TRANSDERMAL FORMULATION OF TERBUTALINE SULPHATE

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Summary

Transdermal matrix type patches of terbutaline sulphate were fabricated using ethyl cellulose and cellulose acetate polymer. The highest release rate was observed from CP3 and EP2 patches. Transdermal patches CP3 and EP2 were found to be physically stable with regard to drug content, tensile strength, folding endurance, thickness, and weight variation. The drug permeation from both the patches follows diffusion controlled drug permeation.

INTRODUCTION

Terbutaline Sulphate is widely used for the therapeutic management of chronic as well as prophylaxis of asthma and nocturnal asthma in particular. It is a drug of choice for the treatment of asthma but it has several drawbacks such as

short biological half-life of about 3.6 hours[1], it is readily metabolized in the gut wall and liver when given orally. It has a short duration of action, low peak plasma level of 1.2 μg/ml and poor bioavailability of only 14.8%. These factors necessitated formulation of controlled release transdermal drug delivery system for terbutaline sulphate, as this route of drug administration would reduce the dosing frequency hence better patient compliance.

MATERIALS AND METHODS

Terbutaline Sulphate was obtained as a gift sample from Gitra Lab., Ahmedabad, Cellulose Acetate and Poly Vinyl Pyrrollidone from OTTO KEMI, Ethyl Cellulose from Ases Chem.Works, Jodhpur and Propylene Glycol from E-Merck India Ltd. Mumbai. All the chemicals and reagents used were of analytical reagent grade.

PREPARATION OF TRANSDERMAL PATCHES

The transdermal patches of terbutaline sulphate were prepared by solvent casting technique employing a mercury substrate. Two types of polymeric patches were prepared; cellulose acetate 5% in combination with PVP 5% and Ethyl cellulose 5% in combination with PVP 5%. The polymeric solution was prepared by dissolving the cellulose acetate and PVP combination in acetone in the ratio 1:4, 1:3 and 3:2 respectively using 2% propylene glycol as plasticizer. Similarly the polymeric solution of ethyl cellulose and PVP combination was prepared by dissolving the combination in alcohol: toluene mixture (1:4) in the ratio 1:4, 1:3 and 3:2 respectively using 2% propylene glycol as plasticizer. Weighed amount of drug was dispersed in each of the polymeric solutions while stirring to ensure the uniform distribution of drug.

A measured volume of each of the polymeric solutions (10 ml) was poured into Borosil® Petri dish and dried at room temperature. To prevent the

fast evaporation from the patches a funnel was placed inverted on the mould. After ensuring the complete evaporation of the solvent, patches of 2.5 cm diameter were cut with a borer and packed in aluminum foil and stored in desiccators for future study.

EVALUATION OF TRANSDERMAL PATCHES

The physical parameters such as thickness, weight variation, folding endurance, tensile strength, water vapor transmission[2] and drug content were determined. Patch thickness was measured using digital micrometer screw gauge (Mitutoyo, Japan) at three different places and the mean value was calculated. The patches were weighed using a Fisher brand digital balance. Folding endurance of patches was determined by repeatedly folding a small strip of film (2 cm x 2 cm) at the same place till it broke[3]. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The tensile strength was determined by using a modified pulley system. Weight was gradually increased so as to increase the pulling force till the patch broke. The percentage elongation[4] before the patch broke was noted with the help of a magnifying glass on a graph paper and the tensile strength was calculated as Kg/mm^2. Water vapour transmission studies were carried out using pre-weighed glass vials of 5ml containing 1 gm of fused calcium chloride. Polymeric films were fixed on the brim of the vials with a adhesive and stored in a humidity chamber at RH 80°C with temperature of 25°C for 24 hours and weight gained was determined.

STABILITY STUDY

The prepared patches were subjected to stability study by storing the patches at different storage conditions. The patches were stored for three months at different temperatures 40°C, 60°C, and 80○C and at room temperature as well

and at relative humidity of 55%, 65% and 75%. The stability study was conducted with regard to tensile strength, moisture content and drug content. The patches, which retained their physical properties, were further subjected to in-vitro permeation studies.

IN-VITRO DRUG PERMEATION STUDIES

The in-vitro permeation studies were carried out using a modified Keshary-Chein diffusion cell. A 2.5 cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the topside was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 75 ml of normal saline solution, the whole assembly was kept on a magnetic stirrer, at a speed of 100 rpm and the temperature conditions controlled at 37°± 2°C . The cell contents were stirred with a magnetic stirrer. Sample of 1 ml was withdrawn at time interval of 1, 2, 3, 4, 5, 6 and 8 hour simultaneously replaced with equal volume of fresh normal saline solution. The samples were withdrawn and filtered through Whatman filter paper. The absorbance of the solution was measured by UV at 276 nm[5].

RESULTS

In the present investigation various polymeric transdermal patches of terbutaline sulphate were prepared. The effect of permeability enhancer (PVP) on the permeability of drug from cellulose acetate and ethyl cellulose patches were studies. The physicochemical characteristics of the patches of terbutaline sulphate in the polymeric matrix were satisfactory with respect to weight variation thickness, folding endurance, water vapour transmission and tensile strength. The polymeric combinations showed good film forming properties the method of casting on mercury substrate was found to give good films. Low SD values were found in the patches, which ensured uniformity of thickness of each

film. Water vapour transmission studies indicated that the films were permeable to water vapour and followed Higuchi kinetics. The diffusion studies reveled that as the concentration of PVP increases the rate of drug diffusion also increases. The stability studies conducted reveled that polymeric patches prepared in the combination of Cellulose acetate and PVP in the ratio of 3:2 (CP3) and combination of Ethyl cellulose and PVP in the ratio of 2:3 (EP2) with 1% plasticizer were found to be most stable with respect to drug content and all the physical parameters evaluated (Table-1). Hence the patches CP3 and EP2 were considered for further in-vitro permeation studies.

Table 1: Physical evaluation of transdermal patches of Terbutailne sulphate.

Formulation Code	Polymer used	Ratio of polymer (w/v)	Thickness (mm)	Weight Variation (mg)	Folding Endurance	Tensile strength (kg /mm^2)	Water vapour transmission (gm/cm^2)
CP1	CA:PVP	1:4	0.406 ±0.5	15.2 ± 2	80 ± 5	0.671 ±0.38	0.132±0.0026
CP2	CA:PVP	2:3	0.820 ±1.1	16.8 ± 3	98± 1.8	0.851± 0.34	0.1176±0.0014
CP3	CA:PVP	3:2	0.610 ± 0.3	8.4 ± 4	124± 1.4	0.910 ±0.52	0.1245± 0.003
CP4	CA:PVP	4:1	0.518 ± 0.7	18.6± 5	104± 1.6	0.741± 0.36	0.095± 0.0017
EP1	EC:PVP	1:4	0.520 ± 0.8	18.5 ± 1	51 ± 2.5	0.498 ±0.2	0.1368±0.003
EP2	EC:PVP	2:3	0.642 ± 0.7	10.1 ±2.5	121 ±4	0.789 ±0.4	0.1352±0.004
EP3	EC:PVP	3:2	0.910 ± 1.2	15.4 ± 3	86±1.9	0.710 ±0.5	0.156±0.0061
EP4	EC:PVP	4:1	0.817± 1.3	12.1± 3.2	52± 2.4	0.234± 0.8	0.105± 0.0074

DISCUSSION

The in-vitro release data from the most stable patches CP3 and EP2 in terms of thickness, tensile strength, weight variation, folding endurance and water transmission, were subjected to zero order and Higuchi model. The kinetic

treatment revealed that the drug release from the patch CP3 followed Higuchi model as the correlation coefficient of linear relation ship between the cumulative percent drug released and the square root of time was found to be 0.9966 and for EP2 it was 0.9943, where as the correlation coefficient of linear relation for zero order was found to be 0.9803 for CP3 and for EP2 it was 0.9812.Thus the comparison of coefficient of linear relation ship between the zero order and Higuchi model suggests that the drug permeation is controlled by diffusion in both the transdermal patches (Fig1 & Fig.2).

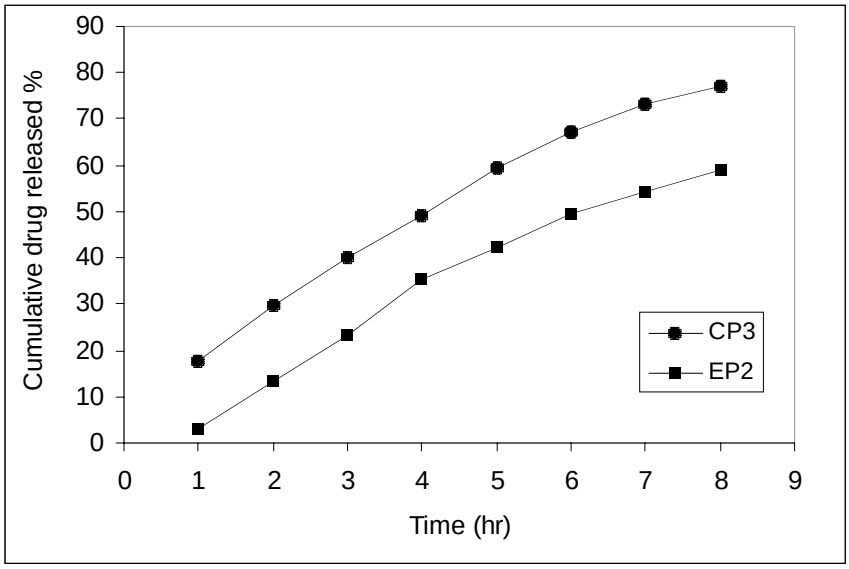

Figure 1: In-Vitro permeation profile (Zero order) of Terbutaline sulphate from CP3 and EP2 patches through human cadaver skin.

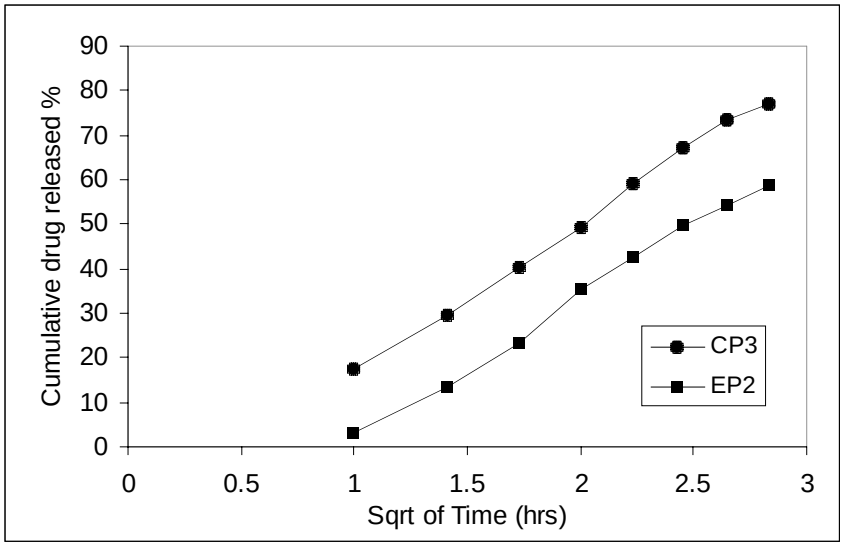

Figure 2: In-Vitro permeation profile (Higuchi Model) of Terbutaline sulphate from CP3 and EP2 patches through human cadaver skin.

The diffusion coefficient of terbutaline sulphate from CP3 was calculated to be 0.2145 ± 0.25 cm^2/h where as for EP2 it was calculated to be 0.1421± 0.28 cm^2/h, from figure 2.

CONCLUSION

The present investigation suggests that the drug release from both the system follows Higuchi kinetics and the higher rates were achieved from CP3 patch as compared to EP2 patch. Thus it could be concluded that higher release rates can be achieved from cellulose acetate patches in combination with PVP where as the same phenomenon was not observed in case of ethyl cellulose patches. Higher drug permeability was observed from cellulose acetate patches as compared to ethyl cellulose patches.

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