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REVIEW ARTICLE

PAMAM Dendrimers mediated solubility enhancement of poorly soluble drugs: a concise review

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Abstract:
High solubility, high permeability and good stability are basic prerequisites for achieving the bioavailability and hence therapeutic effectiveness. Newly developed drugs having poor solubility are rejected or exhibit suboptimal performance. Poor solubility of new chemical entities discovered or already in the market limits their use in formulation development. Poor solubility being a major obstacle in all checkpoints in drug discovery pipeline. Plethora of techniques/methods are used for the improvement of the solubility of poorly water-soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, cosolvency, micellar solubilization, hydrotropy etc. Dendrimers a nanocarrier shows tremendous Solublization potential. These nonmaterial's have unique property to encapsulate the drug inside as well as binding on surface by electrostatic interaction. The dendrimers is hypothesized to have the drug in their internal cavities which are shielded by exterior groups. Various researchers have explored the Solublization potential of dendrimers using poorly soluble drugs to provide the proof of concept. The results, patents and dendrimers based marketed preparations revealed the efficacy of dendrimers for enhancement of solubility.

Keywords: Solubility, Dendrimers, bioavailability

Introduction

Drugs belonging to BCS class –II & IV are dissolution rate limiting .Dissolution being the prerequisite step for the absorption across bio membrane. The therapeutic effectiveness of any poor solubility leads to unavailability of appropriate dose at the site of action[1]. To address this, structural modifications were attempted but often lead to reduce the efficacy of a drug [2]. Various approaches are practiced such as surfactant-based micellar system (i.e., emulsions, liquid crystals or micelles), surfactant (e.g., using tween, span, etc.), complexation (e.g., using cyclodextrin), salt formation, prodrug formation and cosolvent, etc[3, 4, 5]. In 1991 Newkome *et al.* explored the solublization potential of dendrimers by virtue of their unique properties that favors the solubility enhancement [6].

Dendrimer-mediated solubilization has been found to be superior to cyclodextrin-mediated solubilization [7]. Several hydrophobes such as nifedipine, niclosamide, methotrexate, 5-fluorouracil, indomethacin, propranolol, ibuprofen, flurbiprofen etc. have been successfully solubilized in dendrimers [8, 9, 10, 11,12,13,14].

A unimolecular micelle of polyaryl ether dendrimers was prepared by Hawker *et al.*, 1993 & used to investigate solubilization of nonpolar organic molecules [15]. A liner relationship between amount of solubilized pyrene & the dendrimers concentration was observed[16]. A series of inverted unimolecular micelles with hydrophobic shell & hydrophilic interior was prepared by Stevelmans *et al.*, 1996 [17].

The dendritic 'box' prepared by Meijer co-workers by capping dendrimers surfaces with aminoacids could irreversibly solubilize upto 4 molecules of Bengal rose & 8-10 molecules of 4-nitrobenzoic acid per molecule of dendrimers [18.] The use of crown ether dendrimers to solubilize peptides in organic solvents through peptide – NH^{+3}-crowm ether interactions is also reported. The solubility of myoglobin in dimethyl formamide was dramatically increased with first generation dendrimers probably because of binding of lipophilic dendrimers at protein surface **[19].** Hydraamphiphiles dendrimers forms micelles with compact aggregate surface thus can be used for solubility enhancement of poorly soluble compounds [20,21].

1.1 Host guest interaction:

Dendrimers can encapsulate guest molecules in the internal cavities or electrostatically on the surface. Present article explains possible interaction mechanisms between the dendrimer and a bioactive and their possible contribution in drug delivery.

The proposed mechanisms for the host-guest interaction can be broadly categorized into two main classes: (a) covalent binding, in which the guest molecule forms a chemically bonded conjugate (involving hydrophobic interactions, physical entrapment, hydrogen bonding, or electrostatic bonding either alone or in combination with these methods), and (b) non-covalent binding, in which the guest physically interacts with the dendritic architecture.

Jansen et al., 1994, provided the proof of concept about physical entrapment of a guest molecule within the internal cavities of the dendritic structure. [22]. Newkome et al., 1991 were the first to report various type of interaction in dendrimers and their corresponding solubilizing potential. [23]. Dendrimers specifically bespoke to bind hydrophobic guests to the core have been created by the Diederich group under the name 'dendrophanes [24]. Hydrogen-bonding interactions between the dendritic host and the guest molecules like glutarimide and barbituric acid were explored that opened new possibilities for formulation development [25]. 4.0 G PAMAM dendrimers and sodium dodecyl sulfate (SDS) showed that electrostatic interaction between hydrophobe and dendrimer was the major responsible mechanism for solubility enhancement [26,27,28.]

Endoreceptors [29,30]:

1. Physical encapsulation
2. Hydrophobic bonding
3. Hydrogen bonding

Exoreceptors [31,32,33]:

1. Electrostatic interaction

Dendrimers have established themselves as solubilizing agents and has attracted the attention of beginner and advanced scientists across the globe. Mechanisms for the host-guest interaction dendritic architecture can be physical encapsulation, hydrophobic bonding, hydrogen bonding, electrostatic interaction **[34,35,36,37,38].** These poorly water soluble drug are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity [39] .

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micellar nature. Dendrimers have capability of dorming covalent as well as non-covalent complexes with guest materials, which are responsible for its solubilization behaviour. In general various solubility enhancement techniques reported, complexation being the major solubility enhancement principle. Dendrimers enhance the Solubility of hydrophobes probably due to hydrophobic interactions, hydrogen bonding and electrostatic interaction between terminal functional groups of the dendrimers and hydrophobes. **[41.]**

Conclusion:

It can be concluded that in the PAMAM dendrimers are immensely effective and versatile polymeric architecture for solubility enhancement. However, these properties of dendrimers are not restricted to drug molecules but can also be applied to catalysts and organic molecules, where dendrimers function as solubility enhancer and modifier, allowing to mix otherwise immiscible materials. Anticancer drug candidates generally have poor solubility if incorporated in dendrimers may enhance the solubility as well as may release the drug in a sustained manner at targeting site. Improving solubility of active pharmaceutical ingredient facilitates the formulation development in a easy way. Currently top Pharma companies like Starpharma, Lilly, GSK's Stiefel and Elanco have launched products where dendrimers have been used as solubility enhancer for many different drug classes. These encouraging results provide further impetus to design, synthesize, and evaluate dendritic polymers for use in basic drug delivery studies and eventually in the clinic.

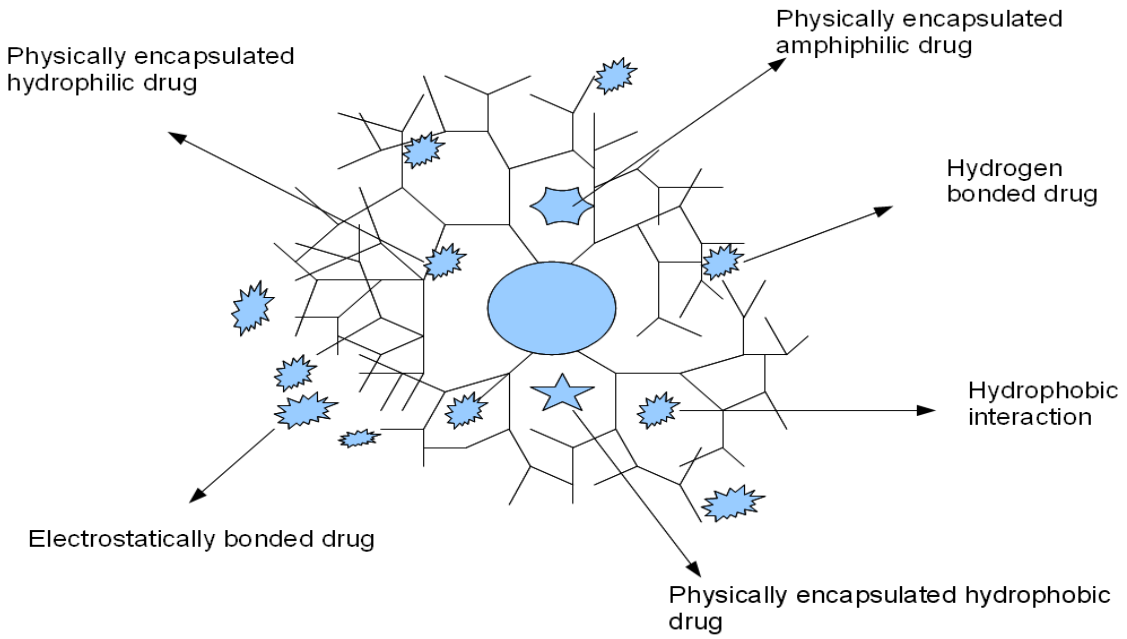

Figure 1:- Dendrimers as Drug Carrier and Mechanism of Drug Entrapment.

Table 1: Dendrimers mediated solubility enhancement of drugs

S. No.	Dendrimers Systems	Solubilizate	References
1.	Amine and Ester-terminated PAMAM dendrimers	Nifedipine	Devarakonda et al, 2004
2.	Hhydroxyl-PAMAM dendrimer	Benzoic acid	Beezer et al, 2004
3.	PAMAM –OH dendrimers	Indomethacin	Chauhan et al, 2003
4.	PEG polyethar dendrimers	Indomethacin	Kwon et al, 1997
5.	PAMAM dendrimers	Flurbiprofen	Asthan et al, 2005
6.	Polyglycerol dendrimer	Paclitaxel	Ooya et al, 2003
7.	PEGylated PAMAM dendrimers	Pyrene	Yang et al, 2004
8.	Polypropylene imine dendrimers	Pyrene	Pistolis et al, 2002
9.	Polyether-PEG dendrimer	Pyrene	Liu et al, 2000
10.	Polyether dendrimer	Pyrene	Hawker et al, 1993
11.	Poly(aryl alkyl ether) dendrimer	Pyrene	Vutukuri et al, 2004

12.	PEGylated PAMAM dendrimer	5-fluorouracil	Bhadra et al, 2004
13.	Polypropylene dendrimer	Bengal Rose	Baars et al, 2000
14.	lysine dendrimer	Orange dye	Chapman et al, 1994
15.	PAMAM dendrimer	Silicone dioxide	Neofotistou et al, 2004
16.	PEG-PAMAM dendrimer	Methotrexate	Kojima et al, 2000
17.	PEG-PAMAM dendrimer	Adriamycin	Kojima et al, 2000
18.	PAMAM dendrimer	Methotrexate	Khopade et al, 2002
19.	Polyether dendrimer	Anthracene	Hawker et al, 1993
20.	PAMAM and Lauroyl PAMAM dendrimer	Propranolol	D'Emanuele et al, 2004
21.	Citric acid-PEG-citric acid dendrimer	Mefenamic acid	Namazi et al, 2005
22.	Amphiphilic dendrimer	Proflavine	Vutukuri et al, 2004
23.	PAMAM dendrimers	Piroxicam	Wiwattanapatapee et al, 1999
24.	PEGylated PPI Dendrimers	Pyrene	Sideratou et al, 2001
25.	PAMAM dendrimers	Ibuprofen	Milhem et al, 2000
26.	PAMAM dendrimers	Niclosamide	Devarakonda et al, 2005
27.	PAMAM dendrimers	Naproxen	Yiyun et al, 2005
28.	PAMAM dendrimers	Nicotinic acid	Yiyun et al, 2005
29.	PEGylated lysine dendrimers	Artemether	Bhadra et al, 2005

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