**Effect of Mannitol Particle Size on Melatonin Dissolution and Tablet Properties using a Quality by Design Framework**

Burcu Mesut¹*, Yağmur Pirinçci Tok¹, Büşra Alkan², Mehtap Kara Vefai³, Mazen Al-Mohaya¹, and Yıldız Özsoy¹
¹Pharmaceutical Technology Department, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey.
²Faculty of Pharmacy, Istanbul University, Istanbul, Turkey.
³Pharmaceutical Toxicology Department, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey.

ABSTRACT
The objective of the current study was to develop an optimized formulation for orally disintegrating tablets (ODTs) containing melatonin. Different particle sizes of mannitol (i.e., filler) were used to study the effects on dissolution and tablet properties using a quality by design (QbD) approach. The quality target product profile was identified, then critical quality attributes (CQAs) were determined. Risk assessment was performed using the Failure Mode Effect Analysis (FMEA) method to identify and rank critical material attributes and process parameters. Thirty-four formulations were prepared and tested. Box-Behnken design (BBD) with response surface methodology was applied to assess the effect of independent factors on CQAs. Finally, the most suitable formulation in terms of tablet properties was determined with Minitab. Specification tests were applied to confirm that the optimized formula met USP requirements. Mannitol with a small particle size had the fastest disintegration time and dissolution rate in ODT formulations containing melatonin.

KEYWORDS: Quality by design, orally disintegrating tablet, dissolution, melatonin, optimization, mannitol

INTRODUCTION
Melatonin (MLT) is a natural hormone that can be found in different biological fluids and synthesized in the pineal glands, providing a circadian presence (1, 2). Endogenous pineal MLT demonstrates chronobiotic influence properties by reducing circadian signals of the suprachiasmatic nuclei to induce sleepiness, improve sleep, and induce GABA-benzodiazepine receptor complex (3).

The British Association for Psychopharmacology reported that MLT is the first-choice treatment for insomnia, parasomnia, and circadian rhythm sleep disorders (4). Specifically, long-term or time zone travelers can confront circadian rhythm confusions (5). MLT reaches a maximum $t_{\text{max}}$ value at 30-60 min after oral administration (6). Taking MLT just before long flights will help eliminate fatigue and circadian rhythm disorders due to flight (7).

The orally disintegrating tablet (ODT) is a solid dosage form that disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue (8). It has many advantages such as solid and liquid dosage form along with the particular benefit that dissolving rapidly in saliva causes the drug to be absorbed in the mouth, pharynx, and esophagus, therefore the pregastric absorption of drugs avoid the hepatic metabolism, and thus the bioavailability of the drug can be increased (9–11). Accordingly, ODTs are among the most patient-friendly dosage forms (12).

Pharmaceutical development is a powerful bridge that links knowledge gained through quality risk management to the improvement of a product and its manufacturing process. Quality by design (QbD) is an effective and systematic approach to pharmaceutical development (13), which commences with pre-determined goals, emphasizes product and process understanding, and process control according to sound science and quality risk management (14, 15).

In accordance with ICH guideline Q8(2), quality cannot be examined into products; it should be built-in by design.
The process and product design performed via the QbD approach decreases the role of finished product tests and therefore ensures control quality at the design stage (17).

QbD consists of elements to provide desired quality, along with a safe and efficient drug product. Identifying the quality target product profile (QTPP) creates the basis of design for the product development and manufacturing process. The next step of the approach identifies critical quality attributes (CQA), which are essential for patients’ health as well as the drug’s physical, chemical, biological, or microbiological properties within an appropriate limit for desired quality. Understanding the development of the drug product and its manufacturing process depends on establishing functional relationships between CQAs and critical material attributes (CMAs). CQAs are for output materials, including product intermediates and finished drug products, whereas CMAs are for input materials, including drug substances and excipients. Process parameters are referred to as the input operating parameters of process steps, and how their variability impacts the CQAs (18–20). A better understanding of the relationship between these variables and product quality aids in risk management, enhances problem detection, raises timely risk control measures (14), and maintains a state of control throughout the lifecycle (21).

Support can be obtained from various artificial intelligence programs to establish a relationship between all statistical methods, formulation inputs and outputs, and facilitate their evaluation (22). Artificial neural networks (ANNs) are applications that learn through experience with appropriate learning examples, not through the program. Moreover, it collects information by identifying patterns and relationships in the data (23). Formulation development and optimization studies are carried out using ANNs and have become increasingly more important in drug development studies, especially in the digital era (24).

The present investigation was performed to develop and optimize an ODT containing MLT using two different types of mannitol as fillers with varying particle sizes. A QbD framework was used with various statistical tools and multi-objective optimization to understand the dissolution behavior and tableting properties of these excipients.

**MATERIALS AND METHODS**

**Materials**

Ready-to-use tablet excipients were received as gifts from suppliers, including Kollidon CL-SF (BASF, Germany), Parteck M100 and M200 (Merck, Germany) with average particle sizes of 70 and 150 μm, respectively, and Parteck LUB (Merck). Melatonin powder was gifted from Swati Spentose Pvt. Ltd. (India). All other chemicals and solvents were of analytical grade and high-performance liquid chromatography (HPLC) grade. Water for the study was generated using a Milli Q Water System (EMD Millipore, Germany).

**Defining the QTPP and CQAs**

The initial step of the QbD framework is defining the QTPP. The desired quality properties of the pharmaceutical product are listed as quantitative attributes (26). Therapeutic indication, route of administration, site of activity, dosage form, dose strength, and details of the QTPP elements, and CQAs of MLT ODTs along with justification and reasonable limits to ensure desired product quality are presented in Table 1.

**Risk Assessment**

Risk assessment methodology was applied to MLT ODTs according to the ICH Q9 guideline (14). A risk assessment of the overall process was performed to identify the high-risk procedures that may impact the CQAs of the final drug product. This was achieved using Failure Mode Effect Analysis (FMEA) methodology. Severity, probability, and detectability of possible risks were assessed, and a risk priority number (RPN) was calculated to rank the risks.

Pareto charts were used to identify the critical factors (CMAs and CPPs) that affect quality (CQAs). In addition, a pareto chart helps to identify which factors to focus on (27).

**Experimental Design**

Response surface methodology (RSM) has dependent and independent variables within a particular series of statistical designs that investigates the impact on the response surface of independent process variables (28). Variability in the formulations (e.g., lubricant and superdisintegration concentration) and process variables (e.g., tablet compression pressure) may result in product quality failures throughout the shelf life, which may impact patients’ health. It is essential to specify CMAs and critical process parameters (CPP) for CQAs in the QbD approach.

For this purpose, ICH Q9 leads risk management, improves problem detection, and promotes timely risk control (16). Therefore, a Box-Behnken design (BBD) with RSM was chosen to evaluate the effect of three independent factors, including filler particle size, disintegrant, and tablet compression pressure. Dependent factors were dissolution rate, disintegration time, tablet breaking...
force, and friability. Knowledge obtained by identifying, perceiving, and controlling inputs (CMAs and CPPs) and outputs (CQAs) and the manufacturing process facilitate establishment of the design space (16).

Preparation of Orally Disintegrating Tablets (ODTs)
MLT ODTs were prepared by direct compression technique with sufficient strength and rapid disintegration time under standardized conditions. Two types of mannitol (Parteck M100 and M200, 100–150 mg) were used as fillers due to their compressibility. All formulations contained Kollidon CL-SF (15–30 mg) as a super disintegrant. MLT (10 mg) was used as a model active pharmaceutical ingredient (API). The lubricant agent was Parteck LUB (3.5 mg). The tablet compression pressure was between 3.44 and 10.34 MPa. The quantitative composition and compression pressure of MLT ODT formulations are shown in Table 2. This study was designed as two series using both mannitol concentrations separately, thus comprising 34 formulations.

MLT, mannitol, , and the super disintegrant were weighed on an analytical balance with 0.1 mg accuracy (Sartorius, Germany), then were transferred into the cubic mixer (Aymes, Turkey) and mixed for 10 min at 100 rpm. Lubricant was then added to the mixture and blended for an additional 5 min. At appropriate weight and pressure, the final mixtures were directly compressed in a single punch tablet press (Yeniyurt, Turkey). Pressed tablets were stored in well-closed glass containers.

Characterization of MLT ODTs
Tablet Friability and Breaking Force
Tablet friability was evaluated by a friability test apparatus (Aymes, Turkey). Accurately weighed tablets were placed in the friabilator drum, rotated 100 times at 25 rpm, then reweighed. The difference in weight before and after rotation was calculated. The loss due to abrasion was expressed as a percentage. According to USP guidelines, weight loss of less than 1% is generally considered acceptable (n = 10) (29).

Table 1. Quality Target Profile (QTPP) and Critical Quality Attributes (CQAs) for Melatonin (10 mg) ODTs.

<table>
<thead>
<tr>
<th>QTPP Elements</th>
<th>Target</th>
<th>Justification / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic indication</td>
<td>Sleep disorders, others*</td>
<td>Melatonin is considered the first treatment of insomnia</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Easy to administer, patient acceptability and compliance</td>
</tr>
<tr>
<td>Site of activity</td>
<td>Systemic</td>
<td>Melatonin is a hormone produced by the pineal gland and has systemic effects</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Orally disintegrated tablet</td>
<td>Fast drug release, fast activity</td>
</tr>
<tr>
<td>Dose strength</td>
<td>10 mg</td>
<td>Commonly accepted strength</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality attributes of pharmaceutical product</th>
<th>Product Target</th>
<th>Is it a CQA?</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apperance</td>
<td>Color and shape acceptable to the patient. No visual tablet defects observed</td>
<td>No</td>
<td>Color, shape, and appearance are not directly related to safety and efficacy. Therefore, they are not critical</td>
</tr>
<tr>
<td>Odor</td>
<td>Odorless</td>
<td>No</td>
<td>Odor is not directly related to safety and efficacy, but odor can affect patient compliance</td>
</tr>
<tr>
<td>Size</td>
<td>Easily handled by patients</td>
<td>No</td>
<td>Ease of dissolving in the mouth as well as patient compliance</td>
</tr>
<tr>
<td>Friability</td>
<td>Below 1.0%</td>
<td>Yes</td>
<td>Drug must have resistance to mechanical activities such as carrying, packaging, etc.</td>
</tr>
<tr>
<td>Breaking Force</td>
<td>Appropriate value to be hard enough and not affect the other CQAs (friability, disintegration time, and dissolution)</td>
<td>Yes</td>
<td>Affect friability test, disintegration time, and dissolution test of drug</td>
</tr>
<tr>
<td>Disintegration Time</td>
<td>&lt; 30 s (USP)</td>
<td>Yes</td>
<td>Affect dissolution time</td>
</tr>
<tr>
<td>Assay</td>
<td>10 mg ± 5%</td>
<td>Yes</td>
<td>Affect safety and efficacy</td>
</tr>
<tr>
<td>Dissolution</td>
<td>According to the USP, no less than 75% dissolution should occur in one hour (40, 41)</td>
<td>Yes</td>
<td>Affect drug bioavailability</td>
</tr>
</tbody>
</table>

* Insomnia, parasomnia.


*Insomnia, parasomnia.*

Dissolution Technologies | FEBRUARY 2023
www.dissolutiontech.com
Tablet breaking force was determined in a diametric compression tester (Sotax HT1, Switzerland) according to USP guidelines (n=10) (30).

**Disintegration Time**
A standard USP disintegration test apparatus (Sotax DT2) was used to measure tablet disintegration time. The test was carried out in 1000 mL of distilled water, maintained at 37 ± 0.5 °C. The disintegration time (DT) was determined visually for each formulation when all the tablets disintegrated completely (31). The mean value and the standard deviation of these determinations were computed (n = 3).

**Dissolution Test Studies**
An in vitro dissolution study was performed on a dissolution tester (Sotax AT2) using USP apparatus 2 (900 mL of 0.1 N HCl solution, 50 rpm, 37 ± 0.5 °C). Samples (3 mL) for the dissolution test (n = 3) were collected manually at regular time intervals (1, 3, 5, 10, 15, 20, and 30 min) without replacing the dissolution medium (medium loss was considered during the calculations). Samples were filtered through a 0.45-μm cellulose acetate filter (Alwsci, China) (32).

Sample concentration of MLT was determined using a HPLC system (Shimadzu A20, Japan), equipped with a photodiode array (PDA) detector at 220 nm. Chromatographic analyses were carried out at 30 °C on a 5-μm C18 Inertsil ODS-3 column (150 x 4.6 mm, GL Sciences, USA). Separation was achieved by isocratic elution with a flow rate of 1.0 mL/min and injection volume of 100 μL. A mixture of water and acetonitrile (60:40, v/v) was used as the mobile phase. MLT eluted at 3 min with a total run time of 8 min. The method was modified according to the study of Filali et al (33).

**Statistical Analysis**
Data were transferred from Microsoft Excel to Minitab 18 software. Statistical evaluation of the obtained data and effects of the independent variables on CQA parameters were analyzed using Minitab 18 software (Minitab Inc., USA); p < 0.05 was considered statistically significant.

**Cell Viability Assay**
Human colorectal adenocarcinoma Caco-2 cells (HTB-37) were purchased from ATCC (USA). Caco-2 cells were incubated under 5% CO₂ at 37 °C, and cell lines were cultured in Eagle’s Minimum Essential Medium supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, and 100 μg/mL streptomycin. The cells were passaged with trypsin– ethylenediaminetetraacetic acid (EDTA) solution before confluency. In addition, in vitro cell viability was evaluated by the MTT test. Caco-2 cells were seeded in 96-well plates with a density of 10⁴ cells per well with 100 μL Eagle’s medium and incubated for 24 h for cells attachment. Subsequently, the culture medium in each well was removed, and MLT

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Mannitol Filler (Parteck M100 or M200) (mg)</th>
<th>Super Disintegrant (Kollidon CL-SF) (mg)</th>
<th>Tablet Compression Pressure (MPa)</th>
<th>Theoretical Weight of Tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1*/F18**</td>
<td>100</td>
<td>22.5</td>
<td>3.44</td>
<td>136.0</td>
</tr>
<tr>
<td>F2*/F19**</td>
<td>125</td>
<td>22.5</td>
<td>6.89</td>
<td>161.0</td>
</tr>
<tr>
<td>F3*/F20**</td>
<td>150</td>
<td>15.0</td>
<td>6.89</td>
<td>178.5</td>
</tr>
<tr>
<td>F4*/F21**</td>
<td>125</td>
<td>15.0</td>
<td>3.44</td>
<td>153.5</td>
</tr>
<tr>
<td>F5*/F22**</td>
<td>100</td>
<td>15.0</td>
<td>6.89</td>
<td>128.5</td>
</tr>
<tr>
<td>F6*/F23**</td>
<td>150</td>
<td>22.5</td>
<td>3.44</td>
<td>186.0</td>
</tr>
<tr>
<td>F7*/F24**</td>
<td>125</td>
<td>22.5</td>
<td>3.44</td>
<td>161.0</td>
</tr>
<tr>
<td>F8*/F25**</td>
<td>125</td>
<td>30.0</td>
<td>6.89</td>
<td>168.5</td>
</tr>
<tr>
<td>F9*/F26**</td>
<td>100</td>
<td>30.0</td>
<td>6.89</td>
<td>143.5</td>
</tr>
<tr>
<td>F10*/F27**</td>
<td>125</td>
<td>30.0</td>
<td>10.34</td>
<td>168.5</td>
</tr>
<tr>
<td>F11*/F28**</td>
<td>150</td>
<td>30.0</td>
<td>6.89</td>
<td>193.5</td>
</tr>
<tr>
<td>F12*/F29**</td>
<td>100</td>
<td>22.5</td>
<td>10.34</td>
<td>136.0</td>
</tr>
<tr>
<td>F13*/F30**</td>
<td>125</td>
<td>30.0</td>
<td>3.44</td>
<td>168.5</td>
</tr>
<tr>
<td>F14*/F31**</td>
<td>125</td>
<td>22.5</td>
<td>10.34</td>
<td>161.0</td>
</tr>
<tr>
<td>F15*/F32**</td>
<td>125</td>
<td>15.0</td>
<td>10.34</td>
<td>153.5</td>
</tr>
<tr>
<td>F16*/F33**</td>
<td>125</td>
<td>15.0</td>
<td>6.89</td>
<td>153.5</td>
</tr>
<tr>
<td>F17*/F34**</td>
<td>150</td>
<td>22.5</td>
<td>10.34</td>
<td>186.0</td>
</tr>
</tbody>
</table>

*Note – Melatonin (10 mg) was active pharmaceutical ingredient; lubricant was Parteck LUB (3.5 mg).
*Formulations with Parteck M100 (F1–F17), ** Formulations with Parteck M200 (F18–F34.)
with concentrations of 0.3125, 0.625, 1.25, 2.5, 5, and 10 mg/mL were added to the cells and incubated at 37 °C for 24 h. After this incubation period, 20 µL of MTT solution (5 mg/mL in phosphate buffered saline (PBS) was added to each well, then further incubated at 37 °C for 3 h. The culture medium was discharged, then 100 µL dimethyl sulfoxide (DMSO) was added to visualize MTT formazan purple crystals. The absorbance was measured on a microplate reader spectrophotometer (Biotek, USA) at 570 nm (n = 9).

RESULTS AND DISCUSSION
Risk Assessment of MLT ODTs
In the risk assessment study, a risk score of 200 and above was considered a high risk for failure (34). Tablet friability and breaking force, disintegration time, assay, and dissolution were 252, 216, 252, 200, and 250, respectively.

Characterization of MLT ODTs
Tablet Friability and Breaking Force
Friability is impacted by tablet mechanical strength, which defines how easily particles can be displaced from their original locations in the tablet when exposed to an external shear or impact stress (35). According to the USP limit, the weight loss for a single evaluation should be less than 1% (29).

Table 1. Results of tablet friability (n = 10) (a), breaking force (n = 10) (b), and disintegration time (n = 3) (c) for all melatonin ODT formulations. Results are mean values. ODT: oral disintegrating tablet.

Table 1

Tablet Friability (% Chart)

Tablet Breaking Force (N) Chart

Disintegration Time (s) Chart

Figure 1a displays the friability of all formulations. Almost all formulations were within the acceptable limits of weight loss, but a few formulations were more than 1%. Particularly, it was noticed that the friability was higher in formulations containing the smaller particle size of mannitol (M100), which may have poor strength (36).

Tablet breaking force results are presented in Figure 1b. The resulting values increased with an increase in tablet compression pressure, which is consistent with published literature (37). In addition, tablets compressed at 10.34 Mpa showed the highest breaking force values, as expected.

The particle size of excipients affects interparticulate bonds and the bonding force. For instance, smaller particles lead to an increasing number of bonds per cross-sectional area; hence, the bonding force per particle-particle bridging is larger for coarser particles. In other words, raw material with small particle size does not inevitably lead to higher mechanical tablet strength, for example, owing to changing the porosity or deformation behavior of the particles (38).
Disintegration Time
Disintegration time of the ODT formulations was less than 30 seconds, but formulations containing M100 had a faster disintegration time compared with formulations containing larger mannitol particles (M200), as seen in Figure 1 (39). Tablets were prepared using wet granulation followed by tableting, which could produce granules with a smaller size distribution, which can positively impact the mechanical strength of tablets and negatively impact disintegration time and dissolution rate (40).

Dissolution Tests
The HPLC method was validated for selectivity, linearity, accuracy, precision, limit of detection (LOD), and limit of quantification (LOQ). The validation parameters were found to be linear in a concentration range of 1.0–12 µg/ml ($R^2 > 0.9998$), accurate (recovery > 98%), precise (intra and inter-day variations < 2%). LOD and LOQ values were 0.07 and 0.21 µg/mL, respectively.

Figure 2 shows the results of dissolution studies. The prepared formulations with M100 showed the fastest dissolution behavior. The formulations comprised of larger mannitol particles (M200) were affected by compression pressure.

Statistical Analysis
All inputs, including filler particle size, different concentrations of super disintegrant, and different compression pressure applications, were found insignificant ($p > 0.05$) on assay and dissolution behavior at 1, 3, and 5 mins, with low regression values. MLT is BCS class I drug that can rapidly dissolve in the dissolution medium, precisely the parts close to the surface of tablets. Consequently, the inputs had no effect on the dissolution rate within the 5 mins. However, the effects of the inputs on friability, breaking force, disintegration time, and dissolution at 10, 15, 20, and 30 mins were significant ($p < 0.05$), with different regression values. The findings also suggest that the particle size of mannitol, mainly with tablet compression pressure, makes a significant difference on tablet properties (27).

The $p$-value was below 0.05 for all variables whose modeling capability ($R^2$) was also above 0.50. This finding provides evidence that inputs used in this study were critical parameters, having a significant effect on outputs. The greatest effects of inputs were on tablet friability, breaking force, and dissolution at 3 min (Fig. 3).

The parameters that had the highest effect on the breaking force were the tablet compression pressure, (M100 and tablet compression pressure), (M200 and tablet compression pressure), (tablet compression pressure and tablet compression pressure), and (super disintegrant and tablet compression pressure), respectively. M200 and tablet compression pressure were the main parameters affecting the friability. The most significant input parameters for dissolution at 3 min were tablet compression pressure and tablet compression pressure.

M100 and M200 (CMAs) and tablet compression pressure (CPP) affected disintegration time and breaking force (CQAs), as shown in contour plots (Fig. 4).

![Figure 2. Dissolution results of melatonin ODT formulations (F1–F34). ODT: oral disintegrating tablet.](image)
Figure 3. Pareto chart analysis of tablet breaking force, friability, and dissolution (Dis) 3 mins for melatonin ODT formulations. ODT: oral disintegrating tablet.

Figure 4. Contour plots of disintegration time and tablet breaking force for melatonin ODT formulations. ODT: oral disintegrating tablet.
Particle size and tablet compression pressure also affected disintegration time (Fig. 4).

As shown in Figure 4, M100 and M200 exhibited various behaviors, specifically in the disintegration time. For instance, M200 with a large particle size resulted in a longer disintegration time as tablet compression pressure increased.

**CMAs and CPPs of the Optimized MLT ODT Formulation**

As a result of the optimization analysis for MLT ODTs, the values that should be applied to formulation content and process parameters are: M100: 91.795 mg, M200: 0.054 mg, super disintegrant: 20.472 mg, and tablet compression pressure: 3.44 and 3.64 Mpa.

The disintegration time, friability, and breaking force tests were within the pharmacopeial limits (15 s, 0.48%, and 30 N, respectively). The dissolution profile of MLT ODTs showed rapid release around 1 min, a plateau around 5 mins, and more than 80% of drug was released at 30 min.

**Cell Viability Assay**

The cell viability of MLT was evaluated using the MTT test in Caco2 cells. The IC\textsubscript{50} value was calculated as 11.6925 mg/mL. Cell viability decreased in a concentration-dependent manner. It was observed that 2.5, 5, and 10 mg/mL of MLT significantly reduced cell viability compared to the control group.

**CONCLUSION**

MLT ODTs were prepared using two different types of mannitol (Parteck M100 and M200), Kollidon CL-SF, and various tablet compression pressures. ODTs were successfully prepared, characterized, and optimized using the QbD approach. Mannitol showed different tablet characteristics according to particle size. Tablets with smaller particle size mannitol had a fast disintegration time and high friability and breaking force compared with tablets having larger mannitol particles. Tablet compression pressure had the greatest effect on the tablet characteristics. The study reveals how different CMA and CPP parameters affect dissolution studies (e.g., different types of the same excipient can affect different effects on dissolution), which is a primary decision criterion in determining bioavailability of drugs. Evaluation of the effects of both material and process parameters for product specifications can be accomplished using the QbD approach.

**FUNDING**

This work was supported by the Istanbul University Scientific Research Project Foundation, Istanbul, TR (grant no. TSA-2018-31663). The authors also thank Merck and BASF for their support.

**CONFLICT OF INTEREST**

The authors disclosed no conflicts of interest related to this article.

**REFERENCES**


in the development of mini-tablets.


Aksu, B.; Mesut, B. Quality by design (QbD) for pharmaceutical area. J. Pharm. Istanbul Univ. 2015, 45 (2), 233–251.


19. Aksu, B.; Mesut, B. Quality by design (QbD) for pharmaceutical area. J. Pharm. Istanbul Univ. 2015, 45 (2), 233–251.


