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Solubilisation of quercetin: Comparison of hyperbranched polymer and hydrogel

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ABSTRACT

Most of the new chemical entities discovered today are highly lipophilic in nature and show poor solubility and membrane permeability resulting in poor oral bioavailability. Quercetin is a bioactive flavonoid widely used as a health supplement. Being sparingly soluble and chemically unstable in aqueous intestinal fluids, quercetin is poorly absorbed orally. Drug delivery systems, like hydrogels or hyperbranched polymers are able to increase the solubility of drugs, because they carry different functional groups which allow strong interactions with the functional groups of the drug.

The solubility of quercetin, as a flavonoid with disease prevention character, in water or in ethanol and the solubilisation of quercetin in water or ethanol using hyperbranched polymer Boltorn H20 or Poly-(*n*-isopropylacrylamide) hydrogels are investigated experimentally. Additionally, the chemical stability of quercetin at room temperature over a long time period is studied. The most important findings are a) the solubility of quercetin in water is extremely low; b) linear or cross-linked Poly-(*n*-isopropylacrylamide) can be used to avoid the decomposition of quercetin; c) the swelling properties of Poly-(*n*-isopropylacrylamide) hydrogels are not influenced by the presence of quercetin; and d) hyperbranched polymers can be used to improve the quercetin solubility.

1. Introduction

The use of drug-delivery systems to improve the efficacy of drugs remains an important strategy for achieving progress against diseases. All therapies require the administration of stable dosage forms in adequate concentrations and exposure periods to realize their potential. Development of drug-delivery systems requires simultaneous consideration of several factors, such as drug properties, route of administration, nature of delivery vehicle, mechanism of drug release, ability of targeting, and biocompatibility. The solubilisation of drugs may be advantageous for drug delivery purposes because of increased water solubility of sparingly soluble drug, enhanced permeability across the physiological barrier, or substantial changes in drug distribution. Several strategies were developed for enhancing the drug solubility; among them chemical modification, incorporation in liposome or adding a cosolvent. Chemical modifications or conjugations to polymers can additionally help to increase the chemical stability of the drug.

Quercetin belongs to the chemical class of flavonoids and can be found in many common foods, such as apples, nuts, berries, etc. Natural polyphenols are valuable compounds possessing scavenging properties towards radical oxygen species, and complexing properties towards proteins [1–4]. Unfortunately, these properties are also responsible for a lack in long-term stability, making these natural compounds very sensitive to light and heat. Caused by the poor water solubility and the chemical instability, quercetin is poorly absorbed orally [5]. Quercetin is a typical plant flavonoid that possesses diverse pharmacologic effects including anti-inflammatory, cardio-protective, antioxidant, anti-cancer, antiviral, and anti-anaphylaxis effects and against aging [6–11]. Furthermore, the enrichment of flavonoid in nutrition (functional food) became of interest in past years caused by several positive effects on health [12].

However, the application of quercetin in pharmaceutical field is limited due to its poor solubility, low bioavailability, poor permeability and instability [5,13]. Precise knowledge of solubility is highly desirable. For quercetin, despite the great interest in this flavonoid over the recent year, only a few data dealing with their solubility in water are available. The U.S. National Library of medicine presents a value of $c_q = 60$ mg/kg for the solubility of quercetin in water at $T = 298.15$ K [14]. The experimental investigated data were measured by Weester and Bruins [15], however; the authors measured the solubility of several substances in dichlorethylene and not in water. Lauro et al. [16] indicate the solubility at room temperature to be $c_q = 7.7$ mg/L. The solubility was photometrically detected and the calibration was implemented in water between $c_q = (5–20)$mg/L, which is above the solubility in water itself. Chebil et al. [17] measured by equilibrium experiments a

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value of log (c_q[mol/L]) = −4.52. Razmara et al. [18] estimated experimentally the coefficients of the Apelblat equation describing the temperature dependency of the solubility. Kim et al. [19] measured the water solubility, where a small amount of DMSO is present. All these values lead to a scattered picture about the water solubility of quercetin (Table 1).

The poor solubility can be increased by organic solvents [17,18,20–22], ionic liquids [23], supercritical water [24] or supercritical carbon dioxide in combination with ethanol [25]. One of the best solvents for quercetin is ethanol; however, the stability of quercetin in ethanol [26] and in water at higher temperatures [27] is limited. Fiol et al. [28] figured out that the antioxidant activities of the reaction products compensated the "loss" of the antioxidant activity caused by thermal degradation of the original compounds of the uncooked material. To improve the bioavailability of quercetin, numerous approaches have been undertaken, involving the use of promising drug delivery systems such as encapsulation of different types of β-cyclodextrin [29–45], inclusion complexes [16,19,46–50], chemical modification [51,52], liposomes [53–64], solid dispersions [65,66], microparticles [67–73], nanoparticles [74–87] or micelles [88–109], which appear to provide higher solubility and bioavailability. Enhanced bioavailability of quercetin in the near future is likely to bring this product to the forefront of therapeutic agents for treatment of human disease [110,111].

The aim of this work is to measure the solubility in water again in order to clarify the scattering in the data given in Table 1. Additionally, the stability of quercetin using ethanol as solvent is studied in detail as well as their improvement by the addition of different polymers. The solubilisation capacity as well as the chemical stability of quercetin using two different methods is explored. The first method is the application of hydrogels and the second one is the application of hyperbranched polymers. Both methods are widely used for the design of drug delivery systems [112–117].

2. Experimental section

2.1. Used chemicals

For preparation of solutions, solubilisation of quercetin in water or ethanol and production of PNIPAM-hydrogels and loading of hydrogels, the used chemicals are listed in Table 2.

2.2. Solubility measurements of quercetin

The equilibrium experiments were performed in flask wrapped with aluminum foil in order to prevent quercetin from light. Usually, the measurement of the quercetin concentration in the liquid phase after equalization leads to the saturation concentration. Unfortunately, the quercetin concentration in the liquid phase was below the detection limit of the standard analytical methods, like UV–VIS, FTIR, capillary electrophoresis as well as HPLC. Therefore, an enrichment method was applied. The equilibrated solution was filtrated and 100 ml of total volume was vaporized at p = 10 mbar and at T = 308.15 K, in order to prevent thermal decomposition. The remaining solid phase of quercetin was solved in 10 ml ethanol and the concentration was measured using UV–VIS spectroscopy. The observed spectra of ethanol and quercetin are depicted in Fig. 1. The spectrum of quercetin is quite similar to the spectra found in literature [26]. The adsorption maximum or quercetin at λ = 372 nm is not influenced by the presence of ethanol. Hence, the quercetin concentration can be estimated by photometrical detection (Jena AG, Specord 200) at λ = 372 nm. For quantitative detection of quercetin in ethanol solution, a calibration was prepared (*a.u.* = 52763.6 w_q; R = 0.99952), the calibration curve is plotted in Fig. 2. Due to this step of enrichment one was able to detect these extremely low concentrations. For the solubility of quercetin in ethanol at room temperature the well-known shake flask method was utilized. For all measurements several repetitions were performed.

Table 1
Water solubility of quercetin measured in weight fraction, w_q, of quercetin.

T/K	w_q	Ref.
Room temperature	$7.7 \cdot 10^{-6}$	[16]
323	$9.13 \cdot 10^{-6}$	[17]
323	$1.16 \cdot 10^{-3}$[a]	[18]
298.6	$9.2 \cdot 10^{-4}$	[18]
Room temperature	$1.5 \cdot 10^{-5}$	[19]

[a] Calculated using the given correlation equation.

Table 2
Chemicals used.

Chemicals	M [g/mol]	Purity	CAS-Nr.	Producer
Acetone	58.08	>99.8%	67-64-1	Merck
Ammonium-peroxodisulfate	228.2	Reag. Ph Eur	7727-54-0	Merck
Boltorn H20	1750		326794-48-3	Perstorp
Ethanol	46.07	>99.9%	64-17-5	Merck
n-Isopropyl-acrylamide	113.15	>97%	2210-25-5	Aldrich
n,n'-Methylenbis-acrylamide	154.17	>99.5%	110-26-9	Fluka
Quercetin	302.24	>95%	117-39-5	Aldrich
Sodium disulfite	190.11		7681-57-4	Merck

2.3. Solubilisation of quercetin in water by hyperbranched polymers (Boltorn H20)

Hyperbranched polymers are statistically branched macromolecules, with a tree like structure. The properties of these polymers can be tailored by the architecture, like degree of branching, and the number and kind of terminal groups. Quercetin carries five hydroxyl groups. For this reason, a hyperbranched polymer with hydroxyl terminal groups was selected. One example of this type of hyperbranched polymer is Boltorn H20 with a degree of branching of 2. Aqueous Boltorn H20 solutions show a liquid–liquid demixing [118–120]; therefore only a small amount of Boltorn H20 can be added to water. Several aqueous solutions of hyperbranched polymer in water that differ in the polymer concentration (w_{H20} = 0.00025, w_{H20} = 0.0005, w_{H20} = 0.001, w_{H20} = 0.0015) were prepared. The polymer solution was kept for a short time period at T = 363 K [121] and subsequently cooled down with the help of ice water to T = 298 K. For the solubility measurements of quercetin in these aqueous polymer solutions an excess amount of quercetin was added. After equilibration at constant temperature small samples were taken and the amount of quercetin in solution was detected in the same way as the amount of quercetin in water.

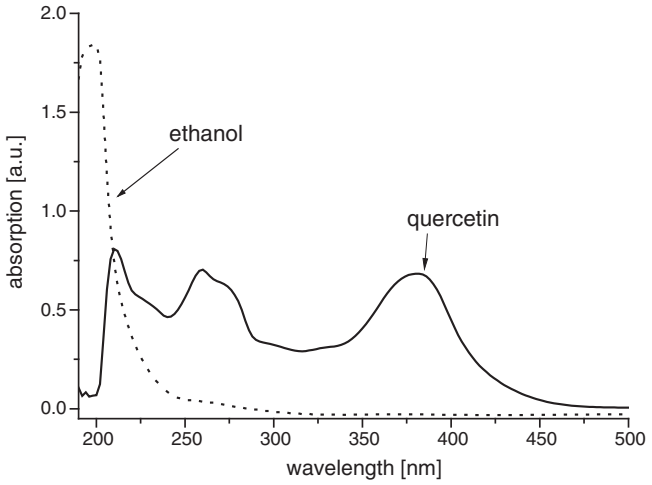

Fig. 1. UV–VIS spectrum of ethanol and quercetin.