Ph.D. theses

# Development of functional polymers for self-healing applications and controlled drug delivery

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# 1. Introduction and objectives

Polymers and plastics constitute one of modern society's most important and versatile classes of materials. Owing to significant strides made over the past decades, their range of applications has continuously expanded, rendering them indispensable in most areas of industry and everyday life. The rapid development of polymer chemistry has fundamentally changed the way macromolecular materials are perceived: whereas earlier research primarily focused on the production of structural materials with appropriate physical and mechanical properties (strength, toughness, fire resistance, etc.), nowadays, there is a growing interest in designing functional polymers, i.e. polymeric materials with special electrical, magnetic, optical, biologically relevant, etc. properties. This paradigm shift of considerable scientific and historical significance has been brought about by the emergence of novel polymerization techniques, post-synthetic modification strategies and computer-assisted molecular design, which together enable precise control over macromolecular structure and functionality. As a result, polymers have come to play a pivotal role in the field of biomedical engineering, electronics, energy, as well as in environmental applications.

For applications requiring a precise combination of properties, it is essential to modify the polymer at the core of the functional system. For this reason, modern materials science increasingly targets polymers with properties that can be tailored in a controlled and versatile manner. Amid this multiplicity of macromolecular materials, however, one polymer in particular stands out: poly(vinyl alcohol) (PVA). PVA has become one of the most extensively studied polymers due to the combination of highly attractive characteristics, including excellent film-forming ability, biocompatibility, biodegradability, water solubility, relative ease of modification, etc. These qualities make PVA a preferred material across many industries, from biomedical technologies to electronics, food processing, construction, pharmaceuticals, cosmetics, and packaging. Despite all these advantages, however, PVA-based products suffer from several serious limitations: the high density of hydroxyl groups renders these materials in their pristine form highly sensitive to water, leading to pronounced swelling and generally inadequate mechanical performance, which can significantly shorten their service life. The overarching goal of modifying PVA, therefore, is not merely to overcome these shortcomings, but to do so while maintaining the advantages – biocompatibility, biodegradability, non-toxicity, processability, etc. – that make the polymer valuable in the first place. Building on this objective, the present work was directed towards developing modification strategies that address PVA's limitations while retaining its promising features.

To address the challenges outlined above, the first part of the present work aimed at developing a PVA-based functional material cross-linked by reversible covalent bonds with the ability to self-heal after sustaining mechanical damage and with thermo-mechanical properties that can be tuned by adjusting the cross-link density. To achieve this, a simple one-pot synthetic approach was employed which, to the best of our knowledge, has not previously been utilised for this purpose. During the modification of PVA, small amounts (0.89–7.12 mol%) of low-molecular-weight compounds bearing formyl and amino groups capable of forming dynamic imine bonds by reacting with each other were incorporated into the macromolecular chains via Steglich esterification. Following confirmation of successful functionalisation, our objective was to investigate the influence of the degree of modification on the mechanical and thermal properties of PVA, and to characterize the self-healing performance of the resulting systems using both qualitative and quantitative methods.

The second part of this study focused on tailoring the wetting properties of PVA. Since both chemical composition and surface roughness determine how water interacts with solid surfaces, PVA was hydrophobised via silanization, while the desired surface texture was achieved by the addition of biocompatible cellulose particles. These modifications transformed the initially highly hydrophilic, water-soluble polymer into a material suitable for the formation of thin films with extremely low wettability. Further objectives included investigating the impact of film composition on wettability and demonstrating that, by finding the optimal composition, the thin films can be converted into controlled drug delivery systems. The practical relevance of this concept was illustrated using mitomycin C (MMC) as a model drug. MMC is a widely used chemotherapeutic agent with moderate water solubility, which, when administered in its free form, is rapidly eliminated from the body. As a result, ensuring therapeutic efficacy often requires relatively high doses and frequencies of administration, which in turn increases the risk of severe side effects. Encapsulation of the drug into composite thin films with tunable wetting characteristics offers a way to modulate its release profile. This enables the maintenance of a more consistent plasma concentration within the therapeutic range over a longer period of time, thereby reducing the likelihood of adverse reactions.

## 2. Experimental

In the first part of my PhD work, a homogeneous, single-component macromolecular system capable of local and autonomous self-healing at ambient conditions, using atmospheric moisture as an external stimulus was developed. To impart dynamic self-healing ability, low concentrations (0.89–7.12 mol%) of 4-formylbenzoic acid (4-FBA) and 3,4-diaminobenzoic acid (3,4-DABA) – small molecules bearing formyl and amino groups capable of forming reversible imine linkages by reacting with each other – were introduced into PVA via a one-pot synthetic method based on Steglich esterification. The reaction was carried out in dimethyl sulfoxide in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). After removing the by-product, concentrating the reaction mixture, and precipitating the polymer, the product was isolated by centrifugation and dried at room temperature until constant mass was achieved. For control, samples with comparable degrees of functionalisation (0.89–7.12 mol%) containing either formyl or amino groups were also prepared. Next, free-standing films were fabricated from native PVA and its derivatives using the solvent casting technique. The chemical composition, the crystallinity and the thermal properties of the cast polymer films were investigated employing infrared spectroscopy (ATR-FTIR), X-ray diffractometry (XRD), and differential scanning calorimetry (DSC) and thermogravimetry (TG), respectively. Bulk and surface processes occurring during self-healing were studied by X-ray microtomography (micro-CT), digital microscopy, and scanning electron microscopy (SEM). To determine the mechanical properties and self-healing efficiency, the films were subjected to uniaxial tensile testing.

The second part of my work focused on the preparation of composite thin films with composition-dependent wettability. For the fabrication of the samples, the matrix material (PVA) was first hydrophobised to a varying extent using a hexane-based silanization solution containing systematically varied amounts (0.01–2 vol%) of n-butyltrichlorosilane (BTS). After completion of the reaction, the liquid phase was removed by decantation, the modified polymers (BTS–PVA) were washed with hexane, and then dried at 50 °C. The success of the silanization reaction was confirmed by IR spectroscopy. The hydrophobic character of the samples (after swelling in distilled water) was verified by TG measurements, while the degree of hydrophobisation was quantified using a titrimetric method based on the acetylation of residual free hydroxyl groups with acetic anhydride. The solubility of both hydrophobised and unmodified PVA was determined gravimetrically in water as well as in a 10 vol% ethanol–water solvent mixture.

Thin films containing 0.25 wt% of the model drug MMC (with respect to the combined dry mass of the polymer and the cellulose mixture) were prepared by solvent casting from PVA treated with a silanizing solution containing 1 vol% BTS (1% BTS–PVA) and from the native polymer. Firstly, for the preparation of the casting solution, the polymers were dissolved in a 10 vol% ethanol–water solvent mixture, after which the required amount of MMC was added to the obtained solutions. To generate surface roughness, varying amounts (0–95 wt%) of a cellulose mixture ("roughening agent") were introduced into the MMC/polymer solutions. The roughening agent consisted of the 1:1 mass ratio physical mixture of cellulose powder (20–150 μm) and microcrystalline cellulose (~20 μm). After thorough homogenization, the MMC/polymer/cellulose suspensions were cast into Petri dishes and dried at 60 °C to constant mass. Drug-free thin films of identical composition were also prepared to serve as control samples. The physical state of the model drug embedded in the films was determined by XRD. Surface morphology was characterized by SEM, surface roughness by contact profilometry, film thickness by a digital profile gauge, and porosity by micro-CT. The the wetting behavior of the samples was analysed by static and dynamic contact angle measurements, while the apparent surface free energy values were calculated using the method of Drelich and the Owens–Wendt–Rabel–Kaelble model. During *in vitro* dissolution tests, the amount of MMC liberated from the dosage forms into the medium (phosphate-buffered saline, PBS) was monitored via UV–Vis spectrophotometry.

## 3. New scientific results

**T1. A facile and versatile functionalisation strategy was developed for linear poly(vinyl alcohol) (PVA), enabling the formation of reversible imine cross-links between polymer chains via the reactions of the introduced formyl and amino groups.**

**T1.1.** It was demonstrated that ester bonds could be formed in a one-pot manner between the hydroxyl groups of PVA chains and the carboxyl groups of 4-FBA and 3,4-DABA in the presence of DCC and catalytic amounts of DMAP.

**T1.2.** It was shown that this one-pot Steglich esterification approach enabled the degree of functionalisation of PVA ($M_w$ = 46.83 kDa, degree of hydrolysis = 86–89 mol%) to be tuned over a wide range (0.89–7.12 mol%).

**T1.3.** The simultaneous presence of formyl and amino moieties on the PVA chains led to the formation of Schiff base linkages between the linear macromolecules, as indicated by the appearance of new IR bands at ~1630 and ~1540 $cm^{-1}$. In contrast, control samples bearing only

one of these functionalities displayed solely the vibrational bands of the corresponding free functional groups, while the characteristic IR peaks of the imine bond were not observed.

**T2. It was demonstrated that the reversible nature of the imine bonds formed by the condensation reaction between the incorporated formyl and amino groups imparted self-healing capability to PVA.**

**T2.1.** X-ray microtomography (micro-CT), scanning electron microscopy (SEM), and digital microscopy clearly revealed that artificially damaged, i.e., bisected specimens, once wetted and rejoined, virtually fused together at room temperature within 24 hours: the dynamic imine bonds present in the samples enabled them to successfully restore their integrity, both in the bulk phase and on the surface.

**T2.2.** It was demonstrated that even a sample with a nominal degree of functionalization as low as 1.78 mol% was capable of complete regeneration, achieving a healing efficiency ($\eta$) of 175%[1] as determined by tensile tests, whereas pristine PVA – apart from minimal self-adhesion – exhibited no self-healing behavior ($\eta \sim 28\%$).

**T3. As a new scientific finding, it was demonstrated that the thermal and mechanical properties of the modified PVA can be tuned over a wide range by varying the nominal degree of functionalisation.**

**T3.1.** Thermal (DSC, TG) analysis and structural characterisation (XRD, FTIR) revealed that the incorporation of bulky substituents into the macromolecules had a pronounced effect on the polymer's thermal transitions ($T_g$, $T_m$). The glass transition temperature ($T_g$) of PVA decreased from 65.3 °C to 35.0 °C with increasing extent of modification, indicating the disruption of interchain hydrogen bonds by the bulky substituents and the consequent enhancement of chain mobility. Similarly, both the melting temperature ($T_m$, 195 °C → 170 °C) and the degree of crystallinity ($X_c^{DSC}$, 36% → 0%) – calculated from the heat of fusion values ($\Delta H_m$) obtained by integrating the melting peaks – exhibited a decreasing trend, consistent with the values estimated by XRD ($X_c^{XRD}$, 37% → 8%) and IR ($X_c^{FTIR}$, 46% → 9%) measurements.

**T3.2.** The appearance of an additional endothermic peak ($T_{crd}$) was also observed in the temperature range of 234–250 °C; its intensity increased progressively with the nominal degree of

[1] The healing efficiency ($\eta$) is a relative measure comparing the mechanical performance (here: the tensile strength) of the healed sample to that of the undamaged specimen. Values exceeding 100% can be attributed to the measurement configuration and to higher local mechanical load-bearing capacity arising from the rearrangement of the dynamic network.

functionalisation and was attributed to the cleavage of imine bonds and the subsequent rearrangement of the dynamic network. TG measurements indicated that the increasing extent of modification led to the reduction of the thermal stability of the polymer ($T_{deg}$ = 307 °C → 232 °C), which could be explained by the disruption of the crystalline domains and the concomitant increase in the amorphous fraction.

**T3.3.** It was demonstrated through uniaxial tensile testing that the mechanical properties of PVA could be tuned across a wide range by varying the nominal degree of functionalisation. As the amount of incorporated bulky substituents increased, the formation of ordered domains held together by hydrogen bonds became more and more hindered, resulting in a reduction in sample crystallinity (see T3.1). The decrease in hydrogen bond density, and thus chain rigidity, together with the gradual increase in imine cross-link density, transformed the initially brittle polymer into a softer, more viscoelastic material: the Young's modulus and the tensile strength decreased from 414.9 MPa to 3.44 MPa and from 34.46 MPa to 3.40 MPa, respectively, while the elongation at break increased from 12.13% to 130.25%.

**T4. It was shown that the hydrophobisation of the polymer chains, combined with the use of appropriate fillers, markedly reduced the intrinsic water solubility of PVA, enabling the fabrication of thin films exhibiting extreme water-repellency (parahydrophobicity).**

**T4.1.** It became evident that even treatment with a silanizing solution containing as little as 1 vol% n-butyltrichlorosilane (BTS) is sufficient to markedly reduce the solubility and wettability of the inherently hydrophilic, water-soluble PVA. By incorporating a filler composed of a 1:1 mass ratio physical mixture of cellulose powder (0.02–0.15 mm) and microcrystalline cellulose (20 μm) – and by finding the optimal filler content (20–95 wt%) –, free-standing composite thin films with extreme water-repellent character ($\Theta^*$ > 150°) could be prepared from the modified polymer (1%BTS–PVA).

**T4.2.** SEM micrographs revealed that increasing the proportion of the "roughening agent" (0, 20, 40, 60, 80, 90, and 95 wt%) in the polymer matrix (PVA and 1%BTS–PVA) resulted in the formation of solvent-cast thin films with more and more textured and porous surfaces.

**T4.3.** It was further shown that the use of fillers composed of particles of different sizes (20 μm and 0.02–0.15 mm) led to the simultaneous appearance of coarse, micrometer-scale protrusions and finer topographical features on the surface of films containing ≥60 wt% filler, indicating the formation of hierarchical surface roughness. As a result, both the arithmetic mean roughness ($R_a$) determined by contact profilometry (e.g., PVA100/CK0: 0.02±0.01 μm → PVA10/CK90: 31.6±4.8 μm) and the porosity values calculated from micro-CT data (e.g., 1%BTS-

PVA100/CK0: 0.7% → 1%BTS-PVA40/CK60: 64.9%) increased systematically with increasing cellulose content.

**T4.4.** According to the results of static contact angle measurements, the composite thin films exhibited composition-dependent wetting behaviour. Increasing the filler content amplified the intrinsic wetting characteristics through surface roughening: the inherently hydrophilic PVA films became superhydrophilic ($\Theta^*$= 60.3° → 0°) as the cellulose content increased, whereas the initially hydrophobic 1%BTS–PVA films gradually developed extreme water-repellent characteristics ($\Theta^*$= 97.4° → 168.2°). Dynamic contact angle measurements revealed that 1%BTS–PVA films at moderate/high filler loading (≥60 wt%) exhibited parahydrophobicity, a wetting behaviour characterised by high advancing angles ($\Theta_A$ = ~160°) and pronounced contact angle hysteresis ($\Delta\Theta = \Theta_A - \Theta_R$ = ~85°). The parahydrophobic nature of the surfaces was further evidenced by the apparent surface free energy values calculated from dynamic contact angle data (e.g., 1%BTS-PVA10/CK90, $\gamma_s^{tot}$ = 1.7±0.7 mJ/m$^2$).

**T5. As a novel scientific finding, it was demonstrated that PVA-based thin films exhibiting composition-dependent wettability can be successfully employed as vehicles for controlled drug delivery.**

**T5.1.** *In vitro* dissolution tests conducted under physiological conditions (PBS, pH ~ 7.4, 0.9 wt% NaCl, 37 °C) showed that the release rate of MMC from the composite thin films could be precisely controlled by varying the carrier composition, and thus the wetting characteristics of the surface. As anticipated, the dissolution rate of the drug embedded in the hydrophilic films (PVA100/CK0, PVA40/CK60) was substantially greater than that of its free form (~80%, $t$ = 8 hours, $k'_{MMC}$ = 1.49×10$^{-4}$ 1/s): 98% of the chemotherapeutic agent was liberated from the smooth PVA100/CK0 film over a two-hour period ($k'_{PVA100/CK0}$ = 2.8×10$^{-4}$ 1/s), whereas the MMC loaded into the thin film containing 60 wt% cellulose was almost immediately released (~100%, $k'_{PVA40/CK60}$ = 6.7×10$^{-4}$ 1/s). In contrast, the films prepared from the hydrophobized polymer (1%BTS-PVA100/CK0) displayed considerably slower dissolution rates (100%, $t$ = 8 hours, $k'_{1\%BTS-PVA10\ /CK0}$ = 8.0×10$^{-5}$ 1/s), while the parahidrophobic 1%BTS-PVA40/CK60 film showed strong retention of the drug, releasing only ~49% of the MMC over 8 hours ($k'_{1\%BTS-PVA40/CK60}$ = 3.7×10$^{-6}$ 1/s).

**T5.2.** XRD measurements revealed that the originally crystalline MMC was embedded in the polymer matrix in a partially amorphous form. This amorphous fraction represents a higher-energy, less stable form of the drug, in which the absence of lattice energy imposes no thermo-

dynamic barrier to dissolution. As a result, dispersing MMC in a hydrophilic polymer matrix promoted faster dissolution and significantly higher solubility (see T5.1), which is expected to enhance its bioavailability. In the composite thin films exhibiting (para)hydrophobic wetting characteristics, MMC also existed in its partially amorphous form; however, the extremely water-repellent nature of the matrix substantially hindered the water imbibition into the porous carrier, thereby decreasing the release rate of the partially amorphous drug (see T5.1).

## 4. Publications

Hungarian Science Bibliography (MTMT) identifier: 10071803

**Papers related to the thesis**

1. **T. Takács**, M.M. Abdelghafour, Á. Deák, D. Szabó, D. Sebők, I. Dékány, L. Róvó, Á. Kukovecz, L. Janovák, *Surface wetting driven release of antifibrotic Mitomycin-C drug from modified biopolymer thin films.* European Polymer Journal, 2020, 139: 109995.
   DOI: 10.1016/j.eurpolymj.2020.109995 SJR indicator: Q1
   Independent citations: 0 Impact factor: 4,598

2. **T. Takács**, M.M. Abdelghafour, Ł. Lamch, I. Szenti, D. Sebők, L. Janovák, Á. Kukovecz, *Facile modification of hydroxyl group containing macromolecules provides autonomously self-healing polymers through the formation of dynamic Schiff base linkages.* European Polymer Journal, 2022, 168: 111086.
   DOI: 10.1016/j.eurpolymj.2022.111086 SJR indicator: Q1
   Independent citations: 26 Impact factor: 6,0

3. **T. Takács**, M.M. Abdelghafour, D. Sebők, Á. Kukovecz, L. Janovák, *Structural and thermoanalytical characterization of self-healing polymer: the effect of cross-linking density.* Journal of Thermal Analysis and Calorimetry, 2024, 149: 2765-2775.
   DOI: 10.1007/s10973-023-12862-2 SJR indicator: Q2
   Independent citations: 6 Impact factor: 3,1

**Other papers**

1. R. Saker, O. Jójárt-Laczkovich, G. Regdon Jr., **T. Takács**, I. Szenti, N. Bózsity-Faragó, I. Zsupkó, T. Sovány, *Surface modification of titanate nanotubes with a carboxylic arm for further functionalization intended to pharmaceutical applications.* Pharmaceutics, 2023, 15: 2780
   DOI: 10.3390/pharmaceutics15122780 SJR indicator: Q1
   Independent citations: 1 Impact factor: 5,4

2. D. Szabó, L. Janovák, M.M. Abdelghafour, **T. Takács**, M. Csanády Jr., G. Spengler, L. Szakács, M. Csanády, L. Rovó, *Új minimálinvazív kezelési lehetőségek jó- és rosszindulatú fül-orr-gégészeti betegségekben nanoszerkezetű hatóanyag-leadó rendszerek alkalmazásával.* Orvosi hetilap, 2024, 165: 370-378.
DOI: 10.1556/650.2024.32978 SJR indicator: Q4
Independent citations: 0 Impact factor: 0,9

**Scientometric data**

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|---|---|
| Peer-reviewed publications: 5 | Related to the thesis: 3 |
| Cumulative impact factor: 19.998 | Related to the thesis: 13.698 |
| Independent citations: 33 | Related to the thesis: 32 |

**Conference presentations**

1. **T. Takács**, M.M. Abdelghafour, Ł. Lamch, I. Szenti, D. Sebők, L. Janovák, Á. Kukovecz, *Dinamikus Schiff-bázis kötéseken alapuló, öngyógyító tulajdonságokkal rendelkező polivinil-alkohol.* XLIV. Chemistry Lectures, Szeged (Hungary), October 26–27, 2021.

2. **T. Takács**, M.M. Abdelghafour, Ł. Lamch, I. Szenti, D. Sebők, L. Janovák, Á. Kukovecz, *Self-healing polyvinyl alcohol with dynamic Schiff base linkages.* Chemietage 2024, Graz (Austria), September 23–25, 2024.