RESEARCH ARTICLE

Preparation and Evaluation of PVA, Chitosan Polymeric Matrixes and *In-vitro* Study for their Controlled Release of Enzalutamide

Oraas A. Hatem*[1], Zainab A. H. Alebady[2]

[1]*Department of Chemistry, College of Science, University of AL-Qadisiyah, Iraq*
[2]*Department of laboratory and clinical science, College of Pharmacy, University of AL-Qadisiyah, Iraq*

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ABSTRACT

Enzalutamide is an effective androgen signaling receptor inhibitor that affects the androgen pathway in various ways. Enzalutamide can reduce the competitive binding of testosterone to the androgen receptor. It also inhibits the translocation of the activated androgen receptor for the cytoplasm to the nucleus, and its binding to DNA and cofactors recruitment to the binding site.

This study evaluated polyvinyl alcohol/chitosan hydrogels as a pH-sensitive matrix drug delivery system for enzalutamide.

The release of enzalutamide from PVA/CS hydrogel were determined at the simulated gastric and intestinal fluid (SGF and SIF, respectively). Various kinetic models were employed to evaluate the drug release's kinetic mechanism. The drug release was influenced by the concentration of polymers, the pH of the release medium, and the amount of cross-linking agent. Hydrogels containing (60:40) PVA to chitosan showed a higher release percentage of about 98% at SIF. The kinetic models showed that the release process follows the Higuchi model in SGF with a regression coefficient of 0.925. In contrast, SIF follows the first-order model with a regression coefficient value of 0.994. The results confirmed that the new formed PVA/CS hydrogels are potential systems for enzalutamide-controlled drug delivery.

Keywords: Chitosan, Drug delivery, Enzalutamide, Hydrogel, pH-sensitive, Prostate cancer, PVA.

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INTRODUCTION

Prostate cancer the sixth-leading cause of death from cancers and the most common male cancer. men. The mainstay of prostate cancer treatment has been to interfere with androgen-receptor signaling since 1941, when the hormonal dependence of prostate cancer was first identified.[1]

High-risk locoregional prostate cancer patients are now living longer due to the advancements in endocrine therapy. However, it has been shown that new hormonal therapies can lengthen a patient's life with a metastatic, castration-resistant condition.[2]

It is possible to treat acquired resistance to the first-generation nonsteroidal antiandrogens bicalutamide, flutamide and nilutamide using the oral androgen receptor inhibitor enzalutamide (MDV3100). Enzalutamide improved patients of castration-resistant prostate cancer survival, whether it was given during the administration of docetaxel chemotherapy or before that.[3,4]

Polymer science advancements have resulted in the development of various innovative medication delivery systems. Surface and bulk qualities should be considered while designing polymers for different applications as drug delivery polymers. Biodegradable polymers are extensively used in drug delivery since they may be broken down inside the body into non-toxic monomers.[5]

The material releases the active agent from it in a particular way when a natural or synthesized polymer is carefully integrated with medication or other active agents. The release of the active agent may eventually occur over a long time, over time, or maybe started by the external environment or other events.[6]

Pharmaceutical applications for polymers range as tablets binders to viscous and flow regulators in liquids, suspensions, and emulsions.[7]

In order to deliver more efficient treatments while lowering the risk of under- and overdosing, drug distribution is regulated. Utilizing controlled-delivery systems has additional advantages, such as minimizing dosage requirements, optimizing pharmaceutical effectiveness, and enhancing patient compliance. Polymers can be used as film coatings

**Author for Correspondence: oraas.adnan@qu.edu.iq*

to adjust the characteristics of medication release, improve drug stability, and mask the unpleasant taste of a treatment. Pharmaceutical polymers are frequently used to mask taste, and controlled release such as extended, pulsatile, and targeted increases stability and bioavailability.[8]

The toxic effect or non-biocompatibility of the materials, undesirable degradation products, any techniques required to implant or remove the system, the potential for postoperative pain from the delivery method, and the higher cost of current control compared to conventional pharmaceutical formulations are some of the drawbacks to consider.

Recent advancements in controlled drug release formulations and the polymers used in these systems allow them to do more than just lengthen a medication's effective release period. For instance, current controlled-release systems can deliver or cease delivering medications in response to changes in the physiological environment. Additionally, materials that could result in active targeting systems have been developed. A specific formulation can determine the precise cellular, tissue, or region where the medication it contains is to be given. In monolithic delivery systems, drugs are dispersed within a polymer and released through diffusion. The original drug concentration and polymeric chain relaxation control the drug release rate from a matrix product, resulting in an extended-release characteristic. Growing technologies give opportunities that researchers have only just begun to consider, though much of this investigation is in its early stages.[9-13]

This work aimed to create and assess polyvinyl alcohol/chitosan hydrogels as a pH-sensitive matrix for enzalutamide delivery. The primed PVA/CS hydrogels were evaluated for morphology and swelling behavior.

METHODS AND MATERIALS

Materials

Enzalutamide raw material (Scinopharm, Tawin, China), chitosan and polyvinyl alcohol (Sigma Aldrich, Germany), glutaraldehyde (CDH, India), hydrochloric acid, acetic acid, potassium phosphate monobasic, sodium chloride and sodium hydroxide (BDH, India). Sodium dodecyl sulphate (SDS) (AK Scientific, USA), were of analytical grade and were used without further purification.

Methods

Preparation of PVA/CS Matrix Hydrogel

For the preparation of PVA/CS matrix hydrogel, two different solutions (A and B) were prepared. To prepare a solution (A), 10 g of PVA were added to 20 mL of distilled water. The volume was completed to 100 mL and placed on a magnetic stirrer, heated to 60°C for up to 60 minutes, stirring constantly until a clear solution emerged.

To prepare a solution (B), the beaker was filled with chitosan powder and 1% acetic acid (1 g: 100 mL). The system was covered, sealed, and stirred magnetically to ensure total dissolution for 1-hour. The PVA solution was mixed thoroughly with the chitosan solution at room temperature (for 30 minutes then put in ultra sonicator for 30 minutes to degassing), resulting in mixtures with PVA to chitosan mass ratios of (100:0, 80:20, 60:40, and 40:60) abbreviated as MX1, MX2, MX3, MX4, respectively.

A total of 1-mL of cross-linking agent (Glutaraldehyde) was added to the solution mixture, mixed continuously until hydrogel formed, transferred into a petri dish, and dried off at room temperature.

Effect of Cross Linking Agent on a Swelling Ratio of a Polymeric Matrix

For the optimal matrix the impact of varying the cross-linking agent's volume was studied, as the matrix swelling behavior was studied without adding a cross-linking agent, in addition to the effect of adding volumes of 0.5, 1, 2, 3 mL of the cross-linking agent.

Swelling Properties

Samples were dipped in 50 mL of distilled water at room temperature for 24 hours, the extra water on the surface was wiped off with filter paper, and the swollen samples were weighed repeatedly until equilibrium was reached. The following equation was used to calculate the swelling index (SI):

$$SI = \frac{Ws - Wd}{Ws} * 100$$

Where W_s is the weight of the gel after swelling and W_d is the weight of the dry gel

Preparation of SGF and SIF

NaCl (3 g) was dissolved in approximately 1450 mL of deionized water to prepare the simulated gastric fluid (SGF), and the pH was then adjusted to 1.2 ± 0.1 using diluted HCl. Potassium phosphate monobasic (10.2 g) and SDS (3.75 g) were dissolved in 1000 mL of deionized water to produce the simulated intestinal fluid (SIF), which was subsequently pH-amended to 6.8 ± 0.1 with 1 N NaOH. Finally, deionized water was employed to adjust the volume of each fluid to 1500 mL.

Calibration Curve of Enzalutamide

The standard solution of enzalutamide(Mw.t=464.44 g/mol) was prepared at a concentration of 2.0 x 10^{-4}. The maximum wavelength, λ_{max}(223 nm) of enzalutamide solution, was determined using UV spectroscopy with a 200–400 nm range.

The calibration curve of the drug was studied in the simulated gastric fluid and simulated intestine fluid by preparing eight solutions of successive dilution of the standard solution with concentrations ranging between (0.01–2.00)x10^{-4} M using UV spectroscopy at the maximum wavelength (223 nm) Figures 1 and 2.

Kinetics of Drug Release

Enzalutamide was employed as a model drug to investigate the drug release from PVA/CS hydrogels, 9.3 mg of the drug was dissolved in PVA/CS mixture before the addition of cross-linking agent. Gels were immersed into 100 mL of SGF and SIF, and a batch was taken out at regular intervals. The release

Table 1: The values of the reaction rate constants and regression coefficients for drug release kinetics in different media

Medium	*Zero order*		*First order*		*Higuchi model*	
	R^2	$K(M\ min^{-1})$	R^2	$K(min^{-1})$	R^2	KH
SGF	0.800	$2x10^{-7}$	0.831	0.001	0.925	$5x10^{-6}$
SIF	0.909	$4x10^{-7}$	0.994	0.007	0.982	$9x10^{-6}$

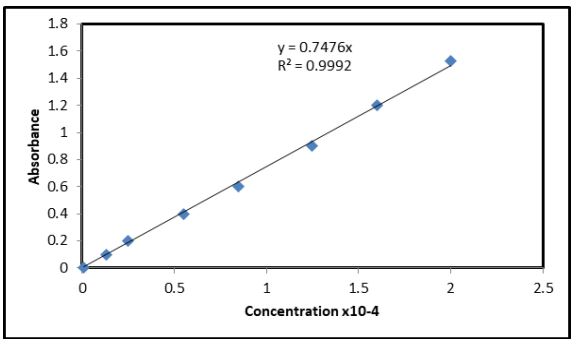

Figure 1: Calibration curve of Enzalutamide at λ_{max} (223 nm) in SIF.

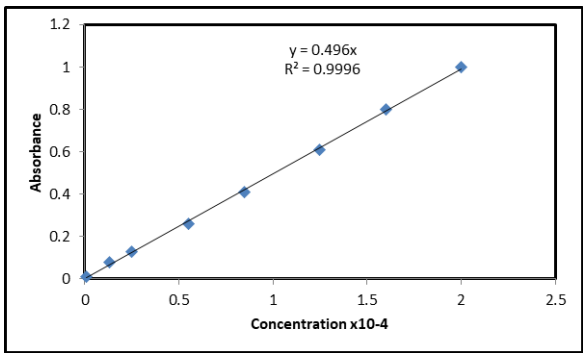

Figure 2: Calibration curve of Enzalutamide at λ_{max} (223 nm) in SGF

of, enzalutamide was determined by UV spectrophotometry at 223 nm.

Three different mathematical models that determined the kinetics of drug release from polymeric matrix were considered:

- Zero-order

$$Qt = K_\circ t \ldots\ldots\ldots\ldots (2)$$

- First-order

$$\ln \frac{Q_\circ}{Q_\circ - Q_t} = K_1 t \ldots\ldots\ldots (3)$$

Where Q_o is the concentration of the drug-loaded to the hydrogel matrix and Qt the concentration of released drug

- Higuchi Model

$$f_t = Q = k_H t^{1/2} \qquad \ldots\ldots (4)$$

K_H is the Higuchi dissolution constant, and Q is the concentration of the released drug.

RESULT AND DISCUSSION

A scanning electron microscope was applied to investigate surface morphology considering the polymeric matrix's size and shape, as well as the nature of the surface which has been prepared. Figure 3, from the study of the surface morphology of the polymeric matrix before and after loading the drug, it was noted that the matrix formed in the form of irregular curvy sheets with micro-dimensions, but it appears to be more regular after loading the drug.

The swelling behavior of the prepared samples in SGF and SIF was studied. Figure 4 shows the swelling ratio after 24 hours. It was noted that the sample MX3 gave the best swelling ratio in both SIF and SGF. The reason may be that the system's polyvinyl alcohol-based gel polymers exhibit a high water absorption capacity with the appropriate amount of chitosan, which could well be governed by the PVA's molecular weight and cross-linking degree.

It was observed that the matrix exhibited a decreasing swelling ratio in SGF compared with SIF, indicating that the polymeric matrix was pH-sensitive.

It was observed that the matrix exhibited decreasing swelling ratio in SGF compared with SIF, which indicates that the polymeric matrix was pH-sensitive

For MX3,cross-linking agent concentration's impact has been investigated; the higher the cross-linking agent quantity, the lower the swelling ratio of the matrix was noticed. As a result of increasing interactions and binding between PVA and chitosan, which hinders the swelling, 1-mL of glutaraldehyde gave the best value for the swelling ratio Figure 5.

The percentages of enzalutamide release from the polymeric matrix (Figure 6) were measured according to the following equation:

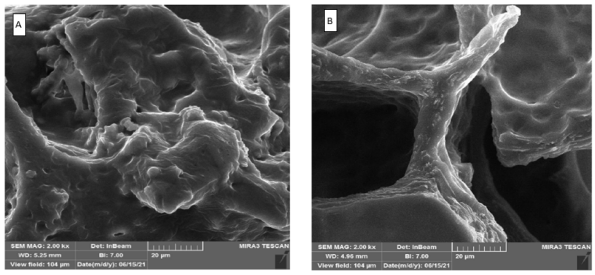

Figure 3: FE-SEM images of the polymeric matrix at 50 µm magnification (A) before loading the drug and (B) after loading the drug.

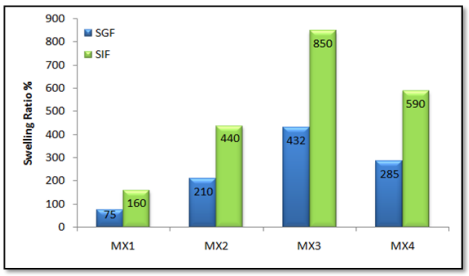

Figure 4 : Swelling ratio of polymeric matrix in SGF and SIF.

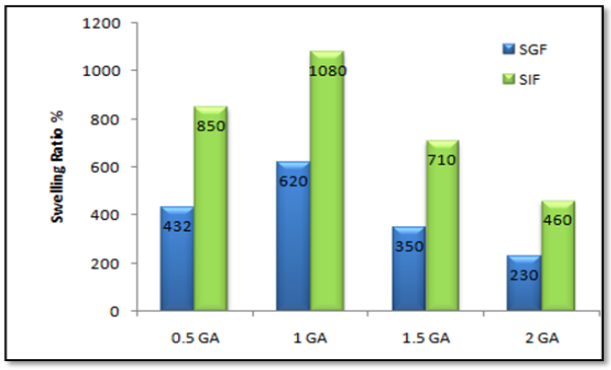

Figure 5: Effect of the concentration of cross-linking agent on the swelling behavior of MX3

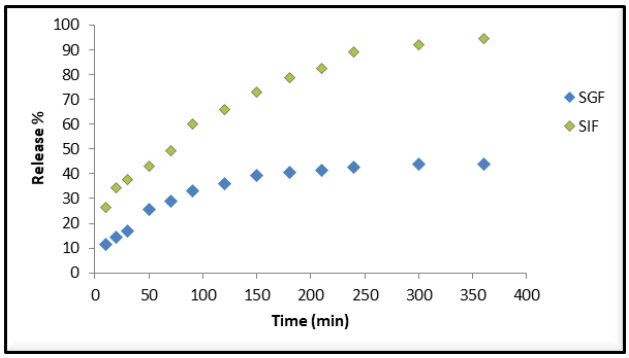

Figure 6 : The released percentage of drugs in SGF and SIF.

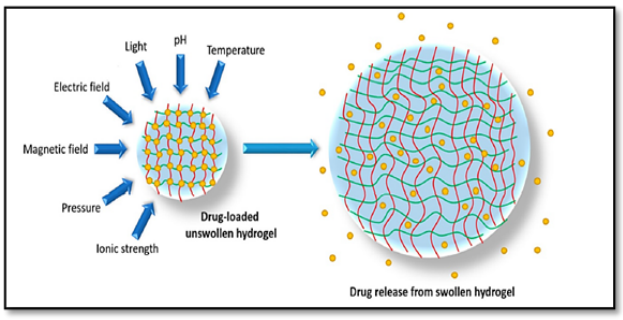

Figure 7: The release of drug from the smart hydrogel by swelling–diffusion mechanism.

$$Release\ \% = \frac{W_t}{W_i} x100 \ldots\ldots 5$$

The results demonstrated an increase in drug release percentage in SIF compared to SGF; this might be due to the shrinking of the polymeric matrix in the acidic medium, which restricts drug release.

In the drug release system used in the study, the drug was inserted into the polymer to form a homogeneous system called the matrix system. Diffusion occurs in this system when the drug passes through the network of the swelling gel to the external environment through the swelling mechanism, followed by diffusion (Figure 7).

Erosion and diffusion are the two ways biodegradable polymers release medications. The relative rates of erosion and diffusion have an impact on the *in-vivo* drug release from biodegradable polymers since both processes are involved. The concentration and type of drug will have an impact on both polymer degradation and release mechanisms.

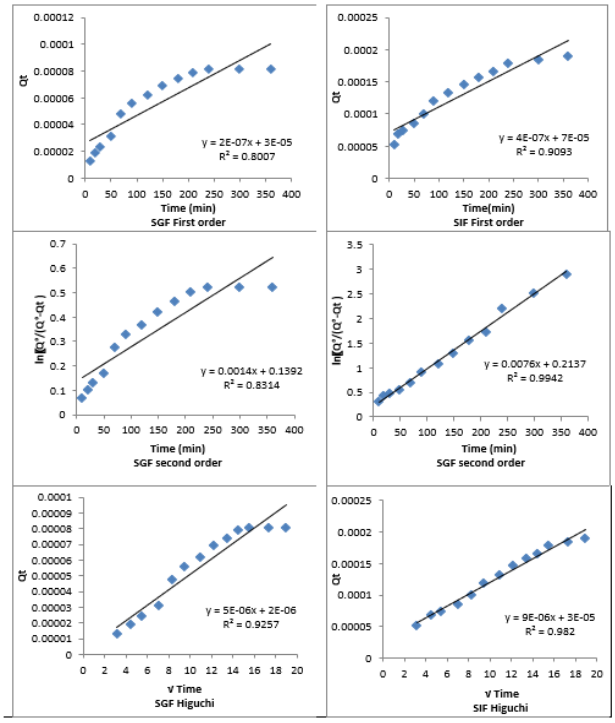

Figure 8: Kinetic models of enzalutamide release in SIF and SGF.

The kinetics study of the drug release within SGF and SIF according to equations 3, 4, and 5 (Table 1) and what is shown in Figure 8 revealed that the release process follows the Higuchi model in SGF with a regression coefficient value of 0.925. In contrast, SIF follows the first-order model with a regression coefficient value of 0.994.

CONCLUSIONS

To conclude, the above explicit data demonstrated the possibility of using the freshly created PVA/CS hydrogels as drug delivery vehicles for the enzalutamide in an attempt to reduce stomach upset and nausea which is usually occurred in patients treated with enzalutamide, which can also be recommended to be tested for other drugs that have unpleasant stomach effect, in order to enhance the accompanying side effect.

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