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Review Article

A Comprehensive Review on Terbutaline Sulphate Tablet in Sublingual Route for The Treatment of Asthma

Chand Ratan Rathi [1], Vijay Sharma [2], N Ravindra [3], Virender Singh [4]

[1] Research Scholar, Goenka College of Pharmacy, Lachhmangarh, Sikar.
[2] Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.
[3] Principal and Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.
[4] Assistant Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.

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Corresponding author: Chand Ratan Rathi
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Abstract:

The demand for fast disintegrating tablets has been growing during the last decade, due to the characteristics of fast disintegrating sublingual tablets for the potential emergency treatment. The sublingual course is a quick onset of activity and preferred patient consistency over orally ingested tablets. Sublingual from the Latin for "under the tongue", alludes to the pharmacological course of the organization by which drugs diffuse into the blood through tissues under the tongue. Sublingual drug delivery can be an alternative and better route when compared to oral drug delivery as sublingually administered dosage forms bypass hepatic metabolism. Rapid onset of pharmacological effect is often desired for some drugs, especially those used in the treatment of acute disorders. Sublingual tablets disintegrate rapidly and the small amount of saliva present is usually sufficient for achieving disintegration of the dosage form coupled with better dissolution and increased bioavailability. Terbutaline is a β2-adrenergic agonist used to treat asthma and COPD. It works by relaxing bronchial smooth muscles, improving airflow.

Keywords: Sublingual Tablets, Better Bioavailability, Fast Disintegration, Tongue, Mucus, terbutaline sulphate.

Introduction

The sublingual route is a promising alternative for systemic drug delivery, offering improved patient compliance, robustness, and accessibility, with the added benefit of easy dose removal in emergencies. This route bypasses the first-pass metabolism, making it ideal for drugs like cardiovascular medications, analgesics, steroids, barbiturates, enzymes, vitamins, peptides, and minerals. Current research focuses on developing advanced delivery systems and enhancing permeation to maximize efficiency. Sublingual delivery ensures rapid absorption and onset of action, making it particularly effective for drugs requiring immediate therapeutic effects, while also improving bioavailability and minimizing metabolic degradation in the liver [1,2]. Research on rapid-release delivery systems focuses on addressing oral cavity disorders for both local and systemic treatment. The unique anatomy and physiology of the sublingual mucosa facilitate efficient drug absorption. Current studies explore mechanisms and strategies for sublingual permeation enhancement to improve drug efficacy. Historical and modern theories of sublingual delivery are reviewed, offering insights into its evolution. Various dosage

forms, including those in development, are also analyzed for their effectiveness and practicality. These advancements highlight the potential of sublingual systems to provide fast, efficient, and patient-friendly drug delivery solutions for diverse therapeutic needs. [3,4]

Sublingual Drug Delivery System

Within the oral mucosal cavity, delivery of drugs is classified into three categories:

Sublingual delivery refers to the systemic administration of drugs through the mucosal membranes under the tongue. This method allows rapid absorption into the bloodstream, bypassing the digestive system and first-pass metabolism in the liver. It provides quick onset of action and is ideal for drugs requiring fast therapeutic effects, such as cardiovascular medications or pain relievers. Sublingual delivery is non-invasive, improves patient compliance, and is particularly useful for drugs that are poorly absorbed orally.

Buccal delivery refers to the administration of drugs through the mucosal membranes of the cheeks. In this method, the drug is placed between the cheek and gum, where it is absorbed directly into the bloodstream through the buccal mucosa. This route bypasses the gastrointestinal tract and first-pass metabolism in the liver, providing rapid onset and increased bioavailability. Buccal delivery is often used for drugs that require steady, prolonged release or for patients who have difficulty swallowing. It is non-invasive, convenient, and can improve patient compliance.

Local delivery refers to the administration of drugs directly into the oral cavity for targeted treatment at a specific site, such as for conditions like oral infections, gum disease, or mouth ulcers. This method allows the drug to act locally without being absorbed into the bloodstream, minimizing systemic side effects. Local delivery forms include gels, lozenges, mouthwashes, and ointments, which are applied directly to the affected area in the oral cavity. This approach offers effective relief and treatment with a higher concentration of the drug at the site of action. [5,6]

Sublingual gland: -

The sublingual glands are salivary glands located in the oral cavity, positioned beneath the mucous membrane of the floor of the mouth and under the tongue, anterior to the submandibular glands. These glands are drained by 8 to 20 excretory channels. The primary duct, known as the sublingual duct (of Bartholin), joins the submandibular duct to discharge saliva through the sublingual caruncle, a small prominence near the base of the tongue. [7,8,9]

The sublingual glands are classified as mixed glands, primarily consisting of mucous acini with serous demilunes. This composition makes them responsible for producing a mucous-rich saliva. Most of the minor sublingual ducts open independently into the oral cavity along the sublingual fold (plica)—a raised ridge of mucous membrane located on either side of the frenulum linguae. [10,11,12]

The secretomotor function of the sublingual glands is controlled by the chorda tympani nerve, a branch of the facial nerve, which relays signals through the lingual nerve. This autonomic innervation facilitates the secretion of saliva, playing a key role in oral lubrication, digestion, and maintaining mucosal health. The anatomical positioning and functional features of the sublingual glands are critical for their role in oral physiology. [13,14]

Benefits of Rapidly Disintegrating Sublingual Tablets: -

- Sublingual administration allows medications to be taken without water, offering convenience and flexibility for use anytime and anywhere, ensuring ease for patients in diverse settings.
- Sublingual tablets enhance bioavailability, especially for insoluble and hydrophobic drugs, by ensuring rapid disintegration and dissolution,

enabling efficient absorption through the mucosa and bypassing gastrointestinal degradation.

- Sublingual tablets offer prolonged stability by retaining their solid dose form until use, combining the stability advantages of solid dosage forms with the enhanced bioavailability benefits of liquid forms.
- Sublingual tablets are ideal for geriatric and pediatric patients with dysphagia and others facing challenges with standard oral forms, including individuals with mental illness, developmental disabilities, noncompliance, restricted liquid intake, or nausea, ensuring convenient and effective administration.
- Sublingual administration is highly effective in situations requiring immediate action, such as motion sickness, acute allergic reactions, or coughing, as it enables rapid drug absorption and a swift onset of therapeutic effects. [7,8]

Limitations of Sublingual Tablets: -

- The tablets often lack sufficient mechanical strength, requiring careful handling to avoid breakage or damage during storage and administration.
- If not properly formulated, the tablets may leave an unpleasant taste or cause a gritty sensation on the tongue, affecting patient comfort and compliance.

Sublingual absorption: -

Sublingual drug delivery, meaning "under the tongue," is a method of administering medications orally for rapid absorption into the bloodstream through the highly vascularized sublingual mucosa. Unlike traditional oral routes, sublingual delivery bypasses the digestive system and liver metabolism, enabling direct systemic circulation and faster therapeutic effects.

This technique is widely used in medicine for delivering cardiovascular drugs, steroids, barbiturates, and enzymes. Additionally, it has proven effective for rapidly absorbing vitamins and minerals, offering direct nutritional benefits. Sublingual absorption is particularly beneficial for individuals with gastrointestinal disorders, such as ulcers, celiac disease, or compromised digestion, as it avoids gastric degradation and ensures optimal nutrient delivery. Elderly patients and those with reduced digestive function also benefit from this efficient delivery system.

By circumventing the digestive tract, sublingual drug delivery provides a reliable and effective method for improving bioavailability, making it a practical solution for systemic administration, particularly when gastrointestinal factors might otherwise hinder absorption.[10,11]

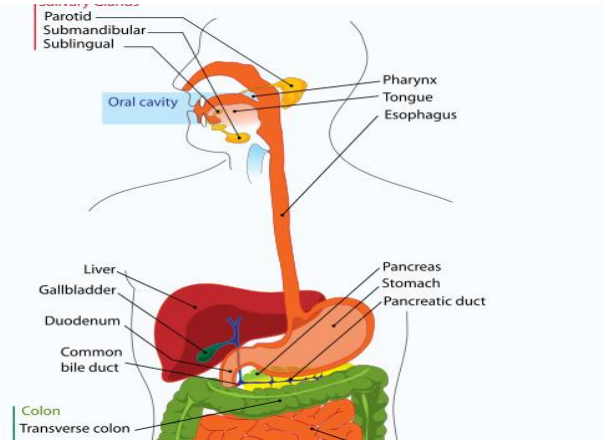

Figure 1. sublingual gland and GIT

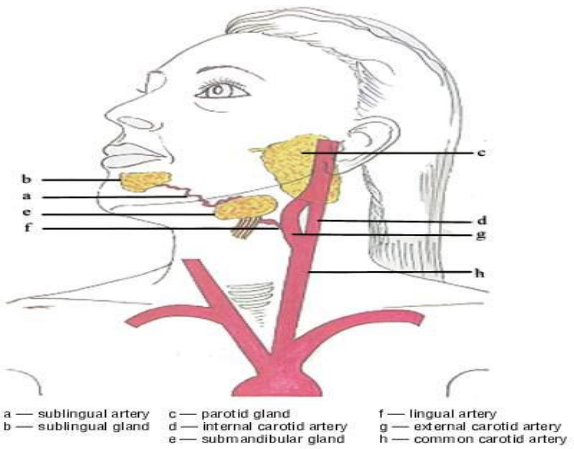

Figure 2. Sublingual Glands

Bronchial Asthma: -

Asthma is a chronic condition marked by intermittent and reversible airway obstruction, triggered by non-harmful stimuli that do not affect non-asthmatic individuals. Patients typically experience episodes of shortness of breath, wheezing, and coughing. It affects over 5% of the population in developed countries, with increasing prevalence and severity. Despite the availability of numerous therapies, asthma-related mortality continues to rise. Experts suggest that this may be due to underutilization of existing treatments and insufficient awareness of recent advances in asthma pathophysiology and management. [12,13]

Asthma is characterized by two key features: bronchial hyperresponsiveness and inflammatory changes in the airways. These alterations in the airways are often linked to bronchial hyperresponsiveness, which can be present even in individuals with moderate asthma and may precede the development of full-blown asthma. Bronchial hyperresponsiveness refers to an exaggerated sensitivity to various stimuli, such as irritants, cold air, and certain medications. Asthma episodes can be triggered by numerous factors, including allergens (in sensitized individuals), physical exercise (often triggered by cold air), respiratory infections, and environmental pollutants like sulfur dioxide. These triggers contribute to the onset and worsening of asthma symptoms in susceptible individuals. [14,15]

An asthmatic attack typically consists of two main phases:

- Early Phase (Immediate Phase): This phase occurs within minutes of exposure to an asthma trigger (such as allergens, irritants, or exercise). It involves the immediate release of inflammatory mediators like histamines, leukotrienes, and prostaglandins, leading to smooth muscle contraction, bronchoconstriction, and increased mucus production. As a result, the airways narrow, causing symptoms like wheezing, shortness of breath, and coughing. This phase is usually rapid in onset and can last for several hours.
- Late Phase (Delayed Phase): This phase occurs 4 to 6 hours after the initial exposure and is characterized by prolonged inflammation in the airways. It involves the infiltration of inflammatory cells, including eosinophils, neutrophils, and T lymphocytes, which lead to further airway edema, mucus hypersecretion, and bronchoconstriction. The late phase exacerbates symptoms, contributing to sustained airway narrowing, coughing, and increased bronchial hyperresponsiveness. It can last for days if untreated, and is often more difficult to manage without proper intervention. [16,17]

Drugs Used to Treat Asthma: -

Bronchodilator Drugs: -

β2-adrenoceptor agonists are the primary pharmacological agents used for treating the acute phase of an asthma attack, functioning through a dual mechanism. The most significant effect is the bronchodilation achieved by direct stimulation of the β2-adrenoceptors on bronchial smooth muscle, which alleviates bronchospasm regardless of the spasmogen involved. These agents also help by reducing mediator release from mast cells and modulating vagal tone, further contributing to symptom relief. Salbutamol and terbutaline are the most commonly used β2-adrenoceptor agonists, typically administered via inhalation through aerosol, powder, or nebulized solutions. In more severe asthma attacks, these medications can be given parenterally for faster action.

Xanthine Drugs-

Three pharmacologically active naturally

occurring methylxanthines include theophylline, theobromine, and caffeine, with theophylline being the most commonly used in clinical practice for asthma management. Theophylline, chemically known as 1,3-dimethylxanthine, is often administered as aminophylline (theophylline ethylenediamine), which is more soluble and used for intravenous treatments. Caffeine and theophylline are components of common beverages like coffee and tea, while theobromine is primarily found in chocolate. Both theophylline and aminophylline have bronchodilatory effects, though they are less potent than beta-adrenergic agonists. [18,19]

Terbutaline Sulphate

Terbutaline is a β2-adrenergic agonist used to treat asthma and COPD. It works by relaxing bronchial smooth muscles, improving airflow. Available in oral, inhaled, and injectable forms, it provides rapid relief, with effects lasting 3-5 hours. Common side effects include tremors, palpitations, and headache**.**

Clinical uses

Terbutaline is primarily used for the management and treatment of asthma, chronic obstructive pulmonary disease (COPD), and other conditions involving bronchospasm. Its clinical uses include:

- Acute asthma attacks: It acts as a bronchodilator to relieve symptoms of wheezing, shortness of breath, and chest tightness.
- Exercise-induced bronchoconstriction: Terbutaline can be used to prevent bronchospasm triggered by physical exertion.
- Chronic obstructive pulmonary disease (COPD): It helps in managing symptoms like wheezing and difficulty breathing in patients with COPD.
- Premature labor: It is sometimes used off-label to delay preterm labor by relaxing uterine smooth muscle.

Terbutaline provides quick relief and is often used as a short-acting bronchodilator or in combination with other treatments. [20,21]

Mode of action

Terbutaline works by stimulating the beta-2 adrenergic receptors on the smooth muscles of the airways. This leads to the activation of adenylate cyclase, which increases cyclic AMP (cAMP) levels in the cells. Elevated cAMP causes the smooth muscle to relax, resulting in bronchodilation, or the widening of the airways.

This bronchodilation helps to relieve the symptoms of asthma, chronic obstructive pulmonary disease (COPD), and other conditions associated with bronchoconstriction, such as wheezing, shortness of breath, and chest tightness.

Additionally, terbutaline has some anti-inflammatory effects, reducing the release of inflammatory mediators like histamine and leukotrienes from mast cells and other immune cells. This contributes to its overall therapeutic effect in asthma and related respiratory conditions.

Terbutaline is often used as a short-acting beta-agonist (SABA) for quick relief during acute asthma attacks. [22,23]

Pharmacokinetic data

The pharmacokinetics of terbutaline involve its absorption, distribution, metabolism, and excretion:

Absorption:

Terbutaline is well absorbed when administered via oral, inhalation, or subcutaneous routes. However, it is subject to first-pass metabolism when taken orally, which can reduce its bioavailability. Inhaled terbutaline bypasses this first-pass effect, leading to a higher concentration reaching the lungs.

Distribution:

After absorption, terbutaline is distributed

throughout the body. It is moderately bound to plasma proteins (about 60–80%). Terbutaline crosses the placenta and is also excreted in small amounts in breast milk.

Metabolism:

Terbutaline undergoes hepatic metabolism, primarily by glucuronidation and to a lesser extent by sulfation. The metabolites are pharmacologically inactive.

Elimination:

Terbutaline is primarily excreted renally (through urine) as its inactive metabolites. The half-life of terbutaline is relatively short, around 3 to 6 hours, which is why it is often used as a short-acting beta-agonist for quick relief.

The pharmacokinetic profile of terbutaline supports its use in both quick-relief treatments and for ongoing management, particularly in inhaled form for more targeted delivery. [24,25]

Adverse effects

The adverse effects of terbutaline are primarily due to its action on β2-adrenergic receptors, and some spillover effects on β1-receptors, especially at higher doses. Monitoring is crucial when administering terbutaline, particularly in high-risk populations or when used in higher doses. [26,27]

Summary And Conclusion

This study focused on formulating sublingual tablets by selecting appropriate diluents, super disintegrants, preparation methods, and permeation enhancers. The evaluation involved assessing disintegration time, hardness, friability, wetting time, percentage permeability, in vitro dissolution time, content uniformity, and drug content. The review states that a number of sublingual manufacture in various technologies. The study let out that sublingual tablets are proved better for asthma patient compliance and a better way of drug delivery for pediatrics and geriatrics patients. and it also gives the rapid on set of action because of the systemic circulation through capillaries present in the sublingual cavity. these tablets overcome the difficulties in swallowing.

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