In recent years, there has been a substantial increase in the risk of civilization diseases, described as the greatest threat to the health of the Polish population. On the list of the civilization diseases are cardiovascular diseases (including hypertension (NT), myocardial infarction and stroke). According to the nationwide NATPOL 2011 report, approximately 32% of the population (10.5 million people) suffer from arterial NT, which is almost every third Polish citizen. Forecasts from this study indicate that by 2035, the number of people suffering from arterial NT will have increased to around 14 million, or 36%, of Polish citizens. As a result, the preparation of novel, alternative antihypertensive drug formulations is currently being conducted in a variety of research centers. These new drug forms could determine a precise drug release pharmacokinetics and reduce side effects. Despite extensive studies, there is no commercial solution on the market in this field. ***On that account, the goal of the proposed project is the studies under development of an innovative formulation of carvedilol (CDL) in the form of thermosensitive suppositories composed of a carvedilol/biodegradable micro- or nanocarrier system for hypertension therapy. This dosage form may be suitable for non-cooperating and unconscious patients or patients with digestive problems, but also for people with mental or metabolic disorders***. Despite the fact that so far a number of scientific studies have been undertaken on the pharmacokinetics and anti-hypertensive effect of CDL rectal delivery systems in the form of solid suppositories, ***the formulation indicated in this project has not yet been obtained and characterized.*** It is also worth mentioning that according to the ESC Guidelines for the Prevention of Cardiovascular Disease (CVD), CDL is a drug that has been authorized for use in the treatment of hypertension, angina pectoris, and heart failure. Because of the considerable first pass metabolism, its oral bioavailability is only approximately 20-25 %. This drug causes gastrointestinal adverse effects such as diarrhea, gastrointestinal discomfort, and gastric irritation. ***The significant novelty of our findings relies on using new and branched biodegradable matrices with different microstructure as an efficient solution for the modification of CDL release properties. We believe that the developed thermosensitive suppositories composed of micro- and nanocarriers with a well-defined microstructure, can be practically applied as "long-", "medium-", or "short-term controlled delivery systems of pointed active substance.*** The biodegradable polymeric carriers (matrices) will be synthesized from the heterocyclic monomers (cyclic carbonates and esters) in the presence of non-toxic pentaerythritol as an initiator process. Importantly, the obtained biodegradable materials will possess a well-defined topology, microstructure as well as appropriate physicochemical and biological properties. The synthesized materials will be firstly subjected to the toxicity and mutagenicity assays and then to the preparation of biodegradable micro- or nanocarriers of CDL. The carvedilol/biodegradable nanocarriers-loaded suppositories as an innovative formulation of CDL will be after developed, characterized and subjected to *in vitro* evaluation of drug release properties. ***The release data points will be subjected to zero-order, first-order kinetics, Higuchi and Korsmeyer-Peppas models to evaluate the kinetics and release mechanisms of CDL from the formulations.*** Our intention in this project, is to demonstrate the influence of the polymer microstructure on the amount of drug released. ***In the further step of our study, the cytotoxicity of the selected innovative formulation of CDL will be evaluated with the in vitro methods recommended by the EN ISO 10993 guideline with mammalian cells.*** All changes in the viability or condition of cell cultures induced by the tested samples will be assessed qualitatively and quantitatively. The quantitative estimation of cells viability after treatment will be evaluated spectrophotometrically with the neutral red uptake assay. Whereas, the qualitatively evaluation of cells condition will be examined microscopically and recorded in the test report descriptively and graphically. ***It is very important to mention that the developed innovative formulation will also be subjected to the pharmacokinetic studies as well as determining CDL antihypertensive efficacy after its rectal application in vivo.*** Blood pressure and heart rate will be measured by a catheter inserted into the femoral artery using a BP-2 blood pressure monitor. Mean blood pressure (MAP) and heart rate (HR) values will be calculated by averaging the variables measured in breathing cycles just prior to drug rectal administration and at selected post-challenge phase time points. Furthermore, the rats will be subjected to the procedure of collecting tail vein blood repeatedly at specified time points. ***Finally, the histopathology and immunohistochemistry as well as determination of the distribution of innovative CDL formulation in tissues (e.g., brain, liver, heart, etc.) will be conducted in details.***

We assume that the data/results obtained in the proposed project can provide reliable elements for further application. This in turn, could contribute to the development of a new formulation of cardiovascular control.

This project is interdisciplinary and connects biomaterials engineering, chemistry and pharmacy. We are persuaded that such a holistic approach could increase awareness in all of the areas listed.