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Review Article

Approaches to Improve Oral Bioavailability of Antihypertensive Drugs: A Mini-Review

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Abstract



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Hypertension elevates the risk of heart disease and stroke which are one of the most frequent causes of death. Fortunately, hypertension is manageable with the use of anti-hypertensives and a healthy lifestyle. However, patient non-adherence to the prescribed dosing regimen is the primary reason for uncontrolled blood pressure levels. Daily multiple doses of medication are one of the major reasons for patient non-compliance to the dosing regimen. Multiple doses of medication are a result of low solubility and high first-pass metabolism of anti-hypertensives. There are several approaches to improve the bioavailability of anti-hypertensives like polymeric and non-polymeric approaches to enhance solubility, avoiding first-pass metabolism through alternate routes of drug delivery and others. The objective of this review is to discuss different approaches to enhance the oral bioavailability of anti-hypertensive drugs.

Keywords: Solubility enhancements, solid lipid nanoparticles, hot melt extrusion, drug delivery, pharmacokinetics, poorly soluble, oral bioavailability.

Introduction

Hypertension is a cardiovascular disease (CVD) resulting in increased blood pressure. As per the Centers for Disease Control and Prevention, there were 670,000 hypertension-associated deaths in the United States in 2020. WHO estimates that there are 1.28 billion adults who are suffering from hypertension. Hypertension is prevalent in countries with low and middle income compared to high-income countries. As per WHO (Geneva) report in 2008, hypertension caused about 45% of deaths due to ischemic coronary illness and 51% of death as a result of stroke. In 1980, 600 million individuals were experiencing hypertension, while in 2008 this figure increased to 1 billion raising a major concern for its management (WHO, 2013)¹⁻⁷.

The risk of hypertension increases drastically after 45 years. For a forty-five-year-old without hypertension, the risk of developing hypertension in the next 40 years is 93% for African Americans, 92% for Hispanics, 86% for whites, and 84% for Chinese adults. Hypertension was the prominent reason for death and adjusted life due to disability in 2010. Hypertension had more impact on women compared to men and African Americans in comparison to whites. The risk of cardiovascular diseases increases in a log-linear fashion with an increase in systolic blood pressure (SBP) levels from 115-

180 mm of Hg and an increase in diastolic blood pressure (DBP) from 75-105 mm of Hg. A 20 mm Hg increase in SBP and a 10 mm Hg increase in DBP are associated with a doubling in the risk of death due to stroke, heart disease, or other vascular disease. In persons higher than 30 years of age, higher SBP and DBP are linked with increased risk for CVD, angina, myocardial infarction (MI), heart failure (HF), stroke, peripheral arterial disease, and abdominal aortic aneurysm⁸⁻⁹.

The anti-hypertensive drugs that are now on the market may be divided into each of the following groups:

- A. Diuretics
 - a) Thiazides
 - b) High ceiling
 - c) Potassium sparing
- B. Renin angiotensin system inhibitors
 - a) ACE inhibitors
 - b) Angiotensin (AT1) receptor blockers
 - c) Direct renin inhibitors
- C. sympathetic inhibitors

- a) β -Adrenergic blocker
 - b) α -Adrenergic blocker and β -Adrenergic blocker
 - c) α -Adrenergic blocker
 - d) Central sympatholytics
- D. Calcium channel blocker
- a) Phenyl alkyl amines
 - b) Benzothiazepine
 - c) Dihydropyridines
- E. Vasodilator
- a) Arteriolar dilator
 - b) Arteriolar and veno dilator

The vast majority of these drugs have a few substantial limitations, including limited permeability, low bioavailability, a very shorter half-life, and unfavorable side effects. Novel drug delivery methods provide formulation scientists with a chance to address these kinds of problems with antihypertensive medication treatment by offering the following qualities. Increased selectivity, reduced adverse effects, low dosage frequency and improved bioavailability are all desirable characteristics¹⁰⁻¹¹.

Despite the availability of several conventional antihypertensive dosage forms, they predominantly suffer from poor aqueous solubility resulting in poor bioavailability (BA)¹²⁻¹³. Some anti-hypertensive drugs also face the challenge of significant first-pass metabolism causing low bioavailability. The other issues related to anti-hypertensives are short half-lives and frequent dosing. Alternate routes of drug delivery through buccal or transdermal routes can overcome challenges due to high first-pass metabolism. Solubility enhancement can also resolve the issue of low bioavailability for low-soluble drugs¹⁴⁻¹⁶.

Micronization

Micronization increases the dissolution rate and solubility of drugs by increasing the surface area of the drugs¹⁷. Nifedipine is a calcium channel blocker indicated for hypertension along with vasospastic angina, and chronic stable angina. Supercritical fluid process technology was used to prepare microparticles of Nifedipine. The microparticles resulting from this technology led to particles of 15-30 μ m size and were able to release the drug twice faster compared to tablets containing milled nifedipine. Felodipine belongs to a class of dihydropyridine derivatives indicated for hypertension with a similar mechanism of action as Nifedipine. Supercritical fluid technology was also used to micronize felodipine through particles from gas-saturated solutions¹⁸.

Hot Melt Extrusion

Hot Melt Extrusion utilizes thermal energy and shear forces for the preparation of amorphous solid dispersions. The drug is solubilized or dispersed at a molecular state in a hydrophilic polymer to improve the soluble characteristics of water-insoluble drugs¹⁹⁻²⁰. The solubility of Telmisartan was improved by preparing an amorphous solid dispersion in Surplus and a pH modifier (sodium carbonate). Different formulations were prepared by altering the ratios of the drug, polymer, and pH modifier. The solid-state characteristics were studied using DSC and p-XRD. The favorable formulation was subjected to pharmacokinetic evaluation in rats. The results indicate that the amorphous solid dispersion prepared through hot melt extrusion was able to improve the C_{max} and AUC by 6.61 and 5.37 times of powder telmisartan²¹.

In another study, the solubility of Olesmesartan medoxomil was improved by hot melt extrusion. Kollidon VA-64 was used as a hydrophilic carrier. Different formulations were prepared using the design of experiments. Characterization techniques like scanning electron microscopy, atomic force microscopy, DSC, and TGA were used to investigate the solid-state characteristics of the formulations. In-vivo, studies were performed on Sprague-Dawley rats to study the pharmacokinetics. The results indicate the bioavailability doubled through the amorphization of Olesmesartan medoxomil²².

Amorphous solid dispersion of Nisoldipine was prepared using HME technology using Kollidon VA64 as polymer. The selected formulation had drug to polymer ratio of 1:10. The amorphous nature of the drug in the ASD was confirmed by XRD, DSC, and FTIR techniques. The in-vitro release characteristics and in-vivo performance of the final formulation were compared with Nierxin, a commercial tablet formulation. The results indicate that the developed ASD performed on par with the commercially available formulation²³.

Buccal Drug Delivery

Buccal drug delivery could be the most viable option for drugs that undergo extensive first-pass metabolism or drugs which show erratic gastric absorption. Buccal drug delivery of anti-hypertensives which undergo extensive first-pass metabolism can help in improving the bioavailability²⁴. El-Sayed Khafagy et al., prepared a mucoadhesive buccal nano-sponge of carvedilol to counter the high first-pass metabolism. Nano-sponge was prepared using thin-film hydration followed by a sonication technique. A 3²-factorial design was used for the optimization of bilosomes. The bilosomes were incorporated in carboxymethylcellulose/hydroxypropyl cellulose films for buccal drug delivery. In-vivo assessment on rats showed that buccal delivery of carvedilol helped in improving bioavailability²⁵.

A study by Sumedha Bansal et al., was performed on buccal adhesive patches of losartan potassium. Buccal films were prepared with polyvinyl alcohol and chitosan using a solvent casting technique. Propylene glycol was used as the plasticizer. The patches were characterized for thickness, weight uniformity, folding endurance, drug content, swelling index, surface pH, in-vitro release, and ex-vivo permeation. The results indicate that the optimized formulation was successful in delivering losartan in 8h²⁶⁻²⁷.

Transdermal drug delivery

Transdermal drug delivery like buccal drug delivery can be particularly useful for drugs that undergo systemic metabolism and can also deliver the drug in a controlled fashion²⁸⁻³⁰. Mohd et al., prepared transdermal patches of pinacidil monohydrate for drug delivery through a percutaneous route. These patches were tested on hypertension-induced rats through prednisolone acetate. The blood pressure of rats was monitored through the cuff tail technique. The results indicated that the transdermal patch is successful in lowering blood pressure for 48 hours³¹.

A transdermal patch of losartan was developed using polymers ethyl cellulose, polyvinyl alcohol, Eudragit RL100, and Eudragit RS100. In-vitro release studies were performed to study the drug release characteristics. The results indicate that the drug release of losartan was improved by the use of hydrophobic polymers compared to hydrophilic polymers³².

Nadia et al., prepared a pro-transfersomal system of timolol maleate which was delivered through a transdermal route. Timolol has a poor oral bioavailability of 50% due to high

first-pass metabolism. It also has a short half-life of 4h. The formulation was optimized by preparing different formulations using a 2³-factorial design. The variables studied were phosphatidylcholine: surfactant molar ratio, carrier: mixture, and SAA type. The output parameters were particle size, drug entrapment efficiency, and drug release rate. The final optimized formulation was studied on hairless rats and compared with the aqueous administration of Timolol. The results indicate that optimized formulation performed six times better in bioavailability compared to oral administration³³.

Solid Lipid Nanoparticles

Delivering drugs that have low aqueous solubility and/or permeability (BCS class II & IV) is a complicated task due to poor bioavailability caused by pH variation in the gastrointestinal tract (GIT)³⁴⁻⁴³. The pH difference can impact the pharmacological activity of a drug by any of the chemical degradation pathways like oxidation, deamidation, or hydrolysis of both small molecules and large molecules⁴⁴. The oral bioavailability of drugs like candesartan cilexetil is affected as they undergo chemical degradation at acidic pH. Enzymes like liver esterase and cytochrome P450 cause significant degradation of antihypertensives. Protease degrades 94-98% of orally administered protein formulations⁴⁵.

The primary methods of preparation of solid lipid nanoparticles include hot homogenization followed by ultrasonication, microemulsion method, solvent emulsification/evaporation, solvent injection method, supercritical liquid extraction of emulsions and, high-pressure homogenization. In the case of the high-pressure homogenization technique, it can be further sub-classified as hot and cold techniques⁴⁶⁻⁵². Lipids also pose a concern to microbial stability as they are prone to microbial contamination⁵³⁻⁵⁴.

Narendar and Kishan, 2015 formulated SLNs loaded with nisoldipine for enhancing oral bioavailability, through a systematic design of experiments approach. Nisoldipine is a calcium channel blocker and thereby is used in the treatment of hypertension. However, nisoldipine has poor oral BA (5%) because of its poor aqueous solubility and high first-pass metabolism. Studies indicate that nisoldipine-loaded SLNs could enhance the oral BA by 2.45-fold compared to the control suspension formulation. The half-life and mean residence time of SLNs increased significantly compared to the control formulation. This is achieved due to the sustained release of the nisoldipine from the SLNs. Studies were also performed to compare the performance of nisoldipine nanostructured lipid carriers with SLNs. The results indicated that both nanocarrier systems improved bioavailability by enhancing solubility⁵⁵.

Conclusion

Antihypertensives play a very important role in managing cardiovascular diseases which is one of the primary reasons for death. As per recent information from FDA and WHO, the number of patients suffering from hypertension seems to increase day by day. Researchers are actively looking for new targets and new molecules which are more efficient than the existing molecules. It was also important to find ways to utilize the existing molecules to the maximum potential. These new technologies will help to revive the usage of drugs that have been subsided because of low aqueous solubility or high first-pass metabolism.

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