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DESIGN AND DEVELOPMENT OF NDDS OF CAPTOPRIL DRUG USED IN THE TREATMENT OF CHF

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ABSTRACT

Congestive heart failure (CHF) is a prevalent cardiovascular condition characterized by the heart's inability to pump blood efficiently, leading to symptoms such as shortness of breath, fatigue, and fluid retention. Captopril, an angiotensin-converting enzyme (ACE) inhibitor, has been widely used in the management of CHF due to its ability to reduce blood pressure and improve cardiac function. However, its therapeutic efficacy is often limited by poor bioavailability and rapid clearance from the systemic circulation.Liposomes, lipid-based vesicular structures, offer a promising approach to enhance the delivery of captopril to the target site, thereby improving its therapeutic outcomes. The design and development of liposomal formulations of captopril involve encapsulating the drug within lipid bilayers, thereby protecting it from degradation and extending its circulation time in the bloodstream. Additionally, surface modification of liposomes with targeting ligands can facilitate their accumulation in the myocardium, enhancing drug uptake at the site of action.This review discusses the principles underlying the design and formulation of liposomes for captopril delivery, including lipid composition, size optimization, and encapsulation efficiency. Moreover, it explores various techniques for characterizing liposomal formulations, such as particle size analysis, drug release kinetics, and stability studies. Furthermore, the potential advantages of liposomal captopril delivery, including improved bioavailability, reduced systemic toxicity, and enhanced therapeutic efficacy, are highlighted.

Keywords: bioavailability, Congestive heart failure, captopril, Liposomes,

1. INTRODUCTION

Novel Drug Delivery System is to provide a therapeutic amount of drug to the appropriate site in the body to accomplish promptly and then maintain the desired drug concentration. The drug- delivery system should deliver drug at a rate control by the necessarily of the body over a specified term of treatment. Many types of novel approaches of drug delivery system are discovered from which in this research paper liposome is used as drug delivery system for captopril which is used in the treatment congestive heart failure and hypertension. Congestive heart failure (CHF) represents a significant and growing public health concern worldwide, posing substantial challenges for patient, healthcare systems, healthcare providers alike. This chronic condition, characterized by the heart's inability to pump blood efficiently to meet body's metabolic demand's, results in a cascade of symptoms and complications that significantly impact patient's quality of life and overall prognosis. In this thesis, we aim to explore various aspects of chf, including its pathophysiology, etiology, sign's and symptoms, treatment, cardia remodelling, stages, development of heart failure.CHF arises from various etologies, including coronary artery diseases, hypertension, valvular heart disease cardiomyopathies, and congential heart defects, each contributing to impaired cardiac function and structural adnormalities. Despite advances in medical therapy and interventions, CHF remains a leading cause of morbidity and mortality globally, with a substantial economic burden stemming from hospitalizations, outpatient care and loss of productivity.Liposomes are simple microscopic vesicels in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecule. Structurally liposomes are cocenteric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayers mainly composed of natural or synthetic phospholipids.The issues mentioned above are discussed in detail in this review paper.

1.1 CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a chronic and progressive condition characterized by the heart's inability to pump blood effectively to meet the body's needs. It is a significant public health concern globally, affecting millions of individuals and accounting for substantial healthcare expenditures and morbidity. Understanding the pathophysiology, risk factors, clinical manifestations, diagnosis, and management of CHF is essential for healthcare providers and patient like.CHF typically develops as a result of underlying cardiovascular diseases that damage or weaken the heart muscle, impairing its ability to contract and pump blood efficiently.[1]

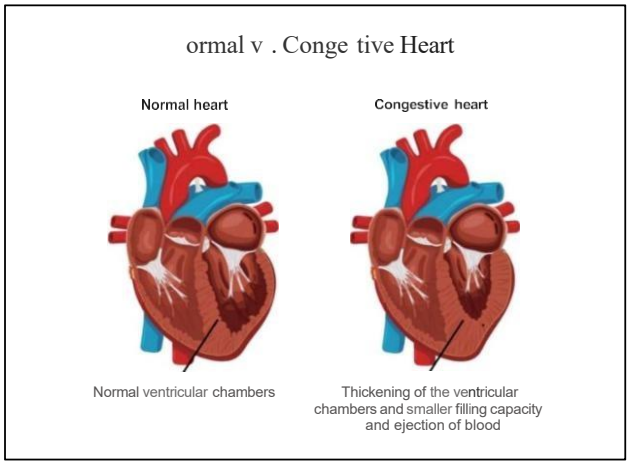


FIG.NO:-1.1 NORMAL HEART VS CONGESTIVE HEART

1.2 Stages:

1. Stage A: At risk for HF. No symptoms, structural heart disease, or evidence of elevated cardiac biomarkers, but risk factors are present. Risk factors include hypertension, diabetes, metabolic syndrome, cardiotoxic medications, or having a genetic variant for cardiomyopathy.

2. Stage B: Pre-HF. Patients have no signs or symptoms of HF but have structural heart disease, evidence of elevated filling pressures (by invasive/noninvasive assessment), or persistently elevated cardio markers in the absence of other reasons for elevated markers, like chronic kidney disease or myocarditis.

3. Stage C: Patients with structural heart disease and current or past history of HF symptoms.

4. Stage D: Patients with refractory symptoms that interfere with daily life or recurrent hospitalization despite targeted guideline-directed medical therapy.[2]

1.3 Sign & Symptoms:

- Shortness of Breath (Dyspnea).
- Fatigue and Weakness.
- Swelling (Edema).
- Rapid or irregular Heartbeat (Arrythmias).
- Persistent Cough or Wheezing.
- Increased Urination at Night (Nocturia).
- Weight Gain.[3]

1.4 Pathophysiology:

HF is a progressive disease. Any acute insult to cardiac structure or acute alteration secondary to following factors given below may initiate the compensatory mechanism, which, once exhausted, results in maladaptation.

- Genetic mutation.
- Cardiac tissue infiltration.
- Ischemia, valvular heart disease.
- Myocarditis.
- Acute myocardial injury

In the initial stages of **CHF,** several compensatory mechanisms attempt to maintain cardiac output and meet the systemic demands. The chronic activation of the sympathetic nervous system results in reduced beta-receptor responsiveness and adrenaline stores. This results in changes occus are given below.

- Myocyte regeneration.
- Myocardial hypertrophy.
- Myocardial hypercontractility.[4]

1.5 Etiology:

There are many etiologies of congestive heart failure:-

- Ishemic heart disease.
- Valvular heart diseases.
- Hypertension.
- Cardiomyopathy.
- Inflammatory cardiomyopathies.[5]

1.6 Classification of Chf Drugs:

1. Inotropic drugs: Digoxin, Digitoxin, Ouabain, Dopamine, Amrinone.

2. Diuretics: Furosemide, Bumetanide, Hydrochlorothiazide, Metolazone, Xipamide.

3. Aldosterone antagonist: Spironolactone, Eplerenone.

4. Inhibitors of Renin-Angiotensin system: Enalpril, Ramipril, Losartan.

5. Vasodilators: Glyceryl trinitrate, Hydralazine, Sod. Nitroprusside.[6]

1.7 Treatment:

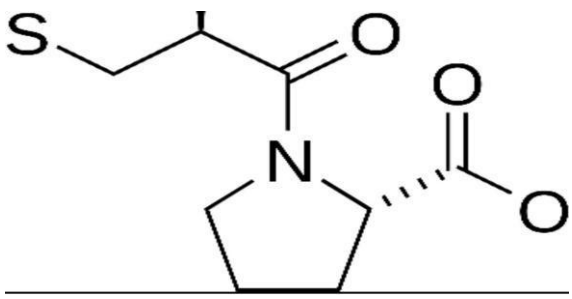
CHF treatment involves medications like ACE inhibitors, beta-blockers, and diuretics, along with lifestyle changes such as a low-sodium diet, exercise, quitting smoking, and managing weight. Medical procedures like implantable devices or heart valve surgery may be necessary, and regular monitoring and follow-up with healthcare providers are crucial for managing symptoms and improving quality of life.

Regular monitoring and follow-up with healthcare providers are crucial for adjusting medications, addressing new symptoms, and ensuring the effectiveness of treatment. Compliance with medications and lifestyle changes is essential for managing CHF effectively and improving overall health outcomes.[7]

2. METHODOLOGY OR MATERIALS AND METHOD.

2.1 Drug profile

Captopril is an ACE inhibitor medication used to treat conditions like hypertension, heart failure, and certain kidney disorders. It works by blocking the action of an enzyme that causes blood vessels to constrict, resulting in relaxation of blood vessels and lowering of blood pressure. By reducing the workload on the heart, it helps improve heart function and manage symptoms of heart failure. Captopril is typically taken orally, and its effects can be observed within an hour, with peak effects occurring within 2 to 4 hours. Common side effects may include dizziness, cough, and elevated potassium levels. It's important to follow dosage instructions and monitor for potential adverse effects.[8]



Molecular Formula - C9H15NO3S.

Molecular Weight - 217.3 g/mol.

Odor - Slight sulfurous odor.

Melting Point -103-104.

Colour -off-white crystalline powder.

Shelf life - Stable under recommended storage conditions.

Solubility: - Freely soluble in water, alcohol, chloroform, methylene chloride, sparingly. Soluble in ethyl acetate.

Decomposition -When heated to decomposition it emits every toxic fumes of /nitrogen oxides and sulfur oxides.

IUPAC Name -(2S)-l-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid.[8]

2.2 PREFORMULA TIONS STUDY

The standardization of drug and drug-excipients interaction was carried out based on the various parameters including physicochemical properties of drug, drug interaction by DSC and FTIR studies.

- **Fourier Transform Infrared Spectroscopy.**

Infrared spectra were generated with an FTIR spectrophotometer.The spectra were obtained using KBr pellet technique. The KBr pellets were prepared by 10 mg sample mixed with 200 mg potassium bromide at high compaction pressure. Thus, the prepared pellets were scanned at a resolution of 4000 cm -1 to 400 cm -1.

- **Differential Scanning Calorimetry.**

DSC thermal studies was carried out to observe the thermal behavior of the captopril and excipients on DSC 25 Mettler (Perkin-Elmer). The samples were heated in sealed aluminum pans which were heated at a rate of 50 °C/min over a temperature range from 50 ± 1°C to 300°C. Nitrogen gas purged at a rate of 30 ml/min. Empty aluminum pan was used as a reference.

- **Solubility.**

The aqueous and lipid solubility characteristics of a drug substance are of fundamental importance in determining whether it is capable of reaching sites of absorption, its interaction with putative therapeutic targets and its ultimate metabolism and excretion. An assessment of solubility characteristics is, therefore, usually a starting point for preformulation studies.

- Absolute solubility.
- Molecular Dissociation pKa.
- Solubility in Various Solvents.
- Solubility in Various Solvents.[9]

- **Partition Coefficient.**

Even when a drug substance is readily soluble at physiological pH's, its ability to transfer across membranes can be highly dependent on its capacity to partition into and cross lipophilic substrates, *e.g.* components of cell walls.

This lipophilicity can be quantified for comparative purposes by determining its partition coefficient *P*

Pclw= (Coi1)/(Cwater) at equilibrium

Which is a measure of the unionised drug distribution between an aqueous and an organic phase at equilibrium.

- **Polymorphism and Crystallinity**

Drugs and excipients can exist in various crys0talline or amorphous states depending on their chemical composition and method of isolation or crystallisation.

During crystallisation, molecules may arrange themselves in different geometric configurations such that the structure of the crystals formed has different packing arrangements or orientations. These different states are refers to as polymorphs. [3]

2.3 VARIOUS METHODS.

There are differnet methods involoved in the preperation liposomes.

General method of preperation- It involves four steps for the preperation of liposomes.[10]

Drying down lipids from organic solvents.

D1•spers1•0n of 11· p·1as/·m aqueous mea·ia.

Purification of resultant liposomes

Analysis of final product.

- **Passive Loading Techniques**

1) Mechanical dispersion methods.

a) Lipid hydration methods
b) Micro emulsification
c) Dried reconstituted vesicles.
d) Freeze thaw method

2) Solvent dispersion method.

a) Ethanol injection method.
b) Ether injection method.
c) Reverxe phase evaporation method.

- **Active Loading Techniques**

a) Proliposomes.

b) Lyophillization.[10]

2.4 PHARMACOKINETIC & PHARMACODYNAMIC

- **In vitro studies**

In vitro drug release testing methods for injectable liposome formulation have been generally grouped into three major categories: sample and separate, dialysis membrane, and continuous flow techniques.[11]

- **In-vivo studies.**

- **Animal model test.**

Considerable time and resources are required to carry out human studies, So animal studies are prefferred at small scale. The most common animal species used for evaluating Ndds are mouse, rat, dog, rhesus monkey etc. Rhesus monkey is one of the most reliable models for in vivo evaluation of Ndds.

In vivo testing follows strict guidelines and human animal use ethics. The protocol for diagnostic of pharmacological action of liposomes in animal follow multiple steps. Animal are injected with microbes that elict pharmacological action of drug encapsulated in liposomes rat is allowed to rest for 1-2 hours , after which blood sample was colllected and tested for drug metabolites and other in vivo studies was conducted on blood sample.

FIG.NO:- 3.7 RAT

Mice, and other rodents such as rats and hamsters, make up over 90% of the animals used in biomedical research. In addition to having bodies that work similar to humans and other animals, rodents are small in size, easy to handle, relatively inexpensive to buy and keep.[29]

- **Human volunteers test**

The final stage of the development of a liposomes encapsulated with captopril involves pharmacokinetic and pharmacodynamic data following appilication of the patch to human volunteers.

- Clinical trails have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc.

- Phase 1 clinical trails are conducted to determine mainly safety in volunteers.
- Phase 2 clinical trails determine short term safety and mainly effectiveness in patients.
- Phase 3 trails indicate the safety and effectiveness in large number of patient population.
- Phase 4 trails at post marketing surveillance are done for marketed patches to detect adverse drug reactions.

Human studies require considerable resources but they are the best to assess the performance of the drug

3. RESULT AND DISCUSSIONS

The aim of the formulation of captopril encapsulated in liposomes is to increase the availability of the novel drug delivery system to the treatment of congestive heart failure. To achieve this goal, captopril encapsulation in liposomes was prepared using ethanol injection metnod, ether injection methods and reverse phase technique using rotavapor method was used.

4. CONCLUSION

Congestive heart failure (chf) is a medical emergency faced by human race. The field of pharmacologic modulation in congestive heart failure is still in its infancy. There are lots of drugs obtained from natural, synthetic and semi synthetic. We chose captopril for the treatment of congestive heart failure. Congestive heart failure is a chronic and progressive condition characterized by the heart's inability to pump blood effectively to meet the body's need. This review would have provided an idea on the medicinal value of captopril and the importance of captopril. Captopril were found to be useful in the treatment of congestive heart failure. Common side effects of May include dizziness, cough, and elevated potassium level. Further this review investigation will be helpful to identify the drug according to their drug profile and also provide valuable information to the researcher to establish the pharcological activities Supported with possible mode of action. If the topical application of captopril is given it show significantly higher rate of treating and reduce the chances of heart attack.

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