Summary

The effectiveness of current intravaginal gynecological therapies remains unsatisfactory. This issue largely stems from the fact that contemporary drug formulations – such as creams, suppositories, tablets, and capsules – often experience uncontrolled leakage from the vaginal cavity due to their physical form. As a result, drug bioavailability is significantly reduced, making it difficult to determine the actual dose absorbed into the body. This limitation results in the necessity for frequent dosing, which can lead to recurring infections, microbial drug resistance, and, in severe cases, infertility. In light of the need to improve women's health and quality of life, it is essential to develop carriers for various bioactive substances used in gynecological therapies that will enhance bioavailability and prolong their interaction time with affected tissues.

The aim of this study was to develop a polymeric material that could serve as a versatile base for preparing effective formulations intended for intravaginal gynecological therapies, including hormonal, antifungal, and anticancer treatments. One of the primary challenges in designing this type of polymer is the requirement to integrate several crucial biological and physicochemical properties, such as biocompatibility, lack of cytotoxicity, suitable rheological properties, good adhesion to the mucosal lining of the vaginal wall, and amphiphilicity – particularly important for carriers designed for hydrophobic substances. Hyperbranched polyglycidol (HbPGL) was chosen for this purpose due to its relatively simple and cost-effective synthesis, high hydrophilicity, and biocompatibility. The structure of this polymer consists of four types of constitutional units: dendritic, terminal, and two types of linear monohydroxyl units. The monohydroxyl units were selectively modified with hydrophobic groups (phenyl or biphenyl) through ester or urethane bonds, imparting an amphiphilic character to the HbPGL macromolecule. The presence of 1,2-diol functional groups in the terminal units ensured adequate solubility of the hydrophobized HbPGL macromolecules in water, enabling the formation of hydrogel systems with dynamic (reversible) network junctions. An acrylamide copolymer containing boric acid units was designed and synthesized to act as a cross-linking agent. Formulations prepared from the materials mentioned above and containing clotrimazole (used as a model antifungal drug commonly employed in gynecological therapies, also known for its anticancer properties against cervical cancer) exhibited rheological properties suitable for syringe administration and showed the ability to self-healing.

The research demonstrated that the degree of modification of the monohydroxy groups with phenyl moieties influenced both the efficiency of encapsulating hydrophobic bioactive substances within the HbPGL macromolecular structure and the rheological properties of

the resulting hydrogels. Insufficient degrees of hydrophobization resulted in very low encapsulation efficiency, while excessively high molar fractions of hydrophobic groups in the macromolecule limited the hydrogel's self-healing ability. It was found that, in addition to dynamic network junctions, hydrophobic interactions involving the aromatic rings present in the structure of hydrophobized HbPGL also play a role in forming the hydrogel.

Formulations based on hyperbranched polyglycidol modified with biphenyl groups exhibited characteristics of viscous non-Newtonian liquids and, more importantly, enabled molecular dispersion of clotrimazole within the polymer matrix (not observed for phenyl-modified HbPGL derivatives), significantly enhancing its bioavailability and producing an unexpectedly prolonged antifungal effect (up to 7 days). Additionally, it was observed that aqueous solutions of HbPGL hydrophobized with phenyl groups exhibit thermoresponsive properties, with the type of bond used to covalently immobilize the aromatic ring in the HbPGL structure significantly affecting both the phase separation mechanism and the transition temperature. The phase transition of the polymer was shown to involve conformational changes within the HbPGL ether chains and the tendency of the aromatic rings to become exposed on the macromolecule's exterior. In the case of the urethane derivative, which was demonstrated to be more hydrophobic than the ester derivative, aggregation of hydrophobic domains was observed.

It was shown that the use of a hydrogel matrix based on hydrophobized HbPGL enhanced the anticancer effect of the drug 5-fluorouracil and contributed to its selective action against cervical cancer cells. Given the formulations currently employed in cancer treatment, a system that operates selectively at the disease site would represent a breakthrough material for intravaginal oncological therapy.

An attempt to create a hormone carrier (for progesterone and estradiol) highlights the broad potential applications of hydrophobized hyperbranched polyglycidol, although further optimization of these formulations is required.