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Self-assembly strategy for the design of soft nanocontainers with controlled properties

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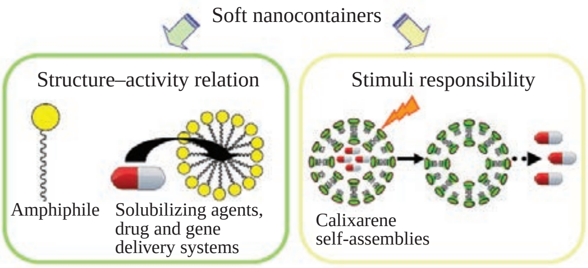
Organized systems based on amphiphiles are discussed from the viewpoint of their application as solubilizing agents and drug and gene delivery systems with structure–activity relationships and stimuli responsibility emphasized. Special attention is paid to cationic surfactants, including gemini and naturally originated compounds. Practically important lipid formulations, *i.e.*, liposomes and solid lipid nanoparticles, are discussed in terms of their stability, loading capacity, surface modification and therapeutic efficacy. The stimuli responsibility of formulations is analyzed and exemplified by smart supramolecular systems based on a calixarene platform.



Recent research activity in organic chemistry is mainly directed towards the synthesis of drug molecules. Meanwhile, many problems should be solved before these potential drugs can reach clinical practice. To succeed in this way, it is necessary (i) to increase the water solubility of hydrophobic medicines, (ii) to protect them from biodegradation, (iii) to improve their bioavailability and biocompatibility, (iv) to provide conditions for targeted delivery and (v) to minimize toxicity and side effects. To solve these problems, nanocontainers are developed based on amphiphilic compounds.[1–3] So-called lipid formulations (micelles,

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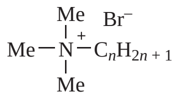
microemulsions, vesicles, liposomes and lipid nanoparticles) make it possible to incorporate active components inside nanoaggregates (nanocontainers), thereby isolating them from a bulk medium and generating a specific microenvironment. This may result in an increase in the solubility, concentrating and stabilization effects, improvement in bioavailability, *etc*. While a wide number of lipid formulations have been worked out, only few of them were approved for medical application. Therefore, the design and synthesis of novel amphiphiles answering biotechnological criteria remain a challenging task.[1–5] These criteria emphasize high efficacy (high therapeutic effect and loading capacity), patient friendly approach (low toxicity, noninvasive administration route), suitable size characteristics and colloidal and biological stability.

This review is focused on the problems conjugated with different features of soft colloidal carriers responsible for their functionality, including the design of amphiphiles fitting the above criteria and study of their self-assembly. Special attention is paid to the functional activity, exemplified by the solubilization capacity of amphiphilic systems toward hydrophobic probes and drugs and their ability to DNA condensation. Formulations based on synthetic amphiphiles are exemplified by our recent publications reflecting main trends in this field, which are supplemented with literature data on drug delivery systems based on natural lipids. Different formulations and profit/limitation analysis are compared. The final part of the review is focused on calixarene-based systems. A calixarene platform provides many advantages in the biotechnological applications of supramolecular systems, such as low toxicity, multi-centred binding mechanism involving the macrocyclic cavity, molecular recognition of guests, versatile morphological behaviours, *etc*.

Synthetic amphiphile based strategies

Factors determining structural behaviour. The nature of amphiphilic molecules plays an essential role in their biotechnological applications. In recent years, much attention has been paid to cationic amphiphiles due to their high affinity to negatively charged nucleotide units of DNA, cell membranes, *etc*.[2] In our work, homological series of cationic surfactants are designed. Their aggregation properties are reported to be strongly determined by the nature of head group and alkyl chain length.[2,4,6–14] One of the key properties of surfactants from the viewpoint of their functionality is a critical micelle concentration (CMC).[15–38] As documented, amphiphilic compounds with a positively charged nitrogen atom demonstrated very similar aggregation ability with CMC values mainly depending on their hydrophobicity (Table 1).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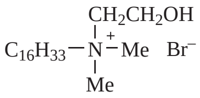
TMA-16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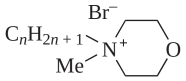
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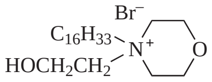
MP-*n*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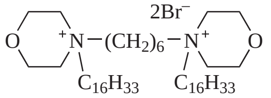
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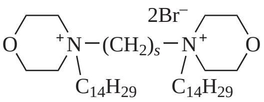
MP 16–6–16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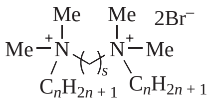
MP 14–*s*–14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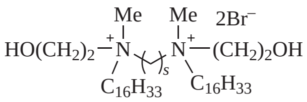
m–*s*–*m*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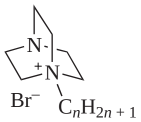
16–*s*–16(OH)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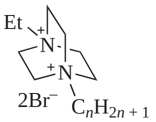
DABCO-*n*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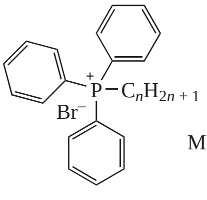
DQD-*n*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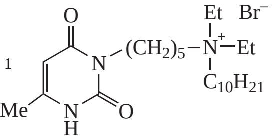
TPPB-*n*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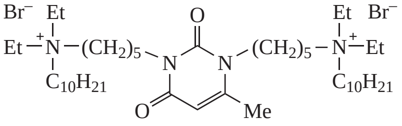
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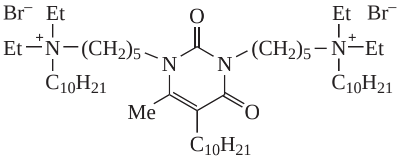
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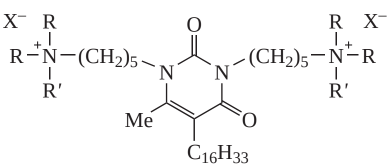
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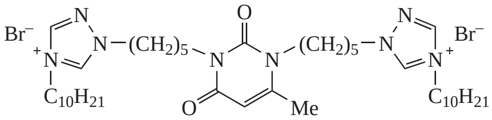
APB: X = Br, R = R′ = Et
APT: X = OTs, R = Et, R′ = Me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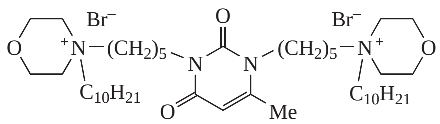
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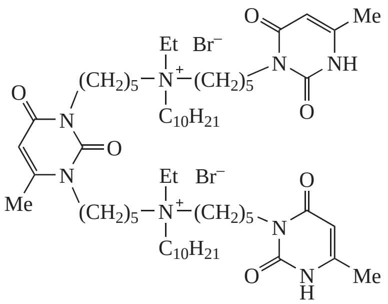
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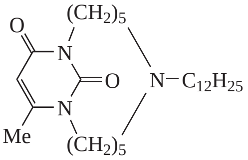
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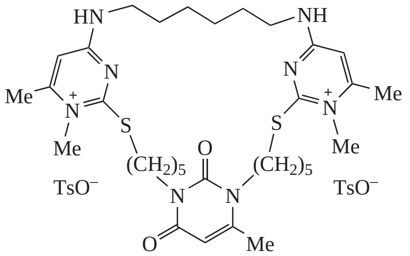
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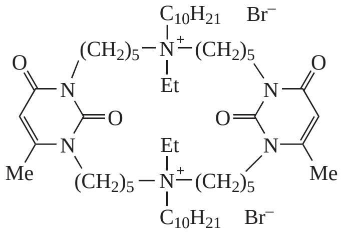
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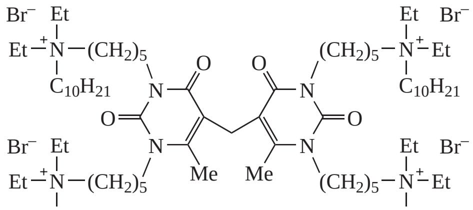

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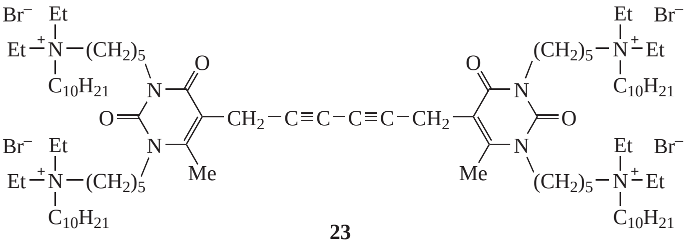

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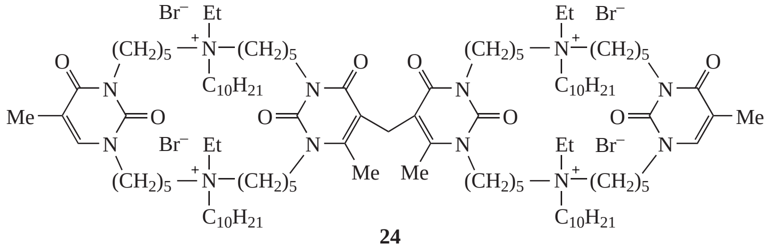

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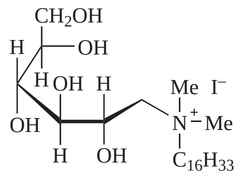
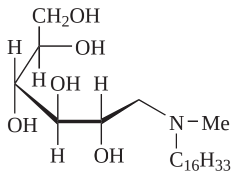


26
GM-16



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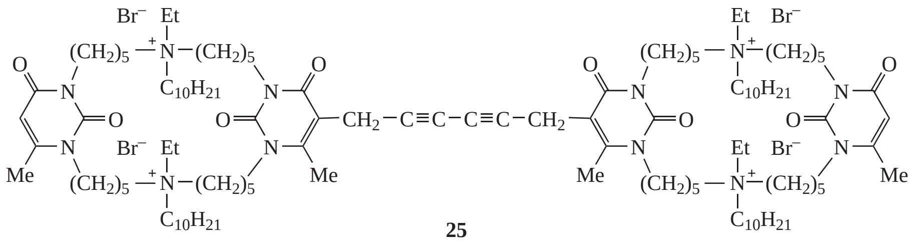
GAM-16



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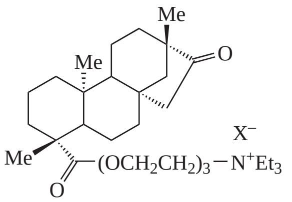


28

At the same time, transition to a triphenylphosphonium bromide (TPPB) series resulted in a marked decrease in CMCs,[7,8] with the slope of ln CMC *vs.* n being unchanged (about 0.3) (here, n is the number of carbon atoms in the alkyl tail).

Many advantages may be provided by the use of amphiphiles with natural fragments, *e.g.*, amino acid, nucleotide base, sugar and terpene.[39,40] The occurrence of such residues may increase the affinity of artificial amphiphiles toward biological species and improve the biocompatibility of systems. Our work is focused on the design and self-organization of amphiphiles bearing these moieties, positively charged pyrimidinic compounds being investigated in detail. In these studies, the structure of pyrimidinic amphiphiles has been systematically varied from acyclic to macrocyclic scaffolds, from monocationic to multicharged compounds and from single-tailed monomeric surfactants to oligomeric amphiphiles with several alkyl tails.[8,27–38,41,42] Systematic investigations aimed at the uniform task provide obvious advantages of the systems developed. In particular, they can be optimized based on structure–activity correlations. Importantly, the nanocontainer properties can be tuned due to differentiated factors controlling the self-organization, morphological behaviour and functional activity. Among key factors, the number of charge centres, a macrocyclic *vs.* open-chain structure effect, the size of a macrocyclic cavity, the occurrence of mobile protons capable of H-bonding and the rigidity of molecules should be mentioned. The manipulation by these factors makes it possible to tailor the structural behaviour of pyrimidinic amphiphiles, solution pH, reactivity and complexation with nucleic acids in a wide range. This can be exemplified by the concentration-dependent gel-like behaviour of sulfide bridged pyrimidinophane **20**[34] and the fabrication of nontoxic pH-responsive nanocontainers for hydrophobic guests (**19**).[33]

Unlike known systems, pyrimidinic amphiphiles exhibit an unusual micellar rate effect toward the degradation of organophosphorus ecotoxicants, acetylcholinesterase inhibitors, differing from that of typical cationic surfactants. Thus, they accelerate the basic hydrolysis of highly hydrophobic phosphonates, while retard or show zero effect on the nucleophilic cleavage of less hydrophobic esters.[8,30,41,42] Probably, one of the reasons for this phenomenon is the fact that the solutions of pyrimidinic amphiphiles undergo acidification with an increase in their concentration.[29–31] A similar effect has been revealed in TPPB series,[4] which can be explained by the ionization and partial dissociation of water molecules in the solvate shells of sterically hindered charged groups.

Another novel family of amphiphiles based on natural compounds affiliates amphiphiles bearing diterpenoid fragments (**28**).[10,43] It was demonstrated that two cationic diterpenoid compounds with the same surface active ion and different counterions (bromide and tosylate) dramatically differ in their morphological behaviours and functional activity, although self-assemble within similar concentration ranges (see Table 1).[10,43]

From the viewpoint of green chemistry, very attractive amphiphilic compounds are gemini surfactants composed of two head group/tail pairs connected with spacer groups of different nature. Typical *m*–*s*–*m* gemini with ammonium charged groups and a polymethylene spacer (here, m is the number of carbon atoms in alkyl tails and s is the number of carbon atoms in a spacer fragment) are rather well studied.[44–48] Unlike single-tailed surfactants, gemini can form aggregates in a micromolar concentration range, more considerably decrease surface tension at the interfaces, demonstrate enhancing solubilization properties, *etc*., which provides many profits upon their involvement in biotechnological applications. Due to their practical importance, gemini attract much fundamental research interest, including the thermodynamics of micellization, morphology behaviour, estimation of aggregation number, counter-ion association degree, *etc*.,[44–46] which makes it possible to reveal the structure–activity correlation and to give recommendations for the design of novel amphiphiles.

Unlike a conventional single-head surfactant, an additional factor is responsible for the structural behaviour of gemini. The structure of a spacer fragment markedly influences aggregation properties, including CMC values, the morphology of aggregates and their surface characteristics. In contrast to the effect of alkyl chain length, the influence of a spacer fragment is less unambiguous, *e.g.*, aggregation characteristics often show nonmonotonic dependences on the spacer length. For example, this is

Table 1 CMC and solubilization powers (S) of cationic surfactants.

Compound		CMC/ mmol dm^{-3}	S/mole of dye per mole of surfactant[a]
1	TMA-16	0.97[4]	0.033 (alanine-substituted calix[4]arene)[15] 0.082 (valine-substituted calix[4]arene)[15] 0.3 (BBI)[16] 0.015 (Orange OT)[17] 0.0159 (Orange OT)[4]
2	TMA-16(OH)	0.65[18]	0.035 (alanine-substituted calix[4]arene)[15] 0.049 (valine-substituted calix[4]arene)[15]
3	MP-10	20[19]	
	MP-12	9.6[19]	
	MP-14	4.0[19]	
	MP-16	1.0[17,19]	0.042 (Orange OT)[20] 0.099 (indomethacin)[6]
	MP-18	0.33[19]	
4	MP-16(OH)	1.0[18]	
5	MP 16–6–16	0.02[20]	0.06 (Orange OT)[20]
6	MP 14–4–14	2.2	0.492 (indomethacin)[6] 0.044 (thymolphthalein)[6]
	MP 14–6–14	2.3	0.497 (indomethacin)[6] 0.070 (thymolphthalein)[6]
	MP 14–8–14	1.6	0.423 (indomethacin)[6] 0.036 (thymolphthalein)[6]
	MP 14–10–14	2.7	0.414 (indomethacin)[6] 0.019 (thymolphthalein)[6]
7	12–2–12	0.8[21]	0.017 (Orange OT)[21]
	12–4–12	1.2[21]	0.0196 (Orange OT)[21]
	12–6–12	1.25[24] 1.0[21]	0.017 (Orange OT)[21]
	14–2–14	0.11[17]	0.394 (indomethacin)[22] 0.0084 (thymolphthalein)[23]
	14–3–14	0.11[22]	0.394 (indomethacin)[22] 0.019 (thymolphthalein)[23]
	14–4–14	0.14[17]	0.295 (indomethacin)[22] 0.031 (thymolphthalein)[23]
	14–6–14	0.22[17]	0.32 (indomethacin)[22] 0.042 (thymolphthalein)[23]
	16–6–16		0.67 (indomethacin)[22]
8	16–6–16(OH)	0.0045[25]	0.742 (indomethacin)[22] 0.043 (Orange OT)[b]
	16–4–16(OH)	0.0014[25]	0.075 (Orange OT)[b]
	16–12–16(OH)	0.008[25]	0.029 (Orange OT)[b]
9	DABCO-12	11[26]	
	DABCO-14	4.0[26]	
	DABCO-16	1.0[26]	0.0340 (Orange OT)[7]
	DABCO-18	0.12[26]	
10	DQD-12	26.5[12]	0.00658 (Orange OT)[12]
	DQD-14	10.3[12]	0.013 (Orange OT)[12]
	DQD-16	3.0[12]	0.020 (Orange OT)[12]
	DQD-18	0.80[12]	
11	TPPB-8	32[4]	0.00092 (Orange OT)[4]
	TPPB-10	6.1[4]	0.0093 (Orange OT)[4]
	TPPB-12	2.0[4]	0.0134 (Orange OT)[4] 0.0295 (Sudan I)[13]
	TPPB-14	0.33[4]	0.020 (Orange OT)[4] 0.0431 (Sudan I)[13]
	TPPB-16	0.1[4]	0.0277 (Orange OT)[4] 0.0544 (Sudan I)[13]
	TPPB-18	0.018[4]	
12		2.0; 10.0[27]	
13		3.0[28]	
14		0.045[27]	
15	APB APT	0.4[29] 0.1[29]	
16		3.0[30]	0.0016 (Orange OT)[30]
17		3.4[31]	0.0014 (Orange OT)[31]
18		0.1; 2.0[32]	
19		5.0 (pH < 4)[33]	
20		1.7; 10[34]	
21		0.85[35]	
22		0.87[36]	
23		0.72[36]	
24		1.0[36–38]	
25		1.3[36]	
26	GM-16	0.7[11]	0.0237 (Orange OT)[11]
27	GAM-16	0.1 (pH ⩽ 4.0)	0.023 (Orange OT; pH ⩽ 3.0) 0.014 (Ind-1; pH ⩽ 3.0)
28	X = Br X = OTs	10.2[10] 8.4[10]	0.0047 (Orange OT)[10] 0.0058 (Orange OT)[10]

[a] The guest is indicated in parentheses. [b] Unpublished results.

observed in the case of the CMC of *m*–*s*–*m* series, demonstrating the maximum values of s = 4–6. Aggregation numbers are reported to be lower than those in monocationic analogues, and they increase with the spacer length.[45] Interestingly, a rather good agreement was observed for the data obtained by different techniques, *e.g.*, for a 2 mM solution of 12–2–12, the aggregation numbers of 42[21] and 48[49] were obtained by dye solubilization and SANS methods, respectively.

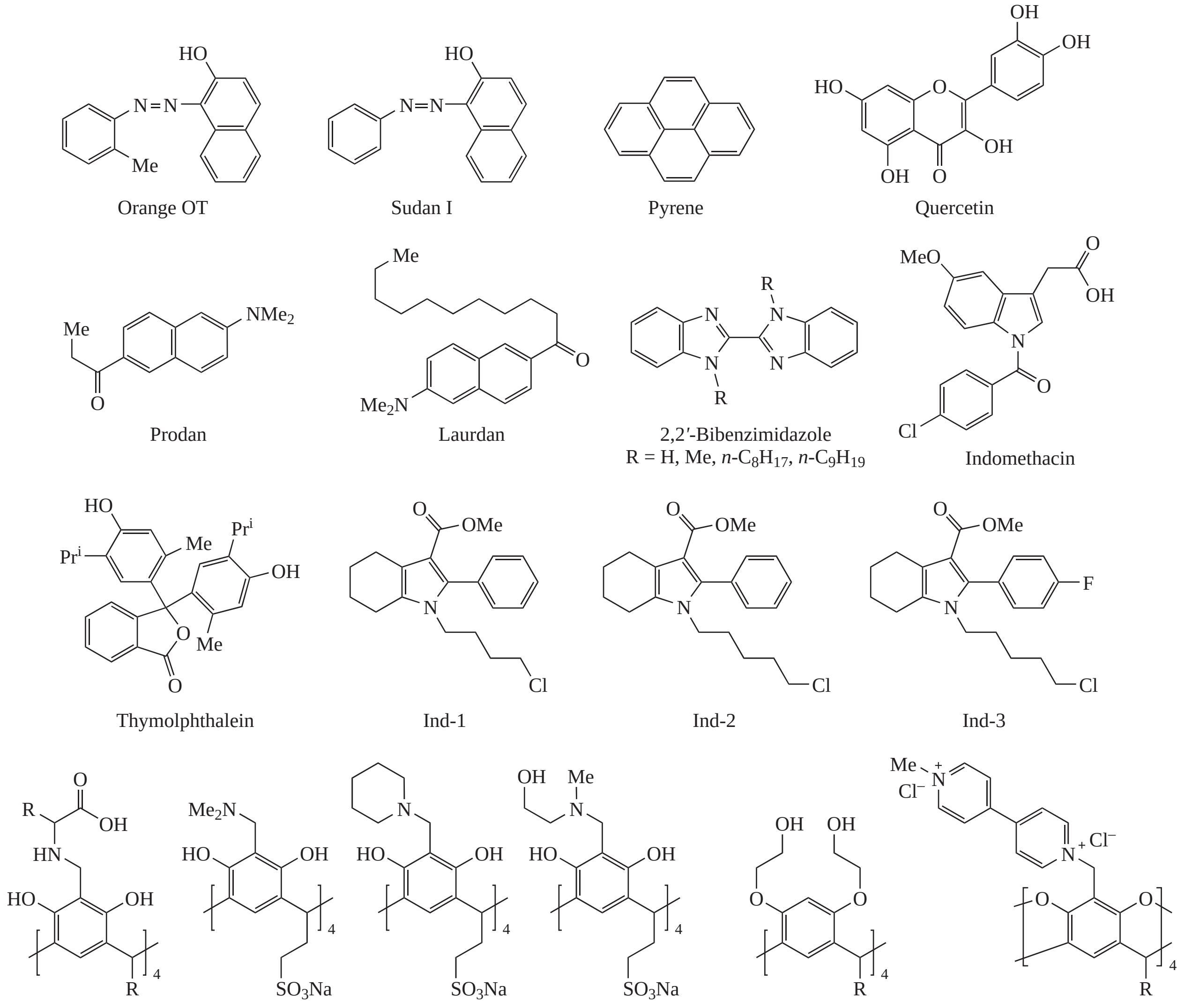
The rigidity of a spacer is a very essential factor influencing both CMC and the morphology of aggregates. The role of the spacer was considered in detail,[45] with the effect of spacer length prevailing over the flexibility/rigidity factor. Much attention is paid to gemini surfactants containing natural fragments in the spacer, which can be exemplified by amino acid derivatives[40,47] susceptible to structural transitions.

The structure of head groups is a factor affecting the aggregation behaviour of gemini, which is exemplified in the recent literature by studies of different surfactants with heterocyclic polar groups or functionalized ammonium analogues.[48,50] In our work, the nature and number of cationic groups are systematically varied, including conventional ammonium analogues with hydroxyethyl substituents,[25,51] heterocyclic polar groups with morpholine,[6,20] uracile,[31,32,52] purine[38,42] triazole[30] or diazobicyclooctane containing residues (DABCO derivatives).[12,53,54] The marked advantages of these series of amphiphiles include the occurrence of functional groups capable of H-bonding, which enriches interactions between species and provides additional tools for the control of solution behaviour. Moreover, unlike conventional surfactants, cyclic or bicyclic polar groups promote diverse morphological behaviours, thereby facilitating a smart character of nanocontainers. The series of DABCO-based surfactants (**9**, **10**) include mono- and dicationic surfactants of two types, namely, single- and double-tailed analogues, thereby allowing one to compare the role of numbers of charged groups and tails. Along with direct micelles formed in aqueous media, reverse micelles occurring in nonpolar solvents have been documented.[53] Contrary to typical gemini (two-tailed two-head surfactants), dicationic DABCO derivatives with a single long tail (**10**) demonstrate higher CMC compared to their monocationic analogues,[12] strongly emphasizing the role of the hydrophobicity factor.

Importantly, due to their versatile morphological behaviours, geminis demonstrate stimuli responsive properties, showing sphere-to-rod or micelle-to-vesicle transitions,[45,55] which allow us to recommend them as soft and smart nanotechnological materials.

Solubilization of hydrophobic probes and drugs. Solubilization ability is one of the key properties of surfactant aggregates, which arises from the microheterogeneous nature of micellar solutions. The amphiphilic structure of surfactant molecules provides the occurrence of a gradient of polarity in direct micelles, which are composed of nonpolar interior formed by hydrophobic tails and polar periphery region formed by head groups. For this reason, direct micelles existing in aqueous solution can incorporate hydrophobic compounds and function as nanocontainers to improve their water solubility. We studied the solubilization capacity of surfactant nanocontainers toward spectral probes, drugs and insoluble compounds used as modifiers for the nanocontainer properties, *e.g.*, calixarenes (Figure 1).

Before the preparation of a formulated drug, the properties of nanocontainers should be characterized. Useful information can be provided by the exploration of spectral probes, including the location site of hydrophobic molecules and microenvironmental characteristics (polarity, viscosity, charge, *etc*.). This is based on changes suffered by probe molecules in micelles, such as pK_a shifts and solvatochromic effects. This can be exemplified by the indicator thymolphthalein, for which a decrease in pK_a is observed in dicationic surfactant solutions reflected in the shift in colour change pH range.[23] Important micelle characteristics such as surface potential were determined[4] for a series of cationic surfactants with phosphonium and ammonium head groups with the use of *p*-nitrophenol (PNP) as a spectral probe suffering the decrease in pK_a value in cationic micelles. The phenomenon of solvatochromism is successfully employed for the evaluation of changing the microenvironmental properties of mixed micelles based on cationic gemini 14–*s*–14 and typical cationic surfactant cetyltrimethylammonium bromide (CTAB) with the use of methyl orange, Reichart's betain, and PNP spectral probes.[17] For these systems, a negative deviation from ideal mixed behaviour is demonstrated, and nanocontainer facilities are testified by hydrophobic dye incorporation. The surface potential and micropolarity are reported to decrease smoothly with the transfer from single CTAB micelles to their mixture with gemini.[17] Important information can be obtained by the use of fluorescent probes such as pyrene, laurdan and prodan (Figure 1). These techniques make it possible



Orange OT

Sudan I

Pyrene

Quercetin

Prodan

Laurdan

2,2′-Bibenzimidazole
R = H, Me, n-C_8H_{17}, n-C_9H_{19}

Indomethacin

Thymolphthalein

Ind-1

Ind-2

Ind-3

Amino acid-substituted calix[4]resorcine

Amino-substituted sulfonated calix[4]resorcine

Oxyethylated calix[4]resorcine
R = Et, n-C_5H_{11}, n-C_7H_{15}, n-C_8H_{17}, n-C_9H_{19}, n-$C_{11}H_{23}$

Viologen-substituted calix[4]resorcine

Figure 1 Structural formulae of compounds used as spectral probes, drugs and macrocyclic building blocks.

to characterize the micropolarity in location site, to calculate the number of aggregation and to quantify critical concentrations corresponding to the aggregation threshold and morphological transitions. We focus on these studies since the use of the same spectral probes allows us to compare the solution behaviours of homologues within a series of surfactants and different amphiphiles against each other, which provides the basis for the structure–activity correlation including the effectiveness of surfactant nanocontainers. Thus, an increase in solubilization capacity toward hydrophobic probes occurs with the transition from lower to higher homologues within the series of phosphonium and ammonium surfactants and dicationic DABCO derivatives.[4,12] The comparison of various homological series, *i.e.* well known trimethylammonium (TMAB-*n*), with TPPB-*n*, morpholinium (MP-*n*) and DABCO-*n* reveals that solubilization capacity of aggregates toward Orange OT increases in the order TMAB-*n* < < TPPB-*n* < DABCO-*n* ≈ MP-*n*,[4,7,20] thereby strongly emphasizing the role of head groups. High solubilization efficacy of morpholinium surfactants probably indicates that the presence of ether groups stimulates the solubilization. Similar effect of improving the binding capacity of surfactant aggregates toward organic guests including drugs, dyes and reagents is documented for hydroxyethylated cationic surfactants.[18,19] In these cases, additional contribution of hydrogen bonding is probably observed, resulting in both host and guest stabilization.

The solubilization capacity of nanocontainers depends on the structures of both a surfactant and a drug. This can be exemplified by the studies of biologically active heterocyclic compounds, including newly synthesized substances and commercial drugs (Figure 1), for which a tenfold increase in water solubility is achieved with the help of micellar systems. For the antiviral and antitumor drug bibenzimidazole (BBI), typical nonionic (Tween 80) and ionic (CTAB, sodium dodecyl sulfate, SDS) surfactants are explored as the enhancers of water solubility.[16] The solubilization capacity of the systems increases in the order SDS < CTAB < Tween 80. The highest extinction coefficient is observed for SDS micelles, which is of practical importance for improving the analytical technique of BBI detection.

Nanocontainers for the anti-inflammatory drug indomethacin were developed[21] based on different surfactants. In general, low-toxic nonionic surfactants have the advantage of ionic analogues; however, superior activity and low CMC of dicationic gemini surfactants can give them priority over a nonionic amphiphile. Solubilization of indomethacin is reported to increase in the order Tween 80 < 16–6–16 < 16–6–16(OH). Gemini with shorter tails (14–*s*–14 family) demonstrated lower solubilization capacity with only a slight effect of the spacer length.[21] Effective solubilization action toward indomethacin is demonstrated by morpholinium surfactants, with the activity increasing in the case of gemini.[6] Additional factors contributing to the binding of the drug are the pK_a shift of carboxylic group of indomethacin and electrostatic and hydrogen bond interactions between host and guest molecules. Importantly, nanocontainers undergo a load-induced structural modification, including size characteristics and polydispersity, *i.e.*, mutual influence occurs between the nanocontainer components and the load.

It is of practical importance that marked substrate specificity occurs in some cases, which is obvious from the solubilization data of TPPB series toward Orange OT and Sudan I dyes. For the latter, twofold higher *S* values are observed despite the fact that the structures of probes differ only slightly (Figure 1). An analogous result was obtained for DABCO-16 nanocontainers in regard to these probes.

In the case of gemini supplementary factor influencing the solubilization capacity is the structure of spacer fragment. It is possible to compare the effects of polymethylene spacer length for different gemini families and different loads. For the 12–*s*–12 series (*s* = 2–6), the solubilization power toward Orange OT little changes,[22] while that toward indicator thymolphthalein increases.[23] Non-monotonous changes in the solubilization effect occur within the same homological series toward the drug indomethacin,[22] as well as in the series 16–*s*–16(OH) (*s* = 4–12) in regard to Orange OT. For the gemini series MP 14–*s*–14 solubilization of indomethacin smoothly decreased, when *s* changed from 4 to 10, while the solubilization of thymolphthalein decreased nonmonotonically.[6]

Despite the fact that the solubility of drugs in nanocontainers markedly increases (by orders of magnitude) compared to free drugs, absolute values of the concentration of solubilized drugs achieved are insufficient. Therefore, additional efforts are needed to improve the situation. One of the ways is to impart the amphiphilic or charged character to therapeutic molecules. Alkylated BBI derivatives with methyl and octyl tails (BBI-1 and BBI-8, respectively) were synthesized and their solubility in water and micellar systems was tested.[56] We failed to prepare quaternized derivatives; therefore, we used micellar nanocontainers to achieve their solubility in water. For BBI-8, the solubilization capacity in nonionic micellar nanocontainers changed in the order Pluronic 17 R4 << Tyloxapol < Tween 80 ≈ Pluronic F127, while markedly increases under acidic conditions due to arising of effectively hydrated charged nitrogen. Fundamental benefits of nanocontainers based on BBI-8 is their stimuli responsive behaviour since they form homogeneous solution under acidic conditions and precipitate at higher pH. This can be used for the control of binding/release mechanisms and both nanocontainer and drug regeneration in the case of *ex vivo* assays.

Cationic nanocontainers can be modified by additives, *e.g.*, hydrotropes. Unlike typical surfactants, hydrotropes are low-molecular-weight compounds, many of which are amphiphilic and able to aggregate at high concentrations. In our work[57] salts of acetic and aromatic acids, *N*-methyl glucamine (MG), thymol, *etc*. are explored as hydrotropic agents. The solubility of spectral probes in micellar (CTAB) nanocontainers increases in the order salicylate < benzoate < tosylate < acetate << MG. Additional factor contributing to the improvement of nanocontainer properties is a decrease in the toxicity of cationic surfactants. Thus, the modification of DABCO-16-based nanocontainers with MG (equimolar mixture) resulted in a marked increase in the solubility of quercetin compared to single cationic micelles, with the toxicity of modified nanocontainer essentially decreasing.[58] Taking into account the excellent effects of an increase in the solubility and a decrease in the toxicity demonstrated by MG, we synthesized a surfactant bearing a glucamine moiety[11] and a hexadecyl tail (GM-16) (**26**). This cationic surfactant aggregates at 0.7 mM and undergoes structural transition beyond ~10 mM, which is supported by viscosity and NMR self-diffusion data, with the solubilization capacity changing above the morphological rearrangement.[11] As predicted, GM-16 exhibited an excellent nanocontainer behaviour toward hydrophobic probes and a solubilization capacity exceeding that of typical surfactant CTAB in combination with controlled morphology and lower toxicity.[11]

To achieve the stimuli responsive behaviour, amine analogue of GM-16 with pH-dependent properties (GAM-16, **27**) has been synthesized. This amphiphilic compound is water soluble under acidic conditions and forms aggregates of about 8–10 nm beyond 0.1 mM. Their solubilization capacity is testified toward Orange OT (*S* = 0.023) and newly synthesized indole derivative Ind-1 (Figure 1) (*S* = 0.014), which is comparable with CTAB. As beneficial properties, a renovation behaviour of these nanocontainers should be mentioned, *i.e.*, they can be reversibly destroyed with loads retained in the precipitation. Nanocontainers can be repeatedly regenerated under basic conditions.

Based on the data obtained, practical recommendations can be given for the improvement of nanocontainers. One of the desirable properties of surfactants as nanocarriers is the morphological variability since the structural transition can initiate the targeted release of drug loaded. The variation of head groups may serve as a tool for reaching this transition. It can be exemplified by amphiphilic derivatives of DABCO, for which the formation of non-spherical aggregates of $\geqslant 100$ nm was documented within a concentration range close to CMC,[26] and the vesicle–micelle morphological transition of aggregates at low surfactant concentrations was shown.[12] Apart from the direct solubility effect additional factors can be involved in the case of hydrotropic agents due to their ability to induce structural rearrangements. This is exemplified by sphere-to-rod transition of cationic micelles initiated by aromatic acid salts[59] or gel-like behaviour observed in CTAB–thymol or DABCO–16-thymol systems.[57] Such morphological transitions may considerably modify the solubilization activity of surfactants.

DNA carriers based on cationic amphiphiles. Synthetic cationic amphiphiles are a very attractive alternative to natural DNA carriers since they make it possible to avoid such limitation as an immune response. The so-called non-viral vectors provide many advantages, *e.g*. the relative simplicity of formulations, high efficacy of DNA binding resulting in the condensation and compaction of giant polyanions. On the other hand, there are few examples of the use of synthetic gene delivery systems in clinical practice due to the low transfection efficacy mediated by non-viral vectors. Therefore, the design of novel cationic surfactants for these purposes remains a challenging task for interdisciplinary researchers at the intersection of physical chemistry, biology and medicine.[60,61] Moreover, fundamental knowledge on the factors responsible for DNA delivery to different cells is insufficient and should be elucidated.

Our work focuses on the design of novel cationic vectors with different molecular fragments systematically varied. This allows us to reveal structure–activity relationships and to select the most promising candidates for *in vivo* assays. To answer modern biotechnological criteria several trends should be maintained upon the fabrication of non-viral carriers, including the low concentration of foreign compounds used, low toxicity, the absence of side effects, bioavailability, biocompatibility, nanosized dimensions, *etc*. Therefore, gemini surfactants with a low aggregation threshold, especially those bearing natural fragments are of particular importance. DNA transfer to both prokaryotic and eukaryotic cells mediated by hydroxyethylated dicationic surfactants 16–*s*–16(OH) with polymethylene spacer fragments ($s =$ $= 4, 6, 12$) was studied, and factors responsible for the transfection efficacy were discussed.[25,62] For the pEGFP/gemini lipoplexes superior effect has been achieved, exceeding that of a commercial preparation. Note that, unlike the majority of literature data, high functionality was demonstrated by individual surfactant systems with no helper lipids or PEGylation technique involved. The activity changes as 16–4–16(OH) < 16–6–16(OH) < 16–12–16(OH), which is strongly supported by the same order of the condensation effect and the capacity of integrating with lipid bilayer. Inverse regularity is observed in the case of transformation of bacterial cells, with 16–12–16(OH)-based lipoplexes demonstrating the inhibitory effect on the plasmid DNA transferring.[25] The latter can be due to the negative influence of cationic surfactants on electroporation procedure and/or their antibacterial activity.

The role of head groups in morpholinium surfactants was studied[20] and compared with that in CTAB. The correlation between aggregation activity, surface and microenvironmental characteristics and nanocontainer properties was revealed. Nanosized aggregates based on dicationic morpholinium surfactants demonstrated higher solubilization capacity and binding affinity toward oligonucleotide compared to monocationic morpholinium analogue and CTAB. Lipoplex formation with a monomodal size distribution (~50 nm) was supported by a dynamic light scattering (DLS) technique, ethidium bromide quenching study and ζ-potential measurements. Note that morpholinium gemini shows advanced ability to integrate with a lipid bilayer,[20] which makes it possible to recommend this amphiphile as a potential gene carrier.

Pyrimidinic (uracilic) amphiphiles are very promising for the fabrication of gene delivery systems due to their capability of complementary binding with nucleotide units of DNA. In our work systematic variation of the molecular structure of mono-, di- and multi-charged pyrimidinic surfactants has been carried out, which allowed us to emphasize the role of hydrophobic tails, their location, molecular scaffold (acyclic *vs*. macrocyclic), number of cationic centres, occurrence of H-bonding, *etc*. (**12**–**24**) in both the aggregation behaviour and functional activity including DNA transferring to mammalian and bacterial cells.[27,31] The structure–activity correlation is the focus of the self-assembly and lipoplex formation studies exemplified by the series of pyrimidinic surfactants starting from dicationic bolaform analogue with two short tails and monocationic surfactant capable of H-bonding, passing through dicationic amphiphile with two tails to the analogue with three tails. The crucial role of hydrophobicity and cooperative interactions is emphasized, with three-tailed surfactants revealing the highest complexing activity toward the DNA decamer. Bolaform analogue incapable of self-assembling appeared to fail to compensate anionic charges of oligonucleotide, although it can form lipoplexes at a high N/P ratio (here, N and P are the numbers of charged nitrogen and phosphate groups in the surfactant and DNA, respectively).

One of the high-potential way to design the drug and gene carriers is connected with the combining of various structural units of amphiphilic molecules showing high activity. This can be exemplified by the study of novel dicationic pyrimidinic surfactant with morpholinium head groups,[31] which demonstrated high complexing activity toward plasmid pK18. The lipoplex formation (250 nm in diameter) is strongly supported by DLS and ethidium bromide exclusion studies. Low isoelectric point (N/P ratio) corresponding to the charge neutralization of phosphate backbones and effective integration with lipid membrane allows one to recommend this amphiphile as a candidate for DNA carrier.

Another family of cationic surfactants with natural fragments is diterpenoid amphiphiles, tested as non-viral vectors.[10,43] While two surfactants studied differed only in the counterions (bromide or tosylate) (**28**), their morphological behaviours differed dramatically. Tosylate derivative shows typical surfactant properties, with the micelle-like aggregates occurring above the CMC. Contrary to this, bromide derivative undergoes a micelle–vesicle–micelle transition with an increase in the concentration, which is testified by fluorescence spectroscopy, DLS, TEM data, NMR self-diffusion, conductivity measurements, *etc*. Unlike the former, the latter demonstrates high ability to integrate with the lipid bilayer and form lipoplexes with DNA decamer. The versatile morphological behaviour encouraged us to test a bromide analogue as a complexing agent for plasmid DNA. The transformation of *E. coli* Nova Blue cells with plasmid/diterpenoid surfactant lipoplexes reveals that the effect is strongly dependent on the techniques used. In the case of electroporation the inhibition of the transformation occurs, while in the case of chemical treatment no effect is observed with the surfactant added. This result is in agreement with the above data on the DNA transfer in bacterial cells mediated by hydroxyethylated gemini.[25]

Lipid-based strategies: vesicles, liposomes and solid lipid nanoparticles as drug delivery systems

Different encapsulation technologies have been proposed over the past few decades and are now in clinical trials or have already received approval for chemotherapeutic small molecules and RNA. This part of the review is focused on recent trends in the fabrication and application of lipid-based nanocarriers (liposomes, lipid-based nanoparticles and lipid nanoemulsions) with improved properties in clinical practice. It is known that nanocarriers consisting of lipids possess a number of advantages (Figure 2): (i) due to the fact that the cell membrane is composed of lipid bilayer, the lipid nanocarriers are capable of interacting with the cell membrane; (ii) lipid-based nanostructures demonstrate biocompatibility and biodegradability and are commercially available materials; (iii) in the case of lipid system the protection against capture by immune cells is higher compared to polymer particles; (iv) prolongation of drug action is also one of the advantages of lipid nanoparticles. Loading, encapsulation efficiency and release of drug from lipid particles depend on drug lipophilicity and particle structure and composition.

The advantage of lipid nanoparticles is the possibility to encapsulate genetic material and their controlled release with low toxicity and high biocompatibility maintained. Recent trends in the delivery of genetic material were surveyed.[63] The efficiency of the cellular uptake of RNA may be improved by conjugation with polyethylene glycol (PEG) or the so-called PEGylation of nanoparticles. The effect of PEG additives on their physical and chemical properties, RNA encapsulation efficiency, toxicity, targeting efficiency and suppression of cancer cells was evaluated.[64] Neutral lipid liposomes effectively accumulate in cancer cells with RNA encapsulated. The lipid systems described were very stable and long circulating, which gives great hope for their use in clinical trials for the treatment of cancer.[65]

Lipid nanoparticles and liposomes, due to their biocompatibility and facility of large-scale production, are promising for vaccine delivery systems.[66] A thorough understanding of HIV and cancer diseases, namely, the microenvironment and metastatic processes, allowed researchers to detect a variety of target receptors for the attack of infected cells. Lipid systems applicable to the development of new drug delivery systems for the administration of anti-retroviral drugs to the central nervous system were described.[67]

The effective lipid delivery systems in tumor cells were reviewed.[68] Despite the fact that many lipid formulations are effective in the treatment of cancer, the lipid systems are in preclinical trials today.

From a wide range of systems, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers, due to their unique characteristics, are promising candidates for drug delivery to the lymphatic tissue.[69] It was noted that the liposomes and SLNs provide better penetration into the lymphatic system with the size being an extremely important criterion.[70]

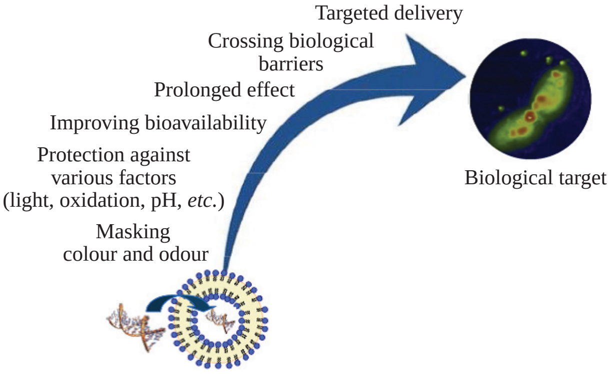


Figure 2 Schematic diagram of factors responsible for the improvement of effectiveness of formulated preparations compared to free drugs.

The use of nanoscale lipid systems during the passage of the route through the lungs can improve the treatment of pulmonary arterial hypertension. A recent review shows that the liposome systems may be delayed in the pulmonary area, underscoring the effectiveness of liposomes as delivery systems for long-term and targeted drug delivery.[71] Colloidal systems based on lipids have an additional advantage, when administered *via* the lungs due to the physiological components of the composition. It is known that liposome compositions passed the process of freeze-drying reached the third phase of clinical trials and have the prospect for successful commercialization of nanoparticles for inhalation.[72]

Ocular drug delivery systems are capable of remaining on the ocular surface for a longer period than eye drops; that is, in this case, the concentration of drug substances, which can penetrate through the eye segments, increases. Each system has its own contribution to the bioavailability of drugs in the eye. Lipid-based systems usually contain penetration enhancers such as surfactants that facilitate drug diffusion through the membrane.[73] Modification of the properties of nanoparticle delivery systems, such as the size and surface charge, is a strategy to increase the retention time and to improve the penetration of drugs.[74] A review[75] presents successful examples on nanostructured nanoparticles based on lipids to deliver drugs in the eye, including commercial preparations based on liposomes, for example, loaded with verteporfin. It was concluded that the liposomal formulations are more acceptable to the system (parenteral administration) rather than direct/topical administration to the eye to obtain a non-invasive eye drops.

Liposomes comprised of phospholipids and cholesterol presented the first platform from a wide range of drug delivery systems. It is well known that, by combining various lipids in the preparation of liposomes and their surface modification, different effects can be achieved. For example, the PEGylation of particles can reduce the adsorption of proteins and increase the circulation time of liposomes.[76] Cationic liposomes are most effective in the delivery of genetic material for the treatment of ocular diseases. However, there are no effective transfectants exhibiting low toxicity and efficacy *in vivo*. The lipid carriers for RNA and possible strategies for the solution of existing problems were described.[77] Surface coating and modification of liposomes are important in targeted drug delivery. One approach to improve the delivery in tumor cells is the creation of liposomal systems with photosensitizers. The use of photodynamic therapy makes it possible to orient systems to specific types of tumors reaching internal organs, improve permeability, retain and increase retention time in the malignant tissue.

Transfersomes, *i.e.*, liposomes containing sodium cholate, Span 80, Tween 80 and ethosomes enriched in alcohol have proven themselves as effective delivery systems that enhance the penetration of drugs through the skin.[78]

Liposomes having a negative surface charge and coated with mannose can be effectively absorbed by the lymphatic system. Such systems have diverse perspectives in the creation of drugs for the treatment of the immunodeficiency virus.[79] The delivery systems with different receptors-markers on the virus cell are used to effectively reduce immunodeficiency virus infection.[80] Liposomal systems may be used to deliver antibiotics.[81] It is possible to modify the liposome surface with other nanoparticles or targeting moieties to improve the site/specific delivery and to control the release of antibiotics.

Bionanovesicles received as a result of the encapsulation of quercetin and curcumin showed anti-inflammatory effects on cutaneous wounds. In accordance to epidemiological data and the results of *in vitro* assays, it can be assumed that a daily topical application of curcumin loaded in nanovesicles can provide effective protection for patients with skin wounds.[82]

Liposome-based systems in comparison with other colloidal systems exhibit higher therapeutic activity in the treatment of leishmaniasis, murine candidiasis and cryptococcal. Imunnoliposomes obtained exhibit high antiviral and antifungal activity, as compared to a free drug.[83] The use of liposomal forms for drug trifluralin and its analogues resulted in improved *in vivo* performance against *Leishmania infantum* infection.[84] Further modification of liposomes may improve the bioavailability of formulated drugs and favor their targeted delivery.[85,86]

Unlike liposomes, solid lipid particles have a solid core and possess high stability, low toxicity, high encapsulation efficiency, possibility of sterilizing and a large scale producing.[87] The second generation of the SLN, namely, nanostructured lipid particles (NLC), is the most successful example.[88] Surface modification of nanoparticles plays an important role in the delivery efficacy. Jain *et al*.[89] found that the galactosylation of SLN surface improved their performance in the treatment of cancer. The lipid particles modified by galactosylation and having a hydrodynamic diameter of 240 nm, an encapsulation coefficient of 72.3, highest cellular uptake, lower cytotoxicity, higher nuclear localization against A549 cells showed superior efficacy of the drug. Therefore, these carriers can be recommended as promising candidates for the treatment of cancer. The modification of solid lipid particles by cationic surfactants makes it possible to obtain lipoplexes to transfect cells. Recently, the possibility of SLN technology to deliver genes to the retina was demonstrated.[90]

Lipid nanoparticles are most suitable for the delivery of antituberculous drugs[91] because mycobacteria have a special affinity for lipidic substances.

A significant advantage of SLN formulations is their ability to pass through the blood-brain barrier and their prospective use in the treatment of neurodegenerative diseases.[92]

The comparison of different lipid systems for the delivery of retinylpalmitate through the horny layer of the skin was undertaken. It was found that the characteristics related to penetration and retention properties depend on the choice of the type of particle. The retention of the drug in the surface layers of the skin is more likely using the SLN, whereas nanoemulsions improve the penetration into the deeper layers of the skin.[93]

Self-assembly in calixarene-based systems for the fabrication of multifunctional nanocontainers

A growing interest in the self-assembly processes is primarily caused by the fabrication of micro- and nanoscale structures for various molecular device applications. Self-assembly inducing the formation of supramolecular assemblies has been widely explored as a kind of facilitated nanocontainers. This application requires the development of self-assembly mechanisms to produce nanocontainers with controlled structures and functions. There are several strategies for their creation and, alternatively, the nanocontainer structure can be achieved through the self-assembly of macrocyclic platforms. Within the latter methodology, the calixarene platform has demonstrated its potential for building up these systems. Therefore, we will briefly overview the calixarene-based systems that appear as most promising and present several prominent works.

The calixarene skeleton is a useful stable frame for the building of smart molecules and supramolecular assemblies. A suitable substitution on the upper and/or lower rim leads to unusual and surprising properties in the calixarene-based systems. The organic molecular cavities of calix, thiacalix- and resorcin[*n*]arenes offer great potential for the encapsulation of key molecules for technological applications.[94,95] These building blocks afford molecular capsules based on the self-assembly of several units, which is primarily driven by the interplay of weak attractions that act over short distances between molecules, including hydrogen bonds, electrostatic interaction, aromatic π-stacking and van der Waals interactions. Many encapsulation approaches were developed and related to controlling the capture–release processes, the reversibility of the systems and the type of guests that can be captured.[96] Therefore, calix[*n*]arene-based systems are versatile molecular capsules providing different nanospaces, some of which are controllable and adjustable, can encapsulate different kinds of interesting guests in solution.

The ability of synthetic receptors based on a calixarene platform to recognize biopolymers is determined by receptor conformation, type of functional groups and ability of a macrocycle to self-assembly. According to the reported data, calixarenes that interact with biomacromolecules contain amino groups,[97] quaternary ammonium substituents,[98] phthalimide[99] and peptide fragments.[100] The water-soluble *p-tert*-butylcalix[5]arene molecules were studied with the aim of exploiting their inner cavities as binding sites for biogenic amines.[101,102] In addition, glucocalix[4]arenes are regarded as a desired multivalent scaffold, where functional groups are anchored at the rims of macrocycles, and demonstrate enhanced bioactivities, such as lectin recognition and targeting property.[103,104]

The assembly properties of calixarenes are of considerable interest for drug transport in medical applications. Hydrophobic drugs, such as ciprofloxacin, could be loaded into amphoteric calix[8]arene nanoaggregates and released due to the pH-sensitive disassembly of calix[8]arenes.[105] The nanoparticles based on amphoteric calix[6]arene hexacarboxylic acid and calix[8]arene octocarboxylic acid are stable in a 4.5% bovine serum albumin solution and buffers (pH 5–9) and exhibit good paclitaxel loading capacity and a sustained drug release *in vitro*.[106]

Targeted drug delivery is a rapidly emerging field, where the calixarenes gained importance due to their ability to exhibit multivalency.[107] A multivalent fluorescent folate–calix[4]arene conjugate was shown to penetrate and localize inside cancer cells *via* folate receptor-mediated endocytosis.[108]

Solid lipid nanoparticles are also advanced tools for encapsulation of the active pharmaceutical ingredients in drug targeting. The amphiphilic calix- and resorcin[*n*]arenes were investigated to generate solid lipid nanoparticles that showed a great similarity to the commercial lipid-based nanoparticles in terms of stability and hence showed a potential for future applications.[109]

The capability of calixarenes to immobilize and transport drug molecules makes the macrocycles functionalized with amino acid residues attractive components of supramolecular systems. However, their use in aqueous solutions including biological fluids is limited because of extremely low water solubility (<1 μM). This problem can be solved by solubilizing them in surfactant micelles resulting in mixed aggregate formation[15,110–112] that finds application in pharmaceutics for drug delivery systems.[113]

The use of surfactants in supramolecular amphiphiles based on calixarenes is also widespread.[114,115] From the viewpoint of structural features of calixarenes, they incorporate single-headed, gemini- and bola-type amphiphiles into a single molecule.[116,117] As a result, calixarene amphiphiles exhibit special assembling properties that cannot be easily obtained by other traditional amphiphiles.[117] Meanwhile, the inclusion of guests may affect the assembling behaviour of calixarene amphiphiles,[118] like calixarene-induced aggregation. For example, complexation with sulfonatocalix[*n*]arenes promotes the aggregation of aromatic or amphiphilic guest molecules.[119,120] In addition, the ability of calix[4]arenes to form noncovalent assemblies with amphiphilic and polymeric amines allows one to create high-efficient catalytic systems[121] and may have prospective impact on nanomedicine and healthcare.[122] The superamphiphilic system based on resorcin-

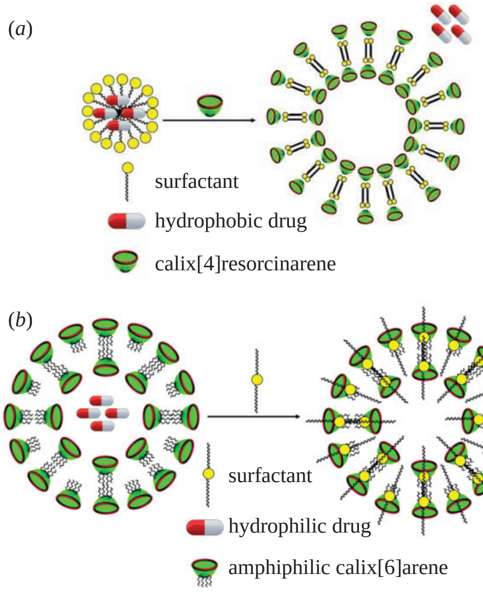


Figure 3 Schematic diagram of self-assembly in the aqueous calixarene–surfactant systems and the subsequent release of encapsulated (*a*) hydrophobic and (*b*) hydrophilic drugs.

[4]arene and a surfactant was tested as a nanocontainer for model hydrophobic substrates and dyes.[123,124]

Supramolecular interactions between calixarenes and surfactants can be used to control the binding and release of guests. An addition of ionic calix[4]resorcinarene to oppositely charged surfactant micelles solubilizing hydrophobic guest molecules induced the collapse of spherical micelles into vesicles, which can be used to trigger the release of encapsulated guests [Figure 3(*a*)].[125] The reverse case is also possible, where the surfactant added leads to the release of a substrate encapsulated into calixarene-based vesicles [Figure 3(*b*)].[126]

Amphiphilic calixarenes and calixresorcinarenes can form inclusion complexes with dyes.[127–129] Efficient binding of substrates with these macrocycles occurs due to their significant aggregation enabling binding by neighbouring aggregated molecules. The binding and release of guests generates a colour change in the colloidal macrocycle–dye system due to dye displacement and variation in aggregate dimensions.[130]

The calixarenes with specific functional groups were also used for the creation of electro-switchable systems.[131] Molecular switches capable of reversibly changing the supramolecular structure were created at the calixarene platform.[132] It was shown that octacationic amphiphilic calix[4]resorcine containing viologen groups on the upper rim and different length tails on the lower rim can be applied to the design of electron driven systems in organic (acetonitrile, DMF and DMSO), aqueous-organic or aqueous media.[132–134] The reduction of octacharged pentyl and decyl cavitands to tetracharged cavitands induces a selective reversible electroswitch interconversion between bound and unbound states of dianions in the aggregates of supramolecular complexes.

Conclusions

A significant health problem is the development of effective drugs. Amphiphilic compounds provide a suitable and rational platform for the fabrication of soft and smart materials for nano- and biotechnological applications. The fabrication of drug and gene delivery systems can be performed with the use of amphiphiles. To rationalize the development of effective nanocontainers, the structure–activity relations should be elucidated. Amphiphilic nanocontainers provide many benefits from the viewpoints of enhancing the solubility and stability of practically important hydrophobic probes and drugs. Application of geminis and naturally originated compounds allows one to minimize toxicity of formulations and side effects. Lipid nanocarriers, namely liposomes and solid lipid nanoparticles are very promising candidates for clinical applications. Their modification through various strategies, *e.g.*, PEGylation and galactosylation, as well as functionalization with residues sensitive to external stimuli (pH, redox, *etc*.) are promising ways to develop formulations for the treatment of serious diseases. To attain high efficacy of drug formulations, the tools for their controlled binding/release profile should be developed. From this viewpoint calixarene platform has many benefits, making it possible to fabricate the morphologically labile nanocontainers demonstrating selective multicentered binding of guest molecules and their triggered release under the microenvironmental conditions around diseased cells.

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