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New transdermal bioadhesive film containing oxybutynin: In vitro permeation across rabbit ear skin

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Abstract

Oxybutynin is used extensively in the treatment of patients with overactive bladder. The aim of this work was to realize and test in vitro a new transdermal bioadhesive film containing oxybutynin. Transdermal films were prepared by dissolving in water an adhesive (Plastoid®), a film-forming polymer (polyvinyl alcohol), a plasticizer (sorbitol) and the drug. The mixture was then spread on siliconized paper and oven-dried. Permeation experiments were conducted in Franz-type diffusion cells using rabbit ear skin as barrier. The donor compartment contained a water solution, the prepared film (with or without backing) or the commercial patch (Oxytrol®). The experiments were performed for 24 h. Oxybutynin showed good permeation characteristics across the skin. When the film was applied in occlusive conditions the release profiles were much higher than in non-occlusive conditions, reaching 50% of drug permeated after 24 h. Compared to the commercial patch Oxytrol®, the film was more efficient suggesting that a smaller area or a lower drug loading could be employed. The results obtained show that the bioadhesive film can be a promising and innovative therapeutic system for the transdermal administration of oxybutynin.

Keywords: Oxybutynin; Transdermal delivery; Rabbit ear skin; Overactive bladder

1. Introduction

Overactive bladder is a common condition characterized by urinary frequency and urgency, with or without incontinence and nocturia (Wein and Rackley, 2006). Recent findings estimate the prevalence at about 17% in the adult population (Wein and Rackley, 2006), increasing markedly with age in both men and women (Staskin, 2005).

Several antimuscarinic agents are currently available for the pharmacological treatment of overactive bladder in adults, including oxybutynin (OXY), tolterodine, trospium chloride, darifenacin and solifenacin (Andersson, 2004; Getsios et al., 2005). The antimuscarinics all appear to exert their clinical effect through inhibition of the bladder muscarinic receptors, but they vary both in structure and in their functional profile.

Oxybutynin is used extensively in the treatment of patients with overactive bladder (Andersson and Chapple, 2001; Hay-Smith et al., 2002). Oral administration produces a high incidence of anticholinergic adverse events, such as dry mouth. This is due to the high serum concentration of the active metabolite *N*-desethyloxybutynin that follows hepatic first pass metabolism in the gut and liver (Andersson and Chapple, 2001).

Attempts to increase tolerability have included the development of advanced formulations that regulate release of the active ingredient (Dmochowski, 2005). In a randomized cross-over pharmacokinetics study OROS® oxybutynin chloride tablets showed a relative bioavailability higher (153%) for oxybutynin and lower (69%) for *N*-desethyloxybutynin, compared with immediate release oxybutynin tablets (Gupta and Sathyan, 1999). New administration routes were also investigated, such as the transdermal route. Clinical trials involving a transdermal formulation of oxybutynin have shown that this delivery method may be associated with a lower incidence of anticholinergic adverse events compared with both the immediate-release and the extended-release oral formulations (Dmochowski, 2005; Dmochowski et al., 2003; Dmochowski et al., 2005). Local reactions at the site of application included mild to moderate erythema and pruritus (Dmochowski et al., 2003).

We have recently described an innovative transdermal drug delivery system, a water-based and vapor permeable bioadhesive

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film intended for dermal and/or transdermal delivery (Padula et al., 2003; Nicoli et al., 2004a; Nicoli et al., 2005). The transdermal film is not adhesive in the dry state, but only when applied on wet skin, and is water permeable thus reducing the risk of skin irritation (Zhai and Maibach, 2002). The permeation kinetics across the skin of model drugs included in the transdermal film, namely lidocaine (Padula et al., 2003) and caffeine (Nicoli et al., 2004a; Nicoli et al., 2005), was unusual, showing a sort of "burst" effect in the early times of permeation. Overall, the permeation profiles resulted linear with the square root of time, suggesting a matrix-type control of drug delivery by the film.

The aim of this work was to realize and test in vitro transdermal bioadhesive films, with or without backing, containing oxybutynin hydrochloride. A water solution of oxybutynin hydrochloride and the commercial transdermal patch Oxytrol® were used as reference. Rabbit ear skin was used as permeation barrier, because it has been shown to be a reasonable model for human skin in vitro (Nicoli et al., 2001, 2003; Artusi et al., 2004).

2. Materials and methods

2.1. Materials

Oxybutynin hydrochloride (MW = 393.95, pK_a of the free base: 8.04) (Miyamoto et al., 1994) was a gift from Lisapharma (Erba, Como, Italy). Eudragit® E100 (Rohm) used for the preparation of the adhesive Plastoid® E35H, was purchased from Rofarma (Gaggiano, Milan, I) and polyvinyl alcohol (PVA) (MW 83400; degree of hydrolysis: 87%) from Nippon Ghosei (Osaka, J). All other chemicals used were of analytical grade. For HPLC analysis, acetonitrile (HPLC grade) and distilled water were used.

Plastoid® E35H was prepared according to the Rohm protocol: Eudragit® E100 (15.9% w/w), lauric acid (9.2% w/w) and adipic acid (1.8% w/w), were added to hot water (72.1% w/w), ($T \approx 80\,^{\circ}C$). The mixture was stirred, maintaining the temperature at about 80 °C until getting a clear solution. The solution was cooled down to 60 °C and glycerol (1.0% w/w) was added. The mixture was then gradually cooled down to ambient temperature stirring during the cooling process.

The backing used for the occlusive experiments with films was a polyester film (Scotchpack™ 1220, 3M, USA).

The commercial formulation tested was Oxytrol® (Watson Laboratories Inc, Salt Lake City, USA), a matrix type transdermal system composed of three layers: a PET/EVA occlusive backing, an acrylic adhesive containing OXY free base (36 mg in 39 cm^2) and triacetin as penetration enhancer (Quan et al., 2003), and a siliconized liner.

2.2. Film preparation

Films containing oxybutynin hydrochloride were prepared as previously described (Padula et al., 2003). The composition of the mixtures to be laminated is reported in Table 1. A solution of oxybutynin hydrochloride in water/sorbitol was added to PVA water solution and to the adhesive Plastoid® E35H. The resulting mixture was slowly stirred overnight using a magnetic bar. All mixtures were laminated on siliconized paper using a film casting knife (BYK Gardner, Silverspring, MD, USA; gap 400 μm) and oven dried at 80 °C for 30 min.

Table 1
Composition (% wet weight) and oxybutynin content of the prepared patch

Component (% wet weight)	1% film	8% film	Oxytrol®
PVA (30% solution)	62.0	62.0	–
Plastoid E35H®	27.0	27.0	–
Sorbitol 70%	4.0	4.0	–
Oxybutynin HCl	0.3	3.2	–
Water	6.7	3.8	–
Oxybutynin content			
% w/w	1.1 ± 0.4	7.9 ± 0.3	15.5
μg/cm^2	85.6 ± 3.4	870 ± 165	923

2.3. Film characterization

Once dried, three circles 20 mm in diameter were cut from each film. Each circle was measured for weight and thickness (Absolute Digimatic 547–401, Mitutoyo, Milan, I, resolution 0.001 mm) and then was dissolved in 50–100 mL of water (according to OXY loading) under sonication for 1 h. The solutions obtained were analyzed by HPLC in order to determine the amount of oxybutynin contained in the patch. The results were expressed as both μg of oxybutynin per cm^2 and % of oxybutynin (w/w) (Table 1).

2.4. Oxybutynin analysis

Oxybutynin analysis was performed by HPLC (Gilson, Serie 200 Iso Pump, Cinisello Balsamo, I), using a Novapak® C8 column (Waters, Milford, MA, USA). The mobile phase was a mixture of water, acetonitrile and 1 M ammonium acetate (37:61:2 v:v:v) buffered at pH 7 with acetic acid, pumped at 1 mL/min. UV detection (Gilson 117 UV detector) at 220 nm was employed. In these conditions, the retention time of OXY was about 5 min. The method was validated according to USP 26. The method resulted linear in the interval 0–520 μg/mL, with a tailing factor of 1.3. The relative standard deviation (RSD%) resulted 5.7%.

2.5. Permeation experiments

Permeation experiments were conducted in vertical Franz-type diffusion cells (Disa, Milan, I), with an exposed surface area of 0.6 cm^2. Rabbit ear skin was used as barrier. Rabbit skin was excised post-sacrifice from the inner part of rabbit ears (6 months old) obtained from a local slaughter's house. When not used immediately, the skin was kept refrigerated (2–5 °C) and used within 3 days.

The donor compartment was filled with 1 mL of oxybutynin hydrochloride solution 2 mg/mL (pH 6) or 10 mg/mL (pH 4.75) in water, with the commercial patch or with the prepared films.

All the patches tested were cut at 0.6 cm^2 in order to fit the cell permeation area. In the case of film, the exposed skin area was wetted with a measured volume of water (about 15 $\mu L/cm^2$) before film application, according to Padula et al. (2003).

The receptor phase was 0.9% sodium chloride solution, thermostatted at 37 °C and magnetically stirred in order to prevent any boundary layer effects. At predetermined time intervals the receptor solution was sampled and analyzed by HPLC for the determination of drug permeated.

Each permeation experiment was replicated at least 6 times.

The permeation profiles were then fitted to the following equation (Moser et al., 2001):

$$Q = (\mathrm{KH})C_{\mathrm{Veh}}\left[\frac{D}{H^2}t - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{n}\frac{(-1)^2}{n^2}exp\left(\frac{-Dn^2\pi^2 t}{H^2}\right)\right] \quad (1)$$

where Q is the cumulative amount of drug permeated per unit area at time t, C_{veh} the concentration of the drug in the donor vehicle, K the stratum corneum/vehicle partition coefficient, D the diffusion coefficient and H the diffusion path-length. The permeability coefficient P was calculated as the product between KH and D/H^2. The fitting was performed using KaleidaGraph® 3.6.2 (Synergy Software) running on a MacIntosh Power Book G4.

2.6. Statistical analysis

The results were expressed as the mean ± S.E.M. Statistical differences were determined by Student's t-test.

3. Results and discussion

Oxybutynin free base (pK_a 8.04) (Miyamoto et al., 1994) is a very lipophilic substance, with a log P of 4.9. Its hydrochloride salt is water-soluble and obviously shows a log P decreasing with decreasing the pH value. In particular, the apparent log P of OXY hydrochloride (Miyamoto et al., 1994) at pH 6.2, which is close to the pH value of the transdermal films object of this work, was 2.89, optimal lipophilicity value for transdermal delivery.

3.1. Permeation from solution

Initially, the skin penetration of OXY was studied from aqueous solutions of its hydrochloride salt, to characterize the permeation properties of the drug. In fact no fundamental permeation data is available in the literature to our knowledge. Additionally, we found essential to characterize OXY permeation across the skin starting from a water solution, because the bioadhesive film object of this work is water based.

Rabbit ear skin was used as animal model skin, because of its similarity with human skin in vitro (Nicoli et al., 2001, 2001; Artusi et al., 2004). OXY hydrochloride water solutions 2 mg/mL (pH 6.0) and 10 mg/mL (pH 4.75) were used as donors and the resulting permeation profiles are reported in Fig. 1. Despite the small percentage of OXY in the non-ionized form

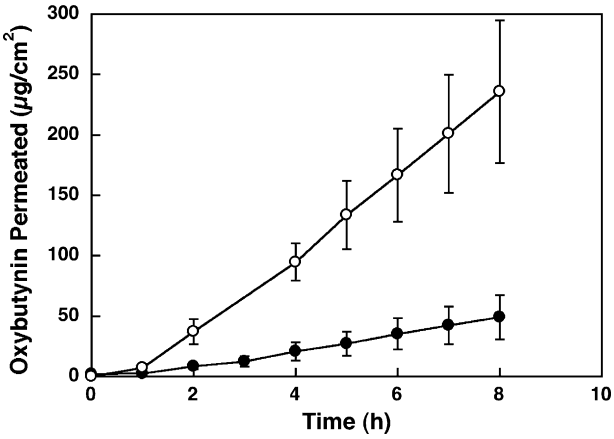

Fig. 1. Oxybutynin permeation profiles across rabbit ear skin from water solution 10 mg/mL (◯) (pH 4.75) and 2 mg/mL (●) (pH 6.0). Mean values ± S.E.M.

(0.05% and 1% at pH 4.75 and 6.0, respectively), the drug permeated the skin to a significant extent, with a short lag time. The flux, calculated as the slope of the regression line in the interval 2–8 h, resulted 13.8 ± 5.8 and 33.4 ± 10.7 $\mu g\,cm^{-2}\,h^{-1}$, for 2 and 10 mg/mL respectively. Since OXY was used as hydrochloride salt, the overall flux was due to the permeation of both the ionized and un-ionized species. The permeability coefficient of the two species was estimated from the flux data, using the approach of Hayashi et al. (Hayashi et al., 1992). The permeability coefficient of the ionized form resulted 6.7×10^{-3} cm/h, while the value for the non-ionized was 2.9×10^{-2} cm/h. The latter is in good agreement with the permeability coefficient value (4.7×10^{-2} cm/h) predicted by the equation of Potts and Guy (1992). Overall, these results indicate that the permeability of the two forms is in agreement with the pH-partition theory, being higher for the un-ionized form. However, at the pH value of the prepared film (approx. 6), the contribution of the ionized form prevails over that of the unionized form, owing to the pK_a value of OXY (8.04).

3.2. Permeation from the bioadhesive films and commercial patch

The film object of this study is composed of water-soluble substances, namely a film forming agent, an adhesive and a plasticizer (Nicoli et al., 2004b). Film application requires preventive skin wetting to partly dissolve the adhesive thus restoring skin adhesiveness. Water used for film application has been shown to evaporate quickly, within 60 min of application, although the film remains adhered to the skin up to 24 h (Nicoli et al., 2005). The permeation profiles obtained with films containing lidocaine (Padula et al., 2003) and caffeine (Nicoli et al., 2004a, 2005) resulted linear with the square root of time, suggesting a matrix-type control of drug delivery by the film.

Table 1 reports the composition of the mixtures used for transdermal film preparation, together with the respective values of OXY content in the finished product. The films prepared were identified with their OXY content, expressed as % w/w.

Fig. 2 reports the permeation profiles of OXY obtained. Despite the difference in drug loading, the two films produced

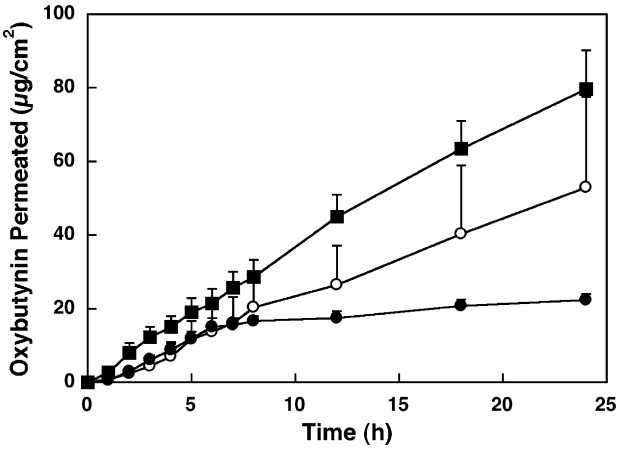

Fig. 2. Oxybutynin permeation profile across rabbit ear skin from Oxytrol® (◯) and from the transdermal films prepared, containing 1 (●) or 8 (■) % of the drug (%w/w). Mean values ± S.E.M.

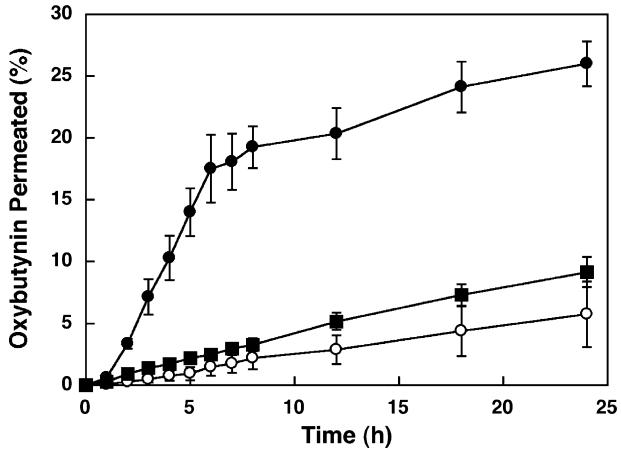

Fig. 3. Percentage of oxybutynin permeated from Oxytrol® (◯) and from the transdermal films prepared, containing 1 (●) or 8 (■) % of the drug. Mean values ± S.E.M.

comparable permeation profiles up to 7 h. After that, the 1% film showed a marked decrease in permeation rate, while the 8% film kept increasing in an almost linear way up to 7 h. Comparing these kinetics to those obtained with films containing other drugs, such as lidocaine (Padula et al., 2003) and caffeine (Nicoli et al., 2004a, 2005) for which the transport was linear with the square root of time up to 24 h, it appears that OXY behaves in a different way. The behavior of OXY is more similar to sumatriptan (Femenia-Font et al., 2006): in the case of sumatriptan, we hypothesized that drug diffusion within the dry patch was more difficult than with caffeine and lidocaine. Probably OXY release takes place only from the more superficial layers of the film: when the first layers are depleted, release stops, because OXY diffusion within the polymeric matrix is very slow. In the case of 8% film, the permeation profile does not show the abrupt change because depletion in the superficial layers has not taken place yet, owing to the higher drug loading.

The commercial patch Oxytrol® produced a permeation profile non significantly different from the 8% film. When the permeation data were expressed as percentage permeated (Fig. 3), the 1% film showed a significantly different trend, releasing 26% after 24 h. The percentage of OXY penetrated from Oxytrol® and the 8% film were 5.7 ± 2.7% and 9.2 ± 1.2% after 24 h, respectively. Then, the bioadhesive film showed a similar or better performance, compared to the commercial product, in terms of drug delivery efficiency. Oxytrol® contains triacetin as penetration enhancer; the bioadhesive film contains lauric acid, adipic acid and glycerol, which can potentially act as penetration enhancers as well.

The permeation data obtained with the 8% film and the commercial patch were then elaborated, to try to understand the exact mechanism of drug delivery control. The permeation data up to 7 h (see Fig. 2) were fitted to the appropriate solution of Fick's law for non steady state conditions (Eq. (1)) (Moser et al., 2001), to calculate the relevant parameters, i.e. diffusive and partitioning parameters which are reported in Table 2, together with the respective data obtained from solutions. The two water solutions gave similar results, while the values were much different for the films. The partitioning parameter KH, which gives an indication as to the partitioning of the permeant between the stratum corneum and the formulation (Artusi et al., 2004), was in the range (6.1–6.9) × 10^{-2} cm^{-1} for the solutions, while it decreased to a significant extent for the 8% film (0.06 × 10^{-2} cm^{-1}) and for the commercial patch Oxytrol® (0.013 × 10^{-2} cm^{-1}). The lower partitioning parameter of the film compared to solution (both with pH around 6) indicates that the inclusion of OXY Hydrochloride in a mixture of polymers/adhesives reduced the partitioning into the stratum corneum (assuming that the diffusive path length remained unchanged). In the case of Oxytrol®, which contains OXY free base, the reduction of partitioning parameter can probably be explained considering that matrix itself is quite lipophilic and

Table 2
Permeation parameters of oxybutynin across rabbit ear skin (mean values ± sem)

Formulation	KH (×10^2 cm^{-1})	D/H^2 (h^{-1})	P (×10^3 cm/h)	Lag-time (h)
2 mg/mL solution[a]	6.12 ± 1.91	0.18 ± 0.06	7.13 ± 1.99	1.3 ± 0.2
10 mg/mL solution[b]	6.89 ± 3.91*	0.14 ± 0.06	4.85 ± 1.93*	1.8 ± 0.7
Film[c]	0.06 ± 0.03*	0.30 ± 0.13	0.05 ± 0.01*	2.2 ± 1.3
Film[c] occluded	0.20 ± 0.04*◦	0.14 ± 0.03	0.25 ± 0.04*	1.4 ± 0.2
Oxytrol®	0.013 ± 0.005◦	0.18 ± 0.03	0.02 ± 0.01*	1.1 ± 0.1

* and ◦ significantly different among them ($p < 0.05$).
[a] pH 6.0
[b] pH 4.75.
[c] 8% Film.

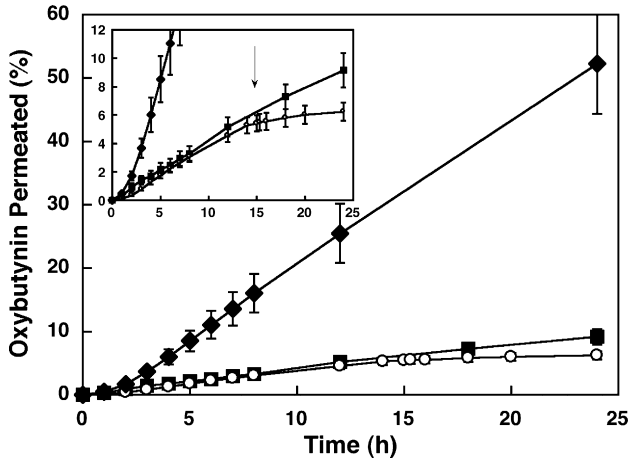

Fig. 4. Oxybutynin permeation profiles across rabbit ear skin from the 8% transdermal film applied for 24 h (■), removed after 15 h (◯) and applied in occlusive conditions for 24 h (♦). Mean values ± S.E.M.

then the drug does not have the tendency to migrate into the stratum corneum.

Considering the diffusive parameter D/H^2, its value varied but in a non significant way for the various formulations. This indicates that OXY diffusion was not influenced by the presence, and potential penetration, of other components of the formulations. The permeability coefficient varied according to the partitioning parameter, while the lag-time was more or less constant for all formulations tested.

To evaluate the possibility of a reservoir formation of OXY in the stratum corneum, the same 8% patch was applied to the skin for 15 h and then the permeation of the drug was followed up to 24 h. The insert in Fig. 4 highlights the two curves, where it can be seen that OXY does not accumulate into the stratum corneum because the profile flattened just after patch removal. This can be an advantage in practical use, since it guarantees the immediate interruption of drug input when the patch is removed.

Finally, the effect of occlusion on OXY skin penetration from the film was evaluated. Occlusion (i.e., the application of an impermeable baking on the surface of the formulation to avoid water evaporation) is known to improve drug penetration (Zhai and Maibach, 2002), although to a different extent according to the physico-chemical properties of the permeant. On the other hand, the commercial patch Oxytrol® includes an occlusive backing. A previous work on sumatriptan, included in the same film object of this work, showed that occlusion improved to a significant extent the permeation of the drug (Femenia-Font et al., 2006). The main reason for this improvement proved to be the avoidance, in occlusive conditions, of patch drying over time.

The film containing 8% of OXY was applied on the skin in occlusive conditions, i.e., was covered with an impermeable backing. The profiles obtained, reported in Fig. 4, show that in occlusive conditions OXY flux is much higher than in non-occlusive conditions, producing a significant improvement of efficiency, because 50% of drug permeated the skin after 24 h of application. Additionally, the permeation profile was linear up to 24 h. Concerning the permeation parameters, as can be seen in Table 2, the partitioning parameter increased significantly compared to the film applied in non-occlusive conditions, although it did not reach the value of water solution. The increase in partitioning can be due to the conserved hydration of the occluded film, which favors OXY partitioning out of the film into the stratum corneum. Additionally, the presence of water into the film can facilitate OXY diffusion within the film, due to an increase in drug mobility.

4. Conclusions

From the results obtained in the present work it can be concluded that the bioadhesive film can be a promising and innovative therapeutic system for the transdermal administration of oxybutynin. When the film was applied in occlusive conditions the release profiles were much higher than in non occlusive conditions, reaching 50% of drug permeated after 24 h. Compared to the commercial patch Oxytrol®, the film was more efficient up to 24 h of wearing. The consequence is that a smaller area or a lower drug loading could be employed.

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