1. INTRODUCTION:

1.1. Cancer:

Cancer is anticipated to be a vital reason for cause of morbidity and mortality in the upcoming few decades worldwide. It can be defined as an uncontrollable growth of abnormal cells in the body. Genetic modification is the leading cause of the tumor generation. It has been proven that a number of genes are having key role in cancer metastasis. The molecular mechanism for the tumor generation involves deregulation of the tumor suppressor gene and overexpression of oncogene both individually or together responsible for the tumor progression (1-3).

1.2. Epidemiology:

The statistical data showed that over 7 lakh new cancer cases are registered every year and the approximate cancer related death is more than 5 lakh in the age group between 30-69 years. Furthermore, the lung and oral cavity cancer in male and cervix and breast cancer in female accounted for over 50% cancer mortality in India. Thus second most common carcinoma observed in females is breast cancer (4, 5). It is the leading cause of cancer in the females between age of 15 and 54 and the second leading cause of death of women in the United states (6).

1.3. Pathogenesis:

Breast carcinoma is a malignant tumor initiated in the breast cells and associated with various risk factors as seen in other cancers as well. Pathogenesis of breast carcinoma includes, genetic mutation (viz., BRCA1, BRCA2, and P53) of the cellular DNA which subsequently leads to activation of growth promoting oncogenes and inactivation of tumor suppressor genes with alteration in the genes that control the apoptosis. This all factors combined together leads to unregulated proliferation and differentiation of cancer cells in milk duct thereby nourishing the growth of malignant tumors. Apart from this, a family history, lifestyle, physical activity age, geography, diet and alcohol *etc.* are also having a significant influence on the breast cancer genesis (1, 7). The diagrammatic representation of pathophysiology of breast cancer is depicted in figure 1.1.

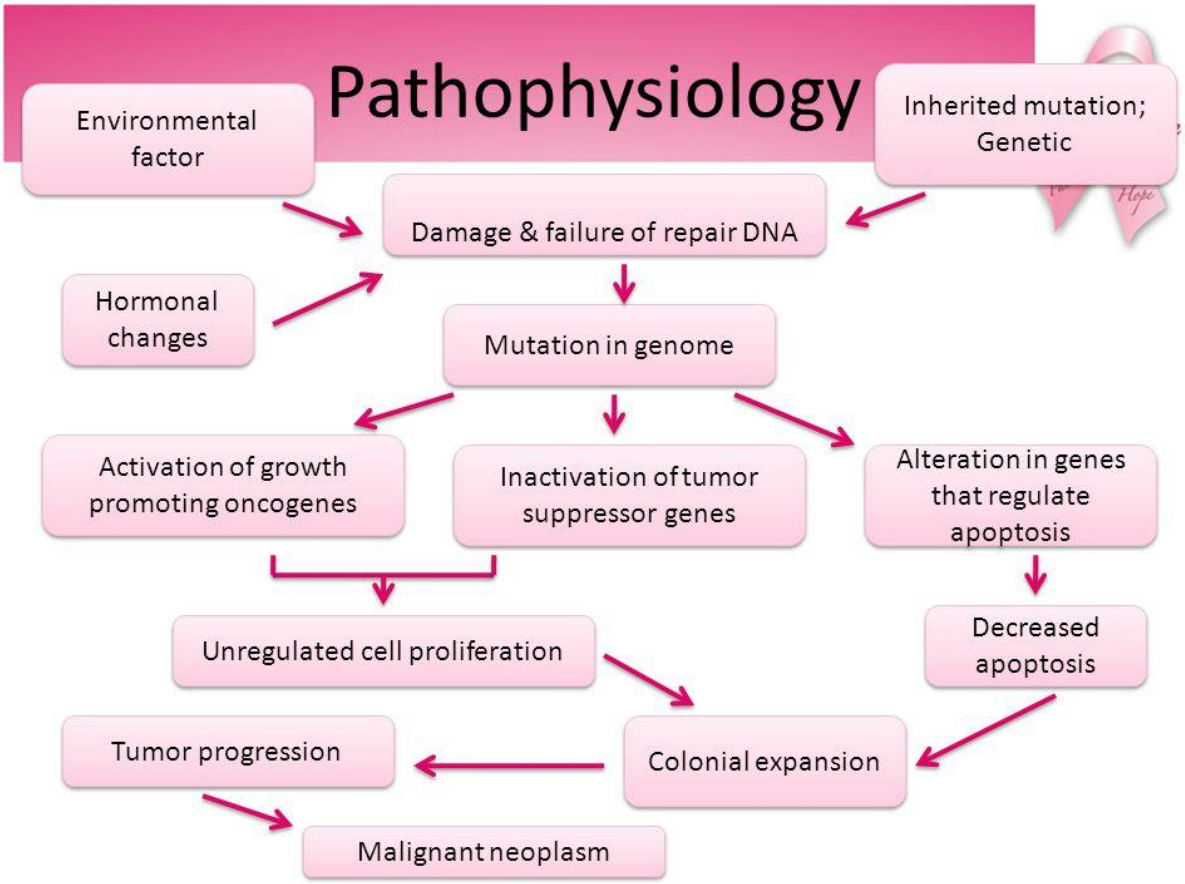

Figure 1.1: Pathophysiology of breast cancer

1.4. Diagnosis and management of breast cancer:

The advances in the technology have contributed handsomely to the ease of cancer diagnosis with techniques like mammography, MRI, ultrasound imaging, *etc*. Estrogen receptor and progesterone receptor status, HER2 protein expression and gene amplification, commercially available gene assay like Oncotype DX assay, Amsterdam 70-gene profile, Mammaprint are also helpful indicators in cancer diagnosis (8). Depending upon the stage and the type of the tumor, it can be managed by mastectomy (surgical removal of the entire breast) or lumpectomy (removal of lump). The radiation therapy uses high energy rays like X-rays or gamma rays that target a tumor or post-surgery tumor site. But, most commonly used treatment for cancer is a chemotherapy. Which encourages the application of different anticancer moieties like Doxorubicin, Raloxifene, Tamoxifene, Methotrexate, Anastrazole, Cyclophosphamide, Exemestane, 5-Fluorouracil, Toremifene, Letrozole, *etc*. (9, 10).

1.5. Current challenges for chemotherapy:

In chemotherapy, the present treatment strategies rely heavily on the utilization of ordinary cytotoxic medications which have adverse effects and restricted efficacy. Currently available drug molecules for cancer treatment include peptides, steroids and oligonucleotides. Most of the anti-cancer drugs are hydrophobic in nature and hence, having low solubility and bioavailability. Therefore, the desired therapeutic dose will not reach to the target, necessitating a need of higher dose administration for therapeutic efficacy. This may damage healthy cells and tissues, leading to severe side effects, *e.g.* severe hair falls resulting in baldness, acute vomiting and nausea, low blood cell counts making patients more susceptible towards developing infection or anaemia (11).

Furthermore, many of the anticancer drugs are available in the oral dosage form due to the patient comfort, ease of convenience over parenteral administration and their capability to formulate chronic treatment regimens. However, having all aforementioned advantages, the efficacy of oral drug delivery system is hampered due to poor aqueous solubility and bioavailability of drugs. The probable reasons for this could be patient specific or pharmaceutical specific. Later part might be a major contribution to low bioavailability by either of the following reasons. The pre-systematic metabolism in the gut wall and liver of existing anticancer moiety, high molecular weight, which could decrease the intestinal permeability and the formulation framework has a greater impact on the solubility and bioavailability of the drug. Besides this, one can never think of enhancing the oral dose of existing anticancer drug to make it more bioavailable for a longer period of time as they are having narrow therapeutic window. Since last couple of decades, research breakthroughs have been made in outlining pharmaceutical medications to tame the aforementioned obstacles. The smart way of enhancing the solubility and bioavailability of BCS class II and IV drugs is engineering them in a such way which would alter the physicochemical parameters of anticancer moieties to alter their absorption and release behaviour. This has significantly propelled the learning of physicochemical properties of these medications and cellular uptake mechanisms, thereby generating effective therapeutic strategies. (12-14).

1.6. Recent scenario in the field of drug delivery:

Current scenario has shifted toward tuning of particle size toward nano size *i.e.* development of nano drug delivery system. Nanotechnology has wider advantages and applications over other delivery systems available. It can be used as a highly sensitive diagnostic as well as a

therapeutic element (15). Moreover, it offers various advantages like extended half-life, enhanced bio-distribution, higher circulation time of the drug, controlled and sustained release of the drug, flexibility in route of administration, increased intracellular concentration of drug, tissue/organ specificity along with promising outcomes concerning stability, biocompatibility and biodegradation (16-18).

An ideal drug delivery system should encourage the intracellular accumulation of drug in the targeted cells and maintain drug concentration at its effective level. This is possible by two ways *viz.,* (a) by designing a formulation that gives controlled or sustained release *i.e.* modified release or (b) by targeting the drug to its target *i.e.* tumour cell. The research thrust these days is on designing a targeted drug delivery system that will deliver a therapeutic dose to the cancerous cell and ultimately reducing its reach to healthy cells thereby decreasing their side effects. Targeting concept is now in focus and vast researches are involved in formulating a nano system, including liposomes (19-22), solid lipid nanoparticles (23), self-micro emulsifying drug delivery system (SMEDDs) (24) having tumour-targeting efficiency. Mesoporous silica nanoparticle (MSNs) is one of the nano carriers, which are in focus for various advantages associated with them (25, 26).

1.7. Mesoporous silica nanoparticles:

In nanotechnology, mesoporous silica nanoparticles (MSNs) based targeted delivery offers a promising tool for increasing the intra tumoral concentration of anti-cancer drugs and limiting its toxic effects to normal cells as they bind to cell membrane receptors which are over expressed in cancer cells only. This has led to a great research interest towards targeting the drug loaded MSNs into tumor cells. The flexible surface of MSNs plays an important role in reaching their targets. Unique properties of MSNs like porosity, shape, size, surface functionalization *etc* collectively decide mechanism of action, their interaction with living body components such as cells, tissues and biomolecules and release pattern of formulation in biological systems, with considerable increment in therapeutic ability. Combined together, all these have a direct impact on safety, biodistribution and theranostic potential (27). Moreover, theranostic application of MSNs is also in the limelight where, the name theranostic itself suggests dual application of MSNs in therapeutic and diagnosis filed. This dual characteristic is solely attributed to its flexible surface that can easily be modified to achieve the desired objective (28). MSNs with particle size ranging from 50-200 nm have been studied as nanocarriers for the delivery of small drug molecules and antigen and it has been proved that

MSNs are having high drug loading capacity. MSNs can be used to enhance solubility and in turn the bioavailability of many drugs. This is due to its unique and tailor made nano size and also due to ability to convert the crystalline nature of drug into amorphous form once it gets embedded inside the pores. Further, by attaching various receptor selective ligand can help in formulating a receptor based targeted drug delivery system (29-33). Despite all this, MSN based formulations are yet to be commercialized. Presently, few silica nanoparticles available commercially are Nanoceuticals™ Chocolate slim shake and Lancome® Renergie microlift, a cosmetic product (34). Recently, Cornell dots (C-dots form of MSNPs) have been approved by the USFDA for stage 1 clinical trial in the year 2014 (35, 36). Cornell dots are a type of inorganic silica nanoparticles designed for fluorescence imaging applications. They are to be utilized for lymph node mapping in cancer and they include cyclic RGDY peptides as a targeting moiety, a polymer layer and NIR fluorescent dye labelled internal silica core (37). As such silica is recognized as GRAS (Generally regarded as safe) by the USFDA. A first trial in human in 5 patients indicated a favorable pharmacokinetic and safety as a tumor targeting agent, creating opportunities for further trials in future (38).

1.8. History and mechanism of synthesis:

MSNs have been firstly discovered by Kresge et al at the Mobile Oil Company in 1990s. They had prepared a mesoscopic highly ordered inorganic material wherein the template moiety is surrounded by inorganic mater through hydrolysis and condensation via the sol-gel mechanism. Further the porous honeycomb network was gained after successful removal of template from the core (39).

In depth investigation demonstrated that the two mechanisms are involved in the formation of mesoporic assembly as depicted in figure 1.2. In the liquid-crystal templating (LCT), the surfactant concentration is so high that under optimum pH and temperature condition it will form mesopores even in the absence of the initial precursor moiety. Whereas, in the second mechanism the hexagonal, cubic or laminar arrangement is formed by the cooperative self-assembly of surfactant which present at the lower concentration and the already added inorganic species (40).

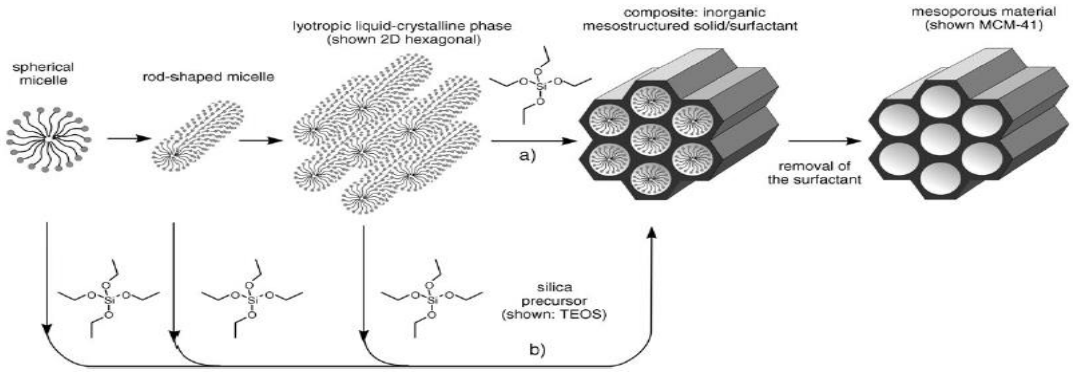

Figure 1.2: Mesoporous material formation (a) Liquid crystal template mechanism; (b) cooperative liquid crystal template mechanism

The development of mesoporous assembly was initiated by Mobil Oil Company and the discovered mesopore classified under M41S category having a pore diameter of 2 to 10nm (figure 1.3). The well-known representative of this category is MCM-41 having a hexagonal arrangement with space group *p6mm*. Apart from this, MCM-48 having cubic mesoporic arrangement with space group *Ia3d*), and MCM-50 with laminar structure having space group *p2* have also fallen under the M41S category. In this research work two types of carriers form this family *i.e.* MCM-41 and MCM-48 was selected to carry out the research work. Beside these mesoporous carriers, others are also available and synthesised widely as listed in the table 1.1 (41-43).

Table 1.1. List of various MSNs carriers (41-43)

Name	Full Form	Structure
MCM-41	Mobil Composition of Matter	2D-hexagonal, cylindrical pores
MCM-48	Mobil Composition of Matter	cubic
MCM-50	Mobil Composition of Matter	Lamellar
SBA-1	University of California at Santa Barbara	Cage-type, cubic, spherical cavities
SBA-3	University of California at Santa Barbara	Hexagonal, cylindrical
SBA-11	University of California at Santa Barbara	Cubic
SBA-12	University of California at Santa Barbara	3D-hexagonal
SBA-15	University of California at Santa Barbara	2D-hexagonal
SBA-16	University of California at Santa Barbara	Cubic KIT-1 (Korea Advanced Institute of Science and Technology)
Disordered MSU-X	MichiganStateUniversity	Large Pore, 2D hexagonal
Disordered TUD-1	TechnischeUniversiteit Delft	3D, foam-like

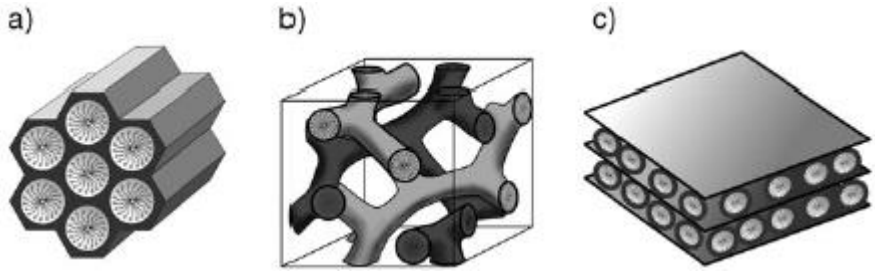

Figure 1.3: Different carriers of M41S category. (a) MCM-41, (b) MCM-48, (c) MCM-50

1.9. Surface modification of MSN:

1.9.1. Pore Gating

This system involves unifying of bulky molecular moieties like proteins and peptides or incorporation of metals like iron (superparamagnetic iron oxide nanoparticles; Fe-NP) and gold (a gold nanoparticle; Au-NP). Giri S, *et al.,* formulated the mesoporous silica nanorods with iron oxide (Fe-NP) cap, possessing a redox responsive cleavable disulphide linker which upon cleavage releases the cargo (44). One more pore gating MSNs has been designed by researchers A Schlossbauer, *et al.,* which deals with the strategy of melting of DNA linkers by MSNs decorated with temperature programmable molecular valve system comprising avidin caps (45).

1.9.2. External surface modification of MSNs

Outer layer of MSNs carrier is feasible for surface modification and provides an opportunity to prepare tunable MSNs. This external surface decoration may affect the release profile and may possess targeting efficiency (46). Two basic mechanisms exist for grafting of functional groups on the surface of carrier *viz.,* physical and chemical. These also depend on the solubility of the drug. Physical adsorption is commonly seen in external grafting of MSNs. Hydrogen bonding, electrostatic and hydrophobic interactions are the representative forms of the physical adsorption. In case of non-functionalized MSNs, where plenty of OH groups are available on the surface, hydrogen bond becomes a representative of physical adsorption, but once the surface is functionalized latter two types of interaction will represent physical adsorption (47). Two main strategies are applied for surface modification *viz.,* co-condensation and post-synthetic grafting method. In the former technique, functionalizing ligand is administered during the synthesis of bare MSNs, whereas in the latter, functionalizing moiety is incorporated once the unmodified MSNs carrier is synthesized (48).

1.9.2.1. Co-condensation process

The process of co-condensation involves direct functionalization of MSNs' outer surfaces during synthesis only. This strategy modifies mesoporous silicate surface by sol-gel chemistry between tetra-alkoxysilane and one or more organo-alkoxysilanes with Si-C bonds and this will synthesize hybrid inorganic-organic mesoporous silicates. This method is also applicable for synthesis of MSNs for imaging purposes. *E.g.* use of co-condensation method for incorporation of two different Gd^{3+} complexes at very high loading (15.5%–28.8 %w/w) and this synthesized, MCM-41 carrier was successfully characterized by SEM, TEM, TGA, PXRD, DCP. General steps involved in synthesis of MSNs (addition of silica source, *i.e.* TEOS, surfactant, water *etc.*, autoclaving, and calcination) are displayed in Figure 1.4 (49).

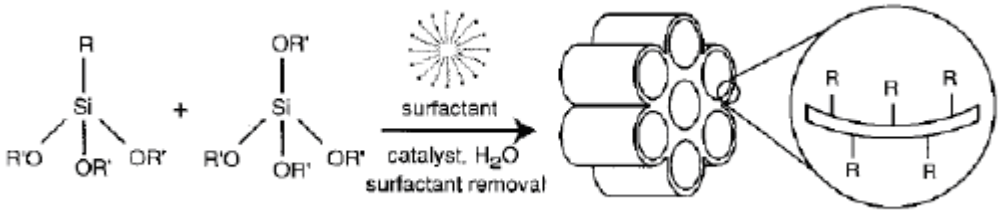

Figure 1.4: Basic steps involved in MSNs synthesis (49)

1.9.2.2. Post synthesis strategy

This process involves the surface modification after synthesis, *i.e.* post synthesis functionalization method. It involves modification of the surface of MSNs usually after removal of surfactant. Here, the Si-OH group which is present on the surface of MSNs act as an anchoring moiety for functionalization. It is mostly carried out by sialylation process. Grafting can be done on internal as well as external surface. The detailed pictorial representation is depicted in figure 1.5 (49). The co-condensation method is preferred as found in most of the literature due to more uniformity. *e.g.* Surface of MCM-41 was functionalized by vinyl group using both the above mentioned techniques. Lim and Stein have compared the relative distribution of surface groups based on powder X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), and bromination kinetics data. Results showed a wider distribution of vinyl groups on the surface of MCM-41 prepared by direct co-condensation method, whereas for those prepared by the post grafting method, the results showed a lack of uniformity with a large proportion of vinyl groups on the external surface of the crystallites or inside channels but lesser number near the channel openings (50). In products obtained from a direct co-condensation reaction, the vinyl groups appeared to be more uniformly distributed

throughout the channels. A number of functional groups have been tried to set the functionalized MSNs which could be used as drug carriers. E.g. Outer decoration of MSNs with disulphide linked polymer to achieve the redox responsive release of drug has been done by author Liu R, *et al* (51). A variety of functional group or moieties can be attached on the surface of MSNs by either of the above mentioned techniques as listed in the Table 1.2 (26, 52-63).

Comparing between the two modification methods, one realize that the post modification does not much affect the size and size distribution of the particles, where as one-pot synthesis produces a much bigger particles, of course, with low aggregation with relatively homogenous incorporation of modifier to the interior and exterior (64).

Backfilling strategy is another approach used for MSNs fabrication. It is a simple approach to introduce active molecules into the empty pores of mesostructured silica wherein, these empty pores are exposed to the solution or vapour of active molecules and are allowed to diffuse. However, this strategy does not involve chemical modification of the material and hence is a less widely used method (65).

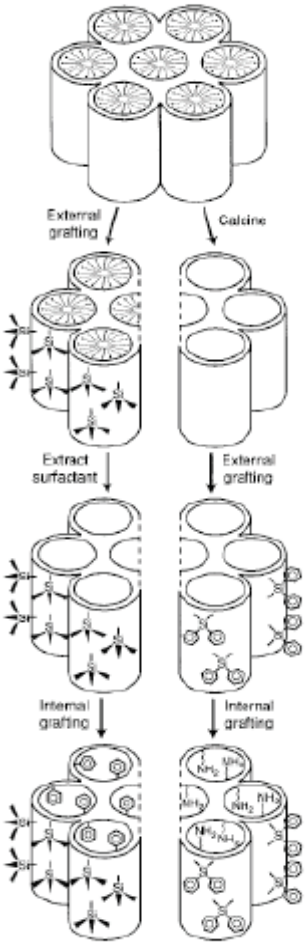

Figure 1.5: Two different strategy for functionalization of carrier (49)

Table 1.2. Varieties of moiety used for surface modification of carrier

Type of modification	Reagent	Name of Drug	Application	Reference
Amino	APTES	5-FU	Controlled Release	(52)
Cyano	CPTES	5-FU	Controlled Release	(52)
Carboxyl	CPTES + Reduction by 50 % v/v of H_2SO_4	5-FU	Controlled Release	(52)
Methyl	OTMS	5-FU	Controlled Release	(52)
Pegylation	PEG 2000	Doxorubicin	To enhance cytotoxicity of prepared formulation against Hela and NIH3T3 cells	(53)
Chitosan	Chitosan	Doxorubicin	For preparation of pH sensitive nano drug delivery system	(54)
Folic acid	Chitosan + folic acid	Anisomelic acid	Targeting drug delivery system to cancer cells	(55)
Sugar	Glucose + Galactose	Celastrol	Controlled and Targeting drug delivery system to cancer cells	(56)
Cyclodextrin	β-CD	Doxorubicin	pH responsive and controlled release nano drug delivery system	(57)
Lactose	Lactose	Docetaxel	To prepare Asialoglycoprotein receptor targeted nano drug delivery system	(26)
Eudragit	Eudragit S-100(ES-100)	DoxazosinMesylate	To release the drug at pH 7.4	(58)
Gold nanoparticles	Gold	-	63% selective killing of cancer cell with enhanced two photon imaging property	(59)
Iron oxide nanoparticles	Fe_3O_4	-	Controlled release under the influence of an external magnetic field.	(60, 61)
Hyaluronic acid	MSN-NH_2, EDC, NHS, Hyaluronic acid	Doxorubicin	Targeting nano drug delivery system to CD44-overexpressing cancer cells	(62)

Lactoferrine	Oleic amine, iron oxide, lactoferrine,	Paclitaxel	Tumor targeted and on-demand drug release with combination of lactoferrine cap on Mesoporous uiron oxide nanoparticles.	(63)

1.10. Targeted drug delivery system using MSNs:

Various overexpressed receptors can be easily targeted with the help of different targeting ligands. This will help in reducing the adverse effects on the healthy cells. There are two types of targeting approaches as described follow.

1.10.1. Active targeting in cancer

It involves the receptor based targeting strategy wherein the specific receptor is focused by attaching the receptor targeting ligand over the surface of nanoparticles which will have an affinity to selectively bind to it. E.g. application of folate modified nanoparticles to target the folate receptors through the receptor mediated endocytosis (36, 66).

1.10.2. Passive targeting in cancer

This approach relies on the enhanced permeation and retention effect (EPR). Leaky vasculature in the blood vessel epithelial layers and inefficient drainage system are the characteristic of tumor tissues and it is ideal for the passive targeting. Because of the nano size, the nano drug delivery systems having higher circulation time and will stay for a longer time in the circulation. For this purpose, various coating materials decorated on the external surface of the nanoparticles viz., PEG. Such materials will enhance the bulk of nanosystem and can be scavenged from the reticular endothelial system (RES) (36, 67).

1.11. Toxicity, biocompatibility and biodegradation of MSNs:

Although having a tremendous application in the pharmaceutical world, the biocompatibility of MSNs is still debatable and it is essential to discuss about their biocompatibility and safety profile. Numerous parameters have direct influence on the safety profile of MSN which covers surface properties, particle size, charge, shape *etc*. At the cellular level, MSNs can interact with the biological system through many of the mechanisms like mitochondrial dysfunction, glutathione depletion, membrane peroxidation and DNA damage *etc*. Research also says that the pristine MSNs are having less hemocompatibility as compared to surface decorated MSNs. Furthermore, apart from having targeting properties, the surface decoration exhibits reduced undesirable interaction with the internal organelles (36). Moreover, Lu et al concluded 50nm

particle size is the optimal size for the drug delivery by MSNs with respect to 30nm or even 200nm (68). Whereas, He et al demonstrated that as the size of MSNs increases, the excretion from urine also increases correspondingly. Further, they also claimed that smaller size MSNs *i.e.* 190nm and 420nm size MSNs are more cytotoxic with respect to bigger sized MSNs *i.e.* 1220nm (69). Further the smaller nanoparticles are having a more haemolytic effect as compared to bigger sized nanoparticles (70). Overall, there are dual thoughts for biocompatible nature of MSNs, and it further requires an in depth exploration. Their biodegradation is debatable. Chen et al have demonstrated a detailed degradation of MSNs in human embryo kidney 293T cells by measuring the silica content in culture medium and performing depth TEM analysis. They claimed, upon degradation of MSNs into the cells, the size and dispersibility of cells were unchanged, and hence the toxicity due to accumulation of silica aggregates in the tissues would be reduced (71). Further, Zhai et al inferred that the degradation of MSNs took place in cytoplasm initially followed by in lysosomes later on. Moreover, the culture of MSNs with human endothelial cells experiments revealed higher accumulation of MSNs in the culture media *i.e.* outside the cell supports the claim that MSNs are not having cell toxicity (72). Additionally, research also says that the MSNs are converted into silanoic acid inside the body, which is excreted through kidney majorly. Further, the study also says that the silica particles mainly converts into its bioavailable form *i.e.* monomeric orthosilicic acid, which is essential for bone and connective tissue hemostasis (36).

1.12. Drug delivery by MSN:

- **Oral** route is a widely employed route of drug administration due to patient compliance. But the poor aqueous solubility and permeability hampers its availability and henceforth having unfavourable pharmacokinetic properties. BCS has divided the drugs into four categories according to their solubility and permeability performance. Around 70% of the discovered NCEs fall under BCS class II and IV categories (73). Therefore, various attempts to improve the in vitro dissolution profile and in vivo pharmacokinetic performance. MSNs are now emerging field to satisfy above goal and many authors have explored it to the depth.
- **Intravenous** route has many advantages over oral route, as the drug directly reaches to the blood circulation and demonstrate the quick onset of the action. Various NCEs are also unstable at the acidic condition of the stomach and may show the inactivation or degradation of drug or peptide like biomolecules. In such a case, it becomes essential to

inject such a drug to the target site only. So in such cases the administration through parenteral route becomes beneficial. This route also makes it possible to work on receptor based targeting. Many researchers have explored the MSNs to formulate a cancer cell targeted nano drug delivery system.

- In this investigation, both oral and intravenous route have been explored in detail.

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