CHAPTER 2:
LITERATURE SURVEY

CHAPTER-2: LITERATURE REVIEW

2.1 Introduction

Cancer is one of the most challenging disease to treat as it is nothing but excessive unbound growth of body's own cells. Since no other foreign substance is involved, the immune system of the body fails to fight against the metastasis. The major obstacles in its treatment are off site biodistribution and drugs leaking out during blood circulation (1). However, a lot of progress has been made and several treatment options are available like surgery, radiation and chemotherapy either individually or in an collective form. In spite of the several treatment options available the major challenge to be addressed is providing an effective and targeted therapy for cancer such that the tumor cells are exclusively targeted and healthy cells are spared from the ill effects of anticancer drugs. Thus, for achieving success in treating fatal diseases controlled drug delivery systems play a crucial role due to reduced toxicity, dose reduction, improved therapeutic efficiency and gaining patient compliance as well (2).

Anticancer drugs are known to be highly potent and hence though effective in killing tumor cells are exerting similar strong harmful effect on normal cells. The major issues faced by anticancer drugs which mars their efficacy is that of solubility, permeability and ultimately bioavailability. The drug molecules belonging to Biopharmaceutical classification system (BCS) class II and IV in specific suffer such limitations. More than half of the marketed products possess low solubility (3-5) and about 70 percent of new chemical entities (NCEs) discovered suffer low solubility issues resulting in limited efficacy (6, 7). Low solubility leads to low bioavailability limited by low dissolution rate in GIT (7). Hence, this is the foremost issue which needs to be addressed i.e. increment in solubility of the anticancer drugs.

There are many approaches available for achieving the goal of solubility and ultimately bioavailability enhancement. Some of them are solid dispersion, hydrotropy, complexation, self-emulsifying systems, micronization, nanonization etc. Nano drug delivery systems have

proved to be highly successful in achieving the objective mainly credited to their highly favorable and unique physicochemical properties (8). Mesoporous silica nanoparticles classify under one such nano drug delivery carriers which have proved to be highly successful in various applications like solubility improvement, bioavailability enhancement, targeted drug delivery and various other environmental applications apart from cargo delivery and biomedical applications. This can be attributed to their distinctly advantageous features like open pore system and well defined large surface area coupled with ease of surface functionalization, nil premature leakage and good biocompatibility(9). Various organic and functional groups which can be attached with ease include amine, chloropropyl, phenyl, benzyl, mercaptopropyl, cyanopropyl, butyl groups etc. (10-12). Other ligands like hyaluronic acid, folic acid and others targeted the respective receptors overexpressed in cancer cells can also be fastened with ease.

Notably, surface functionalized MSNs offer several more advantages than their bare counterparts. They are known to be more effective, more biocompatible and cause only minor haemolysis in comparison to unfunctionalized carriers. Their use in targeted therapy of cancer is useful in attaining exclusive drug accumulation at tumour site. Stimuli based and receptor based targeting both the approached have borne fruits and given positive results in treating the menace of cancer.

The stimuli based systems are basically of two types endogenous stimuli based and exogenous stimuli based systems. Endogenous stimuli based systems exploit the differences existing between environment of normal cells and cancer cell like reduced pH and acidic environment of cancer cell, elevated redox potentials and enhanced expression of some enzymes. Exogenous stimuli is concerned with external physical amendments like variations in magnetic field, temperature, light and electric fields (1, 13, 14). pH stimuli based drug delivery systems hold a special importance as the extracellular tumours and endosomes both having respective pH 6.8 and 5.5 are more acidic as compared to normal tissues with pH 7.4 (15-17). Thus, chances of

drugs being selectively amassed at the tumor site are increased. Of all the polymers and other pH sensitive coatings employed Polyacrylic acid (PAA) has been relatively less researched upon. Herein, PAA was used as a pH sensitive coating and was first choice due to its good biocompatibility, minimal toxicity, hydrophilicity, carboxylic group and eccentric physicochemical properties. It has been reported to have worked wonders as a candidate for pH stimuli based delivery systems (18-20). The PAA capped MSNs synthesized exhibited excellent pH responsiveness. PAA molecules acted as active gate keepers in serving the mission of controlled drug release at required specific acidic pH.

Folate receptors are one of the most overexpressed receptors in many types of cancer. Prostate cancer cell lines LNCaP and PC-3 have been reported of overexpressing folate binding proteins on their membrane (21-23). Folate overexpression has been widely exploited in other types of cancer but studies targeting these receptors for prostate cancer treatment are scarce (24, 25). Herein, we synthesized surface functionalized MSNs using a facile strategy. The FA MSNs are more useful in exhibiting internalization and causing toxicity to prostate cancer cells as compared to their unfunctionalized version.

In the present research; the applicability of bare and surface functionalized MCM-41 MSNs in prostate cancer treatment has been studied in depth. Their role in solubility and bioavailability enhancement by oral route and as intravenous targeted drug delivery carriers based on pH stimuli and Folate receptor overexpression has also been investigated along with the hem compatibility and biocompatibility studies in healthy mice.

2.2 Selection of active pharmaceutical ingredients

2.2.1 Etoposide (ETO)

Etoposide is one of the most potent and widely used anticancer drug used in treatment of cancers of various organs like lung, prostate, gastric, and testis. Chemically, it is a D-glucose

derivative and less toxic than podophyllotoxin. Its route of administration include both oral and intravenous. It is a derivative of podophyllotoxin exhibiting good antitumor activity (26, 27). ETO is Topoisomerase II inhibitor and hampers DNA synthesis by forming complex with Topoisomerase II and DNA (28, 29). It basically acts on S and G2 phase of cell cycle. Cancer cells are more likely to rely on such enzyme than healthy cell attributed to their uncontrolled multiplication. This leads to introduction of breaks in double strand DNA and prevent further repair. There remains no scope of re-ligation leading to faulty error based DNA synthesis and cancer cell death. Being a BCS class IV drug it suffers from both low solubility and permeability.

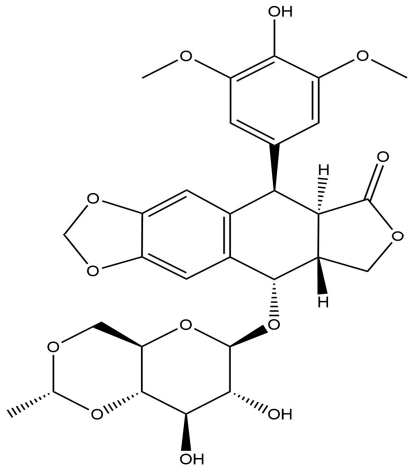
Much research has been done on ETO; investigating it for various purposes by different research groups. The various formulations tried so far for various aims like solubility enhancement, targeting and bioavailability enhancement of ETO include PLGA(30, 31), PLGA and PCA Nanoparticles (NPs) (32), glyceride-lipid NPs (33), Strontium carbonate NPs (34), Solid Lipid NPs (35-38), tripalmitin NPs (39), Self-emulsifying drug delivery systems (40, 41) etc.

So far, no research work has been carried out on formulating mesoporous silica nanoparticles for ETO, surface functionalizing the carriers and also studying pH responsive and receptor based efficacy of ETO loaded MSN formulation.

2.2.1.1 Physicochemical properties and Pharmacological characteristics of ETO

- Description: It is a DNA topoisomerase -II inhibitor used in treatment of cancer of various organs like lung, prostate, testis and gastric. It is effective in causing breaks in DNA strands, inhibiting DNA re-ligation and causes lethal error in DNA at premitotic stage itself. It basically acts at S and G2 phase of cell cycle.

- IUPAC Name:(5R,5aR,8aR,9S)-9-(((2R,4aR,6R,7R,8R,8aS)-7,8-dihydroxy-2-methylhexahydropyrano[3,2-d][1,3]dioxin-6-yl)oxy)-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one
- Structure:



- Formula: $C_{29}H_{32}O_{13}$
- Available marketed formulations: Vepesid (capsules), Lastet (capsules), Toposar (injection), Etopophos as powder
- Melting point: 236-251℃
- BCS Classification: BCS Class IV
- Log P: 1.16
- pKa: 9.33
- Solubility: 0.08mg/mL in water
- Chemistry: ETO is a semisynthetic and less toxic derivative of Podophyllotoxin, from the rhizome of the wild mandrake. It is a glycoside of podophyllotoxin with a D-glucose derivative (26).

- Mechanism of action: ETO forms a ternary complex with DNA and topoisomerase II enzyme. And prevents the relegation of DNA strands thereby causing breaks in DNA strands and hence errored DNA synthesis of cancer cells promotes apoptosis.
- Dose: 50 mg oral, 20mg/mL concentrated solution for infusion.
- Protein binding: 97%
- Metabolism: Primarily hepatic through O-demethylation through CYP450 3A4 isoenzyme pathway. It also undergoes glutathione and glucuronide conjugation. Prostaglandin synthetase are responsible for conversion of etoposide to O-demethylated metabolites (quinone).
- Route of elimination: It is excreted by both renal and non-renal processes i.e. metabolism as well as biliary excretion. Glucuronide conjugates of ETO are also excreted in human urine.
- Major side effects: Myelosuppression, Hypersensitivity, Hypotension, Secondary leukaemia, impaired hepatic function, mutagenic potential and Tumour lysis syndrome.

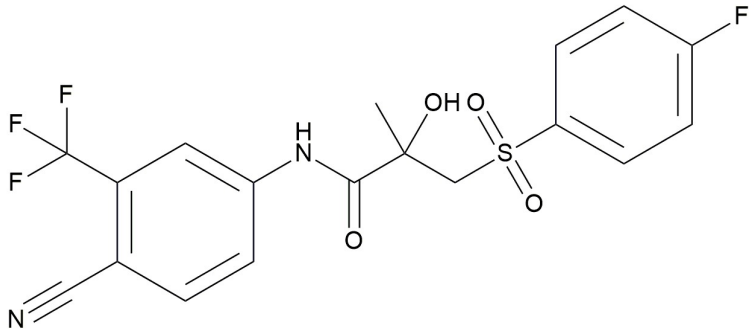
2.2.2 Bicalutamide (BIC)

Bicalutamide is the major treatment option for people suffering from Prostate cancer. It belongs to BCS class II and suffers hindered solubility issues limiting its therapeutic efficacy. It is approved for use in high doses in monotherapy of Locally advanced prostate cancer and in metastatic prostate cancer along with gonadotrophin releasing hormone analogue (42). Additionally, it is also employed for treating androgen dependent hair and skin conditions and high testosterone levels due to polycystic ovary syndrome in women (43). Various formulations of BIC are researched upon like Nano dispersion for dissolution rate enhancement (44), PLGA NPs (24, 45), nanostructured lipid carrier (46), polymeric NPs (47) in prostate cancer treatment and also BIC loaded magnetic nanoparticles (48).

No mesoporous formulation for BIC is available till date exploring the oral and iv route for the same.

2.2.2.1Physicochemical properties and Pharmacological characteristics of ETO

- Description: Bicalutamide is an androgen receptor antagonist.
- IUPAC: N-(4-cyano-3-(trifluoromethyl)phenyl)-3-((4-fluorophenyl)sulfonyl)-2-hydroxy-2-methylpropanamide
- Structure:



- Formula:$C_{18}H_{14}F_4N_2O_4S$
- Available marketed formulations: Casodex®, Cassotide, Bicalox, Bicamide all as oral tablets.
- Melting point: 191-193℃
- BCS classification: BCS class II
- Log P: 2.7
- pKa: 11.95
- Solubility: 0.00928 mg/mL
- Chemistry: Bicalutamide is a racemic mixture consisting of equal proportions of (R)- & (S)- Bicalutamide. It has a molecular weight of 430.73 g/moL. It is a synthetic and non-steroidal agent derived from flutamide. It possesses two rings ad referred to as diary propionamide or anilide.

- Mechanism of action: BIC competes with the androgen for binding to the androgen receptors. It is a highly competitive silent androgen receptor antagonist. Due to competitive antagonism it has no capacity to activate AR under normal physiological conditions.
- Dose: 50 mg oral dose
- Protein binding: 96%
- Metabolism: Bicalutamide undergoes hepatic stereo-specific metabolism. The inactive S isomer is metabolised primarily by glucuronidation. The R isomer also undergoes same treatment but it is mostly oxidized to an inactive metabolite followed by glucuronidation.
- Route of elimination: Bicalutamide has a long plasma elimination half life of about 1 weeks in humans. It is eliminated in faeces and urine(49) whereas its metabolites are eliminated through urine and bile(50). Both BIC and its metabolites are excreted as glucuronide conjugates(51).
- Major side effects: Hot flashes, night time excessive urination, lower back and pelvic pain, high blood pressure, infection, trouble breathing and anaemia.

2.3 Need for the study

A large number of newer cancer cases are being reported annually. Cancer still remains a lethal disease with no definite cure. Despite many technological advances in medical field, improvements in cancer treatment is still lagging behind. Current cancer treatments including chemotherapy kills healthy cells as well and causes toxicity to patients. The biggest challenge in current cancer treatment is the design of a smart drug delivery system for targeted delivery of anticancer agents. Due to lack of specification and solubility of drug molecules, patients have to take high doses of the drug to achieve the desired therapeutic effects for the treatment of cancer. Hence, designing new targeted drug delivery systems becomes imperative.

There is a dire need of a sure shot targeted treatment of cancer which can be achieved with the novel drug delivery systems like MSNs. They hold lot of potential and can prove to be far more effective over the conventional chemotherapeutics.

Apart from the issues mentioned above the major challenge that the drug formulation is facing today is that most of the NCEs discovered suffer from solubility and permeability limitations. This is likely to affect their bioavailability and inn turn efficacy. Thus, it becomes imperative to design a nanoparticle based drug delivery system which can provide an enhanced surface area for good drug loading and release and in turn increase the solubility by providing improved dissolution kinetics and drug release properties. This can in turn aid in permeability and bioavailability enhancement as well.

Mesoporous silica materials become known as a promising candidate that can overcome above problems and produce effects. The unique mesoporous structure of silica facilitates effective loading of drugs and their subsequent release of the target site. Other features such as tunable pore size, and uniform pore size leading to uniform release, zero premature release and good biocompatibility and biodegradability are added feather to the cap. Therefore, encapsulation of drug into mesoporous silica nanoparticle, capable of selectively targeting the cancer cells leads to greater therapeutic effectiveness with minimal side effects.

2.4 References

1. Yang K-N, Zhang C-Q, Wang W, Wang PC, Zhou J-P, Liang X-J. pH-responsive mesoporous silica nanoparticles employed in controlled drug delivery systems for cancer treatment. Cancer biology & medicine. 2014;11(1):34.

2. Uhrich KE, Cannizzaro SM, Langer RS, Shakesheff KM. Polymeric systems for controlled drug release. Chemical reviews. 1999;99(11):3181-98.

3. 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.

4. 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.

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. 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.

7. 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.

8. Zhang L, Gu F, Chan J, Wang A, Langer R, Farokhzad O. Nanoparticles in medicine: therapeutic applications and developments. Clinical pharmacology & therapeutics. 2008;83(5):761-9.

9. Vallet-Regí M, Ruiz-González L, Izquierdo-Barba I, González-Calbet JM. Revisiting silica based ordered mesoporous materials: medical applications. Journal of Materials Chemistry. 2006;16(1):26-31.

10. Huh S, Wiench JW, Trewyn BG, Song S, Pruski M, Lin VS-Y. Tuning of particle morphology and pore properties in mesoporous silicas with multiple organic functional groups. Chemical Communications. 2003(18):2364-5.

11. Xu W, Gao Q, Xu Y, Wu D, Sun Y, Shen W, et al. Controlled drug release from bifunctionalized mesoporous silica. Journal of Solid State Chemistry. 2008;181(10):2837-44.

12. Wang G, Otuonye AN, Blair EA, Denton K, Tao Z, Asefa T. Functionalized mesoporous materials for adsorption and release of different drug molecules: A comparative study. Journal of Solid State Chemistry. 2009;182(7):1649-60.

13. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nature reviews Drug discovery. 2014;13(11):813.

14. Zhu L, Torchilin VP. Stimulus-responsive nanopreparations for tumor targeting. Integrative Biology. 2012;5(1):96-107.

15. Peng H, Dong R, Wang S, Zhang Z, Luo M, Bai C, et al. A pH-responsive nano-carrier with mesoporous silica nanoparticles cores and poly (acrylic acid) shell-layers: fabrication, characterization and properties for controlled release of salidroside. International journal of pharmaceutics. 2013;446(1-2):153-9.

16. Engin K, Leeper D, Cater J, Thistlethwaite A, Tupchong L, McFarlane J. Extracellular pH distribution in human tumours. International Journal of Hyperthermia. 1995;11(2):211-6.

17. Lee ES, Oh KT, Kim D, Youn YS, Bae YH. Tumor pH-responsive flower-like micelles of poly (L-lactic acid)-b-poly (ethylene glycol)-b-poly (L-histidine). Journal of Controlled Release. 2007;123(1):19-26.

18. Yuan L, Tang Q, Yang D, Zhang JZ, Zhang F, Hu J. Preparation of pH-responsive mesoporous silica nanoparticles and their application in controlled drug delivery. The Journal of Physical Chemistry C. 2011;115(20):9926-32.

19. Xiao X, Liu Y, Guo M, Fei W, Zheng H, Zhang R, et al. pH-triggered sustained release of arsenic trioxide by polyacrylic acid capped mesoporous silica nanoparticles for solid tumor treatment in vitro and in vivo. Journal of biomaterials applications. 2016;31(1):23-35.

20. Li H, Yu H, Zhu C, Hu J, Du M, Zhang F, et al. Cisplatin and doxorubicin dual-loaded mesoporous silica nanoparticles for controlled drug delivery. RSC Advances. 2016;6(96):94160-9.

21. Hattori Y, Maitani Y. Folate-linked nanoparticle-mediated suicide gene therapy in human prostate cancer and nasopharyngeal cancer with herpes simplex virus thymidine kinase. Cancer gene therapy. 2005;12(10):796.

22. Martínez-Carmona M, Lozano D, Colilla M, Vallet-Regí M. Selective topotecan delivery to cancer cells by targeted pH-sensitive mesoporous silica nanoparticles. Rsc Advances. 2016;6(56):50923-32.

23. Singh R, Singh S, Sharma PK, Lillard Jr JW. T regulatory and prostate cancer cell-specific drug targeting using novel XPclad© nanoparticles (42.7). Am Assoc Immnol; 2009.

24. Dhas NL, Ige PP, Kudarha RR. Design, optimization and in-vitro study of folic acid conjugated-chitosan functionalized PLGA nanoparticle for delivery of bicalutamide in prostate cancer. Powder technology. 2015;283:234-45.

25. Bonvin D, Bastiaansen JA, Stuber M, Hofmann H, Ebersold MM. Folic acid on iron oxide nanoparticles: Platform with high potential for simultaneous targeting, MRI detection and hyperthermia treatment of lymph node metastases of prostate cancer. Dalton Transactions. 2017;46(37):12692-704.

26. Hande K. Etoposide: four decades of development of a topoisomerase II inhibitor. European journal of cancer. 1998;34(10):1514-21.

27. Gordaliza M, Garcıa P, Del Corral JM, Castro M, Gómez-Zurita M. Podophyllotoxin: distribution, sources, applications and new cytotoxic derivatives. Toxicon. 2004;44(4):441-59.

28. Pommier Y, Leo E, Zhang H, Marchand C. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. Chemistry & biology. 2010;17(5):421-33.

29. Baldwin E, Osheroff N. Etoposide, topoisomerase II and cancer. Current Medicinal Chemistry-Anti-Cancer Agents. 2005;5(4):363-72.

30. Yadav KS, Sawant KK. Formulation optimization of etoposide loaded PLGA nanoparticles by double factorial design and their evaluation. Current drug delivery. 2010;7(1):51-64.

31. Yadav KS, Chuttani K, Mishra AK, Sawant KK. Long circulating nanoparticles of etoposide using PLGA-MPEG and PLGA-pluronic block copolymers: characterization, drug-release, blood-clearance, and biodistribution studies. Drug Development Research. 2010;71(4):228-39.

32. Snehalatha M, Venugopal K, Saha RN, Babbar AK, Sharma RK. Etoposide loaded PLGA and PCL nanoparticles II: biodistribution and pharmacokinetics after radiolabeling with Tc-99m. Drug delivery. 2008;15(5):277-87.

33. Reddy LH, Murthy R. Etoposide-loaded nanoparticles made from glyceride lipids: formulation, characterization, in vitro drug release, and stability evaluation. AAPs PharmSciTech. 2005;6(2):E158-E66.

34. Qian W-Y, Sun D-M, Zhu R-R, Du X-L, Liu H, Wang S-L. pH-sensitive strontium carbonate nanoparticles as new anticancer vehicles for controlled etoposide release. International journal of nanomedicine. 2012;7:5781.

35. Reddy LH, Adhikari JS, Dwarakanath BSR, Sharma RK, Murthy RR. Tumoricidal effects of etoposide incorporated into solid lipid nanoparticles after intraperitoneal administration in Dalton's lymphoma bearing mice. The AAPS journal. 2006;8(2):E254-E62.

36. Athawale RB, Jain DS, Singh KK, Gude RP. Etoposide loaded solid lipid nanoparticles for curtailing B16F10 melanoma colonization in lung. Biomedicine & Pharmacotherapy. 2014;68(2):231-40.

37. Kuo Y-C, Hong T-Y. Delivering etoposide to the brain using catanionic solid lipid nanoparticles with surface 5-HT-moduline. International journal of pharmaceutics. 2014;465(1-2):132-42.

38. Kuo Y-C, Lee C-H. Inhibition Against Growth of Glioblastoma Multiforme In Vitro Using Etoposide-Loaded Solid Lipid Nanoparticles with ρ-Aminophenyl-α-D-Manno-Pyranoside and Folic Acid. Journal of pharmaceutical sciences. 2015;104(5):1804-14.

39. Reddy LH, Sharma RK, Chuttani K, Mishra AK, Murthy RR. Etoposide-incorporated tripalmitin nanoparticles with different surface charge: formulation, characterization, radiolabeling, and biodistribution studies. The AAPS journal. 2004;6(3):55-64.

40. Wu Z, Guo D, Deng L, Zhang Y, Yang Q, Chen J. Preparation and evaluation of a self-emulsifying drug delivery system of etoposide–phospholipid complex. Drug development and industrial pharmacy. 2011;37(1):103-12.

41. Akhtar N, Talegaonkar S, Khar RK, Jaggi M. Self-nanoemulsifying lipid carrier system for enhancement of oral bioavailability of etoposide by P-glycoprotein modulation: in vitro cell line and in vivo pharmacokinetic investigation. Journal of biomedical nanotechnology. 2013;9(7):1216-29.

42. Schellhammer PF, Sharifi R, Block NL, Soloway MS, Venner PM, Patterson AL, et al. Nical benefits of bicalutamide compared with flutamide in combined androgen blockade for

patients with advanced prostatic carcinoma: Final report of a double-blind, randomized, multicenter trial. Urology. 1997;50(3):330-6.

43. Moretti C, Guccione L, Di Giacinto P, Simonelli I, Exacoustos C, Toscano V, et al. Combined oral contraception and bicalutamide in polycystic ovary syndrome and severe hirsutism: a double-blind randomized controlled trial. The Journal of Clinical Endocrinology & Metabolism. 2017;103(3):824-38.

44. Li C, Li C, Le Y, Chen J-F. Formation of bicalutamide nanodispersion for dissolution rate enhancement. International journal of pharmaceutics. 2011;404(1-2):257-63.

45. Ray S, Ghosh S, Mandal S. Development of bicalutamide-loaded PLGA nanoparticles: preparation, characterization and in-vitro evaluation for the treatment of prostate cancer. Artificial cells, nanomedicine, and biotechnology. 2017;45(5):944-54.

46. Kudarha R, Dhas NL, Pandey A, Belgamwar VS, Ige PP. Box–Behnken study design for optimization of bicalutamide-loaded nanostructured lipid carrier: stability assessment. Pharmaceutical development and technology. 2015;20(5):608-18.

47. Arya A, Khandelwal K, Ahmad H, Laxman TS, Sharma K, Mittapelly N, et al. Co-delivery of hesperetin enhanced bicalutamide induced apoptosis by exploiting mitochondrial membrane potential via polymeric nanoparticles in a PC-3 cell line. RSC Advances. 2016;6(7):5925-35.

48. Lee K-J, An J-H, Shin J-S, Kim D-H. Synthesis and characterization of bicalutamide-loaded magnetic nanoparticles as anti-tumor drug carriers. Journal of nanoscience and nanotechnology. 2012;12(2):1611-5.

49. Weber GF. Hormone Therapy. Molecular Therapies of Cancer: Springer; 2015. p. 303-32.

50. Fradet Y. Bicalutamide (Casodex®) in the treatment of prostate cancer. Expert review of anticancer therapy. 2004;4(1):37-48.

51. Schellens JH, McLeod HL, Newell DR. Cancer clinical pharmacology: Oxford University Press; 2005.