UNIVERSITI TEKNOLOGI MARA

PRODUCTION OF GRISEOFULVIN NANOPARTICLES VIA WET-GRINDING METHOD

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Thesis submitted in fulfillment of the requirements

for the degree of

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulation of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any other degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Poorly water soluble drugs pose formulation problem and low oral bioavailability. Size reduction is among the several approaches to improve the solubility of such drugs. Wet grinding is a relatively new technology used to reduce the particle sice down to sub-micron range. Griseofulvin a BCS II Class model drug was used to assess the feasibility of the above method to reduce the particle size to nanoscale with narrower distribution of particle size. Different factors such as type of the surfactants, concentration of surfactants, grinding speed, grinding time and the size of the grinding media (grinding beads) was varied to find the optimized conditions to achieve the desired particle size and size distribution of the griseofulvin particles. The lowest mean particle size of 123 ± 0.0 nm for griseofulvin was accomplished with 5% w/v blend of 1.65% w/v of Tween 80 and 3.35% w/v of Span 80 at 1200 rpm using grinding media of 1 mm in diameter for 60 minutes followed by using 0.2 mm in diameter for 90 minutes (total 150 minutes). The next procedure considered the storage stability of nanosuspension. The type and concentration of stabilizers were varied. This study focused on the particle size growth control (Oswald ripening) during storage (monthly up to 3 months). The results showed that manitol 3% w/v used as a stabilizer could maintain the particle size at 158 nm with uniformity of 0.336 at 3 months storage condition (room temperature). *In vitro* dissolution rate of griseofulvin was significantly increased by reduction of particle size. Griseofulvin of different particle sizes rapidly dissolved in different dissolution media. The results showed that griseofulvin in nanosize almost 100 % dissolved in the aqueous solution after 120 minutes. The oral bioavailability of griseofulvin of different particle size was found to be significantly increased by reduction of particle size. The results showed that griseofulvin in nanosized form had greater bioavailability compared to the macrosized and microsized forms. The $AUC_{(0-24)}$, C_{max}, and T_{max} of nanosized griseofulvin after oral administration were greater than the macrosized and microsized griseofulvin. The $AUC_{(0-24)}$ of nanosized griseofulvin was one (1) fold greater than the microsized form and three (3) folds greater than the macrosized griseofulvin. The C_{max} of nanosized griseofulvin was one (1) fold of the macrosized form and two (2) folds of the microsized form. The T_{max} of the three (3) suspensions were not statistically significantly different. The tissue distribution study showed that a higher concentration of griseofulvin in tissues (kidney, liver, skin and brown adipose) was achieved by the nanosized griseofulvin than the macrosized griseofulvin. After two (2) hours of oral administration, the hightest concentration of nanosized griseofulvin was found in the liver. This study shows that wet grinding is a possible method for the preparation of griseofulvin nanoparticles for improved oral bioavailability of this antibiotic.

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