Preparations And Evaloution of Paracetamol Tablet

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Abstract- *Musculoskeletal pain conditions are age-related, leading contributors to chronic pain and pain-related disability, which are expected to rise with the rapid global population aging. current medical treatments provide only partial relief. Furthermore,non-steroidal anti-inflammatory Drugs (NSAIDs) and opioids are effective in young and otherwise healthy individuals but are often contraindicated in elderly and frail patients. As a result of its favorable safety and tolerability record, paracetamol has long been the most common drug for treating pain. Strikingly, recent reports questioned its therapeutic value and safety. This review aims to present guideline recommendations. Paracetamolas been assessed in different conditions and demonstrated therapeutic efficacy on both acute and chronic pain. It is active as a single agent and is additive or synergistic with NSAIDs and opioids, improving their efficacy and safety.However, a lack of significant efficacy and hepatic toxicity have also been reported. Fast dissolving formulations of paracetamol provide superior and more extended pain relief that is similar to intravenous paracetamol. A dose reduction is recommended in patients with liver disease or malnourished.*

Genotyping may improve efficacy and safety. Within the current trend toward the minimization of opioid analgesia, it is consistently included in multimodal, non-opioid, or opioid-sparing therapies. Paracetamol is being recommended by guidelines as a first or second-line drug for acute pain and chronic pain,especially for patients with limited therapeutic options and for the elderly.

Keywords- pain; musculoskeetal; cancer; headache; elderly; paracetamol; guidelines

I. INTRODUCTION

Pharmaceutical tablets may be manufactured through three different methods. These include direct compression, dry granulation and wet granulation. Current usage of the term "direct compression" is the process by which tablets are compressed directly from the powder blends of active ingredient/s and suitable excipients. Dry granulation and wet granulation involve processes in which powdered particles are made to possess cohesive qualities, aggregate or adhere to form regular larger sized multi-particulate entities called granules. Granulation of drug particles is usually carried out to impart cohesiveness to the tablet formulation and to improve on the flow characteristics of the individual particles in order to improve the inherent poor compression properties and to prevent segregation of the constituents which may arise primarily from differences in size or density. Direct compression as a procedure of tablet production has great advantages because the drug,even with addition Of certain additives, is compressed without previous granulation. While in most cases the advantages of this procedure are economy, production of tablets containing drugs sensitive to moisture and heat, it is also a selective method either for high or low dosage preparations. It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible adjuvants may yield satisfactory tablets for such materials. These directly compressible adjuvants are most often based on sugar, cellulose or inorganic saIts. Many researches have been performed with dispersed dextrose (Emdex), aggregates of mechanically disintegrated a-cellulose (Elcema G 250), microcrystalline cellulose (Avicel) and dicalcium phosphate dehydrate (Emcompress).Different directly compressible adjuvants have different effectiveness in the formulation of tablets through direct compression. Paracetamol powder, a potent analgesic agent, with apparent poor flow properties as indicated in its inability to flow through a 13 mm diamneter glass funnel was compressed directly by the careful selection of previously examined directly compressible adjuvants. Previously examined wet binders were aso used in the wet granulation of paracetamol powder.

History:-

This mild pain reliever has a history that dates back to 1893.This was the first time it got clinical use. It wasn't available for commercial use in the United States until 1950. Australia started using it commercially in 1956.Originally sold under the name Triagesic, this drug was a combination of paracetamol, caffeine, and aspirin.After the initial introduction in 1950,the manufacturers removed it from commercial use until 1953. The SterlingWinthrop Company began marketing it under the name Panadol.McNeil Laboratories sold it under the name of Children's Tylenol Elixir in 1955in the United States.You could only get Paracetamol by prescription until 1959.It then switched to an over-the-counter medication.In

1956,Frederick Stearns &Co began selling this drug in the United Kingdom in 500-milligram tablets under the name Panadol. From the 1960s to the 1980s, the drug's popularity increased rapidly. It is now considered to be a household drug. Any patents have expired and there are dozens of generic versions of Paracetamol available today.

DRUG PROFILE OF PARACETAMOL

1.DURG DESCRIPTION:

NAME:PARACETAMOL
SYNONYM-Acetaminophen,Paracetamol,Paracetanol
CHEMICAL FORMULA-C8H9NO2
IUPAC NAME-4-Hydroxy acetanilide
Average molecular weight-151.2g permole
Other characteristics-Awhite,crystallinepowder,sparingly soluble in water,freely soluble in alcohol, very slightly soluble inmethylene chloride

Sr.No.	Genetic Name	Dose	Dosage	Brand names	Manufacturer
1	Paracetamol	500mg	Tablets	Panadol	GSK
2		500mg	Tablets	Pedrol	Stanley
3		120mg\5ml	suspension	Samophen	Adamjee

Indication
Paracetamol is one of the most commonly used "over the counter"analgesic for:

·Headache
·Musculoskeletal pain
·Dismennorhea

Novel Uses:

1g.iv Paracetamol was found to be equally successful to ketamine in preventing remifentanil-induced hyperalgesia, with the added advantage of reduced the time to extubation and full anaesthetic recovery.

During i.v. regional anaesthesia, adding paracetamol to the injected lidocaine was shown to improve the overall quality of the block. Onset of motor block was sooner, tourniquet pain was reduced, and recovery of motor and sensory block was delayed, resulting in lower intraoperative pain scores and total systemic analgesic requirements.
Side effects:-1.Liver Damage
2.Skin reactions
3.asthma

Other some usual side effects are as follow:
4.Nausea
5.Vomiting
6.Stomach pain
7.Loss of appetite

Mechanism of action:-

Although paracetamol was discovered over 100 years ago and has been widely used in medical practice for more than half the century, its mechanism of action has not been elucidated until now).It has analgesic and antipyretic properties similarly to NSAIDs,but contrary to them, it does not possess any anti-inflammatory activity. When applied in recommended doses, it does not induce typical for NSAIDs gastrointestinal side effects.However,it suppresses prostaglandin production likewise NSAIDs. Due to lack of an anti-inflammatory component, paracetamol has not been regarded as a member of the NSAIDs family in pharmacological text-Books,although what is interesting, it has been Always discussed together with these drugs. Therefore, the discussion on the mechanism Action of paracetamol should begin from the analysis of NSAIDs action. Paracetamol (acetaminophen) is generally considered to be a weak inhibitor of the synthesis of prostaglandins (PGs). However, the in vivo effects of paracetamol are similar to those of the selective cyclooxygenase-2 (COX-2)inhibitors.Paracetamol also decreases PG concentrations in vivo, but, unlike the selective COX-2 inhibitors,paracetamol does not suppress the inflammation of rheumatoid arthritis. It does,however,decrease swelling after oral surgery in humans and suppresses inflammation in rats and mice. Paracetamol is a weak inhibitor of PG synthesis of COX-1 and COX-2 in broken cell systems,but,by contrast, therapeutic concentrations of paracetamol inhibit PG synthesis in intact cells in vitro when the levels of the substrate arachidonic acid are low (less than about 5 μmol/L). When the levels of arachidonic acid are low, PGs are synthesized largely by COX-2 in cells that contain both COX-1 and COX-2.Thus,the apparent selectivity of paracetamol may be due to inhibition of COX2-dependent pathways that are proceeding at low rates. This hypothesis is consistent with the similar pharmacological effects of paracetamol and the selective COX-2 inhibitors. COX-3, a splice variant of COX-1, has been suggested to be the site of action of paracetamol, but genomic and kinetic analysis indicates that this selective interaction is unlikely to be clinically relevant. There is considerable evidence that the

analgesic effect of paracetamol is central and is due to activation of descending serotonergic pathways,but its primary site of action may still be inhibition of PG synthesis.The action of paracetamol at a molecular level is unclear but could be related to the production of reactive metabolites by the peroxidase function of COX-2,which could deplete glutathione, a cofactor of enzymes such as PGE synthase.

Additionally,paracetamol influences transient receptor potential (TRP)channels and voltage-gated Kv7 potassium channels and inhibits T-type.2calcium channels. It also exerts an impact on L-arginine in the nitric oxide (NO)synthesis pathway. However, not all of these effects have been clearly confirmed. Therefore, the aim of our paper was to summarize the current state of knowledge of the mechanism of paracetamol action with special attention to its safety concerns.

Excipients Used In solid dosage form:-

Excipients are inert substances used as diluents or vehicles for a drug.In the pharmaceutical industry it is a catch-all term which includes various subgroups comprising diluents or fillers, binders Or adhesives,disintegrates,lubricants,glidant,flavours', colors and sweeteners. All of these must meet certain criteria as follows:-

a)Physiologically inert.
b)Acceptable to regulatory agencies.
c)Physiologically and chemically stable.
d)Should not interfere with the bioavailability of the drug.
e)Commercially available in the form and purity commensurate to pharmaceutical standards.f) inexpensive.

Excipient category	Function in formulation	Working principle	Examples
Diluents	Fillers	Make up the bulk of solid unit dosage forms when drug itself is inadequate to produce the bulk	Lactose,Directly compressible Starches,Dextrose,Sorbitol, Microcrystalline
Binders and Adhesives	Impart cohesive qualities to powdered material.	Improves free flow qualities by formulation of granules to desired hardness and	Acacia,Gelatin, Starch paste,
Lubricants	Reduce interparticular friction,prevent adhesion of tablet material to the surface of dies and punches facilitate easy ejection of tablet from die cavity and improve the rate of flow tablet granulat	Interpose a film of low shear strength that interface between the tabletting mass and die wall	Talc,Stearic acid, Magnesium stearate,Calcium stearate, Polyethylene glycol. Surfactants, vegetable oil.
Glidants	Improve flow characteristics of powder mixture.	Added in dry state prior compression,it reduces friction between particle	Colloidal Silicone dioxide (Carbosil). Asbestos free starch Corn starch.
Disintegrants	Facilitate breakup or disintegration after administration	Function by drawing water into the tablet,swelling it and burst apart	Starches,Clays, Cellulose,Cross linked polymers, Modified starches such as Primogel
		causing the tablet burst apart	and Explotab Veegum HV. Crosscarmalose, Cross Povidone, Sodium starch glycolate.

Flavors	Limited to chewable tablets/tablets intended to dissolve in mouth.	Mask unpleasant taste	Spray dried and other flavors,syrup
Sweeteners	Impart sweet taste to the formulation;use is limited to chewable tablets.		Mannitol, Saccharin.etc

Coloring agents	Impart aesthetic appearance to dosage form. disguising off color drugs,product identification		FD and C, D and C dyes and lakes.

Pharmacokinetics data:-

1.Absorption

Regular-release

Oral acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract primarily in the small intestine. This absorption process occurs by passive transport. The relative bioavailability ranges from 85% to 98%.

Extended-release

Each bilayer acetaminophen extended-release,650-mg caplet contains 325 mg of immediate-release acetaminophen on one side and, on the other side, 325 mg of acetaminophen in a matrix formulation designed to slowly release. In vitro data indicate that two 650-mg extended-release caplets (containing a total of 1300 mg of acetaminophen) release 88% and 95% of the drug within 3 and 5hours,respectively.

Administration of a single dose of two 650-mg, extended-release caplets,the average maximal plasma concentrations occurred within 0.5 to 3 hours following ingestion and ranged from 6.9 to 14.1 μg/mL.

2.Distribution

Acetaminophen appears to be widely distributed throughout most body fluids fat. The apparent volume of distribution of acetaminophen is 0.95 L/kg.A relatively small proportion (10% to 25%) of acetaminophen is bound to plasma proteins and binding is only slightly increased in plasma concentrations associated with overdose. The sulfate and glucuronide metabolites do not bind to plasma proteins even at relatively high concentrations.Spinal fluid low protein binding and low molecular weights allow acetaminophen to pass through the blood-brain barrier. The peak concentration of acetaminophen incerebrospinal fluid is reached after 2 to 3 hours. Placental barrier analysis of urine samples has demonstrated the passage of unconjugated acetaminophen via placental transfer. When given to the mother in therapeutic doses,acetaminophen crosses the placenta into fetal circulation as early as 30 minutes after ingestion,although the difference in serum concentration between maternal and cord blood is not statistically significant. In the foetus,acetaminophen is effectively acetaminophen metabolized by sulfate conjugation. Breast miIk maternal ingestion of acetaminophen in recommended analgesic doses does not present a risk to the nursing infant. Amounts in milk range from 0.1% to 1.85% of the ingested maternal dose. These studies have established that, even at the time of peak acetaminophen concentration in human breast milk, the nursing infant would receive less than 2% of the maternal dose. Accordingly, breast feeding need not be interrupted because of maternal ingestion of recommended doses of acetaminophen.

3.Metabolism

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

a) Conjugation with glucuronide
b)Conjugation with sulfate
c) Oxidation via the cytochrome, P450-dependent, mixed-function oxidative enzyme pathway to form a reactive intermediate metabolite,which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

Two additional minor pathways also are possibly involved in acetaminophen metabolism:-

a) Hydroxylation to form 3-hydroxy-acetaminophen
b) Methoxylation to form 3-methoxy-acetaminophen.

These metabolites are further conjugated with glucuronide or sulfate.Inadults,the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants,theSulfate conjugate predominates.

4.Excretion

The biologic half-life of acetaminophen in normal adults is approximately 2to 3hours in the usual dosage range. It is somewhat shorter in children and somewhat longer in neonates and in patients with cirrhosis. The elimination half-life is approximately 3 hours for the extended-release product.The elimination half-life of acetaminophen in the cerebrospinal fluid according to pooled data is 3.2 hours. Acetaminophen is eliminated from the body primarily by formation of glucuronide And sulfate conjugates in a dose-dependent manner.

Method of preparation:-

D Direct compression:-

As its name implies,direct compression involves direct compression of powdered materials into tablets without modifying the physical nature of the materials itself. The technology involved in this method assumes great importance in the tablet formulations,because it is often the cheapest means,particularly in the production of generics that the active substance permits.

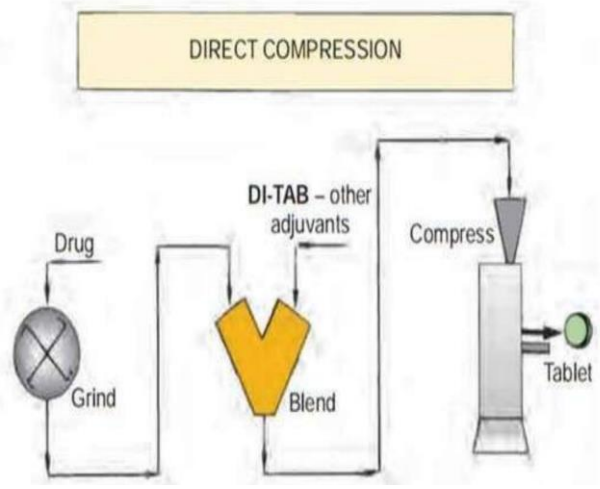
Direct compression avoids many of the problems associated with wet and dry granulations.

Its successful application in tablet formulation rests on two fundamental issues:-

1.availability of suitable excipients
2.The availability of suitable machinery.

A stepwise summary of the manufacturing steps used in the manufacture of tablets by the dry granulation method are listed below:-

1)Milling of therapeutic agent and excipients
2)Mixing of milled powders, disintegrants and lubricants
3)Compression into tablets.

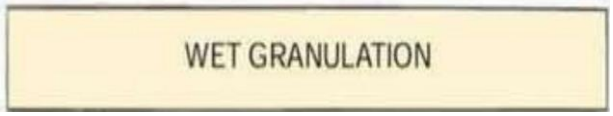


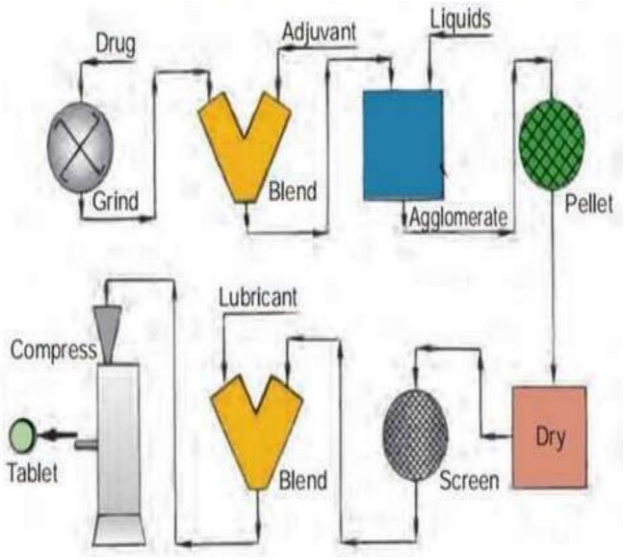
I. Wet granulation:-

Wet granulation is a widely used method for the production of compressed tablet. It is essentially a process of size enlargement involving several steps and the use of an adhesive substance known as binder. The granules produced using this method of granulation has a greater probability of meeting all the physical requirements for tablet formation.

A stepwise summary of the manufacturing steps used in the manufacture of tablets by the wet granulation method are listed below:-

1)Weighing,milling and mixing of the APIs with powdered excipients (excluding the lubricant)
2)Preparation of binder solution
3) Mixing of binder solution with powders to form a damp mass
4)Screening the dampened powder into pellets or granules (wet screening)using 6-12 mesh screen 5) Drying of moist granules
6) Sizing the granulation by dry screening using 14-to 20-mesh screen
7) Mixingof the dried granules with lubricant and disintegrants
8)Compression of granules into tablets





II. Drygranulation:-

Dry granulation also referred to as precompression or double compression Dry granulation is typically used in the manufacture of tablets if the formulation ingredients are too fluffy or too susceptible to flowability problems for direct compression

Methods of dry granulation:-

1) Slugging technique:-

This process involves compression of primary powder particles into large flat tablets or pallets using a tablet press or, more usually,a large heavy-duty rotary press.The resultant compact is then milled using a hammer mill or other conventional milling equipment. The milled slugs are passed through a screen of desired mesh for sizing.Lubricant is added in the usual manner, and the granules compressed into tablets.

2) Roller compaction:-

Roller compaction also referred to as ribbon blending.It is a process where formulation ingredients are continuously passed between two counter-rotating rollers where it is densified and consolidated into a sheet of solid mass.Depending on the type of rollers used,the feed material may be compacted into dense ribbon-like materials known as flakes(smooth rolls) or dense briquettes (almond or stick-shaped) if the rollers have grooved or etched surfaces. The compacted materials are further milled, sized, lubricated and compressed into tablets.

Evolution of paracetamol tablet,:- Official test:-

1)weightuniformity 2) Content uniformity 3) Dissolution 4) Disintegration

1)Weight uniformity

Twenty (20) tablets were weighed .Individually on the Mettler electric balance (P163 Mettler instrument AG) from which the mean was calculated and the percentage deviations and standard error of the mean (SEM) determined.

USP Official Limits

Tablet weight	Limit
130mg or less	±10%
130-324mg	±7.5%
>324mg	±5%

BP official Limits:-

Tablet weight Limit	
80mg or less	±10%
80-250mg	±7.5%
>250mg	±5%

IP Official Limits:-

Tablet weight Limit	
80mg or less	±10%
80-250mg	±7.5%
>250mg	±5%

2)Content Uniformity:-

Content Uniformity is a pharmaceutical analysis parameter for quality control of tablets.Multiple tablets are selected at random and a suitable analytical method is applied to assay the individual content of the active ingredient in each capsule or tablet.The preparation complies if not more than

one (all within limits)individual content is outside the limits of 85 to 115% of the average content and none is outside the limits of 75 to 125% of the average content.The preparation fails to comply with the test if more than 3 individual contents are outside the limits of 85 to 115% of the average content or if one or more individual contents are outside the limits of 75% to 125% of the average content.

3)Dissolution:-

Dissolution is a process in which a solid substance solubilise in a given solvent mass transfer from the solid surface to the liquid phase.

Based on sink or non-sink conditions dissolution apparatus are classified as-

1)Closed Compartment Apparatus
2)Open Compartment Apparatus

Types of Dissolution Apparatus:-

USP BP	IP		
TYPE-1	Rotating basket	Basket type	Paddle type
TYPE-II	Paddle type	Paddle type	
TYPE-III	Reciprocating cylinder	Flow through cell	
TYPE-IV	Flow through cell		
TYPE-V	Paddle over disc		
TYPE-VI	Rotating cylinder		
TYPE-VII	Reciprocating Disc		

3)Disintegration test:-

Disintegration is the break down process of tablet into smaller particles and is the first step towards dissolution used to determine the time of the medication in the human body.

Disintegration time for tablet

Types of tablet	Disintegration time		
	IP	BP	USP
Uncoated	15min	15min	5min
Coated	60min	30min	-
Film	30min	-	-
Enteric	120min		
Dispersible	3min	3min	3min

1 + 2

Non-Official Tests of Tablets:-

1)Description/Appearance
2)Thickness and Diameter
3)Hardness
4)Organoleptic properties
5)Friability

1)Description/Appearance:-
Thickness of tablets:-
The thickness of the tablet is the only dimensional variable related to the tablet compression process. Generally, it is measure with a micrometer. The thickness should control within ±5% variation of a standard value.
2)Diameter and Shape of Tablets:-

The diameter and shape of the tablets should control by the diameter and shape of the die and punches during the compression process. USFDA recommends that the diameter of the tabet should be 8 mm or less than 8 mm and should not exceed 22 mm.

3)Hardness of Tablets:-

The breaking force of tablets is commonly called "hardness" in the pharmaceutical literature; however, the use of this term is misleading according to USP. Certainly tablets require a definite amount of hardness to withstand mechanical

shocks of handling in manufacture, packaging, and transportation without affecting the disintegration limit.

4)Organoleptic properties:-

Color: Tablet colour is crucial for identification and patient acceptance.
Odour: Some types of tablets such as ODT tablets,chewable tablets have an odour to make a pleasant taste and improve patient acceptance.Besides in some tablets, flavouring agents are used within coating material to mask bad odour.
Taste: Taste is important for patient acceptance especially for ODT tablets,chewabletablets,and dispersible tablets.

5)Friability:-

Is another major of strength along with hhardneshardness.Rochefriabilater is used for checking the friability is shown below.Tabletsundergoes combined process of abrasion and shock during Friability.
Operated at 25 rpm at 4 minute that is 100rotations
Tablets are dropped from 6 inches
Tables weighing ≤650 mg 10 tablets are taken for testing.Limit:-0.5-1%.

SPECTROPHOTOMETRIC METHOD DEVELOPMENT

Ultraviolet-Visible spectrophotometry.

UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in soluion.Instrument which measure the ratio, or function of ratio,of the intensity of two beams of light in the U.V-Visible region are called Ultraviolet-Visible spectrophotometers.

In qualitative analysis, organic compounds can be identified by use Of spectrophotometer, if any recorded data is available, and quantitative Spectrophotometric analysis is used to ascertain the quantity of molecular species absorbing the radiation. Spectrophotometric technique is simple, rapid,moderately specific and applicable to small quantities of compounds. The fundamental law that governs the quantitative spectrophotometric analysis is the Beer-Lambert law.

Beer's law: It states that the intensity of a beam of parallel monochromatic radiation decreases exponentially with the number of absorbing molecules. In other words, absorbance is proportional to the concentration.

Lambert's law: It states that the intensity of a beam of parallel monochromatic radiation decreases exponentially as it passes through a medium of homogeneous thickness. A combination of these two laws yields the Beer-Lambert law.

Beer-Lambert law: When beam of light is passed through a transparent cell containing a solution of anabsorbing substance,reduction of the intensity of light may occur. Mathematically, Beer Lambert law is expressed as
A=abc
Where,A=absorbance or optical density
A=absorptivity or extinction coefficient
B=path length of radiation through sample(cm)C=concentration of solute in solution.
Both b and a are constant so a is directly proportional to the Concentration c
When c is in gm/100 ml, then the constant is called A(1%,1cm)

$$A = A\frac{1\%}{1cm}bc$$

Quantification of medicinal substance using spectrophotometer may carried out by preparing solution in transparent solvent and measuring it's absorbance at suitable wavelength. The wavelength normally selected is wavelength of maximum absorption (λmax), Where small error in setting the wavelength scale has little effect on measured absorbance. Ideally, concentrationshould be adjusted to givean absorbance of approximatel0.9, around which the accuracy and precision of the measurements are optimal.

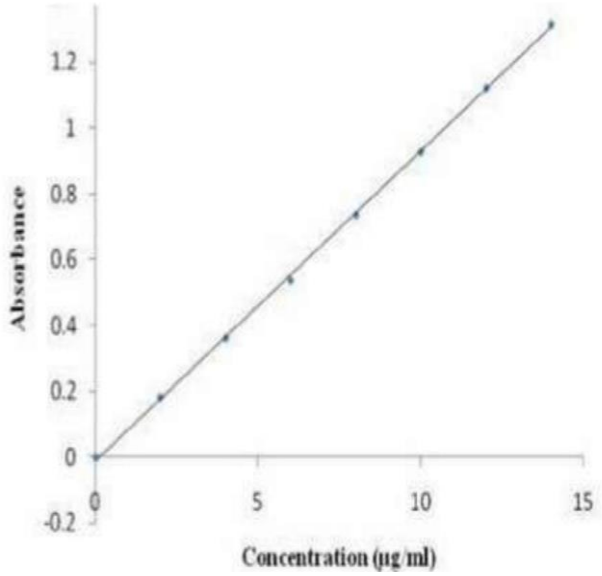
The assay of single component sample,which contains other absorbing substances, is then calculated from the measured absorbance by using one of three principal procedures. They are, use of standard absorptivity value,calibration graph and single or double point

standardization. In standard absorptive value method, the use of standard A (1%, 1 cm) or E values are used in order to determine its absorptivity. It is advantageous in situations where it is difficult or expensive to obtain a sample of the reference substance.In calibration graph method, the absorbances of a number of standard solutions of the reference substance at concentrations encompassing the sample concentrations are measured and a calibration graph is constructed.The concentration of the analyte in the sample solution is read from the graph as the concentration corresponding to the absorbance of the solution. The single point standardization procedure involves the measurement of the absorbance of a sample solution and of a standard solution of the reference substance.The concentration of the substances in the sample is calculated from the proportional relationship that exists between absorbance and concentration.

Ctest=(AtestxCstd)/Astd

Where Ctest and Cstd are the concentrations in the sample and standard solutions respectively and Atest and Astd are the absorbances of the sample and standard solutions respectively. For assay of substance/s in multi component samples by spectrophotometer; the following methods are being used routinely, which includes

Simultaneous equation method
Derivative spectrophotometric method
Absorbance ratio method (Q-Absorbance method)
Difference spectrophotometry
Solvent extraction method



Calculation formula used

1.Calculation formula for % assay of Paracetamol

Mean Test Absorbance ilution of Standard Mean Test Weight %Assay xPotency of Standard Mean Standard Absorbance Dilution of Sample Label Claim.

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