FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF VORTIOXETINE HBr FOR AVOIDANCE OF FIRST-PASS METABOLISM

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ABSTRACT: The oral route is the most common way to deliver drugs, but traditional pills and capsules can be slow to take effect and lose potency due to stomach acids and liver processing. To overcome these challenges, the sublingual route placing a tablet under the tongue—has emerged as a powerful alternative. It allows for rapid absorption directly into the bloodstream, avoiding digestive breakdown and first-pass metabolism. This review explores sublingual tablet drug delivery in detail. It starts by examining the structure and function of the sublingual mucosa and the principles of drug absorption through this membrane. The benefits of this approach, such as faster action, better bioavailability, lower doses, and improved patient convenience, are weighed against its limitations, including taste issues, dosage constraints, and variations in saliva. The ideal drug properties for sublingual delivery and analyze the critical role of formulation ingredients like super disintegrants, fillers, sweeteners, and flavouring agents. The discussion covers common manufacturing methods, including direct compression and effervescent systems, along with key factors for optimizing tablet performance. The review also highlights recent innovations, clinical applications, and commercially available sublingual products. Finally, it considers future directions for this field.

Keywords: Vortioxetine, Sublingual Tablets, mannitol, solid dispersion, taste masking, First pass Metabolism

INTRODUCTION

Major depressive disorder (MDD) is a chronic and recurrent psychiatric illness characterized by persistent low mood, loss of interest, cognitive impairment, and reduced quality of life. Vortioxetine hydrobromide is a novel multimodal antidepressant that acts as a serotonin reuptake inhibitor and modulator of multiple serotonin receptor subtypes. It is clinically effective in the management of MDD and is well known for improving cognitive dysfunction associated with depression. However, after conventional oral administration, vortioxetine undergoes extensive hepatic first-pass metabolism, which can reduce systemic bioavailability and delay the onset of therapeutic action.

The oral route remains the most convenient and commonly used route of drug administration. However, conventional oral tablets and even fast-dissolving tablets deliver the drug to the gastrointestinal tract, where it is subjected to enzymatic degradation and significant first-pass metabolism in the liver. This metabolic loss not only reduces bioavailability but also contributes to inter-individual variability in drug response and delays therapeutic onset. Therefore, alternative drug delivery strategies capable of bypassing hepatic metabolism are highly desirable, particularly for drugs requiring rapid systemic action at low doses.

The sublingual route of drug administration offers a distinct advantage by allowing the drug to be absorbed directly into the systemic circulation through the sublingual mucosa, thereby

bypassing the gastrointestinal tract and hepatic first-pass metabolism. The sublingual region is highly vascularized, possesses a thin epithelial membrane, and provides excellent permeability for lipophilic drugs. As a result, drugs administered via this route exhibit rapid absorption, faster onset of action, improved bioavailability, and reduced dose variability compared to conventional oral delivery systems.

Sublingual tablets are specifically designed to disintegrate rapidly in small volumes of saliva and release the drug directly for transmucosal absorption. Unlike orally disintegrating tablets, which mainly depend on gastrointestinal absorption after swallowing, sublingual tablets aim for direct systemic delivery through the oral mucosa. This makes the sublingual route especially suitable for drugs intended for rapid therapeutic action and for molecules that undergo extensive first-pass metabolism, such as vortioxetine.

In addition to rapid absorption, patient acceptability and palatability play a crucial role in the success of sublingual dosage forms. Since the tablet remains under the tongue for sufficient time to allow absorption, taste masking becomes essential. The incorporation of sweetening agents such as sodium saccharin and flavoring agents like menthol not only improves palatability but also enhances saliva secretion, thereby aiding faster disintegration and dissolution of the tablet.

Based on these considerations, the present study was designed to formulate and evaluate sublingual tablets of vortioxetine hydrobromide with the objective of avoiding hepatic first-pass metabolism, enhancing bioavailability, and ensuring rapid onset of antidepressant action. The formulation approach involves the use of suitable superdisintegrants, palatability enhancers, and optimized excipient combinations to achieve rapid disintegration, acceptable mechanical strength, efficient drug release, and effective transmucosal permeation

Anatomy and Physiology of Sublingual Mucosa

The sublingual mucosa refers to the specialized tissue lining the floor of the oral cavity beneath the tongue. Anatomically, this region is distinct from other parts of the oral cavity such as the hard palate and gingiva, which are keratinized and primarily adapted to withstand mechanical stress. In contrast, the sublingual mucosa is composed of non-keratinized stratified squamous epithelium, lacking the protective keratin layer that normally acts as a diffusion barrier. The absence of keratin results in a relatively thin and flexible membrane, a feature that significantly enhances its permeability and makes it highly suitable for transmucosal drug delivery. One of the most important anatomical characteristics of the sublingual mucosa is its minimal epithelial thickness. It is among the thinnest mucosal surfaces in the human body, providing a short diffusional path for drug molecules to cross the epithelial barrier. Although the available surface area under the tongue is comparatively limited, its high permeability effectively compensates for this constraint, allowing rapid absorption of suitable drug molecules. https://doi.org/10.3390/pharmaceutics17091212 This unique structural arrangement makes the sublingual region an efficient site for systemic drug administration, particularly for potent drugs administered in low doses. From a physiological perspective, the sublingual mucosa is highly vascularized, containing a dense network of capillaries and larger blood vessels, including branches of the sublingual artery. This rich blood supply plays a crucial role in maintaining a steep concentration gradient that favors rapid drug diffusion across the mucosal membrane. Once absorbed, drugs enter the venous circulation through the sublingual and deep lingual veins, which drain directly into the internal jugular vein and subsequently into the superior vena cava. https://doi.org/10.3390/pharmaceutics17020148

Principle of Sublingual Drug Absorption

In addition to conventional oral drug delivery, absorption through the oral mucosa represents an important alternative route in pharmacotherapy. The oral cavity is lined by a structurally diverse mucosal membrane, the characteristics of which vary according to regional function. Beneath the tongue, the sublingual mucosa consists of a superficial epithelial layer supported by the basement membrane, lamina propria, and submucosa, which together contain blood vessels, minor salivary glands, and sensory receptors. This structural organization plays a decisive role in determining the efficiency of drug absorption. Sublingual drug delivery shares several advantages with traditional oral administration, such as high patient acceptability, ease of use, and low cost, while offering additional therapeutic benefits. Medications administered sublingually do not require swallowing or water for intake, making them especially useful for patients with dysphagia. More importantly, drugs absorbed through the sublingual mucosa bypass the gastrointestinal tract and hepatic first-pass metabolism, allowing direct entry into the systemic circulation. As a result, a faster onset of action and improved bioavailability can be achieved compared to conventional orally swallowed dosage forms. https://doi.org/10.1016/j.jsps.2022.07.004

Drug absorption from the sublingual region is primarily influenced by physiological and physicochemical factors. After placement beneath the tongue, the dosage form dissolves in saliva, releasing the active pharmaceutical ingredient, which then permeates across the mucosal barrier into the underlying vascular network. Saliva plays a crucial role by providing the dissolution medium and maintaining an environment suitable for drug stability. Although the fluid volume in the oral cavity is relatively low (approximately 1 mL), the pH remains within a narrow and favorable range (5.5–7.0), and enzymatic activity is significantly lower than in the gastrointestinal tract. This environment reduces the risk of enzymatic degradation, particularly for peptide and protein-based drugs. The permeability of the sublingual mucosa is significantly higher than that of keratinized oral regions and the skin. This enhanced permeability is attributed to the non-keratinized nature of the epithelium and its relatively thin structure, which reduces diffusional resistance. Drug permeation across the sublingual mucosa occurs mainly via passive diffusion through either the transcellular or paracellular pathways. https://doi.org/10.1016/j.ijpharm.2020.119807 Hydrophilic drugs tend to permeate through aqueous intercellular spaces, while lipophilic molecules preferentially traverse the lipid-rich cell membranes. In certain cases, carrier-mediated transport mechanisms have also been reported, involving specific uptake or efflux transporters present on epithelial cell membranes. Despite these advantages, several physiological factors can influence the extent of sublingual absorption. Variations in saliva flow may lead to premature swallowing of the drug, a phenomenon known as saliva washout, which can reduce absorption efficiency. The mucus layer covering the mucosa, composed mainly of mucin glycoproteins, may also act as a diffusional barrier https://doi.org/10.4103/0250-474x.180244 . Additionally, the rapid turnover of epithelial cells in the oral cavity, occurring approximately every 14–21 days, reflects the dynamic nature of this tissue and may influence drug transport characteristics.

Overall, the principle of sublingual drug absorption is based on rapid dissolution in saliva, efficient permeation through a thin and highly vascularized mucosal membrane, and direct transport into the systemic circulation. These features make the sublingual route particularly suitable for potent drugs requiring rapid therapeutic action and avoidance of hepatic first-pass metabolism. https://doi.org/10.3390/pharmaceutics17020148

Advantages of Sublingual Drug Delivery System

The sublingual route of drug administration offers several therapeutic and patient-related advantages that distinguish it from conventional oral dosage forms. These benefits primarily arise from the unique anatomical and physiological features of the sublingual mucosa, which enable rapid and efficient systemic drug absorption. One of the most significant advantages of sublingual drug delivery is the avoidance of hepatic first-pass metabolism. Drugs absorbed through the sublingual mucosa enter the systemic circulation directly via the venous drainage of the oral cavity, thereby bypassing the gastrointestinal tract and liver. This results in higher bioavailability and allows a greater proportion of the administered dose to remain pharmacologically active compared to swallowed oral formulations https://doi.org/10.1038/s41575-021-00539-w . The rapid onset of action is another major benefit of sublingual administration. Due to the thin, non-keratinized epithelium and rich vascularization of the sublingual region, drugs can be absorbed quickly into the bloodstream. This makes sublingual dosage forms particularly useful in conditions where immediate therapeutic effect is required, such as cardiovascular emergencies, pain management, and acute neurological disorders. Sublingual delivery also enables reduction in dose size, as improved bioavailability often allows lower drug quantities to achieve the desired therapeutic effect. Reduced dosing can minimize systemic side effects and improve overall safety, especially for potent drugs with narrow therapeutic windows. https://doi.org/10.22214/ijraset.2024.58175

From a patient perspective, sublingual tablets offer enhanced convenience and compliance. They do not require water for administration and are easy to use, making them suitable for pediatric, geriatric, and dysphagic patients. This route is also beneficial for patients experiencing nausea or vomiting, where swallowing conventional tablets may be difficult. Another important advantage is the protection of drugs from gastrointestinal degradation. Drugs administered sublingually are not exposed to the acidic gastric environment or digestive enzymes of the gastrointestinal tract, which is particularly advantageous for acid-labile molecules and peptides that are otherwise unstable when administered orally https://doi.org/10.1055/a-2560-9884 . Sublingual drug delivery provides flexibility in dosage form design, allowing the development of tablets, films, sprays, and drops. This versatility enables formulation scientists to tailor products according to therapeutic needs and patient preferences. Additionally, rapid disintegration and dissolution under the tongue contribute to improved patient acceptability when combined with appropriate taste-masking strategies. The sublingual drug delivery system offers a combination of pharmacokinetic, therapeutic, and patient-centric advantages, making it a valuable alternative to conventional oral administration for achieving rapid, efficient, and reliable systemic drug delivery.

Limitations and Challenges of Sublingual Tablets

Despite their advantages, sublingual tablets present several limitations that must be addressed during formulation and use. The limited surface area of the sublingual region restricts drug loading, making this route suitable mainly for potent drugs administered in low doses. Taste masking remains a major challenge, as prolonged contact with taste buds can reduce patient compliance, especially in pediatric and geriatric populations. https://doi.org/10.3389/fphar.2019.01328

Variability in saliva flow and composition may lead to premature swallowing of the drug, reducing transmucosal absorption and causing inconsistent therapeutic outcomes. Additionally, the short residence time under the tongue can limit drug absorption unless specialized formulation strategies are employed. Drug-related factors such as poor solubility, instability in saliva, or mucosal irritation may further compromise effectiveness. From a formulation

standpoint, achieving a balance between rapid disintegration and adequate mechanical strength is also challenging. These factors highlight the need for careful drug selection and formulation optimization in sublingual tablet development. https://doi.org/10.3390/pharmaceutics17020256

Excipients Used in Sublingual Tablets

Excipients play a critical role in the successful design of sublingual tablets, as they directly influence disintegration behavior, drug release, absorption, stability, and patient acceptability. Since sublingual tablets are intended to disintegrate rapidly in a small volume of saliva and remain in contact with the mucosa for effective absorption, careful selection of excipients is essential. The excipients used must ensure rapid wetting and disintegration, pleasant mouthfeel, minimal irritation, and adequate mechanical strength. The major categories of excipients commonly employed in sublingual tablet formulations are discussed below.

Superdisintegrants

Superdisintegrants are key excipients in sublingual tablets, as they promote rapid tablet breakup upon contact with saliva. Their primary function is to facilitate quick penetration of saliva into the tablet matrix, leading to swelling, wicking, or deformation of the tablet structure. Rapid disintegration is crucial for sublingual formulations to ensure fast drug release and subsequent transmucosal absorption. Commonly used superdisintegrants include crospovidone, croscarmellose sodium, and sodium starch glycolate. Crospovidone acts mainly by capillary action and has minimal gelling tendency, making it particularly suitable for sublingual tablets. Croscarmellose sodium swells rapidly in the presence of moisture, while sodium starch glycolate exhibits high swelling capacity. The concentration and combination of superdisintegrants must be optimized, as excessive amounts can negatively affect tablet hardness and mouthfeel.

Diluents

Diluents, also known as fillers, are used to increase the bulk of sublingual tablets and improve compressibility, especially when the drug dose is low. In sublingual formulations, diluents are selected not only for their compressional properties but also for their effect on mouthfeel and palatability. Mannitol is the most commonly used diluent in sublingual tablets due to its pleasant cooling sensation, non-hygroscopic nature, and good solubility in saliva. Lactose and microcrystalline cellulose are also used, either alone or in combination, to enhance tablet strength and uniformity. Mannitol is particularly preferred because it dissolves quickly in saliva, contributing to rapid tablet disintegration and improved patient acceptance. The choice of diluent significantly influences tablet porosity, disintegration time, and overall sensory perception.

Sweetening Agents

Sweetening agents are essential components of sublingual tablets to improve palatability and mask the unpleasant taste of many active pharmaceutical ingredients. Since sublingual tablets remain in close contact with taste buds during administration, inadequate taste masking can lead to poor patient compliance. Both natural and artificial sweeteners are used in sublingual formulations. Commonly employed sweeteners include sodium saccharin, aspartame, sucralose, and acesulfame potassium. Sodium saccharin is widely used due to its high sweetness intensity and stability over a wide pH range. Artificial sweeteners are often preferred over sugars to avoid excessive tablet weight and caloric intake. Sweeteners are frequently combined with flavoring agents or advanced taste-masking techniques to achieve optimal sensory acceptability without compromising tablet performance.

Flavoring Agents

Flavoring agents are added to sublingual tablets to enhance patient acceptability and improve the overall sensory experience. These agents help to mask residual bitterness and provide a pleasant

taste and aroma during tablet disintegration. Commonly used flavoring agents include menthol, peppermint oil, spearmint, orange, and lemon flavors. Menthol is particularly popular in sublingual formulations because it produces a cooling sensation and can stimulate saliva secretion, which aids tablet wetting and disintegration. Flavoring agents are usually used in small quantities to avoid irritation of the oral mucosa. The selection of flavor depends on the target patient population, drug taste profile, and compatibility with other excipients. Proper optimization ensures that the flavor enhances acceptability without interfering with drug release or absorption.

Lubricants and Glidants

Lubricants and glidants are necessary to ensure smooth manufacturing and prevent problems during tablet compression. Lubricants reduce friction between the tablet formulation and the die wall, while glidants improve powder flow properties. Magnesium stearate is the most commonly used lubricant in sublingual tablet formulations, although it must be used cautiously, as excessive amounts can create a hydrophobic layer around particles and delay disintegration. Talc and colloidal silicon dioxide are frequently used as glidants to improve powder flow and uniformity. In sublingual tablets, the concentration of lubricants is kept as low as possible to maintain rapid disintegration and dissolution. Proper balancing of lubricants and glidants is essential to achieve acceptable tablet hardness without compromising performance.

Taste Masking Agents

Taste masking agents are particularly important in sublingual tablet formulations due to prolonged exposure of the drug to taste receptors. In addition to sweeteners and flavors, advanced taste-masking techniques are often employed for drugs with strong bitterness. These include ion-exchange resins, solid dispersions, microencapsulation, inclusion complexes with cyclodextrins, and polymer coating. Ion-exchange resins form complexes with the drug, preventing its immediate interaction with taste buds while allowing release in saliva. Solid dispersion techniques improve drug solubility while reducing bitterness. Although these approaches are effective, they can increase formulation complexity and cost. Often, a combination of basic sweetening and advanced taste-masking strategies is used to achieve optimal palatability and patient compliance.

Category	Role in Sublingual Tablets	Key Characteristics / Rationale	Common Examples
Superdisintegrants	Promote rapid tablet disintegration in saliva	Enable fast water uptake by swelling or wicking; essential for quick drug release and absorption through sublingual mucosa	Crospovidone, Croscarmellose sodium, Sodium starch glycolate
Diluents (Fillers)	Increase tablet bulk and improve compressibility	Provide pleasant mouthfeel, enhance tablet porosity, and aid rapid dissolution in small saliva volume	Mannitol, Lactose monohydrate, Microcrystalline cellulose (MCC)
Sweetening Agents	Improve palatability and	High sweetness intensity; reduce bitterness without	Sodium saccharin, Aspartame,

	mask bitter drug taste	increasing tablet size; improve patient compliance	Sucralose, Acesulfame potassium
Flavoring Agents	Enhance sensory acceptance	Mask residual bitterness, provide pleasant aroma and cooling sensation; may stimulate saliva secretion	Menthol, Peppermint oil, Spearmint, Orange flavor, Lemon flavor
Lubricants	Reduce friction during compression	Prevent sticking to punches and dies; used in minimal amounts to avoid delayed disintegration	Magnesium stearate, Stearic acid
Glidants	Improve powder flow properties	Ensure uniform die filling and consistent tablet weight	Talc, Colloidal silicon dioxide
Taste Masking Agents	Reduce direct contact of bitter drug with taste buds	Physically or chemically block drug–taste receptor interaction while allowing release in saliva	Ion-exchange resins (Kyron T-114, T-134), Cyclodextrins
Advanced Taste Masking Techniques	Improve palatability of highly bitter drugs	Used when sweeteners alone are insufficient; enhance patient acceptability	Solid dispersion, Microencapsulation, Spray drying, Inclusion complexes

Evaluation Parameters for Sublingual Tablets

Evaluation of sublingual tablets is essential to ensure product quality, safety, performance, and patient acceptability. Since sublingual tablets are intended to disintegrate rapidly in a small volume of saliva and deliver the drug directly into systemic circulation, both conventional tablet evaluation tests and sublingual-specific parameters are required. These evaluation parameters assess physical integrity, drug content uniformity, disintegration behavior, dissolution performance, and absorption potential.

Weight variation is carried out to confirm uniformity of tablet mass and ensure consistent dosing. Tablets are individually weighed and compared with the average weight according to limits.

Thickness and diameter are measured using a vernier caliper or micrometer screw gauge to ensure uniform tablet size, which affects packaging and patient handling. **Hardness** testing determines the mechanical strength of the tablets. Sublingual tablets require sufficient hardness to withstand handling while still allowing rapid disintegration. **Friability** assesses tablet resistance to abrasion during handling and transport; a friability value below 1% is generally considered acceptable.

Drug content uniformity (assay) ensures that each tablet contains the intended amount of active pharmaceutical ingredient. This test is critical for low-dose sublingual formulations, where dose variation can significantly impact therapeutic efficacy.

Wetting time evaluates the ability of the tablet to absorb saliva quickly, which is an important indicator of rapid disintegration and patient comfort.
In-vitro disintegration time is one of the most critical parameters for sublingual tablets. It measures the time required for the tablet to break down completely in simulated salivary conditions, with typical acceptance criteria being within 2 minutes.
In-vitro dissolution studies are performed to assess the rate and extent of drug release from the tablet. Since sublingual tablets act rapidly, dissolution sampling is often carried out at short time intervals.
Ex-vivo permeation studies using buccal or sublingual mucosa in diffusion cells provide valuable information on drug transport across the mucosal membrane and help predict in-vivo absorption behavior.
Taste evaluation is important due to prolonged contact of the dosage form with taste buds. Sensory evaluation or electronic tongue analysis may be employed to assess palatability.
Stability studies are conducted under ICH guidelines to evaluate the effect of storage conditions on physical appearance, drug content, and performance over time. Together, these evaluation parameters ensure that sublingual tablets possess adequate mechanical strength, rapid disintegration, efficient drug release, and acceptable sensory characteristics, ultimately supporting consistent therapeutic performance.

Conclusion

Sublingual drug delivery systems represent a promising and patient-friendly alternative to conventional oral dosage forms, particularly for drugs that undergo extensive hepatic first-pass metabolism or require rapid onset of action. The unique anatomical and physiological features of the sublingual mucosa—such as its thin, non-keratinized epithelium, high vascularity, and low enzymatic activity—facilitate fast and efficient systemic absorption, leading to improved bioavailability and reduced inter-individual variability in drug response. As highlighted in this review, sublingual tablets are especially suitable for potent, low-dose drugs like vortioxetine hydrobromide, where rapid therapeutic action and enhanced cognitive benefits are clinically desirable in the management of major depressive disorder. The successful development of sublingual tablets depends on careful selection and optimization of excipients, including superdisintegrants, diluents, sweetening agents, flavoring agents, lubricants, and taste-masking agents, to achieve rapid disintegration, acceptable mechanical strength, efficient drug release, and good patient compliance. Although challenges such as limited drug loading capacity, taste masking, saliva washout, and formulation stability persist, advances in formulation technologies and evaluation methodologies have significantly improved the feasibility and reliability of sublingual dosage forms. Overall, sublingual tablets offer a robust platform for rapid and effective systemic drug delivery, and continued research in this area is expected to further expand their clinical applications and therapeutic potential.

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