

Evaluation and characterization of orally disintegrating films loaded donepezil hydrochloride for Alzheimer's disease

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Received: 15 November 2022 / Revised: 14 December 2022 / Accepted: 14 December 2022

ABSTRACT: Nowadays, innovative and more effective drug dosage forms continue to be researched and developed compared to traditional drug dosage forms. The importance of orally disintegrating films (ODFs) in current studies and advancements cannot be overstated. This study aims to create the optimum ODF formulations using pullulan and lycoat with donepezil hydrochloride (donepezil HCl). Plasticizers such as polyethylene glycol 400 (PEG-400) and glycerine were used to form flexible films. In the characterization studies of the films produced by the solvent casting technique: determination of morphology, determination of folding, determination of disintegration time, determination of thickness, determination of swelling, determination of pH, determination of mass uniformity, determination of *In vitro* release, and determination of content uniformity studies were carried out. According to the results obtained, the non-brittle, smooth-surfaced films were disintegrated in the mouth in an average of 35 seconds. Since the 10th minute, more than 85% of the active pharmaceutical ingredient (API) has been revealed. These values suggested that the pullulan polymer showed better film-forming capacity when used with lycoat polymer. Ultraviolet (UV)-visible spectrum studies were carried out to validate donepezil HCl. Thanks to the ODFs containing donepezil HCl, an effective and safe, innovative clinical use has been achieved in the treatment of diseases such as dementia and Alzheimer, which are characterized by a decrease in daily life activities and atrophy in cognitive abilities.

KEYWORDS: Orally disintegrating film; donepezil hydrochloride; pullulan; lycoat.

1. INTRODUCTION

Donepezil HCl is a reversible acetylcholinesterase (AChE) inhibitor that was first introduced to the market in 1997. It is used to treatment of mild to moderate dementia-related Alzheimer's disease. Donepezil HCl provides acetylcholine transmission in the brain by blocking the activity of the enzyme responsible for the breakdown of acetylcholine [1]. Alzheimer is a disease that causes mood changes in patients, prevents correct thinking and perception, prevents them from doing their daily activities, and provides atrophy of cognitive and mental abilities [2]. In recent years, it has been seen quite frequently in the elderly parts of modern societies. It is a disease caused by a deficiency of high levels of acetylcholine in the cerebral cortex and hippocampus of the brain [3]. Donepezil HCl has demonstrated significant efficacy in maintaining cognitive activities and treating symptoms of Alzheimer's and dementia compared to placebo at dose of 5 mg or 10 mg once daily. The optimum dose of donepezil HCl to be used in clinical should be decided for each patient to prevent the side effects of the drug and to ensure maximum effectiveness [4,5]

In the late 1970s, orally disintegrating tablets (ODTs) were developed that can be used without water in geriatrics, pediatrics, non-adherent patients, who have swallowing difficulties, and nausea patients due to the difficulty of traditional drug administration routes [6]. Later, it was observed that; these patients may be at risk of suffocation. At the same time, ODTs can become brittle in the mouth and disperse to different points. ODFs, which are a new dosage form have been designed to tolerate such undesirable effects. ODFs prepared with hydrophilic polymers are placed on the tongue, they come into contact with saliva and disperse quickly without the need for water, revealing the API and exerting the systemic effect [7].

How to cite this article: Özen M.İ., Kerimoğlu O., Evaluation and Characterization of Orally Disintegrating Films Loaded Donepezil Hydrochloride for Alzheimer's Disease. J Res Pharm. 2023; 27(2): 893-902.

ODFs have a flexible structure with high bioavailability and rapid onset of action compared to traditional drug delivery [8]. This study aimed to design and evaluate ODF formulations, especially by using pullulan and lycoat polymers.

2. RESULTS AND DISCUSSION

In this study, a total of 12 main formulations containing donepezil HCl were studied. Among these films, which were prepared by solvent casting method, three films with the best morphological appearance were selected, taking into account the features such as being easy to separate from the Petri dish, being flexible, and having a smooth surface. The characterization studies were carried out for each of them. The films to be used for characterization studies were cut in 2x2 cm² dimensions, with n = 3 parallels outputs from each petri dish.

2.1. Determination of morphology

When the optimum formulations were examined morphologically, it was seen that the F-9 formulation produced a clearer image in liquid and solid form than the F-5 formulation. This is because, unlike the F-5 formulation, cross-linked povidone (cross-PVP) was used in the F-9 formulation. Because this agent provides clarity and consistency to the formulation. At the same time, cross-PVP has a good binder and film-forming properties [9]. We can explain that the reason why the F-9 formulation is more flexible is due to the presence of cross-PVP in the formulation. The F-12 formulation is even more transparent and more fluid than the others. In this formulation, the amount of Metolose 90 SH-100 was used less than in other optimum formulations. Thanks to the cross-PVP it contains, the F-12 formulation has a clear appearance in liquid and solid form.

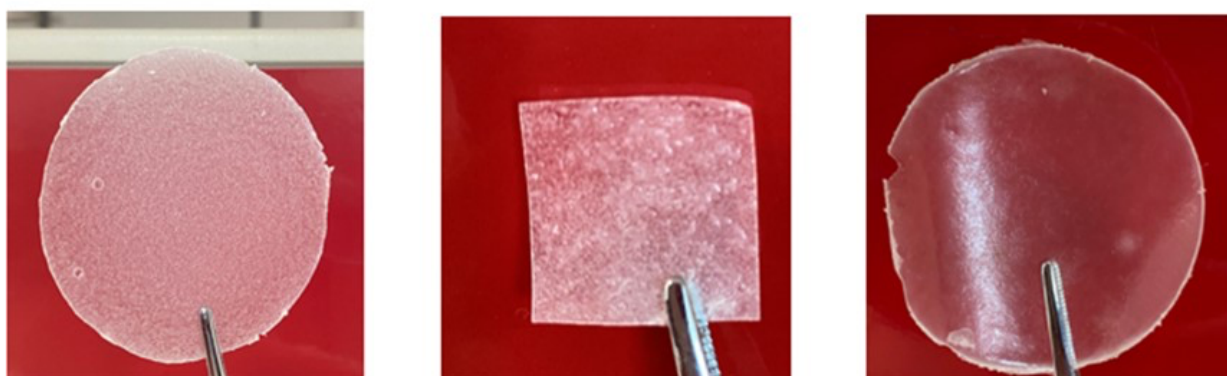


Figure 1. Optimum morphological formulations, from left to right of the page; F-5, F-9, F-12

2.2. Determination of disintegration time

The determination of the disintegration time for the F-5, F-9, and F-12 formulations in the experiments performed as n = 6 parallels for each formulation. According to the results, it was observed that the F-5 formulation dispersed in 90.33 ± 2.42 seconds, the F-9 formulation dispersed in 35 ± 2.36 seconds, and the F-12 formulation dispersed in 43.2 ± 3.11 seconds. The F-9 and the F-12 formulations are better dispersed. It is thought that the main reason for this is that, unlike the F-5 formulation, sodium starch glycolate (Na-starch glycolate) and cross-PVP were added to the F-9 formulation, and cross-PVP was added to the F-12 formulation. Because these excipients are superdisintegrants [10]. Cross-PVP can swell without gelling. This allows the films to swell more when they come in contact with saliva, and thus to disperse and dissolve faster [11]. Likewise, Na-starch glycolate has a high water-holding capacity. Therefore, it swells quickly and breaks down easily [12].

2.3. Determination of folding

The folding endurance of the F-5 formulation was found to be 413.33 ± 8.32 , the F-9 formulation was found to be 208 ± 4.58 , and the F-12 formulation was found to be 436.33 ± 4.93 . Accordingly, the plasticizer properties of both three formulations were evaluated as good.

2.4. Determination of swelling

In the experiments carried out in $n = 3$ parallels for each formulation, the swelling of F-5 was found to be $83.04\% \pm 1.82$, the swelling of F-9 was found to be $90.54\% \pm 3.95$, and the swelling of F-12 was found to be $109.32\% \pm 0.81$. Accordingly, it was observed that the F-9 formulation swelled more due to the Na-starch glycolate and cross-PVP content. Likewise, due to the addition of cross-PVP to the F-12 formulation, it swelled more [12].

2.5. Determination of thickness

In the experiments carried out in $n = 6$ parallels for each formulation, it was observed that the F-5 formulation had a thickness of 0.225 ± 0.009 mm, the F-9 formulation had a thickness of 0.268 ± 0.015 mm, and the F-12 formulation had a thickness of 0.198 ± 0.013 mm.

2.6. Determination of mass uniformity

It was observed that the F-5 formulation weighed 107.7 ± 4.29 mg. It was observed that the F-9 formulation weighed 122.6 ± 3.16 mg and the F-12 formulation weighed 99.2 ± 4.47 mg.

2.7. Determination of pH value

In the experiments carried out in $n = 3$ parallels for each formulation, the pH of the F-5 formulation was found to be 5.68 ± 0.04 , the pH of the F-9 formulation was found to be 6.25 ± 0.09 , and the pH of the F-12 formulation was found to be 5.72 ± 0.02 . Values were determined in the pH range compatible with the intraoral pH [13].

2.8. In vitro release study

In vitro release values of the F-5, F-9, and F-12 formulations in the experiments performed as $n = 3$ parallels for each formulation were shown in figure 2. While the total release content was $98.76\% \pm 1.07$ for the F-5 formulation, it was found to be $99.53\% \pm 0.07$ for the F-9 formulation and $99.52\% \pm 0.12$ for the F-12 formulation at the 30th minute.

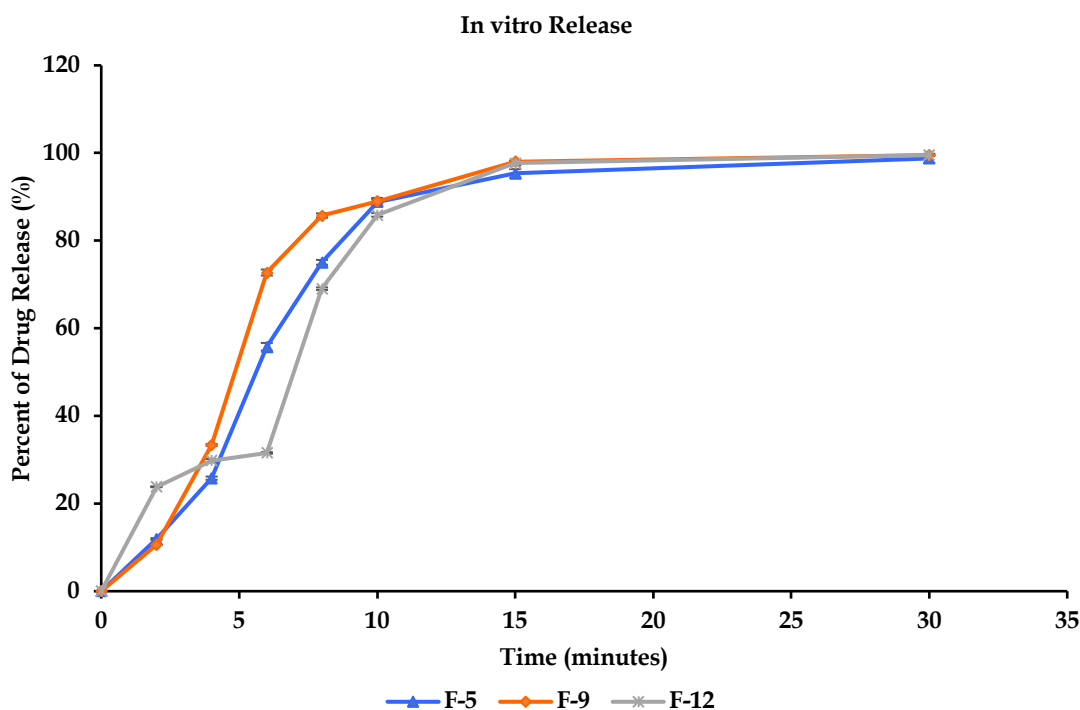


Figure 2. *In vitro* release of each formulation ($n = 3, \pm$ SD)

2.9. Content uniformity

Content uniformity (%) of the F-5, F-9, and F-12 formulations in the experiments performed as $n = 6$ parallels for each formulation were shown in the graph. According to the data obtained: the dissolution medium can dissolve more than three times the dosage amount of ODFs. Depending on the saturation of the solution, the suitability of the sink condition can be expressed as $(\phi) < 1/3$ [14]. Content uniformity was found to be 4.96 ± 0.05 for the F-5, 4.97 ± 0.04 for the F-9, and 4.93 ± 0.04 for the F-12.

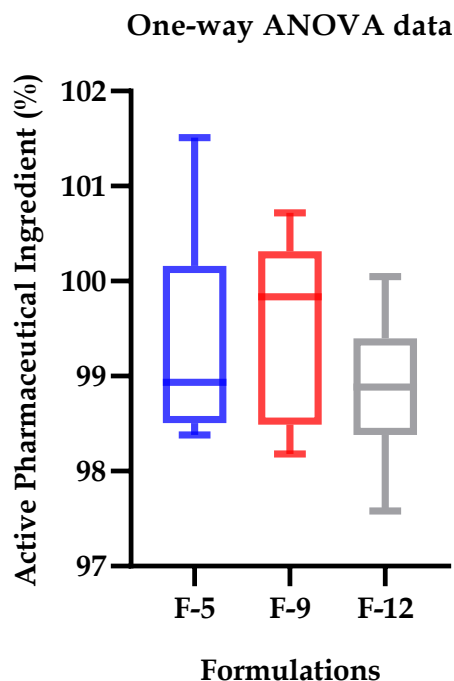


Figure 3. API (%) of each formulation ($n = 6$)

2.10. Validation of analysis method

According to the validation results: a linear equation was obtained by analyzing the values of the solutions of different concentrations prepared with donepezil HCl with a UV-Visible spectrophotometer. It has been observed that the equation formed due to the linear relationship between concentration and absorbance follows Beer's Lambert law [15].

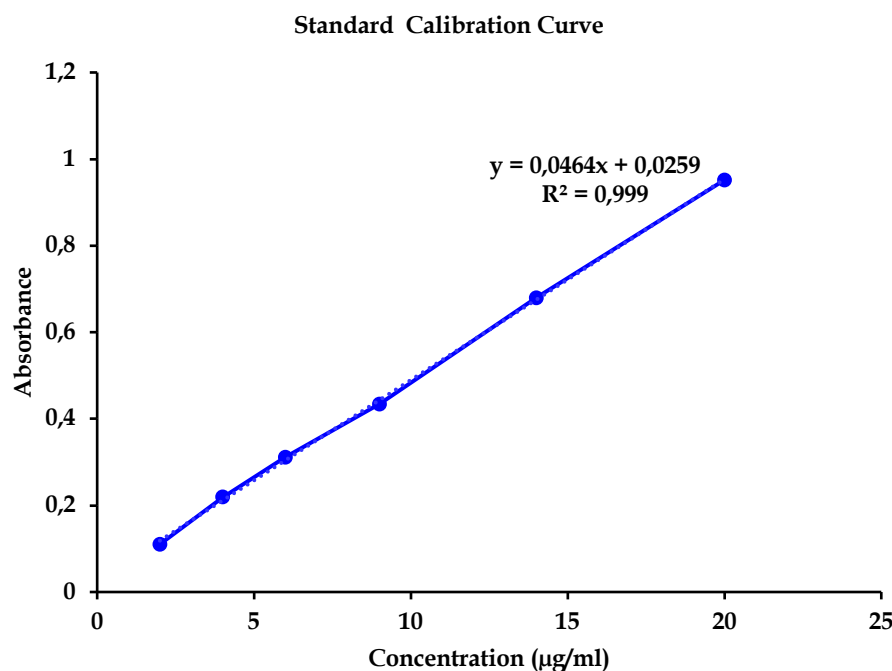


Figure 4. Standard calibration curve of donepezil HCl (n = 3)

2.11. Drug excipients interference in analysis method

UV-visible spectrophotometer was used to analyze the pre-formulations at various times (minutes of 5th and 10th). It was found that donepezil HCl and other excipients did not interfere with each other. The F-5 formulation was 0.047 the F-9 formulation was 0.022, and the F-12 formulation was 0.041. This study was conducted for three parallels for each time interval.

2.12. Statistical analysis

According to ANOVA, the p-value was found to be 0.49 for content uniformity and the p-value was found to be 0.94 for *In vitro* release, which means that deviation from the null hypothesis, is not statistically significant, and the null hypothesis is not rejected. Likewise, pH values, disintegration time values, folding values, swelling values, thickness values, and mass values do not differ significantly according to the Brown-Forsythe test.

3. CONCLUSION

In this study, unlike other ODFs containing donepezil HCl, ODF formulations were designed by using pullulan and lycoat polymers together. The combination of pullulan and lycoat polymers led to the development of novel, efficient, and unique ODF formulations. It has been observed that the ODFs containing pullulan and lycoat disperse in the mouth within seconds and release the API within minutes. These optimal ODF formulations promise a glimmer of hope in clinical usage, especially in patients with Alzheimer's and dementia, for reasons such as being able to be used without requiring water and not causing the risk of suffocation. The results of this study can be compared with similar studies and addressed more comprehensively and improved.

4. MATERIALS AND METHODS

4.1. Materials

Donepezil HCl, Deva Pharmaceuticals, Türkiye; Lycoat® RS 720 (E002R-E003R), Roquette, France; Pullulan, USP-NF Hayashibara NAGASE, Japan; HPMC, Metolose® 90 SH 10.000, Metolose® 90 SH 4.000 Metolose® 90 SH 400, Metolose® 90 SH 100, and Methocel™ K-15, Shin-Etsu Chemical Co. Ltd., Japan; PEG-400, ABCR GmbH & Co. KG, Germany; Na-starch glycolate, Bilim Pharmaceuticals Co. Ltd., Türkiye; Avicel® PH-101, NF FMC BioPolymer, USA; Cross-PVP, BASF Aktiengesellschaft, Germany; Sodium carboxymethyl

cellulose (Na-CMC), Santa Farma Pharmaceutical Co. Ltd., Türkiye; Glycerine, Sigma Aldrich Biochemic. GmbH, Germany; Propylene glycol, Tekkim Chemical Co. Ltd., Türkiye. All excipients used were of analytical quality.

4.2. Methods

4.2.1 Preparation of orally disintegrating films

First, 12 donepezil HCl-free pre-formulation studies were completed. According to the results obtained from pre-formulation morphology studies: F-5, F-9, and F-12 formulations were selected as the optimum formulations. 5 mg of donepezil HCl was added to these formulations for characterization studies of ODFs. The ODFs containing donepezil HCl were prepared by the solvent casting method using pullulan and lycoat as a film-forming polymer. According to this method; hydrophilic polymers are dissolved in distilled water and the API along with other excipients was dissolved in another distilled water, then both of the solutions are mixed and stirred with a magnetic stirrer. Finally, cast into the petri dishes and dried [16,17,18]. In the formulations shown in the table, all excipients except distilled water were added in grams. Distilled water was added to 15 ml for each formulation.

Table 1. Formulations of ODF (F: Formulation, L: Lycoat, P: Pullulan, M: Metolose, M K-15: Methocel K-15, A 101: Avicel 101, Na SG: Na-starch glycolate, G: Glycerine PG: Polyethylene glycol)

F	L	P	HPMC	M 100	M 4.000	M 100.000	M K-15	Na CMC	A 101	Cross PVP	Na SG	PEG 400	G	PG
1	0.20	0.10	0.20	-	-	-	-	-	-	0.05	0.10	0.30	-	-
2	0.20	0.10	0.20	-	-	-	-	-	0.10	-	0.10	0.30	-	-
3	0.20	0.15	0.10	-	-	-	-	-	0.10	-	0.10	0.30	0.15	-
4	0.20	0.10	-	-	-	-	0.10	-	0.10	-	0.05	0.20	0.10	-
5	0.20	0.10	-	0.20	-	-	-	0.10	0.10	-	-	0.30	0.10	-
6	0.20	0.10	-	-	0.20	-	-	-	-	0.05	0.05	0.25	0.10	-
7	0.20	0.10	-	-	-	0.10	-	-	0.10	0.05	0.05	0.30	0.10	-
8	0.20	0.10	-	0.20	-	-	-	0.10	0.10	-	0.10	0.10	0.10	0.10
9	0.20	0.10	-	0.20	-	-	-	-	0.10	0.05	0.05	0.30	0.10	-

10	0.20	0.10	-	0.20	-	-	-	0.10	0.10	0.10	-	0.30	0.10	-
11	0.20	0.10	-	-	0.20	-	-	0.10	0.10	0.05	0.05	0.10	0.10	0.10
12	0.20	0.10	-	0.10	-	-	-	0.05	-	0.05	-	0.30	0.10	-

4.2.2. Determination of pH value

The optimum pH range for the oral cavity is between 5.8 and 7.4. If the pH of the ODF is lower than 5.5, it may irritate the mouth [19]. Each of the 2x2 cm² cut films was transferred to beakers (n = 3). After adding 5 ml of the distilled water and waiting for 30 minutes, pH values were measured with a pH meter [20].

4.2.3. Determination of disintegration time

Disintegration time was determined by the petri dish method. Each of the 2x2 cm² films were transferred to petri dishes and 5 ml of phosphate buffer solution (pH 7.4) was added to them (n = 6). The time when the films started to disintegrate was recorded with the help of a chronometer [21].

4.2.4. Determination of folding

The folding endurance value is calculated after testing three ODF (size of 2x2cm²) samples. ODFs were folded several times in the middle with the help of the hand. This process continued until the films ruptured [22].

4.2.5. Determination of swelling

Each film has been pre-weighed on an electronic balance. Then, it was transferred to petri dishes containing phosphate buffer solution. The weight of the film was increased until a maximum swelling weight was observed. The swelling films were transferred to the watch glass and weighed again on an electronic balance. The swelling determination was calculated using the following formula [23].

$$\%S = (W_t - W_0) / W_0 \times 100$$

%S: Swelling percentage

W_t: Swelling weight of the film after t time

W₀: Initial (dry) weight of the film

4.2.6. Determination of thickness

This test was performed by cutting the ODFs of size 2x2 cm². Their thickness was measured by a caliper (electronic micrometer) from the five separate points (from the center and four different corners). Their averages were taken as a basis [24].

4.2.7. Mass uniformity

This test was performed by cutting the ODFs of size 2x2 cm². It was conducted for 7 parallels for each formulation. The average weight is determined by weighing each one separately on an electronic balance then weight variation was observed [25].

4.2.8. In vitro release study

This test was performed by cutting the ODFs of size 2x2 cm². The film was put in 100 ml of phosphate buffer solution in the beaker, which at placed in a shaking water bath fixed at 37 ± 0.5 °C. One ml sample was withdrawn from the dissolution medium at different time intervals (2, 4, 6, 8, 10, 15, and 30 min), and the same amount of fresh dissolution medium was added to maintain sink conditions. The UV-visible spectrophotometer was used to examine the samples at 229 nm. The *In vitro* release test was conducted for three parallels and protected from light and heat during the studies. *In vitro* release values were calculated with the aid of the predetermined donepezil HCl standard calibration curve equation [26, 27].

4.2.9. Content uniformity

This test was performed by cutting the ODFs of size 2x2 cm². The film was put with 100 ml of phosphate buffer solution in a beaker. Then it was placed for 30 minutes in the shaking water bath. After 30 minutes, 1 ml of the sample from the beaker was transferred to the volumetric flask, and dilutions were made. Absorbance values were found by using a UV-visible spectrophotometer. The standard calibration curve equation for donepezil HCl was used to calculate the content uniformity by taking the average of the observed values (n = 6) [28]. According to European Pharmacopeia (EP), standards for content uniformity of solid single-dose dosages have been considered. The content of API in films containing donepezil HCl should be in the range of 85-115% [29].

4.2.10. Preparation of buffer

The phosphate buffer solution (pH 7.4) was prepared according to the EP; First, 0.2 M potassium dihydrogen phosphate was added to 250 ml distilled water. It was mixed until dissolved with a magnetic stirrer. Then, 0.1 M sodium hydroxide was added to 393.4 ml distilled water and mixed in the same way with the magnetic stirrer. Finally, the second solution was added to the first solution and measured with a pH meter, and the pH was fixed at 7.4 [30].

4.2.11. Validation of analysis method

Validation studies were carried out to show that the method used in the analysis of the API is accurate and reproducible under certain conditions. For this; linearity, precision, accuracy, specificity, and stability parameters were examined [31]. First, 10 mg of donepezil HCl was weighed on an electronic balance. Then it was completed to 100 ml with phosphate buffer solution after being API dissolved within some amount of the buffer solution in an ultrasonic bath. Then, dilutions were prepared from this stock solution at concentrations of 2 µg/ml, 4 µg/ml, 6 µg/ml, 9 µg/ml, 14 µg/ml, and 20 µg/ml. Measurements were observed with a UV-visible spectrophotometer at a wavelength of 229 nm (n = 3) to see the wavelength of the maximum absorbance (λ_{\max}) of the solutions prepared in the phosphate buffer solution (blank solution). Linear equation and R² value were calculated with the help of the values found to be, and the standard calibration curve was obtained [32].

4.2.12. Statistical analysis

All analytical values were presented as mean ± standard deviation. GraphPad® software was used to analyze the data found. One-way ANOVA test and Brown-Forsythe test were used while analyzing [33].

Acknowledgments: Authors are thankful to Ali Raif Pharmaceutical Industry Co., Ltd. for supplying pullulan and lycoat. The authors are also thankful to Prof. Dr. Timuçin Uğurlu for supplying other excipients.

Author contributions: Concept - O.K., M.İ.Ö.; Design - O.K., M.İ.Ö.; Supervision - O.K.; Resources - O.K., M.İ.Ö.; Materials - O.K.; Data Collection and/or Processing - M.İ.Ö.; Analysis and/or Interpretation - M.İ.Ö.; Literature Search - M.İ.Ö.; Writing - M.İ.Ö.; Critical Reviews - O.K., M.İ.Ö.

Conflict of interest statement: The authors declare that there are no conflicts of interest.

REFERENCES

- [1] Sutthapitaksakul L, Dass CR, Sriamornsak P. Donepezil – An updated review of challenges in dosage form design. *Journal of Drug Delivery Science and Technology*. 2021; 63: 102549. <https://doi.org/10.1016/j.jddst.2021.102549>
- [2] Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev*. 2018; 6: 1-29. <https://doi.org/10.1002/14651858.CD001190.pub3>
- [3] Sugimoto H. Donepezil hydrochloride: a treatment drug for Alzheimer's disease. *The Chemical Record*. 2001; 1(1): 63-73. [https://doi.org/10.1002/1528-0691\(2001\)1:1<63::AID-TCR9>3.0.CO;2-I](https://doi.org/10.1002/1528-0691(2001)1:1<63::AID-TCR9>3.0.CO;2-I)
- [4] Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, Pratt RD. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology*. 2003; 61(4): 479-486. <https://doi.org/10.1212/01.WNL.0000078943.50032.FC>
- [5] Whitehead A, Perdomo C, Pratt RD, Birks J, Wilcock GK, Evans JG. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials. *International Journal of Geriatric Psychiatry*. 2004; 19(7): 624-633. <https://doi.org/10.1002/gps.1133>

- [6] Nagaraju T, Gowthami R, Rajashekar M, Sandeep S, Mallesham M, Sathish D, Shravan Kumar Y. Comprehensive review on oral disintegrating films. *Current Drug Delivery*. 2013; 10(1): 96-108. <https://doi.org/10.2174/1567201811310010016>
- [7] Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films: a modern expansion in drug delivery system. *Saudi Pharmaceutical Journal*. 2016; 24(5): 537-546. <https://doi.org/10.1016/j.jsps.2015.02.024>
- [8] Lee Y, Kim K, Kim M, Choi DH, Jeong SH. Orally disintegrating films focusing on formulation, manufacturing process, and characterization. *Journal of Pharmaceutical Investigation*. 2017; 47(3): 183-201. <https://doi.org/10.1007/s40005-017-0311-2>
- [9] Sumaiyah S, Mentari J, Suryanto S. The effect of crospovidone on the dissolution profile of amlodipine besylate from fast orally dissolving film. *Macedonian Journal of Medical Sciences*. 2019; 7(22): 3811-3815. <https://doi.org/10.3889/oamjms.2019.510>
- [10] Tang ESK, Liew CV, Er DZL, Liu X, Wigmore AJ, Heng PWS. Study of coat quality of tablets coated by an on-line supercell coater. *AAPS PharmSciTech*. 2007; 8(3): E92-E98. <https://doi.org/10.1208/pt0803063>
- [11] Hiremath P, Nuguru K, Agrahari V. Chapter 8 - Material Attributes and Their Impact on Wet Granulation Process Performance. In: Narang AS, Badawy SIF. (Eds). *Handbook of Pharmaceutical Wet Granulation*. Academic Press, Cambridge, 2019, pp. 263-315. <https://doi.org/10.1016/B978-0-12-810460-6.00012-9>
- [12] Parfati N, Rani KC, Charles N, Geovany V. Preparation and evaluation of atenolol- β -cyclodextrin orally disintegrating tablets using co-process crospovidone-sodium starch glycolate. *International Journal of Applied Pharmaceutics*. 2018; 10(5): 190-194. <https://doi.org/10.22159/ijap.2018v10i5.27982>
- [13] Choi JE, Loke C, Waddell JN, Lyons KM, Kieser JA, Farella M. Continuous measurement of intra-oral pH and temperature: development, validation of an appliance and a pilot study. *Journal of Oral Rehabilitation*. 2015; 42(8): 563-570. <https://doi.org/10.1111/joor.12294>
- [14] Liu P, De Wulf O, Laru J, Heikkilä T, van Veen B, Kiesvaara J, Hirvonen J, Peltonen L, Laaksonen T. Dissolution studies of poorly soluble drug nanosuspensions in non-sink conditions. *AAPS PharmSciTech*. 2013; 14(2): 748-756. <https://doi.org/10.1208/s12249-013-9960-2>
- [15] Mayerhöfer TG, Popp J. Beer's Law - Why absorbance depends (almost) linearly on concentration. *Chemphyschem: A European Journal of Chemical Physics and Physical Chemistry*. 2019; 20(4): 511-515. <https://doi.org/10.1002/cphc.201801073>
- [16] Wang LF, Rhim JW, Hong SI. Preparation of poly (lactide)/poly (butylene adipate-co-terephthalate) blend films using a solvent casting method and their food packaging application. *LWT - Food Science and Technology*. 2016; 68: 454-461. <https://doi.org/10.1016/j.lwt.2015.12.062>
- [17] Preis M, Breikreutz J, Sandler N. Perspective: concepts of printing technologies for oral film formulations. *International Journal of Pharmaceutics*. 2015; 494(2): 578-584. <https://doi.org/10.1016/j.ijpharm.2015.02.032>
- [18] Gökay Y. Master's Thesis. Preparation and evaluation of orally dispersing films containing verapamil hydrochloride. Department of Pharmaceutical Technology, Faculty of Pharmacy, Marmara University, Haydarpaşa, İstanbul, Türkiye, 2020.
- [19] Pechová V, Gajdziok J, Muselík J, Vetchý D. Development of orodispersible films containing benzydamine hydrochloride using a modified solvent casting method. *AAPS PharmSciTech*. 2018; 19(6): 2509-2518. <https://doi.org/10.1208/s12249-018-1088-y>
- [20] Abouhoussein D, El Nabarawi MA, Shalaby SH, El-Bary AA. Cetylpyridinium chloride chitosan blended mucoadhesive buccal films for treatment of pediatric oral diseases. *Journal of Drug Delivery Science and Technology*. 2020; 57: 101676. <https://doi.org/10.1016/j.jddst.2020.101676>
- [21] Zhang L, Aloia M, Pielecha-Safira B, Lin H, Rajai PM, Kunnath K, Davé RN. Impact of superdisintegrants and film thickness on disintegration time of strip films loaded with poorly water-soluble drug microparticles. *Journal of Pharmaceutical Sciences*. 2018; 107(8): 2107-2118. <https://doi.org/10.1016/j.xphs.2018.04.006>
- [22] Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: a new approach to oral drug delivery system. *International Journal of Pharmaceutical Investigation*. 2013; 3(2), 67-76. <https://doi.org/10.4103/2230-973X.114897>
- [23] Karki S, Kim H, Na SJ, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. *Asian Journal of Pharmaceutical Sciences*. 2016; 11(5): 559-574. <https://doi.org/10.1016/j.ajps.2016.05.004>
- [24] Garsuch V, Breikreutz J. Comparative investigations on different polymers for the preparation of fast-dissolving oral films. *Journal of Pharmacy and Pharmacology*. 2010; 62(4): 539-545. <https://doi.org/10.1211/jpp.62.04.0018>
- [25] Sultana F, Arafat M, Pathan SI. Preparation and evaluation of fast dissolving oral thin film of caffeine. *International Journal of Pharmacy and Biological Sciences*. 2013; 3(1): 153-161.

- [26] Jelvehgari M, Montazam SH, Soltani S, Mohammadi R, Azar K, Montazam SA. Fast dissolving oral thin film drug delivery systems consist of ergotamine tartrate and caffeine anhydrous. *Pharmaceutical Sciences*. 2015; 21(2): 102-110. <https://doi.org/10.15171/PS.2015.24>
- [27] Deepthi A, Reddy BV, Navaneetha K. Formulation and evaluation of fast dissolving oral films of zolmitriptan. *American Journal of Advanced Drug Delivery*. 2014; (2): 153-163.
- [28] Nafee NA, Boraie NA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. *Acta Pharmaceutica (Zagreb)*. 2003; 53(3): 199-212.
- [29] European Pharmacopoeia, 2.9.6. Uniformity of Content of Single-Dose Preparations, seventh ed., France, Council of Europe, 2011.
- [30] European Pharmacopoeia, 4.1.3. Buffer Solutions, seventh ed., France, Council of Europe, 2011.
- [31] Kumari B, Khansili A. Analytical method development and validation of UV-visible spectrophotometric method for the estimation of vildagliptin in gastric medium. *Drug Research (Stuttgart)*. 2020; 70(9): 417-423. <https://doi.org/10.1055/a-1217-0296>
- [32] Koeber R, Klunemann HH, Waimer R, Koestlbacher A, Wittmann M, Brandl R, Doerfelt A, Jahner T, Melchner D, Haen E. Implementation of a cost-effective HPLC/UV-approach for medical routine quantification of donepezil in human serum. *Journal of Chromatography B*. 2012; 881-882: 1-11. <https://doi.org/10.1016/j.jchromb.2011.10.027>
- [33] Sow MT. Using ANOVA to examine the relationship between safety & security and human development. *Journal of International Business and Economics*. 2014; 2(4): 101-106. <https://doi.org/10.15640/jibe.v2n4a6>

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