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AN INNOVATIVE REVIEW ON TARGETED DRUG DELIVERY SYSTEM BY USING FORMULATION SOFTWARE

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ABSTRACT

A targeted drug delivery system enhances therapeutic concentration by selectively delivering drugs to specific areas, minimizing side effects and protecting healthy tissues. It utilizes various carriers to maintain the drug's integrity while targeting diseased organs. Over the past 60 years, drug delivery technologies have evolved through three generations, with the first focusing on controlled release and the recent generation addressing biological barriers. Key principles for successful drug targeting include effective drug loading, avoidance of degradation, precise delivery, and timed release. The application of targeted systems is essential for medications with instability, poor absorption, short half-lives, and low specificity. Advantages over traditional methods include reduced dosage frequency, improved bioavailability, and increased treatment efficacy. Different drug delivery approaches are employed for the central nervous system, including both invasive and non-invasive methods. Quantum dots and transdermal patches are examples of innovative delivery mechanisms.Targeted drug delivery shows promise in treating various diseases, including diabetes and cancer, and utilizes methods like liposomes and nanoparticles for high stability and specific targeting. Future research aims to further refine these systems to improve drug efficacy and reduce side effects.The application of Design of Experiment (DOE) methods

aids in optimizing drug formulations, with a focus on enhancing the effectiveness of targeted therapies. A study on olanzapine showcased the potential of polymeric nanoparticles to reduce adverse effects while maintaining therapeutic action, revealing a trend towards more effective antipsychotic treatments with improved patient compliance.

KEYWORDS: Targeted drug delivery system, Dose Dumping, Factorial design, Olanzapine, DoE.

INTRODUCTION

A targeted drug delivery system is a method that selectively and effectively targets specific regions, enhancing therapeutic concentration and preventing non-targeted areas like organs or tissue. This approach can enhance therapeutic activity with less adverse effects and events, as it allows for the delivery of the active moiety to the targeted region, thereby reducing the risk of adverse events.[1]

A medication's pharmacological characteristics determine its biological effects in a patient. The drug-target interaction is compromised unless the drug is delivered to the site of action at a concentration and pace that maximizes therapeutic effects while minimizing side effects. Targeted drug delivery aims to deliver the therapeutic agent's pharmacological effect to diseased organs exclusively, sparing healthy ones. This system uses various carriers to preserve and deliver the intact drug to the chosen tissue or organ. Unlike traditional dose forms, targeted drug delivery releases the medication in a dose form, which has drawbacks such as immediate effects and intrusiveness. Oral administration is not suitable for many medications, including peptide pharmaceuticals, due to poor oral absorption.[2]

Modern drug delivery technology, which is 60 years old, has developed numerous systems over the years. The first generation (1950-1980) was successful in developing controlled release formulations for clinical applications, while the second generation (1980-2010) struggled with physicochemical and biological barriers. The third generation (from 2010) aims to overcome both. Drug delivery systems increase drug administration efficiency, with excipients enhancing drug efficacy. Occasionally, a new drug can become a blockbuster by exceeding annual sales expectations.

HISTORY

Prior to 1950, medications were made as pills or capsules with instantaneous release mechanisms. Smith Klein Beecham introduced the first sustained release formulation in 1952, allowing controlled drug release kinetics through Spansule technology. This technique helped control the kinetics of drug release at a preset pace, reducing disparities between 1G and 2G delivery systems. The lack of clinical applications of 2G technologies is due to the limitations of transdermal and oral medication delivery methods, which are directly influenced by changes in in vitro drug release kinetics. This lack of development is hindering the development of 3G-based clinical solutions. The limited effectiveness of 2G drug delivery techniques stems from their incapacity to manage the uncertainties and unpredictabilities of the biological environment, while 1G formulations' inventiveness is primarily responsible for controlling their physicochemical properties, such as cell and water solubility.[3]

DRUG TARGETING NECESSITATES THE FOLLOWING FOUR PRINCIPLES

1. Drug loading to the target site
2. Avoiding drug degradation by bodily fluids
3. Reaching the target site
4. Releasing the medication at the designated spot at the predetermined time.

Depending on the route to be taken, different drug delivery mechanisms must be used at different body areas of interest.

IN DRUG TARGETING, THE DRUG MAY BE DELIVERED TO

• The capillaries of the target site.

• The specific type of cells as in the case of cancer cells.

• Specific tissues or organs which recognize the drug.

CAUSES OF USING THE TARGETED DRUG DELIVERY SYSTEMS

There are several causes for the application of a targeted drug delivery system which include:

1. Low drug stability.
2. Poor drug absorption.
3. The short half-life of the drug.
4. The large volume of distribution of the drug.
5. Low drug specificity.[3]
6. Narrow therapeutic index of the drug.

TAILORED MEDICATION DELIVERY SYSTEMS VS TRADITIONAL DRUG DELIVERY

• Reduces dosage variation and frequency.

• Improves site-specificity, bioavailability, and absorption.

• Lower dosage eliminates therapeutic value with minimal side effects.

• Increases dosage stability and active moiety storage.

• Simplifies dosage delivery process for targeted areas.

• Demonstrates appropriate treatment efficacy quickly.

Drug Targeting Biochemical Processes

• Cellular uptake and processing.

• Transport across epithelial barrier.

• Extravasation.

• Lymphatic uptake.

CELLULAR UPTAKE AND PROCESSING OVERVIEW

• Endocytosis is a process that takes up macromolecular assemblies, involving internalization of the plasma membrane and extracellular material absorption.

• Pinocytosis captures molecules proportional to concentration and size, occurring more slowly than phagocytosis.

Transport across the epithelial barrier

• Drugs with low molar mass can pass through the epithelial barrier through selective and non-selective endocytosis.

• Active transport depends on the structural integrity of epithelial cells, while passive transport is more prevalent in damaged mucosa.

Extravasation

• Diseases often result from malfunctioning cells outside the cardiovascular system, requiring drug extravasation to leave the central circulation.

Lymphatic uptake

• Drug molecules can either reabsorb directly into the bloodstream or enter the lymphatic system, entering systemic circulation.

APPROACHES TO CNS DRUG DELIVERY

A. INVASIVE APPROACHES OR NEUROSURGICAL APPROACHES

- Intra cerebro- ventricular (ICV) infusion
- Convection-enhanced delivery (CED)
- Intra-cerebral injection or implants
- Disruption of the BBB.

B. NON-INVASIVE

- **Chemical techniques** a. Prodrug b. Drug conjugate
- **Colloidal Techniques** a. Nano particles b. Liposome

Quantam dots are in all three spatial directions, the motion of conduction band electrons, valence band holes, or excitons—bound couples of conduction band electrons and valence band holes—can be contained within a quantum dot, a semiconductor nanostructure.

Because of their theoretically high quantum yield, quantum dots are especially important for optical applications. The transdermal approach involves the topical administration of medications in the form of patches, which are designed to deliver pharmaceuticals for systemic effects at a controlled and preset rate. A transdermal medication delivery system, which comes in both passive and active designs Pharmaceuticals can now be administered across the skin barrier thanks to these devices. Transdermal patches operate quite simple in theory. Folate Targeting: A drug delivery technique used in biotechnology is called folate targeting.[4]

APPLICATION OF DRUG DELIVERY IN DISEASE TREATMENT

- Targeted drug administration is used in treating diseases like diabetes and cardiovascular disorders.
- Regenerative techniques are being used to treat cardiac conditions.
- Stem cell therapy uses targeted medication delivery to restore heart's contractile function.
- Liposome therapy is a treatment for tuberculosis, improving targeted site concentration and microphage penetration.
- 3D printing is used to target cancerous tumors, showing therapeutic effect at the targeted location.
- Other applications include protein detection, bio detection of pathogens, tissue engineering, MRI contrast enhancement, drug and gene therapy, DNA structure probing, and drug discovery.

FUTURE PROSPECTS

• Future researchers focus on targeted drug delivery due to benefits like target specificity, improved bioavailability, stability, and reduced side effects.

• Methods like liposomes, nanoparticles, microspheres, microsponges, niosomes, and aquasomes focus on specific target locations for high stability and consistent release rates.

• Nanoparticles offer low dosage, target specificity, and excellent bioavailability of poorly soluble medications due to their high lipophilicity.[5]

DESIGN OF EXPERIMENT

The Design of Experiment (DOE) is a statistical method used in various scientific and industrial domains to create, advance, and optimize processes and products. DOE approaches involve establishing goals, response variables, levels, components, experimental design, and method of experimentation. The type of research, process type, and available resources typically determine variables in the DOE.

A DOE consists of a sequence of actions: preparation, experiment execution, and analysis of experimental data using statistical techniques. The first stage involves identifying the investigation problem and choosing a system or process. The second stage defines variables influencing performance indicators, the number of experimental runs, and an appropriate array. The third stage covers the experiment's execution and data gathering. The final step involves data analysis using statistical tools and result interpretation.

Factorial experiments are also used to investigate the effects of multiple elements. Full factorial design (FFD) is a factorial experiment that includes every possible combination of selected factors and levels. The resolution level of the design determines the order of confounding primary effects and their interactions. Some designs, such as definitive screening or response surface methodology (RSM), are derived from factorial designs and can be considered partial factorial designs.[6]

STATISTICAL TOOLS OVERVIEW

• Analysis of variance (ANOVA): Determines if group means in a sample differ and if these variations are due to chance or a known cause.

• DOE: Sample is a collection of experimental runs chosen based on design.

• ANOVA quantifies the impact of different predictors on the dependent variable.

• Regression analysis: Creates a quantifiable relationship between variables using a regression equation.

• ANOVA assesses the influence of factors, interactions, and randomness on response amount.

METHODOLOGY

This study aims to investigate an issue by identifying independent and dependent variables, creating a numerical representation for simulations, determining the appropriate Decision Support Methods (DOMs), applying numerical simulations to apply multiple DOMs, analyzing the data post-processing, assessing the quality of data from various DOEs, and creating recommendations for choosing the best DOM based on lessons learned and literature review. The study also conducts data analysis and post-processing to determine the "ground truth" of the data.

GENERAL RECOMMENDATION

The general recommendation is to provide broad recommendations for researchers and designers in choosing the best Design Energy Efficiency (DOE) systems, focusing on a DOE-based approach that results in a more deliberate and grounded decision process. This approach is particularly useful for studies with limited resources that seek to study complex systems or processes with some degree of nonlinearity, which is typically present in natural and architectural physics processes.

The recommendation also highlights the importance of careful assessment when determining categorical aspects in building science challenges. Discrete product classification, such as components with preset mechanical, thermal, or optical qualities, is often encouraged by technology in the building business. However, many variables that seem categorical at first glance are actually continuous from a physics standpoint. To comprehend the "true" nature of the factor's physical attributes behind technical implementations, the researcher's familiarity with the physics and phenomena stated in the problem is crucial. This approach helps researchers and designers make informed decisions about DOEs and their effectiveness in various scenarios.[6]

AN OVERVIEW USING DOE TECHNOLOGY OF THE DRUG OLANZAPINE

This study aimed to encapsulate different nano-antipsychotics, such as olanzapine, in polymeric nanoparticles to investigate the possibility of reducing drug-related extrapyramidal

side effects. The polymeric nanoparticle systems were prepared using FDA-approved polycaprolactone and a simple nanoprecipitation technique using a factorial design and DoE approach. Factors selected for optimization during formulation development included polymer content and surfactant concentration at three different levels (32 factorial design). The formulation was modified with a surfactant (polysorbate 80) to increase the efficiency of the brain targeting the nanoparticles developed through endocytosis.

Catalepsy was induced in a rodent model, and the designed formulations were investigated in comparison with pure drug solution for efficiency in decreasing extrapyramidal adverse effects. In vitro characterization studies demonstrated a narrow size distributed nanoparticles with high stability indicating zetapotential and high encapsulation efficiency. In vitro release studies resulted in an extended release of atypical antipsychotic for 60 hours from drug-loaded optimized nanoparticulate formulations. The catalepsy studies in rodent model demonstrated a significant decrease in extra pyramidal adverse effects compared to the pure atypical antipsychotic.

The designed antipsychotic loaded polymeric nanoparticulate system may be highly promising for the tremendous improvement of antipsychotic therapy with reduced adverse effects. Non-adherence to antipsychotic medication often leads to poor tolerance, which can reduce the effectiveness of treatment. Most of these side effects are dose- and concentration-dependent. Positron emission tomography (PET) can estimate the D2-like receptor uptake in the brain required for an antipsychotic effect and the level above which EPS occurs.

There is a need for long-acting antipsychotic medications that control or eliminate psychotic symptoms with fewer or fewer side effects and can be designed to increase patient consent. A small number of oral and intramuscular formulations of olanzapine are currently available on the market, but the oral route is not the first choice for the treatment of acute phase schizophrenia. Intra-muscular controlled release dosage forms of Olanzapine are designed for very prolonged duration, but this is not effective for acute phase treatment.The authors have developed a systematic approach to include a detailed study of antipsychotic-induced extrapyramidal effects using a new nanoparticle formulation of the atypical antipsychotic agent olanzapine.

FORMULATION CONSIDERATION NANOPRECIPITATION ASPECT

The nanoprecipitation method is used to incorporate hydrophobic drugs into nanoparticulate systems, such as polymeric nanoparticulate systems. This technique involves rapid solvent diffusion across the solvent-polymer and aqueous phase interface. Olanzapine-loaded poly-caprolactone nanoparticulate systems were prepared using this method, exhibiting narrow size distribution, high encapsulation efficiency, and extended drug release characteristics. Variables like polymer and surfactant concentration significantly influenced these responses.[7]

CONCLUSION

Our Review provides a quick overview of how the two systems have integrated for the formulation based on the new technology, DoE. The use of targeted drug delivery systems and DoE-based formulations has grown significantly in recent years. The targeted drug delivery system significantly enhances therapeutic efficacy by selectively delivering medications to specific sites, thereby minimizing adverse effects and improving patient outcomes. This innovative approach, supported by advancements in drug formulation technologies, holds promise for more effective treatments across various medical conditions.

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