REVIEW ARTICLE

Dendrimers - Reflections on host-guest interaction mechanism towards solubility enhancement

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Hydrophobicity of a bioactive is one area of major concern that poses as a great hindrance in the development of a therapeutically effective dosage form and prevents sufficient delivery of the drug to the target site. Since the last decade, dendrimers have emerged as highly promising drug delivery modules because of their unique structure and properties. Solubility enhancement is an important aspect of dendrimers and this is a synergy with site-specific drug delivery. The hydrophobic guests when entrapped in the hydrophobic channels of dendrimers are solubilized in the aqueous solution. The present article explores the various complex interaction mechanisms between the dendrimer and a bioactive. Hence the objective of this review is to reflect the host-guest interactions with the potential role of the proposed system, to enhance drug solubility and bioavailability.

Key words: *Dendrimer, host-guest interactions, solubilization*

INTRODUCTION

In the context of drug delivery, solubility issues are one of the major factors that are of concern for the development of pharmacologically effective dosage forms. The precise value of the solubility parameter of a drug is of significance, in terms of bioavailability. Lower solubility of a therapeutically active substance is often associated with bioavailability problems, lack of *in-vivo* and *in-vitro* correlation, lack of patient compliance, and inter-subject variations. These variations assume a practical significance for drugs with a low safety margin, for example, Digoxin. There are 40% new drugs / bioactives, which confine their possible application in formulation development, because of poor aqueous solubility and hydrophobicity. In order to acquire the desired bioavailability and subsequent therapeutic response, the drug must be soluble in aqueous solutions, which leads to its absorption at an optimum rate and extent and also facilitates the systemic delivery of the drug to the body. Solubility is an intrinsic physiochemical property of bioactives, which can be used to explain the drug action,[1] structure activity relationships,[2] drug transport kinetics,[3] and *in-situ* drug release profile.[4]

The therapeutic efficacy of any drug is often diminished by its incapability to gain access to the site of action and it is often in close proximity with poor solubility of the drug in the body's aqueous compartment. Various techniques have been proposed to overcome the solubility problems of therapeutic moieties. In this aspect a surfactant-based system and cyclodextrins (CDs) have been used to enhance the solubility and bioavailability. However, these systems have few shortcomings, including premature and incomplete release of the drug, due to their thermodynamic instability of micelles above the critical micellar concentration (CMC). Also, the solubilization capacity of unimolecular micelles is confined due to the conformational collapse of the hydrophobic core in aqueous media. However, dendrimers are better than conventional polymeric micelles because of their ability to maintain the micellar structure at all concentrations. All the conventional approaches of solubility enhancement have limitations, such as, nephrotoxicity of CDs, limited choice of co-solvents in cosolvency, limited pH dependence of drugs concerning solubility, and so on.[5] Some research groups had also studied microemulsion technology in order to develop formulations for hydrophobic drugs such as flurbiprofen. However, this technique was also not so successful owing to long-term stability problems associated with microemulsions.[6]

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To achieve good bioavailability, advances are being made with innovations in nanotechnology. Dendrimers are novel, synthetic, three-dimensional, highly branched, monodisperse, globular, nanopolymeric configurations, synthesized by repetitive sequence of reaction steps, giving a precise branching structure, having precisely placed functional groups.[7] These unique novel materials have emerged as potential drug delivery devices and a number of applications of dendrimers in the biomedical field have been reported, a major contribution being in the field of solubility enhancement.[8]

Dendrimers are one of the most researched macromolecules of recent times. Emergence of dendrimers was a phenomenon in the bulk of the published work in the last decade and has received much attention as controllable nanoscale vehicles. Polyamidoamine (PAMAM) and Polypropylene imine (PPI) dendrimers have been extensively explored for their role in drug delivery, and more importantly, are commercially available. Dendrimers are composed of a hydrophobic core and hydrophilic exterior functional moieties and hence they resemble the micellar architecture.[9] The groups present in the inner channels of dendrimers are called endo-receptors and those present on the surface are called exo-receptors[10] [Figure 1]. The hydrophobic core of the dendrimers imbibes them with the ability to encapsulate and carry hydrophobic guest moieties within their interior core. Hydrophilic terminal moieties of dendrimers make them soluble in aqueous and other polar media, while the core can solubilize hydrophobic small molecules without fear of change in their hydrophobic area. The solubilization process is normally reversible and the guest molecules are free to diffuse out of the micelles under favorable conditions. Owing to this reason, dendrimers can be of immense use for drug delivery. The utility of dendrimers has been explored as solubilizing agents. Several types of host-guest interactions have been involved in encapsulating the guest molecules within the core and the solubilization process.

In light of the above background and the potential upcoming role of the proposed dendrimers in enhancing drug solubility and bioavailability, this review explores the host-guest interactions and critically examines the postulated mechanisms of drug/hydrophobe-dendrimer interactions.

Host-guest interaction

The mechanisms for the host-guest interaction can be broadly grouped into two main classes: (a) covalent binding, in which the guest molecule forms a chemically bonded conjugate (involving hydrophobic interactions, physical entrapment, hydrogen bonding, or electrostatic bonding either alone or in combination with these methods), and (b) non-covalent binding, in which the guest physically interacts with the dendritic architecture[11,12] [Figure 2, Table 1].

Hydrophobic interaction

A hydrophobic interaction has been predicted to be a major mechanism involved in the interaction of a hydrophobic core of dendrimer with hydrophobic solute/drug molecules. A hydrophobic drug would be expected to associate with a dendrimer core to achieve maximum contact with its hydrophobic domain. Newkome *et al*., were the first to report this type of interaction in dendrimers, to solubilize hydrophobic solutes in aqueous media. The dendritic micelles consisted of a hydrophobic core (apolar core) derived from an alcohol unit and outer functionalities comprised of tetra methyl ammonium carboxylate ions. The system was found to enhance, by four times, the aqueous solubilities of hydrophobic solutes such as naphthalene and diphenylhexatriene.[13]

Naylor *et al*., investigated the hydrophobic interior binding properties of PAMAM dendrimers with methyl ester groups of acetyl salicylic acid and 2, 4 di chlorophenoxy acetic acid, and predicted that a similar mechanism was responsible for the increased solubility of the drug.[14]

Liu *et al*. reported that the hydrophobic model drug indomethacin was encapsulated in the hydrophobic core of the dendritic micelles and the drug could be released

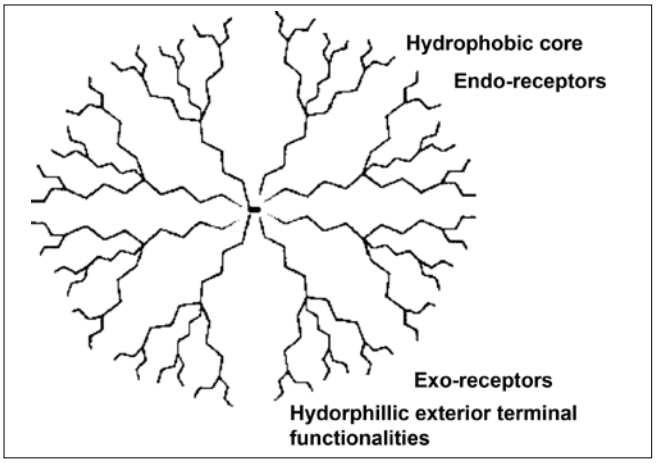

Figure 1: Structure of a typical dendrimer

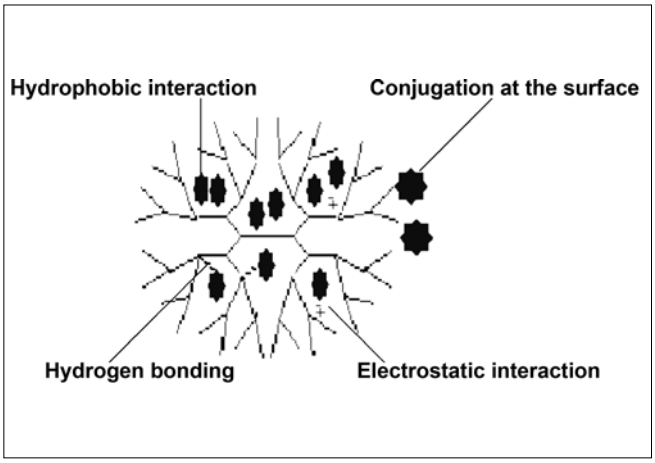

Figure 2: Dendrimers: As mediators for solubility enhancement

Table 1: Various mechanisms of solubility enhancement

Type of interaction	Dendritic system	Reference
Hydrophobic	Dendritic micelles	Newkome *et al*., 1991
	PAMAM	Naylor *et al*.,1989
	Dendritic micelles	Liu *et al*.,2000
	Polyaryl ether dendrimer	Hawker *et al*., 1993
	PAMAM	D'Emanuele *et al*., 2004
	PAMAM	Pistolis *et al*., 199
	Ester terminated PAMAM	Beezer *et al*., 2003
Physically locked in guest	PPI based dendrimer box	Jansen *et al*., 1995
	Ester terminated PAMAM	Prieto *et al*., 2006
	-OH-terminated PAMAM	Beezer *et al*., 2003
	-OH-terminated PAMAM and G4.5-PAMAM	Chauhan *et al*., 2003
	NH2-terminated PAMAM	Wiwattanapatapee *et al*., 1999
Hydrophobic and hydrogen bonding	Conjugated G3-NH2 PAMAM	Yang *et al*., 2004
Hydrophobic and hydrogen bonding	Mannosylated PPI dendrimer	Vijay Kumar *et al*., 2006
Hydrogen bonding	PAMAM	Yiyun *et al*., 2005
Hydrogen bonding	PAMAM	Devarakonda *et al*., 2004
	PAMAM	Santo *et al*., 1999
Electrostatic interaction	PAMAM	Milhem *et al*., 2000
	Amphiphilic PAMAM	Baars *et al*., 2000
	PAMAM	Kohle *et al*., 2003
	G4-NH2 PAMAM	Chauhan *et al*., 2004
	PAMAM	Namazi *et al*., 2005
	PAMAM	Asthana *et al*., 2005
	G0-PAMAM	Najlah *et al*., 2006
Electrostatic and hydrogen bonding	G4-PAMAM	Yiyun *et al*., 2005
conjugation	G4-OH PAMAM	Kolhe *et al*., 2006
	Acetylated and hydroxyl PAMAM	Patri *et al*., 2005
	Cyclic core dendritic polymer	Zhuo *et al*., 1999
Electrostatic entrapment	Positively charged PAMAM	Khopade *et al*., 2002
Hydrophobic interaction with liposome	Partial dendrimer or dendron	Purohit *et al*., 2001
Electrostatic and H-bonding	Dendriosomes	Al-Jamal *et al*., 2003
Encapsulation	PEGyated PAMAM	Kojima *et al*., 2000
	Peptide based PAMAM	Bhadra *et al*., 2003
	PEGylated lysine-based dendrimer	Bhadra *et al*., 2005

slowly in a sustained manner. The results showed that about nine to ten indomethacin molecules were loaded per dendrimer. It was indicated that the proposed system could be of potential application in controlled release delivery of the drug. The authors suggested that dendritic micelles were capable of enhancing the solubility and encapsulation of indomethacin.[9]

Hawker *et al.*, used a polyaryl ether dendrimer to solubilize a range of polycyclic compounds in aqueous media. Solubility enhancement was proposed to occur due to $\pi - \pi$ interactions. The authors also observed a linear relationship between solubilizing the capacity of the dendrimer and the amount of pyrene solubilized. The solubilization efficiency was comparable to that of sodium lauryl sulfate (SLS) micelles. Although the dendritic system could solubilize as low as 5×10^{-7} mol/L concentrations of pyrene, SLS required its critical micelle concentration (CMC), that is, (8.1×10^{-3} mol/L of pyrene). One molecule of dendrimer was able to solubilize approximately 0.45 molecules of pyrene.[15]

D'Emanuele *et al.*, recently reported solubility and bioavailability improvement of propranolol using PAMAM dendrimers. Poor water solubility and p-glycoprotein efflux transport mechanism were considered responsible for poor oral bioavailability of propanolol. Its aqueous solubility was significantly increased by about 106-fold using G3.0-PAMAM dendrimers. Dendrimers were hypothesized to be contributing to the manner of bypassing an efflux transporter, rather than inactivating it, and the increased solubility invariably improved the oral bioavailability. The efflux transporter inhibitors did not affect permeation of the dendrimer-propranolol complex, which supported the system to bypass the efflux transporter rather than block it.[16]

Pistolis *et al.*, postulated the hydrophobic binding of pyrene with terminal functionalities of PAMAM dendrimers. The aqueous solubility of pyrene was increased 10-fold (8.0×10^{-7} M to 7.6×10^{-6} M).[17] In another attempt Kumar *et al*, developed mannosylated PPI dendrimer for delivery of rifampicin. The authors observed that rifampicin solubility

was enhanced owing to hydrophobic interaction with the dendritic core. The work was performed in our laboratory.[18]

Physical locking for encapsulation

In this type of interaction the guest molecules (like hydrophobic drugs, etc.) get physically entrapped within the internal cavities of the host molecule, that is, dendrimers. The concept of the 'dendritic box' developed by Jansen *et al.*, 1994, conceives the mechanism of the physical entrapment of a guest molecule within the internal architecture of the dendritic box, and this has been explored during their formulation process, while entrapping the guest molecules in these boxes. The diffusion of guest molecules out of the dense surface shell of the boxes is prevented even during solvent extraction; sonication, and heating phenomena and the guest molecules can be released from the core of the dendritic box when the 'dense outer shell' is disrupted.[19]

The authors synthesized the dendritic boxes based on PPI dendrimers. The rigid shell was constructed through modification of outer amine functionalities of the PPI by the N-hydroxy succinimide ester of a tertiary butyloxy carbonyl (t-Boc). $^{1}H;^{13}C$ NMR, infrared, ultraviolet, and circular dichroism spectroscopy were used for structure elucidation of the modified dendrimers. The size of the fifth generation dendritic box was found to be 5 nm. Dendritic boxes encapsulated a large variety of dye molecules into their internal cavities, for example, Eriochrome black T; 7, 7, 8, 8-tetra cyanoquinodimethane (TCNQ) and Rose Bengal. It was found that Eriochrome black T displayed an increased solubility profile and its diffusion out of the box was unmeasurably slow due to close packing of the shell. In case of Rose Bengal one molecule was encapsulated per box. Moreover, the authors also proposed that the potential application with these systems might be in the studies concerning, photochemistry and photophysics of isolated molecules in a well-defined cage.[20]

In another approach, Esfand and Tomalia, studied the varying drug release profile of guest molecules from Dendrilock™, in which the terminal functionality of PAMAM dendrimers was modified as a congested dense outer shell. Guest molecules were captured within the Dendrilock™ and led to a slow release of guest molecules, yet, low generation dendrimer Dendripores™, with a less close packed surface, displayed time-dependent release of guest molecules.[21]

Hydrogen bonding interaction

Hydrogen bonding interactions are possible between guest molecules and suitable surface functional groups of dendritic micelles or the core. Hydrogen bonding or hydrogen bridge interactions are due to the small size of the hydrogen atom on both components and its large electrostatic field, which led to the movement toward the electrostatic atom. Hydrogen bonding interactions are ubiquitous in biological systems.

Newkome *et al.*, reported hydrogen-bonding interactions between the dendritic host and the guest molecules, such as, glutarimide and barbituric acid.[22] Furthermore, recently Prieto *et al.*, designed two dendrimer complexes with amine- and ester-terminated functionalities, namely, sulfadiazine-4.0G and Sulfadiazine-4.5G complexes, as potential candidates for antitoxoplasmic therapy. Two different mechanisms for solubility enhancement were pointed out by these dendrimers having amine- and ester- terminated functional groups. It was found that the solubility of sulfadiazine was increased linearly with increasing the dendrimer concentration. The proposed mechanism for interaction with ester-terminated dendrimers was hydrogen bonding, whereas, electrostatic interaction was a major mechanism for solubilization with amine terminated dendrimers.[23]

Beezer *et al.*,[5] and Twyman *et al.*,[24] synthesized hydroxyl-terminated dendrimers by reaction between ester-terminated PAMAM dendrimers and TRIS (tris hydroxymethylamino methane). The complex formation between the carboxyl groups of benzoic acid and internal tertiary nitrogens of the dendrimer was suggested to be due to hydrophobic and hydrogen binding. The authors concluded that solubility enhancement was possibly due to the ion pair formation between the acidic hydrophobe and tertiary nitrogens of the dendrimers. The internal tertiary nitrogens were strongly basic (pKa ~9.5), and hence involved in deprotonating the acidic guest molecules and this aptly increased the ability of the carboxylate or phenolate counter ions, to bind with the quaternized nitrogen dendritic cavities.

The role of dendritic architecture with uniformly positioned functionalities for the solubility enhancement of a hydrophobe has been reported by Chauhan *et al.* The phase solubility of indomethacin was examined using 4.0 G-NH_2, 4.0 G-OH, and 4.5 G-ester terminated PAMAM dendrimers. The authors suggested that hydrogen bonding was the possible mechanism by which G4-OH dendrimer exerted its solubilizing effect and improved the bioavailability of indomethacin in transdermal drug delivery applications.[25]

In another attempt, Wiwattanapatapee *et al.*, examined the solubility enhancement of the poorly water-soluble drug piroxicam. In this study, the pyroxicam molecules were complexed within the 3.0 G-NH_2 dendrimer by hydrogen bonding or electrostatic complexation. It was also reported that piroxicam molecules were not electrostatically complexed by 2.5 G-carboxylated dendrimer due to similar charge on the compounds. Solubility enhancement of piroxicam might be the consequence of increase in the pH of the solution by the highly basic dendrimer.[26]

Yang *et al.*, prepared a series of PEG-polyamidoamine unimolecular dendritic micelles by the conjugation of polyethylene glycol (PEG) of different molecular weights (750, 2000, and 5000) with 3.0 G-NH_2 terminated PAMAM dendrimers. It was found that

three mechanisms, that is, hydrophobic interaction between hydrogen bonding and acid base interaction were involved in increasing the solubility of pyrene. PEG arm length also played an important role in the solubility of the hydrophobe because an increase in arm length of PEG increased the steric hindrance in the coupling reaction. PEG 5000 with increased length of the PEG chain dendrimer displayed less solubility than PEG 2000 dendrimer, owing to its shell disruption caused by inter-penetration of individual micelles adjacent to each other. The PEG-2000 dendrimer displayed a higher capability of solubility enhancement of pyrene as compared to PEG-750 dendrimer because of a thick network of PEG chains at the dendrimer surface and a longer arm length.[27]

Very recently Kumar *et al.*, explored the potential of mannosylated PPI dendrimer for selective delivery of an anti-tubercular drug, rifampcin, to alveolar macrophages. Hydrogen bonding and hydrophobic interactions were the mechanisms by which the dendrimer complexed with rifampcin and the aqueous solubility increased two-folds. PPI of 5.0 G displayed higher aqueous solubility of rifampcin as compared to mannosylated PPI dendrimer. The authors suggested that it was possibly the increase in the steric hindrance on the surface of the mannosylated dendrimer that reduced the molecular gap present in the dendrimer. Deprotonation of hydroxyl groups present on the surface of the mannosylated dendrimer might also be the reason. Solubility enhancement of rifampcin was increased to a lesser extent because the protanoated/deporonated state of the dendrimer was one of the most important factors to affect the solubility of hydrophobes.[18]

Yiyun and Tongwen, used 1.0 G, 2.0 G, 3.0 G, and 4.0 G PAMAM dendrimers for solubilization of a water insoluble hydrophobe, nicotinic acid. It was proposed that hydrogen bonding between the tertiary amines of PAMAM dendrimers and hydrogen of pyridine moiety of nicotinic acid could be the possible mechanism for solubility enhancement. The authors pointed out that generation size, pH of the solution, concentration of the dendrimer, and surface area played a significant role in the nicotinic acid solubility.[28]

Devarakonda *et al.*, employed different generations of PAMAM dendrimers for solubility enhancement of a calcium channel blocking agent, nifedipine. Primary amines on the surface and tertiary amines in the internal cavities of the dendrimer could act as donors and acceptors of the hydrogen atom. Covalently bonded hydrogen with nitrogen in the dihydropyridine moiety of nifedipine could act as a hydrogen bond donor. Hydrogen bonding between primary nitrogen atoms on the dendrimer surface and hydrogen atom of nifedipine could be a major mechanism responsible for solubility enhancement. The authors also found that generation size, surface group, and pH of the medium significantly influenced the solubility of nifedipine. Ester-terminated PAMAM dendrimers were protonated to a lesser degree as compared to amine-terminated PAMAM dendrimers at pH 7.0. Hence, deprotonated tertiary amines in dendritic cavities were more available for hydrogen bonding with nifedipine and the aqueous solubility of drug was enhanced more in the case of ester-terminated PAMAM dendrimers. Both amine-and ester-terminated PAMAM dendrimers showed Higuchi A_L type of solubility profile at pH 4.0 and pH 10 values. Solubility of nifedipine increased in the following order 2.5 G > 3.0 G > 1.5 G > 2.0 G > 0.5 G < 1.0 G < 0.0 G. At pH 7.0, it was suggested that the proposed system offered designing the dendrimers as pH-dependent controlled release delivery systems.[29] Santo *et al.*, devised PAMAM dendrimers by hydrogen-bonding interaction of various biological molecules such as pyridine and trimethadione.[30]

Electrostatic interaction

Solubility enhancement was explored on the basis of electrostatic bonding of both the positively charged primary amines and tertiary amines of dendrimers, with negatively charged hydrophobes. It is one of the major interaction mechanisms between host and guest moieties in solubilization.

Studies by Milhem *et al.*, using an aqueous solution of 4.0 G PAMAM dendrimers and sodium dodecyl sulfate (SDS) showed that electrostatic interaction between hydrophobe and dendrimer was the major responsible mechanism for solubility enhancement. It was found that electrostatic bonding could result between the amine groups of the dendrimer and the carboxyl groups of ibuprofen at pH 10. The solubility of ibuprofen in the dendrimer solution was directly proportional to the dendrimer concentration and inversely proportional to the temperature. At pH 2, there were fewer chances that the ibuprofen molecules would interact electrostatically because its molecules remained in a unionization state.[31]

Electrostatic interaction of benzoic acid or salicylic acid with amphiphilic PAMAM dendrimer was demonstrated by Baars *et al.* Evidence of electrostatic bonding was monitored by ^{1}HNMR spectroscopy. The host-guest complexes were stable and considered as potential drug delivery systems.[32]

Kohle *et al.*, investigated the complex formation ability of PAMAM dendrimers with ibuprofen. These drug dendrimer complexes were stable and efficacious in deionized water and methanol over a period of eight hours. The mechanism of a complex formation was ionic interaction between the surface amino groups of G4 PAMAM and the carboxyl groups of ibuprofen molecules. It was reported that 32 and 78 drug molecules were incorporated per G3 and G4 PAMAM molecule, respectively. However, 24 drug molecules were encapsulated with hydroxyl terminated hyper-branched polyol. Drug dendrimer complexes followed a slow release pattern in RPMI 1640 culture medium. This result could be due to a high degree of ionic interaction and salt concentration.[33]

Chauhan *et al.*, explained solubility enhancement of poorly water-soluble drug indomethacin. The effect of three different PAMAM dendrimers on the aqueous solubility of indomethacin and the bioavailability improvement was investigated. Authors used G4.0-NH_2, G4.0-OH, and G4.5 PAMAM dendrimers and found the order of solubility enhancement of indomethacin as G4.0-NH_2 > G4.0- OH > G4.5. It was noticed that with amine terminated dendrimers the solubility was enhanced on the basis of electrostatic interactions between the carboxyl group of indomethacin and the amino groups of the dendrimer. In case of G4.5 PAMAM and G4-OH PAMAM the proposed mechanism was molecular encapsulation and hydrogen bonding, respectively. Ionization of primary and tertiary nitrogen was more at pH∼4.5 than at pH 7.0 and least at pH 10.5 because - NH_2 and > N- have pKa values of 7.9 and 6.5, respectively. Indomethacin (pKa∼4.5) was 50 and 99.7% ionized at pH 7.0 and 4.5, respectively. Therefore, electrostatic interactions could be held responsible for increasing the indomethacin solubility at the respective pH values. From this study with dendritic polymers it could be concluded that the proposed system displayed better drug- targeting efficiency to the arthritic regions with sustained drug delivery.[34]

Namazi and Adeli synthesized biocompatible G1.0, G2.0, and G3.0 dendrimers using PEG 600 as the core and citric acid as a branching unit. These triblock dendrimers have been successfully explored for the solubilization of various hydrophobes such as 5-amino salicylic acid (5-ASA), pyridine, mefenamic acid, and diclofenac. The role of dendrimers in the aqueous solubility of hydrophobes could be explored by electrostatic interactions. The electrostatic host-guest interaction was demonstrated by ^{1}HNMR studies and these versatile polymeric complexes were stable up to 10 months.[35]

Asthana *et al.*, highlighted the controlled site-specific delivery of flurbiprofen using the G4-PAMAM dendrimer. It was observed that the solubility of flurbiprofen in the G4-PAMAM solution increased linearly with an increase in dendrimer concentration. FTIR spectroscopy of drug dendrimer complex demonstrated the electrostatic bonding between the carboxyl group of flurbiprofen and the amino groups of the dendrimer. This proposed system was revealed to be effective in increasing the solubility and bioavailability of flurbiprofen.[36]

Najlah *et al.*, recently reported an electrostatic interaction of a poorly aqueous soluble drug naproxen with the G0 PAMAM dendrimer. Authors disclosed that drug dendrimer complexes were stable at pH 1.2, 7.4, and 8.5. These complexes were verified by the HPLC method and it was concluded that conjugates were able to solubilize and improve the bioavailability of naproxen.[37]

The ability of the G4-NH_2 PAMAM dendrimer to interact with the hydrophobic guest molecule was demonstrated by Yiyun and Tongwen. The aqueous solubility problem was overcome by this attempt. It was pointed out that electrostatic interactions as well as hydrogen bonding involved between the surface amino groups of the G4.0-NH_2 and the carboxyl group of the nicotinic acid were the possible mechanisms for solubility enhancement and the solubility increased in a linear manner with an increase in the dendrimer concentration.[38]

Drug-dendrimer conjugation

In addition to enhancing the solubility of a biopharmaceutical substance, drug dendrimer conjugation offers the drug, opportunities for controlled delivery of bioactives. Kolhe *et al.*, conjugated ibuprofen with the G4-OH PAMAM dendrimer via the ester bond. These conjugates yielded a high drug payload via the ester bond formation between the carboxyl group of ibuprofen and hydroxyl group of dendrimers. Up to 58 ibuprofen molecules were covalently conjugated with one G4.0-OH molecule upon conjugation to this dendrimer, and the carrier system showed an enhanced intracellular delivery. Also the conjugates of the analgesic agent could be utilized for site-specific targeting by attaching antibodies and ligands.[39]

Patri *et al.*, designed PAMAM dendrimers with covalently attached folic acid to target the anticancer drug, methotrexate. Acetylated and hydroxyl functionalized dendrimers enhanced the aqueous solubility of methotrexate via the formation of nonspecific "inclusion complex". It was demonstrated that covalently coupled drug dendrimer conjugates were stable in phosphate buffer saline and aqueous solution. These drug dendrimer conjugates were promising drug carriers for selective targeting, avoiding uncontrolled and premature delivery of the drug moieties in biological environments.[8]

Duncan and Malik, synthesized PAMAM dendrimer conjugates with cisplatin, a potent effective anticancer hydrophobe. It was demonstrated that conjugation improved the solubility of the drug in aqueous media and decreased its toxic side effect.[40]

Based on the time sequenced propagation technique, a series of dendritic polymers using cyclic cores of 1, 4, 7, and 10 tetrazacyclododecan (tetra-amine core) were synthesized by Zhuo *et al*. The conjugation of 5-Fluorouracil to the dendrimer periphery displayed enhanced solubility and sustained release behavior.[41]

Dendrimer-liposomes interactions

Electrostatic entrapment of dendrimer in liposome

An alternative approach to the development of dendrimers as anticancer drug carriers was explored by Khopade *et al.* The authors enhanced the entrapment efficiency of methotrexate in liposome using PAMAM dendrimers. Positively charged PAMAM dendrimers were electrostatically entrapped in negatively charged liposomes. It was pointed out that the pH gradient was created by highly basic dendrimers in the liposomal aqueous compartment and this increased the influx of methotrexate into the aqueous compartment of the

liposome. This interaction showed increased solubility of the water-insoluble drug, methotrexate, and led to an improved entrapment efficiency of the liposomes.[42]

Hydrophobic interaction of dendrimer-liposomes

Purohit *et al.*, synthesized partial dendrimers or dendrons (dendrimers having no branching core) and studied the interaction mechanisms with three different types of liposomes, namely, positive, negative, and neutral charges. Interaction / entrapment efficiency of partial dendrimers was maximum in the neutrally charged liposome, followed by the negative and positive charged liposomes. It was noticed that the possible mechanism of the interaction might be a hydrophobic interaction between the partial dendrimers and liposomes[43] [Figure 3].

Dendriosomes-drug interaction

Novel types of dendrons were created by stepwise solid-phase peptide synthesis, by Al-Jamal *et al*. These novel dendrons self assembled in water, forming vesicular structures and were termed as 'dendriosomes'. Cholesterol-free dendriosomes had higher entrapment efficiency as compared to dendriosomes with cholesterol. It was thought to be simply due to reduced drug accumulation at the dendron sites in the bilayers as a consequence of dendron replacements, since it was a potential site for electrostatic interaction or H-bonding, with cholesterol.[44]

Influence of dendritic architecture on solubility

With increase in the generation of dendrimers, there is an increase in void spaces within the core and hence the capability to encapsulate the drug molecules is enhanced. The solubilization or encapsulation of bioactives within the dendrimers and their controlled release is a phenomenon that depends on dendritic architecture [Figure 4, Table 2]. Effect of dendritic architecture on the solubility enhancement and controlled release of paclitaxel was investigated by Ooya *et al.* They synthesized the ethylene glycol-based, star-shaped dendrimers. The solubility of paclitaxel in 3.0 G, 4.0 G, and 5.0 G polyglycol dendrimers at a concentration of 10% w/w increased by 270, 370, and 430-folds, respectively. Star shaped poly oligo ethylene glycol methyl-acrylate (OEGPA) enhanced the aqueous solubility of paclitaxel by 130-folds. Hence it was clearly observed that 3.0 G, 4.0 G, and 5.0 G dendrimers were more effective than graft and star-shaped draft polymers. This difference in the paclitaxel solubility was due to the influence of the density of ethylene glycol chains. The release trend of solubilized paclitaxel was strongly dependent on the dendrimer generation, being highest for 5.0 G and lowest for 3.0 G polyglycerol dendrimers. On account of more solubilization capacity of 5.0 G as compared to 3.0 G, the highest release rate was achieved.[45]

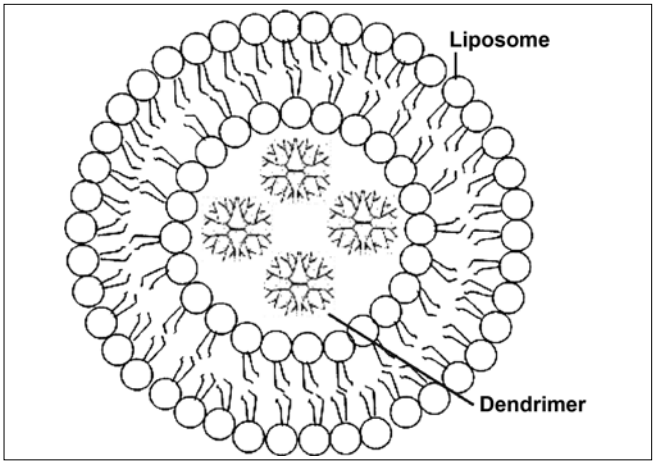

Figure 3: Dendrimer encapsulated within the liposome

Encapsulation of drug within PEgylated dendrimers

Modification of terminal functionalities of dendrimers with biocompatible polymers like PEG has been explored for solubilization and safe drug delivery [Figure 5]. Kojima *et al.*, prepared various formulations of water-soluble G-3 and G-4 PAMAM dendrimers coated with PEG, having different molecular weights (550 Da to 2000 Da). Methotrexate and adriamycin were successfully encapsulated in PEGylated dendrimers. It was found that the arm length of PEG on dendrimers influenced the solubility enhancement of methotrexate and adriamycin. Methotrexate molecules were encapsulated electrostatically by the acid-base reaction, while adriamycin molecules were complexed with polyethyleneglycol-monoethyl ether (MPEG) PAMAM dendrimers. *In vitro* studies showed sustained release of methotrexate from a dendritic carrier. Moreover, encapsulation ability increased with an increase in the dendrimer generation and molecular weight of PEG.[46]

Bhadra *et al.*, designed a peptide-based new class of PAMAM dendrimers for safe and effective delivery of 5-flurouracil. G4-NH_2 PAMAM dendrimers were PEGylated using MPEG-5000, and it was found that PEGylated dendrimers increased the drug loading capacity 12-folds. PEGylated Peptide-based dendritic nanocontainers displayed that they significantly increased the solubility of 5-fluorouracil

Table 2: Solubility enhancement of hydrophobes by various dendritic systems

Dendritic sysetm	Hydrophobe	Fold	References
Dendritic micelle	Naphthalene	4	Newkome *et al*., 1991
PAMAM	Propranolol	106	D'Emanuele *et al*., 2004
PAMAM	Pyrene	10	Pistilis *et al*., 1997
Mannosylated PPI	Rifampcin	2	Kumar *et al*., 2006
Polygycerol G-3, G-4, G-5 dendrimer	Paclitaxel	270,370,430	Ooya *et al*., 2003
PAMAM	Flurbiprofen	268	Asthana *et al*., 2005

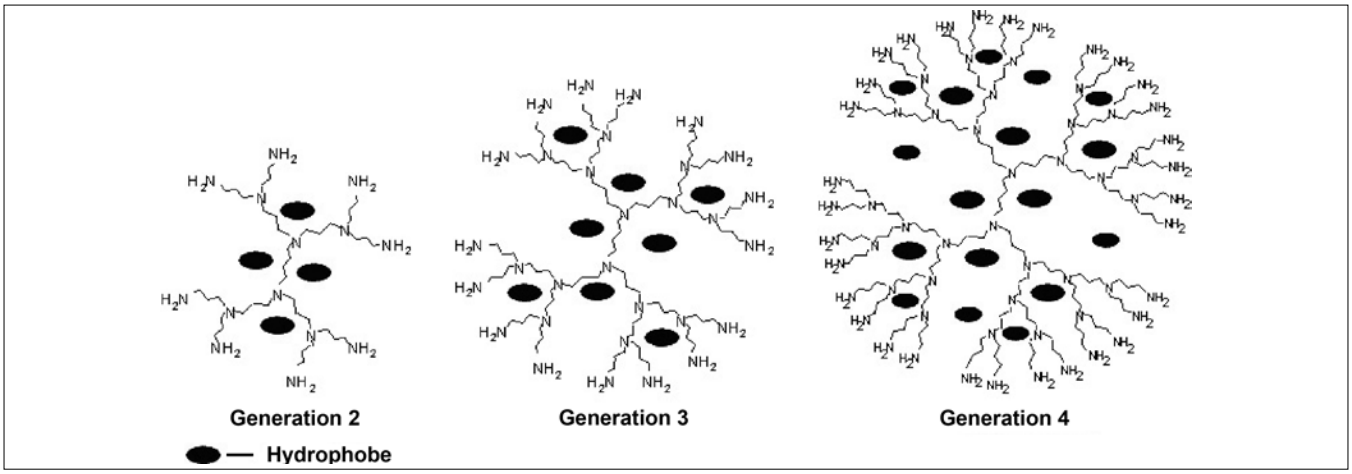

Figure 4: Increase in encapsulation efficiency with rise in dendrimer generation

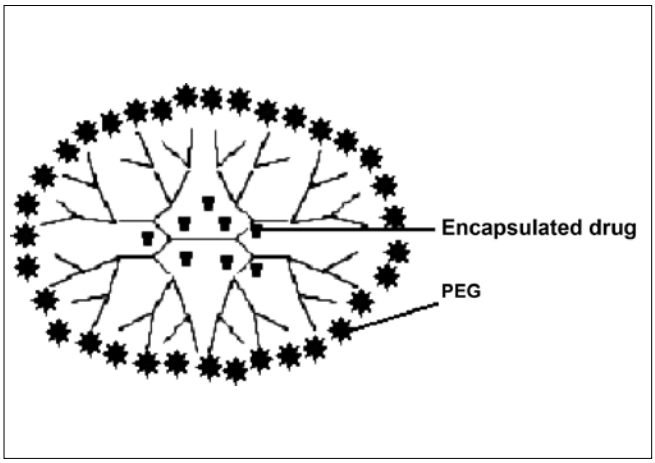

Figure 5: Pegylated dendrimer

and reduced the hemolytic toxicity as compared to simple dendrimers.[47]

CONCLUSION

The hydrophobic nature of any therapeutic moiety imposes a constraint in achieving the required bioavailability and has always been a matter of concern in the development of a new chemical entity. A number of drug delivery vehicles such as CDs, microemulsions, micelles, invert micelles, and so on, have been studied to overcome problems related to solubility of therapeutic substances. However, neither of them are predicted to be a very satisfactory tool in achieving the desired objective. Since the last decade dendrimers have emerged as promising tool for drug delivery. A variety of dendrimers in their original and modified form have been studied successfully to increase the solubility of hydrophobes. However, there is a need for further investigation on the effect of pH, temperature, and generation of dendrimers upon solubility of bioactives. Although a number of interaction mechanisms have been reported for solubilization of bioactives in dendritic cavities, this area still needs rigorous studies. Increased solubilization only matters when there is a subsequent enhancement of the bioavailability of bioactives at the desired site. Thus the potential of dendrimers in navigating the therapeutic moiety to the desired site and delivering the therapeutic payload at the target epitopes is also one area that is yet to be optimized.

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