RESEARCH ARTICLE

Synthesis and Characterization of Inclusion Complex of Carbamide with Extremely Branched, Globular, Mono-Disperse, Nanometric Starburst PAMAM Dendrimer

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All Dendrimers are the emerging polymeric architectures known for their defined structure, low polydispersity, nanometric size and high functionality. These nanostructure macromolecules have shown their potential abilities in entrapping and conjugating the high molecular weight hydrophobic or hydrophilic entities by host-guest interaction and covalent bonding respectively. Dendrimer is the irresistible candidature for the formation of inclusion complexes capable of accomplishing the various applications. This is due to the presence of various terminal groups with varied functionalities. PAMAM Dendrimer has been growing interest because of their unique characteristics like globular, nanoscale, macromolecule with different functionalities at periphery. PAMAM is comparatively novel group of these distinctive materials that is grown from the core side and each half or complete generation needs some repeating reactions. Also it has potential applicability in a wide range of areas makes it the promising candidate for lots of applications.Herein, we have synthesized Polyamidoamine (PAMAM) dendrimer of various generations and characterized by Fourier transform infrared (FTIR) spectroscopy and Mass spectrometry. The -0.5G PAMAM has differential functionality and special characteristics which allows the formation of inclusion complexes with various molecules. At this place, the inclusion complexes formed with carbamide molecules, which implant more functionality through host-guest interaction compared to the host molecules alone. Due to this modification in dendrimer variety of functional groups added to it which increases the hydrophilicity in -0.5G PAMAM and can become a promising candidate for lots of applications.

Introduction

Dendrimer are synthetic, nano-sized, three-dimensional, mono disperse, highly branched and new class of polymeric macromolecules. The size of dendrimers is in range of 1 to 15 nanometres. Structurally dendrimers has a great impact on their chemical and physical properties [**1**]. This Mono dispersed and highly branched macromolecules werefore mostly discovered by Fritz Vogtle in 1978, further worked by Donald Tomalia and Coworkers in the early 1980. In the same period George R. Newkone also discovered dendrimer [**2**]. The word 'dendrimer' coined from two words 'dendron' originally from the Greek meaning tree and another word 'meros' meaning unit or part. Together forms 'dendrimer' molecule like a part of a tree.The 'dendrimer' is mostly used term but another term 'cascade molecule' is also used but it is not as much established as 'dendrimer' **[3]**. Buhleier, Wehner and Vögtle [**4**] Tomalia, Baker, Dewald, Hall, Kallos, Martin, Roeck, Ryder and Smith [**5**] ,and Newkome, Yao, Baker and Gupta [**6**] were the first researchers who hoist the dendrimer chemistry . The terms arborols, hyperbranched polymers, arborescent polymers, and cascade molecules are handed-down till now, but "dendrimer" is well thought of now. Dendrimers are considered as the latest nano-tools to nano-encapsulate and deliver a wide spectrum of bioactives. In fact, dendrimers are artificial macromolecules, structuring like a tree in order to effectively encapsulate and deliver bioactive compounds. These macromolecules have been indicated as the "Polymers of the 21st century" [**7**]. According to Tomalia, dendritic structures categorized into four sub-classes that are random hyperbranched polymer, dendrigraft polymers, dendrons, and dendrimers**.** Among all the dendrimers poly(amidoamine) PAMAM dendrimer is used enormouslyas applying materials in supramolecular chemistry. PAMAM provides theperfect structure for the development of active drug carriers, gene transfer devices, host-guest interactions [**8**]. Dendrimer for solubility enhancement of the drugs came a long way in last 15 years. The complexation of water-insoluble molecules with dendrimer for increased solubility, highdrug loading, enhanced dissolution and increased physicochemical stability closely correlates the dendrimer potential as excipients. Dendrimer as solubility enhancers can be used through all possible drug delivery routes of administration [**9**]. Experimentally, dendrimers were introduced by Newkome and Tomalia and their initial publications suggested a plethora of applications including those related to controlled release of pharmaceuticals.

Now, almost 20 years later, this field of host-guest properties of dendritic molecules has grown into a special area of supramolecular chemistry [**10**]. Previous studies have demonstrated that polyamido-amine (PAMAM) and polypropylenimine (PPI) dendrimers form inclusions or ionic pairs with a list of drugs. Also the surface charge on dendrimers plays an important role in drug loading and release processes. The recent study provides a new insight into dendrimer-based host−guest systems, especially for those guest molecules bearing multiple charges [**11**]. Dendrimers are strongly and successfully proven as beneficial additives in drug delivery systems with different routes of drug administration because dendrimer has provided greater solubility of drugs in water and its biocompatibility. Dendrimers have very well defined guest entrapment properties. Dendrimers are very useful in pharmaceutical as well as non-pharmaceutical applications [**12-14**].

Among the various dendrimers, polyamidoamine (PAMAM) dendrimers are multifaceted materials and are capable of undergoing several interactions between their branch end groups and different functional materials. Due to their distinctive properties of regular structure, monodispersity, hydrophilicity, high mechanical and chemical stability, PAMAM dendrimers are regarded as eminent matrices for electrochemical applications [**15**].Linear Polymers, which are synthesized by classical polymerization process are generally having large or small branches and random in shape. In contrast, dendrimer has controlled size and the shape, which results in better physical and chemical properties. Special architectural structure of dendrimer makes it suitable for various applications in various fields of light harvesting materials, Drug delivery, chemical and fluorescent chemosensor, adhesives, etc. [**16**].

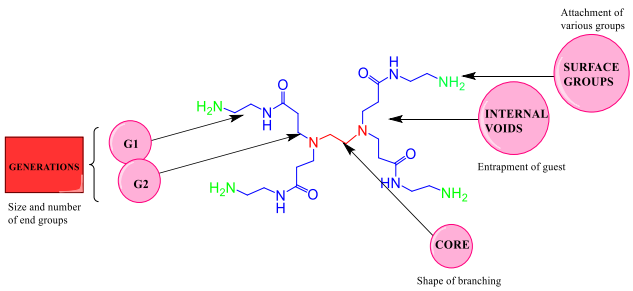


Fig. 1. Molecular Structure of PAMAM dendrimer.

Molecular structure of dendrimer

The typical dendrimer is comprised of three distinct parts, including a central core, generations i.e.; branches radially attached to central core and terminal groups consisting of various functional groups attached to outermost branches. Structurally dendrimer has a great impact on its physical and chemical properties [**17,18**]. As the functional group attached to the terminal branched is varied there is a variation in the chemical and physical properties of dendrimers. Multiple functional groups can be added in a single dendrimeric molecule to show the different properties. The internal generation form the interior cavities which are useful in encapsulation of various materials forming dendrimer composites [**19**]. A typical dendrimer structure consists of three components, namely;

- An initiator core determines the size and shape of the dendrimer;
- Interior layers or generations composed of repeating units, radially attached to the interior core, determines the amount of void space that can be enclosed by the dendrimer; and
- Exterior layer attached to the outermost interior generations, allows growth of the dendrimer or other chemical modifications [**20**].

The core structure includes cavities which build cages and channels to create the branching units easily and to accommodate the bioactive ingredients. The branches give some abilities to dendrimers such as high miscibility, solubility, and reactivity. The surface of dendrimers can be complexed with numerous active compounds; also, they are modifiable units [**7**].

The generation of dendrimer is hyperbranching when going from the centre of the dendrimer towards the periphery of the dendrimer, resulting in homostructural layers between the focal or branching points [**21,22**]. The number of focal points when going from the core of the dendrimer towards the dendrimer surface is the generation number, i.e. a dendrimer having four focal points when going from the centre to the periphery is denoted as the 4th generation dendrimer. Here, this term is abbreviated to simply a G4- dendrimer [**23,24**]. The Synthesis used for dendrimer synthesis allows the control over molecular design parameters like size and shape. Many synthetic techniques depend upon the chemical reactions like Williamson ether synthesis, Michael addition reaction [**25, 26**]. Divergent synthesis is a method where dendrimer is synthesized from its core to the terminal groups i.e.; it is initiated at the core and expand out to the terminal groups. The core molecule is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups, leading to the formation of first generation dendrimers. This process is repeated until the desired size of dendrimer is obtained [**25**]. This method was developed by Tomalia and newkomes in the early 1980. The mostly developed dendrimer from divergence in this is his polyamidoamine (PAMAM). The greatest disadvantage of this approach is that the incomplete growth and the side reactions lead to imperfect dendrimers. To reduce these side reactions and imperfections, it's recommended to use a large excess of reagents [**27**].

Poly (amidoamine) dendrimers can be called as PAMAM Dendrimer which was first synthesised by the divergent method. It is a major type of dendrimer. In PAMAM dendrimer ethylenediamine or ammonia is used as initiator core reagents. The PAMAM dendrimer has a generation level of range from 1 to 10 having diameter in a range of 1.5 nm to 14.5 nm. PAMAM Dendrimers are

commercially available as starburst PAMAM dendrimer by Dendritech. PAMAM dendrimer are widely used by researchers all over the globe to solubilise insoluble drug molecules such as Nifedipine and NSAID's [**27**]. Dendrimers have various applications in pharmaceutical and non-pharmaceutical industries. There are now more than fifty families of dendrimers, each with having unique and special properties. The surface, interior and core can be tailored to different sort of applications. Many potential applications of dendrimers are based on their molecular uniformity, multifunctional surface and presence of internal cavities. These specific properties make dendrimers suitable for a variety of high technology uses including biomedical and industrial applications.

Carbamide is employed as fertilizer providing nitrogen in soil for plants growth. Therefore, carbamide exhibits dual purpose of serving as a component of fertilizer for providing fixed nitrogen for growth of plants as well as host moiety for preparing inclusion complexes [**28**]. These host–guest complexes are based on the reversible association of a large, usually cavity-bearing, molecule (the "host") with a smaller molecule that is encapsulated within the host cavity (the "guest"). The interaction involves a complementarily between the physicochemical parameters of the cavity of the host (e.g., size, shape, charge, hydrophobicity) and the corresponding parameters of the guest molecule in order to ensure a good fit and a thermodynamically stable complex. Other paramount factors that can modulate the formation and stability of the host−guest complexes are the environmental conditions such as the solvent, pH, and temperature, which are frequently used to provide stimuli-responsiveness of the host−guest systems [**29**]. Guest-host chemistry in dendrimers is divided into endo or exo-complexation which is determined by whether the guest molecule is bound in the interior or to the surface of the dendrimer. Both types of guest-host chemistry have been a popular topic due to the potential applications in drug-delivery. Recently reported a study of endo-complexation of the γ-lactam antibiotic oxacillin in a G4 1,4-diaminobutane-core 1-(4-carbomethoxy) pyrrolidone functionalized PAMAM Dendrimer [**30**]. An Inclusion complex formation is totally based on the host-guest chemistry. An inclusion complex includes the two chemical compounds. The compound which has the cavity in it is called as host molecule and the other chemical compound which is accommodated in the cavity is called as guest molecule [**31**]. The more general term inclusion compound was introduced in 1952 by the German chemist Cramer. One of the salient features of Carbamide is to form inclusion complexes with various compounds [**32**]. Inclusion complexes formed with a host–guest molecule may exhibit ameliorate chemical or biological properties compared to the host molecule alone. Such as ameliorates aqueous solubility, dissolution, and bioavailability [**33**] Dendritic architectures are regarded as 'static unimolecular micelles' since they offer opportunities for various guest molecules to be solubilized via covalent or non-covalent complexation. Guest molecules can form non-covalent inclusion complexes with dendrimers where they interact electrostatically and hydrophobically -via ionic interactions, hydrogen bonding and Vander-Waals forces- with the surface functional groups and the internal tertiary amino groups of dendrimers [**34**]. There has been an immense interest in the use of dendrimers as hosts or carriers of a variety of guest molecules. host-guest chemistry involving dendritic hosts, the substrate was bound to the interior of the dendrimer, either non-specifically or by well-defined multiple hydrogen-bonding interactions as found in the 'dendroclefts' [**35**]. Inclusion complexes can be formed either in solution or in the crystalline state. Water is usually used as solvent, although inclusion complex formation also takes place in dimethyl sulfoxide and in dimethyl formamide [**31**].The physical entrapment of guest molecule takes place by depending upon dendrimer and drug type, involving the mechanism of electrostatic interaction, hydrophobic interactions, hydrogen bonding, either alone or all in combination [**36**]. Besides mixing molecular solutions of the host and of the guest, the neutralization, co-precipitation, slurry mixing, kneading and grinding are other common methods that can be used for generating host–guest complexes [**29**].

In the Present work, we elucidated the synthesis of different generations of PAMAM dendrimer. This synthesized dendrimers are used as host in our inclusion complex. The carbamide is used as the guest and novel inclusion complex of carbamide and dendrimer is synthesized. The synthesized Carbamide-Dendrimer inclusion complex is characterized using XRD, SEM, FT-IR techniques.

Experimental

Chemicals details

Chemicals used in the experiments were Ethylenediamine (Sigma Aldrich, Merck India Ltd., ≥ 99.5%), Methyl Acrylate (Sigma Aldrich, Merck India Ltd., 99%), Carbamide (Sigma Aldrich, Merck India Ltd., 99.5%), Methanol (Sigma Aldrich, Merck India Ltd., 99.8%), Copper Sulphate (Sigma Aldrich, Merck India Ltd., 98%). Allthe chemicals are of commercial grade and used without further distillation and purification. The reaction was monitored using the Copper Sulphate reagent which is 1% w/v with water.

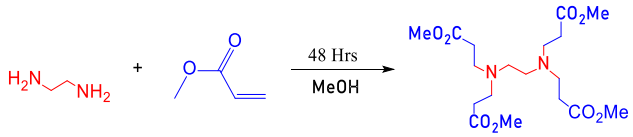
Material synthesis

The synthesis of PAMAM Dendrimer is done by two methods i.e., Divergent method and convergent method. In the laboratory scale the PAMAM Dendrimer is synthesised by the divergent method. In this method, synthesis is done from core to terminal groups. In this work Ethylenediamine is used as core. In the very first step Michael addition reaction is carried out, were the primary amine i.e., Ethylenediamine, the core is added to Methyl Acrylate forming the esters. The second step is

done to increase the generation of PAMAM dendrimer i.e., amidation of formed ester with Ethylenediamine.

Synthesis of -0.5 G PAMAM dendrimer

This synthetic technique leads to the synthesis of half generation of PAMAM dendrimer (-0.5 G). Here the starting material used is Ethylenediamine. The -0.5 G PAMAM dendrimer, the tetra ester is formed when each amino groups of Ethylenediamine is fasten by the four acrylate molecules (**Scheme 1**).

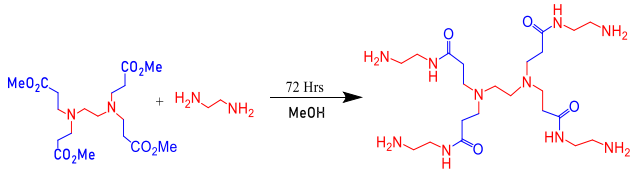


Scheme 1. Synthesis of -0.5 G PAMAM dendrimer.

Ethylenediamine (3.1 ml) dissolved in Methanol; in a RBF till fumes disappear. Methyl Acrylate (17.5 ml) dissolved separately in Methanol is added to Ethylenediamine solution drop by drop with constant stirring at Room Temperature. After complete addition, the formed solution is kept in a dark chamber for 48 hours at room temperature. Completion of reaction is monitored by Copper Sulphate reagent test. Once the reaction is completed, the excess Methyl Acrylate is removed using Rota Vacuum Evaporator at 60°C. The obtained product is -0.5 G PAMAM Dendrimer.

Synthesis of 0.0 G PAMAM dendrimer

This synthetic technique leads to the synthesis of full generation or zero generation of PAMAM dendrimer (0.0 G). In this the -0.5 G PAMAM dendrimer, the tetra ester formed in the first step is leading with amidation reaction. Thus tetra ester reacts with excess of Ethylene Diamine forming the 0.0 G PAMAM dendrimer, tetra amine (**Scheme 2**).

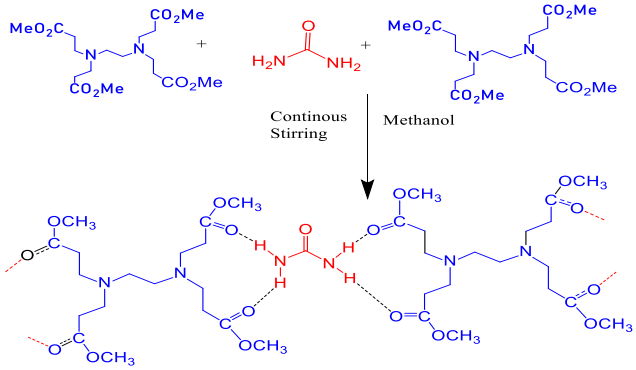


Scheme 2. Synthesis of 0.0 G PAMAM dendrimer.

-0.5 G PAMAM dendrimer (2.1 gm) dissolved in methanol in RBF. Ethylenediamine (39.6 ml) dissolved separately in methanol is added to -0.5 G PAMAM solution at Room temperature. After addition, the formed solution is kept in a dark chamber for 72 hours at room temperature. Completion of reaction is monitored by Copper Sulphate reagent test. Once the reaction is completed, the excess Ethylenediamine is removed using Rota Vacuum Evaporator at 116°C. The obtained product is 0.0 G PAMAM Dendrimer.

Synthesis of inclusion complex

The PAMAM dendrimer and Carbamide is reacted in methanol to form the Inclusion Complex (**Scheme 3**).



Scheme 3. Synthesis of inclusion complex.

-0.5 G PAMAM (1 gm) dendrimer is dissolved in Methanol (20 ml). In this solution the Carbamide is saturated with continuous stirring. This saturated solution is kept aside at room temperature for 24 hours. The obtained product is Inclusion Complex of Carbamide.

The same procedure is repeated for the 0.0 G PAMAM dendrimer.

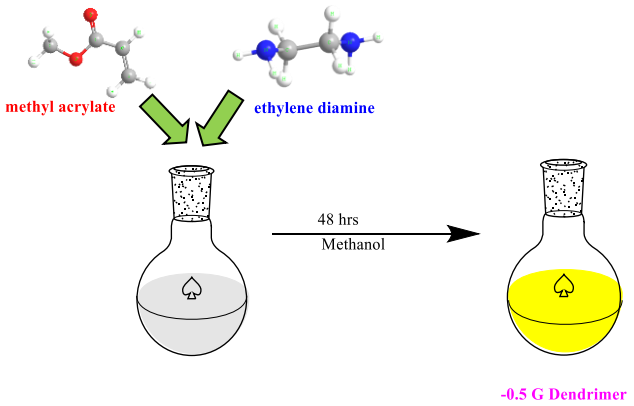


Fig. 2(a). Schematic image of synthesis of -0.5 G PAMAM dendrimer.

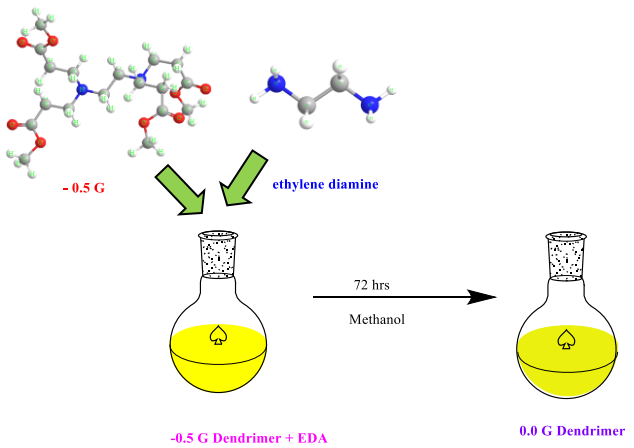


Fig. 2(b). Schematic image of synthesis of 0.0 G PAMAM dendrimer.

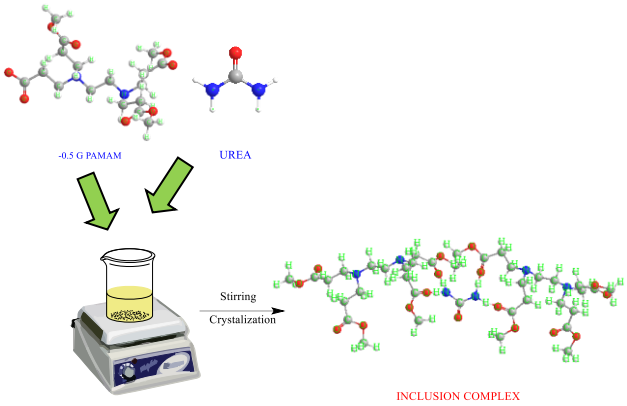


Fig. 2(c). Schematic image of synthesis of Carbamide-Dendrimer inclusion complex.

Characterizations

The structural characterizations were carried out by using SEM, FT-IR, LC-MS,X-ray diffraction techniques. The shape and structure of the sample was estimated by Zess Evo 18 Scanning Electron Microscope. The Absorption spectrum of the sample was recorded on Brucker FT-IR Spectrophotometer. The Mass spectrum of the sample was recorded from Shimadzu LC-MS Triple Quadruple. The crystal struture was determined from Rigaku's Miniflex 1800 X-ray powder diffraction also, the preliminary analysis of sample is done by copper sulphate reagent(1% w/v).

Results and discussion

The Preliminary assessment of the dendrimer is carried out by its physical characteristic like colour, state, also by the copper sulphate reagent test.

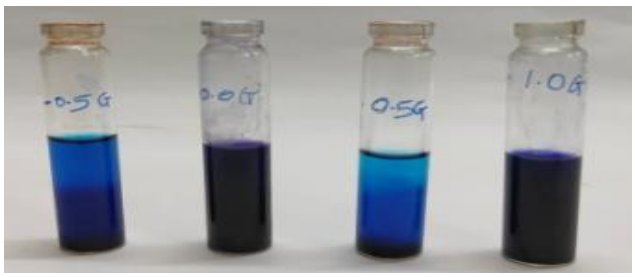


Fig. 3. $CuSO_4$ Reagent test for PAMAM dendrimer.

Table. 1. Physical Characteristic of PAMAM dendrimer.

Sr. No.	Generation of dendrimers	Molecular weight	Colour as concentrated	Physical state	Identific-ation by $CuSO_4$ Test
1.	- 0.5 G	405	Light Yellow	Oily	Deep blue
2.	0.0 G	517	Light greenish yellow	Oily	Violet

FT-IR spectroscopy

The most characteristic peaks of -0.5 G PAMAM dendrimers were at 1730cm^{-1} which indicates the presence of ester group. The Absorption peaks at 2952cm^{-1} and 2826cm^{-1} indicates the presence of aliphatic C-H stretching. The peak at 1194cm^{-1} indicates the C-C bending. Absence of N-H stretching shows that all -NH_2 of Ethylenediamine is consumed by acrylate moieties. Thus, indicates the formation of -0.5 G PAMAM dendrimer.The most characteristic peaks of 0.0 G PAMAM dendrimers were at 3354cm^{-1} which indicates the presence of N-H stretch of primary amine. The peak at 3280cm^{-1} shows the N-H stretch of secondary amine. The Absorption peaks at 2924cm^{-1} and 2854cm^{-1} indicates the presence of aliphatic C-H stretching. The peaks at 1654cm^{-1} indicates the presence of amide group. The presence of N-substituted amide is indicated by peaks at 1597cm^{-1}, 1447cm^{-1}, 1356cm^{-1}. The peak at 1036cm^{-1} indicates the C-C bending. The obtained results are given in table. The FT-IR spectra of -0.5 G and 0.0 G PAMAM is shown in figure.

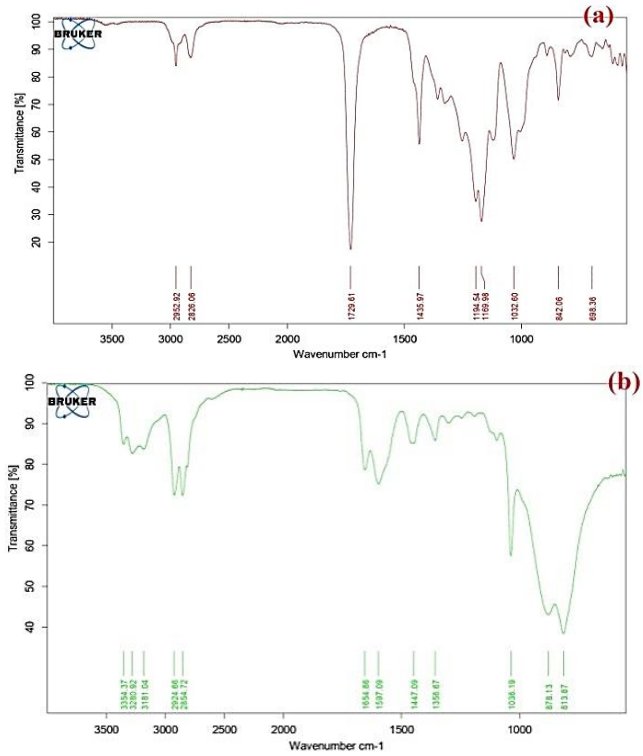


Fig. 4.1. IR Spectra for PAMAM dendrimers (a) -0.5 G (b) 0.0 G.

Table. 2. IR Interpretation of PAMAM dendrimers.

Genera-tion	S. No.	Peaksvalue	Interpretation
0.5 G	1.	1730 cm^{-1}	Ester group
	2.	2952 cm^{-1} and 2826 cm^{-1}	Aliphatic C-H stretch
	3.	1194 cm^{-1}	C-C bending
0.0 G	1.	3354 cm^{-1}	N-H stretch of primary amine
	2.	3280 cm^{-1}	N-H stretch of secondary amine
	3.	2924 cm^{-1} and 2854 cm^{-1}	Aliphatic C-H stretch
	4.	1654 cm^{-1}	Amide group
	5.	1597 cm^{-1}, 1447 cm^{-1}, 1356 cm^{-1}	N-substituted amide
	6.	1036 cm^{-1}	C-C bending

LC-MS spectrometry

The Molecular mass of the -0.5 G and 0.0 G PAMAM dendrimer were determined from the Shimadzu Triple Quadruple Spectrometer. The LC-MS analysis for -0.5 G PAMAM dendrimer $C_{18}H_{32}N_2O_8$ is (m/z), 405 $[M+1]^+$. The LC-MS analysis for 0.0 G PAMAM dendrimer $C_{22}H_{48}N_{10}O_4$ is (m/z), 517 $[M+1]^+$. The Mass spectra of -0.5 G and 0.0 G PAMAM are shown in figure.

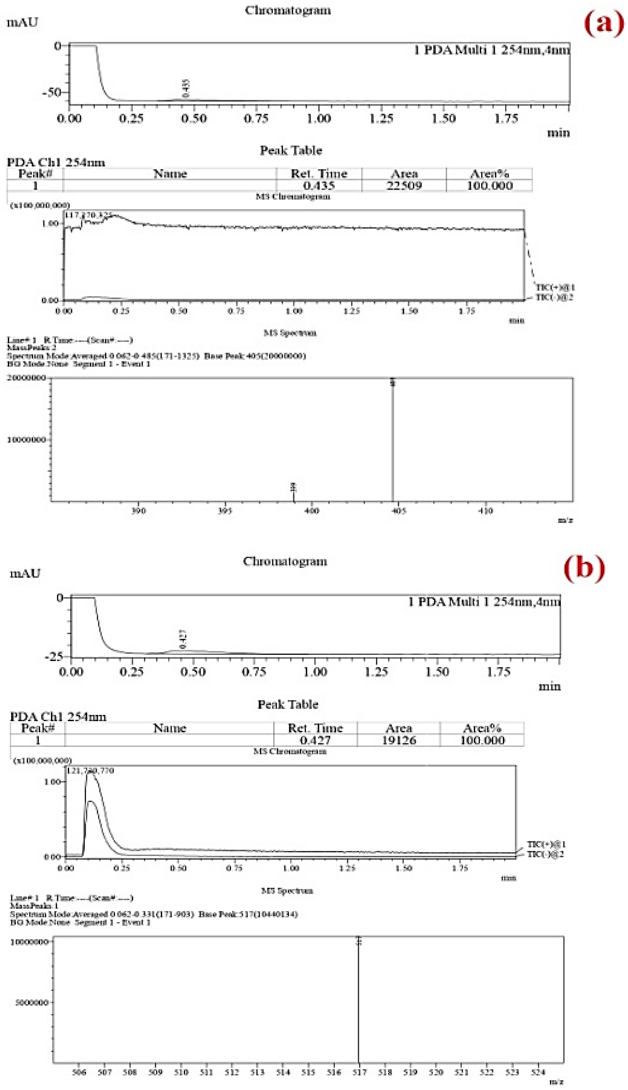


Fig. 4.2. Mass spectra for PAMAM dendrimers (a) -0.5 G (b) 0.0 G.

Analysis of inclusion complex of carbamide and dendrimer

The synthetic procedure for synthesis of Inclusion complex of carbamide was carried out with both the synthesised generations of PAMAM dendrimer i.e., -0.5 G and 0.0 G. Out of this two generations the -0.5 G which contains ($–COCH_3$) group at the periphery forms the Inclusion complex with carbamide, while the other generation 0.0 G which contains ($-NH_2$) group at the periphery fails forms the Inclusion complex with carbamide.

Fig. 5. Synthesised Carbamide-Dendrimer Inclusion Complex

Scanning electron microscopy

The Scanning electron Micrographs of the inclusion complex of carbamide with -0.5 G PAMAM dendrimer is shown in the figure. The Inclusion complex shows the needle like white coloured crystals.

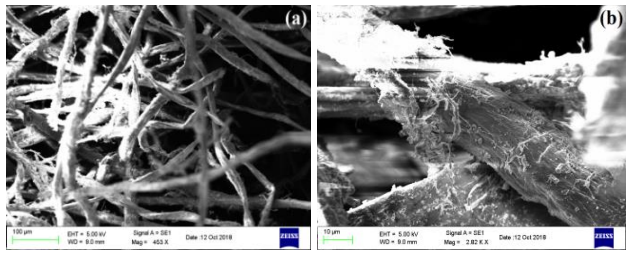


Fig. 6.1. (a), (b) SEM images of Carbamide-Dendrimer inclusion complex.

FT-IR spectroscopy

The most characteristic peaks were at 1730 cm^{-1} which indicates the presence of ester group. The Absorption peaks at 2952 cm^{-1} and 2826 cm^{-1} indicates the presence of aliphatic C-H stretching. The peak at 1194 cm^{-1} indicates the C-C bending. The absorption peak at 3345 cm^{-1} indicates O-H stretching.

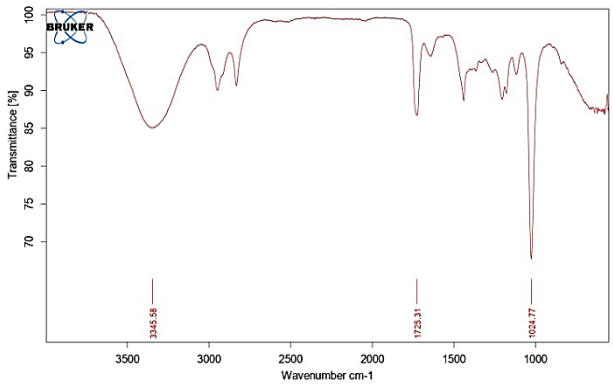


Fig. 6.2. IR Spectra of Carbamide-Dendrimer inclusion complex.

XRD diffractograms

The XRD patterns of the Inclusion complex of carbamide with -0.5 G PAMAM dendrimer is shown in the figure. The figure shows XRD pattern of prepared carbamide containing -0.5 G PAMAM dendrimer. The XRD analysis was done in RIGAKU-X-Ray diffraction. The Peaks are

well matched with standard Carbamide with reference code (00-001-0444).

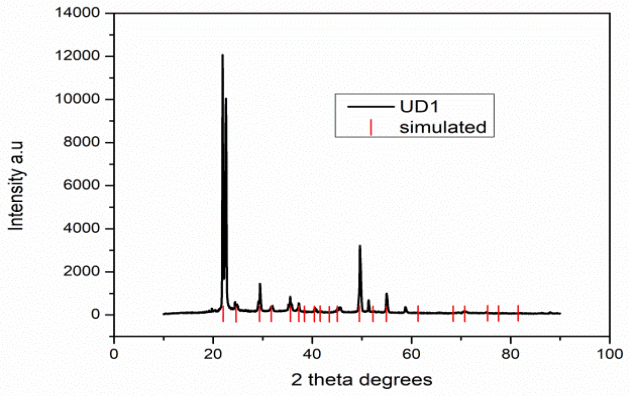


Fig. 6.3. XRD Pattern of Carbamide-Dendrimer inclusion complex.

Conclusion

The synthesised -0.5 G PAMAM dendrimer which has special characteristic like globular, nanoscale, macromolecule with different functionalities at periphery makes it a promising candidate for lots of applications. A novel Carbamide-Dendrimer Inclusion complex was successfully synthesized and characterized using SEM, FT-IR and X-Ray diffraction techniques. Synthesised dendrimer was characterized by FT-IR, LC-MS and at preliminary level by Copper Sulphate Reagent.

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Conflicts of interest

There are no conflicts to declare.

Keywords

Dendrimer, PAMAM, host-guest, inclusion complex.

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