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Review Article

SPECTROSCOPIC CHARACTERIZATION OF DENDRIMERS

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ABSTRACT

Dendrimers acclaimed its fascinating position in the nanoworld. By virtue of its unique polymeric architecture, it exhibits precise compositional and constitutional properties. Spectroscopy is a technique that uses the interaction of energy with a sample to perform an analysis. This review is a study of the main analytical techniques used for the characterization of the chemical composition, the morphology, the shape, the homogeneity of dendrimers, synthesis, conjugation, reaction rate, determination of the molecular weight, structural defects of dendrimer, determination of polydispersity and purity of dendrimers. It includes Ultra-violet–visible (UV–vis), Infra-red (IR), Nuclear Magnetic Resonance (NMR), Mass spectrometry, Raman spectroscopy, Fluorescence spectroscopy, Atomic Force Spectroscopy, X-ray photoelectron spectroscopy (XPS), Electron Paramagnetic Resonance (EPR) Spectroscopy, and X- Ray Absorption Spectroscopy. Dendrimer characterization with the help of spectroscopic techniques is very useful and has wide application in the field of dendrimer chemistry.

Keywords: Dendrimers, Conjugation, Analytical techniques.

INTRODUCTION

Dendrimers are branched, synthetic polymers with layered architectures[1]. Dendrimer is a carefully architected, highly branched and organized, polymer sphere. By virtue of its unique polymeric architecture it exhibits precise compositional and constitutional properties[2,3]. Dendrimers are hyper branched, highly ordered 3-D structure, having definite molecular weight, size, shape, in which all the bonds are converging to a focal point[4,5]. The size, shape, and surface properties of the polymer are used to modulate the pharmacokinetic and pharmacodynamic behavior of drugs conjugated with or encapsulated in the polymeric carrier. Recently, a class of well-defined, monodisperse, and tree-like polymers called dendrimers has attracted attention because of the flexibility they offer in terms of their size, shape, branching, length, and surface functionality[6, 7, 8]. Characterization of polymeric materials is vital for predicting and elucidating polymer properties and morphology until recently, no single technique could completely describe the above characteristics of a polymer sample. The word 'spectroscopy' is used as a collective term for all the analytical techniques based on the interaction of light and matter. Spectrophotometry is used for both qualitative and quantitative investigations of samples. The principal objective of the work presented here is to analytically characterize and investigate dendrimers using UV-Vis spectrometry, FT-IR spectroscopy, Differential Scanning Calorimetry (DSC), NMR spectroscopy, as well as ESI Mass spectroscopy, etc. Spectroscopy techniques are vital tools for analyzing dendrimer. This provides the information about the structure, reaction rate, appearance-disappearance-reappearance chemistry of characteristic peaks, conjugation etc[9].

Spectroscopy and Spectrometry

Various spectroscopy techniques used in dendrimer characterization are enlisted as:

1. Ultra-violet–visible (UV–vis)
2. Infra-red (IR)
3. Nuclear Magnetic Resonance (NMR)
4. Mass spectrometry
5. Raman spectroscopy
6. Fluorescence spectroscopy
7. Atomic Force Spectroscopy
8. X-ray photoelectron spectroscopy (XPS)
9. Electron Paramagnetic Resonance (EPR) Spectroscopy
10. X- Ray Absorption Spectroscopy

Dendrimers UV spectroscopy

UV-Vis spectroscopy is an important analytical tool for characterization of dendrimers. UV-vis range lies between 200-800nm. UV-Vis spectrometry provides the proof of synthesis as well as the conjugation (surface modification) on dendrimers due to characteristic absorption maximum or shift in value of lambda max (Bathochromic shift: Red shift). UV-Vis spectrometry is used to detect the functional moieties attached on dendrimer molecules. Characteristic curves in UV-Vis exhibits the specific maximum absorption peaks at specific wavelength, which is ascribed to the contribution of the conjugated moiety. This suggests the successful conjugation of surface modifiers to dendrimers[10]. UV-Vis is also used to determine the conjugation of dendrimer–star polymers, shifts in the peaks supports the conjugation[11]. UV method is also used for characterization of dendrimer-Gold Nanocomposite materials[12]. UV–Vis spectral studies shows reaction rate, attaching a solvatochromic probe at the core of dendrimers from G0 to G6 shows a dramatic change in the absorption maximum from G3 to G4, which is consistent with a transition from an open to a more globular shape[13].

Dendrimers IR spectroscopy

IR spectroscopy is an analytical method used in the determination of synthesis, for determination of functional group, conjugation and drug-dendrimer interaction of dendrimer. The infrared portion of the electromagnetic spectrum is usually in between 0.8-1000µm. In determination of drug dendrimer interaction by IR spectroscopy the identification of the vibrational signature of the drug–dendrimer interactions is only possible by comparison of the interacting systems to the spectra of the dendrimers and drug. Unfortunately, the vibrational investigation and structural understanding of PAMAM dendrimers is still very limited[14]. Appearance-Disappearance-Reappearance of characteristic peaks provides the proof of synthesis progress. Disappearance of nitrile groups in the synthesis of PPI dendrimers, Disappearance-Reappearance of amine groups in PAMAM dendrimers generation, Pegylation of PAMAM dendrimers, the occurrence of hydrogen bonding in PPI glycine functionalized dendrimers, or the disappearance of the aldehydes during the synthesis of PMMH dendrimers reflects the synthesis and surface modifications[15, 16, 17].

Dendrimers NMR spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy is valuable technique in the characterization of dendrimers. Nuclear magnetic resonance (NMR) spectroscopy permits determination of the structure and dynamics of molecules in solution. PAMAM dendrimers and complexed PAMAMs are characterized by Rotational-Echo Double Resonance (REDOR) solid-state NMR spectroscopy[18]. One-dimensional (1D) and two-dimensional (2D) NMR studies are used to probe the conformation of a melamine dendrimer bearing unique NMR signals from the core to the

periphery[19]. ^{31}P NMR was utilized for phosphorus dendritic structures, their characterization and to ascertain their purity. High-resolution solution NMR spectroscopy is used to characterize the structure of Pd dendrimer-encapsulated nanoparticles (DENs). If heteroatoms are present in the dendrimer scaffold then not only ^{1}H-NMR and ^{13}C-NMR spectroscopy but also other NMR techniques (e.g. 15N, 19F, 29Si, and 31P) can be used for characterizing dendrimers**.** Characterization of dissolved dendrimers by routine (1D)-NMR spectroscopy becomes increasingly difficult with increasing generation number[20].

Multidimensional NMR spectroscopy ((2D)-NMR, (3D)-NMR) is also acquiring increasing importance in the characterization of dendrimers**.** NOESY experiments permit quantitative determinations of internuclear distances for nuclei in different parts of the dendrimer molecule. In the interpretation of (2D)-NOESY (NOESY=nuclear Overhauser enhancement spectroscopy) spectra, a knowledge of the spatial interrelationships between protons in different parts of the dendrimer scaffold can be acquired from proton-proton NOE interactions. Principal use of diffusion NMR in dendrimer chemistry is for size determination of dissolved dendrimers[21].

Table 1: Applications of spectroscopic techniques in dendrimer characterization

Analytical Techniques	Interpretation
Dendrimers UV spectroscopy	-Synthesis [Characteristic curves exhibits the specific maximum absorption peaks] [10]. - Conjugation(surface modification) [Shift in peak] [11]. -Reaction rate [12, 13].
Dendrimers IR spectroscopy	-Synthesis [Characteristic peaks corresponding to functional groups] [14]. -Conjugation (surface modification) [Shifts in Characteristic peaks corresponding to functional groups) [15]. -Appearance-Disappearance-Reappearance chemistry of characteristic peaks [16, 17].
Dendrimers NMR spectroscopy: ^{1}H-NMR and ^{13}C-NMR Rotational-Echo Double Resonance (REDOR) Solid-state NMR spectroscopy One-dimensional (1D) and two-dimensional (2D) NMR (2D)-NMR-techniques [e.g. (2D)-NOESY, (2D)-TOCSY (TOCSY=Total Correlation Spectroscopy) NMR Diffusions NMR spectroscopy (e.g. PGSE = Pulsed Gradient Spin Echo; STE = Stimulated Echo; DOSY = Diffusion Ordered Spectroscopy)	-Synthesis of dendrimers [Characteristic peaks in the spectra] [18]. -Conjugation chemistry [shielding deshielding effects shifts in peaks] [19]. -Hydrodynamic radii [NMR pulse-field gradient spin–echo] [19]. -Number of protons [intensity of peaks and integral value] [20]. -Conformational changes [unique NMR signals from the core to the periphery] [One-dimensional (1D) and two-Dimensional (2D) NMR.] [20]. (i)Isomer populations observed by 1 H NMR reveal the onset of globular Structure. (ii)NOE complexity emerges with globular structure: variable temperature NOESY studies show that the peripheral groups. (iii)Variable temperature coefficients measured for NH protons suggest that solvent is largely excluded from the interior of the dendrimer [20]. -Relaxation studies show that peripheral groups are more dynamic than groups at the core [21]. -Mobility of group [Relaxation times (T1) measurement by lH- and 13C NMR] Since the mobility of a dendrimer segment is proportional to its T1 value 21. -Encapsulation and extraction [Increase in the NMR intensity in 1D and 2D NMR spectra] [21].
Mass spectroscopy: MALDI-TOF-MS ESI-MS	-Determining the molecular weight [22]. -Structural defects in dendrimers [23]. -Determination of the polydispersity [24]. -Purity of dendrimers [24].
Raman Spectroscopy	-Structure [25]. -Librations of terminal groups in dendrimers [26]. -Interaction between PAMAM dendrimer with lipid membranes [27, 28].
Fluorescence Spectroscopy	-Binding to PAMAM dendrimer /interaction, polymer binding mode, the binding constant /complexation [29]. -The size and shape of the molecules [30]. -Peripherally modification [30].
Atomic Force Spectroscopy	-Characterize the structure [31]. -Interaction of the different dendrimer therapeutics with a lipid bilayer, behavior of the dendrimer agents [31].
X-ray Photoelectron Spectroscopy	-Elemental composition [32, 33]. -Empirical formula [34]. -Chemical state [35]. -Thickness of one or more thin layered dendrimers [36, 37].
Electron Paramagnetic Resonance Spectroscopy.	-Determining the numbers [38]. -Distributions of numbers [39]. -Spatial distribution of molecule [40].
X-ray Absorption Spectroscopy (XAS)	-Structural information [41]. Local geometric and electronic structures [41].

Mass spectroscopy

Mass spectroscopy is an analytical technique that measures mass to charge ratio of charged particle. The powerful capabilities of Matrix Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) Mass Spectrometry is realized with the fast and accurate determination of molar masses, the sequencing of repeat units, and recognition of polymer additives and impurities[22, 23].

MALDI-TOF-MS and ESI-MS number among the few analytical methods suitable for detailed studies of structural defects in dendrimers on the basis of characteristic fragmentation pattern.

It is used in the determination of the polydispersity and the purity of dendrimers, which is defined as the percentage of defect-free dendritic material.

Mass spectroscopy is used in the determination of fragmentation pattern of different dendrimers. Fragmentation of different generations of poly (amidoamine) dendrimers was explored in five common MALDI matrices: 2, 5-dihydroxybenzoic acid (DHB), 4-hydroxy-3-methoxycinnamic acid (FER), a-cyano-4-hydroxycinnamic acid (ACH), 2, 4, 6-trihydroxyacetophenone (THAP), and 3-hydroxypicolinic acid (HPA). Determining the molecular weight of the higher-generation dendrimers are under way using MALDI TOF mass spectroscopy, GPC analysis and Diffusion-ordered NMR spectroscopy (DOSY NMR)[24].

Raman spectroscopy

Raman spectroscopy is a spectroscopic technique used to study vibrational, rotational, and other low-frequency modes in a system[25]. Raman spectroscopy give relevant information about the degree of cyclodehydrogenation of polyphenylene dendrimers and the characterization of PPI and phosphorus dendrimers[26].The low frequency Raman spectra in $R(\nu)$ representation is used to investigate the librations of terminal groups in dendrimers. FT-Raman spectroscopy provides unique detailed information about the structure of the technologically relevant materials[27]. Raman spectroscopy is used in determination of interaction of PAMAM dendrimers with lipid bilayer. Raman spectroscopy were applied to assess the thermodynamic changes caused by PAMAM G4 and G3, and to specify the exact location of these dendrimers into the DPPC lipid bilayer. This study is helpful to rationally design new liposomal drug carriers for bioactive molecules by combining dendrimeric and liposomal technologies[28].

Fluorescence spectroscopy

Fluorescence spectroscopy is a type of electromagnetic spectroscopy which analyzes fluorescence from a sample. Fluorescence spectroscopy provides valuable information regarding the interaction between the drug and dendrimers. Size and shape of molecules can be determined with the help of fluorescence spectroscopy[29, 30].

Atomic force microscopy (AFM)

AFM provides a three-dimensional surface profile and better resolution. Atomic force microscopy (AFM) is a very useful technique to characterize the structure, Interaction of the different dendrimer therapeutics with a lipid bilayer and behavior of the dendrimer agents. Polyamidoamine dendrimer modified multi-walled carbon nanotubes (dMNTs) was fabricated and characterized by AFM [31].

X-ray photoelectron spectroscopy (XPS)

X-ray photoelectron spectroscopy (XPS): XPS is also known as ESCA, an abbreviation for Electron Spectroscopy for Chemical analysis[32]. X-ray photoelectron spectroscopy (XPS) is a quantitative spectroscopic technique utilized to measures the elemental composition, empirical formula, chemical state, thickness of one or more thin layered dendrimers (1–8 nm) and electronic state of the elements that exist within dendritic framework[33]. Specific groups of starburst macromolecules such as P = S, aromatic rings, C-O, and C = O can be identified and characterized by X-ray photoelectron spectroscopy (XPS). Synthesis, characterization of melamine-based dendrimers, NiSn Dendrimer, electro catalysis using Pt and Pd dendrimer, Immobilization of Poly (amidoamine) dendrimers can be performed[34, 35, 36, 37].

Electron Paramagnetic Resonance (EPR) Spectroscopy

Electron paramagnetic resonance (EPR) or electron spin resonance (ESR) spectroscopy is a technique for studying chemical species that have one or more unpaired electrons, such as organic and inorganic free radicals or inorganic complexes possessing a transition metal ion. EPR is found useful for dendrimer characterization-specifically, for determining the numbers, distributions of numbers, and spatial distribution of molecule[38, 39, 40].

X-ray Absorption Spectroscopy (XAS)

X-ray absorption spectroscopy (XAS) is a widely-used technique for determining the local geometric and/or electronic structure of matter. X-ray absorption spectroscopy (XAS) is a characterization technique used to determine structural information of a compound. It is specific for finding the *local* geometric and electronic structures [41].

CONCLUSION

A spectroscopic technique has vast application in the field of dendrimer characterization. UV-Vis spectrometry provides the proof of synthesis as well as the conjugation (surface modification) on dendrimers. Appearance-Disappearance-Reappearance of characteristic peaks in IR spectra provides the proof of synthesis progress. Nuclear magnetic resonance (NMR) spectroscopy permits determination of the structure and dynamics of molecules in solution. PAMAM dendrimers and complexed PAMAMs are characterized by Rotational-Echo Double Resonance (REDOR) solid-state NMR spectroscopy. MALDI-TOF-MS and ESI-MS number among the few analytical methods suitable for detailed studies of structural defects in dendrimers on the basis of characteristic fragmentation patterns. Thus combination of all spectroscopic techniques is vital tool for the characterization of dendrimers in the era of this new molecular chemistry world.

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