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ORIGINAL ARTICLE

# Formulation and Evaluation of Triamcinolone Acetonide-Loaded Oral Disintegrated Film with Different Polymers *via* Solvent Casting Method

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## ABSTRACT

**Objectives:** The study aimed to investigate the effect of different polymers and plasticizers on oral disintegrating films (ODFs) containing triamcinolone acetonide (TA), a glucocorticosteroid indicated for the treatment of oral wounds.

**Materials and Methods:** Thirteen different formulations with the same amount of polymer and plasticizer were prepared by solvent casting. Briefly, the solutions containing polymer, plasticizer, and other ingredients were poured into Petri dishes and kept at room temperature for 20 hours to obtain ODFs. Physical properties of ODFs such as visual appearance, weight and thickness uniformity, pH, mechanical durability (tensile strength, elongation at break and folded insurance), and disintegration time were assessed and drug content analysis was performed on ODFs.

**Results:** Suitable ODFs were produced with hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol, carboxymethylcellulose, gelatin, and pectin, while film integrity was not achieved with polyethyleneglycol 4000 (PEG 4000), chitosan and starch. Glycerin made ODFs more transparent, reduced their thickness, and improved their mechanical properties. On the other hand, PEG 400 reduced the weight variation. Regarding drug content, PEG-containing gelatin-based ODF (ODF10) and pectin-based ODF (ODF12) complied with pharmacopeial limits. In addition, all ODFs except HPMC-based ODFs had an appropriate pH range.

**Conclusion:** When all features were evaluated together in terms of the applicability of an ODF to the patient, the most convenient formulation was found to be gelatin-based with PEG 400 ODF (ODF10). In short, patients will benefit from ease of application and transportation and effective therapy with correct dosing with the development of ODF forms of TA for which there are no preparations except for cream, gel, and pomade forms for topical use in Türkiye.

**Keywords:** Triamcinolone acetonide, oral disintegrating films, solvent casting method, PEG 400, glycerin

## INTRODUCTION

Oral mucositis is an acute ulceration and inflammation of the oral mucosa caused by various factors, such as cancer, infectious diseases, immunologic diseases, and trauma lesions.[1,2] It occurs in 20-100% of patients with cancer, depending on the dose of chemotherapeutics received, and significantly reduces the patient's quality of life as it causes pain, bleeding, ulcers, and difficulty in eating, drinking, and even speaking. Although many different approaches, such as zinc, aloe vera, and amifostine, have been used to treat oral mucositis, progress of oral mucositis can be serious enough to require hospitalization.[3]

Triamcinolone is a moderate-potency corticosteroid with a chemical structure of 9α-fluoro-11β, 16α, 17α, 21-tetrahydroxy-1, 4-pregnadiene-3, 20-dione and is used in the treatment of mouth sores.[4] Triamcinolone acetonide (TA) is a more potent derivative of triamcinolone, a synthetic glucocorticosteroid, with antiallergic, immunosuppressive, anti-inflammatory, and anti-scarring activities. TA can be administered systemically or

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topically, but its systemic use at high doses for a long time causes many adverse reactions that limit its clinical use.[5] It is indicated for the temporary relief of symptoms of oral inflammatory and ulcerative lesions and is used as mouthwashes, buccal formulations, or ointments.[6] Fast-acting products are needed to treat oral mucositis due to the painful process; furthermore, the concentration of corticosteroids in the oral mucosa must be increased by preventing systemic absorption as much as possible to treat effectively.[6,7] However, due to saliva flow and mechanical effects, the contact time of mouthwashes with the oral mucosa and their action time are short.[8]

Buccal formulations may decrease patient comfort due to their large size and prolonged stay in the oral cavity. In ointments, on the other hand, the active substance may be released from the dosage form during storage, and its efficacy may decrease because the drug is administered at insufficient doses. It can also be separated easily from the drug administration site during speaking and by salivation, which may lead to treatment failure.[6] In addition, TA has been shown to have low chemical stability in ointment forms.[9] Orally disintegrating films (ODFs) are a novel drug delivery system in which a stable solid film form is quickly disintegrated and absorbed in contact with saliva in the oral cavity. Therefore, ODFs containing TA may be a therapeutic option because of dispersing quickly due to their large surface areas along with its rapid onset of action. They exhibit high stability due to their solid form. Packing is also easier because they are not fragile, unlike orally disintegrating tablets.[10,11] Additionally, ODFs allow easy and safe application, especially in pediatric, geriatric, and dysphasia patients. These systems can be applied without water, which is very important when there is no access to water.[12,13]

ODFs have been prepared using various methods, including solvent casting, hot-melt extrusion, semisolid casting, solid dispersion extrusion, rolling, solvent spraying, and new technologies (Soluleaves™, XGel™, Wafertab™, etc.).[13,14] Among them, solvent casting is a highly preferred method with high reproducibility, a simple procedure, and no equipment requirement. Using organic solvents is one of the limitations of solvent casting, which can be eliminated by using distilled water (DW).[10,15] In the formulation of ODFs, water-soluble polymers are usually used to ensure rapid oral disintegration and makeup at least 45% of the film weight. They also contain plasticizers (increase film flexibility), saliva stimulants, super disintegrants, and surfactants (facilitate film disintegration), sweeteners and flavorings (better taste), and coloring agents in certain proportions to give the formulation various properties.[10,11] The polymers used may have natural or synthetic structures. Natural polymers include pectin, pullulan, maltodextrin, sodium alginate, sodium starch glycolate and gelatin; synthetic polymers include cellulose derivatives [hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC), methylcellulose], vinyl polymers [polyvinylpyrrolidone, polyvinyl alcohol (PVA) and polyethylene oxide (PEO)], and acrylic polymers (Eudragit) are widely used.[10]

The purpose of this study was to compare TA-loaded ODFs prepared using different polymers (synthetic or natural) and plasticizers, which are frequently preferred in the preparation of ODFs, in terms of organoleptic properties, weight and thickness variation, mechanical strength, pH, disintegrating time, and drug amount. ODFs were prepared using the solvent casting method. Several characterization studies were conducted on TA-loaded ODFs for comparative evaluations.

## MATERIALS AND METHODS

*Materials*

Materials used for the preparation of the formulation: HPMC (ShinEtsu, Japan), PVA (85-124 kDa, 99% + hydrolyzed, Sigma, USA), polyethyleneglycol 4000 (PEG 4000) (Merck, USA), CMC (Doğa İlaç, Türkiye), chitosan (190-375 kDa, Sigma, USA), starch (Yasin Teknik, Türkiye), gelatin (Doğa İlaç, Türkiye), pectin (Doğa İlaç, Türkiye), PEG 400 (Merck, Germany), glycerin (99.5%, Farma Kalite, Türkiye), monopotassium phosphate ($KH_2PO_4$, ≥ 99.5%, Isolab, Germany), disodium phosphate dihydrate ($Na_2HPO_4.2H_2O$, Merck, Germany), sodium chloride (NaCl, ≥ 99.5%, Merck, Denmark), phosphoric acid (Sigma, USA), citric acid (anhydrous) (› 99.5%, Tekkim Kimya, Türkiye), sodium saccharin (Na-saccharin, ≥ 98%, Sigma, USA), vanillin (≥ 99%, Merck, Germany), ethanol (absolute) (EtOH; ≥ 99.9%, Isolab, Germany). DW was obtained using a Millipore Milli-Q ultrapure water system in the laboratory.

*TA-loaded ODFs*

Eight different polymers were used to prepare the TA-loaded ODFs. Four of them were HPMC, PVA, PEG 4000, and CMC as the synthetic polymers, and the others were chitosan, starch, gelatin, and pectin as natural polymers. Furthermore, two different plasticizers (PEG 400 and glycerin) were selected to evaluate their effectiveness on the properties of ODFs. The active substance (TA) and excipients used in the formulations and their amounts are given in Table 1. The ODF preparation process for HMPC, PEG 4000, CMC, and gelatin, which are easily water-soluble polymers, was briefly described as follows: The polymer (0.68 g) was added part by part onto 20 mL of DW on a magnetic stirrer (Heidolph Instruments, Germany), and mixing was continued until it was completely dissolved at room temperature. The citric acid (0.05 g) as a saliva stimulant, Na-saccharin (0.05 g) as a sweetener, PEG 400 or glycerin (0.2 g) as a plasticizer for film flexibility, and vanillin (0.01 g) as a flavor were added to the polymer solution. Since TA is not water-soluble, 0.01 g of TA was first dissolved in 1 mL EtOH using bath sonication (Weightlab Instruments, Türkiye), followed by its addition to the polymer mixture.

The amounts of TA and excipients were kept constant in all formulations (Table 1). However, the preparation method had to be modified for PVA, chitosan, starch, which are not freely water-soluble polymers, and pectin. For example, PVA dissolves in hot water. Therefore, for the PVA-based ODFs, PVA was added to 20 mL of DW, heated to about 100-120 °C,

**Table 1. Formulation of the TA-loaded ODFs**

| Formulations | Quantity in 20 mL dw (g) | ODF1 | ODF2 | ODF3 | ODF4 | ODF5 | ODF6 | ODF7 | ODF8 | ODF9 | ODF10 | ODF11 | ODF12 | ODF13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Polymer** | 0.68 | | | | | | | | | | | | | |
| HPMC | Synthetic | + | + | | | | | | | | | | | |
| PVA | Synthetic | | | + | + | | | | | | | | | |
| PEG 4000 | Synthetic | | | | | + | | | | | | | | |
| CMC | Synthetic | | | | | | + | + | | | | | | |
| Chitosan | Natural | | | | | | | | + | | | | | |
| Starch | Natural | | | | | | | | | + | | | | |
| Gelatin | Natural | | | | | | | | | | + | + | | |
| Pectin | Natural | | | | | | | | | | | | + | + |
| **Plasticizer** | 0.2 | | | | | | | | | | | | | |
| PEG 400 | | + | | + | | + | + | | + | + | + | | + | |
| Glycerin | | | + | | + | | | + | | | | + | | + |
| Citric acid | 0.05 | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Na-saccharin | 0.05 | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Vanillin | 0.01 | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Triamcinolone acetonide | 0.01 | + | + | + | + | + | + | + | + | + | + | + | + | + |

ODF: Oral disintegrating film, HPMC: Hydroxypropyl methylcellulose, PVA: Polyvinyl alcohol, PEG 4000: Polyethylene glycol 4000, CMC: Carboxymethylcellulose, PEG 400: Polyethylene glycol 400, Na-saccharin: Sodium saccharin, Dw: Distilled water

and stirred vigorously until all the PVA had dissolved. After cooling to room temperature, the volume was increased to 20 mL with DW. Excipients (citric acid, Na-saccharin, PEG 400 or glycerin, vanillin) and then 1 mL ethanolic solution of TA were added to the PVA solution at room temperature, as mentioned above.

For chitosan-based ODFs, since chitosan dissolves in an acidic environment, citric acid was first dissolved in DW, and then chitosan in parts was added to this solution under a magnetic stirrer at room temperature. Subsequently, Na-saccharin, PEG 400 or glycerin, and vanillin were added to the polymer solution, respectively, and mixing continued. Finally, 1 mL of the TA solution in ethanol was added to the solution.

For starch-based ODFs, a plasticizer (PEG 400 or glycerin) was first added to the DW under a magnetic stirrer to decrease the phase-transition temperature of the starch and protect it from temperature-related degradation.[16]

Starch was added to this solution and mixed for 30 minutes to disperse it. Afterwards, the temperature was turned on and the mixture was mixed at 80 °C for 30 minutes to gel. After cooling to room temperature, the volume was increased to 20 mL with DW. Citric acid, Na-saccharin, and vanillin were added to the polymer solutions, and the mixing was continued. Finally, 1 mL of the TA solution in ethanol was added to the solution.

For pectin-based ODFs, pectin was added to 20 mL of DW and left at room temperature for one day without mixing to prevent bubble formation. The next day, citric acid, Na-saccharin, PEG 400 or glycerin, and vanillin were added to the polymer solution under gentle stirring with a glass rod. Subsequently, 1 mL of TA solution in ethanol was added to the solution.

Each final polymer solution containing TA, prepared as mentioned above, was mixed under a magnetic stirrer for 10 minutes, and then it was rested outside for a further 10 minutes without mixing to remove the formed bubbles. After that, it was poured into a 10 cm Petri dish. Petri dishes wrapped in aluminum foil with holes punched on them were placed in a fume hood (second-degree) and left to dry for 20 hours at room temperature.

*Characterization of TA-loaded ODFs*

*Film-forming capacity and physical appearance*

The film-forming capacity is the ability of a polymer to form films that can be separated

from the surface on which they are cast. The films were characterized as easy-moderate-difficult-very difficult depending on the difficulty level of getting out of the mold. The film's appearance was evaluated by visual observation. The parameters like homogeneity and transparent/blurry images of the films were evaluated.[17]

*Weight and thickness variation*

After the prepared ODFs were cut into 2 x 2 $cm^2$ dimensions, the weight and thickness of 3 samples for each formulation were measured with an analytical balance (Ohaus Corporation, USA) and a caliper, respectively.

*Mechanical strength*

Two different methods (folding endurance and tensile strength) were used to determine the mechanical strength of the films. For folding endurance, the prepared ODFs were cut in 2 x 2 $cm^2$ dimensions and folded manually on top of each other from the same place. The number before the fold number at which the first break occurs was accepted as the fragility parameter.[14] In the tensile strength analysis, a TA-XT Plus Texture Analyzer (Stable Micro Systems, UK) equipped with a 5 kg load cell in TPA mode was used. Films with dimensions of 1 x 3 $cm^2$ were held between two clamps of the TA-XT probe positioned at a distance of 1 cm. The lower clamp was held stationary, and the ODF strips were stretched by the upper clamp at a rate of 1 mm/s until the strip tore. The tensile work performed during this process and the tensile deformation/elongation of the film at the moment of tearing were measured.[18]

*pH analysis*

2 x 2 $cm^2$ cut films were added to 2 mL of artificial saliva. After they were completely dissolved, their pH was measured using a digital pH meter (Ohaus Starter 3000, USA).[14] Three samples were tested for each formulation. Films containing only PVA had to be heated at high temperatures to dissolve after expulsion into the salivary fluid.

*Disintegrating time*

There are no official guidelines for determining the degradation time of ODFs. 2 x 2 $cm^2$ cut films were placed in 10 mL of artificial saliva at 37 °C, and the stirring rate was set to 100 rpm. The time taken for complete film disintegration was determined using a stopwatch.[19] Three samples were tested for each formulation.

*Drug content*

A certain amount of TA was weighed on an analytical balance and dissolved in EtOH. After sonication, the same volume of DW as EtOH was added to this solution to prepare a stock solution. Calibration samples were prepared at concentrations of 1000, 800, 400, 200, 100, and 50 µg/mL using the stock solution. Dilutions were made using an EtOH: DW mixture (1:1 *v/v*). Spectrum scanning was performed in the 200-800 nm range using an ultraviolet-visible (UV-Vis) spectrophotometer (Thermo Scientific Multiskan G0, USA), and the maximum absorbance was observed at 286 nm. 20 mL of DW was added to the films cut in 2 x 2 $cm^2$ size, and their weights were measured. The films were homogenized *via* Ultraturrax (Heidolph Instruments, Germany) at 15,000 rpm for 5 minutes in an ice bath. A certain volume of the samples obtained as a result of this process was taken, and the same volume of EtOH was added to it. After filtering through a 0.45 µm filter, absorbance was measured at 286 nm wavelength using a UV-Vis spectrophotometer. Measurements were performed in triplicate for each formulation.

*Statistical analysis*

Data were presented as mean ± standard deviation (SD) and analyzed using GraphPad Prism Version 5.0 (GraphPad Software Inc., USA). Statistical analyses were performed using Student's t-test or One-Way analysis of variance followed by Tukey's test, as appropriate.

## RESULTS

The results of the film-forming capacity and physical appearance are listed in Table 2. Among the formulations in which the film can be removed from the Petri dish; HPMC (ODF1), PVA (ODF3), CMC (ODF6), and gelatin (ODF10) formulations prepared with PEG 400 had homogeneous, semi-transparent, easy-to-remove properties (Figures 1a, c, e, and 2a), while HPMC (ODF2), PVA (ODF4), CMC (ODF7), and pectin (ODF13) formulations prepared

**Table 2. Results of the film-forming capacity, physical appearance analysis and total score of ODF formulations**

| Formulations | Film-forming capacity | Physical appearance | Total score |
|---|---|---|---|
| ODF1 | Easy to remove from the mold | Homogeneous, semi-transparent | ++++ |
| ODF2 | Easy to remove from the mold | Homogeneous, transparent | +++++ |
| ODF3 | Easy to remove from the mold | Homogeneous, semi-transparent | ++++ |
| ODF4 | Easy to remove from the mold | Homogeneous, transparent | +++++ |
| ODF5 | Do not remove from the mold | Homogeneous, semi-transparent, sticky | + |
| ODF6 | Easy to remove from the mold | Homogeneous, semi-transparent | ++++ |
| ODF7 | Easy to remove from the mold | Homogeneous, transparent | +++++ |
| ODF8 | No film formation was observed. | | |
| ODF9 | Very difficult to remove from the mold | Non-homogeneous, non-transparent, fragmentary, brittle | + |

**Table 2. Continued**

| Formulations | Film-forming capacity | Physical appearance | Total score |
|---|---|---|---|
| ODF10 | Easy to remove from the mold | Homogeneous, semi-transparent | ++++ |
| ODF11 | Difficult to remove from the mold | Homogeneous, transparent, fragmented | ++ |
| ODF12 | Easy to remove from the mold | Homogeneous, transparent but bubble view | +++ |
| ODF13 | Easy to remove from the mold | Homogeneous, transparent | +++++ |

ODF: Oral disintegrating film, +++++: Very good, ++++: Good, +++: Average, ++: Poor, +: Very poor

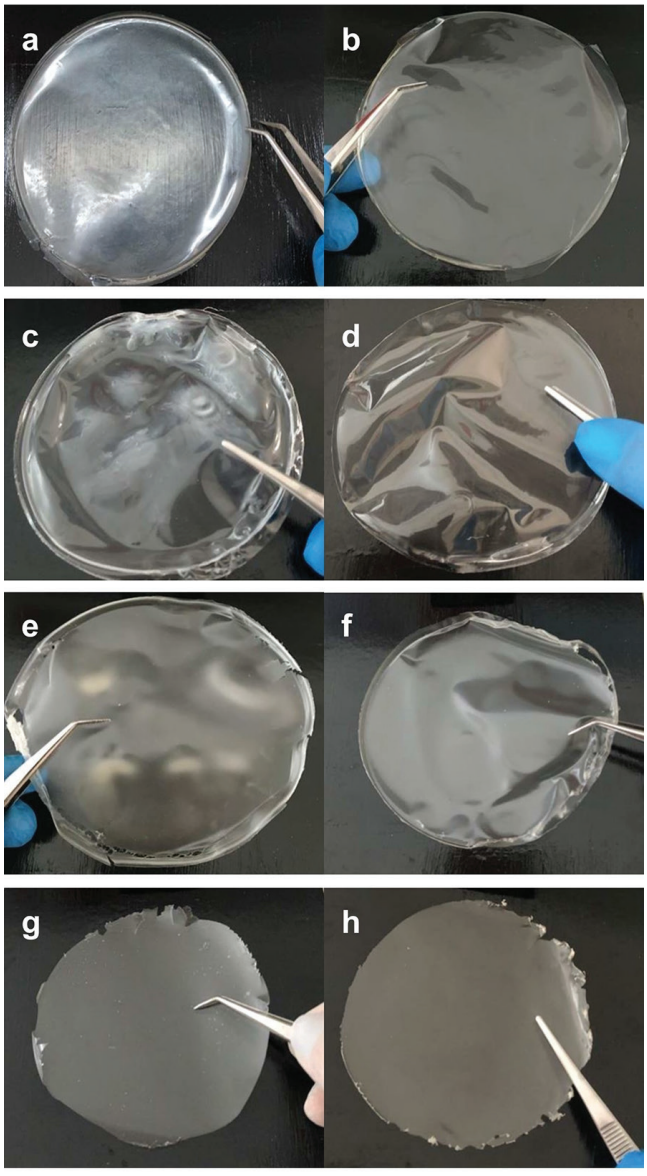


**Figure 1.** Images of HPMC formulation prepared with PEG 400 (ODF1) (a) and glycerin (ODF2) (b); PVA formulation prepared with PEG 400 (ODF3) (c) and glycerin (ODF4) (d); CMC formulation prepared with PEG 400 (ODF6) (e) and glycerin (ODF7) (f); pectin formulation prepared with PEG 400 (ODF12) (g) and glycerin (ODF13) (h)

HPMC: Hydroxypropylmethyl cellulose, PEG 400: Polyethylene glycol 400, ODF: Oral disintegrating film, PVA: Polyvinyl alcohol, CMC: Carboxymethylcellulose

with glycerin exhibited homogeneous, transparent, and easy-to-remove properties (Figure 1b, d, f, h). Films containing pectin plus PEG 400 (ODF12) exhibited a homogeneous and transparent appearance, were easily demolded, and contained bubbles (Figure 1g). On the other hand, ODF11 films prepared with gelatin and glycerin exhibit homogeneous and transparent properties; however, they break up when removed from the mold (Figure 2b). Finally, no film formation was observed in the formulation in which PEG 4000 (ODF5) or chitosan (ODF8) were used as the polymer, and PEG 400 was used as the plasticizer (Figure 3a, b). In addition, although starch formulations prepared with PEG 400 (ODF9) can be removed from the mold, it cannot be asserted that a film has been formed (Figure 3c).

The values obtained as a function of weight, thickness, folding endurance, tensile strength, pH, *in vitro* disintegration time, and drug content of ODFs prepared using different polymers and plasticizers are shown in Table 3. The weights of the ODFs ranged from 28.6 ± 3.2 mg to 75.6 ± 4.0 mg, and the highest film weight was obtained using HPMC plus PEG 400 film (ODF1). The general trend in films other than those prepared with CMC is that lower-weight films are formed when glycerin is used as a plasticizer. In the ODFs with glycerin as the plasticizer, the film thickness was similar to or lower than that of PEG 400. When the mechanical properties were examined, the films with HPMC exhibited low mechanical strength. The pH values of the ODFs differed between 4.02 ± 0.18 and 6.11 ± 0.06. Only four ODFs (ODF1, ODF2, ODF7 and ODF10) dispersed within 5 minutes, and the shortest disintegration time was observed in the ODF1 formulation containing HPMC plus PEG 400, with a value of 59.43 ± 15.12 s. Although the formulations prepared with PVA

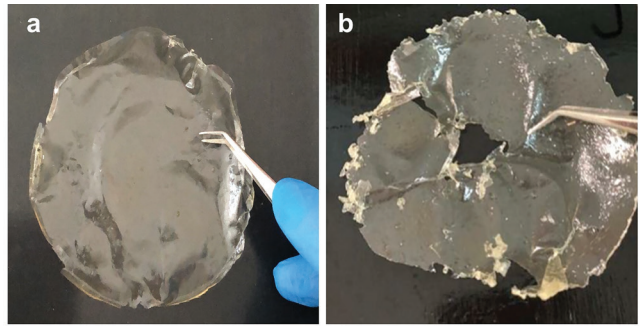


**Figure 2.** Images of gelatin formulations prepared with PEG 400 (ODF10) (a) and glycerin (ODF11) (b)

PEG 400: Polyethylene glycol 400, ODF: Oral disintegrating film

were kept for more than five minutes, no disintegration was observed, and the film remained intact (data not shown). In addition, ODFs exhibited high drug loading capacity overall; only ODFs with PVA had the lowest drug content with 58.8 ± 2.1% and 51.0 ± 1.0% (Table 3).

## DISCUSSION

ODF formulations have several advantages, such as an effective therapeutic response that can be achieved as a result of the active substance being released in a shorter time and improved patient compliance. In this regard, ODFs are expected to have a suitable appearance, sufficient mechanical strength, short disintegration time, and high drug content.[15,20] In the present study, we found that PEG 4000, chitosan or starch-containing fomulates did not form films. On the contrary, easily demoldable films with a homogeneous appearance were obtained when HPMC, PVA, CMC, gelatin, and pectin were used as polymers. Furthermore, more transparent films were produced when glycerin was used as the plasticizer, which is similar to the results presented by Okonogi et al.[21] (Table 2). PEG has been mentioned as a polymer that can be used in ODFs in the literature; however, its high molecular weight version, PEO, has been used rather than PEG.[22] Similarly, there are ODFs prepared with chitosan and starch in the literature; however, the amounts of the polymers and the contents of the formulations used are quite different from those in our study.[23-25] In addition, polymers and plasticizers were compared in this study, and polymers were used at a fixed ratio; thus, film formation was not observed due to insufficient solubility at the concentration determined for chitosan and starch.

In this study, ODFs with glycerin generally had a lower average film weight than those with PEG 400; however, the difference was not significant ($p > 0.05$), except for PVA-based ODFs ($p < 0.001$). On the other hand, CMC-based ODFs did not show a

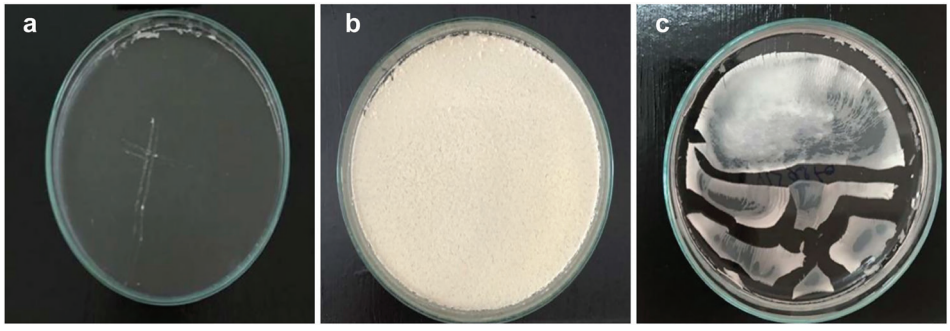


**Figure 3.** Images of PEG 4000 (ODF5) (a), chitosan (ODF8) (b) and starch (ODF9) (c) formulation prepared with PEG 400
PEG 4000: Polyethylene glycol 4000, ODF: Oral disintegrating film, PEG 400: Polyethylene glycol 400

**Table 3. Characterization analysis results in terms of weight variation, thickness variation, mechanical strength, pH, disintegration time, and drug content of ODF formulations**

| Formulations | Weight (mg ± SD) | Thickness (mm ± SD) | Tensile strength (mPa) | Elongation at break (%) | Folding endurance | pH ± SD | Disintegration time (s ± SD) | Drug content (% ± SD) |
|---|---|---|---|---|---|---|---|---|
| ODF1 | 75.6 ± 4.0 | 0.33 ± 0.03 | 4.62 ± 1.01 | 11.31 ± 4.70 | 40 ± 18 | 4.08 ± 0.08 | 59.43 ± 15.12 | 115.6 ± 0.5 |
| ODF2 | 65.3 ± 6.4 | 0.23 ± 0.03 | 8.76 ± 1.33 | 17.91 ± 3.47 | 73 ± 22 | 4.02 ± 0.18 | 147.68 ± 51.9 | 115.2 ± 0.2 |
| ODF3 | 68.3 ± 5.5 | 0.35 ± 0.09 | 25.66 ± 5.71 | 276.74 ± 37.13 | > 300 | 4.92 ± 0.19 | ** | 58.8 ± 2.1 |
| ODF4 | 32.0 ± 4.4 | 0.20 ± 0.00 | 4.44 ± 0.48 | 342.00 ± 185.76 | > 300 | 6.11 ± 0.06 | ** | 51.0 ± 1.0 |
| ODF5* | - | - | - | - | - | - | - | - |
| ODF6 | 39.0 ± 1.0 | 0.23 ± 0.03 | 6.76 ± 0.60 | 18.50 ± 3.08 | > 300 | 5.13 ± 0.14 | ≥ 300 | 74.3 ± 0.3 |
| ODF7 | 46.6 ± 6.7 | 0.22 ± 0.03 | 5.68 ± 1.14 | 67.73 ± 25.51 | > 300 | 5.06 ± 0.05 | 271.6 ± 4.04 | 78.3 ± 3.3 |
| ODF8* | - | - | - | - | - | - | - | - |
| ODF9* | - | - | - | - | - | - | - | - |
| ODF10 | 63.3 ± 4.2 | 0.33 ± 0.03 | 10.38 ± 5.19 | 8.35 ± 6.39 | > 300 | 4.84 ± 0.10 | 121.71 ± 21.16 | 109.8 ± 0.3 |
| ODF11 | 53.0 ± 3.6 | 0.26 ± 0.03 | 2.46 ± 0.23 | 46.91 ± 15.02 | > 300 | 4.65 ± 0.17 | ≥ 300 | 63.8 ± 1.0 |
| ODF12 | 32.0 ± 1.7 | 0.20 ± 0.00 | 11.20 ± 1.25 | 27.62 ± 5.59 | > 300 | 5.53 ± 0.09 | ≥ 300 | 85.6 ± 0.7 |
| ODF13 | 28.6 ± 3.2 | 0.20 ± 0.00 | 4.52 ± 0.40 | 41.06 ± 9.74 | > 300 | 5.98 ± 0.11 | ≥ 300 | 77.4 ± 0.3 |

*Analysis results are not available as they could not be removed from the mold. **Analysis results were not measured. SD: Standard deviation, ODF: Oral disintegrating film

trend like the other films. The slightly higher average weight obtained in CMC-based ODFs containing glycerin ($p > 0.05$) may be because glycerin films retained more water.[26]

It was concluded that PEG 400 improved the weight variation of ODFs, including HPMC, CMC or pectin, with lower SD values observed (Table 2). Moreover, ODFs with HPMC had significantly higher weights even though they contained the same amount of polymer (ns vs. ODF3, ODF10, and ODF11; $p < 0.01$ vs ODF7; $p < 0.001$ vs. ODF4, ODF6, ODF12, and ODF13). The differences between the weights of ODFs may be related to the viscosity of the polymers used, such that the weight of the ODF may increase as the viscosity of the polymer increases.[27]

Since dose accuracy is directly related to film thickness, it is important to ensure uniform film thickness. Considering that an ideal ODF should exhibit a thickness between 0.05 and 1 mm, the thickness of all ODFs prepared in our study (0.20 ± 0.00 mm to 0.35 ± 0.09 mm) was within these limits. However, the thickness of the ODFs containing glycerin was lower than that of the other formulations, including PEG 400, which is similar to other studies.[23,28,29] The difference between the thickness values of PEG 400 and glycerin was not significant ($p > 0.05$), except for the PVA-based ODFs ($p < 0.01$). For ODFs containing HPMC, PVA, pectin, or gelatin, a linear relationship between the weight and thickness of the films was observed, as expected.[30]

ODFs are expected to have sufficient tensile strength, high elongation at break, and good folding endurance to demonstrate the desired flexibility and stretchability during transportation, handling, and application. However, an excessively high tensile strength is undesirable as it delays drug release from the ODF.[28,31] There is no limit value for the tensile strength and elongation at break, whereas formulations with folding endurance exceeding 300 are considered durable and flexible.[31] In line with the data in the literature, the ODFs had tensile strength values from 2.46 ± 0.2 Mpa to 25.66 ± 5.71 Mpa and elongation at break values from 8.35 ± 6.39% to 342.00 ± 185.76% (Table 3).[28,32] One of the factors affecting the durability of ODFs is the type and amount of plasticizer in the formulation. In our study, two different plasticizers (PEG 400 and glycerin) were used in fixed amounts. In all ODFs except HPMC, glycerin slightly decreased the tensile strength compared with PEG ($p > 0.05$), however; the effect of glycerin on the tensile strength was more prominent in PVA-based ODFs ($p < 0.001$). In addition, according to the elongation at break values, glycerin gave more elasticity to the film than PEG 400 in all ODFs, the difference was not statistically significant ($p > 0.05$), though. Although no plasticizer effect was observed in formulations with a fold number ≥ 300, the elasticity-increasing effect of glycerin was observed in ODF1 and ODF2 formulations prepared with HPMC. Similar results have been obtained in various studies, and this effect of glycerin has been attributed to the effective insertion of its molecules into polymer chains due to its hydroxyl groups and smaller molecular size, as well as the replacement of the intermolecular bonds in the polymer matrix by hydrogen bonds formed between polymer and glycerin.[28,33] The highest tensile strength was obtained with ODF3, and the highest elongation percentage was obtained with ODF4, which may be due to the use of high molecular weight PVA, and the disintegration time results also support this situation.

The surface pH of ODFs is a crucial parameter that should be considered when predicting the stability of dosage forms and mucosal irritation. The pH values of ODFs should be close to the pH value of the oral mucosa (6.2-7.6) so that they do not irritate the oral mucosa and facilitates their administration to patients.[31] However, films developed by Visser with a surface pH of 4.5-6.5 were also found not to cause local irritation (Visser, J. C. Orodispersible films as pharmacy preparations: Let's get flexible, University of Groningen, 2017). In this respect, it was observed in this study that, except for HPMC-based ODF1 and ODF2, the other films had a suitable pH range (Table 3).

A time limit of three minutes has been reported for the *in vitro* disintegration times of ODFs.[34] The ODF1, ODF2, and ODF10 formulations were disintegrated in less than three minutes, whereas ODF1 had the minimum disintegration time (59.43 ± 15.12 s), which is in agreement with the literature.[35] Besides, PEG decreased the disintegration time of HPMC- and gelatin-based ODFs ($p < 0.05$ and $p < 0.001$, respectively). Although PVA is a water-soluble polymer, the disintegration time of films prepared with PVA (ODF3 and ODF4) was more than five minutes, which may be due to the very high molecular weight (MW) of PVA, since PVA with a 16,000 Da MW is generally used in ODF formulations and the disintegration time of these products is less than 127.36 s.[36]

According to the Pharmacopeia, the content uniformity limit is 85-115%.[37] The drug contents of the prepared ODFs varied between 115.6 ± 0.5% and 51.0 ± 1.0%. However, ODF10 and ODF12 met the criteria in terms of pharmacopeial standards (Table 3). The formulation with the highest drug content was ODF1 with 115.6 ± 0.5% (not-significant vs. ODF2; $p < 0.01$ vs. ODF10; $p < 0.001$ vs. the others), whereas the formulation with the lowest drug content was ODF4 with 51.0 ± 1.0%. The difference between these values may be due to the use of different types of polymers and plasticizers. In addition, higher drug content was observed in PEG-containing films, except for CMC-based ODFs. This effect of PEG was not significant for HPMC-based ODFs and CMC-based ODFs ($p > 0.05$), but was highly significant for the other ODFs ($p < 0.001$) and may be due to its higher solubility-enhancing effect.[38]

*Study limitations*

Although different polymers and plasticizers were used in the study, their amounts were kept constant. Therefore, whereas ODFs could not be obtained with some polymers, unacceptable ODF results, such as higher disintegration time and lower pH, were obtained with some polymers. Further studies are required to obtain formulations with more suitable properties that can be obtained using DoE design. In addition, the superiority of the developed formulation over the marketed product in terms of effectiveness can be evaluated by *in vitro* oral mucositis cell culture or *in vivo* animal models.

## CONCLUSION

ODFs of TA, a glucocorticosteroid indicated for treating oral wounds, have been successfully developed using various polymers and plasticizers. In general, successful results were obtained with HPMC, PVA, CMC, gelatin, and pectin, whereas film integrity was not achieved with PEG 4000, chitosan, and starch. The most suitable formulations were obtained for HPMC-based ODF1 and ODF2 and gelatin-based ODF10 in terms of ease of demolding, homogeneous weight and thickness variation, high mechanical durability, suitable pH value, short disintegration time, and high drug content. However, considering that the oral flora can tolerate low values, such as pH 4.5, we conclude that ODF10 is the most appropriate formulation for assessing pH, mechanical durability, disintegration time, and drug content. To summarize, PEG-containing gelatin-based ODF-containing TA is a promising candidate for patients with oral mucositis, and the efficacy of this formulation should be evaluated in future studies.

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*Ethics*

**Ethics Committee Approval:** Not required.

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*Authorship Contributions*

Concept: Ö.Ç., K.Ö., M.S., Design: Ö.Ç., K.Ö., B.T., Data Collection or Processing: Ö.Ç., K.Ö., B.T., M.S., Analysis or Interpretation: Ö.Ç., K.Ö., S.E., B.T., Literature Search: Ö.Ç., K.Ö., S.E., Writing: Ö.Ç., K.Ö., S.E.

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