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RESEARCH ARTICLE

EFFECT OF HYDROPHILIC POLYMER IN THE RELEASE PATTERN OF TERBUTALINE SULPHATE TRANSDERMAL PATCH

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ABSTRACT

The aim of the study is to formulate matrix based transdermal patch for water soluble drug like terbutaline and to study the effect of formulation composition on physical property, to study permeation profile of the patches through hairless mice skin and to study release profile of the patches. Five monolayered terbutaline sulphate transdermal patches bearing a rate controlling membrane were prepared by solvent-casting technique. Five formulations were prepared with varying concentrations of sodium alginate- FI, FII, FIII, FIV and FV with 350mg, 450mg, 250mg, 400mg and 300mg respectively. The 15mg terbutaline sulphate, 0.5ml glycerine and 0.1% chlorocresol were used along with sodium alginate in preparation of drug matrix. A mixture of ethylcellulose, chloroform and dichloromethane were used for preparation of rate controlling membrane using dibutylphthalate as a plasticizer.

The physicochemical characteristics of the patches were evaluated by standard techniques. In-vitro drug release test was done in Keshary Chein diffusion cell by using skin of albino mice for 6 hours study. From the in-vitro permeation release study, formulation FII, FIV and FV followed Higuchi order kinetics while FI followed Peppas equation and FIII followed first order kinetics. Formulation FII showed more permeability than other formulations due to high concentration of sodium alginate in the FII. Thus the release of drug was found to be directly related to the concentration of SA.

Key words: Sodium alginate; Terbutaline Sulphate; Drug matrix; Rate controlling membrane; Drug release study; In-vitro drug permeation study

INTRODUCTION

Drug delivery technologies are now receiving considerable attention from pharmaceutical companies. The main purpose of developing alternative drug delivery technologies is to increase efficiency and safety of drug delivery and provide more convenience for the patient. Substantial research conducted during the past several years has lead to the development of technologies that meet the requisite criteria for delivering the drug through a non-invasive route [1]. One of such technologies is transdermal drug delivery. Transdermal drug delivery system is topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate [2].

Transdermal drug delivery is the non-invasive delivery of medications from the surface of the skin which is the largest and most accessible organ of the human body through its layers, to the circulatory system. Medication delivery is carried out by a patch that is attached to the body surface. Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin [1].

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks -- namely poor bioavailabiltity due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.[3]

To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (ie site specific) , spatial and temporal placement within the body thereby reducing both the size and number of doses.[4]

Terbutaline Sulphate is widely used for the therapeutic management of chronic as well as prophylaxis of asthma and nocturnal asthma in particular. But it has several drawbacks such as short biological half-life of about 3.6 hours [5], 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% [6]. These factors necessitated formulation of controlled release transdermal drug delivery system for terbutaline sulphate.

MATERIALS AND METHODS

Materials

Terbutaline sulphate, Chlorocresol and Ethyl cellulose MCCP PH 102 was received as a gift sample from Nepal Pharmaceutical Pvt. Ltd. (NPL), Bara. The rest ingredients and reagents were of analytical grade.

Equipments and Instruments

Keshary Chein diffusion cell, Analytical Balance, UV/Visible spectrophotometer, Microprocessor pH meter, Magnetic Stirrer with Hot plate, Micrometer screw gauge, Hot Air Oven, Albino mice received from animal house, Aluminium foil, Glass mould

Preparation of Terbutaline Drug Matrix

The drug polymer solution (composition given in Table 1) was transferred into a mould of size 22×22 cm^2, previously covered with a backing membrane, aluminium foil. The mould was then kept in a hot air oven and maintained at a temperature of 60°C for 12 hours. The composition of the drug matrix is shown in Table 1.

For the preparation of drug polymeric solution for each 4.9cm^2, 15mg of terbutaline sulphate was dissolved in 5 ml water. 0.5 ml glycerine and chlorochresol 1% was also added. Then sodium alginate (SA) was added with continuous stirring. The solution was homogeneously mixed. Sufficient water was added to maintain the viscosity.

Table 1: Formulation of Drug Matrix

Formulation	Terbutaline Sulphate (mg)	Sodium Alginate (mg)	Water (ml)	Glycerine (ml)	Chlorcresol (%)
FI	15	**350**	5	0.5	0.1
FII	15	**450**	5	0.5	0.1
FII	15	**250**	5	0.5	0.1
FIV	15	**400**	5	0.5	0.1
FV	15	**300**	5	0.5	0.1

Preparation of Rate Controlling Membrane

Ethyl cellulose was dissolved in a mixture of chloroform and dichloromethane. Dibutylphthalate was used as a plasticizer, and the solution was poured in the previously dried drug matrix and left for drying. The composition of rate controlling membrane for each patch is given in the Table 2.

Table 2: Formulation of rate controlling membrane

Composition	Amount
Ethyl Cellulose	25 mg
Chloroform	2.5 ml
Dichloromethane	3 ml
Dibutyl Phthalate	45 mg

Evaluation of physical parameters

Weight Variation: The patch of diameter 2.5 cm were cut and was weighed for 10 patches of each formulation. The data were presented in ± standard deviation. [7]

Thickness Variation: Thickness was measured using screw gauze at different points of the film. The thicknesses of 10 patches were measured. The data were presented in ± standard deviation. [7]

Diameter Variation: For each patch, diameter was measured at two spots by vernier calliper and its average was taken. It was done for 10 patches. The data were presented in ± standard deviation. [7]

Folding Endurance: For each patch, folding endurance was determined by repeatedly folding the small strip of film at the same place until it break. The number of times the films could be folded at the same place without breaking was the folding endurance value. [8]

Moisture content: For determination of moisture content the prepared patches were weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films were weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using the following formula. [7]

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Standard Calibration Curve

A stock solution of Terbutaline Sulphate (500 µgm per ml) was prepared. Five samples of concentration 25, 50, 75,100 and 125 µgm per ml were prepared from the stock solution with proper dilution using saline phosphate buffer (pH 7.4). The absorbance of these solutions was measured at 277 nm.

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Absorbance against concentration was plotted and R^2 value showed that there was linear relationship among the measured value. The equation for the calculation of concentration of drug in content, release study and permeation study were calculated using the equation obtained from standard calibration curve.

Assay

The drug containing patch of 4.9cm^2 area was cut into pieces and kept in 100 ml volumetric flask containing the saline phosphate buffer (pH 7.4). The volumetric flask was kept in the magnetic stirrer for 2 hour. The absorbance of the samples was measured with the help of spectrophotometer. The total drug content of the patch was determined.

Drug Relase Study

The patch to be studied was stuck to the inner surface of the lid with the glue such that the blocking membrane (aluminum foil) was stuck to the lid. The release apparatus was set such that receiver fluid (saline Phosphate buffer pH 7.4) would be in contact with the patch of the lid maintained at the temperature of 32°C ± 2° C. The rotation of the magnetic bead was maintained at 120 ± 50 rpm. The 3.4ml sample was drawn at interval of 0.5 hour. The amount of drug release was estimated by using the equation obtained from the standard calibration curve.

In-vitro Drug Permeation study

The patch to be studied was adhered to the outer surface of the mice skin. The skin containing patch was then fitted to the receiver compartment of the Keshary Chein diffusion cell. Receiver compartment along with skin and upper compartment was held together with the rubber band. The phosphate buffer was filled in the receiver compartment such that it was in contact with the skin. The magnetic stirrer was maintained at 120 ± 50rpm. The temperature of the phosphate buffer in the receiver compartment was maintained at 32°C ± 2°C. Sample of 3.4 ml was drawn at the predetermined interval of 0.5hours and after withdrawing, 3.4 m1 was replaced in the receiver compartment at each interval. The amount of drug permeated was estimated by using the equation obtained from the standard calibration curve.

In-vitro Drug permeation kinetics

The various mathematical models were used to see whether or not permeation of drug via the mice skin followed zero order, First order, Peppas equation or Higuchi equation.

Result and Discussion

Evaluation of Physical parameters

The physical properties of the patches are recorded in table 3.

Table 3: Physical parameters of formulated patches

Formulation	Weight variation (gm)	Diameter	Thickness	Average Folding Endurance	% Moisture Content
FI	0.461 ± 0.17	2.5 ± 0.1	0.42 ± 0.05	721	2.990 ± 0.06
FII	0.483 ± 0.14	2.5 ± 0.05	0.55 ± 0.10	650	8.765± 0.08
FIII	0.488 ± 0.10	2.5 ± 0.05	0.60 ± 0.07	597	8.371± 0.04
FIV	0.366 ± 0.11	2.5 ± 0.08	0.40 ± 0.06	743	6.250± 0.02
FV	0.555 ± 0.14	2.5 ± 0.07	0.90 ± 0.03	197	4.393± 0.06

The weight variation of FIII was found least deviated and FI was found highly deviated in comparison with other formulations. The deviation in the patch may be due to improper mixing or due to irregular surface of the oven used for drying. The thickness was found to be highest in FV and lowest in FIV. This may be due to improper mixing or due to irregular surface of the oven used for drying purpose. Folding endurance for all the formulations was very good. Folding endurance measures the ability of patch to withstand rupture. The moisture content was found to be least in FI i.e. 2.990% and greatest in FII i.e. 8.765%. Generally the moisture content for transdermal patches should be 2-5 %. Thus moisture content studies showed strong moisture absorbing capacity, this is due to inherent property of the sodium alginate polymer. This observation indicates the use of proper packaging material.

The physicochemical studies show the unpredictable characteristics of sodium alginate concentration in physicochemical parameters of the patch. Thus SA does not interfere the physicochemical parameters of the patch.

Assay

The maximum assay was found to be 91.46% of formulation FV and minimum was found to be 82.13% of FII. The assay was found to be less; this may be due to errors in mixing, thickness, weight variation, etc.

Drug Release Study

In the release study, release from FII was found greatest in comparison with other formulations. The drug release from the patch increased compared to the permeation study due to absence of skin as barrier. The release seems to be dependent on the concentration of SA except FI which contain SA 350mg. This may resulted due to error in the rate controlling membrane, weight variation or due to improper mixing.

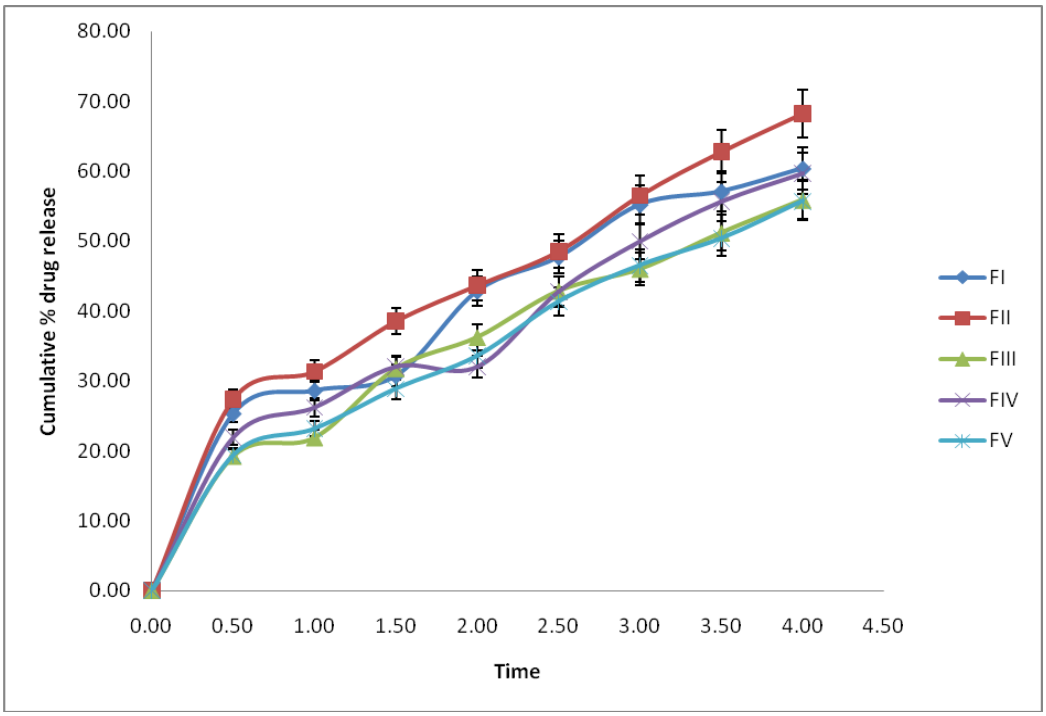

Fig 1: Drug release profile of formulated patches

In-Vitro Drug Permeation Study

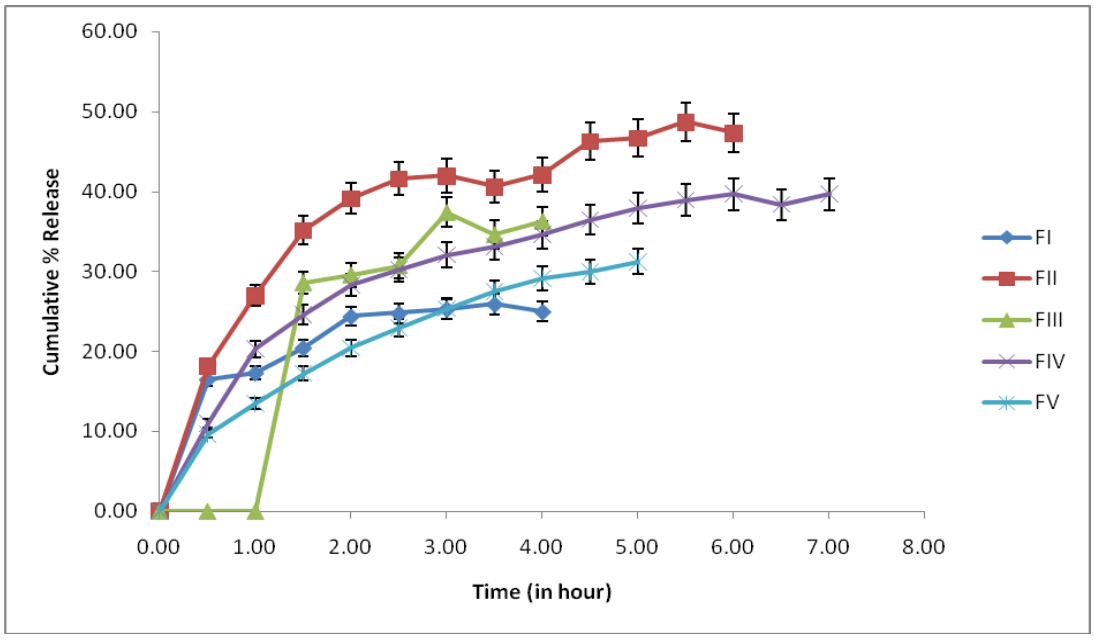

Fig 2: In-vitro drug permeation profile of formulated patches

The graph plotted between cumulative percentages of drug permeated against time, shows the permeation of drug in FII was greatest among the five formulations. It could be due to higher concentration of Sodium alginate in the formulation, 450mg of SA was used. SA was used in the formulation as a thickening and suspending agent which also helps in the formation of gels. The main function was to isolate and entrap the drug in the drug matrix. SA is hydrophilic polymer which is not suitable for transdermal formulation. So the membranes formed from hydrophobic polymers were used as rate controlling membrane.

The curve obtained from in FIV and FV was nearly similar but the cumulative percentage drug release in FIV was higher due to higher concentration of SA i.e., 400mg than FV (300mg).For the formulation FI and FII the release study could only be carried out for 4 hours due to constrain in time and electricity.

The graph showed direct relation between concentration of SA and drug permeation except FIII. This may be due to more lag time because of the temperature of the receptor compartment was not maintained initially.

In-Vitro Permeation kinetics

The in-vitro release data was treated with kinetic equations such as the zero order rate kinetic equation, first order rate kinetic equation, Higuchi's diffusion equation and Peppas equation, to understand the release kinetics and mechanism of release from the formulated patch. From the in-vitro permeation release study, formulation FII, FIV and FV followed Higuchi order kinetics. One of the assumptions of Higuchi equation was the maintenance of perfect sink condition. The multilayered structure of skin could provide perfect sink condition and could be the reason for following Higuchi equation. Due to the hydrophilic property of the drug, aqueous layer of the skin could maintain perfect sink condition for the drug. This also signifies that the initial drug concentration in the system is much higher than the matrix solubility, the diffusivity of the drug is constant and the swelling of the polymer is negligible. FI followed Peppas equation and FIII followed first order kinetics.

Table 4: In-vitro drug permeation kinetics of formulated patches

Formulation	Zero Order Kinetics		First Order Kinetics		Higuchi Order Kinetics		Peppas Equation	
	R^2	K	R^2	k	R^2	n	R^2	n
I	0.668	0.639	0.795	0. 057	0.894	1.593	**0.901**	0.246
II	0.721	0.749	0.683	0.056	**0.917**	2.311	0.914	0.360
III	0.794	1.380	**0.989**	0.043	0.780	2.949	0.951	0.249
IV	0.785	0.627	0.688	0.060	**0.952**	2.059	0.930	0.439
V	0.912	0.747	0.880	0.104	**0.997**	1.919	0.996	0.526

CONCLUSION

Transdermal patches with different concentration of Sodium Alginate were prepared using terbutaline sulphate as an active drug ingredient. Other excipients of drug matrix and rate controlling membrane were kept constant to evaluate the role of SA in drug permeation. The five formulations were prepared formulations I, II, III, IV and V using 350mg, 450mg, 250mg, 400mg and 450mg SA respectively and keeping other excipients and drug constant. The physiochemical parameters were determined. The physiochemical parameters do not show significance of concentration of SA.

From the permeation study, it was found that the release and permeation of FII was greater than other formulations. This is due to use of higher concentration of SA in this formulation. From the in-vitro permeation release study, formulation FII, FIV and FV followed Higuchi order kinetics. FI followed Peppas equation and FIII followed first order kinetics.

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CONFLICT OF INTEREST

We authors do not have any personal or financial conflict regarding the publication of this manuscript.

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