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Evaluation of the physical properties of an orodispersible tablet containing melatonin and pyridoxine HCl (Vitamin B6)

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ABSTRACT: Individuals deficient in melatonin are more prone to experiencing difficulties with sleep. The creation of an orally disintegrating tablet formulation of melatonin (MT) would enable a rapid and efficacious response to the population's needs. This formulation is suitable for all individuals, including the elderly and children, and is also preferred due to its pleasant taste. The text in question discusses the role of pyridoxine (PY) as a vital coenzyme involved in a number of physiological processes within the human body. The text emphasises the necessity of obtaining pyridoxine (PY) from external sources, given that the body is incapable of producing it autonomously. Moreover, the text delineates the formulation of a tablet containing both MT and PY, which is designed for convenient use and enhanced efficacy. Moreover, the text delineates the exhaustive testing regimen, which encompasses weight deviation, friability, disintegration time, moisture content, diameter and height measurements, and hardness tests, to ensure the physical stability of the manufactured tablets. The aforementioned tests demonstrated that the tablet satisfied the criteria set forth in the European Pharmacopoeia. The results of the physical tests conducted on the tablet containing MT and PY demonstrated that the values obtained were within the desired range and in accordance with the standards set forth in the European Pharmacopoeia. The mean hardness of the manufactured tablets was determined to be within the range of 27 ± 3.2 to 35 ± 1.5 Newton. In the friability test, the efficiency ratio was calculated to be 99.793. It is a widely accepted principle that the diameter and thickness of tablets should be 1/4. The results demonstrate that all ODTs exhibit this characteristic. The tablets were found to possess both hardness and friability, which ensures that the tablet remains stable and reduces losses to a minimum. The mean diameter of the tablets was found to be 7.08 ± 0.01 mm, with a mean height of 2.50 ± 0.01 mm. Furthermore, the mean diameter was determined to be 6.97 ± 0.01 mm, with a mean height of 3.21 ± 0.01 mm. The standardisation of the tablets was successfully accomplished. The disintegration test yielded an average disintegration time of between 20 and 28 seconds for the tablets in the oral cavity, which was deemed optimal. In conclusion, the text suggests that further evaluation through in vivo and in vitro tests could be conducted to further develop the formulation.

KEYWORDS: Melatonin; pyridoxine (vitamin B6); orodispersible tablet; formulation; physical analysis.

1. INTRODUCTION

A multitude of factors influence the bioavailability of drugs, cosmetics and foods [1]. The most significant of these factors is the carrier system of the cosmetic, food supplement, or drug. It has been asserted that the carrier system is instrumental in enhancing the absorption of the active ingredient in cosmetic products[2] and in safeguarding the barrier function in the urine-contact areas of the skin in infants [3]. These systems are effective for enhancing the bioavailability of synthetic and herbal compounds with antioxidant, antibacterial, and antidiabetic properties [4-6]. In the context of food supplements, carrier systems have been employed to prepare alcohol-free products, particularly for use in children [7]. In the context of drug carrier systems, liposomes have demonstrated considerable efficacy in enhancing the anticonvulsant effect [8], accelerating wound healing [9,10], and augmenting the antifungal activity of essential oils [11]. For vitamins, nanofibre transdermal patches have been demonstrated to enhance

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bioavailability [12]. Furthermore, transdermal carrier systems designed to mitigate the first-pass effect in the liver when hormones are administered topically have been developed [13]. Melatonin is one of the hormones that presents bioavailability issues. The most prevalent utilisation of MT is in the management of sleep disorders. The medication facilitates the onset of sleep and improves the quality of sleep. PY plays an active role in the synthesis of proteins. Proteins serve as the fundamental structural units of the human body [14]. MT (N-acetyl-5-methoxytryptamine) is an indole amine produced by several organs within the human body. The pineal gland is the primary source of MT production in response to darkness. Additionally, other organs are capable of producing MT, including the skin, bone marrow, lymphocytes, retina, and gastrointestinal tract [15}. MT was initially identified by Aaron Lerner in 1958 and has since been demonstrated to regulate circadian rhythms and exert numerous other beneficial effects [16]. In this study, the objective was to transform MT and PY into orally disintegrating tablets, with the aim of developing a formulation that would be suitable for individuals. The objective of the fast-disintegrating formulation was to provide rapid relief to individuals in a short time. Physical tests were conducted on the orally disintegrating tablet produced via the direct compression method, and the quality and control of the tablets were evaluated [17].

Orodispersible tablets disintegrate and/or dissolve rapidly in the oral cavity and are not intended for ingestion [18]. Tablet formulations are designed in such a way that the active pharmaceutical ingredient can be released and absorbed in the gastrointestinal tract as intended, with the objective of maximising the effectiveness of the active ingredient. In the context of pharmaceutical development, routine tests are conducted to evaluate the efficiency with which a drug is released from the dosage form and to ascertain its physical stability throughout the manufacturing phase [19,20]. In the pharmaceutical industry, tablets are primarily manufactured through one of three fundamental production processes: dry granulation, wet granulation, and direct compression [21,22]. Granulation is a crucial process in the production of pharmaceutical solid oral dosage forms. It is typically employed to enhance the flowability of powders and prevent their mixing [23]. The process ensures the uniformity of particle formulations and prevents the separation of active pharmaceutical ingredients and the formation of dust, thereby enhancing stability. The granules produced are used as a pharmaceutical dosage form, though they are more frequently employed as an intermediate step in the production of tablets. Granulation processes can be broadly classified into two categories: wet granulation and dry granulation [24]. Granulation is a process of size enlargement whereby small particles coalesce to form larger, more permanent aggregates, which retain the original particles as identifiable components. Granulation is achieved through the agitation of moistened powders in mixing equipment, compaction, extrusion, and size enlargement by spheronization [25]. The process is employed for the purpose of developing and enhancing the formulation properties of a given substance, including those pertaining to fluidity and compressibility. The selection of an appropriate granulation process in pharmaceutical production is dependent on a number of factors, including the specific production conditions and the characteristics of the formulation in question [26]. The advancement of immediate-release and modified-release tablet formulations represents a substantial area of investigation within the domain of oral solid dosage form development. In comparison to other forms of tablet, this one has the advantage of a rapid effect and ease of use.

2. RESULTS

2.1 Preformulation study

The characteristics of the active ingredients were analysed using a combination of organoleptic, physicochemical and spectrophotometric methods. The results demonstrated that the colour, odour and texture of MT and vitamin PY were consistent with the official values. Furthermore, the spectrophotometric measurement results indicated that the absorption peak value of MT was 225 nm, while that of PY(B6) was 290 nm.

2.2 Experimental studies on powder mixtures

The direct printing method was selected to produce tablets. The values of the powder mixtures' bulk density, tapped density, Hausner's ratio and compressibility index are presented in Table 1 for reference. Upon analysis of the flow properties of the powder mixtures, it was observed that the Hausner ratio ranged between 1.15 ± 0.33 and 1.25 ± 0.37, while the compressibility index (in percentage) ranged between 14.71 ± 0.24 and 28.57 ± 0.22. It was stated that the Hausner ratio was between 1.25 and 1.00, and the compressibility value was between 20% and 1%. These flow properties were deemed suitable for the direct printing method of the powder mixtures.

Table 1. Precompression properties of powder mixtures (n=6).

Formulation Code	Bulk Density(g/mL) (n=6)	Tapped Density (g/mL) (n=6)	Hausner's Ratio	Compressibilty Index (%)
MT/PY-F1	0.34 ± 0.13	0.39 ± 0.05	1.15 ± 0.33	14.71 ± 0.24
MT/PY-F2	0.35 ± 0.17	0.41 ± 0.08	1.17 ± 0.42	17.14 ± 0.20
MT/PY-F3	0.38 ± 0.14	0.45 ± 0.07	1.18 ± 0.35	18.42 ± 0.21
MT/PY-F4	0.24 ± 0.15	0.30 ± 0.04	1.25 ± 0.37	25.00 ± 0.22
MT/PY-F5	0.30 ± 0.19	0.37 ± 0.06	1.23 ± 0.38	23.33 ± 0.20
MT/PY-F6	0.32 ± 0.15	0.38 ± 0.07	1.19 ± 0.35	18.75 ± 0.20
MT/PY-F7	0.32 ± 0.11	0.37 ± 0.05	1.16 ± 0.41	15.63 ± 0.21
MT/PY-F8	0.31 ± 0.12	0.37 ± 0.06	1.19 ± 0.40	19.35 ± 0.24
MT/PY-F9	0.29 ± 0.14	0.35 ± 0.09	1.21 ± 0. 31	20.69 ± 0.25
MT/PY-F10	0.28 ± 0.16	0.36 ± 0.10	1.23 ± 0.33	28.57 ± 0.22
MT/PY-F11	0.30 ± 0.11	0.37 ± 0.08	1.16 ± 0.36	23.33 ± 0.21

2.3. Organoleptic Control

The colour, shape, smell and taste of ODT tablets may be significant factors in determining the dosage form to be administered and may influence the efficacy of the treatment, with potential psychological implications for the patient. All tablets exhibited satisfactory organoleptic characteristics, including colour, shape, smell and taste.

2.4. Weight Variation

A random selection of 20 tablets was subjected to a weight uniformity analysis. The results demonstrated that no more than 2 tablets exhibited a weight variation exceeding 7.5% of the mean weight value.

2.5. Hardness Test

The mean hardness was determined to be 118.1 Newton and is presented in Table 2. The hardness of standard tablets is typically within the range of 25-35 Newtons, while tablets that disintegrate over an extended period, such as sublingual tablets, exhibit higher hardness values. These findings are optimal for tablets that disintegrate within the oral cavity (Table 2).

2.6. Tablet Diameter and Height

In accordance with the results of the size measurement, ODT tablets exhibiting a flat surface were selected at random. The average diameter of the tablets was calculated to be 7.08 ± 0.01 mm, while the average height was calculated to be 2.66 ± 0.01 mm. The data are presented in Table 2.

2.7. Friability and abrasion

Following a comprehensive examination of the tablets, they were placed in the friabiliser. Following 100 cycles, the machine was terminated, and the tablets were weighed. It is established that the results of the crumbling determination should fall within the range of 0.1 to 0.8%. A crumbling loss exceeding 1% is indicative of suboptimal crumbling. In order to print the ODT tablets, a pressure of 1N and a printing time of 30 seconds were applied. The crumbling results of the tablets exhibited a range of 0.88% to 1.25%.

Table 2. Tablet weights and deviations, hardness, diameter and width, diameter and height values.

Formulation Code	Weight (mg)	Hardness (N)	Diameter(mm)	Height(mm)
MT/PY-F1	96.41 ± 0.61	35 ± 1.5	7.06 ± 0.01	2.51 ± 0.01
MT/PY-F2	97.32 ± 0.65	30 ± 2.1	6.97 ± 0.01	2.48 ± 0.01
MT/PY-F3	97.12 ± 0.67	28 ± 3.4	7.04 ± 0.01	2.61 ± 0.01
MT/PY-F4	96.21 ± 0.59	27 ± 3.2	7.05 ± 0.01	2.47 ± 0.01
MT/PY-F5	95.23 ± 0.56	28 ± 2.4	7.04 ± 0.01	2.28 ± 0.01
MT/PY-F6	94.31 ± 0.58	29 ± 2.3	7.05 ± 0.01	2.57 ± 0.01
MT/PY-F7	96.12 ±0.72	34 ± 2.5	7.04 ± 0.01	2.66 ± 0.01
MT/PY-F8	98.21 ± 0.55	32 ± 2.6	7.03 ± 0.01	2.64 ± 0.01
MT/PY-F9	95.65 ± 0.46	30 ± 2.7	7.05 ± 0.01	2.56 ± 0.01
MT/PY-F10	94. 23 ± 0.76	28 ± 2.4	7.08 ± 0.01	2.65 ± 0.01
MT/PY-F11	96.34 ± 0.71	31 ± 2.3	7.07 ± 0.01	2.56 ± 0.01

2.8. Disintegration time

In accordance with the stipulations set forth in the European Pharmacopoeia, orally disintegrating tablets are required to disintegrate within the oral cavity within a period of three minutes. The results of the test, which was conducted with six tablets, indicated that the average disintegration time had decreased from 28 seconds to 20 seconds. This is consistent with the data presented in Table 3 of the European Pharmacopoeia.

Table 3. The results of the ODTs; friability, disintegration and dissolution.

Formulation Code	% Friability	Disintegration time (s)
MT/PY-F1	0.88	25
MT/PY-F2	0.94	24
MT/PY-F3	0.98	20
MT/PY-F4	1.25	27
MT/PY-F5	1.19	25
MT/PY-F6	1.13	22
MT/PY-F7	0.86	25
MT/PY-F8	0.93	23
MT/PY-F9	0.96	20
MT/PY-F10	1.17	27
MT/PY-F11	1.09	28

2.9. Dissolution test

The outcomes of the dissolution test of ODT tablets in which crospovidone and croscarmellose sodium were employed as superdispersants are presented in Figure 1 and Table 4. It is anticipated that effervescent tablets will release a minimum of 75% of the active substance within a 30-minute period. It was observed that samples of 5 mL taken at different times released between 50.08 ± 0.97% and 71.28 ± 1.08% of

the active substance after five minutes, 65.48 ± 1.17% and 83.28 ± 1.28% at 10 minutes, 75.21 ± 1.21% and 91.18 ± 1.31% at 15 minutes, and that all tablets released more than 75% of the active substance at 30 minutes.

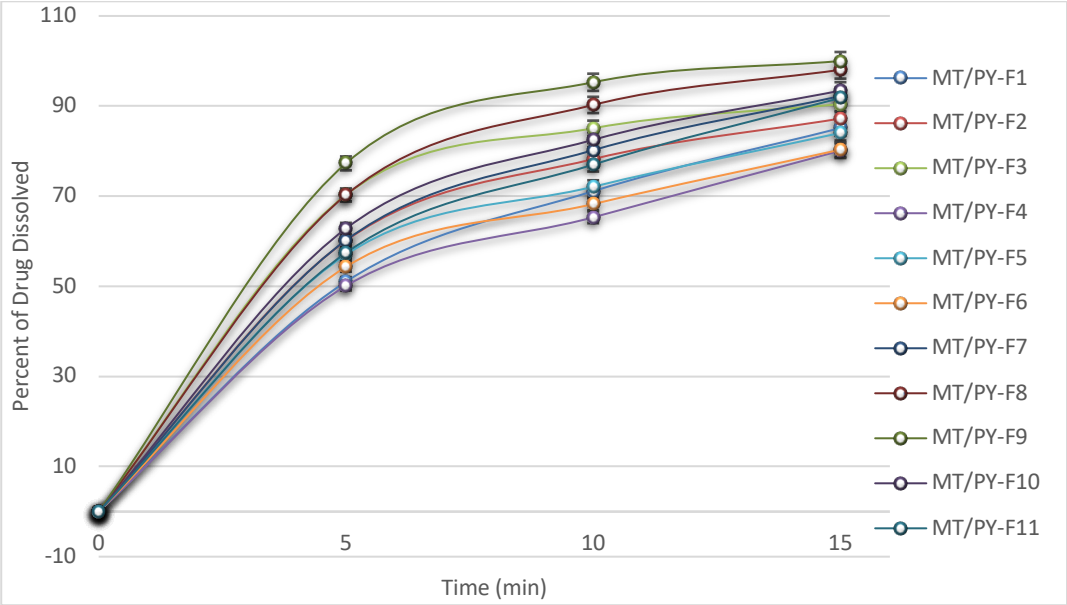

Figure 1. *In-vitro* dissolution parameters in pH 6.8 phosphate buffer (n=3 ± SD).

3. DISCUSSION

MT is soluble in both water and fat, thereby circumventing any potential impediments and facilitating effective functioning in a multitude of bodily systems. The MT hormone exerts a variety of effects, thereby enabling its utilisation for a multitude of purposes [27]. Moreover, the absence of any stated side effects provides an opportunity for the safe use of MT [28]. It is hoped that this review of the literature has demonstrated the continued relevance of MT and that further studies will be conducted in this area. Moreover, it is anticipated that the data and documentation pertaining to the mechanisms of action of MT may not be exhaustive and comprehensive. It is similarly hoped that the identified deficiencies will be addressed in subsequent studies.

This marks the inaugural investigation of an oral MT pharmaceutical formulation, designed to dissolve in the mouth. The pharmacological effects of this formulation were confirmed by the inclusion of PY. The objective of the tablet is to enhance patient compliance due to its straightforward administration and rapid onset of action [29,30].

In consideration of the properties of the powder mixtures, the Hausner ratio ranged from 1.15 ± 0.33 to 1.25 ± 0.37, while the printability values ranged from 14.71 ± 0.24 to 28.57 ± 0.22. The Hausner ratio should fall within the range of 1.00-1.25, while the printability index should be between 1-20, in order for direct printing to be an acceptable option. The powder blend with the optimal flow properties was identified as MT/PY F1. Melatonin is employed as a bulking agent in the highest proportion in this formulation. The bulk density of melatonin is 0.47 g/cm^3, while the tapped density is 0.57 g/cm^3. Additionally, sodium croscarmellose is utilised at the lowest concentration. The findings indicated that alterations in the ratios of dispersant and super-dispersant resulted in modifications to the flow properties of the powders.

The results of the physical tests conducted on the tablet containing MT and PY demonstrated that the values obtained were within the desired range and in accordance with the standards set forth in the European Pharmacopoeia. The mean hardness of the manufactured tablets was determined to be within the range of 27 ± 3.2 to 35 ± 1.5 Newton. In the friability test, the efficiency ratio was calculated to be 99.793.

Table 4. *In vitro* dissolution test result for MT concentration (n=3).

Formulation Code	D_5 (%)	D_{10} (%)	D_{15} (%)
MT/PY-F1	51.02±1.14	71.11±1.32	85.12±1.24
MT/PY-F2	60.12±1.18	78.23±1.08	87.23±1.02
MT/PY-F3	70.28±1.12	85.07±1.34	90.45±1.02
MT/PY-F4	50.08±0.97	65.31±1.21	80.08±1.07
MT/PY-F5	57.02±1.44	72.09±1.14	84.02±1.15
MT/PY-F6	54.32±1.11	68.25±1.27	80.32±1.19
MT/PY-F7	60.21±1.17	80.21±1.35	92.21±1.18
MT/PY-F8	70.25±1.03	90.25±1.87	98.05±1.03
MT/PY-F9	77.28±1.08	95.28±1.15	100.00±0.94
MT/PY-F10	62.82±0.98	82.51±1.02	93.43±0.85
MT/PY-F11	67.42±1.08	77.01±1.67	91.80±1.81

It is widely acknowledged that the diameter and thickness of tablets should be 1/4. The results demonstrate that all ODTs exhibit this characteristic. The tablets were found to be both hard and friable, which ensures that the tablet remains stable and reduces losses to a minimum. The mean diameter of the tablets was determined to be 7.08 ± 0.01 mm, with a mean height of 2.50 ± 0.01 mm. The mean diameter was also determined to be 6.97 ± 0.01 mm, with a mean height of 3.21 ± 0.01 mm. The standardisation of the tablets was successfully achieved. The disintegration test yielded an average disintegration time of between 20 and 28 seconds for the tablets in the oral cavity, which was deemed optimal. The low degree of ambient humidity sensitivity and the resulting stability confer advantages.

4. CONCLUSION

Subsequently, *in-vivo* and *in-vitro* studies can be conducted on the tablet to examine the parameters associated with its absorption, distribution, metabolism, and elimination, as well as to investigate the efficacy of the formulation in the context of treatment. The incorporation of diverse active and excipient substances into the tablet composition enables the formulation of a novel composition.

5. MATERIALS AND METHODS

5.1 Materials

The rapidly disintegrating melatonin and pyridoxine tablets comprise the following components: Melatonin (Sigma Aldrich, Germany), Pyridoxine (Sigma Aldrich, Germany), Aerosil (Colloidal silicon dioxide; Evonik Rohm GmbH, Germany), Mannitol (Sigma Aldrich, Germany), Polyvinylpyrrolidone K-30 (Crospovidone; Fluka, Germany), Microcrystalline cellulose (Avicel PH 101; FMC Biopolymer, Philadelphia), Aspartame (Deva Holding, Turkey), Magnesium stearate (Riedel de Haen, Germany), Sodium Bicarbonate (Sigma Aldrich, Germany), Citric Acid (Sigma Aldrich, Germany), Sucralose (Sigma Aldrich, Germany), Orange Flover (Sigma Aldrich, Germany).

5.2 Methods

The physicochemical properties of MT and vitamin PY were investigated with a view to characterising the powder mixture and guaranteeing its efficacy before proceeding to the production of rapidly disintegrating tablets in the oral cavity.

The UV-vis spectrum of MT and PY was performed with the Cary 60 UV-Vis (USA) instrument. This was used to determine the precision, security and accuracy values for the validation of the analytical method.

The bulk density, tapped density, compressibility index and Hausner ratio of MT/PY ODT blends were evaluated in order to assess the prepressibility properties of the mixture.

5.2.1. Determination of weight variation

The powder mixture was introduced into a 10 mL tared tape measure, which was then left to stand without any disturbance or compression. The volume was filled to the 10 mL line, after which the weight was re-determined. This procedure was repeated ten times.

5.2.2. The determination of bulk and tapped densities

The determination of bulk and tapped densities was conducted in accordance with the United States Pharmacopeia (USP) methods I and II, respectively. The former involved the use of a standard device, whereas the latter employed a specialised apparatus. Subsequently, the compressibility index and Hausner ratio were calculated using the formulations delineated in Equations 1 and 2. The aforementioned investigative procedures will facilitate the estimation of the pre-pressibility characteristics of the powder mixtures that constitute MT/PY oral dissolving tablet (ODT) formulations, thereby enabling the prediction of their flow properties.

Table 5. Orodispersible tablet formulation containing MT and PY.

INGREDIENTS	MT/PY-F1	MT/PY-F2	MT/PY-F3	MT/PY-F4	MT/PY-F5	MT/PY-F6	MT/PY-F7	MT/PY-F8	MT/PY-F9	MT/PY-F10	MT/PY-F11
Melatonin (%)	2	2	2	2	2	2	2	2	2	2	2
Pyridoxine(B6) (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Silica colloidal anhydrite (%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol (%)	74.5	64.5	54.5	34.5	34.5	44.5	74.5	64.5	54.5	34.5	44.5
Crosscarmellose Sodium	10	20	30	0	10	10	0	0	0	0	0
Crospovidone (%)	0	0	0	0	0	0	10	20	30	10	10
Magnesium stearate (%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sodium Bicarbonate (%)	0	0	0	30	24	18	0	0	0	24	18
Citric acid (%)	0	0	0	20	16	12	0	0	0	16	12
Sucralose (%)	5	5	5	5	5	5	5	5	5	5	5
Orange Flavor (%)	5	5	5	5	5	5	5	5	5	5	5
Total	100	100	100	100	100	100	100	100	100	100	100

The following tests were conducted on the tablets produced: weight deviation determination, calculation of tablet diameter and height, determination of hardness, determination of crumbling and abrasion, determination of disintegration time, and determination of moisture content. Furthermore, an investigation was conducted to ascertain the durability and stability of the tablets. The aforementioned data are of significant importance throughout the production, packaging and transportation of the tablets.

5.2.3. Determination of weight deviation

In order to ascertain the weight deviation of ODT tablets, a random sample of 20 tablets was selected and weighed using the aforementioned device. Subsequently, the mean weight (in mg) and standard deviation (SD) values were calculated. The weight deviation was evaluated in accordance with the maximum deviation values accepted in the Turkish Pharmacopoeia.

5.2.4. Determination of tablet diameter and height

A caliper, a precision instrument, is utilised for this procedure. Ten tablets were measured with the OEM KMP150 digital caliper, and the diameter and height values of each were recorded. Subsequently, the mean and standard deviation values were calculated.

5.2.5. Determination of hardness

The determination of tablet hardness was conducted utilising the Sotax MT 50 hardness tester device. The device is capable of precisely measuring a number of characteristics of the tablet, including width, length, diameter, hardness, and weight. Ten tablets were selected for hardness testing using the aforementioned hardness tester. The tablet was positioned between two probes, one of which was a moving probe and the other a stationary probe of the hardness tester. Subsequently, a force was applied by the

moving probe. The breaking force of the tablet, which was taken as the hardness of the tablet, was recorded. The values for hardness, diameter, and width were calculated for each of the ten tablets.

5.2.6. Determination of friability

The friability test was conducted using the Sotax FT2 device, in accordance with the established protocol. Twenty tablets were randomly selected and weighed on a precision electronic balance, and the total weight was recorded. In accordance with the stipulations set forth by the Turkish Pharmacopoeia, the maximum permissible deviation resulting from the comminution process is employed as a general criterion for acceptance. Moreover, the friability was calculated as a percentage change in weight under controlled conditions.

5.2.7. Determination of disintegration time

The apparatus for determining the disintegration time of tablets comprises a motor, an arm, and a thermostatic water bath. Each arm is connected to a basket, which contains six tubes. The experiment was conducted using the Sotax DT 50 device. In accordance with the USP and IP, six tablets were placed in six baskets to simulate in vivo conditions, forming one sample for the determination of the disintegration time of tablets. The tablets must be dispersed within three minutes in a distilled water environment at 37°C.

5.2.8. Dissolution test

The rate of *in-vitro* drug release represents a significant limiting factor, as the dissolution of the tablet is a prerequisite for the absorption of the active substance. The majority of pharmacopoeias describe a variety of devices. In this study, the Sotax AT7 Smart (Germany) apparatus, designated XXIV (paddle assembly) in accordance with the United States Pharmacopeia (USP), was utilised. The following test conditions were employed: The test conditions were as follows: the apparatus was placed in a "sink" environment at 37±5°C, a sufficient volume of phosphate buffer (pH 6.8) was added, and the pedal was rotated at a speed of 50 rpm for 30 minutes. The quantity of MT released was determined by filtering the solution through Whatman filter paper and measuring the absorbance at 222 nm using a spectrophotometer.

5.6. Statistical analysis

Data from the physicochemical, and quality control studies were statistically analyzed with the aid of the Statistical Analysis Software (SPSS version 22. Inc.). One-way analysis of variance (ANOVA) was performed for comparison ($P<0.05$).

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