INVESTIGATION OF THE CHEMICAL STABILITY OF SOME PEPTIDE AND PROTEIN DRUGS BY HPLC AND CE

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Many cellular processes in biological systems require proteins and peptides acting as modulators. Since recombinant DNA technology has enabled pharmaceutical industries to realize commercial production of these compounds, either native or modified, peptides and proteins have become increasingly important as pharmaceutical agents. The number of these compounds that are in Phase I trials or has been approved by the FDA is steadily increasing. The emerge of peptides and proteins as pharmaceutical entities requires a more comprehensive understanding of protein stability, both physical and chemical, in order to be able to cope with problems in synthesis, purification, formulation, storage and delivery of these compounds. A special problem with higher molecular peptides and proteins is the appearance of higher order structures in addition to the primary structure. Instability of these higher structures (physical instability) and modifications in the primary structures (chemical Instability). Both degradations can result in the loss of biological activity of the compounds of interest.

The primary objective of our research group has been the chemical stability of proteins and peptides. These studies have been performed using RP-HPLC and various forms of capillary electrophoresis. In the lecture the features of these techniques with respect to stability problems concerning proteins and peptides will be discussed.

Stability studies of several peptides, such as substance P-antagonist G, gonadorelin and several of its analogues, as well as proteins, more specifically recombinant human granulocyte colony-stimulating factor and interleukin-2 will be explained. These studies involve the kinetics and mechanisms of degradation under various condition, among which pH dependency and redox conditions are the most prominent. A theoretical approach of the pH dependency will be given, while also some practical implications, such as the introduction of interleukin-2 into sustained release pharmaceutical formulations will be mentioned.