Design of Nanocarriers for Chemotherapy of Prostate Cancer

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KEYWORDS

Health, Health care, drug, pharmaceutical care

ABSTRACT

Any part of the body might become cancerous. It begins when regular cells are pushed out by out-of-control cells. This can spread to other parts of the body and interfere with normal bodily functions. Globally, cancer is considered to be a huge burden that will only get worse as the population ages and grows. Given the various drawbacks and adverse effects of the traditional formulations, novel strategies for medication delivery to prostate cancer cells are being researched and explored. With their many advantages over traditional chemotherapy, including improved drug solubility, protection from macrophage uptake, which lengthens the drug's blood residence time, and controlled drug delivery to the target prostate cancer, polymeric nanoparticles have been identified as promising candidates for drug delivery to prostate cancer.

1. Introduction

A collection of disorders known as cancers are characterized by aberrant cell development that has the capacity to infiltrate or spread to other bodily regions. With trillions of cells making up the human body, cancer can begin practically anywhere. Human cells normally proliferate and divide to create new cells as needed by the body. New cells replace old ones when they die as a result of ageing or injury. This well-organized process is disrupted when cancerous growth occurs, leading to increasingly aberrant cell behaviour, extended cell survival, and the formation of new cells when none are required [1]. These additional cells continue to mutate unchecked, growing into growths known as tumours. Due to the ageing and growth of the global population, prostate cancer is predicted to become the sixth most common cause of cancer-related death in males globally by 2030, accounting for 4,99,000 new deaths and 1.7 million new cases [2]. Men between the ages of 65 and 79 are most likely to get this kind of cancer, with men under the age of 65 accounting for 25% of cases. Currently, radiation therapy, chemotherapy, hormone therapy, and surgery are the available treatments for prostate cancer. These medical procedures either have severe adverse effects or are highly intrusive [4]. While chemotherapy can be somewhat effective, its chief disadvantages include the inability of the medications to reach the tumour tissues at high doses, unacceptable toxicity, the emergence of multiple drug resistance, and the nonspecific targeting of the treatments [3]. A strong nonsteroidal anti-androgen called flutamide (FLT) is used to treat advanced prostate cancer. It suppresses the growth of androgen-dependent cells and disables the androgen receptors on cancerous cells. Flutamide is typically taken orally three times per day at a dose of 250 mg. After a single dosage, it quickly absorbs via the mouth and reaches its maximal plasma concentration in one hour. Its elevated hepatic metabolism results in less active metabolites (hydroxyl flutamide), which is exacerbated by its shortened elimination half-life of five to six hours.

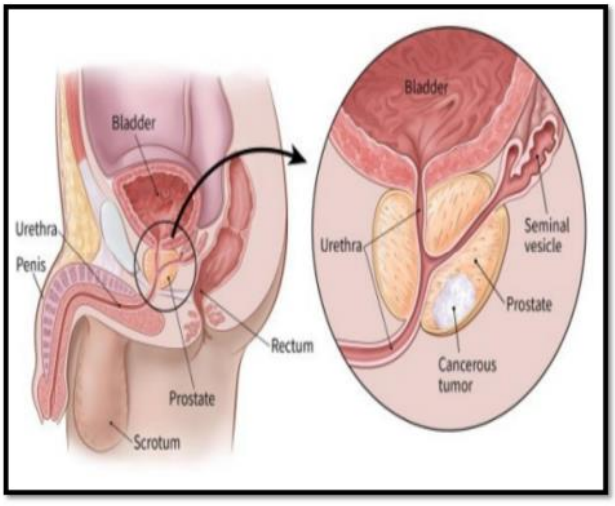

Figure 1. Prostate cancer

Flutamide's poor therapeutic profile is partly caused by its quicker metabolism, which also results in a delayed bioavailability. Its weak wettability and low water solubility, which continuously lower testosterone, may be the cause of its low bioavailability. Flutamide treatment may result in a wide range of adverse effects, such as hepatotoxicity at high doses, fatigue, impotence, enlargement of the male breast, and diarrhoea. A prolonged release formulation of flutamide is preferred in order to reduce both the frequency of drug administration and the incidence of side effects [14]. Flutamide can be placed into nano drug carriers to produce decreased hepatic impairment, reduced incidence and severity of side effects, optimised release at the necessary site of action, enhanced plasma half-life, and improved bioavailability.

2. Literature Review

[5] talked about the global prostate cancer epidemiology. Estimates from GLOBO-CAN 2018 show that 1,276,106 new cases of prostate cancer were reported globally in 2018, with developed nations having a greater prevalence. Variations in the incidence rates across the globe are indicative of variations in the application of diagnostic testing. The incidence and fatality rates of prostate cancer are closely correlated with age, with older men (over 65) having the highest incidence. In comparison to White men, African-American men experience higher incidence rates and a more aggressive form of prostate cancer. [6] created and characterised flutamide-loaded polyacrylamide (PAM) and punicic acid (PA) nanomicelles by employing film casting for self-assembly and ultrasonication afterward. Upon preparation, the nanoparticles (NPs) exhibited an 88 nm particle size, 0.246 PDI, í9 mv zeta potential, 94.5% drug EE, and 85.6% drug release up to 10 hours at pH 7.4. The findings imply that Flutamide's cytotoxic effects on prostate cancer may be amplified by using PAMPA copolymeric nanomicelles. produced and assessed gold nanoparticles coated with flutamide while the extract of Dracocephalum Kotschyi Boiss was present [11]. The spherical size of the gold nanoparticles, which ranged from 30 to 70 nm, was shown using the scanning electron microscope (SEM). The volume of extract, the volume of nanogold solution, temperature, the length of the extraction process, and the pH of the sample solution were found to be the key determinants of the flutamide loading capacity.

Conventional chemotherapy has several disadvantages when treating prostate cancer, including poor biodistribution profiles, unfavourable pharmacokinetics, limited water solubility, and an inability to deliver a sufficient amount of the drug to the tumour site without causing unwanted side effects [7]. Drug delivery methods based on nanotechnology have been created as solutions to many of the problems that occur with traditional formulations. The main goal of employing cutting-edge drug delivery technologies in pharmaceutical delivery is to facilitate effective therapeutic agent delivery to target locations at the right dosage with fewer adverse effects on the patient [8]. The potential for tailored delivery to the tumour, their capacity to wrap or bind millions of molecules of a drug and deliver to the necessary spot, and their ability to get over solubility and stability concerns are the main benefits of employing nanoparticles as a carrier for anticancer treatments. A lot of work has gone into creating nanoparticles for the delivery of anticancer medications in order to attain desired biological features, given the advantages that nanotechnology offers. [13].

3. Materials And Methods

To reduce side effects and increase the efficacy of traditional chemotherapeutic medicines, better therapeutic alternatives must be developed for the treatment of prostate cancer [12]. From this angle, significant progress has been achieved in improving the pharmacokinetic and bioavailability of these medications through the development of nanotechnology-based products. Because of their ability to target tumours and deliver anti-cancer drugs more precisely to cancer cells, nanoparticle-based therapeutic systems have garnered a lot of attention [9]. This is because these systems have the potential to revolutionise cancer therapy and diagnosis while also greatly improving therapeutic outcomes without affecting surrounding tissue. Indeed, the distinct dimensions, surface features, and morphology of nanoparticles (NPs) significantly influence their in vivo biodistribution. Numerous recent research have already shown that employing nanomedicine for prostate cancer treatment and prevention may

be a practical way to lower the disease's death and morbidity rates. It has been documented that flutamide can be effectively encapsulated in chitosan nanoparticles via the ionic cross-linking method [10], in methacrylic acid nanoparticles via the solvent evaporation method, and in casein nanoparticles via the ionic cross-linking method. and by the emulsion solvent diffusion approach in the PLGA nanoparticles. However, safer Flutamide hasn't been contained in PCL, mPEG-PLA, or m-PEG-PCL nanoparticles. Therefore, PCL, m-PEG-PLA, and m-PEG-PCL have been selected as the materials for the particle matrix in this investigation. In contrast to other lactide-derived polymers, these polymers have a slower rate of degradation and are susceptible to hydrolysis of the ester linkages within the human body (Kumari et al., 2010). This study's formulation may be superior to earlier research in that it will produce smaller particles, improved surface characteristics, the intended in vitro drug release kinetics, and a longer half-life.

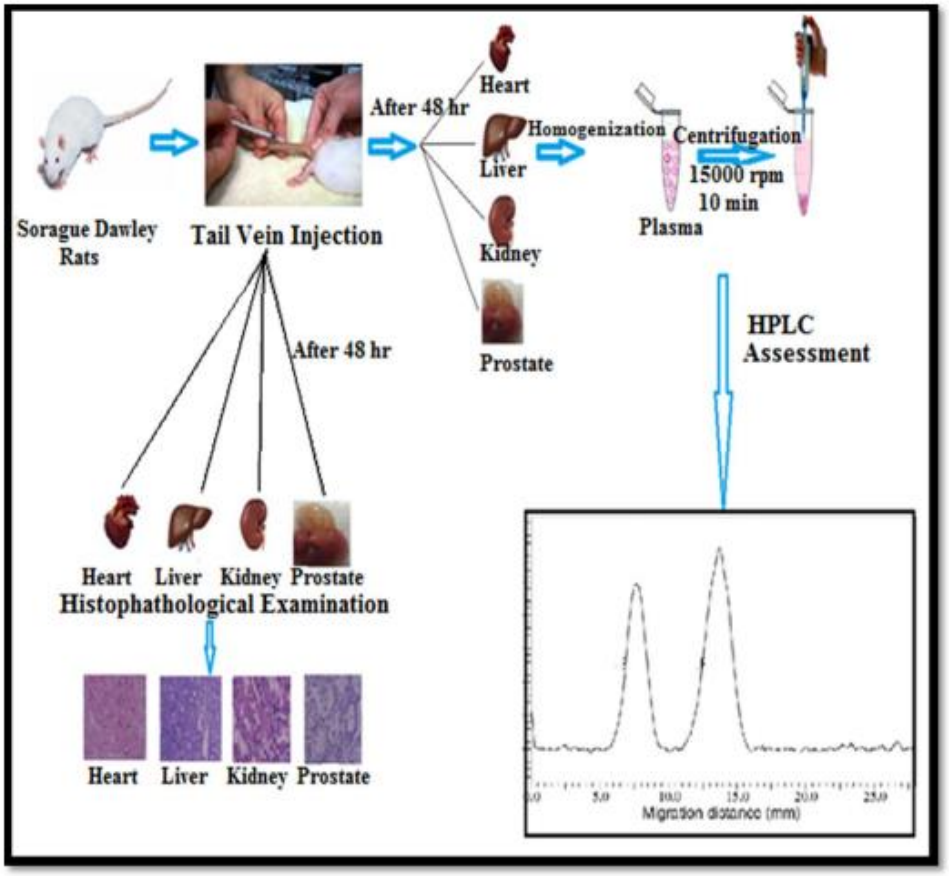

Figure 2. Scheme of In- vivo Biodistribution Study

The initial stage in developing a drug's dosage forms rationale is preformulation testing. In order to establish a stable, safe, and effective dosage form, it is defined as the stage of the research and development process where the physical, chemical, and mechanical properties of a new therapeutic ingredient are characterised both alone and when mixed with excipients. Preformulation testing aims to provide formulators with knowledge that will help them create stable, bioavailable dosage forms that can be mass manufactured.

4. Experimental Analysis

Using the KBr pellet technique and a Brunauer spectrophotometer, the infrared spectra of flutamide was recorded. To identify the functional group contained in the pure drug sample, FT-IR spectroscopy was employed. Pure flutamide's FTIR spectra reveals the distinctive peaks at 554.28, 3360.06, 1717.71, 1541.46, and 1344.97 cm.

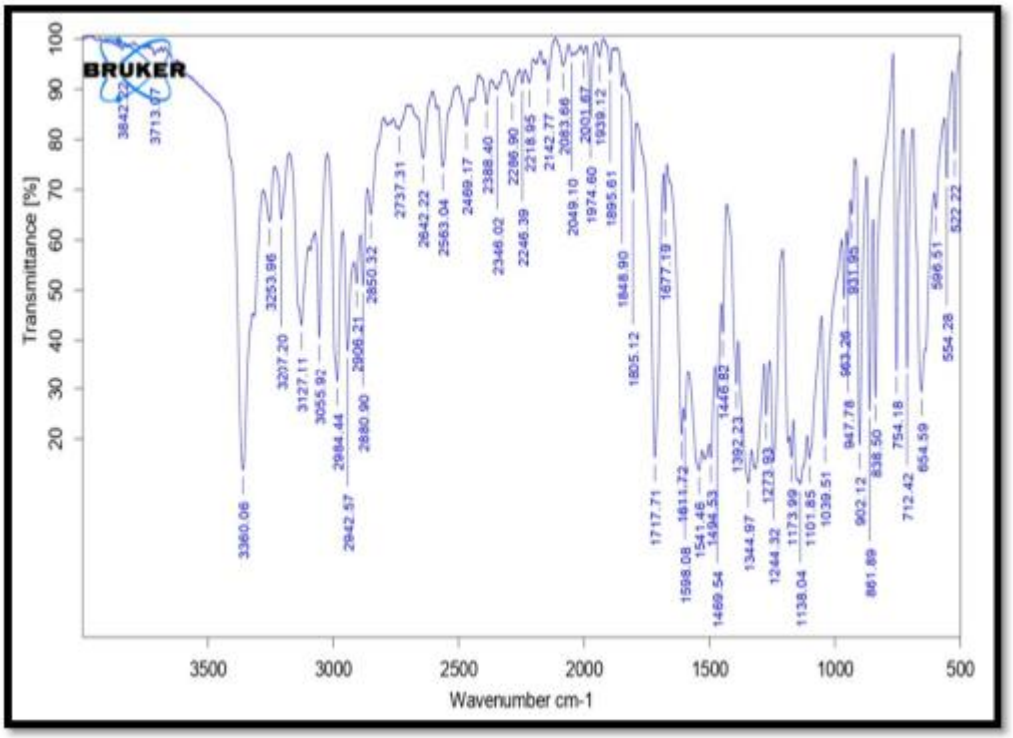

Figure 3. IR Spectra of Flutamide

The interaction between Flutamide, PCL, mPEG-PLA, mPEG-PCL, and Pluronic F-127 utilised in the synthesis of NPs was discovered using FTIR. The medication and excipient mixture was utilised for FTIR analysis after being manufactured in a 1:1 w/w ratio. The formulation's FTIR spectra revealed peaks that were similar to those of the pure medication. Flutamide's FTIR spectra show that the distinctive peaks of -NH, C=O, N = O, C - N, and C - F3 are located at 3360.06, 1717.71, 1541.46, 1344.97, and 554.28 cm-, in that order.

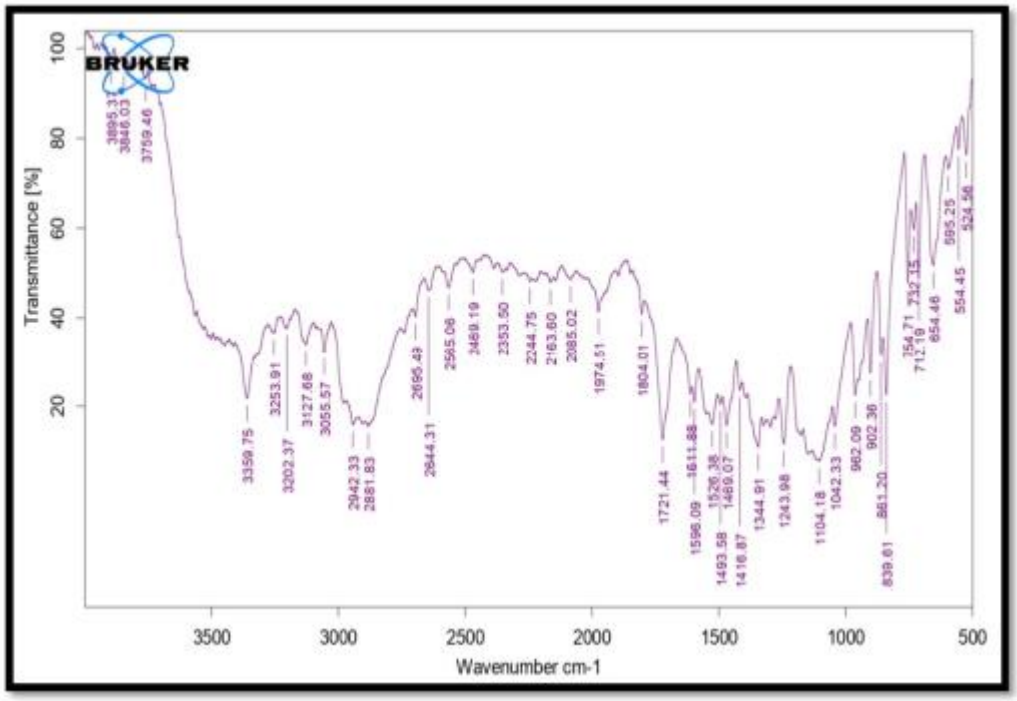

Figure 4. IR Spectra of Flutamide + mPEG-PCL + Pluronic F 127

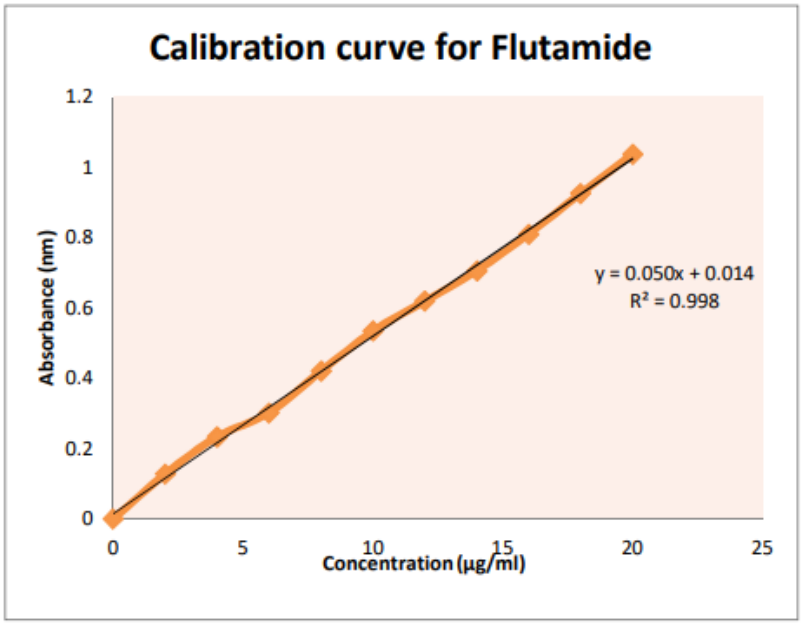

Figure 5. The Standard Calibration Curve of Flutamide in PBS pH 7.4

The nanoprecipitation process was used to create flutamide-loaded nanoparticles. This entails the polymer precipitating in acetone and the acetone diffusing into an aqueous media that contains pluronic F-127. The formulation was created statistically using 23 factorial designs, where three variables were maintained at two levels: the percentage of stabiliser, the volume of organic solvent, and the polymer concentrations. A total of 24 formulations (F1–F24) were created using the polymers PCL, mPEG–PLA, and mPEG–PCL. Eight formulations were created for each polymer, and each formulation was examined for a number of factors, including drug content, percentage yield, entrapment efficiency, particle size, Zeta potential, scanning electron microscopy (SEM), and in vitro drug release and kinetics.

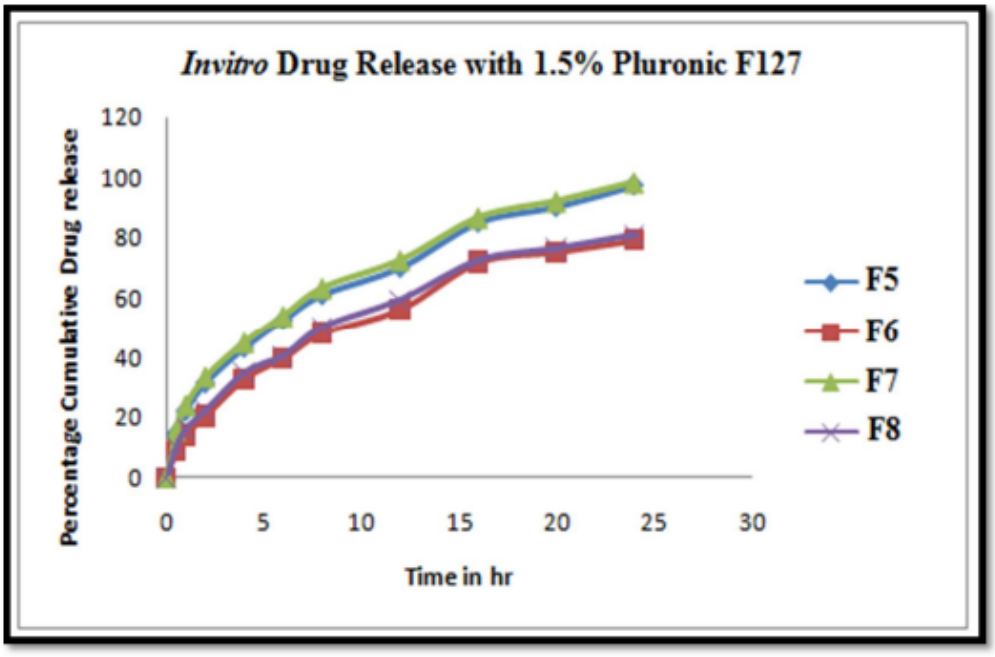

Figure 6. Invitro Drug Release of FLT loaded PCL NPs (F1 – F8) with 1.5% Pluronic F127

There were two stages to the drug release: a rapid release and a delayed release. The in vitro release

showed a rapid release for the first four hours, then a slower, continuous release for the next twenty-four hours. Out of all the formulations tested, F2, F10, and F18 demonstrated superior sustained and controlled drug release over a 24-hour period. These formulations included 50 mg of polymer, 10 ml of acetone, and 1% pluronic F127. The drug release from the F2 nanoparticles produced with PCL was 77.32% ± 1.32 in a 24-hour period. In a 24-hour period, the formulation F18 demonstrated sustained drug release of 80.13% ± 1.75, while the nanoparticles F10, produced with mPEG-PLA, demonstrated controlled drug release of 71.24% ± 1.53.

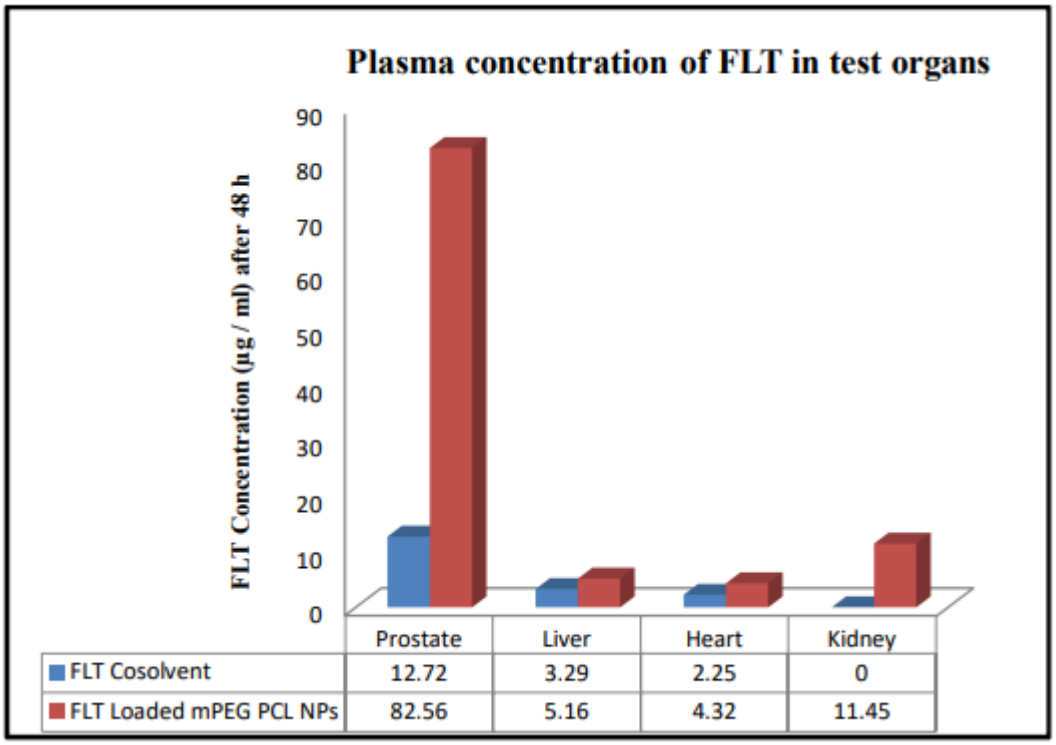

Figure 7. Plasma concentration

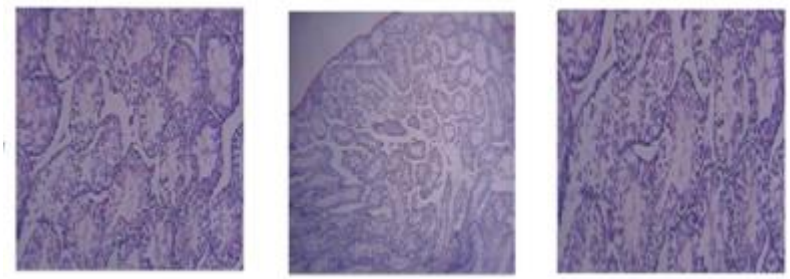

Figure 8. Histopathological examination of Prostate

Figure 8 displayed the distribution profiles of FLT in the kidney, liver, heart, and prostate. Compared to FLT cosolvent, the prostate's FLT concentration was significantly higher with mPEG-PCL NPs. Compared to FLT cosolvent, the clearance of FLT was slower when mPEGPCL NPs were given to rats because it was still present in the kidney 48 hours after treatment.

5. Conclusion

The prostate is a little gland that is only present in men that is situated in the pelvis between the bladder and the penis. It aids in the generation of semen. The growth of cancer in the prostate that has the potential to spread to the lymph nodes and bones is known as prostate cancer. A strong nonsteroidal anti-androgen called flutamide is used to treat advanced prostate cancer. It suppresses the growth of

androgen-dependent cells and disables the androgen receptors on cancerous cells. Flutamide is typically taken orally three times per day at a dose of 250 mg. The medication has a short half-life and a high first pass metabolism. Flutamide treatment may result in a number of adverse effects, including as fatigue, impotence, breast fullness, diarrhoea, and liver dysfunction. To reduce the frequency of drug administration and thus the likelihood of side effects, a formulation of Flutamide-loaded polymeric nanoparticles with sustained release was created. In this work, PCL, mPEG–PLA, and mPEG–PCL were used as polymers in the nanoprecipitation process to prepare flutamide loaded polymeric nanoparticles. The produced NPs were assessed, and the effects of three formulation excipients on the NPs' characteristics were carefully examined. In terms of encapsulation efficiency, percentage yield, and in vitro drug release, the polymer mPEG–PCL produces the most optimal nanoparticles when compared to PCL and mPEG–PLA.

References

[1] Sun, Guanxing, Kai Sun, and Jie Sun. "Combination prostate cancer therapy: Prostate-specific membranes antigen targeted, pH-sensitive nanoparticles loaded with doxorubicin and tanshinone." *Drug Delivery* 28, no. 1 (2021): 1132-1140.
[2] Johnson, Renjith P., Chandrahas Koumar Ratnacaram, Lalit Kumar, and Jobin Jose. "Combinatorial approaches of nanotherapeutics for inflammatory pathway targeted therapy of prostate cancer." *Drug Resistance Updates* 64 (2022): 100865.
[3] Ashique, Sumel, Prathap Madeswara Guptha, Satish Shilpi, Saurabh Sharma, Shubneesh Kumar, Mohammad A. Altamimi, Afzal Hussain, Sandhya Chouhan, and Neeraj Mishra. "Nanocarrier-mediated delivery for targeting for prostate cancer." In *Multifunctional Nanocomposites for Targeted Drug Delivery in Cancer Therapy*, pp. 355-392. Academic Press, 2024.
[4] Madhavi, M., Sasirooba, T., & Kumar, G. K. (2023). Hiding Sensitive Medical Data Using Simple and Pre-Large Rain Optimization Algorithm through Data Removal for E-Health System. *Journal of Internet Services and Information Security*, *13*, 177-192.
[5] Zhao, Jiang, Chi Zhang, Weihao Wang, Chen Li, Xupeng Mu, and Kebang Hu. "Current progress of nanomedicine for prostate cancer diagnosis and treatment." *Biomedicine & Pharmacotherapy* 155 (2022): 113714.
[6] Suresh, G., Narayana, K.L., Kedar Mallik, M., Srinivas, V., Jagan Reddy, G.
[7] Processing & characterization of LENS™deposited Co-Cr-W alloy for bio-medical applications (2018) International Journal of Pharmaceutical Research, 10 (1), pp. 276-285.
[8] Tiburcius, Steffi, Kannan Krishnan, Jae-Hun Yang, Fatemeh Hashemi, Gurwinder Singh, Deepika Radhakrishnan, Hoang Trung Trinh, Nicole M. Verrills, Ajay Karakoti, and Ajayan Vinu. "Silica-Based Nanoparticles as Drug Delivery Vehicles for Prostate Cancer Treatment." The Chemical Record 21, no. 6 (2021): 1535-1568.
[9] Bobir, A.O., Askariy, M., Otabek, Y.Y., Nodir, R.K., Rakhima, A., Zukhra, Z.Y., Sherzod, A.A. (2024). Utilizing Deep Learning and the Internet of Things to Monitor the Health of Aquatic Ecosystems to Conserve Biodiversity. Natural and Engineering Sciences, 9(1), 72-83.
[10] Hema, Soundararajan, Selvarathinam Thambiraj, and Dhesingh Ravi Shankaran. "Nanoformulations for targeted drug delivery to prostate cancer: an overview." Journal of Nanoscience and Nanotechnology 18, no. 8 (2018): 5171-5191.
[11] Ramakrishnan, J., Ravi Sankar, G., & Thavamani, K. (2019). Publication Growth and Research in India on Lung Cancer Literature: A Bibliometric Study. Indian Journal of Information Sources and Services, 9(S1), 44–47.
[12] Ashrafizadeh, Milad, Shahin Aghamiri, Shing Cheng Tan, Ali Zarrabi, Esmaeel Sharifi, Navid Rabiee, Firoz Babu Kadumudi et al. "Nanotechnological approaches in prostate cancer therapy: integration of engineering and biology." Nano Today 45 (2022): 101532.
[13] Choksi, Ankur U., Amir I. Khan, Soum D. Lokeshwar, Daniel Segal, Robert M. Weiss, and Darryl T. Martin. "Functionalized nanoparticles targeting biomarkers for prostate cancer imaging and therapy." American Journal of Clinical and Experimental Urology 10, no. 3 (2022): 142.
[14] Ramana, R.H.V., & Ravisankar, V. (2024). Precision in Prostate Cancer Diagnosis: A Comprehensive Study on Neural Networks. Journal of Wireless Mobile Networks, Ubiquitous Computing, and Dependable Applications (JoWUA), 15(2), 109-122. https://doi.org/10.58346/JOWUA.2024.I2.008
[15] Omabe, Kenneth, Clément Paris, François Lannes, David Taïeb, and Palma Rocchi. "Nanovectorization of prostate cancer treatment strategies: a new approach to improved outcomes." Pharmaceutics 13, no. 5 (2021): 591.
[16] Panda, Pritish K., Shivani Saraf, Ankita Tiwari, Amit Verma, Sarjana Raikwar, Ankit Jain, and Sanjay K. Jain. "Novel strategies for targeting prostate cancer." Current drug delivery 16, no. 8 (2019): 712-727.