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Synthesis, Properties, and Biomedical Application of Polyolefin-Polyglycerol Hybrid Systems

DISSERTATION

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Maike C. Lukowiak

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1. Gutachter: Prof. Dr. Rainer Haag

2. Gutachter: Priv.-Doz. Dr. Christoph Böttcher

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Für meine Familie.

A mi familia.

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Table of Contents

Abbreviations

2-BPB	2-bromopropinoyl bromide
A	absorbance
aq.	aqueous
ATR	attenuated total reflection
ATRP	atom transfer radical polymerization
A549	adenocarcinomic human alveolar basal epithelial cell line
BP	benzophenone
br	broad
BSA	bovine serum albumin
CAE	constant analyzer energy
cLSM	confocal laser scanning microscopy
CMC	critical micelle concentration
CMS	core-multishell
Cryo	cryogenic
CWC	chain walking catalyst
CWP	chain walking polymerization
δ	chemical shift (NMR)
DAPI	4,6-diamidino-2-phenylindole
DDS	drug delivery systems
DLS	dynamic light scattering
DMEM	Dulbecco's modified eagle medium
DMSO	dimethyl sulfoxide
dPE (DPE)	dendritic polyethylene
dPG	dendritic PG
dPGS	dPG sulfate
ε	molar extinction coefficient
EA	elemental analysis
E. coli	Escherichia coli
EPR	enhanced permeability and retention
eq.	stoichiometric equivalent(s)
EtOH	ethanol
FA	formaldehyde

FACS	fluorescence-activated cell sorting
FCS	fetal calf serum
FDA	US Food and Drug Administration
FIB	fibrinogen
FITC	fluorescein isothiocyanate
FM	Fairbrother-Mastin
FTIR	Fourier transform infrared spectroscopy
GA	glutaraldehyde
GPC	gel permeation chromatography
h	hour(s)
HDPE	high-density polyethylene
hPG	hyperbranched PG
HPLC	high-performance liquid chromatography
I	fluorescence intensity
ICI	Imperial Chemical Industries, Great Britain
λ	wavelength
LB	Luria-Bertani
LDPE	low-density polyethylene
lPG	linear PG
LS	light scattering
LYS	lysozyme
m	multiplet (NMR)
M	molar
MALLS	multi-angle laser light scattering
MAO	methylaluminoxane
MeOH	methanol
min	minute(s)
M_n	number-averaged molecular weight
MOPS	3-(*N*-morpholino)propane sulfonic acid
mPEG	poly(ethylene glycol) monomethyl ether
M_w	weight-averaged molecular weight
MW	molecular weight
MWCO	molecular weight cut-off
ND	nanodiamond

NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NR	Nile red
N-V	nitrogen-vacancy
OD	optical density
OEG	oligo(ethylene glycol)
OH	hydroxyl groups
ox.	oxidized
P. aeruginosa	Pseudomonas aeruginosa
PAMAM	poly(amido amine)
PBS	phosphate buffered saline
PDI	polydispersity index
PE	polyethylene
PEG	poly(ethylene glycol)
PEI	polyethyleneimine
PEO	poly(ethylene oxide)
PFA	paraformaldehyde
PG	polyglycerol
pH-CMS	pH-responsive CMS
PHEMA	poly(2-hydroxyethyl methacrylate)
POEGMA	poly(oligo(ethylene glycol) methacrylate)
PP	polypropylene
PPI	poly(propylene imine)
PPM	postpolymerization modification
PTFE	polytetrafluoroethylene
PY	pyrene
Q	quartile
RC	regenerated cellulose
Ref.	reference
RF	radio frequency
RI	refractive index
ROMBP	ring-opening multibranching polymerization
rpm	revolutions per minute
r.t.	room temperature

RTCA	xCELLigence real-time cell analyzer
s	second(s)
s	strong (IR)
SAM	self-assembled monolayer
SEC	size-exclusion chromatography
TBAF	tetrabutylammonium fluoride
TEM	transmission electron microscopy
TGA	thermogravimetric analysis
THF	tetrahydrofuran
TBDPS	*tert*-butyldiphenylsilyl
UCI	University of California, Irvine
UV	ultraviolet
Vol	volume
VUV	vacuum UV
w	weak (IR)
XPS	X-ray photoelectron spectroscopy
ζ	zeta potential

1 Introduction

1.1 Amphiphilic Polyolefin-Polyglycerol Systems

1.1.1 Polyolefins

Polyolefins, such as polyethylene (PE) and polypropylene (PP) (Figure 1), are a class of synthetic polymers with the simplest chemical composition which consists of only carbon and hydrogen atoms.[1] Polyolefins are made from the corresponding alkene (olefin) monomers, e.g., polyethylene is made from the monomer ethylene and polypropylene from propylene.

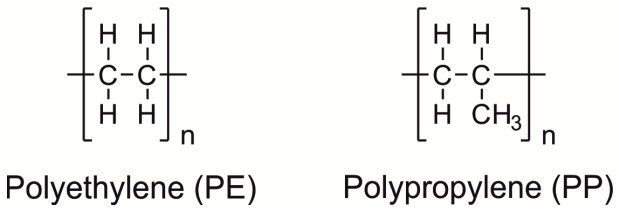


Figure 1. The two most common polyolefins polyethylene (PE) and polypropylene (PP).

Nowadays, more than 50% of all synthetically produced polymers worldwide are polyolefins with an annual production volume of 130 million tons in 2013 and an unbroken production increase.[1] This may be explained with the many advantages that polyolefins offer. They are inexpensive, light in weight, sustainable, recyclable, have outstanding processability, low production cost, offer a wide variety of properties, and the production needs only easily available and non-toxic monomers.[1] Today, many different types of polyolefins are available on the market, for example, high-density polyethylene (HDPE) or low-density polyethylene (LDPE). Many of the polyolefins have found daily use in packaging, but they have also found application in the biomedical field, which has been somewhat limited because of their strong hydrophobicity and non-biodegradability.[2–4] Traditionally, polyethylene was synthesized by high-pressure ethylene polymerization as invented by ICI (Imperial Chemical Industries, Great Britain) in 1935.[1] In contrast, the catalyzed olefin polymerization using titanium compounds like $TiCl_4$ and aluminum-alkyls, e.g., $[(C_2H_5)_2AlCl]$ as co-catalysts, which was developed by Ziegler and Natta in the 1950s, requires only low pressure and temperature.[1,5] Ziegler and Natta were both awarded with the Nobel prize in chemistry in 1963 for this achievement, and heterogeneous Ziegler-Natta catalysts have been globally very popular ever since.[1,5–7] There has been a push to develop and improve catalysts though, which has resulted

in the important discovery of homogeneous metallocene catalysts based on Ti, Zr, or Hf complexes and activated by methylaluminoxane (MAO) with only one active site (single site catalysts) and therefore leading to more defined polyolefin structures.[1,5,6,8] While historically, most catalysts' design has been focused on early transition metals, in the last two decades, late transition metals have also attracted the attention of many researchers.[8–12] Late transition metals have a high tendency to undergo β-hydride elimination reactions, which is, for example, used in the Pd-catalyzed Heck coupling reaction, but their ability to yield high molecular weight polyolefins is limited by the subsequent associative chain transfer of the olefin by the incoming monomer.[13] In 1995, Brookhart and co-workers made the seminal discovery that high molecular weight polyolefins could be obtained by Ni^{II}- and Pd^{II}-α-diimine complexes.[14,15] Even though the Ni^{II}-catalysts were more active, the Pd^{II}-catalysts could afford highly branched polyolefins and could tolerate and incorporate polar olefins.[16] The key insight was that the introduction of sterically bulky axial substituents on the α-diimine ligand retards the rates of chain transfer and can therefore lead to high molecular weights.[13,14,17] Brookhart and Fink both proposed that the observed branching formation in polyethylenes was caused by isomerization of the catalyst or by "walking" of the catalysts along the polymer backbone during the migratory insertion polymerization.[13,14,18] The proposed mechanism for chain walking polymerization (CWP) includes iterative β-hydride elimination, bond rotation, and retransfer of the hydride in opposite stereochemistry that leads to the chain walking of the Pd^{II}-catalyst (Figure 2).[13,14,18–20]

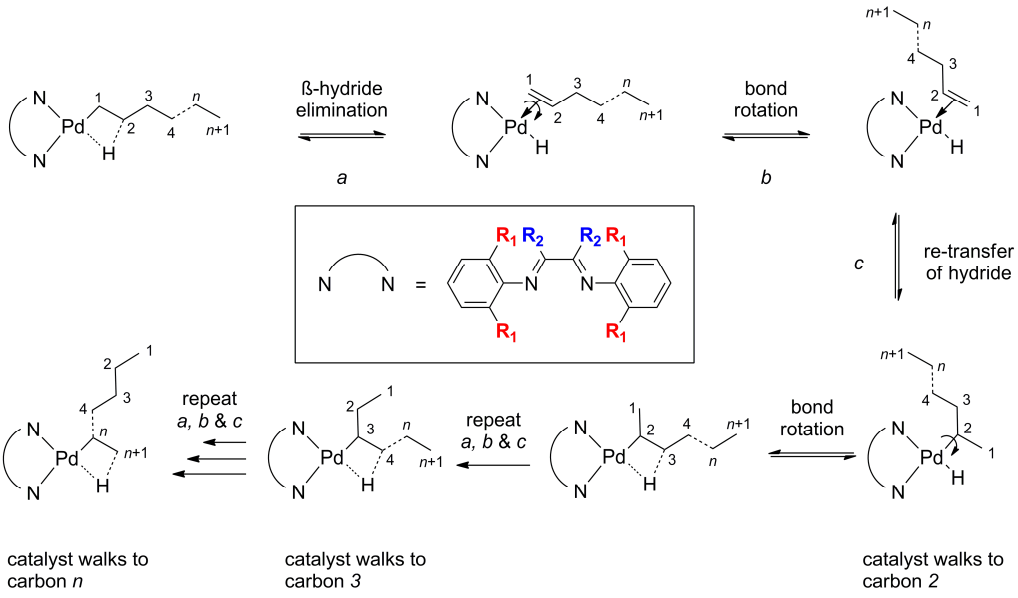


Figure 2. Proposed chain walking mechanism through iterative β-hydride elimination and hydride transfer. Figure adapted from the literature.[13,14,18–20]

Inspired by this breakthrough and motivated by the fact that the polymer architecture can strongly influence the polymers' properties, Guan et al. showed in 1999 that CWP can be used to control the polymers' topology (Figure 3).[19,20] Simply by changing the ethylene pressure, either linear polyethylenes with short branches, hyperbranched, or dendritic polyethylenes could be obtained (Figure 3, bottom).[20]

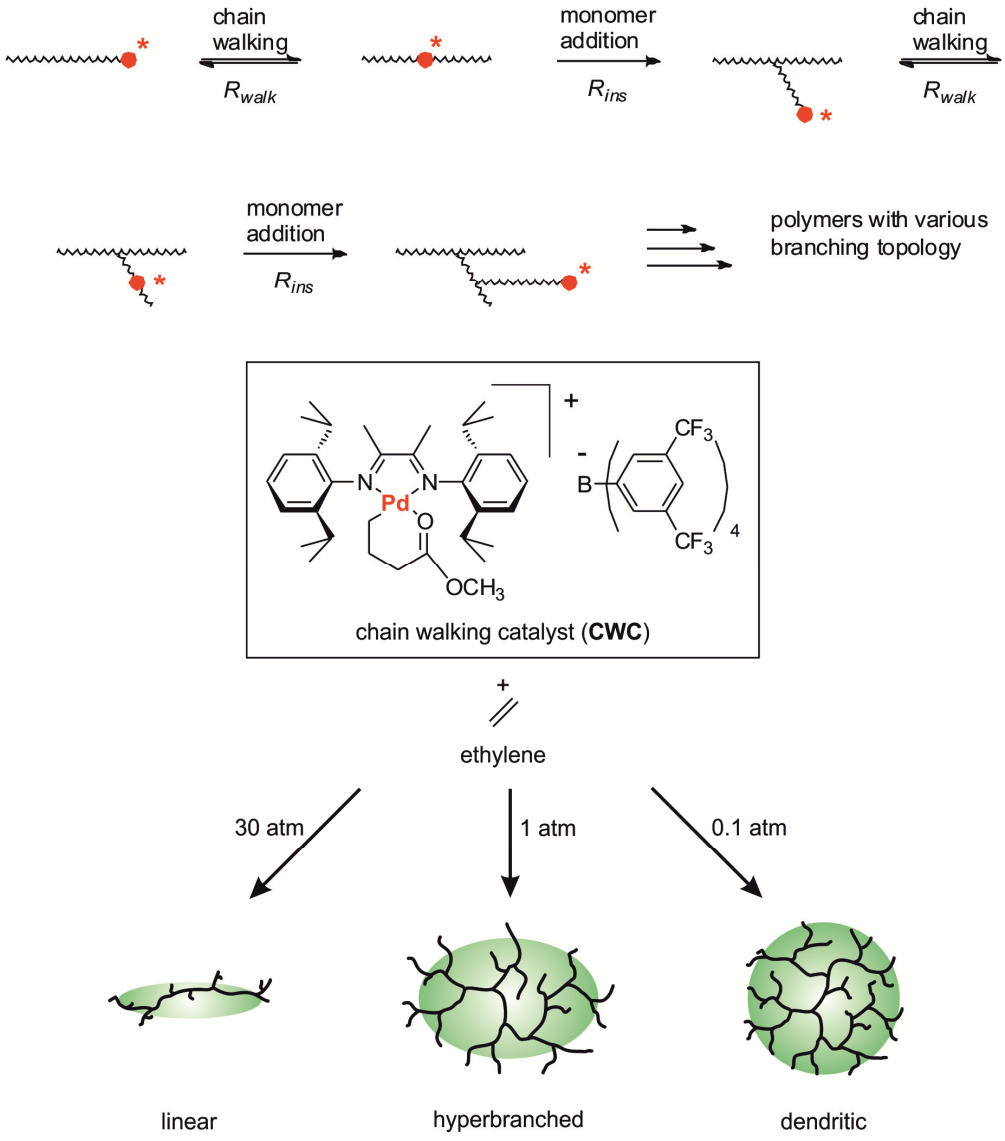


Figure 3. Top: schematic representation of the chain walking process that can lead to polyethylenes with various branching topologies. Middle: a typical chain walking catalyst (CWC). Bottom: the different topologies (linear, hyperbranched, and dendritic) obtainable by chain walking polymerization (CWP) at different ethylene pressures. Figure adapted from the literature.[13,19,20]

The topology is dependent on the relative rates of the migratory insertion (R_{ins}) which leads to chain growth and chain walking (R_{walk}) which causes branching formation. At polymerization conditions where the chain walking is very competitive, e.g., at low ethylene pressure, the catalyst should walk randomly and extensively through the polymer backbone and therefore create a hyperbranched or dendritic polymer topology.[13,20] This feature could be also obtained for CWP by tuning the electronic structure of the catalyst with electron-donating or -withdrawing substituents on the α-diimine ligand. The latter kind of catalyst favors the formation of more dendritic PEs.[13,21] The complete elucidation of the PEs topologies was very challenging and required several different analytical methods, including ^{1}H and ^{13}C NMR, size-exclusion chromatography with a multi-angle laser light scattering detector (SEC-MALLS), neutron scattering, solution properties, as well as rheological studies.[13,20,22,23]

It is worth mentioning that branching in dendrimers or hyperbranched polymers, which both have a tree-like fractal cascade structure but with more perfectly formed dendrimers, usually has to be build up with monomers that already have the branching feature encoded in them.[13,19] Dendrimers are synthesized by either a convergent (periphery to core) or divergent (core to periphery) approach that involve iterative organic multistep reactions.[24,25] The synthesis of hyperbranched polymers can be more easily achieved by the condensation of AB_x-type monomers with $x \geq 2$ whereby A and B are mutual functionalities.[13,26–28] In contrast to this, one-pot CWP introduces the branching as a feature of its catalytic process while the monomer can be unbranched and as simple as ethylene ($H_2C{=}CH_2$).[13,19,20,29] Tremendous progress has already been made in the investigation of CWP and the catalyst design.[9,30,31] For example, a change in the bulkiness of the substituents R^1 or R^2 on the α-diimine ligand (Figure 2) has led to highly branched PEs with different sizes and molecular weights with the bulkier substituents yielding larger PEs.[9,17,30,32]

Polymers with polar functionalized side groups are highly desirable materials, because, compared to their unfunctionalized analogs, their properties can be beneficial.[33,34] If combined with the already outstanding properties of unfunctionalized polyolefins, this could lead to new areas of application.[33] Conventionally, polar comonomers could only be introduced by free radical polymerization with ethylene at extremely high temperatures and high pressures, which yielded uncontrolled structures and incorporations.[13] Guan and co-workers were able to successfully incorporate polar α-olefin comonomers in a one-pot CWP process (Figure 4) and still retain the possibility to create different topologies (linear, hyperbranched, and dendritic).[29] For example, they could synthesize dendritic copolymers

with multiple hydroxyl, epoxide, and saccharide groups. The ratio of comonomer incorporation could be adjusted with the initial comonomer concentration.[29]

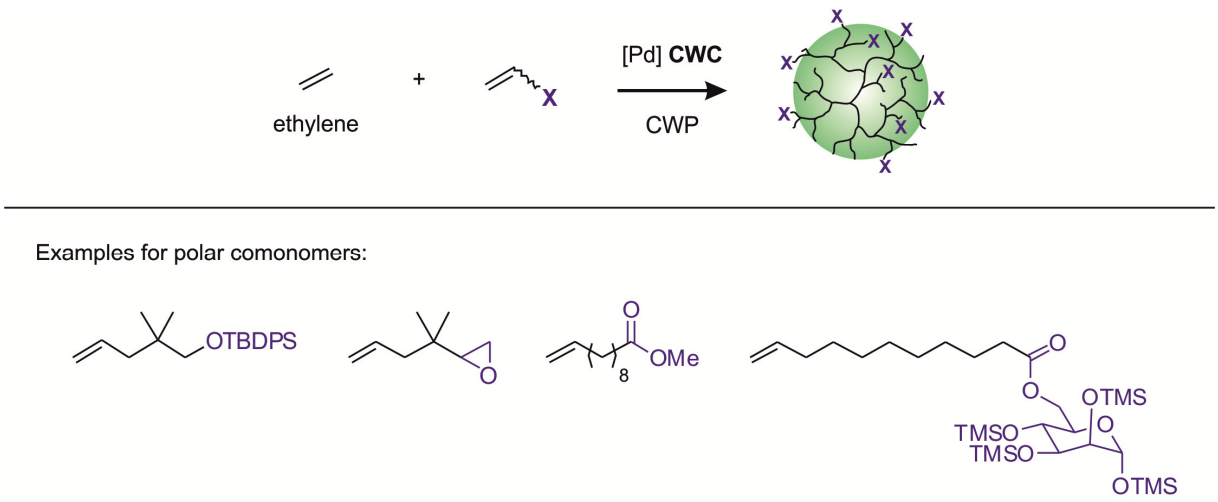


Figure 4. Synthesis of functional copolymers via CWP of ethylene and polar comonomers to yield controlled topologies (linear, hyperbranched, and dendritic; see also Figure 3). Only the dendritic example is shown here. Figure adapted from the literature.[29]

Some design rules for comonomers could be determined. For certain functionalities in the comonomer, e.g., ethers, a quartenary carbon blocking group needs to be introduced to prevent the deactivation of the CWC, because the CWC cannot walk over quatenary carbons.[29] Comonomers bearing ester functionalities lead to chelate formation with the Pd center, which slows down the polymerization, but if the ethylene coordinates again, the polymerization can still proceed. Therefore, the quartenary carbon blocking group is not needed in ester bearing comonomers.[13,30,35]

Brookhart and co-workers could show that substituted olefins have a much lower reactivity for insertion for the Pd^{II}-α-diimine catalyst, which means that they can only be incorporated if the catalyst walks to primary carbon atoms, i.e., chain ends.[36] Therefore the differences in the reactivity lead to preferential incorporation of the polar comonomers on the surface of dendritic copolymers.[13] This unique feature can be useful for many applications that require surface accessible multivalent groups and additionally makes dendritic PE copolymers great candidates for the use as the core in core-shell architectures (see also Chapter 1.2.2).[13,37]

The Pd-diimine CWP can be also carried out under “living” polymerization conditions (typically between 5-25 °C) and thus lead to even more complex and controlled chain

architectures like the ones demonstrated in Figure 5.[38,39] A "living" or quasi-living polymerization is featured with instantaneous chain initiation and simultaneous chain propagation, while the chain breaking reactions (chain transfer and termination) are present but only on a low level, whereas in true living polymerizations chain breaking reactions are absent.[38]

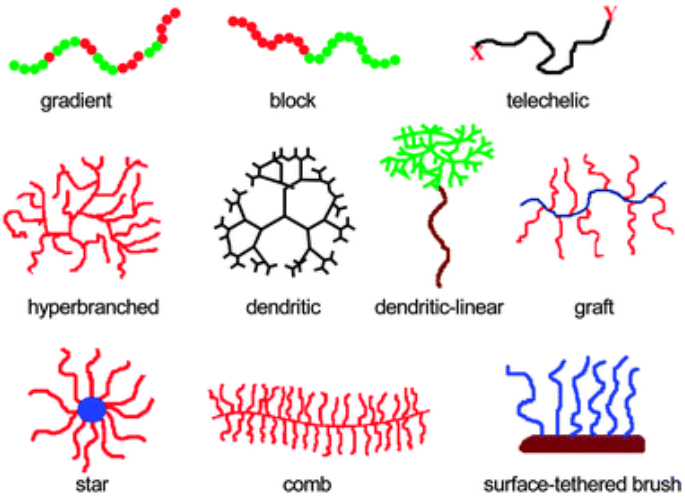


Figure 5. Representative complex polymer chain architectures. Reproduced from Ref. [38] with permission from The Royal Society of Chemistry.

1.1.2 Polyglycerol

Polyglycerol (PG), a polymer with a polyether backbone and polyol functionalities, can be synthesized with different degrees of branching ranging from 0 for linear PG and typically around 0.5-0.6 for hyperbranched PGs to 1 for perfect PG dendrons or dendrimers.[40–44] Many different PG structures have been prepared, some of which are summarized in Figure 6 according to their size range from 1 nm up to 30 µm.[45]

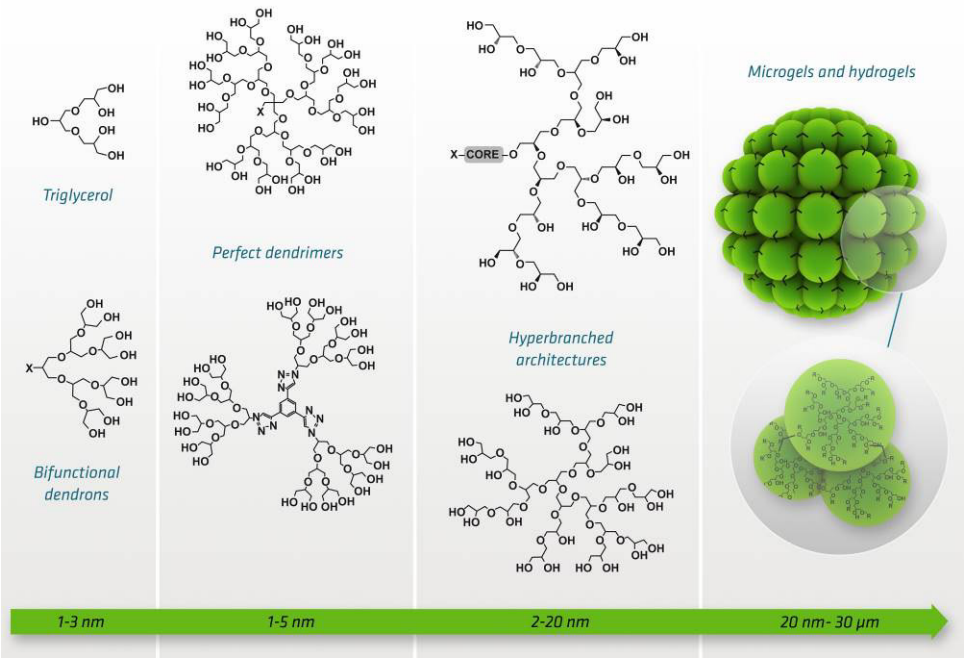


Figure 6. Examples of different synthesized dendritic PGs that range from dendrons to megamers which have been ordered according to their increasing size. Figure was reprinted with permission from Ref. [45]. Copyright © 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

PG polymers have found many applications including polymer supported catalysis, drug delivery, and bioinert surfaces.[45–51] The chemical structure of PG is very similar to the one for poly(ethylene glycol) (PEG), which is still the most commonly applied non-ionic hydrophilic polymer and thus regarded as the gold standard for biomedical applications. In the field of drug delivery, PEGs have many advantages like stealth behavior, prolonged blood circulation, and successful approval from the Food and Drug Administration (FDA). Therefore introduction of PEG (PEGylation) is a widely used method to improve materials' biocompatibility and applicability. However, PEG also has some drawbacks, because it can cause hypersensitivity, it degrades relatively easy under stress, and it is non-biodegradable.[52]

In the search for potential alternatives, PG is regarded a likely candidate.[43,45,52] Several studies have demonstrated PG's excellent biocompatibility and potentially safe *in vitro* and *in vivo* profile. The biocompatibility profile of both linear and hyperbranched PGs is similar to or even better than PEG's.[46] Furthermore, it could be shown that PG has higher thermal and oxidative stability than PEG.[51] While perfect PG dendrons or dendrimers can only be synthesized in tedious organic multi-step reactions, hyperbranched PG can be obtained in an easy one-pot synthesis via anionic ring-opening multibranching polymerization (ROMBP) in a controlled way by slow monomer addition, which makes it available on a kilogram scale.[40,44] Typical polydispersity indexes (PDI) for hyperbranched PG are between 1.2-1.7, which is exceptionally low for hyperbranched polymers.[45] The mechanism for the ROMBP of glycidol, which relies on rapid cation exchange, is shown in Figure 7.

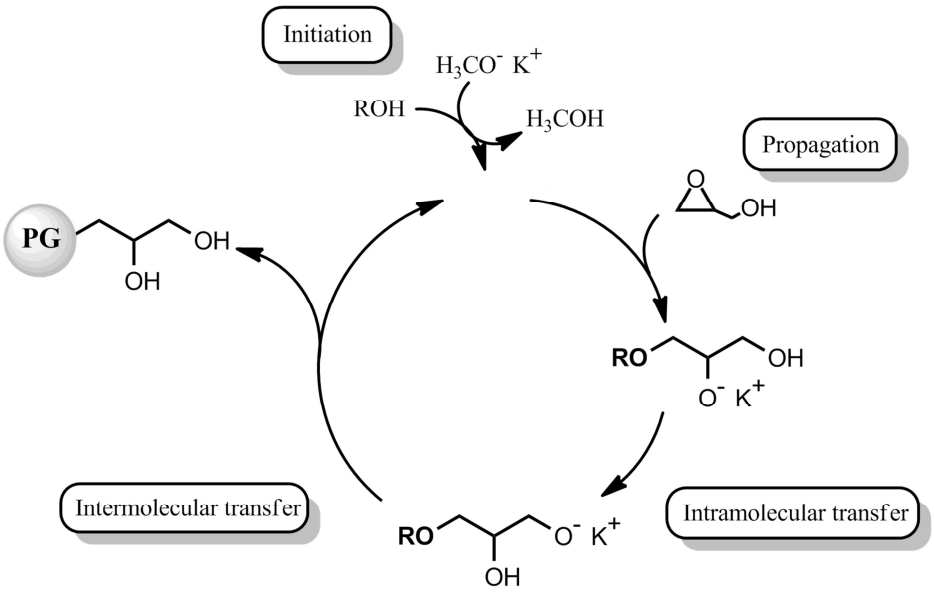


Figure 7. Mechanism of an anionic ring-opening multibranching polymerization (ROMBP) that can be used to form well-defined hyperbranched PGs under slow monomer addition.[40] Figure adapted from Ref. [45] with permission from John Wiley and Sons. Copyright © 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Moreover, the high loading capacity of hyperbranched and dendritic PGs (dPGs) because of their polyol structure can be very useful for investigating multivalent interactions.[53–57] The hydroxyl groups of dPG can be converted into a variety of different functionalities with standard organic reactions. dPGs that have been obtained with various charges according to the different functionalities, have been used for all kinds of biomedical

applications (Figure 8).[45,46,58] For example, positively charged dPGs with amine functionalities have been recently applied in gene delivery and negatively charged dPG sulfates (dPGS) as heparin analogs for anti-inflammatory purposes.[56,59–62]

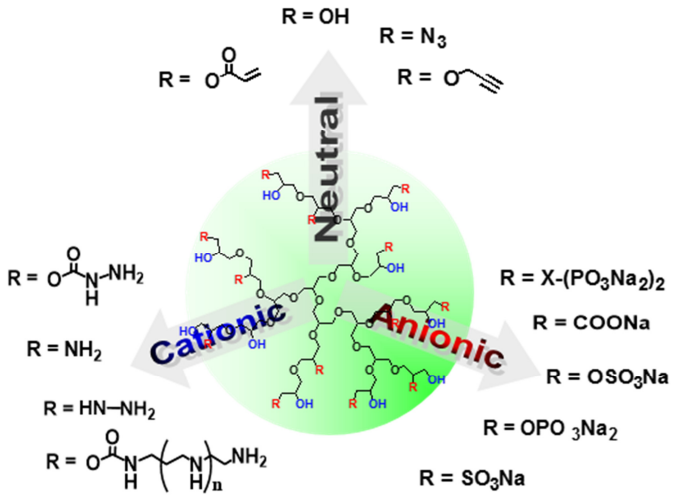


Figure 8. Schematic representation of differently functionalized dPG derivatives that were developed for the field of biomedicine. The depicted structure is idealized and represents only a small part of the PG scaffold. Reproduced from Ref. [46] with permission from The Royal Society of Chemistry.

1.2 Biomedical Application of Amphiphilic Polyolefin-Polyglycerol Systems

1.2.1 Bioinert Surfaces

Biofouling is of great concern in numerous applications, particularly for biomedical devices and implants, food packaging, or biosensors.[63–66] For example, when a biomedical device comes in contact with living tissue and human blood, within seconds nonspecific protein adsorption occurs, which can be followed by a cascade reaction that eventually even leads to foreign body reaction and rejection of the device.[67,68] This hinders the biomedical device's effectiveness and can cause serious infections.[69] Proteins can slowly denature on the surface and eventually lead to irreversibly adsorbed protein layers. This has prompted a tremendous amount of developmental research on surface coatings that prevent the nonspecific protein adsorption in the first place (Figure 9).[65,67,70–74]

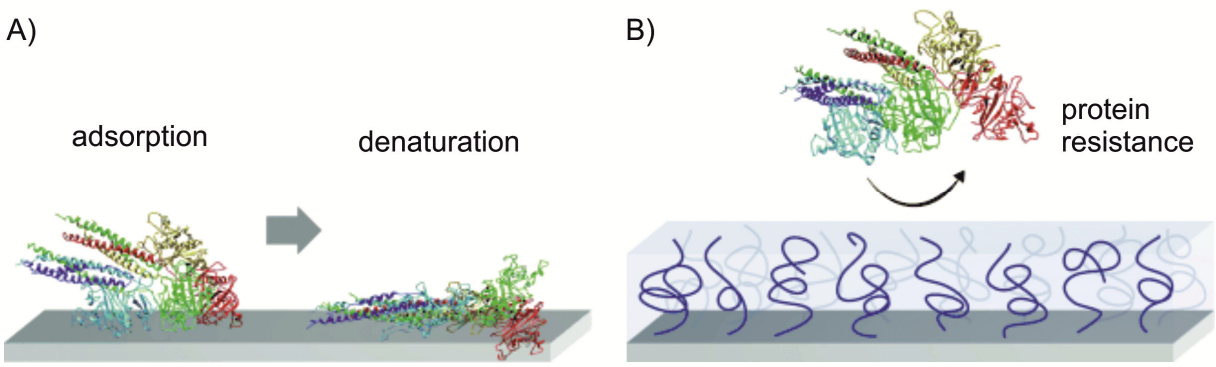


Figure 9. Schematic representation of (A) the dynamic adsorption and denaturation of proteins on a bare surface and (B) the protein resistance of polymer coated surfaces. Figure adapted from Ref. [67] with permission from John Wiley and Sons. © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

The adsorbed protein layer also provides a conditioning layer, e.g., for the attachment of bacteria to the surface, which leads to microbial colonization and biofilm formation (Figure 10).[65,66,75]

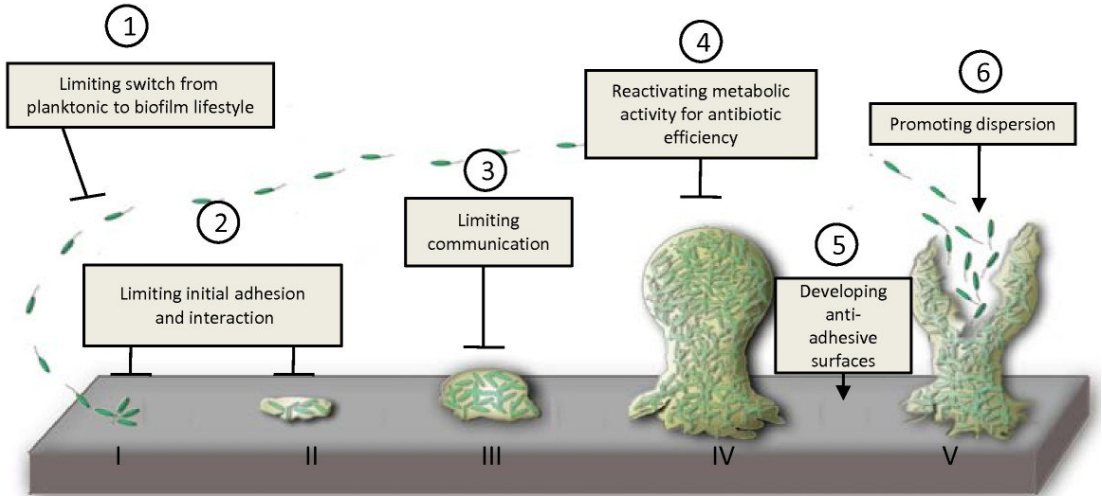


Figure 10. Schematic representation of the temporal evolution of biofilm formation. Schematization of the four-stage universal growth cycle of a biofilm with common characteristics, including initiation (I), maturation (II and III), maintenance (IV), and dissolution (V).[66] Figure adapted from the literature.[66] © 2011 Bordi and de Bentzmann; licensee Springer.

The processes of protein adsorption and biofilm formation are extremely complex and, despite considerable scientific efforts, the processes and interactions with biomaterials are still poorly understood.[67] Water-mediated hydrophobic and hydration forces as well as electrostatic interactions are believed to be the main factors in the protein adsorption process.[67] Some empirical rules have evolved from the many investigations that help predict a material's bioinert properties. One of them is "Berg's law" or "Berg's limit" which states the protein adsorption depends on the hydrophilic/hydrophobic ratio.[76] Surfaces that have a contact angle θ above 65° are considered hydrophobic and prone to protein adsorption, while if $\theta < 65°$, the protein should not be able to displace the water from the hydrophilic surface and therefore should not adsorb on the surface.[67,76] Whitesides and co-workers performed a systematic study on self-assembled monolayers (SAMs) to find ways to suppress protein adsorption and came up with a set of characteristics for bioinert surfaces. According to the "Whitesides rules", these polymers should be (1) hydrophilic, i.e., have polar functional groups, (2) have hydrogen bond accepting groups, but (3) should not have hydrogen bond donating groups, and finally, (4) should have no net charge.[67,70,77,78]

Obviously, these empirical rules have some limitations and further studies are needed for a more comprehensive understanding. The strategies for bioinert polymeric surfaces can be divided into two main categories for either passive or active surface coatings (Figure 11). In the passive approach, the polymer coating is intended to make the materials' surface "stealthy" with regard to the surrounding tissue or fluids, and thereby reduce biofilm formation (Figure 11A).[67,69] In the active approach, additional biocidal agents should kill any microbes that eventually adhere on the surface. They can be incorporated in the surface and act on contact, be released over time or upon external stimuli, e.g., by cleavable linkers (Figure 11B). For example, silver nanoparticles, antibiotics, and polycations are used as biocidal agents.[65,79]

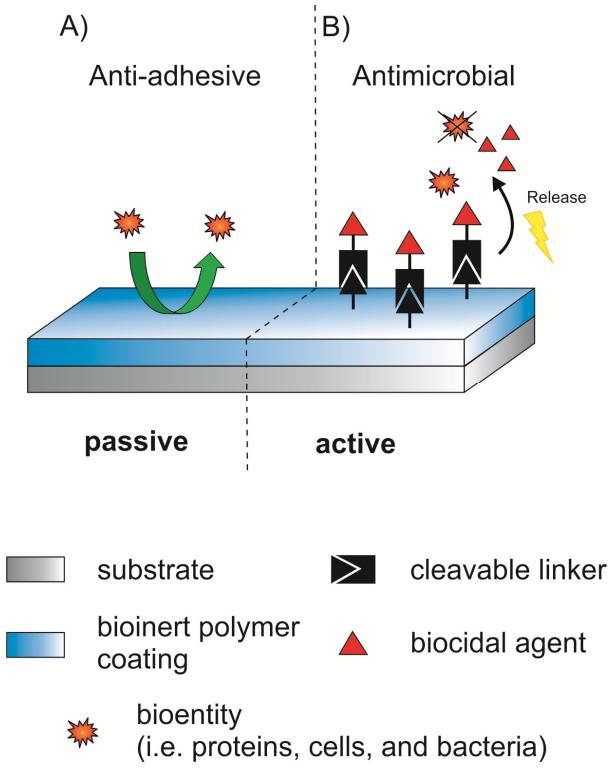


Figure 11. Schematic of two strategies for bioinert surfaces. (A) The passive approach that prevents nonspecific protein adsorption in the first place and (B) the active approach that kills adhered microbes, e.g., by the release of biocides.[70,80]

Since Merrill described the resistance of polymeric surfaces to proteins in 1987, numerous different polymers have been examined for the use as bioinert surface coatings.[70] Conventionally, the polymer coating strategy has been classified into physisorption and chemisorption (covalent bond formation) and one can further differentiate how the polymers chains are grafted onto a surface.[70] The grafting of hyperbranched or dendritic polymers can be performed either by a step-by-step or graft-on-graft approach, by grafting-to, and by grafting-from.[81] While the first two methods involve multistep procedures, the grafting-to and grafting-from approach work in one-step. In the grafting-to approach polymers are prefabricated and functionalized in the desired way in solution and are then coupled to functional groups on the surface by coupling chemistry. In the grafting-from approach the polymerization is initiated from functional groups on the surface. The grafting-to approach has the advantage that homogeneous surface-grafts can be produced when using well-defined preformed polymers, however, this approach suffers from low reproducibility and kinetic limitations in the density of polymer chains due to steric restriction.[70,81] The grafting-from approach can generally lead to high grafting densities and complete surface coverage. Additionally, thicker polymer films can be produced in a controlled way.[50,82]

The most commonly used bioinert polymers, shown in Figure 12, can be divided into non-ionic hydrophilic polymers and zwitterionic polymers. Poly(ethylene glycol) (PEG) or oligo(ethylene glycol) (OEG) coatings have been extensively used and studied and still demonstrate the gold standard in the prevention of biofouling. However, due to some limitations of PEG based coatings, like their limited stability under the presence of oxygen at elevated temperatures or enzymes *in vivo*, zwitterionic polymers have especially become a new benchmark in bioinert materials.[67,70]

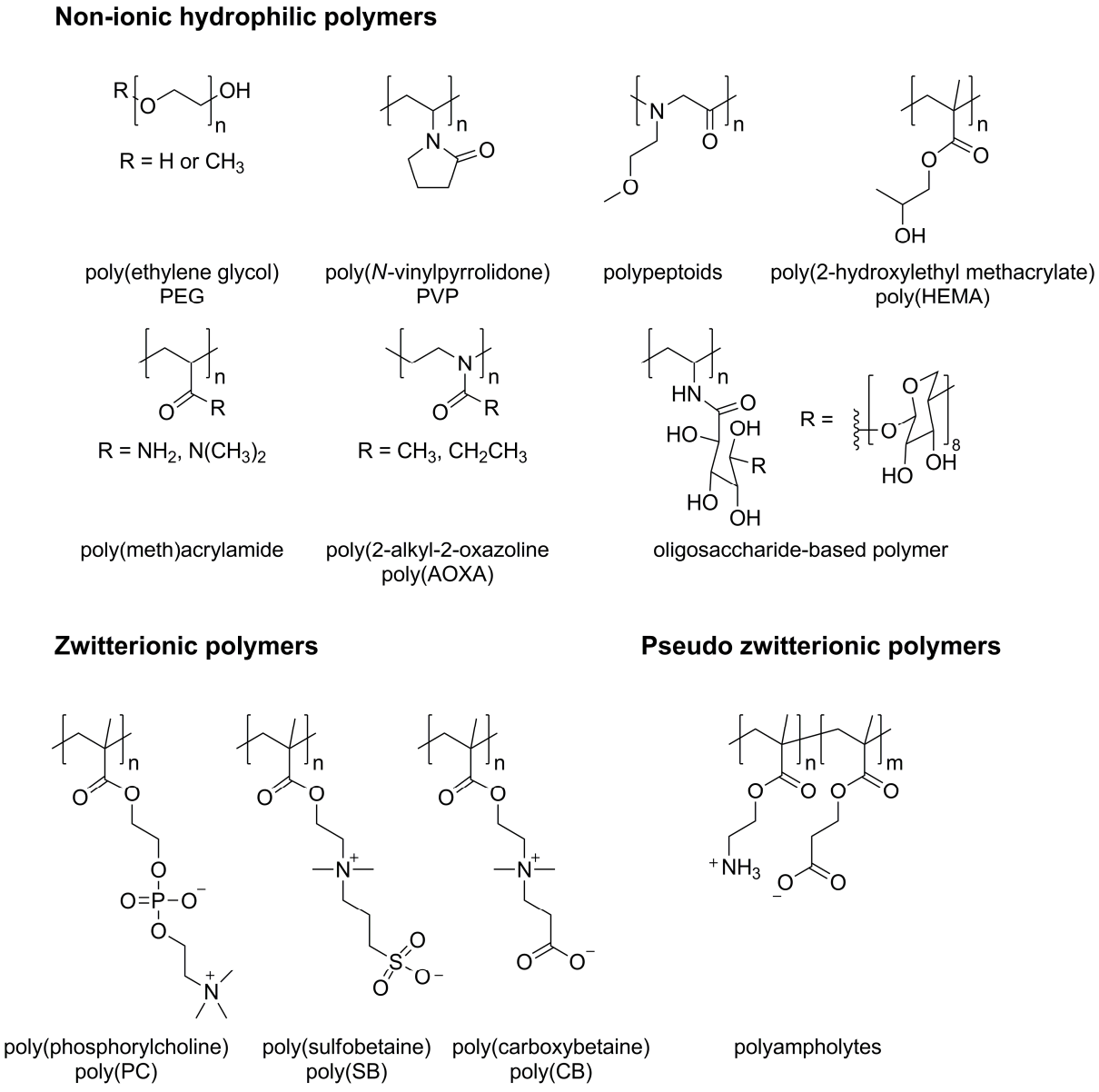


Figure 12. Some typical bioinert polymers' structures. Figure adapted from the literature.[70]

Another alternative to OEG- and PEG-based coatings are PGs with linear or branched architectures. PGs have been shown to be more resistant to heat and oxidation, have had less thrombocyte activation and similar or better protein resistance than PEG.[67] Inspired by the term PEGylation, introduction of PG is also called "PG-lation." While the dPG structure is built up in the grafting-from or "hypergrafting" approach by polymerizing the monomer glycidol from surface initiator sites, preformed and prefunctionalized dPG is introduced in the grafting-to approach with coupling chemistry to functional groups on the surface.[81,83–85]
The protein resistant behavior of dPG, PG dendrons, and linear PG (lPG) could be demonstrated as SAMs on gold surfaces (Figure 13).[51,86–88]

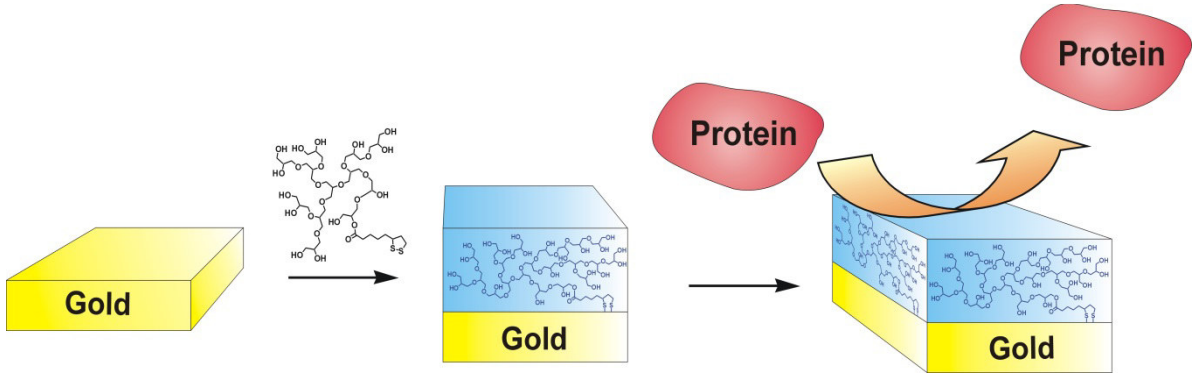


Figure 13. SAM formation with dPG on gold for protein resistance. This figure was reprinted with permission from Ref. [45]. Adapted from [51]. Copyright © 2004 and 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Furthermore, hyperbranched as well as linear PGs have been introduced on glass surfaces by first cleaning and activating the glass and then attaching them in a grafting-to approach (Figure 14).[89] The PG polymers were prefabricated and modified with triethoxysilane groups in solution and then these polymers were introduced to the surface by silanization. The produced glass surfaces not only showed excellent protein resistance to the commonly used model proteins bovine serum albumin (BSA) and fibrinogen (FIB), but also to cells and several model biofilm forming bacteria like *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*).[89] Linear PG analogs have also exhibited thermoresponsive behavior which could be beneficial for bioinert surfaces and cell culture application.[90]

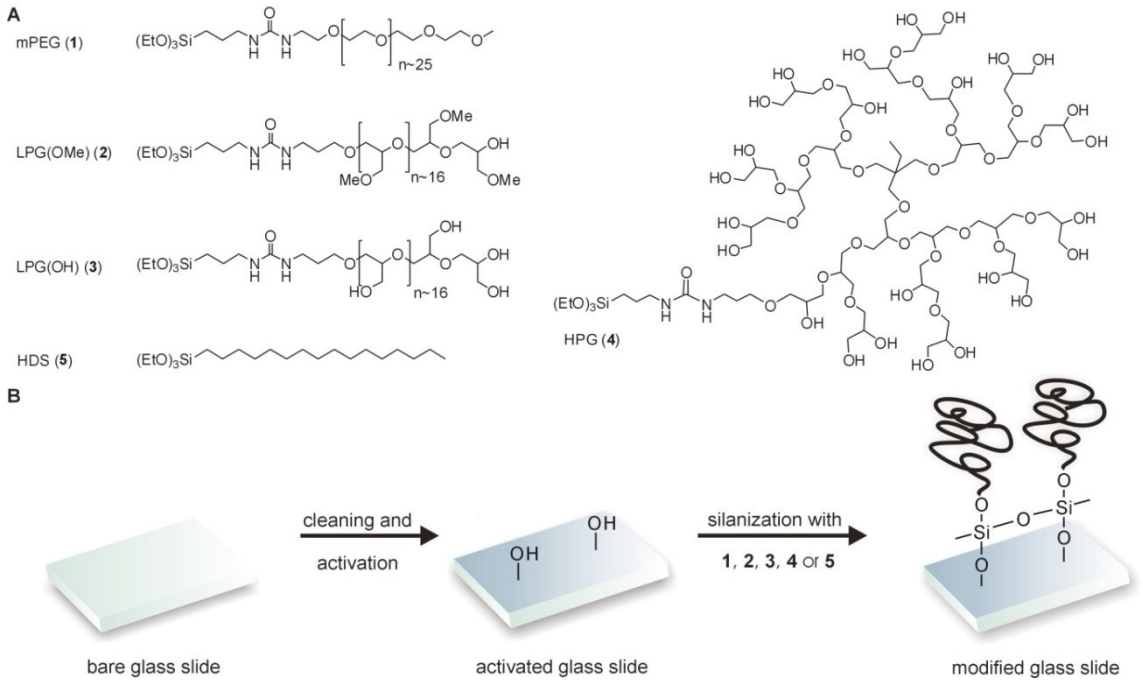


Figure 14. Introduction of linear and hyperbranched PGs by a grafting-to approach on glass surfaces for resistance to proteins, cells, and bacteria. Figure was adapted with permission from Ref. [89]. Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

In a recent study, Paez et al. investigated up to which level of amino functionalization of dPG coated on gold surfaces the protein resistant behavior of PG could be retained.[91] The results demonstrated that surfaces which were coated with PG-NH_2 with up to 9% amino functionalization (of all PG hydroxyl groups) had very good protein resistance. Moreover, the remaining amine groups were still accessible for specific ligand or biomolecule binding and can thereby enabled PG based bioassays (Figure 15).[91] Recently, Moore et al. introduced polyglycerol based cell microarrays to the literature as well.[92]

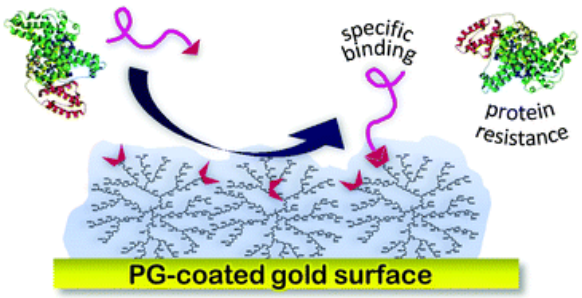


Figure 15. Schematic representation of dPG-amine coated gold surfaces, which exhibited resistance to nonspecific protein adsorption. The remaining amine groups were still accessible for specific ligand and biomolecule binding. Reproduced from Ref. [91] with permission from The Royal Society of Chemistry.

Surface independent universal coatings with dPGs also recently became available which bare catechol anchoring groups for building stable bioinert multilayers of PG.[57,93]

All of the above-mentioned examples for PG-lated surfaces were produced by the grafting-to approach. In 2003, Huck et al. reported the grafting-from strategy (Figure 16) by surface-initiated polymerization of glycidol on Si/SiO_2 surfaces. In this approach, the Si-OH bonds were deprotonated with sodium methoxide and were then used as initiators for the anionic ring-opening multibranching polymerization of glycidol to yield hyperbranched PG (hPG) on the surface. PG coatings of controlled thickness could be produced.[82] Recently, Moore et al. reported the grafting-from approach on activated glass, silicon, and porous silicon substrates using the same strategy and showed that the hPG coatings resulted in ultralow-fouling.[94] Terfort and co-workers could also demonstrate PG coating onto the oxide surfaces of steel, aluminum, and silicon by a grafting-from process.[95,96]

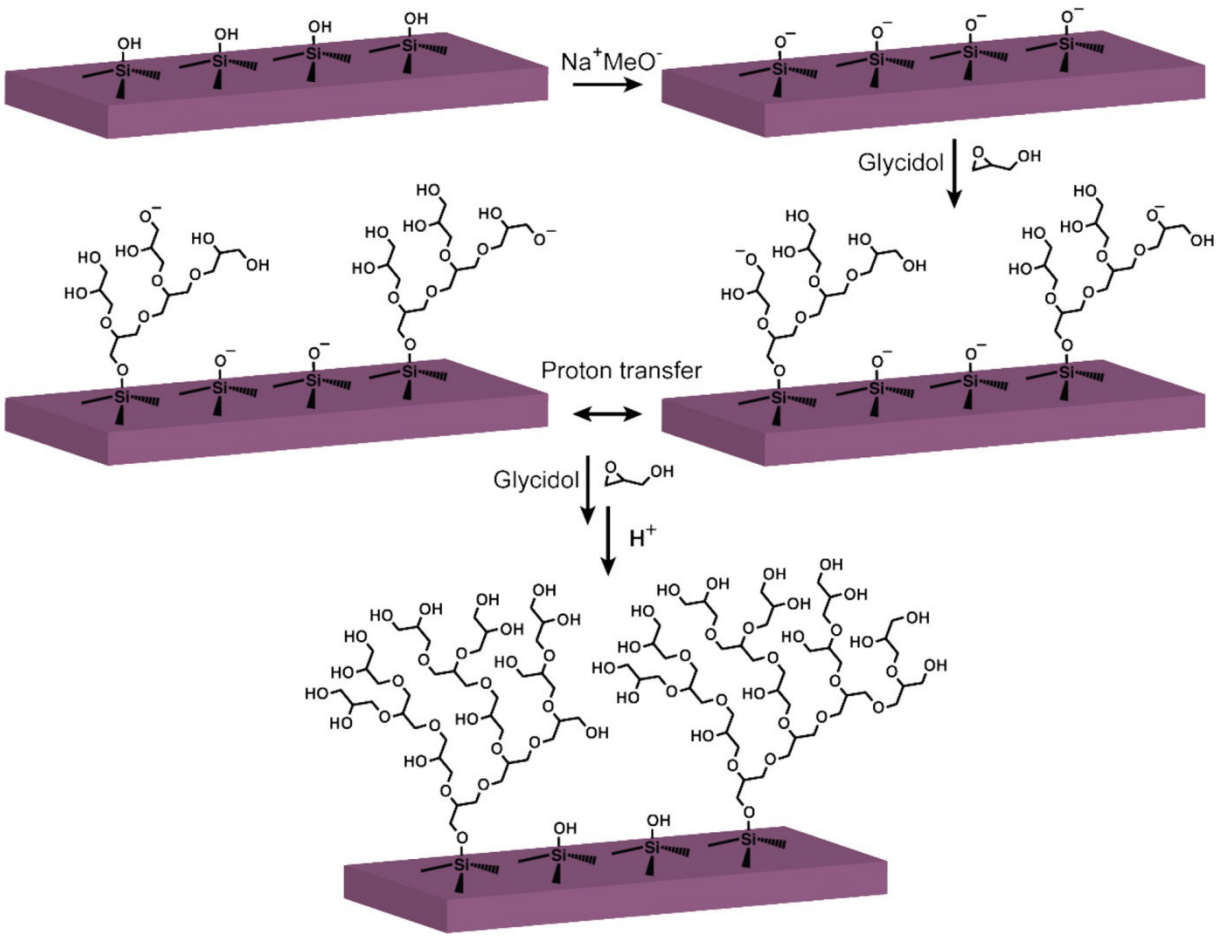


Figure 16. Proposed growth mechanism for surface-initiated hPG synthesis by the grafting-from strategy.[82,94] Reprinted with permission from Ref. [94]. Copyright © 2014 American Chemical Society.

As outlined in the first section of this introduction, polyolefins are one of the most produced and applied polymers worldwide. Especially PP has also found many applications in the biomedical field, where it has been used as syringes, surgical sutures, mesh implants, and blood bags, as well as for packaging purposes.[2–5] All of these examples benefit from polyolefins' robustness and stability. Unfortunately, polyolefins are also prone to strong protein adsorption due to their hydrophobicity, which complicates their use. Furthermore, the chemical inertness of polyolefins necessitated the development of methods to introduce functionalities on polyolefin surfaces for bioinert coating.[97,98] These methods usually require quite harsh conditions for the surface activation like UV-irradiation, corona, and plasma treatment.[97,99]

An example for polyolefins' surface modification, the mechanism for a UV-induced graft polymerization initiated by benzophenone (BP), can be seen in Figure 17.[97]

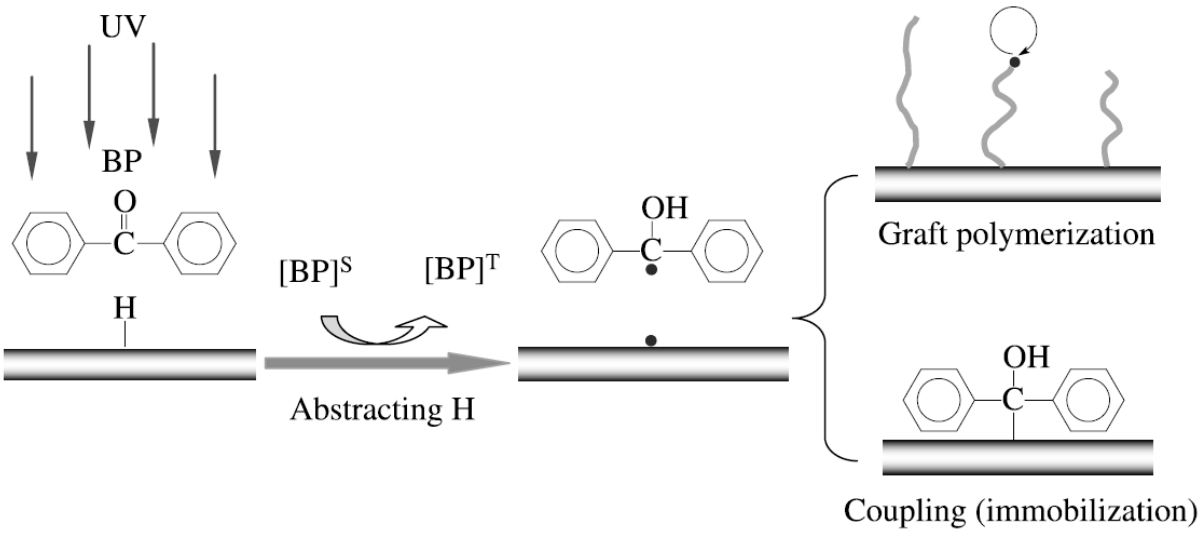


Figure 17. Mechanism of the UV-induced graft polymerization initiated by benzophenone (BP) on polyolefin surfaces. Figure reprinted from the literature Ref. [97] with permission from Taylor & Francis.

One especially elegant and mild way to produce bioinert PP surfaces, i.e., PP nonwoven fibers was reported very recently by Goli et al. (Figure 18).[98] The authors made use of the intrinsic hydrophobicity of PP by adsorbing denatured proteins (lysozyme (LYS) or FIB) on them as the first step, which were stabilized by cross-linking with glutaraldehyde (GA) in the presence of sodium borohydride ($NaBH_4$). Afterwards, the remaining functional amine and hydroxyl

groups of the denatured protein layer were used for the deposition of 2-bromopropinoyl bromide (2-BPB). Then poly(2-hydroxyethyl methacrylate) (PHEMA) was introduced by a grafting-from procedure via atom transfer radical polymerization (ATRP). Finally, the terminal hydroxyl groups of HEMA's pendent groups were modified with fluorinated moieties of different chain lengths by subsequent postpolymerization modification (PPM) to yield amphiphilic brush structures. The produced coated PP fibers were characterized by several analytic methods such as ellipsometry, contact angle measurement, or X-ray photoelectron spectroscopy (XPS), among others. The protein resistance was tested by incubation with fluorescein isothiocyanate (FITC)-labeled BSA as model protein and observed by merging optical and fluorescence microscopy images, which showed reduced protein adsorption for the fluorinated PP films (Figure 18, bottom).[98] They also used the same approach to synthesize active biocidal PP surfaces with incorporated silver nanoparticles.[100]

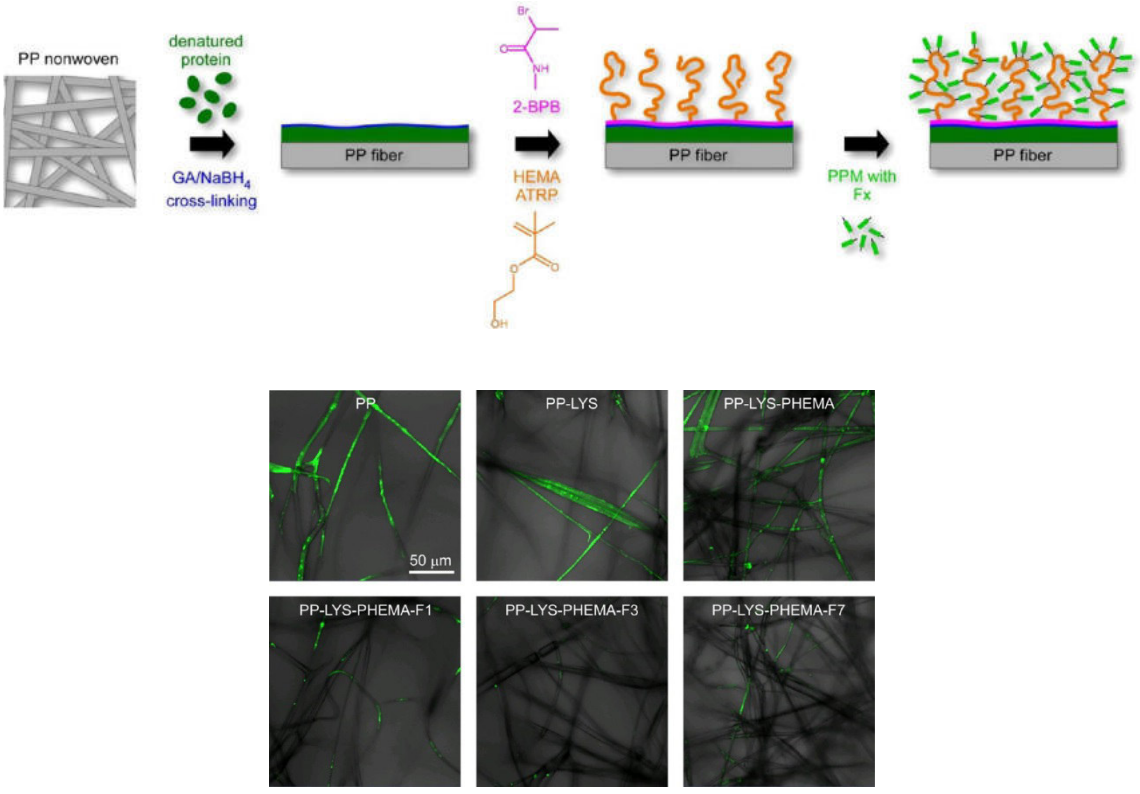


Figure 18. Top: synthetic scheme used by Goli et al. for the synthesis of fluorinated PHEMA-brushes on PP fibers. Bottom: merged optical and fluorescence microscopy images after incubation of LYS-PHEMA fluorinated (F) films with the model protein BSA-FITC. Adsorbed protein can be seen as green fluorescence. Adapted with permission from [98]. Copyright © 2012, American Chemical Society.

Another commonly used method to introduce functional groups on polyolefin surfaces that deserves further attention and description is the plasma treatment.[97,101–104] During plasma exposure, the polymer surface is bombarded with a highly energetic mixture of ions, electrons, neutrals, and very hard vacuum UV (VUV) irradiation.[101] The high energy is needed to break up the inert polyolefin structure, specifically for the scission of C-H bonds, but unfortunately also causes some C-C bonds to break and normally leads to rather uncontrolled functionalization. The main challenge in plasma techniques lies in controlled surface activation. Usually plasmas produce a variety of functional groups on the polyolefin surface due to the high energy level of the plasma and post-plasma oxidation. Oxygen plasma, for example, introduces a broad mixture of O-functional groups (hydroxyl, carbonyl, epoxides, etc.) on the surface (Figure 19A).[101] In contrast, the recently developed plasma bromination by Wettmarshausen et al. leads to selective monotype functionalized polyolefin surfaces through the introduction of reactive bromine groups (Figure 19B).[101,105,106]

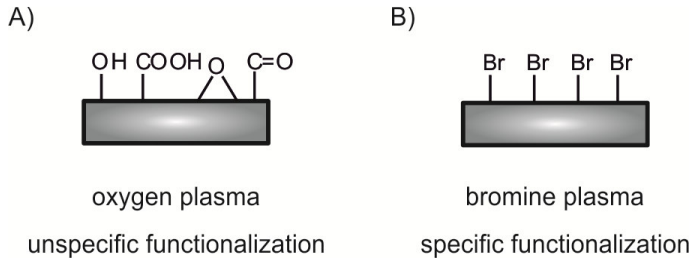


Figure 19. Unspecific plasma functionalization like in the case of (A) oxygen plasma and (B) specific functionalization by plasma bromination. Figure adapted from the literature.[101,105,106]

Two reasons for the high selectivity can be named. Firstly, the only possible side reaction instead of the desired reaction to C-Br is the formation of Br^-, which has no significance because the formed HBr is continuously removed by the high vacuum. Secondly, bromine and bromine-containing precursors have low dissociation energies and thus the excess of energy and side reactions can be minimized. Furthermore, since only low radical formation is caused, the post-plasma oxidation can be nearly eliminated. For these reasons, plasma bromination leads to the selective introduction of bromine groups in high yields.[105–110] Friedrich and co-workers could further show that the density of bromine functionalities could be varied by changing the plasma exposure time and power and that the bromine groups proved to be suitable as anchor points for the introduction of, e.g., hydroxyl- or amino-functionalized linkers by substitution reactions.[105,106,111] Plasma bromination hence displays a very promising first step on the way to bioinert polymer coated polyolefin surfaces.

1.2.2 Macromolecular Carriers for Drug Delivery

In the last decade, the fields of nanomedicine and polymer therapeutics have attracted considerable attention in the research community.[112,113] Polymer therapeutics use drug delivery systems (DDS) for the improvement of therapeutically active agents and the reduction of side effects for the treatment of cancer or other diseases.[114] Polymer therapeutics include several different classes of polymeric DDS like polymer-drug conjugates, polymeric micelles, polymer-protein conjugates, and polyplexes.[46] Nanocarriers, which typically are between 1-200 nm, can deliver the bioactive agent (e.g. drug) at the targeted site with an improved therapeutic activity than for the free form of the drug.[46,115] Macromolecular carriers can especially increase the blood circulation time, which decreases the number of treatments/injections, and side effects. A better biocompatibility and lower immunogenicity is often caused by a stealth effect of the polymers used for DDS. PEG has been very often used in this context.[52] PEGylation of peptides, proteins, antibodies, and drugs is therefore one of the most employed techniques in the field of polymer therapeutics.[116–118] Moreover, polymeric DDS can benefit from the enhanced permeability and retention effect (EPR) that was introduced by Maeda et al. (Figure 20).[119] The EPR effect describes a passive accumulation of macromolecules in tumor tissue which is caused by the hyperpermeability of tumor vasculature.[46,112] Normally, small molecular weight drugs penetrate both normal healthy as well as tumor tissue and therefore cause the well-known side effects in chemotherapy. Macromolecular DDS, however, only penetrate the disordered barrier of leaky tumor tissue but not normal tissue so that they accumulate in the tumor tissue (Figure 20A).[46] Figure 20B shows the different cellular uptake mechanisms for macromolecular DDS.

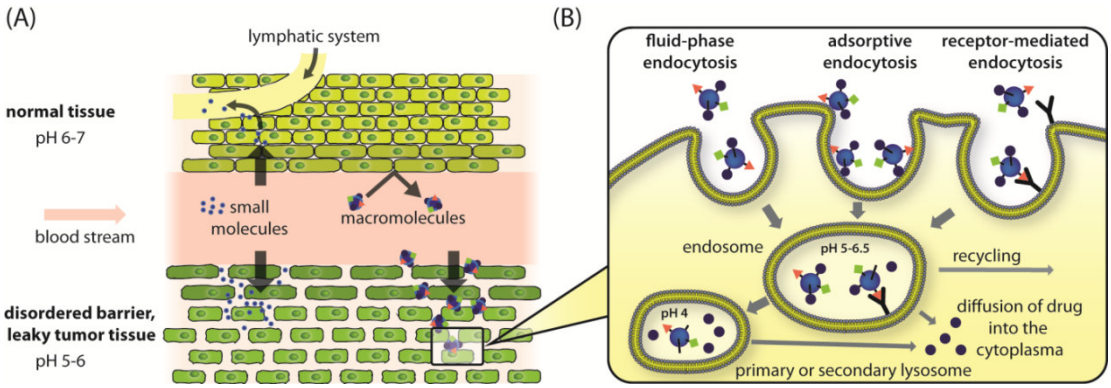


Figure 20. Schematic representation of (A) the EPR effect and (B) the cellular uptake mechanisms. Reproduced from Ref. [46] with permission from The Royal Society of Chemistry.

One of the major limitations in the development of new chemotherapeutic drugs is their poor solubility in aqueous environment due to their hydrophobicity.[120–122] Dendritic macromolecular carriers, which often consist of core-shell architectures, can solve this problem by either (A) encapsulation of the drug or (B) by conjugation of the drug to the nanocarrier's scaffold with cleavable linkers for the later release of the payload (Figure 21).[45] The use of dendritic DDS is of particular interest because of their high number of functional groups and their tree-like well-defined architecture. Dendritic DDS include dendrons, dendronized polymers, dendrimers, and hyperbranched polymers as scaffolds.[123]

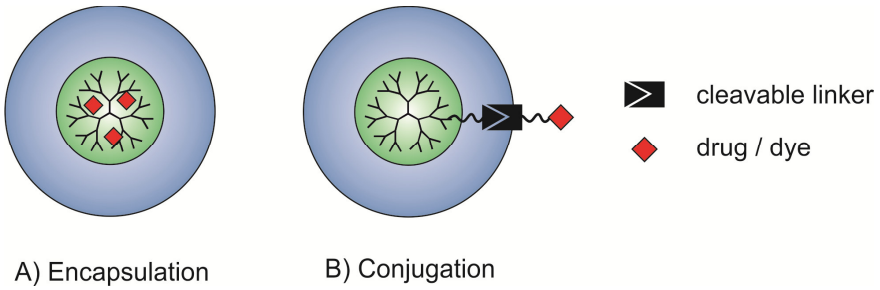


Figure 21. Drugs or dyes can be either (A) physically encapsulated within core-shell nanocarriers or (B) chemically conjugated to the nanocarrier's scaffold, often with the use of cleavable linkers.

Furthermore, dendritic core-shell nanocarriers are also investigated for diagnostic bioimaging purposes, for gene delivery, and others.[124,125] The focus in this work lies on the use of macromolecular core-shell carriers via encapsulation.

In addition to dendritic core-shell architecture, amphiphilic supramolecular systems like small molecule micelles, vesicles, and liposomes are used for the formulation and encapsulation of dyes/drugs.[126–129] In comparison, amphiphilic core-shell nanocarriers, which resemble covalently bound micelles and are therefore called unimolecular micelles, have been shown to be beneficial because of their higher stability under dilution conditions, where supramolecular micelles eventually fall apart (Figure 22).[130–134]

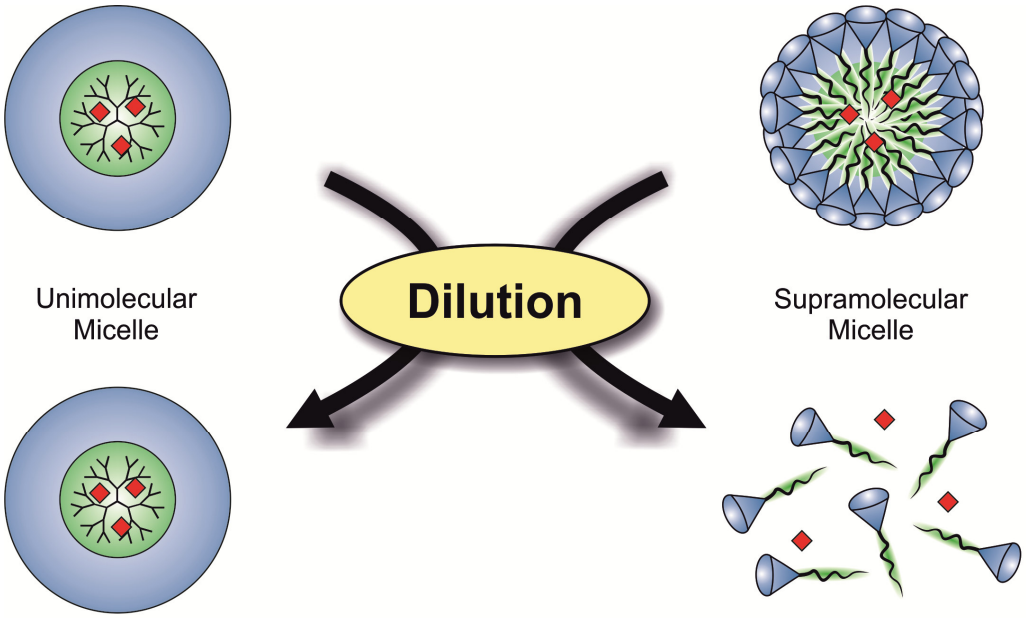


Figure 22. Schematic representation of the benefits from encapsulation with unimolecular micelles which stay intact under dilution due to their chemically bound structure, while supramolecular micelles can fall apart.

Although the release of the guest remains the focus of most research,[135–139] the solubilization process is unclear and little is known about the factors that influence the encapsulation of a certain guest in a certain carrier.[140,141] It was found that the encapsulation mechanism of amphiphilic core-shell systems is not necessarily unimolecular but can be also based on aggregates of unimolecular micelles with the encapsulated guest (Figure 23D).[142–146] There are three pathways for unimolecular encapsulation within amphiphilic core-shell nanocarriers that are (1) in the core, (2) in the shell, or (3) at the interface of core and shell (Figure 23A-C). In the efforts to decrease the lack of mechanistic understanding for molecular transport systems, dyes are often used as model systems for drugs because of the better investigation possibilities. For example, the fluorescent dye pyrene is commonly used because its fluorescence depends on the local environment in the nanocarrier and can therefore lead to knowledge about the encapsulation pathway.[147]

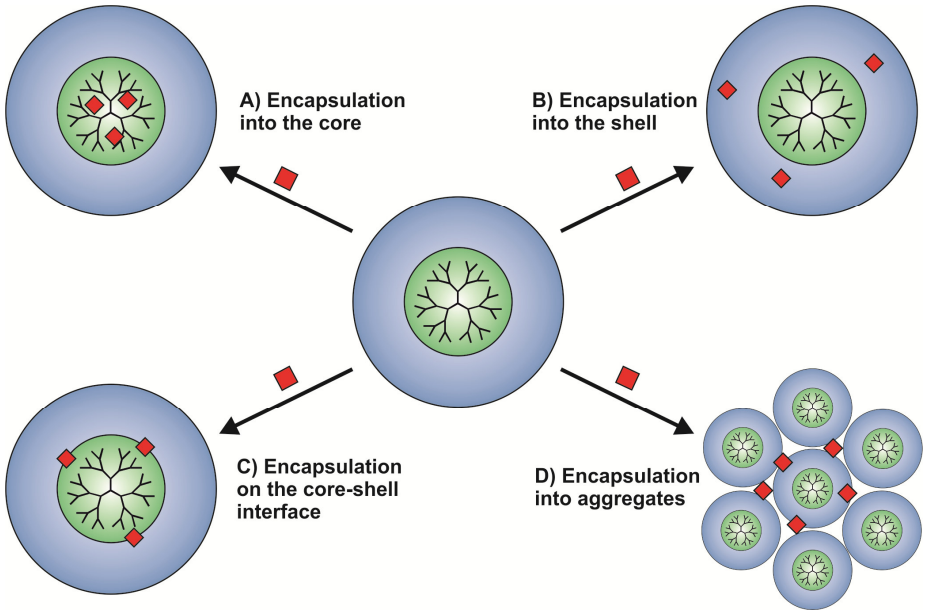


Figure 23. Different pathways for encapsulating of drugs or dyes in core-shell nanocarriers: (A) into the core, (B) into the shell, (C) on the core-shell interface, or (D) into aggregates of unimolecular micelles.

In 1991, Newkome et al. introduced the term unimolecular micelle. They could show that a dendritic cascade polymer with multiple carboxylic acid groups on the periphery (Figure 24) could encapsulate hydrophobic guests in water without showing a concentration dependence which is traditionally seen in small amphiphilic molecules.[131,148]

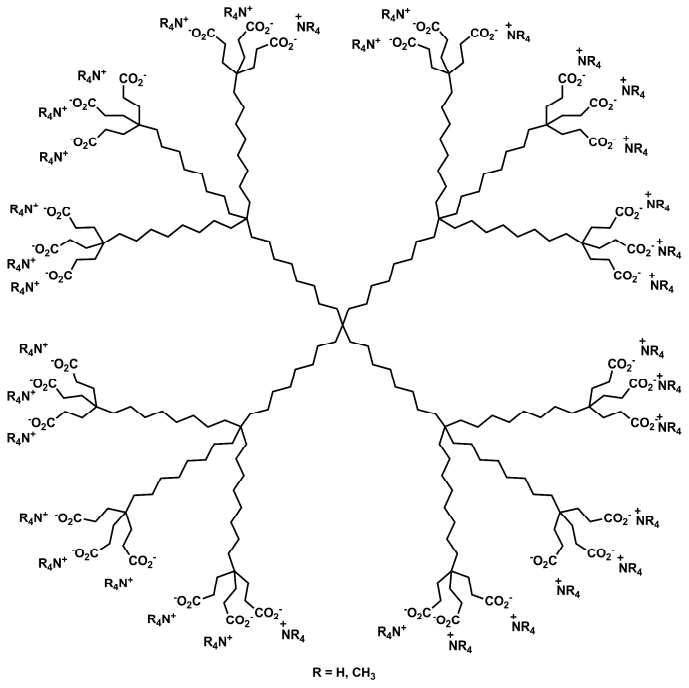


Figure 24. The first example of unimolecular micelles was reported by Newcome et al.[131]

While Newkome et al. used the divergent approach, Fréchet and co-workers reported the first amphiphilic dendrimer synthesized by a convergent approach in 1993.[134,148] Meijer and co-workers pioneered the investigation on the encapsulation behavior by developing the so-called "dendritic box" that could effectively "lock" guests by steric blocking the dendrimers and release them after steric "de-blocking" (Figure 25).[148,149]

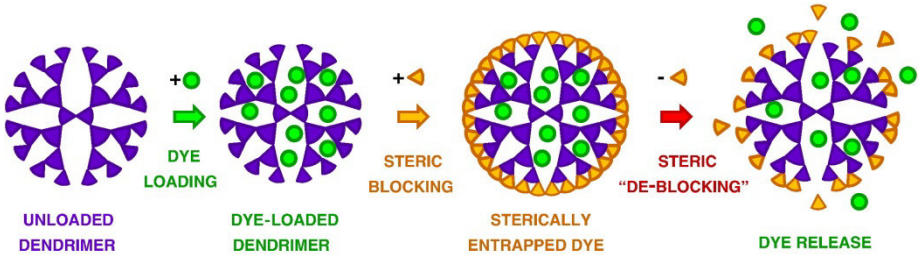


Figure 25. Schematic representation of the "dendritic box" in which the payload can be entrapped by steric blocking and released again after steric "de-blocking."[148,149] Reprinted from [148] Copyright (2012), with permission from Elsevier.

In all of these early examples, the "shell" only consisted of distinct functional or the above-mentioned sterical blocking groups, on the periphery of the dendrimers. Afterwards, the design of specific core-shell architectures first began by introducing PEG as the shell building block to increase the water solubility.[130] A huge amount of different polymers are now being used as core and shell materials, but inorganic materials have also been investigated.[124,125] Decheng Wan and co-workers published several very interesting studies for a better understanding of encapsulation processes by systematically varying core-shell structures, for example, by core engineering.[150–155] They also tried to understand what influences encapsulation in aggregates or as unimolecular micelles and studied the cooperative entrapment of different guests.[156] Unfortunately, these early studies were mostly conducted on the encapsulation of hydrophilic compounds in organic solvents, which is not necessarily transferable to the encapsulation of hydrophobic compounds in aqueous solutions. These organo-soluble systems with hydrophilic cores and hydrophobic shells are called inverse unimolecular micelles.[157] However, for application as DDS water-soluble systems for the encapsulation of hydrophobic guests are of much greater interest.

Some of the typical examples for dendritic polymer scaffolds used as DDS are shown in Figure 26. Next to amino containing polymers like polyethyleneimine (PEI), poly(propylene imine) (PPI), and poly(amido amine) (PAMAM), dendritic polyglycerol (dPG) could be also established as a new platform for nanomedicine.[46,123]

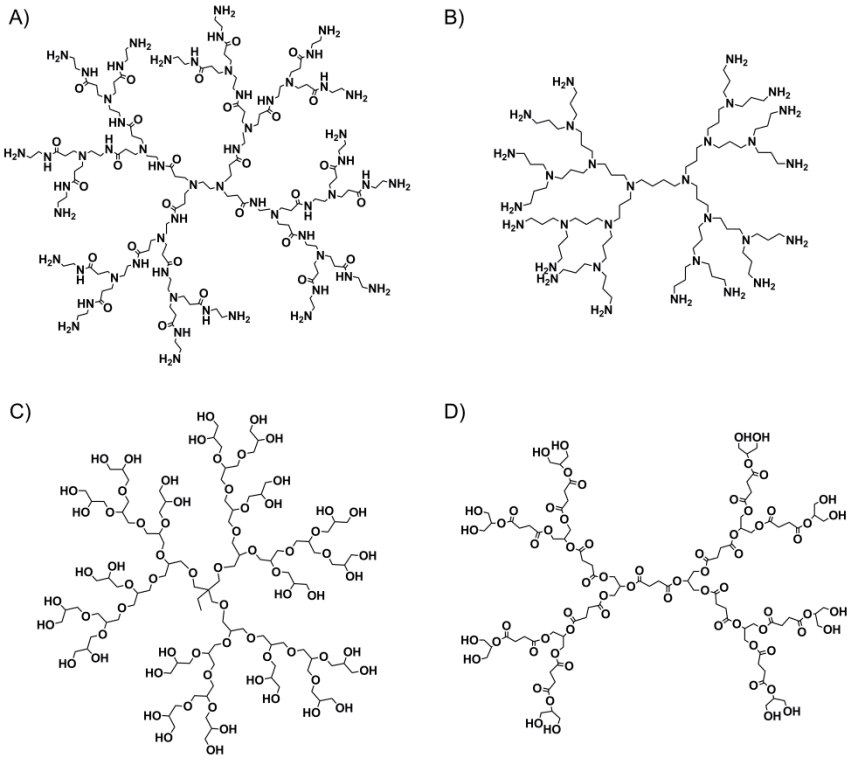


Figure 26. Examples of frequently used polymeric scaffolds for dendritic DDS. (A) Polyamidoamine (PAMAM), (B) poly(propylene imine) (PPI), (C) polyglycerol (PG), and (D) poly(glycerol-succinic acid) dendrimer. Figure adapted from the literature.[46,123]

In general, the encapsulation capacity depends on the hydrophilicity or hydrophobicity of both the nanocarrier and the guest, which means that hydrophilic cores can usually encapsulate hydrophilic guests (like in the above-mentioned inverse micelles) and hydrophobic cores can encapsulate hydrophobic guests. PG, for example, is very hydrophilic, so naturally when it was used as the core material with a shell built from alkyl chains, it could encapsulate hydrophilic guests, like the dye Congo red, in organic solvents.[158] However, dendritic PG-based core-shell nanocarriers could also be successfully developed by modifying the interior of dPG in such a way that the core became more hydrophobic than the shell. This can be also considered as the introduction of hydrophobic "pockets" within the hydrophilic scaffold. For this purpose, alkyl chains, aromatic units, and perfluorinated chains were introduced to be able to encapsulate hydrophobic guests within the PG nanocarriers as well.[143,159–163] The shell was usually made from PEG. Some of the reported PG cored nanocarriers showed either a unimolecular encapsulation or an aggregates-based one, depending on the type of drugs and dyes used.

Inspired by liposomes, core-multishell (CMS) nanocarriers were developed that had a hydrophilic core, a hydrophobic inner shell, and a hydrophilic outer shell. The first generation was based on a hyperbranched PEI core, a linear alkyl chain, and a PEG outer shell.[142] In the next generation, the PEI core was exchanged for a dPG one because of PEI's potential toxicity and the much better biocompatibility of PG.[144,145,164] In most of the studied examples, encapsulation with CMS nanocarriers was based on aggregates and not as initially intended based on unimolecular nanocarriers (Figure 27).

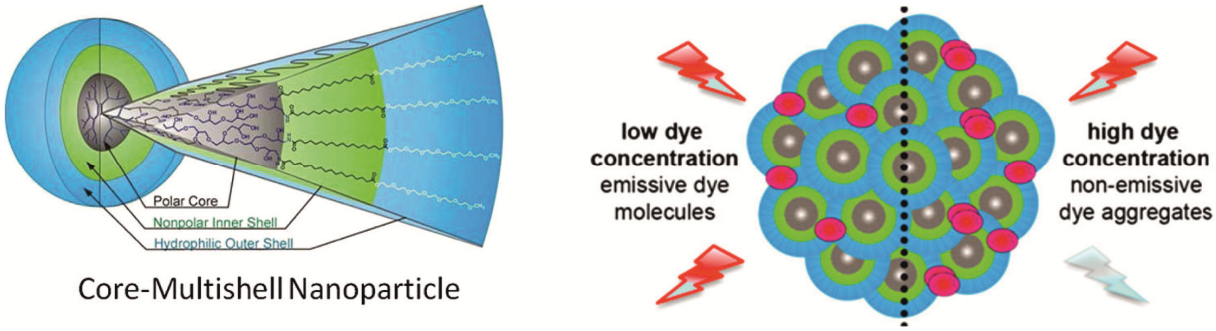


Figure 27. Example for a core-multishell nanoparticle and a representation of its aggregation upon the encapsulation of Nile red (NR, oval red circles). At low dye concentrations, the dye molecules stayed emissive, while at high dye concentrations, NR aggregates formed within the CMS aggregates, which were non-emissive. Adapted with permission from Ref. [144]. Copyright © 2012, American Chemical Society.

In one study, it seemed that the introduction of a rather uncontrolled hyperbranched PG shell could prevent the aggregation.[165] However, in another study, where perfect PG dendrons of generation 1 or 2 were used as the shell building block, it was found that the aggregation of CMS nanocarriers could not be generally prevented in this way.[145] Moreover, the authors concluded that the aggregation or non-aggregation was strongly influenced by the guest molecules.[145] Very recently pH-responsive CMS (pH-CMS) nanocarriers could also be presented.[166] The new system could encapsulate the anti-tumor drug doxorubicin at physiological pH (7.4) but could cleave the shell at lower pH (starting around pH 5), which is also present in tumor tissue, and thereby release the drug. Interestingly, in this case the transport of doxorubicin was achieved by unimolecular CMS and pH-CMS nanocarriers and not in aggregates, as was observed for other guest molecules such as Nile red (NR).[166] In any case, further systematic studies will be needed to learn more about the influencing factors for encapsulation by structure-property relationships.

As explained above, the real challenge lies in the encapsulation of hydrophobic guests in water. Core-shell systems based on hydrophobic cores have been less explored for synthetic difficulties. It is envisioned that very hydrophobic cores, which show a big polarity gradient from the shell to the core, should exhibit high encapsulation capacities. In 2004, Guan and co-workers published a very elegant one- or two-step procedure to obtain dendritic, highly hydrophobic polyethylene cores with hydrophilic PEG shells (Figure 28).[37] They either copolymerized ethylene by CWP with a comonomer bearing a PEG-chain or alternatively first synthesized hydroxyl-functionalized dendritic PE cores and grafted the PEG shell to it. The reported nanocarriers were water-soluble and could encapsulate the hydrophobic dye NR in a unimolecular fashion. Quantitative data indicated that the dye encapsulation capacity was nearly proportional to the M_n of the hydrophobic core.[37]

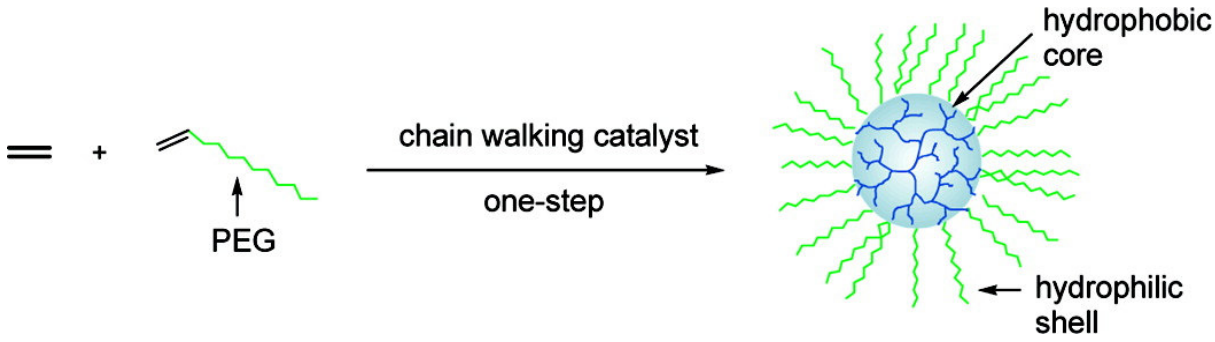


Figure 28. Schematic representation of the one-step procedure by CWP to obtain dendritic PE cores with PEG shells. Reprinted with permission from Ref. [37]. Copyright © 2004, American Chemical Society.

Several more manuscripts on PE-based core-shell systems have been recently published.[138-141] One interesting study by Wu and co-workers compared the encapsulation of a coumarin dye (C153) in nanoparticles with either a dendritic or hyperbranched PE core whereby both had a poly(oligo(ethylene glycol) methacrylate) (POEGMA) shell.[171] The study suggested that coumarin 153 sensed a slightly more polar environment for the dendritic core than for the hyperbranched one.[171] In 2013, the same group also published the synthesis and investigation of a series of dPE core-mPEG (here named PEO) shells (Figure 29).[172] In a first step, hydroxyl-functionalized dPE was synthesized. The hydroxyl-groups were then converted into alkyne groups and the azide-functionalized mPEG was introduced by click chemistry. Due to a low amount of hydrophilic mPEG chains on the hydrophobic dPE core,

the dPE-mPEG core-shell nanoparticles were not directly water-soluble but were soluble in organic solvents like tetrahydrofuran (THF).

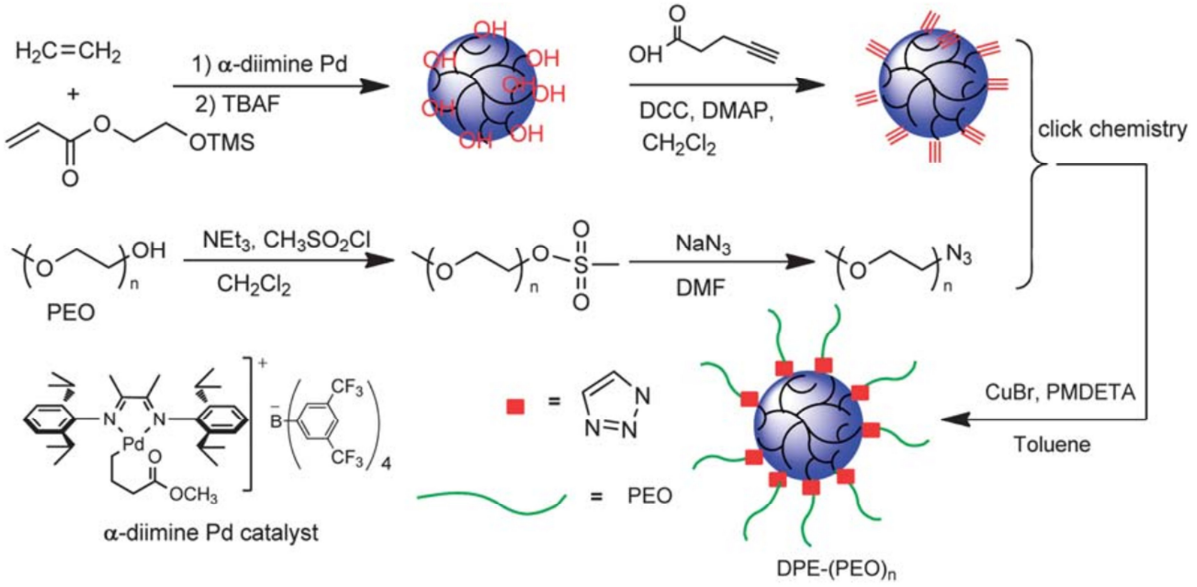


Figure 29. Synthetic scheme for the synthesis of amphiphilic DPE-$(PEO)_n$ nanoparticles by click chemistry. Reproduced from Ref. [172] with permission from The Royal Society of Chemistry.

The authors studied the self-assembly of the core-shell nanoparticles into supramolecular architectures in water and hexane after using a slow solvent exchange method by dialysis from THF to the respective solvent. Vesicular structures were observed in water. The sizes of the vesicles grew with increasing mPEG chain length. In hexane the amphiphilic nanoparticles exhibited a critical micelle concentration (CMC of 0.8 mg/mL) above which the nanoparticles self-assembled into multi-molecular micelles but under which they were present as unimolecular micelles (Figure 30). The multi-molecular micelles again increased in size with longer PEG chains. Furthermore, with one of their nanoparticles, they investigated the encapsulation of the hydrophilic dye Rhodamine B in hexane which increased considerably above the CMC because of the more hydrophilic environment provided by the multi-molecular micelles.[172]

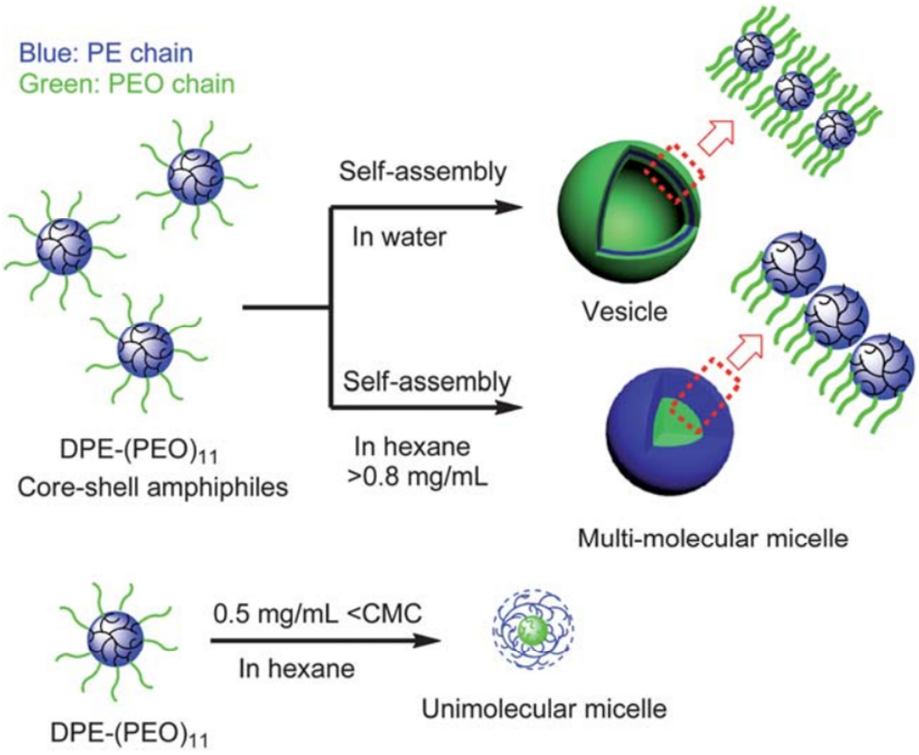


Figure 30. Self-assemblies of amphiphilic DPE-$(PEO)_n$ nanoparticles in different solvents and at different concentrations. Reproduced from Ref. [172] with permission from The Royal Society of Chemistry.

The questions or issues and probably biggest challenges that remain when using hydrophobic cores like dPE are firstly, if and how the encapsulated guests could be released again from the nanocarriers and, secondly, the non-biodegradability of dPE that currently limits the application of these systems in biomedical applications.

Another possible core that deserves a short introduction in the context of this thesis is the carbon-based nanodiamond (ND). ND has emerged as a highly interesting material for biomedical application because of its inertness, low toxicity, and especially because of its possible non-bleaching and non-blinking strong fluorescence of NDs with nitrogen-vacancy (N-V) centers.[173–175] NDs were already discovered in the 1960s but the scientific community needed 20-30 years to become aware of their relatively easy production and unique properties, including high hardness, stiffness, and strength.[173,175] One of the ways to produce NDs is by the detonation technique, which usually yields ND sizes of ~5 nm.[176] NDs consist of sp^3-hybridized carbon atoms in a diamond lattice structure and have a perturbed carbon shell with different functional groups.[176] The structure and composition of the shell differ

depending on how the NDs were prepared.[176] Figure 31 shows the octahedral nanodiamond model as well as bulk diamonds in comparison to nanodiamond powder.

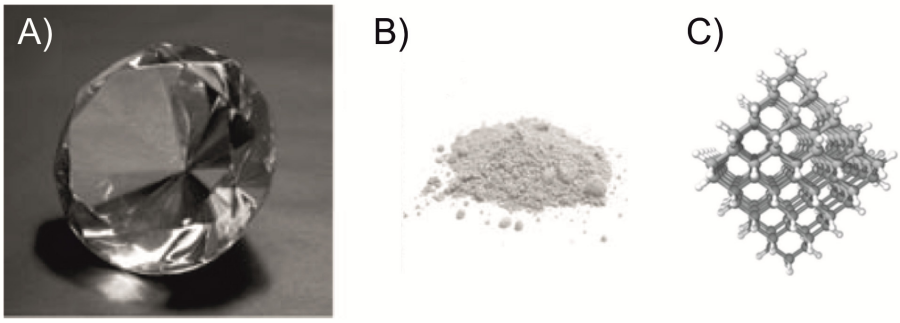


Figure 31. (a) Bulk diamonds, (b) nanodiamond powder, (c) the octahedral nanodiamond model. Adapted from Ref. [177] with permission from The Royal Society of Chemistry and from Ref. [174] with permission from John Wiley and Sons. Copyright © 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

The obtained NDs have a variety of functional groups on their surface, which can be unified by several modification strategies (Figure 32). For example, carboxyl groups can be obtained by harsh oxidation with very strong acids, e.g., H_2SO_4/HNO_3 3:1, under heating and sonication.[174,178]

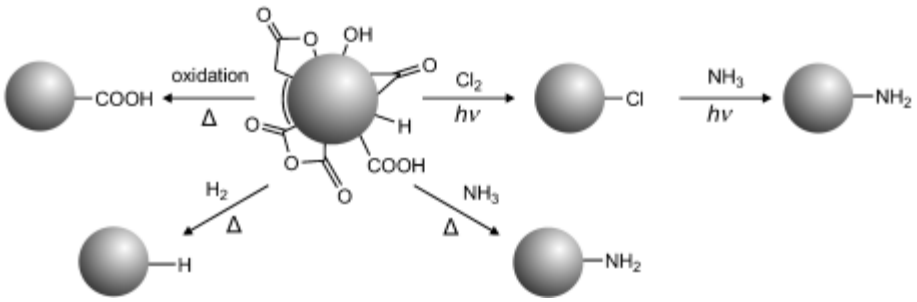


Figure 32. Examples of possible ways to unify the functional groups on NDs. Adapted from Ref. [174] with permission from John Wiley and Sons. Copyright © 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

NDs usually have a strong tendency to agglomerate. This agglomeration results in poor dispersibility in physiological environment, i.e., in phosphate buffered saline (PBS) or in cell culture medium, which limits their biomedical application.[179] Therefore, strategies like PEGylation or PG-lation have been employed to improve their water dispersibility.[179–181]

PEGylated NDs were able to adsorb doxorubicin and to transport the drug into tumor cells.[182] In 2011, Komatsu and co-workers reported the synthesis of highly soluble PG-coated NDs that could even be purified and size separated by chromatography. They first oxidized the NDs and then grafted PG by ring-opening polymerization of glycidol in bulk under neutral conditions and at high temperature (Figure 33).[181]

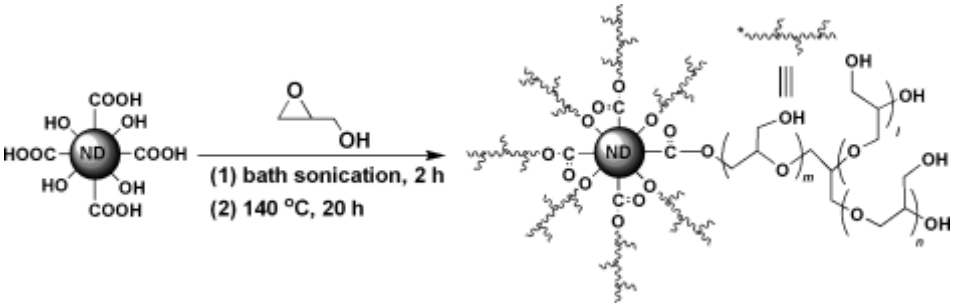


Figure 33. Komatsu's synthesis of ND functionalized with hyperbranched PG by grafting-from through the ring-opening polymerization of glycidol. Reproduced from Ref. [181] with permission from John Wiley and Sons. Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Furthermore, recently it could be shown that fluorescent NDs keep this property even after PG functionalization[183] and ND-PG has been also been used as a new macrophage-evading platform for targeted drug delivery and for gene delivery.[184,185] Ongoing investigations indicate that further advances will be made in the field of ND-based systems in the near future.

2 Scientific Goals

As outlined in the introduction, polyolefins such as polypropylene and polyethylene have many advantages that make them some of the most commonly used polymers in the world. However, polyolefins have some drawbacks like their hydrophobicity that limit their use in biomedical applications. In this work, polyglycerol (PG) was introduced to overcome these limitations, because it makes them amphiphilic, and thus more hydrophilic and biocompatible. The objective of this thesis is therefore to modify polyolefins with polyglycerols (PG-lation) to increase the materials' hydrophilicity. The biomedical application of these new amphiphilic polyolefin-polyglycerol systems shall be investigated as bioinert surfaces and as macromolecular carriers for drug delivery (Figure 34).

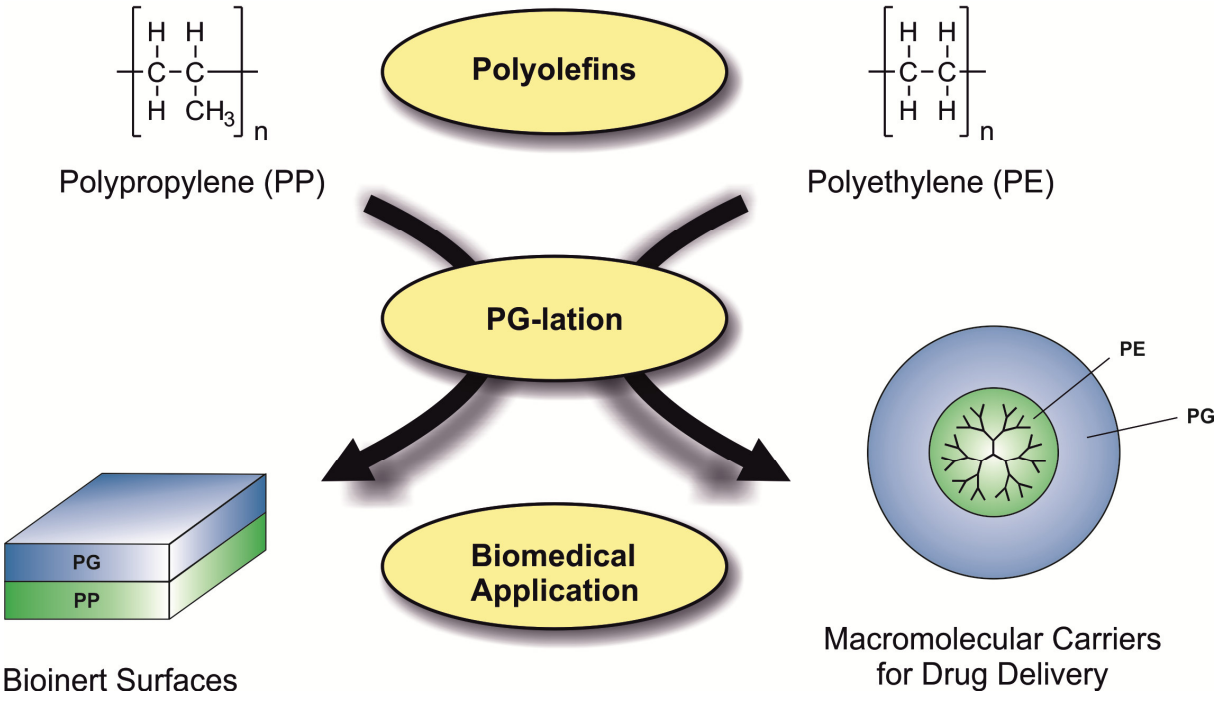


Figure 34. Schematic of the scientific goal of this thesis, which is the PG-lation of polyolefins and the biomedical application as bioinert surfaces and macromolecular carriers for drug delivery.

In the first part of this work, amphiphilic polyolefin-polyglycerol surfaces shall be synthesized in a simple two-step approach and investigated for their application as bioinert surfaces. Since polyolefins have no reactive functional groups on their surfaces, they need to be introduced by an activation method. Reactive bromine anchoring groups will therefore be introduced in this work on commercial polypropylene (PP) films by plasma bromination. The

coating with PG shall be performed by a grafting-to procedure with PG-amines. Different molecular weights and amounts of amino functionalities will be grafted onto the PP surfaces to investigate if the sterical hindrance of bigger molecular weight PGs can be overcome by more binding sites to the surface. Furthermore, it shall be investigated if this multivalent binding led to higher long-term stability of the coated PP films. The successfulness of the PG-lation shall be analyzed by various characterization methods. To investigate the applicability as bioinert surfaces, the resistance to protein adsorption and bacteria attachment will be studied for the different PG-PP films.

In the second part of this work, the application of amphiphilic polyethylene (PE)-polyglycerol core-shell copolymers as macromolecular carriers for drug delivery shall be studied. The poor solubility of hydrophobic compounds in an aqueous environment strongly limits their biomedical application. The use of amphiphilic unimolecular transporters for enhancing the solubilization of hydrophobic guests through encapsulation is a possible solution as was described in the introduction. Therefore, PE-PG core-shell nanoparticles will be synthesized with a simple two-step approach. The first step shall be to synthesize hydroxyl-functionalized dendritic PE copolymers as the core building block. It is necessary to introduce hydroxy groups as attachment points to build up the PG shell, which shall be, in contrast to the first part of this work, introduced by a grafting-from procedure through the hyperbranched polymerization of glycidol. The resulting PE-PG core-shell copolymers will be analyzed by various characterization methods. The nanocarriers' ability to encapsulate hydrophobic guests in aqueous media and the encapsulation mechanism shall especially be studied. The investigations will be divided into two studies. In the first one, the benefits from using unimolecular nanocarriers rather than supramolecular micelles shall be proven for the transport of a hydrophobic guest into tumor cells. In the second study, the influence of the flexibility of the core shall be investigated in comparison to hard nanodiamond (ND) cored nanoparticles.

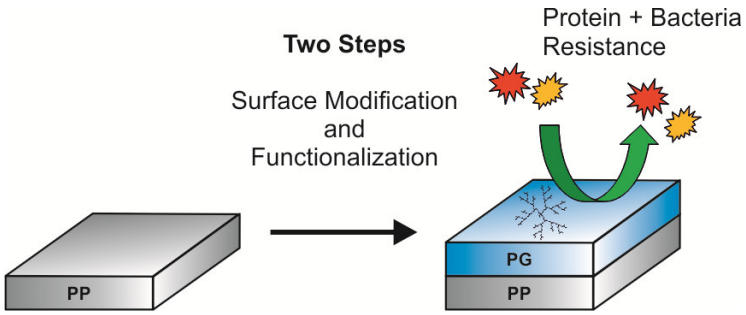
3 Publications and Manuscripts

3.1 Polyglycerol Coated Polypropylene Surfaces for Protein and Bacteria Resistance

This chapter was published in:

Maike C. Lukowiak, Sascha Wettmarshausen, Gundula Hidde, Petra Landsberger, Viola Boenke, Karsten Rodenacker, Ulrike Braun, Jörg F. Friedrich, Anna A. Gorbushina, Rainer Haag,* *Polymer Chemistry* **2015**, *6*, 1350-1359.

http://dx.doi.org/10.1039/C4PY01375A



The Author's Contributions:

- Synthesis of PG-amines (one PG was obtained on azide stage from Cathleen Schlesener)
- Synthesis of PG-coated PP films and mPEG-coated control
- Characterization by contact angle and zeta potential measurements
- Protein adsorption study
- Coordination of the cooperations
- Discussion and evaluation of all results
- Preparation of the manuscript

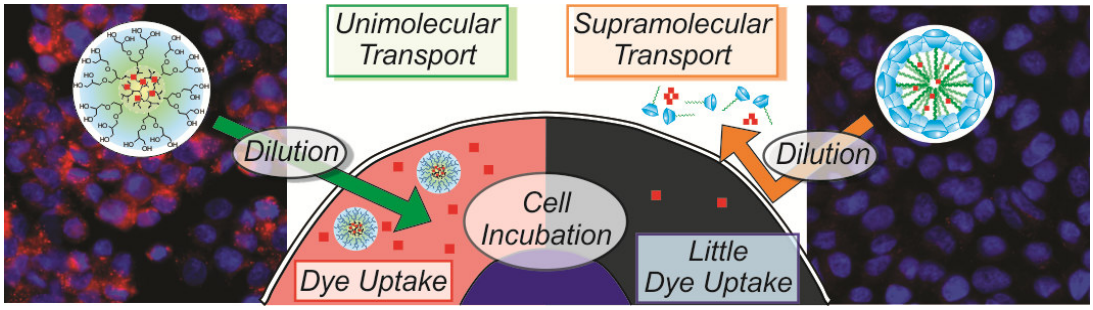
3.2 Tandem Coordination, Ring-Opening, Hyperbranched Polymerization for the Synthesis of Water-Soluble Core–Shell Unimolecular Transporters

This chapter was published in:

Chris S. Popeney,[#] Maike C. Lukowiak,[#] Christoph Böttcher, Boris Schade, Pia Welker, Dorothea Mangoldt, Gesine Gunkel, Zhibin Guan,* Rainer Haag,* *ACS Macro Letters* **2012**, *1 (5)*, 564–567.

[#] These authors contributed equally.

http://dx.doi.org/10.1021/mz300083y



The Author's Contributions:

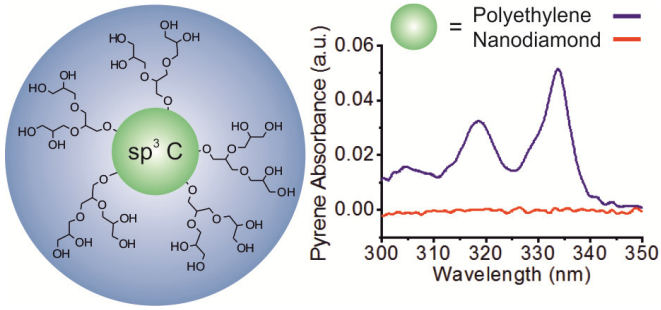
- Synthesis and purification of PE-PG core-shell copolymer as well as all needed reagents
- Characterization by NMR, GPC-MALLS, and DLS
- Loading of core-shell nanocarrier and amphiphilic micelle
- UV/Vis, Fluorescence, and DLS experiments for investigation of encapsulation
- Design of in vitro experiment with the help of Pia Welker
- Performance of FACS experiments with the help of Dorothea Mangoldt
- Discussion and evaluation of the results
- Manuscript preparation together with Chris Popeney

3.3 Carbon-Based Cores with Polyglycerol Shells – The Importance of Core Flexibility for Encapsulation of Hydrophobic Guests

This chapter was published in:

Maike C. Lukowiak, Benjamin Ziem, Katharina Achazi, Gesine Gunkel-Grabole, Chris S. Popeney, Bala N. S. Thota, Christoph Böttcher, Anke Krueger, Zhibin Guan, Rainer Haag,* Journal of Materials Chemistry B **2015**, *3*, 719-722.

http://dx.doi.org/10.1039/C4TB01858C



The Author's Contributions:

- Synthesis and purification of PE-PG core-shell copolymer as well as all needed reagents
- Characterization by NMR and GPC-MALLS
- Characterization of both nanocarriers by DLS and TGA
- Loading of core-shell nanocarrier and amphiphilic micelle
- UV/Vis, Fluorescence, and DLS experiments for investigation of encapsulation
- Design of in vitro experiment with the help of Katharina Achazi
- Discussion and evaluation of the results
- Preparation of the manuscript

4 Summary and Conclusion

The aim of this work was to modify hydrophobic polyolefins with hydrophilic polyglycerol (PG) for improved properties and to investigate their potential biomedical application. The work was divided into two areas of research, bioinert surfaces and macromolecular carriers for drug delivery (Figure 35).

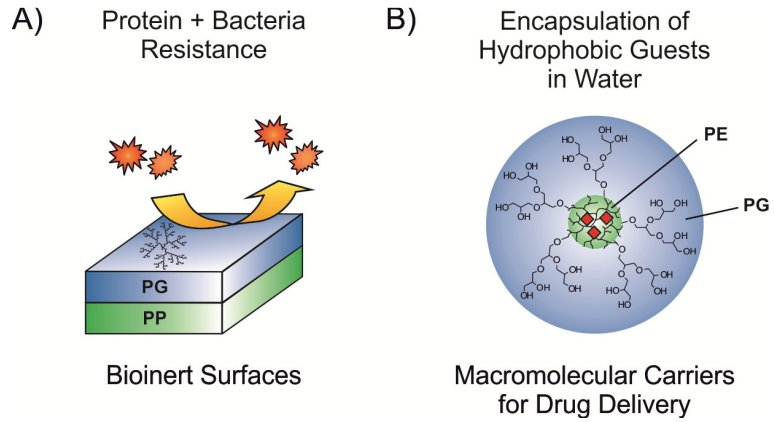


Figure 35. Biomedical application of amphiphilic polyolefin-polyglycerol systems investigated in this work. (A) Polyglycerol (PG) coated polypropylene (PP) films as bioinert surfaces. (B) Polyethylene (PE)-PG core-shell nanoparticles as macromolecular carriers for drug delivery.

The first part of this work focused on the biomedical application of amphiphilic polyolefin-polyglycerol systems as bioinert surfaces (Figure 35A). Polyolefins are commonly used for biomedical purposes, but their strong hydrophobicity results in protein adsorption and biofilm formation. Therefore, the goal was to modify polyolefin surfaces with polyglycerol to increase their inertness. PG-coated PP films were synthesized in an easy two-step protocol by plasma bromination and subsequent grafting-to of PG-amines. The first step was to introduce reactive bromine anchoring groups on the surface of PP with high yield and selectivity. In the second step, the bromine groups could be replaced under very mild conditions by the amino functionalities of PG, which was used with different molecular weights and amounts of amine groups. Grafting polymers with bigger molecular weights becomes increasingly difficult. It could be shown that the rising sterical hindrance of bigger PGs could be overcome by adding more potential binding sites to the surface. The PG-coated films were characterized by contact angle, X-ray photoelectron spectroscopy (XPS), ATR-FTIR, and surface zeta potential measurements. Successful grafting was demonstrated by reducing the contact angle from very

hydrophobic contact angles for pure PP films to very hydrophilic contact angles for PG-coated PP films. An increased oxygen content in XPS and a shoulder in the C1s spectra at a binding energy of 286.5 eV that is specific for alcohol and ether bonds gave further evidence. Surface zeta potential and ATR-FTIR measurements suggested a higher water uptake than for untreated PP. Longer plasma bromination times and multivalent introduction of PG resulted in better long-term stability. The applicability of the PG-coated films was studied by investigating the protein adsorption. Fluorescently-labeled proteins (BSA-FITC and FIB-FITC) were incubated with the PG-coated or mPEG-coated films for comparison, since poly(ethylene glycol) coatings still represent one of the gold standards for bioinert surfaces, and the amounts of adsorbed proteins were measured by fluorescence microscopy. All PG-coated PP films showed good protein resistance that reached values as low as 2% in comparison to bare PP and the results were as good as or better than the mPEG-coated control. However, no structure-property relationships could be found for the different PG-coated PP films. The resistance to bacteria attachment was furthermore investigated for the best surfaces for two different model biofilm-forming bacteria (*E.coli* and *P.aeruginosa*). A small difference in the amino group concentration of the originally prepared PGs had a surprisingly major effect on the bacteria attachment. Only the lower original amino functionalization of PG proved to be beneficial for reduction of bacterial attachment and the results were superior to the mPEG-coated control.

In summary, the amphiphilic modification of PP surfaces with PG by a very simple two-step method could be successfully applied as bioinert surfaces with protein and bacteria resistance. The knowledge that was generated can be used to design better real-life bioinert polymer surfaces in the future.

The second part of this work focused on the biomedical application of amphiphilic polyolefin-polyglycerol systems as macromolecular carriers for drug delivery (Figure 35B). Macromolecular carriers, like unimolecular micelles, can improve the solubilization of hydrophobic compounds in aqueous environment by encapsulation. The mechanism for encapsulation is not necessarily unimolecular but can also be aggregate-based. Until now, little knowledge has been available about the factors that determine encapsulation and most studies have been conducted in organic instead of aqueous solution and therefore for encapsulation of hydrophilic instead of hydrophobic guests. The solubilization and transport of hydrophobic guests/drugs is, however, more useful for biomedical application. Hence, in the second part of this work, PE-PG core-shell nanoparticles were synthesized in a simple two-step procedure by tandem coordination and ring-opening polymerization, and the ability

of the PE-PG copolymers to function as nanocarriers was investigated. Special focus was given to understanding the encapsulation mechanism. The second part of the work was divided into two further studies. In both of them, hydroxyl-functionalized dendritic PE core was synthesized by palladium-catalyzed chain walking polymerization (CWP) as the first step. Two different CWP catalysts were used to obtain a very big dendritic PE with a high molar incorporation of hydroxy groups for the first study and a smaller dendritic PE with a low amount of hydroxy groups for the second study. In a second step, these hydroxy groups were used in both cases as initiation points for the ring-opening polymerization of glycidol to obtain hyperbranched PG as the shell. A much bigger shell was necessary in the second case to achieve good water solubility. Both PE-PG core-shell copolymers were characterized by NMR, static (GPC-MALLS) and dynamic (DLS) light scattering techniques, and cryo-TEM. Two commonly used hydrophobic model compounds, pyrene (PY) and Nile red (NR), were used to investigate the core-shell nanocarriers' encapsulation behavior. In the first study, we found that the PE-PG nanocarrier solubilized both guests in a unimolecular fashion. The benefit of the higher stability of this unimolecular transporter under dilution conditions was proven in comparison to a compositionally similar supramolecular amphiphile for the transport of NR into tumor cells. In the second study, we compared the encapsulation and transport efficiency of the second PE-PG nanoparticle to another sp^3-hybridized carbon-cored core-shell nanocarrier with nanodiamond (ND) core that had different core flexibility but the same hyperbranched PG shell. While the dendritic PE core is soft and flexible, the nanodiamond core is hard and rigid. No solubilization higher than the natural water solubility of the guest PY was found for ND-PG. The solubilization of NR was also clearly lower for ND-PG than for PE-PG. Moreover, we found that both core-shell nanoparticles were able to transport NR into tumor cells, but due to the better loading of the flexible PE-PG the latter showed better results than the rigid ND-PG. The applicability of the rigid nanocarrier (ND-PG) would be very limited because of its extremely low encapsulation capacity.

In summary, the amphiphilic modification of the synthesized dendritic PE nanoparticles with hyperbranched PG resulted in PE-PG core-shell copolymers that could be successfully applied as macromolecular carriers for the solubilization of hydrophobic guests in aqueous media. Special focus was given to encapsulation and transport behavior. The flexible PE-PG nanocarriers could be shown to be superior to supramolecular amphiphiles as well as to rigid nanodiamond-cored nanocarriers. The knowledge that was gained in the studies from the second part of this thesis should be helpful for designing better nanocarriers in the future.

5 Outlook

This thesis demonstrated a way to improve the properties of polyolefins by modification with polyglycerols for biomedical application in two different fields as bioinert surfaces and as macromolecular carriers for drug delivery.

In the first project, it would be of further interest to find the mechanistical reasons for the surprising bacteria attachment results. However, one has to keep in mind that biofilm formation, including protein adsorption and bacterial attachment, are extremely complex multi-parameter problems which would probably require an even more simplistic approach. Apart from the study of the protein and bacteria resistance, it would be worthwhile to investigate the hemocompatibility of the produced PP-PG films since many biomedical applications come in contact with blood. Furthermore, since these films' passive bioinertness might not be sufficient for real-life application, these systems should be further developed to include an active, biocide-releasing surface.

For the use of PE-PG nanoparticles as macromolecular carriers for the study of the encapsulation of hydrophobic guests, additional parameters should be adjusted in the building blocks of the nanocarrier for a deeper understanding of the encapsulation mechanism and the structure-property relationships. For example, one could further change the topology or the sizes of the core or the shell. The two biggest limitations for application as drug delivery devices are the release of the hydrophobic cargo from the hydrophobic core and the polyethylene core's non-biodegradability. Therefore, the development of a triggered release system and biodegradable core-shell architectures remain still a challenge.

6 Kurzzusammenfassung/ Short Summary

6.1 Kurzzusammenfassung

Das Ziel dieser Arbeit war die Modifizierung von hydrophoben Polyolefinen mit hydrophilen Polyglycerinen um verbesserte Eigenschaften zu erreichen und die potentielle biomedizinische Anwendung zu untersuchen.

Der erste Teil der Arbeit fokussierte sich auf die biomedizinische Anwendung von amphiphilen Polyolefin-Polyglycerin-Systemen als bioinerte Oberflächen. PG-beschichtete PP-Oberflächen konnten in einem einfachen, zweistufigen Verfahren über (1) Plasmabromierung zur Einführung von reaktiven Brom-Ankergruppen und (2) das Aufpfropfen von PG-Aminen unter milden Bedingungen hergestellt werden. Der Erfolg der Beschichtung wurde über Kontaktwinkel-, XPS-, ATR-FTIR- und Zetapotential-Messungen untersucht. Die Schwierigkeit hochmolekulare PGs aufzupfropfen konnte über die Einführung von mehr Amin-Linkern überwunden werden. Eine längere Plasmabromierungsdauer und die multivalente Präsentation von PG führte zu einer höheren Langzeitstabilität. Die Proteinadsorption konnte für alle PG-PP-Folien im Vergleich zu reinem PP stark reduziert werden und war gleich gut oder besser als die der mPEG-beschichteten Kontrolle. Die besten Oberflächen wurden auf ihre Resistenz gegen Bakterienadhäsion getestet. Überraschenderweise führte ein kleiner Unterschied im ursprünglichen Amingehalt zu einer großen Änderung der Bakterienadhäsion. Oberflächen mit extrem geringen Amingehalt zeigten gute Resistenz gegen Bakterien und waren der mPEG-Kontrolle überlegen. Diese neuen Ergebnisse können für das Design von besseren, anwendungsbezogenen, bioinerten Polymeroberflächen verwendet werden.

Der zweite Teil der Arbeit fokussierte sich auf die biomedizinische Anwendung der amphiphilen Polyolefin-Polyglycerin-Systeme als molekulare Transporter für Wirkstoffe. PE-PG Kern-Schale-Nanopartikel wurden über ein einfaches, zweistufiges Verfahren über eine Tandem Koordinations-, Ringöffnungs-Polymerisation hergestellt. Die Fähigkeit von PE-PG-Copolymeren als Nanocarrier zu agieren wurde untersucht. Zwei verschiedene PE-PG-Nanocarrier wurden synthetisiert und über NMR, GPC-MALLS, DLS und Kryo-TEM charakterisiert. Die Beladung der Nanopartikel mit zwei häufig verwendeten hydrophoben Modell-Farbstoffen wurde mittels UV/Vis, Fluoreszenz und DLS Messungen untersucht. In einer ersten Studie zeigten die PE-PG-Nanocarrier unimolekulares Transportverhalten und der Vorteil gegenüber supramolekularem Transport konnte über die Aufnahme unter hoher

Verdünnung von transportiertem NR in Tumorzellen gezeigt werden. In einer zweiten Studie wurde der weiche PE-PG-Nanocarrier mit einem ND-PG-Nanopartikel mit hartem Nanodiamanten als Kern verglichen. Der weiche PE-PG-Nanocarrier war dem harten ND-PG in Bezug auf Verkapselungskapazität und Aufnahme von transportiertem NR in Tumorzellen überlegen. Das in diesen Studien generierte Wissen dient nun für das Design optimierter Nanocarrier.

6.2 Short Summary

The aim of this work was to modify hydrophobic polyolefins with hydrophilic polyglycerol in order to achieve improved properties and to investigate their potential biomedical application. The first part of this work focused on the biomedical application of amphiphilic polyolefin-polyglycerol systems as bioinert surfaces. PG-coated PP surfaces could be synthesized in an easy two-step approach by (1) plasma bromination for the introduction of reactive bromine anchoring groups and (2) grafting of PG-amines under very mild reaction conditions. The successfulness of the coating was investigated by contact angle, XPS, ATR-FTIR, and zeta potential measurements. The difficulties grafting bigger molecular weight PGs could be overcome by introducing more amino linkers to the surface. Longer plasma bromination times and multivalent presentation of PG resulted in higher long-term stability. The protein adsorption could be more strongly reduced for all PG-PP films in comparison to bare PP and was as good as or better than the mPEG-coated control. The best surfaces were tested for their resistance to bacteria attachment. Surprisingly, a small difference in the original amine amount already led to a big change in bacteria attachment. Surfaces with extremely low amine content showed good resistance to bacteria, which was superior to the mPEG-coated control. These new results can be used to design better real-life bioinert polymer surfaces

The second part of this work focused on the biomedical application of amphiphilic polyolefin-polyglycerol systems as macromolecular carriers for drug delivery. PE-PG core-shell nanoparticles were synthesized in a simple two-step procedure by tandem coordination, ring-opening polymerization. The ability of the PE-PG copolymers to function as nanocarriers was investigated. Two different PE-PG nanocarriers were synthesized and characterized by NMR, GPC-MALLS, DLS, and cryo-TEM. The loading of the nanoparticles with two commonly used hydrophobic model dyes was investigated by UV/Vis, fluorescence, and DLS measurements. In a first study, the PE-PG nanocarrier showed unimolecular transport behavior, and the advantage over supramolecular transport could be shown by the uptake of transported NR into tumor cells under high dilution. In a second study, the soft PE-PG nanocarrier was compared to a hard nanodiamond cored ND-PG nanoparticle. The soft PE-PG nanocarrier was clearly superior to the rigid ND-PG nanocarrier with regard to encapsulation capacity and the uptake of transported NR into tumor cells. The knowledge generated from these studies is useful for designing better nanocarriers in the future.

7 References

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8 Curriculum Vitae

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