IMPROVED ANTIFUNGAL ACTIVITY OF ITRACONAZOLE USING MULTIMPLE COMBINATION OF BIOADHESIVE-THERMOSENSITIVE IN SITU VAGINAL GEL-GEL FLAKES- SOLID DISPERSION IN CANDIDIASIS RAT MODEL

Andi Dian Permana[1*], Emilia Utomo[2], Muhammad Rezky Pratama[1], Muh. Nur Amir1, Qonita Kurnia Anjani[2], Sandra Aulia Mardikasari[1], Sumarheni Sumarheni[1], Achmad Himawan[1,2], Andi Arjuna[1], Usmanengsi Usmanengsi[1], Ryan F. Donnelly[2]

[1]Faculty of Pharmacy, Universitas Hasanuddin, Makassar 90245, [2]School of Pharmacy, Queen's University Belfast, Belfast, UK BT9 7BL

Background: The treatment of vaginal candidiasis using conventional dosage form resulted in ineffective therapy. Furthermore, as one of antifungal agents, the effectiveness of itraconazole (ITZ) is hampered by its poor aqueous solubility. Here, we developed mucoadhe-thermosensitive *in situ* vaginal gel containing gel flake- solid dispersion of ITZ to overcome the problems

Methods: The optimization of solid dispersion and gel-flake formulations of ITZ was performed using a composite central design. The gel flakes- solid dispersions were further incorporated into *in situ* vaginal gel using PF-127 and PF-68, as the gelling agents, with the addition of hydroxypropyl methylcellulose (HPMC) as the mucoadhesive polymer.

Results: The results exhibited that the optimized formulation of solid dispersion was able to significantly improve the solubility of ITZ in water and simulated vaginal fluid to reach the values of 4.211 ± 0.23 and 4.291 ± 0.21 mg/mL, respectively. In addition, the optimized formulation of gel flakes had optimum entrapment efficiency and drug-loading capacity. The obtained *in situ* vaginal gel provided desirable physicochemical characteristics and could retain more than 4 mg of ITZ in the vaginal tissue after 8 h. Importantly, as per the *in vivo* antifungal activity using infection animal models, the incorporation of the solid dispersion technique and gel-flake system in the formulation of the bioadhesive-thermosensitive in situ vaginal gel led to the most significant decrease of the growth of Candida albicans reaching <1 log colony-forming units (CFU)/mL or equivalent to <10% of the total colony after 14 days, indicating the improvement of ITZ antifungal activity compared to other treated groups.

Conclusions: The incorporation of ITZ into bioadhesive-thermosensitive *in situ* vaginal gel and gel flakes-solid dispersions could significantly enhance the solubility of ITZ and improve *in vivo* antifungal activity in candidiasis rat model.