# KINETIC SOLUBILITY OF MEBENDAZOLE NANOCRYSTAL

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## ABSTRACT

MBZ nanosuspensions were produced by high pressure homogenization and transformed into dry powder by lyophilization. MBZ nanocrystals were intensively evaluated regarding their physicochemical properties with respect to particle size analyses, crystallinity and kinetic solubility. The particle size was determined by photon correlation spectroscopy (PCS. DSC and X-ray diffraction were used to study the crystalline state of MBZ nanocrystals. In a period of 1 week, the kinetic solubility was determined using a shaker water bath at $37^{O}$ C. DSC and X-ray diffraction analyses showed that lyophilized MBZ nanocrystals prepared by high pressure homogenization remained in crystalline state. Lyophilized MBZ nanocrystals could be re-dispersed completely in water and the kinetic solubility in water increased 9 fold, from 60,57 ηg/ml to 598 ηg/ml.

**Keywords**: **mebendazole, nanocrystal, kinetic solubility**

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## INTRODUCTION

Mebendazole (MBZ, Methyl-5-benzyl-2-benzimidazole carbamate used as an anthelmintic drug. The drug is known to act through irreversible inhibition of glucose uptake in the parasite, leading to depletion of glycogen store which results in a decrease in adenosine triphosphate activity. Only 5–10% of the ingested drug is absorbed from the human gastrointestinal tract (Eskandari *et al*, 2011). It has poor solubility and poor oral bioavailability. The drug has dissolution rate limited bioavailability and therefore formulating as nanosuspension might improve its dissolution rate thereby enhance oral bioavailability (Kumar *et al*, 2008).

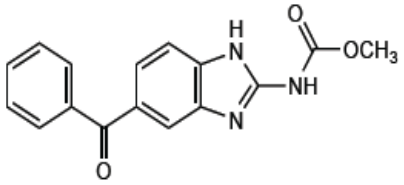


**Fig. 1 –Chemical structure of mebendazole**

Over the last decade, there has been increase in the number of newly developed drug molecules that exhibit poor water solubility as well as poor bioavailability. So, one of the most challenging tasks in drug development is to improve solubility and oral bioavailability of these novel drugs. Various methods to enhance solubility of poorly water-soluble drugs include solubilization (Dulfer *et al*,1995), formation of complexes β-cyclodextrin (Calabro et al, 2005), solid dispersions (Kanaze et al, 2006), liposomes (Dupont,

2002), emulsions (Nakano, 2000) and microemulsions (Lawrence and Rees, 2000). However, these methods are successful in some instances and are specific to drug candidates.

The fundamental basis for the observation that size influences the solubility is found in the Kelvin equation (Buckton and Beezer, 1992). The Kelvin equation is equally applicable to the solid–liquid interface, because the vapor pressure in a liquid–gas system corresponds to the dissolution pressure in a solid–liquid phase system. Replacing the pressure terms with solubilities (*c*s), as activity coefficients are effectively set equal to the unity in the dilute solutions considered here, produces the so-called Gibbs–Kelvin relation.

The aim of this study is to assess of kinetic saturation solubility of mebendazole nanocrystal. The physicochemical properties of the MBZ nanocrystals and the nanocrystal powder have been investigated regarding crystallinity and kinetic solubility.

## MATERIAL AND METHODS

### *Materials*

MBZ raw material was purchased from PT Indofarma (Bekasi, Indonesia). Polyvinyl alcohol (PVA) were kindly gifted from BASF. Sodium lauryl sulphate (SLS) was obtained from Cognis Indonesia Ltd. Polysorbate 80 (Tween 80®) was obtained from Shino Japan Chemical. All other reagents were of analytical grade.

### *Methods*

#### *Production of mebendazole nanosuspensions*

Mebendazole nanosuspensions were produced by high pressure homogenization (HPH) in aqueous solution of surfactant and polymer using Nano DeBEE (USA). The nanosuspensions were produced at room temperature, applying main-milling 20 homogenization cycles at 1500 bar (equal to
150,000 kPa and 21,756 psi).

#### *Particle size analyses*

The particle size and zeta potential value of the mebendazole nanosuspensions were determined by the DelsaTM Nano C Particle Analyzer (Beckman Coulter GmbH, Germany). The samples were adequately diluted with deionised water and placed in an elec- trophoretic cell.

#### *Lyophilization*

The mebendazole nanosuspensions were dried by lyophilization. Each mebendazole nanosuspension (10 mL) was freeze-dried at −80◦C in a 20 mL vial using Martin Christ " 1–2/LD plus freeze dry system (Martin Christ Gefriertrocknungsanlagen GmbH, 37507 Osterodeam Harz, Germany) with 50 mbar vacuum for 24 h. The dried powder was stored in a desiccator.

***Characterization by DSC***

Differential scanning calorimetric (DSC) measurements were carried out using a TA DSC 60 thermal analyzer (TA-60 WS DE 19720, Shimadzu, JAPAN) in a temperature range of 30◦C–300◦C at a heating rate of $10^{O}$C/min in nitrogen gas

***Powder X-ray diffraction (PXRD)***

X-ray diffraction was studied using the Bruker AXS D8 Advance X-ray diffractometer (Bruker AXS, Madison, USA) Cu K" targets at a scanning rate of 0.010 2$\theta$/s, applying 40 kV at 40 mA, to observe the crystallinity of samples.

***Kinetic solubility***

Solubility studies were performed with shaking water bath (SW 22 Shaking Water Bath, Julabo GmbH, Eisenbahnstr, Germany ) at $37^{O}$ C. Vials were sealed to avoid changes due to evaporation and placed for 1 week in a thermostated storage at 37±0,5$^{O}$C. After the equilibrium was reached, suspensions were filtered through Sartorius® 0.1 mm filters (Sartorius AG, Germany). An aliquot from each vial was withdrawn by a 1 ml glass syringe (Poulten & Graf GmbHGermany) and assayed by spectrometrically at 287 nm using an ultraviolet spectrometer (Beckman D270, Beckman Coulter GmbH, Germany) to evaluate the amount of MBZ dissolved.

**Table 1. Composition of MBZ nanosuspension**

| | Formulation (%) | | |
|---|---|---|---|
| | **A** | **B** | **C** |
| MBZ | 10 | 10 | 10 |
| PVA | 2 | - | - |
| SLS | - | 0,5 | - |
| Tween 80 | - | - | 0,5 |
| Water | 88 | 89,5 | 89,5 |

## RESULT AND DISCUSSION

***Production of aqueous nanosuspensions and Lyophilization***

MBZ nanosuspensions stabilized by tree different stabilizers were successfully produced. The PCS particle size data of all nanosuspensions are shown in Table 2. The nanosuspension stabilized by PVA (formulation A) was chosen for further investigations. Dried MBZ nanocrystals were obtained by lyophilization using the freeze dryer. After 24 h, lyophilized MBZ nanocrystals were collected. The physical characteristics of the lyophilized MBZ nanocrystals were investigated with regard to crystalline state and kinetic solubility.

**Table 2. Mean PCS particle size and PI MBZ nanosuspension**

| | Formulation | | |
|---|---|---|---|
| | **A** | **B** | **C** |
| z-average (nm) | 201 | 310 | 564 |
| PI | 0,212 | 0,253 | 0,277 |

***Crystalline state evaluation by DSC***

Thermal analysis of the MBZ nanocrystal powder was performed and compared to the raw material and to the data in the literature. The MBZ nanocrystal powders investigated were obtained by lyophilization. The results of thermal analysis by DSC can be seen in Fig. 2. According to these results, the melting

points of MBZ (raw material and both nanocrystal powders) are similar. The only difference observed was a slight shift in melting temperature (from 320,53$^{O}$C to 323$^{O}$C). This modification was attributed to the presence of PVA as stabilizer and mannitol as cryoprotectant. The results of the thermal analyses are shown the melting points of the MBZ nanocrystals have not changed significantly. The presence of stabilizers has a minor influence on the melting temperature and has not altered the crystallinity of the drug

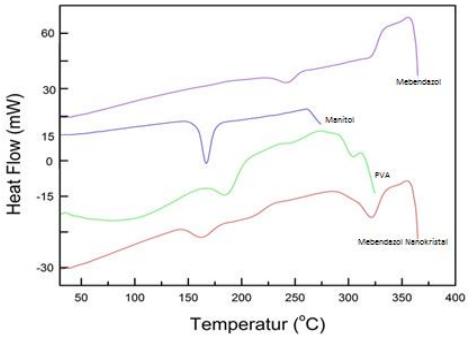


**Fig. 2 – DSC thermogram of lyophilized, MBZ nanocrystals and raw material**

***Crystalline state evaluation by XRD***

To confirm the crystalline state of the dried MBZ nanocrystals, X-ray diffractionwas performed of the lyophilized MBZ nanocrystals. X-ray diffraction patterns were visualized in diffractograms can be seen in Fig. 3. The crystallinity of lyophilized MBZ nanocrystals with PVA as stabilizers. The diffractograms reveal no different peaks for MBZ nanocrystals. According to these results, MBZ nanocrystals were still in the same crystalline state as the raw material. Applying energy by being homogenized and subjecting them to the drying processes did not transform MBZ nanocrystals to be fully or partially amorphous. In general, more crystalline substances are physically more stable compared to amorphous forms.

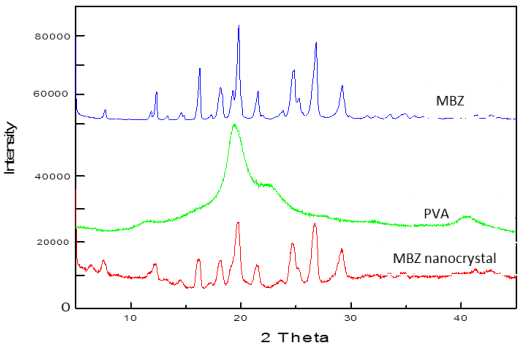


**Fig. 3 – X-ray diffractogram patterns of lyophilized MBZ nanocrystal formulations and the raw material**

***Kinetic solubility***

Thermodynamic solubility is the concentration in the solute in equilibrium with a normal sized powder, this condition being physically stable. Kinetic solubility, e.g. achieved by size reduction or from amorphous powders, is higher than the thermodynamic solubility but physically not long-term stable (Mauludin *et al*, 2009). The kinetic solubility of MBZ nanocrystals was investigated over 1 week. The results of this testing showed that the solubility of the MBZ nanocrystals in water was increased at 37$^{O}$ C. The kinetic solubility was with 598 µg/ml higher than of the raw material (60,57µg/ml) (Fig. 4).

According to the crystalline state investigation, the solubility enhancement of the MBZ nanocrystals is not due to the presence of the MBZ amorphous form. It

is due to the particle size reduction to the submicron range. This result is in agreement with the Kelvin–Gibbs equation and Ostwald–Freundlich equation (Buckton and Beezer, 1992; Müller and Akkar, 2004)

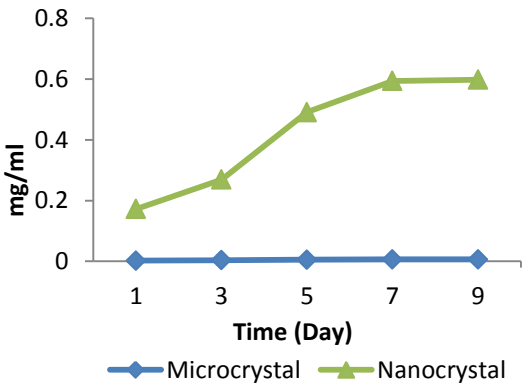


**Fig. 4 – Kinetic saturation solubility of the MBZ nanocrystals and MBZ microcrystals in water at 37$^{O}$ C.**

## CONCLUSION

MBZ nanocrystals could provide superior physicochemical properties. Lyophilized MBZ nanocrystals improved the kinetic saturation solubility from 60,57 ηg/ml to 598 ηg/ml, comparison to MBZ microcrystals.

## ACKNOWLEDGEMENTS

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