Journal of Research in Pharmacy

Research Article

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Stability studies of compression coated ornidazole tablets for colon specific drug delivery

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Received: 22 May 2018 / Revised: 09 August 2018 / Accepted: 14 August 2018

ABSTRACT: In our previous study, colon targeted tablets of ornidazole were prepared with compression coating technique. Pectin was used as the coating layer and different ethyl cellulose (EC) types (EC N7, N 10 and N 100) were added to Pectin to enhance mechanical and release properties. The object of the present study was performed stability testing of these coated tablets of ornidazole in a high density polyethylene plastic bottle with/without silica gel as per ICH guidelines. For this aim, several quality-control parameters such as uniformity of weight, diameter and thickness of tablets, tablet hardness, friability, content uniformity and tablet dissolution rate are determined in stability conditions (25±2°C / 60±5% relative humidity and 40±2°C / 75±5% relative humidity). These parameters were evaluated at 0 month, 3 month, 6 month and 12 month intervals. It was concluded that the coated ornidazole tablets should be stored in a high density polyethylene plastic bottle with silica gel at controlled room temperature (25°C) or below their relative humidities and the presence of desiccant in the market package was essential.

KEYWORDS: Stability studies; compression coated ornidazole tablet; ethylcellulose; characterization of tablet; dissolution study.

1. INTRODUCTION

Stability of a pharmaceutical dosage form is defined as the time lapse during which the drug product retains, within specified limits and throughout its period of storage and use, same properties and characteristics that it possessed at the time of its manufacture. USP defines stability of pharmaceutical product as, "extent to which a product retains within specified limits and throughout its period of storage and use. It is a routine performed at various stages of product development and it must be demonstrated that pharmaceutical product characteristics from the production haven't changed until the patient's use. So, the stability is the most important quality indicator [[1]-[3]].

The stability of product is expressed as the expiry period or technically as shelf life which is valuable quality attribute for all pharmaceutical dosage forms [[1]]. It is important for patient's safety, drug efficacy, build in quality and expiration date of the product. These studies are performed by exposing the representative sample of pharmaceutical product to environmental factors such as temperature, humidity and light [[3], [5]]. Stable tablets retain their original size, shape, weight, roughness, colour variation, cracking under normal handling and storage conditions throughout their shelf life.

In general, a dosage form should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use. The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period [[6], [7]].

The aim of this study was to evaluate the stability of compression coated ornidazole tablets as per ICH guidelines [[8], [9]]. For the preparation of tablets, pectin was used as the coating layer and mixed with ethyl cellulose to enhance the mechanical and release properties. The stability of tablets were evaluated with the parameters of weight variation, diameter, thickness, hardness, friability, content uniformity and dissolution at different time intervals of 0, 1, 3, 6 and 12 months as function of temperature and relative humidity.

How to cite this article: Rençber S, Şenyiğit Y, Özyazıcı M. Stability studies of compression coated ornidazole tablets for colon specific drug delivery. J Res Pharm. 2019; 23 (1): 34-43.

https://doi.org/10.12991/jrp.2018.106
ISSN: 2630-6344

2. RESULTS AND DISCUSSION

2.1. Preparation of tablets

Compression coated ornidazole tablets were successfully prepared. They showed a uniform, smooth and shiny surface, without coating defects.

2.2. Stability studies

Stability testing was carried out to provide evidence of how the quality of the manufactured tablets may change with time under the influence of environmental factors such as temperature and humidity and storage clousure with silicagel or without silicagel. They were important and necessary for observing drug's degradation in the process of time. Stability study was carried out in climatic chamber at 25±2°C/60±5% relative humidity for 12 months and 40±2°C/75±5% relative humidity for 6 months. In stability studies, compression coated ornidazole tablets were evaluated by weight variation, diameter, thickness, hardness, friability, content uniformity and tablet dissolution rate.

2.2.1. Uniformity of weight

In this study, at the beginning the average weights of F1-F6 were found to be 0.61±0.00 g, 0.61±0.00 g, 0.60±0.00 g, 0.60±0.00 g, 0.60±0.00 g and 0.60±0.00 g, respectively. The pharmacopoeial limit for the percentage deviation for the tablets of more than 250 mg is ± 5% of the weight [[17], [17]]. At the end of stability studies, the average weight of all tablet formulations was found to be within the pharmacopeia limitations, and hence all formulations passed the test for uniformity of weight as per official requirements (Table 2). Also, the results showed at the end of 12 months the average weight of tablets in a high density polyethylene plastic bottle without silica gel increased due to relative humidity but the increase in weight is not significantly different ($p \geq 0.05$). However, no visible changes were observed in the tablets after storage in a high density polyethylene plastic bottle with silica gel for 6 / 12 months.

2.2.2. Diameter and thickness studies

The diameter and thickness values of all tablets in a high density polyethylene plastic bottle without silica gel were increased (Table 1). No visible changes were observed in the tablets after storage in a high density polyethylene plastic bottle with silica gel for 12 months (Table 2). In pharmacopoeias, there is no records about the diameter/thickness ratio of the tablets, however it is a general relationship that generally thickness should not be more than 1/2 of the tablet diameters. According to Güven [[16]], diameter / thickness ratio must be four. In the literature, it was seen that there were tablets which did not have diameter / thickness ratio as four but nothing clear about what could be the harmful. Diameter/thickness ratio results of the tablets were presented in Table 1 and 2 and these ratios of all tablet formulations were below 4 during stability studies.

2.2.3. Tablet hardness

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping. The force required to break a tablet along its diameter is defined as the hardness or crushing strength of a tablet [[19]]. The recommended value for oral tablet hardness is 4-8 kg [[20], [21], [22]]. At the beginning, all of the formulations showed a high hardness value in the range of 7.23-8.17 kg/Monsanto (Table 1-2). After keeping in stability chamber for 12 months at controlled temperature and humidity, hardness values of tablets in a high density polyethylene plastic bottle without silica gel were changed significantly. However, no visible changes were observed in the tablets after storage in high density polyethylene plastic bottle with silica gel for 12 months (Table 2). Tablet hardness is not an absolute indicator of strength. Therefore, the ability of the compressed tablet to avoid fracture and breaking was also tested with friability studies.

2.2.4. Friability

Tablets are constantly subjected to mechanical shocks and aberration during the manufacturing, packing and transportation process. Therefore, tablets should be formulated to withstand such stress. In order to see the resistance of tablets, friability tests are routinely performed. Friability refers the ability of the compressed tablet to avoid fracture and breaking during transport and it is defined as the % weight loss of tablets during the test. Shafer et. al. [[23]], mentioned that a loss was not more than 1 % was normal but especially less than 0.8 % of loss was also considered as normal. In the present study, friability values of all tablet formulations were below 1%, indicating that the friability is within the limits ($p \geq 0.05$) (Table 2).

2.2.5. Content uniformity

At the beginning, coated tablets were found to contain 94-97% of amount indicating uniformity of content uniformity (Table 1 and 2) . The results showed that at the end of 12 months the content of tablets in a high density polyethylene plastic bottle with silica gel are not significantly different ($p \geq 0.05$) (Table 2). However, the content uniformity values were decreased in a high density polyethylene plastic bottle without silica gel slightly.

2.2.6. In vitro drug release study

In vitro release studies were performed to evaluate the ability of the coat layer to remain intact and prevent drug release in the physiological environment of stomach and small intestine. Therefore, conditions mimicking mouth to colon transit were used and tablets were tested in pH 1.2 HCl buffer for 2 h and then the dissolution medium was replaced with pH 6.8 phosphate buffer for 3 h. After that, pectinolytic enzymes (Pectinex 3XL) were added to dissolution medium to evaluate the susceptibility of the coat layer to bacterial enzymatic break down in colon. These pectinolytic enzymes were good for degrading soluble and insoluble pectins with varying degrees of esterification [14, [24]].

The release rate of ornidazole was found to be ≈89-96% in the mimicking conditions of colon at the end of 24 h (Table 3-4). However, in both of the stability conditions, drug release rate of tablets in a high density polyethylene plastic bottle without silica gel decreased significantly in 24 hours at the end of 6/12 months (Table 3). However, no visible changes were observed in the tablets after storage a high density polyethylene plastic bottle with silica gel for 12 months (Figure 1, Table 4). Similar results were found in the literature for *in vitro* drug release of tablets ([2], [25]).

Table 1. Summary of stability studies in a high density polyethylene plastic bottle without silica gel

Code	Time (month)	Appearance	Weight (mg)	Diameter/ thickness ratio	Hardness (kg /monsanto)	Friability (%)	Content Uniformity	Drug Released (%) (24 h)
F1	t=0	Appropriate	0.61±0.00	3.61±0.03	7.83±0.83	0.12	96.32±0.29	94.91±0.54
	t=12 (25°C)	Appropriate	0.64±0.02	3.29±0.09	7.30±1.32	0.10	90.82±0.61	85.22±0.85
	t=6 (40°C)	Appropriate	0.66±0.01	3.16±0.05	6.76±1.20	0.08	85.72±0.38	79.00±0.86
F2	t=0	Appropriate	0.61±0.00	3.57±0.04	8.17±0.29	0.10	95.23±0.34	89.50±0.64
	t=12 (25°C)	Appropriate	0.64±0.01	3.07±0.06	7.96±1.03	0.08	86.28±0.35	80.56±1.02
	t=6 (40°C)	Appropriate	0.65±0.02	3.00±0.06	6.20±0.90	0.06	79.91±0.37	75.12±2.90
F3	t=0	Appropriate	0.60±0.00	3.67±0.08	7.95±0.62	0.11	96.14±0.53	94.06±0.49
	t=12 (25°C)	Appropriate	0.64±0.01	3.09±0.16	7.60±1.01	0.08	85.50±0.36	82.97±1.31
	t=6 (40°C)	Appropriate	0.65±0.02	2.96±0.16	6.70±1.03	0.07	77.05±0.63	78.00±1.93
F4	t=0	Appropriate	0.60±0.00	3.65±0.10	8.53±0.23	0.16	100.0±0.56	96.84±0.35
	t=12 (25°C)	Appropriate	0.63±0.01	3.24±0.07	7.20±1.03	0.11	87.98±0.46	87.00±1.05
	t=6 (40°C)	Appropriate	0.64±0.03	3.12±0.07	6.30±1.00	0.09	78.28±0.57	79.25±1.99
F5	t=0	Appropriate	0.60±0.00	3.51±0.06	7.87±0.63	0.19	96.46±0.53	91.67±1.92
	t=12 (25°C)	Appropriate	0.64±0.01	3.35±0.26	7.30±1.05	0.15	82.85±0.29	79.03±1.24
	t=6 (40°C)	Appropriate	0.65±0.01	3.32±0.26	6.40±0.46	0.12	78.01±0.38	77.78±2.29
F6	t=0	Appropriate	0.60±0.00	3.48±0.08	7.23±0.23	0.13	94.45±0.19	94.31±1.25
	t=12 (25°C)	Appropriate	0.64±0.01	3.12±0.09	6.60±1.30	0.10	85.78±0.55	83.72±1.56
	t=6 (40°C)	Appropriate	0.66±0.02	3.07±0.09	5.71±029	0.08	72.15±0.76	76.00±2.29

Table 2. Summary of stability studies in a high density polyethylene plastic bottle with silica gel .

Code	Time (month)	Appearance	Weight (mg)	Diameter/ thickness ratio	Hardness (kg /monsanto)	Friability (%)	Content Uniformity	Drug Released (%) (24 h)
F1	t=0	Appropriate	0.61±0.00	3.61±0.03	7.83±0.83	0.12	96.32±0.29	94.91±0.54
	t=12 (25°C)	Appropriate	0.61±0.00	3.60±0.05	7.81±0.35	0.12	96.50±0.32	94.85±0.48
	t=6 (40°C)	Appropriate	0.62±0.01	3.59±0.04	7.79±0.42	0.11	95.12±0.18	93.21±1.74
F2	t=0	Appropriate	0.61±0.00	3.57±0.04	8.17±0.29	0.10	95.23±0.34	89.50±0.64
	t=12 (25°C)	Appropriate	0.61±0.00	3.56±0.03	8.15±0.52	0.10	95.61±0.21	89.85±0.96
	t=6 (40°C)	Appropriate	0.62±0.00	3.55±0.05	8.12±0.32	0.09	94.02±0.38	86.14±2.23
F3	t=0	Appropriate	0.60±0.00	3.67±0.08	7.95±0.62	0.11	96.14±0.53	94.06±0.49
	t=12 (25°C)	Appropriate	0.60±0.00	3.67±0.06	7.93±0.46	0.10	94.41±0.45	94.64±1.71
	t=6 (40°C)	Appropriate	0.61±0.00	3.65±0.03	7.91±0.61	0.09	92.97±0.26	91.71±1.23
F4	t=0	Appropriate	0.60±0.00	3.65±0.10	7.53±0.23	0.16	96.64±0.56	96.84±0.35
	t=12 (25°C)	Appropriate	0.60±0.01	3.64±0.04	7.50±0.35	0.15	96.00±0.42	97.42±1.26
	t=6 (40°C)	Appropriate	0.61±0.00	3.62±0.08	8.48±0.48	0.13	95.24±0.51	94.16±1.75
F5	t=0	Appropriate	0.60±0.00	3.51±0.06	7.87±0.63	0.19	96.46±0.53	91.67±1.92
	t=12 (25°C)	Appropriate	0.60±0.00	3.50±0.07	7.85±0.55	0.18	96.03±0.23	90.93±1.35
	t=6 (40°C)	Appropriate	0.61±0.01	3.48±0.04	7.81±0.62	0.17	94.34±0.36	88.04±1.69
F6	t=0	Appropriate	0.60±0.00	3.48±0.08	7.23±0.23	0.13	94.45±0.19	94.31±1.25
	t=12 (25°C)	Appropriate	0.60±0.01	3.47±0.05	7.20±0.71	0.12	93.95±0.28	93.12±1.14
	t=6 (40°C)	Appropriate	0.61±0.00	3.45±0.04	7.18±0.28	0.11	92.05±0.35	91.55±1.62

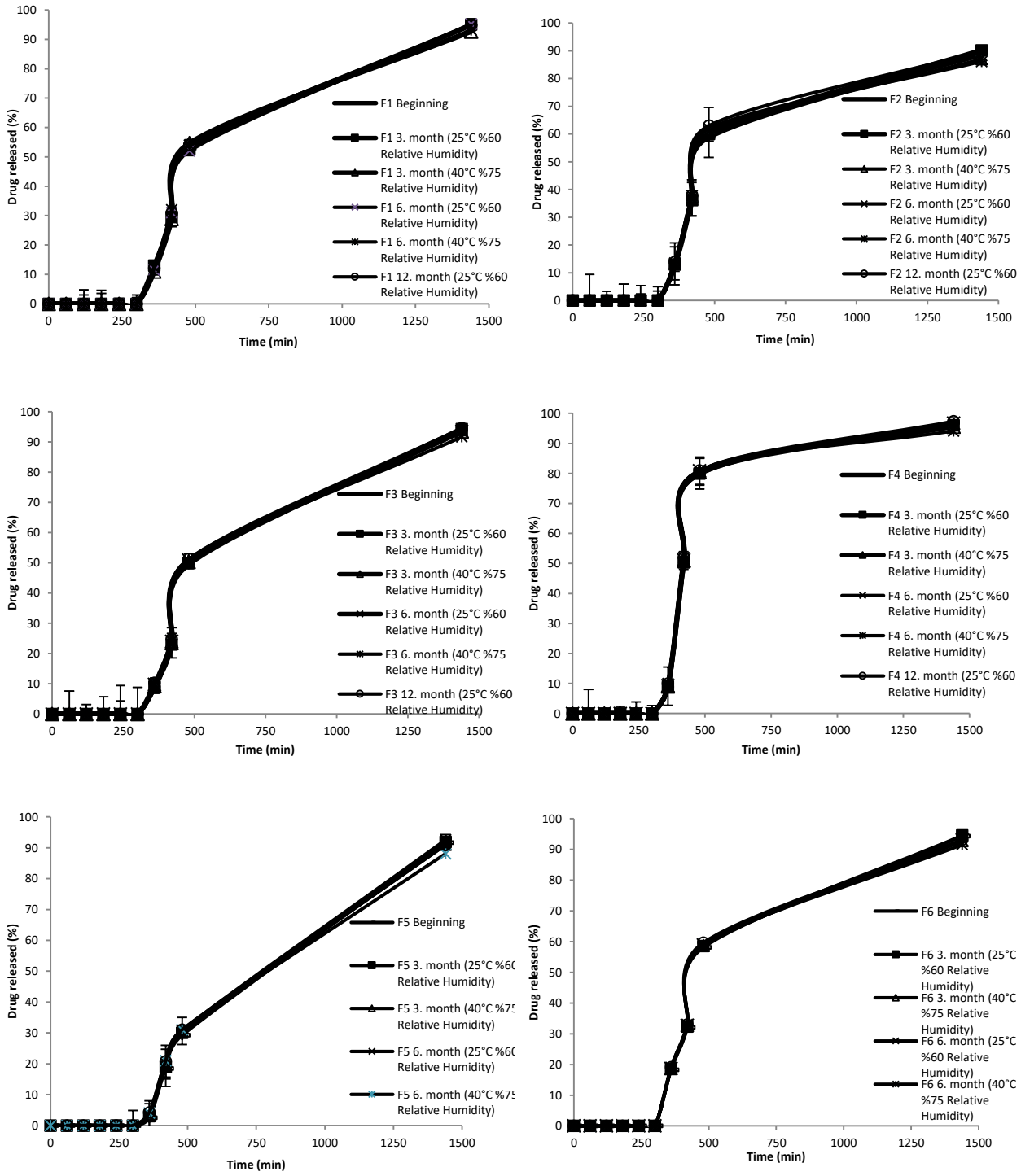

Figure 1. *In vitro* drug release profiles of compression coated ornidazole tablets in a high density polyethylene plastic bottle with silica gel.

Table 3. *In vitro* drug release results of compression coated ornidazole tablets in a high density polyethylene plastic bottle without silica gel.

Code	Dissolution Time (hour)	Drug Released (%)			
		Beginning	3. month	6. month	12. month
		25°C/60±5% Relative Humidity			
F1	2	0±0	0±0	0±0	0±0
	24	94.91±0.54	90.00±1.79	88.21±2.76	85.22±0.85
F2	2	0±0	0±0	0±0	0±0
	24	89.50±0.64	85.44±2.76	83.69±2.93	80.56±1.02
F3	2	0±0	0±0	0±0	0±0
	24	94.06±0.49	89.00±2.76	86.81±2.02	82.97±1.31
F4	2	0±0	0±0	0±0	0±0
	24	96.84±0.35	92.00±2.20	90.00±2.98	87.00±1.05
F5	2	0±0	0±0	0±0	0±0
	24	91.67±1.92	88.34±2.27	82.22±2.66	79.03±1.24
F6	2	0±0	0±0	0±0	0±0
	24	94.31±1.25	90.45±1.15	88.61±1.70	83.72±1.56
		40°C/75±5% Relative Humidity			
F1	2	0±0	0±0	0±0	-
	24	94.91±0.54	87.53±2.44	79.00±0.86	-
F2	2	0±0	0±0	0±0	-
	24	89.50±0.64	79.20±2.31	75.12±2.90	-
F3	2	0±0	0±0	0±0	-
	24	94.06±0.49	86.71±2.51	78.00±1.93	-
F4	2	0±0	0±0	0±0	-
	24	96.84±0.35	89.47±1.65	79.25±1.99	-
F5	2	0±0	0±0	0±0	-
	24	91.67±1.92	84.52±2.32	77.78±2.29	-
F6	2	0±0	0±0	0±0	-
	24	94.31±1.25	86.00±2.49	76.00±2.29	-

Table 4. *In vitro* drug release results of compression coated ornidazole tablets in a high density polyethylene plastic bottle with silica gel.

Code	Dissolution Time (hour)	Drug Released (%)			
		Beginning	3. month	6. month	12. month
		25°C/60±5% Relative Humidity			
F1	2	0±0	0±0	0±0	0±0
	24	94.91±0.54	95.02±0.98	95.20±2.01	94.85±0.48
F2	2	0±0	0±0	0±0	0±0
	24	89.50±0.64	90.21±1.52	88.26±0.98	89.85±0.96
F3	2	0±0	0±0	0±0	0±0
	24	94.06±0.49	94.31±0.95	93.45±1.19	94.64±1.71
F4	2	0±0	0±0	0±0	0±0
	24	96.84±0.35	96.03±1.55	96.78±1.88	97.42±1.26
F5	2	0±0	0±0	0±0	0±0
	24	91.67±1.92	91.94±1.62	92.55±1.86	90.93±1.35
F6	2	0±0	0±0	0±0	0±0
	24	94.31±1.25	94.54±1.23	93.05±1.23	93.12±1.14
		40°C/75±5% Relative Humidity			
F1	2	0±0	0±0	0±0	-
	24	94.91±0.54	92.66±2.01	93.21±1.74	-
F2	2	0±0	0±0	0±0	-
	24	89.50±0.64	87.00±1.88	86.14±2.23	-
F3	2	0±0	0±0	0±0	-
	24	94.06±0.49	93.56±1.48	91.71±1.23	-
F4	2	0±0	0±0	0±0	-
	24	96.84±0.35	95.61±1.34	94.16±1.75	-
F5	2	0±0	0±0	0±0	-
	24	91.67±1.92	90.95±1.36	88.04±1.69	-
F6	2	0±0	0±0	0±0	-
	24	94.31±1.25	92.68±1.27	91.55±1.62	-

3. CONCLUSION

In this study, core tablets containing ornidazole were compression coated with different Pectin - EC mixtures and stability studies were performed in a high density polyethylene plastic bottle with/without silica gel under at 25±2°C/60±5% relative humidity and 40±2°C/75±5% relative humidity. The stored tablets were evaluated for various tablet characteristics including weight, diameter, thickness, hardness, friability, content uniformity and dissolution rate. No visible changes were observed in the tablets after storage in high density polyethylene plastic bottle with silica gel for 12 months. It was concluded that the coated ornidazole tablets should be stored in a high density polyethylene plastic bottle with silica gel at controlled room temperature (25°C) or below their relative humidities and the presence of desiccant in the market package was essential.

4. MATERIALS AND METHODS

4.1. Materials

Ornidazole was a kind gift from Abdi İbrahim İlaç San. ve Tic. A.Ş. (Turkey). Pectin was donated by Wyeth İlaçları A.Ş. (Turkey). Ethylcellulose (EC) N7, N10 and N100 were obtained from Hercules (England). Pectinex 3XL was a gift from Novo Nordisk (Switzerland). All other solvents and reagents were of analytical grade.

4.2. Preparation of tablets

Tablets were prepared in accordance with Özyazıcı et al's study [[10]]. Core tablets were prepared with ornidazole and polyvinylprolidone (1%, PVP) by wet granulation method.

Core tablets containing 200 mg ornidazole were compression coated with 400 mg coating material. Briefly, half of the coating material was placed in the flat-faced punches. The core tablet was carefully positioned in the centre of the die cavity and was filled with the other half of the coating material. The coating material was compressed around the core using a hydraulic hand press tablet machine (Perkin Elmer) with a pressure to 5.0 tons for 10 s [[11], [12]]. Compositions of compression coat are given in Table 5.

Table 5. Composition of the compression coat

Formulation Code	Composition of Compression Coat
F1	%80 Pectin - %20 EC N7
F2	%60 Pectin - %40 EC N7
F3	%80 Pectin - %20 EC N10
F4	%60 Pectin - %40 EC N10
F5	%80 Pectin - %20 EC N100
F6	%60 Pectin - %40 EC N100

4.3. Stability studies

The compression coated ornidazole tablets were submitted to stability test and they were maintained in a high density polyethylene plastic bottle with/without silica gel according to ICH guidelines at 25±2°C / 60 ±5% relative humidity for 12 months and 40±2°C / 75 ± 5% relative humidity for 6 months [[7], [13], [14]]. Physical attributes of the tablets, i.e., appearance, uniformity of weight, diameter, thickness, hardness, friability, content uniformity and *in vitro* drug release profiles were tested over a period of 12 months.

4.3.1. Uniformity of weight

20 tablets were randomly selected and weighed individually using an electronic balance (Sartorius) and the mean weights of tablets were calculated.

4.3.2. Diameter and thickness studies

The diameter and thickness measurements were conducted on 3 tablets using Mitutoyo Absolute Digimatic Caliper and diameter/thickness ratio was calculated. Results are expressed as the mean and standard deviation.

4.3.3. Tablet hardness

Ten tablets were randomly selected and individually placed between two anvils of the hardness tester (Monsanto type) and force is applied. Then, the hardness of tablets reported in kg/monsanto.

4.3.4. Friability test

Friability of the tablets was determined using friabilator (Roche friabilitor). 10 tablets were weighted and subjected to the combined abrasion and shock in a plastic chamber revolving at 25 rpm for 4 minutes. In each revolution, tablets were dropped at a height of 6 inches. Tablets were de-dusted using a brush and reweighed. The percentage of the tablets friability was calculated as Equation 1. The desirable friability was determined as lower than 1%.

$$\text{Friability} = \frac{initial\ weight\ of\ tablets - final\ weight\ of\ tablets}{initial\ weight\ of\ tablets} \times 100 \qquad \text{(Equation 1)}$$

4.3.5. Content uniformity

For content uniformity test, tablets were pulverized, pH 6.8 phosphate buffer was added to adjust the volume to 10 mL and then extracted by shaking for 1 h. The mixture was filtered and the drug was assayed spectrophotometrically at 319 nm [[15]].

4.3.6. In vitro drug release study

In vitro drug release studies were performed using paddle method according to USP 34 and 900 mL medium was maintained at 37 °C. Tablets were tested for drug release for 2 h in pH 1.2 HCl buffer as the average gastric emptying time is about 2 h. Then, the dissolution medium was replaced with pH 6.8 phosphate buffer and drug release was tested for 3 h as the average small intestinal transit time is about 3 h. At the end of these time periods, 1% pectinolytic enzyme was added to dissolution medium to simulate colonic transit and the study continued up to 24 h. At various time intervals, samples were withdrawn and the amount of ornidazole released from was estimated spectrophotometrically (Shimadzu, UV 1208). The λ_{max} values were 277 nm for pH 1.2 HCl buffer and 319 nm for pH 6.8 phosphate buffer, respectively [[10]].

4.3.7. Statistical data analysis

Statistical data analysis was performed using the Student's t-test with $P<0.05$ as the minimal level of significance.

Acknowledgments: This study was supported by a research grant from Ege University (03/ECZ/006 and 04/ECZ/028).

Author contributions: Conception – S.R., Z.Ş., M.Ö.; Design – S.R., Z.Ş., M.Ö.; Supervision – S.R., Z.Ş., M.Ö.; Resources – S.R., Z.Ş., M.Ö.; Materials – S.R., Z.Ş., M.Ö.; Data Collection and/or Processing – S.R., Z.Ş., M.Ö.; Analysis and/or Interpretation - S.R., Z.Ş., M.Ö.; Literature Search – S.R., Z.Ş., M.Ö.; Writing Manuscript– S.R., Z.Ş., M.Ö.; Critical Review – S.R., Z.Ş., M.Ö.

Conflict of interest statement: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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