The magic particle silica: Past to present

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Abstract
The challenges in the field of chromatographic separation mainly fast and efficient separation for variety of samples has led to the changes in particle size, improvement in packing material design, development of synthetic method has provided the possibility of fabricating silica nanoparticle with different sizes in nanometer ranges. In present review, we have tried to show the journey of silica particle over the years and changes in the size, surface, internal pore size and packings. Their applications especially the mesoporous nanoparticles have also been mentioned.

Keywords: Silica, Amorphous, Crystalline, Cores shell, Hybrid, Monoliths.

Introduction
Silica: Silica is a hard, unreactive, colorless compound which occurs as a principle constituent of sandstone and is one of the most abundant compounds on earth. Silica gel, a highly porous, non-crystalline form of silica used to remove moisture from gases and liquids, to thicken liquids, to impart a dull surface to paints and synthetic films, and for other purposes.

History of Silica: Silica gel was in known as early as the 1640s as a scientific curiosity. In 1918 Professor Walter A. Patrick at Johns Hopkins University patented the synthetic route for producing silica gel. Its adsorptive properties were found in World War I for the adsorption of vapors and gases in gas mask canisters. In World War II, silica gel was indispensable in the war effort, used as a dehydrating agent to protect military and pharmaceuticals. Other uses includes, as a fluid cracking catalyst for the production of high octane gasoline, as a catalyst support for the manufacture of butadiene from ethanol. The evolution of silica particle is shown in Fig. 1. The general forms of silica are given in Table 1.

Table 1: General forms of silica

S. No	Types	Pore Diameter	Appearance	Uses
1.	Type A	2.5 nm	Clear pellets	Catalyst carriers, separators, variable-pressure adsorbent
2.	Type B	4.5-7.0 nm	Translucent white pellets	Liquid adsorbents, drier, perfume carriers catalyst
3.	Type C	>7.0 nm	Translucent, micro-pored structure	Raw material for preparation of silica gel cat litter, drier, adsorbent and catalyst carrier

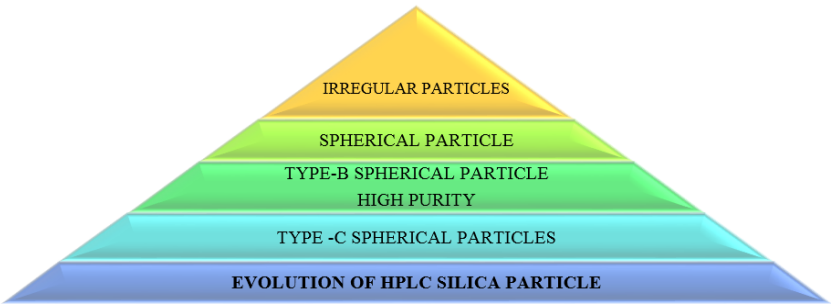


Fig. 1: Evolution of silica particles

Occurrence and Different forms: It occurs either as crystalline or non-crystalline (amorphous) form. Different forms of silica are shown in flow chart (Fig. 2).

Porosity of Various Silica Particles: Pores are the voids present in a certain structure and useful for a lot of industrial applications, ranging from catalysis over chromatography to even controlled drug release and micro-electronics.[1]

According to IUPAC, porous materials can be classified on the basis of pore diameter into one of these 4 classes[2]:

1. Micropores : < 2 nm
2. Mesopores : 2 nm < 50 nm
3. Macropores : 50 nm < 7500 nm
4. Megapores : > 7500 nm

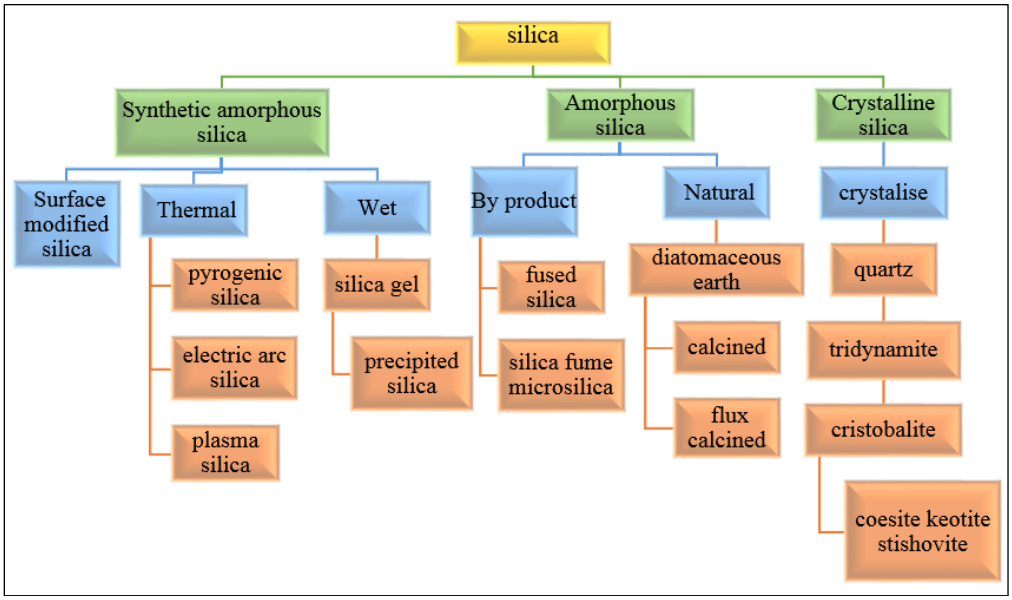


Fig. 2: Different forms of silica particles

Microporous materials inherently possess a higher surface area than mesoporous materials, which in turn has a larger surface area than macroporous materials.

Porosity brings instability, which is related to the more open structure towards destructive substances. To overcome these problems, the pore walls either are made thicker or they are functionalized. Thicker walls reduce the surface area per gram and functionalization reduces the pore diameter of the particle.[2]

Synthesis of Silica: Silica is mainly synthesized from an aqueous solution, with dissociated monomeric silicic acid, Si(OH), or from a vapor of a silicon compound such as silicon tetrachloride. Waterglass is a sodium salt of silicic acid that forms silicic acid upon acidification. Colloidal silica particles are formed when the concentration of Si(OH) exceeds about 2.10M and condensation to polysilicic acids occurs. The polymerization and the formation of silica can be represented as follows:

$[Si_{n\ O2n-nx/2}\ (OH)_{nx}\ ] + m\ Si(OH)_4 \rightarrow [Si_{n+m\ O2n-nx/2+2m(2-p)}\ (OH)_{nx+4(m-p)}\ ] + 2_{pm}\ H_2O$

Where:

n = number of silicon atoms in a polysilicic acid molecule or particle,

x = number of OH groups per silicon atom in the polymer ($0 \leq \times \leq 3$),

m = number of monomeric silicic acid molecules added to the polymer,

p = fraction of the hydroxyl groups per monomeric silicic acid molecule that are converted to water during the polymerization reaction.[3]

Colloidal Silica: The partial neutralization of alkaline silicate solution with mineral acid can be achieved by electro dialysis resulting into formation of colloidal silica.[3]

Alkaline silicate solution → Electro dialysis → Colloidal silica suspension

Types of Silica Particle: Mainly three types of silica are available-

1. Amorphous silica
2. Crystalline silica
3. Synthetic amorphous silica

Amorphous Silica: Amorphous silica includes the pure forms of SiO_2 such as colloidal silica, precipitated silica, silica gel, pyrogenic silica, silica fume, quartz glass, fused silica and also the skeletons of Radiolaria and diatoms in the form of diatomaceous earth. These silica skeletons are comprised of an amorphous opaline substance.

Synthesis of Amorphous Silica: Amorphous silica are synthesized by the polymerization of Si $(OR)_4$ (tetra alkyl orthosilicate, where R is the alkyl chain) to form a network of SiO_2 groups. The synthesis is given as follows-

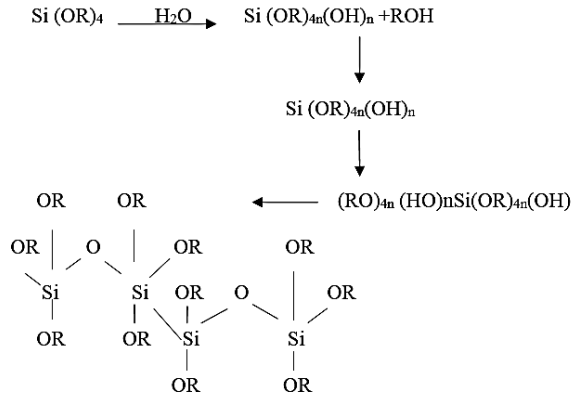


Fig. 3: Synthesis of amorphous silica

Amorphous silica is available in two different forms –

1. Naturally occurring amorphous silica
2. By products of amorphous silica

Naturally Occurring Amorphous Silica: Silica occurs naturally in the solid amorphous state as flint, opal or diatomaceous earth.

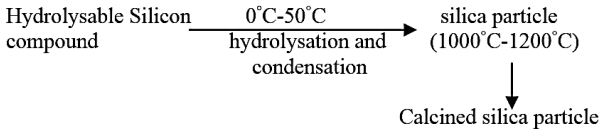
It includes: Diatomaceous earth, calcined and flux calcined.

Diatomaceous Earth: Diatomaceous Earth, also known as D.E., diatomite, or kieselgur/ kieselguhr, is a naturally occurring, soft, siliceous sedimentary rock that is easily crumbled into a fine white to off-white.

1. Particle size :< 3 μm to > 1 mm, but typically 10 to 200μm.
2. The typical chemical composition of oven-dried diatomaceous earth is 80 to 90% silica, with 2 to 4% alumina and 0.5 to 2% iron oxide.[4,5]

Calcined Silica Particle: Calcined silica particle having low hygroscopicity, narrow range of particle size distribution, even particle diameter.

Calcined silica can be synthesized as follow:



1. Organic solvent preferably contains:

a. Silicon compound - 0.05 to 1.2 mol/L
b. Water - 2.0 to 25.0 mol/L
c. Catalyst - 0.8 to 9.4 mol/L

2. Average particle diameter - 0.04μm and 5.0μm
3. Moisture absorption - 0.2 wt % or less[6].

Byproduct of Amorphous Silica: It includes - fused silica, silica fumes and micro silica.

Amorphous silica is also available in various forms such as vitreous silica, silica M, micro-amorphous silica. These silicas have high surface area generally greater than $3m^2g^{-1}$.

Crystalline Silica: Crystalline silica is a basic component of soil, granite and many other minerals, in which the silicon and oxygen atoms are arranged in a tetrahedron structure, exists in several forms, or polymorphs.

The importance of the crystalline feature is that it is highly stable, insoluble in water, possesses on its surface reactive oxygen species when fractured.

There are four main features for classification of solid silica. These are

1. Crystal structure - Surface composition
2. Porosity - Dispersity

Different forms of crystalline silica are available:

1. Quartz 4. Keotite
2. Tridymite 5. Stishovite
3. Cristobalite 6. Coesite

The other crystalline forms such as Silica W, Silica O and Hydrated Crystalline Silica are also available.[2]

Toxic Properties of Crystalline Silica: The toxicity of crystalline silica varies according to polymorphic form; cristobalite and quartz appear more reactive and more cytotoxic than coesite, shishovite and tridymite.[7]

1. Silicosis
2. Chronic obstructive pulmonary disease (COPD)
3. Pulmonary tuberculosis
4. Chronic bronchitis

Synthetic Amorphous Silica (SAS): Synthetic amorphous silica is a form of silicon dioxide (SiO_2) that is intentionally manufactured. The different forms of SAS are synthesized by various processes like wet process, thermal process and by surface modification process.

By wet process: By thermal process:

1. Silica gel 1. Pyrogenic Silica
2. Precipitated silica 2. Electric arc silica
3. Plasma silica

Wet Process

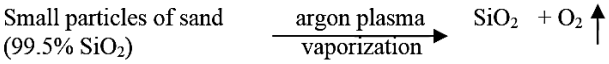
Silica Gel: Silica gel is a granular, vitreous, porous form of silicon dioxide made synthetically from sodium silicate by wet process. Most applications of silica gel require it to be dried, hence also known as silica xerogel.[8]

Precipitated Silica: They are produced from mineral acid. Sulphuric acid and sodium silicate solution are added simultaneously with agitation to water. Primary particles have a diameter of 5-100 m^2/g.

Thermal Process

Pyrogenic Silica (Fumed Silica): It is produced in a flame, consists of microscopic droplets of amorphous silica fused into branched, 3D secondary particles which then agglomerate into tertiary particles.[9]

Plasma Silica: For producing ultrafine silica particles a plasma transferred-arc reactor was developed (Plas-macan) The process is as follow:



Advanced Forms of Silica Particles

Core Shell Particles: Core–shell particles consist of a solid core coated with a layer of porous silica that is deposited either in layers or a single coating, depending on the manufacturer. The diameter of the solid core and porous layer vary between different manufacturers and the required overall particle size. For chromatographic applications, the core–shell silica particles are also widely known as fused-core, solid core or superficially porous particles. The particle diameter generally is 2.7µm or even smaller eg 1.3µm.

The important advantages of core shell particles includes speed, resolution, sensitivity, peak capacity, high number of theoretical plates, high productivity and solvent saving. There are a number of core–shell columns like Kinetex™ *core-shell*, BlueShell R, Accucore™, Capcell core, HALO™.

Preparation of Core Shell Particles: Core–shell particles are usually synthesized by a two-step or multiple-step process. The core particles are synthesized first and the shell is then formed on the core particle via different methods, depending on the type of core and shell materials and their morphologies. Many approaches have been used by the scientist for preparation of core shell particle like layer by layer via electrostatic interactions, Multilayer by multilayer, shell synthesis on preformed cores, one pot synthesis and sphere-on-sphere silica particle, Droplet based fluidic approach.[10]

Applications of Core shell Microspheres and Nanoparticles:[10,11] Core–shell silica microspheres have shown better results in liquid chromatography while core/shell nanoparticles have many potential and exciting applications in the biomedical field.

In the biomedical field, core/shell nanoparticles are mainly used for controlled drug delivery, for bioimaging, for cell labeling, as biosensors and tissue engineering applications etc.

Reversed-phase HPLC: The most common mode of HPLC is done through Reversed-phase analysis. Core–shell particles of size 1.7–1.5µ have provided better efficiency with more number of theoretical plates. Aromatic hydrocarbon, pesticides, and explosives gave fast and high resolution separation when analysed on Halo C18 and C8 columns. Similar results were obtained for large biomolecules as well.

Capillary Electrochromatography Separation: Capillary electrochromatography (CEC) is a separation technique in which the mobile phase moves by an electro-osmotic flow rather than pressure in HPLC. Core–shell particles have shown a great success in chiral separations.

Controlled Drug Delivery and Specific Targeting: The use of nanoparticles in controlled and targeted drug delivery to the specific region have been successfully achieved which resulted in overall efficacy in the delivery system.

Bio-imaging: Various molecular imaging techniques such as magnetic resonance imaging (MRI), ultrasound imaging, optical imaging (OI) and positron emission tomography are used for the imaging of both in vivo and in vitro biological specimens.

Sensors, Replacement, Support, and Tissues: Magnetic-based nanocomposites coated with any other material, such as a fluorescent one, a metal, silica, or a polymer, are used as bio-analytical sensors for the detection of damaged cells, DNA, RNA, glucose, cholesterol, etc. But they require the presence of antibody for selective binding to analyte.

Mesoporous Silica Nanoparticles (MSN):[12,13] It is one of the recent developments in nanotechnology. Mesoporous silica materials have attracted special attention after the discovery of new family of molecular sieve called M41S, MCM-41, MCM-48 and SBA-15 are the most common mesoporous silica materials with the pore size ranging from 2 -10 nm and 2D-hexagonal and 3D-cubic structural characteristics.

Morphology of Mesoporous Silica Nanoparticles

Particle Size: The silica particle size will determine the permeability of the packed bed as well as the efficiency of the column. The variables that involve controlling the size and morphology of MSNs include:

1. Rate of hydrolysis and condensation of silica source.
2. Level of interaction between assembled template and silica polymer.

Pore Size: The parameters that are used to control the pore structure of MSNs includes:

1. Amount of silica source and surfactant.
2. Packing capacity of surfactant.

To adjust the pore width, hydrothermal treatment, Surfactant or mesitylene as swelling agent plays an important role.

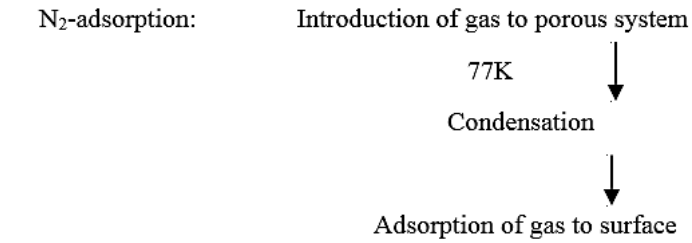
Surface Area: To control the amount of incorporated drug in the matrix two different approaches are used –

1. Increasing or decreasing the surface area
2. Modifying the surface drug affinity

Pore Volume[9]: The amount of drug adsorbed can be determined by pore volume. Pore volume and amount of drug loaded are directly proportional to each other.

Generally, when the pore size is less than 15 nm and surface area is about 1000 m^2g^{-1}, the pore volume is in the of range 2 cm^3g^{-1}.

Porosity:[2] Porosity is generally measured by N_2-adsorption which determines the pore width. XRD and TEM are used to measure pore structure of MSNs.



Various phases of silica with their pore size are available:

Mesophases in silica	*Structure*	*Pore size*
p6m (MCM-41)	2D hexagonal	2 – 5 nm
Ia3d (MCM-48)	3D cubic	
p2 (MCM-50)	lamellar	
p6m (MSNs)	2D hexagonal	6-20 nm

Properties of Mesoporous Silica

The unique properties of mesoporous silica nanoparticles (MSNs) such as-

1. They have controlled particle size; porosity, morphology, and high chemical stability make nanoparticles highly attractive as drug carriers, diagnostic catalysis, separation and sensing.
2. Rapid internalization by animal and plant cells without causing any cytotoxicity inside the body.[2]

Applications of MSNs[13]

1. **Imaging and Diagnostic Agents:** Bio-distribution, cancer cell targeting efficiency, cytotoxicity is observed well by imaging of mesoporous silica nanoparticles. The core material can be filled with therapeutic agents, quantum dots and fluorescent dyes like Fluorescein isothiocyanate (FITC) and rhodamine B isothiocyanate (RITC). The most commonly used Near-IR dyes for imaging includes AlexaFluor 700 and Dy Light 680.
2. **Target Specificity:** Target specificity of mesoporous silica nanoparticles decreases the dosage of drug and eliminates the harmful toxic effects of drugs after administration. Passive targeting increases permeability of tumor blood vessels and allows the accumulation of nanocarriers at tumor site.
3. **Dispersibility:** For biomedical application MSN must remain dispersed for its stability and its aggregation must be avoided by chemical modification of the surface of MSNs, coating with proteins and polymers and lipid bilayer coating.
4. **Bio Sensing and Cell Tracing:** The capability of mesoporous silica nanoparticles to functionalize its surface with greater amount of cell recognizing agents or other site-directing compounds make MSNs an excellent cell tracing agent.

Hybrid Organic and Inorganic Particle:[14] The disadvantage silica based reversed-phase materials; they have a limited usable pH range, typically pH 2–8. The bonded phase is susceptible to hydrolysis below pH 2 and above pH 8, hydroxide ions (OH ion) can attack and dissolve the silica, which leads the crumble of the packed stationary bed and a drastic loss in efficiency. Second, tailing occurs when basic solutes interact strongly with residual silanols groups and in turn loss in resolution as well as to the accuracy and precision of quantitation. The best properties of bonded silica having high efficiency and stability towards pH led to the synthesis of hybrid organic-inorganic particles. They are best prepared by Sol-gel synthesis using organosilanes.

Some of hybrid particle based columns used in chromatographic analysis includes Symmetry C18, XTerra MS C and XTerra RP18 columns from Waters and Zorbax Eclipse XDB-C18 double end capped dimethyl–C18 bonded sol-gel columns from Agilent Technologies.

Monolithic Silica Stationary Phase:[15,16] The recent invention and development of monolithic silica stationary phase is a major technological change in column technology with higher column efficiency and with minimum back pressure. The monolithic stationary phases are made of continuous porous silica or organic polymer.

There are several types of monolithic silica stationary phases like:

1. Agglomerates of polyacrylamide particles
2. Polymethyacrylate block
3. Agglomeration of micron-size silica beads
4. Polystyrene-divinylbenzene block
5. Silica rods

The chromatographic properties of monolithic silica gel depends largely on pore size/skeleton size ratio and high porosities, resulting in high permeability

and a higher number of theoretical plates per unit pressure drop.

They are manufactured by sol-gel process leading to formation of rod shaped silica, which possess a defined bimodal pore structure with macro and meso pores in the micro- and nanometer range

Monolith stationary phases have

1. **Flow-through Pores with Macro Porosity (1–2µm in width):** It determines the column permeability, by mercury intrusion porosimetry.
2. **Diffusive Pores (Called Meso Pores):** It determines the column performance and the average size of mesopores ranges from 2 to 50 nm. Mesopores form the internal porosity of the column which is approximately 0.20 for the neat silica.

Important characteristics for current silica monolith columns:

1. Efficiency of column: 3–5µm silica particles.
2. Pressure drop: 30–40% lower than a 5µm silica particle.

Applications: The monoliths silica columns have been used in HPLC for analysis of basic drugs, large biomloecule, plant virus, bacteriophages and in capillary electro chromatography. The difference between monolithic and particulate based packing is shown in Table 2.

Table 2: Difference between particulate and monolithic packings

S. No.	Particulate based Packing	Monolithic Packing
1.	Characteristics of column: Inter particulate void volume determines the permeability and column back pressure.	Macro pore determine the permeability and column backpressure.
2.	Plate number (N) is inversely proportional to particle diameter.	Plate number is directly proportional to particle diameter.
3.	Inter particle volume depends on particle size. Diameter <3µm (small permeability) Diameter>11µm (large permeability)	Macro pore size determines the particle performance.
4.	Column performance: a. Flow rate : less b. Back pressure: high c. Porosity: less d. Run time: higher e. Efficiency (HETP): lesser	 High Less High Lesser Higher
5.	Precision and reproducibility: a. Retention time: higher b. Resolution factor: lesser c. Tailing factor: higher	 lesser higher lesser
6.	Structure: a. Frit: present b. Sample and mobile phase usage: more c. Absorption and separation capacity : lesser d. Loadability: less	 Absent Less 30-40% higher capacity More

Conclusion

This review highlighted many exciting progresses on various silica particles. The particles with diverse nature and even size smaller than eukaryotic cell have capability to cross the cell. Morphological changes help in modifying mesoporous silica material to produce diversified forms of material. By changing pH and stirring rate produces hundreds of microns up to milliliters of particle size and different pore structures. Core-shell structure provides high magnetization which gives sufficient pore volume and surface area to store and release the drug. Hybrid silica particles provide wide pH range to operate at low back pressure and monoliths provide greater stability and porosity. The uniqueness of various particles is summarized in the Table 3.

Table 3: Summary of Silica particles, its porosity and applications

S. No.	Types of Silica Particles	Porosity	Applications
1.	Crystalline silica	1- 10 µm	Food and Pharmaceuticals Hydraulic fracturing Sand casting Precursor to glass and silicon
2.	Amorphous silica	5-50nm	Chromatography Thickening agent Catalyst Microelectronics Semiconductor systems
3.	Colloidal silica	1-5nm	Catalysis Ceramics Paper and textiles Tobacco treatment Strength enhancement in rubber
4.	Synthetic amorphous silica	3-4µm	Food materials Fabricating three layered nanocables
5.	Core shell silica particle	2.6-2.7µm	Rp-HPLC analysis Capillary electro-chromatography Bio-imaging Controlled and Target specificity Sensors, Replacement, Support, and Tissues
6.	Mesoporous silica nanoparticle	200nm	Imaging and diagnostic agent Target specificity Dispersibility Optoelectronic devices Cds nanoparticle capped MSN

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