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Studies on the Film Coating Potential of *Anacardium Occidentale* (Cashew Tree) Gum

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirement for the Master of Philosophy (Mphil) Pharmaceutics Degree

By

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DECLARATION

The experimental work outlined in this thesis was carried out in the Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, KNUST. This work has not been submitted for any other degree.

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DEDICATION

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This thesis is **DEDICATED** to my dear mum, Mama Lydia and my cherished siblings for their love and constant support in prayer.

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Great is Thy faithfulness, O Lord my God. I give all thanks, praises and glory to my God and Father above for all His provisions and protection. It is He, who has brought me to this great height and still holding me up.

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ABSTRACT

This research work involved the study of *Anacardium occidentale* (cashew) gum as a material for pharmaceutical film coating. Both the crude and purified forms of the gum were evaluated for some physicochemical properties. The percentage yield for the purification was appreciable. The gum was found to be acidic and its viscosity significantly increased with increasing concentration and storage time. Both crude and purified gums had acceptable insoluble matter and moisture content. Polymeric films were prepared from homogenous solutions of the purified cashew gum only and mixtures of the cashew gum with either hydroxypropyl methylcellulose (HPMC) or carboxymethyl cellulose (CMC) using the solvent casting method in plastic petri dishes, using different plasticisers. The physical (weight and thickness) and mechanical (folding endurance, tensile strength, percentage elongation, Young's modulus) properties of these films were determined. Paracetamol tablets were prepared and used as the model drug for the research work. The tablets were film coated with solutions of the cashew gum using different coating times. Quality tests including uniformity of weight, thickness, hardness, friability, disintegration time, assay and dissolution on both the uncoated and film coated tablets were conducted. The results obtained established that propylene glycol is not a suitable plasticiser for cashew gum and that blending cashew gum with hydroxypropyl methylcellulose or carboxymethyl cellulose produced non – uniform and films of poor clarity respectively. Cashew gum on its own produced transparent and smooth, but brittle films. Addition of plasticisers to the gum imparted flexibility to the films. Increasing cashew gum and plasticiser concentrations in the films increased the folding endurance and elongation of the films. Tensile strength was enhanced when gum amount was increased but a decrease in tensile property was observed when plasticiser amount was increased. Young's modulus decreased when both cashew gum and plasticiser amounts were increased. Both uncoated and coated tablets passed all the quality tests. Application of the gum as a film coat to paracetamol tablets enhanced the mechanical strength of the tablets, in terms of friability and hardness. The rate of drug release was higher for the uncoated paracetamol tablets than for the film coated ones. The percentage drug release in phosphate buffer (pH-6.8) was higher than in 0.1M HCl dissolution medium. Film coating of core paracetamol tablets did not significantly impact on the immediate-release nature of the tablets. The mechanism of drug release from the tablets was found to be by diffusion. Cashew gum can therefore be used successfully as a film coating agent for immediate-release tablets.

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CHAPTER ONE

1.0 GENERAL INTRODUCTION

1.1 BACKGROUND

Today, once a good tablet has been formulated, it is often coated. This is because coated tablets have several advantages over the uncoated ones. Coated tablets have enhanced mechanical strength thereby facilitating handling; unpleasant tastes and odours are effectively masked aiding patient compliance, and special drug release characteristics are imparted so that enteric and modified drug release can be achieved. Coating also protects drugs from the environment, particularly light and moisture. Sugar coating was one of the earliest methods to achieve this but it is an arduous, time consuming process resulting in a shift to film coating.

A film coating solution consists of a polymer (the film former), plasticiser, pigments and the solvent. Various polymers, mostly ethers of cellulose such as hydroxypropyl methylcellulose, ethyl cellulose and methylcellulose are being used as film coating agents. There is however a high demand for natural excipients since they are less costly, non-toxic and freely available.

Naturally occurring gums with desired pharmaceutical properties are needed to replace synthetic ones. Gums are translucent amorphous substances and polymers of a monosaccharide or mixed monosaccharides and many of them are combined with uronic acids. The nature of the compounds involved influences the properties of different gums.

Cashew plantations abound in Ghana and the tree produces a lot of gum. Gum from the cashew tree (*Anacardium occidentale)*, which is a plant exudate, has physico-chemical and rheological properties similar to gum Arabic, which is obtained from *Acacia Senegal*. Gum Arabic serves as a coating agent and film former in panned confections such as chocolate pebbles (Ohr, 2001). However, its high cost has led to the assessment of other tree gums. Evaluation of cashew gum for film forming properties is therefore a step in the right direction. Many parts of the cashew plant are used. It is mainly known for its nuts, which are used as food ingredients, but the fruit can also be utilised in the making of cashew wine. Cashew gum extraction represents one more source of revenue for the producer and an essential raw material for the local pharmaceutical companies.

1.1.1 JUSTIFICATION OF WORK

In the pharmaceutical industry gums and mucilages are widely used for conventional and novel dosage forms. They are used for their demulcent nature in cough preparations, as bulk laxatives, as excipients such as binders, disintegrants, and emulsifiers, among others. Being natural, they have several advantages over synthetic and semi-synthetic ones because they are biodegradable, biocompatible, non-toxic, less expensive, environmentally-friendly, widely available, better tolerated and edible. They can also be tailored by modification processes so as to possess properties that would give them the ability to compete with the synthetic ones or even have better formulation properties.

Most solid oral dosage forms, particularly tablets are more often than not film-coated for several reasons including protection from the environment (light and moisture), to mask unpleasant taste and odour, to improve appearance, impart enteric properties and to modulate the release of medicaments. Film coating materials that are usually employed are the cellulose derivatives hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), ethyl cellulose (EC)

and others such as polyvinyl pyrrolidone (PVP). Local manufacture of medicines is very expensive since most companies have to import these raw materials thereby making products expensive.

There is therefore a need to have natural, locally available alternatives to these synthetic, imported film coating agents. In order for this substitution to be appropriate, the natural gums must be investigated to ensure that they possess the requisite qualities that would make them useful and comparable with the synthetic ones. This would encourage the cultivation of these gums, one of which is the cashew gum for use in the local pharmaceutical industries.

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1.1.2 SCOPE OF RESEARCH

The research would basically entail:

- Physicochemical characterization of cashew tree gum
- Formulation of polymeric solutions of cashew gum only
- Formulation of polymeric solutions containing a combination of cashew gum and other polymers [hydroxypropyl methylcellulose (HPMC) and carboxymethyl cellulose (CMC)]
- Preparation of free films from solutions of cashew gum only and cashew gum in combination with HPMC and CMC
- Evaluation of physical and mechanical properties of drug-free films
- Formulation of Paracetamol tablets (as the model drug for research) and their assay
- Film coating of Paracetamol tablets with varying concentrations of cashew gum solutions
- Evaluation of both uncoated and film-coated tablets using British Pharmacopoeial as well as and other tests
- Study of the release profile of film coated tablets

- Study of the kinetics and mechanism of release for the uncoated and coated tablets

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1.2 INTRODUCTION

1.2.0 TABLETS AS A DOSAGE FORM

Tablets are oral solid preparations containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Some are swallowed whole, others are chewed; some are dissolved or dispersed in water before administered and others are retained in the mouth where the active ingredient is liberated. They are usually right, circular solid cylinders, the end surfaces of which are flat or convex. They may have break-marks and may bear a symbol or other markings.

Tablets are prepared primarily by compression. They are often coated to provide protection from the environment (i.e. air, light, moisture) for drug stability purposes, or from the acid contents of the stomach, as well to mask unpleasant tastes or odours. They are more popular than other dosage forms for a number of reasons. These include the convenience and safety of the oral route, their physical and chemical stability, accurate drug dosing due to their preparation procedure and ease of handling. Others are the fact that tablets can be mass produced, and have

consistent quality due to the quality-controlled production procedures which are available for the dosage form (Aulton, 2001).

1.2.1 TABLET TYPES

Tablets can be classified as follows (based on their drug-release profile):

- Immediate-release tablets: These are the most common type of tablets, where the drug is rapidly released after administration or the tablet is dissolved and administered in the form of a solution. They include;
    - Disintegrating tablets
    - Chewable tablets
    - Effervescent tablets
    - Sublingual and buccal tablets
- Extended-release: Here, the drug is released slowly at a nearly constant rate
- Delayed-release: For this type, the drug is released from the dosage unit some time after administration.
    - Enteric tablets

Other tablet classes are coated, uncoated, soluble/ dispersible and lozenges. Lozenges dissolve slowly in the mouth and are intended for local action in the mouth or throat. They are thus described as slow-release tablets for local drug treatment (Aulton, 2001).

1.2.2 QUALITY CHARACTERISTICS OF TABLETS

It is essential that tablets contain the right dose of the drug, and must have an elegant appearance with consistent weight, size and appearance. Tablets must be biocompatible and the drug, bioavailable to the patient. It is very necessary that they are very stable under chemical, microbiological and physical conditions in the course of their lifetime. Finally, a tablet must be safely packaged, have sufficient mechanical strength and be acceptable to the patient (Aulton, 2001).

1.2.3 BIOAVAILABILITY OF TABLETS

The rate and/or extent of absorption of a drug from the gastrointestinal tract is influenced by many physiological factors and physicochemical properties associated with the drug itself. The

bioavailability of a drug is also influenced by factors associated with the formulation and production of the dosage form. Presently, many dosage forms are being designed to affect the release and absorption of drugs, for example controlled- release systems and delivery systems for poorly soluble drugs.

The type of dosage form and its method of preparation or manufacture can influence bioavailability. The type of oral dosage form also influences the number of possible intervening steps between administration and the appearance of dissolved drug in the gastrointestinal fluids and finally in circulation. In general, drugs must be in solution in the gastrointestinal fluids before absorption can occur. Thus the greater the number of intervening steps, the greater will be the number of potential obstacles to absorption and the greater will be the likelihood of that type of dosage form reducing the bioavailability exhibited by the drug (Aulton, 2001).

1.2.3.1 UNCOATED TABLETS

When a drug is formulated as a compressed tablet there is an enormous reduction in the effective surface area of the drug, owing to the granulation and compression processes involved in tablet making. These processes necessitate the addition of excipients, which serve to return the surface area of the drug back to its original precompressed state (Aulton, 2001).

Disintegration of the tablet into granules causes a relatively large increase in effective surface area of drug and the dissolution rate may be likened to that of a coarse, aggregated suspension. Further disintegration into small, primary drug particles produces a further large increase in effective surface area and hence dissolution rate. The dissolution rate is probably comparable to that of a fine, well dispersed suspension. Disintegration of a tablet into primary particles is thus important, as it ensures that a large effective surface area of a drug is generated in order to facilitate dissolution and subsequent absorption. However, simply because a tablet disintegrates rapidly does not necessarily guarantee that the liberated primary drug particles will dissolve in the gastrointestinal fluids, and that the rate and extent of absorption are adequate (Aulton, 2001).

1.2.3.2 FILM COATED TABLETS

The presence of a coating presents a physical barrier between a tablet core and the gastrointestinal fluids: coated tablets therefore not only possess all the potential bioavailability problems associated with uncoated conventional tablets, but are subject to the additional potential problem of being surrounded by a physical barrier. In the case of a coated tablet which is intended to disintegrate and release drug rapidly into solution in the gastrointestinal fluids, the coating must dissolve or disrupt before these processes can occur. The physicochemical nature and thickness of the coating can thus influence how quickly a drug is released from a tablet.

The coating of a tablet core by a thin film of a water-soluble polymer, such as hydroxypropyl methylcellulose, should have no significant effect on the rate of disintegration of the tablet core and subsequent drug dissolution, provided that the film coat dissolves rapidly and independently of the pH of the gastrointestinal fluids. However, if hydrophobic water-insoluble film-coating materials, such as ethyl cellulose or certain acrylic resins, are used, the resulting film coat acts as a barrier which delays and/ or reduces the rate of drug release. Thus these types of film-coating materials form barriers which can have a significant influence on drug absorption.

1.2.4 TABLET COATING

Tablet coating is the application of a coating material to the exterior of a tablet with the intention of conferring benefits and properties to the dosage form over the uncoated variety. On few occasions coatings may also be applied to hard-shell and soft elastic capsules.

1.2.4.1 TYPES OF TABLET COATING

1.2.4.2 FILM COATING (MOST POPULAR)

It involves the deposition, usually by spraying, of a thin uniform film of a polymer formulation around a tablet. This process confers several benefits and properties over the uncoated variety such as masking of bitter/unpleasant taste or odour, making swallowing easy and protecting moisture and light sensitive drugs which all aid in patient compliance and ensures that a non-degraded drug is consumed by the patient. Also in handling and packaging, film coating enables tablets to maintain their integrity due to the mechanical strength imparted by the coating. Film

coating (coloured) also aids in easy identification of products as well as imparting controlled release properties on the dosage form if desired.

A suitable formulation for film coating must contain a suitable polymer, plasticiser, an appropriate solvent or combination of solvents, a pigment/colourant if desired and a surfactant may also be added to modify some properties of the formulation such as viscosity. For a good formulation these constituents have to be present in fitting proportions.

Types of film coating:

- Immediate-release (non-functional) film coating:

They do not affect the biopharmaceutical properties of the tablet. They are readily soluble in water.

- Modified-release (functional) film coating:

This allows the drug to be delivered in a specific manner; i.e. it affects drug release behavior. Modified release film coatings are sub-classified into;

1. Delayed-release coating (enteric coating): This type of coating is only soluble in water at pH ≥5-6 and is intended to protect the drug from gastric acidic pH (for acid labile drugs). It is used for colonic drug delivery systems.

2. Extended-release coating: This coating is mostly water-insoluble. It is designed to ensure a consistent drug release manner over a long period of time (6-12 hr) and thus decreasing dosing regimen and improving patient compliance (Aulton, 2001).

1.2.4.3 SUGAR COATING

It involves successive application of sucrose-based coating formulations to tablet cores. Water evaporates from the syrup leaving a thick sugar layer around each tablet which is often shiny and highly colored. It involves a number of steps (six), making the procedure time consuming.

The process begins with sealing (waterproofing), which is the application of one or more coats of a waterproofing substance, such as pharmaceutical shellac (traditionally) or synthetic polymers, such as cellulose acetate phthalate (CAP). The next step is subcoating, where large quantities of sugar-coatings are usually applied to the tablet core (typically increasing the tablet weight by 50-

100%) in order to round off the tablet edge. Antiadherents e.g. talc may be added after partial drying to prevent sticking of the tablets together. This is followed by smoothing, (since the subcoating results in tablets with rough surfaces) using a thick sucrose syrup coating to facilitate the color application (which requires a smooth surface). The color coatings usually consist of thin sucrose syrup containing the requisite coloring materials producing a smooth tablet but somewhat dull in appearance. For a glossy finish, the final stage (polishing) involves the application of waxes (beeswax or carnauba wax). Lastly, printing of manufacturer' logo, product name, dosage strength or other appropriate code using special edible inks for identification may be done (Aulton, 2001).

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1.2.4.4 COMPRESSION/ PRESS COATING (LESS POPULAR)

This has gained interest for creating modified-released products. It is dry process involving the compaction of granular materials around a preformed tablet core using specially designed tableting equipment. It is a complex process, as the tablet may be tilted when transferred to the second die cavity. Compression coating is usually done to separate incompatible materials (one in the core and the other in the coat). It may also be used to create modified-release products (Aulton, 2001).

1.2.4.5 GELATIN COATING (NOT COMMON)

This is a quite recent innovation. The innovator product, the gelcap, is a capsule shaped compressed tablet coated with gelatin layer. This type of coating allows the coated product to be about one-third smaller than a capsule filled with an equivalent amount of powder. It also facilitates swallowing and the coated tablet is more tamper evident than an unsealed capsule. It may be also performed for granules (coated granules) to be compressed into tablet or filled into a capsule.

1.2.5 SHIFT FROM SUGAR TO AQUEOUS FILM COATING

Sugar was the first choice as coating agent however, sugar coating is a time consuming process, and the quality of finished product is dependent on the skills of operator.

These have led to the development of film coating technique which is mainly based on solutions of different polymers in various organic solvents, which are toxic in nature. As the level of

understanding regarding the toxic effects of these solvents increased, their use and exposure of workers to them were limited. Another area of concern too is their high cost.

A better choice is therefore to eliminate the use of organic solvents and start using water as the solvent system for tablet coating though it has some disadvantages. The main reason for using organic solvents was to avoid possible decomposition of active ingredients and many other process related problems such as over wetting, picking and sticking etc. which may occur with aqueous coating systems. However, decomposition of active ingredients, possible coating difficulties and all such problems are being sorted out by scientific evaluation (Pareek and Rajsharad, 2003b).

1.2.6 THE FILM COATING PROCESS

Film coating of tablets is a multivariable procedure, with many different factors, such as tablet core properties, coating equipment, coating liquid and process parameters which affect the final quality of a pharmaceutical product.

Tablet coating takes place in a controlled atmosphere inside a perforated rotating drum. The tablets are lifted and turned from the sides into the centre of the drum, exposing each tablet surface to an even amount of sprayed coating. The liquid spray coating is then dried onto the tablets by heated air drawn through the tablet bed. The air flow is regulated for temperature and volume to provide controlled drying and extraction rates, and at the same time, maintaining the drum pressure slightly negative relative to the room in order to provide a completely isolated process atmosphere.

The coating process is usually a batch driven task basically consisting of loading of tablets into pan, warming to the desired process temperature, spraying (application of the atomized coating formulation and rolling are carried out simultaneously), drying to remove the solvent, cooling and unloading/ product discharge (Amrutha, 2009).

The thickness of a film coat is usually from 20-100 μm after the film coating process is fully completed (Hogan, 1995).

1.2.7 THE COATING FORMULATION

Coating liquid may affect the final quality of the tablets. Different film formers have different chemical nature and different characteristics. Viscosity may affect the spreading of coating liquid across the surface of substrate. Surface tension may also affect in wetting of surface. Formulations may contain optional surfactants, plasticisers or pigments. These additional excipients can affect the viscosity of the coating solution, however the major factor controlling the formulation is the viscosity of the polymer grade being used and the concentration of polymer in the solution (METHOCEL, 2002).

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The optimization of film coating formulation is necessary to improve adhesion of the coating to the core, decrease bridging of intagliations, increase coating hardness or to improve any other property. Three major factors affect the film quality: tensile strength of the film coating formulation (mainly dependant on polymer properties), elasticity of the resultant film (mainly dependant on properties and quantity of plasticizer used) and the film-tablet surface interaction, which all depend on the coating liquid preparation (Pareek and Rajsharad, 2003a).

1.2.7.1 PROPERTIES OF COATING SOLUTION

Successful film coating depends not only on the core tablets and coating equipment but also on the coating solution. Several properties of the solution viscosity including the following have to be enhanced to achieve a successful film coat.

Solution viscosity is due to solids level. As viscosity is increased (above 200–250 cps), the droplet size produced by the spray guns increases. Large droplets, which are not easy to eliminate, result in a lower coating efficiency, and a rougher film surface. A low solids level in the coating solution also needlessly increase the process time and the time required to provide a protective film coating, thus resulting in increased tablet attrition. However, if a high solids level does not create an excessively viscous solution, it provides an excellent opportunity to reduce the volume of coating solution, and thus the coating time. High solution viscosity also has adverse effects on spreading of sprayed drops, which has to be optimized to achieve a good and

continuous film (Porter et al., 2009). The coating solution must therefore be formulated to have a sprayable solution viscosity (i.e. containing the right percentage solid content) regardless of the delivery system, since it affects the coating efficiency. Higher viscosities may however be possible under certain equipment conditions (METHOCEL, 2002).

The degree of tackiness of the coating preparation increases with an increase in plasticizer concentration due to softening of the polymer. To reduce the stickiness of a film and minimize agglomeration of the coated substrates, antiadherent compounds (e.g. talc) are generally included in coating formulations (Wesseling et al., 1999).

Also, the coating solution must be stable (chemically and physically) during the coating time. For example, settling-out of solution solids which occurs with solutions that contain an excessive percentage of solids or when the coating has insufficient suspending capacity can lead to blockage of the solution lines or the spray guns. There also has to be compatibility of the coating materials and also between the film-coating and the tablet core (Porter et al., 2009).

1.2.7.2 COMPOSITION OF FILM COATING FORMULATION

Film coating formulations usually contain the following components: polymer, plasticizer, colorants / opacifiers, solvent / vehicle, flavours and sweeteners, surfactants, antioxidants and antimicrobials/ preservatives.

1.2.7.3 POLYMER

This is the most important component of a film coating solution. It is the film former and must be capable of producing smooth thin films reproducible under the prescribed coating conditions.

As tablet coating technique was changed from sugar coating to film coating, polymers like methyl cellulose, hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC) etc. became the main coating materials in place of sugar. The higher viscosity grades of HPMC provide films with good tensile strength but having poor adhesion with the core tablet surface. The same

HPMC when dissolved in water give rise to many other problems like high solution viscosity. Water is a poor solvent for HPMC as compared to organic solvents; therefore, solution preparation is difficult.

The selection of a correct polymer system is very critical for the success of aqueous coating formulations. By selecting the lower viscosity polymers, the solid content in the coating formulation can be increased which will result in lesser amount of water required which in turn can increase the coating speed and reduce coating time (less time for solvent evaporation) (Pareek and Rajsharad, 2003b).

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1.2.7.4 POLYMERS (GUMS) USED AS FILM COATING MATERIALS

Polymers that are used as film formers are usually synthetic and semi-synthetic and include:

- Immediate - release coating polymers
    1. Cellulose derivatives e.g. hydroxy propyl methyl cellulose, HPMC (most widely used), methylcellulose, hydroxy propyl cellulose (HPC)
    2. Vinyl derivatives e.g. polyvinyl pyrrolidone (PVP), which as a result of inherent tackiness is usually used as a copolymer with vinyl acetate
- Modified – release coating polymers
    1. Extended - release
        a) Cellulose derivatives (that is the highly substituted forms) such as ethyl cellulose (EC)
    2. Enteric – coating
        a) Methacrylic acid copolymers
        b) Phthalate esters e.g. cellulose acetate phthalate (CAP)

1.2.7.4.1 BLENDING POLYMERS

It may at times be advantageous to blend polymers of varying types. For example, HPC is much more brittle than HPMC but it is a better adhesive. Used alone, the films from HPC may be tacky and cause problems like sticking or picking of tablets. But when used in combination with HPMC, a better film is produced and the HPC imparts a better adhesion.

Blends of methylcellulose (MC) and polyvinyl pyrrolidone (PVP) have also been used commercially. While PVP has poor film formation properties, it can be used at very high concentrations with very low viscosity in water unlike MC alone. This could be a method of increasing polymer concentration without detrimentally raising solution viscosity (METHOCEL, 2002).

1.2.7.5 SOLVENT

An ideal solvent system should contain not less than 30% and not more than 50% of the solvent that can dissolve the polymer. The most commonly used organic solvents were isopropanol alcohol and methylene chloride. Modern techniques now rely on water as a solvent because of the apparent drawbacks with the use of organic solvents (environmental, safety, financial and solvent residue issues). For conventional film coating the polymer should have good solubility in aqueous fluids to facilitate the dissolution of the active ingredient from the finished dosage form. However, where a modified-release action is required then a polymer system of low water solubility or permeability is chosen.

1.2.7.6 PLASTICISER

Films coatings prepared from pure polymers tend to be brittle and crack upon drying. The function of a plasticiser in a coating formulation is to soften films or make them less brittle. The addition of plasticisers to the coating liquid decreases the intermolecular forces along the polymer chains by relieving molecular rigidity.

Generally, water-soluble plasticizers are chosen for use in aqueous systems. Using a plasticizer can lead to smoother films, increase adhesion to the tablet surface, reduce logo bridging, and actually reduce cracking or chipping by improving film toughness (METHOCEL, 2002).

Recommended levels of plasticisers range from 1-50 % by weight of the film former. Commonly used plasticisers are oils/glycerides (e.g. castor oil, fractionated coconut oil), polyols (e.g. polyethylene glycol (PEG), glycerin, propylene glycol (PG)), organic esters (e.g. diethyl phthalate) and surfactants (e.g. tweens, spans). For aqueous coating PEG and PG are more used while castor oil and spans are primarily used for organic-solvent based coating solution. In general, only water-miscible plasticisers (PEG) can be used for aqueous-based spray systems and

vice versa. The plasticiser and the film former must be at least partially soluble or miscible in each other. The amount of plasticiser used is very important to film properties because if the film is over-plasticised it will lose toughness or may exceed the capacity of the polymer to hold the plasticiser (METHOCEL, 2002).

1.2.7.6 PIGMENTS

Pigments are used for coloration of tablets. The use of pigments (insoluble colours) has replaced the use of water-soluble dyes because they tend to be more chemically stable towards light, provide better opacity and covering power and optimise the impermeability of a given film to water vapour. Pigments or pigment dispersions are added to polymer solutions in amounts required to achieve the desired coloring while hiding or masking taste effects. Generally, the level of pigment used will be from 50-200% of the polymer weight in a coating solution. Examples of pigments are iron oxide, titanium dioxide and aluminium lakes. If the coating solution contains insufficient pigment, it will be impossible to develop the desired color intensity and also to minimise color variation, due to poor opacity of the coating solution. Excessively high pigment levels can reduce the mechanical strength of the coating (METHOCEL, 2002).

1.2.7.7 SURFACTANTS

Surfactants are sometimes used to aid in color dispersion and development of the tablet coating. The use of surfactants may also depress the viscosity of the polymer solution. Reduction of pigment flocculation through the use of surfactants can also improve the coating gloss. The use of surfactants is generally not advised except to solve specific performance problems.

1.2.7.8 OTHER ADDITIVES

Flavours and sweeteners are added to mask unpleasant odours or to develop the desired taste. Examples are aspartame, fruit spirits (organic solvent), water soluble pineapple flavour (aqueous solvent) etc. Antioxidants such as oximes, phenols are also sometimes incorporated to stabilize a dye system to oxidation and colour change. Antimicrobials /preservatives can also be added to put off microbial growth in the coating composition. Some aqueous cellulosic coating solutions are prone to microbial growth so long storage of the coating composition should be avoided. Examples are alkylisothiazloinone, carbamates, benzothiazoles etc. Other additives include film adhesion enhancers and anti-tacking agents.

1.2.8 CHARACTERISTICS OF CORE TABLETS TO BE FILM COATED

Coating at any scale involves the understanding of the interactions between the product being coated, the film coating formulation, the equipment installation and the processing parameters.

Granule characteristics: Active Pharmaceutical Ingredient (API) characteristics, excipients, multicomponent tablets (where more than one granulation step is employed) and unoptimised granulation could result in granules that are fragile, of poor compressibility among others, finally producing poor tablets for coating.

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Tablet shape and hardness: The shape of the tablet may have a considerable effect on the tablet hardness, tablet friability, edge erosion (in case of sharp edged tablets) and the mixing characteristics of the tablets in the coating pan.

In order to withstand the high mechanical stress during film coating, core tablets ought to be strong. As mentioned, the core shape plays a major role while optimising hardness. For instance, a small diameter tablet with higher core thickness is less prone to breakage during film coating than a large size caplet with break-line. A flatter tablet with sharp edges will also give rise to high attrition during film coating. Rounded tablet cores are therefore more preferred to caplet and flat round tablets.

Friability: Highly friable tablets will result in rough surface after film coating either due to surface or edge erosion or more importantly the powder generated by such friable tablets getting re-deposited on the tablet surface during coating process

Lubricants: Magnesium stearate is essential for smooth operation of the compression machine. It could however make the tablet surface quite hydrophobic causing poor film adhesion of aqueous film coating. Further, the high surface tension of water may not provide enough surface wetting on such a hydrophobic surface causing very uneven or patchy coated surfaces.

Super-disintegrants: like sodium starch glycolate which are used to achieve drug release characteristics / dissolution profile can create serious problems during aqueous film coating. If the initial drying phase of aqueous coating is not good, moisture absorption may happen which

may activate the super-disintegrant and the core surface may start disintegrating, resulting in very rough tablet surfaces.

Logos / break-lines: Logo bridging or filling will be observed only on the tablets with logos. The depth and calligraphy of logo can play a role in logo filling. The presence of break-lines on large size tablets with lower thickness are likely to break inside the coating machine (Pareek and Rajsharad, 2001).

1.2.9 COATING EQUIPMENT

Tablet coating equipment may include spray guns, coating pan, polishing pans, solution tanks, blenders and mixers, homogenizers, peristaltic pumps, fans, steam jackets, exhaust and heating pipes and filters.

Different types of coating pans used for coating were conventional coating pans, manesty accelacota, driam (driacoater), butterfly coater etc. Nowadays the side-vented, perforated pan-coater is the most commonly used coating device of tablets (Amrutha, 2009; Heinamaki et al., 1997).

Shallow bed depths, a large number of spray guns and fully optimized baffle systems produce the best coating. Most coating processes use one of the three general types of equipment: Standard coating pan, perforated coating pan and fluidized bed (air suspension) coater. Generally, more energy efficient, automated systems are preferred, to shorten the total coating time and reduce operator participation in the coating process.

Standard/ Conventional Pan System consists of a circular metal pan (8 to 60 inches in diameter) mounted angularly on a stand. It is rotated on its horizontal axis by a motor. Heated air is directed into the pan and onto the tablet bed surface and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied to the tablets by spraying on to the rotating tablet bed using an atomizing device.

A perforated pan system on the other hand consists of perforated or partially perforated drum that is rotated on its horizontal axis in an enclosed housing (Zhang and McGinity, 2000).

Fluidized bed (air suspension) coaters are also highly efficient drying systems. The air flow is controlled so that more air enters the center of the column, causing the tablets to rise in the center. Coating solutions are continuously applied from a spray nozzle located at the bottom of the chamber or are sprayed on to the top of the cascading tablet bed by nozzles located in the upper region of the chamber.

Irrespective of the type of coating equipment used, coating preparations are generally applied using a spray-atomization technique and two types of spray nozzles are employed. With pneumatic nozzles, high-pressure air is passed across the fluid stream as it exits the nozzle opening. In contrast, hydraulic nozzles rely on the fluid being pumped at relatively high pressures through a small opening. One of the advantages of pneumatic nozzles is that the atomized droplet size can be controlled independently of the polymer flow rate, whereas changing the spray rate of a hydraulic nozzle without adjusting the nozzle will result in changes in the atomization spray pattern (Mehta, 1997).

A variety of pumps may be used to deliver the coating material to the spray nozzle. The peristaltic pump (most commonly used and is also the easiest to clean) is ideal for delivering latex and pseudolatex polymeric dispersions that may coagulate at high pressure. To control the delivery of the liquid polymeric material more precisely, a gear pump may be employed but problems with undissolved solids in the coating formulation may arise. The gear pump is also more difficult to clean as compared with the peristaltic system. A piston pump utilizes both air and hydraulic systems. One of the advantages of the piston pump is that minor clogs in the nozzle may be easily cleared due to the pressure reserve. Polymeric materials, however, may coagulate due to the high pressures used and the piston system is quite difficult to clean (Felton, 2007).

1.2.10 PROCESS PARAMETERS/ FILM COATING PARAMETERS

Many quality aspects of the final coated product are greatly influenced by the combined effect of process parameter values used in aqueous film coating. These parameters affect the spreading, penetration and drying (i.e. evaporation of water) of the coating formulation on the tablet surface and subsequently, the surface roughness and the residual moisture of the coated tablets (Twitchell et al., 1995; Obara and McGinity, 1995). The variable inputs to a film coating

process derived from differences in equipment installations include but are not limited to the following:

1.2.10.1 AIR FLOW RATE

This affects the drying efficiency of the coating unit and subsequently, the quality of the coated tablets. Franz and Doonan (1983) found that an increase of the inlet air flow rate causes a linear increase in the tablet bed temperature, increasing the evaporative capacity of the coating unit and eliminating over wetting problems of tablets.

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1.2.10.2 SPRAY RATE

Spray rates for aqueous film coating vary from 6 to 30 g/min for a small 2.0 L pan, to 80 to 250 g/min/gun in a large production-scale pan. Some key factors that limit the maximum spray rate per gun are the viscosity of the coating solution (which cannot be too low or too high) and the type of spray gun used (Porter et al., 1997). The spray rate affects the moisture content of the formed coating and the quality and uniformity of the film.

Factors such as movement of the tablet cores must also be considered in determining the spray rate because if this movement is consistent and a higher spray rate is to be delivered, an acceptable level of film-coating uniformity would be achieved (Porter et al., 1997). A low rate causes incomplete coalescence of polymer due to insufficient wetting, which could result in brittle films. A high rate may result in over wetting of the tablet surface and in subsequent problems such as picking and sticking. If the spray rate is high and the tablet surface temperature is low, films are not formed during the spraying but the post drying phase, and rapid drying often produces cracks in the films.

1.2.10.3 ATOMISING AIR PRESSURE

This influences the volume of coating solution that impacts the tablet surface and hence their wettability and surface roughness. It must therefore be optimised to achieve a successful coat. For instance, increasing the spraying air pressure decreases the surface roughness of coated tablets and produces denser and thinner films. If spraying air pressure is excessive, the spray loss is great, the formed droplets are very fine and could spray-dry before reaching the tablet bed, resulting in inadequate droplet spreading and coalescence. In addition, with low spraying air

pressure big droplets could locally over wet the tablet surface and cause tablets to stick to each other (Khan et al., 2001; Tobiska and Kleinebudde, 2003).

1.2.10.4 INLET AIR TEMPERATURE

The inlet air temperature affects the drying efficiency (water evaporation) of the coating pan and the uniformity of coatings. High inlet air temperature causes an increase in the drying efficiency of the film coating process and a decrease in the water penetration into the tablet core, which also decreases the residual moisture content of coated tablets. Too much air temperature however, causes an increase in the premature drying of the spray during application and subsequently decreases the coating efficiency (Porter et al., 1997, Pourkavoos and Peck, 1994, Rege et al., 2002).

1.2.10.5 ROTATING SPEED OF PAN

To effectively optimize film-coating quality, the tablets must be mixed such that each tablet has the same probability of being in the spray region for an equal length of time. The pan speed selected should be the lowest speed that produces a rapid and continuous tablet flow through the spray zone. This allows for uniform application of the coating solution to produce a consistent film coat, while subjecting the tablets to a minimal amount of abuse. In general, if tablet friability is less than 0.1%, then tablet attrition will not be a problem. A smaller tablet can be slightly softer, since these tablets produce a less abusive tumbling action (Porter et al., 2009).

1.2.10.6 HUMIDITY CONTROL

The humidity of the coating process air is an important factor affecting the penetration and evaporation of water on the tablet surface. The water removal efficiency of the coating process is linearly correlated with the residual moisture content, tensile strength and porosity of the core tablet (Pourkavoos and Peck, 1994).

1.2.10.7 SPRAY GUN-TO-TABLET-BED DISTANCE

For small scale coating systems, the gun-to-bed distance can be as little as 2.5 to 5.0 cm and 20 to 25 cm for a production sized pan. Changing this distance implies a corresponding change in a process parameter must be effected. For instance, for a distance of less than 20 cm, either spray

rate must be reduced or the pan temperature increased to optimize evaporation time (Porter et al., 2009).

1.2.10.8 NUMBER OF SPRAY GUNS

To maximize the uniformity and application of the coating, the spray zone should cover from the front to the back edge of the tablet bed. The objective is to produce a uniform "curtain" of spray through which the tablets pass but overlapping of spray patterns leads to localized over-wetting of the tablet bed (Porter et al., 2009).

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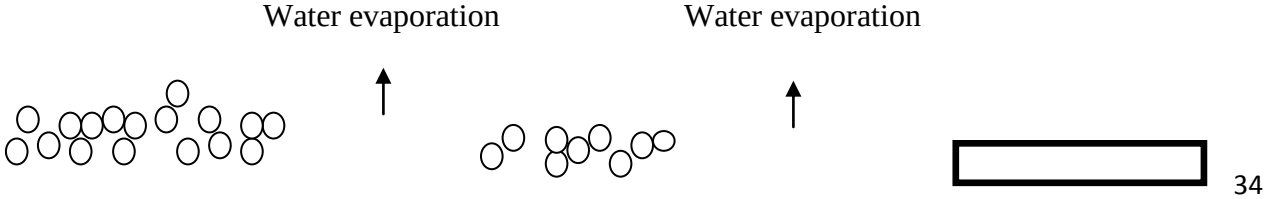
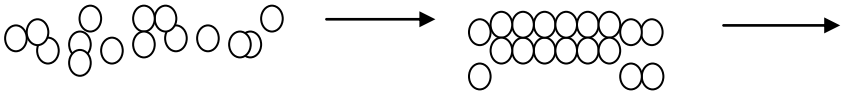
1.2.11 THE MECHANISM OF FILM FORMATION

Aqueous film coating applications are either solutions or dispersions, depending on the water solubility of the film forming polymers. Film formation from the polymer solution occurs through a series of phases. When the polymer solution is applied to the surface of a tablet, cohesion forces form a bond between the coating polymer molecules (Banker, 1966).

Film formation occurs when the polymeric particles coalesce to form a continuous film. The coalescence is initiated by water evaporation since it causes the dispersed polymer particles to pack closely, in an ordered array with water filling the voids. After the polymer particles come into contact with each other, they then deform and coalesce into the film (Ruotsalainen, 2003). Coalescence only occurs above a minimum film forming temperature (MFFT) of the coating polymer, and so temperature/water evaporation is considered to be major process-related factor affecting the process (Obara and McGinity, 1995).

Film formation, that is the coalescence, is a complex process and dependent on environmental (humidity and temperature) conditions, polymer properties (such as storage/age, molecular weight, particle size and viscosity), solvent properties like surface tension and on other constituents of the coating liquid (Dobler and Holl, 1996; Eckersley and Rudin, 1996). This could be illustrated as:





aqueous dispersion deposited on the tablet surface

polymer particle compaction and deformation

coalescence into a continuous film

1.2.11.1 MINIMUM FILM FORMING TEMPERATURE (MFFT)

This can be defined as the minimum temperature at which a polymer will coalesce to form a thin film when laid on a substrate. When this process occurs in the absence of pigmentation or other opacifying materials, a clear transparent film is formed. At temperatures lower than the MFFT, a white, powdery, cracked film will result because considerable particle deformation can only take place if drying is at temperatures well above the polymer's MFFT and close to or above its glass transition temperature (Tg). If drying is very close to the MFFT, particle deformation would be only partial and incomplete. The MFFT is usually closely related to the Tg but not synonymous with it; whilst the Tg may be determined by predicted calculation, the MFFT is best determined by the use of a MFFT Bar (Rhopoint, 2002).

1.2.11.2 GLASS TRANSITION TEMPERATURE (Tg)

The glass transition temperature (Tg) of a polymer is a characteristic temperature at which there is a major change in properties. If the sample is stored below the Tg the amorphous form will be brittle and is described as the glassy state. If the sample is above its Tg it becomes rubbery. It however differs from the melting point. Below Tg, polymer molecules are immobile and above it, the molecules can wiggle around (Nutan, 2004; Aulton, 2001).

Under normal coating conditions, polymers would be in the glassy state being rigid, tough and brittle. To make these polymers more flexible, the Tg can be lowered by adding a small molecule, called a plasticizer, which fits between the glassy molecules, giving them greater mobility. Water, for instance, is a good plasticizer for many materials, and so the glass transition temperature will usually reduce in the presence of water vapour. The greatest stability during storage of a polymer is therefore obtained at temperatures below Tg where subtle changes in polymer properties (e.g., tackiness) are reduced (Swarbrick, 2007; Aulton, 2001).

The glass transition temperature of the coating system (dictated by the properties of the polymer, and the properties and concentration of the plasticizer, where needed) determines the minimum film-forming temperature (MFFT). The product temperature within the coating pan must exceed the MFFT for film coalescence to occur (Porter et al., 2009).

1.2.12 POLYMER FILMS (FREE FILMS)

When gum solutions are cast on a surface and dried, they leave a film that possesses specific plasticity, tensile strength, clarity, solubility and other characteristics. The ability of these gums to form micelles, gives them this film-forming property. Structural differences such as the presence or absence of branching and electrical charges impact such properties (Nieto, 2009).

Free films are generally used to assess properties, chiefly mechanical, of polymers because these properties are greatly determined by the nature of the polymer, and to a lesser extent, the method used for their preparation. They are prepared by solvent-casting or compression moulding from aqueous-based formulations. They have to be free of any substrate, and so their ease of removal from the casting substrate is important. Some methods for assisting with this problem include: casting onto photographic paper and removing the film by soaking in warm water to dissolve the gelatin, casting onto aluminium foil followed by amalgamation with mercury, casting onto silanised glass plates or into polytetrafluoroethylene (PTFE) dishes, in which case the film is removed by gently peeling it from the substrate (Steward, 1995).

1.2.12.1 MECHANICAL PROPERTIES OF FILMS

One of the most useful mechanical tests for polymeric and pharmaceutical materials in general is to determine their tensile strength and the accompanying stress–strain curve. This is generally done by using a mechanical testing machine, and continuously measuring the force developed as the material is elongated at a constant rate of extension. Important mechanical properties of a material include the modulus which is a measure of the material stiffness, yield stress, strength, ultimate strength, elongation at break and toughness (area under the curve).

For polymer films, an increase in molecular weight tends to increase film tensile strength, elongation, and flexibility. This can be explained on the basis that longer polymer chains exhibit

greater flexibility and elasticity. They can thus be extended further before rupture, as compared with short polymer chains (Brady et al., 2009).

Tensile strength (TS) (formerly known as ultimate tensile strength), is based on the maximum load sustained by the test-piece, e.g. a polymer film, when it is tested to destruction. It indicates the strength of the film telling if the sample is strong or weak. The higher the TS value of a material, the stronger or tougher it is. The numerical value of tensile strength is calculated as a

$$TS = \frac{\text{maximum load applied}}{\text{original cross-sectional area of sample}}$$

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The units used are megapascals (MPa) or Newtons per square millimetre (N/mm2) (Vernon, 1992).

Young's Modulus (sometimes referred to as modulus of elasticity) is also an extremely important characteristic of a material. It is the numerical evaluation of Hooke's Law, namely, ratio of stress to strain (the measure of resistance to elastic deformation). It is a measure of hardness, stiffness or rigidity of a material (Muhammad et al., 1992) and it is useful in predicting adhesion, that is, the lower the Young's modulus, the better film adhesion is to tablet substrates.

Toughness of a film coat is the best predictor of overall film performance as it includes both the film strength and ability to deform without breakage**.** Though studies of the mechanical properties of free films are informative of polymers/gums, the results may not necessarily be a true reflection of the film coating. It is however usual that linear, high molecular weight, non-ionic gums form strong films.

1.2.13 ADHESION OF FILM COATING TO TABLETS

Fundamentals of tablet film coating include optimised adhesion to the core tablets and improved physical characteristics tablet. Adhesive force is the force required to pull a film coating from the tablet surface while adhesiveness is defined as the force required in removing the film coating from a unit area of the tablet surface (Fung and Parrott, 1980).

The adhesion of the coat to the tablet will depend on a complex set of interacting factors related to the coating formulation, the tablet core and processing conditions. A primary requirement is

that the coating formulation spreads completely over the surface of the tablet. The adhesion will be enhanced if penetration into the pores of the tablet is controlled. Processing conditions aside, adhesion will be controlled by the interaction of the fluid with the tablet core. A high positive spreading coefficient is necessary for complete wetting of the tablet cores (Khan et al., 2001).
Loss of adhesion may compromise the mechanical protection that the film coating provides to the tablet and may lead to an accumulation of moisture at the film-tablet interface, affecting the stability of moisture-labile drugs (Okhamafe and York, 1985).

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1.2.14 SURFACE ROUGHNESS

Aesthetically, a smooth and glossy film coat is desirable because film coated tablets with a rough appearance appear dull. Surface roughness is one of the most important parameters in engineering the surfaces of tablets to be coated. Roughening the surface of these solids could change many aspects of the surfaces including adhesion and bond formation, in this instance, between a film coat and the core surface. The measurement of surface roughness not only quantifies surface characteristics of the film but also helps to provide information on the behaviour of the atomised droplets of film coating solution on the core surface, and facilitates the optimization of the coating process. The surface roughness of the tablet compact and the force of compression used during tableting will also affect polymer adhesion, by altering the effective area of contact between the film coating and the surface of the solid. A scanning probe microscope is suitable for evaluating surface roughness of films quantitatively (Twitchell et al., 1995; Orafai and Spring, 2007; Fisher and Rowe, 1976).

1.2.15 DEFECTS IN FILM COATING OF TABLETS

Over-wetting of tablets, under-drying or poor tablet quality results in removal of a film coat. This is known as picking. Another fault is bridging, which occurs when the coating fills in the lettering or logo on the tablet and is typically caused by improper application of the solution, poor design of the tablet embossing, high coating viscosity and high percentage of solids in the solution or improper atomisation pressure.

Improper tablet compression could also result in capping; that is when the tablet separates in laminar fashion. Soft tablets, an over-wetted tablet surface, inadequate drying or lack of tablet surface strength could also result in erosion of the coated tablet.

Twinning is a common problem with capsule shaped tablets when two tablets stick together. A good balance in the pan speed (increase) and spray rate (reduction) could help reduce this problem. Again, if the coating solution does not lock into the tablet surface due to either a defect in the coating solution or an unoptimised film coating process, the coating easily peels away from the tablet surface in a sheet.

Also, a high pan speed, friable tablet cores, or a coating solution which lacks a good plasticizer would most definitely result in chipping of coated tablets. Orange peel, that is, a coating texture that resembles the surface of an orange would be obtained when high atomization pressure in combination with too high spray rates that are employed. Lastly, a mottled colour could be observed on film coated tablets when the coating solution is improperly prepared or the tablet cores are cold (Tousey, 2005).

1.3.0 GUMS

1.3.1 ORIGIN, FORMATION AND COMPOSITION

The most common gum sources are trees in the tropics and sub-tropics. Plant gum exudates are produced by the trunk, branches and fruit. They are plant hydrocolloids considered to be pathological products formed following mechanical injury to the plant as a form of response, or owing to unfavorable conditions, such as drought or by a breakdown of cell walls (extra cellular formation; gummosis). They can also be produced after microbial invasion or infection (Jones and Smith, 1949; Ovodov, 1975).

Gums are non-crystalline, amorphous substances (colloids); polysaccharides or mixed monosaccharides, and many of them are combined with uronic acids. They contain hydrophilic

molecules and can therefore combine with water to form viscous solutions or gels. The wide industrial application of gum exudates is due to their water-holding capacity to produce gels or highly viscous solutions, and their ability to enhance the stability of emulsions and foams. These properties depend on the chemical structure of gum exudate polysaccharides and their conformation in the solvent. For this, rheometry is an important tool to analyze such physicochemical properties of gum exudates (Rinaudo, 2001; Rincon et al., 2009; Whistler, 1993; Simas-Tosin et al., 2010)

These gum exudates have complex structures, with a great number of monosaccharides and glycosidic linkages, most of them having highly branched structures. The nature of the compounds involved influences the properties of different gums. For instance, linear polysaccharides occupy more space and are more viscous than highly branched compounds of the same molecular weight. The branched compounds form gels more easily and are more stable because extensive interaction along the chains is not possible (Jani et al., 2009).
They dissolve in and form intensive hydrogen bonds with water. Because of the size and configuration of their molecules, these polysaccharides have the ability to thicken and/or gel aqueous solutions as a result of both hydrogen bonding between polymer chains and intermolecular friction when subjected to shear (Nieto, 2009).

Gums may contain functional groups such as esters (methoxyl e.g., tragacanth and acetyl residues e.g., xanthan, khaya) and alkyl (methyl) groups as derivatives of the sugar and sugar acids.

1.3.2 CLASSIFICATION OF GUMS

Gums perform a number of metabolic and structural functions and are available in high quantities in a number of plants (largest producers), animals, seaweeds and microbes.
Some commonly used classifications of commercially available gums are as follows:

- Charge
    a) Non-ionic gums (neutral): guar, locust bean, xanthan
    b) Anionic gums (acidic): karaya, tragacanth
- Source

a) Marine/ algal(seaweed): agar, alginic acid
b) Animal: chitin and chitosan, hyaluronic acid
c) Microbial (bacterial and fungal): xanthan, dextran
d) Plant:
    i. Shrub/ tree exudates – e.g. cashew, albizia, tragacanth, khaya
    ii. Seed gums – e.g. guar, locust bean, starch
    iii. Extracts – e.g. pectin
    iv. Tuber and roots –e.g. potato starch

- According to shape
    a) Linear: algins, amylose, cellulose, pectins.
    b) Branched:
        i. short branches – e.g. xanthan, xylan, galactomanan.
        ii. branch-on-branch – e.g. amylopectin, gum arabic, tragacanth (Jani et al., 2009).

Other classifications include natural (e.g. chitin, acacia, tragacanth and xanthan), modified or semi - synthetic (e.g. carboxymethylcellulose, hydroxymethyl cellulose and microcrystalline cellulose) and synthetic (e.g. carboxypolymethylene and colloidal silicon dioxide). They are also sometimes classified as either water swellable (e.g. albizia) or water soluble (e.g. acacia).

1.3.3 ADVANTAGES AND DISADVANTAGES OF GUMS AND MUCILAGES

Gums have certain advantages over synthetic polymers which include being edible, biodegradable, renewable, low cost (in terms of purchase and production), biocompatible and non-toxic (they are made up of repeating sugar units hence they have no adverse impact on humans or environmental health e.g., skin and eye irritation). The production cost is also much lower compared with that for synthetic materials.

However, gums have some disadvantages too such as significant microbial contamination due to their moisture and carbohydrate contents which can support microbial growth. Also, due to environmental and seasonal variation, there is batch to batch variation even for a produce from the same plant as well as hydration rate that is difficult to control as a result of differences in collection sites, species and climatic conditions (Jani et al., 2009).

1.3.4 METHODS FOR DETECTING GUMS

Gums and mucilages can be detected by a simple phytochemical test. An amount of the test sample is dissolved in distilled water and to this; absolute alcohol is added with constant stirring. A white or cloudy precipitate indicates their presence.

In their natural state, individual specimens of gums may sometimes be recognised by their physical characters (size, shape, taste, colour, brittleness, appearance on fracture etc.). For example, tragacanth gum occurs in flattened ribbons up to 25 mm long and 12 mm wide and is white or very pale yellowish-white in colour. It is translucent and horny and it breaks with a short fracture. It is also odourless and has little taste. Acacia on the other hand occurs in rounded or ovoid tears up to about 3 cm in diameter or in angular fragments. The outer surface bears numerous fine cracks which form during the 'ripening' and make the tears opaque. The gum is white or very pale yellow in colour and the tears break rapidly with a somewhat glassy fracture and much of it consists of small pieces. It is odourless and has a bland and mucilaginous taste.

Also, tragacanth swells into a gelatinous mass when placed in water but only a small portion dissolves. On the addition of a dilute solution of iodine to a fragment previously soaked in water relatively few blue points are visible due to its starch content unlike karaya which contains no starch and rather stains pink with solution of ruthenium red (Evans, 2002).

Commercial samples of gums cannot be recognised in this way since most of them are used in the powdered form. Some can be recognised by the way they dissolve or disperse in water. Thus gum arabic dissolves in water easily and can be readily distinguished from tragacanth and khaya gums which partially dissolve in water.

1.3.5 PURIFICATION OF GUMS

Gums, while on their source trees become contaminated with lot of impurities. They are therefore purified before use. Some gums are readily soluble in water, which is therefore used in their purification.

Raw gum from the same botanical origin is a blend of gum nodules with different mesh sizes,

containing some vegetable, mineral and microbial impurity. Dry purification, such as kibbling, sieving and pulverization, could be used. Here, the level of impurities could be slightly reduced but bacterial contamination cannot be enhanced resulting in raw gums not meeting international specifications for use either as pharmaceuticals or food. Purification in aqueous solutions (more efficient), is therefore employed (Thevenet, 2010).

The gum is fully dissolved in water and the impurities are removed by a number of filtration steps. Microbial contamination is also reduced by a plate heat exchanger and the resulting gum syrup is then either roller or spray dried. These two different methods for recovering the purified gum result in differences in emulsification and hydration properties of the gum among other physical and functional properties (Thevenet, 2010).

Another method, most commonly used is to precipitate the pure gum from the filtered gum solution instead of outright drying is by gradually adding alcohol or a suitable polar solvent, followed by air or oven drying at a suitable temperature. In certain cases, highly polar organic solvents, e.g. dimethyl sulphoxide, are used.
In the purification, dissolution may be accelerated using dilute acids, aqueous salt or alkalis depending on the nature of the gums, that is, if it does not readily dissolve in water. Heating must be avoided if either dilute acid or water is employed, since partial hydrolysis may occur in gums which contain heat labile sugar residues. Application of too much heat is inadvisable during alkali extraction, for although undesirable protein is eliminated, decomposition of the uronic acid building units may occur.

Gums can be further purified by heating under reflux with an alkali (KOH) on a water bath, filtering the hot solution and then centrifugation. The gel obtained is then poured into a mixture of ethanol and acetic acid, washed with ethanol, then ether and then dried. Purification could also be done by electrodialysis, but a lower yield may be obtained.

Yield, rheological properties and compositional characteristics of the extracted gum are dependent upon the pH, gum:water ratio, temperature and processing time (Koochecki *et al*., 2009; Kleczkowski and Wierzchowski, 1940).

1.3.6 PHYSICOCHEMICAL PROPERTIES OF GUMS

The nature of the compounds in the structures of different gums greatly influences their properties. For example, linear polysaccharides occupy more space and are more viscous than highly branched compounds of the same molecular weight. Also, branched compounds form gels more easily and are more stable because extensive interaction along the chains is not possible. These different properties or similar properties of varying degrees, to a very large extent determine the uses and commercial values of the gums.

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Differing climatic conditions and hence, geographical locations, as well as different soils would result in the same species of a plant producing gums showing different properties. Even for the same tree, seasonal variations and age may affect certain physicochemical properties of its gum (Jani et al., 2009; Panda, 2010). The physical properties may also be affected by age of the exudates and the treatment of the gum after collection such as washing, drying, sun – bleaching and storage conditions (Glicksman, 1969).

1.3.6.1 TASTE AND SMELL

Water soluble gums are usually odourless and so differ markedly from the oil soluble resinous exudates which have distinctive smells. Gums are usually tasteless and bland, except for some species which have a sweet, carbohydrate or glycerine taste while some types that have been contaminated with tannins have a harsh, bitter flavor (Panda, 2010).

1.3.6.2 COLOUR AND FORM

Many gums when first secreted appear to be colourless. In the solid state; gums vary from almost water white (colourless) to various shade of yellow, amber, pink, black and orange to dark brown. In commercial valuation of gums, there is a strong preference for those that are light coloured. Colour is mainly due to the presence of impurities and tannins. Often it appears as the gum ages on the tree many substances are washed on it. Colour could also appear as the gum is dried or heated while on the plant for example, due to the effects of scorching caused by bush or grass fires (Evans, 2002, Panda, 2010).

Natural gums are exuded in varieties of shapes and forms, the best known being the tear drop or globular shapes of acacia gum. Other characteristic shapes are flakes or threadlike ribbons as with tragacanth, still others resemble stalactites and after collection and fracturing, yield irregular rod- shaped fragments as seen in khaya gums. The surface of most of gums is perfectly smooth when fresh but may become rough or covered with small cracks or striations upon weathering, resulting in an opaque appearance. These fissures or striations are often restricted to the surface, but may be deep in some gums (Panda, 2010).

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1.3.6.3 POLARISATION

The aqueous solutions of gums, as well as mucilages are laevorotatory (Kokate et al., 2008).

1.3.6.4 HARDNESS AND DENSITY

Gums vary in hardness, which is obviously governed by the amount of moisture present. This generally ranges between 12 and 16 %. Density also shows variability. This may depend on the amount of air that may have been incorporated in the gum during formation. Most gums break with glassy fracture when properly dried, and may be readily pulverised (Panda, 2010). Gums are hygroscopic and will absorb moisture and become soft in humid atmosphere unless they are tempered with alum or formalin. This power to hold water or lose it may have an important repercussion in gum trade.

1.3.6.5 SOLUBILITY

Gums are easily distinguished from resins by their solubility characteristics, that is, resins are typically soluble in organic solvent while gums are typically water soluble. Most gums yield some amount of insoluble residue when mixed with water but they could be said to be soluble in water, to varying degrees. Some gums are readily soluble in water, which is therefore used to extract them. Generally, there are three solubility patterns: soluble in water, forming a transparent solution; partially soluble in water; and insoluble in water, forming a gel and possibly a very thick, transparent solution (Maynor and Van der Reyden, 2011).

A lot of gums cannot be dissolved in water at concentrations higher than 5 % because of their very high viscosities. However, acacia for example, is almost completely soluble in an equal weight of water, which is up to 50% concentration, solution taking place rather slowly. Gum solubility in solvent is affected by the temperature of the solvent as with every solute. Others,

such as sterculia gum have low solubility but swell to many times their original volume. Tragacanth also swells into a gelatinous mass when placed in water but only a small portion dissolves, because it consists of a small water-soluble fraction known as tragacanthin and a water-insoluble fraction known as basorin (Evans, 2002).

It is very important to note however that, due to the different chemistries of different gums, aqueous solutions prepared from different gums may not always be miscible. Gums are generally insoluble in oil and in most organic solvents. They may be soluble in aqueous ethanol, up to some limits. Some degree of solubility can also be obtained in glycerol and ethylene glycol. The overall solubility properties of gums can be improved by freeze drying or by the purification of the gum.

1.3.6.6 VISCOSITY AND RHEOLOGICAL PROPERTIES OF GUMS

This property which is about the thickness of a gum is an important factor in determining the quality of the gum, that is, the higher the viscosity the better the gum. Normally, when gums come into contact with water there is an increase in the viscosity of the formulations and many useful industrial and pharmaceutical applications of gums are based on this character. However, due to the complex nature of gums (monosaccharides to polysaccharides and their derivatives), there is reduction in viscosity with storage/ age of the gum (Jani et al., 2009). Other factors which can affect rheological properties exhibited by a dispersion of a gum in a solvent include concentration and temperature effects. Heating or fine powdering of gums result in a loss of viscosity as occurs with tragacanth.

The physical properties of gums, such as their rheological behavior are manifestations of their chemical structure, the kind and amount of solvent, and the kind and concentration of ions and other substances dissolved in the solvent. Gums are commonly composed of several different kinds of monomer units with many possible variations in regard to degree of branching, length of branches, and types of linkages. Forces (hydrogen bonding, ionic charges, dipole and induced dipole interactions, van der Waals forces) act between molecules, between different parts of the same molecule, and between polymer and solvent affecting such properties as gel-forming tendency, viscosity and adhesiveness.

The types of linkages in gum structures, due to their effects on chain flexibility are important also in determining physical properties. For example, linear molecules make more viscous solutions than do long-branched molecules of similar molecular weights, but they have a tendency to precipitate because of association of the chains. If this association is prevented, stability can be achieved without much sacrifice of viscosity. While it is known that solutions of some gums are slimy or mucilaginous whereas others are tacky (for reasons unknown), rheological properties of different gum solutions also differ (Whistler, 2008).

However, as with all macromolecules/ polymers, gum solutions exhibit pseudoplastic flow. In this property, the apparent viscosity decreases as the shear rate increases and is reversible, with the original viscosity returning upon the reduction of the shear rate thereby having an effect on the pouring and texture of the finished products (Phillips and Williams, 2000).

1.3.6.7 pH OF GUM SOLUTIONS

On hydrolysis, gums yield sugars like arabinose, galactose, glucose, mannose and xylose along with various uronic and methyl sugars. The sugar acids, when present in appreciable amounts, tend to lower the pH of their solutions enabling the gums to occur frequently as salts of sodium, potassium, calcium or magnesium (Daniel, 2006). A number of some natural gums such as locust bean are however neutral.

1.3.7.0 SOME FACTORS AFFECTING BEHAVIOUR OF GUM SOLUTIONS

The structure of the gum molecules can be disrupted by various factors, which in turn affects their performance. They can be hydrolysed by acid or enzymes, and heat can increase this effect. Temperature also can affect the viscosity, and these changes may be reversible.

1.3.7.1 CONCENTRATION

The concentration of gum dispersions prepared determines the viscosity they would show, that is, the higher the concentration, the greater the viscosity. At quite low concentrations, a directly proportional increase in viscosity is observed and the flow tends to be Newtonian. However for most gums, viscosity increases more rapidly above certain concentrations.

1.3.7.2 TEMPERATURE

For some gums, such as xanthan, their solutions provide uniform viscosities over the temperature range freezing to near boiling with excellent thermal stability (Sharma et al., 2006). Heating of most gums however results in a permanent loss/reduction of viscosity but this may be more pronounced at much lower concentrations. This is usually due to loss of the polymer conformation. High storage humidity or high storage temperature also contributes to loss of viscosity (Wang, 2000). The extent to which this can happen depends on properties of individual gums. Increasing temperature to some extent however, increases solubility of gums.

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1.3.7.3 AGING

Viscosity decreases with increasing age and also, finely ground powder gum loses more viscosity compared to a coarse powder or the whole exudates and is most noticeable soon after grinding.

1.3.7.4 pH STABILITY

Most gums are slightly acidic and so are quite stable at acidic pHs. Tragacanth for instance is one of the most acid-resistant gums. The addition of strong mineral and organic acids causes a drop in solution viscosity of gums in general. Di - and trivalent cations also cause a drop in viscosity or may cause precipitation, depending on the metal ion type and concentration. Raising the pH of a gum solution (by adding an alkali) also changes the texture of the solution; for karaya gum for instance, the solution becomes ropy and cohesive. This phenomenon does not occur if the alkali is added prior to gum addition (Phillips and Williams, 2000).

1.3.8.0 CASHEW

1.3.8.1 BOTANY AND SOURCE

Family: Anacardiaceae

Genus: *Anacardium*

Species: *occidentale*

Synonyms: *Acajuba occidentalis, Anacardium microcarpum, Cassuvium pomiverum*

Common name: cashew

In Ghana, is found mainly in cashew growing districts like Sampa, Wenchi, Bole and Jirapa. There are also cashew plantations like Ejura farms.

Parts Used: Leaves, bark, fruit, nut

The cashew is in the family Anacardiaceae. Its English name derives from the Portuguese name for the fruit of the cashew tree, *caju*, which in turn derives from the indigenous Tupi name, *acajú*. It is widely grown in tropical climates for its nuts and apples

The name *Anacardium* refers to the shape of the fruit, which looks like an inverted heart (*ana* means "upwards" and -*cardium* means "heart"). In the Tupi language *acajú* means "yellow head".

The tree is small and evergreen, growing to 10 - 12 m (32 ft) tall, with a short, often irregularly shaped trunk. The leaves are spirally arranged, leathery textured, elliptic to obovate, 4 to 22 cm long and 2 to 15 cm broad, with a smooth margin. The flowers are produced in a panicle or corymb up to 26 cm long, each flower small, pale green at first then turning reddish, with five slender, acute petals 7 to 15 mm long.

The fruit of the cashew tree is an accessory fruit (sometimes called a pseudocarp or false fruit). What appears to be the fruit is an oval or pear-shaped structure that develops from the pedicel and the receptacle of the cashew flower. Called the cashew apple, better known in Central America as "marañón", it ripens into a yellow and/or red structure about 5–11 cm long. It is edible, and has a strong "sweet" smell and a sweet taste. The pulp of the cashew apple is very juicy, but the skin is fragile, making it unsuitable for transport (Varghese and Pundir, 1964).

1.3.8.2 ORIGIN AND DISTRIBUTION

It is originally native to northern South America but the Portuguese took it to India from where it spread to Southeast Asia and eventually to Africa. The cashew is native to the relatively dry areas of the Caribbean and the northern region of South America. It is now cultivated throughout the tropics for the cashew nut (Ross, 2001).

1.3.8.3 CLIMATE AND SOIL

Cashew tolerates wide range of ecological factors. Its distribution is restricted to altitudes below 700 m. However, best production is noticed up to the altitude of 400 m with at least 9 hr sunlight/day from December-May. Cashew grows well at reasonably high temperatures (not above 36^{o}C) and does not tolerate prolonged periods of cold and frost especially during the juvenile period.

Cashew trees are often found growing wild on the drier sandy soils in the central plains of Brazil and are cultivated in many parts of the Amazon rainforest. It however grows in almost all soil types and performs well in red sandy loams, laterite soils and coastal sands. It can adapt very well to dry conditions because it is hardy and drought resistant. It is very sensitive to water logging and hence heavy clay soils with poor drainage conditions are unsuitable for its cultivation. Cashew comes up well when the soil pH is in acidic range (i.e. pH > 8 is not suitable for cultivation). It responds well to supplementary irrigation during the summer month (June-March).

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1.3.8.4 PROPAGATION

Cashew was propagated only through seeds for which it takes about 5-6 years for first bearing. Hence, vegetative propagation planting is necessary to obtain higher and early yield. Many techniques of vegetative propagation like grafting (soft wood and epicotyl), budding and layering (air-layering being the easiest method) have been tried in cashew with varied degrees of success. Soft wood grafting is the most successful and commercially viable technique, giving 70% success rate.

1.3.8.5 CHEMICALS FOUND IN CASHEW TREE

In addition to being delicious, cashew fruit is rich in vitamins, minerals and other essential nutrients. It has up to five times more vitamin C than oranges and contains a high amount of mineral salts. Volatile compounds present in the fruit include esters, terpenes and carboxylic acids. The bark and leaves are a rich source of tannins, a group of plant chemicals with documented biological activity. These tannins, in a 1985 rat study, demonstrated anti-inflammatory and astringent effects, which could be why cashew is effective in treating diarrhoea (Taylor, 2005).

Anacardic acids (2-hydroxy-6-alkylbenzoic acid) are found in cashew, with their highest concentration in the nutshells. Several clinical studies have shown that these chemicals curb the darkening effect of aging by inhibiting tyrosinase activity, and that they are toxic to certain cancer (breast) cells (Kubo et al., 1993). It can also kill the methicillin-resistant Staphylococcus aureus (MRSA) cells rapidly.

The main chemicals found in cashew are alanine, alpha-catechin, alpha-linolenic acid, anacardic acids, anacardol, antimony, arabinose, caprylic acid, cardanol, cardol, europium, folacin,

gadoleic acid, gallic acid, gingkol, glucuronic acid, glutamic acid, hafnium, hexanal, histidine, hydroxybenzoic acid, isoleucine, kaempferols, L-epicatechin, lauric acid, leucine, leucocyanidin, leucopelargonidine, limonene, linoleic acid, methylglucuronic acid, myristic acid, naringenin, oleic acid, oxalic acid, palmitic acid, palmitoleic acid, phenylalanine, phytosterols, proline, quercetin-glycoside, salicylic acid, samarium, scandium, serine, squalene, stearic acid, tannin, and trans-hex-2-enal tryptophan (Taylor, 2005).

1.3.8.6 TRADITIONAL MEDICINAL USES OF CASHEW

Cashew (kaju) is a useful tree as different parts of it are used either individually or collectively to treat several diseases. Fresh or hot water extract of different plant parts is used orally as aphrodisiac, antidysenteric, antihaemorrhagic and externally as anti-inflammatory.

Hot water extracts of dried leaf are used orally for diabetes in Brazil and Thailand; diarrhea in Tanzania and externally to wash ulcers in West Indies. The seeds are consumed orally in Colombia and India as aphrodisiac and to cure impotence whereas in Cuba, seeds are first toasted and then their powder is mixed with sugar to be consumed as an aphrodisiac. Hot water extract of the seed is used orally in Peru as an antidysentric, antihaemorrhagic, purgative, respiratory stimulant and externally as anti-inflammatory agent. In Peru, it is common to use hot water extract of the seeds to cure warts. People in West Indies treat uterine disorders with juice of the seed.

Hot water extract of the bark is used to treat amenorrheoa in Haiti, to increase fertility in women in Ghana and to help people manage diabetes in Jamaica. In Madagascar, it is used for dysentery, hypertension and diabetes but as an external anti-inflammatory agent in Panama. It is consumed to treat diarrheoa in Panama and Senegal.

Indians use hot water extract of the dried kernel as an aphrodisiac while it is used for diabetes mellitus in Europe. The unripe fruit juice is taken orally to treat haemorrhage and diarrheoa and juice of ripe fruit used as a diuretic and anti-scorbutic in Guinea. In Ghana, hot water extracts of the dried fruit is used as a wash to treat yaws. Exudate of the fresh pericarp is used externally as an emollient for chilblains and also as an insecticide to prevent termite attack in India. It is

believed that throat pain gets relieved if fruit is consumed on an empty stomach in Panama. (Ross, 2001)

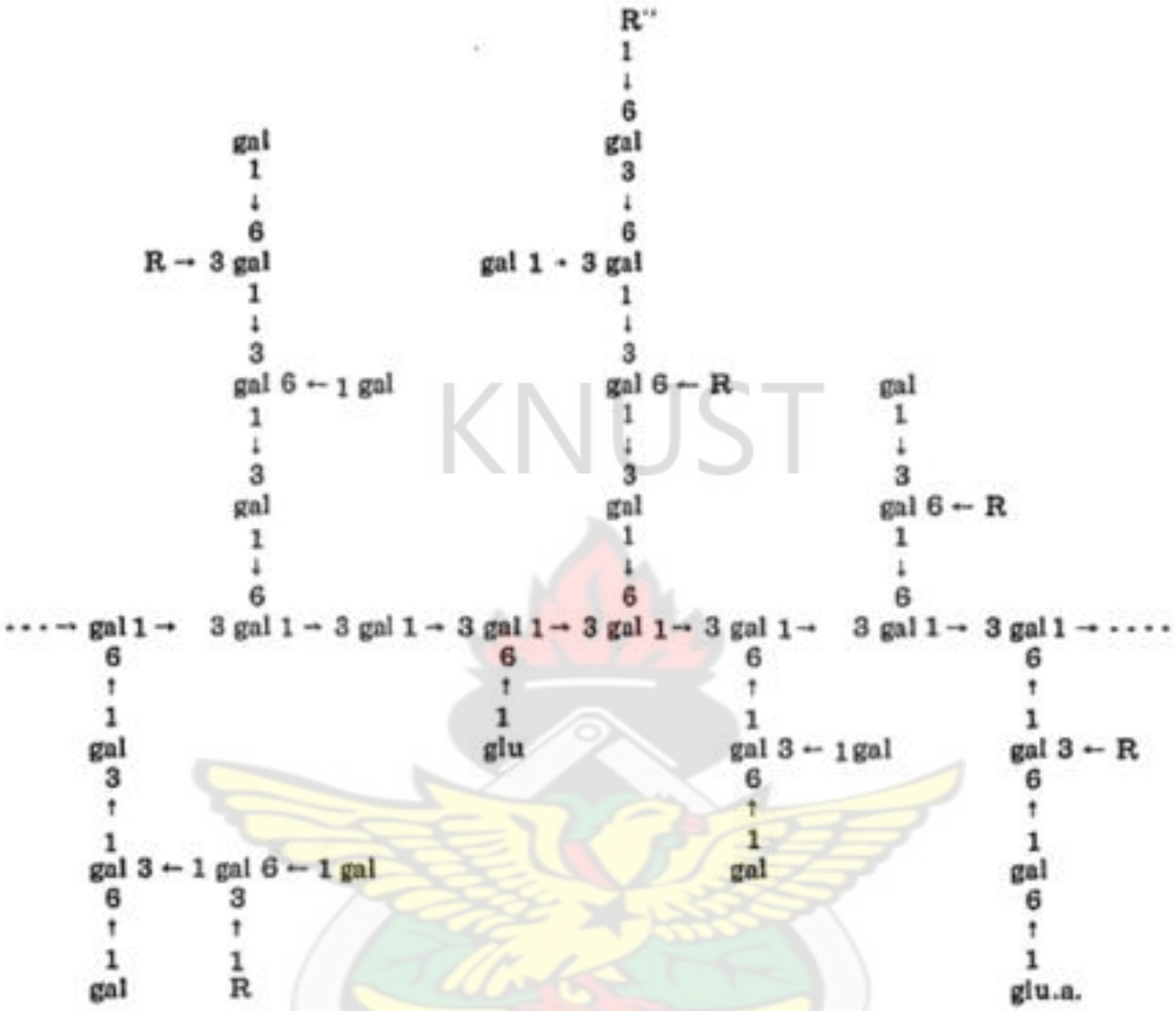
1.3.9.0 CASHEW GUM

Cashew gum is a complex, highly branched polysaccharide of high molecular mass which after hydrolysis yields galactose and galacturonic acid. The sticky exudates from this tree darken and thicken rapidly on exposure to air. When applied as a varnish, provides remarkable protection, as is unchanged by acids, alkalis, alcohols or heat up to 70^{o}C (Lima et al., 2002).

1.3.9.1 CHEMICAL PROPERTIES AND COMPONENTS OF CASHEW GUM

Due to its chemical nature, when cashew gum is applied as a varnish, it provides remarkable protection, as is unchanged by acids, alkalis, alcohols or heat up to 70^{o}C (De Paula and Rodrigues, 1995).

The gum exudate from *Anacardium occidentale* contains galactose (61%), arabinose (14%), rhamnose (7%), glucose (8%) and glucuronic acid (5%) in addition to small amounts (< 2%) of each of mannose, xylose and 4-0 methylglucuronic acid. Contrary to earlier findings, the main aldobiuronic acid present is 6-O-(β-D-glucopyranosyluronic acid)-D-galactose; smaller amounts of the 4-O-methyl analogue are also present. Mild acid hydrolysis showed only two galactobioses, 3-O-β-D-galactopyranosyl-D-galactose (major component) and 6-O-β-D-galactopyranosyl-D-galactose (minor component) (Anderson and Bell, 1975). Kjeldahl nitrogen, proteins, phenols and enzymes such as polyphenoloxidase, peroxidase, chitinase and trypsin-, chymotrypsin-, subtilisin- and papain-inhibitors have also been shown to be present in cashew gum. It has also been proved to have some antimicrobial (antifungal and antibacterial) and insecticidal activities thereby suggesting its possible role in the defence mechanisms of the plant (Marques and Xavier-Filho, 1991; Marques et al, 1992).



Above is a possible structural fragment of cashew gum (R - D-mannose, D-xylose, L-rhamnose, L-arabinose or 1, 2-linked arabinose chains. R'' - D-glucose or D-glucuronic acid) (Anderson and Bell, 1975)

1.3.9.2 USES OF CASHEW GUM

The gum is used largely in industrial application as a binder/adhesive for books, envelopes, labels, stamps and posters. It is also used as an additive in the production of chewing gum because of its thickening power. In the food industry, it is used as a jellying agent for canned food and fruit jam. It is also used as a stabiliser for fruit juices, as well as in preparing salad dressings and making cashew wines.

Cashew gum (similar to gum Arabic) can be used as a substitute for liquid glue for paper, and in the pharmaceutical industry, as an agglutinant for capsules and pills (Smith and Montgomery, 1959). Other possible uses are as an emulsifying and a suspending agent in the pharmaceutical

industry.

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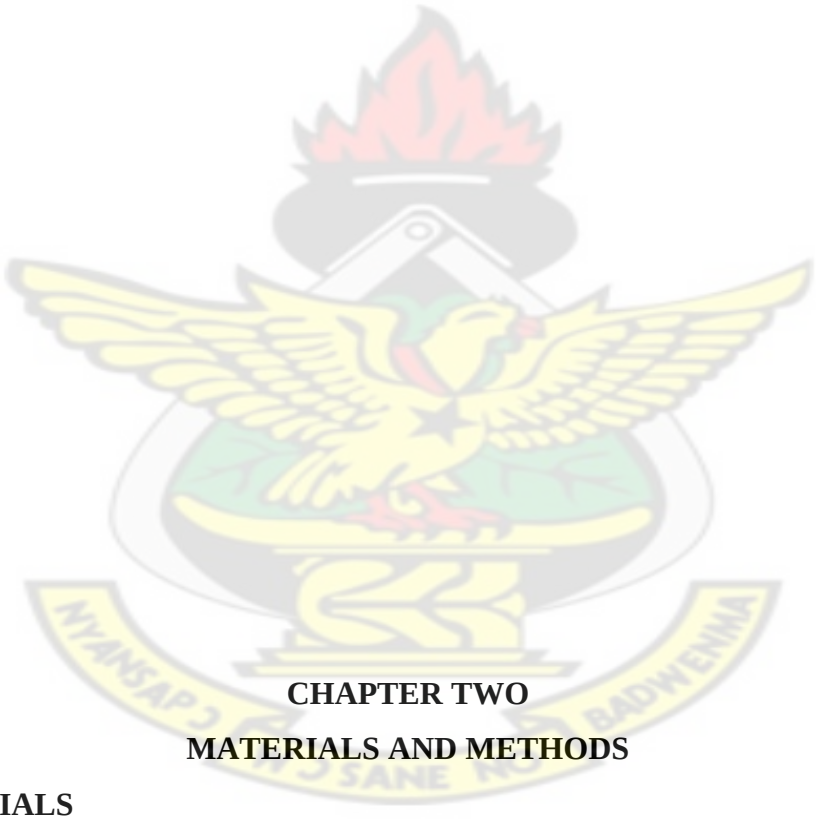

CHAPTER TWO
MATERIALS AND METHODS

2.1.0 MATERIALS

Crude and purified cashew gums were used for the study. The crude gum was obtained from a cashew plantation at Nkoranza in the Ashanti Region of Ghana, as natural exudates from the stem barks of the tree *Anacardium occidentale*, family Anacardiaceae. Mad. Augustina Addai, a retired worker at the Forestry Research Institute of Ghana, FORIG, Fumesua in Kumasi authenticated the plant, collected and supplied the crude gum. Other materials include Paracetamol powder BP, Lactose, Magnesium stearate, (Kinapharma Ltd., Ghana), Maize starch,

Polyvinyl pyrrolidone, Carboxymethyl cellulose (Tradewinds Chemists, Kumasi), Hydroxypropyl methylcellulose, HPMC E15 (i.e. viscosity of 2% solution is 15 cPs) (Amponsah-Effah Pharmaceuticals Ltd., Kumasi), Talc.

2.1.1 REAGENTS

96% ethanol, diethylether, distilled water, glycerol, propylene glycol, sodium hydroxide (NaOH) pellets, potassium dihydrogenphosphate (KH_2PO_4), dilute hydrochloric acid were obtained from the chemical stores of the Departments of Pharmaceutics and Pharmaceutical Chemistry, KNUST, Kumasi.

2.1.2 APPARATUS AND EQUIPMENT

pH meter (Eutech instruments, Cyberscan), ADAM Analytical balance (Milton Keynes, United Kingdom), T90+ UV/VIS Spectrometer (PG Instruments Ltd, Leicestershire, England), Erweka Dissolution Apparatus (Type DT 6, GmbH Heusenstamm, Germany), Brookfield Viscometer (Model DV-ll+, PHYWE, Gottingen, Germany), Retsch laboratory sieves, Erweka Disintegration Apparatus (ZT3, GmbH Heusenstamm, Germany), Erweka Friabilator (TA 20, GmbH Heusenstamm, Germany), Universal Testing Machine (Hounsfield Ltd., Surrey, England), Micrometer (Clarke Instruments Ltd., Salisbury, England), Monsanto hardness Tester (Missouri, USA), Manesty Tablet Coater (GRYPHON, Huddersfield, England), Oven (Gallenkamp 300 Plus Series, Apeldoorn Zuid, Netherlands), Single punch tabletting machine (DP 30, Pharmao Ind. Co., Ltd. Liaoning, China), magnetic stirrer, beakers, conical flasks, petri dishes (glass and plastic), sintered glass filter (No. 1), hot plate, Whatman filter papers, measuring cylinders, water bath, among others were the equipment and apparatus used for this project.

2.2.0 PURIFICATION OF CRUDE CASHEW GUM

The process was started by removing the bark attached to the gum with the aid of a knife, and also by hand picking debris and breaking the tears into smaller pieces. The lighter grade of the collected cashew gum was selected for purification. The gum was dried in a hot air oven at 50^{o}C (for about 6 h) until it became easily breakable after which it was ground using a porcelain mortar and pestle till fine. Some of this was used as crude cashew gum for some of the subsequent tests and analyses. For the purification, 900 ml of distilled water was added to 300 g

of the ground crude gum and stirred. The mixture was then allowed to stand for 24 h with intermittent stirring. The mucilage obtained was then strained through a two-fold calico cloth to remove any insoluble matter or impurities. The gum was then precipitated by adding 1200ml of 96% ethanol with stirring. It was then washed with diethylether and dried in a hot air oven at 60^{o}C for 8 h. The dried purified gum was then ground with a mortar and pestle and screened through a180 μm sieve. The gum was then stored in an air-tight container and used for subsequent tests.

Percentage Yield Determination

The weight of the dry crude gum (before purification), W1 and that of the dry purified gum (after purification), W2 were determined using a balance. The percentage yield was then calculated using the formula;

$W2/W1 \times 100$

2.3.0 EXAMINATION OF PHYSICO-CHEMICAL PROPERTIES OF CASHEW GUM

2.3.1 MACROSCOPIC EXAMINATION

Macroscopic properties of the cashew gum determined included colour, odour, taste, surface appearance, size, form and shape and fracture.

2.3.2 MOISTURE CONTENT (LOSS ON DRYING) British Pharmacopeia (BP) method

One gram (1 g) of the crude gum was weighed into a glass petri dish of known weight and dried in a hot air oven at 105^{o}C till constant weight. The final (constant) weight of the gum was taken, and the moisture content (loss on drying) was then calculated and expressed as a percentage. The process was repeated for the purified gum.

2.3.3 INSOLUBLE MATTER IN CRUDE AND PURIFIED GUMS (B.P. method)

To five grams (5 g) of the crude gum in a conical flask, 100 ml of distilled water was added, followed by 14.0 ml of dilute hydrochloric acid. The mixture was boiled gently for 15min with frequent shaking, filtered while hot through a tared sintered glass filter (No. 1) and washed with hot distilled water. The residue was then dried at 105^{o}C till constant weight. This was repeated using the purified cashew gum. The weight of the insoluble matter (residue) on the filter was then expressed as a percentage.

2.3.4 SWELLING CAPACITY

Five grams (5 g) of the purified and dry cashew gum powder was placed in a 100 ml capacity measuring cylinder and tapped 200 times manually. The initial volume of the gum, V1 was recorded and this was followed by the addition of 85 ml of distilled water. The mouth of the cylinder was covered and shaken. The volume was made to 100 ml and left to stand for 24 h after which the new volume occupied by gum, V2 was recorded. The swelling capacity was computed as the ratio of final volume to initial volume, V2/V1 (Bowen and Vadino, 1984). Two other media; 0.1M HCl and phosphate buffer (pH – 6.80) were also used.

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2.4.0 EFFECT OF CONCENTRATION AND STORAGE TIME ON VISCOSITY

Four different concentrations of the purified gum were prepared i.e. 5, 10, 15 and 20%w/v dispersions. They were each prepared by weighing the required amount of the gum into a clean beaker and adding three quarters of the required volume of water and then stirred using a magnetic stirrer. They were then left to stand overnight to ensure full dissolution and then stirred again for 10 min to obtain good homogenous solutions. The viscosities of the four concentrations of gum dispersions prepared were determined in triplicate, using a Brookfield viscometer (speed-30 rpm: temperature-25^{o}C). This was done weekly over six weeks.

2.5.0 EFFECT OF CONCENTRATION AND STORAGE TIME ON pH

Mucilages of the purified gum were prepared with distilled water at concentrations of 5, 10, and 15 and 20%$^{w}/_{v.}$ The pH of the samples was determined weekly over a six-week period using a standardised pH meter (at room temperature – 27-28^{o}C).

2.6.0 PREPARATION OF FREE FILMS FROM PURIFIED CASHEW GUM

Free films were prepared by the solvent casting method. The components of the film formulations are shown in Table 1.0. For each formulation, the required amount of gum(s) was weighed into a beaker and 15 ml of distilled water added. The mixture was stirred with a stirrer, plasticised with the required amount of propylene glycol and then stirred again with a magnetic

stirrer for 2 h (by which time no concentration gradients were observed in the preparation(s)). The solution was made up to the final volume (20 ml) with more distilled water. It was then left to stand overnight to enhance dissolution (by diffusion) and also to remove any trapped air bubbles. The mixture was then stirred again for 1 h using the magnetic stirrer. The 20ml formulation was then carefully poured into the centre of a 9cm diameter plastic petri dish and then left to dry in an oven at 60^{o}C . The drying times of the films varied from 4 to 6 h. The films were then carefully removed and placed in labeled petri dishes which were stored in a dessicator for further evaluation. Using the same values in Table 1.0, another set of films were prepared using glycerol as plasticiser in place of propylene glycol.

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Table 1.0 Formulas of polymeric solutions for preparing free films

Formulation	**A**			**B**					**C**			
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
CG (%)	7.5	10.0	12.5	12.5	12.5	12.5	12.5	12.5	10.0	10.0	10.0	10.0
Amount of CG (g)	1.50	2.00	2.50	2.50	2.50	2.50	2.50	2.50	2.00	2.00	2.00	2.00
CMC (1%) Amount (g)	-	-	-	-	-	-	-	-	0.20	-	-	-

CMC (2%) Amount (g)	-	-	-	-	-	-	-	-	-	0.40	-	-
HPMC (1%) Amount (g)	-	-	-	-	-	-	-	-	-	-	0.20	-
HPMC (2%) Amount (g)	-	-	-	-	-	-	-	-	-	-	-	0.4
Plasticiser concentration (%)	20	20	20	0	5	10	20	30	20	20	20	20
Plasticiser amount (g)	0.30	0.40	0.50	-	0.125	0.25	0.50	0.75	0.44	0.48	0.44	0.48
Plasticiser volume(ml)	0.24	0.32	0.40	-	0.10	0.20	0.40	0.60	0.35	0.38	0.35	0.38
Water to (ml)	20	20	20	20	20	20	20	20	20	20	20	20

CG-cashew gum, CMC-carboxymethyl cellulose, HPMC- Hydroxypropyl methyl cellulose (E15), Plasticiser- glycerol/ propylene glycol

A – Effect of gum content, B – Effect of plasticizer content, C – Effect of blending CMC or HPMC with cashew gum

2.7.0 EVALUATION/ CHARACTERISATION OF FREE FILMS

The films were evaluated for the following properties

2.7.1 WEIGHT DETERMINATION

Six films (2 cm×2 cm each) from each formulation were taken and weighed individually on an electronic balance. The average weights and standard deviations were then calculated.

2.7.2 THICKNESS

The thickness of the films (1 cm×1 cm) was determined at five different locations (centre and four peripheral locations) using a micrometer screw gauge and a mean value of the five measurements was used as the film thickness and the standard deviation was calculated.

2.7.3 MECHANICAL PROPERTIES

2.7.3.1 FOLDING ENDURANCE

A strip of film (2 cmx2 cm) of each formulation was cut by using a sharp scissors. Folding endurance was determined by repeatedly folding the film at the same place. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

2.7.3.2 TENSILE STRENGTH, YOUNG'S MODULUS AND PERCENTAGE ELONGATION

These mechanical properties were evaluated using a Hounsfield Universal Testing Machine with a 500 N load cell. Film strips of dimensions 5cm×1cm, and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min until the force applied was sufficient to break each film. The force at break (N) and elongation were then recorded from the screen connected to the machine. The determinations were done in triplicate for each formulation. Three parameters, namely tensile strength, Young's modulus and percent elongation were computed for the evaluation of the films using the following equations:

$$\text{Tensile strength (N/ mm}^2\text{)} = \frac{\text{Force at break (N)}}{\text{Initial cross-sectional area of the sample (mm}^2\text{)}}$$

$$\textbf{\%}\ \text{Elongation} = \frac{\text{Increase in length of film}}{\text{Original length of film}} \times 100$$

$$\text{Young's modulus (N/mm}^2\text{)} = \frac{\text{Force at break (N)}}{\text{Change in length}} \times \frac{\text{Original length of film}}{\text{Cross-sectional area of film}}$$

2.8.0 FORMULATION OF PARACETAMOL TABLETS

2.8.1 PREPARATION OF POLYVINYL PYRROLIDONE (PVP) MUCILAGE

10 g of PVP powder was weighed into a clean mortar. About 30 ml of distilled water was added bit by bit with trituration till a uniform solution was formed. This was then transferred into a 100

ml measuring cylinder and made up to volume with more distilled water to produce a 10%$^{w}/_{v}$ preparation. The resulting mucilage was then used as the binding agent for the preparation of paracetamol granules.

Table 2.0 Formula for preparing Paracetamol granules for compression into tablets

Ingredients	1 tablet/ mg	600 tablets/ g
Paracetamol	250	150
Lactose	101	60.6
Maize starch	32	19.2
PVP	10	6.0
Talc	6	3.6
Magnesium stearate	1	0.6

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2.8.2 PREPARATION OF GRANULES AND COMPRESSION INTO TABLETS

The granules were prepared by the wet granulation method. 150 g of paracetamol powder, 60.6 g of lactose and 19.2 g of maize starch were weighed and mixed by geometric dilution in a clean porcelain mortar. The 10%w/v PVP mucilage prepared was added in bits to the powder mix while carefully kneading. This was done until a suitable damp mass was achieved after which the volume of the mucilage used was recorded. The damp mass was screened using laboratory sieve number 8. The wet granules obtained were then dried in a hot air oven at 60^{o}C for 1 h. The dried granules were then screened using sieve number 16 and lubricated with 3.6 g of talc and 0.6 g of magnesium stearate by hand mixing. The granules were dried again at 60^{o}C for 5 min and then compressed into tablets using a single punch tabletting machine. The tablets produced had an average diameter of 10 mm and each contained approximately 250 mg of paracetamol.

2.9.0 QUALITY CONTROL TESTS ON UNCOATED PARACETAMOL TABLETS

2.9.1 UNIFORMITY OF WEIGHT

Twenty (20) tablets from the batch produced were randomly selected. The tablets were weighed together, after which the average tablet weight was calculated. The tablets were then weighed

individually. The weight of each tablet was subtracted from the average tablet weight (deviation) and the percentage deviation of each tablet from the mean was also calculated.

2.9.2 FRIABILITY TEST

A sample of whole tablets of total weight as near as possible to 6.5 g was weighed initially, Wo and dedusted. They were then placed in the drum of the friabilator and all the parameters set on the machine. The drum rotated and tumbled the tablets for 4 min (100 times), after which the machine stopped automatically. Any loose dust from the tablets was removed and their final weight, W_f taken and the percentage weight loss calculated as $[(Wo - W_f) /Wo] \times 100$. The tablets were observed for cleavages, breakages and cracks.

2.9.3 HARDNESS TEST

Ten (10) tablets were selected randomly from the tablet batch. Each tablet was placed in between the test jaws of the tablet hardness tester. The force applied to each tablet till it broke was recorded, and the mean value computed as the breaking strength/hardness of the tablets.

2.9.4 THICKNESS

The thicknesses of ten tablets (crown) were determined using a micrometer and the average calculated.

2.9.5 DISINTEGRATION

One (1) dosage unit was placed in each of the 6 tubes of the basket of a disintegration apparatus. The apparatus was operated using distilled water as the immersion fluid, maintained at 37 ± 2 °C. The machine was put on and the rack with tubes moved up and down in the immersion fluid, until all tablets disintegrated in each of the tubes. The time was then recorded. The procedure was repeated with two other media: 0.1 M HCl and phosphate buffer of pH 6.80.

2.9.6 ASSAY OF PARACETAMOL TABLETS

2.9.6.1 PREPARATION OF STANDARD SOLUTIONS FOR CALIBRATION PLOT

The following solutions of pure paracetamol powder using 0.1M NaOH as solvent were prepared: 0.00025%w/v, 0.00050%w/v, 0.00075%w/v, 0.0010%w/v and 0.0015%w/v. The

absorbances of these solutions were determined at a wavelength of 257nm. A calibration curve showing the relationship between concentration and absorbance was then plotted. The equation and correlation value were then determined.

2.9.6.2 ASSAY

Twenty (20) of the uncoated paracetamol tablets were weighed and powdered. A quantity of the powder containing 0.15 g of paracetamol was added to 50 ml of 0.1M NaOH. This was then diluted with 100 ml of distilled water, shaken for 15 min and sufficient water added to produce 200 ml of solution. The solution was further shaken and filtered. 10 ml of the filtrate was taken and diluted to 100 ml with more distilled water. 10 ml of the resulting solution was taken and to it, 10 ml of 0.1M NaOH was added, and the solution diluted to 100 ml. The absorbance of this final solution was then measured in triplicate, at a wavelength of 257 nm by UV spectrophotometry, using 0.1M NaOH as the reference solution. Using the regression statistics obtained from the calibration plots of the standard solutions, the amount of paracetamol in the tablets was calculated.

2.9.7 DISSOLUTION OF TABLETS

2.9.7.1 PLOTTING CALIBRATION CURVES

The appropriate amounts of pure paracetamol powder were weighed to prepare solutions of the following concentrations; 0.00025%w/v, 0.00050%w/v, 0.00075%w/v, 0.0010%w/v and 0.0015%w/v, using 0.1M HCl as the solvent. The same concentrations were prepared using a phosphate buffer (pH 6.80). The absorbances of these solutions were determined at a wavelength of 257 nm. A calibration curve showing the relationship between concentration and absorbance was then plotted for drug for each solvent used. The equations and correlation coefficient values for each curve were then determined.

2.9.7.2 IN VITRO DISSOLUTION TESTING

This test was carried out using an Erweka Dissolution machine (paddle method). The dissolution parameters used: 37 ± 0.5^{o}C; 50 rpm; 900 ml of 0.1M Hydrochloric acid. One dosage unit was placed in each of the vessels of the dissolution machine and operated at the specified rate. Extreme care was taken to exclude air bubbles from the surface of the dosage unit. At specified

time intervals of 5 min, 10 min, 15 min , 20 min, 30 min, 45 min, 60 min and 90 min, 5 ml samples were withdrawn from a zone midway between the surface of the dissolution medium and the top of the rotating paddle blade, not less than 1 cm from the vessel wall. To replace the 5 ml sample withdrawn, 5 ml of fresh dissolution medium was added to the vessel from which the volume was withdrawn. The vessel was kept covered for the duration of the test and the temperature of the medium maintained at 37 ± 0.5 °C at all times. The withdrawn samples were filtered using Whatman filter paper and diluted 20 times with some of the dissolution medium. The diluted filtrates were then analysed by UV spectrophotometry at a wavelength of 257 nm using a 1cm cell and 0.1M HCl as blank solution.

Using the equation obtained from the calibration curve, the concentration of paracetamol in samples taken at the specified times were calculated and the percentage release values were then calculated. A plot of percentage drug release against time was established. The test was repeated using phosphate buffer (pH 6.80).

2.10.0 FILM COATING OF TABLETS

2.10.1 PREPARATION OF FILM COATING SOLUTION

Composition of coating liquid:

- Polymer (CG) -7.50%w/v
- Glycerol - 20% of weight of the gum
- Distilled water - to volume

The required amount of the gum was weighed and dispersed into a beaker containing distilled water, three-quarters of the final volume of the formulation. The mixture was stirred with a mechanical stirrer for five (5) hours, during which it was plasticized with the calculated volume of glycerol, the plasticiser. The mixture was allowed to stand overnight to enhance dissolution (by diffusion) and also to remove any trapped air bubbles. The mixture was then stirred again for a further two (2) hours.

2.10.2 CALIBRATION OF SPRAYING DEVICE

The volume of the spraying device was determined by initially washing and drying the spray gun. It was then filled to capacity with water. The water was then transferred into a measuring

cylinder and the volume noted. This procedure was repeated three times and the average value recorded as the volume of the spraying device.

2.10.3 DETERMINATION OF SPRAY RATE

The spray gun of the spraying device was filled with water and the water discharged with the aid of the pump. The volume of water discharged per minute was recorded as the average of three readings. The procedure was repeated using the coating solutions prepared. The number of pumping (depression of valve of spraying device) done per minute of spraying was also recorded.

Table 2.1

Operating Conditions for Coating

ITEM/ FACTOR	VARIABLE
Charge per batch	150 tablets
Speed of pan	25 rpm
Spray rate	48.33 ± 0.577 ml/ min
Drying air temperature	60 ± 3^{o}C
Distance of spray gun from pan	13 cm
Spray gun nozzle diameter	1 mm
Coating times	4 minutes
	8 minutes

2.10.4 THE FILM COATING PROCESS

A Manesty tablet coater was used for the film coating. The equipment was switched on for some time to allow the drying air to reach a temperature of 60^{o}C. One hundred and fifty (150) tablets of paracetamol were loaded into the pan coater previously cleaned. The process was started by pre-warming of the tablets for 5 min while they tumbled in the pan. As the tablets rolled, the film coating solution was sprayed and the drying air caused the solvent to evaporate simultaneously.

A cycle of 30 seconds of spraying (6 sprays) followed by 5 min of drying was employed. The cycle was repeated eight (8) and sixteen (16) times to obtain coating times of four (4) and eight (8) minutes respectively. The tablets were then labelled appropriately and dried in glass petri dishes in a hot air oven at 40^{o}C overnight.

2.11.0 QUALITY CONTROL TESTS ON COATED PARACETAMOL TABLETS

Uniformity of weight, friability, hardness, thickness, disintegration and in vitro dissolution tests were carried out on both the four (4) and eight (8) minutes coated tablets as was done for the uncoated tablets.

N.B The average thickness of the film coats was computed as the difference between the thickness of the coated and uncoated tablets.

2.12.0 STATISTICAL ANALYSIS

Results obtained were analysed and graphs drawn using Microsoft Office Excel and Graph Pad prism.

2.12.1 DATA ANALYSIS

The dissolution/drug release data obtained were treated according to the Hixson-Crowell, Higuchi and Korsmeyer - Peppas equation models to evaluate the release mechanism and kinetics.

CHAPTER THREE

RESULTS AND CALCULATIONS

3.1.0 PURIFICATION OF CASHEW GUM

Percentage Yield Determination

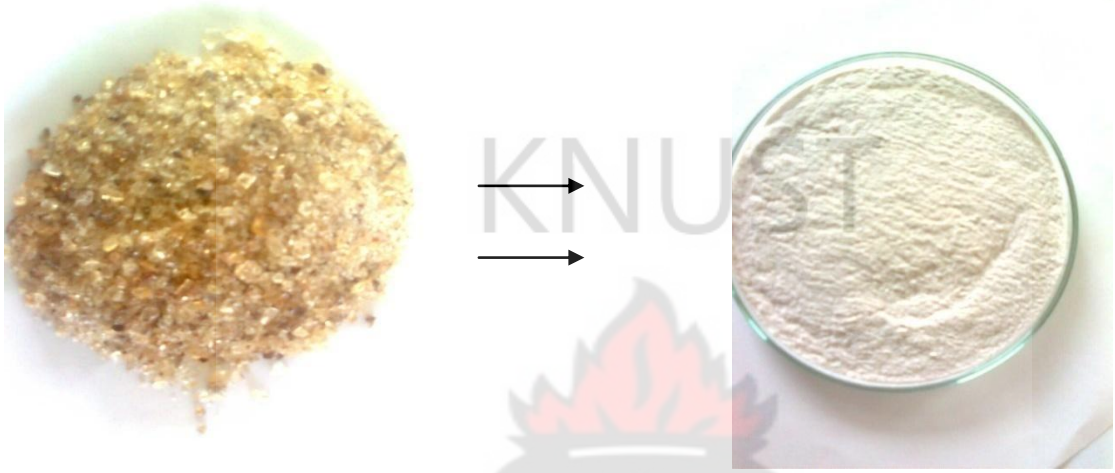
Weight of crude gum, W1 = 300 g

Weight of purified gum, W2 = 229.77 g

% yield = $\frac{W2}{W1} \times 100$

= $\frac{229.77\ g}{300\ g} \times 100$

= 76.59%



Crude gum Purified gum

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3.2.0 PHYSICAL EXAMINATION OF CASHEW GUM

Table 3.1.0

Macroscopic properties of cashew gum

Property	Characteristic of gum	
Colour	Crude gum	-Glassy white, golden

	brown Purified gum -Off-white to buff
Taste	Bland
Surface appearance	Crude gum -Somewhat smooth surface
Size	Crude gum -Variable
Form and Shape	Crude gum -Thin long cylindrical tears, short and rounded
Fracture	Crude gum -Rounded ones fracture with difficulty and the thin ones did so easily

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Table 3.1.1

Moisture content and insoluble matter of cashew gum

Gum	Moisture content (%)	Insoluble matter (%)
Purified gum	11.20±0.141	0.20±0.028

Crude gum	13.00±2.828	0.40±0.071

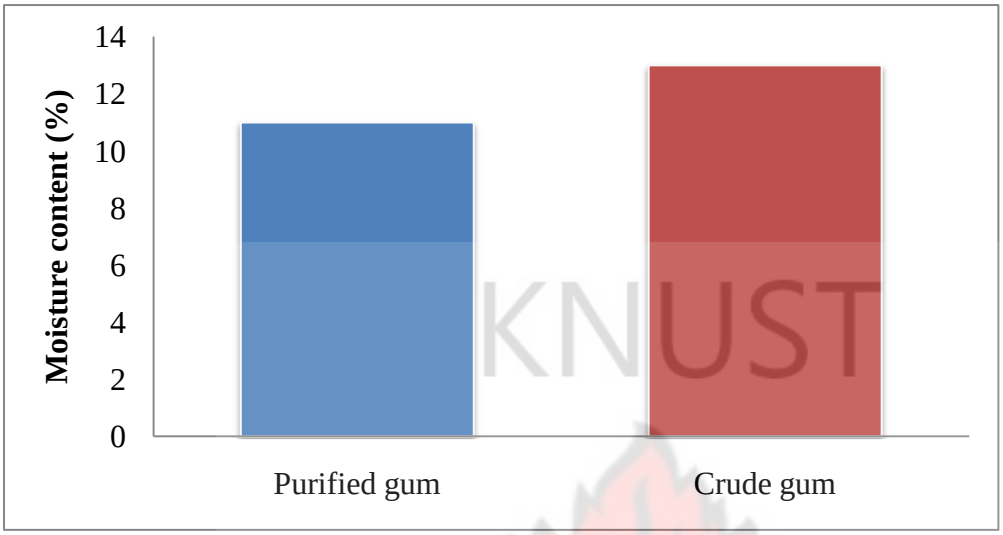

Figure 3.0 Moisture content of purified and crude cashew gum

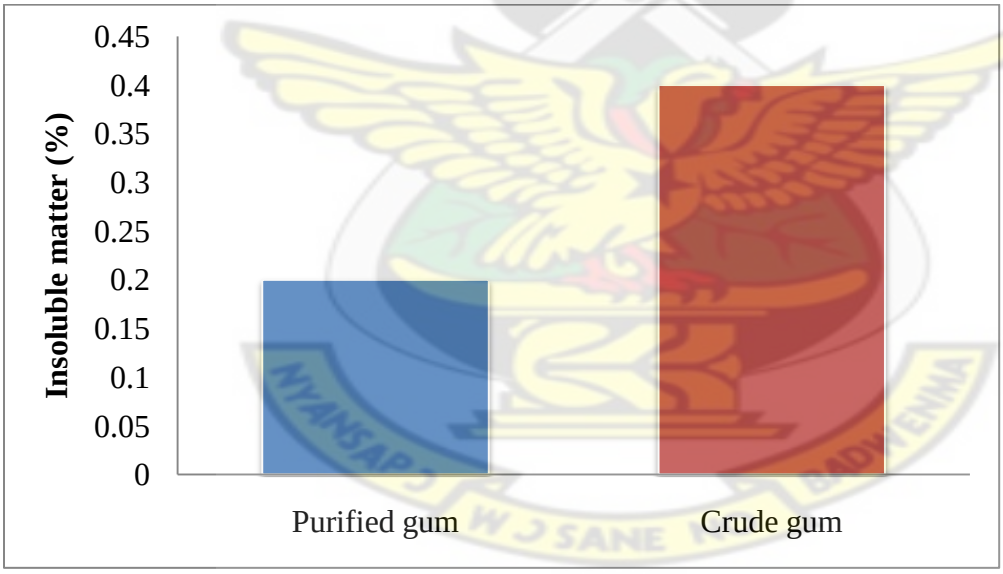

Figure 3.1 Insoluble matter of purified and crude cashew gum

Table 3.1.2

Swelling capacity of purified cashew gum in different media

Medium	Swelling Capacity
Distilled water	3.29

0.1M HCl	3.53
Phosphate buffer (pH-6.80)	3.83

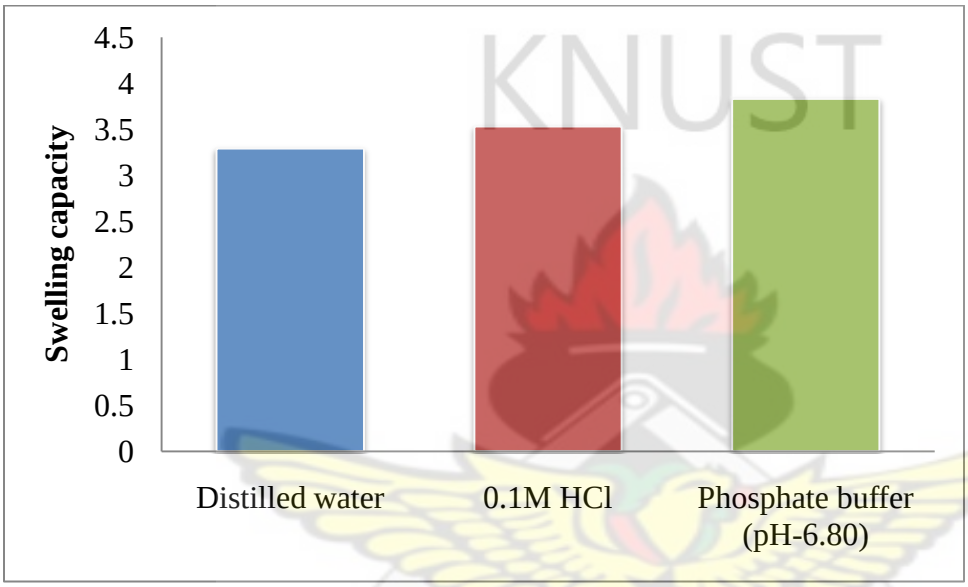

Figure 3.2 Swelling capacity of purified cashew gum in different media

Table 3.1.3

Viscosity with concentration

Concentration (%w/v)	Viscosity (cPs)
5	2.67±0.58

10	5.00±0.00
15	26.27±0.23
20	86.93±1.85

Values are mean ± S.D, (n = 3)

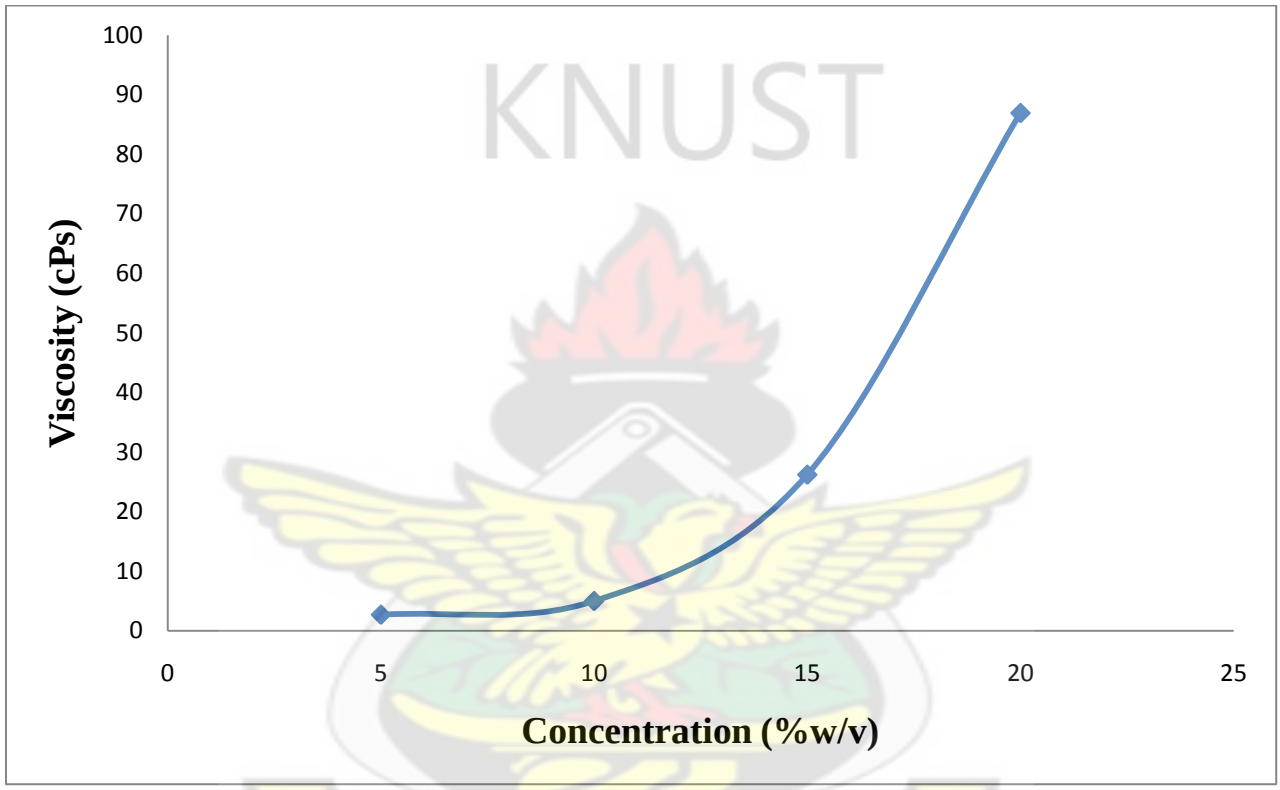

Figure 3.3 Viscosity of cashew gum as a function of concentration

Table 3.1.4

Change in viscosity with time

	Viscosity (cPs)

Storage Time	5%w/v	10%w/v	15%w/v	20%w/v	P value
Week 0	2.67±0.58	5.00±0.00	26.27±0.23	86.93±1.85	< 0.001
Week 1	3.20±0.00	8.67±0.58	35.07±0.12	95.00±0.00	< 0.001
Week 2	2.33±0.58	5.33±0.58	41.00±0.00	109.93±0.12	< 0.001
Week 3	3.00±0.00	10.00±0.00	42.53±0.46	110.40±0.17	< 0.001
Week 4	2.00±0.00	10.00±0.00	44.67±0.58	110.33±0.58	< 0.001
Week 5	2.00±0.00	10.00±0.00	43.20±0.35	110.13±0.23	< 0.001
Week 6	2.00±0.00	10.00±0.00	42.00±0.00	110.00±0.00	< 0.001

Values are mean ± S.D, (n = 3); P value summary = *** (Means are significantly different)

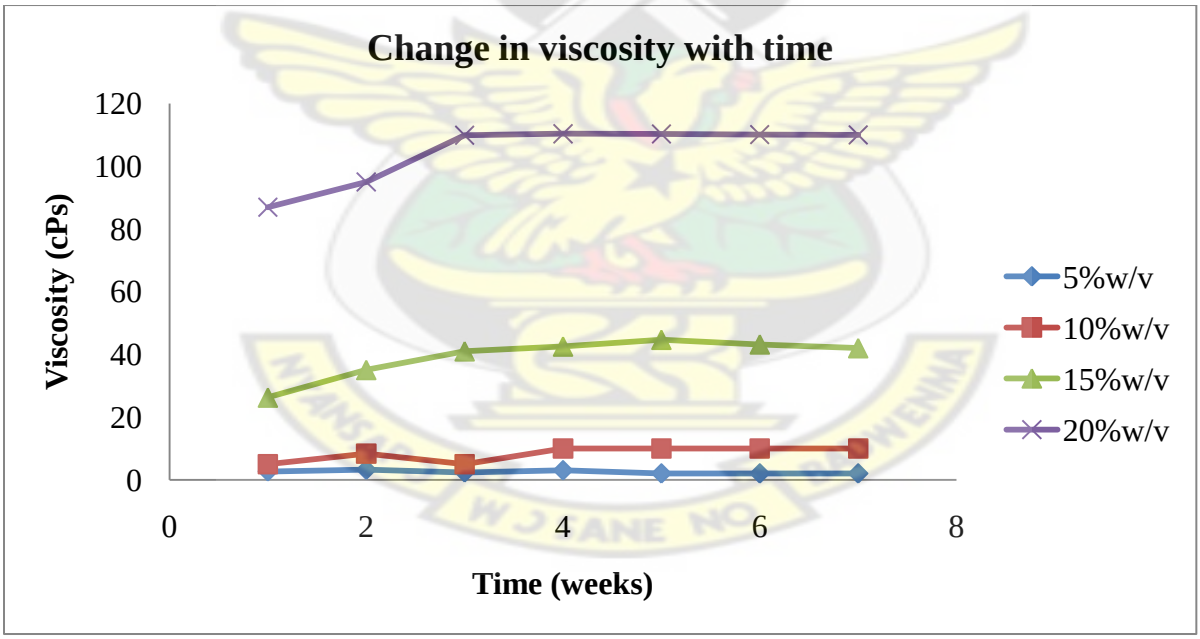

Figure 3.4 **Relationship between viscosities of purified cashew gum preparations and storage time**

Table 3.1.5

pH with concentration

Concentration (%w/v)	pH
5.0	4.44
10.0	4.35
15.0	4.32
20.0	4.28

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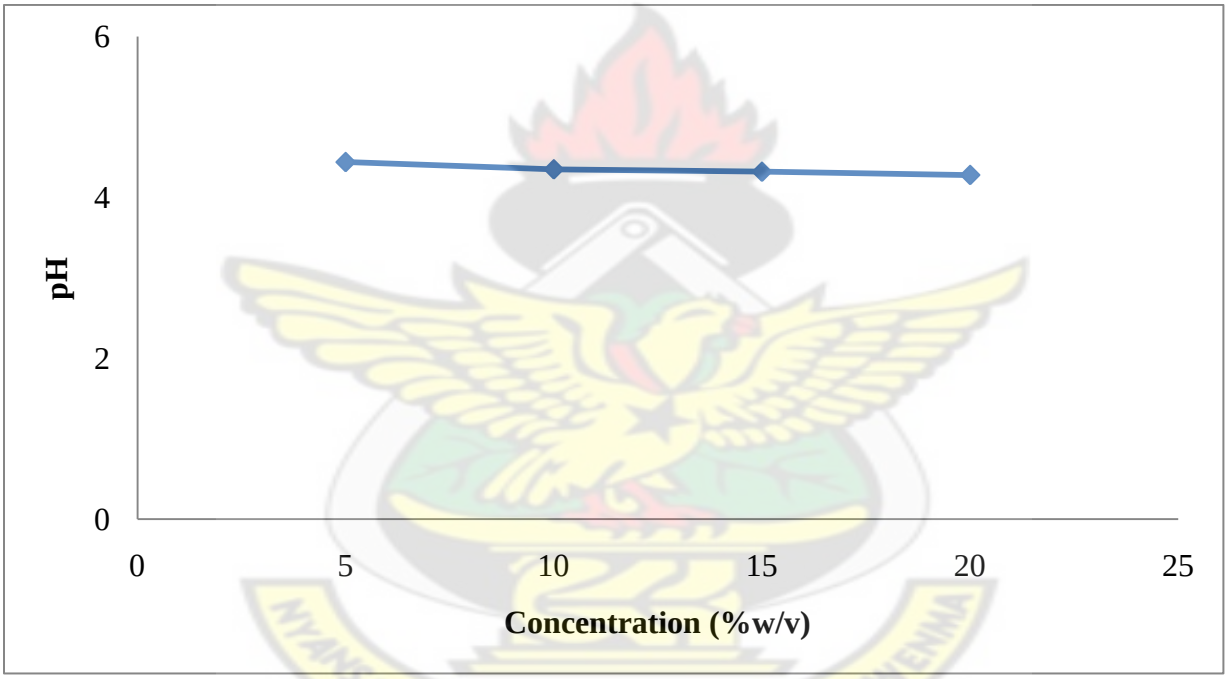

Figure 3.5 **pH of cashew gum as a function of concentration**

Table 3.1.6

Change in pH with time

Storage Time	pH			
	5%w/v	10%w/v	15%w/v	20%w/v
Week 0	4.44	4.35	4.32	4.28
Week 1	4.27	4.17	4.14	4.07
Week 2	4.20	4.10	4.08	4.06
Week 3	4.14	4.07	4.05	4.02
Week 4	4.17	4.17	4.07	4.06
Week 5	4.29	4.27	4.18	4.17
Week 6	4.43	4.32	4.21	4.17

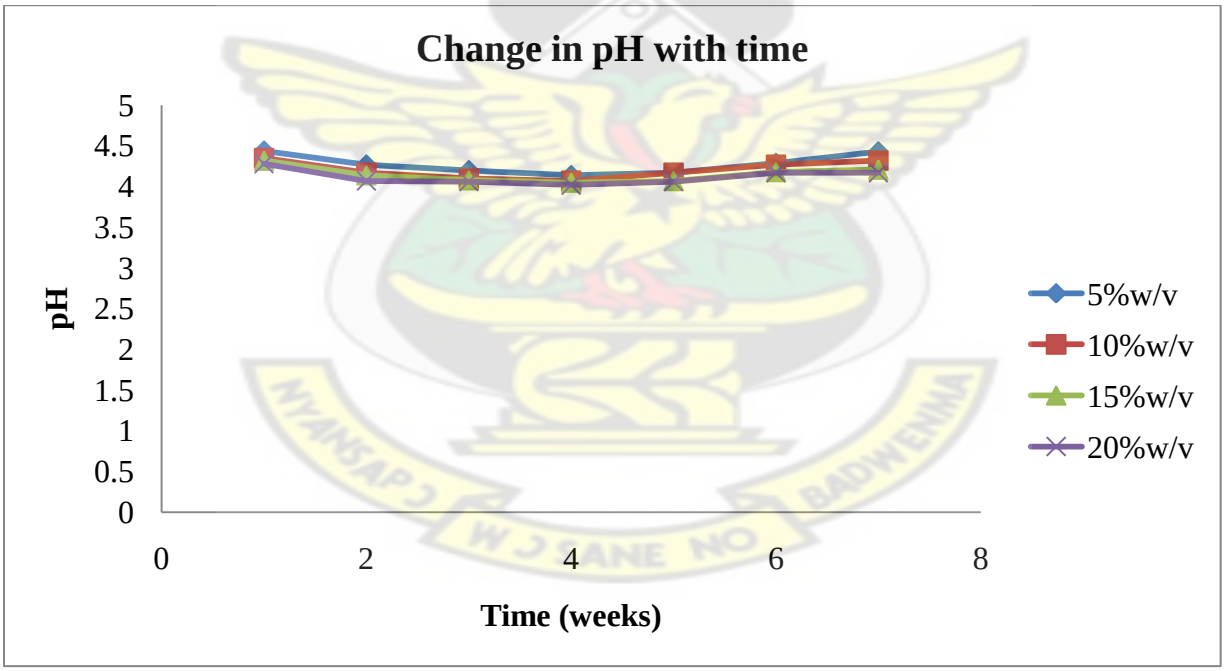

Figure 3.6 Relationship between pH of purified cashew gum preparations and storage time

3.3.0 FREE FILMS EVALUATION

Table 3.2.0 Appearance and texture of free films

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Formulation	Appearance	Texture
F1	Transparent and uniform	Smooth
F2	Transparent and uniform	Smooth
F3	Transparent and uniform	Smooth
F4	Transparent and uniform	Smooth
F5	Transparent and uniform	Smooth
F6	Transparent and uniform	Smooth
F7	Transparent and uniform	Smooth
F8	Transparent and uniform	Smooth
F9	Opaque but uniform	Rough
F10	Opaque but uniform	Rough
F11	Transparent but non-uniform	Slightly rough
F12	Transparent but non-uniform	Slightly rough

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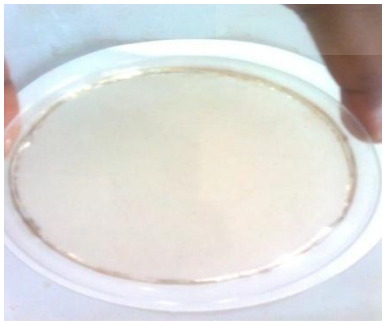

Cashew gum only, using glycerol as plasticiser

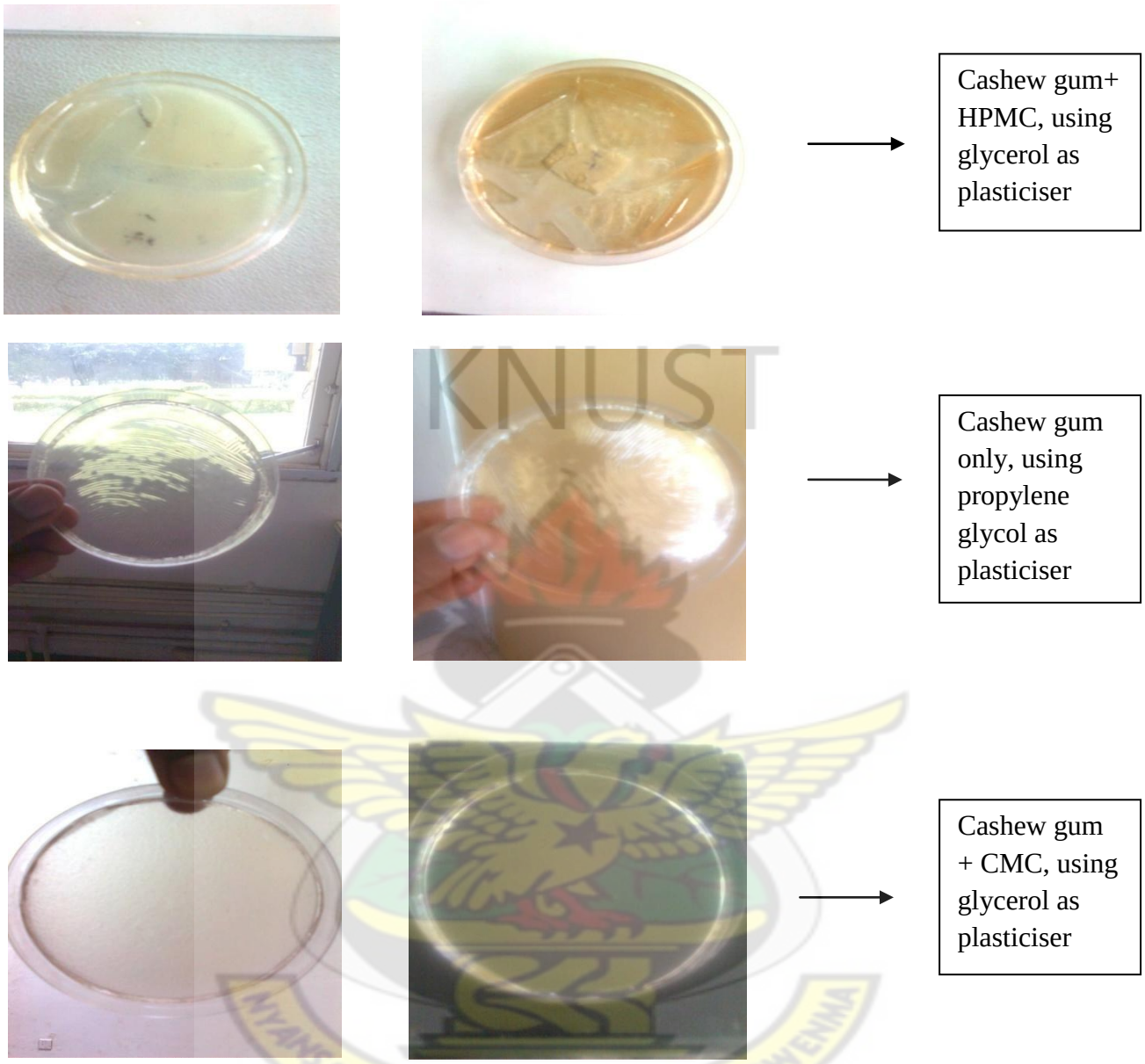

Figure 3.7 Sample pictures of the free films

Table 3.2.1 Properties of Free Films

Formulation	Weight (g) (mean ± S.D, n = 6)	Thickness (mm) (mean ± S.D, n = 5)	Folding endurance	% Elongation (mean ± S.D, n = 3)	Tensile strength (N/mm^2) (mean ± S.D, n = 3)	Young's modulus (N/mm^2) (mean ± S.D, n = 3)

A	**F1**	0.0337±0.006	0.21±0.007	289	54.34±9.455	0.56±0.044	1.03±0.115
	F2	0.0354±0.003	0.24±0.004	299	65.88±2.330	0.65±0.046	0.98±0.060
	F3	0.0412±0.003	0.26±0.009	249	84.53±4.894	0.71±0.026	0.81±0.080
B	**F4**	-	-	-	-	-	-
	F5	0.0439±0.005	0.32±0.006	-	-	-	-
	F6	0.0423±0.005	0.31±0.004	98	41.85±9.717	3.62±0.380	8.98±2.325
	F7	0.0412±0.003	0.26±0.009	249	84.53±4.894	0.71±0.026	0.81±0.080
	F8	0.0558±0.005	0.29±0.009	356	89.09±7.425	0.47±0.079	0.58±0.068
C	**F9**	0.0462±0.003	0.31±0.004	210	76.39±6.480	1.53±0.113	2.32±0.578
	F10	0.0492±0.005	0.32±0.009	>400	80.01±4.703	4.44±0.241	5.574±0.635

A – Effect of gum content, B – Effect of plasticizer content, C – Effect of blending CMC with cashew gum

Table 3.3.0

Calibration of Spraying Device and Determination of Spray Rate

Parameter	**Variable**

Volume of spraying device	300 ± 0.00 ml
Spray rate (per minute)	48.33 ± 0.577 ml/ min
Pumps per minute	88 ± 1.00 pumps/min
Volume per spray/discharge	0.55 ml

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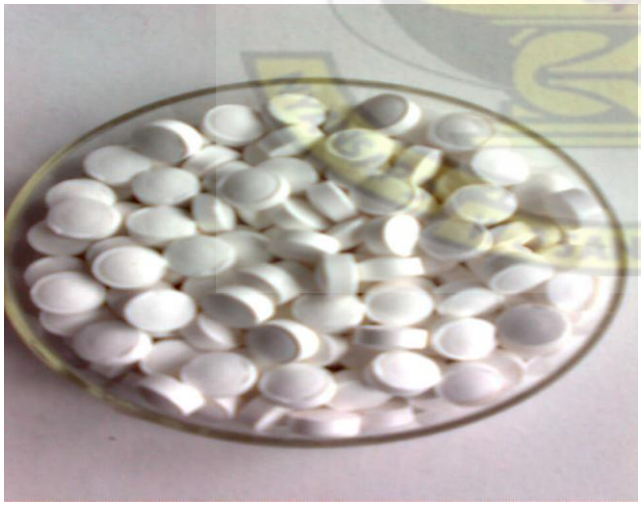

Uncoated tablets

Coated
(4 minutes)
tablets

Coated
(8 minutes)
tablets

Figure 3.8 Pictures of the uncoated and coated tablets

3.4.0 QUALITY CONTROL TESTS CONDUCTED ON UNCOATED AND COATED PARACETAMOL TABLETS

3.4.1 UNIFORMITY OF WEIGHT

CALCULATION

The percentage deviations of the tablets from the mean were calculated using:

$$\text{Percentage deviation} = \frac{(A - B)}{B} \times 100,$$

Where, A = Initial weight of tablet, B = Average weight of 20 tablets

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Table 3.4.0

Uniformity of weight of Uncoated tablets

Tablet no.	Tablet weight, A(g)	Deviation (A-B), g	Percentage deviation
1	0.4043	0.0003	0.074
2	0.4027	-0.0013	-0.322
3	0.4058	0.0018	0.445
4	0.4072	0.0032	0.792

5	0.4055	0.0015	0.371
6	0.4056	0.0016	0.396
7	0.4039	-0.0001	-0.025
8	0.4050	0.0010	0.248
9	0.4034	-0.0006	-0.149
10	0.4051	0.0011	0.272
11	0.4014	-0.0026	-0.645
12	0.4034	-0.0006	-0.149
13	0.4007	-0.0033	-0.817
14	0.4021	-0.0019	-0.470
15	0.4035	-0.0005	-0.124
16	0.4048	0.0008	0.198
17	0.4047	0.0007	0.173
18	0.4061	0.0021	0.520
19	0.4028	-0.0012	-0.297
20	0.4017	-0.0023	-0.569
Total weight (g)		8.0797	
Average weight (g), B		0.4040	
Standard deviation		0.0017	

Table 3.4.1

Uniformity of weight of Coated tablets - 4 minutes

Tablet no.	Tablet weight A(g)	Deviation (A-B), g	Percentage deviation
1	0.4212	0.0089	2.159
2	0.4077	-0.0046	-1.116
3	0.4114	-0.0009	-0.218
4	0.4117	-0.0006	-0.146

5	0.4170	0.0047	1.140
6	0.4113	-0.0010	-0.243
7	0.4074	-0.0049	-1.188
8	0.4031	-0.0092	-2.231
9	0.4180	0.0057	1.382
10	0.4016	-0.0107	-2.595
11	0.4035	-0.0088	-2.134
12	0.4244	0.0121	2.935
13	0.4096	-0.0027	-0.655
14	0.4112	-0.0011	-0.267
15	0.4291	0.0168	4.075
16	0.4013	-0.0110	-2.668
17	0.4120	-0.0003	-0.073
18	0.4165	0.0042	1.019
19	0.4074	-0.0049	-1.188
20	0.4198	0.0075	1.819
Total weight (g)		8.2452	
Average weight (g), B		0.4123	
Standard deviation		0.0077	

Table 3.4.2

Uniformity of weight of Coated tablets - 8 minutes

Tablet no.	Tablet weight A(g)	Deviation (A-B), g	Percentage deviation
1	0.4141	-0.0070	-1.662
2	0.4204	-0.0007	-0.166
3	0.4249	0.0038	0.902

4	0.4338	0.0127	3.016
5	0.4190	-0.0021	-0.499
6	0.4257	0.0046	1.092
7	0.4058	-0.0153	-3.633
8	0.4305	0.0094	2.232
9	0.4313	0.0102	2.422
10	0.4226	0.0015	0.356
11	0.4196	-0.0015	-0.356
12	0.4283	0.0072	1.710
13	0.4192	-0.0019	-0.451
14	0.4318	0.0107	2.541
15	0.4148	-0.0063	-1.496
16	0.4246	0.0035	0.831
17	0.4150	-0.0061	-1.449
18	0.4118	-0.0093	-2.209
19	0.4174	-0.0037	-0.879
20	0.4112	-0.0099	-2.351
Total weight (g)		8.4218	
Average weight (g), B		0.4211	
Standard deviation		0.0077	

3.4.2 Weights of tablets before and after coating

Table 3.4.3

Batch	Average tablet weight/g	Weight (150 tablets) before coating/g	Weight (150 tablets) after coating/g	Weight gain/ g	% Weight gain

Uncoated	0.4040	-	-	-	-
Coated (4 min)	0.4123	60.23	60.51	0.28	0.46
Coated (8 min)	0.4211	60.41	61.58	1.17	1.94

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3.4.3 Thickness of uncoated and coated tablets

Table 3.4.4

Batch	Average crown thickness (mm)	Thickness of film coat (mm)
Uncoated	5.817±0.063	-
Coated (4 min)	5.820±0.055	0.0015
Coated (8 min)	5.850±0.062	0.0165

Values are mean ± S.D, (n = 20)

3.4.4 Friability test

Table 3.4.5

Batch	Initial weight, A/ g	Final weight/ g	Weight loss, B/ g	% Friability [B/A ×100]
Uncoated	6.40	6.37	0.03	0.47
Coated (4min)	6.48	6.48	0.00	0.00
Coated (8 min)	6.52	6.52	0.00	0.00

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3.4.5 Resistance to crushing /Hardness

Table 3.4.6

Batch	Hardness (Kg/cm^2)
Uncoated	3.58 ± 0.504
Coated (4min)	7.12 ± 1.401
Coated (8 min)	8.83 ± 1.194

Values are mean ± S.D (n =10)

3.4.6 Disintegration time

Table 3.4.7

Batch	Disintegration time (min)		
	Distilled water	0.1M HCl	Phosphate buffer (pH – 6.80)
Uncoated	1.09	1.00	0.45
Coated (4min)	2.51	2.28	2.26
Coated (8 min)	3.26	2.57	3.13

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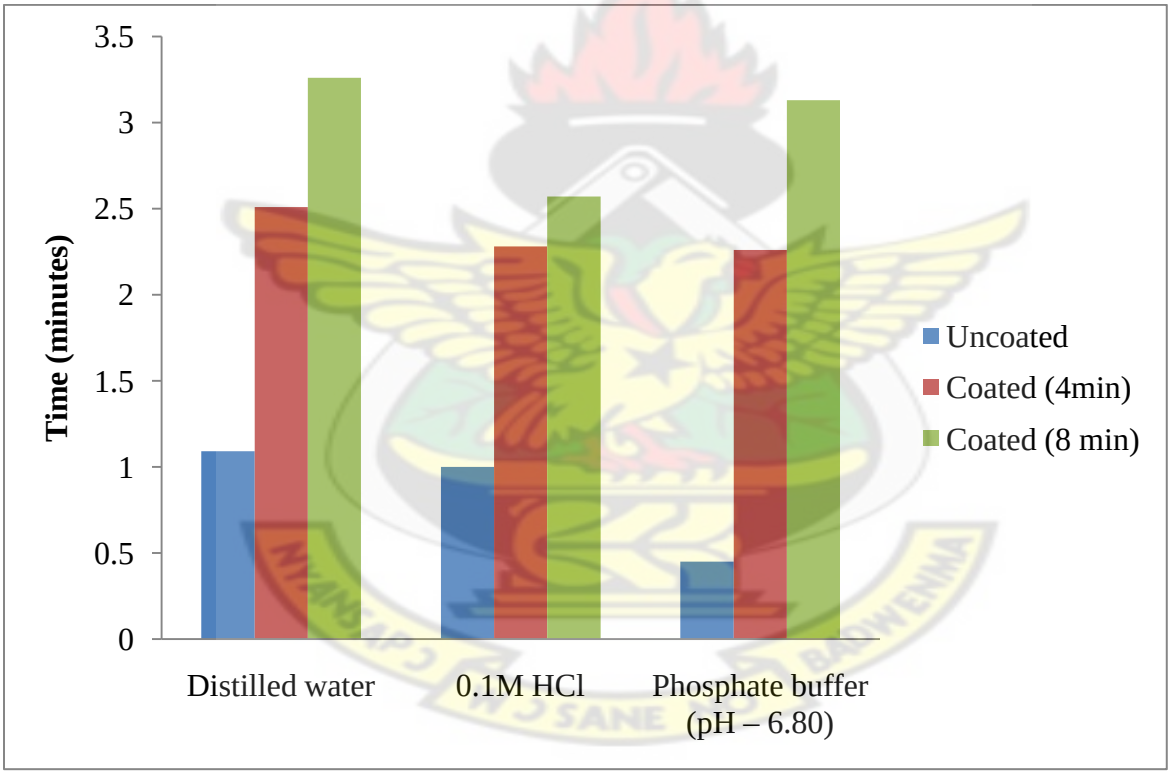

Figure 3.9 Disintegration times of uncoated and coated tablets in different media

3.5.0 ASSAY OF PARACETAMOL TABLETS

Table 3.5.0

Absorbance of pure paracetamol in 0.1M NaOH

Blank solution: 0.1M NaOH

Concentration (%w/v)	Absorbance
0.00025	0.704
0.00050	0.877
0.00075	1.050
0.0010	1.221
0.0015	1.584

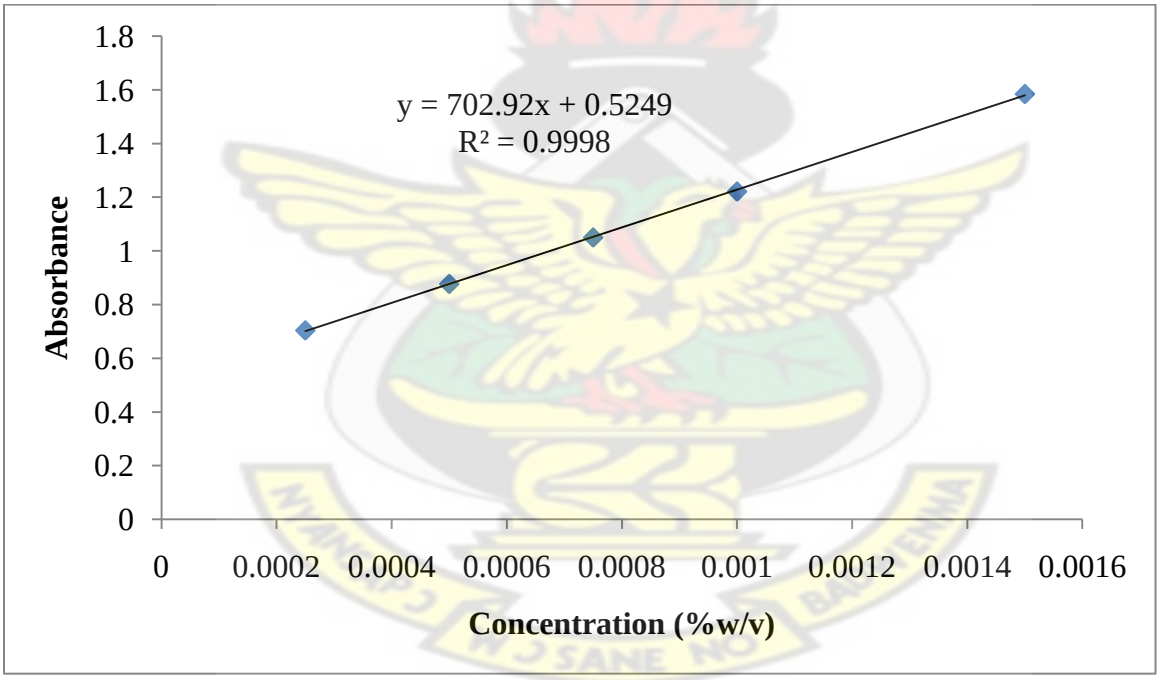

Figure 3.10 Calibration curve for pure paracetamol in 0.1M NaOH

Calculation of paracetamol content in tablets

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From the calibration curve, the equation of the graph of pure paracetamol powder dissolved in 0.1M NaOH is:

$y = 702.9x + 0.524$

where y= absorbance, and x = concentration

hence,

$x = (y-0.524) / 702.9$

For an absorbance of 1.037, its concentration,

$x = (1.037 – 0.524)/ 702.9$

$x = 7.3 \times 10^{-4}$ %w/v

Calculation of expected concentration of paracetamol in the assay

0.15 g Paracetamol (P) was diluted to 200 ml = Solution A

10 ml of A was diluted to 100 ml

If, 0.15 g P = 200 ml

7.5×10^{-3} g = 10 ml

10ml of A (7.5×10^{-3} g P) was diluted to 100 ml = Solution B

Solution B contains 7.5×10^{-3} g P

Finally, 10 ml of B was diluted to 100 ml = Solution C

If, 100 ml of B = 7.5×10^{-3} g P

Then, 10 ml of B = 7.5×10^{-4} g P

Therefore the final solution, C whose absorbance was measured contained 7.5×10^{-4} g Paracetamol and the corresponding concentration is 7.5×10^{-4} %w/v.

The paracetamol content of the tablets

= Actual concentration obtained after assay × 100%

Expected concentration

= $\frac{7.3 \times 10^{-4}\ \%w/v}{7.5 \times 10^{-4}\ \%w/v} \times 100\%$

= **97.33%**

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Table 3.5.1

Paracetamol content of tablets

Absorbance	Paracetamol content (%)	Mean paracetamol content ± S.D
1.037	97.33	
1.036	97.12	**97.32±0.1904%**
1.038	97.50	

3.6.0 DISSOLUTION OF TABLETS

Table 3.6.0

Absorbance of pure paracetamol in 0.1M HCl

Blank solution: 0.1M HCl

Concentration(%w/v)	Absorbance
0.00025	0.150
0.00050	0.300
0.00075	0.428
0.0010	0.544
0.0015	0.836

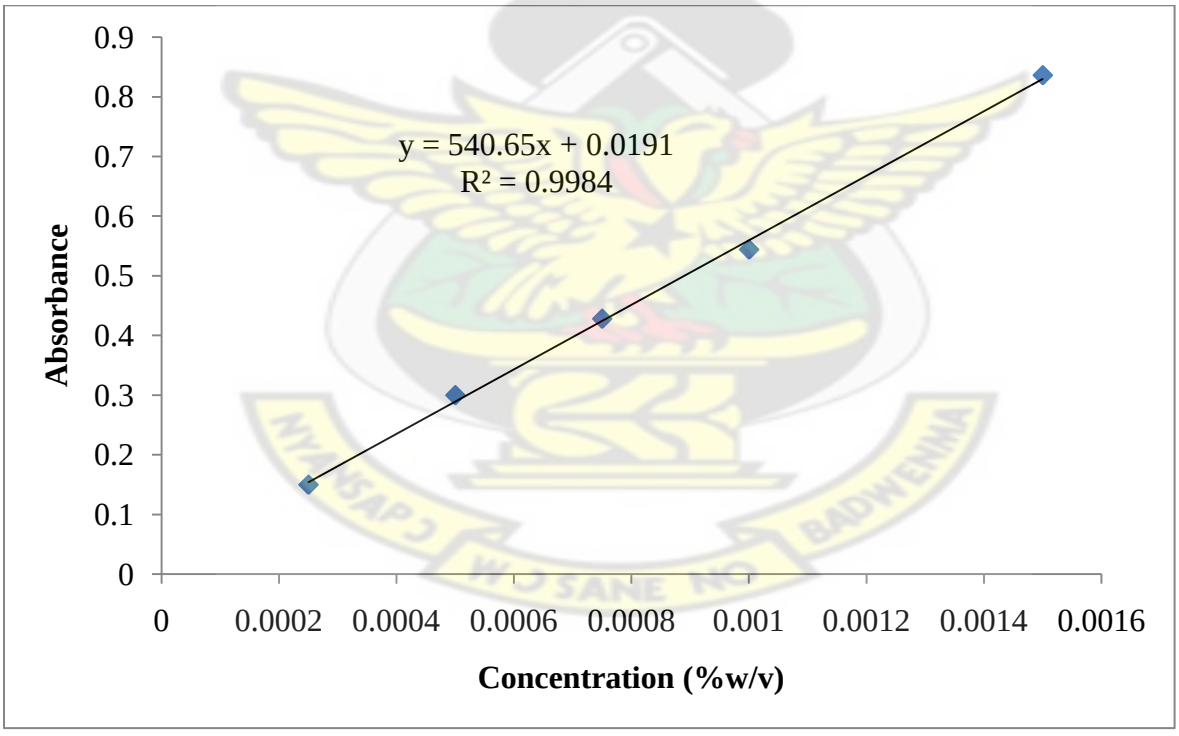

Figure 3.11 Calibration curve for pure paracetamol in 0.1M HCl

Table 3.6.1

Absorbance of pure paracetamol in Phosphate buffer (pH-6.80)

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Blank solution: Phosphate buffer (pH-6.80)

Concentration (%w/v)	Absorbance
0.00025	0.120
0.00050	0.240
0.00075	0.383
0.0010	0.449
0.0015	0.741

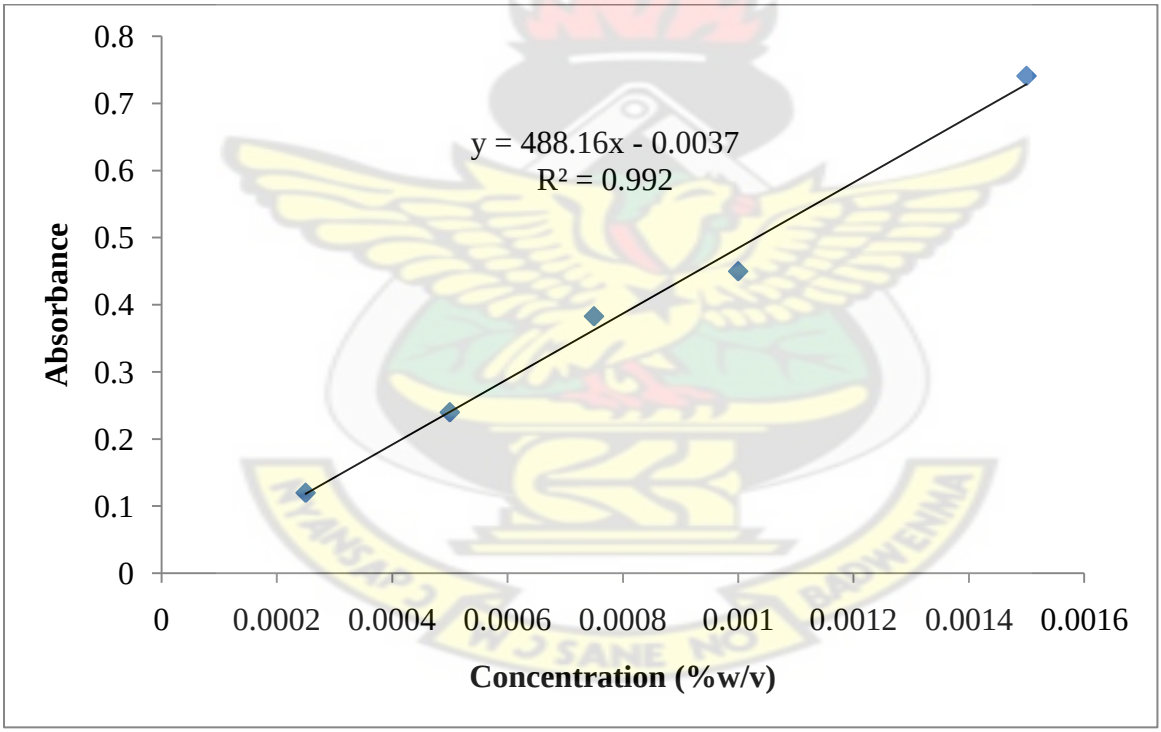

Figure 3.12 Calibration curve for pure paracetamol in Phosphate buffer (pH - 6.80)

Calculation for concentration of Paracetamol

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From the calibration curve, the equation of the graph of pure paracetamol powder dissolved in 0.1M HCl is:

$y = 540.6x + 0.019$

where y = absorbance, and x = concentration

hence,

$x = (y - 0.019) / 540.6$

For a solution with an absorbance of 0.558, its concentration,

$x = (0.558 – 0.019)/ 540.6$

$x = 9.90 \times 10^{-4}$ %w/v

Multiplying 'x' by the dilution factor of 20 gives the concentration of drug dissolved.

9.90×10^{-4} %w/v x 20 = 1.994×10^{-2}%w/v

= 0.01994%w/v

0.01994%w/v was contained in the 5 ml of solution pipetted

Calculation of percentage release

For a 100% release of the paracetamol,

250 mg of drug is in 900 ml of dissolution medium

Concentration = 0.027778%w/v

Then % release

= (0.01994%w/v / 0.027778%w/v) x 100

= **71.79%**

[NB: Similarly, the various concentrations of paracetamol in the phosphate buffer (pH-6.80) were calculated using the equation, y = 488.1x – 0.003]

3.6.1 DRUG RELEASE PROFILES IN DIFFERENT DISSOLUTION MEDIA

Table 3.7.0

Drug release for uncoated paracetamol tablets in 0.1M HCl

Time (minutes)	Mean absorbance	Amount of drug (g) in 900ml of medium	Concentration (%w/v)	Percentage release (%)
0	0	0	0	0
5	0.558	0.1795	0.01994	71.79
10	0.604	0.1945	0.02161	77.91
15	0.663	0.2144	0.02382	85.77
20	0.664	0.2148	0.02387	85.90
30	0.676	0.2188	0.02431	87.50
45	0.678	0.2194	0.02438	87.77
60	0.682	0.2208	0.02453	88.30
90	0.703	0.2277	0.0253	91.10

Table 3.7.1

Drug release for coated (4 minutes) paracetamol tablets in 0.1M HCl

Time (minutes)	Mean absorbance	Amount of drug (g) in 900ml of medium	Concentration (%w/v)	Percentage release (%)
0	0	0	0	0
5	0.475	0.1518	0.01687	60.73
10	0.588	0.1895	0.02106	75.78
15	0.607	0.1958	0.02176	78.31
20	0.640	0.2068	0.02298	82.71
30	0.652	0.2108	0.02342	84.31
45	0.653	0.2111	0.02346	84.44
60	0.670	0.2168	0.2409	86.70
90	0.675	0.2184	0.02427	87.37

Table 3.7.2

Drug release for coated (8 minutes) paracetamol tablets in 0.1M HCl

Time (minutes)	Mean absorbance	Amount of drug (g) in 900ml of medium	Concentration (%w/v)	Percentage release (%)
0	0	0	0	0
5	0.427	0.1358	0.01509	54.34
10	0.529	0.1698	0.01887	67.92
15	0.544	0.1748	0.01942	69.92
20	0.555	0.1785	0.01983	71.39
30	0.594	0.1915	0.02128	76.58
45	0.594	0.1915	0.02128	76.58
60	0.639	0.2064	0.02293	82.57
90	0.650	0.2101	0.02334	84.04

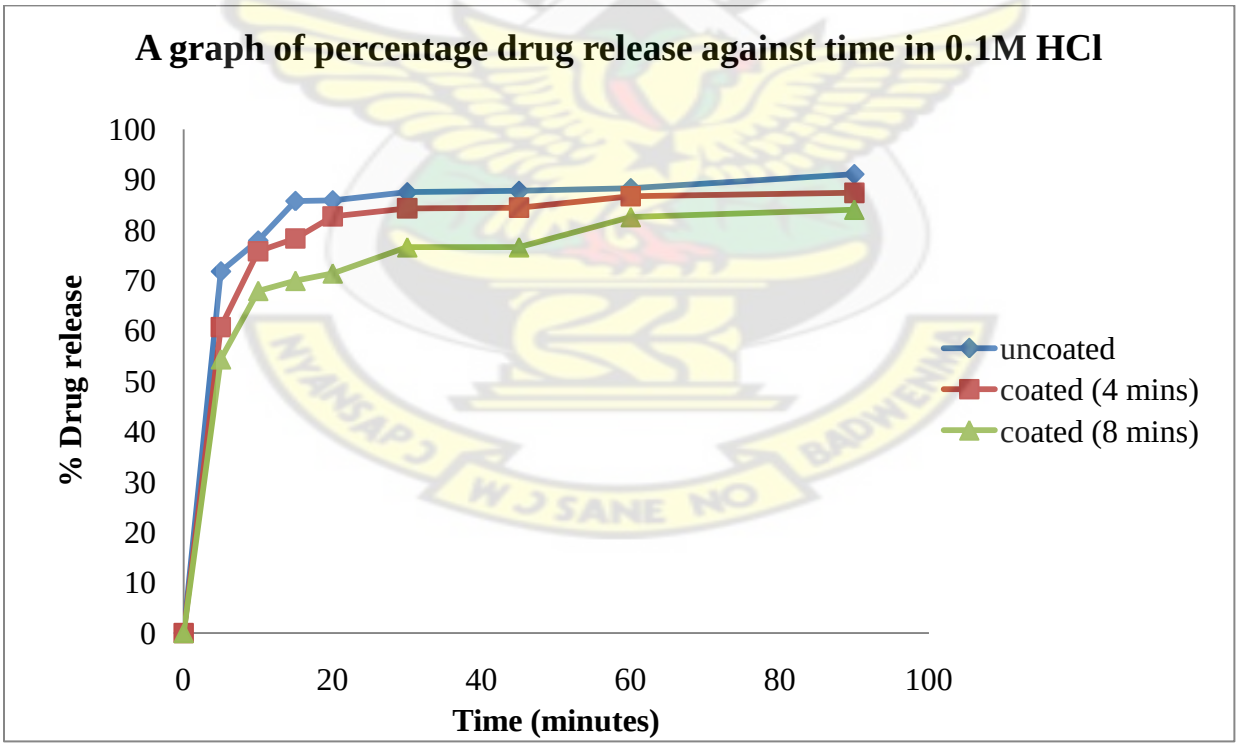

Figure 3.13 Release of paracetamol from uncoated and coated tablets in 0.1M HCl

Table 3.7.3

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Drug release for uncoated paracetamol tablets in phosphate buffer (pH-6.80)

Time (minutes)	Mean absorbance	Amount of drug (g) in 900ml of medium	Concentration (%w/v)	Percentage release (%)
0	0	0	0	0
5	0.487	0.1807	0.02008	72.27
10	0.544	0.2016	0.02240	80.64
15	0.585	0.2168	0.02409	86.72
20	0.594	0.2203	0.02448	88.13
30	0.601	0.2230	0.02478	89.20
45	0.636	0.2360	0.02622	94.37
60	0.655	0.2426	0.02696	97.04
90	0.662	0.2453	0.02726	98.11

Table 3.7.4

Drug release for coated (4 minutes) paracetamol tablets in phosphate buffer (pH-6.80)

Time (minutes)	Mean absorbance	Amount of drug (g) in 900ml of medium	Concentration (%w/v)	Percentage release (%)
0	0	0	0	0
5	0.397	0.1477	0.01641	59.08
10	0.489	0.1816	0.02018	72.63
15	0.540	0.2000	0.02222	80.11
20	0.557	0.2065	0.02294	82.61
30	0.566	0.2101	0.02334	84.03
45	0.581	0.2154	0.02393	86.17
60	0.582	0.2159	0.02399	86.35
90	0.586	0.2172	0.02413	86.89

Table 3.7.5

Drug release for coated (8 minutes) paracetamol tablets in phosphate buffer (pH-6.80)

Time (minutes)	Mean absorbance	Amount of drug (g) in 900ml of medium	Concentration (%w/v)	Percentage release (%)
0	0	0	0	0
5	0.367	0.1366	0.01518	54.63
10	0.470	0.1744	0.01938	69.77
15	0.533	0.1976	0.02196	79.04
20	0.542	0.2011	0.02234	80.47
30	0.546	0.2025	0.02250	81.00
45	0.575	0.2132	0.02369	85.28
60	0.580	0.2150	0.02389	85.99
90	0.582	0.2159	0.02399	86.35

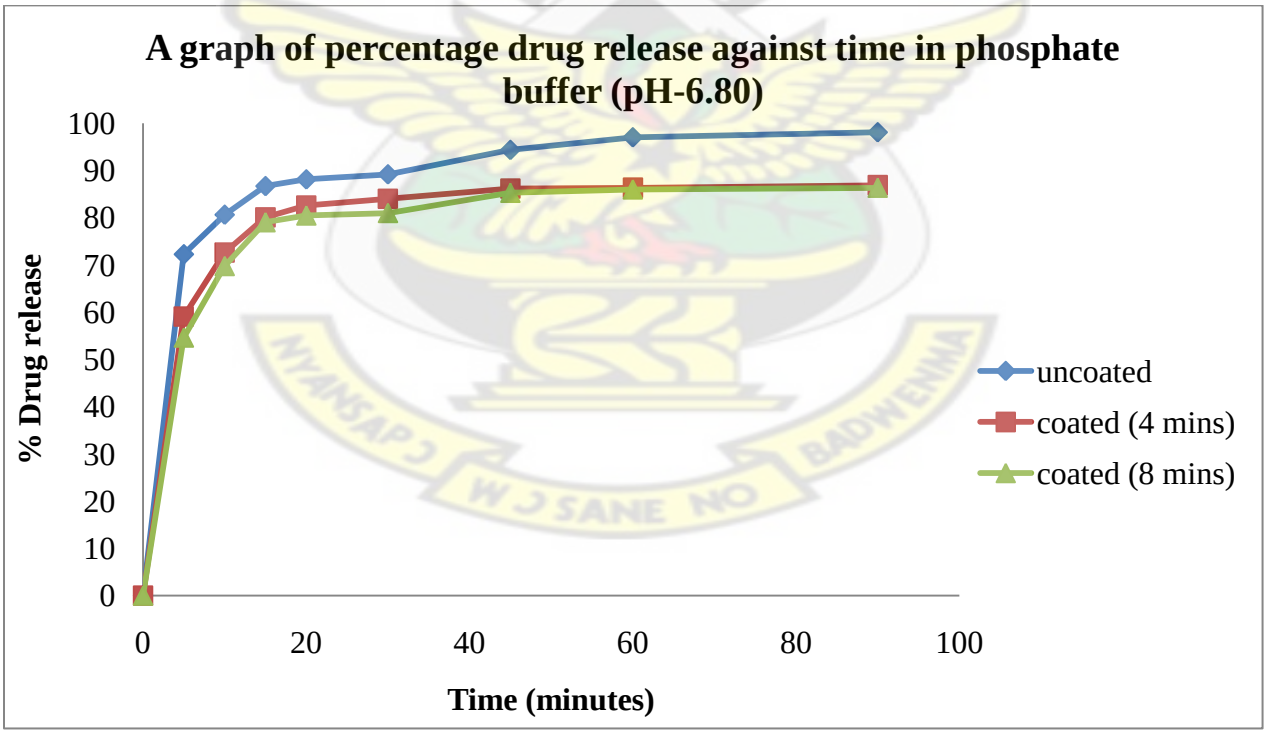

Figure 3.14 Release of paracetamol from uncoated and coated tablets in phosphate buffer (pH - 6.80)

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3.6.2 RELEASE PROFILES OF EACH TABLET BATCH IN BOTH DISSOLUTION MEDIA

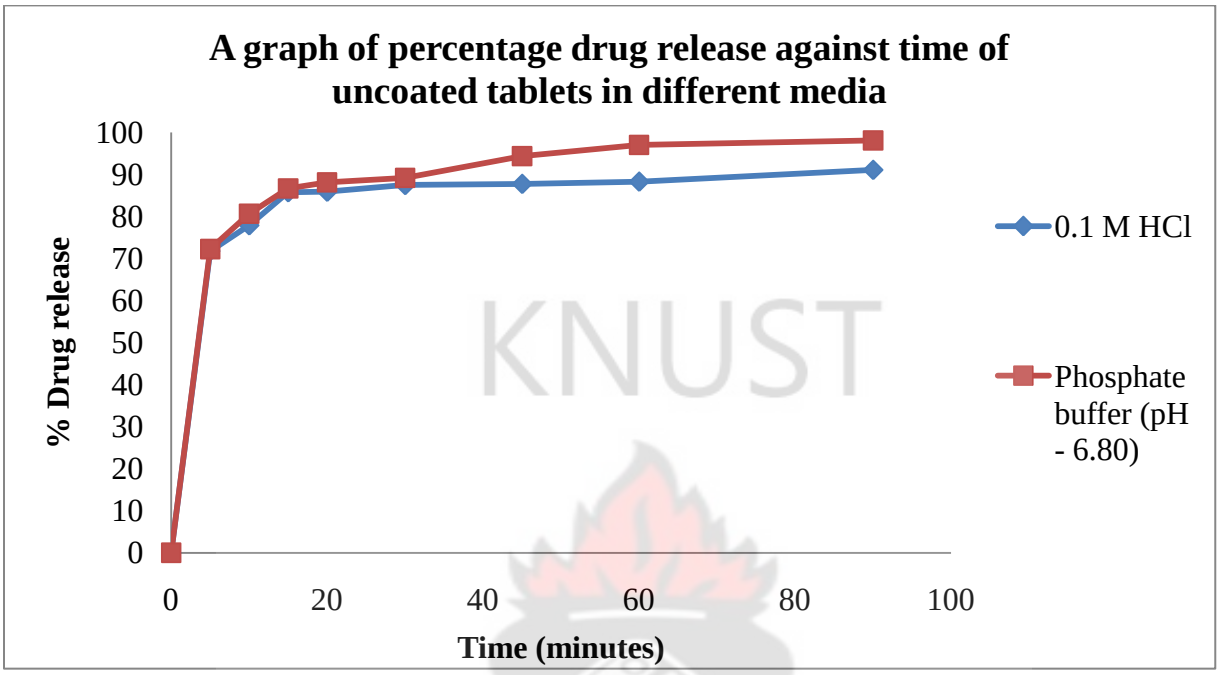

Figure 3.15 Release of paracetamol from uncoated tablets in both 0.1 M HCl and phosphate buffer (pH - 6.80)

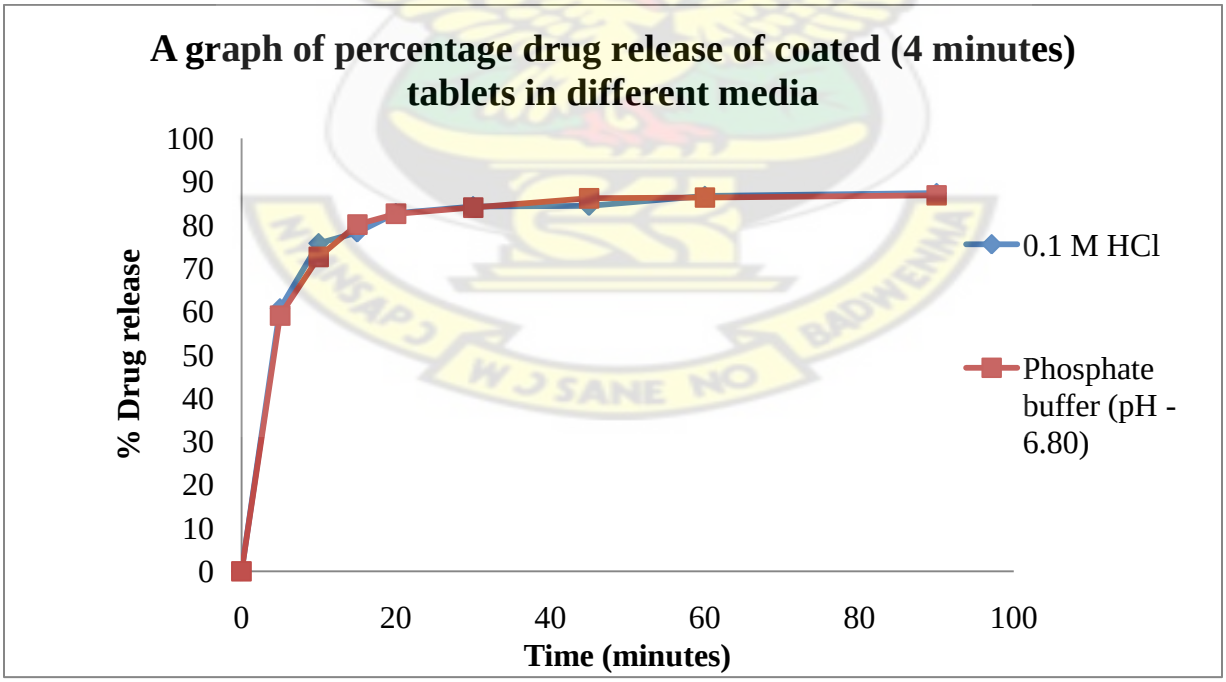

Figure 3.16 Release of paracetamol from coated (4 minutes) tablets in both 0.1 M HCl and phosphate buffer (pH - 6.80)

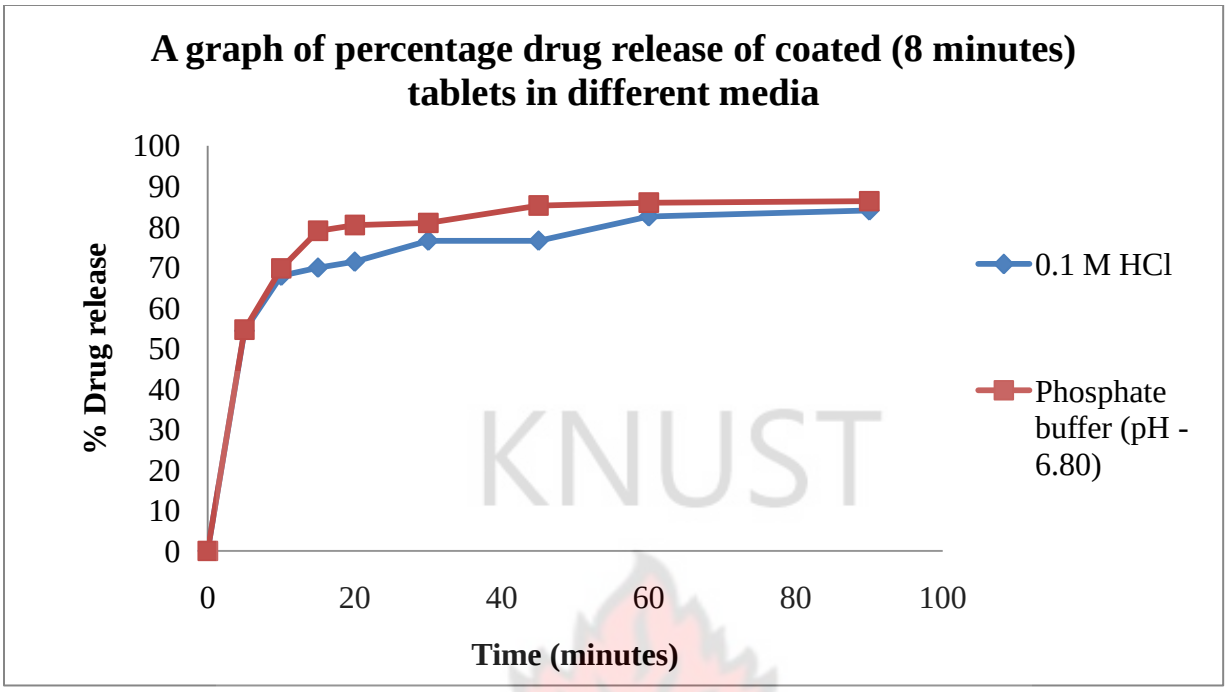

Figure 3.17 Release of paracetamol from coated (4 minutes) tablets in both 0.1 M HCl and phosphate buffer (pH - 6.80)

Table 3.7.6

t_{15}, $t_{50}$and t_{90} of the uncoated and coated tablets

	0.1M HCl			Phosphate buffer (pH – 6.80)		
Batch	**t_{15}**	**t_{50}**	**t_{90}**	**t_{15}**	**t_{50}**	**t_{90}**
Uncoated	71.79	88.00	91.10	86.72	95.50	98.11
Coated (4 min)	60.73	84.50	87.37	80.11	86.20	86.89
Coated (8 min)	54.34	78.5	84.04	79.04	85.50	86.35

Where:

t_{15}, t_{50} and t_{90} are the percentage drug release at times 15, 50 and 90 minutes respectively.

3.6.2 DRUG RELEASE KINETICS AND MECHANISM

Table 3.8.0

In vitro release data according to mathematical models

Dissolution medium	Formulation	Hixson-Crowell release model	Higuchi release model	Korsmeyer-Peppas model	
		R^2	R^2	R^2	n
0.1M HCl	Uncoated tablets	0.758	0.703	0.923	0.118
	Coated (4 minutes)	0.715	0.663	0.903	0.183
	Coated (8 minutes)	0.756	0.844	0.912	0.181
Phosphate buffer (pH-6.80)	Uncoated tablets	0.746	0.868	0.930	0.122
	Coated (4 minutes)	0.727	0.641	0.917	0.203
	Coated (8 minutes)	0.667	0.663	0.879	0.229

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Hixson - Crowell release equation,

$K_{HC}.t = Q_0^{1/3} - Q_t^{1/3}$

Where,

Q_0 - Initial amount of drug,

Q_t - Cumulative amount of drug release at time, t

K_{HC} – Hixson - Crowell release constant

t - time in hours

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Higuchi release equation,

$Q = K_H t^{1/2}$

Where,

Q - cumulative amount of drug release at time, t

K_H - Higuchi constant and

t - time in hours

Korsmeyer – Peppas equation model,

$Mt/ Mu = kt^n$

Where,

Mt/ Mu - the fraction of drug released into dissolution medium at time t,

k - constant which incorporates the properties of the macromolecular polymeric system and drug

t – time and

n – release/ diffusional exponent, which characterizes the drug transport/ release mechanism

CHAPTER FOUR

DISCUSSION AND CONCLUSION

4.1.0 DISCUSSION

- **Macroscopic properties of cashew gum**

The macroscopic properties of cashew gum are shown in Table 3.1.0. The crude cashew gum samples were thin long cylindrical tears, and some were short and rounded with their colour ranging from glassy white to golden brown. The purified gum was however somewhat buff in colour. The thick gums fractured with much difficulty whilst the thin one fractured easily. The odour of the gum was characteristic and not that strong, but its use in formulation did not affect the odour of the formulation. The taste of the gum is bland and makes it suitable for pharmaceutical use.

- **Moisture content and insoluble matter of cashew gum**

From Table 3.1.1, moisture contents of the purified and crude gum were 11.0 % and 13.0 % respectively. The difference between the moisture content of the purified and crude gums can be attributed to the purification process. The moisture content calculated, complied with the required standard set in the B.P. (2009) as 15 % w/w for acacia gum, which is commonly used in both the pharmaceutical and food industries. This test is important because excess moisture, in combination with a suitable temperature leads to the activation of enzymes and with suitable conditions, to the thriving of microbes.

Fig 3.1 shows that the purified form of the gum had a relatively low insoluble matter compared to the crude form. The purification process without doubt removed most of the impurities in the crude gum. The gum was dissolved in water, filtered and precipitated with alcohol so as to obtain the gum in its purified form. Crude cashew gum had 0.40 % of insoluble matter present. Though this value falls within the B.P. limits (0.5 % w/w) for gums such as acacia, comparing it to that of the purified gum which was 0.20 % w/w, the percentage of insoluble matter in the crude was high. This implies that, improving upon the process of harvesting and cleaning/purification of gum would result in decreased levels of impurity and contamination.

- **Swelling capacity of purified cashew gum in different media**

The value of swelling capacity/index of a polymer shows the extent of its hydration or water retention. Generally, the higher this value is in a particular medium, the longer would disintegration and hence, dissolution of a core substrate be in that medium. This is because swelling of a gum, for example when used as a coating around a tablet could slow down capillary flow of the disintegrating liquid into the tablets. This value may vary even for particular tree species due to seasonal and edaphic changes as well as treatments/modifications the gum may have been subjected to. Also, the lower the viscosity of a polymer, the lower is its swelling capacity.

Gums (being polysaccharides) often swell when they are hydrated. They also develop electrical charges when they are wet. This happens because they contain exposed hydroxyl (OH) groups with negatively charged oxygen atoms and positively charged hydrogen atoms, from their sugar and uronic acid units. Water molecules permeate these polymers, adhering to the charged surfaces as well as cohering to adjacent water molecules. This influx of water molecules and chemical bonding (i.e. hydrogen bonding) causes the gums/polymers to swell (Armstrong, 2012).

According to Table 3.1.2, the order of swelling capacity of the cashew gum in the various media was as follows: distilled water < 0.1M HCl < phosphate buffer (pH-6.80), and was from 3.29-3.83. The differences in the values for the different media may be attributed to the variation in pH. Altering the pH of distilled water increased the swelling capacity slightly. However, the swelling was greatest in the less acidic medium (pH 6.80). This low swelling capacity of the cashew gum used indicates minimal effect on drug release, depending on the concentration employed.

- **Viscosity of Gums**

Tables 3.1.3 and 3.1.4 and Figs. 3.3 and 3.4 show viscosities of the cashew gum with concentration and the effect of storage time on its viscosity. The viscosities of the gum dispersions increased with increasing concentration but this increase was more rapid at concentration 10%w/v and above. The 5% mucilage was just about thrice as viscous as water (1.00 cP), unlike other gums like guar, alginates and tragacanth: just to mention a few, which have viscosities of over 10 cPs at concentrations as low as 1%.

Being a low viscosity gum/ polymer, cashew gum is therefore very suitable for film coating of pharmaceutical dosage forms. This is because, by selecting the lower viscosity polymers, the solid content in the coating formulation can be increased which will result in lesser amount of water required for coating, which in turn can increase the coating speed and reduce coating/process time (less time for solvent evaporation). Deposition of the film on the tablets is also made faster and also, a much better film is obtained since there would be more polymer gum molecules available to coalesce into the film (Pareek and Rajsharad, 2003b; Rottmann et al., 2009). A good and tough film is therefore achieved.

There was a gradual increase in viscosity in the first two weeks for the 15 and 20%w/v preparation after which the viscosities were fairly constant. This increase in viscosity is due to the hydration of the gums that results in an increase in gum volume. On the whole, all four concentrations of the mucilages had fairly constant viscosities with increase in storage time.

From the statistical evaluation done using ANOVA, all the P values obtained for each individual concentration (that is 5, 10, 15 and 20%w/v) as well each one compared with another were $P < 0.001$. This means that there is significant increase in viscosity with increasing concentration and also, there is significant change in viscosity of all the four concentrations of cashew gum used with increasing storage time.

- **Acidity of gum**

It can be observed in Tables 3.1.5 and 3.1.6, the pH of the purified gum mucilages were acidic. The acidic nature of the gums could be attributed to the presence of the acidic functional group (uronic acid) of sugar units in the gum. The 5 - 20%w/v preparations gave pH values from 4.44 - 4.28; where the higher the concentration of the gum was, the slightly more acidic it was which could probably be due to the higher content of these uronic acid units in the more concentrated preparations. Over a six-week period, the pH values were between 4.02 and 4.44, meaning there was no major change in pH over time as observed in Fig. 3.6. The slight reduction in pH for the first four weeks in all four preparations could be attributed to fermentation of the sugar units and the gradual hydrolysis of the uronic acid units which made the solutions more acidic.

- **Evaluation of cashew gum containing free films**

Free films were prepared from the purified cashew gum and evaluated. This is because free films are generally used to assess properties, chiefly mechanical, of gums when they are intended for use in tablet coating (or other processes involving film preparation), because these properties are greatly determined by the nature of the gum/polymer. The compositions of the free films prepared using different amounts of cashew gum and plasticisers are shown in Table 1.0, and their physical properties, Table 3.2.0 and 3.2.1. Sample pictures of the films are also shown in Fig. 3.7.

The films were initially prepared using propylene glycol as plasticiser. Though these films were transparent/clear, they showed some folds, and as the concentration of the plasticiser was increased, the areas of these folds also increased. Propylene glycol can therefore be said to be an unsuitable/ineffective plasticiser for cashew gum because an effective plasticiser is one that melds homogenously with the polymer in a suitable solvent and remains melded when the solvent is evaporated. It was also observed that films containing combinations of the cashew gum and HPMC at concentrations of 1%w/v and 2%w/v of the total formulation volume that was cast were not uniform in appearance as seen in Fig. 3.7. Since films formulated with either polymer, that is the cashew gum alone and the HPMC alone were uniform and transparent, it could be said that the two are chemically incompatible possibly as a result of repulsive interactions between them. However, slight chemical (acid or alkaline hydrolysis or introduction of the relevant functional groups) and enzymatic modifications of cashew gum may result in improvement of some of its properties and also make it more suitable for blending with other gums; natural or semi-synthetic.

All these films (that is, those with propylene glycol as plasticiser, those prepared from a blend of HPMC and cashew gum) were therefore discarded, together with the F4 and F5 formulations because they were too brittle to handle. F4 contained no plasticiser and F5 contained 5% (of total polymer weight) plasticiser. Since plasticisers help to make films flexible, the brittle nature of F4 and F5 could be attributed to the absence or low level of the plasticiser respectively. The F4 formulation was prepared with no plasticiser, so as to ascertain the film forming ability of the cashew gum only. Those containing carboxymethyl cellulose (CMC) were also rough to touch and quite opaque but were the most easily removable.

Inter - formulation variations in the properties investigated; weight, thickness, folding endurance and mechanical, namely percentage elongation, tensile strength and Young's modulus were observed. These were due to the different proportions of the polymer (cashew gum) and/or plasticiser used.

The weights of the films varied from 0.0337±0.006 to 0.0492±0.005g and the thicknesses, from 0.21±0.007 to 0.32±0.009 mm. The differences in weights and thicknesses of the films are attributable to the fact that as the amount of the cashew gum increased and also as CMC was added, there was a corresponding increase in both the weights and thicknesses of the films. For the group B batch where plasticiser effect was investigated, there was a decrease in both weight and thickness as the plasticiser concentration was increased (cashew gum content being the same) till a concentration of 30% was reached. This could be due to the fact that for the lower concentrations, the plasticiser amounts were not very sufficient to ensure adequate flexibility and spreading of the films in the casting substrate (petri dish), thus causing those unit areas of the films to be heavier and thicker.

The folding endurance of a film is frequently used to estimate the ability of the film to withstand repeated bending, folding, and creasing and may be used as a measure of film quality. The folding endurance was observed to vary among the batches with the range of 98- > 400. It increased with an increase in the cashew gum amount, which indicates the film forming property of the gum. It also increased with increase in plasticiser concentration. This is because plasticisers reduce brittleness, impart flexibility, increase toughness, and thereby increasing the tear resistance of a film. The results indicated that the films would not crack and so maintain their integrity with moderate to quite frequent folding or handling. A folding endurance of up to 300 is considered satisfactory to reveal good film properties (Khana et al., 1997). F5 (5% plasticiser) could not be tested for folding endurance due to its very brittle nature while F6 (10% plasticiser) showed the least value for this property; both as a result of very low plasticiser content. Addition of CMC (1%) to cashew gum decreased the folding endurance but increasing the CMC content to 2% produced the film with the highest folding endurance but as mentioned, these were discarded because they were neither smooth nor transparent. Therefore aside the formulations mentioned, all the other films had satisfactory folding endurance showing good flexibility and elastic characteristics.

A soft and weak polymer is characterised by low tensile strength and low elongation while a hard and brittle polymer is defined by a moderate tensile strength and low elongation. A soft and tough polymer is characterised by moderate tensile strength and high elongation, whereas a hard and tough polymer is characterised by high tensile strength and high elongation (Bharkatiya et al., 2010).

The percentage elongation, which is a measure of the capacity of the films to deform, increased with increase in both polymer (gum) and plasticiser concentration. This is because, the more flexible a film is; the longer it can be stretched before tearing. Lower elongation indicates a low deformation capacity of the film and a brittle film structure.

Tensile strength also increased as gum concentration increased but a decrease was observed with an increase in plasticizer concentration. As mentioned earlier, plasticisers increase film flexibility, thus making the films less tough, with lower tensile strength. All the films had quite low tensile strength.

Increasing the plasticiser amount decreased the value of Young's modulus of the films. A low value however contributes to an increase in adhesion between the film and the coating surface (Okhamafe and York, 1985).

The small tensile strength values suggest the risk of film cracking but there was no sign of cracking in either the free films or coated tablets which is due to the lower values of Young's modulus obtained.

The cashew free films therefore possessed a good balance of mechanical properties studied. On the whole, the films were of sufficient toughness and had good adhesion properties. The film containing 7.5% of cashew gum (the smallest gum amount investigated) and 20% plasticiser had reasonable values for the mechanical properties tested so that proportion of the gum to the plasticiser was used for film coating of the model paracetamol tablets.

- **Quality control tests on paracetamol tablets**

The coated tablets did not stick to each other and were generally good looking with smooth coats as seen in Fig. 3.8. Also, a rub of the coated tablets against white paper did not reveal any peel.

The uniformity of weight test shows how much individual tablet weights deviate from the average tablet weight. According to the British Pharmacopeia, B.P. (2009), the permitted

percentage deviation for a tablet of weight greater than 250 mg is 5 % and that not more than two of the individual tablets should deviate from the average weight by more than 5% and none should deviate by twice the permitted deviation. From Tables 3.4.0 - 3.4.2, the tablets complied with this standard.The uniformity of weight test carried out on both the uncoated and film-coated tablets showed that all three batches have uniform weights. This means that the flow properties of the granules used for compression were good, and also that the film coats applied were also somewhat uniform.

The increase in weight of the tablets coated for four (4) and eight (8) minutes were 0.46% and 1.94% respectively, as recorded in Table 3.4.3. In film coating, weight increase due to coating materials is usually 2-3% (Aulton, 2001). The values obtained though not in this range, could be said to be acceptable since the only components of the coating formulation were the gum/polymer, plasticizer and the solvent. If other components such as colourants/pigments were added, a much higher increase in weight would have been obtained.

Table 3.4.4 shows the thicknesses of the uncoated and coated tablets. The thicknesses of the actual coats were 1.5 µm and 16.5 µm respectively for 4 and 8 minutes of coating. According to Hogan (1995), the thickness of a film coat is usually from 20 -100 µm after the film coating process is fully completed. However, in view of the low concentration of the cashew gum used and the exclusion of other constituents in the coating formula such as pigments, the film coat thicknesses obtained are considerably good. Coating of the tablets increased the tablet thicknesses. Also, film coat thickness increased slightly with an increase in coating time because the higher the coating time, the more solids are deposited on substrate surface and hence, the thicker the coat.

Table 3.4.5 shows the friability of uncoated and film-coated paracetamol tablets. Friability measures the ability of tablets to withstand stress, abrasion and how easily they can chip, and as such, a measure of great importance in terms of tablet robustness. In film coating, friability accurately reflects the stresses tablets encounter when tumbling in a coating pan. According to the B.P. (2009), the maximum weight loss of a sample of tablets after being subjected to the friability test must be 1%. However, for film coating, it is good that the friability of the core tablets have a maximum value of 0.3% and preferably less than 0.1% regardless of their size or shape due to the mechanical stresses of coating (Levina and Cunningham, 2005).

The uncoated paracetamol tablets formulated had a friability of 0.46%, though slightly higher than the desired 0.3%, it is appropriate because none of the tablets broke up during the coating procedure nor suffered any physical defects. The coated tablets had zero friability indicating that the coating procedure improved the stress resisting ability of the tablets.

Table 3.4.6 shows the results of the hardness test on the three batches of tablets investigated. Tablet breakage and surface erosion are typically seen when the mechanical strength and friability of the tablet core are inadequate (Levina and Cunningham, 2005). The force required to break a tablet is measured in kilograms and a crushing strength of 4kg is usually considered to be the minimum for satisfactory tablets however for oral tablets, hardness of 4 to 10 kg is acceptable. The uncoated tablets (3.58 kg/cm^2) were therefore of moderate hardness. The coated ones (7.12 and 8.83 kg/cm^2 for 4 and 8 minutes coating respectively), on the other hand were of adequate strength. Film coating of the tablets increased the tablet hardness from 3.58 to 7.12 and 8.83 kg/cm^2, which are about twice the value for the uncoated tablets. Increasing coating time further increased the tablet hardness due to the barrier coat applied.

The disintegration test gave the results presented in Table 3.4.7. All three batches of tablets disintegrated in less than five (5) minutes, in all the three media used. These values are within the accepted criteria of within 15 minutes for uncoated and immediate-release coated tablets (British Pharmacopoeia, 2009). However, the uncoated tablets had the least disintegration times in all the three media used, followed by the 4 minutes coated tablets and then the tablets coated for 8 minutes. Also, the times were observed in the order: phosphate buffer (pH - 6.80) < 0.1M HCl < distilled water, meaning that pH differences influenced tablet disintegration, the process, being quickest in the less acidic medium. The slightly higher values for the coated tablets, was due to the coating barrier/ film coat applied, which had to be eroded to give way for the tablets to come into contact with the disintegrating medium in order to break up. Since the order of hardness was the same as that of the disintegration times, it could be said that increasing the coating time increases tablet hardness which also results in increased disintegration time.

- **Assay of paracetamol tablets**

The correlation coefficient obtained from the calibration curve that is, Fig. 3.10 used for assaying the paracetamol was 0.999 which indicates very good linearity thereby making any deductions from the curve justifiable. The mean paracetamol content of the tablets was obtained as

97.32±0.1904%. According to the B.P. 2009, the paracetamol content of paracetamol tablets must be 95.0 to 105.0% of the stated amount. The value obtained fell within this range indicating that the tablets were well prepared and also that, they contained the acceptable amount of the active ingredient needed for the desired therapeutic action.

- **Dissolution/ drug release from tablets**

The calibration curves plotted for paracetamol in 0.1M HCl and phosphate buffer (pH-6.80) shown in Figs. 3.11 and 3.12 gave R^2 values of 0.998 and 0.992 respectively which show that the curves have good linearity, making the successive calculations from them valid.

Tables 3.7.0 – 3.7.2 and Figs. 3.13 and 3.14 show the release profiles of uncoated and coated tablets in the different dissolution media used while Figs. 3.15, 3.16 and 3.17 show the release of each of the tablet batches studied in both dissolution media.

According to the B.P. (2009), the percentage release of paracetamol from the tablets formulated must be at least 75% of the active ingredient within 45 minutes of the dissolution test. In 30 minutes, all the formulations in both media had achieved this release.

The rates of release from the uncoated tablets were higher than that from the coated tablets showing the role of the applied film coat as a barrier around the tablet cores. This is due to the fact that the cashew gum had to be hydrated and eroded by the dissolution medium before dissolution of the tablet substrate could occur. From Figs. 3.15 – 3.17 and Table 3.7.6, it is observed that for the uncoated and coated (8 minutes) tablets, a slightly higher drug release was achieved in the phosphate buffer (pH-6.80) which is the simulated intestinal pH than in the 0.1M HCl, the simulated gastric pH, indicating slower dissolution of the paracetamol in the latter medium. At time 15 min (t_{15}), more than 75% drug release had been achieved for all three formulations in the phosphate buffer (pH-6.80) unlike in the 0.1M HCl, where 75% release occurred after t_{15}, but by 45 min. Also, in the phosphate buffer (pH-6.80), the release profiles of the 4 minutes and 8 minutes coated tablet were almost the same. The highest drug release was obtained for the uncoated tablets in the phosphate buffer (pH-6.80) at time of 90 min, t_{90}.

Coating of the tablets did not therefore have a significant impact on release of the active drug. For this reason, bitter/ unpleasant taste and odours could be effectively masked, swallowing can be eased and mechanical integrity of tablet cores could be improved without bioavailability

being reduced, when cashew gum is used as a film coating agent for immediate-release tablets at a concentration of 7.5%w/v of the coating formulation.

- **Kinetics and release mechanism**

Table 3.8.0 shows the kinetics and mechanism of release for both the uncoated and coated tablets using various mathematical models. The mechanism of drug release from the uncoated and film coated tablets was assessed using the Korsmeyer - Peppas model (Korsmeyer et al., 1983). The R^2 values obtained were between 0.879 and 0.930 with all n values being less than 0.45. n is the diffusion or release exponent which indicates the drug release mechanism, which being < 0.45 suggests that the drug release was by quasi - fickian diffusion meaning that diffusion was the process by which paracetamol was released from the tablets.

Comparing the results obtained using other equations, it is observed that R^2 values from the Higuchi equation (0.640 – 0.868) were higher than those from the Hixson – Crowell equation (0.667 – 0.758) which also suggests that the drug release was by diffusion. This is because high correlation values (R^2), from the Higuchi equation suggests that drug release is by diffusion while high R^2 values from the Hixson – Crowell equation suggests that drug release is by dissolution with changes in surface area and diameter of particles/ tablets respectively.

4.2.0 CONCLUSION

From the results obtained in this study, it can be concluded reasonably that:

- Purification of cashew gum can be attained with a good yield.
- Films of good mechanical properties, that is, flexible and yet tough films with good adhesion on tablet cores can be obtained from cashew gum solutions.
- Physical and mechanical properties of films formed from cashew gum depend on the amount of the gum, as well as the type and amount of plasticiser employed.
- Glycerol is a very good and better plasticiser for cashew gum than propylene glycol.
- Tablets can be efficiently coated with cashew gum solution containing as low as 7.5% of the gum.
- Film coating tablets with cashew gum (7.5%) preparations does not significantly modify their drug release profiles.
- Cashew gum is a non-functional film coating agent.

4.3.0 RECOMMENDATIONS

- The inclusion of other coating formulation constituents, such as pigments, flavours and surfactants and their effect on the film forming capacity of cashew gum could be determined.
- Further work on the stability of cashew gum film coated tablets should be ascertained.
- Slight modifications of the gum in terms of its colour and some chemical properties may be attempted to observe if improved properties may be obtained.

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4.5.0 APPENDIX – PREPARATION OF TEST SOLUTIONS USED

1. 0.1M HCl solution: 0.97 ml of stock HCl (36% purity, 1.18 g/ml), was measured into a beaker already containing about 30 ml of distilled water. The mixture was swirled and then transferred into a 100 ml volumetric flask. The beaker was qualitatively rinsed into the volumetric flask and more distilled water was added to make up to the 100 ml volume. (Using the same ratios of stock HCl to distilled water, larger volumes were prepared).
2. Phosphate buffer (pH - 6.80): 250 ml of 0.2 M potassium dihydrogenphosphate (KH_2PO_4) was placed in a 1000 ml volumetric flask. 112 ml of 0.1M NaOH was then added and the solution was diluted to make up to the 1000 ml volume. (Using the same ratios of the ingredients, larger volumes were prepared).
3. 0.2M KH_2PO_4: 27.22 g of $KH_2PO_4$was weighed into a beaker containing 300 ml of distilled water and stirred with the aid of a mechanical stirrer. The solution was transferred into a 1000 ml volumetric flask. The beaker was rinsed quantitatively into the volumetric flask and solution was made up to the 1000 ml volume. (Using the same ratios of the ingredients, larger volumes were prepared).
4. 0.1M NaOH: 4.04 g of NaOH pellets were weighed into a beaker containing water to dissolve the pellets. The solution obtained was then transferred quantitatively into a 1000 ml volumetric flask and made up to volume. (Using the same ratios of the ingredients, larger volumes were prepared).

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