Formulation and Evaluation of Pseudolatex Transdermal Drug Delivery System of Terbutaline Sulphate

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Accepted 11 October 2001
Revised 7 September 2001
Received 9 February 2001

Since oral bioavailability of terbutaline sulphate is poor, pseudolatex transdermal patches incorporating terbutaline sulphate were prepared as an effective mode of therapy for nocturnal asthma in particular. The pseudolatex patches were formulated using combinations of Eudragit RS 100 and RL 100 and Eudraflex as plasticizer. The physicochemical characterization of the films were evaluated for suitability and drug release profile from the films as well as skin permeation aspects were evaluated for therapeutic efficacy. The resulted medicated patches were of average thickness (95-155 μm), and content uniformity of the drug varied from 94.5 to 99.1 percent. The formulation F3 showed least and F7 showed highest percentage of elongation. The percentage of moisture absorption varied from 2.91 to 3.65 at 63 percent relative humidity. The release profiles from the patches followed apparent zero order pattern up to a period 12 h, after which it levels off. The cumulative amount of drug permeated over a period of 24 h was found to be 4.8 mg/cm², which was about 50 percent of the loaded dose. The skin permeation took place at a steady rate over a period of 12 h after which the rate was reduced.

Pseudolatex type of transdermal patches can overcome the side effects associated with the transdermal system[1]. Pseudolatex can be described as two-compartment system, one compartment being a hydrophilic polymer forming a three dimensional network and the other compartment being water. Pseudolatices are widely studied biomaterials and materials for the preparation of sustained released drug dosage form. Their high biocompatibility in a number of applications makes them promising candidates for preventing the side effects[1]. It provides more reliable and steady release of drugs[2]. A wide range of applications of pseudolatex have been described, among them the contactness, maintenance of the blood concentration and the transport properties of pseudolatex makes them useful as a drug delivery system.

The successful development of transdermal drug delivery system depends on the choice of drug. Terbutaline sulphate (TBS) is widely used for the therapeutic management of chronic as well as prophylaxis of asthma and nocturnal asthma in particular. It has a mean biological half-life of about 3.6 h[3]. However, it is readily metabolized in the gut wall and liver when given orally[4]. Consequently it has a short duration of action, low peak plasma level of 1.2 μg/ml and the poor bioavailability of only 14.8 percent. Inhalation therapy is also not suitable since only 10-20 % of the inhaled dose of TBS reaches the lungs[5]. For the chronic management or prophylactic therapy of asthma particularly nocturnal asthma, a long-acting formulation particularly transdermal delivery would be of benefit[6,7]. Therefore long acting formulation of TBS is needed for the effective treatment of all types of bronchial asthma, particularly for the treatment of all types of reversible airway obstruction to inhalation therapy[8]. In the present investigation pseudolatex transdermal patches containing TBS has been developed to provide a satisfactory sustained action medication for controlling asthma. Also its various physicochemical properties, release profile and skin permeation properties, of drug have been studied and reported.

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TBS USP was obtained from Wockhardt Ltd., Aurangabad, Eudragit RS-100 and RL-100, Eudraflex and Eudragit NE-30D were obtained form Rohm Pharma GmbH, Germany. Acetone was purchased from Loba Chemie, Mumbai.

Eudragit NE-30D suspension was dried in air. The films thus obtained were crushed to pieces. Two hundred and fifty milligrams of the polymer was dissolved in 5 ml of acetone and was poured over an aluminum foil of area 4.8 cm^2 and dried overnight. Dryness of the casted films were monitored by judging the degree of transparency.

Films were prepared using 7 ml of solution of the required amount of drug and polymer prepared by dissolving in a mixture of acetone and pH 7.0 buffer solution in different combination and casted over backing membrane. Eudraflex was used as plasticizing agent. The films were dried under controlled condition. The films were cut into pieces of 1 cm^2. The films prepared with 1:0, 1:1, 1:2, 1:3, 2:3, 0:3, 37: 63 combination of Eudragit RL–100 and RS-100 and 10mg/1cm^2 of TBS were selected for evaluation.

The physical parameters such as thickness, weight variation, tensile strength and percentage of elongation of various films were determined. The thickness of the films was measured at different places using micrometer and the average was taken. Weight variation test was done by weighing each film individually, the average weight of the film was taken as the weight of the films. The tensile strength and percentage of elongation of the free films was measured using tensile strength instrument. It was done in triplicate and the average was calculated using equation reported by Allen *et al*[9]. The percentage of elongation of the films was calculated according to the A.S.T.M. standards. The physical characteristics are shown in Table 1. The content uniformity of the films were determined by dissolving in acetone, diluting with distilled water and analysing for drug content at 270 nm.

The method of Utzemi *et al.* was adopted for the determination of moisture absorption (MA)[10]. The MA of various films was studied at 63% relative humidity. The film of known thickness was fixed over the edge of the glass vial containing 3 g of fused calcium chloride as a desiccant using an adhesive. The charged vial was weighed and kept in a disiccator maintained at 63% relative humidity. The vial was taken out periodically and weighed for a period of 72 h. The experiment was performed in triplicate and the average values were calculated using equation, reported by Crowford and Esmerian[11].

The skin irritation tests of the films was done according to the Bhalla *et al*[12] and Panigrahi *et al.*[13], on albino rats. The animals were observed for 7 d for any sign of oedema or erythrema.

The diffusion study using Keshary-Chien diffusion cell was performed[14]. The cell was locally fabricated and it had a volume of 12 ml in the receptor compartment. The solution (phosphate buffer, pH 6.8) in receptor compartment was

TABLE 1: EVALUATION OF TBS PSEUDOLATEX TRANSDERMAL PATCHES.

Formulation	Thickness (μm)	Weight variation (mg)	Skin irritation test	% elongation	Tensile strength (g/cm^2)	Content uniformity (%)	Water Vapour transmitted in 24 h(g)
F1	115±0.9	27.5±0.25	+	23.34±0.25	280.5	98.11±1.01	3.01
F2	103±0.62	23.8±0.18	+	22.15±0.16	212.89	99.12±0.75	2.91
F3	97±0.75	21.7±0.21	+	22.24±0.23	180.04	97.98±0.95	2.92
F4	95±0.55	31.4±0.22	+	21.67±0.22	160.75	96.84±1.25	3.16
F5	105±0.89	24.9±0.26	+	20.89±0.24	220.54	98.58±0.85	3.50
F6	101±0.83	22.5±0.23	+	24.5±0.25	210.84	95.99±0.75	3.46
F7	108±0.43	25.8±0.25	+	23.5±0.17	263.46	97.34±0.91	3.65

The table indicates the various parameters studied of pseudolatex transdermal patches (F1 to F7), indexed as F1, F2, F3, F4, F5, F6 and F7 containing different proportion of Eudragit RI-100 and Eudragit RS-100 as follows.

stirred at controlled speed at 37±1°. At suitable interval of time 1 ml of medium was withdrawn and the same volume was replaced by phosphate buffer of pH 6.8. The sample withdrawn was analysed for the drugs content at 270 nm. The result were plotted as cumulative percentage release versus time was shown in fig. 1.

Skin permeation study was performed as described by Kakkar and Gupta[15]. Young albino mice aged between 6 to 8 w were taken and killed by cervical dislocation. The abdominal skin was carefully separated from the body, with the dermis part remaining intact. The inner part of the skin was washed with distilled water thoroughly to separate the adhering fat. Finally the hair on the skin were carefully removed by means of fine forceps. The skin so obtained was examined microscopically for the presence of any possible damage.

The drug permeation from the films through the mouse skin was determined. The contents of donor and receptor compartments were separated by placing freshly excised mouse skin in between two compartments. The skin was mounted in such a way that stratum corneum side of the skin continously remained in an intimate contact with the transdermal patch in the donor compartment. The receptor contained phosphate saline buffer of pH 6.8 at 37 ±1°. Samples of 1 ml were withdrawn periodically for 24 h and analysed for drug content at 270 nm. The result were plotted as cumulative percentage release versus time as shown in fig.2.

The formulation prepared using different ratios of Eudragit RS-100 and RL-100 shows thickness between 95 μm to 155 μm. Weight variation varies from 21.4 to 27.5 mg. The formulation F3 shows least percentage of elongation, where as F7 shows highest percentage of elongation. The result indicates that the thickness is directly proportional to the tensile strength. The drug content uniformity of the formulation varies from 95.45 to 99.1%. The percentage of moisture absorption at 63% RH varies from 2.91 to 3.65. The animals subjected for the primary skin irritation test did not show any sign of oedema or erythrema on observing for a period of 7 d. The results indicated that the formulation prepared using 2:3 ratio of Eudragit RL-100 and RS-100 was found to be superior to the others. All the transdermal films shows more that 50% of *in vitro* flux release. The order of diffusion F3>F4>F6>F2>F5>F7> F1. The release rate varies from 48.25 to 83.43%. The TLC was carried out for all the formulations and was found to be intact[16].

The *in vitro* flux followed an apparent zero order kinetics. The skin permeation of TBS took place at a higher constant rate over a period of about 12 h after which the rate slightly reduced but was found to be steady. The cumulative amount of TBS permitted per sq cm through the mice abdominal skin over a period of 24 h was found to be

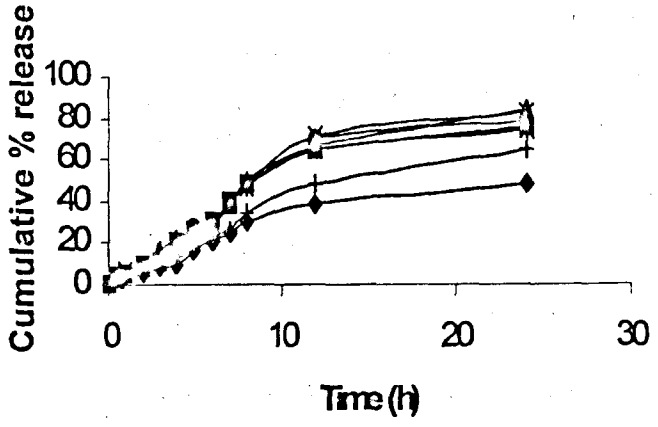

Fig. 1: *In vitro* diffusion of TBS from various pseudolatex films.

Release profile of TBS from various pseudolatex films of different composition, viz.F1(-◆-): -1:0, F2 (-■-): -1:1, F3 (-▲-):-1:2, F4 (-x-):-1:3, F5(-✱-):-2:3, F6 (-●-):-0:3, F7 (-+-):-37:63.

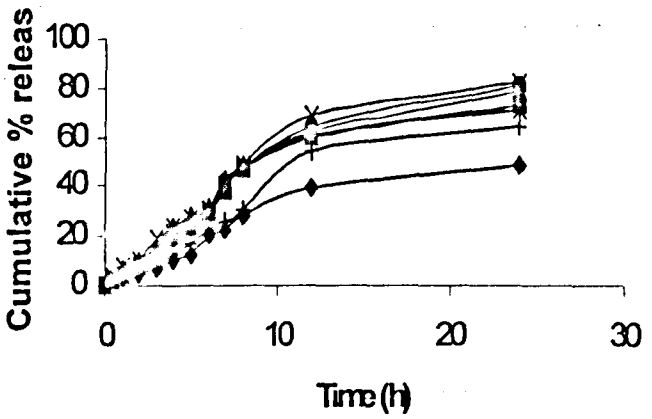

Fig. 2: *In vitro* permeation of TBS from different pseudolatex films.

Permeation profile of TBS through mice abdominal skin from various pseudolatex films of different composition, viz. F1(-◆-): -1:0, F2 (-■-):-1:1, F3 (-▲-):-1:2, F4 (-x-):-1:3, F5(-✱-):-2:3, F6(-●-):-0:3, F7 (-+-):-37:63.

4.8 to 8 mg which was varied from 50 to 80% of the loading dose per sq cm of the pseudolatex patch.

The various physicochemical properties of the pseudolatex films, such as thickness, weight variation, tensile stength, percentage of elongation, uniformity of drug content and moisture absorption properties were found to be within limits and satisfactory. The skin irritation test conducted over rabbits showed that there was no irritation at all for a period of 7 d, establishing the superiority of pseudolatex patches over other types of transdermal films. The *in vitro* release profile and skin permeation studies showed that the pseudolatex patches could be used as suitable sustained released transdermal drug delivery system over a prolong period of time.

ACKNOWLEDGEMENTS

The authors would like to thank Wockhardt Ltd., Aurangabad, India for the gift sample of terbutaline sulphate. They would also like to thank Department of Pharmaceutical Technology, Jadavpur University and the College of Pharmaceutical Science, Tamando, Bhubaneshwar for providing the facilities to carry out the research work.

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Novel Method of Synthesis of Curcuminoids and Derivative of Ibuprofen as Potent Antiinflammatory Agent

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Accepted 12 October 2001

Revised 24 September 2001

Received 30 January 2001

A novel method of synthesis of curcumin-I has been successfully developed using Claisen-Dieckmann condensation where dehydrozingerone is condensed with methyl ferulate in presence of sodium ethoxide in dimethyl sulphoxide. Various curcuminoids are prepared by changing the esters and α, β-unsaturated ketones. This reaction is utilized to prepare dehydrozingerone-

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