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Review Article

A REVIEW ARTICLE ON DENDRIMER TOXICITY

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ABSTRACT

PAMAM Dendrimer is highly branched polymer with low polydispersity and water soluble. The cationic Dendrimer are highly toxic to as the comparison of anionic Dendrimer with high generation (G5, G6, G7) Dendrimer. The toxicity caused by the high generation of Dendrimer is more as the comparison to low generation of Dendrimer.

The following Dendrimer toxicity is reported that mortality, sub lethal toxicity, hatching effect shown in the zebrafish and also caused cytotoxicity in blastomers in zebrafish. In the lethal toxicity like as reduce the body weight, bent trunk, small head and eye.

The PAMAM Dendrimer toxicity also reported that haemolytic, change the erythrocyte shape. Also reported that haemobilia and spleenomegaly (inlargment of spleen) with the high generation of Dendrimer G7 with 500mg/Kg orally dose.

INTRODUCTION

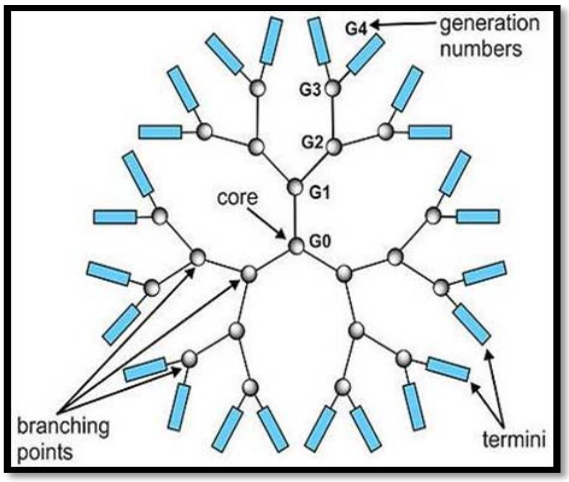
The Dendrimer word derived from a Greek word 'Dendron'. The Dendrimer have a tree like structure. The Dendritic molecule carriers for Drug Delivery, Gene delivery, Diagnosis and Biological application.[1] They are highly branched molecule. Their reasonable cost of manufacture, toxicological profile and biocompatibility distinguish them from other nanosised species used for polyvalent or multivalent drug discovery[1].

Dendrimer are polymers which are the water soluble in nature. Dendrimers are nanosized, three-dimensional polymers characterized by tree-like branching and compact spherical geometry.[2] It is possible to control on molecule size, shape, dimension, density, polarity, flexibility, and solubility by choosing different building/branching units and functional groups.[3]

Dendrimers are a novel class of polymeric materials. A dendrimers are typically symmetrical about the core and often adopt a sphere-shaped 3D structural design that provides a high level of surface functionality and flexibility. The term originates from "Dendron" sense a tree in Greek. Dendrimers are building from a starting atom, such as nitrogen, carbon and other elements are added by a repeat series of chemical reactions that create a spherical branching structure.[10]

Polyamidoamine (PAMAM) dendrimers contain a well-defined, mono-dispersive and stable molecular architecture that is beneficial for targeted drug delivery. The highly branched, multivalent and multifunctional shell of dendrimers allows for exploitation of their surface chemistry, and the comparatively solvent-filled interior core renders them helpful for drug delivery.[11]

General structure of Dendrimer



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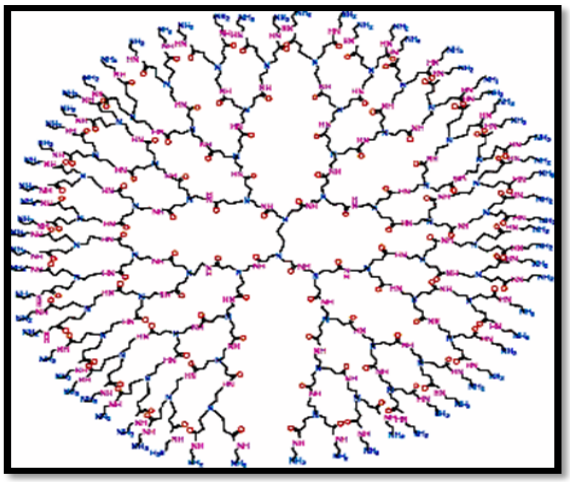
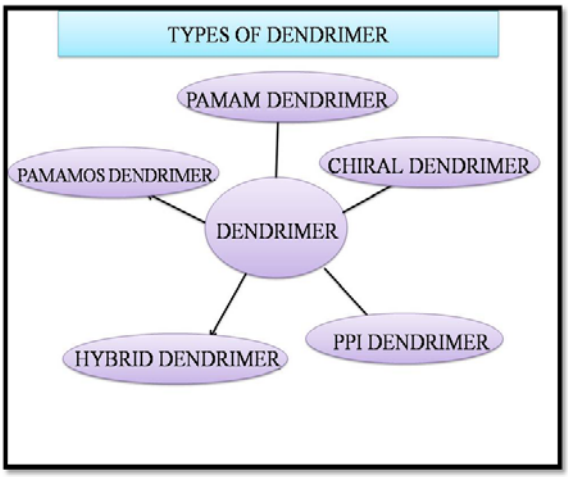
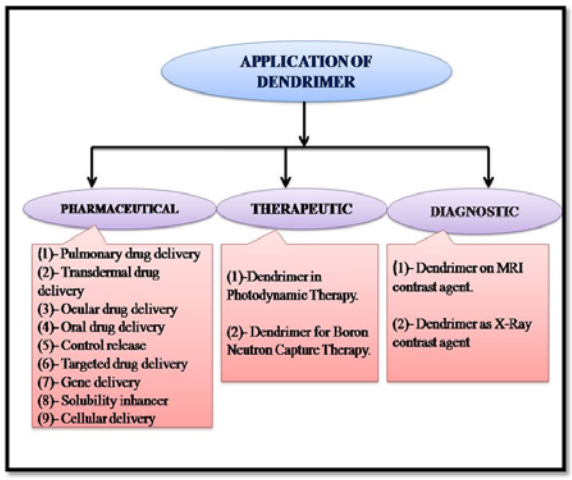


Types of Dendrimer[11]





Application of Dendrimer[11]

Cytotoxicity:

PAMAM Dendrimer (G-3.5 & G-4) was shown toxicity in Zebrafish embryo. The G-4 Dendrimer have amino functional group on the end of the terminal. Mainly toxicity of the PAMAM Dendrimer G-4 caused due to cationic charge of molecule. The G-3.5 Dendrimer have carboxylic group on the end of the terminal. The carboxylic group is low toxic with compare of the amino group. The low generation of PAMAM Dendrimer has high biocompatibility show.

The Dendrimer toxicity is depend on the generation, the generation are increase that means the increase toxicity. Cationic Dendrimer are more toxic as the compare of anionic dendrimer, because cationic group have the positive ion charge and anionic groups have negativity charge.

In the Zebrafish G-4 PAMAM Dendrimer caused cytotoxicity in fibroblast which is depend on the concentration of Dendrimer. If the G-4 PAMAM Dendrimer will modify with RGD (Arg-Gly-Asp) they are reduced the cytotoxicity in Zebrafish but which is not completely abolished[4]. The G-4 PAMAM Dendrimer was caused the sublethal toxicity in zebrafish and which is not arrest the embryonic development but produce the impair development of embryo.

Haemolytic Activity:

PAMAM Dendrimer of G-2, G-3 and G-4 caused the erythrocyte shape and also caused the cell aggregation of the different concentration of Dendrimer[4]. In the leving being, blood constituents are the first target of drug action. The drug binding plasma protein, platelets, leucocyte and erythrocyte show action and may be lead to serious problem[4]. The PAMAM Dendrimer G-2, G-3 and G-4 were examined haematotoxicity which is the influence of Red Blood Cell morphology[4]**.** The erythrocyte cells have the biconcave shape. The increase concentration of the G-4 PAMAM Dendrimer in blood cells which is change the shape of RBCs which observed by the optical microscope[5].

Cationic (amino group) Dendrimer has changed the erythrocyte cells due to interact with the erythrocyte membrane as the compare to anionic Dendrimer[5]. The erythrocyte cells surface have negative charge due to the presence of glycolipid and protein so the cationic Dendrimer interect with the erythrocyte membrane due to the electro static attraction. The electro static repulsion prevent in RBCs by self aggregation[6]. Cationic PAMAM Dendrimer attached to RBCs surface and produce the electrostatic

attraction, they are caused erythrocyte aggregation by cross linking of Dendrimer.[7,8]

Oral toxicity:

Cationic (positive charge) Dendrimer caused more toxicity, the high generation (G-6 & G-7) of PAMAM Dendrimer have terminal group of amine (-NH_2) or hydroxyl (-OH), they are caused haemobelia and spleenomegaly (increase spleen shape).[9] The tolerable dose of high generation of PAMAM Dendrimer by oral route 200mg/kg and low generation of PAMAM Dendrimer (G-3 & G-4) by oral route 500mg/kg.[9]

The high generation of PAMAM Dendrimer is caused more toxic as compared to low generation of PAMAM Dendrimer. The oral toxicity of hydroxic group (-OH) PAMAM Dendrimer G-7 caused toxicity at the dose of greater than 300mg/kg proved.[9] The animal was lost 10% body weight over the three days after oral administration of the dose, which is caused the abnormally enlarged spleen (spleenomegaly). They are also caused the RBCs damage and inflammation by the orally administration of G-7 –OH PAMAM Dendrimer and G-7 –NH_2 PAMAM Dendrimer orally administered 50mg/kg caused haemobilia and loss of 10% body weight.

References:

1. Gajbhiye V, Palanirajan VK, Tekade RK and Jain NK. (2009), "Dendrimers as therapeutic agents: a systematic review", JPP 2009, 61: 989–1003.
2. Scott H. Medina and Mohamed E. H. El-Sayed. (*2009*), "Dendrimers as Carriers for Delivery of Chemotherapeutic Agents", *Chem..rev.2009, 109,3141-3157.*
3. Yiyun C, Zhenhua XU, Minglu MA, Tongwen XU. (2007) "Dendrimers as Drug Carriers: Applications in Different Routes of Drug Administration", Published online in Wiley Inter Science (www.interscience.wiley.com). DOI 10.1002/jps.21079.
4. Tisha C King Heiden et al. (2007). "Development toxicity of low generation PAMAM Dendrimer in Zebrafish," Toxicology and Applied Pharmacology 2007, 225: 70-79.
5. Domanski DM, Klajnert B, Bryszewska M. (2003). "Influence of PAMAM Dendrimer of human red blood cells," Biochemistry 2004. 63: 189-191.
6. N. Malik, R. Wiwattanapatapee, R. Klopsch, K. Lorenz, H. Frey, J.W. Weener, E.W. Meijer, W. Paulus, R. Duncan, Dendrimers: relationship between structure and biocompatibility in vitro, and preliminary studies on the biodistribution of 125I-labelled polyamidoamine dendrimers in vivo, J. Control. Release 2000. 65: 133– 148.
7. T.L. Zhang, J.F. Lu, Y.X. Gao, K. Wang, Arsenite, arsenate and vanadate affect human erythrocyte membrane, J. Inorg. Biochem. 2000. 79: 195–203.
8. Z.-Y. Zhang, B.D. Smith, High-generation polycationic dendrimers are unusually effective at disrupting anionic vesicles: membrane bending model, Bioconjug. Chem. 2000. 11: 805–814.
9. Thiagarajan G, Greish K, Ghandehari H. (2013). "Charge affect the oral toxicity of poly (amidoamine) dendrimers," Europian Journal of Pharmaceutical and Biopharmaceutics 2013. 5-9.
10. Surendra Tripathy and Malay K Das, (2013) Dendrimers and their Applications as Novel Drug Delivery Carriers Journal of Applied Pharmaceutical Science Vol. 3 (09),142-149
11. Tisha C. King Heiden, Emelyne Dengler, Weiyuan John Kao Warren Heideman, Richard E. Peterson, (2007) Developmental toxicity of low generation PAMAM dendrimers in zebrafish Toxicology and Applied Pharmacology 225 (2007) 70–79.