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Dendrimers: a Review on Synthetic Approaches

Vivek Gupta, Surendra Kumar Nayak

School of Pharmaceutical Sciences, Lovely Faculty of Applied Medical Sciences, Lovely Professional University, Phagwara, Punjab, India.

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ABSTRACT

This review article is focused on different synthetic strategies used in dendrimer synthesis at commercial and laboratory scale. These synthetic strategies includes their own advantages and disadvantages. This review will cover divergent (from core to surface) and convergent (from surface to core) approaches used in dendrimer synthesis and the problems associated with these synthetic strategies. This article also covers the important applications of dendrimers in the field of pharmaceutical sciences. This data of review is collected from various articles, research papers and patents available on dendrimers.

INTRODUCTION

Dendrimers are highly branched polymer of nano size. These are three dimensional, monodisperse, globular macromolecules having high number of functional groups on their surface. Dendrimers are synthesized by series of repetitive steps. The idea of repetitive growth with branching was first reported by Vogtle (Buhleier *et al.,* 1978). This was followed by independent development of the divergent, macromolecular synthesis of "true dendrimers" by Tomalia (Tomalia *et al.,* 1984, Tomalia *et al.,* 1985). They were the first who coined the term dendrimer for these macromolecules and described the synthesis of poly (amidoamine) (PAMAM) dendrimer in detailed manner. Then a convergent synthetic method of dendrimer synthesis was introduced by Frechet (Hawker and Frechet, 1990).Afterwards there was explosion of scientific interest in dendrimers as a new class of polymeric nanomaterial because of its various cutting edge structural advantages over simple polymers. Dendrimers are highly branched polymers which have special characteristics like different functional end groups, higher density and lesser viscosity (Fréchet *et al.,* 1996,Jikei and Kakimoto 2001, Aulenta, 2003, Voit and Lederer2009). Due to these unique features this class of polymeric nanomaterial have various applications in different fields like as drug delivery (Florence, 2005, Gillies and Fréchet, 2005, Emanuele and Attwood, 2005, Wolinsky and Grinstaff, 2008, Medina and El-Sayed, 2009), dendrimer based nanomedicine (Majoros and Baker 2008), gene delivery (Mintzer and Simanek, 2009), light harvesting (Adronov and Frechet, 2000), dendritic nanomaterials (Grimsdale and Mullen 2005), electrode design (Guldi and Prato, 2004), solubility enhancers (Gupta *et al.,* 2006) and for various biotech applications (Grinstaff, 2008).

Table 1: Dendrimer families.

S. No.	Type of Dendrimer	Discovered by
1.	Polyamidoamine (PAMAM) Dendrimer	Tomalia (Tomalia et al.)
2.	Arborols	Newkome (Newkome *et al.,* 1985, Newkome *et al.,* 1996)
3.	Polypropyleneimine (PPI) Dendrimer	De Brabander and Meijer (De Barbender and Meijer, 1993)
4.	Polyether dendrimer	Frechet (Grayson and Frechet, 2001)

There are different dendrimer families with different synthetic routes but common in all is repeated sequence reactions and their purification steps. These dendrimer families are summarized in table 1.

** Corresponding Author*
Vivek Gupta, School of Pharmaceutical Sciences, Lovely Faculty of Applied Medical Sciences, Lovely Professional University, Phagwara, Punjab, India. Email: siaram.vivek@gmail.com

Synthetic Approaches

Literature survey shows us that there arehuge number of synthetic strategies available for dendrimer synthesis. Broadly these strategies can be subdivided into two categories that are divergent and convergent approaches.

Divergent Synthesis

Divergent synthesis is initiated with a multifunctional core molecule like ethylenediamine (EDA), then with the help of Michael addition reaction four arms are added on nitrogen of EDA (two arms possible on each nitrogen), after this in second step EDA is again reacted on these formed four arms through amidation reaction as shown in following figure 1. These two steps can be repeated multiple times to form different generations of dendrimers, in each generation number of arms doubles from previous generation.

To avoid structural defects at higher generations a large excess of Michael donor (EDA) is used in this approach. This divergent route (Tomalia, 1984) is advantageous to get higher yield ofdendrimer with lower purity (Hummelen, 1997)or we can say that purity is compromised for getting higher yield. That's why this approach of synthesis is very useful and used worldwideat commercial scale for production of dendrimers. Lesser purity in divergent synthesis of dendrimers is basically due to one of the following reasons:

Missing repeat units

As divergent synthesis proposing that nitrogen of EDA (Michael donor) is reacting with methyl acrylate (Michael acceptor) through Michael addition reaction but if only one hydrogen of amine replaced and second one is missed to react, thenthis missing unit remain as such and synthesis proceed further and creating impure dendrimer. This defect is shown in figure 2.

Intramolecular and intermolecular cyclization

In second step of amidation there arechances of amidation between two arms with same molecule of ethylenediamine that is called intramolecular cyclization that would stop further growth of dendrimer at these two arms. Similarly amidation with single EDA molecule between two different dendrimer molecules creates intermolecular cyclization as shown in figure 2. This type of dimer formation by intermolecular cyclization stops the growth of both dendrimermolecules at these two arms.

Ester Hydrolysis

There is a chances of hydrolysis of ester bond of Michael acceptor (like methyl acrylate) during dendrimer synthesis. This ester hydrolysis creates acid group that is non-reactive to amine to form an amide in reaction conditions.So ester hydrolysis also generatesdefects in dendrimer synthesis as shown in figure 3.

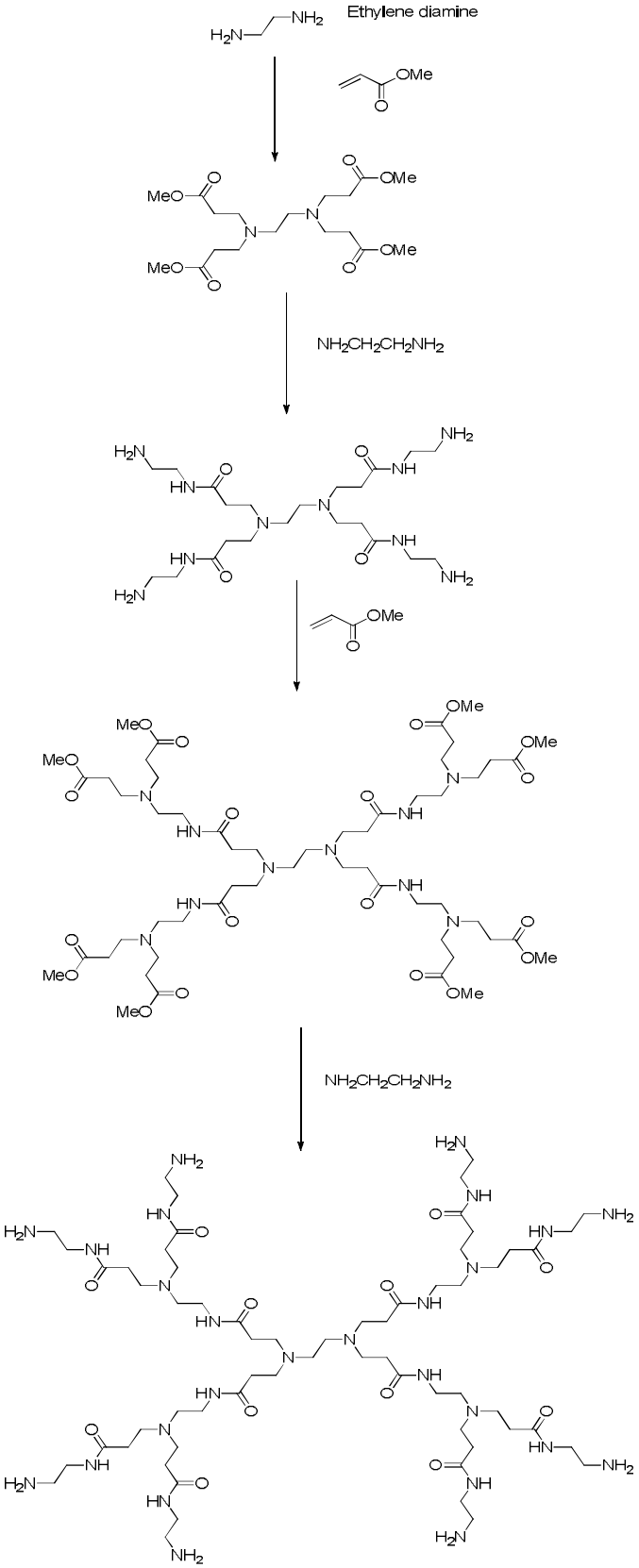

Fig. 1: Divergent approach of dendrimer synthesis.

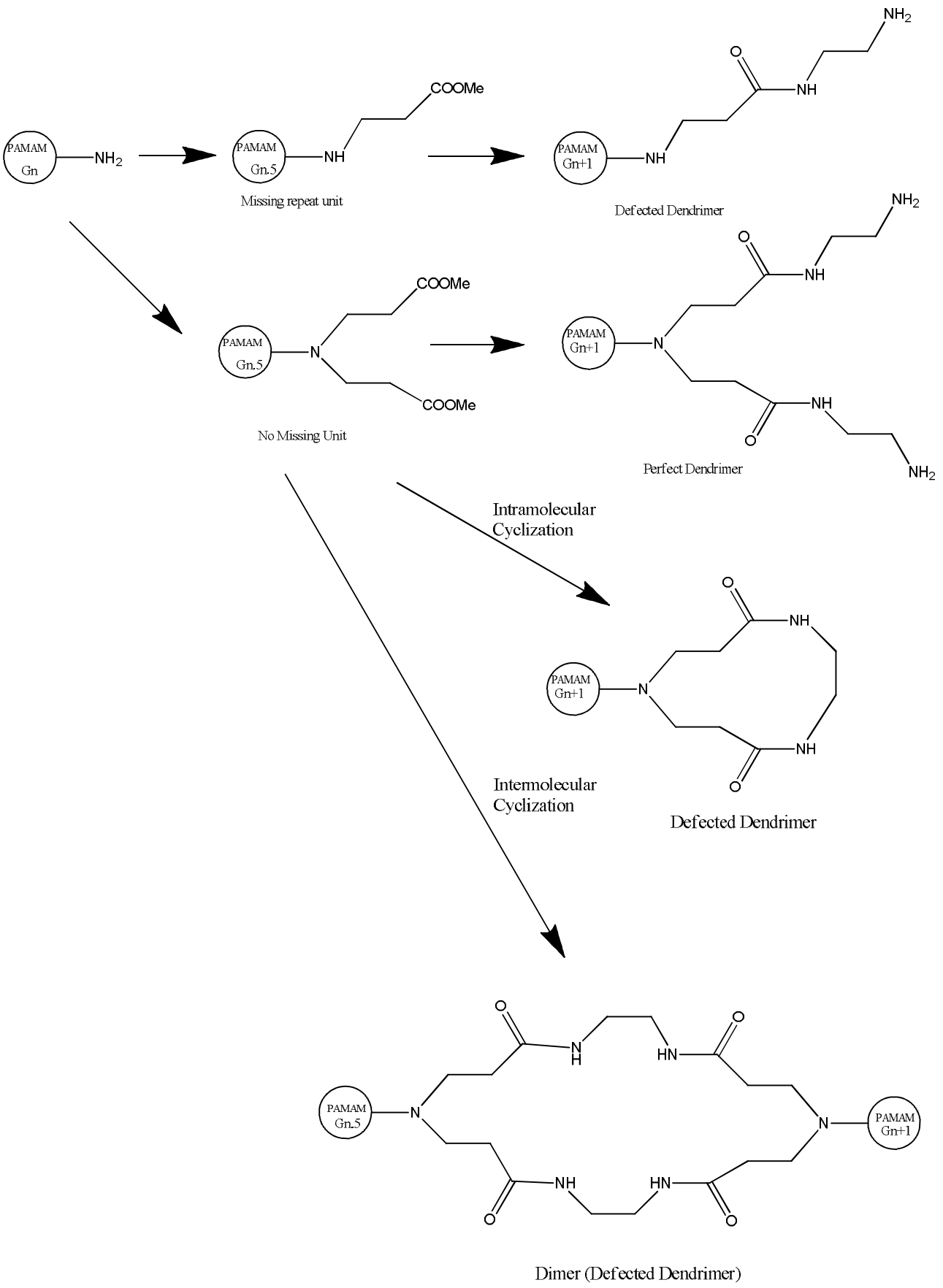

Fig. 2: Various possible defects in divergent dendrimer synthesis.

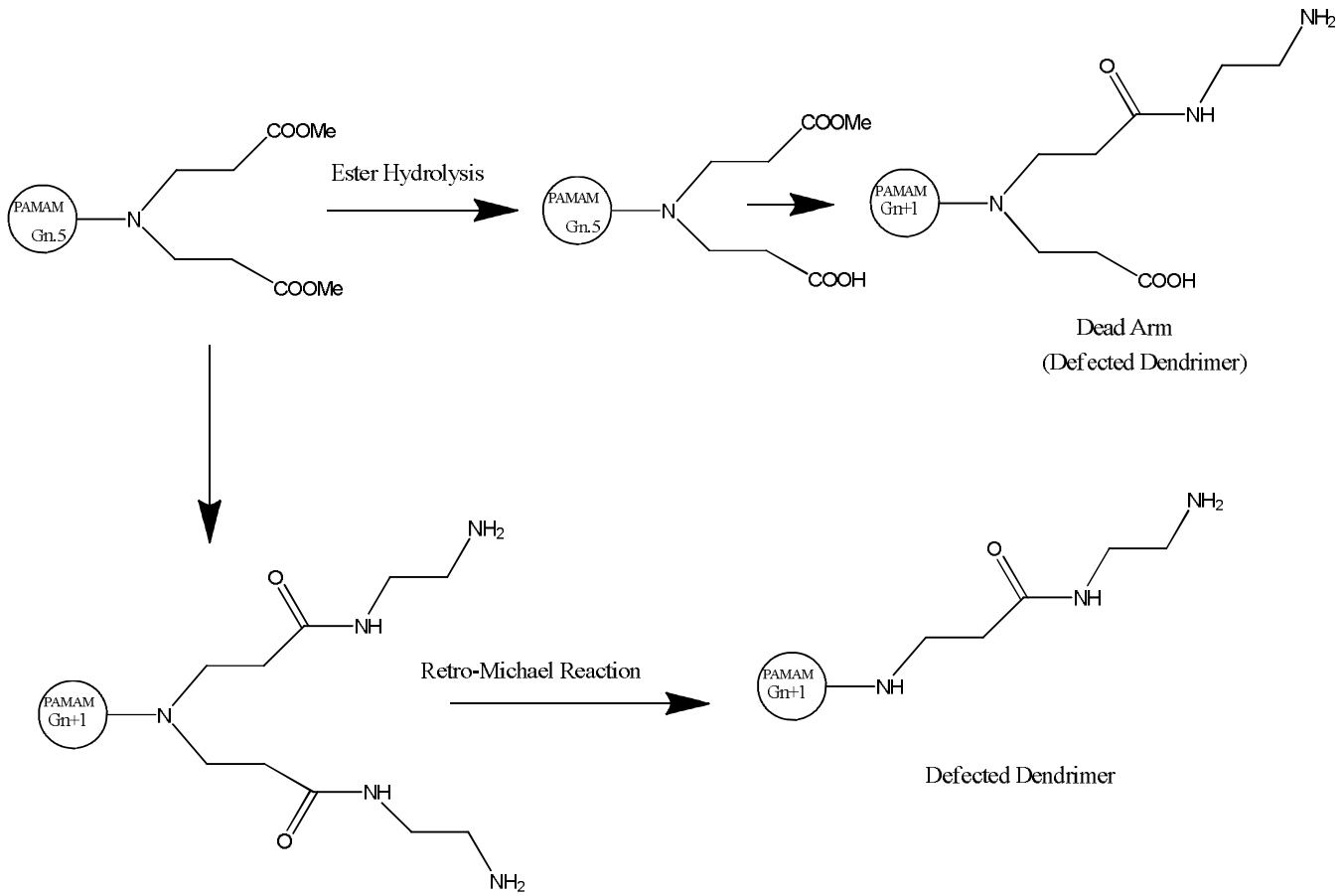

Fig. 3: Ester hydrolysis and Retro-Michael Reactions in divergent dendrimer synthesis.

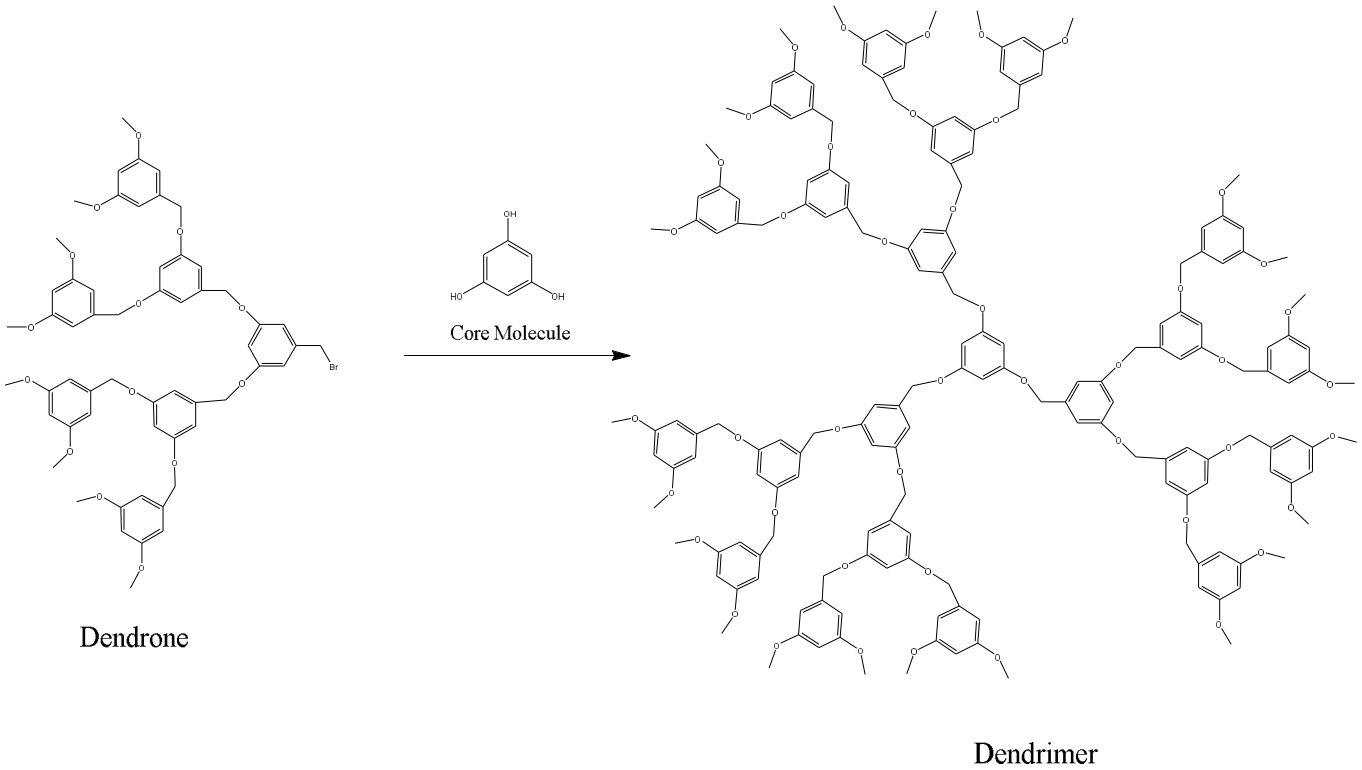

Fig. 4: Convergent approach of dendrimer synthesis.

Retro Michael Reaction

Sometimes there is chances of retro Michael reaction in which reverse of Michael reaction occurs and synthesized arm degrades back to free –NH group as shown in figure 3. Dendrimer synthesis involves stepwise synthesis and purification step after every synthetic step to remove incomplete (defected) dendrimer produced during synthesis. But the purification process is based on molecular properties like mass, size, chemical behavior etc. In divergent synthesis when dendrimer size becomes bigger these differences in molecular properties becomes smaller in each generation. So purification process becomes less efficient at this stage and we have to compromise with lesser purity in divergent process of dendrimer synthesis.

Convergent Synthesis

Convergent approach (Grayson and Frechet, 2001) of dendrimer synthesis overcomes the purity and structural defect issues of divergent synthesis. By this approach more uniform and symmetric dendrimers can be synthesized but with lower overall yield. In other words yield is sacrificed for purity and this approach is generally used for laboratory scale dendrimer synthesis. For commercial scale production, divergent synthesis is still favored. Most commonly used commercially available dendrimers are PAMAM (Tomalia, 1985) and PPI (De Barbender and Meijer, 1993), which are structurally somewhat different in every batch due to structural defects.

Convergent approach of dendrimer synthesis was first introduced by Jean Frechet (Hawker and Frechet, 1990).In this approach dendrons that ends up to terminal groups are synthesized first and in final step these are linked together to a core molecule for getting complete dendrimer structure as shown in figure 4. Dendrimers synthesized by this way have less impurities, more monodispersity and symmetry because better purification is possible of dendrons before final attachment to core. But the size of dendrimer synthesized by convergent approach have limitation due to steric hindrance between dendrons going to attach with core. This size limitation is not with divergent approach of dendrimer synthesis.

IMPORTANT APPLICATIONS OF DENDRIMERS

When drug is conjugated with dendrimer (Figure 5 and Figure 6), it increases its half-life. For example half-life of methotrexate is increased to 24 hours from 24 minutes when conjugated with dendrimer. This longer circulating half-life also increase its efficacy due longer contact time with target site. This also decrease the frequency of drug administration as well as increases patient compliance. Solubility of drug is found greatly enhanced when conjugated with dendrimer. For example paclitaxel solubility is enhanced by 9000 fold when conjugated with dendrimer. Polyethylene glycol (PEG) attached between drug and dendrimer (Figure 7) also plays an important role in enhancing solubility of drug (Owen and Paul Barrett, 2010).

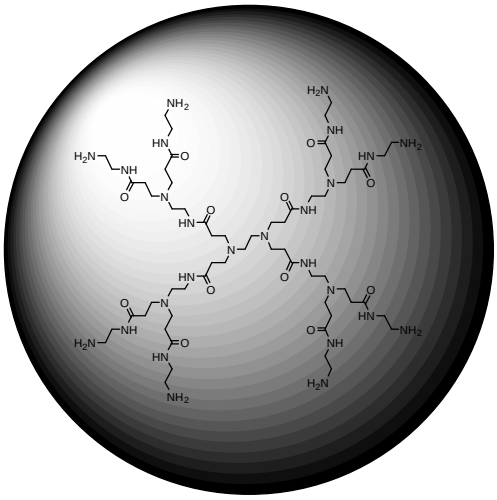

Fig. 5: Structure of PAMAMDendrimer.

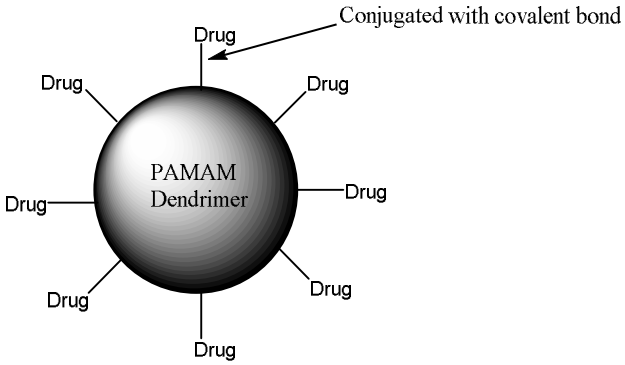

Fig. 6: Drug attached with dendrimer via covalent bond.

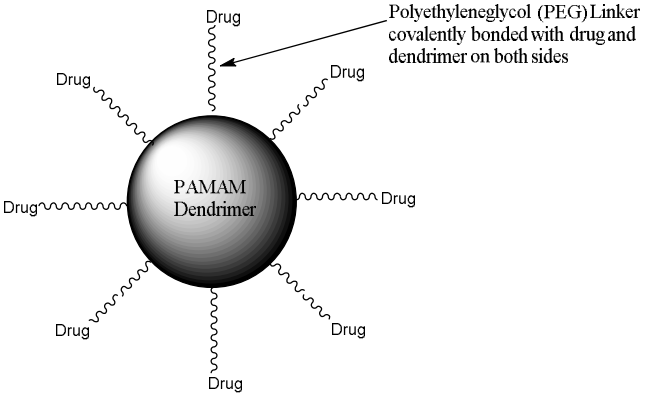

Fig. 7: Drug Dendrimer Conjugate through PEG Linker.

CONCLUSIONS

We have reviewed various synthetic strategies for dendrimer synthesis. In general dendrimers can be synthesized by two techniques that is divergent and convergent approach. In divergent approach, synthesis is started with a core molecule which grows outwards. In convergent approach, dendrons are synthesized first and then connected to the core molecule inward. Divergent approach is used for commercial scale production of dendrimers because by this approach good yield is obtained but purity is sacrificed. Various types of structural defects are possible

in divergent synthesis of dendrimers like missing repeat unit, intramolecular and intermolecular cyclization, ester hydrolysis, retro Michael reaction etc. Convergent approach is used for laboratory scale production of dendrimers with higher purity and lesser defects but yield is sacrificed. Dendrimers synthesized from convergent approach are more uniform and symmetrical with lesser defects because purification can be done at dendron stage that is before attaching to core molecule. Dendrimers have various applications. In the field of pharmaceutical sciences these are specially used for enhancing half-life of drugs and reducing frequency of drug administration. Dendrimers are also used for enhancing solubilities of various drugs.

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