Abstract: The purpose of the present study was the development and characterization of a reservoir-type transdermal patch loaded with dexamethasone gel through physicochemical and biopharmaceutical tests to generate an innovative pharmaceutical form. The reservoir-type transdermal patch consists of three parts: i) the adhesive film, ii) an impermeable film with a reservoir function, and iii) dexamethasone formulated in a PF-127 gel. The patch was evaluated based on area, thickness, resistance to fracture, bioadhesion, and post-wetting bioadhesion of the adhesive film. In addition, release studies were conducted on the reservoir-type transdermal patch. The characterization tests were for i) an impermeable film with an area of 247 ± 0.19 cm², a thickness of 0.22 ± 0.01 mm, and tensile strength of 1463.9 ± 300.30 gf; ii) an adhesive film with a tensile strength of 64.21 ± 18.74 gf, bio-adhesion of 879.71 ± 205.67 gf, and a post-wetting bio-adhesion of 505.10 ± 34.39 gf; and finally, iii) dexamethasone gel with a relative density value of 0.938 ± 0.01, non-Newtonian fluid, 99.06% of drug content, dexamethasone release test adjusted to the zero-order kinetic model and skin permeation studies with a Flux (Jss) = 140.98 μg/cm²*h. As a result of these tests, the reservoir type transdermal patch presents adequate characteristics for dexamethasone transdermal administration.

Keywords: transdermal reservoir-type patch; transdermal drug delivery; patch; polyvinylpyrrolidone; skin; dexamethasone; PF-127; Eudragit E100.

© 2022 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

The innovation in pharmaceutical forms has been increasing primarily in forms that improve the properties of drugs and the acceptance and comfort of patients. Despite this, the oral route continues to be one of the most-used administration routes due to its low production cost and ease of administration. However, it has disadvantages that compromise the bioavailability of the drug within the body, such as the effect of the first hepatic step and the degradation of the drug in the gastrointestinal tract. Bioavailability and degradation are two
reasons pharmaceutical research have a great interest in different administration routes to avoid these disadvantages, such as the transdermal route [1]. Transdermal patches offer great advantages over the oral route, primarily by avoiding the effect of the first step and increasing its bioavailability.

According to the Pharmacopoeia of the United Mexican States, a patch is defined as a flexible adherent film of variable size containing one or more drugs applied externally and may be of local or systemic action. The routes of administration may be topical or transdermal [2]. In a reservoir transdermal patch, the patch has a drug reservoir with a diffusion membrane. Moreover, it can differ in the type of content, which can be liquid, solid, or semi-solid, but the membrane must always be present to control the drug release [2,3].

For this reason, this work aimed to develop a reservoir transdermal patch with a PF-127 gel of dexamethasone. Dexamethasone is a glucocorticoid with great anti-inflammatory properties, which are 25 to 30 times greater than those obtained with cortisone. Its mechanism of action is primarily based on the dilation of capillaries, inhibition of fibrin deposits, and migration of leukocytes to the inflamed area. It also inhibits phagocytic activity, the proliferation of fibroblasts, and the deposition of collagen [4]. Dexamethasone has anti-inflammatory (steroid) and immunosuppressive effects and increases protein catabolism and glucose availability and mobilizes fatty organs and lipolysis. Dexamethasone belongs to Group II of the biopharmaceutical classification, with low solubility and high permeability [5].

The reservoir-type transdermal patch consists of three parts: i) the adhesive film, ii) an impermeable film with a reservoir function, and iii) dexamethasone in a PF-127 gel. The components of the transdermal patch are characterized by area, thickness, and resistance to fracture. The patch is also evaluated based on the adhesive film's bioadhesion and post wetting bioadhesion. The dexamethasone in a gel is characterized by the relative density, viscosity, and chemical content. In addition, release studies were conducted on the reservoir-type transdermal patch to determine the dexamethasone release mechanism.

2. Materials and Methods

We used the following analytical grade reagents that comply with Analytical Chemistry Society specifications: dexamethasone sodium phosphate (Global Chemicals), Eudragit E100 (HELM de México), Ethocel (HELM de México), polyvinylpyrrolidone K30 (Droguería Cosmopolita), methanol (J.T. Baker), ethanol (J.T. Baker), Pluronic F-127 (BASF, USA), Kollicoat IR (BASF, USA), Kollisolv polyethylene glycol (PEG) E400 (Sigma-Aldrich), triacetin (Sigma-Aldrich), distilled water Milli-Q (Millipore Inc.), dibasic sodium phosphate (Fermont), sodium hydroxide (MEYER), and Milli-Q quality distilled water (Millipore Inc.).

2.1. Transdermal film preparation.

Polymeric films were prepared based on the method reported by Escobar-Chávez et al. (2011) [6]. Four formulations (Tables 1 and 2) were developed for the two films that comprise the reservoir-type transdermal patch: the first with a waterproof film and the second with drug release properties and skin adhesion. The following tests characterized the film formulations: area, thickness, tensile strength, bioadhesion, and post wetting bioadhesion (Table 1).
2.2. Area and thickness.

An area of 4 cm$^2$ for the formulation was measured using a Truper digital caliper. The areas and thicknesses of three different points on the films were determined [7].

2.3. Tensile strength.

A texturometer (Brookfield CT3 Texture analyzer, USA with TexturePro CT software) with a load charge of 4.5 kg was used for this test. Determinations were made for each film. Films with an area of 7.55 cm$^2$ were held with tweezers in the texturometer in the following conditions: pre-test velocity of 2 mm/s, an activation charge of 6.8 g, and a test speed of 0.5 mm/s. The probe was withdrawn at a speed of 4.5 mm/s, with a total distance of 100 mm, determining the necessary force at which the patches can be broken [7].

2.4. Bioadhesion tests.

The studies were conducted using a texture analyzer (Brookfield model CT3 Texture analyzer, USA with TexturePro CT software). The skin samples were glued into place with cyanoacrylate at the bottom of the texturometer. At that moment, the cylindrical probe (perplex cylinder, 1.27 cm$^2$) started to descend to the film (1.1309 cm$^2$) at a pre-test velocity of 2 mm/s until the film made contact at a load force 6.8 gf and a speed of 0.5 mm/s. Finally, the cylinder was removed at a speed of 4.5 mm/s until reaching a separation distance of 100 mm [7]. In the post wetting bioadhesion test, the procedure was carried out using the same methodology and characteristics as the bioadhesion test. The difference was that the films of the transdermal patch were hydrated for 10 min before the test using an atomizer with distilled water at approximately 30 cm [7].

2.5. Characterization of dexamethasone gel.

The gel was prepared with Pluronic F-127 at a concentration of 30% w/w of the polymer. The appropriate amounts of PF-127 were weighed and added slowly to a solution of distilled water at a temperature of 5°C; then the dexamethasone was added at a concentration of 20 μg/mL with gentle agitation with a magnetic stirrer (TUV Rheinland, USA MED MSH-S10). Afterward, the solution was placed in refrigeration for 24 h until the solution was clarified [10-12].

2.6. Relative density.

To determine the relative density of the systems, a metal pycnometer was used, and the test was performed in triplicate at a temperature of 25°C. The empty metal pycnometer was weighed alone then was weighed with distilled water. Finally, the measurement was taken with the sample. The relative density was calculated using the following formula:

$$\text{Relative density} = \frac{\text{Weight of pycnometer with sample} - \text{Weight of empty pycnometer}}{\text{Weight of pycnometer with water} - \text{Weight of empty pycnometer}}$$

2.7. Viscosity.

The viscosity measurements were carried out on the Brookfield viscometer (Model DV-E), with an S-63 needle, and the sheer force was measured at different shear rates (1 to
100 rpm). For this test, approximately 20 mL of the sample was poured into a sample holder, waiting for 1 min for each measurement to record the viscosity in cP.

2.8. Drug content.

Ten samples of 500 μL of the Pluronic® F-127 gel with dexamethasone were taken. Each of these samples was dissolved in 40 mL of cold deionized water under constant agitation using a magnetic stirrer (Science USA) for 10 min. Once dissolved, the content was transferred to a 250 mL volumetric flask by performing the corresponding rinses with deionized water to ensure the total transfer of the sample to the flask. It was brought to the capacity mark with deionized water. Subsequently, an aliquot of 5 mL of the previous solution was taken and brought to capacity in a 100 mL volumetric flask. Finally, the absorbance of each of the samples was measured at a length of 240 nm in an ultraviolet-visible spectrophotometer (Velab USA).

2.9. Release test of reservoir transdermal patch.

The studies were conducted in a dissolutor (MAYASA model APPM-0250, México) with apparatus number 5 USP (paddle-over-disk method) to assess the dexamethasone release from releasing the prepared patches. The conditions were 500 mL of phosphate buffer with a pH of 5.5, referring to the physiological skin pH [6], at 37.5°C with stirring (50 rpm), and 3 mL of the samples taken at 5, 10, 15, 20, 30, 60, 120, 180, 240, 300, 360, and 420 min. Subsequently, the amount of drug released as a function of time was quantified by spectrophotometry at 240 nm.

2.10. In vitro percutaneous absorption studies.

*In vitro* skin permeation studies by passive diffusion were performed on the human abdominal skin (Hospital Regional de Alta Especialidad de Zumpango. Protocol number CEI/HDAEZ/2020/12). The fatty and connective tissue were removed, and the samples were stored in the freezer at -21°C for no than 15 days. *In vitro* percutaneous absorption studies were performed using vertical Franz-type diffusion cells under sink conditions. As a membrane between the two compartments, the human abdominal skin was used. The transdermal patch was placed on the skin, and the receiver compartment was filled with a buffer solution of HEPES at pH 7.4. Sampling was performed at different intervals for 32 h, and the drug content was determined by UV-Vis spectrophotometry at 240 nm with a previously validated method. The cumulative amount of drug permeated per unit area (Q, mg/cm²) as a time (h) function was plotted. The steady-state flux (JSS, μg/cm²/h) of dexamethasone was estimated from the slope of the graph by linear regression analysis. The lag time (tLag) was ascertained from the x-intercept of the slope obtained to estimate the JSS. The drug's permeability coefficient (Kp, cm/h) through mucosa was calculated by dividing JSS by initial drug concentration in the patch [7].

3. Results and Discussion

The formulations for the impermeable films and adhesive film are shown in Table 1.
### Table 1. Experimental formulations for the impermeable film and adhesive film.

| Components                  | Impermeable film |            | Adhesive film |            |
|-----------------------------|------------------|------------|---------------|------------|
|                             | Formulation 1 (%) | w/w       | Formulation 2 (%) | w/w       |
| Ethylcellulose (Ethocel)    | 4                | -         | -             |            |
| Triacetin                   | 2                | -         | 2             | -          |
| Eudragit E 100              | -                | 4         | 4             | -          |
| Kollisolv PEG E 400         | -                | 2         | -             | 2          |
| Kollicoat IR                | -                | -         | 4             |            |
| Polyvinylpyrrolidone K30    | -                | -         | 2             |            |
| Methanol (mL)               | 25               | -         | 25            |            |
| Water (mL)                  | -                | -         | -             | 25         |

### 3.1. Area and thickness.

The dimensions are a fundamental part of the transdermal patch design, which implies having strict control in the final area of the transdermal patch so that both films are perfectly spliced and sealed correctly and avoid loss of the drug. The results in the impermeable film with a reservoir function are shown in Table 2. For Formulation 1, an average area of $4.24 \pm 0.19 \text{ cm}^2$ and a thickness of $0.228 \pm 0.01 \text{ mm}$ were obtained, whereas an average area of $4.42 \pm 0.244 \text{ cm}^2$ and an average thickness of $0.243 \pm 0.0291 \text{ mm}$ were found for Formulation 2. The results are represented in Figures 1 and 2, and they were compared in both formulations. No significant difference ($p > 0.05$) in area and thickness was found because the same cutting technique was used for both formulations.

### Table 2. Results for area and thickness for the impermeable and adhesive films.

| Film | Impermeable film | Adhesive film |
|------|------------------|---------------|
|      | Formulation 1    | Formulation 2 | Formulation 1 | Formulation 2 |
|      | Area (cm²) | Thickness (mm) | Area (cm²) | Thickness (mm) | Area (cm²) | Thickness (mm) | Area (cm²) | Thickness (mm) |
| 1    | 4.1            | 0.22          | 4.3          | 0.25          | 4.1          | 0.68          | 4.5          | 0.23          |
| 2    | 4.2            | 0.21          | 4.3          | 0.28          | 4.2          | 0.62          | 4.3          | 0.38          |
| 3    | 4.4            | 0.23          | 4.8          | 0.25          | 4.2          | 0.34          | 4.2          | 0.32          |
| 4    | 4.5            | 0.24          | 4.7          | 0.26          | 4.5          | 0.32          | 4.5          | 0.57          |
| 5    | 4.62           | 0.24          | 4.6          | 0.26          | 4.1          | 0.38          | 4.3          | 0.32          |
| 6    | 4.05           | 0.25          | 4.5          | 0.27          | 4.1          | 0.24          | 4.2          | 0.47          |
| 7    | 4.1            | 0.21          | 4.0          | 0.25          | 4.3          | 0.25          | 4.3          | 0.43          |
| 8    | 4.2            | 0.22          | 4.2          | 0.21          | 4.2          | 0.26          | 4.4          | 0.74          |
| 9    | 4.1            | 0.23          | 4.3          | 0.20          | 4.1          | 0.23          | 4.3          | 0.24          |
| 10   | 4.2            | 0.23          | 4.3          | 0.20          | 4.2          | 0.24          | 4.3          | 0.24          |
| Mean | 4.247          | 0.228         | 4.42         | 0.234         | 0.1247       | 0.1633        | 0.119        | 0.1685        |
| Std deviation | 0.193     | 0.01         | 0.244        | 0.0291        | 0.1247       | 0.1633        | 0.119        | 0.1685        |

**Figure 1.** Area measurement results of the impermeable film (reservoir function) and adhesive film, comparing their respective formulations (1 and 2) (n=10).
Figure 2. Thickness measurement results of the impermeable film (reservoir function) and adhesive film, comparing their respective formulations (1 and 2) (n=10).

3.2. Tensile strength.

The importance of this test is focused on maintaining the integrity of the transdermal patch, helping to ensure the therapeutic efficacy of the pharmaceutical form. The films must withstand manipulation from manufacturing and use by patients. If a rupture occurs in any of the films, the dosage of the pharmaceutical form would be compromised, affecting the absorption of the drug and, therefore, its therapeutic action [13]. Table 3 shows the results for the adhesive and waterproof films and their respective formulations. For the adhesive film, in Formulation 1, an average of 64.219 ± 18.743 gf was required to break the film, whereas Formulation 2 required a force of 1102.45 ± 121.05 gf. A statistically significant difference exists between the formulations (p < 0.05). For Formulation 1, triacetin improves its properties. The excipient provides plasticizing properties to the polymer, resulting in flexible films with ideal conditions for forming the transdermal patch [14].

Table 3. Rupture resistance test results for adhesive and impermeable films with a reservoir function.

| Sample | Adhesive film | Impermeable film |
|--------|---------------|------------------|
|        | Formulation 1 (gf) | Formulation 2 (gf) | Formulation 1 (gf) | Formulation 2 (gf) |
| 1      | 51.59          | 1073.5           | 1052              | 694.5          |
| 2      | 94.5           | 1330.5           | 1951.5            | 381.5          |
| 3      | 89.5           | 1073            | 1874.5            | 573           |
| 4      | 58.5           | 1063.5          | 1567              | 103.5         |
| 5      | 31.5           | 940             | 1551.5            | 245           |
| 6      | 56.8           | 1065            | 1435.5            | 703           |
| 7      | 79             | 989             | 1289              | 89.5          |
| 8      | 63.5           | 1209            | 1040              | 247          |
| 9      | 60.5           | 1036            | 1489              | 323          |
| 10     | 56.8           | 1245            | 1389              | 127          |
| Mean   | 64.21          | 1102.45         | 1463.9            | 348.7         |
| Standard Deviation | 18.74 | 121.09 | 300.30 | 234.45 |

The waterproof film obtained the following results: in Formulation 1, the force required was 1463.9 ± 300.30 gf, whereas for Formulation 2, the average was 348.7 gf to fracture the film. A significant difference exists (p < 0.05) between the impermeable films. Formulation 1 has a triacetin plasticizer, which increases the viscous properties of the excipients. In Formulation 2, polyethylene glycol 8000 can interact with the polymer chains, causing an extension and generating a greater resistance than Formulation 1. Figure 3 illustrates the results of the fracture resistance test for both polymeric films with their respective formulations.
Figure 3. Rupture resistance of the impermeable (reservoir function) and adhesive films, comparing their respective formulations (1 and 2), (n=10).

3.3. Bioadhesion test.

The bioadhesion test is crucial in the characterization of the transdermal patch for the following reasons. The adhesion in the skin allows the pharmaceutical form to remain for a long time at the application site, favoring the bioavailability of the drug. With the help of the correct bio-adhesives, it is possible to direct the drug to specific sites and tissues, increasing permanence. Moreover, if a controlled release is added, the frequency of administration can be reduced [15]. The test evaluates the force required to detach the film or transdermal patch from the skin, which is joined by interfacial forces [16,17].

Table 4. Bio-adhesion and post-wetting bio-adhesion test results for adhesive film formulations.

| Sample | Formulation 1 (gf) | Formulation 2 (gf) | Formulation 1 (gf) | Formulation 2 (gf) |
|--------|--------------------|--------------------|--------------------|--------------------|
| 1      | 917                | 160.5              | 499.75             | 263.5              |
| 2      | 702.3              | 160                | 424.3              | 168                |
| 3      | 521.8              | 150.5              | 581                | 167                |
| 4      | 1130               | 156                | 456                | 256                |
| 5      | 1098               | 167                | 578                | 189                |
| 6      | 817                | 142                | 489                | 154                |
| 7      | 867                | 103.5              | 501                | 284.5              |
| 8      | 915                | 114.7              | 524                | 301                |
| 9      | 689                | 130                | 487                | 136                |
| 10     | 1140               | 156                | 511                | 245                |
| Mean   | 879.71             | 144.02             | 505.10             | 216.40             |
| Standard Deviation | 205.67             | 21.30              | 48.34              | 59.89              |

Figure 4. Bioadhesion and post-wetting bio-adhesion test results for the adhesive formulations (1 and 2), (n=10).

Because the adhesive film has contact with the skin, it was the only one that applied this test. The results are shown in Table 4 and Figure 4. For Formulation 1, $879.71 \pm 205.67$ gf was needed to detach the film from the skin, whereas $144.02 \pm 21.30$ gf was needed for
Formulation 2. Both formulations were compared (p <0.05), finding a statistically significant difference, which indicates that, for Formulation 1, a greater force is needed to detach it because the Eudragit E100 polymer confers greater adhesiveness to the film when interacting with the organic esters of triacetin.

3.4. Post wetting bioadhesion.

This test simulates the external conditions to which the skin is exposed, which may affect the adhesion of the patch, such as perspiration and/or washing [18,19]. In the same way as the previous test, the largest values were obtained in Formulation 1 at 505.105 ± 34.394 gf, whereas Formulation 2 resulted in values of 216.4 ± 59.898 gf. The results are shown in Table 4 and Figure 4. A significant difference between Formulations 1 and 2 exists (p < 0.05) due to the properties conferred by the combination of Eudragit E100 and triacetin; therefore, Formulation 1 is more bio-adhesive.

3.5. Characterization of dexamethasone gel.

3.5.1. Relative density.

The relative density test is based on the relationship between the weight of the volume of the evaluated substance and the weight of the same volume of water at a specific temperature (i.e., the density of the substance divided by the water density), and the measurement is made with a pycnometer [2]. The sample of the Pluronic-F127 gel with dexamethasone was subjected in triplicate to the relative density measurement test. The results are illustrated in Table 5. The average result is 0.9389 ± 0.01, with a lower value for the water.

| Sample | Relative Density |
|--------|------------------|
| 1      | 0.9377           |
| 2      | 0.9381           |
| 3      | 0.9408           |
| Mean   | 0.9389           |
| Standard Deviation | 0.01              |

3.5.2. Viscosity.

Viscosity is one of the tests used to study rheology, which describes the flow of fluids and the deformation of solids. In this sense, viscosity is the expression of fluid flow. The higher the viscosity is, the greater the resistance. Based on this, the fluids can be classified into two large groups: Newtonian and non-Newtonian [20,21]. The results are shown in Table 6 and Figure 5. Increasing the shear rate up to 100 rpm and, subsequently, the same operation in the opposite direction (i.e., decreasing the viscosity varies considerably) verifies that PF-127 gel loaded with dexamethasone is a non-Newtonian fluid. These fluids do not follow Newton’s law, and their viscosity does not remain constant as the shear rate increases [22]. Within non-Newtonian fluids, we have different classifications whose criteria are based on the type of deviation concerning Newton’s law. In this case, it is a pseudoplastic fluid because the viscosity increases as the speed of the displacement decreases [15,23]. Figure 5 shows the relationship between the viscosity and shear rate for Pluronic® F-127 gel.
Table 6. Measurement results of the relative density in Pluronic-F127 gel with dexamethasone.

| Speed (rpm) | Ascendant (cP) | Descendant (cP) |
|-------------|----------------|-----------------|
| 6           | 45             | 2120            |
| 12          | 60             | 1180            |
| 20          | 90             | 430             |
| 30          | 128            | 264             |
| 50          | 162            | 212             |
| 60          | 178            | 202             |
| 100         | 182            | 188             |

3.5.3. Drug content.

The uniformity of drug content in the pharmaceutical form is a quality parameter that ensures the content of the drug as indicated in the formulation, which ensures the appropriate dosage for the patient, thereby ensuring the therapeutic effect [23]. The results when evaluating the chemical content of the dexamethasone gel are shown in Table 7, obtaining an average recovered percentage of the dexamethasone of 99.0675%, with a standard deviation of 1.30% and a coefficient of variation of 1.35%, which indicates that it complies with the specification because, in spectrophotometric methods, the percentage of CV should not be greater than 3%, guaranteeing a homogeneous distribution of the drug in the Pluronic® F-127 gel according to the Pharmacopoeia of the United Mexican States [24].

Table 7. Results of the gel chemical content test of Pluronic-F127 with dexamethasone.

| Sample | Absorbance | Dexamethasone Concentration (μg/mL) | Recovered Dexamethasone (mg) |
|--------|------------|------------------------------------|------------------------------|
| 1      | 0.494      | 19.73                              | 98.69                        |
| 2      | 0.49       | 19.57                              | 97.89                        |
| 3      | 0.493      | 19.69                              | 98.49                        |
| 4      | 0.506      | 20.21                              | 101.07                       |
| 5      | 0.489      | 19.53                              | 97.69                        |
| 6      | 0.506      | 20.21                              | 101.07                       |
| 7      | 0.494      | 19.73                              | 98.69                        |
| 8      | 0.493      | 19.69                              | 98.49                        |
| 9      | 0.49       | 19.57                              | 97.89                        |
| 10     | 0.504      | 20.13                              | 100.67                       |
| Mean   | 0.4959     | 19.81                              | 99.06                        |
| Standard Deviation | 0.0068 | 0.2681 | 1.34 |
| % of CV | 1.3626 | 1.35 | 1.35 |

3.6. Release test of the reservoir transdermal patch.

After analyzing the results of the polymeric films and checking that the physical characteristics satisfy the needs of the reservoir-type transdermal patch, Formulation 1 of the impermeable film was selected, which presented better properties to be used as a reservoir film.
For the adhesive film, Formulation 1 was chosen because it had better properties. Therefore, these films were united, adding into their interior the Pluronic® F-127 gel with dexamethasone to perform the release test.

Release tests are performed to measure the amount of drug that passes to the medium of dissolution at defined time intervals. Since the absorption of the drug and its physiological availability depend on its release, the characteristics suitable for its dissolution are important for pharmaceuticals [18,25]. In the case of the reservoir-type transdermal patch, the dissolution profile guarantees that the amount of the drug in the reservoir of the patch is released. Figure 6 shows the gradual release of dexamethasone for the reservoir-type transdermal patch, which ensures the total release of the drug at approximately 93% within a period of about 7 h, indicating that the dexamethasone is available for absorption through the skin.

Figure 6. Dexamethasone release profile in the reservoir-type transdermal patch.

To describe the mechanism of release of the drug through the adhesive film, the main kinetic release models were evaluated. The use of mathematical models allows predicting the release kinetics of the pharmaceutical form to investigate the release of dexamethasone in the transdermal patch. The data were analyzed using the following mathematical models [26]:

- **Zero-order** \( Q = k_0 \times t \),
- **First-order** \( \ln(100-Q) = \ln Q_0 - k_1 \times t \),
- **Higuchi** \( Q = kH \times t^{1/2} \),
- **Korsmeyer-Peppas** \( \frac{M_t}{M_\infty} = Kt^n \),

where \( Q \) is the percentage of drug dissolved at time \( t \), and \( k_0, k_1, \) and \( kH \) are the speed constants of the zero-order, first-order, and Higuchi models, respectively. For Korsmeyer-Peppas, \( \frac{M_t}{M_\infty} \) is the fraction of the drug dissolved at time \( t \), \( K \) is the release rate constant that incorporates structural and geometric characteristics of the delivery system, and \( n \) is the release exponent that indicates the mechanism by which the release occurs. The values of \( n \) and the predictions [27] are listed as follows:

- \( 0.45 \leq n \leq 0.89 \) corresponds to a Fickian release mechanism.
- \( 0.45 < n < 0.89 \) corresponds to non-Fickian or anomalous release.
- \( n = 0.89 \) is transport Case II, and the rate of drug release is controlled by the relaxation of polymer chains.
- \( n > 0.89 \) corresponds to a non-Fickian diffusion release, Super Case II.

The Korsemeyer-Peppas model explains drug release mechanisms where erosion and/or dissolution of the matrix occurs, being a model generalized Higuchi equation. It has been widely used for describing the release of drugs from polymeric systems. Table 8 shows the parameters obtained from the mathematical models indicated above for the release kinetics in a medium at a pH of 5.5. The kind of release kinetics is given by the profile with the coefficient of determination (r2) closest to 1. The best adjustments in the kinetics were the
zero-order and first-order models. The above indicates that the reservoir-type transdermal patch released dexamethasone in a concentration-dependent manner, showing a time-dependent release profile. Figures 7 and 8 show the mathematical zero-order and first-order models applied to the kinetics of the release of dexamethasone in the reservoir-type transdermal patch.

Table 8. Kinetic profile results of dexamethasone release in the transdermal patch type reservoir.

| Model          | R²   |
|----------------|------|
| Zero-order     | 0.9324 |
| First-order    | 0.9123 |
| Higuchi        | 0.809 |
| Korsmeyer-Peppas | 0.8841 |

Figure 7. Zero-order kinetic model for the release of dexamethasone.

Figure 8. First-order kinetic model for the release of dexamethasone.

3.7. In vitro percutaneous absorption studies.

*In vitro* percutaneous absorption studies using Franz-type diffusion cells are of great relevance to determining many drugs' percutaneous absorption parameters; this represents an important role when designing and developing transdermal systems.

Figure 9. *In vivo* skin dexamethasone permeation profile of the reservoir-type transdermal patch.
Results of the *in vitro* drug permeation from the transdermal patch formulation revealed that the maximum permeation flux (Jss) of dexamethasone was 140.98 μg/cm²·h with lag time (tLag) of 18.7374 h and a permeability coefficient (Kp) 7.049x10^-4 cm²/h. Figure 9 contains the drug permeation profile. Based on the skin permeation results, therapeutic concentrations of dexamethasone can be reached by using the optimized transdermal patch area of 4.14 cm² that delivers a 15 mg dose of dexamethasone for 14.28 days.

Finally, in figures 10 and 11, we can observe the layers that compound the transdermal patch and the already assembled reservoir-type transdermal patch containing the dexamethasone gel.

**Figure 10.** Layers that form the reservoir-like patch: A) Impermeable layer, B) Adhesive layer.

**Figure 11.** Assembled reservoir-type transdermal patch containing dexamethasone in a PF-127 gel.

4. Conclusions

A reservoir-type transdermal patch loaded with dexamethasone formulated in a Pluronic F-127 gel was developed. Before the characterization tests of the films, the choice of Formulation 1 for both the adhesive film and waterproof film was determined because they offer greater resistance to fracture and, therefore, handling, and they provide excellent bio-adhesion. This is increased by being previously moisturized, which gives it adequate thickness and ideal characteristics for the permanence of the reservoir-type transdermal patch on the patient's skin. The formulated gel had a lower density than water. In terms of its viscosity, it was determined that it is a non-Newtonian fluid of the pseudoplastic type.

Regarding the release profiles, in a period of about 7 h, 93.76% of the dexamethasone content in the reservoir-type transdermal patch is released, with a zero-order kinetic release profile. From the results of the in vitro skin permeation studies, the following results were obtained: Flux (Jss) =140.98 μg/cm²·h, Kp =7.049x10^-4 cm²/h, and tLag = 18.7374 h. Based on these results, therapeutic concentrations of dexamethasone can be obtained using an area of approximately 4.14 cm² of the transdermal patch for 14 days.

**Funding**

This research was funded by the Universidad Nacional Autonóma de México (project number: PAPIIT IG 100220, PAPIME PE 201420 and Cátedra PIAPI 2015), and Consejo Nacional de Ciencia y Tecnología (project number: CF 140617).
Acknowledgments

We thank Helm México for donating the Eudragit E100.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Peña-Juárez, M.C.; Guadarrama-Escobar, O.R.; Escobar-Chávez, J.J. Transdermal Delivery Systems for Biomolecules. J Pharm Innov 2021, https://doi.org/10.1007/s12247-020-09525-2.

2. Comisión permanente de la Farmacopea de los Estados Unidos Mexicanos Farmacopea de los Estados Unidos Mexicanos. 9a ed. Secretaría de Salud, México, 2008.

3. Suñé, N.J. Nuevas aportaciones galénicas a las formas de administración. Grupo Ferrer (España); 2012.

4. Government of California Drugbank. Dexamethasone. Available online: https://www.drugbank.ca/drugs/DB01234 (accessed on 10 December 2019).

5. Escobar-Chávez, J.J.; Merino, V.; Díez-Sales, O.; Nácher-Alonso, A.; Ganem-Quintanar, A.; Herráez, M.; Merino-Sanjúan, M. Transdermal nortriptyline hydrochloride patch formulated within a chitosan matrix intended to be used for smoking cessation. Pharmaceutical Development and Technology 2011, 16, 162-169, https://doi.org/10.3109/10837450903584902.

6. Serrano Castañeda, P.; Escobar-Chavez, J.; Arroyo-Vazquez, J.; Rodriguez-Cruz, I.M.; Melgoza Contreras, L.M. Pravastatin transdermal patch: Effect of the formulation and length of microneedles on in vitro percutaneous absorption studies. Iranian Journal of Pharmaceutical Research 2020, 19, 127-133, https://doi.org/10.22037/ijpr.2019.1100914.

7. Castañeda S.P.; Domínguez Delgado C.L.; Cruz Rodriguez, I.M.; Melgoza Contreras, L.M.; Molina Trinidad, E.M.; Lopez Cervantes, M.; Escobar-Chávez, J.J. Development of Poly (Methyl vinyl ether-alt-maleic acid) Microneedles for Transdermal Delivery of Atorvastatin Calcium, Curr Pharm Biotechnol 2020, 21, 852-861, https://doi.org/10.2174/1389201210216620217103302.

8. Singh, A.; Bali, A. Formulation and characterization of transdermal patches for controlled delivery of sulfoxetine hydrochloride. J Anal Sci Technol. 2016, 7, https://doi.org/10.1186/s40543-016-0105-6.

9. Chaibva, F.; Walker, R. The Comparison of In Vitro Release Methods for the Evaluation of Oxytocin Release from Pluronic® F127 Parenteral Formulations. Dissol Technol. 2007, 15-25, https://dx.doi.org/10.14227/DT140407P15.

10. Escobar-Chávez, J.J.; Quintanar Guerrero, D.; Ganem Quintanar, A. In vivo skin permeation of sodium naproxen formulated in pluronic F-127 gels: effect of Azone and Transcutol. Drug Dev Ind Pharm. 2005, 31, 447-54, https://doi.org/10.1080/03639040500214662.

11. Escobar-Chávez, J.J.; López Cervantes, M.; Naik, A.; Kalia, Y.N.; Quintanar Guerrero, D.; Ganem Quintanar, A. Applications of thermo-reversible pluronic F-127 gels in pharmaceutical formulations. J Pharm Pharm Sci. 2006, 9,339-58.

12. Saltzman, M. Drug Delivery: Engineering principles for drug therapy. Oxford University Press (USA); 2001; https://doi.org/10.1093/oso/9780190585891.001.0001.

13. Food and Drug Administration. CFR - Code of Federal Regulations Title 21: Sec. 184.1901 Triacetin. 2016 April. Available on line: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?frr=184.1901 (Accessed April 1, 2019).

14. Yang, D.; Chen, M.; Sun, Y.; Jin, Y.; Lu, C.; Pan, X.; Quan, G.; Wu, C. Microneedle-mediated transdermal drug delivery for treating diverse skin diseases. Acta Biomater. 2021, 121, 119-133, https://doi.org/10.1016/j.actbio.2020.12.004.

15. Wang, B.; Hu, L.; Teruna, J. Drug Delivery: Principles and applications. 2nd ed; Wiley: USA; 2016.

16. Kováčik, A.; Kopečná, M.; Vávrová, K. Permeation enhancers in transdermal drug delivery: benefits and limitations. Expert Opin Drug Deliv. 2020, 17, 145-155, https://doi.org/10.1080/17425247.2020.1713087.

17. Pineda-Álvarez, R.A.; Bernard-Bernad, M.J.; Rodríguez-Cruz, I.M.; Escobar-Chávez, J.J. Development and Characterization of Starch/Gelatin Microneedle Arrays Loaded with Lecithin–Gelatin Nanoparticles of Losartan for Transdermal Delivery. Journal of Pharmaceutical Innovation 2020, https://doi.org/10.1007/s12247-020-09494-6.

18. Gennaro, A.; Remington, J.P. Remington Farmacia. 20ª ed Tomo 1. Argentina (Buenos aires): Panamericana; 2003; pp. 970-1079.

19. Anguiano Almazan, E.; Serrano Castañeda, P.; Díaz Torres, R.; Escobar-Chavez, J.J. Design and Evaluation of Losartan Transdermal Patch by Using Solid Microneedles as A Physical Permeation Enhancer. Iran J Pharm Res 2020, 19, 138-152, http://doi.org/10.22037/ijpr.2019.1100912.
20. Escalona-Rayo, C.F.; Serrano-Castañeda, P.; López-Cervantes, M.; Escobar-Chavez, J.J. Optimization of Unidirectional Mucoadhesive Buccal Patches Based on Chitosan and Pluronic® F-127 for Metoprolol Controlled Release: In Vitro and Ex Vivo Evaluations. *J Pharm Innov* 2020, 15, 556–568, https://doi.org/10.1007/s12247-019-09401-8.

21. Constantino-González, K.S.; Serrano-Castañeda, P.; Guadarrama-Escobar, O.R.; López-Cervantes, M.; Domínguez-Delgado, C.L.; Escobar-Chávez, J.J. Development and Characterization of Amikacin Loaded Emulgel for the Treatment of Mycetoma. *Pharmaceutical Chemistry Journal* 2021, 54, 1024-1032, https://doi.org/10.1007/s11094-021-02315-1

22. Martín, A.; Swarbrick, J.; Cammarata, A. *Physical Pharmacy.* 3rd ed; Lea & Febiger, Philadelphia. USA; 1983.

23. Aulton M. Farmacia: Ciencia y diseño de formas farmacéuticas. 2nd ed; Elsevier. Madrid España; 2004.

24. Malana, M.A.; Zohra, R. The release behavior and kinetic evaluation of tramadol HCl from chemically cross linked Tr polymeric hydrogels. *DARU Journal of Pharmaceutical Sciences* 2013, 21, https://doi.org/10.1186/2008-2231-21-10.

25. Martínez Hernández J. Liberación transdérmica de Pravastatina Sódica formulada en microagujas poliméricas biodegradables. Tesis de Licenciatura en Farmacia., FESC-UNAM. Méx; 2014. https://ru.dgb.unam.mx/handle/DGB_UNAM/TES01000720243

26. Guadarrama-Escobar, O.R.; Sánchez-Vázquez, I.; Serrano-Castañeda, P.; Chamorro-Cevallos, G.A.; Rodríguez-Cruz, I.M.; Sánchez-Padrón, A.Y.; Anguiano-Almazán, E.; Peña-Juárez, M.C.; Méndez-Albores, A.; Domínguez-Delgado, C.L.; Mercado-Márquez, C.; Rodríguez-Pérez, B.; Escobar-Chávez, J.J. Development, Characterization, Optimization, and In Vivo Evaluation of Methacrylic Acid–Ethyl Acrylate Copolymer Nanoparticles Loaded with Glibenclamide in Diabetic Rats for Oral Administration. *Pharmaceutics* 2021, 13, https://doi.org/10.3390/pharmaceutics13122023.

27. Dash, S.; Murthy, PN.; Nath, L.; Chowdhury, P. Kinetic modeling on drugs release from controlled drug delivery systems. *Acta Pol Pharm.* 2010, 67, 217-223.