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Mesoporous Silica Nanoparticles: A Multifunctional Carrier for Drug Delivery System

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ABSTRACT

From the last few years, the rapid increase in research on the mesoporous silica nanoparticles for the diagnosis and treatment of various diseases has been observed & has potential advances in various drug delivery systems. Mesoporous silica nanoparticles due to its multifunctional properties such as particle size range, pore size, loading capacity & surface fictionalization play an important role in controlled and sustained drug delivery systems. Mesoporous material use as a versatile carrier for loading of the micro molecules proteins, siRNA. These unique characteristics of MSNs provide a promising approach for the precision of cancer treatment and attained extensive attention as an efficient drug delivery system.

INTRODUCTION

For the oral drug administration solubility & rate of dissolution in GIT, this is the challenging step during the absorption process of the drug. About 40% of the drugs discovered by the pharmaceutical industry have problems associated with poor solubility as well as permeability. This solubility problem affects drug delivery and has a poor correlation to in-vivo absorption.

There are major challenges to overcome the solubility issues and to increase the oral bioavailability of drug many strategies are developed such as solid dispersion techniques, emulsion-based system, etc. but all those techniques have some limitations to improve the solubility problems, so there is need to increase the new types of approaches.

Nanotechnology has become great advances in the field of science & technology. Nanotechnology has now a day's wide applications in the formulation of targeted drug delivery system, the use of nanoparticles in such targets have some disadvantages to reach to the target. Recently the porous materials have shown a significant feature in the formulation of the dosage form. The main advantage of the porous material is its surface area, high efficiency for the loading of drug particles. The driving force, the presence of surface atoms on the pores increases the surface area of porous solids.

The pore structure of solid particles is categorized into three types i.e., macroporous, mesoporous, and microporous, and has to size range is 2nm, 2-50nm; more than 50nm different pore size solid material have different structural properties. (1)

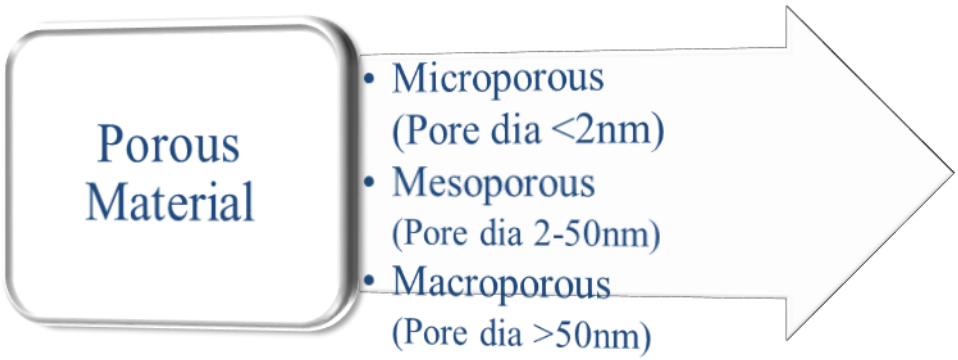

Figure No. 1: size range of porous materials

Recently the new approach of the porous material is been used for the drug delivery system and also to increase the bioavailability of the drug. Among the various porous materials,

mesoporous material is having unique structural features. A Mesoporous silica nanoparticle is the promising class of the porous material. A unique feature of the mesoporous includes it is having high loading efficiency of the drug into it, also it has main advantages like MSNs is biocompatible, biodegradable, non-toxic has a high surface area, pore volume and homogenous distribution of therapeutic molecule.

The large surface area and pore volume present on mesoporous silica is the well suitable carrier or reservoir for the loading of the therapeutic agent and also for a diagnostic agent. In addition to this MSNs possess good biocompatibility, the ability of surface modification & have good controllable size, etc that make the mesoporous material an excellent candidate for various biomedical & drug delivery applications. Now a day's mesoporous silica is used as an effective carrier and physical and chemical modification on the surface of MSNs leads to increase the biocompatibility and the rate of absorption of the drug. It is very easy to chemically modify the surface of MSNs due to the presence of the silanol group. Modification on the surface of MSNs can enhance the opportunities in challenging treatments in a disease such as cancer. (1,2)

The mesoporous material is the pharmaceutical carrier system for various immediate as well as controllable drug delivery systems & also it can be used for medical devices because of the well-organized structure.

The particle size, pore size & morphological properties of MSNs can be modulated by changing the reaction conditions such as a change in temperature and pressure, etc.

Particle size

Controlled particle size is an important aspect of the drug delivery & the biomedical applications of the MSNs as a drug carrier.PH range of medium, speed of reaction, additive agents have a direct relationship with the particle size of MSNs.

The control over the particle size can effectively be achieved by the addition of suitable inorganic salts, inorganic bases, amines, etc. they speed up the rate of reaction and eliminate the hydrolysis & condensation of silica. By increase with the speed of reaction results into smaller particle size change in the molar ratio of silica precursor have a direct influence on the particle size TEOS: TEA ratio change from 1:1 to 1:4 larger particle size observed with 1:4 molar mass ratio. (3)

Also change in the PH of medium generally affects the particle size of silica particles as PH goes on increases particle agglomeration of silica nanoparticles is takes place.

Reaction parameters such as temperature influence the particle size of MSNs with an increase in temperature from 30to70˚c the increase in particle size observed, this is because with an increase in temp the rate of reaction is speeds up resulting into dense silica structure and larger particle size. (4)

Shape of MSN's

Shape of silica nanoparticles affects the distribution and drug delivery of drug molecules. control over the shape of silica nanoparticles is important in in-vivo effects and cellular uptake of the drug (5) spherical shaped MSNs are widely used for the drug delivery potential. The concentration of reactants like silica precursor, catalyst, surfactants have an impact on the morphological characteristics of the MSNs & non-spherical shaped like a rod, ellipsoid, plate-like, cube & shut shapes could be generated. (6)

Pore volume and pore size of MSN's

The pore size of the nanoparticles is varied by the type of surfactant, surfactant with longer chain length are produce larger pore sized silica particles and with use of short length surfactants the pore size of the nanoparticles get decrease. (6,9)

Also, the concentrations of surfactant molecules such as CTAC & CTAB have a significant impact on the arrangement of the particles. If the concentration is too high then the disordered structure of MSNs is formed. CTAC & CTAB are pore generating templates that produce the mesoporous silica nanoparticles like a wormhole.

The concentration of CTAC influence the structural arrangement of silica nanoparticles, higher the amount of TEOS produced disordered structure of mesoporous silica nanoparticles. Whereas lesser amount is also not sufficient to form the mesoporous silica nanoparticles.

Due to the structural feature of the MSNs they are widely used for the various drug delivery applications, as it is having high loading capacity, larger pore size & have ability of surface modification both internal as well as external surface is better for targeting drug molecules.

Drug loading and their release from MSN's

Loading of drug:

The main advantage of MSNs is both the hydrophobic & hydrophilic drugs can be incorporated into the pores of MSNs. The drug loading based on the adsorption property, MSNs have large pore size increases the drug loading capacity. Various methods such as solvent dispersion method, solvent evaporation, etc. are used for the loading of drug. The drug loading capacity can be increase by functionalization of the MSNs, silanol group present on the surface of MSNs can be replaced by various functional groups such as amino; phosphate, etc. effectively increase the drug loading capacity.

Drug release from MSN's-

The release pattern of drug from MSNs is based on the diffusion mechanism. The important factor responsible for controlling the drug release is interaction between the drug molecules & the surface groups present on the pores. Drug molecule is adsorbed in the pore surface that surface is prevented by APTES which prevents the early release of drug.

If sometimes the surface of MSNs is functionalized & then drug is loaded, drug gets adsorb on the surface of MSNs & it may be able to release by burst effect. The drug release study of Aspirin was studied in this case post-synthetic grafting and condensation methods are used. It was shown that there was weak interaction observed between the plane silanol group and Aspirin, faster drug release took place by Fick's diffusion mechanism. Functionalization on the surface of MSNs with the amino group slowed down the release of drug and drug release observed in a controllable manner. (11)

Due to the uniqueness & multifunctional properties of MSNs are used in various drug delivery applications to set target therapy & also for diagnostic purposes.

Mesoporous silica nanoparticles produce a great advantage for the intelligent & controllable delivery of drugs at its target site.

The stimuli-responsive drug delivery involves stimuli such as PH, temperature, redox, enzymes, etc. the channel of pores is only open when it is in response to certain stimuli.

PH responsive drug delivery -

PH is the most important factor which is responsible for the release of drug at a particular PH range. Alteration in the PH environment, have a direct effect on the drug release. Drug molecules loaded into mesoporous channels to protect the early release of drug and allow the release of drug at specific PH range PH dependent drug release is achieved.

Prednisolone loaded into MSN-48 and their pore surface was coated with succinylated polylysine (SPL) which shows PH dependent release in the region of the colon.

The *in-vitro* release study was performed it as showed that prolonged release of the drug took place in colon region & successful PH responsive drug delivery achieved. At acidic PH range, the coating of succinylated polylysine (SPL) protect the drug early release due to its unionized form & at the colon region particular range of PH, SPL get convert into ionized form and drug release was takes place by the diffusion mechanism from MSN. (16)

The PH responsive drug delivery is the most promising approach in the targeted tumor therapy. The tumor region is slightly acidic than that of normal tissues, so loading of drug into MSNs the pore surface protected with the PH sensitive chitosan, polysaccharides to achieved the controllable release of curcumin in the treatment of cancer. The rate of curcumin improved at PH range of 7.4 to 5.5. (14)

In case of Doxorubicin PH responsive polymers such as polyacrylic acid was used it was observed that sustainable drug release & increase in the cellular uptake of drug was successfully rated.

β-cyclodextrin also used as a PH sensitive polymer which is capped on the pores of MSNs, the PH sensitivity of MSNs was evaluated at PH range 7.4 to 5.5. PH dependent release of drug P-anisidine was observed.

Redox responsive drug release-

Redox is another strategy for control the release of drugs from MSNs carriers.

Redox responsive drug deliveries have been widely used for the delivery of most anticancer drugs &making the use of an endogenously present reducing agent. The disulfide bonds are present in redox cleavage used.

The disulfide-linked polyethylene glycol synthesized to MSNs for the redox modified drug delivery.

Glutathione (GSH) is equal to the intracellular concentration & Rhodamine is used as a model drug added to release media for in-vitro release study.

It was studied that in absence of Glutathione the release of Rhodamine is less & drug release was blocked. Apart from this modification on the release of MSNs with PEG which forms the biocompatible nanoparticles. (19)

In-vitro experiment performed to confirm the redox responsiveness of the carriers by using hydrogen peroxide as redox stimuli with increase in the concentration of hydrogen peroxide increases the release rate of drug because oxidation of ferrocenyl molecule took place. There is strong interaction occurred between the β-CD & ferrocenyl molecule which results in dissociation of the β-CD capping & allows the release of the drug from pores of MSNs. (19)

Temperature responsive drug release:

Temperature is an important factor for the release of drugs from the carrier system. An increase or decrease in temperature has direct relation with controlling drug release. The release of drugs mainly occurred at 37ºC change in temperature is the important point for the release of drug from MSNs. It was observed that mainly the temperature at the site of inflammation & at the tumor site than that of normal tissues. At the tumor side, there is higher temperature and normal tissue has lesser temperature this temperature difference used for drug delivery at the tumor site.

Now day's temperature-sensitive polymer poly (N-isopropyl acrylamide). (PNIPAM) is considering as a temperature control stimuli. 31ºC which is critical solution temperature of PNIPAM at this temperature it gets swells and release of drug can be carried out at higher temperatures.

MSNs are coated with the temperature-sensitive polymer PNIPAM to study release profile of Doxorubicin. It was observed that release of DOX takes place at 37ºC which is a relatively high temperature than the room temperature. (21, 22)

Enzyme based drug deliver

y: The enzyme responsive materials were developed to obtain control of the delivery. Mesoporous silica nanoparticles are coated by various polymers & the degradation of polymer coat occurred by specific enzymes. Polymers such as polyethylene glycol diacrylate (PEGDA), matrix metalloproteinase (MMP), polypeptides are coated on pores of MSNs carrier NADPH: quinine oxidoreductase 1(NQ 01) is used as an enzyme stimulus for the release of Doxorubicin.

The drug-loaded on the MSNs & further functionalization of MSNs by alkyl successively done. To avoid the early release of drugs from MSNs the pores were blocked by rotoxane tethering to benzoquinone. Benzoquinone gets reduced by opening the pores release of Doxorubicin carried out.

The in-vivo experiment in nude mice having tumor (lung) it was shown that a decrease in the tumor volume in the mice significantly observed when it heated with MSN-NQ 01 enzymes & compared to those was treated with saline & free doxorubicin. (23)

Light responsive & chemical reaction responsive drug delivery

Irradiation of the surface of nanoparticles is another tool to control the release of a drug. Exposure to the light of certain chemical substances triggered the release of certain entrapped molecules due to the mechanism of photodegradation of chemical groups. The functionalization of MSNs was carried out by mercaptopropyl & the pores of MSNs capped sulforhodamine when it is expressed to the visible light the light-responsive release of entrapped drug mercaptopropyl was takes place due to the photodegradation. This approach was usually utilized for the delivery of anticancer agents. (24)

Chemical reactions this is another approach used for the release study of certain drugs, which is based upon cleavage of bonds reducing molecules that allows the release of specific molecules.

In the study used of collagen which was loaded on the pores of MSNs with the use of molecules such as dithiothreitol is a reducing agent through disulfide bonds the release of drug took place.

Magnetic responsive drug release:

Magnetic responsiveness is another strategy for control the drug release in the presence of external magnetic field.

Single-stranded DNA was immobilized on the surface of MSNs after that magnetic bead was tethered to DNA through complementary sequence, pores of MSNs capped with the magnetic nanoparticles, upon higher temperature & with the use of external magnetic field, double-stranded DNA strand gets melted, followed by uncapping of the pores of MSNs which releases the model drug fluoxetine. (21)

Mesoporous silica for the improving solubility of drug

Mesoporous silica nanoparticles can be act as effective carrier for the drugs are having poor solubility. Due to the modified surface chemistry of the MSNs, they are used for poor solubility drugs to tackle their solubility issues. Mesoporous silica is used as an alternative to the other carrier members to improve the solubility issues & bioavailability of the drugs. The oral bioavailability of drug Telmisartan which is a BCS class II drug having poor solubility, their solubility & bioavailability was improved by loading Telmisartaninto pores of MSNs. The in-vivo release study was conducted on a beagle dog.

In in-vivo absorption study, TEL-loaded MSNs in beagle dogs 1.29 times increase as compared to the marketed tablet & plane MSNs. Also in-vitro cellular uptake study was showed that the TEL-MSN enhanced cellular uptake in Caco-2 cells. (35, 36,37)

Mesoporous silica nanoparticles could be widely exploited for improving drug bioavailability & absorption of poorly water-soluble drugs.

Mesoporous silica nanoparticles in Anti-inflammatory therapy

Different characteristics of MSNs have been used for various anti-inflammatory drugs. With the use of MSNs to control the release rate & improves the anti-inflammatory activity of drugs effectively. The most widely used anti-inflammatory agents i.e. Ibuprofen often was loaded on the multifunctional mesoporous channels & their effect was studied. SBA-15 & MSM-41 are the most widely used silica carriers. Ibuprofen was loaded on the pore surface of MSNs initially it was loaded in small pores of peripheral surface & finally drug is

incorporated deep in the length of mesoporous channels it was found that with used of MSNs effective delivery of anti-inflammatory drug i.e. Ibuprofen was successively carried out.

Surface fictionalization modification on the surface of the silanol group significantly improves the drug release rate and also stabilizes it. (12,13)

Here SBA-15 was used as a carrier for the loading of ibuprofen, the surface of the MSNs was altered by the use of functional group aminopropyl. SBA -15 alone not control the release of ibuprofen because of weaker interaction between the silanol group & the carboxy groups of ibuprofen.

So, surface functionalization of MSNs with amino groups effectively controls the release of ibuprofen because of the strong interaction takes place between silanol group, amino group & the carboxy group of ibuprofen. (14)

Also, this approach was successively studied for the other anti-inflammatory agents like aspirin & indomethacin for effective drug loading & prolonged release rate profiles. (11,15)

MSNs in antibiotic therapy:

Micro-organisms that provide resistance to the antimicrobial drugs, to prevent resistance & to achieve successive therapeutic effect, so controlled & targeted release is important for the antibiotics. Mesoporous silica nanoparticles are having different morphological properties & different structural arrangements due to these MSNs have different release kinetics. It was studied that for the study of release kinetic, amoxicillin was the model drug, amoxicillin loaded on the MSNs which is having hexagonal structural arrangement releases drug in a slower rate than the disk form whereas faster rate of release of the drug observed in case of powder comparing to the disk formulation. (38, 39)

Effective drug delivery & reduced side effects of chemotherapeutic effects:

Many of the cancer drugs are suffering from the problem of poor solubility, instability of drug & poor cellular uptake due to certain issues efficient therapy of anticancer drugs get hampered. Also, anticancer drugs are having a narrow therapeutic index & frequent side effects. So to decrease such side effects & protects the drug from degradation, improves the cellular uptake of drug and generate target-specific delivery of drug is necessary for many of the anticancer agents.

The mesoporous silica nanoparticles are highlighted approach which is suitable for the delivery of small molecules to load the drug effects of poor solubility, 40% of the drug is discovered which are having poor water solubility. MSNs have produced high interest as a drug carrier. Delivery of anticancer agent Doxorubicin (DOX) to the tumor site (40).DOX loaded into MSNs and empty nanoparticles were also injected subcutaneously directly into the tumor or intraperitoneally in mice and compared with the free DOX. It was shown that the particle mediated delivery enhanced the cellular uptake of DOX & improved therapeutic efficiency. (30)

Active tumor-targeting therapy:

Targeting tumors can be achieved by either passive or active targets by the accumulation of therapeutic or diagnostic nanoparticles to the tumor. In active targeting, there is a specific interaction between the delivery carrier and the tumor cells whereas passive targeting occurs to form leaky vasculature improved lymphatic function of tumor cells. By actively targeting the intracellular concentration of drug increases & retaining drug inside the tumor tissues.

In vivo study demonstrated as, active targeting by MSNs using folic acid as a targeting ligand. (31)

It was shown that results for folic acid conjugate camptothecin loaded MSNs which inhibits the tumor growth of the pancreatic cell. (41)

In vivo study showed that IV administration of mannose functionalized mesoporous silica nanoparticles to target the lectins on cancer cells which demonstrated successful targeting increases therapeutic effectiveness.

MSNs in multidrug therapy and its resistance:

It is an alternative approach which combines therapeutic agents & targeting specific site of action. Multidrug resistance is the main cause that can be responsible for therapy failure. The mechanism of MDR multifaced it can be cellular or pharmacological MDR have different circumstances such as pharmacokinetic profiles, insufficient dose, inadequate infusion & effect of the tumor microenvironment.

Cellular mechanisms are classified as pump & non-pump such as cell apoptosis and DNA repairing. The study describes a multifunctional nanoparticulate drug delivery system which is combined with MSNs and with an anticancer drug Docetaxel (DOX) or Cisplatin. Suppressor of the pump or non-pump drug resistance i.e., siRNA target to MRP1 or BCL2 mRNA & increases the anticancer activity successively achieved the target. (33)

Another approach to overcome the multidrug resistance, mesoporous silica nanoparticles was investigated. Where Doxorubicin was conjugated with PH sensitive hydrazone linkers who provides sustained release of DOX.

Verapamil & MSNs with DOX & hydrazone have better cellular uptake & high retention of drugs in a tumor cell. Another modification used as PH responsive MSNs is used to overcome multidrug resistance. MSNs containing porogen CTAB & DOX where the surfactant is used as a chemosensitizer for preventing the MDR &increases drug efficiencies. (34)

CONCLUSION

In this review, we have mainly focused upon the mesoporous silica nanoparticles and their utilization in various drug delivery systems. Mesoporous silica nanoparticles are used as a carrier system for the various therapeutic and diagnostic applications. The unique properties of the mesoporous silica nanocarriers such as pore size, pore-volume, high loading capacity, biocompatibility make them widely exploited carriers. With the use of different concentrations of reactants and the reaction conditions such as temperature, stirring ratemesoporous silica nanoparticles obtained with different particle sizes, pore-volume, and particle shape. In this review how mesoporous silica nanoparticles are used to deliver the drug at various sites by various stimuli such as PH, temperature, light, chemical, magnetic, etc. mesoporous silica nanoparticles is an advantageous carrier for cargo release due to their non-toxic nature, biocompatibility with body and biodegradability. Also one of the special characteristics is the ability of surface modification on the surface of the mesoporous silica nanoparticles by various functional groups helps to enhance the loading capacity and also modify the drug release profile. With the use of mesoporous silica nanoparticles, it is possible to protect the drug from the external environment and also achieve the premature release of drugs.

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