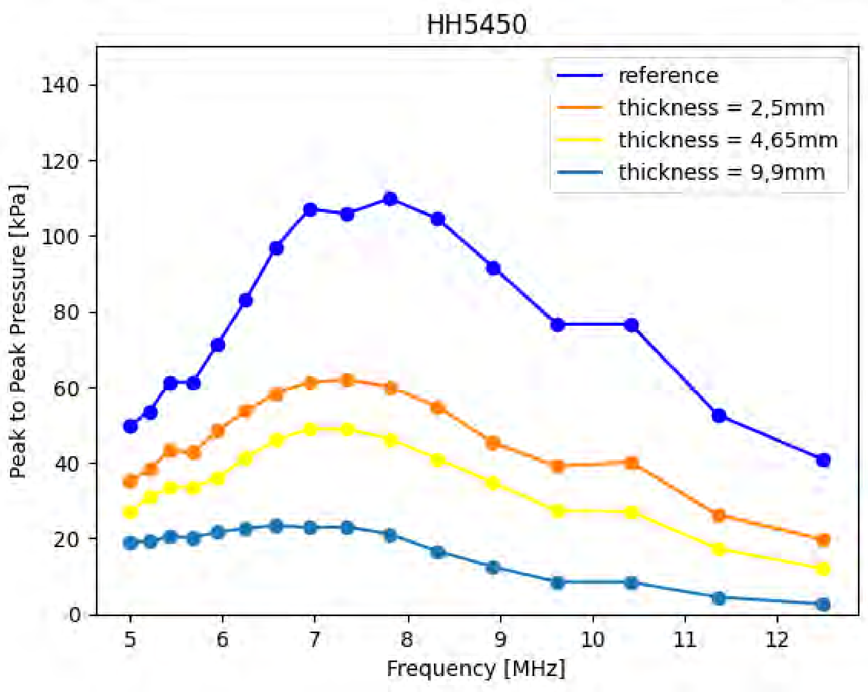

Figure 7.41: Peak-to-peak pressure signal of the three HH5450 samples with different thicknesses and reference measurement.

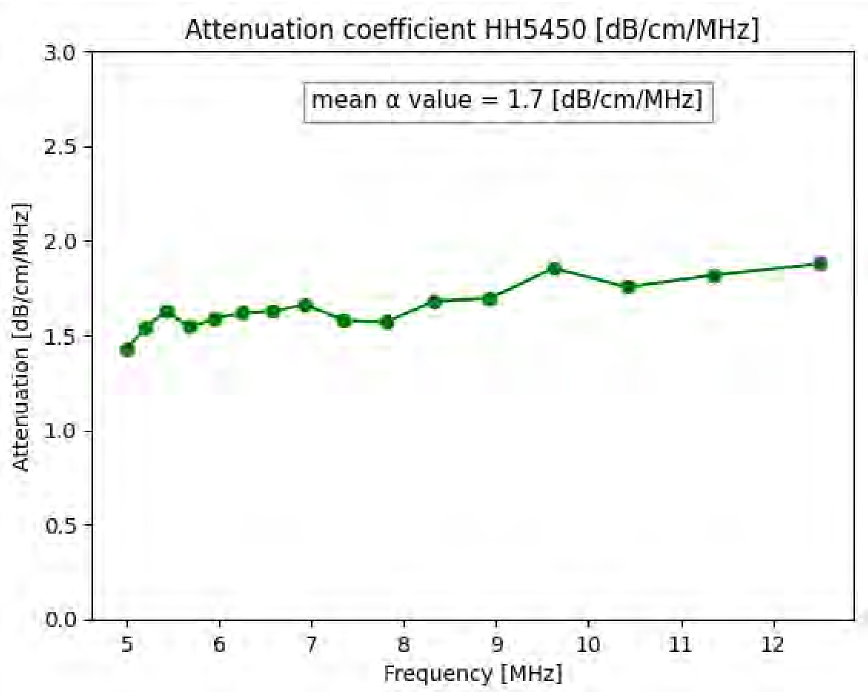

Figure 7.42: Attenuation values of HH5450 in decibel per centimeter per MHz. The HH5450 $\langle\alpha\rangle = 1,7$ dB/cm/MHz.

7.4. Skin-compatibility

To analyze skin compatibility, interviews with experts in medical devices and medical professionals were conducted and reviewed. From these interviews, it was concluded how to validate skin compatibility of the material listed in Table 4.2. The compatibility was validated according to ISO standards 10993, parts 5, 10, and 23, and intended use was checked. The information on these topics was found in the interview notes and datasheets of the materials. Below in Table 7.2, this validation is summarized.

7.4.1. Interviews

Six interviews were conducted; interview notes and responses are captured below. The questions per interview were slightly adjusted where needed to obtain desired information.

The following questions were asked during the interviews with an employee at NovioScan

- What type of wearable device does NovioScan make?
  Wearable bladder sensor for kids. Using ultrasound transducer to sense if a child's bladder is full. When it is full, the child will get a notification.
- Are there regulations or guidelines for long-term use (t > 48 hours) of wearable ultrasound devices?
  No, according to NovioScan, there are no regulations for the long-term use of wearable ultrasound devices on a patient.
- What regulations do you turn to for guidance?
  NovioScan consulted regulations for medical plasters, ISO standards 10993, 14971, 14155, and 13485, cosmetic regulations, and intended use of the materials like wound care.
- Have you experienced skin irritation difficulties during long-term ultrasound use?
  No skin irritation is experienced while testing the ultrasound SENS-U bladder sensor.
- Have you experienced difficulties with skin irritation during the long-term use of acoustic interface materials on the skin?
  Novioscan has not experienced skin irritation due to the acoustic interface material but has experienced slight skin irritation after removing the medical plaster.
- For how long is it placed on the skin?
  A person can wear the SENS-U for the whole night and/or day. Generally, it is attached to the skin to the stomach for 10 hours.
- What type of acoustic interface material is used?
  The interface material used is an ultrasonic gel encapsulated between the ultrasound transducer and the skin with a medical plaster.
- Have you experienced difficulties with the dehydration of this material?
  For the time the SENS-U is used, NovioScan did not experience problems with dehydration of the gel.
- Have you experienced other difficulties with this material?
  No, there have not been difficulties.

The following questions were asked during the interviews with an employee at Mepy:

- What products does Mepy make?
  Ultrasound acoustic gel and acoustic probe covers as interfaces for ultrasound imaging.
- What regulations do you turn to for guidance?
  Intended use classification of the materials in question.
- Have you experienced skin irritation difficulties during long-term ultrasound use?
  Long-term continuous exposure to ultrasound waves can cause skin heating and, eventually, skin irritation.
- What difficulties with skin irritation would you foresee for wearable ultrasound patches?
  Among others, a challenge could be the weight of the patch and where it would be positioned on the body. If it turns out to be too heavy on the skin, it could cause irritations.

The following questions were asked during the interviews with an employee at Philips working on the Avalon

- What type of wearable device does Philips make?
  Avalon FM50 is a fetal monitor device that uses Doppler ultrasound and can monitor fetal and maternal heart rates.
- What type of ultrasound monitoring does it use?
  It uses Doppler ultrasound.
- Have you experienced skin irritation difficulties during long-term ultrasound use?
  No, they do not experience skin irritation due to the long-term use of ultrasound. The ultrasound transducer was not ON continuously but turned ON for three minutes and OFF for hours.
- For how long is it placed on the skin?
  This varies, but it is intended to be used for hours.
- Have you experienced difficulties with skin irritation during the long-term use of acoustic interface materials on the skin?
  No, there was no skin irritation due to the use of acoustic interface materials, though they did experience heating of the skin due to when the cleaning solutions of the skin were not removed completely before placing the patches of the Avalon
- What type of acoustic interface material is used?
  General ultrasonic gel, Aquasonic, is used.
- Have you experienced difficulties with the dehydration of this material?
  No, for this period, there were no difficulties with dehydration. When the gel does dry out, it can be easily reapplied.
- Have you experienced other difficulties with this material?
  No, other than the skin irritation due to cleaning agents.

The following questions were asked during the interview with a cardiologist-electrophysiologist:

- Do you have experience with ECG patches on the skin for an extended period?
  Yes, at Haga Ziekenhuis, in the cardiology department, they have many heart patients who get attached to a heart monitor and or Holter test for a couple of days
- What skin irritations would you expect/have you observed with ECG materials?
  They experience minimal skin irritation after removing the ECG stickers.
- Do you think ECG-like adhesive patches can be used long-term (>5 days) on a patient's skin without causing too many skin problems?
  According to the cardiologist-electrophysiologist, long-term adherence to ECG stickers to the skin would not cause too many skin problems.
- Could this also be done at home?
  Yes, during a Holter test, a patient is attracted to a mobile heart monitoring device and is sometimes taken home.
- Do you have ideas for possible applications of wearable ultrasound devices in your medical field?
  Heart movies can be made with ultrasound; it would be convenient if this could be done with a wearable patch deployed once at a specific location.
- What are your thoughts on using a skin-mimicking phantom for testing these materials?
  This is an excellent way to start testing materials, though testing on patients is better. The cardiologist-electrophysiologist even suggested doing patch tests on volunteers among their patients.

The following questions were asked during the interview with a plastic surgeon:

- Do you have experience with ECG patches on the skin for an extended period?
  After an operation, the ECG patches are stuck on a patient for heart monitoring.
- What skin irritations would you expect/have you observed with ECG materials?
  There could be some skin irritation, though this is gone in a couple of days and, in their experience, never severe.

- Do you think ECG-like adhesive patches can be used long-term (>5 days) on a patient's skin without causing too many skin problems?
  The plastic surgeon removed an ECG adhesive patch from a patient after it had been there for a couple of weeks. There is redness at first when removed slowly and with care, but this goes away.
- Can the skin stay moist for such a long time?
  Yes, the skin can stay moist for a long time. It does get wrinkly, but if there is no wound or ulcer, she cannot think of why this would cause problems.
- Can the skin endure prolonged tension?
  yes, the skin is elastic and can easily heal itself.
- Do you have ideas for possible applications of wearable ultrasound devices in your medical field?
  After skin grafting, the new skin must be monitored at specific points. Currently, this is done manually with a mobile Doppler device, which causes much time stress among the team. A wearable ultrasound patch would, in this case, ease this stress and give the medical workers more time for other care.
- What are your thoughts on using a skin-mimicking phantom for testing these materials?
  She thought it was a good way to start the initial testing.
- What is your opinion on the phantom, especially the 'skin' layer?
  It is a good idea to make the phantom mimic aspects of the skin, which are important for the performance decrease of the material. Though it does not say anything about how the skin will react.

The following questions were asked during the interview with a dermatologist:

- Do you have experience with ECG patches on the skin for an extended period?
  Yes, but not extensively. After operations sometimes.
- What skin irritations would you expect/have you observed with ECG materials?
  A rash could occur, which will probably heal in a couple of days.
- Do you think ECG-like adhesive patches can be used long-term (>5 days) on a patient's skin without causing too many skin problems?
  The skin is a strong and resilient organ. It can heal fast if the patient does not have underlying medical conditions like diabetes,any open wounds or ulcers.
- Can the skin stay moist for such a long time?
  Yes, if the materials are like ECG solid hydrogels, this would not form a problem. If the patient does have underlying medical problems with the skin, it is not recommended.
- Can the skin endure prolonged tension?
  The skin is a resilient organ and can handle a lot.
- What are your thoughts on using a skin-mimicking phantom for testing these materials?
  The outcomes will probably not exactly mimic the properties of the skin, but it could be similar.
- What is your opinion on the phantom, especially the 'skin' layer?
  The skin is a living and breathing organ, a phantom will probably not exactly mimic these properties of the skin.

From the interview with experts on medical devices, it was derived to validate the material; it had to be tested against ISO 10993, listed in the approved cosmetic products, or intended for medical applications. From the interviews with medical professionals, it was derived that they do not expect long-term attachment of wearable ultrasound devices with acoustic interface materials like ECG solid hydrogels to cause skin irritation. However, it would still need to be patch-tested on the skin.

7.4.2. Validated materials

Information was collected from the interviews and literature to validate the materials. The results are shown in Table 7.2. All materials complied with the ISO norm 10993 parts 5, 10, and 23. The intended use for the materials was all in the medical field and used on human skin. The time periods the materials are usually in contact with human skin differ. Information on the intended use time on the skin was difficult to verify. Hence, this information was derived from the interviews.

Table 7.2: The table below contains the validation of skin compatibility found in the datasheets of the potential acoustic interface materials. Medical professionals were interviewed, and literature was consulted for information on intended use and time on the skin.

Name	**Material**	**Intened use**	**intened time on skin**
AquaFlex	solid hydrogel	Ultrasound	10 min
HydroAid	solid hydrogel	Wound dressing Ultrasound	10 min
EcoFlex	silicone	Prosthetic appliances and cushioning for orthotics	-
Envision	silicone	Ultrasound	10 min
Axelgaard	solid hydrogel	ECG	5 days
HH5023	ECG solid hydrogel	ECG	5 days
HH5450	ECG solid hydrogel	ECG	5 days

Name	**Cytotoxicity, Irritation, Sensitixation**	**reference**
AquaFlex	Hazards: no known significant effect or critical hazards.	[43]
HydroAid	non-toxic non-irritating non- allergic	[44]
EcoFlex	Certified skin safe and certified by an independent laboratory.	[47]
Envision	In compliance with the MDR: it indicates the product is a medical device.	[37]
Axelgaard	non-cytotoxic non-irritating non-sensitizing	[45]
HH5023 HH5450	The ECG Series has passed biocompatibility under ISO 10993-5, 10, 23: cytotoxicity - zero skin irritation - zero skin sensitization- zero	[46]

8 Discussion

8.1. Ultrasound Phantom

In this section, Phantom Model 5 will be discussed. The phantom was given a score of 52 out of 63, providing 80% all-round score. While looking at the photos taken during the eight days the phantom was placed in the oven at T=34 °C, some observations stand out and will be discussed below.

Data collection

Two Phantom model 5 containers were assembled with three wearable patches with different acoustic materials. These phantoms were placed in an oven at T = 34 degrees C for eight days. Pictures of the phantoms and ultrasound images of all six wearable patches were captured during the first five days of observation. After this week, the containers were left in the oven over the weekend until day 8. On day 8, the phantoms could be observed again, which is the reason for the two-day gap in the ultrasound and observation data. However, it did not raise a concern for this research due to the set requirement of a lifetime of five days and the phantoms were observed every day for a period five days.

Hydration layer

The shrinking of the agar surface has been touched upon in the Results section 7.1.5. Throughout the five days, this seemed not to form a problem for making the ultrasound images at the correct spots. When looking at Fig. 7.13, all the images from day one until day five are taken at the same place; no repositioning due to the shrinking of the agar layer seems to occur. Also, no mold growth was observed on the phantom on day 5. However, on day 8, the agar layer started to cause problems. Shown in Fig. 7.12 are the before and after images of the two containers. Before, the agar layer was uniform, but after eight days in the oven, it started to shrink and misform. This gave issues while making ultrasound images through the wearable patches. Because of this shrinkage and deformation, the patches had moved from their original position, causing non-consistency in the ultrasound images. Moreover, the agar layer in container 2 had begun to grow mold on it, also seen in the Fig. 7.12.

This issue is also clearly seen in the ultrasound images made on day 8 (Fig. 7.13). The agar layer, indicated by the two bright horizontal stripes, as shown in Fig. 7.14, remains straight for the first five days but is found to be deformed in the images on day 8. This is especially clear in the image on day 8 made through HH5023; here, the layer seems to have a bend in it.

Re-usablility of the phantom

After eight days, the wearable patches with interface materials were disassembled, and the shrunken agar layer with PET foil was peeled off the gel wax surface. This surface was as flat and smooth as initially shown in the Fig. 7.12 the bottom images. This, however, does not cause a problem because gel wax reforms slowly. After a week, the surface layer was much smoother and the phantom could be used again. Also, the gel wax surface was slightly deformed because the agar was so deformed after eight days. If the agar layer had been removed earlier, for instance, on day five, the surface of the gel wax filling would have been smoother. In addition, before and after ultrasound images were made on the gel wax filling. A week after removal of the agar layer there were no distortions or abnormalities in the images compared to before. Gel wax is not affected by the degradation of agar.

8.2. Lifetime experiments of acoustic interface materials using the phantom

The lifetime experiments were conducted with the developed phantom model 5. Due to time restrictions, this was only done once. Therefore, deriving a conclusion from the results in Fig. 7.15 is difficult. This is the reason only careful conclusions will be given.

While looking at the ultrasound images made through the interface materials in Fig. 7.13, there are some observations to discuss. On day 8, all the images look distorted in some way, probably due to the degradation of the agar layer.

This issue is most visible in the image made on day 8 through AquaFlex; the ultrasound image shows a grey haze over the image. HydroAid, on day 8, shows a slight downward bend in the agar layer. Images made with EcoFlex show some distortions that could indicate non-conformal contact with the surface of the phantom due to, for instance, small air bubbles. EcoFlex is also the only material that was not made with water and does not 'stick' to a surface like others do. From the images made with the interfaces on container 1, AquaFlex gave the most consistent outcome, ultrasound images made through HydroAid resulted in brighter images, and the images with Ecoflex were least consistent due to the artifacts in the images and gave the darkest images.

The images made with Axelgaard show a 'growing' interface layer on top op the agar layer in the images. This is probably a reason why the agar layer deforms as time passes. The ultrasound images of HH5023 clearly show a thicker growing interface layer on top of the agar layer. Following the growth of a thicker interface material, the agar layer on day 8 is visibly deformed. This is probably due to the fact that the ECG solid hydrogel HH5023 soaks up a lot of water. The images made through ECG solid hydrogel HH5450 indicate a change in the material's composition after day 1; the images become increasingly grey. On day 8, this grey haze distorted the entire image.

Some of the images show bright stripes below the scattering objects. It is theorized this is likely due to the bounced ultrasound waves in the agar layer, which reach the wire at a later point in time, resulting in a reflection deeper in the ultrasound image.

When analyzing the graphs with plotted brightness values of the ultrasound images shown in Fig. 7.15, it must be kept in mind that the data collected on day 8 (160 hours) is not reliable because of the dehydration of the agar layer causing distortion of the ultrasound images.

Some observations that can be made from analyzing the plotted brightness values in Fig. 7.15 derived from the ultrasound images made through the different interface materials will be listed here. The brightness values of the ultrasound images made through AquaFlex appear to decrease over a period of five days. The last value is very high due to the degradation of the agar layer. Also, as discussed, the images through HydroAid have a higher brightness value. The brightness values of the images captured through HH5450 increase over the duration of the experiment and has the highest brightness values at day 8. The data seems to indicate that throughout the eight days, HydroAid, Axelgaard, and HH5023 stayed consistent in acoustic performance when analyzing the data of the brightness of the ultrasound images.

8.3. Acoustic performance

To evaluate the acoustic performance of materials commonly used in ultrasound phantoms or as ultrasound interface materials, through-transmission measurements were conducted, and the acoustic attenuation coefficient was calculated. The acoustic attenuation coefficients (α) of twelfth different materials were measured using the setup. Due to the inconsistencies in the measurement setup, not all the reference measurements are identical. However, for calculating the attenuation coefficient, this is not an issue. As previously stated, the difference between the ultrasound signal through thick and thinner material samples is calculated (Eq. 6.14). It is assumed, that the reflections of ultrasound due to a difference in acoustic impedance (Z) values at the interfaces of water to material and back to water are canceled out when taking the difference between the two measurements.

The plotted peak-to-peak pressure signals through the ECG hydrogel material, HH5023, show an inconstancy of the ultrasound transducer, see Fig. 7.39. At a transmission frequency of 9 MHz, the transducer faltered. This was also apparent and noted during this measurement. The 'dip' in the plotted graphs at 9 MHz Fig. 7.39 can be interpreted as a shortcoming of the experimental setup. Since the attenuation coefficient is calculated with the peak-to-peak pressure values, this also applies to the ’peak’ in the attenuation coefficient graph shown in Fig. 7.40.

Initially, the desire was to compare the measured attenuation coefficients to those found in the literature. This proved difficult to do. The attenuation coefficient measured in this research was measured for frequencies between [5-12,5 MHz]. The attenuation coefficient values found in the literature were rarely measured for frequencies in this range. In addition, the acoustic properties of all the potential interface materials were difficult to find. The materials, gelatin, agar, and PVA that were used in the phantom were all measured by Chen P. et al. (2022) [24]. The researchers used a transmission frequency range of 1-6 MHz, which is not fully comparable. The attenuation coefficients measured at the highest transmission frequencies of the research in Chen P. et al. and the lowest transmission frequencies in this research were compared. The attenuation coefficients measured by Chen P. et al. had slightly higher values than those measured in this research. The differences were $\pm$0,5 dB/cm at 6 MHz. This could be due to the fact that the researchers used two different ultrasound transducers during the measurements, one for the frequency range of 1-4 MHz and one for 4-6 MHz. This could result in more accurate results. However this is hard to say, due to the difference in the transmission frequency range of both setups.

8.4. Skin-compatibility

To assess the skin compatibility of the potential acoustic interface materials, the datasheets and medical professionals with experience were consulted. To fully examine this, patch tests on skin have to be conducted. The validation report shown in Table 7.2 gives an indication of the outcome but is not a complete validation.

9 Conclusion

For the conclusions of this research, this chapter is divided into three main parts, as was done previously.

- Ultrasound Phantom 9.1;
- Acoustic performance 9.2;
- Skin-compatibility 9.3.

9.1. Ultrasound Phantom

In this section, the phantom model is assessed for meeting the defined requirements and the lifetime experiments with the phantom are being evaluated. And conclusions for both are being derived.

9.1.1. Assesment of phantom model 5

At the start of developing the ultrasound phantom, a set of requirements and wishes to be met were established. Below, the defined requirements are evaluated to see if they were satisfied.

1. **Transparent to ultrasound;**
   The acoustic impedance values of the materials were not measured. To evaluate if this requirement of $Z_{phantom} \approx Z_{water} = 1,48$ MRayl/m² was met, the acoustic impedance values were found in the literature. The acoustic impedance of Agar 5% ranges from $Z_{agar} = 1,54 * 10^6$ - $1,56 * 10^6$ MRayl/m² [24]. The acoustic impedance values found in the literature for gel wax was $Z_{gelwax} = 1,22 \pm 0,01$ MRayl/m² [68]. The impedance of Z_{agar} is 17% smaller than that of water, and the impedance of Z_{gelwax} is 4% larger than that of water. In Table 4.1, the acoustic impedance values of water, skin, breast, muscle, and bone tissue found in the literature are listed. Both the agar and gel wax impedance values are in the range for which it is visible with ultrasound imaging. As shown in the Fig. 7.13 with an ultrasound transducer, clear ultrasound images can be made inside phantom model 5. From this, it can be concluded that ultrasound phantom model 5 is transparent to ultrasound transmitted from a Philips Lumify L12-4 probe.
2. **Lifetime t > 5 days;**
   As shown in the observations of the phantom model 5 over eight days Fig. 7.11. The model kept fully functioning for at least five of the eight days, after which it started to falter. This was primarily due to the dehydration of the agar layer, which caused it to shrink and deform. Phantom model 5 met the lifetime requirement of five days.
3. **Includes scattering objects, which are visible with ultrasound;**
   Two types were evaluated for the scattering objects: stainless steel and nylon wires. As shown in Fig. 4.3, nylon wires were the preferred scattering objects for this phantom. They formed more minor reflection spots on the ultrasound, not 'tails' as the stainless steel wires caused (Fig. 7.2), and were easier to assemble straight. The wire holder had been altered a few times because the structure would deform. This was because of the strain force of the strung nylon wires pulling the side toward the middle or due to high temperatures while pouring in the phantom filling. The finalized wire holder was designed so that it would not deform under force or temperature and was printed with a very rigid material with an SLA printer. In Fig. 6.2, the finalized version of the wire holder is shown.

4. **The phantom must mimic human skin conditions: human skin water evaporation;**
   The hydrating layer with the top layer containing pores was placed in an oven to examine the water evaporation rate of the phantom model 5. The average amount of water evaporating is 139,5 nL/(min*cm²). The water evaporation rate eventually was 92,90 nL/min*cm². This results in a ratio of [agar: skin] = [0,7:0]. The evaporation rate was an average of the values found in the literature. The amount of water evaporation of a human being could be between 10 - 250 nL/(min*cm²) [27]. An evaporation rate of 92,90 nL/min*cm² is in this range. Therefore, this evaporation rate is still deemed sufficient enough, although this is slightly less than the desired amount.
5. **The phantom must mimic human skin conditions: human skin temperature;**
   With an oven set on a temperature of T= 34 °C, the temperature requirement of mimicking skin temperature of 33 °C - 36 °C was met. The live temperature inside the oven was noted on the outside; this varied between 33-35 °C but was mostly 34 °C.
6. **The phantom must mimic human skin conditions: acoustic impedance (Z) and attenuation coefficient (α) similar to those of human tissue.**
   The acoustic impedance and attenuation values of human soft tissue were found in literature: $Z_{tissue} = 1,54$ - $1,99$ MRayl and $\alpha_{skin} = 0,44$ dB/cm. For comparing acoustic impedance values to skin, the values of Table 4.1 were consulted.

   - $Z_{agar} = 1,55 * 10^6$ MRayl/m²;
   - $Z_{gelwax} = 1,22$ MRayl/m²;

   Although the acoustic impedance values of agar and gel wax are not the same, they are similar. The acoustic impedances of agar and breast tissue are very similar, $Z_{agar} \approx Z_{\text{breast tissue}}$. Also, the acoustic properties of gel wax can be altered using paraffin; this is what Maneas E. et al. (2018) did to mimic specific human tissue types [68].

   With the through-transmission measurement setup, the attenuation coefficients of the materials used in this phantom model have been measured and calculated.

   - $\langle\alpha_{Gelwax}\rangle = 0,2\ dB/cm/MHz$;
   - $\langle\alpha_{Agar}\rangle = 0,2\ dB/cm/MHz$;
   - $\langle\alpha_{plastic}\rangle = 0,1\ dB/cm/MHz$.

   The attenuation coefficients of human tissue vary between 0,44 - 0,75 dB/cm/MHz. The attenuation coefficients of gel wax, agar, and plastic are smaller than those of human tissue. Making these materials less attenuating for ultrasound than human skin.

Further wishes for a phantom for lifetime experiments:

- **The phantom is reusable;**
  Phantom model 5 is a model with three different functioning layers. Because of this design, it is possible to reuse the container, filling it with wire holders and nylon wires. The hydration layer and top layer with pores are the only disposable parts.
- **The phantom is made in 1-2 hours;**
  This wish can be interpreted in two different manners: the initial assembling of the full phantom and the assembly of the hydration layer and wearable patches. The full assembly of the phantom model 5 took about 8 hours to complete. The phantom assembly was only the hydrating and top layers, and sticking the patches on top. This did take up to 2 hours when the materials were prepared. So, when resuing the phantom model, it could be made in 2 hours, and it took four times longer to make a fresh model.

The three-layer model made with gel wax, agar, and PET foil gave a well-performing skin-mimicking phantom for five days. The phantom was easy to assemble, and the filling with scattering objects is reusable.

9.1.2. Lifetime experiments of acoustic interface materials using phantom model 5

It is difficult to form a conclusion with the data of the 'lifetime' performance experiments, because it was only conducted once for the interface materials. The lifetime experiment was performed over eight days due to the limited lifetime of the hydrating layer of phantom model 5.

First, the ultrasound images made during the experiment, shown in Fig. 7.13, will be evaluated. A conclusion that can be taken is that the agar layer of the phantom distorted the images when it was too dehydrated. AquaFlex delivered the most consistent ultrasound images. EcoFlex did not have a stable adhesion to the surface of the phantom. ECG solid hydrogel HH5023 soaks up a lot of water, resulting in the material to swell, changing the thickness and form. Axelgaard provided consistent ultrasound images during the eight days. The image quality through HH5450, decreased over time.

When combining the observations of the ultrasound images in Fig. 7.13, phantom model 5 Fig. 7.11 and the plotted brightness values of the ultrasound images in Fig. 7.15 some conclusions can be made. There seems to be a relation between an increase in brightness values of the ultrasound images over a period and the degradation of the acoustic interface material or hydration layer.

This relation seems clear when looking at the results of the images made through ECG solid hydrogel HH5450. On day 8, the scattering objects were not visible, indicating a distortion, and the ultrasound image could not be properly captured. This connection is also derived from the images made through the solid hydrogel Aquaflex. Throughout the first five days, the images in Fig. 7.1 do not show any signs of degradation or poor image quality. On day 8, the image has a grey haze. This indicated a distortion in the hydrating layer or acoustic interface.

In the pictures of phantom model 5 after the experiment, some mold and decolorization are visible in the agar layer. A mold spot was localized underneath the position of the wearable patch with HH5450 inside on day 8; see Fig. 7.12. However, it is not possible to conclude with certainty that this graduate increase in brightness of the image over this period since it was not localized before day 8, see Fig. 7.11. When looking in the experiment notes and the Fig. 7.12, it was concluded that the distortion in the image on day 8, made through AquaFlex, was due to the agar layer degradation over the last two days.

The main outcome from this experiment is that the acoustic interface materials seem to have a longer lifetime than eight days on skin-mimicking phantoms.

9.2. Acoustic performance

The attenuation of the ultrasound signal can be observed in the Fig. 7.17. The signal that traveled through thicker samples showed lower peak-to-peak pressure values. In this research, the main focus was placed on the attenuation of the signal to calculate the attenuation coefficient for different transmitted frequencies. This decrease in signal is most likely because the ultrasound waves had to travel longer through a specific material. This complies with the unit of the attenuation coefficient α in $[dB/cm/MHz]$. The table below is the same table shown in the Results Table 7.1 but ordered differently. In Table 9.1, the materials are ordered in relevant groups to be compared more easily.

Table 9.1: Main attenuation values of potential acoustic interface materials, ordered in different group types.

type of material	name	$\langle\alpha\rangle$ in $[db/cm/MHz]$ over a frequency range of 5-12 MHz
solid hydrogel	AquaFlex	0,2
	HydroAid	0,2
silicon	EcoFlex	1,6
ECG hydrogel	Axelgaard	5,0
	HH5023	4,2
	HH5459	1,7
protein product	Gelatin	0,2
	Agar	0,2
synthetic polymer	PVA	0,3
candel wax	Gel wax	0,7

The ECG hydrogel measured the highest mean attenuation coefficients from all the materials, which implies the lowest acoustic performance compared to the other materials. The mean attenuation coefficients range from 1,7 - 5,0 db/cm/MHz. This is probably due to the woven material inside the hydrogels, initially used for conducting electrical signals. As expected, the solid hydrogels had the lowest mean attenuation coefficients, with a 0,2 dB/cm/MHz value. The silicon material, EcoFelx, measured just lower than the ECG hydrogels. The solid hydrogels AquaFlex and HydroAid have the highest acoustic performance when considering acoustic attenuation values. Though EcoFlex and ECG hydrogel HH5459 also measured low attenuation coefficients and are serious contenders for acoustic interface materials.

9.3. Skin-compatibility

From the interview with experts on medical devices, it was derived how to validate the material; it had to be tested against ISO 10993, listed in the approved cosmetic products or had an intended use in medical applications. From the interviews with medical professionals, it was derived that they do not expect long-term attachment of wearable ultrasound devices with acoustic interface materials like ECG solid hydrogels to cause skin irritation. However, it would still need to be patch tested on skin.

For interface materials to be approved for wearable ultrasound patches, these have to be compatible with human skin and not cause medical problems. To assess the compatibility of these materials, the following requirements for the acoustic interface material between the ultrasound transducer and skin were established.

- **Conformable to the body: flexible and creating an airtight seal with the skin;**
  This requirement has been assessed during the 'lifetime' performance experiments of the acoustic interface materials. All materials are flexible and conform to a surface to make an airtight seal. The good conformability of the materials to the miniature gaps and holes of the skin is probably because the materials consist of a lot of water. Ecoflex was the only material that did not contain of water. This material also was less flexible and did not make an airtight seal with the phantom surface. The ECG solid hydrogels (Axelgaard, HH5023, and HH5450) have a more sticky composition. These properties make them conform to the curvature of the body. The other solid hydrogels, AquaFlex and hydroAid, are less sticky, making them easier to slide over a surface.
- **Biocompatible with human skin;**
  The materials that are included in Table 7.2 are validated for being non-toxic, non-irritable, and non-sensitizing for human skin.
- **Prolonged duration of functional use, t > 5days;**
  It is difficult to make a conclusion with the data of the 'lifetime' performance experiments, because it was only conducted once for the interface materials. For this experiment run, the materials AquaFlex, HydroAid, Ecoflex, Axelgaard, HH5023, and HH5450 were functional as interface materials for longer than five days.

- Hydration: The materials AquaFlex, HydroAid, Axelgaard, HH5023, and HH5450 were not dried up or shrunken after eight days. They seemed to soak up the water from the hydration layer so they did not dry out. When placed in wearable patches on an ultrasound phantom that mimics skin properties, these materials could stay hydrated enough for a period longer than five days.
- Adherence to skin: The ECG solid hydrogels (Axelgaard, HH5023, and HH5450) have a more sticky composition and stay adhered to the surface of the phantom. However, if these materials soak up too much water, they become less sticky. The other solid hydrogels, AquaFlex, and hydroAid, are less sticky and adhere less tightly to a surface. The EcoFlex patch does not adhere to the surface without taping the wearable patch to the surface.

9.4. Closing Remarks

In this thesis, an ultrasound phantom was developed that mimics skin properties. These types of ultrasound phantoms have not yet been made or written about in literature. This phantom model can be used to test the lifetime performances of acoustic interface materials. Also, the attenuation of these acoustic interface materials and the materials used for the development of this phantom model have been measured. Furthermore, interviews were conducted for information on the skin compatibility of potential acoustic interface materials and how to validate these for skin compatibility. With consultation of the interviews and literature, a theoretical validation of skin compatibility of the acoustic interface materials was done.

The ultrasound phantom, which was developed, model 5 - a three-layer model, was evaluated for the established requirements. It can be concluded that five of the six requirements were fully met, and one was not. This was the requirement of having acoustic properties similar to that of human tissue. Phantom Model 5 was developed with materials with lower attenuation coefficients than human skin. This implies that the phantom materials attenuate an ultrasound wave less than human tissue. For this particular ultrasound phantom, it does not form an issue. In the case where the primary research revolves around the lifetime performance of acoustic interface materials, the developed phantom model 5 is suitable to use.

The phantom model had a lifetime of eight days. Although the lifetime requirement of five days was satisfied, for other experiments that required longer periods, this could form a problem. The bottleneck of phantom model 5 was the shrinking and deformation of the hydrating layer, which was made from agar. An opted solution for this issue could be to remove the agar layer every five days. The patches are attached to the top layer of PET foil, which can easily be removed and assembled on the phantom model. This will form a slight relocation of the patches, resulting in slightly different ultrasound images. But if the aim is to test the dehydration of the interface materials, this could be a solution.

While looking at the data of the measured acoustic attenuation coefficients and the skin-compatibility assessments, it can be concluded that Aquaflex, HydroAid, ECG materials, and silicon are promising acoustic interface materials. They have low mean attenuation coefficients, resulting in high acoustic performance and making high-resolution ultrasound imaging or monitoring possible. According to the literature, all the materials are compatible with the skin, though they still need to be patch-tested on human skin. A one-time 'lifetime' performance experiment of eight days was conducted on ultrasound phantom model 5, mimicking human skin conditions. What could be concluded from this experiment is that the materials did not dry out in a period of eight days. Medical professionals with experience with ECG stickers and patients with skin irritations do not expect long-term attachment of wearable ultrasound devices with acoustic interface materials like ECG solid hydrogels to cause skin irritation. Skin is a resilient organ; it can withstand a lot and heals quickly. However, it would still need to be patch-tested on patients.

9.5. Research Questions

The research questions posed in Problem Statement 3 are repeated below for convenience.

Objective: Develop an ultrasound phantom for testing acoustic interface materials through answering the following questions:

Research Question 1

Can an ultrasound phantom be developed which mimics skin properties and can be used for a prolonged period of time?

Yes, an ultrasound phantom model was developed to mimic skin properties like water evaporation, temperature, and acoustic performance. It is a three-layer model, with a filling material (gel wax) with scattering objects inside, a hydrating layer (agar), and a regulation layer with holes (PET foil) to make sure the amount of water evaporation of the phantom is similar to that of the skin. The phantom performed as a human skin for five days, where after, it started to falter. The bottleneck of this phantom is the hydration layer, which is dehydrated and starts to deform after five days.

Research Question 2

How do the promising acoustic materials perform over a time period of 5 days?

With the ultrasound phantom model 5, the lifetime experiments were conducted with six potential interface materials: AquaFlex (solid hydrogel), HydroAid (solid hydrogel), Ecoflex (silicone), Axelgaard (ECG solid hydrogel), HH5023 (ECG solid hydrogel), and HH5450 (ECG solid hydrogel). Over a period of five days, the materials were performing well. For this experiment, the bottleneck was the hydration layer of the phantom model.

Research Question 3

what are the acoustic properties of the promising interface materials and the materials used in the phantom?

The acoustic attenuation coefficients of the interface materials and the materials used in the phantom can be found in Table 7.1. All the materials that were evaluated in this thesis have great potential to be used as interface materials in wearable ultrasound devices. The materials are AquaFlex (solid hydrogel), HydroAid (solid hydrogel), Ecoflex (silicone), Axelgaard (ECG solid hydrogel), HH5023 (ECG solid hydrogel), and HH5450 (ECG solid hydrogel). After interviewing medical professionals and evaluating the acoustic attenuation coefficients of the materials, ECG materials came out as very reliable interface materials. They stay adhered to the skin for long periods, have an attenuation coefficient sufficient for ultrasound imaging, and do not show signs of drying out after a week on a skin-mimicking phantom.

Research Question 4

How can the interface materials be evaluated for skin biocompatibility?

From the interviews with experts on medical devices, how to validate the material was derived; it had to be tested against ISO 10993, listed in the approved cosmetic products or had an intended use in medical applications. However, to fully evaluate the skin compatibility of these materials, patch tests on the skin still need to be conducted.

10 Recommendations

This chapter provides a brief overview of the primary recommendations for the future continuation of this research project.

In the process of developing a phantom that mimics skin properties such as water loss and temperature, PVA was deemed not appropriate for this type of model. This is due to the amount of water evaporation of PVA, which was too little to regulate with a top layer but too much to mimic skin. Also, the PVA material started to 'melt' and shrink after af 1-2 hours in an oven at T= 34°C. However, PVA is a very suitable material for ultrasound phantoms; it has a low attenuation coefficient and stays stiff at room temperature for a few hours, but not for days. For other applications, this could be a good alternative.

For future recommendations, it is suggested that the lifetime experiments be repeated using the phantom model for these six different interface materials. It could also be an option to renew the hydration layer every seven days to prevent the agar layer from dehydrating over the acceptable limit if the experiment requires longer periods. To further examine the lifetime performance of potential acoustic interface materials it is recommended to do longer-duration experiments. Since, during the eight days duration of the experiment conducted in this thesis, the acoustic interface materials did not show clear signs of dehydration or degradation.

While doing the interviews with the medical professionals in the hospitals, it was apparent that there were applications for wearable ultrasound devices in all three departments: cardiology, plastic surgery, and dermatology. A recommendation for the future is for TNO Holst and/or the TU Delft to engage in conversations with such doctors so that innovative and purposeful collaborations can be formed.

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