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RESEARCH PAPER

Development and In Vitro Evaluation of Polymeric Responsive Release Matrix Type Transdermal Patches of Two Anti-asthmatic Drugs

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Abstract
Ketotifen fumarate, a mast cell stabilizer, and salbutamol sulfate, a bronchodilator, are frequently prescribed together for chronic asthma. This study aimed to combine both anti-asthmatic drugs in single polymeric responsive matrix type transdermal patches. Drug release from polymeric device was optimized by varying ratios of hydrophilic (polyvinyl pyrrolidone) and hydrophobic (ethyl cellulose) polymers. Propylene glycol was used as plasticizer and solvent system including mixture of chloroform and methanol. Physicochemical evaluations like thickness, weight variation, folding endurance, tensile strength, content uniformity and % moisture absorbance of developed patches were carried out. Developed patches were also subjected for in vitro release of drugs, and formulation of P6 with equal proportion of polyvinyl pyrrolidone and ethyl cellulose found optimized formulation with respect to release rate of both drugs. 76.49% of ketotifen fumarate and 77.49% of salbutamol sulfate were released from P6, and release of both drugs sustained up to 24 h. In the next step, permeability enhancers like Tween 20, isopropyl myristate, eucalyptus oil and span 20 were added to the formulation P6 and subjected to in vitro permeation study on Franz diffusion cell using rabbit skin. Results of in vitro permeation study revealed that transdermal patches with permeation enhancers permeate the significant amount of drugs in comparison with the formulation without enhancer.

Keywords Anti-asthmatics · Transdermal patches · Polymers · Enhancers · Release · Permeation

1 Introduction

Oral route of drug administration is the most common and popular route, but due to some disadvantages like first pass metabolism, degradation of drug in stomach and gastrointestinal tract (GIT) and irritation of GIT due to extreme pH of some drugs lead to less patient adherence to oral route of drug administration. Therefore, oral route is not considered as ideal route of drug administration. In order to overcome the problems associated with conventional routes of drug administration, there is a need to develop a novel route of drug delivery like transdermal drug delivery system or patches (Banker et al. 1990; Chien 1992; Guyz 1996). Transdermal drug delivery system consists of medicated patches which intend to stick on intact skin in order to permeate the drug into systemic circulation at predetermined rate for desired period of time. Rate and extent of release and permeation of drug(s) from transdermal device can be controlled to the desired rate by appropriate combination of different polymers (hydrophilic and hydrophobic) (Alexander et al. 2012; Misra 1997). Polymers are considered the backbone of transdermal drug delivery system. Matrix of patch is prepared by dissolving the polymer in a solvent, followed by dispersion of drugs in prepared solution. Polymers intended to use in formulation of transdermal device should be biocompatible and chemically inert with drug

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and other excipients of system like enhancers, plasticizers, solvents and adhesive materials. Polymer should remain stable throughout the products shelf-life. It is well known that the popular polymers such as PVP, EC, Eudragit RL and Eudragit RS are compatible with a number of drugs (Rama and Diwan 2000). From transdermal drug delivery system, drug can be delivered at desired rate by using appropriate combination of polymers (Keith 1983; Chien 1987; Walter 1991; Misra 1997). Cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan are natural polymers used in transdermal drug delivery system. Synthetic polymers frequently used to fabricate transdermal drug delivery system are polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone, polymethyl methacrylate and crossed linked polymers like polyethylene glycol, eudragits, ethyl cellulose and hydroxypropyl methylcellulose (Verma and Lyar 2000; Ubaidulla et al. 2007; Bromberg 1996). Ketotifen fumarate is mast cell stabilizer having anti-asthmatic, anti-allergic and anti-conjunctivitis activity (Yousuf et al. 2013). Salbutamol sulfate is a bronchodilator used to treat the compliance associated with bronchial asthma. Ketotifen fumarate and salbutamol sulfate are frequently prescribed together in case of chronic asthma (Misra 1997; Yousuf et al. 2013).

Prescription of complex drug regimens by the physicians is one of the contributing factors to poor medication adherence; therefore, formulating them in single dosage regimen may prove helpful to increase patient's adherence to the prescribed medicines (Brown et al. 2011).

In the present project, matrix type polymeric responsive transdermal drug delivery system of two anti-asthmatic drugs, ketotifen fumarate and salbutamol sulfate was designed. Release of drugs from polymeric devices was optimized by varying ratios of hydrophilic and hydrophobic polymers. Physicochemical properties of patches were evaluated and found satisfactory. In vitro release of drug from patches with different polymeric combination was also studied. The formulation P6 founded optimized formulation with respect to release of both drugs and release of both drugs sustained up to 24 h. The optimized formulation was subjected for in vitro permeation of drugs using Franz diffusion cell, through excited rabbit skin membrane, and further, the effect of different permeation enhancers was also examined on the permeation of drugs. Results of in vitro permeation study revealed that transdermal patches with permeation enhancers permeate the significant amount of drugs in comparison with the formulation without enhancer.

2 Experimental

2.1 Materials

Salbutamol sulfate (SS) was obtained as gift sample from GlaxoSmithkline (Karachi, Pakistan). Ketotifen fumarate (KF) was supplied as gift sample from Barrett Hodgson (Karachi, Pakistan). Ethyl cellulose (EC $\sim$ 5.1 cps), poly vinyl alcohol 72,000 amu (PVA) and polyvinyl pyrrolidone (PVP) were purchased from Sigma-Aldrich (UK). Eucalyptus oil was purchased from George Rennie (France). Isopropyl myristate (IPM) was purchased from Panreac Quimica (USA). Tween 20, span 20 and chloroform were purchased from BDH (UK). Methanol and propylene glycol (PG) were purchased from Merck (Germany). All other chemicals used were of analytical grade.

2.2 Preparation of Backing Membrane

Polyvinyl alcohol as backing membrane was used, which was prepared by slight modification in method reported by Gupta and his coworker (Gupta and Biswajit 2003). For fabrication of backing membrane, 100 ml of double distilled water was taken in conical flask, and water was stirred continuously on hot plate stirrer at 80 °C. 4 g of polyvinyl alcohol was gradually added to water, and stirring was continued for 1 h. After 1 h, polymeric solution of polyvinyl alcohol (4% w/v) was cooled and the entrapped air was removed by sonicator (Elmasonic, Elma E 30 H) for 5 min. Finally, 15 ml of the homogenous solution was transferred in glass petri dishes with an area of 61 cm^2, and petri dish having solution for backing membrane was dried at room temperature for 24 h.

2.3 Preparation of Polymeric Matrix

Table l shows formulation variables of transdermal patches with various polymeric combinations. Polymeric matrix was prepared by taking 100 ml of solvent mixture of chloroform and methanol (1:1) in 250-ml conical flask. Weighed amount of polymers, ethyl cellulose and polyvinyl pyrrolidone (given in Table 1) were added into the flask gradually. 1.75 gm of plasticizer propylene glycol (PG) was also added to the flask. The flask was covered with aluminum foil in order to prevent the loss of solvent by evaporation. The solution was stirred at 500 rpm by magnetic stirrer (Velp Scientifica, Germany) for 30 min. After 30 min, weighted amounts (0.620 g KF and 2.480 g SS) of both anti-asthmatic drugs were added and the stirring was continued for further 30 min in order to obtain a homogenous dispersion of drugs in matrix solution. Then, the entrapped air was removed by sonicating matrix

Table 1 Formulations variables of polymeric matrix type transdermal patches

Formulations	Propylene glycol (g)	Chloroform–methanol mixture 1:1 (ml)	Polymeric combinations (g)	
			Ethyl cellulose	Polyvinyl pyrrolidone
P1	1.75	100	10	0
P2	1.75	100	9	1
P3	1.75	100	8	2
P4	1.75	100	7	3
P5	1.75	100	6	4
P6	1.75	100	5	5
P7	1.75	100	4	6
P8	1.75	100	3	7
P9	1.75	100	2	8
P10	1.75	100	1	9
P11	1.75	100	0	10

dispersion (Elmasonic, Elma E 30 H) for 5 min. Finally, 10 ml of prepared matrix dispersion was poured in petri dish already containing backing membrane. A funnel was inverted on the petri plate in order to avoid the rapid evaporation of solvent, because rapid evaporation of solvent leads to produce the rigid and tough membrane. For drying the matrix solution, petri plate was placed on horizontal surface at room temperature for 24 h. After drying, fabricated patches were removed from petri plate, wrapped in aluminum foil, labeled and stored at 25 °C[14]. For in vitro evaluation, patches were cut into an area of 1.5 cm^2 circular disk.

2.4 Addition of Permeation Enhancer to Polymeric Matrix

For preparation of transdermal patches with permeation enhancers, polymeric matrix was prepared by the same method described above. Before casting the matrix into petri plate, weighed amount of permeation enhancer (Tween 20, isopropyl myristate, eucalyptus oil and span 20) was added to polymeric matrix dispersion and solution was stirred for 10 min, followed by sonication for 2 min. Table 2 depicts the formulations variables of transdermal patches with various permeation enhancers. The solution casting for patch preparation, drying, removing, cutting and storing of transdermal patches was carried out by the same method as applied for formulation without enhancers.

2.5 Thickness Uniformity

The thickness uniformity test was performed to ensure the uniformity of patches with regard to thickness. The test was performed by measuring the thickness of formulated film at five different places ($n = 5$) using micrometer screw gauge (Sharpfine Type-A, China). Average values were calculated from the given readings (Shivaraj et al. 2010).

2.6 Weight Uniformity

Uniformity in weight of fabricated film was insured by conducting the weight uniformity test. Five patches of an area of 1.5 cm^2 were randomly selected, and each patch was weighted individually on digital balance (Shimadzu AUX220, Germany). The mean values were calculated from obtained weight (Saxena et al. 2006; Sathyapriya et al. 2008).

2.7 Percentage Moisture Absorption

Percent moisture absorption study was performed to determine the extent to which formulated transdermal patches uptake the moisture or water. In order to evaluate the moisture absorption by patches in percentage, patches was precisely cut in circular disk of 1.5 cm^2, weighted and stored in desiccator at 84% relative humidity maintained by a saturated solution of aluminum chloride and having room temperature. Patches were weighed again after 24 h, and percent moisture absorption was calculated from differences in initial and final weight of films by using formula:

$$\text{Percent moisture absorption} = \frac{W_f - W_i}{W_i} \times 100$$

W_i = initial weight; W_f = final weight (after 24 h).

2.8 Folding Endurance

Strength of patches was determined by conducting the folding endurance test. The test was performed manually; a film of 2 × 5 cm was cut and folded repeatedly at same place till the film was broken or showed any crack. The number of times patches was fold at same place without any damage elaborating the values of folding endurance. For each formulation, five patches were checked and average was computed (Sankar et al. 2003).

2.9 Tensile Strength

Mechanical properties of fabricated polymeric patches were determined by measuring the tensile strength of formulated films. Tensile strength of patches was measured by modified pulley system, the instrument has fixed scale on horizontal wooden platform, and it has two clips: One is fixed on a side of platform and the other is movable. For measuring the tensile strength, a strip of 2 cm width and 5 cm length was cut, and one end of strip was held in fixed

Table 2 Formulation variable of transdermal patches with various permeation enhancers

Ingredients	Formulations				
	PE1	PE2	PE3	PE4	PE5
Ethyl cellulose (g)	1.5	1.5	1.5	1.5	1.5
Polyvinyl pyrrolidone (g)	1.5	1.5	1.5	1.5	1.5
Propylene glycol (g)	1.75	–	–	–	–
Tween 20 (g)	–	5	–	–	–
Isopropyl myristate (g)	–	–	5	–	–
Eucalyptus oil (g)	–	–	–	5	–
Span 20 (g)	–	–	–	–	5
Chloroform–methanol mixture (1:1 v/v) (ml)	100	100	100	100	100

clip of apparatus and other end in movable jaw of instrument. The weight was gradually increased until strip was broken, and tensile strength was calculated by formula given below.

$$\text{Tensile strength} = \frac{F}{a.b(1 + L/l)}$$

where F is the force required to break; a is the width of film; b is the thickness of film; L is the length of film; l is the elongation of film at break point.

The experiment was performed on five formulations of single batch, and average values were computed from the given readings (Kulkarni et al. 2002; Baichwal 1985).

2.10 Drug Content Uniformity

Uniformity of drug content was assured by comparing drug-loaded patches with blank patches (without drug). The films were cut into small pieces of an area of 1.5 cm^2 and placed in 100 ml of water in conical flask and stirred continuously on magnetic stirrer for 36 h. Then, the solution was sonicated for 30 min and filtered. The suitable dilutions were prepared with distilled water, and samples analyzed on double-beam UV–visible spectrophotometer (Shimadzu-1601, Germany) at wavelength of 300 nm for ketotifen fumarate and 276 nm for salbutamol sulfate (Garala et al. 2009).

2.11 In Vitro Release Study

In vitro release of both anti-asthmatic drugs, i.e., ketotifen fumarate and salbutamol sulfate from developed transdermal patches, was studied using dissolution apparatus (PTDT7 Pharma Test, Germany). 500 ml phosphate buffer (pH 6.8) at a temperature of 32 ± 0.5 °C was used as dissolution media. An accurately cut patch of an area of 1.5 cm^2, containing 1.5 mg of ketotifen fumarate and 6 mg of salbutamol sulfate, was placed in watch glass of diameter 3 inch, with releasing surface facing upward. Patch on watch glass was covered with stainless steel mesh (25 µm) using stainless steel clips. The disk assembly holding transdermal patch is given in Fig. 1. The compact disk assemblies containing transdermal devices are placed at the bottom of vessel. Dissolution medium was keep stirring continuously with paddle over a speed of 50 rmp through experimentation period. 2 ml of sample from dissolution medium was collected with auto sampler (PTFC II, Pharma Test, Germany) at various time intervals at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20 and 24 h. The amounts of both the drugs ketotifen fumarate and salbutamol sulfate released at specified time points were analyzed by UV spectrophotometric method. In vitro release study of newly developed transdermal patches was conducted on five patches of each formulation, and average values were computed.

2.12 In Vitro Permeation Studies

In vitro permeation study of newly developed combined anti-asthmatic transdermal patches of ketotifen fumarate and salbutamol sulfate was conducted on Franz diffusion cell (Permegear, Bethlehem USA) having an area of 1.5 cm^2, and volume of receptor compartment was 12 ml. Depilated, excised hair-free skin membrane of rabbit was used in permeation study due to difficulty in obtaining human skin samples (Chi et al. 2010). Phosphate buffer (pH 7.4) was used as receptor fluid. The receptor medium (phosphate buffer) was filled in receptor compartment of Franz diffusion cell, and temperature of outer jacket was set at 37 ± 1 °C, by continues circulation of water from thermostatic water bath (Brookfield, USA). Diffusion cell assembly comprised of magnetic stirrer, Franz diffusion cell and water bath with pump. 37 ± 1 °C temperature of outer jacket maintains temperature of inner jacket at 32 ± 1 °C (temperature of skin); difference in temperature is due to loss of heat in plastic tubes that supply the water to outer jacket of Franz diffusion cell from water bath (Hyun and Kyun 2002; Girish et al. 1996). A piece of

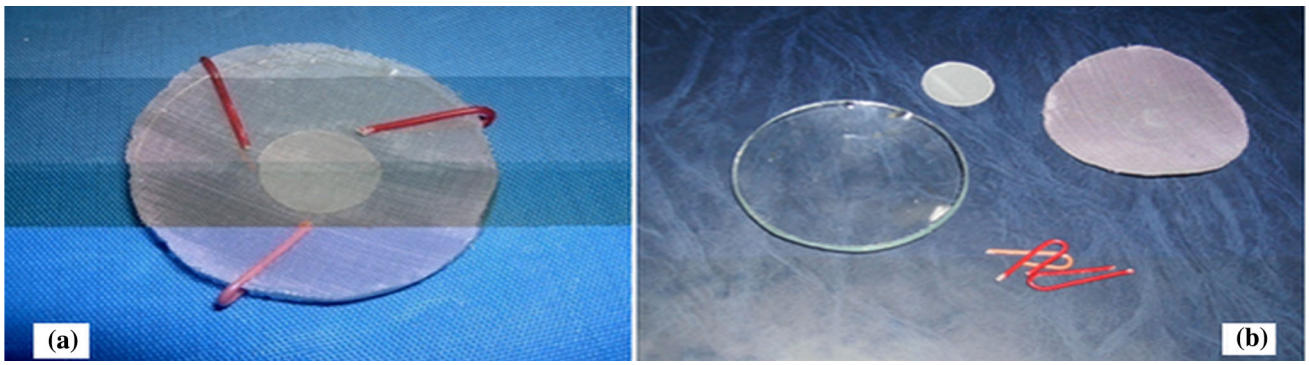

Fig. 1 Transdermal patch dissolution setup **a** disk assembly; **b** watch glass, clips, wire mesh and patch

Table 3 Physical properties of newly developed transdermal patches

Formulations	Physical properties of transdermal patches				
	Weight variation (mg) ± SD $n = 5$	Thickness (μm) ± SD $n = 5$	Moisture absorption (%) SD $n = 5$	Folding endurance SD $n = 5$	Tensile strength (kg/cm^2) SD $n = 5$
P1	26.56 ± 0.001	22 ± 0.001	3.4 ± 0.08	135 ± 0.9	0.51 ± 0.03
P2	27.01 ± 0.004	24 ± 0.015	3.6 ± 0.05	136 ± 1.2	0.54 ± 0.07
P3	27.94 ± 0.002	23 ± 0.029	3.7 ± 0.07	142 ± 1.5	0.60 ± 0.02
P4	28.13 ± 0.005	25 ± 0.005	3.8 ± 0.06	149 ± 1.0	0.61 ± 0.09
P5	29.07 ± 0.004	25 ± 0.006	3.8 ± 0.04	153 ± 1.7	0.63 ± 0.06
P6	29.92 ± 0.009	26 ± 0.012	3.9 ± 0.03	155 ± 1.6	0.66 ± 0.04
P7	30.51 ± 0.008	27 ± 0.009	4.1 ± 0.10	159 ± 1.4	0.69 ± 0.01
P8	31.22 ± 0.003	27 ± 0.007	4.2 ± 0.90	161 ± 1.8	0.71 ± 0.08
P9	31.00 ± 0.013	28 ± 0.004	4.2 ± 0.12	164 ± 1.5	0.74 ± 0.10
P10	29.00 ± 0.020	29 ± 0.001	4.4 ± 0.05	166 ± 0.8	0.73 ± 0.50
P11	29.92 ± 0.018	30 ± 0.008	4.5 ± 0.07	170 ± 1.6	0.70 ± 0.12

The values are expressed as mean ± SD, where SD is standard deviation

depilated hair-free rabbit skin membrane was cut in size equal to open end of receptor compartment of Franz diffusion cell and placed over the receptor compartment so that skin cover the open end of cell completely. Circular disk of patch having an area of 1.5 cm^2 with releasing surface toward the skin was placed over the skin membrane fitted to receptor compartment. The donor compartment of cell was set over the receptor compartment with stainless steel clamp, and junction of assembly was covered with petroleum jelly in order to provide the occlusive condition. The settled assembly was placed over the magnetic stirrer (Velp Scientifica, Germany), and the receptor fluid was kept under stirring continuously at a speed of 500 rpm during tests by using magnetic bars.

Sample of 1 ml was taken at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20 and 24 h through the sample port and replaced with equal volume of fresh receptor medium, using long needle syringe. After suitable dilution, sample was analyzed on UV–visible spectrophotometer (Shimadzu 1601, Japan) at a wavelength of 300 nm for ketotifen fumarate and 276 nm for salbutamol sulfate.

3 Results and Discussion

3.1 Weight Variation Test

Results of weight variation study revealed that weight of individual patch of 1.5 cm^2 lies in range of 26.56 ± 0.001–31.22 ± 0.003 mg. Weight of individual patches was found to increase slightly as amount of hydrophilic polymer increased, and this may be due to absorption of water by hydrophilic polymer in matrix of patch. Table 3 indicates the weight of transdermal patches along with standard deviation, and low values of standard deviation ensure the uniformity in weight of developed transdermal patches.

3.2 Thickness Uniformity Test

Table 3 shows the thickness of transdermal patches in micrometer and their standard deviations. Results of thickness evaluations show that thickness of patch was 22 ± 0.001–30 ± 0.008. Thickness of developed patches also increased slightly with increasing amount of hydrophilic portion of film former. Low values of standard deviation revealed that plate casting is a reliable method to develop the transdermal patches with uniform thickness.

3.3 Moisture Absorption

Results of moisture absorption study show that formulations absorbed 3.4 ± 0.08–4.5 ± 0.07% of moisture, and Table 3 represents the results of moisture absorption capacity of formulated patches. Absorption capacity varies from patch to patch depending upon the composition of polymers used to fabricate the film. Formulation with high ratio of hydrophilic polymer absorbed more amount of moisture. This may be attributed to hydrophilic nature of polyvinyl pyrrolidone, and the presence of polyvinyl pyrrolidone made the film spongier due to the irregular arrangement of molecule and spaced the molecules further apart than in fabricated film which ultimately increases the capacity of matrix to absorb the water. Results of moisture absorption study are in agreement with the previous studies conducted by Arora (2002). The presence of PG further supports the absorption of moisture due to its humectants nature. The formulated films should not absorb large amount of moisture content as low amount of moisture absorbed by patches is in the favor of patches to keep them stable and intact, and dry films are also remains protected from microbial growth (Mutalic and Udupa 2004).

3.4 Folding Endurance

Folding endurance test was performed to determine the strength of fabricated films. Table 3 lists the results of folding endurance test of transdermal formulations with various ratios of hydrophilic and hydrophobic polymers, and the values were in range of 135 ± 0.9–170 ± 1.6. The films formulated with large proportion of polyvinyl pyrrolidone showed high folding endurance and vice versa. This increase in tensile strength by increasing the hydrophilic polymer may be explained by fact that formulations with large amount of polyvinyl pyrrolidone have capability to absorb the more amount of water, and in polymeric film, water acts as plasticizer and makes film flexible which ultimately increases the folding endurance (Minoura 1996).

3.5 Tensile Strength

Mechanical property of formulated films was determined by measuring the tensile strength of developed film. Table 3 gives the readings for obtained results of tensile strength in kg/cm^2, and value was in the range of the 0.51 ± 0.03–0.70 ± 0.12 kg/cm^2. Results of study reveal that tensile strength increased with an increasing ratio of polyvinyl pyrrolidone. This may be attributed to the hydrophilic nature of polymer, which increases the capacity of matrix to absorb the water, and water acts as plasticizer and make membrane flexible, thus increasing the tensile strength of fabricated film.

3.6 Content Uniformity

In order to judge distribution of both anti-asthmatic drugs in polymeric matrix, content uniformity test was conducted. Table 4 elaborates the results (%) of both drugs distributed in polymeric matrix. Percent content of ketotifen fumarate was between 97.63 ± 0.07 and 103.87 ± 0.02%, and salbutamol sulfate was 98.32 ± 0.06–103.81 ± 0.05%. Low difference among formulations and less values of standard deviation ensured the uniform distribution of both drugs in polymeric matrix. From obtained results of study, it can be concluded that solvent casting is a suitable method for developing transdermal patches of multiple drugs with uniform distribution.

3.7 In Vitro Drug Release Study

In vitro release study for transdermal patches was carried out for 24 h. Percent release data of ketotifen fumarate and salbutamol sulfate at various time periods are depicted in Figs. 2 and 3, respectively. Developed patches showed considerable amounts of both drugs released within 10 to 12 h, but release rate varies depending upon ratio of hydrophilic and hydrophobic polymers used to fabricate the patches. Maximum amounts of both drugs were released from formulation P11 (99.33% of ketotifen fumarate and 99.09% of salbutamol sulfate) within 6 h. However, transdermal formulations with high portion of hydrophilic polymers were not suitable to sustain the release of drugs for prolonged period of time. Rapid release of both drugs from the system was due to addition of hydrophilic polymer and polyvinyl pyrrolidone. Polyvinyl pyrrolidone has strong co-enhancing property in aqueous medium and dissolves rapidly in dissolution medium. Dissolution of hydrophilic portion of membrane leads to formation of pores in ethyl cellulose matrix. The spongy structure of membrane allows fast permeation of dissolution medium causing rapid dissolution of surface

Table 4 Content % of ketotifen fumarate and salbutamol sulfate in transdermal drug delivery system

Formulations	Contents % ± SD	
	Ketotifen fumarate	Salbutamol sulfate
P1	97.63 ± 0.07	98.32 ± 0.06
P2	99.43 ± 0.06	101.54 ± 0.05
P3	103.87 ± 0.02	100.01 ± 0.03
P4	98.71 ± 0.03	99.35 ± 0.04
P5	101.12 ± 0.09	98.86 ± 0.07
P6	100.24 ± 0.05	102.02 ± 0.017
P7	99.42 ± 0.15	101.48 ± 0.09
P8	102.67 ± 0.07	98.73 ± 0.08
P9	97.89 ± 0.01	99.42 ± 0.02
P10	100.29 ± 0.03	103.81 ± 0.05
P11	98.11 ± 0.06	101.09 ± 0.07

The values are expressed as mean ± SD, where SD is standard deviation

hydrophilic drugs and higher release rates (Guyot and Fawaz 2000; Gannu et al. 2007). Results of dissolution studies revealed that formulation P6 with equal proportion of hydrophilic and hydrophobic polymers showed release of drugs more suitable and sustained patron in comparison with all other formulations. The patches P6 released 76.49% of ketotifen fumarate and 77.49% of salbutamol sulfate at the end of 24 h. The present formulation neither showed rapid release nor retarded the release of both drugs during the period of dissolution. On the basis of results of release rate and release pattern, patches P6 were selected for further permeation study. Effects of various permeation enhancers were also checked on permeation of both anti-asthmatic drugs through excited rabbit skin membrane.

3.8 In Vitro Permeation Study

Developed transdermal patches P6 with equal ratios of hydrophilic and hydrophobic polymers (EC:PVP 1:1) were considered as optimized formulation on the basis of release rate and extended duration of release. The present formulation was selected for further in vitro permeation study, and effects of various permeation enhancers were also studied on the permeation of drug through rabbit skin membrane. Table 2 gives formulation variable of developed transdermal patches with various permeation enhancers. Permeation studies of optimized formulations with various enhancers like Tween 20, isopropyl myristate, eucalyptus oil and span 20, were conducted for 24 h on Franz diffusion cell. The cumulative amounts of ketotifen fumarate and salbutamol sulfate were calculated in microgram and plotted against the time in graph, and Figs. 4 and 5 depict the amount of both anti-asthmatic drugs permeated at various time points.

Formulations PE1-PE5 showed significant amounts of both drugs permeated within 24 h. PE3 showed the highest amounts (1272.83 µg or 84.85% of ketotifen fumarate and 5043.10 µg or 84.05% of salbutamol sulfate) of both anti-asthmatic drugs permeated in 24 h. However, formulation PE1 without permeability enhancer showed a permeation of 752.52 µg or 50.16% of ketotifen fumarate and 3068.22 µg or 51.13% of salbutamol sulfate. Flux for both the drugs was also calculated and is given in Table 4. Amount of drugs released from patches is accumulated on surface of skin and available for permeation through membrane. Rapid release of ketotifen fumarate and salbutamol sulfate was due to the addition of hydrophilic polymer polyvinyl pyrrolidone. PVP increases the rate of release of both drugs. Addition of permeability enhancer increases permeations of both drugs through rabbit skin membrane. All formulations with permeability enhancers

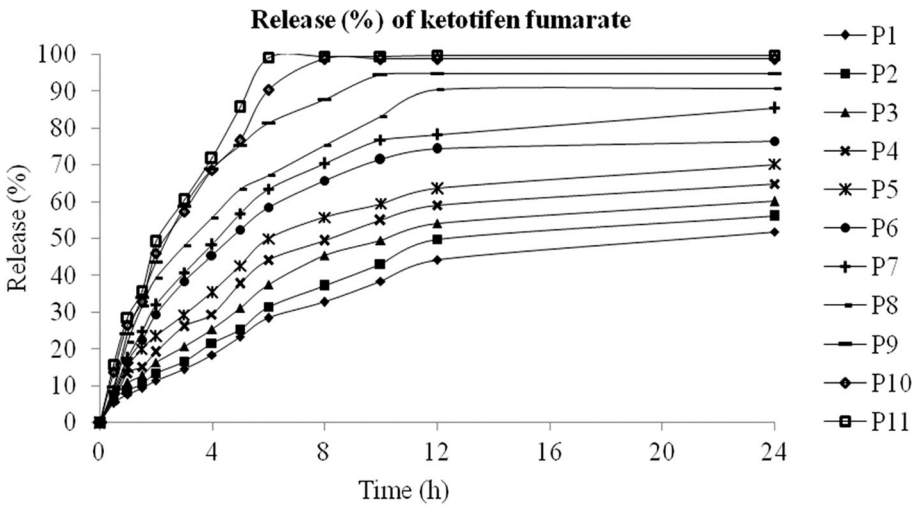

Fig. 2 Release (%) of ketotifen fumarate from patches with various polymeric ratios

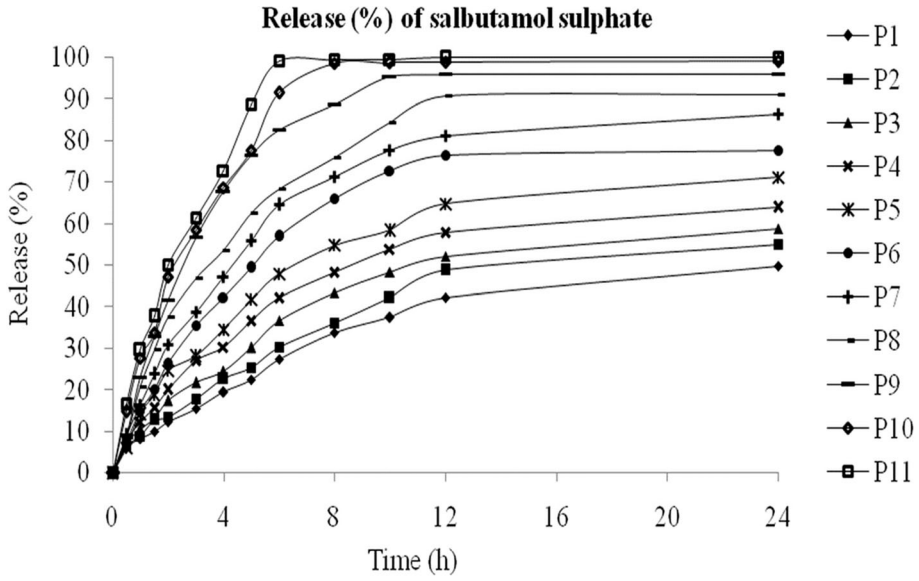

Fig. 3 Release (%) of salbutamol sulfate from patches with various polymeric ratios

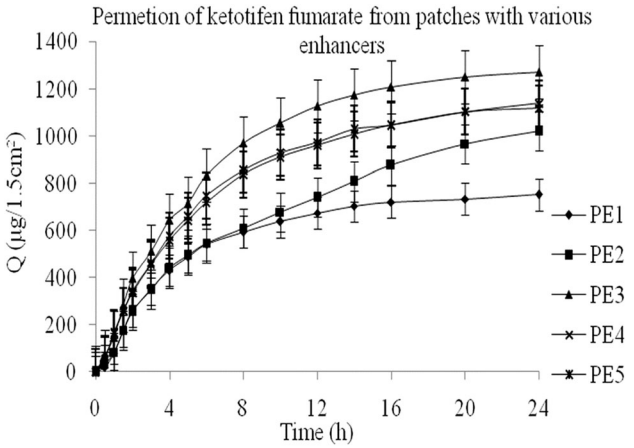

Fig. 4 In vitro permeation profile of ketotifen fumarate, from formulations with various permeation enhancers

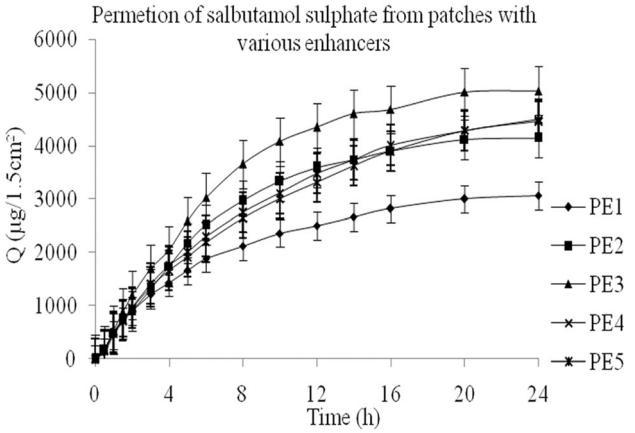

Fig. 5 In vitro permeation profile of salbutamol sulfate, from formulations with various permeation enhancers

showed significant amounts of both anti-asthmatic drugs permeated. The slight difference was noted in cumulative amounts of drugs permeated through rabbit skin from transdermal patches with various enhancers. This difference in permeation may be due to the reason that each enhancer has its unique mechanism of permeation like Tween 20 being a non-ionic surfactant used to enhance the permeability of drug though stratum corneum. The permeation promoting activity of non-ionic surfactants (Tweens) may be due to reduction in surface tension, improvement in wetting of skin and enhanced distribution of drug in matrix patch (Tanwar 2005). Tween 20 increases partitioning of polar molecules across the barrier more easily. Non-ionic surfactants in aqueous media lead to form large micelles. These micelles have the potential to remove lipid molecules from skin membrane rendering skin more porous and favorable for permeation of hydrophilic drug (Ibrahim et al. 2004). Among transdermal patches of polymeric combinations, formulations having isopropyl myristate showed the superior behavior in terms of cumulative permeation of both anti-asthmatic drugs. This desired behavior of PE3 may be attributed to the use of an optimized combination of hydrophilic and hydrophobic polymers and pronounced enhancing effect of isopropyl myristate. Isopropyl myristate is an ester-type enhancer. Isopropyl myristate interacts more easily with lipid portion of stratum corneum and modifies reversibly the structure of stratum corneum of skin. Thus, permeability of drugs from transdermal patches is increased (Lalatendu et al. 2005).

The penetration enhancing effect of eucalyptus oil is primarily believed to be due to promotion of membrane

vehicle partitioning tendency of drug with oils. Penetration of oil into intracellular lipid phase of membrane may increase the degree of fluidity, resulting in decreased resistance to permeation. Eventually, eucalyptus oil increases flux of drugs (Suchika et al. 2010).

Solvent-drag effect is another important step considered to enhance the permeation of drugs. Span 20 is believed to increase the partitioning of drugs into solvent very rapidly resulting in formation of small drug-polyion complex of about 3 μm. Polyion complex is pushed by solvent into systemic circulation by appendages. Gradient in chemical potential is responsible to push these complexes through various membranes of skin.

4 Conclusion

Based on the results of the present investigations, it was concluded that two anti-asthmatic drugs can be administered simultaneously by developing transdermal patches. Findings of this study suggest that appropriate combination of polymers determines the performance of transdermal drug delivery system. Transdermal patches with permeation enhancers permeate the significant amount of both drugs, but formulation with isopropyl myristate showed promising permeation capability. Isopropyl myristate is the best enhancer for promoting permeation of drugs through skin membrane from transdermal drug delivery system. Permeation of both ketotifen fumarate and salbutamol sulfate through skin membranes can be optimized in terms of sustained and extended release by utilizing suitable combinations of polymers and enhancers.

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Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest in this work.

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