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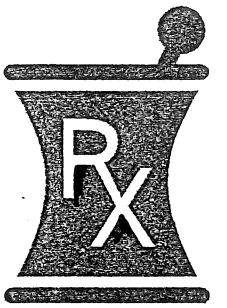

LECTURES
AND
PODIUM PRESENTATIONS

PDD LECTURE
Improvement In Drug Solubility And Availability By The Use of Cyclodextrins

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Hydrophilic cyclodextrins, by their ability to include poorly water-soluble molecules inside theri hydrophobic cavity, can lead to an increase in the apparent solubility of the guset molecule. This increase depends on the nature of the host cyclodextrin, and of the guest molecule. However, a low affinity constant between host and guest can result in a progressive decrease in solubility. Such a drawback can be prevented by polyvinylpyrrolidone, in the surrounding medium. This can be prevented by the presence of macromolecules, such as cellulose deriavtives or polyvinylpyrrolidone, in the surrounding medium. This can be advanteagously used to prepare dermal hydrogels of water-insoluble products such as tretinonin. Nowadays, nanoparticles are proposed for parenteral or gastrointestinal administration; however, the most frequently used polymers can entrap only hydrophilic drugs. It is possible to overcome this problem by the use of cyclodextrins. In fact, hydrophilic cyclodextrins can be associated to classic nanoparticle polymers such as polyisobutyl cyanoacrylate, and dramaticaly increase their loading capacity in water-insoluble drugs, resulting in a rapid release of drug. Similarly, amphiphilic cyclodextrins can be used to prepare nanoparticles capable of entrapping water-insoluble drug in molecular state. A series of steroids has been incorporated in these nanoparticles and the data are discussed.

PODIUM PRESENTATION I.
(PDD)

Polyhydroxyalkanoates In The Controlled Sulperazone Delivery For The Treatment of Osteomyelitis

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A random copolyester of 3-hydroxybutyrate-3-hydroxyvalerate, P(3Hb-3HV) and 3-hydroxybutyrate-4-hydroxybutyrate, P(3HB-4HB), were produced by the fermentation of Alcaligenes eutrophus and Alcaligenes latus. Polymers were extracted and purified from the microbial biomass and used in the construction of an implant containing sulperazone as an antibiotic. Studies using 50% loaded P(3HB-3HV) and P(3HB-4HB) rods showed that the drug was completely released in less than 3 days. To decrease the release rate, rods were coated using the same polymer solution. Cumulative release was about 70% of its initial content at the end of 12 days. In vivo studies were conducted with male New Zealand rabbits (1.5-2.0 kg). At 2 week intervals, The rods were retrieved and biodegradation, drug release, morphological and histopathological investigations were carried out. Following determination of performance in healthy animals, rods were implanted 3 weeks after bacterial inoculation (Staphylococcus aureus, 0.5 ml, 1.0 x 10^6 CFU/ml) of right hind leg. Thereafter the rabbits were sacrificed at 1st, 3rd, and 6th week post-implantation and radiological, histopathological and microbiological results ere obtained. Preliminary results showed that PHA rods are effective in treating experimental osteomyelitis.

PODIUM PRESENTATION II.
(PDD)
Studies On Chlorzoxazone Matrix Tablets

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In this study Chlorzoxazone matrix tablets were prepared by means of wet granulation method using Eudragit RS 100, lactose and primojel in different ratios. Including Half Change studies The in vitro release of Chlozoxazone from matrix tablets was carried out by USP XXII paddle method both in simulated gastric and intestinal media. Release data were examined kinetically and the ideal kinetic models were estimated. Micromeritic investigations were carried out on Chlorzoxazone and the granules (250 μm) in order to standardize the matrix tablet product and to optimize the pilot production of the matrix tablets prepared from these granules. Tablet controls were also done on these prepared tablets.

The results obtained showed that the matrix tablets prepared from the granules of 250 μm, particle size compressed under 0.25 t. Pressure and with the 1:0.5:0.8:%20 (Drug: Eudragit RS 100: Lactose: Primojel) ratio has the best release behavior. The findings of the micromeritic studies also showed that by the granulation process the micromeritic properties of Chlorzoxazone powder were changed significantly.

This study put forward a matrix tablet form of Chlorzoxazone which has been investigated in physical respect from crude materials to packing such as formulation, preparation, in vitro dissolution kinetic and micromeritic properties including tablet controls.

RPh LECTURE

Applications of Gamma-Scintigraphy In Development And Delivery of Pharmaceutical Dosage Forms

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The non-invasive technique of gamma-scintigraphy as a powerful imaging tool has been used in the nuclear medicine departments of hospitals all over the world. The potential applications of the technique in pharmaceutical drug development and delivery has recently diversified. In the course of development of oral dosage forms, gamma scintigraphy has been utilized to assess the fate of dosage forms and formulations, rate and extent of drug absorption from different regions of gastrointestinal (GI) tract and delivery of drugs to the specified location in the GI tract at a pre-defined time. In combination with the InteliSite® capsule (a radiofrequency activated remote control drug delivery device) to deliver drugs at specific regions of the GI tract, it is possible to study the regional variations in drug absorption and bioavailability down the GI tract.

The influence of some physiological variables such as the presence of food in the stomach and body position on the transit of solid dosage forms through the GI tract and integrity of modified release formulations have been studied using gamma imaging. The technique has also been used to characterize delivery device for other routes of administration such as; pulmonary, rectal, vaginal, ocular and nasal routes. The majority of gamma scintigraphy studies reported in the literature have been carried out in human volunteers under normal physiological conditions.

PBIO LECTURE

Mucosal Delivery of Macromolecules: Is The Nasal Route The Ultimate Choice?

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Recently, the number and importance of drugs with peptide structures have been increasing. While the availability of new peptide protein drugs represents a progress in pharmaceutical and biomedical sciences, it would be highly desirable if these drugs could be administered non-parenterally and preferably orally. One of the biggest challenges for pharmaceutical scientists in the future will be to develop and apply novel technologies to overcome the three main obstacles to the oral availability of peptide drugs. These are: a) presystemic degradation, b) low and variable absorption and c) hepatic clearance. This has captured the imagination of many scientists from all over the world and many research groups have already been partially successful in solving some of the compounds in two of these major problem areas through the use of inhibitors, enhancers and colloidal carriers and some smaller peptides such as cyclosporin, are successfully administered by the oral route. However, many other large peptides, especially the ones with significant plasma level related toxicity such as insulin, are still far from being formulated into oral products. On the other hand the nasal route offers an ideal-non invasive alternative to parenteral and oral routes of administration. It is also convenient and effective for administering drugs that undergo extensive hepatic first pass elimination and/or GIT metabolism. The nasal route was among the earliest non-oral routes that were investigated extensively for peptide and protein delivery. These studies have led to a better understanding of proteolytic, transport and clearance barriers to nasal peptide and protein absorption and to an assortment of strategies to overcome them. Both protease inhibitors and the penetration enhancers demonstrate efficacy in enhancing peptide protein drug absorption. Nevertheless, the issues related to their safety profile are needed to be cleared. Recent developments in the area of colloidal carriers and mucoadhesives in improving nasal bioavailability is also quite exciting. As well as retarding the clearance of the applied dose from the nasal cavity these vehicles also lower the transport barrier function. In this category biodegradable particles of natural or synthetic polymers and chitosan are quite promosing. The nasal route also shows potential for the delivery of vaccines for achieving comprehensive immune defenses.

This presentation will summarize and evaluate the existing techniques for making macromolecules mucosally available by increasing the extent of absorption and reducing degradation. Recommendations will be made with regard to the best use of existing methods and to the future research that is needed.

PODIUM PRESENTATION III.
(PBIO)
Controlled Release of Antibiotics From Biodegradable Microspheres

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A controlled release device was constructed using a novel, biodegradable polyester, poly(3-hydroxybutyrate-co-3-hydroxyvalerate), and a well-known antibiotic, tetracycline (TC) which is known to be effective against many of the periodontal disease relted microorganisms. Tetracycline HCl loaded microcapsules of PHBV were prepared using w/o/w double emulsion and their encapsulation efficiency, loading, release characteristics, morphological properties were invstigated. In these, copolymers with various hydroxyvalerate (HV) contents (7, 14, 22) were used. The antibiotic was used both in highly water soluble and in neutralized form (TCN). It was found that concentration of the emulsifiers, polyvinyl alcohol and gelatin, influenced the encapsulation extent. With TCN a much higher loading was observed. The release trend fitted reasonably well to Higuchi's release from spherical microspheres. Biodegradability of the polymer was not influential on the release from microcapsules. The slopes of release curves of M_t/M_∞ vs $t^{1/2}$ plots were 0.0254, 0.0484, and 0.0144 $h^{-1/2}$ for PHBV 7, 14, and 22, respectively. PHBV foams were loaded with the same drugs and release behaviors were studied. It was seen that the release rates were considerably higher than those from the microparticles. The antimicrobial activities of the antibiotics after loading were also tested by using a tetracycline sensitive microorganism. Results indicated that both antibiotics maintained their original activity and were, therefore, found to be suitable for application in vivo.

PODIUM PRESENTATION IV.
(PDD)

Effect of Capsaicin –Containing Gel Emulsion on The Innervation And Vascular Reactions of The Skin

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Epidermal application of capsaicin is widely used for treatment of a variety of pathological conditions associated with pain. However, The burning sensation and the concominant hyperalgesia and irritation induced by capsaicin limits its clinical use.

The aim of our study was to develop a transdermal controlled drug delivery system in order to eliminate these disadvantages of capsaicin.

We prepared several different systems (e.g. ointments, multiple emulsions) and found that gel emulsions showed the best parameters. The polymer concentration and the type of the emulsifier were varied to influence the drug release. The in vitro percutaneous absorption was determined by using a Hanson cell, and simultaneously rheological measurements were carried out by a Paar Physica Rheometer.

The aim of our in vivo experiments was to study the effect of repeated epicutaneous applications of capsaicin (1%) dissolved in ethanol or Miglyol 812, on the innervation pattern and vascular reactions of the rat skin. Immunohistochemical localization of protein gene product 9.5 was used to demonstrate cutaneous nerve fibers. Neurogenic inflammation was studied using the vascular labeling technique. Capsaicin treatment resulted in a rapid and almost complete loss of epidermal axons and a diminution of the inflammatory response. Innervation of dermal structures were less affected. The prenet findings suggest that loss of epidermal sensory axons may underlie the significant antinociceptive effect of epicutenously administered capsaicin.

PODIUM PRESENTATION V.
(PDD)
A New Formulation Type of Famotidine HCl As Suppositories

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In this study, a new formulation type of famotidine HCl was developed and rectal suppositories were prepared. On these suppositories prepared by using two different groups of suppository bases (lipophilic and hydrophilic) after tests of melting point, pH, hardness, melting and dispersion time and quantitative content analysis were applied, in vitro release of the active substance was studied. In addition to this the effect of particle size on in vitro release from lipophilic bases was investigated. It was observed that the release of famotidine HCl from suppositories fitted to $(bt)^a$ kinetic model commonly.

According to the in vitro dissolution test results it was thought that famotidine HCl suppositories may show a faster effect than its film coated tablets available on market. Furthermore, it was found out that particle size has an important effect on in vitro release of famotidine HCl lipophilic bases.

PODIUM PRESENTATION VI.
(PT)
Study of The Compressibility of The Avicel PH-301 And PH-302

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There are many papers in the literature about different types of cellulose, particularly the Avicel PH-101, but the newer Avicel types PH-301 and PH-302 (manufactured by FMC Corp., Philadelphia, Pennsylvania, USA) is not yet sufficiently well-known. Therefore, the aim of this work was to study their compressibility behavior in comparison with Avicel PH 101 using Korsch EKO instrumented eccentric tablet machine. Force-Displacement and Force-Time curves were constructed and used to study their compressional behavior. The compressional parameters were calculated on the bases of the compressional curves, and the physical characteristics of the comprimates were also evaluated.

From the results of this work, it was found that, the deformation properties of A301 and A302 were closely resembled those of A101. They deformed mainly by plastic deformation but they showed more inclination to elastic behavior than that of A101, and their comprimate strength was clearly smaller than that of A101 comprimates. A301 and A302 have nearly the same comprimate weight variation and thickness, which are lower than those of A101, and they have lower friction and better lubrication than those of A101. They can be compressed at higher compressional forces giving thinner tablts at a given hardness and weight. A301 and A302 have good compressional parameters and they can be compressed succesfully, although the compressibility factors (Pr) of A302 are slightly smaller than those of A301.

PODIUM PRESENTATION VII.
(CADD)

"N6-N7" – A Modification of The "N6-C8" Model For The Binding Site On Adenosine A1 Receptors With Improved Steric And Electrostatic Fit

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A modification of "N6-C8" model, named "N6-N7", is proposed for the binding site on adenosine A1 receptor. The steric and electrostatic fit of the two models is tested on the basis of eight reference compounds. The steric fit is assessed by the parameter mean value of the root mean squares RMS(mean) of the distances between atoms producing areas with negative electrostatic potential and between atoms that act as donors in H-bond formation. The "N6-N7" model demonstrates better steric and electrostatic fit in comparison with the "N6-C8" model.

PDD LECTURE

Colonic Drug Delivery Systems: Design And Gamma Scintigraphy Evaluation of A Novel Antibacterial Agent

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Nisin is a peptide antimicrobial agent. It was found to be active against Clostridium difficile which causes severe repulsing diarrhea, and vancomycin resistant enterococci, which causes a large increase in the number of untreatable or difficult to treat bacterial infections. Both organisms colonize in the colon. Therefore, nisin must be formulated in a dosage form which immediately releases the intact antimicrobial agent in the colon. Nisin is being a polypeptide is digested by the proteolytic enzymes in the small intestine. Therefore, protection of nisin through the gastrointestinal tract until it reaches the colon is essential. Colonic delivery systems can be classified to two main approaches: 1) chemical/microbiological approach, which depends on that colonic bacteria is capable of extensive enzymatic activity and colonic targeting is achieved by compounds selectively degraded by the microbial enzymatic activity (prodrugs or universal systems), but most of the materials are not approved for human use. 2) Technological/physiological approach, which utilizes The physiological differences in pH or transit time between different segments of the GIT. This is accomplished by the use of pH dependant or time dependent polymers or the combination of both mechanisms. Developing colonic drug delivery system, using currently available materials, with potential to succeed should be based on utilization of pH and transit time of the different segments of the GIT. In this study Eudragit®L30D coating was used to target nisin to the colon.

The nisin was formulated into a tablet containing 100 mg of nisin using roller compaction technique. The core tablet production process was found to be efficient in producing tablets of sufficient hardness to withstand coating in the fluidized bed. Triple compaction was required in order to minimize raw material to lot to lot variability and producing tablets of comparable physical properties. The combination of sodium chloride and disintegrant in the tablet was found to be essential for tablet disintegration in the intestinal environment. Effect of sodium chloride and disintegrate levels on tablet physical properties were studied. The production process was validated and mixing times for intra- and extra-granular ingredients were optimized. The tablet production process had no effect on the integrity of the nisin molecule. The tablets were coated in a Glatt GPCG-1 fluid bed (Wurster attachment) using EUDRAGIT L30D at different weight gains, then tested using USP dissolution apparatus II in 0.1 N HCl for two hours, then phosphate buffer pH 6.8 until complete disintegration. The effect of coat thickness/weight on the onset of tablet disintegration was studied. The coated tablets resisted disintegration in 0.1 N HCl for two hours. A linear relationship was observed between the coat thickness or Percent weight gain and the time to beginning of disintegration. Coated tablets with varying coat weight/thickness, containing samarium oxide, were neutron activated and tested in gamma scintigraphy study showed that the time to tablet disintegration depended largely on the coat thickness. Dosage forms with the optimal coat thickness, administered to six subjects, exhibited disintegration in or near the colon and with the exception of only one subject the dosage forms spread completely through out the colon. It was concluded that it is possible to develop a colonic delivery system for the polypeptide drug nisin and EUDRAGIT L30D can be used for time targeting based on the established linear relationship between coat thickness and time to the beginning of disintegration. A proof of concept was demonstrated using gamma scintigraphy. The in vivo results correlated with in vitro results in that the time to tablet disintegration depended largely on the coat thickness. A coat thickness of 0.381 mm equivalent to a coat weight gain of 40% was sufficient for targeting nisin to the colon.

PODIUM PRESENTATION I.
(PDD)
The Emulsion Base <<Mustela – mink>> Raises The Effectivity of Ointments In Treatment of Skin And Fungoid Diseases

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We summarized the experience of treating the skin and fungous diseases with medicines made using emulsion base: <<Mustela-mink>>. More than two thousand patients with different skin disorders, who used this drug for outward application were observed. The base of <<Mustela>> is highly dispersed emulsion of mustel's oil in water, which was prepared by using emulsion wax. It contents glycerine, citrate, cigerole, concervants – parabens and fragrances. We used the oitment Ac. Salicylici –2%, Ac. Salicylici and Dermatoli %10- on 987 patients. The oinment with sulfur 20% was applicated to 520 patients with microsporia and tricophytia of the skin and the hair. We had good results of usage of 0.5% Prednisolon cream and Zinc emulsion 3-5% based on <<Mustela>> on more than 200 patients with acute and chronical eczema.

The treatment with << Mustela-mink>> and 1% Metranidazoli considered in 18-25 applications two times a day on 20 patients with tinea pedis complicated onychomycosis. The other ointsments with 0.2% Furacillini, 1-5% Lacvomucetini, 1-5% Accoli, 5-10% Dimexidi are also applied.

We prepare the creams on the emulsion base <<Mustela – mink>> for the most of medicines for outward applications at our clinic.

PODIUM PRESENTATION II.
(PDD)
Effect of The Addition of Lubricants In The Flowability And Compression Characteristics of Maltodextrins

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Maltodextrins are composed of water-soluble polymers obtained from the reaction of starch with acid and/or enzymes in the presence of water. They are used in the food and pharmaceutical industry, in latter as direct compression excipients. The grade M150 presents manufacturing problems due to high ejection and residual forces as well as stickiness in comparison with other maltodextrins. Therefore, the use of lubricants is necessary in the formulation to reduce friction between the tablet and die wall and to prevent adhesion of the tablet material to the punches or die wall. The aim of this study was to evaluate the effect of the addition of three lubricants (magneisum stearate, PRUV® and PRECIROL®) in the flowability and compression characteristics of two maltodextrins (M150 and M510). The flow rate was measured with an integrated system of data acquisition for the measurement of flow characteristics using a funnel as a vessel. The compression characteristics of the powders were investigated on an instrumented single-punch tablet machine. Quantitative parameters as well as graphical methods have been used to evaluate The compression characteristics. The variables under study were concentration of lubricant added, mixing time and applied pressure during compression. The best lubricant in improving the flowability of the maltodextrins was magnesium stearate followed by PRUV® and PRECIROL®. The influence of mixing time and concentration of lubricant on the flowability vary depending on the lubricant considered. M150 shows higher friction during compression and ejection than M510. The most efficient lubricant in decreasing the friction during compression and ejection in M510 was PRUV® while in M150 was magnesium stearate. Therefore, the efficiency of the lubricant depends not only in the intrinsic characteristics of itself, but also in the excipient properties.

PBIO LECTURE
HIGH MOLECULAR WEIGHT ANTINEOPLASTIC GLYCANS FROM BACTERIAL CELL WALLS

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Complex high molecular weight sugars represent a significant fraction of many bacterial cell walls. Structural elements include long-chain fatty acid derivatives such as mycolates which constitute a major portion of mycobacterial cell walls and these were reported to have significant biological activity over 50 years ago. However, sugar or sugar/protein components were first reported in Mycobacterium tuberculosis and these materials were sufficiently stable to be extracted from the intact cells by boiling with water. Structurally the complex sugars usually consist of β(1-6) or β(1-3) glucose which often have a reduced solubility. Biological activity, usually measured against a simple murine S-180 sarcoma, has been manifest and there have been limited human trials against cancers. Similar β-glycans (made up of different sugars) and β-glucans (entirely glucose) have been obtained from other organisms such as yeasts and mushrooms and been described as immunomodulators and antineoplastics. A well-characterized example is lentinan, obtained from the edible Chinese mushroom Lentinus edodes.This β(1-3)-glucan (with β(1-6) -glucopyranoside side chains) has a molecular weight of 400-800 kDa. Biological activity is claimed to be directly related to size, the bigger the molecule, the higher the activity. Bacillus Calmette Guérin, (BCG) is a living bacterial culture that was originally developed as a tuberculosis vaccine but is now the major approved for human superficial bladder cancer. It was therefore of interest to if there was a soluble glycan or glucan associated with this organism, already proven to have direct antineoplastic activity in its own right. Boiling water extracts of BCG proved to have significant activity against a number of in vivo models, including murine sarcoma and human colon and breast cancers. The main compound responsible for this activity has been isolated and characterized as PS1A1, a α(1-6) glucan with a molecular weight of around 65 kDa. Similarly, M. vaccae, an organism used experimentally as an immuno adjuvant in tuberculosis and cancer treatment, has been shown to have one main active component although surprisingly this has proved to be a α(1-3) polymannan attached to a polypeptide core. What is even more surprising is that, like BCG and PS1, this new component is active orally. This observation appears to open the way to oral treatment of, for example, human breast cancer and its metastases, an exciting prospect.

PODIUM PRESENTATION III.
(PBIO)
Significance of Protein And Peptide Adsorption At Interfaces For Drug Development

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The interfacial adsorption of proteins is important in several areas of pharmaceutics:

- The physical stability and the available concentration of solutions of the new peptide and protein drugs are affected by interfacial adsorption.
- Phagocytic uptake of intravenously injected particulate delivery systems is often initiated by interfacial adsorption of blood proteins.
- The interfacial properties of proteins are utilized in the preparation of emulsions and microcapsules.

Proteins and peptides have an affinity for interfaces. Interfacial adsorption of proteins often leads to molecular conformational changes, driven by change in environment (pH, ionic strength, etc.). This may result in loss of physiological/pharmacological activity and physical activity. This may affect the dosing of a protein/peptide drug.

One of the important objectives in present day drug therapy is the selective delivery of drugs and diagnostic agents to specific target sites or organs in the body. Colloidal systems such as microcapsules prepared using natural and synthetic polymers are currently being investigated as drug delivery devices for the purpose of drug targeting. A major obstacle to the effective use of these microparticulate drug delivery systems, administered by the parenteral route, is the rapid uptake of small particles by the cells of the RES (phagocytosis). In the body blood proteins adsorb onto microparticulates as a result of opsonization which can lead to phagocytosis. This process depend on: the size and surface characteristics of the particles. The more hydrophobic the particles and the greater the probability of opsonization occurring.

In this study, interfacial adsorption of proteins and peptides were investigated with respect to the aspects of drug development mentioned above. The experiments were conducted at air/aqueous and oil/aqueous interfaces under different conditions using interfacial tension, rheology, and charge studies.

PBIO LECTURE
STRATEGIES FOR PERORAL PEPTIDE ABSORPTION AND PERORAL VACCINATION

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The peroral route of peptide and protein administration is currently the greatest challenge in developing suitable dosage forms, because it offers the highest ease of application to the patient. However, particular difficulties are met in designing effective delivery systems for gastro-intestinal application. The challenge to achieve sufficient peptide drug absorption for systemic action is to overcome the very efficient absorption barriers of the gastro-intestinal tract . These barriers can be divided into three main parts: (1) the metabolic barrier consisting of the proteolytic activity of luminal and membrane-bound enzymes, (2) the mucosal transport barrier, whereby the passive absorption of hydrophilic macromolecules such as peptides is mainly controlled by the integrity of intercellular junctions and (3) the mucus layer which covers the epithelial cells as a blanket and forms a highly viscous network of glycoproteins hampering the diffusion of peptides.

For peroral vaccination, the delivery system must fulfill the following requirements: it must be stable for the toxin during the passage of the gastro-intestinal tract and be selectively taken up by the sampling ports for antigens in the intestinal tract, the so-called Peyers Patches (PP). The dome of the PP is covered by a monolayer of M-cells which allow transcytosis of suitable particles of the vaccine delivery system depending on their size and surface hydrophobicity/hydrophilicity balance.

In the first part of the lecture strategies and mechanisms will be discussed how to timely and locally deactivate enzyme activity of the predominant luminal enzymes in the intestinal tract and how to reversibly open tight junctions in order to allow for paracellular transport of the peptides across the enterocytes based on two classes of mucoadhesive polymers, i.e. negatively charged and crosslinked poly-acrylates and positively charged chitosan salts and derivatives as the trimethyl chitosans. The toxicity aspects of these polymers as a new class of safe penetration enhancers will be discussed as well. In the second part of the lecture some strategies for peroral vaccine delivery systems will be discussed based on gel state vesicular systems (niosomes) in which ovalbumin is incorporated as toxin. First results of IgA and IgG production after oral application of these systems to mice will be presented.

PT LECTURE

Some Aspects of Sustained-Release Matrix Tablets Prepared With New Modified Polymeric Carbohydrates

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Recently, study of sustained-release matrix system has become prominent. The compaction of a mixture constituted by a drug and a polymer, first proposed by Higuchi, is still one of the most efficient techniques to obtain oral controlled release tablets. Although the matrix systems offer a major advantage in the ease of fabrication and manufacture on large scale, release kinetics are directly influenced by formulation and physico-chemical factors.

The importance of matrix material choice on drug release in formulation of sustained-release tablets is illustrated by many studies. Alderman found that the release of a drug by a matrix system was produced by two simultaneous mechanisms: erosion or attrition of the outermost, least consistent gel layer and dissolution of the active principle in the liquid medium and diffusion through the gel barrier when formed. The diffusion of the drug will not only be via water-filled pores, also via the free volume between polymer chains. The incidence of the latter depends on the polymer's physical structure, its crosslinking degree, its degree of crystallinity and also on the possible solute-polymer interactions. Direct compression is the preferred method of manufacture to produce tablets intended for immediate or sustained drug release, due to the environmental issues that are making other processes less tolerable and more expensive. The selection of polymers for tableting depends on the development of highly compressible and free flow powders.

Whereas cellulose derivatives have been the most widely used polymers for hydrophilic matrix tablets, only some investigators mentioned the possibility to use modified starches in this field.

Accordingly, the polymer is the element in the formulation that is most responsible, by hydration, of the diffusion of the drug and the formation of erosion-resistant gel layer. Different aspects of a controlled release tablet using a new family of modified polymeric carbohydrates will be described. The copolymers were obtained by graft copolymerization of methyl methacrylate (MMA) on different carbohydrates: carboxymethyl and hydroxypropyl starch, and carboxymethly and hydroxypropyl cellulose.

The different topics to be covered are:

A. Preparation of the new copolymers: in order to obtain the pure copolymer, the removal of the unreacted carbohydrate and the acrylic polymer formed out of the carbohydrate (homopolymer) will be necessary.
B. Rheological properties and compression behavior of the copolymers
C. Dissolution profiles and kinetics of the matrix systems using theophylline as model drug.
D. Effect of the addition of a direct compression excipient.

PODIUM PRESENTATION IV.
(BPK/PD)

Modeling of Drug Release From Different Geometrical Erodible Tablets Using Hopfenberg Equation

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The aim of this study was to make it clear statistically how the hydrogel matrix tablets in various geometrical shapes affect the release rate of the geometrical shape, by comparing the release rates of the matrix tablets, with the classical cylinder shaped tablets. I tried to express this effect by mathematical equation.

Hydrogel matrix tablets were prepared with HPMC (E-50) possessing different geometrical shapes as triangular, cylindrical and spherical cup using experimental design.

Drug release from surface-eroding devices with various geometries was analyzed by Hopfenberg. Hopfenberg developed a general mathematical equation describing drug release from slabs, spheres and infinite cylinders.

In our study, modified Hopfenberg equation was evaluated to describe drug release from erodible triangular and spherical cup tablets undergoing surface erosion.

PODIUM PRESENTATION V.
(PDD)
PHOTOAGİNG OF SKİN: MECHANİSM AND PREVENTİON

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Skin is the only human organ which continuously exposed to chemicals and environmental influences that affect its health and appearance. UV exposure is one of the ways which convert natural substances into free-radical containing derivatives. Exposure to UV radiation from sun modifies and accelerates biological aging a process which is usually called photoaging. Under physiological and pathophysiological conditions, reactive forms of oxygen is created. They are formed in a normal metabolic process. These enzymatically generated free radicals contribute to systemic aging and some diseases as cancers and immune deficiencies.

On the skin, however, free radical formation (via reactive oxygen species-ROS) from ionizing and less energetic radiations may be assumed to be a major contributor to aging. They are constantly being formed, starts rhe oxidative stress and thought to damage cells. Oxidative damage to cell components is accepted as one of several factors for many diseases including aging. Among the major cellular and extracellular targets for these reactive oxygen radical species are proteins, enzymes and DNA/RNA. However, an important primary target of oxidative damage is probably the unsaturated fatty acid components of cell membranes. Excess production ROS, especially hydroxy radicals, can easily initiate lipid peroxidation in cell membranes to form lipid peroxides and also accelerate aging. The level of these compouds is held constant by the cooperation of nonenzymatic and enzymatic detoxification antioxidant systems.Oxidative stress which plays an important role in photoaging and skin cancer may be decreased by antioxidants. Three main groups of antioxidant system protects tissue from the effects of free radicals. Primary antioxidants work by preventing the formation of new free radical species. Superoxide dismutase, glutathione peroxidase and metal binding proteins could be included in this group. Secondary antioxidants trap radicals, preventing chain reactions. Examples include vitamin E (alpha tocopherol), vitamin C (ascorbate), beta carotene, uric acid, bilirubin and albumin. Tertiary antioxidants repair biomolecules damaged by free radicals. These include DNA repair enzymes and methionine sulphoxide reductase. If deficiencies develop in the antioxidant system, tissues no longer have any protection from the effects of free radicals.

In order to protect skin from photoaging by the harmful effects of UV radiation, photoprotection strategies should be established. Since now, photoprotection has relied only on the use of sunscreens, especially UVB filter. Then UVA filters have been added. More recently biochemical protection, a new notion, which introduces antioxidizing and DNA repair agents have been put into progress and the subject will be reviewed in this lecture.

PDD LECTURE
Modified Drug Delivery Systems For Drugs With Gastroenteric Irritant Effect

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One of the most significant side effect of oral dosage forms is their irritative effect on stomach mucosa. This problem can be overcome introducing enteric coating. It is well-known that enteric coated oral dosage forms dissolve in intestinal fluid rather than gastric fluid, consequently, avoiding gastric irritation. Enteric-coated dosage forms may be prepared by means of enteric coating tablets or preparing enteric-microcapsules. The release of drug is modified by enteric-coating.

Both natural (zein, gluten, gelatin, etc.) and synthetic polymers (cellulose derivatives, etc.) have been used as enteric coating agents for decades. These polymers are insoluble in acid media,but dissolve at pH values in the range of 4.5 – 7.0, depending on the feature of the carboxyl groups. Carboxyl groups dissociate at these pH values. Thus, the film formed on the surface of the coated tablets withstands prolonged contact with gastric fluids; however, it dissolves rapidly in the mild acidic to neutral medium of the small intestine. This pH – dependent dissolution behavior can be of great benefit preventing the release of the active ingredient when suspended in acidic medium.

Cellulose acetate phthalate (CAP) is soluble at pH 6.5 whereas cellulose acetate trimellitate (CAT) is soluble at pH 5.0. Cellulose derivatives have been widely used in formulation of enteric coated tablets. The advantage of these two polymers is that they allow active ingredient to release at lower pH values. Eudragit L and Aquateric also found wide application in pan or fluidizing bed coating procedures. In spite of interest of using some of these polymers in formulation of enteric coated tablets, there have not been intensive research conducted in the formulation of enteric-microcapsules. Enteric- microencapsules have better advantages as they may also provide better flow properties and modified release of the drug.

In this lecture, both enteric-tablets and –microcapsules will be discussed with respect to the theory of modified release of the drug with gastric irritation from enteric-coated tablets and microcapsules, their applications, and in vitro and in vivo studies. They will be compared to the conventional dosage forms.

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PODIUM PRESENTATION VI.
(PT) .
Effect of Roller Compaction On The Characteristics of Nisin Granules And Corresponding Tablets

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Nisin is apeptide antimicrobial agent which has low and inconsistent bulk and tap densities, and very fine and inconsistent particle sizes. The raw material also exhibits poor flow properties. Nisin gels in some gastrointestinal fluids, and it loses activity in alkaline pH. Therefore, this study was performed to evaluate the effect of roller compaction in overcoming the raw material difficulties, flowability, and capping of nisin. The effect of single, double, and triple compaction, using a Freund TF-Mini roller compactor, was evaluated.

It was found that although single pass roller compaction improved the raw material characteristics, at least three passes were necessary to produce acceptable flowability for compression and minimize raw material lot-to-lot variability. Roller compaction increased the bulk and tap densities of nisin and decreased the percent of fines. The patented formula was not directly compressible, however, the number of roller compaction passes decreased the tablet capping. After three passes, excellent tablets were produced which could withstand the vigorous agitation in the Wurster fluid bed coating for colonic targetting.

PODIUM PRESENTATION VII.
(PDD)
A Preliminary Investigation On The Estimation of The Sustained Release of Mefenamic Acid Microspheres

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The main objective of the present study was to formulate sustained release mefenamic acid microspheres based Eudragit.

The microspheres which contained mefenamic acid were prepared by using spheric cristallization method.

Mefenamic acid (MA), N-(2,3-Xylyl) antranilic aicd, has analgesic, antiinflammatory and antipyretic properties. MA is freely absorbed from gastrointestinal tract. The reported half-life is 2 hours.

In this study, Eudragit RL 100, RS 100, L 100 and S 100 were used as polymer.

Microspheres were prepared with mixer by spheric cristtalization method. We supplied different particle sizes microspheres by stirring at 750, 1000 and 1250 rpm, respectively.

The MA content was determined spectrophotometrically at 290 nm. Microspheres were placed in 400 ml of phosphate buffer (pH 6.2).

The USP XXII rotating basket method was used for dissolution studies.

All of the experiments were carried out in triplicate. Kinetic assesment of release data was evaluated with a computer program.