Porous Inorganic Drug Delivery Systems – *A Review*

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Abstract

Innovative methods and materials have been developed to overcome limitations associated with current drug delivery systems. Significant developments have led to the use of a variety of materials (as excipients) such as inorganic and metallic structures; marking a transition from conventional polymers. Inorganic materials, especially those possessing significant porosity, are emerging as good candidates for the delivery of a range of drugs (anti-biotics, anti-cancer and anti-inflammatories), providing several advantages in formulation and engineering (encapsulation of drug in amorphous form, controlled delivery and improved targeting). This review focuses on key selected developments in porous drug delivery systems. The review provides a short broad overview of porous polymeric materials for drug delivery before focusing on porous inorganic materials (e.g. Santa Barbara Amorphous (SBA) and Mobil Composition of Matter (MCM)) and their utilisation in drug dosage form development. Methods for their preparation and drug loading thereafter are detailed. Several examples of porous inorganic materials, drugs used and outcomes are discussed providing the reader with an understanding of advances in the field and realistic opportunities.

Keywords: Porous materials, mesoporous, nanoparticles, drug delivery, inorganic

1. Introduction

Drug delivery is the approach of administering therapeutic agents (in various formulations) to attain desired therapeutic effect (s) (1,2). Over the years, drug delivery methods have improved and evolved significantly to enhance patient compliance, drug bioavailability, safety and therapeutic index (3). Advances in routes of administration also impact both drug efficacy and pharmacokinetics (4), and the oral route is the most popular and convenient for patients (5). However, there are some limitations including; dysphagia (inability to swallow), erratic absorption and drug degradation in the gastrointestinal tract (e.g. peptides and proteins) resulting in reduced bioavailability (4-6). Innovative methods have been developed to overcome such limitations. Size reduction is an advanced approach for the delivery of an accurate therapeutic dose, controlled drug release, targeted delivery, improved pharmacokinetics and to reduce adverse reactions (2,7). Moreover, several unorthodox strategies have been explored to utilise structures on the nano- and micro-meter scales that are promising candidates and emerging systems for drug delivery. These include microspheres (8,9), dendrimers (10,11), nano-particles (12,13), nano-emulsions (14,15), nano-fibers (16,17), micelles (18), niosomes (19,20), liposomes (21,22) and proniosomes (23,24).

This review focuses on selected developments in porous inorganic drug carriers. A short overview of organic materials is also provided before various aspects of inorganic materials (structure, synthesis, applications and toxicity) are discussed with selected findings summarised in three tables.

2. Materials used for drug delivery

A broad range of natural and synthetic materials have been used as excipients (and device platforms) for several applications in drug delivery; such as polymers, lipids, surfactants, ceramics, inorganic and porous materials.

Progression in polymer science has contributed significantly towards novel drug delivery technologies (25) for enhanced, sustained and controlled release (26,27). Polymers (natural and synthetic) are either biodegradable or non-biodegradable. They provide therapeutic benefits in which they can serve as bio-active agents or simply as carriers for molecules of interest (hydrophilic and hydrophobic). Ideally, they must be both biocompatible and biodegradable, which improves drug release kinetics and enables a systematic method for

their removal from the body (26). Natural polymers (e.g. collagen, alginate, chitosan and carrageenan) which are generally extracted from natural compounds have the advantage of being biocompatible and biodegradable. In contrast, synthetic polymers are synthesised as either biodegradable (e.g poly(glycolic acid) (PGA), poly(adipic acid), polyamino acids, poly(ε-caprolactone) (PCL) and polyphosphonates) or non-biodegradable (e.g. polyvinyl pyrrolidone, carboxymethyl cellulose, poly(methyl methacrylate) (25). The use of synthetic polymers for drug delivery system development provides distinct advantages over naturally occurring types, largely due to the ability to tailor their chemical and physical properties (e.g. chain structure, solubility, size and biodegradability) (28).

Lipid based drug delivery systems work on the basis of improving hydrophobic drug solubility, absorption and bioavailability by encapsulation/solubilisation (6). These are available in different forms; such as drug in lipid solutions (e.g. halofantrine (29)), microemulsions (e.g. etodolac (30)), emulsions (e.g. bupivacaine (31)), liposomes (e.g. doxorubicin (32)) and solid-lipid nanoparticles (e.g. minoxidil (33)).

Surfactants have also contributed towards the development of advanced drug delivery systems (34). They are used in all pharmaceutical disperse systems (e.g. emulsions, suspensions, foams, gels and composites) (35). Moreover, they can be used as drug vehicles/carriers or targeting systems (36) and in topical formulations to enhance drug penetration across epithelial barriers (37,38). There are several types of surfactants; anionic (e.g. carboxylates and sodium lauryl sulphate), cationic (e.g. cetyltrimethyl ammonium bromide and benzalkonium chloride), non-ionic (e.g. Tween® 80 and Span® 80) and zwitterionic (e.g. sulphobetaine and dodecyl betaine) (37).

Ceramic nano-powders provide an alternative approach for drug delivery. Ceramics are non-immunogenic materials which are compatible with biological tissues, excipient chemicals and drugs (39). Bioceramics (e.g. silica-based glasses and calcium phosphates) have been utilised for local drug delivery; such as treating osteoporotic fractures, large bone defects, bone tumours and bone infections (40).

Nanoparicles prepared from oxides of silver, gold, silica, titanium, iron, copper and zinc have potential use in several biomedical applications including drug delivery, cellular and bimolecular labelling, cancer targeting and biosensing (41). These nanoparticles are capable of delivering multi-functional properties e.g. antibody functionalised gold has been shown to provide both selective imaging and photo-thermal apoptosis of cancerous cells (42).

Among the various carrier systems, porous materials are evolving as an innovative class of host/guest systems (43). Their porous structure permits encapsulation of a variety of active molecules (44) and have also shown great promise in many miscellaneous medical fields. Furthermore, as is the case with synthetic polymers; porous materials can be designed as fibres, micro- and nanoparticles, coatings and monoliths (44).

3. Porous materials

Porous materials have been used as controlled drug delivery carrier systems with optimistic properties, such as well-organised stable architectures, modifiable and uniform pore sizes and large surface areas (43-45). For inorganic porous materials, the porous state is classified according to the pore size boundary i.e. macroporous (pore size >50 nm), mesoporous (pore diameter 2-50 nm), and microporous (pore diameter <2 nm) (44). A variety of polymeric and inorganic porous carriers are widely available and extensively used in different types of biomedical and pharmaceutical applications such as active loaded tissue engineering construct, oral, topical and injectable drug delivery.

3.1 Porous polymeric carriers

Porous polymeric carriers are available in different morphologies i.e. microspheres, porous fibres, porous microneedles, as well as hydrogel systems. They are utilised for various pharmaceutical applications. Porous polymeric microspheres with interconnected pores and large surface areas have been used as carriers for several therapeutic drugs, vaccines and genes (46,47). These particles have been engineered/synthesised from a variety of synthetic polymers (i.e. poly(lactic-co-glycolic acid) (PLGA) (46,47), poly lactic acid (PLA) (48,49), poly(methyl methacrylate) (50), poly-(methyl ethyl cyanoacrylate)(51), polyacrylamide (52) and Eudragit (53)). In addition, several natural polymers (such as; chitosan (54), polysucrose (55) and alginate (56)) have also been used for porous particle synthesis.

As for their applications, porous polymeric microspheres have been explored for pulmonary, tissue engineering (as scaffolds), topical and oral delivery systems (e.g. microsponges). Large porous microspheres are considered as optimal drug carriers for pulmonary delivery (57). Their porous structure and large size can achieve deep lung deposition and therefore enhance drug delivery (58). Furthermore, porous particles with diameters greater than 5 μm in diameter and possessing mass densities less than 0.4 g/cm^3 were inhaled deeply into the lungs and bypassed clearance mechanisms (59).

Porous biodegradable polymeric microspheres have been utilised as scaffolds for tissue engineering (60) with highly open inter-connecting porous microspheres ideal for cell delivery *via* impregnation. In this instance, the highly porous structure is essential to attain adequate cell seeding density and to facilitate oxygen and nutrient transportation across selected cells to promote their growth and proliferation (61).

Microsponges are porous polymeric microspheres, and have been used for topical and oral drug delivery (62). They have been developed to enhance encapsulated drug stability against environmental and physical degradation (62,63). Also, microsponges can be used to improve the safety profile for various drugs and their efficacy (63). For instance, microsponges used in topical drug delivery can entrap topical ingredients (e.g. sunscreens, emollients, essential oils, fragrances and topical anti-inflammatory agents) and control their release onto skins surface (62) by gradually releasing the entrapped active to avoid its accumulation within the dermis and epidermis (64). For oral dosage form applications; entrapping poorly water soluble drugs in microsponge pores is one way to enhance their solubility (63,64) and to provide controlled release mechanisms to the lower gastric intestinal tract (63).

Fibrous matrices (with interstitial porous features) offer large surface areas. These have been employed in several areas of tissue engineering and drug delivery (encapsulation and controlled drug release systems) (65-67). Various biodegradable (e.g. PCL (65), poly (L-lactic acid) (PLLA) (66), PLGA (68)) and non-biodegradable (e.g. polystyrene (69)) polymers has been used.

Porous microneedle arrays have been developed with potential applications in drug and vaccine delivery (70). This approach is valuable for applications requiring large surface areas, such as the insertion of microneedles into the skin to serve as tissue engineering scaffolds or biosensors. Microneedles may disengage from their substrate and remain embedded in the tissue for controlled drug delivery (71). Utilising microneedles from biodegradable polymers (e.g. PLA (71)) which degrade safely at the site of insertion is advantageous (70). Porous microneedles are naturally weaker than solid microneedles, and this may hinder their ability to penetrate the skin (70,71). Therefore, this approach still requires further exploration in order to deliver ideal platforms for dermal delivery (70).

Hydrogels are cross-linked networks of water insoluble polymers (e.g. chitosan (72), poly(acrylic acid) (73) and alginate (74)) which are able to swell significantly in aqueous media (75). They are classified according to their network structure (porous to nonporous);

microporous, macroporous and superporous hydrogels (75). The network structure of porous hydrogels allows entrapment of drugs into their matrix (76). They are utilised as drug carriers with the ability to release the entrapped drug in a sustained profile (77). The release rate of the entrapped drug can be controlled by the pore size, the polymer biodegradability and the affinity of the drug to the polymer (78). Superporous hydrogels contain large quantities of interconnected and open pores within their network. Their highly porous structure is very useful for a range of novel drug delivery approaches, such as intestinal delivery of therapeutics and gastric retention (79).

The aforementioned porous carriers are usually produced using biodegradable/non-biodegradable polymers. Natural polymers are mostly biodegradable and provide high biocompatibility (25,28). For instance, gelatine, chitosan, collagen and dextran are natural, biodegradable, biocompatible, nontoxic and non-immunogenic. While, sodium alginate is an example of a naturally occurring polymer, it does not undergo degradation *via* mammalian enzymatic action (28). Biodegradable polymers are preferred as they degrade *in vivo* to non-toxic monomers (25). For example, PLA degrades to form lactic acid which is then metabolized through the Krebs cycle and excreted as carbon dioxide and water, mostly through respiration. PGA is another biodegradable polymer which degrades to glycolic acid; which is later excreted in urine (80). Most biodegradable polymers (e.g. PCL, PLA, PGA and PLGA) have proven to be biocompatible and nontoxic (80,81). However, the biocompatibilities of some polymers (e.g. PGA and PLA) maybe compromised when used in certain orthopaedic applications. They may release small fragments during their degradation stimulating foreign inflammatory reactions (80,81). These small fragments are finally phagocytised by multinucleated giant cells and macrophages (80). Some polymers produce acidic degradation products (e.g. PLA, PGA and PLGA) which affect cell integrity in their microenvironment by lowering the surrounding pH (82). Poly (methyl cyanoacrylates) is another biodegradable polymer but its degradation products (cyanoacetic acid and formaldehyde) are toxic (28).

The elimination of non-biodegradable polymers is highly dependent on their molecular weight. Large non-biodegradable polymers may persist within tissue after cellular death or be eliminated through renal glomerular filtration if their molecular weight is lower than the renal excretion threshold (83,84). However, accumulation is a potential problem for all non-biodegradable polymers. Even if the molecular weight of the polymer is below the renal

excretion threshold, some quantities of polymer (tail end of the molecular chain distribution) will still possess a higher molecular weight (84).

3.2 Mesoporous inorganic porous carriers

Inorganic porous materials are promising carriers for various types of drugs, genes and proteins. Their porous structure is beneficial to attain a controlled, sustained or pulsatile release in drug delivery applications. The diffusion rate of entrapped drug, gene or protein can be controlled by the materials porous and hydrophilic characteristics. Moreover, porous inorganic materials demonstrate high mechanical and chemical stability under a range of physiological conditions (44). They are classified into three classes according to their pore size; microporous inorganic materials (e.g. zeolites molecular sieves), mesoporous inorganic materials (e.g. MS and mesoporous metal oxides) and macroporous inorganic materials (e.g. macroporous aluminophosphate) (85). A transmission electron micrograph of mesoporous silica is shown in **Figure 1**.

The term meso means “in between”, and is used by International Union of Pure and Applied Chemistry (IUPAC) to describe porous materials having pore size between the micropore and macropore range (2-50 nm). IUPAC classify mesoporous materials according to the nature of the materials network; ordered or disordered materials (86). Mesoporous materials are excellent matrices for controlled drug delivery and in recent times greater research efforts have been dedicated to develop various types of mesoporous materials with variable porous structure and functionality (87,88).

The attractive features of these materials include their stability, well-defined surface properties, high pore volume, narrow pore diameter distribution and high surface area. These features allow the entrapment of drugs, proteins and other biogenic molecules and release them in a more predictable and reproducible pattern (87-90). Moreover, the size of their pores can be tailored from 1.5 to several tens of nanometres allowing their matrices to encapsulate a range of molecules (87). A variety of mesoporous materials have been utilised as substrates for drug delivery; such as mesoporous silica-based materials (91-97), carbon (98,99), zirconia (100), alumina (101,102), titanium oxide (103) and composites (104,105). Ordered mesoporous silica-based materials have drawn great research focus in the last decade because of their evolving applications in drug delivery and various other biomedical applications (97,106,107). They are made of SiO_4 tetrahedra and exhibit ordered arrangements of pores (channels and voids) with different geometries. The pore size and geometry of these materials

can be tuned using several synthetic techniques (108). In 1992, family of silicate and alumina silicate ordered mesoporous materials called M41S was synthesised using liquid crystal templating (109,110). This family includes different members with different geometries. For example, MCM 41 (Mobil Composition of Matter 41) has arrays of two-dimensional cylinderical pores (2-5 nm) in a hexagonal arrangement, MCM-48 exhibits cubic three-dimensional structure with unique bi-continuous channels (2-5 nm) and MCM-50 has a laminar structure (89,111). In 1998, Zhao and co-workers synthesised ordered mesoporous silica (MS) (20−300 Å) using non-ionic triblock copolymers. This type of mesoporous material is called SBA (Santa Barbara Amorphous) and the most representative members of this family are hexagonally ordered MS (SBA-15) and cubic MS (SBA-16) (112). SBA-15 and SBA-16 have thicker walls and larger pore sizes compared to MCM-X type silica's (113). MCM-41 and SBA-15 are presumably the most studied ordered MS materials (97). Other types of MS have been synthesised such as MSU (Michigan State University) (114), TUD (Technische Universiteit Delft) (115) and FSM (Folded-Sheet Mesoporous Material) (116) and MPS (synthesized mesoporous silica) (117) by using various synthetic techniques.

Much work has been carried out applying synthetic mesoporous silica-based materials as controlled (90,118), targeted (106,107) and responsive (119) drug delivery systems. This is owing to their high thermal and chemical stability, biocompatibility, large surface areas and good compatibilities with other materials (89). In addition, these systems have the advantage of improving the utilisation of poorly soluble drugs. This is related to the interactions between the organic functional groups of the drug with germinal and single silanol groups available in the pore walls of mesoporous materials (120). Both small and large drug molecules have been encapsulated within mesoporous materials *via* solvent impregnation (89). The mechanism of drug release from such matrices is largely diffusion controlled and depends on many parameters such as chemical composition of their surface, pore size, pore connectivity, drug loading method, drug physicochemical properties and hydrophilicity of the platform (91,97,121).

The release kinetics of drug from their matrices can be controlled by modifying the pore size (118), pore geometry (122), drug loading method (123) and surface functionalisation (90). Vallet-Regi *et al,* developed two types of MCM-41's with different pore sizes using ibuprofen (model drug) with drug loading weight percent ratio of 30% (drug/MCM-41). Ibuprofen release (under static conditions) exhibited varying release profiles depending on the method of ibuprofen charging and not the pore size (123). Another work conducted by the

same group demonstrated release profiles of ibuprofen (under stirring conditions) were highly influenced by the pore size of MCM 41. The release rate of ibuprofen decreased as the pore size was reduced. Thus controlled drug delivery can be modulated by careful selection of mesoporous material pore size (118).

MS pores can be tailored to various geometries and sizes. Pore size has a significant effect on drug loading and release rate. There are several architectures of mesoporous materials (such as those possessed by MCM-41, MCM-48 and SBA-15) that have an influence on the diffusion rate and the route of drug loading into the material. Mesoporous materials with short two-dimensional hexagonal pore can also be characterised by direct diffusion of loaded drug into the release medium. While in three-dimensional cubic pore channels the loaded drug will require more time for the same quantity to diffuse due to longer non-linear pore channels (124). The release kinetics of drug molecules from silica matrix can be modified by functionalising its surface (silica) with different chemical moieties (89,125). For example, SBA-15 silica functionalised with amine groups was investigated as controlled drug delivery matrices for ibuprofen and bovine serum albumin (BSA, as model drugs). The time to functionalise the SBA-15 (post-synthesis or during one-pot synthesis, detailed later) was found to affect the adsorption capacity and release behaviour of both drugs. The release profiles of ibuprofen and BSA from SBA-15 were more effectively controlled by functionalising SBA-15 *via* post-synthesis (using ibuprofen) and using one-pot synthesis (for BSA). In addition, release profiles were highly dependent on different surface properties of SBA-15 materials (90).

MS have been extensively utilised as MSN (107), MS-microspheres (126), MS-fibres (127) and MS-beads (128) or simply by inclusion/adsorption of therapeutic drug in the silica matrix (120). These drug delivery systems have shown promise as useful candidates for oral, topical or injectable drug carrier systems.

For oral drug delivery, ordered silica-based mesoporous materials (e.g. MCM-41 and SBA-15) have been used to design fast onset therapeutic effect formulations (120), to increase the dissolution rate of poorly soluble drugs (129) and to enhance drug bioavailability (97). The dissolution improvement associated with the utilisation of MS can be established by changing the solid state property of the entrapped drug from the crystalline to amorphous form. This in turn increases drug absorption from the intestine and consequently results in enhanced bioavailability (122). For instance, the inclusion of the hydrophobic drug ‘Itraconazole’ into

ordered MS accelerated its release and significantly enhanced its systemic bioavailability (97,130). The oral delivery of ibuprofen loaded into MS materials (SBA-15, MCM-41, and TUD-1) has shown to reduce the dependency of drug dissolution profile on the pH of the *in vitro* assessment medium. Thus at acidic pH, ibuprofen release demonstrated a significant improvement when using mesoporous silica, which in turn enhanced the drugs bioavailability (122). Furthermore, MSN has been developed as an oral drug delivery system, where the oral absorption of telmisartan was improved significantly *via* greater permeability and a reduction in drug efflux (131).

With regards to topical delivery, silica nanoparticles are widely utilised for cosmetics and dermal therapies such as antioxidants, UV ray filters and antifungals (132). Flavonoids (e.g. quercetin (133) and rutin (134)) are used in topical cosmetic products to offer protective effects against photo-degradation because of their antioxidant and radical scavenging properties. However, their use is limited due to their low physicochemical stability (132). Encapsulation of quercetin in octyl-functionalised MCM-41 has also shown to improve its stability and performance without undermining its antioxidant properties (133). In another study, rutin (the glycoside of quercetin) was loaded into aminopropyl-functionalised MCM-41 (NH_2-MCM-41) maintaining the chemicals antioxidant property whilst also increasing the metal-chelating activity (134). Trolox is another antioxidant that has been loaded into MCM-41 clearly demonstrating improvements to photostability, while maintaining its radical scavenging property; which was demonstrated through slow diffusion from MCM-41 pores (135). In addition, MS has been used to entrap UV ray filters (e.g. benzophenone-3 (136), octal methoxycinnamate (137)). It was found that encapsulation of octal methoxycinnamate in the MS matrix (MCX-MS) was ~65 wt. % of MCX-MS and increased its SPF value by 57% (137).

A topical powder of econazole nitrate (an antifungal agent loaded into MCM-41) also demonstrated enhanced drug dissolution rate with high antifungal activity. In addition, the adsorption capacity of MCM-41 further assisted in the treatment of fungal infections by reducing moisture availability (found between folds in skin) which is usually ideal for fungal growth (138).

With respect to intravenous drug delivery, MSNs have been explored for the delivery of anticancer drugs (12,119,139) and genes (140). Numerous anticancer drugs have low aqueous solubility and therefore cannot be administered intravenously thus MSNs have been deployed

as carrier systems to increase their solubility (12). Moreover, MSNs are able to increase the accumulation of anticancer drugs at the tumor site, thus improving their efficiency (139). MSN's can be used intravenously for intracellular delivery of drug, especially where the entrapped drug is inside pores (not on the surface) and is released once in intracellular compartments (106). Inflammed tissue and tumors are more acidic than blood and normal tissue, and pH responsive drug delivery systems based on MSN have been developed for site targeted controlled release (124,141,142).

3.3 Synthesis of mesoporous silica

The basic synthesis of MS particles involves the addition of silica into a surfactant template solution which induces a reaction between the incorporated materials. The second step involves aging, filtration and calcination to obtain MS particles (143). Amongst these, the most employed templating technique for ordered MS synthesis is *via* liquid crystal mechanism (110,112,114,144). Here, liquid crystal structures (within the selected surfactant micellar solution as ordered arrays with different geometries i.e. cubic, hexagonal, or lamellar) serve as organic templates for the formation of silica mesoporous materials. The inorganic silicate precursor in the reaction mixture condenses around these arrays and forms silica walls reflecting their geometry. This is followed by removal of the templete *via* calcination, leaving the materials with a well-ordered mesoporous structure (110,114).

In this regard, the role of template used in the preparation of MS (and applied temperature) is crucial as they are directly linked to MS pore size, where the temperature has a positive correlation with pore capacity. Amphiphilic molecules are used for the synthesis of MSNs and they serve as a template to dictate the internal shape. In general, different types of templates are used in the synthesis of mesoporous materials such as ionic surfactant (e.g. quaternary ammonium surfactants (92,110)), non-ionic block copolymers (e.g. Pluronic (112)) and organic non-surfactant template (e.g. triethanolamine (115)). (ADDED)

The calcination step in MS synthesis plays a critical role in determining drug delivery potential and biocompatibility because surfactant elimination is known to impede the porous silica network. For instance, calcined silica has exhibited a greater opened silica network compared to non-calcined samples. In addition, non-calcined silica is known to show greater quantities of silanol groups compared to their calcined counterparts (145). **Table 1** shows selected synthesis methods (and geometrical impact) for silica

3.4 Biodegradation and elimination of mesoporous silica

Various biodegradability studies have indicated that functionalised and non-functionalised MS can be biodegraded in simulated body fluids and human cells (146-149). Degradation rate is significantly influenced by the surface area and initial concentration of mesoporous silica. Functionalisation of MS also influences the rate of degradation, for instance; functionalisation of MS with phenyl groups increased the degradation rate while functionalisation of MS with PEG resulted in slower kinetics (147).

Hollow MSNs (HMSNs), a specific type of MS particle system, was shown to degrade inside human cells. *Zhai et al*, for the first time investigated the ability of HMSNs to degrade inside human umbilical vein endothelial cells. It was found that HMSNs degrade in the cytoplasm and lysosomes through two steps. The first degradation step occurs in both the cytoplasm and lysosome. The second is restricted to the lysosome. The degradation rate of HMSNs in cells was found to be fast in the first two days followed by slower rates in the following 48 hours. Furthermore, by-products of degradation were excreted into the culture medium (149). Another study performed by *Chen et al* demonstrated Stöber MSN (uniform spherical colloidal silica particles; synthesised by hydrolysis and condensation of tetraethoxysilan), almost degrade completely in SBF and human embryo kidney cells. This indicates such materials are promising canddiates for biomedical (drug delivery) applications (150).

In relation to the elimination of MS particles, nearly 100% of injected silica nanoparticles were reported to be effectively removed post *in vivo* administration through hepatobiliary clearance, without inducing any hepatic toxicity (151). However, *in vivo* bio-distribution and urinary excretion studies of spherical MSNs found particles mainly distributed in the liver and spleen, with lower quantities also evident in the lung, kidney and heart. PEGylated MSNs were found to have a lower excretion in urine without causing any toxicity effect after one month of monitoring (152).

3.5 MS based materials in drug delivery

MS based materials have been developed successfully for potential to deliver a host of drug types (e.g. anticancer, anti-inflammatory and antibiotics). Also, they serve as promising excipients and carriers for emerging biomedical and therapeutic applications such as tissue engineering and gene delivery, while their potential in co-delivery has also been explored. **Table 2** shows selected drug delivery studies involving mesoporous inorganic materials.

Conventional chemotherapy has various drawbacks such as the inability of providing required drug concentrations at the tumor site, intolerable cytotoxicity and development of multi drug resistance. Moreover, ~40–60% of anticancer drugs have low bioavailability because of their poor solubility, high first pass metabolism, poor permeability through biological membranes and rapid clearance (106). Several research studies have been carried out in order to develop nano-carriers and tissue targeting systems that are able to overcome such medical barriers which retard the therapeutic effect of anticancer drugs (12,106,139,153,154). MS based materials are emerging as valuable carrier systems for the efficient treatment of cancer which is underpinned by multi-disciplinary research arising from complex materials, their physical properties and biological interactions (107). Studies have shown MS nano-carriers to enable suppressing effect cancerous tissue, whilst providing an effective dose, rapid excretion and reduced toxicity of loaded anticancer drug (139). The ability to control their pore size provides flexibility and tailored routes for drug encapsulation (153). Additionally, MSNs are capable of enhancing dissolution of poorly soluble anticancer drugs, thus increasing their bioavailability and efficiency (12,154). Silica based materials have been used for achieving intracellular targeted delivery of anticancer drugs which remain encapsulated within tunable pores; inhibiting premature release and degradation of drug in route to target tissues (106,139). They are promising for specific cell targeting as they can be covalently modified with targeting ligands (153). For instance, functionalisation of MSNs external surface with cancer specific ligands (e.g. antibodies and folic acid) allows selective targeting of nanoparticles to cancerous cells. These ligands can selectively bind to receptors that are extensively expressed on effected cell surface thus enhancing cellular uptake of anticancer drug (107,139). For example, folic acid was used as a ligand to target folate receptors which are overexpressed in various cancers (e.g. lung, colorectal, endometrial, breast, ovarian and renal cell carcinoma). Thus using folic acid as a targeting ligand enhances the uptake of anticancer drug within these cell types (107,155) and MS based materials have already been used successfully to encapsulate doxorubicin (153), camptothecin (12), paclitaxel (154) and methotrexate (155). Also several attempts have been made to overcome multi-drug resistance displayed by cancerous cells and to enhance chemotherapeutic efficiency *via* co-delivery of siRNA with anticancer actives (156-158).

MS materials have been effectively developed as carriers for several anti-inflammatory drugs (e.g. ibuprofen (90,118,122,123), piroxicam (120), sulfasalazine (141) and naproxen (159)). MSs were used to enhance the dissolution properties of anti-inflammatory drugs (120,122), to provide controlled release (118,123) and to target their release at the preferred site of action

(141). For instance, the entrapment of piroxicam (a poor water soluble drug) (~%14) into MCM-41 mesoporous silicate (characterised by a large surface area and the presence of pores with diameters larger than the piroxicam molecular size. was shown to enhance piroxicam's dissolution rate considerably and attained a rapid analgesic onset that was comparable to the analgesic effect of the marketed product Brexin® (120). Also, the use of MS as a carrier for ibuprofen was found to improve the drugs dissolution rate at low pH conditions (122). Controlling the delivery rate of ibuprofen entrapped in silica matrices was also investigated by functionalising the pore wall (90,96) and modifying the pore size (118). A slow release formulation of ibuprofen was obtained by loading ibuprofen into functionalised micron-sized MCM-41 spheres, which demonstrated a unique sustained release rate compared to irregularly shaped drug carriers (96).

A pH targeted, responsive system for the delivery of sulfasalazine (anti-inflammatory prodrug) to colonic tissues was designed by functionalising MSNs with trimethylammonium. This novel system achieved minimal sulfasalazine release under acidic pH (stomach) and maximum release rate at neutral pH (colon). Therefore, the formulation offered targeted delivery of the prodrug to the colon, protecting it from degradation in the stomach and reducing its side effects (141).

Several antibacterial agents have also been loaded into mesoporous silica, such as levofloxacin (145), vancomycin (160), gentamicin (95), amoxicillin (161) and erythromycin (162). MS has been used as a matrix for the incorporation of levofloxacin by both impregnation and surfactant-assisted drug loading methods. The antibacterial effect of this formulation was tested against *Escherichia coli*. Both drug loading methods resulted in matrices exhibiting similar levofloxacin release profiles (*in vitro*); displaying an initial fast release within the first ten hours followed by sustained release up to the end of the test period (350 hours). The lasting antibacterial activity of both systems indicated the suitability for local administration for the treatment of bone infections and osteomyelitis (145). Vancomycin was also loaded into sol-gel silica microspheres to design a sustained release formulation for the treatment of osteomyelitis. Optimization of the synthetic parameters achieved varied controlled release kinetics of vancomycin enabling selection of the desired therapeutic profile (160). Hexagonally ordered mesoporous SBA-15 were used to incorporate amoxicillin (161) and gentamicin (95) with controlled delivery properties. Two types of 'SBA-15' were used for each drug: calcined powder and disk conformation. *In vitro* controlled release of amoxicillin was achieved by using SBA-15 as disks while the release

rate was faster when deploying SBA-15 calcined powder platform. *In vitro* controlled release of amoxicillin from SBA-15 (disk) system was comparable to traditional administration forms of amoxicillin formulations (such as suspension, tablets and capsules) (161). With regard to gentamicin, no significant difference between disk and calcined powder was detected for *in vitro* release study. Release profiles of both forms showed a high initial burst release (~60%) followed by a sustained release phase. When compared with traditional gentamicin dosage forms (e.g. injection, cream, suspension and ointment), the dissolution of SBA-15-gentamicin system was instantaneous (95). Amoxicillin remains the choice of treatment for infections such as bronchitis, pneumonia, and those related to the ear, nose, skin, and urinary tract. Gentamicin is used to treat infections caused by staphylococcus or resistant staphylococcus. Controlled delivery of amoxicillin and gentamicin in SBA-15 material exhibited advantages when compared to conventional dosage forms where antibiotic dissolution is fast and immediate. These systems help by reducing the frequency of administration although the desired dose of antibiotic is achieved in controlled fashion (95,161). Ordered cubic three dimensional MS materials have been employed as carriers for the delivery of erythromycin. The release of erythromycin was controlled by modifying the pore size and functionalising the surface of mesoporous silica. A slow release was obtained as the pore size of the silica reduced. Also, functionalisation of silica surface decreased the release rate by a factor of ~six (162).

MS materials have also been applied in tissue engineering research as they are promising bioactive materials (163). The bioactivity of silica materials, when in contact with physiological fluids, is attributed to the presence of silanol groups on their walls. Here, silanol groups are capable of forming interfacial bonds with tissues through carbonated apatite formation (163,164). Both pores (165) and silanol groups (166) act as nucleation sites for apatite layer formation. The silanol group concentration at the surface has a crucial effect on the bioactivity of materials. Moreover, the presence of mesoporous larger than 2 nm in the silica matrix not only enhances the formation of the carbonated apatite layer; but also increases tissue oxygenation (163). Also, such pores act as nutrient depots for cells by adsorbing growth factors and biomolecules thus promoting cell proliferation (167). Investigations into the bioactivity of MCM-41, MCM-48 and SBA-15 have elucidated that SBA-15 and MCM-48 are bioactive materials while MCM-41 is not. This can be explained due to the higher surface silanol concentration exhibited by MCM-48 and SBA-15 compared

to MCM-41 (163). Although, MCM-41 does not exhibit bioactivity, surface modification of MCM-41 is a route to induce bioactive behaviour (165).

Silica based mesoporous materials have been investigated as scaffolds in reconstruction of hard tissue such as tooth and bone due to their bioactivity, biocompatibility, structure and textural properties (166). Furthermore, combining bioactivity and controlled drug release properties can be achieved by entrapping therapeutic drugs within meso-pores of silica based materials. This promising combination may result in a significant enhancement on their performance as biological scaffolds (163,168). MS based scaffolds used for bone tissue engineering have been prepared as different types of morphologies such as spheres (169), nanofibres (169) and nanoparticles (170).

Gene delivery is rapidly emerging as an important treatment for genetically induced diseases; such as cancer, sickle-cell anemia and hepatitis C (171,172). Gene carriers must be on the nano-scale to function efficiently for gene transfection because large particles are problematic for uptake by mammalian cells (173). Various nano-scaled carriers such as polymers, lipids and inorganic nanoparticles have been used extensively to improve the cellular delivery of large range of nucleic acid agents (171). Among these carriers, MSNs have shown great potential for gene delivery (171,174) largely due to their small size permitting endocytosis into cells. They allow stable delivery of DNA directly in to the cytoplasm and also the nucleus for transcription (140). Furthermore, MSNs also protect encapsulated genes from enzymatic action such as degradation (171,175). Surface modification of MSNs is an additional aspect being explored in the formulation of porous drug delivery systems. The use of various moieties to serve functions outside of targeting (e.g. optimization of nucleic acid adsorption and release characteristics) has also been explored (174,175). For example, functionalisation of MSNs with histidine has demonstrated enhanced gene transfection efficiency (176) and when using degradable poly (2-dimethylaminoethyl acrylate) controlled release of siRNA in to cells is achievable (174). However, the loading of large bimolecular genes into meso-pores of MSN is not straightforward, and many studies have shown DNA adsorption on the outer surface rather than encapsulation within pores (175,177). Accordingly, the use of larger meso-pore diameters to increase gene entrapment within MSNs has been demonstrated (171,172,177).

3.6 Drug loading methods for mesoporous materials

Various approaches have been used to load drugs into mesoporous matrices such as physical mixing, solvent based techniques, melt methods, supercritical fluids, microwave irradiation and co-spray drying. Physical mixing involves blending suitable amounts of drug and mesoporous materials until a uniform dispersion is obtained (138,178). The most employed approaches are solvent based techniques (solvent impregnation) which involves dissolving of drug in organic solvent followed by impregnation of the mesoporous material in a concentrated drug solution, followed by agitation of the mixture for several hours and solvent evaporation (90,120,130). The 'incipient wetness procedure' is an alternative solvent based technique which is achieved by several impregnation steps of the carrier in drug solution. Successive impregnations improve drug encapsulation significantly through complete pore filling (179). The melt technique is a simple and solvent-free process which is performed by melting the drug and the carrier together yielding a physical mixture at high temperatures (117,138), although drug stability and thermal properties are critical which could limit process applicability (180).

The aforementioned 'manual' methods are only suitable where small quantities of encapsulated materials are required and are problematic on the industrial scales (180). In addition these conventional methods have intrinsic disadvantages such as the use of organic solvents that will require a subsequent solvent elimination process; impacting on time and cost factors (129). Therefore, supplementary approaches have been proposed to load drug into mesoporous carriers without affecting active stability such as supercritical fluids method (129,181), co-spray drying (182,183) and microwave irradiation (184). The supercritical fluid method (e.g. supercritical carbon dioxide) has yielded mesoporous materials with improved encapsulation properties. The supercritical fluid mediums liquid like density allows solubilisation of large quantities of drug and in tandem gas like diffusivity facilitates molecular access to the mesoporous matrix (129,181). Moreover, this process does not require solvent removal steps commonly associated with process involving organic solvents. Supercritical processing conditions, such as the pressure, can greatly affect drug loading into mesoporous silica, the drug solid state and resulting release profile. For instance, increasing the pressure can reduce drug loading efficiency. This process is a promising approach for loading poorly aqueous soluble drugs into silica mesoporous materials to improve their dissolution rate and oral bioavailability (129).

Another loading technique is co-spray drying of the drug with the mesoporous carrier. This approach involves dispersing the carrier in a solution of the drug in a volatile solvent followed by spray drying of the dispersion. Compared to solvent based techniques, this method produces more stable amorphous state of the drug with considerably enhanced dissolution rate and oral bioavailability (182,183).

Microwave based methods have been explored to load drugs into mesoporous silica, which involves microwave irradiation of drug and MS mixture in a controlled temperature environment. This method avoids undesirable drug degradation as it ensures an ideal constant temperature throughout the process not exceeding critical values. In this method the drug melts inside silica pores in the amorphous form and resulting products have shown improved release properties (184).

Surfactant assisted drug loading method (also termed one-pot synthesis) is a more recent approach when using mesoporous materials. In this method, drug is loaded during the synthesis of the mesoporous material, thus the drug is entrapped inside the surfactant micelle structure. This approach exploits the presence of the surfactant template as an adjuvant for loading the drug to increase its loading efficiency, enhance its release kinetic pattern and improve its stability. For example, loading levofloxacin using the surfactant assisted method increased the loading efficiency to 100% (145).

3.7 Toxicity of mesoporous silica

The current data on MSN toxicity is limited and controversial (185). However, MSNs are biocompatible materials at concentrations suitable for some pharmaceutical applications (185,186). The free surface silanol group in silica materials can interact and damage biomolecules such as cellular membrane proteins and lipids (187), and certain haemolytic activity has also been reported (188). However, most silanol groups in MSNs (unlike amorphous silica nanoparticles) are located in the internal surface of the particles and only a minor percentage of silanol groups are accessible to the bulk solution resulting in improved biocompatibility (188). Therefore, surface functionalisation of MS nanoparticles (MSNs) has the potential to decreases surface reactivity and enhancing their biocompatibility (187).

MSNs exhibit higher biocompatibility than nonporous amorphous silica particles towards red blood cells. It was found that the intravenous administration of MSNs at concentrations up to 100 μg/ml did not induce any haemolytic activity towards red blood cells (188).

With regards to tissue toxicity, intravenous administration of MSN into mice revealed no detectable histopathological abnormalities in spleen, liver, heart, kidney and lung. These findings suggest that MSNs do not cause tissue inflammation or toxicity. This could be attributed to stable physicochemical properties, biocompatibility of such particles and their degradation products (152). Moreover, Malvindi *et al*, conducted an *in vitro* cytotoxicity study using three different sizes of silica nanoparticles (25, 60 and 115 nm) and two surface charges (negative and positive) on five cell lines. The results showed no cytotoxic indications when using particle concentrations of up to 2.5 nM (on all cell lines). The cellular uptake of particles was mediated *via* endocytic process that is highly dependent on silica particle size and not the particle charge (189). Other studies have found that cytotoxicity of silica particles is highly dependent on particle size, concentration (148,190) and the presence of residual surfactant (148). For example, nano-sized MS particles demonstrated low cytotoxicity for concentrations up to 25 μg/ml whereas micron-sized particles showed slight cytotoxicity over a broad MS concentration up to 480 μg/ml. Subsequently, nano-sized particles are endocytosed more readily than micro-sized systems (148). However, a cytotoxicity study on MCM-41 and its functionalized analogs toward human neuroblastoma cells found these materials to be cytotoxic between concentrations of 40 to 800 μg/ml (191). Another research work performed on the effect of MCM-41 and SBA-15 nanoparticles on cellular respiration showed SBA-15 inhibited respiration rate, while MCM-41 had no detectable effect. The inhibition induced by SBA-15 nanoparticles was time and concentration dependant (192). Table 3 summarizes different toxicity studies performed on mesoporous silica particles.

3.8 Future perspectives

There are many physiological obstacles for the nano carriers preventing them from reaching to selective target sites, such as circulating from the blood to the tumor extracellular matrix, attaching to tumor-cell membrane for endocytosis, releasing the drug inside the cells and targeting the subcellular sites. Therefore, efforts have been devoted to design multifunctional nano carriers aims to overcome these physiological obstacles (193). Among different nano-carriers, silica based nano-carriers are very attractive delivering the drug into selective sites (194), intracellular co-delivery of the drug and other therapeutic molecules such as genes (174) chemosensitisers (195) and peptides (193).

Controlled release of the drug from MS materials can be achieved by adjusting their pore size, morphology and surface characteristics. However, these approaches results in ordinary

release profiles which cannot achieve the desired clinical outcomes (196). Therefore, it is essential to design responsive controlled delivery systems that can achieve a site targeted release that is triggered by intracellular or external stimuli (175). MSNs system (e.g. MSN and nanotubes) are interesting candidates capable of achieving stimuli responsive release (194,196,197). Responsive drug release from MS can be achieved by two main methods: covalent bonding of the drug to the silica via cleavable bonds or functionalisation of the outer surface of the MSN using removable coating or capping (gatekeepers) (175). In the later approach, pores loaded with the drug can be blocked by different gatekeepers which can prevent the carriers from releasing of the drug prematurely. The release of the encapsulated drug is triggered by certain stimuli that are capable of removing theses gatekeepers (194,198) and are classified into physical stimuli (e.g. temperature, light, electricity and magnetism) and chemical stimuli (enzymes, ionic strength and redox potential). However, the design of bio-responsive systems that release drugs upon exposure to intracellular stimuli such as redox potential, enzymes and acidic pH are more valuable in biomedical applications (194,197). For instance, the pH responsive release system is an effective method for controlling drug release into selective sites (198). This is because of the pathological tissues which exhibit different pH from normal tissues, for example cancerous and inflammatory tissues have more acidic pH than normal tissues. For example, tannin functionalised MSNs were found to be potential carriers to design pH responsive drug delivery system for cancer and stomach treatment. Using tannin as a gatekeeper resulted in an efficient entrapment of the model drug inside the mesopores of MSN in the pH 7.4. By lowering the pH, tannin was cleaved rapidly with increasing the release of model drugs (142). Another interesting bio-responsive system is enzyme triggered strategy in which the enzymatic hydrolysis results in opening the coated mesopores and hence releasing the entrapped drug. An example for this system is demonstrated by lactose functionalised MS wherein a lactose derivative grafted on the surface of MS act as the gatekeeper (197).

Multifunctional MSNs were utilised for intracellular co-delivery of therapeutic molecules with a great efficacy for enhancing the anticancer cytotoxicity and minimizing the multidrug resistance (156,157,193,195). Multidrug resistance (MDR) is the resistance of tumor cells to the chemotherapy where cancerous cells become resistant to different types of drugs simultaneously. MDR causes the most challenges for scientists to develop efficient chemotherapeutic treatment for the tumors (195). MDR is multifactorial and can be classified into two main mechanisms; pump resistance (caused by certain membrane-bound proteins

that form efflux pumps) and non-pump resistance (caused by activation of cellular anti-apoptotic proteins). Thus it is important to inhibit these mechanisms simultaneously via targeting all of the intracellular molecular targets (156). A novel strategy to overcome the MDR can be achieved by co-delivery of the drug with nucleic acids (e.g. siRNA), wherein siRNA is capable of silencing genes responsible for MDR. MSNs have been reported to be successful systems for the delivery of anticancer drugs simultaneously with siRNA (156,157). The use of MSNs for simultaneous delivery of doxorubicin with siRNA into multidrug resistant ovarian cancerous cells enhanced the anticancer efficacy of doxorubicin. As this co-delivery system significantly inhibited the non-pump resistance mechanism, decreased the extracellular premature release of doxorubicin, delivered doxorubicin intracellularly into the perinuclear region and exerted synergistic cytotoxic effects to the cancerous cells. Functionalisation of MSNs with targeting moieties selective to cancerous cells will further enhance the anticancer efficiency of the system and decrease it's adverse effects on normal cells (156). The co-delivery of the chemosenstiser with anticancer drug (paclitaxel) is able to supress the MDR of breast cancer cells and guarantee pH responsive release behaviour thus decreased adverse effects and toxicities to normal cells (195).

3.9 Concluding Remarks

Multifunctional MS based nano-carriers which possess unique features such as tunable pore size, high surface area, highly accessible free silanol groups, bioactivity and responsive release properties have significant potential in medical applications for enhancing clinical outcomes for a variety of drug delivery therapies. Though unconventional, such materials are a useful route to tailor drug delivery systems where polymeric materials may become problematic. The multi-variate design of drug delivery systems (associated with inorganic carriers), from synthesis to loading, provides a bottom up approach for emerging and existing APIs.

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Tables and Figures

Tables

Figures

Table 1. Selected synthesis methods for silica particles and resulting impact on pore geometry.

Type of mesoporous silica	Method of synthesis	Pore size	geometry	comments	Ref.
MCM-41	Liquid crystal templating synthesis	2-5 nm	Ordered two dimensional hexagonal arrangement of pores with uni-directional channel	Direct diffusion of loaded drug into the release medium is characteristic of such systems	(89,111,124)
MCM-48		2-5 nm	Cubic three-dimensional with bi-continuous channels	Loaded drug requires more time for the same quantity to diffuse due to longer non-linear pore channels (sustained release)	(89,111,124)
SBA-15	Non-ionic triblock copolymer synthesis	5–10 nm	Ordered two-dimensional hexagonal structure, with uni-directional channel	Thicker walls and larger pore sizes compared to MCM-X type silica	(89,112)
SBA-16		Min 1-6 nm Max 4-9 nm	Cage-like cubic structure	Promising material in separation and catalysis due to its cage structure and large cell parameter	(89,112)
MSU	Non-ionic surfactant templating	2-5.8 nm	Disordered hexagonal type channel structure	Non-ionic surfactant templating offers a general method for mesoporous metal oxide synthesis (e.g. mesostructured pure alumina)	(114)
TUD-1	Non-surfactant templating method	Bimodal pore distribution: 3.5–5.0 and 15–25 nm	Three dimensional foam-like mesoporous structure with bimodal mesopores	Unique bimodal pore distribution, offers wide possibilities for chemical applications such as imparting functionality.	(115)

Table 2. A summary of key selected drug delivery studies involving porous inorganic materials

Drug name	Drug type	Delivery route	Type of Mesoporous carrier	Pore size	Method of loading	Loading content/ Loading efficiency	Results	Reference
ibuprofen	Anti-inflammatory	Oral	MCM-41	3.6-2.5 nm	Solvent impregnation.	11-34 %	The delivery rate of ibuprofen in stimulated body fluid solution is influenced by MCM-41 pore size. Smaller pores lead to reduced release rates.	(118)
Ibuprofen and BSA	Anti-inflammatory and model protein	Oral	Amine-functionalised SBA-15	78-86 Å	Solvent impregnation.	14.6-37.2% and 1.1-34.5 %, respectively	SBA-15 was functionalised with amine groups using two methods (post-synthesis and one-pot synthesis). The release profiles of ibuprofen and bovine serum albumin from SBA-15 were more effectively controlled. The release profiles were highly dependent on SBA-15 material surface properties.	(90)
Ibuprofen	Anti-inflammatory	Oral	3-aminopropyltriethoxysilane functionalised MCM-41	2.1-3.7nm	Solvent impregnation.	25-36 %	A slow release formulation of ibuprofen was obtained by loading the drug into functionalised micro-sized MCM-41 spheres. In which micro-sized spheres showed a unique slower drug release rate than irregularly shaped carriers	(96)
Ibuprofen	Anti-inflammatory	Oral	MCM-41	3 - 3.6 nm	Solvent impregnation. and Incipient witness(IP)	184 mg/g and 500 mg/g, respectively	Drug loading within MCM-41 was influenced by the method used. Both loading methods improved drug dissolution, but more loading efficiency was observed by using incipient wetness method	(179)
Ibuprofen	Anti-inflammatory	Oral	SBA-15	6 nm	Co-spray drying	75 %	Co-spray drying of SBA-15 with ibuprofen improved drug solubility for rapid	(183)

							dissolution and exhibited excellent physical stability, even under harsh experimental conditions	
Piroxicam	Anti-inflammatory	Oral	MCM-41	3.21 nm	Solvent impregnation.	14 ± 2 %	Entrapment of piroxicam into MCM-41 mesoporous silicate enhanced the drugs dissolution rate considerably and attained a rapid analgesic onset that was comparable to the marketed rapid product Brexin®	(120)
sulfasalazine	Anti-inflammatory prodrug	Oral	Trimethylammonium functionalised MCM-41- type MSN	2.7 nm	Solvent impregnation.	4.7 - 103.1 µmol \g	Novel system achieved minimal sulfasalazine release under acidic pH (stomach) and maximum release rate at neutral pH (colon). Therefore, the formulation offered targeted delivery of prodrug to the colon, protecting it from degradation in the stomach and reducing side effects	(141)
Camptothecin	Anticancer	Intravenous	MCM-41-type fluorescent MSN	2 nm	Solvent impregna-tion.	NA	Camptothecin was successfully loaded into MCM-41 MSN and delivered into human cancer cells to prompt apoptosis.	(12)
paclitaxel	Anticancer	Intravenous	MSN containing the fluorescence dye fluorescein isothiocyanate	2 nm	Solvent-impregnation	Not reported	MSN containing dye was taken up efficiently by human cancer cells	(154)
levofloxacin	Antibiotic	Local bone administration	Calcined and non calcined mesoporous silica	8.5 nm	Solvent impregena-tion. and one pot synthesis	4.3 and 100 %, , respectively	Both drug loading methods resulted in matrices with similar levofloxacin release profiles (in vitro study) which displayed an initial rapid release within the first ten hours followed by sustained release up to the end of	(145)

							the test. Antibacterial activity of both systems was effective prolonged.	
Amoxicillin	Antibiotic	oral	SBA-15-powder and SBA-15 disk	8 nm for calcined samples	Solvent impregna-tion.	24 % wt	In vitro controlled release of amoxicillin was achieved using SBA-15 as discs while the release rate was faster using SBA-15 calcined powder. In vitro controlled release of amoxicillin from SBA-15 discs system was comparable to traditional administration forms of amoxicillin such as suspensions, tablets and capsules	(161)
Gentamicin	Antibiotic	Oral, intravenous and topical	SBA-15-powder and SBA-15 disk	5.5 nm	Solvent impregnation.	20 and 17 %, respectively	No significant difference between disc and calcined powder was detected in the in vitro release study. Release profiles of both forms showed a high initial burst release (~60%) followed by a sustained release period. When compared to traditional gentamicin dosage forms the dissolution of gentamincien:SBA-15 system was instantaneous	(95)
Erythromycin	Antibiotic	Oral	MCM-48 And large pore LP- Ia3d	3.6 and 5.7 nm, respectively	Solvent impregnation.	28 and 41 %, respectively	The release of erythromycin was controlled effectively by modifying the pore size and functionalising the surface of MS. Sustained release was obtained by reducing silica pore size. Functionalisation of silica surface reduced release rate by a factor of ~6.	(162)
Econazole	Antifungal	Topical	MCM-41 Powder formulation	3.25 nm	melt technique	25 %	Econazole-loaded MCM-41 showed enhanced drug dissolution rate with	(138)

							high antifungal activity. Moisture absorbance capacity of MCM-41 increased, which indirectly assisted in anti-fungal action (reducing bacterial growth).	
Fenofibrate	Lipid Lowering Drug	Oral	MPS	Not reported	Solvent impregnation and Melt method	20-33 % and 20-66 %, respectively	Fenofibrate was loaded into MPS in the amorphous state and drug loading was dependent pore volume. Overloading of drug resulted in drug re-crystallisation.	(117)
Fenofibrate	Lipid Lowering Drug	Oral	SBA-15	5–8 nm	supercritical carbon dioxide method	12.62-25.94 wt. %	Drug loading increased as with drug:silica ratio	(129)
Fenofibrate	Lipid Lowering Drug	Oral	MCM-41 And SBA-15	2.5nm And 6.5nm	Solvent impergenation and co-spray drying	30 and 50%, respectively	Co-spray drying was more effective in enhancing dissolution rate and bioavailability of the drug when compared to solvent impregnation.	(182)
Fenofibrate	Lipid Lowering Drug	Oral	core shell, core shell rehydrox, SBA-15 and silica gel	Not reported	microwave irradiation	50, 25, 16 %	Drug was melted inside silica pores in the amorphous form and showed significant improvements in release profiles	(184)

Table 3. A summary of selected toxicity studies performed on mesoporous silica particles.

Silica type	Concentration\ Dose	Particle size	Toxicity	comments	Ref.
MCM-41-type MSN	up to 100 µg/ml	100 and 300nm	No significant haemolytic activity was detected at a concentration of 100 µg/ml	MSNs showed high biocompatibility at concentrations suitable for therapeutic applications	(188)
MSNs and PEG–MSNs	5 µl/g	80–360 nm	Both types did not cause tissue toxicity. No noticeable histopathological abnormalities in spleen, liver, heart, kidney and lung.	MSNs do not cause tissue inflammation or toxicity. This could be attributed to stable physicochemical properties, biocompatibility of such particles and their degradation products	(152)
MSN	50 mg/kg	110 nm	MSN did not cause any changes in liver, spleen, kidney and lung morphology following exposure through different routes (at 50 mg/kg).	Mesoporous silica are biocompatible when adminsterted by intravenous and oral methods.	(199)
Mesoporous Silica Nano and Microparticles	10–480 µg/ml	190–1220 nm	nano-sized MS particles demonstrated low cytotoxicity for concentrations up to 25 µg/ml, whereas micron-sized particles showed slight cytotoxicity over a broad MS concentration up to 480 µg/ml	The cytotoxicity of silica particles was dependant on particle size	(148)
MCM-41 and SBA-15	25–500 µg/ml	300–650 nm Hundreds of nanometres, respectively	SBA-15 supressed cellular respiration rate at 25–500 µg/mL, while MCM-41 had no detectable effect on respiration rate.	The cellular respiration inhibition of SBA-15 was concentration and time-dependent. The insignificant effect of MCM-41 is due to limited cellular uptake because of high surface area per unit mass	(192)
Functionalized and non-functionalized MCM-41	40 to 800 µg/ml	250 nm	MCM-41 and its functionalized analogues killed human cells under the test	The highest cytoxicity is caused by MS with the largest surface area. However surface area is not the only factor contributing towards cytotoxicity. Other factors such as size and shape may also have an impact	(191)

FIGURES

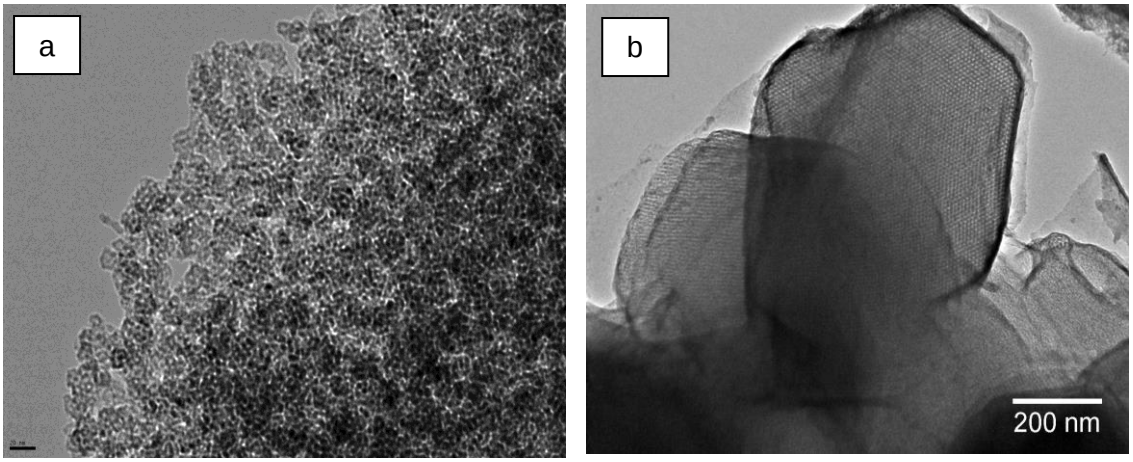

Figure 1: TEM images of (a) MCM-41 (110) and (b) CMK-3.

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