J. Mat. NanoSci. 2020, 7(1), 1-18 Review

Journal of
Materials NanoScience

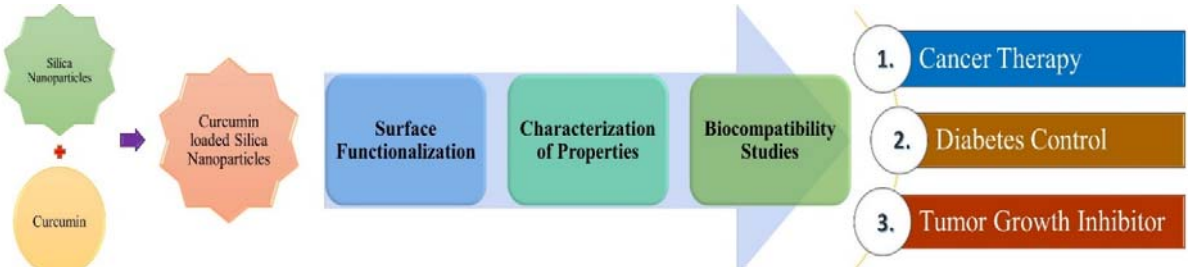
Curcumin loaded Silica Nanoparticles and their therapeutic applications: A review

Parul Pant,[1] Chetna Gupta,[1] Sagar Kumar,[2] Apoorva Grewal,[1] Shivani Garg,[1] Aishwarya Rai[1]

[1]Department of Chemistry, Hansraj College, University of Delhi, Delhi, India. [2]Department of Inorganic and Physical Chemistry, Indian Institute of Sciences, Bengaluru, Karnataka, India.

Submitted on: 10-Oct-2019, Accepted on: 31-Dec-2019 Published on: 07-Jan-2020

ABSTRACT



Silica nanoparticles offer a promising platform for the delivery of drugs, in particular for the drugs which lack water solubility, target capability and have non-specific distribution, systematic toxicity and low therapeutic index. In this review, we focus on the synthesis and therapeutic (particularly, anti-cancer) applications of Curcumin loaded Silica Nanoparticles. Various surface modifications of silica nanoparticles have been discussed that are used to enhance their therapeutic applications. The characterization techniques and study of their biocompatibility have also been presented.

Keywords: Silica, nanoparticles, curcumin, cancer, therapeutics, drug delivery, biomedical

INTRODUCTION

Nanomedicine, the use of nanotechnology for biomedical applications, has potential to change the landscape of the diagnosis and therapy of many diseases. Use of nano-carriers such as solid nanoparticles, liposomes, polymeric micelles, polymeric nanoparticles, drug-polymer conjugates, dendrimers etc. for controlled and sustained delivery of drugs, such as Curcumin, which has low biocompatibility, has been extensively studied to overcome several problems in conventional drug delivery systems in past years.[1,2] Each delivery system has its advantages and disadvantages. For example, O'Brien et al. have achieved high drug loadings in liposomes,[3] but also their intrinsic structural stability is undesirably low during circulation. Inorganic Drug delivery systems, such as Silica nanoparticles (SiNPs), which can overcome the disadvantages of organic drug delivery systems, offer an effective way to enhance the outreach of nanomedicine applications. Their hydrophilic surface increases their circulation efficiency, have excellent biocompatibility,[4] and can be easily mass produced at low capital. Nanoparticle (NP) based drug delivery is receiving attention due to these unique properties and as these NPs can easily encapsulate poorly soluble drugs,[2] protect therapeutic molecules from degradation,[5] modify their blood circulation and reduce side effects of drugs.[6] On the other hand, Curcumin is a well-renowned drug having anti-oxidant, anti-inflammatory, anti-proliferative, anticancer, antidiabetic,[7] antirheumatic, anti-invasive, antiangiogenic and anti-viral applications however, its potential is limited due to its lack of solubility in aqueous solvents, rapid elimination from body and

*Corresponding Author: Dr. Parul Pant
Department of Chemistry, Hansraj College, University of Delhi, Maurice Nagar, Delhi -07. India.
Tel:
Email: parulpant@hrc.du.ac.in

Cite as: *J. Mat. NanoSci., 2020, 7(1), 1-18.*
URN:NBN:sciencein.jmns.2020.v7.99

 ISSN 2394-0867
http://pubs.thesciencein.org/jmns

inadequate absorption. Studies indicate that Curcumin exhibits a versatile range of pharmacological value against many chronic diseases such as type-II Diabetes, rheumatoid arthritis, multiple sclerosis, Alzheimer's disease and Atherosclerosis. It also restricts platelet aggregation, Thrombosis and HIV Replication. Moreover, it enhances wound healing and is found to protect against Liver injury, cataract formation, pulmonary toxicity and fibrosis.[7-17] Finally, the anti-cancer activities of Curcumin have been exploited for both prevention and treatment of large variety of various cancers including gastrointestinal, melanoma, genitourinary, breast, lung, hematological, head and neck neurological and sarcoma.[17-20] So, Curcumin with these many advantageous applications can be brought into use by applying delivery approach based on nanotechnology,[21-22] which overcomes its above-mentioned limitations. This review discusses different aspects of research work done on Curcumin loaded silica nanoparticles in the recent years.

1.1. CURCUMIN – THE DRUG

Vogel et al.[23] were first to extract an impure form of a natural yellow-colored phenolic antioxidant, curcumin. Curcumin present in many kinds of herbs, particularly in *Curcuma longa* Linn (turmeric) (family Zingiberaceae) has been used in its crude form as spice and dietary supplement as well as component of many traditional Asian medicines.[24] The commercially available Curcumin products contain not only curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)], but have three curcuminoids present in them, namely ~17% demethoxy curcumin, 3% bisdemethoxycurcumin and rest is curcumin [Figure1].[25]

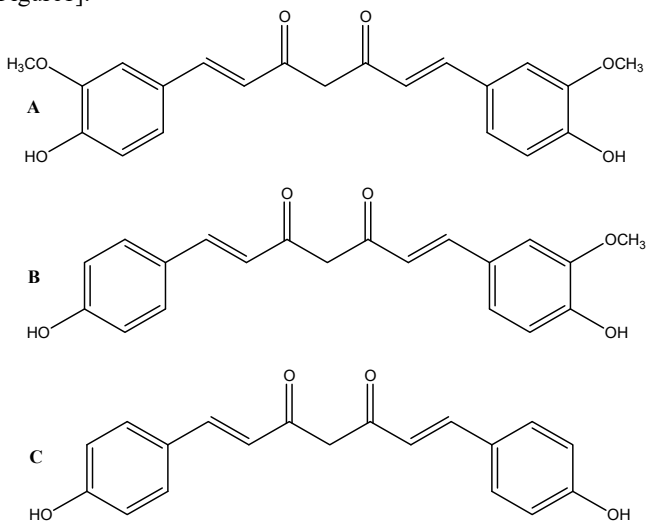


Figure 1. Structures of Curcumin (Curcumnoids) Curcumin(A), demethoxycurcumin(B) Bisdemethoxycurcumin(C)

Keto form of curcumin dominates in acidic and neutral conditions and solid phase. It has a pKa value of 8.54.Curcumin also acts as a Michael acceptor because it exhibits keto-enol tautomerism.[26] It is less soluble in water, only about 0.6 µg/mL, at pH<=7 and is extremely susceptible to degradation under basic conditions,[27-29] but soluble in organic solvents like methanol, ethanol, dimethylsulphoxide (DMSO) and acetone because of its chemical structure.

Curcumin acts as an anti-oxidant,[30] which is responsible for its wound healing properties as free radicals are the major cause of inflammation.[31] It enhances wound healing through tissue remodeling, granulation tissue formation and collagen deposition.[32] Its anti-inflammatory,[33] and anti-infectious activities,[34] increase its wound healing potential. The positively charged metals found in the active sites of target proteins are chelated by the enol form of curcumin. Curcumin chelating potential of the type 1:1 and 1:2 have been reported for several metal cations.[35] Out of all the curcuminoids, curcumin has the most anti-oxidant potential. Curcumin protects liver against injury and fibrogenesis by suppressing hepatic inflammation, attenuating hepatic oxidative stress,[36] increasing expression of the xenobiotic detoxifying enzymes,[37,38] inhibiting hepatic stellate cells activation[39] and supporting the mitochondrial function.[40]

Curcumin has a glucose lowering effect because of its actions on various glucose and lipid metabolism related targets, oxidative stress, cell growth, inflammation and apoptosis.[41] The various nanoformulations which can be used to increase the solubilisation of curcumin and protect it against inactivation by hydrolysis include: liposomes,[42] polymeric Nanoparticles,[43] polymeric micelles,[44-51] conjugates,[52] peptide/protein carriers,[53] cyclodextrins,[54] solid dispersions etc.[55]

1.2. SILICA NANOPARTICLES- THE DELIVERY VEHICLE

Silicon dioxide or Silica (SiO_2) is found in nature in crystalline and amorphous forms.[56] The packing of SiO_4 units form a three-dimensional network structure which terminates at the surface in two ways: siloxane group with oxygen group on surface or silanol group with –OH group on the surface. There are three types of silanol groups vicinal, germinal, isolated silanol sites as illustrated in figure 2.

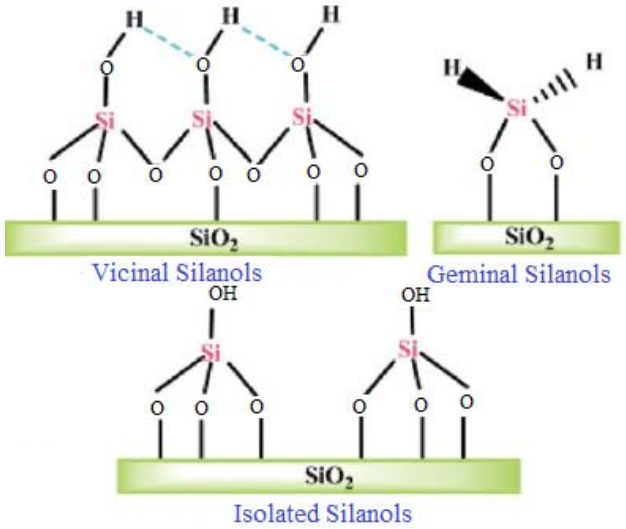


Figure 2. Structures of silanol groups present in silica nanospheres.

SiNPs have unique physiochemical properties such as high surface area, nanometer size and rigid framework, with excellent thermal, chemical and mechanical stability.[57-59] The inherent inactive nature of silica can be utilized by using it as a support material and the functionalization of its exterior and interior pore surfaces with several organic moieties and hybrid atoms.

SiNPs may further be classified into Hollow SiNPs and Mesoporous SiNPs.

a) Hollow SiNPs consists of a nano-sized hollow interior surrounded by a solid silica shell. Their versatile properties include high specific surface area,[60-63] thermal insulation,[64-66] and optical property.[67]

b) Mesoporous SiNPs (MSNPs) have a unique mesoporous structure. They have high potential in biomedical applications because of high surface area and mesoporous structure.

Other nanocarriers face some key barriers in their translocation.[68-70] These include difficulty in developing nanocarriers that encapsulate sufficient therapeutic agents with activated release, difficulty in their delivery to the target molecule, toxicity of engineered nanomaterials and finally their cost-effective preparation. Therefore, MSNPs can be used as nanometer sized drug carriers because they overcome some of the problems of other nanoformulations.

2. Preparation of SiNPs

Traditional techniques used to synthesize SiNPs involve flame synthesis, reverse micro emulsions, hydrothermal synthesis and widely used sol-gel technique. It overcomes the disadvantages of above-mentioned techniques as through systematic monitoring of reaction parameters, it can control the particle size, size distribution and morphology of particles.

Sol-gel Process

SiNPs can be obtained as a pure and homogeneous product at mild conditions through sol-gel process. It is a widely used wet chemical technique to synthesize SiNPs. This technique comprises of hydrolysis and condensation of Silica precursors such as TEOS or Sodium silicate in the presence of mineral acid (HCl) or base (NH_3) as catalyst.[71-73]

The reaction involved in sol-gel technique for SiNPs using TEOS can be written as:[72-75]

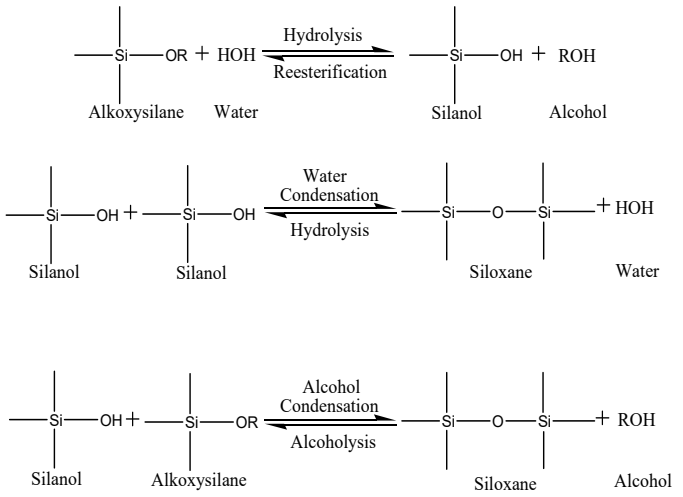


Figure 3. The hydrolysis of TEOS molecules forms silanol groups. The condensation/polymerization between the silanol groups or between silanol groups and ethoxy groups creates siloxane bridges (Si–O–Si) that form entire silica structure.

Stöber et al. were first to synthesize spherical and monodispersed SiNPs (5nm-2000nm) from aqueous alcohol solution of silica alkoxides in presence of ammonia as a catalyst.[73] Base catalyzed Stöber method has an advantage over acid catalyzed systems as it reduces monodispersed spherical silica particles while the latter produce gel structures. Subsequent methods for the synthesis of SiNPs evolved from the Stöber method.

Size of Nanoparticles can be reduced by slowing down the rate of reaction (polycondensation) by varying reaction parameters.[74,,75] Most of the works prove that increased ammonia concentration increases the particle size.[76-82] Replacing ammonia with ammonium salts of Br, I, Cl reduce particle size by 73%-78%. Therefore, addition of small amount of anion electrolyte produces monodispersed SiNPs ~20nm to ~34nm[83] depending on the anion used. Particle size and distribution of SiNPs also depends on mixing modes provided concentration of reactants and temperature are kept constant.[84] Rahman et al. reported homogeneous, highly dispersed and stable SiNPs ~7.1nm in size'[81]' using low frequency ultrasound and optimum conditions of sol-gel process. Therefore, it can be concluded that the optimum conditions for a reaction can be set depending upon the desired particle size and morphology of SiNPs to be produced.

SiNPs need to be dried to convert them from fluid to solid form. Some of the drying techniques include supercritical drying, freeze drying, spray drying and thermal drying. A careful controlled drying process leads to the formation of well dispersed particles whereas drying in the presence of water can result in agglomeration phenomena. The effect of alcohol dehydration, freeze drying, and oven drying techniques on the size, size distribution, dispersion and agglomeration of ~7nm nanosilica produced by sol-gel method were described by Rahman and co-workers.[85] According to the results, the most efficient technique was found out to be alcohol dehydration as it produced SiNPs with improved dispersion and reduced agglomeration. Thus, synthesized SiNPs can be surface-functionalized with multiple organic and inorganic groups, polymers, and proteins which serve as caps and gatekeepers for controlled drug release and further enhance their biocompatibility and cellular uptake.[86,87]

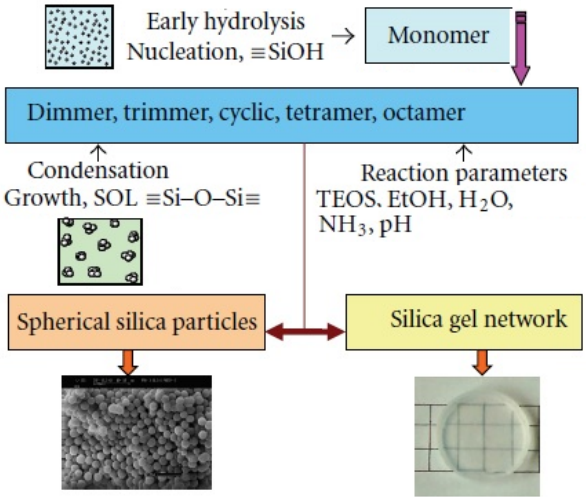


Figure 4. Schematics of Sol-Gel.

2.1. Preparation of Curcumin loaded SiNPs

In this review we are focusing on the preparation of SiNPs in conjugation with curcumin by using sol-gel process.

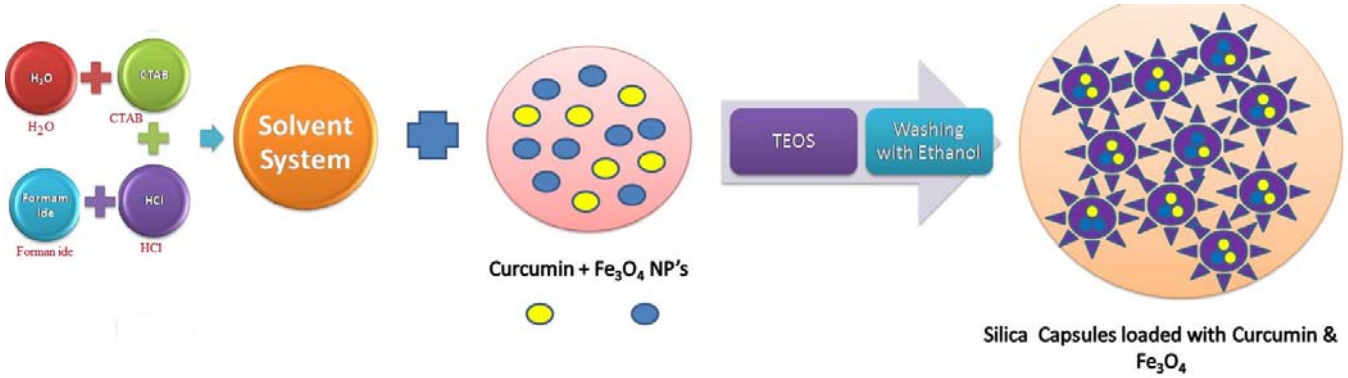


Figure 5. Schematic representation of loading of SiNPs with Curcumin and Fe_3O_4.

Curcumin conjugated SiNPs can be prepared using modified Stöber method '73' and adding curcumin during the reaction. Over the years, various researchers have worked on curcumin conjugated SiNPs using novel techniques. In 2009, Vishwanatha et al. formulated a delivery system where curcumin was encapsulated in poly (lactic-co-glycolic acid) (PLGA) nanospheres by solid-in-oil-in-water (s/o/w) solvent evaporation technique.[88] Their studies showed that smooth, spherical PLGA nanospheres were formed and exhibited high yield and drug entrapment efficiency with a narrow size range of 35nm to 100nm and mean particle diameter of 45nm. The in vitro curcumin release studies from the nanospheres showed that curcumin was released in a sustained manner over a prolonged period. Recently it was shown that, hydrophobic curcumin can be effectively encapsulated into porous silica capsule through a multistep self-assembly approach.[89] Chin et al. reported the formation of magnetic nanocomposites of silica with curcumin in the cetyltrimethylammonium bromide (CTAB) micellar rod in the presence of super paramagnetic Fe_3O_4 Nanoparticles (8nm-10nm). This method endowed ultrahigh loading of magnetite inside the porous silica matrix which imparted high magnetophoretic mobility for targeted delivery.[90]

Mesoporous spherical hollow SiNPs were prepared by Jin et al. using a self assembled alanine-based amphiphile as a template and then they were functionalized with curcumin molecules attached to the internal surface of the nanostructure by covalent bonding. [91] Approximately, 35% of the curcumin was selectively immobilized onto the internal surfaces of the mesoporous hollow silica particles by covalent bonds. The curcumin molecules from the hybrid material were effectively released by the cleavage of the amide bond by the base.

Patra et al. introduced a novel method for encapsulation of curcumin by synthesizing microcapsule containing self-assembled Nanoparticles using poly (L-lysine), trisodium citrate and silica sol. [92,93]

Micro-curcumin was prepared by PLL mediated self-assembly method where the first step involved was ionic-linking of the PLL chains with the multivalent counter anions (trisodium citrate) to form spherical aggregates.[93,94] Due to their net positive charge, these aggregates later assisted the congregation of negatively charged silica nanoparticles to shape the ordered microcapsule structure. In the microcapsules formed, the shell wall consists of positively charged PLL chains interspersed with the negatively charged silica nanoparticles. Curcumin was added to the PLL solution to encapsulate curcumin inside the microcapsules. The structure of the microcapsules was found to be dependent upon the solubility of curcumin in the solvent environment and such microcapsules could only be prepared in neutral and alkaline environment. Therefore, it was easy to prepare and purify micro-curcumin and the process was fast. Poly (L-lysine) is a non-toxic and highly stable material that prevents metabolic degradation therefore it was used in this method for pH triggered curcumin release. The only disadvantage was found to be the size of the microcapsules which could affect the cell membrane penetration efficiency compared to 100nm particles commonly used in drug delivery.

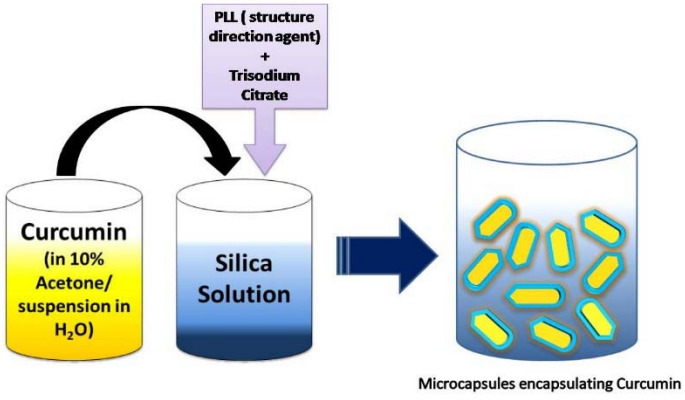


Figure 6. Synthesis of microcapsules encapsulating PLL-mediated self-assembled nanoparticles

Hamam et al. prepared curcumin formulation using Mesoporous Silica nanoparticles (MPSPs) and oleic acid and investigated in vitro penetration through the skin and in vivo anti inflammatory and analgesic effects.[95] Result showed a very high loading efficiency (98.72%) of curcumin which could be explained based on chemical interaction. The resultant delivery device of curcumin resulted in improved solubility of curcumin

Figure 7. Preparation of Curcumin loaded MPSP's.

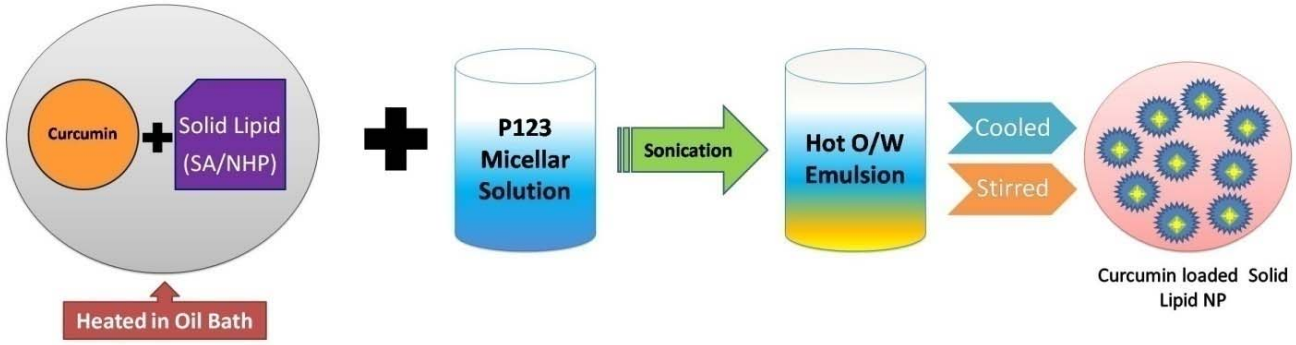


Figure 8. Synthesis of curcumin loaded nano matrix combining solid lipid nanoparticles and mesostructured silica.

loaded MSNPs in aqueous media and enhanced permeation of curcumin through skin.

Kim et al. designed a drug delivery system aimed to increase the stability, bioavailability and sustainability of released curcumin through a double encapsulation of the drug into a core shell nano matrix combining solid lipid nano particles and mesostructured silica.[96]

The release of curcumin was found to be pH dependent for both stearic acid and cetyl palmitate-based materials due to interactions between curcumin and silanols of the mesopore surface.

Radhakrishnan et al. reported the fabrication of a bioresponsive and targeted drug delivery system which utilized MSNPs as the drug carrier and chondroitin sulphate as the degradable cap. [97] The cap in addition to being biodegradable provides targetability to the particles towards CD44 over expressing cells.

A novel nanocarrier was constructed by combining two kinds of drug carrier (MSNPs and F127 micelles) by Xu et al. providing a suitable method for the design of multifunctional stimuli-responsive drug delivery and self-fluorescent imaging systems.[98]

The system was fabricated using curcumin loaded micelles (F127) as gating agents and fluorescent labels of MSNPs via Schiff base. This study provided a potential drug delivery system for biomedical imaging diagnosis and simultaneous therapy for lesion sites such as cancers.

In a similar approach, Xu et al.[99] developed self-fluorescent and stimuli-responsive drug nanocarriers based on curcumin gatekeeper on a platform of mesoporous silica nanoparticles with large pores for drug delivery. The curcumin gatekeeper was anchored to the surface of large pores via thiol-ene ‘‘click” chemistry, and the pluronic polymer, F127, was coated to the out surface of the nanocarrier by self-assembly through hydrophobic interactions to provide a hydrophobic micro-environment. In vitro drug release profiles indicated that curcumin could be entrapped in the pores with nearly no leakage and induced rapid drug release in the existence of GSH at pH 5.5 condition through the hydrolysis of β-thioesters.

Dinda et al.[100] reported the synthesis of curcumin loaded organically modified silica (ORMOSIL) nanoparticles to vanish the major hinderance i.e. poor aqueous solubility for it's oral bioavailability and therapeutic use. ORMOSIL nanoparticle comprises of the non polar core of Tween80/1-butanol/water micelles to which sample of curcumin in chloroform was dissolved by magnetic stirring.[101] At final stage 3-aminopropyltriethoxysilane was added at room temperature to get curcumin loaded ORMOSIL NP. The study aimed at the evaluation of the toxicity of ORMOSIL NP to the tumor cells in-vitro as well as in-vivo animal tumor models.

Gangwar et al.[102] reported simple wet chemical protocol which delineates the conjugation of curcumin with silica nanoparticle. For the synthesis of this conjugate simple modified Stober[73] method was followed.

This conjugation was also examined against the cancerous lines and primary cell lines which showed its potential application in biomedical domain.

Jin et al.[91] prepared curcumin-immobilized mesoporous hollow silica nanoparticles (C-MHSP) using a self-assembled alanine-based amphiphile as a template and then functionalization with curcumin molecules that are covalently attached to the internal

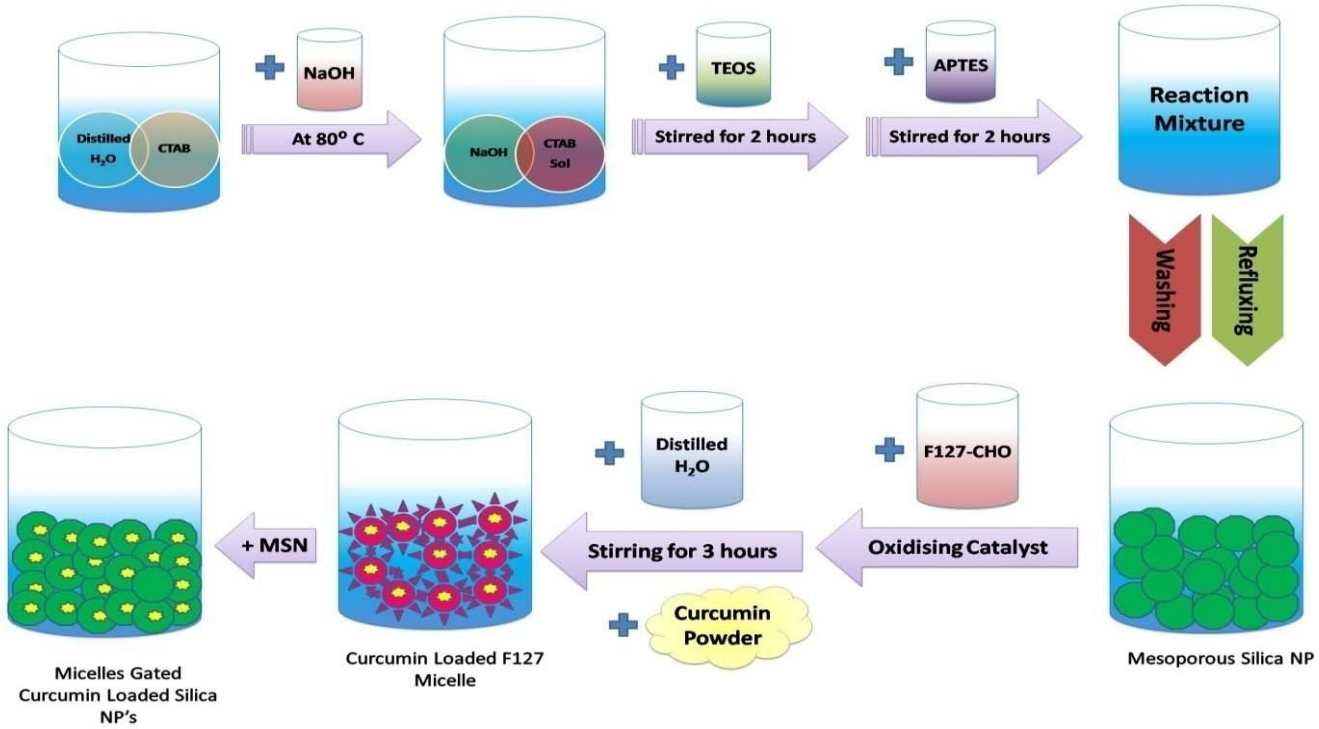


Figure 9. Synthesis of F127 micelle gated curcumin loaded SiNPs for multifunctional stimuli-responsive drug delivery and self-fluorescent imaging systems

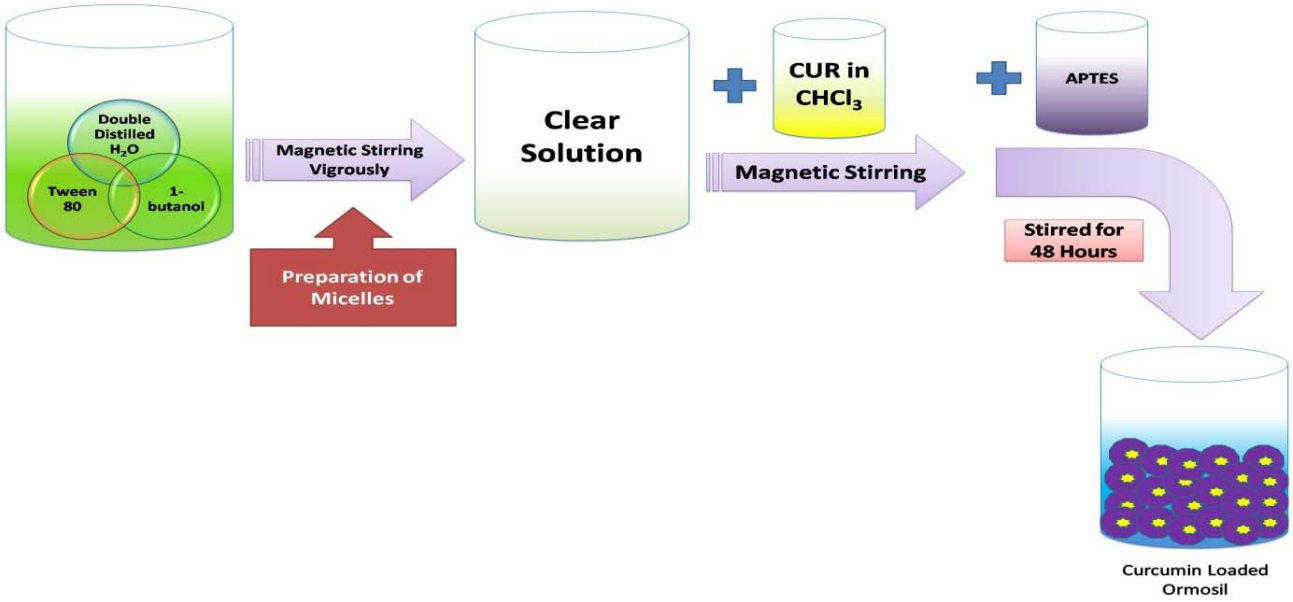


Figure 10. Synthesis of curcumin loaded organically modified silica (ORMOSIL) nanoparticles by Dinda et al. [100]

surface of the nanoparticles. In their study, they reported the selective immobilization of organic functional molecules at the inner surface of MHSP, and described the operation of a novel, biocompatible, controlled-release of the cargo molecule.

Bolluet al.[103] synthesized two different silica based (MSU-2 and MCM-41) curcumin loaded mesoporous materials namely V3 and V6. Both materials were found to be biocompatible while exhibiting significant cytotoxicity in different cancer cell lines. Studies conducted with the materialsshowed slow andsustained release of curcumin, which could be proved as alternative treatment strategies for cancer therapy through nanomedicine approach. Firstly, preparation of non-functionalized mesoporous silica materials is performed in accordance with previously reported synthetic protocol.[76,104] In order to enhance the loading efficiency of curcumin, Bollu et al.[103] in their study preformed two step functionalistion of MSU-2 and MCM-41, silica based

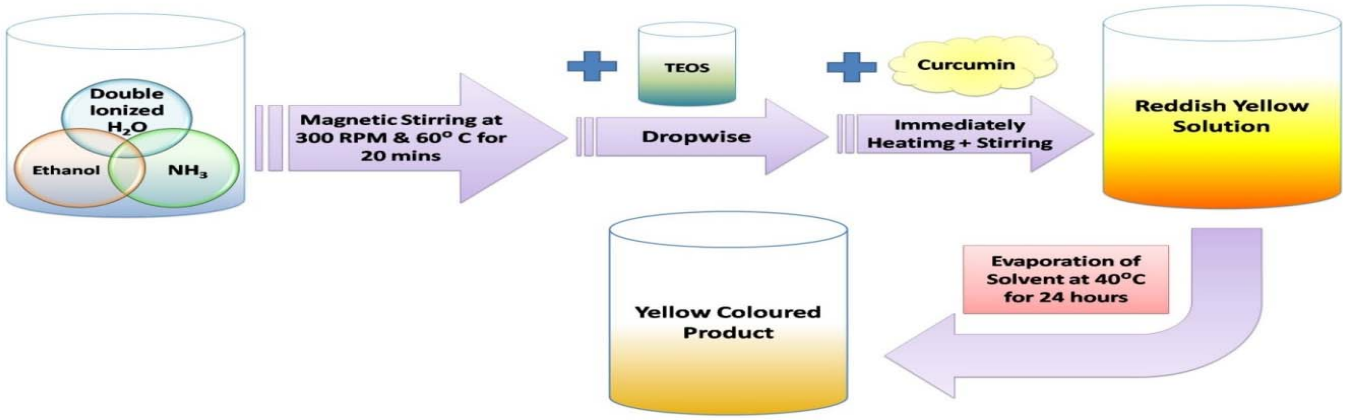


Figure 11. Synthesis of curcumin conjugated SiNPs (yellow coloured product) by Gangwar et. al. (ref. 102)

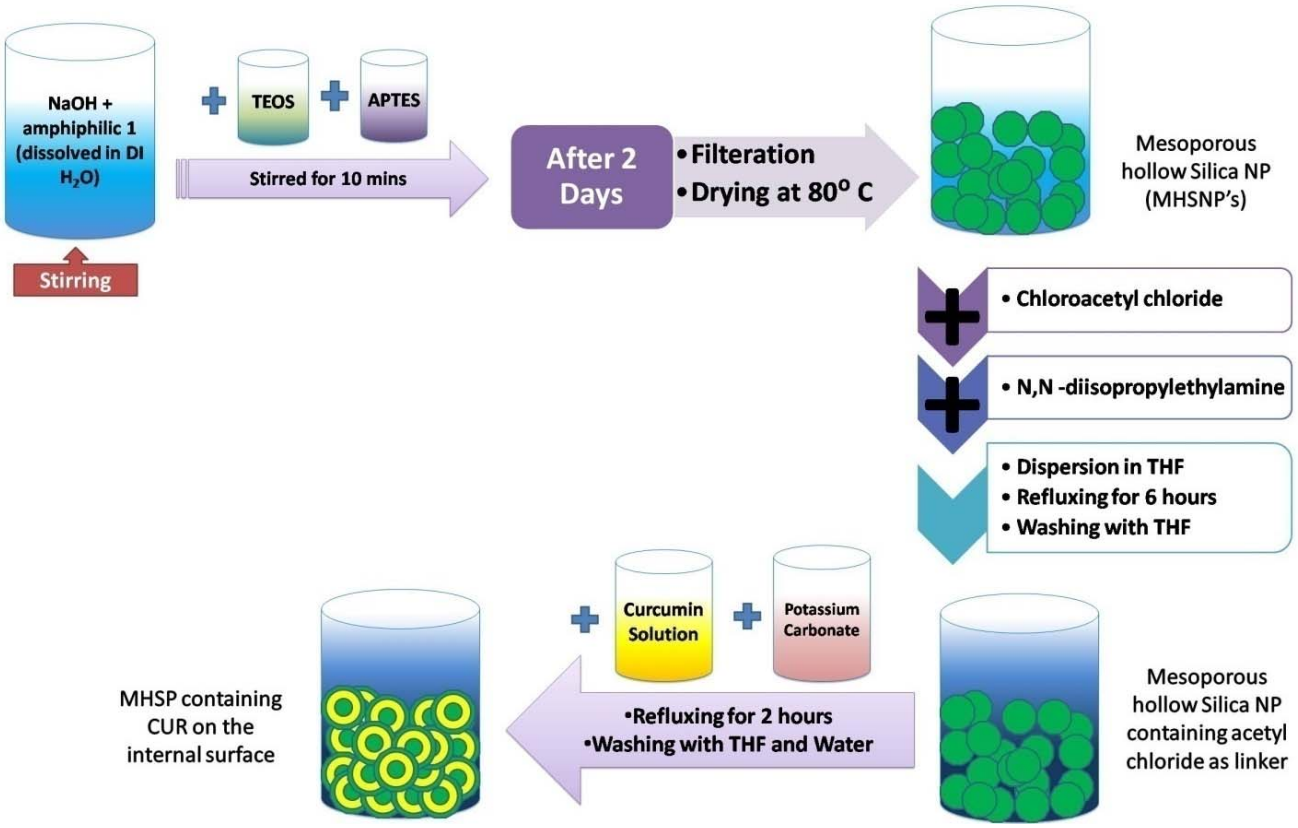


Figure 12. Synthesis and functionalization of C-MHSP using self-assembled alanine-based amphiphile as a template[91]

materials (MSU-2 and MCM-41) were initially functionalized with 3-chloropropyltriethoxysilane followed by amine functionalization with polyamino ligand (tris (2-aminoethyl) amine) and finally the loading of curcumin to these silica based materials.

Daryasari et al.[105] prepared normal and large pore size mesoporous silica nanoparticles (NMSNs and LMSNs) by co-condensation method and coated with (3-aminopropyl)triethoxysilane (APTES) to prepare amine functionalized MSNs (MSN-NH_2). Then conjugated with succinic anhydride (SA) to obtain carboxylic acid functionalized MSNs (MSN-COOH). Curcumin (CUR) was loaded into the synthesized MSNs with two different pore size and their loading capacity and efficiency were compared. Chitosan (CS), a pH-sensitive polymer, was also conjugated to folic acid (FA) as an active targeting agent and then coated on the surface of carboxylic acid enriched MSNs. Studies confirmed the selective targeting and successful delivery of CUR by the designed MSNs and suggested LMSN-COOH-CUR@CS-FA as a promising candidate for targeted hydrophobic anticancer delivery.

Sanghoon et al.[106] were able to design microcapsules (MC) combining a core of solid lipid nanoparticle (SLN) and a mesoporous silica shell and explored them as oral delivery system of curcumin.It was found that SLN acts as reservoir of

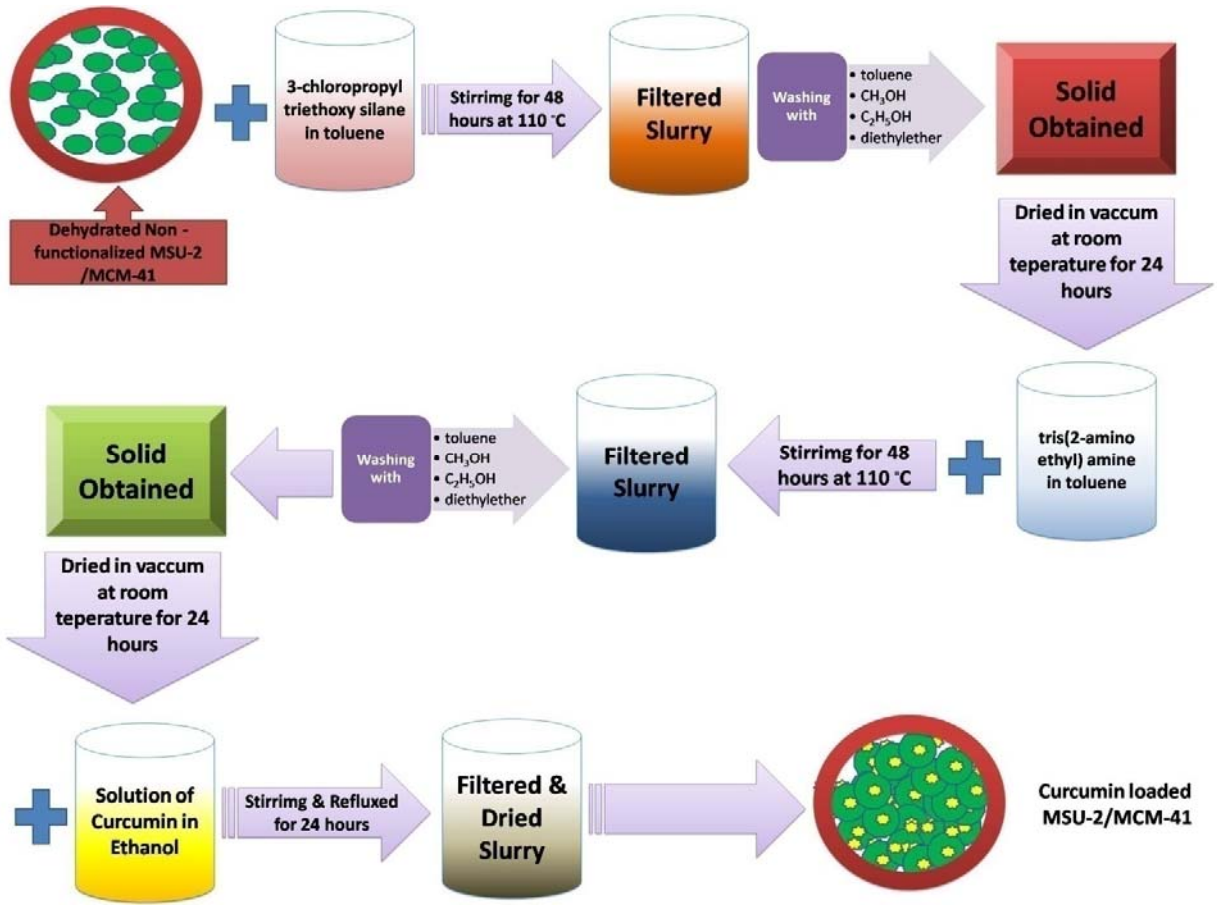


Figure 13. Synthesis of curcumin loaded MSU-2/MCM-41 by Bollu et al.[103]

curcumin while themesoporous shell insures the protection and the controlled release of the drug. These findings suggest that organic core-silica shell microcapsules are promising drug delivery systems with enhanced bioavailability for poorly soluble drugs.The resulting hybrid silica microcapsules showed pH-dependent curcumin releaseas the stability of lipid core has been shown to have a correpondance with pH value.

Dejian et al. prepared curcumin-loaded mesoporous silica incorporated nanofiber mats using blend electrospinning of curcumin-loaded mesoporous silica nanoparticles (CCM-MSNs) and polyvinyl pyrrolidone (PVP) for hemostasis.Thedetermination of structure, biocompatibility and antibacterial activity was done, especially focusing on the hemostatic effect using an in vivo liver injury model. The hybrid nanofiber mats were shown to exhibit enhanced in vitro antibacterial effects against methicillin-resistant Staphylococcus aureus (MRSA).[107]

3. Characterization of Nanoparticles

The effort to prepare Silica NPs with precisely controlled physicochemical properties has been of utmost importance as the excellent control over syntheses is the prerequisite for the biomedical application of silica NPs. So, the availability of techniques that allow the characterization of their physical and chemical properties at the nanoscale is as important as their synthesis itself. Nanoparticles are generally characterized by their size, shape, morphology and surface charge. The average particle diameter, their size distribution and charge affect the physical stability, the toxicity, physical stability and the in vivo distribution and redispersibility of the nanoparticles. In this section we discuss various techniques employed over the years to examine and verify the physical characterstics of the synthesized Silica NP's.

3.1. Particle Size

The size of nanoparticles as well as the uniformity, are two important parameters of a drug delivery system based on nanoparticles, as they determine the in vivo distribution, toxicity, and targeting ability.[108-110] More importantly, altering their size can influence drug loading, drug release, and in vitro and in vivo stability. There are several tools for determining nanoparticle size like Dynamic Light Scattering (DLS) or Photon-correlation Spectroscopy (PCS), Atomic Force Microscopy etc. The fastest, most advanced and one of the popular method of determining particle size is photon-correlation spectroscopy (PCS) or dynamic light scattering (DLS). DLS is used to determine the size of Brownian nanoparticles in colloidal suspensions in the nano and submicron ranges. Shining monochromatic light onto a solution of spherical particles in Brownian motion causes a Doppler shift when the light hits the moving particle, changing the wavelength of the incoming light. This change is related to the size of the particle. This relation helps to extract the size distribution and gives a description of the particle's motion in the medium, measuring the diffusion coefficient of the particle and using the autocorrelation function. The photon correlation spectroscopy (PCS) represent the most frequently used technique for accurate

estimation of the particle size and size distribution based on DLS.[111] Other important technique, Atomic force microscopy (AFM) offers high resolution in particle size measurement which involves physical scanning of samples at sub-micron level using a probe tip of atomic scale.[112] AFM provides the most accurate measurements of size and size distribution. It requires no mathematical treatment and singly provides a real picture of size of the particles which helps largely in the study of its biomedical behavior. Singh et al. measured particle size and zeta potential of drug loaded SiNp using a Zetasizer Instrument.[113]

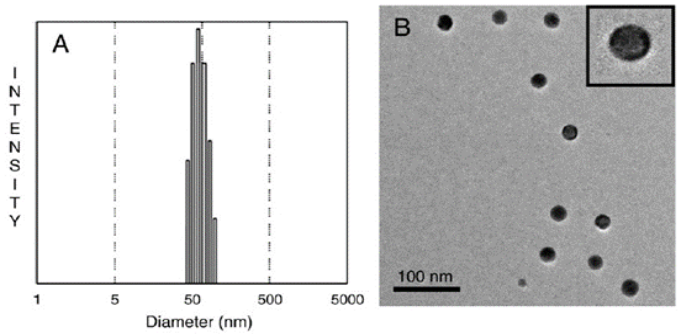


Figure 14. Representative (A) dynamic light scattering and (B) transmission electron microscopic images of the gadolinium oxide-doped and DNA-coated silica NPs. (Reproduced with permission from Ref. 166. Copyright 2011 Nanomedicine: Nanotechnology, Biology, and Medicine)

3.2. Particle Shape and Surface Morphology

The shape of nanoparticles is of equal importance as their size in drug delivery. For example, spherical nanoparticles are good candidates for drug delivery, but anisotropic structure of NPs can sometimes provide higher efficiencies because of their larger ratios of surface area to volume. Even the slightest changes in the shape and surface morphology of the NPs can adversely effect the parameters of its biocompatiabilityand also the drug encaplsulation and targeting. In addition to both size and shape, the surface characteristics of nanoparticles represent another critical parameter in determining their drug-loading efficiency and release profile, circulation half-life, tumor targeting, and clearance from the body. Electron microscopy (both SEM & TEM) techniques are very useful in determining the overall shape of synthesized nanoparticles. AFM also can give a characterstic image of the shape and even the delicate microstructure of the nanoparticles. Without any specific pre-treatment. The techniques based on electron microscopy offer several benefits in morphological and sizing analysis; but, they convey limited information about the size distribution. Scanning electron microscopy (SEM) gives morphological surface examination with direct visualization of the surface. The surface characteristics of the sample are obtained from the secondary electrons emitted from the sample surface. The nanoparticles sample dry powder should be prepared first and then investigated using SEM. The NP's should also be able to withstand vacuum for the examination. The mean size obtained by SEM is comparable with results obtained by DLS. SEM techniques are time consuming, costly and frequently need complementary information about sizing distribution.[114] TEM operates on different principle than SEM, yet it often brings same type of data. The sample preparation for TEM is complex and time consuming because of its requirement to be ultra-thin for the electron transmittance. [115] By utilizing more sophisticated microscopy techniques, surface images are constructed using a physical probe that scans the specimen in order to view the chemical composition near the surface of the nanocomposites.[116,117] In other techniques, often used is the Solid-state NMR spectroscopy,that can confirm the covalent grafting of organic functionalities onto silica NP surfaces.[115] The crystalline structure and the phase purity of (modified or simple) silica NP's are determined using X-Ray Diffraction. The diffraction peak positions of Silica NPs and drug (Curcumin) loaded Silica NPs can be studied simultaneously using XRD and change in their ordered crystalline structure can be verified. Jambhrunkaret al. and group reported that mesoporous silica nanoparticles (MCM-41) before and after Curcumin encapsulation showed same diffraction peak positions in XRD analysis, demonstrating the retention of the ordered structure.[118] Also, TGA was employed to predict the thermal stability, moisture content and possible decomposition of drug and functionalities in/on the nanoparticles. The physical state of the nanoparticles can be characterized using Differential Scanning Calorimetric studies (DSC Thermogram Analysis).

Ideally, the NPs should have a hydrophilic surface to resist the adsorption of plasma proteins and escape the uptake by macrophages.[119] The Surface hydrophobicity of the NPs can be characterized by various techniques like Hydrophobic Interaction Chromatography (HIC), Biphasic Partitioning, adsorption of probes and contact angle measurements. Moreover, several advanced and sophisticated analytical techniques are reported in literature for surface study of nanoparticles. X–ray Photon Correlation Spectroscopy (XPS) and Energy-Dispersive X-ray Fluoroscence Spectroscopy (ED-XRF) permits the identification of specific chemical groups on the surface of nanoparticles.[120]

Other than that Nitrogen adsorption/desorption isotherms for determination of active surface area can be done. Some groups calculated mesopore size distribution by the BJH (Barret, Joyner, Halenda) method.[113]

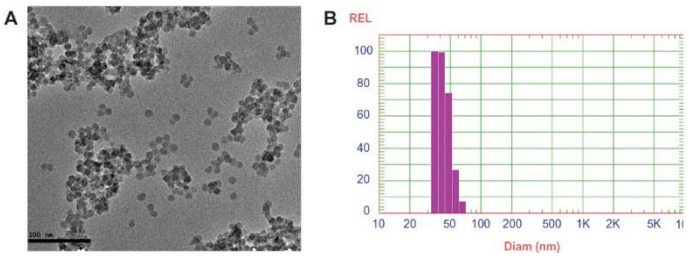


Figure 15. (A) Transmission electron microscopic image and (B) dynamic light scattering of silica nanoparticles coencapsulating gadolinium oxide and horseradish peroxidase.(Reproduced with permission from Ref. [167]. Copyright 2012 International Journal of Medicine)

3.3. Surface Charge

The zeta potential of a nanoparticle is commonly used to characterize its surface charge.[121] Actually, it is an indirect measure of the Surface Charge of the particle. The Zeta Potential

of the surface reflects the electrostatic potential of a particle and is influenced by the composition of the particle as well as the medium in which the nanoparticle is suspended. The characterization of nature and intensity of the surface charge of nanoparticles is very important as it governs their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds. For example, it is a general accepted and experimentally proven fact that nanoparticles with a cationic charge would induce more immune response and cytotoxicity than the neutral and anion counterparts but are advantageous for transvascular transport in tumors, whereas particles with a neutral charge show favorablly long circulation times and interstitial transport in tumors.[122-123] High zeta potential values, either positive or negative, should be achieved in order to ensure stability and avoid aggregation of the particles. The quantitative measurement of surface hydrophobicity can also be predicted from the values of zeta potential. It can also provide information about the nature of material encapsulated in the nanocapsules or functionalized on the surface of the nanoparticles. [124] The most common technique used for the measurement of Zeta Potential is using a Zetasizer which works on the principle of quasi-elastic light scattering. Use of Malvern Zetasizer Nano ZS, Malvern Instruments Ltd., U.K. has been reported in works of Singh et al. and Mohanty et al. for the measurements of Zeta Potential of nanoparticulates.[113,125] Siddharth et al. characterized the zeta potentials of mesoporous silica NPs and their surface functionalized counterparts , compared and reported the results.[118]

3.4. Drug Loading

A successful drug-delivery system using nanoparticles should have a high drug-loading capacity to minimize the quantity of materials and increase the efficiency needed for administration. The efficiency of drug loading and entrapment in a nanoparticle is determined by the properties of both the drug molecules and the carrier material i.e. nanoparticles. The drug loading of the nanoparticles is generally defined as the amount of drug encapsulated per mass of NPs (usually moles of drug per mg NPs or mg of drug per mg NPs). More widely used parameters used for drug loading characterization are Encapsulation Efficiency or Entrapment Efficiency (EE) and Drug Loading (DL) content determined by following equations.

EE (%) = 100 × (Total amount of curcumin − Free curcumin)/ Total amount of curcumin

DL (%) = 100 × Weight of curcumin in nanoparticle/ (Weight of the curcumin in nanoparticle + Weight of nanoparticle)

The techniques used for this analysis of above parameters is classical analytical techniques such as UV spectroscopy or High Performance Liquid Chromatography (HPLC) after ultracentrifugation, ultra filtration, gel filtration, or centrifugal ultrafiltration [126]. Quantification is performed with the UV spectroscopy, HPLC or Fluorimetry. Absorption and Fluorescence spectra of Silica NPs, free drug (Curcumin) and Curcumin functionalized/encapsulated Silica NP's can be studied using an absorption spectrophotometer and Fluorimeter respectively. The concentration of free curcumin in the solvent can be determined by comparing with the standard curve obtained by measuring the absorbance of known concentrations of Curcumin in appropriate solvent (like DMSO). [113] The unknown terms in the two equations on RHS can be easily then determined using above methods.

The surface functionalization and modification, encapsulation of Curcumin can also be verified by FTIR analysis. [118] FTIR helps in identifying the nanocomposites via the analysis of functional groups. It can also be used to study the interactions between the drug and the nanoparticle's matrix.

Jiahao et al prepared highly ordered mesoporous silica nanoparticles (MSNs) with etching method and then coated homogeneous PEGylated lipid bilayer with 10–15 nm thickness around the surface of MSNs using film hydration method. Systematic optimization and characterization of co-encapsulation process of curcumin into PEGylated lipid bilayer coated mesoporous silica nanoparticles (PLMSNs) was performed carrying out single factor test, associated with Box-Behnken Design. The concentration of encapsulated drugs was measured by reversed phase high performance liquid chromatography (RP-HPLC) method. [127]

4. Biocompatibility

The most important factor in the design of Curcumin loaded Silica Nanoparticle for in vivo application is the biocompatibility of the Nanoparticle itself as it the one acting as drug carrier or vehicle. It's the nanoparticle which is in contact with the biological fluids like blood and other biological components. For in vivo biomedical applications, the particles should fully perform the desired function and avoid non-specific and deleterious changes to the body's biological system. At conference of the European Society for Biomaterials in 1986, the word "biocompatibility" was defined as "the ability of a material to perform with an appropriate host response in a specific application". But in present context the scope of biocompatibility widens and "being biocompatible" means that the nanoparticle must have limited toxicity to the organism's system at its effective dose, it must be able to perform its function without interference from the organism's healthy mechanisms, and it must be able to circulate sufficiently long to accomplish its intended task. While discussing the biocompatibility of Curcumin loaded Silica particles all the physical factors such as their size, shape, structure, surface characterstics and the toxicity of Silica NPs comes into consideration. The biocompatiability of the nanoparticle ensures the effectiveness of the Curcumin loaded Silica Nanoparticles.

Many researchers have observed that the cytotoxicity of silica NPs is size dependent. [128-134] Mou et al. reported the effect of particle size on the cellular uptake of mesoporous by Hela cells.[135] The cellular uptake is size-dependent in the order 50 nm > 30 nm > 110 nm > 280 nm > 170 nm. The cellular uptake of 50 nm nanoparticles by Hela cells was about 2.5 times higher than that of 30 nm particles and thus, these 50 nm particles showed maximum cellular uptake.[136,137] The cellular uptake indirectly defines how much drug is released into the cells depending of the Drug Loading Efficiency of the Curcumin Loaded Silica Nanoparticles. Gao et al. studied the cellular uptake and cytotoxicity of monodisperse 80 nm and 500 nm silica NPs in the human dermal

fibroblasts.[130] The studies reflected that cell viability and mitochondrial membrane potential are more strongly affected by the smaller NPs than the larger NPs, but the adhesion and migration ability of the fibroblasts are impaired by NPs of both sizes. Shi et al. the in vivo biodistribution and urinary excretion of spherical mesoporous silica NPs with a size of 80, 120, 200, and 360 nm.[138] They found the particles of smaller size had longer blood-circulation lifetime and the excretion from urine remarkably increased with the increase of particle size, which may reflect the in vivo degradation rates. Passagne et al. reported in his research that 20 nm nonporous silica NPs are more toxic than 100 nm NPs and concluded that cytotoxicity is associated to stress oxidative with up-production ROS and lipid peroxidation [134]. Lin et al. reported that porous silica particles (25, 42, 93, 155, and 225 nm) caused a concentration and size dependent hemolytic activity.[139] The smaller particles have higher hemolytic activity than the larger ones.

In vitro studies have shown that the surface characteristics of silica NPs also plays an important role in their cytotoxicity.[128,130,140-143] Brown et al. reported that uncoated silica NPs induce an increased release of lactic acid dehydrogenase and

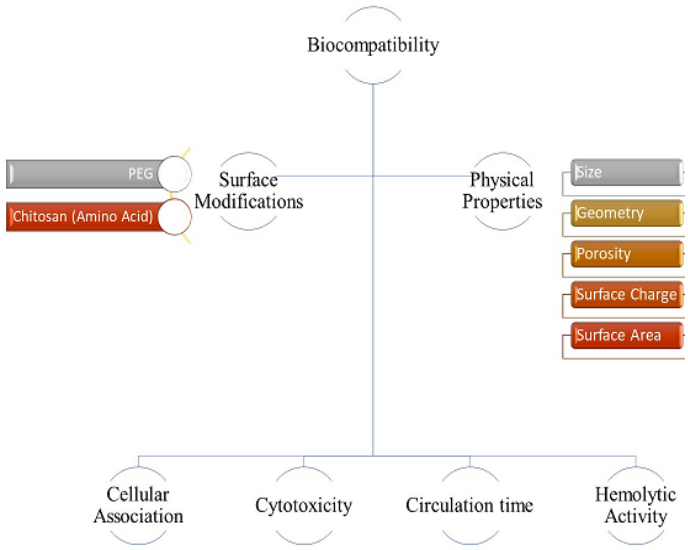


Figure 16. Dependency of biocompatibility of modified silica nanoparticles on various parameters.

interleukin-8, but when PEGylated , this effect is reduced. [144] Polyethylene glycols (PEGs) can form a hydrophilic layer around particles with increased dispersity and can greatly increase the half-life by delaying opsononization (association with opsonin serum) which makes them the most efficient surface modification [145]. Chang et al. observed that the cytotoxicity of silica NPs to various human cells can be reduced by modifying their surface with chitosan (which bears amino groups).[143] But Oh et al. studies contradict this and reports that amine-functionalized silica NPs with positively charged surfaces are more toxic to macrophage J774A.1 cells than silica NPs with anionic or neutral surface charge.[128] These contradictory results may be explained by the fact that the effects of the physicochemical properties of silica NPs on cytotoxicity are also cell-type dependent.[143] Yu et al. evaluated the impacts of geometry, porosity, and surface charge of silica NPs on cellular toxicity and hemolytic activity in their studies. [140] They observed that surface charge and porosity of the NPs are the major factors that affected the cellular association and cytotoxicity of the silica NPs. Nonporous silica nanoparticles are less toxic than mesoporous silica nanoparticles and this was demonstrated in the studies of Herd et al.[146] In another study, Rabolli et al. observed the effect of silica NP size, surface area, and microporosity on in vitro cytotoxic activity in four types of cells: macrophages, fibroblasts, endothelial cells, and erythrocytes. The physicochemical parameter that governs the response to the NPs varies by cell types, which again supports the fact that cell type plays an important role in determining the in vitro toxicity. The various results of their research were as follows: in murine macrophages, the cytotoxic response increases with external surface area and decreases with micropore volume; in human endothelial cells and mouse embryo fibroblasts, cytotoxicity increases with increasing surface roughness and decreasing diameter; in human erythrocytes, hemolytic activity increases with particle diameter. [147]

6. THERAPEUTIC APPLICATIONS

The pharmacological properties of curcumin have been subjected to detailed research in recent years. It is evident that multi-faceted mechanisms of curcumin result in its vast contribution to a diversity of effects on biological systems. Curcumin has been shown to have significant vitro antioxidant, diabetic complication, antimicrobial agent, neuroprotective, anti-cancer, antithyroid, cancer cells detection of hypochlorous acid, wound healing, treatment of major depression, healing of paracentesis, and treatment of carcinoma and optical detection of pyrrole properties.

To improve the poor biopharmaceutical properties of curcumin, its aqueous solubility has to be improved. This can be done using nanocarriers such as SiNPs for targeted delivery of drugs. A successful formulation of drug delivery system involves preparing carrier system capable of encapsulating the desired drug within its structure and then delivering the drug to the cancerous tissue in its active form. Most nanoformulations are administered parenterally. However, noninvasive routes of administration such as oral, transdermal and pulmonary are preferred for patients. The appropriate route of administration depends upon the targeted region in the body and the characteristics of the formulations.

Therapeutic regimen of curcumin loaded SiNPs is pronounced in:

Ma'mani et al. synthesized Curcumin loaded guanidine functionalized PEGylated I3ad mesoporous silica nanoparticles KIT-6 as an efficient drug delivery system for breast cancer cells. This new system exhibited high drug loading capacity, sustained drug release profile, and high and long-term anticancer efficacy in human cancer cell lines. It showed pH responsive controlled characteristics and highly programmed release of curcumin leading through the results in in vitro breast cancer therapy. The results depicted that pure nanoparticles have no cytotoxicity against human breast adenocarcinoma cells (MCF-7), mouse

breast cancer cells (4T1), and human mammary epithelial cells (MCF10A).[148]

In another study by Chen et al.novel multifunctional MSN with folate (FA) receptor-targeting functionality and intracellular pH-responsive release properties were constructed and examined for controlled release of curcumin. Compared to the native parent drug, this nano-delivery system improved solubility and biocompatibility of curcumin under physiological conditions. Studies showed that the FA-MSN N=C-Cur could effectively target to FA-receptor-rich MCF-7 cells via FA receptor-mediated endocytosis and showed significantly higher cytotoxicity to MCF-7 cells than to FA receptor deficient HEK-293T cells, mainly due to the high efficiency of cellular uptake by FA receptor-mediated endocytosis and subsequent pH-triggered curcumin release in the targeted cells.[149]

Wang et al. assessed the curative effect of a potential nanoformulation, i.e. Cur-loaded and calcium-doped dendritic mesoporous silica nanoparticles modified with folic acid (Cur-Ca@DMSNs-FA) for breast cancer therapy. They developed multifunctional dendritic mesoporous silica nanoparticles (Ca@DMSNs-FA). Studies demonstrated that this delivery system promoted intracellular delivery of Cur and enhanced the anticancer effect against MCF-7 breast cancer cells, mainly due to the targeted delivery, pH responsible drug release, excellent biocompatibility, and higher bioavailability.[150]

Cytotoxicity of organically modified silica nanoparticle-curcumin complex conjugated with hyaluronic acid (HA-SiNP-cur) was investigated by Surya Prakash Singh et al. in human colon carcinoma cells. Curcumin was loaded in SiNPs and resulting complexes were conjugated with HA, which has a strong affinity for cancer cells expressing CD44.The study showed that the conjugation of SiNPs-curcumin complex with oligomers of HA results in enhanced uptake of curcumin possibly through CD44 mediated endocytosis and improvement in cytotoxicity in colon carcinoma cells.[113]

Nuclear factor kappa B (NF-κB) is a ubiquitous transcription factor which plays a critical role in the immune system and controls the expression of various cytokines and the major histocompatibility complex gene. Curcumin has been shown to target and inhibit activated NF-κB to restrict tumor cell growth in various cancer types. [151-153] This phenomenon is amplified by using curcumin loaded SiNPs, resulting in increased preferential cytotoxicity to cancer cells. The results of studies done by Vishwnatha et al. [88] indicated that LNCaP cells treated with curcumin loaded PLGA SiNPs showed a distinct decrease in NF-κB activity, possibly due to absence of NF-κB binding to the kappa oligonucleotide. Therefore, this curcumin loaded PLGA nanoparticle might be a better therapeutic approach than free curcumin for treating prostate cancer.

A novel delivery system of curcumin through transdermal route using sub-micronized particles composed of MSNPs and oleic acid was prepared by Hamam et al.[95] The in vitro penetration of the MSNPs through the skin and in vivo anti-inflammatory and analgesic effects were studied. The results showed high loading efficiency (98.72%), significantly enhanced curcumin penetration through the rabbit skin. Anti-inflammatory study using formalin induced mouse oedema assay clearly showed that curcumin encapsulated into MSNPs had anti-inflammatory effect, while analgesic effect was carried out using the standard Eddy's hot plate assay. Curcumin formulation showed higher analgesic activity compared to the placebo as indicated by higher response time.

Curcumin loaded mesoporous silica–chondroitin sulphate hybrid nanoparticles prepared by Radhakrishnan et al.[97] proved promising as a drug delivery system. This was demonstrated using a cervical cancer line. On interacting with cancer cells, the chondroitin sulphate present on the surface recognized and attached onto the CD44 receptors facilitating the uptake of these particles. The phagocytized particles were then exposed to the degradative enzymes, such as hyaluronidase present inside the cancer cells, which degraded the cap resulting in drug release. It was observed that the system can enhance the anticancer activity of the hydrophobic drug curcumin.

A protease called trypsin is overexpressed in certain cancers such as leukemia, colon cancer, and colorectal cancer. Mesoporous silica nanoparticle (MSN)−protamine hybrid system (MSN−PRM) was fabricated by Radhakrishnan et al. [154] which selectively released drugs in presence of trypsin. On exposure to the enzyme trigger (trypsin), the protamine cap disintegrated, opening up the molecular gates and releasing the entrapped drug molecules. The system exhibited minimal premature release in the absence of the trigger and selectively released the encapsulated drugs in the presence of the proteases secreted by colorectal cancer cells. The ability of the MSN–PRM particles to deliver anticancer drugs to colorectal cancer cells was demonstrated. Curcumin-loaded MSN–PRM nanoparticles were incubated with colorectal cancer cells (COLO 205), and the cell viability was studied using an MTT assay.Enhanced anticancer activity of curcumin in MSN–PRM was observed which may be due to the slow release of curcumin into the acidic intracellular compartment from MSN–PRM aiding in better stabilization as opposed to free curcumin, which is easily prone to hydrolytic degradation.

Amino-functionalized silica nanoparticles loaded with curcumin weresuccessfully synthesized via sol-gel approach, the targeting ligand, folate, was covalently attached to amino groups of nanoparticle surface through amide bond formation. [155] The cytotoxic effect of nanoparticles on prostate cancer cells line was evaluated and compared to normal cells line (prostate epithelial cell). Cytotoxicity experiments demonstrated that folate-functionalized nanoparticles were significantly cytotoxic to tumor cells, whereas normal cells were much less affected by the presence of these structures.

Huang et al. functionalized beta cyclodextrin hydrate (β-CD), a hydrophilic non-toxic carrier for hydrophobic drugs, inside magnetic mesoporous silica as the physical binding sites for the model drug curcumin. Studies and various characterization explored the fabrication of two kinds of bifunctionalizednanostars for the delivery of nano-formulations of the curcumin drug, in which the drug delivery nanocarriers could effectively increase the cytotoxicity to cancer cells, such as SK-HEP1 cells and HepG2 cells, compared with free curcumin, in order to kill them more effectively.[156]

Amino-functionalized curcumin-loaded SiNPs were prepared by Oliveira et al. which were found to have bactericidal activity

when evaluated against E.coli, a typical gram-negative bacterium, using viable cell count method. Based on the observations it was concluded that, since, amino group provides positive charge to the nanoparticle surface, they are better attracted by and able to interact with negative cell surface resulting in superior antimicrobial activity by suppressing the biosynthesis of the cell wall, disrupting the mass transport and accelerate the death of the bacteria. As curcumin is also negatively charged, this functionalization lead to better loading of curcumin as well, resulting in further increase of the bactericidal activity. Thus, nanoparticle surface properties were modified to enhance biological response and generate a tailored dual bactericidal system to substitute conventional antibiotics.[157]

α-Synuclein (α-Syn) is a protein found to accumulate in Lewy bodies, or protein clumps which cause toxic effects in the brain of the patients suffering from Parkinson's disease and often leads to neuronal death. Curcumin is shown to exhibit therapeutic effect against such neurological diseases, but its applications are limited by its poor aqueous solubility and bioavailability. Taebnia et al. [158] developed curcumin loaded amine-fuctionalized SiNPs which were shown to have increased drug loading efficiency and enhanced stability and reduced toxic effects of the drug. It was also revealed that α-Syn species interacted strongly with the curcumin loaded amine-fuctionalized SiNPs, leading to a significant inhibition of the fibrillation process and reduced its cytotoxicity-associated effects.

The overexpression of P-glycoprotein (P-gp) and the capture of drugs in endolysosomesposes a major problem of multidrug resistance (MDR) in chemotherapy. Sun et al. [159] reported peptide (GFLGHHHRRGDS)-functionalized mesoporous silica nanomedicine (MSN) for encapsulation of curcumin (CUR) and doxorubicin (DOX) with high-loading efficiency to significantly reverse the MDR in consequence of rapid endolysosomal escape and the inhibition of P-gp function. Confocal fluorescence imaging, flow cytometry and MTT assays demonstrated that the combination of CUR and the peptide-functionalized MSN markedly enhanced the intracellular DOX concentration and achieved a successful chemotherapeutic treatment to MCF-7 or MCF-7/ADR cells, working as an effective strategy to overcome MDR.

Singh et al. investigated the relative uptake efficacy and phototoxic potential of curcumin organically modified silica nanoparticle complexes and free curcumin in multicellular spheroids of human oral cancer cells by spectroscopy. The results showed that silica nanoparticles loaded with curcumin could penetrate better in oral cancer spheroids compared to free curcumin and the efficacy of uptake was found to be higher for small (~195 μm) spheroids. Further exposure to light amplified the antimetastatic ability in small spheroids and enhanced the generation of ROS scavengers. Therefore, it can be concluded that curcumin loaded SiNPs and light treatment could be effective for small avascular tumors of oral cancer.[160]

Xiubin Xu et al. fluorescent mesoporous silica nanoparticles curcumin polymer which was able to multiple function of acting as fluorescent agent, increasing the drug loading ratio of curcumin, and controlling the opening and closing of the pores. Author proposed the idea of development of smart and self-fluorescent drug nanocarrier for imaging and cancer therapy after getting positive results.[161]

Cheng et al. developed mesoporous silica nanoparticle approach for neurodegenerative therapy. This approach involved targeted co-delivery of Curcumin to protect Reactive oxygen species cell damage. The group proposed the curcumin modified nanoparticle has the ability to slowdown or prevent neurological disorders such as Alzheimer's, Parkinson's etc.[162]

Hadisoewignyo et al. designed an oral curcumin-MSN drug delivery system which exhibited strong anti-inflammatory properties with very low side effects. The group proposed use of curcumin modified Mesoporous silica nanoparticles as drug for treatment of diseases like cancer, diabetes etc.[163]

Li et al. synthesized Homogeneous PEGylated Highly ordered mesoporous silica nanoparticles (MSNs) co-encapsulated with Paclitaxel (Tax) and Curcumin (Cur). In-vitro release experiments of the curcumin and paclitaxel modified silica nanoparticles revealed definite and persistent cytotoxic effect against canine breast cancer cells.[164]

So far, the emphasis of these nanoparticles is particularly on the treatment of cancer, but some studies have shown that the nanoparticles also have potential for the treatment of the other chronic and life threatening diseases including Alzheimer, diabetes, infections, as well as different liver, kidney and cardiovascular diseases. Extensive human clinical trials must be conducted to establish the safety, especially after chronic and repeated use and effectiveness for treatment of cancer and other diseases.

CONCLUSION

This review presents an updated summary on the various advances undertaken in the field of Nanomedicine and Nano drug delivery. It throws lights on the anti-cancer and anti-inflammatory effects of Curcumin and Curcumin loaded Silica Nanoparticles. Curcumin, an otherwise versatile drug, has low solubility in aqueous solvents which leads to its rapid elimination from the body. This property further limits the therapeutic potential of Curcumin related drugs. However, conjugating it with Silica Nanoparticles improves its aqueous solubility and makes it more bioavailable.

The silica curcumin conjugate provides a unique drug delivery platform paving way for the development of powerful nanomedicine. This helps in early diagnosis and specific personalized therapy of many other diseases such as various tumors, diabetes, rheumatoid arthritis, multiple sclerosis, Alzheimer's etc.

Thus, Curcumin loaded Silica Nanoparticles have tremendous potential in the field of nano drug delivery, it is only a matter of time before they change the face of modern medicine.

REFERENCES

1. K. Loomis, K. McNeeley, R.V. Bellamkonda. Nanoparticles with targeting, triggered release, and imaging functionality for cancer applications. *Soft Matter*. **2011**, 7, 839-856.
2. A.Z. Wang, R. Langer, O.C. Farokhzad. Nanoparticle delivery of cancer drugs. *Annu. Rev. Med*. **2012**, 63, 185–198.
3. M.E.R. O'Brien, N. Wigler, M. Inbaret.al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin

HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann. Oncol*. **2004**, 15, 440-449.
4. K. Unger, H. Rupprecht, B. Valentin, W. Kircher. The Use of Porous and Surface Modified Silicas as Drug Delivery and Stabilizing Agents. Drug Deliv. *Ind. Pharm*. **1983,** 9, 69-91.
5. B.S. Chhikara. Current trends in nanomedicine and nanobiotechnology research. *J. Mater. Nanosci.* **2017**, 4 (1), 19–24.
6. Y. Wang, X. Wei, C. Zhang, F. Zhang, W. Liang. Nanoparticle delivery strategies to target doxorubicin to tumor cells and reduce side-effects. *Ther. Deliv*. **2010**, 2, 273-287.
7. R. Dabur, B. Sharma, A. Mittal. Mechanistic approach of anti-diabetic compounds identified from natural sources. *Chem. Biol. Lett.* **2018**, 5 (2), 63–99.
8. B.B. Aggarwal. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annu Rev Nutr*. **2010**; 30: 173-199.
9. R. Olszanecki, J.N Jawie, M. Gajda, L. Mateuszuk, A. Gebska, M. Korabiowska. Effect of curcumin on atherosclerosis in apoE/LDLR-double knockout mice. *J Physiol Pharmacol*. **2005**, 56, 627-635.
10. S.K. Shin, T.Y. Ha, R.A. McGregor, M.S. Choi. Longterm curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. *Mol Nutr Food Res.,* **2011**, 55, 1829-1840.
11. B.H. Shah, Z. Nawaz, S.A. Pertani, A. Roomi, H. Mahmood, A. Saeed. Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor and arachidonic acid-mediated platelet aggregation through inhibition of thromboxane formation and Ca2þ signaling. *Biochem Pharmacol.,* **1999**, 58, 1167-1172.
12. B.B. Aggarwal, A. Kumar, A.C. Bharti. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res*., **2003**, 23, 363-398.
13. G.C. Jagetia, B.B Aggarwal. "Spicing up" of the immune system by curcumin. *J Clin Immunol.* **2007,** 27, 19-35.
14. B.B. Aggarwal ,C. Sundaram , N. Malani , H. Ichikawa . Curcumin: the Indian solid gold. *Adv Exp Med Biol.* **2006**, 595, 1-75.
15. A. Goel , A.B. Kunnumakkara , B.B. Aggarwal . Curcumin as ''curecumin'': from kitchen to clinic. *BiochemPharmacol*. **2008**, 75, 787-809.
16. B. Thorat. Chemical extraction and biomedical importance of secondary organic metabolites from plants – A review. *J. Biomed. Ther. Sci.* **2018**, 5 (1), 9–42..
17. A. Duvoix, R. Blasius, S. Delhalle, M. Schnekenburger, F. Morceau ,E .Henry. Chemopreventive and therapeutic effects of curcumin. *Cancer Lett.* **2005**, 223, 181-190.
18. P. Anand, C. Sundaram, S. Jhurani, A.B. Kunnumakkara, B.B. Aggarwal. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett*. **2008**, 267, 133-164.
19. G. Bar-Sela, R. Epelbaum, M. Schaffer. Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. *Curr Med Chem*. **2010**, 17, 190-197.
20. J. Ravindran, S. Prasad, B.B. Aggarwal. Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? *AAPS J*. **2009**, 11, 495-510.
21. P. Ruenraroengsak, J.M. Cook, A.T. Florence. Nanosystem drug targeting: facing up to complex realities. *J Control Release* **2010**, 141, 265-276.
22. P. Anand, H.B. Nair, B. Sung, A.B. Kunnumakkara, V.K. Yadav, R.R. Tekmal, B.B. Aggarwal . Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo. *Biochem. Pharmacol*. **2010**, 79, 330-338.
23. H.A. Vogel, J. Pelletier. Curcumin-biological and medicinal properties. *J Pharmacol* **1815**, 2, 50-50.
24. R. Sharma, A. Gescher, W. Steward. Curcumin: the story so far. *Eur J Cancer*. **2005**, 41, 1955-1968.
25. O. Naksuriya, O.S. Okonogi, R.M. Schiffelers, W.E. Hennink. Curcumin nanoformulations: a review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. *Biomaterials* **2014**, 35, 3365-3383.
26. J. Fang, J. Lu, A. Holmgren. Thioredoxin reductase is irreversibly modified by curcumin: a novel molecular mechanism for its anticancer activity. *J. Biol. Chem.* **2005**, 280(26), 25284-25290.
27. B.T. Kurien, A. Singh, H. Matsumoto, R.H. Scofield. Improving the solubility and pharmacological efficacy of curcumin by heat treatment. Assay Drug Dev Tech. **2007,** 5, 567-576.
28. H.H. Tønnesen, M. Másson, T. Loftsson. Studies of curcumin and curcuminoids. XXVII. Cyclodextrin complexation: solubility, chemical and photochemical stability. *Int J Pharm*. **2002**, 244, 127-135.
29. Y.J. Wang, .M.H. Pan ,A.L. Cheng, L.I. Lin, Y.S. Ho, C.Y. Hsieh . Stability of curcumin in buffer solutions and characterization of its degradation products. *J Pharm Biomed* **1997,** 15, 1867-1876.
30. B. Meng, J. Li, H. Cao. Antioxidant and anti-inflammatory activities of curcumin on diabetes mellitus and its complications. *Curr. Pharm. Des*. **2013**, 19, 2101-2113.
31. C. Mohanty, M. Das, S. Sahoo. Sustained wound healing activity of curcumin loaded oleic acid based polymeric bandage in a rat model. *Mol. Pharmacol*. **2012**, 9, 2801-2811.
32. B. Joe, M. Vijaykumar, B. Lokesh. Biological properties of curcumin - cellular and molecular mechanisms of action. *Crit. Rev. Food Sci. Nutr*. **2004**, 44, 97-111.
33. G. Liang, S Yang, H. Zhou, L. Shao, K. Huang, J. Xiao. Synthesis, crystal structure and anti-inflammatory properties of curcumin analogues. *Eur. J. Med. Chem*. **2009**, 44, 915-919.
34. S.H. Mun, D.K. Joung, Y.S. Kim, O.H. Kang, S.B. Kim, Y.S. Seo. Synergistic antibacterial effect of curcumin against methicillin-resistant Staphylococcus aureus. *Phytomedicine* **2013**, 20, 714-718.
35. S.C. Gupta, S. Prasad, J.H. Kim, S. Patchva, L.J. Webb, I.K. Priyadarsini, B.B. Aggarwal. Multitargeting by curcumin as revealed by molecular interaction studies. *Nat. Prod. Rep*. **2011**, 28, 1937-1955.
36. N. Mathuria, R. Verma. Effect of curcumin on rat sperm morphology after the freeze-thawing process. *Acta Pol. Pharm*. **2007**, 63, 413-416.
37. R. Hemeida, O. Mohafez. Curcumin attenuates methotraxate-induced hepatic oxidative damage in rats. *J. Egypt. Natl. Cancer Inst*. **2008 ,** 20, 141-148.
38. H. Farghaly, M. Hussein. Protective Effect of Curcumin Against Paracetamol-induced Liver Damage. *Aust. J. Basic Appl. Sci*. **2010**, 4, 4266-4274.
39. S. Priya, P. Sudhakaran. Curcumin-induced recovery from hepatic injury involves induction of apoptosis of activated hepatic stellate cells. *Indian J. Biochem. Biophys*. **2008**, 45, 317-325.
40. U. Subudhi, K. Das, B. Paital, S. Bhanja, G. Chainy. Alleviation of enhanced oxidative stress and oxygen consumption of L-thyroxine induced hyperthyroid rat liver mitochondria by vitamin E and curcumin. *Chem. Biol. Interact*. **2008**, 173, 105-114.
41. A. Noorafshan, S.A. Esfahani. A review of therapeutic effects of curcumin. *Curr. Pharm. Des*. **2013**, 19, 20.
42. A. Karewicz, D. Bielska, B. Gzyl-Malcher, M. Kepczyn, R. Lach, M. Nowakowska. Interaction of curcumin with lipid monolayers and liposomal bilayers. *Colloid Surf B.* **2011**, 88, 231-239.
43. M. Sun, X. Su, B. Ding, X. He, X. Liu, A. Yu. Advances in nanotechnology-based delivery systems for curcumin. *Nanomedicine UK* **2012**, 7, 1085-1100.
44. K. Kataoka, A. Harada, Y. Nagasaki. Block copolymer micelles for drug delivery: design, characterization and biological significance. *Adv Drug Deliv Rev.* **2001**, 47, 113-131.
45. R. Kumar, M. Sharma. Herbal nanomedicine interactions to enhance pharmacokinetics, pharmaco-dynamics, and therapeutic index for better bioavailability and biocompatibility of herbal formulations. *J. Mater. Nanosci.* **2018**, 5 (1), 35–58.
46. G. Gaucher, P. Satturwar, M.C. Jones, A. Furtos, J.C. Leroux. Polymeric micelles for oral drug delivery. *Eur J Pharm Biopharm* **2010**, 76,147-158.
47. C. Oerlemans, W. Bult, M. Bos, G. Storm, J.F.W. Nijsen, W.E. Hennink. Polymeric micelles in anticancer therapy: targeting, imaging and triggered release. *Pharm Res.* **2010**, 27, 2569-2589.
48. B.S. Chhikara. Prospects of Applied Nanomedicine. *J. Mater. Nanosci.* **2016**, 3 (1), 20–21..

49. Y. Matsumura, K. Kataoka. Preclinical and clinical studies of anticancer agent-incorporating polymer micelles. *Cancer Sci.* **2009**, 100, 572-579.
50. C. Deng, Y. Jiang, R. Cheng, F. Meng, Z. Zhong. Biodegradable polymeric micelles for targeted and controlled anticancer drug delivery: promises, progress and prospects. *Nano Today* **2012**, 7, 467-480.
51. Y. Lu, K. Park. Polymeric micelles and alternative nanonized delivery vehicles for poorly soluble drugs. *Int J Pharm.* **2013**, 453, 198-214.
52. K. Parvathy , P. Negi , P. Srinivas . Curcumin-amino acid conjugates: synthesis, antioxidant and antimutagenic attributes. *Food Chem* **2010**, 120, 523-530.
53. F. Kratz. Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles. *J Control Release* 2008, 132, 171-183.
54. V.R. Yadav, S. Prasad, R. Kannappan, J. Ravindran, M.M. Chaturvedi, L. Vaahtera. Cyclodextrin-complexed curcumin exhibits anti-inflammatory and antiproliferative activities superior to those of curcumin through higher cellular uptake. *BiochemPharmacol* **2010**, 80, 1021-1032.
55. M.A. Alam, R. Ali, F.I. Al-Jenoobi, A.M. Al-Mohizea. Solid dispersions: a strategy for poorly aqueous soluble drugs and technology updates. *Expert Opin Drug Del*. **2012**, 9, 1419-1440.
56. D. Napierska, L.C.Thomassen, D. Lison, J.A. Martens, P.H. Hoet. The nanosilica hazard: another variable entity. *FibreToxicol*. **2010**, 7, 39.
57. T. Suteewong, H. Sai, J. Lee, M. Bradbury, T. Hyeon, S.M. Gruner, U. Wiesner. Ordered mesoporous silica nanoparticles with and without embedded iron oxide nanoparticles: structure evolution during synthesis *J. Mater. Chem*. **2010**, 20, 7807–7814.
58. V. Polshettiwar, V.D. Cha, X. Zhang, J.M. Basset. High-Surface-Area Silica Nanospheres (KCC-1) with a Fibrous Morphology. *Angew. Chem., Int. Ed*., **2010**, 49, 9652–9656.
59. N. Linares, E. Serrano, M. Rico, A.M. Balu, E. Losada, R. Luque, J. Garcia-Martinez. Incorporation of chemical functionalities in the framework of mesoporous silica. *Chem. Commun*. **2011**, 47, 9024–9035.
60. M. Fuji, C. Takai, Y. Tarutani, T. Takei, M. Takahashi. Surface properties of nanosize hollow silica particle on a molecular level. *Adv. Powder Technol*. **2007**, 18(1), 81–91.
61. J. Hu, X. Wang, L. Liu, L. Wu. A facile and general fabrication method for organic silica hollow spheres and their excellent adsorption properties for heavy metal ions. *J. Mater. Chem,* **2014**, A, 19771–19777.
62. Y. Yin, M. Chen, S. Zhou, L. Wu. A general and feasible method for the fabrication of functional nanoparticles in mesoporous silica hollow composite spheres. *J. Mater. Chem*. **2012,** 22, 11245–11251.
63. M. Sasidharan, D. Liu, N. Gunawardhana, M.Yoshio, K.Nakashima. Synthesis, characterization and application for lithium-ion rechargeable batteries of hollow silica nanospheres. *J. Mater. Chem*. **2011**, 21, 13881–13888.
64. Q. Yue, Y. Li, M. Kong , J. Huang, X. Zhao, J. Liu , F.R. Willifor. Ultralow density, hollow silica foams produced through interfacial reaction and their exceptional properties for environmental and energy applications. *J. Mater. Chem*. **2011**, 21, 12041–12046.
65. M. Fuji, C. Takai, H. Watanabe, K. Fujimoto. Improved transparent thermal insulation using nano-spaces. *Adv. Powder Technol.* **2011**, 26 (3), 857–860.
66. Y. Liaoa, X. Wu, H. Liu, Y. Chen. Thermal conductivity of powder silica hollow spheres. *Thermochim. Acta* **2011**, 526(1–2), 178–184.
67. Y. Du, E.L. Luna, W. STan, F.M. Rubner, E.R. Cohen. Hollow silica nanoparticles in UV-visible antireflection coatings for poly (methyl methacrylate) substrates. *ACS Nano*. **2011,** 4(7), 4308–4316.
68. R.K. Jain, T. Stylianopoulos .Nat. Rev. Clin, Delivering nanomedicine to solid tumors. *Oncol*. **2010**, 7(11), 653-664.
69. P. Mittal, S. Singh, A. Singh, I.K. Singh. Current advances in drug delivery systems for treatment of Triple negative breast cancer (TNBC). *Chem. Biol. Lett.* **2020**, 7(1), 1–12.
70. S.S. Malapure, S. Bhushan, R. Kumar, S. Bharati. Radiolabelled nanoparticles in cancer management: current status and developments. *Chem. Biol. Lett.* **2018**, 5 (1), 25–34.
71. K.J. Klabunde, J. Stark, Koper. Nanocrystals as stoichiometric reagents with unique surface chemistry. *The Journal of Physical Chemistry* **1996**,100, 12142–12153.
72. L.L. Hench, J.K. West. The Sol-Gel process. *Chemical Reviews* **1990**, 90, 33–72.
73. W. Stöber, A. Fink, E. Bohn. Controlled growth of monodisperse silica spheres in the micron size range. *J. Colloid Interface Sci.,* **1968**, 26, 62–69.
74. G.H. Bogush, M.A. Tracy, C.F. Zukoski. Preparation of monodisperse silica particles: control of size and mass fraction. *J. Non-Crystalline Solids* **1988,** 104, 95–106.
75. J. Singh, S. Kumar, B. Rathi, K. Bhrara, B.S. Chhikara. Therapeutic analysis of *Terminalia arjuna* plant extracts in combinations with different metal nanoparticles. *J. Mater. Nanosci.* **2015**, 2 (1), 1–7..
76. G.H. Bogush, C.F. Zukoski. Studies of the kinetics of the precipitation of uniform silica particles through the hydrolysis and condensation of silicon alkoxides. *J. Colloid Interface Sci.* **1991**, 142(1), 19–34.
77. S.K. Park, K.D. Kim , H.T. Kim . Preparation of silica nanoparticles: determination of the optimal synthesis conditions for small and uniform particles. *Colloids and Surfaces A* **2002**, 197, 7–17.
78. J.K. Bailey, M.L. Mecartney . Formation of colloidal silica particles from alkoxides. *Colloids and Surfaces* **1992**, 63(1- 2), 151–161.
79. K. Lee , A.N. Sathyagal, A.V. McCormick . A closer look at an aggregation model of the Stober process . *Colloids and Surfaces A* **1998**, 144, 115–125.
80. D.L. Green , J.S. Lin ,Y.F. Lam , M.Z.C. M. Hu, D.W. Schaefer , M.T. Harris. Size, volume fraction, and nucleation of Stober silica nanoparticles. *Journal of Colloid and Interface Science* 2003, 266, 346–358.
81. I.A. Rahman, P. Vejayakumaran , Sipaut . An optimized sol-gel synthesis of stable primary equivalent silica particles. *Colloids and Surfaces A* **2007**, 294, 102–110.
82. K.S. Rao, K. El-Hami , T. Kodaki , K. Matsushige , K. Makino . A novel method for synthesis of silica nanoparticles. *Journal of Colloid and Interface Science* **2005**, 289, 125– 131.
83. I.A. Rahman, P. Vejayakumaran, Sipaut. Effect of anion electrolytes on the formation of silica nanoparticles via the sol-gel process. *Ceramics International* **2006**, 32, 691–699.
84. M. Jafarzadeh, I.A. Rahman, C.S. Sipaut. Synthesis of silica nanoparticles by modified sol-gel process: the effect of mixing modes of the reactants and drying techniques. *Journal of Sol-Gel Science and Technology* **2009**, 50, 328–336.
85. I.A. Rahman, P. Vejayakumaran, C.S. Sipaut, J. Ismail, C.K. Chee. Effect of the drying techniques on the morphology of silica nanoparticles synthesized via sol-gel process. *Ceramics International* **2008,** 34, 2059–2066.
86. B.G. Trewyn, I.I Slowing, S. Giri, H.T. Chen, V.S. Lin. Synthesis and Functionalization of a Mesoporous Silica Nanoparticle Based on the Sol−Gel Process and Applications in Controlled Release. *Acc. Chem. Res*. **2007**, 40, 846−853.
87. B.G. Trewyn,, J.A. Nieweg, Y. Zhao, V.S.Y. Lin. Biocompatible mesoporous silica nanoparticles with different morphologies for animal cell membrane penetration. *Chem. Eng. J*. **2008,** 137, 23−29.
88. A. Mukerjee , J.K. Vishwanatha. Formulation, Characterization and Evaluation of Curcumin-loaded PLGA Nanospheres for Cancer Therapy. *Anticancer Research* **2009** , 29, 3867-3876.
89. N.W. Cliffordn, K.S. Iyer, C.L. Raston. Encapsulation and controlled release of nutraceuticals using mesoporous silica capsules. *J. Mater. Chem*. **2008 ,** 18, 162-165.
90. S.F. Chin, K.S. Iyer, M. Saunders, T.G. St. Pierre, C.Buckley, M. Paskevicius, C.L. Raston. Encapsulation and Sustained Release of Curcumin using Superparamagnetic Silica Reservoirs. *Chem. Eur. J*. **2009,** 15, 5661 – 5665.
91. D. Jin , K.W. Park , J.H. Lee , K.Song , J.G. Kim , M.L. Seo, J.H.Jung . The selective immobilization of curcumin onto the internal surface of mesoporous hollow silica particles by covalent bonding and its controlled release. *J. Mater. Chem* **2011**, 21, 3641-3645.
92. D. Patra, F. Sleem. A new method for pH triggered curcumin release by applying poly (l-lysine) mediated nanoparticle-congregation. *Analytica chimica Acta* **2013,** 795, 60-68.
93. D. Patra, A.J. Amali, R.K. Rana. Preparation and photophysics of HPTS-based nanoparticle-assembled microcapsules. *J. Mater.Chem.***2009,** 19, 4017–4021.

94. A.J. Amali, N. Rangaraj, D. Patra, R.K. Rana. Pyranine-3 in poly(l-lysine)-mediated nanoparticle – assembled microcapsules: its pH sensitive release while acting as a ratiometric optical pH sensor. *Chem. Commun*. **2012**, 48, 856–858.
95. F. Hamam, M. Al-Remawi. Novel delivery system of curcumin through transdermal route using sub-micronized particles composed of mesoporous silica and oleic acid. *J. Functional Foods* **2014**, 8(1), 87–99.
96. S. Kim, M.J. Ste´be, J.L. Blin, A.Pasc. pH-controlled delivery of curcumin from a compartmentalized solid lipid nanoparticle@ mesostructured silica matrix. *J. Mater. Chem. B* **2014,** 2, 7910-7917.
97. K. Radhakrishnan, J. Tripathy, A. Datey, D. Chakravortty, A.M. Raichur. Mesoporous silica–chondroitin sulphate hybrid nanoparticles for targeted and bio-responsive drug delivery. *New J. Chem*. **2015**, 39, 1754-1760.
98. X. Xu , S. Lü, C. Gao , X. Wang , X. Bai , H. Duan , N. Gao , C. Feng , M. Liu . Polymeric micelle-coated mesoporous silica anoparticle for enhanced fluorescent imaging and pH-responsive drug delivery. *Chemical Engineering Journal* **2015**, 279, 851-860.
99. X. Xu, S. Lü, C. Gao , C. Feng , C. Wu, X. Bai , N. Gao , Z. Wang , M. Liu . Self-fluorescent and stimuli-responsive mesoporous silica nanoparticles using a double-role curcumin gatekeeper for drug delivery. *Chemical Engineering Journal* **2016**,300, 185–192.
100. K.A. Dinda , K.C. Prashant ,S. Naqvi , J. Unnithan , M. Samim , A. Maitra . Curcumin loaded organically modified silica (ORMOSIL) nanoparticle; a novel agent for cancer therapy. *Intl. Journal of Nanotech*. **2012**, 9, 862-871.
101. D.J. Bharali, I. Klejbor, E.K. Stachowiak, P. Dutta, I. Roy, N. Kaur, E.J. Bergey, P.N. Prasad, M.K. Stachowiak. Organically modified silica nanoparticles: a nonviral vector for in vivo gene delivery and expression in the brain. *Proc. Natl. Acad. Sci.* **2005**, 102, 11539–11544.
102. R.K. Gangwar, G.B. Tomar, V.A. Dhumale, S. Zinjarde, R.B. Sharma, S. Datar. Curcumin Conjugated Silica Nanoparticles for Improving Bioavailability and Its Anticancer Applications. *J. Agricultural Food Chem.* **2013**, 61(40), 9632-9637.
103. V.S. Bollu, A.V.Barui, S.K. Mondal, S. Prashar, M. Fajardo, D. Briones, A. Rodriguez-Dieguez , C.R. Patra ,S.G. Ruiz. Curcumin loadedsilica-based mesoporous materials: Synthesis, characterization and cytotoxic properties against cancer cells. *Materials Science and Engineering: C.* **2016**, 63, 393-410.
104. D. Perez-Quintanilla, A. Sanchez, I. delHierro, M. Fajardo, I. Sierr. Synthesis and characterization of novelmesoporous silicas of the MSU-X family for environmental applications. *J. Nanosci. Nanotechnol*. **2009**, 9, 4901–4909.
105. M.P. Daryasari, M.R. Akhgar, F. Mamashli, B. Bigdeli, M. Khoobi. Chitosan-folate coated mesoporous silica nanoparticles as a smart and pH-sensitive system for curcumin delivery. *RSC Adv*. **2016**, 6, 105578–105588.
106. K. Sanghoon, D. Roudayna, J. Olivier, C. Nadia, P. Andreea. Core–shell microcapsules of solid lipid nanoparticles and mesoporous silica for enhanced oral delivery of curcumin. *Colloids and Surfaces B: Biointerfaces* **2016**, 140, 161–168.
107. L. Dejian, N.Wei, C. Liang,Y. Miao,X. Zhang,F. Chen, Y. Bin, A. Rongguang ,Y. Bioking. Fabrication of curcumin-loaded mesoporous silica incorporated polyvinyl pyrrolidone nanofibers for rapid hemostasis and antibacterial treatment. *RSC Adv.* 2107,3, 7973-7982.
108. V.J. Mohanraj, Y. Chen , Nanoparticles - A Review. *J. Pharm. Res.* 2006, 5, 561 –573.
109. N. Kamaly , Z. Xiao, P.M. Valencia , A.F. Radovic-Moreno , O.C..Farokhzad . Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. Chem. *Soc. Rev*. 2012, 41, 2971 – 3010.
110. X.H. Xia , M.X. Yang ,Y.C. Wang , Y.Q. Zheng , Q.G. Li , J.Y. Chen, Y. Xia . Quantifying the Coverage Density of Poly (ethylene glycol) Chains on the Surface of Gold Nanostructures. *ACS Nano* 2012, 6, 512 – 522.
111. D.N. DeAssis, V.C. Mosqueira, J.M. Vilela, M.S. Andrade, V.N. Cardoso. Release profiles and morphological characterization by atomic force microscopy and photon correlation spectroscopy of 99m Technetium – fluconazole nanocapsules. *Int J Pharm*. **2008**, 349, 152 – 160.
112. A.Z. Muhlen, E.Z. Muhlen, H. Niehus, W. Mehnert. Atomic force microscopy studies of solid lipid nanoparticles. *Pharm Res.* **1996**, 13, 1411-1416.
113. S.P. Singh, M. Sharma, P.K. Gupta. Cytotoxicity of curcumin silica nanoparticle complexes conjugated with hyaluronic acid on colon cancer cells. *Int. J. Biological Macromolecules* **2015**, 74, 162-170.
114. J. Molpeceres, M.R. Aberturas, M. Guzman. Biodegradable nanoparticles as a delivery system for cyclosporine: preparation and characterization. *J Microencapsul*. **2000**, 17, 599-614.
115. I. Roy, A. Anuradha. Synthesis and characterization of iron phosphate NPs and applications in magnetically guided drug delivery. *J. Mater. Nanosci.* **2016**, 3 (1), 1–7.
116. M.Q. Zhang, M.Z. Rong, H.M. Zeng, S. Schmitt, B. Wetzel, K.J. Friedrich. Atomic force microscopy study on structure and properties of irradiation grafted silica particles in polypropylene-based nanocomposites *Appl. Polym. Sci.* **2001**, 80, 2218–2227.
117. R.H.Y. Chang, J. Jang, K.C. W. Wu . Cellulase immobilized mesoporous silica nanocatalysts for efficient cellulose-to-glucose conversion. *Green Chem*. **2011**, 13, 2844–2850.
118. S. Jambhrunkar , Z. Qu , A. Popat . Effect of Surface Functionality of Silica Nanoparticles on Cellular Uptake and Cytotoxicity. *Mol Pharmaceutics* **2014**, 11, 3642-3655.
119. K. Yang, Y.Q. Ma. Computer simulation of the translocation of nanoparticles with different shapes across a lipid bilayer. *Nat. Nanotechnol*. 2010, 5, 579–583
120. P.D. Scholes, A.G. Coombes, L. Illum, S.S. Davis, J.F. Wats, C. Ustariz, M. Vert, M.C. Davies . Detection and determination of surface levels of poloxamer and PVA surfactant on biodegradable nanospheres using SSIMS and XPS. *J control Release*. **1999**, 59, 261-278.
121. P. Couvreur, G. Barratt, E. Fattal, P. Legrand, C. Vauthie . Nanocapsule technology: A review. *Drug Carrier Syst*. **2002**, 19, 99–134.
122. A.E. Nel, L. Madler, D. Velegol, T. Xia, E.M.V. Hoek, P. Somasundaran, F. Klaessig, V. Castranova, M. Thompson. Understanding biophysicochemical interactions at the nano-bio interface. *Nat. Mater*. **2009**, 8, 543-547.
123. A. Verma, F. Stellacci. Effect of surface properties on nanoparticle-cell interactions. *Small* **2010**, 6, 12-21.
124. Z. Pangi, A. Beletsi, K. Evangelatos. PEG-ylated nanoparticles for biological and pharmaceutical application. *Adv. Drug Del Rev.* **2003**, 24, 403-419.
125. C. Mohanty, S.K. Sahoo. The in vitro stability and in vivo pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation. *Biomaterials* **2010**, 31, 6597-6611.
126. B. Magenhein, M.Y. Levy, S. Benita. A new in vitro technique for the evaluation of drug release profile from colloidal carrier's ultrafiltration technique at low pressure. *Int. J. Pharm*. **1993**, 94, 115-123.
127 L. Jiahao, C. Qiang, T. Yinian. PEGylated Lipid bilayer coated mesoporous silica nanoparticles for codelivery of paclitaxel and curcumin: Design, characterization and its cytotoxic effect. *International Journal of Pharmaceutics* 2018, 536, 272–282.
128. W.K. Oh, S. Kim, M. Choi , C. Kim, Y.S. Jeong, B.R. Cho, J.S. Hahn, J. Jang. Cellular uptake cytotoxicity, and innate immune response of silica–titania hollow nanoparticles based on size and surface functionality. *ACS Nano* 2010, 4, 5301-5313.
129. H.H. Yuan, F. Gao, Z.G. Zhang, L.D. Miao, R.H. Yu, H.L. Zhao, M.B. Lan. Study on Controllable Preparation of Silica Nanoparticles with Multi-sizes and Their Size-dependent Cytotoxicity in Pheochromocytoma Cells and Human Embryonic Kidney Cells. *J. Health Sci*. 2010, 56, 632-640.
130. Y.Y. Zhang, L. Hu, D.H. Yu, C.Y. Gao. Influence of silica particle internalization on adhesion and migration of human dermal fibroblasts. *Biomaterials* **2010**, 31, 8465-8474.
131. K.O. Yu, C.M. Grabinski, A.M. Schrand, R.C. Murdock, W. Wang, B.H. Gu, J.J. Schlager, S.M. Hussain. Toxicity of amorphous silica nanoparticles in mouse keratinocytes. *Nanopart. Res*. **2009**, 11, 15-24.
132. M.V.D.Z. Park , W. Annema , A. Salvati, A. Lesniak , A. Elsaesser , C. Barnes , G. McKerr, C.V. Howard , I. Lynch , K.A. Dawson , A.H. Piersma , W.H. de Jon. In vitro developmental toxicity test detects inhibition of stem

cell differentiation by silica nanoparticles. *Toxicol. Appl. Pharmacol*. **2009**, 240, 108-116.
133. S. Quignard , G. Mosser , M. Boissiere , T. Coradin . Long-term fate of silica nanoparticles interacting with human dermal fibroblasts. *Biomaterials* **2012**, 33, 4431-4442.
134. I. Passagne , M. Morille , M. Rousset , I. Pujalte , B. L'Azou . Implication of oxidative stress in size-dependent toxicity of silica nanoparticles in kidney cells. *Toxicology* **2012**, 299, 112-124.
135. F. Lu , S.H. Wu , Y. Hung , C.Y. Mou . Size effect on cell uptake in well-suspended, uniform mesoporous silica nanoparticles. *Small* **2009**, 5, 1408-1413.
136. B.D. Chithrani , A.A. Ghazani , W.C.W. Chan . Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. *Nano Lett*. **2006**, 6, 662-668.
137. F. Osaki , T. Kanamori , S. Sando , T. Sera , Y. Aoyama. A quantum dot conjugated sugar ball and its cellular uptake on the size effects of endocytosis in the subviral region. *J. Am. Chem. Soc*. **2004**, 126, 6520-6521.
138. Q.J. He , Z.W. Zhang , F. Gao , Y.P. Li ,J.L. Shi . In vivo Biodistribution and Urinary Excretion of Mesoporous Silica Nanoparticles: Effects of Particle Size and PEGylation. *Small* **2011**, 7, 271-280.
139. Y.S. Lin , C.L. Haynes . Impacts of mesoporous silica nanoparticle size, pore ordering, and pore integrity on hemolytic activity. *J. Am. Chem. Soc*. **2010**, 132, 4834-4842.
140. T. Yu , A. Malugin, H. Ghandehari . Impact of silica nanoparticle design on cellular toxicity and hemolytic activity. *ACS Nano* **2011**, 5, 5717-5728.
141. A.J. Nan , X. Bai , S.J. Son , S.B. Lee , H. Ghandehari. Cellular Uptake and Cytotoxicity of Silica Nanotubes. *Nano Lett*. **2008**, 2150-2154.
142. T. Morishige, Y. Yoshioka , H. Inakura , A. Tanabe, X.L. Yao ,S. Narimatsu , Y. Monobe , T. Imazawa , S. Tsunoda , Y. Tsut- sumi , Y. Mukai , N. Okada , S. Nakagawa .The effect of surface modification of amorphous silica particles on NLRP3 inflammasome mediated IL-1β production, ROS production and endosomal rupture. *Biomaterials* **2010**, 31, 6833-6842.
143. J.S. Chang, K.L.B. Chang, D.F. Hwang , Z.L. Kong . In vitro cytotoxicitiy of silica nanoparticles at high concentrations strongly depends on the metabolic activity type of the cell line. *Environ. Sci. Technol.* **2007**, 41, 2064-2068.
144. S.C. Brown, M. Kamal, N. Nasreen , A. Baumuratov, P. Sharma, V.B. Antony , B.M. Moudgil . Influence of shape, adhesion and simulated lung mechanics on amorphous silica nanoparticle toxicity. *Adv. Powder Technol*. **2007**, 18, 69-79.
145. F.M. Veronese, G. Pasut . PEGylation, Successful Approach to Drug Delivery. *Drug Discov. Today* **2005**, 10, 1451-1458.
146. H.L. Herd, A. Malugin , H. Ghandehari . Silica nanoconstruct cellular toleration threshold in vitro. *J. Controlled Release* **2011**, 153, 40-48.
147. V. Rabolli , L.C.J. Thomassen , C. Princen , D. Napierska , L. Gonzalez , M. Kirsch-Volders , P.H. Hoet , F. Huaux , C.E.A. Kirschhock , J.A. Martens , D. Lison . Influence of size, surface area and microporosity on the in vitro cytotoxic activity of amorphous silica nanoparticles in different cell types. *Nanotoxicology* **2010**, 4, 307-318.
148. L. Ma'mani, S. Nikzad, H. Kheiri-manjili, S. al-Musawi, M. Saeedi, S. Askarlou, A. Foroumadi, A. Shafiee. Curcumin-loaded guanidine functionalized PEGylated I3ad mesoporous silica nanoparticles KIT-6: Practical strategy for the breast cancer therapy. *European Journal of Medicinal Chemistry* **2014**, 83, 646-654.
149. C. Chen, W. Sun , X. Wang , Y. Wang , P. Wang. Rational design of curcumin loaded multifunctional mesoporous silica nanoparticles to enhance the cytotoxicity for targeted and controlled drug release. *Materials Science & Engineering C* **2018**, 85, 88–96.
150. J. Wang , Y. Wang , Q. Liu , L. Yang , R. Zhu , C. Yu , S. Wang . Rational Design of Multifunctional Dendritic Mesoporous Silica Nanoparticles to Load Curcumin and Enhance Efficacy for Breast Cancer Therapy. *ACS Applied Materials and Interfaces* **2016**, 8, 26511−26523.
151. S. Singh , B.B. Agarwal . Activation of transcription factor NF-κB is suppressed by curcumin (diferulolymethane). *J. Bio Chem* **1995**, 270(42), 24995-25000.
152. A.S. Jaiswal , B.P. Marlow , N. Gupta S. Narayan . Beta-cateninmediated transactivation and cell-cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells. *Oncogene* **2002**, 21, 8414-8427.
153. K. Balasubramanyam , R.A. Varier , M. Altaf , V. Swaminathan , N.B. Siddappa , U. Ranga , T.K. Kundu . Curcumin, a novel P300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/non-histone proteins and histone acetyltransferase-dependent chromatin transcription. *J Biol Chem* **2004**, 279, 51163-51171.
154. K. Radhakrishnan , S. Gupta , D.P. Gnanadhas , P.C. Ramamurthy , D. Chakravortty, A.M. Raichur. Protamine-Capped Mesoporous Silica Nanoparticles for Biologically Triggered Drug Release. *Particle and Particle Systems Charact*. **2014**, 31, 449–458.
155. L.F. de Oliveira, K. Bouchmella, K. DeA. Gonçalves, J. Bettini, J. Kobarg, M.B. Cardoso. Functionalized Silica Nanoparticles as an Alternative Platform for Targeted Drug-Delivery of Water Insoluble Drugs. *Langmuir* **2016**, 32(13), 3217–3225.
156. P. Huang , B. Zeng, Z. Mai , J. Deng , Y. Fang , W. Huang , H. Zhang, J. Yuan, Y. Wei, W. Zhou. Novel drug delivery nanosystems based on out-inside bifunctionalized mesoporous silica yolk–shell magnetic nanostars used as nanocarriers for curcumin. *J. Mater. Chem. B* **2016**, 4, 46—56.
157. L.F.de Oliveira, K. Bouchmella, A.S. Picco, L.B. Capeletti, K.A. Gonçalves, J.H.Z. dos Santos, J. Kobarg, M.B. Cardoso. Tailored Silica Nanoparticles Surface to Increase Drug Load and Enhance Bactericidal Response. *J. Braz. Chem. Soc*. **2017**, 28(9), 1715-1724.
158. N. Taebnia , D. Morshedi , S. Yaghmaei , F. Aliakbari , F. Rahimi , A. Arpanaei . Curcumin-Loaded Amine-Functionalized Mesoporous Silica Nanoparticles Inhibit α-Synuclein Fibrillation and Reduce Its Cytotoxicity-Associated Effects. *Langmuir* **2016**, 32, 13394−13402.
159. X. Sun, Y. Luo , L. Huang ,B. Yu , J. Tian . A peptide-decorated and curcumin-loaded mesoporous silica nanomedicine for effectively overcoming multidrug resistance in cancer cells. *RSC Adv*. **2017**, 7, 16401-16409.
160. S.P. Singh, M. Sharma, P.K. Gupta . Evaluation of Phototoxic Effects of Curcumin Loaded in Organically Modified Silica Nanoparticles in Tumor Spheroids of Oral Cancer Cells . *BioNanoSci*. **2015**; 5:10–21
161. X. Xu , S. Lü, C. Wu, Z. Wang, C. Feng, N. Wen, M. Liu, X. Zhang, Z. Liu, Y. Liu, C.Ren. Curcumin polymer coated, self-fluorescent and stimuli-responsive multifunctional mesoporous silica nanoparticles for drug delivery, *Microporous and Mesoporous Materials* **2018**, 271, 234-242.
162. C.S. Cheng,T.P. Liu,F.C. Chien,C.Y. Mou ,S.W. Wu ,Y.P Chen. Co-delivery of Plasmid and Curcumin with Mesoporous Silica Nanoparticles for Promoting Neurite Outgrowth, *ACS Appl. Mater. Interfaces* **2019**, 11, 17, 15322-15331.
163. N.A. Nasab, H. H. Kumleh ,M. Beygzadeh, S. Teimourian , M. Kazemzad , Delivery of curcumin by a pH-responsive chitosan mesoporous silica nanoparticles for cancer treatment, *Artificial Cells, Nanomedicine, Nanomedicine and Biotechnology* **2018**, 46(1), 75-81.
164. L. Hadisoewignyo , S..B. Hartono, A. Kresnamurti, I. Soeliono , Y. Nataline, G.A. Prakoso , D.A.R. E.AuliaEvaluation of anti-inflammatory activity and biocompatibility of curcumin loaded mesoporous silica nanoparticles as an oral drug delivery system, *Advances in Natural Sciences: Nanoscience and Nanotechnology* **2018** 9(3) 035007.
165. J. Lin, Q.Cai, Y. Tang, Y. Xu, Q. Wang, T. Li, H. Xu, S. Wang, K. Fan, Z.Liu, Y. Jin, D. Lin. PEGylated Lipid bilayer coated mesoporous silica nanoparticles for co-delivery of paclitaxel and curcumin: Design, characterization and its cytotoxic effect, *International Journal of Pharmaceutics* **2018**, 536(1), 272-282.
166. G. Bhakta, R.K. Sharma, N. Gupta, S. Cool, V. Nurcombe, A. Maitra. Multifunctional silica nanoparticles with potentials of imaging and gene delivery. *Nanomedicine: Nanotechnology, Biology, and Medicine* **2011**, 7, 472–479.
167. R.K. Sharma, N. Gupta, A. Shrivastava. Silica nanoparticles coencapsulating gadolinium oxide and horseradish peroxidase for imaging and therapeutic applications. *Int. J. Nanomedicine* **2012**, 7, 5491-5500.

AUTHORS BIOGRAPHIES

Dr. Parul Pant is currently teaching Chemistry in Hansraj College, University of Delhi. Her research areas of expertise include Inorganic, Analytical and Green Chemistry. She has co-authored books on environmental Studies. She has published many research papers in international journals of repute. Dr. Pant is a Life member of Green Chemistry Network Centre and Indian Chemical Society.

Dr. Chetna Gupta has been teaching Chemistry in Hansraj College, University of Delhi since 2009. Her research interests are in the broad area of Green Chemistry where she focuses on the therapeutic applications of drug doped silica nanoparticles. She has published various research papers in renowned national and international journals. She is the lifetime member of Green Chemistry Network Centre and Indian Society of Analytical Scientists.

Sagar Kumar received his bachelor's degree in Science from Hansraj College, Delhi University in 2017. He is current pursuing Integrated Masters-PhD course in Department of Inorganic & Physical Chemistry, Division of Chemical Sciences, Indian Institute of Science. He is currently working in the field of Chemical Biology and Bioinorganic Chemistry exploring the working of metalloenzymes involved in Endothelial Dysfunction.

Aishwarya Rai, completed her graduation in B.Sc. (hons) Chemistry from Hansraj College, University of Delhi. She has worked as research intern in a project related to Curcumin loaded Silica Nanoparticles.

Shivani has done her graduation and post Graduation in Chemistry from Hansraj College, University of Delhi. She has worked as research intern in a project related to Curcumin loaded Silica Nanoparticles.

Apoorva has done BSc(H) in Chemistry from Hansraj College, University of Delhi. She has worked as research intern in a project related to Curcumin loaded Silica Nanoparticles. Her research interests include inorganic and green Chemistry.