carbohydrate of RTA significantly decreased uptake by liver and kidney, and resulted in prolonged circulating half-life. These results suggest that RTA prepared by carbohydrate-directed PEGylation would be more effective when constructed as immunotoxin for tumor targeting.

[PE1-31] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Comparative re-evaluation of protein denaturation for PLG microspheres prepared by W/O/W multiple emulsification processes.

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The purpose of this study was to re-evaluate the degree of protein denaturation during microencapsulation with poly (lactide-co-glycolide) (PLG) polymer. Ovalbumin(OVA), a model antigen, was entrapped in PLG microspheres by W/O/W multiple emulsification method in various conditions, i.e. with or without addition of polyvinylpyrrolidone(PVP) as a stabilizer for primary emulsification. PLG microspheres were suspended in PBS solution(pH 7.4) and incubated with shaking at 37.5℃. Release medium was collected periodically and analyzed using the micro-BCA protein assay method and ELISA method. In preliminary study with SDS-PAGE, typical bands for OVA showed that the primary structure of protein was not affected significantly. However, there was a decrease in immunoreactivity of OVA. In order to express the degree of protein denaturation, antigenicity ratio(AR) was introduced as follows: amount of immunoreactive of OVA / total amount of OVA released × 100(%). Especially the addition of primary emulsification stabilizer greatly influenced on protein denaturation : i.e. about 65% of AR with stabilizer versus less than 35% of AR without stabilizer. Therefore, in order to obtain information on structural integrity of protein, it is better to re-evaluate the protein denaturation employing immunoreactivity measurement for antigen entrapped in PLG microspheres.

[PE1-32] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Intranasal Delivery of Poly(ethylene glycol) Conjugated Salmon Calcitonin in Rats

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Activated PEG molecules (2000 and 5000 Da) were attached to salmon calcitonin via covalent linkage. Mono-PEG-sCT was then separated by size exclusion chromatography and characterized by CE and MALDI-TOF mass spectrometry. Six Male Sprague-Dawley rats (220-280 grams) per group were used. sCT (2 IU/kg) and PEG-sCT (2 IU/kg) were dissolved in saline solution and directly applied onto the nasal mucous membrane of rat by using micropipet (50 ul/rat) under anesthesia, respectively. Blood was withdrawn at a certain time intervals and centrifuged to collect the plasma samples. Serum calcium concentration was measured by o-cresolphthalein complexone complex assay using UV spectrophotometer. Serum calcium concentrations following nasal placebo administration remained around 100 % of the basal calcium levels during 6 hours. Nasal administration of native sCT (2 IU/kg) resulted in a slight decrease in serum calcium with a maximum decrease of less than 10 % at 30 min and returned to the control level within two hours. Significantly prolonged decrease of serum calcium were observed over six hours after nasal administration of PEG-sCTs. It was also observed that PEG5000-sCT had the less hypocalcemic effect that PEG2000-sCT. Therefore, these results indicate that PEG attachment to sCT can be investigated as a novel nasal delivery system of therapeutic peptides.

[PE1-33] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Effect of Enhancers on the in vitro Skin Permeation of Ciclopirox from novel Soft

Hydrogel

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The purpose of this study was to evaluate the effects of various enhancers on the in vitro rat skin permeation of ciclopirox olamine from novel soft hydrogel (S-Gel).
A number of 1% ciclopiroxe S-Gel formulations with and without one of various enhancers were prepared and compared with each other. The in vitro rat skin permeation of drug was investigated using Keshary-Chien permeation cells at 37℃. The drug concentrations were determined by gas chromatography and the fluxes of ciclopiroxe were calculated from the slope of linear portion of the permeation profiles.
Among various enhancers used in this experiment, dodecylamine, HPE-101 and oleic acid were the most effective enhancers. The fluxes of 1%ciclopiroxe S-Gel containing one of the three enhancers, dodecylamine,
HPE-101 and oleic acid were 2.35, 2.24 and 2.12㎍/㎠/hr, respectively, comparing with 1.80㎍/㎠/hr of the control S-Gel without any enhancers.
From these results, this study demonstrated a good feasibility of a new dosage form, ciclopirox S-Gel for the treatment of cutaneous candidiasis, and other fungal skin infections, namely dermatophytosis and pityriasis versicolor.

[PE2-1] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

IN VITRO METABOLISM OF A NEW PROTON PUMP INHIBITOR KR60436 IN RAT AND HUMAN LIVER MICROSOMES

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KR60436, 1-(2-methyl-4-methoxyphenyl)-4-[(2-hydroxyethyl)amino]-6-trifluoro methoxy-2,3-dihydropyrrolo-[3,2c]-quinoline is a new proton pump inhibitor under development for the treatment of gastric ulcer. The objectives of this study were to investigate the in vitro metabolism of KR-60436 in rat and human liver microsomes, and to identify the KR60436 metabolites.
KR60436 was incubated individually with male rat and human liver microsomes in the presence of NADPH generating system. Unchanged KR60436 plus five oxidized metabolites were profiled, and tentatively identified from the incubation using electrospray LC/MS and MS/MS techniques. Electrospray-MS and MS/MS analysis of unchanged KR60436 and its metabolites revealed intense protonated molecular ions and prominent as well as informative daughter ions for stuctural elucidation of metabolites. Four metabolic pathways are proposed for the formation of metabolites in both species: O-demethylation, N-dehydroxyethylation, hydroxylation and N-acetylation. OH-KR60436 (M1) and O-demethyl-KR60436 (M2) was major metabolites in rats and human, respectively. In conclusion, KR60436 is substantially metabolized in rat and human liver microsomes.

[PE2-2] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

METABOLISM OF A NEW PROTON PUMP INHIBITOR DBM-819 by LC-MS/MS

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