CHAPTER 44

PHARMACY

Doctoral Theses

01. ARYA (Amit)
Design and Evaluation of Novel pH-Sensitive Polymers for colon Targeted drug Delivery.
Supervisor : Prof. D P Pathak
Th 23615

Abstract
(Not Verified)

Conventional treatment options for inflammatory bowel diseases are anti-inflammatory drugs, corticosteroids, Immunosuppressants, antibiotics etc. Non-specificity of these drugs causes serious adverse effects. Thus, targeting a drug molecule directly to the site of disease i.e. colon wouldmaximize the local concentration of drug and lower the dose required for the treatment, thereby minimizing the side effects. Acrylic acid-co-butyl methacrylate (AA: BMA) and Methacrylic acid-cobutyl methacrylate (MAA: BMA) copolymers were synthesized in different molar ratio. AA: BMA (4:6 and 5:5) and MAA: BMA (3:7 and 4:6) showed less swelling and erosion at pH 1.2, while at pH above 6.8, the swelling and erosion was high. This suggested that these polymers would protect the drug release in the stomach and release it at the distal ileum or colon. The copolymers were characterized by FTIR, DSC, XRD and GPC. The copolymers were found to be highly hemocompatible. Therefore, there use as biomaterials for drug delivery purpose would be safe. The selected copolymers were used for the preparation of aceclofenac loaded microparticle formulations. The microparticles were characterized using FTIR, XRD, DSC and SEM. The percentage aceclofenac loading was about 5- 6%, while the drug loading efficiency was about 30 %. Average particle size of microparticles was about 105 µm. In vitro drug release profiles in buffers of different pH showed the colon targeting behavior of the formulations. As these formulations release major portion of the drug at pH ≥6.8, these would act as enteric formulation, and target the drug to the distal ileum or colon. The in vivo studies were are also in accordance with the in vitro release studies, and the microparticle formulation showed significant improvements in the TNBS induced colitis in rats.

Contents

02. BAJAJ (Sakshi)
Identification, Isolation, Characterization and Biological evaluation of Some herbal Drugs.
Supervisor : Dr.S R Wakode
Th 23613

Abstract
(Verified)

Swertia alata and *Artabortrys hexapetalus* were selected on the basis of their Traditional claims for FEVER. Standardization of a crude drug is an integral part of establishing its correct identity. Hence, the selected medicinal herbs were identified and authenticated using macroscopic, microscopic and physico chemical characters which were find complied with the standards prescribed in the official books. Preliminary phytochemical screening of the extracts resulted in presence of variety of secondary metabolites in both plants showing its potential for biological activity. The rich content of total phenols, flavonoids showing its strong anti-oxidant potential. All the extracts were analyzed by HPTLC for development of fingerprinting, which will surely help in determining identity, purity and adulterants of the herbs to ensure correct identity. Three phytoconstituents have been isolated and characterized from *S.* alata*.* All these compounds were novel except SA-1. Oil of leaves of *A. hexapetalus* were isolated by hydro-distillation followed by GCMS analysis resulted in identification of many new bioactive compounds, which can lead to be helpful in Drug Discovery. In pharmacological activities, it was found that crude extracts of selected medicinal plants exerted significant activities by different methods. Ethanolic extract showed maximum activity due to presence of majority secondary metabolites in it. Further *In vivo* studies may reveal the exact mechanisms of action responsible for the activities. In antileishmanial studies, petroleum ether extract showed maximum activity, it may be due to presence of terpenoids as characterized in the GCMS spectra of *A. hexapetalus. Potent activity of extract reveals that these drugs can be taken as lead as single or in combination for development of new PHYTOPHARMACEUTICAL for KALAZAR.*

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03. DONGARE (Shirish S)

Investigate the Protective and therapeutic Role of Herbal Drugs in the Management of Diabetes and its Complications by In-Vitro and In-Vivo Techniques.

Supervisors: Dr. Rajani Mathur and Dr. Rohit saxena

Th 23611

Abstract
(Not Verified)

The chronic hyperglycemia is the primary causal factor underlying the development of various macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular damage including retinopathy, nephropathy and neuropathy. Due to the limitations of the current treatments of Diabetes and its complications, new drug regimens are the need of the hour. WHO recommends the evaluation of the effectiveness of medicinal plants in conditions where we lack the conventional allopathic treatment of diabetes. Based on the literature survey for established antihyperglycemic, anti-inflammatory, antioxidant and/or antiangiogenic activities, we selected standardized ginger extract and soya bean extract for to evaluate their potential in the management of diabetic retinopathy, diabetic cardiomyopathy and diabetic nephropathy in STZ induced diabetic rats and high glucose induced toxicity in cultured human RPE cells (ARPE-19) for diabetic retinopathy. The current study was aimed to find out therapeutic potential of herbal drugs for the prevention of diabetes and its complications in experimental models besides to study their effects were studied on several biochemical parameters like blood glucose, HbA1c, TNF-alpha, VEGF, Aldose reductase, total antioxidant etc. and histopathological, Immunohistopathology, TEM studies were carried out. Current study

showed that the standardized extract of Zingiber officinale and soya bean extract attenuates retinal as well as kidney microvascular and cardiac macrovascular changes in STZ-induced diabetic rats through its anti-inflammatory, anti-angiogenic, and antioxidant actions. Although, these effects, could result from anti-hyperglycaemic effects of ginger extract containing 5% gingerol and soya bean extract containing 98% genistein. However, the results of the in-vitro study clearly demonstrate that ginger extract and soya bean extract protects RPE cells from high glucose toxicity. Despite the fact that precise molecular targets remain to be determined, ginger extract and soya bean extract seems to be a potential candidate for further investigations.

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04. HIMANGINI

Synthesis, Computational Studies and Biological Evaluation of New Pyrazoline Derivatives.

Supervisor: Prof. D P Pathak

Th 23612

Abstract
(Not Verified)

Software repositories, such as bug repositories, source control repositories, archived communications, deployment logs and code repositories contain a rich and detailed information about the evolution of a software project. These repositories help software developers/triagers in the bug fixing process and software managers in the maintenance and evolution of the software products. Reporting a bug requires several attributes to be filled at the time of bug submission in the form of bug report.Bug report data is useful in various bug attributes prediction, namely bug priority, severity, CC list, fix time and assignee. Cross project validation is an important concern in empirical software engineering where we train classifier on one project and test it for prediction on other projects in the absence of historical data for training. A clear understanding of bug attributes, their interdependence and their contribution in predicting the other attributes will help in improving the quality of software.It is the need of the hour to discover the association of bug fix time and assignee with other bug attributes.Open source software is evolved through an active participation of the users in terms of reporting of bugs, request for new features and feature improvements. The code changes done in source code files due to these issues fixing increase the complexity of code which is used to predict the possible code changes in the software over a long run (potential complexity of code changes).A software is upgraded with the inclusion of new features and improvements in existing features. Some of the issues remain unresolved in the current release. These unresolved/leftover issues are added to the initial issue content of the next release and get fixed in subsequent releases. For the release time problem, the source code changes and left over issues of the previous release can be considered

Contents

05. RAWAT (Ashwani Singh)
Provesicular Approach for Combination Therapy.
Supervisors : Dr. Meenakshi K Chauhan and Dr. P.K.Sahoo
Th 23610

Abstract
(Not Verified)

Present research comprises of the development of a novel Pro Transferosome (ProT)-Gel based transdermal drug delivery system for delivering a combination of LAC and GLC with the aim of reducing pill burden and enhancing bioavailability. Two methods were developed for simultaneous detection of LAC and GLC through UV and HPLC. HPLC conditions included: mobile phase: acetonitrile, Na HPO buffer and methanol (55:40:5) at 1.2 mL/min; column oven temperature: 40^{0}C; sample cooler temperature: 25^{0}C; detector wavelength: 240 nm. Taguchi (L) design was used to ensure the robustness of the method. ProT-Gel was prepared by using phase separation coacervation method. A hybrid statistical design composed of Plackett–Burman (PB), Box-Behnken (BB), and Central Composite (CC) methods was used for optimization of formulation. Characterisation studies included scanning electron microscopy (SEM), confocal laser scanning microscopy (CLSM), encapsulation efficiency, and storage stability. E*x-vivo* and *in-vivo* studies were also conducted. PB suggested GLC/lipid ratio, solvent, buffer pH, soya phosphatidylcholine (SPC), and sodium deoxycholate (SDC) significantly impacted the transferosome characteritics. The optimised values obtained using BB were: GLC/lipid=7.49, solvent=tert-Butyl alcohol, buffer pH=5.0; and using CC were: SPC=83.89%, SDC=24.99%. Average diameter using SEM was 206.76nm with a PDI of 0.235. The encapsulation efficiency after hydration was 90.46% and 95.46% for GLC and LAC, respectively. *Ex-vivo* study showed enhancement ratio of 2.11 and 4.64 for GLC and LAC loaded ProT-Gel, as compared to drugs' suspension. CLSM confirmed penetration capability of upto 180 µm. Relative bioavailability was 156.20% and 219.02% for LAC and GLC, respectively with a single-dose of optimized ProT-Gel formulation. The formulation was stable under refrigerated conditions (4±1^{0}C). A novel ProT-Gel was succesfully developed to deliver LAC and GLC combination transdermally. Method designed to analyse and quantify the drugs simultaneously was rapid, accurate, and sensitive. Hybrid statistical design led to an optimized formulation with minimum resources, time, and effort.

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06. SACHIN KUMAR
Anticancer Activity of Few selective Plants.
Supervisor : Dr. Ramesh Babu Bodla
Th 23734

Abstract
(Not Verified)

Plant constituents are on the forefront as anticancer remedies. *Hamelia patens* Jacq. is an herbaceous perennial plant of family Rubiaceae. Extracts of different parts of the plant have shown antidiarrheal, antifungal and cytotoxic properties. *Aegle marmelos* is a medium size perennial tree which belongs to family Rutaceae. Various studies have reported that leaf extracts of *A. marmelos* have produce anticancer, cardiotonic,

antidylipidemic and hypoglycemic effects. Leaves of *Hamelia patens* and *Aegle marmelos* were found to have free radical scavenging and antioxidant properties which could be accrued to the presence of phenolic and flavonoid compounds. Previous studies have shown the anticancer effects of *Hamelia patens* and *Aegle marmelos* in different cancer cell lines. Here, we studied the anticancer effects of *Hamelia patens* and *Aegle marmelos* in other cancer cell lines i.e., MCF-7 (breast cancer), H-460 (lung cancer), SF-268 (Glioma cancer). Leaves of *Hamelia patens* were found to contain oxindole alkaloids and have shown cytotoxic effect in breast cancer cell line. Quercetin was also found to be present in leaves of *Hamelia patens* which might be responsible for the cytotoxic effects of *Hamelia patens* in breast cancer, lung cancer and glioma cancer cell lines. Leaves of *Aegle marmelos* were found to have cytotoxic effects in breast cancer, lung cancer and glioma cancer cell lines which could be attributed to retinoic acid, stigmasterol and umbelliferone other than imperatorin.

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07. SHARMA (Navneet)
Development and Evaluation of the Efficacy and Safety of the Dermal Nanoformulation and Wipe Against CBRN Contaminants.
Supervisors: Dr. D P Pathak and Dr. R K Sharma
Th 23614

Contents

08. SHARMA (Vidushi)
Identification and biological Evaluation of Novel and Selective Phosphodiesterase-4B Inhibitors.
Supervisor: Dr. Sharad Wakode
Th 23609

Abstract
(Verified)

Phosphodiesterases hydrolyse cyclic nucleotides and thus regulate their intracellular levels. Among different family members, phosphodiesterase 4 (PDE4) selectively hydrolyse cyclic adenosine monophosphate (cAMP). PDE4 is predominantly expressed in immune and inflammatory cells and thus reported to suppress a wide spectrum of inflammatory responses in animal models of different inflammatory disorders, such as asthma, COPD, psoriasis, inflammatory bowel diseases, and rheumatoid arthritis. Therefore, PDE4 is a proven therapeutic target for inflammatory and autoimmune diseases. However, the non-selective PDE4 inhibitors like rolipram are associated with severe side effects like nausea and emesis. The behavioural correlation of emesis in mice by deleting the PDE4D encoding gene confirmed that the inhibition of PDE4D is responsible for the emetic effect of non-selective PDE inhibitors. Among four PDE4

isoforms (PDE4A, PDE4B, PDE4C and PDE4D), PDE4B is abundant in inflammatory cells, immune cells and smooth muscle cells. The role of PDE4B has been thoroughly studied in inflammatory pulmonary disorders. Therefore, selective PDE4B inhibitors can provide anti-inflammatory efficacy without PDE4D associated side effect. However, conserved active site residues of the two enzymes make it difficult to design selective PDE4B inhibitors. The thesis entitled “Identification and biological evaluation of novel and selective phosphodiesterase- 4B inhibitors” describes our studies on PDE4 using various computational approaches viz. molecular dynamics simulation, binding free energy calculation, per residue energy decomposition, molecular docking, shape-based pharmacophore mapping, virtual screening and crystal structure analysis. It aims to identify selective and potent PDE4B inhibitors using the knowledge generated by carrying out these studies. It also includes new computational methodologies and biological testing of serendipitous hypotheses to address some of the current challenges involved in the identification of new small molecules that selectively inhibit PDE4B. In conclusion, this thesis enlists the potential, novel and selective PDE4B inhibitors having additional antioxidant properties.

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