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

*A project report submitted to the Department of Pharmacy, University of Asia Pacific in partial fulfillment of the requirements for the degree of  
Bachelor of Pharmacy (Honors)*

Submitted By

Registration No.: 18103051

Submission Semester: Fall 2021

Submission Date: 31 May 2022

******

Department of Pharmacy

University of Asia Pacific

**Abstract**

Paracetamol (acetaminophen) is considered as the 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 carried out to analyse the quality of marketed brands of paracetamol tablet formulation manufactured in Bangladesh. The selected tablet formulations were tested for various parameters such as weight variation, diameter & thickness, hardness, friability, disintegration time, potency and dissolution profile by the use of standard technic to evaluate the quality of the tablet. After completing all the test then the values were compare to the standard value. Weight variation value requirement was compiles with the standard value . In case of diameter & thickness size and shape of all tablets was uniform.Three tablets were taken for hardness test and all the tablet met the the standard specification.All tablets showed impressive friability values and also remained within the specification according to BP. Disintegration time for all tablets was within 15 minutes also complying the USP (United State of Pharmacopeia) recommendation. The percentage content of active ingredient of all the paracetamol tablets show values within the monograph specifications (90-110%). Moreover, the release rate of different brands of paracetamol was satisfactory; all tablets attained 80% dissolution within 30 minutes, according to USP monograph. The selected brand that was evaluated in this study could be considered bio-pharmaceutically and chemically equivalent. Therefore, it can be concluded that the selected brand of paracetamol that are available in Bangladesh met the USP specification for quality control analysis.

**Table of contents**

|  |  |  |
| --- | --- | --- |
| **SI. No.** | **Topic** | **Page** |
|  | Summary of the Study |  |
|  | Table of Contents |  |
|  | List of Tables |  |
|  | List of Figures |  |

**Chapter 1-Introduction**

|  |  |  |
| --- | --- | --- |
| **SI. No.** | **Topic** | **Page** |
| 1.1 | General Introduction |  |
| 1.2 | History of Paracetamol |  |
| 1.3 | Chemistry of Paracetamol |  |
| 1.4 | Synthesis of Paracetamol |  |
| 1.5 | Impurities of Paracetamol |  |
| 1.6 | Physico-chemical Properties of Paracetamol |  |
| 1.6.1 | Description |  |
| 1.6.2 | Melting Point |  |
| 1.6.3 | Boiling Point |  |
| 1.6.4 | Molecular Formula |  |
| 1.6.5 | Molecular Weight |  |
| 1.6.6 | Solubility |  |
| 1.6.7 | Spectroscopy Data |  |
| 1.6.8 | Stability |  |
| 1.6.9 | Dissociation Constant |  |
| 1.6.10 | Density |  |
| 1.6.11 | λmax |  |
| 1.6.12 | Storage |  |
| 1.6.13 | Refractive Index |  |
| 1.6.14 | Molar Volume |  |
| 1.6.15 | Shelf Life |  |
| 1.6.16 | Vapor Density |  |
| 1.6.17 | Partition Coefficient |  |

**Chapter 1-Introduction (contd.)**

|  |  |  |
| --- | --- | --- |
| **SI. No.** | **Topic** | **Page** |
| 1.7 | Pharmacology of Paracetamol |  |
| 1.8 | Mechanism of Action of Paracetamol |  |
| 1.9 | Toxicology of Paracetamol |  |
| 1.10 | Pharmacokinetics of Paracetamol |  |
| 1.10.1 | Absorption |  |
| 1.10.2 | Distribution |  |
| 1.10.3 | Metabolism |  |
| 1.10.4 | Exceretion |  |
| 1.10.5 | Plasma Half-life range |  |
| 1.10.6 | Volume of Distribution |  |
| 1.10.7 | Protein Binding |  |
| 1.10.8 | Bioavailability |  |
| 1.10.9 | Clearence |  |
| 1.11 | Pharmacodynamics of paracetamol |  |
| 1.12 | Therapeutic use of Paracetamol |  |
| 1.12.1 | Indication |  |
| 1.12.2 | contraindication |  |
| 1.12.3 | Dosage |  |
| 1.13 | Adverse Effect of Paracetamol |  |
| 1.14 | Major side Effects |  |
| 1.15 | Excessive use of Paracetamol Symptoms |  |
| 1.16 | Drug Interactions |  |
| 1.17 | Evaluation of tablet |  |
| 1.17.1 | Weight Variation Test |  |
| 1.17.2 | Hardness Test |  |
| 1.17.3 | Measurement of Thickness |  |
| 1.17.4 | Measurement of Diameter |  |
| 1.17.5 | Dissolution Test |  |
| 1.17.6 | Friability Test |  |
| 1.17.7 | Disintegration Test |  |

**Chapter 1-Introduction (contd.)**

|  |  |  |
| --- | --- | --- |
| **SI. No** | **Topic** | **Page** |
| 1.17.8 | Potency Test |  |
| 1.18 | Objective of the study |  |

**Chapter 2-Materials and Method**

|  |  |  |
| --- | --- | --- |
| **SI. No.** | **Topic** | **Page** |
| 2.1 | Sample Collection |  |
| 2.2 | Standard Collection |  |
| 2.3 | Materials Used in the Experiment |  |
| 2.4 | Equipment Used in the Experiment |  |
| 2.5 | Essential Apparatus Used in the Experiment |  |
| 2.6 | Figures of Instruments Used in this Test |  |
| 2.7 | Methods of Testing Quality Parameters |  |
| 2.7.1 | Weight Variation Test |  |
| 2.7.1.1 | Procedure |  |
| 2.7.1.2 | Specification |  |
| 2.7.1.3 | Acceptance Criteria |  |
| 2.7.2 | Thickness and Diameter Test |  |
| 2.7.2.1 | Procedure |  |
| 2.7.2.1.1 | Measurement Of Thickness |  |
| 2.7.2.1.2 | Measurement Of Diameter |  |
| 2.7.2.2 | Specification |  |
| 2.7.3 | Hardness Test |  |
| 2.7.3.1 | Procedure |  |
| 2.7.3.2 | Specification |  |
| 2.7.4 | Friability Test |  |
| 2.7.4.1 | Procedure |  |
| 2.7.4.2 | Specification |  |
| 2.7.5 | Disintegration |  |
| 2.7.5.1 | Procedure |  |
| 2.7.5.2 | Specification |  |

**Chapter 2-Materials and Method (contd.)**

|  |  |  |
| --- | --- | --- |
| **SI. No** | **Topic** | **Page** |
| 2.7.6 | Preparation of standard Curve For paracetamol |  |
| 2.7.7 | Dissolution Test |  |
| 2.7.7.1 | Procedure |  |
| 2.7..7.2 | Specification |  |
| 2.7.8 | Potency Test |  |
| 2.7.8.1 | Procedure |  |
| 2.7.8.2 | Specification |  |

**Chapter 3-Results and discussion**

|  |  |  |
| --- | --- | --- |
| **SI. No.** | **Topic** | **page** |
| 3.1 | Weight Variation Test |  |
| 3.2 | Diameter |  |
| 3.3 | Thickness |  |
| 3.4 | Hardness |  |
| 3.5 | Friability |  |
| 3.6 | Disintegration Time |  |
| 3.7 | Dissolution Profile |  |
| 3.8 | Potency |  |
| 3.9 | Conclusion |  |
|  | References |  |

**List of Tables**

|  |  |  |
| --- | --- | --- |
| **SI. No.** | **Topic** | **Page** |
| 1.5 | Chemical Structure of Paracetamol and its Impurities |  |
| 2.3 | Materials Used In the Experiment |  |
| 2.4 | Equipment Used In this Experiment |  |
| 2.7.1.2 | Specification for Weight Variation Test |  |
| 2.7.5.2 | Specification for Disintegration Test |  |
| 3.1 | Weight Variation Test of Paracetamol tablets |  |
| 3.2 | Diameter of Parcetamol Tablets |  |

**List of Tables (contd.)**

|  |  |  |
| --- | --- | --- |
| **SI. No** | **Topic** | **Page** |
| 3.3 | Thickness of Paracetamol Tablets |  |
| 3.4 | Hardness of paracetamol Tablets (kp) |  |
| 3.5 | Friability of paracetamol Tablets |  |
| 3.6 | Disintegration Time of paracetamol Tablets |  |
| 3.7 | Dissolution profile of Tab-1  Dissolution Profile of Tab-2  Dissolution Profile of Tab-3 |  |
|  |
|  |
| 3.8 | Potency of Paracetamol Tablet |  |

**List of Figures**

|  |  |  |
| --- | --- | --- |
| **SI. No** | **Topic** | **Page** |
| 1.3 | Structure of paracetamol |  |
| 1.4.1 | Flowchart for the Synthesis, Characterization and Purification of Paracetamol |  |
| 1.4.2 | Synthesis of Paracetamol |  |
| 1.8 | Metabolism of Arachidonic Acid |  |
| 1.9.3 | Metabolism of paracetamol |  |
| 2.6.1 | Electronic Balance |  |
| 2.6.2 | Friability Tester |  |
| 2.6.3 | Disintegration Tester |  |
| 2.6.4 | Pipette and Pipette Filler |  |
| 2.6.5 | Mortar and Pestle |  |
| 2.6.6 | Digital Vernier Calipers |  |
| 2.6.7 | Dissolution Apparatus |  |
| 2.6.8 | UV- Visible Spectrophotometer |  |
| 2.6.9 | Hardness Tester |  |
| 2.6.10 | pH meter |  |
| 2.7.6 | Standard Curve of Paracetamol |  |

**Chapter 1:**

**Introduction**

1. **Introduction**

**1.1 General Introduction:**

Paracetamol (proposed international non-proprietary name) (acetaminophen) is an OTC drug and also it belongs 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 was first introduced in the market of USA with the brand name called Tynelol. No intravenous formulation of acetaminophen was available in the market of USA before November 2010, then the USFDA 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 adequately absorbed from the small bowel in addition to that this drug is not showing any significant first-pass 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 has not sufficient capability in binding to plasma proteins so the apparent volume of distribution of this drug is comparatively much more high 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 achieved. This peak plasma concentration is known as C-max.For an orally administered paracetamol the C-max 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.That’s 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 of using this particular type of drug and the patient must 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 happened 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) popularly known as paracetamol belongs to acetanilide derivative with a chemical formula of [Oscier and Milner, 2009]. This drug is chemically known as 4-hydroxy acetanilide and this drug is a metabolite of phenacetin which is also named as 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]. Structure of Paracetamol is given in figure 1.3 [Audu *et al*.,2012].

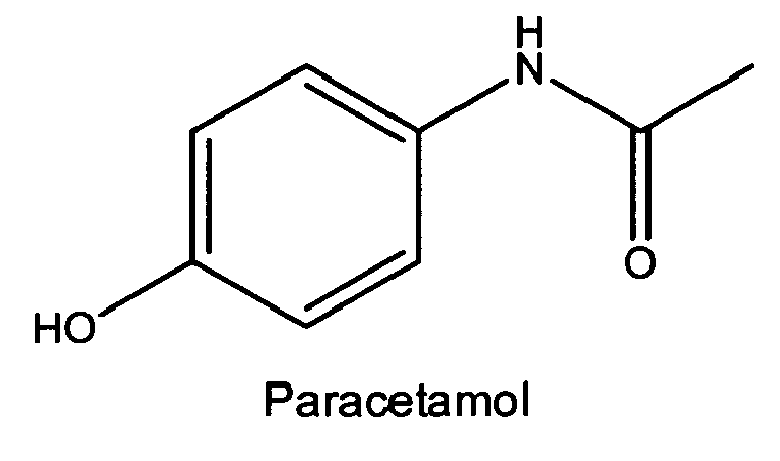


Figure 1.3: Structure of Paracetamol

**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 1.4.1 synthesis, purification and characterization of paracetamol is given in a flowchart [Graham *et al*., 2013]. Chemical reaction of paracetamol synthesis is given in figure 1.4.2 [Audu *et al*., 2012].

4 Aminophenol (2.75g; 25.2 mmol)

7.5 ml H2O

Acetic anhydride (3ml; 31.8 mmol)

Heat, Stirring, 10 min

Vacuum filtration

Residue

Filtrate

(Aqueous acid solution)

Wash

Purification

(Recrystallization)

(Discard)

Crystal

Filtrate

Constant weight yield

Characterization/Identification

,

TLC

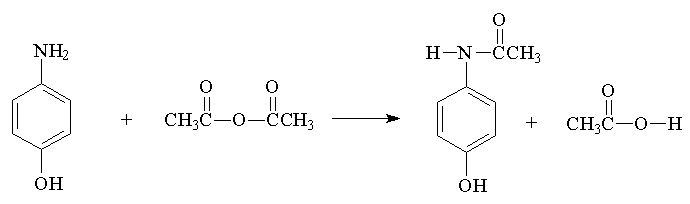
1H-RMN

13C-RMN

IR

Melting point

Figure 1.4.1: Flowchart for the Synthesis, Purification and Characterization of Paracetamol



aminophenolAcetic anhydrideParacetamol Acetic acid

Figure 1.4.2: 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 | C8H9NO2 | Graphic |
| 4-Aminophenol | C6H7NO | Graphic |
| Hydroquinone | C6H6O2 | Graphic |
| 4-Nitro phenol | C6H5NO3 | Graphic |
| 4'-Chloroacetanilide | C8H8ClNO | Graphic |
| P-Benzoquinone | C6H4O2 | Graphic |

**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:**

**1.6.5 Molecular Weight:** 151.16 g/mol

**1.6.6 Solubility:** NAPA isInsoluble 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/

**1.6.11 λmax:** 243nm

**1.6.12 Storage:** Must bestored in well closed, light resistance containers.

**1.6.13 Refractive index:** 1.62

**1.6.14 Molar Volume:** 120.93 cm3

**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]

**1.7 Pharmacology of Paracetamol**

The drug Paracetamol is vastly used by the people of all over the world for its analgesic activity and capability of reducing fever. This drug has similar mechanism of action as like NSAIDs and alsohave the similarity 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**

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 H2 synthetase which is responsible for the arachidonic acid consequences in the volatile PGH2. 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 PGG2  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 PGG2. 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 1.8 shows the arachidonic acid metabolism schematically [Graham and Scott, 2005].

Phospholipids

Inhibition caused by steroids Phospholipase A2

Arachidonic Acid + lysophospholipids

Inhibition caused by NSAIDs  cyclo-oxygenase

PGG2(prostaglandin G2)

Peroxidase enzyme

PGH2

PGF2α PGE2  PGI2 TXA2

synthetase synthetase synthetase synthetase

PGF2α PGE2  PGI2 TXA2

Figure 1.8: 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 and this is liable for the damage of liver. 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 significant hepatocyte toxicity but in 50% cases this dysfunction occurs by the hepatic failure [Bertolini *et al*., 2006].

**1.10 Pharmacokinetics of Paracetamol**

**1.10.1 Absorption:**

After oral administration the drug paracetamol is taken up significantly from the gastrointestinal tract and also not force to undergo significant first pass metabolism. In adults the oral bioavailability of paracetamol is observed at 63 to 89% [Oscier and Milner, 2009]. Intake of caffeine during administration time of paraectamol accelerates the absorption rate but drug food interactions slowdown the rate of paracetamol absorption. Metaclopromide accelerate the gastric emptying rate thus increase the rate absorption in the meanwhile other drugs such as morphine decreases the rate of gastric emptying thus reduce the absorption and this lead to the the prevention of therapeutic plasma levels [Oscier and Milner, 2009]. In the healthy aspects of fasting, the absorption of paracetamol in the solution is very fast and the maximum plasma concentration often occurs between the range of 15 to 30 minutes of eating. The absorption of tablet is usually low and the plasma concentration may range up to 80 fold in 1 hour after taking the therapeutic dose in the clinical practical situations [Prescott, 1980]. Rectal paracetamol absorption is slow and unpredictable and bioavailability ranges between 24% to 98% [Oscier and Milner, 2009]. Rectal route absorption depends on the various aspects such as on the size, anatomy, number of used suppositories and the pH. Usually the drug paracetamol has not the enough ability to bound to the plasma protein. The drug paracetamol shows more reliable therapeutic plasma concentration compare to that of oral administration. The orally administered groups of paracetamol yielded less plasma concentration taht was after 150 min but the intranvenous administration groups yielded higher plasma concentration [Oscier and Milner, 2009].

**1.10.2 Distribution:**

Usually the drug paracetamol has not the enough ability to bound to the plasma protein and its distribution amount is approximately 0.7 -1.1 L / kg. This drug is not in ionized state at physiological pH and it has the ability to pass through the placenta and blood brain barrier easily. After the process of hydrolysis one gram of paracetamol provides only 0.5 gram of paracetamol. The concentration of red blood cells and plasma have ratio of 1.2 : 1. Thus this drug shows insignificant binding to the plasma protein. The volume of distribution of paracetamol ranges between 0.9 - 1 L /kg [Oscier and Milner, 2009].

**1.10.3 Metabolism:**

The drug paracetamol metabolized by the function of liver and then dispelled from the body through kidney. 90% of the drug is metabolized by glucoronidation and sulfation process and then to form metabolites which is non toxic in nature and then that are completely removed in the urine [Osier and Milner, 2009]. Through the oxidation caused by the cytochrome P450 enzyme a small fraction produce the highly reactive metabolism known as N-acetyl-p-benzoquinoneimine (NAPQI). Usually NAPQI reacts with glutathione, forming a conjugate which is then excreted in the urine. But when the large amount of paracetamol is ingested then the hepatic glutathione is removed and as a consequences NAPQI accumulates thus lead to the process of hepatic necrosis. In neonates the hepatic clearence is lowest in severe cases, whose value increases from infancy. In adults with healty physical strength elimination half life is increased form 2 to 4 hours and 4 to 5 hours in the consideration of newborns and this value increased upto 11 hours in infants. Patients who have severe renal dysfunction among them the GFR is less than 10 ml/min and then it is recommended to increase the dose interim to 6-8 hours [Oscier and Milner, 2009]. Figure 1.9.3 displays metabolism of paracetamol [Graham and Scott, 2005].

**Paracetamol**

**(Acetaminophen)**

**Phase I Metabolism CYP2E1**

1. **acetyl-p-benzoquinone**

**N-acetylcystein (NAPQI)**

**Normal doses Toxic doses**

**Glutathione Glutathione**

**Phase II metabolism**

**Cystein Mercapturic acid NAPB complexes with membrane**

**Sulphydryl groups**

**Liver Damage**

**(Hepatocyte Necrosis)**

Figure 1.9.3: Metabolism of Paracetamol

**1.10.4 Excretion:**

If a subject was given a paracetamol at a rate of 20mg/kg then average renal clearence is about 13mg/min. Clearance depends on the rate of the flow of the urine but it is not depended on the pH of the urine.With the help of subsequent tubular reabsorption paracetamol drug appears to be filtered from the glomeruli. In the process of sulfation and glucoronidationthe average renal clearence of paracetamol is 166 and 130 ml/min respectively and this clearence has no accordance with urine flow or urine pH. In case of a renal patient the plasma half life of paracetamol is not increased in the contrary the conjugates are deposited and retained [Forrest *et al*., 1982].

**1.10.5 Plasma Half-life Range:** 1–4 hours.

**1.10.6** **Volume of Distribution (Vd):** 65 L

**1.10.7 Protein Binding:** 10-25%

**1.10.8 Bioavailability:** Oral bioavailabilty: Ranges in between 70% -90%

Rectal bioavailability: Ranges in between 30% - 70%

**1.10.9 Clearance :** 20 Litre/hour

**1.11 Pharmacodynamics of Paracetamol:**

The drug paracetamol belongs to the group of para-aminophenol that shows analgesic and antipyretic activity. Prostaglandin synthesis is inhibited in the central nervous system and the neutralization of pain monitor the mechanism of action of paracetamol. This drug is applied in the prophylaxis of mild to moderate fever and pain. Paracetamol is processed by metabolism with the functioning of liver. Then removed in the urine by the action of kidney mainly as glucuronide and sulfate conjugate; the unchanged portion of paracetamol excreted through the kidney is less tahn 5%. This drug has poor capacity to bind with plasma protein in therapeutic concentration. High doses of paracetamol (more than 2,000 mg per day) increase the chances to damage the upper gastrointestinal region 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). An experimental study of 2008 on the long term effect of paracetamol tablets in children shows that taking the drug paracetamol to treat feverin the first year of life enhances the asthma symptoms at the age of 6 to 7. It further states that the use of paracetamol both in the child aged at 6 to 7 and in the first year of life enhances the occurence of rhino conjunctivitis and eczema. Hypersensitivity reactions such as rash and difficulties in breathing and disorders relted to blood resulting in sore or bleeding preparations such as thrombocytopenia or reduced white blood cell count known as leukopenia are unlikely to cause a serious allergic reaction to this drug, if this is happening to someone then consult a doctor must be needed. The symptoms of a severe hypersensitivity reaction including rash , itching, swelling in mouth or tongue or throat, diziness, shortness of breath are most common.Most necessary concern in the consideration of paracetamol and its effect on the liver there are some issues that has to be needed immediate attention. As for example yellow eyes or yellow skin is one of the signs of liver damage by the paracetamol drug that is often seen with the administration of large doses of paracetamol and the extended use of paracetamol.Another sign may be outlined by examine urine and stool and if the urine and stool is bloody then it can be concluded that it is the side effects of paracetamoland stomach irritation. Most usual side effects that are related to paracetamol poisoning are nausea and vomiting and these side effects are commonly appear within the 24 hours of the administration of the drug paracetamol [Malar and Bai, 2012].

**1.12 Therapeutic Use of Paracetamol**

**1.12.1 Indication**

The drug paracetamol is an effective painkiller in the consideration of moderate pain such as headache, myalgia, postpartum pain and such other condition. Acetaminophen or paracetamol alone has insufficient therapeutic action for inflammatory conditions such as rheumatoid arthritis but with this short effectiveness it can also be used as an analgesic with anti-inflammatory therapy. Acetaminophen is the drug of choice in the consideration of mild pain for the patients who have allergy to aspirin or the poor tolerance of salicylates. 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, the drug paracetamol does not counteract the effects of uricosoric agents; this drug can also be used in the combination with probenecid to treat the disease gout. The drug paracetamol is preferred over aspirin in children to treat viral infection [Prescott, 2000].

**1.12.2 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].

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

**1.13 Adverse Effects of Paracetamol**

Adverse effects means the undesirable effects that may produce during the use of any drug. Large doses of acetaminophen cause dizziness, agitation and confusion. Taking 15 grams of acetaminophen can be fatal, leading to death due to serious hepatotoxicity with centrilobular necrosis as well as acute renal tubular necrosis. Usually greater than 4 to 6 gram/day of paracetamol doses are not recommended and this dose is contraindicated by drinking alcohol concurrently. Symptoms like nausea, vomiting, diarrhea and abdominal pain is preliminary symptoms of paracetamol intoxication.Even kidney damage may occur without the hapatic damage after the normal doses of paracetamol. There are some very rare adverse events like hemolytic anemia and methemoglobinemia. The use of paracetamol also enhances the cardiovascular risk. Clinical studies and many epidemiological report have been shown that non-steroidal anti-inflammatory drug as well as non selective and selective cox inhibitors can increase blood pressure and cardiovascular events. This health issues should not be ignored at all [Sudanot *et al*., 2012].

### 1.14 Major Side Effects

Major side effects that are related to the use of paracetamol are discussed below:

### Bloody or black, tarry stools

* Bloody or cloudy urine
* Fever with or without chills
* Pain in the lower back
* Pinpoint red spots on the skin
* Skin rash, hives, or itching
* Sore throat
* 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].

**1.15 Excessive Use of Paracetamol Symptoms:**

**Symptoms of paracetamol that are related to the excessive use are discussed below:**

* 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].

**1.16 Drug Interactions:**

Paracetamol strengthens the anticoagulant effects of warfarin, thus increasing the risk of bleeding. So paracetamol should be used in a limited dose incase of using concurrently with warfarin or other anticoagulants. Administration of Carbamazepine with paracetamol increases the risk of hepatic intoxication induces hepatic metabolism of paracetamol and this leads to the increase formation of toxic metabolites. Bio-availability of paracetamol is low in the patient who have epilepsy or patients who are taking enzyme induction anticonvulsants drug like phenytoin and phosphenytoin. Concurrent use of Lamotrigine sulfinpyrazone with paracetamol increases the excretion of urine and paracetamol with zidovudine resulting neutropenia and hepatotoxicity. The main concern of paracetamol interaction is the interaction with alcohol. Alcohol - Paracetamol syndrome is defined as the development of acute toxic hepatic symptoms in long-term alcoholics [Stiffit *et al*., 1990]. Patients with alcohol-paracetamol syndrome are more prone to taking higher doses of paracetamol compare to than that of non-alcoholic patient. 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].

**1.17 Evaluation of Tablet**

**1.17.1 Weight Variation Test:** Thistest is a compensatory test of pharmaceutical product**.** Weight variation 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].

% of weight variation = × 100

**1.17.2 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].

**1.17.3 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].

**1.17.4 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].

**1.17.5 Dissolution Test:**

Dissolution test of seleceted sample measure the value of drug release from any dosage regimen. Tests usually shows the report of the percentage of drugs released at specific times. Dissolution experiments determine the causes 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].

**1.17.6 Friability Test:**

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

**1.17.7 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 degree celcius. 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].

**1.17.8 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].

**1.18 Objective of the Study**

A comparative study is done to confirm the quality parameters of a particular drug. Various quality indicators established by the United States Pharmacopoeia (USP), British Pharmacopoeia (BP). This research study is done to check the quality parameters of paracetamol (500 mg) tablet that are obtainable 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**

1. **Materials and Methods**
   1. **Sample Collection**

The purpose of our study was to asses the quality of various paracetamol tablet brands available in the pharma-market of Bangladesh. In the consequences 500mg Renova (paracetamol) tablets were collected from the University laboratory. To complete this test 20 tablets of Renova(paracetamol) were taken. Then the sample information was properly checked such as manufacturer name, batch number, date of manufacture, expiration date, production license number.

**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 Renova 500mg (paracetamol) tablet | University Laboratory |
| 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 |
| **In-Vitro Test** | **Main Apparatus** | **Manufacturer** |
| 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:**

The instruments that is used in this test are provided by University laboratory. All the instruments are highly valuable and digital.So very intensive care must be needed when the instruments are used. It is necessary to work in the laboratory with patience and care.

|  |  |
| --- | --- |
| U-S-Solid-200-x-0-001g-1mg-Lab-Analytical-font-b-Balance-b-font-Digital.jpgFig 2.6.1:Electronic balance | Fig 2.6.2: Friability tester |
| vtd-dv.png  Fig 2.6.3: Disintegration apparatus | AC136544l.jpgFig 2.6.4:Pipette and pipette filler |
| Figure 2.6.5: Mortar and pastlesmall-porcelain-mortar-and-pestle-3.gif | Figure 2.6.5: Digital vernier calipers |

|  |  |
| --- | --- |
| http://t2.gstatic.com/images?q=tbn:ANd9GcSA2WJz_J-IT7iJtNj4Nr8p9Ama-ggxpy65mK7bgFIfYYuO9lfmpgFigure 2.6.7: Dissolution apparatus | UVmini-1240.jpg  Figure 2.6.8:UV- visible spectrophotometer |
| Figure 2.6.9: Hardness tester | R410139-01.jpgFigure 2.6.10: pH meter |

**2.7 Methods of Testing Quality parameters**

In-Vitro Test of Quality control Parameters are:

* 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, X1, X2, X3… Xz.

• The average weight determination, X= (X1+X2 +X3+…+ Xz)/20

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

Weight variation (%) =

% of Deviation (+) =

% of Deviation (‒) =

**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 measured 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 weredetermined 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 tabletsfrom 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 = W1
* 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= W2
* % of Friability = × 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 370 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 (PH 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.

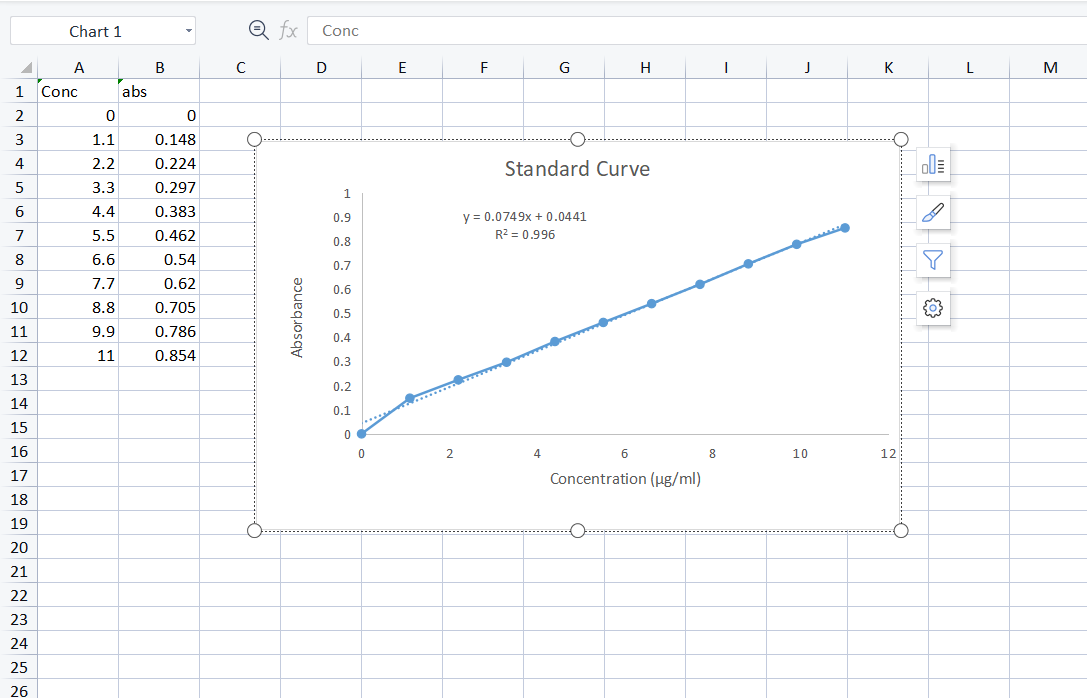


Figure 2.7.6: Standard Curve of Paracetamol

**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 PH 6.8 was used as a medium. Temperature was maintained at 370C using water bath. 1000 ml media was made by adding 6.8gm of KH2PO4 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 λmax 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

% Potency = × 100

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

**2.7.8.2 Specification:**

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

**Chapter 3:**

**Results and Discussion**

1. **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:

% of Friability = × 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 3 Paracetamol Tablets are given below in sepearate table for each tablet

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/10ml | 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 |

Table 3.7: Comment of Dissolution Testing

**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:

% Potency =

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.

**3.9 Conclusion**

Paracetamol is an over the counter. Hence, it should be necessary to manufacture paracetamol by maintaining the Good Manufacturing Practice (GMP).The various quality control parameters including weight variation, hardness, friability, disintegration time, dissolution and potency were evaluated of marketed Paracetamol tablet named as Renova 500mg (paracetamol). This present study was undertaken with an aim to evaluate the quality parameters of paracetamol preparations available in Bangladesh. After completing this study we can say that the pharmaceutical companies of our country are doing a great job as they are maintaining good quality products in order to serve this country. Since the life of a patient depending on which kind of drug is taken by the patient so the drug should be safe, having no toxicity and must have good efficacy. So we did various official and non-official and in-vitro studies like weight variation, friability, hardness, disintegration, dissolution and potency tests and we did this test to know that the patients who are taking paracetamol can be sure that the drug they are taking is safe and have good efficacy and whether this drug met the USP specification or not.Fortunately we found all the different brands met USP specification and as a result, patients can safely switch from one brand to another. So, these type of studies should be conducted more frequently so that this study are capable of building mass awareness as well as helps in the betterment of our pharmaceutical sector.

**References:**

Aronoff D.M., Oates J.A., Boutaud O. *New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases*. **Clinical Pharmacology and Therapeutics; 2006,** 79; 9–19.

Forrest J.A.H., Clements J.A., Prescott L.F. **Clinical pharmacokinetics of paracetamol; 1982,** 7(2); 93.

Irshad M., Malik M., Furqan A. *Intravenous paracetamol in pediatrics: A global perspective.* **An International Journal of Anesthesiology, Pain Management, Intensive Care & Resuscitation; 2012,** 16(3); 311-314.

Shep D., Ojha A., Patel S., Rathod R., Nivsarkar M., Jaiswal V. *et al. Bioequivalence and evaluation of two formulations of paracetamoler 650 mg: a single dose pharmacokinetic randomized two period crossover comparison in healthy indian adult volunteers.* **International Journal of Current Pharmaceutical Research; 2010,** 2(4).

Graham G.G., Scott K.F. *Mechanism of action of paracetamol.* **American Journal of Therapeutics; 2005,** 12; 46–55.

Malar V.H.L., Bai S.M.M. *Beware of paracetamol toxicity.* **Clinical Toxicology; 2012,** 2(6); 1-3.

Prescott, Laurie F., Steel R.F., Ferrier W.R. *The effects of particle size on the Absorption of phenacetin in man.* **Journal of Clinical Pharmacy and Therapeutics; 1974,** 11; 496-504.

Bertolini A., Ferrari A., Ottani A., Guerzoni S., Tacchi R., Leone. *et al. Paracetamol: new vistas of an old drug.* **CNS Drug Reviews; 2006,** 12(3-4); 250-275.

# Mathur N., Kumar R., Tiwari K., Singh S., Fatima N. *Evaluation of quality control parameters on various brands of paracetamol tablet formulation.* World Journal of Pharmacy and Pharmaceutical Sciences; 2015, 4(07); 976-984.

# Oscier C.D., Milner Q.J.W. *Peri-operative use of paracetamol.* Anaesthesia; 2009, 64(1); 65-72. Paracetamol for Oral Use [Internet]. 2013. Available from: <https://www.tga.gov.au/otc-medicine-monograph-paracetamol-oral-use>

# Paracetamol IRAC Monograph73 [Internet]. 1999. Available from: <https://monographs.iarc.fr/ENG/Monographs/vol73/mono73-20.pdf>

Forrest J.A.H., Clements J.A., Prescott L.F. **Clinical pharmacokinetics of paracetamol; 1982,** 7(2); 93.

Graham GG, Scott KF. *Mechanism of action of paracetamol.* **American Journal of Therapeutics; 2005,** 12; 46–55.

Prescott, Laurie F., Steel R.F., Ferrier W.R. *The effects of particle size on the Absorption of phenacetin in man.* **Journal of Clinical Pharmacy and Therapeutics; 1974,** 11; 496-504.

Vidhya M., Bai S.M.M. *Beware of Paracetamol Toxicity.* **Journal of Clinical Toxicology; 2012,** 2; 142.

Web Health Centre. [Internet]. **2017**. Available from: http://www.webhealthcentre.com/drugix/Paracetamol\_di0105.aspx#top.

Paracetamol Information Centre. Paracetamol Dosage [Internet]. Available from:

<http://www.pharmweb.net/pwmirror/pwy/paracetamol/pharmwebpicm.htm>

Prescott, Laurie F., *Paracetamol: past, present, and future.* **American Journal of Therapeutics; 2000.**

Drugs.com [Internet]. **2016.** Available from:

http://www.drugs.com/sfx/paracetamol-side-effects.html

Easton, P.A. *Remington's Pharmaceutical Sciences.* In: Easton, P.A. editors. **Mack Publishing Company; 1995,** 1109-1110.

Prescott L.F. *Kinetics and metabolism of paracetamol and phenacetin.* **British Journal Clinical Pharmacology; 1980,** 10; 291-298.

Smith H. *Potential analgesic mechanism of acetaminophen.* **Pain Physician; 2009,** 12; 269-280.

Steffe E.M., King J.H., Inciardi J.F. *The effect of acetaminophen on zidovudine metabolism in HIV-infected patients.* **Journal of Acquired Immune Deficiency Syndrome; 1990,** 3(7); 691–694.

*IARC monographs on the evaluation of carcinogenic risks to humans.* **International Agency for Research on Cancer of World Health Organization; 1993,** 73; 401-404.