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Research Paper

Hydroxypropylmethylcellulose films for prolonged delivery of the antipsychotic drug chlorpromazine

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Abstract

Objectives The aim of this study was to develop transdermal films based on hydroxypropylmethylcellulose with the purpose of improving transdermal permeation of chlorpromazine hydrochloride, an antipsychotic drug used to alleviate the symptoms and signs of psychosis.

Methods Hydroxypropylmethylcellulose films were prepared and evaluated for their drug content, film thickness, residual water content and bioadhesive properties. In-vitro permeation experiments were performed in the absence and in the presence of permeation enhancers (oleic acid, polysorbate 80, or both) with the purpose of improving drug availability. Other formulative parameters, such as drug and plasticizer concentration and hydroxypropylmethylcellulose type, were investigated.

Key findings Both oleic acid and polysorbate 80 had significant effect on drug permeation with respect to the control formulation. In particular films containing a mixture of oleic acid and polysorbate 80 provided the best enhancement activity for chlorpromazine. Moreover, a decrease in propylene glycol or chlorpromazine content or an increase of hydroxypropylmethylcellulose viscosity provided lower cumulative amounts of drug permeated.

Conclusions The results obtained confirm that chlorpromazine permeation can be easily modulated by varying the composition of hydroxypropylmethylcellulose-based films. These formulations could serve as candidates for transdermal delivery of antipsychotic drugs.

Keywords chlorpromazine; hydroxypropylmethylcellulose film; transdermal permeation

Introduction

Chlorpromazine is an antipsychotic drug used to alleviate the symptoms and signs of psychosis. Most formulations currently available have been designed for oral administration. After oral administration chlorpromazine undergoes biodegradation in the gastrointestinal lumen, metabolism during absorption in the gastrointestinal mucosa and the hepatic first-pass effect. An alternative approach would be transdermal drug delivery, which offers many advantages, including the improvement of patient compliance, the ability to bypass the first-pass metabolism and the maintenance of relatively stable blood levels and long-term therapy from a single dose.[1] The average daily oral dose is 25–75 mg (mild cases) or 75–150 mg (more severe cases). Since chlorpromazine has an oral bioavailability of approximately 30%, the anticipated transdermal dose for mild cases is 7.5–30 mg daily. An interesting approach to transdermal drug delivery has involved films where the drug was dispersed in an inert polymer matrix.[2] Despite the advantages of these drug delivery systems, drug absorption across the skin remains a major obstacle due to the presence of the stratum corneum, which presents a rate-limiting barrier. An interesting strategy to enhance percutaneous absorption is the use of permeation enhancers, such as fatty alcohols and acids, organic solvents, terpenes and azone.[3] Enhancers facilitate the absorption of a drug through the skin by temporarily diminishing the impermeability of the skin. An ideal permeation enhancer should be nontoxic, nonirritating, nonallergenic, inert and compatible with drug and excipients. Moreover the skin should immediately regain its barrier properties after removal of the enhancer.

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The aim of this research was the formulation of transdermal hydroxypropylmethylcellulose (HPMC)-based films containing chlorpromazine hydrochloride for the treatment of psychotic disorders. In fact the chlorpromazine log P value (octanol–water, 3.4) is considered optimal for absorption through membranes. Nevertheless its high molecular weight (MW 355.33) and a high dissociation (pKa 9.20) at physiological pH is the major obstacle for chlorpromazine diffusion across the skin.[4–6] Film composition was therefore modified by incorporating a chemical permeation enhancer or binary enhancer combinations (oleic acid or polysorbate 80, or both). [7–9] Oleic acid, an unsaturated C18 fatty acid, and polysorbate 80, an anionic surfactant, are considered powerful permeation enhancers and their application in transdermal formulation has been widely studied.[10] Moreover, their disruption of the barrier does not lead to irritation.[11] Propylene glycol was chosen as a plasticizer and for its ability to act synergistically with many enhancers.[12] In fact many studies have shown that the skin-permeability-enhancing effects of fatty acids, such as oleic acid, are greatest with propylene glycol. This association disorganizes the multilaminate hydrophilic–lipophilic layers located intercellularly in the stratum corneum, consequently promoting percutaneous absorption of drugs.[13,14] Also the non-ionic surfactant polysorbate 80 is able to enhance skin permeation by solubilizing the lipids within the stratum corneum and modifying the permeability characteristics of biological membranes.

Materials and Methods

Materials

Chlorpromazine hydrochloride and polysorbate 80 were purchased from Fluka (Milan, Italy), while hydroxypropylmethylcellulose (HPMClv: Methocel E50 Premium LV, viscosity of 2% solution in water 40–60 cps; HPMChv: Methocel E4M Premium, viscosity 3000–5600 cps) was from Dow (Milan, Italy). Propylene glycol and ethanol were obtained from Carlo Erba (Milan, Italy), while oleic acid was obtained from Avocado (Morecambe, UK). Karl Fischer reagents were from Riedel-de Haen (Seelze, Germany). All other chemicals used were of analytical grade and purchased from Carlo Erba (Milan, Italy). Backing (3M Scotchpak 9734 Polyester Film Laminate) was a kind gift from 3M (St Paul, USA).

Film preparation

Chlorpromazine hydrochloride was solubilized in a mixture of water, propylene glycol and ethanol. Eventually oleic acid or polysorbate 80, or both, were added and the mixture was stirred overnight. HPMClv or HPMChv was slowly incorporated to the mixture and once it was fully hydrated and gel consistency was obtained, 20 g of the mixture was spread on a polyester sheet (3M Scotchpak 9734 Polyester Film Laminate Backing) placed in a 105-mm diameter Petri-dish. After oven-drying at 70°C for 6 h, the film layer was cut into appropriate sizes, packed in aluminium foil and stored at 4°C for further studies. To evaluate the influence of propylene glycol concentration, chlorpromazine hdyrochloride concentration and HPMC type on transdermal drug permeation, the composition of the mixture used for film preparation was modified as reported in Table 1.

Photo-correlation spectroscopy

The presence of oleic acid in the mixtures used for film preparation allowed the formation of biphasic systems. In particular the mixtures prepared without chlorpromazine hydrochloride appeared macroscopically opaque. On the other hand the presence of the drug in the mixtures produced clear and translucent systems due to the ability of chlorpromazine hydrochloride to reduce the size of the inner phase of the emulsion. In fact as reported in other works,[15,16] chlorpromazine hydrochloride, due to its amphiphilic character, is able to form micellar systems with nanometric size. Before the addition of HPMC, all the mixtures containing oleic acid and chlorpromazine hydrochloride were analysed in terms of size of the inner phase by means of photo-correlation spectroscopy (PCS; Brookhaven 90-PLUS; New York, USA) with a He–Ne laser beam at a wavelength of 532 nm (scattering angle of 90°).

Characterization of transdermal films

Once dried, three circles 2.10 cm in diameter were cut from each film. Each circle was measured for thickness (Mitutoyo pocket thickness gauge; Mitutoyo Mfc. Co. Ltd, Tokyo, Japan) and then was dissolved in 100 ml of 0.9% w/v sodium chloride solution. The solutions obtained were spectrophotometrically analysed at 254 nm (UV-1601; Shimadzu, Tokyo, Japan) to determine the amount of chlorpromazine hydrochloride contained in the film. The results were expressed as milligrams of drug per square centimetre (mg/cm^2). The water content was determined using the Karl Fischer (KF) method (Karl-Fischer DL-38, Mettler-Toledo, Milan). The KF

Table 1 Composition of the mixtures used for film preparation

	F_0	F_1	F_2	F_3	F_4	$F_{4(C3/4)}$	$F_{4(C1/2)}$	$F_{4(P3/4)}$	$F_{4(P1/2)}$	$F_{4(HPMChv)}$
Drug	11.80	11.80	11.80	11.80	11.80	8.85	5.90	11.80	11.80	11.80
Water	31.80	31.80	31.80	31.80	31.80	31.80	31.80	31.80	31.80	31.80
Ethanol	27.30	26.40	26.40	25.95	25.50	28.45	31.40	32.33	39.15	25.50
Propylene glycol	27.30	27.30	27.30	27.30	27.30	27.30	27.30	20.47	13.65	27.30
Oleic acid	0	0.90	0	0.90	0.90	0.90	0.90	0.90	0.90	0.90
Polysorbate 80	0	0	0.90	0.45	0.90	0.90	0.90	0.90	0.90	0.90
HPMClv	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	0
HPMChv	0	0	0	0	0	0	0	0	0	1.80

Amounts are expressed as % w/w on wet basis.

reagent (Hydranal Methanol Dry) was standardized using Hydranal composite J. All determinations were carried out in triplicate. The in-vitro bioadhesion was measured in terms of the force needed to pull out a freshly excised pig ear skin (surface area 1 mm^2) from a film with an adapted tensiometer (Krüss 132869; Hamburg, Germany). The skin was fixed to a support with cyanoacrylate adhesive and then suspended from the tensiometer spring. The zero resetting of the instrument had been regulated until the force measured by the torsion balance was zero dyne, indicating a perfect compensation of the weight of the membrane and its support. The skin was lowered until it just contacted the surface of the film. A 40 dyne force, measured by the torsion balance of the instrument as a negative force, was applied to the film for 5 s. Then the skin was raised until it was separated from the film. This point represented the adhesive bond strength between these elements. This value was expressed as a positive force in dyne. For each mixture, the assay was performed for three different films and averaged.

In-vitro transport experiments

The permeation of chlorpromazine hydrochloride from the prepared films was determined by introducing single film in the donor compartment of a vertical Franz diffusion cell, with an exposed surface area of 3.46 cm^2. Pig ear skin was used as the test membrane. The skin from the inner face was excised from the ear using a surgical blade and used immediately. The receptor compartment was filled with 0.9% w/v sodium chloride solution to solubilize chlorpromazine hydrochloride and to ensure sink conditions, maintained at 37 ± 0.5°C and continuously stirred at 100 rev/min. Samples of the receptor solution were withdrawn at predetermined time intervals of over 100 h and analysed by UV/Vis spectrophotometer for the determination of drug permeated. Sink conditions were maintained at all times. All experiments were carried out in triplicate. The results of the permeation experiments are shown as cumulated drug amount (mg) permeated per unit of surface area (cm^2) plotted as a function of time.

Statistical analysis

All the experiments were done in triplicate. Results are expressed as mean ± SD. Statistical data were analysed by Kruskal–Wallis test. The criterion for statistical significance was $P < 0.05$.

Results

Dimensional analysis of the inner phase of all formulations (mixtures employed for film preparation before the addition of HPMC) containing oleic acid and chlorpromazine hydrochloride was performed. The mean diameter of formulation F1 globules was 199.5 ± 6.3 nm. The presence of polysorbate 80 decreased the inner phase size of oil–water systems proportionally to its concentration (105.1 ± 4.8 and 71.6 ± 4.1 nm for F3 and F4, respectively). Moreover, decreasing amount of drug in the mixtures ($F_{4(C3/4)}$ and $F_{4(C1/2)}$) induced the formation of globules of 220.8 ± 6.6 and 252.2 ± 6.9 nm in size, respectively. Finally different amounts of propylene glycol produced a less efficiently dispersed inner phase: the mean diameter for $F_{4(P3/4)}$ and $F_{4(P1/2)}$ was 380.3 ± 5.9 and 399.2 ± 7.0 nm, respectively.

The drug content and thickness of the films are shown in Table 2. The different thickness of films can be related to the different composition used for their preparation. In particular, decreasing the content of propylene glycol produced differences in the film thickness. Moreover the experimental drug content of all the formulations was close to the theoretical one (6.79 mg/cm^2 for F_0, F_1, F_2, F_3, F_4, $F_{4(P3/4)}$, $F_{4(P1/2)}$, $F_{4(HPMChv)}$; 5.10 mg/cm^2 for $F_{4(C1/2)}$; 3.40 mg/cm^2 for $F_{4(C3/4)}$) with low standard deviation (relative to the mean of three determination: three circles 2.10 cm in diameter cut from each film), suggesting that the method employed for their preparation was capable of giving a uniform drug distribution. After drying, the residual water content was approximately 1.30% (w/w). The results revealed that the presence of permeation enhancers did not change water content value. On the contrary, films containing a higher percentage of propylene glycol showed a higher water content. As can be seen in Table 2, the bioadhesion values were similar for all films. In fact the bioadhesive excipient in all formulations is HPMC. This polymer contains a large number of hydroxylic groups that enable formation of hydrogen bonds with the epidermal layer of the skin.[17,18]

The effect of enhancers on the permeation profiles of chlorpromazine from HPMC films is shown in Figure 1. Oleic acid (F_1) or polysorbate 80 (F_2) alone had an effect on drug permeation with respect to the control formulation (F_0). Moreover, films containing a mixture of oleic acid and polysorbate 80 (F_3 and F_4) provided the best enhancement

Table 2 Characteristics of the different films

Film formulation	Drug content (mg/cm^2)	Film thickness (mm)	Water content (% w/w)	Detachment force (dyne)
F_0	6.72 ± 0.04	0.50 ± 0.02	1.30 ± 0.06	16.0 ± 0.8
F_1	6.72 ± 0.03	0.52 ± 0.05	1.33 ± 0.03	15.8 ± 0.3
F_2	6.67 ± 0.08	0.54 ± 0.03	1.32 ± 0.02	16.5 ± 0.4
F_3	6.68 ± 0.01	0.57 ± 0.01	1.32 ± 0.02	16.1 ± 0.8
F_4	6.78 ± 0.01	0.58 ± 0.06	1.33 ± 0.06	16.2 ± 0.4
$F_{4(C3/4)}$	5.04 ± 0.02	0.52 ± 0.01	1.28 ± 0.03	16.3 ± 0.5
$F_{4(C1/2)}$	3.41 ± 0.03	0.47 ± 0.02	1.25 ± 0.05	16.3 ± 0.9
$F_{4(P3/4)}$	6.68 ± 0.03	0.36 ± 0.01	1.15 ± 0.02	16.2 ± 0.5
$F_{4(P1/2)}$	6.74 ± 0.05	0.17 ± 0.02	0.92 ± 0.04	16.3 ± 1.0
$F_{4(HPMChv)}$	6.77 ± 0.03	0.55 ± 0.01	1.43 ± 0.03	16.5 ± 0.7

Data are expressed as mean ± SD, $n = 3$.

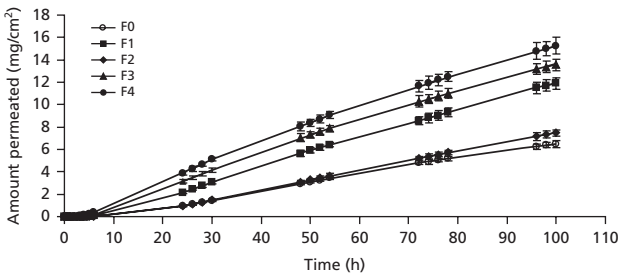

Figure 1 Permeation profiles of chlorpromazine hydrochloride through pig ear skin from HPMC films with different penetration enhancers. Data are means ± SD, $n = 3$.

Table 3 Effect of permeation enhancers, amount of propylene glycol, drug concentration and HPMC viscosity on the percutaneous parameters of chlorpromazine hydrochloride

Formulation	Flux (μg/cm^2/h)	Q_{100} (mg/cm^2)	Lag time (h)
F_0	58.0 ± 2.6	6.5 ± 0.3	6.1 ± 0.3
F_1	121.3 ± 5.8	11.9 ± 0.5	5.4 ± 0.2
F_2	58.0 ± 2.3	7.5 ± 0.3	6.1 ± 0.4
F_3	167.2 ± 6.3	13.6 ± 0.5	5.2 ± 0.3
F_4	194.7 ± 6.8	15.2 ± 0.7	4.0 ± 0.2
$F_{4(C3/4)}$	68.2 ± 3.4	7.5 ± 0.4	6.0 ± 0.1
$F_{4(C1/2)}$	37.8 ± 1.5	3.7 ± 0.2	5.8 ± 0.3
$F_{4(P3/4)}$	87.3 ± 3.7	10.4 ± 0.5	5.5 ± 0.1
$F_{4(P1/2)}$	59.5 ± 2.0	5.9 ± 0.3	5.2 ± 0.1
$F_{4(HPMChv)}$	88.7 ± 4.3	7.8 ± 0.3	4.7 ± 0.3

Q_{100}, cumulative amount of chlorpromazine hydrochloride permeated after 100 h. Data are expressed as means ± SD, $n = 3$.

activity for chlorpromazine hydrochloride. The effect of different concentrations of propylene glycol on the permeation of chlorpromazine hdyrochloride from HPMC films is shown in Table 3. A decreased amount of propylene glycol reduced drug availability. As can be expected the chlorpromazine hydrochloride concentration in the HPMC film influenced permeation (Table 3). In particular, a decrease in chlorpromazine hydrochloride concentration provided lower cumulative amounts of drug permeated. Finally, the effect of varying HPMC viscosity on the permeation is shown in Table 3. Intrinsic viscosities at 25°C were determined on gels (mixtures used for film preparation after the addition of HPMC and before the drying process) using a rotational viscometer (Visco Star-R; Fungilab S.A., Barcelona, Spain). The results show that the more viscous mixtures ($F_{4(HPMChv)}$; viscosity of 2% solution in water: 3000–5600 cps) had decreased drug permeation with respect to the control mixture (F_4; 40–60 cps).

Discussion

The presence of oleic acid in the formulations produced biphasic systems stabilized by polysorbate 80 and chlorpromazine hydrochloride. The study of the mixtures employed for film preparation before the addition of HPMC provided preliminary information about the characteristics of these biphasic systems. In particular, polysorbate 80 has the ability to reduce the interface tension of oil–water biphasic systems and in all formulations analysed we observed a decrease of the inner phase size as a function surfactant concentration. Moreover chlorpromazine hydrochloride, which is an amphiphilic compound able to distribute between lipophilic and hydrophilic phases, was found to induce the formation of globules with lower size with increasing its concentration.[19,20] Finally we found that propylene glycol influenced the dispersion of the inner phase too. This effect can be explained due to polarity and viscosity changes of the external phase of the emulsions. In fact $F_{4(P3/4)}$ and $F_{4(P1/2)}$ formulations were prepared using an excess of ethanol with respect to other films. In particular, a decreased polarity limited the emulsifying ability of the surfactant system, while a decreased viscosity favoured the formation of globules with larger size.

To obtain the films, all the mixtures were added with cellulose and oven-dried. The drying process favoured the elimination of ethanol and water. The percentage of water present in the different formulations was similar, apart from films containing a different amount of propylene glycol. This can be explained by the hygroscopic character of propylene glycol, which can reduce the elimination of water during the drying step.

One of the approaches used to improve drug permeation and achieve the desired therapeutic plasma level makes use of enhancers. In this study, oleic acid and polysorbate 80, in the presence of propylene glycol as plasticizer, were selected to modulate the in-vitro permeation of drug through the skin. Moreover, binary enhancer combinations (both oleic acid and polysorbate 80) were tested with the aim of evaluating possible synergistic effects. Oleic acid, polysorbate 80, or their mixtures produced an increase in drug permeation with respect to control formulation. In this study propylene glycol was selected as plasticizer, but a satisfactory solvent power for chlorpromazine hdyrochloride can also be achieved. Moreover propylene glycol has been widely used as enhancer in its own right and as a vehicle for other enhancers.[13,21,22] Therefore a decreased amount of propylene glycol reduced drug availability due to different effects: the improved drug solubility in the films and the enhancing effect. As percutaneous absorption involves the passage of drug molecules from the skin surface into the stratum corneum under the influence of a concentration gradient and their subsequent diffusion through the stratum corneum, different chlorpromazine hydrochloride concentration in the films provided significant differences in the cumulative amounts of drug permeated. Finally also the choice of HPMC type allowed modulation of drug permeation. HPMC added to the mixtures employed for film preparation induced the formation of a gel with a particular viscosity as a function of its molecular weight. After drying, the more viscous mixtures produced a more packed network in which drug diffusion can be limited.[23]

Conclusions

On the basis of these results, it can be concluded that chlorpromazine can be transdermally administered by HPMC films. Drug permeation through the skin can be easily

modulated by varying the composition of HPMC-based films and by the addition of permeation enhancers. In particular the synergistic action of oleic acid–polysorbate 80 mixture provided the best enhancement activity for chlorpromazine. These formulations could serve as candidates for transdermal delivery of antipsychotic drugs.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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