

## MUCOADHESIVE DRUG DELIVERY SYSTEM WITH ENHANCED PERMEABILITY CAPACITY FOR INTRAVESICAL THERAPY

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**Introduction and objective:** Bladder cancer (BC) represents 3% of the new diagnosis of cancer. 70% of the patients present the non-muscle-invasive type of the disease [1]. This type of BC is usually treated by the transurethral resection of the visible tumor, followed by intravesical immuno- or chemotherapy. The instillation of chemotherapy into the bladder is not totally efficient as it faces limitations such as short residence time and permeability restrictions of the bladder mucosa [2]. Thus, the main objective of this work was to develop drug delivery formulations for intravesical chemotherapy that enhance its residence time and permeation capacity. **Methodology:** Carboxymethylcellulose (CMC) and polyvinyl alcohol (PVA) polymers were used to prepare a physical hydrogel with mucoadhesive properties. Papain, a thiol proteolytic enzyme, was added to the formulations as a permeation enhancer. The mucoadhesive capacity of the formulation was evaluated by its interaction with mucin, bioadhesion strength and retention on bladder urothelium. *Ex-vivo* drug permeation was also elucidated using Franz cells to observe the papain effect.

**Results and discussion:** The CMC + PVA formulations showed positive bioadhesion components, confirming their interaction with the urothelium. The significant decrease of  $\eta_b$  in the formulation containing enzyme suggests that papain was cleaving the glycoproteins present in the mucin. On bioadhesion strength assays, the prepared formulations required a slightly higher detachment force than the control. In terms of work of adhesion, all formulations had values higher than those recorded for the control ( $p < 0.05$ ), confirming that there were mucoadhesive interactions between the bladder tissue and the gels. Hydrogel retention assay revealed that the formulations had higher bioadhesion capacity than the control (FITC solution), especially after the third wash (15 mL). By drug permeation analysis, it was possible to observe that the lag time decreased for CMC + PVA hydrogels with and without papain in comparison to the control. At the timepoint of 2 h, the formulation containing papain presented the highest capacity of permeation.

**Conclusions:** The biocompatible hydrogel containing papain as a permeability enhancer was an innovative approach for BC treatment to address the poor permeation of the tissue and short residence time. The formulation developed in this work could represent a very notable improvement in clinical practice, ensuring a longer retention time of the formulation in the bladder tissue, with a more sustained release of the drug and greater permeation capacity.

### References

[1] International Agency for Research on Cancer; pp. 1–2, 2020. [2] Kolawole, O.M. et al., *Int. J. Pharm.* 532, 105–117, 2017.

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