Journal of Molecular Liquids 242 (2017) 732–738

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Surfactant solutions for enhancing solubility of new arylquinolin-2-ones

Alla B. Mirgorodskaya [a], Vakhid A. Mamedov [a,b], Lucia Ya. Zakharova [a,b,*], Farida G. Valeeva [a], Vera L. Mamedova [a], Venera R. Galimullina [a], Rushana A. Kushnasarova [b], Oleg G. Sinyashin [a,b]

[a] A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, 8, ul. Arbuzov, 420088 Kazan, Russian Federation
[b] Kazan National Research Technological University, 68, ul. K. Marx, Kazan 420015, Russian Federation

ARTICLE INFO

Article history:
Received 26 May 2017
Received in revised form 13 July 2017
Accepted 15 July 2017
Available online 17 July 2017

Keywords:
Micelle
Microemulsion
Solubilization
Arylquinolin-2-ones

ABSTRACT

Micellar solutions and microemulsions have been used for the increase in the solubility of a series of arylquinolin-2-ones in water. Using spectrophotometry, the solubilization capacity of systems has been characterized with respect to arylquinolin-2-ones. As micelle-forming compounds nonionic amphiphiles are used, whose application is approved in medicinal and pharmacological practice, namely, Tween 80, Pluronic F127, Brij 35, and Tyloxapol. For comparison typical ionic surfactants are explored as well. It has been demonstrated that micellar solutions of Tween 80 can increase the content of test compounds in water up to 20 times, while microemulsions exhibit a higher effect. It has been found out that the solubilization process of arylquinolin-2-ones is accompanied by a remarkable change of their acid-base properties: the value pK_a may increase by 4 units with the transition from the solutions of cationic surfactants to anionic.

1. Introduction

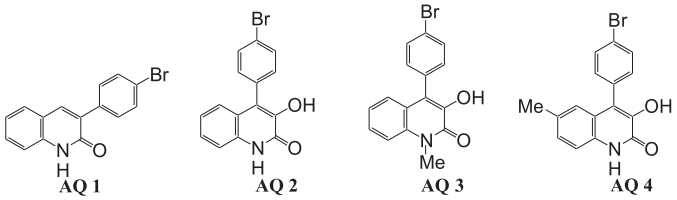
Quinolines are important class of nitrogen-containing heterocycles with a wide range of medicinal properties such as antimalarial, antiasthmatic, antihypertensive, antibacterial, anti-inflammatory, and tyrosine kinase inhibitors [1–6]. In addition to medicinal properties, quinolines are known to undergo hierarchical self-assembly into a variety of nanostructures and mesostructures with improved electronic and photonic function [7–9].

Quinolin-2-ones are omnipresent in naturally occurring and synthetic compounds displaying a broad range of pharmacological activities [10, 11]. For example, this core is present in the antibiotics *nybomycin* and *deoxynybomicin* [12–16], isolated from streptomycete cultures. Strong fluorophoric properties coupled with chemical and thermal robustness of quinolin-2-ones enable them to be used in laser dyes [17], optical probes [18] and as donor chromophores in FRET systems [19].

3-Arylquinolin-2-ones could inhibit the migration of tumor cells with no cytotoxicity in vitro or in vivo [20]. The combination of 3-arylquinolin-2-ones and doxorubicin or etopoiside led to additive in vivo benefits compared with individual administration of the drugs [21]. 3-Arylquinolin-2-ones were also efficient tools in the treatment of osteoporosis [22]. They are selective non-competitive antagonist receptors [23] and could serve as precursors of a new class for nonpeptide gonadotropin releasing hormone receptor antagonists [24].

4-Arylquinolin-2-ones constitute a valuable class of biologically active molecules [25], including an orally active antitumor agent [26]. Naturally occurring viridicatin, viridicatol and 3-*O*-methylviridicatin, compounds containing the 3-hydroxyquinolin-2(1*H*)-one skeleton, which fungal metabolites isolated from *Penicillium* species, have been reported to inhibit the replication of human immunodeficiency virus (HIV) [27]. In addition, a series of 3-hydroxy-4-arylquinolin-2-ones have been found to act as maxi-K channel openers with antibacterial activity [28].

In this work a series of arylquinolin-2-ones (AQ) structurally similar to the known biologically active compounds have been obtained. Formulas of these compounds are given below.



Compounds AQ 2 and AQ 4 are obtained and characterized at the first time, while previously known compound AQ 3 is synthesized through original scheme.

Despite the fact that AQs are of practical importance their investigations and especially biotechnological application are prevented by their scarce water solubility. Therefore this study is devoted to the problem of enhancing of the solubility of AQs in water, which would facilitate

* Corresponding author at: 8, ul. Akad. Arbuzov, Kazan 420088, Russian Federation.
E-mail addresses: luciaz@mail.ru, lucia@iopc.ru (L.Y. Zakharova).

http://dx.doi.org/10.1016/j.molliq.2017.07.055
0167-7322/

their practical use. Importantly, the majority of commercial drugs are hydrophobic compounds and need special formulations to increase their solubility and bioavailability. For this purpose surfactant systems are of particular interest [29–31]. Therefore our recent research activity focuses on the design of novel amphiphiles answering criteria of biotechnologies and estimation of their aggregation and solubilization properties [32–34]. The analysis of recent literature revealed that different types of organized systems based on synthetic and natural amphiphilic compounds are used for the encapsulation of hydrophobic drugs, e.g. single surfactant or polymer micelles [35,36], binary surfactant/cosurfactant or surfactant/polymer systems [37,38], nanoemulsions [39] etc. Typically surfactants play role of building blocks capable of self-assembling with the formation of nanosized aggregates. Due to nonpolar interior such nanoaggregates demonstrate the host activity toward hydrophobic molecules, e.g. water-insoluble drugs and probes, thereby increasing their stability and concentration in aqueous media. In addition, surfactants are successfully used for modifying the morphological and binding/release behavior of formulated drugs [40,41]. Noteworthy, the effectiveness of solubilization is determined by a variety of factors, such as the structure of surfactant and drug molecules, the morphology of aggregates, the presence of additives and solution conditions, e.g. pH, ionic strength, etc.

Based on this information we focus herein on several tasks, with different types of micellar systems (nonionic and ionic) involved, namely: (i) to improve solubility of AQs; (ii) to compare the efficacy of formulations, (iii) to analyze the correlation between surfactant/AQ structures and solubilization capacity; (iv) to optimize the fabrication of nanocontainers for AQs and similar types of biologically active compounds.

2. Methods and materials

2.1. Materials

3-(4-Bromophenyl)quinolin-2(1*H*)-one (AQ 1) was obtained in 95% yield by H_2SO_4-mediated cyclization of 3-(4-bromophenyl)-*N*-phenyloxirane-2-carboxamide, which was, in turn, synthesized in 84% yield under mild conditions Darzens condensation using EtONa (1.2 mol equiv) in EtOH, at 0–5 °C to room temperature for 24 h (Scheme 1) according to the reported method [42].

3-Hydroxy-4-(4-bromophenyl)quinolin-2(1*H*)-one (AQ 2), 3-hydroxy-4-(4-bromophenyl)-1-methylquinolin-2-one (AQ 3) and 3-hydroxy-4-(4-bromophenyl)-6-methylquinolin-2(1*H*)-one (AQ 4) were obtained in moderate yields from 4-bromobenzaldehyde and 2,2-dichloro-*N*-phenylacetamide, 2,2-dichloro-*N*-phenyl-*N*-methylacetamide and 2,2-dichloro-*N*-(4-tolyl)acetamide, respectively, with using *t*-BuOK (1.2 mol equiv) in toluene at −45 °C to room temperature for 24 h, and followed by treatment of the reaction mixture by HCl (gas) completed by the product precipitation (Scheme 2).

Physico-chemical characteristics of AQ 1 have been described previously [42]. Here we present data for compounds AQ 2–4.

AQ 2: yield 57%, white powder, mp 253 °C; IR (Nujol): γ 3307, 1684, 1128, 722 cm^{-1}; ^1H NMR (400 MHz, DMSO d_6): δ 7.08 (dd, $J = 8.1, 8.0$, 2H, H6,7 in quinolone ring system), 7.30 and 7.35 (d and d, $J = 8.0$ and 8.0, 1H and 1H, H5 and H8 in quinolone ring system);7.30 and 7.68 (d and d, $J = 8.4$ and 8.4, 2H and 2H, C_6H_4-Br-p), 12.18 (NH). Anal. Calcd for $C_{15}H_{10}BrNO_2$: C, 56.99; H, 3.19; Br, 25.27; N, 4.43. Found: C, 57.02; H, 3.17; Br, 25.32; N, 4.45.

AQ 3: yield 37%, white powder, mp 252–255 °C (252–254 °C[18]); IR (Nujol): γ 3240, 1627, 1272, 1118, 808, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.91 (c, 3H, NMe), 7.23, 7.37 and 7.42–7.53 (dd, $J = 6.9$, 7.1, d, $J = 7.3$ and m (dd + d), 1H, 1H and 2H, quinolone ring system), 7.33 and 7.69 (d and d, $J = 8.3$ and 8.3, 2H and 2H, C_6H_4-Br-p); Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; Br, 24.20; N, 4.24. Found: C, 58.24; H, 3.62; Br, 24. 29; N, 4.28.

AQ 4: yield 55%, light yellow powder, mp 249–251 °C; IR (Nujol): γ 3315, 1671, 1112, 1011, 799 cm^{-1}; ^1H NMR (400 MHz, DMSO d_6): δ 2.21 (c, 3H, Me), 6.82 (c, 1H, H5 in quinolone ring system), 7.16 and 7.28 (d and d, $J = 7.4$ and 7.4 Hz, 1H and 1H, H7 and H8 in quinolone ring system); 7.29 and 7.70 (d and d, $J = 8.2$ and 8.2 Hz, 2H and 2H, C_6H_4-Br-p); 12.13 (br c, 1H, NH); Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; Br, 24.20; N, 4.24. Found: C, 58.29; H, 3.58; Br, 24.17; N, 4.23.

2.2. Instruments and methods

Commercial specimens of nonionic and ionic surfactants represented by Pluronic F-127 and Tyloxapol (Sigma) with 99% assay were used to prepare solutions without preliminary purification. As a solubilization medium, micellar solutions with the surfactant concentration from 0 to 0.015 M were used, which were obtained using water purified on a Direct-Q 5 UV system. Another type of the systems prepared were microemulsions with the volume fraction of water of 0.74. Microemulsions are typically composed of 9.4 g Tween 80 (or CTAB), 9.4 g butanol, 2.0 g decane and 79.2 g water.

UV–Vis spectra of samples studied were recorded in 1 or 0.10 cm quartz cells using Specord 250 Plus (Analytik Jena) spectrophotometers equipped with a thermosttated cell unit. The extinction coefficient (ε) of a probe was determined from the absorbency (*A*), measured at the wavelength corresponding to the absorption maximum from the relation $\varepsilon = A / (l \times C)$, where *C* is a concentration of the probe, and *l* is the path length. The average values of three to five measurements were used, with the reproducibility being of ±0.05.

The apparent pK_a values ($pK_{a,app}$) of arylquinolinons were calculated on the basis of their absorbency at different pH values according to the Henderson-Hasselbalch equation:

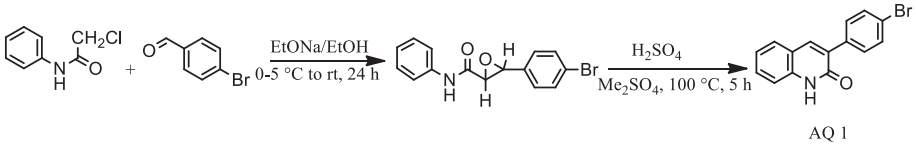
$$pK_{a,app} = pH + \log[\text{neutral form}]/[\text{anionic form}]$$

The acidity was monitored by a pH-meter Hanna 213 with the electrode HI 1330.

The solubilizing capacity of micellar systems toward arylquinolons was determined for its saturated solution as follows. The excess of a crystalline probe was placed in the surfactant solution at neutral pH, stirred vigorously for 2 h and then equilibrated for 48 h at 25 °C. The undissolved probe was filtered, and the filtrate was put to a cuvette, after which absorbency at the maximum in the area 320–340 nm was measured. The error of all experiments was <4%.

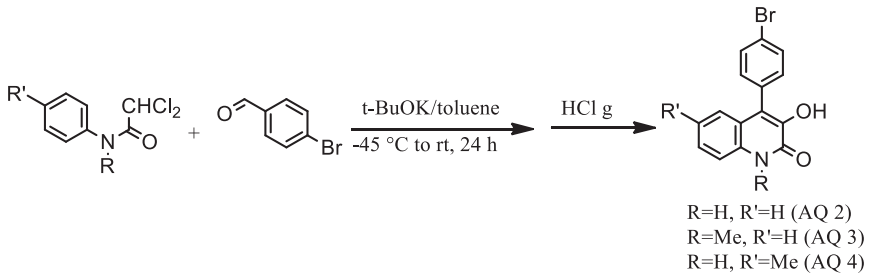
In special experiments an additional 1–2 h ultrasonication at 25 °C (Elmasonic S 15H; the operating frequency of 35 kHz) of the samples was performed. Ultrasonication was carried out in ultrasonic bath (volume of 1.75 L) supplied with function of the thermostat (30 to 80 °C) and the built-in frequency modulation device. The frequency of ultrasonic generator is of 37 kHz.

The size of particles in the supramolecular systems was determined using a Malvern ZetaSizer Nano (Malvern Instruments, UK). 4 MW He-



AQ 1

Scheme 1. Synthesis of 3-(4-bromophenyl)quinolin-2(1*H*)-one AQ 1.



Scheme 2. Synthesis of 3-hydroxy-4-(4-aryl)quinolin-2(1*H*)-ones AQ 2–4.

Ne laser with 633 nm wavelength acted as radiation source. Obtained signal analysis was performed on the basis of frequency and phase analysis of scattered light using software supplied with the device. The measurements were performed at least 5 times in 10 runs, so that ≥50 scans were obtained for each sample.

3. Results and discussion

3.1. Properties of arylquinolin-2-ones in aqueous solutions without surfactant

One of the essential criteria of bioavailability of drug preparation or biologically active substance is its sufficient solubility in aqueous systems. In order to evaluate the content of arylquinolin-2-ones in water, the procedure for its analytical control should be primarily developed. For these purposes we used electronic spectra of arylquinolin-2-ones recorded at various pH (Figs. 1–3, Fig. S1) demonstrating intense absorption in the range of 220–250 nm and the broad band around of 300–370 nm, which is more convenient for the application as analytical signal. Due to the low water solubility of the compounds, their spectra were recorded in the aqueous solution containing up to 20% dimethylformamide. Spectral characteristics of arylquinolin-2-ones (absorption maxima and molecular absorption coefficients), which were used in subsequent analyses of their solubility, are summarized in Table 1.

The spectral behavior of arylquinolin-2-ones is caused by their molecular structure and the ability to participate in acid—base interactions. In the arylquinolin-2-ones studied (except for AQ 3), N-H group is present, which exhibits weak acidic properties. In addition, the molecules of AQ 2, AQ 3 and AQ 4 contain ionizable hydroxy-group. In the case of AQ 1, the spectrum remains unchanged in the broad range up to pH 12 (Fig. 1) and only a slight bathochromic shift occurs in more alkaline media. Probably this compound is present in its neutral form in the above range, while the elimination of hydrogen from amino-group is possible only under rigid conditions (strongly alkaline media). Analogous spectral response to the change of pH is observed for compounds AQ 2, AQ 3 and AQ 4. Spectra remain unchanged in acidic and neutral medium, while in weakly basic solutions the absorption band shifts to the longer wavelength range due to the dissociation of hydroxyl-group (Figs. 2, 3, Fig. S1). It should be noted that the introduction of methyl substituent into the aromatic ring of arylquinolin-2-ones (AQ 4) leads to the slight bathochromic shift of the absorption bands (by 7 nm with respect to AQ 2) both in neutral and alkaline media, with insignificant drop of intensity observed (Fig. 3). Spectra of AQ 3 (Fig. S1) containing methyl fragment at nitrogen atom differ little from spectra of AQ 2.

Based on the spectral data of AQ 2, AQ 3 and AQ 4 at various pH we evaluated pK_a of hydroxyl-group using the Henderson-Hasselbalch equation (Table 1). It should be noted that in the case of AQ 3, which does not contain hydrogen at nitrogen atom, pK_a is higher than that for arylquinolin-2-ones AQ 2 and AQ 4. This may presumably be related to the fact that intramolecular hydrogen bond may be formed in the case of two latter compounds, which stabilizes anionic form and leads to the decrease in pK_a. Based on the pK_a values obtained, we can state that these compounds are in the neutral form under conditions of the solubility measurement carried out at pH 6–7.

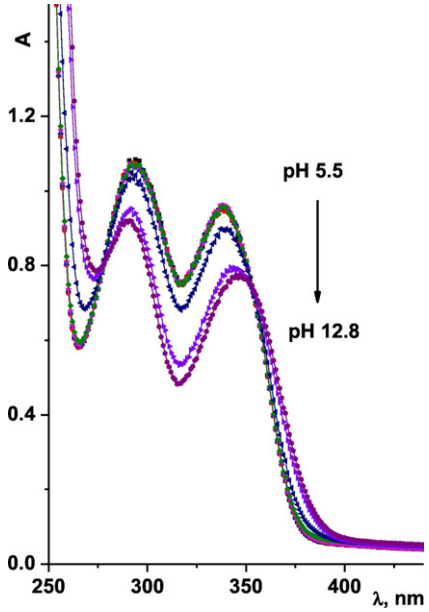


Fig. 1. UV–vis spectra of AQ 1 (0.2 mM) in the water-DMF mixture (20 vol%) at different pH varied as 5.50; 6.80; 8.35; 9.30; 10.45; 12.0; 12.4; 12.8; l = 1 cm.

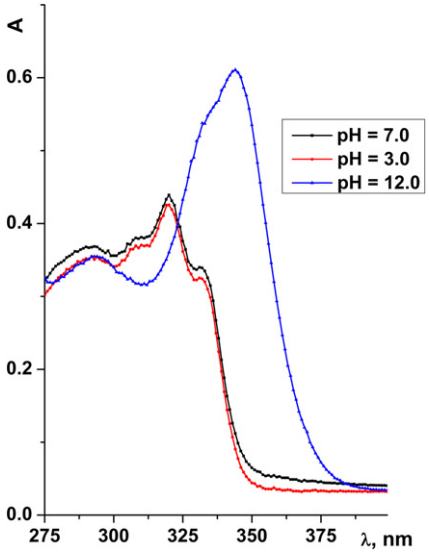


Fig. 2. UV–vis spectra of AQ 2 (0.1 mM) in the water-DMF mixture (20 vol%) at various pH, l = 1 cm.

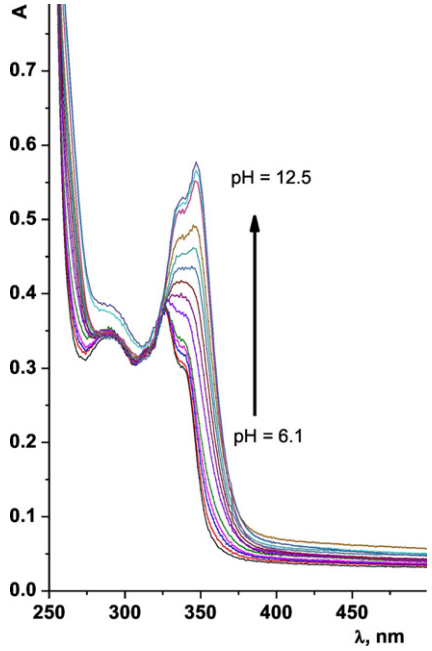


Fig. 3. UV–vis spectra of AQ 4 (0.2 mM) in the water-DMF mixture (20 vol%) at different pH varied as 6.1; 7.3; 7.7; 7.9; 8.2; 8.5; 8.8; 9.0; 9.2; 9.3; 9.5; 9.6; 10.3; 11.0; 12.5; l = 1 cm.

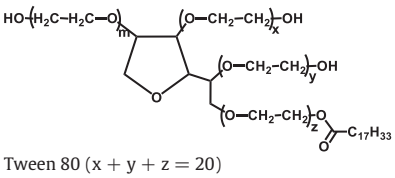
A general approach to the evaluation of the limiting solubility of compounds in water involves the preparation of saturated solutions and subsequent quantitative determination of their concentration. In the case of arylquinolin-2-ones, this concentration was determined spectrophotometrically from the analysis of the absorbency of solutions in the absorption maxima (see Experimental). The values obtained indicate an extremely low solubility of these compounds (Table 1), which can prevent their further application and investigation. Notably, in aqueous solutions at pH > 9, the solubility of arylquinolin-2-ones grows by 2–5 times due to their transition to the anionic form. However, strongly basic solutions do not meet the requirements of biocompatibility and an increase in pH may not be a satisfactory approach to solve the problem of the solubility of these compounds.

3.2. Solubilization of arylquinolin-2-ones in micellar solutions

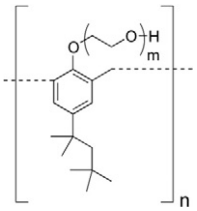
In this study, we focus on the supramolecular strategy for the improvement of water solubility of arylquinolinones, which based on the use of self-assembling surface-active substances. The ability of such systems to solubilize low-polar organic compounds is one of the key features, which determines the application of surfactants for the solution of a variety of fundamental and applied problems in technology, medicine, food and agriculture [43–46]. The solubilization process represents the distribution of low-soluble substances between the disperse phase and dispersion medium, which leads to the growth of the solubility of compounds due to their localization in hydrophobic domains of supramolecular systems, in particular, in nonpolar core of micelles or microemulsions [29,30,47]. In this case, supramolecular systems act as nanocontainers, which can immobilize the target organic compound and provide its controlled release from the aggregate. Based on this phenomenon, a large number of delivery systems for drug and biologically active substances were formed, which provide high therapeutic effect upon the interaction of the loaded nanocontainer with biotargets [31, 45,48]. Effectiveness of solubilization is determined by a series of factors, such as the nature and hydrophilic—lipophilic properties of surfactant, morphology of the formed aggregates, the presence of various additives and pH of the medium, as well as the structure of solubilizate [31,49].

In this work, we tested known amphiphiles as solubilizing agents, namely Tween 80, Brij-35, Pluronic F127, and Tyloxapol, because these compounds are low-toxic and were approved in medical and pharmacological practice [50–54]. The chosen compounds differ in their hydrophilic—lipophilic balance (HLB) and possess low values of critical micelle concentration (cmc), which provides their solubilizing action at micromolar content in aqueous solutions. The employment of cationic surfactants as solubilizers is related to the fact that these compounds display high affinity to the lipid cell components in spite of their marked toxicity (II or III toxicity level). In addition, they are used as carriers upon transdermal delivery of the drug and widely used in ophthalmology [55,56].

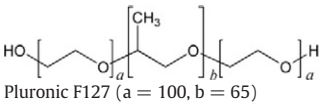
The formulas of the used amphiphilic compounds are given below.



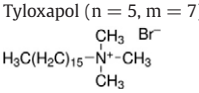
Tween 80 (x + y + z = 20)



Tyloxapol (n = 5, m = 7)



Pluronic F127 (a = 100, b = 65)



Cetyltrimethylammonium bromide (CTAB)

$CH_3(CH_2)_{10}CH_2(OCH_2CH_2)_nOH$
Brij 35 (n = 23)

$CH_3(CH_2)_{10}CH_2(OCH_2CH_2)_nOH$
Sodium dodecylsulfate (SDS)

To evaluate the ability of micellar systems to increase the solubility of hydrophobic substances, limiting content of the test substance at various surfactant concentrations was measured. In the case of arylquinolin-2-ones, their concentration was determined spectrophotometrically from the absorbency of the samples at the absorption maximum. This approach allows us to obtain quantitative characteristics and to compare the solubilization capacity (S) of various micellar systems. The value of S is contributed by the number of molecules of solubilized compound, which are related to the molar concentration of aggregated surfactant and calculated from the equation $S = b / \varepsilon$, where b is the slope of the dependence of absorbency of the solution at the maximum of the absorption of solubilizate on the concentration of surfactant; and ε is the molecular absorption coefficient, which is determined for each arylquinolin-2-one in surfactant solutions. In Fig. 4, the spectra of saturated solutions of AQ 2 recorded at pH 6.5 at various concentration of Tween 80 are exemplified, while in Fig. 5 the change of the absorbency (A) of saturated solution of this arylquinolin-2-ones at various surfactant concentration is given. At the surfactant concentration below cmc, the

Table 1
Spectral characteristics of arylquinolin-2-ones in aqueous solutions.

AQ	pH 3.0		pH 7.0		pH 12.0		pK_a	Solubility in water, μM
	λ, nm	ε, l mol^{-1} cm^{-1}	λ, nm	ε, l mol^{-1} cm^{-1}	λ, nm	ε, l mol^{-1} cm^{-1}		
AQ 1	339	4750	339	4800	340	4400	–	3.5
AQ 2	320	4300	320	4400	346	6100	8.6	6.8
AQ 3	324	1580	325	1550	348	2650	9.7	5.2
AQ 4	327	1900	327	1950	348	2800	8.7	3.8

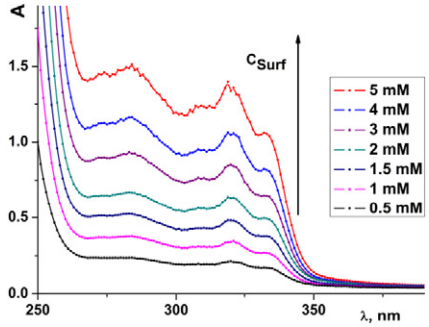


Fig. 4. UV–vis spectra of AQ 2 saturated solutions in the presence of different Tween 80 concentrations (path length is 1 cm, pH 6.5, 25 °C).

solubility of these heterocyclic compounds in aqueous solutions is very low and almost does not change, while a significant increase in their solubility is observed above this threshold. This behavior is a substantial argument toward the principal role of the solubilization of arylquinolin-2-ones by surfactant micelles. Analyzing the values of solubilization capacity (Table 2), it can be seen that the highest effect of nonionic surfactants is observed for arylquinolin-2-one AQ 2 and the solubilizing action grows in the following order: Pluronic F127 > Brij 35 ≅ Tyloxapol > Tween 80.

Solubilizing effect of CTAB toward arylquinolin-2-ones in neutral media is markedly higher compared to nonionic surfactants, which indicates the involvement of electrostatic interactions between micelle and solubilizate. It should be noted that, in the case of the substances involved in acid—base equilibria a selective binding of their neutral or ionic forms with micellar surface can occur. The effect is determined by the micelle charge and is reflected by the change of pK of solubilizates. We demonstrated the effect of surfactant on the example of AQ 2, for which pK_a values was spectrophotometrically determined in surfactant solutions of various natures. The effect of nonionic Tween 80, cationic CTAB, and anionic sodium dodecyl sulfate (SDS) was estimated. The experiment was carried out at the concentration, which exceeds cmc by three times. It was determined that the pK_a value of arylquinolin-2-one AQ 2 in Tween 80 solutions is 8.5, which almost coincides with the value in water. In the case of ionic surfactants, the remarkable effect is observed: pK_a of AQ 2 is 6.2 and 10.4, respectively, in CTAB and SDS solutions. Thus, the transition from cationic surfactants to anionic allows one to change the acid—base equilibrium constant of AQ 2 by four orders.

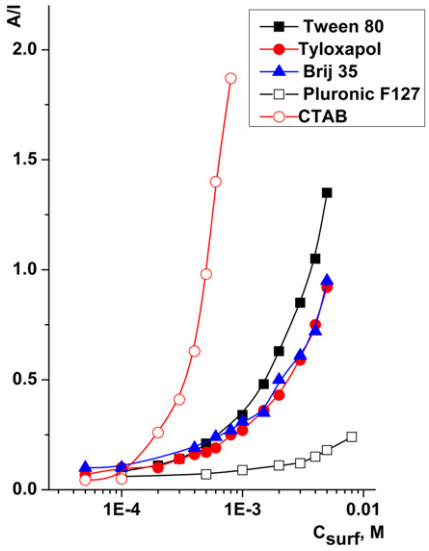


Fig. 5. Absorbency of micellar solutions saturated with AQ 2 as function of surfactant concentration (λ = 320 nm, pH 6.5, 25 °C).

Table 2
Solubilization capacity of micellar systems with respect to arylquinolin-2-ones.

Surfactant	HLB[a]	AQ 1		AQ 2	
		b	*S*	*b*	*S*
Tyloxapol	13	66	0.0137	168	0.036
Tween 80[b]	15	71	0.0148	254	0.055
Brij 35	16.9	61	0.0127	159	0.034
Pluronic F-127	22	24	0.0050	23.1	0.005
CTAB	16.4	112	0.0233	399	0.095

[a] According to the manufacturer data.
[b] For AQ 3 and AQ 4 in Tween 80 solutions, S is 0.041 and 0.031, respectively.

This is important from the viewpoint of of the affinity between arylquinolin-2-ones and micelles, which make it possible to increase the loading of nanocontainers and to control the interaction of solubilizates with biological species.

One of the approaches used to improve the solubility of compounds, is the ultrasonic treatment of the system. As was exemplified by AQ 2, sonication for 1 h leads to the increase in its solubility both in water and micellar solutions by 1.2–1.4 times; additional 1-h treatment provides the increase of its content in the solution by <5% (Fig. 6).

3.3. Solubilization of arylquinolin-2-ones in microemulsions

Another type of supramolecular systems based on nonionic surfactants, which was used to improve the solubility of arylquinolin-2-ones, were microemulsions. Microemulsions are macroscopically homogeneous, thermodynamically stable, self-organizing dispersions with aqueous and hydrocarbon (oil) phases, at the interface of which the molecules of micelle-forming surfactants and cosurfactants (usually low-molecular-weight alcohols) are present [57,58]. Microemulsions differ from their predecessors represented by micellar solutions by slightly larger aggregates, higher concentration of surfactants, and a large volume of the disperse phase. Highly developed interface and large hydrophobic core assigns these systems unique solubilizing features [59,60]. The employment of cationic CTAB gives higher S values, which indicates the involvement of electrostatic interactions between the micelle and micellar surface. In this work, we obtained direct four-component microemulsions based on Tween 80 and *n*-butyl alcohol using decane as oil. Dynamic light scattering showed that in these optically transparent macroheterogeneous systems particles with the hydrodynamic diameter of ~3 nm for CTAB-based microemulsions and 5 nm for those based on Tween 80 (polydispersity index is 0.20–0.35) are observed. The prepared microemulsions were stable; reproducible results were obtained while testing their properties within one month. It was shown that the limiting solubility of arylquinolin-2-ones in the Tween 80-based microemulsion amounts to 0.58 mM in the case of AQ 2 and 0.42 mM in the case of AQ 4, that is higher almost by two orders as compared to water. In the case of microemulsions based on CTAB, even larger growth of the solubility of arylquinolones

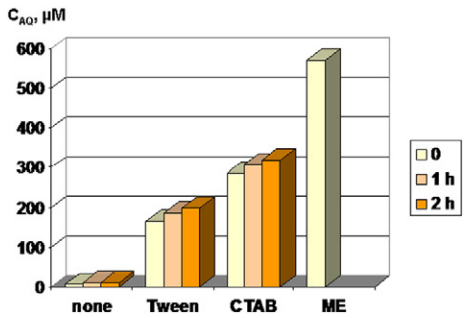


Fig. 6. Maximum concentration of AQ 2 in micellar solutions of surfactants (C_{surf} 3 mM) and microemulsion (ME) as function of ultrasound treatment. The composition of microemulsion is Tween 80–9.43 g, butanol 9.42 g, decane 1.96 g and water 79.2 g.

is observed: maximum available concentration is 0.75 mM. The use of microemulsions as solubilizers for arylquinolin-2-ones with the aim of their application in biosystems requires their further modification and optimization of composition and the decrease in toxicity conjugated with the presence of butanol and decane in the composition. However, upon their in vitro application these limitations are not so important, which reveals wide perspectives for microemulsions as solubilizers of arylquinolin-2-ones and other heterocyclic compounds weakly soluble in water.

4. Conclusions

Thus, supramolecular systems based on surfactants (micellar solutions and microemulsions) have been successfully used for the increase in the solubility of a series of arylquinolin-2-ones in water. Using spectrophotometry, the solubilization capacity of systems based on nonionic micelle-forming compounds has been characterized, whose application is allowed in medicinal and pharmacological practice, namely, Tween 80, Pluronic F127, Brij 35, Tyloxapol, as well as the systems based on ionic surfactants with respect to arylquinolin-2-ones. It has been demonstrated that micellar solutions of Tween 80 can increase the content of test compounds in water up to 20 times. Microemulsions also exhibit a higher effect; however, the existence of a significant amount of butanol as a cosurfactant, restricts their application in pharmacological practice. It has been determined that the solubilization process of arylquinolin-2-ones is accompanied by a remarkable change of their acid—base properties: the value pK_a may increase by 4 units with the transition from the solutions of cationic surfactants to anionic. This is principal from the viewpoint of the affinity between arylquinolin-2-ones and micelles, which make it possible to increase the loading of nanocontainer and to control the interaction of immobilized solubilizates with biological species.

Acknowledgements

This work is supported by the Russian Science Foundation (grant no 14-23-00073).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.molliq.2017.07.055.

References

[1] R.D. Larsen, E.G. Corley, A.O. King, J.D. Carrol, P. Davis, T.R. Verhoeven, P.J. Reider, M. Labelle, J.Y. Gauthier, Y.B. Xiang, R.J. Zamboni, Practical route to a new class of LTD_4 receptor antagonists, J. Org. Chem. 61 (1996) 3398–3405.
[2] Y.L. Chen, K.C. Fang, J.-Y. Sheu, S.L. Hsu, C.C. Tzeng, Synthesis and antibacterial evaluation of certain quinoline derivatives, J. Med. Chem. 44 (2001) 2374–2377.
[3] G. Roma, M.D. Braccio, G. Grossi, F. Mattioli, M. Ghia, 1,8-Naphthyridines IV. 9-Substituted *N*,*N*-dialkyel-5-(alkylamino or cycloalkylamino) [1,2,4]triazolo[4,3-a][1,8]naphthyridine-6-carboxamides, new compounds with anti-aggressive and potent anti-inflammatory activities, Eur. J. Med. Chem. 35 (2000) 1021–1035.
[4] B. Kalluraya, S. Sreenivasa, Synthesis and pharmacological properties of some quinoline derivatives, Farmaco 53 (1998) 399–404.
[5] D. Doube, M. Blouin, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J.P. Falgueyret, R.W. Friesen, M. Girard, Y. Girard, J. Guay, P. Tagari, R.N. Young, Quinolines as potent 5-lipoxygenase inhibitors: synthesis and biological profile of L-746,530, Bioorg. Med. Chem. Lett. 8 (1998) 1255–1260.
[6] B.A. Subba Reddy, A. Venkateswarlu, G. Niranjan Reddy, Y.V. Rami Reddy, Chitosan-SO_3H: an efficient, biodegradable, and recyclable solid acid for the synthesis of quinolone derivatives via Friedlander annulation, Tetrahedron Lett. 54 (2013) 5767–5770.
[7] A.K. Agarwal, S.A. Jenekhe, New conjugated polyanthrazolines containing thiophene moieties in the main chain, Macromolecules 24 (1991) 6806–6808.
[8] X. Zhang, A.S. Shetty, S.A. Jenekhe, Electroluminescence of multicomponent conjugated polymers. 1. Roles of polymer/polymer interfaces in emission enhancement and voltage-tunable multicolor emission in semiconducting polymer/polymer heterojunctions, Macromolecules 33 (2000) 2069–2082.
[9] S.A. Jenekhe, L. Lu, M.M. Alam, New conjugated polymers with donor-acceptor architectures: synthesis and photophysics of carbazole-quinoline copolymers and oligomers exhibiting large intramolecular charge transfer, Macromolecules 34 (2001) 7315–7324.
[10] C.B.M. Poulie, L. Bunch, Heterocycles as nonclassical bioisosteres of α-amino acids, ChemMedChem 8 (2013) 205–215.
[11] S. Heeb, M.P. Fletcher, S.R. Chhabra, S.P. Diggle, P. Williams, M. Camara, Quinolones: from antibiotics to autoinducers FEMS, Microbiol. Rev. 35 (2011) 247–274.
[12] R.M. Forbis, K.L. Rinehart, Nybomycin. VII. Preparative routes to nybomycin and deoxynybomycin, J. Am. Chem. Soc. 95 (1973) 5003–5013.
[13] A.M. Nadzan, K.L. Rinehart, Hydroxynybomycin: isolation, structure and bioactivity, J. Antibiot. 30 (1977) 523–524.
[14] F. Strelitz, H. Flon, I.N. Asheshov, Nybomycin, a new antibiotic with antiphage and antibacterial properties, Proc. Natl. Acad. Sci. U. S. A. (1955) 620–624.
[15] K.L. Rinehart, G. Leadbetter, R.A. Larson, R.M. Forbis, Nybomycin. III. Revised structure, J. Am. Chem. Soc. 92 (1970) 6994–6995.
[16] H. Naganava, T. Wakashiro, A. Yagi, S. Kondo, T. Takita, M. Hamada, K. Maeda, H. Umesawa, Deoxynybomycin from a streptomyces, J. Antibiot. 23 (1970) 365–368.
[17] W.M.F. Fabian, K.S. Niederreiter, G. Uray, W. Stadlbauer, Substituent effects on absorption and fluorescence spectra of carbostyrils, J. Mol. Struct. 477 (1999) 209–220.
[18] M.S. Tremblay, M. Halim, D. Sames, Cocktails of Tb3+ and Eu3+ complexes: a general platform for the design of radiometric optic probes, J. Am. Chem. Soc. 129 (2007) 7570–7577.
[19] L. Clima, W. Bannwarth, Building-block approach for the straightforward incorporation of a new FRET (fluorescence-resonance-energy transfer) system into synthetic DNA, Helv. Chim. Acta 91 (2008) 165–175.
[20] Y. Luo, F. Tao, Y. Liu, B. Li, G. Zhang, Intramolecular amidanion – an efficient synthesis of 3-aryl-2-quinolines, Can. J. Chem. 84 (2006) 1620–1625.
[21] B. Joseph, F. Darro, A. Bard, F. Lesur, C. Collignon, A. Decaestecker, A. Frydman, G. Guillaument, R. Kiss, 3-Aryl-2-quinolone derivatives: synthesis and characterisation of in vitro and in vivo antitumor effects with new emphasis on a new therapeutical target connected with cell migration, J. Med. Chem. 45 (2002) 2543–2555.
[22] M. Croisy, C. Huel, E. Bisagni, Synthesis of 3-(4-methoxyphenyl)-5,7-dimethoxy-(1H)quinolin-2- or 4-ones and derivatives, Heterocycles 45 (1997) 683–690.
[23] P.D. Lesson, R. Baker, R.W. Carling, J.J. Kulagowski, I.M. Mawer, M.P. Ridgill, M. Rowley, J.D. Smith, I. Standsfield, Amino acid bioisosteres: design of 2-quinolone derivatives as glycine-site *N*-methyl-D-aspartate receptor antagonists, Bioorg. Med. Chem. Lett. 3 (1993) 299–304.
[24] J.L. Jiang, R.J. DeVita, M.T. Goulet, M.J. Wyvratt, J.L. Lo, N. Ren, J.B. Yudkovitz, J.S. Cui, Y.T. Yang, K. Cheng, S.P. Rohrer, Synthesis and structure-activity relationship studies of piperidine-substituted quinolones as nonpeptide gonadotropin releasing hormone antagonists, Bioorg. Med. Chem. Lett. 14 (2004) 1795–1798.
[25] Y. Kobayashi, T.A. Harayama, Concise and versatile synthesis of viridicatin alkaloids from cyanoacetanilides, Org. Lett. 11 (2009) 1603–1606.
[26] P.R. Angibaud, M.G. Venet, W. Filliers, R. Broeckx, Y.A. Ligny, P. Muller, V.S. Poncellet, D.W. End, Synthetic routes towards the farnesyl protein transferase inhibitor ZARNESTRA™, Eur. J. Org. Chem. (2004) 479–486.
[27] S.-Y. Sit, N.A. Meanwell, 4-Aryl-3-hydroxyquinolin-2-one derivatives as ion channel modulators, U.S. Patent 5,892,045, 1999.
[28] A. Heguy, P. Cai, P. Meyn, D. Houck, S. Russo, R. Michitsch, C. Pearce, B. Katz, G. Bringmann, D. Feineis, D.L. Taylor, A.S. Tyms, Isolation and characterization of the fungal metabolite 3-*O*-methylviridicatin as an inhibitor of tumour necrosis factor α-induced human immunodeficiency virus replication, Antivir. Chem. Chemother. 9 (1998) 149–155.
[29] A.R. Tehrani-Bagha, K. Holmberg, Solubilization of hydrophobic dyes in surfactant solutions, Materials 6 (2013) 580–608.
[30] R. Thipparaboina, R.B. Chavan, D. Kumar, S. Modugula, N.R. Shastri, Micellar carriers for the delivery of multiple therapeutic agents, Colloids Surf. B. Biointerfaces 135 (2015) 291–308.
[31] L.Ya. Zakharova, R.R. Kashapov, T.N. Pashirova, A.B. Mirgorodskaya, O.G. Sinyashin, Self-assembly strategy for the design of soft nanocontainers with controlled properties, Mendeleev Commun. 26 (2016) 457–468.
[32] G.A. Gaynanova, G.I. Vagapova, F.G. Valeeva, E.A. Vasilieva, I.V. Galkina, L.Ya. Zakharova, O.G. Sinyashin, A novel supramolecular catalytic system based on amphiphilic triphenylphosphonium bromide for the hydrolysis of phosphorus acid esters, Colloids Surf. A Physicochem. Eng. Asp. 489 (2016) 95–102.
[33] D.A. Samarkina, D.R. Gabdrakhmanov, V.E. Semenov, F.G. Valeeva, L.M. Gubaidullina, L.Ya. Zakharova, V.S. Reznik, A.I. Konovalov, Self-assembling catalytic systems based on new amphiphile containing purine fragment, exhibiting substrate specificity in hydrolysis of phosphorus acids esters, Russ. J. Gen. Chem. 86 (2016) 656–660.
[34] A.B. Mirgorodskaya, L.Ya. Zakharova, E.I. Khairutdinova, S.S. Lukashenko, O.G. Sinyashin, Supramolecular systems based on gemini surfactants for enhancing solubility of spectral probes and drugs in aqueous solution, Colloids Surf. A Physicochem. Eng. Asp. 510 (2016) 33–42.
[35] C. Faustino, C. Serafim, I. Ferreira, L. Pinheiro, A. Calado, Solubilization power of an amino acid-based gemini surfactant towards the hydrophobic drug amphotericin B, Colloids Surf. A Physicochem. Eng. Asp. 480 (2015) 426–432.
[36] D. Xia, H. Yu, J. Tao, J. Zeng, Q. Zhu, Ch. Zhu, Y. Gan, Supersaturated polymeric micelles for oral cyclosporine a delivery: the role of Soluplus–sodium dodecyl sulfate complex, Colloids Surf. B. Biointerfaces 141 (2016) 301–310.
[37] A. Kumar, G. Kaur, S.K. Kansal, G.R. Chaudhary, S.K. Mehta, (Cationic + nonionic) mixed surfactant aggregates for solubilisation of curcumin, J. Chem. Thermodyn. 93 (2016) 115–122.
[38] S. Parmar, P. Chavda, P. Bahadur, Pluronic–cationic surfactant mixed micelles: solubilization and release of the drug hydrochlorothiazide, Colloids Surf. A Physicochem. Eng. Asp. 441 (2014) 389–397.
[39] E. Gué, M. Since, S. Ropars, R. Herbinet, L. Le Pluart, A. Malzert-Fréon, Evaluation of the versatile character of a nanoemulsion formulation, Int. J. Pharm. 498 (2016) 49–65.

[40] P. Knöös, S. Onder, L. Pedersen, L. Piculell, S. Ulvenlund, M. Wahlgren, Surfactants modify the release from tablets made of hydrophobically modified poly(acrylic acid), Results Pharma Sci. 3 (2013) 7–14.
[41] P. Knöös, M. Wahlgren, D. Topgaard, S. Ulvenlundand, L. Piculell, Effects of added surfactant on swelling and molecular transport in drug-loaded tablets based on hydrophobically modified poly(acrylic acid), J. Phys. Chem. B 118 (2014) 9757–9767.
[42] V.A. Mamedov, V.L. Mamedova, S.F. Kadyrova, G.Z. Khikmatova, A.T. Gubaidullin, I.Kh. Rizvanov, Sh.K. Latypov, Metal-free intramolecular transannulation of *N*,3-diaryloxirane-2-carboxamides: a concise and versatile route to 3-aryloxirane-2-carboxamides: a concise and versatile route to 3-arylquinolin-2(1*H*)-ones, Tetrahedron 71 (2015) 2670–2679.
[43] G.M. Kontogeorgis, S. Kiil, Introduction to Applied Colloid and Surface Chemistry, 367, J. Wiley & Sons, 2016.
[44] L.L. Schramm, E.N. Stasiuk, D.G. Marangoni, Surfactants and their applications, Annu. Rep. Prog. Chem. Sect. C 99 (2003) 3–48.
[45] C.O. Rangel-Yagui, A. Pessoa Junior, L.C. Tavares, Micellar solubilization of drugs, J. Pharm. Pharm. Sci. 8 (2005) 147–165.
[46] M. Cheng, G. Zeng, D. Huang, Ch. Yang, C. Lai, Ch. Zhang, Ya. Liu, Advantages and challenges of Tween 80 surfactant-enhanced technologies for the remediation of soils contaminated with hydrophobic organic compounds, Chem. Eng. J. 314 (2017) 98–113.
[47] A.S. Narang, D. Delmarre, D. Gao, Stable drug encapsulation in micelles and microemulsions, Int. J. Pharm. 345 (2007) 9–25.
[48] D.J. McClements, Encapsulation, protection, and release of hydrophilic active components: potential and limitations of colloidal delivery systems, Adv. Colloid Interf. Sci. 219 (2015) 27–53.
[49] K.L. Mittal, in: K.L. Mittal (Ed.), Micellization, Solubilization, and Microemulsions, vols. 1 and 2, Plenum, New York 1977, p. 487 (945 pp).
[50] R. Sharma, D. Nandni, R.K. Mahajan, Interfacial and micellar properties of mixed systems of tricyclic antidepressant drugs with polyoxyethylene alkyl ether surfactants, Colloids Surf. A Physicochem. Eng. Asp. 451 (2014) 107–116.
[51] S.K. Mehta, N. Jindal, Mixed micelles of lecithin–tyloxapol as pharmaceutical nanocarriers for anti-tubercular drug delivery, Colloids Surf. B. Biointerfaces 110 (2013) 419–425.
[52] D.A. Chiappetta, A. Sosnik, Poly(ethylene oxide)-poly(propylene oxide) block copolymer micelles as drug delivery agents: improved hydrosolubility, stability and bioavailability of drugs, Eur. J. Pharm. Biopharm. 66 (2007) 303–317.
[53] F. Shakeel, N. Haq, F.K. Alanazi, I.A. Alsarra, Solubility and thermodynamics of tenoxicam in (PEG-400 + water) binary solvent systems at different temperatures, J. Mol. Liq. 213 (2016) 221–227.
[54] J. Shokri, A. Nokhodchi, A. Dashbolaghi, D. Hassan-Zadeh, T. Ghafourian, M.B. Jalali, The effect of surfactants on the skin penetration of diazepam, Int. J. Pharm. 228 (2001) 99–107.
[55] S. Klang, M. Abdulrazik, S. Benita, Influence of emulsion droplet surface charge on indomethacin ocular tissue distribution, Pharm. Dev. Technol. 5 (2000) 521–532.
[56] Ph. Daull, F. Lallemand, J.S. Garrigue, Benefits of cetalkonium chloride cationic oil-in-water nanoemulsions for topical ophthalmic drug delivery, J. Pharm. Pharmacol. 66 (2014) 531–541.
[57] S.E. Friberg, P. Bothorel, Microemulsions: Structure and Dynamics, 320, CRC Press, Boca Raton, 1987.
[58] D.P. Acharya, P.G. Hartley, Progress in microemulsion characterization, Curr. Opin. Colloid Interface Sci. 17 (2012) 274–280.
[59] S.P. Moulik, A.K. Rakshit, Physicochemisty and applications of microemulsions, J. Surf. Sci. Technol. 22 (2006) 159–186.
[60] M. Fanun, Microemulsions as delivery systems, Curr. Opin. Colloid Interface Sci. 17 (2012) 306–313.