Nano-sponges: A Novel Carrier for Delivery of Chemo-therapeutic Drugs

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ABSTRACT
Nano-sponges belong to the category of hyper-cross linked polymer which is based on the colloidal structure. Nano-sized carriers are developed recently and are being used to deliver poorly water soluble drug by modifying the pharmaco-kinetic parameter and provide enhanced prolonged release. As a new class of chemo-therapeutic agents is being developed, formulation is getting difficult to issues such as poor solubility, low loading capacity and less entrapment of the drug in the drug delivery system. Nano-sponges have shown to deliver the most complex and challenging Chemo therapeutic drugs due to its amphiphilic nature. Nano-sponges tend to adhere to the tumor through complex bonding and release the drugs at the tumor site, in response to the stimuli such as temperature and pH thus providing the much needed targeted drug delivery. Nano-sponge delivery system has been able to resolve the bio-availability, dose regime, enhanced formulation flexibility issues and fewer side effects while delivering the chemo-therapeutic drugs. Nano-sponges are usually prepared by cross-linking suitable polymer such as Beta-cyclodextrin with cross-linkers. The below comprehensive articles is a brief review of all chemo-therapeutic agent formulated in the Nano-sponge and various methods for the synthesis of Nano-sponges and loading of the active components in the Nano-sponge drug delivery system.

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INTRODUCTION
The delivery of the sought after drug to target site has been a prevailing problem faced by the research fraternity for ages. The Science of Drug Discovery is progressing over years; new molecules are being brought into the market for the various problems associated with solubility, compatibility and formulation. Advancement of superior and dense carrier molecules called Nano sponges have the prospective to change the way drug delivery takes place. Nano sponges as such are a superior newer class of materials consisting of microscopic particles having nanometers scale broad cavities. Nano sponges are capable of conveying lipophilic and hydrophilic substances thus altering the solubility nature of hydrophobic drug molecules. Nanotechnology has influenced the pharmaceutical industry over the last six decades. During the same timeline comprehensive research with respect to the cyclo-dextrins took place owing to their toxicological safety and boundless pharmaceutical application. The key component that has influenced the treatment of many diseases condition is its resemblance with the mesh. Early study and clinical trials are of the view that nano sponge drug delivery system is superior and precise in delivering the molecules for various cancers when compared to the conventional drug delivery system. In the present scenario cancer tops the chart for leading cause of death in most emerging
economy with lung cancer prevalent among males and breast cancer rampant among females. The wide and most accepted therapy with respect to cancer are narrowed down to radiation, chemotherapy and finally to the surgery. This article is intended to introduce latest Nano sponge drug delivery as an anti-Carcinogenic Anti-Cancer agent.

**Advantages of Nano sponge**

1. Challenging delivery of pulmonary and venous drugs is viable by enclosing the drugs in the Nano-sponge given their tiny size (Subramanian et al., 2012).

2. Amphiphilic nature gives the Nano-sponge edge of incorporating difficult to formulate water insoluble molecules in the Cyclo-dextrin cavity meant for hydrophobic molecules & hydrophilic molecules in cavities between the single Cyclo-dextrin moieties. The Solubility of hydrophobic is possible by Nano-sponge drug delivery.

3. Nano-sponge is a promising drug delivery system owing to their basic chemistry of particles. Cross linking the cyclodextrin leads to formation of Nano structured pores which works as a drug loading site for the drugs (Valle, 2004).

4. Nano-sponge attributes the property of tunability. Tunability is it’s inherit capability to influence particle structure while the size of the aperture and nature can be modified as desired. Altering cross-linker to Polymer proportion, desired cross linkage is achieved which has a direct influence on the drug molecule loading and kinetics release of the drug (Ahmed et al., 2013).

5. Anticipated, controlled drug release gives the edge to the Nano-sponge system (Bhowmik et al., 2018).

6. Patient adherence is increased by tagging specialized linkers to the intended affected cells thus attaining higher efficiency with alleviated side-effects and a lower dose and frequency.

7. Self-sterilizing activity is owed to the average pore size of 0.25μm preventing penetration of bacteria in the Nano sponge (Bhowmik et al., 2018).

8. Effective targeted drug delivery system is developed as the drug is delivered at the tumor site in comparison to the drug delivery where in drug is extensively circulated throughout the body (Arkas et al., 2006; Trotta et al., 2008).

**Disadvantage of Nano sponge**

1. The shortcoming of Nano sponges is to incorporate only small molecules.

2. The Nano sponges can possible be either Para crystalline or in crystal-line form.

3. The loading capacity of Nano sponges be influenced by the degree of crystallization. Para crystalline nano sponges demonstrate different loading capacities.

4. The nano sponges can be synthesized to be of specific size and to release drugs over time by varying the proportion of cross linker to polymer.

5. Incidence of dose dumping are possible at times (Singh et al., 2016).

**MATERIALS AND METHODS**

**Material used for Preparation of Nano-sponges**

The major components that are mainly used for preparation of Nano-sponge are a polymer system And a cross linker system to incorporate the drug within the system. The following Figure 1 depict Polymer and cross linker used for preparation of Nano-sponge system containing the Chemo-Therapeutic Drug.

**Methods of Preparation**

Nan-sponges are prepared by the below listed Method,

**Solvent method**

Solvent method consists of incorporating such a polymer that is compatible with the solvent, most preferred polar aprotic solvent like dimethyl sulfoxide. The following mix was introduced in excess amount of the cross-linker, most sort molar ratio of cross-linker in polymer is 4:16 (Shivani and Poladi, 2015). Optimum temperature for the was selected ranging from 10 °C to the solvents reflux temperature, time frame ranging from 1 to 48 hours .Carbonyl compounds cross linker (dimethyl carbonate and carbonyl diimidazole) are preferred (Trotta et al., 2003). The solution was cooled till room temperature, further steps involve the product to be incorporated in excess of water which is distilled twice, with the assistance of separation technique of filtration in presence of vacuum, the product was recovered and purified with the assistance of prolonged Soxhlet extraction, ethanol used as a solvent (Rita et al., 2011). Residual moisture was
### Table 1: Prior techniques used for synthesis of Nano-sponge for chemotherapeutic Drugs

| Drug                | Techniques Employed                          | Cancer Type                  | Cross linker          | Route of Administration | Outcome                                                                 | Refer No                        |
|---------------------|----------------------------------------------|------------------------------|-----------------------|-------------------------|---------------------------------------------------------------------------|---------------------------------|
| Camptothecin        | Hyper cross-linked - (β-cyclodextrins),       | All types of cancer         | Diphenyl carbonate    | Oral Route              | Prolonged release profile                                                | (Swaminathan et al., 2010)     |
| Tamoxifen           | Hyper cross-linked Cyclodextrins,            | Breast Cancer                | Carbonyldiimidazole   | Ocular Route            | Higher Drug entrapment with slow release                                 | (Torne et al., 2013)            |
| Resveratrol         | Hyper cross-linked (β-Cyclodextrin)          | All Types of Cancer         | Carbonyldimazole      | Oral Route              | Better permeation, stability                                              | (Ansari et al., 2011)           |
| Dexamethasone       | Ultrasound-assisted synthesis of (β-Cyclodextrin) | To Treat Chemotherapy Induced Nausea | Diphenyl carbonate    | Ocular route            | Enhanced permeation coupled with retention                                | (Swaminathan et al., 2013)      |
| Paclitaxel          | Hyper cross-linked (β-Cyclodextrin)          | Ovarian, Breast Cancer, breast, | Carbonyldiimidazole   | Oral Route              | Higher Plasma Concentration                                               | (Torne et al., 2010)            |
| Erlotinib           | Hyper cross-linked (β-Cyclodextrin)          | Non - small cell lung Cancer | Carboxyl diimidazole  | Oral Route              | Enhanced Oral bioavailability                                             | (Dora et al., 2016)             |
| Meloxicam           | Polymer condensation method                  | Colorectal cell Cancer      | Pyromellitidianhydride (PMDA) |                         | Dissolution Rate Improved                                                 | (Shende et al., 2015)           |

### Figure 1: Different Types of Polymer and co-polymer Used

**Polymer**
- β-Cyclodextrin
- Methyl β-Cyclodextrin
- 2-HydroxyPropyl β-Cyclodextrin
- PVA & ethyl cellulose
- Hyper cross linked polystyrenes

**Cross Linker**
- Diphenylcarbonate,
- Carbonyldiimidazole,
- Pyromellitidianhydride,
- Poly-L- Lysine17
- 2, 2-bisacrylamidoceticacid
- Pyromellitidianhydride

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Table 2: Prior Techniques Employed For Loading of Chemo-Therapeutic drug in Nano-sponge

| Drug             | Techniques Employed for loading the drug | Cross linker | Cancer Type                | Route of Administration | % Drug Loading Efficiency | Refer No                |
|------------------|------------------------------------------|--------------|----------------------------|-------------------------|--------------------------|-------------------------|
| Camptothecin     | Freeze Drying Technique                   | β-Cyclodextrin | All Types of Cancer        | Oral Route              | 37% w/w                  | (Swaminathan et al., 2010) |
| Tamoxifen        | Mixed with assistance of magnetic stirrer, sonicated followed by Freeze drying | β-Cyclodextrin | Breast Cancer              | Oral Route              | 25% w/w                  | (Torne et al., 2013)     |
| Resveratrol      | Freeze Drying Technique                    | β-Cyclodextrin | All Types of Cancer        | Oral Route              | 40% w/w                  | (Ansari et al., 2011)    |
| Dexamethasone    | Freeze Drying Technique                    | ——           | To Treat Chemotherapy Induced Nausea | Ocular route           | 10% w/w                  | (Swaminathan et al., 2013) |
| Paclitaxel       | Freeze drying technique                    | β-Cyclodextrin | Pancreatic Cancer          | Oral Route              | 19% w/w                  | (Torne et al., 2010)     |
| Erlotinib        | Freeze drying technique                    | β-Cyclodextrin | Non-small cell lung Cancer | Oral Route              | 74.29% ± 6.81% w/w       | (Dora et al., 2016)      |
| Meloxicam        | Freeze Drying                             | β-Cyclodextrin | Colorectal cell Cancer     | Oral Route              | 23% w/w                  | (Shende et al., 2015)    |
| Tamoxifen        | Freeze Drying                             | β-Cyclodextrin | All Types Cancer           | Oral Route              | 32% w/w                  | (Torne et al., 2013)     |

removed under vacuum and homogeneous powder was obtained by grinding in the mechanical mill (Swaminathan et al., 2010).

**Ultrasound-assisted synthesis**

Ultrasound-assisted synthesis comprise a crosslinking reaction between the polymer and the cross linker deprived of solvent in the assistance of sonication. Sphere shaped homogeneous nano-sponges were obtained by ultrasound assisted synthesis (Tejashri et al., 2013). Optimum molar ratio of Polymer + cross linker was introduced within the flask. Flask was arranged within the ultrasound bath filled with water and optimum heat of 90 degree was introduced. Sonication assisted ultrasound synthesis was carried for mixture for 5 hours. Product mixture was allowed to reach acceptable temperature and product was crumbled subsequently. Further purification of the synthesized product was carried out by water to eliminate the traces of non-reacted polymer with further refinement was done with assistance of Soxhlet extraction method with the assistance of Ethanol as a solvent. Vacuum drying was further carried out to eliminate the traces of the water and stored at ambient temperature of 25°C (Swaminathan et al., 2007).

**Application**

Nano-sponge has a wider application in the delivery of chemo-therapeutic drugs as they tend to be highly effective in retarding or delaying the growth of tumor cancer as compared to the already available chemotherapeutic regime. The Nano sized sponges are loaded and expose targeting peptide which further tend to bind to the tumor surface leading to triggering of Nano sponge and release of the active components in a targeted manner. Prior work done for preparation of Nano-sponge for chemotherapeutic
drug and their loading techniques are depicted in the Table 1 and Table 2.

**CONCLUSIONS**

Nano-sponges are the most emerging and the competent drug delivery system for the Anti-cancer drug, which provides the much desired drug delivery to overcome the emerging formulation difficulties of newer class of the anti-cancer drug. As the ongoing drug delivery system is incompetent, the Nano-sponge will provide the target delivery thus alleviating the side effects associated with the chemotherapy.

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