DOCTORAL DISSERTATION ABSTRACTS

IN VITRO AND IN VIVO STUDIES ON DRUG DELIVERY SYSTEMS DEVELOPED FOR DIAGNOSIS AND SCINTIGRAPHIC IMAGING OF DEEP VEIN THROMBOSIS

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The aim of this research is to investigate the feasibility of drug delivery systems such as liposomes, niosomes, sphingosomes containing fibrinolytic enzymes like streptokinase and urokinase having the ability to accumulate in thrombi and used for the treatment of thrombus. Streptokinase and urokinase produced Lancefield Group C β-hemolitic streptococci and isolated form human urine, respectively, are proteolitic enzymes directly activating fibrinolitic system.

Film method followed by extrusion and freeze-thawing was used for the preparation of streptokinase/urokinase liposome, niosome, sphingosome dispersions and enhancing the amount of encapsulation of active substance, respectively. DMPC was used for liposome bilayer as phospholipid. SUR I was used for niosome bilayer as surfactant and SPH was used for sphingosome bilayer. SA and DCP were incorporated into streptokinase and urokinase dispersions, respectively. CHOL was added to all formulations as bilayer condenser. Molar bilayer compositions of (10:1:4) for all dispersions were used. The amount of entrapped drug, liposomal phospholipid content, particle size were determined for all dispersions. It was found that entrapment efficiency of dispersions were between 9 and 13%. The highest entrapment efficiency was obtained with niosome dispersions. Phospholipid yield of liposome vesicles was bigger than sphingosome vesicles both containing streptokinase and urokinase. After extrusion technique, particle size of all dispersions was reduced to 150-200 nm. In vitro release of drug from vesicles was investigated in buffer and buffer containing albumine and results were evaluated kinetically. The highest release rate was obtained with niosome vesicles containing streptokinase or urokinase both in buffer and buffer containing albumine medium. Physical stability of liposome, niosome, sphingosome vesicles containing streptokinase/urokinase was investigated. Liposome dispersions containing streptokinase/urokinase were found the most stable formulations stored at refrigerator and room temperature, both.

In vivo experiments were carried on rabbits which have thrombus formed in jugular vein and biodistribution of liposome, niosome, sphingosome vesicles containing radiolabeled streptokinase or urokinase was invastigated with the free streptokinase or urokinase. It was found that Trombus/Ven ratio was enhanced by encapsulating these enzymes into liposome, niosome, sphingosome vesicles, when compared with the free streptokinase or urokinase. After the biodistribution studies, scintigraphic imaging studies were carried out on rabbits. It was succeed to have imaging of thrombi by liposome formulations containing streptokinase.

After the sterilisation studies by gamma irradiation, it was found that dispersions can be sterilised by 15 kGy radiation dose and no big changes were occurred the chemical structure of raw material composed to dispersions.

Briefly, as far as release, stability and scintigraphy studies are concerned, streptokinase liposomes [DMPC:SA:CHOL+streptokinase (10:1:4)] was found as the most convenient formulation. However, niosomes were evaluated as the best formulation when entrapment efficiency results are taken into consideration. But, there is still a need further studies on the formulations to improve the scintigraphic images

Key Words: Liposome, Niosome, Sphingosome, Streptokinase, Urokinase, Thrombus, Scintigraphic Imaging, Gamma Irradiation, Sterilisation

Doctoral Dissertation Abstracts

TO DEVELOP THE MODIFIED RELEASE TABLET FORMULATIONS CONTAINING KETOPROFEN LOADED MICROSPONGES AND TO INVESTIGATE *IN VITRO-IN VIVO* PROPERTIES

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In our study, we aimed to prepare ketoprofen loaded microsponges by emulsion-solvent diffusion method and to evaluate them by *in vitro* control methods so as to choose the best formulation for preparing their tablets by direct compression method and to investigate the behavior of microsponges under pressure. After that a comparison was made by *in vivo* tests among the commercially available reference product (carrying the equal amount of ketoprofen with our tablets) and the prepared tablets.

In order to prepare microsponges, two different polymers Eudragit RS 100 and ethylcellulose were used. First of all, drug and polymer were dissolved in ethanol. Then this ethanolic solution was poured into 200 ml of distilled water which contained the emulsifying agent (PVA 72.000). After 30-45 minutes of stirring, the solid particles were filtered and washed with distilled water and dried in vacuum oven overnight. By *in vitro* control methods, formulations which were prepared with Eudragit RS 100 and containing the drug in the highest ratio was choosen the best one.

In tablet studies two different direct compression agents were used; Ludipress and Flow-Lac 100 and with 1000, 2000, 3000 and 3800 kgf/cm^2 pressure values were applied with hydraulic press. With SEM analysis and other *in vitro* control methods, tablets were evaluated and tablets which were pressed with 2000 kgf/cm^2 with Flow-Lac 100 were chosen to use in vivo studies. It was seen in SEM analysis that tablets which were pressed with 3800 kgf/cm^2, have cracks on microsponge surfaces. This was confirmed by dissolution tests also. We usually expect that when compression pressure increases, drug release from tablets will decrease. When 1000, 2000 and 3000 kgf/cm^2 pressure values were applied, it was seen from the dissolution profiles that when pressure value increased, drug release from the tablets decreased but when 3800 kgf/cm^2 were applied, a burst effect in the drug release was noted. This was explained with the deformation of the microsponge structure.

In *in vivo* studies the pharmacokinetic parameters of the modified release tablets which were prepared from ketoprofen loaded microsponges. were evaluated and a comparison was made with the commercially available ketoprofen tablet. Commercial ketoprofen tablets showed a more rapid absorption rate than modified release tablets and peak levels were reached within almost 5 hours after administration. However, modified release tablets showed a slower absorption rate and peak levels were reached 8 hours after administration. A correct dosage interval for modified release tablets (24 hours) maintain the well-known safety of ketoprofen and ketoprofen administered as commercial retard form tablets.

Key words: Ketoprofen, Microsponges, Emulsion-solvent diffusion technique, Tablets, Pharmacokinetic study.