REVIEW ARTICLE

Exploring the Intranasal Medication Delivery Methods for the Management of Hypertension

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Abstract

Intranasal drug delivery systems (INDS) have attracted interest as a possible tactic to enhance the bioavailability and absorption of medications. The use of INDS to treat hypertension (HTN), a prevalent cardiovascular ailment, is examined in this review study. The paper describes the ability for medication to cross the nasal barrier and gives a summary of the cellular and structural makeup of the nasal cavity. It talks about many options and strategies to improve the way nasal drugs are delivered, with an emphasis on devices that make use of nanotechnology. The paper also includes a thorough analysis of the various approaches to treating HTN and a discussion of how INDS can enhance medication efficacy and lessen systemic side effects. This review compiles available literature on formulation strategies, relevant *in vivo*, *ex vivo*, and *in vitro* assessment technologies, as well as the advancement of studies concerning the role of the nasal epithelium in the systemic circulation of antihypertensive medications. With intranasal delivery, the first-pass impact is removed, doses are lowered, and drug bioavailability is enhanced. Future research in this area may lead to more effective and patient-friendly HTN therapies.

Key words: Hypertension, intranasal, nanotechnology, nasal cavity

INTRODUCTION

A major issue in general medical care for both developed and developing countries is hypertension (HTN). Globally, almost one billion people suffer from high blood pressure.[1] In Egypt, the prevalence of this grave health concern is 26.3% of the adult population. The incidence of HTN rises with age; approximately half of persons over 60 have HTN.[2] The term HTN, also known as elevated blood pressure, describes an increasing pressure in the blood arteries. It is the most common disease in humans; it affects both sexes and all age groups mostly in old age people. Elevated blood pressure is sometimes referred to as HTN, which is short for HTN resulting from an overly rapid heartbeat.[3] Some of the main conclusions drawn from the report are as follows: After 115/75 mmHg, the risk of cardiovascular diseases (CVD) rises with every 20/10 mmHg increment. Ninety percent of 55 year old with normo-tension will develop HTN at some point. A larger risk factor for CVD is found in systolic blood pressure measurements over 140 mmHg as opposed to diastolic blood pressure.[3-5]

The following are a few of the typical pathophysiological reasons of HTN

- Overproduction of hormones which promote salt retention and constriction
- A diet low in calcium and potassium may be linked to a chronically excessive salt consumption
- Adrenaline secretion abnormalities lead to increased production of aldosterone and angiotensin II
- Moreover, there is a higher activity of associated vascular growth factors, diabetes, insulin resistance, obesity, and overweight.

In addition to renal parenchymal illness, endocrine and central nervous system (CNS) disease, renal infarction, and

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vascular complications, pregnancy (hypoxemia) are other secondary causes of HTN that may lead to a hypertensive crisis. In addition to renal parenchymal illness, endocrine and CNS disease, renal infarction, and vascular complications, pregnancy (hypoxemia) are other secondary causes of HTN that may lead to a hypertensive crisis.[6] It is unclear what causes HTN, or high blood pressure. On the other hand, a number of things may influence its growth. Depending on whether there is an underlying cause, HTN can be categorized as primary or secondary.

Primary HTN

The most typical and usually develops over an extended length of time.

For the majority of adults, no clear reason exists. On the other hand, a few risk factors might raise the possibility of primary HTN, such as:

- Age: As people age, their risk of high blood pressure rises
- Family history: Family history can be major factor for HTN
- Race: African Americans have a higher risk of severe consequences and early onset of high blood pressure
- Obesity: Overweight or obesity increases the risk of high blood pressure
- Absence of physical activity: Insufficient exercise can lead to the development of high blood pressure
- Unhealthy diet: Eating a diet heavy in fat, salt, and cholesterol raises the risk of HTN
- Alcohol intake: Excessive alcohol drinking might cause blood pressure to rise.

Secondary HTN

Usually manifesting abruptly, secondary HTN raises blood pressure above that of primary HTN and is brought on by an underlying medical issue. Secondary HTN can result from a number of illnesses and circumstances, including:

- Kidney illness
- Tumors of the adrenal glands
- Thyroid issues
- Tablets for birth control and other prescribed medications
- Illegal substances, such amphetamines and cocaine
- Congenital cardiac conditions
- Apnea obstructive sleeper.

There are a many risk factors that might raise the chance of having primary HTN even when the actual etiology of the illness is unknown. Higher blood pressure than primary HTN is caused by secondary HTN, which often manifests abruptly and is brought on by an underlying illness or circumstance.

TREATMENT

HTN, often known as high blood pressure, is treated with a combination of medicines and lifestyle modifications. The purpose of therapy is to lower the HTN and prevent damage to vital organs, including the heart, brain, and kidneys.

Lifestyle adjustments

A lifestyle change may effectively lower blood pressure in hypertensive patients currently using antihypertensive medicines and prevent HTN in healthy individuals, allowing for a considerable reduction in the quantity and frequency of antihypertensive medications.[7]

The most popular lifestyle changes advised by the European Society of HTN and the European Society of Cardiology in 2013 include cutting back on salt, consumption.[8-12]

Medications

For those over 65 and those with risk factors including diabetes and high cholesterol, pharmaceutical treatment is advised to decrease blood pressure to <130/80. Drugs of several kinds are used to treat high blood pressure, such as:

- Angiotensin-converting enzyme inhibitors: These agents reduce kidney injury by relaxing blood arteries. Lisinopril and enalapril are two examples
- Angiotensin II receptor blockers: They reduce kidney injury by relaxing blood arteries. Telmisartan and losartan are two examples
- Blockers of calcium channels: These dilate blood arteries. Amlodipine and felodipine are two examples
- Diuretics: They reduce blood pressure by flushing out excess water from the body. Chlorthalidone and hydrochlorothiazide are two examples
- Beta-blockers: They lower blood pressure by slowing and lessening the power of the heartbeat. When other therapies have failed, they are typically utilized
- Aldosterone antagonists: The treatment of resistant HTN may involve the use of aldosterone antagonists. They prevent the body from accumulating salt and fluid due to the action of a naturally occurring molecule. Spironolactone and eplerenone are two examples
- Renin inhibitors: Aliskiren reduces the kidney's synthesis of renin, an enzyme that initiates a series of chemical reactions that raise blood pressure
- Combination therapy: In some circumstances, it may be necessary to take two or more drugs together to successfully decrease blood pressure
- HTN that resists: Further therapies may be taken into consideration if blood pressure persists in being high even after taking at least three different blood pressure medications, including a diuretic.

INTRANASAL DRUG DELIVERY

One non-invasive way to give medication through the nose cavity is by intranasal delivery. This method has a number of benefits over oral and parenteral (injection) methods, which makes it a desirable choice for some drugs, particularly those that target the CNS or are used locally to treat nose ailments. Compared to more conventional modes of administration, intranasal drug delivery allows for a faster onset and greater absorption of medication. Because the olfactory nasal neuroepithelium creates a special link between the CNS and the external environment, this delivery system has drawn interest for its potential to carry medications to the brain. Oral medicine administration is regarded as the most effective drug delivery technique for achieving systemic effects. Finding better systemic delivery methods has become necessary, nevertheless, due to certain drugs' low oral bioavailability.[13-16] The parenteral method, sometimes known as the injection route, is the second most common way to administer drugs. Parenteral administration often seeks to induce rapid systemic effects in order to prevent systemic adverse effects and/or acquire higher drug concentrations at the targeted target. This procedure's primary drawback is that it is intrusive, which might hurt patients and lead to noncompliance.[17-19] The use of IN drug administration has become commonplace as a secure and reliable alternative to parenteral and oral methods.

Mechanisms of nasal mucosa-mediated intranasal drug delivery and absorption: Because of the nasal cavity's high vascularization, medications can enter the bloodstream and circulate throughout the body quickly. By avoiding the liver's first-pass processing, this approach may improve the medication's bioavailability. Direct delivery from nose to brain: When given intranasally, medications may be able to pass through the blood-brain barrier and enter the CNS through the trigeminal and olfactory nerve pathways. This is especially advantageous for medications used in neurotherapy.

LIMITATION OF INTRANASAL ROUTE

The "IN" route is used to describe the administration of a medication or chemical through the nasal passages. Although intranasal administration has many advantages, there are also disadvantages and considerations that need to be made. The following are some disadvantages of administering drugs intranasally:

- Limited volume and dosage: The quantity of medication that can be inhaled is restricted due to the nasal passages' restricted capacity to absorb liquids. Getting large dosages or medications that require large amounts delivered could be difficult.
- Mucociliary clearance: The cilia and mucus lining the nasal passages can be used to remove foreign objects from them. This natural defense mechanism may reduce the amount of time that drugs are in contact with the nasal mucosa, potentially affecting absorption.
- Irritation and sensation: Some intravenous medications may cause skin irritation or a burning sensation. This could make patients uncomfortable, leading them to quit taking their prescription.
- Nasal congestion: Nasal congestion might make it difficult to take medication intranasally. When there is nasal congestion or obstruction, the absorption of intranasal medications may be affected. The correct administration of intranasal medications usually requires the involvement of the patient and the use of suitable skills. Ineffectiveness could result from mishandling the medication.
- Quick absorption: This can occasionally be beneficial, but it can also have negative effects. When it comes to treatments that require a slower, continuous release, intranasal delivery might not be the ideal choice.
- Limitations: Not every drug can be used orally. Medication transport through the nasal mucosa may be impacted by the physicochemical properties of the drug, including its molecular size and lipophilicity.
- Risk of nasal damage: Using intranasal medications inappropriately or frequently carries the risk of causing damage to the nasal mucosa in addition to other adverse effects.
- Local tolerance: The nasal mucosa may not tolerate some medications well, which could result in localized pain or side effects.
- Treatment delivery depth: It could be challenging to properly deliver the medication to certain places inside the nasal passages if a specific target location is required for the treatment to be effective [Table 1].

TECHNIQUES FOR ENHANCING NASAL ABSORPTION

Several strategies were investigated to enhance drug absorption through the nasal mucosa.[20] It is imperative to improve nasal absorption of medications and chemicals in order to increase the effectiveness of intranasal medication administration. A few strategies can be employed to increase nasal absorption:

- Nasal formulation design: Offer formulations with intranasal administration optimized. This entails choosing the right vehicle (such as solutions, suspensions, or gels) and adjusting the PH to improve drug solubility and stability.
- Distribution of particle size and size: Use smaller particle sizes in solid formulations (such as powders and aerosols) to increase the surface area accessible for medicine absorption.
- Prodrug design: By altering their structural composition, prodrugs can become more lipophilic and hence have a higher permeability across the nasal mucosa.
- Enhancers of permeation: Add permeation enhancers (PE) (such surfactants and absorption enhancers) to formulations to boost a drug's permeability through the nasal mucosa. However, one should carefully assess the security and potential irritation of utilizing PEs.

- Mucoadhesive concoctions: Prepare mixtures referred to as muco-adhesives that have the potential to adhere to the nasal mucosa and prolong the period of time a medication is in contact with the mucosal surface.
- Liposome and nanoparticle formulations: If medications are encapsulated in liposomes or nanoparticles utilizing nanotechnology, they may be more stable and easier to pass through the nasal mucosa.
- Nasal cavity target: Drug formulations intended to target the olfactory region ought to be designed in a manner that promotes drug deposition in this specific area.
- Use of cyclodextrins: The solubility and stability that cyclodextrins provide may be advantageous for drugs meant for intranasal delivery.
- Optimal drug concentration: Adjust the drug's concentration in the formulation to ensure maximal absorption without causing irritation or congestion.
- Patient alignment and techniques: Correct medicine administration may help ensure that the drug is deposited in the nasal cavity.
- Reducing nasal congestion: Using decongestants or other methods to reduce nasal congestion may enhance drug absorption by enhancing contact with the nasal mucosa.
- Physiological aspects: Consider individual physiological factors, such as age and nasal structure that may affect how well nasal medications are absorbed. Make the necessary composition and dose adjustments [Table 2].

TRADITIONAL METHODS OF DISTRIBUTION

Nasal sprays and drops

When distributing formulations the IN route, nasal drops are considered to be among the simplest and most effective techniques [Figure 1]. Its main drawback is that the dose administration is not accurate with this method. Nevertheless, metered dosage pumps and actuators are fitted to nasal sprays, whether they are suspensions or solutions, so they can provide precise doses between 25 and 200 µL [Table 3].

Semi-solid dosage forms

Nowadays, the most popular semi-solid systems used in the design of nasal drug delivery systems include gels, ointments, and liquid systems including polymers that gel *in situ*. Nasal gels are suspensions or solutions that are very viscous. Due to its high viscosity, nasal gels have the benefit of reducing anterior formulation leakage, lessening flavor impact from reduced swallowing, and reducing post-nasal dripping.

Pharma carriers with excellent, persistent release effects include sorbitan monostearate (SMS) organogels. The nasal method of intranasal propranolol hydrochloride solution exposure was effectively carried out on human volunteers. Its quick biological half-life and rapid absorption, however, meant that the drug's levels in the systemic circulation were not maintained. Solution difficulties may be solved using SMS organogels. An *in vitro* study found that, in comparison to aqueous solution and emulsion, organogels released over 90% of the medicines they contained by trans-nasal administration. Organo-gels offered a potent barrier against propranolol diffusion, resulting in a brief release of the medication.[21] Losartan potassium (LK) mixed into gel system is another example of a nasal semi-solid dosage form. Using triethanolamine for pH correction and ethanol or PEG 4000 (5% w/v) as an absorption enhancer, LK solution (10 mg/mL) was created. Derived from the *ex vivo* research. The manufactured LK gel with ethanol was shown to be an excellent absorption enhancer, as evidenced by the considerable increase in drug release percentage (76.77 ± 1.55%, $P < 0.05$) after 1 h compared to the LK gel without the inclusion of an absorption enhancer (72.87 ± 1.4%). PEG addition did not change the drug release from LK (72.30 ± 1.8%) [Figure 2].[22]

SOLID DOSAGE FORM

The vasculature inside the nasal mucosa's epithelium might be covered by solid dosage forms. If the medicine is not stable enough to generate solution and suspension dosage forms, one workable dose form that may be used is nasal powder. The two primary advantages of powder dose forms are their lack of preservatives and the medication's increased stability in the formulation. Particle size, aerodynamic characteristics, and the nasal irritancy of the active ingredient and/or excipients are only a few of the many variables that affect powder stability.[23] Metoprolol tartrate used orally to treat HTN only produced 50% of the prescribed amount in the systemic circulation; to increase its bioavailability, metoprolol tartrate was developed in a nasal powder dosage form. The pharmacokinetic investigation found that nasal delivery of metoprolol tartrate resulted in a faster release and greater bioavailability than oral treatment.

ADVANCEMENTS IN TARGETED DRUG TRANSPORT

Lipid-based nanocarriers

Liposomes

The Greek terms "lipo," which denotes their fat content, and "soma," which denotes their structure, are the source of the word "liposome." Liposomes are tiny, spherical, microscopic vesicles that contain an aqueous volume and a lipidic bilayer membrane made of cholesterol and phospholipid. This membrane allows for the incorporation of lipophilic or hydrophilic drugs into lipid bilayers or the aqueous compartment.[24] Liposomes' capacity to efficiently encapsulate both small and large molecules with a range of hydrophobicity and pKa values is one advantage of using them to administer drugs. Modifying the liposomal surface to reduce clinical drug dosages and side effects while targeting

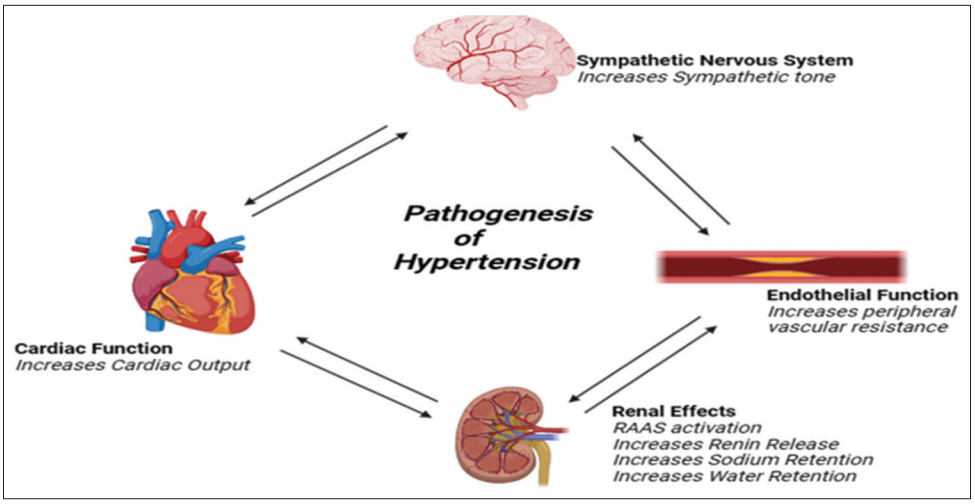

Figure 1: Pathogenesis of hypertension

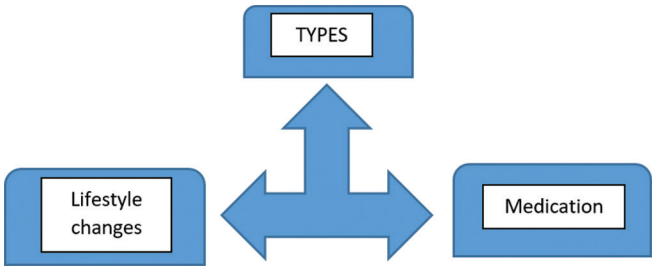

Figure 2: Diagrammatic representation of types of treatment

the therapeutic agent and prolonging its release.[25] Drug molecules can be encapsulated in liposomes to shield them from metabolism. Liposomal drug delivery may offer advantages such as reduced toxicity, enhanced pharmacological efficacy, and controlled drug release at the intended site.[26]

Niosome

Niosome vesicles are created when non-ionic surfactants self-assemble in an aqueous environment. Niosomes are helped to create a closed bilayer structure by heat or physical agitation. While keeping the hydrophobic components apart, the aqueous solution is used to join the hydrophilic head groups. Their cost-effectiveness and higher chemical stability are advantages over liposomes. Niosomes may be the ideal vesicular system for nasal administration, taking into account nasal delivery and having better chemical and physical stabilities than liposomes. Both lipophilic and hydrophilic medications may be transported by them. Their non-ionic nature plays a part in their low toxicity. They pass through biological membranes and gain a high degree of permeability because of their biodegradability, the body can readily get rid of them.

Microemulsions (MEs)

MEs exhibit droplet sizes ranging from 10 to 100 nm and are characterized as transparent, homogeneous, and thermodynamically stable systems composed of surfactant, water, and oil, with the potential inclusion of a cosurfactant. Their minimal interfacial tension between oil and water phases distinguishes them from other systems like water-in-oil (w/o), oil-in-water (o/w), or biphasic systems, contingent upon their internal structure. Despite their belated emergence, MEs have fortuitously emerged as promising vehicles for targeted drug delivery.[27] Notably, MEs have garnered significant attention for their potential to enhance oral drug absorption, facilitated by the incorporation of mucosal adhesive polymers which extend mucosal retention time, thereby accelerating systemic drug uptake and augmenting bioavailability via hepatic metabolic bypass mechanisms. Moreover, the lipophilic properties and non-spherical morphology of MEs render them a compelling alternative for drug delivery applications.[28]

SOLID LIPID NANOPARTICLES (SLNs)

SLNs, colloidal particles ranging in size from 1 to 1000 nm, remain solid at room temperature due to their lipid makeup, which has melting temperatures greater than ambient settings. The drug is often found in a lipid matrix within SLNs, similar to lipoid nanospheres. One significant advantage of SLNs is their capacity to be applied to wounded or inflamed biological surfaces, which is aided by the primarily lipidic matrix and the presence of safe excipients. Drug encapsulation inside lipid matrix frequently results in increased stability and reduced breakdown. SLNs' controlled drug release allows for sustained therapeutic concentrations, which improves therapy efficacy over longer periods of time. The nanosize, lipidic composition, and presence of surfactants in SLNs promote enhanced transcellular absorption across the nasal mucosa, allowing for systemic drug delivery. The SLN formulation process is low-cost and scalable.

Nano-structured lipid carriers (NLCs)

NLCs aimed to overcome the drawbacks of the new SLN. NLCs also appear as stable lipid matrices at room temperature

Table 1 : Medication classes used to treat hypertension

Drug class	Action	Example
Angiotensin-converting enzyme inhibitors	Reduce blood pressure by preventing the conversion of angiotensin I to angiotensin II, a strong vasoconstrictor	Lisinopril, enalapril
Angiotensin II receptor blockers	Avoid vasoconstriction by preventing angiotensin II from attaching to its receptors	Losartan, valsartan
Beta-blockers	Reduce heart rate and cardiac pumping capacity to reduce blood pressure	Atenolo, metoprolol
Calcium channel blocker	Stop calcium from entering the heart's and the arteries' cells, causing the heart to contract less forcefully and the arteries to relax	Verapamil, amlodipine
Diuretics	Reduce blood volume and blood pressure by increasing the body's excretion of water and sodium	Loop diuretics, thiazide diuretics

Table 2: Various kinds of nanocarriers that are injected nasally to treat hypertension

Type of nano carriers	Active ingredient
Glycerosomes	Lacidipine
Nano-emulsion	Nitrendipine
Nano-gels	Amlodipine
Chitosan	Olmesartan
Niosomes	Diltiazem

Table 3: Examples of systemic intranasal drugs loaded microparticulate for the treatment of hypertension

Types of microparticulates	Active ingredient
Hydrogel micro-particles	Sildenafil citrate
Chitosan microsphere	Diltiazem hydrochloride
Alginate microsphere	Carvedilol
Gelatin microsphere	Oxprenolol
Microsphere	Valsartan

and body temperature. When oils are used instead of solid fats alone, the fatty acids are disorganized, resulting in higher levels of drug concentration and reduced drug absorption during storage. Systemic drug delivery has been successfully achieved by delivering NLCs in IN.

Lipid nanocapsules (LNCs)

LNCs are biomimetic nanocarriers with structures such as polymeric nanoparticles and liposomes. The lipid core of LNCs consists of medium-chain triglycerides, surrounded by a surfactant shell of PEGylated surfactant and sometimes lecithin or other co-surfactants. One advantage offered by LNCs is that they are packed with lipophilic solvents. In addition to being safe, it can be synthesized in an easily reproducible manner without the need for synthetic organic chemicals or large amounts of reagents and conjugates to use the right. LNCs are a great alternative to liposome emulsions and MEs because of their stability and small size.

Transferosomes

Sevak and Bloom first proposed the notion of transferosomes in 1992, describing a unique technique to drug administration characterized by flexible membranes largely made of phospholipids and PE. Notably, PE's distinctive trait is its capacity to provide higher flexibility to the lipid bilayer than typical liposomes, allowing for fast shape changes and cellular penetration, hence increasing permeability. Transferosomes have increased encapsulation capacity for a wide range of chemicals, particularly lipophilic ones, thanks to their extraordinary flexibility and network efficiency, as well as their ease of scalability and intrinsic resistance to metabolic degradation. This makes them ideal for nasal medication delivery applications. A significant example of using transferosomes to increase oral drug delivery is the development of composite chitosan transferosomes with the goal of increasing verapamil bioavailability. The composite vesicles are created by dispersing phospholipid, drug, and penetration enhancer in an organic solvent mixture (methanol and chloroform, 2:1 v/v) using the thin-film hydration process. Studies have shown that transferosomes can encapsulate drugs with an entrapment efficiency of up to 64%. Furthermore, the addition of chitosan enabled rapid drug release within the 1st h, followed by continuous release thereafter. Verapamil composite chitosan vesicles had a considerably greater Cmax (10.05 ± 0.06 µg/mL) than conventional oral dose forms (7 ± 0.12 µg/mL) or sustained-release formulations (2.52 ± 0.01 µg/mL). Furthermore, these vesicles had an absolute bioavailability of 81.83%, significantly increasing verapamil's oral bioavailability, decreasing early drug absorption inhibition and perhaps minimizing adverse effects.[29]

POLYMER-BASED NANOCARRIERS

Polymeric nanocarriers are solid colloidal particles with a size range of 1–1000 nm. These carriers are made of macromolecular materials or polymers that are biocompatible and biodegradable. They are versatile tools that can be used as vaccination adjuvants or drug delivery vehicles, allowing

active substances to be dispersed, entrapped, encapsulated, adsorbed, or chemically bonded. Notably, nanoparticles have specific advantages due to their size, however only a small number can cross mucosal membranes through the paracellular route after tight attachment. Nanospheres and nanocapsules are two examples of polymeric nanoparticles, with nanospheres acting as reservoirs and nanocapsules as matrix systems. These carriers offer exciting opportunities for focused and regulated medication delivery, seeking to reduce adverse effects while improving therapeutic outcomes. The use of polymeric nanoparticles for nasal medication administration seeks to strike a balance between low side effects and maximum therapeutic efficacy. Their small size provides unique physicochemical and biological properties, making them appropriate for a variety of biological applications. These characteristics include the ability to cross tissue and cell barriers, as well as a larger reactive surface area, which allows for interactions with biological systems.

MULTIPARTICULATE DRUG DELIVERY

Microparticles and microspheres, a common component of multi-particulate drug delivery systems, offer both technical and medical advantages based on their structural functions. Depending on the formulation, it can be used in a variety of pharmaceutical dosage forms, including liquid (pills, capsules, and gums), and semi-solid (gels, creams, and pastes), and solids (capsules, tablets, and sachets). The overall size of the microparticles ranged from 1 to 1000 nm. They are useful for safe and efficient drug delivery by a variety of routes, and act as multiclass drug delivery systems with unique physiological and pharmacological advantages of efficacy, tolerability, and compliant patients homogeneous or heterogeneous depending on how microparticles are produced and processed there must be order. Circular shapes are generally preferred because they facilitate later work such as coatings. The drug is uniformly dispersed, dispersed, or suspended in microspheres, which form matrix structures. Typically, a solid or liquid microsphere system is dispersed or dispersed in the matrix.

CONCLUSION

We have walked a path that opens up a potential future for the treatment of hypertensive patients by investigating the cutting-edge field of intranasal medication delivery systems. With its straightforward and non-invasive methodology, the intranasal route offers a strong substitute for conventional parenteral and oral approaches, possibly transforming the way HTN is managed. The main attraction of intranasal delivery is its capacity to bypass the gastrointestinal system and first-pass metabolism, which increases the antihypertensive medications' bioavailability. This benefit is especially important for drugs that are heavily processed by the liver or have a low oral bioavailability. Moreover, the nasal mucosa's quick absorption can provide immediate therapeutic benefits, which is crucial for treating acute hypertensive crises. In summary, research into intranasal drug delivery strategies for HTN reveals a promising new area for improving patient care. There is a chance that HTN can be managed in a way that is more patient-friendly and effective as long as science and technology continue to push the boundaries. However, to fully realize this promise, novel research, formulation science, and device engineering must be used to overcome current obstacles. Intranasal medication delivery may establish itself as a key component of the future of HTN therapy with the combined efforts of scientists, physicians, and pharmaceutical companies. This will provide patients with a new, effective, and more controllable method of controlling their blood pressure.

REFERENCES

1. Malik A, Yoshida Y, Erkin T, Salim D, Hamajima N. Hypertension-related knowledge, practice and drug adherence among inpatients of a hospital in Samarkand, Uzbekistan. Nagoya J Med Sci 2014;76:255-63.
2. Gee ME, Bienek A, McAlister FA, Robitaille C, Joffres M, Tremblay MS, *et al*. Factors associated with lack of awareness and uncontrolled high blood pressure among Canadian adults with hypertension. Can J Cardiol 2012;28:375-82.
3. Chobanian AV, Bakris George L, Black HR, Cushman WC, Green LA, Izzo JL Jr., *et al.* The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. JAMA 2003;289:2560-72.
4. Böhm M, Schumacher H, Teo KK, Lonn E, Mahfoud F, Mann JF, *et al*. Achieved diastolic blood pressure and pulse pressure at target systolic blood pressure (120-140 mmHg) and cardiovascular outcomes in high-risk patients: Results from ONTARGET and TRANSCEND trials. Eur Heart J 2018;39:3105-14.
5. Li J, Somers VK, Gao X, Chen Z, Ju J, Lin Q, *et al*. Evaluation of optimal diastolic blood pressure range among adults with treated systolic blood pressure less than 130 mm Hg. JAMA Netw Open 2021;4:e2037554.
6. Bhalerao KK, Dange SM, Kamble MS, Bhosale AV, Nanjwade BK, Shinde SA, *et al*. Development and evaluation of amlodipine besylate nanogel. J Bionanosci 2015;9:22-7.
7. Cuspidi C, Tadic M, Grassi G, Mancia G. Treatment of hypertension: The ESH/ESC guidelines recommendations. Pharmacol Res 2018;128:315-21.
8. Vispute M, Nazim S, Khan T, Shaikh S. An overview on exploring nasal microemulsion for treatment of CNS disorders. Int J Pharm Sci Res 2013;4:1294-11.
9. Puddey IB, Beilin LJ, Vandongen R. Regular alcohol use raises blood pressure in treated hypertensive subjects. A randomised controlled trial. Lancet 1987;329:647-51.
10. Venkatalaxmi A, Padmavathi BS, Amaranath TJ.

A general solution of unsteady Stokes equations. Fluid Dyn Res 2004;35:229-36.
11. Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. Lancet Neurol 2018;17:1006-15.
12. Priano SM, Hong OS, Chen JL. Lifestyles and health-related outcomes of U.S. hospital nurses: A systematic review. Nurs Outlook 2018;66:66-76.
13. Harris R, Acosta N, Heras A. Chitosan and inhalers: A bioadhesive polymer for pulmonary drug delivery. In: Inhaler Devices. United Kingdom: Woodhead Publishing; 2013. p. 77-93.
14. Ban MM, Chakote VR, Dhembre GN, Rajguru JR, Joshi DA. *In-situ* gel for nasal drug delivery. Int J Dev Res 2018;8:18763-9.
15. Vigani B, Rossi S, Sandri G, Bonferoni MC, Caramella CM, Ferrari F. Recent advances in the development of *in situ* gelling drug delivery systems for non-parenteral administration routes. Pharmaceutics 2020;12:859.
16. Xu Y, Shrestha N, Préat V, Beloqui A. Overcoming the intestinal barrier: A look into targeting approaches for improved oral drug delivery systems. J Control Release 2020;322:486-508.
17. Moeller EH, Jorgensen L. Alternative routes of administration for systemic delivery of protein pharmaceuticals. Drug Discov Today Technol 2008;5:e89-94.
18. Raza A, Sime FB, Cabot PJ, Maqbool F, Roberts JA, Falconer JR. Solid nanoparticles for oral antimicrobial drug delivery: A review. Drug Discov Today 2019;24:858-66.
19. Nikam TH, Patil MP, Patil SS, Vadnere GP, Lodhi S. Nanoemulsion: A brief review on development and application in parenteral drug delivery. Adv Pharm J 2018;3:43-54.
20. Ghadiri M, Young PM, Traini D. Strategies to enhance drug absorption via nasal and pulmonary routes. Pharmaceutics 2019;11:113.
21. Pisal S, Shelke V, Mahadik K, Kadam S. Effect of organogel components on *in vitro* nasal delivery of propranolol hydrochloride. AAPS PharmSciTech 2004;5:e63.
22. Pisal PB, Patil SS, Pokharkar VB. Rheological investigation and its correlation with permeability coefficient of drug loaded carbopol gel: Influence of absorption enhancers. Drug Dev Ind Pharm 2013;39:593-9.
23. Prajapati M, Mandloi R, Pillai S, Birla N. The review on the nasal drug delivery. Asian J Pharm Res 2020;10:110-6.
24. Migliore MM, Vyas TK, Campbell RB, Amiji MM, Waszczak BL. Brain delivery of proteins by the intranasal route of administration: A comparison of cationic liposomes versus aqueous solution formulations. J Pharm Sci 2010;99:1745-61.
25. Gabizon A, Shmeeda H, Barenholz Y. Pharmacokinetics of pegylated liposomal doxorubicin: Review of animal and human studies. Clin Pharmacokinet 2003;42:419-36.
26. Rommasi F, Esfandiari N. Liposomal nanomedicine: Applications for drug delivery in cancer therapy. Nanoscale Res Lett 2021;16:95.
27. Abd Sisak MA, Daik R, Ramli S. Study on the effect of oil phase and co-surfactant on microemulsion systems. Malays J Anal Sci 2017;21:1409-16.
28. Elshafeey AH, Bendas ER, Mohamed OH. Intranasal microemulsion of sildenafil citrate: *In vitro* evaluation and *in vivo* pharmacokinetic study in rabbits. AAPS PharmSciTech 2009;10:361-7.
29. Mouez MA, Nasr M, Abdel-Mottaleb M, Geneidi AS, Mansour S. Composite chitosan-transfersomal vesicles for improved transnasal permeation and bioavailability of verapamil. Int J Biol Macromol 2016;93:591-9.

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