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Mechanistic insights into the regulation of alternative NF-kB pathway: A promising step towards identifying novel drug targets in inflammation and cancer

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NF-kB signalling plays a central role in inflammation and cancer by controlling various processes including cell survival, proliferation, regulation of inflammatory cytokine expression etc. Fine-tuning of NF-kB response is therefore important to achieve normal homeostatic regulation of above processes as loss of control over NF-kB regulation would lead to pathological conditions such as inflammatory disorders and cancer. While the regulation of classical NF-kB has been extensively studied the mechanism by which the alternative pathway is regulated has remained elusive. Moreover whether loss of control over the alternative NF-kB contributes to inflammation and tumorigenesis has not been clear. Recent reports indicated that TNF receptor associated factors (TRAF) TRAF3, TRAF2 and cIAP play an important role in negatively regulating the alternative pathway by controlling the turnover of NF-kB inducing kinase (NIK), an essential kinase in this pathway. In resting cells TRAF3 forms a bridge between NIK and TRAF2-cIAP2 complex via its TRAF domain. In this complex cIAP2 acts as a E3 ubiquitin ligase that mediates K-48 linked ubiquitination of NIK leading to the proteasome dependent degradation of the latter. Deletion of TRAF3 or TRAF2 or cIAP disrupts the NIK-TRAF3-TRAF2-cIAP complex that results in NIK stabilization and constitutive activation of the alternative pathway. Interestingly, in some forms of B-cell malignancies such as Multiple Myeloma (MM) deletion of TRAF3 and cIAP as well elevated expression of NIK resulting in the constitutive activation of the alternative pathway were frequently observed. However, the mechanism by which NIK contributes to inflammation and cancer has ramined elusive. The current focus of our lab is to find novel insights into the regulation of this pathway and to study its role in inflammation and tumorigenesis.

Biography

Sivakumar Vallabhapurapu (Siva) is an Assistant Professor in the Department of Cancer and Cell Biology, University of Cincinnati, Cincinnati, Ohio, USA. He completed his graduate training in 2004 at the University of Karlsruhe, Karlsruhe, Germany, and was a postdoctoral fellow at the Fritz Lipmann Institute for Age Research in Jena, Germany and at the University of California, San Diego. At UCSD he worked with one of the world's famous scientists, Dr. Michael Karin and studied the regulation of NF-kB transcription factors in the immune system. Siva received fellowships from organizations such as GATE (1994) from The Government of India, Indian Institute Science (1997) and Boehringer Ingelhelm (2001). Siva has published very high impact papers in journals such as Nature Immunology, Science, Journal of Experimental Medicine etc., and has also contributed significantly to the field of immunology by writing a review on NF-kB signaling in the immune system, published in the journal Annual Reviews of Immunology.

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Transdermal needle-free delivery of peptides and proteins using water-in-oil microemulsions: High bioavailability, with drug dependent pharmacology

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The technical problems involved in the needle-free transdermal delivery of peptides and proteins have largely been resolved through the development of water-in-oil microemulsions. Biodistribution studies have shown that transdermally administered proteins remain resident in the skin for an extended period of time, with very little material appearing in the circulation. The resultant "dermal depot" of these pharmaceuticals results in significantly different biodistribution and pharmacology of the dermally applied pharmaceuticals when compared to sub-cutaneously administered material. Thus topical administration of IGF1, GHRP-6 or insulin lead to a much higher anabolic effect on muscle tissue than similar doses administered sub-cutaneously. Furthermore, there was a dose-dependent reduction in the weight of adipose tissue, following transdermal delivery of insulin, which was much greater than could be achieved with sub-cutaneously administered insulin, and which occurred without modification of serum glucose levels. Transdermal delivery of peptides and proteins formulated in water-in-oil microemulsions provides a novel means for altering the pharmacology of many sub-cutaneously administered drugs, with the added potential advantage of directly targeting a multitude of skin diseases, such as psoriasis, eczema, rosazea and skin cancer. This mode of delivery is currently under development at Transgene Biotek Ltd, Hyderabad for a range of applications.

Biography

Dr Russell-Jones completed his Ph.D at the University of Adelaide and postdoctoral studies at the Rockefeller University NY. He has published more than 50 papers in reputed journals, has presented at over 40 international meetings, and has over 50 filed provisional patents, the majority of which have proceeded to grant. Dr Russell-Jones is a preeminent scientist in the fields of oral and transdermal delivery of peptides and proteins. In addition he has worked extensively on the development of vitamin mediated targeting systems for the detection and treatment of tumours. He is the co-inventor on several ongoing projects in collaboration with Transgene Biotek Ltd.

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Oral drug delivery: Pharmaceutical technology archetypes

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Globally, pharmaceutical R&D has witnessed radical transformation in the area of drug delivery science. Several products have been tailored to meet the demand of the market with major focus on improving patient therapy compliance, and reducing toxicity profile. Dosage forms via different routes of administration engineered in this direction have given rise to a variety of Modified Release systems. Oral drug delivery products include those that modulate the drug release including controlled, prolonged, delayed, pulsatile and regiospecific drug delivery like gastroretentive, colonic release etc. The principle objective of such drug delivery technology archetypes is not only to modulate the pharmacokinetic profile but they also help to address unmet medical needs. This talk would focus on the growing emergence of diverse pharmaceutical drug delivery technology platforms, their benefit in product life-cycle management, regulatory perspectives, market potential and imminent prospects.

Biography

He earned his Ph.D. from University of Mumbai (India) and Post-doctorate from Kyoto Pharmaceutical University (Japan). He has published and presented several original research papers, articles and abstracts in peer reviewed journals and conferences. He has conceptualized innovative drug delivery platform technologies and is an inventor in number of patents. He is an invited speaker at international scientific meetings and conferences. He serves as reviewer for more than 30 scientific international journals and is on Editorial/Advisory board of various journals.

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Effect of bioenhancers on permeability and In-vitro release of various anti-tubercular agents

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Tuberculosis (TB) is a chronic infection caused by the Mycobacterium tuberculosis. It remains one of the leading infectious disease killers around the world. Moreover it is probably the most important single cause of morbidity and mortality among HIV-infected people. WHO has estimated that at the end of 2010 there were about 17.5 million persons with M. tuberculosis and HIV co-infection worldwide.

The treatment of TB involves administration of several drugs to which the organisms are susceptible and the response of mycobaterial infections to chemotherapy is slow, so the patient must take the medication on a regular basis for months to years. Otherwise microbial resistance develops rapidly. Higher frequency of drug administration, fluctuation in drug plasma level, resulting in poor patient compliance and increased microbial resistance are the major challenges before Anti-TB therapy.

Sustained release microspheres delivery system that releases the drug in the body in such a manner to keep the drug plasma concentration constant throughout the regimen.

Bioenhancers are the substances which, when given along with other drugs in various treatments, enhance the bioavailability and bioefficacy of the drug without altering the drug properties.

In a present research work, we have attempted to improve the Anti-TB therapy through a combination of microspheres and bioenhancer approaches. Sustained release microspheres of anti-tubercular drugs using various methods like modified emulsification and complex coacervation method were formulated and the effect of bioenhancers i.e. piperine and Carum carvi on the permeability and in-vitro release were studied. It has been found that, there was significant increase in permeability (studied using Franz diffusion cells) and in-vitro release (increment upto 70-80% when used single and 80-90% when used in combination). Other parameters like % yield, particle size (μ), % drug entrapment efficiency, % bioadhesion and drug-excipient study using FTIR were also studied.

Biography

Mr. Prashant L. Pingale has completed his M. Pharm. from Dept. of Pharmacy, Annamalai University, Tamil Nadu and pursuing his doctoral research studies at School of Pharmacy and Technology Management, NMIMS Shirpur Campus, a distinguished institute in Pharmacy and Management Education. He has 8 national / international publications in his credit. He has presented 10 research / oral presentations in international / national conferences, workshops and symposia.

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Transdermal delivery of lopinavir loaded ultradeformable vesicles (UDVs): An alternate way to circumvent its limited oral bioavailability

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Lopinavir, (2S)-N-[(2S,4S,5S)-5-[2-(2,6-dimethylphenoxy)acetamido]-4-hydroxy -1,6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-1,3-diazinan-1-yl)butanamide, is one of the specific reversible inhibitors of the HIV protease, an enzyme that has an essential role in HIV replication and the formation of an infectious virus. Sensitivity of lopinavir towards intestinal metabolizing enzyme cytochrome P450 3A4 severely limits its oral bioavailability. In addition, its high molecular weight (~628Da), poor aqueous solubility (~0.01mg/ml), high log P value (~4.56) and susceptibility for P-glycoprotein efflux transporters further adversely affect the oral absorption.

To overcome such a problem, the transdermal route could be a better alternative in providing sustained levels of drug for a greater time period, bypassing presystemic metabolism, and hence increasing patient compliance. However, its clinical application has found limited due to the presence of the outermost barrier layer of skin, the stratum corneum (SC). Several physical and chemical methods have been developed till date for increasing permeation of active moiety through skin. In the present investigation, elastic liposomes are selected as a drug delivery module for their ultradeformable nature and ability to improve solubility of poorly water-soluble drugs which leads to a greater concentration gradient across the skin and subsequently improves permeation.

The current work includes development of lopinavir loaded elastic liposomes, its characterization and investigation of its transdermal drug delivery potential. The prepared elastic liposomes were extensively optimized for various process variables along with drug:lipid and lipid:surfactant ratio. The optimized UDVs were characterized to be spherical, unilamellar structures having low polydispersity (PDI=0.109), nanometric size range (mean vesicular size = 128.0±3.6nm), and considerable percentage entrapment efficiency (79.86±0.230). Ex vivo skin permeation studies of lopinavir across rat abdominal skin indicated significantly ($P < 0.05$) greater percent drug release (19.08%) and skin deposition (23.19%) while poor surface drug retention (56.34%) when compared to conventional liposomes and plain drug solution.

Biography

Dr. (Mrs.) Hetal P Thakkar has completed her Ph.D at the age of 33 years from The M.S. University of Baroda. She is lecturer in Pharmacy Department, Faculty of Technology & Engineering, The M.S. University of Baroda, a premier department. She has published more than 15research papers and review articles in reputed journals and has presented papers in various conferences. She is a recipient of "Career Award for young teachers" from All India Council of Technical Education, for which a grant of Rs. 10.5 Lakhs is sanctioned.

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Design, development and evaluation of ultra-deformable vesicular drug delivery system for topical delivery of Itraconazole

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In the last decade, topical and transdermal delivery of poorly soluble drugs by lipid based particulate systems have gained much attention in the pharmaceutical field due to their suitable properties for the delivery of the drugs through the skin, which is a barrier against the systemic absorption of drugs. Recently, innovative, flexible, vesicular systems termed as "Ethosomes" and "Transferosomes" have been developed for topical/ transdermal delivery of various drugs. These systems have wonderful property to permeate intact through the human skin due to their high elasticity, which has an immense consequence for design of carrier system both for local and systemic delivery of hydrophilic and lipophilic drugs by topical application. Itraconazole is an antifungal drug with broader spectrum of activity compared to ketoconazole or fluconazole. Topical route for local or systemic delivery of itraconazole has not been explored extensively as indicated by the availability of fewer publications. Thus, in the present work, it is being attempted to deliver itraconazole with improved efficacy, lower absorption variability and improved bioavailability by topical route using ultra-deformable vesicular drug delivery systems. Different formulations of ethosomes as well as transferosomes were prepared by employing design of experiment techniques. The formulations were evaluated for viscosity, vesicle size, drug content and in-vitro drug release studies. Both types of ultradeformable delivery systems were evaluated for their performance in terms of skin penetrability and formulation stability. Computer assisted design of experiment is very wise approach to find out the optimum formulation. Itraconazole can be entraped into the ethosomal vesicles. Itraconazole can be delivered to systemic circulation using ethosome, having the deeper penetration in skin. Further in-vivo release study is required to confirm that this formulation have the tendency to deliver systemic circulation through topical application.

Biography

Dr. Shivprasad Majumdar has completed M.Pharm. (Biopharmaceutics) in 2006 from Govt. College of Pharmacy, Karad, affiliated to Shivaji University, Kolhapur and Ph.D. in 2011 from NMIMS, Mumbai. He is working as Assistant professor in NMIMS and awarded as Best Faculty of 2010-11. He has published more than 10 papers in reputed journals and presented over 25 papers at various International and National conferences. He won best presentation awards in different events like PharmaGlow's Power Point Presentation Competition – 02 arranged by Pharmainfo.net, Canada, National Level Workshop on "Coating Technology of Solid Dosage Forms" organized by Gurunanak College of Pharmacy, Nagpur, etc.

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Bioavailability assessment of topically applied ufasomal formulation for treatment of Arthritis

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Cutaneous route for drug administration has many advantages over other pathways, including avoidance of first pass effect, delivering drugs continuously, having fewer side effects, and improving patient compliance. This work describes comparison of bioavailability between novel vesicular drug carrier systems called ufasomes encapsulating dexamethasome with marketed formulation and explores its potential as surrogate drug delivery system for efficient topical application. Cost effectiveness and ease of preparation are two main edges oleic acid vesicles over transfersomes and conventional liposomes. An in vitro technique has been developed for evaluating the delivery performance of topical formulations. A thin and uniform layer of formulation was applied in facsimile to actual usage conditions by troweling the vehicle across a thin, circular copper template (250 pm in thickness). Ufasomal gel, liposomal gel, vehicle and plain drug solution each containing a range of concentrations of minoxidil, were applied over rat skin within a defined circular area of 1.54 cm'. The rates of permeation of model drug from these formulations were determined by finite dose diffusion experiments. For formulations containing 2% model drug , the flux from the ufasomal gel formulation was about 4 times higher than fluxes from the liposomal gel . Even though all ufasomal gel formulations were initially saturated with drug, the flux of minoxidil from these creams increased as the concentration of model drug was increased from 0.5% to 2%. In contrast, the delivery rates from the liposomal gel and vehicle did not appear to be dependent on the model drug concentration applied .Under the operative experimental conditions, the percent coefficients of variation of flux of model drug from these formulations were less than 15%. To achieve this low level of variability, the skin samples were all obtained from the same cadaver abdomen. If one assumes that the efficacy of a particular formulation is dependent on the ability of the drug to be released from the vehicle and diffuse through the skin, the studies show that the nature of the vehicle can profoundly affect delivery even when excess solid drug is present. They also indicate that reliable in vitro comparisons of drug delivery are possible as long as one performs the studies on skin samples taken from the same section of skin.

Key words: - ufasomes, topical delivery

Biography

I, Arvind Sharma have completed his M.pharmacy from Punjabi university Patiala Punjab India and persuading PhD from chitkara university Punjab. I am working as Assistant professor (pharmaceutics) in Chitkara College of pharmacy. I have published more than 20 papers in reputed journals and attended more than 20 national and international conferences

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Investigation of DNA integration into reproductive organs following intramuscular injection of DNA in mice

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DNA immunization with plasmid DNA encoding bacterial, viral, parasitic and tumor antigens has been reported to trigger protective immunity. The use of plasmid DNA vaccination against many diseases has produced promising results in animal and in human clinical trials. However, several safety concerns about the use of a DNA vaccine exist such as the possibility of integration into the host genome and elicitation of adverse immune responses. In this study, we examined the potential integration and bio-distribution of pcDNA3.1+PA, a new vaccine candidate with Gen Bank accession number: EF550208 encoding the PA63 gene, in reproductive organs of mice, ovaries and uterus in female and testis in male mice. Animals of both sexes were injected with pcDNA3.1+PA in intramuscular route. Host genome integration and tissue distribution were examined using PCR and RT-PCR methods, twice a month during 6 months. The results confirmed that pcDNA3.1+PA was not integrated into the host genome and they could not enter to reproductive organs. This finding has important implications for the use of pcDNA3.1+PA plasmid as a vaccine and opens new perspectives in DNA vaccine area.

Keywords: DNA, Integration, Intramuscular injection, Reproductive organs, Mice

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