GENERAL INTRODUCTION

Asthma is defined as a chronic inflammatory disease of the airways. Inflammation is usually associated with airway hyperresponsiveness (an exaggerated airway narrowing response to triggers, such as allergens and exercise). This leads to recurrent symptoms such as wheezing, dyspnea (shortness of breath), chest tightness and coughing. Symptom episodes are generally associated with widespread, but variable, airflow obstruction within the lungs that is usually reversible either spontaneously or with appropriate asthma treatment ***(Shah et al., 2010).***

Asthmatics usually have airway hyper responsiveness, variable airflow obstruction, episodes of wheezing, breathlessness, and cough. Asthma is widespread for all classes of age, including the elderly and children ***(Melani, 2013)***.

Asthma symptoms and exacerbations are linked with significant morbidity. Asthma causes that more than 14.5 million workdays and 14 million schooldays are missed. Yearly, there are almost 2 million emergency department (ED) cases and 500, 000 hospitalizations for this disease. Asthma negatively affects quality of life. The changing pattern of the disease control reflects both the exposure to triggers and adherence with controller medications ***(Stempel et al., 2005)***.

Physician can diagnose asthma in many cases on the basis of the characteristic findings in a patient's clinical history and examination. Asthma is strongly supposed if a patient suffers from allergic conditions as eczema or has a family history of asthma. Diagnosis in adults can be done through measurement of airway function as it is possible for adults, while children who are unable to perform such tests. Diagnosis is based on a careful collection and analysis of the patient's medical history ***(Prabakaran et al., 2004)***.

Classification of asthma:

The classification is according to severity which is evaluated by symptoms and lung function tests.

1) Intermittent persistent asthma

- Symptoms: Less than 2 days a week and don't interfere with normal activities.
- Nighttime symptoms: Less than 2 days a month.
- Lung function tests: Both forced expiratory volume (FEV1) and peak expiratory flow rate (PEFR) >80%.

2) Mild persistent asthma

- Symptoms: More than 2 days a week but do not occur every day.
- Attacks interfere with daily activities.
- Nighttime symptoms occur more than twice a month (3-4 times).
- Lung function tests: Both FEV1 and PEFR>80% ***(Current Clinical Practice, 2007)***

3) Moderate persistent asthma

- Symptoms: occur daily and inhaled short- acting asthma medication is used every day.
- Attacks interfere with daily activities.
- Nighttime symptoms occur more than 1 time a week but do not happen every day.
- Lung function tests: FEV1 and PEFR more than 60% to less than 80% predicted.

4) Severe persistent asthma

- Symptoms occur daily and severely limit daily physical activity.
- Nighttime symptoms occur often, sometimes every night.

- Lung function tests: FEV1 and PEFR are less than 60% predicted. **(*http://www.nhlbi.nih.gov/guidelines/asthma/index.htm*).**

Goals of Asthma Treatment *(Current Clinical Practice, 2007)*

1. Prevent chronic symptoms.
2. Keep normal pulmonary functions.
3. Keep and Maintain normal activity levels
4. Minimize any need for emergency treatment or hospitalization and Prevent recurrence of the disease.
5. Offer optimal treatment with minimal side effects.
6. Meet expectations of patients for asthma control.

Medications: *(Petrov and Wenzel, 2010)*

- **Short Acting Beta-2 Agonists (SABAs)**

They are rescue medicines act within 10 minutes and have duration of action of 4–5 h.

EX: Salbutamol.

- **Anticholinergics**

Slower onset of action (30–60 min to maximum effect) and is less potent than short acting beta-2 agonists.

Ex: Ipratropium bromide.

2) Controllers

- **Glucocorticosteroids (GCs)**

They should be used on a regular basis once or twice a day but can also be used for acute exacerbations.

EX: Fluticasone and mometasone which are the most potent IGCs.

- **Cromones**

They are less effective than GCs

Ex: Sodium cromoglycate and nedocromil sodium.

- **Long Acting Beta-2 Agonists (LABA)**

They are similar to short acting beta-2 agonists, but unlike SABAs, they have a longer duration of action on the receptor.

EX: salmeterol and formoterol.

- **Methylxanthines**

They are less effective than beta-2 agonists and may have significant side effects

EX: Theophylline and aminophylline

- **Leukotriene Modifiers (LMs)**

LMs are effective in the treatment of acute asthma in adults and used as controllers in persistent asthma.

EX: Montelukast, Zafirlukast.

- **Anti-IgE Therapy**

EX: Omalizumab

β2 adrenoreceptor agonists bronchodilators are commonly used in asthma treatment as they can provide rapid and effective symptoms relief. The main action of these drugs is to oppose lung smooth muscle contraction accompanied with asthma***. (Petrov and Wenzel, 2010)***

Salbutamol Sulphate (SS) as a model drug:

Chemical structure: Salbutamol Sulphate is the (1RS)-2-(1, 1-Dimethylethyl)amino)-1-(4-hydroxyl-3- (hydroxymethyl)phenyl)ethanol) sulfate. It is $(C13H21NO3)_2$. H2SO4 with a molecular weight 576.7. It has the following structure: ***(Clarke, 2011; British Pharmacopoeia, 2013).***

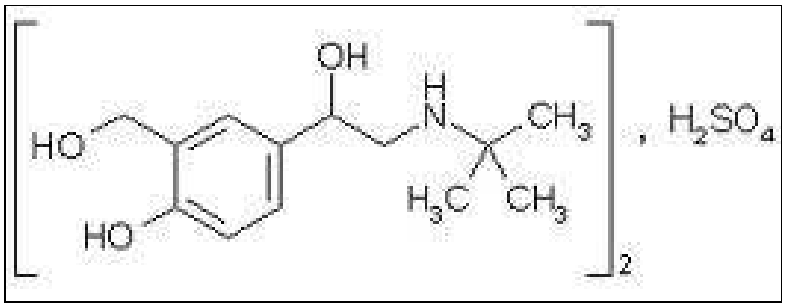

Figure (I): Chemical structure of Salbutamol Sulphate.

Synonymus:

Albuterol sulfate, salbutamol hemi sulfate.

Solubility:

Freely soluble in water, practically insoluble or very slightly soluble in ethanol and methylene chloride with pka 9.3.

Apperance:

White or almost white crystalline powder. It shows polymorphism with a melting point 151 -156***(B.P, 2013).***

Indication:

Salbutamol or albuterol is a short-acting β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma

and chronic obstructive pulmonary disease in both children and adult ***(Melani, 2013).***

Mechanism of action:

Salbutamol Sulphate binds to β2-adrenergic receptors on bronchial smooth muscle cells. This results in the activation of adenyl cyclases, which in turn results in the cyclic adenosine monophosphate (cAMP)–mediated activation of proteinkinase A, so lead to smooth muscle relaxation ***(Hoshang, 2012)***.

Pharmacokinetics:

Salbutamol Sulphate is readly absorbed from gastrointestinal tract. When it is given by inhalation from 10 to 20% of the dose reaches the lower airways. The reminder is retained in the lung or swallowed and absorbed from the gut. It is subjected to first pass metabolism in the liver and possibly in the gut wall. It doesn't metabolite in the lung. The main metabolite is the inactive sulfate conjugate. It is rapidly excreted in the urine as metabolites and unchanged drug, a smaller proportion is excreted in the faeces. The plasma half life range from 4 to 6 hours ***(Martindale, 2013)***.

Historic development of Salbutamol Sulphate:

It was the first selective β2-receptor agonist to be marketed in 1968. It was first sold by Allen & Hanburys (UK) under the brand name Ventolin®. The drug was an instant success, and has been used for the treatment of asthma from that time. However, in the U.S., FDA agreement of this life saving drug was delayed by 14 years, and it was not available until May 1982 **(www.steroidal.com/fat-loss-agents/albuterol)**.

Available dosage forms:

Prolonged release salbutamol capsules, prolonged release salbutamol tablet, salbutamol injection, salbutamol neubiliser solution, salbutamol oral solution, salbutamol powder for inhalation, salbutamol pressurized inhalation, salbutamol tablet ***(Martindale, 2013).***

Dose and administration:

A typical dose for the prevention and or treatment of acute asthma is two inhalations as needed every 4–6 h. Oral salbutamol in a dose of 2 to 4 mg three or four times daily. Salbutamol Sulphate can be given by intra mascular injection in a dose of 500µg every 4 hours.

Interaction:

Salbutamol Sulphate interacts with corticosteroids, diuretics and xanthenes. This interaction results in increasing risk of hypokalaemia so monitoring of potassium level is required ***(Matindal, 2013).***

Adverse effects:

The high doses of Salbutamol Sulphate cause tremors of skeletal muscle (particarly the hands), tachycardia, nervousness, headache and Hyperglycemia especially in children. These side effects are usually not seen with standard therapeutic doses ***(Petrov and Wenzel, 2010)***.

Previous researches:

Salbutamol Sulphate has been formulated as fast dissolving buccal tablet by Dineshmohan et al.(2010), mucoadhesive buccal patches by Shah et al.(2010), , oral film with thermal ink-jet by Buanz et al.(2011) mucoadhesive buccal tablet by Arya et al.(2011), mucoadhesive buccal bilayered tablet by Rao and Kulkarni.(2012) and *in-situ* gel by Farid et al.(2013)

Dosage forms exist to optimize the drug delivery to its site of action. To this end, various inventive delivery systems have been developed. Attainment of suitable blood concentration / time profiles in controlled studies is regarded as validation of the effectiveness of the specialized dosage form. However, it should be remembered that "delivery" also encompasses the role of patient actually consuming the medication in an uncontrolled setting ***(Rathbone, 2003).***

The appropriate design and formulation of a dosage form needs to take in consideration many factors:

1) Biopharmaceutical factor: involving factors affecting drug absorption from different dosage forms.
2) Physicochemical factor: involving physical and chemical properities of the drug ingredients used in manufacturing of the dosage form.
3) Therapeutic factor: involving disease to be treated, patient correlated factors. Thus it is important to relate the drug to the clinical indication that have been treated before the combination of drug and dosage form can be formulated ***(York, 2002).***

Asthma medications can be administered via inhaled, oral, or parentral routes. Inhalers are the preferred method of delivery for most asthma medications because of direct deposition of drug to the airways and few systemic side effects ***(Petrov and Wenzel, 2010).***

Different routes for drug administration e.g oral, parentral, and inhalation. Every route has its specific function, advantages and disadvantages ***(Blackburn, 2010).*** The most commonly and rapidly route is injection as it results in rapid increase in the drug concentration in the blood but it is painful and may lead to toxic or autoimmune response by the time. Many attempts were done to find alternative routes to produce systemic drug effect ***(Kamimori, 2002).*** Inhaler drug therapy requires that patients become skilled at specific inhalation techniques for each type of inhaler devices.

When the technique is not optimized, this can result in decreased drug delivery and potentially reduced efficacy ***(Petrov and Wenzel, 2010)***.

The oral route still the preferred way of administration for both patients and clinicians due to its several advantages e.g accurately dosing, easily manufactured, posses good physical and chemical stability as it is dry in nature, pain free, ease-self administration, cheap and improved patient compliance compared to the other routes ***(Vranic´and Uzunovic, 2008).***

Oral solid dosage forms (OSDs e.g Tablets and hard gelatin capsules) represent majority of drug delivery systems which are now available. However, many patient groups such as the elderly, children, mentally retarded patients, nauseated and those who have reduced liquid intake having difficulties in swallowing these dosage forms. Also oral route sometimes become ineffective due to first pass hepatic effect resulting in reduced drug bioavailability, slow onset of action which is not suitable in emergencies ***(Deshpande and Ganesh, 2011).*** Also half of patient´s surveyed to have experienced difficulty in taking medication and felt that tablet is better and easier formulation compared to other formulations such as capsules or powder ***(Popa and Gafitanu, 2003).*** Beside increase the intake of water for swallowing conventional dosage forms results in frequent urination and nocturia ***(Murpani et al., 2003).*** These difficulties are often responsible for poor compliance with the dosage, or even stopping the treatment and therefore resulting in ineffective therapy ***(Kearney, 2003).*** Thus there is a need for patient friendly, convenient dosage forms that result in patient convenience and leads to compliance with the prescribed dosing regimen and, as a consequence, enhanced therapy ***(Rathbone et al., 2003).***

For the last few decades, researchers have been developing intraoral dosage forms (IODS). These dosage forms can produce desirable drug exposure for optimum therapeutic effect. The scientific and patent literature over the last twenty years, nontraditional oral dosage forms (e.g., buccal,

sublingual, etc.) have been or are being developed.The emphasis on pregastric absorption by the various tissues of the oral cavity to avoid first-pass, thus enhance bioavailability and improve convenience of dosing. The intraoral dosage forms (IODs) are formulated for local as well as systemic drug delivery. However, most of IODs are intended to disintegrate, dissolve, or release the drug in the oral cavity. The drug has the opportunity to either be locally absorbed, in part or whole, and/or swallowed and subsequently absorbed along the GIT ***(Tapash, 2005)***.

Several intra oral dosage forms have been developed, including sublingual and rapid-melt tablets, mucoadhesive films, lyophilized wafers, patches, bioerodible disks, and microparticles ***(Teubl et al., 2013)***.

Classification of intra oral dosage forms (IODS) ***(Teubl et al., 2013)***

These dosage forms can be classified according to their dissolution and/or disintegration kinetics as.

- **Quick-dissolving (QD)**

They are systems disintegrate within a few seconds to a minute upon contact with saliva without the need of water or chewing. They offer several benefits, including enhanced efficacy and convenient administration.

- **Slow-dissolving (SD)**

They are systems also dissolve in the oral cavity within 1–10 min

- **Non-dissolving (ND)**

They are systems do not dissolve entirely and are therefore fitting systems for controlled drug delivery.

Composition of oral mucosa:

The oral mucosa consists of an outermost layer of stratified squamous epithelium, below which lies a basement membrane, and below it a lamina propria and submucosa as illustrated in the following figure.

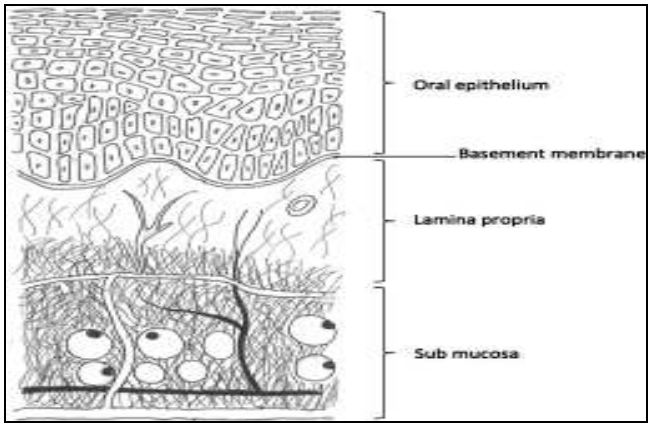

Figure (II): The schematic diagram of the structure of oral mucosa ***(Lam et al., 2013).***

There are three types of oral mucosa that can be found in the oral cavity; the specialized mucosa that found on the dorsal surface of the tongue. The masticatory mucosa which is found on the hard palate (the upper surface of the mouth) and the gingiva.The linning mucosa which covers the rest of the oral cavity (sublingual mucosa and buccal mucosa) ***(Patel et al., 2011).*** The oral mucosa has a unique structural and physiological properties which offers several opportunities for systemic drug delivery. As the mucosa is highly vascularized any drug diffusing across the oral mucosa membranes has direct access to the systemic circulation through capillaries and venous drainage and will bypass hepatic metabolism ***(Munasur et al., 2006)***. The gingival and the palatal mucosa are keratinized, and hence are like the epidermis of the skin. The buccal and sublingual. mucosae have a non-keratinized surface linning ***(Chen, 1999).*** The non-keratinized areas have a higher permeability to water and hydrophilic compounds than keratinized areas ***(Veuillez et al., 2001)***.

Advantages of oral transmucosal drug delivery

Absorption across the oral mucosa provides a rapid onset of action, as that seen with intravenous administration. Additionally, oral mucosal drug delivery offers an alternative route in patients who have difficulty in swallowing, nausea and vomiting, or intestinal failure. Oral mucosal delivery is non-invasive and less threatening for many patients compared with other routes of administration (e.g. intravenous, intramuscular). Also, drugs administered via the oral mucosa do not require technical equipment (e.g. infusion pumps) and expertise, thus are more cost-effective than invasive therapies. This route of drug delivery increases the systemic bioavailability of drugs with low oral bioavailability as peptides and proteins ***(Madhav et al., 2009)***.

Clinical application of oral transmucosal drug delivery:

Oral transmucosal delivery has received considerable attention. Oral transmucosal deliveries of sedatives, anti-nausea, drugs for erectile dysfunction and Formulations of sublingual testosterone and estrogen show good results with clinical advantages over other routes of administration although many drugs have been evaluated for oral transmucosal delivery, few are commercially available. The clinical need for these drug delivery systems should be high enough to compensate the high need with developing this type of product ***(Lam et al., 2013)***.

The following figure illustrate application site of oral mucosal dosage forms:

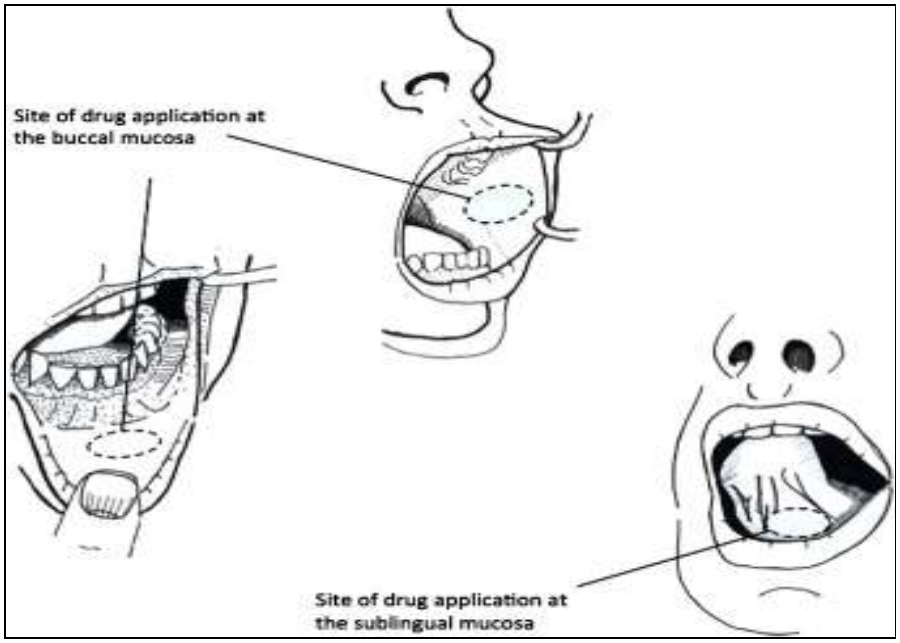

Figure (III): The common sites of drug application to buccal and sublingual mucosa ***(Lam et al., 2013)***.

Drug delivery via membrane of the oral cavity can be subdivided into the following:

1) Sublingual delivery, which the drugs administration via sublingual mucosa to the systemic circulation.

2) Buccal delivery, which is administration of drugs via the buccal mucosa (the linning of the cheek and area between the gums and upper& lower lips) to the systemic circulation.

3) Local delivery, for the treatment of conditions of the oral cavity, principally ulcers, bacterial and fungal infections, and periodontal diseases ***(Tapash, 2002)***.

As metioned before Salbutamol is one of the most commonly short-acting B2-adrenergic receptor agonist used as anti-asthmatic drug. Because of its poor bioavailability through oral route due to first pass metabolism. This drug satisfies the requirements of buccal and sublingual drug delivery system ***(Rao and Kulkarni, 2012)***.

Sublingual drug administration can offer an excellent alternative route of dug administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation. It by passing enzyme degradation in the gut and liver. The thin sublingual mucosa (about 190 in compared to 500 –800 μm of the buccal mucosa) also the abundance of blood supply at the sublingual region allow excellent drug penetration or absorption.This leads to achieve high plasma drug concentration with a rapid onset of action ***(Bayrak et al., 2011)***.

Fast dissolving dosage forms (FDDs) include tablets and films are used to attain an instant high concentration of drug in the body for immediate actions ***(Kumari, 2010)***. Beside they have the advantages of liquid formulations, such as easy administration and no risk of suffocation resulting from traditional dosage forms. These dosage forms can result in improvement of the bioavailability of some drugs. They offer absorption of drug in oral cavity and pregastric absorption of saliva containing dispersed drugs that pass down into the stomach ***(Chauhan et al., 2013)***.

We planned to formulate SS as fast dissolving sublingual tablet and fast dissolving sublingual film. The tablets were prepared by direct compression technique and the films were prepared by casting method.

The work in this thesis is divided into three chapters:

Chapter I: Formulation, evaluation of Salbutamol Sulphate fast dissolving sublingual tablets and stability study of the best formula.

Chapter II: Formulation, evaluation of Salbutamol Sulphate fast dissolving sublingual films and stability study of the best formula.

Chapter III: Bioavailability and clinical study of the selected Salbutamol Sulphate fast dissolving sublingual tablet and film in humans.