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Design and Evaluation of Nano spheres for Gastro retentive Drug Delivery System in Selected Hypertensive Drug

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Abstract: Hypertension is an ongoing heart condition that requires long-term pharmacotherapy so as to achieve the optimal blood pressure by removing associated complications such as heart attack, stroke, and kidney failure. Although oral drug delivery is the most preferable route of antihypertensive therapy, the majority of the traditional dosage delivery routes are constrained by the following factors: low bioavailability of gastrointestinal absorption, low GIT residence, high first-pass metabolism, and high dosage frequency. The gastro retentive drug delivery systems (GRDDS) have a number of antihypertensive agents that have a narrow absorption profile in the upper gastrointestinal tract with short biological half-lives. [1–3] [4–6]

One of the potential solutions to these problems suggested is the use of the gastro retentive nanosphere-based drug delivery system that could extend gastric retention, enhance the solubility of the drug, and deliver it under controlled and sustained methods. Among the advantages of nanospheres, whose diameter ranges between 10 and 1000 nm, is the fact that they are typified by high surface area, high mucoadhesive property, high drug loading capacity, and protection of the drug contained in the nanoparticle against adverse gastric conditions.[10] [11] [12] [13]

This review is a general discourse on the design principles, formulation methodology, and characterization schemes in the design of nanospheres to enable gastro retentive delivery of selected hypertensive drugs. It lays emphasis on the methods of preparation, polymer-drug complexes, the particle size, surface morphology, encapsulation efficiency, dynamics of drug release in vitro, mucoadhesive force, and stability measurements.

Keywords: Nano spheres, Hypertension, Gastro retentive drug delivery system.

INTRODUCTION

The health problem of hypertension is crucial at the global scale and is regarded as one of the greatest risk factors of morbidity and mortality of the cardiovascular system. The world health statistics indicate that the presence of chronic high blood pressure in the arteries puts one at a very high risk of being exposed to coronary artery disease, stroke, heart failure, and chronic kidney disease. The hypertension management is commonly grounded on long-term or life-long use of antihypertensive medications. Despite the large number of drug classes, the optimal therapeutic response is hard to achieve due to the issues of drug pharmacokinetics, adherence, and inter-subject variations in gastrointestinal absorption. [20–22]

Oral antihypertensive application is the most preferred drug administration method as it is easy to use, cheap, and most patients do not object to it. However, the traditional methods of oral delivery, such as tablets and capsules, are likely to possess such drawbacks as fast gastric emptying, erratic plasma drug concentrations, frequent administration, and even reduced bioavailability. The inefficiencies become particularly conspicuous with antihypertensive drugs, which possess either brief biological half-lives, narrow therapeutic indices, or region-specific absorption in the upper gastrointestinal tract. This means that patients require repeated doses to maintain

therapeutic plasma concentrations, which may pose a problem of non-adherence in patients and accelerate the occurrence of adverse events.

In an attempt to nullify these deficiencies, there has been research into more intricate systems of delivering drugs to improve the pharmacodynamics and pharmacokinetics of the antihypertensive agents. The gastro retentive drug delivery systems (GRDDS) have drawn much attention among them, as they promise to increase the gastrointestinal retention time and deliver drugs in a favorable and steady release. GRDDS have been developed to remain longer in the stomach, and therefore to enhance drug absorption in the upper gastrointestinal tract, and decrease differences in plasma drug concentration. A number of gastro retentive techniques have been developed, and these include floating systems, mucoadhesive systems, expandable systems, high-density systems, and raft-forming systems. [4–6]

Nanotechnology has also developed the gastro retentive drug delivery area through the capability of developing nanoscale carriers, which have enhanced functionality. One potential platform that has been proposed to be used in gastro retentive applications is Nano spheres, which are a type of polymeric nanoparticles where the drug is homogenously distributed within a solid polymer structure. Nano spheres have the ability to promote drug dissolution and stability and intimate contact with the gastric mucosa due to their small size and large surface area. Moreover, Nano spheres that are prepared by utilizing mucoadhesive polymers may adhere to the stomach wall and thus resist gastric emptying and increase the time of drug residence. [7–9]

The potential selection of suitable polymers is extremely vital in the successful development of nanosphere-based GRDDS. Natural polymers, such as chitosan and alginate, are better biocompatible, biodegradable, and mucoadhesive, whereas synthetic polymers, such as poly(lactic-co-glycolic acid) (PLGA) and Eudragit, are more competent to control the kinetics of drug release and structural stability. Polymers' composition and the drug influence the most significant formulation parameters such as encapsulation efficacy, particle diameter, repulsion, and release opposition. Therefore, there has to be a systematic design approach to simplify Nano sphere preparations towards the gastro retentive delivery. [10] [11] [12] [13]

Various antihypertensive agents, such as verapamil, propranolol, metoprolol, atenolol, and enalapril, were named as drugs that could be delivered via the gastrointestinal tract because of their selective uptake in the stomach or proximal small intestine and their high vulnerability to first-pass metabolism. Enhancement of bioavailability, extension of therapeutic effect, decreasing the dosing frequency, and increasing patient compliance through incorporation of these drugs into gastro retentive nanospheres have been demonstrated. Moreover, regulated diffusion of drugs through nanospheres can be effective in maintaining constant plasma drug concentrations to reduce side effects of drugs in their peaks, as well as enhance their overall safety.

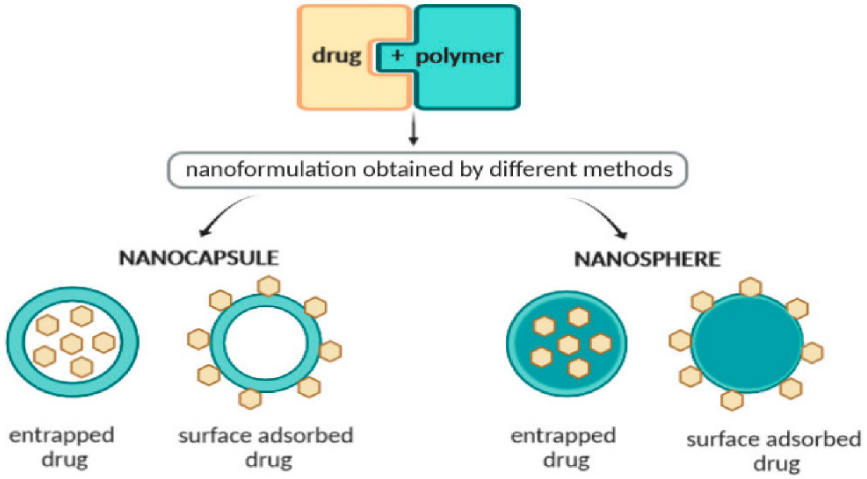

Fig 1: Nanosphere

2. Design Principles of Nano particulate GRDDS:

The efficient design of the nanosphere-based gastro retentive drug delivery systems (GRDDS) is dependent on the rational design approach encompassing the choice of polymers, compatibility of the drug and polymer, and optimization of the formulation variables. All these design principles have an impact on the gastric retention, drug release, stability, and the therapeutic effect of the formulation. Nanospheres of antihypertensive drugs should be formulated with special consideration, since they are usually used on a chronic basis and do require constant plasma levels of the drugs in these cases. [4–6] [20–22]

2.1. Polymer Selection:

Polymer is among the most critical aspects to determine the performance of nanospheres that will be used to deliver a drug to the stomach. The polymers are also used to encapsulate the drug and are also crucial in defining the particle size, surface properties, mucoadhesive, degradation rate, and the kinetics of drug release. The perfect type of polymer to be used in gastro retentive nanospheres must be biocompatible, biodegradable, non-toxic, and able to preserve the stability of the drug-carrying nanoparticle in the acidic gastric environment.

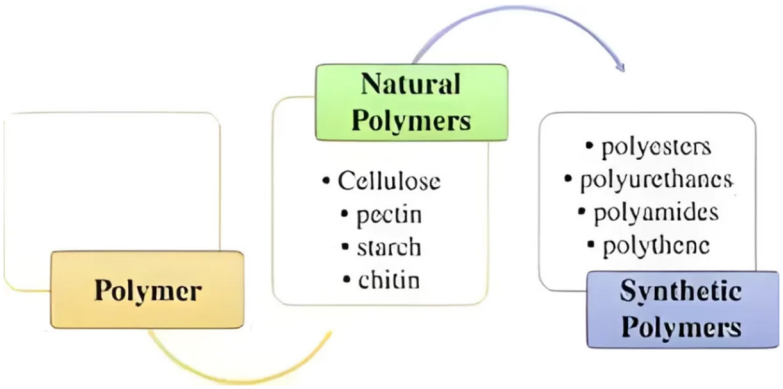

Fig 2: Polymers

Natural Polymers

- Chitosan, alginate, and gelatin are natural polymers that have been extensively studied in gastro retentive nanosphere formulations because of their natural biocompatibility and biodegradability characteristics. [11]
- A cationic polysaccharide, the chitosan, which is a derivative of chitin, has excellent mucoadhesive properties due to the electrostatic forces between its positively charged amino group and the negatively charged gastric mucin. This property greatly improves the gastrointestinal residence time. Moreover, chitosan may temporarily open tight junctions and enhance the absorption of drugs. [10]
- Alginate is an anionic polymer that forms a gel matrix in the presence of divalent cation e.g., calcium ions. Nanospheres made of alginate are able to swell in gastric fluid, which also leads to a long gastric Gelatin is a protein-derived polymer and, therefore, it has good film-forming and is biodegradable. Its amphotericity enables it to be versatile encapsulated with drugs; however, its mechanical stability could be enhanced by crosslinking.
- Natural polymers can be batch-to-lot variants, have low mechanical strength despite their merits, and require optimization during formulation development.

Synthetic Polymers

- The synthetic polymers used include poly (lactic-co-glycolic acid) (PLGA) and Eudragit variants, which give more control over the formulation characteristics and drug release kinetics. [12] [13]
- PLGA is a popular biodegradable polymer that is accepted by the regulatory agencies. With the option of changing the lactic acid to glycolic acid ratio, the rate of degradation and drug release profile may be accurately manipulated. PLGA nanospheres have good structural integrity and prolonged drug release.
- Eudragit polymers, in particular, Eudragit RS and Eudragit RL, are used to release drugs with controlled release and pH-free properties. Their solubility within the gastric fluid is low, which enables extended retention and slow diffusion of the drug and can be used in gastro retentive preparations. [13]
- Synthetic polymers tend to be more reproducible, stable, and scalable than natural polymers, but can have worse mucoadhesive properties without modification or bio adhesive agents.

Characteristics of the polymer are desired.

Polymers used in gastro retentive nanosphere formulations need to have:

I. Gastric Mucoadhesiveness, to guarantee long adhesion to the gastric mucosa and to the ability to resist emptying.
II. Monitored erosion behavior, which facilitates the synchronization of polymer erosion and the release of drugs.
III. Chemical and biological inertness, which guarantees non-toxicity and antihypertensive drugs. [20–22]
IV. Stability in acidic solutions, to ensure the drug is not degraded in the gastric conditions.

2.2. Drug–Polymer Interactions

The interaction of drugs with polymers is a crucial factor in encapsulation efficiency, stability, and release of nanosphere-based GRDDS. Effective formulation needs a good balance between interaction that can enable an efficient drug incorporation without affecting chemical stability and therapeutic activity.

Drug Charging and Loading and Encapsulation:

The loading and encapsulation efficiencies of the drugs should be high in order to reduce the frequency of drug intake and enhance patient compliance, particularly in chronic diseases like high blood pressure. The concentration of polymer, the solubility of the drug, the methodology of preparation, and the affinity of the drug and the polymer are all factors that affect the drug loading. Encapsulation efficiencies of more than 70 are usually the goal of optimized formulations, and they are deemed to be clinically significant.

Chemical Stability and Compatibility:

The compatibility of the drug and polymer is critical to ensure that it does not degrade, crystallize or lose its therapeutic activity during formulation or storage. The negatively contacting interactions can cause a decreased bioavailability or instability of the nanospheres. Thus, compatibility studies play a central role in the development of formulation.

Drug Release Kinetics:

The gastro retentive nanospheres are preferred to have a desired drug release profile that is sustained or near zero-order that facilitates constant plasma drug levels and minimizes variations in cases of traditional dosage forms. Depending on polymer properties and formulation, drug release of nanospheres can be by diffusion, polymer erosion, or a mixture of both.

Drug-Polymer Interactions Characterization:

Characterization: This method allows the evaluation of both the solubility and cellular structure of the polymer containing the drug Successful drug encapsulation and stability are confirmed using the following techniques: physicochemical characterization.

- The difference in thermal behavior is determined by Differential Scanning Calorimetry (DSC), and it suggests the possibility of interaction or the change of crystallinity.
- Fourier Transform Infrared Spectroscopy (FTIR) is used to determine the chemical compatibility through analyzing the interactions between the functional groups.
- To determine the amorphous character of crystallinity of the encapsulated drug, X-ray Diffraction (XRD) can be utilized.
- These analysis instruments ensure that the integrity of the nano sphere and drug activity do not collapse during formulation and storage.

3. Methods of Preparation

Preparation method is also significant in defining the physicochemical properties, drug loading capacity, release kinetics, and gastro retentiveness of the nanospheres. To choose a preparation method, a number of factors should be taken into consideration, and those are physicochemical characteristics of the antihypertensive drug, nature of the polymer, targeted size of the particle, scalability of the formulation, and stability. The literature has reported different approaches that can be used to prepare nanospheres, which can be used to deliver gastro retentive drugs.

I Emulsion Solvent Evaporation Process:

One method that is most commonly used to prepare polymeric nanospheres, especially of hydrophobic antihypertensive drugs, is the emulsion solvent evaporation. The drug and polymer in this technique are dissolved in a volatile organic solvent like Dichloromethane, ethyl acetate, or Chloroform to form the organic phase. The emulsification phase is then high-speed homogenized or sonicated into an aqueous phase with a stabilizer or surfactant, e.g., polyvinyl alcohol. [14, 15] [20–22]

With constant stirring, the organic solvent will evaporate slowly, so the polymer will precipitate, and solid nanospheres containing the drug will be formed. Polymer concentration, type and concentration of surfactant used, stirring rate, and rate of solvent evaporation are among the aspects that determine the size and distribution of the nanospheres. The method provides reasonable control of particle size and encapsulation efficiency; however, it might require the use of organic solvents, which will have to be carefully removed in order to be safe and in compliance with regulations.

II Ionic Gelation Method:

The ionic gelation approach is especially appropriate with regard to preparing the nanospheres by means of natural polymers like chitosan and alginate. It is a method that is based on the electrostatic interaction between oppositely charged polymers and crosslinking agents. An example is chitosan, which is a positively charged polymer that forms nanospheres when it interacts with negatively charged crosslinkers, e.g., sodium tripolyphosphate. [10] [11] [16]

Under this technique, the polymer solution is gradually mixed with the crosslinking agent after dissolving or dispersing the drug. This process uses the ionic crosslink formation to create a nanospace immediately without adverse conditions and organic solvents. Ionic gelation is regarded as a gentle and environmentally-friendly procedure, which is especially beneficial to acid-pragmatic antihypertensive drugs. Nevertheless, it needs to be optimized to ensure that the particle size is uniform and encapsulation is high. [20–22]

III Nanoprecipitation (Solvent Displacement) Technique:

The solvent displacement technique (or nanoprecipitation) is a simple and reproducible method of nanoparticle preparation of synthetic polymers like PLGA. In this technique, both the drug and the polymer are dissolved in an organic solvent that is water-soluble, like acetone or ethanol, and then added in drops into an aqueous phase subjected to continuous stirring.

The organic solvent is rapidly diffused into the aqueous phase, thus causing supersaturation and precipitation of the polymer to form a nanosphere. This technique does not need any high shear forces or high temperatures, and it can be used with thermolabile drugs. Nanoprecipitation has a small particle size distribution and is well scalable, but not effectively used with drugs that are highly soluble in water, because of loss to the aqueous solution

IV Spray Drying Technique:

Spray drying is a scalable method for producing nanospheres, where a liquid feed is transformed into dry particulate form in one step. In this technique, a solution or a suspension of drug and polymer is atomized into a hot drying chamber, and fast solvent evaporation results in the creation of solid nanospheres.

Different parameters that control the size of the particles, such as the inlet temperature, feed rate, atomization air pressure, and polymer concentration, can be controlled in spray drying. The technique is especially convenient in the case of large-scale production and has a high reproducibility. Its use in the heat-sensitive antihypertensive drugs, however, may be restricted due to exposure to high temperatures, unless the optimum conditions are used. [20–22]

V Emulsion–Diffusion Method:

The emulsion diffusion method comprises the creation of an oil-in-water emulsion wherein a partially water-miscible solvent system is used. The polymer and drug are dissolved in a solution that is saturated with water, and the solution is emulsified into an aqueous solution. The next step is the further addition of surplus water, which causes the diffusion of the solvent, and then the precipitation of the polymer and formation of a nanosphere.

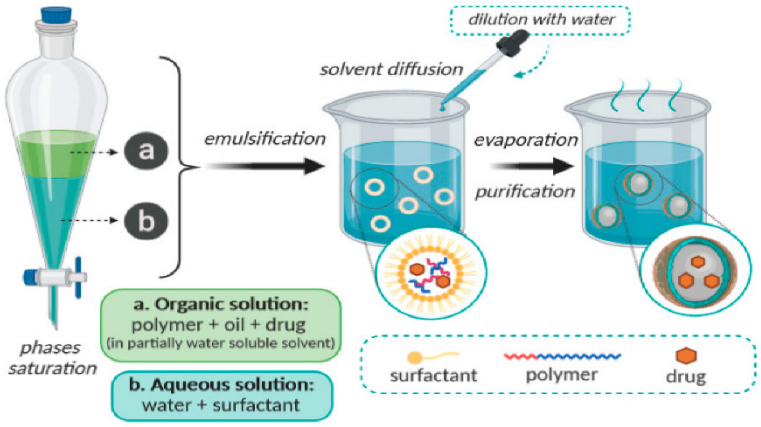

Fig 3: Emulsion Diffusion Method

This technique will be beneficial in decreasing the quantity of organic solvent utilized and attaining an even distribution of particle sizes. It has been effectively used in the making of nanospheres with elevated encapsulation proficiency and controlled drug discharge characteristics.

Factors that affect the formation of a Nanosphere

No matter the method of preparation, several formulation and process variables impact nanosphere properties, and they are:

a. Type of polymer and polymer concentration.
b. Drug solubility and drug-polymer ratio.
c. Surfactant concentration
d. Stirring speed or homogenization speed.
e. Medium temperature and PH.

These parameters should be optimized to achieve nanospheres with a favorable gastro retentive behavior, prolonged release of the drug, and stability.

3.7. Applicability to Gastro retentive Drug Delivery

Gastro retentive applications are of particular interest to preparation procedures that allow incorporation of mucoadhesive polymers or nanospheres, which have the correct surface characteristics. Methods like ionic gelation and emulsion-based methods can be used to create nanospheres, which can be attached to the gastric mucosa, resist the emptying of the gut, and release antihypertensive drugs in a controlled way over long durations. [16] [20–22]

4. Characterization of Nano particulate GRDDS

It is important to characterize nanospheres as accurately and comprehensively as possible to guarantee the performance of nanospheres, their safety, stability, and reproducible behavior. Characterization studies can give important data on the physicochemical properties of the formulation, encapsulation efficiency of the drug, drug release, mucoadhesive potential, and long-term stability. All of these parameters define the efficacy of nanosphere-based gastro retentive drug delivery systems (GRDDS), especially of antihypertensive drugs necessitating a sustained and controlled therapeutic exposure. [4–6] [20–22]

4.1. Physical and Morphological Characterization:

- **Particle size and size distribution**

  Particle Size Particle size data is considered to be the mean or median particle size measured in nanometers, mcm, or feet.

  The size of particles is considered one of the most significant properties of nanospheres because it directly affects the surface area, rate of drug release, mucoadhesive properties, and gastro-retention. Nanospheres to be used in gastro retentive have a size of 100-1000 nm, usually being large enough to interact with the gastric mucosa but small enough to avoid rapid gastric emptying.

  Dynamic Light Scattering (DLS) is usually used to measure particle size and size distribution. DLS delivers data about the hydrodynamic diameter and polydispersivity index (PDI), which is an indicator of the homogeneity of the particle size distribution. The low PDI (less than 0.3) shows that the size distribution is narrow and homogenous, meaning it is preferable to obtain reproducible drug release and uniform performance in vivo. [17]

- **Surface Charge (Zeta Potential)**

  Measurement of Zeta potential gives information on surface charge and colloidal stability of nanospheres. The positively charged nanospheres (especially nanospheres that are prepared using chitosan) are the ones that have an improved mucoadhesion attributable to the attraction of the negatively charged gastric mucin via electrostatic interactions. Also, an increase in the absolute zeta potential values helps enhance the physical stability by avoiding the aggregation of particles. [10]

- **Morphological Analysis**

  Nanospheres' surface and shape are important factors that determine drug release and stability. SEM and TEM are common methods used to observe the morphology of a nanosphere. These methods verify the sphericity, flatness of surfaces, and non-aggregation. Predictable and controlled drug release profiles of uniform and spherical nanospheres with smooth surfaces are linked to sustained plasma drug concentrations and are vital to the preservation of constant drug levels in the plasma.

4.2. Efficiency of Encapsulation and Drug Loading.

The most important parameters to consider in regard to the clinical applicability of nanosphere formulations are encapsulation efficiency and drug loading capacity. High encapsulation efficiency implies that a sufficient concentration of drug is entrapped into the nanospheres; hence, low dosing is required, and the dosing frequency is lowered, which is significant in chronic diseases like hypertension.

Encapsulation efficiency is normally expressed as a percentage of drug encapsulated to the total amount of drug consumed in the formulation. A larger value of 70 or more is usually regarded as acceptable as far as therapeutic relevance is concerned. The efficiency of drug loading and encapsulation is measured analytically through UV -Visible spectrophotometry, high-performance liquid chromatography (HPLC), or fluorometric techniques based on the physicochemical characteristics of the drug. The studies also allow assessing drug wastage during preparation and maximizing preparation conditions.

4.3. In Vitro Drug Release Analysis.

An in vitro drug release experiment is conducted to test the release profile of antihypertensive drugs of nanospheres at simulated gastrointestinal conditions. Such studies are typically done in simulated gastric fluid (SGF) at pH 1.2 with or without enzymes to simulate the physiological conditions of the stomach. [20–22]

The profile of release gives useful data on the mechanism of drug release, which could be by diffusion of the drug through the polymer mass, erosion or degradation of the polymer, or a mix of both. The gastro retentive systems must have a sustained and controlled release of drugs over long periods of time so as to maintain a constant level of plasma drugs.

The kinetic models of equations, which include zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations, are mathematical models that can be used to explain the overall release mechanism. These models are needed to compare formulations and optimize the parameters of polymer composition and processing. [18]

4.4 Mucoadhesive Strength

It is evaluated using a spruing machine simulator test apparatus (Fisher, 2008). Mucoadhesive Strength Evaluation: An evaluation of Mucoadhesive Strength is through a spruing machine simulator test apparatus (Fisher, 2008). [19]

The determination of the gastro retentive ability of nanospheres will be based on mucoadhesive strength. Good mucoadhesion allows a longer period of adherence of nanospheres to the gastric mucosa, which prevents the emptying of the stomach and increases the absorption of the drug.

Mucoadhesive properties are traditionally measured with the help of mucin-binding assays, where the interaction between nanospheres and mucin is measured. Other techniques are ex vivo adhesion tests of gastric mucosal tissues. High mucoadhesive potential is especially beneficial when using nanospheres that are developed using materials like chitosan that bind with the gastric mucus layer using the electrostatic mechanism of interaction. [10.]

4.5. Stability Studies

The stability tests are carried out to determine the physical and chemical stability of nanospheres when stored. Such studies assess variations in the particle size, morphology, drug content, and release behavior in different environmental conditions, such as different temperatures, humidity levels, and pH levels. [23]

The determination of shelf life and storage conditions is guided by accelerated and long-term stability tests, which are commonly conducted in line with ICH guidelines. The formulations based on nanospheres are of particular concern to stability analysis because aggregation, polymer degradation, or leakage of drugs may abort the therapeutic efficacy and safety. [23]

5. Application to Hypertensive Drugs:

5.1. Hypertensive Agents\ Selection Criteria.

The selection of antihypertensive agents to be included in the gastro retentive nanosphere systems is vital in the quest to attain the best therapeutic outcome. The desired drug candidates are usually associated with physicochemical and pharmacokinetic constraints, which can be circumvented by increasing the gastric residence time and controlled release of the drug.
Some of the critical selection criteria will be:

- Short biological half-life: Drugs that are quickly eliminated require a lot of repeat administration, and this may result in poor patient compliance. Gastroretentive nanospheres facilitate the release of drugs in a sustained manner, keeping the plasma levels of the therapeutic levels within a long period of time.

- Site-specific absorption: Drugs with a selective absorption form in the stomach or in the upper small intestine: The drugs are better absorbed in the proximal gastrointestinal tract, leading to high gastric retention, resulting in increased absorption efficacy in decreasing the variability of bioavailability.
- Low oral bioavailability as a result of the first-pass metabolism: There are a lot of antihypertensive drugs that experience a lot of hepatic metabolism, and as a result, the systemic availability gets reduced. Plasma peak concentrations can be reduced by controlled release of nanospheres, and overall bioavailability can be enhanced. [20–22]
- Narrow therapeutic window: Drugs with sustained and predictable release have a narrow therapeutic index, causing minimal sub- or overdose effect or drug toxicity.

Examples of these would be:

- **Verapamil:** It has a short half-life and high first-pass metabolism; hence, it is a good drug to be used in gastro retentive nanosphere systems to have a long effect.
- **Metoprolol:** This drug must maintain a continuous plasma level to provide blood pressure control; controlled-release formulations will aid in the maintenance of the level.
- **Propranolol:** It exhibits absorption in the upper gastrointestinal tract, and the gastro retentive delivery systems can increase the absorption and therapeutic effect of propranolol.

5.2. Research Results in the Literature.

It has been shown in many studies that gastro retentive nanosphere-based drug delivery systems can enhance the pharmacodynamics and pharmacokinetics of antihypertensive agents.

The major findings given in the literature are:

- The chitosan-based nanospheres have a good mucoadhesive activity as a consequence of positive surface charge, which leads to an increase in the gastric residence time and the sustained release of antihypertensive drugs (e.g., verapamil and metoprolol) through the nanospheres. [10] [20–22]
- It has been demonstrated that the release profile of the nanospheres of poly-lactic-co-glycolic acid (PLGA) can be controlled and predictable at 12 to 24 hours, due to the biodegradable polymer backbone and diffusion-controlled release properties of the nanospheres.
- The nanosphere formulations are always known to exhibit excellent oral bioavailability and low dosing rate, as well as effective therapeutic efficacy as compared to traditional dosing forms. These benefits play a role in enhancing patient adherence and sustainable hypertension treatment.

6. Comparative Advantages

Feature	Conventional Oral	GRDDS Nanospheres
Gastric Residence	Short	Prolonged
Bioavailability	Variable	Enhanced
Release Profile	Immediate	Sustained/Controlled
Patient Compliance	Moderate	Higher
Side Effects	Peaks/Valleys in plasma levels	Smoother plasma profiles

Evaluation Tests of Gastro retentive Nanospheres:

1. Particle Size and Size Distribution:

- The size of particles is very important in dictating how the drug will be released, its stability, and the amount of surface area of the nanospheres. Smaller particles have more surface area that can be used to increase dissolution and release of drugs.
- To prevent multiple scattering of light, the prepared nanosphere suspension is diluted with distilled water or filtered buffer solution.
- The sample cuvette of a Dynamic Light Scanning (DLS) particle size analyzer has the diluted sample.
- The instrument registers changes in the scattering of light due to Brownian motion of particles.
- Out of these variations, the hydrodynamic diameter of particles is determined.
- The device will also give the Polydispersity Index (PDI), which is used to show the evenness of the particle size distribution.

Particle size range: 10-1000 nm

PDI value: A value smaller than 0.3 means that it has a very narrow size distribution and is quite uniform.

2. Surface Morphology (SEM/TEM):

- The surface morphology analysis gives details of the shape of nanospheres, surface texture, and structural integrity.
- The SEM uses the electron beam to create an image (scanning) of the electron beam onto the body under examination. Scanning Electron Microscopy (SEM):
- A single dose of dried nanospheres is spotted on an aluminum stub with a double-sided adhesive tape.
- A sputter coater is used to coat the sample with a thin layer of gold or platinum in order to enhance conductivity.
- The sample is then subjected to a Scanning Electron Microscope with various magnifications.
- Photographs are taken in order to monitor the shape of particles, surface smoothness, and aggregation.

Transmission Electron Microscopy (TEM):

- A drop of nanosphere suspension is then applied to a carbon-coated copper grid.
- Filter paper is used to remove excess liquid.
- The grid is dried, and it is viewed under TEM.
- Higher resolution images can give a lot of internal and external structural features.
- Nanospheres that are well prepared would usually exhibit a smooth surface, spherical shape, and uniform distribution.

3. Zeta Potential Measurement:

- Zeta potential is used to determine the charge of the particles at their surfaces, and it determines the physical stability of the colloidal system. Highly charged particles repel, and the particles are not aggregated.
- A nanosphere suspension is diluted with either distilled water or electrolyte solution.
- The sample is diluted and then put in a cell of zeta potential.
- The sample is measured with a zeta potential analyzer that works on the electrophoretic mobility.
- The charged particles move towards the electrode with opposite charges against which an electric field is applied.
- The instrument is used in measuring particle velocity and determining the zeta potential value (mV).

High stability: Greater than +30mV or lower than -30mV

Moderate stability: +-20-30 mV

Low stability: less than +-20 mV

4. Drug Entrapment Efficiency:

- Entrapment efficiency is used to establish the percentage of a drug that has effectively been encapsulated within the nanospheres as compared to the amount of the drug utilized during the formulation process.
- A known amount of nanosphere suspension is centrifuged into a centrifuge tube.
- A centrifugation at 10,000-15,000 rpm for approximately 30 minutes is done.
- Nanospheres will be deposited on the bottom to form a pellet and leave the free drug in the supernatant.
- The supernatant is taken with care.
- The amount of free drug is ascertained with the help of a UV-visible spectrophotometer or HPLC.
- Elevated entrapment efficiency implies that there is efficiency in drug incorporation and formulation performance.

5. Drug Loading Capacity:

- Drug loading refers to the number of drugs available in the nanospheres when compared to the weight of the nanospheres.
- The nanospheres are weighed accurately to a known amount.

- A suitable solvent or a buffer solution is used in the dissolution or disruption of the nanospheres.
- The drug is totally liberated from the polymer matrix.
- The concentration of the drug is determined by the Folin UV spectrophotometry or the HPLC.
- Increased drug loading is beneficial in enhancing dose efficiency and lowering the amount of carrier material that is needed.

6. In-Vitro Drug Release Study:

- This paper assesses the drug release rate and percent under the influence of simulated gastric conditions out of nanospheres.
- A predetermined number of nanospheres that is equal to a certain dose of drug is added to a dissolution basket or dialysis bag.
- The sample is added to the USP dissolution apparatus Type II (paddle type).
- Dissolution medium: 900 mL of 0.1 N HCl (pH 1.2) to imitate gastric fluid.
- It is kept at a temperature of 37 +- 0.5degC.
- In most cases, paddle speed is set to 50-100 rpm.
- Five milliliters of the samples are withdrawn at fixed time intervals (e.g., 1, 2, 4, 6, 8, 12 hours).
- The same volume of fresh dissolution medium is added to sustain constant volume.
- The filtered samples are detected by means of UV spectroscopy or HPLC.

Kinetic models may be fitted with the data of the release of drugs as:

Zero-order kinetics

First-order kinetics

Higuchi model

Korsmeyer-Peppas model

The models are useful in comprehending how drugs are released.

7. Mucoadhesion Study:

Mucoadhesion tests are the tests used to find out the capacity of nanospheres to adsorb to gastric mucosal surfaces, which increases gastric retention time.

In-vitro Wash-Off Method

- Fresh animal (goat or pig) gastric mucosa is cut off and adhered to a glass slide.
- The mucosal surface is spread with a known amount of nanospheres.
- The slide is put in the USP disintegration apparatus with simulated gastric fluid.
- The device causes the slide to rise and fall to imitate the actions of the stomach.
- Specifically, the amount of particles left on the mucosa is determined at certain intervals.
- The more the proportion of particles attached to the mucosa, the higher the mucoadhesive characteristics.

7. Challenges and Limitations

Although gastro retentive nanospheres hold a promising potential in the treatment of hypertension, there are several scientific, technical, and clinical challenges that are yet to be met before the wide clinical acceptance.

- **Scale-up and manufacturing expense:** The nanosphere formulations at the laboratory scale are difficult to translate to the industrial scale of the manufacturing process because of difficult fabrication strategies, the need for quality control regulations, and high manufacturing expenses. The reproduction of batch-to-batch properties whilst preserving particle dimensions, drug loading, and release properties is especially challenging.
- **Drug stability at acidic gastric conditions:** The stability of the chemical of some antihypertensive drugs and polymer carriers may be affected by the acidic pH of the stomach. The degradation of the drug or carrier material can cause loss of therapeutic efficacy and unpredictable release patterns, and hence, protective coating or pH-controlling excipients are required. [20–22]

- **Inter-patient variability of gastric motility:** The resultant variations in gastric emptying time, fed or fasted state, age, and disease conditions can play an important role in determining residence time and work of gastro retentive systems. This inconsistency can lead to a lack of consistent drug absorption and therapy in patients.
- **Stable mucoadhesion behavior with time:** Although the initial action of mucoadhesive polymers is to increase the gastric retention, it is difficult to ensure strong and long-term mucoadhesion in a hostile gastric environment. Polymer-mucus interactions can be weakened by continuous mucus turnover and mechanical stress due to gastric motility, which decreases the retention efficiency.

8. Future Directions

Development of future studies in gastro retentive nanosphere-based drug delivery systems should aim at developing further strategies to address the prevailing shortcomings and maximize the healing effect.

- **Smart nanospheres:** To facilitate site-specific release of drugs, including pH-responsive or enzyme-activated nanospheres, it is possible to develop stimuli-responsive nanospheres, which can be site-specific, on-demand, and reduce degradation of drugs in adverse conditions.
- **Ligand-mediated delivery via ligand-decorated surfaces:** The ligands can be used as a functional group to target nanospheres to the gastric mucosa to improve retention duration and drug uptake.
- **In vivo imaging methods:** Sophisticated imaging techniques such as gamma scintigraphy and magnetic resonance imaging (MRI) may be used to retrieve the gastric retention behavior and drug release patterns in real time, which is a useful translational phenomenon in human subjects.
- **Clinical trials to validate therapeutic:** To pass the regulatory and clinical pathway and demonstrate clinical superiority in antihypertensive gastro retentive nanosphere formulations over existing antihypertensive dosage forms, clinical trials are required, which are well-coordinated and designed trials to validate the safety, efficacy, and therapeutic superiority of the antihypertensive formulations.

Conclusion

The design and development of antihypertensive drugs exemplifies great improvement in the oral drug delivery technology. These systems have definite therapeutic benefits over traditional oral preparations in that they increase the residence time of gastrointestinal tract contents, promote drug absorption in the upper region, and provide the capability to do controlled and sustained drug release. [20–22]

To translate these promising systems into clinical use, continued research on optimization of formulation, overall physicochemical-biological characterization, and thorough clinical trials will be needed. Further innovation and validation can make gastro retentive nanospheres potentially fruitful in better management of hypertension and patient quality of life.

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