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Formulation development-overview on formulation of antihypertensive drug used in hypertension

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ABSTRACT
hypertension is the most important modifiable risk factor for all-cause morbidity and mortality worldwide and is associated with increased risk of cardiovascular disease . Fewer than half of those with hypertension are aware of their condition, and many others are aware but not treated or inadequately treated, although successful treatment of hypertension reduces the global burden of disease and mortality. The etiology of hypertension involves the complex interplay of environmental and pathophysiological factors that affect multiple systems, as well as genetic predisposition. Evaluation of patients with hypertension includes accurate standardized blood pressure measurement, assessing patients' predicted risk of atherosclerotic cardiovascular disease, evidence of target organ damage, detection of secondary causes of hypertension and presence of comorbidities, including Cardiovascular disease and kidney disease. Lifestyle changes, including dietary modifications and increased physical activity, Amlodipine is a calcium channel blocker that is mainly used in the treatment of hypertension and angina. Amlodipine is a photosensitive drug and requires protection from light. Nifedipine is a calcium channel blocking agent used in the treatment of various cardiovascular diseases, long term treatment of hypertension and angina pectoris. Earlier, short acting nifedipine was used sublingually in emergency management of severe hypertension. Losartan Potassium is an angiotensin II receptor antagonist with anti hypertensive activity. It belongs to class 1 of Biopharmaceutical Classification System . It is readily absorbed from the GI tract following oral administration but the bioavailability is about 33% due to substantial first-pass metabolism.

Keywords: Amlodipine,nifedipine,losartan potassium, cardiovasculardisease,hypertension,blood pressure BCS class

I. INTRODUCTION

Systemic arterial hypertension (hereafter referred to as hypertension) is characterized by persistently high blood pressure (BP) in the systemic arteries. BP is commonly expressed as the ratio of the systolic BP (that is, the pressure that the blood exerts on the arterial walls when the heart contracts) and the diastolic BP (the pressure when the heart relaxes). The BP thresholds that define hypertension depend on the measurement method (Table 1). Several etiologies can underlie hypertension. The majority (90–95%) of patients have a highly heterogeneous 'essential' or primary hypertension with a multifactorial gene-environment etiology. A positive family history is a frequent occurrence in patients with hypertension, with the heritability (a measure of how much of the variation in a trait is due to variation in genetic factors) estimated between 35% and 50% in the majority of studies1,2. Genome-wide association studies (GWAS) have identified ~120 loci that are associated with BP regulation and together explain 3.5% of the trait variance3,4,5. These findings are becoming increasingly important as we search for new pathways and new biomarkers to develop more modern 'omics'-driven diagnostic and therapeutic modalities for hypertension in the era of precision medicine6. Several rare, monogenic forms of hypertension have been described (for example, the Liddle syndrome, glucocorticoid-remediable aldosteronism (a mineralocorticoid excess state) and mutations in PDE3A (which encodes cGMP-inhibited 3',5'-cyclic phosphodiesterase A)), in which a single gene mutation fully explains the pathogenesis of hypertension and indicates the best treatment modality7,8,9. If hypertension is caused by another condition (for example, primary aldosteronism, pheochromocytoma (a neuroendocrine tumor of the adrenal glands or other neuroendocrine tissues) or renal artery stenosis), it is referred to as secondary hypertension. Hypertension is the most common preventable risk factor for cardiovascular disease (CVD; including coronary heart disease, heart

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failure, stroke, myocardial infarction, atrial fibrillation and peripheral artery disease), chronic kidney disease (CKD) and cognitive impairment, and is the leading single contributor to all-cause death and disability worldwide10. The relationship between BP and the increased risk of CVD is graded and continuous, starting as low as 115/75 mmHg, well within what is considered to be the normotensive range. Successful prevention and treatment of hypertension are key in reducing disease burden and promoting longevity in the world's population. In treating hypertension, it is important to consider a person's predicted atherosclerotic CVD (ASCVD) risk more than the level of BP alone, as persons with high CVD risk derive the greatest benefit from BP lowering treatment11This Primer will discuss the epidemiology and pathophysiology of primary hypertension, prevention strategies for slowing the progression of BP elevation, management strategies (including optimal BP targets) for lowering BP and preventing CVD outcomes in patients with established Hypertension and the effects of antihypertensive treatment on quality of life;

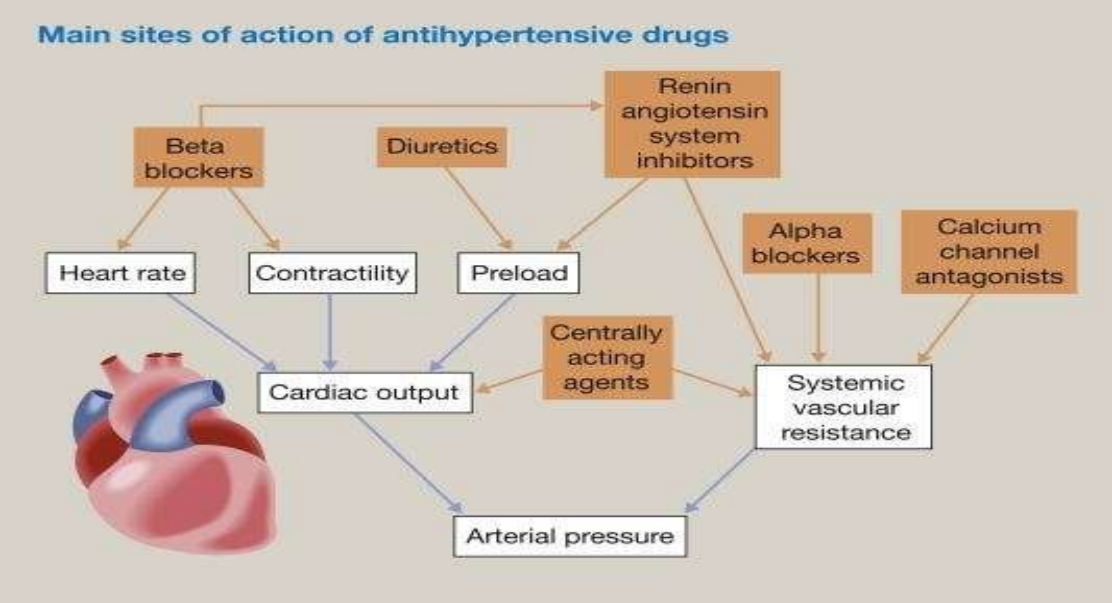

Fig. Main Site of action of antihypertensive drug

finally, we will explore knowledge gaps, future trends and the outlook for hypertension research and treatment over the next decade. Amlodipine (AD) belongs to the group of calcium channel blockers. The newer calcium channel blockers such as dihydropyridines, AD, felodipine, and nisoldipine have improved vascular selectivity and longer durations of action.

They bind to target receptors in a slow and sustained pattern producing a smooth onset of action with a 24 h control of blood pressure. Once daily dosing of these longer acting calcium channel blockers improves patient compliance and is associated with minimum encounter of side effects. The calcium channel blockers are suitable for a wide range of hypertensive patients including the elderly, black, and those with concomitant diseases that preclude the use of other antihypertensive [1].

AD is commonly used in the treatment of heart diseases like angina and hypertension [2]. Efforts have been made to prepare various dosage forms of AD to improve its efficacy and stability. Therefore, a comprehensive review of various formulations of AD reported in the literature has been made which would be helpful for pharmaceutical scientists and formulators in identifying and developing the most suitable dosage form of AD. CDDS are those convenient means of drug delivery systems which are meant to obtain a reduction of daily administration of drugs with fast absorption and elimination.

Many controlled release systems have been developed for maintaining a therapeutically effective concentration of drug in systemic circulation for longer period of time as well as to reduce side effects 1. Nifedipine is a calcium channel blocking agent used in the treatment of

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various cardiovascular diseases, long term treatment of hypertension 7and angina pectoris8. Earlier, short acting nifedipine was used sublingually in emergency management of severe hypertension.

Later it was established that there is an increased risk of myocardial infarction or mortality in patient receiving short acting nifedipine for hypertensive emergencies 9, 10. The objective of present work is the formulation of floating Nifedipine matrix system using HPMC polymer. Losartan Potassium is an angiotensin II receptor antagonist with anti hypertensive activity. It belongs to class 1 of Biopharmaceutical Classification System (BCS).

It is readily absorbed from the GI tract following oral administration but the bioavailability is about 33% due to substantial first-pass metabolism. Peak plasma concentration occurs at about

1hr after an oral dose and has short terminal elimination half-life is about 1.5 to 2hrs respectively, thereby requiring two to three times daily dosing in large number of patients, which often leads to non-compliance.6 Thus, there is a strong clinical need and market potential for a dosage form that will deliver Losartan Potassium in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance.

The present study was aimed towards the development of extended release formulations of Losartan potassium based on osmotic technology. In this study, osmotic drug delivery matrix tablets of Losartan potassium were developed. The core tablets of Losartan Potassium consisted of drug along with an osmotic agent (mannitol) and swellable polymer Hydroxy propyl methylcellulose7-10 (methocel). The core tablets were coated with ethyl Cellulose 7 cps11,12 and PEG-4000. After coating, the optimized coated tablets were further subjected to micro drilling on the upper face to get 0.5µm orifice diameter that release the drug at controlled manner. This study was intended to evaluate the influence of formulation variables like levels of swellable polymer, amount of mannitol concentration and coating solution ratios of semi permeable membrane (SPM) on the drug release from the tablet formulations.

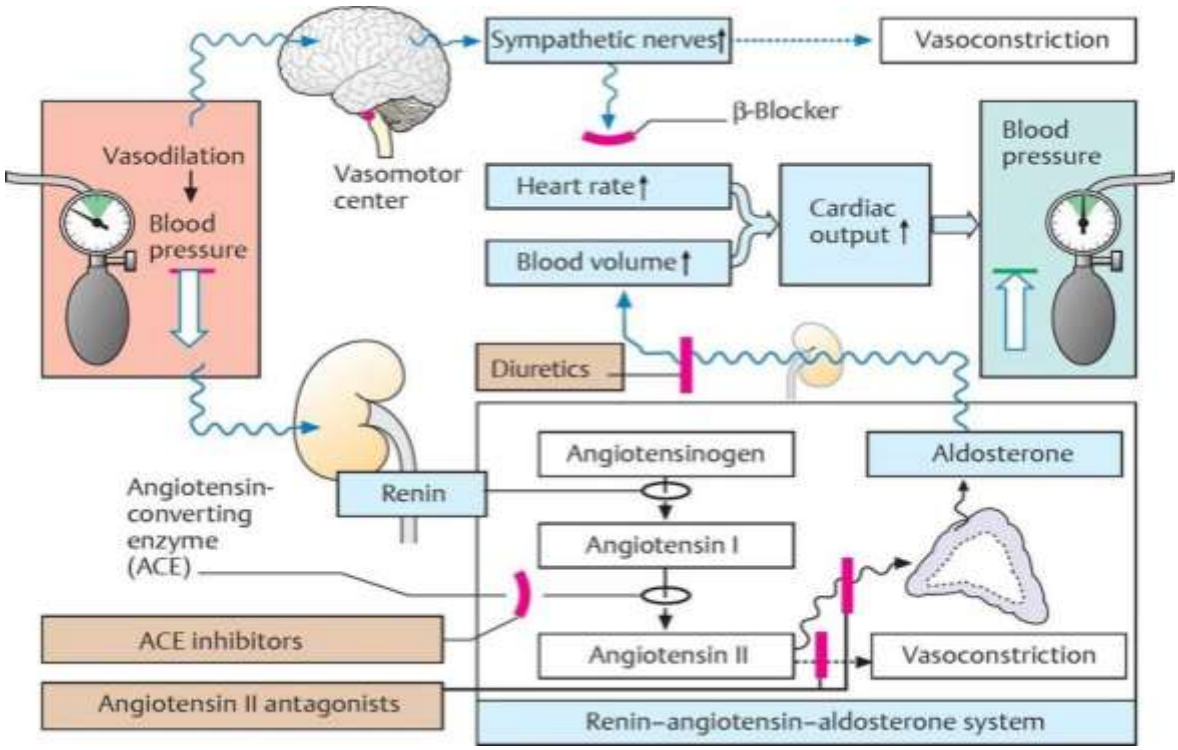

Fig. Pharmacology - An Illustrated ReviewAntihypertensive Drugs

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Formulation development

Floating drug delivery system: Floating drug delivery system or hydrodynamically balanced system (HBS) is a formulation of drug in gel forming hydrocolloid meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also does so in an area of the GIT that would maximize drug reaching its absorption site.

In the formulation of the FDDS, polymers play an important role. They not only hold the formulation ingredients together but also give a floating property and sustained release. The most commonly used polymers are HPMC and sodium alginate HPMC comes in various grades like Methocel K4M, Methocel K50M, Methocel K100M, Methocel E4, Methocel E50, Methocel E100 etc 2. These excipients absorb a significant amount of water (more than 20% of their dry weight) while maintaining a distinct 3-dimensional structure.

When a dosage form is immersed in a specific medium, hydration occurs, which leads to gel formation. The process of erosion causes the de-aggregation and the creation of new gel layers, affecting both the volume and the weight of the dosage form. This in turn causes the controlled drug release. It has been observed that only hydrophilic polymers are not sufficient for floating characteristics and better results are possible with use of some soluble or gas-evolving excipients 3.Floating drug delivery systems have various advantages like sustained release, site specificity, absorption enhancement, maintenance of constant blood levels etc 4.

The novel design of an oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs. But there are several physiological difficulties, which include restraining and localizing the drug delivery system within the regions of the gastrointestinal tract and the highly variable nature of gastric emptying process (a few minutes to 12 hours).

This variability, in turn may lead to unpredictable bioavailability and the time to achieve peak plasma levels, since the majority of drugs are preferentially absorbed from the upper part of small intestine. Furthermore, the relatively brief gastric emptying time in humans, which normally averages 2 to 3 hours through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose Therefore, restraining a drug delivery system in a specific region of the gastrointestinal tract offers numerous advantages, especially for drugs exhibiting an absorption window or for drugs with a stability problem. Overall, the intimate contact of the drug delivery system with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption 5, 6.

These considerations have led to the development of oral controlled-release dosage forms possessing gastric retention capabilities. Nifedipine is a calcium channel blocking agent used in the treatment of various cardiovascular diseases, long term treatment of hypertension 7and angina pectoris8. Earlier, short acting nifedipine was used sublingually in emergency management of severe hypertension. Later it was established that there is an increased risk of myocardial infarction or mortality in patient receiving short acting nifedipine for hypertensive emergencies 9, 10. The objective of present work is the formulation of floating Nifedipine matrix system using HPMC polymer.

II. MATERIALS AND METHODS:

Materials: Nifedipine was gift sample from Sharon Biomedicine Ltd. Raigad, Hydroxy Propyl Methyl Cellulose K4M (Research Lab Fine chemicals Mumbai), sodium bicarbonate (Poona Chemicals, Poona), Carbopol 934P (S. D. Fine chemicals Mumbai), talc, magnesium stearate.
The equipments used were tablet compression machine (Rotary Tablet Press F. P. Machinary, Ahmedabad), UV visible spectrophotometer (Shimadzu Corporation), dissolution test apparatus, electronic balance, hardness tester and friability test apparatus.

Method:

Fabrication of Floating Tablets: Nifedipine, HPMC, Carbopol, and sodium bicarbonate were passed through sieve no. 80 separately. The drug was then mixed with the polymers and other ingredients in the weight proportion and compressed on an eight station tableting machine using flat-faced Punch (diameter 5 mm). Formulations are shown in Table 1 **Osmotic controlled matrix tablet:**

Materials and method:

Materials: Losartan Potassium was obtained as gift sample from M/S AUROBINDO Pharma Ltd,

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Hyderabad. Hydroxy propyl methyl cellulose (Methocel/HPMCK15M) was obtained as gift sample from M/S Colorcon Asia Pvt. Ltd, Mumbai. Microcrystalline Cellulose (Tabulose) and Mannitol was obtained as Gift Sample from M/S Matrix Pharma Ltd, Hyderabad. Talc and magnesium stearate were obtained commercially from
Loba Chemie Pvt. Ltd, Mumbai. Ethyl cellulose-7cps was obtained commercially from S.D.Fine Chem. Ltd, Mumbai. Poly Ethylene Glycol-4000 was obtained as gift sample from Sisco Research Laboratories Pvt. Ltd, Mumbai.

PREPARATION OF OSMOTIC TABLETS:

Preparation of Core Tablets: The osmotic core tablet of Losartan potassium were prepared by direct compression process.13,14Losartan Potassium was blended with HPMC K15M in a double cone blender for 10 min. The mixture was passed through #30 mesh sieve, and osmotic agent (mannitol), MCC were added in geometric dilution and blending is continued for additional 10 min.

To this mixture talc and magnesium stearate which were passed through #60 mesh sieve were added and blending is continued for additional 5 min. The blend was then compressed into tablets using Clit 10 station mini press. The same procedure was employed for preparing different batches of tablets with varying mannitol concentration. To minimize processing variables all batches of tablets were compressed under identical conditions. The compressed core tablets were further evaluated for their physical parameters such as weight uniformity, friability, Hardness and Drug content. The composition of different tablet formulations of Losartan Potassium were given in (Table 1).

Coating and Drilling:

Core tablets of Losartan Potassium were coated in a conventional laboratory coating pan (Scientific instrument, New Delhi, India) fitted with three baffles placed at angle of 120° having outer diameter of 10 cm.

The components of coating solution were added to solvent mixture in sequential manner. The component added first was allowed to dissolve before next component was added. Coating process was done on a batch of 100 tablets. Pan speed was maintained at 50 rpm and hot air inlet temperature was kept at 38-42°C. The manual coating procedure based on intermittent spraying and coating procedure was used with spray rate of 4-5 ml/min. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process . Coating was continued until desired coat thickness was obtained on the core tablets. In all cases coated tablets were dried at 50°C for 6 hrs before further evaluation.

The composition of coating solutions used for coating of core tablets was given in (Table 2). An appropriate size orifice (0. 5µm) is made on one face of all coated tablets using micro drill. (Kamlesh Engineers, Udaipur, India).

Mouth dispersible tablet:

Materials:

Amlodipine besylate was obtained as gift sample from copella laboratories limited Hydrabad India Crospovidone Croscarmellose sodium,sodium starch glycolate, aspartame lactose and magnesiun stearate was produced S.D fine chemicals Mumbai, India and all other chemicals /solvent used were of analytical grade.

Method:

Preparation of tablet:

Fast dispersible tablet containing 10mg of amlodipine besylate were prepared by direct compression method and various formula used in the study are shown in [Table1].All the ingredient without magnesium stearate and talc were mixed uniformly followed by addition of magnesium stearate and talc super disintegrants like sodium starch glycolate, Crospovidone and Croscarmellose sodium were used in different ratio and effect of combination of superdisintegrants was studied the prepared powder blend was evaluated for various parameter like bulk density, tapped density, angle of repose, compressibility index and Hausner ratio.after evaluation of powder blend the tablet were compressed single station tablet punching machine [Rimek mini press 1] using 6 mm flat punches set.

III. CONCLUSION:

Hydrodynamically balanced systems of nifedipine with shorter lag time can be prepared by direct compression method using HPMC and NaHCO3 as gas generating agent.

As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent (NaHCO3) increases, the drug release increases and at the same time floating lag

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time decreases. Most of the designed formulations of nifedipine HBS displayed first order release kinetics, and drug release follows Korsmeyer Peppas kinetic model.

The present study has shown that it is possible to extend the release of losartan potassium by formulating it as osmotic controlled release tablets employing HPMC K 15M as polymeric material and mannitol as osmogen. The formulation with micro-orifice after coating with ethyl cellulose 7cps and PEG-4000 exhibited zero order drug release profile with constant release rate.

The study shows that mouth dissolving tablets of amlodipine besylate can be successfully prepared by direct compression technique using selected superdisintegrants for better patient compliance and effective therapy.

IV. RESULT:

In the present study, hydrodynamically balanced systems of nifedipine were prepared by using HPMC at different drug to polymer ratios along with a gas generating agent, sodium bicarbonate. Extended release formulation of Losartan Potassium osmotic tablets were developed. Extended release Osmotic tablets of Losartan Potassium were prepared by direct compression process. Losartan Potassium osmotic tablets were prepared b y using HPMCK15M as release rate retardant.

First nine formulations of amlodipine besylate were prepared with different concentrat ion of three superdisintegrants namely Sodium Starch glycolate, Croscarmellose sodi um, Crospovidone. Microcrystalline cellulose was used as the direct compressible ve hicle. Talc and silicone dioxide are used as glidants to improve the flow property of the formulation. Magnesium stearate, which found to be having a deleterious effect o n the dissolution, was used at very low concentration as antiadherent. The formulation F1 , F2, F3 having croscarmellose as superdisintegrants at a concentration of 4, 6, 8% respectively. F4, F5, F6 having SSG as disintegrants at a concentration of 4, 6, 8 % respectively. F7, F8, F9 containing cros PVP as superdisintegrant at a concentration of 4, 6, 8% respectively. The last three formulations (F9F12) were prepared by using combination of superdisintegrants. The bittertaste of the drug is masked by using so dium saccharin as sweetening agent.

Abbreviation:

Blood pressure (BP), Genome-Wide association studies(GWAS), cardiovascular disease(CVD), chronic kidney disease(CKD), amlodipine(AD), controlled drug delivery system(CDDS), Hydoxypropyl methylcellulose(HPMC), Biopharmaceutical Classification System(BCS), semi permeable membrane(SPM), Hydrodynamically Balanced System(HBS), Microcrystalline cellulose(MCC), Polyethylene glycol(PEG).

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