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RESEARCH PAPER

The Influence of Hydrocolloid Patch Composition on the Bioavailability of Triamcinolone Acetonide in Humans

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ABSTRACT

Triamcinolone acetonide (TACA) is a corticosteroid; it is used in the systemic and topical treatment of a variety of inflammatory conditions, including eczema and psoriasis. Conventionally, for topical use, the drug is formulated in a cream or ointment. However, it has been observed in vitro that percutaneous penetration of corticosteroids can be influenced by hydrocolloid patches. Corticosteroids produce a pallor or blanching when applied to the skin that correlates with anti-inflammatory activity; this property has been used extensively as a bioassay. The aim of this study therefore was to evaluate the occlusive properties of a range of hydrocolloid patches containing TACA on the drug's penetration in vivo using visual assessment and a graded multiple measurement. The in vivo hydration of these dermatological patches was also investigated. Statistical analysis of the weight gains of patches containing either NaCMC 39% or pectin 39% showed that there was a significant difference in the rates of hydration of the two types of patch ($p < .005$). An increase in application time of the hydrocolloid patches allowed more TACA to be released, which was illustrated by an increase in both the maximum percentage total possible score (%TPS) values and AUC, although changes in the hydrocolloid composition did not significantly alter the blanching response. All of the patches adhered well, were

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unobtrusive to the normal activity of the wearers, and showed great potential for the convenient, localized, prolonged delivery of drugs to the skin.
Key Words: *Blanching; Corticosteroid; Occlusion; Topical.*

INTRODUCTION

Triamcinolone acetonide (TACA) is a corticosteroid that is used in the systemic and topical treatment of a variety of inflammatory conditions, including eczema and psoriasis. Conventionally, for topical use, the drug is formulated in a cream or ointment. However, studies have shown that an occlusive covering to the skin promotes the hydration of the underlying stratum corneum (1–5), which in turn increases the absorption of the topically applied drug (6–10) and therefore the bioavailability and efficacy (11,12). It has also been observed in vitro that the extent of hydration afforded to the stratum corneum, and thus enhancement of percutaneous penetration of drugs, may be related to the properties of the applied covering (13).

However, the use of creams under a patch is problematic in that it is a two-stage process involving the inconvenience of spreading the cream on the skin followed by occlusion. In addition, the presence of cream excipients at the interface between patch and skin reduces adhesion. Consequently, considerable research effort has been exerted in the development of transdermal patches for the systemic delivery of drugs (14). However, in comparison, there have been few studies that have considered the use of patch technology for the more efficient delivery of drugs that act locally.

Corticosteroids, as well as possessing topical anti-inflammatory activity, produce pallor or blanching when applied to the skin. Such an effect has been used as a bioassay in a variety of studies since the early 1960s for the evaluation of the potency of corticosteroids (15–22). A number of instrumental methods have been employed to assay the magnitude of the blanching response, including reflectance (23), thermographic (24), photographic (25), and colorimetric methods (26). However, these methods have been shown to be laborious; currently, the most favored technique is the relatively facile method of visual assessment (27). Typically, the blanching responses for all volunteers at each time point are summed and expressed as a percentage of the total possible score (%TPS). This %TPS value gives an indication of the amount of drug that has penetrated the skin at each time point. The area under the curve (AUC) for the plot of %TPS versus time can also be calculated; it is used as an estimation of the total topical bioavailability of the steroid (28).

The aim of this study was therefore to evaluate the occlusive properties of a range of hydrocolloid patches containing TACA on the drug's penetration in vivo using visual assessment and the graded multiple-measurement procedure initially described by Barry and Woodford (29). The in vivo hydration of these dermatological patches, which have been shown to exhibit different water uptake properties in vitro (13), was also investigated, and the proportion of the weight increase of patch material that was attributable to water uptake was assessed.

MATERIALS AND METHODS

Materials

TACA was donated by E. R. Squibb and Son (Moreton, UK; now Bristol-Meyers Squibb). For the patch preparation, the adhesive premix was supplied by Conva-Tec (Deeside, Clwyd, UK) and comprised a mixture of hydrophobic synthetic and semisynthetic elastomers, tackifying resins, and mineral oil. Sodium carboxymethylcellulose (71/35XF) was obtained from Aqualon Company (Wilmington, DE) and pectin (HM) from A/S Kobenhavns Pektinfabrik (Lille Kensved, Denmark). All solvents were high-performance liquid chromatography (HPLC) grade and were obtained from BDH (Poole, Dorset, UK).

Patch Manufacture

Patches were prepared by addition of the hydrocolloid powders (pectin and/or sodium carboxymethylcellulose [NaCMC]) and TACA to the heated adhesive premix (13) in a Sigma blade mixer (S330C, Brabender OHG, Duisberg, Germany) to produce a homogeneous dispersion. Subsequent to cooling, the hydrocolloid premix was extruded (measuring extruder 10DW, Brabender OHG) using a ribbon die adjusted to give an adhesive sheet of uniform thickness (0.425 mm). This was then laminated between a sheet of polyethylene film and a silicone release paper (which was removed prior to use).

In Vivo Patch Hydration Studies

The volar forearms of 20 volunteers (age range 21 to 35 years) were employed in the study to investigate the effect of patch composition on hydration. Volunteers were excluded if they suffered from skin diseases, had general allergies, or if they were sensitive to Elastoplast® or other dressing materials. Arm contact with water was minimized, but careful bathing was permitted after 48 hr.

Twenty rectangles of patch material, 4 cm × 2 cm were applied to the forearms of each volunteer with reference to randomization charts. Each site was allocated a treatment group consisting of NaCMC 39%; NaCMC 26%, pectin 13%; NaCMC 19.5%, pectin 19.5%; NaCMC 13%, pectin 26%; and pectin 39% applied for 24 hr, 48 hr, 72 hr, and 96 hr.

Immediately prior to application, patches were removed from their release liners and weighed. After periods of 24, 48, 72, and 96 hr, the appropriate patches were removed and reweighed. Any erythema, itching, discomfort, and patch loss were also recorded. Increase in weight of the patches was recorded as milligrams increase per patch.

In the hydration study, volunteers were asked to complete a diary sheet relating to activities carried out during the trial and were asked to comment on the state of the patches.

In Vivo Percutaneous Absorption Studies

For the trial, 10 Caucasian volunteers (7 female, 3 male; age range 22–40 years) who had not been treated with topical or systemic corticosteroids for at least 1 month were employed. There were 20 sites utilized per arm, and they were allocated, by reference to randomization charts, as follows: 3 per treatment group for 39% pectin with and without 0.1% TACA and 39% NaCMC with and without 0.1% TACA and 2 per treatment group for 19.5% pectin and 19.5% NaCMC with and without 0.1% TACA. Patches without drug were employed as controls.

A 20 mm × 20 mm square patch of the appropriate type was applied to all test sites. The location of all patches was marked precisely with permanent ink immediately after application. One square was removed from the 39% pectin with and without 0.1% TACA and 39% NaCMC with and without 0.1% TACA treatment groups after 6, 9, and 14 hr contact with the skin, while a square was removed after 9 hr and 14 hr for 19.5% pectin and 19.5% NaCMC with and without TACA.

Skin blanching was assessed under standard lighting conditions provided by a light box (Hancocks size A3, 2 × 18 Watt Phillips Graphica fluorescent lamp LDL 400) fitted about 350 cm above the arm at times of 1, 2, 3, 6, 8, 10, 25, 32, 50, 74, and 98 hr after the removal of patches. The degree of pallor was estimated using a 0–4 scale with half-point rating (30). All estimations of blanching were made without reference to application charts.

All volunteers were asked to avoid excessive alcohol consumption, elevated temperatures, and excessive arm contact with water during the trial.

Areas under the plot of %TPS versus time were calculated using the trapezoidal rule (29). This AUC was taken as a measure of the total bioavailability of TACA over the time period studied.

Data Analysis

All data were analyzed using the Mann Whitney U test (31).

RESULTS

In Vivo Hydration of Patch Material

Figure 1 shows the mean hydration levels of the five patches with different hydrocolloid compositions over 96 hr when applied to the skin in vivo. Table 1 shows the number of patches that were lost over each 24-hr period as a function of the pectin and NaCMC content of each patch. Although many volunteers commented that the patches were uncomfortable over the first 24 hr, none reported excessive discomfort or itching. Three volunteers lost many of their patches over the first 72 hr, whereas the majority of the volunteers lost only one or perhaps two patches. Reference to the diary sheets of the former group failed to identify any specific activities, such as excessive exercise or frequent washing, that would explain such patch loss.

Figure 1 clearly indicates how patch composition affected water uptake in vivo; patches containing NaCMC 39% showed a linear weight increase of approximately 0.13 mg cm^{-2} hr^{-1} over the 96-hr period ($r = 0.994$). Patches containing 39% pectin, however, showed a hydration rate of 0.07 mg cm^{-2} hr^{-1} over the first 24 hr, falling to 0.02 mg cm^{-2} hr^{-1} over the following 72 hr of the study. The patches composed of varying proportions of the two hydrocolloids exhibited intermediate behavior. Statistical analysis of the weight gains of patches containing NaCMC 39% and pectin 39% showed that there

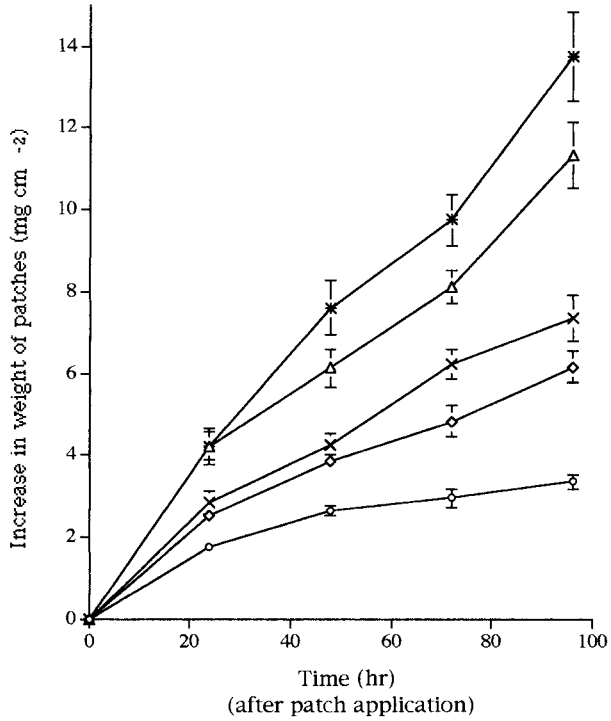

Figure 1. The effect of varying hydrocolloid content on the in vivo hydration of patches ($n = 20 \pm$ SEM): ○, pectin 39%; ◇, pectin 26%, NaCMC13%; ×, pectin 19.%, NaCMC19.5%; □, pectin 13%, NaCMC 26%; *, NaCMC 39%.

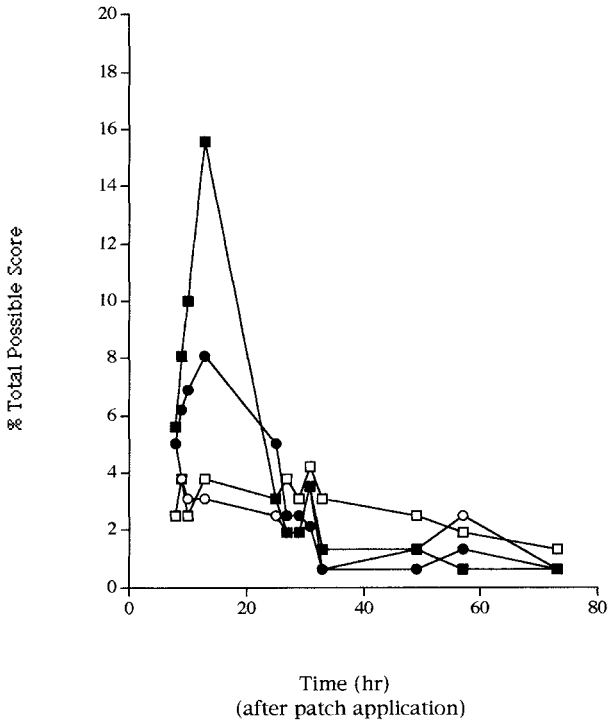

Figure 2. The blanching response of dermatological patches containing 0.1% TACA of different hydrocolloids with controls after application for 6 hr: ■, pectin 39%/TACA patch; ●, NaCMC 39%/TACA patch; □, pectin control patch; and ○, NaCMC control patch.

was a significant difference in the rates of hydration of the two types of patch ($p < .005$).

In Vivo Percutaneous Absorption of Triamcinolone Acetonide

The percutaneous penetration of TACA from patches containing the drug as a 0.1% dispersion for 6 hr is shown in Fig. 2. Maximum blanching was observed 12 hr after patch application, with maximum %TPS values being 15.6 and 8.1 for patches containing 39% pectin and 39% NaCMC, respectively. However, although maximum blanching induced by both patch types was found to be significantly different from that of their controls ($p < .05$), maximum %TPS values produced by the patches were not significantly different from each other.

Table 1

Patches Lost During the In Vivo Study

	0–24 hr	24–48 hr	48–72 hr	72–96 hr	Total
Pectin 39%	1	3	5	9	18
Pectin 26%/NaCMC 13%	0	1	3	5	9
Pectin 19.5%/NaCMC 19.5%	0	2	1	2	5
Pectin 13%/NaCMC 26%	0	0	4	3	7
NaCMC 39%	0	2	3	5	10

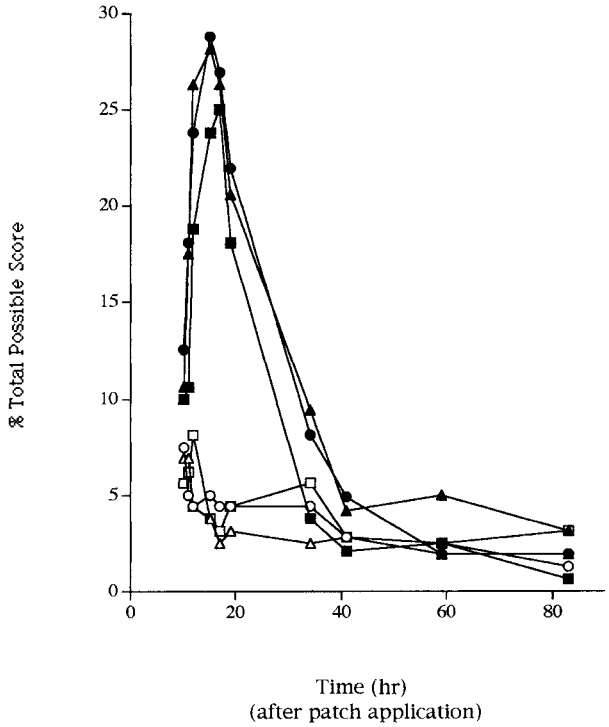

Figure 3. The blanching response of dermatological patches containing 0.1% TACA of different hydrocolloids with controls after application for 9 hr: ■, pectin 39%/TACA patch; ▲, pectin 19.5%, NaCMC 19.5%/TACA patch; ●, NaCMC 39%/TACA patch; □, pectin control patch; △, pectin 19.5%, NaCMC 19.5%/TACA patch; and ○, NaCMC control patch.

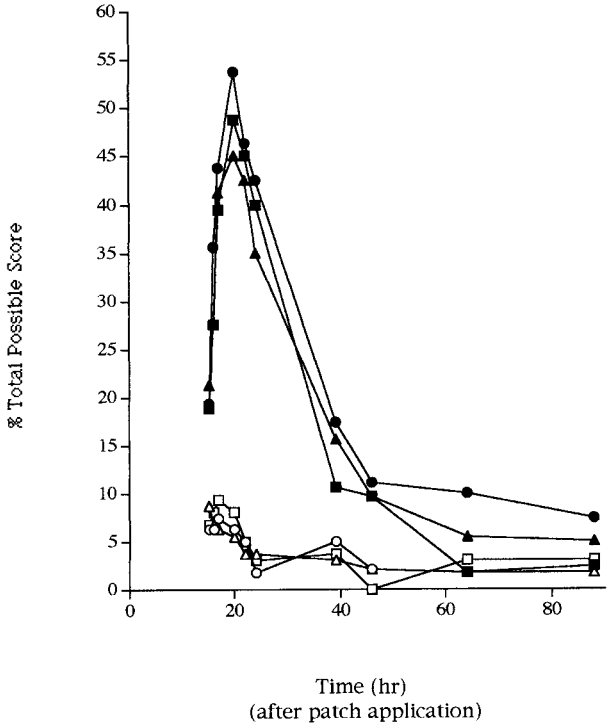

Figure 4. The blanching response of dermatological patches containing 0.1% TACA of different hydrocolloids with controls after application for 14 hr: ■, pectin 39%/TACA patch; ▲, pectin 19.5%, NaCMC 19.5%/TACA patch; ●, NaCMC 39%/TACA patch; □, pectin control patch; △, pectin 19.5%, NaCMC 19.5%/TACA patch; and ○, NaCMC control patch.

Figure 3 shows the blanching response after application of patches containing 0.1% TACA for 9 hr. The patch material also contained either 39% pectin and 39% NaCMC or 19.5% pectin and 19.5% NaCMC. The figure shows that all patches induced significantly higher maximum blanching scores than their corresponding controls ($p < .01$), for which maximum blanching was observed 15 hr after application for both patches containing 39% NaCMC and 19.5% pectin and 19.5% NaCMC. Maximum blanching was observed 17 hr after application for patches containing 39% pectin. Although the data suggest that the induced blanching profile that results after a 9-hr application is lower for patches containing 39% pectin compared to the two other patches, these differences were not significant.

Blanching responses after a 14-hr application of patches containing a dispersion of 0.1% TACA are shown in Fig. 4; they show trends similar to induced blanching after a 9-hr application. The parameters derived from the blanching curves are shown in Table 2. Maximum blanching and AUC values for patches containing 0.1% TACA were significantly different from those observed for control patches ($p < .01$). Maximum blanching was observed 20 hr after application for all patch types, and the extent of blanching was not significantly different among patches of varying hydrocolloid composition.

DISCUSSION

A number of TEWL values for the human forearm, determined using commercially available equipment such as the Evaporimeter® and Corneometer®, have been quoted in the literature; they range between 2 and 6 gm^{-2} hr^{-1} (13,32–37).

Aly et al. (34), in fact, measured TEWL before and after application of Saran Wrap®, a polyethylene film, to the forearm and found that values increased from 5.6 g

Table 2

Observed Peak Blanching Response and Cumulative Area Under the Curve for the Different Test Patches Applied for 6, 9, and 14 hr

Test Preparation	Observed Peak (%TPS)	Cumulative Area Under the Curve (% TIPs · hr)
Applied for 6 hr		
Active 39% pectin	15.6	243
Active 39% NaCMC	8.1	183
Control 39% pectin	4.2	182
Control 39% NaCMC	3.8	141
Applied for 9 hr		
Active 39% pectin	25.0	493.0
Active 19.5% pectin, 19.5% NaCMC	28.1	724.5
Active 39% NaCMC	28.8	658.2
Control 39% pectin	5.0	263.9
Control 19.5% pectin, 19.5% NaCMC	6.9	218.8
Control 39% NaCMC	8.1	293.1
Applied for 14 hr		
Active 39% pectin	48.8	1106.7
Active 19.5% pectin, 19.5% NaCMC	45.0	1247.6
Active 39% NaCMC	53.8	1515.8
Control 39% pectin	9.4	297.9
Control 19.5% pectin, 19.5% NaCMC	8.8	266.3
Control 39% NaCMC	7.5	279.3

TPS = total possible score.

m^{-2} hr^{-1} before application to 18.7 g m^{-2} hr^{-1} after removal of the film. Grice et al. (33) and Rietschel (35) also showed similar effects. Ladenheim et al. (13) showed that application of Actiderm to the skin results in a decrease in TEWL compared with unoccluded values. Such work provides some support for the hypothesis that application of patch material increases the hydration of underlying skin.

The effect of hydrocolloid composition on the weight increase of patches when placed on the skin is shown in Fig. 1. The figure shows that increasing the NaCMC composition enhanced the ability of the patch to take up water vapor from the skin. In previous studies involving Actiderm (38), it was determined that 86.7% of the weight gain of the patch material was attributable to uptake of water, with the remainder of the weight gain probably due to electrolytes, skin, and hair adhered to the patch. Consequently, assuming that 86.7% of the weight increase was due to water uptake, the TEWL of the skin beneath the patches can be calculated as a function of time; the values are shown in Table 3.

Comparison of the these values with those in the literature indicates that application of all five patch types caused a reduction in TEWL compared to values for unoccluded skin. However, different patch types reduced TEWL to different extents, suggesting that hydrocolloid composition may affect the extent of hydration induced to the underlying stratum corneum. Patches containing 39% NaCMC, for example, only caused TEWL to be reduced to 1.26 g m^{-2} hr^{-1} over the final 24 hr of patch application, whereas patches containing 39% pectin caused TEWL to be reduced to 0.15 g m^{-2} hr^{-1} over the same time period.

Table 3 also shows that patches containing 39% NaCMC caused a reduction in TEWL of 15.4% from the first to the last 24 hr, whereas patches containing 39% pectin caused a 76.6% reduction in calculated TEWL values. There are two possible explanations for this phenomenon. The patches containing 39% pectin have been shown to have a lower capacity for water vapor uptake than patches containing 39% NaCMC (Fig. 1). Therefore, the former patch types will absorb less water when placed on the skin. The patches containing 39% pectin, due to their low water uptake capacity, may therefore have induced a greater level of hydration to the stratum corneum than patches containing 39% NaCMC. An alternative hypothesis is that both patch types induced the maximum

Table 3

Calculated TEWL Values Beneath Patch Material with Different Hydrocolloid Compositions

	TEWL ($g\ m^{-2}\ hr^{-1}$)		
	First 24 hr	Final 24 hr	Decrease (%)
Pectin 39%	0.69	0.15	78.3
Pectin 26%/NaCMC 13%	0.91	0.48	47.3
Pectin 19.5%/NaCMC 19.5%	1.02	0.45	55.9
Pectin 13%/NaCMC 26%	1.53	1.13	26.1
NaCMC 39%	1.49	1.26	15.4

possible hydration to the stratum corneum; however, patches containing 39% pectin may also have limited diffusion of water from the dermis through the stratum corneum. In contrast, patches containing 39% NaCMC, due to their more hygroscopic nature, may have induced greater diffusion of water from the dermis through the maximally hydrated stratum corneum, resulting in relatively high TEWL compared to patches containing 39% pectin. Patches with varying proportions of the two hydrocolloids showed intermediate water vapor uptake characteristics in vivo.

Duration of application affected TACA-induced blanching for all three patch types (Figs. 2–4). An increase in application time allowed more TACA to be released from the patches, thus allowing more drug to penetrate the stratum corneum and to induce a greater blanching response. This was illustrated by an increase in both the maximum %TPS values and the AUC (Table 2).

The blanching assay has been used extensively to examine the effect of a number of parameters on the percutaneous penetration of topically applied corticosteroids. For example, the assay was utilized to demonstrate the difference in potency between triamcinolone and TACA. A dramatic increase in activity was produced when the 16α and 17α hydroxyl positions on triamcinolone were united through the acetonide group (39). The same assay has been used to demonstrate a tachyphylactic response to repeated applications of the same dose of TACA (40), and the blanching response induced by TACA has been correlated with clinical efficacy of the steroid (41). Stoughton (42) showed that the blanching response induced by TACA was not related to its concentration in the applied vehicle. The effect of formulation variables on TACA-induced blanching was studied by Barry and Woodford (29,43), who found that incorporation of TACA in an ointment base reduced the bioavailability of the drug compared to cream formulations. Similar trends were also shown by Stoughton (42) and Jackson et al. (17), who demonstrated that different formulations of TACA induced different levels of blanching even though they contained the same concentration of steroid. Hollingsbee et al. (2) found that Actiderm markedly increased the bioavailability of TACA from creams and alcoholic solutions. In contrast, only a slight effect on bioavailability from an ointment application was demonstrated.

Application of patches containing TACA and different hydrocolloid ratios showed that changes in hydrocolloid composition did not significantly alter the blanching response (Figs. 2–4). This may have been due to a number of reasons. As observed by Stoughton (42), maximum blanching responses elicited by TACA were induced at low concentrations (0.025%). Therefore, the maximum possible blanching response at the respective time points may have been induced by all patches, and although some patch formulations may have caused increased percutaneous absorption of TACA, this would not have been reflected by an enhanced blanching response.

The effect of the hydrocolloid composition of patches on both drug release from the matrix and on hydration of the underlying stratum corneum must also be considered. Patches containing 39% pectin exhibited low rates of hydration when placed on the skin (Fig. 1), and although this may not facilitate drug release, it was thought that this might enhance hydration of the stratum corneum. Since hydrated stratum corneum is known to be more permeable to corticosteroids than unhydrated skin, then enhanced blanching might be expected after application of patches containing 39% pectin. Conversely, patches containing 39% NaCMC hydrated to a greater extent than those containing 39% pectin (Fig. 1), which could have led to enhanced drug release from the patch matrix. However, the increased water uptake might induce lower levels of hydration to the underlying stratum corneum. An enhanced drug release from the matrix, combined with reduced levels of stratum corneum hydration induced by

patches containing 39% NaCMC, may therefore result in a similar blanching response to that induced by patches containing 39% pectin, for which the opposite is true. For the patches containing 19.5% NaCMC, 19.5% pectin, intermediate levels of drug release and stratum corneum hydration would also result in a similar blanching profile.

It can therefore be concluded that, although the TACA-containing hydrocolloid patches varied in their affinity to take up water lost from the skin, the resultant activity of the corticosteroid, as determined by blanching, was independent of the nature of hydrocolloid composition. Nevertheless, the response to the applied patches was directly dependent on their time of application to the skin. Such patches show great potential for the convenient, localized prolonged delivery of drugs to the skin, which would be desirable for the topical use of other corticosteroids, cytotoxic agents, anesthetics, retinoids, biopharmaceuticals, and antifungal, antibacterial, and antiviral agents since the uncontrolled entry of such agents into the systemic circulation can cause side effects.

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