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Interpenetrating Polymer Network Hydrogel Membranes of PLA and SA for Control Release of Penicillamine Drug

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ABSTRACT:
The study presents, the experimental results on the successful encapsulation of Penicillamine drug using Sodium Alginate (SA)/Poly(lactic acid) (PLA) blend as controlled release (CR) polymer matrices. The Penicillamine-containing polymer blend membranes have been prepared by changing the experimental variables such as PLA, SA and drug content by solution casting evaporation method. The membranes were characterized by swelling studies, FTIR, DSC, XRD, SEM, tensile strength measurements and in-vitro release studies. The swelling results indicated that swelling of polymer membranes decreases with the increasing the amount of PLA. However, no significant variation in swelling was observed with different amount of Penicillamine loading. The absence of chemical interactions between active ingredients and polymer was confirmed by FT-IR spectral measurements. Differential scanning calorimeter (DSC) and X-ray diffraction (XRD) studies were performed to understand the crystalline nature of drug after encapsulation into the membranes. Scanning electron microscopy (SEM) was used to study the surface morphology of the membranes. The in vitro studies were carried out in phosphate buffer pH 7.4 at 37 ^{o}C. The results of controlled release tests showed that the amount of Penicillamine release increased with the increasing the amount of SA in the membrane. Moreover, the release rate of drug increased as the amount of drug loaded in the membranes increased. All the results indicated that the prepared membrane was potentially useful in drug delivery systems and the prolonged release rate was observed.

Keywords: *Interpenetrating Polymer Network, Penicillamine, Encapsulation, Poly(lactic acid).*

1. INTRODUCTION

In recent years, biodegradable polymers have attracted attention to be used as biomaterials particularly, for tissue engineering, gene therapy, wound healing and controlled drug delivery systems [1]. The most important advantage of biodegradable polymers is the disappearance of implanted foreign materials from the body as a result of their biodegradation. Most important biodegradable polymers used in biomedical applications are poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(e-caprolactone) (PCL), poly(3-hydroxyl butyrate) (PHB), co-polymers of polyglycolide, chitosan, alginate and soy protein [2-5]. In drug delivery systems, various drug preparations like micro-capsules, microspheres, implants, pallets and membranes have been fabricated by using above bio-degradable polymers as drug matrix.

Membranes, is a major importance in medical applications, in particular in a number of lives saving treatment methods. Membranes are used in drug delivery, artificial organs, tissue regeneration, diagnostic devices, as coatings for medical devices, bio-separations, etc. The total membrane area produced for medical applications almost matches all industrial membrane applications together [6-10]. In fact in fiscal terms, the value of medical membrane products is far larger than all other applications combined [11-14]. Only in the US for example, the medical membrane market approaches 1.5 billion dollars per year and grows steadily. The biggest part of the medical market involves membranes in drug delivery, hemo-dialysis, other artificial organs (oxygenators, pancreas, etc.) and tissue engineering.

Poly(lactic acid) (PLA) and its derivatives, with their outstanding biocompatibility and biodegradability, have become increasingly important in the development of biomedical fields [15-17]. These polymers can either function as a matrix to control diffusion of the drug, followed by polymer bio-control diffusion of the drug, followed by polymer bio-degradation and elimination of the degradation products from the body, or participate in and control the rate of drug release by polymer hydration and degradation. PLA is a versatile new

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compostable polymer that is made from renewable resources such as corn, sugar beets, or rice by Cargill Dow's [18]. In contrast to conventional plastics, such as polypropylene and polyethylene, which require hundreds or even thousands of years to degrade, PLA can degrade into naturally occurring products in just a few years [19]. Hence, PLA is used for many applications, with its properties such as high degrees of transparency and biocompatibility and high melting point (155-175 ^{o}C). Currently, there is an increasing interest in using PLA for biodegradable materials even in biomedical application for it s biocompatibility [20-26]. As there were no reports on the drug delivery applications of PLA/SA blends the author thought to work on this system. To tailor its crystallization behaviour, degradation rate and other material properties for the applications, blending PLA with other biocompatible polymers like sodium alginate is a practical and economically new approach in drug delivery studies.

Among the biocompatible and natural polymers, sodium alginate (SA) is a water-soluble polysaccharide having good membrane forming properties [27]. Alginate is a linear chain structure of (1→ 4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues arranged in block wise fashion (Scheme 1). These blocks are constructed in three different ways: homopolymeric MM blocks, homopolymeric GG blocks and heteropolymeric sequentially alternating MG blocks [28,29]. Presence of α-L-guluronic acid in various ratios and molecular weight alters physico-chemical properties of the polymer [30]. These factors contribute towards the overall drug delivery performance of the membrane.

D-Penicillamine (D-P) (Scheme 1) is a chelator drug which is used for treatment of lead toxicity for several years [31]. The efficacy of D-P in reducing blood lead level (BLL) has made it a good choice for treatment of chronic lead poisoning in adults [32]. D-P administration can increase the urinary excretion of lead because of complexes which it forms with this heavy metal [33]. In many cases BLL fell down to acceptable range after D-P treatment [34]. However, long period of administration and side effects of D-P have complicated its use in the treatment of lead poisoning [35].

In the present research program, we have prepared SA/PLA blend membranes for controlled release of Penicillamine. It also deals with the *in-vitro* release studies on membrane formulations loaded with different amounts of Penicillamine. Drug loaded membranes were characterized by using Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (X-RD), diffraction scanning calorimetry (DSC). The kinetics of the drug delivery system has been reported.

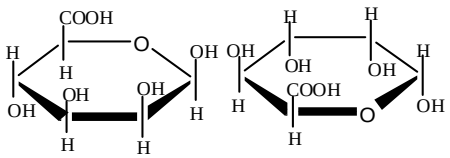
2. EXPERIMENTAL

2.1. Materials

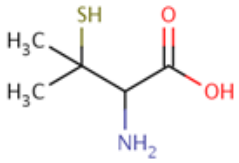
SA of medium viscosity grade (viscosity of 1%w/v solution at 25 ^{o}C, 5.5 ±2 counts per second) was obtained from Hi-media, Hyderabad, India. Poly lactic acid (PLA), is purchased from Aldrich chemicals (St. Louis) USA, Penicillamine was received as a gift sample from VVS Pharmaceutics & Chemicals (Hyderabad, India). Double-distilled water was used throughout the research work.

2.2. Preparation of drug loaded blend membrane

The membranes of SA/PLA were prepared by a solvent-casting method. 2% Aqueous solution of SA was prepared by dissolving SA in water overnight under constant stirring conditions, to this the required amount of Penicillamine drug was added slowly until a clear homogeneous solution is obtained. PLA solution is prepared separately by dissolving 100-200 mg of PLA in 20 ml of dichloro methane and pouring it into the drug containing SA solution at room temperature under magnetic stirring for 15 min. The milky suspension was ultrasonicated for 10 min at 60 magnitudes and 2 cycles for better colloidal dispersion. The organic solvent was removed on a rotavapour. The final solution obtained was used to carryout films by casting on a glass plate, followed by drying at 30 ^{o}C for 72 h and films with thickness 100-200 μm were obtained. The schematic diagram of the formation of cross-linked blend membrane is shown in Scheme 2. The compositions of films carried out from SA and SA/PLA mixtures with or without drug are presented Table 1.

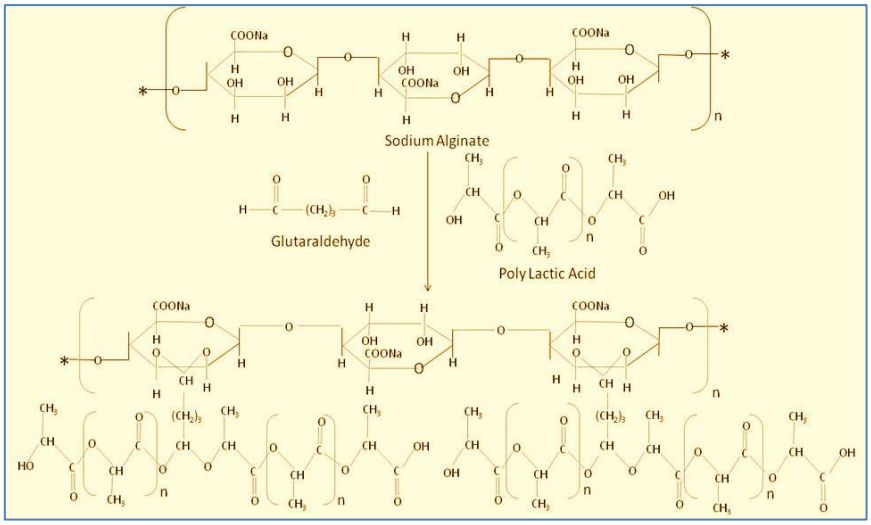


(a)



(b)

Scheme 1. The model structure of (a) Sodium alginate (b) Penicillamine.



Scheme 2. The model structure of cross-linked SA/PLA blend membranes

2.3. Swelling properties

Squares of 1.5 cm^2 were cut and dried at 60 ^oC until constant weight (W_d). Then, they were immersed into 5ml of distilled water at 37 ^oC in 7.4 phosphate buffer solution at least 24 hours. Afterwards, the samples were taken out from bottles and wiped with blotting paper to remove the surface adhered water molecules and weighed (W_s). Here, the degree of swelling ratio (*DS*) is defined as the weight of water absorbed by the membrane (W_s) divided by the dried weight of the membrane (W_d).

$$\% DS = \frac{(W_d)}{(W_s) - (W_d)} \; X\,100 \qquad (1)$$

2.4. Estimation of drug and encapsulation efficiency

Polymer blend membranes equivalent to 100 mg was stirred in 20ml of phosphate buffer solution (pH 7.4) and the drug content was analyzed by UV spectrophotometer (Lab India, Mumbai, India) at a λ_{max} of 200 nm. Encapsulation efficiency (EE) was calculated as the percentage (w/w) of the theoretical drug content (Equation 1). Results were based on triplicate and the average values are compiled in Table 2.

$$\% \text{ Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) x100 \qquad (2)$$

2.5. In vitro release studies

The drug loaded blend membranes were suspended in baskets containing 500 ml of phosphate buffer Solution (pH-7.4, acts as simulated intestinal fluid) and incubated on a shaking bed (Lab India, Mumbai, India) at 37 ^oC with a rotating speed of 100 rpm. At appropriate time intervals aliquot of the samples were withdrawn and the amount of Penicillamine released from the membranes were evaluated by UV spectrophotometer (Lab India, Mumbai, India) at a λ_{max} of 200 nm. Then an equal volume of the same dissolution medium was added back to maintain a constant volume. All the experiments were done in triplicate and results are average.

2.6. Fourier transform infrared spectroscopy

The FT-IR spectra were recorded on a FT-IR Spectrophotometer (Bomem, Model: MB3000, Canada). About 2mg of the samples was ground thoroughly with KBr and pellets were made by using hydraulic press under a pressure of 600kg/cm^2. Spectra were scanned between 4000 and 500 cm^{-1} at ambient temperature.

2.7. Scanning Electron Microscopy (SEM)

SEM images of plain SA/PLA blend membrane in dry powder form were recorded using a JSM 6400 SEM (JEOL Ltd., Akishima, Tokyo, Japan) at 100× and 80× magnification. Working distance of 39 mm was maintained and the acceleration voltage used was 20 kV, with the secondary electron image (SEM) as a detector.

2.8 Thermal gravimetric analysis (TGA)

Thermo gravimetric analyses (TGA) curves of Penicillamine, placebo SA/PLA blend membrane and Penicillamine-loaded SA/PLA blend membranes were recorded using a Waters apparatus DSC-TGA Q-600 model instrument (UK) at the following conditions: the weight of the sample 9-12 mg, the heating rate 10 ^oC/min, the maximum heating limit 700 ^oC under an inert atmosphere.

2.9. X-Ray diffraction (X-RD)

X-Ray diffraction patterns of Penicillamine, placebo SA/PLA blend membrane and pencilamine-loaded SA/PLA blend membrane were recorded using Shimadzu Lab-XRD-6000X diffractometer [Japan], using Nickel-filtered Cu Kα radiation [λ=0.154 nm]. Dried membrane sample were mounted on a sample holder and the patters

were recorded in the range of 10-50^0 at the speed of 5^0/min to know the crystallinity.

2.10. Tensile strength measurements:

The mechanical measurements of the membranes were recorded with INSTRON 3369 universal Testing Machine (Norwood, Massachusetts, USA) type tensile test apparatus at a drawing speed of 30 mm/min. Test samples were cut into 1X10cm. The tensile parameters were measure using 10 Kg load cell. For all samples 3 determinations were carried out and the result was given as an average.

3. RESULTS AND DISCUSSION

The different formulations of SA, PLA, GA and Drug variations have been shown as SA/PLA-0 to SA/PLA-9 codes and are incorporated in the Table.1.

Table 1. Polymer blend composition at various concentrations of reaction mixture components

Sample code	SA	PLA	GA	Drug
SA/PLA-0	0.9	0.1	0.01	-
SA/PLA-1	0.9	0.1	0.01	0.1
SA/PLA-2	0.85	0.1	0.01	0.1
SA/PLA-3	0.8	0.1	0.01	0.1
SA/PLA-4	0.9	0.1	0.01	0.2
SA/PLA-5	0.9	0.1	0.01	0.3
SA/PLA-6	0.9	0.15	0.01	0.1
SA/PLA-7	0.9	0.2	0.01	0.1
SA/PLA-8	0.9	0.1	0.05	0.1
SA/PLA-9	0.9	0.1	0.1	0.1

3.1 Fourier transform infrared spectroscopy

FT-IR spectra of drug (penicillamine), PLA, SA, SA/PLA blend membrane and Drug loaded SA/PLA membrane are presented in Figure1. FTIR studies were performed to confirm the crosslinking between SA and PLA membrane by GA.As shown in Figure 1 (b), the absorption bands around 1613 and 3414cm^{-1} are due to stretching bands of carboxylate and hydroxyl groups, respectively. Similarly, the characteristic PLA peaks of C=O stretching at 1760 cm^{-1}, C-H stretching at 2900-3000 cm^{-1}, C-C stretching at 870 cm^{-1}, C-H deformation at 1350-1500cm^{-1}, are also shown in Figure. In case of pure SA a characteristic broad band at 3443 cm^{-1} is detected and attributed to O-H stretching vibrations of SA as shown in Figure 1(c). A characteristic peaks observed at 1617 cm^{-1} and 1409 cm^{-1} corresponds to the asymmetric stretching vibration and symmetric stretching vibration of -COO group of -COONa respectively, present in SA. Figure1(d) shows the FT-IR spectra of PLA/SA blend with a proportion of 10% PLA and 90% SA, at 1% GA chemical cross-linker. It can be noted the bands at 1617, 3413, 2900 and 1120 cm^{-1} mainly associated with SA and also the presence of peaks related to carboxylic acid and the acetals form by the cross-linking reaction by glutaraldehyde of alcohol group from SA and acid groups from PLA. These bands confirms the crosslinking between chains by GA.

From Figure 1(a), it is observed that penicillamine shows peaks at 3066, 2662 and 1655 cm^{-1} were due to -N-H, -S-H and -CO_2 stretching vibrations. But in Figure 1(e) i.e. penicillamine drug loaded membrane showed the peaks at 3350, 2662 cm^{-1}due to -COOH, -S-H,stretching and bending vibrations, it relatively showed the above drug peaks in the drug loaded membrane, which indicates the drug present in the drug loaded membrane. At the same time in Figure 1(e) no new characteristic absorption bands of drug loaded membranes were observed, this clearly explains there was no chemical reaction between membrane and drug. As a result, the drug did not lose its activity in the drug loaded membranes.

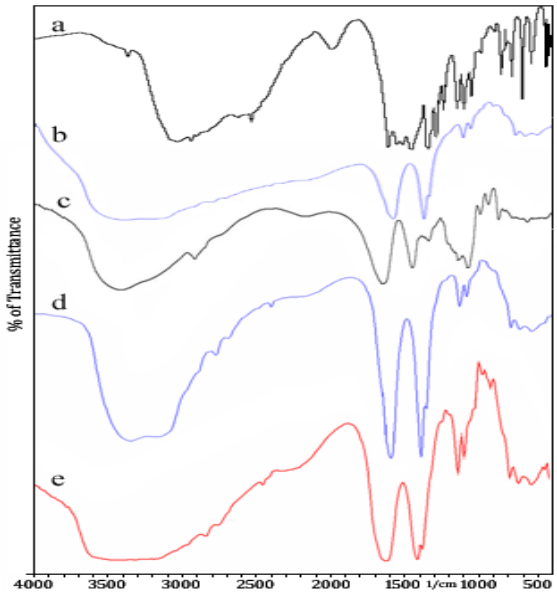


Figure 1. FT-IR spectra of plain Penicillamine (a), PLA (b), SA (C) SA/PLA blend membrane (d) and Drug loaded SA/PLA blend (e)

3.2 Thermal gravimetric analysis (TGA)

Thermo grametric analysis (TGA) was employed to characterize the thermal stability of the Drug loaded SA/PLA blend membrane in comparison with blank SA/PLA blend membrane. TGA curves of blank SA/PLA blend membrane (a) and Drug loaded SA/PLA blend membrane (b) are shown in Figure 2 Thermal stability of drug loaded SA membranes is well improved and is obvious from TGA curves. In case of SA-PLA-5, about 6-8% weights loss was observed below 110^{o}C. This was attributed to the removal of water. Figure 2 shows the degradation of pure blend membrane is faster than drug loaded blend membrane. In drug loaded SA/PLA membrane sample, a residual weight of

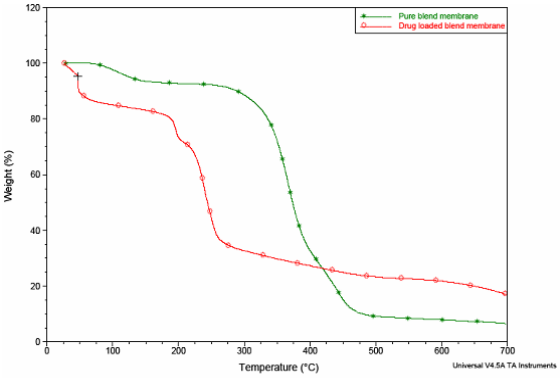


Figure 2. TGA curves of pure SA/PLA blend membrane (a) and Drug loaded SA/PLA blend membrane.

70% was observed at 300 ^{o}C. These studies indicate that drug loaded SA/PLA blend leads to an overall improvement in the thermal stability of the membranes.

3.3. X-Ray diffraction (X-RD)

X-RD analysis provides a clue about the crystallinity of drug in the blend membrane. The X-Ray diffractions of Penicillamine loaded SA/PLA blend membrane; plain SA/PLA blend membrane and Plain Penicillamine are presented in **Figure 3**. Penicillamine peaks observed at 2θ of 12^{o}, 14^{o}, 18^{o}, 24^{o} and 30^{o} are due to crystalline nature of Penicillamine whereas, all these peaks were not observed but few peaks are observed with very less intensity in the case of drug loaded blend membrane. This confirms the presence of drug in the blend membrane as well as its crystalline nature [36].

3.4 Scanning Electron Microscopy (SEM)

The membrane obtained from SA/PLA blend solution by conventional casting method were morphologically studied with the help of SEM analysis. In Figure 4(a**)** shows the SEM image of SA/PLA (90/10) membrane cross-linked with 0.1% GA without drug content. The presence of two phases is belonging to the polymers such as SA and PLA. The photography presented in Figure 4(b) belongs to a SA/PLA (90/10) film with drug and cross-linked with 0.1% GA. In this case, we can also see the drug molecules are physically associated and adsorbed at the surface of the phase. This clearly indicates good compatibility between the polymer matrix and drug, Penicillamine.

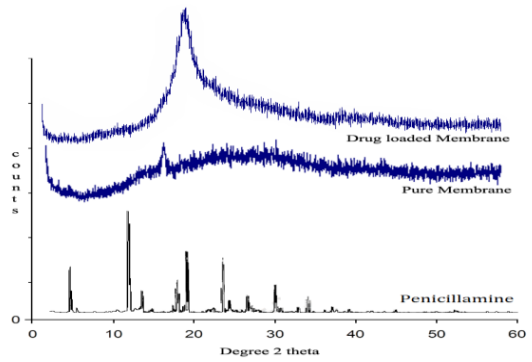


Figure.3. X-Ray diffraction patterns of Penicillamine loaded SA/PLA blend membrane (a) plain SA/PLA blend membrane (b) and Plain Penicillamine drug

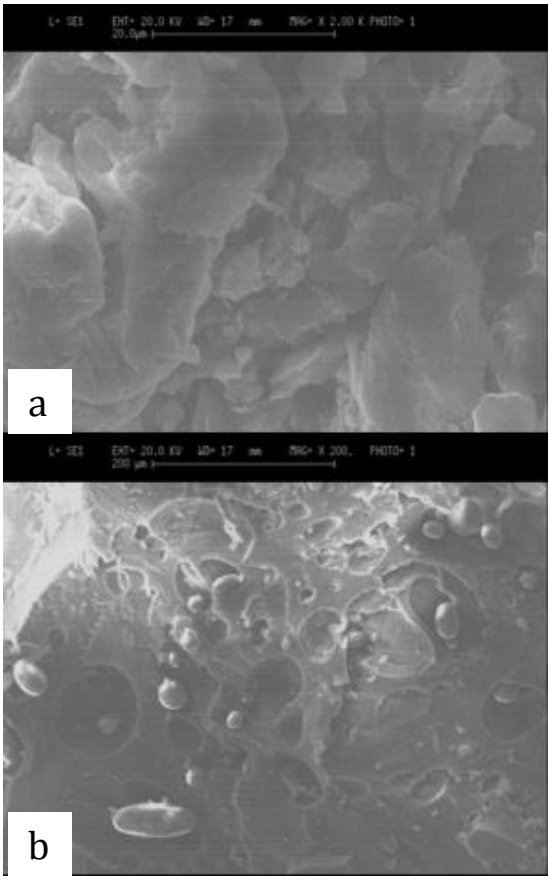


Figure 4. SEM micrograms of plain blend membrane (a) and Penicillamine Loaded blend membrane (b)

3.5. Tensile strength measurements:

The improved mechanical strength of SA/PLA blend membranes was confirmed by tensile strength (TS) measurements. The SA/PLA-0 blend membrane made of pure SA showed TS of 2.4 kg/cm^{2}. While, blend membranes prepared including SA and PLA have shown higher TS as shown in Table2. Results indicate that the blend membranes showed higher TS as compared to SA alone. This may be due to formation of large number of links amount the polymer chains as results of blend formation, thereby increasing strength of the matrix. Among the blend membranes, TS increased with an increase in concentration of GA, indicating an increased strength of matrix with increasing cross-linking. The mechanical strength values of blend membranes are shown in Table2.

3.6. Swelling properties

The ability of a blend membrane to preserve water is an important aspect to be investigated for drug delivery applications. The water uptake (swelling) percent of blend membrane with different concentration of SA, PLA and GA at distilled water is given in Figure 5 (a). As seen here, the blend membranes did absorb water rather fast in about 4h, and then gradually reached equilibrium in about 24h. The water binding ability of the bend membrane could be mainly attributed to the hydrophilic nature of Sodium Alginate present in the blend membrane. In general, the water uptake decreases as the cross-linking degree is increased because of the decrease in the number hydrophilic groups as well as the more difficulty in the structural expansion due to the more dense covalently linked network [37]. For the specific case of Sodium Alginate, a more complex relationship is found between cross-linking degree with Glutaraldehyde and swelling capability, because the crystalline content in the material is

Table.2 The values of Tensile Strength for different blend membranes

Sample code	Tensile Strength
SA/PLA-0	2.40±0.25
SA/PLA-1	3.15±0.23
SA/PLA-2	2.86±0.25
SA/PLA-3	2.42±0.05
SA/PLA-4	3.21±0.15
SA/PLA-5	3.39±0.18
SA/PLA-6	4.18±0.29
SA/PLA-7	4.25±0.32
SA/PLA-8	3.51±0.05
SA/PLA-9	4.15±0.09

also changing [38]. The results in Figure 5 (b) indicate that the percent of swelling increases with increasing sodium alginate concentration or with decreasing cross-link density. The maximum swelling percentage (110%) was achieved by using the highest concentration of Sodium Alginate (1%) with the lowest cross-link densities.

3.7 Encapsulation efficiency

Three different concentrations of Penicillamine (0.1, 0.2 and 0.3%) were loaded during the preparation of blend membranes. Results of % encapsulation efficiency are included in Table 3. The percentage of entrapment efficiency depending on the preparation conditions and the type of the matrix material used to prepare the membranes. Table shows that % of encapsulation efficiency increased with increasing amount of drug loaded and with increase in SA content of the encapsulation efficiencies are in the range of 63 to 71%. Encapsulation efficiency decreased with increase in cross-linker (GA) and PLA concentration, this decrease might be due to the increase in cross-linker of the polymer matrix (Table 3). The increase in cross-linking density leads to the formation of rigid structure as a result, reduction in free volume within the polymer matrix, thereby reducing their encapsulation efficiencies. The % of encapsulation of blend membrane prepared with SA/PLA (90:10) cross-linked with different amounts of GA (0.01, 0.05 and0.1) are 71, 65 and 62% respectively and different amounts of PLA (0.1, 0.15 and 0.2) are 71, 70 and 63 respectively.

3.8. In-vitro release study

In-vitro release studies were performed by dissolution test apparatus in pH 7.4 buffer solutions, and the results are discussed below.

3.8. Effect of Polymers

To understand the release profiles of Penicillamine from cross-linked SA/PLA blend membranes, in-vitro release studies was carried out in pH 7.4 phosphate buffer solutions at 37 ^{o}C. Figure 6 displays the cumulative release of Penicillamine through membranes containing SA/PLA ratios, and at constant GA (0.1%) concentration. From figure 6a it was observed that the highest cumulative release is obtained for SA/PLA- formulation, which has 0.1% PLA ratio. On the other hand, the least cumulative release (Penicillamine) is obtained in 0.2% PLA ratio. When the amount of PLA is increases in the SA/PLA blend membrane, a decrease in the drug release observed. This could be because as the amount of PLA increases in the membrane, the hydrophobicity of the overall matrix increases due to presence of ester linkages and methyl groups of PLA, which increases the hydrophobicity of the matrix, thereby decreasing the release rates from Penicillamine thus a regaining type responses of polymer chains is possible due to the stress induced by the surrounding solvent media during the dissolution step, resulting in a decrease of chain dimensions of the polymer matrix. This will further decrease the molecular volume of the hydrated polymer due to decreased swelling of PLA component of the polymer matrix, thereby reducing the free volumes spaces of the matrix. Hence, with an increase of PLA in the SA/PLA blend membranes a decrease in % of cumulative release is observed.

3.8.2. Effect of drug concentration

Figure 6b displays the release profiles of SA/PLA blend membranes loaded with different amounts of drug (0.1, 0.2 and 0.3). Release data showed that formulations containing highest amount of drug displayed fast and higher released rates than those formulations containing a small amount of Penicillamine. A prolong released was observed for the formulation containing lower amount of Penicillamine. In other words, with decreasing

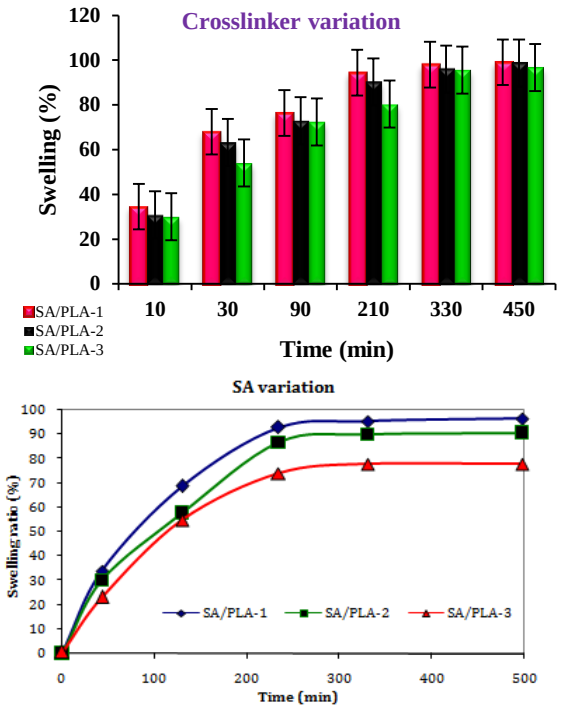


Figure 5. Variation of % swelling ratio with (a) concentration of SA and (b) crosslinker

amount of drug in the matrix, it is noticed that the released rate becomes quite slower, this is due to the availability of more free void spaces through which lesser number of drug molecules will transport. Because drug release from the blend membranes is sustained by diffusion mechanism, the release rates are slow at lower amount of Penicillamine. Similar release profiles were also reported by various researchers [39].

3.8.3. Effect of cross-linking agent

The percent of cumulative release data vs. time plots for blend membranes with varying amount of GA (0.01, 0.05 and 0.1) at a fixed amount of drug (0.1g), and polymers are displayed in Figure 6 (c). The % cumulative release is quite fast and large, at lower amount of GA, whereas the release is quit lower at higher amount of GA. Probably, at higher concentration of GA, polymeric chains become rigid due to the contraction of micro voids, thus decreasing % cumulative release of Penicillamine through the polymeric matrices. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA.

3.8.4. Drug release kinetics

In order to establish a link between drug release and molecular transport parameters, we have fitted the release data to an empirical equation [40]:

$$(M_t/M_\infty) = kt^n \qquad (3)$$

Table 4. Results of % of Encapsulation Efficiency and Release Kinetics parameters (k and n) of Different formulations

Sample code	% of Encapsulation	K	n
SA/PLA-0	41.7±1.5	0.0147	0.740
SA/PLA-1	71.7±1.2	0.0180	0.862
SA/PLA-2	67.8±0.9	0.0171	0.832
SA/PLA-3	63.3±0.9	0.0210	0.718
SA/PLA-4	69.7±1.2	0.0188	0.925
SA/PLA-5	78.4±1.1	0.0021	1.161
SA/PLA-6	70.2±0.3	0.0161	0.817
SA/PLA-7	63.1±0.5	0.0236	0.700
SA/PLA-8	65.2±0.2	0.0429	0.658
SA/PLA-9	62.1±0.5	0.0299	0.598

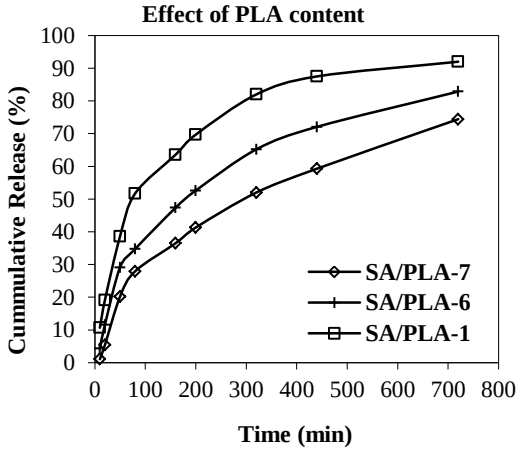


Figure 6(a): % of Cumulative release of Penicillamine through SA/PLA blend membranes containing différent amounts of PLA.

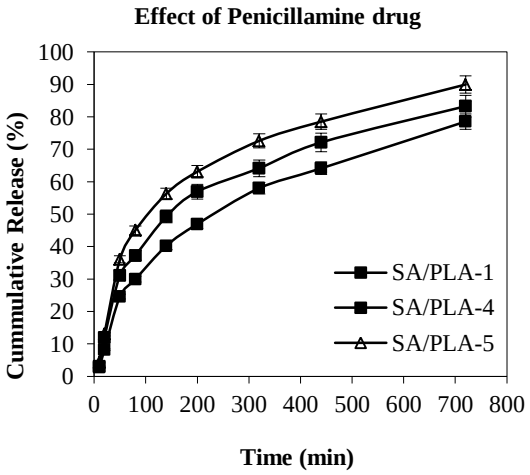


Figure 6(b): % of Cumulative release of Penicillamine through SA/PLA blend membranes containing différent amounts of Penicillamine Drug.

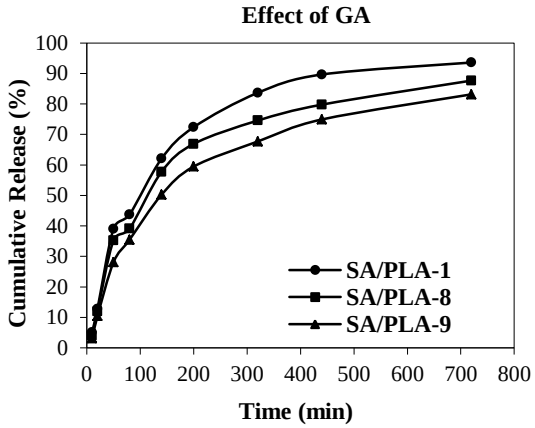


Figure 6(c): % of Cumulative release of Penicillamine through SA/PLA blend membranes containing différent amounts of cross-linking agent.

were M_t/M_α represents the fractional drug release at time *t*, *k* is a constant characteristic of the drug-polymer system and n is an empirical parameter characterizing the release mechanism. Using the least-squares procedure, we have estimated the values of *n* and *k* for all formulations using equation (4) and these results are presented in Table 3. If *n*=0.5, drug diffuses and release out of the polymer matrix following Fickian diffusion. For *n*>0.5, anomalous or non-Fickian type drug diffusion occurs. If *n*=1, a completely non-Fickian or case II release kinetics is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to anomalous type of diffusion transport [41]. The values of *k* and n have shown a dependence on the extent of cross-linking, the percentage of drug loading, and PLA content in the matrix. Values of *n* for membranes are calculated by varying the amount of PLA (0.1, 0.15 and 0.2 g), keeping Penicillamine (10%) and GA (2 ml) constant , and range from 0.700 to 0.862, leading to a shift transport of anomalous type. The Penicillamine loaded membranes containing different amount of Penicillamine and GA exhibited n values ranging from 0.862 to 1.169, and the values for different formulations are presented Table 3, indicating the shift transport of anomalous-type release. This may be due to the reduction in the regions of low micro-viscosity and closure micro-cavities in swollen state of the polymer. Similar findings were also observed by Lyu et al [42] wherein the effect of monomer, drug, and cross-linker content on dissolution kinetics.

4. CONCLUSIONS

The SA/PLA blend membranes were prepared by using PLA with different concentrations of SA and glutaraldehyde. The concentration of PLA and glutaraldehyde had an influence on the morphology, mechanical, and swelling property of the blend membranes. The blend membranes exhibit a much higher stiffness than pure SA membrane, indicating that this strategy may allow for the use of SA-based structures in tissue engineering applications requiring some mechanical features. The % of swelling of the blend membranes increased with either increasing SA content or decreasing crosslink densities and PLA content. The maximum swelling of the membranes (around 110%) was achieved in about 24 h. The developed membranes were found to be adequate to release previously loaded drugs. The drug release profile was affected by the composition of the blend membranes. The drug release was fast at the initial period, in agreement to the water uptake behavior; however, almost constant drug release was observed at the later time period. The blend membranes prepared with the lowest amount of PLA and cross-linking agent showed the highest percent of drug release. These preliminary results suggested that SA/PLA blend membranes could be suitable to release bioactive components for stimulating cell differentiation and proliferation or drugs, such as anti-inflammatory and antibiotics, to induce therapeutic effects in tissue engineering strategies.

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