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Polymeric Nanocarriers for the Delivery of Flutamide in Prostate Cancer Therapy

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Abstract
Prostate cancer poses a significant health burden globally, necessitating innovative approaches to enhance the efficacy of therapeutic interventions. This study focuses on the design and characterization of polymeric nanocarriers as delivery vehicles for flutamide, a nonsteroidal antiandrogen with proven efficacy in prostate cancer treatment. The primary objective is to address the limitations associated with flutamide, including poor aqueous solubility, by encapsulating it within polymeric nanocarriers. The nanocarriers were synthesized and optimized to efficiently encapsulate flutamide, offering controlled release and enhanced drug stability. Physicochemical characterization was conducted to assess the particle size, surface charge, and morphology of the developed nanocarriers. In vitro release studies were performed to evaluate the sustained release profile of flutamide from the nanocarriers. The potential of the polymeric nanocarriers to improve drug delivery was further assessed through cellular uptake studies using prostate cancer cell lines. The findings from this research provide valuable insights into the design and characterization of nanocarriers for flutamide, offering a promising strategy to overcome existing challenges associated with its administration.
Keywords: *Flutamide, Loaded, Polymeric, Nanocarriers*

I. Introduction

Prostate cancer remains a significant global health concern, representing one of the most prevalent malignancies affecting men. Despite advances in diagnosis and treatment modalities, the efficacy of conventional therapeutic agents is often hindered by limited drug solubility, systemic toxicity, and inadequate drug delivery to the target site. In recent years, nanotechnology has emerged as a promising avenue to address these challenges, offering precise and targeted drug delivery systems that can enhance therapeutic outcomes while minimizing adverse effects.

Flutamide, a nonsteroidal antiandrogen, has demonstrated efficacy in managing prostate cancer by antagonizing androgen receptors. However, its clinical utility is constrained by poor aqueous solubility, which affects its bioavailability and therapeutic potential. In response to these limitations, the present study focuses on the design and characterization of polymeric nanocarriers to encapsulate and deliver flutamide, with the aim of improving its pharmacokinetics and therapeutic efficacy.

Polymeric nanocarriers provide an innovative platform for drug delivery, offering benefits such as controlled release, enhanced drug stability, and the ability to target specific tissues. This research endeavors to engineer nanocarriers that can encapsulate flutamide efficiently, protect it from premature degradation, and facilitate its targeted delivery to prostate cancer cells.

In this context, the objectives of the current investigation encompass the synthesis and optimization of polymeric nanocarriers loaded with flutamide, followed by a comprehensive characterization of their physicochemical properties. The ultimate goal is to establish a novel therapeutic approach that maximizes the therapeutic potential of flutamide while minimizing systemic side effects, thereby contributing to the advancement of prostate cancer treatment.

This paper presents a comprehensive exploration of the rationale, methodology, and potential implications of utilizing polymeric nanocarriers for the delivery of flutamide in prostate cancer therapy. By addressing the existing challenges associated with flutamide administration, this research aims to contribute valuable insights to the ongoing efforts in improving the precision and efficacy of prostate cancer treatment.

II. RESEARCH METHODOLOGY

Poly-Ɛ-Caprolactone (PCL) (C6H10O2, 80,000 MW; CAS-No 24980-41-4)/ (C6H10O2, 65,000 MW)/ (C6H10O2, 10,000 MW), Flutamide (FLT) 2-methyl-N-[4-nitro-3 (trifluoromethyl) phenyl] propanamide (CAS-No. 13311-84-7), Chloroform (99%) (CHCl3, CAS-No. 67-66-3) and Ethanol (99%) (C2H6O, CAS-No. 64-17-5) were all purchased from Sigma-Aldrich (Sigma-Aldrich inc, 3050 Spruce St., St. Louis, MO63103). Fluka Analytical was the originator of the Poly Vinyl Alcohol (13-23 and 30-70 kDa) that was purchased. Oxoid Microbiology was the distributor of the Phosphate Buffer Saline (Dulbecco A) that was acquired. Sigma-Aldrich (Sigma-Aldrich inc, 3050 Spruce Street, St. Louis, Missouri 63103) was the supplier of the dialysis membrane bags that were purchased. The Pur-ALyzerTM Mega Dialysis Kit ranged from 3 to 20 millilitres and had a molecular weight of 3.5 kilodaltons.

Equipment

Homogenizer (IKA Labortechnik ULTRATURRAX TP 18/10 – 1000 – 10000 rpm), Rotovap Buchi Rotovapor re120, Varian 705 DS Dissolution Apparatus, Mastersizer (Malvern Mastersizer 3000 laser diffraction particle size analyzer), Zeiss EVO50 SEM operated at (EHT) 10.00 kV, and UVspectrophotometer, Perkin Elmer Lambda XLS (430nm) were all provided by the University of Wolverhampton and were all utilised in the experiment.

METHODS DEVELOPMENT

Before beginning this laboratory examination, independent research was conducted in order to facilitate the continued development of the techniques that are currently being utilised in the Tang laboratory.

When it comes to the manufacture of microsphere particles, the solubility of the medicine and polymer (PCL) in different solvent systems is the fundamental factor that determines the procedure. A couple of the most prevalent systems are:

- Single emulsion solvent evaporation (Perez et al., 2000).
- Double emulsion solvent evaporation (Dhanaraju et al., 2006; Cleek et al., 1997).

This inquiry will be carried out using the single emulsion oil/water (O/W) solvent evaporation technique (figure 4), which is the most popular way for manufacturing PCL microspheres. This method will be employed to carry out this investigation. Figure 4 is a schematic that provides a summary of the process of producing polymeric microspheres that are loaded with drugs. Based on Li et al. (2008), there are four main processes involved in the process.

1. The first step is to dissolve the synthetic polymer in an optimal volatile organic solvent. Next, the active component is added to the mixture. The active molecule can either be dissolved or simply distributed in the organic phase.
2. The emulsion of the organic phase is transferred into an aqueous phase that is incompatible with all other phases, resulting in the formation of the oil-water emulsion.
3. The process of removing the solvent from the dispersed phase by the use of solvent evaporation. Producing solid particles from the dispersed phase by transformation.
4. The process of collecting the microspheres and dried them out.

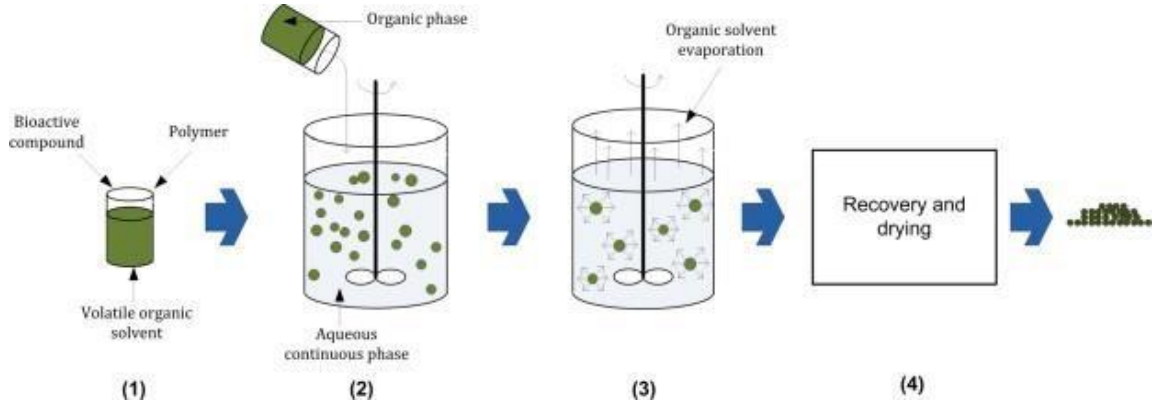

Figure 1 Main steps of the oil/water single emulsion-solvent evaporation method (Li et al., 2008).

III. RESULTS

As the molecular weight of PCL drops from 80 kDa to 10 kDa, it is clear that the diameter of microspheres reduces on average. This is an observation that can be made by studying the micrographs that are presented in figure 4.1. The microspheres comprised of PCL 80kDa exhibit a diameter of around 8.4µm, which

decreases to 5.5µm when PCL 10kDa is utilised on the microspheres. In terms of size, there is a little reduction in particle size after FLT was integrated, as can be seen visually after comparing the microspheres that were empty and those that were encased with FLT to each other. "

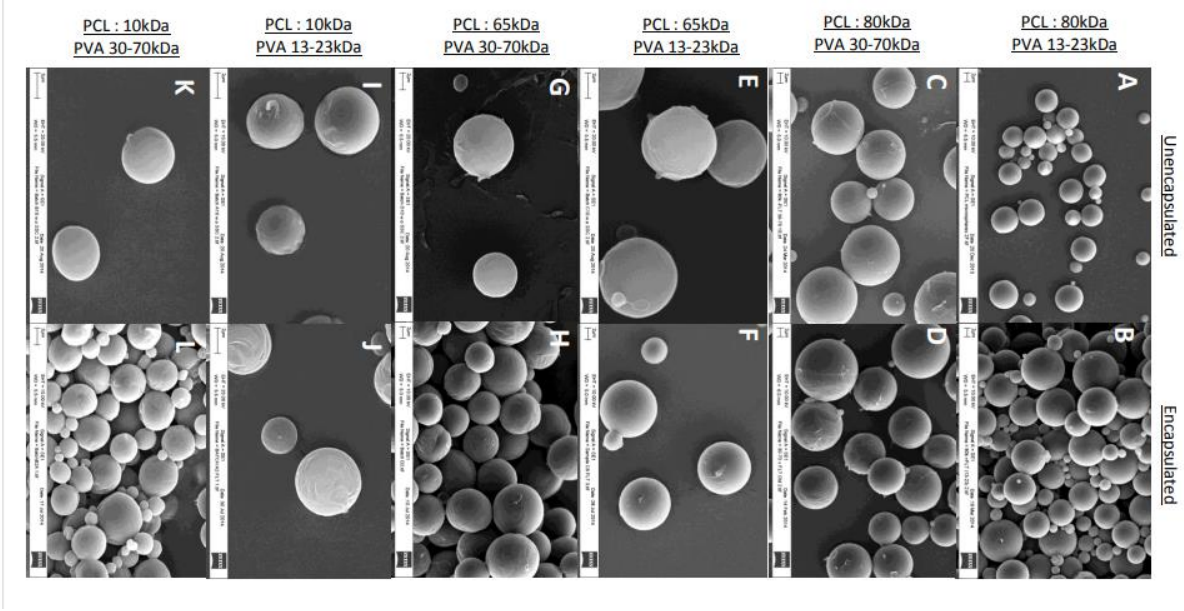

Figure 2 .SEM Micrographs of Unencapsulated and Encapsulated Flutamide Microspheres. A= (4000x mag), B= (5000x mag), C= (5000x mag), D= (5000x mag), E= (12,000x mag), F= (10,000x mag), G= (12,000x mag), H= (10,000x mag), I= (12,000x mag), J= (12,000x mag), K= (12,000x mag), L= (10,000x mag). (See Table 4.1 for detailed formulations).

In the formulation of PCL 80kDa that is seen in figure 3, two different molecular weights of PVA were added, and both of them created smooth microspheres. Figure 2micrographs C and D revealed the most consistent microspheres out of all the formulations. These micrographs also included a higher surfactant molecular weight range than the other formulations. Based on the findings of this visual examination, it appears that attaining a better level of microsphere homogeneity may be accomplished by increasing the molecular weight range of PVA from 30 to 70 kDa. When comparing micrographs E, F to G, H and micrographs I, J to K, L, it is possible to observe the impact that the use of PVA operating at a greater molecular weight range has.

Figure 2 micrographs C and D demonstrated the microspheres that were the best suitable for dissolving analysis overall. Following the evaluation of their morphology, it was determined that the PVA 30-70kDa at 0.5% weight/volume had stabilised the aqueous phase during the formulation process, resulting in the formation of microspheres that were extremely uniform and spherical, as shown in the SEM micrograph.

The microspheres that are partially formed and seen in picture A of figure 4.2 are relatively smooth, although they exhibit a significant degree of clumping due to their formation. Through the use of the identical experimental methods throughout the formulation process, it has been seen that in this particular instance, either the solvent has not been completely evaporated or the medication has not completely encapsulated (Scale Bar: 2µm).

Figure 3: Image (A) Formulation :

- Batch : B22
- Drug : Flutamide - (50 mg)
- Solvent : Chloroform - (10.0 mL)
- Polymer : Poly-(epsilon-caprolactone) 10kDa - (500 mg)
- Surfactant : Poly Vinyl Alcohol 30-70kDa - (1250 mg)
- Homogenisation Speed: 5,000 rpm
- Drug : Polymer Ratio = 1 : 20
- Oil : Water Ratio = 1 : 3

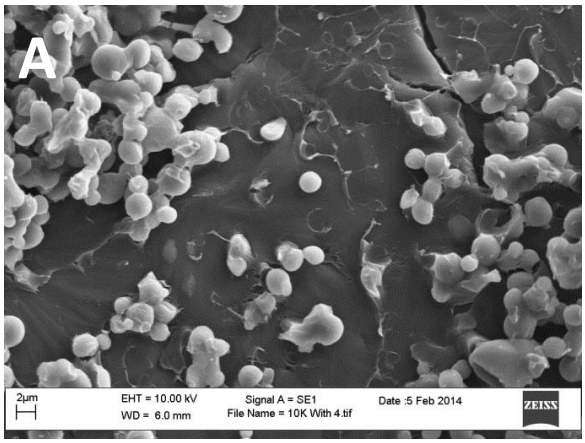

Figure 3 A = SEM image of the FLT loaded PCL 10kDa - PVA 30-70kDa microspheres (4,000x mag) (See Table4.1.1. for detailed formulations).

PERCENTAGE ENCAPSULATION EFFICIENCY (DIRECT METHOD)

distinct molecular weights of PCL polymer are presented These molecular weights are 80 kDa, 65 kDa, and 10 kDa. These molecular weights are then further classified into two PVA surfactant molecular weight ranges: 13-23 kDa and 30-70 kDa. After that, the direct encapsulation approach was utilised to conduct tests on each and every specific formulation of FLT loaded microspheres. For the purpose of determining the average percentage, this study was performed three times (Table 1). There was a comparison made between the % encapsulation efficiency of the PVA 13-23kDa formulations and the PVA 13-23kDa formulations using the p-value of the two-tailed t-test. Statistical significance is defined as a p-value that is less than 0.05, accompanied with a confidence interval that is at least 95%. The purpose of doing a multiple comparison of column data was to determine if there is a significant difference between the control and other sets of data (Table 1). This was accomplished by employing a Holm-Šídák's test inside a one-way analysis of variance (ANOVA) study, which was carried out using Graph Pad Prism 6. The multiple comparison test developed by Holm and Sidak demonstrated, via the use of p-values, that there is a statistically significant distinction between the control group and the other data sets tested.

Table 1A table illustrating the direct percentage of encapsulation effectiveness achieved by FLT in the various formulations utilised for testing (N=3)

	Direct Percentage Encapsulation Efficiency of FLT					
(Polymer)PCL MW	80kDa		65kDa		10kDa	
(Surfactant) PVA MW	13-23kDa	30-70kDa	13-23kDa	30-70kDa	13-23kDa	30-70kDa
Average (%)	90.12 ±0.56	90.92 ±1.08	80.88 ±2.04	79.25 ±1.92	74.33 ±4.51	72.05 ±1.81
(T-test) P value	0.3210		0.3701		0.4605	
Holm-Sidak's test (1)	Control		**		**	
Holm-Sidak's test (2)		Control		***		****

(ns : P>0.05, * : P≤0.05, ** : P≤0.01, *** : P≤0.001 or **** : P≤0.0001)

In order to construct, the data that was collected and presented in table 1 was utilised. The data demonstrates that among the three PCL molecular weights that were evaluated, the 80kDa molecular weight exhibited the greatest average %EE, with its values of 90.12% ±0.56% and 90.92% ±1.08%. It was shown that the percentage of encapsulation efficiency decreased in tandem with the decrease in the molecular weight of PCL.

IV. CONCLUSIONS

Here, we report the effective preparation, development, and testing of a controlled drug delivery system encapsulating the prostate cancer chemotherapeutic medication FLT in Poly-(epsilon-caprolactone). During development, the microspheres formulation was fine-tuned to accommodate for the molecular weight range of poly-(epsilon-caprolactone) and poly vinyl alcohol. Visually, the SEM results show that the best drug delivery system is made using PVA with a high molecular weight (MW) range of 30-70 kDa and a high PCL MW of 80 kDa at a concentration of 0.5% wt/v. All of the microspheres are the same size, shape, and distribution, and they're smooth and round. that the average percentage of FLT encapsulation is 1.60 percentage points greater when using a lower PVA molecular weight range (13-23 kDa) as compared to PVA 30-70 kDa. It appears, however, that the PVA molecular weight ranges are not significantly different (p>0.05) according to the statistical analysis (t-test). When comparing PVA 13-23 kDa to PVA 30-70 kDa, it is visually evident in table 3

that the former yields 1.00% more product on average. Once again, following statistical analysis (t-test), the p-value indicates that the ranges of PVA molecular weights are not significantly different ($P>0.05$). When the 80kDa PCL was employed, the SEM micrographs and mastersizer samples revealed a little increase in particle size.

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