Comparative Analysis of In Vitro Release Kinetics Of Sultolin® and Salbutal®

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

Submitted by: Shamsunnaher
ID: 2006-2-70-117
Submission date: 24 December 2009

Department of Pharmacy
East West University

ACKNOWLEDGEMENTS

All praise is for all mighty Allah who has given me the opportunity to complete my B.Pharm research & the opportunity to study the subject.

I would like to express my deep sense of gratitude to my supervisor and respected teacher, Mr. Atiqul Haque Pathan, Senior Lecturer, Department of Pharmacy, East West University, for his constant supervision, intense support, enthusiastic encouragements and constructive criticism during the research work. His timely advice and encouragement have made it possible for me to accomplish the task as per schedule.

After that I want to demonstrate my gratitude for our honorable Chairperson Dr. Chowdhury Faiz Hossain for his superior supervision.

I must gratefully acknowdge Incepta Pharmaceuticals Ltd. for providing the gift of crude sample of salbutamol.

I also want to thank our Lab Instructor Razia sultana to help us run the dissolution tester and UV spectrophotometer authentically.

I am thankful to my other co-researchers Shahreen Raihana, Kazi Ireen, Md. Faisal Mahmud without whose enthusiastic cooperation this study would not have been completed.

I am especially thankful to my very best friend Sazib, for secretarial assistance, and help me in a million other ways which enabled me to spend on this research work.

Finally, I express my sincere gratitude to my caring parents for guiding me all through my life and encouraging me to carryout this research.

Shamsunnaher

Shamsunnaher

26-12-09

Declaration of Guide

This is to certify that Shamsun naher, student of Department of Pharmacy, East West University, has performed this research titled "Comparative analysis of in vitro release kinetics of Sultolin® (Square Pharmaceuticals Ltd.), and Salbutal® (Sunofi Aventis Pharmaceuticals Ltd.)"

Her work is genuine. I have gone through the research and the work is up to my satisfaction.

A.H. Pathan
06.12.09

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

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

ABSTRACT

Purpose*:** The purpose of this research work was to investigate the release pattern of Salbutamol Sulphate from two different brands (SULTOLIN® & SALBUTAL®) of Bangladesh. ***Method: Thirty tablets of each brand were collected from the market and were characterized by physical parameters like hardness, thickness, weight variation and dissolution studies. Salbutamol Sulphate release was investigated using the method inscribed in dissolution study part. Dissolution tests for tablets and capsules of British Pharmacopoeia. Hardness of the withdrawn samples from the market was measured by hardness tester (Veego, Germany). Thickness of the samples was measured by Vernier Calipers. Friability of the samples was measured by using Roche Friability Tester. Dissolution of the taken samples was investigated using dissolution tester (RC6, Vanguard Pharmaceuticals, USA) to evaluate release kinetics. Because with the help of in vitro release data we can also predict the in vivo release as well as bioavailability of the drug. For this purpose stomach like environment was created. ***Result*:** Mean hardness value of Salbutamol (Sultolin; Salbutal) tablets was found to be (9.99; 13.03) N. Mean thickness value of Salbutamol (Sultolin; Salbutal) tablets was found to be (8.17; 6.32) cm. Average weight of Salbutamol (Sultolin; Salbutal) was (o.1710; 0.1008). And % loss of Salbutamol (Sultolin; Salbutal) was (0.37; -0.10). ***Conclusion:*** The release pattern of Salbutamol Sulphate 4mg tablet did not fulfill its requirement to provide desired and optimum release of the drug with the increase of time due to prior limitation.

Keywords: **Salbutamol Sulphate, Dissolution, Hardness, Thickness, Friability, Stomach, Release pattern.**

TABLE OF CONTENT	
Topic	Page no.

AIM OF THIS RESEARCH WORK:

The aim of my research work is to compare in vitro release kinetics between two Salbutamol Sulphate brands (**SULTOLIN® & SALBUTAL®**) in Bangladesh.

OBJECTIVES OF THIS RESEARCH WORK:

- To assess the overall production quality.
- To assess uniformity of the rate of release of the active ingredient from tablet matrix of different manufacturers in Bangladesh.
- To assess the rate of drug absorption, as well as bioavailability & efficacy of that drug.

INTRODUCTION:

Asthma is excessively common among the individuals (up to 10% in adults and 35% in children). Asthma is differently distributed in the world. Asthma incidence is 1%/y in average. Children are at greater risk of asthma than adults, which could be due to a cohort effect. Severe asthma is reported by 1-3% of the general population (children and adults respectively). Recent population-based data show that the asthma prevalence increase observed worldwide in the past 30 years has now stopped in industrialized countries. Such phenomenon has been paralleled by an increase in the use of asthma medications. The development and phenotypic expression of asthma depends on a complex interaction between genetic and environmental factors. Gene-environment interactions already in early life should be explored to understand asthma epidemiological evolution.[1]

Asthma is a chronic disease associated with substantial morbidity, mortality, and health care use. Between 1980 and 1994, the self-reported prevalence of asthma increased 75% among all race, sex, and age groups in every region of the United States. Although an estimated 14.6 million persons had asthma in the United States in 1996.[2] In 1999, approximately 16.9 million American adults reported having been told by a healthcarebprofessional that they had asthma. It has been estimated that 7.8 million children age 18 years and younger have asthma. Asthma improves in many children as they age; 50% appear to have "outgrown" asthma by their mild-teens.

However, it is incorrect to consider that these individuals no longer have asthma, because many eventually have a return of symptoms. In 1999, there were 10.8 million office and outpatient visits for asthma, and 2.0 million asthma-related visits to emergency departments. Although death from asthma remains uncommon, death rates had been increasing in recent years but appear to have reached a plateau. In 1999, there were 4657 deaths attributed to asthma. The most common cause of death is believed to be in adequate assessment of the severity of airway obstruction by either practitioner or patient, leading to suboptimal therapy. The cost to society of asthma is substantial. In 2000 alone, it is estimated that direct costs related to asthma exceeded $8.1 billion. These costs include $2.4 billion for medications and $3.5 billion for hospitalizations. Indirect costs of asthma are estimated at $4.6 billion.[4] Asthma affects more than 30 million people in the U.S.--111 people per 1,000--and more than 4,000 died of the disease in 2002, according to the Centers for Disease Control & Prevention 2002 National Health Interview Survey.[5]

More recent studies have suggested a plateauing of the prevalence of the disease. Because establishing the diagnosis of asthma and characterizing the features of the disease have long been difficult for both the clinician and the researcher, studies determining the frequency of asthma across different countries and over time, seeking clues to the etiology of the disease, and monitoring for untoward variations provide the clinician with additional resources to manage patients with asthma.[2]

Local and national studies have also provided insights into the epidemiology of exacerbations of asthma. For example, epidemics of asthma exacerbations in Barcelona, Spain, were eventually linked to exposure to atmospheric soybean dust released during cargo handling at the local port. The highly predictable annual epidemic of asthma exacerbations in school-age children in the northern hemisphere every September, peaking some 17 days after the return to school, appears to be predominantly driven by seasonal rhinovirus infection, probably compounded by other risk factors for asthma exacerbations, including reduction in use of asthma controller therapy over the summer months, exposure to seasonal allergens and possibly the stress of returning to school.

Asthma comprises a range of heterogeneous phenotypes that differ in presentation, etiology and path physiology. The risk factors for each recognized phenotype of asthma include genetic, environmental and host factors. Although a family history of asthma is common, it is neither sufficient nor necessary for the development of asthma. The substantial increases in the incidence of asthma over the past few decades and the geographic variation in both base prevalence rates and the magnitude of the increases support the thesis that environmental changes play a large role in the current asthma epidemic. Furthermore, environmental triggers may affect asthma differently at different times of a person's life, and the relevant risk factors may change over time. Short-term studies of risk factors may suggest a lower likelihood of asthma, whereas the same factors may be associated with greater risk if follow-up is more prolonged. This pattern may relate to overlap between different wheezing phenotypes in early childhood, only some of which persist as asthma in later childhood and adulthood. Because of this phenomenon, we examine here the risk factors for persistent asthma at different ages, specifically the prenatal period, infancy, childhood and, briefly, adulthood.

Sex affects the development of asthma in a time-dependent manner. Until age 13–14 years, the incidence and prevalence of asthma are greater among boys than among girls. Studies through puberty have shown a greater incidence of asthma among adolescent and young adult females and a greater proportion of males with remission of asthma. Before age 12, boys have more severe asthma than girls with higher rates of admission to hospital. In contrast, adult females have more severe asthma than males, with more hospital admissions, slower improvement, longer hospital stays and higher rates of

readmission. Most authors have attributed these changes in prevalence and severity to events of puberty, although mechanisms for differences between the sexes have not been established. In childhood, airway hyper responsiveness is more common and more severe among males; however, airway hyper responsiveness increases in females during adolescence, such that by adulthood it is both more common and more severe among adult women. The influence of some environmental risk factors such as allergens may be modified by sex. In one study of adults, 18% of women with asthma, but only 2.3% of men with asthma, had normal results on common tests related to atrophy (negative skin prick tests, immunoglobulin E < 100 IU/mL and eosinophilia < 5%), which suggested different disease mechanisms between the sexes.[3] The Global Initiative for Asthma estimates that 300 million people worldwide currently have asthma and an additional 100 million people will be diagnosed by 2025. Although asthma can be managed, there is no cure for it.[5]

OVERVIEW OF ASTHMA:

Asthma is a chronic disease that affects ten million patients, resulting annually in two million emergency room visits, 500,000 hospitalizations, and 5000 deaths.[7] Asthma is a chronic inflammation of the body's bronchial (airway) tissues. People with asthma experience shortness of breath, chest tightness, coughing and wheezing. These symptoms intensify during an asthma attack, which occurs when exposure to allergens or other stimuli further inflame the airways, leading to an inability to expel trapped air from the lungs.[8]

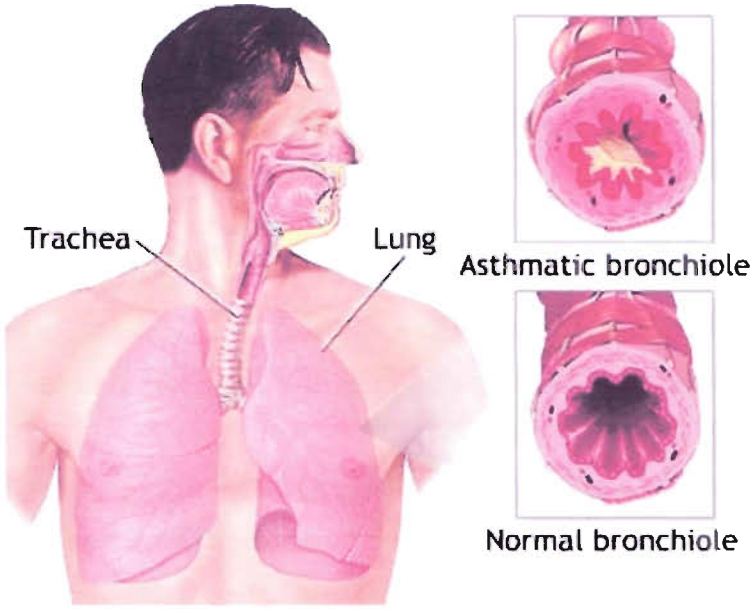


Figure: Asthma with inflamed bronchi tube.[6]

During an asthma attack, the smooth muscle surrounding the bronchi contracts and the lining of the bronchi swells; this swelling is life-threatening because the airways can become blocked.[5] Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased mucous secretion. The symptoms of asthma may be effectively by several drugs, but no agent provides a cure for this obstructive lung disease. Drugs used to treat asthma can be delivered to the lungs by inhalation, or by oral or parenteral route. Inhalation is often preferred, because the drug is delivered directly to the target tissue.[7]

PATHOPHYSIOLOGY OF ASTHMA:

Major Contributing Process

a. Inflammatory Cells (i.e., mast cells, eosinophils, activated T cells, Macrophages, and epithelial cells) secrete mediators and influence the airways directly or via neural mechanisms.

b. Airway Obstruction is responsible fir many of the clinical manifestations of asthma.

(1) Severity of obstruction is variable and believed to be a result of bronchoconstruction, airway wall edema, mucus plug formation, airway remodeling, smooth muscle hypertrophy, and hyperplasia.

(2) Airway Obstruction reduces ventilation to some lung regions, which causes a ventilation/perfusion (V/Q) imbalance that leads to hypoxemia. This is reflected by a reduction in the partial pressure of arterial oxygen observed in moderate to severe exacervations.

c. Hyper responsiveness, an exaggerated response to certain stimuli, is an important feature of asthma and appears to correlate with clinical severity and medication requirements. Increased levels of inflammatory mediators and infiltration by inflammatory cells are thought to be the primary mechanisms responsible for airway hperresponsiveness.

d. Airway inflammation is crucial to development of asthma and contributes to airway hperresponsiveness, airflow obstruction, respiratory symptoms, and disease chronicity. Inflammatory cells and their mediators are responsible for altered mucociliary function, epithelial disruption ranging from minor ciliary loss to severely denuded epithelium, increased airway permeability and reduced clearance of inflammatory mediators.

(1) Acute inflammation is associated with early recruitment of cells to the airway.

(2) Subcute inflammation is associated with recruited and resident cell activation, resulting in more persistent inflammation.

(3) Chronic inflammation is associated with persistent cell damage and ongoing repair, resulting in airway abnormalities that may become permanent.

e. Alteration in autonomic neural control also contributes to obstruction.

(1) Elevated parasympathetic tone and reflex bronchoconstriction may occur as a result of increased cholinergic sensitivity or a change in muscaranic receptor function.

(2) Increased smooth muscle responsiveness may be the result of smooth muscle hypertrophy. Exposure of the nerve endings, caused by inflammation, may also contribute.

f. Airway remodeling can result from inflammation when asthma is poorly controlled. The resulting damage can yield permanent airway abnormalities because of subbasement membrane collagen deposition and fibrosis. Hypertrophy of the airway smooth muscle is another form of tissue remodeling in asthma. These events may occur even in the face of mild disease but does not necessarily occur in asthma patients.

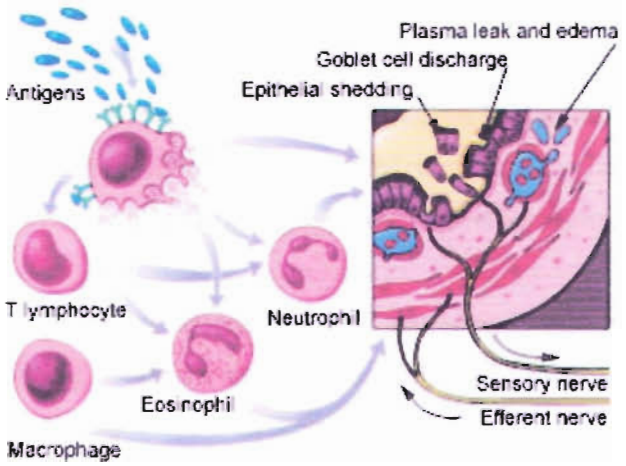


Figure: Pathophysiology of asthma.[6]

GUIDELINES FOR ASTHMA:

During the past two decades, we have witnessed many scientific advances that have improved our understanding of asthma and our ability to manage and control it effectively. However, the diversity of national health care service systems and variations in the availability of asthma therapies require that recommendations for asthma care be adapted to local conditions throughout the global community. In addition, public health officials require information about the costs of asthma care, how to effectively manage this chronic disorder, and education methods to develop asthma care services and programs responsive to the particular needs and circumstances within their countries.

In 1993, the **National Heart, Lung, and Blood Institute** collaborated with the World Health Organization to convene a workshop that led to a Workshop Report: Global Strategy for Asthma Management and Prevention. This presented a comprehensive plan to manage asthma with the goal of reducing chronic disability and premature deaths while allowing patients with asthma to lead productive and fulfilling lives.

At the same time, the **Global Initiative for Asthma (GINA)** was implemented to develop a network of individuals, organizations, and public health officials to disseminate information about the care of patients with asthma while at the same time assuring a mechanism to incorporate the results of scientific investigations into asthma care. Publications based on the **GINA** Report were prepared and have been translated into languages to promote international collaboration and dissemination of information. To disseminate information about asthma care, a **GINA** Assembly was initiated, comprised of asthma care experts from many countries to conduct workshops with local doctors and national opinion leaders and to hold seminars at national and international meetings. In addition, **GINA** initiated an annual World Asthma Day (in 2001) which has gained increasing attention each year to raise awareness about the burden of asthma, and to initiate activities at the local/national level to educate families and health care professionals about effective methods to manage and control asthma.

In spite of these dissemination efforts, international surveys provide direct evidence for suboptimal asthma control in many countries, despite the availability of effective therapies. It is clear that if recommendations contained within this report are to improve care of people with asthma, every effort must be made to encourage health care leaders to assure availability of and access to medications, and develop means to implement effective asthma management programs including the use of appropriate tools to measure success.

In 2002, the **GINA** Report stated that "it is reasonable to expect that in most patients with asthma, control of the disease can, and should be achieved and maintained." To meet this challenge, in 2005, Executive Committee recommended preparation of a new report not only to incorporate updated scientific information but to implement an approach to asthma management based on asthma control, rather than asthma severity. Recommendations to assess, treat and maintain asthma control are provided in the document.

The **GINA** program has been conducted through unrestricted educational grants from AstraZeneca, Boehringer Ingelheim, Chiesi Group, GlaxoSmithKline, Meda Pharma, Merck, Sharp & Dohme, Mitsubishi Tanabe Pharma, Novartis, Nycomed, PharmAxis, and Schering-Plough. The generous

contributions of these companies assured that Committee members could meet together to discuss issues and reach consensus in a constructive and timely manner. The members of the **GINA** Committees are, however, solely responsible for the statements and conclusions presented in this publication.[19]

In 2007, the **National Asthma Education and Prevention Program (NAEPP)** published its third report, Guidelines for the Diagnosis and Management of Asthma, based on the findings of the Expert Panel Report-3 (EPR-3). The EPR-3 followed the EPR-2, released in 1997, and an interim update published in 2002. The EPR-2, while helping greatly with the treatment of asthma, was a report based on expert opinion. The advantage of the EPR-3 is that it is evidence-based.[18]

APPROACHES TO TREATMENT:

Prevention of AG: AB reaction—avoidance of antigen, hyposensitization—possible in extrinsic asthma and if antigen can be identified.

Suppression of inflammation and bronchial hyperreactivity—corticosteroids.

Prevention of release of mediators—mast cell stabilizer.

Antagonism of released mediators—leukotriene antagonists, antihistamines, PAF antagonists.

Blockade of constrictor neurotransmitter—anticholonergics.

Mimicking dilator neurotransmitter—sympathomimetics.

Directly acting bronchodilators—methylxanthines.[9]

Drugs used are—

i. Bronchodilators

A. Sympathomimetics: Adrenaline, Epinephrine, Isoprenaline, Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol.

B. Methylxanthines: Theophylline, Aminophylline, Choline theophyllinate.

C. Anticholinergics: Atropine methonitrate, Ipratropium bromide, Tiotropium bromide.

ii. Leukotriene antagonists

Montelukast, Zafirlukast.

ii Mast cell stabilizers

Sodium cromoglycate, Nedocromil, Ketotifen.

iii Corticosteroids

Systemic: Hydrocortisone, Prednisolone and others.

Inhalation: Beclomethasone dopropionare, Budesonide, Fluticasone propionate, Flunisolide.9

In my research work, we used salbutamol sulphate. It is short acting beta-2 agonists, which relieves the symptoms of asthma quickly.

SALBUTAMOL:

Salbutamol (INN) or albuterol (USAN) is a short-acting β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and COPD.

Salbutamol sulphate is usually given by the inhaled route for direct effect on bronchial smooth muscle. This is usually achieved through a metered dose inhaler (MDI), nebuliser or other proprietary delivery devices (eg. Rotahaler or Autohaler). Salbutamol can also be given orally or intravenously. However, some asthmatics may not respond to these medications as they will not have the required DNA base sequence in a specific gene.

Salbutamol became available in the United Kingdom in 1969 and in the United States in 1980 under the trade name Ventolin.[10] Oral salbutamol still forms the mainstay of treatment for asthma in patients who are unable or unwilling to use the inhaled route of delivery. Cultural preferences has made the oral route the main form of administration in the asian countries.[11]

Salbutamol is one of the β-agonist bronchodilators, the largest group among the various classes of inhaled asthma drugs. The recent evolution of β-agonists can be traced back to adrenal extracts that were used to treat asthma in the late 1800s and the synthesis of epinephrine, also known as adrenaline, at the turn of the 20th century. Adrenaline is the body's natural bronchodilator, so the benefits of epinephrine were recognized in the 20th century for treating asthma. By the 1920s, injectable epinephrine was a preferred asthma treatment, followed by nebulized epinephrine in the 1930s. Adrenaline is released in the body by the adrenal glands when a person is confronted with stress. Unfortunately, injected epinephrine comes with adverse side effects, such as anxiety, heart palpitations, tremors, and increased blood pressure.

Epinephrine and other ß-agonists are categorized as sympathomimetics, meaning they mimic the natural stimulation of the sympathetic nervous system. The unwanted side effects led researchers to search for an adrenaline analog that would retain the bronchodilating quality without the cardiovascular side effects. In the 1940s, isoprenaline was synthesized. It was a more effective bronchodilator that did not increase blood pressure, and it eventually displaced epinephrine as the preferred asthma treatment.

Isoprenaline wasn't an ideal solution, however. It still led to increased heart rate, and the effects were short-lived because it was metabolized quickly. In the 1960s, an increase in asthma deaths in Britain coincided with the increase in sales of isoprenaline inhalers. The circumstantial evidence implicated the high-strength isoprenaline (known as isoprenaline-forte) used in the inhalers. There was also evidence that some patients had used it more frequently despite worsening asthma, although the exact cause of the deaths remains unknown.

Because isoprenaline's brief effect was due to the enzyme catechol-*O*-methyltransferase, a senior medicinal chemist on the team decided to make a noncatechol analog of isoprenaline. The chemistry proved to be difficult--it was not until 1966 that the saligenin analog of isoprenaline was first tested. The tests revealed that the β-agonist was active on the bronchial muscle but did not affect the heart. The next drug in the series to be tested was salbutamol, which was found to be more active at the β_2-receptors, to act even more selectively on bronchial muscle with minimal cardiovascular side effects, and--best of all--to last about four hours.

Salbutamol was one of the earliest drugs developed by rational design. At the time there were no models of the β-receptors to guide the work; the human β-receptor was not characterized until the 1990s. So the researchers relied on an iterative process based on what they knew about the structure and properties of adrenaline and isoprenaline. Asthma is an ancient disease--the history of its treatment goes back about 5,000 years. Salbutamol revolutionized asthma treatment and management within months of appearing on the market, leading to other bronchodilators and an improved quality of life for asthma sufferers.[5]

PHYSICAL PROPERTIES OF SALBUTAMOL:

DESCTIPTION: A white or almost white, crystalline powder. Clear solution in methanol, very pale clear yellow solution.

MELTING POINT: 157-158 °C (with decomposition).

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

IR SPECTRUM:

Salbutamol (potassium bromide disk):

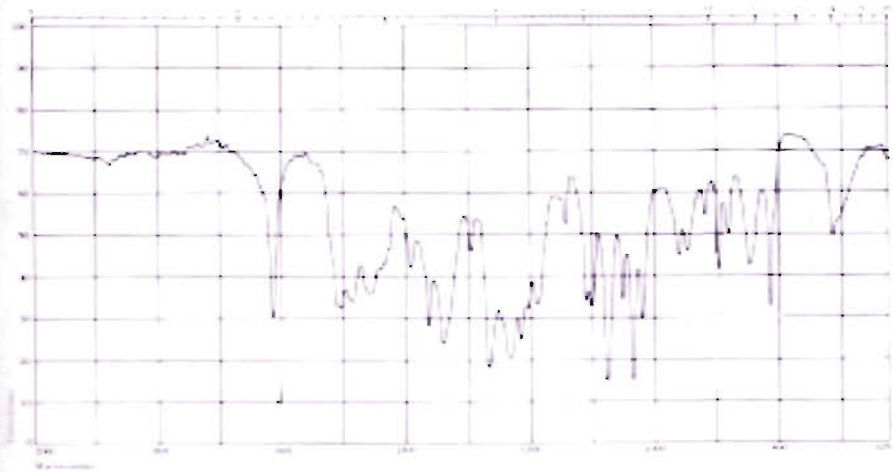


Figure: IR Spectra of Salbutamol.

CHEMICAL PROPERTIES:

CHEMICAL NAME: (±) alpha1-[(tert-butylamino) methyl]-4-hydroxy-m-xylene-alpha, alpha'-diol.

COMPOSITION:

C65.25

H8.84

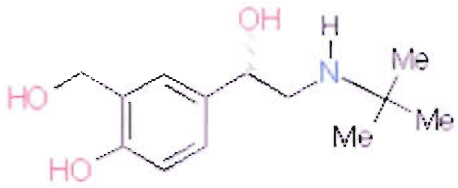
N5.85

O 20.06

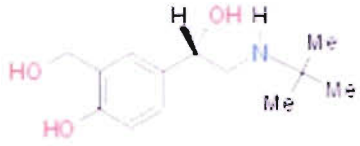
MOLECULAR FORMULA: $C_{13}H_{21}NO_3$.

MOLECULAR WEIGHT: 239.31 g/mol.

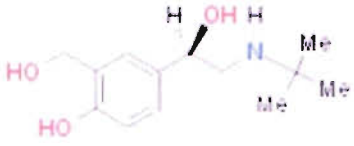
STRUCTURE:



ISOMERS:



R SALBUTAMOL



S SALBUTAMOL [12]

PHARMACOLOGICAL PROPERTIES:

PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Selective beta-2-adrenoceptor agonist. ATC code: R03A C02. Salbutamol is a selective beta-2 adrenoceptor agonist. At therapeutic doses it acts on the beta-2 adrenoceptors of bronchial muscle, with little or no action on the beta-1 adrenoceptors of the heart. It is suitable for the management and prevention of attack in asthma. [13]

MECHANISM OF ACTION:

Salbutamol is a beta (2)-adrenergic agonist and thus it stimulates beta (2)-adrenergic receptors. Binding of albuterol to beta (2)-receptors in the lungs results in relaxation of bronchial smooth muscles. It is believed that salbutamol increases cAMP production by activating adenylate cyclase, and the actions of salbutamol are mediated by cAMP. Increased intracellular cyclic AMP increases the activity of cAMP-dependent protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular calcium concentrations. A lowered intracellular calcium concentration leads to a smooth muscle relaxation. Increased intracellular cyclic AMP concentrations also cause an inhibition of the release of mediators from mast cells in the airways. [14]

PHARMACOKINETIC PROPERTIES:

Salbutamol administered intravenously has a half-life of 4 to 6 hours and is cleared partly renally and partly by metabolism to the inactive 4'-O-sulphate (phenolic sulphate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. The majority of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.

After oral administration, salbutamol is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulphate. Both unchanged drug and conjugate are excreted primarily in the urine. The bioavailability of orally administered salbutamol is about 50%.

DOSAGE & METHOD OF ADMINISTRATION:

Salbutamol has duration of action of 4 to 6 hours in most patients.

Increasing use of beta-2 agonists may be a sign of worsening asthma. Under these conditions a reassessment of the patient's therapy plan may be required and concomitant glucocorticosteroid therapy should be considered.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

Adults: - The usual total daily dose is 12 to 32mg in three or four divided doses.

Children: - 2 - 6 years: The usual total daily dose is 3 to 8mg in three or four divided doses.

6 - 12 years: The usual total daily dose is 6 to 8mg in divided doses.

Over 12 years: The usual total daily dose is 6 to 16mg in divided doses.

Special patient groups:-

In elderly patients or in those known to be unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with 5ml of oral solution (2 milligram salbutamol) three or four times per day.

ADVERSE EFFECT:

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 and <1/10), uncommon (≥ 1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data.

Immune system disorders Very rare: Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse.
Metabolism and nutrition disorders Rare: Hypokalaemia.
Nervous system disorders Very common: Tremor. Common: Headache. Very rare: Hyperactivity.
Cardiac disorders Common: Tachycardia, palpitations. Rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles Unknown: Myocardial ischemia*. * reported spontaneously in post-marketing data therefore frequency regarded as unknown
Musculoskeletal and connective tissue disorders Common: Muscle cramps. Very rare: Feeling of muscle tension.

INTERACTION WITH OTHER MEDICINAL PRODUCTS & OTHER FORMS OF INTERACTION:

Salbutamol and non-selective beta-blocking drugs, such as propranolol, should not usually be prescribed together.

Salbutamol is not contra-indicated in patients under treatment with monoamine oxidase inhibitors (MAOIs), however the effects of salbutamol may be altered by guanethidine, reserpine, methyldopa and tricyclic antidepressants. Caution should be exercised in its use with anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents.

SPECIAL WARNINGS & PRECAUTIONS FOR USE:

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely too normal after a bronchodilator. These patients will require high dose inhaled (e.g. >1mg/day beclomethasone dipropionate) or oral corticosteroid therapy. With this primary background corticosteroid treatment, Ventolin provides essential rescue medication for a severe asthmatic in treating acute exacerbations. Failure to respond promptly or fully to such rescue medication signals a need for urgent medical advice and treatment.

Increasing use of short-acting inhaled beta-2 agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients considered at risk, daily peak flow monitoring may be instituted. Patients should be warned that if either the usual relief is diminished or the usual duration of action reduced, they should not increase the dose or its frequency of administration, but should seek medical advice.

Salbutamol causes peripheral vasodilation which may result in reflex tachycardia and increased cardiac output. Caution should be used in patients with angina, severe tachycardia or thyrotoxicosis.

Potentially serious hypokalaemia may result from beta-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 by hypoxia. It is recommended that serum potassium levels are monitored in such situations.
In common with other beta-adrenoceptor agonists, Ventolin can induce reversible metabolic changes, for example increased blood sugar levels. The diabetic patient may be unable to compensate for this and the development of ketacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of myocardial ischemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

PREGNANCY & LACTATION:

Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. Salbutamol has been in widespread use for many years in human beings without apparent ill consequence; this indicates its well-established use in the management of premature labor. However, as with the majority of drugs, there is little published evidence of its safety in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the fetus at very high dose levels.

During worldwide marketing experience, rare cases of various congenital anomalies, including cleft palate and limb defects have been reported in the offspring of patients being treated with salbutamol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

As salbutamol is probably secreted in breast milk its use in nursing mothers is not recommended unless the expected benefits outweigh any potential risk. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

INCOMPATIBILITY:

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.[13]

HALF LIFE:

1.6 hours.[14]

TOXICITY:

LD_{50}=1100 mg/kg (orally in mice).[14]

SHELF LIFE:

3 years

Diluted solution: 4 weeks. Discard any unused diluted solution.

PRECAUTIONS FOR STORAGE:

Do not store above 25°C.

Store in the original container to protect from light.

For storage of the diluted product, see section 6.3 and protect from light.[13]

EVALUATION OF TABLETS:

To design tablets and later monitor tablet production quality, quantitative evaluations and assessments of a tablet's chemical, physical, and bioavailability properties must be made. Not only could all three property classes have a significant stability profile, but the stability profiles must be interrelated, i.e., chemical breakdown or interactions between tablet components may alter physical tablet properties, greatly changing the bioavailability of a tablet system.

GENERAL APPEARANCE:

The general appearance of a tablet, its visual identity and overall "elegance", is essential for consumer acceptance, for control of lot-to-lot uniformity and general tablet-to tablet uniformity, and for monitoring trouble-free manufacturing. The control of the general appearance of a tablet involves the measurement of a number of attributes such as a tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying markings.

SIZE AND SHAPE:

The size and shape of the tablet can be dimensionally described, monitored, and controlled. A compressed tablet's shape and dimensions are determined by the tooling during the compression process. At a constant compressive load, tablet thickness varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed, and with tablet weight, while a constant die fill, thickness varies with variations in compressive load.

Tablet thickness is consistent with batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in good working order. The crown thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other techniques employed in production control involve placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliperscale.

The method is much more rapid than measurement with a micrometer in providing an overall estimate of tablet thickness in production operations, but it does not as readily provide information on variability between tablets; however, if the punch and die tooling has been satisfactorily standardized and the tablet machine is functioning properly, this method is satisfactory for production work.

UNIQUE IDENTIFICATION MARKINGS:

Pharmaceutical companies manufacturing tablets often use some type of unique markings on the tablets in addition to color, to aid in the rapid identification of their products. These markings utilize some form of embossing, engraving, or printing. A look into the product identification section of the current Physician's Desk Reference (PDR) to the multitude of marking variations, both artistic and informational, that can be produced.

The type of informational markings placed on a tablet usually includes the company name or symbol, a product code such as that from the National Drug Code (NDC) number, the product name, or the product potency. In the future, these identifying marks, in conjugation with a greater diversity of tablet sizes and shapes, may provide the sole means of identification of tablets, if the pharmaceutical industry continues to lose the use of approved Food, Drug, and Cosmetic (FD&C) colors.

ORGANOLEPTIC PROPERTIES:

Many pharmaceuticals tablets use color as a vital means of rapid identification and consumer acceptance. The color of a product must be uniform within a single tablet (referred to as "mottling"), from tablet to tablet, and from lot to lot. Nonunifomity of coloring not only lacks esthetic appeal but could be associated by the consumer with nonunifomity of content and general poor quality of the product. The eye cannot discriminate small differences in color nor it precisely defines color. The eye has limited memory storage capability for color, and the storage of visually acquired data is difficult, which results in people perceiving the same color differently and a single person describing the same color differently at different times.

In addition, visual color comparisons require that a sample be compared against some color standard. color standards themselves are subject to change with time, thus forcing their frequent redefinition, which can lead to a gradual and significant change in acceptable color. Efforts to quantitiate color evaluations have used reflectance spectrophptometry, tristimulus colorimetric measurements, and the use of a microreflectance photometer to measure the color uniformity and gloss on a table surface. The presence of an odor in a batch of tablets could indicate a stability problem, such as the characteristic odor of acetic acid in degrading aspirin tablets; however, the presence of an odor could be characteristic of the drug, (vitamins have a characteristic odor).

Taste is important in consumer acceptance of chewable tablets. Many companies utilize taste panels to judge the preference of different flavors and flavors levels in the development of a product. Owing to the subjectiveness of "taste" preference, however, the control of taste in the production of chewable tablets is often simply the presence or absence of a specified taste. A tablet's level of flaws such as chips, cracks, contamination from foreign solid substances (e.g., hair, drops of oil, and "dirt"), surface texture ("smooth" versus "rough"), and appearance ("shiny" versus "dull") may have a zero –defect specification, but the visual inspection techniques used for detecting or evaluating these characteristics are subjective in nature. Electronic devices that are currently being developed hold promise for making inspection a more quantitative and reproducible operation.[16]

HARDNESS STUDY OF SULTOLIN & SALBUTAL:

Methodology:

Objective: The objective of this experiment is to measure the hardness of tablets by using hardness.
Theory: Too 'soft' tablets can disintegrate during transportation. Too 'hard' tablets could damage tooth. An acceptable 'hardness' is required & tablet strength testing is necessary for both, research &

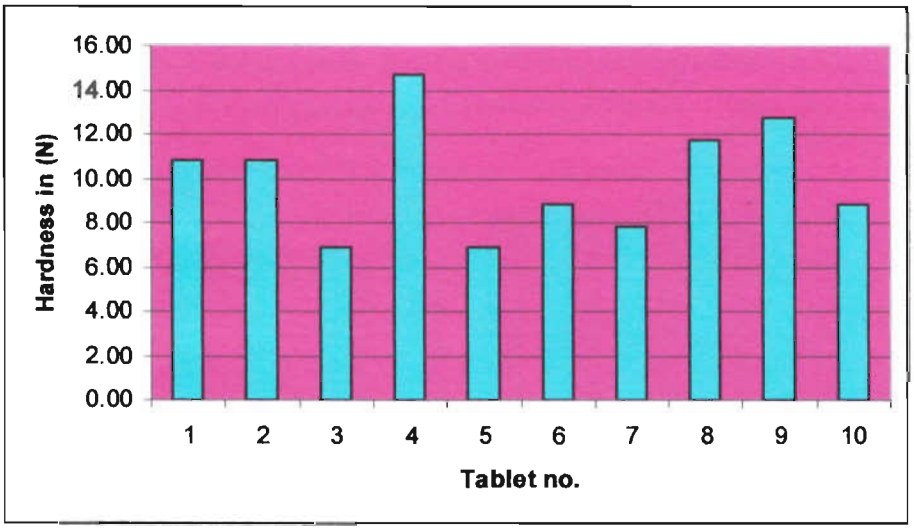
development of new formulations, and for quality control & release pattern. In my research work Monsanto hardness tester was used.

Procedure: First the sliding scale of the hardness tester was kept in zero position. After that one sultolin tablet was placed vertically between two jaws. Then force was applied with a screw thread & spring until the sultolin tablet fractured. Then reading was taken in kg from the sliding scale. The procedure was then repeated for another nine sultolin tablets and another ten sulbutal tablets. Most materials testing is performed using the International System of Units. 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 (for sultolin)** & in **Table 2 (for sulbutal)**.

1.1TABLE 1: HARDNESS TEST OF SULTOLIN TABLETS

Tablet SI no.	Hardness of Sultolin Tablets in kg	Hardness of Sultolin Tablets in Newton
1	1.1	10.78
2	1.1	10.78
3	0.7	6.86
4	1.5	14.70
5	0.7	6.86
6	0.9	8.82
7	0.8	7.84
8	1.2	11.76
9	1.3	12.74
10	0.9	8.82

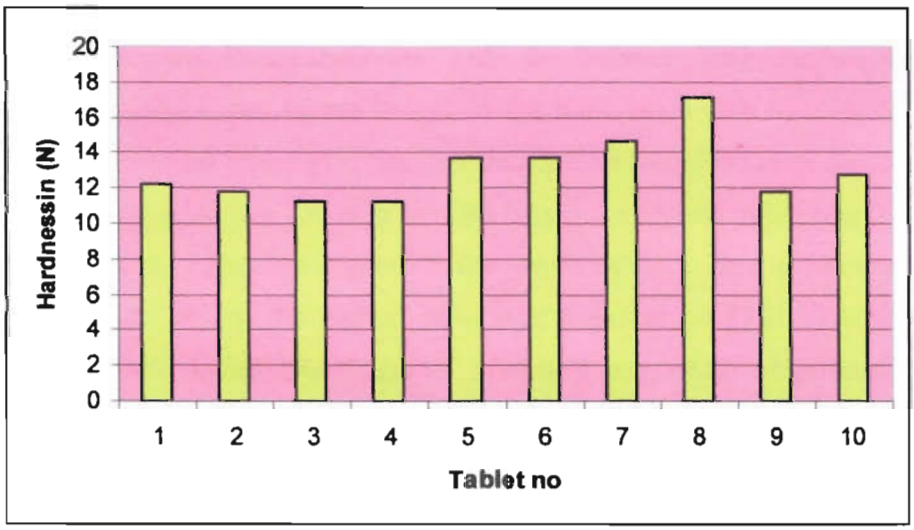
1.1 FIGURE 1: BAR DIAGRAM OF SULTOLIN TABLETS



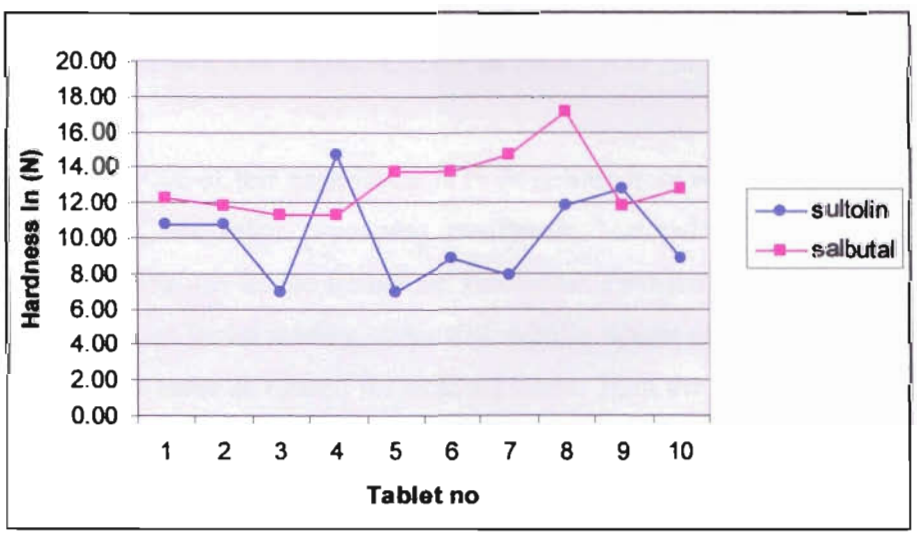
1.1TABLE 2: HARDNESS TEST OF SALBUTAL TABLETS

Tablet SI no.	Hardness of Salbutal Tablets in kg	Hardness of Salbutal Tablets in Newton
1	1.25	12.25
2	1.20	11.76
3	1.15	11.27
4	1.15	11.27
5	1.40	13.72
6	1.40	13.72
7	1.50	14.70
8	1.75	17.15
9	1.20	11.76
10	1.30	12.74

1.1 FIGURE 2: BAR DIAGRAM OF SULTOLIN TABLETS



1.1 LINE CHART 3: COMPERISION OF HARDNESS BETWEEN SULTOLIN & SALBUTAMOL



DISCUSSION:

Hardness is thus sometimes termed the tablet crushing strength. Tablet hardness has been defined as the force required to break a tablet in a diametric compression test. In my research work, Monsanto hardness tester was used to break tablets of two salbutamol brands, which was Sultolin 4mg manufactured by Square Pharmaceuticals Ltd. & Salbutal 4mg manufactured by Aventis Pharmaceuticals Ltd. These two tablets belong to the same batch (Jan 09). Ideally all the different varieties of testing machines would give the same result if tablets of the same batch are used. . In case of Sultolin, the lowest value was found to be 6.86 N and the highest value was found to be 14.70 N which is almost more than double compared to the lowest value. In case of Salbutal, the lowest value was found to be 11.27 N and the highest value was found to be 17.15 N which is almost equal compared to the lowest value. Die filling & lubricants can affect tablet harness. At a constant compression force (fixed distance between upper & lower punches), hardness increases with increasing die fills and decreases with lower die fills. When lubricants are used in too high a concentration or mixed for too long a period.[16]

RESULT:

In case of Sultolin, the mean hardness value is 9.99 N. The crushing strength rages from 6.86 N to 14.70 N.

In case of Salbutal, the mean hardness value is 13.03 N. The crushing strength ranges from 11.27 N to 17.15.

These values represent that variation is more in sultolin tablets than in Salbutal tablets.

FRIABILITY STUDY OF SULTOLIN & SULBUTAL:

Methodology:

Objective: The objective of this experiment is to determine how well tablets withstand up to coating, packaging, shipping, and other processing conditions. Materials: Electronic weighing balance & Friability Tester, which was Roche friabilator. Procedure: First ten tablets of sultolin were weighed, it was considered to be an initial reading. After that sultolin tablets were placed in the section one of the drum of the friability tester & rotated for hundred times. Then the sultolin tablets were re-weighed, it was considered to be as a final reading. The percent loss was then calculated. The whole process was then repeated for another ten tablets of salbutal.[16] According to USP, the tablets should not loose more than one percent of their total weight. Then % loss is presented in **Table 1 (for sultolin)** & in **Table 2 (for sulbutal).**

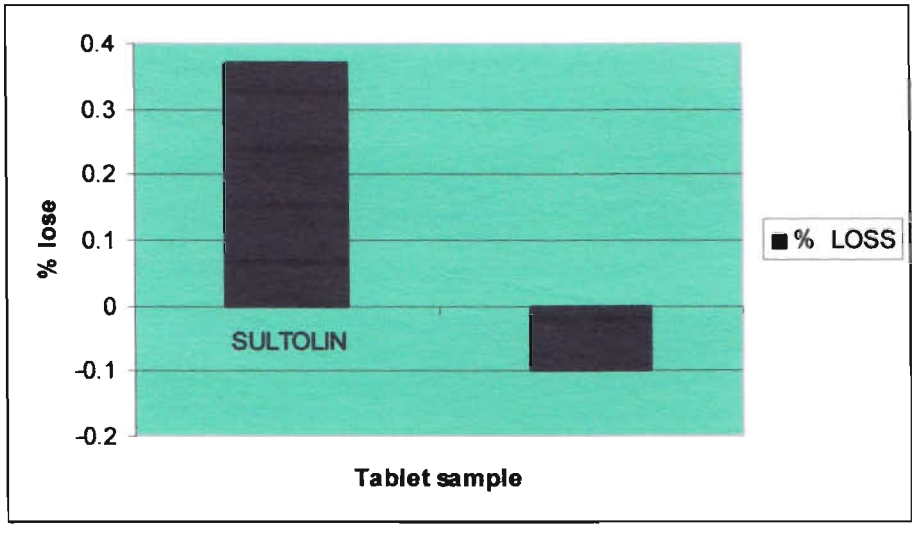
2.1 TABLE 1: FRIABILITY TEST OF SULTOLIN TABLETS

Initial Weight of 10 Tablets in (gm)	Final Weight of 10 Tablets in (gm)	% Loss = (Initial Weight – Final Weight / Initial Weight) × 100
1.7103	1.7166	0.37

2.1 TABLE 2: FRIABILITY TEST OF SALBUTAL TABLETS

Initial Weight of 10 Tablets in (gm)	Final Weight of 10 Tablets in (gm)	% Loss = (Initial Weight – Final Weight / Initial Weight) × 100
1.0086	1.0076	-0.10

2.1FIGURE 1: BAR DIAGRAM OF SULTOLIN & SALBUTAL TABLETS



DISCUSSION:

Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets, tend to "cap" on attrition, losing their crown portions. Therefore, another measure of a tablet's strength, its friability, is often measured. In my research work, Roche friabilator was used for friability testing. Conventional compressed tablets that lose less than 0.5 to 1 % of their weight is considered acceptable. Sometimes, moisture content may affect the tablets friability, and negative result predominates.[16] As we know that Salbutamol Sulphate is a highgroscopic substance, so it can absorb moisture rapidly. And thatiswhy Salbutal gives negative result.

RESULT:

In case of Sultolin tablets, the percent lose of tablets is 0.37.

In case of Salbutal tablets, the percent lose of tablets is -0.10.

THICKNESS STUDY OF SULTOLIN & SULBUTAL:

Methodology:

Objective: The objective of this test is to measure the thickness of tablets by using vernier calipers. Materials used: Vernier caliper was used in this experiment. Procedure: First one tablet was placed horizontally between two jaws. The screw of the calipers was run to hold the tablet. Then reading was taken in cm (centimeter) from the scale. The process was then repeated for remaining nine sultolin tablets. Again, the thicknesses of other ten salbutal tablets were determined by using the same procedure. The average thickness was determined and the thickness determination procedure is presented in **Table 1 (for sultolin) & in Table 2 (for salbutal)**.[17]

3.1 Table 1: Thickness test of Sultolin Tablets

Tablet SI no.	Reading of cm Scale	Reading of Vernier Scale	Vernier constant	Vernier error	Thickness of Tablet (cm)
1	0.8	3.0	0.05	0.02	8.17
2	0.8	3.0	0.05	0.02	8.17
3	0.8	3.0	0.05	0.02	8.17
4	0.8	3.0	0.05	0.02	8.17
5	0.8	3.0	0.05	0.02	8.17
6	0.8	3.0	0.05	0.02	8.17
7	0.8	3.0	0.05	0.02	8.17
8	0.8	3.0	0.05	0.02	8.17
9	0.8	3.0	0.05	0.02	8.17
10	0.8	3.0	0.05	0.02	8.17

3.1 Table 2: Thickness test of Salbutal Tablets

Tablet SI no.	Reading of cm Scale	Reading of Vernier Scale	Vernier constant	Vernier error	Thickness of Tablet (cm)
1	0.6	6	0.05	0.02	6.32
2	0.6	6	0.05	0.02	6.32
3	0.6	6	0.05	0.02	6.32
4	0.6	6	0.05	0.02	6.32
5	0.6	6	0.05	0.02	6.32
6	0.6	6	0.05	0.02	6.32
7	0.6	6	0.05	0.02	6.32
8	0.6	6	0.05	0.02	6.32
9	0.6	6	0.05	0.02	6.32
10	0.6	6	0.05	0.02	6.32

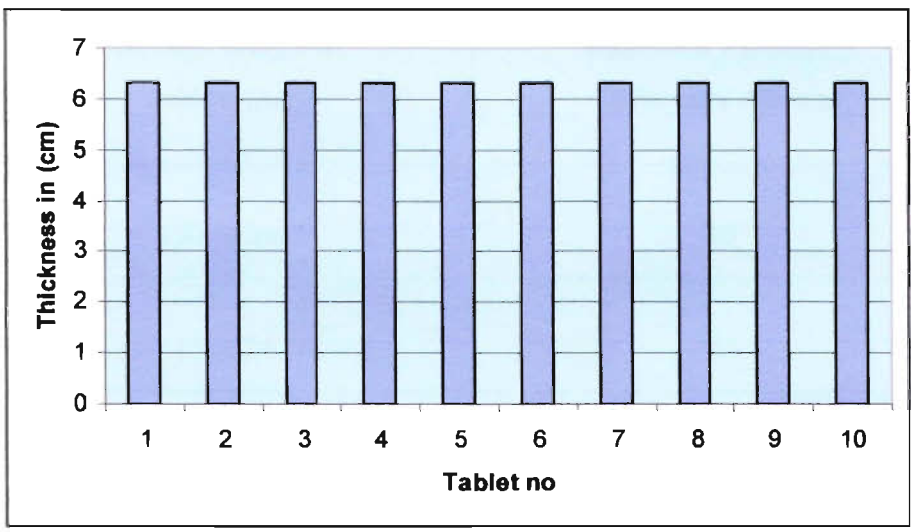
CALCULATION:

Thickness of the tablet is:

Reading of cm scale + Reading of Vernier scale + Vernier error

3.1 FIGURE 1: BAR DIAGRAM 0F THICKNESS TEST OF SULTOLIN TABLETS

3.1 FIGURE 2: BAR DIAGRAM 0F THICKNESS TEST OS SALTOLIN TABLETS



DISCUSSION:

Ten out of ten Sultolin & Salbutal tablets (Salbutamol Sulphate) were found to have a thickness of 8.17 & 6.32 cm. Variation in thickness of the tablets of the same batch were less.

RESULT:

The average thickness was found to be 8.17 (for Sultolin) & 6.32 (for Salbutal) cm.

WEIGHT VARIATION STUDY OF SULTOLIN & SULBUTAL:

Methodology:

Objective: The objective of this experiment is to determine the uniformity of tablet weights. Materials Required: Electronic Weighing Balance was used to weigh the tablets. Procedure: First ten sultolin tablets were taken. After that all the tablets were weighed and average weight was calculated, it was considered as the standard weight of an individual tablet. Then all the tablets were weighed individually & observed whether the individual tablet were within the range or not. Then weight variation test is performed for the ten salbutal tablets by using the same procedure. Then data are plotted in the **Table 1** & **Table 2**. The variation from the average weight in the weights not more than two tablets must not differ more than the percentage listed below:

4.1 TABLE 1: WEIGHT VARIATION TOLERANCES FOR UNCOATED TABLETS

Average Weight of Tablets (mg)	**Maximum Percentage Difference Allowed**
130 or less	10
130-324	7.5
More than 324	5

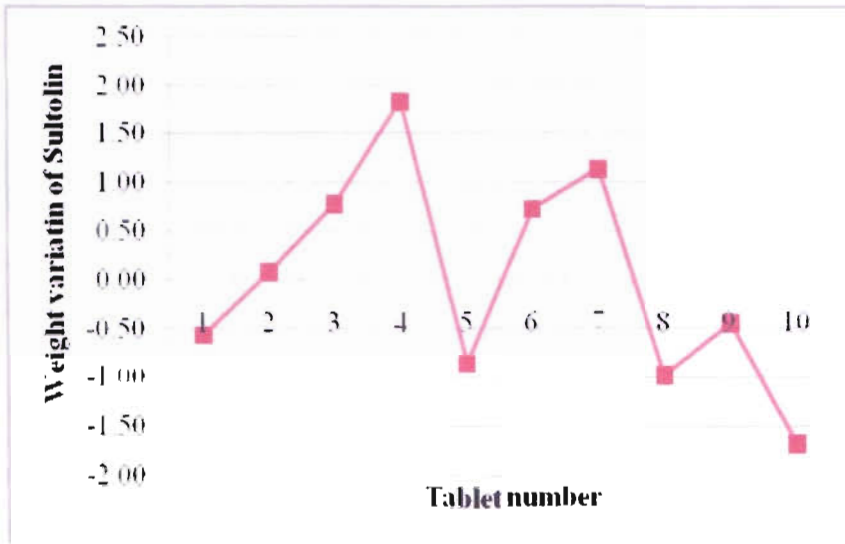
4.1 Table 2: Weight Variation test of Sultolin Tablets

Tablet SI no.	Individual Weight (gm)	Average weight = sum of individual weight/10	Weight variation = (Avg Wt. - Ind. Wt.)×100/A Wt.
1	0.1720	0.1710	-0.42
2	0.1709		0.08
3	0.1697		0.78
4	0.1679		1.83
5	0.1725		-0.86
6	0.1698		0.72
7	0.1691		1.13
8	0.1727		-0.98
9	0.1718		-0.45
10	0.1739		-1.68

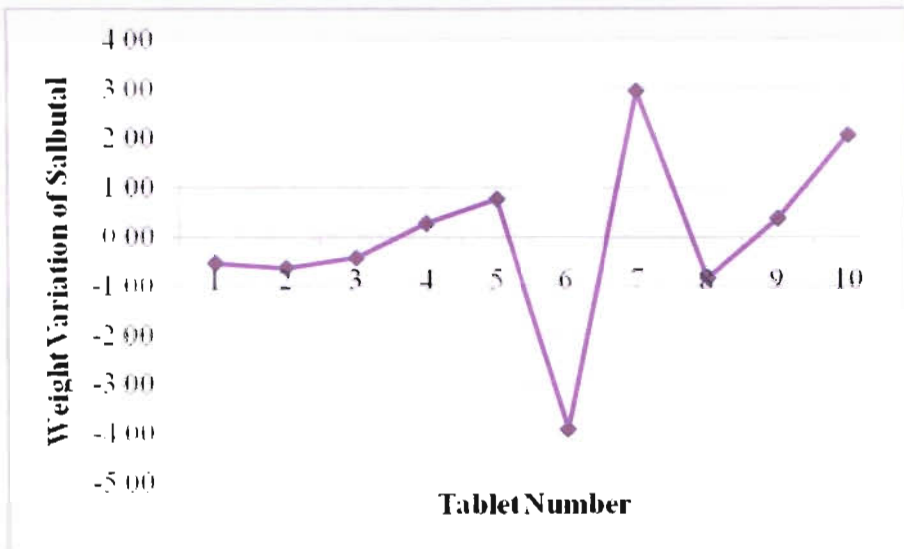
4.1 Table 3: Weight Variation test of Salbutal Tablets

Tablet SI no.	Individual Weight (gm)	Average weight = sum of individual weight/10	Weight variation = (Avg Wt. - Ind. Wt.)×100/A Wt.
1	0.1014	0.1008	-0.53
2	0.1015		-0.40
3	0.1013		-0.43
4	0.1006		0.25
5	0.1001		0.75
6	0.1048		-3.90
7	0.0979		2.93
8	0.1017		-0.83
9	0.1005		0.35
10	0.0988		2.04

4.1 Line diagram 1: Weight Variation test of Sultolin Tablets



4.1 Line diagram 2: Weight Variation test of Salbutal Tablets



DISCUSSION:

The weight variation test would be a satisfactory method of determining the drug content uniformity of tablets if the tablets were all or essentially all (90 to 95%) active ingredient, or if the uniformity of the drug distribution in the granulation or powder from which the tablets were made were perfect. The weight variation test is clearly not sufficient to assure uniform potency of tablets of moderate or low-dose drugs, in which excipients make up the bulk of the tablet weight. [16] 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 Sultolin & Salbutal 4 mg tablet the average weight was found to be 0.1710 gm & 0.1008 gm. So it is within the range and acceptable.

RESULT:

The average weight of the Sultolin & Salbutal (Salbutamol) was found to be 0.1710 gm & o.1008gm. The percentage difference or the weight variation did not exceed the ± 10% limit.

DISSOLUTION STUDY OF SULTOLIN & SULBUTAL TABLETS:

OBJECTIVE: The objective of this experiment is to –

- Evaluate the potential effect of formulation and process variables on the bioavailability of a drug;
- Ensure that preparations comply with product specifications;
- Indicate the performance of the preparations under in vivo conditions.[17]

PREPARATION OF THE DISSOLUTION MEDIUM:

Methodology: The supplied HCL from the East West University laboratory of Pharmacy Department was 32% w/v. As the molecular weight of HCL is 36.5, the 1 M HCL solution contains 36.5 gm theoretically. So, 100ml contains 32gm. Therefore, 10gm contains (BP).[15]

In vitro release studies: The most direct assessment of a drugs release from various tablet formulations or products is accomplished through in vivo bioavailability measurements. The use of in vivo studies is restricted, however, for several reasons: the length of time needed to plan, conduct, and interpret the study; the highly skilled personnel required for human studies; the low precision and high cost of the studies; the use of human subjects for "nonessential" research; and the necessary assumption that a perfect correction exists between diseased patients and the healthy human subjects used in the test.

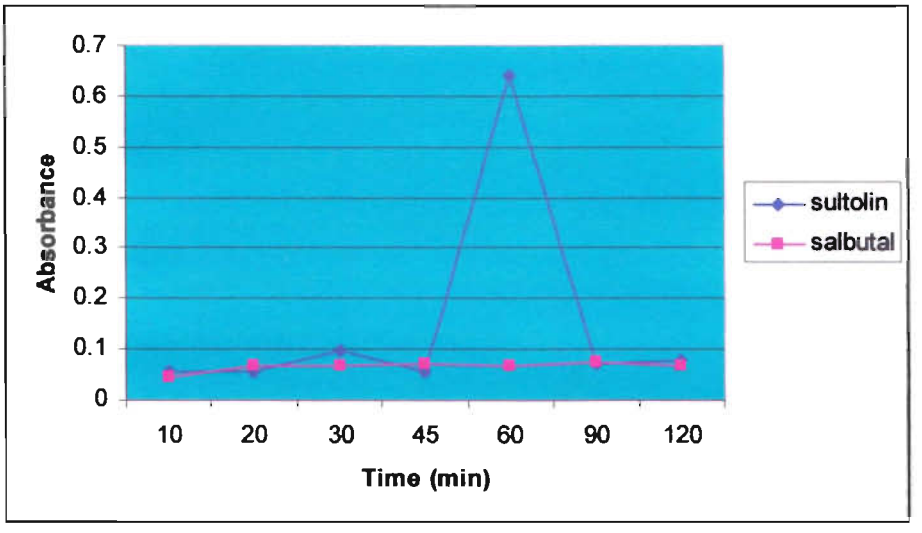
Consequently, in vitro dissolution tests have been extensively studied, developed, and used as an indirect measurement of drug availability, especially in preliminary assessments of formulation factors and manufacturing methods that are likely to influence bioavailability. As with any in vitro test, it is critically important that the dissolution test be correlated with in vivo bioavailability tests.[16]

Methodology: In vitro drug release studies of the collected tablets were conducted using BP XII D Apparatus 1 (Paddle apparatus) by dissolution tester (RC6, Vanguard Pharmaceuticals, USA) at 37° C (± 0.5 °C) and 100 revolutions per minute speed in accordance with BP. Dissolution studies were carried out by using 900 ml 0.1 M HCL solution as a dissolution medium in every vessel. Eight milligram (mg) 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 and 276nm as directed by the BP. Reference Salbutamol solution was prepared by taking 8mg of. Then the absorbance of those solutions of different concentrations was observed with single beam spectrophotometer at and 276nm.[15] The data of absorbance at 276 nm are inscribed in Table 1 and plotted graphically in Line diagram.

5.1 Table 1: Dissolution test of Sultolin & Salbutal Tablets

	Absorbance	
Time	**Sultolin**	**Salbutal**
10	0.054	0.045
20	0.055	0.066
30	0.098	0.067
45	0.055	0.069
60	0.064	0.067
90	0.072	0.076
120	0.077	0.066

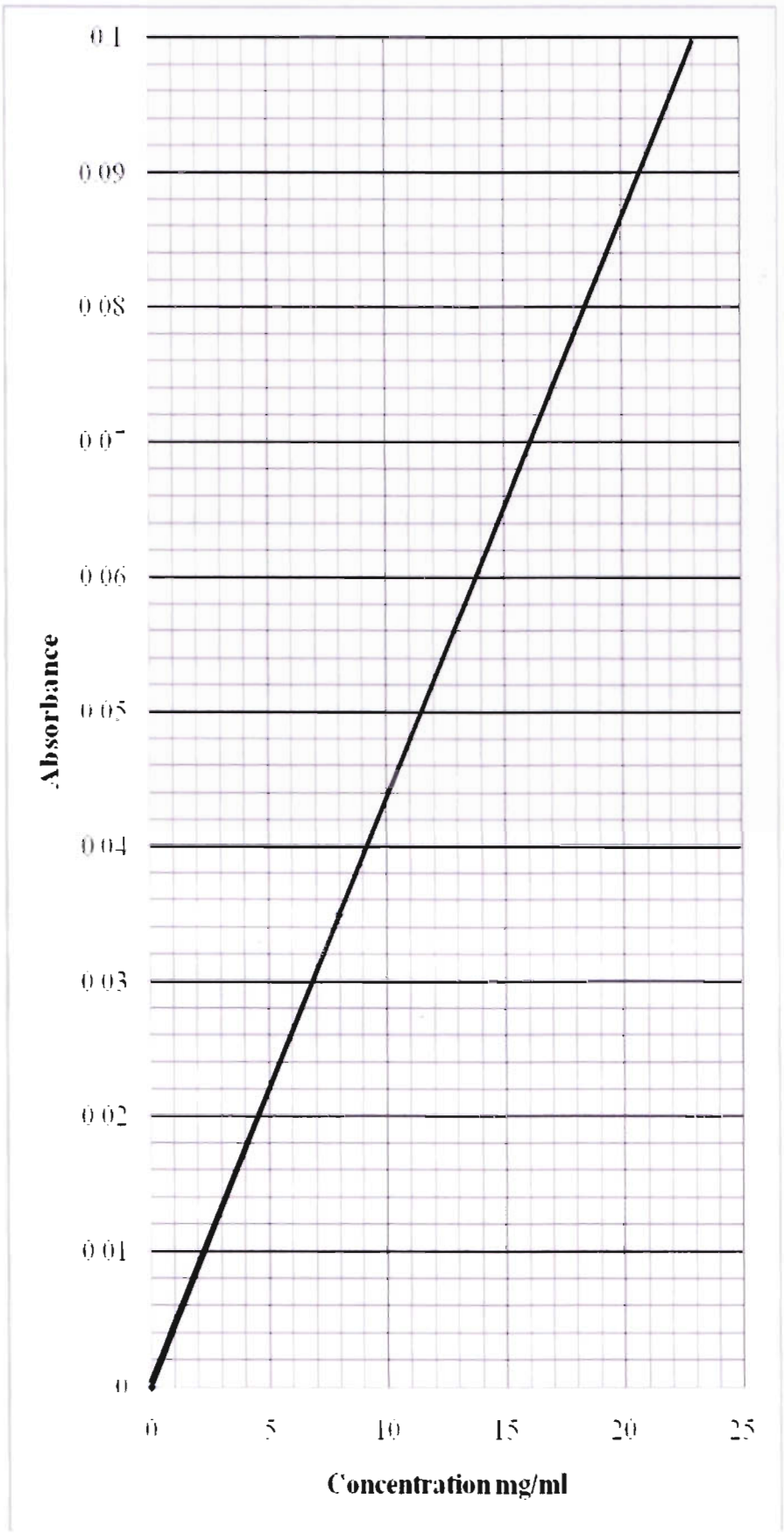
5.1 Line diagram 1: Dissolution test of Sultolin & Salbutal Tablets



PREPARATION of STANDARD CURVE:

As the concentration of the different withdrawn solution of Salbutamol taken at different time intervals namely at 10, 20, 30, 45, 60, 90, 120 minutes was unknown, it was decided to prepare a standard curve of pure Salbutamol which was a kind gift from **Incepta Pharmaceuticals Ltd.** To begin with o.008gm 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 10 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 1mg/ml. Similarly it was diluted four times to a solution having concentration of 0.0001mg/ml. Both the solution having concentration of 0.001mg/ml and 0.0001mg/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 0.001mg/ml and 0.002 for the solution 0.0001 mg/ml. By plotting the value in Microsoft Excel 2003 application the following line **chart 1** was found in which each 1 block of X axis was assumed to be equal to 1 and each 5 block of Y axis was assumed to be equal to 0.01 units.

5.1 LINE CHART 2: STANDARD CURVE of CRUDE SALBUTAMOL SULPHATE at 276 nm


0 1
0 09
0 08
0 07
0 06
0 05
0 04
0 03
0 02
0 01
0
Absorbance
0
5
10
15
20
25
Concentration mg/ml

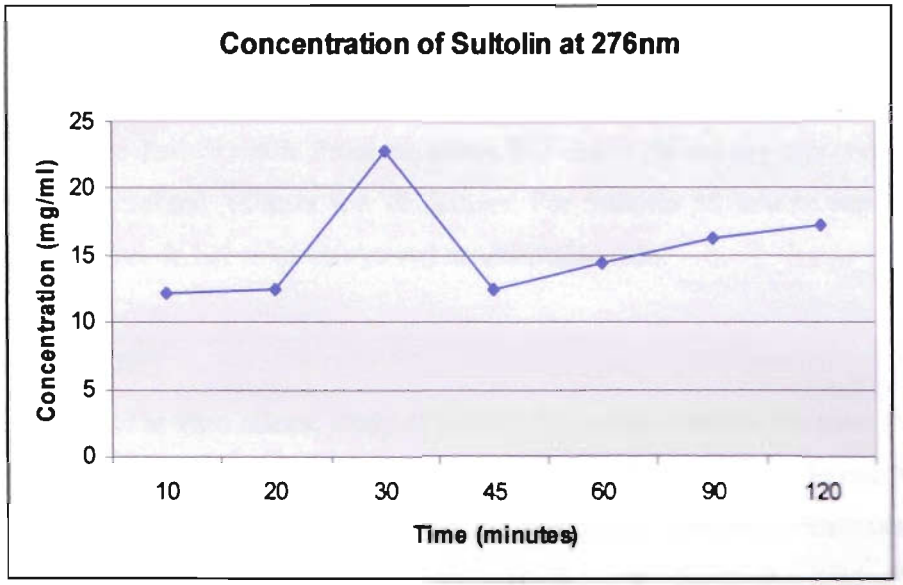
DETERMINATION OF THE CONCENTRATION OF SULTOLIN & SALBUTAL

From the standard curve of the crude Salbutamol Sulphate concentrations of Sultolin & Salbutal were determined after 10, 20, 30, 45, 60, 90 and 120 minutes. Absorbances of different Salbutamol brands were plotted in the Y- axis of the curve. From each absorbance point of Y-axis a horizontal line was drawn which intersected on a point of the standard curve. From each intersected point on standard curve a line was drawn perpendicularly downward to the X-axis. Each line intersected at different points on X-axis representing the concentrations of different brand of Salbutamol at different time intervals. The determined concentrations were listed in Table5.

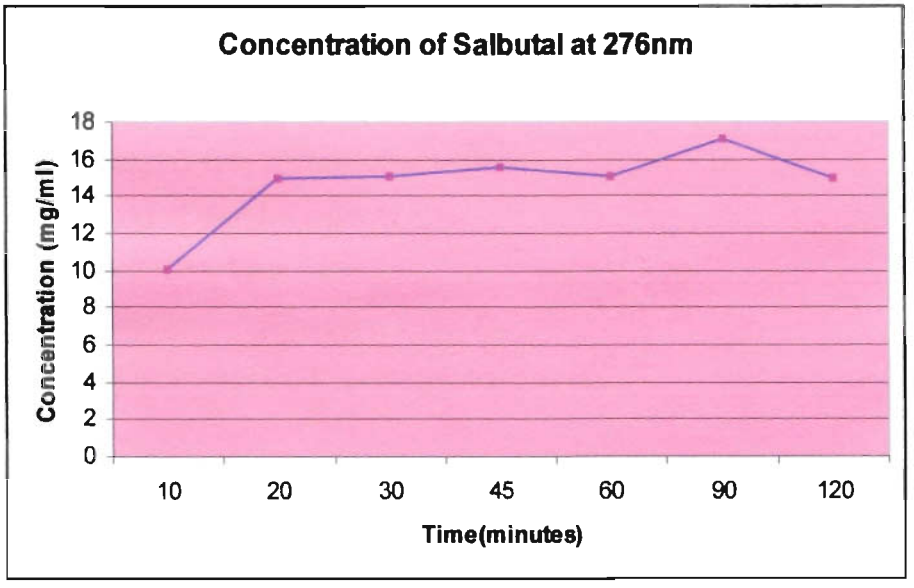
5.1Table 2: Concentration of Sultolin & Salbutal determined from the Standard Curve

	Concentration (mg/ml)	
Time	Sultolin	Salbutal
10	12.2	10.1
20	12.5	15
30	22.7	15.1
45	12.5	15.6
60	14.4	15.1
90	16.2	17.1
120	17.2	15

5.1 FIGURE 3: LINE DIAGRAM of CONCENTRATION OF SULTOLIN at 276nm



5.1 FIGURE 4: LINE DIAGRAM of CONCENTRATION of SALBUTAL at 276nm



DISCUSSION:

In vitro dissolution test was performed to determine the rate of release of the drug. Because absorption as well as overall bioavailability and efficacy of the drug. But, during the testing there were some limitations, like the rpm of the dissolution tester was not fixed. For this reason the matrix of the tablet was came to the top portion of the beaker. We do not have the supply of distill water. Salbutamol is a highly hygroscopic substance; we did not maintain the temperature properly. For these reasons, we did not able to get the desired result. From the above line charts we can say that concentration of Sultolin & Salbutal were increased, excepts few deviations. For Sultolin 30 minute was not accepted. And for Salbutal 60 minutes & 120 minutes showed unacceptable data.

CONCLUSION:

The importance of in vitro release study of tablet is knows-no-bounds. Because absorption is dependent on the rate of release of the tablets. Without absorption no drugs will able to reach the site of action and subsequently, it will not be bioavailable and therapeutically effective. Thereafter, by observing the in vitro release kinetics data of this drug we will further predict the in vivo bioavailability of this. But in my research work, there were some limitations like- drastic change in rpm of dissolution tester, unavailability of distilled water, uncontrolled temperature, improper functioning of hardness tester, improper functioning of UV spectrophotometer etc. For those reasons, we would not be able to comply with the in vivo release kinetics data.

RECOMMENDATIONS:

If we will be able to minimize our limitations then the study will show linear relationship with the extent of time. Limitations include:

- Drastic change in rpm of dissolution tester,
- Unavailability of distilled water,
- Uncontrolled room temperature,
- Improper functioning of hardness tester &
- Improper functioning of UV spectrophotometer etc.

References

http://www.ncbi.nlm.nih.gov/pubmed/16138594

http://www.tripdatabase.com/doc/342705-Current-epidemiology-of-asthma--emerging-patterns-of-asthma-

http://www.cmaj.ca/cgi/content/full/cmaj;181/9/E181

Shargel, L., Mutnick, A.L., Soney, P.F., & Swansan, L.N., (2007). *Comprehensive Pharmacy Review* (6th ed.). pp.1044-1045. New Delhi, India: Wolters Kluwer Health (India) Pvt. Ltd.

http://pubs.acs.org/cen/coverstory/83/8325/8325salbutamol.html

http://images.google.ca/images?gbv=2&hl=en&q=PATHOPHYSIOLOGY+OF+ASTHMA&sa=N&start=20&ndsp=20

Harvey, R.A., Champe, P.C., Howland, R.D., & Mycek, M.J., (2006). *Lippincott's Illustrated Reviews (pharmacology)* (3rd ed.).pp. 315- 316. India: B.I. Publications PVT. LTD.

http://yourtotalhealth.ivillage.com/asthmabasics?ivNPA=1&sky=ggl|hco|al|asthma|PPCD379a|s

Tripathi, KD.,(1996). *Essentials of Medical Pharmacology* (5th ed.).pp. 198-199. New Delhi, India: Brothers Medical Publishers (P) LTD.

http://www.medic8.com/medicines/Salbutamol.html

http://www.springerlink.com/content/r201847322572331/

http://www.ch.ic.ac.uk/local/projects/j_hettich/salbutamol/noframes/nfproperties.html

http://www.medicines.ie/medicine/2040/SPC/Ventolin+2mg+5ml+Oral+Solution/

http://www.pharmgkb.org/do/serve?objId=PA448068

British P harmacopoiea-2004, 4th edition

Lachman, L., Liberman, H.A., & Kanig, J.L., (1986). *The Theory and Practice of Industrial Pharmacy* (3rd ed.). pp. 296-297,299-302. Bombay, India: Varghese Publishing House

Aulton, M.E., (2002). Pharmaceutics The Science of Dosage Form Design (2nd ed.). pp. 418-420. New York: Churchill Livingstone

http://www.rtmagazine.com/issues/articles/2009-05_01.asp

http://www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=60