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Reviews

Dendrimers: Novel Polymeric Nanoarchitectures for Solubility Enhancement

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Poor solubility and hydrophobicity of drugs/bioactives limit their possible applications in drug delivery and formulation development. Apart from conventional methods of solubility enhancement, there are some novel methods which can be used in solubilization. Dendrimers represent a novel type of polymeric material that has generated much interest in many diverse areas due to their unique structure and properties. Dendrimer-mediated solubility enhancement mainly depends on factors such as generation size, dendrimer concentration, pH, core, temperature, and terminal functionality. Added advantage in solubilization can be achieved considering these factors. Available literature suggests that ionic interaction, hydrogen bonding, and hydrophobic interactions are the possible mechanisms by which a dendrimer exerts its solubilizing property. This review presents various mechanisms and reports relating to solubility enhancement using dendrimers. Also, micellar behavior and future possibilities in relation to solubilization via dendrimers are included.

Introduction

Up to 40% of new chemical entities (NCEs) discovered by the pharmaceutical industry today are hydrophobic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies.

Relative to highly soluble compounds, low drug solubility often manifests itself in a host of in vivo consequences including decreased bioavailability, increased chance of food effect, incomplete release from the dosage form, and higher interpatient variability. Poorly soluble compounds also present many in vitro formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the in vivo absorption. These in vivo/in vitro correlations are often sufficiently formidable to halt development of many newly synthesized compounds due to solubility issues.

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Poorly soluble drugs such as Nifedipine and Felodipine have motivated the development of drug delivery technologies to overcome the obstacles to their solubilization through either chemical or mechanical modification of the environment surrounding the drug molecule or physically altering the macromolecular characteristics of aggregated drug particles. These technologies include both traditional methods of solubility enhancement such as particle size reduction via comminution and spray drying, miceller solubilization, and cyclodextrin-mediated inclusion complexes.[1−3]

Cyclodextins and micelles share something in common: their hydrophobic interior is capable of encapsulating hydrophobic drugs and their hydrophilic exterior is responsible for solubilization. Bountiful literature reporting cyclodextrin-mediated solubilization of drugs is available.[4−7] High costs and nephrotoxicity on parenteral administration limit the use of cyclodextrins. Moreover, the aqueous solubility of the most commonly used cyclodextrin, β-CD (1.8 g/100 mL at 25 °C), is often insufficient to stabilize drugs at therapeutic doses.[8]

The reports on micelle- and polymeric-micelle-mediated solubilization are also in abundance.[9−25] The disruption of micellar structure on dilution with body fluids below critical

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Table 1. List of the Solubilizates Whose Aqueous Solubility Is Enhanced by Using Various Dendrimers

no.	dendrimer used for solubilization	solubilizate
1	amine- and ester-terminated polyamido amine (PAMAM) dendrimers[40]	Nifedipine
2	-OH-terminated PAMAM dendrimer[53]	benzoic acid
		3-amino 1,5 -dibromo phenol
		iodine
		salicylic acid
		2, 6 dibromo 4-nitrophenol
3	[Gn]-PGLSA-OH dendrimers[67]	Reichardt's dye
		(2,8-diphenyl)
		4-(2,4,6-triphenyl
		pyridinio phenolate)
		10 hydroxy camptothecin
		(10-HCPT)
4	PAMAM NH_2 and PAMAM -OH dendrimers[41]	Indomethacin
5	PEG polyethar dendrimers[20]	Indomethacin
6	PAMAM dendrimers[46]	Flurbiprofen
7	Polyglycerol dendrimer[52]	Paclitaxel
8	PEGylated PAMAM dendrimers[58]	pyrene
9	polypropylene imine dendrimers[44]	pyrene
10	polyether−PEG dendrimer[17]	pyrene
11	polyether dendrimer[51]	pyrene
12	poly(aryl alkyl ether) dendrimer[60]	pyrene
13	PEGylated PAMAM dendrimer[56]	5-fluorouracil
14	polypropylene imine−oligoethyleneoxy dendrimer[55]	Bengal Rose
		4,5,6,7-tetra chloro-fluorescein
15	PEO- and t-BOC-terminated poly-α-∈- lysine dendrimer[63]	Orange OT
16	ester- and NH_2-terminated PAMAM dendrimer[64]	SiO_2
17	PEG-PAMAM dendrimer[57]	Methotrexate
18	PAMAM dendrimer[62]	Methotrexate
19	PEG−PAMAM dendrimer[57]	Adriamycin
20	polyether dendrimer[51]	Anthracene
		1,4-diamino anthraquinone
		2,3,6,7-tetranitro fluorescein
21	PAMAM and Lauroyl PAMAM dendrimer[61]	Propranolol
22	citric acid-PEG−citric acid dendrimer[42]	5-amino salicylic acid
		pyridine
		Mefenamic acid
		Diclofenac
23	amphiphilic dendrimer[60]	Proflavine
24	PAMAM dendrimers[68]	Piroxicam
25	PEGylated diaminobutane PPI dendrimers[59]	pyrene
		β-methasone valerate
		β-methasone dipropinate
26	PAMAM dendrimers[47]	Ibuprofen
27	PAMAM dendrimers[50]	Niclosamide
28	PAMAM dendrimers[45,48]	Naproxen
		Ibuprofen
		Diflunisal
		Ketoprofen
29	PAMAM dendrimers[49]	nicotinic acid
30	PEGylated lysine dendrimers[69]	Artemether

micellar concentration (CMC) leads to the burst release of the entrapped drugs.[17]

Since application of micelles as drug vehicles mainly depends on their morphology and stability, it is important to seek micelles with stable structure and well-defined size and narrow size distribution.[26] Dendrimers with hydrophobic core and hydrophilic periphery have shown to exhibit micelle-like behavior and have container properties in solution.[17] The use of dendrimers as unimolecular micelles was proposed by Newkome in 1985.[27] This analogy highlighted the utility of dendrimers as solubilizing agents.[28]

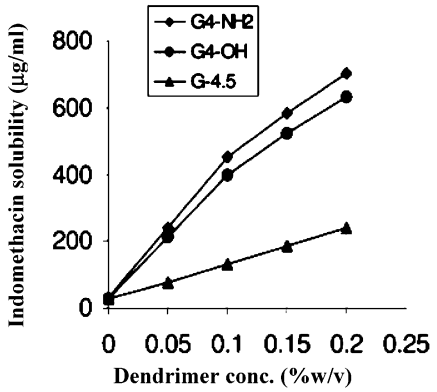

Figure 1. Solubility profile of Indomethacin in the presence of differing concentrations of G4−NH_2, G4−OH, and G−4.5 dendrimers at pH 7.0.[41] Reproduced with permission from Elsevier.

Dendrimers represent a novel type of polymeric material that has generated much interest in diverse areas due to their unique structure and properties. Their unique structural features include highly branched and well-defined structure, globular shape, and controlled surface functionalities. Wide ranging applications of dendrimers as drug delivery devices,[29−32] as gene carriers,[33−36] and in magnetic resonance imaging[37−39] have been reported. Here we have attempted to comprehensively review the work done in the field of dendrimer-mediated solubility enhancement (Table 1). Our major focus was to derive the conclusions from recently published data/ reports. Use of dendrimers in solubility enhancement is studied extensively. A plethora of available studies can be discussed more meaningfully by subgrouping them under the following headings.

Effect of Generation Size

Scientists have examined the effect of dendrimer generation on solubility enhancement. Most of them have observed that the solubility of a hydrophobe increased with increasing generation number. There is tendency, however, to select dendrimers up to generation 3 as they are less immunogenic and more biocompatible as compared to higher generations. Studies on the fourth generation are also available but comparatively rare. Experiments on generation five and onward are almost nonexisting.

Devarakonda et al. reported the solubility enhancement of Nifedipine using different generations of PAMAM dendrimers. The authors used both amine- and ester-terminated dendrimers and found that the aqueous solubility of Nifedipine increased several-fold with dendrimer generation in both cases. They proposed that hydrogen bond formation between the tertiary nitrogen of PAMAM dendrimers and the hydrogen of the dihydropyridine moiety of Nifedipine could be the possible mechanism of solubility enhancement. It was suggested that the hydrophobic microenvironment of dendritic microcavities could also be the contributing factor in solubility enhancement.[40]

Chauhan et al. used G4−NH_2, G4−OH, and G4.5 ester-terminated PAMAM dendrimers for solubility enhancement of Indomethacin. It was observed that at pH 7 aqueous solubility of Indomethacin increased in following order: G4−NH_2 > G4−OH, > G4.5 (Figure 1). Three different mechanisms for

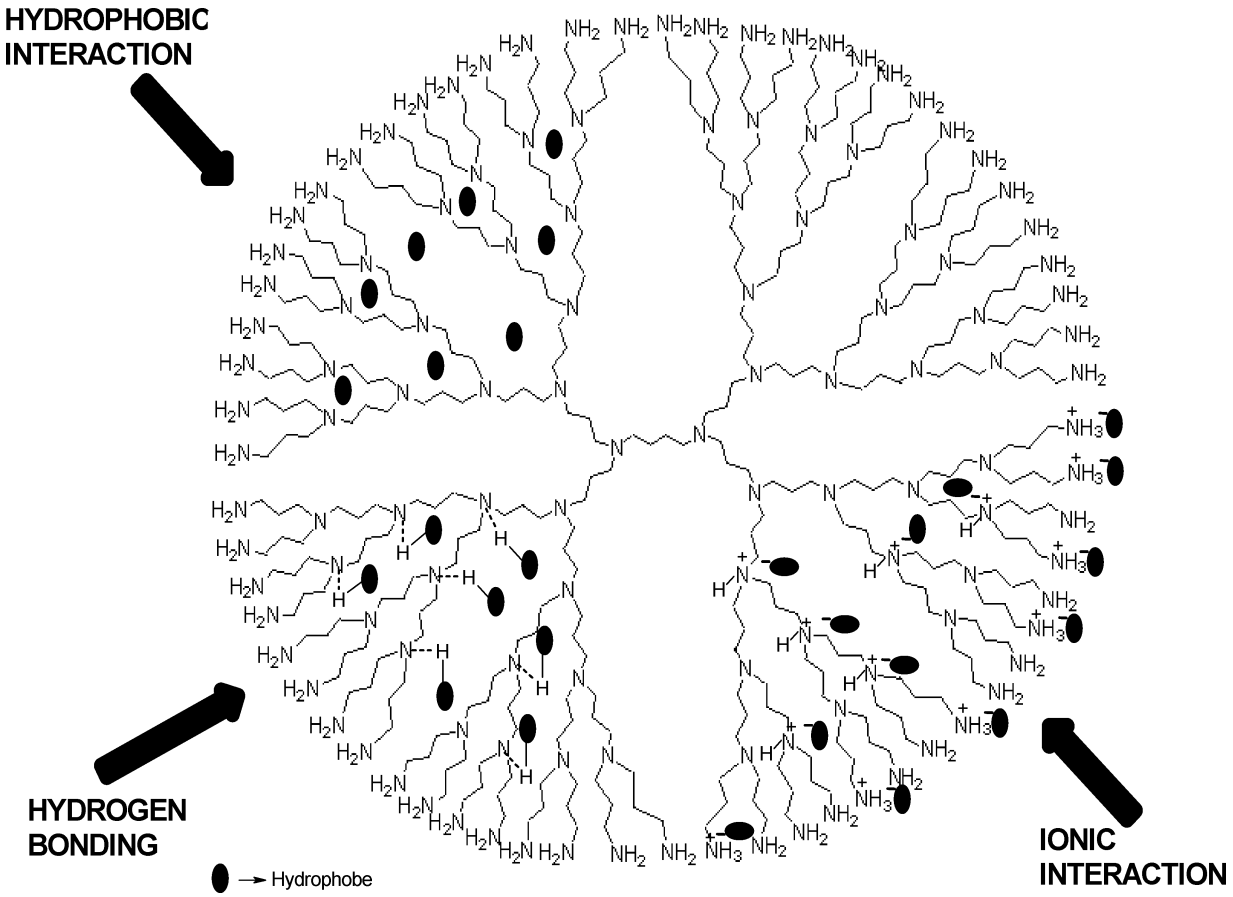

Figure 2. Possible mechanisms of dendrimer-mediated solubility enhancement. Reproduced with permission from Elsevier.

solubility enhancement were proposed for these generations having different terminal functionalities. With amine-terminated dendrimers, the proposed mechanism for solubility enhancement was electrostatic interactions between the terminal amine groups of dendrimers and the carboxylic group of Indomethacin and molecular encapsulation. The −OH-terminated dendrimers were found to increase solubility by weak hydrogen bonding, whereas molecular encapsulation was the primary mechanism involved in solubility enhancement by ester-terminated dendrimers (Figure 2).[41]

Very recently Namazi et al. reported the synthesis of a new type of dendrimer with poly(ethylene glycol) (PEG) as the core and citric acid as the branching unit. The authors used three generations (G_1, G_2, and G_3) of these dendrimers for the solubility enhancement of different hydrophobes and found that the solubility of all the hydrophobes (e.g., pyrene, 5-amino salicylic acid, Mefenamic acid, and Diclofenac) increased with generation number. It was proposed that electrostatic interaction was the mechanism responsible for solubility enhancement. They pointed out that trapping of guest molecules in the cavities of the dendritic host was yet another possibility. It was suggested that the size of the guest molecule has some influence on solubility enhancement. This was evident from the fact that the solubility enhancement of smaller guests (pyridine and 5-amino salicylic acid) was greater as compared to that of larger ones, i.e., Diclofenac and Mefenamic acid.[42]

Some other workers have also studied the effect of generation on solubility enhancement. Kaanumalle et al. reported that aqueous solubility of pyrene increased by 5-, 8-, and 24-fold with generation 1, 2, and 3, respectively, of poly(alkyl aryl ether) dendrimers having a phenolic hydroxy group at periphery.[43]

Pistolis and Malliaris employed poly(propylene imine) (PPI) dendrimers for solubility enhancement of pyrene. Solubilization of pyrene increased linearly with increasing dendrimer generation. Exciplex formation was the mechanism the authors proposed for solubility enhancement.[44] Yiyun et al. solubilized different NSAIDs using PAMAM dendrimers and studied their generation as well as concentration-dependent studies using generation 2, 3, and 4 dendrimers. Results indicated that dendrimer-mediated solubilization was proportional to the concentration of dendrimers. Also, higher generations were found to solubilize more drugs. The order of solubility enhancement of NSAIDs at a constant dendrimer concentration and fourth generation was Naproxen > Ketoprofen > Ibuprofen > Diflunisal.[45] All of these studies have reported that solubility increases with generation number. At lower generation numbers, dendrimers have open structures, which becomes increasingly globular with an increase in generation number. Generation number dependent enhancement in solubility could be attributed to this conformational change.

Effect of pH

Electrostatic interaction between hydrophobes and peripheral, as well as internal, tertiary amines of dendrimers is a major mechanism responsible for solubility enhancement. The protonation of nitrogen whether at periphery or at dendrimer interiors is influenced by pH. Recent reports reveal attempts to study the effect of pH on the acid−base properties of these nitrogens and the impact on solubility enhancement.

Devarakonda et al. found that Nifedipine solubility increased linearly with increasing concentration of amine-terminated PAMAM dendrimers at pH 7 and pH 10 but not at pH 4 (Figure

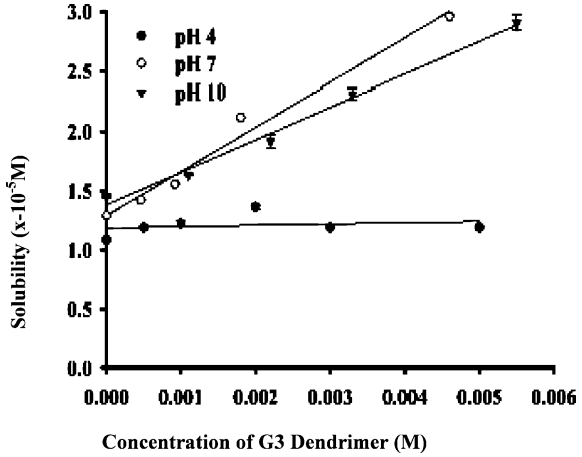

Figure 3. Solubility profiles of Nifedlipine in the presence of increasing concentrations of amine-terminated G3 PAMAM dendrimer.[40] Reproduced with permission from Elsevier.

3). On the contrary, the aqueous solubility of Nifedipine increased linearly with increasing dendrimer concentration at pH 4, 7, and 10 in case of ester-terminated half-generation PAMAM dendrimers. The authors also found that the Nifedipine solubility was highest at pH 7, less at pH 10, and least at pH 4 (Figure 4). It was suggested that at pH 4 the protonation of tertiary amines in amine-terminated dendrimers created an environment with considerable polarity inside the dendrimer microcavity, and hence no increase in solubility of Nifedipine was observed at pH 4 in full generation PAMAM dendrimers. As compared to amine-terminated PAMAM dendrimers, the protonation was less in the case of ester-terminated half-generation PAMAM dendrimers at pH 4. This means that more unprotonated tertiary amines were available for hydrogen bonding with drug molecules. Hence, the aqueous solubility of Nifedipine increased linearly with increasing dendrimer concentration at pH 4 as well. At pH 7 (neutral), both primary and tertiary amines are less susceptible to protonation as compared to that at pH 4 and 10. That is why the highest solubility of Nifedipine was attained at this pH.[40]

A similar trend was observed by Asthana et al.[46] The authors found that the increment in the aqueous solubility of weakly acidic drug Flurbiprofen using a fourth generation PAMAM dendrimer was maximum at pH 7, less at pH 10, and least at pH 2 (Figure 5 and Table 2).

Milhem et al. studied the solubility enhancement of weakly acidic Ibuprofen using G4 PAMAM dendrimers as a function of pH. The authors also reported that the electrostatic interaction between host and guest was responsible for the solubility enhancement of Ibuprofen. The increase in solubility was highest at pH 10.5, whereas at pH 2 no significant increase in solubility was recorded (Table 3). The authors concluded that, at highly basic pH, weakly acidic Ibuprofen is ionized and interacts electrostatically with surface amine groups of dendrimers, whereas at pH 2, this interaction is not possible because Ibuprofen largely remained un-ionized.[47] Very recently, Yiyun et al. investigated the solubility enhancement of nicotinic acid and ketoprofen using PAMAM dendrimers in a separate study. A concentration- and generation-dependent solubility enhancement was observed. The solubility was highest at pH 6.0 and least at pH 3.0. The authors proposed electrostatic interaction between surface amine groups of the dendrimer and the carboxylic group of guests and also hydrogen bonding between atoms of nicotinic acid and the tertiary amine groups of the dendrimers as possible mechanisms for the solubility enhancement. Solubility enhancement was greater in amine-terminated dendrimers than in the corresponding generation of the ester-terminated ones.[48−49] In another study, Devarakonda et al. compared the role of PAMAM dendrimers and cyclodextrins (HPβCD, βCD) in the solubility enhancement of Niclosamide. It was observed that, in general, the amine-terminated dendrimers have a superior ability to enhance solubility of Niclosamide as compared to CD (as characterized by higher stability constants and complexation efficiency). A concentration-dependent increase in the solubility of Niclosamide was observed in the case of amine-terminated dendrimers at pH 7 and 11 and in water. The electrostatic interaction between the positively charged primary amines of dendrimers and the negatively charged Niclosamide molecule was the proposed mechanism of action for solubility enhancement. The solubility enhancement was highest in water.[50]

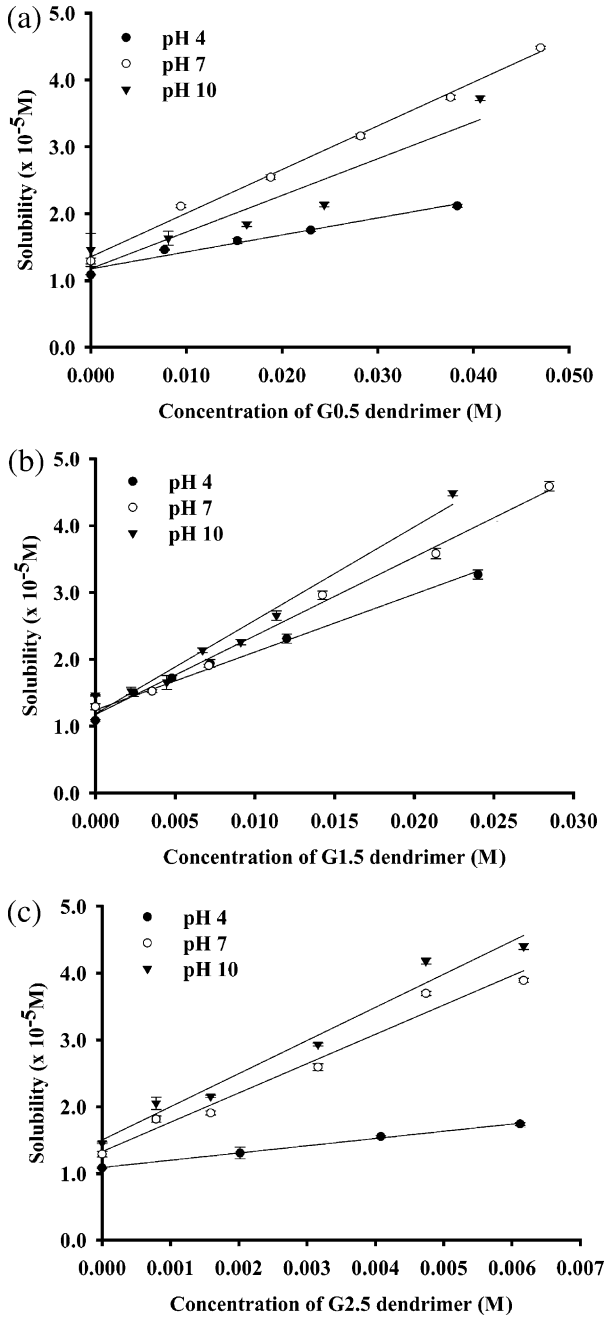

Figure 4. Solubility profiles of Nifedipine in the presence of increasing concentrations of ester-terminated PAMAM dendrimers (A) G 0.5, (B) G 1.5, and (C) G 2.5.[40] Reproduced with permission from Elsevier.

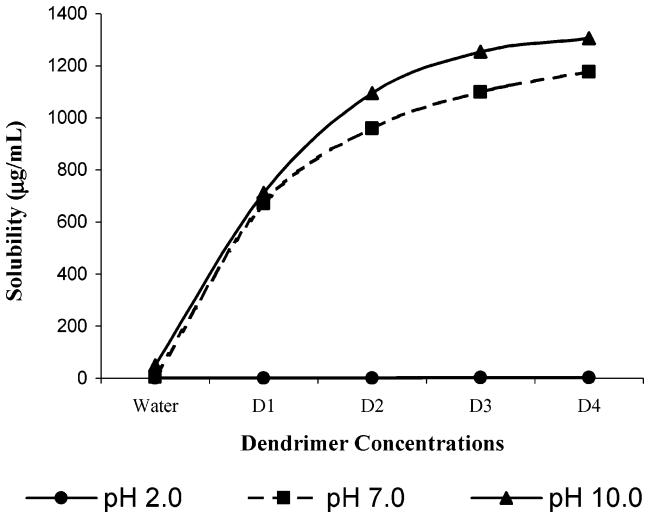

Figure 5. Comparison of the solubility profile of FB in different concentrations of dendrimer at pH values 2.0, 7.0, and 10.0 at 25 ± 2 °C.[46] Reproduced with permission from Elsevier.

Table 2. Effect of pH on Solubility of Flurbiprofen (FB) in Water with Different Concentrations of G4 PAMAM Dendrimer Solutions at 25 ± 2 °C[46]

		water solubility of FB (µg/mL) in different pH at 25 ± 2 °C		
no.	system[a]	pH 2.0	pH 7.0	pH 10.0
1	water	0.23	3.57	50.41
2	D_1	0.74	671.52	712.11
3	D_2	1.02	959.89	1095.56
4	D_3	1.22	1098.01	1254.34
5	D_4	1.34	1177.02	1305.23

[a] D_1, D_2, D_3, and D_4 are, respectively, 0.1%, 0.2%, 0.3%, 0.4% aqueous concentrations of G4 PAMAM dendrimers.

Table 3. Effect of pH on the Solubility (mg/mL) of Ibuprofen in PAMAM G4 Dendrimer Solutions at 27 °C[47]

2% G4 pH 10.5	3% G4 pH 10.5	water pH 5.8	2% G4 pH 2	3% G4 pH 2
12.16	18.11	0.09	0.07	0.05

Effect of Core

In 1993 Hawker and co-workers synthesized dendritic unimolecular micelles using 3,5-dihydroxy benzyl alcohol as the building block.[51] These unimolecular micelles were used to increase the solubility of pyrene. It was found that the aqueous solubility of pyrene was increased by about 120-fold (Figure 6). Liu et al. synthesized analogous unimolecular micelles.[17] The difference was the building block (Figure 7): instead of using the widely used 3,5-dihydroxybenzyl alcohol, these workers used 4,4-bis(4-hydroxyphenyl) pentanol as the building block. This change ensured larger internal cavities and imparted greater flexibility to the unimolecular dendritic micellar structure. The influence of available larger internal cavities was quite evident as the enhancement in the aqueous solubility of pyrene this time was 356-fold as compared to 120-fold in the previous study. The beauty of dendrimer chemistry is that it offers great flexibility in the selection of the core for synthesis. This makes synthesis of dendrimers with a difference in container properties (and solubilization ability, in turn) possible simply by alteration in a core molecule.

Effect of Temperature

In a preliminary examination, Milhem et al. have reported the effect of temperature on solubility enhancement of Ibuprofen using G4 PAMAM dendrimers. They studied the solubility enhancement of Ibuprofen at different temperatures, viz., 27, 35, 40, 45, and 50 °C. It was found that the solubility enhancement was inversely proportional to an increment in temperature (Figure 8). However no explanation was offered for the unusual trend.[47] Temperature is one of the most important factors influencing solubility. Unfortunately, apart from the study described above, this area has somehow remained unexplored.

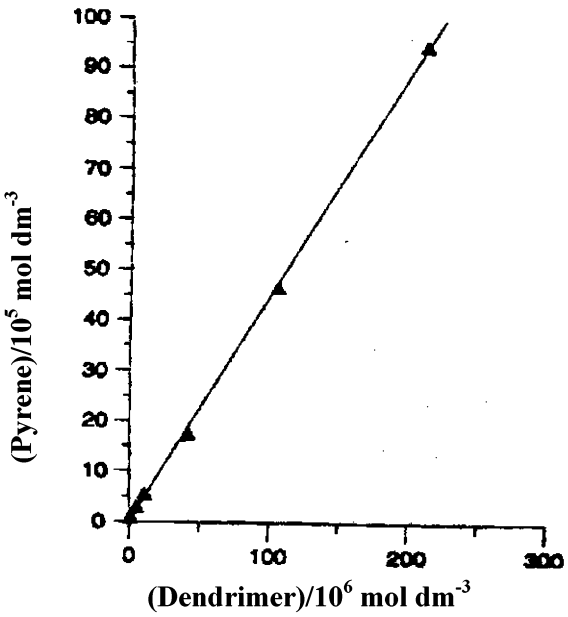

Figure 6. Solubility of pyrene as a function of dendrimer concentration in water.[51] Reproduced with permission from Elsevier.

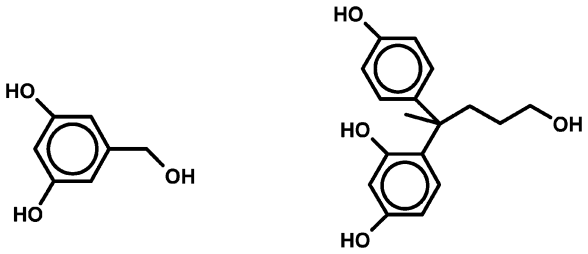

Figure 7. Structure of the monomers used to build dendrimers.[17] Reproduced with permission from Elsevier.

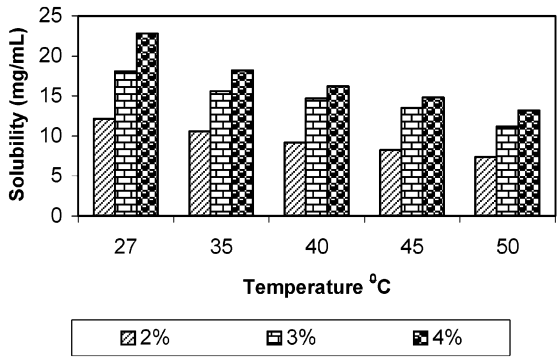

Figure 8. Effect of temperature on Ibuprofen solubility solubilized via different concentrations of dendrimers (% w/v).[47] Reproduced with permission from Elsevier.

Effect of Polymeric Architecture

The effect of polymeric architecture on solubilization and controlled release of Paclitaxel was studied by Ooya et al. In

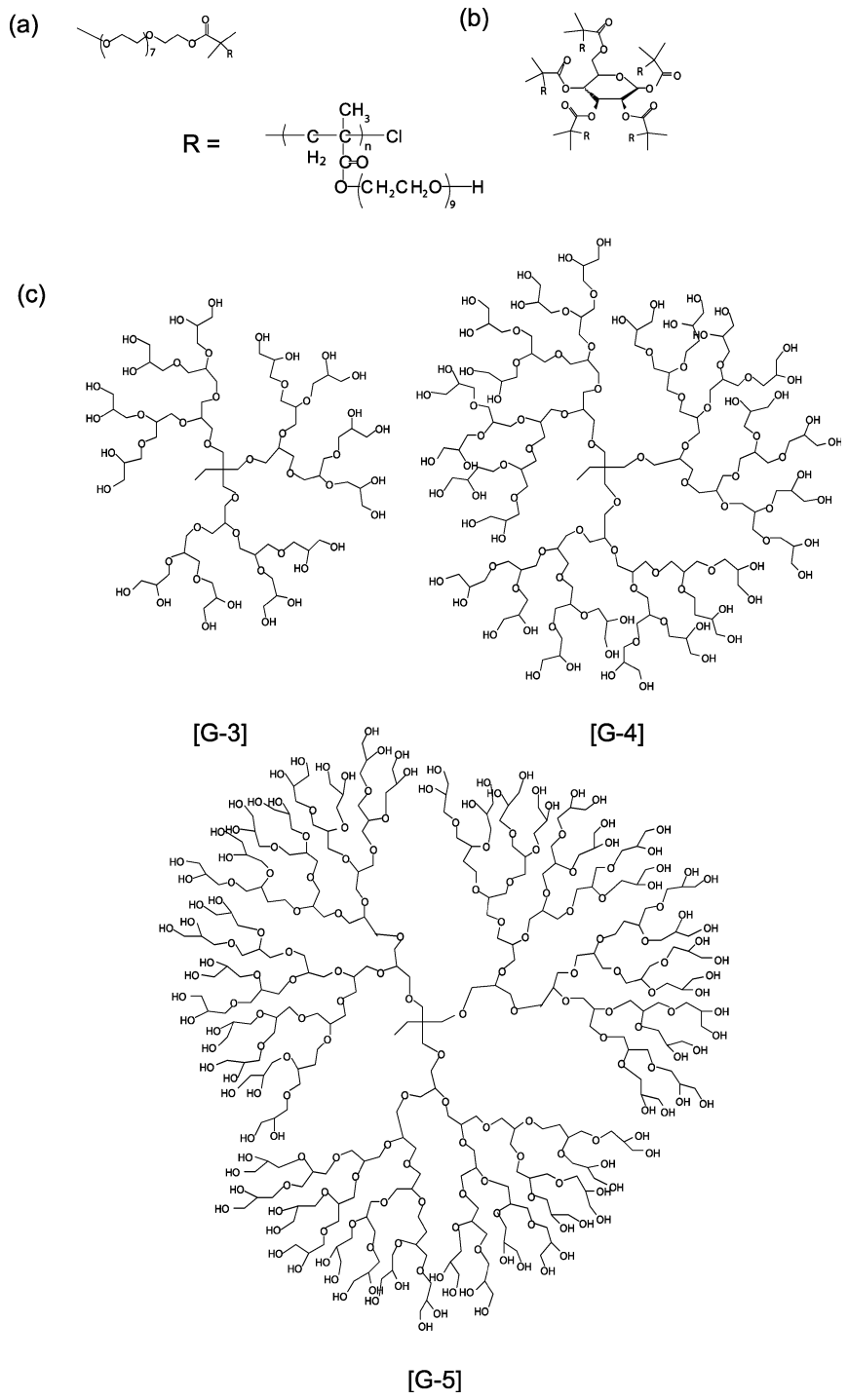

Figure 9. Chemical structure of (a) poly [oligo(ethylene glycol) methacrylate] [poly(OEGMA)], (b) five-arm star poly(OEGMA), and (c) polyglycerol dendrimers with generation 3 (G-3), 4 (G-4), and 5 (G-5).[52] Reproduced with permission from Elsevier.

this study, the effect of the density of ethylene glycol chains on the solubility enhancement of Paclitaxel was investigated. They synthesized poly(oligo ethyl glycol methacrylate) (OEGMA), five-arm star-shaped polyOEGMA, and Polyglycerol dendrimers G-3, G-4, and G-5 (Figure 9) and found that solubility of Paclitaxel was increased in all polymer solutions as compared to PEG-400. The ability to enhance Paclitaxel solubility was in the order described in (Table 4). The results clearly indicated the influence of density of ethylene glycol chains on Paclitaxel solubility. While star polyOEGMA increased the aqueous solubility of Paclitaxel 130-fold, G3, G4, and G5 polyglycerol dendrimers increased it by 270, 370, and 434-fold, respectively.[52]

Table 4. Paclitaxel Solubility in Different Polymer Solutions[52]

		Paclitaxel solubility (mg/mL)[a]	
sample	MW (g/mol)	10 wt %	80 wt%
PEG400	400	0.0004 ± 0.0001	16.17 ± 0.35
poly(OEGMA)	10 300	0.0116 ± 0.0005	
five-arm star poly(OEGMA)	98 700	0.0397 ± 0.0028	
G-3 dendrimer	1690	0.0804 ± 0.0051	1.873 ± 0.158
G-4 dendrimer	3508	0.1100 ± 0.0062	1.817 ± 0.078
G-5 dendrimer	7087	0.1282 ± 0.0091	2.305 ± 0.056

[a] The aqueous Paclitaxel solubility in the absence of any polymers is 0.0003 mg/mL. Mean ± SD (n = 3).

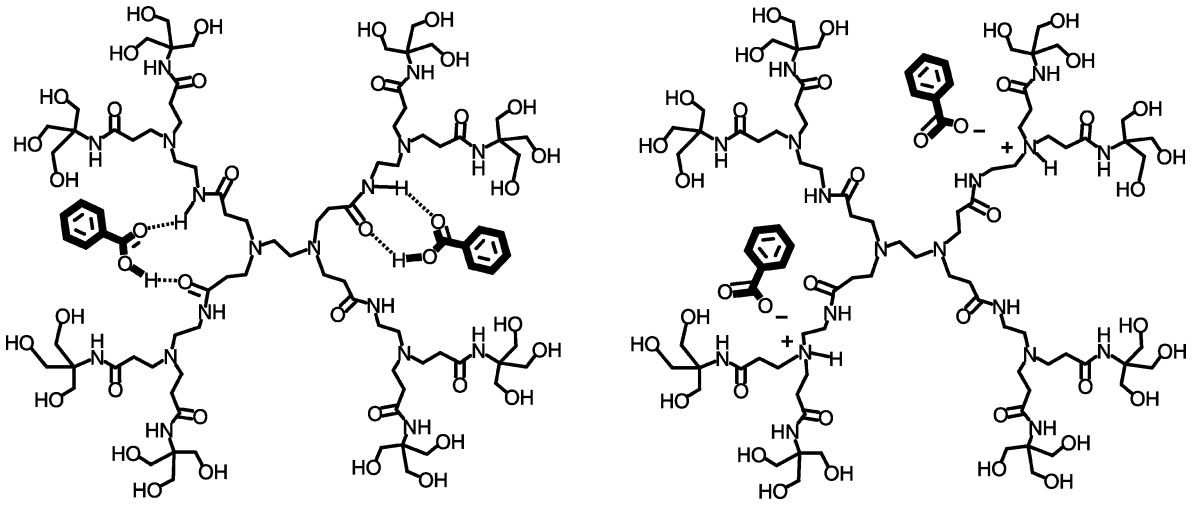

Figure 10. Likely hydrogen bonding interaction and ion pairing interaction.[53] Reproduced with permission from Elsevier.

Variations: Modification of Terminal Functionality

Researchers have exploited terminal functional groups of dendrimers to tailor-make their properties. In an attempt to enhance the clinical utility of dendrimers, Beezer et al. and Twywan et al. modified ester-terminated PAMAM dendrimers to hydroxyl-terminated dendrimers by treating the former with TRIS group (tris hydroxymethyl amino methane). This served two purposes. First, the inherent haemolytic toxicity associated with amine-terminated dendrimers was expected to be reduced. Second, one ester terminus generated three hydroxyl end groups. This was expected to increase the water solubility of the dendrimer dramatically. The authors then studied the influence of these terminals on the solubility enhancement of small hydrophobic acidic molecules. It was observed that the solubility of a complex of dendrimer and hydrophobe was infinite, and hence the solubility of bound hydrophobic guest could also be considered infinite. A simple ion pair interaction between host and guest (Figure 10) was indicated to be the mechanism involved in solubilization.[53−54]

Baars et al. studied the localization of guest molecules in water-soluble oligoethyleneoxy-modified PPI dendrimers. PPI dendrimers having a DAB core and NH_2 functionality were modified with 3,4,5-tris(tetraethyleneoxy)benzoyl units, which have a basic interior of tertiary amine and hydrophillic periphery, and were able to encapsulate guest molecules, e.g., Bengal Rose and 4,5,6,7-tetrachloro fluorescein in these unimolecular water-soluble micelles (Figure 11). Though many researchers have used modified dendrimers for solubility enhancement, among lots of reported variations PEGylated dendrimers find the most common place and hence need special mention.[55]

PEGylated Dendrimers. Many workers have PEGylated dendrimer periphery and examined the utility of PEGylated dendrimers in solubility enhancement and drug delivery. Bhadra et al. devised PEGylated nanocontainers by PEGylation of G4 PAMAM dendrimers. The authors observed that PEGylated dendrimer display improved entrapmaent efficiency of sparingly water-soluble anticancer agent 5- Fluorouracil.[56] The effect of arm length of poly(ethylene glycol) on dendrimer-mediated solubility was also studied by Kojima et al. Anticancer drugs were encapsulated using a PAMAM dendrimer having MPEG (poly(ethylene glycol) monomethyl ether) grafts of different molecular weights. Two anticancer drugs—methotrexate (MTX), a practically water insoluble drug, and Adriamycin (ADR), a hydrophobic drug—were successfully encapsulated in the hydrophobic interior of MPEG-550 G3, MPEG-2000 G3, MPEG-550 G4, and MPEG- 2000 G4 PAMAM dendrimers. Varying amounts of MTX molecules associated with the MPEG-550 G3, MPEG-2000 G3, MPEG-550 G4, and MPEG-2000 G4 PAMAM dendrimers were approximately 10, 13, 20, and 26 mol/mol of dendrimer, while for ADR the results were 1.2, 2.3, 1.6, and 6.5 mol/mol of dendrimers, respectively. It was observed that most of the ADR was complexed and solubilized on the surface of MPEG chains, while in case of MTX, an acidic drug, the number of encapsulated molecules increased due to electrostatic interaction resulting from an acid−base reaction between dendrimer and MTX. It was found that with increasing dendrimer generation and PEG molecular weight, more drug molecules could be encapsulated.[57] In another attempt, Yang et al. used G3 PAMAM dendrimers and conjugated it with PEGs of different molecular weight, viz., 750, 2000, and 5000. The authors found that a relatively higher conversion of dendrimer periphery was obtained with PEG-750, which is attributed to reduced steric hindrance in the coupling reaction due to the decrease in PEG arm length. The results suggest that PEG arm length has a significant effect on pyrene water solubility (Figure 12). Short PEGs (e.g., PEG-750) do not have much interaction between each other and thus produce a relatively loose cavity. It was suggested that PEGylation with short-armed poly(ethylene glycol) has a limited value in solubility enhancement of hydrophobes. PEGylation with PEG having a longer arm, e.g., PEG-2000, produces a thick network of PEG chains at the dendrimer surface and thus a higher capacity for solubility enhancement. Interestingly, the authors found that a dendrimer PEGylated with PEG-5000 has a lower capability for solubility enhancement of pyrene than a dendrimer PEGylated with PEG-2000. They attributed this to the agglomeration of the former and interpenetration of PEG chains (Figure 13), thus the occupying cavities available for guest.[58] Sideratou et al. studied the effect of extent of PEGylation of DAB-64-poly(propylene imine) dendrimer on the solubility enhancement of pyrene. Higher pyrene loading was achieved by DAB64−8PEG than the DAB64−4PEG, and it was proposed that pyrene exists not only in the dendrimer interior but also in PEG chains.[59]

Amphiphilic Dendrimers. The amphiphillic dendrimers were reported by Hawker et al. back in 1993.[51] The authors have shown that the dichloromethane/ water emulsion produced with carboxyl- and phenyl-terminated dendritic diblock copolymer at interface persisted for a few weeks. This indicated the surfactant-like behavior of amphiphillic dendrimer. Recently, Vutukuri et al. investigated the utility of amphiphillic dendrmers

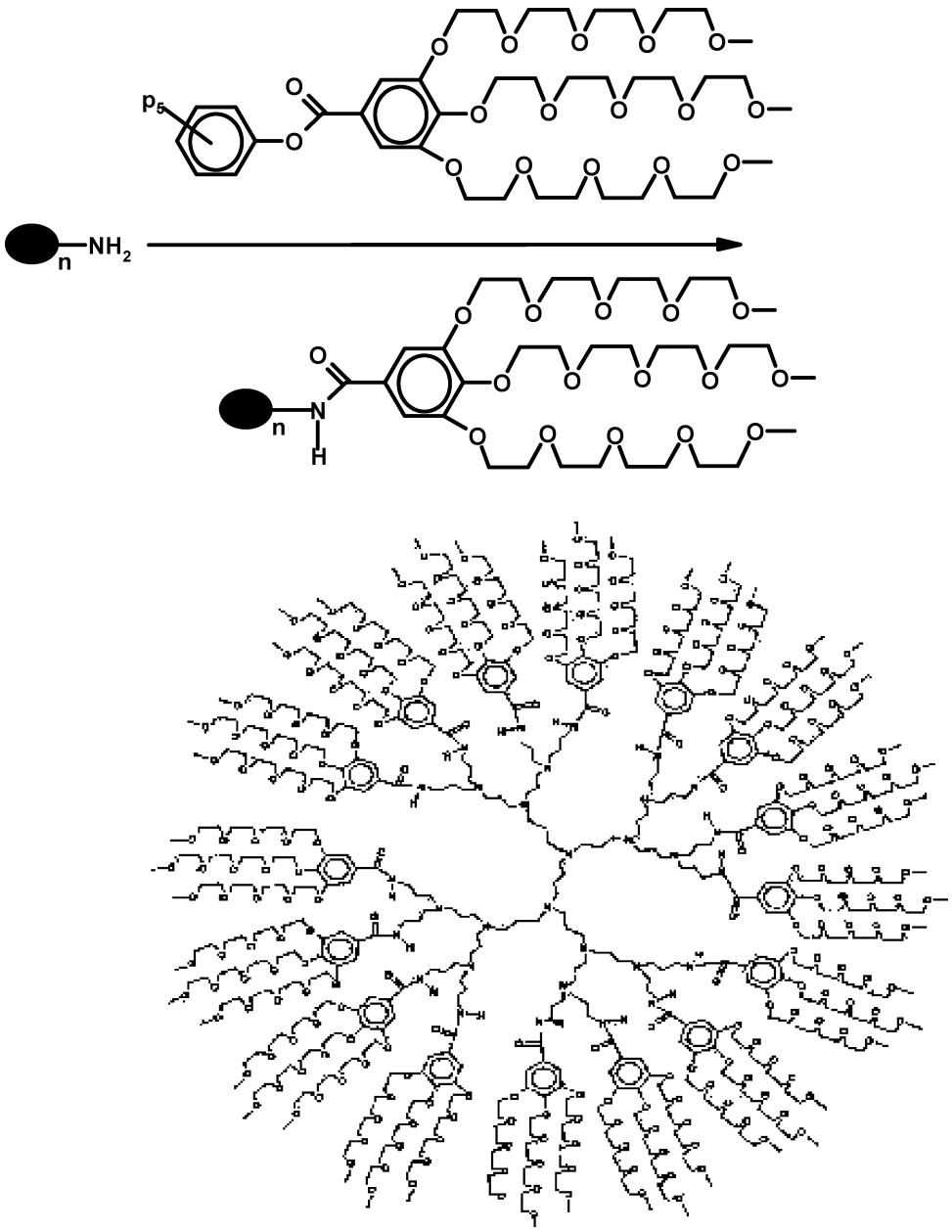

Figure 11. Synthesis of oligoethyleneoxy functionalized poly(propylene imine) dendrimers: $n = 4$:1, $n = 16$:2, $n = 32$:3, and $n = 64$:4 (top). Schematic structure of host 2 (bottom).[55] Reproduced with permission from Elsevier.

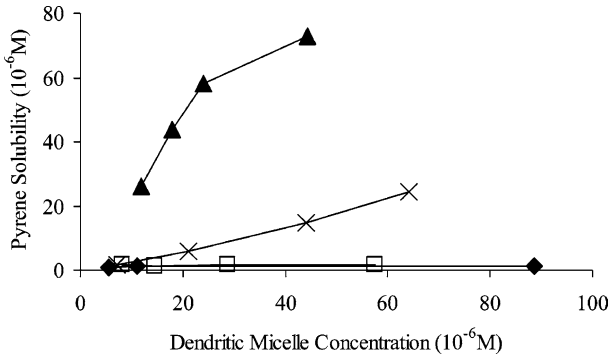

Figure 12. Effect of PEG arm length on the water solubility of pyrene: (♦) parent dendrimer, (□) micelle-750, (▲) micelle-2000, (×) micelle- 5000).[58] Reproduced with permission from Elsevier.

in solubility enhancement. They synthesized and characterized "amphiphilic dendrimers", so-called because these particular dendrimers exhibited both polar and nonpolar nanocontainer properties. The authors used a molecule called biaryl monomer having both carboxylic acid (as hydrophilic moiety) and a decyl chain (as hydrophobic moiety) as a repeat unit with 3,5-dihydroxybenzyl alcohol at the periphery. The dendrimers produced in this way were able to solubilize both hydrophobic and hydrophilic compounds. The third generation of this dendrimer was able to encapsulate 6.5 molecules of Reichardts dye, which is a hydrophobic dye. The solubility of a hydrophilic dye Proflavine in toluene was also increased using the same amphiphilic dendrimers. The authors believed that the amphiphillic dendrimer they synthesized could act as a micelle as well as a reverse micelle in respective solvents.[60]

Dendritic Prodrug. Propranolol is a poorly water-soluble drug. D'Emanuele et al. in a unique study reported solubility enhancement of Propranolol by chemically conjugating it with PAMAM dendrimers. The aqueous solubility of Propranolol increased by about 106-fold by conjugating it to G3 PAMAM dendrimers.[61]

Dendrimers "Locked in" Liposomes. Khopade et al. utilized the solubility enhancement of methotrexate by PAMAM den-

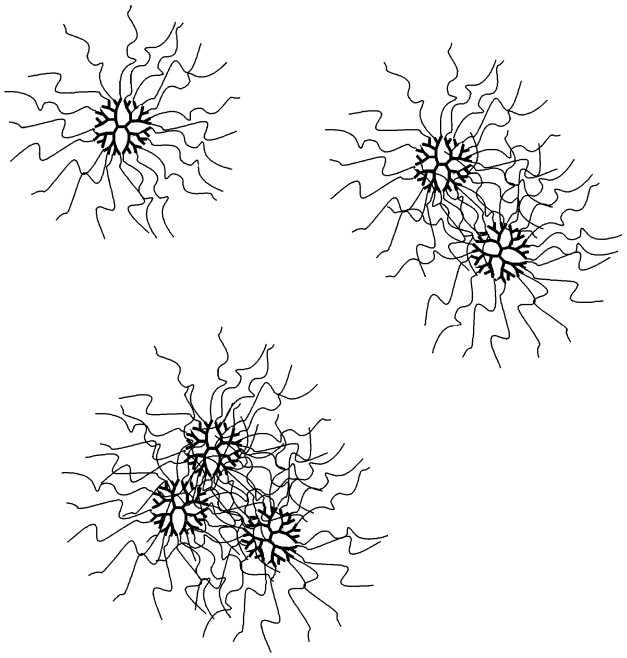

Figure 13. Two-dimensional schematic diagram of a unimolecular dendritic micelle, an agglomerate of two micelles, and an agglomerate of three micelles. (The long flexible lines represent PEG arms around a dendrimer surface, and inside are dendritic cores with 32 surface sites which are potential sites for conjugation with PEG arms.[58]) Reproduced with permission from Elsevier.

drimers for a novel purpose. Low entrapment efficiency of liposomes is their known limitation, and Khopade et al. entrapped PAMAM dendrimers in liposomes made up of phosphatidyl choline based on ionic interaction. This created the pH gradient within the liposome interior acting as a relatively basic sink due to presence of dendrimers and increased the influx of MTX (acidic in nature) into liposomal interiors. Solubilization of methotrexate in PAMAM dendrimers improved its entrapment in liposomes.[62]

Hydraamphiphiles. Chapman et al. reported the synthesis of amphiphilic copolymers derived from t-BOC-terminated poly-(α-ϵ-L-lysine) dendrimer and poly(ethylene oxide) (PEO). They termed it "Hydraamphiphile". The Hydraamphiphile contains three sections: one hydrophiphilic, one hydrophobic, and a central polar segment. An aqueous solution of G4 Hydraamphiphiles solubilized the dye Orange OT. The solubility of the dye showed a linear relationship with Hydraamphiphile concentration. The authors suggested that Hydraamphiphile could be useful in solubilization of both polar and water insoluble molecules.[63]

Inverted Micelles. Stevelmens et al. synthesized inverted dendritic micelles by conjugating long hydrophobic chains of alkyl acid chlorides ($ClCOC_n$ with $C_n = (CH_2)_{n-1}CH_3$ with $n = 5, 9-15$) with terminal amino groups of polypropylene imine dendrimers from 1 to 5 generation. The inverted micelles were able to solubilize hydrophilic Rose Bengal dye successfully.[28]

Nonpharmaceutical Applications

Apart from application of dendrimers in the pharmaceutical field, dendrimers have also been used as solubilizing agents in nonpharmaceutical areas. Neofotistou et al. used dendrimer solubilizing capacity as a tool in a desalination system. In this study, the ability of starburst PAMAM dendrimers (generation 0.5, 1, 1.5, 2, and 2.5) to inhibit scaling was investigated. It was clearly demonstrated that PAMAM dendrimers can be used to make silica more soluble and thus inhibit scale deposition. In general, the NH_2-terminated PAMAM dendrimer is reported to be a better inhibitor, i.e., can solubilize more SiO_2, in comparison to odd generation or COOH-terminated dendrimers. This was possibly due to more electrostatic interaction between positively charged $-NH_2$-terminated dendrimer with SiO_2, as compared to negatively charged −COOH-terminated dendrimer.[64]

Ogava et al. studied the potential of water-soluble dendrimers as a potential fluorescent detergent to form micelles at very low CMC. The self-assembly of pyrene-cored poly(aryl ether) dendrimers have been studied, and it was shown that poly(aryl ether) dendrimers act as surfactant, which aggregate at quite low concentration in aqueous solution (1.8×10^{-5} M) to form micelles. This was rather different from the CMC of usual detergents ($\sim 10^{-2}$ M). This ability of dendrimers was generation-dependent. A study on the use of dendrimers in a liquid extraction process based on its property to solubilize the hydrophilic compound in its interior is reported.[65] Cooper et al. synthesized a fourth generation hydrophilic dendrimer, DAB-dendr-$(NH_2)_{32}$, which was functionalized with a CO_2-philic shell derived from a heptamer acid fluoride of hexafluoro propylene oxide, $(CF_3\ CF_2\ CF_2\ (OCF\ (CF_3)\ CF_2)_5$. These dendritic surfactants were able to extract the hydrophilic compound methyl orange (an CO_2 insoluble dye) from an aqueous solution of liquid carbon dioxide.[66]

Conclusion

The hydrophobicity of a new chemical entity is a major drawback encountered during its product development and presents a major hindrance in achievement of satisfactory bioavailability. Hence, solubility enhancement of these hydrophobic drugs has always been a challenge to the investigators. The use of dendrimers as solubilizing agent has attracted the attention of many scientists due to its characteristic static micelle-like properties, which are different from those of conventional micelles. Range of dendrimers in their original or modified form has been tried successfully for enhancing solubility of hydrophobes. Studies comparing potential of dendrimers in solubility enhancement with micelles and cyclodextrins are available and suggest that dendrimers might prove significantly superior to both of these systems. The inherent toxicity of the amine-terminated dendrimers limits the clinical applications, yet due to its multifunctional nature, scientists have various options to overcome this problem. Studies are reported which show that masking the terminal amine groups by some means not only dramatically improved the efficiency of dendrimers in solubility enhancement but also made them more biocompatible. Various studies suggest that generation number, pH of the medium, size of dendritic microcavities, temperature, and dendritic architecture are the factors that influence the efficiency of dendrimers as solubilizing agent. Careful examination of available literature suggests that ionic interaction, hydrogen bonding, and hydrophobic interactions are the possible mechanisms by which dendrimers exert their solubilizing effect. Although a good number of studies investigating the effect of generation, pH, and concentration are available, the effect of core and temperature still largely remain uninvestigated. An alteration in core might have a dramatic influence on solubility as shown by the few available studies. This opens a possibility of trying newer materials as initiator cores to modulate the property of dendrimer as a container for hydrophobes. The scarcity of studies investigating the effect of temperature on dendrimer-mediated solubility enhancement is yet another aspect

which needs increased attention. As pharmaceutical products are manufactured and stored subject to various temperature conditions and they are exposed to 37 °C in the body, the necessity of relevant study design exploring these effects intensifies. The role of dendrimers in solubility enhancement can become meaningful only if it results in subsequent enhancement in drug bioavailability. A detailed experimentation correlating in vitro and in vivo performance of dendrimers can yield substantial information, which could be useful in their development as drug delivery devices. Finally, it can be concluded that in the form of dendrimers we have an immensely effective and versatile polymeric architecture for solubility enhancement.

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