Evaluation of In-Vitro Quality Study of Paracetamol Tablets (500mg) Commercially Available in Bangladesh

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Abstract

Paracetamol (acetaminophen) is considered as the most popular and is vastly used drugs in the indication of pain and fever. Among the available pain killers this drug hold a unique position. Unlike most of the NSAIDs, this drug is considered to be safe as this drug has no anti-inflammatory action and it does not cause any gastrointestinal destruction or unexpected cardiac and renal failure.The present study was conducted to analyse the quality of three marketed brands of paracetamol tablet formulation manufactured by different companies in Bangladesh. The tablet formulations of different brands were tested for various parameters like weight variation, diameter & thickness, hardness, friability, disintegration time, potency and dissolution profile using standard techniques to evaluate their quality. The values were compared with the standards. Weight variation value requirement was compiled by all brands. In case of diameter & thickness size and shape of all tablets was uniform. Two tablet brands were not complied with the standard specification for tablet hardness. All brands showed impressive friability values and also remained within the specification according to BP. Disintegration time for all brands was within 15 minutes also complying the USP (United State of Pharmacopeia) recommendation. The percentage content of active ingredient of all brands of Paracetamol tablets show values within the monograph specifications (90-110%). Moreover, the release rate of different brands of paracetamol was satisfactory; all samples attained 80% dissolution within 30mins, according to USP monograph. All the three brands evaluated in this study could be considered biopharmaceutically and chemically equivalent. Therefore, it can be concluded that almost all the selected brands of paracetamol that are available in Bangladesh met the USP specification for quality control analysis.

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Introduction

1.Introduction

1.1 General Introduction:

Paracetamol (proposed international non-proprietary name) (acetaminophen) is an OTC drug and also it is belonging to the group of non-steroidal anti-inflammatory drug (NSAIDs) which are vastly used as a painkiller.This drug has also antipyretic action but has a little effectivity to reduce inflammation.The peroxides that obtain at the site of inflammation are inhibited by the Cyclo-oxygenase (COX) [Mathur et al., 2015]. In 1955 this product was firstly available in the market of USA and then in the following year this drug was availble in the market of UK. Since then, the paracetamol was used as analgesia and in the treatment of fever. Probably this drug is vastly prescribed medicine in children [Bertolini et al., 2006].

The FDA approved Acetaminophen and introduced in the market of USA under the brand name Tynelol.Before November 2010, no intravenous (IV) formulation of v acetaminophen was available in the market of USA, then the FDA approved the IV form of acetaminophen and introduced the formulation in the market of USA under the brand name of Ofirmev. Currently, IV formulation of acetaminophen is used all over the world.[Irshad et al., 2012]. Paracetamol is used as analgesia and it is effective to reduce fever.This drug has also some other indication like headaches, muscle aches, menstrual cramps, colds and sore throats, toothaches, back pain and osteoarthritis. This drug is now available in the form of a tablet, capsule, suspension, drops, extended-release (long acting) tablet, suppository and IV as well as IM form. Paracetamol has a safety index and also able to be endured for human being in a proper therapeutic doses. Unlike NSAIDs, its incidence of gastrointestinal side effects in therapeutic doses is also low [Mathur et al., 2015].

The drug paracetamol is smoothly absorbed from the proximal part of the small bowel and this drug is not showing any significant firstpass metabolism by the liver.The bioavailability of acetaminophen is estimated at between 63–89% in adults when this drug is administered orally.As this drug is not sufficiently bound to plasma proteins so the volume of distribution is comparatively much more and this value ranges between 0.7–1 L/kg. The maximum effectivity like analgesic and antipyretic action occurs when the peak plasma levels is acchieved. This peak plasma concentration is known as Cmax.For an orally administered paracetamol the Cmax is achieved approximately at 45min after the time of administration. Like all the other analgesics, this drug has also a short half-life which is around around 2–3

hours.Thats why it is necessary to frequent dosing to maintain the peak plasma concentration.The dosage regimen of acetaminophen In UK is 500–1000 mg every 4–6 hours. However, the advantageous feature is that if the duration of action of any dosage is longer then it will require a fewer daily doses thus it could maintain therapeutic plasma levels.This things would improve the patient convenience and compliance to use this particular type of drug and the patient mjust be benefited at night time [Shep et al., 2010].

1.2 History of Paracetamol

Acetaminophen also known as paracetamol was firstly synthesized by the scientist named Harmon Northrop Morse in favor of the reduction process of P-nitro phenol through Tin within glacial acetic acid in the year 1878.But this synthesized form was not used as the intention of treating disease for another 15 years. Then the scientist named Von Mering used acetaminophen or so called paracetamol for the intention of treating diseases in the year 1893. This drug was not commercially available in the market of USA until 1950 and it is not also available in Australia before in the year 1956.Then in the decade of 1960s and 1970s, there was a growing worry about the toxicological effect of painkillers without a prescription, but that time acetaminophen or so called paracetamol showed its consistent safety index in general use. However, a large overdose of paracetamol can cause the severe damage of the liver and this study have been reported in the year 1996.Luckily there is an antidote known as N-acetyl cystein that works against the liver toxicity caused by the the overdose of paracetamol.In the year 1980 an serious issue was hapenned related to aspirin as the drug aspirin is associated with the Reyes syndrome in children.After that incidence paracetamol became the main painkiller and was used to treat fever in children and that subsequently reduced the damage related to Reyes syndrome. Currently, paracetamol is the leading choice for pain management and to treat fever in different ages of patients like infants, pregnant women as well as adulte patients .Using paracetamol in a proper way,this drug rarely causes the undesired effects and there have been no reports of harmful side effects.This drug has a wide tolerance and is effective to treat patients who have problem with the non-steroidal anti-inflammatory drugs such as aspirin-sensitive asthma patients and the patient who have gastrointestinal perplexity.After certain time a better understanding may be gained about the mechanism of action of paracetamol for a full understanding of cyclo-oxygenase enzymes. Meanwhile, paracetamol may be applied to other therapeutic cases, such as preventing

atherosclerosis by the antioxidant activity.Briefly, since the first clinical use of paracetamol has passed over a century but this drug is considered as the primary choice of drug first-line for both adult and children to treat fever and pain [prescott and Laurie, 2000].

1.3 Chemistry of Paracetamol

Acetaminophen or N-acetyl-P-aminophenol(NAPA) also popularly known as paracetamol belongs to the acetanilide derivative with a chemical formula of $C_8H_9NO_2$ [Oscier and Milner, 2009]. This drug is chemically known as 4-hydroxy acetanilide and this drug is an active metabolite of phenacetin which is a so-called coal tar analgesic.But that active metabolite has been withdrawn from the market due to several undesired events are caused by this analgesic [Mathur et al.,2015].

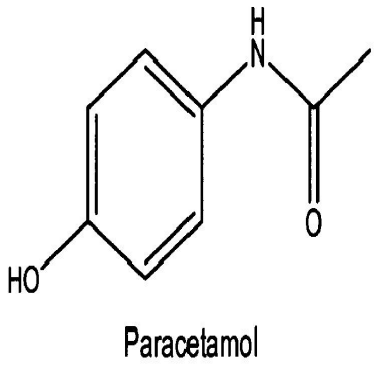


Figure 01: Structure of Paracetamol

1.4 Synthesis of Paracetamol

For the synthesis of NAPA or paracetamol 250 mL round-bottom flask, reflux condenser, stirring magnet, heating plate, oil bath, Büchner funnel and filter flask, vacuum pump, 100 mL beaker, watch glass are required to synthesize paracetamol in laboratory. In figure 02 synthesis, purification and characterization of paracetamol is given in a flowchart [Graham *et al*., 2013]. Chemical reaction of paracetamol synthesis is given in figure o3 [Audu *et al*., 2012].

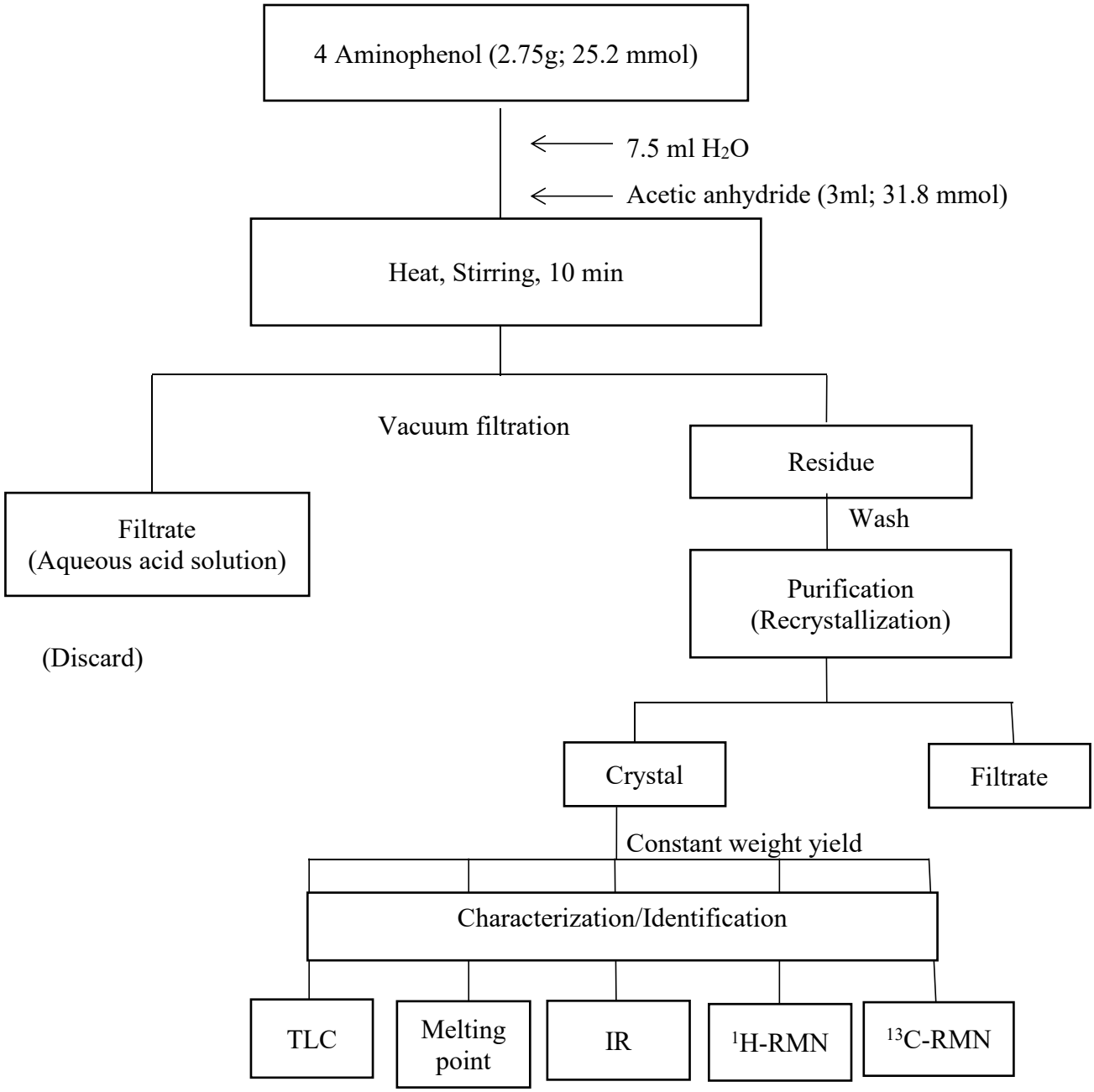
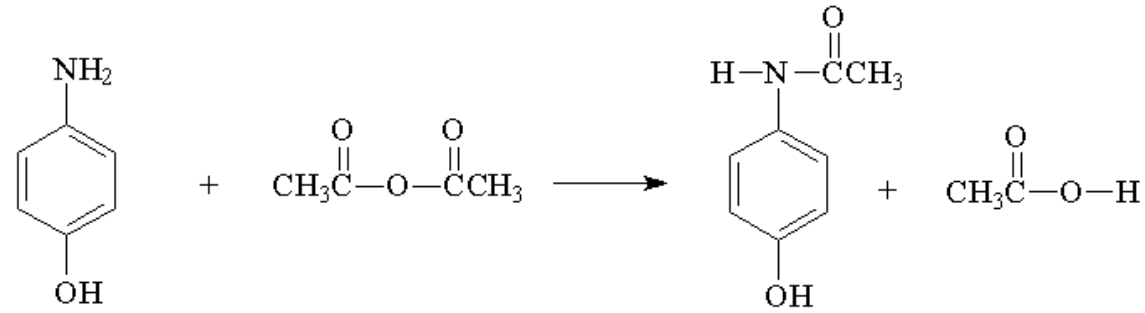


Figure 04: Flowchart for the Synthesis, Purification and Characterization of Paracetamol



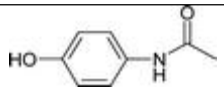
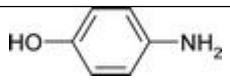
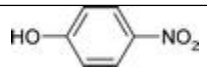
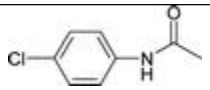
aminophenol Acetic anhydride Paracetamol Acetic acid

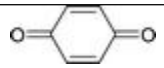
Figure 03: Synthesis of Paracetamol

1.5 Impurities of Paracetamol

Chemical Structures of Acetaminophen and its Impurities with chemical structure and molecular formula are described in a table below[Calinescu *et al.*, 2012].

Table 1.5: Chemical Structures of Paracetamol and its Impurities

Compound Name	Molecular Formula	Chemical Structure
Acetaminophen	$C_8H_9NO_2$	
4-Aminophenol	C_6H_7NO	
Hydroquinone	$C_6H_6O_2$	
4-Nitro phenol	$C_6H_5NO_3$	
4'-Chloroacetanilide	C_8H_8ClNO	

P-Benzoquinone	$C_6H_4O_2$	

1.6 Physical and Chemical Properties Of Paracetamol

1.6.1 Description: White odorless crystalline solid powder.

1.6.2 Melting Point: 169-170.5℃

1.6.3 Boiling Point: 420℃

1.6.4 Molecular Formula: $C_8H_9NO_2$

1.6.5 Molecular Weight: 151.16 g/mol

1.6.6 Solubility: NAPA is Insoluble in water but very soluble in ethanol

1.6.7 Spectroscopy Data: IR, UV, NMR, fluorescence and mass spectra have been reported as a spectroscpic data for paracetamol.

1.6.8 Stability: The dry and pure form of NAPA must be satble at 45°C.

1.6.9 Dissociation Constant: pKa= 9.0-9.5

1.6.10 Density: 1.293 g/ cm^3

1.6.11 λmax: 243nm

1.6.12 Storage: Must be stored in well closed, light resistance containers.

1.6.13 Refractive index: 1.62

1.6.14 Molar Volume: 120.93 cm^3

1.6.15 Shelf Life: 3 years

1.6.16 Vapor Density: 5.2

1.6.17 Partition Coefficient: 6.237

[Remington's Pharmaceutical science, 1995];[Rxlist, 2016]

1.7 Pharmacology of Paracetamol

NAPA or Paracetamol vastly used by the people of all over the world for its analgesic activity and capability of reducing fever.This drug has similar mehanism of action to that of NSAIDs and also match to the action of COX-2 selective inhibitors. But this drug has not as much as effetivitycompared to other NSAIDs or COX-2 selective inhibitors.After that this drug is is the first line therapy due to its good tolerability. As this drug is almost similar to the NSAIDs the pharamacological activity of NAPA or paarcetamol is not certain,however the fact is this drug is now generally acceted by the people of all over the world that COX-1 and COX-2 are effectively inhibited through the metabolism by the the peroxidase function of

this isoenzyme.from the tyrosine residue phenoxyl radicals is formed which is responsible for the cyclooxygenase effectivity of COX-1 and COX-2 are inhibited b y the action of isoenzyme called peroxidase and this isoenzyme also is the primary cause to the inhibition of prostaglandin (PG) synthesis.NAPA also known as paracetamol has the activity for inhibiting the synthesis process of prostaglandins.This is occur only when the minimum doses of arachidonic acid is present if the sufficient doses of arachidonic acid is present then the peroxidase activity has been suppressed.Rheumatoid arthritis and acute gout are effectively suppressed by the action of paracetamol, however this drug also prevents inflammation that is resulting from tooth extraction and also this drug is effective in several type of afflicting tests in animal model.NAPA also known as paracetamol has a capability of COX-2 selectivity.The apparent COX-2 selectivity of NAPA also known as paracetamol effectivity would easily demonstrated by observing its lower activity as anti platelet and this drug don cause any gastroinstestinal discmofort. In contrast to the NSAIDs that are non selective in nature and COX-2 inhibitors that are selective, other peroxidase enzymes like myeloperoxidase is effectively inhibited by the action of NAPA. Myeloperoxidase The resistance of myeloperoxidase is responsible in the simultaneous reduction of paracetamol oxidation.This whole process is associated with several type of diseases like rheumatic disease and atherosclerosis.As most of the analgesic drug ,selective and non selective NSAIDs have central and peripheral effects thats why NAPA also known as paracetamol has also the same effect [Alloui et al., 1996].

1.8 Mechanism of Action

NAPA also known as paracetamol has an analgesic action on central and peripheral nervous system which is produced by activating the descending inhibitory pain pathways known as serotonergic pathway which is the major component of endogenous pain inhibitory system [Pickering et al., 2008]. Controversy is created about the location of this drugs main activity, which is responsible for the inactivation of prostaglandin sysnthesis or the cannabinoid receptor that is affected by an active metabolism. The enzyme named as prostaglandin H_2 synthetase which is responsible for the arachidonic acid consequences in the volatile PGH_2. PGHS-1and PGHS-2 are the two main forms of this enzyme.The enzyme PGHS consists of 2 different sites and the sites are named as COX elaborately cyclooxygenase site and POX elaborately known as peroxidase site .At the COX site arachidonic acid is converted into the PGG_2 by the action of tyrosine 385 radical. At the POX site tyrosine 385 radical is converted

into the radical form with the help of ferril protoporphyrin IX radical cation.At the POX site NAPA function as a reducing agent and this action lessen the presence of ferril protoporphyrin IX radical cation.This type of action can be minimized by the availability of hyroxy peroxide producing lipoxygenesis enzyme and another way is to swamp the POX site with the help of a substrate molecule like PGG_2. The lack of anti platelet effect of paracetamol can be explained by observing the peroxide tone and swamping the peripheral analgesic action.

In contrast, an active metabolite of paracetamol called p-aminophenol may induce the effect of NAPA.By the action of the enzyme named amide hydrolase p-aminophenol may bind with arachidonic acid acting through the cannabinoid recerptor like AM404.This drug has also function in PGHS in the areas where high concentration of amide hydrolase is present [Aronoff et al., 2006].

Figure 04 shows the arachidonic acid metabolism schematically [Graham and Scott, 2005].

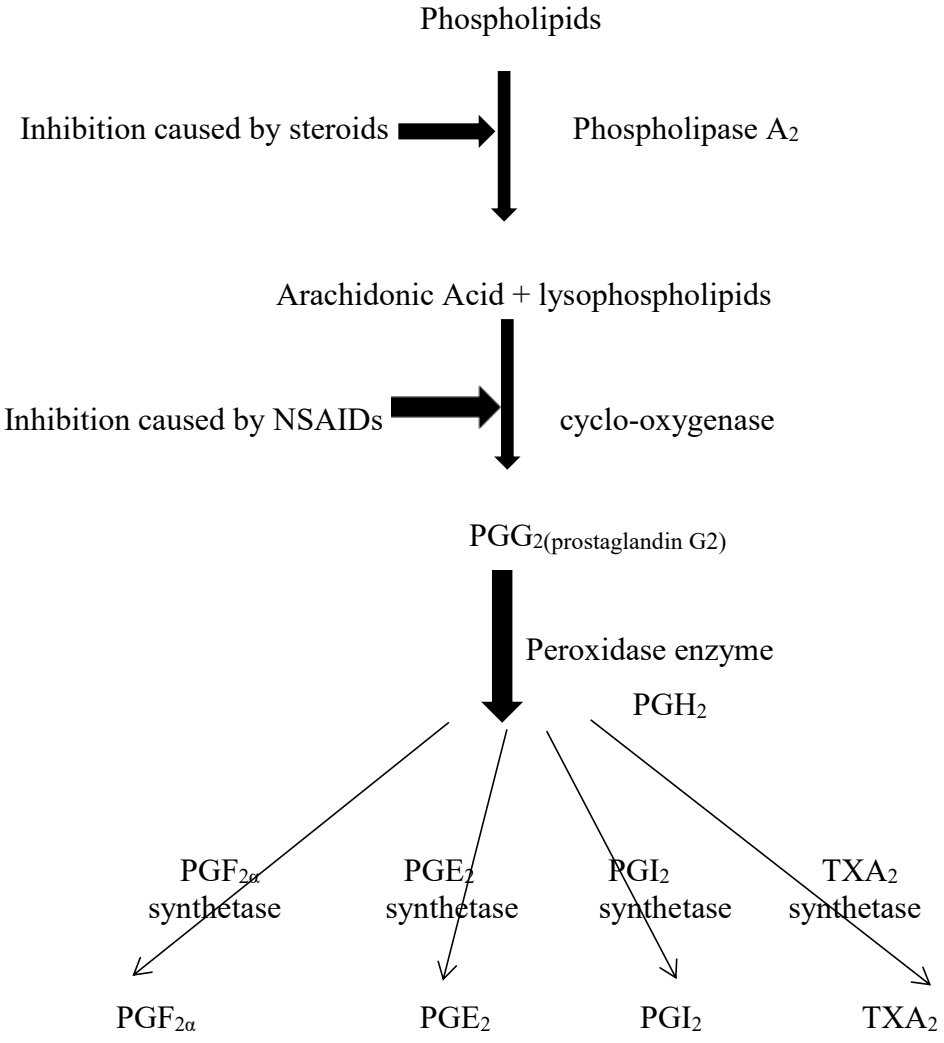


Figure 04: Metabolism of Arachidonic Acid schemitically

1.9 Toxicology of Paracetamol

In accurate doses paracetamol has always a safety therapeutic index.In adult this drug shows toxicological effect at the doses around 7.5 mg or higher and in children doses like 150 mg/kg may cause toxicity [Bertolini et al., 2006].

More than normal use may cause paracetamol toxicity.The most common effect of paracetamol toxicity is that it is resposible for the destruction of hepatocytes.After the excessive use of NAPA also known as paracetamol has no sign and symptoms in the first 24 hours in almost many of the patient.Meanwhile some others may realize some symptoms like abdominal pain, nausea vomiting e.t.c.Symptoms of liver failure, such as low blood sugar, are associated with increased paracetamol toxicity.If the toxicity of NAPA can treate immediately then it could be curable otherwise this can lead to serious damage even it could lead to death of the patient.Paracetamol is metabolized to a metabolite known as N-acetyl-p-benzoquinone shortle known as NAPQI which is actually responsible for liver damage.The natural antioxidant glutathione of liver is consumed by the NAPQI which directly destroy the liver cells thus leadind to the liver failure. The chance of paracetamol poisoning is increased by the more than normal use of alcohol consumption.Another factors that can also cause the pracetamol toxicity are the use use of certain drugs like isoniazid and even fasting may increase the toxicity of paracetamol [Malar and Bai., 2012].

Paracetamol toxicity can also damage the function of kidney.In 25 % cases dysfunction relating to the kidneys occurs by the sinificant hepatotoxicity but in 50% cases this dysfunction occurs by the hepatic failure [Bertolini et al., 2006].

1.9 Pharmacokinetics Of Paracetamol

1.9.1 Absorption:

Paracetamol is well absorbed from the gastrointestinal tract after oral administration and is not subject to significant first-pass metabolism in the liver, with oral bioavailability estimated at 63-89% in adults [Oscier and Milner, 2009]. However, drug-food interactions slow down the rate of paracetamol absorption, while caffeine accelerates absorption. Prokinetic drugs

(such as metoclopramide) accelerate gastric emptying, increase the rate of absorption, while drugs reduce the rate of gastric emptying (such as morphine), slow absorption, and in some cases prevent therapeutic plasma levels [Oscier and Milner]. In the healthy aspects of fasting, the absorption of paracetamol in the solution is very fast and the maximum plasma concentration often occurs within 15-30 minutes of eating. Absorption from tablets is usually slow, and in practical clinical situations the plasma concentration may range up to 80-fold 1 hour after taking the therapeutic dose [Prescott, 1980].Rectal paracetamol absorption is slow and less predictable, with bioavailability between 24% and 98% [Oscier and Milner, 2009]. This variability depends on the size, anatomy and number of suppositories used and the rectal pH. Paracetamol is not significantly bound to plasma proteins and its distribution amount is 0.7-1 l.kg − 1 [Oscier and Milner, 2009]. Paracetamol gives more reliable therapeutic plasma concentrations intravenously than orally. Differences between the venous and oral groups were marked less after 150 min but intravenous preparations yielded higher plasma concentrations.

1.9.2 Distribution:

Paracetamol is not significantly bound to plasma proteins, and its distribution amounts to 0.7-1 l kg − 1. It is non-ionized at physiological pH and freely crosses the placenta and blood-brain barrier. One gram of paracetamol provides 0.5 g of paracetamol after hydrolysis. The ratio of concentrations in red blood cells and plasma is about 1.2:1 and binding to plasma proteins is insignificant. The apparent volume of distribution of paracetamol in man is about 0.9- 1/kg [Oscier and Milner, 2009].

1.9.3 Metabolism:

Metabolism of paracetamol occurs primarily in the liver, while elimination occurs almost entirely through the kidneys. Upon absorption of the therapeutic dose, about 90% is metabolized by glucuronidation and sulfation to form non-toxic metabolites that are excreted in the urine [Osier and Milner, 2009]. A small fraction forms the highly reactive metabolism N-acetyl-p-benzoquinoneimine (NAPQI) through oxidation by the cytochrome P450 system. NAPQI reacts with glutathione, forming a conjugate which is then excreted in the urine.

After ingestion of large amounts of paracetamol, hepatic glutathione is depleted and NAPQI accumulates, resulting in sub-acute hepatic necrosis, and in severe cases, hepatic clearance is lowest in neonates, whose value increases from infancy. The elimination half-life increased to 2-4 hours in normal adults, 4-5 hours in newborns, and up to 11 hours in premature infants

[Oscier and Milner, 2009]. One to four percent of urine is excreted unchanged, and in patients with severe renal impairment (GFR less than 10 ml.min − 1) it is recommended to increase the dose interval to 6-8 hours [Oscier and Milner, 2009].

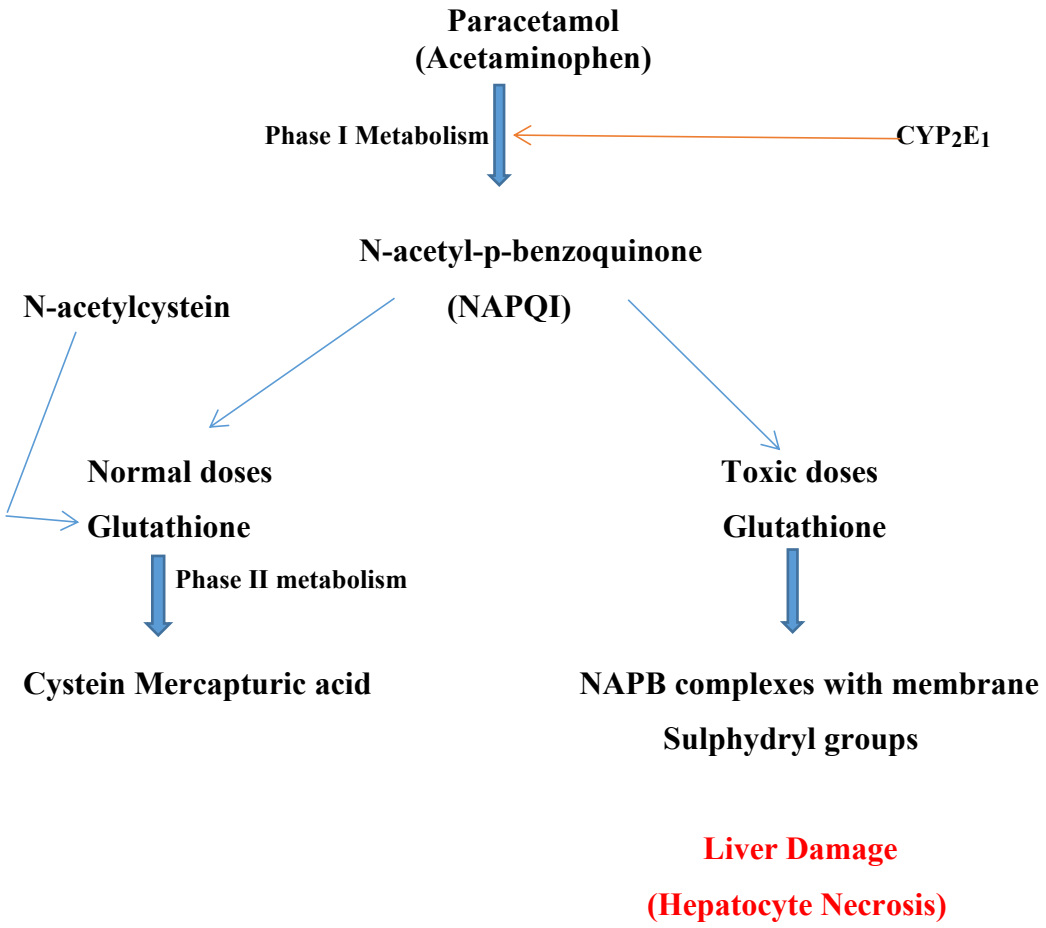


Figure 05:Metabolism of Paracetamol

1.9.4 Excretion:

The average renal clearance of paracetamol in healthy subjects given 20 mg / kg was 13 mg / min. Clearance depends on the rate of urine flow but not the pH. Paracetamol appears to have been filtered into the glomeruli with subsequent extensive tubular reabsorption. The average renal clearance of paracetamol sulfate and glucuronide was 166 and 130 ml / min, respectively, and no correlation with urine flow or pH. Plasma half-life of paracetamol is not increased in patients with impaired renal function, but conjugates are deposited and retained [Forrest et al., 1982].

1.9.5 Plasma Half-life Range: 1–4 hours.

1.9.6 Volume of Distribution (Vd): 65 L

1.9.7 Protein Binding: 10–25%

1.9.8 Bioavailability: Oral bioavailability: 70% - 90%

Rectal bioavailability: 30% - 70%

1.9.9 Clearance (CL): 20 L/h

1.10 Pharmacodynamics of Paracetamol

Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity. The mechanism of action is dependent on the inhibition of prostaglandin synthesis in the central nervous system (CNS) and inhibits the development of pain peripherally. It has no anti-inflammatory activity. It relieves mild to moderate pain and fever. Paracetamol is metabolized by the liver and excreted in the urine mainly as glucuronide and sulfate conjugate; Less than 5% is excreted as unchanged paracetamol. Binding to plasma proteins in therapeutic concentrations is minimal. High doses of paracetamol (more than 2,000 mg per day) increase the risk of upper gastrointestinal complications such as abdominal bleeding. Excessive use of paracetamol (300 g per year or 1 g per day on average) has been linked to a condition known as 'small indented and calcified kidney' (SICK). A 2008 study on the long-term side effects of paracetamol tablets in children found that taking paracetamol for fever in the first year of life was associated with an increased incidence of asthma symptoms at age 6-7. It further states that paracetamol use (both in the first year of life and in children aged 6-7 years) was associated with an increased incidence of rhino conjunctivitis and eczema. Hypersensitivity reactions (rash and shortness of breath), blood disorders resulting in sore or bleeding preparations (such as thrombocytopenia) or low white blood cell count (leukopenia) are unlikely to cause a severe allergic reaction to this drug, but consult a doctor immediately. Symptoms of a severe allergic reaction include: rash, itching / swelling (especially of the mouth / tongue / throat), dizziness, shortness of breath. The most serious concern with paracetamol is its effect on the liver, and so there are some issues that need immediate attention. Yellow eyes or skin can be a sign of liver damage due to taking paracetamol and is often seen with large doses or extended use. Bloody urine and stool suggest side effects of

paracetamol and stomach irritation. The most common side effects of paracetamol poisoning are nausea and vomiting. These effects usually appear within 24 hours of medication [Malar and Bai, 2012].

1.11 Therapeutic Use of Paracetamol

1.11.1 Indication

Although aspirin is said to be equivalent to analgesic and antipyretic agents, acetaminophen differs in that it has no anti-inflammatory properties. It does not affect uric acid levels and lacks platelet-blocking effects. The drug is an effective painkiller for mild to moderate pain such as headache, myalgia, postpartum pain and other conditions. Acetaminophen alone is insufficient therapy for inflammatory conditions such as rheumatoid arthritis, although it can be used as an analgesic with anti-inflammatory therapy. For mild pain, acetaminophen is the drug of choice for patients with an allergy to aspirin or when salicylates are poorly tolerated. Aspirin is recommended for patients with a history of hemophilia or peptic ulcer and for those whose bronchospasm is induced by aspirin. In contrast to aspirin, acetaminophen does not counteract the effects of uricosuric agents; It can be used in combination with probenecid to treat gout. It is preferred over aspirin in children with viral infections.

1.11.2 Contraindication

Patients are prohibited to use paracetamol who are known to any hypersensitivity of this drug. It is also contraindicated for those who have renal and hepatic impairment [prescott, 2000].

1.11.3 Dosage

Dosage regimen of paracetamol(500mg) for an adult must be 1 to 2 tablets in every 4 to 6 hours that should not exceeding the limit of 7.5gm [Aronff et al., 2006].

Dosage regimen of paracetamol for children aged between 6-12 years shoul not exceed the limit of 150mg / kg [Aronoff et al., 2006].

1.12 Adverse Effects of Paracetamol

Large doses of acetaminophen cause dizziness, agitation and confusion.Taking 15 grams of acetaminophen can be fatal, leading to death due to severe hepatotoxicity with centrilobular necrosis, sometimes associated with acute renal tubular necrosis. Doses greater than 4-6 g / d are not recommended and history of alcoholism even contradicts this dose.Early symptoms of

hepatic damage include nausea, vomiting, diarrhea, and abdominal pain. Kidney damage has occurred without hepatic damage, even after normal doses of acetaminophen.Hemolytic anemia and methemoglobinemia are very rare adverse events. These drugs have recently been linked to increased cardiovascular risk. Indeed, epidemiological and clinical studies have shown that non-selective non-steroidal anti-inflammatory drugs, as well as selective cyclooxygenase-2 inhibitors, can increase blood pressure and cardiovascular events. However, the effects of paracetamol (acetaminophen) on blood pressure and cardiovascular health should also not be ignored [Sudanot et al., 2012].

1.13 Major Side Effects

- Bloody or black, tarry stools
- Bloody or cloudy urine
- Fever with or without chills (not present before treatment and not caused by the condition being treated)
- Pain in the lower back and/or side (severe and/or sharp)
- Pinpoint red spots on the skin
- Skin rash, hives, or itching
- Sore throat (not present before treatment and not caused by the condition being treated)
- Sores, ulcers, or white spots on the lips or in the mouth
- Sudden decrease in the amount of urine
- Unusual bleeding or bruising
- Unusual tiredness or weakness
- Yellow eyes or skin

[Paracetamol adverse effect, 2014].

1.14 Excessive use of paracetamol symptoms:

- Diarrhea
- increased sweating
- loss of appetite

- nausea or vomiting
- stomach cramps or pain
- swelling, pain, or tenderness in the upper abdomen or stomach area

[Paracetamol adverse effect, 2014].

1.15 Drug Interactions:

Paracetamol strengthens the anticoagulant effects of asinocomorol and warfarin, increasing the risk of bleeding. Patients taking oral anticoagulants should be warned to limit paracetamol intake.

Administration of Carbamazepine with paracetamol increases the risk of hepatotoxicity, induces hepatic metabolism of paracetamol and thus increases the formation of toxic metabolism.

Bioavailability of paracetamol has been shown to be low in epilepsy patients taking enzyme induction anticonvulsants including phenytoin and phosphenytoin.

Lamotrigine sulfinpyrazone, like paracetamol carbamazepine, increases urine excretion, hepatotoxicity increases the risk of paracetamol toxicity by increasing metabolite formation.

Co-administration of paracetamol with zidovudine may result in neutropenia or hepatotoxicity. The main concern is the interaction with alcohol. Alcohol - Paracetamol syndrome is defined as the development of acute toxic hepatic symptoms in long-term alcoholics who take paracetamol, generally considered non-toxic [Stiffit et al., 1990].

Patients with alcohol-paracetamol syndrome are more prone to taking higher doses of paracetamol than non-alcoholic patients. The overall mortality rate in alcohol-paracetamol syndrome is about 20%, and exceeds 75% in acute liver failure. Concomitant use of alcohol and paracetamol may increase the CYP2E1-mediated metabolism of paracetamol to higher hepatotoxic metabolism, N-acetyl-p-benzoquinoneimine (NAPQI). Among non-alcoholics, NAPQI is detoxified by a combination of glutathione. In alcoholics, NAPQI accumulates as a result of a combination of CYP2E1 induction and glutathione reduction. In these cases, the highest risk of paracetamol toxicity occurs after a brief (12-hour) withdrawal from alcohol, since CYP2E1 is still induced, but alcohol is not present to compete for CYP2E1 metabolism [Bertolini et al., 2006].

1.16 Evaluation of Tablet

1.16.1 Weight Variation Test: Variation in weight test is a compensatory test of pharmaceutical product**.**Variations in the weight of the capsule have an importance in measuring process control. Variation in weight test is done to check compatibility of each company's tablets. This is also done to ensure that the sample tablet's weight variation complies with the USP specification [Latchman et al., 2009].

$$\% \text{ of weight variation} = \frac{individual\ weight - average\ weight}{average\ weight} \times 100$$

1.16.2 Hardness test:

This is the amount of energy needed to break a tablet (in kilograms, pounds or arbitrary units). The hardness of a tablet is an important quality criterion. The properties of many tablets, such as isolation, solubility and thinness, are affected by hardness.The weight of the tablet must be needed to crush when it is placed on the edge is called the hardness or crushing power of the tablet. The hardness of the tablet should be between 40 and 80 N according to the harness test specification, USP [Lachman et al., 2009].

1.16.3 Measurement of Thickness:

The thickness of the die and the amount of filling of content must be needed to to enter the die, the filling materials compaction properties and the pressure applied at the time of compression may effect on the thickness of the tablet. Attention should be paid to using the same fill, dye and pressure parameters to achieve uniform tablet thickness during and during batch production for the same formulation.The level of pressure affects the thickness of the tablet as well as its hardness; Hardness is probably the more necessary criterion because it affects separation and dissolution. So for tablets of consistent thickness and hardness, controlling the pressure is doubly important. The consistent thickness of the tablets is used as a counting process in equipment admission; So the thickness of the tablet becomes an essential feature of the packing operation and tablet calculation [Lachman et al., 2009].

1.16.4 Measurement of Diameter:

Measurement of diameter of tablet is done to check either the uniform shape pf the tablet is maintained for each tablet or not. The diameters uniformity of the materials has an important effect on increasing the patient's compliance and to reduce the confusion with the different sizes of tablets. Due to the different sizes of tablets, the patient may feel that the medicine or tablet contains different amounts of active ingredients [Latchman et al., 2009]

1.16.5 Dissolution Test:

Dissolution surveys measure the rate and range of drug release from any dosage form. Tests usually report the percentage of drugs released at specific times. Dissolution experiments determine the factors that affect the bioavailability of drugs.In accordance with the USP specification for dissolution analysis content of the must be dissolved more than 80% after 30 minutes of [Lachman et al., 2009].

1.16.6 Friability Test:

Friability test may be done due to the tablet have the tendency to convert into powder.This problem can create the destruction of the elegant appearance of the tablet.the uniformity of weight of tablet or content of the tablet may effect on the buyers acceptancy. This process has been related to the hardness of the tablet.To check the withstand friction of atablet in packaging as well as handling and storage. The USP specification for friability is less than 1% [Lachman et al., 2009].

1.16.7 Disintegration Time:

The time it takes for a particle of a tablet or capsule to break down in a certain liquid media is called dissociation time. The test is performed by inserting one tablet unit into each of the six tubes in the basket, then a disc is attached. Unless otherwise indicated, the device should be operated using water as immersion fluid and kept at a temperature of (37) o C. After that, the dosage form unit and time are measured. When all the pills are detached, the DT is calculated. Since tablets take different amounts of time to dissolve, the largest DT tablet is considered to be the time of batch dissolution.According to the USP the disintegration time for uncoated tablet must be not more than 15 minutes and for coated tablet time must not excced 30 minutes.But disintegration time is longer for enteric coated tablet.It almost take 2 hrs in gastric fluid and 1hr in phosphate buffer to disintegrate [Lachman et al., 2009].

1.16.8 Potency Test:

Potency is a measure of drug activity that is defined in terms of the amount needed to produce a certain level of effect. An extremely strong drug produces a large response at low doses, whereas a less potent agent produces a lower response at lower concentrations. It

varies with relationships and effectiveness. Active's ability to evaluate whether it is present in the pile.Specification According to the USP specification, the strength of the drug must be between 95 and 105 percent. [Lachman et al., 2009]

1.17 objective Of The Study

A comparative study is evaluated to confirm the quality parameters of a particular drug. Various quality indicators established by the United States Pharmacopoeia (USP), British Pharmacopoeia (BP).This reseach study is done to check the quality parameters of paracetamol tablet 500 mg that are available in the market of Bangladesh whether this drug match the criteria of USP, BP etc or not.This study also give information about general understanding of the physical and chemical parameters of marketed paracetamol brands and to compare the quality between the sample brands.

Chapter 2:

Materials and Methods

2. Materials and Methods

2.1 Sample Collection

The purpose of our study was to evaluate the quality of various paracetamol tablet brands available in the pharma-market of Bangladesh. Then 500mg tablets of different brands of paracetamol were bought from a local pharmacy in Farmgate, Dhaka. Tablets of 7 brands were collected and marked as A, B, C, D, E, F,G. Sample information was properly checked such as manufacturer name, batch number, date of manufacture, expiration date, production license number and purchase of DAR number & maximum retail price at the time of purchase.

2.2 Standard Collection:

Reference standard of paracetamol (99.98%) was collected from the University laboratory.

2.3 Materials Used in the Experiment:

Table 2.3: Materials Used in the Experiment

Items	Names	Source
Drug(API)	Paracetamol standard (500mg)	University Laboratory
Marketed Samples	Marketed formulations of Paracetamol tablet (500)mg	Local Pharmacy
Chemicals and Solvents	Potassium Monobasic Phosphate	University Laboratory.
	Sodium Hydroxide	University Laboratoy.
	Distilled Water	University Laboratory.

2.4 Equipment Used in the Experiment

Table 2.4: Equipment Used in this Experiment

In-Vitro Test	Main Apparatus	Manufacturer
Weight variation	Analytical balance	Shimadzu corporation, Japan
Thickness	Digital vernier caliper	SDK
Friability	Roche friabilator	Veego, Indian
Hardness	Tablet hardness tester	Model Dr. Schleuniger,Switzerland
Disintegration	Disintegration apparatus	Veego, India
Dissolution	USP dissolution apparatus (paddle type)	Electrolab, SAKA International Ltd
Potency	UV spectrophotometer	UV-1700 Shimadzu, Japan

2.5 Essential equipments used in the experiment:

- Glass test tube
- Pipette
- Filter paper
- Funnel
- Conical flask(100 ml)
- Glass rod
- Volumetric flask (100 ml, 50 ml)
- Mortar – Pestle
- Wax paper
- Filter paper

- Spatula
- Test tube holder
- UV-Pyrex cell
- Beaker (1000 ml, 100 ml)

2.6 Figures of instruments used in this test:

Fig 01:Electronic balance

Fig 02: Friability tester

Fig 03: Disintegration apparatus

Fig 04:Pipette and pipette filler

Figure 05: Mortar and pastle

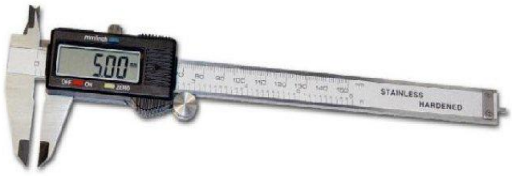


Figure 06: Digital vernier calipers

Figure 07: Dissolution apparatus

Figure 08: UV- visible spectrophotometer

Figure 09: Hardness tester

Figure 10: pH meter

2.7 Methods of Testing Quality parameters

In-Vitro Test of Quality Parameters:

- Weight variation
- Thickness
- Diameter
- Hardness
- Friability -
- Disintegration &
- Dissolution
- Potency

2.7.1 Weight Variation Test:

Weight variations are performed to test whether the tablets produced have a uniform weight. To evaluate the effectiveness of the tablet, it is necessary to monitor the amount of the drug in each tablet. A tablet contains a certain amount of medicine weighing a certain amount of tablets. So the weight of the tablet and its uniformity can help ensure that a tablet contains the right amount of medicine[Latchman et al., 2009].

2.7.1.1 Procedure:

• 20 tablets were selected at random and weighed each one individually, X_1, X_2, X_3… Xz.

• The average weight determination, $X= (X_1+X_2 +X_3+…+ Xz)/20$

Total weight and average weight of 20 tablets were determined. The percent of weight variation was calculated by the following formula

$$\text{Weight variation (\%)} = \frac{\text{Total weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

$$\text{\% of Deviation (+)} = \frac{\text{Maximum weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

$$\text{\% of Deviation (–)} = \frac{\text{Minimum weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

2.7.1.2 Specification:

According to USP,the specification is shown in the following table

Table 2.7.1.2: Specification for weight variation test:

Average Weight of tablets	Maximum Percentage deviation
80 mg or less	± 10%
More than 80mg and less than 250 mg	± 7.5%
250 mg or more	± 5%

2.7.1.3 Acceptance criteria:

USP Specification for uncoated tablets**,**

- Not more than two deviate from the average weight by the above percentage.
- None deviates from the average weight by more than twice of that percentage**.**

2.7.2 Thickness and Diameter Test:

Tablet thickness and diameter should be controlled to ensure uniformity in tablets appearance and fitting into the containers for packaging process.

- Materials: 20 Tablets of each brand.
- Instrument: Digital Vernier Caliper

2.7.2.1 Procedure:

2.7.2.1.1 Measurement Of Thickness: During testing, the thicknesses of 20 tablets from each brand were determined by using Vernier Caliper. Place each tablet one by one in the Jaw and note the thickness reading in mm.

2.7.2.1.2 Measurement Of Diameter: During diameter testing, the diameters of round shape of 20 tablets from each brand were determined by using Vernier Calipers. Place each tablet one by one in the Jaw and note the diameter reading in mm of round shape tablet. The tablets which are capsule in shape their width and length was determined.

2.7.2.2 Specification:

The thickness should be controlled within ±5 of standard value. The deviation of individual unit from the mean diameter should not exceed ± 5% for tablets with diameter of less than 12.5 and ± 3% for diameter of 12.5 mm or more.

2.7.3 Hardness Test:

The hardness of a tablet is an important quality parameter. Strength affects many tablet properties including isolation, dissolution and weakness. The hardening or crushing strength of the tablet is the load required to crush it when placed on the edge of the tablet.

2.7.3.1 Procedure:

- The Monsanto hardness tester was used to determine the tablet hardness. The tablet was placed between affixed and moving jaw.
- Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gave a measure of the hardness of the tablet.
- Measurements were carried out for 3 tablets randomly. Before each reading all the fragments of the broken tablets were removed.

2.7.3.2 Specification:

According to USP, hardness of the tablet ranges from 5-8 kgF (1 Kg= 10 newton).

2.7.4 Friability test:

Friability refers the ability of the compressed tablet to avoid fracture and breaking during transport. Friability is defined as the % of weight loss by tablets due to mechanical action during the test.

2.7.4.1 Procedure:

7 tablets from each of the seven brands were weighed and placed in a Rochefriabilator and revolved at a speed of 25 rpm for 4 minutes. The tablets were removed, de dusted and weighed again. The percent weight loss or friability percentage was calculated

- Initial weight of 7 tablets = W_1
- Put these tablets in the Friabilator and adjust the instrument at 100 rpm (i.e. = 25 rpm for 4 min)
- Final weight of seven tablets= W_2

- % of Friability = $\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$

2.7.4.2 Specification:

According to USP, it must be less than or equal to 1%.

2.7.5 Disintegration time:

Disintegration time is the time required for the tablet to break into particles. This tests are performed to find out if it takes time for a solid oral dosage form, such as a tablet or capsule, to be completely isolated. Measurement of quality during disintegration.

2.7.5.1 Procedure:

3 tablets of paracetamol were employed randomly for the test in distilled water at 37^0 C using Tablet Disintegration Tester (Model:VDT-2, Veego, India). The disintegration time was recorded as the time required passing the tablet completely through the sieve and no particle remained on the basket of system.

2.7.5.2 Specification:

According to USP,the specification is shown in the following table

Table 2.7.5.2: Specification for Disintegration test:

Types of tablets	**Disintegration time**
Uncoated Tablets	Not more than 15 minutes
Coated Tablets	Not more than 30 minutes
Enteric coated tablets	According to BP Disintegrate in 2 hour in gastric fluid in (0.1 N HCl) and 1 hour in phosphate buffer (P^H 6.8)

2.7.6 Preparation of Standard Curve for Paracetamol:

The calibration curve was very significant in this study because all drugs released at different time intervals were compared with the calibration curve and thus the percentage release was calculated. To prepare this calibration curve, 20 mg of pure paracetamol powder was taken and dissolved in 100 ml of phosphate buffer with a pH of 5.8. The solution was then filtered and 10 ml from the filter was taken in another 100 ml volumetric flask and the volume was adjusted up to 100 ml with 5.8 phosphate buffer. It was stock solution and the concentration was 20 µg / ml. Finally, we diluted 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml, 9ml and 10ml stock solution in 10 separate test tubes by diluting the required amount to 10 ml. Phosphate buffer. Then, we took readings of each serial dilution at U max 243 nm on a UV spectrophotometer.

2.7.7 Dissolution Test

Dissolution may be defined as the amount of drug substance that goes into solution under standardized conditions, temperature and solvent composition.

- Materials: Phosphate buffer (pH 6.8) and 3 tablets of paracetamol were taken randomly.
- Instrument: Dissolution Tester, pH meter.
- Specification of Instrument: Electrolab Dissolution tester, India.

2.7.7.1 Procedure:

Dissolution test was performed using USP apparatus II. 900ml of phosphate buffer of P^H 6.8 was used as a medium. Temperature was maintained at 37^0C using water bath. 1000 ml media was made by adding 6.8gm of KH_2PO_4 and 0.98gm of NaOH. Finally, single tablet of each brand was placed in the each vessel separately. Then the apparatus allowed running at 50rpm for 60 min. 10ml sample was withdrawn from each beaker with the help of pipette at 5 min, 15 min, 30 min, 45 min and 60 min and 10 ml of medium was added to the vessel at the time of each withdrawal. The withdrawn sample than filtered and each ml of sample were

diluted to 50 times, and then absorbances were taken at 243nm using UV-Spectrophotometer. Percent release of drug at different times was calculated for each and every sample by using the equation of calibration curve.

2.7.7.2 specification:

According to USP specification for dissolution study, drug must be dissolved > 80% of labeled amount after 30 minute.

2.7.8 Potency test:

The potency of tablets is expressed in terms of grams, milligrams, or micrograms (for some potent drugs) of drug per tablet and is given as the label strength of the product.

2.7.8.1 Procedure:

The potency was determined by crushing four tablets of each brand randomly. The powders were mixed properly and 20 mg equivalent weight of paracetamol was taken and dissolved in 100 ml phosphate buffer (pH= 5.8) medium and then filtered through 0.45-µm membrane filter paper. 10 ml of the filtrate was taken in another 100 ml volumetric flask and diluted up to 100 ml by using same medium. Absorbance was measured for this solution by using UV spectrophotometer at λ_{max} 243 nm. From this absorbance value, concentration was calculated using calibration curve equation and finally potency was determined. It was calculated by using the following formula

$$\% \text{ Potency} = \frac{\text{Experimental value (Drug present in a single tablet)}}{\text{Theoretical value (strength)}} \times 100$$

Again, Drug present in a single tablet was calculated by the following formula-

$$\frac{Conc\left(\frac{mg}{ml}\right) \times Dilution\ Factor \times Total\ volume\ (ml) \times average\ weight(mg)}{Sample\ taken\ (mg)}$$

2.7.8.2 Specification:

According to USP, specification of potency for tablet should be within (95-105) %.

Chapter 3:

Results and discussion

3. Result and Discussion

For the comparative study, we analyzed the weight change test, thickness, dimensions and shape, hardness, separation time of seven different brands of paracetamol tablet 500mg with Innovator products. The in vivo study was done only with brand innovative products.

3.1 Weight variation test:

The tablets were tested for uniformity of their weight and for tablet-to-tablet variation which should be within the current deviation limits approved by the USP; Typically% 10% for tablets weighing 130mg or less, ± 7.5% for tablets weighing 130mg to 324mg, and ± 5% for tablets weighing more than 324mg [Lachman et al., 2009].

Table 3.1:Weight Variation Test of Renova (Paracetamol 500mg) Tablets:

Brand	Number of tablets taken	Average Weight (mg)	Maximum Weight (mg)	Minimum Weight (mg)	Minimum(-) % Deviation	Maximum(+) % Deviation
A	20	623.15	644	613	-1.62%	+3.34%

Calculation of standard deviation:

- (+) Deviation= (maximum weight- average weight)/average weight ×100
- (-) Deviation= (minimum weight- average weight)/average weight ×100

Discussion:

We know that, limit of weight variation test for Paracetamol is ±5%. We can see that the minimum % deviation and maximum % deviation of brand A is within the limit.

3.2 Diameter :

The dimensions of 20 paracetamol tablets were measured using vernier calipers.The results are given below:

Table: 3.2 Diameter of Paracetamol Tablet

Brand	Average Diameter (mm)	Minimum(-) % Deviation	Maximum(+) % Deviation	Shape	Figure
A	12.3	0%	0%	Round	

Calculation for thickness:

- Average Thickness = Total thickness / Number of tablets.
- (+) Deviation= (maximum diameter - average diameter) /average diameter × 100
- (-) Deviation= (minimum diameter - average diameter) /average diameter × 100

Discussion:

we have found that brand A possessed the round shape. The diameter of this tablet is in a uniform state all the tablets diameter is same as a result no deviation occurs.

3.3 Thickness:

The thickness of the tablet can vary without any change in its weight because of the difference in the density of the tablet and the speed of compression of the tablet as well as the pressure applied to the tablet.

Table 3.3: Thickness of Paracetamol Tablet

Brand	Number of tablets taken	Average thickness (mg)	Maximum thickness (mg)	Minimum Diameter (mg)	Minimum(-) % Deviation	Maximum(+) % Deviation
A	20	4.167	4.15	4.12	-0.40%	+0.79%

Calculation for thickness:

Average Thickness = Total thickness / Number of tablets.

Discussion:The % deviation of thickness of Brand A is within the limi

3.4 Hardness:

The hardness of the tablet depends on the materials used, the space between the upper and lower punches during compression and the pressure applied during the compression process. The hardness also depends on the nature and quality of the excipients used during formation [Lachman et al., 2009].

Table 3.4: Hardness of Paracetamol Tablets (kp)

Brand	Tab-1	Tab-2	Tab-3	Average	SD
A	12.31 kp	6.78kp	10.03 kp	9.70	2.78

3.5 Friability Test:

Table 3.4: Friability of Paracetamol Tablets

Brand	W1	W2	%Friability
A	4340 mg	4336 mg	0.09%

Calculation:

$$\textbf{\% of Friability} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{Initial weight}} \times \textbf{100}$$

Discussion:

According to BP, range of friability should not be more than 1 %. Here % friability of brand A is within the limit.

3.6 Disintegration Time:

Table 3.6: Disintegration Time of paracetamol Tablets

Brand	Tab-1	Tab-2	Tab-3	Average	SD	Comment
A	49 sec	50 sec	52 sec	50.33 sec	1.53	Within the limit

3.7 Dissolution Profile:

Dissolution Profile of Paracetamol Tablets

Table 3.7: For Tab-1

Time(min)	Absorbance	mcg/ml	mg/10ml	mg/900ml	Cumulative Amount release	% release .
0	0	0	0	0	0	0
5	0.445	5.325	2.676	240.861	240.861	48.17
15	0.662	8.250	4.125	371.235	373.911	74.78
30	0.782	9.852	4.926	443.331	450.132	90.03
45	0.845	10.693	5.346	481.182	492.909	98.58
60	0.806	10.172	5.085	457.750	474.824	94.96

Table 3.7: For Tab-2

Time(min)	Absorbance	mcg/ml	mg/10 ml	mg/900ml	Cumulative Amount release	% release .
0	0	0	0	0	0	0
5	0.413	4.925	2.463	221.636	221.636	44.33
15	0.682	8.517	4.258	383.251	385.714	77.14
30	0.795	10.025	5.013	451.142	457.862	91.57
45	0.832	10.519	5.260	473.371	485.105	97.02

60	0.812	10.252	5.126	461.355	478.348	95.67

Table 3.7: For Tab-3

Time(min)	Absorbance	mcg/ml	mg/10ml	mg/900ml	Cumulative Amount release	% release .
0	0	0	0	0	0	0
5	0.436	5.232	2.616	235.454	235.454	47.09
15	0.653	8.130	4.065	365.828	368.444	73.69
30	0.768	9.665	4.832	434.920	441.601	88.32
45	0.856	10.840	5.420	487.790	499.304	99.86
60	0.817	10.319	5.159	464.359	481.292	96.258

Discussion:

The above profile shows that within 30 minutes, over 80% drug was released. So it can be said that all the three tablets of brand A released the desired amount of drug at specific time according to USP specification.

Brand	% Release at 30 minutes	Result according to USP Specification at 30 minutes (%)	Comment
A	Tab-1: 90.03%	More than 80% at 30 min	Accepted
	Tab-2: 91.57%		Accepted

	Tab- 3: 88.32 %		Accepted

3.8 Potency:

Four tablets were taken. The tablets are powdered and the powder is thoroughly mixed. A portion of the powder is dissolved in a solvent and diluted if necessary. Absorption is measured on a spectrophotometer. From the average absorption concentration and ultimately the potency of the drug can be determined.

Table 3.7**:** Potency of paracetamol 500mg Tablets

Brand	Absorbance	mcg/ml	mg/ml	Total Vol (ml)	Dilution Factor	Average Tablet weight	Sample taken	Drug in a tablet	Strength (mg)	%Potency.
A	0.774	9.74	0.00974	100	10	622	12.44	496.125	500	97%

Calculation:

$$\% \text{ Potency} = \frac{Conc\left(\frac{mg}{ml}\right) \times Dilution\ Factor \times Total\ volume\ (ml) \times average\ weight(mg)}{Sample\ taken\ (mg)}$$

Discussion:

The % potency of brand A is found 97% which is within the accepted range according to the USP specification as well as BP specification.

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