Formulation and stability study of chlorpheniramine maleate transdermal patch

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Administration of drugs through skin has received great attention through the last decade. Hence this study aims to formulate an anti-histaminic drug Chlorpheniramine maleate (CPM) as transdermal patch using different bioadhesive polymers such as ethyl cellulose, cellulose acetate, and polyvinyl pyrrolidone with different plasticizers such as propylene glycol (PG) and polyethylene glycol 400 (PEG400). Patches were prepared through solvent evaporation method, evaluated for their physical and mechanical properties and then subjected to stability study to select the best formulae to be evaluated in vitro and in vivo. The selected formulae were examined for CPM release in phosphate buffer saline pH 5.5 and also tested for CPM permeation through ear rabbit skin. Finally, one formula was evaluated in vivo in comparison with multiple oral doses of commercial CPM oral tablets and results showed that CPM transdermal patch has higher bioavailability than an oral tablet of the same dose, with lower plasma fluctuation and less administration frequency.

Key words: Transdermal patch, chlorpheniramine maleate, polymers, bioadhesive

INTRODUCTION

A transdermal patch is a medicated adhesive patch placed on the skin to deliver a time-released dose of medication through the skin for treating topical or systemic illness. Since early 1990, this dosage form of transdermal therapeutic system has been available in the pharmaceutical market. Such a system offers a variety of significant clinical benefits over others, such as tablet and injection.

Transdermal drug delivery system (TDDS) can deliver certain medication to systemic circulation in a more convenient and effective way than is possible with conventional dosage form. The potential of skin as a path of drug administration has been amply demonstrated by the acceptability of marketed therapeutic systems. Administration of systemic drugs using a transdermal patch represents a noninvasive route, with improved patient compliance. This route of administration prevents passage through the gastrointestinal tract and maintains constant plasma levels for prolonged periods of time.

Also, for the transdermal route of administration, peak plasma levels of drug are reduced leading to decreased side-effects and it avoids presystemic and systemic first pass metabolism and eliminates the need for intravenous access.

Transdermal route is a potential mode of delivery of lipophilic drugs in the systemic circulation. It controls of the area of application, amount applied, release kinetics and prolongation of application time.

Low turnover rate of transdermal products from pharmaceutical research and development departments could be attributed to the disadvantages encountered with this route of administration including the outermost stratum corneum layer of the epidermis as a significant barrier to penetration across the skin, skin irritation associated with some drugs, limitation of dose that could be incorporated in the patch, lag time for drug absorption and onset of action, and metabolism of some drug in the skin.

MATERIALS AND METHODS

Material
Cellulose acetate (CA) (40% acetyl groups), Ethyl cellulose (EC) (about 200cps, 48-49.5% Ethoxy groups), Fluka Biochemica, Switzerland. Polyvinyl pyrrolidone (PVP) K-30 (Luna Co. from Bf. Goodrich, USA), Chlorpheniramine maleate (CPM) (Al Gomhoria Co.,
Cairo, Egypt), Acetonitrile, Methanol, and Ether were of HPLC reagent grade: Romil, London, UK.

Methodology

**Formulation and evaluation of different CPM transdermal patches**

**Partition coefficient of CPM in n-octanol/ Phosphate buffer (PB) system**

The partition coefficient of the drug was determined by taking equal volumes of n-octanol and aqueous solution (PB pH 7.4) in a separating funnel. In case of water-soluble drugs such as CPM, a drug solution of 25 µg/ml was prepared in the buffer saline. Twenty-five milliliters of this solution was taken in a separating funnel and shaken with equal volume of n-octanol on mechanical shaker for 24 hours. The mixture was then centrifuged at 2000 rpm for 10 minutes and concentration of CPM in aqueous phase was determined spectrophotometrically by measuring absorbance at 261 nm. The partition coefficient (Kp) was calculated from this equation:

\[
K_p = \frac{\text{Concentration of the drug in organic phase}}{\text{Concentration of the drug in aqueous phase}}
\]

**Design of the experiment and preparation of the films**

A 2^4 factorial design was used for construction of CPM film formulations to result in 16 different formulations, as illustrated in Table 1. Preparation of the films was done using solvent-casting technique.

**Two types of patches were formulated:**

a) 2.5% CA with 2.5% PVP patches.

b) 2.5% EC with 2.5% PVP patches.

The predetermined amounts of CA or EC and PVP polymers were dissolved in 1:1 mixture of methanol and chloroform, then the drug (0.1% W/V), preservatives (in concentration of 0.1% w/w for methyl parabens and 0.01% for propyle parabens), and plasticizer were added, this solution was stirred with the aid of mechanical stirrer to ensure complete drug and plasticizer distribution, 10 ml of this solution were taken and poured in dry glass petri dish (5.5 cm diameter) and dried at room temperature. To prevent fast evaporation from the patches, a funnel was placed inverted on the dish. After ensuring the complete evaporation of the solvent, patches were packed in aluminum foil and stored in dessicator for further study.

**Evaluation of the prepared films**

**Physical and mechanical parameters**

**Thickness**

Patch thickness was measured using micrometer at three different places and the mean value plus standard deviation (S.D.) was calculated.

**Weight**

Five different films from individual batches were weighed individually, and the average weight was calculated, the individual weight should not deviate significantly from the average weight, so the standard deviation was calculated. The tests were performed on films which were dried at 60°C for 4 hours prior to testing.

**Tensile strength**

Tensile strength was determined using tensile strength apparatus, weight was gradually increased so as to increase the pulling force till the patch broke, and the tensile strength was calculated.

\[
\% \text{Elongation} = \frac{L_1 - L_2}{L_2} \times 100
\]

Where \(L_1\) = final length of each strip; and \(L_2\) = initial length of each strip.

**Moisture content**

The film was weighed and kept in a dessicator containing calcium chloride at 40°C and dried for at least 24 hours. The film was weighed until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage (by weight) moisture content.

**Moisture uptake**

The weighed film was kept in a dessicator at room temperature for 24 hours. It was then taken out and exposed to 84% relative
humidity using a saturated solution of potassium chloride in a dessicator until a constant weight was achieved\[23\].

The per cent moisture uptake was calculated by using the following formula:

\[
\text{Per cent moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

Swelling index (SI)
Medicated films were dried until constant weight \(W_1\) using dessicator over anhydrous CaCl\(_2\) at room temperature for one day. The films were then immersed in 100 ml of distilled water at 37°C and reweighed after removal of excess water by pressing it gently between two filter papers \(W_2\).

The reweighed films were retained to the dessicator and allowed to be dried to constant weight \(W_3\).

Swelling index is calculated from the following formula:\[24,25\]

\[
\text{SI} = \frac{W_2 - W_3}{W_3}
\]

Where \(W_2\) = the weight of immersed film
\(W_3\) = the weight of redried film.

Drug content
Determined area \((1 \text{ cm}^2)\) of each patch was taken and dissolved in about 30 ml phosphate buffer pH 5.5 with the aid of magnetic stirrer, the solution was filtered through filter paper and completed to 50 ml with the buffer, the amount of drug was determined by measuring the absorbance spectrophotometrically at wave length 261 nm with respect to the standard calibration curve of CPM. This experiment was done five times taking parts from different places in the patch as to assure well drug distribution through the patch.

Stability study
The prepared patches were subjected to stability study by storing the patches at different storage conditions. The patches were stored for three months at refrigeration (2-5°C) and ambient conditions (25°C).\[26\] They were then subjected to further physical evaluation involving test for weight, tensile strength, and percent elongation, also they were tested for actual drug content in order to select the best formulae to be in vitro and in vivo evaluated.

In vitro release of CPM from different films
Dissolution of the selected films was done using USP type II dissolution test apparatus according to the following method.\[27\]

The matrices were fixed on watch glasses covered with stainless screen about 150 mesh/inch which was cut to fit circle on the watch glass, the back of the this assembly was covered with aluminum foil to prevent drug dissolution from this side and then the hall assembly was immersed in 900ml phosphate buffer pH 7.4, temperature was maintained at 32°C.\[28\] speed of rotation was 100 rpm. Samples were collected periodically at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours and replaced with fresh medium. Solutions were filtered through Whatman filter paper, measured spectrophotometrically at 261 nm to determine amount of drug released with time.

Results were analyzed to find the best fit using linear regression according to zero order,\[29\] first order,\[30\] Higuchi diffusion model\[31\] and Korsmeyer Peppas equation.\[32\]

\[
\frac{mt}{m} = k t^n \quad \text{(Korsmeyer equation)}
\]

Where \(mt/m\) is the fraction of drug released, \(k\) is the kinetic constant, \(t\) is release time and \(n\) is the diffusion exponent for drug release. The value of \(n\) gives an indication about the release mechanism: when \(n = 1\), the release rate is independent of time (zero-order) (case II transport), \(n = 0.5\) stands for Fickian diffusion (Higuchi model) and when \(0.5<n<1\), this indicates anomalous or non-Fickian release. Lastly, when \(n>1\), super case II transport is apparent, \(n\) is the slope value of log \(mt/m\) versus the log time curve.

In vitro diffusion and permeation study of CPM films
Franz diffusion cell was used for the study of the in vitro release patterns of the prepared film formulations. This type of cell has been used in majority of the published in vitro transdermal patch studies.\[30,34\]

Rabbit ear skin was used as in vitro membrane for studying drug permeation from different patches.\[5,21\] The skin \((0.1\text{ cm thickness})\) was stabilized for two hours using phosphate buffer (pH 7.4) and the test was done as fellow.\[35,36\] The films were placed in between the donor and receptor compartments, after application of skin membranes, in such a way that the drug-releasing surface faced the receptor compartment. The receptor compartment was filled with the elution medium (PB pH 7.4), and a small bar magnet was used to stir the medium at a speed of 60 rpm with the help of a magnetic stirrer. The temperature of the elution medium was maintained and controlled at 32±0.5°C by a thermostatic arrangement. An aliquot of 1 ml withdrawn at predetermined intervals for a period of eight hours. The drug concentration in the aliquots was determined spectrophotometrically at \(\lambda_{\text{max}}\), 261nm, after suitable dilution, and was calculated with the help of a standard calibration curve of CPM.

To examine the drug permeation kinetics and mechanism, the data were fitted to models representing zero-order, first-order, Higuchi diffusion model, and Korsmeyer-Peppas.\[37-39\]
The permeation parameters of CPM from its films including: Permeability Coefficient (P: cm/min), Diffusion Coefficient (D: cm²/min), Partition coefficient (K), Lag time (t₀; min) and the Apparent Steady State Flux (Jss; µg/cm² min) were calculated.

Bioavailability and in vivo study
Formula C was selected to be evaluated in vivo in comparison with multiple doses of oral tablets of the commercial product Allergy®.

Six New Zealand white rabbits weighting 2-2.25 kg were used. In cross over study with at least one week apart as washing out period, the six animals were divided into two groups, for the first group, patch C was applied on the rabbit ear region (containing 8 mg CPM), The second group received one oral tablet at zero time and then another tablet at the fourth hour of the experiment (each tablet contain 4 mg CPM).

Blood samples were collected from the eye vein in tubes washed with dilute heparin solution to prevent blood coagulation. Samples were collected at time intervals of 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours, they were centrifuged at 3000 rpm for 10 minutes and clear plasma was collected in polyethylene capped tubes and deep frozen at -20°C till extraction and analysis. Drug was extracted and analyzed using chromatographic conditions (HPLC) according to method described by Hament et al.[40] From the results, Cmax (ng/ml), Tmax (hour), AUC₀-₈₈ (ng.hr/ml), AUC₀-₈₈ (ng.hr/ml) and relative bioavailability (AUC₀-₈₈ test/AUC₀-₈₈ commercial product) × 100 were calculated. Statistical tests of significance were performed using one-way ANOVA with multiple comparison by LSD method, and the differences were considered significant when p≤0.05.

RESULTS AND DISCUSSION

Partition coefficient of drug in n-octanol/PB system
n-Octanol and in vitro study fluid (here phosphate buffer, pH 7.4) are considered the standard system for determining the drug partition coefficient between skin and in vitro fluid. Partition of CPM in n-octanol-PB system was found to be 7.1 with logarithmic value (log P) equals 0.851. The results obtained indicated that the drug possesses sufficient lipophilicity which meets the requirements of formulating it into a transdermal patch.[41]

Evaluation of fresh films
The formulations resulted in films which were homogenous, coherent, and free from crystallization, with equal parties and uniform color, but for formulae F1, F5, and F9, no film was formed but sticky heterogenous mass resulted. Thickness of the prepared films ranged from 0.275mm to 0.342mm with small variation between batches of the same patch while weights of fresh films after drying for four hours at 60°C ranged from 0.865gm for F8 to 1.156gm for F14 with small variations in the weight of different batches of the same patch. Our films have relatively good tensile strength values (ranged from 1.84 to 3.85[kg/cm²]) these values guarantee films to be elastic on handling.[42]

The per cent elongation values of fresh films whose were directly proportional to values of tensile strength. The presence of moisture may not affect hardness of the patch in normal conditions, but it may affect in exaggerated conditions.[43] For values of moisture content, with increasing amount of the hydrophilic polymer PVP in the formulation, moisture content also increases.[23]

Moisture content and moisture uptake can cause significant changes in properties such as reduced crushing strength, increased pore diameter in the patches containing hydrophilic polymer. But the moisture content in our preparations was found to be low [2.125-4.232% weight], and it varied very little in the formulations. This little moisture content helps the formulations to be stable and prevents them from becoming a completely dried, brittle product. Low moisture uptake also protects the materials from microbial contamination and avoids bulkiness of the patches.[18]

Swelling index of the preparations was directly proportional to the percent of the hydrophilic polymer PVP and that of the plasticizer.

Drug content
Drug content of the prepared films was found to be ranged from 98.4 to 100.08% of the labeled amount with very small variations between different places in the same patch.

Stability study
After storage in refrigerator, both formulae F2 and F10 are deformed and not available for further study, while for formulae F4, F6, F7, F11, F13, and F14, an observable increase in their weight (might be due to moisture absorption) occurred while sharp decrease in the tensile strength and % elongation was observed. For formulae F3, F8, F12, F15, and F16, the increase in weight was very small and also slight decrease in their tensile strength and % elongation was found. For all formulae (except F2 and F10), no change occurred in their drug content.

After storage at ambient conditions, three formulae (F2, F6, and F10) became very brittle and not available for further study, while for formulae (F4, F7, F11, F13, and F14) they have observable decrease in their weight (might be due to moisture loss) and decrease in their tensile strength and % elongation. The decrease in weight, tensile strength, and % elongation was less for formulae (F3, F8, F12, F15, and F16), thus these formulae have approved their stability upon storage in refrigerator and at ambient conditions, and so these formulae were selected for further studies and given new codes as shown in Table 2.
Table 2: Selected formulae for \textit{in vitro} and \textit{in vivo} studies

<table>
<thead>
<tr>
<th>Plasticizer</th>
<th>PVP (%)</th>
<th>Polymer (%)</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%PG</td>
<td>25</td>
<td>75 CA</td>
<td>A(3)</td>
</tr>
<tr>
<td>15%PEG400</td>
<td>25</td>
<td>75 CA</td>
<td>B(8)</td>
</tr>
<tr>
<td>15%PG</td>
<td>25</td>
<td>75 EC</td>
<td>C(12)</td>
</tr>
<tr>
<td>10%PEG400</td>
<td>25</td>
<td>75 EC</td>
<td>D(15)</td>
</tr>
<tr>
<td>15%PEG400</td>
<td>25</td>
<td>75 EC</td>
<td>E(16)</td>
</tr>
</tbody>
</table>

CA: cellulose acetate; EC: ethyl cellulose; PVP: polyvinyl pyrrolidon

\textbf{In vitro} release of CPM from selected films

Drug release from swellable and erodible hydrophilic matrix can be attributed to polymer dissolution (matrix erosion mechanism), drug diffusion through the gel layer or combination of both,[42] however, polymer dissolution and drug release from polymeric matrix is known to ensure sustained release characteristics, as well as reproducibility of rate and duration of drug release.[44]

Figure 1 illustrates per cent of cumulative amount of CPM released from different patches with time per unit area. From the results, formula C has drug release of about 96.27\% after eight hours.

The dissolution data of most of the formulations fitted well into the Higuchi model; revealing linearity in the Q versus square root of time plots confirming square root kinetics; and the data fitment of the release profile done using Korsmeyer-Peppas model showed values of (n) obtained to be in the range of 0.801-0.963. The mechanism of drug release in these cases was known to follow anomalous transport mechanism, i.e., the drug was released by initial swelling and followed anomalous transport.

\textbf{In vitro} permeation of CPM patches through ear rabbit skin

Release of the drug from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane.[41]

Figure 2 illustrates the per cent of cumulative amount of CPM permeated per cm\(^2\) versus time, from the results, we can observe that formula (C) has the highest cumulative percent of CPM released and permeated after 8 hours (95.92\%). Kinetic analysis of CPM permeation data through skin resulted in that the permeation data of most of the formulations fitted well into the Higuchi model as it has the highest linear regression coefficient (R\(^2\)) for all formulae except for formula D as its linear regression coefficient assumes zero order kinetics, and the data fitment of the release and permeation profile done using Korsmeyer-Peppas model showed values of (n) obtained to be in the range of 0.952-0.979. The mechanism of drug release in these cases was known to follow anomalous transport mechanism, i.e., the drug was released by initial swelling and followed anomalous transport.

Table 3 shows permeation parameters of CPM through ear rabbit skin. From the table, we can detect that propylene glycol (PG) has higher effect as penetration enhancer than PEG.
at the same ratio (incorporated in formula E), and it is mostly effective in 15% with the same ratios of the used polymers.

Bioavailability and in vivo study

Figure (3) illustrates CPM plasma concentrations versus time for both the transdermal patch and multiple oral doses of the commercial tablet (Allergyl®), it is clear that, for the transdermal patch, it has one C\text{max} at 1.5 hours followed by nearly steady state concentration, while for oral doses, there were two C\text{max} at 1.5 and five hours accompanied by observable fluctuation in CPM plasma concentrations, also the C\text{max} of the transdermal patch is higher than both of these of the oral tablets meaning that the transdermal patch could achieve higher plasma concentration than multiple oral doses of the drug. Concerning the AUC\text{p} achieved by the transdermal patch it was 392.88 ng/ml.hr while for the multiple oral doses it was 280.13 ng/ml.hr, and when compared statistically using one-way ANOVA test at p≤0.05, there was significant difference between both of them which means that bioavailability of the transdermal patch was significantly higher than that of the oral doses, this was also clear when we calculated the bioavailability of the transdermal patch relative to that of the oral doses as it was 140.25% compared to that of the oral doses.

Thus, transdermal formulation of CPM using bioadhesive polymers such as EC, CA, and PVP has approved its ability to give controlled release and higher absorption of CPM. These results are similar to Sadashivaiah et al.,[18] who studied the design and in vitro evaluation of haloperidol lactate transdermal patches containing EC povidone as film formers, also similar to Biswajit et al.,[23] who formulated diclofenac diethylamine as transdermal patch using polymer combination of EC and PVP in different ratios. Our finding also agrees with Sirnivas and Nayanabhirama,[40] who reported that application of glibenclamide as transdermal patch resulted in more hypoglycemic level than oral glibenclamide in mice.

CONCLUSION

Formulation of CPM as transdermal patch could enhance its bioavailability due to bitter absorption from the skin and, avoiding first-pass effect and metabolism in the gut mucosa, it increases patient compliance due to decreasing dose frequency.

REFERENCES


Source of Support: Nil, Conflict of Interest: None declared.

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