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Formulation and Evaluation of Oral Microsphere of Anti Hypertension Drug

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Abstract: *High blood pressure (hypertension) is a serious health problem that often requires long-term treatment. Many antihypertensive drugs have drawbacks such as a short half-life, low absorption, and frequent dosing, which can reduce patient compliance. Microspheres are tiny particles that can carry drugs and release them slowly in the body. They improve drug stability, extend release time, reduce side effects, and increase effectiveness. Different types of microspheres, such as bioadhesive, floating, magnetic, and polymer-based, can be made using natural or synthetic polymers. In hypertension treatment, drugs like losartan, diltiazem, and metoprolol have been successfully formulated into microspheres, showing better control of blood pressure and reduced dosing frequency. This review highlights the methods of preparation, advantages, limitations, and applications of microspheres, with special focus on their role in improving antihypertensive therapy. Microsphere-based drug delivery offers a promising approach for safer, more effective, and patient-friendly hypertension management.*

Keywords: Microspheres, Antihypertensive drugs, Controlled drug delivery, Sustained release, Bioavailability, Losartan potassium, Hypertension management, Mucoadhesive microspheres, Oral drug delivery, Polymer-based microspheres

I. INTRODUCTION

[1]Microspheres are small, round particles (1 to 1000 micrometers in size) that can hold medicines in solutions or tiny crystal forms. In skin treatments, these particles help the drug stay at the site of application instead of spreading into the whole body unnecessarily. This ensures the medicine is released directly into the skin where it is needed. Microspheres act like tiny storage units that slowly release the drug, keeping the right amount of medicine in the skin while reducing unwanted side effects. This controlled release also prevents too much or too little medicine being delivered, which is especially important in reducing antibiotic resistance during infection treatment. Using the right delivery systems with microspheres can also make products safer.

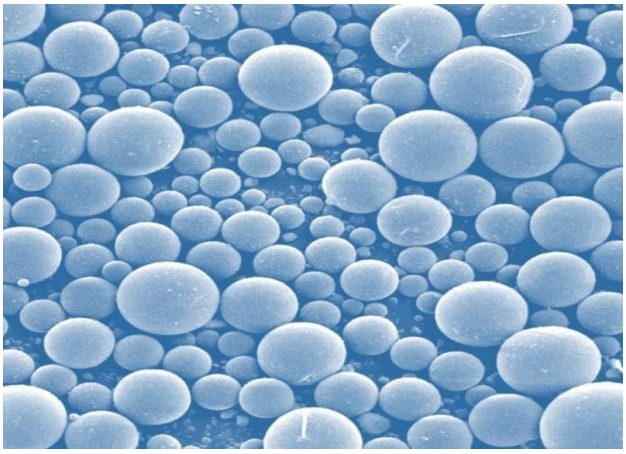

Fig 1: Microsphere.

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Compared to regular treatments, microspheres improve how well medicines work. Many types of drugs—such as NSAIDs, hormones, proteins, peptides, and tissue-based medicines—can be loaded into microspheres. There are two main types of microspheres.

[2]The therapeutic efficacy of any pharmacological treatment can be characterized by the attainment of an optimal drug concentration within systemic circulation or target tissues, such that the levels remain therapeutically effective yet non-toxic over an extended duration. Accomplishing this objective necessitates the rational design of an appropriate dosage regimen. Among various strategies, microspheres represent a promising vehicle for controlled and sustained drug delivery.

Losartan potassium, a potent antihypertensive agent, demonstrates extensive plasma protein binding and is associated with several adverse effects, including gastrointestinal disturbances, neutropenia, acute hepatotoxicity, migraine, and pancreatitis. Consequently, the incorporation of this compound into a sustained-release delivery system is considered advantageous. The present investigation was directed toward the formulation of controlled- release Losartan-loaded microspheres employing both emulsification and water-in-oil (w/o) solvent evaporation techniques.

[3]Microspheres represent a widely utilized drug delivery system, notable for their inherent mucoadhesive characteristics. They are fabricated employing a diverse range of polymers and demonstrate broad pharmaceutical applicability. However, their therapeutic effectiveness is often constrained by the relatively brief residence time at the absorption site. Consequently, the development of strategies that facilitate prolonged and intimate interaction between the delivery system and the absorptive mucosal surfaces would be highly advantageous for enhancing drug bioavailability and therapeutic outcomes.

[4]Microencapsulation is employed to modulate and prolong the release of a therapeutic agent. As illustrated in the figure, the drug is entrapped within a polymeric capsule. Upon exposure to the acidic gastric environment (pH ~1.3), the polymeric matrix undergoes dissociation, thereby enabling the gradual release of the drug. This controlled release mechanism facilitates the maintenance of therapeutic drug concentrations over an extended period while minimizing fluctuations in plasma levels.

[5]In the present investigation, Losartan potassium was employed as the model drug. Alginate, a naturally occurring polysaccharide polymer derived from brown algae, is composed of two distinct monomeric units: β-D-mannuronic acid and α-L-guluronic acid. Losartan potassium-loaded microbeads were formulated using the ionotropic gelation technique, wherein the natural anionic polysaccharide sodium alginate interacts with oppositely charged calcium ions. The calcium ions act as cross-linking agents (counter ions), leading to the instantaneous formation of microbeads.

Although various synthetic polymers have been utilized for the preparation of microbeads, each is associated with certain advantages and limitations. Losartan potassium (LP) is a potent and highly selective angiotensin II type 1 (AT1) receptor antagonist with established antihypertensive activity. It is rapidly absorbed from the gastrointestinal tract, exhibiting an oral bioavailability of approximately 33%, with a plasma elimination half-life ranging between 1.5 and 2.5 hours.

[6]Microspheres are commonly used as a drug delivery system and also stick well to mucus surfaces. They have many uses and are made with different types of polymers. However, their success is limited because they stay only for a short time at the absorption site. Therefore, it would be better if there were ways to keep the drug delivery system in close contact with the absorption surface.

[7]Controlling blood pressure with just one type of medicine often doesn't work. Treatment plans can use either fixed-dose combinations (two or more drugs in one tablet) or separate drugs taken one after another. Using a combination makes the medicine easier to take, allows lower doses of each drug, reduces side effects, and helps patients follow treatment better. In many cases, more than one drug is needed to reach the target blood pressure.Amlodipine besylate is a calcium channel blocker that relaxes blood vessels and improves blood flow. Losartan potassium is an angiotensin II receptor blocker that also helps lower blood pressure.

[8]The study was carried out to check how different process and formulation factors affect HPMC-based spray-dried mucoadhesive microspheres. The goal was to improve the preparation method and test if giving the drug through the nose could be an effective non-invasive way for systemic drug delivery, using dexamethasone-induced hypertensive rats as the model.

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Polymer used for formulation of microspheres:-

[9]Polymers are often used to make microspheres, and they are grouped into two main types:

Synthetic polymers:-

These are man-made and can be:

- Non-biodegradable polymers (do not break down easily)

-poly methyl methacrylate (PMMA)
-Acrolein
-Glycidyl methacrylate
-Epoxy polymers

- **Biodegradable polymers** :-(can break down naturally)

-Lactides, Glycosides and their copolymers
-Poly alkyl cyano acrylates
-Poly anhydrides

Natural polymers:-

These come from natural sources like proteins, carbohydrates, or modified carbohydrates.

- Proteins:-

-Albumin
-Gelatin
-Collagen

- Carbohydrates:-

-Agarose
-Carrageenan
-Chitosan
-Starch

- Chemically modified carbohydrates:-

-Poly dextran
-Poly starch

Type of Microspheres:-

Bioadhesive microspheres → Microspheres that stick to body tissues

Magnetic microspheres → Microspheres that move or can be directed using a magnet

Floating microspheres → Microspheres that float in stomach fluid to stay longer in the stomach. **4)Radioactive microspheres** → Microspheres that carry radioactive substances, usually for treatment. **5)Polymeric microspheres** → Microspheres made from polymers (special long-chain molecules).

Biodegradable polymeric microspheres → Made from polymers that can break down naturally in the body.

Synthetic polymeric microspheres → Made from man-made polymers that may or may not break down naturally.

[10] **Bioadhesive microspheres** → Microspheres that stick to body tissues.

-Adhesive means the process by which a drug sticks to a membrane with the help of water-soluble polymers. When a drug delivery system attaches to mucosal membranes like those in the mouth, eyes, nose, or rectum, it is called bioadhesion. These microspheres can stay longer at the target site, which helps the drug work better.

[11]**Magnetic microspheres** → Microspheres that move or can be directed using a magnet.

-Magnetic microspheres are special types of microspheres that deliver drugs directly to the disease site. Instead of spreading large amounts of free drug through the whole body, only a small amount of drug is guided to the target using a magnetic field. These microspheres are very small (less than 4 μm), so they can move easily through blood capillaries without blocking them. An external magnetic field of 0.5–0.8 tesla is used to direct them. For example, they can remove neuroblastoma cells from bone marrow using antibodies attached to magnetic microspheres.

- Types of magnetic microspheres:-

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Therapeutic magnetic microspheres

Used to treat liver tumors by carrying chemotherapy drugs directly to the site. Often loaded with proteins or peptide drugs for targeted delivery.

Diagnostic magnetic microspheres Used mainly for imaging liver metastases.

Can also form nano-particles (like superparamagnetic iron oxides) that help distinguish bowel loops from other abdominal structures in imaging.

[12]Floating microspheres → Microspheres that float in stomach fluid to stay longer in the stomach.

Because floating types are lighter than stomach fluid, they stay on top and are not affected by how quickly the stomach empties. While floating in the stomach, the drug is released slowly at a controlled rate. This helps the medicine stay in the stomach longer, keeps drug levels in the blood more steady, reduces the risk of irritation or sudden overdose, and provides a longer-lasting effect. An example of such medicine is ketoprofen.

[13]Radioactive microspheres → Microspheres that carry radioactive substances, usually for treatment.

Radioactive microspheres used in radioembolization therapy are 10–30 nm in size, which is bigger than capillaries, so they get trapped in the first capillary they reach. These microspheres are injected into the arteries that supply the tumor. This way, they deliver a high dose of radiation directly to the tumor without damaging the surrounding healthy tissue. The main types of radioactive microspheres are α, β, and γ emitters.

Polymeric microspheres → Microspheres made from polymers (special long-chain molecules).

▫Types of polymeric microspheres:-

Biodegradable polymeric microspheres:-

Natural polymers like starch are used to make these microspheres. They are biodegradable, compatible with the body, and can stick to mucous membranes. Because they swell in contact with water, they form a gel and stay longer at the site. The amount and rate of drug release depend on the polymer concentration and follow a sustained release pattern. The main drawback is lower drug loading and release efficiency. These microspheres are used in various treatments, for example, polylactic acid microspheres loaded with 5-fluorouracil.

Synthetic polymeric microspheres:-

These microspheres are widely used in medicine as drug carriers, fillers, bulking agents, or embolic particles. They are safe and compatible with the body. The main drawback is that they may move from the injection site, which can cause blockages or damage to other organs. An example is phenobarbitone microspheres made with the polymer Eudragit RL.

Porous microspheres:-

Glass microspheres:-

Porous microspheres:-

Porous microspheres have tiny holes on the outside or inside where the drug can be placed. These holes are made using substances called porogens, which are removed later. Examples of porogens include ammonium bicarbonate, hydrocarbon waxes, sodium chloride, sugar, gelatin, and ice. The outer structure of the microsphere is made from materials like calcium carbonate, mesoporous silica, hydroxyapatite, or biodegradable porous starch. These microspheres are useful for delivering proteins and peptides.

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Glass microspheres:-

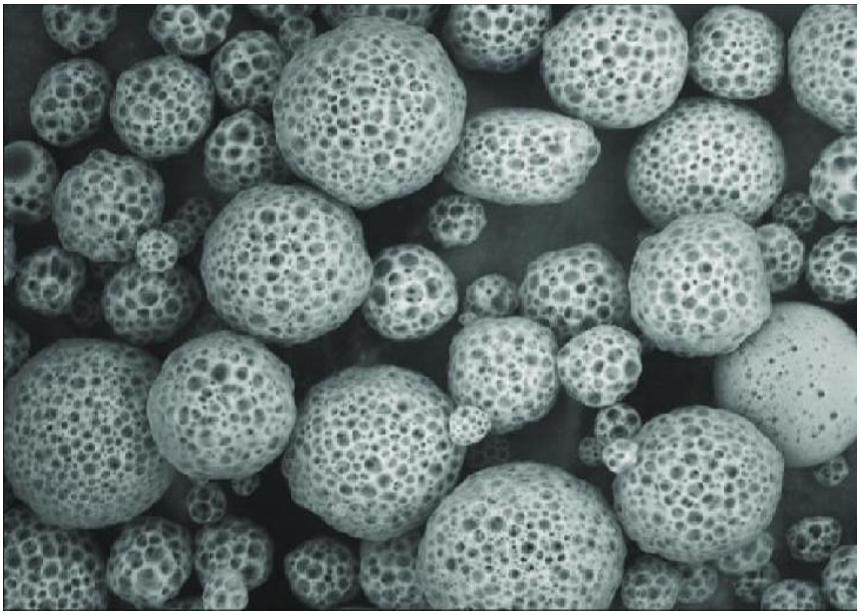

Fig. :-2 Porous microspheres seen under a scanning electron microscope. Image adapted with permission from the Koch Institute Public Galleries, Massachusetts Institute of Technology, Cambridge, USA (https://ki-galleries.mit.edu/2015/tzeng).

Hollow glass microspheres are tiny, free-flowing glass particles with a hollow center. They usually range from 10 µm to 100 µm in size and have a thin silica shell about 1 µm thick. These microspheres can be used as carriers for proteins and genetic material in tissue engineering. For drug delivery, they need to be combined with an organic polymer or have other materials, like metal ions, added to the glass.

Methods of Preparation:-

[14]When making microspheres, these points should be considered:

They should be able to hold enough drug.

They should stay stable after preparation and last long enough for clinical use.

Their size should be easy to control, and they should mix well in water for injections.

They should release the drug slowly and steadily over time.

They must be safe for the body, break down naturally, and allow chemical changes if needed.

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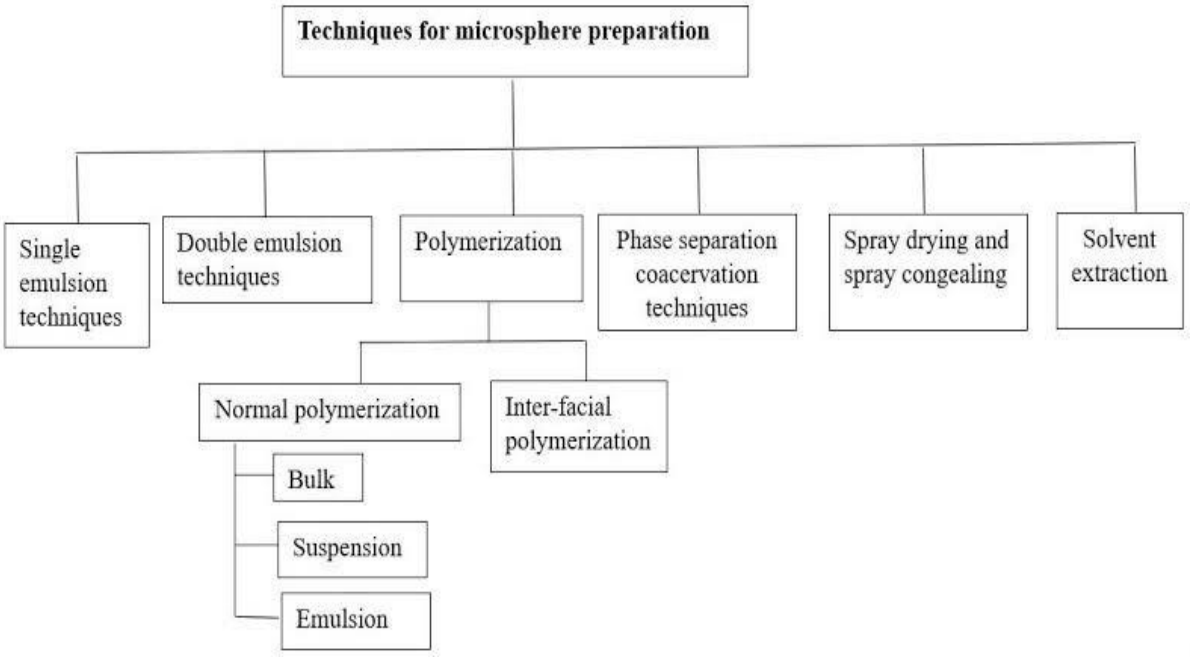

ADVANTAGES:-

▫Advantages of microsphere:-

[15] 1)Making the drug particles smaller increases their surface area, which helps improve the solubility of drugs that do not dissolve well.

[16] 2)Increase stability of the drug and protect it from stomach enzymes.

[17] 3)The shape and structure of microspheres can be designed in a way that controls how fast they break down and release the drug.

[18] 4)Safe to swallow without the risk of choking, making it safer to use.

[19] 5)Smaller microspheres have a larger surface area, which helps improve the effectiveness of poorly soluble drugs

[20] 6)Microspheres and microcapsules help slow down drug release and deliver it to the desired site in the body.

DISADVANTAGES :-

▫Disadvantages of microsphere :-

[21] 1) Controlled-release medicines usually have more drug in them, so if the release is disrupted, it could cause toxicity. Factors like food or how fast the medicine moves through the gut can change the release rate.
This type of medicine should not be chewed or crushed.

[22] 4)The medicine stays stable after being made and can be stored safely for a suitable time.

[23] 5)The release rate of controlled dosage can change based on factors like food intake and how the drug moves through the intestines.

[24] 6)Microspheres carry a lot of drug, so there is a chance of sudden release that could be harmful.

APPLICATION :-

[25]Microspheres in Vaccine Delivery:-
Controlling how the antigen is released in the body.
Making the antigen more effective at triggering immunity.
Keeping the antigen stable.

[26]Microspheres in Gene Delivery:-

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-Gene delivery can be done using viral vectors, non-ionic liposomes, plication complexes, or microcapsules. Viral vectors are very effective and can target many types of cells. However, when used in the body, they can trigger the immune system and cause harmful effects.

[27]Oral Drug Delivery:-

-The use of a polymer matrix to deliver diazepam by mouth has been tested in rabbits. The studies showed that even a film made with a 1:0.5 ratio of drug to polymer could work well as a dosage form, performing similarly to commercial tablets.

[28]Transdermal Drug Delivery:-

-Polymers are good at forming films. How the drug is released from these films depends on their thickness and how tightly the film is crosslinked.

[29]Targeting Using Microparticle Carriers:-

-Targeting drugs to specific sites is an important and widely studied approach today. The effectiveness of a drug depends on how available it is in the body and how well it binds to its target.

-One common method is the pellet technique, which can be made using extrusion and spheronization methods, using materials like microcrystalline cellulose (MCC) and chitosan.

[30]Monoclonal Antibodies:-

Non-specific adsorption

Specific adsorption

Direct coupling

Coupling using a reagent

[31]Other Applications of Microspheres:-

-Carbonless copy paper

-Photosensitive paper

MICROBES IN THE PATHOGENESIS OF HYPERTENSION:-

[32]High blood pressure (hypertension) is one of the main risk factors for heart disease. Recent results from the INVEST study have added new knowledge about the link between gum disease (periodontal disease) and high blood pressure. Unlike earlier studies that used indirect signs like tooth loss, gum attachment loss, or pocket depth, this study directly tested for the presence of periodontal bacteria.

The study by Desvarieux et al.showed a clear connection between certain bacteria under the gums—such as Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola—and hypertension. People with the highest levels of these bacteria were more than three times more likely to have high blood pressure compared to those with the lowest levels. They also had, on average, a 9 mmHg higher systolic BP and a 5 mmHg higher diastolic BP. This pattern was seen in both men and women, though it was stronger in men. Even when using a simpler clinical measure of gum disease (pocket depth less than 3 mm), the results remained reliable.

Another study looked at bacterial infections during pregnancy and their effect on blood pressure. Petry et al.found that pregnant women who required antibiotics for bacterial infections showed a small rise in average arterial BP. This matched older research from the 1960s involving over 6,000 women, where those with serious infections had slightly higher systolic BP (about 3 mmHg), though the results were not statistically significant at that time.

Overall, these findings suggest that bacterial infections—even if their impact on BP is small—may contribute to high blood pressure and are linked to complications like pre-eclampsia during pregnancy.

[33]Microspheres, a new drug delivery system, offer a promising way to improve antihypertensive drug formulations. Antihypertensive drugs include ACE inhibitors, angiotensin antagonists, calcium channel blockers, diuretics, and vasodilators. Many of these drugs have limitations, such as a short half-life, low bioavailability, poor absorption, and unwanted side effects. Microspheres are designed to overcome these problems.

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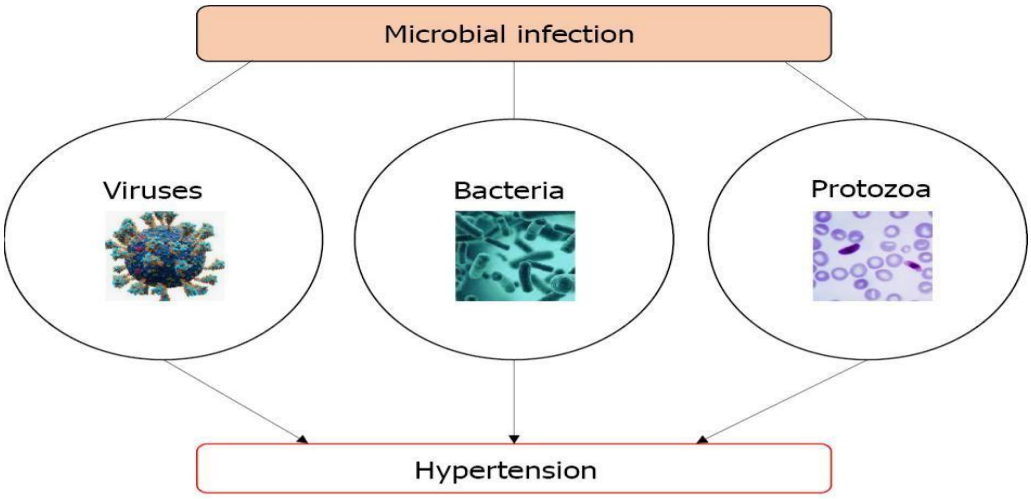

-Recent studies show that metoprolol tartrate, a β-adrenergic receptor blocker used to treat mild to moderate hypertension and angina, is rapidly absorbed in the stomach, which can affect patient compliance. By preparing metoprolol tartrate in microspheres, it is possible to achieve prolonged drug release, improve patient adherence, reduce dosing frequency, and lower side effects.

-Losartan potassium, another antihypertensive drug, can cause side effects like gastrointestinal issues, neutropenia, liver problems, migraine, and pancreatitis. Formulating losartan into microspheres can increase its biological half-life, reduce the frequency of doses, and help reduce drug resistance. Studies have shown that losartan can provide sustained effects for more than 12 hours.

-Diltiazem HCl is used to prevent angina and hypertension but has a short half-life of 3–5 hours. Microsphere formulations of diltiazem HCl can provide sustained drug release for up to 12 hours and extend the half-life to about 14.8 hours.

[34]CHARACTERIZATION & EVALUATION PARAMETERS:-

▫Characteristics of gut microbiota in healthy individuals:-

The human digestive system has more microorganisms than the total number of human cells. These microorganisms carry about 100 times more genes than the human genome. Because of this, they are often called the "second human genome," as they play an important role in overall health. Together, these microorganisms are called the gut microbiota. They include fungi, viruses, archaea, protozoa, and mainly bacteria.

▫Mechanisms linking gut microbiota and hypertension:-

- Gut microbial metabolites and hypertension:-

Gut microbes produce different substances (called metabolites) that can affect blood pressure. The main ones studied are short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), bile acids (BAs), hydrogen sulfide (H_2S), and serotonin (5-HT). These substances have been widely researched, and their effects on blood pressure and the ways they work are shown in Figure 1 and Table 1.

▫Short-chain fatty acids (SCFAs):-

SCFAs are produced when dietary fiber.. The main SCFAs are acetate, propionate, and butyrate, which together make up about 95% of all SCFAs. They help control blood pressure and influence nerve activity.

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Studies in humans show that people with high blood pressure often have lower SCFA levels. Animal studies also support this: when SCFAs were added to the drinking water of hypertensive rats, it stopped their blood pressure from rising further. In another experiment with mice treated with excess mineralocorticoids, SCFAs reduced both systolic and diastolic blood pressure

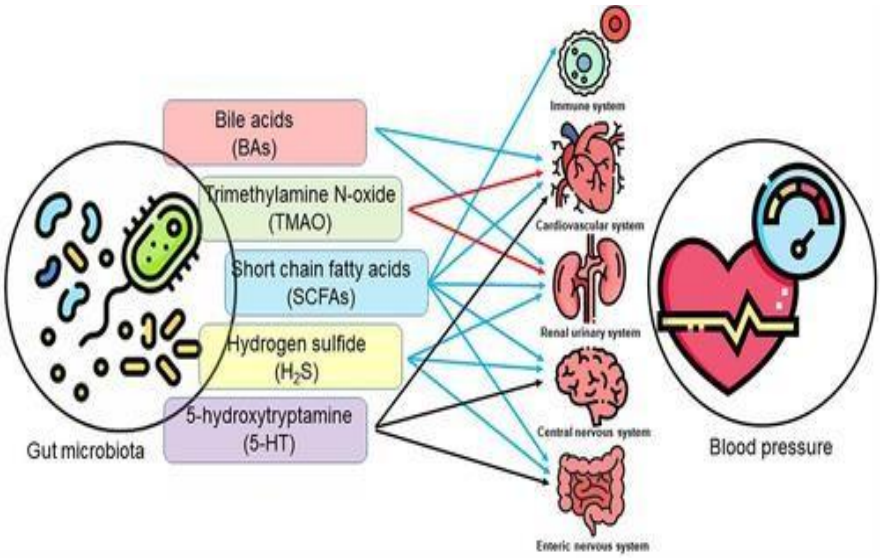

Figure :-3 Gut microbes produce or change certain metabolites that affect blood pressure. These metabolites act on five major body systems to regulate blood

▫Trimethylamine N-oxide (TMAO):-

Trimethylamine (TMA) is a substance made by gut bacteria from choline. In the liver, TMA is converted into TMAO. Recent studies show that TMAO is linked to a higher risk of high blood pressure.

A meta-analysis found that people with high TMAO levels were more likely to develop hypertension than those with normal levels. Another updated study showed that higher TMAO levels were related to higher systolic blood pressure, but not to diastolic blood pressure.

▫Bile acids (BAs):-

Primary bile acids are made in the liver from cholesterol. To make them more soluble, they are joined with glycine or taurine. Gut bacteria have special enzymes that can remove glycine/taurine and change primary bile acids into secondary bile acids.

▫H_2S:-

Hydrogen sulfide (H_2S) is an important signaling molecule in the body and works as a reducing agent. It is found in large amounts in the colon, mainly produced by intestinal cells and gut bacteria. H_2S helps regulate blood pressure. Studies show that diet restriction, protein intake, and certain plants can increase H_2S levels in feces.

▫5-Hydroxytryptamine (5-HT):-

About 80–90% of the body's 5-HT (serotonin) is made by special enterochromaffin cells in the intestine. Studies show that gut bacteria, especially pore-forming bacteria, can influence its production. Substances like butyrate, cholate, propionate, tyramine, and deoxycholate can stimulate 5-HT release from intestinal cells. In further studies, deoxycholate was shown to increase blood 5-HT levels in germ-free mice.

▫Gut microbiota and blood pressure medications:-

People respond differently to blood pressure medications. Recent studies suggest that gut bacteria can influence how well these drugs work. Evidence shows that gut bacteria can metabolize drugs in ways similar to the liver.

▫Calcium channel blockers:-

Amlodipine is broken down in the liver, forming pyridine metabolites. These metabolites then go through further changes, including oxidation, removal of amino groups, and modification of fatty parts.

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▫ACE inhibitors (ACEis):-

ACE inhibitors play a role in the renin-angiotensin system. In hypertension, they reduce muscle and scar tissue in the intestinal wall and increase the length of intestinal villi. This suggests that lowering blood pressure with ACE inhibitors may also help restore the intestine to a healthier state.

▫Diuretics:-

Spironolactone, a drug that blocks mineralocorticoid receptors, was shown to restore the gut F/B ratio and increase acetate-producing bacteria in hypertensive rats to levels seen in healthy rats. It also reduced Th17 immune cells in the gut and aorta, improved aortic function, and lowered blood pressure.

▫Beta Blockers:-

Metoprolol is mainly broken down in the liver by the enzyme CYP2D6, which also processes many hormones and about 25% of other drugs. Found that patients taking metoprolol had higher levels of hippuric acid, hydroxyhippuric acid, and methyluric acid—compounds produced with the help of gut bacteria. This suggests that metoprolol may alter gut bacterial species or their activity. Overall, long-term metoprolol use may affect gut microbial metabolism.

Alexandra et al. Analyzed 1,135 stool samples and found connections between the gut microbiome and 19 drug groups, including beta blockers and ACE inhibitors.

▫Antibiotics and Hypertension:-

Antibiotics can change the gut microbiota and may affect blood pressure. Current research on how antibiotics influence blood pressure and gut bacteria is summarized in Table 2. Honour et al. First found that giving neomycin by mouth lowered blood pressure in male Sprague-Dawley rats with cortico-sterone-induced hypertension.

▫Gut microbiota-targeted intervention and its effect on hypertension:-

▫**Probiotic supplementation:-**

Probiotics are live microorganisms that provide specific health benefits. Studies have shown that probiotics can lower blood pressure in people with hypertension and have a mild effect on blood pressure in healthy individuals.

▫High-fiber diet:-

Changing the gut microbiota through diet may be a new way to manage high blood pressure. Studies show that eating more fiber, such as oat bran, reduced the need for blood pressure medicines, lowered both clinic and 24- hour blood pressure, and increased the levels of beneficial bacteria like Bifidobacterium and Spirillum.

Machine learning-based gut microbiota analysis in hypertension:-

In the past decade, scientists have collected a large amount of microbiota data. To make better use of this, they applied machine learning methods to analyze the data from many different angles. Unlike simple statistical comparisons, machine learning can handle complex calculations and automatically find patterns and relationships between different factors.

[35]RESULTS:-

▫Compatibility study:-

FT-IR spectroscopy was used to check if hydralazine hydrochloride (the pure drug) was compatible with bovine serum albumin after making the microspheres. The IR spectrum of the pure drug matched its standard reference spectrum.

The pure drug showed clear peaks at:

N-H stretch: 3217.1 cm^{-1} Aromatic C-H stretch: 3028.1 cm^{-1} C=C stretch: 1591.4 cm^{-1}

Out-of-plane bending of adjacent H atoms on an aromatic ring: 786.6 cm^{-1}

These same peaks also appeared in the spectrum of the microsphere formulation. This confirms that the drug was successfully present in the microspheres and was compatible with the polymer.

▫Entrapment efficiency:-

The entrapment efficiency values are shown in Table 2. The highest efficiency was seen in F6 (68.20±1.03%) and the lowest in F1 (57.39±1.48%)

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For formulations F1, F2, and F3 (with different amounts of glutaraldehyde), the efficiencies were 57.39±1.48%, 59.78±1.43%, and 62.60±2.03%, respectively. This shows that increasing the glutaraldehyde amount improves entrapment efficiency.

Similar results were observed for F4, F5, and F6. The results also showed that polymer concentration has a strong effect—entrapment efficiency increased as polymer concentration rose from 10% w/w to 20% w/w.

▫Surface morphology:-

The surface structure of the microspheres was studied using a scanning electron microscope (SEM). SEM is commonly used because it is easy to prepare samples and operate. The SEM images of formulation F6 (Figure 1) showed that all microspheres were spherical in shape with smooth surfaces.

▫Particle size analysis:-

Particle size was measured using laser particle size analysis (Table 2). Results showed that particle size mainly depended on albumin concentration. Increasing albumin concentration from 10% w/w to 20% w/w significantly increased particle size, while glutaraldehyde amount had little effect. Figure 2 shows the effect of polymer concentration and glutaraldehyde on particle size.

▫Sterility test:-

After 14 days of incubation, no microbial growth was observed on the filters. This confirms that the formulation was sterile and passed the sterility test.

▫In vitro drug release studies:-

The drug release pattern helps to predict how the delivery system will work inside the body. All six microsphere formulations were tested for drug release under laboratory conditions. The study was carried out in pH 7.4 buffer, and the results are shown as mean ± SD (n=3).

The drug release study was carried out using phosphate buffer saline in 100 ml glass vials. The results for all formulations are shown in Figure 3. After 24 hours, the

cumulative drug release was 97.51%, 96.13%, 95.48%, 97.18%, 96.37%, and 95.69% for formulations F1 to F6, respectively.

During the first hour, the initial release was 48.59%, 43.59%, 35.98%, 46.14%, 42.14%, and 27.88% for F1 to F6, followed by a slower and continuous release phase polymer concentration also influenced the release: increasing polymer concentration slowed down drug release. Formulations F4, F5, and F6 showed slightly reduced release compared to F1, F2, and F3 because of higher polymer content.

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To study the release mechanism, the data were fitted into different mathematical models: Korsmeyer–Peppas, Higuchi matrix, and Hixson–Crowell. The correlation coefficients (r^2) for these models are listed in Table 3. The model with the highest r^2 value was considered the best fit.

For formulation F6, the Higuchi matrix model showed the best fit ($r^2 = 0.9910$), indicating that drug release was mainly controlled by diffusion through pores. For formulations F1 to F5, the Korsmeyer–Peppas model gave the best fit, and the release exponent (n value) was used to explain the release mechanism.

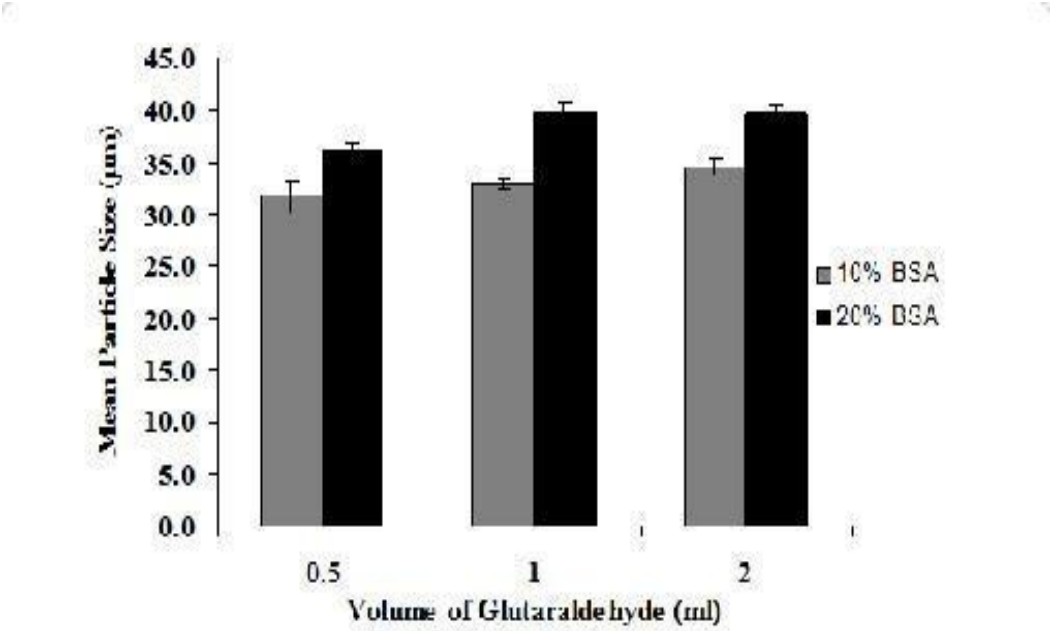

Figure 4 :-Effect of polymer concentration and glutaraldehyde volume on the average particle size of hydralazine hydrochloride microspheres. BSA means Bovine Serum Albumin. The error bars show the standard deviation (SD) for 3 samples (n=3).

Figure 5:- In vitro release behavior of hydralazine hydrochloride microspheres.

To study different drug release patterns using the Korsmeyer-Peppas model, the 'n' values showed that formulations F1, F2, F3, F4, and F5 followed Fickian release.

▫In vivo studies:-

Formulation F6, which had the best particle size, high drug entrapment, and good in vitro release, was chosen formin vivo studies. The goal was to compare the antihypertensive effect of F6 with the pure drug (Hydralazine HCl). The results are shown in Table.

In the control group (Group I), the baseline systolic and diastolic blood pressure were 120±0.40 mmHg and 91±0.7 mmHg. After giving DOCA to Groups II, III, and IV for 30 days, blood pressure increased:

DOCA salt group (Group II): 162±1.35 / 119±1.08 mmHg

DOCA + F6 formulation (Group III): 164±1.08 / 118±0.82 mmHg

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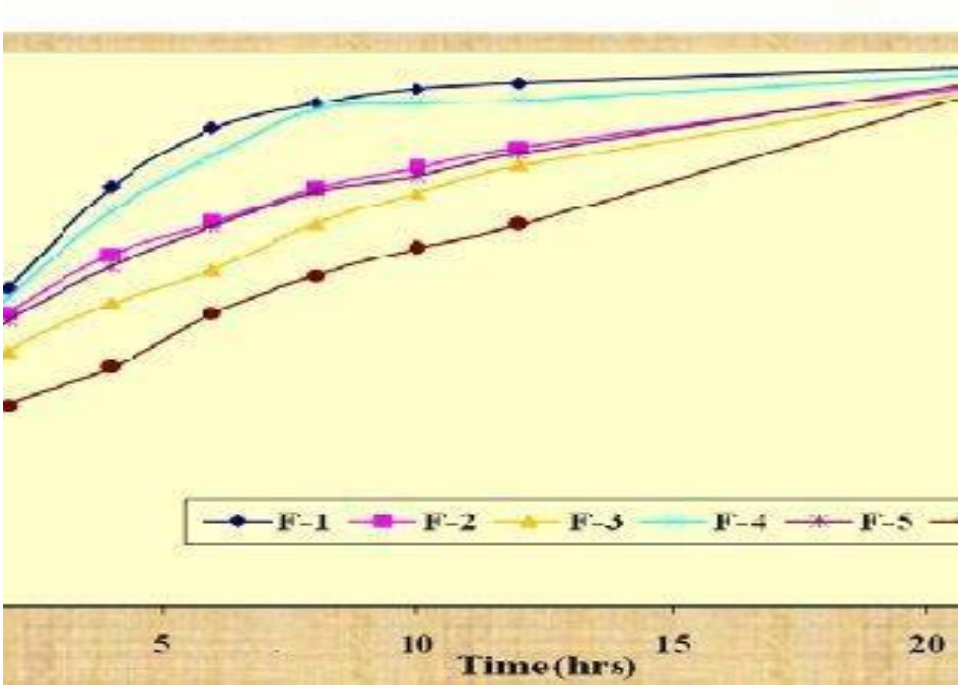

DOCA + pure drug (Group IV): 163±0.71 / 119±0.42 mmHg
On day 31, 1 hour after administration, a sudden drop in blood pressure was observed: Group IV: 142±1.08 / 108±1.07 mmHg
Group III: 153±1.58 / 115±0.91 mmHg
After 12 hours:
Group IV: Slight increase to 137±1.0 / 100±1.04 mmHg
Group III: Reduced further to 129±0.91 / 97±1.23 mmHg After 24 hours:
Group III: Maintained near-normal blood pressure at 126±0.41 / 94±1.08 mmHg (close to Group I) Group IV: 139±0.87 / 101±0.85 mmHg

DISCUSSION

Albumin Microspheres for Drug DeliveryAlbumin microspheres are widely studied as controlled-release systems for delivering drugs. There are several ways to make albumin particles, either by incorporating the drug during particle formation or after.

In the first method, the process uses thermal denaturation (heating) or chemical cross-linking in liquids like vegetable oil or isooctane. This is called the emulsion cross-linking or emulsion polymerization method. One reason this method is used is that both BSA (albumin) and Hydralazine hydrochloride are water-soluble.

▫In this method:-

Albumin and the drug are dissolved in water, forming the aqueous phase.Small droplets of this aqueous solution are formed in a non-mixing liquid, light liquid paraffin, creating a water-in-oil emulsion.

A fat-loving (lipophilic) surfactant, Span 80, stabilizes the emulsion.

Since albumin is soluble, it needs chemical cross-linking to become stable at body temperature (37 ºC). Glutaraldehyde is used for this.

Glutaraldehyde is added after 15 minutes of stirring at 2500 rpm. This allows enough time for droplets to form and reach a stable size. An important point of this method is that the droplets keep their size and shape while being turned into solid, rigid microspheres.

BP – Blood pressure, DOCA – Deoxycorticosterone acetate. Data are shown as Mean ± SEM (n = 4).

Statistical analysis was done using One-way ANOVA followed by Tukey's test.

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*P<0.001 – significantly different from the Control group #P<0.05 – significantly different from the DOCA-treated group ##P<0.001 – highly significant compared to the DOCA-treated group

The antihypertensive effect of Formulation F6 and pure Hydralazine HCl was measured using the tail-cuff method to check blood pressure. The results showed that Group III (F6 microspheres) kept blood pressure low for up to 24 hours. In contrast, Group IV (pure drug) showed a rise in blood pressure after 6 hours. These findings match the in vitro drug release pattern of Formulation F6.

[36]CONCLUSION

This study shows the key features of Losartan Potassium microbeads. Ionic gelatin can be used to make these microbeads. Factors like drug amount, polymer concentration, cross-linking agent, stirring speed, and curing time affected the particle size, drug loading, entrapment efficiency, and swelling of the microbeads.

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