JAPR

Vol. 01, Issue, 02, pp. 7-12, February, 2024

RESEARCH ARTICLE

Docetaxel: Strategy to Enhance Their Efficiency Using Polymeric Nanocomposite

Ayesha Bibi [a], Ajmal Shah [a], Maryam Israr [a], Shagufta Rani [a], Nayab Tariq [a], Rabia Habib [a], Muhammad Ahsan [a]*, Mansoor Ali Khan [a]*

[a] *Department of Chemistry Abdul Wali Khan University, Mardan 23200, KPK, Pakistan.*

ARTICLE INFO

Article History:
Received 15 *January*, 2024
Received in revised form 2 *February*, 2024
Accepted 15 *February*, 2024
Published online 17 *February*, 2024

Keywords:
MNPs
MNPs @SiO_2
@p(AN-co-AA-co-EGDMA)
Docetaxel
Loading

Corresponding author: Muhammad Ahsan and Mansoor Ali Khan
E-mail addresses:
mahsan94544@gmail.com
mk940084@gmail.com

ABSTRACT

Docetaxel (DTX) is a semi-synthetic anticancer drug from the taxoid family. DTX is a good anti-mitotic anticancer agent that can be used to treat many types of human cancer. DTX does have some problems, such as not dissolving well in water, being highly poisonous overall, and not being distributed in a specific way. To solve these issues, researchers have been working on making nanocarriers that can carry DTX to the targeted site. Polymeric nanocomposites have gained great attention as carriers for drugs delivery. In this study, magnetite coated silica (MNPs@SiO_2) were made and covered with a polymer of organic ligands that is acrylonitrile (AN), acrylic acid (AA), and ethylene glycol dimethacrylate (EGDMA) to load the DTX. The polymeric nanocomposite (MNPs@SiO_2@p (AN-co-AA-co-EGDMA)) was collected as a white powder and studied using FTIR, EDX, and SEM techniques. The prepared polymeric nanocomposite was studied for loading of docetaxel. The effect of contact time, pH, and polymeric nanocomposite amount on the loading of the drug were also evaluated. The maximum loading for docetaxel (93.4%) was observed at 10mg of the polymeric nanocomposite, pH of 4, and time of 6 h.

1. Introduction

Prostate cancer (PC) is one of the most common types of cancer in men, and with the highest incidence rate reported among Africans. The World Health Organization (WHO) says that cancer is still the leading cause of death and that number will likely rise to 17.5 million by 2050. In the UK in 2017, about 1,60,000 men were diagnosed with it [1]. Radiotherapy and chemotherapy are the most common treatments, but they have a lot of side effects and toxins that affect the whole body. Additionally, advanced prostate cancer, also known as metastatic cancer, can still be cured with the help of chemotherapy and other treatments that extend life. To better manage and increase the survival percentage of patients with advanced PC, it is vital to create a viable medication delivery method [2]**.** The creation of highly efficient medications and the delivery of those drugs in a manner that is selective to malignant cells while minimizing harmful effects on normal cells is the primary challenge. A great number of studies on the development of chemotherapies for prostate cancer have been designed and produced by researchers [3]**.** One of the substances that shows potential is DTX, which is a toxoid and is widely used as an anticancer medication against cancers of the prostate, breast, neck, hepatic, pancreatic, and stomach. As a result of its high affinity for the binding site of the β tubulin protein, which is responsible for initiating the assembly of tubulin into microtubules, the DTX exerts its influence by blocking the process of microtubule depolymerization. Therefore, stopping of microtubule depolymerization during the G2/M phase ultimately results in the arrest of the cell cycle and the initiation of apoptosis [4,5]. DTX also shows an anti-angiogenic effect [6]. When compared to other cancer therapies such as doxorubicin,

paclitaxel, and fluorouracil, it is believed to be a more effective anti-microtubule agent [7]. DTX is a more powerful medicine than paclitaxel; hence, a lower doses of docetaxel was able to produce a considerable amount of apoptosis in cancer cells, but a higher dose of paclitaxel was able to do precisely the same thing [8]. DTX, on the other hand, has a few drawbacks, including its break down as a result of a high metabolism in the liver by a member of the cytochrome P450 family (CYP3A4), its insolubility in water, its limited bioavailability, its non-uniform bio distribution, its high renal clearance, its sensitization, and its dose dependent hazardous side effects [1].Taking into consideration these limitations, a wide range of innovative nanotechnology based techniques, designed and assessed such as liposomes [9], Carbon nanotubes [10]**,** micelles [11]**,** Nano conjugates [12]**,** and inorganic nanoparticles [13] for DTX that have been identified as a potentially beneficial addition to enhance the effectiveness of treatment by increasing solubility, improving pharmacokinetics (PK), and increasing bioavailability. Nevertheless, solid tumours exhibit a growing incidence of treatment resistance as a result of the lack of a lymphatic system, acidic milieu, oxygen deprivation, and heightened vascular permeability. These factors contribute to the presence of heterogeneous vasculature and elevated interstitial fluid pressure (IFP). Furthermore, the abnormal growth of blood vessels (aberrant angiogenesis) has modified the mechanisms that prevent cell death (antiapoptotic) and promote cell division (proliferative). This has resulted in medication resistance, which can be attributed to changes in the tumour microenvironment [1]. Since docetaxel became known as the first choice for treating advanced or metastatic prostate cancer, resistance to it has been a big problem in the field [14]**.** It has been very important to come up with a nanoformulation that might make docetaxel more soluble or improve circulation and permeability by turning around prostate cancer cells resistance to it [15]. Magnetic nanoparticles (MNPs) have gotten a lot of attention lately as a medical tool. For example, they can be used as a drug carrier or a contrast agent in magnetic resonance imaging. Because iron oxide MNPs can be changed into a natural form of iron in the body, like haemoglobin in red blood cells, they are widely used in medicinal fields as non-toxic and biodegradable materials. Iron oxide MNPs stick together because they have a lot of surface area and interact with each other using dipoles. This makes the particles bigger. To get around this problem, designing the surface of MNPs is a good way to keep them from sticking together. To reach this goal, various polymers and inorganic materials can be used, or proteins can be chemically attached to other molecules. One of the most important parts of creating new drug delivery systems is picking the right organic molecules to act as surface modifiers or drug trapping agents. This is done so that the drugs can be loaded and released efficiently [16]. Using a magnetic iron oxide core covered in the right organic or inorganic coat has worked well in many biological tasks, ranging from separating large molecules to using magnetic resonance imaging. When it comes to coating materials, silica is likely the most studied and most widely used one. The silica coat not only makes magnetic nanoparticles more stable in water, but it also gives different functional groups a place to connect [17]. Nanoparticles with polymers on them can stop grains from growing and clumping together and make it easier for other nanoparticles to stick to them [18]. Different types of polymerization methods are used to make the polymer coating. The microwave assisted polymerization method is one of the best ways to polymerize. The microwave assisted polymerization technique has slowly become a popular synthetic tool because it has many benefits, including shorter reaction times, higher yields, fewer by-products, and the ability to be scaled up without any negative effects. This is because the microwave heating process, high temperatures, and short periods of high pressure make reactions happen faster than with traditional methods [19]. The physical qualities of the polymer that is made this way have also been seen to improve. Microwave-assisted polymerization is very useful in polymer study because it has many benefits, such as direct heating, high temperature uniformity, a fast reaction rate, and lower energy use. As was already said, it also leads to big changes in yield, selectivity, and the physical and chemical properties of new material phases [20, 21, 22, 23]. A lot of people are interested in controlled drug delivery methods, and big changes are likely to happen soon. They can direct the drug to certain parts of the body, like an organ, tissue, cell, or tumor, or they can control how fast or how much of the healing agent is released. There are some controlled delivery methods that can do both at the same time. Because of these features, the bad side effects are lessened, the drugs don't hurt healthy parts of the body, the effective level is kept, and large doses of the drug are avoided. These features are particularly important for anticancer drugs that kill cells [24,25,26,27]. In the current study DTX is loaded onto the polymeric nanocomposite for enhancing the efficiency of anticancer drug medication DTX.

2. Materials and Methods

2.1 Chemicals

All the chemicals used were of analytical grade. Acrylonitrile (AN), Acrylic acid (AA), Azobisisobutyronitrile (AIBN), Ethylene glycol dimethaacrylate (EGDMA) and Docetaxel anticancer drug were purchased from sigma Aldrich.

2.2 Preparation of iron oxide nanomaterials

Fe_3O_4 MNPs were synthesized by the chemical co-precipitation method as mentioned in our earlier publication [28].

2.3 Silica coating on MNPs

Silica coating on MNPs were done by the stober method as mentioned in our earlier publication [28].

2.4 Polymer coating over MNPs@SiO_2

To prepare polymeric nanocomposites of Silica coated MNPs and polymeric shell, 0.3 g of the synthesized MNPs@SiO_2 was reserved and added to the 80 mL mixture of acetonitrile and dist.H_2O (3:1 v/v) in a vessel and 40 min sonicated. After sonication 0.06 g of AN, 0.0404 ml of AA, 6 mg of AIBN and 0.244 ml of EGDMA was added to the reaction mixture. Then the mixture was 10 min purged with N_2 and 40 min sonicated at 353.15K and then the reacting mixture was kept for 25 min in oven at 403.15 K and then for few min at 423.15 K till polymerization. The product was filtered, washed several times with methanol and deionized water. The product was dry for 2h in an oven at 373.15 K and grinded [29].

2.5 Characterization

A Shimadzu Corporation made FTIR spectrophotometer was used to identify the functional groups in polymeric nanocomposite. SEM analysis were done to know about the structures of polymeric nanocomposite and to know about the elemental analysis of the synthesized polymeric nanocomposite an Oxford EDX (Inca-200) was used.

2.6 Docetaxel adsorption for its potential loading

20 ml of 20 ppm docetaxel working solution was used for every adsorption study. Then the 20 mL solution was taken in a 100mL beaker and placed at room temperature in a shaker with 120 rpm speed. Various adsorption analysis were done with different desired pH, adsorbent weight, and time interval. The adsorbent polymeric nanocomposite was removed via an external magnet after the adsorption of docetaxel. The reacting solutions were then compared with parent solution of 20 ppm at 272 nm by a spectrophotometer of double beam. The % adsorption of drug docetaxel via polymeric nanocomposites was evaluated by given formula.

$$\% \text{ Ads.} = C_i - C_f \times 100/Ci$$

Where C_i is the initial concentrations and C_f is the final concentration

3. Results and discussion

3.1 FTIR Analysis

Figure 1 displays the FTIR spectrum of the magnetite coated silica coated polymeric nanocomposite. The peak at 2950 cm^{-1} showed that the CH_3 and CH_2 groups of AA, AN, and EGDMA were stretching vibrations. The peak at 2200 cm^{-1} showed the C–N group of AN. The sharp rise in absorption seen at 1725 cm^{-1} was caused by the C=O groups of AA and EGDMA. The peaks seen at 1400 and 1330 cm^{-1} show that the bending vibration of CH_3 in the C-CH_3 of the EGDMA. The broad peak at 1158 cm^{-1} is because the C-O is stretching. The results showed that the polymer changed the surface of the MNPs@SiO_2 nanocomposite.

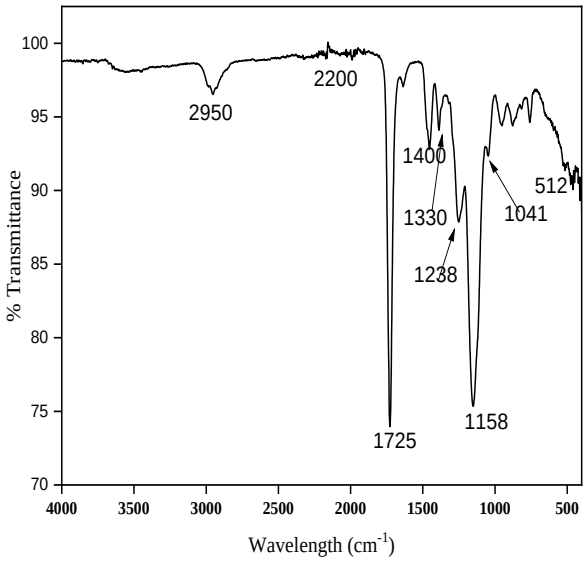

Figure 1. FTIR Analysis of polymeric nanocomposite

3.2 SEM Analysis

Figure 2 shows the SEM pictures of the polymeric nanocomposite. The image showed that the polymeric nanocomposite has flowers like porous morphology. It can be seen from the SEM image that the particles are bigger and their edges are brighter. Before, Javidi et al. (2015) used molecular imprinting to put a polymer layer on MNPs@SiO_2 and revealed that the polymer was shaped like a sphere and had a smooth surface [29].

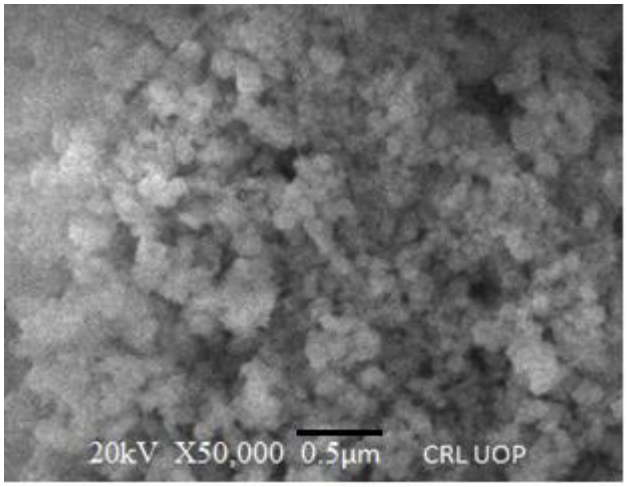

Figure 2. SEM image of polymeric nanocomposite

3.3 EDX spectrum

An EDX spectrum confirmed the elements that made up the synthesised polymeric nanocomposite. The EDX spectrum of the polymeric nanocomposite is shown in Figure 3. The fact that oxygen and carbon are present on the MNPs@SiO_2 shows that a polymer (AN-co-AA-co-EGDMA) is there. It was easy to see from the EDX spectrum that the polymeric shell surrounds the iron and silica elements. The results show that this simple, cheap, and quick method can be used to make multi-component core-shell hybrids.

Table 1. Elemental composition of polymeric nanocomposite

Element	Weight%	Atomic%
C	73.10	79.29
O	24.77	20.17
Si	0.26	0.10
Fe	1.87	0.44
Totals	100.00	100.0

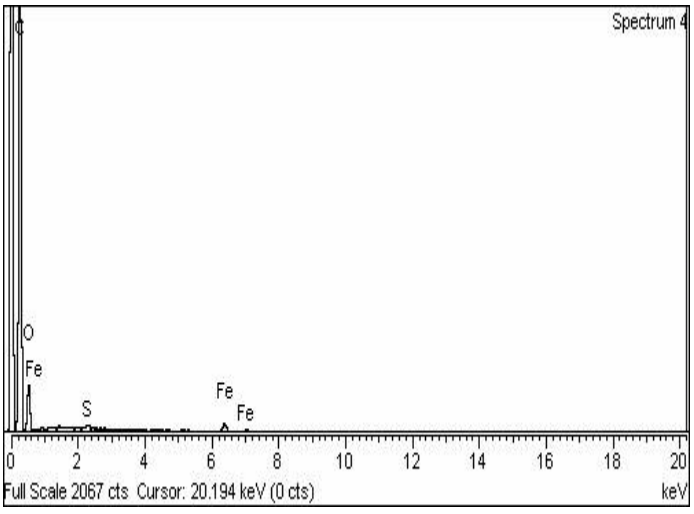

Figure 3. EDX spectrum of polymeric nanocomposite

3.4 Adsorption studies

3.4.1 Spectroscopic determination of docetaxel

DTX was assessed for its maximum absorbance (max) at 272 nm by scanning a 20 µg/mL prepared drug solution with a double-beam UV/Visible spectrophotometer from 200 nm to 800 nm. To determine the impact of docetaxel concentration on absorbance value, the solutions absorbance with different concentrations (5.0, 10.0, 15.0, 20.0, 30.0 µg/mL) was calculated at 272 nm with a reference of 90% ethanol and is plotted in figure number 4. To find out the straight line equation absorbance versus concentration plot was used and the graph provide a linear lapse which facilitated us for concentration calculations in additional studies.

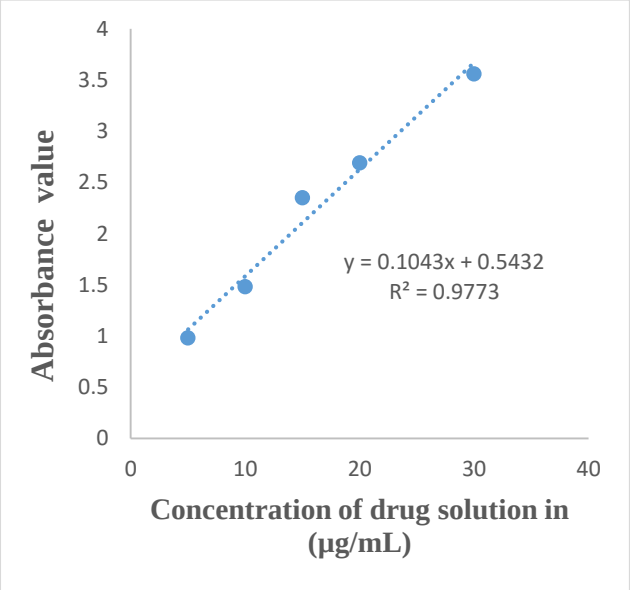

Figure 4. Docetaxel concentration effect on absorbance

As straight line equation is,

y =mx + c……..eq 1

X=y-c /m……eq 2

X= y –0.5432/0.1043……eq 3

3.4.2 Effect of polymeric nanocomposite on docetaxel adsorption

Utilizing 20 mL of working solutions with a range of concentrations from 05 to 40 mg, the docetaxel adsorption was carried out in a shaker incubator at 120 rpm speed and set time interval. The docetaxel adsorption values with reference to various concentrations of adsorbent dose are plotted in figure 5. As the amount of adsorbent was raised from 05 to 10 mg, the adsorption of docetaxel increased. After that, a little rise was noticed, but it was not significant

statistically. Therefore, optimum adsorbent dose of 10mg was chosen and drug concentrations of 20µg/mL was chosen optimum.

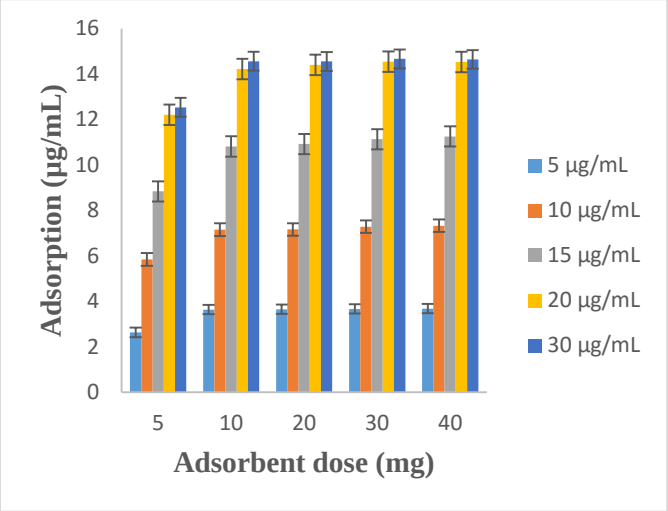

Figure 5. Docetaxel adsorption values with reference to various concentrations of adsorbent dose

3.4.3 Influence of time on docetaxel adsorption

Adsorption was carried out in a shaker incubator at 120 rpm speed and at various interval of times including 02.00 hours, 03.00, 04.00, 05.00, 06.00, and 12.00 h, with constant conditions, adsorbent dose (10mg) and concentration of drug (20µg/mL), with increase in time the adsorption also increased and the maximum adsorption was found in 6 h. Therefore, the optimum time was selected 6 h. Effect of time on docetaxel adsorption are plotted in figure 6.

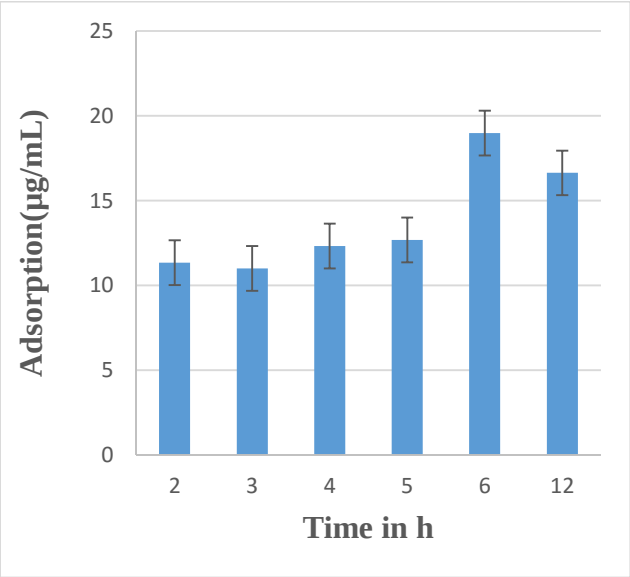

Figure 6. Effect of time on docetaxel adsorption

3.4.4 Effect of pH on adsorption of docetaxel

Docetaxel adsorption was also done while examining how pH levels between 2 and 10 affected the process. Other reaction parameters, such as the amount of adsorbent (10 mg), the volume of DTX solution (20 µg/mL), the adsorption period (6 h), and the speed of shaking in the shaker incubator (120 rpm), were maintained constant. A UV-Visible double beam spectrophotometer was used to measure the results for each pH value at a fixed wavelength of 272 nm. The results of adsorption are plotted in figure 7. The results confirmed that the produced adsorbent has the capacity to adsorb docetaxel at all pH levels, but that it absorbs the most docetaxel (93.4%) at 4 pH. Therefore, the optimum pH was nominated as 4 for docetaxel adsorption. The final shape of the synthesized adsorbent, the fundamental structure of docetaxel, and the site of zero-charge are responsible for this (PZ-Ch). At the adsorbent surface, PZ-Ch has a positive (+ve) charge when the pH is less than 4, and a negative (-ve) charge when the pH is higher.

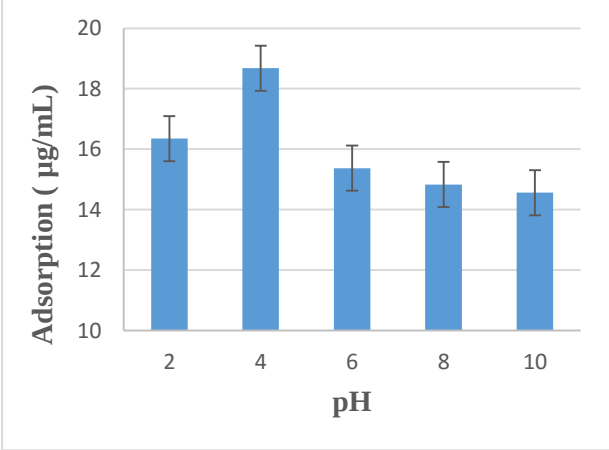

Figure.7 Effect of pH on adsorption of docetaxel

4. Conclusion

The co-precipitation method was used to make iron oxide nanoparticles, which were then covered with silica using the Stober method. The magnetite coated silica were then covered with a polymer made of AN, AA, and EGDMA through microwave assisted precipitation polymerization. We used FTIR, SEM and EDX to study the magnetite coated silica covered with a polymer that was made. We looked at how well the magnetite coated silica covered with a polymer nanocomposite loaded with anticancer drug, specifically docetaxel. The results showed that docetaxel were loaded onto the polymeric nanocomposite successfully.

Acknowledgement: Authors are grateful to the Department of Chemistry, Abdul Wali Khan University Mardan,

Pakistan, for providing the facilities for all the experimental work.

Date availability statement: No supplementary data is available.

Ethics approval statement: Not applicable.

Funding: Not applicable

Authorship contribution statement: The study's conceptualization, design, preparation of the materials, data collection, analysis, and paper writing were all done by the authors.

References:

[1]. Korake S, Bothiraja C. and Pawar A. (2023). Design, development, and in-vitro/in-vivo evaluation of Docetaxel-loaded PEGylated Solid Lipid Nanoparticles in Prostate Cancer Therapy. Eur J Pharm Biopharm.

[2]. Crabb SJ, Birtle AJ, Martin K, Downs N, Ratcliffe I, Maishman T, Ellis M, Griffiths G, Thompson S, Ksiazek L, and Khoo V. (2017). ProCAID: a phase I clinical trial to combine the AKT inhibitor AZD5363 with docetaxel and prednisolone chemotherapy for metastatic castration resistant prostate cancer. Invest New Drugs. *35*: 599-607.

[3]. Ganju A, Yallapu MM, Khan S, Behrman SW, Chauhan SC, and Jaggi M. (2014). Nanoways to overcome docetaxel resistance in prostate cancer. Drug Resist. Updat. *17*(1-2): 13-23.

[4]. Cho HJ, Park JW, Yoon IS, and Kim DD. (2014). Surface-modified solid lipid nanoparticles for oral delivery of docetaxel: enhanced intestinal absorption and lymphatic uptake. Int J Nanomedicine. 495-504.

[5]. Xu Z, Chen L, Gu W, Gao Y, Lin L, Zhang Z, Xi Y, and Li Y. (2009). The performance of docetaxel-loaded solid lipid nanoparticles targeted to hepatocellular carcinoma. Biomater. *30*(2): 226-232.

[6]. Vacca A, Ribatti D, Iurlaro M, Merchionne F, Nico B, Ria R, and Dammacco F. (2002). Docetaxel versus paclitaxel for antiangiogenesis. Stem Cell Res. *11*(1): 103-118.

[7]. Sumera Anwar A, Ovais M, Khan A, and Raza A. (2017). Docetaxel-loaded solid lipid nanoparticles: a novel drug delivery system. *IET* J. Nanobiotechnology. *11*(6): 621-629.

[8]. Grant DS, Williams TL, Zahaczewsky M, and Dicker AP. (2003). Comparison of antiangiogenic activities using paclitaxel (taxol) and docetaxel (taxotere). Int. J. Cancer. *104*(1): 121-129.

[9]. Kobayashi D, Kawai N, Sato S, Naiki T, Yamada K, Yasui T, Tozawa K, Kobayashi T, Takahashi S, and Kohri K. (2013). Thermotherapy using magnetic cationic liposomes powerfully suppresses prostate cancer bone metastasis in a novel rat model. Prostate 73(9): 913-922.

[10]. Wang L, Zhang M, Zhang N, Shi J, Zhang H, Li M, Lu C, and Zhang Z. (2011). Synergistic enhancement of cancer therapy using a combination of docetaxel and photothermal ablation induced by single-walled carbon nanotubes. Int J Nanomedicine. 2641-2652.

[11]. Dou J, Zhang H, Liu X, Zhang M, and Zhai G. (2014). Preparation and evaluation in vitro and in vivo of docetaxel loaded mixed micelles for oral administration. Colloids Surf. B. 114: 20-27.

[12]. Khatun Z, Nurunnabi M, Reeck GR, Cho KJ, and Lee YK. (2013). Oral delivery of taurocholic acid linked heparin–docetaxel conjugates for cancer therapy. J.control.release. 170(1): 74-82.

[13]. Thambiraj S, Vijayalakshmi R, and Ravi Shankaran D. (2021). An effective strategy for development of docetaxel encapsulated gold nanoformulations for treatment of prostate cancer. Sci. Rep 11(1): 2808.

[14]. Albano JM, de Morais Ribeiro LN, Couto VM, Messias MB, da Silva GHR, Breitkreitz MC, de Paula E, and Pickholz M. (2019). Rational design of polymer-lipid nanoparticles for docetaxel delivery. Colloids Surf. B. 175: 56-64.

[15]. Desale JP, Swami R, Kushwah V, Katiyar SS, and Jain S. (2018). Chemosensitizer and docetaxel-loaded albumin nanoparticle: overcoming drug resistance and improving therapeutic efficacy. Nanomed. J. 13(21): 2759-2776.

[16]. Tarasi R, Khoobi M, Niknejad H, Ramazani A, Ma'mani L, Bahadorikhalili S, and Shafiee A. (2016). β-cyclodextrin functionalized poly (5-amidoisophthalicacid) grafted Fe_3O_4 magnetic nanoparticles: A novel biocompatible nanocomposite for targeted docetaxel delivery. J. Magn. Magn. Mater. 417: 451-459.

[17]. Sharafi Z, Bakhshi B, Javidi J, and Adrangi S. (2018). Synthesis of silica-coated iron oxide nanoparticles: preventing aggregation without using additives or seed pretreatment. IJPR. 17(1): 386.

[18]. Murugan E, Ariraman M, Rajendran S, Kathirvel J, Akshata CR, and Kumar K. (2018). Core–Shell Nanostructured Fe_3O_4–Poly (styrene-co-vinylbenzyl chloride) Grafted PPI Dendrimers Stabilized with AuNPs/PdNPs for Efficient Nuclease Activity. ACS omega. 3(10): 3685-13693.

[19]. Shah N, Nisar N, Rehan T, Naeem M, and Ul-islam M. (2022). Microwave-assisted synthesis of a magnetic core–shell material composed of Fe_3O_4@ SiO_2@ poly (methacrylamide-co-acrylic acid) for an anticancer drug loading. Appl. Nanosci. 12(11): 3547-3554.

[20]. Sierra J, Palacios J, and VivaldoLima E. (2006). Effect of microwave activation on polymerization rate and molecular weight development in emulsion polymerization of methyl methacrylate. Journal of Macromolecular Science Part A: Pure Appl. Chem. 43(3): 589-600.

[21]. Kempe K, Becer CR, and Schubert US. (2011). Microwave-assisted polymerizations: recent status and future perspectives. J. Biol. Macromol. 44(15): 5825-5842.
[22]. Wiesbrock F, Hoogenboom R, and Schubert US. (2004). Microwave-assisted polymer synthesis: state-of-the-art and future perspectives. Macromol. Rapid Commun. 25(20): 1739-1764.
[23]. Shi S. (2003). Microwave-assisted wet chemical synthesis: advantages, significance, and steps to industrialization. JMMCE. 2(02): 101.
[24]. Wicki A, Witzigmann D, Balasubramanian V, and Huwyler J. (2015). Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. J Control Release. 200: 138-157.
[25]. Xu X, Ho W, Zhang X, Bertrand, and Farokhzad O. (2015). Cancer nanomedicine: from targeted delivery to combination therapy. Trends. Mol. Med. . 21(4): 223-232.
[26]. Yee Kuen C, and Masarudin MJ. (2022). Chitosan nanoparticle-based system: A new insight into the promising controlled release system for lung cancer treatment. Mol. 27(2): 473.
[27]. Ummadi S, Shravani B, Rao NR, Reddy MS, and Sanjeev B. (2013). Overview on controlled release dosage form. Syst. J. 7(8): 51-60.
[28]. Ahsan M, Qasim S, Shah A, Nawaz I, Kashif M, and Ahmad W, (2024). Loading of anticancer drug anastrozole using Fe_3O_4@SiO_2. Braz. J. 3(2): 93-101.
[29]. Javidi J, Esmaeilpour M, and Khansari MR. (2015). Synthesis, characterization and application of core–shell magnetic molecularly imprinted polymers for selective recognition of clozapine from human serum. RSC Adv. 5(89): 73268-73278.