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d-LIVER

ICT-enabled, cellular artificial liver system incorporating personalized patient management and support

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D4.1: Report on choice of appropriate polymer materials for fluidic systems

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1. Executive Summary

Within Workpackage WP4 “Microfluidics, packaging and integration”, two different fluidic systems will be developed: (i) a microfluidic cartridge for the blood biochemistry instrument and (ii) a closed-loop control of the bio-artificial liver support unit. For that purpose, suitable polymer materials as well as potential coatings were identified within the scope of the present deliverable D4.1 “Report on choice of appropriate polymer materials for fluidic systems”.

In the first main part of this document, important terms like “biocompatibility” and “haemocompatibility” associated with D4.1 are defined in a first instance. Additionally, safety assessment requirements for medical devices were briefly reviewed on the basis of regulations like various EU directives, the international standard ISO 10993 and the guidelines of Unites States Pharmacopeia Class VI.

In the subsequent second part, suitable polymer materials for the fluidic devices were identified with regard to processability and performance. Polycarbonate proved to be the most favourable material. Specifically, micromilling, injection moulding, solvent bonding and γ-sterilization can be applied to this material. Furthermore, adequate types are optically transparent, acceptably hydrophilic, bio- and haemocompatible, comparatively cheap and already tested at IMM.

In the case that the fluidic cartridges have to be coated due to undesirable unspecific adsorption processes, suitable coating materials and strategies were ascertained in the final third part. In detail, a surface passivation, using a polyethylene oxide based coating, was found to meet optimally the requirements.

2. Introduction

The essential aim of d-LIVER is the "development of ICT-enabled bio-artificial liver support systems with associated remote monitoring to assist in the treatment and management of liver patients in care settings extending from the hospital to the home".[1] Among other things, this includes the development of equipment for analysis of biological parameters. Specifically, d-LIVER targets the following topics:

1.) "Sensor-based monitoring of patient health status at home, concentrating on […] discrete measurement of a defined set of biochemical species."
2.) "Monitoring and control of the bio-artificial liver."[1]

For these two purposes, a blood biochemistry instrument, which monitors eight different patient blood parameters (System 1) and a closed-loop control of the bio-artificial liver support unit, which measures parameters associated with bio-artificial liver performance and functionality (System 2), will be developed. Both systems will be based on microfluidic cartridges which will accommodate adequate mechanical, optical, fluidic and electrical interfaces to the whole instrument as well as suitable sensors, valves and membranes. Special attention has to be paid to the selection of all materials of these two systems, which will be in direct contact with the biological samples, since they have to meet a number of additional basic requirements:

- Due to contamination issues, they have to be disposable.
- The disposable material itself may not contaminate the samples, since blood samples circulating through the bio-artificial liver will be returned to the patient, i.e., it has to be biocompatible. In addition, measurements could be falsified in case of contaminated samples.
- The materials have to be applicable to continuous re-use for a defined period of time
- In order to avoid non-specific binding of blood components and thus e.g. blood clotting, all materials have to be haemocompatible. Alternatively, suitable haemocompatible coating materials could be utilized.

Taking into account these and further requirements (e.g. mechanical, chemical), which will be specified later, suitable polymer materials for the systems 1 and 2 will be identified within the present deliverable D4.1.

The following discussion will be divided into three main chapters: (i) Existing relevant regulations for medical applications in relation to biocompatibility and haemocompatibility will be reviewed. (ii) Suitable polymer materials for the microfluidic cartridges will be identified as well as (iii) potentially required appropriate coating materials.

3. Basic information about medical devices

In the previous paragraph, essential requirements of materials, being in contact with biological samples, were introduced. In this section, related definitions and regulations will be overviewed which one has to keep in mind, when looking for suitable polymeric materials.

3.1. Biocompatibility

Currently, there is no standardized strict definition of the term biocompatibility.[2] Generally, this term is used to describe the compatibility of a material or a medical product with biological systems, e.g. the tissue or physiological system of a patient. A material or a product is regarded as biocompatible if it performs its desired function without causing deleterious changes in the body. Depending on the particular application, a variety of tests, as defined in USP (United States Pharmacopoeia) Class VI or ISO 10993 (see below), have to be conducted in order to identify biocompatibility.

3.2. Haemocompatibility

Haemocompatibility is a sub-area of biocompatibility. Similar to biocompatibility, the term haemocompatibility has not been defined in an unambiguous manner. Generally it describes the impact of a material, when contacting blood, i.e. haemocompatible materials ideally are not "detected" as foreign object or do not harm blood components. Hence, such materials do not elicit blood clotting for instance. According to the ISO standards, haemocompatibility covers the categories haemostasis, haematology and immunology.[3]

3.3. Regulations

Medical devices sold in the EU have to be in compliance with the EU directives 93/42/EEC (medical devices), 98/79/EC (in-vitro-diagnostics) and 90/385/EEC (active implantable medical devices). For d-LIVER, the latter directive for implantable devices is irrelevant. However, the first two directives have to be taken into account, since within d-LIVER medical devices and in-vitro diagnostics in terms of those directives will be developed. Specifically, instruments for (i) monitoring of diseases and (ii) in-vitro analysis of blood are for instance medical devices and in-vitro diagnostics, respectively. The directives have been transposed in turn into national laws of the EU members, e.g. the "Medizinproduktegesetz (MPG)" governs the commerce of medical devices in Germany.

The directives mentioned above specify safety assessment requirements of medical devices in order to assure that patients are not exposed to unnecessary risks. According to directive 93/42/EEC, biological assessment is always mandatory when the patient is in close contact with the medical product or material. The directive uses the safety assessments of the international standard ISO 10993 (Biological Evaluation of Medical Devices) as a method to define the testing required for various devices that are directly or indirectly in contact with the body or body fluids ("biocompatibility tests"). It is divided into the following 19 parts:

- 10993-1: Evaluation and testing within a risk management process
- 10993-2: Animal welfare requirements
- 10993-3: Tests for genotoxicity, carcinogeniticity and reproductive toxicity
- 10993-4: Selection of tests for interactions with blood
- 10993-5: Tests for in vitro cytotoxicity
- 10993-6: Tests for local effects after implantation
- 10993-7: Ethylene oxide sterilization residuals
- 10993-9: Framework for identification and quantification of potential degradation products
- 10993-10: Tests for irritation and skin sensitization
- 10993-11: Test for systemic toxicity
- 10993-12: Sample preparation and reference materials
- 10993-13: Identification and quantification of degradation products from polymeric medical devices
- 10993-14: Identification and quantification of degradation products from ceramics
- 10993-15: Identification and quantification of degradation products from metals and alloys
- 10993-16: Toxicokinetic study design for degradation products and leachables
- 10993-17: Establishment of allowable limits for leachable substances
- 10993-18: Chemical characterization of materials
- 10993-19: Physico-chemical, morphological and topographical characterization of materials
- 10993-20: Principles and methods for immunotoxicology testing of medical devices

Originally, the standards of ISO 10993 were supposed to supersede the guidelines of the Unites States Pharmacopeia Class VI (USP class VI), which also define methods of biocompatibility testing for medical devices. However, the standards of USP class VI are still frequently used for biological assessment of polymeric materials.

For the development of medical devices, materials manufacturers often offer so-called "medical grade" materials. The attribute "medical grade" indicates that the material complies with various requirements for medical devices,[4] e.g. it already passed certain tests according to ISO 10993 or USP class VI. Usually, medical grade materials also satisfy regulations of food contact materials as defined by the U.S. Food and Drug Administration (FDA) or in different EU directives for instance. This demonstrates the toxicological innocuousness of the raw materials, even though this is not mandatory for medical devices.

3.4. Conclusion

All materials used in a medical device have to meet a number of requirements. They basically have to be: (i) biocompatible to the levels necessary for the particular application and (ii) in compliance with various legislative requirements.

At this stage of d-LIVER it is reasonable to choose appropriate polymer materials for fluidic systems, which in particular already comply with parts of ISO 10993 and / or USP class VI (e.g. medical grade polymers). This ensures that the materials meet the necessary degree of biocompatibility and already observe the legal requirements. Note that manufacturers also frequently offer polymeric materials not yet tested according to ISO 10993 or USP class VI, which does not coercively mean that they are not biocompatible and inapplicable in medical devices. Thus, also such polymers could be chosen for d-LIVER, if necessary, even though this would come along with additional tests on biocompatibility and therefore would not be a preferable solution.

Apart from standardized biocompatibility tests for the materials themselves as elucidated above, the final integrated medical device has to be tested with respect to the particular application, in order to ensure compliance with the respective EU directives.

4. Choice of appropriate polymer materials

4.1. Processability of polymers

The right choice of suitable polymer materials for the microfluidic cartridges, which will be developed within WP4, is a critical issue in order to ensure manufacturability, performance and biocompatibility. Therefore, a list of polymers already used in microfluidic devices[5] together with critical properties relevant for their processability was compiled as illustrated in Table 1 in a first instance. Note that the properties evaluated in the table can vary significantly depending on producer and material grade, due to the influence of additives. The assessment therefore applies for most common polymer grades.[5]

Table 1: Polymeric materials used in microfluidic devices and their eligibility for selected processing techniques. Indexed information is extracted from literature. Unsubscripted information is IMM-knowledge ("+" = suited, "±" = conditionally suited, "–" = not suited).

Material	*Solvent bonding*	*Injection moulding*	*Micromilling*
COC (Cyclic Olefin Copolymer)	+	+[5]	+
PC (Polycarbonate)	+	+[5]	+[5]
PDMS (Polydimethylsiloxane),	–	–[5]	–[5]
PEEK (Polyether Ether Ketone),	–	+[5]	+[5]
PET (Polyethylene Terephthalate)	–	+[5]	+[6]
HDPE (High-Density Polyethylene)	–	+[5]	+[5]
LDPE (Low-Density Polyethylene)	–	+[5]	–[5]
PI (Polyimide)	–	–[5]	+[5]
PMMA (Polymethyl Methacrylate)	+	+[5]	+[5]
PS (Polystyrene)	+[7]	+[5]	±[5]
PTFE (Polytetrafluoroethylene)	–	–[5]	–[5]
PVC (Polyvinyl Chloride)	–	+[5]	+[5]
PVDC (Polyvinylidene Chloride)	±	–[5]	±
PVDF (Polyvinylidene Fluoride)	–[7]	+[5]	–[5]
PP (Polypropylene)	–	+[8]	–
COP (Cyclic Olefin Polymer)	+	+[9]	+
PSU (Polysulfone)	+[10]	+[11]	+[12]
POM (Polyoxymethylene),	–	+[11]	+
PBT (Polybutylene Terephthalate),	–	+[11]	+[13]
LCP (Liquid Crystal Polymer)	–	+[14]	+[15]
PA (Polyamide)	–	+[16]	+[17]
PEI (Polyetherimide)	+[7]	±[18]	+[19]

The material most suitable for the development of d-LIVER cartridges should in the first instance be machinable via micromilling, enabling rapid prototyping and thus a fast and flexible development of single microfluidic cartridges. However, for the fabrication of a large number of pieces, which will be necessary for evaluation studies in a second step, micromilling is too time-consuming and therefore not acceptable. In contrast, injection moulding is capable of mass-production, i.e., large quantities of directly usable mouldings can be produced very quickly with high precision. Hence, injection moulding compatibility is also a desirable property of the cartridge material selected for d-LIVER.

Almost all microfluidic devices are based on fully enclosed and sealed microfluidic structures. By means of micromilling and injection moulding, however, only open fluidic structures can be produced. This implies that additional bonding and sealing techniques have to be applied for the assembly of a complete microfluidic device.[5] Various methods of polymer bonding have been used in the past, which frequently either rely on an additive mediated bonding or on sophisticated techniques. However, for d-LIVER it is highly desirable to: (i) limit the number of

materials which will be in contact with the biological samples to as few as possible, due to contamination issues and (ii) apply well-established bonding techniques. Hence, "solvent bonding" seems to be the best compromise for polymer joining, since IMM is adept in this technique and since the only additive in this case is an organic solvent, which should be more or less volatilized in the final cartridge. Alternatively, the polymeric devices could also be sealed via laser welding, which should be applicable to all thermoplastics. For the implementation of this technique, however, these thermoplastics usually have to be blackened by dispersed soot particles, giving rise to possible contamination problems and to limitations for optional subsequent optical detection methods.

Taking into account these basic restrictions of the polymer cartridge material, i.e. the suitability for micromilling, injection moulding and solvent bonding, only a few of the polymers listed in Table 1 come into consideration. Accordingly, the polymers best suited from the point of view of processability are:

- COC (Cyclic Olefin Copolymer)
- PC (Polycarbonate)
- PMMA (Polymethyl Methacrylate)
- COP (Cyclic Olefin Polymer)
- PSU (Polysulfone)

If necessary, materials like PS (Polystyrene) or PEI (Polyetherimide), which exhibit restrictions associated with micromilling and injection moulding, respectively, might also be an option.

4.2. Performance of selected polymers

On the basis of Table 2, the best processible cartridge materials (PC, PMMA, PSU, COC, COP) will be analysed further in the following, in particular with respect to their expected performance in system 1 and 2. Note that – similar to Table 1 – the assessment of polymer properties like transparency, biocompatibility, etc. can vary depending on manufacturer and the specific type of polymer. Specifically, bio- or haemocompatible polymers should be understood as polymers, where specific types are available on the market in a quality, that complies with parts of ISO 10993 and USP class V. This does not mean, however, that all types of the same polymer necessarily meet these requirements.

As already mentioned above, the material for the bioanalytical cartridges should be bio- and haemocompatible. Specifically, it should prevent harmful contamination and changes of the samples in order to: (i) allow a safe return of the sample to the patient where necessary and (ii) ensure an undisturbed and sensitive detection of all relevant biological parameters. There are bio- and haemocompatible products based on all polymers listed in Table 2 on the market, making them equally suited for a possible application in a first instance.

A criterion that is in general linked with the extent of haemocompatibility is hydrophilicity. A high hydrophilicity is a highly desirable property due to two main reasons: First, hydrophilic materials usually interact little with proteins or blood[3] and thus frequently exhibit a better haemocompatibility. Second, if applied in microfluidic devices, such materials ease microfluidic operation (in case of a hydrophilic liquid), e.g. by inherent prevention of bubble formation. From this point of view, PSU is more favourable than COC, PC, PMMA and COP. However, a comparison with the water contact angles, which are 71°[20] for PSU, 92° for COC, 82°[20] for PC, 80°[21] for PMMA and 93° for COP, shows that the resulting differences are rather small.

Properties that might also be relevant for the final polymer cartridge are optical transparency, autofluorescence and possibility of sterilization. Optical transparency and absence of

autofluorescence are essential in case of applying optical detection methods. Sterilization methods might be necessary, in particular, when samples are returned to the patient. Among other possibilities such as ethylene oxide or steam sterilization, sterilization by gamma radiation is the most reasonable method to sterilize microfluidic chips, since the entire enclosed microfluidic channel-structure is only accessible by radiation and not by material flow (sterilization prior to the bonding process makes no sense). PC, PMMA, PSU, COP and COC should basically all be suited for gamma sterilization as well as for optical detection methods. However, PSU exhibits minor limitations regarding optical transparency and possibly autofluorescence, for which no data was available.

Table 2: Suitability of selected polymer materials for bioanalytical devices. Indexed information is extracted from literature. Unsubscripted information is IMM-knowledge ("+" = suited, "±" = conditionally suited, "–" = not suited).

Material	*Biocompatible*	*Hemocompatible*	*Hydrophilicity*	*γ-Sterilization*	*Optical transparency*	*Autofluorescence*	*Cost*	*IMM experience*
PC	+[22]	+[23]	±[20]	+[22]	+[5]	+[5]	+[5]	+
PMMA	+[24]	+[24]	±[21]	+[25]	+[5]	+[5]	+[5]	+
PSU	+[26]	+[26]	+[20]	+[27]	±[12]	?	–[28]	–
COC	+[29]	+[29]	±	+[29]	+[29]	+[5]	±[5]	+
COP	+[30]	+[30]	±	+[31]	+[9]	+[9]	±	+

For many potential applications of bioanalytical devices, especially in disposable parts of point-of-care devices, high material costs are not acceptable. Specifically, this applies also to d-LIVER cartridges, which should on the one hand be disposable and on the other be suited for mass-production. Even slightly higher material costs would rapidly add up and significantly increase production costs and ultimately medical treatment costs for the patient. In order to ensure a cost-efficient solution, it is therefore highly desirable to use materials in such cartridges which are as cheap as possible. From such an economical point of view, PSU is the least favourable of all materials listed in Table 2. In contrast, costs for PMMA and PC are similarly low.

IMM has lot of knowledge in the processing and development of microfluidic bioanalytical devices made from various polymeric materials. However, PSU has not been used for such purposes up to now at IMM. In order to reduce the risk of unpredictable problems associated with the use of a completely new material, it is advisable to use well tested materials like PC, PMMA, COC or COP.

4.3. Conclusion

All in all, PC and PMMA should be the most promising and suitable materials for d-LIVER devices. They ensure both a good processability and an excellent performance combined with low costs as discussed in the first and second part of the present section, respectively (cf. Table 1 and Table 2). Therefore, it is recommended to use these materials for the development of the bioanalytical cartridges. Specifically, it is suggested to use PC as starting point, since PC is already approved in applications related to d-LIVER, e.g. in components of dialysis machines.[4] It is further suggested to use PMMA as an adequate fall-back option, in particular when very small channel structures on the microfluidic chips are required (the minimal producible size is limited by the efficiency of the solvent bonding process, which is maximal for PMMA). Depending on the course of the project, COC and COP might be further justifiable possibilities. Compared to PC and PMMA, they exhibit similar beneficial properties, however, at slightly increased costs.

5. Surface Coating

5.1. Interaction between surfaces and blood

In the previous chapter, the discussion about suitable polymer materials for the bioanalytical devices was basically confined to bulk properties. However, whenever a biological sample (blood) is transferred into such a device, it does not come into contact with the bulk, but with surfaces, which are known to play a decisive role for bio- and in particular haemocompatibility. Thus, even though both materials proposed before (PC, PMMA) exhibit promising (bulk) properties, it might still be necessary to implement an adequate surface coating.

There are different features that govern the interaction of blood with a surface, such as blood composition, blood flow and the surface of the contacted material. The latter is characterized by distinct physical and chemical properties like roughness, crystallinity, hydrophobicity/hydrophilicity, outermost structure and surface chemistry.[3,32] Specifically, smooth, hydrophilic and uncharged surfaces have turned out to be frequently advantageous for haemocompatibility for instance.[3]

When blood is exposed to a foreign material, the initial step is usually the unspecific adsorption of proteins or other molecules, often referred to as “biofouling”. This adsorption leads to further biological processes like cell adhesion or activation of enzyme cascades of coagulation, i.e. blood “recognizes” the foreign surface as injury and reacts basically with coagulation in order to close the assumed vascular damage.[2,3] In a bioanalytical cartridge, processes like adsorption of blood components and coagulation are highly undesirable, since they may cause a depletion of target molecules (decrease of device sensitivity) or even a device failure, respectively.[5,33]

5.2. Strategies of surface coating

In order to circumvent such problems, surfaces have to be modified in a way that blood does not “recognize” them as foreign. This can be achieved to some extent by the following three strategies: (i) passivation of the surface in order to minimize the interaction with blood cells and proteins; (ii) surface immobilization of bioactive molecules; and (iii) promotion of the growth of endothelial cells, forming the natural inner lining of blood vessels.[3]

5.2.1. Surface passivation

The interaction between blood proteins and a surface can be minimized by applying an inert coating to the surface. In many cases such inert coatings are polar, electrically neutral and possess hydrogen bond acceptors.[2] Inorganic coatings based on metal oxides or nitrides as well

as organic ones based on polyethylene oxide (PEO), parylene or albumin have been shown to improve biocompatibility for instance.[5]

For a possible implementation in polymeric d-LIVER cartridges, inorganic coatings are not convenient, since they usually require extensive or harsh preparation procedures, which is not worthwhile for low cost polymer disposables. Hence, inorganic coatings are generally used to coat metallic devices for long-term use, such as medical implants. Except for parylene coatings, which are deposited via chemical vapour deposition (CVD), organic PEO or albumin coatings usually require comparatively mild and easy preparation procedures in contrast. From this point of view, both PEO and albumin could be possible coating materials for bioanalytical d-LIVER devices. However, albumin coatings suffer from various problems, in particular associated with shelf life, degradation and sterilization, which basically results from its proteinaceous nature. In contrast, PEO coatings usually exhibit excellent stability, robustness and biocompatibility. As a result, PEO coatings have been already used in dialysis membranes.[3]

5.2.2. Bioactive Coating

Coating a surface with specific bioactive molecules in order to promote a favourable reaction is another strategy to improve the haemocompatibility of surfaces. Specifically, anticoagulants, immobilized on a surface, can inhibit thrombin, the most important enzyme of blood clotting. Prominent examples for this approach are coatings based on the anticoagulant heparin, an indirect thrombin inhibitor, which is able to produce thrombin-resistant surfaces.

Similar to coatings based on albumin, bioactive coatings frequently suffer from problems associated with degradation processes, sterilization and shelf stability. The use of such coatings in bioanalytical d-LIVER devices is therefore primarily not advisable, provided that there are superior alternatives.

5.2.3. Promotion of endothelial cell growth

The haemocompatibility of surfaces can also be improved by mimicking the inner lining of blood vessels, which consists of endothelial cells. In detail, this can be achieved by surface immobilization of extracellular matrix compounds, supporting adhesion and growth of endothelial cells.

This approach, however, is just mentioned for the sake of completeness, because it is not suitable for d-LIVER due to the following main restrictions (there are even further ones not specified subsequently). First, the cells used are autologous endothelial cells, i.e. they are specific to a patient, meaning that this approach is rather more feasible for implants than for disposable bioanalytical devices. Second, endothelial cells cultivated on microfluidic cartridges would not survive a solvent based bonding process as described above as well as ordinary storage conditions.

5.3. Conclusion

In conclusion, there are different strategies to coat surfaces for the purpose of improving their haemocompatibility. For cartridges developed within d-LIVER, it is recommended to apply the approach of surface passivation, provided that surface coating is necessary. Specifically, PEO-based coatings are most favourable, since they combine ease of preparation with sufficient performance.

6. Summary and conclusions

With relevant regulations in mind, in particular ISO 10993 and USP class VI, suitable materials for the blood biochemistry instrument and the closed-loop control, which should be developed within d-LIVER, were identified with regard to processability and performance. As a result, PC is particularly recommendable, with PMMA as a fall-back option. In the course of d-LIVER, it could further turn out that surface coatings to enhance biocompatibility are still necessary. For this case, suitable strategies and coatings were identified. Specifically, the passivation of surfaces via PEO based coatings is recommended for that purpose.

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