IPORSIP-2000

BIOPHARMACEUTICS, PHARMACOKINETICS/PHARMACODYNAMICS (BPK/PD)

POSTER PRESENTATIONS

POSTER PRESENTATION I.
(BPK/PD)

Determination Of Isoniasid, Rifampicin, And Desacetylrifampicin In Plasma By On-line Solid Phase Extraction And Column Liquid Chromatography

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A high performance liquid chromatography (HPLC) method has been developed for the determination of isoniasid, rifampicin, and desacetylrifampicin in plasma samples. Samples were extracted using on-line solid-phase extraction followed by reversed phase HPLC with UV detection at 260 nm.

The drugs and rifampicin metabolite were separate from the organic material automated on-line solid-phase extraction using the sample preparator Marathon II HPLC Pump (Hewlett Packard). Samples were loaded for extraction onto cartridge using 100 mM KH_2PO_4, adjusted for pH 7.5. The mobile phase used for desorbtion from the cartridge and elution onto the analytical column consisted of a linear gradient formed by combination of 100 mM KH_2PO_4, pH 7.5 (eluent A) and 10 mM KH_2PO_4, pH 7.5-acetonitrile (eluent B).

Linear calibration curves were obtained in the range of 0.1 -10 μg/ml for rifampicin and desacetylrifampicin and 0.05-25 μg/ml for isoniasid.

The main advantage of this method used for a bioequivalence study is the high degree of automation allowing a high speed in analysis. The time required for the fully automated analysis of one sample was less than 13 min.

The Effect Of Recombinant Human Erythropoietin On Serum Zinc Levels In Hemodialysis Patients

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One of the most frequently used therapeutic approaches in the chronic renal failure treatment is hemodialysis. Formerly androgens were used to overcome anemia, which is among leading complications of chronic renal failure, they had to be replaced with recombinant human erythropoietin (RhEPO) almost fifteen years ago. RhEPO treatment has been providing promising results with its efficiency, improving quality of life and fewer side effects. On the other hand, the levels of trace elements reduce due to both chronic renal failure and maintenance hemodialysis. This study was designed to evaluate the pharmacokinetic interaction potential of RhEPO with zinc (Zn) during four months. Thirty one adult hemodialysis outpatients participated in this study. Ten of them, not on any drug therapy to interact with RhEPO, named as "Controlled group", and the remainder, on RhEPO therapy, as "RhEPO group". Blood was drawn from the control group at the beginning of the study, and from the RhEPO group at every month for four months. Serum erythropoietin levels were measured by a radioimmunoassay method and Zn status by an atomic absorption method. Serum Zn levels were found higher in the RhEPO group (the difference between means was significant thus, $p= 0.0185$). This observation indicates that RhEPO therapy increases serum Zn levels.

POSTER PRESENTATION III.
(BPK/PD)

Determination Of Metoclopramide In Human Plasma By High-Performance Liquid Chromatography

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Metoclopramide concentration in human plasma were determined by high-performance liquid chromatography (HPLC), using a cyanopropylsilane column and UV detection. The mobile phase consisted of 0.03 M sodium acetate and methanol. The validation of method were demonstrated by the analysis of samples containing 1-200 ng/ml. The method have been applied to the analysis of plasma obtained from human volunteers.

POSTER PRESENTATION IV.
(BPK/PD)

The Influence Of Gentian On The Metabolism Of Peroxide And Free Radical Compound

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The authors (A. Bakuridze, D. Berashvili, T. Dargaeva) have been worked on preparation of Gentian tablets from overgrown parties of Gentiana Lutea with gastroprotective activity.

The majority of pathological states exist with the changes in free radical peroxide oxidation of lipids (FPOL), the level, which is defined with the correlated system activating (FPOL), and the system making an antiradical protection. In various pathologies the destruction of protective system is most frequently observed and the appropriate preparation for therapy is required to have an antioxidative properties.

The results of the analysis performed in recent years indicated the important role of the active condition of lipid peroxide oxidation of biological membrane in the pathogenicity of ulcerous diseases of gastroduodenal zone of GI. However, administration of antioxidant preparations shows expressed antiulcerous effect. Therefore, the main goal of this project was set as to determine not only anti-ulcerous, but also, anti-oxidant activity.

The anti-oxidant activity of Gentian was important with respect to: a) its influence upon the speed of the interception of superoxide radicals, b) at the extent to form the colored complex of malonic dyaldegis with the thyobarbituric acid, c) its influence on the model systems and at the levels of dienes, ketodienes, and Schiff's foundation as well. All these aspects were investigated and these methods of approach allow measurement of possible anti-oxidant quality of tested phytopreparates.

Gentian exhibits immediate potential influence on the process of peroxide oxidation of lipids (POL). This influence is the indicative of its ability to impede POL as on the level of formation of dienes and ketodienes and especially on the level of the formation of Schiff's foundations. Gentian practically reduces the formation of Schiff's foundations one after another and for this reason, it is presented as high capacity anti-oxidant having strong defensive effect.

Among the three methods used, the most accepted method is to produce POL while pre-incubating mitochondria with phytopreparates. The difference among the data indicates the fact that Gentian has wide spectrum of action, which is different, and realizes in different conditions, which is important to use as a remedy.

POSTER PRESENTATION V.
(BPK/PD)

The Influence Of Gentian On Energetic Metabolism Of Lymphocyte Thymus

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To study energetic condition of mitochondria in lymphocytes cell permits itself to determine the influence of biological active substances on their viability and express toxic effects in a number of chemical compounds, in particular on the process of oxidation and phosphoryzation. Three lymphocytes of thymus appears as convenient test object for such research since they are isolated easily in homogenous form without any short comes and the prolonged period is kept in intact condition.

The availability of semiprecious membrane in lymphocytes allows us to conduct experiments with remedies, approaching the in vivo condition.

While studying the influence of Gentian on mitochondria, energetic metabolism of lymphocytes of thymus were investigated with respect to their action on respiration, phosphorilization. Also, the influence of these preparations on the integrity of plasmatic membrane of lymphocytes were studied.

Gentian in high concentrations exerts noticable discontinuous influence on the respiration of lymphs. It is due to the fact that in the presence of the preparations mentioned above, the respiration of lymphs increases against a background of olygomycin and the concentration of DHF is diminished , causing maximum discontinuity of respiration.

The doses of investigated substance can be varied within the wide limits, not exceeding 2.5-3 mg/ml so that higher concentrations expression of negative action on bioenergetics processes take place. Phytopreparation of Gentian exert firm influence on energetic interchange of lymphs, allowing aging process to take place.

POSTER PRESENTATION VI.
(BPK/PD)

Investigations On The Activity Of Aloe Polysaccharide Complex

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To search for a plat with hypoglycemic activity is really a problem for modern pharmacy. In this study aloe leaves were selected. Polysaccharide complexes of arborescent aloe leaves with hypoglycemic activity were isolated. Experiments were conducted to investigate:

- The influence of polysaccharides on blood sugar level on glucose administered white mice.
- The influence of polysaccharide complex on the treatment of alloksanic diabetes.

Polysaccharide complex of aloe possesses hypoglycemic activity. Blood glucose level is reduced to 48% after 7 hours following the administration of aloe.

Experimental diabetes was developed after 48 hours following a momentary injection of Alloksan to animals. Serum glucose levels were compared with the data of intact animals. 4 time increase at 48 and 37% concentration of a-amellas and lipase were determined.

At the same time, dysfunction of pancreas of mice administered alloksan was investigated by activating peroxide oxidation of lipids, on which it is the evidence of increasing speed of reduction in blood glucose levels after 24 hours at 33°C, and 48 hours at 67°C. Polysaccharide samples were administered to the mice with experimentally developed diabetes.

POSTER PRESENTATION VII.
(BPK/PD)

The Validation Of High-Performance Liquid Chromatographic (HPLC) Method Of Pentoxifylline For Pharmacokinetic/Bioequivalence Studies

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Pentoxifylline (PX) is a hemorrheologic agent used in the treatment of intermittent claudication or other circulatory disorders. The major metabolite, hydroxypentoxifylline (MI) is also present in the blood of patients treated with PX. An HPLC method obtained from the literature was further developed in this study. Bioanalytical method validation parameters (accuracy, precision, repeatability, reproducibility, specificity, sensitivity, limit of detection (LOD), limit of quantitation (LQD), calibration curve and its linearity or nonlinearity, analysis range, recovery, stability of the analyte in spiked plasma samples, quality control samples (QC), daily calibration) and system suitability specificiations and tests [capacity factor (k^0), precision-injection repeatability (IR), relative retention (α), resolution (R_0), theoretical plate number (N), bandwidth (t_w), retention time (t_r) were assesed. Acceptance criteria and coeff. of variation (CV) was determined. Linear and nonlinear regression (parabolic, reverse parabolic, log parabolic, log reverse parabolic) were done between peak-height ratio and concentration of PX in plasma samples and the results were compared by goodness of fit. Liquid-liquid extraction method was used for the sample preparation and PX and MI were separated. Retention time of PX was 5.15 min. under 1 ml/min. flow rate. α and R_0 values were determined as 1.15 and 1.40, respectively. There was no interference from endogenous plasma components. The plasma extracts were stable for at least three days when kept at 4°C. General calibration was a ten point plot ranging from 10 to 2000 ng/ml. The best calibration equation was fitted to the log reverse parabolic equation [$\ln C = 0.0661 (\ln h)^2 + 1.48 (\ln h) + 1.90$]. LOD and LOQ were found to be 5 ng/ml and 10 ng/ml, respectively. The average recovery was determined as 103% (CV 7.17%) . This assay is sensitive and rapid enough to be easily applicable to human pharmacokinetic studies. As an application, plasma concentrations and plasma profiles were found using this validated HPLC method in a bioavalability/bioequivalence study of ours.

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Pharmacokinetic Evaluation Of Molsidomine Sustained-Release Hydrophilic Matrix Tablets In Rabbits

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Molsidomine (N-carboxy-3-morpholino-syndonimine-ethylester) is a peripheral vasodilator used for the treatment of angina pectoris. It is soluble in water (2.5 g/l at room temperature). It has a short biological half-life (2.1-2.7 h) in man. For this reason, a number of sustained-release dosage forms have been developed.

The aim of the study was to evaluate the in vivo biopharmaceutic characteristics of newly developed molsidomine sustained-release tablets prepared with mixture of HPMC/pre-gelatinized starch forming hydrophilic matrices. The model was selected. The model hydrophilic matrices were administered orally to rabbits at a dose of 13 mg/kg. Corvaton retard® tablets were used as standard. Plasma molsidomine concentrations were determined by means of a sensitive and specific HPLC-method (limit of detection 1.0 ng/ml) with UV detection (λ = 312 nm). Pharmacokinetic parameters for both tested sustained-release systems: C_{pmax}, t_{max}, AUC $_{0\rightarrow24}$, $t_{1/2}$, k_{el} and MRT, were calculated. They were compared statistically (ANOVA) at $p \leq 0.05$. Results were expressed as the mean values ± SD. The pharmacokinetic data suggest that the pharmacokinetic behavior of molsidomine HPMC/pre-gelatinized starch matrices is similar to that of Corvatan retard tablets, regardless of the differences in the sustained-release system type.

POSTER PRESENTATION IX.
(BPK/PD)

Antiarrhythmic And Antihypertensive Activity Of Novel 7,8-Disubstituted Theophylline Derivatives

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Previously, we reported [1] the synthesis and biological activities of novel 7,8-disubstituted theophylline, one of which, 7-β-hydroxy-γ-(N_4-phenoxy-ethylpiperazine)-propyl-theophylline (CH-1), exhibited potent antiarrhythmic, hypotensive and α-adrenoceptor blocking activity. In continuation of our study on the structure-antiarrhythmic and antihypertensive activity relationships in this series compounds, we synthesized of new CH-1 analogues and tested for electrocardiographic, antiarrhythmic and antihypertensive activity.

The antiarrhythmic effects of novel compounds were examined on rats, using two models of arrhythmia (protection against adrenaline- and barium chloride- induced arrhythmia). Antihypertensive activity was evaluated after single i.v. administration to normotensive rats.

Some of the tested compounds, given 15 min before arrhythmogen in doses of 1/10-1/5 $LD_{50\ i.v.}$, prevented or attenuated the adrenaline-induced arrhythmia, but only compound 7-β-hydroxy-γ-(N_4-phenoxy-ethylpiperazine)-propyl)-8-[2-2'-pirydylethyl)-amino]-theophylline (CH-12) possesses potent antiarrhythmic and a slight hypotensive properties. The biological activity of compound CH-12 was comparable to that reported for CH-1. The results suggest that the antiarrhythmic and hypotensive effect of these compounds depend on the presence of a phenoxyethylpiperazine moiety.

[1] J. Sapa, M. Zygmunt, B. Filipek, S. Charakchieva-Minol, M.J. Mokrosz, G. Chłoń, A. Zejc: Pharmacodynamic studies on novel 7,8-disubstituted theophylline derivatives with antiarrhythmic, antihypertensive, and α-adrenoceptor blocking activity. IPORSIP'98, Abstracts. Acta Pharmaceutica Turcica, Suppl. 1998, 48.

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POSTER PRESENTATION X.
(BPK/PD)

Synthesis, Antiarrhythmic, Antihypertensive, And α-/β-Adrenoceptor Blocking Activity Of Novel Aryloxyalkylamine Derivatives

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In an attempt to develop a new antiarrhythmic and antihypertensive drug, we synthesized a series of aryloxyalkylamine derivatives and tested for antiarrhythmic, and antihypertensive activity as well as for α_1-, α_2 and $\beta_1$adrenoceptor binding affinities. The synthesis of the most active compounds was carried out from appropriate phenoxyethyl bromide with N-subtituted of piperazine, respectively, in toluene, in the presence of potassium carbonate. The tested compounds were isolated and characterized as hydrochlorides. Finally for examined compounds the pKa, logP (partition coefficient) and logD (distribution coefficient) were calculated using the Pallas program. Four compounds, given intravenously and orally, attenuated or prevented the adrenaline-induced arrhythmia, reduced significantly the blood pressure in normotensive anaesthetized rats and reversed the pressor response to adrenaline, and displayed low (nM or μM) binding affinity for α_1-, α_2 and β_1-receptors. The results suggest that the antiarrhythmic and hypotensive effect of this compounds is related to their adrenolytic properties, and that those properties depend on the presence of a phenylpiperazine moiety.

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POSTER PRESENTATION XI.
(BPK/PD)

Synthesis, 5-HT_{1A} And 5-HT_{2A} Receptor Affinity Of New 1-Phenylpiperazinylpropylamine Derivatives Of Purine-2,6-Dione

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Our chemical and pharmacological studies on a group of new derivatives with n-alkyl or ester substituent in the 7-position of 1,3-dimethyl-8-[3-(4-phenyl-1-piperazinyl)-propylamine]-purine-2,6-dione shown that these compounds have 5-HT_{1A} and 5HT_{2A} receptor affinity about of 10^{-7} M and low 5-HT_{2A}/5-HT_{1A} selectivity [1]. As a continuation of our research on the structure-activity relationship we have presently obtained a new set of 1,3-dimethyl-7-arylalkyl-8-[3-(4-phenyl-1-piperazinyl)-propylamine]-purine-2,6-dione derivatives.

The new compounds were evaluated for their affinities for 5-HT_{1A} and 5-HT_{2A} receptors by determining their ability to displace [^{3}H]-8-OH-DPAT and [^{3}H]-ketanserin, respectively, from the rat hippocampus or cortex membrane. We have found that these compounds are new selective 5-HT_{1A} ligands (K_i are within a range of 8 – 50 nM), with moderate affinity for 5-HT_{2A} receptors (K_i = 300-500 nM). We have also showed that the increasing of lipophilic properties by introduction of an arylalkyl moiety enhanced affinity and selectivity for 5-HT_{1A} receptors.

[1] M. Pawłowski, G. Chłoń, J Obniska, A. Zejc, S. Charakchieva-Minol, M. J. Mokrosz: Synthesis, 5-HT_{1A} and 5-HT_{2A} receptor affinity of new 1-phenyl-piperazinylpropyl derivatives of purine-2,6- and pyrrolidine-2,5-diones. Il Farmaco, 2000 (in press).

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Synthesis And Antiarrhythmic Activity Of Some Aminopropanol Xanthone Derivatives

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A new xanthone derivatives of aminopropanol, has been synthesized in the Department of Chemical Technology of Drugs at Medical College of the Jagiellonian University. Continuing our synthesis and studies of new xanthone derivatives which potential activity towards circulatory system has been suggested, we examined aminopropanol xanthone derivatives designated MH-5, MH-6 and MH-7. The present studies were aimed at evaluating their influence on the blood pressure, respiration and therapeutic efficacy in experimental models of arrhythmia induced by adrenaline, calcium chloride, and barium chloride, in rats. All the studied compounds diminished the heart rate from 10 - 20%, lengthened the duration of the P-Q section, the QRS complex and the Q-T interval in the statistically significant way ($p<0.001$). Among the three studied compounds, the aminopropanol xanthone derivatives – MH-7 in the adrenaline model of arrhythmia has the most beneficial antiarrhythmic effects in comparison to control. Among the three compounds studied, the 2-xanthonemethyl derivatives, MH-5 and MH-7 are of particular interest. They combine a negative influence on the coronary blood flow and frequency with a positive inotropic effect. The obtained results permit a conclusion that studies with compound MH-7 should be conducted on isolated rat's heart and on other models of arrhythmia, using various modes of administration.

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POSTER PRESENTATION XIII.
(BPK/PD)

The Influence Of New GABA Monoterpene Homologues On The Central Nervous System Activity In Mice

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Investigations of compounds' SL-1, SL-2, SL-3 on the spontaneous motor activity in mice showed that the compounds SL-2 and SL-3 increased locomotor activity in mice. Nootropil in doses of 100 mg/kg and 200 mg/kg did not change spontaneous locomotor activity in mice. Compound SL-1, did not affect the period of hexobarbital sleeping time. By contrast compound SL-3 reduced the sleeping time induced by hexobarbital by 34.6%. Higher doses of the compound SL-3 (500 mg/kg and 800 mg/kg) did not influence on the duration of hexobarbital induced sleep. Nootropil in doses of 100 and 200 mg/kg prolonged the sleep 55.7% and 77.4%, respectively. Among the tested compounds, only SL-1 in doses of 200 and 400 mg/kg had a significant anticonvulsant activity in the pentylenetetrazol-induced convulsions, in the both used doses it produced decrease in number of animals exhibiting clonic convulsions. The tested compound SL-2 - SL-3 and nootropil did not affect lethality of mice induced by pentylenetetrazol. Summing up, we may say that the carried tests showed that new monoterpene homologues of GABA are virtually not toxic to mice; SL-2 and SL-3 have some stimulating influence on the CNS in mice (enhancing locomotor activity in mice) and reducing (SL-3) the duration of hexobarbital sleep. Moreover SL-1 shows anticonvulsant activity in the pentylenetetrazol-induced seizures. Mechanism of observed effects induced by tested compounds remains unknown. Obtained results may qualify the investigated compounds to undergo extended pharmacological tests, to provide precise estimate on the potential anticonvulsant and/or nootropic activity of the tested compounds.

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Piperazine Xanthone Derivatives As Potential Antiarrhythmic And Hypotensive Compounds

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Continuing our pharmacological studies of new xanthone derivatives which potential hypotensive and antiarrhythmic activity has been suggested, we examined piperazine xanthone derivatives designated MH-10, MH-11 and MH-12. The present studies were aimed at evaluating their influence on the blood pressure and respiration and therapeutic efficacy in experimental models of arrhythmia induced by adrenaline, calcium chloride, and barium chloride, in rats according to the procedure described by Szekeres. The influence of investigated compounds on ECG components, we suggested that activity of MH-10 compound is similar to class 1a antiarrhythmic compounds according to Voughan-Williams, because of prolonged the P-Q and Q-T intervals and extended QRS complex. Compounds administered at a dose equal to 1/5 LD_{50} not produced a significant influence in arterial blood pressure during one hour of observation. They did not have a significant influence on either the amplitude or frequency of respiratory movements. Among the three studied compounds, MH-10 in the adrenaline model of arrhythmia has the most beneficial antiarrhythmic effects in comparison to control. MH-10 prevent the adrenaline-induced blocks and extrasystoles and considerably diminished the mortality in investigated group ($p<0,05$). In the calcium model of arrhythmia the tested compounds were inactive. In barium-induced model of arrhythmia the most effective activity have compounds MH-11 and MH-12. He intensified blocks and the extrasystoles, slightly prevented bigeminy and diminished (60%, $p<0,01$) mortality of animals. During the study of antiarrhythmic activity of some new piperazine xanthone derivatives, the best effect was demonstrated by MH-10 compound.

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POSTER PRESENTATION XV.
(BPK/PD)

Xanthine Derivatives As A New Group Of Adenosine Deaminase Inhibitors

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It is well known that xanthines can imitate adenosine binding to adenosine A1 and A2 receptors. To describe this process three different models (called standard, flipped and N6-C8) were proposed. The base of our studies is the hypothesis that these models can also be used for new compounds modelling which can bind to active centers of adenosine deaminase (ADA) enzymes which metabolise adenosine. It seems that model N6-C8 best describes the interaction between adenosine and receptor. Because of that, we initiated our research. The structure of the synthesized compounds fit to N6-C8 model and structurally the derivatives are similar to EHNA (eryhthro-9-(2-hydroxy-3-nonyl)adenine)- well known deaminase adenosine inhibitor. All obtained compounds are theobromine derivatives with amine group at 8 position and different lipophilic alkyl-, aminoalkyl-, and ketoalkyl-substituent at 1 position. The chain of the substituent with some functional group have a different length from 3 to 8 carbon atoms, with hydroxy- akloxy-, or amino group at the end of a chain. The affinity of tested compounds was better than starting methylxanthines but still weak (micromolar range). We noticed that compounds with 6-carbon atoms chain and with oxygen at the end had higher affinity. Nevertheless we established that the most active already synthesized compounds could be the leading structure for further investigations. Simultaneously, other models : standard and flipped will be verified and the results allow to compare and to find the optimal model for structure programming of new derivatives in this group of methylxanthines.

Determination Of Rifampin And Deacetylrifampin In Human Urine Using HPLC Method

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Rifampin, 3-[[(4-methyl-1-piperazinyl)-imino-]-methyl-rifamycin is a widely used antituberculosis agent. Rifampin is biotransformed in the liver mainly to desacetylrifampin which is an active metabolite, therefore, evaluating the concentration of intact drug and its metabolite has an important role in drug therapy. Several procedures have been described for determination of rifampin and desacetylrifampin in human urine. The extraction steps used are often time-consuming and tedious. In this study we describe a simple and rapid method without any extraction step. Direct injection of diluted spiked urine samples (1:10) was successfully used for determination of rifampin and desacetylrifampin concentration simultaneously, using the HPLC system consisted of a C8 column, mobile phase of acetonitrile-phosphate buffer with flow rate of 0.5 ml/min and UV detection at 334 nm.

The information of validation analysis for rifampin and desacetylrifampin are summarized in the table below:

Drug	Linearity range (μg/ml)	r^2	CV (%) Within day	CV (%) day to day	Quantitation limit (μg/ml)
Rifampin	0.1-20	0.998	6.79	8.57	0.1
Desacetylrifampin	0.5-30	0.989	5.77	5.67	0.5

The Kinetic Evaluation Of Paracetamol Buccal Tablets

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The aim of this study was to offer the dosage form for buccal drug administration developed as an alternative to conventional dosage forms. Buccal tablet was prepared using paracetamol that have high solubility and high permeability and Hydroxypropylmethyl cellulose (E5, E50, E4500) at (1:1) and (1:2) drug:polymer ratios. Furthermore, for formulation optimization study, paracetamol buccal tablets were prepared at different surface area. Using rotating paddle and modified diffusion methods carried out the release of these formulations. The results obtained from in vitro dissolution tests were applied to Zero order, First order, Higuchi, Hixson Crowell kinetic models. Formulations chosen as ideal formulations were evaluated with Peppas equation and the "n" values were determined.

Electronic Format-Biologics Marketing Applications and ARGEFAR

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