Various approaches are in progress for synthesis of PAMAM Dendrimers and targeted delivery of anticancer drugs. Even though dendritic polymers only have a short history of nearly three decades, but dendritic polymers have proved themselves to be promising material. Therefore a literature survey on PAMAM dendrimer and cancer was carried out which is briefly summarized here:

**Mintzer et al., 2012** explored dendrimer multivalency to combat emerging and re-emerging infectious diseases. Dendrimers, a specific class of monodispersed macromolecules, have recently shown potential to function as antibacterial and antimicrobial agent. This review discusses the limitations with currently used antibacterial agents and describes how various classes of dendrimers, including glycodendrimers, cationic dendrimers, anionic dendrimers, and peptide dendrimers, have the potential to improve upon or replace certain antibiotics. Furthermore, the unexplored areas in this field of research were mentioned to present opportunities for additional studies regarding the use of dendrimers as antimicrobial agents.

**Surya et al., 2012** reported spectroscopic characterization of Dendrimers. This review is a study of the main analytical techniques used for the characterization of chemical composition, homogeneity, synthesis, conjugation, reaction rate determination, structural defects, 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, X-Ray Absorption Spectroscopy. Thus combination of all spectroscopic techniques is vital tool for the characterization of dendrimers in the era of this new molecular chemistry world.

**Anupama et al., 2011** have done synthesis and characterization of 4.0G PAMAM Dendrimers-Gallic acid conjugate for cancer targeted drug delivery. 4.0G PAMAM dendrimer was conjugated with Gallic acid (GA) and characterized through UV, FT-IR, 1H NMR and MASS spectroscopy. Cytotoxicity study of dendrimer conjugate was carried out against MCF-7 cell line using MTT assay. The study revealed that the conjugate is active against MCF-7 cell line and might perform synergistically with anti-
cancer drug. Gallic acid–dendrimer conjugate might be a promising nano-platform for cancer targeting and cancer diagnosis.

<table>
<thead>
<tr>
<th>Analytical Techniques</th>
<th>Interpretation</th>
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| UV spectroscopy       | -Synthesis [Characteristic curves exhibits the specific maximum absorption peaks]  
                        | -Conjugation (surface modification) [Shift in peak]  
                        | -Reaction rate |
| IR spectroscopy       | -Synthesis [Characteristic peaks corresponding to functional groups]  
                        | -Conjugation (surface modification) [Shifts in Characteristic peaks corresponding to functional groups]  
                        | -Appearance-Disappearance-Reappearance chemistry of characteristic peaks |
| NMR spectroscopy:     | -Synthesis of dendrimers [Characteristic peaks in the spectra]  
                        | -Conjugation chemistry [shielding deshielding effects shifts in peaks]  
                        | -Hydrodynamic radii [NMR pulse-field gradient spin−echo]  
                        | -Number of protons [intensity of peaks and integral value]  
                        | -Conformational changes [unique NMR signals from the core to the periphery]  
                        | [One-dimensional (1D) and two-Dimensional (2D) NMR.]  
                        | (i)Isomer populations observed by 1H NMR reveal the onset of globular Structure. |
| ¹H-NMR and ¹³C-NMR     | Rotational-Echo Double Resonance (REDOR) |
| Solid-state NMR       | One-dimensional (1D) and two-dimensional (2D) NMR |
| spectroscopy          | (2D)-NMR-techniques [e.g. (2D)-NOESY, (2D)- |
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TOCSY (TOCSY=Total Correlation Spectroscopy) NMR Diffusions NMR spectroscopy (e.g. PGSE = Pulsed Gradient Spin Echo; STE = Stimulated Echo; DOSY = Diffusion Ordered Spectroscopy) (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.

- Relaxation studies show that peripheral groups are more dynamic than groups at the core.
- Mobility of group [Relaxation times (T1) measurement by 1H- 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].

Mass spectroscopy:

MALDI-TOF-MS
- Determining the molecular weight.
- Structural defects in dendrimers.

ESI-MS
- Determination of the polydispersity.
- Purity of dendrimers.

Raman Spectroscopy
- Structure.
- Librations of terminal groups in dendrimers.
- Interaction between PAMAM dendrimer with lipid membranes.

Fluorescence Spectroscopy
- Binding to PAMAM dendrimer /interaction, polymer binding mode, the binding constant /complexation.
- The size and shape of the molecules.
- Peripherally modification.
Sebestik et al., 2011 studied Glyco-dendrimers and their biomedical applications. The size of information that can be stored in nucleic acids, proteins, and carbohydrates was calculated. Dendrimers can be used for creation of libraries, catalysts, and solubilizing agents. Biocompatibility and toxicity of dendrimers was discussed, as well as their applications in nanoscience, nanotechnology, drug delivery, and gene delivery. Carbohydrate interactions of Glyco-dendrimers (bacteria, and cancer) were described.

Barata et al., 2011 reported structural studies of biologically active glycosylated polyamidoamine (PAMAM) dendrimers. Partial modification of carboxylic acid terminated polyamidoamine (PAMAM) dendrimers with glucosamine has been reported to give dendrimer glucosamine conjugates having novel immunomodulatory and anti-angiogenic Properties. The structural features and the dynamic behavior of the partially glycosylated generation 3.5G PAMAM dendrimer showed that its flexibility and polarity changed with the incremental addition of glucosamine.
These peripheral glucosamine molecules remained available on the dendrimers surface for interaction with the biological target.

**Hemant et al., 2010** have developed a new approach for PEGylation of dendrimers. The main drawback of dendrimers is, due to the presence of –NH₂ group at the surface, which causes hemolytic toxicity. The PEGylated dendrimers were evaluated for color reaction UV, FT-IR and NMR studies. The results revealed that this approach for PEGylation gives considerable amount of PEGylation, requires less time duration and hence it could gives a better option for PEGylation of dendrimers.

**Fischer et al., 2010** studied influence of surface functionality of poly (propylene imines) dendrimers on protease resistance and propagation of the scrapie prion protein. Branched polyamines, including PPI (poly (propylene imines) dendrimers, are able to remove protease resistant PrP (Sc) and abolish infectivity, offering possible applications for therapy. These dendrimer types were thought to act through their positively charged amino surface groups. In the present study, the molecular basis of the anti-prion activity of dendrimers was further investigated, employing modified PPI dendrimers in which the positively charged amino surface groups were substituted with neutral carbohydrate units of maltose (mPPI) or maltotriose (m3PPI). Modification of surface groups greatly reduced the toxicity associated with unmodified PPI but did not abolish its anti-prion activity, suggesting that the presence of cationic surface groups is not essential for dendrimer action. Assays revealed that total levels of PrP (Sc) in scrapie-infected mouse neuroblastoma (ScN2a) cells were reduced by mPPI.

**Ottaviani et al., 2010** investigated evolution of the aggregation process of peptides involved in neurodegenerative diseases and preventing aggregation effect of phosphorus dendrimers. Dendrimers have revealed their ability to prevent fibril formation and therefore cure neurodegenerative diseases. It is proposed that dendrimers mainly impede in the lag (nucleation) phase of the prion peptide.

**Thomas et al., 2010** reported the synthesis and biological evaluation of G5 PAMAM dendrimer conjugated with riboflavin as a targeting ligand.

**Shi et al., 2010** reported dendrimer entrapped gold nanoparticles for targeting and imaging of cancer cells. The Au DENPs were linked with targeting ligand folic acid...
(FA) and imaging moiety fluorescein isothiocyanate (FI) molecule. The functionalized Au DENPs are stable, biocompatible and can be used for specific targeting and imaging of cancer cells with over-expressing folate receptor. The Au DENPs linked with defined numbers of folic acid (FA) and fluorescein isothiocyanate (FI) molecules are water soluble, stable, and biocompatible. In vitro studies show that the FA and FI modified Au DENPs can specifically bind to KB cells (a human epithelial carcinoma cell line) that over express high-affinity folate receptors. These findings demonstrate that Au DENPs may serve as a general platform for cancer imaging and therapeutics.

Kumar et al., 2009 reported recent developments in cancer therapy by the use of nanotechnology. He had given an overview of the use of bioconjugated nanoparticles for the delivery and targeting of anticancer drugs. Nanotechnology is definitely a medical boon for diagnosis, treatment and prevention of cancer disease. It will radically change the way we diagnose, treat and prevent cancer to meet the goal of eliminating suffering and death from cancer. The integration of nanotechnology into cancer diagnostics and therapeutics is a rapidly advancing field, and there is a need for wide understanding of these emerging concepts.

Gohel et al., 2009 reviewed dendrimer and its properties. The dendrimers holds a promising future in various pharmaceutical applications and diagnostic field in the coming years as they possess unique properties, such as high degree of branching, multivalency, globular architecture and well-defined molecular weight, thereby offering new scaffolds for drug delivery. Also as research progresses, newer applications of dendrimers will emerge and the future should witness an increasing numbers of commercialized dendrimer based drug delivery systems.

Chen et al., 2009 reported gallic acid as a major anti-cancer compound in Toona Sinensis leaf extracts. GA acts as an anti-proliferative agent in cancer cells, through the generation of ROS, the down-regulation of Bcl-xL and up-regulation of Bax, the reduced mitochondrial membrane potential, cytochrome c release from mitochondria to cytosol, the activated caspases 9 and 3 which led to PARP cleavage, DNA damage and fragmentation and eventually the induction of apoptosis.

Nanjwadea et al., 2009 studied on Dendrimers as new class of polymeric materials. It is generally described as a macromolecule, 3D structure and that provides a high
degree of surface functionality and versatility. The unique properties associated with these dendrimers such as uniform size, high degree of branching, water solubility, multivalency, well-defined molecular weight and available internal cavities make them attractive for biological and drug-delivery applications. Commercialization of dendrimers is now forthcoming. The present review briefly describes about dendrimer synthesis strategies, types of dendrimers with different functionalities, properties which having crucial importance and their potential applications.

Waite et al., 2009 had found that Primary amine acetylation of PAMAM dendrimers reduced their cytotoxicity to U87cells, and promoted the release of siRNA from dendrimer / siRNA complexes. A modest fraction (approximately 20%) of primary amines of PAMAM can be modified while maintaining the siRNA delivery efficiency of unmodified PAMAM.

Tristan et al., 2009 investigated the anticancer agent cisplatin has been conjugated to 3.5G PAMAM dendrimer. Dendrimer-platinate released platinum slowly. The dendrimer-Pt conjugate was between 3- and 15-fold less toxic than cisplatin and its selective accumulation in solid tumour tissue by the enhanced permeability and retention (EPR) effect was appreciably higher. The road to the clinical application of dendrimer-based macromolecular imaging/therapeutic agents has become a hot topic, which remains to be investigated and discussed by scientific researchers and administrative sides in numbers of aspects including synthesis, purity of agents, toxicity, pharmacokinetics and excretion.

Svenson et al., 2009 reviewed the high level of control over the dendritic architecture (size, branching density, and surface functionality) which makes them ideal carriers. Anticancer, anti-inflammatory, and antimicrobial activity have been successfully associated with dendrimers such as poly (amidoamine) (PAMAM), poly(propylene imine) (PPI or DAB) and poly(etherhydroxylamine) (PEHAM) dendrimers, either via physical interactions or through chemical bonding (‘prodrug approach’). Targeted delivery is possible via targeting ligands conjugated to the dendrimer surface or via the enhanced permeability and retention (EPR) effect.

Yang et al., 2009 reported conjugation of partially acetylated G5 PAMAM dendrimer with the targeting moiety (biotin) and the imaging moiety (fluorescein isothiocyanate,
FITC) for targeting cancer cells. They characterized the conjugates by $^1$H NMR, UV-Vis spectrum.

**Kumar et al., 2009** reported recent developments in cancer therapy by the use of nanotechnology. He had given an overview of the use of bioconjugated nanoparticles for the delivery and targeting of anticancer drugs.

**Lammers et al., 2008** had given a review on tumors-targeted nanomedicines. They summarized the most important targeting and future directions in the development of tumor targeted nanomedicines.

**Byrne et al., 2008** reviewed about various active targeting schemes for nanoparticle systems in cancer therapeutics. They had given an outline of current major cancer targets for nanoparticle systems. The major targeting strategies used for the delivery of therapeutic or imaging agents to cancer are angiogenesis associated targeting, targeting to uncontrolled cell proliferation markers and tumor cell targeting.

**Wolinsky et al., 2008** given a review on therapeutic and diagnostic applications of dendrimers for cancer treatment. They focused on dendrimer developments for oncological applications, with emphasis on distinct architectures and the biological responses these structures elicit.

**Niederhafner et al., 2008** reviewed glycopeptide dendrimers. Use of glycopeptide dendrimers in immunotherapy, diagnosis of cancer and viral diseases. Glycopeptide dendrimers containing different types of tumor associated-carbohydrate antigens (T(N), TF, sialyl-T(N), sialyl-TF, sialyl-Le(x), sialyl-Le(a) etc.) were used in diagnosis and therapy of different sorts of cancer. Best results were obtained with multiantigenic vaccines, containing, e.g. five or six different TAAs. The topic of TAAs and their dendrimeric forms at molecular level are reviewed, including structure, syntheses, and biological activities. Use of glycopeptide dendrimers as antiviral vaccines against HIV and influenza is also described. Their syntheses, physico-chemical properties, and biological activities are given.

**Faried et al., 2007** reported the anti-cancer effects of gallic acid isolated from Indonesian herbal medicine *Phaleria macrocarpa* on human cancer cell lines. Gallic acid demonstrated a significant inhibition of cell proliferation in a series of cancer cell
lines and induced apoptosis in esophageal cancer cells (TE-2) but not in non-cancerous cells (CHEK-1).

Giovannini et al., 2007 stated that polyphenols can directly interact with specific steps and/or proteins regulating the apoptotic process in different ways depending on their concentration, cell system, type or stage of the pathological process. Polyphenols may serve as potential candidates for chemoprevention, treatment of cancer and cardiovascular diseases.

Lesniak et al., 2007 reported synthesis of a stable and clinically relevant nanodevice (cRGD-BT-ND) that exhibits superior binding to the biologic target α,β₃ integrins, when either compared to the same free cRGD peptide or to the biotinylated nanodevice without covalently attached peptides (BT-ND). Partially acetylated G5 PAMAM dendrimer was conjugated with biotin and cyclic RGD peptide (Phe (f)-Lys-Arg-Gly-Asp.

Vladimir et al., 2007 summarized currently available information regarding targeted pharmaceutical nanocarriers for cancer therapy and imaging. Some popular pharmaceutical nanocarriers such as liposomes and polymeric micelles are addressed, as are different ways to target tumors via specific ligands and via the stimuli sensitivity of the carriers.

Faried et al., 2007 reported the anti-cancer effects of gallic acid isolated from Indonesian herbal medicine, Phaleria macrocarpa, on human cancer cell lines. Gallic acid demonstrated a significant inhibition of cell proliferation in a series of cancer cell lines and induced apoptosis in esophageal cancer cells (TE-2) but not in non-cancerous cells (CHEK-1).

Gupta et al., 2006 reported solubility enhancement of the poorly water soluble drug indomethacin Piroxicam in the presence of a series of G4, G4.5 PAMAM dendrimers and also G4 dendrimers with surface hydroxyl groups was examined. Both G3 and G2.5 PAMAM dendrimers were shown to enhance significantly the aqueous solubility of piroxicam at pH 6 and 8. Solubility increases with increasing generation. Increased solubility was explained on the basis of electrostatic bonding between the carboxyl group of indomethacin and the amino groups of the dendrimer.
Okuda et al., 2006 performed synthesis of Dendritic poly (L-lysine) (DPKs), dendritic poly (L-ornithine) (DPOs), which are constructed as novel amino acid dendrimers, PEGylated KG6 (the sixth generation of DPKs), and evaluated the physicochemical properties, biodistribution characteristics of these dendrimers. PEGylation of KG6 caused great changes in particle size, zetapotential, blood retention and organ distribution in vivo, indicating that the PEGylation is applicable strategy to improve biodistribution characteristics of dendrimeric molecules.

Srinivasan et al., 2006 studied the influence of ferulic acid on gamma-radiation induced DNA damage, lipid peroxidation and antioxidant status in primary culture of isolated rat hepatocytes. They investigated that the ability to spare healthy tissue from radiation induced cellular damage is the reason behind the usefulness of antioxidants for patients undergoing radiation therapy.

Heegaard et al., 2006 studied dendrimer based anti-infective and anti-inflammatory drugs. Dendrimers are a relatively new class of structurally well-defined, i.e. Monodispersed, synthetic polymers with hyper branched structures which enable a given molecular motif to be presented in a highly multivalent fashion. The surface of dendrimers can be modified relatively easily and, depending on the surface motif, the pharmacological properties of the dendrimer such as cytotoxicity, bacteriocidal effect, biodistribution and biopermeability may be modulated to fit a specific medicinal purpose. Hence the use of dendrimers for the development of antiviral or antibacterial drugs, destroying the infective agent or disrupting multivalent binding interactions between the infective agent and cells of the host organism has become a highly active research field.

Ming et al., 2005 studied the properties of ethylenediamine (EDA) core and amine surface poly(amidoamine) (PAMAM) dendrimers of generation 1 through 7. All the generations were spherical in shape, while the higher generations showed edges or slightly polyhedral shape. Radius of gyration indicates the PAMAM dendrimers are densely compact structures which result from the high flexibility confirmed by the terminal group distribution.
Juhan et al., 2005 studied 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). At the threshold, in addition to the main component peak at 1430.02 Da PAMAM dendrimers showed a complicated fragmentation behavior in the MALDI experiments, with multiple fragmentation channels that depend on the matrices and on the laser pulse energy. Different fragmentation mechanisms may be due to different protonation pathways.

Hirata et al., 2005 studied the inhibitory effect of Ferulic Acid dimer on Lipopolysaccharide-stimulated Cyclooxygenase-2 expression in Macrophages. COX-2 is closely involved in inflammation, arthritis, Alzheimer’s disease, pain and cancer. Studies revealed that bis FA and isoferulic acid showed potent inhibition of COX-2 expression.

Hu et al., 2005 performed synthesis of novel dendrimer derivatives combining the temperature and pH-sensitivities. Their macromolecular structures are characterized by FT-IR, 1H NMR, DSC and particle size analysis, and their aqueous solutions are inspected by UV spectroscopy for understanding their thermo and pH-sensitivities. The CLB released was analyzed by spectrophotometer using 211.5 nm (pHZ 1.4) and 242.0 nm (pHZ 10.0) as characteristics bands, respectively. All solutions withdrawn were kept at 37°C for 48 h prior to measurements. Results indicate that the rate of the drug release can be effectively controlled by the pH value of its environment.

Namazi et al., 2005 reported citric acid–PEG–citric acid triblock copolymers formed inclusion complexes with a range of guest molecules including 5-aminosalicylic acid, mefenamic acid and diclofenac. The amount of entrapped drug increased with increasing dendrimer generation from G1 to G3 and was greatest for 5-aminosalicylic acid, probably because of its small size and high polarity. The rate of release of complexed drug was pH dependent and increased with dendrimer generation.

Furer et al., 2004 performed comparison of FT-IR and Raman spectra of 12 generations of the phosphorus-containing starburst dendrimers containing P=S and
P=O bonds with terminal aldehyde and P–Cl groups. The influence of the encirclement on the band frequencies and intensity was studied. Due to the predictable, controlled and reproducible structure of the dendrimers the information usually inaccessible was obtained. Bands in the IR difference \((G-2(P=O)-G-2(P=S))\) spectra have characteristic EPR-like form. The strong band at 1600 cm\(^{-1}\) show marked changes of the optical density in dependence of the aldehyde (–CH=O) or azomethyne (–CH=N–) substituents in the aromatic ring.

Yang et al., 2004 designed unimolecular dendritic micelles as solubility enhancers by coupling polyethylene glycol (PEG) to polyamidoamine (PAMAM) dendrimers. Micelles 750, 2000, and 5000 have a generation 3.0 dendrimer core (32 primary amine end groups) and PEG arms with molecular weights of 750, 2000, and 5000, respectively. The conjugate of dendrimer core and PEG was characterized by MALDI-TOF MS and 1H NMR. 1H NMR was also used to estimate the average number of PEG arms on each dendrimer molecule. A typical hydrophobic compound, pyrene, was sonicated in an excess amount together with micelles at 50\(^\circ\)C for 6 h to produce its saturated water solution. The change of the solubility of pyrene was monitored at 334 nm, its maximum adsorption wavelength, by UV–VIS spectra. Micelle-2000 could solubilize more pyrene than micelle-750.

Rukkumani et al., 2004 analyzed the protective role of ferulic acid (FA), a naturally occurring nutritional component on alcohol and PUFA induced oxidative stress. Also, Ferulic acid has been known to be effective against cancer, cold, flu, skin aging, muscle wasting and influenza.

Gregory et al., 2004 reported that some cells, such as those of rapidly dividing, aggressive tumors and over-express surface receptors involved in the uptake of vitamin B12, folic acid and biotin. Targeted chemotherapy for cancer treatment offers a great potential advantage in tumor treatment due to greater specificity of delivery which leads to increased dose of the cytotoxin delivered to the tumor relative to the rest of the body. In order to achieve such selective targeted delivery one needs to identify generic markers that are over-expressed on the surface of tumor cell but are not over-expressed on normal tissue.
Marcucci et al., 2004 reviewed about active targeting with particulate drug carriers in tumor therapy: fundamentals and recent progress. The derivatisation of particulate drug carriers with a ligand leads to the selective targeting of the particulate to selected cells, thereby focusing drug delivery.

Shaunak et al., 2004 reported polyvalent dendrimer glucosamine conjugates prevent scar tissue formation. Anionic polyamidoamine 3.5G dendrimers, water-soluble conjugates of D (+)-glucosamine and D (+)-glucosamine 6-sulfate with immunomodulatory and antiangiogenic properties respectively. Dendrimer glucosamine inhibited Toll-like receptor 4-mediated lipopolysaccharide induced synthesis of pro-inflammatory chemokines (MIP-1 alpha, MIP-1 beta, IL-8) and cytokines (TNF-alpha, IL-1 beta, IL-6) from human dendritic cells and macrophages but allowed up regulation of CD25, CD80, CD83 and CD86. Dendrimer glucosamine 6-sulfate blocked fibroblast growth factor-2 mediated endothelial cell proliferation and neoangiogenesis in human matrigel and placental angiogenesis assays. It was concluded that synthetically engineered macromolecules such as the dendrimers described can be tailored to have defined immuno-modulatory and antiangiogenic properties and they can be used synergistically to prevent scar tissue formation.

Boas et al., 2004 studied dendrimers in drug research. Dendrimers are versatile, derivatisable, well-defined, compartmentalized chemical polymers with sizes and physicochemical properties resembling those of biomolecules e.g. proteins. The use of dendrimers in biological systems was reviewed, with emphasis on the biocompatibility of dendrimers, such as in-vitro and in-vivo cytotoxicity, as well as biopermeability, biostability and immunogenicity. The review deals with numerous applications of dendrimers as tools for efficient multivalent presentation of biological ligand in biospecific recognition, inhibition and targeting. Dendrimers may be used as drugs for antibacterial and antiviral treatment and have found use as antitumor agents.

Solassol et al., 2004 studied cationic phosphorus-containing dendrimers reduce prion replication both in cell culture and in mice infected with scrapie. The anti-prion activity of new cationic phosphorus-containing dendrimers (P-dendrimers) with tertiary amine end-groups was tested. These molecules had a strong anti-prion activity, decreasing both PrP (Sc) and infectivity in scrapie-infected cells at non-
cytotoxic doses. They can bind PrP and decrease the amount of pre-existing PrP (Sc) from several prion strains, including the BSE strain. More importantly, when tested in a murine scrapie model, the dendrimers were able to decrease PrP (Sc) accumulation in the spleen by more than 80%. These molecules have a high bio-availability and therefore exhibit relevant potential for prion therapeutics for at least post-exposure prophylaxis.

Jevprasesphant et al., 2003 studied cytotoxicity of dendrimers has been primarily studied in-vitro, however, a few in-vivo studies have been published. As observed for other cationic macromolecules, including liposomes and micelles, dendrimers with positively charged surface groups are prone to destabilize cell membranes and cause cell lysis. Comparative toxicity studies on anionic (carboxylate-terminated) and cationic (amino-terminated) PAMAM dendrimers using Caco-2 cells have shown a significantly lower cytotoxicity of the anionic compounds. Furthermore, the cytotoxicity was found to be generation dependent, with higher generation dendrimers being the most toxic.

Jevprasesphant et al., 2003 reported the influence of surface modification on the cytotoxicity of PAMAM dendrimers. Dendrimers were modified by conjugating either lauroyl chains or polyethylene glycol (PEG) 2000 onto the surface of cationic PAMAM dendrimers (G2, G3, G4). The cytotoxicity of unmodified dendrimers towards Caco-2 cells was appreciably higher for cationic (whole generation) compared with anionic (half generation) dendrimers and for both types increased with increasing size (generation) and concentration. A marked decrease in the cytotoxicity of cationic PAMAM dendrimers was noted when the surface was modified, with the addition of 6 lauroyl or 4 PEG chains being particularly effective in decreasing cytotoxicity.

Waleczek et al., 2003 investigated molecular associations of β-CD with pure (−)-α-bisabolol or (−)-α-bisabolol as a component of camomile essential oil, phase solubility studies were undertaken. ABs type solubility with an apparent complex constant of 273 M$^{-1}$ for the pure (−)-α-bisabolol and 304 M$^{-1}$ for (−)-α-bisabolol as a constituent of the essential oil were obtained.

Newkome et al., 2003 reported the synthesis of arborols.
Cloninger et al., 2002 studied biological applications of dendrimers. In the past year, significant advances have been made in the synthesis and study of glycodendrimers and peptide dendrimers. Application of these dendrimers to the study of carbohydrate-protein and protein-protein interactions has facilitated the understanding of these processes. In addition, dendrimers showed great promise as DNA and drug-delivery vehicles.

Lee et al., 2002 reported the selective delivery of anticancer drugs by polyethylene glycol (PEG)-coated liposomes that contained a new cationic lipid 3,5-dipentadecycloxybenzamidine hydrochloride (TRX-20). They reported that the Chondroitin sulfate targeted delivery of anticancer drugs by novel cationic liposomes represents a potentially useful strategy to prevent the local growth and metastasis, particularly to the liver, of tumor cells that have enhanced expression of Chondroitin sulfate.

Janek et al., 2001 synthesized Generations 0 through 5 of ethylenediamine core poly (amidoamine) dendrimers. The generations –0.5, 0.5, and 1.5 were purified by column chromatography on silica gel and G2.5, G3.5, and G4.5 by column chromatography on Sephadex LH-20. Methanol or its mixture with dichloromethane was used as the chromatographic eluent. Capillary zone electrophoresis was applied to characterize the homogeneity of the individual generations.

Janek et al., 2001 studied on the decomposition of ethylenediamine core poly (amidoamine) (PAMAM) dendrimers (generation 0.5) was investigated by gas chromatography. The decomposition of PAMAM dendrimer G 0.5 into triester is caused by the retro-Michael reaction. Equilibrium between the Michael and retro-Michael reactions is shifted towards the retro-Michael reaction at an elevated temperature. Similar decomposition is possible in the case of higher PAMAM dendrimer generations.

Kojima et al., 2000 studied the influence of dendrimer generation (G3 and G4) and PEG molecular weight (550 or 2000) on the ability of PEG grafted dendrimers to encapsulate the hydrophobic drugs Adriamycin and Methotrexate. It was found that drug loading increased with dendrimer size and increasing chain length of PEG grafts, with up to 6.5 adriamycin or 26 methotrexate molecules incorporated per dendrimer (G4) molecule. The application of dendrimer drug complexation in the enhancement
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of drug solubility and bioavailability and the use of the complexes as vehicles for the controlled release of drugs and drug targeting was discussed.

Malik et al., 2000 used polyamidoamine (PAMAM, poly (propyleneimine) with either diaminobutane or diaminoothane as core, and poly (ethylene oxide) (PEO) grafted carbosilane (CSi–PEO) dendrimers were used to study systematically the effect of dendrimer generation and surface functionality on biological properties in vitro. PAMAM dendrimers exhibit generation dependent haemolysis and changes in red cell morphology were observed after 1 h even at low concentrations (10 mg/ml). At concentrations below 1 mg/ml CSi–PEO dendrimers and those dendrimers with carboxylate (COONa) terminal groups were neither haemolytic nor cytotoxic towards a panel of cell lines in-vitro. In general, cationic dendrimers were cytotoxic (72 h incubation), displaying IC values 550–300 mg/ml dependent on 50 dendrimer-type, cell-type and generation.

Hudson et al., 2000 investigated potential colon and breast tumor suppressive properties of rice, testing the hypothesis that rice contains phenols that interfere with the proliferation or colony-forming ability of breast or colon cells. Eight phenols, protocatechuic acid, p-coumaric acid, caffeic acid, ferulic acid, sinapic acid, vanillic acid, methoxycinnamic acid, and tricin, were identified in the extracts of bran and intact brown rice.

Slavin et al., 2000 stated that whole grains are protective against cancer, especially gastrointestinal cancers such as gastric and colonic and hormonally-dependent cancers including breast and prostate. Phenolic acids, particularly the hydroxycinnamic acid, ferulic acid and p-coumaric acid are found in plant cell walls generally linking cellulose to other polysaccharide components. Also he concluded caffeic and ferulic acids as inhibitors acting both by preventing the formation of carcinogens from precursor compounds and by blocking the reaction of carcinogens with critical cellular macromolecules.

Sudimach et al., 2000 studied targeted drug delivery via folate receptor. The folate is a highly selective tumor marker overexpressed in greater than 90% of ovarian cancer. Two strategies have been developed for the targeted delivery of drugs to folate
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receptor-positive tumor cells: by coupling to a monoclonal antibody against receptor and by coupling to a high affinity ligand, folic acid.

Ren et al., 1999 Series of dendritic polymers were synthesized having cyclic cores of 1, 4, 7, 10-tetraazacyclododecane with full and half generations ranging between 0.5, 5.5 reported their conjugation with 5-fluorouracil. Hydrolysis of the conjugates resulted in a slow in-vitro release of drug over a period of several days, so reducing the toxic side effects of this potent antitumor drug.

Franco et al., 1999 studied doxorubicin-polymer conjugates. Doxorubicin has been a favorite target for developing strategies directed at changing its therapeutic index. Not only has its activity against various solid tumors been an attractive feature, but many studies have pursued its mechanisms of action and differential effects on the heart versus other tissues and tumors

Srinivas et al., 1998 had reported the dependence of generation or size on the physical properties of PAMAM dendrimers. He had reported various molecular, solution and bulk properties of 5.0G PAMAM dendrimers.

Page et al., 1997 reported conjugation of starburst PAMAM dendrimers with mannopyranoside residues \([p\text{-isothiocyanatophenyl 2, 3, 4, 6-tetra-}O\text{-acetyl-}\alpha\text{-d-}\text{mannopyranoside.}}\]

Watkins et al., 1997 reported interactions of dendrimers with anionic surfactants generated supramolecular assemblies which greatly enhance their ability to accommodate the dye. Fluorescence polarization and emission as a function of pH were also studied in an effort to elucidate the interaction of the probe with the dendrimer-surfactant assemblies.

Zimmerman et al., 1996 described the synthesis of molecules containing two isophthalic acid units covalently attached to a rigid aromatic spacer. By normal pairing of carboxylic acids into hydrogen-bonded dimers, these molecules self-assemble in organic solvents to form either a series of linear aggregates or a cyclic hexamer. These molecules were linked to the core of a family of polyether dendrimers, which caused the hexamer to be formed preferentially. The stability of the hexamer depended on the generation number of the dendrimer. The largest of
these hydrogen-bonded macromolecular assemblies is roughly disk-shaped with a 9 nanometer diameter and a 2 nanometer thickness. Its size and molecular mass (34,000 daltons) are comparable to that of small proteins.

**Hawker et al., 1990** reported new convergent approaches to monodisperse dendritic macromolecules. A novel convergent approach for the synthesis of dendritic macromolecules is presented and versatility demonstrated with the synthesis of a series of monodisperse dendritic polyether macromolecules based on 3,5-dihydroxybenzyl alcohol as the monomer unit up to a molecular weight of 40,689.

**Launay et al., 1994** reported fourth-generation neutral phosphorus-containing dendrimers are prepared in good yields. The only byproducts are NaCl and H₂O, and the products contain highly reactive functional groups along the periphery.

**Worner et al., 1993** synthesized Polynitrile- and Polyamine-Functional Poly (trimethylene imine) Dendrimers. By quantitative cyanoethylation of polyamines combined with catalytic hydrogenation (Raney nickel) of the resulting polynitriles, poly (trimethylene imine) cascade molecules are accessible in high yields and high purities. Starting from ammonia, five generations of highly symmetrical dendrimers without structural defects were prepared with this reaction sequence.

**Frechet et al., 1989** reported contributions by key researcher’s significantly expanded the realm of dendrimer chemistry with the “convergent synthesis”.

**Tomalia et al., 1989** described the preparation of dendrimers and their use as fundamental building blocks that may be covalently bridged to form poly (dendrimers) or so-called “starburst polymers”. These poly(dendrimers) are now referred to as “megamers.

**Tomalia et al., 1985** described the first synthesis of a new class of topological macromolecules which we refer to as “starburst polymers. Fundamental building blocks to this new polymer class are referred to as dendrimers. These dendrimers differ from classical monomers/oligomers by their extraordinary symmetry, high branching and maximized (telechelic) terminal functionality density. The dendrimers possess “reactive end groups” which allow (a) controlled molecular weight building
(monodispersity), (b) controlled branching (topology), and (c) versatility in design and modification of the terminal end groups. Dendrimer synthesis is accomplished by a variety of strategies involving “time sequenced propagation” techniques. The resulting dendrimers grow up in a geometrically progressive fashion as shown: Chemically bridging these dendrimers leads to the new class of macromolecules known as starburst polymers.

**Tomalia et al., 1984** reported development of the divergent, macromolecular synthesis of “true dendrimers” in the tomalia group. The first article using the term “dendrimer” and describing in great detail the preparation of poly (amidoamine) (PAMAM) dendrimers was presented in 1984 at the 1st International Polymer Conference, Society of Polymer Science, Japan (SPSJ). It was then published in 1985.

**Buhleier et al., 1978** reported first concept of repetitive growth with branching and applied it to the construction of low molecular weight amines.

**Flory et al., 1941** defined the variables involved on modeling the position vectors of atoms in macromolecules. The first successful laboratory synthesis of such dendritic complexity did not occur until the late 1970s. It required a significant digression from traditional polymerization strategies with realignment to new perspectives. New synthesis concepts that have led to nearly Monodispersed synthetic macromolecules. This was the first time in the history of synthetic polymer science that precise abiotic macromolecules could be synthesized without the use of a biological system. The result was a unique core-shell macromolecular architecture, now recognized as dendrimers.

Exhaustive literature survey made me to think of exploring the possibilities and innovative concepts in dendrimers for targeted drug delivery.
2.2 Underlying principle for research work:

Drug [Anticancer drug]  
Disease [Cancer]  
Delivery system [PAMAM Dendrimers]

Formulation design: Rule of 3

Drug targeting: Right drug at right time at right place

The latest report from the International Agency for Research on Cancer (IARC), a branch of the World Health Organization, states that cancer has emerged as a major public health problem in developing countries, matching its effect in industrialized nations. In 2005, a total of 7.6 million people died due of cancer. More than 11 million people are diagnosed with cancer every year. It is estimated that there will be 16 million new cases every year by 2020. Around 60% of the new cases will occur in the less developed parts of the world. Global cancer rates are expected to increase 50 percent by the year 2020, according to the latest report from the International Agency for Research on Cancer.

The major drawback associated with anticancer drugs is their cytotoxic side effects and non-availability of appropriate dose at the desired site. Conventional mode of administration of such bioactive leads to their interaction with cancerous as well as normal cells. This not only precipitates toxicity but also adds to slightly modify the chemical structure of the drug thus may reduce its efficacy. The effectiveness of a cancer therapeutic device is measured by its ability to reduce and eliminate tumors without damaging healthy tissue. Therefore, a distinct capacity to target tumors is essential in the success of the therapeutic device. An increased site specificity and internalization can improve the efficacy of treatment and decrease the possibility of the serious side effects that cancer patients often experience. The ultimate goal of cancer therapeutics is to increase the survival time and the quality of life.
Nanoparticle systems offer major improvements in therapeutics through site specificity, their ability to escape from multi-drug resistance, and the efficient delivery of an agent.

Cancer has a physiological barrier like vascular endothelial pores, heterogeneous blood supply, heterogeneous architecture etc. For a treatment to be successful, it is very important to get over these barriers. Cancer represents an enormous biomedical challenge for drug delivery. Cancer treatment is very much dependent on the method of delivery. In the past, cancer patients were using various anticancer drugs, but these drugs were less successful and had major side effects. The treatment of cancer using nanoparticles targeted drug delivery is the latest achievement.

Any route of administration, formulation play an important role i.e. the way drug is introduced into the body is as important as the drug itself in attaining the desired therapeutic efficacy. Nanoformulations have already been used as drug delivery systems with great success and nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumor therapy. Selective targeting of anti-tumor agents with concomitant elimination of toxic effects is the prime objective in cancer chemotherapy. The clinical outcome of systemic therapy rests on administrated anti-neoplastic agents to destroy aberrant tumor cells and doing relatively less damage to host cells. Currently, the therapeutic index of most of the anti-neoplastic agents used in systemic therapy remains marginal, despite efforts to modify the drugs to achieve tumor specificity. The lack of success of systemic therapy to achieve tumor specificity is barred on the fact that biochemical differences between tumor and host cells are minimal and almost always quantitative rather than qualitative.

**Rationale for selection of drug:**

Cisplatin is the member of platinum compounds proven efficient for treating a variety of cancer including pulmonary small-cell carcinomas, carcinoma of testis and epithelium carcinoma of head and neck. When solution of drug is given directly by injection form the drug is distributed and taken by the whole body and kills the tumor cells (along with normal cells) by inducing the process of apoptosis. But when it
induces the process of apoptosis in normal cells it causes toxicity of that particular organ for e.g in case of ears cisplatin induces apoptosis in auditory sensory cells resulting in deafness. Along with this the other side effects include toxicities of bone marrow, digestive tract and skin rash or itching. Vomiting occurs in about half the patients, and a further 25% had nausea without vomiting.

Till date cisplatin is available only in the injection form for clinical use but its normal injection results in variety of side effects as mentioned above due to distribution and uptake of drug in whole body.

To overcome these undesirable side effects of cisplatin and to increase the concentration of drug at the tumor site, cisplatin could be entrapped in colloidal drug carriers, such as PAMAM dendrimers, which may provide a better means of delivery in terms of enhanced uptake of drug carriers by the tumor cells only and increased local concentration of the drug at the receptor site because of “Enhanced Permeation Retention Effect” i.e., property of tumor vasculature which is leaky, disorganized and possesses an enhanced capability for the uptake of particulate drug carriers and to retain them because of undeveloped lymphatic drainage system as compared with the normal blood vessels that have intact and continuous vasculature. Studies have suggested that tumor vasculature is hyperpermeable and selectively takes up macromolecules and colloidal carriers of diameter up to 780 nm. Thus, if a drug loaded particulate carrier reach the tumor site it would remain inside the tumor for a longer time releasing the drug either in the vicinity of the tumor cells or internalized by the cell and releases the drug. Thus, such a delivery method could improve the selectivity of treatment by increasing the ratio of cisplatin absorbed by the tumor cells to cisplatin absorbed by other tissues. In the present study, we have entrapped cisplatin in novel PAMAM dendritic system as drug carrier. Although acrylate moieties used in synthesis are cytotoxic in nature yet they being covalently linked with ethylenediamine groups in dendritic units, are not exposed to normal cells while its retention in biological environment. Through dendritic structure the drug is released in controlled manner. This system is proposed to perform dual function, first through retention of drug within minicontainers of system and secondly, controlled and sustained release of drug. The formulation based on proposed hypothesized
system for the present study may be drug loaded 4.0G PAMAM dendrimers and drug loaded PEGylated dendrimers.

2.3 Rationale of selecting Polyamidoamine (PAMAM) dendrimer

This system serves to fulfill following objectives:

- Biocompatible and nonimmunogenic.
- Extension in circulation time essential to produce clinical effect.
- Able to cross bio- barriers like blood brain barrier, cell membrane, etc.
- Free surface groups can form complex or conjugates with drug molecules or ligands by using cross linkers.
- Dimensional stability and controlled method of synthesis.
- Exhibits minimum cytotoxicity up to 5.0 generation
- Hollow cavity for encapsulation of drug.
- Suitability for intracellular accessibility.
- Prolonged delivery of bioactive.
- Dendrimer drug complex or conjugate exhibits better stability of bioactive

in -vivo.

The problems in vesicular system like chemical instability, drug leakage, aggregation and fusion during storage, solubility in physiological environment, lyses of phospholipids. Purity of natural phospholipids, cost of production also lack in dendritic system.

Rational of selecting polyethylene glycol (PEG)

The advantages of PEGylation technology are the following:

- Increased bioavailability
- Increased blood circulation of the drug
- Optimized pharmacokinetics
- Decreased immunogenicity
- Decreased frequency of administration.
Reduced antigenicity and immunogenicity of the molecule to which PEG is attached.

Markedly improved circulating half life in *in-vivo* due to either evasion of renal clearance as a result of the polymer increasing the apparent size of the molecule to above the glomerular filtration limit, and/or through evasion of cellular clearance mechanisms.

PEG has been found to be soluble in many different solvents, ranging from water to organic solvents such as toluene, methylene chloride, ethanol and acetone.

Enhanced proteolytic resistance of the conjugated molecules.

Improved thermal and mechanical stability of PEGylated molecule.

Improved formulation into materials used for some slow release (depot) administration strategies.

An additional benefit of PEGylation related to solubility, is the ability to achieve high concentrations of PEGylated proteins in aqueous solution, without causing aggregation.

In this current context and scope, the research is designed to target tumor cell with anticancer drug loaded dendrimers conjugated with targeting moieties. Entire problems can be addressed with the novel dendritic system in order to improve drug’s release profile and to improve bioavailability by complexing it with dendritic system. The system is hypothesized to have the drug in their internal cavities, which are shielded by exterior groups. Further conjugation of Poly Ethylene Glycol (PEG) chain will sustain the release of drug and targeting moieties will be attached with the help of linker. Also conjugation on dendritic surface will be used in targeting of anticancer drug to cancerous cell, which will reduce the frequency of dosing and hence increases patient compliance. PAMAM dendrimers based drug delivery may contribute by:

- Tremendous solublization potential will improve the aqueous solubility of anticancer drugs, especially having poor solubility.

- Conjugation of PEG on surface will further reduce the cytotoxicity of dendritic system displaying amine groups on the surface.
Targeting moieties attached with surface groups will deliver drug at the site of interest.

Enhanced circulation time of dendrimers based formulations will reduce the frequency of dosing.

Selective targeting with the help of dendrimers will deliver higher drug at targeted site thus less side effects.

Clinical application by improving biodistribution, safety profile, reduced frequency of dosing and poor water solubility.

Research findings would be helpful for the exploitation of dendrimers as future drug delivery carriers.

2.4 Proposed Methodology of Research Work (Plan of Work)

1. Literature survey
2. Preformulation studies of the drug
   - Identification
   - Physical appearance
   - Melting point
   - FT-IR spectra
2. Solubility study of drug
3. Determination of Partition coefficient
4. Standard curve for the quantitative estimation of drug
3. Synthesis of PAMAM Dendrimers by divergent method
4. Characterization of Synthesized PAMAM Dendrimers
   - Physico-chemical characteristics and identification of Dendrimers
     - Boiling point determination
     - Measurement of intrinsic viscosity
   - Ultraviolet-Visible spectroscopy
   - Fourier transform infrared spectroscopy
5. Complexation of Drug with Dendrimers and Identification By
   - Ultraviolet-Visible spectroscopy
   - Fourier transform infrared spectroscopy
   - Nuclear magnetic resonance spectroscopy

6. Surface Modification of PAMAM 4.0G Dendrimers
   - Conjugation of polyethylene glycol (PEGylation)
   - Conjugation of acetyl moiety (Acetylation)
   - Conjugation of gallic acid

7. Characterization of prepared Surface Modified Dendrimers
   - Ultraviolet-Visible spectroscopy
   - Fourier transform infrared spectroscopy
   - Nuclear magnetic resonance spectroscopy
   - Mass spectroscopy
   - Differential scanning calorimetry

8. Complexation of drug with Surface Modified Dendrimers and identification by:
   - Ultraviolet-Visible spectroscopy
   - Fourier transform infrared spectroscopy
   - Nuclear magnetic resonance spectroscopy

9. *In-vitro* characterization of prepared PAMAM formulations
   - Hemolytic toxicity

10. *In-vitro* Cytotoxicity Studies
    - Plain dendrimers
    - Surface modified dendrimers

11. Stability studies
Drug selected for the present study is Cisplatin which is useful in the management of cancer chemotherapy.

2.1 CISPLATIN:

(Clarke’s analysis of Drugs and Poisons 2006; B.P. 2003; Martindale).

**Synonym:**
CDDP; Cis-platinum; Cisplatina; Cisplatine;

**Structure:**

![Structure of Cisplatin](image)

**Chemical Name:**
cis-Diamminedichloroplatinum

**Molecular Formula:**
(NH₃)₂.PtCl₂

**Molecular Weight:**
300.06 g/mol

**Category:**
Cytotoxic

**Definition:**
Cisplatin contains not less than 97.0% and not more than the equivalent of 102.0 percent of cis-diamminedichloroplatinum.

**Description:**
A yellow powder or yellow or orange-yellow crystals.

**Melting Point:**
270°C

**Solubility:**
Slightly soluble in water; practically insoluble in alcohol; sparingly soluble in dimethylformamide.

**pH:**
A 0.1% solution in sodium chloride 0.9% has a pH of 4.5 to 6.0 immediately after preparation.

**Partition coefficient:**
Log P (octanol/water), -2.19.
**Storage:** Store in airtight containers. Protect from light.

**Stability:** Decomposition of cisplatin in aqueous solutions is primarily due to reversible substitution of water for chloride, and its stability is enhanced in sodium chloride solutions because of the excess of chloride ions available.

**Incompatibility:** Cisplatin is rapidly degraded in the presence of bisulfite or metabisulfite. Sodium bicarbonate may also increase the loss of cisplatin from solution, and in some cases may cause precipitation. The stability of cisplatin when mixed with fluorouracil is reported to be limited, with 10% loss of cisplatin in 1.2 to 1.5 hours. Mixtures with etoposide in sodium chloride 0.9% injection formed a precipitate if mannitol and potassium chloride were present as additives. Turbidity has been reported within 4 hours of mixing 0.1% solutions of cisplatin and thiotepa in glucose 5%. Cisplatin exhibits variable incompatibility with paclitaxel, depending on the paclitaxel concentration and the temperature. Cisplatin reacts with aluminium causing loss of potency and precipitate formation.

**Pharmacology:** It is a platinum coordination complex that causes cross linking of DNA favoured site being N⁷ of guanine residue. It can also react with –SH groups in proteins and has radiomimetic property.

**Pharmacokinetics:** After intravenous doses cisplatin disappears from the plasma in a biphasic manner and half-lives of 25 to 49 minutes and 3 to 4 days have been reported for total
platinum.

**Absorption:** It is not absorbed orally and must be given intravenously and intraperitoneal route. Cisplatin is well-absorbed on intraperitoneal use.

**Distribution:** More than 90% of the platinum from a dose is protein bound within 2 to 4 hours, only the unbound fraction has significant antitumor activity. Cisplatin is concentrated in the liver, kidneys, and large and small intestines. Penetration into the CNS appears to be poor. It is distributed into breast milk.

**Metabolism:** The chlorine atoms in cisplatin undergo chemical displacement reactions with water and sulphydryl groups (for example, on proteins) rather than undergoing enzyme-catalyzed metabolism.

**Excretion:** Excretion is mainly in the urine but is incomplete and prolonged: up to about 50% of a dose has been reported to be excreted in urine over 5 days and platinum may be detected in tissue for several months afterwards. The unbound fraction which is more rapidly cleared may be actively secreted by the renal tubules.

**Volume of distribution:** 11 to 12 L/m² also reported as 20 to 80L.

**Half-Life:** Plasma unbound cisplatin, 25 to 48 min and protein-bound platinum, 58 to 73h.

**Clearance:** Plasma, 15 to 16 L/h/m².

**Adverse Effects:** Severe nausea and vomiting occur in most patients during treatment with cisplatin, nausea may persist for up to a week.
Toxicity: Serious toxic effects on the kidneys, bone marrow, and ears have been reported in up to about one third of patients given a single dose of cisplatin, the effects are generally dose-related and cumulative.

Drug Interactions: Use with other myelosuppressive, nephrotoxic or ototoxic drugs may exacerbate the adverse effects of cisplatin. The effects of cisplatin on renal function may also affect the pharmacokinetics of other drugs excreted by the renal route.

Clinical Efficacy: It is used in various first-choice combinations for the treatment of metastatic carcinoma of the testes, ovary, prostate and cervix, squamous cell carcinoma of head and neck, small–oat–cell and non-squamous cell cancer of the lung, advanced cancer of the bladder, medulloblastoma and retinoblastoma that has proved refractory to surgery or radiation. It also is used alone in the treatment of bladder cancer and other types of solid tumors.

Dose and administration: Cisplatin is given by intravenous infusion in sodium chloride 0.9% or in a mixture of sodium chloride and glucose. In monotherapy, it is usually given as a single dose of 50 to 120 mg/m² every 3 to 4 weeks. Alternatively, 15 to 20 mg/m² are given daily for 5 days every 3 to 4 weeks. Lower doses are generally used for combination chemotherapy regimens than for single agent therapy, 20 mg/m² or more is given once every 3 to 4 weeks. A dose of 20 mg/m² daily for 5 days every 3 to 4 weeks has been used in combination chemotherapy of testicular tumours.
Chapter 2

Literature review


Infrared absorption spectroscopy in USP 2003.


Official Formulations:

a) Cisplatin for Injection USP

b) Cisplatin Injection I.P. 1996

Marketed Preparations:

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CISPLATIN KOREA (Inj.)</td>
<td>Shree Ganesh</td>
</tr>
<tr>
<td>CADIPLAT (Vial)</td>
<td>Oncomed</td>
</tr>
<tr>
<td>CISTEEN (Inj.)</td>
<td>VHB Life Sciences</td>
</tr>
<tr>
<td>CISPLATIN (Vial)</td>
<td>Khandelwal</td>
</tr>
<tr>
<td>KEMOPLAT (Vial)</td>
<td>Dabur PHARMA</td>
</tr>
<tr>
<td>CISPLATIN (Vial)</td>
<td>Pharmacia India</td>
</tr>
<tr>
<td>CISPA (Vial)</td>
<td>Novatech</td>
</tr>
<tr>
<td>CISPLAT (Inj.)</td>
<td>Biochem</td>
</tr>
</tbody>
</table>

Identification:

a) By Infrared absorption spectrophotometry. (B.P. 2003)

b) Add 50mg to 2ml of dilute sodium hydroxide solution in a glass dish. Evaporate to dryness.
Dissolve the residue in a mixture of 0.5ml of nitric acid and 1.5ml of hydrochloric acid. Evaporate to dryness. The residue is orange. Dissolve the residue in 0.5ml of water and add 0.5ml of ammonium chloride solution. A yellow, crystalline precipitate is formed.