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Formulation and Evaluation of Transdermal Patches of Salbutamol

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ABSTRACT

Transdermal drug delivery system of Salbutamol using sodium carboxy methyl cellulose and other additives was prepared by solvent casting technique. Salbutamol, a β_2 adrenergic receptor agonist used as an antiasthmatic agent. Propylene glycol (10%) was used as permeation enhancer and Dibutyl pthalate (5%) as plasticizer. The prepared films exhibited satisfactory physicochemical characters such as thickness, weight, drug content, percentage dissolution and swelling index [1]. *In vitro* drug release was determined using egg membrane using Franz diffusion cell. The patches were found to be thin and smooth. The release pattern of the drug extends up to 21 hr. The permeation followed zero order kinetics and the mechanism involved may be matrix diffusion. The sustained release of Salbutamol by Transdermal Drug Delivery System can minimize the frequent administration of conventional Salbutamol dosage form.

Keywords: Salbutamol sulphate, Sodium carboxy methyl cellulose, Propylene glycol, Dibutyl Pthalate, Transdermal.

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INTRODUCTION

Transdermal drug delivery systems (TDDS) are adhesive drug-containing devices of defined surface area that delivers a predetermined amount of drug to the intact skin at a preprogrammed rate. The transdermal delivery has gained importance in recent years. The major advantages claimed for TDDS include avoidance of gastro-intestinal incompatibility and variable absorption; avoidance of hepatic first pass metabolism and consequent degradation and reduced bioavailability; reduced frequency of dosing with improved patient compliance and rapid termination of drug input by removal of the system from the skin [2]. Salbutamol, a β_2 adrenergic agonist with bronchodilatory effect and useful in the treatment of asthma. As the oral dosage form undergoes hepatic first pass metabolism, its systemic bioavailability is 50%. In the present study transdermal films of Salbuatamol sulphate were prepared and evaluated with a view to prevent its first pass metabolism and to achieve a controlled drug release with improved bioavailability.

MATERIALS AND METHOD

Salbutamol sulphate, sodium carboxy methyl cellulose (Na-CMC), propylene glycol (PG), dibutyl pthalate (DBP).

Preparation of Salbutamol Transderml Patches

The transdermal patches of Salbutamol sulphate were prepared by a solvent casting technique using different ratios of sodium carboxy methyl cellulose (Na-CMC) [11% to 15%]. 5 mg of Salbutamol sulphate was weighed and dispersed in 10 ml distilled water [3]. Na-CMC was added to each aqueous drug solution while stirring to ensure uniform distribution. Finally, propylene glycol was added to protect the polymeric patches from brittleness upon storage. The dispersion proceses were made using a magnetic stirrer providing constant stirring (500 rpm) at room temperature until clear solution is obtained. The composition of the tested transdermal patches is shown in Table 1. Measured volumes (10 ml) of the polymeric solution was poured onto a prepared cavity (circular dish of 57 mm² diameter & 8 mm depth) and dried at room temperature for 24 hr with an inverted funnel overhead to provide a uniform rate of evaporation [3,10 & 11]. The formulated patches were allowed to equilibrate in a desiccator over anhydrous calcium chloride for another 24 hr before the evaluation process to ensure total hydration and to exclude entrapped air. The patches were evaluated within one week from the date of casting.

Table 1. Salbutamol loaded Na-CMC patches

S.No	Formulation	Salbutamol (mg)	Sodium carboxy methyl cellulose (%)	Propylene glycol(%)	Dibutyl phthalate (%)
1	F1	5	11	10	5
2	F2		12		
3	F3		13		
4	F4		14		
5	F5		15		

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***In vitro* characterization of Salbutamol transdermal patches**

Initial drug content

For drug content determination, the total content of transdermal patch was placed in a 100 ml volumetric flask and dissolved in water. The solution was filtered through a Whatman filter membrane (0.45µm) prior to spectrophotometric drug analysis at 276 nm (Shimadzu, model UV-1601 PC, Kyoto, Japan) [4 & 9].

Patch weight and thickness

Three randomly selected patches of each formulation were weighed and their average weights were calculated. Patch thickness was determined using Vernier Caliper and recorded [4 & 9]. Results were reported as the mean of five measurements (the 4 corners and the center of each patch).

Percentage dissolution and swelling index of the transdermal patches

The patches were dried in a desiccator over anhydrous calcium chloride at room temperature until a constant weight was obtained (W_1), then they were immersed in 100 ml distilled water at 37°C for 3 days. Excess water present on the swollen patches was removed carefully, by blotting with filter paper. The patches were reweighed (W_2), kept in the desiccator and dried to a constant weight, then they were reweighed again (W_3).

$$\% \text{ dissolution} = \frac{W1 - W3}{W1} \times 100$$

The swelling index (SI) was determined by calculating the amount of water absorbed per unit weight of undissolved patches retrieved from the distilled water after immersion [5].

$$SI = \frac{W2 - W3}{W3} \times 100$$

Results were tabulated as the mean of three replicates.

Moisture absorption capacity of the patches

The water absorption capacity of various films was determined at 33, 65, and 97% relative humidity (RH) [6-8]. Films were cut into 1 × 1 cm strips. The strips were placed in a desicator at 40°C for 24 hr, removed and exposed to conditions of 33% RH (saturated solution of magnesium chloride), 65% RH (saturated solution of sodium nitrate) and 97% RH (saturated solution of potassium sulphate) in different desiccators at room temperature. Weight was taken periodically every 48 hr for 14 days until a constant weight was obtained. The moisture absorption capacity of the films (weight %) was calculated in terms of percentage increase in the weight of film over the initial weight of the specimen.

In vitro dissolution studies

The *in vitro* release was carried out with the egg membrane using Franz diffusion cell. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 37 ± 0.5^{o} C and receptor compartment was provided with sampling port. The diffusion medium used was PBS (pH 7.4). The drug containing film with a support of backing membrane was kept in the donor compartment and was separated from the receptor compartment by egg membrane. The egg membrane was previously soaked for 24 hr in PBS. The donor and receptor compartments were held together using a clamp. The receptor compartment with 15 ml of PBS was maintained at 37 ± 0.5 ^{o}C and stirred with magnetic stirrer, to prevent the formation of concentrated drug solution layer below the dialysis membrane [12-14]. Samples of 3 ml were collected at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by UV Spectrophotometer at 276nm.

RESULTS AND DISCUSSION

Uniformity of drug content, weight and thickness

The drug content analysis of the prepared formulations showed that the process employed to prepare patches in this study was capable of providing films with a uniform drug content and minimum batch variability. All the prepared patches complied with the pharmacopoeial limits for content uniformity. The prepared patches had a thickness ranging from 0.129 to 0.159 mm and their weight was uniform, varying from 0.491 to 0.678 g/patch (Table 2) [4 & 9]. These ranges are suitable for application to the skin as reported earlier.

Percent dissolution and swelling index of the transdermal patches

The incorporation of plasticizer in Na-CMC patches has weakened its resistance to solubility in distilled water. This can be attributed to the fact that plasticizer increases the flexibility of Na-CMC molecules and render the patches more permeable to the water molecules. PG was found to be the most effective in reducing the water resistance of Na-CMC patches while DBP was least effective. The water uptake capacity of the patch was measured by the swelling index (SI). The data in Table 2 revealed that transdermal patch F3 exhibited the highest SI in comparison to other formulations. These results suggest that the patches would be more permeable to the drug [5]. This may be due to the porosity generated in the remnants of the patches after dissolution of Salbutamol.

Moisture absorption capacity of the patches

Moisture absorption of polymeric patches affects both the mechanical properties and the drug release pattern. Moisture absorption capacities under different humidity conditions (Fig 1) revealed that the moisture uptake of the patches depended on the type of Na-CMC and plasticizer used. Moisture absorption in 97% RH is relatively high and the weight of most

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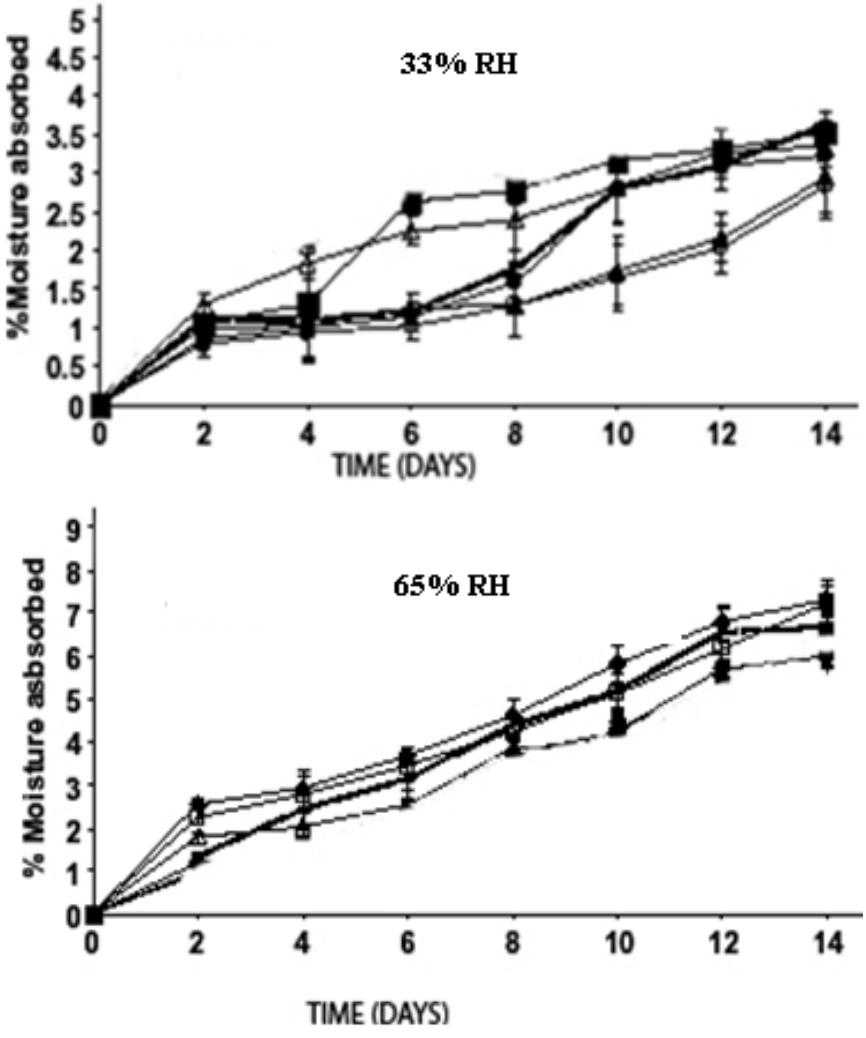
patches significantly increased in comparison to other levels of RH. The highest absorption capacities within 2 weeks were 10.73% for those prepared using Na-CMC (15%) and propylene glycol while the lowest 1.81% was recorded for Na-CMC (13%) patches containing Dibutyl phthalate at 33%, 65%, and 97% RH, respectively. As is apparent, Na-CMC (15%) formulated patches plasticized with any of the mentioned plasticizers absorbed water to a greater extent than patches containing Na-CMC (13%) [6-8].

Table 2. Drug content, Physical characterization, % dissolution and SI of Salbutamol transdermal patches

Formula	Drug content [a]	Uniformity of weight (gm) [b]	Uniformity of thickness (mm) [b]	% Dissolution [b]	Swelling index [b]
F1	91.62± 0.877	0.547± 0.076	0.131 ± 0.003	14.82 ± 0.255	0.282 ± 0.030
F2	93.61 ± 5.020	0.622 ± 0.013	0.129 ± 0.003	12.75 ± 0.650	0.403 ± 0.088
F3	94.47 ± 2.046	0.507 ± 0.068	0.135 ± 0.038	11.18 ± 2.574	1.362 ± 0.172
F4	89.24 ± 2.503	0.628 ± 0.023	0.144 ± 0.023	14.32 ± 0.720	0.175 ± 0.011
F5	88.24 ± 1.782	0.523 ± 0.016	0.159 ± 0.001	14.74 ± 0.976	0.087 ± 0.018

[a] (% ± S.D.) [b] (Average ± S.D.)



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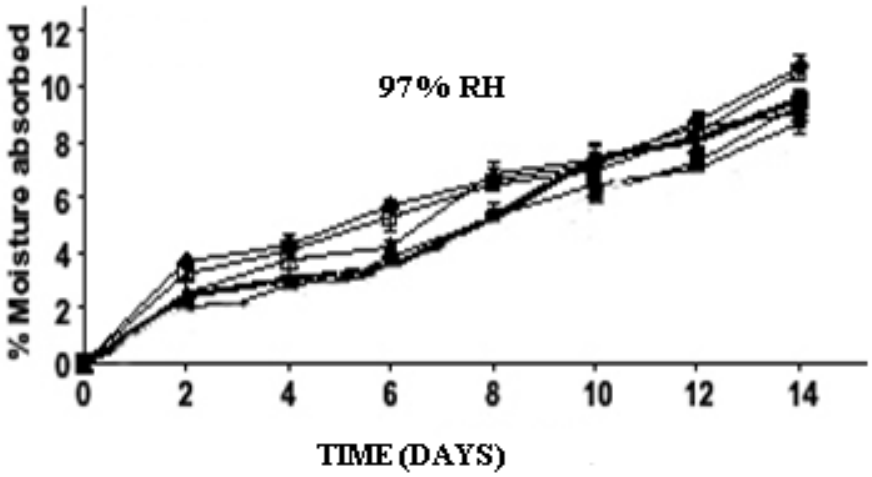

Fig1. Moisture absorption capacity of Salbutamol transdermal patches at 33 % RH, 65% RH and 97% RH.

In vitro release studies

The results of *in vitro* drug release studies from transdermal patches are depicted in Fig 2. The cumulative percent of drug release from formulations was 89.55, 91.6, 95.52, 94.4 and 70.7 respectively. The drug release from different formulations was increased in the following order: F3>F4>F2>F1>F5.

Variable release profiles of Salbutamol from different experimental patches composed of various ratio of Na-CMC. The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains.

Release rates were increased when the concentration of Na-CMC increased in the formulations. This is because as the proportion of this polymer in the matrix increased, there was an increase in the amount of water uptake and hydration of the polymeric matrix and thus more drugs was released. Formulation F5 showed less drug release compared to formulation F3, this is because of the high proportion of HPMC. Swellable polymer further increases the tortuosity and diffusional path length, resulted in decreased drug release; however, the difference was statistically insignificant [12-14].

Table 3. *In vitro* drug release and skin permeation of developed TDDS

Formulation	Cumulative % of drug release ($Q^{r}_{24}{}^{a}$)	Cumulative % of drug permeate ($Q^{p}_{24}{}^{a}$)	Flux (µg/cm^2/h) (J^{a})	Permeability Coefficient (cm h^{-1}) (Kp X $10^{-2\,a}$)
F1	89.55 ±1.97	71.45 ±1.04	162.23 ± 0.27	3.02 ± 0.028
F2	91.6 ± 1.24	75.55 ±1.87	168.23 ± 0.32	3.13 ± 0.054
F3	95.52 ± 1.76	84.89 ±1.89	183.87 ± 0.24	3.43 ± 0.024
F4	94.4 ± 1.54	80.97 ± 1.43	177.83 ± 0.27	3.31 ± 0.032
F5	70.70 ± 1.13	61.94 ± 1.27	139.83 ± 0.31	2.60 ± 0.067

[a] **Values presented are mean ± S.D (n=3)**

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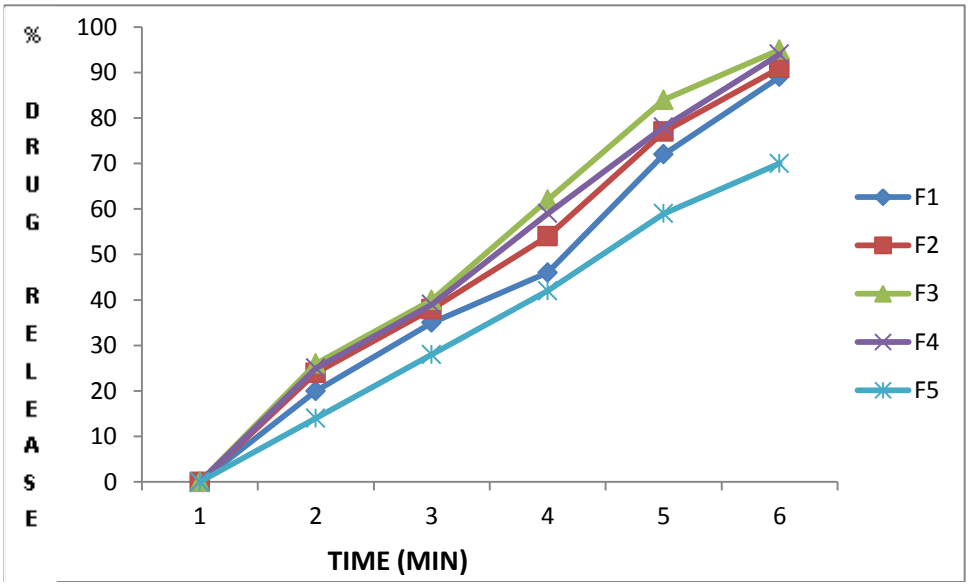

Fig 2. *In vitro* release profiles of Salbutamol from TDDS using Franz diffusion cell.

CONCLUSION

The films of Salbutamol sulphate obtained by the solvent casting method had acceptable mechanical characteristics and satisfactory % drug release. The prepared films were transparent and had a smooth surface without any interactions between the drug and polymer. The study demonstrates the feasibility of formulating transdermal drug delivery system to deliver Salbutamol in the asthma management. The transdermal formulations were found to be safe and non-reactive. Transdermal delivery of Salbutamol appears to be a better route for patients who respond well to β_2 agonists. In the light of the present results, formulations for the transdermal delivery of Salbutamol should be further improved for durations up to several days. This is especially relevant in a country like Egypt, Swiss, Australia, India and Europian countries where inhalers are too expensive devices to be routinely used by asthmatic patients.

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