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Evaluation of Intraocular Penetration of Levofloxacin after Administration Drop Solution by High Performance Liquid Chromatography and Comparison with Ciprofloxacin

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Abstract

Introduction: Levofloxacin is used to treat a wide variety of bacterial infections. Levofloxacin belongs to a class of drugs called quinolone antibiotics. It works by stopping the growth of bacteria.

Fluoroquinolones are suitable for the treatment of ocular infections because of their excellent bactericidal activities and ocular penetration. Among different types of chromatographic methods, HPLC is found to be more effective to achieve quantification of various compounds. In this project, we studied the aqueous penetration of levofloxacin, in patients undergoing cataract surgery and compared with ciprofloxacin.

Methods: 33 volunteer patients received one drop of levofloxacin every six hours over three days before cataract surgery and on the day of surgery administration of drug was stopped one hour before surgery. Aliquot of Aqueous samples were stored at -20˚C. The samples were thawed, mixed for one minute and centrifuged for 10 minute at 3000 g and 20 µl of the clear supernatant injected into the column of HPLC analysis to be assayed by reversed-phase HPLC method. The mobile phase consisted of a mixture of acetonitrile and aqueous solution. Levofloxacin concentration was evaluated by HPLC method with fluorescence detector. Peak area was selected as the best parameter for plotting calibration curves by an integration pack program.

Results: The sensitive HPLC assay for determination of levofloxacin in human ocular aqueous was validated. Linearity was shown for levofloxacin concentration over a wide range of 1.95×10^{-3}-1.50 µg/ml. The average level of the levofloxacin in the ocular aqueous was found to be higher than the MIC values that have been reported in the literature for a common bacterium. On the other hand, penetration of levofloxacin into aqueous humor in the patients

who received eye drops of levofloxacin is much better than patients who received eye drops of ciprofloxacin. The result of experiments shows that, levofloxacin is a favorable antibiotic because of its ability to penetrate the surgical site with effective concentration.

Conclusion: The results of experiments reveal that administration of levofloxacin as an eye drop can be more effective than ciprofloxacin because of its high concentration detected in human ocular aqueous rather than ciprofloxacin. In conclusion, this protocol is applicable for drug monitoring in patients undergoing prophylactic antibiotic therapy prior to surgery.

Key Words: Levofloxacin, Ocular aqueous, HPLC, MIC.

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A Brief Review of Pharmacokinetics Properties of Monoclonal Antibodies

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Abstract

Introduction: Monoclonal antibodies (mAbs) have been used in treatment of various human diseases since many years ago. High specificity and low toxicity are the main reasons for growing the role of mAbs in effective therapy. Unlike small drug molecules, mAbs are high molecular weight hydrophilic proteins with unique and complex pharmacokinetics properties. The large size of mAbs has restricted their distribution into the tissues by diffusion, renal elimination, and metabolism by hepatic enzymes such as cytochrome P450 (CYP). There are different routes for elimination of mAbs, which may lead to linear or nonlinear pharmacokinetics. Saturable mechanisms are probably important in distribution and elimination processes of mAbs, which save them from degradation.

Conclusion: Like small molecule drugs, absorption, distribution, and elimination processes of mAbs are important for Successful Therapy. This Review aims to provide a brief overview of pharmacokinetics properties of monoclonal antibodies.

Key words: mAbs, pharmacokinetics, therapy.

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a Multifnctional Magnetic Fe_3O_4 CD PHIS Nanocomposite for pH-Responsive Drug Delivery to Tumor Cells

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Abstract

Introduction: Breast cancer is one of the major health problems in the world. Some common ways to treat breast cancer include surgery and chemotherapy .The toxic effects of chemotherapy drugs is one of the problems in treatment.Therefore, introducing new drug delivery systems is necessary for better treatments. In this study, we have developed a pH-sensitive amphiphilic magnetic nanocomposite containing Super Paramagnetic Iron Oxide Nanoparticles (SPIONs) and CycloDextrin bonded to PolyHistidine (PHIS) for targeting drug delivery and Magnetic Resonance Imaging applications

Methods: Pure magnetic nanoparticles were prepared by coprecipitation method, surface modification, and functionalization performed with cyclodextrin polymer and histidine. Physical characterization of nanoparticle and magnetic amphiphilic system was performed by DLS, VSM, NMR, FTIR, XRD, TGA, SEM, and TEM.The Doxorubicin loading and release was estimated using Uv/vis spectrophotometer. Cell cytotoxicity was evaluated in MCF-7 cells using an MTT cell proliferation assay.

Results: FTIR indicated that Fe_3O_4 nanoparticles surface-functionlalized with CycloDextrin (CD) and PolyHistidine have been successfully synthesized.The SEM results showed that the size of magnetic nanoparticles in the core of all our nanoparticles was equidimentionally distributed and around 20 nm. Magnetic curves of Magnetic Nano Particles (MNPs) demonostrated that our drug delivery system was superparamagnetic. Synthesis of CycloDextrin polymer was confirmed by NMR spectroscopy.The doxorubicin release rate increased at acidic pH compared with basic pH

Conclusion: Our results indicated that nanomagnetic amphiphilic system including polymer of cyclodextrin, SPION, and pH-responsive layer to that prepared in this study promises to be a useful candidate and appropriate drug delivery system in cancer therapy.

Key words: cancer therapy, Super Paramagnetic Iron Oxide Nanoparticle (SPION),targeting drug delivery.

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Bioequivalance Study of Danazol 200mg Capsule in Comparison of Danatrol 200mg Capsule in Iranian Healthy Male Volunteers

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Abstract

Introduction: Danazol is a synthetic steroid derived from ethisterone. Danazol is indicated in endometriosis, fibrocystic breast disease, and hereditary angioedema. Danazol suppresses the pituitary-ovarian axis and depresses the output of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).Present study aimed to evaluate the bioequivalence between the generic Danazol capsule and a reference product (Danatrol) when gave as equal labeled doses (200mg) in healthy subjects under fasting condition.

Methods:A randomized, open label, single dose, two treatments, two periods, two sequences, crossover design between 200mg of danazol administration under fasting condition was conducted in 12 healthy, Iranian male subjects. Each subject was assigned randomly to receive a single oral dose of test or the reference formulation of 200mg danazol capsule. Study periods were separated by a 7 days washout period. Blood samples were collected at 0, 1, 2, 3, 4, 5, 6, 8 and 24 hours after drug administration. A sensitive and specific HPLC method was used for quantification of danazol in plasma. Pharmacokinetic parameters were analyzed including C_{max}, T_{max}, $t_{1/2}$ and $AUC_{(0-24)}$.

Results: 12 healthy male adult volunteers were enrolled aged 23.3 ± 1.4 years and weight 64.08 ± 1.2 kg. 11 subjects completed both periods of the study. The mean C_{max} values were 76.09 ± 10.50 and 82.11 ± 12.70ng/ml and also the mean $AUC_{(0-24)}$ were 481.739 ± 65.812 and 547.144 ± 97.832 ng/ml.hr for test and reference formulation respectively.

With 90% CI of the ratios, the range of relative bioavailability for C_{max} and $AUC_{(0-24)}$ between test and reference tablets were 79.9 – 130.5% and 79.03 – 126.25%

Conclusion: Based on variability of danazol pharmacokinetics, the limits of acceptance of 70–142.9% for Cmax and 80–125% for $AUC_{(0-24)}$ were established to conclude bioequivalence.

Based on the results of this study, it is concluded that the formulations of danazol tested are bioequivalent.

Keywords: Danzol, bioavailability, HPLC.

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A Review on Different APIs Used in Fast Dissolving oral Films

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Abstract

Introduction: Fast dissolving oral films (FDOFs) are the most advanced types of oral solid dosage form due to more flexibility and comfort. These films improve the efficiency of APIs by dissolving in about less than a minute in oral cavity after the contact with less saliva compared with fast dissolving tablets, without chewing and need of water for administration.

Quickly releasing makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. This fast dissolving drug delivery system (FDDS) is suited for the drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and also make it cost effective. Orally fast dissolving film is the type of drug delivery system which when placed in the oral cavity, disintegrate or dissolve within few seconds without the intake of water. OFDFs are very similar to postage stamp in their shape, size and thickness prescriptions of fast dissolving films have been now approved in US, EU and Japan which are the three major regions. These approved films, have potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin film market will grow significantly. However, not all drugs can be incorporated into this dosage form. Therefore, it is necessary to make a special classification of drugs used in this dosage form. The disadvantage of OS is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active can be improved up to 50% per dose weight.

Conclusion: Oral fast dissolving films have emerged as revolutionary trend and extensive research activities involving various categories of drug are going on in this field. A diverse group of drugs could be produced by fast-

dissolving buccal films, whereas those drugs which a higher dose is needed or their rapid absorption is harmful for the body [for instance heart attack probability increase] are not suitable for this special dosage form. Advantages are over other dosage forms like enhanced bioavailability, and faster action, so it can be concluded that the oral films with so many advantages and high patient compliance have glowing futuristic opportunities.

Key words: Buccal drug delivery, Fast dissolving oral films, Oral strips.

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Amget® a Free Package Based on R for Population PK/PD: Advantages and Disadvantages

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Abstract

Introduction: Pharmacokinetics (PK) and pharmacodynamics (PD) of a drug product through population-based approaches and mathematical modeling of the relationships between exposure, safety, and efficacy are essential for the approval process at regulatory agencies. R® is statistical language developed from S®. S® is language is originally implemented as Fortran libraries. R was created in New Zealand by Ross Ihaka and Robert Gentleman in 1991. The last version of R version 3.0.2 is released in December 2013. The most famous population-based softwares for PK/PD are such as: NONMEM, ADAPT, Monlix and S-ADAPT. AMGET is an external package written in the open source R programming language, was developed specifically to support efficient post processing of ADAPT 5 runs, as well as NONMEM and S-ADAPT runs. AMGET was written by Guiastrennec 2012. AMGET 1.0 is available online for free download on the Comprehensive R Archive Network (CRAN) website at http://cran.r-project.org. The optimization of population PK and/or PD models can be a time-consuming process, largely dependent on the number of observations and parameters, the processing power available, and the software algorithm used. On the other hand, the time required to create diagnostic plots for each model run is highly dependent on the skill of the user. Automated graphing tools, such as the ones provided in AMGET, save the user a

considerable amount of time by streamlining very repetitive tasks, and also decrease the probability of errors by manipulating the data automatically and consistently rather than manually

Conclusion: This package has advantages and disadvantages. Advantages are such as: 1) this package is free, 2) are able analysis population are non-population-based model for Pharmacokinetic and Pharmacodynamic, 3) AMGET is the powerful package for all graphical curve such as: spaghetti plot and so on, 4) seven different GOF plots can be created: observations vs. individual and population model predictions on both linear and logarithmic scales, standardized residual vs. time, and standardized residual vs. individual and population model predictions, 5) are able in post-hoc analysis. Disadvantages are few such as: 1) is based on R, and user should write code for analysis, 2) is new package and was not public familiar, 3) every export for ADAPT and user should now a little about this software. Although this software has advantages and disadvantages we suggest this software for the Iranian system pharmacology researchers.

Key words: Buccal drug delivery, Fast dissolving oral films, Oral strips.

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Biodistribution of Solid Lipid Nanoparticles Incorporated into In-situ Forming Gel as a Controlled Nanoparticle Delivery System; Effect of Probe Lipophilisity

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Abstract

Purpose: Nanoparticulate drug delivery systems, including solid lipid nanoparticles (SLNs), have attracted a lot of attention over recent years. Such systems face different challenges such as rapid clearance by reticuloendothelial system after in-vivo application. In an attempt to solve this problem, this investigation aimed to prepare an in-situ forming SLN-containing poloxamer gel for controlled nanoparticle delivery.

Method: SLN formulations, containing lipophilic fluorescent probes (DiR and Nile Red), were prepared by diluting a warm oil-in-water (O/W) microemulsion of stearic acid, surfactants, and cosurfactants in cold water. After

purification, the mean particle size and zeta potential of the particles were determined and encapsulation efficacy was measured. Nanoparticles were then dispersed in a thermosensitive polymer solution (sol) at 4°C. Sol-gel transition temperature of the system was investigated 4 to 37°C. In vitro release of the probes from the nanoparticles and also release of nanoparticles from the gels after gel erosion were evaluated at 37°C. Probes solution, nanoparticle aqueous dispersion and sol-gel systems containing SLNs (SLN-gel) were injected intraperitoneal into mice. Then organ distributions of probes were then evaluated using small animal imaging Kodak F-pro system.

Results: size and zeta potential of the SLN nanoparticles were found to be around 200 nm and -50 mV respectively. Sol-gel transition temperatures of plain and nanoparticle-loaded systems were found to be 28 ± 0.1°C and 30 ± 0.5 °C respectively. Release and erosion studies indicated that the main release mechanism of the nanoparticles from the gels in-vitro is erosion and that the leakage of probes from the nanoparticles is negligible in-vitro. Loading into in-situ forming system showed nonsignificant effect on release behavior of probe from nanoparticles. Body imaging studies revealed that SLN-Gel system provides a delayed but prolonged delivery for both probes in comparison to aqueous dispersion of nanoparticles and aqueous solution of the probes. In addition, results indicated that DiR with logP of about 20 shows more liver uptake than Nile Red with logP of about 5. This might be due to a difference between molecular release behaviors of two probes in the body.

Conclusion: Present results showed that the prepared system has proper thermoresponsive properties and delivers nanoparticles in a controlled manner. Such systems can be used for drug targeting and increasing the duration of action of nanoparticles.

Keywords: Controlled drug delivery, Imaging, SLN; Solid lipid nanoparticles; Sol-gel systems.

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Biological Tests Methods about Pharmaceuticals and Determine Pharmacokinetic and Toxicokinetic Parameters Indicating Drug Metabolism

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Abstract

Introduction: To produce a new pharmaceutical product with the use of international source data, the main thing we need is gather a perfect collection of information of effective materials of the product. To avoid toxicity, pyrogenicity, carcinogenicity, sensitivity and irritation, it is important to evaluate candidate materials with biological tests in order to simulate the inner conditions such as Toxicokinetic and Pharmacokinetic analyses, Immunogenicity, Antimicrobial Effectiveness Test (AET), Rabbit Pyrogen Test and bacterial endotoxins. Metabolism assays and drug delivery studies are the ones in which the candidate material (in radiolabeled form) should be injected into the bodies of animals which are physiologically like humans. The evaluation of biocompatibility, toxicity factors, protection and maintenance of samples and monitoring of testing environment are very efficient to develop a pharmaceutical with good quality; so in most laboratories, environmental monitoring is unavoidable. Most tests are developed in an exploratory way and will be performed depending on the standards of each sample test. In this article, it is tried to achieve important parameters in producing and developing pharmaceuticals with more efficiency through introducing different biological tests.

Conclusion: It is important to support the development and manufacture of small molecule and biologics in vivo toxicological studies about pharmaceuticals. Pharmacokinetic (PK) and toxicokinetic (TK) analyses are key activities to drug development. ADME (Absorption, Distribution, Metabolism, and Excretion) studies provide a way to evaluate the bioavailability, tissue distribution, active metabolite formation, and elimination of test materialsby using a radiolabeled compound. An immune response may impact a drug's safety and efficacy; so it is possible to determine the toxicity of different cells both qualitatively and quantitatively. We can also conduct the safety test to detect toxic contaminants.Gathering the data of the stability test on drug products is a necessary step in the process of drug approval to determine an overall stability. Antimicrobial Effectiveness Test is performed to determine whether the chosen preservative is appropriate for a product formulation. The LAL (Limulus Amebocyte Lysate) Assay is an"*in vitro*"one used to detect the presence and concentration of bacterial endotoxins in biological products. Water is widely used as a solvent in the pharmaceutical products.Chemical purity of water samples can be assessed by Total Organic Carbon testing. For the production of safe pharmaceuticals, manufacturing environment conditions are extremely important. By controlling and monitoring the manufacturing environment, potential biological compounds contamination can be limited.

Keywords: Biological tests, Biocompatibility, Metabolism, Pharmaceutical, Pharmacokinetic.

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Brush Border Membrane Vesicle (BBMV) and Caco-2 Cell Lines: Two Experimental Models for Evaluation of Absorption Enhancing Effects of Saponins, Bile Salts and Synthetic Surfactants

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Abstract

Introduction: Drug administration through oral rout is the most preferred route by patients and has many advantages including, being proper for children, ease of administration, avoidance of pain and elimination of possible infections caused by unsuitable use of needles. Intestinal absorption of water-soluble drugs is usually limited due to their poor membrane permeability characteristics. The aim of the study was to investigate the influence of absorption enhancers in uptake of hydrophilic compounds. **Methods:** The permeation of the two hydrophilic drug models gentamicin sulfate and 5(6)- carboxyfluorescein (CF) across the brush border membrane vesicles (BBMVs) and Caco-2 cell lines were evaluated using total saponins of *Acanthopyllum squarrusom* (ATS*), Quillaja saponaria* (QTS), sodium lauryl sulfate (SLS), sodium glycocholate (SGC), sodium taurodeoxycholate (STDC) and Tween 20 as absorption enhancers. Transepithelial electrical resistance (TEER) measurement was utilized to assess paracellular permeability of cell lines. Confocal laser scanning microscopy (CLSM) was performed to obtain images of the distribution of CF in Caco-2 cells. **Results:** Tween 20 at concentration 3.33 µg/ml could increase gentamicin about 95.08±1.70%. It was observed that all of the permeation enhancers could improve the uptake of CF through Caco-2 cells. These compounds were able to loosen tight junctions, and increase paracellular permeability. CLSM confirmed the effect of these absorption enhancers on CF transport across Caco-2 lines and showed increased Caco-2 permeability *via* transcellular route. It was also confirmed that the decrease in TEER was transient and reversible after removal of permeation enhancers. The flux of gentamicin and CF were significantly enhanced when permeation enhancers was applied. They could increase the permeability of hydrophilic compounds *via* both the paracellular and transcellular route. **Conclusion:** It is suggested that these absorption enhancers can

potentially be used to increase the oral bioavailability of therapeutic drug molecules towards intestinal epithelial cells.

Key word: absorption enhancers, brush border membrane vesicles, Caco-2 cell, transepithelial electrical resistance.

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Changes in CYP2E1 Activity after MDMA Administration Using Chlorzoxazone as a Probe Drug in Rat Liver Perfused Model

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Abstract

Introduction: Social use of ecstasy has been known as one of the most prevalent of drug abuse among youth during recent decades because of happiness and spree feelings.The metabolic reactions of this material results in ortho-Quinone formation which is able to perturb, similar to Quinone structures which are able to react with intercellular nucleophile structures such as intercellular macro molecules and enzymes in cells leading severe cellular damage in liver, kidney, and heart organs. Thus, any change in metabolic processes due to simultaneous use of other materials is important and can be significant in incidence of toxic side effects of these drugs. In this work, the possibility of metabolic inhibition incidence on 2E1 cytochrome, as a CYP iso-enzyme having no direct role in ecstasy metabolism, was investigated.

CYP2E1is involved in metabolism of a variety of materials including ethanol and drugs such as Chlorzoxazone, Acetaminophen, volatile anesthetics, and environmental carcinogens. Among these drugs, Chlorzoxazone is widely used as an appropriate probe to determine this enzyme activity. Thus, in this study, Chlorzoxazone was chosen as probe substance to study the activity of mentioned iso-enzyme after perfusion of isolated rat liver with different concentrations of ecstasy in perfusion rat liver model.

Methods: Chlorzoxazone was chosen as probe substance to study the activity of mentioned iso-enzyme after perfusion of isolated rat liver with different concentrations of ecstasy in perfusion rat liver model.

Results: A dose dependent effect of ecstasy on CYP2E1activity despite the fact that no considerable change was observed in parent drug concentration after exposure to 300 ng./ml of ecstasy, the metabolite concentration showed about 47% increase after exposure to to 300 ng./ml of ecstasy. After exposure of perfused liver to 600 ng/.ml of MDMA, the drug concentration was increased by 20% while the metabolite concentration was decreased by about 25%.

Conclusion: the ecstasy may damage the activity of liver enzymes, which are not directly involved in its metabolism, probably through formation of active ortho-Quinone compounds besides the inhibition of enzymes directly involved in its metabolism and hence the drug interaction is remarkable after its abuse.

Key words: Ecstasy, Metabolism, Perfused rat liver.

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Comparison of Different Heteroscedastic Calibration Curve Models of Propofol in Human Plasma Determined by HPLC Method: an Application for pharmacokinetic studies

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Abstract

Introduction: Propofol (2, 6-diisopropylphenol) is a fast acting anesthetic drug which is a very common drug for induction and maintenance of anesthesia and also for sedation in intensive care unit patients. Pharmacokinetics of propofol has been the subject of several studies. It shows a high degree of inter-individual variability and could be affected by factors such as patient age, sex and genetic polymorphism.A fully validated, accurate and precise method for measurement of propofol in biological fluid is necessary for pharmacokinetic investigations on this drug. Since the quality of the bio analytical data is completely under the influence of the calibration model, a well-designed and interpreted calibration curve in required for any analytical methodology.The aim of this study was to

select the best calibration model for determination of propofol plasma concentration in future pharmacokinetic studies by high-performance liquid chromatography method.

Methods: Determination of propofol in plasma after deproteinization with acetonitrile containing thymol (as internal standard) was carried out on a C18 column with a mixture of acetonitrile and trifluoroacetic acid 0.1% (60:40) as mobile phase which delivered at the flow rate of 1.2 mL/minute . Fluorescence detection was done at the excitation and emission wavelengths of 276 and 310 nm, respectively. After fitting different equations to the calibration data using weighted regression, the adequacy of models were assessed by lack-of-fit test, significance of all model parameters, adjusted coefficient of determination (R2adjusted) and by measuring the predictive performance with median relative prediction error and median absolute relative prediction error of the validation data set.

Results: The best model was a linear equation without intercept with median relative prediction error and median absolute relative prediction error of 4.0 and 9.4%, respectively in the range of 10-5000 ng/mL. The method showed good accuracy and precision.

Conclusion: Application of the weighted least squares regression method with a proper weighting factor could result in better estimation of the unknown concentration near the lowest level of the analyte in the calibration curve (limit of quantitation). On the other hand with the weighted regression model, it is possible to cover the entire range of calibration curve (up to 500 fold) using one simple equation with good accuracy and precision.Also the presented statistical framework could be used to choose the best model for heteroscedastic calibration data for analytes like propofol with wide range of expected concentration in any pharmacokinetic study.

Keywords: Calibration; Heteroscedasticty, Propofol, Weighted least squares regression.

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System Pharmacology and Pharmacometrics

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Abstract

Introduction: Systems pharmacology is the application of systems biology[1], the computational and mathematical modeling of complex biological systems, using a holistic approach (holism instead of the more traditional

reductionism) principles to the field of pharmacology. Pharmacometrics try to help systems pharmacology as a branch of science concerned with statistics and mathematical models of biology, pharmacology, disease, and physiology used to describe and quantify interactions between xenobiotics and patients (human and non-human), including beneficial effects and adverse effects[2]. It is normally applied to quantify and produce drug, disease and trial models and then with these models drug development, regulatory decisions and rational drug treatment in patients will improve. It seeks to understand how medicines work on various systems of the body. Pharmacometrics and systems pharmacology uses bioinformatics and statistics techniques to integrate and interpret these networks. There are many softwares as population softwares e.g. Monolix, NONMEM, Symcyp, Winnonmix that are trying to improve these research types.

Conclusion: A major focus of pharmacometrics is to understand variability in drug response. Variability may be predictable (e.g. due to differences in body weight or kidney function) or apparently unpredictable (a reflection of current lack of knowledge). With producing bigger and more precise databases (considering metabolism, membranes, pharmacogenetic, pharmcogenomics, drug interactions, food - drug interactions, formulation effect, etc., database articles is recommended in this field (3)) and related topics in pharmaceutics we can move to achieve better understandings of drug variability. With proper modelling considering proper databases more accurate and individual dosage regimens and clinical outcomes could be established. Some examples will be discussed.

Keyword: bioanformatic, modeling, pharmacology.

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Comparison of Regional Brain Distribution of Typical and Atypical D2 Antagonists

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Abstract

Introduction: The treatment of schizophrenia with D_2-antagonists is often problematic due to the extrapyramidal side effects. This is due to D_2 receptors are blocked not only in the frontal cortex (site of action) but also in the

striatal area. The pharmacological effects are related to unbound concentration, in both plasma and in the brain. Therefore, the extent of unbound drug transport across the BBB is measured through $K_{p,uu}$, a ratio of brain interstitial fluid to plasma unbound drug concentrations at steady state. The aim of this study was to determine whether there are any regional differences in the extent of drug transport across the BBB, assessed by $K_{p,uu}$ between the following regions (*i*): hypothalamus, cerebellum, cortex, striatum, hippocampus, brainstem and the spinal cord for D_2-antagonists, haloperidol (typical) and risperidone and paliperidone (atypical).

Methods: The unbound ratio in brain to plasma (of $K_{p,brain}$) was calculated from the results of *in vivo* iv infusion studies in rats and fraction unbund ($f_{u,brain}$, $f_{u,plasma}$) was measured using equilibrium dialysis.

Results: There were significant differences in $K_{p,uu,brain,i}$ ($p \leq 0{,}0001$) between the brain structures for haloperidol versus risperidone and paliperidone. The mean $K_{p,uu}$ values for haloperidol were varying between 0.7± 0.1 (brainstem) and 1.4 ± 0.15 (cortex). $K_{p,uu}$ for paliperidone varied between 0.02 ± 0.007 (hippocampus) and 0.07 ± 0.02 (cortex). Individual regions that varied significantly from the others were striatum and cortex for both paliperidone and haloperidol as well as hippocampus for haloperidol. These regions all had higher $K_{p,uu}$ than the others. Haloperidol had $K_{p,uu}$ values around unity which indicate that it is mainly distributed across the BBB through passive diffusion. Risperidone and Paliperidone are known to be a substrate for the efflux transporter P-glycoprotein, had low $K_{p,uu}$ values .

Discussion: The observed regional differences in BBB transport for haloperidol versus risperidone and paliperidone, with higher $K_{p,uu}$ in cortex and striatum, could provide a better understanding of both the effects and side effects of haloperidol and paliperidone. The observed higher BBB transport in striatum and cortex could indicate that these regions are less protected by the BBB than the other studied regions. These results are offering a promising lead for further research in the area which may provide a better understanding of the pharmacokinetic-pharmacodynamic relationship of drugs targeting the CNS as well as clinical decision-making in the treatment of schizophrenia.

Keywords: brain distribution, D2 antagonists, regional.

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Design, Optimization and Evaluation of Orally Disintegrating Tablet of Meloxicam Using its Menthol Based Solid Dispersions

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Abstract

Introduction: Meloxicam (MLX) is known as a non-steroidal anti-inflammatory drug and a selective cox-2 inhibitor. Various studies indicated that this drug can be used as one of the main treatments of rheumatoid arthritis and osteoarthritis. This drug shows some problems such as low water solubility that lead to poor bioavailability after oral administration and high onset of action. Preparation of MLX as solid dispersion (SD) represents a good method for the enhancement of its solubility. Moreover preparation of orally disintegrating tablets (ODT) from MLX SDs could decrease MLX onset of action. In addition ODT is a suitable dosage form for improving care for elderly patients with osteoarthritis that suffering from dysphagia. In the current study, we aimed to improve the solubility of MLX by preparation of its SDs and decrease its onset of action after preparation of MLX ODT using its prepared SDs.

Methods: MLX SDs were prepared by solvent evaporation method. MLX, PVP k30 as hydrophilic carrier and crospovidone and SLS as solubilizer and stabilizer with different ratios were dispersed in molten menthol as solvent. Menthol was separated from prepared SDs using freeze drying. The solid state of prepared SDs was characterized using differential scanning calorimetry (DSC) and X-ray diffraction (XRD). The saturation solubility of prepared SDs was determined in water. The optimum SD with highest saturation solubility was used for preparation of MLX ODT. ODT were prepared by direct compression method by using crospovidone as superdisintegrant and optimized by 2^3 factorial designs. The effect of the superdisintegrant concentration, mannitol/avicel ratio and the level of compression force were evaluated on the disintegration time, hardness, friability and percent of dissolved MLX after 30 min of prepared MLX ODTs.

Results: DSC and XRD analysis approved amorphous form of MLX in SDs. The optimum SD, which consists of MLX, PVP, crospovidone and SLS at ratio 1:1:1:0.03, showed the highest saturation solubility (12.59±1.2 mg/ml). The optimized ODT formulation selected by the Design-Expert software was prepared by 10% of superdisintegrant, mannitol and avicel at ratio of 2 and with a high level of compression force. Optimised formulation showed hardness

(48±4.35 N), friability (0.81±0.1%).This formulation provided rapid disintegration in 19±2 seconds which 82.14±2.4% drug released within 30 minutes.

Conclusion: Present study demonstrated an effective method for preparation of suitable dosage form of meloxicam with improved solubility and onset of action. This dosage form could be suitable for administration in elderly patients with dysphagia.

Keywords: meloxicam, menthol based solid dispersion, Oral disintegrating tablet.

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Development and Characterization of Ocular Sustained Release Matrix Containing Acyclovir

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Abstract

Introduction: For the treatment of ocular keratitis acyclovir, as a highly specific inhibitor of herpes virus replication, is applied topically into the eye. The objective of this study was formulation and evaluation of bioadhesive and biodegredable acyclovir ocular matrix as ocular insert for prolonged local drug action.

Methods: Inserts containing acyclovir were prepared using a watersoluble polymeric matrix of polyvinyl alcohol and cellulose derivatives and chitosan by the film casting method. The ocular inserts were characterized for thickness, uniformity of weight, drug content uniformity, % moisture absorption or moisture loss, and surface pH. The *in vitro* Permation studies were carried out by putting insert on sheep eye fixed between donor and receptor compartment.

Results: Drug release was found to be affected by the type and concentration of polymer. Water uptake study, dissolution rate of the polymers and viscosity measurements could explain the different release profiles of the drug from the polymers. Chitosan was chosen for its significant sustained release and good bioadhesive property. The

matrix showed a good permeation into the cornea in comparison to eye solution in sheep eye model. Storage of the prepared inserts at 25˚C for six months showed no change.

Conclusion: The physicochemical properties of inserts were found in satisfactory range. The formulation F3 showed maximum *in vitro* drug release profile, better sustained action. Chitosan, as a sustained drug release polymer showed promising sustained action *in vitro* condition in the sheep eye model. Stability studies showed no significant changes in the inserts which suggest that the inserts were stable. However, more exhaustive preclinical and clinical studies need to be performed to show further information about these approaches.

Key words: Acyclovir, Insert, In vitro sheep model release, ophthalmic drug delivery.

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Drugs Used in Cancer Chemotherapy

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Pharmacogenetic Markers for Oxaliplatin and 5-fluorouracil (5-FU)

Abstract

Background and aim: Pharmacogenetics is the study of genetic variations in drug response which are determined by specific genes involved in the metabolism of drugs. Adverse drug reactions are one of the leading causes of death in the United States that pharmacogenetics studies can reduce mortality caused by adverse drug reactions. Indeed pharmacogenetics is a new cornerstone in medicine. Pharmacogenetics studies in cancer chemotherapy is very important because can it can make chemotherapy safer and more effective for an individual patient. Application of pharmacogenetics in cancer chemotherapy drugs can predict prognosis of the drug response and incidence of side effects. Oxaliplatin and 5-fluorouracil (individually or in combination) are among drugs which are the focus of pharmacogenetics studies in the world because they are extensively used in treatment of many solid tumors. The aim of this review study was to identify candidate genes for prediction of fluoropyrimidine and Oxaliplatin toxicity and treatment outcomes.

Methods: we used PubMed and science direct database. The key words used are as follows: gastrointestinal cancer, drug resistance, 5-fu, oxaliplatin, side effect, survival, clinical trial in combination with the words: Studies, meta

analysis and response. In this review, we found genes that were introduced as pharmacogenetics markers and responsible for metabolism of these two drugs and also the variants of these genes that cause inactivation or reduction of enzyme activity. These genes were stated as pharmacogeneticsmarkers : Thymidylate synthase(TYMS), dihydro pyrimidine dehydrogenase (DPYD) methylene tetrahydro folate reductase(MTHFR), Glutathione S-transferases (GSTP), excision repair cross complementation group 1 (ERCC1) and xeroderma pigmentosum group D (XPD).

Result: Some of these polymorphisms had a significant impact in the treatment process including TYMS 3-untranslated region del/del genotype that substantially increased the risk of severe toxicity in carriers of AA genotype. GSTP1 rs1695 increased neurotoxicity. MTHFR c.1298CC homozygous variant genotype predicted hand–foot syndrome. DPYD sequence variants (c.1905þ1G4A, c.2846A4T, c.1601G4A and c.1679T4G) were significantly associated with grade 3–4 toxicity. Carriers of the CC genotype in XRCC1 rs25487 had decreased risk of neuropathy.

Conclusions: We identified a panel of clinically useful pharmacogenetic markers that predict toxicity to fluoropyrimidin and oxaliplatin drugs used in cancer chemotherapy. Patients carrying these variants are good candidates for dose reduction or stopping treatment.

Keywords: pharmacogenetic markers, 5-fluorouracil, oxaliplatin, chemotherapy, polymorphism.

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Effect of Cinnamon on Liver Metabolic Capacity in Rats

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Abstract

Introduction: Cinnamon has a long history as an herbal remedy. It is the brown bark of the cinnamon tree; it is unique healing ability come from its three essential oils plus a wide range of volatile substances. Anti-clotting, anticancer, Anti-Microbial, antioxidant, inhibition of Alzheimer's disease actions and Blood Sugar Control were

investigated largely. Besides the beneficial effects and boosting up lipid metabolism, it may affect drug metabolism and it is advantageous to understand.

Methods: The objective of this study was to define the pharmacokinetic changes of tramadol and its main metabolites in ex vivo perfused liver study in rat model. Six male Sprague-Dawley rats were feed one week with 100mg daily dose of cinnamon by NG-tube. Then their liver perfused by 500ng/ml tramadol, the drug which metabolized by cytochrome P-450 isoenzymes 2D6, 2B6 and 3A4. The concentration of tramadol and its three main metabolites O-desmethyltramadol (M1) and N-desmethyltramadol (M2) and N, O-didesmethyltramadol (M5) were determined in perfusate samples by a rapid HPLC method.

Results: The results of this study showed that pharmacokinetic of tramadol and its three metabolites are influenced by cinnamon. There was a significant difference between AUC (0-180 min) as well as metabolic ratios of metabolites when control and treatment groups were compared. This finding might be of clinical importance as the use of cinnamon as an herbal medicine is growing up.

Conclusion: Some diabetic patient have to use Tramadol for their neuropathy, our findings may help for considering how tramadol metabolism changes and its dose adjustment.

Keyword: cinnamon, liver metabolism, pharmacokinetic, tramadol.

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EGFR Targeted Thermosensitive Liposomes: a Novel Multifunctional Platform for Simultaneous Tumor Targeted and Hyperthermia Responsive Drug Delivery

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Abstract

Introduction: The epidermal growth factor receptor (EGFR) is a promising target for anti-cancer therapy. The aim of this study was to design thermosensitive liposomes (TSL) functionalized with anti-EGFR ligands for targeted

delivery and localized triggered release of chemotherapy. For targeting, we used EGFR specific peptide (GE11) as well as Fab´ fragments of cetuximab.

Methods: Calcein and doxorubicin loaded non-targeted as well as ligand decorated TSL were prepared and extensively characterized in terms of size, PDI, morphology, temperature- and time-dependent release profiles. The prepared multifunctional nanoparticles were also characterized in regards to cellular binding, uptake, subcellular localization and cytotoxicity studies via flow cytometry, live-cell confocal imaging and cell viability assay in cell lines with different expression of EGFR under normothermic (NT) and hyperthermic (HT) conditions. The effect of ligand density of GE11 and Fab´ on in vitro tumor targeting was investigated.

Results: Ligand conjugation did not significantly change physicochemical characteristics of liposomes. Calcein and doxorubicin loaded Fab´-decorated TSL (Fab´-TSL) showed adequate stability at 37 °C in serum and a temperature dependent release at >40 °C. Fab´-TSL can specifically and more efficiently bind to the EGFR overexpressed cancer cells compared to GE11 modified TSL. FACS analysis and live cell imaging revealed efficient cellular association as well as dramatic intracellular cargo release upon hyperthermia. Under competitive free cetuximab as well as low temperature condition cellular uptake of Fab´-TSL was markedly reduced ($P < 0.01$), indicating involvement of EGFR mediated energy-dependent uptake process. Fab´-conjugation and hyperthermia induced enhanced tumor cell cytotoxicity of doxorubicin loaded TSL. The relative cytotoxicity of Fab´-TSL was also correlated to EGFR density on the tumor cells.

Discussion and conclusion: Specific binding capacities, internalization, intracellular trafficking, HT mediated intracellular release properties and cytotoxicity studies in EGFR expressing cell lines proved that this new combinatory active targeting and triggering strategy by Fab´-TSL may offer a promising approach for selective treatment of EGFR high-expressing tumors while restricting drug delivery to the tumor site by localized HT.

Keywords: Cetuximab, EGFR, GE11 peptide, Hyperthermia, Targeting, Thermosensitive liposomes.

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Enhanced Oral Bioavailability of Repaglinide in a Poloxamer 407-Modified Nanoemulsion Drug Delivery System

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Abstract

Introduction: Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Repaglinide (RPG), a member from meglitinide class, is a post prandial glucose regulator used in management of type II diabetes. It is practically insoluble in water (solubility of 34 μg/mL) with a half life of 1 hour. Moreover, RPG reported to possess low and variable bioavailability of 50% with high inter-individual variability in plasma concentrations. These problems results into poor bioavailability after oral administration. Nanoemulsions containing small oil droplets (d < 100 nm) are finding increasing interest as drug delivery systems particularly, in increasing the bioavailability of lipophilic active agents. The aim of present study was to develop and evaluate of RPG loaded in a poloxamer 407-modified nanoemulsion for enhancement of drug bioavailability.

Method: The O/W nanoemulsions were prepared by adding of oil phase (containing the drug and surfactants) into aqueous phase under high speed homogenization. The hydrodynamic sizes, polydispersity, zeta potentials, drug-loading content (DLC) and encapsulation efficiency (EE) of the prepared nano-structured systems were determined. The *in vitro* release kinetics of RPG was also investigated in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). Finally, after oral administration and blood sampling through the implanted cannula in jugular veins of SD rats, pharmacokinetic of RPG was investigated.

Results: The mean diameters, PDI, and zeta potential of RPG-nanoemulsion droplets were about 85 ± 2.5, 0.14, and –33 mV, respectively. The EE and DLC were 98% and 2±0.25 mg/ml, respectively. The optimized formulations were stable for the effect of centrifugal stress, thermal stress, dilution stress and storage for four months. The cumulative release of RPG from nanoemulsions could reach up to 38% after 1 h in GIF while it was 46% after 12 h in SIF. From the pharmacokinetic study, the Cmax and $AUC_{0\text{-}12h}$ of RPG-nanoemulsion were 4.63 and 3.88 -fold increased in comparison to free drug.

Conclusion: In this study, nanoemulsion formulation of RPG was developed with good drug release profiles in both SGF and SIF. The prepared formulations showed significant increase of plasma concentration of RPG for 12 h in comparison to free drug. In conclusion, the poloxamer 407-modified nanoemulsion was able to enhance both the rate and extent of drug dissolution and absorption with possible avoidance of the presystemic metabolism.

Keywords: Bioavailability, Nanoemulsion, Poloxamer 407, Repaglinide.

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Evaluation of the Rout Dependency of the Pharmacokinetics and Neuro-Pharmacokinetics of Tramadol and Its Main Metabolites in Rat

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Abstract

Introduction: Tramadol hydrochloride is an orally-active and centrally-acting opioid-like analgesic used for the treatment of moderate to severe pains. It has three main metabolites O-desmethyltramadol (M1), N-desmethyltramadol (M2) and O, N-didesmethyltramadol (M5).

By considering the importance of tramadol in pain relief and its frequent use by patients, drug abusers and addicted people, the ability to determine tramadol and its metabolites in plasma and cerebrospinal fluid is of great importance in order to calculate pharmacokinetic parameters and to estimate the risk of toxicity and the possibility of drug addiction.

Methods: A pharmacokinetic approach was applied in two groups of rats which were administered tramadol intravenously or intraperitoneally. Five male Wistar rats were used in each group to collect plasma and CSF samples at 5-360 min following tramadol dose of 20 mg/kg. The sample concentrations were determined by using a validated HPLC method.

Results: The result showed that, firstly, tramadol and its metabolites (M1 and M2) penetrate the CSF to a lesser extent compared with the plasma. Secondly, M5 due to its high polarity hardly penetrates the CSF. Thirdly, there is no significant difference between the AUC_{0-t} of tramadol in plasma (414043.67±149246.36 ng.min/ml) and CSF

(221810.59±83023.35 ng.min/ml) in IP group. Fourthly, the amount of M1 and M2 in CSF showed no significant difference following the different routes of administration.

Conclusion: By considering the same amount of M1 in CSF following IV and IP administration and also its main analgesic effect, it seems that both routs of administration may cause the same amount of analgesia.

Key words: Area under the curve, Cerebrospinal fluid, Metabolite, Tramadol, Rat.

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Evaluation of Metabolism Inhibition by MDMA, Study on Mirtazapine in Isolated Perfused Rat Liver

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Abstract

Introduction: Nowadays MDMA (3, 4-methylendioxymethamphetamine), known as ecstasy, is widely abused among youths since induce happiness, elevated self-esteem and empathy in acute exposure. However, abusers are predisposed to depression in chronic consumption of this illicit compound due to serotonergic and dopaminergic nerve deterioration.Mirtazapine (MRZ), as an antidepressant agent, could be prescribed in MDMA-induced depression. MRZ is extensively metabolized in the liver by means of CYP450 isoenzymes. 8-hydroxymirtazapine (8-OH) is mainly produced by CYP2D6. N-desmethylmirtazapine (NDES) is generated by 3A4.

MDMA is also metabolized by mentioned isoenzymes and demonstrates mechanism-based inhibition (MBI) in association with CYP2D6. Moreover, several studies revealed that MDMA shows inhibitory effects on CYP3A4.

Our attempt in the present study was to evaluate the impact of MDMA on metabolism of MRZ in the liver. Therefore, isolated perfused rat liver served as a sophisticated model in this assessment.

Methods: Two experimental groups, control and treatment, were applied. Rats presented in control group were received MRZ-containing Krebs-Henselit buffer (1µg/ml). Rats in treatment group were received aqueous solution

of 1mg/ml MDMA (3mg/kg) intraperitoneally one hour before receiving MRZ-containing medium (1µg/ml) through the single pass mode of liver perfusion.

Results: Analysis of perfusate samples showed that parent drug concentration showed 80% increase in treatment group in comparison with control group. While, both metabolite concentrations showed 50% decrease in treatment group compared with control group.Besides, AUC $_{(0\text{-}120)}$ of parent drug demonstrated 50% increase in treatment group compared with control group.AUC $_{(0\text{-}120)}$ of 8-OH and NDES showed 70% and 60% decrease in treatment group compared with control group. Moreover, observed decrease in metabolic ratios were 83% and 79% for 8-OH and NDES in treatment group compared with control group, respectively. Additionally, hepatic clearance (CL_h) and intrinsic clearance (Cl_{int}) showed 20% and 60% decrease in treatment group compared with control group.

Conclusion: All these finding prove the inhibitory effects of ecstasy on both CYP2D6 and CYP3A4 hepatic isoenzymes. Furthermore, eighty percent enhancement of MRZ concentration in treatment group compared with control group may propose the importance of dose adjustment in clinic referring to two case reports related to interactions between MRZ and fluvoxamine.In conclusion this study is the first investigation of metabolism of MRZ in presence of MDMA in isolated perfused rat liver model.

Key words: Ecstasy, Isolated perfused rat liver model, Metabolism, Mirtazapine.

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Evaluation of Three Vancomycin Dosing Targeting High Trough Concentrations in Iranian Patients

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Abstract

Introduction: In recent years, Vancomycin is one of the most used antibiotics for methicillin-resistant staphylococcal infections. Due to pharmacokinetic differences resulting to variable responses, recent guidelines have recommended trough concentration monitoring which should be maintained at 15–20 mg/l for serious infections. In addition, there are several nomograms to determine the optimized dose of vancomycin which improve the cost-efficiency compared to conventional dosing.Given that in Iran, a constant dose of vancomycin still is prescribing for

all patients without any monitoring, we decided to assess the compatibility of vancomycin dosing regimen with the recommended dose based on the nomograms designed in other countries, in the limited number of patients and determine the rate of achievement to target trough levels in patients receiving proper dose to evaluate their applicability in Iranian patients.

Method: This retrospective study has been conducted on patients admitted to the infectious diseases ward of Imam Khomeini hospital in Tehran on Mehr 1392 to Ordibehesht 1393 who received vancomycin for serious infections and their serum trough level was checked. . The compliance of received dose with the recommended dose based on nomograms (based on creatinine clearance and patient weight) and achieving to target trough level is evaluated. In this study, three different nomogram from Canada (Thalakada et al.), America (Kullar et al. method) and Taiwan (Leu et al.) have been evaluated.

Result: Fifty-nine patients are included to study. Based on Kullar et al., Thalakada et al. and Let et al. nomograms. 25%, 43.6% and 30.5% of patients received appropriate doses, respectively. Among them, 26.7%, 29.17% and 44.4% achieved target serum concentration which was not significantly higher comparing with patients who did not received vancomycin based on nomograms (P value= 0.74, 0.063, and 0.87, respectively).

Conclusion: According to the results, it seems that Canadian nomogram did best prediction of achievement to vancomycin target trough level for Iranian population, but none of them was the perfect fit for the Iranian population. We recommend performing pharmacokinetic studies on vancomycin dosing in Iran to design specific nomogram for Iranian patients.

Keyword: nomogram, trough level, vancomycin.

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Fabrication Silk Hydrogel for Sustained Release of Risperidone and Release Kinetic Evaluation

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Abstract

Introduction and Background: Silk hydrogels are composed of hydrophilic homopolymer or copolymer and it can be produced using a water-based method that enables exact control of structural and mechanical properties.

Silk hydrogels are currently receiving a great deal of interest for local, controlled and sustained drug release because of their versatility, biodegradation and biocompatibility [1]. Also,silk hydrogel has demonstrated strong potential for cartilage tissue engineering [2]. In this work, we have fabricated a subcutaneous implant using silk hydrogel for sustained release of rispridone.

Methods: Silk hydrogels have been prepared using different solvent:

1) Using HCl/acetone solutions to induce β-sheet. 2) Using methanol solvent to induced β-sheet. Also, silk hydrogels of risperidone were prepared in the drug: polymer ratio of 1:3,1:6 and 1:15 and we measured the risperidone release rate from silk hydrogels in phosphate buffer (PH 7.4) in the sink condition with HPLC.

Results: Gelation time can be customized by adjusting the PH of the hydrogel. The results indicated that gelation with hcl/acetone solution occurred after 6 hours and gelation was achieved with using methanol solution just at 4 min.silk hydrogels induced by hcl/acetone as a gelling agent showed higher stiffer gel and slower release rate than silk hydrogels induced by methanol (30 days). the 1:6 drug polymer ratio was optimum for sustaine release of risperidone in one month and the best fit with the highest correlation coefficients was shown by both the higuchi (r^2 = 0.969) and zero-order

(r^2 = 0.943) models.

Discussion and conclusion :Silk protein demonstrates flexibility for processing into hydrogels with good properties. In the current study, we have fabricated a subcutaneous implant using silk hydrogel by inducing β-sheet with HCl/acetone or methanol solutions. The results showed that using hcl/acetone as a gelling agent increases stiffer gel, encapsulation efficiency and decreases release rate from silk hydrogel. Generally, the hydrogel properties improved with using hcl/acetone

Keywords: Rispridone, Silk hydrogels, Sustained release.

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The Use of Mucoadhesive Polymers in Ocular Drug Delivery

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Abstract

Introduction: The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by the use of polymeric soft device that are instilled into cul-de-sac. The present work describes the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, ofloxacin.The present report describes the development and in vitro testing of rod-shaped mucoadhesive ophthalmic inserts fitting the upper or lower conjunctival fornix.

Methods: Cylindrical devices (diameter 0.5-0.8, length 6–12 mm, weight 15 mg) containing ofloxacin were prepared from appropriate mixtures of hydrophyl polymers and Glycerin- Propylene glycol as plastisizer. Film casting method was used for device preparation.The ocular inserts were evaluated for drug-excipient interaction, physico-chemical characteristics, microbiological and in vitro release studies in sheep eyes as model.

Results: Mucoadhesion studies in vitro showed good mucoadhesive properties. A nearly zero-order release rate for 10h was observed in vitro for some types of inserts. In particular, they showed good hydration properties, water vapor transmission rate and mechanical properties.

Conclusion: The presently described mucoadhesive polymer inserts might prove efficient therapeutic systems for chemotherapy of ocular bacterial infections, such as trachoma.

Keywords: ofloxacin, Sustained delivery, *In vitro* release, Ocular drug delivery.

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Mechanism Based Inhibition of CYP2D6 by Ecstasy in Isolated Rat Liver Model

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Abstract

Introduction: 3, 4-Methylenedioxymethamphetamine (MDMA, ecstasy) has a psychotropic effects and is one of the most commonly abused drugs in the world. In vitro studies revealed that MDMA during metabolization process can inhibit CYP2D6 isoenzyme irreversibly; such inhibition is known as mechanism based inhibition (MBI). In this study, the MBI related parameters (Ki and Kinat) for ecstasy were calculated in isolated male Sprague-Dawley rats.

Methods: Isolated rats liver were encountered to ecstasy (50-1200 ng/ml) for 0-30 min, after this periods livers were washed for 15 min with Krebs buffer and non-inhibited CYP2D6 was determined via the dextromethorphan (20 – 800 μM) as a probe of CYP2D6 isoenzyme. All the perfusion study was conducted in single pass mode.

Results: The results indicated that the washing period of 15 min can reduced the concentration of ecstasy at higher concentration with maximum contact time to a suitable reported dilution range and dextromethorphan can saturated rat liver at concentration of 200 μM with no effect on liver function. In this condition, the obtained data for Ki (μM) and Kinact (min^{-1}) in isolated rat liver was 0.430 ±0.513 and 0.108 ± 0.030, respectively.

Conclusion: Kinact was similar to reported value for human microsomes and was greater than human hepatocytes which mean ecstasy inhibit CYP2D6 faster in isolated liver model.

The obtained Ki was about 8 and 2 times smaller than the reported value for human microsomes and human hepatocytes, respectively. This effect can be explained by accumulation of ecstasy in isolated liver in comparison with human microsomes and human hepatocytes.

Key words: CYP2D6, Ecstasy, MDMA, Mechanism Based Inhibition (MBI).

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In-Vitro Plasma Protein Binding of Cefovecin in the Koala (Phascolarctos Cinereus) Vs the Horse (Equus Caballus)

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Abstract

Introduction: Stress is a frequent cause of death in hospitalized wildlife; therefore the use of an injectable antibiotic with a long dosing interval would be desirable to decrease the frequency of handling of animals for treatment. Cefovecin is a semi-synthetic third generation cephalosporin antibacterial developed in 2006 for subcutaneous administration in dogs and cats as an aqueous solution. Because of the long elimination half-life of cefovecin in dogs and cats, cefovecin seems to have attracted interest for the treatment of wildlife and zoo animals. Cefovecin has a high plasma protein binding in dogs, cats and monkeys (more than 90%). Binding of drugs to plasma proteins is an important factor that influences drug disposition and efficacy. Consequently, determination of the degree of cefovecin binding to plasma proteins, especially in non-domesticated species, provides valuable information as to whether a single bolus of administered cefovecin may have a prolonged therapeutic action. The aim of the present study was to determine the *in-vitro* plasma protein binding of cefovecin in the koala (an iconic marsupial with significant economy importance to the Australian economy) and in the horse.

Methods: An HPLC method to determine cefovecin concentrations in plasma was developed and validated. Protein precipitation method by adding 1:1 volume of acetonitrile was used to prepare plasma samples. The plasma protein binding of cefovecin in koala and horse plasma was determined by the ultrafiltration. Cefovecin was added to plasma aliquots to yield 10, 50 and 100 µg/mL concentrations. Samples were incubated in a water bath at 37 °C for 30 minutes. To determine the total drug concentration, 100 µL plasma of each tube was removed and after sample preparation, (which included addition of an internal standard [25 µg/mL]) was injected to the HPLC machine. The remaining plasma was then transferred to the reservoir of the ultrafiltrate device which had a membrane of a molecular weight cut-off of 30 kDa. The ultrafiltrate device was centrifuged with a fixed 45 degree angle rotor and spun at 5800 g for 18 minutes at room temperature. After centrifugation, the filtrate was used for determining the free drug concentration. All samples were prepared and analysed in triplicate.

Results: all intra-assay and inter-assay validation satisfied the ICH (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines. The average of *in-vitro* plasma protein binding of cefovecin in koala and horse was approximately 13 and 93%, respectively.

Conclusion: The low proportion of cefovecin binding to koala plasma proteins , indicates that cefovecin may have a much shorter duration of action in the koala and this should be confirmed by further *in-vivo* studies.

Key words: Cefovecin, Horse, HPLC, Koala, Plasma Protein Binding.

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Metabolic profiling of *Leishmania major* promastigotes after *in vitro* exposure of green synthesis silver nanoparticles

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Abstract

Introduction: Leishmaniasis is a group of diseases caused by intracellular protozoan parasites of the genus Leishmania. Leishmaniasis remains one of the major infectious diseases with 350 million people at risk in 88 countries worldwide and 2 million estimated new cases every year. The lack of effective chemotherapy and emergence of drug resistance highlights the need for an improved knowledge of the parasite's cell biology to discover peculiarities that could potentially be explored as drug targets. The aim of this study is to evaluate the metabolome profiling of Leishmania parasite exposed to silver nanoparticles.

Methods: The effects of different concentrations of silver nanoparticle were assessed on the metabolome profile of leishmania in comparison with control group. We used ^{1}HNMR technique to record the data and chemometrics methods to analyze the data.

Results: The results of this study showed that promastigotes of *Leishmania major* at stationary stage, 22 metabolites of 40 ones significantly altered in the glucose metabolic pathway. D-glucose, melibiose and isomaltose showed most changes between metabolites.

Conclusion: The identification of altered metabolites in the glucose pathway could be used for the further understanding of the parasite biology and its biological responses to silver nanoparticles. Thus, detecting the important enzymes encoding these metabolites for the parasite in this pathway can help in drug discovery strategies.

Keywords: Drug discovery, Leishmania, Metabolomics, Silver nanoparticles.

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Optimized Release of Dexamethasone from a Soluble Ocular Insert for the Treatment of External Ophthalmic Drug Delivery

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Abstract

Introduction: In the case of external ophthalmic inflamatory, administration of a corticosteroid is needed. However, repeated administration of a corticosteroid can increase intraocular pressure and thus lead to glaucoma.To overcome the disadvantages of repeated instillations of products and to avoid the side effects of dexamethasone(DEX), a semi-soluble insert containing DEX was developed.

Methods: Reservoir-type ocular inserts were prepared by the film casting technique in teflon coated Petri dishes and characterized in vitro by drug release studies using a flow-through apparatus that simulated the eye conditions.Ten formulations were developed, which differed in the ratio of polymers Eudragit RL 100 used for the preparation of the rate controlling membrane. All formulations carried Dex, Eudragit RL100, *Polyvinylpyrrolidone* (PVP), plasticizers, propylene glycol. The inserts were then evaluated for their physicochemical parameters. All formulations were subjected to release studies.

Results: On the basis of in vitro drug release studies, the formulation with Eudragit RL 100(8%) was found to be better than the other formulations and it was selected as an optimized formulation. On the basis of microbiological, in vitro drug release, interaction and stability studies, it can be concluded that this ocular insert formulation provided the desired drug release in vitro for 5-12h and remained stable and intact at ambient conditions.

Conclusion: Ophthalmic film delivery systems, in general, bring about a considerable increase in extent of drug release compared to the suspension dosage form.

Keywords: Dexamethasone, Eudragit RL100, Extent release, ocular Insert.

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Oral Liposomes for Improving Bioavailability of Doxorubicin Hydrochloride: Investigating the Role of Surface Charge through In Vitro and In Vivo Studies

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Abstract

Introduction: Oral delivery is the most preferred route of drug administration. Recently, nanoparticulate delivery systems have provided an alternative solution for oral administration of poorly absorbable drugs. Among them, liposomes are very distinct and have shown encouraging potential in enhancing oral absorption of drugs. Doxorubicin hydrochloride (DOX) which is widely used in the treatment of various tumors has a very low oral bioavailability (less than 5%). Due to advantages of liposomes and the fact that surface characteristics are important factors affecting the potentials of liposomes, we investigated the effect of liposomal carrier and its surface charge in improving oral bioavailability of DOX by in vitro and in vivo studies. We introduced suitable liposomes in this regard and studied the underlying mechanism of absorption.

Methods: Doxorubicin loaded liposomes with different surface charges were prepared by active loading method using ammonium sulfate gradient. Liposomes were mainly composed of distearoyl phosphatidylcholine (DSPC) and

cholesterol. Distearoyl phosphatidyl glycerol (DSPG) or 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) were added with different ratios (5% and 10%) to have different negative and positive surface charges, respectively. Liposomes were characterized in terms of size, zeta potential and encapsulation efficiency. The stability and release of formulations were studied in different media including simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), with or without bile salts. The In vivo oral bioavailability of DOX solution (control) and liposomal formulations were studied in male Sprague-Dawley rats. In order to clarify the possible underlying mechanisms, cellular uptake and transport studies were conducted in caco-2 cells

Results: In vivo pharmacokinetic studies in rats demonstrated that the compared to control and all other liposomal formulations, liposomes containing 5% DOTAP (zeta potential 26 mV) markedly improved DOX oral absorption and showed a higher mean AUC value (i.e. 4-fold compared to drug solution). However, higher percentage of DOTAP was not beneficial; indicating that inclusion of positive charge over an optimum range could be favorable. Results of Caco-2 cell line studies suggested that multiple transcytosis mechanisms, including caveolin and clathrin-dependen endocytosis are involved in oral absorption of the aforementioned liposomal formulation.

Conclusion: The findings suggest that positively charged liposomes provide an effective nanoplatform for oral delivery of DOX as a drug with poor membrane permeability and low oral bioavailability. However, a moderate increase in the zeta potential of liposomes is preferred rather than very high zeta potential values.

*Key words***:** oral liposome, bioavailability, doxorubicin hydrochloride, Caco-2 transport

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Population Pharmacokinetics of Propofol in Patients Undergoing Surgical Procedure

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Abstract

Intruduction: Propofol is a rapid acting anesthetic drug which is commonly used for induction and maintenance of anesthesia and for sedation in intensive care unit patients. High clearance and large apparent volume of distribution of this drug make it a good controllable intravenous anesthetic agent.

Pharmacokinetics of propofol has been the subject of several studies. It shows a high degree of inter-individual variability and could be affected by factors such as patient age, sex and genetic polymorphism. The current study was designed and conducted to assess the population pharmacokinetics of propofol in a group of Iranian patients.

Methods: Thirty one adult patients of class ASA-I which were underwent different otolaryngological surgeries and propofol infusion was used for maintenance of anesthesia in them where included in the study. Blood sampling were done up to four hours post end of propofol infusion and propofol concentrations were determined by HPLC with florescence detector. Propofol population pharmacokinetics model was developed by non-linear mixed effect modeling approach using Monolix software. Model qualifications was based on checking the uncertainty in the estimated model parameters, visual predictive check and other diagnostic plots. Covariates tested were patient age, height, weight, infusion rate and sex. Final evaluation of the model parameters was carried out by constructing the 95% Jackknife confidence interval for each of the parameters.

Results: Pharmacokinetics of propofol was best described by a two-compartment structural model. Inclusion of covariates that showed significant relationship with individual Bayesian estimates of model parameters into the population model did not lead to significant improvement in the final model. The final fixed effect parameters of the population model (percent of relative standard error) were 2.7(8%) liter/minute, 14.8(24%) liter, 2.4(10%) liter/minute, 184 liter(13%) for CL, V1, Q and V2, respectively. The percent of inter-individual variability of pharmacokinetic parameters were 40%, 159%, 40% and 52% for the above mentioned parameters, respectively.

Conclusion: Estimated population value of propofol clearance in the current study is higher that some of the previously reported estimates in other populations.

Keywords: HPLC, Population Pharmacokinetics, Propofol, Two-Compartment Structural Model.

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Prediction of Pharmacokinetic Parameters Using Genetic Algorithm Combined with Artificial Neural Network for a Series of Alkaloid Drugs

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Abstract

Introducing simple methods for determining human pharmacokinetic parameters is the prominent aim in the pharmaceutical industry. Computational tools increase the ability of scientists in precisely selecting chemical compounds with the custom pharmacokinetic and safety profile. In this work, we describe a method to predict clearance, plasma protein binding, and volume of distribution of alkaloid drugs. A novel QSPkR (Quantitative Structure-Pharmacokinetic Relationship) technique combined with genetic algorithms and neural network was applied to choose descriptors that are more relevant, and construct suitable predictive models. Developed models were able to predict Systemic clearance, volume of distribution, and plasma protein binding with correlation coefficients 0.972, 0.957, and 0.991 for test sets, and results indicate their effectiveness in comparison with other works.

*Keywords***:** Alkaloid Drugs, Artificial Neural Network , Genetic Algorithm, QSPkR,Structural Descriptors.

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Preparation of spray freeze dried powders intended for systemic delivery of parathyroid hormone (1-34) via inhalation

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Abstract

Systemic delivery of peptides and proteins via inhalation remains a potent, noninvasive means of administration due to the possibilities of high bioavailability and patient compliance. Optimization of particle properties for deep lung deposition after inhalation as well as preserving peptides and proteins stability continues to be the key challenges. Preparation of highly dispersible particles which can reach to the alveoli is succeeded by different techniques. This work investigates the use of spray freeze drying as a particle engineering technique to produce micronized porous parathyroid hormone (1-34) loaded particles suitable for pulmonary delivery. In SFD process, the solution is atomized by a nozzle into a cryogenic fluid and frozen particles are then transferred into the lyophilizer to be dried. The cooling rate in SFD is exceedingly rapid and it is a candidate in the processing of peptides and proteins that are sensitive to high temperatures. However some stresses affect the peptide stability during each step of SFD and it is necessary to add a stabilizer to the peptide solution. In this study influence of different excipients (trehalose, leucin or hydroxypropyl-β-cyclodextrin (HPβCD)) in the medium of water or citrate buffer on microparticles characteristics (size, shape and aerosolization efficiency), peptide chemical and structural stability and its systemic delivery in rats were evaluated. Results showed that using leucin at 10% (w/w) and HPβCD at 0.04% (w/w) in water or citrate buffer medium could preserve parathyroid hormone (1-34) chemical and structural stability via spray freeze drying. Aerosol performance showed that leucin is found more effective than HPβCD in producing inhalable microparticles, and leucin containing powders produced higher fine particle fraction in comparison to HPβCD containing formulations (77.89-82.95% versus 49.10-51.13%). Nevertheless there was no statistical difference between bioavailabilities of HPβCD containing formulations and leucin containing formulations in the presence of citrate buffer; and even in the presence of water, HPβCD lead to higher bioavailability compared to leucin.The high absolute bioavailability (up to 47.25%) of formulations prepared in citrate buffer could purpose replacement of injection form of parathyroid hormone (1-34) by dry powder inhaler form.

Keywords: bioavailability; dry powder inhaler; fine particle fraction, parathyroid hormone, pulmonary drug delivery.

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Preparation, In Vitro Characterization and Pharmacokinetic Evaluation of Brij Coated Doxorubicin Liposomes as a Potential Nanocarrier for Cancer Therapy

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Abstract

Introduction: PEGylated liposomal doxorubicin has revealed several benefits over free drug including less side effects, extended blood circulation time and increased drug accumulation in tumor tissues. However, these advantages do not translate to higher treatment efficacy mainly due to limited cellular uptake related to long PEG chain length, slow release rate of drug and hypersensitivity reactions contributed to DSPE-PEG2000. The aim of this research was to pursue the possibility of replacing this PEGylated phospholipid in vesicle bilayer by a single-chain surfactant with short PEG chain length (Brij 78) to obtain stable, stealth liposomes. Brij 78 has also been shown to efficiently inhibit p-glycoprotein efflux transporter and restore the sensitivity of multiple drug resistance cells to chemotherapy drugs.

Methods: Brij-enriched liposomal dispersions containing 5% and 10% of Brij 78 as well as conventional liposomes were prepared from egg phosphatidylcholine and cholesterol by a thin-film hydration and extrusion technique. Doxorubicin (DOX) was encapsulated into vesicles by remote loading methodology. Liposomes were characterized for drug encapsulation efficiency (EE), particle size, surface charge, storage stability, morphology, and drug release profile. In vivo pharmacokinetics of various liposomal formulations was studied after a single intravenous administration to male Wistar rats. The control group was received doxorubicin solution. The pharmacokinetic parameters were calculated by non-compartment model.

Results: EE was higher than 97% in all prepared formulations. The uncoated and Brij coated liposomes showed a narrow size distribution with an average diameter of 92 ± 13 nm. AFM images confirmed the particle size obtained by DLS technique. The Brij coated liposomes showed controlled cargo release and about 50-60% drug released after 72 h incubation in plasma. Based on the pharmacokinetic results, $AUC_{0\text{-}inf}$ values of conventional, Brij5%, and Brij10% liposomes were 38830 ± 10848, 76988 ± 28398, and 35806 ± 3082 ng·h/mL, respectively. These values were respectively 22.6-, 44.8-, and 20.8- times higher than the control group. The Brij 5% group showed the lowest

apparent steady state volume of distribution (V_{ss}). It was demonstrated that the percentage of Brij 78 had a significant influence on stealth behavior of the nanoparticles

Conclusion: High drug entrapment, satisfactory stability and increased drug exposure suggested that Brij modified liposomes could be an effective chemotherapeutic drug delivery platform.

Keywords: Brij, doxorubicin, in vitro characterization, liposomes, pharmacokinetics, surface modification.

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Radiolabeling of Niosomes by ^{99m}tc-HMPAO Complex as an Approach for Pharmacokinetic and Biodistribution Studies

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Abstract

Introduction: Niosomes are spherical bilayer vesicles formed by self-assembly of non-ionic surfactants They are structurally similar to liposomes in having a bilayer but they offer several advantages over liposomes such as higher chemical stability and lower costs. Labeled niosomes can be used to evaluate the in vivo behavior of different niosomal formulations, as well as for radionuclide therapy and diagnostic imaging. In the present study, for the first time to our knowledge, niosomes were labeled by Tc-HMPAO complexes.

Methods: Glutathion loaded niosomes with the composition of Tween 60 and cholesterol (80:20 %w) were prepared by thin film hydration method. The un-entrapped GSH was separated from niosomal suspension via dialysis membrane overnight at 4 ˚C. The prepared vesicles were characterized for particle size, size distribution and zeta potential. In order to label niosomes with ^{99m}Tc, the preformed GSH loaded niosomes were incubated with the complex of ^{99m}Tc and HMPAO. Labeled niosomes were separated from any free ^{99m}Tc by passage over either a Sephadex G-25 or PD-10 column. For evaluation of labeling efficiency, the activity of the volume fractions containing niosomes was divided to the total activity loaded to the columns before separation. The influence of

different variables such as incubation time, sonication period and GSH concentration on labeling efficiency were studied. Finally, radio-stability of niosomes was checked by dialysis membrane.

Results: All vesicles had a mean diameter of about 305.1± 0.15 nm and polydispersity index of about 0.5 ± 0.18. In comparison to PD-10 column, Sephadex G-25 column was found to be rather suitable as it efficiently isolated labeled niosomes from other impurities. Among different incubation times studied (15, 30, 45 and 60 min), the highest labeling efficiency (43.3 ± 5.0) was achieved following 45 min incubation which was not improved by longer incubation time. Increase of GSH concentration in hydration buffer from 100 to 200 mM resulted in enhancement of labeling efficiency from 43% to 96%. Stability study in plasma performed by dialysis membrane showed only about 22% reduction of niosomes radioactivity after 24 h.

Conclusion: ^{99m}Tc labeled niosomes were prepared successfully (labeling efficiency > 90%) and they had an acceptable radio-labeling stability in plasma. Niosomes carrying radionuclide can be used for tracking the in vivo disposition of these carriers, detection of pathological processes and for imaging.

Key words: niosomes, radio-labelimg, ^{99m}Tc.

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Reducing Neuropathic Hyperalgesia Induced by Cisplatin in Rats by Pretreatment with Aspirin

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Abstract

Complications induced by the chemotherapeutic agent cisplatin, such as neuropathy and hyperalgesia, occur frequently, are often dose limiting, and have an impact on quality of life and survival in cancer patients. The recently discovered aspirin is a potent COX2 inhibitor has neuroprotective properties that may prevent or ameliorate these complications. The objective of this study was to determine the effects of aspirin pretreatment on mechanical hyperalgesia, mortality, and amnesia induced by cisplatin. Adult female rats were given cisplatin (12 mg/kg, i.p.), aspirin (15 and 150 mg/kg, i.p.), aspirin-cisplatin, or vehicle i.p. Body weight were measured daily. Von ferry tests

to assess the development of hyperalgesia were conducted by measuring mechanical sensitivity. Passive avoidance responses of rats were also measured by shuttle box. Our results indicate that aspirin pretreatment significantly inhibits the development of cisplatin-induced mechanical hyperalgesia, and amnesia induced by cisplatin. Although aspirin treatment had analgesic effect on control rats, it also prevented the reduction of amnesia induced by cisplatin. In conclusion, aspirin administration may be useful in the treatment or prevention of chemotherapy induced neuropathy and cognitive impairment. Attenuation of hyperalgesia, mortality and amnesia in the rat by aspirin pretreatment suggest a new application for aspirin as a COX inhibitor for neuroprotection against cisplatin complications.

Keywords: Aspirin, Chemotherapy; Neuropathy; Neuropathic pain.

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In-Vitro & In-Vivo Study of Isosorbide Mononitrate 50mg SR Capsules with Two Different Sources in Comparison of Elantan 50mg Capsule

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Abstract

Introduction: Isosorbide mononitrate (IMN), an organic nitrate and the major biologically active metabolite of isosorbide dinitrate (IDN), is a vasodilator with effects on both arteries and veins. The principal pharmacological action of IMN and all organic nitrates in general is relaxation of vascular smooth muscle, producing dilatation of peripheral arteries and veins, especially the latter.

In present study two source of IMN in the formulation of IMN SR capsule were compared with Elantan 50mg capsule as a reference product.

Methods:

In-vitro test: Dissolution profile: One capsule was placed in a stainless steel metal helix into the beaker containing the dissolution medium (water) and stirring (50rpm) was started. At regular intervals (1, 2, 4, 8 and 12 hours) 2ml samples were withdrawn from the medium and following filtration, 100µl was injected into HPLC.

In-vivo test: A randomized, open label, single dose, tree treatments, tree periods, tree sequences, crossover design between 50mg of ISM SR capsule administration under fasting condition was conducted in 12 healthy, Iranian male

subjects. Each subject was assigned randomly to receive a single oral dose of test formulation1 or 2 and or the reference formulation of 50mg ISM capsule. Study periods were separated by a 7 days washout period. Blood samples were collected at 0, 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours after drug administration. A sensitive and specific HPLC method was used for quantification of ISM in plasma. Pharmacokinetic parameters were analyzed including C_{max}, T_{max}, $T_{1/2}$ and $AUC_{(0-24)}$.

Results:

In-vitro test: Statistical difference between the percent of drug release from test formulation 1 and reference formulation was significant in all sampling time and these two products weren't similar, while there was no significant difference between formulation 2 and reference formulation.

In-vivo test: 12 healthy male adult volunteers were enrolled aged 31.5 ± 3.84 years and weight 71.17 ± 2.50 kg. 12 subjects completed both periods of the study for test formulation 1 and reference and 9 for test formulation 2.

The mean C_{max} values were 489.49 ± 34.98, 498.87 ± 31.43 and 458.10 ± 56.12 ng/ml and the mean AUC_{0-24} were 5647.12 ± 596.06, 5358 ± 351.54 and 6417.38 ± 836.62 ng/ml.hr. for test1, test 2 and reference formulation respectively. With 90% CI of the ratios between test1 and reference tablets, the range of relative bioavailability for C_{max} and AUC_{0-24} were 82 – 104% and 91.3 – 124.7% and between test 2 and reference tablets were 92.8 – 122.1% and 86.9 – 112.5%.

Conclusion: In spite of significant difference between test 1 and reference formulation in dissolution test, both products are bioequivalent with reference formulation, so we can conclude that comparative dissolution profile for sustained release formulations isn't enough to predict the in-vivo results.

Keywords: Dissolution, HPLC, Isosorbide mononitrate.

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Role of Pharmacokinetics in Interpretation of Postmortem Forensic Toxicology Results: A Review

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Abstract

Introduction: Inter- and intra-individual variations in pharmacokinetics parameters related to physiological, pathophysiological, genetic and environmental parameters. In postmortem forensic toxicology, consideration of differences between antemortem and postmortem pharmacokinetics parameters has a critical role in interpretation of analytical results. Changes in the composition of biosamples after death depending on the site of collection and the time elapsed since death. Other phenomena such as postmortem drug redistribution (PMR) and putrefaction are affected the pharmacokinetic parameters at postmortem. Considerable changes occur in the concentrations of some drugs at postmortem. In some cases, drug concentrations increase, others fall and some do not change. From this issue, application of published data about therapeutic, toxic and lethal concentrations in clinical and antemortem circumstances may are misleading when used for postmortem situation. PMR is a main concern should be considered for interpretation of postmortem analysis results. PMR involves the redistribution of drugs into blood from solid organs such as the lungs, liver, stomach and myocardium. Therefore, postmortem drug concentrations do not necessarily reflect concentrations at the time of death, as drug levels may vary according to the sampling site and the interval between death and specimen collection. The underlying mechanisms of PMR are complex and different Passive drug release from drug reservoirs may occur immediately after death and, later on, cell autolysis and the putrefactive process participate in redistribution. There are evidences that basic lipophilic drugs with a large distribution volume (greater than 3 L/Kg) are particularly susceptible to PMR. Consequently, it is of great importance to analyze specimens from different sampling sites in order to detect potential PMR and avoid misinterpretation of results. The tricyclic antidepressants, digoxin, calcium channel blockers, long-acting barbiturates, phenothiazines, opioid analgesics and the amphetamine type stimulants could be considered for PMR. This review presents relevant information to assist in the interpretation of analytical results in postmortem toxicology with some examples of drugs interesting in forensic toxicology practice.

Conclusion: In forensic toxicology, pharmacokinetic differences between antemortem and postmortem circumstances due to PMR and other postmortem biochemical process could be considered for interpretation of toxicological analysis results.

Key words: Forensic Toxicology, Pharmacokinetics, Postmortem.

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SABT: Statistical Analysis of Bioequivalence studies Tool

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Abstract

Introduction: Bioequivalence studies compare the rate and extent of the active pharmaceutical ingredient systemic absorption from generic and reference preparations statistically. Here we present new software to perform non-compartmental analysis of average bioequivalence (ABE) which can be 2x2x2 crossover or repeated crossover or a parallel study. Thanks to its user-friendly environment, SABT does not require any specific computing knowledge and allows the user to save time in the analysis of bioequivalence studies.

Method: A laptop running on Windows8® with an Intel™ Core-i7 processor and 16 GB RAM was used for all programming and analytical experiments. All coding procedures were performed based on MATLAB® 2012. The statistical analysis for bioavailability measurements (AUCs and Cmax) was based on the two one-sided tests as reported by Schuirmann et al. ABE involves the calculation of 90% confidence intervals for the ratio of the averages of the measures for the test and reference product data. The Bioequivalence will be concluded based on the calculated 90% CIs falling within 80-125% (or user defined values).

Results: Comparing exported results and graphs to those results obtained with EquivTest/PK, SAS, WinNonlin, Kinetica and R; revealed reasonable efficiency of our software in different models. The reference data sets used to test the accuracy and applicability were based on (Schütz 2014) and (Fuglsang 2015) for crossover and parallel

design studies, respectively. Further tests performed to ensure that output results be the same as those generated by commercial softwares.

Conclusion: SABT provides a complete descriptive statistics and a series of parametric and non-parametric statistical analysis to evaluate the presence of bioequivalence between two compounds or formulations. Reports include both pharmacokinetics and statistical analysis obtained from the bioequivalence study built in a standard format in lowest runtime with the help of high performance programing. It's time to direct our strategies toward in-house software development.

Keywords: Bioequivalency studies, Non-compartmental analysis, Statistical analysis tool.

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The Effect of the Designed Feed on the Main Quality Attributes of a Therapeutic Monoclonal Antibody

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Abstract

Todays, the quality targets serve as the basis for process development activities and guide the selection of process steps, material attributes, equipment design and operation controls for the manufacturing process of biopharmaceuticals. Some quality attributes are dependent on host cell line, clone, process conditions, and media composition. Consequently, analyzing these product quality features in process development is very valuable to match the desired quality target product profile.In this study, in order to enhance the therapeutic recombinant monoclonal antibody (mAb) productivity in Chinese Hamster Ovary (CHO) cells, an optimized amino acid feed was developed through the design of experiment (DOE) methods, after the design of the optimized feed, the product was analyzed for N-glycan profiles, charge variant distribution, low molecular weight forms and binding potency. These analyses were performed by HPLC, capillary electrophoresis and ELISA. The results indicated that, in addition to mAb productivity, the target mAb quality has been improved using this feeding strategy compared with the control group. This strategy supplies a logical approach for process development which can save time and resources.

*Key words***:** CHO cells, design of experiment (DOE) methods, mAb quality targets, N-glycan profiles.

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Utilization of Active Metabolites in Detection of Benzodiazepine and Tricyclic antidepressant Drugs in Biological Postmortem Samples

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Abstract

Introduction: Benzodiazepines (BZS) and Tricyclic Antidepressant (TCA) are the most frequently prescribed drugs and many of them are used for addiction, abuse and sexual assault. Thus, their analysis seems to be more Important In clinical and forensic toxicology. Metabolism is the major contributor to the systemic exposure and total in vivo clearance of many drugs and thus an important consideration in Drug Discovery and Development. The extensive metabolism of BZS and TCA drugs can alter potency or duration of action of parent drug. The aim of this study is detection of these drugs by their common active metabolites in biological postmortem samples and determination cause of death in Legal Medicine in acute and chronic uses.

Methods: In this cross-sectional study, BZS and TCA and their metabolites were detected in biological specimens (blood, urine, tissue and bile) from cadavers that referred to Legal Medicine Organization, Tehran, Iran (2014-2015).Drug analysis was performed on each sample by Thin Layer Chromatography (Screening test) and HPLC and GC/MS (Confirm ting test).

Results: From 35 cases of Diazepam detected, 19 cases had Nordazepam (major metabolite of diazepam) and in 11 cases of them Nordazepam was detected without Diazepam, in 17 and 8 samples that consist of Flurazepam and Chlordizepoxide respectively with or without their metabolites (Desalkylflurazepam and Demoxapine). From 41 cases of imipramine detected, 11 cases had Desipramine and in 28 cases Desipramine was founded alonely that show acute use of main drug in victims. (Suicides or Homicide)

Conclusion: Results show that BZS and TCA drugs can be detected by utilizing their active metabolites ever without parent drugs and they represent different diagnosis between acute and chronic uses and determine cause of death in forensic toxicology in victims.

Key Words: Benzodiazepines, Forensic Toxicology, Metabolites, Tricyclic Antidepressant.

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Vancomycin Dosing Nomograms Targeting High Serum Trough Levels in Different Populations: Pros and Cons

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Abstract

Introduction: Vancomycin dosing nomogram is a useful and cost saving method in comparison with conventional dosing for achievement to target trough levels. Recent guidelines have recommended trough concentration 15-20 mg/l for complicated infections. To date, several nomograms have been constructed to reach to this optimal trough level range in different populations. In this review, we have collected available nomograms, particularly their advantages and limitations. The data were collected by searching Scopus, PubMed, Medline, and Cochrane database systematic reviews. The key words used as search terms were “vancomycin”, “high trough level”, “dosing nomogram”, “dosing strategy”, “neonates”, “critically ill”, “pediatrics” and “hemodialysis”. We have included all related human studies up to the date of publication.

Conclusion: Most of available nomograms determine the doses according to body weight and renal function. Based on validation studies’ findings using vancomycin dosing nomogram can improve and accelerate target trough concentrations achievement. But it should be noted that there are limited data about their clinical and microbiological outcomes and they are just validated in specific groups of patients. Thus, their widespread application could not be encouraged for all populations before performing adequately powered prospective randomized studies.

Key word: high trough level, nomogram, vancomycin.

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A Disposition Kinetic Study of Tramadol in Intoxicated Rats Induced by Ethanol and Acetaminophen in Perfused Rat Liver Model

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Abstract

Introduction: Tramadol hydrochloride (TrHC) is a synthetic analgesic drug presenting opioid and non-opioid properties, acting generally on the central nervous system (CNS). This drug is structurally related to codeine and morphine, but it is 6000-times less potent than morphine and 10-times less potent than codeine. Damage to the liver can Lead to changes in the metabolism of tramadol. Decreased metabolism causes Maintaining levels of unmetabolized tramadol which increases Side effects such as seizures and other complications. Acetaminophen is a mild analgesic and antipyretic agent Known as the cause centrilobular hepatic necrosis in toxic doses. Ethanol causes clinical and morphological changes such as fatty liver, liver inflammation, fibrosis, cirrhosis, and lipid peroxidation in many organs. The aim of the present study was to Measuring the amount of tramadol and its metabolites in intoxicated rats by ethanol in perfused rat liver model.

Materials and methods: After determining the proper dose of ethanol and acetaminophen, the rats were divided into three groups: The control group (a) (0% APAP, 0% ethanol, n = 7), and the groups received APAP (b) at the dose of 250 mg/kg n = 7, group(C) at first received 3 g/kg/day and over time increased to 6 g/kg/day n=7. All animals on the standard diet were followed for 45 days. Animals were weighed every week to check for changes. At the end of the experiment, serum of liver enzymes (ALT, AST, ALP) were assayed and histopathological examinations performed. After insuring liver damage, tramadol pharmacokinetics was evaluated in a rotating system of hepatic perfusion and analyte concentrations were determined with HPLC. Tramadol was added to perfusion with concentration 500ng / ml. The samples were collected during 180 minutes and analyte concentrations were determined by HPLC. Fluorescence detector was used in this method, and the samples were detected using a C18 column or ODS.

Results: The liver enzyme in the group (a) and (b) compared to the control group showed a significant increase. Histopathologic examination revealed ethanol and acetaminophen cause liver damage. According to calculations done in groups B and C, elimination half-life of tramadol was increased and the clearance was reduced.

Conclusion: Liver damage caused by ethanol and acetaminophen during 45 days in animals lead to a significant reduction in the level of tramadol metabolites. Metabolite M1 is 6-fold analgesic effect of tramadol and 200 times more potent than Tramadol binds to μ. Due to reduced analgesic effect as well as maintaining tramadol in high level and increase in the risk of complications, it needs to select the appropriate dose.

Keywords: acetaminophen, ethanol toxicity, hepatic perfusion, HPLC, lipid peroxidation, liver damage, Tramadol.

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Design and Evaluation of Polymeric Controlled Release Azithromycin Ocular

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Abstract

Inroduction: many ocular surface disorders involving the tear film, eyelids, and adnexal structures are associated with chronic, low-grade bacterial infection and may potentially lead to decreased vision secondary to corneal scarring. Various topical antibiotic and steroid combinations are commonly used with variable clinical response and known potential side effects. However, the long-lasting antibacterial and additional anti-inflammatory properties of topical azithromycin (az) might offer an effective treatment. Transport of drugs applied by traditional dosage forms is restricted to the eye, and therapeutic drug concentrations are not maintained for a long duration since the eyes are protected by a unique anatomy and physiology so repeated instillations of antibiotics are required to reach therapeutic level, above the minimal inhibitory concentration (mic). Direct intravitreal implants, using biodegradable or non-biodegradable polymer technology, have been widely investigated for treatment of chronic vitreoretinal diseases. We have incorporated az in insert polymeric drug delivery system, with a mucoadhesive and hydrophilic properties in order to extent release.

Method: Solvent casting technique was followed to prepare ocular films using different polymers such as, eudragit RL-100, hydroxy propyl methyl cellulose and hydroxyl ethyl cellulose at various proportion and combinations using glyserol as plasticizer. The prepared insert were evaluated for their physicochemical parameters; drug content,

weight uniformity, folding endurance, thickness, % moisture absorption and water vapour transmission rate. The *in vitro* drug release from the formulations was studied and the *in vitro* release kinetic datas were treated according to the diffusion models proposed by Higuchi and Peppas in order to access the mechanism of drug release.

Results: All the formulations showed no change in the physical appearance and the FTIR studies indicated no possibility of interaction between drug and polymer. In vitro release studies revealed that the best ocular inserts formulation followed near to zero-order release kinetics. The controlled release ocular insert was more suitable as compared to conventional dosage form. Shelf-life of the product was found to be more than one year.

Conclusion: The insert ophthalmic formulations of azithromycin, have been shown to have long half-lives in the conjunctiva while providing very low systemic exposure. It can potentially be administered at a much lower dosing frequency than the marketed anitbiotics for the treatment of bacterial conjunctivitis.

***Keywords*:** Azithromycin, controlled release, Ocular Insert.

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The Biopharmaceutical Drug Disposition Classification System and Biopharmaceutical Classification and Sub-classification System of the Iran's official drugs

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Abstract

Introduction: The physicochemical and physiological parameters as well as the properties related to the dosage form affect the bioavailability of the active pharmaceutical agents. These factors are characterized in the Biopharmaceutics Classification System (BCS) by three dimensionless numbers: absorption number (A_n), dissolution number (D_n), and dose number (D_0). Also, based on the Biopharmaceutical Drug Disposition Classification (BDDCS), if the main route of elimination of a drug is metabolism, then the drug is high-permeable

and if the major route of elimination is renal and biliary excretion of unchanged drug, then that drug should be classified as low-permeability. In addition, it is well known that the pKa of an active pharmaceutical ingredient has a significant impact on the solubility/dissolution of drug from the drug product both in vitro and in vivo for BCS Class II and IV acids and bases, and it is usually utilized for a sub-classification extension of the original BCS classification.In order to be used in researches and modeling purposes and more efficient in vitro-in vivo correlations, we developed a classification of Iran's official drugs list. Values for drug solubility were obtained from standard references, and the maximum dose strengths were readily available in the list being classified, enabling the calculation of the dimensionless dose number (D_0). A dose number lower and higher than 1 indicated high-solubility and low-solubility compound, respectively. Log P and Clog P values were used for permeability classifications. Drugs exhibiting n-octanol/water partition coefficient value greater than metoprolol (Log P 1.72) were categorized as high-permeability. Also, for the BDDCS the cutoff was originally set at ≥50% metabolism.

Conclusion: The information provided by these classifications of the Iran's official drugs could help researchers and also pharmaceutical manufacturers to avoid unnecessary human experiments and reduce cost and time of the researches. In addition, science computational modeling lead to more efficient investigations and decreasing drug development timeline, the results of this study will remain an invaluable tool in the future as well.

Key words: Absorption number, Dissolution number, Dose number, Permeability, Solubility.

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Evaluation of Double-Peak Phenomenon of Oral Gliclazide Pharmacokinetics

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Abstract

Introduction: Gliclazide is a second-generation sulphonylurea drug used in the treatment of type 2 diabetes. The pharmacokinetics (PK) of gliclazide after oral administration in healthy volunteers was studied.

Methods: Gliclazide tablet (80mg) test and reference were administered to 12 healthy overnight fasted volunteers in a double blind cross-over design. Blood samples (3 ml each) were drawn before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5.5, 7, 8.5, 10 and 24 hours after drug administration, separated serum parts were stored frozen until analysis for

gliclazide by a validated HPLC method. The noncompartmental parameters including C_{1max}, $C_{2max,}$ t_{1max}, t_{2max} have been reported to describe the concentration and location of the two peaks.

Results: The concentration-time profiles after administration of 80 mg Gliclazide exhibited a double-peak phenomenon in some of the volunteers (in test n=6, in reference n=10). This phenomenon is not seen clearly in the mean concentration-time profiles. The time between the two peaks was different in volunteers. The C_{1max}, $C_{2max,}$ t_{1max}, t_{2max}, are (4.98+/- 1.16 ug/ml, 4.44+/- 1.31ug/ml, 2.92+/-0.85hr, 4.70+/- 2.24hr) for reference and (4.83+/- 0.92 ug/ml, 3.98+/-1.03 ug/ml, 3.46+/- 0.78, and 5.33 +/- 1.86hr) for test product.

Conclusion: We suggest that the mechanism underlying the double-peak phenomenon is due to either enterohepatic recirculation and/or two or more sites of absorption of gliclazide in the healthy volunteers. This is the first report of double peaks for oral gliclazide in healthy volunteers. In addition of difficulties in pharmacokinetics parameter estimation, double-peak phenomenon caused by the hypothesized mechanism may have important therapeutic effects. The double-peak phenomenon was also seen in the decrease of blood glucose level (dBGL) as a pharmacodynamic (PD) response, which will reported in future.

Keywords: Double-Peak Phenomenon, Gliclazide, PK.

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In Vitro and *In Situ* Effects of Atorvastatin and Ezetimibe on Intestinal Efflux Pump

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Abstract

Introduction: P-glycoprotein is a membrane transporter responsible for the active efflux and secreting passively diffused drugs out of the cell .P-gp expresses on several barrier epithelia and has broad substrate specificity. It plays

critical roles in the absorption, excretion, and distribution of drugs. The transport activity of P-gp can be inhibited by a variety of drugs, which may affect the absorption of the drugs and leads to clinically significant DDIs affecting the drugs bioavailability and effectiveness. It is critical to understand which drugs are inhibitors of P-gp so that adverse DDIs might be minimized or avoided. This study performed to investigate the effects of Atorvastatin and Ezetimibe on the function and expression of P-gp.

Methods: The assay of rhodamine-123 efflux in caco-2 cells was used for in-vitro studying of the effect of atorvastatin and ezetimibe on P-gp function. The effect of the drugs on expression of P-gp in Caco-2 cells was assayed by Western Blotting technique. Rat *in situ* single-pass intestinal permeability model using digoxin as a known substrate, and verapamil as a known inhibitor, was performed for studying the effect of the drugs on p-gp function. Digoxin levels of intestinal perfusion samples were analyzed by HPLC method.

Results: Rho-123 intracellular accumulation in atorvastatin, ezetimibe (100 µM), and verapamil (300 µM) treated caco-2 cells were 646.0 ± 13.1, 681.7 ± 135.0 and 749.4 ± 32.1 pg/mg protein, respectively and were significantly higher than the control cells (424.4 ± 89.3; $P < 0.05$). In western-blotting results, 100 µM atorvastatin and also ezetimibe decreased the expression of P-gp in caco-2 cells *in vitro*. Intestinal effective permeability (P_{eff}) of digoxin (20 µM) in presence of 3 and 100 µM atorvastatin, 10 and 100 µM ezetimibe, and 300 µM verapamil were significantly increased in compare with digoxin alone ($p<0.05$ and $p<0.01$).

Conclusion: Our findings showed that atorvastatin and ezetimibe inhibit P-gp efflux activity *in vitro* and *in situ*. Both of the drugs down regulate the expression of P-gp *in vitro*. The P-gp inhibitory effects of atorvastatin and ezetimibe must be considered for predicting potential drug–drug interactions. Further investigations are required to confirm our results and also clear the P-gp inhibitory mechanisms of atorvastatin and ezetimibe.

Keywords: Atorvastatin, Ezetimibe, intestinal efflux.

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Investigation of the Ecstasy's Effects on the Omeprazole Metabolism by 2C19 in Rat Perfused Liver

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Abstract

Introduction: The recreational use of MDMA (ecstasy) has been become rife among youth over the past decade. The drug induces intense feelings of euphoria, empathy and hyperactivity after ingestion through acting as a potent releaser and/or reuptake inhibitor of presynaptic neurotransmitters. Severe acute toxic effects including multi-organ failure, hyperthermia, tachycardia, hypertension, myocardial ischemia, psychosis and the serotonin syndrome are associated with MDMA abuse, which can finally lead to death. Phase I metabolism of MDMA involves two main routes including the chain conversion by N-dealkylation to 3,4-methylendioxyamphetamine (MDA) or O-demethylenation of the ring substitute of both MDMA and MDA into the highly reactive catechol metabolites of 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA). These two later metabolites can be further oxidized to the corresponding ortho-quinones, which are able to enter in a redox cycling leading to generate reactive oxygen and nitrogen species that have been proposed to be the reason of cytotoxicity in several tissues such as liver, brain, kidney and heart.CYP2C19 is involved in the biotransformation of antidepressants and a miscellaneous group of drugs including PPIs, antiepileptics, and the anticoagulants. Among these drugs, omeprazole has been extensively used as an appropriate probe substrate. In rats Similar to humans Omeprazole has been metabolized by 2C19 to 5-OH-omeprazole and formation of this metabolite determines CYP2C19 activity.

Methods: the present study was carried out to investigate the possibility of CYP2C19 inactivation after encountering of an isolated perfused rat liver (IPRL) to different inlet concentrations (300 and 600 ng/ml) of MDMA. One direction perfusion with buffer contains Omeprazole has followed by same process with MDMA and again Omeprazole.

Results: 5-OH-omeprazole was reduced in both mentioned concentrations. The analysis of four latest sample intervals taken after exposure to MDMA, showed about 18% and 16.8% decrease in metabolite concentrations from 18.4 ± 7.0 to 15.3 ± 7.9 and from 19.4 ± 6.8 to 15.9 ± 5.7 μM after administration of administration of 300 and 600 ng/ml of MDMA respectively (pvalue<0.05).Similarly, the $AUC_{(0-t)}$ of metabolite also showed decrease from 461.4 ± 169.9 to 355.5 ± 187.3 and from 467.6 ± 192.2 to 371.5 ± 148.9 μM.min after administration 300 and 600 ng/ml of MDMA respectively (pvalue<0.05). In conclusion: the metabolic activity of CYP2C19 after exposure to MDMA is decreased where the reduction is concentration-independent.

Key words: CYP2C19, liver perfusion, MDMA, mechanism based inhibition, omeprazole.

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In vitro-In vivo Characterization of Hydrogel-Coated Solid Lipid Nanoparticles

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Abstract

Introduction: Upon intravenous administration, solid lipid nanoparticles (SLN) are highly susceptible to phagocytosis by reticuloendothelial system (RES) due to their hydrophobic surface and this problem is counted as the main obstacle against the popular use of these carriers. To overcome this problem, a novel hydrogel-coated SLN structure was developed and evaluated in this study. SLN surface was coated by a poly-cationic polymer, chitosan, via electrostatic attraction with the negatively charged SLN surface. The resulting polymer-coated SLN showed a positive net surface charge, which, then, hosted an inorganic poly-anionic agent, tripolyphosphate, to form the final lipohydrogel structure via the 3D crosslink formation on the surface of the nanocarrier. **Methods**: To obtain this structure, SLNs were prepared by solvent diffusion method and, then, the SLN dispersion was added onto chitosan aqueous solution and, finally, tripolyphosphate (TPP) was added to cross link chitosan chains and to form the final lipohydrogel nanoparticle (LHN). The physicochemical and biological properties of the prepared nanoparticles were investigated. **Results**: Compared to the bare SLN, LHNs showed a significant increase in size and zeta potential. The release profile showed lower burst release and lower release rate for LHN compared to SLN. FTIR analysis showed no covalent bond formation between the drug and the nanocarriers and also confirmed the core-shell structure of LHNs. SEM results demonstrated the formation, size and morphology of SLNs as well as LHNs. The particle size, zeta potential and microscopy data plus FTIR analysis demonstrated the formation of the supposed

lipohydrogel nanoparticles. LHN nanoparticles released the model antidiabetic drug, repaglinide, in a more sustained manner with lower burst effect compared to the corresponding SLN structure. Cytotoxicity studies via cell culture and MTT assay revealed no bio-toxicity of the SLNs and LHNs. In addition, intravenous administration of repaglinide-loaded SLNs and LHNs in rats showed longer drug residence time in circulation for LHNs, a trend also evident for the blood glucose level-time profile. **Conclusion**: The results of this study demonstrated the formation of hydrogel coated SLNs and all the benefits and superior characteristics of LHNs contrast to SLNs, proposes it as a promising candidate for controlled release of the drugs.

Keywords: bio-toxicity, reticuloendothelial system, solid lipid nanoparticles.

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Microsomal Epoxide Hydrolase (mEPXH|) Polymorphism in the Workers of Sour and Sweet Natural Gas Refineries and Its Relation To Lung Functional Parameters

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Abstract

Introduction: Hydrogen sulphide (H_2S) is a potent oxidant known to induce a variety of respiratory effects including increased airway reactivity and bronchoalveolar inflammation. In this cross-sectional study, the effects of genetic polymorphism of microsomal epoxide hydrolase-1 (mEPXH1) exon 4 on the lung function in the subjects exposed chronically to H_2S were investigated.

Methods: The spirometric results of 120 sour gas refinery (SoGR) workers were compared to 110 non-exposed sweet gas refinery (SwGR) workers. The polymorphism His139Arg at exon 4 of mEPXH1 gene was determined using polymerase chain reaction –restriction fragment length polymorphism (PCR-RELP). Multiple linear regression including age and height were used to determine the association of mEPXH gene polymorphisms and spirometric result. Effects of genetic polymorphism on the obstructive and restrictive pulmonary problems were evaluated using logistic regression.

Result: FVC and PEF values were significantly lower in the SoGR subjects. No decreases in FEV1% and FEV1/FVC values were noted in H_2S exposed subjects. The frequency of obstructive and restrictive lung dysfunction was 11% and 40% respectively in the SoGR subjects which were significantly different from the SwGR population (5% and 29%, respectively). There was no association between mEPXH1 gene polymorphism at exon 4 and spirometric parameters and frequency of the restrictive and obstructive lung dysfunction in the subjects exposed to H_2S.

Conclusion: The result of this study that chronic H_2S exposure increases the risk of pulmonary dysfunctions which are not affected by polymorphism in the exon 4 of mEPXH1 enzyme.

Keywords: Genetic polymorphism, Microsomal epoxide hydrolase, Respiratory toxicology.

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Pulmonary Pharmacokinetics of Sildenafil after Oral, IV and Inhaled Administration

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Abstract

Introduction: Pulmonary arterial hypertension is a pathophysiological hemodynamic condition in which average pressure in the pulmonary arteries at rest is higher than 25 mmHg. High concentrations of phosphodiestrase type 5 have been found in the pulmonary vascular smooth muscles and its activity can lead to impaired vasodilatation and abnormal vascular growth. Administration of sildenafil citrate (SC) is considered as a strategy in the treatment of pulmonary hypertension. This study reports production of the inhalable microparticles containing SC-loaded poly (lactide-co-glycolic acid)-nanoparticles.

Methods: SC-nanoparticles were prepared by the double emulsion solvent evaporation method. Next, free SC and SC-loaded nanoparticles were spray dried in the presence of appropriate excipients (lactose, maltose and trehalose). Physicochemical properties and aerodynamic behavior of prepared powders were evaluated. In addition, drug accumulation from selected formulations in the rat lung tissue was compared with oral and IV administration.

Results: Size and fine particle fraction of selected nanocomposites and free SC microparticles were 7 and 4.5 mm, and 60.2% and 68.2%, respectively. In vivo study revealed that route of administration and formulations of sildenafil has significant effects on the kinetics of drug in the body. Following oral and IV administration, the drug

was not detectable in the lung after 4 and 6h, respectively, but in SC-loaded nanoparticles, the drug was detectable in the lung even after 12h of inhalation. The lower concentration of drug after oral administration in the lung tissue is partly because of the first pass metabolism. In addition, rapid disappearing of drug after maximum concentration of drug is related to the physicochemical properties of SC. The low uptake of SC by the lung tissue after oral and IV administration could be attributed to the physicochemical properties of SC as a weak base with pK 8.7; where lung uptake is particularly higher for basic amines with pK values greater than 8.

Conclusion: The spray-drying technique produced powder suitable for inhalation. In vivo study demonstrated that pulmonary administration of sildenafil and sildenafil nanoparticles produced longer half-life and higher concentration of the drug in the lung tissue as compared to oral and IV administration. So, these formulations could be more effective than oral and IV administration of this drug. However, this research work was the first step in the pulmonary delivery of SC dry powder and sustained release SC. Although in vivo evaluation of these formulations showed valuable data, development of these formulations needs more pharmacologic, pharmacokinetic and toxicological evaluation.

Keywords: IV and inhaled administration, Sildenafil, oral

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The Effects of Cetirizine on P-Glycoprotein Expression and Function *In Vitro* and *In Situ*

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Abstract

Introduction: P-glycoprotein (P-gp) plays a major role in drug absorption due to its expression on several barrier epithelia. Induction or inhibition of P-gp by drugs contributes to variability of its transport activity and often results in clinically relevant interactions. It is critical to understand which drugs are inducers or inhibitors of P-gp to

minimize or avoid adverse interactions**.** The purpose of this study was to investigate the effect of cetirizine, a second generation H_1 antihistamine, on P-gp function and expression *in vitro* and *in situ*.

Methods: The in-vitro Rhodamin-123 efflux assay in caco-2 cells was used for studying the effect of cetirizine on P-gp function. Western Blotting Analysis was used for surveying the effect of cetirizine on expression of P-gp in Caco-2 cells. Rat *in situ* single-pass intestinal permeability and P-gp inhibition assay using digoxin, a known substrate, and verapamil, a known inhibitor, were performed for studying the effect of cetirizine on P-gp function. Digoxin and cetirizine levels of intestinal perfusion samples were analyzed by HPLC method.

Results: *In vitro*, the intracellular concentration of Rho123 in cetirizine and verapamil treated cells (88.8 ± 2.3 and 420.6 ± 25.4 pg/mg protein, respectively) were significantly increased compared with Caco-2 control cells (50.2 ± 6.0) ($P < 0.05$). Immunoblotting results showed that cetirizine down-regulate expression of P-gp in Caco-2 cells. *In situ*, digoxin (20 µM) intestinal effective permeability (P_{eff}) in the presence of 10 and 100 µM cetirizine, and also 300 µM verapamil, were significantly ($p < 0.01$) increased compared with digoxin alone (6.8 ± 0.4, 8.7 ± 1.0, and 8.9 ± 0.7 in compare with 3.4 ± 0.8 cm/s). P_{eff} of 10 and 100 µM cetirizine was 6.7 ± 0.7 and 3.4 ± 0.4 cm/s, respectively.

Conclusion: Our results suggest that cetirizine is a P-gp inhibitor and its inhibition activity is dose dependent. The activity must be considered in co-administration with P-gp substrates like digoxin. More investigations are needed to know the mechanisms of the inhibition activity.

Keywords: P-Glycoprotein, Cetirizine, $H_{1,}$ caco-2 cells

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Investigation of the Ecstasy's Effects on the Omeprazole Metabolism by 2C19 in Rat Perfused Liver

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Abstract

Introduction: The recreational use of MDMA (ecstasy) has been become rife among youth over the past decade. The drug induces intense feelings of euphoria, empathy and hyperactivity after ingestion through acting as a potent

releaser and/or reuptake inhibitor of presynaptic neurotransmitters. Severe acute toxic effects including multi-organ failure, hyperthermia, tachycardia, hypertension, myocardial ischemia, psychosis and the serotonin syndrome are associated with MDMA abuse, which can finally lead to death. Phase I metabolism of MDMA involves two main routes including the chain conversion by N-dealkylation to 3,4-methylendioxyamphetamine (MDA) or O-demethylenation of the ring substitute of both MDMA and MDA into the highly reactive catechol metabolites of 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA). These two later metabolites can be further oxidized to the corresponding ortho-quinones, which are able to enter in a redox cycling leading to generate reactive oxygen and nitrogen species that have been proposed to be the reason of cytotoxicity in several tissues such as liver, brain, kidney and heart.CYP2C19 is involved in the biotransformation of antidepressants and a miscellaneous group of drugs including PPIs, antiepileptics, and the anticoagulants. Among these drugs, omeprazole has been extensively used as an appropriate probe substrate. In rats Similar to humans Omeprazole has been metabolized by 2C19 to 5-OH-omeprazole and formation of this metabolite determines CYP2C19 activity.

Methods: the present study was carried out to investigate the possibility of CYP2C19 inactivation after encountering of an isolated perfused rat liver (IPRL) to different inlet concentrations (300 and 600 ng/ml) of MDMA. One direction perfusion with buffer contains Omeprazole has followed by same process with MDMA and again Omeprazole.

Results: 5-OH-omeprazole was reduced in both mentioned concentrations. The analysis of four latest sample intervals taken after exposure to MDMA, showed about 18% and 16.8% decrease in metabolite concentrations from 18.4 ± 7.0 to 15.3 ± 7.9 and from 19.4 ± 6.8 to 15.9 ± 5.7 μM after administration of administration of 300 and 600 ng/ml of MDMA respectively (pvalue<0.05).Similarly, the $AUC_{(0-t)}$ of metabolite also showed decrease from 461.4 ± 169.9 to 355.5 ± 187.3 and from 467.6 ± 192.2 to 371.5 ± 148.9 μM.min after administration 300 and 600 ng/ml of MDMA respectively (pvalue<0.05). In conclusion: the metabolic activity of CYP2C19 after exposure to MDMA is decreased where the reduction is concentration-independent.

Key words: CYP2C19, liver perfusion, MDMA, mechanism based inhibition, omeprazole.

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The Effects of Ph, Temperature and Protein Concentration on the *In Vitro* Binding of Flutamide to Human Serum Albumin

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Abstract

Human serum albumin (HSA), the most abundant protein in plasma, is best known for its extraordinary ligand binding capacity. In the present study the binding properties of flutamide to HSA at different temperatures, pHs and percentages of HSA were investigated. Thermodynamic parameters were also determined to describe the nature of binding interaction. A modified ultrafiltration method was used for accurate determination of flutamide-HAS binding parameters. Samples were extracted and analyzed by developed HPLC-UV method. Analysis of binding data was performed in terms of Scatchard, Klotz and Hill plots. Although kinetic parameters (n, K_a) were found to be affected by temperature, pH, and HSA concentration, flutamide-HSA binding percentage did not show significant differences under different experimental conditions. The negative value of Gibbs free energy (ΔG) indicated that the binding was spontaneous. Moreover, the negative value for enthalpy and entropy changes suggested that hydrogen bonding and van der Waal's forces played major role in the binding of flutamide to HSA.

Keywords: Albumin, Flutamide, pH, Thermodynami,.

Last Name	First Name	Proceeding Number
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Samarai	Vafa	P.1
Dibaei	Maryam	P.2
Rouini	Mohammadreza	P.2
Akbari Javar	Hamid	P.3
Gholibygloo	Elham	P.3
Khoobi	Mehdi	P.3
Roghayeh	Rastegar	P.3
Ghaznavi	Habib	P4
Hadizadeh	Maryam	P.4
Mahmoudian	Massoud	P.4
Tayebi	Ladan	P.4
Arghand Aliabadi	Zeinab	P.5
Shafiee	Kimia Shafiee	P.5
Taghizadeh	Seyed Mojtaba	P.5
Bakhtiari	Nima	P.6
Rashidi	Mohamad Reza	P.6
Taghavi Moghadam	Pouria	P.6
Dadashzadeh	Simin	P.7
Dorraj	Golnar	P.7
Erfan	Mohammad	P.7
Moghimi	Hamid Reza	P.7
Mirmusavi	Seyed Mohammad Hosein	P.8
Zadenajar	Parisa	P.8
Handali	Somayeh	P.9
Löbenberg	Raimar	P.9
Moghimipour	Eskandar	P.9
Ramezani	Mohammad	P.9
Sajadi Tabassi	Sayyed Abolghassem	P.9
Hosseinzadeh Ardakani	Yalda	P.10
lavasani	Hoda	P.10
Rasouli	Mona	P.10
Rouini	Mohammad-Reza	P.10
Valipour	Fatemeh	P.10
Goudarzi	Niloufar	P.11
Nesioonpour	Sholeh	P.11
Pipelzadeh	Mohammad Reza	P.11
Rezaee	Saeed	P.11
Saki	Nader	P.11
Taghavi Moghaddam	Pooria	P.11

Sadri	Sima	P.12
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Jansson	Britt	P.13
König	Frida	P.13
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Melander	Erik	P.13
Payan	Maryam	P.13
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Dehghani	Hossein	P.14
Taheri	Azadeh	P.14
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Mirzaei	Shahla	P.15
Abbasian	Mohammad Hadi	P.16
Ardekani	Ali	P.16
Hamedi	Fahimeh	P.16
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Karami	Zahra	P.19
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Saghatchi Zanjani	Mohamadreza	P.19
Rouini	Mohammadreza	P.20
Sheikholeslami	Behtaj	P.20
Bardia	Jamali	P.21
Hosseinzadeh Ardakani	Yalda	P.21
Jamshidfar	Sanaz	P.21
Lavasani	Hoda	P.21
Rouini	Mohammadreza	P.21
Elyasi	Sepide	P.22
Niazi moghadam	Mohammad Reza	P.22
Ebrahimi	Atefeh	P.23
Fattahi	Ali	P.23
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Lavasani	Hoda	P.25
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Ghayeni	Samaneh	P.26
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Ostad	Seyed Nasser	P.29
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Shafiei	Mohammad	P.31
Zandkarimi	Majid	P.31
Poursina	Narges	P.32
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Vatanara	Alireza	P.32
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Daeihamed	Marjan	P.33
Fazel	Mohammadtaghi	P.33
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Almasi	Ameneh	P.34
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hassanpour Ezatti	Majid	P.35
Malakijoo	Noorolhoda	P.35
Mousavi	Seyed Zahra	P.35
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Kiafar	Mohammad Reza	P.44
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Lavasani	Hoda	P.52
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Rouini	Mohammad Reza	P.52
Esmaeelzadeh	Sara	P.53
Valizadeh	Hadi	P.53
Zakeri-Milani	Parvin	P.53