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Exploring Patient-Centric Drug Delivery System: Recent Advances in Hypertensive Management and their Clinical Impact

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Abstract

Hypertension management continues to be a significant global health challenge, with patient non-compliance to prescribed therapies serving as a major obstacle to achieving effective blood pressure control. Hydrochlorothiazide (HCTZ), a widely used thiazide diuretic, effectively lowers blood pressure but often faces adherence problems, particularly because its conventional tablet form can be difficult for some patients to swallow. Oral disintegrating tablets (ODTs) have emerged as a potential solution, offering the advantage of rapid dissolution in the mouth without the need for water, making them especially suitable for patients who have difficulty swallowing pills. Furthermore, fast-release formulations of HCTZ can improve its bioavailability by promoting quicker dissolution and absorption, leading to a more rapid onset of action and enhanced blood pressure control. Additionally, solubility-enhancing technologies such as solid dispersions or nanoparticles can address the drug's poor solubility, improving its dissolution rate and ensuring more effective therapeutic outcomes. These advanced drug delivery systems not only enhance HCTZ's pharmacokinetic properties but also help to improve patient adherence and clinical outcomes in hypertension therapy, highlighting the importance of patient-centered formulation innovations in modern medicine.

Keywords: Hypertension,Compliance in therapy, Patient-centric drug delivery, Oral Disintegrating Tablets, Fast-Release Formulation and Evaluation, Impact on Hypertension Management

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Introduction:

Hypertension is a widespread risk factor associated with cardiovascular diseases, strokes, heart failure, atrial fibrillation, peripheral arterial disease, renal impairment, and significant neurocognitive disorders. As a result, it poses a critical public health challenge worldwide. Various antihypertensive therapies are employed to reduce blood pressure in individuals with hypertension, focusing on different pathways and mechanisms that contribute to its development.[1] According to the 2021 World Health Organization (WHO) Guideline for the Pharmacological Treatment of Hypertension in Adults. Globally, around 1.28 billion adults aged 30 to 79 are estimated to have hypertension, with the majority (two-thirds) residing in low- and middle-income countries. Alarmingly, 46% of individuals with hypertension are unaware of their condition. Fewer than half (42%) of those affected receive a diagnosis and appropriate treatment, and only about 21% successfully manage to keep their blood pressure under control. Hypertension remains a leading cause of premature mortality worldwide. A key global health goal for non-communicable diseases is to decrease the prevalence of hypertension by 33% between 2010 and 2030**.**Hypertension, or high blood pressure, is a condition where the force of blood against the walls of blood vessels is consistently high, typically measured at 140/90 mmHg or above. It is often asymptomatic, making regular monitoring essential for detection. Risk factors include advancing age, genetics, obesity, physical inactivity, high salt intake, and excessive alcohol consumption. Lifestyle changes, such as adopting a healthier diet, increasing physical activity, and quitting tobacco, can help lower blood pressure, though some individuals may require medication. Blood pressure is measured with two values: systolic pressure, representing the force during heartbeats, and diastolic pressure, indicating the pressure when the heart rests between beats. Hypertension is confirmed if readings on two separate days show systolic levels of ≥140 mmHg and/or diastolic levels of ≥90 mmHg.[2]

Managing high blood pressure with pharmacotherapy is highly effective in reducing cardiovascular risks and mortality. However, it often leads to side effects such as low blood pressure, dizziness, and imbalances in electrolytes. As seen in Figure 1. Despite the availability of numerous medications, many individuals with hypertension struggle to achieve target blood pressure levels, underscoring the need for alternative treatment methods. Renal denervation (RDN) has emerged as an innovative approach, focusing on the role of the sympathetic nervous system in blood pressure control, kidney function, sodium regulation, and the renin-angiotensin-aldosterone system.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Initial animal studies revealed that stimulating the dorsal and splanchnic nerves affected blood pressure and kidney dimensions, providing a foundation for RDN. Subsequent clinical studies demonstrated that selectively ablating the renal sympathetic nerves disrupts neurohormonal pathways, effectively lowering systemic vascular resistance and addressing the root causes of hypertension.

RDN holds promise as either a complementary or standalone treatment, particularly for patients who do not respond well to medications or experience intolerable side effects. This approach introduces a novel way to manage hypertension, offering improved outcomes for those unable to achieve adequate blood pressure control with conventional therapies. As research progresses, further optimization of RDN and exploration of its long-term impacts will be vital for its integration into standard medical practice. The physiological pathways affected by RDN, showcasing its role in reducing sympathetic nervous system overactivity in individuals with hypertension.[2,3]

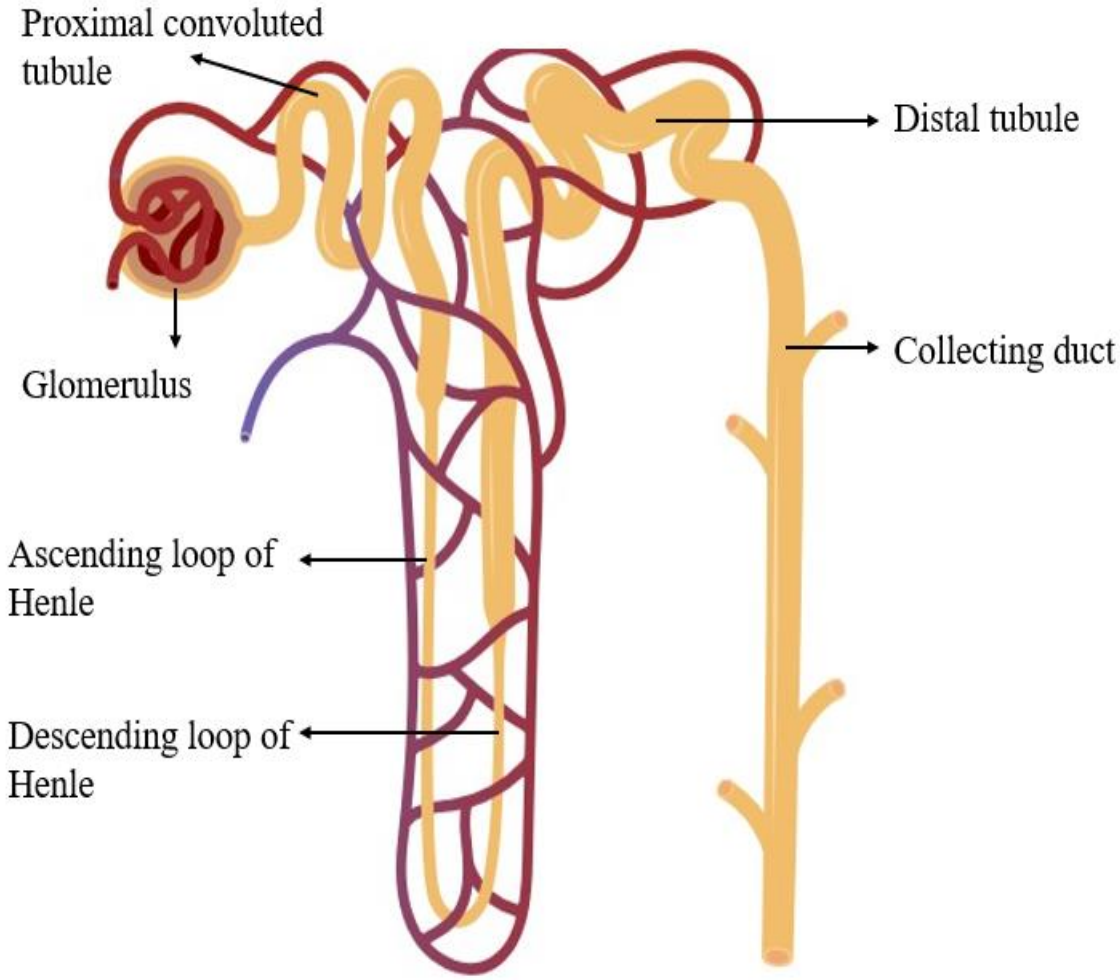

Figure 1: Substances Filtered and Reabsorbed by the Nephron

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Thiazide diuretics were the first well-tolerated and effective antihypertensive medications introduced into clinical practice. For over 50 years, they have been recognized as a first-line treatment option, both as monotherapy and in combination with other medications. Numerous studies have demonstrated their ability to reduce cardiovascular morbidity and mortality. This drug class includes benzothiadiazine derivatives, which gave rise to the name "thiazides," as well as thiazide-like compounds that exhibit similar pharmacological effects despite differing chemical structures. While they share a common mechanism of action and comparable therapeutic effects, their pharmacokinetic properties vary. Chlorothiazide was the first to be used clinically, followed by chlorthalidone, hydrochlorothiazide, indapamide, and xipamide. Among these, hydrochlorothiazide, chlorthalidone, and indapamide are the most commonly used today, with ongoing debates regarding the specific advantages of each. As seen in figure 2.

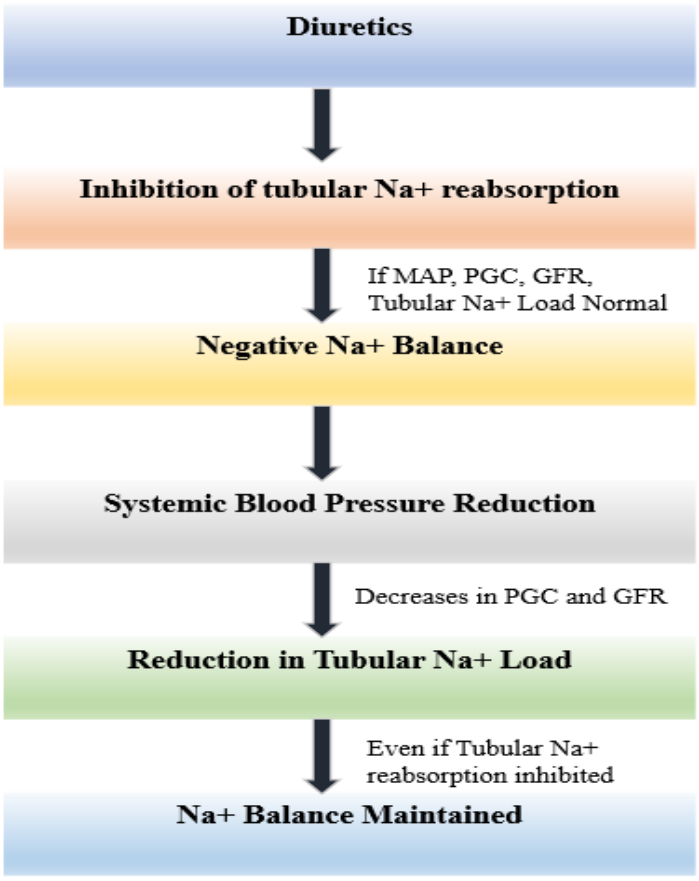

Figure 2: The antihypertensive mechanism of diuretics

Mechanism of action

Diuretics increase urine output by promoting sodium excretion (natriuresis) and accompanying anions like chloride. Prolonged use reduces total body sodium but is limited

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

by compensatory mechanisms, such as activation of the sympathetic nervous system and RAAS. They also affect renal handling of ions like potassium, calcium, and magnesium and may indirectly influence renal hemodynamic.

Thiazide diuretics lower blood pressure by inhibiting the sodium-chloride cotransporter in the distal convoluted tubule, reducing sodium reabsorption and extracellular fluid volume. (Table 1). Over time, their effect shifts to decreasing peripheral resistance, even as cardiac output and fluid volume normalize. Hydrochlorothiazide may also activate potassium channels in vascular smooth muscle and inhibit vascular carbonic anhydrase, reducing vasoconstriction. While these mechanisms remain partly speculative, their primary antihypertensive action relies on blocking the sodium-chloride cotransporter, supported by reduced efficacy in kidney failure and lower blood pressure in individuals with *SLC12A3* mutations.[4]

Table 1. Hydrochlorothiazide impairs the reabsorption of sodium and chloride in the kidney.

Action Site	Normal Function	Effect of Hydrochlorothiazide
Distal Convoluted Tubule	Reabsorption of sodium (Na+) and chloride (Cl-) via the sodium-chloride symporter (NCC)	Inhibition of the sodium-chloride symporter, reducing reabsorption of Na+ and Cl-
Effect on Sodium	Sodium is normally reabsorbed into the blood from the urine.	Sodium remains in the urine, leading to increased excretion.
Effect on Chloride	Chloride is reabsorbed along with sodium.	Chloride also remains in the urine, increasing chloride excretion.
Effect on Water	Water follows sodium and chloride reabsorption, reducing urine volume.	Water is retained in the urine due to decreased sodium reabsorption, leading to diuresis.
Overall Effect	Normal blood volume and blood pressure regulation.	Decreased blood volume and lowered blood pressure due to fluid loss.

Compliance in therapy

Patient compliance with hypertension treatment using hydrochlorothiazide 25 mg tablets can be influenced by several factors that impact both the effectiveness of the drug and the patient's ability to follow the prescribed regimen. One key factor is the ease of administration, as hydrochlorothiazide is often prescribed as a once-daily medication, which tends to improve adherence compared to drugs requiring multiple doses. However, patients who have

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

difficulty swallowing pills may face challenges, although alternative forms like oral disintegrating tablets (ODTs) or liquid versions can help address this issue. Side effects, such as dizziness or low potassium, may also discourage patients from continuing their treatment, but providing guidance on managing these effects can help improve compliance. Additionally, some patients may stop their medication if they don't experience immediate symptoms, so educating them on the long-term benefits of consistent treatment is essential. The cost of hydrochlorothiazide can also affect adherence, especially for those without adequate insurance coverage, but its relatively low cost makes it more accessible. Ensuring that patients have access to the medication is vital for long-term compliance. Patient education on the importance of taking the medication as prescribed, managing side effects, and adopting lifestyle changes like diet and exercise can further encourage adherence. Combining hydrochlorothiazide with other antihypertensive drugs in a single regimen can also simplify treatment and enhance compliance. In conclusion, while hydrochlorothiazide is effective in controlling blood pressure, improving patient compliance requires addressing factors such as ease of administration, side effects, cost, education, and treatment simplicity.[4,5]

Hypertension management involves both pharmacological and non-pharmacological approaches with physicians often prioritizing medication adherence and regular appointments. While medication adherence is crucial for controlling blood pressure and minimizing hypertension-related complications, it is not the sole determinant. Behavioural risk factors, such as a sedentary lifestyle, smoking, alcohol consumption, khat chewing, and excessive salt intake, are commonly addressed by clinicians in Ethiopia. Although counselling on these factors is vital for effective blood pressure management, many patients fail to adhere to the guidance provided.

Poor adherence to counselling on these factors significantly increases the likelihood of hypertension-related complications. Factors influencing compliance include medical insurance, diabetes status, BMI, age, adherence levels, and the quality of the patient-clinician relationship. However, earlier studies have often overlooked the roles of perceived social support and health-related quality of life in patient compliance. While individual factors have been studied extensively, comprehensive analyses integrating these variables are limited. Therefore, this study aims to evaluate the compliance of hypertensive patients with clinician counseling.[6]

Patient-centric drug delivery

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Oromucosal films include mucoadhesive buccal films (MBFs) and orodispersible films (ODFs), which are typically composed of single or multilayered sheets made from appropriate materials. MBFs are designed to adhere to the buccal mucosa when placed in the mouth. These films can be utilized to treat both systemic and local conditions. For systemic therapy, the active pharmaceutical ingredient (API) is absorbed through the mucosal lining, bypassing the gastrointestinal tract, or it may be swallowed with saliva. As seen in Figure 3. In contrast, for local treatments, MBFs are advantageous compared to oral gels or ointments due to their prolonged retention in the mouth, making them less susceptible to removal by saliva. On the other hand, ODFs are designed to dissolve quickly when placed on the tongue.

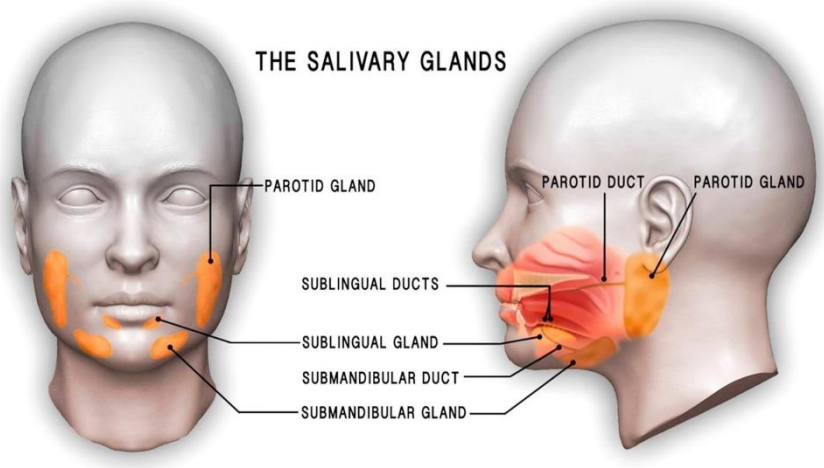

Figure 3: Salivary gland;including parotid glands, submandibular gland and sublingual gland

The API is primarily swallowed with saliva and absorbed through the gastrointestinal tract. ODFs are commonly employed to manage systemic conditions.[7]Oromucosal films are patient-friendly dosage forms that offer high acceptability due to their convenience and ease of use. According to the European Medicines Agency, patient acceptability refers to the willingness and ability of patients to use a medication as prescribed. This aspect has become a crucial consideration in drug development to improve treatment adherence and reduce medication errors. Features like portability, thin and flexible design, dose adjustability, and the option to take them with minimal or no water make these films ideal for individuals with specific needs. They are particularly beneficial for older adults with dysphagia, infants, young children, uncooperative patients, or those experiencing nausea or vomiting.[8] The rapid disintegration or adhesive properties of these films ensure they are not easily spat out. Moreover, their straightforward use without complex preparation steps enhances their suitability for diverse situations, especially for patients who may find it difficult to follow detailed instructions.Oromucosal films can accommodate various drug compounds, including

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

low molecular weight active pharmaceutical ingredients (APIs) with either high or low water solubility, biopharmaceuticals, and herbal extracts. Certain Oromucosal formulations are designed for rapid API absorption, providing a quick onset of action that is particularly beneficial in emergency situations. Alternatively, formulations with controlled or delayed drug release offer a convenient option by reducing the need for frequent dosing. (Table 2).[7] This review highlights the patient-centric attributes of Oromucosal films for delivering drugs locally or systemically through the oral cavity. It also provides a summary of active pharmaceutical ingredients (APIs) recently incorporated into these films.

Table 2. Overview of the characteristics of Oromucosal.

Oromucosal Films	Mucoadhesive Buccal Films	Orodispersible Films
Characteristics	Long residence time in the mouth	Rapid dissolution
	Sufficient mucoadhesion	Stick to the mucosa
	Local and systemic drug delivery	Break down into soft particles
	API absorption mainly via the oral mucosa	Predominantly systemic drug delivery
	Increase of bioavailability	API is mainly swallowed with saliva
		Absorption via gastrointestinal tracts
Multilayer Design	MBF: Non-dissolving backing layer	MBF and ODF: Fixed dose combinations, prolonged drug release
Preparation Method	Conventional solvent casting technique	Novel printing techniques

Additionally, the review explores innovative printing technologies for the production of Oromucosal films, suitable for both small-scale and large-scale manufacturing. 3D printing offers significant advancements in personalized medicine by allowing adjustments to doses and dosage forms based on patient-specific needs, such as body weight and lifestyle. For example, orodispersible tablets can be used instead of conventional tablets for noncompliant

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

patients or those with swallowing difficulties.[9,10] This customization is made possible by the scalability of digital designs, enabling precise dose control through calculated material usage during the design phase. This approach is particularly beneficial for producing orphan drugs for small patient populations and is cost-effective for manufacturing dosage forms with variable doses.

In pediatric and elderly care, factors such as the shape, size, taste, and colour of medicines play a crucial role in therapy. For instance, taste masking can be achieved in methods like fused deposition modeling (FDM), where active pharmaceutical ingredients (APIs) are embedded in a polymer matrix, eliminating the need for additional processes like coating.[11] demonstrated this by producing taste-masked dosage forms in the shape of jelly beans with indomethacin, achieving accuracy, content uniformity, and rapid dissolution.Tablet shape and size also influence patient acceptability. Goyanes et al. studied various shapes, including torus, sphere, disc, capsule, and diamond, finding that torus-shaped tablets were easiest to swallow, especially for elderly patients with swallowing or handling difficulties. Conventional shapes were also acceptable due to their familiarity. The team also noted that tablet geometry minimally affects dissolution, allowing flexibility in design for individual patients. Integrating 3D printing in hospitals and pharmacies has the potential to elevate pharmaceutical compounding and enhance personalized treatments.[12]

Oral Disintegrating Tablets

Orally disintegrating tablets (ODTs) are an innovative and user-friendly dosage form that dissolves rapidly in the mouth without the need for water, providing a convenient method for administering active pharmaceutical ingredients (APIs). This feature ensures a faster onset of action and enhanced ease of use, making ODTs a practical choice for a variety of therapeutic applications. In recent years, their popularity has grown, positioning them as a favored alternative to traditional tablets and capsules in many medical scenarios. The increased adoption of ODTs can be attributed to their numerous advantages, particularly in improving patient compliance. For individuals who struggle with swallowing, such as children, the elderly, or those with psychiatric conditions, ODTs offer a stress-free and effective alternative to standard oral dosage forms. ODTs also play a pivotal role in the lifecycle management of pharmaceutical products. By introducing this innovative dosage form, pharmaceutical companies can extend the appeal and utility of existing medications, addressing the specific needs of niche patient groups. Beyond human medicine, ODTs have proven valuable in veterinary applications, particularly for small animals, where administering medication can be challenging. Their quick dissolution in the mouth simplifies the process, reducing

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

resistance and improving the overall experience for both caregivers and patients.[13]Orodispersible tablets (ODTs) are solid dosage forms that dissolve rapidly in the oral cavity within seconds, eliminating the need for chewing or water intake. They offer a practical solution to enhance patient compliance and simplify drug administration, particularly for geriatric patients, children, and individuals with compromised upper gastrointestinal mucosa. Numerous ODT formulations, including analgesics, antihypertensives, and antidepressants, are already available commercially.[14]as seen in Figure 4.

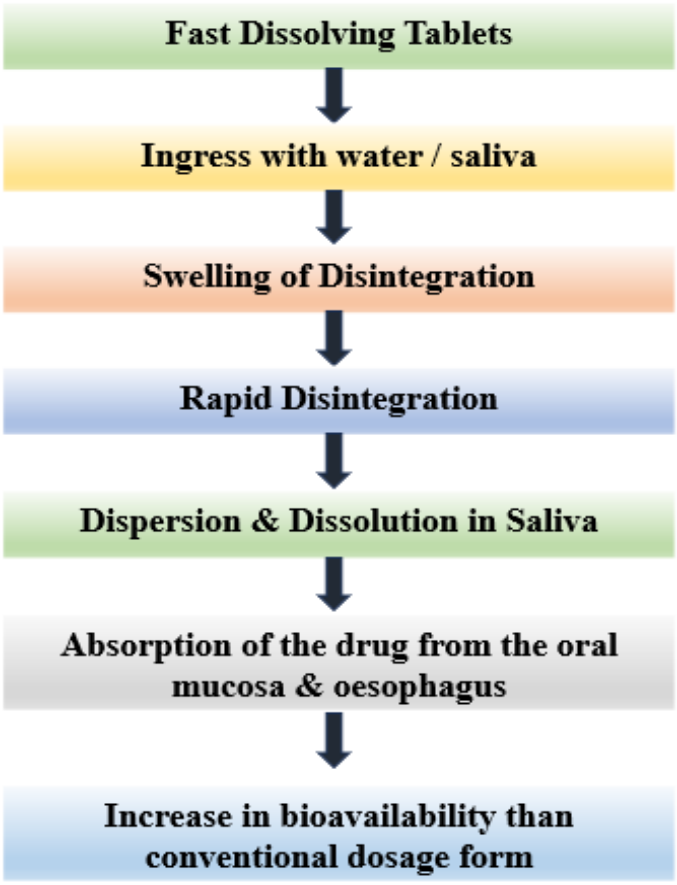

Figure 4: Action of Fast Dissolving Tablets

Various techniques are employed to produce ODTs, such as molding, mass extrusion, freeze-drying, and direct compression. Freeze-drying and direct compression result in tablets with higher porosity, enabling faster disintegration upon contact with saliva. In addition, 3D printing, particularly the binder jetting method, has emerged as a promising technology for creating highly porous structures that meet the physical and biopharmaceutical requirements of ODTs.[15]

Recently, 3D printing has garnered significant attention for its adaptability and innovative potential. This additive manufacturing process constructs objects layer by layer, allowing

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

precise customization. Since its inception in the 1980s, advancements in printing techniques and materials with diverse physical and mechanical properties have significantly expanded its applications. Initially applied in industries like aerospace, construction, and architecture, 3D printing has also gained traction in healthcare.In the medical field, 3D printing is used in areas such as tissue engineering, surgical implants, prosthetics, orthopaedics, and dentistry. It also facilitates the production of surgical tools and enhances operative planning through high-resolution imaging compared to traditional 2D radiological methods. In pharmaceutics, 3D printing has been successfully utilized to manufacture modified-release dosage forms, including rapidly disintegrating tablets and sustained-release drug delivery systems.[16,17]

Orally disintegrating dosage forms (ODDFs) offer numerous benefits from both patient-use and pharmaceutical perspectives. From the patient's viewpoint, ODDFs do not require water for ingestion and dissolve quickly in the mouth, making them highly convenient for use on the go or in areas with limited access to clean water. Unlike liquid dosage forms, ODDFs do not require measurement or manipulation, reducing the risk of dosing errors and the need for caregiver involvement.[18]as seen in Figure 5.

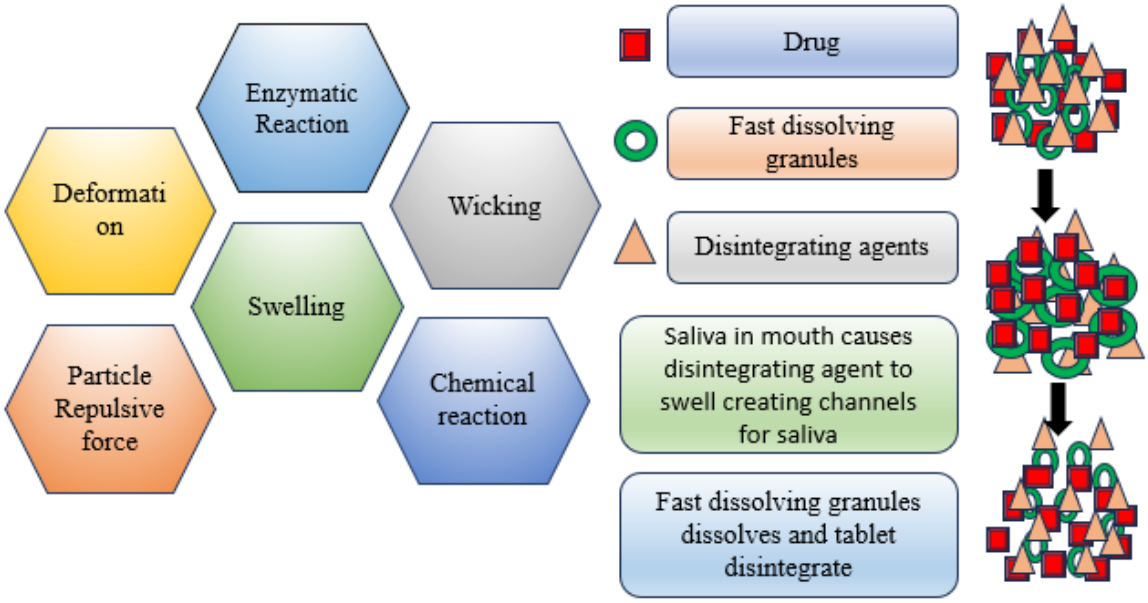

Figure 5: Mechanism of Oral disintegrating tablet

Their ease of swallowing makes ODDFs particularly advantageous for individuals with dysphagia, such as stroke patients. They are also beneficial for paediatric patients, who often struggle to swallow traditional solid dosage forms like tablets and capsules, with studies indicating that most children below six years of age find it challenging. This makes ODDFs an age-appropriate option for children, tailored to meet their needs. Furthermore, about one-

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

third of adults have difficulty swallowing conventional solid dosage forms and ODDFs can help mitigate choking risks associated with swallowing difficulties.In addition to patient-centered advantages, ODDFs offer pharmaceutical benefits. Their rapid disintegration and release of the active pharmaceutical ingredient (API) enable a faster onset of action, which is critical for conditions requiring quick relief, such as migraines. Other conditions benefiting from this fast action include travel sickness, gastrointestinal issues, allergies, and treatments for anxiety and psychosis. Moreover, the rapid dissolution in the oral cavity allows for pre-gastric absorption, enhancing the drug's bioavailability.[18,19]

The pharmaceutical industry is focused on overcoming challenges such as improving the half-life, solubility, stability, and bioavailability of poorly soluble drugs. Key priorities include enhancing safety by minimizing gastrointestinal side effects, improving targeted delivery to specific organs, and boosting patient compliance with sustained-release formulations or easily swallowable dosage forms. Innovation in drug delivery systems is critical for maintaining competitiveness and addressing these demands. Fast-dissolving tablets (FDTs) have become increasingly popular due to their ease of use, self-administration capability, and rapid disintegration without the need for water. They play a crucial role in extending market exclusivity for pharmaceutical companies by providing updated and patient-friendly dosage forms, especially as existing patents approach expiration. Despite higher manufacturing costs, these advanced formulations are seen as investments in meeting patient needs rather than cost burdens to consumers.[20]

Fast-Release Formulation

The formulation of orally disintegrating tablets (ODTs) requires ingredients that ensure rapid drug release and dissolution. These include the active pharmaceutical ingredient (API) and various excipients. Selecting a suitable drug candidate involves considering several factors to enhance dissolution and pregastric absorption. Ideal characteristics include a dose of 20 mg or less, high solubility in water and saliva, small to moderate molecular weight, a lack of bitter taste, partial unionization at the pH of the oral cavity, the ability to diffuse into the epithelium of the upper gastrointestinal tract, and permeability through oral mucosal tissues. While most APIs can be formulated as ODTs, drugs requiring rapid therapeutic action, such as neuroleptics, cardiovascular agents, analgesics, antiepileptics, diuretics, and others, are commonly used. However, certain limitations, such as a short half-life, extremely bitter taste, need for controlled release, or incompatibility with anticholinergics, may make a drug unsuitable for ODTs.[21]

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Excipients play an equally important role in ODT development. Key excipients include disintegrants, diluents, lubricants, and optional agents like sweeteners and flavorings. These excipients should enable quick dispersion and dissolution in the mouth without leaving residue, effectively mask unpleasant drug tastes, provide a pleasant mouthfeel, and remain stable under varying environmental conditions. Additionally, excipients with melting properties around 30–35°C are ideal for enhancing the formulation's rapid disintegration and palatability.[22] Together, the careful selection of APIs and excipients ensures the efficacy and acceptability of ODTs for patients. Detail of excipients is given in table 3.[23]

Table 3. Excipients Used in the Preparation of Orally Disintegrating Tablets.

Excipients	Function	Examples
Superdisintegrants	Promote rapid tablet disintegration and dissolution. Combined with other ingredients like water-soluble excipients or effervescent agents, they enhance the disintegration process, achieving quick-dissolving properties.	Crospovidone, microcrystalline cellulose, sodium starch glycolate, sodium carboxymethyl cellulose, pregelatinized starch, modified corn starch. Sodium starch glycolate offers superior flowability compared to croscarmellose sodium, while crospovidone is fibrous and highly compactable.
Flavors	Improve patient compliance and acceptance by masking unpleasant tastes.	Peppermint flavour, cooling flavours, flavouring oils (e.g., peppermint oil, clove oil, bay oil, eucalyptus oil, thyme oil), vanilla, citrus oils, and fruit essences.
Sweeteners and Sugar-Based Excipients	Provide sweetness, act as bulking agents, and enhance taste masking and mouthfeel properties. Useful for direct compression techniques.	Artificial sweeteners like aspartame; sugar derivatives and bulking agents such as dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, polydextrose, starch hydrolysate, and xylitol.
SurfaceActive	Reduce surface tension to	Sodium dodecyl sulphate, sodium lauryl

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Excipients	Function	Examples
Agents	improve solubilization of the dosage form.	sulphate, polyoxyethylene sorbitan esters (Tweens), sorbitan esters (Spans), polyoxyethylene stearates.
Binders	Maintain the structural integrity of the dosage form during manufacturing and handling.	Polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC).
Coloring Agents	Enhance the appearance and visual appeal of the dosage form.	Sunset yellow, amaranth, red iron oxide.
Lubricants	Reduce friction during tablet compression to protect tablet machinery and ensure uniformity.	Stearic acid, magnesium stearate, zinc stearate, calcium stearate, talc, polyethylene glycol, liquid paraffin, magnesium lauryl sulphate, colloidal silicon dioxide.
Fillers	Increase the bulk of the tablet for easier handling and dosage.	Directly compressible spray-dried mannitol, sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulphate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide.

The preparation of orally disintegrating tablets (ODTs) involves two main categories: conventional and patented techniques. Conventional methods include freeze-drying, spray-drying, molding, phase transition processing, melt granulation, sublimation, mass extrusion, the cotton candy process, and direct compression, each contributing to the development of effective drug delivery systems. Patented techniques, on the other hand, focus on enhancing the rapid-dissolving properties of ODTs by promoting swift water penetration into the tablet matrix for quick disintegration. These technologies differ in parameters such as mechanical strength, porosity, dose, stability, taste masking, mouthfeel, dissolution rate, and bioavailability, with specific advantages and limitations outlined in detailed studies and branded product examples.[24] This review summarizes commonly used techniques for

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

preparing orally disintegrating tablets (ODTs), including molding, mass extrusion, sublimation, spray-drying, direct compression, and lyophilization (freeze-drying), as illustrated in Figure 6. The advantages and limitations of these methods are also discussed. Furthermore, a variety of patented techniques, such as Wowtab®, Orasolv®, Fashtab®, Durasolv®, Zydis®, Flashdose®, and Oraquick®, have been extensively reviewed by Tansel Comoglu and Emine Dilek Ozyilmaz [25].

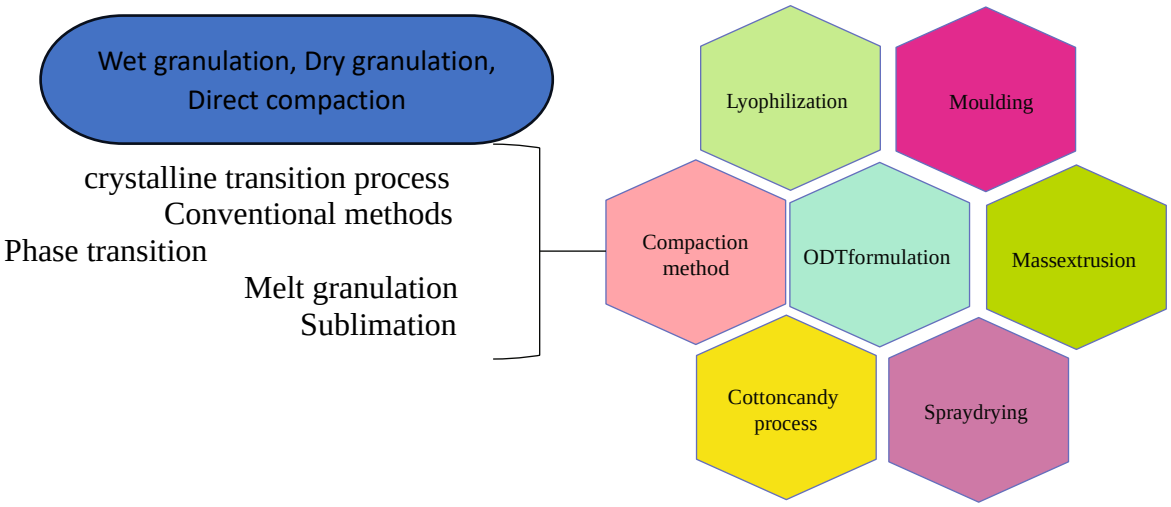

Figure 6: ODT formulation techniques.

Preparation Techniques for Orally Disintegrating Tablets (ODTs)

Molding Method:

ODTs prepared using molding techniques disintegrate rapidly, typically within 5 to 15 seconds. This approach is categorized into heat molding and compression molding. For heat molding, a molten mass containing a dispersed or dissolved drug is utilized. The process begins with suspending the drug in water-soluble sugars (e.g., mannitol, lactose, sucrose, glucose, sorbitol, or xylitol) and agar, which act as binders and improve mouthfeel. This suspension is dispensed into blister packaging or molds, and the solvent is evaporated under vacuum at 30°C, solidifying the agar solution to form ODTs. In compression molding, a powder blend is mixed with a hydroalcoholic solvent and compressed into molds using low pressure, followed by air-drying to create a porous structure with high disintegration and dissolution rates. Despite its effectiveness, this technique has limitations, including high production costs and low mechanical strength, which can lead to tablet breakage during handling. Adding binders such as acacia, polyvinylpyrrolidone, or PEG can mitigate these drawbacks.[26]

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Mass Extrusion:

In this method, water-soluble solvents like polyethylene glycol (PEG) and alcohol are used to soften the powder mixture. The softened mixture is extruded or syringed, and the solvent is removed through evaporation. The resulting gel-like string is crushed into granules, which are subsequently blended with other ingredients and compacted into ODTs. PEG stearate is often employed as a binder to enhance physical strength and disintegration. This technique also enables taste masking by coating the granules with polymers such as Eudragit E 100, ethyl cellulose, or hydroxypropyl methylcellulose (HPMC).[27,28]

Spray-Drying:

This technique produces ODTs with a highly porous structure by spraying a liquid mixture of drugs and excipients into a heated chamber. The resulting microparticles are combined with mannitol, kneaded with water, dried, and compressed into tablets. While this method results in rapid disintegration, its high production cost and the fragility of the tablets make it less suitable for conventional packaging.[29]

Cotton-Candy Process:

This process involves spinning saccharides or polysaccharides (e.g., polymaltodextrin or polydextrose) at high temperatures (180–266°C) to create a candy floss matrix. The matrix is milled, blended with active pharmaceutical ingredients (APIs), and compressed into ODTs. While this method is effective for taste masking and enhancing mechanical strength, it is unsuitable for thermo-labile drugs.[30]

Lyophilization (Freeze-Drying):

Lyophilization involves drying thermo-sensitive APIs at low temperatures under vacuum. The resulting tablets are lightweight, porous, and dissolve rapidly. This method provides accurate dosing and is safer for handling potent APIs in liquid form. However, it is expensive and unsuitable for formulations unstable at high humidity. Techniques such as Zydis and Lyoc employ specific formulations and processes to improve tablet disintegration and mouthfeel while addressing challenges like sedimentation and ethical concerns associated with animal-derived gelatin.[31]

Compaction Methods:

Compaction methods involve applying pressure to agglomerate particlesforming solid tablets through various techniques. One method is sublimation, where a blend containing volatile substances, such as camphor or menthol, is compressed and then sublimated under controlled conditions, resulting in highly porous tablets with rapid disintegration. This technique has been used in the development of Hydrochlorothiazide ODTs, improving rigidity,

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

disintegration speed, and drug release. Another technique, melt granulation, is a solvent-free process that uses binders with low melting points to form granules, which are then compressed into tablets. This cost-effective method allows for controlled drug release, with materials like glycerol fatty acid ester optimizing the formulation. The crystalline transition process takes advantage of the transformation of saccharides from amorphous to crystalline states to enhance tablet hardness and disintegration. For example, combining mannitol and sucrose under specific conditions results in efficient ODTs. Phase transition involves compressing powders containing sugar alcohols with differing melting points and heating them to improve mechanical strength while maintaining porosity, making it ideal for drugs requiring low compression forces. Conventional methods such as wet granulation, dry granulation, and direct compression are widely used in ODT production. Direct compression, commonly used in large-scale manufacturing, incorporates superdisintegrants like crospovidone, croscarmellose, and calcium silicate to achieve rapid tablet disintegration. This method has been successfully applied to produce tramadol hydrochloride and levodopa ODTs, ensuring effective dosing and patient compliance.[32]

Evaluation of ODT

The quality control tests for orally disintegrating tablets (ODTs) largely align with those of conventional tablets, with some minor distinctions. Specific tests unique to ODTs include wetting time, water absorption ratio, moisture uptake, in vivo disintegration time, and taste evaluation. Quality control assessments are categorized into two main groups: precompression tests and post-compression tests.

1.Precompression Tests

Precompression tests assess properties such as the angle of repose, bulk density, tapped density, Hausner ratio, and Carr's index. These evaluations are conducted on the powder blend intended for ODT production to confirm its suitability for further processing.The angle of repose indicates the frictional forces within the powder. A value below 30° suggests good flow properties. The Hausner ratio and Carr’s index are used to predict the flowability and compressibility of the powder, respectively. A Hausner ratio under 1.25 is indicative of good flowability, while a Carr’s index below 15 signals excellent compressibility. Bulk density, closely linked to particle size and adhesion tendencies, is also significant for determining suitable packing materials and ensuring efficient transportation.[33]

2.Post-compression Tests for ODTs

Post-compression tests evaluate the final characteristics of orally disintegrating tablets (ODTs). These tests include weight variation, hardness, thickness, friability, wetting time,

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

water absorption ratio, moisture uptake, disintegration time (in vitro and in vivo), taste evaluation, and dissolution testing, as mentioned in Table 4.

Table 4. Post-compressing tests of ODTs. [40,41,42]

Parameters	Properties	Purpose and Considerations
Weight Variation	The weight of 20 randomly selected tablets is measured, and the average weight is calculated. Tolerable standard deviations (SD) are based on weight: - ≤130 mg: ±10 - 130-324 mg: ±7.5 - ≥324 mg: ±5.	Ensures consistency in tablet weight to meet dosage accuracy.
Content Uniformity	Three tablets are powdered, and the UV absorbance of a sample equivalent to 1 mg of the active pharmaceutical ingredient (API) is measured.	Applies to APIs <25 mg; ensures uniform API distribution. For higher API doses, weight variation suffices.
Hardness	Crushing strength of six tablets is tested using a hardness tester (e.g., Varian), results expressed in Newtons (N).	Assesses the mechanical robustness of tablets.
Porosity	Determined using a mercury porosimeter.	Indicates water penetration potential, affecting disintegration.
Thickness and Diameter	Measurements taken for 10 tablets using a digital Vernier caliper; average values recorded.	Monitors dimensional uniformity of tablets.
Friability	Tablets weighed before and after a friability test (25 rpm, 4 min), and weight loss percentage calculated.	USP standards require <1% friability for acceptable tablets.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Parameters	Properties	Purpose and Considerations
Wetting Time/Water Absorption Ratio	Tablets are weighed before and after placement in a dish containing 10 mL eosin solution; time and weight differences recorded.	Shorter wetting time suggests faster disintegration.
Moisture Uptake	Tablets stored in a desiccator (37°C for 1 day), weighed, then exposed to 75% RH at 25°C for 15 days; weight change recorded.	Evaluates formulation stability under humid conditions.

In Vitro Disintegration Time

ODTs are designed to disintegrate quickly in saliva while maintaining adequate mechanical strength during production and transport. In vitro disintegration tests assess this property using various methodologies. The Ph. Eur. method involves placing tablets in a basket-rack assembly that oscillates in a 37°C water bath, requiring complete disintegration within three minutes for approval. The modified USP method suspends tablets in USP apparatus II, recording the disintegration time as the tablet passes through a sieve. Texture analysis involves pushing a tablet into water using a probe, measuring the extent of penetration. Similarly, the rotary shaft method applies mechanical stress to the tablet on a perforated plate, with disintegration recorded by an electrical sensor. The CCD camera method calculates disintegration time through image analysis by capturing morphological changes in the tablet within a controlled medium. The Aston test replicates oral cavity conditions, maintaining precise temperature (37°C) and humidity (93% RH), with simulated saliva flow disintegrating the tablet, tracked using a texture analyzer.[34]

In Vivo Disintegration, Taste, and Mouthfeel

In vivo disintegration time is evaluated by measuring the time it takes for a tablet to completely disintegrate on the tongue of volunteers, requiring ethics approval if the tablet contains active ingredients with potential side effects. Taste masking is a critical step for bitter drugs to enhance patient compliance, achieved through techniques such as adding sweeteners, adjusting pH, coating active pharmaceutical ingredients (APIs), or employing nanotechnology. Taste and mouthfeel are assessed by volunteers using a scale of 1 to 5, with scores reflecting levels of roughness and bitterness. Evaluating taste for pediatric

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

formulations poses unique challenges, as children's perceptions often differ significantly from those of adults.[35]

Dissolution Test

Dissolution testing uses USP apparatus 1 (basket) or 2 (paddle). For taste-masked ODTs, a paddle speed of 100 rpm is preferred, although 50 rpm enhances profile discrimination. FDA guidelines require at least 85% API dissolution within 30 minutes, analysed via UV-Visspectroscopy or HPLC. These tests ensure ODTs meet pharmaceutical and patient standards for safety, efficacy, and compliance.[36]

Impact on Hypertension Management

Hydrochlorothiazide (HCTZ) is a commonly prescribed thiazide diuretic for managing high blood pressure. Its effectiveness in lowering blood pressure is well-established, with research showing that doses ranging from 12.5 to 25 mg daily can achieve significant reductions. However, compared to other classes of antihypertensive drugs, HCTZ may produce less pronounced reductions in blood pressure. A meta-analysis of randomized trials revealed that HCTZ at these doses lowered systolic and diastolic blood pressure by about 6.5/4.5 mm Hg, which was less effective than the reductions seen with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, and calcium channel blockers.[37]

The impact of hydrochlorothiazide (HCTZ) in the form of an orally disintegrating tablet (ODT) for hypertension treatment. ODTs are formulated to dissolve quickly in the mouth without the need for water, which can improve patient adherence, particularly for those who have difficulty swallowing tablets. Although this formulation may enhance compliance.[38]Oral disintegrating tablets (ODTs) for hydrochlorothiazide (HCTZ) can significantly enhance medication adherence, especially for patients who face challenges such as forgetfulness, difficulty swallowing pills, or lack of water. This convenience is particularly beneficial for elderly and disabled patients, ensuring they can follow their prescribed treatment regimens more easily. Additionally, ODTs reduce "treatment fatigue" by making daily medication-taking less burdensome, which can improve long-term adherence. Consistent use of HCTZ through ODTs can lead to better blood pressure control, reducing the risk of complications such as stroke, kidney disease, and heart failure. By preventing hypertensive crises and maintaining stable blood pressure levels, ODTs can improve overall patient outcomes. Moreover, the ease of use provided by ODTs can enhance patient satisfaction, reduce anxiety about taking medication, and improve both physical and mental health. While ODTs may have a higher upfront cost, their ability to improve adherence can lead to long-term cost savings by preventing hospitalizations and reducing the burden of hypertension-related

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

complications. ODT formulations of HCTZ also allow for more personalized treatment options, particularly for patients with comorbidities or those who have difficulty swallowing traditional pills. Integration with digital health tools can further support adherence by providing reminders and tracking progress. However, more research is needed to compare the effectiveness of ODTs with traditional formulations and evaluate their long-term efficacy and safety in diverse patient populations.[38,39]

Conclusion

Hypertension remains a global health challenge, requiring innovative approaches to enhance patient adherence and treatment effectiveness. Advances in drug delivery systems, such as oral disintegrating tablets (ODTs) and fast-release formulations, have improved the bioavailability and ease of administration of antihypertensive drugs like hydrochlorothiazide (HCTZ). These patient-centric innovations address adherence challenges, particularly for individuals with swallowing difficulties, while offering rapid therapeutic effects and improved clinical outcomes.Renal denervation (RDN) has emerged as a promising non-pharmacological alternative for patients resistant to conventional treatments. By targeting the sympathetic nervous system, RDN effectively lowers blood pressure and provides a long-term solution for hypertension management.Additionally, advancements in technologies like 3D printing and Oromucosal films enable personalized drug delivery, catering to individual patient needs and improving compliance. These breakthroughs represent a significant step forward in managing hypertension more effectively and reducing associated health risks.In summary, integrating novel drug delivery methods with alternative treatments like RDN offers a comprehensive solution to hypertension management. These advancements improve therapeutic outcomes, enhance patient quality of life, and highlight the potential for future innovations in personalized medicine.

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