Radiosintesis dan Karakterisasi Nanopartikel Perak Terstabilisasi Alginat dengan Penyerapan Sistemik Minimal setelah Administrasi Oral Dosis Berulang 14 Hari pada Mencit = Radiosynthesis and Characterization of Alginate-Stabilized Silver Nanoparticles with Minimal Systemic Uptake upon 14-Days Repeated Dose Oral Administration in Mice

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Abstrak

Latar belakang: Nanopartikel perak (AgNPs) telah banyak diteliti karena aktivitas anti-inflamasinya yang berpotensi digunakan sebagai obat yang bekerja secara lokal di saluran gastrointestinal (GI) untuk pengobatan kolitis ulseratif. Namun, disolusi AgNPs secara masif dalam kondisi asam di lambung berpotensi menyebabkan serapan sistemik dan toksisitas. Pendekatan rasional harus dirancang untuk penargetan kolon secara selektif.
Metode: Biomolekul alginat dipilih sebagai agen penstabil untuk radiosintesis dan penghantaran AgNPs karena bersifat biokompatibel, sensitif pH, dan polianionik. Radiosintesis dioptimalkan menggunakan Central Composite Design – Response Surface Methodology (CCD-RSM) yang melibatkan 20 percobaan tanpa penambahan isopropanol sebagai scavenger radikal hidroksil. Stabilitas nanosuspensi dievaluasi selama penyimpanan pada suhu 4°C kondisi gelap selama 40 hari. Disolusi AgNPs secara in vitro ditentukan dalam simulasi cairan lambung pH 1,2 selama 120 menit. Kemudian, serapan sistemik dan toksisitas AgNPs terstabilisasi alginat ditentukan setelah pemberian oral dosis berulang 14 hari pada mencit sehat dengan dosis bervariasi (2,5, 5,0, dan 10,0 mg/kg BB).
Hasil: Radiosintesis berhasil mensintesis AgNPs terstabilisasi alginat tanpa penambahan isopropanol. Kondisi optimal diperoleh pada dosis iradiasi 20 kGy, konsentrasi precursor ion perak 7,78 mM, dan konsentrasi alginat 1,2 % (b/v) yang menghasilkan nilai konversi 65,43 % dengan konsentrasi AgNPs 480,9 ppm. Morfologi AgNPs berbentuk bulat dengan ukuran 10,25 ± 5,03 nm. Menariknya, alginat berperan ganda sebagai agen penstabil sekaligus agen pereduksi selama radiosintesis. Alginat juga berperan menstabilkan nanosuspensi hingga 67 ± 5 hari, dan meminimalkan disolusi pada kondisi asam pH 1.2 hingga kurang dari 1,5 % dalam periode disolusi 120 menit. Setelah administrasi oral dosis berulang 14 hari dosis 2,5 mg/kg BB, mencit sehat tidak menunjukkan tanda toksisitas. Perak tidak terdeteksi pada organ dalam, sedangkan penilaian hstopatologis untuk hepar dan kolon tidak berbeda bermakna dengan kelompok kontrol.
Kesimpulan: Alginat berperan penting dalam radiosintesis AgNPs tanpa penambahan isopropanol. Alginat juga berperan sebagai agen penstabil yang baik untuk menjaga stabilitas selama penyimpanan dan mencegah disolusi dalam kondisi asam. Dosis 2,5 mg/kg BB dapat digunakan sebagai dosis referensi untuk penelitian lebih lanjut mengenai toksisitas/bioaktivitas AgNPs sebagai obat yang bekerja secara lokal di saluran gastrointestinal (GI) untuk pengobatan kolitis ulseratif.
.....Background: Silver nanoparticles (AgNPs) have been extensively investigated due to their anti-inflammatory activity which potentially used as locally-acting drug in the gastrointestinal (GI) tract for treatment of ulcerative colitis. However, massive dissolution of AgNPs in acidic stomach potentially lead to

systemic uptake and toxicity. Rational approaches must be designed for selectively targeting the colon. Methods: Biomolecule alginate was chosen as stabilizing agent for radiosynthesis and delivery of AgNPs due to its biocompatibility, pH sensitiveness, and polyanionic nature. Radiosynthesis was optimized using central composite design – response surface methodology (CCD-RSM) which involved 20 run experiments without addition of isopropanol as a hydroxyl radical scavenger. The stability of nanosuspension was evaluated during storage at 4°C under dark for 40 days. The in vitro dissolution of AgNPs was determined in simulated gastric fluid pH 1.2 for 120 min. Then, systemic uptake and toxicity of alginate-stabilized AgNPs were determined upon 14 days repeated dose oral administration in healthy mice at varied dose (2.5, 5.0, and 10.0 mg/kg BW).

Results: Radiosynthesis had successfully synthesized alginate AgNPs without addition of isopropanol. The optimal condition was found at dose of 20 kGy, precursor silver ion of 7.78 mM, and alginate concentration of 1.2 % (w/v) which resulted the conversion yield of 65.43 % with concentration of AgNPs at 480.9 ppm. The AgNPs was spherical in shape at size of 10.25 ± 5.03 nm. Interestingly, alginate played dual role as stabilizing and reducing agent during radiosynthesis. The alginate allowed stabilization of nanosuspension for 67 ± 5 days, and also minimized the acid dissolution down to 1.5 % during 120 min dissolution time. Upon 14 days repeated dose oral administration of AgNPs at dose 2.5 mg/kg BW, the healthy mice did not showed toxicity sign. Silver was not detected in internal organ, while hstopathological scoring for liver and colon is not significantly different with control group.

Conclusion: Alginate plays important role in radiosynthesis of AgNPs without addition of isopropanol. It also acts as good stabilizing agent for maintaining stability during storage and preventing dissolution in acidic condition. Dose of 2.5 mg/kg BW can be used as a reference dose for further research on toxicity/bioactivity of AgNPs as locally-acting drug in the gastrointestinal (GI) tract for treatment of ulcerative colitis.