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Role of Paclitaxel Nanocrystal Dendrimer for Cancer

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ABSTRACT

Cancer is now the second leading cause of mortality in the United States, after only heart disease. In this regard, the usage of dendrimers including medicines non-covalently encapsulated inside the dendrimer or covalently attached has been demonstrated to be effective against several cancer cell lines. Dendrimers are colloidal polymeric molecules with a specified size that are recognized and controlled by generations of repeating units. Dendrimers have a geometric form and size that is extremely similar to colloidal particles, which is particularly apparent in the upper generations of colloidal dendrimers. These macromolecules, on the other hand, have distinctive structural properties that make them seem like macromolecular colloids. However, developing and testing novel dendrimer drug carriers remains an essential tool in cancer treatment. We discussed in this review the work done with a specific emphasis on the development of dendrimers as a key instrument in the combination with pharmaceuticals, as a possible supplementary agent in anticancer therapy, given the ongoing efforts and research in this area of interest.

INTRODUCTION:

Cancer is a leading cause of death and is predicted to become much more so in the future decades. In 2012, an estimated 14.1 million individuals were diagnosed with cancer, with 8.2 million dying as a result [1]. Lung cancer, liver cancer, and stomach cancer are the most prevalent causes of mortality in the United States, with heart disease being the only cause of death that is more common [2].

Physical, chemical, genetic, or biological variables can promote cancerous cell growth. The illness can manifest itself in a variety of ways, but its underlying pathophysiology involves abnormalities in the molecular machinery that controls the cell cycle, resulting in deregulations. Because a single somatic mutation is insufficient to cause cancer, genetic progression is defined as the accumulation of subsequent mutations. The loss of various controls imposed by the three gene categories: oncogenes, cancer suppressor genes, and apoptosis regulatory genes are required for a tumour to emerge; the accumulation of these mutations is a result of the aberrant cells' genetic instability [3].

Among the proteins that govern the cell cycle and are changed is Cyclin D, which is elevated in a variety of cancers, including stomach and esophageal cancers [4]. The oncoprotein E7, which, like the cyclin D / CDK complex, can block the function of the retinoblastoma protein, a tumor suppressor protein that is altered in many types of cancer by promoting the cell cycle, increases in cases of human papillomavirus (HPVs, human papilloma-viruses) 16 or 18, which are the main cause of cervix cancer in women [5]. Cells overexpressing c-myc are resistant to growth arresting effects promoted by the transforming growth factor β (TGFβ) which induces the expression of p15, p21, and p27 (the same c-myc repressed CKIs). This situation is also found in approximately 80% of cervical tumors [6], and the p53 gene is mutated in half of the known human cancers (of liver, skin, lung, etc.). Myeloid leukemias are part of the other fifty percent where there are no mutations in this gene [7].

Targeted treatment is gaining popularity these days due to its ability to target cancer cells while avoiding damage to non-target cells. Targeted treatment entails the development of medications that inhibit cancer cell growth, enhance cell cycle regulation, or trigger apoptosis or autophagy, as well as the delivery of hazardous compounds to cancer cells selectively to kill them [8]. These highly specific medicines should be able to act on certain proteins or pathways that are overexpressed or abnormal in cancers. This selectivity to destroy tumor

cells is vital to prevent the side effects associated with classic chemotherapies while also improving antitumor activity [9].

Chemotherapy has a nonspecific distribution, with only a tiny proportion of the medication reaching the tumour. Pharmacokinetic factors such as absorption, distribution, metabolism, and elimination (ADME) dictate the quantity of drug and/or active metabolite reaching the tumour [10]. Drug metabolising enzymes and transporters expressed in several organs, including the small intestine, liver, and kidney, are involved in ADME. Xenobiotic-metabolizing enzymes like cytochrome P450 isoforms, in particular, play a vital role in drug metabolism, while transporters like ATP binding cassette (ABC) and solute carrier (SLC) transporters have a significant influence on drug absorption, distribution, and excretion. Drug interactions with enzymes/transporters ultimately dictate pharmacokinetic features, which in turn influence pharmacodynamics. [11]

The mononuclear phagocyte system (MPS), which is made up of monocytes and macrophages in organs like the liver, spleen, lungs, and bone marrow, is well recognized for sequestering injectable materials. Indeed, once in the circulation, unmodified nanoparticle surfaces are swiftly opsonized and removed by the MPS organs' fixed macrophages [12]. As a result, the medications build up in healthy organs, increasing their toxicity and blurring the boundary between tolerance and severe morbidity, as in the case of doxorubicin, a DNA intercalating agent that causes cardiotoxicity [13].

Furthermore, cancer cells have their pH gradient, which creates an environment that is more acidic extracellularly and more alkaline intracellularly. By blunting the immune system, activating endogenous immunosuppressive mechanisms, and suppressing the proliferation of the normal cell population, the tumour micro-environment improves tumour fitness. Furthermore, the tumour microenvironment inhibits the actions of various chemotherapeutic drugs, resulting in drug resistance and failure, either by disrupting drug partitioning, sequestering it intracellularly, or inducing multidrug resistance expression [14]. All of these variables obstruct anticancer medications' ability to repair the tumour, prompting the hunt for more effective drug delivery methods [15].

Paul Ehrlich popularized the term "magic bullet" to describe chemotherapy in light of these limitations. Nanoparticles of $Fe_4[Fe(CN)_6]$, nanotubes, liposomes, polymer-drug conjugates, and others are among the various forms of nanoparticles utilised in medical therapy. Liposomes and polymer-drug conjugates [16] were created in the 1960s and 1970s and are

currently the key platforms in the field of nanomedicine, which is growing as a research topic with substantial implications for existing disease paradigms. The scientific community has embraced the potential of nanomedicine in diseases such as cancer, whose optimal treatment has eluded researchers for decades due to the use of highly toxic compounds that are non-specific to cancer cells, resulting in excessive toxicity to the surrounding healthy cells, and, for many patients, the cancerous cells are discovered only after they have spread too far for treatment to significantly improve life expectancy and quality of life [17].

Paclitaxel (PTX), a taxane plant product derived from the bark of the Pacific yew and discovered in 1962, is one of the most powerful anti-cancer drugs for treating a variety of solid tumours, including breast cancer. Its molecular weight is 853.9 Da and its chemical formula is $C_{47}H_{51}NO_{14}$. Figure 1 shows the chemical formula for PTX. The small-molecule drug's anticancer action includes interfering with normal microtubule breakdown by inhibiting depolymerization during cell division [18, 19].

Taxol® (Bristol-Myers Squibb, Sermoneta, Latina, Italy), a commercial preparation of PTX dissolved in Cremophor EL (a polyoxyethylated castor oil) with dehydrated alcohol at a 50: 50 (v/v) ratio, was approved in 1992 by the US Food and Drug Administration (FDA) to treat ovarian, breast, lung, bladder, prostate, melanoma, esophageal, and other types of solid tumors as well as Kaposi's sarcoma.

Taxol® is beneficial in the treatment of metastatic breast cancer patients, with remission rates of 56–62 percent [20]. Premedication, sophisticated infusion settings, and a significant amount of "chair time" are necessary for drug delivery. Many negative effects have been linked to the excipient used, including allergy, hypersensitivity, and myelosuppression [21]. CrEL-induced complex synthesis, weak water solubility, and P-gp substrate hinder further development. New PTX formulations with lesser toxicity and equivalent or greater anticancer effectiveness are urgently needed in this situation [22].

The anticancer drug PTX is the first-generation taxane. In 1996, the FDA authorized docetaxel (Taxotere®), a semi-synthetic derivative of PTX, for the treatment of advanced breast cancer. Cabazitaxel (Jevtana®), the most current taxane anti-cancer treatment licensed by the FDA, outperforms both PTX and docetaxel due to the presence of methoxy groups at C7 and C10, resulting in a low affinity for P-glycoprotein. As a result, new docetaxel and cabazitaxel formulations have been produced. In 2010, the FDA authorized the "One-vial-

Taxotere" formulation, and a one-pot cabazitaxel formulation was also created. However, in this analysis, we solely look at different PTX formulations for breast cancer therapy [23, 24].

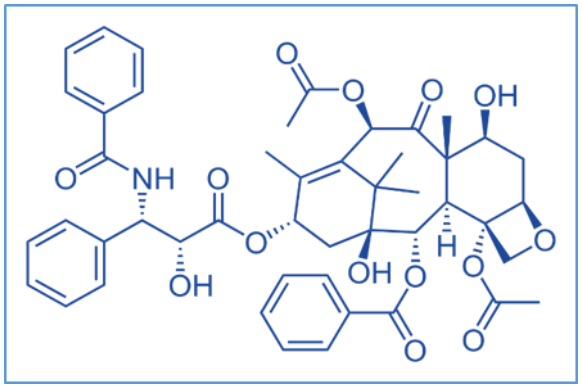

Figure 1: Chemical structure of paclitaxel

DENDRIMERS:

Dendrimers are radially symmetric nanoscale molecules having a well-defined, homogenous, and monodisperse structure consisting of tree-like arms or branches [25]. Fritzn Vogtle discovered these hyperbranched compounds in 1978, Donald Tomalia and coworkers in the early 1980s, and George R. Newkome at the same time, but separately. The second type of synthesized macromolecules is known as arborols, which means "trees" in Latin. Dendrimers are sometimes known as 'cascade molecules,' but this word is less well-known than 'dendrimers' [26, 27]. Dendrimers [28, 29, 30] are virtually monodisperse macromolecules with symmetric branching units constructed around a small molecule or linear polymer core. ‘Dendrimer’ is only an architectural motif and not a compound. Poly-ionic dendrimers do not have a persistent shape and may change in size, shape, and flexibility as a function of increasing generations [31].

End-groups (i.e., the groups reaching the outer perimeter) of dendrimers can be functionalized, changing their physicochemical or biological characteristics [32, 33]. In supramolecular chemistry, dendrimers offer a wide range of uses, notably in host-guest interactions and self-assembly processes. Dendrimers have unique properties that make them intriguing candidates for a variety of applications. Dendrimers are highly defined artificial macromolecules with a tight molecular structure and a large number of functional groups [34]. Dendritic macromolecules are playing an increasingly important role in anticancer therapy and diagnostic imaging.

These well-defined materials are the newest class of macromolecular nanoscale delivery systems [35] due to their benefits. With increased dendrimer production, dendritic macromolecules tend to grow in diameter and take on a more globular form. As a result, dendrimers have emerged as a promising delivery vehicle for investigating the effects of polymer size, charge, and composition on biologically important properties like lipid bilayer interactions, cytotoxicity, internalization, and blood plasma retention time, biodistribution, and filtration [36].

Structure of Dendrimer:

Core: The center might be a multifunctional a great part of (dendrimer core) blessing as a basis or constructing obstructs in a nerve fiber design, which could be a massive colossal atom. The sort of dendrimer is said to be experiencing the center. Because the core is also uniform or heterogeneous, the dendrimer compound is uniform or heterogeneous. The final nerve fiber plan is affected by the shape, size, assortment, and the specific, deliberate bunching of the core. Continuation units or another compound may be first-class as a direct result of the dendrimer center, depending on the desired application. In this approach, the center unit's choice has a big impact on different dendrimer unions [37].

Generation: When going from the core to the border, the area unit of generations results in homo-structural layers between focused functions or branching purposes. Generation selection is defined as the number of focus points that extend from the dendrimer's core to its perimeter. Surface groups (different purposeful groupings) are particularly significant in the search for the best dendrimer application. In general, the number and therefore the shapes of the intentional cluster attached to the dendrimer's exterior surface determine the dendrimer's performance in the field. The purposeful cluster will be reformed to the utmost extent possible on the surface of the dendrimer as required by any chemical process for manufactured materials. [38]

Surface Functionality: Surface teams are critical in determining the read of the dendrimer's eventual use. The amount and hence the shapes of the intentional cluster revealed at the dendrimer bound to determine the dendrimer's effectiveness in an application. The chemical approach will modify and amplify the purposeful cluster according to the application [39].

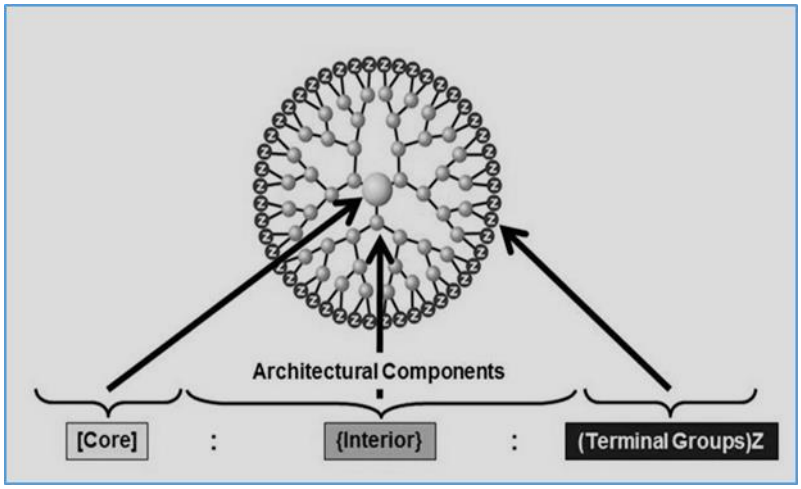

Figure 2: Structure of Dendrimer

Synthesis:

Dendrimers fall between molecular and polymer chemistry. They have a molecular chemistry connection due to their step-by-step regulated synthesis, and they have a polymer connection due to their repeated monomer structure [40, 41]. The three classic macromolecular architectural classes (linear, cross-linked, and branching) are well-known for producing polydisperse products with varying molecular weights. Dendrimer synthesis, on the other hand, allows for the creation of monodisperse, structure-controlled macromolecular structures akin to those found in biological systems [42].

Dendrimers are commonly made using either a divergent or convergent approach [43]. Dendrimer expands outward from a multifunctional core molecule in each approach. The first-generation dendrimer is formed when the core molecule combines with monomer molecules having one reactive and two inactive groups. The molecule's new perimeter is then activated for reactions with additional monomers.

Cascade reactions are the foundation of dendrimer synthesis

Chemists knew about the basic cascade or iterative techniques for synthesis long before they were used. Similar approaches, for example, are used in solid-phase peptide synthesis. In turn, biology has long used similar repeated processes in biochemical synthetic pathways; fatty acid production is one example [44].

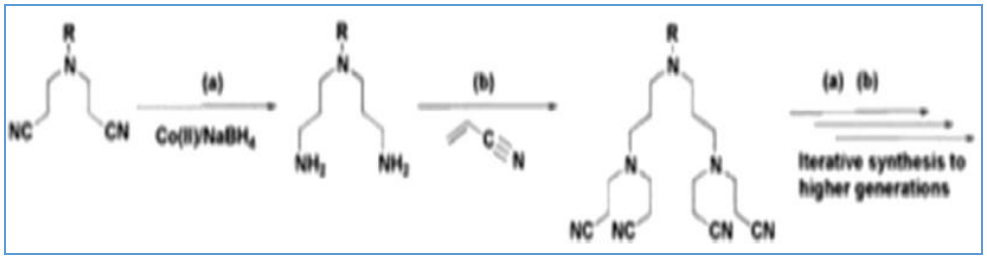

Figure 3: Cascade reactions are the foundation of dendrimer synthesis

The synthesis of dendrimers follows either a divergent or convergent approach

Dendrimers may be made using two different methods. The divergent method, which was popular in the early eras, begins with the core of the dendrimer, to which the arms are connected, and proceeds in a comprehensive and step-by-step way. Synthesis in the convergent method begins on the outside, with the chemical structure that eventually becomes the final dendrimer's outermost arm. The final generation number is predetermined in this technique, which necessitates the synthesis of branches of various sizes in advance for each generation [45].

Properties of dendrimer:

When comparing dendrimers with other nanoscale synthetic structures (e.g., traditional polymers, buck balls, or carbon nanotubes), these are either highly non-defined or have limited structural diversity.

Pharmacokinetic properties

One of the most important things to consider for effective biological applications of dendrimers, such as drug administration, imaging, photodynamic treatment, and neutron capture therapy, is their pharmacokinetic characteristics. Dendrimers are gaining popularity in medicine due to their wide range of possible uses. There are many changes to the peripheral groups of dendrimers that allow for antibody-dendrimer, peptide-dendrimer conjugates, or dendritic boxes that contain guest molecules [46].

Covalent conjugation strategies

For almost three decades, researchers have been testing the method of attaching small compounds to polymeric scaffolds via covalent bonds to increase their pharmacological characteristics [46]. In most situations, however, the conjugated dendritic assembly serves as

a 'pro-drug,' requiring the conjugate to be freed after internalization into the target cell to activate the drug.

Polyvalency

Polyvalency is advantageous since it allows for variable functionalization; it is also critical in the creation of antiviral therapeutic medicines because it allows for various interactions with biological receptor sites.

Self-assembling dendrimers

Self-assembly is another intriguing and quickly emerging field of chemistry. The spontaneous, exact grouping of chemical species by particular, complementary intermolecular interactions is known as self-assembly. The self-assembly of dendritic structures has recently gained popularity [47]. There are three ways for self-assembling dendrimers since they have three separate structural elements (the core, end-groups, and branching units linking the core and periphery).

The first is to make dendrons with a self-recognizing core unit or a ditopic or polytopic core structure, which will result in spontaneous dendrimer production [48]. Gibson and colleagues described a self-assembling dendrimer using pseudorotaxane production as the organizing mechanism. [49]

Electrostatic interactions

The enormous number of frequently similar end-groups exhibited by the dendritic host distinguishes molecular recognition events at dendrimer surfaces. When these groups are charged, the surface can behave as a polyelectrolyte, attracting oppositely charged molecules electrostatically [50]. The aggregation of methylene blue on the dendrimer surface and the binding of EPR probes such as copper complexes and nitroxide cation radicals are two examples of electrostatic interactions between polyelectrolyte dendrimers and charged species [51].

Encapsulation of Drugs within the Dendritic Architecture

Encapsulation

Dendrimers may directly enclose guest molecules into the macromolecule interior due to their ellipsoidal or spheroidal form, unfilled internal cavities, and open architecture [52]. The

hydrophobic nature of these empty interior spaces makes it simple to interact with poorly soluble medicines via hydrophobic interactions. The nitrogen or oxygen atoms in the interior cavities can create hydrogen bonds with the medication molecules.

PEGylated dendrimers

Dendrimers have been modified using poly (ethylene glycol) (PEG) in the development of solubilizing and drug delivery systems. PEG is commonly conjugated to the surface of a hydrophobic dendrimer, forming a hydrophilic shell around the dendrimer's hydrophobic core to create a unimolecular micelle [53]. The hydrophilic component of PEG reduces dendrimer removal from the body. PEG is of special importance in the design of dendrimer systems for pharmaceutical applications because of its high water solubility, biocompatibility, and capacity to change carrier biodistribution.

Dendritic box

Jansen disclosed the synthesis of dendritic boxes based on poly (propylene imine) dendrimers. Even after lengthy heating, solvent extraction, or sonication, guest molecules could be held within the cavities of the dendritic boxes with a thick surface shell, limiting diffusion from the structures [54]. End group modification with a large amino acid derivative results in a thick and hard chiral shell with solid-phase characteristics and a flexible core capable of entrapping molecules.

Cored dendrimers

Zimmerman and colleagues created cored dendrimers that look like hollow nanospheres and can enclose molecules, making them potential delivery vehicles. The dendritic design was modified post-synthesis to achieve encapsulation [55]. In a typical dendrimer, the core unit is critical because it joins the dendrons, or branches, of the structure. Crosslinking the outer surface groups of a dendrimer is an alternate method of preserving structural integrity.

Unimolecular micelles

Unimolecular micelles are dendrimers with a polar core and polar shell. For example, a symmetrical, four-directional saturated hydrocarbon cascade polymer with 36 carboxylic acid moieties and a neopentyl core has been synthesized. Lipophilic probes were found within the dendritic structures' lipophilic infrastructure, leading to the conclusion that the polymers exist

as single molecules capable of molecular inclusion and hence operate as unimolecular micelles [56].

Table 1: Factors Affecting Dendrimer Properties

S. No	Factor	Level	Effect
1	Effect of pH	Low	The structural behavior of PAMAM dendrimers is dependent upon pH At low pH (< 4) the interior is getting increasingly hollow. Repulsion between the positively charged amines both at the dendrimer surface and the tertiary amines in the interior increases at high generation.
		Neutral	-At neutral pH, back-folding occurs which may be a consequence of hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines.
		High -	At higher pH (pH>10) the dendrimer contract as the charge of the molecule becomes neutral, acquiring a more spherical (globular) structure, where the repulsive forces between the dendrimer arms and between the surface groups reach the minimum.
2	Effect of Salt	High	A high concentration of salt has a strong effect on charged PPI dendrimers. Favors a contracted conformation of dendrimers, with a high degree of back-folding somewhat similar to what is observed upon increasing pH or poor solvation.
		Low	The repulsive forces between the charged dendrimer segments result in an extended conformation to minimize charge repulsion in the structure.
	Effect of Solvent		-The solvation power of any solvent to solvate the dendrimer is a very important parameter. -Dendrimers of all generations generally exhibit a larger extent of back-folding with decreasing solvent quality. -The dendrimer arms induce a higher molecular density on

			the dendrimer surface. -NMR studies performed on PPI dendrimers concluded that a nonpolar Solvent like benzene poorly solvates the dendrimers favoring intramolecular interactions between the dendrimer segments and back-folding.
	Effect of Concentration of Dendrimer		-Small-angle X-ray scattering (SAXS) experiments performed on PPI dendrimers (G4, G5) in a polar solvent like methanol show that the molecular conformation of dendrimers upon increasing concentration becomes increasingly contracted. -This molecular contraction may minimize the repulsive forces between the dendrimer molecules and increase the ability of the dendrimers to exhibit a more tight intermolecular packing.

Table 2: Marketed Formulation of dendrimer

S. No	Brand Name	Type of Dendrimer	Company	Application
1	Vivagel	Multiple Antigen	Star pharma	HIV prevention
2	Alert ticket	PAMAM	US army research laboratory Anthrax	Detection
3	SuperFect	Ampiphilic	Qiagen	Gene Transfection
4	Stratus CS	Tecto	Dade Behring	Cardiac Marker
5	Priofect™, Priostar™	Tecto	Starphrma	Targeted diagnostic, therapeutic delivery for cancer cells
6	Avidimer		DOW	Cancer prevention, treatment
7	Dendritic	PAMAM		-
8	Astramol	PPI	DSM	-
9	Starburst	PAMAM		Targeted diagnostic, therapeutic delivery for cancer cells

CONCLUSION:

Dendrimers have unique characteristics that make them promising candidates for a variety of applications. Dendrimers are highly defined artificial macromolecules with a tight molecular structure and a large number of functional groups. Dendrimers can also deliver large amounts of drugs. Dendrimers are useful for medical applications such as biomedicine, drug delivery, and catalysis because of their unique features like as regulated size, monodispersity, and reactive surface groups. The development and study of new dendrimers as drug carriers continues to be an important tool in cancer therapy because they can be functionalized with a variety of ligands to reach tumour tissue through various body barriers with minimal loss of activity in the bloodstream, can selectively kill tumour cells without affecting normal cells, and, most importantly, have an active release mechanism.

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