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Additive effect between maltodextrins and short food agreed organic acids for rutin and quercetin solubilization in aqueous solutions.

Bastian Mueller [a,1], Eva Mueller [a], Didier Touraud [a], Anne-Sylvie Fabiano-Tixier [b], Werner Kunz [a,*]

[a] Institute of Physical and Theoretical chemistry, University of Regensburg, D-93040 Regensburg, Germany
[b] Avignon Université, INRAE, UMR SQPOV, F-84000 Avignon, France

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ABSTRACT

The aim of this study was to achieve an efficient, cost effective and food compatible solubilization of antioxidants by combining two solubilization mechanisms. For this purpose, a complexing agent (polysaccharide molecules) and a small molecule (short organic acids) were combined. Solubilization experiments of rutin and quercetin (two hydrophobic polyphenols) were performed using maltodextrins, cyclodextrins, citric acid and malic acid. We were able to show that maltodextrins at high concentrations are able to solubilize the polyphenols in a similar way to cyclodextrin and thus represent inexpensive and readily available alternatives. Due to their salting-out character we assume a solubilization mechanism via specific interactions, probably complexation. Adding citric or malic acids to maltodextrin solution further increased solubility via additive effects, though the low pH and the salting-out effects of their salts limit practical applications.

1. Introduction

Polyphenols are plant-derived compounds well-known for their antioxidant, anti-inflammatory, and anticancer properties, making them a focal point of nutritional and pharmaceutical research. [1–3] These effects are largely attributed to their ability to neutralize free radicals, thus protecting cells from oxidative damage. [1,2] Additionally, polyphenols have been shown to modulate various signaling pathways and to modulate the immune response, contributing to their anticancer effects by inhibiting the proliferation of cancer cells and promoting apoptosis. [3,4] Due to these properties, polyphenols are increasingly incorporated into dietary supplements and functional foods aimed at promoting health and preventing chronic diseases. [2]

However, their application is limited by their low water solubility, severely affecting their bioavailability, [5–7] their instability against light and oxidation [8] as well as their unpleasant bitter taste, which is problematic for food formulations. [5]

Various additives and chemical functionalizations have been devised to improve the solubility of polyphenols in order to enhance their therapeutic potential. [9] However, all these approaches still bear disadvantages. For example, the use of surfactants, and of many hydrotropes and solvents is often highly restricted due to their toxicity, environmental footprint, taste, cost or negative impact on the total formulation. Thus, overcoming the solubility issues in aqueous environments remains a critical area of research to fully exploit the benefits of polyphenols. [10]

Among the most suitable solubilizing agents are cyclodextrins, which are already used in a multitude of pharmaceutical formulations. Besides solubilization, they can enhance stability and bioavailability of bioactive compounds, inhibit loss of drug molecules and mask their bitter flavor. [11,12]

CD are cyclic oligosaccharides of six, seven or eight α-1,4-glucose units (named α, β, and γ CD, respectively) and possess an overall cone-like structure, with the alcohol groups forming a hydrophilic shell, while the internal cavity is hydrophobic. [13] Herein, hydrophobic molecules with the correct size and chemical structure can be complexed without the formation of covalent bonds. [11,14]

α, β, and γ CD are approved food additives. [16] However, β-CD can only be used in small amounts for practical reasons: In ordinary β-CD, the outer hydroxy groups are oriented in such a way that they form

* Corresponding author.
E-mail address: werner.kunz@chemie.uni-regensburg.de (W. Kunz).
[1] Present address: Institut de Chimie Séparative de Marcoule, CNRS UMR 5257, CEA, Université de Montpelier, ENSCM, F-30207 Bagnols sur Cèze Cedex, France and Physics Department, Technical University of Darmstadt, Darmstadt 64,289, Germany.

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intramolecular hydrogen bonds, drastically reducing its water solubility. [17] This problem can be solved by grafting functional groups to the OH groups so that hydrogen bond cannot form and the CD cannot crystallize. [17] The most commonly used and best studied [18] derivative is hydroxy-propyl-β-cyclodextrin (HP-β-CD). Although it is one of the least toxic β-CD derivatives and is used in pharmaceuticals like eye drops, oral and intravenous solutions, [11] it should not be consumed in large quantities, as it can cause diarrhea and softening of the stool if ingested in excess of 16 g per day. [18,19] Hence, while β-CD is a food additive (E 459), [20] HP-β-CD is not approved as food additive, neither in Europe nor in the US. [21] This raises the question: are there structurally similar compounds that can serve a similar function, but allow for more flexible formulations.

The source material of CDs, starch itself forms remarkable secondary structures with hydrophilic shells and hydrophobic core. [22,23] Notably, one of the polymers forming starch, amylose, has the ability to encapsulate a small solute in its cavity in a single helix that is a bit smaller than CDs. [22]. Common encapsulated solutes are the well-known polyiodide ions, as well as monoacyl lipids and some alcohols. [23,24]

The simple fact that starch is only minimally soluble in water if not heated above 60 °C is a barrier to its use in aqueous solutions. [22] This problem can be overcome by partial hydrolysis into shorter oligosaccharide fragments. The resulting so-called maltodextrins possess characteristics of both starch, such as lack of sweetness, and glucose, such as solubility in cold water. [25,26]

As common food additives, they perform a variety of functions in modern foods: they modulate texture, act as anti-caking and anti-crystallization agents, replace fat in low-fat products by providing a similar mouthfeel, and can extend shelf life and carry flavors and

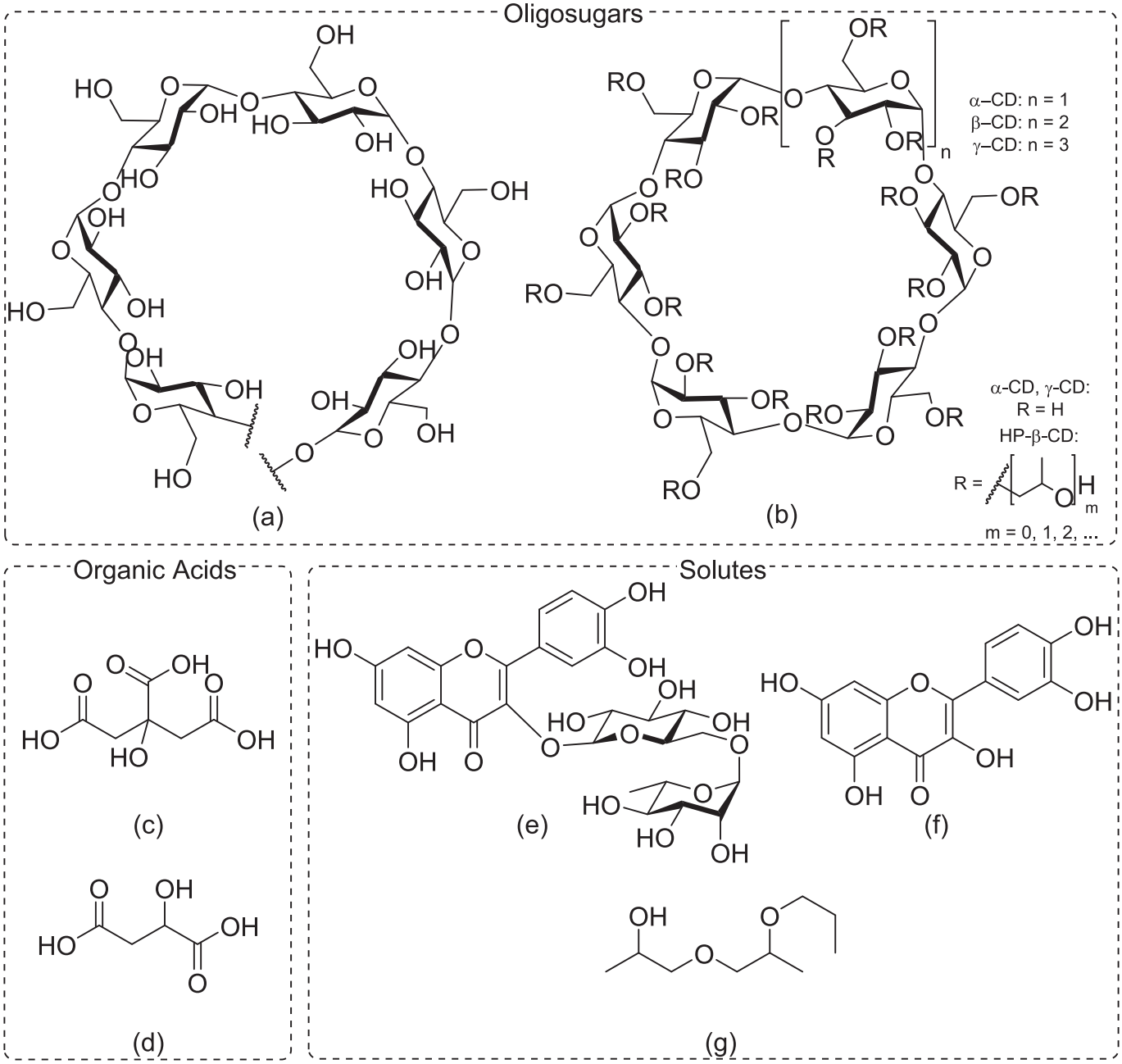

Fig. 1. Structure of the molecules used in this study: a) General structure of a maltodextrin, b) CD, c) Citric acid, d) Malic acid, e) Rutin, f) Quercetin, g) DPnP (dipropylenglycol n-propylether).

fragrances. [25–27] Maltodextrins are less expensive than comparable hydrocolloids and their solutions in water have a barely noticeable texture and taste. [28]

Just like starch, maltodextrin contains mainly α-1,4, but also α-1,6 glycosidic bonds, stemming from the hydrolysis of amylopectin. [26,27] The ratio of these links is dependent on the type of starch that has been hydrolyzed. [26,27]

The fact that the shortest possible α-1,4 connected polyglucan – maltose -already has the same bond angles as those found in the amylose helix, [22] can be taken as evidence that maltodextrin has a helical structure, regardless of their chain length. However, its use as direct molecular encapsulation agent has rarely been investigated.

To address these issues and enhance our understanding of polyphenol formulation, particularly in food-grade media, this study is concerned with the investigation of the use of maltodextrins and short-chain organic acids, both individually and in combination, as well as the influence of pH. Our research was inspired by a recent patent in the field. [29] Herein, a so-called SUPRANADES (supramolecular natural deep eutectic solvent) was described as a combination of maltodextrin and concentrated lemon juice, containing both citric acid and malic acid, that serves as green solvent. We aim to rationalize this concept.

Maltodextrins offer advantages such as high water solubility and lower cost compared to the more established CDs, [27] and they often have fewer regulatory restrictions. However, to our knowledge, no study has reported encapsulation constants for maltodextrins, and these may be lower than for CDs.

In this study, various maltodextrins, CDs, and two organic acids (citric acid and malic acid, just as in the patent [29]) were used to complex and solubilize the polyphenols rutin and quercetin. Rutin was chosen because it is a glucoside of quercetin (Fig. 1) and therefore might need diverging solubilization mechanisms due to size and polarity.

2. Chemicals and methods

2.1. Chemicals

Maltodextrin DE 13.0–17.0 and DE 4.0–7.0 were purchased from Sigma-Aldrich (Munich, Germany). Maltodextrins Glucidex 12, 21D, 29 and IT 47 were a gift from Roquette Frères (Lestrem, France). α-CD, HP-β-CD and γ-CD sold under the trade names CAVAMAX® W6, CAVASOL® W7 HP and CAVAMAX® W8 PHARMA GAMMADEX are a gift from Wacker Chemie AG (Burghausen, Germany). D-(+)-glucose anhydrous (purity = 99 %) was purchased from Alfa Aesar (Karlsruhe, Germany). L-(−)-malic acid (purity >99.0 %) and citric acid (purity ≥99.5 % Ph. Eu.) were purchased from TCI (Eschborn, Germany) and Roth (Karlsruhe, Germany), respectively. Disodium DL-malate (purity 98–101 %) and trisodium citrate for analysis, di-hydrate, were purchased from Sigma -Aldrich (Oakville, Canada). DPnP, mixture of isomers (purity ≥98.5 %) was purchased from Sigma-Aldrich (Munich, Germany). Rutin hydrate (purity ≥ to 94 %, HPLC) and quercetin (purity >95 %, HPLC) were purchased from Sigma-Aldrich (Munich, Germany) and TCI (Eschborn, Germany), respectively. The water in use was deionized Millipore water (18 MΩ·cm) from a Millipore purification system from Merck Millipore (Billerica, MA USA). Monosodium citrate, disodium citrate in solution were prepared by mixing appropriate amounts of citric acid and trisodium citrate. Monosodium malate in solution was prepared in the same manner by mixing appropriate amounts of malic acid and disodium malate.

2.1.1. Sample preparations

Solutions with concentrations over the whole solubility range of citric acid and malic acid and/or their respective sodium salts, with or without an additional 15 wt% maltodextrin DE 13.0–17.0, as well as solutions with maltodextrins of different dextrose equivalents and different CDs were saturated with an excess of a solute and left to stir overnight at room temperature. The success of the solubilization was then evaluated by UV vis absorbance measurements after centrifugation and filtration with a syringe filter at room temperature of the former prepared samples. The used centrifuge is a Sigma 3–18 KS (Osterode am Harz, Germany) at a speed of 14,000 rpm for 10 min. The brand of the used filters is AVANTOR ® hydrophobic PTFE 13 mm, 0.45 μm (VWR international LLC, United States).

2.1.2. UV–visible spectroscopy

Absorbance spectra were recorded from 300 nm to 500 nm using a Perkin Elmer UV/vis Spectrophotometer Lambda 19 (Rodgau, Germany) also at room temperature. A small quantity of the sample was weighed and diluted with water to achieve a concentration suitable for analysis by the photometer. The initial optical density of the sample before dilution was then calculated by multiplying the recorded values by the dilution factor and converted to the solubilized concentration of the polyphenol using the extinction coefficient derived from the calibration curves (see below). The solubilized concentration was then plotted against the weight fraction of the solubilizing additive.

2.1.3. UV–visible calibration curves

A defined amount of rutin or quercetin was dissolved in 100 mL Millipore water to prepare a stock solution. Separate stock solutions were prepared at pH 8 by adding a small amount of sodium hydroxide solution. The stock solution of quercetin at pH 7 also contained 5 % HP-β-CD because the solubility of quercetin in water is too low for a calibration curve. In each case, at least six dilutions of these stock solutions were made with Millipore water to obtain an absorbance of up to 1 a.u. The concentration of the dilutions was plotted against their absorbance, and the slope of the resulting linear curve was interpreted as the extinction coefficient, taking into account the path length of 1 cm.

2.1.4. Salting-out/in behavior determination

The utilized system was a combination of water and DPnP, exhibiting a low-temperature phase separation at approximately 14 °C. [30] A mixture of 3 g of a 45/55 weight ratio mixture of water and DPnP was introduced into a 10 mL glass tube with a specified amount of an additive. A magnetic stirring bar was then introduced, and the tube was subsequently sealed with a Teflon cap. At room temperature, the system displayed biphasic behavior and was driven to an emulsion through agitation. Subsequently, the biphasic system was cooled in an ice bath maintained at a temperature of 0 °C until the samples exhibited a monophasic appearance and consistency, akin to that of water. Subsequently, the temperature of the bath was gradually elevated via the use of a heating stirring plate, with the temperature monitored using a digital thermometer. The emergence of a new phase transition was identified through visual observation. The temperature at which a milky emulsion began to form was noted. The phase transition was reversible by cooling the bath again below the phase transition temperature by the addition of ice. Subsequently, temperature phase transition curves as a function of additive concentration were established. A curve with a positive slope and a negative one, respectively, corresponds to the effect of salting-in and salting-out additives.

3. Results and discussions

3.1. Complexing property of maltodextrins and CDs

To investigate and compare the complexing and solubilizing properties of CDs and maltodextrins, a comparable way to classify these solubilizers had to be established. Maltodextrins are produced by enzymatic or acid hydrolysis of starch. [31] The resulting mixture consists of a broad distribution of glucose, maltose and oligosaccharide fragments of different lengths. [27] In these chains, the anomeric carbon of each monomer is linked to the rest of the chain via 1,4-glycosidic bonds or 1,6-gylcosidic bonds so that only the last monomeric carbon possesses a single reducing end. [28] Maltodextrins can be characterized

by their so-called dextrose equivalent (DE) which is defined as the ratio of an equivalent mass of reducing sugar $m_{reducing}$ (i.e. glucose) that would be able to reduce as much as the maltodextrin over the total mass m_{total}. (32)

$$DE = 100 \cdot \frac{m_{reducing}}{m_{total}}$$

The physicochemical properties of maltodextrin and its solutions in water depend on the DE. In general, maltodextrins with a higher DE are more soluble in water and more hygroscopic, and their solutions have a lower freezing point and are less viscous. [26,27]

A more chemically intuitive parameter that is used for all polymers, including oligo- and polysaccharides, is the degree of polymerization (DP), which represents the number of monomers, in our case glucose units, per polymer chain. [31] The higher the DE number, the lower the DP. [33] For native starches, the DE is essentially zero due to the enormous excess of nonreducing residues in comparison. Trivially, CD have a DE of 0 as they have no reducing end. [31] The DE increases the more the starch is hydrolyzed, which can be adjusted in the production process by changing the temperature of the hydrolysis. [27] Up to a DE of 20, the resulting products are classified as maltodextrins, and above as glucose sirups. [31] The maximum DE is 100, as is clear from the definition. [34]

For the sake of comparability between maltodextrins and CDs, the inverse value of the DE corresponds to the DP. [27] More precisely, the number of glucose units per oligosaccharide chain for an ideally monodisperse maltodextrin can be calculated according to the following eq.

$$DP = \frac{M_{C_6H_{12}O_6}}{M_{C_6H_{10}O_5}} \left(\frac{100}{DE} - 1 \right) + 1$$

The corresponding numbers for the maltodextrins used in this study are shown in Table 1. This is however hypothetical due to the polydispersity and can only be used as a rough estimation. [27] Maltodextrins with identical DE can indeed show different physicochemical properties, if the distribution of chain lengths is different. [32] Additionally, the ratio of α-1,4 glycosidic bonds to α-1,6 glycosidic bonds needs to be considered. [27] While the DE value is usually the only information available for commercial maltodextrins, [28] it is not sufficient to predict all of its physicochemical properties [27,35].

Solubilizations of rutin and quercetin in solutions α-, HP-β-, and γ-CDs were carried out to have our own references for the present studies. Analogous experiments were performed with maltodextrins of different DE ranging from 13.0 to 17.0. Encouraged by the results for rutin, maltodextrins with different DE were also tested for this polyphenol. Although comparative data for CDs have already been extensively reported, see below, investigators have focused on lower CD concentrations due to their restricted use or for practical reasons. Literature on analogous solubilizations with maltodextrins is scarce.

The obtained results are reported in Fig. 2A, B, C and D. Due to the unclear stoichiometry of maltodextrins, all concentrations are expressed as weight fractions.

Table 1
Dextrose equivalents of the maltodextrins in use and their hypothetical degree of polymerization (DP) based von DE assuming monodisperse and common oligosugars of similar size.

DE	DP	Similar oligosugar
4.0–7.0	20.1–15.8	
12	9.1	
13.0–17.0	8.4–6.4	β-CD
15.0–20.0	7.3–5.4	α-CD
16.5–19-5	6.6–5.6	α-CD
21	5.2	
29	3.7	maltotriose
47	2.3	maltose

In Fig. 2A, the linear increase in the concentration of rutin and quercetin with increasing concentration of maltodextrin DE 13.0–17.0 becomes evident. The curve for rutin shows a larger slope than the one for quercetin solubilization.

The presented observations (Fig. 2) support the formation of a complex between the two tested polyphenols and the maltodextrin DE 13.0–17.0. In the case of complex formation, solubilization is only dependent on the concentration of complexing sites on the host molecule and the shape of the solubilization curve is then linear, as the concentration of the host molecule increases. [36] The initial solubility of quercetin is lower, reflecting its well-known lower water solubility compared to its glucoside. [5] The slope of quercetin solubilization with both maltodextrin and all CDs is lower than for rutin, indicating that the smaller size of quercetin in this case does not lead to increased encapsulation.

The efficiency of complexation of a solute with a CD is commonly expressed as the apparent solubility constant K_S, which can be calculated from the solubility S_0 of the solute in absence of a cyclodextrin and the slope of the solubility curve (for this, the x-axis has to be converted to molar concentration). [13]

$$K_S = \frac{\text{slope}}{S_0 \cdot (1 - \text{slope})}$$

Many studies have presented solubility constants for rutin [37–40] or quercetin [12,41,42] with different CDs. However, to the best of our knowledge, we are the first to report solubility constants for these polyphenols, or any solute, for complexation with maltodextrins in an analogous manner. The results are shown in Table 2 for rutin and Table 3 for quercetin. No binding constant was calculated for the complexation of quercetin with γ-CD because the data points do not follow a satisfactorily linear behavior.

The solubilizing efficiency of HP-β-CD exceeds that of the other cyclodextrins and maltodextrins by orders of magnitude. For example, γ-CD, at the highest concentration tested, near its solubility limit, was 2.5 times less effective than HP-β-CD at solubilizing quercetin and as much as 61.6 times less effective for rutin. α-CD, on the other hand, was almost completely unable to facilitate the solubilization of either rutin or quercetin, most likely because its cavity is too small. This indicates that β-CD has the optimal cavity size for the polyphenols considered in this study.

The increase in entropy due to the release of the water inside the cavity is known to be the principal driving force of the complex formation [13] with a multitude of other entropic and enthalpic factors like van-der-Waals interactions, hydrogen bonds or conformational changes also playing a role, depending on the solute. [15]

Molecular dynamics studies have shown that the incorporation of quercetin into a β-CD ring is indeed geometrically possible and energetically favorable, with the additional driving force of a hydrogen bond between one of the phenolic hydroxy groups and an OH group of the CD. [43]

Notably, solubilizations with HP-β-CD did not follow a linear behavior: for rutin, the curve flattens (Fig. 2C) at high concentrations, while for quercetin, it becomes increasingly steep. This indicates that there is an additional effect beyond the formation of a 1:1 stoichiometric complex. [13] Deviations of solubility from linearity at high concentrations are well known and can go in two directions: decreases in complexation efficiency are caused by changes in the bulk solvent, while increases in the slope are due to the formation of a complex with a higher stoichiometry, i.e. more than one solute per CD unit. [11] These deviations are well-known, especially for HP-β-CD, [13] however, can go unnoticed and are not always reported in literature because of the high concentration at which they occur. For example, Nguyen et al. studied the solubilization of rutin with HP-β-CD and reported a linear increase [39], which is in line with our results because they only tested concentrations up to 10 mM (around 14 wt%), whereas in our study deviations from linearity are only observed above 25 wt%.

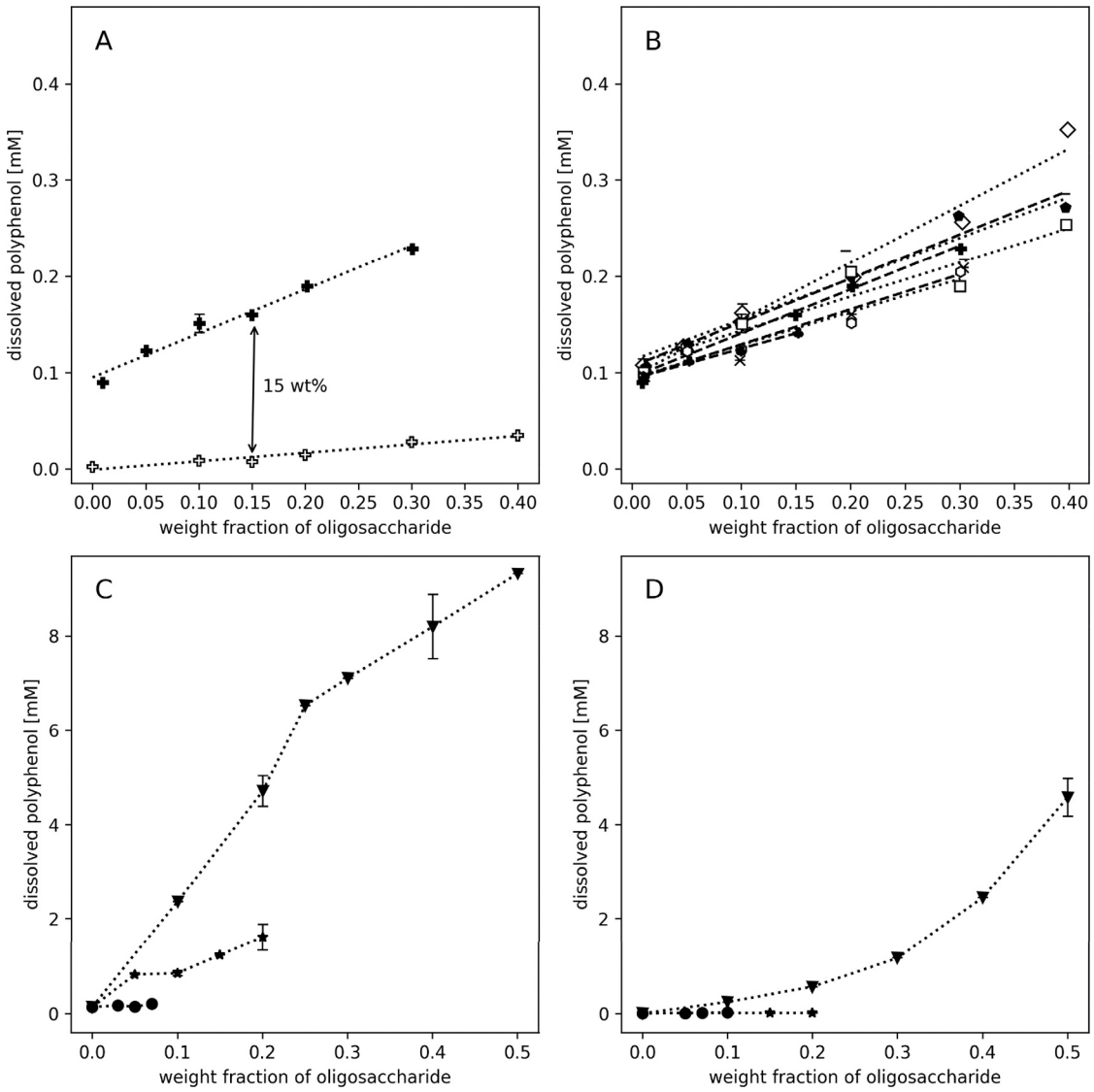

Fig. 2. A) Solubility curves of rutin (✚) and quercetin (✚) in water at room temperature versus maltodextrin DE 13.0–17.0 concentrations. The arrow indicates a maltodextrin content of 15 wt%, which is used for all samples displayed in Fig. 4. B) Solubility curves of rutin in water at room temperature versus weight fractions of maltodextrins of different dextrose equivalents (⬡ DE15.0–20.0, ✚DE 13.0–17.0, ✕ DE16.5–19.5, ♣ DE4.0–7.0, ▬ DE47,□ DE29, ⬟ DE21, ◇ DE12). C) Solubility curves of rutin in water at room temperature versus α-CD (●), HP-β-CD (▼) and γ-CD (★) in weight fraction in water. D) Solubility curves of quercetin in water at room temperature versus α-CD, HP-β-CD and γ-CD in weight fraction in water.

Zheng et al. [42] have shown that the binding constant of the complex of quercetin in HP-β-CD is around ten times higher than in the unsubstituted β-CD. Three hypotheses were proposed to explain this observation: (i) the enlargement of the hydrophobic area of the host molecule by the propyl groups leading to increased interaction with quercetin as the guest molecule, (ii) hydrogen bonding between the side chains and the encapsulated quercetin and (iii) the competition of the hydrophilic isopropyl groups with the hydrophobic quercetin for the interaction with water. Further, Ilyich et al. attributed the greater affinity of quercetin for HP-β-CD than for native β-CD to a conformational change when quercetin is encapsulated with HP-β-CD so that the cavity size is increased. [12]

Although a complex of higher stoichiometry could be a reason for the above observations, another interpretation is probably possible and would allow one to explain the deviations, especially at higher concentrations: the grafted hydroxy-n-propyl groups on β-CD may play the role of a hydrotrope. Hydrotropic solubilization curves typically show little to no solubilization below a certain threshold, the minimum hydrotropic concentration (MHC), after which an exponential behavior begins. [44] The reason is the formation of – comparatively – unstructured nano-inhomogeneities in the solution. [10] High concentrations of HP-β-CD in water could favor the formation of nano-compartments rich in hydroxy-n-propyl groups acting as a solvent and/or hydrotrope. The main problem is the limitation of HP-β-CD for food formulations.

The use of γ-CD seems to be more beneficial than that of maltodextrin DE 13.0–17.0 and α-CD for the solubilization of rutin. α-CD was even less efficient than maltodextrin DE 13.0–17.0. Thus, the maltodextrin tested provided only moderate, but nevertheless significant efficiency.

Table 2
Apparent solubility constants for the encapsulation of rutin with CDs and maltodextrins.

Oligosugar	K_S [M^{-1}]
α-CD	4.1
HP-β-CD	214.4
γ-CD	50.4
Maltodextrin DE 4.0–7.0	7.2
Maltodextrin DE 12	5.6
Maltodextrin DE 13.0–17.0	3.6
Maltodextrin DE 15.0–20.0	2.3
Maltodextrin DE 16.5–19-5	2.4
Maltodextrin DE 21	2.5
Maltodextrin DE 29	1.6
Maltodextrin DE 47	0.9

Table 3
Apparent solubility constants for the encapsulation of quercetin with CDs and maltodextrins.

Oligosugar	K_S [M^{-1}]
α-CD	84.1
HP-β-CD	1555.7
Maltodextrin DE 13.0–17.0	42.9

The primary assumed solubilization mechanism is encapsulation. To form a stable complex and hence efficient solubilization, the size of the cavity must be adequate for the respective solute. Therefore, different binding coefficients with different CDs for any solute are expected and well reported. [13] The question regarding maltodextrin is how this is in the more open helical structure of maltodextrins in contrast to the closed cyclic geometry of CDs. On the one hand, this can render the cavity smaller. On the other hand, a more flexible structure might allow the maltodextrin chain to adapt its conformation to different sizes and geometries of the solutes, but this does not seem to be the case.

Fig. 2B shows the solubilization of rutin for different maltodextrins. A linear increase of the solubilization is observed with almost constant values of the slope. Thus, complexation of the polyphenols by the maltodextrins is likely. Further, many different commercially available maltodextrins seem to have a similar capacity for rutin solubilization in pure water and thus a comparable cavity size.

Overall, the binding constants for rutin in maltodextrins are in a similar range to each other and to α-CD, which makes sense due to their similar cavity size. However, caution should be exercised when differentiating between the different DE, because the molar mass for a monodisperse oligosaccharide derived from the DE was assumed for the calculation of the binding constant, which may not be fully appropriate. Therefore, the binding constants for the lowest and highest DE may have a positive and negative bias, respectively. Nevertheless, it seems that higher DE have a slight tendency to be more effective solubilizers, perhaps because they have a greater proportion of oligosaccharide chains that are long enough to encapsulate a solute. Looking at the graph instead of the binding constant, it seems that the maltodextrin with the lowest DE, DE 4.0–7.0, deviates from the expected trend and shows one of the worst performances. Solutions of this maltodextrin appeared slightly cloudy, as if some of the longer sugar chains were not able to dissolve completely. Therefore, it is possible that they actually encapsulated rutin, as did the other chains, but were removed in the filtration step because they were not in solution.

Since the solubilizing power of inexpensive and unrestricted maltodextrin is poor compared to γ-CD, a way to improve its performance was investigated. For this purpose, further investigations were focused on the effect of citric acid and malic acid and their salts on the solubilization of rutin and/or quercetin in water analogously to the patented SUPRANADES concept, [29] still at room temperature.

3.2. Hydrotropic properties of short organic acids and salting-out effect of their sodium salts

The solubilities of rutin in water with increasing concentration of citric, malic acid and their sodium salt, respectively (Fig. 3A and C) and the solubilities of quercetin likewise versus citric acid and its sodium salts concentrations are depicted in Fig. 3B.

As illustrated in Fig. 3A and B, citric acid serves as a solubilizing agent for both rutin and quercetin in aqueous solutions. From an initial examination of the related curves, it is challenging to discern whether the observed solubilization is attributable to the formation of a complex or to a hydrotropic behavior. To ascertain the precise mechanism, further investigation is required, which is beyond the scope of the present work. Nevertheless, as illustrated in Fig. 3A, the overall solubilization curve of rutin with citric acid resembles a typical hydrotropic behavior. [44]

The pH of solutions containing high concentrations of citric acid and malic acid is too low for practical application. Since an increase in pH can lead to the formation of carboxylate salts, the resulting effects on solubility were investigated by replacing citric acid and malic acid in the experiments with the corresponding mono-, di- or tri-carboxylate sodium salt. This way, a pH so extremely high to deprotonate maltodextrins and CDs cannot be reached. [45] From a formulator's point of view, a basic pH could cause problems, as tri-sodium citrate and di-sodium malate have been reported to be highly salting-out. [46] In addition, the pH of most foods is in between 3 and 7, and elevating the pH can affect taste and texture of an edible formulation in negative ways. [47]

Replacing citric acid with a tri-sodium citrate salt resulted in observable alterations in the absorption parameters of rutin. The addition of only 5 % tri-sodium citrate led to a significant increase of solubility, as rutin and quercetin can be deprotonated at this pH of about 8. [48] To ensure comparability, separate calibration curves were set up. After an initial increase in solubility until a weight fraction of about 5 %, where the polyphenol is then most likely fully deprotonated, the curve decreases again almost linearly with increasing amounts of trisodium citrate. This can be interpreted as a salting-out effect on rutin, in line with the work of Grundl and al. [46] and our work reported in section 3.4. In the frame of that work, trisodium citrate was classified as a salting-out agent for the system DPnP/water, while citric acid was classified as a salting-in agent, while the protonation steps in between have not been studied. [46] DPnP and thus its solubility is not directly influenced by the pH of the solution. Monosodium citrate is classified as a salting-in agent or neutral substance, exhibiting a lesser degree of salting-in compared to citric acid. In the present case, the increased pH is not high enough to form polyphenolates. It seems the higher the degree of ionization of citric molecule and the more dissociated counterions, like sodium, are present, the smaller the salting-in effect. While citric acid itself evidently brings about chaotropic features and loosens the hydrogen bond network in water, the presence of charged and dissociated carboxy groups counterbalance this effect with a strong cosmotropic impact. The impact of mono-, di-, and tri-isodium citrate on the solubility of rutin aligns with the salting-out phenomenon observed in the DPnP/water system. The transition from monosodium salt to disodium salt is less significant than the transition from disodium salt to trisodium salt, since in this case, no chaotropic influence of the molecule is left.

As noted above, the only difference between rutin and quercetin is a sugar group that significantly increases its solubility in water. The overall effect of citric acid and its salts on the solubility of the two polyphenols is similar, but remains low for quercetin because it is difficult to solubilize it in water at all. Monosodium citrate is similarly (in)effective as citric acid, while disodium citrate has very little effect. This shows that short organic acids and their salts are not efficient solubilizing agents for quercetin.

As expected, the solubilization of the phenolics with malic acid at different pH values shows a behavior similar to that of citric acid. A

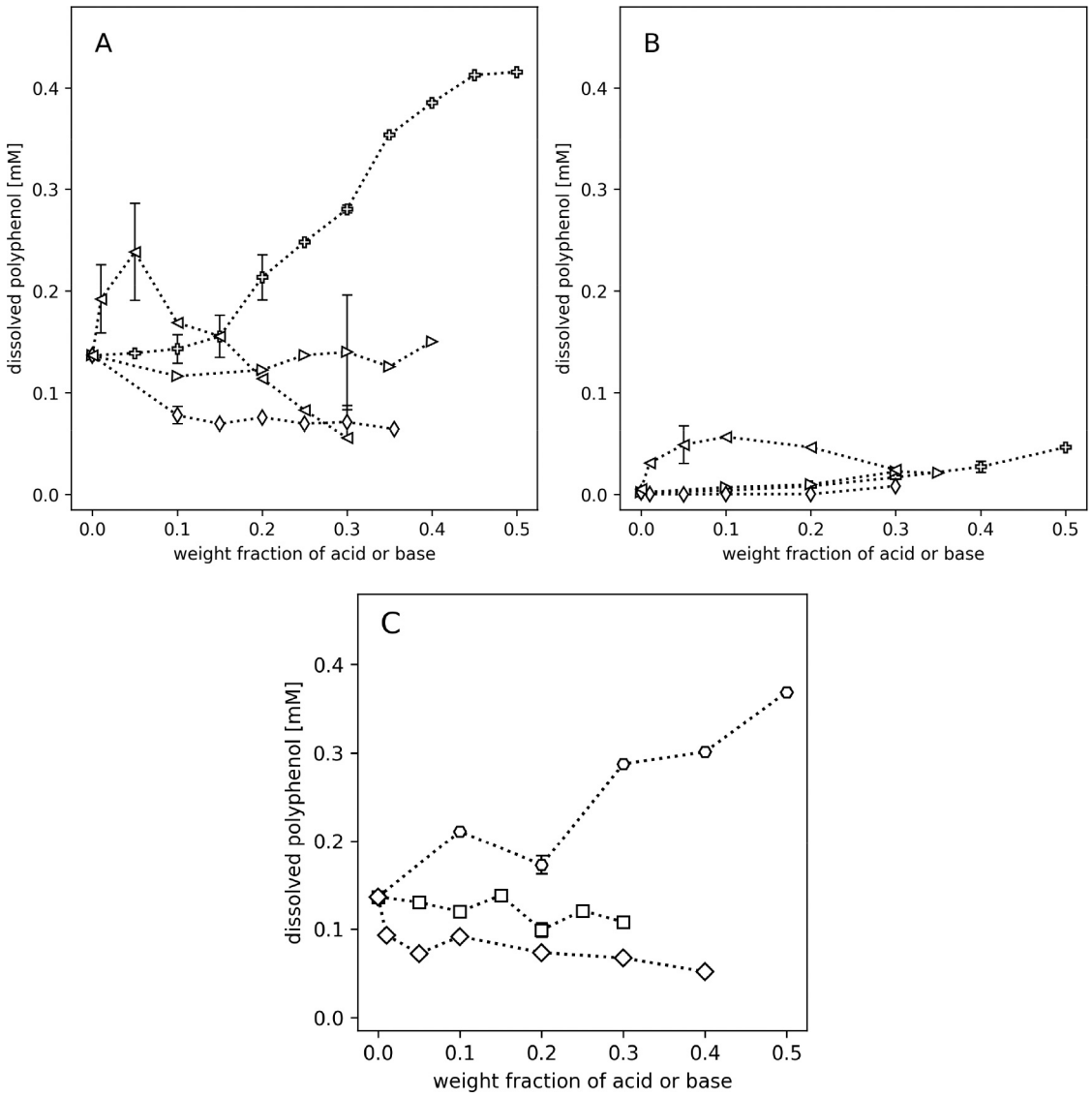

Fig. 3. A) Solubility curves of rutin in water at room temperature versus citric acid and its sodium salts concentrations (✚ citric acid, initial pH = 2, ▷ NaH_2citrate, initial pH = 5, ◊ Na_2Hcitrate, initial pH = 6, ◁ sodium citrate initial pH = 8). B) Solubility curves of quercetin in water at room temperature versus citric acid and its sodium salts concentrations (✚ citric acid, initial pH = 2, ▷ NaH_2citrate, initial pH = 5, ◊ Na_2Hcitrate, initial pH = 6, ◁ sodium citrate initial pH = 8). C) Solubility curves of rutin in water at room temperature versus malic acid and its salts concentrations (○ malic acid, initial pH = 2, □ NaHmalate, initial pH = 4, ◇ sodium malate, initial pH = 7).

similar amount of malic acid is required to solubilize a comparable amount of rutin as for citric acid. Monosodium malate is mostly neutral, perhaps slightly salting-out, and disodium malate is found to be salting-out, although no deprotonation of the polyphenol is observed. The same explanations as given for citric acid can be provided.

3.3. Mixing of complexing maltodextrin and short organic acids (or their sodium salts)

In the next step, we tried to combine the different solubilization mechanisms of oligosugars and short chain acids (and their salts) to check, whether synergistic, additive, or antagonistic solubilization behavior was found.

Fig. 4 shows the solubilities of rutin and quercetin in the presence of 15 % (w/w) maltodextrin DE 13.0–17.0 and varying concentrations of short-chain acids. The solubilization curves of the two phenols follow a trend similar to the one without maltodextrin; however, comparable solubility levels are achieved at lower acid concentrations when the oligosaccharide is present.

A detailed evaluation of the data suggests that the effects of maltodextrin and the short-chain acids are partially additive. This is evidenced by the solubilization curves obtained with 15 % maltodextrin DE 13.0–17.0 and those obtained with only citric or malic acid. The complexing mechanism of the maltodextrin and the hydrotropic solubilizing effect of the short organic acids seem to coexist, as shown in Figs. 3A to 3B and Figs. 4A to 4B, at least within a defined range of concentrations, without impact on one another.

The loss of additivity at high citric acid concentrations for rutin may be due to a competition of the additives for water, resulting in a salting-out effect of citric acid at such high concentrations. The additivity in solubility from the two solubilizers appears to be more consistent for the solubility of quercetin in the presence of citric acid.

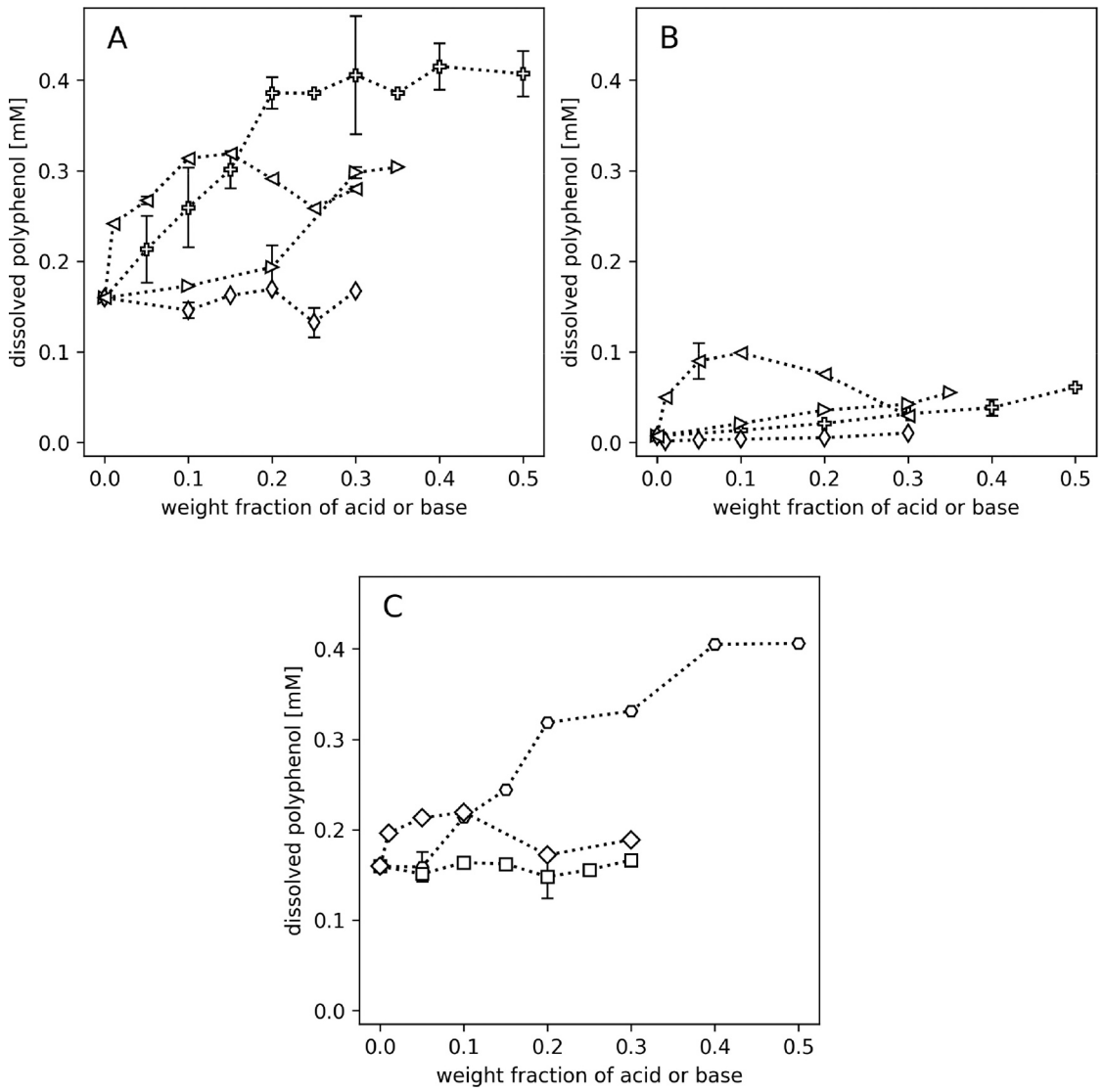

Fig. 4. A) Solubility curves of rutin at room temperature in presence of maltodextrin DE 13.0–17.0 at 15 %(*w*/w) versus citric acid, and its salts concentrations (✜ citric acid, initial pH = 2, ▷ NaH_2citrate, initial pH = 5, ◊ Na_2Hcitrate, initial pH = 6, ◁ sodium citrate initial pH = 8). B) Solubility curves of quercetin at room temperature in presence of maltodextrin DE 13.0–17.0 at 15 % (*w*/w) versus citric acid, and its salts concentrations (✜ citric acid, initial pH = 2, ▷ NaH_2citrate, initial pH = 5, ◊ Na_2Hcitrate, initial pH = 6, ◁ sodium citrate, initial pH = 8). C) Solubility curves of rutin at room temperature in presence of maltodextrin at 15 % (w/w) versus malic acid, and its salt concentrations (⬡ malic acid, initial pH = 2, □ NaHmalate, initial pH = 4, ◇ sodium malate, initial pH = 7).

3.4. Salting-in/out effects of the maltodextrins, CDs, 2-propanol and short organic acids and their sodium salts salts on a water-DPnP mixtures

To gain a deeper understanding of the solubilization process of individual components or monomers, salting-in and salting-out experiments were conducted. Fig. 5A illustrates the relationship between the cloud point of the water-DPnP mixture and the concentrations of the oligoglucose-maltodextrin solubilizers described previously. For each additive, the α coefficient was determined as defined by Bauduin et al. [30]

$$\mathrm{LST}(c) = \mathrm{LST}(c = 0) + \alpha{\cdot}c$$

The results are displayed in Table 4.

All sugars were found to exhibit salting-out behavior, consistent with previous reports. Specifically, all values are notably below the −1.39 °C mol/mmol reported by Grundl et al., who focused exclusively on mono- and disaccharides. [46] This suggests that maltodextrins, like other sugars, deprive the DPnP molecule of its hydration water, resulting in phase separation at lower temperatures. This indicates that all these sugars and their derivatives are salting-out agents. Souza et al. studied a similar aqueous two-phase system of water and acetonitrile and found that all sugars are salting-out in the order maltodextrin > disaccharides > monosaccharides, with little difference between the maltodextrins of different DE tested. [34] As the concentration of the investigated phenols increases with the concentration of maltodextrins, specific interactions, such as complexations, must occur between maltodextrin on the one side and rutin and quercetin on the other side. These interactions are analogous to those observed between CDs and polyphenols (see Fig. 2). In light of its impact on DPnP, the salting-out effect of maltodextrin and CDs should lead to a reduction in the solubility of the two polyphenols in water. However, this outcome has not been observed. It is evident that the salting-out effect of sugars was superseded by the

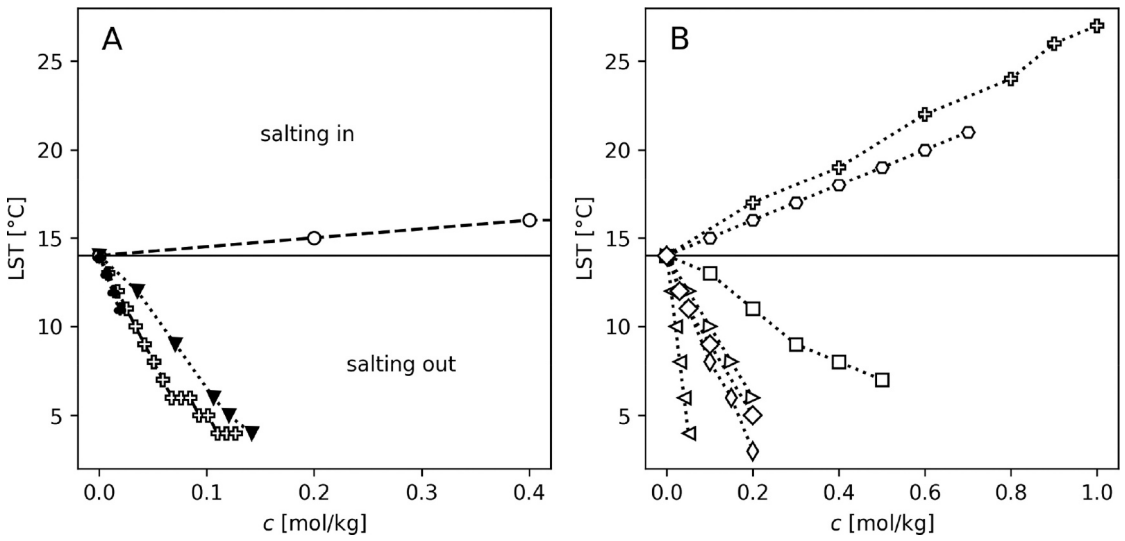

Fig. 5. A) Plot of the temperature phase transition of the system water/DPnP versus polysaccharide and isopropanol concentrations (✙ maltodextrin DE 13.0–17.0, ♣ maltodextrin DE 4.0–7.0, ▼ HP-β-CD, ○ isopropanol). B) Plot of the temperature phase transition of the system water/DPnP versus citric acid, malic acid, and their salts concentrations (✙ citric acid, ▷ NaH_2citrate, ◊ Na_2Hcitrate, ◁ sodium citrate, ○ malic acid, □ NaHmalate, ◇ sodium malate).

Table 4
α coefficients as a measure of the salting-in and salting-out characteristics of each additive.

Compound	α coefficient [°C mol/mmol]
Maltodextrin DE 13.0–17.0	−6.28
Maltodextrin DE 4.0–7.0	−9.15
HP-β-CD	−4.18
Isopropanol	0.28
Citric acid	0.72
NaH_2citrate	−2.25
Na_2Hcitrate	−3.03
Sodium citrate	−11.24
Malic acid	0.56
NaHMalate	−0.83
Sodium malate	−2.44

formation of specific complexes between oligo- and polysugars and polyphenols.

The α- and γ-CDs are insoluble in the DPnP/water system. DPnP precipitates the CDs by taking up the water necessary to solubilize them, thereby salting them out. This finding is consistent with the observation that α- and γ-CDs are less soluble in water compared to maltodextrin DE 13.0–17.0. Water molecules are less tightly bound to the cyclic sugar units than they are to the linear ones as evidenced by the fact that maltodextrins are able to form a gel and bind up to nine times their own mass of water, [27] while no such phenomenon is observed for CD. Contrary to α- and γ-CDs, the HP-β-CD is not salted-out by DPnP. One might assume that the grafted hydroxy-n-propyl groups induce an additional favorable affinity for water, in comparison to pure OH-groups. Nevertheless, the salting-out effect of HP-β-CD is somewhat less pronounced than that of maltodextrin DE 13.0–17.0 in the DPnP/water system and additionally pure 2-propanol is slightly salting-in. In summary, this is consistent with a slight hydrotropic behavior of the ether moieties of the HP-β-CD.

Citric acid and tri-sodium citrate have previously been reported to be salting-in and salting-out agents, respectively. [46] The present work shows that malic acid and mono-sodium malate sodium salts can analogously be classified as salting-in and out, respectively, see Fig. 5B. Disodium malate was already reported as salting-out, too, by Grundel and al., [46] and monosodium malate is found here to be less salting-out than disodium malate, as expected. The orders of salting power for the malate sodium salt is disodium malate > monosodium malate, and for the citrate salts trisodium citrate>disodium citrate>monosodium salts. These findings confirm the salting-out effect of short acid sodium salts, thereby reenforcing our interpretations regarding the solubilization of quercetin and rutin.

4. Conclusion

In conclusion, we could show that maltodextrins can serve similarly to the commonly used CDs to increase the solubility of rutin and quercetin in water. Although the sugars and sugar monomers themselves were shown to have salting-out properties, a specific interaction with the phenols of the oligosugars outcompeted this mode of action resulting in a solubility enhancement. Thus, the tested polysaccharides most likely act as complexing agents for rutin and quercetin, while in the case of HP-β-CD for rutin a more complex solubilization mechanism is plausible.

For the first time, binding constants for encapsulations with maltodextrins have been reported, as is usually done for cyclodextrins. They were found to be slightly lower than for α-CD, which has a similar cavity size, and the dextrose equivalent (DE) did not have a strong influence on the solubilization performance.

In terms of solubilization of quercetin, α- and γ-CD or maltodextrin DE 13.0–17.0 show rather poor performance. γ-CD seems to be better suited to solubilize rutin, which is larger than quercetin. However, the use of maltodextrin is less problematic in terms of toxicity and price. Citric acid, applied at high concentrations, was found to be an adequate agreed hydrotrope. Unfortunately, a very acidic pH (2 and below) is generated in these solutions, making them less interesting for oral applications. For this reason, we have tested progressively higher levels of deprotonation of citric and malic acid and have found them to be less and less effective hydrotropes, in accordance with their increasing salting-out characteristics. Interestingly and encouragingly, the

presence of maltodextrin seemed to reduce the influence of salting-out.

The combination of complexing molecules and short organic acid showed a beneficial additive effect for the solubilization of quercetin and rutin in water. Thus, the complexing solubilization mechanism of oligo- and polysugars and the hydrotropic behavior of short acids can be used additively without impacting each other up to comparatively high concentrations. However, still the resulting pH equal to or below 2 is in an undesirable range. At pH 8, the situation is less clear, since an ionization of the polyphenols occurs, which favors their solubility in water. As the tested phenols are not stable in basic conditions and will degrade oxidatively very quickly [8], further investigation is needed to assess whether maltodextrins protect the polyphenolates from degradation similar to cyclodextrins. [42] At intermediate pH values, no deprotonation of the phenols, favoring their aqueous solubilization, occurs. Yet, the hydrotropic effect is less pronounced than at pure acid conditions. pH and solubility can be better optimized using malic acid than citric acid.

As a general result, we could find that, although less efficient than some cyclodextrins, maltodextrins can be used to enhance the solubility or rutin and quercetin. Since maltodextrin is harmless and cheap, this can be relevant for improved polyphenol water solubility in food or neutraceutical formulations. However, in the case of pharmaceutical formulations, where HP-β-CD can be used, this cyclodextrin is the best choice particularly for injectable formulations.

CRediT authorship contribution statement

Bastian Mueller: Writing – original draft, Validation, Methodology, Investigation, Formal analysis. **Eva Mueller:** Writing – original draft, Supervision, Conceptualization. **Didier Touraud:** Writing – original draft, Supervision, Conceptualization. **Anne-Sylvie Fabiano-Tixier:** Writing – review & editing, Conceptualization. **Werner Kunz:** Writing – original draft, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

[1] R. Tsao, Chemistry and biochemistry of dietary polyphenols, Nutrients 2 (2010) 1231–1246, https://doi.org/10.3390/nu2121231.
[2] S. Quideau, D. Deffieux, C. Douat-Casassus, L. Pouységu, Plant polyphenols: chemical properties, biological activities, and synthesis, Angew. Chem. Int. Ed. Eng. 50 (2011) 586–621, https://doi.org/10.1002/anie.201000044.
[3] X. Han, T. Shen, H. Lou, Dietary polyphenols and their biological significance, IJMS 8 (2007) 950–988, https://doi.org/10.3390/i8090950.
[4] V. Curti, A. Di Lorenzo, M. Dacrema, J. Xiao, S.M. Nabavi, M. Daglia, In vitro polyphenol effects on apoptosis: an update of literature data, Semin. Cancer Biol. 46 (2017) 119–131, https://doi.org/10.1016/j.semcancer.2017.08.005.
[5] A. Munin, F. Edwards-Lévy, Encapsulation of natural polyphenolic compounds; a review, Pharmaceutics 3 (2011) 793–829, https://doi.org/10.3390/pharmaceutics3040793.
[6] V. Dhapte, P. Mehta, Advances in hydrotropic solutions: an updated review, St. Petersburg Polytechnical University Journal: Physics and Mathematics 1 (2015) 424–435, https://doi.org/10.1016/j.spjpm.2015.12.006.
[7] A. Niedzwiecki, M.W. Roomi, T. Kalinovsky, M. Rath, Anticancer efficacy of polyphenols and their combinations, Nutrients (2016), https://doi.org/10.3390/nu8090552.
[8] D.P. Makris, J.T. Rossiter, Heat-induced, metal-catalyzed oxidative degradation of quercetin and rutin (quercetin 3-O-rhamnosylglucoside) in aqueous model systems, J. Agric. Food Chem. 48 (2000) 3830–3838, https://doi.org/10.1021/jf0001280.
[9] L. Lajoie, A.-S. Fabiano-Tixier, F. Chemat, Water as green solvent: methods of Solubilisation and extraction of natural products-past, Present and Future Solutions. Pharmaceuticals (Basel) (2022), https://doi.org/10.3390/ph15121507.
[10] W. Kunz, K. Holmberg, T. Zemb, Hydrotropes, Curr. Opin. Colloid Interface Sci. 22 (2016) 99–107, https://doi.org/10.1016/j.cocis.2016.03.005.
[11] D.-H. Kim, S.-E. Lee, Y.-C. Pyo, P. Tran, J.-S. Park, Solubility enhancement and application of cyclodextrins in local drug delivery, J. Pharm. Investig. 50 (2020) 17–27, https://doi.org/10.1007/s40005-019-00434-2.
[12] T.V. Ilyich, E.A. Lapshina, A.A. Maskevich, A.G. Veiko, A.V. Lavysh, B. Palecz, et al., Inclusion complexes of quercetin with β-Cyclodextrins: ultraviolet and infrared spectroscopy and quantum chemical modeling, BIOPHYSICS 65 (2020) 381–389, https://doi.org/10.1134/s0006350920030070.
[13] E. Del Valle, Cyclodextrins and their uses: a review, Process Biochem. 39 (2004) 1033–1046, https://doi.org/10.1016/S0032-9592(03)00258-9.
[14] E. Schneiderman, A.M. Stalcup, Cyclodextrins: a versatile tool in separation science, J. Chromatogr. B Biomed. Sci. Appl. 745 (2000) 83–102, https://doi.org/10.1016/S0378-4347(00)00057-8.
[15] B. Liu, W. Li, T. Nguyen, an, Zhao J., Empirical, thermodynamic and quantum-chemical investigations of inclusion complexation between flavanones and (2-hydroxypropyl)-cyclodextrins, Food Chem. 134 (2012) 926–932, https://doi.org/10.1016/j.foodchem.2012.02.207.
[16] L. Szente, J. Szejtli, Cyclodextrins as food ingredients, Trends Food Sci. Technol. 15 (2004) 137–142, https://doi.org/10.1016/j.tifs.2003.09.019.
[17] M.E. Davis, M.E. Brewster, Cyclodextrin-based pharmaceutics: past, present and future, Nat. Rev. Drug Discov. 3 (2004) 1023–1035, https://doi.org/10.1038/nrd1576.
[18] T. Irie, K. Uekama, Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation, J. Pharm. Sci. 86 (1997) 147–162, https://doi.org/10.1021/js960213f.
[19] S. Gould, R.C. Scott, 2-Hydroxypropyl-beta-cyclodextrin (HP-beta-CD): a toxicology review, Food Chem. Toxicol. 43 (2005) 1451–1459, https://doi.org/10.1016/j.fct.2005.03.007.
[20] F. Aguilar, U. Charrondiere, B. Dusemund, P. Galtier, J. Gilbert, D. Gott, et al., Inositol hexanicotinate (inositol hexaniacinate) as a source of niacin (vitamin B3) added for nutritional purposes in food supplements, EFSA J. 7 (2009) 949, https://doi.org/10.2903/j.efsa.2009.949.
[21] A. Gonzalez Pereira, M. Carpena, P. García Oliveira, J.C. Mejuto, M.A. Prieto, Gandara J. Simal, Main applications of Cyclodextrins in the food industry as the compounds of choice to form host-guest complexes, IJMS (2021), https://doi.org/10.3390/ijms22031339.
[22] R.D. Hancock, B.J. Tarbet, The other double Helix—the fascinating chemistry of starch, J. Chem. Educ. 77 (2000) 988, https://doi.org/10.1021/ed077p988.
[23] G. Fittolani, P.H. Seeberger, M. Delbianco, Helical polysaccharides, Pept. Sci. (2020), https://doi.org/10.1002/pep2.24124.
[24] S. Pérez, E. Bertoft, The molecular structures of starch components and their contribution to the architecture of starch granules: A comprehensive review, Starch Stärke (Starch - Stärke) 62 (2010) 389–420, https://doi.org/10.1002/star.201000013.
[25] P. Dokic, J. Jakovljevic, L. Dokic-Baucal, Molecular characteristics of maltodextrins and rheological behaviour of diluted and concentrated solutions, Colloids and Surfaces A Physicochemical and Engineering Aspects. 141 (1998) 435–440, https://doi.org/10.1016/S0927-7757(97)00118-0.
[26] Y.-J. Wang, L. Wang, Structures and Properties of Commercial Maltodextrins from Corn, Potato, and Rice Starches. Starch Stärke 52, 2000, pp. 296–304, https://doi.org/10.1002/1521-379X(20009)52:8/9<296::AID-STAR296>3.0.CO;2-A.
[27] I.S. Chronakis, On the molecular characteristics, compositional properties, and structural-functional mechanisms of maltodextrins: a review, Crit. Rev. Food Sci. Nutr. 38 (1998) 599–637, https://doi.org/10.1080/10408699891274327.
[28] C.Y. Takeiti, T.G. Kieckbusch, F.P. Collares-Queiroz, Morphological and physicochemical characterization of commercial maltodextrins with different degrees of dextrose-equivalent, Int. J. Food Prop. 13 (2010) 411–425, https://doi.org/10.1080/10942910802181024.
[29] L. Lajoie, F. Chemat, A.-S. Fabiano-Tixier, Solvant eutectique profond d'origine naturelle supramoléculaire - Supramolecular deep eutectic solvent of natural origin: patent, 2021.
[30] P. Bauduin, L. Wattebled, S. Schrödle, D. Touraud, W. Kunz, Temperature dependence of industrial propylene glycol alkyl ether/water mixtures, J. Mol. Liq. 115 (2004) 23–28, https://doi.org/10.1016/j.molliq.2004.01.001.
[31] X. Qi, R.F. Tester, Is Starch or Maltodextrin "Glucose?", Starch Stärke (Starch - Stärke) (2018) https://doi.org/10.1002/star.201700304.
[32] L. Marchal, Towards a rational design of commercial maltodextrins, Trends Food Sci. Technol. 10 (1999) 345–355, https://doi.org/10.1016/S0924-2244(00)00018-2.
[33] Q. Du, J. Tang, M. Xu, F. Lyu, J. Zhang, Y. Qiu, et al., Whey protein and maltodextrin-stabilized oil-in-water emulsions: effects of dextrose equivalent, Food Chem. 339 (2021) 128094, https://doi.org/10.1016/j.foodchem.2020.128094.
[34] I.N. Souza, C.M. Soares, R.L. Souza, M.G. Freire, A.S. Lima, Aqueous two-phase systems formed by maltodextrin and acetonitrile: phase diagrams and partitioning studies, Fluid Phase Equilib. 476 (2018) 179–185, https://doi.org/10.1016/j.fluid.2018.08.005.
[35] F. Avaltroni, P.E. Bouquerand, V. Normand, Maltodextrin molecular weight distribution influence on the glass transition temperature and viscosity in aqueous

solutions, Carbohydr. Polym. 58 (2004) 323–334, https://doi.org/10.1016/j.carbpol.2004.08.001.
[36] C. Tsunoda, K. Hasegawa, R. Hiroshige, T. Kasai, H. Yokoyama, S. Goto, Effect of Cyclodextrin complex formation on solubility changes of each drug due to intermolecular interactions between acidic NSAIDs and basic H2 blockers, Mol. Pharm. 20 (2023) 5032–5042, https://doi.org/10.1021/acs.molpharmaceut.3c00291.
[37] J. Liu, S. Zhang, X. Zhao, Y. Lu, M. Song, S. Wu, Molecular simulation and experimental study on the inclusion of rutin with β-cyclodextrin and its derivative, J. Mol. Struct. 1254 (2022) 132359, https://doi.org/10.1016/j.molstruc.2022.132359.
[38] M.L. Calabrò, S. Tommasini, P. Donato, R. Stancanelli, D. Raneri, S. Catania, et al., The rutin/beta-cyclodextrin interactions in fully aqueous solution: spectroscopic studies and biological assays, J. Pharm. Biomed. Anal. 36 (2005) 1019–1027, https://doi.org/10.1016/j.jpba.2004.09.018.
[39] T. Nguyen, an, Liu B, Zhao J, Thomas DS, Hook JM., An investigation into the supramolecular structure, solubility, stability and antioxidant activity of rutin/cyclodextrin inclusion complex, Food Chem. 136 (2013) 186–192, https://doi.org/10.1016/j.foodchem.2012.07.104.
[40] K. Miyake, H. Arima, F. Hirayama, M. Yamamoto, T. Horikawa, H. Sumiyoshi, et al., Improvement of solubility and oral bioavailability of rutin by complexation with 2-hydroxypropyl-beta-cyclodextrin, Pharm. Dev. Technol. 5 (2000) 399–407, https://doi.org/10.1081/PDT-100100556.
[41] M. Liu, L. Dong, A. Chen, Y. Zheng, D. Sun, X. Wang, B. Wang, Inclusion complexes of quercetin with three β-cyclodextrins derivatives at physiological pH: spectroscopic study and antioxidant activity, Spectrochim. Acta A Mol. Biomol. Spectrosc. 115 (2013) 854–860, https://doi.org/10.1016/j.saa.2013.07.008.
[42] Y. Zheng, I.S. Haworth, Z. Zuo, M.S.S. Chow, A.H.L. Chow, Physicochemical and structural characterization of quercetin-beta-cyclodextrin complexes, J. Pharm. Sci. 94 (2005) 1079–1089, https://doi.org/10.1002/jps.20325.
[43] C. Yan, X. Li, Z. Xiu, C. Hao, A quantum-mechanical study on the complexation of β-cyclodextrin with quercetin, J. Mol. Struct. (THEOCHEM) 764 (2006) 95–100, https://doi.org/10.1016/j.theochem.2006.02.008.
[44] S. Shimizu, N. Matubayasi, The origin of cooperative solubilisation by hydrotropes, Phys. Chem. Chem. Phys. 18 (2016) 25621–25628, https://doi.org/10.1039/c6cp04823d.
[45] G. Yang, C. Zhu, L. Zhou, Deprotonation and acidity characterization of biomass sugars: a first-principles study, J. Mol. Model. 22 (2016) 104, https://doi.org/10.1007/s00894-016-2972-6.
[46] G. Grundl, M. Müller, D. Touraud, W. Kunz, Salting-out and salting-in effects of organic compounds and applications of the salting-out effect of Pentasodium phytate in different extraction processes, J. Mol. Liq. 236 (2017) 368–375, https://doi.org/10.1016/j.molliq.2017.03.091.
[47] A. Andrés-Bello, V. Barreto-Palacios, P. García-Segovia, J. Mir-Bel, J. Martínez-Monzó, Effect of pH on color and texture of food products, Food Eng. Rev. 5 (2013) 158–170, https://doi.org/10.1007/s12393-013-9067-2.
[48] A. Fusina, P. Degot, D. Touraud, W. Kunz, V. Nardello-Rataj, Enhancement of water solubilization of quercetin by meglumine and application of the solubilization concept to a similar system, J. Mol. Liq. 368 (2022) 120756, https://doi.org/10.1016/j.molliq.2022.120756.