Investigating the influence of aromatic moieties on the formulation of hydrophobic natural products and drugs in poly(2-oxazoline) based amphiphiles

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Abstract:

Many natural compounds with interesting biomedical properties share one physicochemical property, namely a low water solubility. Polymer micelles are, among others, a popular means to solubilize hydrophobic compounds. The specific molecular interactions between the polymers and the hydrophobic drugs are diverse and recently it has been discussed that macromolecular engineering can be used to optimize drug loaded micelles. Specifically, π-π stacking between small molecules and polymers has been discussed as an important interaction that can be employed to increase drug loading and formulation stability. Here, we test this hypothesis using four different polymer amphiphiles with varying aromatic content and various natural products that also contain different relative amounts of aromatic moieties. While in the case of paclitaxel, having the lowest relative content of aromatic moieties, the drug loading decreases with increasing relative aromatic amount in the polymer, the drug loading of curcumin, having a much higher relative aromatic content, is increased. Interestingly, the loading using schizandrin A, a dibenzo[a,c]cyclooctadiene lignan with intermediate relative aromatic content is not influenced significantly by the aromatic content of the polymers employed. The very high drug loading, long term stability, the ability to form stable highly loaded binary coformulations in different drug combinations, small sized formulations and amorphous structures in all cases, corroborate earlier reports that poly(2-oxazoline) based micelles exhibit an extraordinarily high drug loading and are promising candidates for further biomedical applications. The presented results underline that the interaction between the polymers and the incorporated small molecules are complex and must be investigated in every specific case.
Introduction:

For many years, natural products have played an important part in drug discovery. In the late 20\textsuperscript{th} century, a majority of drugs were either natural compounds or their derivatives.[1] At the end of their review concerning the importance of natural products for drug discovery Newman et al. argued that well-defined drug delivery systems could overcome unfavorable physicochemical properties, like aqueous solubility, in the future.[2] Through high-throughput screening, new chemical entities or lead structures are being identified and evaluated every day,[3] but only a minute fraction ever ripen into an approved drug. Obviously, a large proportion of drug candidates are poorly water-soluble[4, 5] which calls for effective formulation strategies. Traditionally used surfactants like Cremophor EL and Tween 80 have drawbacks as they can elicit potentially life-threatening side effects and are limited with respect to their in solubilizing ability.[6, 7] Polymeric micelles have been discussed and evaluated as carriers for hydrophobic molecules for many years and thousands of papers praising the potential of polymer based drug delivery systems are published every year.[8] However, until now, only one micelle-based formulation (Genexol-PM\textsuperscript{®}, South Korea) has been used in the clinic with several other being under clinical development.[9] Zhang et al. argued that the low drug loading capacity and poor \textit{in vivo} stability typically displayed by polymeric micelles is responsible for this major discrepancy.[10] These major problems concerning nanoformulations, drug delivery and the advancement of polymeric micelles for clinical cancer therapy were also critically reviewed by other researchers.[11-13] Polymeric micelles comprising a poly(2-oxazoline) (POx) based amphiphilic triblock copolymer (poly(2-methyl-2-oxazoline)-block-poly(2-butyl-2-oxazoline))-block-poly(2-methyl-2-oxazoline) (PMeOx-b-PBuOx-b-PMeoX \equiv A-pBuOx-A) constitute an unusual exception. Loading capacities (LC) of almost 50 wt.% for one of the most commonly used chemotherapeutic agents, paclitaxel (PTX),[14] were reported by Kabanov, Jordan, Luxenhofer and co-workers.[15-19]. Despite the very low water solubility, PTX is a high affinity substrate for P-glycoprotein (P-gp) which leads to PTX resistance in cancer cells.[20-22] The drug loaded polymer micelles formed stable and injectable formulations and showed significantly increased therapeutic efficacy.[23] The combination of high drug loading and stability was only seen in block copolymers with poly(2-n-butyl-2-oxazoline) as hydrophobic core.[19] Testing a variety of structurally different taxanes led to similar high drug loadings and stability of the formulations.[24] However, with etoposide and bortezomib, two well-
known topoisomerase and proteasome inhibitors, respectively, no stable formulations could be obtained.[15, 17] Lübtow et al. investigated a small library of structurally similar ABA-triblock copolymers based on poly(2-oxazoline)s and poly(2-oxazine)s and explored their solubilization capacity for PTX and curcumin (CUR[25]), another well-known natural compound featuring extremely low aqueous solubility, bioavailability and stability.[26] The authors observed significant and orthogonal specificities dependent on one methylene group. That research outlines the complexity of drug/carrier interactions.[27] More recently, this CUR nanoformulation was characterized in detail and compared in 2D and 3D cell culture with CUR dissolved in DMSO.[28]

Another natural product with low water solubility can be found in fruits of *Schisandra chinensis*, which are widely used in traditional Chinese and Japanese herbal medicine and are said to have hepatoprotective, anti-asthmatic, anti-diabetic and sedative properties.[29, 30] Dibenzo[a,c]cyclooctadiene lignan metabolites are thought to be responsible for the majority of these biological effects.[30] Many of such lignans have been extracted [31, 32] and chromatographically isolated from *Schisandra chinensis* fruits.[33-39] The compounds have been predominantly identified by UV-Vis, IR- and NMR spectroscopy, mass spectrometry and circular dichroism.[33, 40-43] In addition, the absolute configurations of some such lignans were determined via crystal structure analysis.[44] Schobert and co-workers established a simplified extraction method followed by one saponification step to obtain the pure dibenzo[a,c]cyclooctadiene lignan schisandrol A by column chromatography.[45] This was converted to a cinnamate and a titanocene derivative which both showed promising P-gp inhibition and increased activity against cervix and breast cancer cells.[45, 46] The formation of nanoparticles and nanocrystals to formulate schisantherin A, a related dibenzo[a,c]cyclooctadiene lignan, was described by Cheng et al. The drug/carrier aggregates could pass the hemato-encephalic barrier and showed effects potentially useful for the treatment of Parkinson´s disease.[47, 48]

Several strategies for the development of drug specific drug delivery platforms have been followed, lately. In particular, Luo, Nangia and co-workers backed the synthetic work with extensive modeling and achieved very high drug loadings paired with excellent therapeutic efficacy.[49-51] Börner and co-workers employed a high-throughput screening to find an improved drug loading for different cargo.[52-54] The driving forces considered relevant for drug incorporation are hydrophobic and electrostatic interactions, hydrogen bonding, π-π
stacking and van der Waals forces. In the literature, the relevance of these interactions for drug formulation is widely discussed.[55] In order to stabilize polymeric micelles and so increase their loading capacity for PTX (28 wt.%) and docetaxel (34 wt.) Shi et al. synthesized amphiphilic block copolymers comprising the aromatic monomer N-2-benzoyloxypropyl methacrylamide (HPMAm-Bz) as a hydrophobic building block. The π-π stacking effect significantly increased the stability, loading capacity and therapeutic index of drug loaded polymeric micelles.[56, 57] Moreover, this led to a retardation of PTX release compared to polymers that did not contain aromatic moieties.[56] Amphiphilic diblock copolymers containing poly(2-phenyl-2-oxazolin) (PPhOx) and PMeOx were tested on their self-assembly in aqueous milieu. Dependent on different block compositions, the researchers found polymeric micelles, vesicles and larger polymersomes. Furthermore, the hydrophobic drug indomethacin could be successfully formulated.[58] Tiller and co-workers described ABA-triblock copolymers based on PPhOx and PMeOx and discussed their usage in drug delivery. The size and morphology of the aggregates depended strongly on the overall block length and the balance between hydrophilic and hydrophobic moieties.[59]

![Schematic representation of a) the polymers and insoluble small molecules employed in the present study as well as b) the formulation procedure via the thin film method.](figure1.png)

**Figure 1.** Schematic representation of a) the polymers and insoluble small molecules employed in the present study as well as b) the formulation procedure via the thin film method.

Here, we present a small library of POx based amphiphiles, in which the aromatic character was increased systematically and the solubilization capacity for drugs with different aromatic content was investigated.
Materials and Methods:

All substances and reagents for the polymerizations were obtained from *Sigma-Aldrich* (Steinheim, Germany) or *Acros* (Geel, Belgium) and were used as received unless stated otherwise. Curcumin powder from *Curcuma longa* (Turmeric) was obtained from *Sigma-Aldrich* (curcumin = 79%; demethoxycurcumin = 17%, bisdemethoxycurcumin = 4%; determined by HPLC analysis). Paclitaxel was purchased from *LC Laboratories* (Woburn, MA, USA). Deuterated solvents for NMR analysis were obtained from *Deutero GmbH* (Kastellaun, Germany). All substances used for polymerization, specifically methyl trifluoromethylsulfonate (MeOTf), MeOx, BuOx, PheOx, and BzOx were refluxed over CaH₂ and distilled and stored under argon. Benzonitrile (PhCN) was dried over phosphorus pentoxide. The monomers 2-n-butyl-2-oxazoline (BuOx) and 2-benzyl-2-oxazoline (BzOx) were synthesized following the well-known procedure by Seeliger *et al.*[60] The Pt-NHC-complex (Pt-NHC)[61] and the fluorinated curcuminoid derivative (CUR-F₆)[62] were synthesized according to literature (Figure S6). Fruits of *Schisandra chinensis* were obtained from *Naturwaren-Blum* (Revensdorf, Germany) and were dried and powdered prior to the extraction procedure. Schizandrin (SchA) was obtained from powdered *Schisandra chinensis* using the simplified extraction procedure investigated by Schobert *et al.*[45] Thin layer chromatography (TLC), NMR-, IR-, UV-Vis-spectroscopy and electrospray ionization mass spectrometry (ESI-MS) were used for analytical issues. TLC were performed on Sigma-Aldrich® TLC Plates containing silica gel matrix (stationary phase) using n-hexane/ethylacetat (1:1) as mobile (phase). For NMR measurements a small fraction of the purified compound SchA was dissolved in deuterated dichloromethane and ¹H-, ¹³C-, COSY- (correlation spectroscopy), HSQC- (heteronuclear single quantum coherence) and HMBC- (heteronuclear multiple bond correlation) experiments were recorded. For IR-analysis small amount of SchA were recorded on an FT-IR-spectrometer 4100 from 500 to 4000 cm⁻¹ from *Jasco* (Gross-Umstadt, Germany). For the UV-Vis measurement a 1 g/L ethanolic solution of SchA was filtered through 0.2 µm PTFE filters (*Rotilabo*, Karlsruhe) and recorded at 25 °C from 700 to 180 nm.

The purity of SchA was determined to be 97.9% by analytical high pressure liquid chromatography (HPLC). The polymers A-ₚBuOx-A, A-ₚ(BuOx-co-BzOx)-A, A-ₚBzOx-A and A-ₚPheOx-A were synthesized by living cationic ring opening polymerization (LCROP) as described previously.[15] The reactions were controlled by ¹H-NMR-spectroscopy. The
lyophilized polymers were characterized by 1H-NMR and gel permeation chromatography (GPC). The critical micellar concentrations of the ABA-triblock copolymers were determined by pyrene fluorescence measurements.[63, 64] The \( I_2/I_3 \)-ratio in dependence of varying polymer concentrations and the total redshift of \( I_1 \) in dependence of varying polymer concentrations were detected and used for the determination of the CMC-values. Drug loaded polymeric micelles were prepared by thin film method (Figure 1 b). The loading capacities (LC) and efficiencies (LE) were determined by HPLC measurements, according to equation (1) and (2).

\[
LC = \frac{m_{\text{drug}}}{m_{\text{drug}} + m_{\text{excipient}}} \cdot 100\% \quad (1)
\]

\[
LE = \frac{m_{\text{drug}}}{m_{\text{drug,added}}} \cdot 100\% \quad (2)
\]

where \( m_{\text{drug}} \) and \( m_{\text{excipient}} \) are the weight amounts of the solubilized drug and polymer excipient in solution and \( m_{\text{drug,added}} \) is the weight amount of the drug initially added to the dispersion. Therefore, it was assumed that no loss of polymer during micelles preparation occurred. The aggregation behavior of the polymers (10 g/L in PBS) and polymer-drug solutions (1:0.5 g/L in PBS) were investigated by dynamic light scattering (DLS) measurements at 27 different angles (temperature was fixed at 25 °C). The glass transition temperatures (\( T_g \)) and melting points (mp) were determined by differential scanning calorimetry (DSC) measurements. All methods are described in more detail in the supporting information.
Results and Discussion:

Inspired by reports on benefits for drug delivery via π-π stacking between drug carrier and loaded API[65], we wanted to investigate this issue in poly(2-oxazoline) based polymer amphiphiles. In particular, the Hansen-solubility parameters calculated by Dargaville and co-workers suggested a benefit regarding drug loading using polymer amphiphiles comprising a hydrophobic poly(2-phenyl-2-oxazoline) block.[66] In the case of paclitaxel and docetaxel, Hennink and co-workers reported that incorporation of aromatic side chains into thermosensitive block copolymers of modified hydroxypropyl methacrylamides improves drug loading.[56] However, it is important to note that in this study PTX precipitation rather than release was quantified.[56, 57] The authors argue that this was done as it is difficult to upload proper sink conditions for the extremely poorly soluble PTX.

In contrast, in a preliminary study, we did not observe any benefit with respect to PTX formulation when we included aromatic moieties into the hydrophobic block.[19] The inclusion of an aromatic moiety (A-p(BuOx-co-BzOx)-A; LC\textsubscript{PTX}: 36 wt.%) led to significant loss of loading capacity in comparison to A-pBuOx-A (LC\textsubscript{PTX}: 49 wt.%).

Therefore, the present study investigates the influence of different proportions of aromatic moieties within poly(2-oxazoline) based ABA triblock copolymers on the formulation of different hydrophobic drugs with varying aromatic content in more detail. To this end, we used a small library of four different polymers. As in previous work, the hydrophilic block A was poly(2-methyl-2-oxazoline) (pMeOx).[27] The hydrophobic blocks were in order of increasing aromatic content poly(2-butyl-2-oxazoline) (A-pBuOx-A), poly(2-butyl-2-oxazoline-co-2-benzyl-2-oxazoline) (A-p(BuOx-co-BzOx)-A), poly(2-benzyl-2-oxazoline) (A-pBzOx-A) and poly(2-phenyl-2-oxazoline) A-pPheOx-A, respectively. The polymers were prepared by living cationic ring opening polymerization (LCROP) and characterized by \textsuperscript{1}H-NMR and GPC (Table 1 and supporting information).

Table 1. Molecular weight, polydispersity D and yield of the synthesized triblock copolymers.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>M\textsubscript{n}\textsuperscript{(a)} [kg/mol]</th>
<th>M\textsubscript{n}\textsuperscript{(b)} [kg/mol]</th>
<th>M\textsubscript{n}\textsuperscript{(c)} [kg/mol]</th>
<th>D\textsuperscript{(d)}</th>
<th>Yield [%]</th>
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<tbody>
<tr>
<td>A-pBuOx-A</td>
<td>8.6</td>
<td>8.7</td>
<td>5.6</td>
<td>1.10</td>
<td>88</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>9.0</td>
<td>7.8</td>
<td>5.9</td>
<td>1.12</td>
<td>91</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>8.7</td>
<td>10.3</td>
<td>5.2</td>
<td>1.25</td>
<td>77</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>8.5</td>
<td>8.5</td>
<td>5.3</td>
<td>1.10</td>
<td>92</td>
</tr>
</tbody>
</table>

\textsuperscript{a}, theoretical value obtained by \[M\textsubscript{0}/[I]\]\textsubscript{0}.
\textsuperscript{b}, calculated from \textsuperscript{1}H-NMR end-group and side chain analysis.
\textsuperscript{c}, obtained from GPC (T = 40 °C, flow rate was set to 0.7 mL/min (HFIP)).
\textsuperscript{d}, obtained from GPC (M\textsubscript{w}/M\textsubscript{n}).
All polymers exhibited CMC values in the low μM range (determined by pyrene fluorescence, Figure S3), often deemed favorable for intravenous administration (Figure S3, Table S1). Interestingly, in the present library, it appears that the introduction of aromatic side chains has no marked influence on the CMC values. For formulation, we focused on three natural compounds. On the one hand, we employed the well-known and extremely water-insoluble compounds paclitaxel PTX (0.4 mg/L)\cite{20} and curcumin CUR (0.6 mg/L)\cite{26}. On the other hand, we tested the poorly soluble dibenzo[a,c]cyclooctadiene lignan schizandrin (SchA, solubility: 0.19 g/L determined via HPLC). These three natural compounds differ in their relative aromatic content. While PTX contains 3 phenyl rings at a molar mass of 854 g/mol, SchA contains two rings at 432 g/mol and CUR contains also 2 phenyl rings, however connected with a bridging π-system at a molar mass of 368 g/mol. The ratio of $C_{arom}$, the carbon atoms, which are included in the aromatic system, and $C_{total}$, the total number of carbon atoms in the hydrophobic compound, represents the aromaticity of the three different cargos (Table 2).

Table 2. Degree of aromaticity of the hydrophobic drugs PTX, SchA and CUR.

<table>
<thead>
<tr>
<th></th>
<th>PTX</th>
<th>SchA</th>
<th>CUR</th>
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<tbody>
<tr>
<td>$C_{total}$</td>
<td>46</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>$C_{arom}$</td>
<td>18</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>ratio</td>
<td>0.39</td>
<td>0.50</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Additionally, the insoluble compounds Pt-NHC and CUR-F6 (for structures, please see Figure S6) were investigated, the latter of which can be viewed as derivative of natural compound CUR.

All four polymers were tested for the solubilization of PTX and CUR, while A-pPheOx-A was not used to formulate SchA. As previously reported, A-pBuOx-A is an excellent solubilizer for PTX but much less so for CUR.\cite{27} This was corroborated also in the present study (Figure 2).

Interestingly, SchA, having an intermediate relative aromatic content was solubilized very well, but less than PTX. As previously reported\cite{19} and independently reproduced here using a newly synthesized polymer, the introduction of benzylic moieties (A-p(BuOx-co-BzOx)-A) does not help in the formulation of PTX but rather reduces the maximum drug loading. Interestingly, while in the case of SchA the maximum drug loading increased slightly, the LC$_{CUR}$ that could be achieved increased significantly (Figure 2). In the case of A-pBzOx-A, the LC$_{PTX}$ decreased further (35.6±2.1 wt.%), while LC$_{SchA}$ (44.0±0.3 wt.%) and in particular LC$_{CUR}$ (41.0±2.1 wt.%) increased further, compared to A-pBuOx-A based formulations. Interestingly,
within this small library, A-pBzOx-A is the least selective of the tested polymers. Previously, comparable but somewhat higher loading capacities for PTX and CUR could be achieved (LC\textsubscript{PTX}: 40.1±1.5 wt.%, LC\textsubscript{CUR}: 48.5±1.7 wt.%) using A-p(2-n-butyl-2-oxazine)-A.[27] Thus, with increasing aromatic character of the polymeric solubilizer, more CUR (LC\textsubscript{A-pBuOx-A}: 24.4±1.1 wt.%, LC\textsubscript{A-p(BuOx-co-BzOx)-A}: 33.2±3.7 wt.%, LC\textsubscript{A-pBzOx-A}: 41.0±2.1 wt.%) and less PTX (LC\textsubscript{A-pBuOx-A}: 47.5±0.1 wt.%, LC\textsubscript{A-p(BuOx-co-BzOx)-A}: 36.8±1.0 wt.%, LC\textsubscript{A-pBzOx-A}: 35.6±2.1 wt.%) could be solubilized, while little if any influence was found for SchA. Interestingly, this trend was less clear for A-pPheOx-A as solubilizer. While the LC\textsubscript{PTX} did decrease further (28.6±0.6 wt.%), also the solubilization of CUR (LC\textsubscript{CUR}: 33.4±2.3 wt.%) was less efficient. It may be noted that this comparably low loading of PTX using A-pPheOx-A was still higher, albeit only slightly, than the highest PTX loading reported by Hennink et al.[56] In this report, the authors found an increased PTX loading with increasing content of aromatic co-monomer, which was attributed to π-π stacking between polymer and drug molecules. While apparently valid in some cases, it appears that this rationale is not generally helpful to increase drug loading in polymer micelles. Due to insufficient amounts of SchA, this compound was not tested using A-pPheOx-A.

It should be noted that we also attempted formulation of CUR-F\textsubscript{6}, but no stable formulation could be obtained by film hydration method with either polymer. The NHC-Pt-complex was solubilized with A-pPheOx-A by film hydration method using dichloromethane. However, it appears the complex does not exhibit sufficient stability as HPLC analysis revealed multiple signals after formulation whereas the compound was pure initially. Therefore, quantification was not possible.

Figure 2. Maximum solubilized aqueous drug concentrations in formulation with the drug carriers (A-pBuOx-A, A-p(BuOx-co-BzOx)-A, A-pBzOx-A, A-pPheOx-A). Maximum solubilization (LE\textsubscript{minimum} 79 %) of the drugs PTX (blue), CUR (red) and SchA (green) using the four polymers. *1 were taken from Ref[18], *2 were taken from Ref[27]. In all cases, the polymer concentration was fixed at 10 g/L. Data is given as means ± SD (n = 3).
The drug content was quantified immediately after preparation. In order to gain a basic understanding of the stability of the drug formulations, we stored the formulation under ambient conditions and took samples after 10 and 30 days. For A-\textit{pBuOx}-A, we have previously observed excellent stability of the PTX formulation without any precipitation after several months.[15, 17, 18] In general, all tested formulations of PTX, CUR and SchA showed very good stability over 30 days (Figure 3). No significant loss of SchA and very little variability of the drug concentration was observed. In the case of PTX, the variability was somewhat higher, nevertheless overall formulation stability was excellent. The stability compares favorably with π-π interaction stabilized PTX formulations reported by Hennink \textit{et al.} In that report, 50% to 100% of the solubilized PTX precipitated within 10 days, depending on the aromatic content of the micelles.[56] In the case of CUR, we made unexpected observations. First of all, the stability of CUR formulated in the POx based micelles was remarkably high, especially considering the well-established low chemical stability of CUR in aqueous media.[26] In case of A-\textit{p(BuOx-co-BzOx)}-A and A-\textit{pPheOx}-A, we did observe some loss of CUR concentration and increased variability after 30 days, but the average drug loading remained high. Notably, according to HPLC analysis, CUR did not show any signs of degradation, even though it is often reported that CUR is not stable in aqueous environment. Interestingly, in the case of A-\textit{pBzOx}-A, the CUR concentration in solution (after centrifugation and filtration) was much higher on day 10 (LC\textsubscript{CUR}: 45.6±3.3 wt.%) and day 30 (LC\textsubscript{CUR}: 44.6±4.6 wt.%) than on day 0 (LC\textsubscript{CUR}: 20.8±2.1 wt.%). It should be noted, for our stability studies, the drug formulations were stored under ambient conditions over the pellet of unformulated drug (if any). Thus, it appears that CUR that initially precipitated during thin film hydration became incorporated over time into the micelles. Unfortunately, we cannot explain this phenomenon at this point, but further studies are certainly warranted.
Figure 3. Long-term stability of drug/polymer formulations of PTX (a), CUR (b) and SchA (c). For that study the maximum loaded formulations were used. The d0 values were set to 100 %. In all cases, the polymer concentration was fixed at 10 g/L (squares: A-p(BuOx-co-BzOx)-A, circles: A-pBzOx-A, triangles: A-pPheOx-A and stars: A-pBuOx-A). Data is given as means ± SD (n = 3).

In addition to the described single-drug formulations, we also investigated binary co-formulations. Previously, we have reported several POx-based binary and ternary drug-formulations with very high loading of ≥58 wt.%. [17, 27] Here, we investigated A-pBzOx-A for co-formulation of PTX with SchA and CUR, respectively. Both combinations could show interesting pharmaceutical synergies. [67, 68] For these preliminary studies, we fixed the relative drug weight ratio at 1/1 for both combinations (10 g/L A-pBzOx-A and 6 g/L in the case of PTX/SchA and 8 g/L in the case of PTX/CUR). In both combinations, the loading efficiency was excellent and total LC exceeded 50 wt.%. The individual LC for PTX (40.8 wt.%) and CUR (40.1 wt.%) yielded an overall LC of 58.8 wt.%, while with the combination of PTX (35.6 wt.%) and SchA (36.9 wt.%) an overall LCs of 53.2 wt.% was obtained (Figure 4).
Previously, we have investigated PTX formulation with A-pBuOx-A in great detail using electron microscopy, dynamic light scattering (DLS) and small angle neutron scattering.[16, 18] For preliminary elucidation of the aggregation behavior, we investigated aqueous polymer solutions and formulations by DLS (Figure 5). All polymers form aggregates in the size range expected for polymer micelles. The polymers containing aromatic moieties form very small and rather defined polymer micelles. At 10 g/L in PBS hydrodynamic radii between 10-20 nm were found (Figure 5 a, Figure S5 c). In the case of A-pBuOx-A, we found a rather broad distribution centered around a hydrodynamic radius of $R_h = 25$ nm. Previously, using a different batch of the same polymer we observed a bimodal size distribution, originating from spherical and worm-like micelles.[18] Possibly, the broad distribution observed in the present case could be caused by an unresolved bimodal distribution.

Moreover, we investigated drug formulations of A-pBzOx-A by DLS at a polymer/drug-ratio of 10/5 in PBS. The formulation with SchA exhibited three species with the weighted average mean of 23 nm (Figure 5 b, Figure S5 d). A large species at 2000 nm had a very low intensity and may be attributed to an artifact. In addition, two major distributions at about 20 nm and 150 nm were observed. In contrast, for PTX and CUR nanoformulations, only single and rather narrow distributions were observed with hydrodynamic radii of 21 nm (PTX) and 27 nm (CUR) (Figure 5 b, Figure S5 e). Obviously, such small sizes are typically considered favorable for parenteral administration, in particular for cancer chemotherapy.[69]
The drug formulations studied here are not only potentially interesting as drug loaded micelles but also in form of solid dispersions. In this context, it is particularly interesting whether the drug is present in amorphous or crystalline form. Neither polymer exhibited a melting point, therefore being fully amorphous structures with glass transitions temperatures predictable by the Fox equation[70] using the T_g-values of the homopolymers[71-73] (Figure 6 a, Table S9, Equation 6, Table S10). SchA did not undergo thermal degradation at temperatures up to 200 °C, but exhibited a melting point of 129 °C (Figure 6 b), which corroborates values found in the literature.[74] Upon cooling, we did not observe recrystallization at the chosen experimental parameters, but also a T_g-value was detectable. The second heating cycle revealed a T_g of 30.7 °C for SchA. For comparison, we also analyzed a simple physical mixture of SchA and A-pBzOx-A with the nanoformulation (both 1/2, w/w) obtained via thin-film hydration and subsequent lyophilization. For the nanoformulation of A-pBzOx-A and SchA no melting point could be detected in the first heating cycle (Figure 6 c). Only a T_g of 67.5 °C could be discerned, showing that the nanoformulation with a LC of about 30 % was fully amorphous. The fact that only one T_g is observed, elucidates that no independent domains of amorphous drug and amorphous polymer are present, but that the two entities are intimately and molecularly intertwined. In case of the physical mixture, we could clearly observe the melting point of SchA in the first heating cycle (Figure 6 d). Also in this case, no recrystallization of SchA was observed upon cooling. The second heating cycle only revealed a T_g at 70.4 °C. Interestingly, the Fox-equation predicts a much lower T_g for a mixture of 33 wt.% SchA and 66 wt.% A-pBzOx-A. Using the experimentally determined T_g values of both components, the
Fox-equation yields an expected $T_g$ of only 52 °C. The origin of this discrepancy is unclear at this point.

Figure 6. a) DSC analysis of the triblock copolymers (A-pPheOx-A= dark blue line; $T_g=81.3$ °C, A-p(BuOx-co-BzOx)-A= dark red line; $T_g=67.5$ °C, A-pBzOx-A= black line; $T_g=76.7$ °C). The heat flow [W/g] in dependence of the temperature [°C] is shown with the particular glass transition $T_g$ of each polymer marked with vertical lines. DSC analysis of SchA (b), nanoformulation with the polymer A-p(BuOx-co-BzOx)-A (c) and physical mixture of SchA/A-p(BuOx-co-BzOx)-A (d). It is shown the heat flow [W/g] in dependence of the temperature [°C] of the first heating cycle (black), first cooling cycle (red) and second heating cycle (blue). Melting points (endothermal maximum) were determined in the first heating cycle, respectively. The particular $T_g$ values were determined in the second heating cycle. The scans were performed under N$_2$-atmosphere using constant cooling and heating rates of 10 k/min.

Conclusion:

We investigated the influence of incorporation of aromatic moieties into poly(2-oxazoline) based ABA triblock copolymers. In addition to the varying degree of aromaticity within the polymers, three cargo compounds with different relative aromatic content were tested. In contrast to previous reports on a different polymeric system, incorporation of 2-benzyl-2-oxazoline or 2-phenyl-2-oxazoline did not increase drug loading or formulation stability in the case of paclitaxel. Interestingly, the formulation of the natural compound schizandrin A was barely affected while the loading with curcumin benefitted significantly from incorporation of 2-benzyl-2-oxazoline but less so for 2-phenyl-2-oxazoline. Therefore, it appears that π-π stacking can be beneficial for drug loading and formulation stability in some cases, but this
should not be considered a general phenomenon and must be assessed on a case-by-case basis.

Acknowledgement:

This work was supported by the Free State of Bavaria. Start-up funding for R.L. by the University Würzburg and SKZ Das Kunststoff-Zentrum is gratefully acknowledged. M.M.L. would like to thank the Evonik Foundation for providing a doctoral fellowship. We would also like to thank Christian May for technical support. We are very grateful for the HDRC-Software Version 6.3.1., provided by O. Nirschl and K. Fischer, Physical Chemistry of Polymers at the Johannes Gutenberg University Mainz led by Prof. Dr. Sebastian Seiffert (formerly Prof. Dr. Manfred Schmidt).
References


Supporting Information
Investigating the influence of aromatic moieties on the formulation of hydrophobic natural products and drugs in poly(2-oxazoline) based amphiphiles

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Syntheses and extraction procedure

Monomer synthesis: The building blocks for the hydrophobic core of ABA-triblock copolymers

General synthetic procedure 1, GSP 1

For the reaction 1 eq of respective nitrile, 1.2 eq of alkanolamine and catalytic amounts of zinc acetate dehydrate (0.025 eq) were added to a nitrogen flushed flask and heated to 130 °C under reflux for 72 h until the reaction mixture turned dark brown. Reaction progress was controlled by FTIR- and ¹H-NMR-spectroscopy. The mixture was dissolved in dichloromethane and washed with H₂O (3x). The organic phase was dried with MgSO₄, filtered and concentrated under reduced pressure. The raw product was mixed with CaH₂ and purified via vacuum distillation. If necessary, distillation was repeated and the product was kept under nitrogen atmosphere.

2-n-butyl-2-oxazoline (according to GSP1)Ref[27]
2-benzyl-2-oxazoline (according to GSP1)

\[
\text{2-n-butyl-2-oxazoline (according to GSP1)} \text{Ref[27]}
\]

\[
\text{2-benzyl-2-oxazoline (according to GSP1)}
\]

Benzyl cyanide: 204 g (1.7 mol, 1 eq)
Ethanolamine: 128 g (2.1 mol, 1.2 eq)
ZnAc₂·(H₂O)₂: 9.7 g (44 mmol, 0.025 eq)
bp: 78°C (0.3 mbar)
Yield: 140.4 g (0.87 mol, 50.2 %) of clear crystals

\(^1\)H-NMR: (CD\(_3\)OD; 300.12 MHz; 298 K): \(\delta\) [ppm] = 3.70 (t, 2H, \(H^2, J=9\) Hz); 4.18 (t, 2H, \(H^1, J=9\) Hz); 3.52 (s, 2H, \(H^3\)); 7.20 (m, 5H, \(H^4\)).

ABA-triblock copolymer synthesis according living cationic ring opening polymerization

General synthetic procedure 2, GSP 2

The used technique were carried out as described previously.[15] Briefly, 1 eq of initiator (MeOTf) was added to a dried and nitrogen flushed flask and dissolved in the respective amount of benzonitrile. The monomer 2-methyl-2-oxazoline (MeOx) was added and the reaction mixture was heated to 100°C for approximately 4 hours. Reaction progress was controlled by FTIR- and \(^1\)H-NMR-spectroscopy. After complete polymerization of MeOx, the mixture was cooled to RT and the monomer for the second block (A-pBuOx-A: 2-n-butyl-2-oxazoline (BuOx); A-p(BuOx-co-BzOx)-A: mixture of 2-n-butyl-2-oxazoline (BuOx) and 2-benzyl-2-oxazoline (BzOx); A-pBzOx-A: BzOx; A-pPheOx-A: 2-phenyl-2-oxazoline (PheOx)) was added. The reaction mixture was stirred overnight at 100 °C. The procedure was repeated for the third block MeOx. The termination was triggered by addition of 3 eq of 1-Boc-piperazine (PipBoc) at 50 °C for 4 h. For neutralization 1 eq of K\(_2\)CO\(_3\) was added and the mixture was stirred at 50 °C for 4 h again. After removal of the solvent under reduced pressure the supernatant was transferred into a dialysis bag (MWCO 1 kDa, cellulose acetate) and dialyzed against Millipore water overnight. After lyophilization a colorless powder could be obtained.

Figure S1. Reaction scheme of the one-pot synthesis of ABA-triblock copolymers based on Poly(2-oxazolines) by living cationic ring opening polymerization.
A-pBuOx-A (Me-MeOx_{35}-b-BuOx_{20}-b-MeOx_{35}-Pip) Ref[27]  

A-p(BuOx-co-BzOx)-A (Me-MeOx_{35}-b-[BzOx_8-BuOx_{12}]_{rdm}-b-MeOx_{35}-PipBoc):  
According to GSP 2

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Step</th>
<th>Block</th>
<th>Mass (g)</th>
<th>Mol (mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>MeOTf</td>
<td>0.27</td>
<td>1.65 (1 eq)</td>
</tr>
<tr>
<td>1. Block</td>
<td>MeOx</td>
<td>4.94</td>
<td>58.0 (35 eq)</td>
</tr>
<tr>
<td>2. Block</td>
<td>BzOx</td>
<td>2.23</td>
<td>13.4 (8 eq)</td>
</tr>
<tr>
<td></td>
<td>BuOx</td>
<td>2.66</td>
<td>20.0 (12 eq)</td>
</tr>
<tr>
<td>3. Block</td>
<td>MeOx</td>
<td>5.09</td>
<td>59.8 (36 eq)</td>
</tr>
<tr>
<td>Termination</td>
<td>Boc-Pip</td>
<td>0.94</td>
<td>5.01 (3 eq)</td>
</tr>
<tr>
<td></td>
<td>K_2CO_3</td>
<td>0.23</td>
<td>1.67 (1 eq)</td>
</tr>
</tbody>
</table>

Solvent: Benzonitrile  
Concentration: 3.3 M  
Yield: 1  
3.6 g (1.52 mmol; 91 %)  

M_w, theor.: 9.0 kg/mol  
GPC (HFIP): M_n= 5.9 kg/mol; Đ= 1.12  

^1H-NMR: (Me-MeOx_{31}-b-[BzOx_6-BuOx_{10}]_{rdm}-b-MeOx_{32}-PipBoc)  
(CD_3OD; 300.12 MHz; 298 K): δ [ppm] = 7.64–7.42 (br, 32H, H^φ);  
4.07–3.61 (br, 319H, H^1); 3.04–2.90 (br, 3H, H^5); 2.90–2.48 (br, 27H, H^3); 2.47–2.25 (br, 191H, H^4); 1.90–1.48 (br, 57H, H^5,6,7);  
1.24–1.12 (br, 32H, H^φ).
A-pBzOx-A (Me-MeOx35-b-BzOx16-b-MeOx35-PipBoc):
According to GSP 2

Initiation: MeOTf 0.28 g (1.72 mmol; 1 eq)
1. Block: MeOx 5.12 g (60.2 mmol; 35 eq)
2. Block: BzOx 4.76 g (27.5 mmol; 16 eq)
3. Block: MeOx 5.29 g (62.2 mmol; 36 eq)
Termination: Boc-Pip 0.96 g (5.15 mmol; 3 eq)
K₂CO₃ 0.24 g (1.67 mmol; 1 eq)
Solvent: Benzonitrile 31 mL
Concentration: 3.2 M
Yield: 11.6 g (1.32 mmol; 77.4 %)
Mw, theor.: 8.7 kg/mol
GPC (HFIP):
Mₙ = 5.2 kg/mol; Đ = 1.25
Mₙ = 10.3 kg/mol
¹H-NMR:
(Me-MeOx₄₀-b-BzOx₂₀-b-MeOx₄₁-PipBoc)
(CD₃OD; 300.12 MHz; 298 K): δ [ppm] = 7.64–7.42 (br, 101H, H⁶); 4.07–3.61 (br, 423H, H¹); 3.33–3.18 (br, 3H, H²); 2.80–2.48 (br, 7H, H³); 2.47–2.25 (br, 246H, H⁴); 1.68 (s, 9H, H⁵).

A-pPheOx-A (Me-MeOx₃₅-b-PheOx₱₈-b-MeOx₃₅-PipBoc):
According to GSP 2
Initiation: MeOTf 100 mg (0.59 mmol; 1 eq)
1. Block: MeOx 1.76 g (20.7 mmol; 35 eq)
2. Block: PheOx 1.56 g (10.6 mmol; 18 eq)
3. Block: MeOx 1.80 g (21.1 mmol; 36 eq)
Termination: Boc-Pip 327 mg (1.77 mmol; 3 eq)
K₂CO₃ 81 mg (0.59 mmol; 1 eq)
Solvent: Benzonitrile 10.5 mL
Concentration: 3.3 M
Yield: 4.62 g (0.54 mmol; 92.3 %)
Mₔ, theor.: 8.5 kg/mol
GPC (HFIP): Mₐ= 5.3 kg/mol; Đ= 1.10
¹H-NMR:
(Me-MeOₓ₃₃-b-PhOₓ₁₈-b-MeOₓ₃₃-PipBoc)
(CD₂Cl₂; 300.12 MHz; 298 K): δ [ppm] = 7.50–6.95 (br, 90H, H₆);
3.74–3.10 (br, 325H, H₁); 3.01–2.90 (br, 3H, H₃); 2.57–2.20 (br, 5H, H₃);
2.15–2.01 (br, 198H, H₄); 1.44 (s, 9H, H₅).

**Extraction of *schisandra chinensis* fruits**

The extraction procedure of fruits of *schisandra chinensis* was carried out as described by Schobert *et al.*[45] The dried fruit powder (200 mg) was first extracted at RT with *n*-hexane (3.5 L) for 10 h. This extract was filtered off and the remainder was dried and re-extracted with ethyl acetate (2.5 L) for 10 h. After concentration under reduced pressure the raw product was purified three times by column chromatography on Silica Gel (60 Å 230-400 mesh particles) from *Sigma-Aldrich* (Steinheim, Germany) with *n*-hexane/ ethyl acetate (1:1) as the eluent to maintain Schizandrin (SchA) as a colorless powder.
Figure S2: a) Visualization of the extraction procedure. 1. Fruits of *schisandra chinensis*. a) Pulverization 2.) Powder of *schisandra chinensis* fruits. b) Extraction procedure carried out as described by Schobert et al. 3. Raw product. c) Column chromatography using Silica Gel 60. 4. Purified colorless powder of Schizandrin (SchA).

b) Chemical Structure and nomenclature of Schizandrin (SchA) a dibenzocyclooctadiene lignan.

Contrary to their results we couldn’t identify Schisandrol A. By using the simplified extraction method we characterized another known dibenzocyclooctadiene lignan called Schisandrin (SchA).

**Rf-Value:** 0.4  (*n*-hexane/ethyl acetate 1:1)

**$^1$H-NMR:**

$(\text{CD}_2\text{Cl}_2; 300.12 \text{ MHz}; 298 \text{ K}); \delta [\text{ppm}] = 6.60 (s, 1\text{H}, H^7); 6.52 (s, 1\text{H}, H^8); 2.35 (d, 1\text{H}, H'^7, J^7= 15 \text{ Hz}); 2.68 (d, 1\text{H}, H'^8, J^8= 15 \text{ Hz}); 2.38 (dd, 1\text{H}, H'^7, J^7= 12 \text{ Hz}; J^8= 6 \text{ Hz}); 2.67 (d, 1\text{H}, H'^8, J^8= 12 \text{ Hz}); 1.93-1.80 (m, 1\text{H}, H^8); 1.85 (8’-OH); 1.24 (s, 3\text{H}, H^9); 0.81 (d, 3\text{H}, H^9', J^9=6.0 \text{ Hz}); 3.57 (s, 3\text{H}, Ar-OMe); 3.58 (s, 3\text{H}, Ar-OMe); 3.86-3.90 (m, 12\text{H}, Ar-OMe).

**$^{13}$C-NMR:**

$(\text{CD}_2\text{Cl}_2; 300.12 \text{ MHz}; 298 \text{ K}); \delta [\text{ppm}] = 133.8 (C1); 131.8 (C1’); 110.1 (C2); 110.5 (C2’); 152.3 (C3); 152.0 (C3’); 140.3 (C4); 140.8 (C4’); 151.6 (C5); 151.9 (C5’); 122.8 (C6); 124.2 (C6’); 34.3 (C7); 40.9 (C7’); 41.8 (C8); 71.8 (C8’); 56.0 (C3-OMe und C3’-OMe); 60.9 (C4-OMe und C4’-OMe); 60.6 (C5-OMe und C5’-OMe); 15.9 (C8-Me); 29.8 (C8’-Me).

**ESI-MS:**

Exact mass: 432.21 g/mol

Determined: 455.21 [M+Na$^+$], 887.42 [2M+Na$^+$]

**IR ($\nu_{max} \text{ cm}^{-1}$):**

3510 (OH-ν); 3015-2800 (CH- ν); 1580-1570 (C=CAr- ν).
UV-VIS ($\lambda_{\text{max}}^\text{EtOH}$ nm): 217, 253, 286

Purity (HPLC): 97.9%

**Methods**

**Nuclear Magnetic Resonance (NMR) Spectroscopy**

NMR spectra were recorded on a Fourier 300 ($^1$H; 300.12 MHz), *Bruker Biospin* (Rheinstetten, Germany) at 298 K. The spectra were calibrated to the signal of residual protonated solvent (CDCl$_3$: 7.26 ppm; CD$_2$Cl$_2$: 5.31 ppm CD$_3$OD: 3.31 ppm). Multiplicities of signals are depicted as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad.

**Infrared (IR) Spectroscopy**

IR spectra were recorded on a FT-IR-spectrometer 4100 from 500 to 4000 cm$^{-1}$ from *Jasco* (Gross-Umstadt, Germany).

**High Pressure Liquid Chromatography**

HPLC analysis was performed on a LC-20A Prominence HPLC, *Shimadzu* (Duisburg, Germany) equipped with a system controller CBM-20A, a solvent delivery unit LC-20 AT (double plunger), an on-line degassing unit DGU-20A, an auto-sampler SIL-20AC, a photo-diode array detector SPD-M20A, a column oven CTO-20AC, and a refractive index detector RID-20A. As stationary phase, a ZORBAX Eclipse Plus, *Agilent* (Santa Clara, CA, USA) C18 column (4.6 x 100 mm; 3.5µm50mm x 4 mm) was used. For elution a gradient of H$_2$O/CAN from 60/40 (v/v) to 40/60 (v/v) was used.

**Gel Permeation Chromatography (GPC)**

Gel permeation chromatography (GPC) was performed either on a *Polymer Standard Service* (PSS, Mainz, Germany) system (pump mod. 1260 infinity, MDS RI-detector mod. 1260 infinity (*Agilent Technologies*, Santa Clara, California, USA), precolumn GRAM 10 µM (50 x 8 mm), 30 Å PSS GRAM 10 µM (300 x 8 mm) and 1000 Å PSS GRAM 10 µM (300 x 8 mm)) with DMF (containing 1 g/L (11.5 mM) LiBr) as eluent calibrated against PEG standards with molar masses ranging from 106 g/mol to 1015 kg/mol or on a *Polymer Standard Service* (PSS, Mainz, Germany) system (pump mod. 1260 infinity, MDS RI detector mod. 1260 infinity (*Agilent Technologies*, Santa Clara, California, USA), precolumn PFG linear M 7 µm (50 mm x 8 mm) and linear M PSS PFG 7 µm (2 x 300 mm x 8 mm)) with HFIP (containing 3 g/L potassium trifluoroacetate (KTFA)) as eluent calibrated against PEG standards with molar masses ranging from 200 g/mol to 200 kg/mol. Columns were kept at 40 °C and the flow rate was set to
0.7 mL/min (HFIP). Prior to each measurement, samples were filtered through 0.2 µm PTFE filters (Rotilabo, Karlsruhe).

![Figure S3. GPC-elugrams of the polymer structures A-pBuOx-A (a), A-p(BuOx-co-BzOx)-A (b), A-BzOx-A (c) and A-PheOx-A (d).](image)

**Electrospray Ionization Mass Spectrometry (ESI-MS)**

MS-Spectra were recorded on a micrOTOF-Q III spectrometer from Bruker Daltonic. Masses were scanned from 50 to 5000 m/z by 0.7 bar system pressure, 200 °C temperature and 5 L/min inert gas using a sample concentration of 0.1 mg/mL in methanol.

**Pyrene Fluorescence Assay**

60 µL pyrene solutions (25 µM) in acetone were added to glass vials. After evaporation of solvent, 3 mL polymer solutions of various concentrations in deionized water were added to the sample. The samples, with a final concentration of pyrene of 5 x 10^{-7} M, were equilibrated for at least 3 h upon shaking at RT under the exclusion of light. The pyrene fluorescence spectra (λ_{ex}: 330 nm at 25°C) were recorded on a FP-8300 spectrofluorometer system from Jasco (Gross-Umstadt, Germany) in the range of 360 to 400 nm.
Figure S3. Results of the pyrene-fluorescence assay for the aromatic polymers A-p(BuOx-co-BzOx)-A (dark red), A-pBzOx-A (black) and A-pPheOx-A (dark blue). All polymers exhibited CMC values in the μM region. a) $I_1/I_3$ in dependence of varying polymer concentrations. b) Redshift of $I_1$ in dependence of varying polymer concentrations.

Table S1. Summary of pyrene-fluorescence assay. CMC_a determined using decreasing values of $I_1/I_3$-ratio. CMC_b determined by monitoring the redshift of $I_1$.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$M_n$ [kg/mol]</th>
<th>CMC_a [μM]</th>
<th>CMC_a [mg/L]</th>
<th>CMC_b [μM]</th>
<th>CMC_b [mg/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>7.8</td>
<td>0.7</td>
<td>5.5</td>
<td>1.2</td>
<td>9.4</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>10.3</td>
<td>0.3</td>
<td>3.1</td>
<td>1.0</td>
<td>10.3</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>8.5</td>
<td>1.2</td>
<td>10</td>
<td>4.9</td>
<td>42</td>
</tr>
</tbody>
</table>

**Drug Solubilization**

Drug loaded polymer micelles were prepared using the thin film method. Briefly; ethanolic polymer (20 g/L), curcumin (5 g/L), paclitaxel (20 g/L) schisandrin (20 g/L) CUR-F_6 (2 g/L) stock solutions were mixed in desired ratio. For the structure NHC-Pt (5 g/L) dichloromethane was used as solvent. After complete removal of the solvent at 55 °C, the films were dried further in vacuo (≤ 0.2 mbar) for at least 3 h. By addition of preheated (37 °C) H_2O (Millipore) final polymer and drug concentrations were obtained as mentioned in the main text. Complete solubilization was assured by shaking the polymer-drug solutions at 1250 rpm at 55 °C for 15 min with a Thermomixer comfort, *Eppendorf AG* (Hamburg, Germany). Throughout centrifugation for 5 min at 10,000 rpm (5,000 g) with a 3-Speed micro centrifuge, *neoLab* (Heidelberg, Germany) non-solubilized drug (if any) was removed. For long term stability the formulations were stored under the exclusion of light for 10 and 30 days. Precipitated drug during that time was removed by centrifugation before quantification.
Table S2. Data for the long-term stability studies for the drug PTX (day 10). PTXₐ is the added amount of drug in g/L and PTXₗ is the quantified values in g/L. Polymer concentration was constant 10 g/L.

<table>
<thead>
<tr>
<th>polymer</th>
<th>PTXₐ [g/L]</th>
<th>PTXₗ [g/L]</th>
<th>LE [%]</th>
<th>LC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>5</td>
<td>4.0±0.1</td>
<td>78.9±2.3</td>
<td>28.3±1.2</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>7</td>
<td>5.5±0.2</td>
<td>78.5±2.2</td>
<td>35.5±1.5</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>5</td>
<td>4.3±0.2</td>
<td>85.4±3.1</td>
<td>29.9±1.5</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>7</td>
<td>5.8±0.2</td>
<td>83.4±2.5</td>
<td>36.9±1.7</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>3</td>
<td>2.8±0.2</td>
<td>92.8±7.4</td>
<td>21.8±2.2</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>5</td>
<td>4.4±0.1</td>
<td>87.0±2.6</td>
<td>30.3±1.3</td>
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Table S3. Data for the long-term stability studies for the drug PTX (day 30). PTXₐ is the added amount of drug in g/L and PTXₗ is the quantified values in g/L. Polymer concentration was constant 10 g/L.

<table>
<thead>
<tr>
<th>polymer</th>
<th>PTXₐ [g/L]</th>
<th>PTXₗ [g/L]</th>
<th>LE [%]</th>
<th>LC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>5</td>
<td>3.6±0.1</td>
<td>71.9±1.7</td>
<td>26.5±0.9</td>
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<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>7</td>
<td>5.2±0.1</td>
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<td>34.2±1.1</td>
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<tr>
<td>A-pBzOx-A</td>
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<td>83.0±1.0</td>
<td>29.3±0.5</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>7</td>
<td>5.6±0.1</td>
<td>79.9±1.0</td>
<td>35.9±0.7</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>3</td>
<td>2.4±0.0</td>
<td>78.5±0.5</td>
<td>19.1±0.1</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>5</td>
<td>4.0±0.1</td>
<td>78.9±1.6</td>
<td>28.3±0.8</td>
</tr>
</tbody>
</table>

Table S4. Data for the long-term stability studies for the drug CUR (day 10). CURₐ is the added amount of drug in g/L and CURₗ is the quantified values in g/L. Polymer concentration was constant 10 g/L.

<table>
<thead>
<tr>
<th>polymer</th>
<th>CURₐ [g/L]</th>
<th>CURₗ [g/L]</th>
<th>LE [%]</th>
<th>LC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>5</td>
<td>5.0±0.3</td>
<td>99.5±6.6</td>
<td>33.2±3.2</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>10</td>
<td>1.2±0.2</td>
<td>11.7±2.1</td>
<td>10.5±2.0</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>5</td>
<td>5.1±0.2</td>
<td>101.5±3.7</td>
<td>33.7±1.8</td>
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<tr>
<td>A-pBzOx-A</td>
<td>7</td>
<td>4.3±1.2</td>
<td>61.8±17.3</td>
<td>30.2±10.8</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>10</td>
<td>8.4±0.3</td>
<td>83.7±3.4</td>
<td>45.6±3.3</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>5</td>
<td>4.7±0.6</td>
<td>94.4±11.7</td>
<td>32.1±5.5</td>
</tr>
</tbody>
</table>

Table S5. Data for the long-term stability studies for the drug CUR (day 30). CURₐ is the added amount of drug in g/L and CURₗ is the quantified values in g/L. Polymer concentration was constant 10 g/L.

<table>
<thead>
<tr>
<th>polymer</th>
<th>CURₐ [g/L]</th>
<th>CURₗ [g/L]</th>
<th>LE [%]</th>
<th>LC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>5</td>
<td>4.4±0.3</td>
<td>88.8±6.1</td>
<td>30.7±2.9</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>10</td>
<td>1.5±0.5</td>
<td>15.3±4.8</td>
<td>13.3±4.5</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>5</td>
<td>5.2±0.4</td>
<td>103.4±7.2</td>
<td>34.1±3.5</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>7</td>
<td>5.3±1.0</td>
<td>75.3±14.6</td>
<td>34.5±9.3</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>10</td>
<td>8.1±0.5</td>
<td>80.5±4.8</td>
<td>44.6±4.6</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>5</td>
<td>3.5±1.0</td>
<td>70.3±19.9</td>
<td>26.0±9.1</td>
</tr>
</tbody>
</table>

Table S6. Data for the long-term stability studies for the drug SchA (day 10). SchAₐ is the added amount of drug in g/L and SchAₗ is the quantified values in g/L. Polymer concentration was constant 10 g/L.

<table>
<thead>
<tr>
<th>polymer</th>
<th>SchAₐ [g/L]</th>
<th>SchAₗ [g/L]</th>
<th>LE [%]</th>
<th>LC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-pBuOx-A</td>
<td>5</td>
<td>4.8±0.1</td>
<td>96.6±1.0</td>
<td>32.6±0.5</td>
</tr>
<tr>
<td>A-pBuOx-A</td>
<td>8</td>
<td>7.8±0.1</td>
<td>97.0±0.9</td>
<td>43.7±0.7</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>5</td>
<td>4.7±0.2</td>
<td>93.9±3.5</td>
<td>31.9±1.7</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>8</td>
<td>8.0±0.1</td>
<td>100.3±0.8</td>
<td>44.5±0.6</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>5</td>
<td>4.8±0.1</td>
<td>95.2±1.8</td>
<td>32.2±0.9</td>
</tr>
</tbody>
</table>
Table S7. Data for the long-term stability studies for the drug SchA (day 30). SchA is the added amount of drug in g/L and SchAq are the quantified values in g/L. Polymer concentration was constant 10 g/L.

<table>
<thead>
<tr>
<th>polymer</th>
<th>SchA&lt;sub&gt;a&lt;/sub&gt; [g/L]</th>
<th>SchA&lt;sub&gt;q&lt;/sub&gt; [g/L]</th>
<th>LE [%]</th>
<th>LC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-pBzOx-A</td>
<td>8</td>
<td>7.8±0.1</td>
<td>97.7±0.8</td>
<td>43.9±0.7</td>
</tr>
<tr>
<td>A-pBuOx-A</td>
<td>5</td>
<td>4.8±0.0</td>
<td>96.5±0.4</td>
<td>32.5±0.2</td>
</tr>
<tr>
<td>A-pBuOx-co-BzOx)-A</td>
<td>8</td>
<td>7.7±0.3</td>
<td>95.7±3.2</td>
<td>43.4±2.5</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>5</td>
<td>4.7±0.2</td>
<td>93.2±3.2</td>
<td>31.8±1.6</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>8</td>
<td>8.0±0.1</td>
<td>99.9±0.6</td>
<td>44.4±0.5</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>5</td>
<td>4.8±0.1</td>
<td>96.8±2.5</td>
<td>43.6±1.1</td>
</tr>
</tbody>
</table>

For Coformulation two drugs were added in desired ratio. Solubilization experiments were performed with 3 individually prepared samples and results are presented as means ± standard deviation (SD: \( \frac{\sum(x_i-x)^2}{\sum(n_j-1)} \)).

**Quantification of Drug Solubility**

Detection of PTX and SchA were performed by HPLC at 220 nm \( (R_t(PTX): 9.6 \text{ min}, R_t(SchA): 7.6 \text{ min}) \). Paclitaxel and Schisandrin quantification were performed using a calibration curves obtained with known amounts of PTX and SchA. 10 µL of the formulations were dissolved with 990 µL of HPLC solvent prior each measurement. Prior to each measurement, samples were centrifuged (10,000 rpm; 5000 g) with a Speed-micro centrifuge, neoLab (Heidelberg, Germany) and filtered through 0.4 µM filter (Rotilabo, Karlsruhe, Germany). Curcumin quantification was performed by UV-Vis absorption on a BioTek Eon Microplate Spectrophotometer, Thermo Fisher Scientific (MA, USA) using a calibration curve obtained with known amounts of CUR. Samples were prepared in Rotilabo F-Type 96 well plates, Carl Roth GmbH & Co. KG (Karlsruhe, Germany) with a constant volume of 100 µL. Spectra were recorded from 300–600 nm at 298 K. Curcumin absorption was detected at 428 nm. Prior to UV-Vis absorption measurements, the aqueous formulations were diluted with ethanol at least 1/20 (v/v).

The following equations were used to calculate loading capacity \( (LC) \) and loading efficiency \( (LE) \):

\[
LC = \frac{m_{\text{drug}}}{m_{\text{drug}} + m_{\text{excipient}}} \cdot 100\%
\]  
\[
LE = \frac{m_{\text{drug}}}{m_{\text{drug,added}}} \cdot 100\%
\]
where \( m_{\text{drug}} \) and \( m_{\text{excipient}} \) are the weight amounts of the solubilized drug and polymer excipient in solution and \( m_{\text{drug.added}} \) is the weight amount of the drug initially added to the dispersion. Therefore, it was assumed that no loss of polymer during micelles preparation occurred.

![Image](image_url)

**Figure S4.** Calibration curves determined with analytical HPLC (PTX, SchA) and UV-Vis absorption (CUR) using known amounts of particular drug for quantification.

a) Integral under the peak in dependence of PTX, SchA and CUR concentration determined with linear fit function. All data points were performed with 3 individually prepared samples and results are presented as means ± standard deviation (SD).

**Table S8.** Data of solubilization studies for the drugs PTX, CUR and SchA. PTX\(_p\), CUR\(_p\) and SchA\(_p\) is the particular added amount of drug in g/L and PTX\(_q\), CUR\(_q\) and SchA\(_q\) are the quantified values in g/L, respectively. Polymer concentration was constant 10 g/L.

<table>
<thead>
<tr>
<th>polymer</th>
<th>PTX(_p) [g/L]</th>
<th>PTX(_q) [g/L]</th>
<th>LE [%]</th>
<th>LC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>5</td>
<td>4.1±0.2</td>
<td>81.3±3.2</td>
<td>28.9±1.6</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>7</td>
<td>5.8±0.1</td>
<td>83.1±1.4</td>
<td>36.8±1.0</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>10</td>
<td>1.8±1.1</td>
<td>18.8±11.0</td>
<td>15.8±9.9</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>5</td>
<td>4.3±0.1</td>
<td>86.5±2.5</td>
<td>30.2±1.2</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>7</td>
<td>5.5±0.2</td>
<td>79.0±3.1</td>
<td>35.6±2.1</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>10</td>
<td>1.8±0.1</td>
<td>17.7±1.0</td>
<td>15.0±1.0</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>3</td>
<td>2.4±0.0</td>
<td>80.7±1.1</td>
<td>19.5±0.3</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>5</td>
<td>4.0±0.1</td>
<td>79.6±1.2</td>
<td>28.5±0.6</td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>7</td>
<td>1.5±0.3</td>
<td>21.2±3.6</td>
<td>12.9±2.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>polymer</th>
<th>CUR(_p) [g/L]</th>
<th>CUR(_q) [g/L]</th>
<th>LE [%]</th>
<th>LC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>5</td>
<td>5.0±0.4</td>
<td>99.5±7.6</td>
<td>33.2±3.7</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>7</td>
<td>0.4±0.1</td>
<td>5.70±1.7</td>
<td>3.80±1.2</td>
</tr>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>10</td>
<td>0.3±0.0</td>
<td>3.20±0.4</td>
<td>3.10±0.4</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>5</td>
<td>4.9±0.2</td>
<td>98.9±3.6</td>
<td>33.1±1.8</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>7</td>
<td>6.9±0.2</td>
<td>99.1±3.0</td>
<td>41.0±2.1</td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>10</td>
<td>2.6±0.2</td>
<td>26.3±2.1</td>
<td>20.8±2.1</td>
</tr>
</tbody>
</table>
\[
\begin{array}{cccc}
\text{A-pPheOx-A} & 3 & 3.0\pm0.2 & 101.1\pm6.9 & 23.3\pm2.0 \\
\text{A-pPheOx-A} & 5 & 5.0\pm0.2 & 100.3\pm4.7 & 33.4\pm2.3 \\
\text{A-pPheOx-A} & 7 & 2.5\pm0.0 & 36.0\pm0.6 & 20.2\pm0.4 \\
\text{polymer} & \text{SchA} \_ & \text{SchA} \_ & \text{LE} & \text{LC} \\
\text{A-pBuOx-A} & 5 & 4.9\pm0.1 & 98.1\pm2.0 & 32.9\pm1.0 \\
\text{A-pBuOx-A} & 8 & 7.4\pm0.1 & 92.7\pm1.3 & 42.6\pm1.0 \\
\text{A-p(BuOx-co-BzOx)-A} & 5 & 4.8\pm0.1 & 95.1\pm2.8 & 32.2\pm1.4 \\
\text{A-p(BuOx-co-BzOx)-A} & 8 & 7.7\pm0.1 & 95.7\pm1.6 & 43.4\pm1.3 \\
\text{A-pBzOx-A} & 5 & 4.9\pm0.1 & 98.8\pm2.3 & 33.1\pm1.2 \\
\text{A-pBzOx-A} & 8 & 7.9\pm0.0 & 98.3\pm0.4 & 44.0\pm0.3 \\
\end{array}
\]

**Dynamic Light Scattering**

DLS experiments were performed on an ALV CGS-3 *multi detection goniometry*-system (Langen, Germany) equipped with a He-Ne-laser (power 22 mW, \( \lambda = 632.8 \text{ nm} \)) and 8 optical avalanche photodiodes-detectors. Scattering angles between 22 and 151 ° were measured using a 5 ° angle interval (T= 298 K). Prior to each measurement, samples were filtered through 0.45 µm regenerative cellulose filters (*Rotilabo*, Karlsruhe). Sample concentration amounted to 10 or 1 g/L polymer in PBS-solution. The decay of the electric field-time autocorrelation function (ACF) was fitted by the cumulant method (equation 3)

\[
\ln(g_{1}(t)) = A - \Gamma \tau + \frac{\mu_2}{2} \tau^2 - \frac{\mu_3}{3} \tau^3
\]  

with the cumulants \( \Gamma, \mu_2 \) and \( \mu_3 \), the amplitude A and the decay time \( \tau = \frac{1}{q^2 D} \), \( q \) being the absolute value of the scattering vector and D being the Brownian diffusion coefficient which is indirect proportional to the hydrodynamic radius \( R_h \). The z-average diffusion coefficient is available through the first cumulant (equation 4), the polydispersity index (PDI) can be calculated using the quotient of the second cumulant and the squared first cumulant (equation 5).

\[
D_z = \frac{\Gamma}{q^2}
\]

Exponential fit functions (equations 5 and 6), like described detailed by Rausch *et al.* [75],

\[
g_{1}(t) = a_1 \cdot e^{(-\frac{t}{\tau_1})} \\
g_{1}(t) = a_1 \cdot e^{(-\frac{t}{\tau_1})} + a_2 \cdot e^{(-\frac{t}{\tau_2})} + a_3 \cdot e^{(-\frac{t}{\tau_3})}
\]

were used with the amplitudes \( a_i \) and the decay times \( \tau_i = \frac{1}{q^2 D_i} \).
Figure S5. Autocorrelation $g_1(t)$ in dependence of the lag-time $t$ [ms] of the polymer structure A-pBzOx-A of 10 g/L in PBS a) and the nanoformulation A-pBzOx-A/SchA of 1/0.5 g/L in PBS b) fitted by monoexponential a) and triexponential b) fit function. The residuum shows the accuracy of the used fit. c) Hydrodynamic radii $R_h$ [nm] in dependence of the particular scattering vector $q^2$ [cm$^{-2}$] of the Polymers A-pBuOx-A (purple), A-p(BuOx-co-BzOx)-A (dark red), A-pBzOx-A (black) and A-pPheOx-A (dark blue) (10 g/L in PBS) determined using monoexponential fit function. d) Hydrodynamic radii $R_h$ [nm] in dependence of the particular scattering vector $q^2$ [cm$^{-2}$] of the nanoformulation A-pBzOx-A/SchA (1/0.5 g/L in PBS) determined using triexponential fit function (circles: Species 1; triangles: Species 2; stars: Species 3; squares: weighted average). e) Hydrodynamic radii $R_h$ [nm] in dependence of the particular scattering vector $q^2$ [cm$^{-2}$] of the nanoformulations A-pBzOx-A/PTX (blue) and A-pBzOx-A/CUR (red) (1/0.5 g/L in PBS) determined using monoexponential fit function.

Differential Scanning Calorimetry

The DSC measurements were performed in aluminum crucibles on a calibrated DSC 204 F1 Phoenix system from NETZSCH (Selb, Germany) equipped with a CC200 F1 controller unit. The heating and cooling rate was constantly 10 K/min using a constant N$_2$-atmosphere. For each sample three heating cycles and two cooling cycles were performed.
Table S9. Summary of DSC analysis. It shows for all samples the respective sample mass \( m \) [mg], glass transition region \( T_g \) [°C], change of heat capacity \( \Delta c_p \) [J/g-K], melting point \( mp \) [°C] and molar enthalpy of fusion \( H_{mp,m} \) [kJ/mol]. All values were determined using NETSCH Proteus® Analysis 5.0. In the formulation (A-pBzOx-A/SchA(form.)) and a physical mixture (A-pBzOx-A/SchA(phys.)) a polymer/drug-ratio of 10/5 in g/L were used.

<table>
<thead>
<tr>
<th></th>
<th>( m ) [mg]</th>
<th>( T_g ) [°C]</th>
<th>( \Delta c_p ) [J/g-K]</th>
<th>( mp ) [°C]</th>
<th>( H_{mp,m} ) [kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-p(BuOx-co-BzOx)-A</td>
<td>2.0</td>
<td>67.5</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-pBzOx-A</td>
<td>2.5</td>
<td>76.7</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-pPheOx-A</td>
<td>1.8</td>
<td>81.3</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SchA</td>
<td>4.1</td>
<td>30.7</td>
<td>0.42</td>
<td>129.6</td>
<td>13.1</td>
</tr>
<tr>
<td>A-pBzOx-A/SchA(form.)</td>
<td>3.0</td>
<td>67.5</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-pBzOx-A/SchA(phys.)</td>
<td>3.5</td>
<td>70.4</td>
<td>0.41</td>
<td>130.9</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Glass transitions temperatures of ABA-triblock copolymers (binary system) \( (T_g) \) are predictable using the well-known Fox equation[70] and the \( T_g \)-values of the homopolymers \( (T_{g,1}, T_{g,2}) \) and the mass fractions \( (m_1, m_2) \), respectively (Equation 7; Table S10).

\[
\frac{1}{T_g} = \frac{m_1}{T_{g,1}} + \frac{m_2}{T_{g,2}}
\]

Table S10. \( T_g \)-values of the homopolymers used for the prediction of the \( T_g \)-region of ABA-triblock copolymers. References are noted.

<table>
<thead>
<tr>
<th>Homopolymer</th>
<th>Building blocks</th>
<th>( T_g ) [°C]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMeOx</td>
<td>60</td>
<td>75</td>
<td>[71]</td>
</tr>
<tr>
<td>pBuOx</td>
<td>60</td>
<td>25</td>
<td>[71]</td>
</tr>
<tr>
<td>pPheOx</td>
<td>100</td>
<td>103</td>
<td>[73]</td>
</tr>
<tr>
<td>pBzOx</td>
<td>Not noted</td>
<td>61</td>
<td>[72]</td>
</tr>
</tbody>
</table>

**Structures of the hydrophobic drugs Pt-NHC and CUR-F₆**

![Chemical structure of Pt-NHC][61] and CUR-F₆[62].