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Research Article

PREPARATION AND EVALUATION OF POLYVINYL ALCOHOL TRANSDERMAL MEMBRANES OF SALBUTAMOL SULPHATE

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ABSTRACT

The antiasthamatic drug (Salbutamol sulphate) was successfully incorporated into glutaraldehyde crosslinked IPN membranes of PVA, chitosan, and sodium alginate. Mechanical properties such as tensile strength and elongation of the membranes were determined along with permeability properties and drug entrapment efficiency. *In vitro* drug release profile was determined using Keshary-Chien diffusion cell. The membranes produced were found to be thin, smooth and transparent; exhibited high tensile strength and elongation. Rate of swelling as well as water vapor transmission were high for PVA membranes (pure) compared to their IPNs. The results indicated that blending of PVA with other polymers and crosslinking with GA led to the higher entrapment efficiency. The drug release profiles showed that the drug permeated through the membranes was up to 20 hrs.

Keywords: IPN ((Interpenetrating Polymer Network), Chitosan, Crosslinking, Membranes, Transdermal

INTRODUCTION

The biomaterials research field has broadened in the last 3 decades including drug delivery systems, immunological kits and biosensors[1-7]. Extensive efforts have been focused on placing a drug delivery system in a particular region of the body for maximizing drug availability and minimizing the dose dependent side effects. Apart from the development of oral controlled release (CR) formulations, transdermal drug delivery systems (TDDS) using thin polymeric membranes have been widely studied[8,9]. Treatment of chronic diseases such as asthma and rheumatoid arthritis by transdermal route of drug administration might prove to have several advantages over other routes of drug administration[10, 11]. Plasticization of the membranes can be achieved by blending the polymer with another polymer, by crosslinking or by both crosslinking and blending. The advantages of such polymers are not only to create additional free space to accommodate the drug, but also that these systems are biocompatible[12].

The blend materials from either synthetic or natural polymers alone are not always able to meet all the complex demands of the biomaterials. The success of synthetic polymers (as biomaterials) relies on their wide range of mechanical properties, transformation processes, that allow a variety of different shapes to be easily obtained, and low production cost. Biological polymers present good biocompatibility, but their mechanical properties are often poor. Therefore, biologically important polymeric materials based on the blends of synthetic and natural polymers have been prepared, such as poly(N-vinyl-2-pyrrolidone)-kappacarrageenan (PVP/KC), poly(N-vinyl-2-pyrrolidone)-iota-carrageenan(PVP/IC)[12], poly (ethylene oxide)-hydroxypropyl methylcellulose (PEO/HPMC) [13], poly(vinyl alcohol)-chitosan (PVA/C) etc[14].

Numerous studies have been reported on diffusive permeabilities of solutes in PVA gel membranes[15-18]. Chitosan, derived from chitin by deacetylation, is a unique basic polysaccharide. It is water soluble at low pH due to the protonation of the glucosamine moieties. Chitosan hydrogel has some advantages of nontoxicity, biocompatibility and biodegradability[19]. According to Miya et al[20] chitosan forms a clear homogenous blend with PVA and tensile strength of this membrane was greater than the component value. Alginate is a polysaccharide, which is derived from brown seaweed and comprises blocks of guluronic and mannuronic acids. All the polymers are biocompatible, biodegradable and hydrophilic, suitable for the entrapment of water-soluble drugs[21]. The water solubility of the polymers is an advantage in eliminating the use of noxious solvents during processing.

Salbutamol sulphate, an antiasthmatic drug has a biological half-life of 4 hrs and needs to be administered several times a day[22]. For the chronic management or prophylactic therapy of asthma, a long acting formulation particularly transdermal delivery would be of benefit[23]. Hence we have tried to develop PVA transdermal membranes for the release of salbutamol sulphate in this study. Mechanical properties, weight and thickness uniformity, swelling rate, drug entrapment efficiency, and *in vitro* drug release from the membranes were also determined.

MATERIALS AND METHODS

The gift sample of salbutamol sulphate was supplied by Sun Pharma, Baroda, India. The 75-85 % deacetylated chitosan with a viscosity of 200-800 cP measured by Brookfield viscometer in 1% w/v of chitosan solution, in 1% v/v acetic acid solution was purchased from Aldrich Chemical Company, USA. Sodium alginate, polyvinyl alcohol, glutaraldehyde (GA) solution (25 % v/v) and hydrochloric acid were purchased from s.d. Fine-Chemicals Ltd. Mumbai, India and used as received. Distilled water was used throughout the study.

Preparation of drug loaded transdermal membranes[24]

PVA and the IPN with chitosan and sodium alginate were used for the preparation of membranes. PVA and sodium alginate solutions were prepared separately by dissolving the required quantities in distilled water, whereas chitosan solution was prepared by dissolving the polymer in 1 % v/v acetic acid solution with stirring at 40 °C. All the solutions were allowed to stand overnight to remove the air bubbles. As shown in Table 1, varying proportions of polymers in each pair were mixed. The final concentration of mixture of polymers in each solution was 3 % w/v. Salbutamol sulphate (20 w/w of dry weight of polymer) was incorporated in polymer solutions by stirring on magnetic stirrer (30 min), to get homogeneous solution. These polymeric solutions were poured into petri dishes of known diameter. The rate of evaporation of solvent was controlled by inverting a funnel. After complete drying, the membranes were taken out and crosslinked by dipping them in 100 ml of methanol containing 1 % w/w of GA with 0.1 ml of conc. HCl. The temperature was maintained at 40 ºC. After 30 min, the crosslinked membranes were washed in ethanol to remove the surface bound traces of acid and then with distilled water to remove the unreacted GA. The membranes were dried in air and stored in a desiccator.

Thickness and weight variation[25]

The thickness was assessed at six different points of the membranes using micrometer screw gauge. For each formulation, three randomly selected membranes were used. For weight variation test, three membranes from each batch were weighed individually and the average weight was calculated.

Determination of tensile strength and percentage elongation[26]

Membrane strip measuring (10 mm x 50 mm) in dimension and free from air bubbles or any other physical imperfections was held in between two clamps positioned at a distance of 3 cm. During measurement, the membrane was pulled by top clamp at a rate of 0.5 mm/sec, to a distance of 5 cm before returning to the starting point. The force and elongation were measured when the membranes broke. The tensile strength and elongation at break were calculated

Tensile strength = Breaking force (N)/ Cross-sectional area of sample (mm^2)

Elongation (%) = Increase in length at breaking point (mm)/ Original length (mm) x 100

Swelling study[27]

Completely dried membranes with a specified area (1 cm^2) were weighed and put in desiccators for 24 hrs. They were removed and exposed to relative humidity conditions of 75 % in desiccators. Weight was taken on a single pan balance periodically until a constant weight was obtained. The swelling capacity of the membranes (in weight %) was calculated in terms of percentage increase in weight of membrane over the initial weight of the specimen. The experiments were carried out in triplicate and the average values were used for the calculation. The percentage degree of swelling (DS) was calculated as

$DS\ (\%) = W_s - W_{d/}\ W_d \times 100$

Where W_s and W_d indicate the weight of the swollen and dry membranes respectively.

WVTR studies[28]

WVTR studies were carried out using glass vials of equal diameter as the transmission cells. These cells were washed and dried in an oven. About 1 g of fused calcium chloride was taken in the cells and the polymeric membranes (1 cm^2) were fixed over the brim with the help of an adhesive. Then the cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride (200 ml). The humidity inside the desiccator was measured by a hygrometer. The cells were weighed everyday up to seven days and the amount of water vapor transmitted through the membranes was calculated. The experiments were carried out in triplicate and the average values were used for the calculation. The amount of water vapor transmitted was calculated using the formula

$$WVTR=WL/S$$

where, W-water vapour transmitted in g, L is the thickness of film in cm and S is surface area in cm^2.

Entrapment efficiency[10]

Membranes with a specified area (1 cm^2) were cut into small pieces, weighed and put into a 100 ml volumetric flask. About 50 ml of distilled water was added, gently heated to 45 °C for 15 min and kept for 24 hrs with occasional shaking. Contents were diluted upto 100 ml with distilled water. Similarly, a blank was carried out using a drug free membrane. The solutions were filtered and absorbance was measured using a UV spectrophotometer at 276 nm. Corresponding drug concentrations in the samples were calculated from the calibration plot generated by regression of the data taken in triplicate.

Entrapment efficiency = Practical drug content/ Theoretical drug content x 100

***In vitro* skin permeation study**[29]

In vitro drug release study was performed using distilled water in a Keshary-Chien diffusion cell. Appropriate sized polymeric membranes were mounted with excised rat abdominal skin in between donor and receptor compartments of the diffusion cell and were held tightly by springs. The donor compartment was empty, whereas the receptor compartment was filled with distilled water. The magnetic stirrer was set at 100-rpm and the temperature was maintained at 37 ºC. The amount of drug released was determined by withdrawing 5 ml aliquots at regular time intervals. The volume withdrawn was replaced with an equal volume of fresh, prewarmed (37^0C) distilled water. Samples were analyzed using UV spectrophotometer at 276 nm. Amount of drug released was calculated using the calibration curves, constructed from the reference standards.

Skin irritancy test[30]

The primary skin irritation test was performed on seven healthy male albino rabbits weighing between 2 to 3.5 kg. Adhesive tape (Johnson plast) was used as control patch. The transdermal membrane containing the drug and 5 cm^2 in area were used as test patches. The control patch was placed on the left dorsal surface of each rabbit whereas the test patch was placed on the identical site on the right dorsal surface of the rabbit. The patches were removed after a period of 24 hrs with the help of alcohol swab and the skin was examined for erythema/edema.

RESULTS AND DISCUSSION

By using the solvent casting technique, the IPN transdermal membranes of PVA, chitosan and sodium alginate were prepared. Treatment of membranes with an aqueous aldehyde solution (GA was used as a crosslinking agent) containing a small amount of mineral acid converts one of the film components PVA, to insoluble polyvinyl acetal. Sufficient crosslinking was obtained to give tough and water insoluble membranes with little swelling when immersed in aqueous solutions.

The thickness of the membranes (with varying ratios of PVA, chitosan, and sodium alginate) varied between 252 µm to 315 µm. The low values for standard deviation indicate physical uniformity of the membranes. The weights measured for the same ranged between 20 mg to 32 mg.

The results of tensile strength and percentage elongation are mentioned in Table 1. The GA crosslinked PVA membranes had tensile strength of 4.9 kg/cm^2. Sodium alginate is a very strong material with a great stress and Young modulus, and chitosan has good gelling properties. The incorporation of sodium alginate and chitosan into PVA, made the membranes stronger. PVA-chitosan membranes showed better strength i.e. PVA:chitosan in the ratio of 2:1 (7.62 kg/cm^2), 1:2 (13.34 kg/cm^2) and 1:1 (11.88 kg/cm^2) compared to PVA-sodium alginate at the same composition i.e. PVA:sodium alginate 2:1 (5.62 kg/cm^2), 1:2 (9.44 kg/cm^2) and 1:1 (7.81 kg/cm^2) respectively.

Table 1: Composition of various fromulations

FORMULATION CODE	COMPOSITION OF PVA: CHITOSAN	COMPOSITION OF PVA: SODIUM ALGINATE	THICKNESS (µm)	WEIGHT (mg)	TENSILE STRENGTH (kg/cm^2)	PERCENTAGE ELONGATION
F1	1:0	1:0	289 ± 2.6	21.1 ± 0.25	4.9 ± 0.30	39.17 ± 1.11
F2	—	1:1	256 ± 0.10	22.0 ± 1.2	7.81 ± 0.18	38 ± 0.8
F3	—	1:2	286 ± 2.1	28.12 ± 0.2	9.44 ± 0.19	35 ± 0.16
F4	—	2:1	252 ± 0.7	24.4 ± 0.6	5.62 ± 0.22	37 ± 0.22
F5	1:1	—	312 ± 0.11	28.22 ± 0.2	11.88 ± 0.12	31 ± 0.6
F6	1:2	—	315 ± 2.1	31.13 ±0.12	13.34 ± 0.9	23 ± 0.98
F7	2:1	—	270 ± 2.12	29.12 ± 0.66	7.62 ± 0.19	31.82 ± 0.15

The membranes were also having very good elongation properties as shown in Table 1. Here the IPN membranes of PVA with alginate showed better elongation compared to chitosan-PVA membranes. Mechanical properties of the blends were enhanced relative to those of pure PVA.

The swelling of the membranes was calculated from the weight difference relative to the final weight. The results of swelling study are presented in Table 2. GA crosslinked PVA membranes showed swelling of 14.7 %. The IPN membranes with various compositions of PVA and chitosan (2:1, 1:2 and 1:1) showed swelling rate of 8.4 %, 6.1 % and 7.8 % respectively whereas the IPN membranes of PVA-sodium alginate in the composition of (2:1, 1:2 and 1:1) showed to have 12.8 %, 10.2 % and 11.9 % of swelling respectively.

The swelling ratio is significantly dependent on the amount of the crosslinker used for crosslinking. The swelling behavior can be explained by the permeation mechanism in hydrogels, i.e. in the hydrogels the water permeation occurs via a pore mechanism, the reduction in water uptake accompanying increased crosslinking density being an important factor [12].

Water vapor transmission through the membranes determines the permeability characters of the membranes. All the membranes were permeable to water vapor (Table 2), PVA membranes were most permeable to water vapor (1.07×10^{-3} g.cm^2/day). Membrane permeability was reduced after formation of IPN and processing with GA. The membrane permeability was in the order of F4 (8.1×10^{-4} g.cm^2/day) > F2 (5.18×10^{-4} g.cm^2/day) > F3 (3.97×10^{-4} g.cm^2/day) > F7 (3.50×10^{-4} g.cm^2/day) > F5 (2.93×10^{-4} g.cm^2/day) > F6 (2.59×10^{-4} g.cm^2/day). Thickness and area of the membranes available for water vapor transmission were considered when calculating the membrane permeability.

The membranes were analyzed for percentage entrapment efficiency using UV spectrophotometry and these data are presented in Table 2. The entrapment efficiency represents the amount of drug entrapped in the matrix, which varies considerably with the type of network. GA crosslinked PVA membranes were found to entrap 83.06 % of drug. IPN formation and crosslinking with GA led to the increased intermolecular space, which led to the higher percentage of entrapment efficiency. PVA - chitosan IPN in the composition of 2:1, 1:2 and 1:1 showed lesser drug entrapment (86 %, 84 % and 87.1 % respectively) compared to PVA- sodium alginate IPN (88 %, 85 % and 89.6 %) in the same composition.

***In vitro* skin permeation study**

In vitro permeation of salbutamol sulphate through excised rat abdominal skin from different membranes is shown in Fig 1. The *in vitro* drug release studies were carried out in distilled water at 37 °C using the Keshary-Chien diffusion cell. The permeation profiles showed that the cumulative amount of drug permeated was up to 20 hrs, PVA-sodium alginate IPN membranes released more amount of drug compared to those of PVA-chitosan membrane. Pure PVA membrane released about 93% of drug. All the polymers used for preparation of the membranes are hydrophilic in nature and upon crosslinking they have been converted to partially hydrophobic matrices which have less affinity for water; this results in decrease in thermodynamic activity of the drug in the membrane and decreased drug release [31]. Addition of chitosan to PVA retarded the drug release rate.

TABLE 2: CHARACTERIZATION OF IPN TRANSDERMAL MEMBRANES

FORMULATION CODE	SWELLING (%)	WVTR (g.cm^2/day) X 10^{-3}	ENTRAPMENT EFFICIENCY (%)
F1	14.7 ± 0.4	1.07 ± 0.13	83.06 ± 1.2
F2	11.9 ± 2.5	0.51 ± 0.10	89.6 ± 1.7
F3	10.2 ± 1.7	0.39 ± 0.2	85.0 ± 2.1
F4	12.8 ± 3.2	0.81 ± 0.45	88.0 ± 3.1
F5	7.8 ± 0.9	0.29 ± 0.33	87.1 ± 1.1
F6	6.1 ± 1.2	0.25 ± 0.16	84 ± 1.9
F7	8.4 ± 0.6	0.35 ± 0.08	86 ± 1.1

Chitosan can be considered as a microporous material. When a microporous material is below its glass transition temperature(T_g), the thermal movement of the chain segment is restricted in such a way that the pores result from irregularities in molecular packing. The size of the polymer matrix is found to decrease gradually with time, and towards the end of the drug release, the matrix disintegrates into pieces.

On the other hand, the decrease in the permeability is attributable to the remarkable decrease in the diffusion coefficient due to decrease in the mesh size; highly crosslinked membranes have smaller mesh size.

Skin irritation test

After a primary skin irritation test performed on rabbits there was no evidence of erythema/edema either with the control or test membranes, which indicates PVA and its IPN with other polymers are compatible with skin and so the membranes could suitably be used as carriers for transdermal drug delivery system.

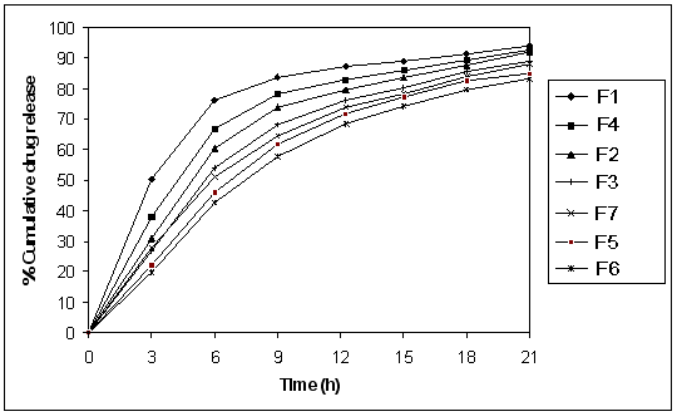

Fig. 1: *In vitro* release profile of salbutamol sulphate from different formulations

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