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A Systematic Review: Chitosan/ Poly (vinyl alcohol) based Hydrogel composites for Drug Delivery Material

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Abstract

This review article aims to systematically describe the synthesis methods, characterization, and performances of CS/PVA based hydrogel composites as drug delivery materials. The literature review was conducted through ScienceDirect and Google Scholar, where the article selection is based on Scopus index in the Q1 and Q2 categories within the past 5 years. The synthesis of CS/PVA hydrogel was performed using various methods, including crosslinking, freeze-thaw, and sol-gel. The synthesis methods of hydrogel composites included crosslinking, freeze-thaw, and sol-gel. Characterization of hydrogel composites was conducted using FTIR spectroscopy, SEM, and swelling ratio measurement. CS/PVA-based hydrogel composites as drug delivery materials have been successfully synthesized using crosslinker, freeze-thaw and sol-gel methods. FTIR spectra indicated that drug was successfully loaded into CS/PVA based hydrogel composite matrix, involving the hydrogen bonding as predominant mechanism of interaction between precursors and drug functionalities. The best swelling capacity was obtained in the CS/PVA/Tetracycline based hydrogel composites, up to 949%. The SEM images indicated the homogeneous morphological structure and surface of hydrogel composites. The CS/PVA/Tetracycline based hydrogel composites exhibited the largest cumulative drug release of 99.44%. The drugs loaded CS/PVA hydrogel composites are promising as a drug delivery material.

Keywords: *chitosan, composite, drug delivery, hydrogel, poly (vinyl alcohol)*

1 Introduction

Drug delivery materials are a cornerstone of modern therapeutics, driving advancements in how drugs are administered, improving patient outcomes, and enabling the development of new treatments for a wide range of diseases. Their importance lies in their ability to optimize drug efficacy, enhance patient compliance, minimize side effects, and support the ongoing innovation in medical treatments [1].

Drug delivery materials can be designed to release therapeutic agents specifically at the site of disease or injury. This localized delivery increases the drug concentration at the target site, enhancing its efficacy. These materials can also provide a controlled release of drugs over an extended period, maintaining optimal therapeutic levels and reducing the frequency of administration. Therefore, targeted drug delivery minimizes the exposure of healthy tissues to the drug, thereby reducing the risk of systemic side effects. The development of drug delivery materials is a multifaceted challenge that requires addressing material selection, biocompatibility, controlled release mechanisms, targeting accuracy, drug stability, manufacturing scalability, regulatory compliance, and patient acceptability [2].

Hydrogels offer numerous advantages for drug delivery, including high water content, biocompatibility, controlled and sustained release, versatility in drug encapsulation, and the ability to be tailored for specific applications [3]. Their unique properties make them ideal for a wide range of biomedical applications, providing effective and safe delivery of therapeutic agents. Hydrogels are hydrophilic polymer networks

capable of holding large amounts of water, making them suitable for various biomedical applications, including drug delivery. The incorporation of additional components into hydrogels can improve their mechanical strength, responsiveness to environmental stimuli, and drug release profiles. Hydrogels composites combine the unique properties of hydrogels with other materials to enhance their functionality. Drug encapsulation into hydrogel composites matrix represents a versatile and promising approach to drug delivery, combining the benefits of hydrogels with enhanced functionalities provided by composite materials [4].

In particular, chitosan (CS) is a naturally-occurring polysaccharide, derived polymer obtained from chitin through deacetylation process, which is found in the exoskeletons of crustaceans like shrimp and crabs. Chitosan is a highly promising hydrogel material for drug delivery due to its biocompatibility, biodegradability, mucoadhesiveness, and versatility. It offers numerous advantages for controlled drug release, stability, and targeted delivery [5]. Besides being biodegradable and biocompatible, making it relatively safe for medical applications, chitosan also has antimicrobial, antioxidant, and cell growth stimulating properties [6]. Therefore, chitosan is very suitable to be used as a drug delivery material.

A part from its excellent properties, CS still has some obstacles in application due to its limited solubility, acks the mechanical strength, poor thermal stability etc. To overcome these drawbacks, the addition of synthetic polymers such as poly (vinyl alcohol) or PVA has been used in the preparation of hydrogels [7]. PVA is a synthetic polymer with hydrophilic and biodegradable properties, which can improve the mechanical strength and water absorption capacity of hydrogels [8].

The selection of an appropriate synthesis method can affect the mechanical strength of the hydrogels. Hydrogels can be synthesized using various methods, depending on the desired properties and applications. The synthesis methods of hydrogels, for instance, free radical polymerization, sol-gel, freeze-thaw, and chemical crosslinking have been frequently reported [9]. In particular, the free radical polymerization involves polymerization of monomers initiated by free radicals while freeze-thaw involves freezing and thawing of polymer solutions [10]. The crosslinking method involves the reaction between polymer molecules and a crosslinking agent to form a three-dimensional network within the hydrogel [11]. Meanwhile, the sol-gel method involves the transition from a liquid sol to a solid gel phase, specifically tailored for creating hydrogel materials. The selection of an appropriate synthesis method will affect the properties and performance of the hydrogel as a drug delivery material [12].

Encapsulation of drug molecules (i.e. ofloxacin [13], enrofloxacin [14], ibuprofen [15], tetracycline [16], and antibacterial compounds (CuO [17], ZnO [18], into hydrogel matrix of CS/PVA for drug delivery materials have been reported.

This study aims to systematically review the information about synthesis methods, properties and performances of drugs encapsulated in CS/PVA based hydrogel composites. In particular, the effect of drug incorporation on the properties and performances of hydrogel composites as controlled drug release materials were reviewed comprehensively.

2 Method

The method used in this study was a literature review conducted by collecting literature sources that relevant to the topics, followed by data analysis and summarization to draw representative conclusions. The review process involved several stages, including planning, identification, selection, and summarization. The planning stage was conducted by determining the topic, objectives, and keywords. The literature search was related to CS/PVA-based hydrogels composites for drug delivery materials shows an excellent publication trend with the number of journal publications increasing every year. The identification stage involved searching reference articles using the specified keywords as presented in **Table 1.** Reference articles were selected based on its relevance to the review topic. To obtain reliable and well-indexed sources, international journals in databases such as ScienceDirect indexed by Scopus in Q1 and Q2 in the last 5 years (2018-2022) were included. The keywords used should cover important aspects of the research topic.

Table 1. Number of articles found by keywords

Database	Keywords	Number of Articles
Science Direct	Hydrogel Composite Chitosan AND PVA AND Drug Delivery	613
	Hydrogel Composite Chitosan AND Poly (vinyl alcohol) AND Drug Delivery	373
	Hydrogel CS AND PVA AND Drug Delivery	349
	Hydrogel composite CS/PVA for "Drug Delivery"	231
	Hydrogel Chitosan AND PVA AND Metal Oxide AND antibacterial	644
	Hydrogel Composite AND Chitosan AND PVA AND Drug Delivery	613

Table 2. The selected reference articles

Title	Author/Year	Ref.
Preparation and properties of *N-glycosylated* chitosan/polyvinyl alcohol hydrogels for use in wound dressings	Yu Yi, et al. /2022	[13]
Controlled release of enrofloxacin by vanillin-crosslinked chitosan-polyvinyl alcohol blends	Karakurt., et al. /2021	[14]
Chitosan polyvinyl alcohol blend films for ibuprofen encapsulation: Fabrication, characterization and kinetics	Aycan., et al. /2020	[15]
Investigating the effect of tetracycline addition on nanocomposite hydrogels based on polyvinyl alcohol and chitosan nanoparticles for specific medical applications	Parsa, et al. /2019	[16]
Fabrication of Chitosan/PVA/ GO/CuO patch for potential wound healing application	Venkataprasana. , et al. /2020	[17]
Nanocomposite framework of chitosan/polyvinyl alcohol/ZnO: Preparation (CS/PVA/ZnO)	Abdeen., et al. /2018	[18]
Incorporation of ZnO nanoparticles into heparinised polyvinyl alcohol/chitosan hydrogels for wound dressing application	Khorasani., et al. /2018	[19]

The selection stage involved sorting and selecting reference articles based on the relevant abstracts. The selected articles were then thoroughly studied to gather the detailed information of the synthesis method, characterization, and performances of CS/PVA based hydrogels composites for drug delivery application. This process was assisted by the JabRef application to organize and manage the selected reference articles. The results of this selection were summarized based on the application of CS/PVA hydrogels as wound dressings. The main reference article titles were collected and summarized in **Table 2.**

3 Result and Discussion

3.1 Synthesis of drug loaded CS/PVA based hydrogel composites

The fabrication methods of chitosan/PVA-based composite hydrogels as drug delivery materials have been intensively reported. The selection of an appropriate synthesis method of hydrogel composites depends on the research objectives, desired properties, and designated application of the composite hydrogels. The most common methods applied in fabrication of hydrogel composites for drug delivery materials were crosslinking, freeze-thaw and sol-gel techniques. **Table 3** demonstrated the fabrication methods of drug loaded CS/PVA based hydrogel composites.

Table 3. The synthesis methods and weight ratio of drug loaded CS/PVA based hydrogel composites

Hydrogel Composites	Synthesis Method	Optimum Compositions			Ref.
		CS (w.t%)	PVA (w.t%)	Drug (mg/mL)	
CS/PVA/ Ofloxacin	Freeze-thaw	1	10	50	[13]
CS/PVA/ Enrofloxacin	Crosslinking	1	1	10	[14]
CS/PVA/GEN/ Ibuprofen	Crosslinking	2	10	20	[15]
CS/PVA/ Tetracycline	Freeze-thaw	5	10	5	[16]
CS/PVA/ GO/CuO	Sol-gel	1	3	3	[17]
CS/PVA/ GA/ZnO	Crosslinking	2	10	2	[18]
CS/PVA/ ZnO	Freeze-thaw	2	10	5	[19]

Table 3 represented a series of drug loaded CS/PVA based hydrogel composites that were synthesized using different methods. It can be

inferred that freeze-thaw, sol-gel, crosslinking techniques are suitable for fabrication of hydrogel composites. In particular, the optimum condition of fabrication of hydrogel composites was indicated by the homogeneous mixture of polymer precursors with drug loaded. It is determined by type and weight ratio of precursors and drug loaded, also environmental factors (pH, temperature, etc.). Since the drugs loaded have different molecular structures, functional moieties, and size (**Figure 1**), then the optimum composition ratio in the composites was variable. In addition, the amount of drug loaded into hydrogel matrix must be suitable for medication purposes.

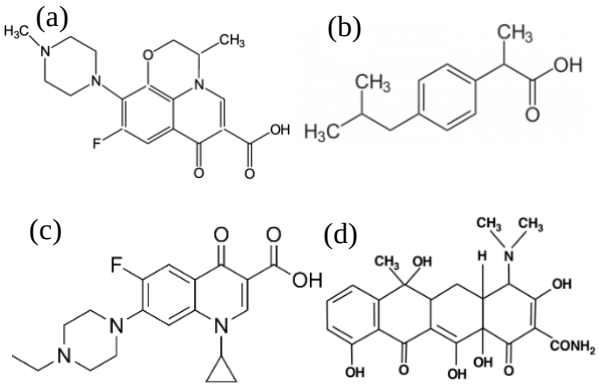

Figure 1. Chemical structures of drug molecules: ofloxacin (a), enrofloxacin (b), ibuprofen (c), and tetracycline (d)

The sol-gel method is the most common method used methods in hydrogel fabrication. This method involves the use of precursor which are then converted into hydrogels through a gelation process [20]. The sol-gel method can produce hydrogels that are strong, stable and can be customized for different applications. In addition, the use of sol-gel method can also improve the mechanical properties and thermal stability of hydrogels [21]. These hydrogels can also be customized to respond to specific pH, which is beneficial for drug delivery in specific environments in the body [22].

The freeze-thaw method involves repeated freezing and thawing of the hydrogel solution, which results in the formation of a stable hydrogel network [23]. This method produces flexible hydrogels with good deformation capabilities making them suitable for applications that require flexible materials [24]. The use of the freeze-thaw method also makes it possible to produce hydrogels with high porosity and swelling capacity [25]. The crosslinking method involves the use of a cross-linking agent, such as glutaraldehyde, which allows the hydrogel molecules to connect and form a network [26]. This method produces hydrogels that are strong, stable, and have well-regulated mechanical properties that are important for long-term drug delivery applications [27,28]. This method allows fine control over the hydrogel network structure, which can promote controlled drug release and prevent hydrogel degradation before the drug reaches its target [29].

In term of hydrogels application as drug delivery materials, the cross-linking is considered as an effective method because it can produce hydrogels with a strong and stable network structure thereby extending the drug release time and preventing degradation of the hydrogel before the drug reaches its target [30]. This method can produce a hydrogel with a strong and stable network structure, thus extending the drug release time and preventing hydrogel degradation before the drug reaches its target. The crosslinking method is also relatively easy to carry out without destroying the drug, thereby, improving the hydrogel performance as a drug delivery material through interactions between drugs and biological targets. Considering the advantages and characteristics of each method, the selection of an effective and efficient synthesis technique is notably crucial depending on the desired properties and target applications of the hydrogel composites.

In addition, various characterization techniques were employed to obtain the information about physicochemical properties of the hydrogels composites, for instance, Fourier Transform Infrared (FTIR) spectroscopy, swelling ratio measurement, and Scanning Electron Microscopy (SEM).

3.2 Characteristics and performances of the hydrogel composites

Chitosan/PVA based hydrogel composites can be characterized through FTIR spectroscopy, SEM observation, and swelling ratio test. In particular, the FTIR spectroscopy is used for functional group identification; swelling test measures the water absorption capacity of hydrogels, and SEM provides information of surface morphology. This characterization method helps in understanding the composition, structure, and drug release control capabilities of hydrogels, providing an important foundation for the development of chitosan/PVA-based hydrogel composites.

3.2.1 Fourier Transform Infrared (FTIR) Spectroscopy

Figure 2 depicts the FTIR spectra of drugs loaded CS/PVA based hydrogel composites. In particular, the FTIR spectrum of chitosan hydrogel indicates the typical peaks at wavenumbers around 1630-1650 cm^{-1} and 1550-1580 cm^{-1} correspond to the presence of amine (NH_2) groups of chitosan. In addition, a peak at wavenumbers at 3300-3500 cm^{-1} represents the hydroxyl (-OH) groups. These results inferred that the interaction between amine and hydroxyl group predominantly occurs via hydrogen bonds.

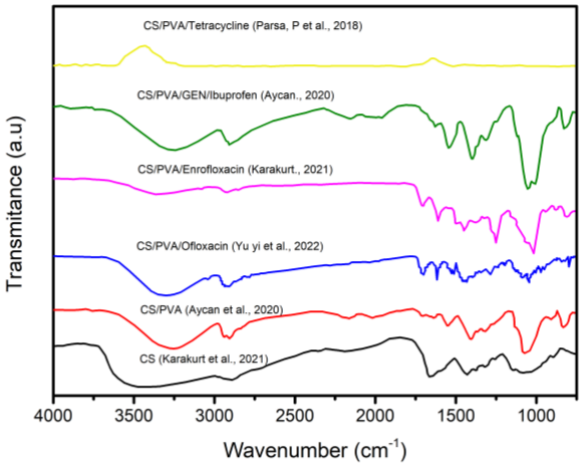

Figure 2. FTIR spectra of drugs loaded hydrogel composites.

These peaks also indicate that chitosan has primary amine groups that can also form hydrogen bonds with surrounding water molecules, increasing its solubility and physical properties [31].

In case of CS/PVA based hydrogel composites, a new peak appeared at wavenumber of 3400-3500 cm^{-1} indicating the existence of hydrogen bonds between the hydroxyl groups of chitosan and PVA and the surrounding water molecules. The peak at 2920 cm^{-1} shows the stretching vibration of the C-H bonds in this hydrogel, indicating the formation of a strong polymer network [32]. This new peak indicates that the addition of PVA increases the formation of hydrogen bonds, which can increase the mechanical strength and stability of the hydrogel composites [33].

Furthermore, the CS/PVA/Ofloxacin hydrogel showed new peaks at wavenumbers of 1442 cm^{-1}, 1621 cm^{-1}, 1710 cm^{-1}, 2789 cm^{-1}, and 3310 cm^{-1}. These peaks indicate the interaction of functional moieties of the drug with the hydrogel composites, reflecting the presence of new bonds formed between ofloxacin and the hydrogel matrix [34]. These peaks showed that ofloxacin was successfully encapsulated in the hydrogel matrix through hydrogen and ionic interactions with the functional groups of CS and PVA [35].

In case of the CS/PVA/vanillin/enrofloxacin hydrogel composites, a new peak was observed at wavenumbers of 1600-1620 cm^{-1}, indicating the aromatic bonds in vanillin. The peak at 1650 cm^{-1} indicates the presence of amide I bonds in chitosan and enrofloxacin, due to a strong interaction between these components in the hydrogel [36]. This peak shift indicates that vanillin and enrofloxacin form hydrogen and covalent bonds with the hydrogel matrix, increasing the drug stability [37].

On the other hand, CS/PVA/GEN/ibuprofen hydrogel composites also showed significant changes in the FTIR spectrum where a new peak at wavenumbers of 1690-1720 cm^{-1} corresponds to the presence of carbonyl bonds from ibuprofen. The peak at 1650 cm^{-1} also indicates the presence of amide I bonds in CS, indicating the conjugation between ibuprofen, GEN, and CS/PVA [38]. This peak indicated that ibuprofen was successfully incorporated into the hydrogel through hydrogen interactions and amide bond formation, which increased the drug loading capacity and drug release properties [39].

In the CS/PVA/tetracycline hydrogel composites, the FTIR spectrum showed the presence of a new peak associated with tetracycline, representing a significant interaction between the hydrogel components [40]. This shows that tetracycline is well integrated in the hydrogel matrix. These new peaks indicate that tetracycline interacts with CS and PVA via hydrogen and electrostatic bonds, which can improve drug delivery efficiency [41]. According to FTIR spectra, it can be inferred that drug was successfully loaded into CS/PVA based hydrogel composite matrix, involving the hydrogen bonding as predominant mechanism of interaction between precursors and drug functionalities.

3.2.2 Swelling ratio (water absorption capacity)

The swelling behavior of hydrogel composites is a pivotal parameter in determining the suitable materials for drug delivery applications. The swelling ratio of hydrogel composites can be influenced by several factors, including the nature of the polymer and the type of functional groups involved.

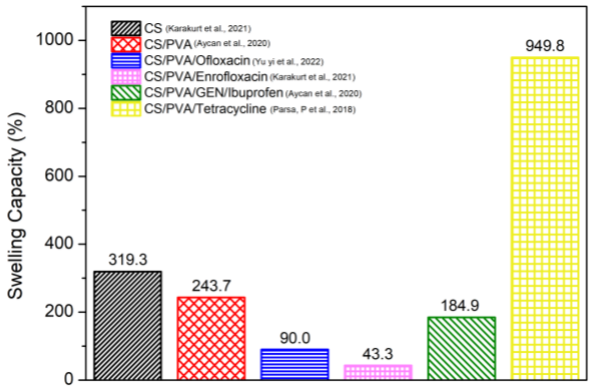

Figure 3. The swelling capacity of hydrogel composites

Figure 3 represents the CS based hydrogel has a swelling *capacity* up to 319.3%, which shows strong hydrophilic properties, as supported by the presence of amino and hydroxyl groups [42]. The CS/PVA hydrogel with a swelling *capacity* of 243.7% also showed good hydrophilic properties, thanks to the hydrogen bonds between the hydroxyl groups of PVA and water molecules, as well as the interaction with the amino groups in CS [43]. On the other hand, CS/PVA/Ibuprofen hydrogel has a lower swelling *capacity* up to 90%, compare to CS/PVA. The decrease is due to the hydrophobic nature of ibuprofen, which reduces water absorption by the hydrogel composites [44]. In contrast, the CS/PVA/GEN/Ibuprofen hydrogel with genipin crosslinking had a swelling *capacity* of 184.9%, due to a denser and stiffer hydrogel network produced by its crosslinking ability [45]. The CS/PVA/Vanillin/Enrofloxacin based hydrogel has the lowest swelling *capacity* of 43.3%, because vanillin and enrofloxacin which are hydrophobic compounds, inhibit water absorption [46]. In contrast, the CS/PVA/Tetracycline based hydrogel composites showed a very high swelling *capacity* of 949%, indicating that tetracycline did not significantly interfere the water absorption capacity of the hydrogel composites, possibly due to specific interactions that increased the overall hydrophilicity [47]. The the use of glutaraldehyde as a crosslinker provides a greater swelling *capacity* compared to other crosslinkers, making it a good choice for drug delivery applications. Glutaraldehyde contributes to the more effective drug delivery through hydrogel composites by enabling slower and more controllable drug release of drugs [48].

3.2.3 Scanning Electron Microscopy (SEM)

The SEM images obtained from the electron microscope observation as presented in **Figure 4** provide visual information about the morphology and surface structure of the hydrogel compo. It can also be correlated with the percentage swelling capacity to provide.

Drug delivery materials can be designed to release therapeutic agents specifically at the site of disease or injury. This localized delivery increases the drug concentration at the target site, enhancing its efficacy. These materials can also provide a controvide a more comprehensive understanding about the relationship between the structure and characteristics of hydrogel composites. If a hydrogel has a high swelling capacity, this indicates that the hydrogel is able to absorb large amounts of water and expand [43]. On the other hand, if a hydrogel has a low swelling capacity, this indicates that the hydrogel has limited ability to absorb water and expand [49].

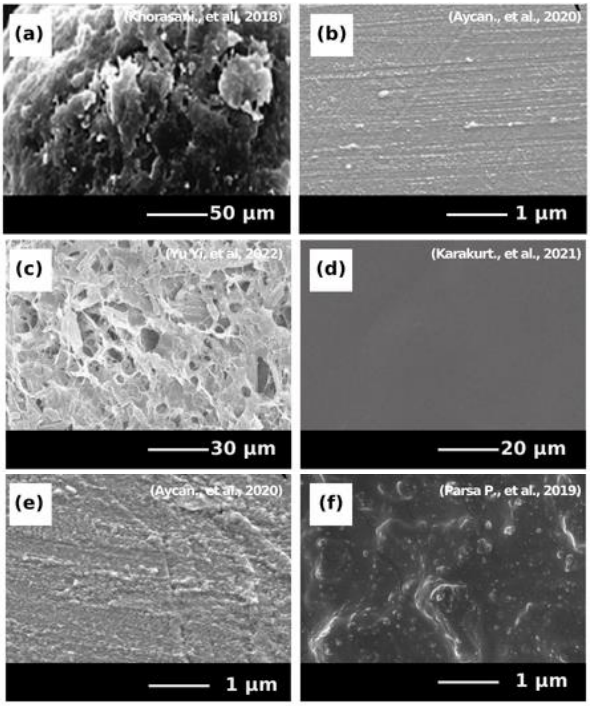

Figure 4. SEM photographs of hydrogel composite

In the CS/PVA/ofloxacin based hydrogel composites, the morphology of the hydrogel composites loaded with 5.0% ofloxacin showed that the ofloxacin loaded did not change the three-dimensional network structure of the hydrogel composites. However, the number of pores increased and the pore size decreased, which may be caused by the dissolution of ofloxacin in the pores of the hydrogel. Strong hydrogen bonds are

formed between ofloxacin and hydrogel, which makes the cross-linked hydrogel composites structure denser [35].

Interestingly, the SEM image of the chitosan/PVA/vanillin/enrofloxacin based hydrogel composites show a smooth and homogeneous surface structure, indicating that the hydrogel has a high density and compact structure [14]. In the CS/PVA/GEN/ibuprofen base hydrogel, the SEM image shows lower porosity. This denser and more organized structure may limit water absorption into the hydrogel composite [39]. Moreover, the SEM image of CS/PVA/Tetracycline based hydrogel composites shows the surface and fracture surface as representative. The well-dispersed structure indicates effective interactions between hydrogel components [50]. The addition of various drugs into the hydrogel matrix not only modifies the pore structure, but also affects the mechanical and functional properties of the hydrogel composites.

3.3 Performance of drug loaded CS/PVA based hydrogel composites

Drug release behavior is an essential aspect in the development of hydrogel composites as drug delivery materials. This determines the efficiency and effectiveness of drugs control release from the hydrogel matrix. Cumulative release (%) of chitosan/PVA based hydrogel composites are presented in **Figure 5.**

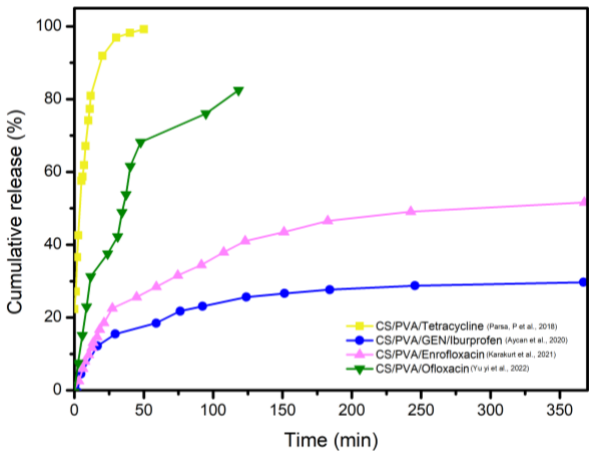

Figure 5. Drug release behavior from hydrogel composites.

The CS/PVA/ofloxacin based hydrogel composites has drug cumulative release of 92.09% and 99.44% after 20 hours and 50 hours, respectively. This is indicated that the hydrogel composites are very effective in releasing drugs in at a relatively short time. On the hand, the CS/PVA/vanillin/enrofloxacin based hydrogel composite showed a controlled drug release profile with a cumulative release of 30%. This indicates that the hydrogel effectively retains the drug and releases it gradually over time, thereby ensuring sustained drug delivery. This controlled release characteristic is beneficial in applications where constant and long-term drug release is desired, such as in the treatment of chronic conditions.

In contrast, the CS/PVA/GEN/ibuprofen hydrogel composite achieved a cumulative release of 50%. This shows a relatively higher release rate compared to previous formulations. A higher release. In addition, the CS/PVA/Tetracycline based hydrogels composite after the first day of release period was stable with a value of 37%, which indicates a more controlled drug release by the hydrogel. Generally, a slow-release profile is more desirable for targeted drug delivery, and in this case, the CS/PVA/Tetracycline based hydrogel composites becomes the most suitable option compared to other series of drug loaded CS/PVA for the slow controlled release drug delivery [41].

4 Conclusion

According to the literature reviewed, CS/PVA-based hydrogel composites as drug delivery materials have been successfully synthesized using crosslinker, freeze-thaw and sol-gel methods. FTIR spectra indicated that drug was successfully loaded into CS/PVA based hydrogel composite matrix, involving the hydrogen bonding as predominant mechanism of interaction between precursors and drug functionalities. The best swelling capacity was obtained in the CS/PVA/Tetracycline based hydrogel composites, up to 949%. The SEM images indicated the homogeneous morphological structure and surface of hydrogel composites. The CS/PVA/ Tetracycline based hydrogel composites exhibited the largest cumulative drug release of 99.44%. The drugs loaded CS/PVA hydrogel composites are promising as a drug delivery material.

References

[1] Anjum, S., Hashim, M., Malik, S.A., Khan, M., Lorenzo, J.M., Abbasi, B.H. et al. 2021. Recent Advances in Zinc Oxide Nanoparticles (ZnO NPs) for Cancer Diagnosis, Target Drug

Delivery, and Treatment. *Cancers*, 13 (18). 10.3390/cancers13184570

[2] Chatterjee, S., Hui, P.C., Wat, E., Kan, C., Leung, P.-C. and Wang, W. 2020. Drug delivery system of dual-responsive PF127 hydrogel with polysaccharide-based nano-conjugate for textile-based transdermal therapy. *Carbohydrate Polymers*, 236 116074. https://doi.org/10.1016/j.carbpol.2020.116074

[3] Mohadi, R., Hidayati, N. and N.R, M. 2007. PREPARASI DAN KARAKTERISASI KOMPLEKS KITOSAN HIDROGEL-TEMBAGA(II). *Molekul*, 2 35. 10.20884/1.jm.2007.2.1.31

[4] Muthohatoh, S. 2012. Sintesis Polimer Superabsorben dari Hidrogel Kitosan Terikat Silang [Skripsi]. Universitas Indonesia, [Depok].

[5] Ali, A. and Ahmed, S. 2018. A review on chitosan and its nanocomposites in drug delivery. *International Journal of Biological Macromolecules*, 109 273–86. 10.1016/j.ijbiomac.2017.12.078

[6] Made Heni Epriyanti, N., Admadi Harsojuwono, B., Wayan Arnata, I., Jurusan Teknologi Industri pertanian, M., Teknologi Pertanian Unud, F. and Jurusan Teknologi Industri Pertanian, D. 2016. PENGARUH SUHU DAN LAMA PENGERINGAN TERHADAP KARAKTERISTIK KOMPOSIT PLASTIK BIODEGRADABLE DARI PATI KULIT SINGKONG DAN KITOSAN. Maret.

[7] Imhitani, Hilya Nur, Wahyuno, Ruri Agung, Pernatasari and Silfiana. 2020. Biopolimer kitosan dan penggunaannya dalam formulasi obat. Graniti.

[8] Hamzah, M., Ndimba, R., Khenfouch, M. and Vallabhapurapu, V. 2017. Blue luminescence from hydrothermal ZnO nanorods based PVA nanofibers. *Journal of Materials Science: Materials in Electronics*, 28. 10.1007/s10854-017-7000-9

[9] Hamedi, H., Moradi, S., Hudson, S.M. and Tonelli, A.E. 2018. Chitosan based hydrogels and their applications for drug delivery in wound dressings: A review. *Carbohydrate Polymers*, 199 445–60. 10.1016/j.carbpol.2018.06.114

[10] Long, J., Etxeberria, A.E., Kornelsen, C., Nand, A. V., Ray, S., Bunt, C.R. et al. 2019. Development of a Long-Term Drug Delivery System with Levonorgestrel-Loaded Chitosan Microspheres Embedded in Poly(vinyl alcohol) Hydrogel. *ACS Applied Bio Materials*, 2 (7) 2766–79. 10.1021/acsabm.9b00190

[11] Figueroa-Pizano, M.D., Vélaz, I., Peñas, F.J., Zavala-Rivera, P., Rosas-Durazo, A.J., Maldonado-Arce, A.D. et al. 2018. Effect of freeze-thawing conditions for preparation of chitosan-poly (vinyl alcohol) hydrogels and drug release studies. *Carbohydrate Polymers*, 195 476–85. 10.1016/j.carbpol.2018.05.004

[12] Ragelle, H., Danhier, F., Préat, V., Langer, R. and Anderson, D.G. 2017. Nanoparticle-based drug delivery systems: a commercial and regulatory outlook as the field matures. *Expert Opinion on Drug Delivery*, Taylor & Francis. 14 (7) 851–64. 10.1080/17425247.2016.1244187

[13] Yi, Y., Huang, T., Xu, Y., Mei, J., Zhang, Y., Wang, X. et al. 2022. Preparation and properties of *N* -glycosylated chitosan/polyvinyl alcohol hydrogels for use in wound dressings. *Journal of Applied Biomaterials & Functional Materials*, 20 228080002211018. 10.1177/22808000221101809

[14] Karakurt, I., Ozaltin, K., Vargun, E., Kucerova, L., Suly, P., Harea, E. et al. 2021. Controlled release of enrofloxacin by vanillin-crosslinked chitosan-polyvinyl alcohol blends. *Materials Science and Engineering: C*, 126 112125. https://doi.org/10.1016/j.msec.2021.112125

[15] Aycan, D., Yayla, N.A. and Aydin, Y.A. 2020. Chitosan polyvinyl alcohol blend films for ibuprofen encapsulation: Fabrication, characterization and kinetics. *Polymer Degradation and Stability*, 181 109346. https://doi.org/10.1016/j.polymdegradstab.2020.109346

[16] Parsa, P., Paydayesh, A. and Davachi, S.M. 2019. Investigating the effect of tetracycline addition on nanocomposite hydrogels based on polyvinyl alcohol and chitosan nanoparticles for specific medical applications. *International Journal of Biological Macromolecules*, 121 1061–9. 10.1016/j.ijbiomac.2018.10.074

[17] Venkataprasanna, K.S., Prakash, J., Vignesh, S., Bharath, G., Venkatesan, M., Banat, F. et al. 2020. Fabrication of Chitosan/PVA/GO/CuO patch for potential wound healing application. *International Journal of Biological Macromolecules*, Elsevier B.V. 143 744–62. 10.1016/j.ijbiomac.2019.10.029

[18] Abdeen, Z.I., El Farargy, A.F. and Negm, N.A. 2018. Nanocomposite framework of chitosan/polyvinyl alcohol/ZnO: Preparation, characterization, swelling and antimicrobial evaluation. *Journal of Molecular Liquids*, 250 335–43. https://doi.org/10.1016/j.molliq.2017.12.032

[19] Khorasani, M.T., Joorabloo, A., Moghaddam, A., Shamsi, H. and MansooriMoghadam, Z. 2018. Incorporation of ZnO nanoparticles into heparinised polyvinyl alcohol/chitosan hydrogels for wound dressing application. *International Journal of Biological Macromolecules*, Elsevier B.V. 114 1203–15. 10.1016/j.ijbiomac.2018.04.010

[20] Biglari, L., Naghdi, M., Poursamar, S.A., Nilforoushan, M.R., Bigham, A. and Rafienia, M. 2024. A route toward fabrication of 3D printed bone scaffolds based on poly(vinyl alcohol)–chitosan/bioactive glass by sol–gel chemistry. *International Journal of Biological Macromolecules*, 258 128716. 10.1016/j.ijbiomac.2023.128716

[21] Zeng, L., Liu, B. and Gao, G. 2023. Physically crosslinked polyvinyl alcohol/chitosan-phytic acid hydrogels for wearable sensors with highly conductive, recyclable and antibacterial properties. *Science China Materials*, 66 (10) 4062–70. 10.1007/s40843-023-2530-4

[22] Seo, B.-B., Kwon, Y., Kim, J., Hong, K.H., Kim, S.-E., Song, H.-R. et al. 2022. Injectable polymeric nanoparticle hydrogel system for long-term anti-inflammatory effect to treat osteoarthritis. *Bioactive Materials*, 7 14–25. 10.1016/j.bioactmat.2021.05.028

[23] Rajan, R., Kumar, N., Zhao, D., Dai, X., Kawamoto, K. and Matsumura, K. 2023. Polyampholyte-Based Polymer Hydrogels for the Long-Term Storage, Protection and Delivery of Therapeutic Proteins. *Advanced Healthcare Materials*, 12 (17). 10.1002/adhm.202203253

[24] Ye, J., Liu, L., Lan, W. and Xiong, J. 2023. Targeted release of soybean peptide from CMC/PVA hydrogels in simulated intestinal fluid and their pharmacokinetics. *Carbohydrate Polymers*, 310 120713. 10.1016/j.carbpol.2023.120713

[25] Soe, H.M.S.H., Kerdpol, K., Rungrotmongkol, T., Pruksakorn, P., Autthateinchai, R., Wet-osot, S. et al. 2023. Voriconazole Eye Drops: Enhanced Solubility and Stability through Ternary Voriconazole/Sulfobutyl Ether β-Cyclodextrin/Polyvinyl Alcohol Complexes. *International Journal of Molecular Sciences*, 24 (3) 2343. 10.3390/ijms24032343

[26] Koosha, M., Raoufi, M. and Moravvej, H. 2019. One-pot reactive electrospinning of chitosan/PVA hydrogel nanofibers reinforced by halloysite nanotubes with enhanced fibroblast cell attachment for skin tissue regeneration. *Colloids and Surfaces B: Biointerfaces*, 179 270–9. 10.1016/j.colsurfb.2019.03.054

[27] Zhang, M., Yuan, Y., Jin, J., Sun, J. and Tian, X. 2023. Polyvinyl alcohol composite hydrogels/epoxidized natural rubber composites (CMCS/PVA/CS-ENR) with core-shell structure as biomass coating material for slow-release nitrogen fertilizer. *Progress in Organic Coatings*, 183 107744. 10.1016/j.porgcoat.2023.107744

[28] Jamal, A., Shahzadi, L., Ahtzaz, S., Zahid, S., Chaudhry, A.A., Rehman, I. ur et al. 2018. Identification of anti-cancer potential of doxazocin: Loading into chitosan based biodegradable hydrogels for on-site delivery to treat cervical cancer. *Materials Science and Engineering: C*, 82 102–9. 10.1016/j.msec.2017.08.054

[29] Boonruam, P. and Wattanachai, P. 2021. EFFECTS OF CHEMICAL COMPOSITIONS OF CHITOSAN-BASED HYDROGEL ON PROPERTIES AND COLLAGEN RELEASE. *ASEAN Engineering Journal*, 11 (2) 85–100. 10.11113/aej.v11.16684

[30] Li, L., Lin, M., Li, L., Wang, R., Zhang, C., Qi, G. et al. 2014. Renal telocytes contribute to the repair of ischemically injured renal tubules. *Journal of Cellular and Molecular Medicine*, 18 (6) 1144–56. 10.1111/jcmm.12274

[31] Zhang, Y., Jiang, M., Zhang, Y., Cao, Q., Wang, X., Han, Y. et al. 2019. Novel lignin–chitosan–PVA composite hydrogel for wound dressing. *Materials Science and Engineering: C*, 104 110002. 10.1016/j.msec.2019.110002

[32] Kamoun, E.A., Chen, X., Mohy Eldin, M.S. and Kenawy, E.-R.S. 2015. Crosslinked poly(vinyl alcohol) hydrogels for wound dressing applications: A review of remarkably blended polymers. *Arabian Journal of Chemistry*, 8 (1) 1–14. 10.1016/j.arabjc.2014.07.005

[33] Yang, W., Fortunati, E., Bertoglio, F., Owczarek, J.S., Bruni, G., Kozanecki, M. et al. 2018. Polyvinyl alcohol/chitosan hydrogels with enhanced antioxidant and antibacterial properties induced by lignin nanoparticles. *Carbohydrate Polymers*, 181 275–84. 10.1016/j.carbpol.2017.10.084

[34] Mirzaeei, S., Taghe, S., Asare-Addo, K. and Nokhodchi, A. 2021. Polyvinyl Alcohol/Chitosan Single-Layered and Polyvinyl Alcohol/Chitosan/Eudragit RL100 Multi-layered Electrospun Nanofibers as an Ocular Matrix for the Controlled Release of Ofloxacin: an In Vitro and In Vivo Evaluation. *AAPS PharmSciTech*, Springer Science and Business Media Deutschland GmbH. 22 (5). 10.1208/s12249-021-02051-5

[35] Mahmood, H., Khan, I.U., Asif, M., Khan, R.U., Asghar, S., Khalid, I. et al. 2021. In vitro and in vivo evaluation of gellan gum hydrogel films: Assessing the co impact of therapeutic oils and ofloxacin on wound healing. *International Journal of Biological Macromolecules*, 166 483–95. 10.1016/j.ijbiomac.2020.10.206

[36] Khanamani, F.S., Hosseinzadeh, A.Y., Akbari, J.H. and ... 2017. Preparation and in vitro evaluation of a novel chitosan-based hydrogel for injectable delivery of enrofloxacin [Internet]. pesquisa.bvsalud.org.

[37] Sen', V.D., Sokolova, E.M., Neshev, N.I., Kulikov, A. V. and Pliss, E.M. 2017. Low

molecular chitosan–(poly)nitroxides: Synthesis and evaluation as antioxidants on free radical-induced erythrocyte hemolysis. *Reactive and Functional Polymers*, 111 53–9. 10.1016/j.reactfunctpolym.2016.12.006

[38] Tian, B. and Liu, J. 2023. Smart stimuli-responsive chitosan hydrogel for drug delivery: A review. *International Journal of Biological Macromolecules*, 235 123902. 10.1016/j.ijbiomac.2023.123902

[39] Mahmood, S., Almurisi, S.H., AL-Japairai, K., Hilles, A.R., Alelwani, W., Bannunah, A.M. et al. 2021. Ibuprofen-Loaded Chitosan–Lipid Nanoconjugate Hydrogel with Gum Arabic: Green Synthesis, Characterisation, In Vitro Kinetics Mechanistic Release Study and PGE2 Production Test. *Gels*, 7 (4). 10.3390/gels7040254

[40] Chen, H., Li, B., Feng, B., Wang, H., Yuan, H. and Xu, Z. 2019. Tetracycline hydrochloride loaded citric acid functionalized chitosan hydrogel for wound healing. *RSC Advances*, 9 (34) 19523–30. 10.1039/C9RA02628B

[41] Luo, Q., Ren, T., Lei, Z., Huang, Y., Huang, Y., Xu, D. et al. 2022. Non-toxic chitosan-based hydrogel with strong adsorption and sensitive detection abilities for tetracycline. *Chemical Engineering Journal*, 427 131738. 10.1016/j.cej.2021.131738

[42] Bi, S., Wang, P., Hu, S., Li, S., Pang, J., Zhou, Z. et al. 2019. Construction of physical-crosslink chitosan/PVA double-network hydrogel with surface mineralization for bone repair. *Carbohydrate Polymers*, 224 115176. 10.1016/j.carbpol.2019.115176

[43] Naidoo, K., Amonsou, E.O. and Oyeyinka, S.A. 2015. In vitro digestibility and some physicochemical properties of starch from wild and cultivated amadumbe corms. *Carbohydrate Polymers*, 125 9–15. 10.1016/j.carbpol.2015.02.066

[44] Enoch, K., S, R.C. and Somasundaram, A.A. 2023. Improved mechanical properties of Chitosan/PVA hydrogel – A detailed Rheological study. *Surfaces and Interfaces*, 41 103178. 10.1016/j.surfin.2023.103178

[45] Constantin, M., Lupei, M., Bucatariu, S.-M., Pelin, I.M., Doroftei, F., Ichim, D.L. et al. 2022. PVA/Chitosan Thin Films Containing Silver Nanoparticles and Ibuprofen for the Treatment of Periodontal Disease. *Polymers*, 15 (1) 4. 10.3390/polym15010004

[46] Bernal-Ballen, A., Lopez-Garcia, J.-A. and Ozaltin, K. 2019. (PVA/Chitosan/Fucoidan)-Ampicillin: A Bioartificial Polymeric Material with Combined Properties in Cell Regeneration and Potential Antibacterial Features. *Polymers*, 11 (8) 1325. 10.3390/polym11081325

[47] Janani, B., Okla, M.K., Abdel-Maksoud, M.A., AbdElgawad, H., Thomas, A.M., Raju, L.L. et al. 2022. CuO loaded ZnS nanoflower entrapped on PVA-chitosan matrix for boosted visible light photocatalysis for tetracycline degradation and anti-bacterial application. *Journal of Environmental Management*, 306 114396. 10.1016/j.jenvman.2021.114396

[48] Jufri, M., Lusiana, R.A. and Prasetya, N.B.A. 2022. Effects of Additional Polyvinyl Alcohol (PVA) on the Physiochemical Properties of Chitosan-Glutaraldehyde-Gelatine Bioplastic. *Jurnal Kimia Sains Dan Aplikasi*, 25 (3) 130–6. 10.14710/jksa.25.3.130-136

[49] Hofman, A.H., ten Brinke, G. and Loos, K. 2016. Hierarchical structure formation in supramolecular comb-shaped block copolymers. *Polymer*, 107 343–56. 10.1016/j.polymer.2016.08.021

[50] Naderi, K., Foroughi, M. and Azqhandi, M.H.A. 2022. Tetracycline capture from aqueous solutions by nanocomposite of MWCNTs reinforced with glutaraldehyde cross-linked poly (vinyl alcohol)/chitosan. *Chemosphere*, 303 135124. 10.1016/j.chemosphere.2022.135124