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Original Article

Formulation and Evaluation of Orally Disintegrating Tablet Containing Aripiprazole in the Context of Quality by Design Approach

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ABSTRACT

Aim/Background: The objective of this research is to develop and enhance the formulation of aripiprazole rapid disintegrating tablets utilizing the Quality by Design (QbD) methodology. **Materials and Methods:** A full factorial experimental design with three levels was employed to analyze the influence of key factors, namely the concentration of the filler (starch), ludipress concentration and disintegrant concentration, on important quality attributes such as disintegration time, friability and hardness. The formulation's drug-excipients interaction was examined using FTIR. Research was conducted to assess the stability of the product in accelerated conditions of 40ºC and 75% relative humidity. **Results:** FTIR analysis indicated that there was no notable chemical interaction seen in the solid form. The Aripiprazole fast disintegrating tablet formulations demonstrated satisfactory friability (0.77±0.16%), rapid disintegration time (66±0.58 sec) and appropriate hardness (48.35±3.22 N). The research revealed that the most favorable combination of independent components consisted of 15.8% filler (starch), 76% ludipress and 1.3% disintegrant. **Conclusion:** The accelerated stability experiments demonstrated that the hardness, friability, disintegration durations and drug release rate were within the permissible limits defined by the compendial standards. Implementing the Quality by Design (QbD) method may facilitate a comprehensive comprehension of how the Critical Material Attributes (CMAs) impact the Critical Quality Attributes (CQAs) of the final product of aripiprazole rapid disintegrating tablets.

Keywords: Aripiprazole, Fast disintegrating tablets, Quality by design QBD, Stability, Super-disintegrants.

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INTRODUCTION

Currently, administering medications by mouth is considered the safest, most convenient and most cost-effective means of delivering drugs, while also having the greatest level of patient compliance. The oral route is the most favored method of administering medication, with tablets and capsules being the most favored forms of dosing.[1] The tablet is the most often used type of medication due to its simplicity for self-administration, small size and ease of production. Geriatric and pediatric patients have challenges while ingesting traditional tablets, resulting in low patient adherence. In order to address this limitation, researchers have created novel medication administration techniques referred to as "melt in mouth" or "Mouth Dissolve (MD)" tablets. These are novel types of tablets that disintegrate/dissolve/disperse in saliva. Their distinctive benefits, such as waterless administration, universal accessibility and flexibility in timing, make them very suitable for elderly and pediatric patients. Additionally, they are appropriate for those with mental illnesses, individuals who are confined to bed and people who lack convenient access to water. These tablets are popular in the present market because they provide advantages such as improved patient compliance, rapid onset of action, higher bioavailability and excellent stability.[2-4] There has been an increasing need for high-quality ODT formulations that include novel disintegrants and provide easy preparation procedures in recent years. The bioavailability of medications may be enhanced by the absorption of drugs in the oral cavity and the pregastric absorption of saliva containing dispersed drugs that then enter the stomach. Furthermore, the quantity of drug that undergoes first-pass metabolism is decreased in comparison to normal tablets.[5]

Schizophrenia is a neurological disorder that disrupts normal brain functioning. It is a psychiatric condition often marked by atypical social conduct and an inability to distinguish reality and it is now emerging as one of the most significant and rapidly

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expanding fields of unaddressed medical need. Schizophrenia is considered one of the most debilitating conditions of all mental illnesses, resulting in substantial financial burdens on healthcare systems worldwide.[6] Aripiprazole (APZ) is a second-generation or atypical antipsychotic drug that specifically attaches to dopamine D2 and serotonin (5-HT2c) receptors in the central nervous system. It is particularly effective in treating the negative symptoms associated with schizophrenia and has a reduced likelihood of causing extrapyramidal symptoms. It is categorized as a BCS Class II drug and has a very low solubility (0.01 µg/mL) in water.[7,8]

The Quality by Design (QbD) approach identifies key quality characteristics from the patient's perspective, translates them into specific attributes that the drug product should have and determines how process factors can be adjusted to consistently produce a drug product with the desired characteristics. The Quality by Design (QbD) strategy starts by establishing a predetermined Target Product Profile (TPP) and thereafter employs a range of concepts and tools at different stages to enhance comprehension of the product. Quality Risk Assessment (QRA) tools, such as Failure Mode Effects Analysis (FMEA) and Risk ranking and filtering, are used to identify an initial list of potential Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). This assessment includes considering and documenting all parameters that could affect the outputs (CQAs) for each unit operation.[9,10]

The study aimed to create an oral disintegrating tablet formulation containing the APZ using the Quality by Design (QbD) approach and MODDE software. This approach involved statistical assessment to understand the impact of formulation and process variables on the quality attributes of the final product. The findings of the present investigation will be valuable for research and development departments in the pharmaceutical industry. The qualities of tablet powder were also examined during the preformulation investigations.

MATERIALS AND METHODS

Materials

Aripiprazole was generously gifted by Santa Farma Pharmaceuticals (Şişli, İstanbul). Starch was obtained from Yasin Teknik (İstanbul, Turkey), Talc powder from Tekkim Laboratories (Tuzla, Turkey), Crospovidone and Ludipress from BASF (Germany) and Magnesium stearate from Doga Pharmaceuticals (Turkey). All other chemicals and reagents were of analytical grade.

Methods

Identifying a quality target product profile (qtpp)

The QTPP is determined based on the intended labeling information that outlines the expected indications, contraindications, dosage form, dose, frequency, pharmacokinetics and other relevant details for a new product.[11,12] Multiple methods exist for expressing a Quality Target Product Profile (QTPP) for Orally Disintegrating Tablets (ODT), with one of these methods being provided in Table 1.

Critical quality attributes (cqa's)

A Critical Quality Attribute (CQA) is a trait or characteristic, whether physical, chemical, biological, or microbiological, that must fall within a certain limit, range, or distribution in order to guarantee the intended quality of a product.[12,13] Table 1 provides a summary of the quality characteristics of ODTs and identifies the specific properties that were designated as Critical Quality Attributes (CQAs) for the medicinal product.

Quality risk assessment

A risk assessment was conducted to analyze 10 process parameters using FMEA as a method to measure the level of risk associated with these materials and the design and process variables. As part of the evaluation, a mechanism called risk qualification was created to score the items. The three ranks, namely Severity (S), Probability (P) and Detectability (D), are used. Severity (S) evaluates the consequences of a failure and how it may impact the quality of a product. The probability of occurrence refers to the likelihood of a failure happening, whereas detectability refers to the ability to identify failure mechanisms. The S, P and D scores are multiplied together to create a Risk Priority Number (RPN), which is used to rank each risk according to its level of importance. Each score is assigned an evaluation point ranging from one to five and the resulting RPN scores are categorized as follows: Low (1-45), Moderate (46-90) and High (91-125). A high-Risk Priority Number (RPN) indicates that the possible hazards have been assessed to have a significant negative impact on the quality of the product.[9]

The Critical Quality Attributes (CQAs) of excipients necessary for the production of Orally Disintegrating Tablets (ODTs) were determined to be a minimum disintegration time and maximum hardness, with a friability not exceeding 1%. The inputs for this research were CMAs, namely the disintegrant type, disintegrant quantity, filler type and filler quantity. The outputs were the attributes of QTPP, namely hardness, friability and disintegration time.

Preformulation studies

Aripiprazole was standardized using UV/Vis spectrophotometers (Shimadzu 1700 and Lab India 2000) to establish a calibration curve for its quantification. Fourier Transform Infrared Spectroscopy (FTIR) (Perkin Elmer 1600, USA), was employed to assess potential drug-excipient interactions. Samples of pure Aripiprazole and its physical mixtures with excipients (Ludipress, Cros-PVP and Starch) were prepared by grinding them uniformly. The mixtures were scanned using a Perkin Elmer 1600 FTIR

Spectrometer within the wavenumber range of 4000-400 cm^{-1} at a resolution of 4 cm^{-1}. The choice of important bands was guided by the distinct functional groups in Aripiprazole, including the N-H stretching (~3472 cm^{-1}) and aromatic C-H vibrations (~3103 cm^{-1} and ~3063 cm^{-1}). Peaks were analyzed for shifts or changes, which would indicate interactions and the result, were cross-validated with baseline spectra of the pure drug.[14]

Formulation method of aripiprazole odt by direct compression method

The tablets were formulated using the direct compression method. Specific proportions of Aripiprazole, Crospovidone, Starch and Ludipress were weighed accurately according to Table 2. These materials were passed through a 710 µm sieve and mixed uniformly in a mortar for 30 min to ensure homogeneity. Talc and Magnesium stearate were added subsequently, sieved through the same mesh and blended with the primary mixture for an additional 15 min. The homogeneous mixture was compressed into tablets using a tablet compression machine (Single Punch Tablet Press Machine) set to a fixed pressure.[3,14-16]

Optimization of odt formulation of aripiprazole

The formulation was optimized using MODDE Pro software and a Box-Behnken experimental design. Independent variables included concentrations of Ludipress (X1), Starch (X2) and Crospovidone (X3). Dependent variables were disintegration time (Y1), hardness (Y2) and friability (Y3). A total of ten formulations (F1-F10) were developed and analyzed for these quality attributes. The design space was mapped to identify the optimal formulation with failure probability under 1%.[17,18]

Pre-compression parameters

Angle of Repose

The angle of repose is the highest angle that may be created between the surface of a pile of powder or grains and a flat horizontal plane. This angle functions as a measure of the internal friction present in the loose powder or granular material.[19] The angle of repose may be calculated by the use of a mathematical equation.

$$Tan\Theta = \frac{h}{r}$$

$$\Theta = \tan -1\left(\frac{h}{r}\right)$$

Θ: is the angle of repose.

h: is the height of the pile.

r: is the radius of the pile base.

Bulk density

The bulk density is obtained by pouring a measured mixture of each recipe into a measuring cylinder without tapping. The calculation is performed by dividing the mass of the powder by the bulk volume,[19] expressed as;

$$\rho b = \frac{w}{v}$$

ρb: Bulk density,

w: weight in grams,

v: volume of bulk.

Tapped density

Tapped density refers to the higher bulk density achieved by manually tapping a container that holds the powder sample. The tapped density was determined by repeatedly tapping a graduated measuring cylinder containing powdered sample (10-500 taps) until there was little additional change in volume (less than or equal to 2 mL). The powdered sample was sufficiently settled after 200 taps, thus, there was no need to continue tapping beyond 500 or up to 1250.[19] The density was determined using this formula.

$$\rho t = \frac{w}{V}$$

ρt: Tapped density,

w: represent the weight in grams,

V: the tapped volume.

Compressibility index (Carr's index)

The compressibility index (Carr's index) is a measure that may be used to quantify the bulk density, shape, size, surface area, moisture content and attraction of materials. The formula was derived by using both tapped and bulk densities.[19,20]

$$C = \frac{\rho t - \rho b}{\rho t} * 100$$

C: Carr's index.

Hausner's ratio

The Hausner's ratio is used as an indirect measure for determining the flowability of powder. The formula utilizes the variables t and b to calculate the tapped density and bulk density, respectively. Lower Hausner's ratios (<1.25) suggest superior flow characteristics in comparison to greater ratios.[19]

$$Hausner's\ ratio\ = \frac{\rho t}{\rho b}$$

Characterizatıon of odt formulation of aripiprazole

Hardness

The tablet's crushing strength, commonly referred to as hardness, was evaluated using a hardness tester (Pharma test, Hainburg, Germany). Five crushed tablets were randomly chosen from each formulation and their crushing strength was evaluated and recorded. This measurement serves as an indicator of the tablets' mechanical robustness and ability to withstand breakage or crumble.[19,21]

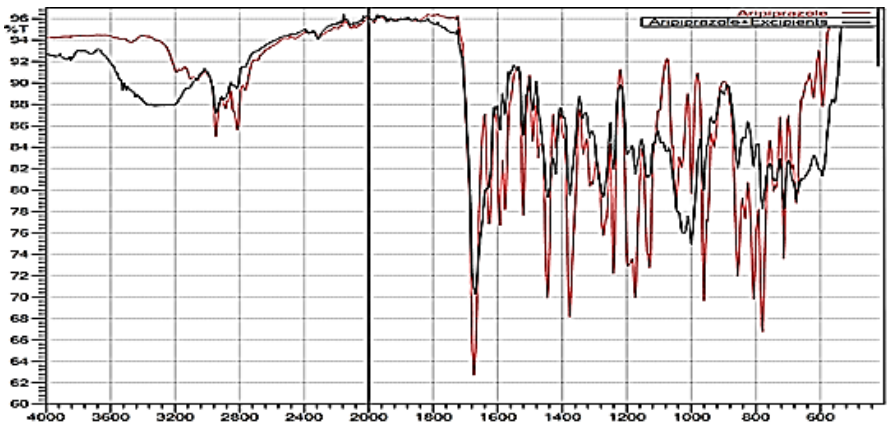

Figure 1: Scanned FTIR spectra of aripiprazole and a physical mixture.

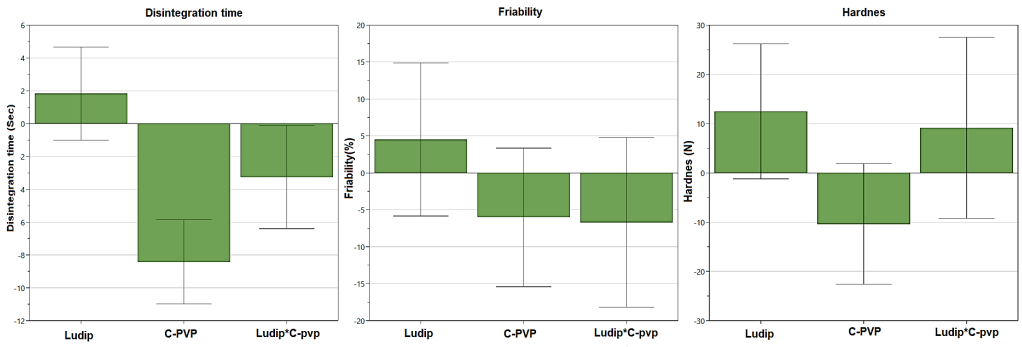

Figure 2: Coefficient plot shows the effect of variables.

Disintegration Time

The *in vitro* disintegration test was conducted at a temperature of 37°C using 900 mL of distilled water, following the guidelines set by the European Pharmacopoeia. The tablets were inserted into each of the 6 tubes of the disintegration apparatus (Pharma test, Hainburg, Germany). Every tube was fitted with a disintegration disk. The duration required for the solid to fully dissolve in the tube was documented. The disintegration time of 6 tablets in a single batch was evaluated and the average value and standard deviation were calculated. This test assesses the tablet's ability to disintegrate into smaller particles when it comes into contact with a solvent.[9]

Friability

The evaluation of friability, which quantifies the weight reduction of tablets caused by the elimination of small particles from their surface, was conducted using the pharmacopeial test (USP, 2011, 34-NF29). A total of twenty tablets (W1) were precisely weighed and put into the friability measuring machine (Pharma test, Hainburg, Germany). The tablets were then rotated at a speed of 25 rpm for duration of 4 min. The tablets were reweighed (W2) after the fines were removed and the percentage weight loss was computed using the formula: 100×(W1-W2)/W1. This test assesses the tablets' durability against abrasion and their capacity to endure mechanical stress while being handled and transported.[9,22]

Characterization of optimum formulation of odt containing aripiprazole

Weight variation

The weight variation test was performed to guarantee uniformity in tablet weight. A sample of ten tablets was taken from each formulation and the weight of each tablet was measured. Precise readings were obtained using an analytical balance (Sarto Elektronik, Istanbul Türkiye). The mean weight of the 20 tablets was calculated in order to evaluate the consistency in tablet weight.[23]

Thickness

In order to determine the thickness of the tablets, a sample of 10 tablets from each formulation was selected at random and measured using an electronic digital caliper. The thickness measurements were marked in millimeters. The average thickness value was determined by using these data, which serves as an indicator of the tablet's physical dimensions.[23]

Hardness

The experiment was conducted using the identical methodology employed in the batch formulation tests, as described previously.

Friability

The experiment was conducted using the identical methodology employed in the batch formulation tests, as described previously.

Table 1: Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) of ODTs.

Quality Target Product Profile (QTPP) for ODT		
QTPP Element	**Target**	**Justification**
Dosage form	ODT	Patient compliance
Route of administration	Oral	Patient compliance
Dosage strength	5 mg	Pharmaceutical limit requirement
	Physical Attributes (hardness, friability)	
	Disintegration time	
	Wetting time	
	Water Content	
	Content Uniformity	
	Drug Release	
	Microbial Limits	

Critical Quality Attributes (CQAs) of ODTs			
Quality Attributes of the Drug Product	**Target**	**Is it a CQA?**	**Justification**
Appearance	Colour and shape acceptable to the patients. No visual tablet defects observed.	No	The safety and effectiveness of a product are not directly influenced by its color, shape, or appearance. Consequently, they are not crucial. The objective is established to guarantee the acceptance of the patient.
Size	5 mg (amount of active ingredient)	Yes	Size is critical as it affects efficacy and toxicity
Odour, taste	No unpleasant odour and taste	Yes	The presence of odor and taste is crucial in Orally Disintegrating Tablets (ODTs) due to the importance of patient convenience.
Friability	<%1	Yes	Increased friability leads to a reduction in size.
Hardness	Pharmacopeia acceptability	Yes	The hardness of a substance has an impact on both the time it takes to disintegrate and the effectiveness of the drugs.
Disintegration time	<3 min	Yes	The efficiency is influenced by the duration of disintegration.
Wetting time	Minimum	Yes	The duration of wetting has an impact on the time it takes for something to break down or disintegrate.
Water absorption capacity	Minimum	Yes	When the water absorption capacity is high, a greater amount of saliva is needed to break down the Orally Disintegrating Tablet (ODT) in the mouth.
Drug release	Pharmacopeia acceptability	Yes	Drug release affects drug efficiency and safety
Content Uniformity	Pharmacopeia acceptability	Yes	Variations in the uniformity substance will have an impact on both the safety and efficiency. The uniformity of Orally Disintegrating Tablets (ODTs) is crucial.

In vitro disintegration

The experiment was conducted using the identical methodology employed in the batch formulation tests, as described previously.

Drug content uniformity

The drug content uniformity test was conducted in accordance with the "USP monograph ‹905› Uniformity of Dosage Units".[24] The phrase "uniformity of dosage unit" refers to the extent to which the quantity of the drug component is consistent across different dosage units. The aripiprazole content of ten tablets was individually evaluated by UV visible spectroscopy (Shimadzu Corporation, Tokyo, Japan). Each tablet was dissolved in a sufficient amount of 0.1 N HCl and the resulting solution was filtered and appropriately diluted before analysis.

The Acceptance Value (AV) was determined using the following equation:

$$AV= (M-X)+ks$$

X is the average individual contents expressed as a percentage, k represents the acceptability constant, s represents the sample standard deviation and M represents the reference value. M is calculated using X and T, where T is the average drug content of 10 tablets represented as a percentage. The highest permissible Acceptance Value (AV) is 15.0.[24]

Wetting time

A total of five circular tissue sheets, each with a diameter of 10 cm, were arranged within a petri dish that also had a diameter of 10 cm. A volume of 10 mm of water at 37°C+0.5°C and containing a dye that dissolves in water was introduced into the petri dish. A tablet was delicately positioned on the surface of tissue paper. The wetting time refers to the duration it takes for water to reach the top surface of the tablets. Randomly, six tablets were selected from each formulation batch and their average reading was recorded.[3]

Water absorption ratio

To determine the water absorption ratio, six tablets were positioned on a folded tissue paper and inserted into a Petri dish measuring 6.5 cm in diameter. To enhance visibility, a solution containing 6 mL of water and a water-soluble red dye was introduced. The duration required for full saturation of the tablets was recorded. The tablets were weighed again after getting wet in order to calculate the water absorption ratio.[25] The water absorption ratio (R) was determined by calculating the percentage using the following equation.

$$R = \frac{Wa - Wb}{Wb} * 100$$

Wa: the specific tablet weight after absorbtion,

Wb: represents the tablet weight before absorbtion.

In vitro drug release

Dissolution investigations of the manufactured Orally Disintegrating Tablets (ODT) were conducted three times using a USP dissolution test equipment, namely type-II (paddle technique), at a temperature of 37±0.5°C. The paddles exhibited a rotational speed of 50 revolutions per minute. The tablets were immersed in a 900 mL solution of Hydrochloric Acid (HCl) at a concentration of 0.1 N. At regular time intervals, 5 mL portions were taken from the dissolving media and passed through Whatman's filter paper. The drug concentration was measured using spectrophotometry at a specific wavelength of 218 nm, as previously stated. Following each withdrawal, 5 mL of new medium was introduced into the dissolving vessel. The cumulative percentage of drug release was determined by using an equation derived from the standard graph.[3,26]

Stability studies

Stability testing was conducted on optimized oral disintegrating tablets of aripiprazole in accordance with the requirements set by the International Council for Harmonisation (ICH). The optimized formulation was maintained at a temperature of 40±2°C and a relative humidity of 75±5% for duration of 3 months. The tablets underwent testing to assess their physical appearance, drug content, disintegration time, hardness, friability and drug dissolution tests.[22]

RESULTS AND DISCUSSION

Preformulation studies

The material was produced and the standard graph was created following the process outlined in the experimental approach. Standard solutions with concentrations of 2 µg/mL, 4 µg/mL, 6 µg/mL, 8 µg/mL, 10 µg/mL and 12 µg/mL were generated. The absorption values for these solutions were measured at a wavelength of 218 nm using a UV spectrophotometer, with 0.1 N HCl serving as the blank. The calibration curve for Aripiprazole was created by graphing the absorbance values on the Y-axis against the concentrations (µg/mL) on the X-axis. The resulting calibration curve, plotting absorbance against concentration, showed a strong linear relationship (R^2>0.99), confirming its suitability for accurate drug quantification in subsequent analyses.

Fourier Transform Infrared Spectroscopy (FTIR) was employed to assess the compatibility of Aripiprazole with the selected excipients. The spectra of pure Aripiprazole and its physical mixtures with Ludipress, Cros-PVP and Starch were recorded using a Perkin Elmer 1600 FTIR Spectrometer within the wavenumber range of 4000-400 cm^{-1} at a resolution of 4 cm^{-1}. Samples were prepared by grinding the drug and excipients into uniform physical mixtures. The selection of important bands focused on the characteristic functional groups of Aripiprazole, including the N-H stretching near 3472 cm^{-1} (secondary amide group in the lactam ring), aromatic C-H stretching vibrations

at 3103 cm^{-1} and 3063 cm^{-1} and C-N stretching at 1375 cm^{-1} (aromatic amine group). These bands were analyzed for any shifts, broadening, or disappearance in the physical mixtures, as such changes could signify interactions between the drug and excipients. Notably, the O-H stretching band observed at 3221 cm^{-1} in pure Aripiprazole shifted to 3400 cm^{-1} in the mixture, suggesting the formation of intermolecular hydrogen bonds. However, no additional peaks or significant alterations were noted in the critical bands of Aripiprazole, confirming the absence of any detrimental chemical interactions and ensuring the stability of the drug in the formulation. Figure 1 displays the FTIR spectra of aripiprazole and a physical combination consisting of aripiprazole, Ludipress, Cros-PVP and Starch.

Pre-compression parameters

Pre-compression parameters, including the angle of repose, bulk density, tapped density, compressibility index (Carr's Index) and Hausner's ratio, are critical for evaluating the flowability and packing characteristics of the powder blend. These properties directly influence the efficiency and quality of the tablet manufacturing process. The angle of repose is a measure of the flowability of the powder blend, with lower values indicating better flow. In this study, the angle of repose ranged between 22.78°±0.25 and 13.63°±0.27, signifying excellent flow characteristics. Good flowability ensures uniform die filling, which is essential for achieving consistent tablet weight and avoiding issues such as weight variation or incomplete filling during compression. Bulk density and tapped density provide insight into the packing behavior of the powder blend. Bulk density reflects the loose packing of the powder, while tapped density represents the maximum packing achieved after tapping. The results showed bulk density values ranging from 0.515±0.041 g/cm^3 to 0.667±0.025 g/cm^3 and tapped density values from 0.66±0.042 g/cm^3 to 0.83±0.027 g/cm^3. A high tapped density compared to bulk density indicates good compressibility, which helps in forming cohesive tablets with adequate hardness during compression. The compressibility index (Carr's Index), derived from bulk and tapped densities, is another measure of powder flow and compressibility. Values in this study ranged from 6.58% to 19.63%, which are within acceptable limits, suggesting good packing and low inter-particulate friction. This ensures uniform tablet compaction and prevents issues such as capping or lamination. Hausner's ratio, another flowability indicator derived from bulk and tapped densities, ranged between 1.07 and 1.24, further confirming the excellent flow properties of the powder blend. A Hausner's ratio below 1.25 indicates minimal cohesion and good flow, which facilitates efficient feeding of the powder into the tablet press and prevents bridging or clogging. In summary, these pre-compression parameters collectively demonstrated that the powder blends used in this study had excellent flowability, compressibility and packing characteristics. These properties ensured consistent and reproducible tablet formation during real-time compression, minimizing weight variability, optimizing mechanical strength and maintaining the overall quality of the tablets. comparable findings were also discovered in a variety of investigations.[21,27,28]

Post-compression quality control tests before optımization

All batches were sent to be compressed and tested. All formulations have a disintegration time that is shorter than 3 min, which is considered acceptable. More precisely, the desired disintegration time is set at 30 sec. The data indicated that Crospovidone reduces the disintegration time of tablets.[29] These data indicate that the formulations have favorable disintegration properties. The friability values exhibit variation across the various tablet formulations. According to the pharmacopeia, the desired level of friability should be below 1%.[3] The friability ratings of F2, F3 and F9 are within the acceptable range, suggesting that they can endure applied pressure and retain their structural integrity. However, F5, F6, F8 and F10 exhibit friability values that are close to the standard limit, indicating the need for precise

Table 2: Composition of ODT preparation using ludipress.

Formulation (mg/tablet)	Aripiprazole	Ludipress	Cros-PVP	Magnesium stearate	TALK	Starch
F1	5	84	0	1.3	2.6	36.6
F2	5	94	0	1.3	2.6	26.8
F3	5	104	0	1.3	2.6	17.1
F4	5	84	3.25	1.3	2.6	33.3
F5	5	94	3.25	1.3	2.6	23.6
F6	5	104	3.25	1.3	2.6	13.8
F7	5	84	6.5	1.3	2.6	30.1
F8	5	94	6.5	1.3	2.6	20.3
F9	5	104	6.5	1.3	2.6	10.6
F10	5	94	3.25	1.3	2.6	23.6
Optimum formulation	5	98.8	1.69	1.3	2.6	20.54

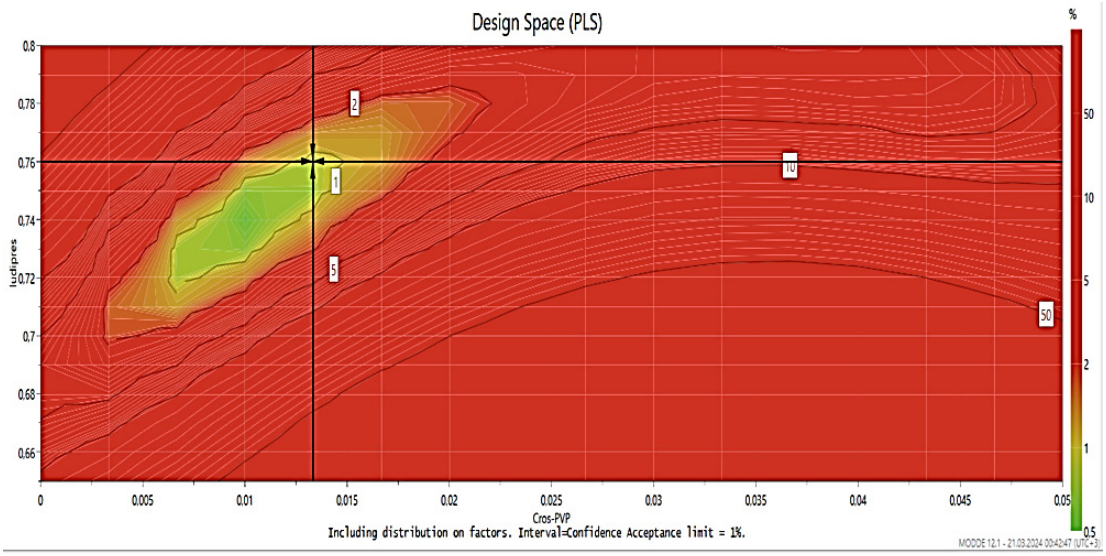

Figure 3: Design space.

modifications to the formula. F4 is characterized by its high friability, which indicates its fragility and tendency to shatter when subjected to pressure. The friability was seen to be increased with the increase in the concentration of the superdisintegrant, whereas it was decreased with the concentration of Ludipress.[30] The hardness values, which varied from 6±0.25 to 94.62±10. The findings indicated that the hardness of the tablets was greatly affected by both the concentration of the superdisintegrant and the concentration of Ludipress. The tablet hardness exhibited a positive correlation with the concentration of Ludipress, owing to the binding efficacy of Ludipress.[31] However, the tablet's hardness noticed a considerable drop as a result of the superdisintegrant.

Optimization of the formulation and data analysis

An investigation was conducted to improve the formulation of Orally Disintegrating Tablets (ODT) containing Aripiprazole. This included studying numerous independent variables, such as various components (Ludipress (X1), starch (X2) and crospovidone PVP (X3)) and their concentrations. The research evaluated many dependent variables, including disintegration time, hardness and friability. Under the Quality by Design (QbD) approach, the modeling parameters were thoroughly assessed in order to determine the most effective formulations. Through the analysis of these Figures, it is feasible to ascertain if each drug exhibits a positive or negative correlation with the given variable. Increasing the ludipress will result in higher hardness and a positive impact on disintegration time. Increasing the amount of crospovidone will result in a reduction in the time it takes for the drug to disintegrate. However, this increase in crospovidone will result in an increasing in friability, as well as causing a drop in its hardness as seen in Figure 2. The design space comprises green zones that represent places with a failure probability of less than 1%. The graphic illustrates locations that have a greater likelihood of failure, which are represented by colors ranging from yellow to red, as seen in Figure 3. The last row of Table 2 presents the optimum formulation resulting from the study, offering a concise summary of the suggested composition for attaining the intended goals.

Table 3: Evaluation of hardness, *in vitro* disintegration study and friability.

Test	Optimum formulation
Hardness (N)	48.35±3.22
Disintegration time	66±0.58
Friability (%)	0.77±0.16
Wetting time	57.6±1.75
Water absorption ratio	70.3±3.27

Post-compression quality control tests after optimization

Size, shape and color

The tablets prepared in this investigation had a circular shape measuring 6 mm in diameter and were determined to be white in color.

Weight variation and thickness

The weight variation range for the best formulation was reported to be 130.66±1.966 mg. This indicates that the powder combination is homogenous, which is expected to result in a high level of effectiveness. When the weight of the tablets falls within the specified range, it is believed that they contain a consistent amount of the active ingredient, which leads to the desired therapeutic response. However, if the weight of the tablets deviates from the specified range, it is believed that they contain either too little or too much of the active ingredient, resulting in an ineffective therapeutic response or a potentially harmful effect, respectively.[32] The thickness measurements for the optimum formulation were around 2.66±0.051 mm. Similar to

weight variation; this also indicates a homogenous combination of powder, which will result in effective performance.[33]

Hardness

The hardness finding is shown in Table 3. Tablet hardness is a measure of the tablet's ability to withstand breaking. To ascertain the hardness of a tablet, a testing procedure entails placing the tablet between the two jaws of the hardness measuring apparatus. One of the jaws slowly approaches the tablet, applying force on the stationary jaw until the tablet breaks. The tablet's failure load throughout the diameter is measured and documented. It is quantified using the unit of force established by Newton. The ideal tablet hardness is essential because tablets that are excessively hard might hinder dissolving and impact the accuracy of dosing, while tablets that are unduly soft can dissolve too rapidly and are susceptible to chipping or breaking during packing and transportation. The finding indicated an optimal level of hardness force.[34]

In vitro disintegration studies

The European Pharmacopeia sets a maximum limit of 3 min for the Disintegration Time (DT) of FDTs when tested using the standard disintegration test.[35] The determined DT of the optimal formulation was 66±0.58, as shown in Table 3. Therefore, the optimized formulation demonstrated satisfactory DT. Superdisintegrants rapidly facilitate Disintegration Time (DT) by swelling and absorbing water, resulting in enhanced wetness of the carrier's surface. This increased the capacity of the tablet to be wetted and dispersed, hence improving its breakdown and dissolving.[36] The key factor contributing to the reduced Disintegration Time (DT) is the strong breaking force and quick swelling of crospovidone in water, without creating a gel. In addition, crospovidone particles are seen to have a granular and extremely porous structure, which promotes the absorption of water into the tablet, resulting in a quick disintegration time.[37]

Friability

For the friability test, a sample of 20 tablets was selected at random. The findings are clearly presented in Table 3. Both the EU and US pharmacopeias specify that a loss of up to at least 1% is considered acceptable for friability.[38] The optimal formulation exhibited a friability of 0.77±0.16%. Tablets are vulnerable to mechanical strains throughout many phases, including handling, packing and transportation. The application of these forces may lead to chipping, breaking, or capping, underscoring the need of designing tablets with enough strength to endure such impacts.

Wetting time and water absorption ratio

The wetting time of the tablet was measured using the approach described in the experimental methodology. The findings are shown in Table 3, revealing that the wetting time ranged around 57.6±1.75 sec. Based on these findings, there is a clear association between wetting time and disintegration time. This implies that an increase in wetness time will result in a corresponding increase in disintegration time and vice versa.[35] On the other hand, the water absorption ratio was assessed and the findings are shown in Table 3, indicating a water absorption ratio ranging around 70.3±3.27. These findings revealed a direct correlation between the wetting time of the Orally Disintegrating Tablets (ODTs) and water absorption, subsequently influencing the tablets' disintegration time.[39]

Drug content uniformity

The drug content uniformity exhibited values of 98.04±1.2%. The (AV) obtained was 6.3, which is within the acceptable limit of <15.0. This indicates that the dosage units are consistent owing to the repeatability of the production technique.[24]

In vitro drug release

Dissolution profiles are essential quality aspects of tablets that significantly impact a drug's bioavailability and, therefore, its pharmacological efficacy.[40] Dissolution profiles are essential quality aspects of tablets that significantly impact a drug's bioavailability and, therefore, its pharmacological efficacy. Figure 4 illustrates the release pattern of the optimized formulation in a 0.1N Hydrochloric Acid (HCl) solution under laboratory conditions. The dissolution study for the optimized Orally Disintegrating Tablets (ODTs) of Aripiprazole was conducted in 0.1 N HCl, simulating the acidic conditions of the stomach. This medium was chosen because Aripiprazole is a Biopharmaceutics Classification System (BCS) Class II drug with low solubility and high permeability and its solubility is maximized in acidic environments. The use of 0.1N HCl provided a relevant model to evaluate the drug release profile under gastric conditions, which is critical for immediate-release formulations like ODTs.

The findings of the *in vitro* release research showed that the optimized formulation exhibited a considerably high dissolution rate. This was attributed to the tablet rapidly breaking down into

Table 4: Stability study of optimized formulation.

Time	Physical appearance	Drug content (%)	Disintegration time (s)	Hardness (N)	Friability (%)
15 days	White colour	97.42±0.87	60±0.18	45.27± 4.45	0.79±0.11
30 days	White colour	98.62±0.25	65±0.42	47.85±1.56	0.75±0.09
60 days	White colour	95.04±0.77	58±0.36	50.17±3.29	0.81±0.19
90 days	White colour	96.85±0.21	62±0.56	46.25±2.36	0.72±0.12

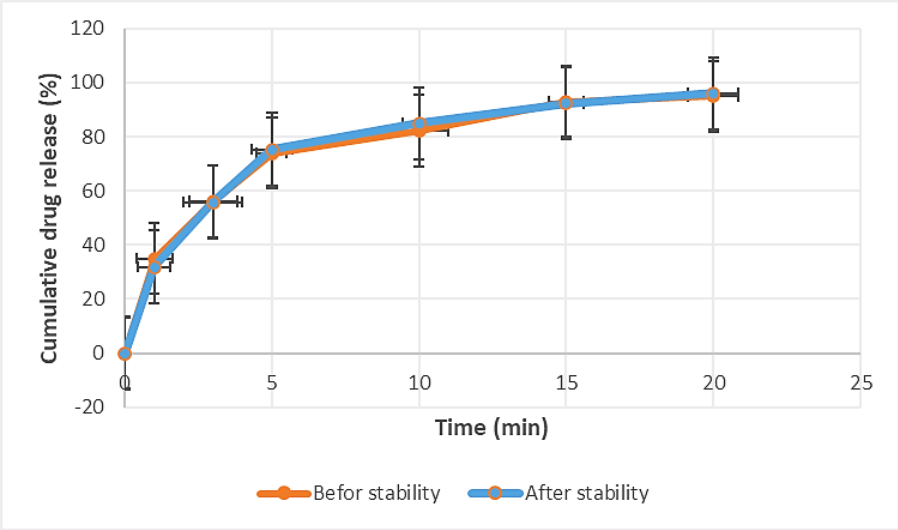

Figure 4: Aripiprazole dissolution profiles during the stability study, both before and following 90 days of storage.

smaller granules and tiny particles, which increased the surface area accessible for dissolving.[41] The dissolution profile revealed that over 80.0% of the drug was released within 30 min, meeting the United States Pharmacopeia (USP) criteria for immediate-release formulations. The rapid disintegration and high dissolution rate observed in 0.1N HCl suggest that the formulation enables a significant portion of the drug to dissolve and potentially be absorbed in the stomach and upper gastrointestinal tract. This is particularly important for drugs like Aripiprazole, which exhibit higher solubility in acidic conditions and may benefit from an increased dissolution rate to enhance bioavailability.[42]

While other dissolution media, such as buffers simulating intestinal pH, were not explored in this study, the results in 0.1N HCl suggest that the formulation effectively facilitates rapid drug release *in vivo* under gastric conditions. To further understand the drug's behavior throughout the gastrointestinal tract, future studies should evaluate the dissolution profile in a broader range of media, including neutral or slightly alkaline conditions, to simulate intestinal environments. This would provide a more comprehensive understanding of the drug's performance *in vivo*.

Stability studies

Stability experiments were conducted on the optimal batch according to the standards set by the International Council for Harmonisation (ICH) for duration of 90 days under accelerated stability conditions (40°C/75% RH). The optimal batch did not exhibit any significant changes in its physical appearance, drug content, disintegration time, hardness, friability and release profile, as seen in Table 4. This demonstrates the excellent stability of the formulation, even under challenging circumstances. Drug release tests were conducted *in vitro* following a 3 months stability test. The results were compared with the initial optimum batch (before stability). Both drug release curves were found to be parallel, showing that there was no change in the drug release behavior for the optimum tablet after 3 months of stability testing, as seen in Figure 4.

CONCLUSION

The adjusted formula of aripiprazole led to a reduction in dispersion time, satisfactory hardness and decreased friability, demonstrated an enhanced *in vitro* dissolving profile and exhibited excellent stability. Optimization outcomes may be achieved by controlling many aspects, such as formulation and process parameters. Implementing the Quality by Design (QbD) method in the development of aripiprazole formulation might assist formulators in gaining a comprehensive knowledge of how Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) impact the Critical Quality Attributes (CQAs) of the end product.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QbD: Quality by Design; **ODT:** Orally Disintegrating Tablet; **APZ:** Aripiprazole; **TPP:** Target Product Profile; **QRA:** Quality Risk Assessment; **FMEA:** Failure Mode Effects Analysis; **CQAs:** Critical Quality Attributes; **CMAs:** Critical Material Attributes; **CPPs:** Critical Process Parameters; **QTPP:** Quality Target Product Profile; **RPN:** Risk Priority Number; **FTIR:** Fourier Transform Infrared Spectroscopy; **AV:** Acceptance Value; **ICH:** International Council for Harmonisation; **DT:** Disintegration

Time; **BCS:** Biopharmaceutics Classification System; **USP:** United States Pharmacopeia.

SUMMARY

This research sought to formulate and enhance Orally Disintegrating Tablets (ODTs) of aripiprazole employing the Quality by Design (QbD) methodology. A complete factorial design was utilized to assess the impact of essential formulation variables-Ludipress, starch and crospovidone-on the Critical Quality Attributes (CQAs) of the tablets, such as disintegration time, hardness and friability. The compatibility between the medicine and excipient was evaluated using FTIR spectroscopy, which confirmed the lack of significant chemical interactions. The improved formulation demonstrated favorable characteristics, including a disintegration time of 66 sec, friability of 0.77% and hardness of 48.35 N. Stability experiments performed under expedited settings demonstrated that the formulation maintained its physical and chemical integrity for 90 days. The research illustrates the effectiveness of the QbD technique in developing a reliable formulation with uniform performance, addressing the requirements of patients needing rapid-onset drugs.

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