Turk J Pharm Sci 2025;22(1):55-63
DOI: 10.4274/tjps.galenos.2024.46116

ORIGINAL ARTICLE

Preliminary Study on the Development of Orodispersible Film Containing Desloratadine

Özden ÇAKMAKYAPAN, Fatma Nur TUĞCU DEMİRÖZ, Zeynep Şafak TEKSİN*

Gazi University Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara, Türkiye

ABSTRACT

Objectives: Orodispersible films (ODFs) are new-generation dosage forms that increase patient compliance, providing ease of drug administration in many patient groups, such as pediatric, geriatric, and patients with physiological and psychiatric disorders. The aim of this study was to conduct preliminary studies to develop ODF containing the poorly water-soluble and oxidation-sensitive drug desloratadine (DL).

Materials and Methods: In this study, the formulation and process parameters, as well as the characterization method were investigated using 20 film formulations manufactured by the solvent casting method. The films were characterized in terms of their appearance, mechanical properties, thickness, disintegration time, and content uniformity. Various strategies have been applied to increase the chemical stability of DL in the formulations and, therefore to choose suitable antioxidants, and morphological and compatibility studies using differential scanning calorimetry were performed. For increasing drug loading, different film compositions were also evaluated.

Results: Among the preliminary formulations tested with a casting height of 400 µm, homogeneous, good mechanical properties with tensile strength values between 6.21-10.34 MPa, flexibility, and ODFs with a disintegration time of less than 60s ODFs were developed. By increasing the solubility of DL in the formulation with the selected components, the drug loading capacity was increased to 3% by the desired level.

Conclusion: One of the enabling formulations, F20, was particle-free with a suitable thickness uniformity (relative standard deviation =4.6%) and content uniformity (acceptance values =5) films were developed.

Keywords: Orodispersible film, solvent casting method, desloratadine

INTRODUCTION

Oral administration is the most preferred route. However, some problems may occur in pediatric, geriatric, and special patient groups with limited swallowing ability in terms of treatment with conventional liquid and solid dosage forms.[1] Orodispersible films (ODFs) are appropriate dosage forms not only for patients who have difficulty swallowing due to physical and cognitive disorders and are at risk of choking but also for those who do not cooperate to take the medication.[2] ODFs offer another advantage in that they enable rapid treatment of various conditions such as allergies, migraines, and nausea without the need for water. On the other hand, one of the most important disadvantages of ODFs is their limited drug-loading capacity.[3]

ODFs are defined in the European Pharmacopoeia (Ph. Eur.) 11.4 as single- or multi-layer strips made of suitable material that disintegrate rapidly when placed in the mouth.[4] Whereas there are no standardized methods or guides for the quality control and characterization of films, it is stated in Ph. Eur. "In the manufacture of ODFs, measures are taken to ensure that they possess suitable mechanical strength to resist handling without being damaged." The tensile strength (TS) is an often used parameter in evaluating the mechanical properties of thin films.[5] The type and concentrations of film-forming polymers that form the main component of orally disintegrating films are largely responsible for producing films with appropriate mechanical strength and integrity.[5,6] Films are manufactured

*Correspondence: zsteksin@gmail.com, ORCID-ID: orcid.org/0000-0001-6359-5935
Received: 11.06.2024, Accepted: 30.12.2024 Epub: 24.01.2025 Publication Date: 07.03.2025

Cite this article as: ÇAKMAKYAPAN Ö, TUĞCU DEMİRÖZ FN, TEKSİN ZŞ. Preliminary study on the development of orodispersible film containing desloratadine. Turk J Pharm Sci. 2025;22(1):55-63.

using different methods such as hot melt extrusion, electrospinning, and solvent casting method.[3] Among these methods, the solvent casting method is the most widely used in the pharmaceutical industry due to its simple production process and low cost.[7] Polymers used in ODFs can basically be classified as cellulose derivatives, starch derivatives, synthetic, and semi-synthetic polymers. Starch derivatives are among the most preferred polymers among all natural biopolymers because of their low price, widespread availability, and biodegradability. Modified starches used in oral films include maltodextrin (Maltrin®, Maltodextrin®), hydroxypropyl pea starch (Lycoat®), pregelatinized starch (Instant Pure Coat®), and Pullulan.[6] Of the cellulose derivatives, hydroxypropylmethylcellulose (HPMC) and hydroxypropyl cellulose (HPC) are most commonly used as film-forming polymers. Other commonly used excipients in the production of ODF include plasticizers [glycerol, propylene glycol (PG), sorbitol, polyethylene glycol], fillers (maltodextrin, mannitol), saliva enhancers (citric acid), solvents, color, flavor, stabilizer, surfactants, and various solubility enhancing agents (CD derivatives, Kleptose® linecaps) depending on the product's quality target product profile and the active ingredient used.[1,2,6,8]

Another factor that may affect mechanical strength is morphological changes in the films, such as crystal formation caused by the active ingredient.[9] Therefore, for mechanical strength in films, in addition to the film-forming materials, different factors, such as the type and amount of active substance in the film, the thickness, and the manufacturing process must be carefully controlled.[5]

Desloratadine (DL) is a 2nd generation H1 antihistamine that is widely used in the treatment of allergic rhinitis and urticaria. The recommended oral dose is 5 mg for adults and adolescents. For the pediatric population from 1 to 5 years old, 1.25 mg of DL can be administered once a day, whereas children aged between 6 and 11 years may be administered 2.5 mg of DL once daily.[10] DL is currently available in the market in the form of a 5 mg film-coated tablet, as well as an oral solution suitable for use at lower doses in pediatric patients and certain patient groups. The development of an ODF formulation for DL provides several advantages over traditional formulations, including enhanced patient compliance, decreased risk of choking, mitigation of stability issues associated with liquid formulations, and accurate dosing. With the growing focus on personalized medicine, ODFs offer the advantage of dose-specification. These formulations can be tailored in terms of dose and size to suit individual age and physiological conditions, facilitating individualized treatment and improving therapeutic outcomes. Given the advantages of ODFs and the necessity to overcome the issue of low drug-loading capacity in this dosage form, we aimed to develop a formulation containing 5 mg of DL that aligns with the highest recommended dosage and ensures therapeutic efficacy.

DL is practically insoluble in water.[11] Moreover, due to its molecular structure, DL is prone to degradation and is especially sensitive to oxidation.[12,13]

Considering the properties of the active substance, the present study aimed to evaluate the appropriate formulation composition, process determination, and characterization methods through preliminary formulation development studies for DL-containing ODF.

Materials and Methods

Materials

DL was a gift sample from Nobel İlaç. Citric acid anhydrous (10024) was obtained from Merck. Pregelatinized hydroxypropyl pea starch (Lycoat RS 780 and Lycoat RS 720), pea maltodextrin (Kleptose Linecaps), and maltodextrin (Glucidex IT6) were kindly donated by Roquette Pharma. HPMC E15 and HPMC E5 (Methocel E15 LVP, Methocel E) were supplied by Colorcon. HP-β-CD (Cavasol W7 HP Pharma) was gifted by Ashland. Sodium Metabisulfite, ascorbic acid, and EDTA were procured as gift samples from Drogsan. Propylgallate was kindly supplied by Ali Raif Pharmaceuticals. Polyvinylpyrrolidone (PVP) (Kollidon® 30 LP), PEG 400, and poloxamer (Kolliphor® P188) were obtained from BASF. Ethanol absolute (Merck) and PG (Merck Emsure) were purchased from local vendors. All other reagents and solvents were of analytical grade.

Method

Compatibility study

Differential scanning calorimetry (DSC) analyses were performed on 2 mg samples of DL, excipient, and drug: excipient in a ratio of approximately 1:1 (*w/w*) and were weighed and placed in aluminum sample containers. After closing the aluminum cover and compressing it with pressure, the cover was placed in the heating cell of the instrument (Shimadzu, DSC-60, Japan). Measurements were performed in the temperature range of 25 °C-300 °C at a heating speed of 10 °C/min under a nitrogen atmosphere.

ODF preparation

ODF was prepared using the solvent casting method. The quantitative compositions of the formulations are listed in Table 1. The ODF preparation steps are illustrated in Figure 1. According to the procedure for the preparation of the polymer solution, film-forming enhancing agents and plasticizers were first added to a measured amount of water, which was heated to 90 °C when using HPMC polymer, and then mixed until a homogeneous solution was obtained. In a separate beaker, solubility-enhancing agents, antioxidants, ethanol, DL, and other excipients were dissolved in a measured volume of water. The mixture was stirred at 1000 rpm for 30 min. The polymer solution was then gradually added to the beaker containing the active ingredient mixture. The resulting mixture containing the active ingredients was stirred using an overhead stirrer (High-Speed Digital, R1042 Dissolver, Ika Eurostar 20) for a total of 30 min, following a stepwise mixing protocol: 10 min at 750 rpm, 10 min at 1000 rpm, and 10 min at 1500 rpm. The bulk wet film was left to degass overnight. Wet film masses were cast using an automated film applicator equipped with a quadruple-layer film applicator (Coatmaster 510, Erichsen). The ODFs were cast at a casting height of 400-1500 µm at a speed of 6 mm/s. Subsequently, the films were dried at room temperature for 24

h and then cut into desired sizes, each containing 5 mg of DL, for further analysis. The prepared films were heat-sealed with polyethylene terephthalate/aluminum sachet foil as the primary packaging.

Characterization of ODFs

ODFs were visually examined for appearance based on the following parameters: homogeneity (absence of insoluble particles and uniform texture), peelability (removability of ODFs from the surface), brittleness, and color alterations. In this respect, following the evaluation of wet mass and films, applicable formulations and casting heights were selected, and further characterization studies were carried out with F17-F20 formulations.

Thickness

The thickness was measured from various regions of the film using a digital micrometer (precision ±0.001 mm Mitutoyo, Japan).

Tensile strength

The TS of the film formulations was measured by attaching a miniature tensile grip accessory to a TA-XT Plus Texture Analyzer (Stable Micro Systems, UK). The distance between the upper and lower handles of the films (2x1 cm) was set to 10 mm. While the upper handle part of the apparatus, whose lower handle part is fixed, moves upwards at a speed of 5 mm/min, the TS is calculated by the device software by dividing the force (N) required to break the film by the cross-sectional area (mm^2).[14]

Table 1. Quantitative composition of formulations for examining drug load and development stable orodispersible film

Ingredients (%)	Formulation code																			
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
Lycoat RS720	18.0	18.0	18.0	20.0	20.0	20.0	20.0	-	20.0	19.25	-	-	-	-	-	-	-	-	-	-
Lycoat RS780	-	-	-	-	-	-	-	-	-	-	-	-	-	5.0	4.0	4.0	5.0	-	-	-
HPMC E15	-	-	-	-	-	-	-	15.0	-	-	12.0	12.0	12.0	10.0	8.0	8.0	10.0	10.0	10.0	9.0
HPMC E5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.0	3.0	3.0
PVP 30LP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.0	4.0
DI	-	-	-	-	-	-	-	-	-	0.3	0.5	0.5	0.5	3.0	2.4	2.4	3.0	3.0	3.0	3.0
Ethanol	-	14.0	14.0	14.0	7.0	7.0	7.0	-	7.0	7.0	7.0	7.0	7.0	7.0	5.6	5.6	7.0	7.0	10.25	10.25
PEG	7.5	7.5	10.0	7.5	-	-	-	-	7.5	7.5	7.5	-	-	7.5	6.0	6.0	7.5	6.5	6.5	7.0
Glycerol	-	-	-	-	7.5	7.5	3.0	5.0	-	-	-	-	-	-	-	-	-	-	-	-
PEG 400	-	-	-	-	-	-	-	-	-	-	-	7.5	7.5	-	-	-	-	-	-	-
Glucidex® IT6	5.0	5.0	5.0	5.0	5.0	3.0	5.0	5.0	5.0	5.0	-	-	-	-	-	-	-	-	-	-
HP-β-CD	-	-	-	-	-	-	-	-	-	-	3.0	3.0	-	5.0	4.0	4.0	-	-	-	-
Pea maltodextrin	-	-	-	-	-	-	-	-	-	-	-	-	3.0	-	-	-	-	-	-	-
Poloxamer 188	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.0	5.0	4.0	3.0
Citric acid	-	-	-	-	-	-	-	-	0.5	0.5	0.2	0.2	0.2	0.2	0.4	0.4	0.2	0.2	0.2	0.2
Ascorbic acid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.5	-	-	-	-	-
Sodium metabisulphite	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.5	0.5	0.5	0.5	0.5
EDTA	-	-	-	-	-	-	-	-	-	-	-	-	-	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Distilled water to	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Assesment remarks																				
Peelability	+/-	+/-	+/-	+/-	-	-	-	+	+/-	-	+	+	+	ND[b]	+	+	+	+	+*	+*
Brittleness	+/-	-	-	-	ND[a]	ND[a]	ND[a]	+	-	+/-	+	+	+	ND[b]	+	+	+/-	+	+*	+*
Homogeneity	+	+	+	+	ND[a]	ND[a]	ND[a]	+	+	-	+	+	+	ND[b]	+/-	+/-	+/-	+	+*	+*

Evaluations obtained from experimental observations: + Desired; +/- Moderate; - Not desired; +*: Best casting solutions.
ND[a]: Not detected because the films could not be removed from the surface, ND[b]: Not detected because the films could not be cast, HPMC: Hydroxypropylmethylcellulose, PVP: Polyvinylpyrrolidone, PEG: Polyethylene Glycol, EDTA: Ethylenediaminetetraacetic acid

Disintegration time

Disintegration times were evaluated using the Petri dish method, and the slide frame method proposed for ODFs in the literature.[15] In the Petri method, a film is placed on the surface of the water in a Petri dish containing 2 mL of distilled water, and the time until the strip disappears completely is recorded. In the slide frame method, films cut in 5x2 cm dimensions were placed on the slide frame. The slide frame was placed on a beaker, and 200 µL of 37 °C distilled water was dropped into the middle of the film using a pipette. The time at which the film dissolved when the first drop fell into the beaker was recorded.

Uniformity of content

DL content was determined by spectrophotometry at 280 nm and was validated according to the International Conference on Harmonisation Q2 (R1) guidelines. The film samples were completely dissolved in 0.1 N hydrochloric acid and diluted to a final concentration 10 µg/mL. Content uniformity was determined by calculating acceptance values (AV) according to the Ph. Eur. 2.9.40.[16]

Statistical analysis

All statistical data were analyzed using Microsoft Excel (Microsoft Office). The Student's *t*-test was used to perform statistical comparisons between two different levels. Results for thickness uniformity results are expressed as mean with relative standard deviation (RSD)%, while mechanical properties and disintegration tests are expressed as mean ± standard deviation (SD).

RESULTS

The preliminary formulations of placebo and DI-containing films and their characteristics are presented in Table 1. The formulation development studies began with the development of orodispersible placebo films (F1) using starch-derived film-forming polymers. Ethanol was added to the F1 formulation to reduce bubble formation. An increase in film brittleness was observed in F2. With the F3 formulation, in which PG amount was increased to reduce brittleness, no improvement in brittleness was achieved, and even increased stickiness was observed. Increasing the amount of PG promoted a significant decrease (p<0.05) in TS. Results of physico-mechanical properties are presented in Figure 2. To support the production of a more cohesive and durable film, the hydroxypropyl pea starch content increased in F4, and an inadequate improvement was observed. Glycerol was tested as a different plasticizer in F5, F6, and F7 with a starch-based film-forming polymer to improve brittleness, and the films could not be removed from the surface. The ODF formulation containing HPMC as a film-forming polymer along with Glycerin in the F8 was easy to remove, non-brittle, and exhibited good mechanical integrity. Placebo F9 films were prepared to evaluate the impact of citric acid on the starch-based films; an increase in brittleness was observed. It was detected that the peelability of the film from the surface became difficult. In F10, the addition of an active ingredient further negatively affects the removability of the film from the surface. The films formed HPMC were flexible, homogenous, and easy to remove from the substrate. F12 and F13 containing PEG 400 showed an improvement in the morphological and mechanical properties of the films as the TS increased. The color of the aqueous casting solutions and films changed to slightly pink. It was intended to contain 3% DI, the amount of HP-β-CD was increased to enhance the water solubility of the active ingredient in the formulation. In F14, due to the presence of an excessive amount of solid mass in the formulation, wetting could not occur, resulting in the formulation could not be cast. To increase the water content and ensure wetting, all excipient ratios except citric acid, as well as DI amount were reduced in F15 and F16. The formulations exhibited high viscosity due to the presence of significant amounts of HP-β-CD, resulting in the entrapment of air bubbles.

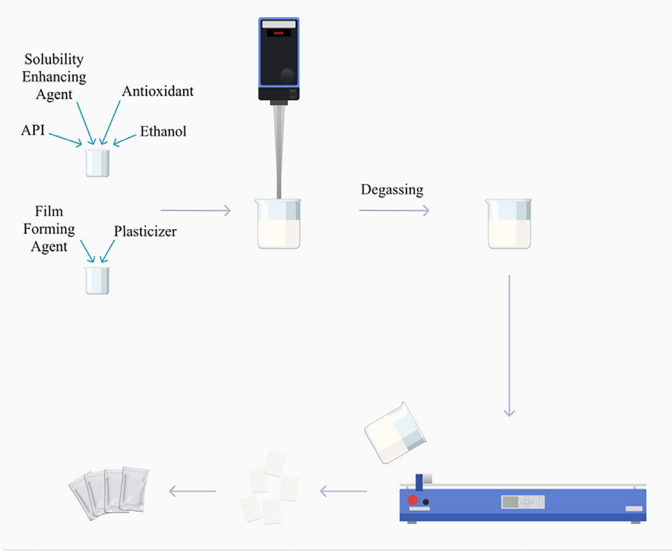

Figure 1. Schematic view of solvent casting procedure of orodispersible film containing DI

DI: Desloratadine

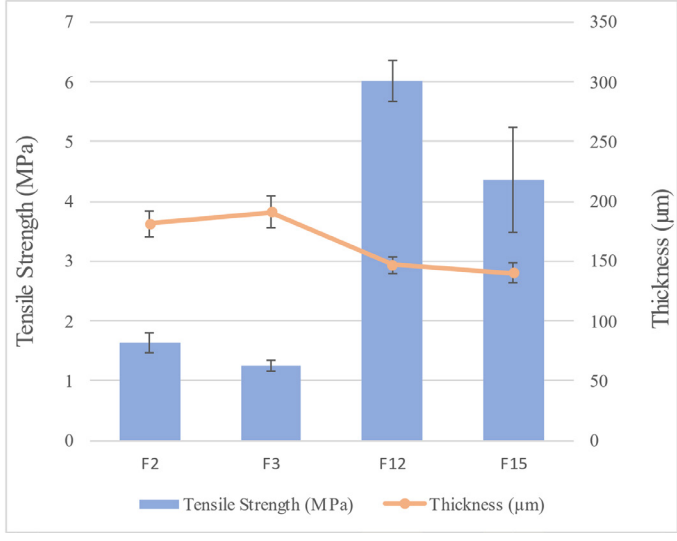

Figure 2. Comparison of TS and dry film thickness characteristics between formulations incorporating HPMC and starch based compositions

HPMC: Hydroxypropylmethylcellulose, TS: Tensile strength

In the preliminary stage, the appropriate antioxidants were investigated by DSC compatibility study. DSC thermograms of DI, antioxidant constituents, and DI: antioxidant in a ratio of 1:1 (*w/w*) are presented in Figure 3. The melting endothermic peak of DI disappeared in the DI: propilgallate binary mixture (Figure 3B). In the DSC thermogram illustrating the 1:1 ascorbic acid mixture, there was a reduction in the peak intensity of the DI, and the peak corresponding to Ascorbic acid disappeared entirely (Figure 3C). To confirm that the formulation containing Ascorbic acid was prepared (F15), it was also observed that the color of DI and ascorbic acid containing casting dispersion changed to light pink (Figure 3E). The influence of casting height on the TS is compared by comparing the disintegration time using the Petri Dish and Slide Frame Method and thickness using F16. These results are shown in Table 2.

Based on the F14 formulation, formulation 17 containing Poloxamer 188 at the same concentration of the film-forming polymer was prepared. It was observed that there was an increase in brittleness and air bubble formation. The particles observed in the wet mass and film surface thickness uniformity (RSD%) were 17.0%. The disintegration time, TS, and thickness measurements of F17-F20 formulations prepared using 400 µm casting height are shown in Table 3. With formulation 18 starch-based polymers excluded, HPMC E5 was added to increase the HPMC ratio in the formulation without further increasing the viscosity to improve the solubility of DI. The amount of particles in the wet mass and on the film surface has decreased significantly. In F19 and F20 formulations with the addition of PVP and Poloxamer, which acts as a film-forming agent and plasticizer, to increase solubility, no particles were observed both in wet mass and homogenous, flexible ODFs were obtained.

DISCUSSION

The preliminary studies of formulation development were conducted to evaluate formulation factors, select the final excipients, determine the process, and choose an appropriate characterization method because no pharmacopeial method has been described and no acceptable limit has been specified.

ODFs typically contain one or a combination of suitable film-forming agents, which constitute a backbone for incorporating drug substances and various excipients.[6,17] A variety of hydrophilic polymers have been extensively investigated in

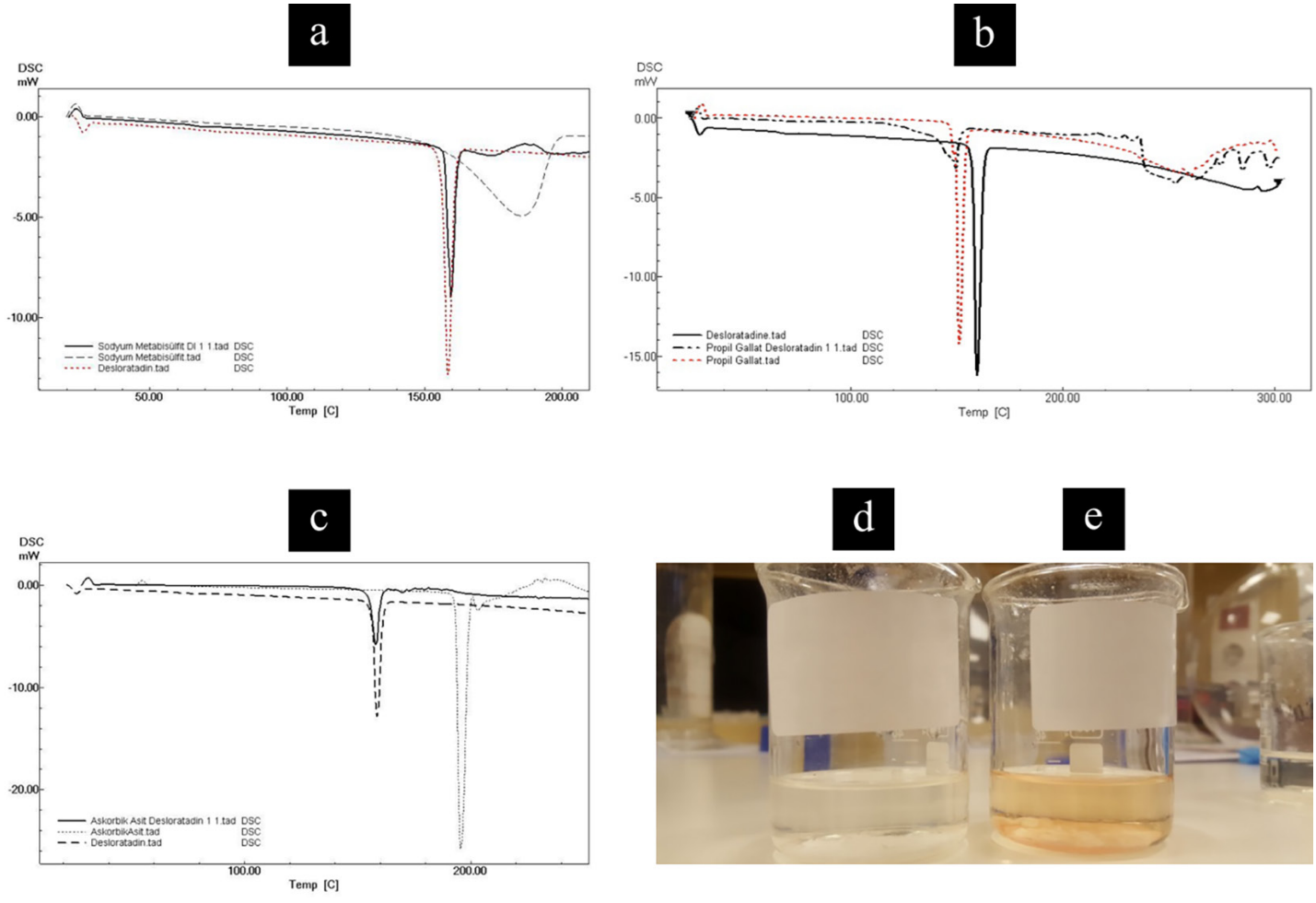

Figure 3. Selected DSC curves of (A) DI, sodium metabisulphite and DI: sodium metabisulphite. (B) DI, propil gallate and DI: propil gallate. (C) DI, ascorbic acid and DI: Ascorbic acid. Wet film formulations containing sodium metabisulfite (D) and ascorbic acid (E) where color change is observed

DI: Desloratadine, DSC: Differential scanning calorimetry

Table 2. Film thicknesses, tensile strengths, and disintegration times measured by the Petri Dish and Slide frame method for prepared orodispersible films with casting heights of 400 µm, 1000 µm and 1500 µm

Formulation code	Casting height (µm)	Dry thickness (µm)	Disintegration time (sec.)		TS (MPa)
			Slide frame	Petri	
F16	400	41.5±8.0	25.3±2.3	31.3±6.1	8.4±0.6
	1000	138.9±8.0	212.3±6.9	380.0±40.0	4.5±0.9
	1500	183.9±8.5	363.0±8.9	483.3±75.1	3.3±1.3

TS: Tensile strength, sec.: Second

Table 3. Characterization of physical and mechanical parameters and disintegration time measured by the sliding frame method for orodispersible films with a casting height of 400 µm

Formulations	Disintegration time (sec)	Thickness (µm)	TS (MPa)	AV
F17	44.3±9.0	68.7±17.0	ND	ND
F18	44.66±3.5	53.9±3.4	10.3±1.7	13.4
F19	44.5±4.5	64.7±4.3	9.1±3.2	6.8
F20	40.5±4.8	56.5±4.6	6.2±3.3	5.0

ND: Not detected, TS: Tensile strength, AV: Acceptance value

the preparation of ODFs, including HPMC; HPC; pregelatinized hydroxypropyl pea starch; PVP and maltodextrin.[17] The different types of HPMC and HPC differ in terms of the degree of substitution and viscosity. It is stated in the literature that appropriate films can be formed by combining different grades of polymers with PVP, HPMC, or starch derivatives.[6,18,19] Although maltodextrin alone can act as film-forming polymers, it has been stated that film properties can be improved by mixing them with other polymers, one of which is modified starches.[6] It was noted that maltodextrin with low dextrose equivalents reduces the brittleness of films.[20] In our study, to improve the mechanical properties of films prepared with Lycoat, such as reducing brittleness and improving removability from the surface, experiments were carried out with the use of Glucidex, different plasticizers, and their ratios, and different film-forming polymer combinations, as shown in Table 1. It was observed that film-forming polymers have a notable effect on mechanical properties. To demonstrate these effects, F2 and F3, containing only Lycoat, F12, containing only HPMC, and F15, containing a combination of Lycoat and HPMC, were selected. As shown in Figure 2, the TS of HPMC-produced films is higher than that of starch-based films. Additionally, when the results obtained from Table 1 in terms of brittleness and film removability were examined, it was found that the major effect in terms of improvement in the mechanical properties of films was obtained with the HPMC polymer. Further studies on HPMC-based films, and the results of formulations of F17-F20 are presented in Table 3. TS values were found to be 1.47%-33.91 MPa in the study evaluating the mechanical properties of commercial ODFs.[21] Our measurement results were within this range, and as the polymer concentrations of HPMC and PVP increased within F19 and F20, flexible films and TS increased as desired; thus, films suitable for handling were obtained. Visser et al.[22] investigated the mechanical properties of polymer films and reported TS values above 2 MPa, with films containing a higher percentage of HPMC exhibiting the greatest TS and being the most preferred.

The results of the investigation of the impact of wet film thickness on TS, disintegration time, and dry thickness show that, in Table 2, the decrease in wet film thickness is associated with an increase in TS and, as expected, a decrease in disintegration time. Since the F16 formulation prepared with a wet film thickness of 400 µm was thin, easy to remove, and flexible with a disintegration time of less than 30s for both methods, a casting height of 400 µm was found appropriate for further studies. Due to the lack of standardized characterization methods for ODFs, the objective of this study was not only to develop DI-containing film formulations but also to assess and compare various characterization techniques. In this context, in addition to evaluating the effect of wet mass thicknesses, different disintegration methods were comparatively evaluated as there is no formal disintegration test for orodispersible films. Disintegration times were evaluated using the Petri dish method and the slide frame method proposed for ODFs in the literature.[1,23] The results are presented in Table 2, and when the Petri dish method was applied, the difference between the disintegration times of the formulations could not be distinguished precisely; therefore, the SD values were found to be higher. In addition, measurement results can vary between individuals. With the Slide Frame method, the endpoint could be easily determined, and the repeatability was high. It is clear from the obtained results that the Slide-frame method is more precise and sensitive than the Petri dish method. An additional advantage of the slide frame method is its simplicity and minimal equipment requirements. The test setup only requires the use of a beaker, slide frame, and small volume of liquid, making it a cost-effective and straightforward technique.[24] However, the slide frame method does not fully correlate with in vivo conditions. Under physiological conditions, the oral film is wetted from both directions, reflecting a more complex and dynamic interaction between the film and saliva. In contrast, this method only involves wetting the film in one direction. In addition, adhesion to the oral mucosa and the force exerted by the tongue are not taken into account.[24, 25] From this point of view, it can be inferred that the disintegration times found with the slide frame method may be longer than physiological conditions, which can effectively simulate the worst-case

scenario. This hypothesis could be further validated through additional studies in the future. The measurement results of the disintegration times of F17-F20 formulations with the Slide Frame method were found to be lower than the 60s (Table 3), and the results obtained were significantly lower than the 180s specified in Ph. Eur. 11.4 for orally disintegrating tablets.[26]

For ODFs, the thickness depends on the wet mass thickness, formulation components, and solid mass content. In the literature, the thickness of 9 commercial preparations was measured, and the results were found to be between 40 and 140 µm.[21] In another study, it was reported that the ideal thickness of buccal films was between 50 and 100 µm.[27] In our study, with the selected formulation content and casting height of 400 µm, homogeneous and suitable films with dry film thicknesses ranging between 50 and 70 µm were obtained (Table 3). Because the thickness uniformity is directly related to the amount of drug in the film, it is important for content uniformity. The RSD% value used in the thickness uniformity evaluation for F19 and F20 was found to be lower than 5%. Another important issue in ensuring content uniformity in ODFs is the homogeneous distribution of the active ingredient in the film. The fact that the film contains particles poses a risk in terms of both content uniformity and mechanical strength. The interaction between the polymer and the crystalline active substance can harden the surface of the film, disrupt its homogeneity, and make it brittle.[28-30] The choice of a film-forming polymer in ODFs is not only important for the mechanical properties and disintegration time but also plays an important role in the dissolution of the drug in the polymer.[31] Studies have shown that some film-forming polymers such as PVP and HPMC increase the solubility of poorly water-soluble drugs by acting as crystallization inhibitors.[32-34] Using these polymers, the crystallization that may occur in the films due to active pharmaceutical ingredients can be reduced or completely prevented during the production and storage of films. It has also been reported in the literature that recrystallization of some active substances, such as Dimenhydrinate, is prevented by the use of maltodextrin and cyclodextrins.[35] Aim of this part of the study was to dissolve Dl in the film to prevent the formation of crystal lumps in ODF. In our previous study, we found that HP-β-CD increased its water solubility by forming a 1:1 stoichiometric complexation with Dl.[36] However, when Dl and HP-β-CD were incorporated into the film formulation, since a very high amount of HP-β-CD was required to form a soluble complex, it was not found suitable for ODF containing Dl. Similarly, in the literature, it was stated that ODFs containing high amounts of CDs negatively affected the mechanical properties.[35] As aimed in this part of our study, Dl could be dissolved in the film at a rate of 3% with the combination of HPMC, PVP, and the surfactant poloxamer P188, and F19 and F20-particle-free homogeneous films were obtained.

In the selection of excipients in addition to their usage purposes, the chemical compatibility between excipients and active ingredients is also critical in the early formulation development stage. Compatibility studies are the first step toward eliminating incompatible excipients.[37] Using DSC as a screening technique, the results showed incompatibility between ascorbic acid and propylgallate, which was also confirmed by further formulation development studies by observing a color change in the bulk formulation containing ascorbic acid (Figure 3E).

The trace amounts of reactive impurities in excipients can cause drug instability. The most common reactive impurities in excipients are peroxides.[38] It is known that peroxides consist of very weak O-O bond and can readily form hydroxyl and alkoxy radicals. Hydroperoxides are commonly formed by the degradation of excipients such as PG and PVP.[38] Formaldehyde and formic acid formed by oxidative degradation are involved in the N-methylation and N-formylation of amine-containing active drug ingredients.[38] The chemical reactions of reactive impurities of formaldehyde and formic acid, majorly formed by the degradation of PG, particularly with amine-containing active drug ingredients, have been investigated extensively.[39-42] Formic acid is often responsible for the formation of N-formyl impurities in active drug ingredients containing primary and secondary amino groups.[39,42,43] It is known that the main degradation product of Dl is N-formyl-Dl.[44] Very small amounts of the degradation product N-formyl desloratadine were found to cause discoloration of Dl.[45] Since an orange-yellow color was observed in the PG-containing formulations and was attributed to oxidation triggering by the mentioned mechanism, PG was excluded from the study. Among the plasticizers tested, PG, one of the solvents in which Dl dissolves well,[46] was found suitable in terms of plasticizing effect, considering the sensitivity of the active substance to oxidation and the need to increase its solubility to increase the amount of drug loading in the film. In the early stages of drug development, understanding the type and degree of degradation of a drug candidate is crucial. As metals found in excipients can catalyze oxidation in drugs at residual levels[38,] in addition to sodium metabisulfite, which is used as an antioxidant, EDTA, which acts as an antioxidant synergist,[47] was also added to the formulations.

CONCLUSION

In this study, it was demonstrated that Dl-containing ODF was successfully developed by taking into account the drug loading and chemical stability of the active substance in combination with selected excipients and process parameters. As a result of preliminary studies, thin, homogeneous, flexible, fast disintegrating (40s), particle-free films were developed with F20, which was found suitable for further studies. The fact that the formulations met the criteria for AV below 15 confirmed that the active ingredient was distributed homogeneously. Based on the obtained promising results, further optimization studies were conducted to develop a generic ODF product of Dl for the effective treatment of allergy and to improve patient compliance.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: Ö.Ç., Z.Ş.T., Design: Ö.Ç., Z.Ş.T., Data Collection or Processing: Ö.Ç., Z.Ş.T., F.N.T.D., Analysis or Interpretation: Ö.Ç., Z.Ş.T., F.N.T.D., Literature Search: Ö.Ç., Writing: Ö.Ç., Z.Ş.T., F.N.T.D.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: This study was supported by the Gazi University Scientific Research Projects Coordination Unit (grant no.: 02/2018-02).

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