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PERILAKU DISOLUSI KETOPROFEN DAN INDOMETASIN FARNESIL TERSALUT GEL KITOSAN-GG

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ABSTRACT

DISSOLUTION BEHAVIOUR OF KETOPROFEN AND INDOMETHACIN FARNESIL COATED WITH CHITOSAN-GUAR GUM GEL

Chitosan, a modification of shrimp-shell waste, has been utilized as microcapsule. However, it's fragile gel property needs to be strengthened by adding glutaraldehyde (glu) and natural hydrocolloid guar gum (gg). This research's purposes were to determine rheological properties of chitosan-guar gum gel, to study diffusion and dissolution behaviour of ketoprofen and infar through optimum chitosan-guar gum gel membrane and microcapsule, respectively, and to test the coating stability of both medicines by the gel microcapsules, which are new drug's preparation, to determine their shelf lives and to predict the degradation mechanisms. This research was designed in six (6) steps: (1) chitin isolation and chitosan synthesis; (2) synthesis and optimization of chitosan-guar gum gel membrane; (3) *in vitro* study of ketoprofen and infar diffusion behaviour through the optimum membrane; (4) synthesis and optimization of chitosan-guar gum gel microcapsule to coat ketoprofen and infar; (5) *in vitro* study of ketoprofen and infar dissolution behaviour from the optimum microcapsule; and (6) physical and chemical microcapsule stability test using relative humidity (RH) and temperature controlled climatic chamber method. Studies on ketoprofen diffusion through chitosan-guar gum membrane showed that the formation of membrane small pores were appeared to be caused by membrane swelling, which was supported by the forcing force resulted from the difference of ketoprofen concentrations in the diffusion cells and from the temperature increase. This unique pore opening process is excellent for drug delivery process as a microcapsule. Spray drying process had successfully coated ketoprofen and infar in chitosan-guar gum microcapsule. Optimization by using Minitab Release 14 software showed that among the microcapsule compositions studied, |gg| and |glu| of 0.35% (w/v) and 3.75% (v/v), respectively were optimum to coat ketoprofen, whereas |gg| and |glu| of 0.05% (w/v) and 4.00% (v/v), respectively were optimum to coat infar, at constant chitosan concentration (1.75% |w/v|). *In vitro* dissolution profile showed that chitosan-guar gum gel microcapsule was more resistant in intestinal pH condition (rather basic) compared with that in gastric pH (very acidic). From stability test, formulation of ketoprofen preparation composed of 1.75% (w/v) chitosan, 0.35% (w/v) gg, and 3.50% (v/v) glu, was relatively the best, with ketoprofen percentage left in microcapsule after 3 months, degradation rate constant, and shelf life of of 80.33%, 0.0351 % $week^{-1}$, and 18.92 months, respectively. The degradation of ketoprofen was seem to follow autocatalytic reaction mechanism controlled by the formation and growth of reaction core. In the other hand, the formulation with composition of 1.75% (w/v) chitosan, 0.19% (w/v) gg, and 5.00% (v/v) glu, was relatively the best microcapsule, with infar percentage left in microcapsule after 3 months, degradation rate constant, and shelf life of 77.67%, 0.0008 $\%^{-2}$ $week^{-1}$, and 4.28 week or about 30 days, respectively. The degradation of infar was presumably caused by hydrolysis.

Keywords: *Chitosan-guar gum*, diffusion, dissolution, stability

ABSTRAK

Kitosan, salah satu modifikasi dari limbah kulit udang, telah dimanfaatkan sebagai mikrokapsul. Namun, sifat gelnya yang rapuh perlu diperkuat dengan menambahkan glu (glu) dan hidrokoloid alami gg (gg). Tujuan penelitian ini ialah menentukan sifat reologis gel kitosan-gg, mempelajari perilaku difusi dan disolusi ketoprofen dan infar berturut-turut melalui membran dan

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mikrokapsul gel kitosan-gg yang optimum, serta menguji stabilitas mikrokapsul gel tersebut, yang merupakan sediaan-obat baru, untuk menentukan usia guna. Penelitian meliputi enam (6) tahap, (1) isolasi kitin dan sintesis kitosan; (2) sintesis dan optimalisasi membran gel kitosan-gg; (3) studi *in vitro* perilaku difusi ketoprofen dan infar melalui membran optimum; (4) sintesis dan optimali-sasi mikrokapsul gel kitosan-gg untuk menyalut ketoprofen dan infar; (5) studi *in vitro* perilaku dissolusi ketoprofen dan infar dari mikrokapsul optimum; serta (6) uji stabilitas mikro-kapsul secara fisik dan kimia menggunakan metode *climatic chamber* yang diatur kelembapan relatif (RH) dan suhunya. Studi difusi ketoprofen melalui membran kitosan-gg menunjukkan bahwa pembentukan pori-pori kecil pada membran disebabkan oleh pembengkakan membran, yang didukung oleh gaya dorong yang dihasilkan oleh perbedaan konsentrasi ketoprofen dalam sel-sel difusi dan oleh kenaikan suhu. Proses pembukaan pori yang khas ini sangat baik untuk proses pengantaran obat sebagai mikrokapsul. Proses pengeringan-semprot telah berhasil menyalut ketoprofen dan infar dalam mikrokapsul kitosan-gg. Optimalisasi dengan perangkat lunak Minilah Release 14 menunjukkan bahwa komposisi |gg| dan |glu| berturut-turut 0,35% (b/v) dan 3,75% (v/v) optimum menyalut ketoprofen |gg| dan |glu| berturut-turut 0,05% (b/v) dan 4,00% (v/v) optimum menyalut infar, pada konsentrasi kitosan tetap, 1,75% (b/v). Profil disolusi *in vitro* menunjukkan bahwa mikrokapsul gel kitosan-gg lebih tahan pada kondisi pH usus (agak basa) dibandingkan dengan pH lambung (sangat asam). Dari uji stabilitas, formulasi sediaan ketoprofen dengan komposisi kitosan 1,75% (b/v), gg 0,35% (b/v), dan glu 3,50% (v/v), relatif paling baik dengan persentase ketoprofen yang masih tersalut setelah 3 bulan, tetapan laju penguraian, dan usia guna berturut-turut 80,33%, 0,0351 (% b/b).minggu^{-1}, dan 18,92 bulan. Degradasi ketoprofen agaknya mengikuti mekanisme reaksi autokatalitik yang dikendalikan oleh pembentukan dan pertum-buhan inti reaksi. Di sisi lain, formulasi sediaan infar dengan komposisi kitosan 1,75% (b/v), gg 0,19% (b/v), dan glu 5,00% (v/v, relatif paling baik dengan persentase infar yang masih tersalut setelah 3 bulan, tetapan laju penguraian, dan usia guna berturut-turut 77,67 %, 0,0008 %$^{-2}$.minggu^{-1}, dan 4,28 minggu atau kira-kira 30 hari. Degradasi infar diduga disebabkan oleh hidrolisis.

Kata kunci: *kitosan-gg*, difusi, disolusi, stabilitas