Determination of the Quality Control Parameters of Paracetamol Tablets in Bangladesh Pharma Market

Submitted by

Zinia Mosharraf

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East West University

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Sufia Islam, PhD

Associate Professor

Department of Pharmacy

East West University

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Certificate

This is to certify that the thesis entitled "**Determination of the Quality Control Parameters of Paracetamol Tablets in Bangladesh Pharma Market"** is a complete record of research work carried out by **Zinia Mosharraf,** in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and submitted to the Department of Pharmacy, East West University, Aftabnagar, Dhaka. It is further certified that all the sources of information and other facilities availed of in this connection are duly acknowledged.

Sufia Islam, Ph.D
Supervisor
Associate Professor
Department Of Pharmacy
East West University
Dhaka, Bangladesh

Mr. Apurba Sarker Apu
Co-Supervisor
Senior Lecturer
Department Of Pharmacy
East West University
Dhaka, Bangladesh

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Abstract

Purpose: The purpose of this research work was to determine the physical quality control parameters of five different brands of paracetamol tablets, each containing three different batches obtained from the Bangladesh Pharma Market.

Method: Hundred tablets from each batch of each brand were taken from the market and were determined by the quality control parameters including weight variation, hardness, friability and disintegration test. The tablets used were Napa (Beximco Pharmaceuticals Ltd.), Parapyrol (GlaxoSmithKline Bangladesh Ltd), Reset (Incepta Pharmaceuticals Ltd.), Zerin (Jayson Pharmaceuticals Ltd.) and Tamen (Eskayef Bangladesh Ltd.). The tablets were evaluated to check if they comply with the specifications of USP.

Result: All the tablets of all the brands met with the specifications of USP except of Batch# 143 of Zerin which did not comply with the acceptable range of ±5 for the percentage weight variation. The range obtained from the test was -9.5 to 11.8%. Hence, only one parameter of Batch# 143 of Zerin did not meet the specification. Further studies are needed to determine the other quality parameters of the product.

Conclusion: Various results were obtained from the test and compared with the specification. The tablets met with the specification and, hence, it can be concluded that the tablets had the desired and optimum therapeutic efficacy.

Key words: Paracetamol, weight variation, hardness, friability, disintegration.

CHAPTER 1
INTRODUCTION

1. Introduction

1.1 Pharmacological properties of paracetamol

Paracetamol (Figure 1) is an over-the-counter non-steroidal anti-inflammatory drug (NSAID) which is commonly used as an analgesic and antipyretic agent but has weak anti-inflammatory effects since it has poor ability to inhibit cyclooxygenase (COX) in the presence of high concentration of peroxides, as are found at sites of inflammation. The most commonly consumed daily dose, 1000mg, (Burke, Smyth, & FitzGerald, 2005) results in roughly 50% inhibition of both COX-1 and COX- 2 in whole body blood assays *ex vivo* in healthy volunteers. It has been suggested that COX inhibitors might be disproportionately pronounced in the brain, explaining its anti-pyretic efficacy. It is used to relieve mild to moderate pain from headaches, muscle aches, menstrual periods, colds and sore throats, toothaches, backaches, osteoarthritis, and reactions to vaccinations (shots), and to reduce fever (Acetaminophen, 2012).

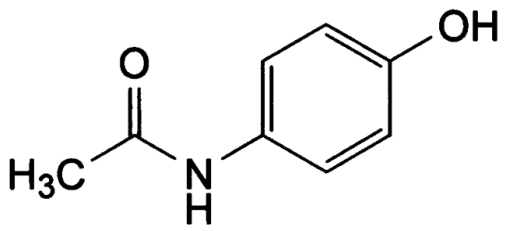


Figure 1. Structure of paracetamol

Unlike opiates it is almost ineffective in intense pain and has no depressant effect on respiration. It is available in a tablet, capsule, suspension or solution (liquid), drops, extended-release (long-acting) tablet, orally disintegrating tablet, suppository, intravenous, and intramuscular form (Acetaminophen, 2012). Paracetamol is generally safe and well tolerated for human use at recommended doses. It also has a low incidence of gastrointestinal side effects at therapeutic

doses in contrast to the NSAIDs (Nayak, 2010). But, acute over dosage can cause severe hepatic damage and in rare individuals, a normal dose can do the same. However, the safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable. The efficacy of pharmaceutical dosage forms generally depend on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary (Nayak, 2010).

1.2 Chemistry of paracetamol

Chemically it is a 4-hydroxy acetanilide and an active metabolite of phenacetin, a so-called coal tar analgesic which is no longer used for medicinal purpose for its adverse effects (Burke *et al.*, 2005). Paracetamol is a white, odorless crystalline powder with a bitter taste, soluble in 70 parts of water (1 in 20 boiling water), 7 parts of alcohol (95%), 13 parts of acetone, 40 parts of glycerol, 9 parts of propylene glycol, 50 parts of chloroform, or 10 parts of methyl alcohol (Paracetamol Information Centre, n.d.a, para 2). It is also soluble in solutions of alkali hydroxides. It is insoluble in benzene and ether. A saturated aqueous solution has a pH of about 6 and is stable (half-life over 20 years) but stability decreases in acid or alkaline conditions, the paracetamol being slowly broken down into acetic acid and p-aminophenol (Paracetamol Information Centre, n.d.a, para 2).

1.3 History of paracetamol

Paracetamol is virtually the sole survivor of the so-called “aniline derivatives” or “aniline analgesics”: acetanilide, phenacetin and paracetamol (acetaminophen). Phenacetin and paracetamol are both derivatives of acetanilide (Bertolini, Ferrari, Ottani, Guerzoni, Tacchi, & Leone, 2006). Acetanilide was serendipitously found to possess antipyretic activity and quickly

introduced into medical practice under the name of antifebrin, and was shown to possess both analgesic and antipyretic activities. But its unacceptable toxic effects, the most alarming being cyanosis due to methemoglobinemia (Bertolini *et al.*,2006), prompted the search of less toxic aniline derivatives. A number of compounds were tested and phenacetin (acetophenetidin) and N-acetyl-p-aminophenol (paracetamol) were found to be the most successful. Paracetamol had been synthesized by Morse in 1878 and was first used in medicine by von Mering in 1893 (Bertolini *et al.*, 2006).

1.4 Pharmacokinetics of paracetamol

Paracetamol is well absorbed from the gastrointestinal tract following oral administration and is not subject to significant first-pass metabolism in the liver, with oral bioavailability estimated at between 63–89% in adults (Oscier & Milner, 2009). However, drug-food interaction tends to slow the rate of absorption of paracetamol, while caffeine accelerates absorption. Prokinetic drugs (such as metoclopramide) accelerate gastric emptying, enhancing the rate of absorption, while drugs that decrease the rate of gastric emptying (e.g. morphine) slow absorption, and in some cases prevent attainment of therapeutic plasma levels.

Rectal absorption of paracetamol is slower and less predictable, with bioavailability between 24% and 98% (Oscier & Milner, 2009). This variability depends on the size, physical composition and number of suppositories used, and on the rectal pH. Paracetamol is not significantly bound to plasma proteins, and has a volume of distribution of 0.7–1 $l.kg^{-1}$ (Oscier & Milner, 2009). It is non-ionised at physiological pH and freely crosses the placenta and blood–brain barrier. Intravenous paracetamol is also available as the prodrug propacetamol, though this

has never held a license in the UK. One gram of propacetamol provides 0.5 g paracetamol after hydrolysis, and bioequivalence has been established.

The minimum plasma paracetamol level required for analgesia and antipyresis is thought to be 10 $\mu g.ml^{-1}$ (Oscier & Milner, 2009), and although not clearly defined, the therapeutic range is usually stated to be 10–20 $\mu g.ml^{-1}$ (Oscier & Milner, 2009). 150 $\mu g.ml^{-1}$ is considered to be the threshold for potential hepatotoxicity. Maximal analgesic and antipyretic activity occurs 1–2 h after peak plasma levels, and the time to achieve this varies with the route of administration. Peak plasma concentration (C_{max}) is achieved approximately 45 min after 1 g orally, at between 3.5 and 4.5 h after rectal administration of both 20 and 40 $mg.kg^{-1}$ (Oscier & Milner, 2009), and approximately 25 min after a 1 g intravenous infusion. Cerebrospinal fluid levels lag behind those seen in plasma, with an equilibration half-time of 0.72 h.

1.5 Metabolism of paracetamol

Metabolism of paracetamol occurs primarily in the liver, while elimination occurs almost entirely through the kidney. Following absorption of therapeutic doses, approximately 90% is metabolised by glucuronidation and sulphation to form non-toxic metabolites (Oscier & Milner, 2009), which are excreted in the urine. A small fraction undergoes oxidation by the cytochrome P450 system to form the highly reactive metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI). NAPQI reacts with glutathione, forming conjugates that are subsequently excreted in urine. Following the ingestion of large amounts of paracetamol, hepatic glutathione is depleted and NAPQI accumulates, leading to sub-acute hepatic necrosis, and in severe cases, to hepatic failure (Figure 2). Clearance is lowest in neonates, with values rising through childhood. Elimination half-life is 2–4 h in normal adults, increasing to 4–5 h in newborns and to 11 h in premature

infants (Oscier & Milner, 2009). One to four percent is excreted unchanged in the urine, and an increased dose interval of 6–8 h is recommended in patients with severe renal impairment (GFR less than 10 ml.min^{-1}) (Oscier & Milner, 2009).

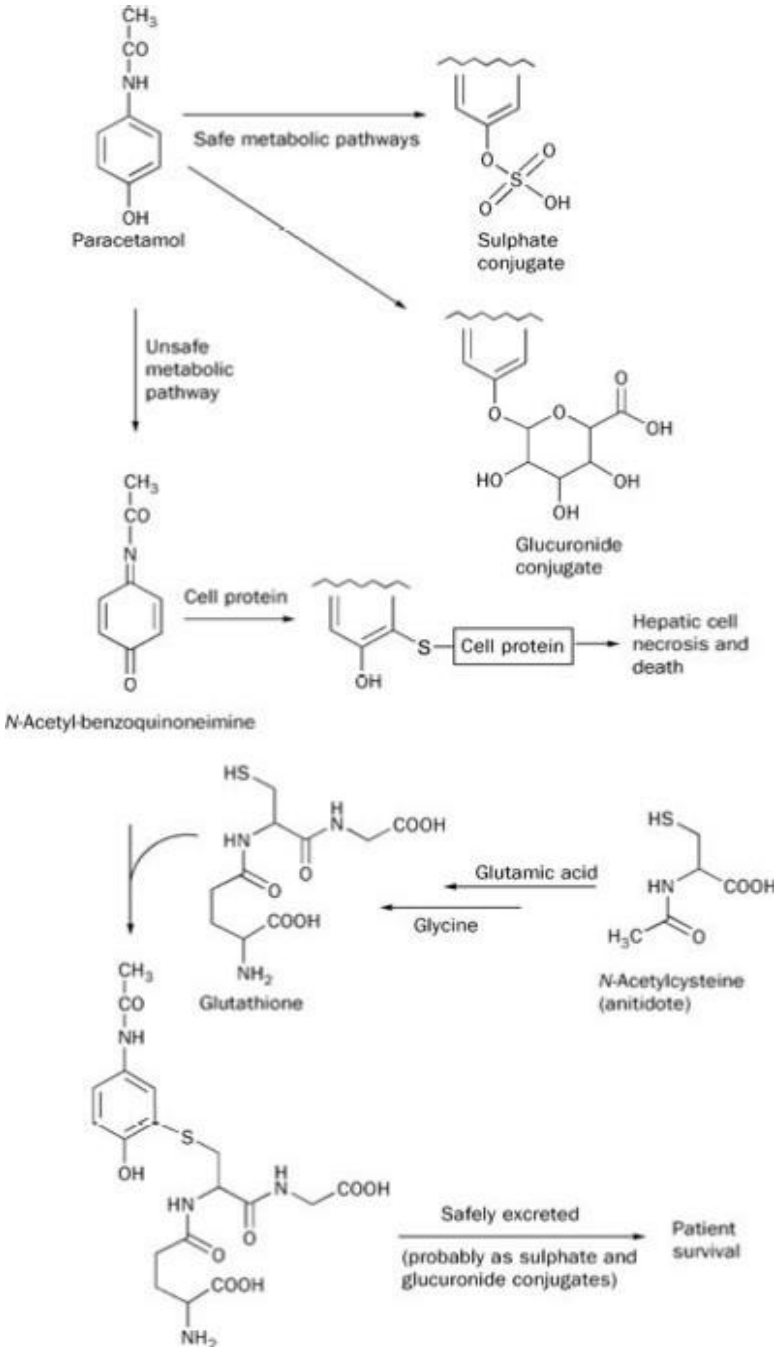


Figure 2. 'Safe' and 'unsafe' metabolic pathways of paracetamol

1.6 Mechanism of action of paracetamol

Paracetamol inhibits both isoforms COX, COX-1 and COX-2. In 2002 (Oscier & Milner, 2009), a COX-1 splice variant, COX-1b (later termed COX-3) was cloned from canine cerebral cortex and was shown to be sensitive to inhibition by paracetamol, but its significance in humans is uncertain. It appears likely that paracetamol is able to inhibit COX most effectively in environments where the ambient concentration of peroxides is low (for example, the brain) (Oscier & Milner, 2009). Peripherally, and especially at sites of inflammation where the peroxide concentration is high, the action of paracetamol on COX is greatly reduced.

However, in about 2005 (Bertolini *et al.*, 2006), a completely new and unforeseen mechanism of action of paracetamol was found when two independent groups, Zygmunt and colleagues and Bertolini and colleagues, produced experimental data clearly demonstrating that the analgesic effect of paracetamol was due to the potentiation of the cannabinoid/vanilloid tone in the brain and in dorsal root ganglia (indirect activation of cannabinoid CB_1 receptors) (Bertolini *et al.*, 2006). In brain and spinal cord, paracetamol, following deacetylation to its primary amine (p-aminophenol), is conjugated with arachidonic acid to form N-arachidonoylphenolamine (AM404), a compound already known as an endogenous cannabinoid (Bertolini *et al.*, 2006), which inhibits the cellular uptake of anandamide, an endocannabinoid, and is an agonist at the vanilloid receptor TRPV1, which is believed to play a central role in nociception. The involved enzyme is fatty acid amide hydrolase. AM404 is an agonist at TRPV1 receptors and an inhibitor of cellular anandamide uptake, which leads to increased levels of endogenous cannabinoids; moreover, it inhibits COXs in the brain, albeit at concentrations that are probably not attainable with analgesic doses of paracetamol. CB_1 receptor antagonist, at a dose level that completely prevents the analgesic activity of a selective CB_1 receptor agonist, completely prevents the

analgesic activity of paracetamol. Thus, paracetamol acts as a pro-drug, the active one being a cannabinoid. These findings finally explain the mechanism of action of paracetamol and the peculiarity of its effects, including the behavioral ones (Bertolini *et al.*, 2006).

1.7 Pharmacological actions of paracetamol

♦**High-altitude headache:** Exposure to high altitude is commonly associated with complication like headache and can appear as high-altitude headache (HAH). HAH occurs in 80% of all individuals at altitudes higher than 3000 meters (FJ, 2012). Increased capillary pressure and oedema maybe provoked due to neurohumoral and haemodynamic response elicited by hypoxia, a probable cause of HAH. Paracetamol can be used as a treatment.

♦**Improves post-operative analgesia after spine surgery:** NSAIDs, as adjuvant to opioids, are commonly used to improve post-operative analgesia associated with scoliosis surgery, reducing the need for opioids. However, by inhibiting cyclooxygenase-enzymes peripherally, NSAIDs may inhibit bone healing. Paracetamol does not have the adverse-effects of NSAIDs and has improved analgesia in children after such surgery as well. However, intravenous paracetamol 90 mg/kg/24h adjuvant to oxycodone did improve analgesia but did not diminish oxycodone consumption during 24hour after major surjery in children and adolscents (Hiller, Helenius, Nurmi, Neuvonen, Kaukonen, Hartikainen, Korpela, Taivvainen, & Meretoja, 2012).

♦**Treatment of chronic low back pain:** Paracetamol-oxycodone versus previous treatments and tramadol-paracetamol versus placebo in experiment were reported as effective for treatment of chronic low back pain (LBP) often characterized by both nociceptive and neuropathic components. While various monotherapies have been reported of only limited efficacy,

combining drugs with different mechanisms of action and targets appears a rational approach (Romano, Romano, & Lacerenza, 2012).

♦**Relief of acute pain:** Paracetamol in combination with tramadol hydrochloride helps relief acute pain. The addition of paracetamol reduces the onset time of analgesia and improves the degree of analgesia while the use of 25% less tramadol in the combination product reduces the incidence of tramadol-related adverse events (Sawaddiruk, 2011). This combination is also found to be effective in the management of postoperative pain. It improves pain relief and provides a faster onset and longer duration of action with fewer adverse events than either component separately. It also reduces the severity of pain, photophobia and phonophobia associated with migraine headache. The combination product has been shown to be most effective in patients with mild to moderate pain and has a lower risk of serious adverse events (Sawaddiruk, 2011).

♦**Dose-dependent inhibition of platelet function:** Paracetamol is a weak inhibitor of platelet COX-1. It has a dose-dependent antiaggregatory effect and this property may become clinically significant in patients with intrinsic or drug-induced impairment of homeostasis (Munsterhjelm, Munsterhjelm, Niemi, Ylikorkala, Neuvonen, & Rosenberg, 2005).

1.8 Dose of paracetamol

In general, children's dosages vary with the age of the child and the type of product, therefore the instructions on the pack should always be followed (table 1). In general, children's dosages are based on a single dose of 10mg paracetamol per kilogram bodyweight, which can be repeated 4-6 hourly, not exceeding four doses per 24 hours (Paracetamol Information Centre, n.d.b).

Table 1

Dose of paracetamol in adult and children

Age group	Dose
Adult	Two 500mg tablets (i.e., 1gm paracetamol) every four to six hours, not exceeding eight tablets (4gms) in any 24 hour period.
Children	**a) 2 month old child:** single dose of 60mg (i.e. 2.5mL paracetamol liquid (oral suspension) at a strength 120mg/5 mL). Paracetamol may be given on a doctor's recommendation only following immunization.
	b) Under 3 months: 10mg paracetamol per kilogram body weight (5mg/kg if jaundiced), on a doctor's advice only.
	c) 3 months to 1 year: Between 60mg and 120mg (i.e. 2.5mL to 5mL of paracetamol liquid (oral suspension) at strength of 120mg/5mL) may be repeated every 4-6 hours to a maximum of 4 doses in 24 hours.
	d) 1 to 5 years: 120mg to 250mg (i.e. 5mL to 10mL of paracetamol liquid (oral suspension) at a strength of 120mg/5mL) may be repeated every 4-6 hours to a maximum of 4 doses in 24 hours.
	e) 6 to 12 years: 250mg to 500 mg (i.e. 5mL to 10mL paracetamol liquid (oral suspension) at a strength of 250mg/5mL) may be repeated every 4-6 hours to a maximum of 4 doses in 24 hours.

(Paracetamol Information Centre, n.d.b)

1.9 Physical parameters of solid dosage forms (Tablets)

1.9.1 Weight variation test

Weight variation test is a very important quality control parameter because it is related with the content uniformity of a drug. A tablet is designed to contain a specific amount of drug in a specific amount of tablet formulation so it is necessary to measure that the drug contains the

appropriate amount. In practice, composite samples of tablets (usually 10) (Lachman, Lieberman, & Kanig, 1986) are taken and weighed throughout the compression process. The composite weight divided by 10, however, provides an average weight but contains 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 the USP/NF provides limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample. According to USP, the weight variation test is run by weighing 20 tablets individually in an analytical balance (figure 3), calculating the average weight, and comparing the individual tablet weights to the average.

Figure 3. Analytical balance (AY220, Shimadzu, Japan)

The tablets meet the USP test if no more than 2 tablets are outside the percentage limit of 1% and if no tablet differs by more than 2 times the percentage limit. The weight variation tolerances for uncoated tablets differ depending on average tablet weight (Lachman *et al.*, 1986). 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. However, the weight variation test is clearly not sufficient to assume uniform potency of tablets of moderate or low-dose drugs, in which excipients make up the bulk of the tablet weight (Lachman *et al.*, 1986).

1.9.2 Hardness

In order to withstand mechanical shocks of handling during its manufacture, packaging and transport, the tablet requires a certain amount of strength, or hardness. In addition tablets should be able to withstand reasonable abuse when in the hands of the consumer. Adequate tablet hardness is a necessary requisite for consumer acceptance (Lachman *et al.*, 1986). Moreover, there is evidence that hardness may influence tablet disintegration and, perhaps more significantly, drug dissolution release rate. It may be especially important to carefully monitor tablet hardness for drug products that possess real or potential bioavailability problems or are sensitive to altered dissolution-release profiles as a function of the compressive force employed.

Figure 4. Hardness tester (Veego, India)

More recently, however, tablet hardness has been defined as the force required breaking a tablet in a diametric compression test (Lachman *et al.*, 1986). To perform this test, a tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded (figure 4). Hardness is thus sometimes defined the tablet crushing strength.

The hardness of a tablet is also a function of the die fill and compression force. At a constant die fill, the hardness values increases and thickness decreases as additional compression force is applies (Lachman *et al.*, 1986). This relationship holds up to a maximum value for hardness and a minimum value for thickness, beyond which increases in pressure causes the tablet to laminate or cap, thus destroying the integrity of the tablet. At a constant compression force, (fixed distance between upper and lower punches), hardness increases with increasing die fills and decreases with lower die fills. In general, tablets are harder several hours after compression than they are immediately after compression. Lubricants can affect tablet hardness when they are used in too long a period. Larger tablets require a greater force to cause fracture and are therefore "harder" than small tablets (Lachman *et al.*, 1986).

1.9.3 Friability

Shock and frictional forces can cause the tablets to get damaged or break. With this test, it is possible to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping which is expressed as a percentage. As the hardness of the tablets is increased gradually there is a markable decrease in the percentage friability in all formulations. The possible reason for this result may be that at high compressional force the granules are packed strongly together and there is low degree of crumbling during friability. So harder the tablets less will be the percentage friability and vise versa (Seitz & Flessland, 1965).

Figure 5. Friability test apparatus

A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test using a friability test apparatus (figure 5) is considered generally acceptable and any broken or smashed tablets are not picked up.

1.9.4 Disintegration

In the context of tablet technology, disintegration implies penetration of the tablet by an aqueous liquid, disruption of internal bonds and the subsequent breakdown of the tablet. It is reasonable to suppose that rapid penetration of liquid is an essential requirement or rapid disintegration of conveniently formulated tablets. Research has established that one should not automatically expect a correlation between disintegration and dissolution. However, since the dissolution of a drug from the fragmented tablet appears to control partially or completely the appearance of the tablet in the blood, disintegration is still used as the guide to the formulator in the preparation of

an optimum tablet formula and as in-process control test to ensure lot-to-lot uniformity (Lachman *et al.,* 1986). Disintegration time may vary considering to its disintegrator used. Higher the disintegration time required lower the dissolution rate and followed to poor absorption. So disintegration is the crucial part of a drug for therapeutic action. Uncoated USP tablets have disintegration time standards as low as 5 minutes, but the majority of the tablets have a maximum disintegration time of 30 minutes (Lachman *et al.,* 1986).

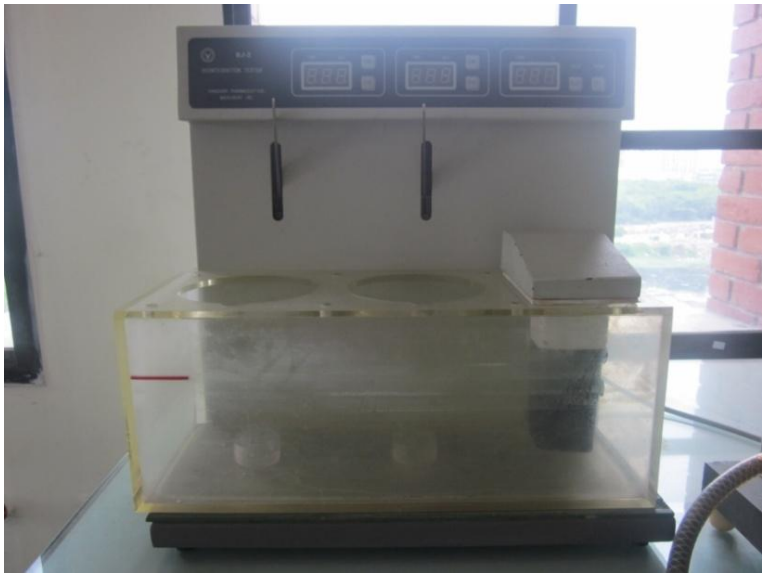


Figure 6. Disintegration tester ((Vanguard Pharmaceutical Machinery INC)

The USP device to test disintegration uses 6 tubes that are 3 inches long, open at the end and held against a 10-mesh screen at the bottom end of the basket rack assembly (figure 6). To test for disintegration time, one tablet is placed in each tube, and the basket rack is positioned in a 1-L beaker of water, simulated intestinal or gastric fluid at 37 ^{o}C ± 2^{o}C, such that the tablets remain 2.5cm above the surface of the liquid on their upward movement and descend not closer than 2.5cm at the bottom of the beaker (Lachman *et al.*, 1986).

1.10 Physical appearances of tablets

Table 2

Physical appearances of the different brands of paracetamol

Brand	Color	Shape	Scoring	Logo
Napa	White	Round	Yes	Yes
Parapyrol	White	Round	Yes	Yes
Reset	White	Round	Yes	Yes
Zerin	White	Round	Yes	Yes
Tamen	White	Cylindrical	No	Yes

1.10.1 Napa

SVA120

SUL330

04450

1.10.2 Parapyrol

591

650

711

1.10.3 Reset

11031

11171

F118

1.10.4 Zerin

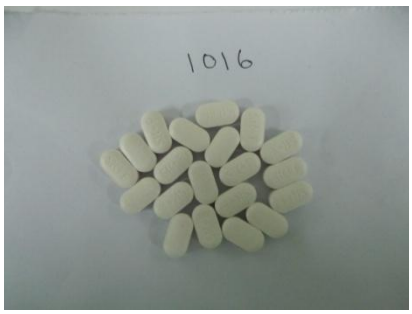
143

191

147

1.10.5 Tamen

1015



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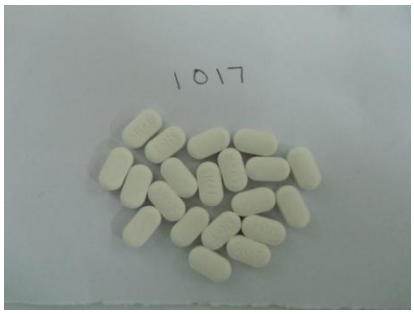

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1.11 Market status of paracetamol brands in Bangladesh Pharma Market

Table 3

Value, % share and growth, and unit sold/year of different brands of paracetamol

Brand	Company	Value in BDT	Share %	Growth %	Sold Unit/Year
Napa	Beximco	680, 596, 845	33.49	44.46	16, 312, 763
Parapyrol	Glaxosmithkline	60, 731, 410	2.99	-12.71	418,703
Reset	Incepta	38, 026, 120	1.87	50.89	1, 683, 599
Zerin	Jayson	17, 203, 902	0.85	-7.97	606, 869
Tamen	Eskayef	16, 166, 778	0.80	-14.11	525, 025

Different brands of paracetamol tablets have established themselves in Bangladesh Pharma market. According to the research conducted by Intercontinental Marketing Services (IMS), 2nd Quarter, 2011 (April - June) (table 3), the following brands of paracetamol tablets were ranked as per their value in market in BDT, with Napa having the highest % share of 33.49% but the 2nd highest % growth of 44.46%. Zerin has the lowest value in BDT at 16, 166, 778 with also the lowest % share at 0.80 and % growth of -14.11.

Significance of the study

It is necessary to carry out study on the quality control parameters of paracetamol tablets available in Bangladesh for the appropriate evaluation of quality, therapeutic efficacy, and safety of the tablets. Moreover, such parameters or physical properties of tablet are also useful tools for maintaining consistency in batch-to-batch manufacturing and it should be performed for every drug product. All of these parameters are closely related to each other and have effect on drug absorption, bioavailability etc. They are important marker to reflect the quality of available paracetamol tablets in Bangladesh. This qualitative data may help in the further improvement of the products. They are very important since inferior, shoddy or poor quality medicines can be a major cause of are a major cause of death and unacceptability of drugs.

Objective of the study

The objective of this study was to conduct the evaluation of the quality control parameters of 15 different batches of five different brands of paracetamol tablets available in Bangladesh market for batch to batch variation and also to perform quality control tests to assess the paracetamol tablets by means of tests including weight variation, friability, hardness, and disintegration tests.

CHAPTER 2

LITERATURE REVIEW

2. Literature review

Ahmed, A., *et al* performed various pharmacopoeial and non-pharmacopoeial control test on Acetaminophen tablets to evaluate the uniformity of weight, diameter, thickness, medicaments, hardness and friability (Ahmed, Ali, Hassan, Ali & Haque, 2001). Four formulations of Acetaminophen tablets were prepared having different hardness using different disintegrants (sodium carboxy methyl cellulose, corn starch, veegum, Avicel 101). Acetaminophen tablets was tested for uniformity of weight, uniformity of thickness, uniformity of diameter for Acetaminophen tablets of different formulation, hardness of tablets, friability of Acetaminophen tablets of different formulation, variation of Acetaminophen contents from tablet to tablet and uniformity of medicament. It was found that the tablets were of an average weight of 600 mg ± 5% which is within the limits of the percentage deviation allowed by USP for tablets weighing 325 mg or more (Ahmed *et al.*, 2001). The deviation in thickness was within ± 5%. The variation in diameter varied from 12.38 to 12.47 mm. The hardness of the formulation with the different disintegrants ranged from 2.8 to 7.5 kg/cm^2. The percentage friability ranged from 1.24 to 3.98% (Ahmed *et al.*, 2001). In all cases the values were less than 2.5% indicating the uniformity of distribution of the active ingredient in tablets. These values are under the limit of B.P. as described by Acetaminophen tablets i.e. ±5%. The uniformity of Acetaminophen content was calculated by average assay method and was found under the B.P. limit i.e. ± 5% (Ahmed *et al.*, 2001). The results have been interpreted statistically and the tablets have been found to be within the limits of B.P. and USP.

Gangwar, S., *et al* compared the disintegrating property of papaya starch and sago starch in paracetamol tablets. The prepared tablets were evaluated for parameters such as weight variation, hardness, friability, and disintegration. Papaya fruit (*Carica papaya*) is a rich source of starch. Unripe papaya fruit contains about 43% of starch (Gangwar, Singh, Garg, Garg, &

Sharma, 2010). Sago starch was obtained from the pith of the plant *Metroxylon sagu* which contains about 27% of the amylose. In this study unriped papaya was taken and pulp powder was obtained by lyophilizing the fresh fruit. Starch extracted from unripe papaya pulp powder was used as the first disintegrant and sago starch obtained was used as the second disintegrant in the paracetamol tablets. The *in vitro* release pattern of the two different formulated paracetamol tablets was compared to determine the disintegrant properties of both starches. The physical properties (bulk density, true density, tapped density, angle of repose, swelling power and paste clarity) of both starches was also evaluated by testing ten batches containing 2%, 4%, 6%, 8%, and 10% concentration of both the starch as disintegrant (Gangwar *et al.,* 2010). The disintegration time of the tablets formulated was compared and it was found that tablets with sago starch disintegrated more rapidly than the tablets with papaya starch. The disintegration time of tablets with papaya starch was found to be 43.5, 41.7, 36.4, 34.6 and 32.3min respectively for 2%, 4%, 6%, 8% and 10% papaya starch as disintegrant. The value of disintegration time for tablets with sago starch as disintegrant was 39.8, 37.9, 36.7, 35.3 and 29.9min respectively for 2%, 4%, 6%, 8% and 10% sago starch.

Sago starch showed significant disintegrant property. It was also found that as the starch concentration was increased, disintegration time decreased but at equal concentration of both starch, sago starch possessed greater disintegrant property. The average weight variation of the tablets was 1.42, 2.56, 3.22, 3.51 and 1.72% respectively for 2%, 4%, 6%, 8% and 10% sago starch. The average weight variation of the tablets was 2.23, 3.07, 1.92, 2.51 and 1.57% respectively for 2%, 4%, 6%, 8% and 10% sago starch (Gangwar *et al.,* 2010). The hardness of the tablet ranged from 6.4 to 6.8 kg/f and 6.2 to 7.0 kg/f for the tablets containing papaya starch and sago starch respectively, which was within the acceptable

limits. The friability of the tablets was found to be between 0.45 to 0.91% and 1.23 to 0.85% for the tablets containing papaya starch and sago starch respectively and this was also within acceptable limits. Sago starch shows higher swelling power than papaya starch and hence it was observed from the study that sago starch possessed higher disintegrating property than papaya starch (Gangwar *et al.*, 2010).

Ngwuluka, N. C., *et al* conducted a test to evaluate the binding properties of dried and milled date palm fruit in comparison with acacia and tragacanth. Various quality control tests were carried out including uniformity of weight, hardness, friability, and disintegration. The granules manufactured using the binders had good flow properties and compressibility. As the concentration of the binders increased, the binding ability improved producing tablets with good uniformity of weight and hardness (Ngwuluka, Idiakhoa, Nep, Ogaji, & Okafor, 2010). The tablets manufactured using dried date palm was found to be less friable than tablets manufactured using acacia and tragacanth. Although, the tablets did not disintegrate, the drug release from the tablets passed the USP and BP specification for dissolution of paracetamol. The tablets also had good uniformity of weight, hardness, friability, thickness and diameter than acacia and tragacanth as its concentration increased and were found to be a better binder than tragacanth. The uniformity of weight ranged from 0.693 to 0.700g, 0.693 to 0.699g and 0.673 to 0.697g for tablets prepared using different concentrations of date palm powder, acacia gum and tragacanth gum respectively (Ngwuluka *et al.*, 2010). The uniformity of diameter ranged from 0.954 to 0.985mm, 0.964 to 0.967mm and 0.965 to 0.967mm for tablets prepared using different concentrations of date palm powder, acacia gum and tragacanth gum respectively.

The uniformity in thickness varied from 0.28 to 0.29mm, 0.21 to 0.29mm and 0.20 to 0.27mm for tablets prepared using different concentrations of date palm powder, acacia gum and

tragacanth gum respectively. The hardness ranged from 6.00 to >14kg for tablets containing date palm powder, >3.50 to 8.50kg for tablets containing acacia gum and 1.00 to >14kg for tablets containing tragacanth gum (Ngwuluka *et al.*, 2010). The friability ranged from 0.93% for tablets containing date palm powder, 12.44 to 26.65% for tablets containing acacia gum. For tablets containing tragacanth gum, there was no loss in weight for tablets containing 2% tragacanth gum but for the other concentration, it ranged from 9.89 to 324.89%. Tablets containing date palm powder had a disintegration time >30mins, tablets containing acacia gum had disintegration time from 23 to >30mins and tablets containing tragacanth gum disintegrated within 5-14mins (Ngwuluka *et al.*, 2010). The results were within the limits.

Eichie, F. E. and Kudehinbu, A. O performed tests to investigate the effect of particle size distribution of paracetamol granules on some tablet mechanical properties of paracetamol tablets. Granules were formed by wet massing paracetamol powder (200g) with 20% (w/w) of maize starch mucilage as binder (Eichie & Kudehinbu, 2009). Resulting granules were classified into different size fractions (212-1700µm) by sieve analysis and samples of granules from the various size fractions were compressed into tablets of weight 500 ± 4.3 mg, diameter 12.3 ± 2.3 mm and thickness 3.6 ± 1.2 mm, using a single punch tablet machine at a compression pressure load of 7 arbitrary units on the load scale. The tablets were equilibrated for 24h before evaluation. Tablet mechanical parameters evaluated were packing fraction (Pf), tensile strength (T), particle density, porosity and friability. The results showed that T values and friability index decreased slightly from 1.48 MNm to 1.35 MNm and 1.77 to 0.93%, respectively, following an increase in the granule sizes from 212 to 1700 µm (Eichie & Kudehinbu, 2009). These differences were, however, not statistically significant.

The packing fraction (Pf) of the tablets increased from 0.853 to 0.960 significantly following an

increase in granule size from 212 to 1700 µm. The indication was that there was a higher degree of consolidation of the compacts formed from larger granules as a result of plastic deformation and fragmentation than those from smaller granules. The study showed that varying the granule size distribution in a powdered bed affects some tablet mechanical characteristics (Eichie & Kudehinbu, 2009). The implication of this is that the granule sizes should be controlled during tableting and/or filling into capsule in order to avoid weight and content variation while ensuring that only tablets with desirable mechanical characteristics are formed.

A. R. Chandrasekaran, et al evaluated six brands of paracetamol (acetaminophen) 500 mg tablets by performing the quality control tests for uniformity of weight, hardness, friability, and disintegration with the aim to assess its bioequivalence. Friability for all brands was below 1%. The average disintegration time ranged from 1.52 to 8.808min (Chandrasekaran, Han, Chung, Cheang, & Ping, 2011). The weight variation test limit was from 0.5223 to 0.6315gm. Tablet hardness ranged from 7.0 to 12.5 kg/square inch. According to USP specification, paracetamol tablets should release more than 80% of drug at 30 min and the results of all the six brands complied with the USP specification (Chandrasekaran *et al.*, 2011).. Based on the finding from this study, it can be concluded that, despite some apparent minor differences in tablet hardness and disintegration time profiles, the dissolution characteristics of various paracetamol tablets appears to be similar and not significantly different from various manufacturers.

CHAPTER 3

METHODS AND MATERIALS

3. Materials and methods

3.1 Weight variation test

Materials: Electronic analytical balance (AY220, Shimadzu, Japan), and Tablets

Method: 20 tablets were taken and each tablet was weighed individually using the electronic balance. The average weight of all the tablets was calculated and considered as the standard weight of the individual tablet. Then all the tablets were individually weighed and the percentage weight variation was calculated to determine whether the individual weight is within the range or not. The tablets meet the USP test if not more than two tablets are outside the percentage limit and if no tablet differ by more than two times the percentage limit (table 3).

Table 4

Limit of weight variation test

Average Weight	Percentage difference
130 mg or less	±10
More than 130	±7.5
324 mg and above	± 5

(Lachman *et al.*, 1986).

3.2 Hardness test

Materials: Hardness tester (Veego, India), and Tablets.

Method: 10 tablets were taken from each batch. Individually, a tablet was placed between two anvils, force was applied to the anvils, and the crushing strength that just caused the tablet to break was recorded. Finally the reading was taken in kg from the sliding scale.

3.3 Friability test

Materials: Veego friability tester, Electronic Analytical Balance (AY220, Shimadzu, Japan), and Tablets.

Method: At first 10 tablets were taken and the tablets were carefully dusted prior to testing. Then the 10 tablets were weighed which was considered as the initial reading. After weighing the tablets, all the tablets were placed in the drum of friability tester and rotated 100 times. After 100 revolutions, the 10 tablets were removed and re-weighed. This was the final reading. The percentage was calculated. According to USP the tablets should not lose more than 1% of their total weight.

3.4 Disintegration test

Materials: Disintegration tester (Vanguard Pharmaceutical Machinery INC), pH meter, 0.1 M HCL, and Tablets

Method: At first, the disintegration tester was assembled. Then 900ml of 0.1 M HCl (pH- 1.2) was placed in each 1000ml beaker (N.B: The volume of the liquid was such that when the assembly is in the highest position the wire mesh was at least 15mm below the surface of the liquid and when the assembly was in the lowest position the wire mesh was at least 25 mm above the bottom of the beaker and the upper open ends of the tubes remain above the surface of the liquid). The temperature was maintained at 37^{o}C. Then one tablet was placed in each of the 6 tubes and the apparatus was operated for the prescribed period. All the tablets must disintegrate within the prescribed time. If 1 or 2 tablets fail to disintegrate completely, the test must be repeated on 12 additional tablets (table 4).

Disintegration is considered to be achieved when no residues remain on the screen, or if there is a residue, it consists of a soft mass having no palpably firm, unmoistened core, or only fragments of coating (tablets) may adhere to the lower surface of the disc.

Table 5

Limit of disintegration time

Type of tablet	Disintegration time
Uncoated tablet	15 minutes
Coated tablet	60 minutes or 1 hour

(Lachman *et al.*, 1986)

CHAPTER 4

RESULTS

4. Results

4.1 Weight variation

4.1.1 Napa

Table 6

Individual weight and percentage weight variation of the three batches of Napa tablets

Brand	Tab no.	Batch# SVA120		Batch# SUL330		Batch # 04450	
		Weight (g)	% Weight variation	Weight (g)	% Weight variation	Weight (g)	% Weight variation
NAPA	1	0.58	1.72	0.58	1.72	0.58	0
	2	0.57	3.51	0.59	0	0.58	0
	3	0.57	3.51	0.59	0	0.58	0
	4	0.58	1.72	0.59	0	0.59	-1.69
	5	0.59	0	0.59	0	0.58	0
	6	0.58	1.72	0.59	0	0.58	0
	7	0.59	0	0.59	0	0.59	-1.69
	8	0.58	1.72	0.59	0	0.59	0
	9	0.60	-1.67	0.59	0	0.59	0
	10	0.59	0	0.59	0	0.58	0
	11	0.58	1.72	0.59	0	0.59	-1.69
	12	0.57	3.51	0.59	0	0.59	-1.69
	13	0.58	1.72	0.59	0	0.58	0
	14	0.58	1.72	0.59	0	0.58	0
	15	0.59	0	0.60	-1.67	0.58	0
	16	0.59	0	0.59	0	0.57	1.75
	17	0.59	0	0.59	0	0.58	0
	18	0.58	1.72	0.59	0	0.58	0
	19	0.59	0	0.60	-1.67	0.58	0
	20	0.59	0	0.59	0	0.58	0

The % weight variation of Batch# SVA120, SUL330 and 04450 ranged from -1.67 to 3.51%, -1.67 to 1.72% and -1.67 to 1.75% respectively (table 5).

Table 7

Mean weight and standard deviation of the three batches of Napa tablets

Brand	Batch	Mean weight (g) (n=20)	Standard Deviation
NAPA	SVA120	0.584	0.008
	SUL330	0.591	0.004
	04450	0.583	0.006

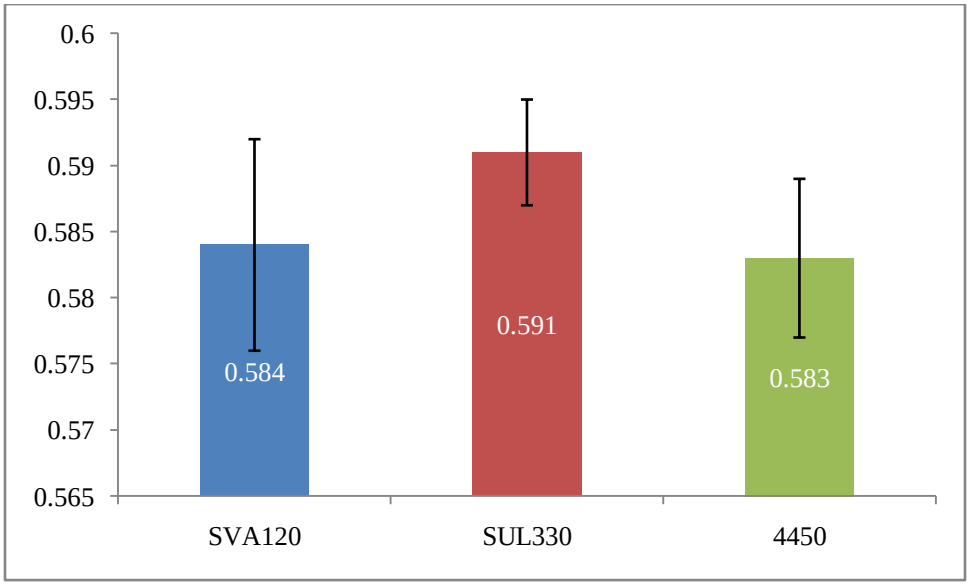

Figure 7. Mean weight of the three batches of Napa tablets

The average weight of Batch# SVA120, SUL330 and 04450 was 0.584g, 0.591g and 0.583g respectively (table 6).

4.1.2 Parapyrol

Table 8

Individual weight and percentage weight variation of the three batches of Parapyrol tablets

Brand	Tab no.	Batch# 711		Batch# 591		Batch # 650	
		Weight (g)	% Weight variation	Weight (g)	% Weight variation	Weight (g)	% Weight variation
PARAPYROL	1	0.59	1.69	0.60	1.67	0.59	1.69
	2	0.59	1.69	0.60	1.67	0.60	0
	3	0.59	1.69	0.60	1.67	0.59	1.69
	4	0.61	-1.64	0.60	1.67	0.58	3.45
	5	0.60	0	0.61	0	0.61	-1.64
	6	0.60	0	0.62	-1.61	0.60	0
	7	0.59	1.69	0.62	-1.61	0.60	0
	8	0.60	0	0.62	-1.61	0.60	0
	9	0.59	1.69	0.61	0	0.61	-1.64
	10	0.59	1.69	0.61	0	0.59	1.69
	11	0.61	-1.64	0.60	1.67	0.59	1.69
	12	0.60	0	0.64	-4.69	0.59	1.69
	13	0.60	0	0.62	-1.61	0.59	1.69
	14	0.60	0	0.60	1.67	0.61	-1.64
	15	0.60	0	0.61	0	0.60	0
	16	0.59	1.69	0.61	0	0.59	1.69
	17	0.59	1.69	0.62	-1.61	0.60	0
	18	0.60	0	0.62	-1.61	0.60	0
	19	0.60	0	0.61	0	0.60	0
	20	0.59	1.69	0.60	1.67	0.59	1.69

The % weight variation of Batch# 711, 591 and 650 ranged from -1.64 to 1.69%, -4.69 to 1.67% and -1.64 to 3.45% respectively (table 7).

Table 9

Mean weight and standard deviation of the three batches of Parapyrol tablets

Brand	Batch	Mean weight (g) (n=20)	Standard deviation
PARAPYROL	711	0.597	0.007
	591	0.611	0.011
	650	0.597	0.008

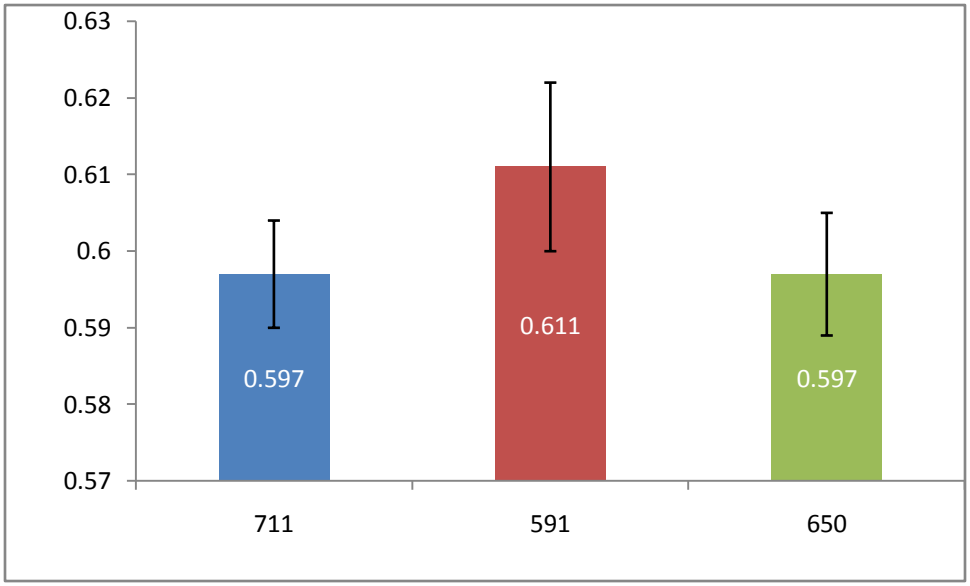

Figure 8. Mean weight of the three batches of Parapyrol tablets

The average weight of Batch# 711, 591 and 650 was 0.597g, 0.611g and 0.597g respectively (table 8).

4.1.3 Reset

Table 10

Individual weight and percentage weight variation of the three batches of Reset tablets

Brand	Tab no.	Batch# 11031		Batch# 11171		Batch # F118	
		Weight (g)	% Weight variation	Weight (g)	% Weight variation	Weight (g)	% Weight variation
RESET	1	0.63	-1.59	0.63	0	0.64	-1.56
	2	0.62	0	0.62	0.61	0.62	1.61
	3	0.62	0	0.62	1.61	0.63	0
	4	0.63	-1.59	0.63	0	0.63	0
	5	0.62	0	0.64	-1.56	0.64	-1.56
	6	0.62	0	0.63	0	0.63	0
	7	0.63	-1.59	0.63	0	0.63	0
	8	0.64	-3.13	0.63	0	0.63	0
	9	0.61	1.64	0.64	-1.56	0.63	0
	10	0.63	-1.59	0.63	0	0.63	0
	11	0.63	-1.59	0.63	0	0.63	0
	12	0.61	1.64	0.63	0	0.63	0
	13	0.61	1.64	0.62	0.61	0.64	-1.56
	14	0.62	0	0.62	0.61	0.64	-1.56
	15	0.62	0	0.64	-1.56	0.63	0
	16	0.63	-1.59	0.63	0	0.62	1.61
	17	0.62	0	0.63	0	0.64	-1.56
	18	0.63	-1.59	0.63	0	0.63	0
	19	0.62	0	0.63	0	0.62	1.61
	20	0.63	-1.59	0.63	0	0.63	0

The % weight variation of Batch# 11031, 11171 and F118 ranged from -3.13 to 1.64%, -1.56 to 1.61% and -1.56 to 1.61% respectively (table 9).

Table 11

Mean weight and standard deviation of the three batches of Reset tablets

Brand	Batch	Mean weight (g) (n=20)	Standard deviation
RESET	11031	0.624	0.008
	11171	0.624	0.008
	F118	0.630	0.006

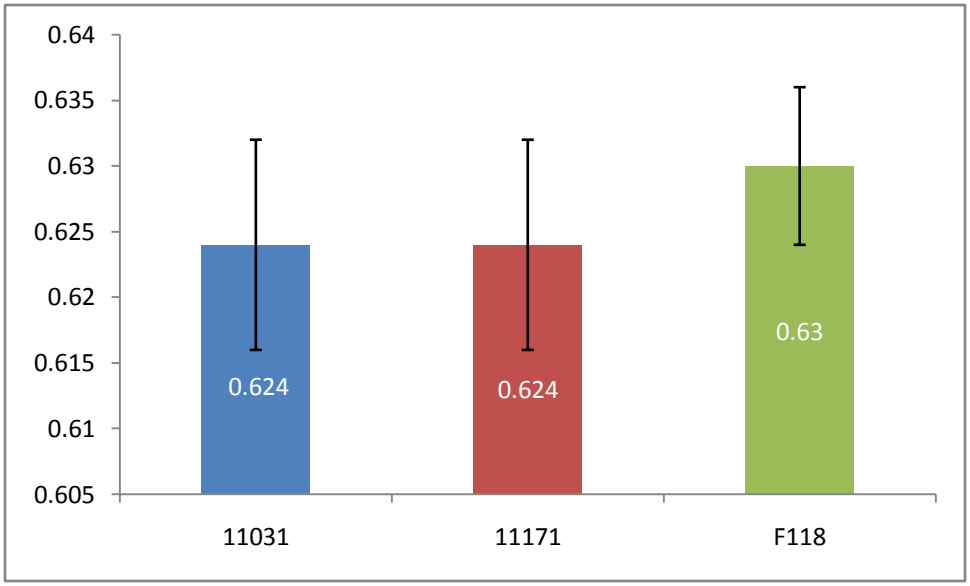

Figure 9. Mean weight of the three batches of Reset tablets

The average weight of Batch# 11031, 11171 and F118 was 0.624g, 0.624g and 0.630g respectively (table 10).

4.1.4 Zerin

Table 12

Individual weight and percentage weight variation of the three batches of Zerin tablets

Brand	Tab no.	Batch# 191		Batch# 147		Batch # 143	
		Weight (g)	% Weight variation	Weight (g)	% Weight variation	Weight (g)	% Weight variation
ZERIN	1	0.55	0	0.58	0	0.63	-9.5
	2	0.55	0	0.59	3.77	0.55	3.64
	3	0.54	1.85	0.59	0	0.57	0
	4	0.54	1.85	0.59	0	0.56	1.79
	5	0.54	1.85	0.59	1.85	0.60	-5
	6	0.56	-1.79	0.59	0	0.62	-8.06
	7	0.55	0	0.59	0	0.63	-9.5
	8	0.53	3.77	0.59	0	0.62	-8.06
	9	0.54	1.85	0.59	1.85	0.62	-8.06
	10	0.52	5.77	0.59	-1.79	0.62	-8.06
	11	0.54	1.85	0.59	0	0.62	-8.06
	12	0.54	1.85	0.59	1.85	0.51	11.8
	13	0.55	0	0.59	1.85	0.53	7.55
	14	0.54	1.85	0.59	0	0.53	7.55
	15	0.56	-1.79	0.60	1.85	0.58	-1.72
	16	0.54	1.85	0.59	-1.79	0.58	-1.72
	17	0.55	0	0.59	-1.79	0.59	-3.39
	18	0.55	0	0.59	0	0.57	0
	19	0.54	1.85	0.60	0	0.61	-6.56
	20	0.57	-3.51	0.59	0	0.59	-3.39

The % weight variation of Batch# 191, 147 and 143 ranged from -3.51 to 5.77%, -1.79 to 3.77% and -9.5 to 11.8% respectively (table 11).

Table 13

Mean weight and standard deviation of the three batches of Zerin tablets

Brand	Batch	Mean weight (g) (n=20)	Standard deviation
ZERIN	191	0.545	0.011
	147	0.548	0.008
	143	0.587	0.036

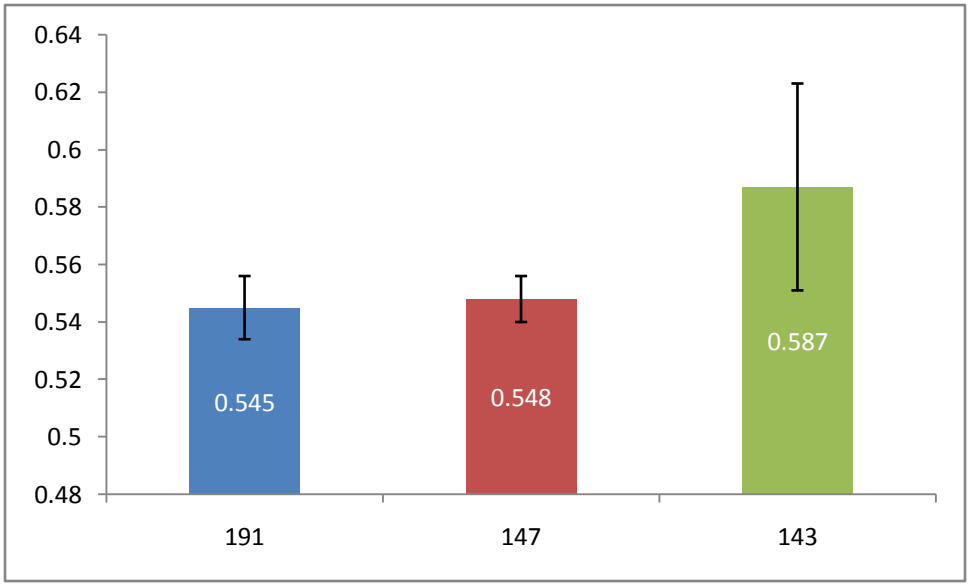

Figure 10. Mean weight of the three batches of Zerin tablets

The average weight of Batch# 191, 147 and 143 was 0.545g, 0.548g and 0.587g respectively (table 12).

4.1.5 Tamen

Table 14

Individual weight and percentage weight variation of the three batches of Tamen tablets

Brand	Tab no.	Batch# 1015		Batch# 1016		Batch # 1017	
		Weight (g)	% Weight variation	Weight (g)	% Weight variation	Weight (g)	% Weight variation
TAMEN	1	0.57	1.75	0.57	0	0.57	0
	2	0.57	1.75	0.57	0	0.56	1.79
	3	0.57	1.75	0.57	0	0.56	1.79
	4	0.56	3.57	0.57	0	0.57	0
	5	0.57	1.75	0.57	0	0.57	0
	6	0.57	1.75	0.57	0	0.57	0
	7	0.57	1.75	0.57	0	0.57	0
	8	0.57	1.75	0.57	0	0.57	0
	9	0.57	1.75	0.57	0	0.57	0
	10	0.58	0	0.57	0	0.56	1.79
	11	0.56	3.57	0.57	0	0.57	0
	12	0.57	1.75	0.57	0	0.57	0
	13	0.57	1.75	0.57	0	0.57	0
	14	0.57	1.75	0.56	1.79	0.57	0
	15	0.57	1.75	0.56	1.79	0.56	1.79
	16	0.57	1.75	0.57	0	0.57	0
	17	0.57	1.75	0.56	1.79	0.57	0
	18	0.57	1.75	0.56	1.79	0.57	0
	19	0.57	1.75	0.57	0	0.58	-1.72
	20	0.57	1.75	0.57	0	0.57	0

The % weight variation range of Batch# 1015, 1016 and 1017 ranged from 1.75 to 3.57%, 0 to 1.79% and 1.75 to 3.57% respectively (table 13).

Table 15

Mean weight and standard deviation of the three batches of Tamen tablets

Brand	Batch	Mean weight (g) (n=20)	Standard deviation
TAMEN	1015	0.584	0.008
	1016	0.591	0.004
	1017	0.583	0.006

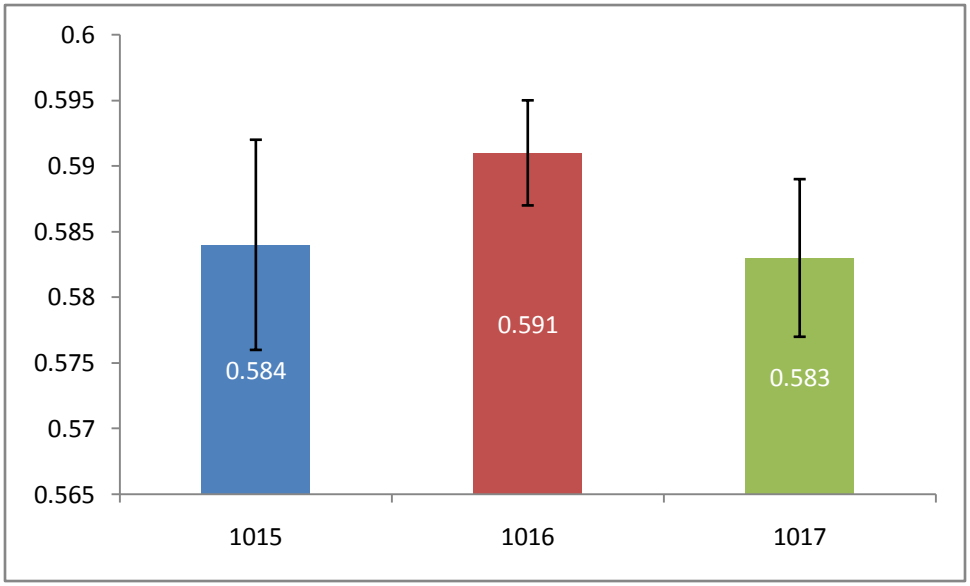

Figure 11. Mean weight of the three batches of Tamen tablets

The average weight of Batch# 1015, 1016 and 1017 was 0.584g, 0.591g and 0.583g respectively (table 14).

4.2 Hardness

4.2.1 Napa

Table 16

Hardness of the three batches of Napa tablets

Brand	Tab no.	Batch# SVA120	Batch# SUL330	Batch # 04450
		Hardness (kg)	Hardness (kg)	Hardness (kg)
NAPA	1	9.1	6.0	13.0
	2	7.8	10.1	16.8
	3	7.2	6.6	15.2
	4	8.3	8.0	15.0
	5	9.0	6.8	13.4
	6	8.8	10.1	17.7
	7	8.6	6.4	15.8
	8	8.6	7.2	15.5
	9	8.5	8.2	16.2
	10	8.2	9.0	16.8

The hardness of Batch# SVA120, SUL330 and 04450 ranged from 7.2 to 9.1kg, 6.0 to 10.1kg and 13.0 to 17.7kg respectively (table 15).

Table 17

Mean hardness and standard deviation of the three batches of Napa tablets

Brand	Batch	Mean hardness (kg) (n=10)	Standard deviation
NAPA	SVA120	8.41	0.572
	SUL330	7.84	1.498
	04450	15.54	1.482

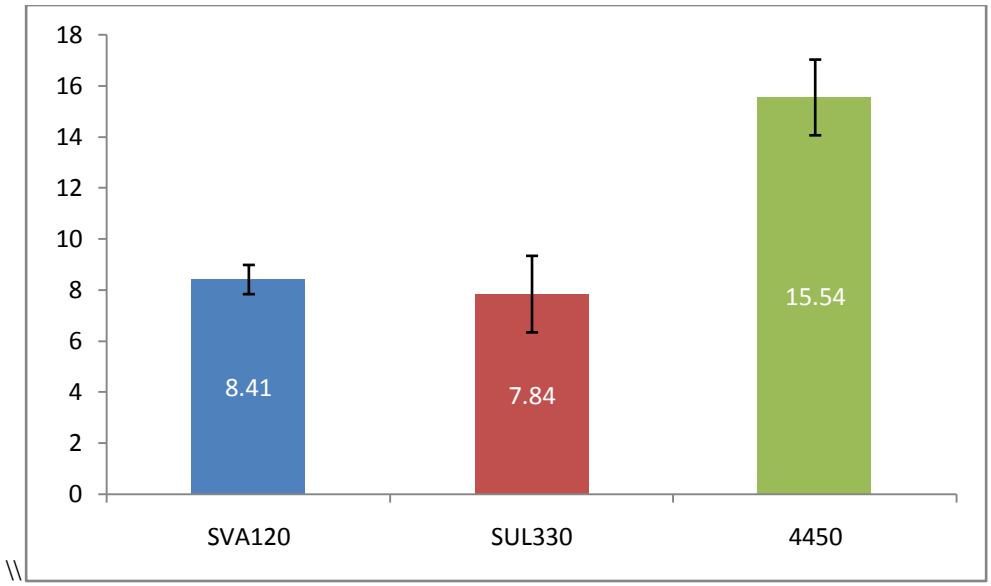

Figure 12. Mean hardness of the three batches of Napa tablets

The average hardness of Batch# SVA120, SUL330 and 04450 was 8.41kg, 7,84kg and 15.54kg respectively (table 16).

4.2.2 Parapyrol

Table 18

Hardness of the three batches of Parapyrol tablets

Brand	Tab no.	Batch# 711	Batch# 591	Batch # 650
		Hardness (kg)	Hardness (kg)	Hardness (kg)
PARAPYROL	1	9.1	11.0	10.8
	2	11.4	12.0	10.8
	3	9.8	12.2	11.6
	4	9.8	14.0	10.2
	5	11.2	10.8	12.4
	6	8.8	13.1	11.8
	7	8.8	11.2	10.5
	8	10.8	10.7	9.8
	9	11.6	10.0	8.4
	10	9.0	12.4	11.4

The hardness of Batch# 711, 591 and 650 ranged from 8.8 to 11.6kg, 10.0 to 13.1kg and 8.4 to 12.4kg respectively (table 17).

Table 19

Mean hardness and standard deviation of the three batches of Parapyrol tablets

Brand	Batch	Mean hardness (kg) (n=10)	Standard deviation
PARAPYROL	711	10.03	1.124
	591	11.74	1.225
	650	10.77	1.143

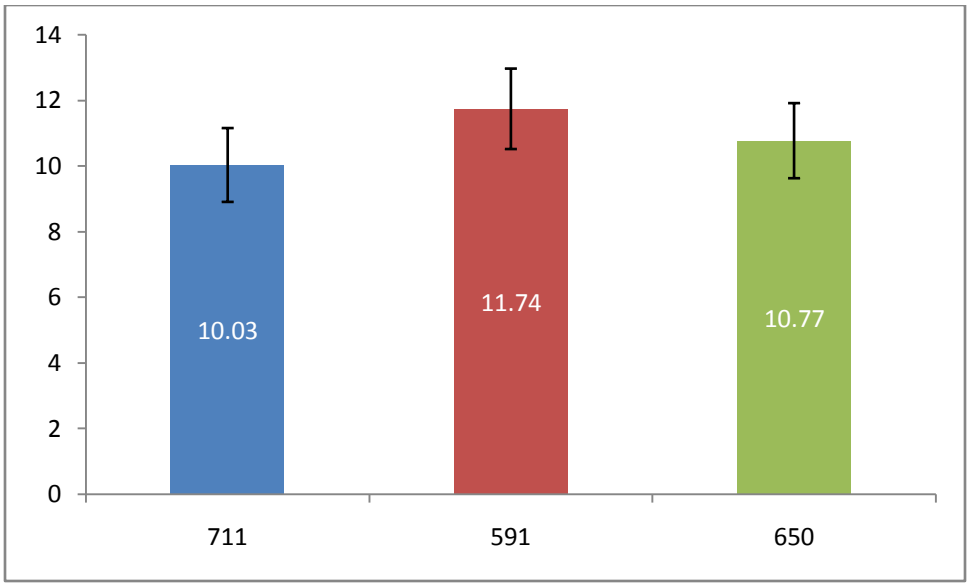

Figure 13. Mean hardness of the three batches of Parapyrol tablets

The average hardness of Batch# 711, 591 and 650 was 10.03kg, 11.74kg and 10.77kg respectively (table 18).

4.2.3 Reset

Table 20

Hardness of the three batches of Reset tablets

Brand	Tab no.	Batch# 11031	Batch# 11171	Batch # F118
		Hardness (kg)	Hardness (kg)	Hardness (kg)
RESET	1	13.7	13.7	14.9
	2	13.5	12.0	16.3
	3	16.8	14.7	17.9
	4	14.7	14.6	12.5
	5	16.2	14.0	14.7
	6	16.0	13.9	16.9
	7	14.4	14.5	19.0
	8	18.7	16.0	12.7
	9	16.6	17.1	13.3
	10	14.0	15.3	13.6

The hardness of Batch# 11031, 11171 and F118 ranged from 13.5 to 18.7kg, 12.0 to 17.1kg and 12.5 to 19.0kg respectively (table 19).

Table 21

Mean hardness and standard deviation of the three batches of Reset tablets

Brand	Batch	Mean hardness (kg) (n=10)	Standard deviation
RESET	11031	15.46	1.673
	11171	14.58	1.380
	F118	15.18	2.258

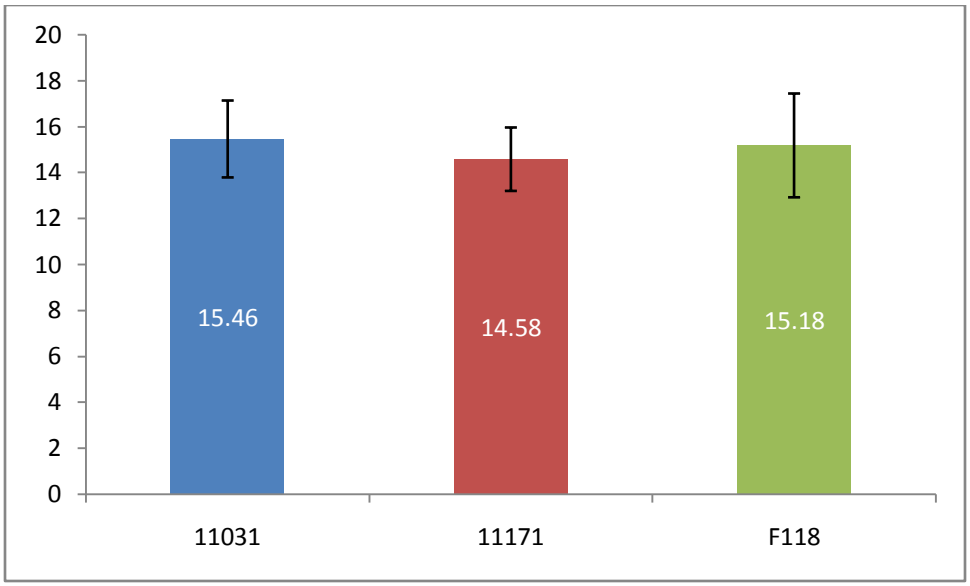

Figure 14. Mean hardness of the three batches of Reset tablets

The average hardness of Batch# 11031, 11171 and F118 was 15.46kg, 14.58kg and 15.18kg respectively (table 20).

4.2.4 Zerin

Table 22

Hardness of the three batches of Zerin tablets

Brand	Tab no.	Batch# 191	Batch# 147	Batch # 143
		Hardness (kg)	Hardness (kg)	Hardness (kg)
ZERIN	1	12.4	12.1	5.4
	2	13.9	15.7	5.6
	3	12.2	15.9	18.4
	4	11.4	12.9	17.2
	5	12.9	15.5	8.2
	6	17.6	16.5	16.2
	7	12.5	15.2	7.6
	8	13.0	14.9	5.0
	9	15.3	16.0	10.4
	10	12.1	14.0	7.5

The hardness of Batch# 191, 147 and 143 ranged from 11.4 to 17.6kg, 12.1 to 16.5kg and 5.4 to 18.4kg respectively (table 21).

Table 23

Mean hardness and standard deviation of the three batches of Zerin tablets

Brand	Batch	Mean hardness (kg) (n=10)	Standard deviation
ZERIN	191	13.330	1.850
	147	14.870	1.434
	143	10.150	5.181

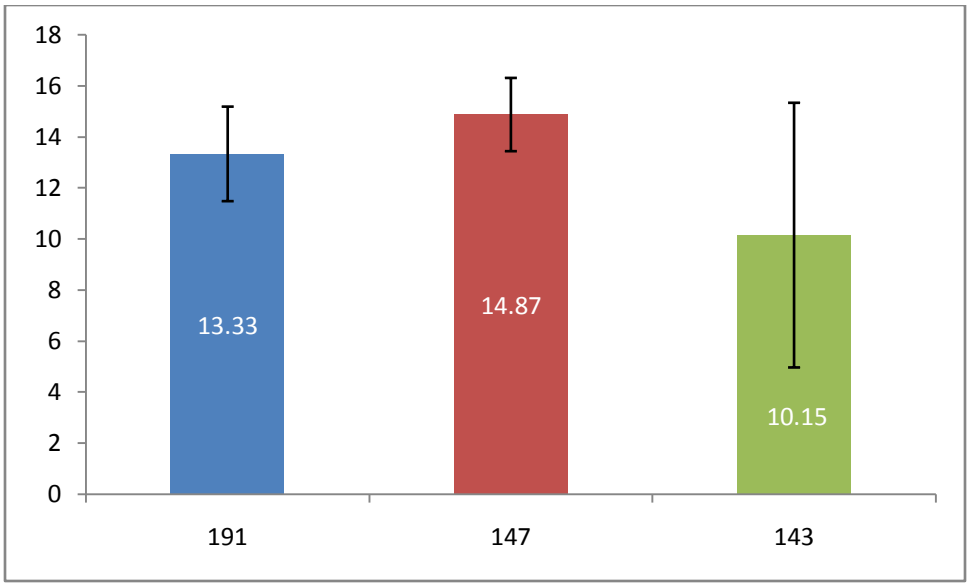

Figure 15. Mean hardness of the three batches of Zerin tablets

The average hardness of Batch# 191, 147 and 143 was 13.33kg, 14.87kg and 10.15kg respectively (table 22).

4.2.5 Tamen

\Table 24

Hardness of the three batches of Tamen tablets

Brand	Tab no.	Batch# 1015	Batch# 1016	Batch # 1017
		Hardness (kg)	Hardness (kg)	Hardness (kg)
TAMEN	1	18.0	14.0	16.0
	2	16.2	18.6	14.3
	3	9.8	17.4	17.5
	4	15.3	16.2	18.1
	5	16.0	17.9	17.9
	6	17.5	16.5	17.6
	7	17.0	13.6	15.9
	8	7.9	17.1	19.0
	9	13.7	17.8	10.0
	10	17.2	13.3	15.5

The hardness of Batch# 1015, 1016 and 1017 ranged from 10.0 to 19.0kg , 13.3 to 18.6kg and 117.9 to 18.0kg respectively (table 23).

Table 25

Mean hardness and standard deviation of the three batches of Tamen tablets

Brand	Batch	Mean hardness (kg) (n=10)	Standard deviation
TAMEN	1015	14.86	1.673
	1016	16.24	1.380
	1017	16.18	2.258

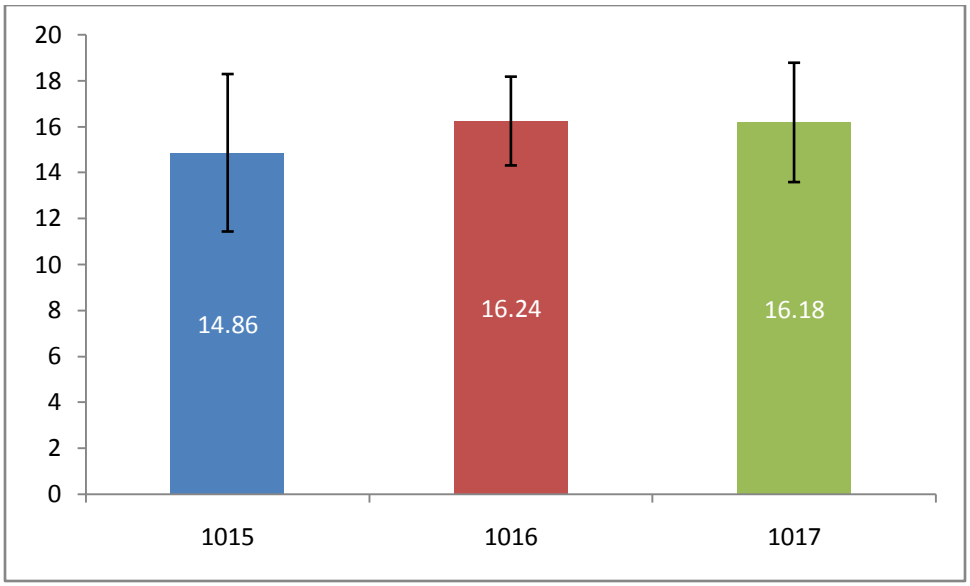

Figure 16. Mean hardness of the three batches of Tamen tablets

The average hardness of Batch# 1015, 1016 and 1017 was 14.86kg, 16.24kg and 16.18kg respectively (table 24).

4.3 Friability

4.3.1 Napa

Table 26

Study of friability of Napa tablets

Batch	Initial weight of 10 tablets	Final weight of 10 tablets	% friability
SVA120	5.85	5.82	0.51
SUL330	5.92	5.87	0.84
04450	5.82	5.80	0.34

The percentage friability of Batch# SVA120 was 0.51%, Batch# SUL330 was 0.84% and Batch# 04450 was 0.34% (table 25).

4.3.2 Parapyrol

Table 27

Study of friability of Parapyrol tablets

Batch	Initial weight of 10 tablets	Final weight of 10 tablets	% friability
711	5.93	5.90	0.51
591	6.09	6.05	0.66
650	5.98	5.96	0.33

The percentage friability of Batch# 711 was 0.51%, Batch# 591 was 0.66% and Batch# 650 was 0.33% (table 26).

4.3.3 Reset

Table 28

Study of friability of Reset tablets

Batch	Initial weight of 10 tablets	Final weight of 10 tablets	% friability
11031	6.23	6.20	0.48
11171	6.26	6.23	0.48
F118	6.34	6.30	0.63

The percentage friability of Batch# 1103 was 0.48%, Batch# 11171 was 0.48% and Batch# F118 was 0.63% (table 27).

4.3.4 Zerin

Table 29

Study of friability of Zerin tablets

Batch	Initial weight of 10 tablets	Final weight of 10 tablets	% friability
191	5.48	5.43	0.91
147	5.49	5.46	0.55
143	5.86	5.81	0.85

The percentage friability of Batch# 191 was 0.91%, Batch# 147 was 0.55 and Batch# 143 was 0.85% (table 28).

4.3.5 Tamen

Table 30

Study of friability of Tamen tablets

Batch	Initial weight of 10 tablets	Final weight of 10 tablets	% friability
1015	5.68	5.67	0.18
1016	5.67	5.65	0.35
1017	5.70	5.68	0.35

The percentage friability of Batch# 1017 was 0.35%, Batch# 1016 was 0.35% and Batch# 1015 was 0.18% (table 29).

4.4 Disintegration time

4.4.1 Napa

Table 31

Disintegration time of the three batches of Napa tablets

Brand	Tab no.	Batch# SVA120	Batch# SUL330	Batch # 04450
		Time (sec)	Time (sec)	Time (sec)
NAPA	1	80	56	99
	2	86	60	100
	3	92	62	100
	4	95	70	104
	5	107	110	106
	6	111	196	106

The disintegration time for Batch# SVA120, SUL330 and 04450 ranged from 80-111sec, 56-196sec and 99-106sec respectively (table 30).

Table 32

Mean disintegration time and standard deviation of the three batches of Napa tablets

Brand	Batch	Mean time (sec) (n=6)	Standard deviation
NAPA	SVA120	95.167	11.957
	SUL330	92.333	54.485
	04450	102.5	3.209

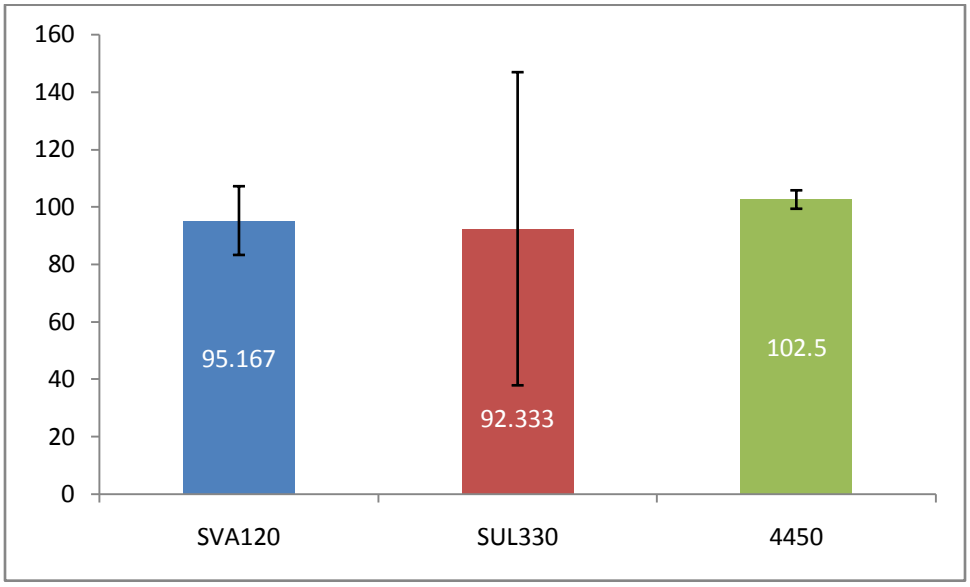

Figure 17. Mean disintegration time of the three batches of Napa tablets

The mean disintegration time of Batch# SVA120, SUL330 and 04450 was 95.167sec, 92.333sec and 102.5sec (table 31).

4.4.2 Parapyrol

Table 33

Disintegration time of the three batches of Parapyrol tablets

Brand	Tab no.	Batch# 591	Batch# 650	Batch # 711
		Time (sec)	Time (sec)	Time (sec)
PARAPYROL	1	3870	3709	230
	2	3889	3712	611
	3	3892	3913	726
	4	3895	3971	1081
	5	3957	4026	1139
	6	3959	4148	1222

The disintegration time for Batch# 591, 650 and 711 ranged from 3870-3959sec, 3709-4148sec and 230-1222sec respectively (table 32).

Table 34

Mean disintegration time and standard deviation of the three batches of Parapyrol tablets

Brand	Batch	Mean time (sec) (n=6)	Standard deviation
PARAPYROL	591	3910.333	37.946
	650	3913.167	175.143
	711	834.833	382.304

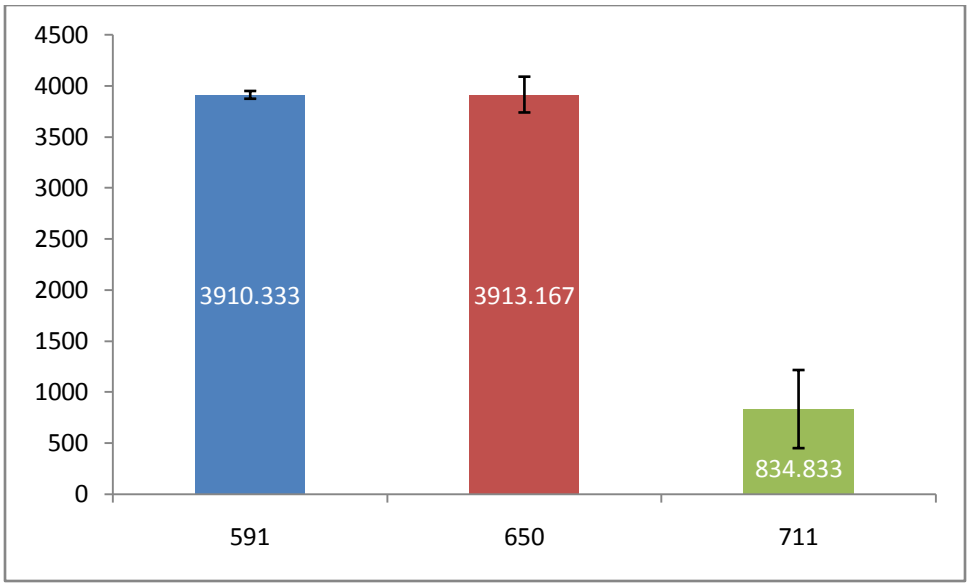

Figure 18. Mean disintegration time of the three batches of Parapyrol tablets

The mean disintegration time of Batch# 591, 650 and 711 was 3910.333sec, 3913.167sec and 834.833sec respectively (table 33).

4.4.3 Reset

Table 35

Disintegration time of the three batches of Reset tablets

Brand	Tab no.	Batch# 11031	Batch# 11171	Batch # F118
		Time (sec)	Time (sec)	Time (sec)
RESET	1	50	74	45
	2	60	81	46
	3	70	99	48
	4	76	119	52
	5	126	131	59
	6	148	139	86

The disintegration time for Batch# 11031, 11171 and F118 ranged from 50-148sec, 74-139sec and 45-86sec respectively (table 34).

Table 36

Mean disintegration time and standard deviation of the three batches of Reset tablets

Brand	Batch	Mean time (sec) (n=6)	Standard deviation
RESET	11031	88.333	39.343
	11171	107.167	26.731
	F118	56	15.556

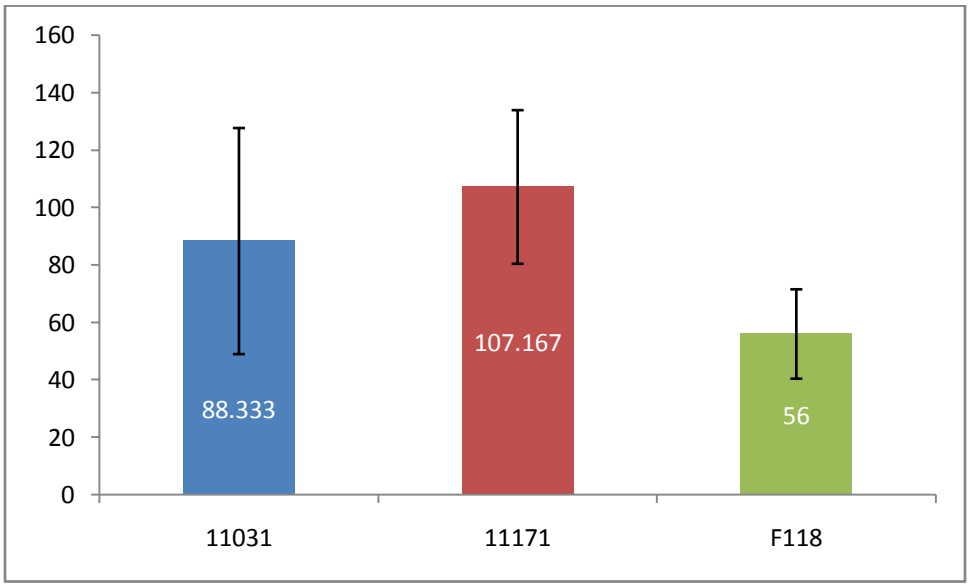

Figure 19. Mean disintegration time of the three batches of Reset tablets

The mean disintegration time of Batch# 11031, 11171 and F118 was 88.333sec, 107.167sec and 56sec respectively (table 35).

4.4.4 Zerin

Table 37

Disintegration time of the three batches of Zerin tablets

Brand	Tab no.	Batch# 143	Batch# 191	Batch # 147
		Time (sec)	Time (sec)	Time (sec)
ZERIN	1	126	370	198
	2	217	375	210
	3	313	378	218
	4	383	400	222
	5	550	405	228
	6	608	416	238

The disintegration time for Batch# 143, 191 and 147 ranged from 126-608sec, 370-416sec and 198-238sec respectively (table 36).

Table 38

Mean disintegration time and standard deviation of the three batches of Zerin tablets

Brand	Batch	Mean time (sec) (n=6)	Standard deviation
ZERIN	143	366.167	187.253
	191	390.667	18.801
	147	219.000	13.957

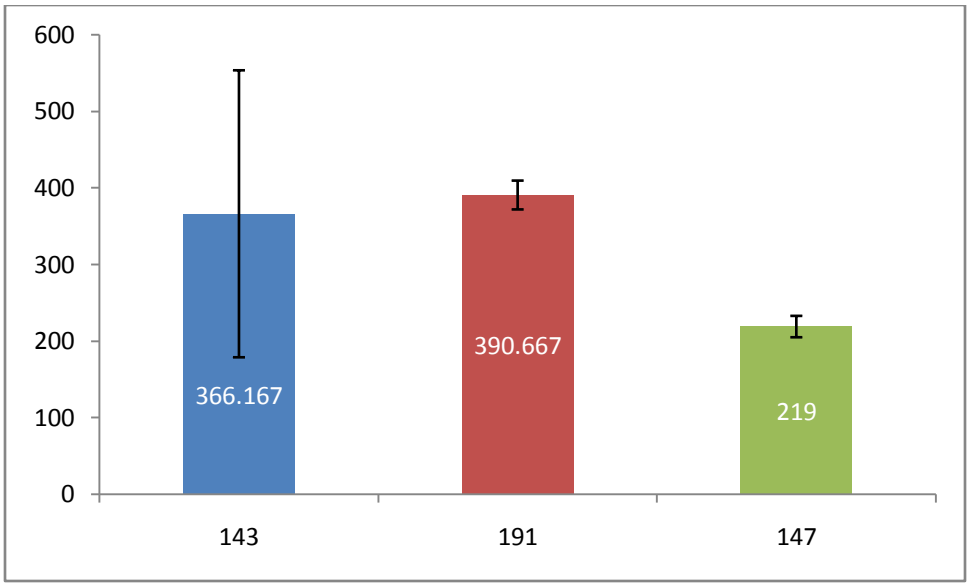

Figure 20. Mean disintegration time of the three batches of Zerin tablets

The mean disintegration time of Batch# 143, 191 and 147 was 88366.167sec, 390.667sec and 219sec respectively (table 37).

4.4.5 Tamen

Table 39

Disintegration time of the three batches of Tamen tablets

Brand	Tab no.	Batch# 1015	Batch# 1016	Batch # 1017
		Time (sec)	Time (sec)	Time (sec)
TAMEN	1	116	196	155
	2	119	220	157
	3	121	222	162
	4	133	226	171
	5	135	230	177
	6	138	249	192

The disintegration time for Batch# 1015, 1016 and 1017 ranged from 116-138sec, 196-249sec

and 155-192sec respectively (table 38).

Table 40

Mean disintegration time and standard deviation of the three batches of Tamen tablets

Brand	Batch	Mean time (sec) (n=6)	Standard deviation
TAMEN	1015	127	9.402
	1016	223.833	17.140
	1017	169	14.043

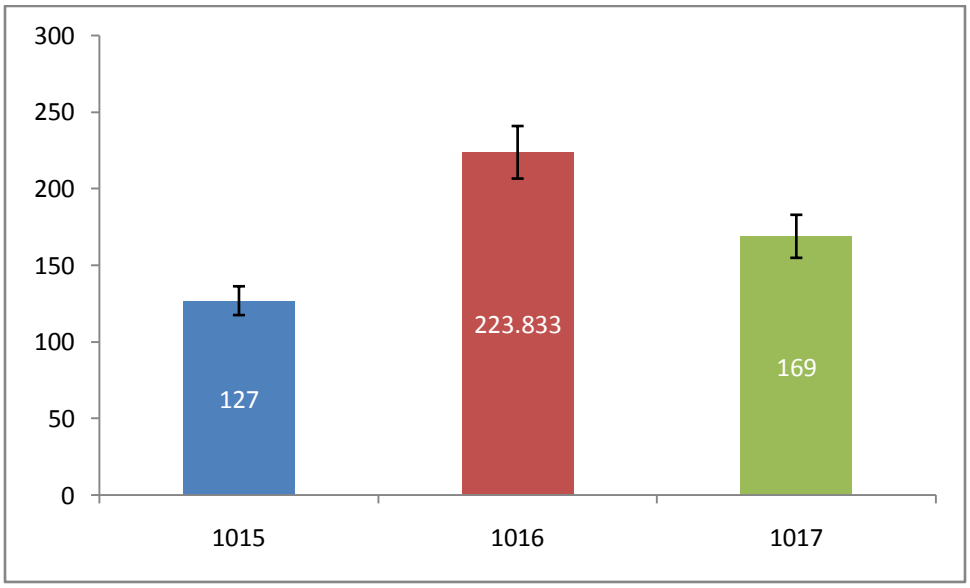

Figure 21. Mean disintegration time of the three batches of Tamen tablets

The mean disintegration time of Batch# 1015, 1016 and 1017 was 127sec, 223.833 and 169sec respectively (table 39).

CHAPTER 5

DISCUSSION

5. Discussion

5.1 Weight variation

The combined effect of the weight variation test is to ensure that all tablets in a batch are within the reasonable limits, of the same batch. Tablets are required to meet a weight variation test were the active ingredient comprises a major portion of the tablet and were control of weight may be presumed to be an adequate control of drug content uniformity. It is necessary that the tablets meet the specification indicating the uniform distribution of the active ingredient within the tablets. All the three batches of Napa (SVA120, SUL330 and 04450), Parapyrol (711, 591 and 650), Reset (11031, 11171 and F118), Zerin (191 and 147) and Tamen (1015, 1016 and 1017) showed a percentage weight variation within the range of ±5 and, therefore, comply with the specification of USP that is mentioned in Table no: 2. However, Batch# 143 of the brand Zerin did not meet the range and was found to have a percentage weight variation of -9.5 to 11.8%, which is outside the acceptable range of ±5% resulting in non-uniform distribution of the active ingredient. All the other remaining 14 batches of the five different brands have passed the quality control parameters.

5.2 Hardness

Tablets require a certain amount of strength, or hardness to withstand the mechanical shocks of handling and transportation yet soft enough to be able to disintegrate properly after swallowing. Since there is also a relationship between hardness and disintegration rate of the tablets, it is essential that the hardness of the tablets are within the acceptable range. Tablets with increased hardness values tend to have increasing disintegration time. However, a minimum hardness of 4kg is essential. All the three batches of Napa (SVA120, SUL330 and 04450), Parapyrol (711, 591 and 650), Reset (11031, 11171 and F118), Zerin (191, 147 and 143) and Tamen (1015, 1016

and 1017) have a hardness within the acceptable range and, therefore, comply with the specification of USP.

5.3 Friability

Tablets should have the ability to resist abrasion when they are subjected to stresses from collision and tablet sliding towards one another and other solid substances, which can result in the removal of small fragments and particles from the tablet surface. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. All the three batches of Napa (SVA120, SUL330 and 04450), Parapyrol (711, 591 and 650), Reset (11031, 11171 and F118), Zerin (191, 147 and 143) and Tamen (1015, 1016 and 1017) have passed the friability test and have met the specification of USP which specifies that if friability study is performed with ten tablets of any batch they must not lose 1% of their initial weight.

5.4 Disintegration

Disintegration test is an important physical parameter of solid dosage form, and is essential for better bioavailability. If the tablet is disintegrated properly, then the dissolution profile of the tablet will be good resulting in better absorption and consequently better therapeutic action. Therefore, the effectiveness of a drug is related to its disintegration time. Disintegration time may vary considering to its disintegrator used. All the three batches of Napa (SVA120, SUL330 and 04450), Parapyrol (711, 591 and 650), Reset (11031, 11171 and F118), Zerin (191, 147 and 143) and Tamen (1015, 1016 and 1017) have a disintegration time that is within the acceptable range and have met the specification of USP where a majority of the tablets have a maximum disintegration time of 30 minutes.

CHAPTER 6
CONCLUSION

Conclusion

Paracetamol is a non-prescription drug. Hence, it is essential that it is manufactured following Good Manufacturing Practice (GMP). In this study, it was observed that all the batches complied with the specification, except for one batch of Zerin (batch# 143) which did not meet the percentage weight variation test, probably resulting in non-uniform distribution of the ingredients. The results meet with the specification of BP and USP which is required for therapeutic efficacy. It is also important that the tablets meet all the parameters because all are essential. If the hardness is increased, then the disintegration rate will increase and this will affect the dissolution profile. It is also necessary that the drugs disintegrate properly because this will influence the dissolution profile. Pharmaceutical equivalence can also be determined from these tests. According to my knowledge, not much work has been done to determine the quality control parameters of paracetamol in Bangladesh. So further study needs to be conducted regarding the quality control parameters because paracetamol, being an OTC drug, is widely used by people and it is necessary that the product is of good and acceptable quality.

CHAPTER 7

REFERENCES

Reference

Acetaminophen. (2012). Retrieved June 5, 2012, from MedlinePlus Web site: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681004.html#other-uses

Ahmed, A., Ali, S. A., Hassan, F., Ali, S. S. & Haque, N. (2001). Evaluation of Acetaminophen Tablets by Control Test. *Pakistan Journal of Pharmaceutical Sciences*. 14(2), pp. 47-55.

Bertolini, A., Ferrari, A., Ottani, A., Guerzoni, S., Tacchi, R., & Leone, S. (2006). Paracetamol: New Vistas of an Old Drug. *CNS Drug Reviews, 12*, pp. 250–275.

Burke, A., Smyth, E., & FitzGerald, G. A. (2005). Analgesic-Antipyretic Agents; Pharmacotherapy of Gout. In L.B. Brunton, J.S Lazo, & K.L. Parker (Eds.), *Goodman & Gilman's the pharmacological basis of therapeutics*. (11th ed., pp. 693). New York: McGraw-Hill.

Chandrasekaran, A. R., Han, C. Y., Chung, A. C. Y., Cheang, L. W., & Ping, L. S. (2011). Post-market *In vitro* Equivalency Evaluation of Paracetamol Tablets in Kedah, Malaysia. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 4(2), pp. 1403-1407.

Eichie, F. E. and Kudehinbu, A. O. (2009). Effect of particle size of granules on some mechanical properties of paracetamol tablets. *African Journal of Biotechnology*. 8(21), pp. 5913-5916.

FJ, C. J. (2012). High-altitude headache and acute mountain sickness [Abstract]. *Cochrane Database of Systematic* Reviews. *Retrieved* May 28, 2012 from *PubMed*.

Gangwar, S., Singh, S., Garg, G., Garg, V., & Sharma, P., K. (2010). To Compare the Disintegrating Property Of Papaya Starch And Sago Starch In Paracetamol Tablets. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2(2), pp. 148-151

Hiller A., Helenius, I., Nurmi, E., Neuvonen, P. J., Kaukonen, M., Hartikainen, T., Korpela, R., Taivvainen, T., & Meretoja, O. A. (2012). Acetaminophen Improves Analgesia but does not Reduce Opioid Requirement After Major Spine Surgery in Children and Adolescents [Abstract]. *Cochrane Database of Systematic* Reviews. *Retrieved* May 20, 2012 from *PubMed*.

Lachman, L., Lieberman, H. A, & Kanig, J. L. (1986). *The Theory and Practice of Industrial Pharmacy*. (3rd ed., pp297, 299-301). Lea &Febiger. Lippincott Williams & Wilkins.

Munsterhjelm, E., Munsterhjelm, N. M., Niemi, T. T., Ylikorkala, O., Neuvonen, P. J., & Rosenberg, P. H. (2005). Dose-dependent inhibition of platelet function by acetaminophen in healthy volunteers [Abstract]. *Cochrane Database of Systematic* Reviews. *Retrieved* May 22, 2012 from *PubMed*.

Nayak, A. K. (2010). Comparative *In Vitro* Dissolution Assessment Of Some Commercially Available Paracetamol Tablets. *International Journal of Pharmaceutical Sciences Review and Research*, 2(1), 29-30.

Ngwuluka, N. C., Idiakhoa, B. A., Nep, E. I., Ogaji, I. & Okafor, I. S. (2010). Formulation and evaluation of paracetamol tablets manufactured using the dried fruit *Phoenix dactylifera* Linn as an excipient. *Research In Pharmaceutical Biotechnology*, 2(3), pp.25-32.

Oscier, C. D. & Milner, Q. J. W. (2009). Peri-operative use of paracetamol. *Anaesthesia*, *64*, 65–

72. doi: 10.1111/j.1365-2044.2008.05674.x

Paracetamol Information Centre. (n.d.a). Paracetamol Chemistry. Retrieved from http://www.pharmweb.net/pwmirror/pwy/paracetamol/pharmwebpicm.html

Paracetamol Information Centre. (n.d.b). Paracetamol Dosage. Retrieved from http://www.pharmweb.net/pwmirror/pwy/paracetamol/pharmwebpicm.html

Romano, C. L., Romano, D., & Lacerenza, M. (2012). Antineuropathic and antinociceptive drugs combination in patients with chronic low back pain: a systematic review [Abstract]. *Cochrane Database of Systematic* Reviews. *Retrieved* May 25, 2012 from *PubMed*.

Sawaddiruk, P. (2011). Tramadol hydrochloride/acetaminophen combination for the relief of acute pain [Abstract]. *Cochrane Database of Systematic* Reviews. *Retrieved* May 25, 2012 from *PubMed*.

Seitz, J. A. and Flessland, G. M. (1965): Evaluation of physical properties of compressed tablets, 1: tablet hardness and friability. *J. Pharm. Sci*., 54: 1353-1357.