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Fund “Nauka” Project № 22023 Resume – Competition-Based Session 2022:

“Evaluation of pharmacokinetic parameters of self-double emulsifying drug delivery systems with alendronate sodium for oral administration”

Project leader: Assoc. prof. Velichka Yordanova Andonova, PhD

The present project is focused on the development and characterization of an oral drug delivery system aiming to improve the oral bioavailability of alendronate sodium. Self-double emulsifying drug delivery system (SDEDDS) models are proposed. SDEDDS have the potential to increase the lipophilicity of many water-soluble drugs, such as alendronate sodium. In this way, the drug’s potential to overcome biological barriers and to be absorbed to a higher degree through traditional mechanisms of transport is increased. SDEDDS also have the potential to favor absorption through the gastrointestinal lymphatic system, which would further increase the bioavailability of alendronate sodium. This formulation approach would lead to a reduction in the administered dose and some adverse drug reactions. The object of investigation of the proposed SDEDDS with alendronate sodium should be the real in vitro and in vivo performance of the models. In this way, it will be possible to follow the kinetics of the drug release, as well as to study the behavior and mechanisms of drug absorption from the systems during in vivo application.

The optimization of SDEDDS with Alendronate Na and the development of a corresponding oral dosage form with an improved efficacy and safety profile with potential application in the treatment of osteoporosis is expected to be the main result of the work of the interdisciplinary team of specialists and researchers.

In consecutive stages are expected:

1. The development of stable and efficient micro- and nano-sized self-double emulsifying drug delivery systems;
2. The development and validation of a chromatographic method for the analysis of Alendronate Na in different matrices;
3. To increase the knowledge about the mechanisms of oral drug absorption;
4. To increase the knowledge on the development of dosage forms with included micro- and nano-sized drug delivery systems;
5. Optimization of the technological and biopharmaceutical characteristics of the obtained solid capsule dosage forms;
6. Proving the safety and effectiveness of the developed drug delivery systems with Alendronate Na – a better oral bioavailability, reduced ADRs on the part of GIT, and, respectively, expected better clinical effect;
7. Development of interdisciplinary dissertation work in the field of the technology of dosage forms and biopharmacy and the field of pharmacology, toxicology, and

pharmacotherapy by one assistant professor from the Department of Pharmaceutical Technologies at the Faculty of Pharmacy of the Medical University of Varna;

8. Development of long-lasting forms of cooperation between the departments participating in the project.

The selected research team members, including specialists in drug technology and biopharmaceutics, pharmacology, pharmacokinetics, organic and pharmaceutical chemistry, biochemistry, and physics and statistics, is a guarantee to successfully conduct wide-ranging and in-depth research for the successful and practical realization of project goals and objectives.

Within the framework of the project, two novel, physically and thermodynamically stable compositions of self-double-emulsifying drug delivery systems (SDEDDS) with a 7% (w/w) sodium alendronate content were successfully developed and fully characterized. The PLG 1.1 formulation, based on phosphatidylcholine, and the Smix1 3.0 formulation, based on polysorbate 80, demonstrated the ability to spontaneously form microemulsions under conditions simulating the gastrointestinal tract, with a mean droplet size of 83.77 nm and 42.14 nm, respectively.

The most significant achieved result is the proven in vivo enhancement of oral bioavailability. Pharmacokinetic studies on an animal model (Wistar rats) reported a 1.8-fold increase in the oral bioavailability of sodium alendronate following the administration of the PLG 1.1 formulation compared to a reference dispersion. This was confirmed by a statistically significantly higher amount of the drug excreted in urine, which amounted to 0.025% of the applied dose for PLG 1.1 versus 0.012% for the control.

To predict this effect, a reliable in vitro permeation model using a biomimetic PermeaPad® membrane was validated, the results of which correlated well with the data from the animal experiments. The foundation for the reliable interpretation of all studies was laid with the development and validation of specific analytical methods for the quantitative determination of sodium alendronate both in the complex formulations and in a biological matrix such as urine.

The achievements and conclusions of the project were effectively disseminated within the scientific community. They form the basis of a successfully defended dissertation and have been presented in a number of publications in peer-reviewed journals, as well as through presentations and posters at national and international conferences.

In conclusion, the project's execution proved that the strategy of incorporating sodium alendronate into double self-emulsifying systems, particularly the PLG 1.1 composition, is an effective approach for significantly improving its oral bioavailability. This discovery has clearly applied potential for the development of more effective oral therapies for socially significant diseases such as osteoporosis.