Comparison of In Vitro Release Kinetics Between Ventolin® and Brodil®

A thesis report submitted to the Department of Pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Faisal
24-12-09

Faisal Mahmud

AIM AND OBJECTIVES

Aim of the study:

To compare the release kinetics of Ventolin® (Sulbutamol CR tablet) and Brodil® (Sulbutamol CR tablet) in the treatment of asthma.

Objectives of the study:

1. To assess and compare

2. To determine the complications.

Declaration of Guide

This is to certify that Faisal Mahmud, student of Department of Pharmacy, East West University, has performed this research titled " **Comparison of In Vitro Release Kinetics Between Ventolin® and Brodil®**"

His work is genuine. I have gone through the thesis and the work is up to my satisfaction.

A. H. Pathan
24.12.05

Atiqul Haque Pathan
Senior Lecturer,
Department of Pharmacy,
East West University.

Dr. Chowdhury Faiz Hossain
Chairman,
Department of Pharmacy,
East West University.

DECLARATON

I sincerely declare that this research titled **"Comparison of In Vitro Release Kinetics Between Ventolin® and Brodil®"** is based on work, carried out by me and no part of it has been presented anywhere previously.

This research work has been carried out in the Department of Pharmacy, East West University, under the guidance of **Atiqul Haque Pathan,** Senior Lecturer, Department of Pharmacy, East West University.

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29.12.09

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Abstract

Purpose: The purpose of this research work was to compare between the release patterns of Ventolin and Brodil tablets. ***Method***: Ten tablets of each of Ventolin (from GlaxoSmith Kline Pharmaceuticals Ltd.) and Brodil (ACI Pharmaceuticals Ltd.) were collected from the market and were justified by physical parameters like hardness, thickness, weight variation, friability and dissolution studies. Release kinetics was measured by using the method inscribed in British Pharmacopoeia. Hardness of the samples from the market was measured by hardness tester. Thickness of the samples was measured by Vernier Calipers. Dissolution of the taken samples was investigated using dissolution tester (RC6, Vanguard Pharmaceuticals, and USA) to evaluate release kinetics. ***Result***: Mean hardness value of Ventolin and Brodil tablets was found to be 11.64N and 14.72 N, respectively. Mean thickness value of Ventolin and Brodil tablets was found to be 8.42 mm and 9.77 mm respectively. Percentage difference of the weight variation test ranges from -2.20% to 3.27 % for Ventolin and-2.40% to 3.44% for Brodil. % friability of Ventolin was found to be 0.17 and of Brodil was found to be – 0.14. ***Conclusion:*** The release pattern of Ventolin tablet not meet the requirement to provide desired and optimum therapeutic efficacy, which is ensured by release kinetics of Brodil.

Keywords: Salbutamol Sulphate, Ventolin, Brodil, Release pattern, Hardness, Thickness, Friability, Dissolution.

Appendix I: List of Tables

Appendix II: List of Diagrams

INTRODUCTION:

Salbutamol Sulphate is a drug used in the treatment of asthma, a chronic lung disease caused by inflammation of the lower airways. Asthma causes the airways to become sensitive, swollen and inflamed, even when there are no visible symptoms and thus causes hyper-responsiveness of tissues lining the bronchi to certain triggers. The most serious symptom is the constriction of the smooth muscle lining the bronchi of the lungs. This symptom was so important that asthma was previously characterised as a periodic bronchospasm. This reduces airflow and thus makes breathing hard or, in fatal cases, impossible. Affecting some 15 million Americans and more than 3 million in the UK, asthma continues to increase in both incidence and severity despite vast improvements in both therapeutic options and understanding of the disease over the years.

These increases have yet to be adequately explained, but the number and frequency of hospitalisations due to asthma, along with the attendant expenditures, continue to escalate. More people of all ages are being treated for asthma now than ever, and the number of children receiving treatment continues to escalate.

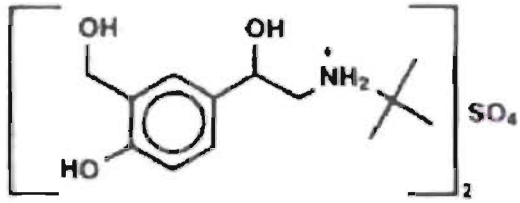
The cost of asthma to the community is truly staggering. An estimated $6 billion is spent on treating asthma in the USA alone. Other expenses such as an estimated $1 billion for the loss in productivity by working parents caring for children who miss school due to asthma mean that asthma treatment is a very important area. (USA)

With asthma affecting 1 in 7 school children in the UK (1 in 25 adults) asthma has an affect on a huge number of families in the United Kingdom. (UK) (Chem. Wiki, 2009)

SALBUTAMOL PHYSICAL DATA:

Generic Class: beta2-adrenergic bronchodilator
FDA Drug Class: Antiasthmatics/Broncodilators
Antihypertensives

Molecular Formula: $C_{13}H_{21}NO_7S$



Chemical Structure of Salbutamol Sulphate (RxList, 2009)

Molecular Weight: 239.31 g/mol

Melting Point: 157-158 °C (with decomposition)

Description: A white or almost white, crystalline powder.

Clear solution in methanol, very pale clear yellow solution.

Solubility: Sparingly soluble in water; soluble in ethanol (96%); slightly soluble in ether.

Composition:

C **65.25**

H **8.84**

N **5.85**

O **20.06** (Chem. Wiki, 2009)

Pregnancy risk category C

Action

Relaxes smooth muscles by stimulating $beta_2$-receptors, thereby causing bronchodilation and vasodilation

Availability

Aerosol: 90 mcg/actuation

Oral solution: 2 mg/5 ml

Solution for inhalation: 0.083% (3 ml), 0.5% (0.5 and 20 ml), 0.63 mg/3 ml, 1.25 mg/3 ml

Syrup: 2 mg/5 ml

Tablets: 2 mg, 4 mg

Tablets (extended-release): 4 mg, 8 mg

Indications and dosages

To prevent and relieve bronchospasm in patients with reversible obstructive airway disease

Adults and children ages 12 and older: *Tablets* - 2 to 4 mg P.O. three or four times daily, not to exceed 32 mg daily. *Extended-release tablets* - 4 to 8 mg P.O. q 12 hours, not to exceed 32 mg daily in divided doses. *Syrup* - 2 to 4 mg (1 to 2 tsp or 5 to 10 ml) three or four times daily, not to exceed 8 mg q.i.d. *Aerosol* - one to two inhalations q 4 to 6 hours to relieve bronchospasm; two inhalations q.i.d. to prevent bronchospasm. *Solution for inhalation* - 2.5 mg three to four times daily by nebulization, delivered over 5 to 15 minutes.

Children ages 6 to 12: *Tablets* - 2 mg P.O. three or four times daily; maximum daily dosage is 24 mg, given in divided doses. *Extended-release tablets* - 4 mg q 12 hours; maximum daily dosage is 24 mg/kg given in divided doses. *Syrup* - 2 mg (1 tsp or 5 ml) three or four times daily, not to exceed 24 mg.

Children ages 2 to 12 weighing more than 15 kg (33 lb): *Solution for inhalation* - 2.5 mg three to four times/day by nebulization

Children ages 2 to 6: *Syrup* - Initially, 0.1 mg/kg P.O. t.i.d., not to exceed 2 mg (1 tsp) t.i.d. Maximum dosage is 4 mg (2 tsp) t.i.d.

To prevent exercise-induced bronchospasm

Adults and children older than age 4 (older than age 12 with Proventil): Two inhalations 15 minutes before exercise

Dosage adjustment

- Sensitivity to beta-adrenergic stimulants
- Elderly patients

Off-label uses

- Chronic obstructive pulmonary disease
- Hyperkalemia with renal failure
- Preterm labor management

Contraindications

- Hypersensitivity to drug

Warnings and Precautions

If a previously effective or recommended dose fails to give relief, the patient should be advised to seek medical advice in order that any further necessary steps may be taken.

- Salbutamol should not be given together with other sympathomimetic agents.
- β-adrenoceptor blocking agents inhibit the bronchodilator activity of salbutamol.
- Consequently β-blockers should not be used in asthmatic patients as they may increase airways resistance.

- Potentially serious hypokaliemia may result from β_2 agonist therapy mainly from parenteral and nebulised administration.
- Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and hypoxia. It is recommended the serum potassium levels are monitored in such situations.

Pregnancy: Administration of medicines during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.During worldwide marketing experience, rare cases of various congenital anomalies, including cleft palate and limb defects have been reported in offspring of patients treated with salbutamol. Some of the mothers were taking multiple medications during their pregnancy. Because no consistent pattern of defects can be discerned, and baseline rate of congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

Lactation: It is not known whether salbutamol has a harmful effect on the neonate. As salbutamol is probably excreted in breast milk, its use in nursing mothers is not recommended unless the expected benefits outweigh any potential risk. (Medsafe, 1999)

Administration

Route	Onset	Peak	Duration
P.O.	15-30 min	2-3 hr	6-12 hr
P.O. (extended)	30 min	2-3 hr	12 hr

Adverse reactions

CNS: dizziness, excitement, headache, hyperactivity, insomnia

CV: hypertension, palpitations, tachycardia, chest pain

EENT: conjunctivitis, dry and irritated throat, pharyngitis

GI: nausea, vomiting, anorexia, heartburn, GI distress, dry mouth

Metabolic: hypokalemia

Musculoskeletal: muscle cramps

Respiratory: cough, dyspnea, wheezing, paradoxical bronchospasm

Skin: pallor, urticaria, rash, angioedema, flushing, sweating

Other: tooth discoloration, increased appetite, hypersensitivity reaction

Interactions

Drug-drug. *Beta-adrenergic blockers:* inhibited albuterol action, possibly causing severe bronchospasm in asthmatic patients

Digoxin: decreased digoxin blood level

MAO inhibitors: increased cardiovascular adverse effects

Oxytoxics: severe hypotension

Potassium-wasting diuretics: ECG changes, hypokalemia

Theophylline: increased risk of theophylline toxicity

Drug-food. *Caffeine-containing foods and beverages (such as coffee, tea, chocolate):* increased stimulant effect

Drug-herbs. *Cola nut, ephedra (ma huang), guarana, yerba maté:* increased stimulant effect. (The Free Dictionary, 2009)

Overdosage:

Peripheral vasodilation and increased irritability of skeletal muscle are signs of overdose due to β receptor sympathomimetics. Sinus tachycardia develops and is partly attributable to a decrease in peripheral resistance associated with a reflex increase in cardiac output. If overdose occurs salbutamol should be withdrawn and if necessary a cardio-selective β blocker such as metoprolol in a single dose of up to 5mg may be given by injection.

Pharmacology of Salbutamol Sulfate

Mechanism of action and use in asthma:

The β adrenergic receptor agonists available for the treatment of asthma are selective for β_2-receptor subtype. The agonists can be classified as short- or long-acting. This sub classification is useful from a pharmacological perspective: Short-acting agonists are used only for symptomatic relief of asthma, whereas long-acting agonists are used prophylactically in the treatment of the disease.

The mechanism of the antiasthmatic β adrenergic receptor agonists is linked with direct relaxation of airway smooth muscle and consequent bronchodilation. Although human bronchial smooth muscle receives little or no sympathetic innervation, it nevertheless contains large numbers of β_2 adrenergic receptors. Stimulation of these receptors activates the G_s adenylyl cyclase-cyclic AMPpathway with a consequent reduction of in smmoth muscle tone. β_2 adrenergic receptor agonists also increase the conductance of large Ca^{2+}-sensitive potassium channels in airway smooth muscle, leading to membrane hyperpolarization and relaxation. This occurs at least partly by mechanisms independent of adenylyl cyclase activity and cyclic AMP production and may involve the regulation of capacitative Ca^{2+} entry by small G proteins.

There are β_2 adrenergic receptors on cell types in the airways other than bronchial smooth muscle. Stimulating β_2 adrenergic receptors inhibits the function of numerous inflammatory cells. Stimulating β_2 adrenergic receptors in these cell types increases intracellular cyclic AMP, activating signaling cascade that inhibits the release of inflammatory mediators and cytokines.

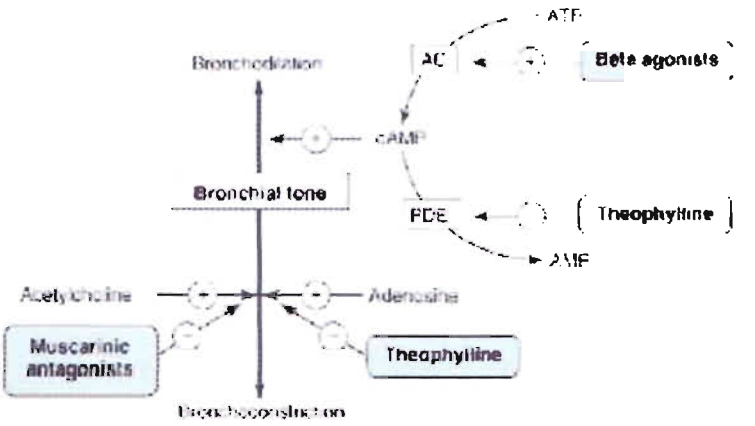


Figure 1: Mechanism of action of β adrenergic receptor agonist (Katzung, B.G., 2007)

Bronchodilation is promoted by cAMP. Intracellular levels of cAMP can be increased by - adrenoceptor agonists, which increase the rate of its synthesis by adenylyl cyclase (AC); or by phosphodiesterase (PDE) inhibitors such as theophylline, which slow the rate of its degradation Bronchoconstriction can be inhibited by muscarinic antagonists and possibly by adenosine antagonists.

Short-Acting β_2 Adrenergic Receptor Agonists:

Drugs in this class include salbutamol, levabuterol, terbutaline and pirbuterol. These drugs are used for acute inhalation treatment of bronchospasm. Terbutaline , salbutamol and metaproterenol also are available in oral dosage form. When given in oral dosage forms, the duration of action is somewhat longer(4-8 hours). Although there are slight differences in the relative β_2/ β_1- receptor potency ratios among the drugs, all of them are selective for the β_2 subtype.

The most effective drugs in relaxing airway smooth muscle and reversing bronchoconstriction are short acting β_2 adrenergic receptor agonists. They are preferred treatment for rapid symptomatic relief of dyspnea associated with asthmatic bronchoconstriction. When the asthma symptoms become persistent, the patient should be reevaluated so that drugs aimed at controlling, in addition to reversing, the disease can be prescribed.

Oral Therapy with β Adrenergic Receptor Agonists:

- Brief courses of oral therapy (salbutamol or metaproterenol syrups) are well tolerated and effective in young children (<5 years old) who can not manipulate metered dose inhalers yet have occasional wheezing with viral upper respiratory infections.
- In some patients with severe asthma exacerbations, any aerosol, whether delivered via a metered dose inhaler or a nebulizer,can worsen cough and bronchospasm owing to local irritation.

In this case, oral therapy with β_2 adrenergic agonists (salbutamol,metaproterenol or terbutaline tablets) can be effective. The frequency of adverse systemic side effects with orally administered agent is higher in adults than in children. (Hardman, J.G. et al, 2006)

Pharmacokinetics:

Salbutamol is readily absorbed from the gastrointestinal tract, maximum plasma concentrations occurring within 2.5 hours. It is subject to first pass metabolism in the liver. The plasma half-life ranges from 2.7-7.0 hours. Elimination occurs by both metabolism and urinary excretion. 76% of an oral dose is excreted over 3 days with the majority of the dose excreted within the first 24 hours.

Salbutamol is metabolised to a sulphate conjugate accounting for 50% of an oral dose. About half is excreted in the urine as an inactive sulphate conjugate, following oral administration (the rest being unchanged salbutamol), whereas rather less is excreted as the conjugate following intravenous administration. Unlike isoprenaline, salbutamol is not inactivated by catechol-o-methyl-transferase (COMT) or sulphatase enzymes.

After inhalation therapy, systemic absorption is low, maximum serum concentrations occurring within 2-4 hours. Salbutamol does not appear to be metabolised in the lung, therefore its behaviour following inhalation depends upon the delivery method used, which determines the proportion of inhaled salbutamol relative to proportion inadvertently swallowed.

Urinary studies indicate an elimination half-life of approximately four hours. Of that which is absorbed, 72% is excreted with 24 hours in the urine, 28% as unchanged salbutamol and 44% as the sulphate conjugate.

Salbutamol does not pass the blood-brain barrier.

Bioavailability:

The relative amount of an administered dose of a particular drug that reaches the systemic circulation intact and the rate at which this occurs is known as the bioavailability. Bioavailability is therefore defined as the rate and extent of drug absorption. The bioavailability exhibited by a drug is thus very important in determining whether a therapeutically effective concentration will be achieved at this site(s) of action.

In defining bioavailability in these terms, it is assumed that the administered drug is therapeutically active form. The definition would not be valid in the case of prodrugs, whose therapeutic action depends on their being converted into a therapeutically active form prior to or on reaching the systemic circulation. In the context of bioavailability, the term 'systemic circulation' refers primarily to venous blood (excluding the hepatic portal vein) and the arterial blood, which carries the intact blood to the tissues.

Therefore, for a drug which is administered orally to be 100% bioavailable, the entire dose must move from the dosage form to the systemic circulation. The drug must therefore:

- be completely released from the dosage form
- be fully dissolved in the gastrointestinal fluids
- be stable in solution in the gastrointestinal fluids
- pass through the gastrointestinal barrier into the mesenteric circulation without being metabolized
- pass through the liver into the systemic circulation unchanged.

Anything that adversely affects either the release of the drug from the dosage form, its dissolution into the gastrointestinal fluids, its permeation through and stability in the gastrointestinal barrier or its stability in the hepatic portal circulation will influence the bioavailability exhibited by that drug from the dosage form in which it was administered. (Aulton, M.E., 2007)

Now, when a drug is perfectly released then it will be absorbed perfectly. Ultimately, the bioavailability of the drug will be high. That is why this research has been done on the release pattern of **Ventolin** and **Brodil.**

What Is Asthma?

Asthma involves chronic inflammation, swelling, and narrowing of the bronchial tubes (airways). The result is difficulty breathing. The bronchial narrowing is usually totally reversible with treatments.

Bronchial tubes that are chronically inflamed may become overly sensitive to allergens (specific triggers) or irritants (nonspecific triggers). The airways may become "twitchy" and remain in a state of heightened sensitivity. This is called "bronchial hyperreactivity" (BHR). In sensitive individuals, the bronchial tubes are more likely to swell and constrict when exposed to triggers such as allergens, tobacco smoke, or exercise. Amongst

asthmatics, some may have mild BHR and no symptoms while others may have severe BHR and chronic symptoms.

The Scope of the Problem

Asthma is now the most common chronic childhood illness, affecting one in every 15 children. In North America, 5% of adults are also afflicted. In all, there are about 1 million Canadians and 15 million Americans who suffer from this disease.

The number of new cases and the yearly rate of hospitalization for asthma have increased about 30% over the past 20 years. Even with advances in treatment, asthma deaths among young people have more than doubled.

Normal Bronchial Tubes

The air we breathe in through our nose and mouth passes through the vocal cords (larynx) and into the windpipe (trachea). The air then enters the lungs by way of two large air passages (bronchi), one for each lung. The bronchi divide within each lung into progressively smaller air tubes (bronchioles), just like branches of an inverted tree. Inhaled air is brought through these airways to the millions of tiny air sacs (alveoli) that are contained in the lungs. Oxygen (O2) passes from the air sacs into the bloodstream through numerous tiny blood vessels called capillaries. Similarly, the body's waste product, carbon dioxide (CO2), is returned to the air sacs and then eliminated upon each exhalation.

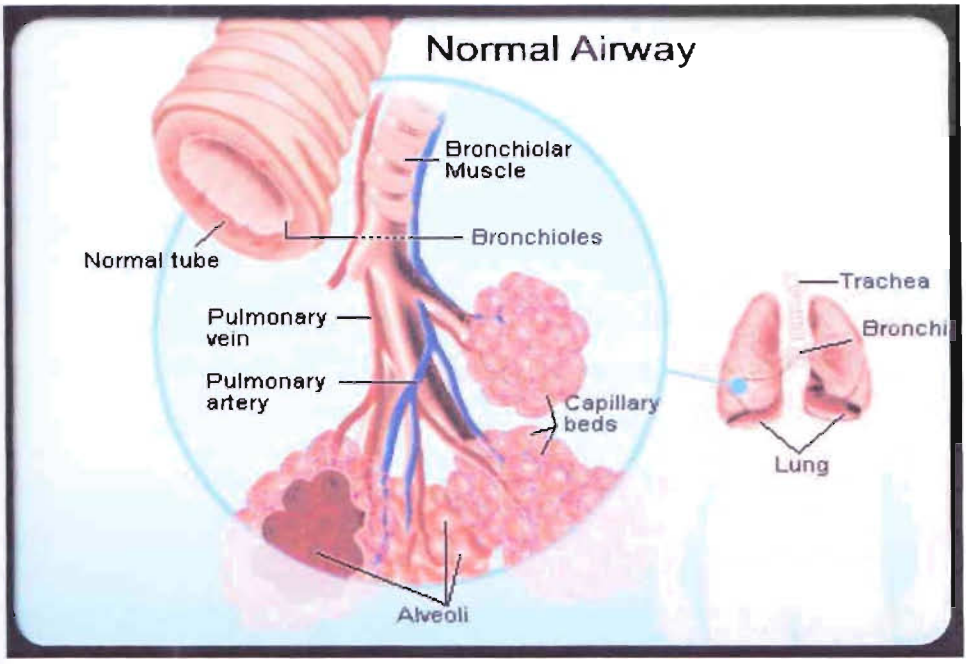


Figure 2: Normal Airway

How Does Asthma Affect Breathing?

Asthma causes a narrowing of the breathing airways, which interferes with the normal movement of air in and out of the lungs. Asthma involves only the bronchial tubes and does not affect the air sacs or the lung tissue. The narrowing that occurs in asthma is caused by three major factors: inflammation, bronchospasm, and hyperreactivity. We'll look at each cause individually on the next few slides.

Inflammation

The first and most important factor causing narrowing of the bronchial tubes is inflammation. The bronchial tubes become red, irritated, and swollen. This inflammation increases the thickness of the wall of the bronchial tubes and thus results in a smaller passageway for air to flow through. The inflammation occurs in response to an allergen or irritant and results from the action of chemical mediators (histamine, leukotrienes, and others). The inflamed tissues produce an excess amount of "sticky" mucus into the tubes. The mucus can clump together and form "plugs" that can clog the smaller airways.

Specialized allergy and inflammation cells (eosinophils and white blood cells), which accumulate at the site, cause tissue damage. These damaged cells are shed into the airways, thereby contributing to the narrowing.

Bronchospasm

The muscles around the bronchial tubes tighten during an asthma attack. This muscle constriction of the airways is called bronchospasm. Bronchospasm causes the airway to narrow further. Chemical mediators and nerves in the bronchial tubes cause the muscles to constrict. Bronchospasm can occur in all humans and can be brought on by inhaling cold or dry air.

Hyperreactivity (Hypersensitivity)

In patients with asthma, the chronically inflamed and constricted airways become highly sensitive, or reactive, to triggers such as allergens, irritants, and infections. Exposure to these triggers may result in progressively more inflammation and narrowing.

Which Triggers Cause an Asthma Attack?

Asthma symptoms may be activated or aggravated by many agents. Not all asthmatics react to the same triggers. Additionally, the effect that each trigger has on the lungs varies from one individual to another. In general, the severity of your asthma depends on how many agents activate your symptoms and how sensitive your lungs are to them. Most of these triggers can also worsen nasal or eye symptoms.

Allergens

- "seasonal" pollens
- year-round dust mites, molds, pets, and insect parts
- foods, such as fish, egg, peanuts, nuts, cow's milk, and soy
- additives, such as sulfites
- work-related agents, such as latex

Irritants

- respiratory infections (caused by viral "colds," bronchitis, and sinusitis)
- drugs, such as aspirin, other NSAIDs (nonsteroidal antiinflammatory drugs), and beta blockers (used to treat blood pressure and other heart conditions)
- tobacco smoke
- outdoor factors, such as smog, weather changes, and diesel fumes
- indoor factors, such as paint, detergents, deodorants, chemicals, and perfumes
- nighttime
- GERD (gastroesophageal reflux disorder)
- exercise, especially under cold dry conditions
- work-related factors, such as chemicals, dusts, gases, and metals
- emotional factors, such as laughing, crying, yelling, and distress
- hormonal factors, such as in premenstrual syndrome

Who Can Develop Asthma?

The many potential triggers of asthma largely explain the different ways in which asthma can present. In most cases, the disease starts in early childhood from 2-6 years of age. In this age group, the cause of asthma is often linked to exposure to allergens, such as dust mites, tobacco smoke, and viral respiratory infections. In very young children, less than 2 years of age, asthma can be difficult to diagnose with certainty. Wheezing at this age often follows a viral infection and might disappear later, without ever leading to asthma. Asthma, however, can develop again in adulthood. Adult-onset asthma occurs more often in women, mostly middle-aged, and frequently follows a respiratory tract infection. The triggers in this group are usually nonallergic in nature.

Types of Asthma: Allergic (Extrinsic)

Extrinsic, or allergic asthma, is more common (90% of all cases) and typically develops in childhood. Approximately 80% of children with asthma also have documented allergies. Typically, there is a family history of allergies. Additionally, other allergic

conditions, such as nasal allergies or eczema, are often also present. Allergic asthma often goes into remission in early adulthood. However, in 75% of cases, the asthma reappears later.

Types of Asthma: Nonallergic (Intrinsic)

Intrinsic asthma represents about 10% of all cases. It usually develops after the age of 30 and is not typically associated with allergies. Women are more frequently involved, and many cases seem to follow a respiratory tract infection. The condition can be difficult to treat and symptoms are often chronic and year-round.

Symptoms and Signs of Asthma

The symptoms of asthma vary from person to person and in any individual from time to time. It is important to remember that many of these symptoms can be subtle and similar to those seen in other conditions. All of the symptoms mentioned below can be present in other respiratory, and sometimes, in heart conditions. This potential confusion makes identifying the settings in which the symptoms occur and diagnostic testing very important in recognizing this disorder.

The following are the four major recognized asthma symptoms:

- Shortness of breath, especially with exertion or at night
- Wheezing is a whistling or hissing sound when breathing out
- Coughing may be chronic, is usually worse at night and early morning, and may occur after exercise or when exposed to cold, dry air
- Chest tightness may occur with or without the above symptoms

How Is Asthma Classified?

Asthma is classified according to the frequency and severity of symptoms, or "attacks," and the results of pulmonary (lung) function tests.

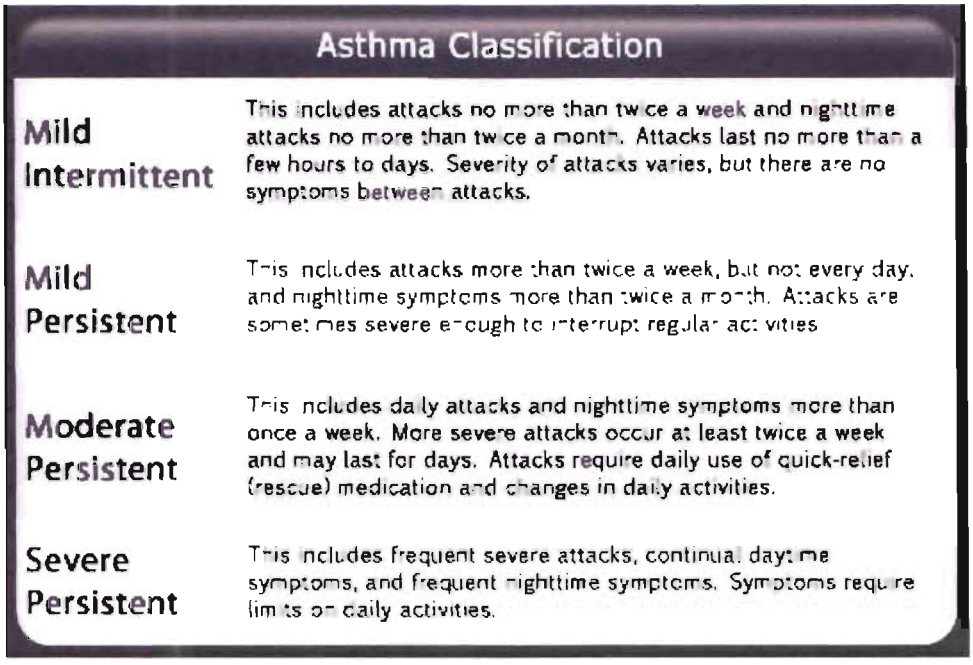


Figure 3: Asthma Classification

Acute Asthma Attack

An acute, or sudden, asthma attack is usually caused by an exposure to allergens or an upper-respiratory-tract infection. The severity of the attack depends on how well your underlying asthma is being controlled. An acute attack is potentially life-threatening because it may continue despite the use of your usual quick-relief medications (inhaled bronchodilators). Asthma that is unresponsive to treatment with an inhaler should prompt you to seek medical attention at the closest hospital emergency room or your asthma specialist office, depending on the circumstances and time of day. Asthma attacks do not stop on their own without treatment. If you ignore the early warning signs, you put yourself at risk of developing a life-threatening asthma reaction called *status asthmaticus*.

Asthma Exams and Tests

There are several asthma tests your doctor may use to make an asthma diagnosis such as lung (or pulmonary) function tests (spirometer, or peak flow meter) which measure lung function. Other asthma tests determine if you are allergic to specific foods, pollen, or

other particles. Blood tests give a picture of your overall health; specific tests also measure levels of immunoglobulin E (IgE), a key antibody that's released during an allergic reaction.

Your doctor may perform an X-ray exam of you in order to visualize the structures inside your chest, including the heart, lungs, and bones. By viewing your lungs, your doctor can see if asthma is causing your symptoms. While a chest X-ray is not an asthma test, it may also be used to make sure nothing else is causing your asthma symptoms.

All of these asthma tests help your doctor determine if asthma is indeed present and if there are other coexisting conditions with asthma, such as allergies, GERD, or sinusitis. Once a proper asthma diagnosis is made, specific medications can be prescribed to help manage your asthma and prevent asthma attacks.

Medical Treatment of Asthma

Most asthma medications work by relaxing bronchospasm using bronchodilators/ inhalers and reducing inflammation with corticosteroids. Inhaled medications are generally preferred over tablet or liquid medicines, which are swallowed. Inhaled medications act directly on the airway surface and airway muscles where the asthma problems initiate. Absorption of inhaled medications into the rest of the body is minimal. Therefore, adverse side effects are fewer as compared to oral medications. Inhaled medications include beta-2 agonists, anticholinergics, corticosteroids, and cromolyn sodium. Oral medications include aminophylline, leukotriene antagonists, beta-2 agonists, and corticosteroid tablets.

Asthma Guidelines:

Present status of Asthma in Central and Southern Asia:

Over 50 million people in Central and Southern Asia have asthma, and many do not have access to the medications that can control the disease, according to a report released today, World Asthma Day. The *Global Burden of Asthma Report*, which details the prevalence, morbidity, and mortality of asthma in 20 regions around the world, reveals a number of alarming facts about the burden of this chronic respiratory disease in Central and Southern Asia.

Due to rapid industrialization and urbanization throughout the region, the prevalence of asthma is predicted to increase rapidly in the coming years. The increase is likely to be particularly dramatic in India, which is projected to become the world's most populous nation by 2050. An absolute 2% increase in the prevalence of asthma in India would result in an additional 20 million people with the disease.

The prevalence of asthma in Central and Southern Asia ranges from 1.5% in Nepal to 4.6% in Uzbekistan—relatively low compared to some other parts of the world. However, the prevalence of asthma has increased markedly in recent years, with up to a threefold increase seen among children in Southern Asia over the last two decades.

Asthma is a chronic lung disease characterized by recurrent breathing problems and symptoms such as breathlessness, wheezing, chest tightness, and coughing. Asthma symptoms vary over time, and also differ in severity from one individual to another. When it is not effectively treated, asthma often leads to hospitalization, missed work and school, limitations on physical activity, sleepless nights and in some cases death.

Although asthma cannot be cured, effective medications to treat and manage the disease exist. One of the authors of the *Global Burden of Asthma Report*, Professor Richard Beasley, of the Medical Research Institute of New Zealand, says, "In Central and Southern Asia, effective asthma management is often limited by lack of availability or affordability of medications." In some areas widespread misconceptions about asthma and its treatment, and reluctance of patients to use the inhaler devices that are key to effective delivery of asthma medicines, also pose challenges. "Low-cost asthma education and management programs are needed to ensure that asthma care is available and affordable for all segments of the population in Central and Southern Asia," adds Professor Beasley.

The high levels of air pollution in Central and Southern Asia are also cause for concern. "The inhabitants of some Indian and Bangladeshi cities are exposed to some of the highest air pollution levels in the world," Professor Beasley says. "Air pollution can trigger asthma attacks, and can also worsen the symptoms of a variety of other respiratory diseases." Indoor air pollution, from burning biomass fuel for cooking and heating in poorly ventilated dwellings, also contributes to the burden of asthma and other respiratory diseases in the region.

Asthma is now one of the world's most common long-term conditions, according to the *Global Burden of Asthma Report*. The disease is estimated to affect as many as 300 million people worldwide—a number that could increase by a further 100 million by 2025.

The *Global Burden of Asthma Report* is a comprehensive survey of the prevalence and impact of asthma around the world, based on standardized data collected in epidemiology studies in more than 80 countries. This groundbreaking report has been written by Richard Beasley, Matthew Masoli, Denise Fabian, and Shaun Holt, of the Medical Research Institute of New Zealand and the University of Southampton in the UK. Initial results of the Report were released on World Asthma Day 2003; the Report is being released in full today.

The Report was commissioned by the Global Initiative for Asthma (GINA), an effort launched in 1993 to work with healthcare professionals and public health officials around the world to reduce the burden of asthma. Guidelines for the diagnosis and management of asthma prepared by GINA have been adapted for use in a variety of settings around the world, illustrating how asthma management programs can be tailored to fit the local culture and level of resources available.

GINA also sponsors World Asthma Day, held each year on the first Tuesday in May. This event aims to raise awareness of asthma around the world and encourage individual countries to take urgent action and make asthma a major health priority within their own regions. (Ginasthma, 2004)

Asthma condition in Bangladesh:

The prevalence of asthma (wheeze in the last 12 months) was 6.9% (95% CI : 6.2–7.6). The prevalence of other asthma definitions were: ever wheeze (lifetime wheeze) 8.0% (95% CI : 7.3–8.7); perceived asthma (perception of having asthma) 7.6% (95% CI : 6.9–8.3); doctor diagnosed asthma (diagnosis of asthma by any category of doctor either qualified or unqualified) 4.4% (95% CI : 3.9–4.9). The prevalence of asthma in children (5–14 years) was higher than in adults (15–44 years) (7.3% versus 5.3%; odds ratio [OR] = 1.41, 95% CI : 1.09–1.82). Asthma in children was found to be significantly higher in households with ≤3 people than in larger households (OR = 2.20, 95% CI : 1.24–3.20). The low-income group (OR = 1.41, 95% CI : 1.04–1.92) and illiterate group (OR = 1.51, 95% CI : 1.01–2.24) were more vulnerable to asthma attacks than the high-income group and more educated people, respectively.

Asthma in Bangladesh appears to be a substantial public health problem: an estimated 7 million people including 4 million children suffer from asthma-related symptoms. (Hassan, M.R., et al, 2002)

Study of Hardness:

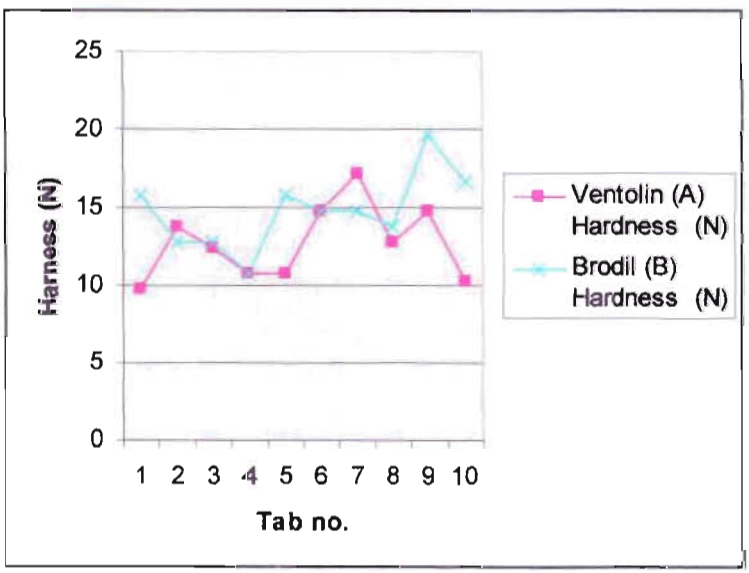
Tablets require a certain of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. Tablets should be able to withstand reasonable abuse when in the hands of the consumer. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. The relationship of hardness to tablet disintegration, and perhaps more significantly, to the drug dissolution release rate, has become apparent. The monitoring of tablet hardness is especially important for drug products that possess real or potential bioavailability problems or that are sensitive to altered dissolution release profiles as a function of the compressive force employed. The hardness of a tablet, like its thickness, is a function of the die fill and compression force. At a constant compression force, hardness increases with increasing die fills and decreases with lower die fills.

Methodology: The hardness of 10 Ventolin(collected from chemist shop manuctured by GlaxoSmith Kline Pharmaceuticals Ltd.) tablets and 10 Brodil(collected from chemist shop manuctured by ACI Pharmaceuticals Ltd.) tablets was determined using hardness tester Monsanto hardness tester was developed fifty years ago. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded and the zero force reading is deducted from it. The Newton is the preferred unit of force as is recognized by the SI System. The average crushing strengths (hardness values) were determined and the data is presented as both in kilogram and Newton unit in **Table 1**. (Lachman, L., et al, 1990)

Table 1: Hardness test of Ventolin and Brodil tablets

	Ventolin (A)		Brodil (B)	
Tab no.	Hardness (kg)	Hardness (N)	Hardness (kg)	Hardness (N)
1	1	9.81	1.6	15.7
2	1.4	13.73	1.3	12.75
3	1.26	12.36	1.3	12.75
4	1.1	10.79	1.1	10.79
5	1.1	10.79	1.6	15.7
6	1.5	14.72	1.5	14.72
7	1.75	17.17	1.5	14.72
8	1.3	12.75	1.4	13.73
9	1.5	14.72	2	19.62
10	1.05	10.3	1.7	16.68

Line Chart 1: Hardness Test of Ventolin and Brodil



Discussion:

Ideally all the different varieties of testing machines would give the same result if tablets of the same batch are used. In our research work we used Monsanto hardness tester to measure the harness of Ventolin and Brodil tablets and the measured values are found to be surprisingly of resonable range. The lowest value for Ventolin and Brodil was found to be 9.81N and 10.79N and the highest value was found to be 14.72 N and 19.62 N, respectively which are almost double compared to the lowest value.

Result:

The mean hardness value of Ventolin is 12.71 N and of Brodil is 14.72 N. For Ventolin, the crushing strength ranges from 9.81 N to 14.72 N. For Brodil, the crushing strength ranges from 10.79 N to 19.62 N.

Study of Thickness:

Methodology: The objective of this experiment was to measure the thickness of tablets by using Vernier Calipers. Each Ventolin tablets and Brodil tablets was placed horizontally between two jaws. The screw of the caliper was run to hold the tablet and reading was taken in cm from the scale. The average thickness was determined and the thickness determination procedure is presented in **Table 2** and **Table 3.**

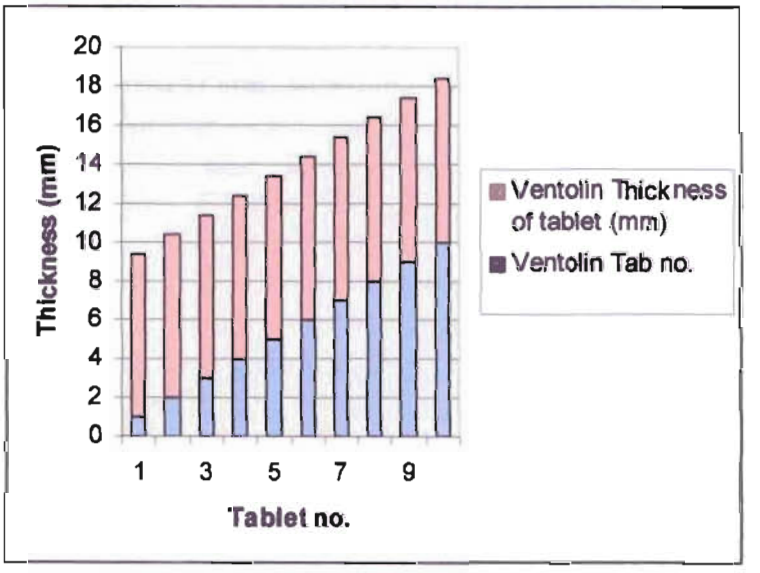
Table 2: Thickness test of Ventolin:

Ventolin					
Tab no.	Reading of cm scale	Reading of vernier scale (mm)	Vernier constant (mm)	Vernier error (mm)	Thickness of tablet (mm)
1	0.8	8	0.05	0.02	8.42
2	0.8	8	0.05	0.02	8.42
3	0.8	8	0.05	0.02	8.42
4	0.8	8	0.05	0.02	8.42
5	0.8	8	0.05	0.02	8.42
6	0.8	8	0.05	0.02	8.42
7	0.8	8	0.05	0.02	8.42
8	0.8	8	0.05	0.02	8.42
9	0.8	8	0.05	0.02	8.42
10	0.8	8	0.05	0.02	8.42

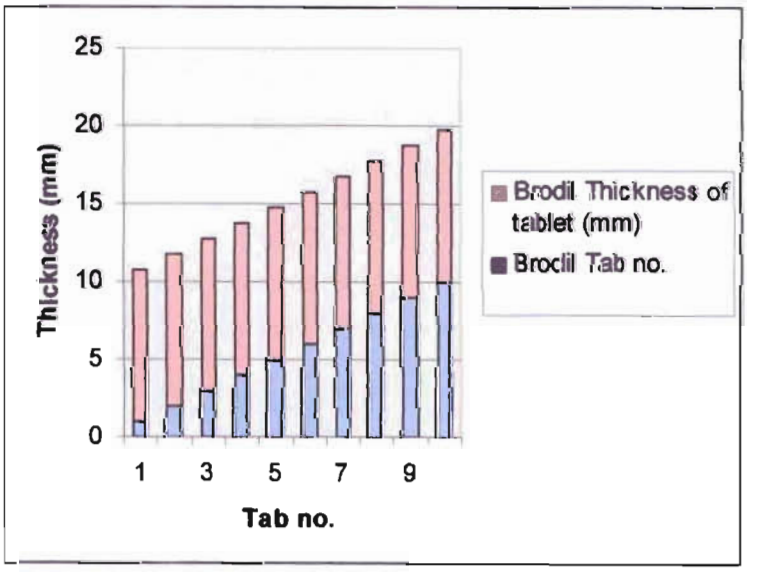
Table 3: Thickness test of Brodil:

Brodil					
Tab no.	Reading of cm scale	Reading of vernier scale (mm)	Vernier constant (mm)	Vernier error (mm)	Thickness of tablet (mm)
1	0.9	15	0.05	0.02	9.77
2	0.9	15	0.05	0.02	9.77
3	0.9	15	0.05	0.02	9.77
4	0.9	15	0.05	0.02	9.77
5	0.9	15	0.05	0.02	9.77
6	0.9	15	0.05	0.02	9.77
7	0.9	15	0.05	0.02	9.77
8	0.9	15	0.05	0.02	9.77
9	0.9	15	0.05	0.02	9.77
10	0.9	15	0.05	0.02	9.77

Bar Diagram 1: Thickness Test of Ventolin



Bar Diagram 2: Thickness Test of Brodil



Discussion:

All the Ventolin and Brodil tablets were found to have a thickness of 8.42 mm and 9.77 mm, respectively. So, there were no variations in the thickness of the tablets of the same batch.

Result:

The average thickness of Ventolin was found to be 8.42 mm. The average thickness of Brodil was found to be 9.77 mm.

Study of Weight Variation:

Methodology: The weight variation test is a satisfactory method of determining the drug content uniformity of tablets if the tablets were all or sentially all(90-95%) active ingredient, or if the uniformity of the drug distribution in the granulation or powder from which the tablets were made were perfect. Composite samples of tablets (usually 10) are taken and weight throughout the compression process. The composite weight is divided by 10, provides an acceptable average weight, there could be tablets excessively underweight or overweight. To solve this problem the USP/NF provides limits for the permissible variations in weights of individual tablets expressed as a percentage of the average weight of the sample. Electronic weighing balance was used to weigh ten randomly withdrawn tablets of both Ventolin and Brodil. The average of the weight was calculated and considered as an individual weight of the tablet. The weight variation test is presented in **Table 4** and **Table 5.** (Lachman,L. et al, 1990)

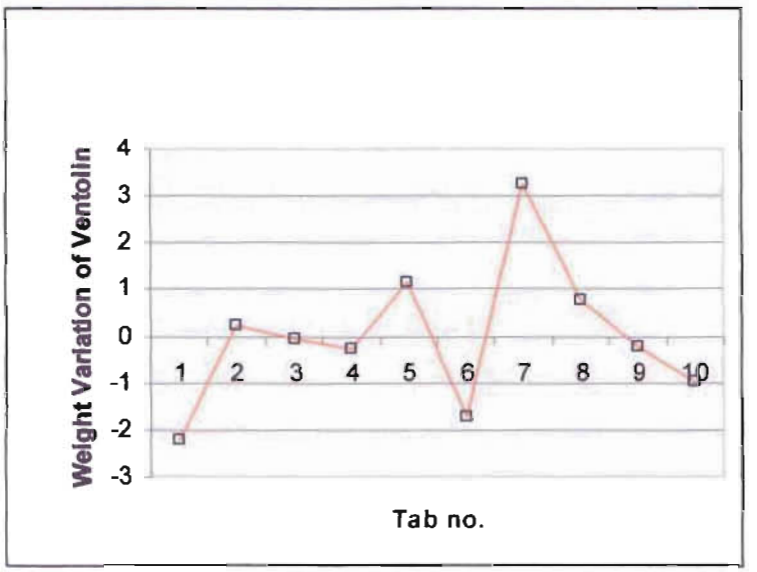
Table 4: Weight Variation Test of Ventolin:

Tab no.	Wt of Ventolin (gm)	Avg wt (gm)	Weight variation [((Avg. wt. - Ini. Wt.)/Avg. wt.)*100]
1	0.2054	0.20097	-2.20
2	0.2005		0.23
3	0.2011		-0.06
4	0.2015		-0.26
5	0.1987		1.13
6	0.2044		-1.71
7	0.1944		3.27
8	0.1994		0.78
9	0.2014		-0.21
10	0.2029		-0.96

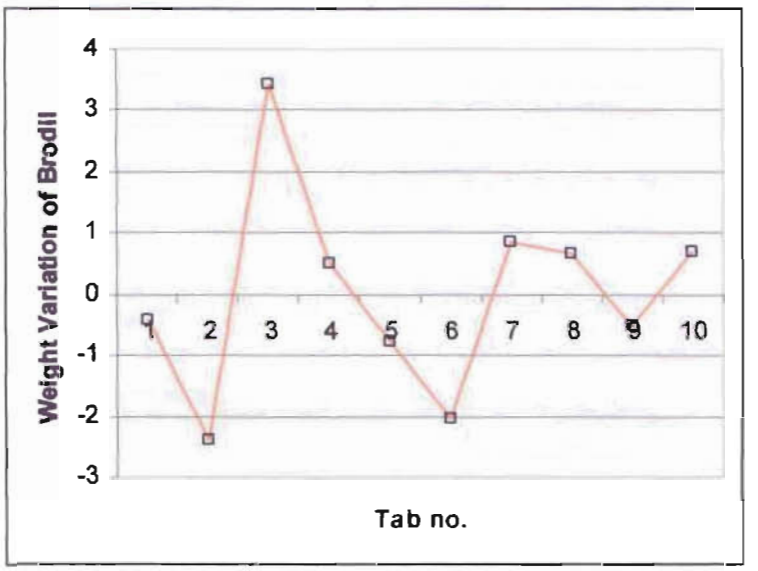
Table 5: Weight Variation Test of Brodil:

Tab no.	Wt of Brodil(gm)	Avg wt (gm)	Weight variation [((Avg. wt. - Ini. Wt.)/Avg. wt.)*100]
1	0.1977	0.19688	-0.42
2	0.2016		-2.40
3	0.1901		3.44
4	0.1959		0.50
5	0.1984		-0.77
6	0.2009		-2.04
7	0.1952		0.85
8	0.1956		0.65
9	0.1979		-0.52
10	0.1955		0.70

Line Chart 2: Weight Variation Test of Ventolin:



Line Chart 3: Weight Variation Test of Brodil:



Discussion:

Tablets are required to meet a weight variation test where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. The variation from the average weight in the weights should be not more than ± 10 if the average weight is 130 mg or less. In my weight variation test of Ventolin tablet the average weight was found to be 0.20097 gm and average weight of Brodil tablet was found to be 0.19688 gm.

Result:

The average weight of Ventolin tablet was found to be 0.20097 gm. The average weight of Brodil tablet was found to be 0.19688 gm. The percentage difference or the weight variation did not exceed the ± 10% limit.

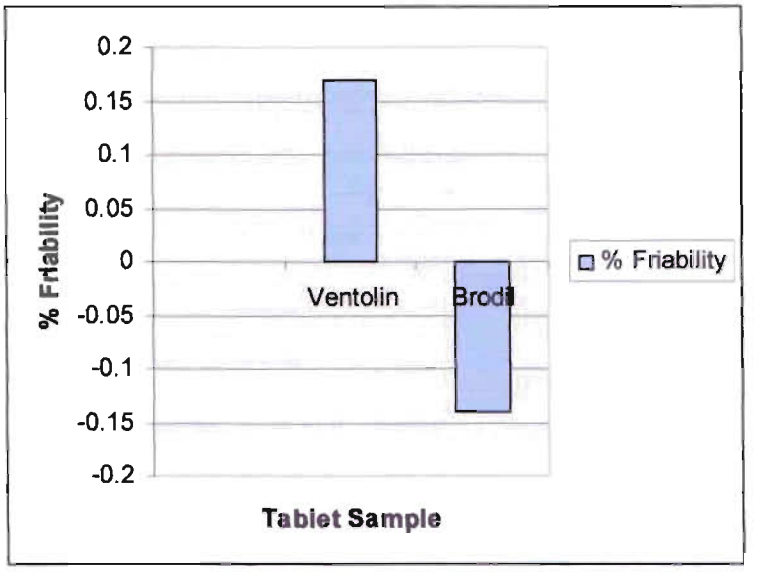
Study of Friability:

Methodology: The laboratory friability tester is known as the Roche friabilitor. This device subjects a number of tablets to the combined effects of abrasion and shock utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets a distance of six inches with each revolution. 10 Ventolin tablets and 10 Brodil tablets were placed in the friabilitor, which was then operated for 100 revolutions. The tablets were then dusted and reweighed. Percent friability of Ventolin and Brodil are shown in the **Table 6.** (Lachman,L. et al, 1990)

Table 6: Friability test of Ventolin and Brodil

Tab Sample	Initial weight (of 10 tabs)	Final weight (of 10 tabs)	% Friability
Ventolin	2.0097	2.0131	0.17
Brodil	1.9688	1.966	-0.14

Bar Diagram 3: Friability Test of Ventolin and Brodil



Discussion:

Normally, a preweighed tablet sample is placed in the friabilitor. The tablet samples are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable. Here, % friability of Ventolin was found to be0.17 and of Brodil was found to be – 0.14.

Result:

% friability of Ventolin was found to be 0.17 and of Brodil was found to be – 0.14. According to the Friability Test, Ventolin tablets were acceptable and Brodil tablets were not acceptable.

Study of Dissolution:

Preparation of the Dissolution Medium:

Methodology: Laboratory of East West University supplied 32% w/v HCl. The molecular weight of HCl is 36.5. 32 gm HCl was dissolved in 100 ml solution. Then calculated with 10 ml of HCl and thus found 31.25 ml HCl solution. This solution was then made upto 1000 ml of HCl solution and 10 ml from this solution was taken and again made up to 1000ml of HCl solution according to British Pharmacopoeia (BP).

In vitro release studies:

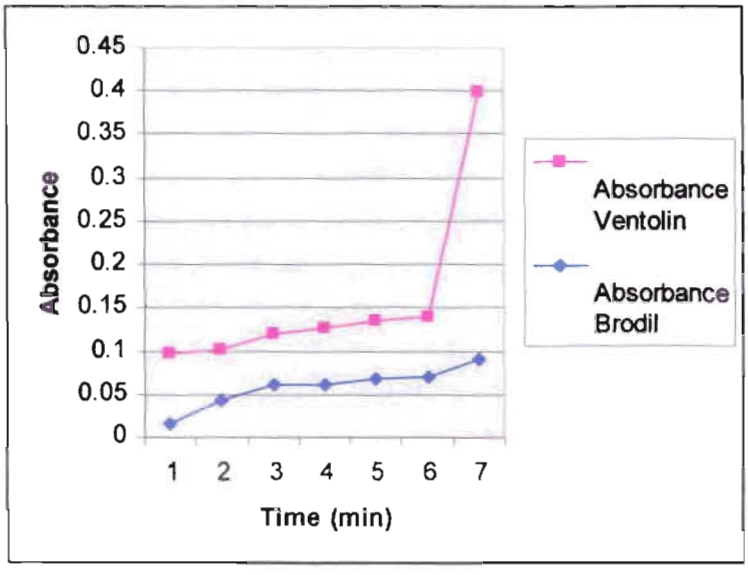
In vitro dissolution test shows (1) that the release of the drug from the tablet is as close as possible to 100% and (2) that the rate of drug release is uniform batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective. A single tablet is placed in a paddle (apparatus 2), formed from a blade and shaft, as the stirring element. The dosage form is allowed to sink to the bottom of the flask before stirring. The paddle is immersed in the dissolution medium contained in a 100ml flask.the flask is maintained at 37 ° C (± 0.5 °C) by a constant temperature bath. The test tolerance is expressed as a percentage of the labeled amount of drug dissolved in the time limit. Dissolution studies were carried out by using 1000 ml HCL solution as a dissolution medium in every vessel. Ten milliliter (ml) samples were taken at regular intervals of 10, 20, 30, 45, 60, 90 and 120 minutes. After each sampling the volume loss was added up by transferring the prepared media in each vessel. Absorbance was measured with single beam spectrophotometer (HACH, Model no DR/400UV-VIS, USA) at 276nm as directed by the BP. Reference solution was prepared by diluting 0.008 mg of Salbutamol sulfate in HCl and then diluted to 100 ml with the same HCl acid. Then 10 ml of the solution was diluted to 100ml with the same HCl acid. Then

absorbance was measured at 276 nm. The data of absorbance at 276 nm are inscribed in **Table 7.**

Table 7: Dissolution Test of Ventolin and Brodil:

	Absorbance	
Time	Ventolin	Brodil
10	0.081	0.015
20	0.059	0.042
30	0.059	0.060
45	0.067	0.060
60	0.067	0.067
90	0.069	0.070
120	0.309	0.090

Line Chart 4: Dissolution Test of Ventolin and Brodil:



Discussion:

The absorbance of the tablets should be increased with the time. In case of Ventolin, initially absorbance had decreased in 20 minutes. Then, absorbance has gradually increased upto 90 minutes. After 120 minutes there was a drastic increase in the absorbance (0.309) which was very abnormal. Absorbance values of Brodil had gradually increased with the time. There was no sudden unexpected change in case of Brodil.

Result:

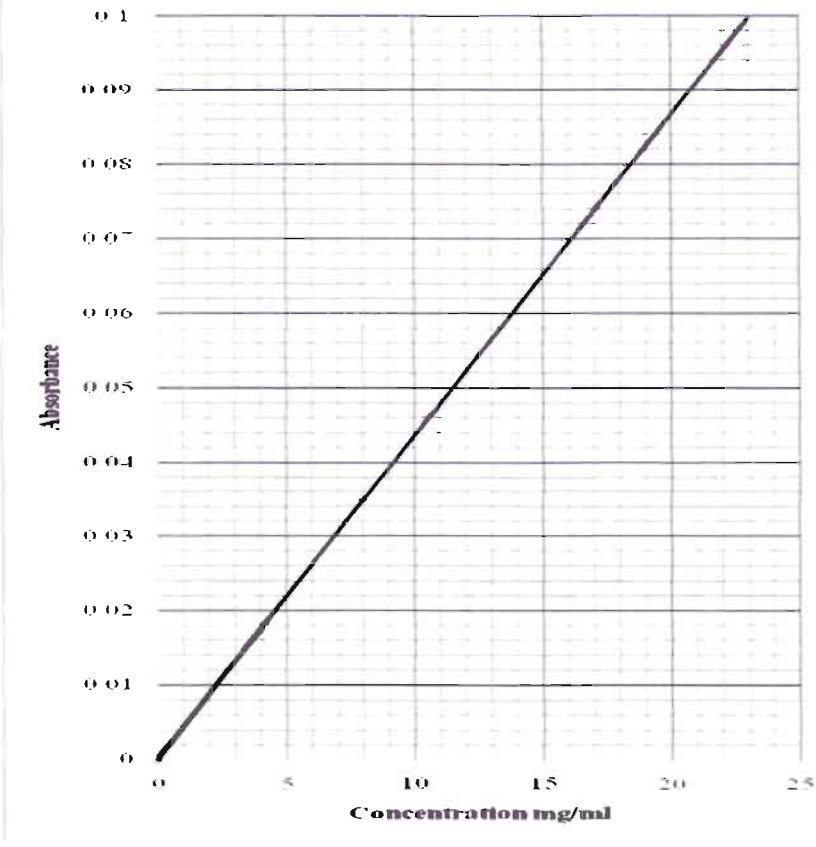
For Ventolin absorbance after 10 minutes and 120 minutes are not acceptable. In case of Brodil the absorbance pattern with time was quite satisfactory.

Preparation of the Standard Curve:

As the concentration of the different withdrawn solution of Salbutamol Sulphate taken at different time intervals namely at 10, 20, 30, 45, 60, 90 and 120 minutes was unknown, it was decided to prepare a standard curve of pure Salbutamol Sulphate. To begin with 0.008g or 8mg of the crude sample was weight in an electronic balance and was dissolved in 100 ml of the prepared medium of 0.1 M HCL in a volumetric flask where the concentration became 0.08 mg/ml. 10 ml of the solution was again diluted with the same medium of 0.1 M HCL to prepare a solution having concentration of 0.008mg/ml. Both the solution having concentration of 0.008mg/ml were taken to measure the absorbance at 276nm in the single beam UV spectrophotometer (HACH, Model no DR/400UV-VIS, USA). Absorbances were recorded as 0.035 for the solution having concentration of 0.008mg/ml. By plotting the value in Microsoft Excel 2003 application the following line

chart 5 was found in which each block of X axis was assumed to be 1 and each 5 block of Y axis was assumed to be 0.01.

Line Chart 5: Standard Curve of Crude Salbutamol Sulphate at 276 nm



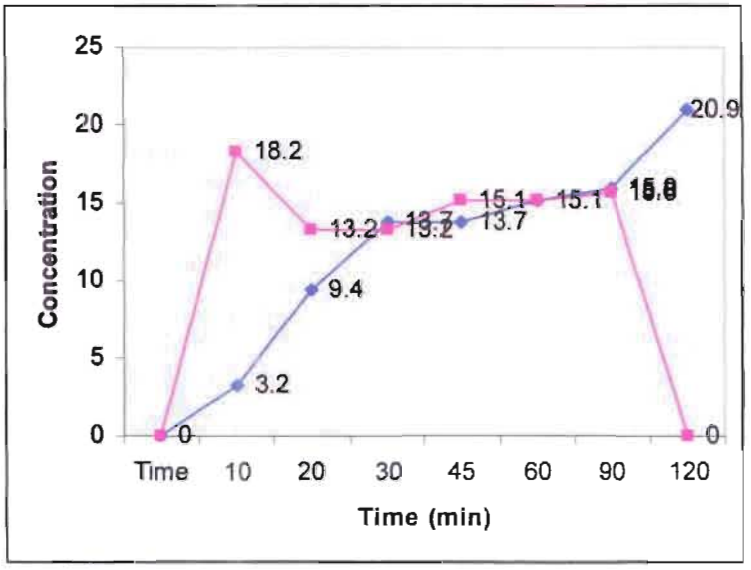
Calculation of concentration of Salbutamol Sulphate:

Calculation of the concentrations of different solution of Salbutamol Sulphate which was previously tested its absorbance at 276 nm were performed by plotting the absorbance data on the Y axis of the graph paper. All the absorbance found at several time intervals namely at 10, 20, 30, 45, 60, 90 and 120 minutes were plotted in the graph paper on the Y axis and a perpendicular was drawn from each of the absorbance value plotted on the Y axis. The point at which the perpendicular intersected was recorded and another perpendicular was drawn from the intercepted point on the slope previously drawn on the standard curve of the crude sample of Salbutamol Sulphate. The point at which the new perpendicular intercepted was found to be the concentration of Salbutamol Sulphate. All the different absorbance of Salbutamol Sulphate solution were plotted in similar way to get the concentration from the standard curve of crude Salbutamol Sulphate. The concentrations of the different solutions of Salbutamol Sulphate are presented in **Table 8.**

Table 8: Concentration of Ventolin and Brodil calculated from the Standard Curve

	Concentration (mg/ml)	
Time	**Ventolin**	**Brodil**
10	18.2	3.2
20	13.2	9.4
30	13.2	13.7
45	15.1	13.7
60	15.1	15.1
90	15.6	15.9
120	-	20.9

Line Chart 6: Concentration of Brodil and Ventolin Tablets at 276nm



Discussion:

The concentration vs time profile graph at 276 nm was found satisfactory as it was observed from the graph that it maintained a steady state concentration. Five values of each Brodil and Ventolin maintained a concentration above the mean steady state concentration which was desired for a sustained release formulation. After 120 minutes the concentration of Brodil was found as 20.9 mg/ml.

Limitations:

A few limitations were found during the entire research work. Among them some were major and some were minor. The limitations were:

- There was no distilled water supply which is one of the most important parameter of studying the release kinetics of tablets.
- The Dissolution Tester used was not a proper functioning one. Sometimes it rotated at more than 150 rpms which was abnormal and unexpected. It mostly hampered the dissolution of Ventolin. Due to mechanical problem, abnormal absorbance of Ventolin was found at 120 minutes interval.
- The Hardness Tester was not giving appropriate readings all the times.
- During Thickness Testing, same values were found for all the tablets which is quite unusual. So, I think something went wrong during measuring the thickness of the tablets.
- The solution taken from the Dissolution Tester should be filtered properly before diluting it in the 100 ml volumetric flask. But no such filtration was followed during the Dissolution Testing.
- Salbutamol Sulphate is highly photo sensitive. But during weighing the crude Salbutamol Sulphate proper sensitive atmosphere was not maintained.

Recommendations:

This research work could have been done more better if -

1) there was proper supply of distilled water,

2) the Dissolution Tester functioned properly,

3) the Hardness Tester Worked properly,

4) the Thickness Tester functioned properly,

5) the dissolute solution was filtered properly and

6) highly-hygroscopic condition was maintained.

Conclusion:

In conclusion, the Salbutamol Sulphate tablets are formulated to normalize abnormal physiological function related to Asthma. Ventolin is more effective oral therapy than Brodil in the treatment of Asthma. Ventolin significantly improve the wanted /unwanted effects which is a general concern in therapeutics. This whole research work concludes that Ventolin marketed by GlaxoSmith Kline Pharmaceuticals Ltd. have an unique release pattern as required by the specified drug release properties. On the other hand, Brodil marketed by ACI Pharmaceuticals Ltd. not provided required unique release pattern and optimum therapeutic efficacy level.

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