

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa



ORIGINAL ARTICLE

Enhanced antibacterial activity of chitosan, guar gum and polyvinyl alcohol blend matrix loaded with amoxicillin and doxycycline hyclate drugs



Dure N. Iqbal^a, Syed Ehtisham-ul-Haque^b, Sundas Ahmad^a, Khadija Arif^a, Erum Akbar Hussain^c, Munawar Iqbal^a, Samar Z. Alshawwa^{d,*}, Mazhar Abbas^e, Nyla Amjed^a, Arif Nazir^{a,*}

^a Department of Chemistry, The University of Lahore, Lahore 53700, Pakistan

^b Department of Pathobiology, University of Veterinary and Animal Sciences, Lahore, (Jhang Campus), 12 km Chiniot Road, Jhang 35200, Pakistan

^c Department of Chemistry, Lahore College for Women University, Lahore, Pakistan

^d Department of Pharmaceutical Sciences, College of Pharmacy, Princess Nourah bint Abdulrahman University, Alriyadh, Saudi Arabia

^e Department of Biochemistry, University of Veterinary and Animal Sciences, Lahore, (Jhang Campus), 12 KM Chiniot Road, Jhang 35200, Pakistan

Received 14 January 2021; accepted 4 April 2021 Available online 15 April 2021

KEYWORDS

Chitosan; Guar Gum; Polyvinyl alcohol; Solution casting method; Drug loading **Abstract** This study focusses on the synthesis of a series of semisynthetic polymeric blended membranes based on chitosan, guar gum and polyvinyl alcohol for the sustained delivery of antibacterial drugs" with "A series of semisynthetic polymeric blended membranes based on GG (guar gum), CS (chitosan) and PVA (polyvinyl alcohol) was fabricated for the sustained delivery of antibacterial drugs. The drug employed in this study includes amoxicillin and doxycycline hyclate. Different ratios of chitosan CS and GG were blended with constant ratio of PVA to synthesize membranes using solution casting method. Fourier transforms infrared (FTIR), scanning electron microscopy (SEM) and X-ray diffraction (XRD) study showed the blend formation, surface morphology and crystalline nature of polymeric membranes respectively. Successful bonding among the ingredients was confirmed by crystalline peak of CS cellulose at 22.6. Swelling test was used to analyze the water absorbing capacity of the membranes, indicating the hydrophilic nature, making these membranes more liable for drug release application. Results revealed that 25 mg was the ideal amount of drug loaded on blended membrane. Antimicrobial activity was promising against selected bacterial

* Corresponding authors.

E-mail addresses: SZAlshawwa@pnu.edu.sa (S.Z. Alshawwa), nyla.amjed@chem.uol.edu.pk (N. Amjed), anmalik77@gmail.com (A. Nazir). Peer review under responsibility of King Saud University.



https://doi.org/10.1016/j.arabjc.2021.103156

1878-5352 © 2021 The Author(s). Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

strains and cytotoxicity assay showed that the polymeric membranes have great potential for biomedical field. The membrane (B-2) was considered best amongst all based on the composition and ratio 3:1 of CS to GG, demonstrated good binding between constituents. These membranes can be employed for sustainable drug delivery process due to good swelling, antimicrobial and absorption characteristics.

© 2021 The Author(s). Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Blending is an unforced approach to bring together the benefits of diverse materials and consequential blend has synergic properties contrary to original polymer (Ezzat et al., 2020; Menazea and Ahmed, 2020c; Menazea et al., 2020b). Semi synthetic polymeric blending is a renowned technique now-a-days to formulate the membranes by mixing the natural and synthetic polymeric materials used for numerous purposes. Currently, the researchers are working with herb based curative products attributed to its safe nature and secure applications. Natural polymers have been broadly discovered as the source for the coating of drugs, delivery of therapeutics and other bioactive particles, which have fascinated remarkable consideration. Their characteristic advantages in excellent biocompatibility, biodegradability, easy availability, definite interactions with some biomolecules and easy adaptation with flexibility in drug delivery (Menazea et al., 2020a; Menazea et al., 2020c; Tommalieh et al., 2020a). Chitosan is a polycationic polysaccharide, chemically called as poly (N-glucosamine) linked by 1, 4-glycosidic bond.

Biopolymers such as chitosan have become a smart choice due to low cost, ecofriendly and good adsorbing capacity (Kajjari et al., 2011; Kalia and Averous, 2011; Sami et al., 2018; Wu et al., 2018). Chitosan (CS) has several biomedical applications e.g. wound healing (Rasool et al., 2019), gene delivery, drug delivery, tissue engineering, bioimaging, protein binding and encapsulation of cells (Shariatinia, 2019; Tommalieh et al., 2021; Tommalieh et al., 2020b; Wu et al., 2018). Chitosan is applied for regenerative skin, scaffold materials, casing materials and in medicinal release attributable to its compatibility (Li et al., 2018; Menazea and Awwad, 2020; Menazea et al., 2021; Morsi et al., 2019; Wang et al., 2018; Yu et al., 2018). The GG is a non-ionic, branched polymer of linear chains of $(1 \rightarrow 4)$ - β -D-mannopyranosyl and α -D-(1 \rightarrow 6) galactopyranosyl units, resulting from seeds of C. tetragonolobus (Prabaharan, 2011). The incidence of huge amount of OH group increases its H-bonding, resulting its high solubility in water, enhanced gumminess and gelling properties of GG solution (Mudgil et al., 2014; Sharma et al., 2018). Properties of GG are modified by derivitization including esterification, grafting and linking taking place at hydroxyl group (Abbas et al., 2019; Bhatti et al., 2020; Iqbal et al., 2020; Sullad et al., 2010). Guar gum is applied as an additive in a variety of foodstuffs, a binder, thickener and in curing of several disorders e.g. hyperglycemia, hyperlipidemic, cholesterol cure, in irrotable bowl disorder, averting the hardening of arteries, weight loss treatment, tissue regeneration and colon tablets (Manna et al., 2015; Menazea and Ahmed, 2020a, 2020b). PVA is a white, tasteless, odorless, granular or powdered semi crystalline or linear synthetic polymer (Abdullah et al., 2017).

It can be chemically modified and due to its simple structure, it is applied in several biomedical fields (Islam and Yasin, 2012).

Controlled drug release system stands for one of the most rapidly taking place part of technological expertise in which chemical engineers and chemists are playing a role to human health care (Yuan et al., 2019). The expression-controlled release drug delivery system (CRDDS) supplies a control on medicine discharge inside the body. Such system assures to sustain drug amount to the directed area as well as to retain the drug concentration in the body (Siepmann and Siepmann, 2012). Drug usefulness and harmless applications can be enhanced by encasing or coupling the pharmaceutical envoy in a polymer or a lipid. This commences a keen interest in mounting the decomposable materials, medicinal carrier systems, and liberation processes via variety of passages in the body of humans and animals (Langer, 1998). Modern drug discharge systems have quite a lot benefits above traditional deliverance systems. Modern systems show good absorption at administration site and defined medicine discharge, economically effective and enhanced medicinal availability (Hardenia et al., 2019).

Doxycycline (α -6-deoxy-5-oxytetracyclin) is a wide spectrum drug used against bacteria that was acquired from oxytetracycline (Beliën and Forcé, 2012; Sahoo et al., 2010). Doxycycline forbids the synthesis of protein of bacteria by interference with t-RNA and m-RNA at ribosomal position (Phaechamud and Charoenteeraboon, 2008). Doxycycline is a member of tetracycline group; consist of wide spectrum antimicrobials which are utilized for healing of contagious disorders within animals and humans. Doxycycline hyclate is explicitly hygroscopic in nature. Due to its nature, it should set aside in a sealed container and sheltered from luminosity. The composition of doxycycline hyclate is (C₂₂H₂₄N₂O₈. HCl)₂. C₂H₆O·H₂O and its molar mass is 1025.89 g.mol⁻¹ (Kogawa and Salgado, 2012; Sloan and Scheinfeld, 2008). Amoxicillin/clavulanate (Augmentin®) is a wide continuum antibacterial drug and furthermore is nowadays employed chiefly for respiratory tract infectivity. Due to its pharmacodynamics and action against bacterial entities, amoxicillin is mainly directed prior to surgical function as well as in veterinary medication (Elmajdoub et al., 2014). The amoxicillinclavulanate combination is the solitary most extensively utilized among antibiotics, recurrently stimulates gastrointestinal after effects, such as queasiness, vomiting, cramping (pervasiveness, 3-6%), or diarrhea occurrence up to 4-15% (Caron et al., 1991; Croydon, 1984).

Based on aforementioned facts, polymeric blended membranes based on chitosan, guar gum and polyvinyl alcohol were prepared for the delivery of antibacterial drugs" with "Based on aforementioned facts, polymeric blended membranes based on CS, GG and PVA were fabricated for the delivery of antibacterial drugs. The drug employed in this study includes amoxicillin and doxycycline hyclate. The membranes were prepared by solution casting method and were characterized by FTIR, SEM and XRD techniques. Swelling, antimicrobial activity and drug loading efficiency of the prepared membranes was also studied.

2. Material and methods

2.1. Chemical and reagents

The reagents and chemicals used in this study were of analytical grade. CS (MW 1526.5 g/mol i.e., 50,000–190,000 Da) was purchased from Sigma-Aldrich Germany and food grade GG (MW 535.15 g/mol i.e., 200,000 to 300,000 Da) from India by Dabur Limited. The drugs amoxicillin and doxycycline hyclate were provided by DON valley pharmaceuticals and NOVA med pharmaceuticals respectively.

2.2. Fabrication of membranes and drug loading

Various compositions of CS/GG/PVA were prepared in order to obtain the optimum formulation for the blended membranes. Amongst all B#2 was considered the best due to its swelling characteristics and porosity. Amoxicillin and doxycycline hyclate drugs were loaded into (B#2) membranes having composition of 60% CS (0.6 g), 20% GG (0.2 g) and 20% PVA (0.2 g). In 2% acetic acid solution CS (60%) was dissolved at 60 °C with continuous stirring. In 20 ml distilled water, 20% PVA was dissolved with constant stirring and heating at 90 °C. After that this prepared solution of PVA was poured into CS solution and blended again for an hour at 60 °C with stirring. In 50 ml distilled water, 20% GG was dissolved and solution of GG was prepared in which later on drug was added via stirring at 40 °C. This solution of GG having drug was added to solution of CS-PVA solution and again blended for an hour at 90-100 °C with constant stirring. With same procedure, membranes having different amounts of drugs were prepared. Composition of polymers and amounts of drugs were given in Table 1.

2.3. Characterization

FTIR investigation of synthesized films done at Happ-Genzel device detector type DTGS with resolution 16 cm⁻¹, background scans are 96 and wavenumber at 4000–650 cm⁻¹. XRD was carried out on X-ray diffraction device with sort D8, Bruker, Germany with series commencing 0 to 70 2Θ . Scanning electron microscope at 10 kx enlargement by means of Evo LS 10, Zeiss, Germany was employed for morphological analysis. Swelling behavior for films was assessed after particular extent of time. Mass of dry membrane piece along with empty petri dish was calculated. Then the membrane was soaked in distilled water for 10 min and after that H_2O was eliminated and the membrane was evaluated another time. Similar practice was repeatedly done, in support of every fabricated film with the same time duration.

2.4. Anti-bacterial activity and cytotoxicity

Anti-bacterial activity (Abbas et al., 2019) and cytotoxicity (Abbas et al., 2018) of membranes was done using disc diffusion method and hemolytic assay respectively via in vitro investigations which showed a pharmacological action against a range of bacteria. Triton-100X was employed as positive control along with phosphate buffer saline was exploited as negative control.

3. Results and discussion

3.1. FTIR analysis

Fourier transform infrared spectroscopy provides the functional group identification for the materials. Fig. 1 shows the IR spectra of blended membranes of GG, CS and PVA. IR spectra of amoxicillin demonstrated a peak due to O-H and N-H stretching (str.) vibrations at around 3470 cm⁻¹ along with C = O stretching of β -lactamic, characteristic bands at 1769 cm⁻¹, C = O stretching of amide at 1688 cm⁻¹ and due to asymmetric stretching of carboxylate at 1587 cm^{-1} . Adtionally, because of C-O bending vibration other peaks were credited at 1008 cm⁻¹ (Songsurang et al., 2011). The IR spectrum of doxycycline shows a broad band between 3000 and 3400 cm⁻¹ of O-H str. and N-H str. at 3166 cm⁻¹, C-H bend at 1450 cm⁻¹, a strong signal at 1666 cm-1 of C = O str, and C-O-H bend at 1390 cm⁻¹ (Junejo and Safdar, 2019). FTIR spectra of B#2 showed distinctive broad band of O-H str. at 3200–3400 cm⁻¹, a precise peak of N-H bending at 1539 cm⁻¹, a characteristic peak due to C-O-H bending at 1407 cm⁻¹, because of C-O str. a strong absortion take placed at 1000–1020 cm⁻¹ and due to C-H bending of alkynes a sharp peak observed at 620 cm⁻¹. whereas in *K*10 and K25 there is variation of values which is correlated with incorporation of amoxicillin drug into the blended membranes of CS, GG along with PVA. The IR spectra of K10 an K25 showed distinctive absorption of O-H str. at 3272 cm⁻¹a broad band, C-H str.

 Table 1
 Identification of samples with codes and concentration of polymers.

	1	1	1 2			
Sr. #	Sample code	Drug	CS (%)	GG (%)	PVA (%)	
1	B#2	_	60	20	20	
2	<i>K</i> 10	10 mg Amoxicillin	60	20	20	
3	K25	25 mg Amoxicillin	60	20	20	
4	K50	50 mg Amoxicillin	60	20	20	
5	S10	10 mg Doxycycline	60	20	20	
6	S25	25 mg Doxycycline	60	20	20	
7	S50	50 mg Doxycycline	60	20	20	



IR spectra of membranes (B#2, K10, S10, K25 and S25) Fig. 1 exhibiting the presence of different functional groups.

2922 cm⁻¹, C = C ring str. 1632–1640 cm⁻¹, C-O-H bending at 1407 cm⁻¹, ether sharp absorption take placed at C-O str. at 1021 cm⁻¹ and because of C-H bending of alkynes a sharp peak observed at 619 cm⁻¹. in K25. The spectrums of S10 and S25 show the shifting of peaks that indicated the development of blended membrane. The spectrums showed characteristics absorption; O-H str. at 3200–3400 cm⁻¹ broad peak, C-H str. at 2922 cm⁻¹, -C \equiv C- str. of asymmetrical alkynes at 2117 cm⁻¹, aromatic C = C str. at 1632–1650 cm⁻¹, C-O-H ben. at 1407 cm⁻¹, ether strong absorption occurs at 1021 cm⁻¹. Table 2 shows the values of absorption peaks along with wavenumber of B#2, K10, S10, K25 and S25 in IR spectra. FTIR results has revealed the successful crosslinking between the constituents materials.

3.2. XRD analysis

For the examination of crystalline or amorphous configuration of chitosan and poly(vinyl) alcohol substances membranes Xray diffraction study was exploited, as such characteristics are proclaimed to influence retention of water as well as degradability characteristics of polymers. Chemical constitution details and crystalline segments were recognized through the crystal construction. (Manikandan et al., 2017; Maruthamani et al., 2017; Prabaharan and Gong, 2008). The crystalline structure indicates the crystalline phase and chemical composition information. X-ray diffraction study revealed (Fig. 2) that



Fig. 2 XRD analysis of fabricated membranes samples.

a prominent peak in B#2 and K10 was observed at 11.02 and was considered to be as a peak of crystallinity, and was absent in among all other loaded membranes (S10, K25 and S25) owing to minor shifting in peak of 2θ due to a new bond formation between the chitosan and PVA functional groups. This indicates that the drugs have minute effect on the crystalline peak. Successful bonding among CS, PVA and GG was confirmed by XRD (at 22.6), which is in accordance with previous reports (Lou et al., 2014).

3.3. SEM analysis

To examine the morphological features of the fabricated blended membranes, scanning electron microscopy was utilized. The smooth surface of synthesized membranes revealed the excellent polymer blending which was confirmed by SEM images (Fig. 3). Some of the samples show rough surface due to porous structure. The magnification of each SEM image was 10 kx which showed the membranes porosity. In swelling characteristics, porosity of the membranes was a significant feature (Islam and Yasin, 2012). The porosity permits the more rapidly swelling plus excellent discharge of drug, hence showing that the nature of prepared membranes is hydrophilic (Boukhouya et al., 2018; Gong et al., 2012).

3.4. Swelling characteristics

Swelling properties of natural materials relies on the nature of medium and swelling is caused by solvent diffusion into mate-

Fuctional groups	B#2 (cm ⁻¹)	K10 (cm^{-1})	S10 (cm^{-1})	$K25 (cm^{-1})$	$S25 (cm^{-1})$
O-H str	3220	3272	3265	3272	3272
C-H str	2877	2922	2922	2922	2922
-C≡C- str	2124	2117	2117	2117	2117
N-H ben	1543	1550	1550	1550	1550
C = C ring str	1632	1640	1640	1632	1640
C-O-H ben	1401	1407	1407	1407	1407
C-O str	1013	1021	1021	1021	1021
C-H ben	620	-	-	619	-

rial structure from extracellular medium. Swelling behaviors of prepared membranes were tested in water and buffer media. The pH of the swelling medium was 5.4–5.6 in distilled water, while the matrix's pH turned 4–4.5 in the buffer solution of 7.4 pH. The sample B#2 with low concentrations of GG and large amount of CS showed good swelling properties among other membranes (Fig. 4). The swelling pattern has indicated the successful crosslinking between CS/GG/PVA. It was concluded that membranes with less amounts of GG and higher amount of CS become porous and absorb more solvent, as a result these membranes expressed good swelling. The swelling can be calculated by the equation (Yasin et al., 2008);

$$Swelling = \frac{(W_S - W_D)}{W_D} \tag{1}$$

The swelling at equilibrium can be studied by the formula; (Sullad et al., 2010)

$$Swelling(\%) = \frac{(W_s - W_d)}{W_d} \times 100s$$
⁽²⁾

 W_s and W_d are the weights of swelled and dry membranes in grams respectively. B#2 due to its swelling characteristics was preferred for drug loading. Breakdown of synthesized loaded membranes was less in the buffer solution of pH 7.4, than acidic medium signifying the good disintegration in the acidic medium. Hence, we can conclude that the polymeric material targets the stomach for the controlled release of drug in acidic environment, thereby polymer disintegrate itself. Results also discovered that sample K25 and S25 showed best swelling amongst the loaded membranes. These results indicated that 25 mg was the ideal amount of drug that was encumbered in 1 g polymer blended membrane.



Fig. 4 Graphical presentation of swelling pattern of fabricated membranes.

3.5. Antimicrobial activity

For the cure of a range of contagious diseases such as swellings and abrasions, there is affluent practice in the exploit of therapeutic flora in the various regions of the globe. Considerable latest attention has been paid to extricate and bio-active substances secluded from species of plant utilized in drug due to aftereffects along with confrontation that pathogenic microbes formulate versus antibiotics. Antimicrobials foundation on



Fig. 3 SEM images of synthesized membranes: (A) B#2 Sample, (B) K10 Sample, (C) S10, (D) K25 and (E) S25 samples at 10 kx magnifications.

plants symbolizes an enormous unexploited foundation for drugs along with additional searching of plant antimicrobials requirements to happen. Antimicrobial's properties of plant source contain vast healing aptitude. They are efficient in the cure of contagious diseases whereas at the same time extenuating a lot of aftereffects which are frequently linked by manmade antimicrobials. The standard was utilized at a concentration of 10 mg/mL. Table 3 indicates the activities of the loaded polymeric membranes against different strains of bacteria. The results has revealed the antibacterial properties of the loaded membranes.

3.6. Biocampatibility

For erythrocyte cellular membrane firmness, fabricated sample treated by means of secluded red blood cells through young individual, investigated. It was in vitro procedure plus very easy for primary inspection of natural and inorganic substances in laboratories, ahead of their initial animal investigation. From findings (Table 4) it was assumed that CS, PVA along with GG with altered amounts of antibiotic (amoxicillin and doxycycline hyclate) did not exhibits red blood cells lysis action. The values of cell lysis have been mentioned in Table 4. As CS and GG along with PVA did not disturb the membrane of red blood cells, it was stated that most of the biologically active substances were tannins liable for cytotoxicity. Moreover, in organic solvent they show solubility. The phytochemical scrutiny of therapeutic plant under inquiry confirmed a substantial concentration of tannins and supplementary phytoconstituent. The outcomes attained in current exploration are found in agreement with preceding investigations. Uddin et al discovered that cytotoxic capability of extricates was of immense importance for their customary applications in the healing of diseases except cancer (Uddin et al., 2011).

Previous studies report on the significance of plant-based membranes and their applications for various purposes. Reddy et al. (Reddy et al., 2006) described the formation of blend microspheres of CS and GG. Cefadroxil was cross-linked with glutaraldehyde and produced semi-interpenetrating polymer network (IPN). The SEM showed non-uniform microspheres and drug was delivered in controlled manner at pH 7.4 up to 10 h. Similarly, Sinha and Kumria (Sinha and Kumria, 2001) stated the use of natural polysaccharides for the development of solid dosage forms for drug delivery to the colon. The reason for using polysaccharide-based system for colon is linked with the presence of variety of bacteria in colon which secrete

 Table 4
 Erythrocytes cell steadiness (cytotoxicity)/red blood cells lysis analysis.

Sr.#	Sample code	Erythrocytes Cell Stability
1	K-10	9.70 ± 0.10
2	S-10	6.55 ± 0.19
3	K-25	13.32 ± 0.16
4	S-25	5.55 ± 0.07
5	K-50	15.56 ± 0.33
6	K-50	11.37 ± 0.15
7	GG	2.52 ± 0.86
8	B#2	3.51 ± 0.63

many enzymes. Some of the approaches for colon-specific delivery system include core coating of the drug, embedding in biodegradable material and formation of conjugate. Variety of polysaccharides have already been discussed and utilized as colon-specific drug carrier, i.e., CS chondroitin sulphate, pectin, cyclodextrin, GG, inulin and amylose.

The blend of pAAm-g-GG and CS was prepared to form IPN hydrogel microspheres using GA as a linking agent by emulsion method. The microspheres used for ciprofloxacin (CFX) release and CFX was released in 12 h. The structure, grafting reaction, stability in IPN hydrogels and molecular dispersion was finalized by the SEM, FTIR, DSC and XRD techniques and drug release kinetics was performed by swelling study pH 7.4 (Kajjari et al., 2011). Similarly, the formulation of hydrogel based on CS and GG was prepared and employed for controlled release of Paracetamol drug. This drug may cause problems in body organs like gastric and may also disturb the metabolism of liver. Hence, for the delivery of this drug, it was combined with alginate beads for safe deliver, which was characterized by swelling and antimicrobial potential. Also, the cytotoxicity and biocompatibility of the developed system using HeLa cell line. The drug released by combining with alginate beads showed promising antiprotease and anti-inflammatory potential. Results revealed that the beads thus prepared was safe to deliver drug since properties of the system did not change. In view of promising properties as well as safe and controlled release of drug, it was suggested for the delivery of Paracetamol in controlled manner (Sami et al., 2018).

Also, CS-ALG based hydrogels was prepared and utilized for targeted drug delivery and protection of lysosomal mem-

Sr. #	Samples	E. coli	P. multocida	B. subtilis	S. aureus
1	K-10	25 ± 2.30	23 ± 3.40	25 ± 2.72	27 ± 1.61
2	S-10	$20~\pm~1.26$	22 ± 4.73	$28~\pm~7.16$	26 ± 5.60
3	K-25	$27~\pm~4.14$	$28~\pm~1.39$	31 ± 2.26	$32~\pm~6.70$
4	S-25	$23~\pm~4.68$	25 ± 2.15	32 ± 1.35	30 ± 3.56
5	K-50	31 ± 2.53	30 ± 6.81	33 ± 3.19	36 ± 4.84
6	S-50	$28~\pm~1.71$	27 ± 5.24	35 ± 6.51	34 ± 2.42
7	GG	13 ± 5.80	12 ± 1.26	15 ± 3.72	14 ± 2.30
8	B#2	15 ± 1.46	13 ± 3.53	16 ± 5.39	16 ± 3.30
9	Rifampicin	33 ± 1.40	34 ± 0.95	35 ± 2.52	36 ± 1.46

E = Escherichia, P = Pasteurella, B = Bacillus and S = Staphylococcus.

branes for the eliminating of food-borne microbes. The CS-ALG based hydrogels was of spherical shape and bears negative charge. The activity of CS-ALG hydrogels was promising and 100% microbes were eliminated using ALG/CS that was loaded with lysozyme. Results depict that the CS-ALG hydrogels are highly efficient against microbes like E. coli and S. aureus which can be employed for the control of food borne microbes for the safety of food (Wu et al., 2018). In another study, a lipid-based hydrogel was prepared by meltemulsification followed by ultra-sonication technique and same was used for release of quercetin (QN) in a control manner. Additionally, CMCS and poloxamer 407 was prepared using genipin linker, which showed promising response for drug deliver and it was revealed that the hydrogel released the quercetin up to 80.52% within 72 h. which suggest the use of CMCS based hydrogels for the controlled release of quercetin for practical applications (Yu et al., 2018). Also, GG based materials showed promising properties for the controlled release of different drugs. One of the drawbacks for GG based hydrogel is the swelling property in water, preclude them for the deliver of drug in a control manner. However, this issue can be solved by modifying the GG based hydrogels by grafting and derivatization for practical. At current, different systems based on GG have been formulated in the form of matrix tablets, coatings and nano/microparticles and these formulations showed excellent performance for the delivery and release of different types of pharmaceutical agents (Prabaharan, 2011).

A GGH modified with OSA and oleic acid having hydrophobic property is fabricated, which was used for the encapsulation of mint oil and efficiency was contrasted with GA and GA-OSA based systems. In this context, the GA-OSA revealed promising retaining of the oil versus GA based system. In view of promising oil retention efficiency of GGH-OSA, it was suggested to use this system to substitute the GA for oil encapsulation (Sarkar et al., 2013). Similarly, CMGG based system was fabricated, which was combined with curcumin and employed as a bioactive material for biological application, which was characterized by advanced techniques. A 90-95% (curcumin) was released in 96 h at pH 7.4 using CMGG-g-gelatin. The CMGG-g-gelatin system was biocompatible with excellent antimicrobial property. Based on the efficiency, it was revealed that the combination of curcumin and CMGG-g-gelatin enhanced the properties of the system and resultantly, the excellent performance was offered by the system as an active biological material (Manna et al., 2015).

Moreover, GG due to its highest viscosity in aqueous solution applied significantly is a promising agent in medical field. In this context, rifampicin drug, which is poorly soluble in water was delivered using GG based micelles. The GG based micelles revealed promising antibacterial property against selected microbes. The biocompatibility was also studied and results revealed that the GG based micelles are safe to use for drug delivery and release in a controlled manner. In drug delivery application, it was observed that the GG based micelles enhanced the drug activity, which was tested for THP-1 cells. A time dependent apoptosis was recorded manner in cell apoptosis study [28]. In another study (Bajpai et al., 2017) reported the preparation of doxycycline hydrogels ladened with GA/PSA for controlled and sustained drug delivery through oral route. The hydrogels were characterized XRD and FTIR. It was further featured by zeta potential and SEM. The release of the drug doxycycline was monitored at 37 °C and pH 7.4 to check the impact under physiological conditions. The drug was also tested against bacterial strains for their antibacterial action e.g. E. coli.On the same line, the exudate GG was modified via graft copolymerization reaction under the influence of microwaves. The 2-hydroxyl ethyl methacrylate (PHEMA) was polymerized to have a graft copolymerization. The ceric ammonium nitrate was applied as a free radical initiator. The different characterization techniques were used to validate the synthesis mechanism including ¹³ C nuclear magnetic resonance, FTIR, CHNSO and thermal gravimetric analysis. These drugs were useful as pH sensitive drug distribution carrier with environment of gastrointestinal tract (GI). The swelling properties of GG-g-P(HEMA) tablets was recorded under physiological stress to be useful for GI (Mahto and Mishra, 2019). Also, Gjoseva et al. (Gjoseva et al., 2018) demonstrated the development of CS microparticulated mucoadhesive DDS with enhanced healing response. A doxycycline hyclate (DOXY) was prepared and ladened with low and medium mol. Mass of CS/TPP MPs. The coacervation/solvent displacement technique was employed for coating with ethyl cellulose. Now we have both coated and uncoated CS/TPP MPs and they did not lay any impact on epithelial cell line and furthermore showed high mucoadhesive potential. The impact generated by MPs was slow and gradual due to the formulation and concentration of the material. Moreover, the it was claimed that CS-based MPs leads to synergy in antiinflammatory activity. Hence, in the light of present investigation, it is concluded that the material based on chitosan, guar gum is efficient biomaterial for biological applications.

4. Conclusions

Blended membranes of chitosan, guar gum and polyvinyl alcohol were synthesized. The varying amounts of CS and GG have significant effect on swelling behavior and permeability of these membranes. PVA modified and upholds the properties of natural polymers. Owing to good swelling, permeability and absorption, membrane (B-2) was considered best amongst all, demonstrating good binding between constituents. Furthermore, hydrophilic nature made this more precise for drug release. Different amounts of drug were loaded in B-2 membrane. These loaded membranes have good pharmacological activity against bacteria. Cytotoxic investigation revealed the effectiveness of these membranes in various biomedical applications. The ternary blends of CS and GG with polyvinyl alcohol have potential for control drug release.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program.

References

- Abbas, M., Ali, A., Arshad, M., Atta, A., Mehmood, Z., Tahir, I.M., Iqbal, M., 2018. Mutagenicity, cytotoxic and antioxidant activities of Ricinus communis different parts. Chem. Cent. J. 12, 3.
- Abbas, M., Hussain, T., Arshad, M., Ansari, A.R., Irshad, A., Nisar, J., Hussain, F., Masood, N., Nazir, A., Iqbal, M., 2019. Wound healing potential of curcumin cross-linked chitosan/polyvinyl alcohol. Int. J. Biol. Macromol. 140, 871–876.
- Abdullah, Z.W., Dong, Y., Davies, I.J., Barbhuiya, S., 2017. PVA, PVA blends, and their nanocomposites for biodegradable packaging application. Polym.-Plast. Technol. Eng. 56, 1307–1344.
- Bajpai, S., Jadaun, M., Bajpai, M., Jyotishi, P., Shah, F.F., Tiwari, S., 2017. Controlled release of Doxycycline from gum acacia/poly (sodium acrylate) microparticles for oral drug delivery. Int. J. Biol. Macromol. 104, 1064–1071.
- Beliën, J., Forcé, H., 2012. Supply chain management of blood products: A literature review. Eur. J. Oper. Res. 217, 1–16.
- Bhatti, H.N., Safa, Y., Yakout, S.M., Shair, O.H., Iqbal, M., Nazir, A., 2020. Efficient removal of dyes using carboxymethyl cellulose/ alginate/polyvinyl alcohol/rice husk composite: Adsorption/desorption, kinetics and recycling studies. Int. J. Biol. Macromol. 150, 861– 870.
- Boukhouya, I., Bakouri, H., Abdelmalek, I., Amrane, M., Guemra, K., 2018. Controlled release of amoxicillin from PMMA and poly (butylsuccinate) microspheres. Chem. Int. 4, 120–129.
- Caron, F., Ducrotte, P., Lerebours, E., Colin, R., Humbert, G., Denis, P., 1991. Effects of amoxicillin-clavulanate combination on the motility of the small intestine in human beings. Antimicrob. Agents Chemother. 35, 1085–1088.
- Croydon, P., 1984. Worldwide clinical review of Augmentin. Postgrad Med 76, 71–78.
- Elmajdoub, A., Elgerwi, A., Awidat, S., El-Mahmoudy, A., 2014. Effects of amoxicillin repeated administration on the hemogram and biogram of sheep. Int. J. Basic Clin. Pharmacol. 3, 676–680.
- Ezzat, H., Menazea, A.A., Omara, W., Basyouni, O.H., Helmy, S.A., Mohamed, A.A., Tawfik, W., Ibrahim, M., 2020. DFT: B3LYP/ LANL2DZ Study for the Removal of Fe, Ni, Cu, As, Cd and Pb with Chitosan. Biointerface Res. Appl. Chem 10, 7002–7010.
- Gjoseva, S., Geskovski, N., Sazdovska, S.D., Popeski-Dimovski, R., Petruševski, G., Mladenovska, K., Goracinova, K., 2018. Design and biological response of doxycycline loaded chitosan microparticles for periodontal disease treatment. Carbohydr. Polym. 186, 260–272.
- Gong, H., Liu, M., Chen, J., Han, F., Gao, C., Zhang, B., 2012. Synthesis and characterization of carboxymethyl guar gum and rheological properties of its solutions. Carbohydr. Polym. 88, 1015– 1022.
- Hardenia, A., Maheshwari, N., Hardenia, S.S., Dwivedi, S.K., Maheshwari, R., Tekade, R.K., 2019. Scientific rationale for designing controlled drug delivery systems. Basic Fundam. Drug Deliv. Elsevier, 1–28.
- Iqbal, D.N., Tariq, M., Khan, S.M., Gull, N., Sagar Iqbal, S., Aziz, A., Nazir, A., Iqbal, M., 2020. Synthesis and characterization of chitosan and guar gum based ternary blends with polyvinyl alcohol. Int. J. Biol. Macromol. 143, 546–554.
- Islam, A., Yasin, T., 2012. Controlled delivery of drug from pH sensitive chitosan/poly (vinyl alcohol) blend. Carbohydr. Polym. 88, 1055–1060.
- Junejo, Y., Safdar, M., 2019. Highly effective heterogeneous doxycycline stabilized silver nanocatalyst for the degradation of ibuprofen and paracetamol drugs. Arabian J. Chem. 12, 2823–2832.
- Kajjari, P.B., Manjeshwar, L.S., Aminabhavi, T.M., 2011. Novel interpenetrating polymer network hydrogel microspheres of chitosan and poly (acrylamide)-grafted-guar gum for controlled release of ciprofloxacin. Ind. Eng. Chem. Res. 50, 13280–13287.

- Kalia, S., Averous, L., 2011. Biopolymers: biomedical and environmental applications. John Wiley & Sons.
- Kogawa, A.C., Salgado, H.R.N., 2012. Doxycycline hyclate: a review of properties, applications and analytical methods. International Journal of Life science and Pharmaceutical Research, ISSN, 2250-0480.
- Langer, R., 1998. Drug delivery and targeting. Nature 392, 5-10.
- Li, M.-F., Chen, L., Xu, M.-Z., Zhang, J.-L., Wang, Q., Zeng, Q.-Z., Wei, X.-C., Yuan, Y., 2018. The formation of zein-chitosan complex coacervated particles: Relationship to encapsulation and controlled release properties. Int. J. Biol. Macromol. 116, 1232– 1239.
- Lou, C.-W., Chen, A.-P., Lic, T.-T., Lin, J.-H., 2014. Antimicrobial activity of UV-induced chitosan capped silver nanoparticles. Mater. Lett. 128, 248–252.
- Mahto, A., Mishra, S., 2019. Design, development and validation of guar gum based pH sensitive drug delivery carrier via graft copolymerization reaction using microwave irradiations. Int. J. Biol. Macromol. 138, 278–291.
- Manikandan, A., Manikandan, E., Meenatchi, B., Vadivel, S., Jaganathan, S., Ladchumananandasivam, R., Henini, M., Maaza, M., Aanand, J.S., 2017. Rare earth element (REE) lanthanum doped zinc oxide (La: ZnO) nanomaterials: synthesis structural optical and antibacterial studies. J. Alloy. Compd. 723, 1155–1161.
- Manna, P.J., Mitra, T., Pramanik, N., Kavitha, V., Gnanamani, A., Kundu, P., 2015. Potential use of curcumin loaded carboxymethylated guar gum grafted gelatin film for biomedical applications. Int. J. Biol. Macromol. 75, 437–446.
- Maruthamani, D., Vadivel, S., Kumaravel, M., Saravanakumar, B., Paul, B., Dhar, S.S., Habibi-Yangjeh, A., Manikandan, A., Ramadoss, G., 2017. Fine cutting edge shaped Bi2O3rods/reduced graphene oxide (RGO) composite for supercapacitor and visiblelight photocatalytic applications. J. Colloid Interface Sci. 498, 449– 459.
- Menazea, A.A., Ahmed, M.K., 2020a. Nanosecond laser ablation assisted the enhancement of antibacterial activity of copper oxide nano particles embedded though Polyethylene Oxide/Polyvinyl pyrrolidone blend matrix. Radiat. Phys. Chem. 174, 108911.
- Menazea, A.A., Ahmed, M.K., 2020b. Synthesis and antibacterial activity of graphene oxide decorated by silver and copper oxide nanoparticles. J. Mol. Struct. 1218, 128536.
- Menazea, A.A., Ahmed, M.K., 2020c. Wound healing activity of Chitosan/Polyvinyl Alcohol embedded by gold nanoparticles prepared by nanosecond laser ablation. J. Mol. Struct. 1217, 128401.
- Menazea, A.A., Awwad, N.S., 2020. Antibacterial activity of TiO2 doped ZnO composite synthesized via laser ablation route for antimicrobial application. J. Mater. Res. Technol. 9, 9434–9441.
- Menazea, A.A., Awwad, N.S., Ibrahium, H.A., Ahmed, M.K., 2020a. Casted polymeric blends of carboxymethyl cellulose/polyvinyl alcohol doped with gold nanoparticles via pulsed laser ablation technique; morphological features, optical and electrical investigation. Radiat. Phys. Chem. 177, 109155.
- Menazea, A.A., El-Newehy, M.H., Thamer, B.M., El-Naggar, M.E., 2021. Preparation of antibacterial film-based biopolymer embedded with vanadium oxide nanoparticles using one-pot laser ablation. J. Mol. Struct. 1225, 129163.
- Menazea, A.A., Ezzat, H.A., Omara, W., Basyouni, O.H., Ibrahim, S. A., Mohamed, A.A., Tawfik, W., Ibrahim, M.A., 2020b. Chitosan/graphene oxide composite as an effective removal of Ni, Cu, As, Cd and Pb from wastewater. Comput. Theor. Chem. 1189, 112980.
- Menazea, A.A., Ismail, A.M., Awwad, N.S., Ibrahium, H.A., 2020c. Physical characterization and antibacterial activity of PVA/Chitosan matrix doped by selenium nanoparticles prepared via one-pot laser ablation route. J. Mater. Res. Technol. 9, 9598–9606.
- Morsi, M.A., Rajeh, A., Menazea, A.A., 2019. Nanosecond laserirradiation assisted the improvement of structural, optical and

thermal properties of polyvinyl pyrrolidone/carboxymethyl cellulose blend filled with gold nanoparticles. J. Mater. Sci.: Mater. Electron. 30, 2693–2705.

- Mudgil, D., Barak, S., Khatkar, B.S., 2014. Guar gum: processing, properties and food applications—a review. J. Food Sci. Technol. 51, 409–418.
- Phaechamud, T., Charoenteeraboon, J., 2008. Antibacterial activity and drug release of chitosan sponge containing doxycycline hyclate. Aaps PharmSciTech 9, 829–835.
- Prabaharan, M., 2011. Prospective of guar gum and its derivatives as controlled drug delivery systems. Int. J. Biol. Macromol. 49, 117– 124.
- Prabaharan, M., Gong, S., 2008. Novel thiolated carboxymethyl chitosan-g-β-cyclodextrin as mucoadhesive hydrophobic drug delivery carriers. Carbohydr. Polym. 73, 117–125.
- Rasool, A., Ata, S., Islam, A., 2019. Stimuli responsive biopolymer (chitosan) based blend hydrogels for wound healing application. Carbohydr. Polym. 203, 423–429.
- Reddy, K.M., Babu, V.R., Sairam, M., Subha, M., Mallikarjuna, N., Kulkarni, P., Aminabhavi, T., 2006. Development of chitosan-guar gum semi-interpenetrating polymer network microspheres for controlled release of cefadroxil. Des. Monomers Polym. 9, 491–501.
- Sahoo, S., Sasmal, A., Sahoo, D., Nayak, P., 2010. Synthesis and characterization of chitosan-polycaprolactone blended with organoclay for control release of doxycycline. J. Appl. Polym. Sci. 118, 3167–3175.
- Sami, A.J., Khalid, M., Jamil, T., Aftab, S., Mangat, S.A., Shakoori, A., Iqbal, S., 2018. Formulation of novel chitosan guargum based hydrogels for sustained drug release of paracetamol. Int. J. Biol. Macromol. 108, 324–332.
- Sarkar, S., Gupta, S., Variyar, P.S., Sharma, A., Singhal, R.S., 2013. Hydrophobic derivatives of guar gum hydrolyzate and gum Arabic as matrices for microencapsulation of mint oil. Carbohydr. Polym. 95, 177–182.
- Shariatinia, Z., 2019. Pharmaceutical applications of chitosan. Adv. Colloid Interface Sci. 263, 131–194.
- Sharma, G., Sharma, S., Kumar, A., Ala'a, H., Naushad, M., Ghfar, A.A., Mola, G.T., Stadler, F.J., 2018. Guar gum and its composites as potential materials for diverse applications: A review. Carbohydr. Polym. 199, 534–545.
- Siepmann, J., Siepmann, F., 2012. Modeling of diffusion controlled drug delivery. J. Control. Release 161, 351–362.
- Sinha, V.R., Kumria, R., 2001. Polysaccharides in colon-specific drug delivery. Int. J. Pharm. 224, 19–38.
- Sloan, B., Scheinfeld, N., 2008. The use and safety of doxycycline hyclate and other second-generation tetracyclines. Expert Opin. Drug Saf. 7, 571–577.

- Songsurang, K., Pakdeebumrung, J., Praphairaksit, N., Muangsin, N., 2011. Sustained release of amoxicillin from ethyl cellulose-coated amoxicillin/chitosan-cyclodextrin-based tablets. Aaps Pharmscitech 12, 35–45.
- Sullad, A.G., Manjeshwar, L.S., Aminabhavi, T.M., 2010. Novel pHsensitive hydrogels prepared from the blends of poly (vinyl alcohol) with acrylic acid-graft-guar gum matrixes for isoniazid delivery. Ind. Eng. Chem. Res. 49, 7323–7329.
- Tommalieh, M.J., Awwad, N.S., Ibrahium, H.A., Menazea, A.A., 2021. Characterization and electrical enhancement of PVP/PVA matrix doped by gold nanoparticles prepared by laser ablation. Radiat. Phys. Chem. 179, 109195.
- Tommalieh, M.J., Ibrahium, H.A., Awwad, N.S., Menazea, A.A., 2020a. Gold nanoparticles doped polyvinyl alcohol/chitosan blend via laser ablation for electrical conductivity enhancement. J. Mol. Struct. 1221, 128814.
- Tommalieh, M.J., Ismail, A.M., Awwad, N.S., Ibrahium, H.A., Youssef, M.A., Menazea, A.A., 2020b. Investigation of Electrical Conductivity of Gold Nanoparticles Scattered in Polyvinylidene Fluoride/Polyvinyl Chloride via Laser Ablation for Electrical Applications. J. Electron. Mater. 49, 7603–7608.
- Uddin, G., Rauf, A., Rehman, T., Qaisar, M., 2011. Phytochemical screening of Pistacia chinensis var. integerrima. Middle-East J. Sci. Res. 7, 707–711.
- Wang, Y., Zhang, X., Qiu, D., Li, Y., Yao, L., Duan, J., 2018. Ultrasonic assisted microwave synthesis of poly (Chitosan-cogelatin)/polyvinyl pyrrolidone IPN hydrogel. Ultrason. Sonochem. 40, 714–719.
- Wu, T., Huang, J., Jiang, Y., Hu, Y., Ye, X., Liu, D., Chen, J., 2018. Formation of hydrogels based on chitosan/alginate for the delivery of lysozyme and their antibacterial activity. Food Chem. 240, 361– 369.
- Yasin, T., Rasool, N., Akhter, Z., 2008. Synthesis of carboxymethylchitosan/acrylic acid hydrogel using silane crosslinker. e-Polymers 8.
- Yu, Y., Feng, R., Yu, S., Li, J., Wang, Y., Song, Y., Yang, X., Pan, W., Li, S., 2018. Nanostructured lipid carrier-based pH and temperature dual-responsive hydrogel composed of carboxymethyl chitosan and poloxamer for drug delivery. Int. J. Biol. Macromol. 114, 462–469.
- Yuan, X., Praphakar, R.A., Munusamy, M.A., Alarfaj, A.A., Kumar, S.S., Rajan, M., 2019. Mucoadhesive guargum hydrogel interconnected chitosan-g-polycaprolactone micelles for rifampicin delivery. Carbohydr. Polym. 206, 1–10.