

**IPORSIP-2000**



**PODIUM PRESENTATIONS  
WEDNESDAY, SEPTEMBER 6, 2000**

## PODIUM PRESENTATION I. (RPh)

### A New Approach For Sterilization/Decontamination: Gamma Irradiation Of Sulfonamides

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No definite rules exist about the radiation sterilization of pharmaceuticals. In the USA, approved pharmaceuticals are considered as "New Drugs" if they are sterilized by radiation. In the UK, some proof should be submitted to special committee like sterility assurance, process has no affected the potency of the drug, any degradation products present are not harmful. Therefore, our intention is to evaluate the gamma irradiation effects on three active substances: Sulfacetamide Sodium (SSA-Na), Sulfametoxazole (SMZ) and Sulfafurazole (SF) in order to help to achieve the radiation sterilization/decontamination of the three members of Sulfonamide group.

Irradiation was performed with <sup>60</sup>Co Source available at TAEK (Turkish Atomic Energy Agency). Powder samples in Type I glass vials were irradiated at the doses of 5, 10, 25, and 50 kGy at room conditions (21°C).

In determination of radiation dose absorbed by the samples; polymethacrylate (Perspex) dosimeters were placed at the furthest point of the <sup>60</sup>Co Source before the irradiation process. After irradiation of samples with 5, 10, 25, and 50 kGy, the absorbances of these dosimeters determined spectrophotometrically and radiation doses absorbed by the samples were calculated.

Powders were analyzed for appearance, pH and melting point changes, specific UV, IR and NMR spectrum area changes, loss of anti-microbial activity and TLC.

Our results indicate that; negligible changes were observed in SSA-Na, SMZ and SFZ powders with gamma irradiation. Therefore, gamma irradiation process is a good alternative for decontamination/sterilization of industrial raw materials. These data will help industry to achieve the radiation decontamination/sterilization of the Sulfonamide group of raw materials. Although 25 kGy is the accepted radiation dose by pharmacopeias for the sterilization there is no reason not to use lower doses. But for the selection of lower doses as appropriate causing minimum chemical degradation on product but enough to sterilize it, further experiments (such as determination of SAL Dose (Sterility Assurance Level) and degradation product assay, HPLC or ESR determinations) must be done. Our experiments on pharmaceutical dosage forms are going on.

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**PODIUM PRESENTATION II.  
(PBIO)**

**Inhibition Of GRB2 and CRKL Proteins Leads To Inactivation Of  
MAPK and AKT Kinases In K562 Cells**

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BCR/ABL, a potent tyrosine kinase, is formed by the reciprocal translocation of chromosomes 9 and 22. In 95% of the cases, chronic myeloid leukemia (CML) is associated with the presence of BCR/ABL gene. GRB2 and CRKL are the most prominent proteins used by BCR/ABL. Both GRB2 and CRKL proteins are important for the transformation of murine hematopoietic cells and rat fibroblasts by BCR/ABL, as well as for the proliferation of BCR-ABL + cell lines. We demonstrate here that inhibition of GRB2 and CRKL proteins expression lead to growth inhibition of BCR/ABL + cells. Our data suggest that BCR/ABL uses GRB2 protein to simulate cell growth by activating MAPK and AKT, while it uses CRKL protein to simulate cell growth by activating AKT, but not MAPK pathway. By elucidating the downstream pathway(s) of BCR/ABL, we may have a better chance to improve therapeutic applications and prevention approaches.

## PODIUM PRESENTATION III. (PP)

### Self-Association Of Human Insulin In Aqueous Solutions Investigated By Modern High-Resolution Techniques

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A convenient and safe administration of insulin to the diabetic patient is still one of the most important challenges in pharmaceutical research. Recently, new insulin formulations and delivery systems have been developed for the nasal, pulmonal and transdermal pathway. Insulin molecules, which consist of A- and a B-chain of amino acids each, show self-association in aqueous solutions. In the established formulations, insulin mainly exists as a hexamer in crystals as well as in solution. Insulin monomers are pharmacodynamically active and are supposed to penetrate membranes more easily. In the present investigations, the level of insulin's self-association in different solutes was determined by novel high-resolution techniques. In preliminary studies, strong concentration-dependent differences of the association tendency of insulin were observed in acetic acid (20% w/w). H-NMR measurements at 600 MHz only show minor variations of the signals in D<sub>2</sub>O/CD<sub>3</sub>COOD mixtures. The calculated molecular structure from NMR data is similar to the x-ray results of the hexamers structure in crystals. Three equal dimers are located around two central zinc atoms and form the hexamer. In highly diluted solutions, molecules with different proportions were observed by atomic force microscopy (AFM). The two dimensional object sizes on the micrographs were evaluated and compared to the three-dimensional extensions of the association structures by the molecular modeling program Hyperchem 5.0. Hence, the molecules observed by AFM can be identified as insulin monomers and dimers. Circular dichroism measurements of insulin solutions support these findings. From the physico-chemical point of view, acetic acid appears as a promising vehicle in future drug delivery systems for human insulin.

## PODIUM PRESENTATION IV. (PDD)

### Preparation Of Modified Release Indomethacin Coprecipitates

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Indomethacin is an effective non-steroidal anti-inflammatory agent and a potent prostaglandin inhibitor. Its use is frequently limited because of its significant ulcerogenic and central nervous system effects. These effects could be reduced by formulating the drug in sustained release dosage forms. In addition, the sustained release dosage forms of indomethacin would be capable to maintain steady plasma level of the drug and reduce the frequency of administration. In this study, modified release coprecipitate formulations containing indomethacin were studied.

Coprecipitates containing indomethacin were prepared by non-solvent addition method. Different ratios of drug to polymer and polymer to polymer were tested. Eudragit® RS 100 and RL 100 were used as polymer. Indomethacin and polymers were dissolved in alcohol and precipitated using distilled water reduced to pH 1.2 at 4°C. Resultant coprecipitates dried at 35°C for 24 hours under vacuum. Coprecipitates were characterized by X-ray diffraction, differential scanning calorimetry, content uniformity and dissolution studies. Comparison of X-ray diffraction patterns of indomethacin and coprecipitates showed a significant reduction of crystallinity in the coprecipitates. This could be due to retardation of indomethacin crystallization by the polymers. According to dissolution studies release rate of indomethacin was increased at low levels of Eudragit® RS 100 and RL 100 ratio while it was decreased at high levels of drug to polymer ratio. The effect of pH on dissolution rate of prepared coprecipitates was also studied using response surface and contour plots. After the tests in three different pH's (5.6, 6.2, and 6.8), it was found that the release rate of indomethacin from coprecipitates increased with pH. It was concluded that Eudragit® was a suitable polymer for modified release indomethacin coprecipitates.

**PODIUM PRESENTATION V.  
(CP)**

**A Pharmacoeconomic Comparison Of Quinolones And  
Chloramphenicol In Treating Typhoid Cases At  
Ciptomangunkusumo Hospital, Jakarta, Indonesia**

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Typhoid fever remains as one of the most common diseases in Southeast Asia that results in high mortality and morbidity. Chloramphenicol has been considered the treatment of choice for this disease since its introduction in 1948. However, with the emergence of resistance pathogens, newer drugs such as quinolones, 3<sup>rd</sup> generation cephalosporin and few others have been explored as an alternative to chloramphenicol.

The objective of this study is to evaluate the effectiveness of quinolones compared to chloramphenicol in treating typhoid fever.

A retrospective study was conducted in Ciptomangunkusumo Hospital, Jakarta, Indonesia. A total of 46 adults patients were included in the study.

Sixteen patients were treated with quinolones and thirty were included in chloramphenicol group. A cure rate of 81% was observed with quinolones group as compared to 93% for the chloramphenicol group. It was noted that non significant difference in the duration of antibiotics therapy ( $p= 0.216$ ), length of hospitalization ( $p= 0.701$ ) and fever clearance time ( $p= 0.944$ ). However, based on the outcomes measures, the cost-effectiveness analysis favored chloramphenicol over the quinolones in all measures.

Based on the data obtained, quinolones may play some role in treating typhoid as a new alternative; however, chloramphenicol is still a drug of choice for the therapy, which is considered as cheap and very effective.

## PODIUM PRESENTATION VI. (PDD)

### Formulation, Rheological Behavior And Clinical Evaluation Of Antipsoriatic Gels

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Topical therapy of psoriasis is the most efficient, riskless as verified until now, method compared to the general treatment.

Wright et al., demonstrated that at the psoriatic damage site there is a deficit in adenylylase which could be genetically based as well as the formation of smaller amounts of cyclic adenosine monophosphate (cAMP) than normal.

It is assured that the decrease in cAMP is caused by an enhanced phosphodiesterase activity or by the diminished levels and function of adenylylase.

It has been experimentally proved the purinic bases applied topically have an inhibitory effect on phosphodiesterase while retinoids increase the number of "gap junction" through which cAMP is transported from one cell to another and they also reduce the mitosis rate which leads to keratinocytes differentiation.

Topical application can produce dermal concentration at higher levels than those obtained by the therapeutical oral doses. Urea's effect on the enzymes is the reduction of keratinocytes DNA synthesis. It also increases transepidermic permeability and makes the epiderma thinner. As excipient, a gel of starch (6%) and tragacanth (1%) containing the following substances was used:

- Formulation I. : 0.5% etretinate, 1% lactic acid, 3% urea, 15% Hypericum oil. It forms an ointment (O/W type emulsion)
- Formulation II. : 1% caffeine, 1% lactic acid, 3% urea, 0,1% calcium acetate, 0.5% EDTA.

The hydrogel formed an emulsion with a lipogel containing Hypericum oil (15%), stearine (2%), cholesterol (2%), and then, obtaining a multiple emulsion of w/o/w type. Both formulations contained 0.5% Tween 80 and 2% propyleneglycole as absorption enhancers. pH, rheological behavior and clinical evaluation was studied. The treatment for plaque psoriasis has to be applied under occlusive dressing. The studied formulations exhibit a uniform spreading and excellent local tolerance.

**PODIUM PRESENTATION VII.  
(PDD)**

**In Vitro Model For Bioadhesive Testing Of Various Polymer  
Solutions**

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Bioavailability problems resulting from a too short stay of pharmaceutical dosage form to the mucous membranes could be solved by using mucoadhesion. An in vitro model was developed to investigate the adhesiveness of various polymer solutions. It is relatively simple, quick and gives a good reproducibility. The test system allows the differences in the adhesive capacity of certain polymers to be determined with sufficient precision and provides full and correct information about the adhesion and the factors it depends on.



# PODIUM PRESENTATION VIII. (BPK/PD)

## In vitro -In vivo Correlation Modelling

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Drug absorption in the human body depends on the dissolution rate of the drug. The procedure to be discussed represents a tool in developing instant or controlled-release dosage forms. The ability to predict the in vivo performance of a speciality dosage form based upon in vitro measurements, in combination with the drug's pharmacokinetic parameters, offer a number of advantages to product development. The optimum formulation in a shorter time, lesser cost and elimination of unnecessary human studies. The ability to predict a plasma level-time curve from a product's dissolution rate or model and its pharmacokinetic parameters implies an excellent in vitro-in vivo correlation.

The procedure employed to predict the plasma level curves may be summarized in the following four steps:

1. Determination of the in vitro dissolution rate and the development of an appropriate dissolution equation or model.
2. Development of a proper pharmacokinetic model for the drug.
3. The redefinition of the pharmacokinetic model equation by putting the in vitro dissolution equation into the differential form of the drug's pharmacokinetic model. When integrated, one obtains an equation which can be used to calculate the expected in vivo performance of the product.
4. Generation of the expected plasma-level time course of the drug employing the constants evaluated in step 1 and 2 and the equation derived in step 3.

$$C_p = \sum_{i=1}^n C_n$$

where  $C_p$ , plasma concentration of the sample;  $C_n$ , plasma concentration of fraction with release rate "n".

From these predictions and simulations, it can be concluded that the dosage form with the desired characteristics would be selected for evaluation in man.