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# NANO IS TOO BIG

## Recent Trends and Advancement in Nanotechnology Applications in Healthcare Sector

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PHARMACEUTICAL NANOTECHNOLOGY CONFERENCE 2017

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Universitas Surabaya, July 21st – 22th, 2017

Faculty of Pharmacy
Universitas Surabaya

**PROCEEDING**

**PHARMACEUTICAL NANOTECHNOLOGY CONFERENCE 2017**

# Nano is Too Big: Recent Trends and Advancement in Nanotechnology Applications in Healthcare Sector

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| Time | Schedule | Speaker | Place | Moderator |
|---|---|---|---|---|
| 08.00 - 09.00 | Registration | | PF 6.1 | |
| 09.00 - 09.30 | Opening ceremony | | PF 6.1 | |
| 09.30 - 09.45 | Coffee break | | PF 5 | |
| 09.45 - 10.45 | Nano is Too Big | Prof. Yashwant Pathak (University of South Florida, USA) | PF 6.1 | Nina Dewi O, M.Farm., Apt (UBAYA) |
| 10.45 - 11.00 | Oral Presentation (session 1) | Johan S (School of Technobiology) | PF 6.1 | Nina Dewi O, M.Farm., Apt (UBAYA) |
| 11.00 - 13.00 | Break (Lunch) | | Poster exhibition (PF 6.1); PF 5 (Lunch) | |
| 13.00 - 14.00 | Chitosan - TPP Nanoparticles and The Implementations on Antibacterial Drug Delivery | Associate Prof. Dr. Haliza Katas (Centre for Drug Delivery Research-Universiti Kebangsaan Malaysia) | PF 6.1 | Moderator : Dr. Tommy Julianto Bustami Effendi (Universiti Teknologi Mara)/Aditya Trias P M.Si., Apt |
| 14.00 - 15.00 | Nanotechnology in topical medication and skin care products | Dr. Tommy Julianto Bustami Effendi (Universiti Teknologi Mara) | PF 6.1 | Moderator : Associate Prof. Dr. Haliza Katas (Centre for Drug Delivery Research-Universiti Kebangsaan Malaysia)/Gabriela Eugresya M.Si., Apt |
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| 15.30 - 16.30 | Nanocrystal for Enhancement of Oral Bioavailability of Poorly Water-Soluble Drugs | Prof. Varaporn Junyaprasert (University of Mahidol, Thailand) | PF 6.1 | Moderator : Agnes Nuniek W, M.Si., Apt (UBAYA) |

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| 10.00 -13.00 | Coffee break, poster presentation | | PF 6 and PF 5 | MC |
| 10.30 -11.00 | PT. Hilab Sciencetama | Supplier | PF 6.1 | MC |
| 11.00 -12.00 | Development of Oral Delivery Solid Dispersion Nanoparticle Using Ultrasonic Spray Drying Method | Dr. Christina Avanti, MS.,Apt (University of Surabaya, Indonesia) | PF 6.1 | Prof. Jagad Kanwar (Deakin University, Australia)/Ike Diah R M.Farm-Klin., Apt |
| 12.00 -13.00 | Lunch | | PF 5 | |
| 13.00-14.00 | Oral presentation (session 2) | 1. Rini Hamsidi, S.Farm., M.Farm., Apt (Halu Oleo University) | PF 6.1 | Nina Dewi O, M.Farm., Apt |
| | | 2. Dr. Farida Suhud, M.Si., Apt (UBAYA) | | |
| | | 3. Aditya Trias, M.Si., Apt (UBAYA) | | |
| | | 4. Karina Citra Rani, M.Farm., Apt (UBAYA) | | |
| 14.00 - 15.00 | Application of Nanoparticles on Herbal Products | Nurul Taufiqurohman M.Eng., Ph.D (LIPI, Indonesia and Precident of Masyarakat Nano Indonesia) | PF 6.1 | Dr. Kartini, M.Si., Apt |
| 15.00 - 15.30 | Coffee break | | PF 5 | |
| 15.30 -16.00 | Closing | Closing ceremony | PF 6.1 | MC |

# FORMULATION AND EVALUATION OF ORALLY DISINTEGRATING TABLETS OF ATENOLOL USING CROSPOVIDONE AS SUPERDISINTEGRANT



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## Abstract

Hypertension is the most common cardiovascular diseases, moreover hypertension is a major risk factor for coronary artery disease and its complications. Hypertension prevalence increases with advancing age. Atenolol is a competitive beta (1) -selective adrenergic antagonists and has been widely used in hypertension therapy. Administration of conventional tablets of atenolol has been reported to exhibit poor patient compliance in geriatric patients. The aim of this study was to formulate and evaluate orally disintegrating tablets of atenolol to overcome poor patient compliance in geriatric patients. In this study, crospovidone were used as superdisintegrant in two different concentrations (10% and 20%). Formula 1 using 0% of crospovidone, formula 2 using 10% of crospovidone, and formula 3 using 20% of crospovidone. It was found that there was significant difference of wetting time, water absorption ratio, in vitro dispersion time, and dissolution parameters (area under curve value (AUC) and dissolution efficiency (ED)) among these formulas. Formula 2 which used 10% crospovidone showed the best physichochemical characteristics and met all requirements of orally disintegrating tablets. Dissolution efficiency of formula 2 (10% crospovidone) increased approximately 2 times compared to formula 1 (0% crospovidone), moreover dissolution efficiency of formula 2 increased 1.25 times compared to formula 3 (20% crospovidone).

**Keywords:** Atenolol, Orally Disintegrating Tablets, Superdisintegrant, Crospovidone

## Introduction

Oral delivery is the most preferred route of drug delivery (Kouchak and Atyabi, 2004). Per oral tablets occupy the broadest and the most significant place among all pharmaceutical dosage forms. Taking one or two tablets a day with a glass of water is the easiest and the most acceptable way of administration of a drug to patient (Turkoglu and Adel Sakr, 2009). However, geriartric patients suffered difficulties when using conventional tablets. In the advanced age, the diminution of organs capacity and functions and additionally the reduced cognitive abilities of some elderly limit the effectivity and safety treatment with drugs (Breitkreutz and Tuleu, 2009).

Data collected over a 30 year period have demonstrated the increasing prevalence of hypertension with age (Lionakis N *et al.*, 2012). According to the data which has been collected by JNC-7, hypertension occurs in more than two thirds of individuals after age of 65 (Chobanian *et al.*, 2003). Hypertension is the most common cardiovascular diseases, moreover hypertension is a major risk factor for coronary artery disease and its complications. Atenolol is a competitive beta (1)-selective adrenergic antagonists and has been widely used in hypertension therapy (Dipiro *et al.*, 2009). Administration of conventional tablets of atenolol has been reported to exhibit poor patient compliance in geriatric patients (Khirwadkar *et al.*, 2013). This condition due to difficulty of swallowing, hand tremors, and lack of memory which has been suffered by geriatric patients (Khirwadkar *et al.*, 2013).

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Orally disintegrating tablets (ODT) offer an advantage for populations who have difficulty in swallowing. Orally disintegrating tablets with good taste and flavor increase the acceptability of bitter drugs by various groups of population, especially geriatric patients (Diaz *et al.*, 2011). Orally disintegrating tablets are novel types of tablets that disintegrate/ dissolve/ disperse in saliva within few seconds. This result in a rapid onset of action and greater bioavailability of the drug than those observed from a conventional tablet dosage form (Chandrasekar *et al.*, 2013). United States Food and Drug Administration (FDA) defined orally disintegrating tablets as a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of second when placed upon the tongue (US FDA, 2008).

Orally disintegrating tablets provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients (Diaz *et al.*, 2012). Orally disintegrating tablets also provide fast disintegration of the tablets results a quick dissolution of the drug and fast absorption that provide rapid onset of action (Behnke *et al.*, 2003; Diaz *et al.*, 2012). The drug may get absorbed from the pharynx and esophagus or from other sections of GIT as the saliva travels down. In such cases bioavailaibility is significantly greater than that observed from conventional tablet dosage form (Brown *et al.*, 2001; Nagar *et al.*, 2011) .

Important desirable characteristics of orally disintegrating tablets are no water requirement for swallowing purpose, but it should dissolve or disintegrate in the mouth usually within fraction of seconds. Moreover, orally disintegrating tablets must provide pleasant feeling in the mouth (Nagar et al., 2011). One of the key component to formulate orally disintegrtaing tablets is superdisintegrants. Superdisintegrants are the class of compound which primarily aid in the rapid disintegration of orally disintegrating tablets in the oral cavity (Mitapalli *et al.*, 2010). The concentration of superdisintegrants which widely used in orally disintegrating fromulation is 10%-20% (Hahm and Augsburger, 2008).

Most disintegrants swell to some extent and the swelling pressure is generally considered as the major factor for tablet disintegration (Fukami et al., 2006). One of the most desirable properties of the disintegrants is rapid swelling without gel formation, since high viscosity on the surface of the tablet will prevent water penetration into the tablet matrix. High swelling capacity along with high water penetration leads to fast tablet disintegration (Hahm and Augsburger, 2008; Mitapalli *et al.*, 2010). Compared to the other superdisintegrants like sodium starch glycolate and croscarmellose sodium, crospovidone appears not to swell as much on contact with water. It is believed that recovery of energy of elastic deformation plays a major role in the disintegrant activity of crospovidone, along with capillary action and disruption of particle-particle bonds on penetration of water into the tablet matrix (Hahm and Augsburger, 2008). The results of previous study also showed that combination of mannitol and crospovidone in orally disintegrating tablets formulation give short wetting time and a sufficient crushing strength (Hahm and Augsburger, 2008).

In this study, orally disintegrating tablets of atenolol were prepared by using direct compression technique. The concentration of crospovidone which were incorporated in each formula are 0% (formula 1), 10% (formula 2), and 20% (formula 3). Formula 1 was used as control in this study. Evaluation was conducted during formulation process. Evaluation consists of pre compression parameters and post compression parameters. This study was conducted to analyzed the impact of different concentration of sodium starch glycolate in orally disintegrating tablets formula to the physichochemical characteristics of the tablets (disintegration time, in vitro dispersion time, water absorption ratio, and dissolution).

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## 1. Materials and methods

### 1.1. Materials

Materials that were used in this study consists of atenolol p.g (Refarmed Chemicals, Lugono Switzerland), *crospovidone* (Kollidon® CL) p.g (BASF South East Asia Pre-Ltd), magnesium stearate p.g (Faci Asia Pacific PTE LTD), aspartame f.g (Ajinomoto Co. Inc.), aqua demineralisata (Laboratorium of qualitative chemistry University of Surabaya), manitol DC p.g (Roquette Freses, Perancis), aerosil p.g (PT. Brataco), *mint flavor* f.g (KH Roberts), sodium dihidrogen fosfat p.a ($NaH_2PO_4.2H_2O$) p.a (Merck), disodium hidrogen fosfat p.a ($Na_2HPO_4.12H_2O$) p.a (Merck), natrium asetat trihidrat p.a. (Riedel), asam asetat glasial p.a (Merck), metanol pro HPLC (Mallinckrodt Chemicals), Avicel PH 102® p.g (Mingtai Chemical Co. LTD), talk (PT. Brataco), and Whatmann filter paper no 41.

### 1.2. Methods

#### 2.2.1 Preparation of Powder Mixture

Preparation of powder mixture was conducted by mixing the component in table 1.

Table 1. Formulation of Orally Disintegrating Tablets of Atenolol Using Crospovidone as Superdisintegrants

| **Materials** | **Formula 1 (mg)** | **Formula 2 (mg)** | **Formula 3 (mg)** |
|---|---|---|---|
| Atenolol | 25 | 25 | 25 |
| Crospovidone | - | 30 | 60 |
| Aspartam | 9 | 9 | 9 |
| Mg Stearat | 4,5 | 4,5 | 4,5 |
| Aerosil | 1,5 | 1,5 | 1,5 |
| Talk | 3 | 3 | 3 |
| *Mint Flavour* | 3 | 3 | 3 |
| Manitol DC | 50,8 | 44,8 | 38,8 |
| Avicel PH 102® | 203,2 | 179,2 | 155,2 |
| **Total weight of tablet** | **300** | **300** | **300** |

Formula 1 using crospovidone 0% (control), formula 2 using crospovidone 10%, and formula 3 using crospovidone 20%. Atenolol and a half of Aerosil 200® mixed for 3 minutes using the tumbling mixer to decrease the electrostatic tendency of atenolol. This mixture then premixed with a portion of Avicel PH 102®. Then, the mixture was mixed thoroughly with crospovidone, Avicel PH 102®, manitol DC, aspartame, and mint flavor for 10 minutes in tumbling mixer. The powder mixture then was evaluated before compression step (pre compression test). After pre compression test, the powder mixture was mixed with talk, magnesium stearate, and Aerosil 200® for 3 minutes. The powder mixture then compressed into tablet using Erweka® tablet compression machine.

#### 2.2.2 Pre Compression Evaluation

The powder mixture from each formula were evaluated by several parameters such as flowability, angle of repose, bulk density, tapped density, compressibility, Hasuner ratio, and moisture content.

##### 2.2.2.1 Flowability and Angle of Repose

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Flowability and angle of repose was determined using fixed funnel method. The powder mixture (± 100 gram) was poured through a funnel that can be raised vertically to a maximum cone height (h) was obtained (Kumare *et al.*, 2013). The radius of the heap (r) was measured and the angle of repose (Θ) was calculated using the formula:

$$\tan \theta = \frac{h}{r}$$

Time for the powder mixture to fall down through a funnel was used to calculate flowability of the powder.

2.2.2.2 Bulk density

Bulk density of powder mixture was determined by pouring the powder into a graduated cylinder. The bulk volume (Vb) and weight of the blend (m) was determined. The bulk density was calculated by this equation (Chandrasekar *et al.*, 2013).

$$\textbf{Bulk density} = \frac{\mathbf{m}}{\mathbf{Vb}}$$

Where,

m = mass of powder mixture
Vb = bulk volume of the powder

*2*.2.2.3 Tapped density

Tapped density of the powder mixture was determined using tapping machine. Tapped density is the ratio of total mass of the powder (m) to the tapped volume of the powder (Vt). Volume was measured by tapping the powder for 500 times. The volume was read every 100 interval (Shirshand *et al.*, 2010). Tapped volume was noted, if the volume did not show a difference between two tapping intervals.

$$\textbf{Tapped density} = \frac{\mathbf{m}}{\mathbf{Vt}}$$

Where,

m = mass of powder mixture
Vt = tapped volume of the powder

2.2.2.4 Compressibility

Compressibility index is one of the methods to evaluate compressibility of the powder and flow property. Compressibility index can be calculated by comparing the bulk density (Db) and tapped density (Dt) of the powder (Aulton and Summers, 2013).

$$\textbf{Compressibility index} = \frac{\mathbf{(Dt - Db)}}{\mathbf{Dt}} \mathbf{\times 100}$$

Where,

Dt is the tapped density of the powder
Db is the bulk density of the powder

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2.2.2.5 Hausner ratio

Hausner ratio is an indirect index to predict powder flow (Aulton and Sumers, 2013). Hausner ratio can be calculated by following formula:

$$\textbf{Hausner ratio} = \frac{\textbf{Dt}}{\textbf{Db}}$$

Where,

Dt is the tapped density of the powder
Db is the bulk density of the powder

Lower Hausner ratio (<1.25) indicates better flow than the higher ones (>1.25).

2.2.2.6 Moisture content

Moisture content of the powder was determined by analyzing approximately 5 grams of the powder. This evaluation was done by using moisture content analyzer. Moisture content of the powder can be calculated using this equation:

$$\%\ MC = \frac{W - Wo}{Wo} \text{ x } 100\%$$

Where,

W is the weight of wet mass
Wo is the weight of dry mass

### 2.2.3 Preparation of atenolol orally disintegrating tablets

The powder mixture was prepared to tableting process after pre compression evaluation. Tableting process was conducted by compress the powder mixture using the Erweka® tablet compression machine. The powder was compressed into 300 mg tablet using 11 mm flat punches.

### 2.2.4 Post compression evaluation

Orally disintegrating tablets of atenolol from all formulations were evaluated considering following parameters like organoleptic, drug content uniformity, dimension, hardness, friability, wetting time, water absorption ratio, in vitro dispersion time, disintegration, and dissolution.

2.2.4.1 Organoleptic

Visual inspection was done to evaluate the color, shape, and taste of orally disintegrating tablets of atenolol.

2.2.4.2 Drug Content uniformity

The content uniformity test was carried out in order to ensure the homogeneity of atenolol in each tablet. Content uniformity of atenolol in orally disintegrating tablet was done by sampling randomly 20 tablets from each formula, and then these tablets were weighed and triturated in a mortar. The powder equivalent to 25 mg atenolol was weighed accurately and dissolved in 10 ml methanol. The solution transferred to 100 ml volumetric flask and a portion of acetate buffer pH 4.6 was added. The solution was sonicated thoroughly, then acetate buffer pH 4.6 was added to the volumetric flask until 100 ml. The undissolved matter was removed by filtration through Whatmann No.41 filter paper. The filtrate was pipetted 10

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ml and diluted with acetate buffer pH 4.6 ad 25 ml in a volumetric flask. This solution was assayed at λ 274 nm, using UV-Visible double beam spectrophotometer (Shimadzu UV-1800).

2.2.4.3 Dimension

Thickness and diameter of tablet were determined using vernier caliper. 10 tablets of each formula were determined its thickness and diameter to ensure uniformity of tablet size.

2.2.4.4 Hardness

For each formula, 10 tablets were determined its hardness using Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm$^2$. Constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted [Chandrasekhar *et al.*, 2013).

2.2.4.5 Friability

Friability of atenolol orally disintegrating tablet was determined using Erweka rolling and impact durability tester. A sample of tablets equal to 6.5 grams was weighed and placed in Erweka rolling and impact durability tester which revolves at a speed of 25 rpm for 4 minutes. The tablets were then dusted and reweighed. Percent weight loss (friability) was calculated using the following equation:

$$\%\text{Friability} = \frac{W1 - W2}{W1} \times 100$$

Where $W_1$ was the weight of the tablet before test and $W_2$ was the weight of the tablet after test.

2.2.4.6 Wetting time

A piece of filter paper with 8 cm diameter was prepared on the petri dish containing 10 ml eosin solutions. Atenolol orally disintegrating tablet was placed carefully on the surface of filter paper. The time of eosin solution to cover the surface of the tablet was noted (Kumare *et al.*, 2013).

2.2.4.7 *Water absorption ratio*

A piece of filter paper was placed in a small Petri dish containing 10 ml eosin solution. Atenolol orally disintegrating tablet was put on the paper and the time required for complete wetting was measured (Kumare *et al.*, 2013). The wetted tablet was then weighed. Water absorption ratio (R) was determined using this equation:

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

Where Wb and Wa were tablet weight before and after absorption.

2.2.4.8 In vitro dispersion time

One tablet was placed in a flask containing 6 ml phosphate buffer pH 6.8 with temperature 37±0.5°C. The time required for complete dispersion was determined.

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2.2.4.9 Disintegration time

Instrument which were used to conduct Hanson and Research disintegration tester. The distilled water at 37±0.5°C was used as disintegration media in 900 ml volume. Six tablets were randomly chosen and each tablet was placed in tube, then the basket rack was positioned in the media. The time for complete disintegration of the tablet with no palpable mass replaced on the screen was measured in seconds.

2.2.4.10 Dissolution study

In vitro dissolution study was performed using USP Type II Apparatus (paddle type) at 50 rpm for 120 minutes. Acetate buffer pH 4.6 was used as a dissolution medium which was maintained at 37±0.5°C. Aliquot (10 ml) was taken at specified time intervals. An equal amount of fresh dissolution medium was replaced immediately following withdrawal of the sample. The absorbance of the medium was analyzed using UV-visible, double beam spectrophotometer (Shimadzu UV-1800) at λ 274 nm.

## 2. Results and discussion

In the present study, orally disintegrating tablets of atenolol were prepared using crospovidone as superdisintegrant. Formula 1 using 0% of crospovidone, formula 2 using 10% of crospovidone, and formula 3 using 20% of crospovidone. These three formulations were prepared by direct compression technique. The formulated powder mixture were evaluated and the results are shown in table 2. These evaluation called as pre compression evaluation.

Table 2. Evaluation of Powder Mixture of Atenolol Orally Disintegrating Tablets

| Evaluation Parameters | Formula 1 | Formula 2 | Formula 3 |
|---|---|---|---|
| Flowability (g/s) | 9.31±0.16 | 6.88±0.10 | 7.37±0.15 |
| Angle of Repose (°) | 32.15±0.00 | 32.15±0.00 | 35.54±0.00 |
| Bulk Density (g/cm$^3$) | 0.393±0.0012 | 0.4211±0.000 | 0.3902±0.000 |
| Tapped Density (g/cm$^3$) | 0.5252±0.0049 | 0.5242±0.000 | 0.5263±0.000 |
| Compressibility (%) | 23.69±0.4990 % | 19.67±0.0000 % | 25.73±0.0000 % |
| Hausner Ratio | 1.32±0.01 | 1.24±0.00 | 1.34±0.00 |
| Moisture Content (%) | 4.80±0.24 | 5.52±0.18 | 5.54±0.07 |

Flowability of the powder mixture was in the range of 4-10 g/s, indicating good flow property (Hahm and Augsburger, 2008; Aulton, 2013). The angle of repose has been used on several branches of science to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles (United States Pharmacopeial Convention, 2017). All the formulas revealed good flow property because the values of angle of repose were between (31°-35°). The compressibility index and Hausner ratio are determined by measuring both the bulk volume and the tapped volume of a powder. The results of compressibility index and Hausner ratio showed that formula 1 was catagorized as passable, fomula 2 was categorized as fair, and formula 3 was categorized as passable. Overall these values indicated good flow properties of powder blend, uniform die fill, and better compression ability (Kumare *et al.*, 2013). Moisture content of the powder blend ranged from 4,00% - 6,00%. Moisture content of the powder mixture must be controlled during production of orally disintegrating tablets to ensure there was no sticking or picking phenomena during tablet compression. Therefore, from the data which was obtained, the powder mixture was decided to compress into orally disintegrating tablets.

The physicochemical properties of different formulas of orally disintegrating tablets are given in table 3.

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Table 3. Physicochemical Properties of Orally Disintegrating Tablets of Atenolol

| Evaluation Parameters | Formula 1 | Formula 2 | Formula 3 |
|---|---|---|---|
| Organoleptic | Round white tablet, sweet and mint odor | Round white tablet, sweet and mint odor | Round white tablet, sweet and mint odor |
| Drug content (%) | 93.99±0.13 | 100.21±2.45 | 98.81±2.31 |
| Hardness (kP) | 2.85±0.24 | 2.40±0.52 | 2.75±0.42 |
| Wetting time (seconds) | 7.00±1.00 | 4.00±0.00 | 7.00±0.00 |
| Water absorption ratio (%) | 126.78±1.89 % | 57.23±1.18 % | 60.47±0.62 % |
| Disintegration time (seconds) | 4.00±0.00 | 15.48±1.16 | 19.85±0.95 |
| In vitro dispersion time (seconds) | 15.00±0.00 | 8.00±1.00 | 13.00±1.00 |
| Friability (%) | 0.20±0.09 | 0.61±0.19 | 2.26±0.66 |
| Dissolution (%Q) | 53.85 | 86.17 | 87.05 |

Orally disintegrating tablets of atenolol which using crospovidone as superdisintegrant were round white tablets, sweet, and mint odor. The content of atenolol in all formulas was ranged from 93.99±0.13 % to 100.21±2.45 %. This results met the specification of atenolol tablets (90.0% - 110.0%) which has been stated in pharmacopeia (United States Pharmacopeial Convention, 2017).The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 2.40±0.52 to 2.85±0.24 kg. Friability values of formula 1 and formula 2 were below than 1%, thus indicating good mechanical resistance of the tablets. Moreover, the friability values of formula 3 were more than 1%. This result showed that the increase of crospovidone level in orally disintegrating tablets caused the increase of friaabilty in orally disintegrating tablets. Crospovidone particles seemed to consist of aggregates of smaller particles that are fused together. The aggregation gives crospovidone a spongy, highly porous appearance (Augsburger *et al.*, 2007). The increase of crospovidone concentration caused increasing of highly porous part of orally disintegrating tablets. Consequently, the friability of the tablets increased.

The wetting time for all the formulated tablets was in the range 4.00 ± 0.00 to 7.00 ± 0.00 seconds. The wetting time of formulations containing 10% crospovidone were significantly faster ($p<0.05$) compare to the other formulas. Unlike the disintegration test, the wetting test uses minimal water, which may be more representative of the quantity of moisture available in oral cavity (Mittapalli *et al.*, 2010). Wetting time process of atenolol orally disintegrating tablets can be seen in figure 1.

Figure 1. Wetting of orally disintegrating tablets of atenolol (F2) at 5, 10, and 15 seconds respectively.

Specifically, the use of crospovidone 10% in atenolol orally disintegrating tablets had faster wetting times, needed less water to disintegrate the tablet. Water absorption ratio values increased concurrently with increases in crospovidone concentrations from 10% to 20%. The increased of water absorption ratio indicating that this formulas had more porous structure, so that the amount of water which was needed to disintegrate the tablets became higher.

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Rapid disintegration within several seconds was observed in all the formulations. All the formulas met the specification of disintegration time which has been stated in compendia (US Departement of Health and Human Services, 2008). Crospovidone is a cross-linked homopolymer of N-vinyl-2-pyrollidone which has good water wicking characteristics and smaller disintegration times due to the hydrophilic pores created in compression However, the increasing of crospovidone concentrations from 10% to 20% caused the disintegration time of atenolol orally disintegrating tablets became slower. This is likely due to partial gelling that potentially could form a viscous barrier and delay the entry of water into the tablets. Based on this facts, crospovidone were found to lengthen disintegration time when utilized in high concentrations (Desai *at al.*, 2014). In vitro dispersion time test was conducted to predict the ability of orally disintegrating tablets to disintegrate in small volumes of saliva (± 6 ml). Formula 2 which was developed with 10% crospovidone showed the fastest in vitro dispersion time. In vitro dispersion time of formula 2 were significantly ($p<0.05$) lower than the in vitro dispersion time of formula 1 (control) and formula 3. Lower in vitro dispersion time of formula 2 indicated their faster dispersion in the mouth (Nagendrakumar *et al.*, 2010). In vitro dissolution study was conducted in a USP apparatus 2, paddle method using acetate buffer pH 4.6 as dissolution medium. The amount of atenolol dissolved in specified time (30 minutes) interval (%Q) from formula 2 and formula 3 met the specification which has been stated in compendia. United States Pharmacopeia 40$^{th}$ edition stated that the amount of atenolol which must be dissolved in 30 minutes (%Q) is 85% (United States Pharmacopeial Convention, 2017). The dissolution profiles of orally disintegrating tablets of atenolol (formula 1, formula 2, and formula 3) are shown in figure 2.

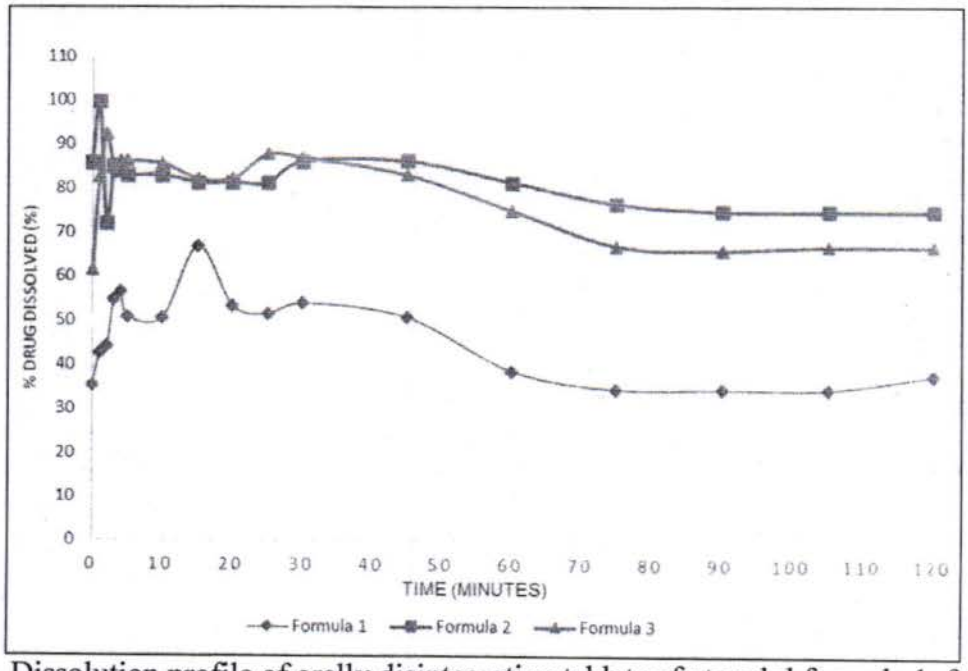


Figure 2. Dissolution profile of orally disintegrating tablets of atenolol formula 1, formula 2, and formula 3.

The dissolution profile for formula 1 (control), formula 2, and formula 3 which contained increasing concentration of crospovidone 10% and 20% is shown in figure 2. It was found that the percentage of drug release within formula 2 and formula 3 was 86.17% and 87.05% respectively. The results of statistical analysis using one way ANOVA showed that the dissolution efficiency of formula 1, formula 2, and formula 3 was significantly different ($p < 0.05$). Formula 2 which using 10% crospovidone showed the highest dissolution efficiency among all formulas. Dissolution efficiency of formula 2 fold approximately 2.2 times

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compare to formula 1 (control). The increased of crospovidone concentration to 20% were found to lengthen the disintegration time, consequently the onset of dissolution became slower (Desai *et al.*, 2014). Moreover, the dissolution efficiency became lower compare to formula 2 which used 10% crospovidone. Crospovidone were found to increase the disintegration time and decrease the dissolution efficiency when utilized in high concentration.

## 3. Conclusions

Thus from above results it can be concluded that crospovidone can be successfully used in the formulation of orally disintegrating tablets of atenolol. Crospovidone mechanism to disintegrate orally disintegrating tablets of atenolol combined wicking (capillary) mechanism and recovery energy of elastic deformation. The difference of crospovidone concentration which was used in orally disintegrating tablets of atenolol affect the physicochemical characteristics of orally disintegrating tablets. The optimum formula in this study was formula 2 (10% crospovidone).

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