1. INTRODUCTION

Cancer, a lethal disease, is the result of uncontrolled growth of the cells and it appears from the extra mass tissue known as tumor.[1] With 8.8 million deaths reported in 2015, cancer still remains a leading cause of death worldwide. Globally, cancer accounts for almost 1 death in 6.[2] Metastases of cancer are associated with a vast majority of morbidity and mortality in cancer patients and is associated with about 90% of all cancer-associated deaths.[3] Among cancers, breast cancer is the most prevalent malignant disease affecting women worldwide.[4] Breast cancer comprised of nearly a quarter (25%) of all cancers with an estimated 1.7 million new cancer cases diagnosed in 2012 and it was the reason for 15% of all cancer deaths among females.[5,6] Various treatment approaches for breast cancer include chemotherapy, endocrine therapy, metronomic chemotherapy, radiotherapy, immunotherapy and surgery.[7] Despite, remarkable progress in breast cancer diagnosis and treatment, 20–30% of patients progress on to metastatic disease after the initial treatment and the median overall survival of metastatic breast cancer (MBC) patients is still only 2–3 years, although the range is wide.[8,9] One of the most crucial parameters in breast cancer therapy is early stage diagnosis, before tumor cells metastasize. Surgery is the first course of action to eliminate the tumor, although systemic chemotherapy, radiotherapy, or a combination of the two are essential, in the event of the spread of metastases throughout the body.[10]

Doxorubicin (DOX), belonging to anthracycline family, is an age old antibiotic and anti neoplastic drug widely used in the treatment of cancer.[11] Excellent anti-tumor efficiency against various solid tumors makes DOX one of the most interesting chemotherapeutic drugs in clinical regimens for breast cancer, especially for metastatic breast cancer.[12] Two mechanisms for anticancer activity of DOX are confirmed. First mechanism involve intercalation into DNA and the subsequent disruption of topoisomerase-II-mediated DNA repair for which candidate pharmacogenes are TOP2A, MLH1, MSH2, TP53, and ERCC2 genes while the second mechanism involves oxidative stress to cellular membranes, DNA and proteins for which candidate genes involve NADH dehydrogenases, nitric oxide synthases, xanthine oxidase, glutathione peroxidase, catalase and superoxide dismutase.[13] However, DOX based chemotherapy suffers from certain drawbacks which include; it affects healthy cells apart from cancer cells, cancer cells develop DOX resistance and sometimes DOX causes biventricular

failure leading to cell death. These negative aspects of cardiotoxicity, drug resistance and normal cell damage associated with DOX are the major hindrances for its efficiency against breast cancer limiting its clinical use and demands the development of new formulation of drug.[14]

Nanotechnology appears an excellent approach to overcome drug resistance by means of targeted delivery and has gained more attention due to their unique accumulation behavior. Hence, to overcome drug resistance and decrease the side effects of doxorubicin, nanotechnology holds promising potential by employing targeted drug delivery approach. Past 2–3 decades have seen rigorous research on nanomedicine for cancer treatment.[11] Over the last two decades, a large number of nanoparticle delivery systems have been developed for cancer therapy, including organic and inorganic materials. Nanoscale drug delivery vehicles have shown the ability to encapsulate a variety of therapeutic agents such as small molecules (hydrophilic and/or hydrophobic), peptides, protein-based drugs, and nucleic acids. Encapsulated molecules can be released from nanocarriers in a controlled manner over time to maintain the drug concentration within its therapeutic window or the release can be triggered by some stimulus unique to the delivery site. Advances in cancer proteomics and bioinformatics have allowed the development of targeted therapies, which were referred to as a "magic bullet". Nanocarriers may be surface functionalized to increase the blood circulation half-life and influence the biodistribution as well as to facilitate the attachment of biomolecules in order to achieve active tumor targeting. Surface ligands include antibodies, aptamers, peptides or small molecules which recognize tumor-specific or tumor-associated antigens in the tumor microenvironment. In general, ligands such as peptides, sugars, and small molecules are more attractive than antibodies due to higher stability, higher purity, ease of production through synthetic routes, and non-immunogenicity. The active targeting mechanism takes advantage of highly specific interactions between the targeting ligand and certain tissues or cell surface antigens to increase cellular uptake and increase tumor retention. The net result of these properties is to lower the systemic toxicity of the therapeutic agent while increasing the concentration of the agent in the area of interest, resulting in a higher therapeutic index for the therapeutic agent. These nanocarriers include polymeric nanoparticles, dendrimers, nanoshells, liposomes, inorganic/metallic nanoparticles, hybrid nanoparticles, micelles, and magnetic and bacterial nanoparticles.[15,16] Figure 1.1 shows the desirable general structure of nanoparticles for targeted drug delivery.

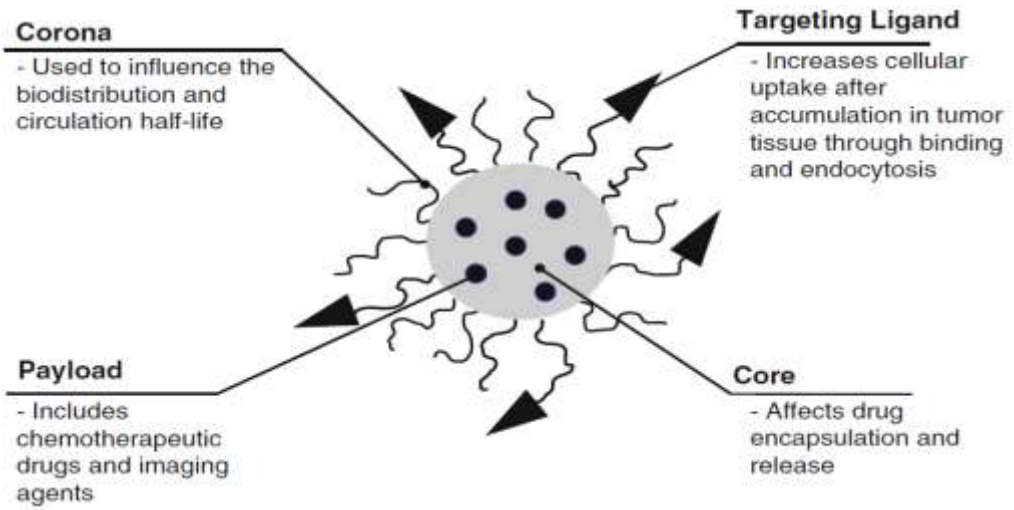


Figure 1.1: Schematic of structure of nanoparticle platform for targeted drug delivery.

Inorganic nanomaterials have special structures and physicochemical properties. Various metal based nanoparticles have shown great prospect as antibacterial agents, in medicine, imaging and drug delivery. In addition to these applications, metal nanoparticles are considered to interfere with different other biological processes such as autophagy induction and angiogenesis. Recently, copper oxide nanoparticles have been characterized for their antimicrobial activity.[17] Copper oxide nanoparticles easily crosses biological barriers and reach target organ.[18] Copper oxide nanoparticles are of great interest due to their high redox cycling property and ability to exert cytotoxicity on different cells via oxidative stress.[17]

Among inorganic nanomaterials, mesoporous silica nanoparticles are centre of focus because of their unique properties. Since the first report using MCM-41 type mesoporous silica nanoparticles (MSNs) as drug delivery system in 2001, the few years have witnessed an exponential increase in research on biomedical applications of MSNs. It has been one of the hottest areas in nanobiotechnology and nanomedicine for designing biocompatible MSNs and multifunctional counterparts in disease diagnosis and therapy.[19] Mesoporous silica nanoparticles (MSNs) have some unique advantages including high surface area and large pore volume, tunable particle size (10-1000 nm) and pore diameter (2-30 nm), uniform mesoporosity, flexible morphology, facile surface functionalization and excellent biocompatibility and biodegradation.[20-22] Textural properties of MSNs provide the possibility to load high amount of drugs within MSNs. On the other hand, there are abundant silanol groups on the surfaces of

mesoporous channels and the outer surfaces of MSNs, which facilitate their surface functionalization.[23] As nanocarriers, mesoporous silica nanoparticles with unique mesoporous structure have been explored as effective drug delivery systems for a variety of therapeutic agents to fight against various kinds of diseases including bone/tendon tissue engineering,[24,25] diabetes,[26] inflammation,[27] and cancer.[28-32]

The biggest challenge in application of MSN for cancer treatment is to obtain "zero premature drug release".[33] Variety of biocompatible and biodegradable polymers such as polyethylene glycol (PEG)[34], poly (acrylic acid)[35], natural polymers like gelatin[36] etc can be used for surface capping of mesoporous silica based nanosystems. These polymer end cappers possessing significant diffusion barrier properties can act as a gatekeeper to provide the intracellular drug release from mesoporous silica nanoparticles. Moreover, some of these polymeric materials are capable of responding to some stimulus due to their intrinsic ability to alter their physical or chemical properties and by using such polymers, nanoparticulate drug delivery systems can be engineered in such a way as to selectively change their properties/functions (for example, facilitate drug release or cellular uptake) in response to specific internal or external stimuli/triggering mechanisms, i.e. behave as smart stimuli-sensitive preparations.[37-40] Such nano-preparations are designed to behave dynamically in response to various internal cues in the microenvironment of the pathological area or to certain external stimuli.[41,42] Internal stimuli that are characteristic for the pathological areas, such as tumors, infarcts, sites of infection, etc., include local changes (compared to normal physiological values) in pH,[43,44] temperature (local hyperthermia that accompanies inflammation),[45-47] redox conditions (such as high intracellular glutathione levels),[48,49] and the expression of certain molecules, including those with enzymatic activity.[50,51] External stimuli or stimuli that could be artificially applied from outside of the body include heat, magnetic fields, light, and ultrasound, and can be employed to facilitate “on-demand” changes of certain functions of nanomedicines.[39,42]

Among the different endogenous and exogenous stimuli, redox potential has recently appeared as the most unique, fascinating, promising and clinically applicable trigger for ‘‘active’’ intra-cellular drug and gene release. As compared to various stimuli such as light and magnetic field that are applied externally and require sophisticated devices, redox is a ubiquitous internal stimulus existing naturally in tumor tissues as well as in cancer cells.[52] The design rationale of reduction-sensitive nanosystems usually involves incorporation of disulfide linkage(s) in the

polymer main chain, at the polymer side chain or in the cross-linker. The disulfide bonds while stable under oxidative conditions are rapidly cleaved, at a time scale from minutes to hours, under a reductive environment through thiol-disulfide exchange reactions.[53,54] Furhtermore, pH sensitive activation is also of particular interest, as delivery can be autonomously activated in vitro and in vivo. When the nanoparticles are taken up by the cells, they enter the cells by endocytosis and will encounter endosomal/lysosomal environments where low pH condition is prevalent. In addition, tumor interior has low pH environment due to hypoxic conditions. This feature provides an advantage that the drug release is more restricted to cancer.[55]

Chitosan (CH) is a non-toxic biodegradable polycation with a high number of primary amino groups. These amine functional groups render cationic character to the polymer and are responsible for a range of significant features including in situ gelation, mucoadhesion, efflux pump inhibition, high cellular permeability for oral administration of drugs which make CH an outstanding candidate in drug delivery systems. CH can swell in cancerous tissues due to their acidic media and this property endows the polymer with the ability of discrimination between normal and cancerous cells for controlled drug release.[56]

Current drug delivery systems, however, do not have the ability to guide themselves to a target. They reach the target area as a result of blood circulation and extravasation followed by intratumoral retention and distribution. So the active targeting is required to guide the drug/drug carriers to a target site.[57] Number of targeting moieties such as Folic acid[58], Lectins[59] etc have been used for effectively targeting the tumor cells, out of which folic acid is an inexpensive, water soluble and stable vitamin without adverse effects on normal cells and low immunogenic response has attracted a great deal of attention for active targeting. The over expression of the FA receptor in epithelial malignancies, such as colorectal, ovarian, and breast cancer cells in comparison with most normal cells make FA conjugates as facile and infallible strategy to promote the receptor-mediated endocytosis of nanoparticles. The vesicular trafficking of FA conjugates makes them able to move through many organelles and release their cargo efficiently into the cell cytoplasm.[60]

1.1. Aims and Objectives:

This work was aimed to develop mesoporous silica nanoparticles as a novel platform for controlled as well as targeted delivery of anticancer agent "Doxorubicin" for improved breast cancer therapy. The research work was designed to achieve efficient breast cancer therapy by synthesizing dual stimuli responsive MSNs which can actively target the breast cancer cells and release the loaded drug within tumor environment and thereby reduce the toxicity associated with conventional anticancer therapy. The incorporation of copper oxide provides synergistic cytotoxicity against cancer cells and improves the therapeutic efficacy of the formulation.

The research work was carried out to achieve following objectives:

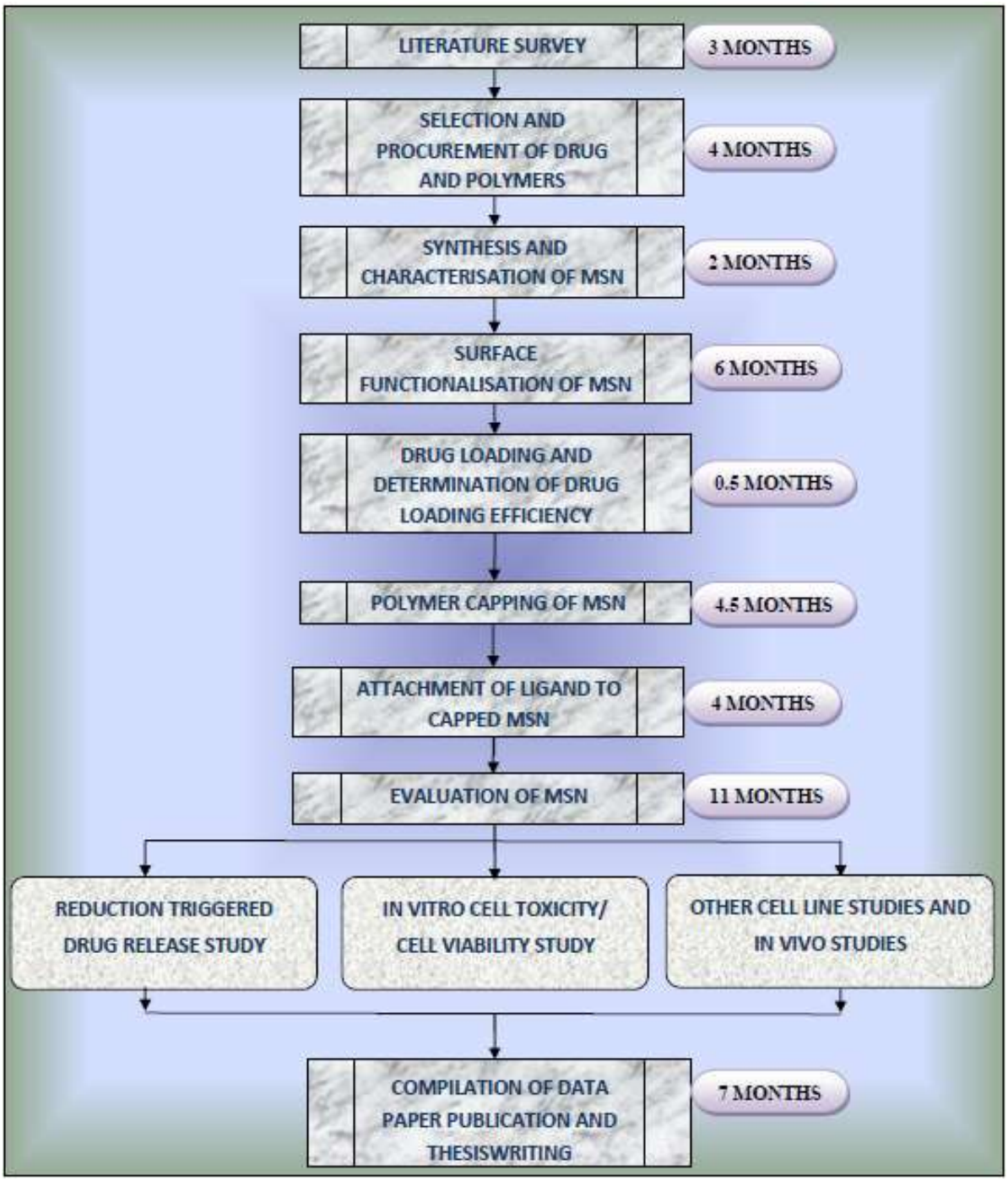
- Synthesis of MSN with required characteristics such as surface area, pore size and pore volume.
- Synthesis of CuO loaded MSN with desired characteristics like surface area, pore size and pore volume.
- Functionalization over MSN surface for improved drug loading and easy polymer conjugation.
- Loading of Dox into functionalised MSN.
- Synthesis of polymer and targeting ligand conjugate.
- Attachment of polymer-targeting ligand conjugate over MSN surface to achieve active targeting to tumor tissue with dual (pH and redox) responsive intracellular drug release and minimum premature drug release.

1.2. Rationale:

Cancer is still one of the most lethal diseases and one of the leading causes of death worldwide. Although there have been significant advances in medical technology, improvements in cancer treatment have lagged behind. Current cancer treatments including chemotherapeutic drugs often kill healthy cells also and cause toxicity to the patient. The biggest challenge in current cancer treatment is the design and synthesis of the controlled biocompatible cap system to obtain "zero premature drug release" and targeted delivery of anticancer drugs in a controlled fashion for smart cancer therapy. Among variety of nanocarriers, mesoporous silica nanoparticles (MSN) are interesting candidates because of their unique characteristics and their safe history, good biocompatibility and biodegradability, and easily “tunable” surface functionality. So the

encapsulation of anticancer drugs within MSN, containing polymeric network as a gatekeeper on surface, capable of selectively targeting diseased cells promises to increase the effectiveness of therapy and reduce the side effects. Additionally, inclusion of copper oxide within pores of MSNs will provide synergistic cytotoxic effect.

1.3. Plan of work:



1.4. Hypothesis:

The formulated mesoporous silica nanoparticles will be able to target folate receptors (over expressed in breast cancer cells) with minimum premature drug release. This will improve the therapeutic efficacy of doxorubicin to great extent with minimum side effects. The incorporation of copper oxide will help to provide synergistic anticancer activity.

References:

1. Pudata V, Subrahmanyam V, Jhansi K. A short note on cancer. Journal of Carcinogenesis and Mutagenesis. 2011, 2(4):1-6.
2. http://www.who.int/mediacentre/factsheets/fs297/en/
3. Zubair H, Ahmed A. Cancer metastasis: an introduction. In: Introduction to cancer metastasis, edited by Ahmed A. Academic Press, USA. 2017:pp. 3-12.
4. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, Thürlimann B, Senn HJ. Tailoring therapies-improving the management of early breast cancer: St Gallen international expert consensus on the primary therapy of early breast Cancer 2015. Annals of Oncology. 2015, 26:1533–1546.
5. Torre LA, Bray F, Siegel RL, Ferlay J, Tieulent JL, Jemal A. Global cancer statistics, 2012. CA: A cancer Journal for Clinicians. 2015, 65:87-108.
6. Malavia S, Bagadi SA, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. Asia-Pacific Journal of Clinical Oncology. 2017, 13:289-295.
7. Tsuji W, Plock JA. Breast cancer metastasis. In: Introduction to cancer metastasis, edited by Ahmed A. Academic Press, USA. 2017:pp. 13-31.
8. EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005, 365:1687–1717.
9. Uhr JW, Pantel K. Controversies in clinical cancer dormancy. Proceeding of the National Academy of Sciences USA. 2011, 108:12396–12400.
10. Bassiouni Y, Faddah L. Nanocarrier based drugs - The future promise for treatment of breast cancer. Journal of Applied Pharmaceutical Science. 2005, 2(5):225-232.
11. Siddharth S, Nayak A, Nayak D, Bindhani BK, Kundu CN. Chitosan-dextran sulfate coated doxorubicinloaded PLGA-PVA-nanoparticles caused apoptosis in doxorubicin

resistant breast cancer cells through induction of DN damage. Scientific Reports. 2017, 7:1-10.

12. Wang C, Sun X, Wang K, Wang Y, Yang F, Wang H. Breast cancer targeted chemotherapy based on doxorubicin-loaded bombesin peptide modified nanocarriers. Drug Delivery. 2016, 23(8): 2697-2702.
13. Shafei A, El-Bakley W, Sobhy A, Wagdy O, Reda A, Aboelenin O, Marzouk A, El Habak K, Mostafa R, Ali MA, Ellithy M. A review on the efficacy and toxicity of different doxorubicin nanoparticles for targeted therapy in metastatic breast cancer. Biomedicine & Pharmacotherapy. 2017, 95:1209-1218.
14. Prados J, Melguizo C, Ortiz R, Velez C, Alvarez PJ, Arias JL, Ruiz MA, Gallardo V, Aranega A. Doxorubicin-loaded nanoparticles: New advances in breast cancer therapy. Anti-Cancer Agents in Medicinal Chemistry. 2012, 12:1058-1070.
15. Alexis F, Pridgen EM, Langer R, Farokhzad OC. Nanoparticles technologies for cancer therapy. In: Drug delivery, Handbook of experimental pharmacology, Edited by Schafer M.-Korting. Springer-Verlag, Berlin. 2010: pp.55-86.
16. Moghimi SM, Hunter AC, Murray JC. Nanomedicine: current status and future prospects. The FASEB Journal. 2005, 19:311-330.
17. Laha D, Pramanik A, Maity J, Mukherjee A, Pramanik P, Laskar A, Karmakar P. Interplay between autophagy and apoptosis mediated by copper oxide nanoparticles in human breast cancer cells MCF7. Biochimica et Biophysica Acta. 2014, 1840:1-9.
18. Sankar R, Maheswari R, Karthik S, Shivashangari KS, Ravikumar V. Anticancer activity of Ficus religiosa engineered copper oxide nanoparticles. Material Science and Engineering C. 2014, 44:234-239.
19. Tang F, Li L, Chen D. Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery. Advance materials. 2012, 24:1504-1534.
20. Kwon S, Singh RK. Silica-based mesoporous nanoparticles for controlled drug delivery. Journal of tissue engineering. 2013, 4:1-18.
21. Hoffmann F, Cornelius M, Morell J, Froba M. Silica based mesoporous organic-inorganic hybrid materials. Angewandte chemie. 2006, 45:3216-3251.
22. Gerardin C, Reboul J, Bonne M, Lebeau B. Ecodesign of ordered mesoporous silica materials. Chemical society review. 2013, 42:4217-4255.

23. Zhu Y. Mesoporous silica nanoparticles with a core-shell structure for drug delivery. Bioanalysis and biomedicine. 2013, 5(3):1-2.
24. Lozano D, Manzano M, Doadrio JC, Salinas AJ, Vallet-Regí M, Gómez-Barrena E, Esbrit P. Osteostatin-loaded bioceramics stimulate osteoblastic growth and differentiation. Acta biomaterialia. 2010, 6:797-803.
25. Zhu M, Wang HX, Liu J, He H, Hua X, He Q, Zhang L, Ye X, Shi J. mesoporous silica nanoparticulate/β-TCP/BG composite drug delivery system for osteoarticular tuberculosis therapy. Biomaterials. 2011, 32:1986-1995.
26. Zhao YN, Trewyn BG, Slowing II, Lin VSY. Mesoporous silica nanoparticle-based dual drug delivery system for glucose-responsive controlled release of insulin and cyclic AMP. Journal of the American chemical society. 2009, 131:8398-8400.
27. Moulari B, Pertuit D, Pellequer Y, Lamprecht A. The targeting of surface modified silica nanoparticles to inflamed tissue in experimental colitis. Biomaterials. 2008, 29:4554-4560.
28. Kardys AY, Bharali DJ, Mousa SA. Amino functionalized silica nanoparticles: Invitro evaluation for targeted drug delivery and therapy of pencreatic cancer. Journal of nanotechnology. 2013:1-8.
29. Gui R, Wang Y, Sun J. Encapsulating magnetic and fluorescent mesoporous silica into thermosensitive chitosan microspheres for cell imaging and controlled drug release in vitro. Colloids and surface B: Biointerfaces. 2014, 113:1-9.
30. Wen H, Guo J, Chang B, Yang W. pH-responsive composite microsphere based on magnetic mesoporous silica nanoparticles for drug delivery. European journal of pharmaceutics and biopharmaceutics. 2013, 84:91-98.
31. Zheng J, Tian X, Sun Y, Lu D, Yang W. pH-sensitive poly (glutamic acid) grafted mesoporous silica nanoparticles for drug delivery. International journal of pharmaceutics. 2013, 450:296-303.
32. Xie M, Shi H, Ma K, Shen H, Li B, Shen S, Wang X, Jin Y. Hybrid nanoparticles for drug delivery and bioimaging: Mesoporous silica nanoparticles functionalized with carboxyl groups and a near-infrared fluorescent dye. Journal of colloid and interface science. 2013, 395:306-314.

33. Yang YW. Towards biocompatible nanovalves based on mesoporous silica nanoparticles. Medchemcomm. 2011, 2:1033-1049.
34. Sun H, Guo B, Cheng R, Meng F, Liu H, Zhong Z. Biodegradable micelles with sheddable poly (ethylene glycol) shells for triggered intracellular release of doxorubicin. Biomaterials. 2009, 30:6358-6366.
35. Li H, Zhang JZ, Tang Q, Du M, Hu J, Yang D. Reduction responsive drug delivery based on mesoporous silica nanoparticle core with crosslinked poly (acrylic acid) shell. Materials science and engineering C. 2013, 33:3426-3431.
36. Zou Z, He D, He X, Wang K, Yang X, Qing Z, Zhou Q. Natural gelatin capped mesoporous silica nanoparticles for intracellular acid-triggered drug delivery. Langmuir. 2013, 29:12804-12810.
37. Jhaveri A, Shvets V, Torchilin V. Stimuli sensitive nanopreparations: Overview. In: Smart pharmaceutical nanocarriers, edited by Torchilin V. Imperial College Press, USA. 2016, pp.1-48.
38. Fleige E, Quadir MA, Haag R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: Concepts and applications. Advanced Drug Delivery Reviews. 2012, 64:866-884.
39. Torchilin V. Multifunctional and stimuli-sensitive pharmaceutical nanocarriers. European Journal of Pharmaceutics and Biopharmaceutics. 2009, 71:431-444.
40. Shim MS, Kwon YJ. Stimuli-responsive polymers and nanomaterials for gene delivery and imaging applications. Advanced Drug Delivery Reviews. 2012, 64:1046-1059.
41. Colson YL, Grinstaff MW. Biologically responsive polymeric nanoparticles for drug delivery. Advanced Materials. 2012, 24:3878-3886.
42. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nature materials. 2013, 12:991-1003.
43. Gerweck LE, Seetharaman K. Cellular pH gradient in tumor versus normal tissue: Potential exploitation for the treatment of cancer. Cancer Research. 1996, 56:1194–1198.
44. Tannock IF, Rotin D. Acid pH in tumors and its potential for therapeutic exploitation. Cancer Research. 1989, 49:4373–4384.

45. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancerrelated inflammation, the seventh hallmark of cancer: Links to genetic instability. Carcinogenesis. 2009, 30:1073–1081.

46. Gromkowski SH, Yagi J, Janeway CA. Jr. Elevated temperature regulates tumor necrosis factor-mediated immune killing. European Journal of Immunology. 1989, 19:1709–1714.

47. Stefanadis C, Chrysochoou C, Markou D, Petraki K, Panagiotakos DB, Fasoulakis C, Kyriakidis A, Papadimitriou C, Toutouzas PK. Increased temperature of malignant urinary bladder tumors in vivo: The application of a new method based on a catheter technique. Journal of Clinical Oncology. 2001, 19:676–681.

48. Russo A, Degraff W, Friedman N, Mitchell JB. Selective modulation of glutathione levels in human normal versus tumor cells and subsequent differential response to chemotherapy drugs. Cancer Research. 1986, 46:2845–2848.

49. Saito G, Swanson JA, Lee KD. Drug delivery strategy utilizing conjugation via reversible disulfide linkages: Role and site of cellular reducing activities. Advanced Drug Delivery Reviews. 2003, 55:199–215.

50. De La Rica R, Aili D, Stevens MM. Enzyme-responsive nanoparticles for drug release and diagnostics. Advanced Drug Delivery Reviews. 2012, 64:967–978.

51. Ghadiali JE, Stevens MM. Enzyme-responsive nanoparticle systems. Advanced Materials. 2008, 20:4359–4363.

52. Cheng R, Feng F, Meng F, Deng C, Feijen J, Zhong Z. Glutathione-responsive nano-vehicles as a promising platform for targeted intracellular drug and gene delivery. Journal of Controlled Release. 2011, 152(1):2-12.

53. Zhao Q, Liu J, Zhu W, Sun C, Di D, Zhang Y, Wang P, Wang Z, Wang S. Dual-stimuli responsive hyaluronic acid-conjugated mesoporous silica for targeted delivery to CD44-overexpressing cancer cells. Acta Biomaterialia. 2015, 23:147-156

54. Meng F, Hennink WE, Zhong Z. Reduction-sensitive polymers and bioconjugates for biomedical applications. Biomaterials. 2009, 30: 2180-2198.

55. He X, Li J, An S, Jiang C. pH-sensitive drug-delivery systems for tumor targeting. Therapeutic Delivery. 2013, 4(12):1499-1510.

56. Suarato G, Li W, Meng Y. Role of pH-responsiveness in the design of chitosan-based cancer nanotherapeutics: A review. Biointerphases. 2016, 11(4):04B201.
57. Bae YH, Park K. Targeted drug delivery to tumors: Myths, reality and possibility. Journal of controlled release. 2011, 153(3):198-205.
58. Narayanan S, Binulal NS, Mony U, Manzoor K, Nair S, Menon D. Folate targeted polymeric green nanotherapy for cancer. Nanotechnology. 2010, 21:1-13.
59. Singh A, Dilnawaz F, Sahoo SK. Long circulating lectin conjugated paclitaxel loaded magnetic nanoparticles: A new theranostic avenue for leukemia therapy, Plosone, 2011, 6(11):1-18.
60. Zwicke GL, Ali Mansoori G, Jeffery CJ. Utilizing the folate receptor for active targeting of cancer nanotherapeutics. Nano Reviews. 2012, 3(1):1-11.