



# Composite nanoparticles derived by self-assembling of hydrophobic polysaccharide derivatives and lignin

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Received: 24 December 2021 / Accepted: 23 February 2022 / Published online: 26 March 2022  
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**Abstract** Composite nanoparticles (NPs) consisting of lignin and different polysaccharide (PS) derivatives were prepared. In this synergistic approach, the PS derivative acts as biocompatible matrix that forms spherical NPs while lignin is a functional compound with therapeutic potential (e.g., antioxidative, antimicrobial, antiviral). Organosolv lignin and three different PS derivatives (cellulose acetate/CA, cellulose acetate phthalate/CAPh, xylan phenyl carbonate/XPC) were used in this study. Nanocomposites with particle sizes in the range of about 200–550 nm containing both types of biopolymers are accessible by dialysis of organic PS/lignin solutions against water.

In particular, XPC and CAPh, which both contain aromatic substituents, were found to be suitable for incorporation of lignin within the PS nanomatrix. The present work paves the way for future studies in which the pharmaceutical potential and biocompatibility of composite NPs of lignin and PS derivatives with tailored properties are investigated.

**Keywords** Nanoparticles · Polysaccharide derivatives · Lignin · Self-assembling · Composites · Biopolymers

## Introduction

Polymer-based nanoparticles (NPs) are of huge interest for biomedical applications such as drug delivery, sensing, and bioimaging (Sur et al. 2019; Calzoni et al. 2019; Suárez-García et al. 2021). Biopolymers in general and polysaccharides (PS) in particular provide unique opportunities in this regard due to their biocompatibility (Bugnicourt and Ladavière 2016; Plucinski et al. 2021). Different top-down and bottom-up methods for preparation of PS-NPs have been reported that show significant differences regarding physical and biological properties of the final materials obtained (Bugnicourt and Ladavière 2016; Quiñones et al. 2018; Paques et al. 2014; Antoniuk and Amiel 2016; Plucinski et al. 2021). Nanoprecipitation is a facile approach for the preparation of PS-NPs that is based on the self-assembling of

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**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s10570-022-04504-x>.

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hydrophobically modified PS derivatives upon the controlled transition from dissolved to non-dissolved state, e.g., induced by dialysis of a polymer solution against the non-solvent water (Gericke et al. 2020). PS-NPs that have been prepared in this manner using different types of PS derivatives (including esters, ethers, carbonates, and carbamates) showed great prospects because they are non-cytotoxic and taken up by cells (Ernsting et al. 2011; Nikolajski et al. 2012). One key challenge in the development of these nanomaterials is their functionalization towards a specific task, which can be achieved by chemical modification with therapeutic agents or by their physical incorporation (Gericke et al. 2020).

Lignin is a highly abundant biopolymer constituting for about 15 to 30% of the plant biomass alongside cellulose and hemicelluloses (Lizundia et al. 2021). Its complex macromolecular structure is very different from PS and composed of various types of randomly cross-linked aromatic monolignol building blocks and corresponding interunit linkages (see Fig. S1 in supplementary material), both depending on biomass origin and isolation process (Ralph et al. 2019). Biomaterials derived from lignin are of great interest in biomedical, pharmaceutical, and personal care applications due to its antioxidant, antimicrobial, and anti-UV activities (Sugiarto et al. 2022; Shu et al. 2021). Nanomaterials and nanocomposites of lignin offer unique application potential in this context (Schneider et al. 2021; Lizundia et al. 2021).

The combination of lignin and PS into composite biomaterials is a very promising approach. The interaction of both biopolymers can be beneficial for the self-assembling and/or provide synergistic effects and enhance the final properties, e.g., bioactivity. As an example, composite films consisting of hydroxypropyl cellulose (as matrix) and lignin (as bioactive component) have been reported previously that showed pronounced antioxidant and antimicrobial activity (Alzagameem et al. 2019). Aim of the present work was to study how composite NPs of lignin and PS derivatives can be prepared by a facile dialysis based approach. Of particular interest were the optimal conditions in terms of type of hydrophobically modified PS derivative and the optimal total amount and ratio of both biopolymers that need to be employed to obtain stable composite NPs. This is crucial in order to prepare tailored nanomaterials and adopt analytical methods to assess their bioactivity in future studies.

## Experimental section

### Materials

Cellulose acetate phthalate (CAPH,  $DS_{\text{acetate}}=2.0$  and  $DS_{\text{phthalate}}=0.7$  as determined by  $^1\text{H-NMR}$  spectroscopy in  $\text{DMSO-}d_6/\text{trifluoroacetic acid}$  to shift the peaks related to hydroxy groups and water), was obtained from Sigma-Aldrich Chemie GmbH. Cellulose acetate (CA,  $DS_{\text{acetate}}=2.4$  as determined by  $^1\text{H-NMR}$  spectroscopy after perpropionylation) was obtained from Eastman Chemical Company. Xylan phenyl carbonate (XPC,  $DS_{\text{carbonate}}=1.9$  as determined by  $^1\text{H-NMR}$  spectroscopy in  $\text{DMSO-}d_6/\text{trifluoroacetic acid}$  to shift the peaks related to hydroxy groups and water) was prepared by homogeneous derivatization of xylan in an ionic liquid/pyridine mixture as described in literature (Gericke et al. 2018). Organosolv lignin was extracted from *Miscanthus x giganteus* according to a previously reported procedure (Bergs et al. 2020). Data on the chemical composition and molecular weight are summarized in Table SI 1 in the supporting information (Bergs et al. 2019).

*N,N*-Dimethylacetamide (DMA, 99% synthesis grade), water of HPLC grade, and regenerated cellulose dialysis membranes (MWCO:  $3500\text{ g mol}^{-1}$ , nominal flat width: 18 mm, Spectra/Por® 3) were received from Carl Roth GmbH & Co. KG. Deionized water was used for dialysis.

### Measurements

The hydrodynamic diameter and polydispersity of the nanoparticles (NPs) were measured by dynamic light scattering (DLS) using a Zetasizer Nano ZS (Malvern Instruments) with an operating wavelength of 633 nm and detection angle of  $173^\circ$ . The mean particle size was approximated as the effective (Z-average) diameter and the width of the distribution as the polydispersity index (PDI) obtained by the cumulants method assuming spherical shape. Each individual measurement was performed in triplicates. Each particle dispersion (obtained after dialysis or after storage) was homogenized in an ultrasonic bath for 5 min and three individual samples (10  $\mu\text{l}$ ) were taken from each particle dispersion and diluted with HPLC grade water (990  $\mu\text{l}$ ). The values for hydrodynamic diameter and PDI are represent as the mean values  $\pm$  standard

deviation obtained for the three samples. For scanning electron microscopy (SEM) images, 10  $\mu\text{l}$  of the NP dispersion that were diluted with water (1:9) were placed on a mica surface, dried, and coated with a thin layer of platinum by sputter coating (CCU-010 HV, Safematic, Switzerland). The SEM images were recorded with a Sigma VP Field Emission Scanning Electron Microscope (Carl-Zeiss AG, Germany) using the InLens detector with an accelerating voltage of 6 kV. Size Exclusion chromatography of the lignin samples was performed in 0.1 N NaOH with polystyrene sulfonate as standard according to literature (Rumpf et al. 2020).

### Nanoparticle preparation

NPs were prepared by a dialysis procedure according to literature (Schulze et al. 2016). Stock solutions of the PS derivatives and lignin in DMA were mixed and, if need be, diluted with DMA, to yield a total volume of 12 ml solution with final mass concentrations in the range of 0 to 8 mg/ml as summarized in Table 1. The polymer solutions were centrifuged ( $8000\text{ min}^{-1}$ , 10 min) to remove dust particles and transferred into dialysis bags. Dialysis was performed against 1 L deionized water for 3 days. Water was renewed three times within the first 3 h of the experiment and subsequently three times per day within similar intervals. After finishing the dialysis, each sample was stored in class vials at 10 °C.

## Results and discussion

The objective of this study was to evaluate the formation of composite nanoparticles (NPs) of lignin (as bioactive component) and hydrophobically modified polysaccharide (PS) derivatives (as biocompatible and particle forming matrix). A facile procedure was employed in which self-assembling is induced by dialysis of an organic polymer solution against the non-solvent water (Gericke et al. 2020). A key requirement for NP formation by this approach is that the polymers are soluble in an organic solvent and insoluble in water. Three different PS derivatives were selected for this study that have been demonstrated to be well suited for PS-NP preparation, namely cellulose acetate (CA), cellulose acetate phthalate (CAPH), and xylan phenyl carbonate (XPC; see Fig. S2 in

supporting information for molecular structure). CA and CAPH form well-defined spherical NPs and both derivatives have been employed successfully for the preparation of PS dye composite NPs (Schulze et al. 2016). Moreover, CAPH-NPs possess reactive moieties that can be functionalized further and the particles disintegrate under alkaline conditions due to deprotonation of the carboxylic acid group, which renders the polymer water soluble (Schulze et al. 2019a). This behavior can be exploited to create stimuli responsive NPs, e.g., for drug release purposes (Wang et al. 2016). XPC has been reported to form very stable reactive PS-NPs with a narrow size distribution that enable direct functionalization of the particles, e.g., with dyes and proteins (Gericke et al. 2021). Organosolv lignin from *Miscanthus x giganteus* was employed in this study because of its a comparably high purity (e.g., regarding residual PS) and narrow molecular weight distribution (Rumpf et al. 2020). Moreover, it possesses a pronounced antioxidant and antimicrobial activity (Alzameem et al. 2018; Alzameem et al. 2019). In preliminary tests it was found that the Organosolv lignin is well soluble in *N,N*-dimethylacetamide (DMA), which is the preferred solvent for PS-NP preparation by dialysis.

Following the procedures previously employed for the preparation of PS-NPs, lignin together with one of the three PS derivatives was dissolved in DMA at different mass concentrations (1 to 4 mg/ml for lignin, 2 to 8 mg/ml for PS derivatives). The two polymer solutions were fully miscible in the ranges employed and showed neither phase separation nor precipitation of one of the biopolymers. For comparison, organic solutions containing only lignin or a PS derivative were prepared. The polymer solutions were dialyzed against water over the course of three days. In all cases, turbid dispersions were formed within about 2 h upon slow exchange of the organic solvents to the non-solvent water. Neither lignin solutions nor mixed solutions containing lignin and a PS derivative yielded macroscopic precipitates, which is an indication that preparation of lignin composite NPs is feasible by this approach. After the dialysis, the particle dispersions were collected and some representative samples were characterized by scanning electron microscopy (SEM, Fig. 1). In addition, all particle dispersions were characterized by dynamic light scattering (DLS; Table 1).

**Table 1** Conditions for and results of the preparation of nanoparticle (NP) dispersions by dialysis of organic solutions containing different polysaccharide derivatives (PS), lignin, or both

NPs	Preparation conditions			Results from dynamic light scattering			
	PS <sup>a</sup>	Mass conc., g/ml		After dialysis		After 7 days storage	
		PS	Lignin	Size, nm <sup>b</sup>	PDI <sup>c</sup>	Size, nm <sup>b</sup>	PDI <sup>c</sup>
1	–	–	1	337 ± 2	0.32 ± 0.01	329 ± 4	0.36 ± 0.01
2	–	–	2	418 ± 10	0.56 ± 0.04	433 ± 3	0.49 ± 0.01
3	–	–	4	315 ± 10	0.58 ± 0.05	336 ± 7	0.44 ± 0.01
4	CA	2	–	200 ± 2	0.15 ± 0.01	250 ± 72	0.25 ± 0.16
5	CA	2	1	402 ± 14	0.49 ± 0.01	388 ± 17	0.51 ± 0.05
6	CA	2	2	421 ± 16	0.56 ± 0.56	357 ± 63	0.42 ± 0.18
7	CA	4	–	234 ± 11	0.13 ± 0.01	235 ± 0	0.12 ± 0.00
8	CA	4	1	315 ± 0	0.31 ± 0.02	305 ± 2	0.34 ± 0.02
9	CA	4	2	418 ± 10	0.56 ± 0.04	433 ± 3	0.49 ± 0.01
10	CA	4	4	305 ± 0	0.54 ± 0.00	307 ± 0	0.53 ± 0.00
11	CA	8	–	268 ± 1	0.18 ± 0.00	310 ± 62	0.24 ± 0.09
12	CA	8	1	388 ± 4	0.36 ± 0.00	407 ± 58	0.50 ± 0.08
13	CA	8	2	523 ± 37	0.62 ± 0.04	429 ± 13	0.66 ± 0.03
14	CA	8	4	642 ± 32	0.69 ± 0.02	463 ± 127	0.49 ± 0.29
15	XPC	2	–	182 ± 1	0.08 ± 0.00	180 ± 1	0.08 ± 0.01
16	XPC	2	1	207 ± 2	0.12 ± 0.01	197 ± 10	0.11 ± 0.02
17	XPC	2	2	260 ± 2	0.23 ± 0.01	289 ± 89	0.24 ± 0.13
18	XPC	4	–	129 ± 0	0.15 ± 0.01	134 ± 1	0.15 ± 0.01
19	XPC	4	1	281 ± 1	0.22 ± 0.01	282 ± 1	0.23 ± 0.00
20	XPC	4	2	406 ± 2	0.20 ± 0.01	396 ± 2	0.20 ± 0.01
21	XPC	4	4	546 ± 7	0.31 ± 0.01	539 ± 5	0.29 ± 0.02
22	XPC	8	–	205 ± 1	0.16 ± 0.01	221 ± 24	0.18 ± 0.03
23	XPC	8	1	396 ± 0	0.18 ± 0.01	386 ± 2	0.19 ± 0.00
24	XPC	8	2	346 ± 3	0.22 ± 0.01	342 ± 3	0.22 ± 0.01
25	XPC	8	4	396 ± 1	0.31 ± 0.02	397 ± 3	0.31 ± 0.00
26	CAPh	2	–	272 ± 7	0.06 ± 0.02	261 ± 59	0.17 ± 0.09
27	CAPh	2	1	185 ± 0	0.24 ± 0.00	220 ± 25	0.27 ± 0.09
28	CAPh	2	2	291 ± 4	0.32 ± 0.02	342 ± 75	0.34 ± 0.08
29	CAPh	4	–	292 ± 5	0.16 ± 0.01	291 ± 4	0.17 ± 0.00
30	CAPh	4	1	216 ± 1	0.22 ± 0.01	196 ± 2	0.20 ± 0.01
31	CAPh	4	2	375 ± 5	0.26 ± 0.02	370 ± 4	0.24 ± 0.00
32	CAPh	4	4	432 ± 3	0.30 ± 0.01	417 ± 2	0.30 ± 0.02
33	CAPh	8	–	406 ± 6	0.21 ± 0.02	466 ± 27	0.24 ± 0.01
34	CAPh	8	1	436 ± 28	0.24 ± 0.01	481 ± 27	0.31 ± 0.05
35	CAPh	8	2	469 ± 86	0.45 ± 0.11	426 ± 6	0.38 ± 0.07
36	CAPh	8	4	934 ± 23	0.61 ± 0.03	492 ± 5	0.49 ± 0.02

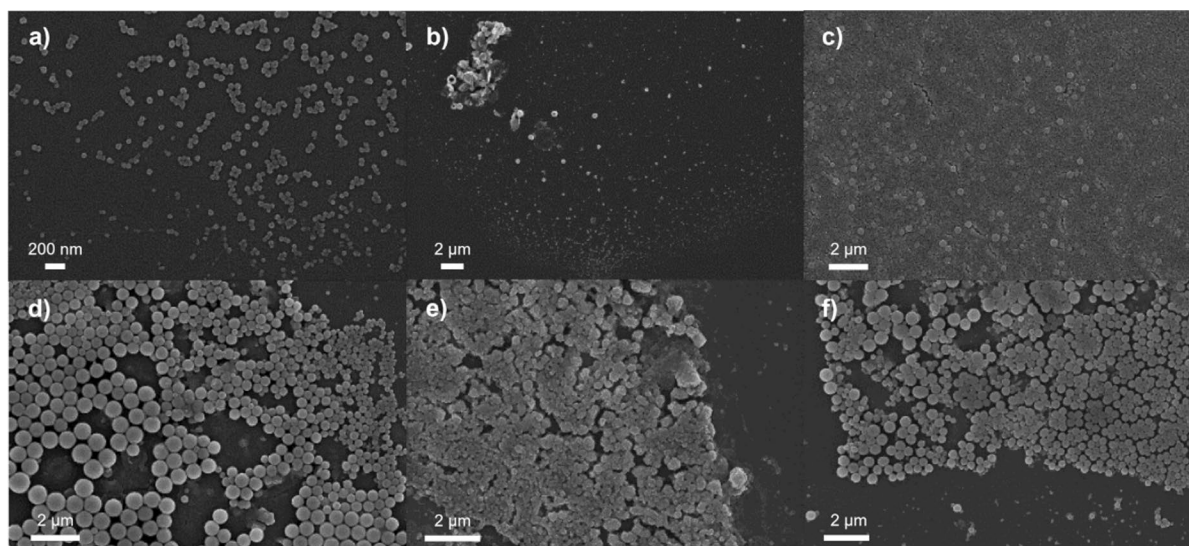
<sup>a</sup>CA cellulose acetate, CAPh cellulose acetate phthalate, XPC xylan phenyl carbonate

<sup>b</sup>Z-Average size (mean value for three samples ± standard deviation)

<sup>c</sup>polydispersity index (mean value for three samples ± standard deviation)

The SEM images of particle dispersions obtained from lignin without any PS derivative revealed the formation of particles in the nm-scale. Compared to the spherical shape of PS-NPs reported before and prepared in this study, the shape of the lignin particles was more irregular (Fig. 1a). A reasonable

explanation for this behavior is the lower solubility of lignin in comparison to the PS derivatives employed (Schulze et al. 2019b). Lower solubility can result in faster regeneration of the polymers upon solvent exchange, thus, yielding more irregular and/or larger particles (Aubry et al. 2009; Chronopoulou et al.



**Fig. 1** Scanning electron microscopy images of different particle dispersions prepared from **a, b** lignin (NP 3), **c** xylan phenyl carbonate (NP 18), and **d–e** mixtures of lignin and

polysaccharide derivatives (from left to right: xylan phenyl carbonate/NP 20, cellulose acetate/NP 8, cellulose acetate phthalate/NP 30)

2009; Gericke et al. 2020). The SEM images also revealed larger particles in the  $\mu\text{m}$ -scale that are likely aggregates of smaller particles. This corresponds with the macroscopic observations that the lignin particle dispersions showed rapid sedimentation over the course of several hours. The NPs obtained from mixtures of lignin with XPC (Fig. 1d), CA (Fig. 1e), and CAPH (Fig. 1f) showed spherical shapes very similar to PS-NPs (Fig. 1c) and no larger aggregates. Due to the fact that the composites showed a regular shape, no aggregates, and a less pronounced sedimentation tendency, it can be concluded that lignin was successfully incorporated into these particles. This finding is strongly supported by the DLS data as well as the deep brown color of the composite particles as opposed to the colorless PS-NP dispersions without lignin (see Fig. S3 in supplementary material).

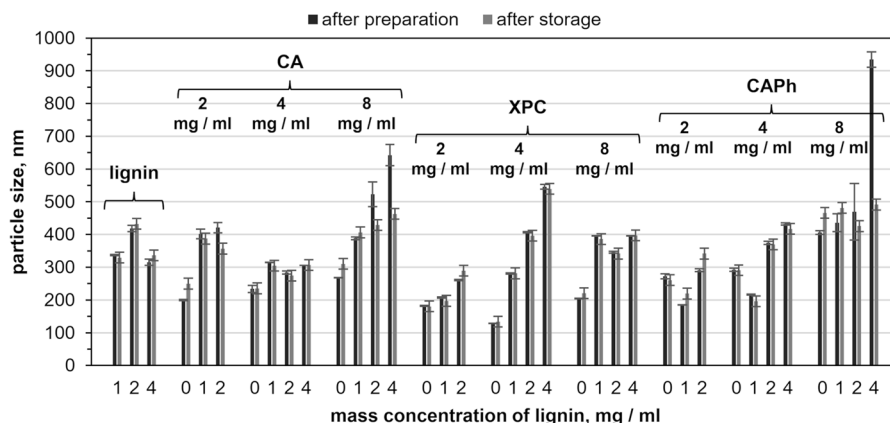
The SEM images revealed different particles sizes in the nm-scale depending on the type of PS derivative and the lignin content. All particle dispersions obtained were characterized by DLS to gain information on the particles size distribution (Table 1). The samples were measured directly after finishing the dialysis. Moreover, they were studied after storing them for 7 days at 10 °C to gain information on the stability of the particles against sedimentation and irreversible aggregation.

Lignin without any PS derivatives present formed particles in the range of about 300 to 400 nm (NP 1 to 3). However, the high polydispersity indices ( $\text{PDI} > 0.5$ ) indicate a very broad particle size distribution. The aqueous lignin particle dispersions also displayed a much more pronounced tendency towards sedimentation compared to the other experiments. For particles obtained by dialysis of PS derivatives, smaller particles (CA: 200 to 270 nm, NP 4, 7, and 11; XPC: 130 to 200 nm, NP 15, 18, and 22; CAPH: 270 to 400 nm, NP 16, 29, and 33) with a narrower size distribution ( $\text{PDI} \leq 0.2$ ) were obtained, which is in accordance with previous reports (Schulze et al. 2016, 2019a; Gericke et al. 2021).

PS lignin composite NPs showed similar properties compared to PS-NPs prepared from the same derivative. As a general trend, it can be stated that when keeping the mass concentration of the PS derivatives constant the particles sizes gradually increased upon increasing the lignin content (Fig. 2). Moreover, the particles became less defined at higher relative lignin content within the composites, as indicated by the general increase in PDI. A factor that determined the particles size in these cases might be the increase in overall polymer concentration within the dialysis solution when lignin is added (Aubry et al. 2009; Chronopoulou et al. 2009; Gericke et al. 2020). The



**Fig. 2** Sizes of nanoparticles prepared by dialysis of organic solutions containing different amounts of lignin or lignin mixed with polysaccharide derivatives (CA: cellulose acetate, XPC: xylan phenyl carbonate, CAPH: cellulose acetate phthalate) against water



specific interactions of lignin with the three different PS derivatives may be another reason for this finding.

For CA-NPs, the least pronounced effect of lignin incorporation on the particle size was observed when using an intermediate mass concentration of 4 mg/ml CA in the starting solution (NP 7 to 10). The size increased by about 30% from 230 to 300–400 nm. The effect of lignin was more pronounced at lower mass concentration (2 mg/ml CA, NP 4 to 6), probably because the relative lignin content was higher in this case. At higher mass concentration (8 mg/ml CA, NP 11 to 14) the impact of lignin was higher as well, probably due to the rather high overall polymer concentration being in the range of the critical overlap concentration (Wondraczek et al. 2013). The PDI values for all CA lignin composite NPs were rather high (0.3 to 0.6) compared to the bare CA-NPs (0.1 to 0.2) as well as to most of the composites of lignin with XPC and CAPH ( $\leq 0.3$ ), which indicates less defined size distribution and shape of the particles. This can also be seen in the SEM images that demonstrated particles of non-spherical shape and some larger aggregates. It can be speculated that introducing lignin disturbs the self-assembling of CA to a certain extend.

The dialysis of mixed solutions of lignin and XPC yielded well-defined composite NPs. The PDI values were  $\leq 0.2$  in almost all experiments and 0.3 when the highest lignin mass concentrations of 4 mg/ml were employed. XPC on its own has been reported to form well-defined PS-NPs (Gericke et al. 2021). The present findings indicate that lignin is well incorporated within the XPC nanomatrix. Only small differences in particle size

were observed for composite NPs using low XPC mass concentrations of 2 mg/ml (NP 15 to 17). A gradual increase of the particle size from about 130 nm (NP 18) to 550 nm (NP 21) occurred using 4 mg/ml XPC solutions with increasing amounts of lignin. At 8 mg/ml of XPC, the particle size showed a steep increase increased from 200 nm (NP 22) to 350–400 nm (NP 23 to 25) independent on the lignin content. As described above, the overall high polymer concentration rather than the absolute or relative lignin content might be the dominating factor in this particular concentration range.

For CAPH based particles, incorporation of lignin showed the least pronounced effect on the particle sizes with the relative increase being less than 50% (Fig. 2). In many cases, no significant increase or a small decrease was observed. The PDI values were  $\leq 0.3$  in all cases, which confirms the formation of uniform composite particles. The only exception were particles NP 35 and 36 obtained at the highest mass concentration of CAPH (8 mg/ml) and lignin (2–4 mg/ml) that featured very high PDI  $> 0.5$ . For the latter case, values for the particles sizes determined by DLS are no longer valid due to multimodal size distributions. Thus, CAPH-based NPs can provide a suitable matrix for the incorporation of lignin. However, the concentration range in which stable composite particles are obtained is narrower compared to XPC, presumably because CAPH-NPs (without lignin) already feature larger particles sizes. Limitation for the formation of stable polymer NPs by nanoprecipitation is the critical overlap concentration at which the individual polymer chains in solution start to entangle (Wondraczek et al. 2013). This issue

becomes very complex when considering mixtures of different polymers in solution.

The particle dispersions prepared in this study showed a certain tendency towards sedimentation over the course of one week. Thereby, bare lignin NPs sedimented faster compared to PS-NPs and composite NPs. After one week of storage, all particle dispersions were characterized again by DLS. Prior to the measurements, the dispersions were treated in an ultrasonic bath for 5 min to gain homogeneous samples. Only minor differences in terms of particle size and PDI values were observed compared to the initial values before storage (Fig. 2). Thus, permanent aggregation of the composite NPs can be excluded, which is an important factor for future applications.

Overall, it can be stated that lignin is well incorporated into XPC- and CAPH-based NPs but not into CA-NPs. Since lignin is a biopolymer primarily composed of different aromatic monolignols, its interaction with the different PS matrices obviously differs. XPC and CAPH feature aromatic substituents as well (see Fig. S2 in supplementary material), which implies that interaction of the aromatic groups between the two different types of biopolymers are beneficial for the formation and stabilization of composite NPs.

## Conclusions

This study reports the fundamental principles of the formation of composite nanoparticles (NPs) derived by self-assembling of polysaccharide (PS) derivatives and lignin. It is demonstrated that lignin is well incorporated in the matrix of PS-NPs obtained from xylan phenyl carbonate (XPC) and cellulose acetate phthalate (CAPH) based on dynamic light scattering (DLS) and scanning electron microscopy (SEM) experiments. Following the procedures that were developed herein, the PS lignin composite NPs will be investigated further in upcoming comprehensive studies, in particular with respect to their antioxidant activity and biocompatibility. The present work provides the basis for evaluating the pharmacological applicability as well as for other potential fields of applications.

**Acknowledgments** The authors are indebted to S. Stumpf and the SEM/TEM facility of the Jena Center for Soft Matter (JCSM) that was established with a grant from the German

Research Council (DFG) and the European Regional Development Fund (ERDF).

**Author contributions** All authors contributed to the study conception and design. Particles preparation and characterization were performed by MG. Isolation and characterization of lignin were performed by JB and MS. The first draft of the manuscript was written by MG and all authors commented on previous versions of the manuscript. Revision of the manuscript was done by MG and MS. All authors read and approved the final manuscript.

**Funding** Open Access funding enabled and organized by Projekt DEAL. The authors have not disclosed any funding

## Declarations

**Conflict of interest** The authors declared that they have no conflict of interest.

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