INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 7, July 2026 | ISSN: 2456-4184 | IJNRD.ORG

AN OVERVIEW OF ADVANCED TECHNOLOGIES IN SUBLINGUAL DRUG DELIVERY SYSTEM

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ABSTRACT

Sublingual drug delivery has gained increasing attention as an effective alternative to traditional oral administration because it enables rapid drug action and improves bioavailability by bypassing first-pass metabolism and gastrointestinal degradation. This approach is particularly helpful for patients including youngsters, the elderly, and those who have trouble swallowing as well as in emergency situations. Despite these advantages, there are a number of disadvantages, including restricted drug dosage, ongoing salivary dilution, and difficulties giving drugs with high molecular weight or poor solubility. Recent advancements to address these problems have focused on novel drug delivery technologies that improve drug retention, permeability, and controlled release. Nanoparticles, nanocrystals, nanoemulsions, nanovesicles, and electrospun nanofibers are examples of nanotechnology-based systems that have demonstrated encouraging outcomes in improving medication solubility, stability, and mucosal absorption, thereby raising overall bioavailability Additionally, these systems aid in prolonging the drug's stay in the sublingual cavity, especially when paired with mucoadhesive qualities. Furthermore, by providing exact control over drug dosage, disintegration, and release patterns, the development of customised and quickly dissolving formulations has been made possible by the advent of 3D printing technology, which has completely changed the design of sublingual dosage forms. Additionally, new microrobotic techniques that actively improve drug release and absorption through fluid dynamics—like microstirring sublingual pills—are being investigated. These techniques have the potential to be used in acute care. Although additional research is still required to address issues with mucosal barriers, drug stability, and the delivery of big macromolecules for successful clinical use, these developments are generally making sublingual medication delivery a more effective, targeted, and patient-friendly strategy.

Keywords: Sublingual drug delivery, Nanotechnology, 3D printing, Microrobotics

INTRODUCTION

Due to its ease of use, patient acceptability, and simplicity, oral administration is the most popular method of medication delivery. But this approach has a number of drawbacks. Many medications undergo first-pass metabolism in the liver, are broken down in the digestive system, and may take longer to start working.[1] Conventional oral dosage forms are frequently unsuitable when a quick beginning of action is required, particularly in emergency situations, due to these disadvantages. The buccal and sublingual routes have drawn

a lot of interest in order to get around these restrictions. By escaping the hostile gastrointestinal environment and first-pass hepatic processing, medications delivered through the oral mucosa are absorbed straight into the systemic circulation.[3] This leads to increased bioavailability and quicker drug absorption, especially for medications with low physicochemical stability like peptides. The sublingual mucosa of the mouth cavity is more porous than the buccal and palatal mucosa. It is an efficient route when a prompt therapeutic response is needed because of its abundant blood flow, which enables medications to enter the bloodstream rapidly.[2] Pediatric, elderly, and dysphagic patients who frequently have trouble swallowing traditional tablets can also benefit from sublingual medicine delivery.Sublingual medication delivery nevertheless confronts a number of difficulties in spite of these advantages. Before enough absorption takes place, the medication may be diluted and removed from the absorption site by constant salivary production. Additionally, the absorption of big or poorly soluble molecules is still restricted, and only tiny therapeutic dosages may typically be supplied through this route. These difficulties have prompted scientists to create sophisticated drug delivery methods that increase mucosal permeability, improve drug retention, and offer more control over drug release. Nanotechnology has emerged as one of the most promising methods for enhancing sublingual medication delivery. A variety of nanocarriers, such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, and electrospun nanofibers, have been created to improve drug solubility, shield unstable drug molecules, and boost oral mucosal penetration. It has also been demonstrated that adding nanostructured drug carriers to oral dosage forms enhances drug release, permeability, and dissolution.[4,5] In order to provide safer, more efficient, and targeted drug delivery via the sublingual route, nanocarrier-based devices are being investigated more and more. Three-dimensional (3D) printing is another significant development that has altered the design and production of sublingual and orodispersible dosage forms. This technique makes personalised medication more feasible by enabling exact control over tablet and film properties, such as drug dose, disintegration time, and drug release profile. Thin, flexible polymeric films that quickly dissolve in the oral cavity are known as orodispersible films. Recent advances in 3D printing have made it possible to create multilayer films, incorporate nanoparticles, and create dosage forms with medications that are poorly soluble in water.[6] Fast-disintegrating films that dissolve in a matter of seconds have been made by printing processes such syringe-based extrusion and hot-melt pneumatic extrusion, making them ideal for sublingual and buccal delivery.

Microrobotic and nanorobotic medication delivery devices are being investigated by researchers more lately.[7,8] By transforming external energy into mechanical motion, these tiny devices can move under control, enabling more accurate delivery of medications to target areas. The same technical approaches are currently being researched for sublingual drug administration, despite the fact that a large portion of current research has concentrated on gastrointestinal and cancer therapies. These systems may promote transport over the sublingual mucosa, regulate medication release, and improve drug retention at the absorption site. Furthermore, mechanically assisted drug delivery methods can help overcome the absorption hurdles that have historically restricted the oral and mucosal administration of peptide medicines, as demonstrated by robotic pill technologies intended for biotherapeutic delivery. Sublingual drug delivery is generally changing due to current developments in nanotechnology, three-dimensional printing, and microrobotic systems.[9] The industry is transitioning from traditional fast-dissolving tablets to more intelligent, effective, and patient-specific medication delivery systems. The functioning principles and therapeutic potential of these developing technologies are discussed in this review, along with the issues that need to be resolved before they may be successfully used in clinical settings.

Advantages of Sublingual Drug Delivery

- Without the need for water or chewing, it has a quick onset of action and dissolves quickly in the mouth. Because of its quick action, it is most frequently utilised in emergency situations such as angina[14].
- The oral cavity offers rapid and thorough medication absorption due to its large contact surface area.

- It avoids the drug's first pass metabolism in the liver and GI tract degradation.
- Low dosages are advantageous since they reduce the chance of adverse effects and offer excellent efficacy.
- This method is more convenient for administering drugs. Because it increases patient adherence as compared to oral drugs.
- Both paediatric and elderly individuals find it easy to give.

Disadvatanges of sublingual drug delivery system[15]

- It is not suitable for a long-term medication delivery method.
- Sublingual medicine cannot be administered to patients who are unconscious.
- This method is not recommended for long-term drug delivery because the medication may interfere with eating, speaking, and drinking.
- When administering sublingual medication, smoking should be avoided since it narrows blood vessels, which reduces the drug's absorption.

Anatomy Of Sublingual Mucosa

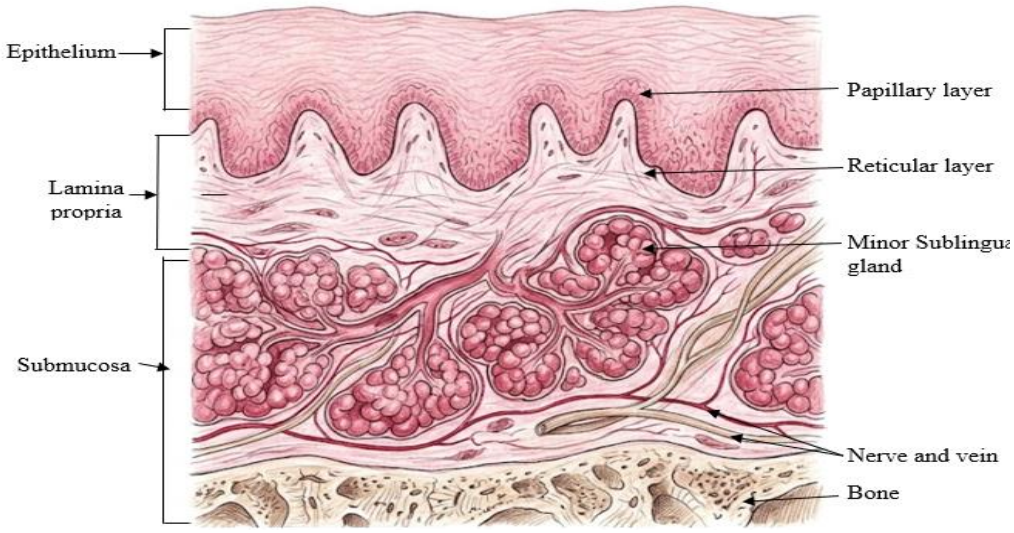

figure 1: anatomy of sublingual mucosa

The sublingual, buccal, gingival, and palatal areas of the mouth cavity can all facilitate drug absorption. The histological structure, metabolic properties, and ability to hold a dose form for adequate drug absorption differ among these sites. Both local and systemic medication delivery are frequently accomplished through the sublingual membrane, which is situated at the floor of the mouth beneath the tongue. Saliva has a pH of 5.5 to 7. Mucus and enzymes make up saliva. Three separate layers make up the oral mucosal membrane. The epithelium, which acts as a barrier and is composed of stratified squamous epithelial cells, is the outermost layer. The basement membrane, lamina propria, and submucosa are located beneath the epithelium. The lamina propria is a low-density, wet layer of connective tissue. This layer contains collagen and elastic fibers, while the oral submucosa is richly supplied with blood vessels. After absorption through the sublingual mucosa, the drug enters the venous circulation directly and passes through the internal jugular, subclavian, and brachiocephalic veins before reaching the superior vena cava. Unlike orally administered drugs, venous drainage from the sublingual region bypasses hepatic metabolism and enters the systemic circulation directly.

Factors influencing sublingual drug delivery system

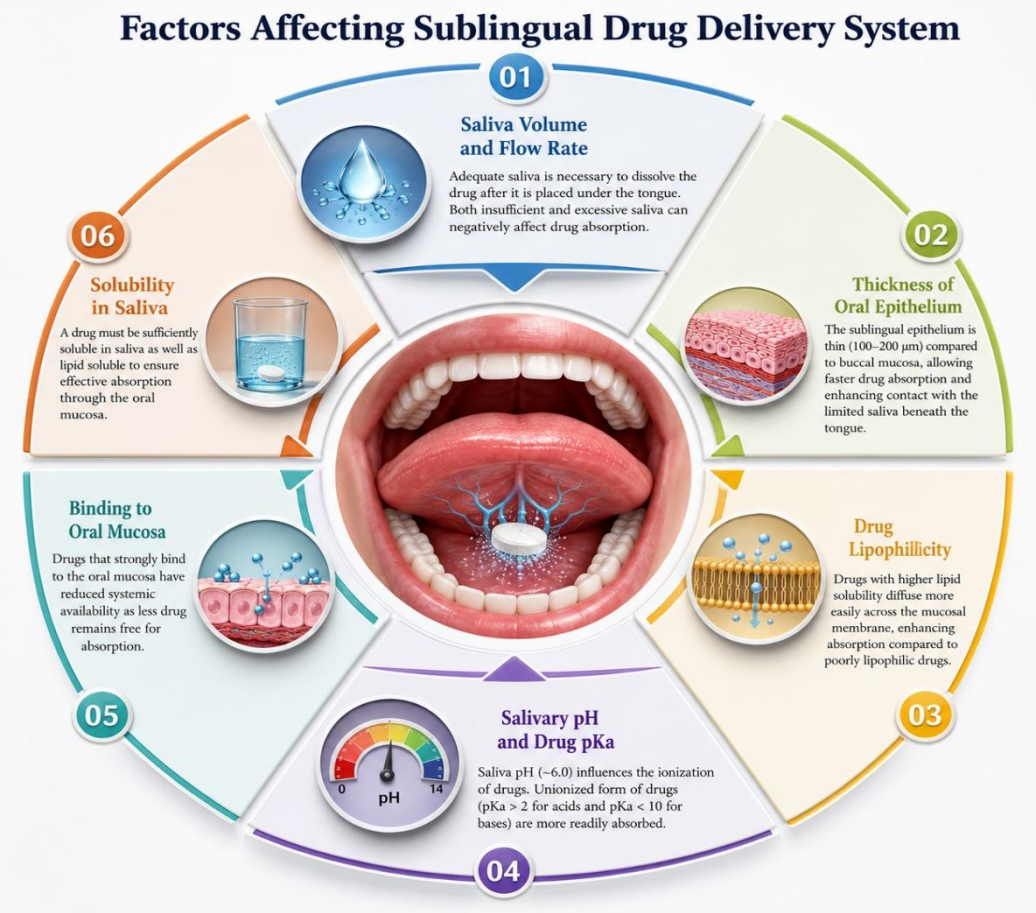

figure 2: factors influencing sublingual drug delivery system [10,11,13,14,17]

Mechanism of sublingual drug absorption

The primary mechanism responsible for drug transport across the sublingual mucosa is passive diffusion, in which unionised, lipophilic drug molecules move across the lipoidal epithelial membrane along a concentration gradient toward the underlying capillary bed.[38] Because the sublingual epithelium is thin, non-keratinised, and richly vascularised, only drugs that possess an adequate balance of lipid solubility and salivary (aqueous) solubility, referred to as biphasic solubility, are absorbed efficiently through this route.[12,38] A smaller subset of small, polar solutes, such as certain sugars and organic acids, cross the epithelium by carrier-mediated transport rather than simple diffusion.[39] Once permeation has occurred, the drug enters the richly anastomosing sublingual venous plexus and drains via the lingual, facial, and internal jugular veins directly into the superior vena cava, thereby bypassing hepatic first-pass metabolism.[38,39] This diffusion-dominated pathway explains the characteristically rapid onset of sublingually administered drugs, while simultaneously restricting the route to potent, low-dose, and moderately lipophilic molecules.[12,39]

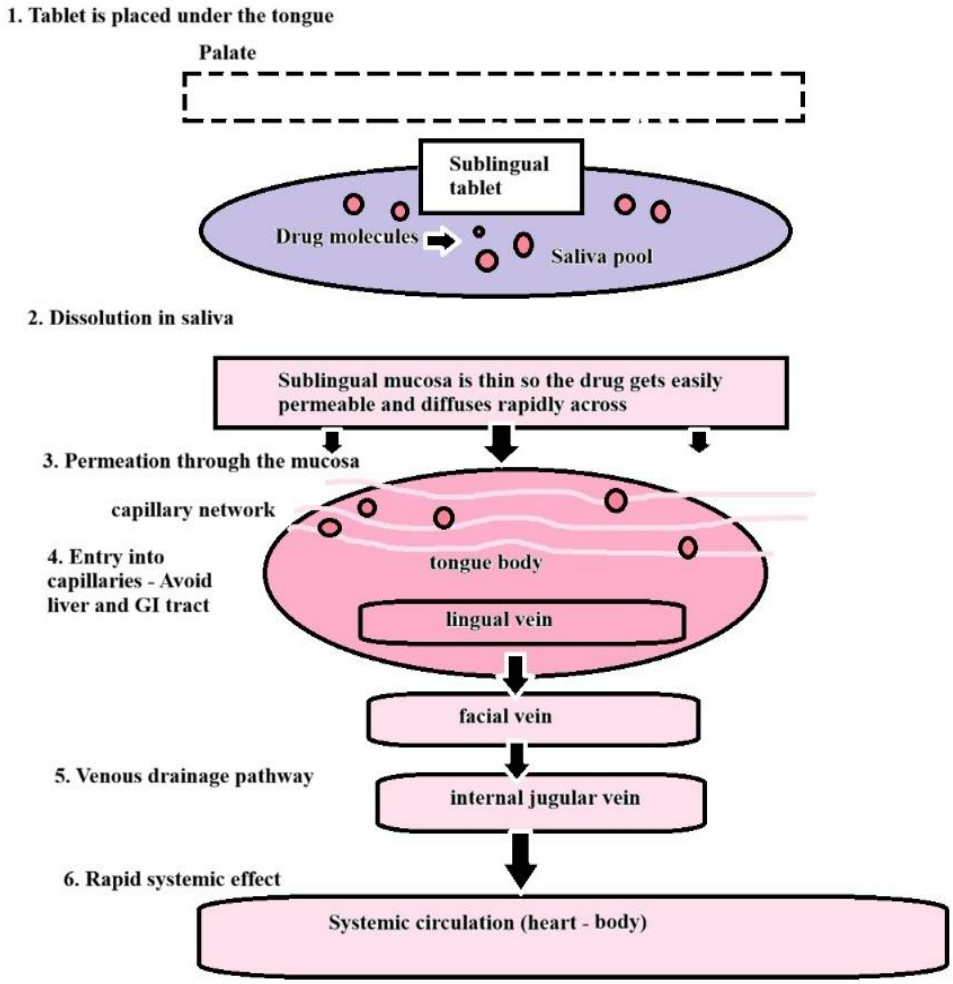

figure 3: mechanism of sublingual absorption

Emerging trends in formulation of sublingual drug delivery system

Nanotechnology

The most interesting drugs delivery now is nano technology. In this method, the drug molecules are encapsulated in tiny carriers called as nanoparticles, nanoemulsions, nanocrystals or lipid nanoparticles.[19] These tiny carriers help to enhance the solubility and absorption of drugs that are poorly soluble in water. Drug delivery systems based on nanotechnology have been extensively investigated to overcome the drawbacks of buccal and sublingual routes, especially for medications with high first-pass metabolism, low permeability, and poor water solubility.[18] Nanoscale formulations improve medication solubility, increase contact with the mucosal surface, and encourage systemic absorption, according to evidence from experimental and review investigations. Nanocrystals are solid particles with nanometric size range between 200–500 nm with crystalline characteristics. It is a simple & effective method which improve bioavailability & dissolution of poorly soluble drugs. Nanocrystals have poor flow properties, which make them difficult to process or handle on a large manufacturing scale.

table 1: recent nanotechnology-based approaches in sublingual drug delivery and their therapeutic applications

Nanomaterial	Drug	Main findings	Therapeutic application	References
Sodium caprate nanocrystals (permeation enhancer)	Canagliflozin	Improvements in sublingual absorption and dissolution rate have been demonstrated by the formulation of nanocrystals. Sodium caprate, a permeation enhancer, has improved mucosal permeability. In vivo research has demonstrated an increase in bioavailability when compared to traditional oral medication delivery.	Diabetes	[20]
Sublingual distribution system based on nanocrystals	Flibanserin	Particle size was decreased, solubility was improved, and the pharmacokinetic profile was improved in the optimised nanocrystal system. Increased bioavailability in comparison to the commercial formulation was validated by in vivo studies.	pre-menopausal female hypoactive sexual desire disorder (HSDD).	[21]
Nanoemulsion based on ascorbyl palmitate	Astaxanthin	Effective sublingual administration with enhanced solubility and absorption was made possible by nanoemulsion. In comparison to traditional formulations, preliminary evidence suggested improved bioavailability.	Nutraceutical	[22]
Polylactic-co-glycolic acid (PLGA) nanoparticles	Glutathione (GSH)	Particle size of 232.57 ± 20.56 nm, zeta-potential of -12.33 ± 0.20 mV, entrapment efficiency of 77.04 ± 1.50 percent, and sustained release profile with a roughly two-fold increase in GSH transmucosal penetration	Sublingual antioxidant delivery with enhanced retention time and sustained drug release profile.	[23]

		(21.9 ± 1.2 percent drug permeation).		
Poly(ε-caprolactone) (PCL) with Eudragit RS 100 nanocapsules	Carvedilol	PCL-nanocapsules demonstrated slower drug diffusion flux than EUD-nanocapsules, spray-dried redispersible nanocapsules with recovery of original nanoparticle properties after drying, improved carvedilol permeation across porcine sublingual mucosa, and increased retention on sublingual mucosa in the presence of simulated salivary flux.	Innovative sublingual solid dose formulations are made possible by sublingual antihypertensive medication administration with enhanced permeability and mucoadhesive qualities .	[24]
Pullulan films containing muco-inert resveratrol-BSA nanoparticles and tamarind seed polysaccharide (TSP)	Resveratrol and Bovine serum albumin (BSA)	Muco-inert resveratrol-BSA nanoparticles showed 3.6 times higher mucus penetration than free drugs, 5% nanoparticle addition dramatically increased initial swelling capacity (435% at 2 min vs 284% at 2 min for TSP-Pul alone), films completely disintegrated within 60 min with accelerated release of both compounds within first 2 hours	Peptides and phytocompounds can be co-delivered sublingually to improve mucosal absorption and extend residence duration.	[25]
Electrospun nanofibers of α-cyclodextrin and polyvinyl alcohol (PVA)	Ondansetron hydrochloride	With a mean fibre diameter of 159 ± 30 nm, electrospun sublingual nanofibers demonstrated good mechanical qualities, quick disintegration, and acceptable physicochemical features. An antiemetic effect similar to oral disintegrating tablets (ODTs) was shown in clinical evaluation, and patient satisfaction was considerably higher ($P < 0.05$).	Ondansetron can be quickly administered sublingually to prevent and cure postoperative nausea and vomiting (PONV); it may be used in individuals who are dysphagic, elderly, or young and need quick pharmacological action.	[26]
Electrospun nanofibers of	Model drug study	Excellent mucoadhesive qualities were shown by	Improved mucosal residence duration with	[27]

chitosan and polyethylene oxide (PEO)	(mucoadhesion evaluation)	chitosan nanofibers; mucoadhesion was linked to swelling capacity; a degree of deacetylation (DDA) of 53–96% enhanced morphological stability in water with robust intermolecular interactions with mucin.	a sublingual medication delivery platform that addresses mucoadhesion issues	

3D Printing

3D printing makes it easier to create personalized medicines. It is also called as additive manufacturing method, which means addition of material layer by layer to create a tablet. FDM based 3D printing has limited drug loading capacity. By using same machine we can prepare different shapes & sizes of tablets. Different specific shapes release medicine slowly or in a special way. There is no need to make big changes to the setup. Different types of materials can be used to make one tablet.

table 2: 3d printing strategies for sublingual drug delivery: formulation design and performance outcomes

3D Printing Technology	Drug/Active	Main Findings	Therapeutic Application	Ref. No.
Melting Solidification Printing Process (MESO-PP)	Domperidone (DOM) nanocrystals	DOM-NC formulations demonstrated enhanced saturation solubility in both water and simulated saliva, as well as quick disintegration in simulated saliva without physicochemical alterations. Improved drug-release profiles were attained by quickly dissolving solid dose formulations.	Sublingual administration to enhance DOM solubility and prevent excessive metabolism; management of gastrointestinal problems, nausea, and vomiting	[28]
3D Scaffold with Freeze-Drying (In Situ Loading)	Atorvastatin nanocrystals (ATV-NCs)	Gyroid scaffolds with a 20 percent infill pattern had the largest nanocrystal load (13.8 ± 0.5 mg) while maintaining nanometric size, and they dissolved completely in 180 seconds. Studies on colloidal stability revealed that the sublingual route was not appropriate in acidic media.	Sublingual delivery system for lipid-lowering medication that avoids the stomach and hepatic first-pass metabolism.	[29]

Microrobotics sublingual pills

Microrobotic sublingual pills represent a novel advancement in sublingual drug delivery systems. In 2025, Askarinam et al. developed the first magnesium-based microstirring sublingual pill designed to enhance drug release and absorption through active hydrodynamic mixing.[30] The formulation incorporated magnesium-gold (Mg/Au) microstirrers that generated hydrogen microbubbles upon contact with saliva, resulting in accelerated tablet disintegration and improved drug transport across the sublingual mucosa. In vivo studies using epinephrine demonstrated significantly higher bioavailability and faster drug absorption compared with conventional sublingual tablets. Although this technology remains in the experimental stage, it has considerable potential for emergency drug delivery applications such as anaphylaxis, cardiac emergencies, and acute pain management.

Challenges In Sublingual Drug Delivery

Sublingual drug delivery isn't without its problems, and several formulation and physiological hurdles still stand in the way of wider clinical use. For one, saliva doesn't stay still — constant secretion and the natural urge to swallow can wash the dose away from the absorption site before it has fully permeated.[10] The sublingual mucosa also has a fairly small surface area and can only hold so much drug at a time, which is why this route works best for potent, low-dose medications and struggles with therapies that need large or sustained blood levels.[16] Bigger, water-loving, or poorly soluble molecules — peptides, proteins, and oligonucleotides in particular — are especially hard to deliver this way, since passive diffusion across the lipoidal epithelium simply isn't efficient for them.[33] On top of that, people don't all produce saliva the same way: differences in pH, flow rate, and mucosal thickness from one person to the next mean absorption and bioavailability can vary quite a bit.[10] There are practical headaches too — bad taste, mucosal irritation, and the need for the dosage form to disintegrate almost instantly all add pressure on excipient choice and formulation design.[16] Getting past these limitations will likely depend on continued progress in permeation enhancers, mucoadhesive polymers, and next-generation nanocarrier or microrobotic platforms that can actively push drug transport across the sublingual mucosa rather than relying on diffusion alone.[33,37]

CONCLUSION

By enhancing drug stability, solubility, and residence time within the oral cavity, cutting-edge technologies like nanoencapsulation, mucoadhesive films, multilayered tablets, 3D-printed dosage forms, nanoparticle sprays, and microrobotic pills have dramatically changed sublingual drug administration.[31] An important development is the incorporation of nanoparticles into orodispersible film (ODF) formulations, which allows for multilayer approaches that separate incompatible drugs and improve permeation across mucosal barriers, especially for oligonucleotides, fragile proteins, and high-molecular-weight polar drugs. [32] In addition to being non-toxic, biocompatible, and biodegradable, oromucosal drug delivery systems based on mucoadhesive biopolymers and their derivatives—particularly thiolated and catecholated derivatives—offer extended residence times, unidirectional and modified drug release capabilities, and improved drug permeability. Nanoparticles, multilayered mucoadhesive systems, paediatric formulations such as fast-dissolving films and tablets, immunotherapy and vaccine delivery, and innovative formulations spanning a wide range of therapeutic agents have all been widely used throughout the innovation and integration phase (2010–2025). While addressing issues like drug stability and taste masking, new developments in sublingual formulations—such as nanoencapsulation, fast-dissolving tablets, and sublingual films—along with personalised medicine strategies and the incorporation of digital health technologies for dose monitoring continue to improve medication performance and patient compliance.[35] Future advancements in nanocarrier systems, bioadhesive polymers, and permeation enhancers are expected to promote more efficient and patient-focused techniques while providing accurate targeting, controlled release, and enhanced therapeutic outcomes

in mucosal drug delivery systems.[36] Sublingual and buccal administration are two of the most advantageous mucosal delivery methods for avoiding first-pass metabolism and gastrointestinal degradation. Nevertheless, successful clinical translation necessitates ongoing progress in overcoming mucosal barriers, especially for newly developed large biological macromolecules like proteins, peptides, and RNA therapeutics.[37]

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