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PHARMACEUTICAL DRUG DESIGN (PDD)

POSTER PRESENTATIONS

POSTER PRESENTATION I.
(PDD)
Theoretical Analysis Of Relaxation Spectra Of Mixed Hydroxypropylmethylcellulose/gelatinized Starch Hydrogel Systems

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Highly concentrated hydroxypropylmethyl cellulose (HPMC), thermally pre-gelatinized starch and mixed HPMC/pre-gelatinized starch hydrogels obtained by swelling of matrix tablets in 0.1 mol/cm^3 HCl (pH 1.0) and Na_3PO_4/HCl phosphate buffer (pH 6.8) have been studied with respect to the viscoelastic behavior. The pre-gelatinized starches produced by spray-drying technique of gelatinization and tested have two different types of chemical compositions, i.e. a) 100% amylopectin (SDWMT) and b) %25 amylose and 75% amylopectin (SDCST). The storage (G') and loss (G'') moduli, as well as the dynamic viscosity (η'), were obtained under dynamic conditions of non-destructive oscillatory tests, in the frequency range from 0.06 to 31.95 rad/s at a temperature of 37 ± 0.5 °C. The mechanical spectra of the gels have been analysed using theoretical rheological.

Clotrimazole Dermal Suspensions- Physical Stability

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Clotrimazole is a synthetic derivative of imidazole with local anti-fungal effect, especially on the mucous membranes as it is very well tolerated (good patient compliance). The following pharmaceutical dosage forms have been used to administer the drug: dermal ointment and endovaginal and buccal tablets.

The objective of this study was to establish the formulation for dermal application. Since Clotrimazole posseses poor water solubility, low density, and is hydrophobic, floating in water. For formulation of a stable suspension, wetting, dispersing and viscosity agents must be added.

15 different suspensions of 1% Clotrimazole were formulated. In this suspensions, the following wetting agents were used: alcohol, glycerole, Tween 80, sodium lauryl sulfate. Methyl cellulose, hydroxypropyl cellulose, sodium carboxy methyl cellulose, polyvinyl alcohol, alginate and aerosil were used as viscosity agents. pH, rate (v) and ratio (F) of sedimentation were determined. Among all the formulations prepared, the Clotrimazole (1%) suspension containing methyl cellulose and Tween 80 was selected for further investigations.

Rectal Hydrogels Containing Dry Extract Of Ruscus Aculeatus L. : Formulation And Biopharmaceutical Characterization

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The present study initiates into the application of a standardized dry extract of Ruscus aculeatus L. for the preparation of rectal hydrogels. Traditionally, these extracts have been used mainly for treatment of circulatory diseases of the lower limbs, some inflammatory conditions of anorectal mucosa, etc. The purpose of this study, was to formulate hydrogels with anti-hemorhroid action, containg 2% dry extract of Ruscus aculeatus L. Several polymers, poloxamers and cellulose derivatives, have been used to develop stable formulations. The main characteristics of the hydrogels: rheological parameters, surface activity, pH, etc. were evaluated. The release profile of the active components and in vitro kinetic properties of the prepared optimal formulations of hydrogels containing dry extract of Ruscus aculeatus L. were also inevtigated.

Evaluation Of Biodegradable Poly(α-Methylmalate) Microspheres

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The aim of present study is to evaluate and to compare in vitro drug release from biodegradable microspheres with poly(α-methylmalate) (PMM_{AL}) and traditionally used PLGA co-polymer.

Microspheres from PMM_{AL} with a drug loading capacity of 30% were obtained by simple solvent evaporation method. Comparatively, microspheres from PLGA co-polymer were loaded with 28% of the same model drug (isopropylantipyrine). Both samples of microspheres have spherical shape and smooth surfaces. The model drug was released from both microspheres in a biphasic manner, characterized by an initial burst effect and continuous and slower release thereafter. Drug release from PMM_{AL} microspheres is much faster compared to the drug release from PLGA microspheres. It is due to the lower molecular weight and faster degradation of PMM_{AL} polymer. SEM of PMM_{AL} microspheres during drug release reveal that they change in size chiefly and no pores occur over their surface. This fact suggests the release from PMM_{AL} micropsheres to proceed as a result from surface erosion unlike the release from PLGA microspheres which increase the porosity of the matrix.

In conclusion, PMM_{AL} polymer can be used as a biodegradable polymer carrier to achieve sustained release from drug loaded microspheres.

In vitro And Ex vivo Permeation Studies Of Chlorpheniramine Maleate Gels Prepared By Carbopol Derivatives

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Chlorpheniramine maleate, an antihistamine commonly used in the treatment of allergy, acts by competitively blocking H1 receptor sites, thereby preventing histamine from causing increased capiller permeability and the formation of tissue edema. It has the known side effects of all antihistamines when given orally. Sedation, dizziness, muscular weakness and gastrointestinal disturbances are the most common ones. It is well absorbed from the gastrointestinal tract. However, only 25-45% of the orally administered dose reaches the blood circulation due to the first pass effect. In order to bypass these disadvantages, the gel formulations have been proposed as topical application.

The objective of this work was to evaluate the invitro release of chlorpheniramine maleate from carbopol bases using different diffussion barriers such as cellulose dialysis membrane, polyurethane membrane, rat skin and human skin. Chlorpheniramine maleate (CM)gel formulations as a ratio of 1% were prepared by using Carbopol derivatives (934, 940, 941, 2984, 980 and 981) at the percentages of 0.5, 1, and 2. Ethanol was incorporated in all formulations at the percentage of 30. Franz diffusion cells with a receiver compartment volume of 14 ml and effective diffusion area of 1.86 cm^2 were utilized for the in vitro diffusion studies. 1 g of sample was placed at the donor part. The receptor chamber was filled with degassed pH 6.0 phosphate buffer. Samples of 300 µl were withdrawn from the receptor chamber at predetermined time intervals and immediately replaced with an equal volume of the flesh buffer solution. Samples were analysed spectrophotometrically at a wavelength of 261 nm. The viscosity values of the all formulations increased with the increasing carbopol concentrations. Because of the inverse relationship between viscosity and diffusion, drug release from the formulations at the higher polymer concentrations decreased except for the formulation prepared with 1% Carbopol 941. It is possible that at the higher polymer concentrations the active substance is trapped in smaller polymer cells and it is structured by its close proximity to that polymer molecules. This increases the diffusional resistance by more than expected. Carbopol derivatives which contain more than 2 ppm benzene residual (Carbopol 934, 940, and 941) have exhibited the same drug release profile with the ones of free benzene residual (Carbopol 2984, 980, 981). In conclusion, CM is a suitable drug entity for use in dermatological gel bases for possible development of diadermatic dosage form.

POSTER PRESENTATION VI.
(PDD)

Elaboration Of Technology And Analytical Methods For Effective Children Medicinal Form

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Creation of effective medicinal forms possesing the ability to induce interferon (IF) is in a great interest in pediatrics. In this aspect, the creation of a rectal medicinal form (a suppository) containing gozalidone and megosine is particularly actual. Gozalidone and megosine are anti-viral preparations which are able to induce IF in organism. It allows not only to treat diseases but also conduct their prophylaxis as well. According to the data of clinical investigations it was revealed that gozalidone had a high anti-chlamydous effect whereas megosine was an effective anti-herpetic agent. In connection with the matter mentioned above, there is a necessity to elaborate a convenient and handy rectal drug as a suppository for infants and pregnant women with herpes and chlamydis virus. With this purpose, we have elaborated technology of suppositoria with Gozalidone and Megosine and investigated the following fatty bases: cocoa oil (base for comparison), hydrogenizate of cotton seeds oil with a 5% content of emulsifier T-2. Physico-chemical properties were determined by generally accepted methods during 15 months. Qualitative content of active substances was determined by spectrophotometric method. Biopharmaceutical on suppositories have been carried out in comparison with other medicinal forms (Gozalidone tablets per 0.1 g and 3% megosine ointment).

As a result of the conducted research, it was determined that the quality of the suppositories met the standard requirements. Physico-chemical, structure-mechanical indices of the suppositories with emulsifier T-2 are as good as with cocoa oil. Quantitative content of active substance is 98%.

Investigations On Preparation Of Papaverine Hydrochloride Tablets Using Microcrystalline Cellulose "Introcel"

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Papaverine hydrochloride tablets per 0.04 g with average mass of 0.35 g on the base of sugar are produced by "Uzchimpharm".

The defects of their technology are as following: undetermined average tablet mass, employment of sugar, dependence of tablet decomposition and strength on the value of compression pressure.

The purpose of this study was to elaborate a new composition and technology of papaverine hydrochloride (PH) tablets using microcrystalline cellulose (MCC) "Introcell" and auxiliary substances to ensure a regulation of bioactive matters release. We have studied physico-chemical and technological properties of PH substantia and concluded that it was a white crystalline powder with prism shaped crystalls, related to anisodiametric group. Non-positive technological characteristics of the substantia required to introduce some auxiliary substances into the tabletting mass composition and to apply a method of wet granulation. For determination of the optimal ratio of substantia and auxiliary matters, we added different amounts of MCC, starch and calcium stearate to the tabletting mass. The results of the experiments showed an expediency of introducing 83% of MCC "Introcell", 2.7% of starch and 1% of calcium stearate in correspondence to the average tablet mass. Afterwards, the obtained mass was pressed on the "Erweka-Apparatebau" machine to produce tablets containing 0.04 g active substance in a tablet with an average mass of 0.30 g. the mass pressed was rather satisfactory, didn't stick to a pressform and the average mass of the produced tablets were determined according to the generall accepted methodology and the obtained results met the standard requirements.

Transport Of Medicinal Agents Through A Semi-permeable Synthetic Membrane And Segment Of The Rectal Intestinal Section

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Elaboration of methods of the biological modeling is an actual problem demanding subsequent investigations. The purpose of our research was to establish a correlation while sulfathiazole and acetylsalicylic acid transport through a semi-permeable synthetic membrane and segment of the rectal intestinal sector in rats. As models, we have used a hydrophilic synthetic membrane with a layer thickness of 0.52 mm and rectal sector of the rats natural intestine; 0.1 mol/l solutions of sodium hydroxide and hydrochloric acid were model media. For conducting the experiment, a suppository was placed in the device, consisting of a glass cylinder of 130 mm in length and 22 mm in diameter and a glass 250 ml capacity. A semi-permeable synthetic membrane, initially kept up in dialysis medium for 45 min., was stretched on the glass cylinder. 100 ml of the dialysis medium was poured to the glass and thermostated until 37°C. After that, the cylinder with a suppository was placed into the glass in such a way so as its lower end to be dipped within 5-7 mm into dialysis medium. Tests were taken in every 30 minutes for 4 hours. Liquid loss was filled up with equal quantity of the solution of the dialysis medium.

During 4 hours, we were conducting a release through the rectal intestinal sector of the rats. Purity and assay of the active ingredients have been carried out according to the methods, elaborated by us. Mathematical analysis of the obtained results showed a presence of positive correlation ($r = 0.81$) between the release through a semi-permeable membrane and through segment of the rectal intestinal sector of rats.

POSTER PRESENTATION IX.
(PDD)

Development Of A Transdermal Therapeutic System For Nicotinic Acid

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Nowadays, development of new highly effective medicinal dosage forms meeting all requirements of the modern pharmacy, is an actual problem. The problem of formulating vitamin preparations in convenient medicinal dosage forms for their administration by patients and prophylaxis of diseases is also important. Nicotinic acid is one of the B-group vitamins and it is known as an antipellagric agent. Industrial pharmacy is producing nicotinic acid in three medicinal dosage forms: powders, tablets (0.05 g) and 1% solution in ampoules. We have elaborated 7 compositions of transdermal systems with nicotinic acid as plasters, containing several types of surface active and auxiliary substances in different ratio, such as 0.5% of Tween 80, 1% of sodium salts of fatty acids, 0.5% of sodium dodecyl sulfate, 0.5% of dodecyl ether triethanolammonium salt of chloroacetic acid, 1% of calcium stearate, 0.1% of polyvinylpyrolidone. For comparison of the results of physico-chemical and biopharmaceutical investigations, we have elaborated the transdermal therapeutic system with nicotinic acid free of surface active agents and auxiliary substances as a control sample. Spectrophotometric method for quantitative determination of the active matters in the transdermal systems has been employed. Biopharmaceutical, microbiological and pharmacological investigations on the transdermal medicinal dosage forms were carried out as well.

Investigations On The Polyox Hydrogel Systems With Nicotine And Cystine Against Nicotinism

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As of 1997, approximately 46 million people in the United States smoke cigarettes. Smoking cigarette has been the cause of 420 000 deaths per year in the US. and about 2 million per year in the developed countries. Hydrogels obtained after irradiation with (γ-rays) induced cross-linking of high molecular weight polyethylene oxide (Polyox) were investigated as a carrier of drugs for replacement therapy.

Nicotine and Cytisine (Laburnum anagyroides, Fabaceae) as a model drugs were used. The release of the drugs depends on drug related factors as well as matrix related factors.

Generally, the release take place as an anomalous diffusion (release exponent n= 0.53 + 0.86). The rate and kinetics of release (t1/2 or zero order prevailing) depend mostly on the drug content in the matrices and the irradiation dose.

As a conclusion, it can be stated that it is not only the type of the matrix (dry or wet) but also irradiation dose (2 or 5 Mrad) and drug concentration as well that determine the kinetics by which the prevailing part of the contained drug is released, which provides greater means for drug release profiles.

Dissolution Characteristics Of Naproxen Sodium Matrix Tablets Prepared From Matrix Granules

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Naproxen sodium is presently marketed as an immediate-release tablet dosage form and is effective for the relief of gout and as an anti-inflammatory/analgesic when administered two to three times a day. The purpose of the present work was to investigate the in vitro performance of compressed matrix tablets which were prepared by granulating using several polymeric substances. Carboxymethylcellulose (CMC), hydroxyproylmethylcellulose (HPMC), Eudragit L 100 and Eudragit RL 100 were used as the polymeric materials to produce sustained-release dosage forms of naproxen sodium. The matrix granules used for the preparation of the tablets sieved through a combined sieve set to four different particle sizes. The matrix tablets were prepared by compacting these granules on a hydraulic press in flat-faced punches of 13 mm diameter with the compaction force of 7540 kg/cm^2. The in vitro dissolution was monitored using a method based on the USP paddle method. The stirring rate was 50 rpm. Simulated intestinal fluid without enzymes was maintained at 37°C± 0.5°C. A UV detector was used to monitor the tablet dissolution at 263 nm. Release data were examined kinetically and the kinetic models were estimated for drug release.

Preparation Of A Floating Dosage Form Containing Diclofenac

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A multiple-unit type oral floating dosage system using ion exchange resins has been prepared in order to prolong the gastric emptying time of preparation. The system is composed of diclofenac-resin complexes which are loaded with bicarbonate and coated with a hydrophobic polymer.

The system is designed so when the beads reach the stomach, chloride ions exchange with bicarbonate and diclofenac ions. The generated carbondioxide entraps in polymeric coated resins and produces floating beads.

In this study, Amberlite-IRA 900 was loaded with diclofenac using a batch method. Bicarbonate was loaded on diclofenac resin beads from different volume of 0.1 M bicarbonate sodium solution. These beads were encapsulated with a hydrophobic polymer, ethyl cellulose or Eudragit RS100, using emulsification-solvent evaporation. Floating ability, core-coat ratio, and release profile of diclofenac in phosphate buffer (pH 6.8) from different samples were determined.

According to obtained results, most of ethylcellulose coated diclofenac-bicarbonate resin complexes can be floated on simulated gastric fluid for more than 24 hours but Eudragit RS100 coated beads sediment rapidly.

Preparation Of Sustained-release Tiaprofenic Acid Beads

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Tiaprofenic acid (TA), 2-(5-Benzoyl-2-thienyl)propionic acid, has analgesic, anti-inflammatory and antipyretic properties; it is an inhibitor of prostaglandin synthetase. The usual oral dose by mouth is 600 mg daily; this may be given in 2 or 3 divided doses or once daily as a sustained-release preparation. TA is readily absorbed from the gastro-intestinal tract. It has a short half-life of about 2 hours.

The wide use of natural polymers as coating barrier or beads forming material has received the attention of many investigators focused on preparation of sustained release dosage forms. Sodium alginate is a natural, biodegradable and biocompatible polymer used as suspending and gelling agent in pharmaceutical technology. Recently, the alginate gel beads, which is a spherical gel prepared by dropping sodium alginate into calcium chloride, has received much attention in sustained-release preparation.

The main objective of the present study was to formulate sustained release TA-beads based sodium alginate. A weighed quantity of MA powder was added to an aqueous solution of sodium alginate (1% w/v) and dispersed homogenously. The bubble-free dispersions were dropped into 100 ml of 0.1 M calcium chloride solution at room temperature using 21 gauge needle. The formed spherical beads were separated, washed with water and dried at room temperature. Drug contents and encapsulation efficiency of the prepared beads and beads properties (e.g. particle size, weight, swelling of the beads) have been investigated. Drug release from the beads were examined using USP XXIII paddle method in 500 ml of phosphate buffer (pH7.4, 37±0.5°C). The released drug amount was determined spectrophotometrically at fixed time intervals and a wavelenght of 316 nm. Kinetic assessment of release data was evaluated using the Higuchi kinetic model for heterogeneous spherical matrices.

The results indicated that drug incorporation efficiency was rather high (>80 %) in all of the examined polymer-MA ratios. In vitro release from prepared beads with different polymer-MA ratios showed a sustained-release profile. Results obtained from release data were in good agreement with the Higuchi model. Hence, the release process was a matrix-type diffusion controlled system.

POSTER PRESENTATION XIV.
(PDD)

Studies on Formulation Of Solid-Lipid Ketoprofen Micropellets

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Ketoprofen is a non-steroidal anti-inflammatory drug which has analgesic and antipyretic properties. It inhibits prostaglandin synthetase. Ketoprofen is not soluble in water and creates local or systemic gastrointestinal disorders. Ketoprofen was reported to cause gastrointestinal side effects requiring withdrawal from the treatment. It is used in romatoid arthritis and in mild to moderate pain.

In this study, prolonged release solid-lipid micropellets of ketoprofen with beeswax in a ratio of (1:3) and (1:4) was prepared by using emulsion congealing technique. Drug was incorporated as solid particles in the melted beeswax, the mixture containing Tween 80 was emulsified in water at 100°C and stirred (800 rpm) at room temperature for 20 min. The beeswax solidified eneveloping the drug. The micropellets produced were washed three times with water. Micropellets were air dried at room temperature.

Ketoprofen content of the micropellets were determined. Dissolution studies of active ingredient from the micropellets were performed by using USP XXII Method I. pH 7.4 phosphate buffer was used as the dissolution medium and the system kept at 37°± 0.5°C for 7 hours. As a result, release of ketoprofen from prepared solid-lipid micropellets was found to be prolonged.