DISERTASI

REKAYASA KRISTAL NIKLOSAMID UNTUK MEMPERBAIKI SIFAT FISIKOKIMIA SERTA UJI EFEKTIVITAS SITOTOKSIK

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ABSTRAK

REKAYASA KRISTAL NIKLOSAMID UNTUK MEMPERBAIKI SIFAT FISIKOKIMIA SERTA UJI AKTIVITAS SITOTOKSIK

Oleh Indra Makmur

Niklosamid merupakan obat antelmintik yang berpotensi dikembangkan kembali *(drug repurposing*) sebagai agen antikanker. Namun, pemanfaatannya masih terbatas oleh kelarutan yang sangat rendah sehingga menghambat laju disolusi dan ketersediaan hayati obat. Penelitian ini bertujuan untuk mengevaluasi pengaruh pembentukan multikomponen kristal niklosamid menggunakan koformer asam kafeat, sakarin, dan piperin melalui metode *solvent drop grinding* terhadap karakteristik fisikokimia, profil disolusi, dan aktivitas sitotoksik pada sel kanker payudara T47D. Penelitian dilakukan secara eksperimental laboratorium dengan pendekatan kuantitatif. Sistem multikomponen kristal niklosamid dibentuk menggunakan metode *solvent drop grinding* dan dikarakterisasi menggunakan *Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), Fourier Transform Infrared Spectroscopy (FT-IR), dan Scanning Electron Microscopy (SEM)*. Selanjutnya dilakukan evaluasi profil disolusi dan aktivitas sitotoksik terhadap sel kanker payudara T47D menggunakan metode *Microculture Tetrazolium Assay (MTT)*. Hasil penelitian menunjukkan bahwa pembentukan sistem multikomponen kristal menyebabkan perubahan karakteristik fisikokimia niklosamid yang ditunjukkan oleh perubahan profil termal, pola difraksi sinar-X, spektrum inframerah, dan morfologi partikel. Sistem niklosamid-piperin menunjukkan perubahan struktur kristal yang paling signifikan dibandingkan sistem niklosamid-sakarin dan niklosamid-asam kafeat. Hasil uji disolusi menunjukkan bahwa seluruh sistem multikomponen kristal meningkatkan profil disolusi niklosamid dibandingkan niklosamid murni. Pada menit ke-120, persentase niklosamid terdisolusi meningkat dari 39,93% pada niklosamid murni menjadi 74,81%, 80,27%, dan 66,08% masing-masing pada sistem niklosamid-asam kafeat, niklosamid-piperin, dan niklosamid-sakarin. Di antara seluruh sistem yang diuji, niklosamid-piperin menunjukkan performa disolusi tertinggi. Seluruh sistem multikomponen kristal juga menunjukkan peningkatan aktivitas sitotoksik terhadap sel T47D dibandingkan niklosamid murni, dengan sistem niklosamid-piperin menghasilkan aktivitas tertinggi yang ditunjukkan oleh nilai IC_{50} sebesar 0,69 µg/mL. Disimpulkan bahwa pembentukan multikomponen kristal niklosamid menggunakan asam kafeat, sakarin, dan piperin melalui metode *solvent drop grinding* mampu memodifikasi struktur kristal, meningkatkan profil disolusi, memperbaiki karakteristik farmasetika, serta meningkatkan aktivitas sitotoksik terhadap sel kanker payudara T47D. Piperin merupakan koformer yang paling prospektif untuk pengembangan lebih lanjut.

Kata kunci: Niklosamid, Rekayasa Kristal, Sifat Fisikokimia, Kokristal, Aktivitas Sitotoksik

ABSTRACT

Crystal Engineering of Niclosamide to Enhance Physicochemical Properties and Evaluate Cytotoxic Activity

By Indra Makmur

Niclosamide is an anthelmintic drug that has recently attracted considerable interest for drug repurposing as a potential anticancer agent. However, its clinical application is limited by its extremely low aqueous solubility, resulting in poor dissolution and low bioavailability. This study aimed to evaluate the effects of niclosamide multicomponent crystal formation with caffeic acid, saccharin, and piperine as coformers using the solvent drop grinding method on its physicochemical properties, dissolution profile, and cytotoxic activity against T47D breast cancer cells. The study was conducted as a quantitative laboratory-based experimental investigation. Niclosamide multicomponent crystal systems were prepared by solvent drop grinding and characterized using Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), Fourier Transform Infrared Spectroscopy (FT-IR), and Scanning Electron Microscopy (SEM). Dissolution studies and cytotoxicity evaluation against T47D cells were subsequently performed using the Microculture Tetrazolium Assay (MTT). The results demonstrated that the formation of multicomponent crystal systems altered the physicochemical characteristics of niclosamide, as evidenced by changes in thermal behavior, X-ray diffraction patterns, infrared spectra, and particle morphology. The niclosamide-piperine system exhibited the most pronounced crystal structure modification compared with the niclosamide-saccharin and niclosamide-caffeic acid systems. Dissolution testing revealed that all multicomponent crystal systems enhanced the dissolution profile of niclosamide compared with pure niclosamide. At 120 min, the percentage of dissolved niclosamide increased from 39.93% for pure niclosamide to 74.81%, 80.27%, and 66.08% for the niclosamide-caffeic acid, niclosamide-piperine, and niclosamide-saccharin systems, respectively. Among all systems evaluated, the niclosamide-piperine multicomponent crystal exhibited the highest dissolution performance. Furthermore, all multicomponent crystal systems demonstrated enhanced cytotoxic activity against T47D cells compared with pure niclosamide, with the niclosamide-piperine system showing the greatest activity, as indicated by an IC_{50} value of 0.69 µg/mL. In conclusion, the formation of niclosamide multicomponent crystals with caffeic acid, saccharin, and piperine through the solvent drop grinding method successfully modified the crystal structure, improved the dissolution profile and pharmaceutical performance, and enhanced the cytotoxic activity against T47D breast cancer cells. Piperine was identified as the most promising coformer for further development.

Keywords: *Niclosamide*, *Crystal Engineering*, *Physicochemical Properties*, *Cocrystal, Cytotoxic Activity.*