Silica particles.

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Mesoporous silica particles (MSP) have gained widespread popularity over recent years. Their advantages of uniform and tunable pore size, easy independent functionalization of the surface, internal and external pores and the gating mechanism of the pore opening make it a distinctive drug carrier. The unique feature of MSPs which makes them a widely exploited carrier for drug delivery is its high loading capacity due to the large pore volume and surface engineering properties both on the external and internal surface for better drug targeting. These versatile carriers can be used for loading a variety of cargos ranging from drugs to macromolecules such as proteins, DNA and RNA.

Mesoporous silica particles

In parallel with organic nanoparticles, such as PLGA-type microspheres, liposomes and lipid nanoparticles, inorganic particles have also been widely explored for their application in biomedicine. One such material is MSPs, where the pore diameter is between 1 and 50 nm together with a large pore volume (0.6–1 cm³ g⁻¹) and a high surface area (100–1,000 m² g⁻¹). Their size (0.05–250 µm), as well as their shape and surface can be custom-designed offering many different possibilities for the loading of anticancer drugs, proteins, DNA and RNA.

There are two main categories of MSNs typified by the following products,

1. MCM-41: Identified in 1990, MCM-41 is hexagonal with a pore diameter of 2.5–6 nm wherein cationic surfactants were used as templates. MCM-41 is one of the most widely explored materials for drug delivery.
2. SBA-15: Six years later, silica nanoparticles with much larger pores of 4.6–30 nm pores were produced at the University of California, Santa Barbara. SBA-15. also has a hexagonal array of pores but with thicker silica walls.

Almost 70% of new drug candidates exhibit low aqueous solubility, ultimately resulting in poor absorption. Nanotechnology is attracting increasing attention, to overcome this solubility obstacle and to improve oral bioavailability. It can be applied in two aspects: processing the drug itself into nano-sized particles or preparing drug-contained particles from various materials. It is feasible to incorporate targeting agents in the external surface of MSPs to direct them to the unhealthy tissues aimed at increasing specificity and therefore MSPs to direct them to the unhealthy tissues aimed at increasing specificity and therefore diminishing undesired side effects.

With excellent features including a huge surface area and ordered porous interior, MSPs can be envisaged as an ideal drug delivery carrier for improving the solubility of poorly water-soluble drugs and subsequently enhancing their oral bioavailability. When water-insoluble drug molecules are contained in mesoporous silica, the spatial confinement within the mesopores can reduce the crystallization of the amorphous drug. Moreover the huge surface area of mesoporous silica facilitates the wetting and dispersion of the stored drug, resulting in fast dissolution.

Release of MSPs’ API cargos can be triggered by activation of a variety of stimulus-responsive, targeted, molecular “gatekeepers”, both internal and external. Internal stimuli include redox potential, enzymes, and pH, while external stimuli include light, ultrasound, and magnetic fields. Temperature can be either internally or externally triggered.

Fig 1: Versatility of MSP as drug carrier constructs: (Wein et al 2013)

5 Karimi 2016, “Smart mesoporous silica nanoparticles for controlled-release drug delivery”, Nanotechnology Reviews Volume 5: Issue 2
Examples include,

> Although numerous reports demonstrate sophisticated drug delivery mechanisms in-vitro, the therapeutic benefit of these systems for in-vivo applications have been under continuous debate. Issues that remain to be resolved, before repeated translation into the clinic include biocompatibility, degradability, pharmacokinetics, blood circulation properties, immunogenicity, and clearance time in the body. Some recent studies have indicated that the encouraging cellular studies can be repeated in-vivo but much progress needs to be made before MSNs can fulfil their therapeutic potential.

### MSP manufacture

Because of the existence of different liquid crystal mesophases and morphologies in the surfactant assemblies, surfactant-templated mesoporous silicas can be tailored to give various mesostructures (e.g. disordered, wormhole-like, hexagonal, cubic, and lamellar), morphologies (e.g. spheres, hollow spheres, fibres, tubules, gyroids, helical fibres and crystals), and dimensions (nm to cm) by controlling the reaction conditions (such as reaction temperature, pH value, surfactants between surfactants and silica species) in order to prepare specific mesoporous silicas. Mesostructural surfactant–silica nanocomposites appear spontaneously to self-assemble.

Four main different types of precursors are used as a source of the silica in the production of MSPs:

1. Glycidoxy-silanes and -siloxanes are unaffected by pH but are affected by ionic concentration and are not suitable for long-term storage.
2. Orthosilicic acid, owing to its slow reaction rate, requiring long preparation times, is not used anymore.
3. Tetraethyl orthosilicate and tetramethoxysilane, owing to their poor water solubility and a requirement for organic solvents and high temperatures, have only received limited use.
4. Tetrakis (2-hydroxyethylorthosilicate) is water soluble, has good biocompatibility and can form gels at relatively low temperatures has been used in many studies.
5. Sodium Silicate can form gels at relatively low temperatures, its water soluble and can be combined with surfactants.

Reproducibility of the synthesis of MSPs at small scale is relatively easy, but at the larger and industrial scale is very difficult to control from batch to batch. In general, and for all nanomedicines, reproducibility is a complicated and expensive process that takes a very long to sort out. For these reasons, the clinical translation of MSPs, in which the therapeutic efficacy alone is not enough, has taken longer than initially desired by researchers in this area.

### The Micropore difference

Micropore Technologies provides aseptic membrane devices for the formation of silica microspheres from lab to full manufacturing scale. Micropore harnesses the well-established condensation polymerization method of silica production with its multi-award-winning membrane emulsification (ME) technology.

Loughborough University together with Micropore has utilized Micropore’s membrane emulsification (ME) technology to manufacture high quality MSPs through an improved, continuous, scalable sol-gel process.

ME offers a narrow size distribution (CV<35%) at tunable sizes between 15-250μm through its precision engineered technology. By regulating the surfactants, pH and silica source the internal structure of the silica particles can be modified.

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7 Karimi 2016, Ibid.
and both micro- and mesoporous (Fig.3) near-monodispersed spherical particles can be produced with a range of internal pores between 1 and 12nm and an average surface area between 300 and 750 m²g⁻¹ (Fig 4).²

Micropore’s value

1. The API can be combined with the sol prior to emulsification or loaded afterwards on porous microspheres.
2. Low shear/temperature during emulsification allows preservation of the drug.
3. “Compartmentalization” of sol gel droplets during emulsification prevents changes in the sol gel structures.
4. Short gelation dependant on the droplet size and initial sol.
5. Preservation of silanol bonds at the surface allowing functionalisation if required.

![Image](image.jpg)

We’re ready to help you with your inorganic microsphere formulations.

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