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PHARMACEUTICAL TECHNOLOGY (PT)

POSTER PRESENTATIONS

POSTER PRESENTATION I.
(PT)

The Effect Of Different Polymers On Microsponge Formation

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During the few years, in pharmaceutical research much attention has been given to the controlled release of systemic drugs. By the use of this approach, controlling the therapeutic efficacy of these drugs, reduction in the total dose needed and a reduction in the side effects can be provided. For this purpose, microsponges are one of the systems which is in trial for controlled drug delivery. Microsponges are porous, polymeric microspheres of that is used mostly for topical and recently for oral administration.

In this study, the aim is to improve the model drug Ketoprofen's pharmacokinetic properties (e.g. $T_{1/2}$= 0.5-2 hours) by preparing its microsponges with different polymers and a comparison is made between them. For this purpose, by using Eudragit RS 100, ethyl cellulose and Eudragit RS 100 and ehtyl cellulose mixtures at different ratios are used for preparing microsponges.

The microsponges were prepared by emulsion-solvent diffusion method. In the first step, outer phase was prepared by mixing sucrose fatty acid ester into certain amount of distilled water and in the second step the outer phase was prepared by mixing the polymer, drug, plasticizer and a solvent that the drug can solubilize in it. Finally, in the last step, the inner phase was poured slowly into the outer phase and mixed together for five hours at 350 rpm. And then, the microsponges were filtered carefully, and put into vacuum oven at 40°C overnight.

After the formulations were prepared, particle size and shape and surface properties of the microsponges were investigated by Scanning Electron Microscopy (SEM). In the second step, among all of the formulations only the suitable ones were chosen and drug release rate studies were investigated by using USP XXIII II. Method (paddle apparatus) in pH 6.8 and 7.4 phosphate buffer solutions. We concluded that among all the formulations that were investigated Eudragit RS 100 formulations gave the best results both with surface properties and the dissolution profiles.

Influence Of Swelling Degree On Release Of Verapamil Hydrochloride From Polymethacrylate Microspheres

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Verapamil Hydrochloride (VRP) is a calcium channel bloker with a phenylalkylamine structure that shows an antihypertensive effect because of the peripheral vasodilation and has nonlinear absorption characteristic. There are different market preparation of VRP's that can be immediate and controlled release. In the recent years, during the preparation of controlled release system, because of the non-linear absorption of VRP, the excess of the absorption difference is determined between patients while they were using the single unit matrix preparation. Because of that reason, according to the single unit dosage form, formulation of multiparticulate matrix systems that contain VRP which has more regular dissolution and absorption at gastrointestinal system bring some advantages.

In this study, VRP loaded microspheres were prepared by solvent evaporation method by using polymethacrylate polymer mixture (Eudragit RS 100 and Eudragit L 100) that show different permeability characteristics in gastrointestinal tract. The particle size and distribution of microspheres were determined and yield value and incorporation efficiency were calculated. Surface morphology of microspheres were observed using scanning electron microscopy and drug release from microspheres were determined using the flow-through cell and half-change method at the different pH of gastrointestinal tract. During the in vitro release studies, swelling of microspheres were determined and increase of diameter of microspheres were observed at the predetermined time interval in the simulated intestinal fluid and swelling degree (Q) were calculated. The effect of Q values to the release of drug from microsphere were determined. All these calculations were evaluated statistically.

As result of our study, at the formulations which were prepared by addition of Eudragit L 100 to Eudragit RS 100, it is seen that drug release increase at the intestinal pH dissolution media and when the in vitro release profile of microspheres at the pH 7.5 were determined, it is seen that the formulations that reached to the desired targeted profile can be prepared parellel to the increasing ratio of L-100 in the formulations, the increase in the Q value is found out. Upon the result of in vitro release studies, parellel to the increasing Q value, increased drug release was also determined.

POSTER PRESENTATION III.
(PT)

Elaboration Of New Anti-Ulcer Drugs On Basis Of Bismuth Biocomplexes

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The extension of bismuth-containing class of anti-ulcer drugs by means of its complex compounds has practical interest, since it's known that the metal co-ordinate-connected possesses as a rule more activity and less toxicity.

Therefore, we used neorganic bismuth (III) and a-aminoacids (DL-tryptophan (Trp) and L-histinde (His)) salts; they are structural units of a protein molecule and have some properties which allow to use them as physiologically active substances.

Complex-formation reactions carried out in alkaline and acid media. There were substances obtained as solid forms which are products of connection and have composition of $Bi(Trp\text{-}H)^2.2H_2O$; $BiCl5(His)^2.10H_2O$.

These compounds were identified by elemental and X-ray analyses. Their melting points and molar electric conductivity were defined. It was deduced about their complex-forming ligands by studying of IR spectrum data of free and co-ordinate ligands as polycrystals and derivatograms.

The biological researchers obtained preliminary data on specific activity of compounds synthesized. In order to determine the harmless properties of complexes, the keen toxicitiy studies were carried out for preparations. Toxicity studies were performed on white mice of both sexes by in-stomach introduction of the drugs. Tests were effected in comparison with colloidal bismuth subcitrate (De-nol, Yamanouchi Europe B.V.). It was established that compounds studied posses 1.5 times less toxicity than compared preparation-colloidal bismuth subcitrate.

Thus, anti-ulcer drugs were synthesized on basis of bismuth (III) and a-aminoacids, their physico-chemical properties and keen toxicity studies were carried out. Pharmacodynamic investigations on complexes obtained are still undergoing.

POSTER PRESENTATION IV.
(PT)

HPLC Method For Qualitative And Quantitative Analysis Of 1,4-Naphtoquinone Derivatives In Plant Row For Pharmaceutical Industry

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A simple, fast and selective method for the assay of 2-methyl-3-phythl-1,4-naphtoquinone (Vitamin K1) and 2-methyl-1,4-naphtoquinone (Vitamin K3) in plant extracts of Zea Mays, Poaceae (Stigmata Maydis) and Kigelia Africana, Bignoniaceae was developed using Rp-HPLC.

Total methanol and chloroform extracts of both plants and particular chloroform, methanol and water fractions of Kigelia Africana isolated with adsorption chromatography from methanol extract were analysed.

We have found that an acetonitrile- nethanol-water mixture is an excellent solvent for reverse phase separation of K1, K3.

Some analytical parameters as standard deviation, confidence interval, relative standard deviation were presented.

POSTER PRESENTATION V.
(PT)

Investigations On Stability of 7-Theophyllinylacetyloxyglycols At Different pH-Values By Means Of Reversed Phase Liquid Chromatography

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In the present study the stability of 7-Theophyllinylacetyloxyglycols-potential pordrugs were investigated in water at different pH -values (1.2, 7.4, and 9.0). For the analysis of hydrolysis product, an HPLC method was developed. The method proposed was sensitive enough and allows complete separation of substances in question. The chromatographic procedure was validated and shows good accuracy, precision and velocity. The separation was performed on a chromatographic column LiChrosorb RP-18, 125 x 4 mm (Merck) and mobile phase methanol-water (50:50) at pH = 3. A chromatograph of Shimadzu -10 A equipped with diode -array detector was used. The detection was at 220 nm. The retention times of separated substances were 1.3 min and 4.6 min, respectively.

POSTER PRESENTATION VI.
(PT)

Characterization and Dissolution Studies Of Carbamazepine In PEG 4000 Solid Dispersion

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The present study has been designed to examine the physical properties and the dissolution behaviour of carbamazepine solid dispersions in a co-polimer of polyethylene glycol 4000. Solid dispersions of carbamazepine in PEG 4000 were prepared in different ratios by the co-evaporation method and melting-solvent method. Physical mixtures of the two molecules in the same ratios were prepared.

The obtained solid dispersions and physical mixtures were characterised using thermal analysis, X-ray diffractometry, infrared spectrophotometry and dissolution studies.

By analyzing X-ray diffraction spectra it was observed that in solid dispersions the specific signals for carbamazepine crystalline structure were reduced. The thermal analysis of the solid dispersions showed a decrease in the entalpy of fusion of the drug, thus, indicating a reduction in drug crystallinity comparing to the carbamazepine alone. Recorded IR spectra sustain the supposition of the formation of the new hydrogene bounds in the studied solid dispersions.

The dissolution rate of the drug was influenced by the co-polymer content in the solid dipserisons. On increasing the weight fraction of the polymer, a faster dissolution rate was obtained. This fact induces to think of a better biovailability of the carbamazepine and to recommend the system for the fast release formulations.

Method For Estimating The Parameters Of First Order Drug Release Delivery System

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The study presents a possibility to estimate the main parameters of first order drug release using aminophylline as a model drug. The main parameters of a matrix drug delivery system (dose and release rate constant) of theophylline releasing according to first order have been determined theoretically on the basis of the main pharmacokinetic parameters of the drug applying the equations for time dependent in vitro drug concentration. The system reaches C_{max} at 5 mg/l, at dose of 256 mg and drug release rate of 0.268 h^{-1}. A matrix tablet based on glycerinomonostearate was developed technologically having the above parameters and containing 300 mg aminophylline equivalent to 257 mg theophylline. The in vitro release rate constant is 0.263 h^{-1}. The model tablets were tested treating 7 healthy volunteers for 24 hours. C_{max} = 5.2 ± 0.72 mg/l was reached for 6.14 ± 0.99 h and is in good correlation with the data for in vitro release rate which confirms the possibility to use the novel method for estimating the specific parameters of the drug delivery system releasing according to the first order reaction.

POSTER PRESENTATION VIII.
(PT)

The Influence Of Distribution Of Hydrocortisone Acetate In Oil-In - Water Creams To The In Vitro Release Of The Drug

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The efficacy of topical pharmaceuticals is related to the differences in the vehicle or base. In this study, we investigated the distribution of hydrocortisone acetate (HA) in the phases of various formulations of creams and the release of the drug from these oil-in-water emulsions. The emulsions were prepared using mineral oil and cetylic alcohol as lipophilic phase and various concentrations of surfactant (polisorbate 80), propylene glycole and water as aqueous phase. HA was suspended in the emulsion. The distribution of HA in the phases of the emulsion was evaluated after separation by ultracentrifugation and ultrafiltration. The quantitative assay of HA was performed spectrophotometrically. The in vitro diffusion was studied in water using a dialysis membrane.

The results show that the amount of HA released decrease with increasing the amount of polysorbate 80 in the emulsions. The release exhibits a parabolic behaviour with increasing the proylene glycole concentration. The release increases when the concentration of the drug in the aqueous phase becomes high.

The Effect Of Excipients On Dissolution And Physical Properties Of Albuterol Tablets Prepared By Direct Compression

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Albuterol sulphate (AS) is a sympathomimetic amine which is used as a bronchodilator in the treatment of reversible bronchospasm. It is absorbed rapidly when administered orally. The plasma half-life of albuterol sulfate was calculated to be 2-7 h. Its usual dose is 2-4 mg, 3-4 times a day. The aim of this study was to investigate the effect of some disintegrants and preparation technique on the physical properties of AS tablet formulation. For this purpose, six different disintegrating agents were used: Emcompress, STA-Rx 1500, Carbonate de Chaux, Corn Starch, Sulphate de Calcium, Primojel. Six different formulations were prepared by direct compression technique. The effect of various adjuvants on the physico-pharmaceutical properties and release profiles of the substance were investigated.

Tablet formulations:

Ingredients/Codes	T1	T2	T3	T4	T5	T6
Albuterol sulfate	4	4	4	4	4	4
Avicel PH 101	85	85	85	85	85	85
Emcompress	105	85				
STA-Rx 1500		20				
Carbonate de Chaux			105	85		
Corn Starch				20		
Sulphate de Calcium					105	85
Primojel						20
Talc	4	4	4	4	4	4
Aerosil	2	2	2	2	2	2
Total weight	200	200	200	200	200	200

Physical properties of the tablets: the prepared tablets were evaluated for uniformity of weight, thickness, hardness, friability, and disintegration time.

Dissolution rate determination: The USP XXIII paddle method (50 rpm) and basket method (100 rpm) were used with 200 ml distilled water as dissolution medium. The temperature of 37 ± 0.5°C was followed. The absorbance of the samples were determined spectrophotometrically at 277 nm. The data were evaluated kinetically. SPSS computer program was used for this purpose.

POSTER PRESENTATION X.
(PT)

In Vitro Release Characteristics Of Marketed Enalapril Maleate Tablets And New Formulation Studies

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The quality assurance of the drugs marketed have gained great importance in the field of industrial and clinical presentation. Some of these studies carried out previously showed quality differences between chemically equivalent formulations.

Enalapril maleate, (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate, a synthetic peptidic derivate, is a long acting oral inhibitor of angiotensin converting enzyme (ACE), which reduces the plasmatic concentrations of angiotensin II and aldosterone and increases the plasmatic activity of renin. The orally absorbed prodrug enalapril maleate is hydrolized in vivo to enalaprilat, an extremely potent inhibitor of converting enzyme. Enalapril maleate is an effective antihypertensive and can be useful in the treatment of congestive heart failure. Enalapril maleate tablets are among the preparations presented by numerous manufacturers. Pharmaceutical properties of enalapril maleate tablets were presented in our previous study. In this study, the dissolution rate studies and kinetic evaluation of dissolution results were carried out.

In order to evaluate the dissolution rates, zero, first order, Hixson Crowell, Modified Hixson Crowell, RRSBW, $Q\sqrt{t}$, Higuchi, Hopfenberg equations have been studied and best fitting equations were found to be Modified Hixson-Crowell and RRSBW kinetics. In addition, different tablet formulations of enalapril maleate were prepared using different excipients. The quality control and dissolution results were evaluated kinetically as mentioned above.

POSTER PRESENTATION XI.
(PT)

In Vitro Study Of Drug Release Processes From Di-Li-DL- Aspartate Sustained Release matrices

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Comparative pharmacological studies of Li-carbonate, Li-DL-aspartate and di-Li-DL-aspartate indicated that di-Li-DL-aspartate has very good antidepressant effect in low doses and this makes it a very efficient drug for treatment of manic depressive disorders. The usual therapeutic dose of 500 mg di-Li aspartate equivalent to 48.3 mg of Li (6.9 mmol) is enough for keeping the concentration within the therapeutic limits of 0.5-1.2 mEq/L for a period of 10-12 hours. The process of Li release from mixed hydrophilic-lipophilic matrices containing di-Li-DL-aspartate was studied in vitro. The influence of the ratio of different matrix agents, particle size of the drug and granules, compression force applied on the matrices, on the Li release kinetics was studied. It has been found out that the studied technological parameters do not change the mechanism of drug release. The process is diffusion - controlled and can be described by the Higuchi equation. Di-Li-DL-aspartate has high solubility in water which is the only parameter that influences drug release process in the studied systems.

POSTER PRESENTATION XII.
(PT)

Stability Study Of Galantamin Hydrobromid In Presence Of 4-Aminopyridin In Tablet Models With Different pH Values

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The combination of Galantamin hydrobromid (Nivalin, an original Bulgarian medicine, Paskov, 1959) with 4- aminopyridin is of interest in connection with their biological activity, expressed in intesifying the synapse delivering in central nervous system (CNS) and peripheral nervous system (PNS). This property may be useful in treatment of different diseasesin which pathogenesis disfunction in the synapses take part or decrease of their function caused by degenerative processes (Alzheimer disease). Mutual potency of 4-aminopyridin and Galantamin hydrobromid was demonstrated on the different levels on the central nervous system (encephalographic experiments) and on peripheral nervous system (neuromuscular synapses). The results were confirmed clinically.

In our previous study, a tablet models of 4-aminopyridin and Galantamin hydrobromid with different pH values were developed.

The objective of this study is to examine the stability of Galantamin hydrobromid in presence of 4-aminopyridin as a function of pH. The stability study was carried out at long term testing conditions (25°C ± 2°C, 60% humidity, RH= 5%) for 12 months and accelerated testing conditions (40°C ± 2°C, 75% humidity, RH= 5%) for 6 months. The samples were tested every month over the first 6 months and once in every three months afterwards.

Based on the obtained results it was determined that the factors which potent the degradation of Galantamin hydrobromid are the high values of pH and percentage of moisture in the tablet models which are in direct relation with quantity of used buffer salts.

POSTER PRESENTATION XIII.
(PT)

Study On Dry Extract Yield On The Different Factors Of Extraction

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Aerva lanata L. is used in folk medicine as a diuretic for treatment of liver, kidneys, stomach and gallbladder diseases. Motherland of this plant is Africa, Asia, and Philippines. We have studied a chemical composition of the extracts obtained by various ways. The content of such biological active substances as flavonoids, tannic matters, essential oils, sugars and ascorbic acid have been established in the organs of the plant, cultivating in Uzbekistan. The purpose of the present investigation was to study the influence of different factors of extraction process ob the yield of dry extract. We have choosen the main factors which influence on the extraction process. They are: extraction time, hydromodulus and multiplicity. Study on influence of the mentioned factors was carried out by the following way: 10 g of Aerva lanata air-dried samples were placed in a conical flask, 100 ml of purified water was added, and then, it was joined up with circular cooling system. The obtained mass was boiled for 10 to 60 minutes under a hydromodulus from 1:10 to 1:35 with multiplicity of 1-3, every time changing the values of the factors under investigation. When time was up, the extract was cooled, filtered and dried at a temperature of 70-80°C in the vacuum drying cabinet. Thus, the highest yield of the dry extract was observed while extracting for 20 minutes with a hydromodulus of 1:35 and 3 multiple extractions. We can conclude that the process of extraction must be conducted for 20 minutes with a hydromodulus of 1:35 and 3 multiple extractions of the raw material. The obtained dry extract has been submitted for pharmacological tests.

POSTER PRESENTATION XIV.
(PT)

Qualitative And Quantitative Analysis Of The Dry Extract Obtained From Inula Grandis

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Natural reserves of Inula grandis are enough in Uzbekistan. Underground organs contain 2-3% of essential oils, 30-40% of polysaccharides (inulin). The decoction obtained from underground organs has been studied pharmacologically and recommended as an expectoral agent for treatment of gastro-intestinal diseases. The objectives of this study were obtaining a dry extract, elaboration of methods of qualitative and quantitative analysis, standardization and preparing tablets. The yield of the dried extract was 40-45 %. Its identification has been conducted by concentrated sulfuric acid and thin layer chromatography (TLC) in the system of ethanol-ethyl ether (3:4) with the Rf value of 0.44 ± 0.02 and butanol-1-acetone-water (2:7:1), Rf value of 0.63 ± 0.02. Silicagel Л 5/40 μ was used as a sorbent. 0.1 mol/l solution of potasium permanganate was a developer. Photoelectrocolorimetric method of quantitative determination of inulin in dry extract has been elaborated. The determination was based on acid hydrolysis of inulin and obtaining colored product by solutions of picric acid and sodium hydrocarbonate. The optical density of the solution was determined at a wave length of 490 nm, the thickness of the layer was 10 mm. Inulin content in dry extract was found by means of the monosaccharide, obtained without acid hydrolysis.

POSTER PRESENTATION XV.
(PT)

Obtaining A Tincture From Phlomis Regelii M. Pop. And Study On Its Properties

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Phlomis regelii M. Pop. Is a perennial herbal plant of Lamiaceae family. It is widely distributed in Uzbekistan and recommended in official medicine as a sedative agent. The plant posseses an appreciable hypertensive and diuretic effect.

The aim of the present study was to obtain a tincture from Phlomis regelii herb and to investigate its numerical indices. Plant raw material was collected in the Chimgan mountains of the Taskent Region in July, 1999. A aerial aprt of the plant was collected by hand, dried in the shade and then, reached a standard level. A tincture was prepared by percolation on the base of 70° alcohol in the ratio of 1:5. The obtained tincture looked like a transparent liquid of dark greenish-brown color with an aromatic odor and a faint bitter taste.

The main component of the flavonoids sum in this plant is hyperoside. Therefore, the content of the active substances has been determined by photocolorimetric method under the indicated flavonoid. We decided to use this method for the tincture as well. For analysis, 5 ml of the tincture which corresponds to 1 g of the herb, was added to 95° alcohol (solution A) and the total volume was made up to 25 ml.

1 ml of the solution was placed into a 25 ml calibrated flask and then, a reaction of diazotization was performed. The mixture volume was diluted to the mark with water and the optical density of the solution was determined photoelectrocolorimetrically. Quantitative content of flavonoids sum has been determined according to the calibrating curve under standard hyperoside. Afterwards, alcohol content and dry precipitation in the tincture were determined. The alcohol content was 67.8% and dry precipitation was 3.4%. The flavonoid content of the obtained tincture was 0.5%. The tincture has passed tests for heavy metals.

POSTER PRESENTATION XVI.
(PT)

Comparative Analytical Investigation Of Silybum Marianum Seeds, Silymarin And Its Pharmaceutical Dosage Forms

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A comparative analytical investigation of Silybum marianum seeds (Cardui martae fructus) in different demographic regions of Bulgaria with respect to content of flavonolignans have been carried out.

Comparative analysis of Silymarin substances of different origin growing in Bulgaria, India, China show that Bulgarian samples contain much more Silibin-Isosilibin and Silidanin -silichristin than others. A comparison regarding qualitative and quantitative content of three Bulgarian pharmaceutical dosage forms and nine sold American preparations were carried out, too. Different analytical methods have been used such as: thin layer chromatography, liquid chromatography and spectrophotometry.

POSTER PRESENTATION XVII.
(PT)

Quality Control Of Different Extracts Obtained From Echium Vulgare L. With Respect To Design Of Future Pharmaceutical Drugs

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Echium vulgare L., named "common viper", belongs to the genus Echium, a member of the family of Boraginaceae. The plant is wide spread in Bulgaria. It is used in folk medicine in the form of extracts for cleaning up the blood and healing wounds, caused by snake bite.

Different extracts against some Gram-positive and Gram-negative bacterial test strains have been investigated.

The presence of pyrolizidine alkaloids such as echimidine and 3'-acetylechimidine is established. These alkaloids are of great interest because of their hepatotoxic, mutagenic and carcinogenic activities.

The preliminary investigations show that the seeds can be used as a source of gama-linolenic acid, preventing and alleviating a wide variety of human diseases as a potential pharmaceutical drugs.

It was determined that the flowers of the plant are rich of anthocyanines. The plant was collected from Vitosha mountain in Bulgaria and identified by L. Vassileva of Botanic Institute at Bulgarian Academy of Scince.

POSTER PRESENTATION XVIII.
(PT)

Determination Of Clenbuterol HCl In Human Serum And Pharmaceuticals And Drug Dissolution Studies By RP-HPLC

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Clenbuterol HCl, a β-agonist drug, is used for the treatment of chronic obstructive pulmonary diseases and reduction of stress symptoms. The reduction of stress symptomes has led to the abuse of Clenbuterol HCl, causing it to be added to the International Olympic Committee's list of doping subtances. The determination of trace amounts of analytes in biological samples, pharmaceuticals is a well-known problem. So, in order to reduce the effect of interfering components and to enrich the analytes of interest, sample pre-treatment is necessary in most cases.

Main objective of this work has been development of a simple, reliable, time and money saving HPLC method which uses UV detection for the determination of Clenbuterol HCl in human serum and pharmaceuticals in order to carry out drug dissolution studies from tablets.

Clenbuterol HCl is well separated on a Waters C18 (5μm, 150 x 4.6 mm) column by using the mobile phase consisted of a mixture of acetonitrile and an ion-pair buffer (32:68; v/v) at a flow rate of 1.5 ml/min. The ion pair buffer contained 0.02 M octanesulfonic acid sodium salt and 0.02 M acetic acid. The pH of the mobile phase was adjusted to pH 3.8 with 0.1 M NaOH. Detection was carried out using a UV detector at 244 nm. Ephedrine Hcl was used as an internal standard. The detector response was linear over the concentration range of 40-50,000 ng/ml (r= 0.9999) with a slope of 3.3 x 10-3. The retention time was 4.25 min for Ephedrine HCl and 9.47 min for Clenbuterol HCl. The limit of detection of the procedure was found to be 3.78 ng/ml.

Within day and between day and recovery tests confirmed the reproducibility, precision and accuracy of the purposed method. This method was successfully applied to the analysis of clenbuterol HCl in human serum. This method was also applied without any interferences from the excipients from the determination of the drug in tablets and in drug dissolution studies.

POSTER PRESENTATION XIX.
(PT)

Design Of Ocular Dispersions Containing Pilocarpine

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The aim of this study was to develop Pluronic containing formulations (based on acetophthalate cellulose) appropriate for delivery of ocular pilocarpine HCl dispersions. Aqueous pH dependent CAP dispersions forming gel "in situ" in the eye were tested as carriers for ophtalmic formulations.

The stability, particle size, and the viscosity of the dispersions were determined using UV-spectrophotometry, HPLC, viscosimetry and particle sizing.

A RP-HPLC method for pilocarpine and isopilocarpine was developed which is suitable for the routine analysis of ophtalmic preparations. Pilocarpine salts are decomposed to pilocarpic acid, isopilocarpine, and isopilocarpic acid. The decomposition products are inactive. Degradation to pilocarpic acid is catalized by both hydrogen and hydroxide ions, while epimerization- only by hydroxide ions. Both hydrolysis and epimerization are pH-dependent processes.

The local tolerance toxicity and pharmacological activity (reactions of the folds, the conjunctive and the cornea) of pilocarpine in the formulations were tested on rabbit eyes. Miosis was measured before and at different time intervals (1,2,3,4,5,6,7,24 and 48 hours) after the application. Intraocular pressure was determined on the 3, 6, 24 and 48 h using a standard tonometer. The results of this investigation indicate that a CAP containing model dispersion with low Pluronic concentrations as a surfactant is suitable for an ophtalmic drug delivery system.

POSTER PRESENTATION XX.
(PT)

Development Of Model Methoclopramide Solutions For Intranasal Application. Part I: Stability Study.

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Model aqueous viscous solutions of methoclopramide were developed on the basis of hydrophilic polymers -hydroxypropylmethylcellulose, methycellulose, carbopol, pluronics- F68™ and F127™ used as vehicles. The characterization of the vehicles included rheological properties and osmolarity studies. It was found that all models were isoosmotic and behave as pseudoplastic systems of viscosity in the range of 10 cP - 30 cP.

The model solutions were stored at three temperatures: 20°, 40°, and 80°C, respectively. The influence of the studied polymer vehicles on the methoclopramide stability was investigated. HPLC method was developed to measure the concentration of the non-degradated drug.

The stability studies showed that the models with Pluronic F68™ and Pluronic F127™ used in concentration between 5-10% posses relatively high stability in comparison to the other samples.

In conclusion, the results gave us good reasons to extend the study of the models with pluronics to develop dosage forms for intranasal application.

POSTER PRESENTATION XXI.
(PT)

Study Of The Solubility Of Piroxicam In Parenteral Solutions

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Piroxicam, a non-steroidal anti-inflammatory drug (NSAID), is highly effective. Unlike short-acting NSAIDs, it has a long biological half-life of over 30 hours. The parenteral form of Piroxicam contributes advantages in the reduction of gastrointestinal complications and rapid pain relief.

Piroxicam is not soluble in water. In an attempt to prepare a parenteral solution, enhancement of its solubility was performed by both cosolvency and complexation methods. N,N-dimethyl formamide (DMF), N,N-dimethyl acetamide (DMA), propylene glycol (PG) and polyethylene glycol (PEG 300) as cosolvents and nicotinamide (NA) as a complex agent were used and their ability to increase drug solubility were investigated. The solubility of Piroxicam increased along with the increase in concentration of cosolvents. The efficacy of cosolvency was in order of:

DMA>PG>DMF>PEG300

The incorporation of Nicotinamide into the solutions significantly increased the solubility of Piroxicam. Although incorporation of NA and DMA resulted in getting desired concentration of Piroxicam in the formulation (i.e. 20 mg/ml), but as DMA was not reported as a common cosolvent in injectable solutions (except in Recerpine injectable solution), this formulation was rejeceted. The investigation was carried on by incorporation of PG and NA, and finally, two formulations of A and B were obtained after passing in vitro tests successfully.

POSTER PRESENTATION XXII.
(PT)

Quality Control And Standardization Of Papain Substance

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The goal of present research is study of physico-chemical properties of papain, prepared from melon-tree that was grown in Uzbekistan.

There was a dried papain substance received with the help of the sublimatical drying after corresponding purification.

Evaluation of the appearance of papin substance was established by visual and instrumental methods on Pulsar spectrocolorimeter. Test results showed that the papain subtance is an almost white amorphous powder.

Solubility of the papain substance was determined during research and it has shown that the papain substance is freely soluble in water and practically insoluble in organic solvents. Also, other quality indices of papain substance such as residual moisture, pH and clarity of substance solution were investigated.

Quantity of evaluation of the substance was performed on proteolytic activity of the preparation.

Comparative results obtained in this study have shown that the papain subtance prepared from melon-tree growing in Uzbekistan corresponds to standard sample on quality indices.

POSTER PRESENTATION XXIII.
(PT)

A Simple And Rapid HPLC Method For Determination Of Cyclosporin A In Pharmaceutical Dosage Form

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Cyclosporin A (CsA) is a lipophilic, neutral, cyclic undecapeptide produced by Trichoderma Polysporum, which is widely used in organ transplantation and treatment of autoimmune diseases. The therapeutic index of CsA is very narrow and the individual therapeutic response and the bioavailability are variable. Several degradation pathways for CsA have been reported. Apparently, most of these derivatives are not immunosuppressive. Determination of CsA in pharmaceutical dosage form to maintain the adequate amount of immunosuppresion and avoiding the advers effects of drug is very important.

For determination of CsA several HPLC methods are reported, but most of them either use high column temperature (70-80°C) which cause rapid deterioration of the column or they suffer the length of analytical time.

In this study, a simple, rapid, sensitive, reproducible and an isocratic HPLC method was developed for determination of CsA, which consisted of: cyano-analytical column (25 x 4 mm), mobile phase (hexan-isopropanol), UV detection (215 nm), flow rate (0.5 ml/min), running at 40°C.

A linear correlation was found over the range of 50-2000 ng CsA Per ml (r^2 = 0.998). Quantitation limit was 50 ng/ml (SD = ± 0.028). The inter-assay variation and the intra-assay variation was 5.24% and .18%, respectively. Therefore, this method can be applied easily to determine the CsA concentration in pharmaceutical products.

POSTER PRESENTATION XXIV.
(PT)

Effects Of Gelucire®44/14 On The Dissolution Of Tiaprofenic Acid From Hard Gelatin Capsules

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Gelucire® 44/14 is a reversible heat meltable excipient and has proved to be of great interest in the manufacturing of semi-solid formulations. Due to its amphiphilic properties, Gelucire® 44/14 forms a very fine (‹1µm) and stable emulsion when brought in contact with physiological liquids at 37°C. In addition, it rapidly disperses in the dissolution medium, independent of the pH value. It is commonly used as an excipient for immediate release dosage form that increases solubility of hydrophobic drugs and enhances bioavailability.

Tiaprofenic acid has analgesic, anti-inflammatory and antipyretic properties. Available conventional dosage forms are capsules and tablets where therapeutic intake is 600 mg daily; this may be given in 2 or 3 divided doses. It is insoluble in water, soluble in alcohol.

In this study, tiaprofenic acid was dispersed in the melted Gelucire® 44/14 and the resulting mixture was filled into hard gelatin capsules. Differential scanning calorimetric and infra-red spectroscopic analysis were performed to determine the physicochemical properties of mixture with tiaprofenic acid and Gelucire®. The solubility studies of the mixtures were made according to solubility monograph in the USP XIX. The release of tiaprofenic acid from capsules was evaluated by the dissolution test according to USP XXIII basket method at 100 rpm. Distilled water (900 ml) was chosen as dissolution medium. Drug amount in the dissolution medium was determined spectrophotometrically (Shimadzu A-1601) at 316 nm. In addition, we also compared the dissolution of hard gelatin capsules containing tiaprofenic acid dispersed in various PEGs with that of the drug alone.

The obtained data showed that Gelucire® 44/14 can be used as the release excipient to increase the release of tiaprofenic acid in a capsule formulation.

POSTER PRESENTATION XXV.
(PT)

Preliminary Studies On Skin Penetration Of Celecoxib

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Celecoxib is a non-steroidal anti-inflammatory (NSAI) drug that inhibits anti-inflammatory, analgesic and antipyretic activities. The mechanism of action of Celecoxib is believed to be due to inhibition of prostoglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2) at therapeutic conecentration in human. Celecoxib doesnot inhibit the cycooxygenase-1 (COX-1) isoenzyme. Celecoxib was found to cause significantly less gastroduedonal ulcers compared to some other NSAI drugs. However, it still has some gastrointestinal side effects. The side effects may be overcome by topical delivery of the drugs.

The aim of this work is to evaluate the release and penetration profile of Celecoxib incorporated into different vehicles. O/W emulsion, oleagenous cream and a gel base (HPMC) were prepared to contain 5% drug. Celecoxib release and penetration was investigated on cellophane memebrane and excised human abdominal skin by using Franz cell. The experiments were run at 37°C ± 0.5. The amount of Celecoxib released and penetrated was determined by UV spectroscopy and HPLC respectively.

As a result, amount of celecoxib released from cellophane membrane was observed as the highest in O/W emulsion base and penetration rate of celecoxib from skin was also found to be the highest in O/W emulsion followed by HPMC gel and oleagenous cream.

POSTER PRESENTATION XXVI.
(PT)

Determination Of Structure Of Kogistin Drug

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Continuing our studies on the syntheses, standardization and elaboration of new form of Kogistin-coordination compound of Co (III) with L-histidine, we established the final structure of this preparation. Formerly it was suggested that the structure in which histidine molecules are bidentant co-ordinated to Co(III) atom.

The results of IR and E-spectra, derivatograms and elemental analysis of several batches show that there are five histidine molecules co-ordinated with two Co(III) atoms and one histidine molecule forms a bridge in Kogestine molecule.

The location of characteristic frequencies in IR-spectrum of free histidine indicates presence of its zwitter ion form. There were broad bands discovered in the field of 2850-3150 cm^{-1} from NH_3 group and intensive bands at 1634 and 1418 cm^{-1} .

In IR-spectrum of the complex , the bands of NH_2 are shown at 3260 and 3130 cm^{-1} because of the participation of ligands of NH_2 groups in co-ordination with cobalt. There are bands of carboxylate group discovered at 1590 and 1400 cm^{-1} being indicater of substituting cobalt atom for carboxylate hydrogen.

Thus, histidine is bidentant co-ordinated by means of nitrogen atom in amino group and oxygen atom in carboxyl group to form stable five members of metal cycle.

There are absorption bands with three maximums at 13400, 21800, 28500 cm^{-1} characteristic of trans-octagon complexes of cobat (III) in ESDR. The complex structure is retained when the dissolution takes place in water. In UV-absorption spectrum of aqueous solution the bands were discovered at 13600, 20800, 27800 cm^{-1} . They are considered to be the evidence of transition 1A1g(1)®*1T2g(1)®3T1g (1-1) of Co (III)-ion in octagonal field of the complex.

The DSC graph of the compounds shows the location of seven water molecules outside the sphere. The complex is dehyrated in teperature range of 70-105°C in one endoeffect. Thus, there was a structure of tetra -(L-β-imidazolilalaninatodihydrochloride)hydroxo-m-β-imidazolilalaninato dicobalt (III) heptahydrate ascribed to complex.

POSTER PRESENTATION XXVII.
(PT)

In Vitro Evaluation Of Bisacodyl Tablets

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Bisacodyl, derivatives of diphenyl methane, is stimulant laxatives used to treat constipation. Bisacodyl often is used to prepare patients for radiological examinations. Bisacodyl tablets are enteric coated. The aim of the study was to investigate the quality control of Bisacodyl tablets and to evaluate the in vitro criteria of Bisacodyl tablets. In vitro evaluation was made according to USP XXIII and the EMA, CPMP, "Note for guidance on investigation of bioavailability and bioequivalence". The enteric-coated tablets were tested in simulated gastric fluid during 1 hour for disintegration time, after that same tablets were washed with water and tested in simulated intestinal fluid. In vitro evaluation of dissolution test was made according to USP XXIII. The tablets were tested in 750 ml 0.1 N HCl during 2 hours, after that, same tablets were tested in pH 6.8 phosphate buffer. Bisacodyl tablets were not dissolved in pH: 1.2 and not less than 95% of bisacodyl tablets was dissolved in 30 minutes at pH: 6.8.