INTISARI

Obat basa lemah memiliki kecenderungan mengalami presipitasi di usus yang menyebabkan bioavailabilitasnya menurun. Terjadinya presipitasi diawali dengan supersaturasi akibat adanya pergeseran pH dari lambung menuju ke usus halus. Penggunaan polimer alami sebagai inhibitor presipitasi masih terbatas dan belum menunjukkan hasil yang optimal. Tujuan penelitian ini untuk mengetahui potensi alginat, gum acacia, pektin, dan karagenan sebagai inhibitor presipitasi ketokonazol.

Tahap pertama dilakukan pengujian sinergisitas kombinasi polimer berupa alginat-gum acacia (AG), alginat-pektin (AP), dan alginat-karagenan (AK) pada rasio 75:25, 50:50, dan 25:75 dengan dan tanpa $CaCl_2$ dengan cara mengukur viskositasnya. Kombinasi polimer tersebut dicampur dengan ketokonazol untuk membentuk suatu *beads* ketokonazol, lalu dikarakterisasi menggunakan *Fourier transform infrared* (FTIR), *Scanning electrone miscroscopy* (SEM), *Differential scanning calorimetry* (DSC), *X-Ray powder diffraction* (XRPD), uji *swelling*, uji disolusi, dan uji kelarutan. Pengujian supersaturasi dilakukan terhadap *beads* ketokonazol menggunakan metode pergeseran pH dengan sistem model 2 kompartemen yang ditransfer menggunakan pompa peristaltik. *Beads* ketokonazol yang paling optimum sebagai inhibitor presipitasi dilanjutkan pengujian *in vivo* pada hewan kelinci. Analisis data menggunakan uji statistika parametrik *independent sample t-test* pada taraf kepercayaan 90% dan uji *one way* ANOVA pada taraf kepercayaan 95%.

Hasil penelitian menunjukkan bahwa dengan penambahan $CaCl_2$ dapat meningkatkan sinergisitas pada kombinasi polimer dibandingkan tanpa $CaCl_2$. Kombinasi polimer yang menunjukkan efek sinergi adalah kombinasi AG75 (75:25), AP75 (75:25), AP50 (50:50), AK75 (75:25), dan AK50 (50:50). Hasil karakterisasi *beads* menunjukkan bahwa semua ketokonazol berhasil terenkapsulasi ke dalam *beads*. *Beads* AL100, AG75, AP75, AP50, dan AK75 mampu meningkatkan kelarutan ketokonazol dalam media FaSSIF pH 6,5. Model disolusi semua kombinasi *beads* dalam media SGF pH 2,0 mengikuti model Korsmeyer-Peppas. Berdasarkan hasil pengujian supersaturasi, *beads* AG75 merupakan *beads* paling optimum dalam menghambat presipitasi ketokonazol, yakni mampu mempertahankan supersaturasi sampai waktu sampling ke-60 menit, sedangkan ketokonazol murni sampai waktu sampling ke-20 menit. Nilai bioavailabilitas relatif *beads* AG75 berbeda signifikan ($p<0,1$) terhadap ketokonazol murni. Nilai bioavailabilitas relatif *beads* AG75 terhadap ketokonazol murni adalah sebesar 156,02±25,46%. Kombinasi polimer alami berupa alginat dan gum acacia dengan rasio 75:25 berpotensi sebagai inhibitor presipitasi ketokonazol yang berperan sebagai obat basa lemah untuk meningkatkan bioavailabilitasnya.

Kata kunci: obat basa lemah; supersaturasi; presipitasi obat; *polymer precipitation inhibitor*; bioavailabilitas

ABSTRACT

Weak base drugs tend to precipitate in the intestine, which causes their bioavailability to decrease. Precipitation begins with supersaturation due to a shift in pH from the stomach to the small intestine. Using natural polymers as precipitation inhibitors is still limited and have not shown optimal results. This study aimed to determine the potential of alginate, acacia gum, pectin, and carrageenan as inhibitors of ketoconazole precipitation.

The first stage was to test the synergism of the combination of polymers in the form of alginate-gum acacia (AG), alginate-pectin (AP), and alginate-carrageenan (AK) at ratios of 75:25, 50:50 and 25:75 with and without $CaCl_2$ utilizing measure the viscosity. The polymer combination is mixed with ketoconazole to form a ketoconazole bead, and then it was characterized using Fourier transform infrared (FTIR), Scanning electron microscopy (SEM), Differential scanning calorimetry (DSC), X-Ray powder diffraction (XRPD), swelling test, dissolution test, and solubility test. Supersaturation testing was carried out on ketoconazole beads using the pH shift method with a 2-compartment model system transferred using a peristaltic pump. The most optimum ketoconazole beads as precipitation inhibitors were continued in vivo testing in rabbits. Data analysis used an independent sample t-test parametric statistical test at a 90% confidence level and one way ANOVA test at 95% confidence level.

The results showed that the addition of $CaCl_2$ can increase synergy in polymer combinations compared to those without $CaCl_2$. Polymer combinations that showed synergy effect were AG75 (75:25), AP75 (75:25), AP50 (50:50), AK75 (75:25), and AK50 (50:50). The results of beads characterization showed that all ketoconazole was successfully encapsulated into the beads. Beads AL100, AG75, AP75, AP50, and AK75 were able to increase the solubility of ketoconazole in FaSSIF media pH 6.5. The dissolution model of all combinations of beads in SGF pH 2.0 media followed the Korsmeyer-Peppas model. Based on the results of supersaturation testing, AG75 beads are the most optimum beads in inhibiting ketoconazole precipitation, which is able to maintain supersaturation until the 60th minute sampling time, while pure ketoconazole until the 20th minute sampling time. The relative bioavailability value of AG75 beads was significantly different ($p<0,1$) to pure ketoconazole. The relative bioavailability value of AG75 beads was 156.02±25.46%. The combination of natural polymers in the form of alginate and gum acacia with a ratio of 75:25 has the potential as a precipitation inhibitor of ketoconazole which acts as a weak base drug to increase its bioavailability.

Keywords: weak base drugs; supersaturation; drug precipitation; polymer precipitation inhibitors; bioavailability