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# Pemodelan Kinetika Reaksi Degradasi Obat Antituberkulosis Isoniazid dan Rifampisin dengan Penambahan Stabilisator Asam Galat atau Asam Askorbat = Kinetic Modeling of Degradation Reaction of Isoniazid and Rifampicin Antituberculosis Drugs with the Addition of Gallic Acid or Ascorbic Acid as Stabilizers

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Abstrak

Tulang belakang menjadi lokasi penyakit tuberkulosis (TB) tulang paling umum yang menyumbang sekitar setengah kasus TB tulang. Pengobatan via oral menggunakan empat obat antituberkulosis (OAT) lini pertama memiliki risiko ketidakpatuhan pasien yang tinggi dan bioavailabilitas obat di jaringan infeksi yang rendah. Penelitian terkini telah membuktikan bahwa implan tulang belakang OAT berpotensi mengatasi masalah ketidakpatuhan pasien dan meningkatkan daya jangkau obat ke daerah terinfeksi. Namun, peningkatan stres oksidatif karena respon tubuh terhadap infeksi patogen berpotensi mengakselerasi degradasi OAT isoniazid (INH) dan rifampisin (RIF). Untuk menghambat degradasi, INH dan RIF ditambahkan stabilisator dari kelas antioksidan yaitu asam galat (AG) untuk INH dan asam askorbat (AA) untuk RIF. Uji degradasi paksa dilakukan dengan terlebih dahulu membuat kurva kalibrasi obat serta menstandardisasi H2O2 stok. Sampel INH dan RIF disimpan selama 21 hari dalam media phosphate buffered saline (pH 7,4) dengan variasi konsentrasi oksidator (H2O2) dan konsentrasi stabilisator. Konsentrasi OAT diukur dengan instrumen high performance liquid chromatography (HPLC) dengan kolom C18 (250  4,6 mm  5 µm). Hasil uji degradasi menunjukkan bahwa sampel INH mengalami degradasi sebesar 82,36%, 96,55%, dan 100% akibat penambahan H2O2 0%, 0,5%, dan 1% (w/v), secara berurutan. Sementara itu, sampel INH mengalami degradasi sebesar 98,34%, 83,68%, dan 60,08% akibat penambahan AG dengan perbandingan massa INH:AG sebesar 4:1, 2:1, dan 1:1, secara berurutan. Penambahan stabilisator dengan konsentrasi yang tepat merupakan upaya untuk mengurangi oksidasi pada OAT yang diimplan di tulang belakang sehingga persamaan kinetika yang akurat dalam merepresentasikan reaksi degradasi OAT diperlukan untuk menentukan konsentrasi stabilisator yang optimal supaya menghasilkan laju degradasi OAT serendah mungkin. Model persamaan kinetika degradasi OAT menunjukkan stabilitas obat yang merupakan fungsi dari konsentrasi oksidator dan konsentrasi stabilisator. Hasil penelitian menunjukkan bahwa untuk reaksi degradasi INH dengan penambahan stabilisator AG dan kehadiran oksidator H2O2, parameter kinetika yang diperoleh yaitu k3 = 1,05 10-4 hari-1, kw = 538,95 mM, KA = 0,71 mM, dan KB = 11,01 mM-1

.....Spine is the most common site of skeletal tuberculosis (TB), which accounts for about half of skeletal TB cases. Oral treatment using four first-line antituberculosis drugs (ATD) has a high risk of patient non-adherence and low bioavailability of drugs in infected tissues. Recent research has proven that ATDs spinal implants have the potential to overcome patient non-adherence problems and it increases the drug's reach to the infected areas. However, an increase in oxidative stress due to the body's response to pathogen infection has the potential to accelerate the degradation of two ATDs, isoniazid (INH) and rifampicin (RIF). To inhibit the degradation, INH and RIF added stabilizers from the antioxidant class, namely gallic acid (GA) for INH and ascorbic acid (AA) for RIF. A forced degradation study was conducted by prior creation of

calibration curves and standardization of H2O2 stock concentration. INH and RIF samples were kept for 21 days in phosphate buffered saline (pH 7,4) aqueous media with varying oxidizer concentrations (H2O2) and stabilizer concentrations. Concentration of ATDs were measured using a high performance liquid chromatography (HPLC) instrument with a C18 (250  4,6 mm  5 µm) column. The results of the degradation test showed that INH samples had a degradation of 82,36%, 96,55%, and 100% due to the addition of 0%, 0,5%, and 1% (w/v) H2O2, respectively. Meanwhile, the INH samples had a degradation of 98,34%, 83,68%, and 60,08% due to the addition of GA with a mass ratio of INH:GA of 4:1, 2:1, and 1:1, respectively. The addition of a stabilizer with the accurate concentration is an effort to reduce oxidation in ATDs implanted in the spine so that an accurate kinetic equation in representing the ATDs degradation reaction is needed to determine the optimum stabilizer concentration to produce the lowest possible ATDs degradation rate. The kinetic equation model of ATDs degradation shows drug stability, which is a function of the oxidizer concentration and the stabilizer concentration. The results showed that for INH degradation reaction with the addition of GA as stabilizer and the presence of H2O2 as oxidizer, the kinetic parameters obtained were k3 = 1,05 10-4 day-1, kw = 538,95 mM, KA = 0,71 mM, and KB = 11,01 mM-1.