JOURNAL OF Materials CHEMISTRY

Surface modification of chitosan membranes by alkane vapor plasma

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Received 4th December 2000, Accepted 1st March 2001
First published as an Advance Article on the web 19th March 2001

Alkane (petroleum ether) vapor plasma technique was used for surface modification of chitosan membranes to control their permeation rate of water-soluble drugs and metabolites. Water contact angles of the chitosan surface increase from 13° to 23° after plasma treatment at 93 W for 60 min, and from 13° to 26° after plasma treatment at 119 W for 30 min, indicating reduced hydrophilicity of the membrane surface. Mechanical properties such as tensile strength and elongation-at-break of the chitosan membranes were also improved. In particular, there was a 6–7 fold increase in tensile strength in the wet state for the chitosan membrane treated at 93 W for 30 min. Permeation coefficients through the chitosan membrane plasma treated at 93 W for 30 min for urea, creatinine, uric acid, and *cis*-DDP decreased by 54.0%, 83.3%, 64.7% and 47.6%, respectively.

1. Introduction

Chitosan is a polysaccharide-based biopolymer and is usually obtained from alkaline *N*-deacetylation of chitin, a natural biopolymer widely found in the shells of crabs, lobster, krill and shrimps. Chitosan and its derivatives have been studied for applications as separation membranes,[1,2] and as biomedical materials such as skin substitutes and wound dressing materials, matrixes for immobilization of enzymes and cells, and carriers for drug and gene delivery[3–7] because of their good biocompatibility and biodegradability.[8] To achieve the desired bulk or surface properties, modification of chitosan by means of polymer blending,[9] cross-linking,[10] and surface chemical modification[5] have been recently carried out. We previously reported that by incorporating gelatin into chitosan membranes, higher release rates of anti-cancer drug (5-Fu) and higher permeation rates of low molecular weight metabolites[9] can be achieved. On the contrary, cross-linking of chitosan membranes with glutaraldehyde leads to lower permeation rates of soluble solutes.[11] Among various kinds of modifications, surface modification by plasma has often proved advantageous because it usually is confined to the top several tens of nanometres of the surface, and has little effect on the bulk membrane materials.

It is known that chitosan membranes are highly hydrophilic and readily form hydrogel membranes in aqueous environments with high permeation rates for water-soluble drugs and small molecule solutes. We are interested in controlling the release rate of water-soluble drugs and solute permeation of a chitosan membrane by adjusting its surface hydrophilicity/hydrophobicity using plasma treatment. Gas plasmas using O_2, N_2, H_2, He, Ar, $CHCl_3$, NH_3, SO_2[12–17] have been used to increase polymer surface hydrophilicity, while aldehyde[18] and fluorocarbon[19,20] plasmas have proved effective in reducing surface hydrophilicity. Here we report a novel alkane plasma technique for chitosan membrane surface modification. A mixture of small alkane molecules, petroleum ether, was chosen as the plasma process gas and characterizations of the plasma modified chitosan membrane including permeation data are reported here.

2. Experimental

2.1. Materials

Chitosan ($M_n = 9.20 \times 10^5$, degree of deacetylation = 90%) was prepared from lobster shells.[4] Acetic acid, sodium hydroxide, petroleum ether (bp 30–60 °C) and other regents were purchased in analytical grade and used as received.

Urea (MW 60), creatinine (MW 113), uric acid (MW168), and cisplatin (*cis*-DDP, MW300) were kindly supplied by the First Affiliated Hospital of Anhui Medical University, Hefei, China.

2.2. Preparation of chitosan membranes

Chitosan was dissolved in dilute acetic acid solution and the solution was maintained at 50 °C for 3 h with stirring. Then the solution was filtered through a filter with 0.2 μm pore diameter and cast on a clean glass dish. The dish was kept at 50 °C until the solvent was completely evaporated. The dry membrane so obtained was immersed in 30 wt% ethyl alcohol aqueous solution at room temperature for 24 h, and then rinsed with distilled water to remove all traces of alkali, followed by drying at 60 °C under vacuum overnight. The as-prepared chitosan membranes were stored in a desiccator for further use. The membrane thickness was in the range of 60–80 μm as measured by a micrometer.

2.3. Plasma treatment

A tubular quartz plasma reactor was used in this study. The rf plasma power at 13.56 MHz could be adjusted between 52.5 to 119 W. The chitosan membrane was placed in the center between the two electrodes. The whole reactor system was evacuated for at least 30 min and then sufficiently purged with petroleum ether. Once the gas pressure was set to 92 Pa by adjusting the petroleum ether flow rate, the plasma reactor was turned on. A light purple discharge glow instantly appeared between the two electrodes, and the chamber pressure dropped

 DOI: 10.1039/b009688l

to 13 Pa. The reactor temperature was kept at a temperature less than 45 °C *via* regular interval discharge.

2.4. Characterization

Thermogravimetric (TG) analysis was conducted with a Model WRT-3 analyzer under N_2 at a heating rate of 10 °C min^{-1}. The morphology of the chitosan membrane was examined before and after plasma treatment with a Hitachi X-650 scanning electron microscope (SEM).

The hydrophilicity of the membranes was characterized by their water contact angles with deionized water using a Model JY-82 contact angle analyzer at 25 °C. The values of θ reported in this study are averages of at least five membranes (deviation < 5%) prepared independently.

Permeation measurements were conducted in a two-compartment quartz cell with the chitosan membrane as the partition membrane. 60 mL of an aqueous solution with a specified initial concentration of the chosen solute was loaded into the left compartment of the cell and the same volume of deionized water was put into the right compartment. Both compartments were well stirred to ensure uniform concentration. The cell was immersed in a constant temperature water bath set at 36 ± 0.5 °C. After a given interval of time, 3 mL aliquots were taken from both compartments, and the concentrations of the solute were determined using a Shimadzu UV–visible spectroscope. The membrane was thoroughly washed with deionized water before another test was conducted. Several tests were usually performed on the same membrane and the average permeation rate (deviation < 5%) was reported. Urea, creatinine, uric acid and cisplatin were used as solutes in the present study. Initial concentrations of the solutes, urea, uric acid, creatinine and *cis*-DDP, are 8.73×10^{-3}, 8.20×10^{-5}, 1.00×10^{-3} and 6.71×10^{-5} mol L^{-1}, respectively. The solute permeation coefficient P was calculated from the following equation, which was obtained from a mass balance equation;[21] that is,

$$P = \frac{-d}{A(1/V_1 + 1/V_2)t} \ln\left[\left(1 + \frac{V_1}{V_2}\right)\frac{C_t}{C_0} - \frac{V_1}{V_2}\right]$$

where V_1, V_2, A, d, C_0, and C_t were the volumes of the concentrate and the dilute compartments, membrane area, membrane thickness, and concentrations in the concentrate compartment at times 0 and t, respectively.

Tensile strength measurements of the membrane in the dry and wet states were carried out at room temperature with a Shimadzu AutoGraph DCS-5000 Test Machine, with samples of 20 mm × 4 mm size at a displacement rate of 20 mm min^{-1} at room temperature. Samples immersed in distilled water for 24 h were used for the wet measurement. Tests of properties of each membrane were repeated five times and the average values (deviation < 10%) were obtained.

3. Results and discussion

3.1. Weight change of chitosan membranes by plasma

The surface of the chitosan membrane was exposed to glow discharge plasma, and its weight was measured before and after the treatment. Fig. 1 shows the weight change of the chitosan membrane with plasma treatment time. Under petroleum ether plasma, the weight of the chitosan membrane initially decreases slightly with time, and remains almost constant after 45 min. For polymers treated by non-deposition gas (O_2, N_2, or He) plasmas, there is only etching and therefore the sample weight decreases linearly with the plasma treatment time.[13,22] In our case, two processes, etching of the membrane and deposition of polymer or oligomer, could occur during plasma treatment. Initially etching dominates and the sample weight drops. Very quickly, however, oligomer deposition starts and these two processes balance each other so that little weight change was observed. Alkane (petroleum ether) molecules can be activated by plasma to produce highly active alkyl radicals that can react with the chitosan membrane surface, and can also readily polymerize to produce oligomers and deposit them on the membrane surface. This was supported by SEM observations. SEM images (Fig. 2) show that the chitosan surface was fairly smooth before plasma treatment while afterward etching lines and deposited oligomer blocks were observed on the membrane surfaces. It is speculated that cross-linking may also take place at the membrane surface molecules during alkane plasma treatment.

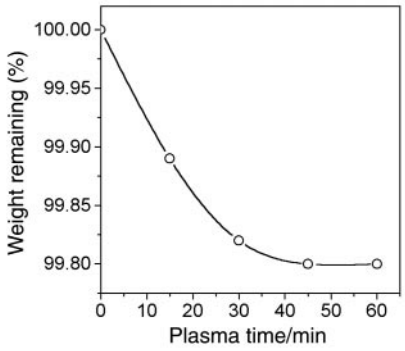

Fig. 1 Weight change of chitosan membrane *versus* plasma treatment time. The membrane was treated with petroleum ether vapor plasma at 119 W.

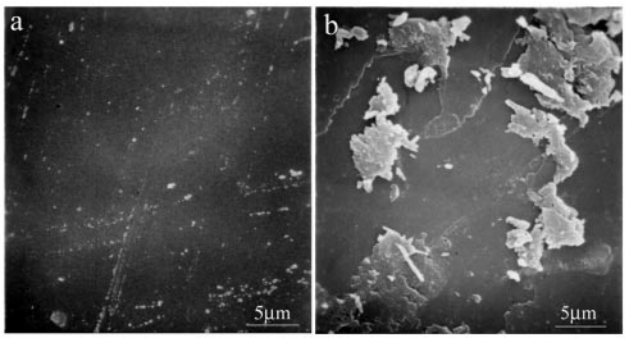

Fig. 2 SEM images of chitosan membrane before and after petroleum ether vapor plasma treatment. (a) untreated; (b) treated at 93 W for 60 min.

3.2. Thermal stability

Thermogravimetric (TG) analysis in nitrogen was used to examine the thermal stability of the chitosan membrane before and after plasma treatment. TG curves of untreated and treated chitosan membranes are presented in Fig. 3. At $T < 125$ °C,

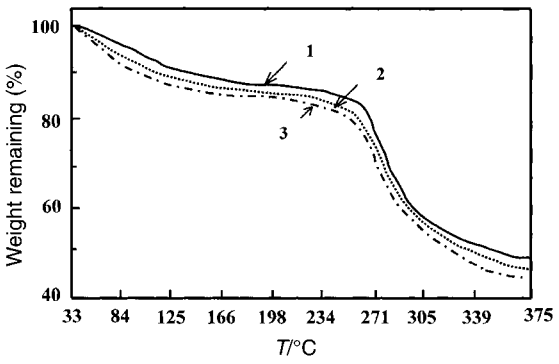

Fig. 3 TG curves of chitosan membranes before and after petroleum ether vapor plasma treatment. (1) untreated; (2) treated at 93 W for 30 min; (3) treated at 93 W for 60 min.

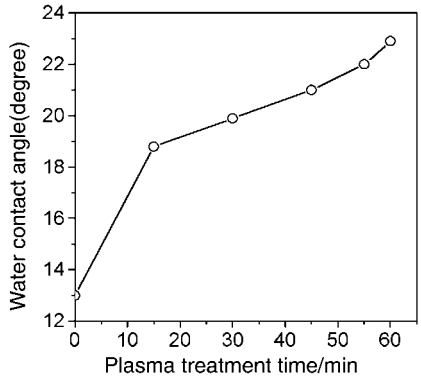

Fig. 4 Water contact angle of chitosan membranes *versus* plasma treatment time. The membrane was treated with petroleum ether vapor plasma at 93 W.

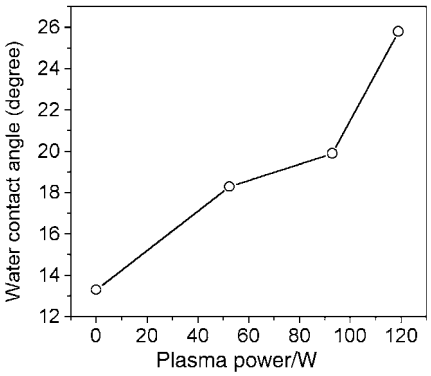

Fig. 5 Water contact angle of chitosan membranes *versus* plasma power for petroleum ether vapor treatment for 30 min.

there is approximately 10% weight loss for the untreated chitosan membrane, which is caused by desorption of water occluded in the chitosan network. The pyrolysis of untreated chitosan membrane starts from around 268 °C. The pyrolysis temperature for plasma-treated membranes is a little lower, and it decreases with treatment time. The slight decrease of pyrolysis temperature may be explained by the fact that plasma-deposited oligomers have a lower decomposition temperature than bulk membrane material. It is noted here, however, that the overall change of pyrolysis temperature is minor and this confirms that the modification by plasma is confined to the surface of the membrane.

3.3. Hydrophilicity reduction of chitosan membranes

The water contact angles of surfaces for the chitosan membranes *vs.* plasma treatment time are plotted in Fig. 4. At the same power of 93 W, the water contact angle of the chitosan surface gradually increases from 13.0° for the untreated membrane to 22.9° after 60 minutes treatment. For the same plasma treatment time of 30 minutes (Fig. 5), the water contact angle increases with plasma power. Clearly petroleum ether plasma treatment reduces the hydrophilicity of chitosan membrane surfaces.

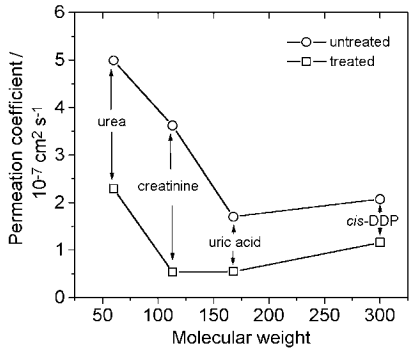

Fig. 6 Permeation coefficients of urea, creatinine, uric acid, and *cis*-DDP *versus* their molecular weights through chitosan membranes before and after petroleum ether vapor plasma treatment at 93 W for 30 min.

3.4. Permeation properties of chitosan membranes

Low molecular weight metabolites such as urea, uric acid and creatinine and anti-cancer drugs such as *cis*-DDP have been commonly used to study the permeation behavior of membranes for biomedical applications.[9,11,23–29] They are also chosen in the present study to illustrate the permeation properties of chitosan membranes before and after modification. There are significant decreases in the permeation coefficients of the metabolites and *cis*-DDP through chitosan membranes that have been plasma treated at 93 W for 30 min (Fig. 6 and Table 1). Permeation coefficients also decrease with plasma treatment time (Table 1). For plasma treatment at 93 W for 30 min, the reduction percentages of permeation coefficients for urea, creatinine, uric acid and *cis*-DDP are 54.0%, 83.3%, 64.7%, and 47.6%, respectively (Table 1).

Solute transport through chitosan hydrogel membranes is generally described by two mechanisms: the pore diffusion mechanism and solution–diffusion mechanism.[21,30] For a highly hydrated chitosan membrane, the former mechanism usually dominates. The diffusion rate of the solute depends on the average pore size of the membrane, the molecular size of the solute and its water solubility. Alkane plasma treatment deposits hydrophobic alkane oligomers and may cause partial cross-linking at the surface, leading to a more hydrophobic and more rigid surface layer that could reduce membrane hydration. As a result, plasma-treated membranes have a lower water content inside the polymer networks. In addition, the pores at the membrane surface may also become smaller after plasma treatment. These explain why plasma treated chitosan membranes possess lower permeation than untreated ones. The dependence of permeation coefficients on molecular weight is plotted in Fig. 6. For both untreated and plasma treated chitosan membranes, permeation coefficients tend to decrease with increase of molecular weight of the solute except for *cis*-DDP. This could be explained by the fact that *cis*-DDP is most easily hydrated.[31]

3.5. Mechanical properties

The mechanical properties of chitosan membranes before and after plasma treatment were investigated. The tensile strength

Table 1 Permeation coefficients of urea, creatinine, uric acid, and *cis*-DDP though chitosan membranes before and after petroleum ether vapor plasma treatment at 93 W for 30 min

		$P/10^{-7}$ cm^2 s^{-1}				Reduction of P (%)			
Sample No.	Plasma conditions	Urea	Creatinine	Uric acid	*cis*-DDP	Urea	Creatinine	Uric acid	*cis*-DDP
1	Untreated	5.0	3.6	1.7	2.1				
2	93 W, 15 min	3.8	3.3	1.0	1.2	24.0	8.3	41.2	42.9
3	93 W, 30 min	2.3	0.6	0.6	1.1	54.0	83.3	64.7	47.6

Table 2 Mechanical properties of chitosan membranes before and after petroleum ether vapor plasma treatment

Sample No.	Plasma conditions (W, min)	Tensile strength/MPa		Elongation at break (%)	
		Dry	Wet	Dry	Wet
1	Untreated	60.8	4.6	9.0	70.0
2	93 W, 15 min	61.0	26.1	13.7	75.7
3	93 W, 30 min	63.0	29.3	11.3	54.5

and elongation-at-break of chitosan membranes in the dry and wet states are listed in Table 2. In the dry state, the tensile strength and elongation-at-break of membranes slightly increase after petroleum ether vapor plasma treatment. After the membrane samples are swollen in distilled water at room temperature for 24 h, however, plasma treated membranes are shown to have tensile strengths that are 6–7 times higher than the untreated membrane. These results suggest again that swelling of the chitosan membranes may have decreased after plasma treatment, and therefore the tensile strength of the membrane is significantly improved. This is consistent with the permeation results discussed previously. It is noted that elongation-at-break of the chitosan membrane is not significantly affected by plasma treatment (Table 2) both in the dry and wet states.

4. Conclusions

Alkane (petroleum ether) vapor plasma surface treatment is an effective technique for control of permeation and drug release rate of chitosan membranes. Membrane weight change during plasma treatment and TG and SEM results seem to suggest that the surface modifications include etching and alkyl oligomer deposition. Contact angle measurements show clearly that hydrophilicity of the membrane surface decreases with plasma treatment time and plasma power. Plasma treatment appears to improve the mechanical properties of chitosan membranes, especially the tensile strength in wet state. Permeation experiments show a significant decrease in the permeation coefficients for urea, creatinine, uric acid, and *cis*-DDP through plasma modified chitosan membranes.

Acknowledgements

The National Natural Science Foundation of China, CE-CERT of U.C.-Riverside are gratefully acknowledged for their financial supports.

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