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Transdermal Drug Delivery of Salbutamol Sulphate with Different Concentration of Polymers

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ABSTRACT

Matrix-type transdermal therapeutic system containing salbutamol sulphate was prepared using different polymers by solvent evaporation technique. Seven different formulations of transdermal patch composed of hydrophilic and hydrophobic polymers as Hydroxypropyl methyl cellulose (HPMC) and Ethyl cellulose (EC) were prepared respectively. Formulations were carring 0.1 ml of di-methyl sulphoxide as penetration enhancer and 0.2 ml of di-butyl phthalate as plasticizer in 5 ml of chloroform: methanol as casting solvent system in each patch separately. The prepared transdermal patches were evaluated for physio-chemical parameters such as thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss, and also evaluated for in vitro release and in vitro permeation rate. The cumulative amount of drug release for seven formulations was found to be 94.589, 76.917, 77.742, 85.101, 87.589, 89.189, 67.16 % respectively. The value for cumulative amount of drug permeated for the said formulations were 95.138, 65.5753, 82.02, 85.1955, 88.297, 90.428, 60.0678 % respectively. On the basis of drug release studies and drug permeation studies formulation F6 emerging as a better formulation than other formulations since it is fulfilling the requirement of better and sustained release for long time (24 hours) which was not possible with HPMC and EC alone which showed maximum % cumulative drug release and maximum permeation rate for short time period.

KEYWORDS: Salbutamol sulphate, Transdermal patch, Solvent evaporation technique, Hydroxypropyl methylcellulose (HPMC), Ethyl cellulose (EC) and goat skin permeation.

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INTRODUCTION

In the recent years there is an increasing recognition that skin can also serve as part of administration in systemically active way. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose.[1] Transdermal delivery of drugs promises many advantages over oral or intravenous administration, such as a better control of blood levels, a reduced incidence of systemic toxicity, an absence of hepatic first-pass metabolism, etc.[2] Chemical enhancers partition into and interact with the SC constituents to induce a temporary, reversible increase in skin permeability where as physical enhancers induce the skin permeability by using physical forces such as magnetic field, electric current, vibration etc.[3] Besides the natural combination, S. Mitragotri suggested controlling the amount of combination of chemical enhancers in TDDS because of side effect due to deep accumulation of the enhancers under the skin.[4] Delivery via transdermal route is better because it is convenient and safe. Because it offers advantages over contional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half life drugs, improving physiological and pharmalogical response, avoiding the fluctuation in drug levels, inter and intra-patient variations, and most significantly it provide patients convenience. To date many chemical and physical approaches have been applied to increase the efficacy of the material transfer across the intact skin, by use of the penetration enhancers, enhancers, iontophoresis, sonophoresis and the use of colloidal carriers such as lipid vesicles (liposomes and proliposomes) and nonionic surfactant vesicles like niosomes and proniosomes.[5] Controlled drug release system (CDDS) can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time.[6,7,8] TDDS has gained a lot of interest during the last decade as it offers many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance.[9] For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin.[10] Salbutamol Sulphate (SS) has been widely used to prevent Bronchiodialater & bronchopulmonary disorders involving bronchospasm.[11] It is a β-adrenergic agonist, which acts by stimulating β -adrenergic receptors. Undergoes first pass metabolism and its metabolite is inactive, and shorter half-life make it suitable for TDDS. However, its low permeability is the main barrier for using

it in TDDS. Further, salbutamol sulphate is an ideal candidate for developing a TDDS because of its superior pharmacological action against asthma at low plasma concentrations.[4] The hydrophilic enhancers DMSO increases the permeation more than, lipohillic enhancer like benzyl alcohol, lauryl chloride and surfactant like sodium lauryl sulphate. Since hydrophilic nature of DMSO, as reported, lowers zeta potential of skin or swells or unfolds the proteins present in the skin. The skin pH (~5.0 to 6.5) makes the drug soluble at the absorption site which causes rapid absorption through skin because of swelling and hydration of the skin. The aim of the present study was to prepare transdermal patches of salbutamol sulphate using different concentration of lipophillic and hydrophilic polymers with DMSO as penetration enhancer and DBP as plasticizer for controlled release of salbutamol sulphate and thus to increase the bioavailability of the drug.

MATERIALS AND METHODS

Materials

Salbutamol Sulphate was received as a gift samples from Plethico Pharmaceuticals Limited, Indore, India. Hydroxypropyl methyl cellulose and Ethyl cellulose was purchased from chemicals and Rolex chemical industries Mumbai, India, respectively. All other laboratory chemicals used in the study were of analytical reagents grade. Double distilled water was used throughout the study.

Preparation of transdermal patch

The drug loaded matrix type transdermal films of salbutamol sulphate by solvent evaporation technique with slight modification. A circular mould of total area of 30.175 cm^2 as fabricated was used. The bottom of the mould was wrapped with aluminium foil, specified quantity in mg of the polymer(s) was accurately weighed as given in Table 1 and dissolved in 5 ml of chloroform: methanol and kept aside to form clear solution. Di-butyl phthalate was used as plasticizer and Di-methyl sulphoxide was used as penetration enhancer. 5 mg of salbutamol sulphate was dissolved in the above solution and mixed for 10 min. The resulted uniform solution was cast on the aluminium foil and dried at 40^{o}C in the hot air oven for 24 hours. An inverted funnel was placed over the mould to prevent fast evaporation of the solvent. After 24 hours the dried films were taken out and stored in desiccators for further studies. Compositions of different formulations are represented in Table 1.

EVALUATION OF TRANSDERMAL PATCH

The prepared transdermal patches were evaluated for their physicochemical characteristics such as thickness, % moisture loss, % moisture absorption, water vapour transmission rate, folding endurance, drug content, in vitro drug release and in vitro drug permeation studies.

Physical appearance:

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

Table 1: Composition of different formulations containing salbutamol sulphate

Formulations	Salbutamol sulphate (mg)	HPMC : EC (mg)	Dibutyl phalate (ml)	Dimethyl sulphoxide (ml)	Chloroform : Methanol (1:1) (ml)
F 1	5	300 : 0	0.2	0.1	5
F 2	5	30 : 270	0.2	0.1	5
F 3	5	60 : 240	0.2	0.1	5
F 4	5	90 : 210	0.2	0.1	5
F 5	5	120 : 180	0.2	0.1	5
F 6	5	150 : 150	0.2	0.1	5
F 7	5	0 : 300	0.2	0.1	5

Thickness uniformity:

The thickness of the prepared patches were measured in 3 different points by using a vernier calliper and determined the average thickness as reported by Shivraj et al (2010) with slight modification.[13] The thickness of the patches was varied from 0.030 mm to 0.056 mm. The film shows increase in thickness was linear with polymer concentration. The result was tabulated in Table 2.

Folding endurance:

The folding endurance was measured manually for the prepared films as reported by Eseldin et al, (2010). A strip of film having specific area (2×2 cm^2) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

Percentage moisture absorption Studies:

The physicochemical studies like moisture absorption (uptake) provide information regarding the stability of the formulations.

The accurately weighed films were kept in desiccators at room temperature for 24 hours, containing saturated solution of potassium chloride in order to maintain 80-90% RH. After 24 hours the films were taken out and reweighed. After 72 hours films are again reweighed. The percentage moisture uptake was calculated from the formula mentioned below as reported by Shivraj et al (2010).[13]

Percentage Moisture Uptake = [Final weight- Initial weight/ initial weight] ×100

Percentage moisture loss determination:

The moisture loss studies provide information regarding the stability of the formulations. The prepared films are to be weighed individually and to be kept in desiccators containing fused calcium chloride at room temperature for 72 hours. After 72 hours the films are taken out and reweighed. The percentage moisture loss was calculated from the formula mentioned below as reported by Shivraj et al (2010).[13]

% Moisture Loss = [Initial weight- Final weight/ Final weight] ×100.

Table 2: Results of Physio-chemical parameter studies of Salbutamol sulphate matrix transdermal patches formulation

Parameters	F1	F2	F3	F4	F5	F6	F7
Thickness (mm)	0.053	0.040	0.046	0.030	0.036	0.043	0.056
Folding endurance	108	53	65	78	90.66	97	105.66
% Moisture absorption	12.8	1.7	2.5	3.4	4.1	6.12	1.52
% Moisture Loss	13.4	6.3	6.5	7.2	7.4	8	11.1
WVTR after 24 hours	0.01161	0.01742	0.01858	0.01724	0.01417	0.01243	0.01977
WVTR after 72 hours	0.02323	0.03484	0.03716	0.03448	0.02834	0.02485	0.03947
% Drug content	97.19	84.09	93.06	94.85	95.96	96.47	82.04
In vitro drug release	94.589	76.917	77.742	85.101	87.589	89.189	67.16
In vitro drug permeated	95.138	65.5753	82.02	85.1955	88.297	90.4286	60.0678
Permeability Coefficient (mg/hr.cm)	0.0182	0.0096	0.0148	0.0099	0.0114	0.0148	0.0125

Water vapour transmission rate:

WVRT is defined as the quality of moisture transmitted through unit area of the film in unit time. This is expressed as gm/ hr cm^2.Glass vials of 5ml capacity were washed, dried to a constant weight in oven. 1gram of fused calcium chloride was taken in each vials and polymer film of 2.25cm^2 was fixed over a brim of each vials separately with the help of adhesive tape. Then the vials were weighed and stored in a humidity

chamber of 80-90% RH condition for a period of 24 hours and 72 hours. Then each vials were removed and reweighed after 24 hours and 72 hours of the storage and weight gain was noted. Transmission Rate was calculated by using formula as:

$$\text{Water Vapour Transmission Rate} = W \times L / S$$

Where, W= gram of water transmitted, L= thickness of the film in centimetre, S= exposed surface area of the film in cm^2.

Drug content uniformity of films:

Drug content of the prepared transdermal patch was determined by the procedure reported by Pullakandam et al (2009) with slight modification. [12] Specified area of patch ($1cm^2$) was cut and added to a beaker containing phosphate buffer pH 7.4 in specific volume of 100 ml. Then this medium was stirred with magnetic beads. The content were filtered through a whatmann filter paper and filtrate was examined for the drug content against the reference solution consisting of placebo films (containing no drug) with the UV spectrophotometer (Shimadzu 1700) at λ_{max} 276nm, and average was calculated.

In vitro drug release studies:

In vitro drug release studies were performed as per procedure with slight modification. By using Franz diffusion cell with a receptor compartment of capacity of 20 ml and by mounting the synthetic cellophane membrane between the donor & receptor compartment of the diffusion cell in vitro drug release studies was performed. The formulated patches were cut into size of $1cm^2$ and placed over the drug releasing membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37°C. Then sample of 5ml was withdrawn at the time interval of 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 & 24 hours and analysed for the drug content spectrophotometrically at λ_{max} 276 nm against blank solution. The receptor compartment (phase) was replenished with an equal volume of phosphate buffer pH 7.4 at each time of the sample withdrawal. The cumulative amounts of drug released per square centimetre of the patches were plotted against time.

In vitro skin permeation studies:

An in vitro permeation study was carried out by using diffusion cell model as reported by Pullakandam et al (2009) with slight modification.[12] Full thickness abdominal skin of male goat was taken from slaughter house. Hair from the abdominal region was removed carefully by using hair removing cream;

the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in phosphate buffer pH 7.4. The diffusion cell was then placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 40 ± 0.5°C using a thermostatically controlled heater. Then isolated skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume (5 ml) was removed from the receptor compartment at regular intervals of 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 & 24 hours and an equal volume was replaced by fresh dissolution medium. Samples are to be filtered through filtering medium and analyzed by UV-spectrophotometer Shimadzu 1700 at maximum wavelength (λ_{max}) of 276nm.

From durg diffusion data the permeability coefficient was calculated by using the equation as reported by Murthy et al (2008), $P = k_{app}$ (H/A); where k_{app} = diffusion rate constant (mg/hr) calculated from slope of the linear drug diffusion (d/p) diffusion profile, H = thickness of the film (cm) & A = Surface area of the film (cm^2).

Table 3: In vitro drug release kinetic studies of Salbutamol Sulphate matrix transdermal patches

Formulation Codes	ZERO ORDER MODEL		FIRST ORDER MODEL		HIGUCHI MODEL		CONCLUSION
	SLOPE	R^2_1	SLOPE	R^2_2	SLOPE	R^2_3	
F1	17.807	0.9835	-0.0852	0.7407	-0.4	0.0371	Follow Zero order kinetic
F2	2.9814	0.7829	-0.0441	0.9756	0.3248	0.1197	Follow First order kinetic
F3	2.9093	0.7902	-0.0314	0.9579	2.3854	0.2452	Follow First order kinetic
F4	3.2129	0.7704	-0.0402	0.9686	2.833	0.275	Follow First order kinetic
F5	3.3689	0.7613	-0.0425	0.965	3.4396	0.3563	Follow First order kinetic
F6	3.4265	0.7758	-0.0459	0.9795	3.4022	0.3367	Follow First order kinetic
F7	2.631	0.8112	-0.0304	0.9596	2.7773	0.4097	Follow First order kinetic

Table 4: In vitro drug permeation kinetic studies of Salbutamol Sulphate matrix transdermal patches

Formulation Codes	ZERO ORDER MODEL		FIRST ORDER MODEL		HIGUCHI MODEL		CONCLUSION
	SLOPE	R^2_1	SLOPE	R^2_2	SLOPE	R^2_3	
F1	3.4337	0.5407	-0.024	0.6802	15.277	0.7028	Follow Higuchi order kinetic
F2	2.3966	0.8867	-0.0274	0.985	1.2292	0.1223	Follow First order kinetic
F3	3.2154	0.766	-0.0382	0.959	3.6182	0.3849	Follow First order kinetic
F4	3.3016	0.8313	-0.0408	0.9842	12.492	1	Follow Higuchi order kinetic
F5	3.1582	0.6775	-0.0436	0.9507	2.4531	0.1189	Follow First order kinetic
F6	3.4519	0.675	-0.0496	0.9401	3.6983	0.2722	Follow First order kinetic
F7	2.2317	0.8602	-0.0225	0.9676	1.6063	0.2361	Follow First order kinetic

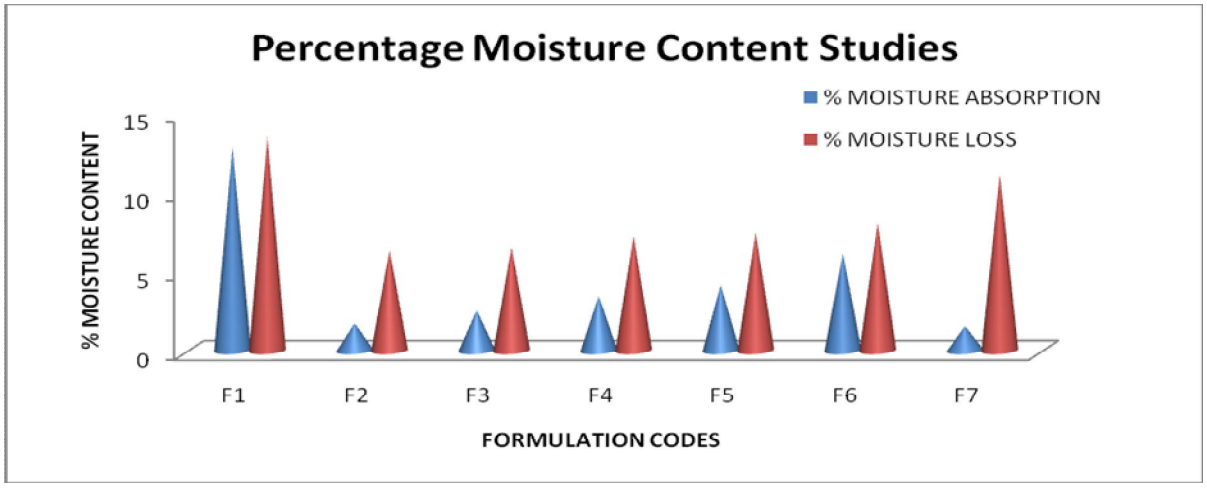

Figure 1: Comparative percentage moisture content studies of all salbutamol sulphate matrix transdermal patches formulations

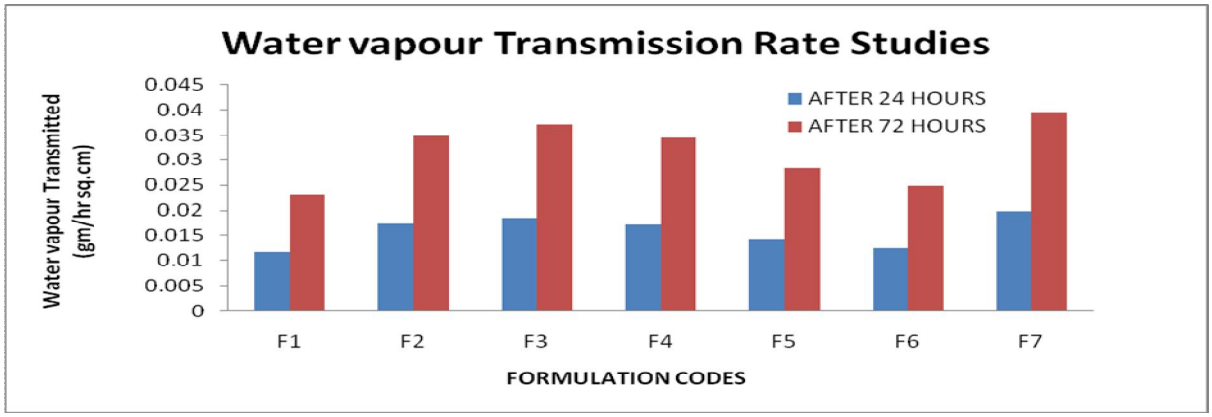

Figure 2: Water vapour transmission rate (WVTR) studies of all salbutamol sulphate transdermal patches formulations after 24 & 72 hours

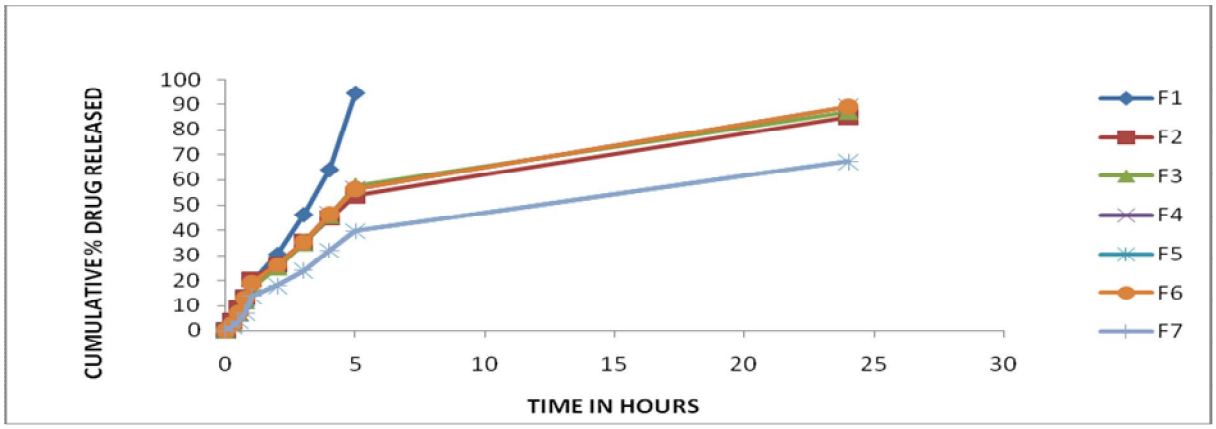

Figure 3: Comparative in vitro drug release studies of various salbutamol sulphate transdermal patches, for Zero order release kinetics model

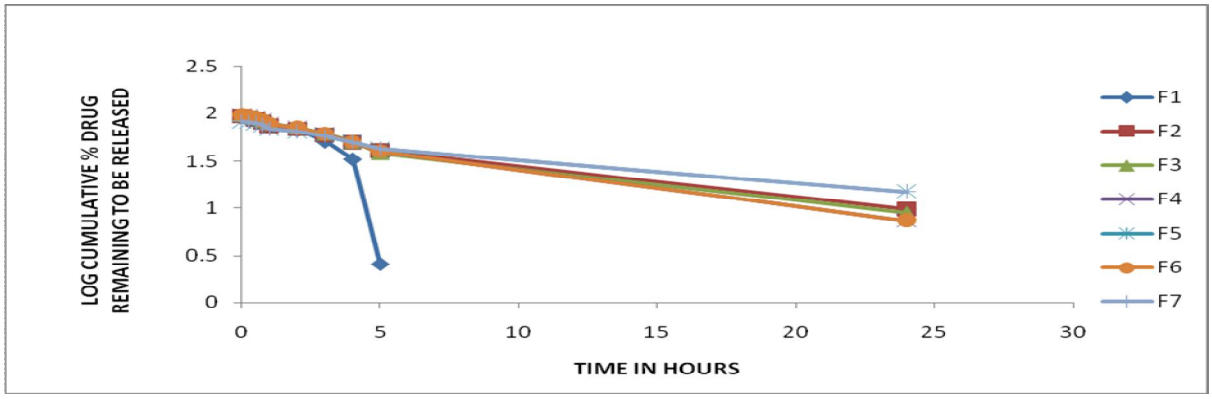

Figure 4: Comparative in vitro drug release studies of various salbutamol sulphate transdermal patches, for First order release kinetics model

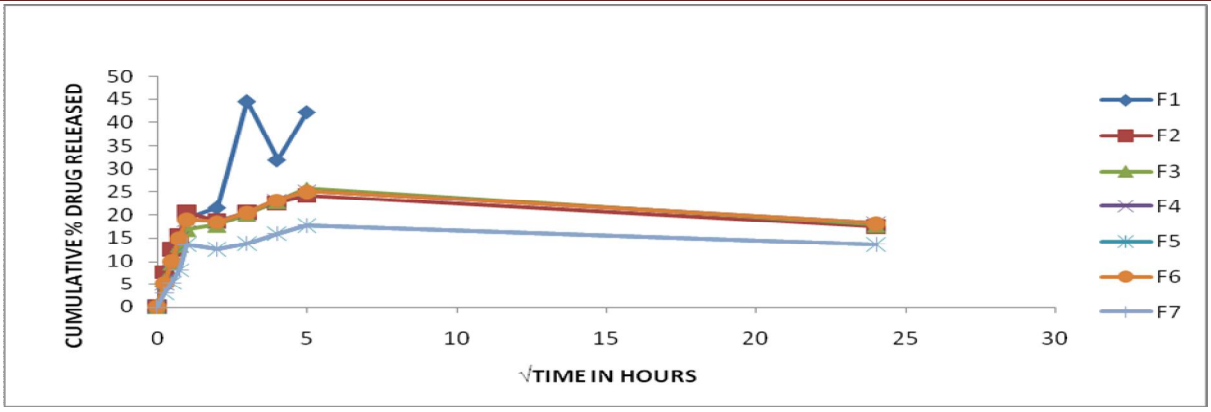

Figure 5: Comparative in vitro drug release studies of various salbutamol sulphate transdermal patches, for Higuchi release kinetics model

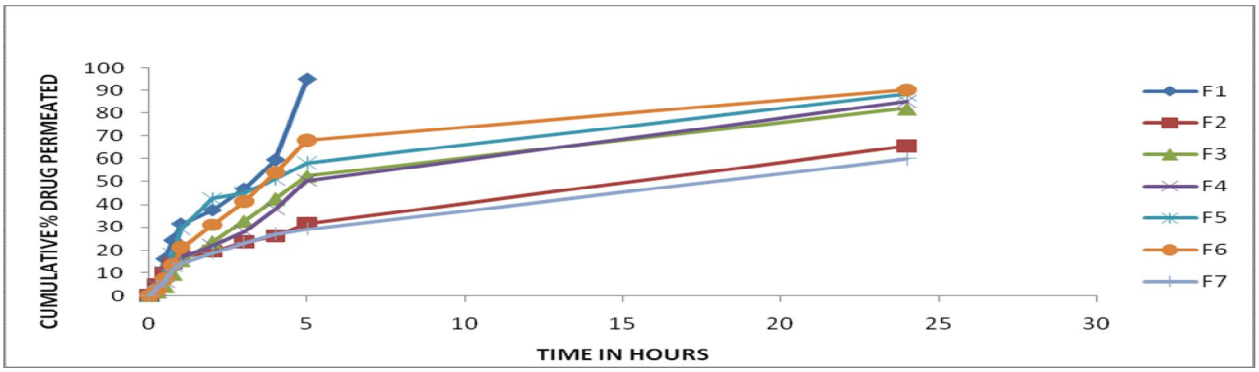

Figure 6: Comparative in vitro drug release studies of various salbutamol sulphate transdermal patches, for Zero order permeation kinetic model

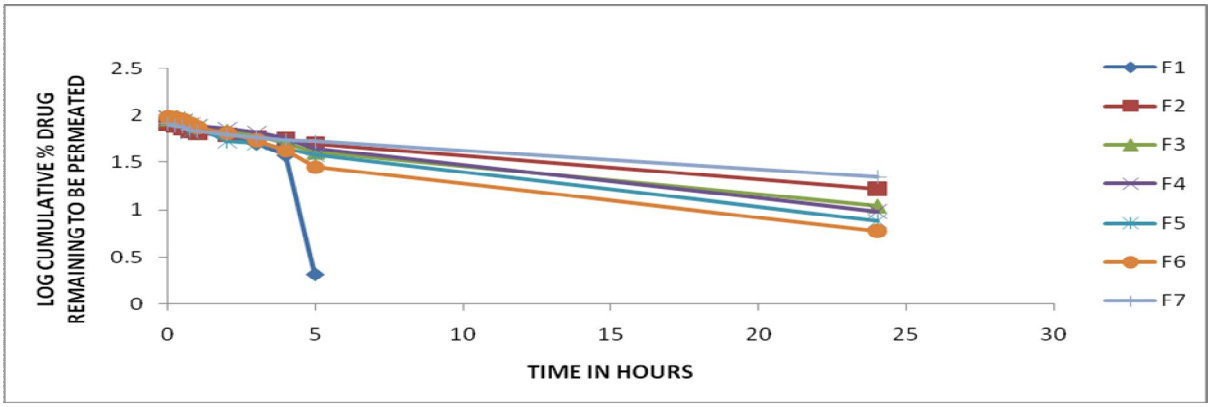

Figure 7: Comparative in vitro drug release studies of various salbutamol sulphate transdermal patches, for First order permeation kinetics model

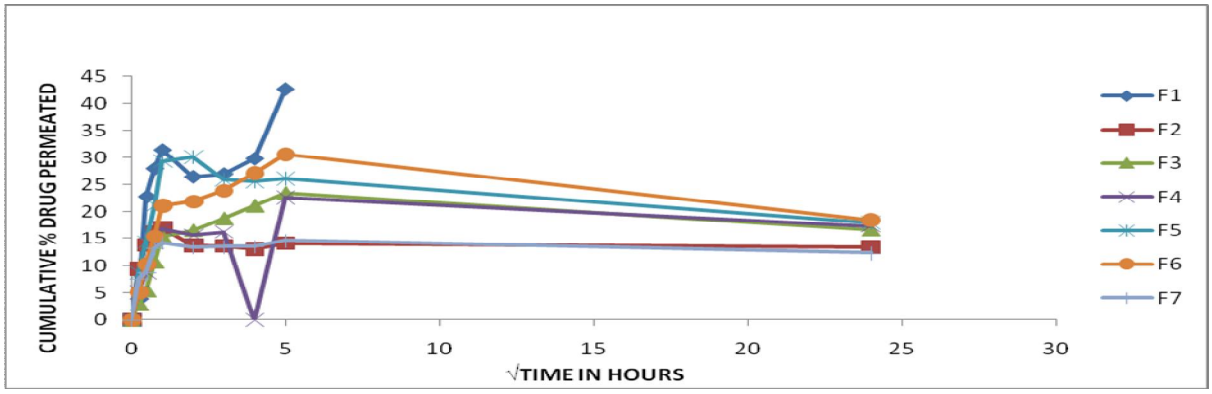

Figure 8: Comparative in vitro drug release studies of various salbutamol sulphate transdermal patches, for Higuchi permeation kinetics model

RESULTS AND DISCUSSION

EVALUATION OF TRANSDERMAL PATCH

Preparation of Salbutamol Sulphate transdermal patches

The salbutamol sulphate loaded matrix type transdermal films were prepared by using "solvent evaporation method". Hydrophilic and lipophilic polymers (such as HPMC and EC respectively) in different ratios separately were dissolved in 5ml of chloroform: methanol (1:1) solvent system and kept aside for formation of clear solutions. Di-butyl phthalate (DBP) was used as plasticizer and dimethyl sulfoxide (DMSO) was used as penetration enhancer. 5 mg of drug was dissolved in above clear solution and mixed for 20 minutes. The resulted uniform solution was casted on the aluminium circular ring of 30.175 cm^2 surface area and dried at 40°C in hot air oven for 24 hours. An inverted funnel was placed over each mould separately to prevent fast evaporation of the solvent. After 24 hours the dried films were taken out and stored in desiccators for further characterization and evaluation of the films/patches.

Physical appearance of the patches:

Film appearance showed that the uniform films were formed. It was observed that patches were found to be almost transparent or white in the colour, smooth, clarity & soft because of addition of Di-butyl phthalate, as plasticizer which helped in preparation of flexible films.

Thickness of the patch:

The thickness of the patches was varied from 0.030 mm to 0.056 mm. The film shows increase in thickness was linear with in polymer concentration. The results are tabulated in table 2. Low standard

deviation values in the film thickness measurements ensured uniformity of the patch prepared by solvent evaporation.

Folding endurance:

The folding endurance were measured manually, the result showed that folding endurance was found to be maximum for formulation F1 (108 folds) whereas, minimum for formulation F7 (53 folds). The result was tabulated in Table 2. This indicates that the maximum folding endurance having films would not break and would maintain their integrity with general skin folding when applied.

Percentage moisture absorption:

The result showed that moisture uptake was found to be maximum for formulation F1 (12.8) whereas moisture uptake observed to be minimum for formulation F7 (1.52). The result are recorded in Table 2 and shown graphically in figure 1. The water absorption capacity was found to be more for hydrophilic polymer HPMC then lipophilic polymers EC at 80-90% R.H., which attributed to the hygroscopic nature of HPMC. The moisture uptake provides information regarding the stability of the formulation, conversely moisture absorbed did not affect film strength and the integrity.

Percentage moisture Loss:

The moisture content studies provide information regarding the stability of the formulations. The result showed that percentage moisture content was found to be maximum for formulation F1 (13.4) whereas, minimum for formulation F6 (8). The result are recorded in Table 2 and shown graphically in figure 1. The moisture content in the formulations was found to increases with increasing concentration of hydrophilic polymer (HPMC) & decreasing concentration of lipophillic polymer EC, because it attributed to the hygroscopic nature while increasing concentration of hydrophilic polymer decreasing concentration of lipophilic polymer (EC). But small moisture content in the formulation maintains stability, & helped patches from being completely dry & brittle.

The optimum moisture content is better requirement for TDDS development which is shown by formulation F6 consisting of both hyrophillic and lipophillic polymers in 5:5 ratio.

Water vapour transmission rate (WVTR) evaluation:

The result showed after 24 hours that water vapour transmission rate was found to be maximum for formulation F7 (0.0198) whereas, minimum for formulation F1 (0.0116) was observed. *Similar results were obtained after 72 hours. *The result are recorded in Table 2 and shown graphically in figure 2. The optimum WVTR was found to be for formulation F6 (0.01243) after 24 hours. The variation in

WVTR may be due to vaporization rate of the casting solvent, which may alternately depend upon its boiling point and vapour pressure during de-solvation of polymer.

Drug content:

The result showed that the drug content of the salbutamol sulphate transdermal patches was ranges from 82.04% to 97.19%. The result showed that drug content was found to be maximum for formulation F1 (97.19) whereas drug content observed to be minimum for formulation F7 (82.04). The results were recorded in Table 2. This indicates minimum batch variability, which demonstrates homogenous distribution of the drug and thus, gives assurance of the strength of slow dose drugs.

In vitro drug release studies:

Released studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance.

The result showed that in vitro drug release of the salbutamol sulphate transdermal patches was found to be maximum for formulation F1 (94.595) in 5 hours and for formulation F6 (89.189) in 24 hours respectively whereas, after 24 hours in vitro drug release observed to be minimum for formulation F7 (67.16). The results are recorded in Table 2. Different release kinetics (zero order, first order & Higuchi order) mechanism were tabulated in table 3 showed zero order release kinetics for formulation F1 having R^2 = 0.9835 & slope = 17.807, as compared to the formulations F2-F7 showed First order release kinetic mechanism because in vitro drug release kinetics varies from R^2 = 0.9596 to 0.9795 which were shown graphically in figure 3-5.

In vitro skin permeation studies:

The cumulative amount of salbutamol sulphate permeated through animal cadavers skin, into a receptor solution, as a function of time from the various patches were observed and different kinetic model were studied for mechanism of permeation.

The result showed that in vitro drug permeation of salbutamol sulphate transdermal patches was found to be maximum for formulation F1 (95.138) in 5 hours and for formulation F6 (90.4286) in 24 hours respectively whereas, after 24 hours in vitro drug permeation observed to be minimum for formulation F7 (60.06). The results are recorded in table 2. F6 emerging as a best formulation since it is fulfilling the requirement of better and sustained release which was not possible with HPMC and EC alone.

Permeation mechanism kinetic reveals that formulation F1 and F4 showed Higuchi mechanism having value of R^2 to be 0.7028 & 1 respectively while, other formulations followed First order permeation kinetics having R^2 ranging from 0.9401 to 0.985, shown graphically in figure 6-8.

The drug release study and permeation studies of matrix films showed that cumulative % drug release (% CDR) and cumulative drug permeation (%CDP) were in the manner, that on increasing concentration of hydrophilic polymer while decreasing concentration of lipophilic polymer increased %CDR and %CDP respectively were obtained.

Increasing the proportion of hydrophilic polymer (HPMC) concentration in the polymer matrix increases the % cumulative drug release and % cumulative drug permeation is observed; because of highly hydrophilic nature of HPMC, which has very less interactions with drug. Due to its high hydrophilicity it absorbs water, dissolution of aqueous soluble fraction of polymer matrix leads to the swelling of polymer which results into more release of drug from gelaneous pores of the films because of adequate porosity & diffusivity. The formation of such pores leads to decrease the mean diffusion path length of the drug molecules to release and permeates into the diffusion medium & hence, to cause higher release rate and permeation rate respectively.

EC attributed to the relatively hydrophobic nature of polymer which were having less affinity for water, results in decrease in thermodynamic activity of the drug in the film & decreased drug release and permeation was obtained. And EC can be used as 'better release retardant' at higher concentration as compared to the HPMC. It is well acknowledged that the addition of hydrophilic component to an insoluble film former tends to enhance its release rate and permeation rate because HPMC is more permeable polymer but for short time period only. By using lipophilic polymer along with hydrophilic polymer combination, release rate and permeation rate can be achieved in controlled manner for longer time period.

CONCLUSION

Controlled release TDDS patches of salbutamol sulphate can be prepared using the polymer & penetration enhancer combinations, HPMC and EC in different concentration with Dimethyl sulphoxide as enhancer and Dibutyl phalate as plasticizer respectively were used for formulation of TDDS. The release rate of drug through patches increased when the concentration of hydrophilic polymer was increased. The drug release and permeation studies of all fabricated patches reveals that

formulation F6 showed maximum release and permeation of drug for longer time period upto 24 hours. So, F6 formulation containing hydrophilic and lipophillic polymers (5:5 ratio) were suitable for development of controlled release patches of salbutamol sulphate. Hence proposed drug delivery system not only overcome the disadvantage of oral drug delivery but also can be exploited for the improvement of the anti-asthamatic therapy without any side effect.

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