2. LITERATURE REVIEW:

2.1. Utility of MSNs in the field of cancer:

One of the severe health menace for human beings is cancer as it leads to a huge burden in all developed, developing and under developed countries alike. A large number of new cases of cancer are being reported annually (1, 2). From the present scenario, it is predicted that by the end of 2030 almost 70% people would be affected by cancer due to the current prevailing conditions (3). In spite of the advances made in tumor therapeutics, the low solubility of many anticancer drugs hampers their genuine application. A large portion of the anticancer medications right now accessible fall into the biopharmaceutical classification system (BCS) II and IV having dissolvability confinements (4-6). Besides 70% of the new therapeutic candidates discovered also face similar complications of low solubility (7, 8). By solving the solubility issues, one can also aim to improve the bioavailability of the same as it is directly associated with the solubility of BCS class II drugs and for class IV drugs, solubility could also improve the bioavailability to a fewer extent due to permeability limitations present. Therefore, increasing the drug solubility has turned out to be the most imperative task to be undertaken. The development of novel delivery systems for these molecules without the use of organic solvents, synthesis of prodrug or salt formation have received noteworthy attention now a days with respect to chemical alteration (9, 10). Amongst wide methodologies available for solubility enhancement, *e.g.* particle size reduction, polymorphs or pseudopolymorphs formation, complexation, solubilisation, preparation of drug dispersions *etc*, the present scenario includes strategies that rely heavily on employing nano sized particles *i.e*. formulating a nano drug delivery system. This concept has been expanded in a couple of decades as the conversion of macro sized particles in nano scale (micronization, nanonization) is a well-established strategy to radically improve the surface area and ultimately boost the solubilisation process (10).

Nanoparticles (NPs) hold an enormous potential as a successful medication conveyance framework. In recent decades, they have gained vital attention owing to their pronounced application in multi-disciplinary fields. They have been successfully used for solubility enhancement, bioavailability enhancement, controlled and sustained drug delivery system, targeting the diseased tissue *etc* (11). For this purpose, many nano systems have been explored so far, nevertheless mesoporous silica nanoparticles (MSNs) are in the limelight because of

their unique features. MSNs are the most sought after candidates in the field of nano drug delivery system. Mesoporous materials are presently in the limelight due to their potential applications in catalysis, adsorption, ecology, nanotechnology, chemical and biological separation, chromatography, photonic and electronic device preparation and medical uses. Since last decade MSNs have shown tremendous potential in drug delivery applications. In the pharmaceutical field, MSNs can be used successfully to satisfy various purposes like enhanced dissolution rate and bioavailability, targeting the desired cells and effective diagnosis of various diseases. Despite the fact that MSNs have high potential in theranostic fields as well, much more research and in depth investigation is needed to fully explore their abilities as nanocarriers (12-14).

Because of the unique and tailor made pore size and particle size, the MSNs have been successfully used for solubility enhancement and this could in turn enhance the bioavailability of many anti-cancer drugs. E.g. She and co-worker has synthesized 5-flouro uracil loaded bare and amine decorated nanoparticles and also had proved that amine coated nanoparticle served as potential intracellular 5-fluorouracil delivery vehicles for cancers (15). Besides, Hartono et al had formulated curcumin loaded amine decorated nanoparticles as drug delivery carriers for bioavailability enhancement of curcumin. Wherein, they had proved improved dissolution and in vivo performance of curcumin loaded nanoparticles as compared to plain curcumin and mesoporous silica micron sized-particles (16). Another group *i.e.* He *et al* had synthesised paclitaxel encapsulated MSNs to improve the solubility of respective poorly soluble drug (17).

Further, the utility of MSNs is not limited to bioavailability enhancement only but it is extensively employed in targeting the various types of cancer cells. The stimuli responsive smart polymeric drug delivery system is gaining an attention now a day especially in tumor targeting. It is very easy to modify the external surface of MSNs to make it stimuli/receptor based drug delivery system. In particular, external surface decoration of mesoporous by different stimuli responsive is in the limelight now days due to its biocompatibility, large surface area, uniform and tunable pore size, noteworthy loading efficiency with zero premature release *etc*. Temperature, pH, redox, *etc* are the various stimuli by which one can focus the drug delivery to target site only (2, 18). For an instant, Daryasari and group had formulated chitosan-folate coated MSNs to serve the purpose of both active and passive targeting of curcumin in the cancer cells. Wherein, they had demonstrated selective uptake of folic acid attached nanoparticles by cancer cells following the active targeting by FA receptors (19). Additionally, Yu et al had coated the Doxorubicin loaded bare MSNs with the hyaluronate to

have active targeting by CD44 receptors and thus this system exhibited an potential to target CD44 overexpressed cancer cells (20). Further, Gang pan and co-worker had formulated 5-FU encapsulated poly(oligo(ethylene glycol) monomethyl ether methacrylate) anchored and RGD functionalized mesoporous silica nanoparticles for colon cancer targeted drug delivery system. They have also proved higher accumulation efficacy of RGD attached MSNs inside the colon cells relative to uncoated MSNs (21). Likewise, Wang and co-authors had engineered paclitaxel filled core-shell MSNs which exhibited improve drug release and pharmacokinetics behaviour. Furthermore, the in vitro cellular uptake study on human lung cancer cell line A549 investigation also demonstrated the potential pulmonary administration of Paclitaxel and its efficacy in lung cancer (22). Moreover, Zhao *et al* have formulated redox responsive MSNs for the co-delivery of si-RNA and doxorubicin by forming a disufide linkage over the surface of bare MSNs which worked as a gatekeeper and was utilized to target intracellular GSH and thus it served as a potential drug delivery system for controlled and targeted release of cargo to the target of choice (23). Besides all this, the other anti-cancer moiety viz., docetaxel (24), anisomelic acid (25), camptothecin (26) *etc* have been actively or passively targeted by framing them into the MSN skeleton successfully.

Apart from the application of MSNs in the cancer filed, MSNs are also widely used for solubility and/or bioavailabilty enhancement of drugs belonging to other category viz., ibuprofen (27) and ketoprofen (28) (anti-inflammatory drugs), Erythromycin (29), amikacin (30), cefuroxime and vancomycin (31) (antibiotics), Telmisartan (32) and captopril (33) (anti-hypertensive), griseofulvin (34) (anti-fungal), budesonide (35) (steroid), cyclosporine (36) (immunosuppressant) *etc*.

With all these options available, pH is the most easiest and feasible way to achieve stimuli responsive drug delivery and Chitosan is the commonly used polysaccharide in the drug delivery system due to its non-toxic, biocompatible, bio degradative nature. The presence of the abundant amine group on the outer surface make chitosan freely soluble in the pH range of 1 to 11. Moreover, being a polysaccharide, it also controls the drug release. Additionally, the unique feature of swelling at lower pH makes chitosan a favourable candidate to formulate a pH responsive (37, 38). Besides chitosan, hyaluronic acid (HA) is also used to serve a dual purpose *i.e.* pH responsive and receptor base targeted nano drug delivery system. HA is a biodegradable, biocompatible and non-immunogenic glycosaminoglycan. It is also essential for proper cell growth, organ structure stability and tissue organization. HA has a dual property *i.e.* pH responsive property along with receptor targeting capacity. The unique pH sensitive

hydrazine bond will direct the higher drug release form HA coated nanoparticles in acidic media. Furthermore, it is also used as a targeting moiety as it is having a specific affinity to bind with the CD44 receptor which selectively overexpressed in cancer (20, 39).

Aforementioned two strategies for formulating pH based nanosystems were implemented along with an active targeting mechanism following active targeting to FA receptor using folic acid in this investigation. Amid, all the mesoporous carriers available, MCM-41 and MCM-48 have explored in this investigation to satisfy the purpose of biovailability enhancement as well as to form the stimuli and receptor based targeted drug delivery system.

2.2. Selection of active pharmaceutical ingredients:

2.2.1. Raloxifene hydrochloride (RLX):

RLX is a potent anti-cancer drug used in the treatment of breast cancer. Besides this, it is having its potential application in the treatment of osteoporosis and cancer especially in breast cancer. It is a second generation selective estrogen receptor modulator (SERM) with established estrogenic activity which make it a potential candidate to be used in the therapy of osteoporosis (40, 41). Being a BCS class II drug (biopharmaceutical classification system), it faces a solubility issue which becomes a major obstacle to its efficacy. Many research groups have explored RLX to satisfy different purposes. E.g. Shah *et al* have synthesized nanostructured lipid carrier for bioavailability enhancement of RLX (42). Bikiaris *et al* have formulated biodegradable polyesters drug carrier to enhance bioavailability and solubility of RLX hydrochloride (43). Similarly, Jay Prakash *et al* have constructed Gellan gum nanoparticles for bioavailability enhancement of the same (44). Fontana *et al* had formulated Eudragit coated RLX nanocapsules to control release to improve the anti-proliferative effect (45). Agardan NB and co-worker had formulated RLX loaded liposomes and cochleats. The efficiency of formulation was tested on human breast carcinoma cell line *i.e.* MCF-7 and they have demonstrated an inhibition of MMP-2 enzymes by RLX loaded cochleates containing DM-β-CD (46). But no research work has yet been carried out to formulate RLX encapsulated mesoporous silica nanoparticles.

2.2.2. Bexarotene (BXR):

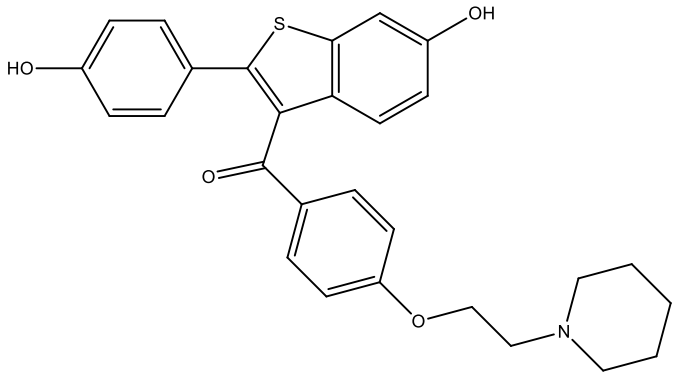
BXR is another API being used in the treatment of breast cancer. As has been BCS class II drug, it faces solubility and permeability problems to show its efficacy. Being a recently discovered molecule, it is not much explored, only a few reports involving formulation of BXR nanoparticle are available. Chen *et al*, have engineered BXR nanocrystals to enhance BXR solubility, where they obtained almost 3 times higher release of BXR from BXR nanocrystal with respect to plain BXR using 0.5% tween 80 surfactant (47). Li *et al* had prepared chitosan folate conjugated nanoparticles as a targeted drug delivery system. They got near to 2.5 times increment in BXR release from its formulation as compared to pure BXR after 120 min of dissolution study in 0.02% Tween 80 and concluded the enhancement in the dissolution rate and the gastrointestinal absorption of the bexarotene loaded folate chitosan coated nanoparticles (48). Another research group had formulated nanocrystal to show its efficacy in lung cancer and they had demonstrated promising effect of BXR in lung cancer using human lung carcinoma cell line A549 (49). Lisi Qi *et al* had incorporated BXR into bovine serum albumin nanoparticles (50). To the best of our knowledge only one mesoporous formulation of BXR has been reported so far wherein Vasile *et al* have synthesized BXR encapsulated bare and amine coated MCM-41 to prepare a pharmaceutical topical formulation (51). However, any reports of mesoporous silica nanoparticle encapsulating BXR and exploring oral and parenteral route are not available till date.

2.3. Physicochemical properties of selected drugs:

2.3.1. RLX:

- Description: It is a second-generation selective estrogen receptor modulator (SERM) used to prevent osteoporosis in postmenopausal women. It has estrogen agonist effects on bone and cholesterol metabolism but behaves as a complete estrogen antagonist on mammary gland and uterine tissue thus also used in the treatment of breast cancer.
- IUPAC name: 2-(4-hydroxyphenyl)-3- (4-[2-(piperidin-1-yl) ethoxy] benzoyl) -1-benzothiophen-6-ol

- Structure:

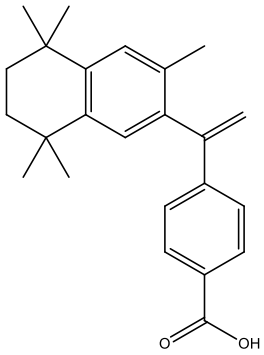


- Formula: $C_{28}H_{27}NO_4S$
- Available marketed formulation: Ralista® (a film coated tablet; RLX equivalent to 60mg)
- Melting point: 143-147 ºC (RLX)
  262-264 ºC (RLX-HCl)
- Log P: 5.45
- pKa: 8.89
- Solubility: 0.000512 mg/mL in water
- Chemistry: Raloxifene is a selective estrogen receptor modulator (SERM) of the benzothiophene class, is similar to tamoxifen in that it produces estrogen-like effects on bone and lipid metabolism, while antagonizing the effects of estrogen on breast and uterine tissue.
- Mechanism of action: Raloxifene binds to estrogen receptors, resulting in differential expression of multiple estrogen-regulated genes in different tissues. It also produces estrogen-like effects on bone, reduces the resorption of bone and increases the bone mineral density in postmenopausal women, thus slowing the rate of bone loss. Additionally, the drug also binds to the estrogen receptor and acts as an estrogen agonist in preosteoclastic cells, which results in the inhibtion of their proliferative capacity. Raloxifene also antagonizes the effects of estrogen on mammary tissue and blocks uterotrophic responses to estrogen. Thus, it prevents the transcriptional activation of genes containing the estrogen response element.
- Absorption: Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. The absolute bioavailability of raloxifene is 2.0%
- Protein binding: 95%
- Metabolism: Hepatic metabolism. It undergoes extensive first pass metabolism to the glucuronide conjugation

- Route of elimination: Primarily excreted through feces.
- Commercial form: Commercially, RLX is available in the form of tablet with 60 mg RLX strength. Various products available are Bonmax, Donmax (Zydus Cadila health care ltd.), Bontact (Cadila Pharmaceutical Ltd.), Essern (Torrent Laboratories Pvt Ltd.), Fiona (Dr. Reddy's Laboratories Ltd.), Ralista (Cipla Limited), Ralofen FC (Lupin Laboratories Ltd) *etc.*

2.3.2. BXR:

- Description: An antineoplastic agent approved by FDA especially for T cell lymphoma. Also used for lung and breast cancer.
- IUPAC name: 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]benzoic acid
- Structure:



- Formula: $C_{24}H_{28}O_2$
- Available marketed formulation: Targretin® capsule (not available in india)
- Melting point: 224-226 ºC
- Log P: 6.9
- pKa: 4.07
- Solubility: 0.000149 mg/mL in water
- Chemistry: Bexarotene (BXR) is a novel oral synthetic retinoid, which shows remarkable anti-tumor potential for treating a variety of tumor cells and has turned out to be a strong chemopreventive and chemotherapeutic agent.
- Mechanism of action: It specifically binds to and activates retinoid X receptors (RXR) that will be significantly useful in the treatment of malignancies. It has already been approved by the food and drug administration (FDA) to treat skin issues caused by cutaneous T-cell lymphoma that is unresponsive to different medicines (52). Moreover, a recent study

conducted also demonstrates the usefulness of BXR in Alzheimer disease by suppressing primary nucleation reaction which initiates the synthesis of β-amyloid peptide - an unique hallmark of Alzheimer's disease (53).

- Protein binding: >99%
- Route of elimination: Primarily excreted through urine
- Commercial form: Commercially, BXR is available in the form of capsule with 75 mg BXR strength. Targretin® is the commercial formulation of BXR but it is not available in India.

2.4. Need for the current study:

It is well known that, the poor solubility and bioavailability hampers the pharmacological action of drug candidate by hampering its release in the body. Although, a solely increment in the bioavailability will not guarantee that the drug moiety will reach to the disease tissue site only and will not harm the healthy cells and tissues. Therefore, it has became prime important to develop such a formulation which will not only satisfy the bioavailability issue, but also fulfil the aim of targeting the drug moiety to the diseased tissue. The similar concept was undertaken here and nanoparticles which have a capacity to be concentrated inside the cancer cells were formulated.

Nanoparticles can easily extravasate into the tumor insterstitum through the leaky vasculature. This leads to higher accumulation of nanoparticles inside the tumor cells as compared to normal cells and this concept is termed as of enhanced permeability and retention (EPR) ability of nanoparticles. Using this concept the nanoparticles are formulated in order to have high retention in the tumor cells. Further, the concept of passive targeting was utilized here to satisfy the goal of higher accumulation of anticancer candidates inside the tumor cells by EPR mechanism. Additionally, the receptor based targeting (active targeting) phenomenon was also studied by selecting folate and CD44 receptor as a targeting receptor which generally overexpressed in the breast cancer (14).

The selected anti-cancer candidates *i.e.* RLX and BXR both are facing a solubility issue as they fall under Biopharmaceutical Classification System (BCS) class II category. The oral bioavailability of the RLX is limited to only 2%, which is accredited to its extensive first pass metabolism (FPM). Roughly 60% of the oral dose undergoes FPM upon oral administration of RLX. The poor aqueous solubility along with significant FPM together contributes towards its lower bioavailability (54, 55). Further, BXR is poorly water soluble with a maximum solubility of about 10–50 µM in pure water. Thus, it became essential to develop a formulation which

can enhance the solubility of selected drug candidate and in turn it could demonstrate a positive impact on their bioavailability (47). Further, the targeting of this moiety using folate and hyaluronate coated MSNs are not yet reported. The coating of external surface with the targeted ligand may direct the drug to reach their target and thereby it can also reduce the adverse effect of the same due their intake by healthy cells. Collectively, in this investigation two formulations were synthesized for each to satisfy the goal of formulating a nanosystem having solubility enhancement and in turn bioavailability enhancement efficiency and targeting efficiency.

2.5. References:

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015;65(2):87-108.
2. Shah PV, Rajput SJ. Facile Synthesis of Chitosan Capped Mesoporous Silica Nanoparticles: A pH Responsive Smart Delivery Platform for Raloxifene Hydrochloride. AAPS PharmSciTech. 2018:1-14.
3. Harding R, Selman L, Agupio G, Dinat N, Downing J, Gwyther L, et al. The prevalence and burden of symptoms amongst cancer patients attending palliative care in two African countries. European journal of cancer. 2011;47(1):51-6.
4. Dahan A, Wolk O, Kim YH, Ramachandran C, Crippen GM, Takagi T, et al. Purely in silico BCS classification: Science based quality standards for the world's drugs. Molecular pharmaceutics. 2013;10(11):4378-90.
5. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced drug delivery reviews. 1997;23(1-3):3-25.
6. Pham-The H, Garrigues T, Bermejo M, González-Álvarez I, Monteagudo MC, Cabrera-Pérez MAn. Provisional classification and in silico study of biopharmaceutical system based on Caco-2 cell permeability and dose number. Molecular pharmaceutics. 2013;10(6):2445-61.
7. Wolk O, Agbaria R, Dahan A. Provisional in-silico biopharmaceutics classification (BCS) to guide oral drug product development. Drug design, development and therapy. 2014;8:1563.
8. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. International journal of pharmaceutics. 2011;420(1):1-10.
9. Lu J, Liong M, Zink JI, Tamanoi F. Mesoporous silica nanoparticles as a delivery system for hydrophobic anticancer drugs. small. 2007;3(8):1341-6.
10. Junyaprasert VB, Morakul B. Nanocrystals for enhancement of oral bioavailability of poorly water-soluble drugs. asian journal of pharmaceutical sciences. 2015;10(1):13-23.
11. Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. Journal of occupational medicine and toxicology. 2007;2(1):16.
12. Shah PV, Rajput SJ. A comparative in vitro release study of raloxifene encapsulated ordered MCM-41 and MCM-48 nanoparticles: A dissolution kinetics study in simulated and biorelevant media. Journal of Drug Delivery Science and Technology. 2017;41:31-44.
13. Saroj S, Rajput SJ. Tailor-made pH-sensitive polyacrylic acid functionalized mesoporous silica nanoparticles for efficient and controlled delivery of anti-cancer drug Etoposide. Drug development and industrial pharmacy. 2018:1-14.
14. Saroj S, Rajput SJ. Composite smart mesoporous silica nanoparticles as promising theranostic candidates: Recent trends and applications. Journal of Drug Delivery Science and Technology. 2018.
15. She X, Chen L, Li C, He C, He L, Kong L. Functionalization of hollow mesoporous silica nanoparticles for improved 5-FU loading. Journal of Nanomaterials. 2015;16(1):108.
16. Hartono SB, Hadisoewignyo L, Yang Y, Meka AK, Yu C. Amine functionalized cubic mesoporous silica nanoparticles as an oral delivery system for curcumin bioavailability enhancement. Nanotechnology. 2016;27(50):505605.
17. He Y, Liang S, Long M, Xu H. Mesoporous silica nanoparticles as potential carriers for enhanced drug solubility of paclitaxel. Materials Science and Engineering: C. 2017;78:12-7.
18. Gulfam M, Chung BG. Development of pH-responsive chitosan-coated mesoporous silica nanoparticles. Macromolecular Research. 2014;22(4):412-7.

19. Daryasari MP, Akhgar MR, Mamashli F, Bigdeli B, Khoobi M. Chitosan-folate coated mesoporous silica nanoparticles as a smart and pH-sensitive system for curcumin delivery. Rsc Advances. 2016;6(107):105578-88.
20. Yu M, Jambhrunkar S, Thorn P, Chen J, Gu W, Yu C. Hyaluronic acid modified mesoporous silica nanoparticles for targeted drug delivery to CD44-overexpressing cancer cells. Nanoscale. 2013;5(1):178-83.
21. Pan G, Jia T-t, Huang Q-x, Qiu Y-y, Xu J, Yin P-h, et al. Mesoporous silica nanoparticles (MSNs)-based organic/inorganic hybrid nanocarriers loading 5-Fluorouracil for the treatment of colon cancer with improved anticancer efficacy. Colloids and Surfaces B: Biointerfaces. 2017;159:375-85.
22. Wang T, Liu Y, Wu C. Effect of paclitaxel-mesoporous silica nanoparticles with a core-shell structure on the human lung cancer cell line A549. Nanoscale research letters. 2017;12(1):66.
23. Zhao S, Xu M, Cao C, Yu Q, Zhou Y, Liu J. A redox-responsive strategy using mesoporous silica nanoparticles for co-delivery of siRNA and doxorubicin. Journal of Materials Chemistry B. 2017;5(33):6908-19.
24. Khosravian P, Ardestani MS, Khoobi M, Ostad SN, Dorkoosh FA, Javar HA, et al. Mesoporous silica nanoparticles functionalized with folic acid/methionine for active targeted delivery of docetaxel. OncoTargets and therapy. 2016;9:7315.
25. Senthilkumar R, Karaman DŞ, Paul P, Björk EM, Odén M, Eriksson JE, et al. Targeted delivery of a novel anticancer compound anisomelic acid using chitosan-coated porous silica nanorods for enhancing the apoptotic effect. Biomaterials science. 2015;3(1):103-11.
26. Yan Y, Fu J, Wang T, Lu X. Controlled release of silyl ether camptothecin from thiol-ene click chemistry-functionalized mesoporous silica nanoparticles. Acta biomaterialia. 2017;51:471-8.
27. Zhang H, Li Z, Xu P, Wu R, Wang L, Xiang Y, et al. Synthesis of novel mesoporous silica nanoparticles for loading and release of ibuprofen. Journal of Controlled Release. 2011;152:e38-e9.
28. Abd-Elrahman AA, El Nabarawi MA, Hassan DH, Taha AA. Ketoprofen mesoporous silica nanoparticles SBA-15 hard gelatin capsules: preparation and in vitro/in vivo characterization. Drug delivery. 2016;23(9):3387-98.
29. Pourjavadi A, Tehrani ZM. Mesoporous silica nanoparticles (MCM-41) coated PEGylated chitosan as a pH-responsive nanocarrier for triggered release of erythromycin. International Journal of Polymeric Materials and Polymeric Biomaterials. 2014;63(13):692-7.
30. Nastase S, Bajenaru L, Matei C, Mitran RA, Berger D. Ordered mesoporous silica and aluminosilicate-type matrix for amikacin delivery systems. Microporous and Mesoporous Materials. 2013;182:32-9.
31. Carmona D, Balas F, Santamaria J. Pore ordering and surface properties of FDU-12 and SBA-15 mesoporous materials and their relation to drug loading and release in aqueous environments. Materials Research Bulletin. 2014;59:311-22.
32. Zhang Y, Wang J, Bai X, Jiang T, Zhang Q, Wang S. Mesoporous silica nanoparticles for increasing the oral bioavailability and permeation of poorly water soluble drugs. Molecular pharmaceutics. 2012;9(3):505-13.
33. Qu F, Zhu G, Huang S, Li S, Qiu S. Effective Controlled Release of Captopril by Silylation of Mesoporous MCM-41. ChemPhysChem. 2006;7(2):400-6.
34. Jambhrunkar S, Qu Z, Popat A, Karmakar S, Xu C, Yu C. Modulating in vitro release and solubility of griseofulvin using functionalized mesoporous silica nanoparticles. Journal of colloid and interface science. 2014;434:218-25.

35. Yoncheva K, Popova M, Szegedi A, Mihály J, Tzankov B, Lambov N, et al. Functionalized mesoporous silica nanoparticles for oral delivery of budesonide. Journal of Solid State Chemistry. 2014;211:154-61.
36. Lodha A, Lodha M, Patel A, Chaudhuri J, Dalal J, Edwards M, et al. Synthesis of mesoporous silica nanoparticles and drug loading of poorly water soluble drug cyclosporin A. Journal of pharmacy & bioallied sciences. 2012;4(Suppl 1):S92.
37. Rampino A, Borgogna M, Blasi P, Bellich B, Cesàro A. Chitosan nanoparticles: preparation, size evolution and stability. International journal of pharmaceutics. 2013;455(1-2):219-28.
38. Woraphatphadung T, Sajomsang W, Gonil P, Treetong A, Akkaramongkolporn P, Ngawhirunpat T, et al. pH-Responsive polymeric micelles based on amphiphilic chitosan derivatives: Effect of hydrophobic cores on oral meloxicam delivery. International journal of pharmaceutics. 2016;497(1-2):150-60.
39. Chen C, Sun W, Wang X, Wang Y, Wang P. pH-responsive nanoreservoirs based on hyaluronic acid end-capped mesoporous silica nanoparticles for targeted drug delivery. International journal of biological macromolecules. 2018;111:1106-15.
40. Jordan V. Beyond raloxifene for the prevention of osteoporosis and breast cancer. British journal of pharmacology. 2007;150(1):3-4.
41. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Jama. 1999;282(7):637-45.
42. Shah NV, Seth AK, Balaraman R, Aundhia CJ, Maheshwari RA, Parmar GR. Nanostructured lipid carriers for oral bioavailability enhancement of raloxifene: design and in vivo study. Journal of advanced research. 2016;7(3):423-34.
43. Bikiaris D, Karavelidis V, Karavas E. Novel biodegradable polyesters. Synthesis and application as drug carriers for the preparation of raloxifene HCl loaded nanoparticles. Molecules. 2009;14(7):2410-30.
44. Prakash SJ, Santhiagu A, Jasemine S. Preparation, Characterization and In Vitro Evaluation of Novel Gellan Gum-Raloxifene HCl Nanoparticles. J Pharm BioSci. 2014;2:63-71.
45. Fontana MC, Beckenkamp A, Buffon A, Beck RCR. Controlled release of raloxifene by nanoencapsulation: effect on in vitro antiproliferative activity of human breast cancer cells. International journal of nanomedicine. 2014;9:2979.
46. Ağardan NBM, Değim Z, Yılmaz Ş, Altıntaş L, Topal T. The effectiveness of raloxifene-loaded liposomes and cochleates in breast cancer therapy. AAPS PharmSciTech. 2016;17(4):968-77.
47. Chen L, Wang Y, Zhang J, Hao L, Guo H, Lou H, et al. Bexarotene nanocrystal—oral and parenteral formulation development, characterization and pharmacokinetic evaluation. European Journal of Pharmaceutics and Biopharmaceutics. 2014;87(1):160-9.
48. Li L, Liu Y, Wang J, Chen L, Zhang W, Yan X. Preparation, in vitro and in vivo evaluation of bexarotene nanocrystals with surface modification by folate-chitosan conjugates. Drug delivery. 2016;23(1):79-87.
49. Wang Y, Rong J, Zhang J, Liu Y, Meng X, Guo H, et al. Morphology, in vivo distribution and antitumor activity of bexarotene nanocrystals in lung cancer. Drug development and industrial pharmacy. 2017;43(1):132-41.
50. Qi L, Guo Y, Luan J, Zhang D, Zhao Z, Luan Y. Folate-modified bexarotene-loaded bovine serum albumin nanoparticles as a promising tumor-targeting delivery system. Journal of Materials Chemistry B. 2014;2(47):8361-71.

51. Vasile A, Ignat M, Zaltariov MF, Sacarescu L, Stoleriu I, Draganescu D, et al. Development of new bexarotene-loaded mesoporous silica systems for topical pharmaceutical formulations. Acta Chimica Slovenica. 2018.
52. Qu L, Tang X. Bexarotene: a promising anticancer agent. Cancer chemotherapy and pharmacology. 2010;65(2):201-5.
53. Habchi J, Arosio P, Perni M, Costa AR, Yagi-Utsumi M, Joshi P, et al. An anticancer drug suppresses the primary nucleation reaction that initiates the production of the toxic Aβ42 aggregates linked with Alzheimer's disease. Science advances. 2016;2(2):e1501244.
54. Shah N, Seth A, Balaraman R, Sailor G, Javia A, Gohil D. Oral bioavailability enhancement of raloxifene by developing microemulsion using D-optimal mixture design: Optimization and in-vivo pharmacokinetic study. Drug development and industrial pharmacy. 2017:1-10.
55. Patil PH, Belgamwar VS, Patil PR, Surana SJ. Solubility enhancement of raloxifene using inclusion complexes and cogrinding method. Journal of pharmaceutics. 2013;2013.