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

Çoban et al. Formulation of Triamsolon-loaded Oral Disintegrated Film

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ABSTRACT

Objectives: The aim of the study was to investigate the effect of different polymers and plasticizers on oral disintegrating films (ODFs) containing triamcinolone acetonide, which is a glucocorticosteroid indicated for the treatment of oral wounds.
Materials and Methods: 13 different formulations which have same amount of polymer and plasticizer were prepared by solvent casting method. 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 ensurance), disintegration time were assessed and drug content analysis were performed on ODFs.
Results: Suitable ODFs were produced with HPMC, PVA, CMC, gelatin, and pectin, while film integrity was not achieved with 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. In terms of 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 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 triamcinolone acetonide 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 acute ulceration and inflammation of the oral mucosa caused by various factors such as cancer, infectious disease, immunologic diseases, and trauma lesions.[1,2] It occurs in 20%-100% of cancer patients, 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, should oral mucositis progress it 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 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 in order 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 is short.[8] Buccal formulations may decrease the patient's 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 the efficacy may decrease because the drug is administered in 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) is a novel drug delivery system, in which a stable solid film-form is quickly disintegrated and absorbed contact with saliva in the oral cavity. Therefore, ODFs containing TA may be a potential therapeutic option. Because they disperse quickly thanks to their large surface areas and provide an effect in a short time. They show high stability due to their being in solid form. Packing is also easier as they are not fragile like orally disintegrating tablets.[10,11] In addition, ODFs allow easy and safe application for especially pediatric, geriatric, and dysphasia patients. These systems can be applied without water, which is very important where 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, simple procedure and no need for equipment. Using organic solvents represent the 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 make up at least 45% by weight of the film. 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 a natural or synthetic structure. Natural polymers include pectin, pullulan, maltodextrin, sodium alginate, sodium starch glycolate and gelatin; Synthetic polymers include cellulose derivatives (hydroxypropylmethylcellulose, carboxymethylcellulose, methylcellulose), vinyl polymers (polyvinylpyrrolidone, polyvinyl alcohol and polyethylene oxide) 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 by solvent-casting method. Several characterization studies were conducted on TA-loaded ODFs for compartive evaluations.

MATERIALS AND METHODS

Materials

Materials used for the preparation of the formulation: Hydroxypropyl methylcellulose (HPMC, ShinEtsu, Japan), polyvinyl alcohol (PVA, 85-124 kDa, 99%+ hydrolyzed, Sigma, USA), polyethyleneglycol 4000 (PEG 4000, Merck, USA), carboxymethylcellulose (CMC, Doğa İlaç, Türkiye), chitosan (190-375 kDa, Sigma, USA), starch (Yasin Teknik, Türkiye), gelatin (Doğa İlaç, Türkiye), pectin (Doğa İlaç, Türkiye), polyethyleneglycol 400 (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). Distilled water was obtained from a Millipore Milli-Q ultrapure water system in the laboratory.

Preparation of TA-loaded ODFs

Eight different polymers were used to prepare TA-loaded ODFs. Four of them are HPMC, PVA, PEG 4000, and CMC as synthetic polymers and the others are 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 formulation 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 as follows: The polymer (0.68 g) was added part by part onto 20 mL of distilled water (DW) on a magnetic stirrer (Heidolph Instruments, Germany) and mixing was continued until it was completely dissolved at room temperature. Respectively, citric acid (0.05 g) as saliva stimulant, Na-saccharin (0.05 g) as sweetener, PEG 400 or glycerin (0.2 g) as plasticizer for film flexibility, and vanillin (0.01 g) for flavor were added to the polymer solution. Since TA is not water-soluble, 0.01 g of it was first dissolved in 1 mL EtOH using bath sonication (Weightlab Instruments, Türkiye) followed by being added 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 PVA-based ODFs, PVA was added to 20 mL of DW, heated to about 100-120°C, and stirred vigorously until all the PVA dissolved. After cooling to room temperature, the volume was made up 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 acidic environment, citric acid was first dissolved in DW and then chitosan in parts was added to this solution under magnetic stirrer and at room temperature. After that, Na-saccharin, PEG 400 or glycerin and vanillin were added to the polymer solution, respectively, and mixing continued. Finally, 1 mL of TA solution in ethanol was added to the solution.

For starch-based ODFs, plasticizer (PEG 400 or glycerin) was first added to DW under a magnetic stirrer to decrease the phase-transition temperature of starch and protect from the temperature related degradation.[16] Starch was added to this solution and mixed for 30 minutes to disperse it. Afterwards, temperature was turned on and mixed at 80°C for 30 minutes to gelling. After cooling to room temperature, the volume was made up to 20 mL with DW. Citric acid, Na-saccharin, and vanillin were added to the polymer solution, respectively, and mixing continued. Finally, 1 mL of 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 in order to prevent bubble formation. The next day, citric acid, Na-saccharin, PEG 400 or glycerin, and vanillin were respectively added to the polymer solution under gentle stirring with glass rod. Then, 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 the 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 it 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: Film-forming capacity is the ability of a polymer to form films that can be separated from the surface on which they are casted. The films were characterized as easy-moderate-difficult-very difficult depending upon the difficulty level of getting out of the mold. The appearance of film was evaluated by visual observation. The parameters like homogeneity and transparent/blurry image of the films were evaluated.[17]

Weight and Thickness Variation: After the prepared ODFs were cut into 2x2 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 2x2 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 was accepted as the fragility parameter.[14] In 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 1x3 cm^2 were held between two clamps of probe TA-XT positioned at a distance of 1 cm. The lower clamp was held stationary and the strips of ODF were stretched by the upper clamp moving at a rate of 1 mm/sec until the strip tore. The tensile work done during this process and the tensile deformation/elongation of the film at the moment of tearing were measured.[18]

pH analysis: 2x2 cm^2 cut films were added to 2 mL of artificial saliva. After they were completely dissolved, their pH was measured using a digital pHmeter (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. 2x2 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 the complete disintegration of the films was determined with 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 distilled water 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 with EtOH:distilled water mixture (1:1 v/v). Spectrum scanning was performed in the 200-800 nm range using a UV-Vis spectrophotometer (Thermo Scientific Multiskan G0, USA) and the maximum absorbance was observed at 286 nm. 20 mL of distilled water was added to the films cut in 2x2 cm^2 size and their weights were measured, and they 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, their absorbance was measured at 286 nm wavelength in a UV-Vis spectrophotometer. Measurements were done in triplicate for each formulation.

Statistical analysis

Data were presented as mean ± standard deviation (SD) and analyzed with GraphPad Prism Version 5.0 (GraphPad Software Inc., USA). Statistical analyses were performed using Student's t-test or one- way ANOVA followed by Tukey test when appropriate.

RESULTS

The results of the film-forming capacity and physical appearance are shown in Table 2. Among the formulations in which the film can be taken 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 from the mold films properties (Fig. 1 a, c, e, and Fig. 2 a), while HPMC (ODF2), PVA (ODF4), CMC (ODF7), and pectin (ODF13) formulations prepared with glycerin had homogeneous, transparent, easy to remove from the mold films properties (Fig. 1 b, d, f, h). Films containing pectin plus PEG 400 (ODF12) exhibited a homogeneous and transparent appearance and were easily de-molded, but contained bubbles (Fig. 1 g). On the other hand, ODF11 films prepared with gelatin plus glycerin displayed homogeneous and transparent properties, however, they broke up when removed from the mold (Fig. 2 b). Finally, no film formations were observed in the formulation in which PEG 4000 (ODF5), and chitosan (ODF8) were used as polymer and PEG 400 as plasticizer (Fig. 3 a, b). In addition, although starch (ODF9) formulations prepared with PEG 400 can be removed from the mold, it cannot be said that a film is formed (Fig. 3 c).

The values obtained as a result of weight, thickness, folding endurance, tensile strength, pH values, *in vitro* disintegration time, drug content of ODFs prepared using different polymers and plasticizers are shown in Table 3. The weight of ODFs ranged from 28.6 ± 3.2 mg to 75.6 ± 4.0 mg, and the highest film weight was obtained with 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 which used glycerin as a plasticizer, the thickness of the film was similar to or lower according to those of PEG 400. When the mechanical properties were examined, it was observed that the films with HPMC exhibited low mechanical strength. The pH values of the ODFs have differenced 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 seen in the ODF1 formulation containing HPMC plus PEG 400 with a value of 59.43 ± 15.12 sec. Although the formulations prepared with PVA were kept for more than five minutes, no disintegration was observed and the film was still intact (data not shown). In additon, ODFs have 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 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 respect, it is expected that ODFs 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, and starch containing fomulations did not form films. On the contrary, easy demoldable films with 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 plasticizer, which is similar to the results presented by Okonogi et al. (Table 2).[21] PEG has been mentioned as a polymer that can be used in ODFs in the literature; however, its high molecular weight version, polyethylene oxide, 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

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

It was concluded that PEG 400 improved weight variation for ODFs including HPMC, CMC, and pectin in that lower SD values were observed (Table 2). Moreover, ODFs with HPMC had significantly higher weight, even though they contained same amount of the 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 the dose accuracy is directly related to the film thickness, it is important to ensure uniformity of their 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. Although the thickness of ODFs contaning glycerin was lower than the other formulations including PEG 400, similar to other studies.[23,28,29] The difference between the thickness values in terms of PEG 400 and glycerin was not significant ($p>0.05$), except for PVA-based ODFs ($p<0.01$). For ODFs containing HPMC, PVA, pectin or gelatin, a linear relationship between weight and thickness of the films was observed, as expected.[30]

ODFs are expected to have sufficient tensile strength and high elongation at break values and folding endurance to demonstrate the desired flexibility and stretchability during transportation, handling and application. However, too high tensile strength is undesirable as it will delay drug release from the ODF.[28,31] There is no limit value for tensile strength and elongation at break, whereas formulations with a folding endurance above 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 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 to 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 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. While no effect of plasticizer 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 literatures 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-glycerin.[28,33] The highest tensile strength was obtained with ODF3 and the highest elongation percentage value 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 to predicted about the stability of the 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 their irritation effects on the oral mucosa

will be lower and provide easy administration to patients.[31] However, films with a surface pH of 4.5 to 6.5 were also found not to cause local irritation (Visser, J. C. Orodispersible films as pharmacy preparations. s: Let's get flexible. [Thesis fully internal (DIV), University of XXX]. XXX. 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 *in-vitro* disintegration times of ODFs.[34] ODF1, ODF2 and ODF10 formulations were disintegrated in less than three minutes, while ODF1 had the minimum disintegration time (59.43±15.12 sec), which is in agreement with the literature.[35] In addition, PEG decreased the disintegration time for HPMC-based ODFs 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 (MA) of PVA, since PVA with an MA of 16 000 Da is generally used in ODF formulations and the disintegration time of these products less than 127.36 sec.[36]

According to the Pharmacopoeia, 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, it can be said that ODF10 and ODF12 met the criteria in terms of pharmacopoeial standards (Table 3). The formulation with the highest drug content was ODF1 with 115.6±0.5% (ns vs ODF2; $p<0.01$ vs ODF10; $p<0.001$ vs the others), while the formulation with the lowest drug content was ODF4 with 51.0±1.0%. This difference between these values may be due to the use of different types of polymers and plasticizers. In addition, higher drug content was found in PEG-containing films except 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 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, while ODFs could not be obtained with some polymers, unacceptable results for ODFs such as higher disintegration time and lower pH were obtained with some polymers. Further studies are need to be performed with formulations having more suitable properties can be obtained by DoE design. Apart from these, 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 triamcinolone acetonide, a glucocorticosteroid indicated for the treatment of oral wounds, have been successfully developed using various polymers and plasticizers. In general, successful results were obtained with HPMC, PVA, CMC, gelatin, and pectin, while 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 easy demolding, homogeneous weight and thickness varitions, high mechanical durability, suitable pH value, short disintegration time and high drug content. However, considering that the oral flora can tolerate a low value such as pH 4.5, we can conclude that ODF10 is the most appropitable formulation for pH, mechanical durability, disintegration time and drug content. To sum up, PEG-containing gelatin-based ODF containing TA would be a promising candidate for the patients suffering oral mucositis and the efficacy of this formulation requires to be evaluated in the future studies.

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Table 1. Formulation contents of TA-loaded ODFs

Formulations		**Amount in 20 mL distilled water (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		0.20													
PEG 400			+		+		+	+		+	+	+		+	
Glycerine				+		+			+				+		+
Citric acid		0.05	+	+	+	+	+	+	+	+	+	+	+	+	+
Na-saccharin		0.05	+	+	+	+	+	+	+	+	+	+	+	+	+
Vanillin		0.01	+	+	+	+	+	+	+	+	+	+	+	+	+
Triamcinolone acetonide		0.01	+	+	+	+	+	+	+	+	+	+	+	+	+

Hydroxypropyl methylcellulose, PVA: Polyvinyl alcohol, PEG 4000: Polyethyleneglycol 4000, CMC: Carboxymethylcellulose, PEG 400: Polyethyleneglycol 400, Na-saccharin: Sodium

Table 2. Results of the film-forming capacity and physical appearance analysis 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	Does 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	+
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	+++++

*+++++: very good; ++++: good; +++: average; ++: poor; +: very poor; -: It could not be scored.

Table 3. Characterization analysis results in terms of weight variation, thickness variation, mechanical streng
drug content of ODF formulations

Formulations	Weight (mg ± SD)	Thickness (mm ± SD)	Tensile strength (mPa)	Elongation at break (%)	Folding endurance	pH ± SD
ODF1	75.6 ± 4.0	0.33 ± 0.03	4.62 ± 1.01	11.31 ± 4.70	40 ± 18	4.08 ± 0.0
ODF2	65.3 ± 6.4	0.23 ± 0.03	8.76 ± 1.33	17.91 ± 3.47	73 ± 22	4.02 ± 0.1
ODF3	68.3 ± 5.5	0.35 ± 0.09	25.66 ± 5.71	276.74 ± 37.13	>300	4.92 ± 0.1
ODF4	32.0 ± 4.4	0.20 ± 0.00	4.44 ± 0.48	342.00 ± 185.76	>300	6.11 ± 0.0
ODF5*	-	-	-	-	-	-
ODF6	39.0 ± 1.0	0.23 ± 0.03	6.76 ± 0.60	18.50 ± 3.08	>300	5.13 ± 0.1
ODF7	46.6 ± 6.7	0.22 ± 0.03	5.68 ± 1.14	67.73 ± 25.51	>300	5.06 ± 0.0
ODF8*	-	-	-	-	-	-
ODF9*	-	-	-	-	-	-
ODF10	63.3 ± 4.2	0.33 ± 0.03	10.38 ± 5.19	8.35 ± 6.39	>300	4.84 ± 0.1
ODF11	53.0 ± 3.6	0.26 ± 0.03	2.46 ± 0.23	46.91 ± 15.02	>300	4.65 ± 0.1
ODF12	32.0 ± 1.7	0.20 ± 0.00	11.20 ± 1.25	27.62 ± 5.59	>300	5.53 ± 0.0
ODF13	28.6 ± 3.2	0.20 ± 0.00	4.52 ± 0.40	41.06 ± 9.74	>300	5.98 ± 0.1

*Analysis results are not available as they could not be removed from the mold. **Could not mesured. SD: Standard deviation.

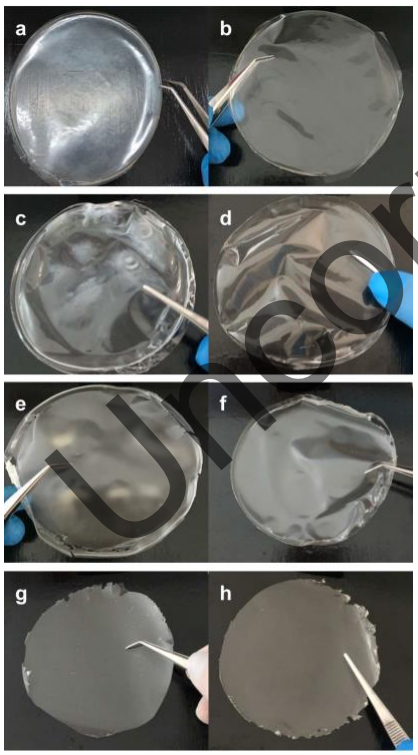

Figure 1. Images of Hydroxypropylmethyl cellulose (HPMC) formulation prepared with PEG 400 (ODF1) (a) and glycerine (ODF2) (b); Polyvinyl alcohol (PVA) formulation prepared with PEG 400 (ODF3) (c) and glycerin (ODF4) (d); CMC formulation prepared with PEG

400 (ODF6) (e) and glycerin (ODF7) (f); Pectin formulation prepared with PEG 400 (ODF12) (g) and glycerin (ODF13) (h)

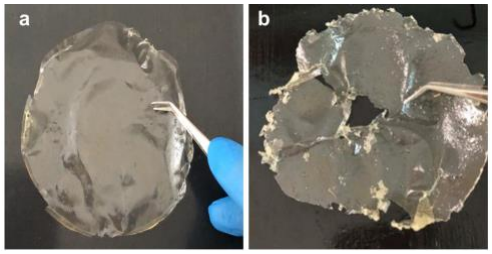

Figure 2. Images of gelatin formulation prepared with PEG 400 (ODF10) (a) and glycerine (ODF 11) (b)

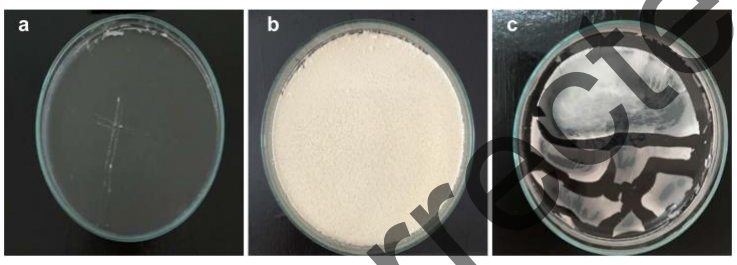

Figure 3. Images of PEG 4000 (ODF5) (a), chitosan (ODF8) (b) and starch (ODF9) (c) formulation prepared with PEG 400