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Formulation, Technology, and Biopharmaceutical Evaluation of Triamcinolone Oral Mucoadhesive Films

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ABSTRACT

Background: Rational pharmacotherapy of oral diseases (lichen planus, pemphigus, pemphigoid) is one of the complex challenges of the modern era. The existing drug forms (gels, tablets, lozenges), despite their mucoadhesiveness, are not characterized by high pharmacological effectiveness. Mucoadhesive films made by nanotechnology provide a new method of treating lichen planus.

Objectives: The research aimed to determine the formulation of triamcinolone oral mucoadhesive, two-layered films based on biopharmaceutical studies and technology development.

Methods: Modern pharmaco-technological, biopharmaceutical, and physicochemical methods were used for the research. The appearance and organoleptic properties of the drug form were controlled (color, smell, consistency). Homogeneity, pH, flexibility, thumb test, and moisture absorption were determined during the research process. The active substance release dynamics were studied under in vitro tests by applying Franz diffusion cells with subsequent spectrophotometry.

Results: Based on biopharmaceutical studies, triamcinolone mucoadhesive, two-layered films are formulated %: (Triamcinolone acetonide—0,20. Lidocaine hydrochloride – 2,0. Ethylcellulose—2,4. METHOCEL K100 – 2,4. Sorbitol 70% solution – 4,0. Polyethylene glycol 400 – 4,0. Glycerin—4,0. Polysorbate 60 – 2,4. Sorbic acid—0,2. Eucalyptus essential oil—0,4. Peppermint essential oil—0,2. 96% ethyl alcohol—up to 100.

Conclusions: Quality indicators of mucoadhesive films are determined. The quality and consumer properties of the provided films are within optimal limits. The dynamics of triamcinolone release are studied. The release of API from the films reaches 70% within 180 minutes. Triamcinolone films maintain stability throughout the study period—3 months when stored under different conditions.

Keywords: Bilayer plates; Lichen planus; mucoadhesive; nanotechnology; triamcinolone.

BACKGROUND

Diseases of the oral mucosa greatly influence the quality of human life. The oral cavity is the central part of the body that provides speech, nutrition, and the sense of taste. In the case of dermatoses—lichen planus, pemphigus, and pemphigoid—there are many lesions on the oral mucosa.

Rational pharmacotherapy of oral cavity diseases is one of the difficult challenges of the modern era, as the existing drug forms (e.g., gels, tablets, lozenges), despite their mucoadhesiveness, are not characterized by high pharmacological effectiveness. The drugs mentioned above have a short exposure time (up to 30 min on the injured mucous membrane). Also, they are washed away with saliva and spread in the oral cavity, which leads to non-targeted, uneconomical consumption of the active pharmaceutical ingredient, which may result in side effects.[1-3]

Oral mucoadhesive films are solid dosage forms of the drug that are applied to the mucous membrane and adsorbed on it, providing a high degree of biological penetration of the active pharmaceutical ingredient.

Recently, research has been carried out primarily related to the development of modern ready-made drug forms of triamcinolone – widely used in dermatoses.[4,5]

METHODS

The research aimed to determine the formulation of triamcinolone oral mucoadhesive, two-layered films based on biopharmaceutical studies and technology development. In order to achieve objectives, we set the following tasks:

- Based on biopharmaceutical studies, drawing up a model oral mucoadhesive, two-layered film composition;
- Based on biopharmaceutical studies, the determination of triamcinolone oral mucoadhesive, two-layered film formulation;
- Drawing up of technological scheme of triamcinolone oral mucoadhesive, two-layered films, and preparation technology development;
- Determination of high-quality indicators of triamcinolone oral mucoadhesive, two-layered films;
- Determination of the stability of triamcinolone oral mucoadhesive, two-layered films.

Pursuant to the functional purpose the subjects of study are provided in Table 1.

Modern pharmaco-technological, physical-chemical, and biopharmaceutical methods were used for the research.[6] The drug form's External image and organoleptic properties (color, smell, consistency, etc.) are controlled.

Investigational medical products also undergo monitoring for the presence of offensive odors and signs of physical instability (aggregation of particles, separation).

TABLE 1. Subjects of study under the functional purpose

	Substance	Purpose
1	Triamcinolone scetonide	Active pharmaceutical ingredient (API)
2	Lidocaine hydrochloride	API
3	Ethyl cellulose	Matrix polymer
4	Methyl cellulose	Matrix polymer
5	Hydroxypropylmethylcellulose	Matrix polymer
6	Carboxymethylcellulose	Matrix polymer
7	Polyvinyl alcohol	Matrix polymer
8	Polyacrylic acid	Matrix polymer
9	Carbopol – 940	Matrix polymer
10	Methocel K15	Matrix polymer
11	Methocel K100	Matrix polymer
12	Sodium alginate	Matrix polymer
13	Polysorbate 60	Surfactant
14	Eucalyptus essential oil	API, penetration enhancer
15	Peppermint essential oil	API, penetration enhancer
16	Glycerin	Plasticizer
17	Polyethylene glycol – 400 (PEG-400)	Solvent
18	Sodium hydroxide	pH-regulator
19	Sorbitol 70% solution	Sweetener
20	Sorbic acid	Preservative
21	Ethyl alcohol, 96%	Solvent

The third edition, named Pharmacopoeia, carries out the determination. Four samples are taken; each sample is 20-30 mg. Two samples are placed on each glass slide. The second glass slide is placed over the samples, and pressure is exerted so that the glass slides tightly stick together and the diameter of spots formed from the samples reaches 2 cm. Obtained spots are observed with the naked eye (about 30 cm from the eye). The sample is homogeneous if there are no visible particles, external inclusions, or signs of physical instability in all four samples: aggregation, coalescence, and coagulation of particles. If one sample fails the test, eight more samples are determined, and all eight must pass the test.

Determination of pH. The pH value is one of the characteristic indicators of the physical-chemical properties of soft dosage forms. The drug's stability, the medical substance's bioavailability, and the soft dosage form's indifference to living tissues depend on its value. The 2.5 g (exact weight) films are placed in a 100 ml capacity beaker. 50 ml of distilled water is added and dissolved by mixing. Then, the pH value is determined potentiometrically.

Bendability: they take a ready film, which is folded in the same place about 50 times. The film structure should not be disturbed in the place of folding, and cracks should not be formed.

Thumb test: to determine adhesion, the thumb test is applied, during which the user presses their finger on the adhesive side of the film and observes its adhesion quality.

Moisture absorption: the ready film is weighed to the nearest thousandth and placed in a desiccator for 24 hours at room temperature, together with 15 ml calcium chloride solution (5g calcium chloride is dissolved in 15 ml distilled water). After 24 hours, the film is removed from the desiccator and weighed with the same accuracy. The formula calculates the amount of absorbed moisture:

Absorbed moisture (%) = final weight – initial weight X 100/ initial weight.

The active substance release dynamics were studied in vitro by applying Franz-type diffusion cells with subsequent spectrophotometry. We used a dual-chamber device separated by a semi-permeable cellophane membrane to evaluate the release of triamcinolone from the films. In the first chamber was placed 1g crushed sample of the test film, and in the second chamber, a phosphate buffer with a pH value of 7.4 (buffer composition: water 400ml, NaCl 8g, KCl 0.2g, NaH_2PO_4 1.44g, KH_2PO^4 0.24g). The test ran at 370C; the diffuse area was mixed through a magnetic stirrer. After each step, we took a sample and added phosphate buffer at an equal volume to the sample in the diffusion area.

RESULTS

We selected the film-forming substance to prepare triamcinolone films, considering its physical-chemical properties and availability.[7] As a result, we composed nine formulations of the test films. The results are shown in Table 2.

We prepared the films from the research formulations using the general scheme: by preliminary saturation of ethyl-cellulose, polyvinylpyrrolidone, and polyvinyl alcohol in 96% ethyl alcohol. Cellulose products, polyacrylic acid, and sodium alginate were included in a mixture of glycerin, sorbitol 70% solution, and polyethylene glycol-400. Triamcinolone, polysorbate-60, sorbic acid, lidocaine hydrochloride, eucalyptus, and peppermint essential oils were successfully added to the prepared model plate mass

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under mixing conditions. We evaluated the films prepared on different film-forming substances according to the leading physical-chemical and technological indicators. The results are provided in Table 3.

TABLE 2. Investigational compositions of triamcinolone films

	Name of ingredients, c	Formulations and composition, (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Triamcinolone scetonide	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
2	Lidocaine hydrochloride	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
3	Ethyl cellulose	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
4	Methyl cellulose	3.2	-	-	-	-	-	-	-	-
5	Hydroxypropylmethylcellulose	-	2.0	-	-	-	-	-	-	-
6	Carboxymethylcellulose	-	-	2.4	-	-	-	-	-	-
7	Polyvinyl alcohol	-	-	-	1.5	-	-	-	-	-
8	Polyacrylic acid	-	-	-	-	1.2	-	-	-	-
9	Polyvinylpyrrolidone	-	-	-	-	-	1.4	-	-	-
10	Methocel K15	-	-	-	-	-	-	2.4	-	-
11	Methocel K100	-	-	-	-	-	-	-	2.4	-
12	Sodium alginate	-	-	-	-	-	-	-	-	2.2
13	Sorbitol 70% solution	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
14	PEG-400	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
15	Glycerin	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
16	Polysorbate - 60	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
17	Sorbic acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
18	Eucalyptus essential oil	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
19	Peppermint essential oil	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
20	Ethyl alcohol, 96%	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0

TABLE 3. Results for the determination of sound quality indicators of triamcinolone test films

Quality indicators	Requirements	F1	F2	F3	F4	F5	F6	F7	F8	F9
Description	Homogenous mass	+	+	+	+	+	+	+	+	+
Homogeneity	Absence of visible inclusions on the glass slide	Matches	Matches	Matches	Matches	Matches	Matches	Matches	Matches	Matches
pH	4.5-8.0	6.8	6.6	7.2	7.2	7.3	7.4	7.1	7.2	7.2
Thumb test	Adhesiveness	Satisfies	Does not satisfy	Satisfies	Does not satisfy	Satisfies	Does not satisfy	Does not satisfy	Does not satisfy	Satisfies
Moisture-absorbing power	±1%	Satisfies	Satisfies	Satisfies	Satisfies	Satisfies	Satisfies	Satisfies	Satisfies	Satisfies
Foldability	The structure should not be broken when folded 50 times in the same place.	Does not match	Matches	Matches	Does not match	Matches	Matches	Matches	Matches	Does not match

Films made under the F1 formulation have uniform structure and good adhesiveness but do not meet the requirement of foldability; F2 formulation films have low adhesiveness features. The films obtained under the F3 formulation are adhesive and solid; Films made under F4 and F6 formulations have low adhesiveness features; And the films made under the F5 formulation, on the contrary, have high adhesive features and also are nonhomogeneous; Films made under F7 and F8 formulation have good adhesiveness feature and also are very solid especially F8 formulation films and according to this indicator, it exceeds to the films made under F3 formulation; The films made under F9 formulation have a good adhesiveness and low solidity. Under the examined parameters, the films made under F8 were found to be favorable, and based on this, further studies were conducted on the films made under F8 formulation.

DISCUSSION

By applying Franz diffusion cells, we examined the degree of triamcinolone release from the films made under the F8 composition. The obtained results are shown in Figure 1.

We studied the stability of triamcinolone films made under F8 formulation during storage under different conditions. The results are provided in Table 4.

Based on theoretical and experimental studies, there is developed a formulation for triamcinolone oral mucoadhesive, two-layered films, %: (triamcinolone

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acetonide – 0.20, lidocaine hydrochloride – 2.0, ethyl cellulose – 2.4, MethocelK100 – 2.4, 70% of sorbitol solution – 4.0, polyethylene glycol 400 – 4.0, glycerin – 4.0, polysorbate 60 – 2.4, sorbic acid – 0.2, eucalyptus essential oil – 0.4, peppermint essential oil – 0.2, 96% ethyl alcohol – up to 100.

FIGURE 1. Statistically processed results of determining the degree of triamcinolone release from the films made under F8 formulation

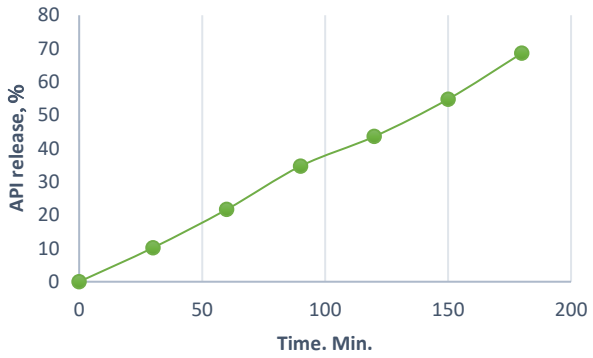

TABLE 4. Statistically processed results of determining the degree of triamcinolone release from the films made under F8 formulation

Evaluation parameters	25±2°C/ 60±5%	30±2°C/ 65±5%	40±2°C/ 75±5%
Description	White	white	White
Homogeneity	Matches	Matches	Matches
pH	7.2	7.0	7.1
Thumb test	Satisfies	Satisfies	Satisfies
Moisture-absorbing power	Satisfies	Satisfies	Satisfies
Foldability	Matches	Matches	Matches

The quality and consumer properties of the provided films are within optimal limits. The dynamics of triamcinolone release are studied. The release of API from the films reaches 70% within 180 minutes. Triamcinolone films maintain stability throughout the study period—3 months when stored under different conditions.

CONCLUSIONS

Quality indicators of mucoadhesive films are determined. The quality and consumer properties of the provided films are within optimal limits. The dynamics of triamcinolone release are studied. The release of API from the films reaches 70% within 180 minutes. Triamcinolone films maintain stability throughout the study period—3 months when stored under different conditions.

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