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## Transdermal Delivery of Antiasthmatic Drug through Modified Chitosan Membrane

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Chitosan has been chemically modified by treating with two different aldehydes *viz* acetaldehyde and propionaldehyde to form Schiff's bases. Schiff bases of chitosan with acetaldehyde and propionaldehyde were named as polymer-I and polymer-II, respectively. FTIR confirmed the reaction carried out on chitosan. Chemically-modified chitosan and plain chitosan were compared for the film forming capacity, swelling property and water permeability rate. Further, the films were incorporated with antiasthmatic drug, salbutamol sulphate by mixing with polymer solution during casting. Drug loading and permeation characteristics were compared for plain chitosan and chemically modified chitosan. Films produced were transparent, smooth and flexible without plasticization. Water permeability for chitosan was  $1.13 \times 10^{-4}$  g.cm<sup>2</sup>/day. It was found to be  $8.10 \times 10^{-4}$  and  $5.18 \times 10^{-4}$  g.cm<sup>2</sup>/day for polymer-I and polymer-II, respectively. Percentage entrapment of salbutamol sulphate in the membranes of plain chitosan, polymer-I and polymer II was 1.22, 1.83 and 1.40 mg/cm<sup>2</sup>, respectively. The time taken for permeation of 50 % of drug ( $T_{50}$ ) through excised rat skin was 118, 62 and 88 min for chitosan, polymer-I and polymer-II, respectively.

Treatment of chronic diseases such as asthma, rheumatoid arthritis by transdermal route of drug administration might prove to have several advantages over other routes of drug administration<sup>1-3</sup>. However, delivery of drugs through transdermal drug delivery system (TDDS) is limited due to its difficulty in absorption of active agents through barriers of skin. Addition of penetration enhancers, modification in membrane delivery system<sup>4,5</sup> and alteration in the physico-chemical properties<sup>6</sup> of the drug may improve the efficiency of TDDS. Polymeric membrane matrix types of transdermal systems have been found to be more effective due to their tailor-made properties<sup>1</sup>.

Chitosan is a naturally occurring biocompatible, cheaply available polymer<sup>7</sup>. This naturally occurring polymer has a repeating structural unit of 2-acetamido-2-deoxy- $\beta$ -D-glucose<sup>8</sup>. Chitosan has been proven to be an ideal polymer not only in biomedical but also in various indus-

trial applications. Chitosan is insoluble in water but soluble in acidic water. Films produced by casting chitosan solution when applied on skin cause irritation due to the presence of traces of acid. Hence it is necessary to wash the films repeatedly to remove any traces of acid. Chemical modification of chitosan and its applications have been reported<sup>9</sup>. Chitosan has been modified by graft co-polymerization and by blending with water soluble polymers<sup>9</sup>. There are also reports of studies on chitosan blend with polyvinyl alcohol (PVA) membranes<sup>10</sup>. According to Miya *et al.*<sup>10</sup> chitosan forms a clear homogenous blend with PVA and tensile strength of the blend membrane was greater than the component value. Uragami, *et al.*<sup>11</sup> prepared a crosslinked chitosan/PVA blend with a fixed amount of crosslinking agent and studied the active transport of the halogen atom through the chitosan/PVA membrane.

Salbutamol sulphate, an antiasthmatic drug was selected for the study. It has a biological half-life of 4 h and needs to be administered several times a day. In this study, we report the possible usage of chitosan and chemically

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modified chitosan for transdermal drug delivery. Salbutamol was incorporated into newly fabricated TDDS. *In vitro* drug release study through excised rat abdominal skin was performed in Keshary-Chien diffusion cell at 37° using distilled water as dilution media.

## MATERIALS AND METHODS

Chitosan was purchased from Aldrich Chemicals, USA. Propionaldehyde, acetaldehyde and acetic acid were purchased from S. D. Fine Chemicals, Mumbai. Gift sample of salbutamol sulphate was obtained from Sun Pharma, Vadodara. Distilled water was used throughout the study. Animal experiments were done as per the approved protocol submitted to the chairman, Institutional Animal Ethics Committee of the college.

### Chemical modification of chitosan:

Chitosan (2% w/v) solution was prepared by dissolving the polymer in 1 % acetic acid solution prepared in distilled water. After ensuring complete dissolution of chitosan, 50 ml of the solution was stirred with 2 g of either acetaldehyde (to prepare polymer-I) or propionaldehyde (to prepare polymer-II). Stirring was continued for 3 h at 60°. Later, the polymer solutions were added to acetone to precipitate the chemically modified chitosan<sup>12</sup>.

### Fourier transform infrared spectroscopy (FTIR) studies:

FTIR measurements were done on Nicolet, Impact 410 at University Sophisticated Instrument Center, Karnataka University, Dharwad. Polymer samples were crushed with potassium bromide and pellets were formed. To ensure the uniform mixing, the pellets were broken and were reformed at high pressure.

### Fabrication of films:

Solutions of polymer-I, polymer-II and plain chitosan were prepared by dissolving 2 g of polymer in 100 ml of 1.0% acetic acid solution. To the above prepared polymeric solutions, 20 % w/w (dry weight of polymer) of salbutamol was added and stirred for half an hour. Drug containing polymeric solutions were poured into a glass bangle (10 cm diameter), placed on a mercury surface in a Petri dish<sup>13</sup> and kept in an oven at 40° for complete drying. Films produced were washed with 50 % ethanol to remove surface bound traces of acid.

### Estimation of % entrapment of drugs:

Membranes with a specified area (1 cm<sup>2</sup>) were weighed and put in to a 100 ml volumetric flask. About 50 ml of dis-

tilled water was added and maintained for 24 h with occasional shaking. Then the volume was made up to 100 ml with distilled water. Similarly, a blank was carried out using drug-free membrane. The solution was filtered and absorbance was measured at  $\lambda_{max}$  of 276 nm using a UV spectrophotometer.

### Permeability measurement:

Water vapor transmission rate (WVTR) studies were carried out according to the method proposed by Rao and Diwan<sup>14</sup> 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<sup>2</sup>) were fixed over the brim with the help of an adhesive. Then the cells were accurately weighed and kept in a closed desiccator containing the saturated solution of potassium chloride (200 ml). The cells were removed and weighed every day for seven days of storage.

### Water absorption measurement:

Membranes with a specified area (1 cm<sup>2</sup>) were weighed and put in to a watch glass containing water. At regular intervals of time, the membranes were taken out, blotted with filter paper and weighed on a digital balance. After attaining equilibrium the membranes were dried and weighed to calculate any weight loss. Membranes showing weight loss of more than 0.01% were not taken for calculation incase experiments were repeated.

### *In vitro* drug permeation study:

*In vitro* drug release was performed in distilled water using Keshary-Chien diffusion cell. The appropriate sized polymeric membranes were mounted with excised rat abdominal skin in between donor and receptor compartments of the diffusion cell and were held securely by springs. The donor compartment was empty and open to air, but the receptor compartment was filled with distilled water. The magnetic stirrer was set at 100 rpm. The temperature was maintained at 37°. The amount of drug released was determined by withdrawing 5 ml aliquots at the selected time intervals up to 24 h. The volume withdrawn was replaced with an equal volume of fresh, prewarmed (37°) distilled water. Samples were analyzed using a UV spectrophotometer at the  $\lambda_{max}$  of 276 nm using distilled water as the blank.

## RESULTS AND DISCUSSION

The free amino group of chitosan was reacted with aldehyde in presence of acid to form Schiff's base<sup>12</sup>. Alde-

hydres were selected based on their film forming capacity with the polymer. The percentage aldehyde conversion and carbon chain length of the aldehyde, affected the film characteristics. Based on the preliminary studies, acetaldehyde and propionaldehyde were selected and polymeric films produced by these aldehydes were named polymer-I and polymer-II, respectively. The reaction was confirmed by performing FTIR on plain chitosan, polymer-I and polymer-II. Chitosan showed peak at  $1647\text{ cm}^{-1}$  corresponding to amino groups. In contrast, after formation of imine group ( $-\text{C}=\text{N}-$ ) a new peak appeared at  $1567\text{ cm}^{-1}$  in both polymer-I and polymer-II<sup>15</sup>. The intensity of peak increased with an increase in aldehyde content during formation of Schiff's base. FTIR spectra of pure salbutamol sulphate and drug loaded membranes were also obtained to find out any chemical interactions between drug and the polymer. Salbutamol sulphate showed characteristic peaks at  $3320$  and  $1370\text{ cm}^{-1}$  and did not alter even after loading into the membrane. This confirms stability of the drug. Chemically modified hydrogels can produce membranes with better properties such as high efficiency due to the change in the polymeric network. Interpenetrating network and grafted polymer membranes have been used for the delivery of various drugs in the form of transdermal delivery systems.

The membranes were analyzed for the drug content. The content of salbutamol sulphate ranged between  $1.22$  to  $1.83\text{ mg/cm}^2$ , the highest was found in polymer-I ( $1.83\text{ mg/cm}^2$ ) followed by polymer-II ( $1.44\text{ mg/cm}^2$ ) and chitosan

( $1.22\text{ mg/cm}^2$ ). Formation of Schiff's base with acetaldehyde might have generated more space within the polymeric network.

The permeability of membranes to water vapor is an important parameter from which permeability of drug can be predicted. The water vapor transmission rate (WVTR) for membranes of chitosan, polymer-I and polymer-II were calculated using Eqn.1',  $\text{WVTR}=\text{WL/S}$ , where W is weight of water vapor transmitted, L is thickness of the membrane and S, the exposed surface area. Results indicated that all the membranes were permeable to water vapor and polymer-I showed highest permeability ( $8.10\times 10^{-4}\text{ g.cm}^2/\text{day}$ ) compared to polymer-II ( $5.18\times 10^{-4}\text{ g.cm}^2/\text{day}$ ) and chitosan ( $1.13\times 10^{-4}\text{ g.cm}^2/\text{day}$ ). A linear plot of WVTR against time for membranes of chitosan, polymer-I and polymer-II was obtained, indicating permeability follows zero order kinetics (displayed in fig.1).

Membranes were further analyzed for water absorption when soaked in water. Since chitosan, polymer-I and polymer-II are insoluble in water, the membranes were not dissolved, and were only swollen. Using water absorption data, diffusion coefficient (D) was calculated as per the procedure<sup>16</sup> using Eqn. 2,  $D=(h\theta/4M_{\infty})^2\pi$ , where h is thickness of the membrane,  $\theta$  is slope obtained by plotting  $M_t/M_{\infty}$  against  $t_{1/2}$ . The calculated D value was high for polymer-I ( $6.11\times 10^{-8}\text{ cm}^2/\text{s}$ ) than polymer-II ( $3.28\times 10^{-8}\text{ cm}^2/\text{s}$ ) and chitosan ( $2.08\times 10^{-8}\text{ cm}^2/\text{s}$ ).

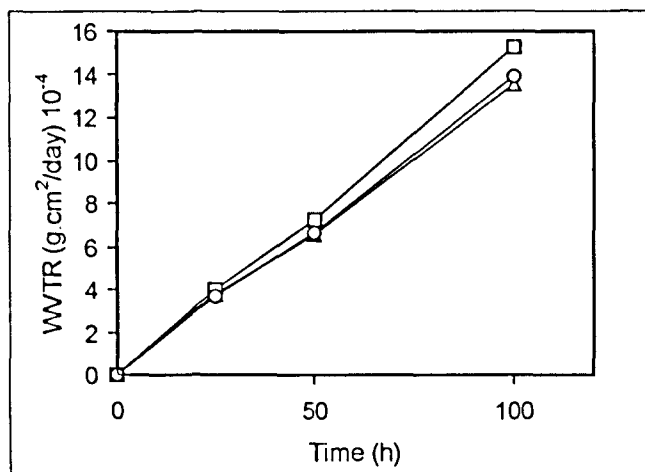


Fig. 1: Rate of water vapor transmission (WVTR) through various membranes at different time intervals.

Water vapor transmission rate through various membranes, chitosan (—Δ—), polymer-I (—□—) and polymer-II (—○—).

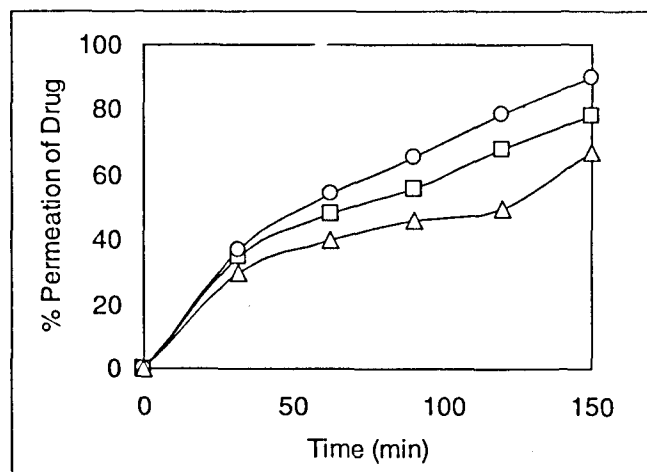


Fig. 2: *In vitro* drug release from different polymeric membranes.

*In vitro* release of salbutamol sulphate from membranes of, chitosan (—Δ—), polymer-I (—○—) and polymer-II (—□—).

*In vitro* release of salbutamol sulphate from membranes of chitosan, polymer-I and polymer-II, through excised rat abdominal skin is displayed in fig. 2. The permeation was high through polymer-I than polymer-II and chitosan. The time taken for permeation of 50 % of salbutamol ( $T_{50}$ ) was 118, 62 and 88 min for chitosan, polymer-I and polymer-II respectively. This indicates formation of Schiff's base with chitosan enhances permeation of drug through skin.

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