Correlation between Hardness and Release Profile of Salbutamol Sulphate Tablets

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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Shahreen Raihana

Declaration by the Research Supervisor and Department Chairperson

December 2009

It is pleasure to certify that the research paper titled 'Correlation between Hardness and Release Profile of Salbutamol Sulphate Tablets' is prepared by Shahreen Raihana, a student of the Department of Pharmacy, East West University, Dhaka. She prepared the paper under our supervision. This is her original work.

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Abstract

Purpose: The purpose of this research work was to investigate the correlation between the release profile and hardness of Salbutamol Sulphate tablets. ***Method:*** Thirty tablets of Salbutamol Sulphate 4 mg were collected from the market and were characterized by physical parameters like hardness, thickness, weight variation, friability and dissolution studies. Salbutamol Sulphate release was investigated using the method inscribed in Appendix XII B: Dissolution tests for tablets and capsules of British Pharmacopoeia. Hardness of the withdrawn samples from the market was measured by Monsanto hardness tester. Thickness of the samples was measured by Vernier Calipers. Dissolution of the taken samples was investigated using dissolution tester (RC6, Vanguard Pharmaceuticals, USA) to evaluate release kinetics. ***Result:*** Mean hardness value of the tablets was found to be – Sultolin 10.01N; Ventolin 12.71N; Brodil 14.72N and Salbutal 13.05N. Mean thickness value of Indapamide tablets was found to be – Salbutal 6.32 mm; Ventolin 8.42 mm; Sultolin 8.17 mm; and Brodil 9.77 mm. Percentage difference of the weight variation test ranged as – Sultolin -1.68 to 1.83%; Ventolin -2.20 to 3.27%; Brodil between -2.4 to 3.44%; and Salbutal between -3.91 to 2.93%. ***Conclusion:*** The release pattern of Salbutamol tablet did not completely fulfill its requirement to provide desired and optimum drug release. Best results were obtained for Brodil of ACI Pharmaceuticals, as it showed a progressive increase in the concentration and released the drug properly. Sultolin of Square Pharmaceuticals, showed more or less acceptable increasing release profile. Salbutal of Sanofi Aventis and Ventolin of GlaxoSmithKline showed less prominent characteristics of hardness and release profile.

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1. Background

Asthma is a disease that is characterized by hyperresponsiveness of tracheobronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretions, mucosal edema and mucous plugging (Tripathi, 2007). According to the Asthma Society of Canada symptoms often include 'shortness of breath, tightness in the chest, coughing, wheezing. Asthmatic lungs are often referred to as "twitchy," meaning they seem to overreact to stimuli such as aero-allergens and cold, dry air. Over time, the airways or bronchial tubes, become inflamed and sensitive. This increased inflammation, if not treated, will often lead to an asthma attack.'

Asthma is a problem worldwide, with an estimated 300 million affected individuals. (Global Initiative for Asthma, 2008). Surveying nearly half a million children 13–14 years of age, this study found great disparities (as high as a 20 to 60-fold difference) in asthma prevalence across the world, with a trend toward more developed and westernized countries having higher asthma prevalence. 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 et al., 2002). Asthma is not a recent condition, in fact there is written evidence of the condition from ancient Egyptian times. The actual term asthma is a Greek word that is derived from the verb 'aazein', meaning to exhale with open mouth, to pant. Asthma, as an inflammatory disease, was not really recognized until the 1960s when anti-inflammatory medications started being used.

Salbutamol Sulphate, with its fast onset of action, is particularly suitable for the management and prevention of attack in mild asthma and for the treatment of acute exacerbations in moderate and severe asthma. At therapeutic doses, it acts on the β_2 adrenoceptors of bronchial muscle with little effect on β_1 adrenoreceptors of cardiac muscle. (Information for Health Professionals, 1999). The drug is a β_2 receptor agonist and serves the purpose to counter the effects of bronco-constriction in various ways. These bind to the beta-adrenergic receptors in airways smooth muscle, leading to activation of adenyl cyclase an increased levels of cyclic-3', 5'adenosine monophosphate (cAMP). Increases in cAMP activate kinases which inhibit the phosphorylation of myosin and decrease intracellular calcium. Decreased intracellular calcium relaxes smooth

muscle airways. This leads to relaxation of airway smooth muscle with subsequent brochodilation (Davis Drug Guide for Nurses, 2007).

In Bangladesh the treatment of asthmatic symptoms generally includes conventional oral dosage forms like tablets, capsules, oral liquids and inhalation. There are other oral Antiasthmatic drugs used in Bangladesh. Some of the mentionable ones are namely; theophyline, levosalbutamol, montelukast, banbuterol HCl. Various companies market these products under various brand names.

Oral preparation is particularly useful for patients unable to use metered dose inhaler properly and for patients to whom the use of inhalation aerosol causes irritation of airways (Information for Health Professionals, 1999). These are suitable for oral therapy mainly for children and adults who are unable to use an inhaler device. In these patients, the controlled-release formulation tablets are helpful in the management of nocturnal asthma (Allen & Hanburys, 2007). As a result the blood levels can be maintained for a prolonged period of time.

Four brands of salbutamol sulphate tablets which are established in the market in Bangladesh were used for this particular study.

1.1 Research Problem

Correlation of the hardness and release profile of various Salbutamol Sulphate controlled release tablets were studied in this paper. Among the various Salbutamol Sulphate tablets available in the market in Bangladesh, the most popularly use strength is that which contains 4mg active ingredient in it. In this study these 4mg strength tablets were used from four companies. These preparations are all supposed to have similar pharmacokinetic properties as in release profile related to disintegration and dissolution, bioavailability, absorption, distribution, metabolism and excretion. The excipients and the matrix used in these preparations need to be of same proportion such that they provide the same benefit to all the patients no matter which brand is prescribed by the physicians, for treatment purpose. The brands used in this study are, Sultolin from Square Pharmaceuticals Ltd. (November 2008 batch), Ventolin of GlaxoSmithKline (January 2009 batch), Brodil of ACI Pharmaceuticals Ltd. (December 2008 batch) and Salbutal of Sanofi Aventis (January 2009 batch). The crude sample used in the study was a kind gift presented by Incepta Pharmaceuticals Ltd. Hence this study was conducted to determine the consistency in the release pattern of four brands in relation to their hardness.

1.2 Objective

1.3.1 General Objective.

To determine if the Salbutamol Sulphate 4mg tablet preparation found in the market exhibit consistency in the release profile in relation with the hardness of the tablets.

1.3.2 Specific Objective.

This study has been conducted in Bangladesh with an aim to develop a specific standard curve with a reference crude sample and compare it with samples collected from the local market. The active drug chosen for the purpose is Salbutamol Sulphate. Various brands from different companies have been collected to serve the purpose.

2. Asthma Overview

Asthma is a serious global health problem. People of all ages in countries throughout the world are affected by this chronic airway disorder that, when uncontrolled can place severe limits on daily life and is sometimes fatal. The prevalence of asthma is increasing in most countries, especially among children. Asthma is a significant burden, not only in terms of health care costs, but also in terms of productivity. During the past two decades there had been many scientific advances that improved our understanding of asthma and the ability to manage and control it effectively. (Global Initiative for Asthma, 2008).

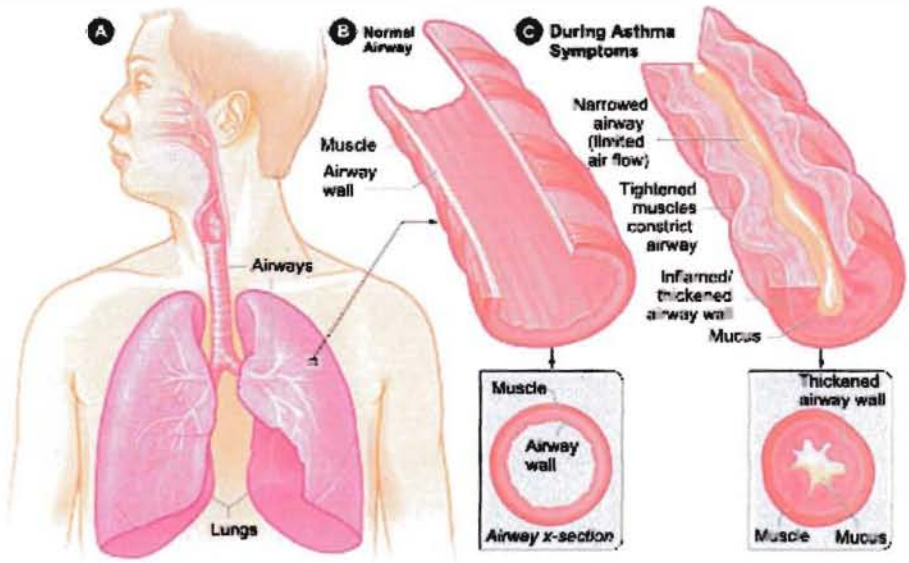

*Figure 1.*the Human lungs. 'A' shows the location of the lungs and airways in the body. 'B' shows a cross-section of a normal airway. 'C' shows a cross-section of an airway during asthma symptoms. (Asthma, U.S. Department of Health & Human Services, 2008)

Asthma is recognized to be a primarily inflammatory conditions: inflammation underlying hyperactivity. An allergic basis can be demonstrated in many adult, and higher percentage of pediatric patients. In others, a variety of trigger factors (infection, irritants, pollution, exercise, exposure to cold air, psychogenic) may be involved (Tripathi, 2007).

In defining the condition called asthma it can be said that 'Asthma is a chronic inflammatory disorder of the airways. It involves complex interactions between many cells (e.g. eosinophills,

mast cells) and inflammatory mediators (interleukins, leukotrienes) that result in inflammation, obstruction (partially or completely reversible after treatment or resolves spontaneously), increased airway responsiveness (i.e. hyperresponsiveness), and episodic asthma symptoms.' (Shargel et al, 2007, p. 1042)

Asthma severity classification were revised by the National Institutes of Health (NIH) in the second expert panel report of the Heart, Lung, and Blood Institute to include mild intermittent asthma in addition to mild, moderate, and severe persistent asthma. A patient's severity classification plays an important role in determining the most important pharmacotherapeutic approach and is determined by: i) Symptoms (daytime and nocturnal), ii) treatment requirements, iii) objective measurements of lung function, including diurnal variations.

Common asthma symptoms include:

i) Coughing – Coughing from asthma is often worse at night or early in the morning, making it hard to sleep,

ii) Wheezing – a whistling or squeaky sound that occurs during breathing,

iii) Chest tightness – may feel like something is squeezing the chest,

iv) Shortness of breath.

Not all people who have asthma have these symptoms. Likewise, having these symptoms doesn't always mean that the patient has asthma. A lung function test, done along with a medical history (including type and frequency of symptoms) and physical exam, is the best way to diagnose asthma for certain. Severe symptoms can be life-threatening. It's vital to treat symptoms when first noticed so they don't become severe. (Signs and Symptoms, U.S. Department of Health & Human Services, 2008)

Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger the asthma symptoms. The former includes host factors (which are primarily genetic) and the latter are usually environmental factors. However the mechanisms by which they influence the development and expression of asthma are complex and interactive. Asthma has a heritable component, but is not simple. Current data shows that multiple genes may be associated in the pathogenesis of asthma. (Global Initiative for Asthma, 2008). Precipitating factors of an acute asthma exacerbation may include – allergens (pollen, house dust

mite, animal dander, mold, cockroaches, food); occupational exposures (e.g. chemical irritants, flour, wood, textile dusts); viral respiratory tract infection; exercise; emotions (e.g. axiety, stress, hard laughter or crying); exposure to irritants (e.g. strong odors, chemicals, fumes); environmental exposures (e.g. weather changes, cold air, sulphur dioxide, cigarette smoke); drugs (e.g. NSAIDS, aspirin, antiadrenegic and cholinergic drugs, and medication containing tartrazine, benzalkonium chloride, sulphites, and other preservative). (Shargel et al, 2007, p. 1042).

2.1 Pathophysiology of asthma

The airways are tubes that carry air into and out of the lungs. People who have asthma have inflamed airways. This makes the airways swollen and very sensitive. They tend to react strongly to certain substances that are breathed in.

When the airways react, the muscles around them tighten. This causes the airways to narrow, and less air flows to the lungs. The swelling also can worsen, making the airways even narrower. Cells in the airways may make more mucus than normal. Mucus is a sticky, thick liquid that can further narrow the airways. This chain reaction can result in asthma symptoms. Symptoms can happen each time the airways are irritated. (Asthma, U.S. Department of Health & Human Services, 2008)

The major contributing process in the pathophysiology of asthma are inflammatory cells, airway obstruction, hyperresponsiveness, airway inflammation, alteration in the autonomic neural control and airway remodeling. Inflammatory cells like mast cells, eosinophills, activated T-cells, macrophages and epithelial cells all secrete mediators and influence the airways directly or via neural mechanisms. Airway obstruction is mainly responsible for the clinical manifestation of asthma. Hyperresponsiveness is an exaggerated response to certain stimuli, is an important feature of asthma and appears to correlate with clinical severity and medication requirements. Air inflammation is crucial to development of asthma and contributes to airway hyperresponsiveness, airflow obstruction, respiratory symptoms, and disease chronicity. Alteration to autonomic neural control also contributes to obstruction. Airway remodeling can result from persistent inflammation when asthma is poorly controlled.

When considering the genetic host factor, the search for genes linked to the development of asthma has focused on four major areas: production on allergen-specific IgE antibodies (atopy); expression of airway hyperresponsiveness; generation of infalammtory mediators, such as cytokines, chemokines and growth factors; and determination of the ratio between the immune responses as relevant to the hygiene hypothesis of asthma. (Global Initiative for Asthma, 2008)

Sometimes symptoms are mild and go away on their own or after minimal treatment with an asthma medicine. At other times, symptoms continue to get worse. When symptoms get more intense and/or additional symptoms appear, it is called an asthma attack. Asthma attacks also are called flare-ups or exacerbations. (Asthma, U.S. Department of Health & Human Services, 2008)

2.2 Guidelines for Asthma

World Health Organization (WHO) estimates that 300 million people currently suffer from asthma. Asthma is the most common chronic disease among children. Asthma is a public health problem not just for high-income countries; it occurs in all countries regardless of the level of development. Most asthma-related deaths occur in low- and lower-middle income countries. Asthma is under-diagnosed and under-treated. It creates substantial burden to individuals and families and often restricts individuals' activities for a lifetime. WHO recognizes that asthma is a major public health importance. The Organization plays a role in coordinating international efforts against the disease. The aim of its strategy is to support Member States in their efforts to reduce the disability and premature death related to asthma. (World Health Organization, 2008)

The diversity of national health care service systems of different countries, and variation in the availability of asthma therapies, require that recommendation for asthma care be adapted to local conditions throughout the global community. In 1993, National Heart, Lung and Blood Institute collaborated with the WHO came up with the Global Strategy for AsthmaManagement and Prevention.

Current IMCI guidelines recommend that if a child is wheezing (even if it disappeared after rapidly acting bronchodilator) give an inhaled bronchodilator for 5 days. However in a footnote mentions that ' In settings where inhaled bronchodilator is not available, oral salbutamol may be second choice' (World Health Organization, 2009).

2.3 Salbutamol Sulphate as Antiasthmatic Drug

Salbutamol Sulphate is used for the relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercise-induced asthma or in other situations known to induce bronchospasm. (Allen and Hanburys, 2007).

2.4 Basics properties of Salbutamol Sulphate

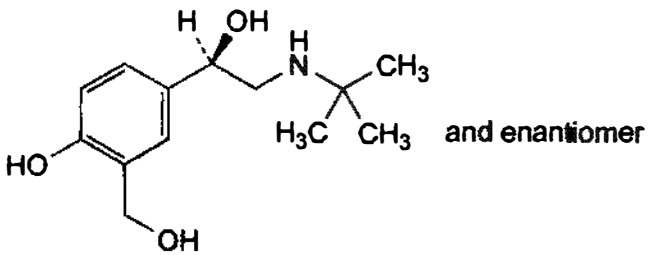

Figure 2. Structure of Salbutamol (British Pharmacopoeia, 2007)

The chemical formula of Salbutamol Sulphate is $C_{13}H_{21}NO_3$. Its molecular weight is 239.3g. the full stereochemical formula of Salbutamol Sulphate is (1*RS*)-2-[(1,1-Dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol. Its content is 98.0 per cent to 101.0 per cent dried substance).

Physical properties of Salbutamol Sulphate – it is White or almost white, crystalline powder in appearance. Its solubility ranges from sparingly soluble in water and soluble in ethanol (96 per cent). Its melting point is about 155 °C, with decomposition. The loss on drying data of Salbutamol SUlphate shows maximum 0.5 per cent loss, determined on 1.000 g by drying in an oven at 100-105 °C. the specified storage conditions for Salbutamol is that it should be protected from light (British Pharmacopoeia, 2007).

2.5 Pharmacology of Salbutamol Sulphate

Inhaled adrenergic agonists with β_2 activity are the drugs of choice for mild asthma, i.e. in patients showing only occasional, intermittent symptoms. Direct acting β_2 agonist are potent bronchodilators that relax airway smooth muscle. Short acting adrenergic agonist are the most

clinically useful β_2 agonist and have a rapid onset of action (15 – 30 minutes) and provide relief for four to six hours. They are for symptomatic treatment of bronchospasm and as "rescue agents" to combat bronchoconstriction. β_2 agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agent for patients with chronic asthma. The dirct acting β_2 selective agonists, such as pirbuterol, terbutaline, and salbutamol (albuterol) offer the advantage of providing maximum attainable bronchodilation with little of the undesired effect of α or β_1 stimulation (Howland, 2006).

These selective adrenergic drugs cause bronchodilation through β_2 receptor stimulation → increased cAMP formation in bronchial muscle cell → relaxation. In addition cAMP in mast cells and other inflammatory cells decrease mediator release. Since β_2 on inflammatory cells are more prone to densensitization, the contribution of this action to the beneficial effect of β_2 agonist in asthma is uncertain. Adrenergic drugs are the mainstay of treatment of reversible airway obstruction but should be cautiously used in hypersensives, ischemic heart disease patients and in those receiving digitalis (Tripathi, 2007).

2.6 Pharmacokinetics of Salbutamol Sulphate

Salbutamol (albuterol) is a highly selective β_2 agonist as mentioned earlier. Cardiac dise effects due action on β_1 receptors are less prominent. Oral administration of salbutamol are also used in place of inhaled preparations. Salbutamol undergoes pre-systemic metabolism in the gut wall and oral bioavailability is 50%. Oral salbutamol acts for 4-6 hours (Tripathi, 2007). 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. (Information for Health Professionals, 1999)

3. Weight Variation Test

The weight of a tablet is determined by the amount of fill placed in the die (is measured by volume and not by weight and therefore depends on the granule size and the void space) during its manufacturing process. With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug. In practice, composite samples (usually 10) of tablets are taken and weighed throughout the compression process. The composite weight divided by 10, however will provide an average weight but contain the usual problems of averaged values. Within the composite sample that has an acceptable average weight, there could be tablets excessively overweight or underweight. To help alleviate this problem that USP/NF provides limits for the permissible variations in the weight of individual tablets expressed as a percentage of the average weight of the sample (Lachman, 2008).

3.1 Methodology

Objective of performing this experiment is to determine if the four commercial brands of Salbutamol Sulphate 4mg tablets fulfill the requirements specified by the USP. For this purpose, each of the tablets of the four different brands Sultolin, Ventolin, Brodil and Salbutal were weighed individually and their weight was recorded in *Table 1, 2, 3* and *4* respectively. The average weight of the 10 tablets of each of the Brands was calculated. Then the weight variation with respect to the average weight was measured using the formula –

$$Weight\ Variation = \left(\frac{Average\ Weight - Initial\ Weight}{Average\ Weight}\right) \times 100$$

All the data were tabulated in the Table... and the process was repeated for each of the Brands used for the study.

Table 1

Weight Variation of Sultolin in Comparison with the Average Weight

Tab sample	Tab no.	Wt of Sultolin (gm)	Avg wt (gm)	Weight variation [((Avg. wt. - Ini. Wt.)/Avg. wt.)*100]
Sultolin	1	0.172	0.17103	-0.57
	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

Table 2

Weight Variation of Ventolin in Comparison with the Average Weight

Tab sample	Tab no.	Wt of Sultolin (gm)	Avg wt (gm)	Weight variation [((Avg. wt. - Ini. Wt.)/Avg. wt.)*100]
Ventolin	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 3

Weight Variation of Brodil in Comparison with the Average Weight

Tab sample	Tab no.	Wt of Sultolin (gm)	Avg wt (gm)	Weight variation [((Avg. wt. - Ini. Wt.)/Avg. wt.)*100]
Brodil	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

Table 4

Weight Variation of Salbutal in Comparison with the Average Weight

Tab sample	Tab no.	Wt of Sultolin (gm)	Avg wt (gm)	Weight variation [((Avg. wt. - Ini. Wt.)/Avg. wt.)*100]
Salbutal	1	0.1014	0.10086	-0.54
	2	0.1015		-0.63
	3	0.1013		-0.44
	4	0.1006		0.26
	5	0.1001		0.75
	6	0.1048		-3.91
	7	0.0979		2.93
	8	0.1017		-0.83
	9	0.1005		0.36
	10	0.0988		2.04

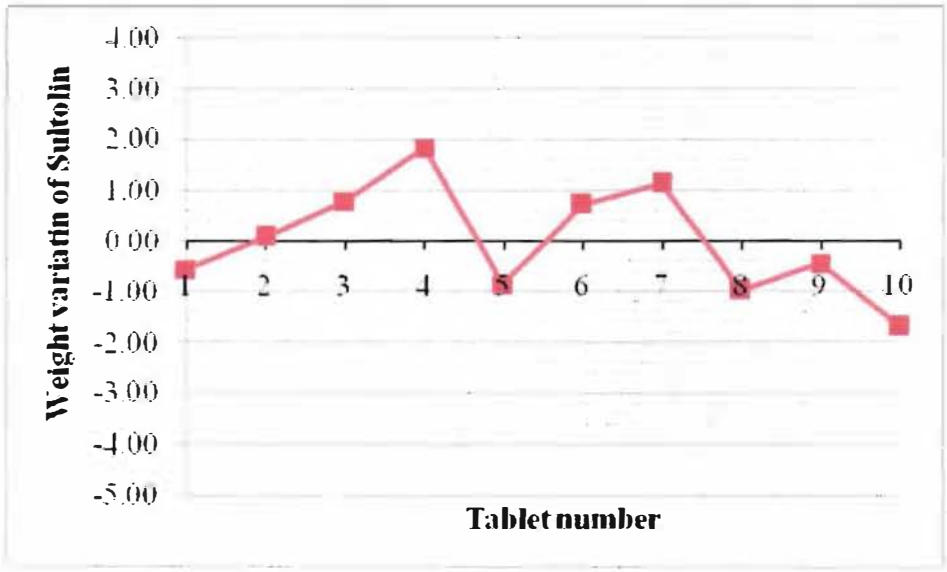

Figure 3. Line Graph to show the weight variation of Sultolin 4mg tablets.

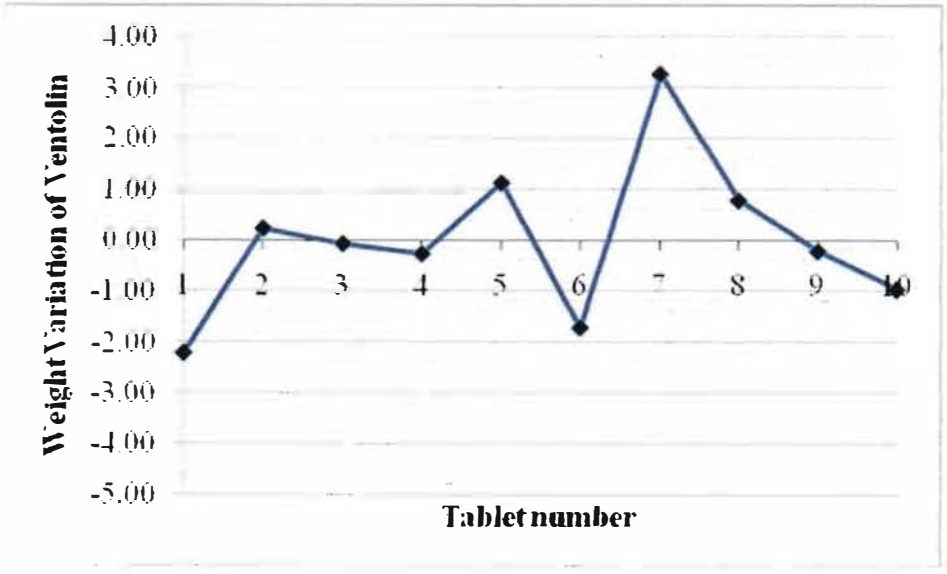

Figure 4. Line Graph to show the weight variation of Ventolin 4mg tablets.

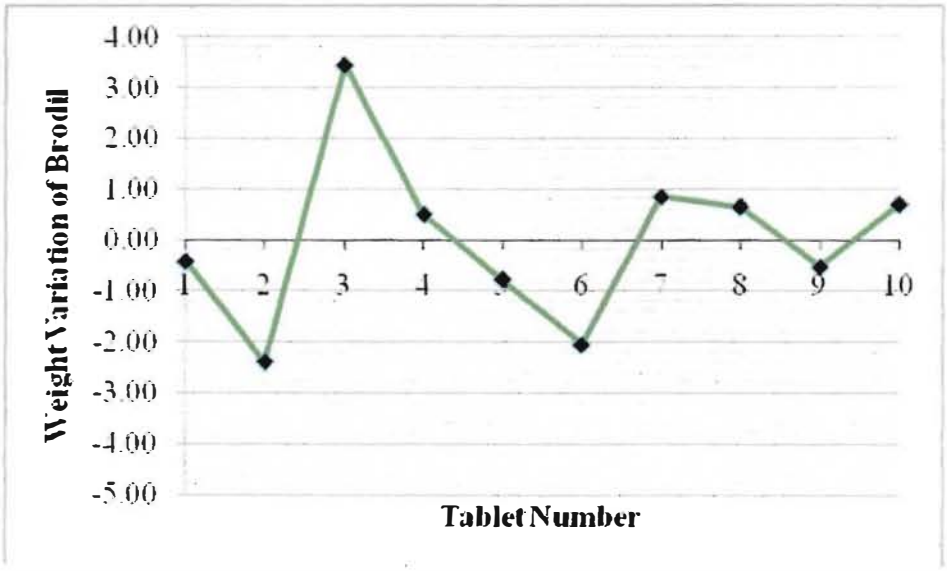

Figure 5. Line Graph to show the weight variation of Brodil 4mg tablets.

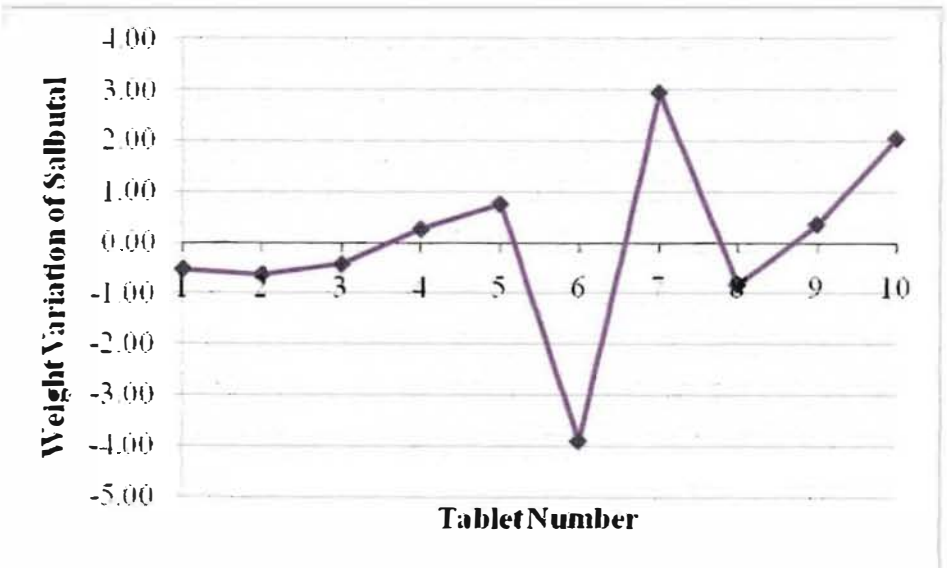

Figure 6. Line Graph to show the weight variation of Salbutal 4mg tablets.

3.2 Discussion

The weight variation of the tablets were found to be – Sultolin between -1.68 to 1.83%; Ventolin between -2.20 to 3.27%; Brodil between -2.4 to 3.44%; Salbutal between -3.91 to 2.93%. The weight variations are supposed to be within ±7.5% range as mentioned in the BP for tablets with average weight within the range of 130 – 324mg. The average weight of the Brands were Sultolin 0.17103gm (171.03mg), Ventolin 0.20097gm (200.97mg), Brodil 0.19688gm (196.88mg), Salbutal 0.10086gm (100.86mg). since the weight variation obtained for all four brands was within ±7.5%, so it can be said that the Salbutamol Suphate 4mg tablets followed the specifications.

3.3 Result

The mean weight for each of the brands were found to be Sultolin 171.03mg, Ventolin 200.97mg, Brodil 196.88mg, Salbutal 100.86mg and the weight variation was within ±7.5% limit.

4. Friability Test

Friability is the tendency of the tablet to crumble. It is important for the tablet to resist attrition. During manufacturing and handling, tablets are subjected to stresses from collision and tablet sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from the tablet surface. The result will be progressive reduction in weight and change in appearance. (Pharos University in Alexandria, Lecture 7, 2008)

Friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The instrument used for such tests is called a friabilator. A number of tablets are weighed and placed in a tumbling chamber which is rotated for 4 minutes or for 100 revolutions. During each revolution the tablet falls from a distance of six inches to undergo shock. After 100 revolutions the tablet are dusted and reweighed. A maximum loss of not more than 1% generally is considered acceptable for most products. Conventionally, the acceptable range of weight loss of compressed tablets according to the USP, is less than 0.5 to 1.0%. (Lachman, 2008)

4.1 Methodology

Objective of this experiment is to determine the percentage friability of 10 Salbutamol Sulphate 4mg tablets of each of the four brands selected from the market. Ten tablets of one brand were weighed altogether using the Electronic weighing balance, and their initial total weight was recorded. Then the tablets were taken into the friabilator and the machine was set to 100 revolutions for 4 minutes. As the start button of the friabilator was pressed, each of the Salbutamol Sulphate 4mg tablets fell a distance of six inches during each revolution. Thus the tablets were exposed to abrasion and collision. After completion of 100 revolutions, the tablets were removed from the fiabilator and dusted with a piece of cloth to rub off any powdered remnants of the tablets. All the 10 tablets were weighed again in the Electronic weighing balance and the new total weight was recorded. The same procedure was repeated for the other three brands of Salbutamol Sulphate 4mg tablets and the initial and final weights were recorded.

The % Friability was calculated using the following formula for each of the four brands (Article 1) –

$$\%Friability = \left(1 - \frac{Initial\ weight}{Final\ weight}\right) \times 100$$

The initial weight, final weight and the %Friability were recorded in the *Table 5.*

Table 5

Percentage Friability of Sultolin, Ventolin, Brodil and Salbutal

Tab Sample	Initial weight (of 10 tabs)	Final weight (of 10 tabs)	% Friability
Sultolin	1.7103	1.7166	0.37
Ventolin	2.0097	2.0131	0.17
Brodil	1.9688	1.966	-0.14
Salbutal	1.0086	1.0076	-0.10

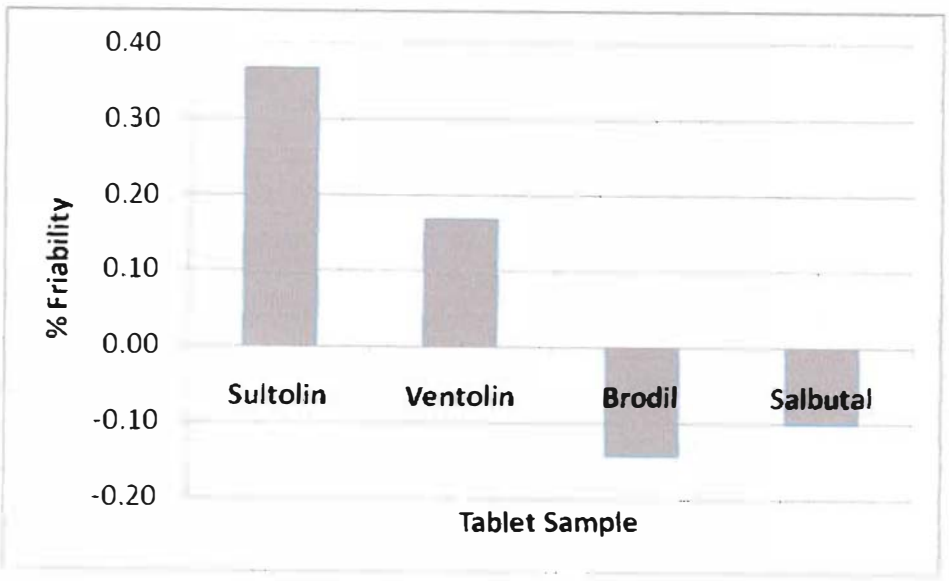

Figure 7. Bar Chart to show percentage friability of Sultolin, Ventolin, Brodil and Salbutal.

4.2 Discussion

The %Friability was found to vary between -0.14 to 0.37% for the four brands of Salbutamol Sulphate 4mg tablets. Hence the %Friability of the four Brands were found to have maintained the specifications of USP. All the tablets were found to be below the 0.5 to 1.0% margin. Ideally any compressed tablet is supposed to comply with the specification. Thus the tablets were found to have enough resistance to withstand the abrasion that may occur during packing, handling and shipping. (Shargel et al, 2007, p. 68-69)

4.3 Result

The variation of the % Friability was found to be within the acceptable range.

5. Hardness Test

In general, tablets should be sufficiently hard to resist breaking during normal handling, packaging and shipping, and yet soft enough to disintegrate properly after swallowing. Hardness of the tablet is controlled by (or is affected by) the degree of the pressure applied during the compression stage. (Pharos University in Alexandria, Lecture 6, 2008). Hardness involves both tablet disintegration and drug dissolution. Certain tablets that are intended to dissolve slowly are made hard. Other tablets that are intended to dissolve rapidly are made soft (Shargel et al, 2007, p. 68-69).

The Hardness test is therefore performed to measure the degree of force required to break a tablet (Shargel et al, 2007, p. 68-69). The test measures crushing strength property defined as the compressional force applied diametrically to a tablet which just fracture (break) it (Pharos University in Alexandria, Lecture 6, 2008). The force will be applied during compression of the tablet. The greater the pressure that needed to be applied, the harder the tablet. The Hardness testers apply increasing pressure on the tablets until the tablet breaks.

5.1 Methodology

Objective of this experiment is to determine the hardness of the Salbutamol Sulphate 4mg tablets of the four brands that are being used for the study. The hardness tester used for this purpose in the laboratory was Monsanto hardness tester. One tablet of one of the brands was placed between the jaws of the hardness tester in a radial direction and pressure was applied manually. As the compression pressure on the tablet was increased the tablet got fixed into the groove and with increasing pressure the tablet broke down at one stage. The scale reading was taken from the tester at the exact force where the tablet gave in to the pressure. The reading was taken in kg. The same was repeated for all the tablets of the brand and the other brands. The results were recorded in the *Table 6.* The hardness in kg were calculated in terms of Newton to present the results in terms of the actual force that was applied to break the tablet.

Table 6

Hardness variation of the Sultolin, Ventolin, Brodil, Salbutal

	Sultolin (A)		**Ventolin (B)**		**Brodil (C)**		**Salbutal (D)**	
Tab no.	**Hardness (kg)**	**Hardness (N)**	**Hardness (kg)**	**Hardness (N)**	**Hardness (kg)**	**Hardness (N)**	**Hardness (kg)**	**Hardness (N)**
1	1.1	10.79	1	9.81	1.6	15.70	1.25	12.26
2	1.1	10.79	1.4	13.73	1.3	12.75	1.2	11.77
3	0.7	6.87	1.26	12.36	1.3	12.75	1.15	11.28
4	1.5	14.72	1.1	10.79	1.1	10.79	1.15	11.28
5	0.7	6.87	1.1	10.79	1.6	15.70	1.4	13.73
6	0.9	8.83	1.5	14.72	1.5	14.72	1.4	13.73
7	0.8	7.85	1.75	17.17	1.5	14.72	1.5	14.72
8	1.2	11.77	1.3	12.75	1.4	13.73	1.75	17.17
9	1.3	12.75	1.5	14.72	2	19.62	1.2	11.77
10	0.9	8.83	1.05	10.30	1.7	16.68	1.3	12.75

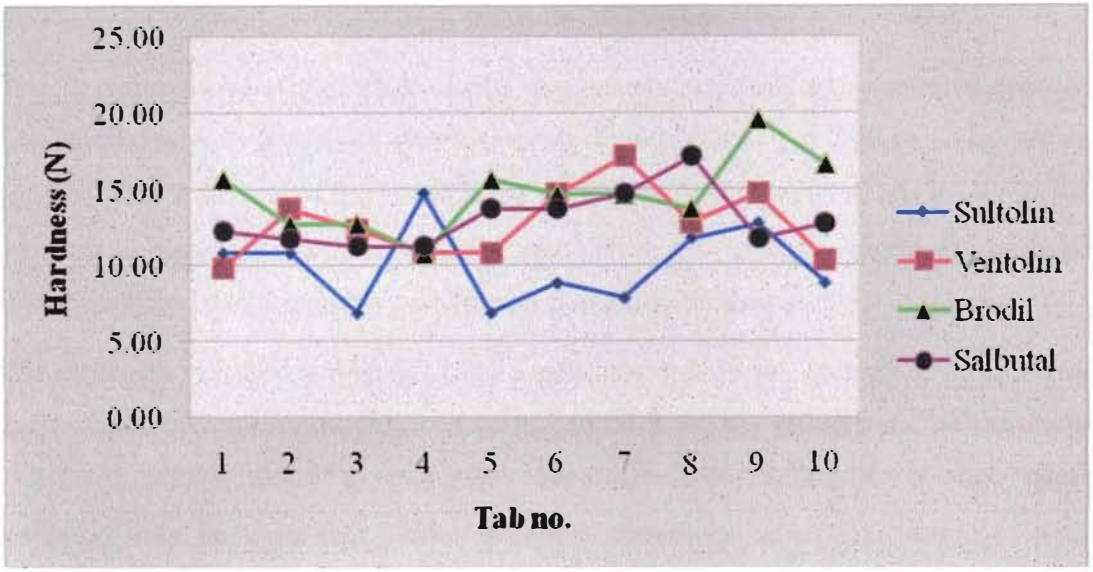

Figure 8. Line Graph to show the weight variation of Brodil 4mg tablets.

5.2 Discussion

The recommended value for tablet hardness is 4-8kg. In this experiment the hardness of the tablets was found in values between 0.7 - 2kg (6.87 – 19.62N) in formulated Salbutamol Sulphate 4mg tablets of all the brands. Individually hardness range of each of the brands was found between 0.7 – 1.5kg for Sultolin, 1.0 – 1.75kg for Ventolin, 1.1 -.2.0kg for Brodil and 1.15 – 1.75kg for Salbutal. so it can be said that the Salbutamol Sulphate 4mg tablets of the various brands were not found to be consistent with the specification. Generally the dissolution times are related to hardness. As the hardness increase, the dissolution rate also delays. But in this case the hardness was found to be less that specified, so the dissolution data is supposed to reflect that by dissolving quickly.

5.3 Result

The mean hardness of the Brands were calculated to be Sultolin 10.01N, Ventolin 12.71N, Brodil 14.72N and Salbutal 13.05N.

6. Study of Thickness

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. The thickness of the tablet is the only dimensional variable related to the 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.

The thickness of individual tablets can be measured using a micrometer or a vernier callipers and their variation from the average can be measured if the die punch was not satisfactory enough (Lachman, 2008). But if the punching instruments were satisfactory enough, then almost no variation may be observed. Tablet thickness should be generally controlled within a ±5% variation of standard value.

6.1 Methodology

Objective of this measurement of thickness of the tablets of the four brands of Salbutamol Sulphate 4 mg, was to get an idea if the die-punch machine used during tablet manufacturing was satisfactory enough to maintain the thickness of all the tablets of a batch within the specified range. The thicknesses of each of the tablets were measured using Vernier calipers and the obtained values were recorded in millimeters in the *Table 7, 8, 9, 10.*

Table 7

Thickness of Salbutal4mg

Salbutal					
Tab no.	**Reading of cm scale**	**Reading of vernier scale (mm)**	**Vernier constant (mm)**	**Vernier error (mm)**	**Thickness of tablet (mm)**
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

Table 8

Thickness of Ventolin 4mg

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 9

Thickness of Sultolin 4mg

Sultolin					
Tab no.	**Reading of cm scale**	**Reading of vernier scale (mm)**	**Vernier constant (mm)**	**Vernier error (mm)**	**Thickness of tablet (mm)**
1	0.8	3	0.05	0.02	8.17
2	0.8	3	0.05	0.02	8.17
3	0.8	3	0.05	0.02	8.17
4	0.8	3	0.05	0.02	8.17
5	0.8	3	0.05	0.02	8.17
6	0.8	3	0.05	0.02	8.17
7	0.8	3	0.05	0.02	8.17
8	0.8	3	0.05	0.02	8.17
9	0.8	3	0.05	0.02	8.17
10	0.8	3	0.05	0.02	8.17

Table 10

Thickness of Brodil 4mg

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

6.2 Discussion

The data obtained following the thickness examination was found to be almost same thickness for all the Salbutamol Suphate 4 mg tablets of the same batch. The thickness of Sultolin was found to be 6.32mm, Ventolin 8.42mm, Brodil 8.17mm, Salbutal 9.77mm.Tablet thickness is consistent 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 punching tooling was of consistent length, and if the tablet was clean and in good working condition.

7. Dissolution Test

Dissolution tests and test specification have been developed for nearly all tablet products. the rate of drug absorption for acidic drug moieties that are absorbed high in the GI tract is often determined by the rate of drug dissolution from the tablets. If the attainment of high peak blood levels of the drug is a product objective, obtaining rapid drug dissolution from tablet is critically important. The rate of dissolution may thus be directly related to the efficacy of the drug product, as well as bioavailability differences between formulations. Therefore, an evaluation as to whether or not a tablet releases its drug contents when placed in the environment of the gastro-intestinal tract is often fundamental concern to the tablet formulator.

In vivo dissolution tests are thus very extensively studied, developed and used as an indirect measurement of drug availability, especially in preliminary assessment of formulation factors and manufacturing methods that are likely to influence bioavailability. As with any in-vitro tests, it is critically important that the dissolution test be correlated with in vivo bioavailability tests. (Lachman, 2008)

The objectives of the in-vitro dissolution tests are –

1. To differentiate between formulations and to evaluate the potential effect of the formulation and other processes variables on drug bioavailability.
2. To ensure bioequivalence from batch to batch.
3. To ensure that the preparation comply with product specification, as it is a requirement for regulatory approval of marketing for the registered product.
4. To indicate the performance of the preparation under the in vivo conditions. (It is possible to correlate dissolution rate of a drug with its bioavailability)

Factors affecting dissolution of a tablet:

1. Disintegration is the important first step to drug dissolution in a tablet.

2. Particle size of drug substance.

3. Solubility and hydrophobicity of the formulation; type and amount of disintegrant, binder and lubricant.

4. Manufacturing method (compactness of the granulation and compression force used in tableting)

These factors could be monitored, according to the dissolution test results, in order to obtain a successful formulation. Dissolution test is performed in-process and on the final product.

Dissolution test is a standard requirement for tablets. USP gives standards for tablet dissolution; there are many apparatus for drug release and drug dissolution for immediate release, extended release and enteric-coated tablets. (Pharos University in Alexandria, Lecture7, 2008)

7.1 Methodology

Objective of performing the dissolution test is to determine if the four brands of Salbutamol Sulphate 4mg tablets dissolve in relation with the hardness data that has been shown previously. The assembly from Apparatus 1 (as mentioned in the BP) has been used, with a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel, at any point, and rotates smoothly without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel was maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. The dosage unit was allowed to sink to the bottom of the vessel before rotation of the blade is started. (British Pharmacopoeia, 2007)

To initiate the process the media for the dissolution had to be made. For this purpose 32% concentrated Hydrochloric acid (HCl) was used. To prepare 10g/l solution of HCl, 31.25 ml of the 32% solution was transferred to a 1000ml beaker and made up to the mark with water. This was the standard solution. 10ml of this solution was then transferred to another 1000ml beaker and made up to the mark with water. The same procedure was followed for four more beakers. These solutions were the blank solution for the media for dissolution test and each contained 10g/l hydrochloric acid. 900ml of this dissolution media was transferred to four of the dissolution vessels and the dissolution tester was set to 20rpm for 120 minutes. Two tablets of each brand were placed in each vessel and the instrument was started. As the paddle rotated within the dissolution vessel, 10ml of the dissolution media were collected at 10, 20, 30, 45, 60, 90 and 120 minutes interval from each of the four vessels. Simultaneously the dissolution media

was replaced by the blank media every time a 10ml sample was collected. When all the samples for all four brands of Salbutamol Sulphate tablets were ready, they were examined under Ultraviolet radiation in an UV spectrophotometer at 276 nm wavelength. Salbutamol Sulphate shows absorption maximum at 276 nm and the specific absorbance at the absorption maximum is 66 to 75. (British Pharmacopoeia, 2007) the value of the absorbance at different time was recorded in *Table 11.*

Table 11

Absorbance of Sultolin, Ventolin, Brodil and Salbutal at 276 nm UV

	Absorbance at 276 nm			
Time (mins)	**Sultolin**	**Salbutal**	**Brodil**	**Ventolin**
10	0.054	0.045	0.015	0.081
20	0.055	0.066	0.042	0.059
30	0.098	0.067	0.060	0.059
45	0.055	0.069	0.060	0.067
60	0.064	0.067	0.067	0.067
90	0.072	0.076	0.070	0.069
120	0.077	0.066	0.090	0.309

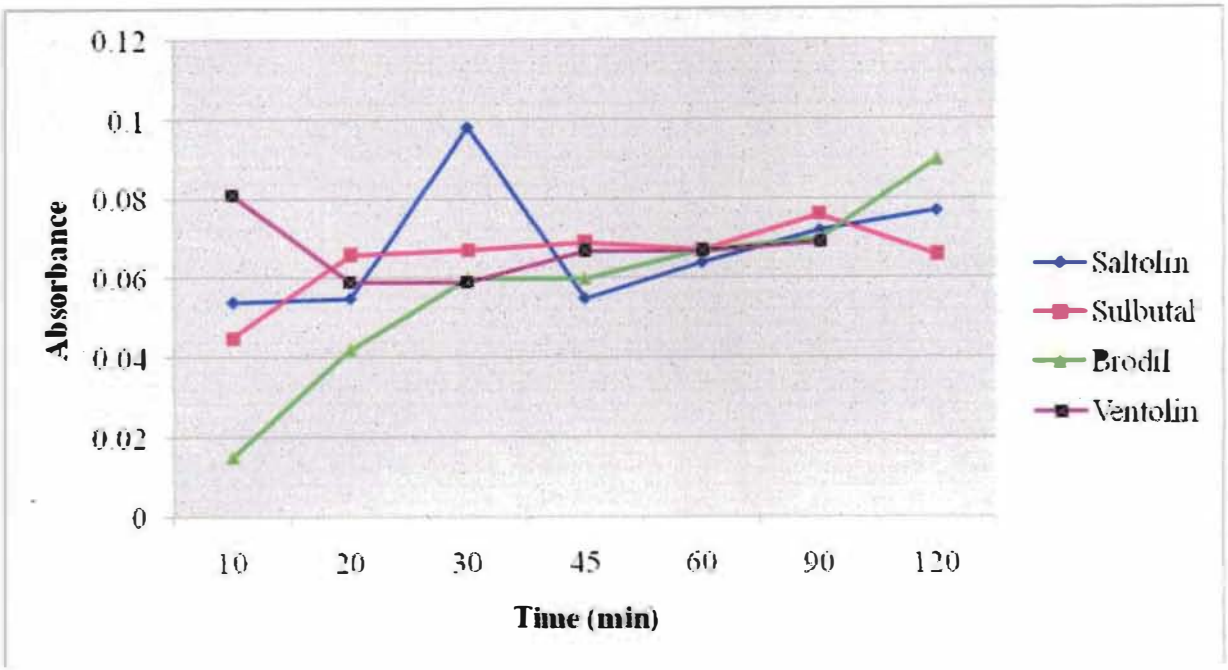

*Figure 9.*Line chart to show the variation in absorbance over time.

7.2 Preparation of the Standard Curve

Crude Salbutamol Sulphate was provided as a kind gift by Incepta Pharmaceuticals Ltd. 8mg (0.008gm) of the crude Salbutamol Sulphate was weighed and transferred to a 100ml volumetric flask and made up to the mark with the dissolution media. 10ml of this was again transferred to another volumetric flask and made up to mark with the blank dissolution media prepared earlier. This solution served as the reference standard for the preparation of the standard curve for Salbutamol Sulphate. This reference standard was also examined under 276 nm wavelength of UV light and the absorbance data was used for the preparation of the standard curve as shown in *Figure 10.*

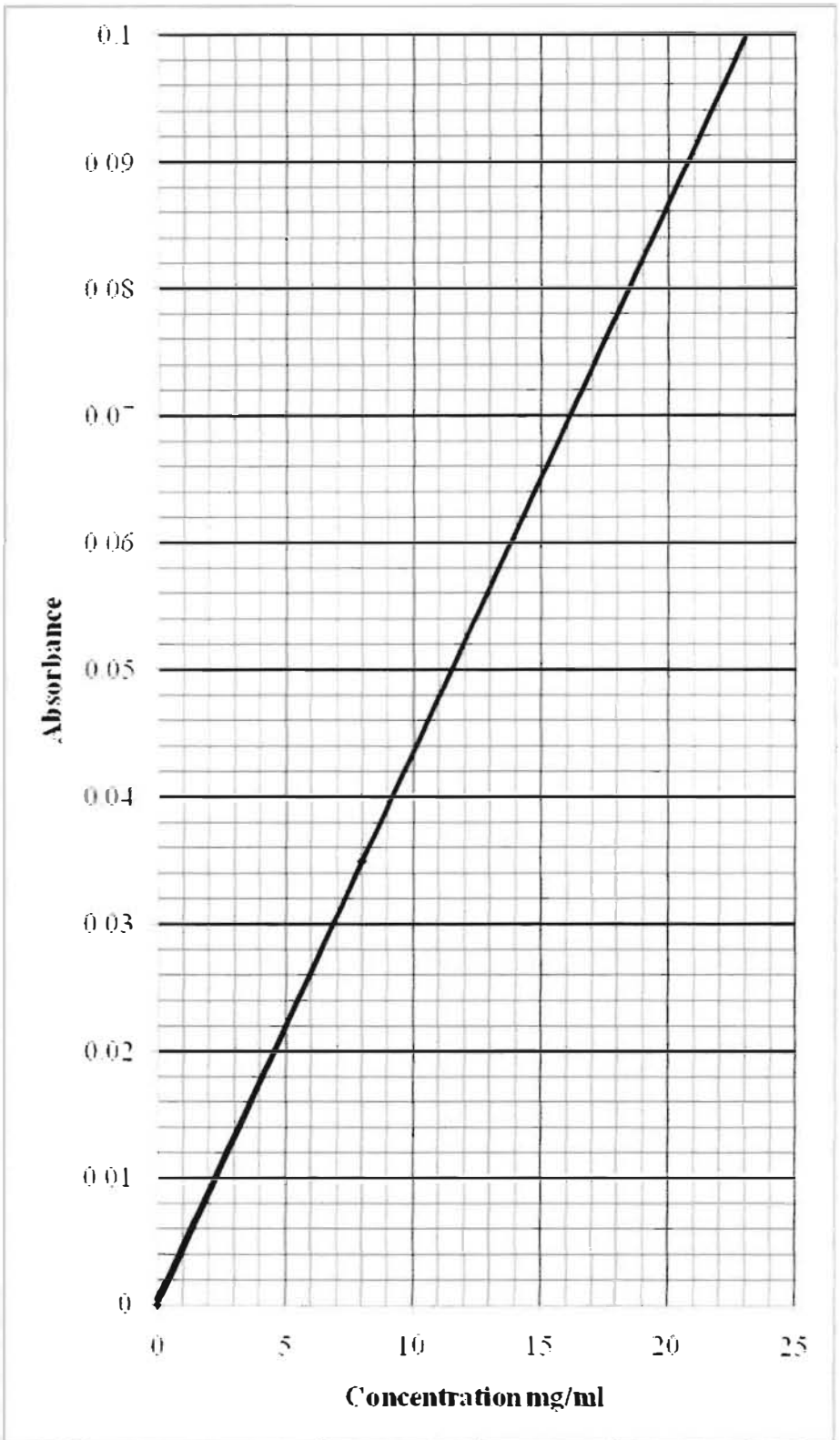

Figure 10. Standard curve for Salbutamol from the reference sample.

This standard curve shows the various concentrations over which the absorbance of Salbutamol Sulphate will vary. Now using the absorbance data that was obtained from the Tablet samples, we can determine the corresponding concentration values and thus find out how much drug went into solution over the two hours dissolution time.

Table 12

Concentration of Salbutamol Sulphate from the Standard curve

	Concentration (mg/ml)			
Time (mins)	**Sultolin**	**Salbutal**	**Brodil**	**Ventolin**
10	12.2	10.1	3.2	18.2
20	12.5	15	9.4	13.2
30	22.7	15.1	13.7	13.2
45	12.5	15.6	13.7	15.1
60	14.4	15.1	15.1	15.1
90	16.2	17.1	15.9	15.6
120	17.2	15	20.9	-

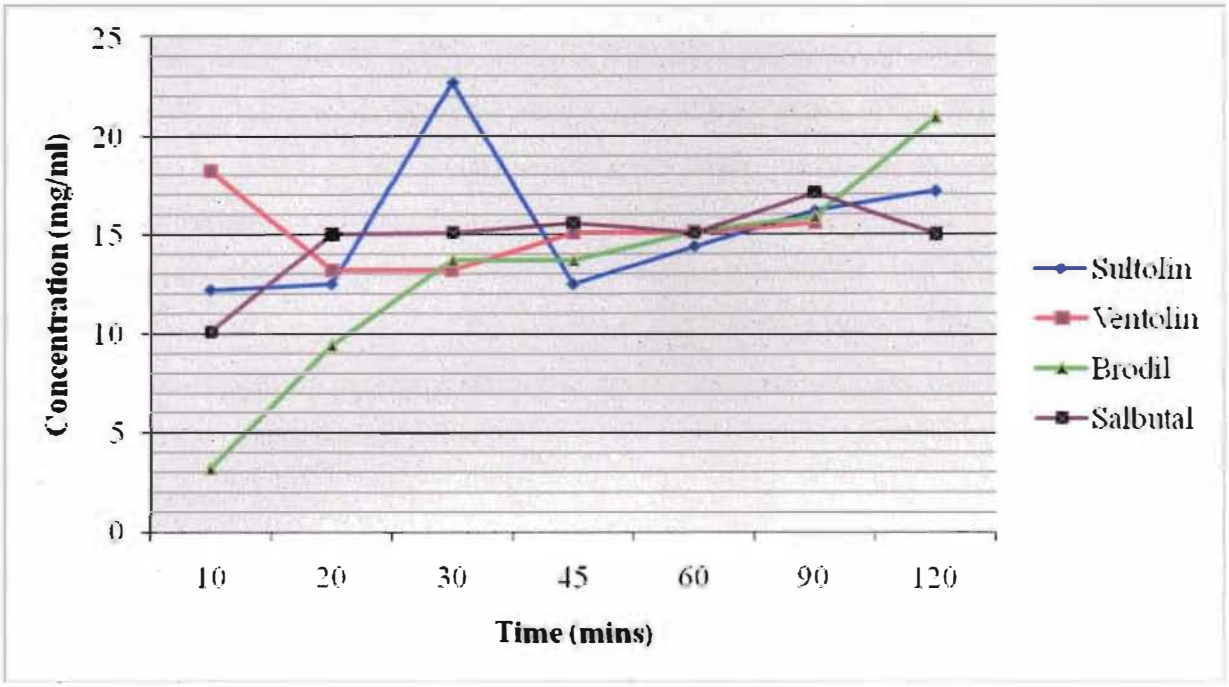

Figure 11. Line chart to show the concentration variation over time

7.3 Discussion

Salbutamol Sulphate is a highly hygroscopic substance and so expected to dissolve in the HCl media very quickly. The dissolution test that was conducted for two hours in the specified media provided the Line Chart... according to the samples that were collected from the vessel in the dissolution tester at times 10, 20, 30, 45, 60, 90, 120 minutes. Absorbance values obtained for each of the samples collected was found to follow an overall pattern of increasing over time during the two hours. The absorbance of Sultolin varied between 0.054 – 0.098; Salbutal varied between 0.045 – 0.076; and Brodil varied between 0.015 – 0.090. But there were many unwanted variation in the absorbance readings of all the brands. As can be seen in the *Table 11* the absorbance value for Ventolin at 120 minutes was found to be extremely high and out of proportion. These deviations were obtained primarily because of some malfunction of the Dissolution tester. But omitting that reading the overall pattern of Ventolin is increasing.

The corresponding concentration values for the absorbance were determined from the standard curve which was extrapolated to obtain most of the values. Unfortunately this should not have

been the case. The values of the concentrations obtained from the tablet dissolutions was supposed to be within the 8mg/ml range as two tablets of each brand were used in each of the vessel in the dissolution tester. Also the **absorbance of 8mg of the crude Salbutamol Sulphate was found to be 0.035.** So the tablets should have shown maximum absorbance at about this value. But unfortunately this had not been the case. This may have been due the tablet matrix and other excipients that were present in the vessel during dissolution. The extra absorbance was obtained because of the presence of the excipients and the tablet matrix. Hence we can conclude that since the pattern of the absorbance was on the increase over the two hours time, so the brands fulfill the release pattern required.

Figure 12. Working with the dissolution tester while the 120 minutes running time was continuing.

8. Limitations

Various limitations were faced throughout the whole of the study process. Some were due instrumental errors. Others were due to some shortcomings on my behalf.

First of all, Salbutamol Sulphate is a hygroscopic substance and absorbs water. During the weight variation test procedure, a slight amount of variation had been due the presence of atmospheric moisture while the weights were taken. Proper mosture free environment was not maintained. This may have also been a contributing factor to the increase in weight after friability was performed. Secondly, the kg scale of the Monsanto Hardness tester used for measuring the hardness was not calibrated to small units such that absolutley accurate measurements could not be taken. Thirdly, the dissolution apparatus was not in proper functioning condition while the experiment was carried on. Throughout the experiment time, the rpm that had been initially set in the dissolution tester was not maintained. As such variation in result was obtained, the reflection of which can be seen in the 120 minute data obtained for Ventolin in *Table 11*. Also, Salbutamol Saulphate is highly light sensitive, but proper suitable condition to avoid any effect could not be maintained but was attempted. And last of all, throughout the experimental procedure tap water had to be used instead of distilled water because of the fact that the distilled water preparing apparatus of the laboratory was out of order. This may have affected the dissolution results to some extent.

In spite of all the limitations faced, it was possible to undertake the overall experimental procedure quite smoothly.

9. Conclusion and Recommendation

The hardness and the release profile of a drug are very intricately correlated. In this study, the data obtained for hardness and dissolution can be observed in order to predict the relation between the hardness and dissolution. Dissolution is a property of a tablet that is directly related to the release profile. This is because when a tablet is injested through oral route, it goes into the gastrointestinal tract where it has to be absorbed to go into the blood and consequently be bioavailable.

Thus in order for a drug to be bioavailable it has to go into solution in the GI tract. For this to happen the drug and the active ingredient must be released in the in vivo environment. That is why we used the in-vitro environment similar to that of the in-vivo so that the drug can come out of the tablet matrix. The matrix and the excipients determine the hardness of a tablet to a large extent and thus control the release of the active drug salbutamol sulphate. Each tablet contains 4.8mg of the active ingredient equivalent to 4mg salbutamol. The other ingredients that make the tablet attain its shape and appearance, are maize starch, lactose monohydrate, dispersed pink erythrosine (E127), carmoisine (E122), titanium dioxide (E171), sodium starch glycollate, talc, magnesium stearate.

In my study the release profile of the tablets of the four different brands found in the market in Bangladesh were observed in comparison with their hardness. Hardness of each of the tablets was found to be of minimum variation and within the BP specifications. Also the dissolution pattern shows an overall increase in the release of Salbutamol over the experiment time.

To take each of the brands individually, the best result were obtained for Brodil of ACI Pharmaceuticals, as it showed a progressive increase in the concentration and released the drug properly. Also the hardness of Brodil was maintained with least variation. Sultolin of Square Pharmaceuticals, was the brand which showed more or less acceptable increasing release profile and the hardness of the tablets were also maintained with less variation. Salbutal of Sanofi Aventis and Ventolin of GlaxoSmithKline showed less prominent characteristics of hardness and release profile.

Thus the use of Brodil, Sultolin, Ventolin and Salbutal has to allow the same anti-asthmatic efficacy as that of crude Salbutamol.

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