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**PODIUM PRESENTATIONS
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PODIUM PRESENTATION I. (PT)

Single Dose Pharmacokinetics And In Vivo Evaluation Of Diflunisal Tablets

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Diflunisal (Dolphin®) is a salicylic acid derivative which has analgesic anti-inflammatory properties. It is rapidly and completely absorbed from the gastrointestinal tract. The aim of the present study was to investigate the single dose pharmacokinetics of diflunisal tablets. Twelve healthy volunteers were included in the in vivo part of the study. After a standart breakfast, 500 mg diflunisal tablets were given and blood samples were collected at different time periods after drug administration. Blood samples were then stored at -20°C until the HPLC analysis. The analytical validation was performed according to USP for the chromatographic studies. Mean blood values were analyzed according to one and two compartmental models. The suitability of one and two compartmental models were found to be 87.5% and 97% respectively. The equation that is derived according to two compartmental model is as follows:

$$C = 54.1 e^{-0.327(t-0.348)} + 31.1e^{-0.046(t-0.348)} - 85.2-1.65(t-0.348)$$

We conclude that in vivo pharmacokinetic results of difunisal tablets are suitable to two in vivo pharmacokinetic results.

PODIUM PRESENTATION II.

(PT)

Stability Study Of W/O/W Viscosified Multiple Emulsions

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W/O/W multiple emulsion systems permit the protection of the entrapped active substances and the prolongation of their release from the inner aqueous phase. There have been various factors affecting the stability of W/O/W emulsions such as the method of preparation, the nature of entrapped materials, the phase volumes, the concentration and the type of emulsifiers, oil and electrolyte and all ingredients introduced in the external aqueous phase.

The aim of this work was to obtain a stable multiple emulsion with much smaller proportion of primary emulsion than the previous formulations and to examine the influence of the nature and the concentration of the viscosifying agents introduced in the external phase on the stability. In order to investigate the influence of the viscosifying on the stability, they were introduced in the external aqueous phase at different concentrations and the proportion of primary emulsion was changed. A two step process was used to prepare the multiple emulsion. The skin feel, consistency and homogeneity of W/O/W multiple emulsions were determined. The microscopic, conductimetric and rheological measurements were also realized. Stability was followed at 25 and 40°C at equal time intervals. The homogeneity of the preparations was examined due to their good properties. The multiple emulsions prepared with 40% of primary emulsion were shown better stability. It appeared clearly that viscosifying agents increased the compacity of the system and a stable multiple emulsion with a quite low proportion of primary emulsion could be obtained by using different thickening and gelling agents such as cellulose derivatives and cabomer.

PODIUM PRESENTATION III.
(BPK/PD)

The Effect Of Some New Aminoalkanolic Derivatives Of Xanthone
In The Anticonvulsant Tests

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In previous studies on chemical compounds with the xanthone structure we found that several of them reveal potential antiepileptic activity coming up to that of phenytoin, carbamazepine and valproate [H. Marona, Z. Górka, E. Szneler.: *Pharmazie*, 53, 219 (1998); H. Marona.: *ibidem*, 53, 405 (1998); H. Marona.: *ibidem*, 53, 672, (1998)]. High protective activities in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (ScMet) tests and a low neurotoxicity in the rotorod test have been shown for (R,S)-2-N-(6-Chloro-2-xanthonemethyl)-amino-1-propanol (**1**). Taking into account promising results of animal studies and the structure-activity relationships two optically active stereoisomers R and S of **1**, compounds **2** and **3**, respectively, were synthesized. Also N-methylation of **1** was carried out resulting in **4**. Moreover, two new aminoalkanolic derivatives of 2- or 4-methylxanthone with corresponding (R,S)-1-amino-2-butanol (**5**) or (R,S)-2-amino-1-propanol (**6**) groups were obtained. All new derivatives of **1** administered in doses from 30 - 300 mg/kg i.p. in mice and in a dose of 30 mg/kg p.o. in rats displayed anticonvulsive properties in the MES and scMet screens. However, at the higher doses the neurotoxic effect was seen in some observation periods. In comparison to the protective activity of **1** the most promising new derivatives seem to be **2** and **3**. Their protective indexes P_i (neurotoxic dose in 50% of animals/median effective dose in 50% of animals, TD50/ED50) for the MES test in mice were 6,23 and < 6,8, respectively. These values correspond with those for the clinically used antiepileptics [D. Mulzac, K.R. Scott.: *Epilepsia*, 34, 1141 (1993)].

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**PODIUM PRESENTATION IV.
(BPK/PD)**

Preparation, In Vitro Dissolution Characteristics And Micromeritic Studies Of Ketoconazole Effervescent Microcapsules Tabletted For Vaginal Delivery

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Ketoconazole is an antifungal agent which is used as the active substance of this study. To overcome its GI disturbances such as nausea and vomiting after the administration by mouth, bioadhesive effervescent tablets were prepared for vaginal delivery.

Microcapsules of ketoconazole were prepared by phase separation technique (Ertan et al.). Sodium carboxymethylcellulose is used as coating material. Microcapsules with core:wall (1:1) and (1:2) ratios were prepared, dried, and sieved from a combined sieve set and then reduced to particle sizes of 250-500 μm , 500-710 μm , and 710-1 mm.

The dissolution studies were carried out with a new basket method by using 600 ml buffers of pH 3, 4.5, and 5 at 37°C with stirring speeds of 50 and 90 rpm. All of the dissolution results were investigated kinetically.

Micromeritic studies were completed on the microcapsules with the particle sizes mentioned above. Bulk volume and weight, tapping volume and weight, fluidity, angle of repose, weight deviation, relative deviation, absolute density and porosities of the sieved microcapsules were determined.

PODIUM PRESENTATION V.

(PP)

The Effect Of The Nature Of H-Bonding Groups On Diffusion Through PDMS Membranes Saturated With Octanol And Toluene

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The permeation of a series of structurally related compounds across two model membranes was studied. The compounds selected were phenol, salicylic acid, benzoic acid, anisole, phenylethanol and benzyl alcohol. These were chosen to represent molecules with different hydrogen bonding capabilities. The membranes selected were silicone rubber impregnated with either octanol or toluene to provide an environment capable or not capable of H-bonding to the permeant as it diffuses. Vertical Franz type diffusion cells were used to study diffusion and the amount of penetrant that diffused were determined by UV spectrometry.

The results were interpreted in terms of diffusion and partition behaviour within the membranes. In the case of octanol there were significant differences in the diffusion behaviour which could be related to solvatochromic effects.

PODIUM PRESENTATION VI.

(PDD)

A Different Approach To Increase Bioavailability And To Reduce Gastric Side Effects Of Water-Insoluble Anti-inflammatory Drugs: Inclusion With Skimmed Milk

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Many nonsteroidal anti-inflammatory drugs (NSAIDs) cause gastrointestinal disturbance and have poor solubility. In order to improve the solubility of NSAIDs, addition of surface active agents and formation of water-soluble salts; and to enhance dissolution and absorptive rate, reduction of particle size have been reported. Formation of solid dispersions (SD) of the drugs with water soluble carriers is one of the several techniques that can be used to improve the dissolution properties of low-water soluble drugs. Use of amino acids in formulations have been reported to reduce gastrointestinal disorders of NSAIDs. In our laboratory, a different approach has been employed to the anti-inflammatory and analgesic agents (indomethacin, sulindac, tenoxicam, dexamethasone, prednisolone) to overcome poor solubility and gastric side effects. In these studies, as carrier to prepare SDs and physical mixtures (PM), skimmed milk was chosen due to its surface active agent and amino acid contents. Freeze-drying method was employed to prepare SDs. Aqueous solubility and in vitro dissolution profiles of SDs were determined based on the methods given in USP XXII. The results were compared to those of PMs and the pure drug substances. It was found that formation of SDs increases the solubility as well as dissolution rate of the drugs. Differential scanning calorimetric (DSC), X-ray powder diffraction, infrared (IR) spectroscopic and scanning electron microscopic (SEM) analysis were also performed to determine the physicochemical properties of PM and SDs in comparison with the plain drug. The data indicated the formation of amorphous ionic state in the SDs.

The effect of formation of SDs on the ulcerogenic activity of the drugs were evaluated on male Wistar albino rats. Pontamine sky blue 6BX in physiological saline were injected to tail venous of rats following a 24 hour-fasting period. Animals were sacrificed 24 hours after the administration of SDs or plain drugs. The stomach of each rat was removed and analysed microscopically. Ulcer indices were statistically compared using Student t-test. The data indicated that preparation of SDs have less ulcer areas than the plain drugs. Thus, it can be stated that SDs cause less local ulcerogenicity than plain drugs. The anti-inflammatory activities of SDs were investigated using carrageenan-induced paw oedema test in rats. It was determined that the anti-inflammatory activity of SDs are significantly higher than that of the plain drugs. In conclusion, SDs prepared with skimmed milk are suitable to overcome the problems of poor solubility and gastric side effects of anti-inflammatory drugs.

PODIUM PRESENTATION VII.
(CADD)

New Computer Aided Drug Design Techniques For Subtype
Selective Adrenergic Ligands

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Computer aided drug design (CADD) methodologies have already played a vital role in the development of novel pharmaceuticals. There are two main methods depending on the availability of structural information on the target receptor. The 3D structure of the receptor, which can be a computer generated model or a crystal structure of the protein, is used in de novo ligand design and docking studies to generate new leads (structure-based method) or if there is no data is available on the actual receptor, then, a ligand-based approach is employed by getting as much information as possible from a collection of available drugs to create a pharmacophore. These methods lead to a small number of candidates which are synthesised and tested for activity at the target.

The aim of this project is to develop novel drug design methodologies by combining those two traditional methods through the development of structure-based pharmacophores using alpha-1 adrenergic receptors (α_1 - ARs) as target receptors. α_1 - Ars regulate several functions including vital responses such as maintenance of blood pressure. α_1 - Ars have a range of subtypes and there are no really selective antagonists available especially for α_{1B} and α_{1D} subtypes. Therefore, we will focus on determining the differences between these subtypes by using a novel CADD technique and this may lead to novel therapeutical approaches to treat a variety of diseases including benign prostatic hyperplasia (BPH).

PODIUM PRESENTATION VIII.
(BPK/PD)

Investigation Of In Vitro/In Vivo Correlation Of Rifampin Capsules

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The development of in vitro/in vivo correlation is of special interest in pharmaceutics. We investigated the in vitro/in vivo correlation in four different rifampin capsules. The dissolution profiles of four different rifampin capsules were determined in USP XXIV medium. The dissolution rate constants (K_{dis}) were calculated according to El. Yazigi method. Area under the dissolution time curve (AUC_{dis}), time to reach 50% and 80% of final amount dissolved ($T_{50\%}$ and $T_{80\%}$ respectively) were also calculated.

Rifampin capsules were administered to healthy volunteers in a double blind crossover design after an overnight fasting, having a washout time of one week. Blood samples were obtained over a 12 hours period and drug concentrations in serum were determined by a validated newly developed HPLC method.

From obtained concentrations, the parameters of K_a (absorption rate constant), K_e (elimination rate constant), C_{max} , T_{max} , $AUC_{(0-C_{max})}$, $AUC_{(0-12)}$, $AUC_{(0-\infty)}$ and C_{max}/AUC were calculated.

There was no correlation between different in vitro and in vivo parameters except from K_{dis} and $AUC_{(0-C_{max})}$. The later parameter could be considered as a measure of absorption rate.

According to the results obtained, we may at least conclude that the dissolution characteristics of rifampin in USP medium are not well correlated to in vivo data, and more in vitro investigation is needed to be done to find a predictive and meaningful correlation.