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Sodium Alginate/Tragacanth Gum Blend Hydrogel Membranes for Controlled Release of Verapamil Hydrochloric Acid

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ABSTRACT

Sodium alginate (SA) and tragacanth gum (TG) blend membranes were prepared by solvent casting method for the controlled release of verapamil an antihypertensive drug. The prepared membranes were crosslinked with glutaraldehyde (GA) and were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffraction (X-RD), and scanning electron microscopy (SEM). FTIR was used to understand the formation of hydrogen bonding due to interaction between SA, TG polymer blend and GA. The DSC and X-RD studies were performed to understand the crystalline nature of drug after encapsulation into hydrogel membranes. SEM was used to study the surface morphology of the membranes. In vitro release studies indicated a dependence of release rate on the extent of crosslinking, amount of drug loading and the amount of blend composition. The results revealed the slow release rates which were extended up to 12 h. Cumulative release data were fitted onto to an empirical equation to compute diffusional exponent (n) which indicates the non-fickian diffusion.

Key words: *Interpenetrating polymer network, Verapamil hydrochloric acid, Encapsulation, Tragacanth gum.*

1. INTRODUCTION

Controlled drug delivery using polymers is one of the emerging technologies, which is generating significant interest because of therapeutic effectiveness of many drugs can be improved [1]. The conventional dosage forms of release pattern of drug at faster rate initially leads to rise in blood level, for the peak and valley patterns of the drug levels in blood [2,3]. The need to minimize blood level fluctuation of drug has lead to the development of controlled drug delivery system. One of the major systems used is incorporation of drug in polymer matrix, which releases a drug in a controlled rate, constant administration of the drug, allowing continuous input of drugs with short biological half-life, but it also eliminates pulsed entry into the systemic circulation, which often causes undesirable side effects [4-7]. In recent years, considerable research efforts have been directed towards the development of safe and efficient drug delivery systems with the use of polymers as agents for the controlled release of drugs from various types of formulated products such as tablets, hydrogel membranes, microspheres, and adhesive strips. Evidence of the high degree of interest in the design of such dosage forms is provided by number of reviews [8-10] that has been concerned with these subjects. The release of drugs, absorbed or encapsulated by polymer, involves their slow and controlled diffusion from or through polymeric material. Therapeutic molecules complexed by polymers may also be released from gels by diffusion.

Sodium alginate (SA), a natural polysaccharide, composed of D-mannuronic acid and D- guluronic acid, is derived from the brown seaweeds. SA is a biodegradable polymer used extensively in drug delivery applications [11-13]. Earlier literature cites many applications of SA in agricultural applications after crosslinking with glutaraldehyde (GA) [14-16]. SA is one of the most versatile natural materials known to form hydrogels and films [17-19]. Drug loaded films of SA are being used in pharmaceutical applications. In the literature, the numerous controlled sustained delivery systems have been described, whereby the active ingredient has been dispersed within these films [20].

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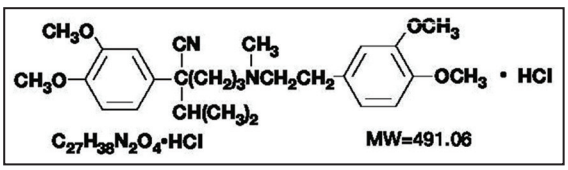
Tragacanth gum (TG) is a natural gum obtained from *Astragalus gummifer* Labillardiere and other species of *Astragalus* [21,22]. The gum consists of a mixture of water-insoluble and water-soluble polysaccharides. Bassorin, which constitutes 60-70% of the gum, is the main water-insoluble portion, while the remainder of the gum consists of the water-soluble material, tragacanth. TG is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations. It is used in creams, gels, and emulsions at various concentrations according to the application of the formulation and the grade of gum used [23]. The drug release property from TG matrices is proceeded by polymer hydration, and processing variables that might affect its hydration would also affect its performance as a controlled-release doses form. Thus, the purpose of the present investigation is to study processing variables at the laboratory and pilot scales that can affect hydration rates of TG. The rate of release from polymer carrier can be tailor made by selecting a suitable polymer blend composition and drug concentration with this idea in mind it is aimed to assess the drug release from SA/TG based matrix formulations for drug released studies.

Verapamil hydrochloric acid (HCl) (VPL) (Scheme 1), the drug selected in present work is a calcium channel blocker used for the treatment of hypertension, angina pectoris, cardiac arrhythmia, and most recently, cluster headaches [24,25]. It is completely absorbed (90%) from the gastrointestinal tract after oral administration but has very low bioavailability of 22±8%. The low bioavailability is owing to the rapid biotransformation in the liver with a biological half-life of 4.0±1.5 h. The short biological half-life and poor bioavailability of drug favors development of controlled release formulations [26-28].

Recently, our group is actively involved in the development of blend polymeric systems for the control release of various types of drugs. Earlier Mallikarjuna *et al.* [29] have prepared blend hydrogel membranes for controlled release of valganciclovir hydrochloride. Prabhakar *et al*. [30] have prepared SA and poly (lactic acid) blend membranes for controlled release of penicillamine. The objective of this work was to develop and characterize SA/TG blend IPN membranes loaded with VPL, which after oral administration could prolong the gastric residence time and increase the drug bioavailability.



Scheme 1: Chemical structure of verapamil hydrochloride

2. EXPERIMENTAL

2.1. Materials and Methods

SA (viscosity [2 W/V%], 1100-1900 cps) was purchased from Merck, Mumbai, India; TG (mol.wt. 840 KDa), GA, HCl, and acetone were all of analar grade purchased from Sd.Fine (India). VPL was purchased from Sigma-Aldrich (St. Louise, USA). Double-distilled water was collected in the laboratory and used throughout this research work. All the chemicals were used as received without further purification.

2.2. Preparation of Drug Loaded Blend Membranes

The blend membranes of SA/TG were prepared by a solvent-casting method. 2 wt.% of SA and 2 wt.% TG was dissolved separately in distilled water under constant stirring (Remi motor) for overnight. The required ratios (Table 1) of SA, TG were taken in 100 ml beaker and to this solution, the antihypertensive drug VPL (10, 15 and 20 wt.%) was added slowly under constant stirring until a clear homogeneous solution was obtained. The obtained solution was filtered for removing of undissolved particles and poured on a Teflon plate of 20 cm×15 cm. The membranes were dried in an oven at 37°C, until it shows constant weight. The dried membranes were dipped into acetone–water mixture containing different ratios (Table 1) of GA and 0.1 HCl for crosslinking up to 30 min. Then, the crosslinked membranes were washed with distilled water to remove the excess of unreacted GA and dried at 37°C for 24 h. The prepared membranes were stored in a closed container for further characterization. The formulation details are given in Table 1.

2.3. Swelling Studies

Squares of 1.5 cm^2 were cut and dried at 60°C until constant weight (W_d) was obtained. Then, they were immersed into 5 ml of distilled water at 37°C in 7.4 phosphate buffer solution for at least 24 h. 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-W_d) divided by the dried weight of the membrane (W_d).

$$\%\,DS = \left(\frac{(W_S)-(W_d)}{(W_d)} \right) \times 100 \quad (1)$$

Where, W_d and W_s were the weights of dried and swollen membranes, respectively.

2.4. Estimation of Drug and Encapsulation Efficiency

The membranes of specified area (1 cm^2) were cut into small pieces and added to 100 ml of phosphate buffer pH 7.4 for complete swelling at 37°C. The swollen membranes were crushed in a glass mortar with pestle. The solution was then heated gently for 2 h to extract

Table 1: Various formulation parameters used in the preparation of membranes and their encapsulation efficiency.

Sample code	SA (w/w%)	TG (w/w%)	GA (ml)	Drug (%)	% Encapsulation efficiency
STV-1	80	20	2	10	68.43±0.57
STV-2	80	20	2	20	75.28±0.92
STV-3	80	20	2	30	82.49±0.62
STV-4	80	20	3	20	72.45±0.52
STV-5	80	20	4	20	69.42±0.65
STV-6	70	30	2	20	71.56±0.34
STV-7	90	10	2	20	78.24±0.35
STV-8	100	-	2	20	72.65±0.34
STV-9	80	20	2	-	-

SA: Sodium alginate, TG: Tragacanth gum, GA: Glutaraldehyde

the drug completely and centrifuged using a table-top centrifuge (R-8C DX Remi, India) at 3000 rpm for 10 min to remove polymeric debris. The clear supernatant solution was analyzed for drug content using UV spectrophotometer (LabIndia-UV3000+) (λ_{max}) at 230 nm. The average of three determinations was considered. The % encapsulation efficiency was calculated using the following Equations 2 and 3.

$$\%\text{Drug loading} = \left(\frac{\text{Amount of drug in membranes}}{\text{Amount of membranes}} \right) \times 100 \quad (2)$$

$$\%\text{Drug encapsulation efficiency} = \left(\frac{\text{Actual drug loading into the membranes}}{\text{Theoretical loading into the membranes}} \right) \times 100 \quad (3)$$

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°C with a rotating speed of 100 rpm. At appropriate time intervals aliquot of the samples were withdrawn and the amount of VPL released from the membranes were evaluated by UV spectrophotometer (Lab India, Mumbai, India) at a λ_{max} of 251 nm. Then, an equal volume of the same dissolution medium was added back to maintain a constant volume. All three experiments were done in triplicate and results are averaged.

2.6. Fourier Transform Infrared (FTIR) Spectroscopy

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

2.7. Scanning Electron Microscopy (SEM)

The membranes were mounted onto stubs using double sided adhesive tape and sputter coated with platinum using a sputter coater (Edward S 150, UK). The coated membranes were observed under SEM (JEOL, JSM-6360, Kyoto, Japan) at the required magnification at room temperature. The acceleration voltage used was 10 kV with the secondary electron image as a detector.

2.8. Differential Scanning Calorimetry (DSC)

The sample membranes were heated from 0 to 400°C at a heating rate of 10°C/min under nitrogen atmosphere (flow rate, 20 ml/min) using a DSC (Model-SDT Q600, USA) and then thermograms were obtained.

2.9. X-ray Diffraction (X-RD)

X-RD patterns of pure VPL drug and drug loaded SA/TG blend membranes were recorded using Shimadzu Lab-XRD-6000X diffractometer (Japan), with the help of Nickel-filtered Cu Kα radiation (λ=0.154 nm). Dried membrane samples were mounted on a sample holder, and the patterns were recorded in the range of 10-50° at the speed of 5°/min to know the crystallinity.

3. RESULTS AND DISCUSSION

3.1. Swelling Studies

The ability of a blend membrane to preserve water is an important aspect to be investigated for drug delivery applications. The variation of % of swelling of the SA/TG (80:20) blend membranes with time for different crosslinker content has been shown in Figure 1. From Figure 1, it is noticed that the blend membranes of different crosslinker content the swelling is fast up to 6 h later gradually reached equilibrium beyond this time. The water binding ability of the blend membrane could be mainly attributed to the hydrophilic nature of both SA and TG 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 of hydrophilic groups as well as the more difficulty in the structural expansion due to the more dense covalently linked network [30], which is also clear from the Figure 1, in this study. For the specific case of SA, a more complex relationship is found between cross-linking degree with GA and swelling capability because the crystalline content in the material is also changing [31].

3.2. FTIR Spectroscopy

FTIR spectra of the pure drug, placebo blend membrane, and drug-loaded blend membranes are presented in Figure 2. The characteristic FTIR absorption peak of VPL (curve 'a') showed the C–H stretching vibrations of the methoxy group at 2840 cm^{-1}. The N–H stretching of the protonated amine group is observed in the range 2800-2300 cm^{-1}, and a strong absorption band due to C–O stretching of the aromatic ester group appeared at 1262 cm^{-1}. FTIR spectra of the VPL-loaded SA/TG (curve c) show a prominent peak for VH at 1517 cm^{-1}, which is due to benzene rings. This indicates that VPL is not involved in any chemical reactions with either the polymer or the cross-linking agent. The absence of this VPL peak in placebo blend membrane further substantiates the above observation.

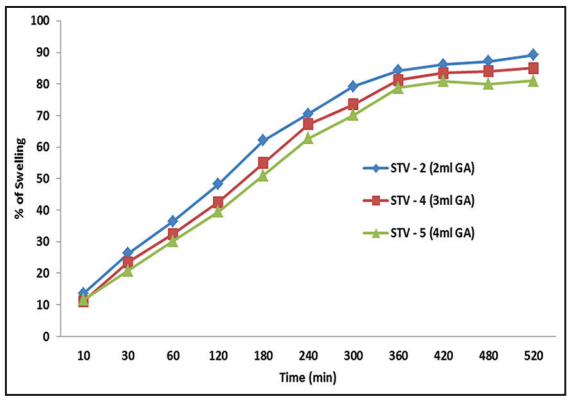


Figure 1: Variation of % of swelling of the sodium alginate/tragacanth gum (80:20) drug-loaded blend membranes with time for different crosslinker (glutaraldehyde) content.

3.3. DSC Studies

DSC thermograms of plain VPL drug (a), drug-loaded blend membrane (b) and plain blend membrane (c) are presented in Figure 3. In the case of plain drug, (a) shows the endotherm peak at 145°C indicates the melting peak [32]. The endothermic sharp peak of drug (145°C) was not appeared in drug-loaded blend membrane (b) which confirms the molecular level dispersion of VPL in the polymer blend matrix. The endothermic peak of the polymeric matrix at 89°C (c) after loading the drug decreased to 84°C (b) due to the possible formation of a loose network as the result of the creation of extra free space after drug loading. Kurkuri *et al.* [32] observed similar observations in their drug release studies of VPL.

3.4. SEM Studies

Without drug (VPL) loaded and with drug-loaded blend membranes of SA/TG are morphologically

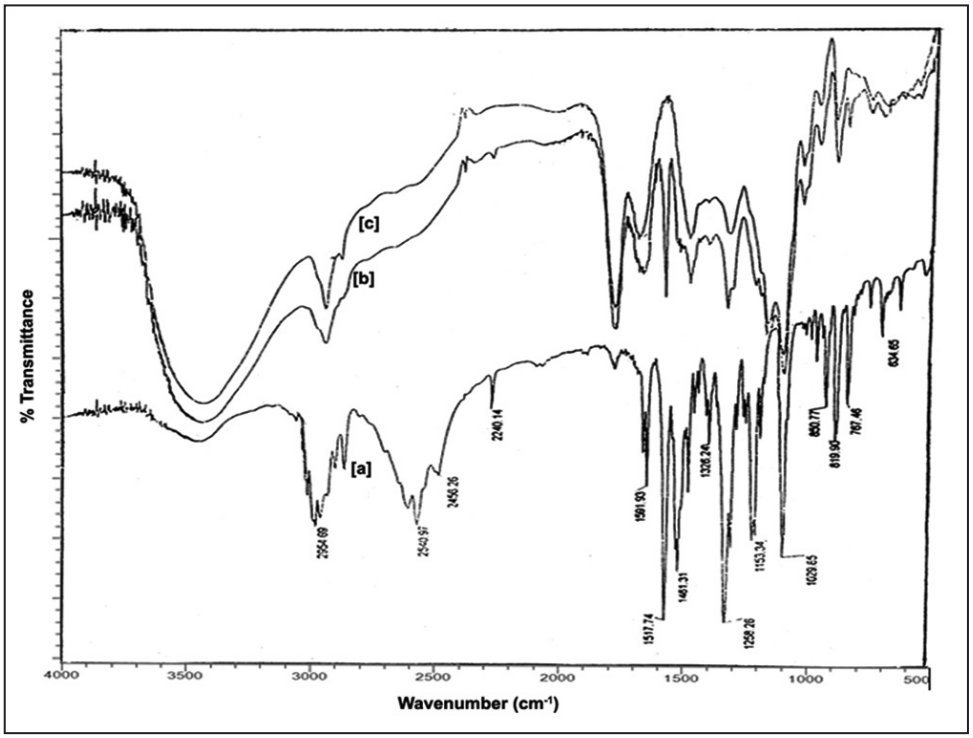


Figure 2: Fourier transform infrared spectra of verapamil hydrochloric acid (a), sodium alginate (SA)/tragacanth gum (TG) blend membrane (b), and drug loaded SA/TG blend membrane (c).

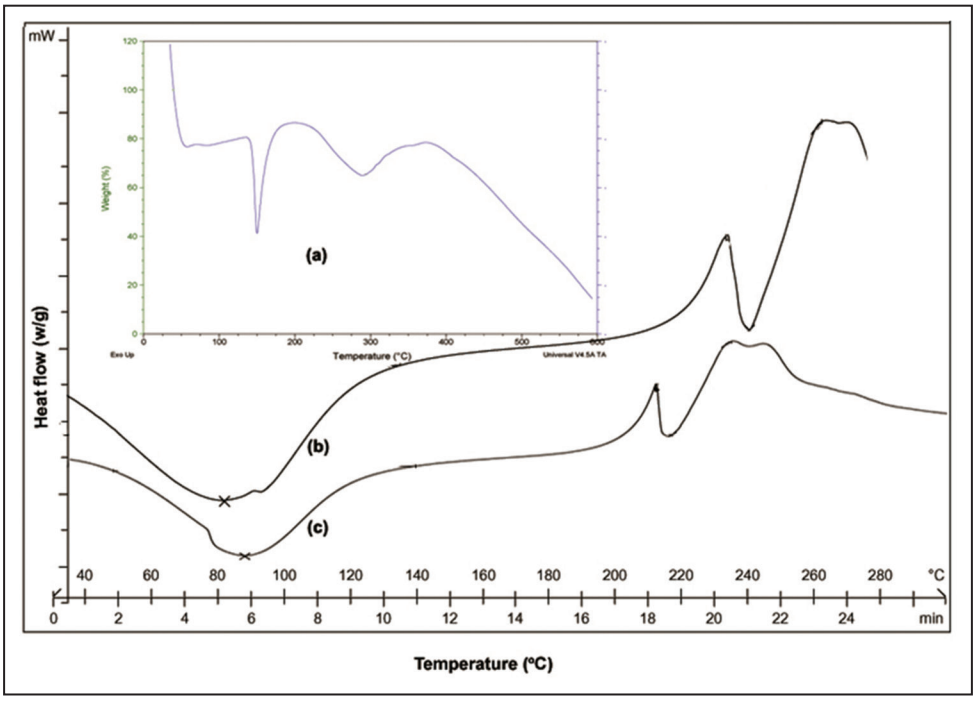


Figure 3: Differential scanning calorimetry thermograms of pure verapamil hydrochloric acid drug (a), drug-loaded blend membrane (b) and pure blend membrane (c).

studied using SEM and these images are showed in Figure 4. a and b shows the SEM image of SA/TG (80/20) membrane cross-linked with 2 ml GA without drug at two different resolutions. Figure 4 (a and b) shows smooth surface which indicates the complete miscibility of these polymers in the blend. Figure 4 (c and d) shows SA/TG (80/20) blend membrane with drug and cross-linked with 4 ml of GA at two different resolutions. Figure 4 (c and d) has a rough and dense surface which indicates the drug molecules are physically associated and adsorbed at the surface of the polymer membrane. The appearance of dense surface may be due to the crosslinker; it shrinks the membrane.

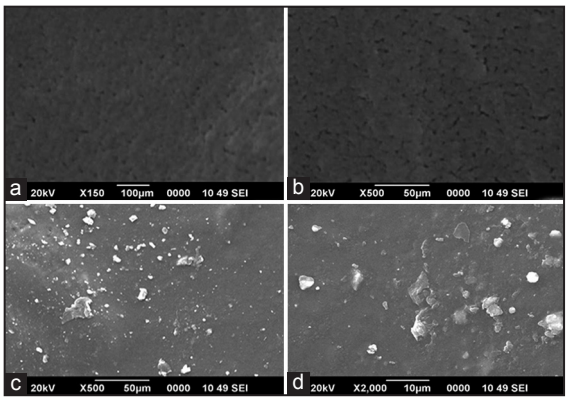


Figure 4: Scanning electron microscopy photographs without drug loaded membranes (STV-9) (a and b) and with drug-loaded membranes (STV-5). (c and d) at different resolutions.

3.5. X-RD Studies

X-RD diffractograms of pure VPL drug Figure 5(a) and VPL loaded SA/TG (80:20) blend membrane Figure 5(b) are presented in Figure 5. From Figure 5(a), it is noticed that the plain drug has shown characteristic peaks at 2Θ=17.2°-24.5° due to it's crystalline nature, whereas the absence of these peaks of drug in drug loaded membrane Figure 5(b) indicates the uniform distribution of VPL in the blend membrane matrix.

3.6. Encapsulation Efficiency

The percentage of encapsulation efficiencies depend on the preparation conditions for various formulation parameters used to prepare the blend membranes are given in Table 1. The values in Table 1 shows that the % of encapsulation efficiency increased with increasing amount of drug loaded in the range of 68-82%. Encapsulation efficiency decreased with increase in cross-linker (GA), this decrease might be due to the increase in crosslinking of the polymer matrix the range of 76-69% (Table 1). 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 encapsulation efficiency decreased within the amount of TG in polymer blend membrane for compositions STV-7, STV-2 and STV-6 from 78% to 71%.

3.7. In Vitro Release Study

In vitro release studies for the drug-loaded blend membranes were performed using dissolution test

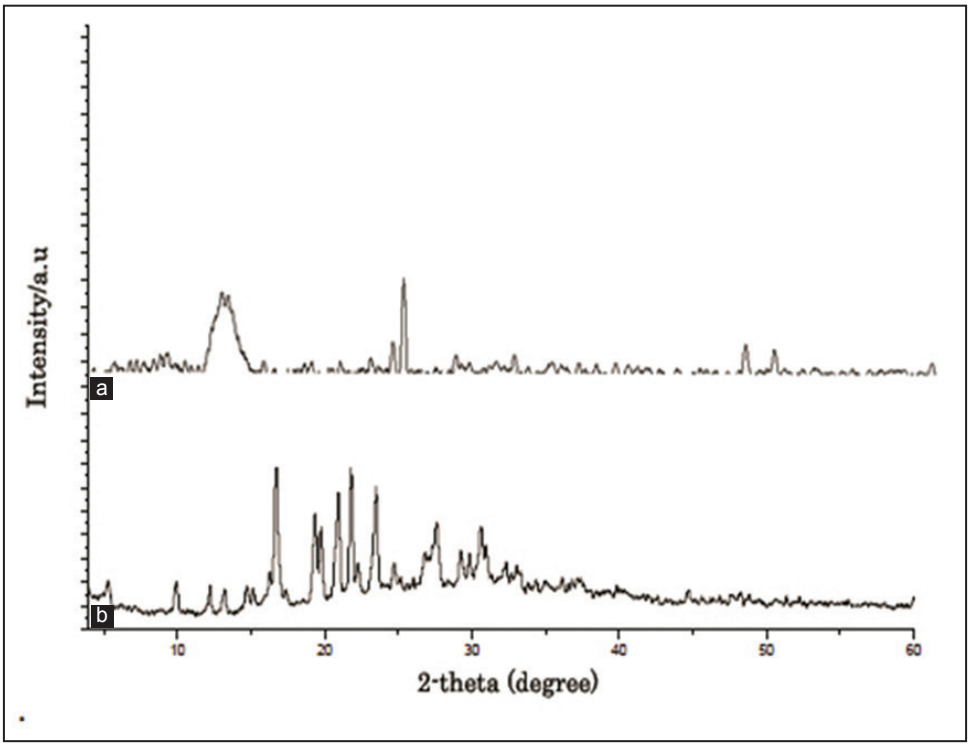


Figure 5: X-ray diffraction patterns of pure verapamil hydrochloric acid drug (a) and drug-loaded sodium alginate/tragacanth gum blend membrane (b).

apparatus in pH 7.4 buffer solution and the results are discussed below.

3.7.1. Effect of polymers

To understand the release profiles of VPL loaded and cross-linked SA/TG blend membranes, *in vitro* release studies were carried out in pH 7.4 phosphate buffer solutions at 37°C and are shown in Figure 6a-c. Figure 6a shows the cumulative release of VPL through membranes containing different ratios of SA/TG ratios at constant GA (2 ml) and at constant drug (20%) content. From Figure 6a, it was observed that the highest cumulative release is obtained for SA/TG-formulation (70% SA+30% TG). On the other hand, the least cumulative release (VPL) is obtained in (90% SA+10% TG). When the amount of TG increases in the SA/TG blend membrane, an increase in the drug release is observed. This could be because as the amount of TG increases in the membrane, the hydrophobicity of the overall matrix increases due to presence of ester linkages and methyl groups of TG, which increases the hydrophobicity of the matrix, thereby showing controlled release rates from VPL 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.

3.7.2. Effect of drug concentration

Figure 6b shows the cumulative release of SA/TG blend membranes loaded with different amounts of drug (10, 20 and 30%). Release data showed that formulations containing highest amount of drug show fast and higher released rates than those formulations containing a lower amount of VPL. A prolong released was observed for the formulation containing lower amount of VPL. In other words, with decreasing 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 Flutamide. Similar release profiles were also reported by various researchers [33].

3.7.3. Effect of cross-linking agent

The percent of cumulative release data versus time plots for drug-loaded blend membranes with varying amount of GA (2, 3, and 4 ml) at a fixed amount of drug (20%), and at a fixed ratio of polymer blend membrane (80% SA: 20% TG) are shown in Figure 6c. 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 microvoids, thus decreasing % cumulative release of VPL through the polymeric matrices. As expected, the release becomes slower at higher amount of GA but becomes faster at lower amount of GA.

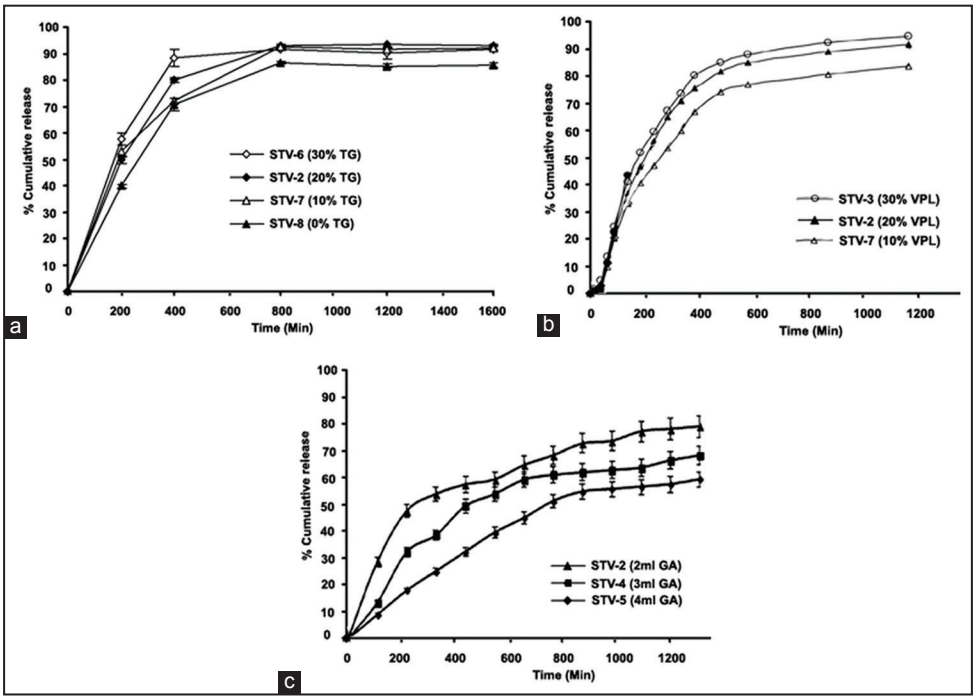


Figure 6: (a) Percentage cumulative release of verapamil hydrochloric acid through sodium alginate/tragacanth gum (TG) blend hydrogel membranes containing different amounts of TG: (◇) 30% TG, (♦) 20% TG, (△) 10% TG, and (▲) 0% TG in pH 7.4 buffer solution. (b) Percentage cumulative release of verapamil hydrochloric acid (VPL) through SA/TG blend hydrogel membranes containing different amounts of Verapamil HCl: (○) 30% VPL, (▲) 20% VPL, (△) 10% VPL at pH 7.4 buffer solution. (c) Percentage cumulative release of flutamide through SA/KG blend hydrogel membranes containing different amounts of crosslinker: (▲) 2 ml GA, (■) 3 ml GA, and (♦) 4 ml GA, and at pH 7.4 buffer solution.

3.7.4. Drug release kinetics

To determine the mechanism of drug release, the initial percentage of drug release versus time profiles have been fitted to the empirical equation [34]:

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

Where 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 diffusion exponent, characteristics the release mechanism. Using the least-squares procedure, we have estimated the values of n, k and r for all formulations using Equation (4), and these results are represented in Table 2. If n=0.5, drug diffuses and releases 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 of "n" ranging between 0.452 and 0.756 are indicative of both diffusion and swelling-controlled drug release, i.e., anomalous-type release [35]. The values of "k" and "n" shown a dependence on the extent of crosslinking, the percentage of drug loading and TG content in the matrix. Values of "n" for membranes are calculated by varying the amount of TG (10, 20, and 30%), keeping VPL (20%) and GA (2 ml) constant, and values range from 0.452 to 0.698, leading to a shift transport of anomalous type. The VPL loaded membranes containing different amount of VPL and GA exhibited n values ranging from 0.489 to 0.756, and the values for different formulations are presented Table 2 indicating the shift transport of anomalous type release. This may be due to the reduction in the reasons of low microviscosity and closure microcavities in swollen state of the polymer. Similar findings were also observed by Kurkuri *et al.* [32] and Kajjari *et al*. [33] from their drug release

Table 2: Results of % of release kinetics parameters (k, n and r) of drug in different blend membrane formulations.

Sample code	k	n	r
STV-1	0.324	0.489	0.987
STV-2	0.387	0.586	0.974
STV-3	0.421	0.756	0.962
STV-4	0.268	0.508	0.992
STV-5	0.326	0.564	0.961
STV-6	0.408	0.698	0.978
STV-7	0.351	0.452	0.985
STV-8	0.315	0.412	0.976

studies where they reported the effect of monomer, drug and crosslinker content on dissolution kinetics.

4. CONCLUSIONS

The SA/TG blend membranes were prepared using different concentrations of SA, drug and GA. The concentrations of TG and GA had an influence on the morphology, mechanical, and swelling property of the blend membranes. The % swelling of the blend membranes increased with either increasing of SA content or decreasing crosslinking densities and TG content. The maximum swelling of the membranes was achieved in about 10-12 h. 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 highest amounts of TG showed the highest percentage of drug release and lowest amount of cross-linking agent which showed the highest percent of drug release. These preliminary results suggested that SA/TG 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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