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ABSTRACT

Biocompatible polymeric materials with precisely controlled macrostructure and their effect on the stability of active substances in binary mixtures

In recent years, polymers used as excipients for active pharmaceutical ingredients (APIs) have become an exceptionally interesting and rapidly developing area of research in pharmaceutical technology. Particular attention is paid to their ability to improve the physical stability of amorphous systems, enhance API solubility, and modify pharmacokinetic parameters. At the same time, the scientific literature still clearly lacks systematic studies addressing the influence of macromolecular architecture on solving key formulation-related challenges, such as effectively inhibiting recrystallization, increasing solubility, or improving the performance characteristics of final formulations. An additional intriguing, yet thus far unexplored, aspect is the effect of polymer topology on promoting and stabilizing different polymorphic forms of APIs. This issue is especially evident in the case of the popular and widely used polymer poly(*N*-vinylpyrrolidone) (PVP), since commercially available materials are exclusively linear macromolecules obtained in an uncontrolled manner (i.e., *via* conventional free-radical polymerization) and characterized by a broad distribution of molecular weights (M_n), and consequently by high dispersity ($Đ$). The lack of availability of PVP polymers with more complex topologies and tightly controlled macrostructural parameters (M_n, $Đ$) significantly limits researchers' ability to investigate the relationship between macromolecular structure and function in pharmaceutical systems. Moreover, the synthesis of nonlinear PVPs remains relatively challenging, as the VP monomer belongs to the group of *"less activated"* monomers, and its controlled polymerization requires advanced and carefully tailored synthetic strategies. In this context, the main objective of this doctoral dissertation was to develop new synthetic routes leading to well-defined PVP polymers with different topologies and tightly controlled parameters (M_n, $Đ$), and then to use the resulting materials as innovative excipients for stabilizing and modifying the properties of selected APIs.

The doctoral dissertation presents a series of four scientific publications published in high-impact journals. The first two papers (**P1** and **P2**) were devoted to investigating the effect of polymer topology and chain length on the efficiency of inhibiting API recrystallization from the amorphous state, specifically in the case of metronidazole and naproxen, respectively. The results obtained clearly demonstrated that differences in macromolecular topology affected both the degree and extent of miscibility in the active substance–polymer system and the nature of intermolecular interactions, which directly translated into differences in the recrystallization kinetics of the API models studied. These findings confirmed that the effectiveness of a polymer as a crystallization inhibitor depends strongly not only on the amount of excipient used, but also on structural features such as topology and chain length. Next, paper **P3** focused on analyzing the influence of PVP homopolymer architecture on changes in the molecular order (smectic and nematic) and phase transition temperatures of liquid-crystalline itraconazole. The study revealed that, in this case as well, polymer topology plays a major role in API–polymer miscibility. Selected PVP macromolecules effectively suppressed the liquid-crystalline order of the API, but only polymers with nonlinear topology were capable of completely disrupting the mesophases and yielding a fully amorphous material, which also contributed to a marked increase in drug solubility. Thus, the results demonstrated that by selecting

a polymer matrix with an appropriate architecture, it is possible to alter the molecular order and liquid-crystalline transition temperatures of drugs in a relatively straightforward manner, and thereby modulate their properties depending on the intended application. In turn, paper **P4** focused on the role of the chemical nature of polymer blocks, in particular the relationship between the hydrophilicity and amphiphilicity of macromolecules, in shaping the physical stability of amorphous binary mixtures and the pharmacokinetic parameters of piribedil. In the course of this work, an important scientific discovery was made: the identification of a previously undescribed second polymorphic form of this active substance. The newly discovered API form exhibited a more favorable release profile, giving this finding not only scientific significance but also clear application potential. This study further showed that the deliberate selection of the nature of macromolecules (i.e., a fully hydrophilic or amphiphilic polymer) may lead to simultaneous improvement in the physical stability of the system and in the parameters determining its pharmaceutical performance.

To sum up, the studies presented make a significant contribution to the advancement of knowledge in the field of chemistry and polymers used in pharmacy. The dissertation provides new and original data on the relationship between polymer macrostructure and the stability and behavior of APIs in binary mixtures. Its innovative character lies both in the development of effective synthetic strategies for obtaining well-defined PVP polymers with diverse topologies and in demonstrating that macromolecular parameters play a key role in controlling the physical and biopharmaceutical properties of APIs (an aspect that has so far been almost completely overlooked due to synthetic challenges). The results presented in this series of publications are important not only from a fundamental perspective, but also in practical terms, as they open up new possibilities for the rational design of modern drug delivery systems based on biocompatible polymeric materials with advanced architecture.