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A Review on Optimizing Medication Delivery: Losartan Potassium and Hydrochlorothiazide in Microbeads and Granules

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The objective of this study was to design and optimize losartan potassium sustained release and hydrochlorothiazide immediate release formulations. The microbeads are prepared by ionic gellation technique. To evaluate the physical parameters, *in-vitro* drug release and stability studies formulated tablets were performed. The in-vitro drug release of the optimized formulation was compared with that of the marketed product. Losartan potassium sustained release microbeads offer slow and sustained release of the medication over a period of time. Furthermore Hydrochlorothiazide granules were prepared and then evaluated. The formulation of immediate release granules of hydrochlorothiazide is a promising approach to improve the bioavailability of the drug and reduce its side effects. Hydrochlorothiazide granules allow for a more rapid onset of

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action, which can be beneficial in patients with acute symptoms. Combining these two medications can be beneficial for patients with hypertension as they can provide both immediate and sustained relief from symptoms.

Keywords: Losartan potassium; sustained release; hydrochlorothiazide; immediate release; gellan gum.

1. INTRODUCTION

"High blood pressure (BP) is a significant public health concern. It is a significant cardiovascular risk factor that has a large impact on cardiovascular mortality" (Rodgers et al., 2000). "According to the Prospective Studies Collaboration, lowering blood pressure can significantly lower cardiovascular risk, cardiovascular mortality, and all-cause mortality. When baseline blood pressure is high, this risk reduction is steeper in younger people than in older subjects. Reducing both systolic and diastolic blood pressure was found to prevent cardiovascular events in a meta-analysis of 61 studies with more than a million hypertensive patients and 12.7 million years of follow-up" [1,2]. "At ages 40 to 69 years, each change in systolic or diastolic blood pressure of 20 or 10 mm Hg was linked to increases in death rates from coronary heart disease, stroke, and other vascular causes that were more than twice as high. While the annual absolute disparities in risk were larger in old age, all of these proportional differences in vascular mortality were around half as dramatic at ages 80-89 yr as at ages 40-49 yr. Therefore, it is necessary to reduce the blood pressure in all patient groups. Both non-pharmacological (lifestyle changes) and pharmaceutical methods can be used to accomplish this goal. Dietary modifications, weight management, smoking cessation, exercise, and stress management are all examples of lifestyle changes. For the initial management of high BP, several pharmacological medications are available, as demonstrated by significant randomized clinical trials. Beta-blockers and thiazide diuretics, such as more recent compounds like dihydropyridine calcium channel blockers (CCB), angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers, are examples of these (ARB). The best strategy for the initial treatment of hypertension should be comprehensive hypertension management, which places a strong emphasis on lowering the overall cardiovascular risk. A two-pronged strategy is used for the initial management of hypertension, with a focus on lifestyle changes and additional pharmacological management" [3,4]. "Non-pharmacological therapy, often known as lifestyle management, is crucial for hypertensive people. Lifestyle changes have the ability to avoid hypertension in non-hypertensive individuals, including those with pre-hypertension, as well as to lower blood pressure and minimize the risk of BP-related clinical consequences. Lifestyle changes can be used as an initial treatment for patients with hypertension before to the start of pharmacological therapy and as an adjuvant to drug therapy in patients already taking medication. These treatments can enable drug step-down in hypertensive patients with medication-controlled blood pressure in those who can maintain lifestyle adjustments" [3,4]. "As essential hypertension is thought to result from interactions between genes and environment, treatment is beneficial when a variety of elements in the patient's life are addressed. Controlling the environmental factors is essential in the therapy of high blood pressure because they are potent and account for the majority of BP differences across individuals and populations. Dietary excess salt and fat, dietary deficit in potassium and fiber, alcohol use, physical inactivity, and psychological stress are significant lifestyle or environmental factors. Obesity, particularly truncal obesity, is a significant risk factor for high blood pressure in Indians, and lifestyle factors play a role in its development. Important lifestyle factors can be controlled to manage hypertension. Lifestyle changes are an essential part for hypertension management. A diet high in calcium, fruits, and vegetables, and low in sodium is effective in treating hypertension, according to the Dietary Approaches to Stop Hypertension (DASH) trial. Exercise is crucial, especially for hypertensive children and adolescents who frequently have elevated sympathetic nervous system activity. Many hypertensive patients experience stress, which worsens their blood pressure" [5,6]. Numerous short-term trials have documented that individuals can make lifestyle changes that lower their BP. A more recent trial documented that individuals can simultaneously make multiple lifestyle changes but a vexing issue is the extent to which individuals can sustain lifestyle changes

over the long term. Numerous long-term studies, including phase 2 of the Trials of Hypertension Prevention (TOHP2) (Stevens et al., 2001) and the Trials of Non-pharmacological Interventions in the Elderly (TONE), have addressed this topic [7,8]. These trials showed that diet- exercise induced weight loss and sodium restriction may be sustained in middle-aged (TOHP2) as well as elderly (TONE) patients with mild to severe hypertension and are associated with significant BP decreases. However, it is necessary to individually examine the importance of various factors in the initial management of hypertension.

2. SUSTAINED RELEASE DRUG DELIVERY SYSTEM

It is well recognized that a sustained release drug delivery method offers quick release of the medication. As a result, to reach and maintain the medication concentration within the medically necessary range for treatment it is often essential to take this type of drug delivery system several times a day, which results in a significant fluctuation in drug levels. For many drug substances, conventional immediate - release formulations provide an appropriate level of patient safety, clinically effective therapy can be maintained while maintaining the necessary balance between pharmacokinetic and pharmacodynamic characteristics. Different well-known benefits of microparticulate drug delivery systems have different well-known benefit [9,10] over single unit dose forms. Additionally, owing in large part to patient acceptance, simplicity, and a manufacturing technique that is both efficient and affordable, oral medication is typically regarded as the first route studied in the discovery and development of new pharmacological entities and pharmaceutical formulations. “Multiple unit dosage form such as microspheres or microbeads have gained popularity as oral drug delivery systems because of the more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation and elimination of unwanted intestinal retention of polymeric material, when compared to non-disintegrating single unit dosage form” [11,12]. “Microencapsulation is one of the most widely used methods for creating delivering microparticulate medication. However, it has several benefits and some disadvantages. Some of the important drawbacks of these techniques include the use of harsh conditions in the formulation process, which limits use of many substances such as proteins, enzymes, as core materials for encapsulation. One solution to the aforementioned issue is the creation of microbead medication delivery systems, that do not require the use of harsh chemicals or high temperature. The traditional methods use polyelectrolyte complexation, ionotropic gelation, and emulsion gelation” [13,14]. “The majority of the work have been conducted on the preparation of microbeads by the ionotropic gelation method rather than other methods owing to its ease of preparation for the treatment of various diseases. Studies are done to assess the release pattern of the drug from microbeads” [15,16].

2.1 Microbeads

Microbeads range in diameter from 0.5 to 1000 m and are virtually spherical in shape. The prolonged release or multiple release patterns of treatment with various active agents are made possible without significant side effects by the crystalline or solution-based solid and free-flowing particulate carriers for dispersed drug particles. The microbeads can include medications to deliver locally at high concentration, ensuring that therapeutic doses are obtained at the target location while minimizing negative effects by maintaining low systemic concentration. They also sustain functionality under physiological settings. The microbeads are made from a variety of polymers, including cationic polymers like chitosan and anionic polymers like sodium alginate, as well as binding substances like gelatin, chondroitin sulfate, and avidin in a certain proportion. The creation of controlled release dosage forms now frequently uses microencapsulation. One technique for the controlled release formulation of different pharmaceutical compounds is the fabrication of polymeric gel beads. The characteristic spherical microcapsules known as beads serve as a stable base for coating or encapsulating the medication on. Thanks to beads, drugs can be delivered more uniformly and with sustained-release properties throughout the gastrointestinal tract. The bioavailability of medicines contained in beads has also increased. Alginate beads have been used as a controlled release carrier in a number of investigations [17,18].

2.2 Advantages of Microbeads

- Limiting fluctuation within therapeutic range.
- Reducing side effects.
- Decreasing dosing frequency.

- Improving bioavailability.
- Improving patient compliance.

2.3 Criteria for Formulation of Sustained Release Microbeads Dosage Forms

There are a number of formulation approaches that have been developed to circumvent the issue with immediate release oral dosage forms. These procedures include embedding the medication in a plastic matrix, ion exchange resins, osmotic pumps, hydrophilic matrices, coatings, hydrophilic and hydrophobic polymer mixtures, and microencapsulation [19]. Drugs are one of the parameters that must also be taken into consideration, along with the physiology of the gastrointestinal tract, physicochemical characteristics of the drug, drug release pattern, and pharmacological effect. The drug's physicochemical properties include aqueous solubility, stability, pKa, and permeability values.

2.4 Different Methods of Preparation of Microbeads

2.4.1 Ionotropic gelation method

In order to start crosslinking, an ionic polymer interacts with ions that have opposite charges. Contrary to simple monomeric ions, the electro-neutrality principle cannot fully account for how polyanion interacts with cations. The ability of cations to conjugate with anionic functions or vice versa depends on the three-dimensional structure and the existence of other groups. Using the ionotropic gelation procedure, beads can be produced in two different ways. The source of the crosslinking ion varies between the procedures. One of the processes positions the cross-linker ion externally, whereas the other way passively incorporates it into the polymer solution [20]. The two categories of ionotropic gelation methods are external gelation method and internal gelation method.

2.4.2 External gelation method

The crosslinking ion source for the external gelation approach is a metal ion solution. A needle is used to inject the drug-containing polymer solution into this solution while gently stirring it. Instant gelation takes place when the polymeric drop comes into contact with the metal ion solution, leading to the creation of self-sustained beads. After being cured in the gelation medium for a predetermined amount of time, the beads are removed and dried. Rapid diffusion of the cross-linker ions into the partially gelled beads causes external gelation [21].

2.4.3 Internal gelation method

Using the internal gelation method, the cross-linker ion is created "in situ". Through this method, insoluble metal salts like calcium carbonate and barium carbonate are used to create the crosslinking cation. By reducing the pH of the solution, the metal cation is liberated in place, solubilizing the metal salt and liberating the metal ion [22].

2.4.4 Emulsion gelation method

The emulsion gelation process is another technique for making microbeads. The weighed amount of sodium alginate is dissolved in deionized water to create the sodium alginate solution. To create a homogenous drug polymeric mixture, a precisely measured amount of the drug is added to the sodium alginate polymeric solution and swirled magnetically with low heat. In order to extrude the crosslinking agent into an oil solution comprising span 80 and 0.2% glacial acetic acid that is held under magnetic control, a certain amount of the crosslinking agent is added to create a viscous dispersion. The distribution of medications to the body can be made more effective and efficient by combining immediate-release granules with sustained-release microbeads. Targeted drug delivery systems are created via sustain-release microbeads, enabling more effective and precise therapies. The creation of immediate-release granules could completely alter the pharmaceutical market [23].

2.5 Polymers Used for the Preparation of Microbeads

Numerous substances, both biodegradable and non-biodegradable, have been investigated for the production of microbeads. These materials are made up of polymers with both synthetic and organic origins as well as modified natural components. Albumin, Gelatin, Sodium Alginate, Chitosan, Starch, Dextran, Polylactide, and olyglycolide Polyanhydride, Polyphosphazene, etc. are some examples of polymers. One of the multiparticulate drug delivery systems, sodium alginate microbeads are designed to achieve prolonged or controlled drug delivery, to increase bioavailability or stability, and to target the drug to certain areas. When compared to non-disintegrating single unit dosage forms, multiple

unit dosage forms, such as microspheres or beads, have gained popularity as oral drug delivery systems due to more uniform drug distribution in the gastrointestinal tract, more uniform drug absorption, reduced local irritation, and elimination of unwanted intestinal retention of polymeric material [24].

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2.5.1 Alginates

Alginates are natural polysaccharide polymers that have been isolated from the Phaeophyceae family of brown algae. Alginate can be transformed into its salts, of which sodium alginate is the most widely utilized type right now. Alginates are used in the delivery of drugs in a variety of ways, including liposomes, matrix type alginate gel beads, the delivery of biomolecules in tissue engineering applications, and changing gastrointestinal transit time. Due to their bioadhesive characteristics, alginates are useful in the pharmaceutical industry. There are many uses for sodium alginate-based drug delivery systems, which can also be created as gels, matrices, membranes, nanospheres, microspheres, and microbeads.Alginate beads can be taken orally by either compressing them into a tablet or adding them to capsules. The creation of systems that can change drug release in response to physiological needs (such as pH-responsive systems based on polymer swelling, magnetically triggered delivery systems, etc.) is a novel use of alginate polymer in the pharmaceutical industry. Alginate also has the physico-chemical characteristics necessary to be a significant contributor to this field of future study [25].

2.5.2 Chitosan

Crab and shrimp shell wastes are the main sources of chitosan, a cationic natural polymer that is generated from the chitin of crustaceans. As a relatively recent invention, its properties—which include the degree of deacetylation, the average molecular weight of the polymer, low toxicity, and good bioavailability—make it a novel excipient in a pharmaceutical formulation. Xanthan, alginate, and carrageenan are examples of natural polyanions that can be coupled with a biopolymer called chitosan to form a variety of polyelectrolyte complex products. A wide range of dosage forms, including ocular, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal, and gene carrier, have recently been created and researched using chitosan and its derivatives. Chitosan is a good choice for biomedical applications since it is biocompatible and exhibits antibacterial and antifungal activity. Numerous studies have demonstrated the value of chitosan in promoting the growth and repair of tissues as well as in therapies that speed up bone regeneration and wound healing [26].

2.5.3 Pectin

Pectin is used as a thickening agent and a gelling agent. Basically, it is a polymer of α-Dgalacturonic acid with 1-4 linkages. The chemistry of pectin and its ability to create gels have made this naturally occurring biopolymer useful in the pharmaceutical sector. Additionally, it has the potential to be employed in the manufacture of pharmaceuticals and the formulation of medications as a carrier for a range of biologically active compounds, not just for sustained release applications but also as a carrier for therapies that are intended to target the colon for either local or systemic action [27].

2.5.4 Xanthan Gum

Extracellular polysaccharides and natural, biosynthetic xanthan gum are edible gums. Glucuronic acid, mannose, and glucose make up xanthan gum. Due to the polyelectrolyte structure of the xanthan molecule, it is extremely soluble in both cold and hot water. Xanthan gum is primarily utilized to increase viscosity and is thought to be a nongelling agent. It quickly hydrates in cold water without lumping to produce a consistent viscosity. As a thickening stabilizer, emulsifier, and foaming agent, xanthan gum is employed. Xanthan may offer the benefit of zero-order release kinetics for medication release. But its main flaw is that the pH and ion content of the medium affect how much medication is released [28].

3. IMMEDIATE RELEASE DOSAGE FORMS

Oral administration is the most favoured route for systemic effects because to its simplicity, absence of discomfort, avoidance of adverse effects, adaptability, and most importantly, patient compliance. Additionally, since they don't have to be created in sterile circumstances, solid oral delivery systems are less expensive to manufacture. Due to patient compliance, extremely accurate dosing, and effective manufacture, tablets are the recommended solid dosage form. These selections will have a big

impact on excipient and equipment choices if solid dosage form technologies develop in response to the amazing advancements in drug discovery, including genomics. Until advanced auto injectors make it possible, patients often do not choose to use injections. Despite the fact that inhalation is a practical alternative delivery mechanism for many treatments, most chemical compounds with low molecular weights have been developed by contemporary biopharmaceutical research. For the delivery of poorly soluble medications containing high molecular weight proteins and peptides, increased oral protein delivery technology using quick release tablets that may release the drugs at an enhanced rate is particularly promising. The oral route is still the most effective approach to administer therapeutic medications since it is inexpensive to treat patients, convenient to manufacture, and has high levels of patient compliance [29]. An immediate release of the medication is required since many patients with a particular therapeutic condition need an action to start quickly. This issue, which is thought to impact 50% of the population, leads to a high rate of ineffective therapy. "Immediate release" refers to any pharmaceutical formulation that does not intentionally or obviously use galenic modifications to slow down the rate of drug release from the formulation or absorption.

3.1 Difficulties

Patients who experience tremors may find it difficult to swallow tablets, powders, and liquids. Physical barriers and adherence to the oesophagus in dysphasia may cause gastrointestinal ulcers. Since young adults' neurological and muscular systems haven't fully matured, solid dose forms like tablets and capsules can be challenging for them to swallow. They can also make elderly people experience dysphasia [30].

3.2 Criteria for Immediate Release Drug Delivery System

If the dosage is solid, it should quickly dissolve or disintegrate in the stomach. It should work with flavor masking when the dosage form is liquid. It should be transportable without being fragile. It ought to feel good in the mouth. Following oral administration, it shouldn't leave any, little, or no residue in the mouth. It shows little sensitivity to temperature and humidity changes in the environment. It should be produced at a reasonable cost utilizing standard processing and packaging machinery. It should have quick drug solubility and absorption, which could result in a quick commencement of action [31].

4. CONCLUSION

Losartan potassium sustained-release microbeads offer a slow and sustained medication release over time. This allows for a more consistent and stable therapeutic effect, and immediate-release Hydrochlorothiazide granules allow for a more rapid onset of action, benefitting patients with acute symptoms. Combining the two medications can help patients with hypertension as they can provide immediate and sustained relief from symptoms. Combining losartan potassium sustained-release microbeads with immediate release Hydrochlorothiazide granules can be a beneficial treatment option for patients with hypertension. Combining the two medications can provide rapid and sustained relief from symptoms. However, consulting a healthcare professional before beginning any new medication regimen is essential.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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