The Role of Clindamycin Phosphate Associated with Adapalene in Three Semisolid Formulations Developed for Topical Acne Treatment

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Despite the fact that in mild-to-moderate acne vulgaris the standard first-line therapy is the topical treatment with fixed combinations of antimicrobial agents and retinoids, the skin type and the skin barrier function should be taken into account when formulating a topical product. The aim of this study was the comparison of three new semisolid formulations developed for topical application by evaluation of their rheological behavior, as well as the evaluation of in vitro percutaneous diffusion through human epidermis membrane of the pharmaceutical ingredients. Clindamycin phosphate and adapalene were incorporated in three different topical bases, an HPLC method for the determination of their content in the new formulations being developed and validated. A higher concentration of drugs was released from the two gel systems (hydroxypropylmethylcellulose 2.5%-F1 and hydroxyethylcellulose 3%-F2) than from the oil-in-water cream (F3) at pH 7.4, whereas at pH 5.5 the drugs were released in higher amounts from the formulation F3. Following the rheological behavior associated with the penetrability through the human epidermis membrane, our study results suggest that F1 and F2 could be appropriate in treating acne lesions in patients with oily skin and unaffected skin barrier function. In contrast, the oil-in-water cream (F3), due to its possible emollient effect and its higher penetrability at pH 5.5 than gel vehicles, may be indicated for patients with dry and sensitive skin associated with an altered skin barrier.

Keywords: clindamycin phosphate, adapalene, glycolic acid, topical preparation, percutaneous diffusion

Topical therapy consisting of an antimicrobial agent and a retinoid is considered the first-line treatment in mild to moderate papulopustular acne, according with Global Alliance to Improve Outcomes in Acne guidelines [1]. It should be taken into account the increasing need to consider the skin condition and environmental factors when selecting medicated or non-medicated dermatological product. In acne vulgaris the patients could present either an oily skin characterized by an alkaline pH and unaffected product. In acne vulgaris the patients could present either a retinoid is considered the first-line treatment in mild to moderate papulopustular acne, according with Global Alliance to Improve Outcomes in Acne guidelines [1]. It should be taken into account the increasing need to consider the skin condition and environmental factors when selecting medicated or non-medicated dermatological product. In acne vulgaris the patients could present either an oily skin characterized by an alkaline pH and unaffected product. In acne vulgaris the patients could present either an oily skin characterized by an alkaline pH and unaffected product.

The obtaining techniques are shown schematically in figure 1 and the used excipients in figure 2. In table 1, the active pharmaceutical ingredients being as an enhancer of drug permeation in order to improve the drugs penetration. Besides this, glycolic acid has its own effect in acne vulgaris, reducing the follicular keratinisation by diminishing the corneocyte cohesion in horny layer of the skin [10]. The purpose of this study was the comparison of three new semisolid formulations developed for topical application, each containing a combination of 1% clindamycin phosphate (CLD), 0.1% adapalene (ADP) and 2% glycolic acid (GA), in terms of their rheological behavior as well as the ability to release their two combined active pharmaceutical ingredients (CLD, ADP) by in vitro diffusion through human heat separated epidermis test. These products differ in composition and the type of semisolid system formed by the approached technique in their preparation: F1- a hydroxypropylmethylcellulose (HPMC) 2.5% gel, F2- a hydroxyethylcellulose (HEC) 3% gel and F3- an oil-in-water cream (O/W).

Experimental part

Materials and methods

The topical products' preparation: The composition of the three formulations developed in our study is indicated in table 1, the active pharmaceutical ingredients being described in figure 1 and the used excipients in figure 2. The obtaining techniques are shown schematically in figure 3.

Quality control of the preparations: pH determination: It was conducted potentiometrically with a Consort C831 multiparameter analyser. Rheological analysis: The spreadability of the formulations prepared was determined using a Poso-Ojeda extensometer and drawing the appropriate curves [12]. Consistency assessment was carried out using a penetrometer (PNR 12 Petrolab, Germany) equipped with a microcone and a suitable
### THE COMPOSITION OF THE PREPARED FORMULATIONS

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Code</th>
<th>Quantity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefalamycin phosphate</td>
<td>CLD</td>
<td>1.00 1.00 1.00</td>
</tr>
<tr>
<td>Adapalene</td>
<td>ADP</td>
<td>0.10 0.10 0.10</td>
</tr>
<tr>
<td>Glycolic acid</td>
<td>GA</td>
<td>2.00 2.00 2.00</td>
</tr>
<tr>
<td>Hydroxypropyl methyl cellulose</td>
<td>HPMC</td>
<td>2.5 3.0</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>HEC</td>
<td>4.0 4.0</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>PG</td>
<td>0.2 0.2</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>PO</td>
<td>1.0</td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td>PEG</td>
<td>0.5</td>
</tr>
<tr>
<td>Polyvinyl alcohol</td>
<td>PVA</td>
<td>-</td>
</tr>
<tr>
<td>Castor oil</td>
<td>CO</td>
<td>-</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>SA</td>
<td>- 6.0</td>
</tr>
<tr>
<td>Cetyl alcohol</td>
<td>CA</td>
<td>- 6.0</td>
</tr>
<tr>
<td>Tween 80</td>
<td>Tw</td>
<td>- 2.05</td>
</tr>
<tr>
<td>Span 60</td>
<td>Sp</td>
<td>- 1.95</td>
</tr>
</tbody>
</table>

**Aqueous solution of parabens**
- (methyl-paraben + propyl-paraben) - 0.75: 0.25 % in distilled water

**Table 1**

**Fig. 1.** Physico-chemical properties of the active pharmaceutical ingredients

**Fig. 2.** Physico-chemical properties of the used excipients [11]
demonstrated that the pH of the skin can be shifted in accordance to W agner H. et al. (2003), as they
5.5 - absolute ethanol 50:50 (v/v). This method is in
7.4 - absolute ethanol 50:50 (v/v) or a mixture of PBS of pH

In vitro diffusion studies: Transdermal diffusion studies for drug release assessment were performed using static
Franz diffusion cells FDC with a diffusion area of 2.833 cm² and a volume of 14 mL for the receptor compartment.
Abdominal skin samples obtained from surgical interventions performed at the Emergency County Hospital
of Tirgu Mures, were used to prepare the epidermis utilized as diffusion membrane. The study was conducted with
the University Ethics Committee approval no. 45/21.03.2016. Informed consent was obtained from the
patients, their identity being masked to the researchers in order to guarantee their anonymity. The epidermis
membrane was prepared from the skin samples according with the method proposed by Kligman et al. [15]. The heat
separated epidermis was placed over a Spectra/Por dialysis
membrane and fitted with the stratum corneum side in
contact with the donor compartment. Two types of
solutions for the receptor compartment were used: either
a mixture of phosphate buffer solution (PBS) 1/15M of pH
7.4 - absolute ethanol 50:50 (v/v) or a mixture of PBS of pH
5.5 - absolute ethanol 50:50 (v/v)

Control solutions – were prepared by dissolving 20.0 mg of
CLD in 10 mL PBS pH 7.4. Five working standard solutions of
different concentrations were prepared: 20, 140, 160,
180 and 200 µg·mL⁻¹. Adapalene – a 20 µg·mL⁻¹ stock
solution was prepared by dissolving 2.0 mg of ADP in a
mixture of ACN:THF in the ratio 95:5 (v/v), in a volumetric
flask of 100 mL. Six working standard solutions with the
concentrations 4, 8, 12, 16, 20 and 40 µg·mL⁻¹ were
prepared.

Stock solutions: Clindamycin phosphate - a 200 µg ·
ml⁻¹ stock solution was prepared by dissolving 2.0 mg of
CLD in 10 mL PBS pH 7.4. Five working standard solutions of
different concentrations were prepared: 20, 140, 160,
180 and 200µg·mL⁻¹. Adapalene – a 20 µg·mL⁻¹ stock
solution was prepared by dissolving 2.0 mg of ADP in a
mixture of ACN:THF in the ratio 95:5 (v/v), in a volumetric
flask of 100 mL. Six working standard solutions with the
concentrations 4, 8, 12, 16, 20 and 40 µg·mL⁻¹ were
prepared.

The rheological characteristics evaluation of the prepared formulations was carried out using a
rheometer Rheotest RV, provided with coaxial cylinders operating with twelve shear rates [14]. All measurements
were carried out in triplicate.

The mobile phase consisted of ortho phosphoric acid 15 mM
solution of pH 2.15 (solvent A) and acetonitrile (solvent B).
The initial ratio of the two solvents 80:20 (A:B) was applied
for 5 min, followed by a ratio of 10:90 from 6 to 14 min. At
the end of each run, the gradient was reversed to its initial
conditions and the column re-equilibrated for 5 min. The
analysis of the samples was carried out at 25°C, with a
flow rate of 1.0 mL/min, an injection volume of 20 µL and
the monitoring wavelength being set at 210 nm.

Analytical performances of the HPLC method: Were
assessed in terms of linearity, precision and accuracy. The
linearity of the method was demonstrated by analyzing
in triplicate five different concentrations of CLD and ADP. A
linear correlation between the areas of the peaks and
concentrations and a regression coefficient higher than
0.999 were used as primary performance criterions for
linearity. The precision of the method was expressed
through the relative standard deviation (RSD%) and the
limit of acceptance was set at 0.2% RSD%. The accuracy
of the method was expressed by mean recovery for three
different standard concentrations, lowest, medium and
highest levels, analyzed in triplicate and the acceptance
limits were set between 98% and 102%.

Thechromatographic conditions: HPLC solvents and reagents were Merck products of analytical grade. Purified
water was used throughout this study was prepared
using a Milli-Q water purification system (Millicore, Milford,
USA). A LaChrom HPLC system (Merck-Hitachi) equipped
with a quaternary pump, degasser, column thermostat,
autosampler with Peltier system, DAD detector and HSM
software, was used for the analysis. The stationary phase
was a reversed phase Kinetic C18 column (150 x 4.60
mm) with a particle size of 2.6 µm (Phenomenex). The
compare the rheological behavior of the prepared formulations, Pearson and one way Anova tests have been used. Differences between CLD and ADP release from the formulation bases at each sampling time were analyzed using Anova test, to compare the mean flow corresponding to the 3 formulations and the control solution. A statistical significant difference was considered for p values lower than 0.05, for a CI of 95%.

Results and discussions

Quality control of the preparations

The visual macroscopic characteristics: The obtained hydrogels (F1 and F2) were homogeneous, slightly opalescent because of adapalene, a highly lipophilic drug, which was dispersed in poloxamer 407. The oil-in-water cream (F3) was homogenous and of white colour.

pH measurement: The pH of the three formulas were in the range of 6.41-6.48, namely: 6.48±0.03 (F1), 6.44±0.01 (F2) and 6.41±0.015 (F3), being within the limits required for topical administration.

The rheological behavior under the rotational shear stress: Each of the three recorded flow curves (fig.4) contains the two different parts generated under acceleration (the up curve) followed by deceleration (the down curve) of the shear rate. The down curve falls to the left of the up curve in the all three studied cases, this demonstrating a thixotropic (time depending) rheological behavior. The size of area in the thixotropic loop of the flow curve is the most evident for the product - F3 and very little obvious for F2. The differences between the approximate values of the yield stress (F1 - 339 dyn/cm², F2 - 569 dyn/cm², F3 - 113 dyn/cm²) demonstrate the plastic characters of the flow, and are also in accordance with the initial appearance of the product.

Glycol increases the viscosity of hydroxypropyl cellulose 4% gel containing propiconazole nitrate [17]. Comparison of the viscosity rheograms by the one way Anova test showed statistical significant differences in the rheological behavior of the studied products, especially in case of F2 product. Taking into account that both formulations contain propylene glycol 4%, this fact is probably due to the influence of polyvinyl alcohol and/or polyethylene glycol on the hydroxyethylcellulose network spatial conformation.

Plastically deformation capacity under vertical forces exerted by pressing with increasing mass: Both, consistency measured by penetration method (fig.6) and the ability of the three studied products to spread on the surface under increasing pressure (fig.7) are largely correlated (= 90 - 95%) to the size of the weight (mass) acting on the product surface, F1 and F2 being advantageous in this regards.

Analytical performances of the HPLC method for clindamycin phosphate and adapalene determination: CLD and ADP analysis was performed by HPLC as it was described in materials and methods. Typical chromatograms for CLD and ADP are shown in figure 8.

Clindamycin phosphate: The retention time of clindamycin phosphate was 3.8±0.2 min. A linear correlation between the chromatographic areas and concentrations was obtained in the concentration's range of 20 to 200 µg·mL⁻¹ corresponding to the mean equation y=1539.1±20 . x - 16117±873, n=3 replicates, N = 5 levels of concentration, R²>0.99. The precision of the method was 1.18% expressed as mean RSD% and accuracy as mean recovery was 99.43% (table 2). The detection limit was 0.84 µg·mL⁻¹ and the quantification limit was 2.80 µg·mL⁻¹.

Adapalene: The retention time of adapalene was 12.3±0.05 min. A linear correlation between the
chromatographic areas and concentrations was obtained in the concentration's range of 4 to 40 \( \mu \text{g} \cdot \text{mL}^{-1} \), corresponding to the mean equation \( y = 32307 \cdot x + 17224 \), \( n=3 \) replicates, \( N = 6 \) levels of concentration, \( R^2>0.999 \). The precision of the method was 3.68\% expressed as mean RSD% and accuracy as mean recovery was 101.47\% (table 2). The detection limit and the quantification limit for adapalene were 0.03 \( \mu \text{g} \cdot \text{mL}^{-1} \) and 0.11 \( \mu \text{g} \cdot \text{mL}^{-1} \), respectively.

Transdermal diffusion parameters for clindamycin phosphate and adapalene: In order to study the influence of the formulation base and the pH on the percutaneous absorption of CLD and ADP, the diffusion of reminded drugs have been studied at two pH conditions, as was described in materials and methods, the obtained data being presented in table 3 and table 4.

In figure 9 and figure 10, were represented the cumulative amounts of CLD and ADP released into the receptor compartment over a period of 9 hours, for both pH conditions.

At both pH of receptor solution, statistically significant greater amounts of CLD than ADP have been released from the vehicle, (table 3 and table 4), with \( p<0.0001 \) (Anova test). After 9 h of penetration through human epidermis membrane, the cumulative amount of CLD (%) released from the analyzed topicals formulations was higher than that released from the control solution (19.69-80.86\% and 7.13\%, respectively) at pH 7.4. Our results are comparable

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**Table 2**

REPEATABILITY AND ACCURACY PARAMETERS FOR CLINDAMYCIN PHOSPHATE AND ADAPALENE

<table>
<thead>
<tr>
<th>Concentration (( \mu \text{g} \cdot \text{mL}^{-1} ))</th>
<th>Crece (( \mu \text{g} \cdot \text{mL}^{-1} ))</th>
<th>Recovery (( \mu \text{g} \cdot \text{mL}^{-1} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Series 1</td>
<td>Series 2</td>
</tr>
<tr>
<td>Clindamycin phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>19.60</td>
<td>19.81</td>
</tr>
<tr>
<td>160</td>
<td>159.83</td>
<td>159.33</td>
</tr>
<tr>
<td>200</td>
<td>201.16</td>
<td>201.38</td>
</tr>
<tr>
<td>Mean</td>
<td>1.18%</td>
<td>1.18%</td>
</tr>
<tr>
<td>Adapalene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.43</td>
<td>4.91</td>
</tr>
<tr>
<td>12</td>
<td>11.01</td>
<td>11.78</td>
</tr>
<tr>
<td>40</td>
<td>39.95</td>
<td>40.30</td>
</tr>
<tr>
<td>Mean</td>
<td>3.68%</td>
<td>3.68%</td>
</tr>
</tbody>
</table>

**Table 3**

IN VITRO DIFFUSION PARAMETERS THROUGH HUMAN HEAT SEPARATED EPIDERMIS, CALCULATED FOR CLINDAMYCIN PHOSPHATE

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Permeated drug amount (( \mu \text{g} \cdot \text{cm}^{-2} )) Mean±SD</th>
<th>Cumulative concentration (( \mu \text{g} \cdot \text{mL}^{-2} )) Mean±SD</th>
<th>Cumul. drug released Mean±SD (%)</th>
<th>Flow (( \mu \text{g} \cdot \text{cm}^{-2} \cdot \text{h}^{-1} ))</th>
<th>( k \times 10^6 ) (cm( \cdot )s(^{-1} ))</th>
<th>( t ) (h)</th>
<th>( D ) (h(^{-1} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>251.56±1.88</td>
<td>46.33±0.46</td>
<td>7.13±1.34</td>
<td>29.3883</td>
<td>0.82</td>
<td>0.52</td>
<td>0.086</td>
</tr>
<tr>
<td>F.1.</td>
<td>2103.68±203.21</td>
<td>382.02±39.30</td>
<td>59.60±6.52</td>
<td>255.8572</td>
<td>7.11</td>
<td>0.11</td>
<td>0.018</td>
</tr>
<tr>
<td>F.2.</td>
<td>2897.84±214.27</td>
<td>338.98±48.84</td>
<td>80.86±6.72</td>
<td>371.0091</td>
<td>10.30</td>
<td>1.35</td>
<td>0.258</td>
</tr>
<tr>
<td>F.3.</td>
<td>695.01±43.01</td>
<td>129.99±8.61</td>
<td>19.69±2.42</td>
<td>86.0762</td>
<td>2.39</td>
<td>1.19</td>
<td>0.198</td>
</tr>
<tr>
<td><strong>Phosphate buffer pH 5.5:Ethanol 39:50 (v/v)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>132.29±26.97</td>
<td>23.06±4.84</td>
<td>3.75±0.89</td>
<td>13.61</td>
<td>0.38</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F.1.</td>
<td>363.98±34.61</td>
<td>66.34±6.61</td>
<td>10.37±1.89</td>
<td>44.83</td>
<td>1.25</td>
<td>0.22</td>
<td>0.036</td>
</tr>
<tr>
<td>F.2.</td>
<td>318.52±22.58</td>
<td>58.83±4.11</td>
<td>9.02±1.63</td>
<td>38.96</td>
<td>1.08</td>
<td>0.72</td>
<td>0.120</td>
</tr>
<tr>
<td>F.3.</td>
<td>800.88±43.93</td>
<td>151.36±8.38</td>
<td>22.94±3.15</td>
<td>96.34</td>
<td>2.68</td>
<td>0.91</td>
<td>0.152</td>
</tr>
</tbody>
</table>
with that obtained by Singh et al (2014), they finding a cumulative released amount (%) of clindamycin phosphate from an HPMC 1.3% base of 49.51 ± 1.30% after 6 h of diffusion through a Cellophane membrane, using as receptor phase phosphate buffer pH 7.4. [18] ADP was released in much lower amount than CLD, namely between 3.77-8.44%. At pH 5.5 the cumulative amount of ADP released (%) from the three formulations (1.33-2.33%) was lower than that released from the control solution (9.49%). The small amount of ADP released compared with CLD, could be explained by the fact that only the dissolved drug in the formulation base, presented to the epidermal membrane is able to enter through its horny layer, as this first layer of the skin is considered the most important barrier for the percutaneous diffusion [19].

In our case, CLD showed a greater penetration than ADP, due to its acceptable in water solubility, in contrast with ADP a highly lipophilic drug, dispersed in our formulations in poloxamer 407 (F1, F2) or in polysorbate 80 (F3), respectively. Regarding the permeability coefficient and lag time, defined as latency time required to reach the steady-state of concentration, an inverse correlation was found, as greater values of k_p have been associated with lower lag time values (table 3 and table 4). At pH 7.4, a statistically significant difference in cumulative amount of drug permeated was observed between all three analyzed topical formulations (p<0.0001, Anova test). A higher concentration of CLD was released from the gel vehicles (F2-80.86%; F1-59.60%), compared with the oil-in-water cream (F3-19.69%). The situation was similar for ADP permeation. This fact could be explained probably due to the easier migration of the drug through the gel vehicles containing a large amount of water, which allows a greater dissolution of the drug, comparing with the oil-in-water cream. In addition, both gel formulations contain propylene glycol, known as a transdermal penetration enhancer. Yamane and Hadgraft suggested in their researches, the ability of propylene glycol to increase drug’s solubility in the vehicle, as well as its capacity to permeate through the skin, altering thus the solubility properties of the tissue and improving the drug partitioning into the membrane in a reversible way [20,21].

Propylene glycol is known as a humectant, safe for use in foods, cosmetics and medicines, being environmentally friendly [22]. It has been found as a permeation enhancer for an antifungal gel with 1.5% propiconazole nitrate [17].

Regarding the adapalene's transepidermal diffusion, Deo et al (2013), in their study found a higher amount released from a marketed topical gel 0.1% (92.02 µg·cm⁻²), than from our formulations (13.31-29.79 µg·cm⁻²), possibly due to a higher concentration of ethanol used in the receptor medium (65%) and also, the diffusion was done through a tuffryn membrane, not human epidermis membrane [23].

Surprisingly, at pH 5.5 a higher amount of CLD has been released from the oil-in-water cream (F3) than the gel vehicles (F1 and F2), most likely due to the possible...
emollient and occlusive effect of the cream, avoiding thus the moisture to escape through the epidermis surface, being known that the hydration of the horny layer allows an easier passage of drug molecules by the intra- and intercellular channels and pathways [19].

Conclusions

F2 spreads well under gentle pressure, having a plastic flow under low intensity friction forces. Rheological behavior indicates this product for managing the sensitive and painful to touch skin, having at the same time an astringent potential, showed by the return to baseline of the viscosity and consistency over a period of time approximately equal to that needed for spreading the product on the application surface. F1 and F3 remain fluid a longer period of time after rubbing, behavior that could generate an emollient effect. F1 could be indicated for pressure- and friction-sensitive areas, while F3 may be appropriate for dry and pressure unsensitive areas. Due to their astringent effects and a greater percutaneous permeability of the drugs at pH 7.4, the gel formulations could be appropriate in treating acne lesions in patients with oily skin and unaffected skin barrier function. In contrast, the oil-in-water cream, due to its emollient effect and its higher penetrability at pH 5.5 than gel vehicles, may be indicated for patients with dry and sensitive skin associated with impaired skin barrier function.

Further investigations are needed for the assessment of in vivo penetrability, efficacy and tolerability of these topical formulations, as well as the formulation’s optimization in order to improve their physico-chemical characteristics and the diffusion parameters of the drugs.

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References

2. PUBCHEM URL: https://pubchem.ncbi.nlm.nih.gov, Date of access 04.11.2015
3. BAOWEI, S., ZHI, W., JIXIAO, W., SHICHANG, W., J Membrane Sci, 251, 2005, p.189
17. SMADI, S., POPOVICI, I., COJOCARU I., BRAHA, S., OCHIUZ, L., DORNEANU, O., Mat. Plast., 46, no. 1, 2009, p.83
22. NEAGU (PETRE), M., CURSARU, D., Rev Chim. (Bucharest), 64, no. 1, 2013, p.92

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