GENERAL INTRODUCTION

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During the past several decades, a steadily growing number of drugs have been discovered. However, about 40 percent of newly designed drugs, especially those which are based on biomolecules such as peptides, oligonucleotides, proteins and DNA, often exhibit low bioavailability and are rejected by the pharmaceutical industry [1]. Therefore, there is an increasing demand for the development of controlled drug delivery systems to minimize drug degradation, manipulate drug pharmacological profile, diversify drug administration routes, decrease detrimental drug side effects and target specific sites. Controlled drug delivery system can be described as formulation that controls the rate and period of drug delivery that is time release doses. It can deliver precise quantity of therapeutic drugs in tailored release manner to enhance drug efficiency (Figure 1) and reduce toxicity. Hence, controlled release of drug using carrier is one of the most promising applications for human health care and represents an ever-evolving field for biomedical materials science.

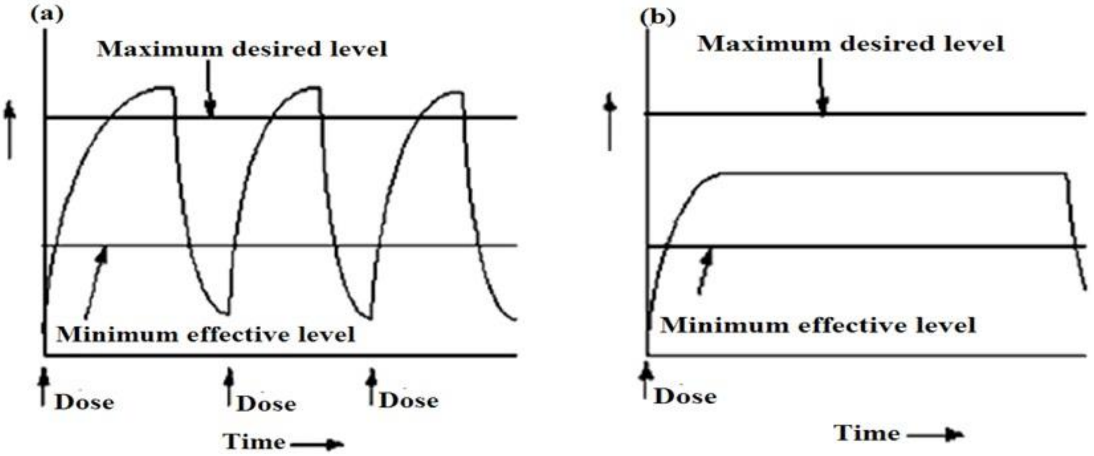


Figure 1. Release profile of drug in (a) traditional and (b) controlled drug delivery system [3]

Different materials have been extensively investigated as carrier for drug delivery (Figure 2), such as amphiphilic block copolymers [2-4], liposomes [5] dendrimers [6, 7] and hydrogels [8, 9].

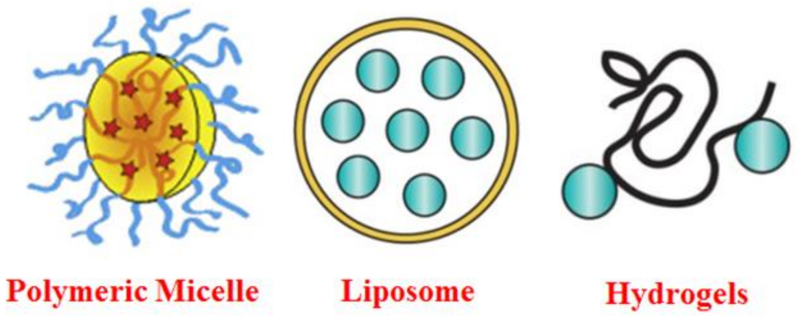


Figure 2. Different drug delivery system [3]

However, they have some limitations such as …..

- Poor chemical stability
- rapid elimination by body functioning processes
- Lack of homogeneous distribution of drug which affects the release rate.
- Specifically designed macroscopic and microscopic structural and chemical features are lacking in polymers.

Compared to the traditional drug carriers, mesoporous silica materials have unique characteristics which make them ideal for hosting as well as delivering drugs and can overcome the above mentioned problems. These are amorphous inorganic materials consisting of silicon and oxygen in their framework. It can be synthesized in the presence of surfactants, which act as templates for the polycondensation of the silicon source (sodium silicate, tetraethyl orthosilicate) [10, 11]. Since 1992, when Mobil Corporation synthesized the MCM-41 material, there have been various types of mesoporous silica in the literature which have been investigated for diverse applications. The factors which determine the physiochemical parameters of mesoporous silica (type of mesostructure, pore diameter, pore volume, wall thickness) dependent on the synthesis conditions such as pH of the medium, type of the silicon source, templating agent and its concentration [12-14].

Advantages of mesoporous silica as carrier

- Ordered porosity at the mesoscale
- Variable pore size
- High specific surface area
- High adsorption capacity

- High concentration of surface Si-OH groups through which it can interact with different functional group of drug
- Their pore size and pore volume can be designed according to substrate molecules for particular application
- Non-toxic, biocompatible and bio-degradable

Further, their pore size and pore volume can be tailored selectively to bind molecules of various size. It is well known that release kinetics of drug from the pores mainly depend on pore size, molecular size of the drug and the drug–surface interaction, which can be done by functionalizing surface of mesoporous silica by proper functional group to increase drug–surface interaction for better control over the drug diffusion kinetics [15]. Functionalization using proper functional group modifies the adsorption capacity of carrier as well as rate of release of the drug.

History of Mesoporous silica as drug delivery systems

1. Major contribution by M. Vallet-Regi and his group. In 2001, they have first time introduced MCM-41 as a drug delivery system for Ibuprofen storage and release. They have synthesized MCM-41 with different pore size and load ibuprofen into it and study the effect of pore size on release rate of drug [16].
2. In 2003, same group have further reported the organic functionalization of MCM-41 having two different sizes by amino propyl group in order to control the release rate of Ibuprofen [17].
3. In 2005, Xue-Feng Qian and his group have reported organic modification of MCM-41 by amino propyl groups using solvothermal process and it’s used as drug delivery system for Aspirin [18a]. Their results show that the release properties of this delivery system are affected by the amount of aminopropyl groups on the pore wall and the ordered structure of mesoporous materials, which indicates that appropriate organic functional groups and post-treated time are favorable for the drug delivery. S. C. Larsen and his group have reported loading and in vitro release of Aspirin from MCM-41 functionalized using aminopropyl group by Co-condensation method. The release data indicated that both the distribution and loading of the amine functional groups in MCM-41 influenced the release properties of Aspirin [18b]. S. Kawi and his group have synthesized and functionlized SBA-15 by amine group using post synthesis

method and studied the in vitro release of Ibuprofen from the same. Their study shows that higher loading as well as controlled release was obtained from functionalized SBA-15 as compared to pure SBA-15 [18c]

4. In 2006, Shilun Qiu and his group have reported synthesis of MCM-41 and MCM-48 with different morphologies, pore geometry as well as pore size and studied the release profile of Ibuprofen [19a]. Their study shows that drug-loading amount was directly correlated to the surface area, pore geometry, and pore volume; while the drug release profiles could be controlled by tailoring the morphologies of mesoporous silica carriers. At the same time, Shilun Qiu and his group have further reported loading and release profile of Captopril from MCM-41 and SBA-15 [19b]. In same year, Shougui Li and his group have reported release study of Captopril from MCM-41 functionalized by trimethylchlorosilane [19c]. M. Vallet-Regı, have reported loading and release of Bisphosphonates from MCM-41 as well as SBA-15 functionlized by amino group [19d].
5. In 2007, V. Ambrogia and his group have reported dissolution rate of piroxicam, a non-steroidal anti-inflammatory drug from MCM-41 [20a]. They have compared the dissolution profile obtained at pH 1.2 with that of marketed product Brexin, a formulation with rapid analgesic effect onset and their results shows higher dissolution rate of drug. In the same year, Carino and his group have reported synthesis of MCM-41 in presence of $Al(OH)_3$ and study the loading as well as release of Methotrexate [20b].
6. In 2008, M. Vallet-Regi and his group have reported functionalization of MCM-41 by 3-aminopropyltriethoxysilane and studied as a potential carrier for controlled drug release, using Ibuprofen as a test drug [21a]. They have reported effect of particle morphology as well as functionalization on release rate of drug. Their study shows that functionalized MCM-41 micro-spheres were found to show a significantly slower drug release rate than irregularly shaped powders. At the same time period, Jun Lin and his group have reported functionlization of MCM-41 by luminescent YVO4:Eu^{3+} layers via the Pechini sol–gel process and studied the release profile of Ibuprofen [21b]. In same time period, R. Martínez-Mañez and his group have reported release of Vitamin B2 at different pH (2 and 7) from MCM-41 functionalized by 3-[2-(2-aminoethylamino)

ethylamino]propyl-trimethoxysilane (pH- and anion-controlled nano-supramolecular gate-like ensembles) [21c].

7. In 2009, V. Ambrogi and his group have reported synthesis of mucoadhesive tablets based on MCM-41, mixtures of hydroxyethylcellulose/MCM-41 and sodium carboxymethylcellulose/MCM-41 and used as carrier for Chlorhexidine diacetate delivery [22a]. M. Vallet-Regi and his group have reported functionalization of SBA-15 by the post-synthesis method with poly(propyleneimine) dendritic precursors, its characterizations and in vitro release of Ibuprofen using this as carrier [22b]. I-B Isabel et al have reported effect of structure type on in vitro release of Ibuprofen using MCM-48 and SBA-15 as drug carrier. They have further functionalized SBA-15 by octadecyltrimethoxysilane and also studied the effect of functionalization on release rate of Ibuprofen [22c].
8. In 2010, Qunli Tang and his group have reported synthesis and functionalization of MCM-41 by dimethylsilyl group and used as drug delivery system for Ibuprofen delivery [23a]. During same year, J.A. Martens and his group have reported in vitro release of Itraconazole from SBA-15 and studied the stability of drug loaded SBA-15 by storing them for 3, 6 and 12 months at 4 and 25 ^{o}C and relative humidity of 0%, 52% and 97 %. Their studied shows that the release behavior was maintained upon storage in dry conditions. Long-term storage at a relative humidity of 52% or 97% had a beneficial effect on the release rate of drug [23b]. Dáˇsa Halamováa and his group have reported synthesis and functionalization of SBA-15 using aminoprpyl group and used as carrier for in vitro release of Naproxen and shown the effect of functionalization on release rate of drug [23c]. R. F. Popovicinad his group have reported functionalization of SBA-15 by 3-aminopropyl group and studied in vitro release of Captopril. They have reported that the loading and release, both were affected by the surface functionalization of SBA-15 [23d].
9. In 2011, Jihong Sun et al have reported functionalization of MCM-41 by 3-aminopropyltriethoxysilane and studied in vitro release of Aspirin. They have reported the Aspirin release kinetic using Korsmeyer–Peppas model and shown the effect of functionalization on release rate of Aspirin [24a]. L. Huang et al have reported controlled release of Captopril in simulated body fluid, using MCM-48 functionalized by hydroxyapatite as drug delivery system. They have

reported that the functionalized MCM-48 loaded with CapH2 still shows strong blue emission centered at 410 nm under UV excitation, and the luminescence intensity increases when drug molecules are gradually released from the carrier [24b]. A. Szegedi and his group have synthesized and functionalized MCM-41 and SBA-15 by 3-aminopropyl group and reported in vitro release of Ibuprofen. They have shown that Surface modification with amino groups resulted in high degree of ibuprofen loading and slow release rate for MCM-41 compared to SBA-15.The adsorbed drug content and the delivery rate can be predetermined by the choice of mesoporous material with the appropriate structural characteristics and surface functionality [24c].

10. In 2012, Gheorghe Maria and his group have reported Cephalosporin release from MCM-41 functionalized by 3-aminopropyl group. They have studied the release kinetics of Cephalosporin using Korsmeyar-Peppas model and Extended Kinetics model [25a]. A. Szegedi and his group have synthesized and functionalized MCM-41 by 3-aminopropyl group and shown that the Amino modification resulted in high degree of Ibuprofen loading and slow release rate in comparison to the parent non-modified MCM-41 [25b]. J. Sun et al have studied the influence of mesoporous structure on drug delivery property of Ibuprofen from the bimodal mesoporous silica with short random mesoporous channels and MCM-41 with long ordered mesopores which were modified with 3-(2-aminoethylamino) propyl group. They have shown that faster release was obtained for bimodal mesoporous silica compared to MCM-41 and also studied the release kinetics of Ibuprofen release using Korsmeyere-Peppas Model [25c]. Marek Laniecki and his group have reported adsorption and in vitro release of Papaverine hydrochloride from SBA-15 with different formulation such as powders, granules and tablets. They have functionalized SBA-15 by Hydroxypropyl cellulose and stearic acid and shown the effect of functionalisation on release rate of drug [25d].
11. In 2013, Siling Wang et al have investigated MCM-48 and MCM-41 type mesoporous silica as carrier for water insoluble Cilostazol and found the faster release from MCM-48 as compared to that of MCM-41. Further, they have reported release kinetic and mechanism using Zero-order, fist order release kinetic model and Higuchi Model [26a]. M.R. Delgado and his group have reported functionalization of sub-micrometric MCM-41 spheres by 3-

aminopropyl as well as carboxyl group and studied in vitro controlled release of Cisplatin [26b]. Daniela Berger et al have reported functionalization of MCM-41 by a postsynthesis grafting procedure with hydrophilic aminopropyl and hydrophobic vinyl group and studied as drug delivery system for Irinotecan. Their studies show that all the drug loaded materials shows exhibited higher cytotoxicity on murine embrionary fibroblastic (MEF) cells than free irinotecan at the same content of the cytostatic agent [26c]. J. Mielcarek et al have reported loading and characterization of calcium channel blocker – lacidipine into SBA-15. No release study was carried out for the same [26d].

12. In 2014, J. Kurczewska and his group have reported in vitro release of Ibuprofen from MCM-41. They have loaded ibuprofen into MCM-41 using Calcium alginate as binder [27a]. However, they have not shown any kinetic study of Ibuprofen release. During same year, Carla D. Nunes and his group have studied in vitro release of Nifedipine from MCM-41 and show that drug inside the MCM-41is more resistant to photo degradation than in its pure form [27b]. Chang-Sik Ha et al have reported comparison of release behavior of MCM-41 and SBA-15 functionalized by alkyl group for Ibuprofen, lysozyme, and Cytochrome C [27c]. D. Berger and his group have studied the effect of structural, textural and surface properties of MCM-41, MCM-48 and SBA-15 on aminoglycoside (amikacin and Kanamycin) uptake and in vitro delivery and shows that slower release was obtained from SBA-15 compared to MCM-48 [27d]. M. Vallet-Regí and his group have studied in vitro release of Chicago Sky Blue (CSB) 6B from SBA-15 functionalized by 3-aminopropyl group. They have reported that the positively charged amino groups could interact with the negatively charged sulphonic groups of CSB allowing controlled the release process [27e]. P.L.O. Volpe et al have studied the Ibuprofen loading and release from SBA-15. They have employed functionalized SBA-15 using glutaraldehyde-bridged silylating agent as carrier for Ibuprofen delivery and observed faster release for pure SBA-15 as compared to that of functionalized SBA-15. They also have reported kinetic study of ibuprofen release using Korsmeyer-Peppas Model [27f].
13. In 2015, Shunai Che and Xiao Liu have studied the effect of particle size on release rate of Itraconazole. They have synthesized MCM-41 and SBA-15 with different particle size, loaded Itraconazole and reported in vitro release of same.

Their studies show that the release profile of drug was not influenced by the particle sizes. However, the release performance increased with increasing pore diameter [28a]. Jan Wasicki et al have reported dissolution of poorly water-soluble drug, Nimodipine using MCM-41 and SBA-15 as carrier [28b]. F. Baltazar et al have studied the in vitro release of Salicylic Acid from microporous zeolite NaY, and the mesoporous SBA-15 and MCM-41.They have reported that SBA-15 and MCM-41 proved to be more efficient in loading drug than microporous zeolite NaY. The release rate of Salicylic Acid increases with increasing pore size for materials. They also have reported drug release mechanism using Higuchi Model [28c].

14. In 2016, M. M. Ayad and his group have synthesized and functionalized KIT-6-SO_3H and SBA-15-SO_3H and used as carrier to deliver Procaine hydrochloride. Their study indicates that the amount and release rate of drug was modulated through functionalization by an SO_3H group on the surface of the pore walls present in the mesoporous silica materials [29].
15. In 2017, M. Monduzzi and his group have studied adsorption and release of Ampicillin using MCM-41, SBA-15 and amino functionalized SBA-15. Their study shows that higher loading was obtained for functionalized SBA-15 as compared to pure silica materials as well as sustainable release of drug was also obtained from amino functionalized SBA-15 [30a]. A. Yilmaz and his group have reported loading of Celecoxib (CLX), a highly hydrophobic nonsteroidal anti-inflammatory drug into SBA-15 and functionalized SBA-15 by 3-aminopropyl group in presence of different solvents. They have studied the effect of solvent (ethanol, methanol and hexane) on loading and release of drug in different pH. Their study shows that higher loading was obtained in case of functionalized SBA-15 in hexane and also shows controlled release for the same [30b]. R.A. García-Muñoz and his group have reported synthesis and functionalization of SBA-15 by various organic group such as 3-aminopropyl, 2,4-chlorosulfonylphenyl, 3-mercaptopropyl, chlorotrimethyl, styrylethyltrimethoxy, trimethoxy(octyl), 1-naphthyltrimethoxy, N-3-methoxysilylpropyl)ethylenediamine, N-3-trimethoxysilylpropyl) diethylenetriamine, (N-henylaminopropyl) trimethoxy and aminoethyl aminomethyl groups and studied the in vitro release of Methylprednisolone sodium hemisuccinate. Their study shows that SBA-15 functionalized with

aminopropyl groups has the largest capacity of drug adsorption and controlled delivery, higher than the provided by materials functionalized with other groups, independently of the synthesis route [30c]. M.E. Mesquita and his group have studied the in vitro release of Efavirenz from MCM-41 and SBA-15 and also reported the release kinetic using Zero order, First order release kinetic model, Higuchi model and Korsmeyer-Peppas model [30d].

After a thorough investigation of the available literature, it was found that MCM-41 and MCM-48 have been used as carriers to deliver large number of drug molecules. Because of differences in structure and geometry of MCM-41 and MCM-48, which results in the apparent difference in their drug release profiles, we also have selected these two for detailed study. SBA-15 was not selected as its structure is similar to that of MCM-41 except for wall thickness.

Further, literature survey also shows that no inorganic moiety has ever been used as functionalizing agent. So it was thought to be of interest to use an inorganic moiety, polyoxometalates (POM) to functionalize the carriers.

A Brief overview of Polyoxometalates

Polyoxometalates (POMs) are discrete anionic metal oxygen clusters which can be regarded as soluble oxide fragments [31]. They are a distinctive class with unique properties of topology, size, electronic versatility as well as structural diversity. Due to the combination of their added value properties such as redox properties, large sizes, high negative charge, nucleophilicity they play a great role in various fields such as material science, catalysis, electrochemistry, photochromism and magnetism. Along with this, they have also been used in medicinal chemistry [32-38]. Further, they have great number of water molecules and presence of terminal oxygen which can bind to the different groups of drug molecules. The literature survey shows that among all the polyoxometalates, the 12-tungstophosphoric acid has been widely used in medicinal chemistry [39–43]. So it is interesting to study the effect of this inorganic molecule on the release of drug.

Among different POMs, Keggin type POM are investigated extensively because of their easy synthesis as well as high stability [44]. The general formula for Keggin type POM is $[XM_{12}O_{40}]^{n-}$, in which X is the hetero atom, usually a main group element (e.g., P, Si, Ge, As), and M is the addenda atom, being a d-block element in high oxidation state, usually V(IV,V), Mo(VI) or W(VI) and formed by different mononuclear oxoanions. For example, the formation of polyoxoanion is shown in the following equation.

$$12MO_4^{m-} + HXO_4^{p-} + 23H+ \rightarrow [XM_{12}O_{40}]^{n-} + 12H_2O \text{ -------- Eq. (1)}$$

The acidic salts of ions are known as heteropoly acids (HPAs).

Structure of Keggin type POMs

The ideal Keggin structure, $[XM_{12}O_{40}]^{3-}$ of α-type has Td symmetry and consists of a central XO_4 tetrahedron (X = heteroatom or central atom) surrounded by twelve MO_6 octahedra (M = addenda atom). The twelve MO_6 octahedra comprise four groups of three edge-shared octahedra, the M_3O_{13} triplet [45, 46], which have a common oxygen vertex connected to the central heteroatom. The oxygen atoms in this structure fall into four classes of symmetry-equivalent oxygens: X-O_a-$(M)_3$, M-O_b-M, connecting two M_3O_{13} units by comer sharing; M-O_c-M, connecting two M_3O_13 units by edge sharing; and O_d-M, where M is the addenda atom and X the heteroatom. The schematic representation of Keggin type is shown in Figure 3**.**

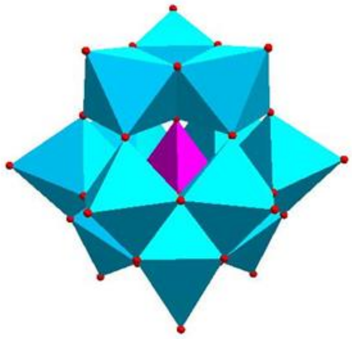


Figure 3. Molecular structure of 12-tungstophosphoric acid

Selaction of biomolecules/Drugs

L-Arginine

L-Arginine is a semi essential amino acid. Molecular structure of L-Arginine is shown in Figure 4. L-Arginine is also substrate for the synthesis of nitric oxide (NO), polyamines and agmatine and influence hormonal release and the synthesis of pyrimidine bases [47-50]. It is the main source of generation of NO via NO synthase (NOS). The 3 NOS isoforms have been found to be expressed in the kidney [50]. In the kidney endothelial NOS is important in the maintenance of glomerular filtration rate, regional vascular tone, and renal blood flow. The neuronal NOS (nNOS) is expressed primarily in the macula densa and participates in the control of glomerular hemodynamic via tubulo-glomerular feedback and rennin release. The inducible (iNOS) is expressed in the kidney under pathological condition in the glomerular mesangium, infiltrating macrophages and tubules [51]. L-Arginine is the substrate for arginases, a group of enzyme that are involved in tissue repair processes and that metabolize L-Arginine to l-ornithine [52] as well as precursor for polyamine synthesis which is also involved in tissue repair and wound healing [53,54]. During the time of stress, body does not provide sufficient amount of L-Arginine for metabolic needs. Hence under this condition, L-Arginine supplementation has been considered as an adjunct treatment for restoring normal function [53, 55, 56]. It was also found that compared to oral administration, intravenous administration of L-Arginine to the patients with coronary artery disease increases the bioavailability of vascular nitric oxide (NO) which shows the vasodilator effect.

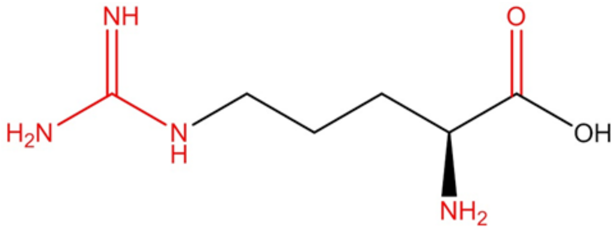


Figure 4. Molecular structure of L-Arginine

Further it was found that in case of oral administration, the bio-availability of L-Arginine decreases as it is utilized by arginase for the production of urea and ornithine and thus competes with NO synthase for substrate availability [47, 57], 40% L-Arginine is degraded in the intestine by arginase [58].

Cysteine

Cysteine is a naturally occurring, sulfur-containing amino acid which has a thiol group and is found in most proteins. Molecular structure of Cysteine is shown in Figure 5. Because it is a sulfur-based amino acid, Cysteine itself can act as an antioxidant in the body. Cysteine pro-drugs are used to treat Schizophrenia and reduce drug cravings [59]. Cysteine is a limiting substrate in the production of glutathione in the body. The reduction of intracellular levels of glutathione contributes to chronic inflammatory conditions, which are associated with cancer, neurogenerative, cardiovascular and infertility diseases resulting in high demand of Cysteine [60-62]. Current Cysteine therapies are administration of different Cysteine derivatives such as N-acetyl-Cysteine. One of the major drawbacks of these therapies is high dosages that can provoke persistent damage and strong allergic reactions [63-66].

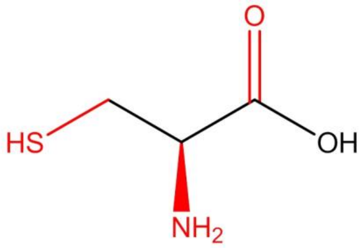


Figure 5. Molecular structure of Cysteine

Aspirin

Aspirin is primarily used for the treatment of cardiovascular diseases [67]. It is a non-steroidal anti-inflammatory drug which acts by inhibiting the enzyme cyclooxygenase [68] and also used for analgesic and antipyretic effects [69]. The molecular dimensions of the Aspirin molecule shown in Figure 6 are 8.1 Å X 6.5 Å X 3.6 Å.

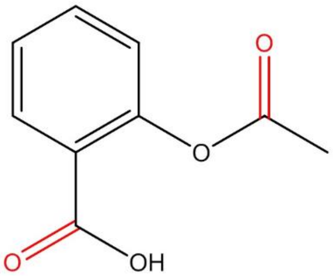


Figure 6. Molecular structure of Aspirin

It has been reported that Aspirin can also reduce the development of different types of cancer such as pancreatic, breast, head, and neck cancer [69-73]. Because of its shorter biological half-life and poor solubility it shows poor pharmacological profile

[74, 75]. The administration of most anti-inflammatory drugs in therapeutic doses can lead to development of gastrointestinal inflammation or ulcers [76]. To avoid these problems, encapsulation of anti-inflammatory drug, Aspirin into various drug carriers should help to achieve the desired goals.

Captopril

Water-soluble drug Captopril is an orally active inhibitor of angiotensin-converting enzyme (ACE), having size of 9.0 × 5.7 × 3.3 A^o (Figure 7) has been widely used for the treatment of hypertension and congestive heart failure. It acts by inhibiting the active sites of the ACE, blocking the conversion of angiotensin I to angiotensin II. According to the Biopharmaceutical Classification System (BCS), captopril is classified as a class III drug with high solubility and poor permeability. It is an orally active inhibitor of ACE used for controlling blood pressure, treating heart failure, preventing cardiac remodeling and left ventricular dysfunction after myocardial infarction, and preventing kidney damage in people with hypertension or diabetes. It is one of the best documented ACE inhibitors [77-79]. However, instability of this drug due to its active functional group, thiol is main drawback of its oral administration. Further, duration of drug in vivo requires a long drug activity. These are the major drawback of oral administration of captopril [80, 81].

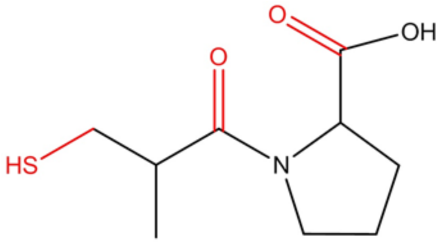


Figure 7. Molecular structure of Captopril

Along with this, its medication required higher dosing. Recently, a new drug, Angiopril has been used for the treatment instead of Captopril. However, the mentioned problem of captopril can be solved by designing proper carrier which can release it in controlled manner and protect it from degradation due to its active thiol group.

Camptothecin

Camptothecin (CPT) is a naturally occurring quinolone alkaloid which shows significant anticancer activity with a broad spectrum of human malignancies (Figure 8) and CPT is an inhibitor of the DNA-replicating enzyme topoisomerase-I [82]. Unfortunately, the clinical application of CPT is hindered by its poor pharmaceutical profile, with extreme aqueous insolubility, low stability of the lactone form at physiological pH, and severe systemic toxicities which included myelosuppression, vomiting, diarrhoea, and hemorrhagic cystitis [83-85]. A better understanding of mode of action, chemistry and pharmacology of the CPT led to the development of water-soluble derivatives such as irinotecan, topotecan and 9-aminocamptothecin [86]. Although less active than the CPT [87], these derivatives have gained approval by the Food and Drug Administration (FDA) for treating cancers. However, these CPT derivatives still suffer from important drawbacks mainly related to the poor stability of the lactone ring, the short half-life of the compounds in blood and a number of non-resolved toxic effects. Therefore, the development of controlled delivery strategies could lead to significant advantages in the clinical use of these drugs. In this sense, CPT has been encapsulated in different vehicles, like PLGA microspheres [88], solid lipid nanoparticles [89], liposomes [90] and micelles [91].

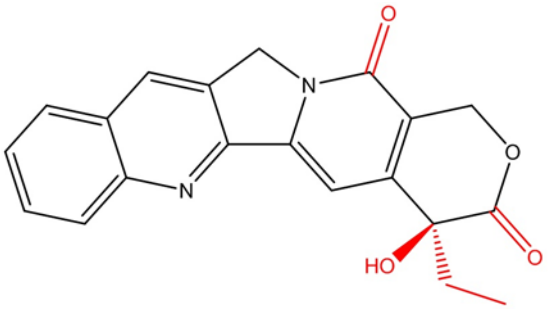


Figure 8. Molecular structure of Camptothecin

Reports are also available for Camptothecin loading and release using functionalized as well as non-functionalized Silica nanoparticles [92] and polymeric nanoparticles [93]. Further, to modulate the release rate of CPT, carriers are functionalized by various organic molecules such as silica nanoparticles functionalized by 3-Mercaptopropyl group [94] and Nucleic acids [95]. Functionalization leads to overcome the mentioned problems faced by CPT.

Different methods for loading of Drugs

There are various methods which are used for loading of drugs into the mesoporous silica.

(a) Melt method
(b) Impregnation method
(c) Soaking Method

Melt method

Melt method is the techniques use for loading of drugs into carrier. In this procedure physical mixture of drug and carrier are heated at the melting point of drug. However, this method is not generalized to all drug molecules. Because the chemical stability of the drug is may be affected thermal heating. Further, this method is not used for drugs which are based on biomolecules such as peptides, oligonucleotides, proteins and DNA. As at higher temperature these drug molecules might show change in their structure.

Impregnation

Impregnation is a technique in which a solution of the Drug is brought in contact with the carrier. Two methodologies exist. In dry impregnation, also referred to as "pore volume impregnation", just enough liquid (solution of the drugs) is used to fill the pore volume of the Carrier. In wet impregnation, the carrier is dipped into an excess quantity of solution containing the drug (Figure 9). Then mixture is heated to evaporate the solvent and dried.

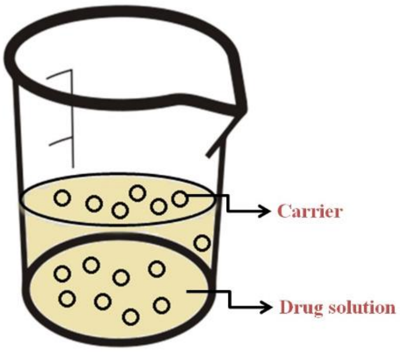


Figure 9. Wet impregnation method for drug loading

Soaking method

This is the anther technique which is used for loading of drug. In this method, carrier/mesoporous silica is soaked in solution of drug in proper solvent for 24 h in sealed glass vials. During the loading process, the solution is magnetically stirred (Figure 10). After 24 h, the mixture is filtered and washed with same solvent to remove excess amount of drug present on surface of carrier. The type of solvent to be used depends on the type and solubility of the drug. Each type of molecule to be confined has its own optimum solvent and an optimum ratio to obtain the highest possible amount of drug adsorbed. The amount of drug loaded is obtained by analyzing a filtrate by different method such as Uv-Visible spectroscopy and HPLC.

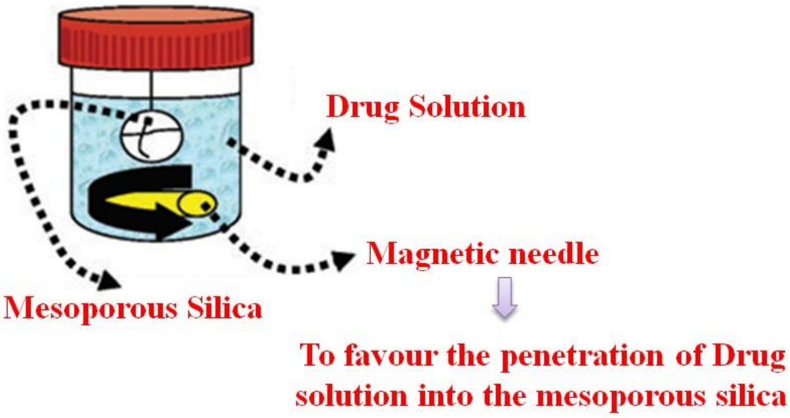


Figure 10. Soaking method for drug loading

Scope of thesis

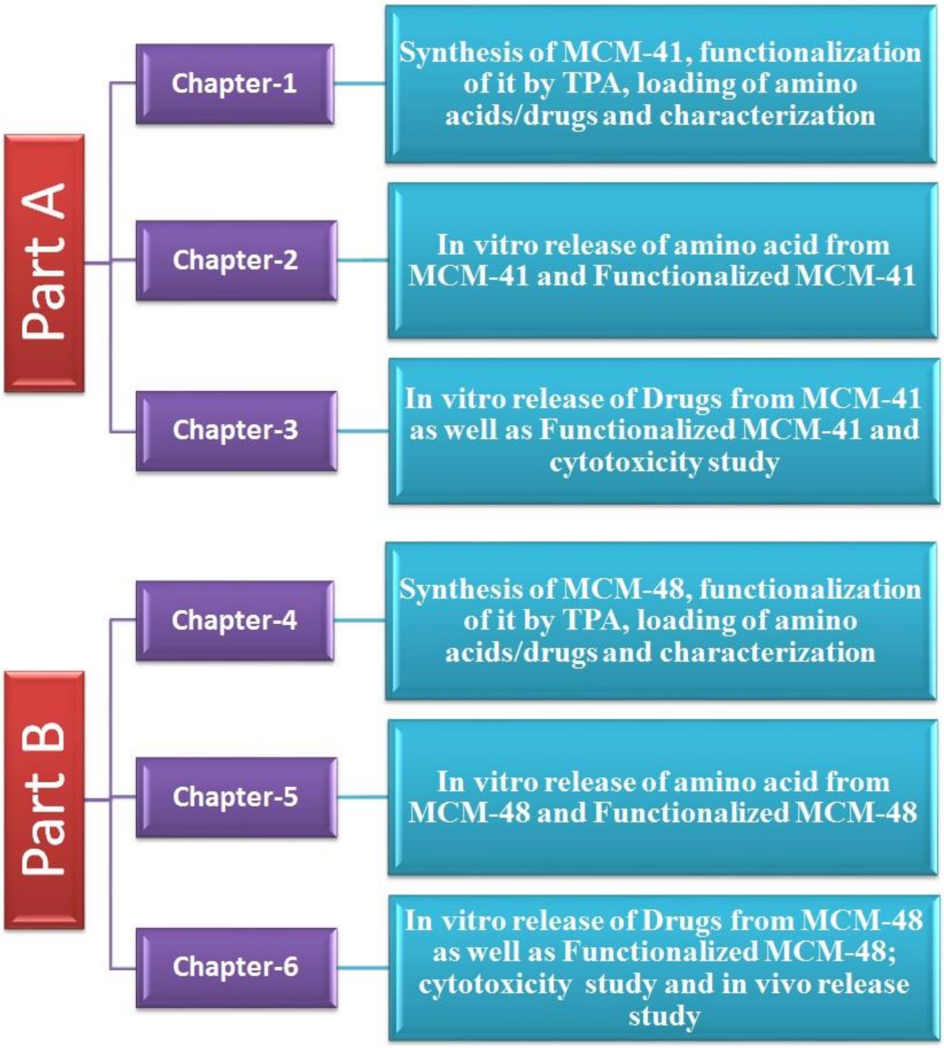
In present, thesis mesoporous silica materials (MCM-41 and MCM-48) were synthesized, functionalized by an inorganic moiety (12-tungstophosphoric acid) and Characterized by various physicochemical techniques. Pure and functionalized MCM-41 and MCM-48 have been studied as carrier to deliver Cysteine, L-Arginine, Aspirin, Captopril and Camptothecin. In vitro release studies of selected drugs were carried out in Simulated Body fluid (SBF pH 7.4) and Simulated Gastric fluid (SGF pH 1.2) under different condition at body temperature. Drug release kinetic and mechanism were also studied using various models such as First order, Higuchi Model, Korsmeyer-Peppas Model (KPM) and Extended Kinetic Model (EKM).

Objective of the work

- To develop controlled drug delivery system based on mesoporous silica (MCM-41 and MCM-48) and the polyoxometalates, 12-tungstophophoricacid.
- To synthesize MCM-41 and MCM-48, to characterize them using various techniques such as XRD, SEM, TEM, FTIR, NMR, TG-DTA, BET analysis as well as to load L-Arginine, Cysteine, Captopril, Aspirin and Camptothecin and to characterize them using same techniques.
- To study the in vitro amino acids/drugs release in simulated body fluid (similar to blood plasma pH 7.4) and gastric fluid (pH 1.2). Amino acids/drugs release will be monitored using UV-Visible spectrometry, under stirring and static condition.
- To functionalize MCM-41 and MCM-48 using 12-tungstophosphoricacid (TPA), loading with the mentioned amino acids/drugs and their characterization.
- To see the effect of functionalization on release profile of drug molecules.
- To study the kinetics and release mechanism of drugs using different models such as 1st order release kinetic model, Higuchi model, Korsmeyer-Peppas model (KPM) and Extended kinetic model (EKM).
- Perform MTT study for Camptothecin loaded systems.
- To study the in vivo Camptothecin release from the selected best systems.
- To design MCM-41 type mesoporous silica nanoparticle and study is application as carrier.

Organization of the thesis

The work was divided into six chapters categorized into two parts.



Annexure

Mesoporous silica nanoparticles (MSN) also have been reported as drug carrier because of having unique properties such as large surface area, large pore volume, highly ordered pore structure, adjustable pore size higher adsorption capacity, biocompatibility and non-cytotoxicity. Further, they are effectively taken by cells because of smaller size. In the present thesis we also have synthesized MCM-41 type mesoporous silica nanoparticle. Further, these are functionalized by TPA and characterized by physicochemical techniques. Functionalized and unfunctionalized MCM-41 nanoparticles have been studied as carrier to deliver L-Arginine, Aspirin and Captopril.

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