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DEVELOPMENT AND EVALUATION OF EXTENDED RELEASE TABLETS OF LOSARTAN POTASSIUM AND ENALAPRIL MALEATE.

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ABSTRACT

The bilayer tablet concept has long been utilized to developed sustained release formulations. Bilayer tablet has a fast releasing layer and contain second layer to sustain the drug release. A fast releasing granules lead to sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug release from the sustaining granules. Bilayer tablet consist of two layers of tablet in a single unit. This approach can be used for the treatment of various diseases which require not only single drug but also combination of drugs. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. In which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining.

Keywords: Extended Release, Bilayer Tablet, Renin, Tablets.

INTRODUCTION

The oral route of drug delivery is considered as the preferred and most patient convenience means of drug administration. Consequently, much effort is directed during drug discovery to identify orally active candidates that will provide reproducible and effective plasma concentration in vivo. The reality is that many compounds are either incompatibility or ineffectively absorbed after oral administration (bioavailability is an issue), or that the required during frequency is too short to enable once or twice daily administration (pharmacokinetic half- life in an issue). Conventional drug delivery systems have little or no control over drug release. This may result from constantly changing, unpredictable plasma concentrations. The rate and extent of drug absorption from conventional drugs may vary greatly depending on factors such as the pysico-chemical properties of drugs, presence of excipients the presence or absence of food, pH of the gastro-intestinal tract, and so on.

The design of modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience.

Modified release formulation technologies offer an effective means to optimize the bio-availability and resulting blood concentration time profiles of drug. Modified release refers to both delayed and extended release systems. For oral administration as well as oral delivery systems designed specially to modify the release of poorly water-soluble drugs. Recent developments in the technology have prompted scientists to develop bilayer tablets with improved patient compliance and convenience.

The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in the proper form, at or over the proper time and in the desired location and to have its chemical integrity protected to that point.

Harris interactive survey for hypertension, in the United States revealed that out of 90 % patients taking medication only 50% to 60% were involved in some form of lifestyle change to control BP. Thus, majority of patients with hypertension rely on medication for the control of their BP. More recent clinical trials suggest that the approach of using monotherapy for the control of hypertension is not likely to be successful in most patients and especially in those with some comorbidity (eg. DM, heart failure). The achievement of BP goal typically requires 2 or more medications in various settings.

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Highest dose combination (telmisartan 80 mg plus amlodipine 10 mg) had the greatest least square mean systolic/diastolic BP reductions (26.4/20.1 mm Hg; P < 0.05 compared with both monotherapies) with over 90% BP response rates. Peripheral edema was most common in the amlodipine 10-mg group (17.8%) but the rate had notably lowered when amlodipine was used in combination with telmisartan. Similar results were observed with other trial of olmesartan medoxomil/amlodipine combination therapy vs. respective monotherapies where more effective BP reduction and BP goals (44.5-54% vs 28.5-30%) were achieved with combination therapy than with either of monotherapies. Over 70% of patients on combination therapy achieved BP goals.

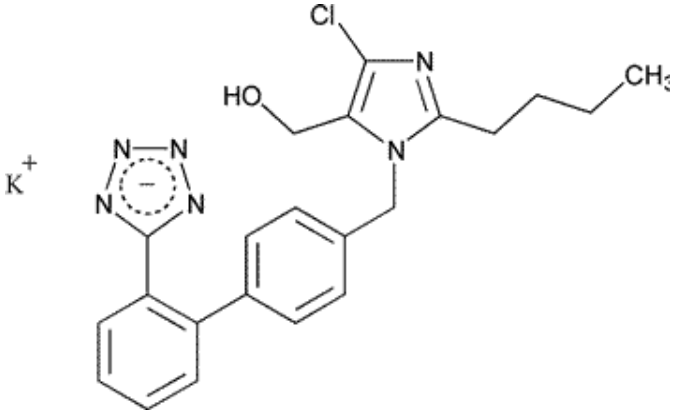
Another double blind, parallel group randomized study for 12 weeks comparing the combination therapy of felodipine and metoprolol (5/50mg) with either monotherapy exhibited significantly greater antihypertensive response (98%) with combination compared to monotherapy (felodipine- 79% and metoprolol- 82%). A significant greater reduction in mean systolic/diastolic BP (28/18 mmHg) with combination therapy was evinced compared to either felodipine (18/12 mm hg) or metoprolol (19/12 mm hg).

Many panels including Hypertension in African Americans Working Group and European Society of Cardiology have strongly supported that treatment initiation with 2 or if needed 3 drugs is justified in many cases of hypertension management. There are other various advantages with combination therapy. Combining the drugs makes them available in a convenient dosing format, lowers the dose and can be given in once daily schedule thus improving compliance. There is an additive or synergistic antihypertensive effect at lower doses of individual components and at the same time the drugs in combination counteract the side effects of each other. This helps more patients to achieve normal BP and even can be effective in hard-to-treat populations. Early normalization of BP may greatly motivate the patients to adhere to lifelong treatment.

MATERIALS AND METHODS

Drug Profile

LOSARTAN POTASSIUM



Empirical Formula: $C_{22}H_{22}ClKN_6O$
Molecular Weight: 461.0 g/mol
IUPAC Name: (2-butyl-4-chloro-1-{[2'-(1H-tetrazol-5-yl) biphenyl-4- yl] Methyl}-1H-imidazol-5-yl) methanol potassium salt
Category: Antihypertensive
Class: Angiotensin II Receptor Antagonist
Dose: Orally – 50 mg twice a day
Description: White to off- white crystalline powder
Odour: Odourless
Melting Point: 183-184˚C
Solubility:
Water: 400mg/ml
Organic solvent:
Methanol: 400 mg/ml
Storage: Keep away from Heat, Spark, and Flame
Uses: Hypertension, Congestive Heart Failure, Diabetic Neuropathy, Myocardial Infarction.

Clinical Pharmacology:

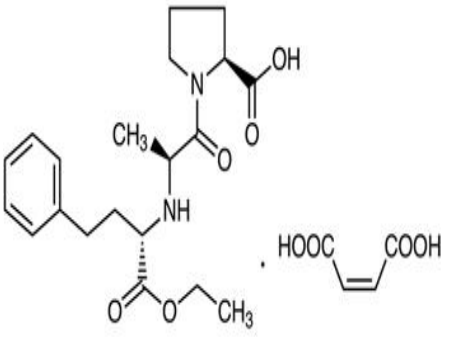
Blocks vasoconstriction and aldosterone - secreting effects of angiotensin II at various receptor sites, including vascular smooth muscle and adrenal glands Also increases urinary flow and enhances excretion of chloride, magnesium, calcium, and phosphate.

Adverse Effect:

Hypotension, Hyperkalemia, Headache, dizziness.

ENALAPRIL MALEATE

Structural formula:



Empirical Formula: $C_{20}H_{28}N_2O_5$
Molecular Weight: 376.447 g/mol
IUPAC Name: (2S)-1-[(2S)-2-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino} propanoyl] pyrrolidine-2-carboxylic acid
Category: Antihypertensive
Class: Angiotensin Converting Enzyme Antagonist
Description: White to off- white powder
Odour: Odourless
Melting Point: 143 – 144.5 ˚C
Solubility:

Water: sparingly soluble
Organic solvent: Methanol: freely soluble
Ethanol: soluble
Storage: Keep away from Heat, Spark, and Flame
Uses: Hypertension, Congestive Heart Failure, Diabetic Neuropathy, Myocardial Infarction.

Clinical Pharmacology:

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II.
Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Adverse Effect:

Hypotension, Hyperkalemia, Angiodema, Dysguesia

Preformulation Studies

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

A thorough understanding of physicochemical properties may ultimately provide a rationale for formulation design or support the need for molecular modification or merely confirm that there are no significant barriers to the compound's development.
The goals of the program therefore are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish its compatibility with different excipients.
- Hence, Preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies.

Preformulation studies are the first step in the development of dosage form of a drug substance. The objective of Preformulation studies is to develop a portfolio of information about the drug substance, so that this information useful to develop different dosage forms. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.
Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic biopharmaceutical properties of the resulting product.
The following tests were performed in present study:

- Appearance
- Solubility
- Physico-chemical characterization
- Identification
- Residue on ignition
- Heavy metals
- Related substances by HPLC
- Assay by HPLC
- Polymorphism
- Particle size
- Drug – excipients compatibility studies
- Methods adopted for above tests are

Appearance:

Take 2 g of sample in a clean, dry Petri dish and observe, visual against black background and observations were recorded.

Solubility:

Solubility was determined in different solvents and solubility characteristics were reported.

IDENTIFICATION TEST

Firstly, clean the sample holder by acetone. Then Switch on the Instrument and take the sample in sample holder, and the results are observed. Fourier transform IR spectra were recorded on FT/IR affinity type A. The scanning range was 400-4000 cm-1, resolution was 2 cm^{-1}. Initially, a FTIR transmittance spectrum of was obtained from a KBr pellet and interpreted following the characteristic IR absorption bands.

RESULTS AND DISCUSSION

The FT-IR spectrum of the obtained sample of drug was compared with the standard FT-IR spectra of the pure drug. The infrared absorbance spectrum of Losartan potassium and Enalapril Maleate was recorded using a Brukar FT-IR Spectrophotometer over the range of 675–960 cm^{-1}. The result obtained was complies with the standard limits and can be have Satisfactory Data. The Appearance of Losartan potassium and Enalapril Maleate was visually observed and found to be complies with the Standard limits. The Appearance of Solution of Losartan potassium and Enalapril Maleate was visually observed against white and black background and found to As a Clear solution The Solubility Profile of drug Of Losartan potassium and Enalapril Maleate was found to be. The melting point of the drug Of Losartan potassium and Enalapril Maleate was found to be 263-265 and 143-145 °C respectively which complies with the standard limits. The pH of the drug Calcium of Losartan potassium and Enalapril Maleate was found to be 7.4 and 6.2 respectively. The LOD of the drug Calcium of Losartan potassium and Enalapril Maleate was found to be 0.1148 & 0.2114. The Tapped Density of the drug Of Losartan potassium and Enalapril Maleate was found to be 0.6968 & 0.7490. The Bulk Density of the drug Of Losartan potassium and Enalapril Maleate was found to be 0.6172 & 0.6622. The Angle of Repose of the drug Of Losartan potassium and

Enalapril Maleate was found to be 28.89 & 33.02. The Carr's Index of the drug Of Losartan potassium and Enalapril Maleate was found to be 11.42 & 11.58.
The Hausner Ratio of the drug Of Losartan potassium and Enalapril Maleate was found to be

1.1289 & 1.310. The Weight Variation of the tablet for B1, B2, B3, B4, B5, B6 was found to be 600 ± 5%, 605 ± 5%, 603 ± 5%, 599 ± 5%, 600 ± 5%, 600± 5%. The thickness of the tablet for B1, B2, B3, B4, B5, B6 was found to be 2.32, 2.43, 2.37, 2.34, 2.40, 2.36. The Friability of the tablet for B1, B2, B3, B4, B5, B6 was found to be 0.87, 0.58, 0.69, 0.79, 0.59, 0.65. The Hardness of the tablet for B1, B2, B3, B4, B5, B6 was found to be5.1, 5.2, 5.1, 5.0, 5.0, 5.0. The Disintegration time of the tablet for B1, B2, B3, B4, B5, B6 for losartan and enalapril was found to be 2, 2, 2, 2, 2, 2 & 5, 8, 8, 6, 9, 7 respectively.

CONCLUSION

Hypertension is one of the most common chronic diseases worldwide. However, many people have hypertension without awareness and treatment of the disease, indicating it is necessary to provide some basic knowledge and essential information of hypertension to our audience, upper primary pupils at early stage of their lifes to prepare them early in prevention or management of this disorder in their future life. Many risk factors are related with hypertension. Avoiding the factors help to prevent hypertension, reduce symptoms and prolong lives. Complications of hypertension are major sources of mortality. Reducing blood pressure with medication or keeping it within normal range will prevent, attenuates or reduce these complications.

Treating hypertension in very old patients reduces stroke and heart failure with no effect on total mortality. The most reasonable strategy is the one associated with significant mortality reduction; thiazides as first-line drugs with a maximum of two drugs. The combinational therapy for hypertension is the need of disease to give patient better compliance. In Bilayer tablet the benefit was that it gives both the immediate and Sustain release. Drug release from the first releasing layer leads to a sudden rise in the blood concentration. The time taken to achieve steady state plasma concentration is minimum. However, the blood level is maintained in steady state, as the remaining drug is releasing slowly from the sustained layer. In this bilayer tablet Enalapril maleate gives immediate release and Losartan Potassium gives sustain release which maintains the blood serum level and give effect for a long time.

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