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Original Article

Design, Optimization, and *in vitro* Evaluation of Orally Disintegrating Tablets Containing Amlodipine Besylate

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ABSTRACT

Background: In this study, it was aimed to prepare orally disintegrating tablet formulations of amlodipine besylate by applying the experimental design. **Materials and Methods:** A face-centered, central composite 3^2 full factorial design was applied to evaluate the effects of filler ratio (MAN: MCC; X_1) and super disintegrant percentage (SSG; X_2) on the critical tablet characteristics such as tensile strength (Y_1), disintegration time (Y_2) and dissolution rate (5th min) (Y_3). **Results:** The Quadratic model showed good predictability ($p<0.0001$) on tablet tensile strength and the linear model was found to be suitable for disintegration time and dissolution time profiles ($p<0.001$ and $p>0.05$ respectively). In addition to the compendial quality control tests for tablet formulations, a texture analyzer with the tablet disintegration rig fixture was also used for the disintegration test and onset of disintegration (s), end of disintegration (s), disintegration rate (mm/s), duration of swelling (s), swelling distance (mm), residual height (mm) values were obtained. **Conclusion:** It was determined that F9, with the highest MAN: MCC (75:25) and SSG (10%) ratios, met all pharmacopeia standards and gave the best disintegration time results (18.55±1.28 s), which is a very crucial factor for orally disintegrating tablet characterization, compared to other formulations.

Keywords: Amlodipine besylate, Design of experiments, Texture analyzer, Orally disintegrating tablet, Direct compression tableting.

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INTRODUCTION

Oral drug administration provides the highest patient compliance, especially when repeated or routine dosing is required. An important place among pharmaceutical forms is oral solid dosage forms in tablet form.[1] In recent years, Orally Disintegrating Tablets (ODTs) are becoming prominent among different tablet formulations.

ODTs can also be referred to as rapidly/fast disintegrating, rapidly/ fast dispersing, rapidly/ fast dissolving, fast melting, or orodispersible tablets.[2-5] According to the European Pharmacopoeia (Ph. Eur.),[6] the definition of the orodispersible tablet is an uncoated tablet that disperses rapidly in the mouth before swallowing. It is also stated in Ph. Eur. that ODTs should disintegrate in less than 3 min in conventional disintegration test apparatus. On the other hand, the United States Food and Drug Administration (FDA) defines these tablets as "a solid dosage form containing an active ingredient that rapidly disintegrates when placed on the tongue, usually within seconds".[7]

The development of ODTs provided ease of use compared to conventional tablets, chewable tablets, and liquid dosage forms and offered more precise dosing compared to liquid products. ODTs have been developed specifically for bedridden patients, the elderly, mentally ill patients, children, and patients suffering from dysphagia. In addition, their use is more common in cancer, AIDS, diabetes, Alzheimer's and cardiovascular diseases. This dosage form provides convenience for patients who are constantly ill, who need to take medication while traveling, that is, who have difficulty in finding water. The rapid disintegration of the drug in saliva, which occurs within 60 sec, results in an easily swallowed suspension, enabling high drug loading capacity. Additionally, the disintegration of the tablet in the mouth may facilitate a degree of absorption through the sublingual or buccal mucosa. Furthermore, drug candidates that undergo pre-gastric absorption when formulated as Orally Disintegrating Tablets (ODTs) may exhibit increased oral bioavailability.[4,8-11] From this point of view, designing ODT formulations provides advantages in terms of ease of use and high patient compliance with hypertension.

Hypertension is a chronic disease with an estimated prevalence of 1.13 billion in 2015. It is defined as having systolic and diastolic

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blood pressure greater than 140 and 90 mm Hg, respectively.[12,13] As a considerable and costly public health problem, controlling blood pressure in hypertension reduces the risk of coronary artery disease, stroke, peripheral vascular disease, congestive heart failure, end-stage renal disease, and overall mortality. In cases where lifestyle modification is inadequate to control blood pressure, different first-line medications such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers are used. As a calcium channel blocker, Amlodipine (AML) is one of the most commonly used oral antihypertensive agents.[14] This basic dihydropyridine derivative inhibits calcium influx in peripheral vascular and coronary smooth muscle cells, leading to vasodilation in peripheral and coronary vascular beds.[15] The besylate salt of AML, the model drug in this study, shows a higher aqueous solubility than the free base form and provides better absorption and subsequently higher bioavailability in tablet formulations.[16] Furthermore, the market offers a variety of tablets containing amlodipine in different strengths, including 2.5, 5, and 10 mg doses. Similarly, Synthon Pharmaceuticals ® has developed ODTs that come in the same dosages. In this study, ODTs were formulated using 13.9 mg amlodipine besylate, equivalent to 10 mg amlodipine base.

ODTs can be formulated at low cost by direct mixing method depending on the properties of the active ingredient. Ideally, the active ingredient in ODTs should preferably have a low-medium molecular weight, have good solubility in saliva, and be partially non-ionized at the pH value of the oral cavity.[4,17,18]

A tablet's rapid disintegration is due to swift water penetration into the matrix. Key strategies for developing fast-disintegrating oral dosage forms involve enhancing matrix porosity, adding effective disintegrating agents, and employing highly water-soluble excipients in the formulation.[19] Super disintegrants can be used in the formulation of ODTs to achieve rapid disintegration while in the mouth. Among those disintegrants, sodium starch glycolate possesses the role of burst disintegration facilitator with good flowability.[20] On the other hand, Microcrystalline Cellulose (MCC) can act as both a filler, binder, and disintegrant, and such multifunctional excipients often result in better compressibility, dilution potential, and possibly faster disintegration.[21] Similarly, sugar alcohols/polyols such as mannitol are often included in ODTs as fillers because they both increase tablets' compressibility and also shorten disintegration time due to their high solubility in water.[22] Moreover, mannitol has a notable advantage over other sugars and sugar alcohols due to its low hygroscopicity, which increases tablet stability.[23]

The determination of ODT disintegration time and behavior is very critical in the evaluation and development of this dosage form. There is no specific disintegration test defined for ODTs in Pharmacopeias. In the disintegration test for tablets performed with the pharmacopeia method, the average data of six tablets are presented as observational results, and the study is carried out in high volume. The use of a texture analyzer device to determine the disintegration time of ODTs has the advantage of simulating oral conditions, such as applying a smaller volume and defined force (not agitation) compared with the compendial test. The texture analysis method presents quantitative data rather than observation-based results. Also, this device can determine the behavior of formulation during disintegration. The tablet, attached to the lower part of the probe with a double-sided adhesive tape, is immersed in a defined volume of distilled water at a constant force, and the disintegration time and distance traveled by the probe are monitored. The time-distance profiles created by the texture analysis software allowed the accurate calculation of the start and end points of the disintegration time.[24,25]

In this study, ODT formulations containing amlodipine besylate were developed and the effects of tablet excipients (independent variables) on tablet characteristics were evaluated by using the Design of Experiment (DoE) statistical approach. DoE was used in the formulation design as it best explains the cause-effect relationship.[26] ODT formulations were prepared by direct compression method due to its low cost and simple process, and quality control tests were carried out on tablets. A comprehensive analysis of disintegration is essential in the formulation development of ODTs to ensure reliable and consistent drug release. Disintegration tests were carried out using a texture analyzer and a compendial disintegration tester to determine the difference between formulations. With the texture analysis method, the detailed disintegration properties of tablets as; swelling distance, duration of swelling, the onset of disintegration, end of disintegration, disintegration rate, and residual height were quantitatively demonstrated.

MATERIALS AND METHODS

Materials

Amlodipine besylate was received from Deva Holding A.Ş. (İstanbul, Turkey). Sodium starch glycolate "Primojel®", mannitol and magnesium stearate were also provided as a gift from Deva Holding A.Ş. (İstanbul, Turkey). Microcrystalline cellulose "Avicel PH102®" was procured from FMC biopolymer (St. Louis, Mo, USA). All other chemicals used were of analytical grade.

Design of experiment and statistical analysis

The response surface approach implements a specific set of statistical designs to evaluate the effects of independent process variables on the responses. It also enables significant variables to be distinguished and potential interactions between them to be recognized. Therefore, preliminary studies were carried out to find the variable ranges that would provide the desired tablet quality. Afterward, the effects of mannitol: microcrystalline cellulose (filler) level (MAN: MCC; X_1) and sodium starch glycolate (super disintegrant) level (SSG; X_2) as independent formulation

variables on the critical quality characteristics of ODTs were investigated by using face-centered, central composite, 3^2 full factorial design. Low, medium, and high independent variable levels were expressed as (-1), (0), and (1), respectively.

Tensile strength (Y_1), disintegration time (Y_2), and dissolution rate at the 5th min (Y_3) were chosen as dependent variables. The influence of both formulation and process variables on tablet hardness is undeniable. This, in turn, has a direct impact on the tensile strength, which is crucial in determining the disintegration and dissolution rates of tablets. Consequently, these factors play a critical role in affecting the bioavailability of the drug. Given these considerations, tensile strength, disintegration time and dissolution rate were determined as critical quality attributes in this study.[27] All experimental batches were investigated in triplicate and expressed as mean±standard deviation. The statistical analysis was performed by Analysis of Variance (ANOVA) using SPSS 22 and design expert (Design Expert® 13, State-Ease Inc. Minneapolis, MN, USA) software, and equations were derived using appropriate models. p-value<0.05 was statistically significant. By comparing different statistical parameters such as multiple correlation coefficient (R^2) or corrected multiple correlation coefficient (corrected R^2), the most suitable experimental model was selected, and a 3D response surface plot and contour plot of the results were also obtained.[28-32]

For the optimization step, the relationship between independent and dependent variables was quantified and fitted into a model using equation- 1 as below.

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_{12}+b_{22}X_{22} \quad (1)$$

where Y is the measured response, b_0 is the intercept, X_1 and X_2 are independent variables, b_1 and b_2 are regression coefficients, b_{12} is a coefficient of interaction between independent variables, and b_{11} and b_{22} are quadratic coefficients.[33]

Preparation of amlodipine containing orally disintegrating tablets

AML ODTs were prepared by direct compression technique under certain conditions. The components of formulations are shown in Table 1. Since the super disintegrant ratios and tablet weights were kept constant in the formulation design, the amounts of other excipients used as fillers varied by weight. These fillers used in the formulation design were studied in three different ratios. For each formulation, a defined amount of AML, SSG, MCC, and MAN were weighed (Shimadzu ATX-224, Japan) and mixed for 5 min in a laboratory size V-mixer and 5 min more after the addition of Magnesium Stearate (MGST). A hydraulic press (Kaan Kalıp, Turkey), equipped with a 12 mm flat-faced punch and die, was used for preparing tablets with 200 bar compression pressure.

Fourier Transform Infrared (FTIR) analysis

FT-IR analysis of AML, excipients (SSG, MCC, MAN, and MGST), and ODT formulation blends was performed using Fourier transform infrared spectrophotometer (Shimadzu IR-Affinity 1S, Japan). The samples were mixed with KBr, and discs were prepared by compression. The scanning range was 4000-400 cm^{-1}. The presence of new bands or absence of characteristic peaks corresponding to the blend components was accepted as incompatibility between the drug and the excipient.[34] All the spectra were recorded in triplicate to obtain reproducible results.

Quality control tests of orally disintegrating tablet formulations

Weight uniformity, thickness and diameter, hardness, friability, disintegration, and dissolution tests were carried out as the quality control tests for ODT formulations.

Table 1: Components of amlodipine besylate ODT formulations.

Formulation	Amlodipine Besylate (% w/w)	SSG (% w/w)	MAN: MCC	MGST (% w/w)	Total Tablet weight (mg)
F1	5.56	2.5	50:50	1	250
F2	5.56	5	50:50	1	250
F3	5.56	10	50:50	1	250
F4	5.56	2.5	25:75	1	250
F5	5.56	5	25:75	1	250
F6	5.56	10	25:75	1	250
F7	5.56	2.5	75:25	1	250
F8	5.56	5	75:25	1	250
F9	5.56	10	75:25	1	250

ODT: Orally disintegrating tablet, **SSG:** Sodium starch glycolate, **MAN:** Mannitol, **MCC:** Microcrystalline cellulose, **MGST:** Magnesium stearate.

Uniformity of weight

Twenty tablets from each batch were selected randomly and weighed individually on a digital weighing balance (Shimadzu ATX-224, Japan), and the results were given as mean±SD. The deviation from the mean weight was evaluated for each formulation as a percentage.

Determination of thickness and diameter

A digital caliper (Mitutoyo CD-15CPX) with a sensitivity of 0.01 mm was used to determine the thickness and diameter (n=10). The diameter and thickness of the tablets were measured in mm, and the results were given as mean±SD.

Mechanical strength

The mechanical strength of tablets can be determined by the parameters of hardness and friability.[35] The hardness of 10 randomly selected tablets was measured using a Hardness Tester (Holland C_{50}, UK). The hardness as mean±SD was calculated. The tensile strength (T) was calculated using the equation-2.[36]

$$T\ (MPa) = \frac{2F\ (N)}{\pi \times d\ (mm) \times t(mm)} \qquad (2)$$

where F, d, and t are the breaking force, diameter, and thickness of ODTs, respectively.

Tablet friability was determined by rotating 20 tablets in the friability tester (Aymes, Turkey) at 25 rpm for 4 min. According to the weight of ODTs before (W_1) and after the test (W_2), weight loss was calculated using equation-3.[6]

$$\text{Friability}\ (\%) = \left(\frac{W1 - W2}{W1}\right) \times 100 \qquad (3)$$

Determination of disintegration time with pharmacopoeial method

The disintegration time of tablets was determined according to the European Pharmacopoeia.[6] The tests were performed in a disintegration tester (Pharmatest PTZ Auto, Hainburg, Germany) in distilled water (900 mL) at 37±0.5°C. The disintegration test continued until the granules of tablets disappeared on the mesh of the apparatus. After the disintegration of 6 randomly selected tablets, results were recorded in sec (s) as mean disintegration time±SD.

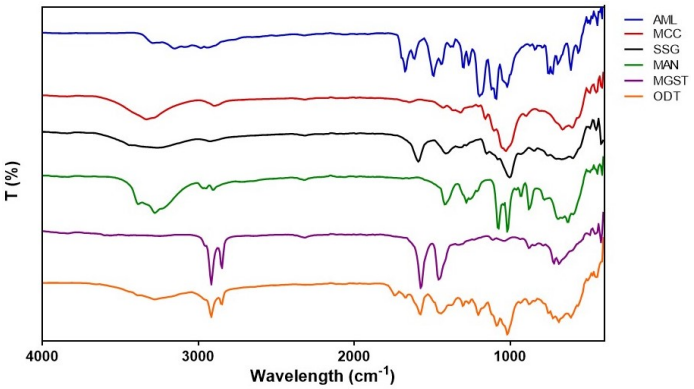

Figure 1: FTIR spectrum of active ingredients and excipients. AML: Amlodipine besylate, MCC: Microcrystalline cellulose, SSG: Sodium starch glycolate, MAN: Mannitol, MGST: Magnesium stearate, ODT: formulation blend prepared by mixing all powders.

Determination of disintegration time with texture analysis method

The study was carried out with a texture analyzer (TA.XT Plus, Stable Microsystems, Godalming, UK) equipped with a tablet disintegration rig. The rig has probe heads that can be magnetically attached to the spindle that is screwed into the load cell carrier.[37] The apparatus was calibrated with a 5 kg load cell. The tablet was attached to the lower part of the probe head with double-sided tape. The probe was immersed in a Perspex vessel filled with 5 mL of distilled water, and compressed with constant pressure until it contacted the perforated platform (30 mm diameter) in the vessel. The onset of disintegration (s), end of disintegration (s), disintegration rate (mm/s), duration of swelling (s), swelling distance (mm), and residual height (mm) of ODTs were calculated by the time-distance profiles generated by texture analyzer software. This method was performed using 6 tablets for each formulation. Changes in disintegration time were determined as a function of excipient concentrations. The test parameters used are; test mode: compression, pre-test speed: 2 mm/sec, test speed: 3 mm/sec, post-test speed: 10 mm/sec, target mode: force, force: 60 g, and trigger force: 5 g.

The definitions of the parameters obtained by the texture analysis method are given below

- Duration of swelling and onset of disintegration; the time when disintegration begins with or without the presence of swelling.
- Swelling distance; the distance at which the sample swells and expands before dispersion begins.
- Disintegration rate; the first gradient of the region descending from the onset of disintegration before the break point where the disintegration velocity decreases or stops.
- End of disintegration; the duration calculated using the intersection of the slopes of the primary descending and final plateau regions.
- Residual height; represents the height of the residue remaining in the disintegration chamber, calculated by subtracting the initial thickness of the tablet from the final height of the probe.

Dissolution studies

Dissolution studies were performed with USP apparatus II (AT7 Smart; Sotax, Switzerland). The rotating speed for the paddles was kept constant at 50 rpm. The dissolution medium was 900 mL of 0,01 N HCl (pH 2.0) and heated to 37±0.5°C. At fixed time intervals (5, 15, 30, and 60 min), 1 mL samples were withdrawn, and the drug content was assayed spectrophotometrically (UV

5, Mettler Toledo, Italy) at 239 nm. The UV-spectrophotometric method was validated with a correlation coefficient value of 0.999. All analyses were performed in triplicate under sink conditions.

RESULTS AND DISCUSSION

Characterisation of amlodipine containing orally disintegrating tablets

FTIR analysis (Figure 1) was performed to determine whether there was an incompatibility between active ingredients and excipients used in ODT formulations.

The characteristic absorption peaks of AML were observed at 3294 cm^{-1} (N-H stretching); 3155-2947 cm^{-1} (C-H stretching bands); 1674 cm^{-1} (C=O stretches of ester carbonyl); 1087 cm^{-1} (aromatic C-Cl stretch); 1018 cm^{-1} (ether C-O-C symmetric stretch); 748, 725 and 694 cm^{-1} (aromatic CH bending). Similarly, distinct peaks were seen at 3332 cm^{-1} for MCC, 3260 cm^{-1} for SSG, 3278 cm^{-1} for MAN representing O-H stretching; 2893 cm^{-1} for MCC, 2924 cm^{-1} for SSG, 2947 cm^{-1} for MAN representing C-H stretching; 1319 cm^{-1} for MCC, 1280 cm^{-1} for SSG, 1280 cm^{-1} representing C-O stretching. Moreover, bands at 1643 cm^{-1} and 1427 cm^{-1} observed in the MCC sample show C=O and CH_2 bending, respectively.[38-40] Twin peaks of MGST at 1573 and 1458 cm^{-1} are associated with asymmetric Carboxylate (COO-) stretching and symmetric carboxylate stretching vibration, respectively. In addition, the peaks at 2916 and 2846 cm^{-1} are attributed to the C-H stretching vibration.[41] The band at about 3248 cm^{-1} is due to OH stretching vibrations of the associated water molecule.[42]

When the FTIR spectrum of the ODT blend is examined, O-H and C-H stretching related to the components were identified at about 3300 cm^{-1} and 2900 cm^{-1}, respectively. There was also an accurate C=O stretching peak from MGST at 1573 cm^{-1}. The peaks of the C-O stretching appeared in the range of 1203-1381 cm^{-1}. It was concluded that the chemical structures were well preserved and there was no incompatibility between the components of ODT formulations.

The weight uniformity, diameter, thickness, hardness, and tensile strength of the ODTs were summarized in Table 2.

As none of the ODTs are outside the 5% weight deviation limit for tablets of 250 mg, each of the nine ODT formulations fulfills the pharmacopoeial requirements. The diameters of the ODT formulations were between 12.06-12.08 mm and the standard deviation values were found to be 0.009 mm at maximum. The thickness values of the formulations were between 1.72-1.76 mm, and the maximum standard deviation was found to be 0.041 mm.

Friability is defined as the wear value of compressed uncoated tablets by mass, and this value should not be greater than 1% for each formulation, according to European Pharmacopoeia 8.0.[6] In this respect, since the friability value for all formulations is below 1%, it has been observed that all tablets comply with pharmacopeia standards. When the crushing strength of ODTs was determined as another measure of tablet strength, it was observed that the tablet hardness ranged between 27 and 73 N as illustrated in Table 2. Friability and hardness were inversely correlated in ODTs. With a low MAN: MCC ratio, low friability and high hardness values were observed. According to the one-way ANOVA studies, when the amount of sodium starch glycolate was increased, there was no significant change in the tablet hardness values ($p>0.05$).

Regression analysis was performed for the tensile strength values which were calculated based on the hardness values of ODTs. The tensile strength of ODTs was increased with the increase in MCC levels (Figure 2A-B). Besides, as shown in Table 3, regression analysis displayed that MAN level ($p<0.0001$) and SSG level ($p<0.05$) had a negatively significant effect on tensile strength. Similar results were observed in a different study by Soeratri *et al.*, 2020, with tablets containing SSG.[43] Sano *et al.*, 2013 also found in their study that ODT hardness decreased due to the presence of mannitol, which supported our findings.[44] Consequently, it is expected that the tensile strength, which is derived from the hardness value, would also decrease. Additionally, since the MCC rate increases as the mannitol rate decreases in the formulation to ensure uniformity in tablet weight, the effect of MCC itself on the increase in hardness and tensile strength values should also be taken into consideration. In this context, various studies have demonstrated that the moisture content of Avicel pH 102 significantly influences the mechanical strength of tablets. Tablets containing MCC exhibit elevated strength and hardness, and when combined with other excipients such as Mannitol and Ac-di-sol, the formulation results in tablets with even superior mechanical strength and hardness.[45,46] Moreover, the MAN level was found to be more effective on tensile strength by its higher coefficient, compared to SSG level or quadratic effects.

The quadratic model showed good predictability ($p<0.0001$) with the best R^2 and the influence of two variables on tablet tensile strength was expressed in equation 4.

$$\text{Tensile strength } (Y_1)=1.48-0.604\,X_1-0.119\,X_2+0.105\,X_1X_2+0.0728X_1^2-0.127\,X_2^2 \quad (4)$$

Disintegration time of orally disintegrating tablets

Pharmacopoeia method

Initially, the classical disintegration test method was used for all ODT formulations to determine the disintegration times (Figure 3) by taking the European Pharmacopoeia 8.0 as a reference.[6]

According to European Pharmacopoeia 8.0, ODTs are required to disintegrate in less than 180 sec. The disintegration times of all formulations were found within this limit in the disintegration test performed according to the pharmacopeia method. Figure 2C-D illustrates that when the ratio of SSG in tablets was kept

Table 2: Characteristics of orally disintegrating tablets containing amlodipine besylate.

Sample	Weight (mg) (*n*=20)	Diameter (mm) (*n*=10)	Thickness (mm) (*n*=10)	Hardness (N) (*n*=10)	Tensile Strength (MPa) (*n*=10)
F1	246.71±0.51	12.06±0.009	1.73±0.032	49.35±3.83	1.50±0.11
F2	246.28±1.06	12.07±0.005	1.73±0.023	49.03±3.18	1.50±0.11
F3	246.67±1.00	12.06±0.009	1.73±0.023	41.05±4.17	1.22±0.14
F4	245.63±1.43	12.07±0.005	1.73±0.023	73.13±2.81	2.23±0.09
F5	245.59±1.43	12.07±0.000	1.72±0.015	70.75±4.96	2.23±0.09
F6	245.53±1.08	12.07±0.000	1.72±0.013	59.09±2.53	1.81±0.08
F7	246.96±0.73	12.07±0.006	1.75±0.041	27.49±8.11	0.83±0.25
F8	246.15±1.04	12.07±0.006	1.74±0.033	30.86±3.44	0.94±0.12
F9	245.59±0.75	12.08±0.009	1.76±0.036	27.30±4.45	0.82±0.14

Values are expressed as mean±standard deviation.

Table 3: ANOVA analysis data of dependent variables for 3^2 full factorial design.

Independent Variable	Y_1: Tensile strength (Quadratic Model)	Y_2: Disintegration time (Linear Model)	Y_3: Dissolution rate (Linear Model)
Intercept	1.48	28.86	89.91
X_1	-0.6038 (p<0.001)	-13.42 (p<0.001)	-1.87 (p>0.05)
X_2	-0.1192 (p<0.05)	-2.62(p>0.05)	3.42 (p>0.05)
X_1X_2	0.1051 (p<0.05)	-	-
P-value	<0.0001	0.0002	0.1115
R^2	0.9991	0.9386	0.5187
Adjusted R^2	0.9975	0.9181	0.3583
Predicted R^2	0.9896	0.8538	-0.1736
Adequate precision	63.8060	15.8761	4.8141

***X_1*:** MAN: MCC level, ***X_2*:** SSG level, X_1X_2 is the interaction effect.

constant and the ratio of MAN: MCC was decreased, a significant prolongation of tablet disintegration time occurred according to the method specified in the pharmacopeia ($p<0.05$). As the SSG concentration increased, there was a slight decrease in the disintegration time nonetheless, a significant response based on SSG level in the ODTs was not observed ($p>0.1$). The disintegration time depending on the MAN: MCC (X_1) and SSG (X_2) levels are explained by equation 5, and the linear model was fit with the most reliable R^2 value for the regression analysis ($p<0.001$). According to equation 5, the MAN level has a higher negative impact than the SSG level on the disintegration time due to a higher coefficient. Sugar alcohols like mannitol increase tablets' compressibility and also shorten disintegration time due to their high solubility in water.[22,47] This property provided by Mannitol has also been supported by different studies that compare it with Avicel® PH102.[46,48]

$$\text{Disintegration time } (Y_2) = 28.86\text{-}13.42\ X_1\text{-}2.62\ X_2 \qquad (5)$$

Texture analysis method

By evaluating the disintegration test results according to the pharmacopeia method, three formulations with the fastest disintegration results were selected. These formulations were also analyzed by the texture analysis method. Different test parameters for the disintegration processes of F7, F8, and F9 formulations were calculated using a texture analyzer, as shown in Table 4. Disintegration graphs of the texture analyzer for F7, F8, and F9 formulations denoting the effect of the increasing SSG ratio on the swelling distance and the onset of disintegration values are shown in Figure 4.

Due to the applied force and less liquid disintegration medium, the texture analysis method could simulate the *in vivo* environment better, whereas only observational results could be obtained with the disintegration test specified in the pharmacopeia. In addition, depending on the excipient ratios in the ODT formulations, responses such as tablet swelling distance, disintegration start and end points, disintegration rate, and residual height were obtained in a more reliable, quantitative, and detailed manner. In the results

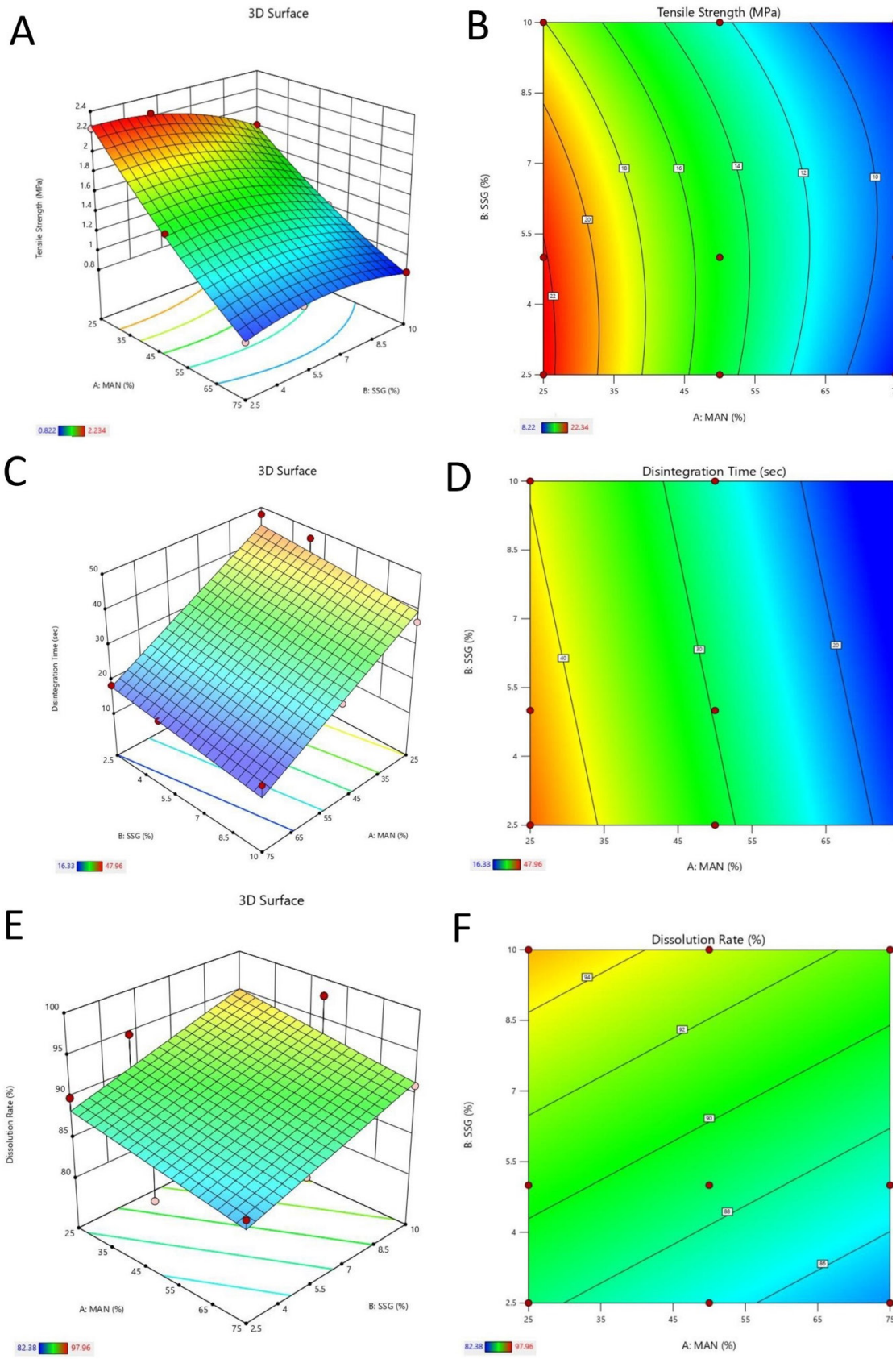

Figure 2: The effect of MAN level and SSG level on tensile strength (Y_1) (A, B), on disintegration time (Y_2) (C, D), and on dissolution rate at 5th min (Y_3) (E, F) of ODTs containing amlodipine besylate.

Table 4: Disintegration data of F7, F8 and F9 formulations using a texture analyzer (*n*=6).

Disintegration Test Parameter	F7	F8	F9
Onset of Disintegration (s)	54.05±19.55	32.42±1.70	18.55±1.28
End of Disintegration (s)	135.88±30.20	67.09±4.21	41.09±4.62
Disintegration Rate (mm/s)	0.00123±0.00057	0.00661±0.00107	0.02576±0.00471
Duration of Swelling (s)	54.04±19.55	32.42±1.70	18.55±1.28
Swelling Distance (mm)	0.15±0.02	0.29±0.03	0.25±0.05
Residual Height (mm)	0.19±0.03	0.38±0.03	0.81±0.06

Values are expressed as mean ± standard deviation.

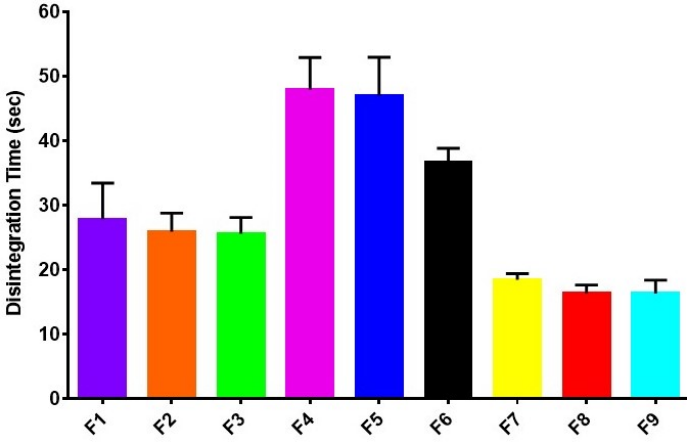

Figure 3: Disintegration time profile of ODTs.

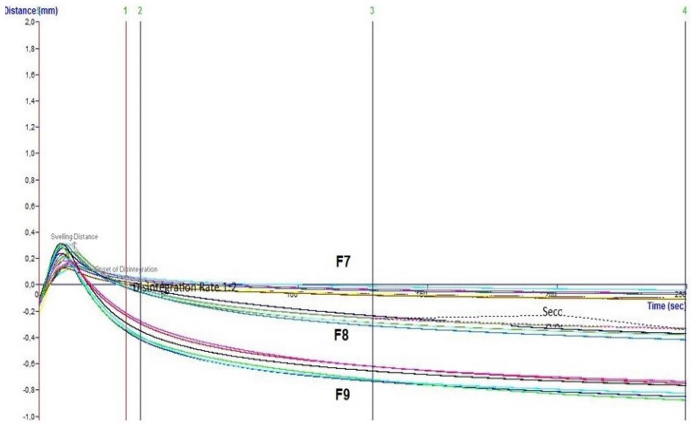

Figure 4: Texture analyzer graphs of F7, F8 and F9 formulations (*n=6*).

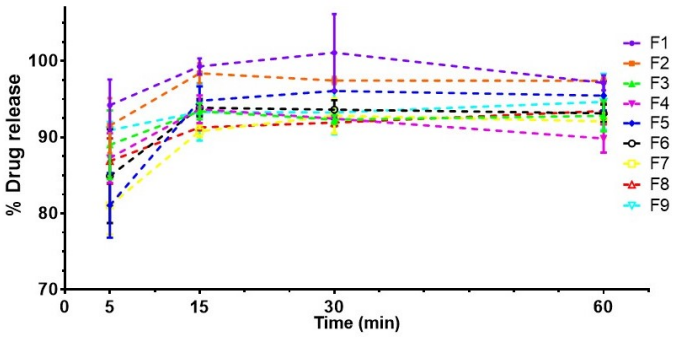

Figure 5: Dissolution profile of ODT formulations containing AML.

obtained according to the pharmacopeia method, the increased SSG in the formulations was found to be inversely proportional to the disintegration time. When F7, F8, and F9 formulations were compared according to the texture analysis method, it was confirmed that the disintegration time was shortened due to the increasing SSG ratio. F7, F8, and F9 formulations started to disintegrate in less than 1 min, according to the texture analysis method. It was observed that F9 with ratios of 75:25 MAN: MCC and SSG 10% was the formulation with the fastest disintegration. In addition, the increasing level of SSG did not have a significant effect on the swelling distance ($p>0.05$).

Dissolution profiles of orally disintegrating tablets

When the dissolution profiles of the formulations were examined, a rapid release within the first five min was observed. When the effect of MAN: MCC (X_1) and SSG (X_2) levels on dissolution rate (5th min) (Y_3) were evaluated by regression analysis, equation 6 was obtained by the linear model. In the equation, it was seen that MAN level had negative, and SSG level had a positive effect on the dissolution rate. Likewise, it was observed that the dissolution rate decreased partially with the increasing amount of MAN, while the dissolution rate increased with the SSG level (Figure 2E-F). However, significant results could not be obtained depending on both variables ($p>0.05$).

$$\text{Dissolution rate } (Y_3) = 89.91\text{-}1.87\ X_1 + 3.42\ X_2 \qquad (6)$$

AML release was observed to be cumulatively more than 90% in 30 min for all formulations (Figure 5). At the end of 5 min, it was seen that when the amount of SSG was increased, there was no significant change in the release rates of the tablets in the dissolution medium ($p>0.05$). Similarly, as the MAN: MCC ratio decreased, the dissolution rate of ODTs increased slightly but did not give a significant result ($p>0.05$).

CONCLUSION

Orally disintegrating tablets are dosage forms that are preferred especially in pediatric, geriatric, and psychiatric patient groups, and have been very popular in recent years due to their high patient compliance. In this study, ODTs were prepared using AML, an antihypertensive agent that mostly elderly patients should use regularly. ODT formulations of AML were prepared by direct compression technique using common excipients (MCC, MAN, SSG, and MGST). All the ODT formulations studied fulfilled the pharmacopeia requirements in the context of diameter, height, weight, hardness, friability, and dissolution rate. No drug-excipient interactions have been observed for ODT formulations. The DoE method was used to interpret the cause and effect in the relationship between tablet properties and excipients. While the MAN: MCC ratio created a statistically significant difference in both disintegration and tensile strength values, the change in SSG ratio created a significant difference only in tensile strength ($p<0.05$). It was determined that F9, which has the highest ratio of MAN and SSG among the obtained formulations, met all pharmacopeia standards and gave the best results among other formulations in terms of disintegration time, which is the determining factor for ODTs. In this study, a mathematical relationship was established between the components and the tablet responses by application of the DoE approach, and thus the study sheds light on other studies for effective time and material savings in formulation development.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AML: Amlodipine; **DoE:** Design of experiment; **FDA:** Food and drug administration; **FTIR:** Fourier transform infrared spectroscopy; **MAN:** Mannitol; **MCC:** Microcrystaline cellulose; **MGST:** Magnesium stearate; **ODT:** Orally disintegrating tablet; **SSG:** Sodium starch glycolate.

SUMMARY

Hypertension is one of the most common chronic diseases worldwide, affecting more than 1 billion people. One of the most preferred active ingredients in antihypertensive treatment is amlodipine. Conventional tablets of amlodipine are available in the market. In addition, ODTs have gained popularity in recent years due to their easy use and high patient compliance, and they can form a very accurate drug delivery system in the treatment of amlodipine. In this study, amlodipine ODTs were formulated, and the effect of formulation parameters on tablet specifications was explained by mathematically expressing with DoE and statistically interpreted. In addition, the Pharmacopeial and texture analysis methods were compared over the disintegration times of ODTs.

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