FORMULATION AND IN-VITRO EVALUATION OF ORAL SUSTAINED-RELEASE DICLOFENAC SODIUM MATRIX TABLETS USING HYDROPHILIC POLYMER BLENDS

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DECLARATION

The experimental work described in this thesis was carried out at the Department of Pharmaceutics, KNUST. This work has not been submitted for any other degree.

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DEDICATION

This thesis is dedicated to my dear and lovely mum, Mrs. Elizabeth Obese, for her love, care, prayer and support all these years.

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I give thanks to God Almighty who has brought me this far and will still see me through.

I want to say a big THANK YOU to all individuals who have contributed immensely for me to undertake this project.

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ABSTRACT

A sustained effect of diclofenac is required for the treatment of some chronic conditions like rheumatoid arthritis, osteoarthritis and chronic pain. Sustained release matrix tablets of diclofenac sodium were formulated using the natural gums, xanthan gum and cashew gum together with the semi–synthetic release modifier, hydroxypropylmethylcellulose (HPMC). Crude and purified cashew gums were found to have satisfactory moisture content and insoluble matter. The gums were analysed for their rheological property and found to show pseudoplastic flow. Fifteen (15) different batches of matrix tablets of diclofenac sodium (dose 100 mg) were produced by wet granulation. Different ratios (100:0, 80:20, 60:40, 20:80, 0:100) of Xanthan: HPMC, Xanthan: Cashew and Xanthan: Cashew: HPMC were used. The flow properties of the granules and the physical properties of the compressed tablets namely, weight uniformity, crushing strength, drug content, friability and tablet thickness were evaluated. In – vitro release studies of the drug was performed in phosphate buffer, pH 7.5 over 24 hours with Voltaren Retard as the reference diclofenac sodium tablet. The granules produced had good flow properties as evidenced by their angles of repose, Hausner ratio and Carr's index values. All the physical characteristics of the formulated tablets fell within acceptable limits. The swelling index of Batch 2 tablets containing only xanthan gum exhibited the highest swelling index followed by Batch 10 tablets containing xanthan and cashew gums in the ratio, 80:20. Different dissolution models were applied to the drug release data in order to evaluate the release mechanism and kinetics. The drug release data fitted well to the Higuchi square root model (R^2 = 0.8308 – 0.9750).The n value obtained for most of the batches ranged from 0.45 to 0.89 which indicates that drug is released through an anomalous or non – Fickian transport. Overall, drug release was found to be a complex mixture of diffusion, swelling and erosion. The similarity factor (f_2) obtained for batches 7 to 15 fell in the range 50 – 100 meaning the drug release profile of the batches was similar to the reference drug. Batches 7 to 13 and 15 had difference factors in the range 0 – 15 signifying a minor difference in the dissolution profile of those batches and the reference drug. From the results obtained, the gums and HPMC used individually could not sufficiently produce sustained release so must be combined in various ratios for effective sustained release to be achieved.

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INTRODUCTION

1.1 GENERAL INTRODUCTION

The term modified – release dosage form is used to describe products that alter the timing and rate of release of drug substance. A modified-release dosage form is defined "as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosages forms (Kamboj *et al.*, 2009).

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years (Allen *et al.*, 2010). There is regular and ongoing research into the use of naturally occurring biocompatible polymeric materials in the design of dosage forms for oral controlled release administration. The search for alternative products from renewable sources has increased significantly over the years (Reddy *et al.*, 2003).

Products that can be utilized over a long period of time will reduce the cost of importing these basic ingredients that are used in the pharmaceutical industry. Normally, plant products serve as a good alternative to the synthetic materials because of local accessibility, eco-friendliness and lower costs compared to the imported synthetic products.

Hydrophilic polymers have attracted considerable attention for use as sustained and controlled release devices for the delivery of both water-soluble and water – insoluble agents. Their characteristics and ability to hydrate and form a gel layer are well known and essential to sustain and control drug release from matrices (Modi *et al.*, 2011). The hydrated gel layer thickness determines the diffusion path of the drug molecules through the polymer mass into the diffusion medium (Emeje *et al.*, 2008).

Gums are natural exudates from the bark of trees and they have been of great pharmaceutical importance. Plant polysaccharides have been shown to be useful for the

construction of drug delivery systems for specific drug delivery. Some natural gums e.g. guar, tamarind, locust bean and okra gums as polymeric materials have been reported to be suitable in the design of controlled drug delivery systems because of their swelling or permeability profiles (Nussinovitch, 2009).

A number of approaches have been used to obtain controlled drug release but hydrophilic matrix is recognized as the simplest and the most widely used method. Upon ingestion of a hydrophilic matrix tablet, drug release results initially from swelling which causes a gel layer to form on the tablet surface. This gel layer retards further ingress of fluid and subsequent drug release. The swelling of the polymer matrix very often occurs with erosion (Varshosaz *et al.*, 2006) and both of them contribute to the overall rate of drug release.
The use of hydrophilic gum blends as the hydrophilic matrix can further be investigated to determine whether the release of the active ingredient can be controlled further. Several gum blends have been researched into and the use of a blend of xanthan and cashew gums will be investigated.

Hydrophilic polymers are widely used in the formulation of modified release oral dosage forms. Their convenience and ease of manufacture may cut down the cost of the final product. Besides, hydrophilic polymer matrix system offers several additional advantages over other technologies for controlled release drug delivery. The mechanism and the influence of various technological and formulation variables on the drug release from hydrophilic systems have been well studied. Until now, a large number of natural and synthetic polymers, single or in combinations, have been listed as hydrophilic matrix excipients (Amit *et al.*, 2008).

Introduction of matrix tablet as sustained release has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical Technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Because of increased complication and expense involved in marketing of new drug entities, scientists have focused greater attention on development of sustained release or controlled release drug delivery systems (Modi *et al.*, 2011). Matrix

system is widely used for the purpose of sustained drug release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers (Kamboj *et al.*, 2009). By the sustained release method, therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous sustained release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed. Intense research has recently focused on the designation of sustained release systems for poorly water soluble drugs (Modi *et al.*, 2011). Various drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets and osmotic pumps with laser drilled holes. These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipients (Kamboj *et al.*, 2009).

Xanthan gum is normally used as food additive and rheology modifier. It is used as a food thickening agent and as a stabilizer (Lachke, 2004). Cashew is readily available in Ghana and the most commonly used part is the nuts which are used as food ingredients (Gyedu-Akoto *et al.*, 2008) but the gum can be worked on and exploited for use in the pharmaceutical industry. The basic idea behind the use of the matrix system is to maintain a constant level of drug in the blood plasma in spite of the fact that the drug does not undergo disintegration. This is very useful when a sustained effect of diclofenac sodium is required for a long time to treat some chronic conditions like rheumatoid arthritis, osteoarthritis, chronic pain, ankylosing spondylitis and actinic keratosis.

1.2 JUSTIFICATION

Gums have a very wide application particularly in the pharmaceutical industry where they are used in emulsions, suspensions, lotions, creams, ointments, jellies, tablets, capsules, pills, suspensions and paste. Thorough studies have been made into the possible uses of

gums in the pharmaceutical industry. Different materials such as polyvinyl pyrollidone are used as tablet binders and hydroxypropylmethycellulose for sustained release formulations. As a result of this, some drugs though locally produced, are more expensive than imported drugs. Patients are therefore not able to afford these quality products and therefore resort to buying cheap and low quality medicines they find on the market. The need therefore for other sources of cheaper pharmaceutical excipients cannot be over emphasised.

Xanthan and cashew gums are natural products that can be used as pharmaceutical excipients in the formulation of sustained/controlled release drugs because they are readily available, non-toxic, biodegradable, cost-effective and simple to use.

1.3 SCOPE OF RESEARCH

The work would essentially consist of:

- Extraction and purification of cashew gum
- Evaluation of the physicochemical properties of xanthan and cashew gums
- Determination of the viscosities and rheological properties of xanthan and cashew gums
- Particle size analysis of xanthan and cashew gums
- Determination of the swelling capacity of xanthan and cashew gums
- Determination of the flow properties of the cashew and xanthan gums
- Formulation and determination of the flow properties of granules
- Preparation of matrix tablet batches using xanthan and cashew gum blends
- Quality control tests on matrix tablets produced.
- In vitro drug release analysis of the matrix tablets produced compared to a sustained release diclofenac on the Ghanaian market.
- Swelling index of the batches of tablets formulated
- Difference and similarity factor determination
- Evaluation of the mechanism and drug release kinetics of batches of tablets produced

Chapter 2

LITERATURE REVIEW

2.1 TIME RELEASE TECHNOLOGY

Time release technology, also known as sustained – release, sustained – action, extended – release, time – release or timed – release, controlled – release, modified release, or continuous – release, is a mechanism used in pill tablets or capsules to dissolve slowly and release a drug over time. The advantages of sustained – release tablets or capsules are that they can often be taken less frequently than immediate - release formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream (Modi *et al.*, 2011).

Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. The sustained plasma drug levels provided by sustained release products often times eliminates the need for night dosing, which benefits not only the patients but the care giver as well (Ravindra *et al.*, 2009).

There is a continuously growing interest in the pharmaceutical industry for sustained release oral drug delivery systems. There is also a high interest for design a dosage formulation that allows high drug loading, particularly for actives with high water solubility. Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of drugs (Ravindra *et al.*, 2009).

In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose (Ravindra *et al.*, 2009).

The basic rationale of a sustained drug delivery system is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route. The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and/or targeting the drug to desired site. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration (Ravindra *et al.*, 2009).

The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

The basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. This objective can be accomplished by maximizing drug availability. This can be done by increasing the drug absorption. The two aspects most important to drug delivery are Spatial Placement: - which relates to targeting a drug to a specific organ or tissue and Temporal Placement: - which refers to the controlling the rate of the drug delivery to the target tissues (Modi *et al.*, 2011).

2.1.1 Conventional Drug Therapy

Conventional drug therapy is of short duration of action. This is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer period of time, for example, by increasing the dose, then toxic level may be produced at early times (Curry, 1983).

Some problems associated with the conventional drug delivery system are:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur (Curry, 1983).

2.2 SUSTAINED RELEASE FORMULATIONS

Sustained Release: - includes any drug delivery system that achieves slow release of drug over an extended period of time. Most sustained release formulations are designed so that the administration of a single dosage unit provides the immediate release of an amount drug that promptly produces the desired therapeutic effect and gradual and continual release of additional amounts of drug to maintain this level of effect over an extended period usually eight to twelve hours (Ravindra *et al.*, 2009).

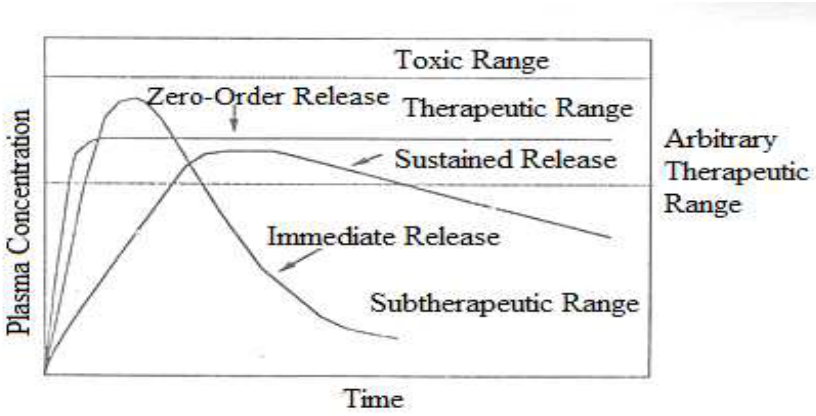

Figure 2-1 Plasma Drug Concentration Profiles for Conventional Tablet Formulation, a Sustained Release Formulation and a Zero Order Controlled Release Formulation

Controlled and Sustained Release has both been used in inconsistent and confusing manner. Both represent separate delivery process. Sustained Release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained Release systems generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order.

Repeat action tablets are an alternative method of sustained release in which multiple doses of drug are contained within a dosage form and each dose is released at periodic intervals. Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example, enteric coated tablet (Colombo *et al.*, 2000).

The ideal way of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant concentration in the body or an organ over an extended time; in other words, the amount of drug entering the system is equivalent to the amount of drug removed from the system. All forms of metabolism and excretion are included in the removal process: urinary excretion, entero – hepatic recycling, sweat, fecal and so on. Since for most of the drugs these elimination processes are first order, it can be said that at certain blood

level, the drug will have a specific rate of elimination. The idea is to deliver drug at this exact rate for an extended period. This is represented mathematically as following,

$$\text{Rate in} = \text{Rate out} = k_{elim} \times Cd \times Vd$$

Where Cd is the desired drug level, Vd is the volume of distribution, and k_{elim} is the rate constant of drug elimination from the body. Often such exacting delivery rates prove to be difficult to achieve through administration routes other than intravenous infusion. Non-invasive routes, for example, oral route is thus preferred (Modi *et al.*, 2011).

2.2.1 Advantages of sustained release dosage forms

a. **Patient Compliance**: Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, and understanding of the need to adhere to a strict treatment schedule. Also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and or systemic side effect of the dosage form. The problem of lack of patient compliance can be resolved to some extent by administering controlled release drug delivery system.

b. **Reduced 'see - saw' fluctuation**: Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see – saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see – saw' or 'peak and valley' pattern is more striking in case of drugs with biological half-lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well designed controlled release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a steadier drug concentration in blood circulation and target tissue cells.

c. **Reduced total dose**: Controlled release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the

total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

d. **Improved efficiency in treatment**: Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A controlled release dosage forms leads to better management of the acute or chronic disease condition.

e. **Economy**: In comparison with conventional dosage forms the average cost of treatment over an extended period may be less. Economy also may result from a decrease in nursing time and hospitalization. Also reduction in blood level oscillation characteristic of multiple dosing of conventional dosage forms. Reduction in the amount of drug administered. Also maximizes the availability with a minimum dose. There is control of drug absorption; high peak level peaks that may be observed after administration of high availability drug can be reduced. Safety margin of high potency drugs can be increased.

f. **Improved therapy**:

   i. Sustained blood level: The dosage form provides uniform drug availability / blood levels unlike peaks and valley pattern obtained by intermittent administration.

   ii. Attenuation of adverse effects: The incidence and intensity of undesirable effects caused by excessively high peak drug concentration resulting from the administration of conventional dosage forms is reduced.

   iii. It is seldom that a dose is missed because of non-compliance by the patient (Brahmanker and Jaiswal, 1995).

2.2.2 Disadvantages 0f Sustained Release Dosage Forms

a. **Dose dumping**: Dose dumping is a phenomenon where by relatively large quantities of drug in a controlled release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital
b. **Less flexibility in accurate dose adjustment:** In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.
c. **Poor *in vitro* – *in vivo* correlation**: In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called 'Absorption window' becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.
d. **Patient variation**: The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient (Brahmanker and Jaiswal, 1995).

2.2.3 Designing of sustained release drug delivery system

Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of

both physicochemical and biological factors that come into play in the design of such system (Modi *et al.*, 2011).

2.2.3.1 FACTORS TO CONSIDER IN THE DESIGN OF SUSTAINED RELEASE DOSAGE FORMS

The therapeutic efficacy of drug under clinical conditions is not simply a function of its intrinsic pharmacological activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions encountered by the drug molecule while traversing the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site.

a. **Pharmaceutics**: This refers to the development/manufacturing of an efficient delivery system in which the drug has maximum physiological stability and optimum bioavailability.
b. **Biopharmaceutics/Pharmacokinetics**: This involves the study of absorption, distribution, metabolism and excretion of the drug, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.
c. **Pharmacodynamics/ Clinical Pharmacology**: It is the study of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, intensity and duration of pharmacological activity (Curry, 1983).

2.2.3.2 BIOPHARMACEUTICAL FACTORS

a. **Dissociation constant "pka"**: For a drug to be absorbed it must dissolve in the aqueous phase surrounding the site of administration and then partition in the absorbing membrane. Two of the most important physicochemical properties of a drug that influence its absorptive behavior are its aqueous solubility and if it is a weak acid or base its pka. These properties play an influential role in the performance of controlled release systems.

   Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pka of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation.

Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media.

These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined. Compounds with very low solubility (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be a poor choice for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low (Jain, 2002).

b. **Partition Coefficient**: The partition coefficient is another important drug property, which influences the design of oral controlled delivery by two ways; it is an important property that governs the permeation of drug particles through biological membrane. The diffusion of drug molecules across rate controlling membrane or through the matrix systems essentially relies on partition coefficient. When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipid; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and retained in the lipophilic tissue for a longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion – limiting membranes must largely depend on the partitioning characteristics of the drug (Lee and Robinson, 1996).

c. **Drug stability**: The stability of the drugs at the site of its release and exposure bio-milieu is one more drug property that can influence the design of oral controlled drug delivery. Drugs that are unstable in gastric pH can be developed as slow release dosage form and drug release can be delayed till the dosage form reaches the

intestine. Drugs that undergo gut-wall metabolism and show instability in small intestine are not suitable for controlled drug delivery systems.

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and hence, is subject to degradation. Propentheline and probanthine are representative examples of such drugs (Banker and Rhodes, 2002).

d. **Absorption**: The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into a controlled – release system. Since the rate limiting step in drug delivery from a controlled – release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of drug relative to its release is essential if the 'system is to be successful. Since the purpose of forming a sustained release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8 – 12 hours, the maximum half-life for absorption should be approximately 3 – 4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete thus corresponds to a minimum apparent absorption rate constant of 0.17 - 0.23 hr^{-1} to give 80 - 95 % over this time period.

Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, a sustained release preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds is trying to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence

of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bioadhesive materials (Brahmanker and Jaiswal, 1995).

e. **Distribution**: The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue to that in plasma at the steady state called T/P ratio. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug dosing regimen and hence the need to employ a controlled – system.

f. **Metabolism**: Drugs that are significantly metabolized before absorption either in the lumen or tissue of the intestine can show decreased bioavailability from slower – releasing dosage forms. Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution. Drugs which are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating a sustained – release dosage form is,

    i. Drug should have low half-life (<5 hrs.)
    ii. Drug should be freely soluble in water.
    iii. Drug should have larger therapeutic window.
    iv. Drug should be absorbed throughout the GIT.

    Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the sustained release dosage form. But during this, the crystallization of the drug, which is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same (Brahmanker and Jaiswal, 1995).

g. **Side Effects and Safety considerations**: The side effects of some drugs are mainly developed due to the fluctuation in the plasma concentrations. The incidences of side effects can be minimized by controlling the concentration within therapeutic range at any given time.

h. **Disease State**: Even, in some cases are considered before the designing of an oral controlled delivery. This can be explained by the following classical examples. Aspirin is a drug of choice for rheumatic arthritis, and it is not a suitable candidate for sustained release dosage form. Still an aspirin sustained release dosage form could be advantageous to maintain therapeutic concentrations, particularly throughout the night, thus alleviating morning stiffness.

2.2.4 Characteristics of drugs unsuitable for oral sustained release forms

a. Not effectively absorbed in the lower intestine e.g. riboflavin, ferrous salts

b. Absorbed and excreted rapidly; short biologic half-lives (< 1hr) e.g. penicillin G, furosemide.

c. Long biologic half-lives (>12 hr.) e.g. diazepam, phenytoin

d. Large doses required (>1g) e.g. Sulfonamides

e. Cumulative action and undesirable side effects; drugs with low therapeutic indices e.g. phenobarbital, digitoxin

f. Precise dosage titrated to individual is required e.g. anticoagulants, cardiac glycosides

g. No clear advantage for sustained release formulation e.g. Griseofulvin

2.2.5 Criteria for choosing drugs for sustained release dosage forms

a. **Desirable half-life**: The half-life of a drug is an index of its residence time in the body. If the drug has a short half-life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the

circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$).

Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all other processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for sustained-release formulations, as this can reduce dosing frequency.

In general, drugs with half-lives shorter than two hours such as furosemide or levodopa are poor candidates for sustained release preparations. Compounds with long half-lives, more than eight hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

b. **High therapeutic index**: Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities e.g. Digitoxin.
c. **Small dose**: If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty. For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5 - 1.0 g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.
d. **Desirable absorption and solubility characteristics**: Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.
e. **Desirable absorption window**: Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the 'absorption window'. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

f. **First pass clearance**: Delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms (Aulton, 2001; Gennaro, 1990).

2.3 ORAL CONTROLLED RELEASE SYSTEMS

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug.
Depending upon the manner of drug release, these systems are classified as follows:

2.3.1 Dissolution controlled release systems

These types of systems are easiest to design. The drug present in such system may have an inherent slow dissolution rate e.g. Griseofulvin and Digoxin. Drugs that produce slow dissolving forms when it comes in contact with GI fluids. Also drugs having high aqueous solubility and dissolution rate. Drugs having high aqueous solubility and dissolution rate, show challenge in controlling their dissolution rate.

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by equation 1.

2.3.2 Matrix (monolith) dissolution controlled systems

As the drug is homogeneously dispersed throughout the rate controlling medium, this system is also called as monolith system. It is very common and employs waxes such as beeswax, carnauba wax which control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release is often first order from such matrices**.**

Today, most time-release drugs are formulated so that the active ingredient is embedded in a matrix of insoluble substance(s) such that the dissolving drug must find its way out through the holes in the matrix. Some drugs are enclosed in polymer – based tablets with a laser – drilled hole on one side and a porous membrane on the other side. Stomach acids push through the porous membrane, thereby pushing the drug out through the laser – drilled hole. In time, the entire drug dose releases into the system while the polymer container remains intact, to be later excreted through normal digestion. In some sustained release formulations, the drug dissolves into the matrix, and the matrix physically swells to form a gel, allowing the drug to exit through the gel's outer surface (Qiu et al., 2000).

2.3.3 Reservoir dissolution controlled systems

In this type, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose and polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of the coating.

2.3.4 Diffusion controlled release systems

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug

delivery systems. Similar to the dissolution-controlled systems, the diffusion controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution controlled systems, the drug is made available as a result of partitioning through the polymer (Jain et. al., 2008).

2.3.5 Matrix diffusion controlled systems

In this type, the drug is dispersed in an insoluble matrix of rigid, non swellable hydrophobic material or swellable hydrophilic substances. Materials used for rigid matrix are insoluble plastics such as poly-vinyl chloride and stearic acid. With the plastic materials, the drug is generally kneaded with the solution of poly-vinyl chloride in an organic solvent and then granulated. The granules are then compressed into tablets; swellable matrix systems are popular for sustaining the release of highly water soluble drugs. The materials for such matrices are,

a. Hydrophilic gums: Guar gum, Tragacanth gum
b. Synthetic: Polyacrylamides
c. Semi-synthetic: Hydroxypropylmethylcellulose, Carboxyl methyl cellulose

The drug release in this type of controlled release systems follows Fickian first order diffusion under equilibrium condition (Modi *et al.*, 2011).

2.4 MICROENCAPSULATION

Microencapsulation may be defined as the process of surrounding or enveloping one substance within another substance on a very small scale, yielding capsules ranging from less than one micron to several hundred microns in size. Microcapsules may be spherically shaped, with a continuous wall surrounding the core, while others are asymmetrically and variably shaped, with a quantity of smaller droplets of core material embedded throughout the microcapsule. All three states of matter (solids, liquids, and gases) may be microencapsulated. This allows liquid and gas phase materials to be handled more easily as solids, and can afford some measure of protection to those handling hazardous materials.

Microencapsulation may be achieved by a myriad of techniques, with several purposes in mind. Substances may be microencapsulated with the intention that the core material be confined within capsule walls for a specific period of time. Alternatively, core materials may be encapsulated so that the core material will be released either gradually through the capsule walls, known as controlled release or diffusion, or when external conditions trigger the capsule walls to rupture, melt, or dissolve (Jyothi et al., 2010).

The substance that is encapsulated may be called the core material, the active ingredient or agent, fill, payload, nucleus, or internal phase. The material encapsulating the core is referred to as the coating, membrane shell, or wall material. Microcapsules may have one wall or multiple shells arranged in strata of varying thicknesses around the core. Microencapsulation processes are usually categorized into two groupings: chemical processes and mechanical or physical processes (Gibbs *et al.*, 1999).

2.4.1 Chemical methods of microencapsulation

This method of encapsulation takes advantage of the reaction of aqueous solutions of cationic and anionic polymers such as gelatin and gum arabic. The polymers form a concentrated phase called the complex coacervate. The coacervate exists in equilibrium with a dilute supernatant phase. As water-immiscible core material is introduced into the system, thin films of the polymer coacervate coat the dispersed droplets of core material. The thin films are then solidified to make the capsules harvestable.

2.4.2 Physical methods of microencapsulation

Spray drying is a mechanical microencapsulation method developed in the1930s. An emulsion is prepared by dispersing the core material; usually an oil or active ingredients immiscible with water into a concentrated solution of wall material until the desired size of oil droplets are attained. The resultant emulsion is atomized into a spray of droplets by pumping the slurry through a rotating disc into the heated compartment of a spray drier. There the water portion of the emulsion is evaporated, yielding dried capsules of variable shape containing scattered drops of core material. The capsules are collected through continuous discharge from the spray drying chamber. This method can also be used to dry small microencapsulated materials from aqueous slurry that are produced by chemical methods (Jyothi *et al.*, 2010).

Fluid bed coating, another mechanical encapsulation method, is restricted to encapsulation of solid core materials, including liquids absorbed into porous solids. This technique is used extensively to encapsulate pharmaceuticals. Solid particles to be encapsulated are suspended on a jet of air and then covered by a spray of liquid coating material. The capsules are then moved to an area where their shells are solidified by cooling or solvent

vaporization. The process of suspending, spraying, and cooling is repeated until the capsules' walls are of the desired thickness. This process is known as the Wurster process when the spray nozzle is located at the bottom of the fluidized bed of particles. Both fluidized bed coating and the Wurster process are variations of the pan coating method. In pan coating, solid particles are mixed with a dry coating material and the temperature is raised so that the coating material melts and encloses the core particles, and then is solidified by cooling; or, the coating material can be gradually applied to core particles tumbling in a vessel rather than being wholly mixed with the core particles from the start of encapsulation (Pardeshi *et al.*, 2012).

2.5 MATRIX TABLET

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively, drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems are shown in Table 2.1, which includes both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Xanthan gum, Sodium alginate, Poly-ethylene oxide and cross-linked homopolymers and copolymers of acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface (Qiu *et al.*, 2000).

Table 2-1 Examples of two classes of retardant material used to formulate matrix tablet

No.	Matrix Characteristics	Materials
1	Insoluble, inert	Polyethylene, Polyvinyl chloride, Ethyl cellulose
2	Insoluble, erodible	Carnauba wax, Stearic acid, Polyethylene glycol

Source: (Kamboj et al., 2009)

2.5.1 Hydrophilic matrix tablet

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion, drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug release behavior from compressed hydrophilic matrices has been studied by number of investigators.

The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follows:

- **Cellulose derivatives:** Hydroxyethylcellulose, Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cps, Sodium carboxymethylcellulose and Methylcellulose 400and 4000 cps.
- **Non-cellulose natural or semisynthetic polymers:** Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of mannose and Galactose, Chitosan and Modified starches.
- **Polymers of acrylic acid:** Polymers which are used in acrylic acid category is Carbopol 934.

Other hydrophilic materials used for preparation of matrix tablet are alginic acid, gelatin and natural gums (Sayed *et al.*, 2009).

2.5.2 Fat-wax matrix tablet

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat – wax is

allowed to solidify and is then comminuted for sustained-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized – bed and steam jacketed blender or granulating with a solution of waxy material or other binders.

The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix (Chandran *et al.*, 2008).

2.5.3 Plastic matrix tablet (hydrophobic matrices)

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Sustained release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles (Basak *et al.*, 2006).

Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,

a. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
b. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.
c. Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses. For example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene (Gothi *et al.*, 2010).

2.5.4 Biodegradable matrices

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by surrounding living cells or by non – enzymatic process into oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic polyesters and poly anhydrides.

2.5.5 Mineral matrices

These consist of polymers which are obtained from various species of seaweeds. Example is alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali. Matrix systems can also be classified according to their porosity and consequently, macro porous, micro porous and non-porous systems can be identified as,

a. **Macro porous systems**: In such systems, the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.
b. **Micro porous system**: Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.
c. **Non - porous system**: Non – porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present (Varshosaz *et al.*, 2006)

Different drugs and polymers used in sustained-release based matrix tablets are given in the following table.

Table 2-2 Drugs and polymers used in sustained-release based on matrix tablet

DRUG	POLYMER
Metoclopramide Hydrochloride	Hydroxy Propyl Methyl Cellulose (HPMC), Carboxymethylcellulose (CMC), Ethyl Cellulose (EC)
Ibuprofen	Ethyl cellulose, Cellulose acetate phthalate
Metoprolol succinate	HPMC K100M, Xanthan gum
Ambroxol Hydrochloride	HPMC
Tramadol Hydrochloride	Xanthan gum, Guar gum.
Tramadol Hydrochloride	Carrageenan gum, Karaya gum, HPMC K15
Aceclofenac	Carbopol 971P, Carbopol 974P

Source: (Modi et al., 2011) .

2.6 DRUG RELEASE FROM MATRIX SYSTEMS

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release,
b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,
c) The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation,

2.6.1 Reservoir devices

These systems are hollow containing an inner core of the drug surrounded by the water insoluble polymer membrane. The polymer can be applied by coating or microencapsulation techniques. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. The polymers commonly used in such devices are ethyl cellulose and poly-vinyl acetate. The disadvantage of reservoir devices over matrix diffusion controlled system is a chance of sudden drug dumping.

2.6.2 Dissolution and diffusion controlled release systems

In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system.

2.7 DELAYED TRANSIT AND CONTINUOUS RELEASE SYSTEMS

These systems are designed to prolong their residence in the GI tract along with their release. Often the dosage form is fabricated to detain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are mucoadhesive systems and size based systems (Brahmanker and Jaiswal, 1995).

2.7.1 Delayed release systems

The design of such systems involves release of drug only at specific site in the GIT. The drugs contained in such a system are those that are:

- Destroyed in the stomach or by intestinal enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site
- Meant to exert local effect at a specific GI site

The two types of delayed release systems are intestinal release systems and colonic release systems (Venkatraman *et al.*, 2000).

2.8 FORMATION AND CLASSIFICATION OF GUMS

Gums and mucilages are polysaccharide complexes formed from sugar and uronic units. They are insoluble in alcohol but dissolve or swell in water (Irvine, 1961). The polysaccharide may be produced naturally from plants or produced synthetically. Natural gums are obtained as exudates or extractives from various plants and plant parts (Trease and Evans, 1983). The gum exudates are obtained mainly from the bark of stems, branches and roots of plants. Examples of gum include khaya, albizia, guar, acacia, tragacanth and xanthan, among others. They are products of normal plant metabolism and may serve as food reserves or act as agents of holding water. Various sea weeds also produce gums such as agar and carrageenan which are obtained by extraction.

The basis and reason for gum formation and exudation of gums are still not fully understood and many theories have been formulated to explain the phenomenon. One theory suggests that the gum formation is a protective mechanism resulting from a pathological condition. Other proposed theories believe that gums are normal physiological metabolites of plants. Some evidence on acacia trees favours the former theory. Healthy acacia trees, grown under favourable conditions of moisture, soil and temperature, do not produce any gum. When grown under adverse conditions offered by high elevations, heat and lack of moisture, the secretion of gum is favoured (Blunt, 1926). Others believe that gums are synthesised as a result of infection of the plant by microorganism in an effort to seal off the infected section of the plant and prevent further invasion of tissue (Nussinovitch, 2009).

The formation of gum has also been attributed to fungi attacking the plant and releasing enzymes that penetrate the tissue and transform the constituent cellulose materials of the cell wall into gum. For example, the parasite Stereum purpureum, which causes lead disease, induces plum trees to produce a considerable amount of gum at the site where the parasite grows. Yet another theory claims the formation of gums caused by bacterial action and suggests that specific bacteria are capable of producing different kinds of gums (Carignatto *et al.*, 2011). The most reasonable explanation however seems to be the simplest one, namely that the plant produces the gum in order to seal of the injured part, primarily to prevent infection. This concept is supported by the fact that gums are produced immediately by gum producing plants once they are injured deliberately. Gums and

mucilages are said by some to arise from starch, whilst others suggest that they are produced at the expense of cellulose or hydrocellulose (Thaysen and Bunker, 1927).

An interesting observation made is that all the neutral sugars in some gums are indeed present in the tissues of the tree in the free state (Smith and Montogomery, 1959). Gums in general may be classified as acidic, neutral or basic. Natural gums are either acidic or neutral. No basic gum occurs in nature. Examples of acidic gums are acacia, tragacanth and albizia gums. Examples of neutral gums are asparagus gum and plantago seed gums.
Gums are also classified into natural (examples are: acacia, tragacanth and xanthan), modified or semi- synthetic (examples are: carboxymethylcellulose, and microcrystalline cellulose) and synthetic (example are: carboxypolymethylene and colloidal silicon dioxide.) Gums are sometimes classified as either water swellable (example albizia) or water soluble (example acacia).

2.8.1 Physical and chemical properties of gums

The physical properties of gums are of primary importance in determining their uses and commercial value. These properties may differ considerably depending on the botanical source of the gum. Gums from the same specie when collected from plants growing under different climatic and edaphic conditions or even collected from the same plant at different seasons of the year, show considerable difference in their physical properties. Another factor that affects the physical properties of gums is the treatment gums receive after collection such as washing, drying and bleaching in the sun as well as storage conditions.

2.8.1.1 COLOUR

In the solid state, gums vary from almost colourless to various shade of yellow, amber and orange to dark brown. In commercial valuation of gums, strong preference is always shown for those that are light coloured. Certain gums when freshly secreted are virtually colourless. 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.

2.8.1.2 TASTE AND SMELL

True gums are generally scented or nearly so, differentiating them from some resins and oleo- resins that are distinctive in smell. They may be tasteless, and are in fact generally devoid of characteristic taste apart from being blandly mucilaginous. Some may be either sweet or bitter, depending on their botanical origin.

2.8.1.3 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 proves variable. 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 pulverized. Gums are hygroscopic and will absorb moisture and become soft in humid atmosphere. This power to hold water or lose it may have an important repercussion in gum trade.

2.8.1.4 SOLUBILITY

For their solubility in water most gums like albizia, khaya and tragacanth swell in water to give viscous or gel like solutions, whilst other gums like acacia literally dissolve in water. A lot of gums cannot be dissolved in water at concentrations higher than 5 % because of their very high viscosities. Gum arabic however can yield solutions up to 50 % concentrations. Gums are generally insoluble in oil and in most organic solvents. They may be soluble in aqueous ethanol, up to a limit of about 60 % ethanol. Limited solubility can also be obtained with glycerol and ethylene glycol. The gums that swell in water usually have a soluble portion and insoluble portion.

The overall solubility properties of gums can be improved by freeze drying or by the purification of the gum (Aspinall *et al.*, 1956). The purification involves dissolving the gum in 4 % sodium hydroxide, acidifying with hydrochloric acid and precipitating with ethanol. The purified gum in contrast with the crude gum is readily soluble in water. There is great loss in viscosity after purification (Trease and Evans, 1983).

2.8.1.5 PHYSICAL PROPERTIES OF GUMS

The physical properties and the appearance of natural gums are of utmost importance in determining the commercial value and their end use. These vary considerably with gums of different botanical source, and there are even substantial differences in gum from the same specie when collected from plants growing under different climatic conditions or even collected from the same plant at different seasons of the year. The .physical properties may also be affected by age of the exudates and the treatment of the gum after collection, which may involve washing, drying, sun – bleaching and storage conditions (Glicksman, 1969).

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. The colour of gums in their natural forms varies from almost water white (colourless) through shades of yellow, amber, pink and orange to dark brown. Many gums when first secreted appear to be colourless, and it is believed that colour is due mainly to the presence of various types of impurities. Colour often appears as the gum ages upon the tree or as it is dried or heated.

The presence of tannins also account for the dark gums yielded by certain trees. The water soluble gums are usually odourless and in this respect differ markedly from the oil soluble resinous exudates which have distinctive smells. The gums are usually tasteless and bland, except for some species which have sweet carbohydrate taste and some types that have been contaminated. Gums contaminated with tannins usually have a harsh, bitter flavour that is a serious disadvantage. Gums vary in hardness but, since this is usually dependent on the amount of moisture present, this therefore cannot be used as a mean of classification (Glicksman, 1969).

2.8.1.6 pH AND OTHER PROPERTIES OF GUMS

Natural gums are mostly acidic with a few being neutral. The acidity is due to the presence of uronic acid unit in addition to the sugar polymer. The pH of gum solutions range from 3-6, albizia gum ranges between 3.5 and 5 and that of tragacanth mucilage ranges between 5 and 6.

Gums are known to reduce the surface tension of water and the interfacial tension between oil and aqueous phases, hence their suspending and emulsifying properties. Some gums may be compatible with others and in most cases modification of properties occur and these are exploited to obtain optimum and conducive properties in their use and applications. For example acacia combines conveniently with tragacanth by lowering the viscosity of tragacanth which in turn produces emulsions with superior quality (Davidson, 2002)

2.8.1.7 VISCOSITY AND RHEOLOGICAL PROPERTIES OF GUMS

Many useful industrial and pharmaceutical applications of gums are based on the viscous character of their solutions. Whereas most gums like khaya form highly viscous solutions at low concentrations of about 1 to 5 %, acacia gum is unique in that it is extremely soluble and not very viscous at low concentrations. High viscosities are not obtained until concentrations of about 40 to 50 % are obtained. Like other physical properties, viscosity and rheological properties of the gum exudates are affected by the age of the parent tree, the climatic conditions or amount of rainfall or sunshine, pH and its variation, ageing of the gum, or mucilage and concentration of mucilage (Davidson, 2002).

2.8.2 Methods used for the purification of gums and mucilages

Gums for analysis are first purified by extraction with water. Dissolution may be accelerated using dilute acids or alkalis depending on the nature of the gums. If either dilute acid or water is employed, heating must be avoided 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 thereby eliminated, decomposition of the uronic acid building units may occur.

The solution of the gum or mucilages is filtered to remove insoluble impurities and the polysaccharide removed by precipitating with alcohol. Repeated precipitation from acidified aqueous solutions with ethanol serves to remove inorganic ions and any proteinaceous impurity. Elimination of inorganic ions may also be effected by electro dialysis or by passing an aqueous solution of the material through cation exchange resin.

Separation and purification can be achieved by crystallisation or precipitating from water. In this case, the polysaccharide is dissolved in hot or warm water, and the solution allowed cooling for the polymer to precipitate. Precipitation with alcohol and other organic solvents have been the main method used for the purification of gums and mucilages. The technique consists of dissolving the polysaccharide in water and adding ethanol gradually to effect precipitation. Although there is the tendency of co- precipitation, this disadvantage can be overcome to an extent by repeated fractional precipitation.

Fractional precipitation with salts has an advantage in that the tendency for co- precipitation is much less since salts have the effect of reducing hydrogen bonding. Fractional precipitation with complexing agents have also been found useful. Complexing agents such as phenols, borates, copper and aluminum ion form gelatinous complexes with mucilage. Some polysaccharides also have the tendency to precipitate others by forming complexes. Proteins used in fractional precipitation are the most selective method to and hold out considerable promise for the purification of polysaccharides (Smith and Montogomery, 1959). When gums contain considerable amount of protein, precipitation of the polysaccharide with ammonium sulphate or acetic acid may be advantageous since such procedure retains the proteins in the solution.

The gum acetates may be purified by precipitation from acetone or chloroform solution with diethyl ether or petroleum ether and the polysaccharide regenerated by deacylation with sodium hydroxide or potassium hydroxide. The purified products thus obtained dries prior to analysis by solvent exchange, azeotropic distillation of the water benzene- ethanol or by freeze- drying.

Freeze drying usually provides light amorphous white powders. When gums which contain moisture are dried by methods other than freeze drying, they often form hard, horny masses that are difficult to manipulate. It is not advisable to dry these polysaccharides by heating, for certain undesirable changes in solubility may develop and in the case of those gums

containing acidic groups, hydrolysis and decomposition may occur (Smith and Montogomery, 1959).

2.8.3 Applications and uses of gums and mucilage

Gums find diverse application in pharmacy and are widely used as emulsifying and suspending agents, depending on their exhibited properties. Gum mucilage performs a stabilising function and imparts viscosity to emulsions thus reducing creaming. They are used to maintain insoluble solids in organic suspensions and to produce mucilaginous ointments and cosmetic hand creams. Acacia gum is used as a suspending agent, emulsifier, adhesive and binder in tableting and demulcent in cough syrups (Ramsden, 2003). In tableting, gums find use as adhesives or binders and also an excipient in the manufacture of pills and plasters. A number of plant gums have been used as binding agents in tablet formulations. They have been found useful in producing tablets of different mechanical strength and drug releasing properties for different pharmaceutical purposes. The fact that gums are naturally available, inexpensive and non-toxic has also fostered interest in developing the gum for pharmaceutical use.

2.8.4 Gum – producing microorganisms

Most phyto-pathogenic bacteria do not form spores. Many of them are resistant to desiccation and survive under dry conditions for more than 50 years at normal surrounding temperature. This is due to the protective layer of the 'ooze' or exudates produced by the bacteria. The layer is nothing but a coating of specific gum that is chemically a polysaccharide. This coating may act as a barrier against attack from bacteriophage, and also helps identification of appropriate sites on the host plant for colonization of the bacteria. *Xanthomonas campestris* synthesizes the xanthan gum. It is a gram negative, yellow-pigmented bacterium and several species of Xanthomonas pathogenize specific plant hosts.

For example, cabbage is attacked by *X. campestris*, sugar cane by *X. vasculorum*, strawberry by *X. fragaria* and walnut by *X. juglandis*. Xanthan gum is a cream coloured powder that is soluble in hot or cold water with a high viscosity even at low concentrations. The molecular weight of xanthan is determined by light scattering, quasi-elastic light

scattering and band sedimentation analysis. These methods however have revealed a wide variation between 2 million to 62 million in the molecular weight of xanthan. The explanations for these variations in the reported values were provided by the quasi-elastic light scattering techniques. Hydrogen bonding appears to be important in stabilizing the aggregates of xanthan in water. In 4M urea solution, a lower molecular weight of 2 million was obtained (Sharma *et al.*, 2006).

2.8.4.1 XANTHOMONAS CAMPESTRIS, DESCRIPTION AND SOURCE

Xanthan gum is a natural polysaccharide. It was discovered in the late fifties in the research laboratories of the US Department of Agriculture during research work into the industrial applications of microbial biopolymers. Extensive research revealed that the bacterium *Xanthomonas campestris* found on cabbage plants produces a high molecular weight polysaccharide which protects the bacterium. This polysaccharide, called xanthan gum, proved to have technically and economically interesting properties. The industrial importance of xanthan gum is based upon its exceptional qualities as a rheology control agent in aqueous systems and as a stabilizer for emulsions and suspensions.

Xanthan gum is a white to cream coloured free flowing powder soluble both in hot and cold water, but insoluble in most organic solvents. Even at low concentrations xanthan gum solutions show a high degree of viscosity in comparison with other polysaccharide solutions. This property makes it a very effective thickener and stabilizer. Xanthan gum solutions are highly pseudoplastic but not thixotropic, i.e. even after high shear rates the initial viscosity is rebuilt instantaneously (Rodríguez and Aguilar, 1997).

Xanthan gum is more pseudoplastic than most other hydrocolloids. This pseudoplasticity enhances sensory qualities (flavour release, mouth feel) in final products, eases processing (mixing and pumping) and guarantees a good pourability. Xanthan gum solutions are very resistant to pH-variations, i.e. they are stable in both alkaline and acidic conditions. The thermal stability of xanthan gum is usually superior to most other water soluble polysaccharides. Xanthan gum is tasteless and does not affect the taste of other food ingredients.

In its powder form xanthan gum can be easily and safely stored over several years. Xanthan gum solutions, however, although more resistant to microbial attack than most other water soluble polymers, should be protected by adequate preservatives when storage time shall exceed 24 hours (Rodríguez and Aguilar, 1997).

2.8.4.2 BACKBONE OF XANTHAN GUM

The main chain of xanthan is built up of D-glucose units linked through the b-1 position of one unit with 4th position of the next unit, a linear backbone identical to the chemical structure of cellulose. The primary structure of xanthan consists of a pentasaccharide repeating units. The presently accepted structure of xanthan consists of (1, 4)-b-D-gluco-pyranose units. Trisaccharide side-chains are attached to alternate sugar residues on the main chain at the C-3 position. The side chain consists of two mannose residues and a glucuronic acid residue. The terminal b-D-mannopyranose residue is (1, 4) linked to the b-D-glucuronic acid residue, that in turn is (1, 2) linked to non-terminal a-D-mannopyranose residue. The 6-OH group of the non-terminal D-mannopyranose residue is present as acetic acid ester. Pyruvate acetyl groups are located on the D-mannopyranosyl end groups of side-chains. The influence of different glycosidic or other linkages in the backbone of any polysaccharide is an important feature in modifying polysaccharide chain conformation and its characteristics. It is not surprising that xanthan of different pyruvate levels (that is 1 to 6 %) display different rheological (flow) properties. Pyruvic acid attached to the terminal carbohydrate of the side chains adds another carboxylate group. The percent composition of xanthan proposed for industrial use is as follows: Glucose 37, mannose 43.4, glucuronic acid 19.5, acetate 4.5 and pyruvate 4.4% (Sharma *et al.*, 2006).

2.8.4.3 PRODUCTION OF XANTHAN GUM

The biosynthesis of microbial hetero polysaccharides such as xanthan is a complicated process involving a multi-enzyme system. The initial step in the biosynthesis of xanthan is the uptake of carbohydrate, which may occur by active transport or facilitated diffusion. This is followed by phosphorylation of the substrate with a hexokinase enzyme that utilizes adenosine 5'-triphosphate. The biosynthesis involves conversion of the phosphorylated substrate to the various sugar nucleotides required for assembly of the polysaccharide-

repeating unit through enzymes such as UDP-Glc pyrophosphorylase. UDP-glucose, GDP-mannose and UDP-glucuronic acids are necessary for the synthesis of xanthan with the appropriate repeating unit.

In the biosynthesis of xanthan on the cabbage plant by *X. campestris*, the cabbage provides the carbohydrate substrates, proteins and minerals for cell growth. In the laboratory conditions or commercial fermentation, carbon sources, nitrogen sources, trace minerals and pH conditions are provided in a way that simulates natural conditions (Rodríguez and Aguilar, 1997).

2.8.4.4 COMPATIBILITY OF XANTHAN GUM WITH OTHER INGREDIENTS

Xanthan gum is compatible with most food, cosmetic and pharmaceutical ingredients. Xanthan gum has an excellent stability in the presence of acids. It can be dissolved directly in many acid solutions. To achieve best results it is recommended to add the acid after the preparation of the gum solution. Xanthan gum solutions have unusually good compatibility and stability in the presence of most salts. The addition of electrolytes, such as sodium and potassium chloride, increases the viscosity and stability. Divalent salts like calcium or magnesium have a similar effect on viscosity. Optimum viscosity is reached at salt concentrations above approximately 0.1%. Higher salt concentration levels do not increase stability any further, nor do they affect the rheological properties of xanthan gum solutions. Most food systems, though, contain the appropriate amount of salts. Even at high concentrations xanthan gum is compatible with most salts. Only at high pH-levels (pH > 10) xanthan gum tends to form gels in the presence of high concentrations of divalent cations. Trivalent cations, such as aluminum and iron, form gels at acid or neutral pH. Gelling may be prevented by high levels of monovalent metal salts.

Xanthan gum is a high molecular weight anionic polysaccharide produced by the fermentation of a carbohydrate source with Xanthomonas campestris. This polymer exhibits three desirable properties: high viscosity at low concentrations, pseudoplasticity; and insensitivity to a wide range of temperature, pH and electrolyte variations. Because of its special rheological properties, xanthan is used in food, cosmetics, pharmaceuticals, paper, paint, textiles, adhesives and oil and gas industry. The flow characteristics of xanthan,

coupled with its stability to salts and extremes of pH, gives it a technical advantage over most polymers used in drilling.

By blending different gums with xanthan gum, varying the ratio and the concentration of the combination, very specific characteristics of the end product may be obtained, e.g. viscosity, pseudoplasticity, texture and mouth feel. Xanthan gum is highly resistant to enzymatic degradation due to the nature of the sugar linkages as well as to the side chain substituents on the polysaccharide backbone. Pure xanthan gum can therefore be safely used in the presence of most enzymes commonly occurring such as galactomannanases, cellulases, amylases, pectinases, proteases etc. Xanthan gum is not directly soluble in most organic solvents. Up to 40 - 50 % of common solvents such as isopropanol, methanol, ethanol or acetone can be added to aqueous solutions of xanthan gum without precipitation of the gum (Rodríguez and Aguilar, 1997).

2.8.4.5 USES AND APPLICATIONS OF XANTHAN GUM

One of the most remarkable properties of xanthan gum is its ability to produce a large increase in the viscosity of a liquid by adding a very small quantity of gum, on the order of one percent. In most foods, it is used at 0.5%, and can be used in lower concentrations. The viscosity of xanthan gum solutions decreases with higher shear rates; this is called pseudoplasticity. This means that a product subjected to shear, whether from mixing, shaking or even chewing, will thin out, but once the shear forces are removed, the food will thicken back. A practical use would be in salad dressing: the xanthan gum makes it thick enough at rest in the bottle to keep the mixture fairly homogeneous, but the shear forces generated by shaking and pouring thins it, so it can be easily poured. When it exits the bottle, the shear forces are removed and it thickens back up, so it clings to the salad. Unlike other gums, it is very stable under a wide range of temperatures and pH.

In foods, xanthan gum is most often found in salad dressings and sauces. It helps to prevent oil separation by stabilizing the emulsion, although it is not an emulsifier. Xanthan gum also helps suspend solid particles, such as spices. Also used in frozen foods and beverages, xanthan gum helps create the pleasant texture in many ice creams, along with guar gum and

locust bean gum. Toothpaste often contains xanthan gum, where it serves as a binder to keep the product uniform. Xanthan gum is also used in gluten-free baking. Since the gluten found in wheat must be omitted, xanthan gum is used to give the dough or batter a "stickiness" that would otherwise be achieved with the gluten. Xanthan gum also helps thicken commercial egg substitutes made from egg whites, to replace the fat and emulsifiers found in yolks. It is also a preferred method of thickening liquids for those with swallowing disorders, since it does not change the color or flavor of foods or beverages (Rodríguez and Aguilar, 1997).

In cosmetics, xanthan gum is used to prepare water gels, usually in conjunction with bentonite clays. It is also used in oil-in-water emulsions to help stabilize the oil droplets against coalescence. It has some skin hydrating properties. Xanthan gum is a common ingredient in fake blood recipes, and in gunge or slime (Sharma *et al.*, 2006).

2.8.5 Anacardium occidentale- botany and source

Family: Anacardiaceae

Genus: Anacardium (Rickson and Rickson, 1998)

Species: occidentale

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

Common name: cashew

It is found mainly in cashew growing districts like Sampa, Wenchi, Bole, Jirapa, and Ejura, Tamale

Parts Used: Leaves, bark, fruit, nut

2.8.5.1 DESCRIPTION

Native to Brazil, it also grows in tropical areas of Central and South America and in the West Indies in tropical forests and grasslands. The evergreen tree grows to about thirty feet, producing low branches with oval leaves and pink-streaked yellow flowers on long spikes. Its greenish-gray fruit or apple is, in fact, a thickened stem. The true fruit is the cashew nut which hangs immediately below the fruit. It is encased in a red or yellow flesh. The gum exuded by the stem wards off ants and other insects. Cashew is a multi-purpose tree of the

Amazon that grows up to 15 m high. It has a thick and tortuous trunk with branches so winding that they frequently reach the ground. 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 (Morton, 2003).

The cashew tree produces many resources and products. The bark and leaves of the tree are used medicinally, and the cashew nut has international appeal and market value as a food. Even the shell oil around the nut is used medicinally and has industrial applications in the plastics and resin industries for its phenol content. Then, there is the pseudo-fruit-a swollen peduncle that grows behind the real fruit that yields the cashew nut. The pseudo-fruit, a large pulpy and juicy part, have a fine sweet flavour and are commonly referred to as the "cashew fruit" or the "cashew apple." Fresh or frozen cashew fruit concentrate is as common a juice product in South American food stores as orange juice is in the United States. It is very perishable, however; therefore, no fresh cashew fruit is exported into the United States or Europe from South America.

The cashew nut is defined botanically as the fruit. It grows externally in its own kidney-shaped hard shell at the end of this pseudo-fruit, or peduncle. The nut kernel inside is covered with an inner shell, and between the two shells is a thick, caustic, and toxic oil called cardol. Cashew nuts must be cleaned to remove the cardol and then roasted or boiled to remove the toxins before they can be eaten (Morton, 2003).

2.8.5.2 PLANT CHEMICALS

In addition to being delicious, cashew fruit is a rich source of 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 of cashew 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 may be why cashew is effective in treating diarrhoea. Anacardic acids 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 cells.

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 (Thomas and Filho, 1985).

2.8.5.3 CHEMICAL PROPERTIES OF CASHEW GUM

Cashew gum is a complex polysaccharide of high molecular mass, on hydrolysis it yields galactose and galacturonic acid. The variation in acid number is influenced not only by the source of the sample but also by its age. The sticky exudates from this tree darken and thicken rapidly on exposure to air. When applied as vanish, provides remarkable protection, as is unchanged by acids, alkalis, alcohols or heat up to 70^{o}C. 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-O-methylglucuronic acid (de Paula and Rodrigues, 1995). 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).

Degraded gum A, prepared by controlled acid hydrolysis, contained galactose, glucose, and uronic acid. A Smith-degradation of degraded gum A gave degraded gum B, which contained only galactose. Sequential Smith-degradations of Anacardium occidentale gum, and methylation analyses of the gum and of its degradation products indicated a highly-branched galactan framework consisting of chains of β-(1–3)-linked D-galactose residues

branched and interspersed with β-(1–6) linkages. Arabinose is present as end-groups or in short (1–2)-linked chains up to five units long. Glucose, rhamnose, mannose xylose, and uronic acid are all present as end-groups (Anderson and Bell, 1975).

2.8.5.4 USES OF CASHEW GUM

Cashew gum is used primarily in industry for binding books, as adhesives for envelopes, label, stamps and posters. It is also used as an additive in the manufacture of chewing gum because of its thickening power. It is used as a jellying agent in canned food and jellies for fruit jam. Cashew gum is similar to gum arabic in rheological properties and can be used as a substitute of liquid glue for paper, in the pharmaceutical and cosmetic industries as agglutinant for capsules and pills and in food industry as a stabilizer of juices. It can also be utilized in the making of cashew wines (Owusu *et al.*, 2005).

Other possible uses are as a binder, emulsifying and suspending agent in the pharmaceutical industry (Ofori - Kwakye *et al.*, 2010)

2.8.5.5 RESEARCH ADVANCEMENT ON POSSIBLE USES

The polysaccharide, combined with water soluble, branched 1,3-β galactose and with other oligosaccharides and proteins, exhibited high inhibitory activity (average 88% $p < 0.005$) against an implanted sarcoma 180 solid tumours in mice, characterizing an antitumor activity of the cashew gum (Mothe' *et al.*, 2008). Himejima and Kubo, (1991) found out that, there are antitumour agents from cashew juice. (Kubo *et al.*, 1993) also found out that, the nut shell oil of Anarcardium occidentale has antibacterial properties.

Some application of cashew gum has been proposed in the last few years, such as superabsorbent hydrogel as soil conditioner, polyelectrolyte complex with chitosan for drug delivery. The polysaccharide has also been modified by carboxymethylation with monochloroacetic acid as the etherifying agent (de Paula and Rodrigues, 1995).
Crude and purified cashew tree gums were tested for their antimicrobial activity against bacteria, yeast and fungi. Their use was also evaluated as a carbon source for microbial

growth. Cashew gum presented only a weak activity against Saccharomyces cerevisiae and no activity was observed against all other microorganisms tested. The possibility that removal of anacardic acid present in the raw gum during purification may explain the negative results obtained was discussed. When purified cashew tree gum was used as carbon source, only Listeria monocytogenes, Saccharomyces cerevisiae and Kluyveromyces marxianus did not grow after 5 days of incubation (Torquato *et al.*, 2004).

2.9 HYDROXYPROPYL METYLCELLULOSE

Hydroxypropyl methyl cellulose (also known as hypromellose or HPMC) is a non-ionic, water soluble polymer derived from cellulose. It is a semisynthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products. As a food additive, hypromellose is an emulsifier, thickening and suspending agent, and an alternative to animal gelatin. It comes as a white or off-white odourless powder that is used to thicken products (Katzhendler *et al.*, 2000).

The cellulose derivatives, like HPMC and hydroxyethyl cellulose (HEC) are created through a reaction of cellulose with ethylene or propylene oxides or both to create these products. The compound forms colloids when dissolved in water. Although non-toxic, it is combustible and can react vigorously with oxidising agents. Hypromellose in an aqueous solution, unlike methylcellulose, does not exhibit thermal gelation property. That is, when the solution heats up to a critical temperature, the solution congeals into a non-flowable but semi-flexible mass. Typically, this critical (congealing) temperature is inversely related to both the solution concentration of HPMC and the concentration of the methoxy group within the HPMC molecule (which in turn depends on both the degree of substitution of the methoxy group and the molar substitution). That is, the higher the concentration of the methoxy group, the lower the critical temperature. The viscosity of the resulting mass, however, is directly related to the concentration of the methoxy group (the higher the concentration, the more viscous or less flexible the resulting mass) (Piriyaprasarth and Sriamornsak, 2011).

In addition to its use in ophthalmic liquids, hypromellose has been used as an excipient in oral tablet and capsule formulations, where, depending on the grade, it functions as controlled release agent to delay the release of a medicinal compound into the digestive tract. It is also used as a binder and as a component of tablet coatings (Katzhendler *et al.*, 2000).

Hypromellose solution is a non-newtonian solution and exhibits pseudoplastic, more specifically, thixotropic behaviour. HPMC is soluble in water and some organic solvents: its aqueous solution is of surface tension, high transparency and stable property. The solubility varies with the viscosity, the lower the viscosity, the higher solubility it has. HPMC has also other characteristics such as thickening property, pH stability, water retention, excellent film-forming property and good disperse and adhesion power (Siepmann *et al.*, 1999).

2.10 TABLETS AS A DOSAGE FORM

Tablets may be defined as a solid pharmaceutical dosage form containing drug substance with or without suitable excipients and prepared either by compression or moulding methods. Tablets remain popular as dosage form because of the advantages afforded both to the manufacturer (e.g., simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (accuracy of dosage, compactness, portability and ease of administration). Tablet technology has undergone great improvement. Factors affecting the availability of the right kind of tablets are always being considered together with factors affecting raw materials, facilities, personnel, validated processes and equipment, packaging and the controls.

2.10.1 Types of tablets

Compressed Tablets: These tablets are formed by compression and they contain no special coating. They are made from powdered, crystalline or granular materials alone or in combination with binders, disintegrants, lubricants and diluents

Sugar Coated Tablets: These are compressed tablets containing a sugar coating. Such coatings may be coloured and are beneficial in covering up drug substances possessing objectionable taste or odour and in protecting materials sensitive to oxidation.

Film Coated Tablets: These are compressed tablets which are covered with a thin layer or film of water soluble material. A number of polymeric materials with film coating properties may be used.

Enteric Coated Tablets: These are compressed tablets coated with substances that resist solution in the gastric fluid but disintegrate in the intestine. They are normally used for drugs that are inactivated or destroyed in the stomach, for those which irritate the mucosa or a means of delayed release of the medication.

Multiple Compressed Tablets: These are compressed tablets made by more than one compression cycle. Examples are layered tablets and press-coated tablets.

Controlled Released Tablet: Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. These tablets can be categorised into three types;

- Those which respond to some physiological condition to release the drug, such as enteric coating.
- Those that release the drug in a relatively steady, controlled manner.
- Those that combine combinations of mechanisms to release pulses of drugs such as repeat-action drugs.

Effervescent Tablets: In addition to the drug substance, these contain Sodium bicarbonate and inorganic acids such as citric acid or tartaric acid. In the presence of water these additives reacts liberating carbon dioxide which act as a disintegrator and produces effervescence.

Buccal And Sublingual Tablets: These are small, oval tablets. Tablets intended for buccal administration by inserting it into the buccal pouch (Zografi *et al.*, 1990).

2.10.2 Tablet Ingredients

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials; these are known as additives or excipients. They may be classified according to the part they play in the finished tablet. The first group contain those which help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders, glidants and lubricants. The second group of added substances help to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, colours etc.

2.10.2.1 DILUENTS

Frequently the single dose of the active ingredient is so small and inert substances are added to increase the bulk in order to make the tablet a practical size for compression. Diluents used for this purpose include dicalcium phosphate, calcium sulphate, lactose, cellulose, kaolin, manning, dry starch and powdered sugar, microcrystalline cellulose)

2.10.2.2 BINDERS

These are agents used to impart cohesive qualities to the powdered materials. They impart cohesiveness to the tablet formulation which insures the tablet remaining intact after compression as well as improving the free flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin, and sugars. Natural and synthetic gums which have been used include acacia, sodium alginate, panwar gum, ghatti gum, carboxymethylcellulose, methyl cellulose and polyvinylpyrrolidine.

The quantity of binder used has considerable influence on the characteristics of the compressed tablet. The use of too much binder or too strong a binder will make a hard tablet which will not disintegrate easily and will cause excessive wear of punches and dies.

2.10.2.3 LUBRICANTS

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of tablet material to the surface of dies and punches, reduce inter particle friction, facilitate ejection of the tablets from the die cavity and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate hydrogenated vegetable oil and polyethylene glycol. In selecting a lubricant, proper attention must be given to its compatibility with the drug agent.

2.10.2.4 GLIDANTS

A glidant is a substance which improves flow characteristics of a powder mixture. These materials are normally added in the dry state just prior to compression. Colloidal silicon dioxide is the most commonly used at usually low concentrations.

2.10.2.5 DISINTEGRANTS

A disintegrant is a substance or mixture of substances, added to a tablet to facilitate its break up or disintegration after administration. The active ingredient must be released for the tablet matrix efficiently as possible for its rapid dissolution. Materials serving as disintegrants have been classified chemically as starches, clays, cellulose, algins, gums and cross linked polymers. The oldest and still the most popular disintegrants are corn and potato starch which have been well dried and powdered. A group of materials known as super disintegrants have gained popularity as disintegrating agents. The name comes from the low levels at which they are very effective. Examples are croscarmelose and crospovidone. The method of addition of the disintegrant in the course of granulation is also of much importance (Aulton, 2001).

2.10.3 Tablet characteristics

Tablets as a dosage form should meet certain specific requirements. The diameter, shape, thickness, accuracy of dosage, weight, hardness, stability, disintegration time and dissolution has to conform to certain parameters.

2.10.3.1 TABLET HARDNESS AND FRIABILITY

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depend on its hardness. Hardness determinations are made throughout the tablet runs to determine the need for pressure adjustment on the tableting machine. A tablet property related to hardness is friability. This parameter assesses the ability of the tablet to withstand abrasion in packaging, handling and shipping.

2.10.3.2 UNIFORMITY OF DOSAGE FORMS

Tablet Weight

The volumetric fill of the die cavity determines the weight of the compressed tablet. The weight of the tablet is the quantity of the granulation which contains the labelled amount of the therapeutic agent. The tablet weights must conform to the set standards as in the USP or BP.

Content Uniformity

Each tablet must contain the intended drug quantity with little variation among the tablets in a batch. The drug quantity per tablet of average weight is determined analytically and compared to standards as set in the monographs.

2.10.3.3 TABLET DISINTEGRATION

To be absorbed, a drug substance must go into solution, but the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. It is therefore recognised that the in vitro tablet disintegration test does not necessarily bear a relationship to the in vivo action of the tablet. The maximum disintegration time often set at 15 minutes for ordinary tablets and 60 minutes for coated tablet. This test does not apply to depot tablets, lozenges and chewable tablets.

2.10.3.4 DISSOLUTION

For certain tablets, monographs specify compliance with limits on dissolution rather than disintegration. Since drug absorption and physiological availability depend on having the drug in dissolved state, suitable dissolution characteristics are an important property of a satisfactory tablet. Like the disintegration test, the dissolution test for measuring the time required for a given percentage of the drug substances in a tablet to go into solution under a specified set of conditions, is an in vitro test. It is intended to provide a step towards the evaluation of the physiological availability of the drug.

2.10.3.5 STABILITY

The stability of the drug substances is investigated when developing the formulation. A suitable method of preparation must be chosen for the tableting of sensitive substances. The stability control proceeds after production by periodic examination of stored reference sample of production batches. Tablets generally have a long shelf life. The physico-chemical properties of the tablet should also be studied during storage (Aulton, 2001).

2.11 METHODS OF PREPARATION OF TABLETS

2.11.1 Wet granulation

The most widely use and most general method of tablet preparation is the wet granulation method. Wet granulation is a process of adding a liquid binder or adhesive to the powder mixture. The amount of liquid can be properly managed, and over wetting will cause the granules to be too hard and under wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvents.

Procedure of Wet Granulation

Step 1: Weighing and Blending - the active ingredient, filler, disintegration agents, are weighed and mixed.

Step 2: The wet granulate is prepared by adding the liquid binder/adhesive. Examples of binders/adhesives include aqueous preparations of corn starch, natural gums such as acacia, and cellulose derivatives such as methyl cellulose.

Step 3: Screening the damp mass into pellets or granules

Step 4: Drying the granulation

Step 5: Dry screening: After the granules are dried, pass through a screen of smaller size than the one used for the wet mass to select granules of uniform size to allow even fill in the die cavity

Step 6: Lubrication- A dry lubricant, anti-adherent and glidant are added to the granules either by dusting over the spread-out granules or by blending with the granules. It reduces friction between the tablet and the walls of the die cavity. Anti-adherent reduces sticking of the tablet to the die and punch (Zografi *et al.*, 1990).

2.11.2 Dry granulation

This process is used when the product needed to be granulated may be sensitive to moisture and heat. Dry granulation can be conducted on a press using slugging tooling or on a roller compactor commonly referred to as a chilsonator. Dry granulation equipment offers a wide range of pressure and roll types to attain proper densification. However, the process may require repeated compaction steps to attain the proper granule end point.

Process times are often reduced and equipment requirements are streamlined; therefore the cost is reduced. However, dry granulation often produces a higher percentage of fines or non-compacted products, which could compromise the quality or create yield problems for the tablet. It requires drugs or excipients with cohesive properties.

- Some granular chemicals are suitable for direct compression (free flowing) e.g. Potassium chloride
- Tableting excipients with good flow characteristics and compressibility allow for direct compression of a variety of drugs.

2.12 FLOW PROPERTIES OF GRANULES

Practically every solid used in pharmacy must be handled as a powder at some stage and this handling is greatly facilitated if the powder is free flowing. This study of the flow and deformation of powders is the science of rheology and is analogous in some respect to the rheology of liquid systems. However, since a powder mass consist of discrete particles; there is an absence of the continuity found in liquids. There are different methods used to determine the flow properties of powders or granules. These methods are generally grouped into two as direct and indirect methods. The indirect methods include angle of repose, shear cell determination, bulk density measurement etc. The direct methods include Hopper flow rate and recording flow meter (Aulton, 2001).

2.12.1 Angle of repose

There are many different methods of determining the angle of repose. The different methods may produce different values of angle of repose for the same powder. For this reason angles of repose tend to be variable and are not always representative of flow under specific conditions. As a general guide, powders with angles of repose greater than 50° have satisfactory flow properties whereas angles close to 25° correspond to very good flow properties. The different methods for determining angles of repose are:

- Fixed height method
- Fixed base method
- Tilting table

2.12.2 Bulk density measurements

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A given mass of granules in a measuring cylinder will have an initial volume, V_o. After tapping for some specific amount of time, it attains a final volume, V_f. The change in volume occurring when void space diminishes is known as 'packing down'. An initial density can be calculated knowing the initial bulk density of fluff or paired bulk density, D_o. The final density can also be calculated. This is known as the final bulk density or equilibrium or tapped or consolidated bulk density, D_f

Hausner found that the ratio D_f/D_0 was related to interparticulate friction and such could be used to predict powder flow properties. Hausner showed that powders with low interparticulate friction had ratios of approximately 1.2, whereas more cohesive, less free-flowing ones had ratios greater than 1.6 (Aulton, 2001).

2.12.2.1 CARR'S INDEX

Carr developed another method of measuring powder flow from bulk density measurements. Carr's index is also known as percentage compressibility and is calculated as % Compressibility = $(D_f - D_o / D_f) \times 100$

2.13 DICLOFENAC, SOURCE AND CHEMICAL DATA

Systematic (IUPAC) name: 2-[2-(2, 6-dichlorophenylamino) phenyl] acetic acid

Formula: $C_{14}H_{11}C_{l2}NO_2$ (Sallmann, 1986)

Molecular Mass: 296.148 g/mol

Half-life: 1.2-2 hrs. (35% of the drug enters enterohepatic recirculation)

Routes: oral, rectal, im, iv (renal- and gallstones), topical

Trade names: cataflam, diclomax, naklofen, olfen, voltaren, voltarol

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). It is used to reduce swelling and to treat pain. Diclofenac is used for musculoskeletal complaints, especially arthritis,

rheumatoid arthritis, polymyositis, dermatomyositis, osteoarthritis, dental pain, TMJ, spondylarthritis, ankylosing spondylitis, gout attacks, and pain management in cases of kidney stones and gallstones. An additional indication is the treatment of acute migraines. Diclofenac is used commonly to treat mild to moderate post-operative or post-traumatic pain, particularly when inflammation is also present, and is effective against menstrual pain and endometriosis (Dastidar *et al.*, 2000).

Diclofenac Sodium and Diclofenac Potassium are two forms of diclofenac. These are actually salts of diclofenac also known as sodium and potassium salts. Both are similar in the sense that their base is diclofenac. The real difference lies in the fact that potassium salt of diclofenac is more soluble in water than sodium salt. As far as response time is concerned, it is Diclofenac potassium that gets absorbed quickly and starts analgesic activity in a much quicker time than Diclofenac sodium. Both sodium and potassium salts of diclofenac are different in nature and function and cannot be treated as equivalent though their dose may be same. Diclofenac potassium is immediate release, while Diclofenac sodium is delayed release (Sallmann, 1986).

2.14 DRUG RELEASE KINETICS

An ideal kinetic profile of drug release from a prolonged release carrier is a zero order curve. The constant amount of an active substance dose within time unit provides the drug presence at a therapeutic level in human body during the long time period. Most often, however, pharmaceutics referred to as controlled release systems (CRS) and composed of biodegradable polymeric matrix enclosing therapeutic agent reveal a complex heterogeneous release profile. The initial stage, so called ‘the burst effect’, is a rapid dissolution of part of drug which is not protected effectively by a carrier. The following stage is a slow release of drug fraction enclosed in matrix, induced by a polymer hydrolytic degradation (Balcerzak and Mucha, 2010).

There are number of kinetic models which describe the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter drug release and *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In this regard, the use of *in vitro* drug dissolution data to predict *in vivo* bio-performance can be considered as the rational

development of controlled release formulations. The methods of approach to investigate the kinetics of drug release from controlled release formulation can be classified into three categories:

- Statistical methods (exploratory data analysis method, repeated measures design, multivariate approach [MANOVA: multivariate analysis of variance]
- Model dependent methods (zero order, first order, Higuchi, Korsmeyer-Peppas model, Hixson Crowell, Baker-Lonsdale model**,** Weibull model, etc.)
- Model independent methods [difference factor (f_1), similarity factor (f_2)] (Suvakanta *et al.*, 2010).

2.14.1 Multivariate analysis of variance (Manova)

These methods were based upon repeated measures designs where time is the repeated factor and percent dissolved is the dependent variable. Since the data were collected as repeated measurements over time on the same experimental unit, a repeated measures design was applied. When compared to students‘t’ and paired‘t’ tests, the major advantage of this design is increased precision. In repeated measures, analysis of variance (ANOVA) containing repeated measures factors with more than two levels, additional special assumptions enter the picture: These are compound symmetry assumption and the assumption of spherocity. Because these assumptions rarely hold, the MANOVA approach to repeated measures ANOVA has gained popularity in recent years.

The compound symmetry assumption requires that the variances and co-variances of the different repeated measures are homogeneous. This is a sufficient condition for the univariate ‘F’ test for repeated measures to be valid. The spherocity assumption is a necessary and sufficient condition for the F test to be valid. When the compound symmetry or spherocity assumptions have been violated, the univariate ANOVA table will give erroneous results. Mauchly’s test of spherocity results are used for the assumption of spherocity (Suvakanta *et al.*, 2010).

2.14.2 Model dependent methods

Model dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters. The model dependent approaches used in this work included zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models.

2.14.2.1 ZERO ORDER KINETICS

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

The equation can be expressed as:

system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the expression is given by equation 17:

the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time (Hixson and Crowell, 1931).

2.14.2.5 KORSMEYER-PEPPAS MODEL

Korsmeyer *et al.* (1983) derived a simple relationship which described drug release from a polymeric system equation:

Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion (Korsmeyer *et al.*, 1983).

2.14.3 Model independent approach using a similarity factor

A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles. The difference factor calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves. It is expressed as:

f_1

Chapter 3

MATERIALS AND METHODS

3.1 MATERIALS

Xanthan gum, a polysaccharide, derived from the bacterial coat of *Xanthomonas campestris* was obtained from the Chemical Store of the Department of Pharmaceutics, KNUST, Kumasi. Crude cashew gum was obtained from the Wenchi Cashew Plantation as natural exudates from the stem barks of the plant *Anacardium occidentale*, family, Anacardiaceae at Wenchi in the Brong Ahafo region of Ghana. The plant was authenticated by the curator of the plantation. Other materials used include Diclofenac Sodium powder (Hubei Prosperity Galaxy Chemical Co., Ltd., China), Hydroxypropyl Methylcellulose (UK Chemicals, Kumasi), Microcrystalline Cellulose (Amponsah-Effah Pharmaceuticals Ltd., Kumasi). Talc and Magnesium stearate were obtained from the Chemical Store of the Department of Pharmaceutics, KNUST, Kumasi.

3.2 CHEMICALS AND REAGENTS

96 % ethanol, diethyl ether, concentrated hydrochloric acid, distilled water were obtained from the Chemical Store of the Department of Pharmaceutics and the Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, KNUST. Kumasi. Sodium hydroxide pellets, phosphoric acid, sodium dihydrogen phosphate and disodium hydrogen phosphate were obtained from Lab Chem. Ltd. Kumasi.

3.3 EQUIPMENT AND APPARATUS

Eutech pH meter (pH 510, pH/mV/^{0}C meter), porcelain mortar and pestle, Analytical balance (Adam Equipment), UV spectrophotometer (T90 UV/VIS spectrometer, PG Instruments Ltd.), Erweka Dissolution Apparatus, (Type DT 6, GmbH Heusenstamm, Germany), Erweka Friabilator (USP), Brookfield Viscometer (Brookfield Engineering Lab Inc., Middleboro, MA, USA), Number 4 sintered glass filter, Stormer Viscometer,

Retsch Laboratory Sieves, Sartorius Electrical Balance, Whatman filter papers (grade 1: 1001- 185), Retsch Mechanical Shaker, dessicator, Monsanto Tablet Hardness Tester (Model: Mht – 20), Single Punch Tableting Machine, Electronic Vernier callipers, among others were the equipment and apparatus used.

3.4 PREPARATION AND PURIFICATION OF CASHEW GUM

The crude cashew gum was cleaned by removing the bark and other extraneous materials by hand picking, breaking and sieving. The gum was dried in an oven at 60 ºC for about 10 hours until it became sufficiently brittle. The dried gum was then sorted into two grades, light coloured grade and dark coloured grade. The light coloured grade was selected for further processing by grinding in a porcelain mortar into fine powder. The powdered gum was used in some of the subsequent test and analysis as crude cashew gum powder. To purify the gum 700 g of the crude gum powder was dissolved in 1400 ml of distilled water and allowed to stand for 24 hours with intermittent stirring as the gum was very soluble in water. Using a piece of calico the gum mucilage obtained was filtered by squeezing to remove any insoluble debris or impurities. The filtered mucilage was re-filtered to ensure that all debris was removed. The filtered mucilage was purified by precipitating the gum out with 96 % ethanol. About 2500 ml of 96 % ethanol was used to precipitate 700 g of the gum, the precipitated gum was filtered and washed with diethyl ether and dried in the hot air oven at 60 ºC for about 8 h. The dried purified gum was milled and sieved through sieve number 80. The powdered gum was used in subsequent test and analysis as purified cashew gum.

3.5 EXAMINATION OF PHYSICAL PROPERTIES OF CASHEW GUM

3.5.1 Macroscopic properties of crude cashew gum

In evaluating the macroscopic properties of the crude cashew gum, its shape, size, surface characteristics, colour and nature, odour and taste were observed.

3.5.2 Moisture content of the gum

Two (2) grams of powdered crude cashew gum was weighed accurately into a porcelain crucible which had previously been dried to a constant weight. The gum was placed in a hot

air oven and maintained at a temperature of 105 °C. After 5 h, the gum was removed and cooled, after which it was placed in a desiccator for 30 min. The weight of the crucible and the gum were recorded. The determination was done in triplicate. The moisture content or loss on drying was expressed as a percentage of the cashew gum sample. The entire process was repeated for purified cashew gum (Tsourouflis et al., 1976).

3.5.3 Insoluble matter in crude and purified gum

Two grams (2 g) each of the crude and purified gums were separately weighed into a 250 ml round bottom flask. To each was added 100 ml of water followed by the addition of 14 ml of 2M HCl. The mixture was boiled gently for 15 min, while shaking frequently, and filtered whilst hot through number 4 sintered glass filters. The residue was then washed with hot water and dried at 105 °C to constant weight. The weight of the insoluble matter was expressed as a percentage.

3.6 RHEOLOGY OF XANTHAN AND CASHEW GUM MUCILAGES

3.6.1 Viscosity of gum mucilage

Mucilages of different concentrations of xanthan gum (0.5 % w/v, 0.75 % w/v, 1 % w/v) and cashew gum (1 % w/v, 2 % w/v, 5 % w/v and 10 % w/v) were prepared using distilled water. The viscosities of the samples were determined at shear rate of 1 rpm using a Brookfield viscometer (spindle number 2).

3.6.2 Flow curves of xanthan and cashew gums

The Stormer Viscometer was used in this determination. The different concentrations of the gums were prepared and introduced into the sample compartment of the viscometer. Weights were introduced and the time taken to achieve 100 revolutions recorded. This was done for both loading and unloading of the shear stresses. Determinations were done in triplicate.

3.7 SWELLING CAPACITY OF XANTHAN AND CASHEW GUMS

A 10 g sample of the gum was weighed into a 100 ml measuring cylinder and tapped 200 times. The volume was then recorded (V1). Distilled water was added to the mass to reach

the 100 ml mark and left to stand for 24 hours. The new volume (V2) of the gum in the measuring cylinder was recorded. The swelling capacity was calculated as the ratio of the final volume to the initial volume of gum (Pawar and D'mello, 2011). The experiment was repeated using phosphate buffer, pH 7.5 as the swelling medium.

3.8 FLOW PROPERTIES OF THE XANTHAN AND CASHEW GUMS

3.8.1 Bulk density measurements for xanthan and cashew gums

10 g of the gum was weighed and poured through a funnel into a 100 ml measuring cylinder. The cylinder was then lightly tapped twice to collect all the granules sticking on the wall of the cylinder. The initial volume, Vo was recorded. The cylinder was tapped from a height of 2 cm, 100 times on a wooden bench top to attain a constant volume reading from the cylinder, Vf. The initial density was calculated as the initial bulk density or fluff or paired bulk density, Do i.e. mass/Vo. The final density was also calculated as the final bulk density or equilibrium or tapped or consolidated bulk density, Df i.e. mass/V_f. The ratio Df/Do was calculated as the Hausner's ratio. Carr's index also known as percentage compressibility was calculated as (Df – Do/Df) x 100% (Carr, 1965). The Hausner ratio and the Carr's index, which are measures of interparticle friction and the potential powder arch or bridge strength and stability, respectively, are used widely to estimate the flow properties of powders (Aulton, 2001).

3.8.2 Angle of repose

The angle of repose was also performed using the fixed height method. The gum was allowed to flow freely from a funnel at a fixed height onto a horizontal surface to form a cone. The base of the cone was marked and the height of the orifice of the funnel from the horizontal surface was also measured. The height of the cone was measured. The angle of repose was calculated from the height of the cone and the radius of its base using the relation, $\tan \theta = h/r$ (Ejikeme, 2008).

3.9 PARTICLE SIZE ANALYSIS OF XANTHAN AND CASHEW GUMS

The particle size and the particle size distribution of xanthan and cashew gum powder were determined by using the Retsch Mechanical Shaker and the nest of sieves was arranged from sieve 8 to sieve 200 on the mechanical shaker. 120 g of the gum powder was weighed and placed on the topmost sieve and covered with the lid. The powder was agitated for a period of 15 minutes at amplitude of vibration of 60^0 after which the amount of powder retained on each sieve was weighed and recorded. The results were then used in further calculations.

3.10 PREPARATION OF GRANULES

The ratio of the polymers in each batch is shown in Table 3.1. Fifteen (15) different batches of granules were prepared by the wet granulation method. The actual amounts of the ingredients used are shown in Tables 3.2 – 3.16. In the preparation of the granules, no disintegrant was added to the powder mix in order to prevent the early breakdown of the matrix tablets. A blend of all ingredients except the lubricant and glidant was mixed in a porcelain mortar using water as the granulating fluid until a damp mass which easily broke into lumps (not powder) when pressure was applied to it using the thumb was formed. The damp mass was screened through sieve number 8 and the wet granules were dried at 60 °C for 1 hour in a hot air oven. The dried granules were screened through sieve number 16. The granules were used in further determinations and compressed into tablets.

Table 3-1 Ratios of polymers used in the formulations

BATCH	FORMULATION	CASHEW GUM	XANTHAN GUM	HPMC
1	C	100		
2	X		100	
3	H			100
4	H_8C_2	20		80
5	H_6C_4	40		60
6	H_2C_8	80		20
7	X_8H_2		80	20
8	X_6H_4		60	40
9	X_2H_8		20	80
10	X_8C_2	20	80	
11	X_6C_4	40	60	
12	X_2C_8	80	20	
13	$C_6X_2H_2$	60	20	20
14	$H_6X_2C_2$	20	20	60
15	$X_6C_2H_2$	20	60	20

KEY: C – Cashew gum, X – Xanthan gum and H – Hydroxypropyl Methylcellulose (HPMC)

Table 3-2 Batch 1

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.260 g	20.80 g

Table 3-3 Batch 2

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Xanthan Gum	0.260 g	20.80 g

Table 3-4 Batch 3

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
HPMC	0.260 g	20.80 g

Table 3-5 Batch 4

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.052 g	4.16 g
HPMC	0.208 g	16.64 g

Table 3-6 Batch 5

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.104 g	8.32 g
HPMC	0.156 g	12.48 g

Table 3-7 Batch 6

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.208 g	16.64 g
HPMC	0.052 g	4.16 g

Table 3-8 Batch 7

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Xanthan Gum	0.208 g	16.64 g
HPMC	0.052 g	4.16 g

Table 3-9 Batch 8

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Xanthan Gum	0.156 g	12.48 g
HPMC	0.104 g	8.32 g

Table 3-10 Batch 9

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Xanthan Gum	0.052 g	4.16 g
HPMC	0.208 g	16.64 g

Table 3-11 Batch 10

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Xanthan Gum	0.208 g	16.64 g
Cashew Gum	0.052 g	4.16 g

Table 3-12 Batch 11

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.104 g	8.32 g
Xanthan Gum	0.156 g	12.48 g

Table 3-13 Batch 12

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.208 g	16.64 g
Xanthan Gum	0.052 g	4.16 g

Table 3-14 Batch 13

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.156 g	12.48 g
HPMC	0.052 g	4.16 g
Xanthan Gum	0.052 g	4.16 g

Table 3-15 Batch 14

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.052 g	4.16 g
HPMC	0.156 g	12.48 g
Xanthan Gum	0.052 g	4.16 g

Table 3-16 Batch 15

INGREDIENTS	MASTER FORMULA	(× 80 tablets) Scaled quantities
Diclofenac Sodium	0.100 g	8.00 g
Magnesium Stearate	0.004 g	0.32 g
Microcrystalline Cellulose	0.0476 g	3.81 g
Talc	0.0084 g	0.672 g
Cashew Gum	0.052 g	4.16 g
HPMC	0.052 g	4.16 g
Xanthan Gum	0.156 g	12.48 g

3.11 DETERMINATION OF FLOW PROPERTIES OF THE GRANULES

3.11.1 Bulk density of granules

The initial bulk density (fluff density) and the final density (tapped density) of the granules were determined as described in Section 3.8.1. From the results, Hausner's ratio and Carr's index were calculated.

3.11.2 Angle of repose of granules

The angles of repose of the granules were performed as described in Section 3.8.2.

3.12 COMPRESSION OF TABLETS

Sustained release tablets each containing 100 mg of diclofenac sodium was prepared. Fifteen (15) different batches was compressed using the Single-punch tableting machine fitted with concave punches and die set. Magnesium stearate and talc were employed as lubricant and glidant respectively. The lubricant and granules were hand mixed for 5 min after which the granules were put in a metallic tray just before compression. In each batch, the estimated weight of the tablet was 420 mg.

3.13 EVALUATION OF TABLETS

3.13.1 Uniformity of weight test

Twenty (20) tablets from each batch were randomly selected and weighed together; the tablets were then weighed individually. The weight of each tablet was subtracted from the mean tablet weight and the percentage deviation of each tablet from the mean was calculated. (British Pharmacopoeia, 2009)

3.13.2 Crushing strength

Crushing strength of the tablets was determined at room temperature by diametral compression using a Monsanto tablet hardness tester. Ten tablets were selected randomly from the different batches of the tablets prepared and used for the experiment. A tablet was placed between the plate of the tester and the knob was screwed until contact was made after which there was enough pressure due to further screwing to cause breakage. The hardness was then read on the side scale of the tester. Results were taken only from tablets which split clearly into two halves without any sign of lamination. All measurements were made in triplicate (Owolabi et al., 2010).

3.13.3 Friability test

A number of tablets of total weight greater than 6 g was dedusted and weighed initially, Wo. They were then placed in the drum of the Erweka Friabilator and all the parameters set on the machine. The drum rotated and tumbled the tablets for four (4) minutes at 25 rpm, after which the machine stopped automatically. The tablets were observed for cleavages, breakages and cracks dedusted again. The final weight, $W_{f,}$ was recorded and the percentage weight loss calculated as

3.14 SWELLING INDEX OF TABLETS

The swelling index of all the tablet formulations was studied. The extent of swelling was measured in terms of percent weight gain by the tablet. One tablet from each formulation was kept in a petri dish containing 20 ml of phosphate buffer pH 7.5. At the end of 1h, the tablet was withdrawn, wiped with tissue paper, and weighed. Then for every 2 h, weights of the tablet were noted, and the process was continued till the end of 18 h. The percent weight gain of the tablets was calculated as:

3.16 DISSOLUTION

3.16.1 Dissolution testing

Dissolution testing was carried out on the various diclofenac sodium matrix tablets as well as on voltaren retard tablets, a commercial product used as a reference (standard) sample. 900 mls of the dissolution medium (Phosphate buffer pH 7.5) was placed in the six vessels of the dissolution machine. The dissolution medium was equilibrated to 37 ± 0.5 °C and the paddle speed set to 50 revolutions per minute. One tablet was placed in each of the vessels of the dissolution machine and operated at the specified rate. At specified time intervals of 5 min, 15 min, 30 min, 1h, 2h, 4h, 6h, 8h, 10h, 12h, 15h, 18h, 21h and 24h. 10 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 10 ml sample withdrawn, 10 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 a Whatman filter paper and diluted 10 times. The diluted filtrate were analysed by UV spectrophotometer at a wavelength of 276 nm using a 1cm cell and phosphate buffer pH 7.5 as reference solution. Using the equation obtained from the calibration curve, the concentration of diclofenac sodium in samples taken at times 5 min, 15 min, 30 min, 1h, 2h, 4h, 6h, 8h, 10h, 12h, 15h, 18h, 21h and 24h were calculated and the percentage release values were then calculated. A plot of cumulative percentage drug released against time was established.

3.17 DIFFERENCE AND SIMILARITY FACTOR S

Results obtained from the dissolution profile were fitted into equations to determine the difference and similarity factors of the various batches compared to a standard.

$$f_1 = \{[\Sigma\, t_{=1}^{n} |Rt-Tt|] / [\Sigma\, _{t=1}^{n} Rt]\} \times 100 \ldots\ldots\ldots\ldots \text{eqn. 21}$$

$$f_2 = 50 + \log \{[1+ (1/n) \textstyle\sum_{t=1} * n (R_t-T_t)^2]^{-0.5} * 100\} \ldots\ldots\ldots\ldots \text{eqn. 22}$$

Where f_1 = difference factor

f_2 = similarity factor

n = time points

Rt = cumulative percentage dissolved at time t for the reference

Tt = cumulative percentage dissolved at time t for the test (Suvakanta *et al.*, 2010).

3.18 DRUG RELEASE KINETICS

3.18.1 Zero order kinetics

The cumulative percentage release of the drug was plotted against time and the correlation coefficient and the slope noted. The equation used was

3.18.4 Hixson – Crowell model

This is based on the Hixson – Crowell cube root law. Here, the cube root of the cumulative percentage release of the drug was plotted against time. The rate constant of release (K_{HC}) and the regression line value (R^2) were extracted from the graph. The equation was

$$Q_0^{1/3} - Qt^{1/3} = K_{HC}\, t \ldots\ldots\ldots\ldots\ldots\ldots eqn\ 24$$

Where Q_0 = is the initial amount of the drug in tablet

Qt = the amount of drug released in time t

K_{HC} = the rate constant for Hixson-Crowell rate equation (Singhvi and Singh, 2011).

3.18.5 Korsemeyer-Peppas model

This simple empirical equation is used to describe general solute release behaviour from controlled release polymer matrices. Here, a plot of the logarithm of the cumulative percentage of the drug released against the logarithm of time and the slope, 'n' and the regression line values (R^2) were extracted from the graph. The equation used is

$$F = (Mt/M) = kt^n$$

Where F = fraction of drug released

Mt = amount of drug released at time t

M = total amount of drug in dosage form

k = kinetic constant

t = release time

n = the diffusional exponent for drug release (Korsmeyer *et al.*, 1983).

Chapter 4

RESULTS

4.1 PURIFICATION OF CASHEW GUM

Percentage Yield calculation

$$\% \text{ yield} = \frac{\text{Final weight of gum (after purification)}}{\text{Initial weight of gum (before purification)}} \times 100$$

Hence for cashew gum

$$\text{Percentage yield} = \frac{505.8 \text{ g}}{700 \text{ g}} \times 100 = \mathbf{72.26}\ \%$$

4.2 PHYSICAL TESTS ON CASHEW GUM

Table 4-1 Macroscopic properties of the crude gum

Property	Characteristic of gum
Colour	Yellowish, glassy white
Taste	Bland
Odour	Characteristic
Appearance	Smooth

Table 4-2 Insoluble matter and moisture content of cashew gum

Gum	Insoluble matter (%)	Moisture content (%)
Purified gum	0.260 ± 0.030	11.14 ± 0.24
Crude gum	0.450 ± 0.115	13.84 ± 0.12

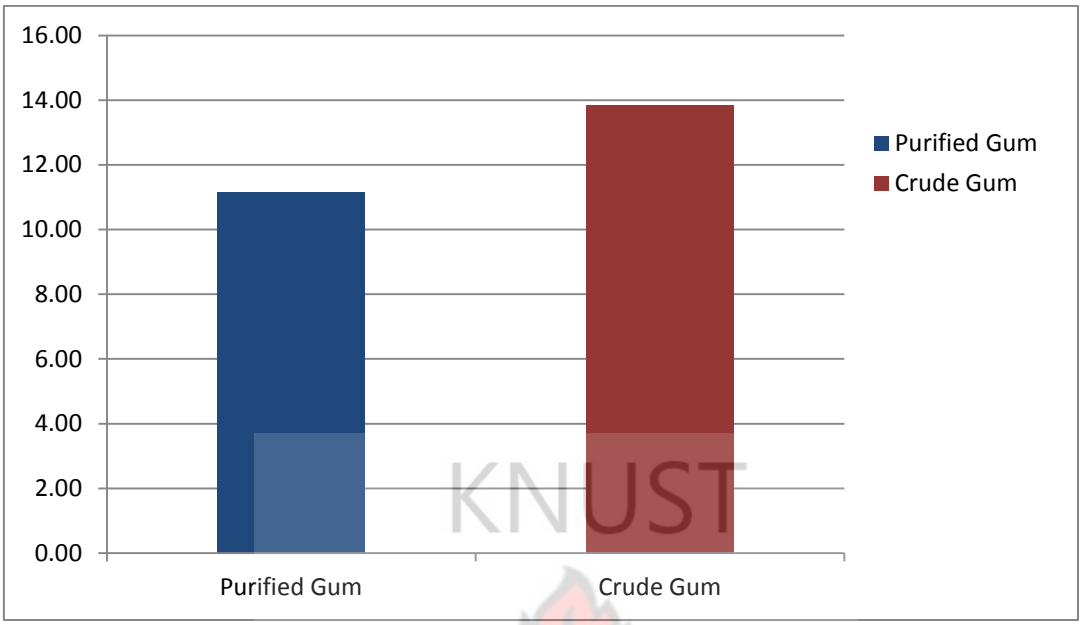

Figure 4-1 Moisture content of crude and purified cashew gum

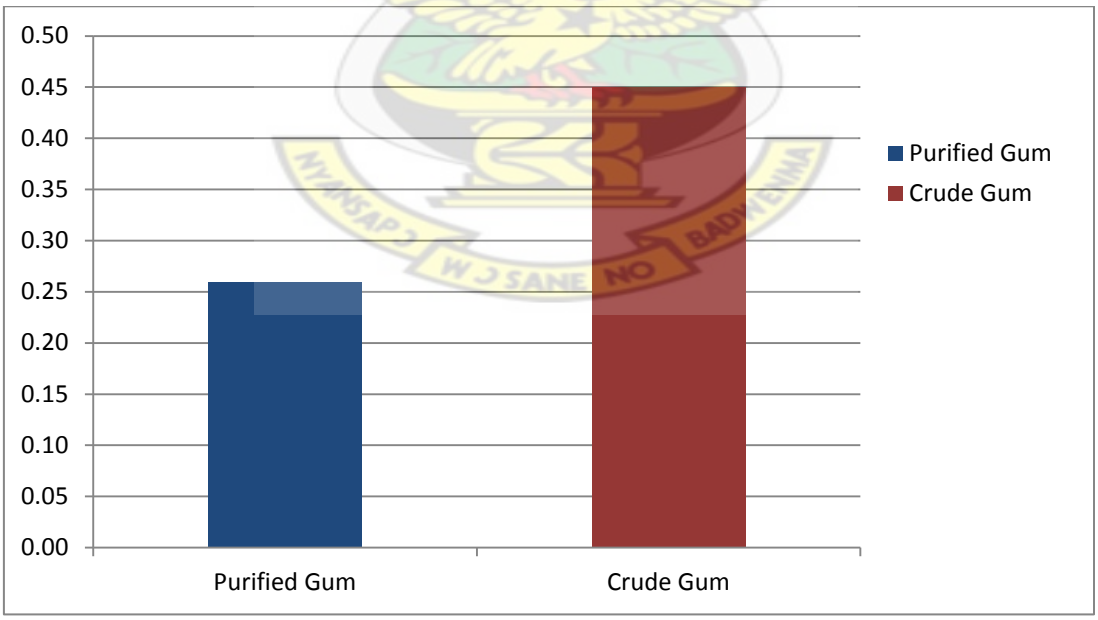

Figure 4-2 : Insoluble matter of crude and purified cashew gum

4.3 RHEOLOGY OF XANTHAN GUM AND CASHEW GUM

4.3.1 Viscosities of different concentrations of xanthan gum mucilage

Table 4-3 Effect of concentration on the viscosity of xanthan gum mucilage

Concentration (%w/v)	Viscosity (cps)
0.50	84.2
0.75	174.0
1.00	312.3

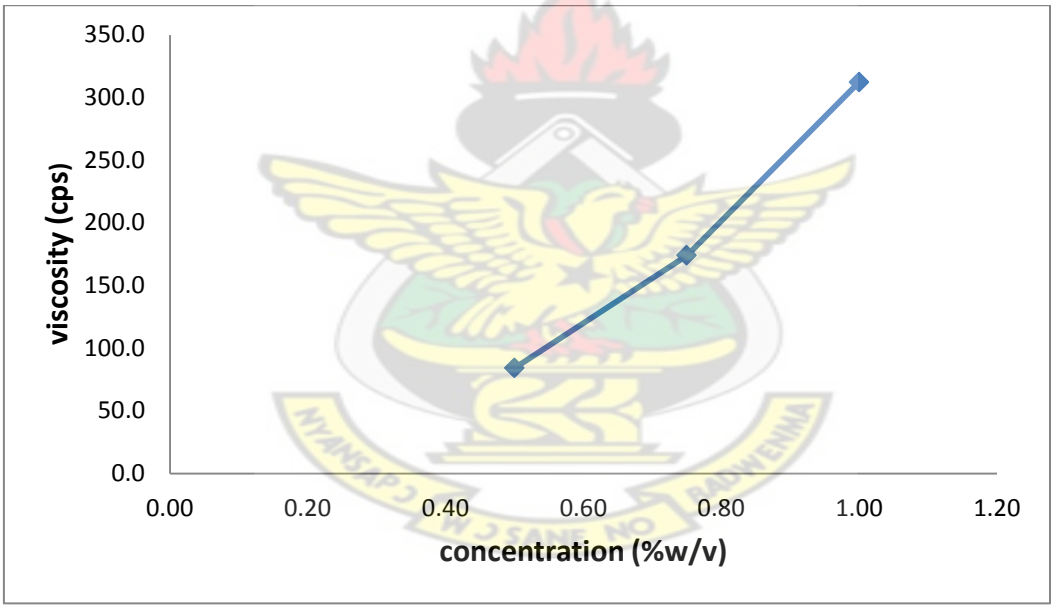

Figure 4-3 Relationship between concentration and viscosity of xanthan gum mucilage

4.3.2 Viscosities of different concentrations of cashew gum mucilage

Table 4-4 Effect of concentration on the viscosity of cashew gum mucilage

Concentration (%w/v)	Viscosity (cps)
1.0	5.2
2.0	12.4
5.0	25.6
10.0	63.5

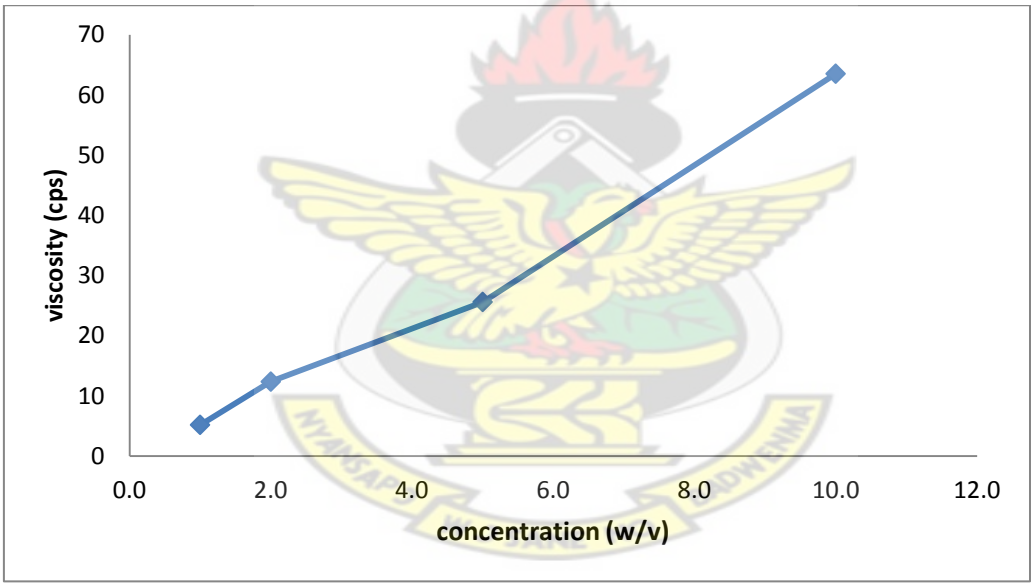

Figure 4-4 Relationship between concentration and viscosity of cashew gum mucilage

4.3.3 Flow curves for xanthan gum mucilage

Table 4-5 Rheogram for 0.5%w/v xanthan gum mucilage

LOADING			UNLOADING		
weight /g	time /sec	revs /sec	weight /g	time /sec	revs /sec
0	35.33	2.83	50	8.98	11.14
5	25.40	3.94	40	10.2	9.80
10	20.40	4.90	30	11.95	8.37
20	14.94	6.69	20	14.82	6.75
30	11.97	8.35	10	19.61	5.10
40	10.27	9.74	5	24.75	4.04
50	8.86	11.29	0	30.70	3.26

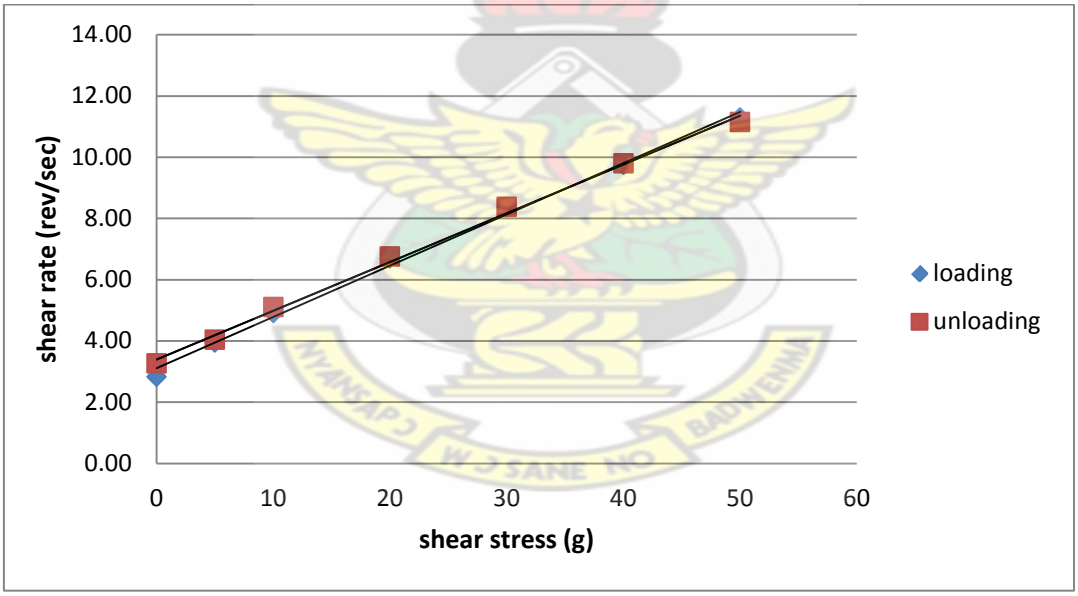

Figure 4-5 Rheogram for 0.5 %w/v xanthan gum mucilage

Table 4-6 Rheogram for 0.75%w/v xanthan gum mucilage

LOADING			UNLOADING		
weight /g	time /sec	revs /sec	weight /g	time /sec	revs /sec
0	43.59	2.29	50	10.79	9.27
5	32.99	3.03	40	12.52	7.99
10	26.52	3.77	30	14.80	6.76
20	19.00	5.26	20	18.48	5.41
30	15.17	6.59	10	25.45	3.92
40	12.57	7.96	5	32.04	3.12
50	10.79	9.27	0	44.06	2.27

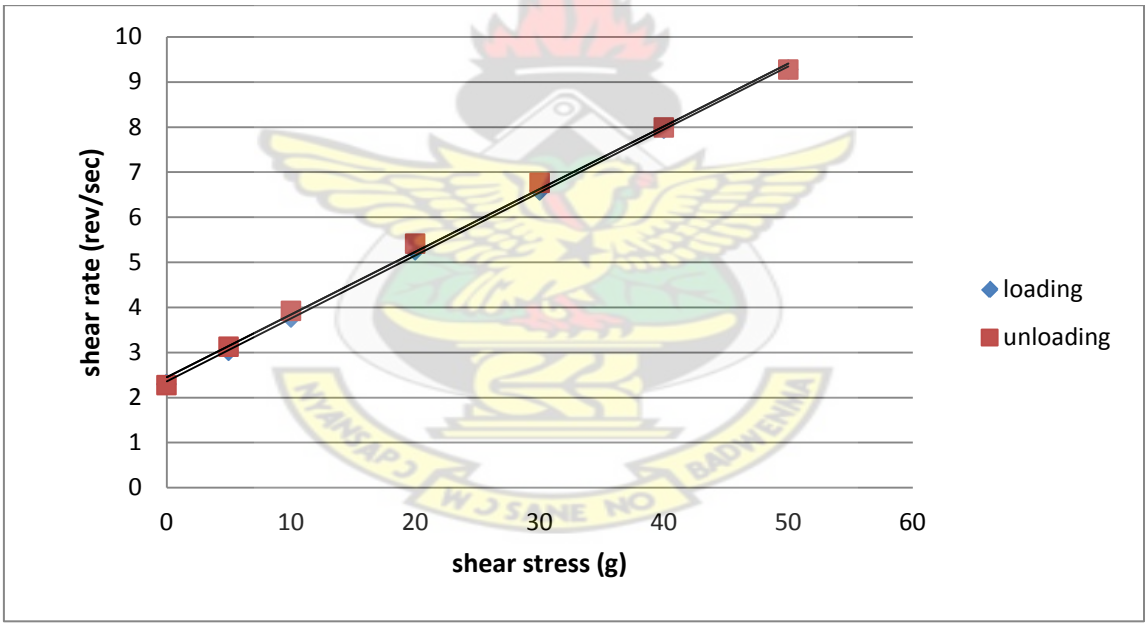

Figure 4-6 Rheogram for 0.75 %w/v xanthan gum mucilage

Table 4-7 Rheogram for 1.0%w/v xanthan gum mucilage

LOADING			UNLOADING		
weight /g	time /sec	revs /sec	weight /g	time /sec	revs /sec
0	187.27	0.53	50	19.54	5.12
5	113.77	0.88	40	24.29	4.12
10	77.78	1.29	30	32.3	3.10
20	45.94	2.18	20	47.16	2.12
30	31.48	3.18	10	82.14	1.22
40	23.96	4.17	5	119.06	0.84
50	19.22	5.20	0	203.27	0.49

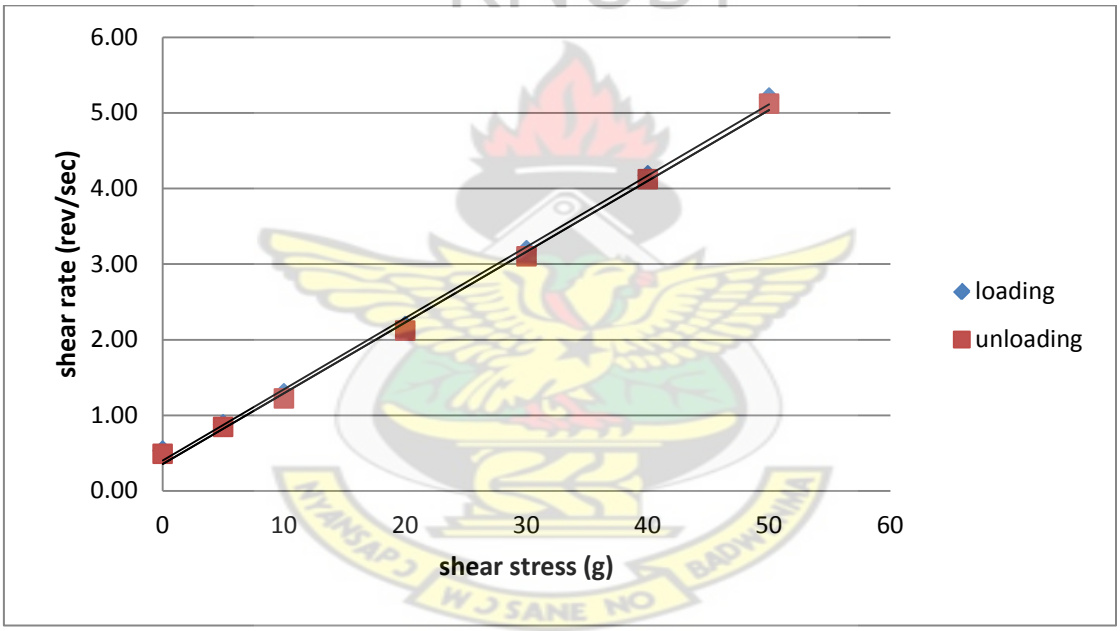

Figure 4-7 Rheogram for 1.0%w/v xanthan gum mucilage

4.3.4 Flow curves for cashew gum mucilage

Table 4-8 Rheogram for 1%w/v cashew gum mucilage

LOADING			UNLOADING		
weight /g	time /sec	revs /sec	weight /g	time /sec	revs /sec
0	64.94	1.54	50	8.65	11.56
5	20.66	4.84	40	9.82	10.18
10	17.73	5.64	30	10.93	9.15
20	12.90	7.75	20	12.69	7.88
30	11.35	8.81	10	16.50	6.06
40	9.60	10.42	5	20.45	4.89
50	8.44	11.85	0	85.47	1.17

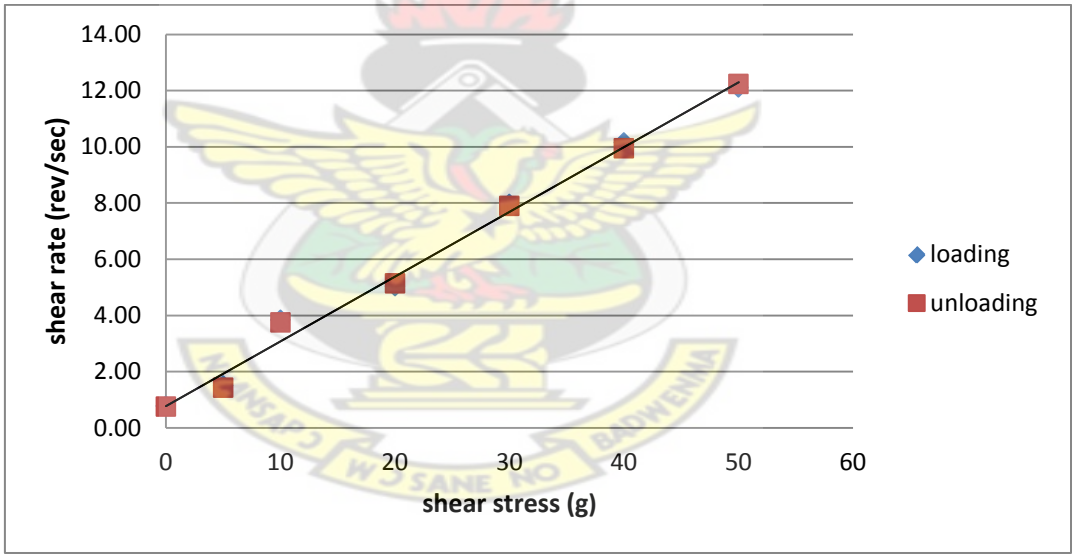

Figure 4-8 Rheogram for 1.0 %w/v cashew gum mucilage

Table 4-9 Rheogram for 2 %w/v cashew gum mucilage

LOADING			UNLOADING		
weight /g	time /sec	revs /sec	weight /g	time /sec	revs /sec
0	31.25	3.20	50	8.45	11.83
5	19.61	5.10	40	9.60	10.42
10	16.10	6.21	30	10.53	9.50
20	12.74	7.85	20	12.76	7.84
30	10.64	9.40	10	16.08	6.22
40	9.50	10.53	5	19.05	5.25
50	8.46	11.82	0	31.15	3.21

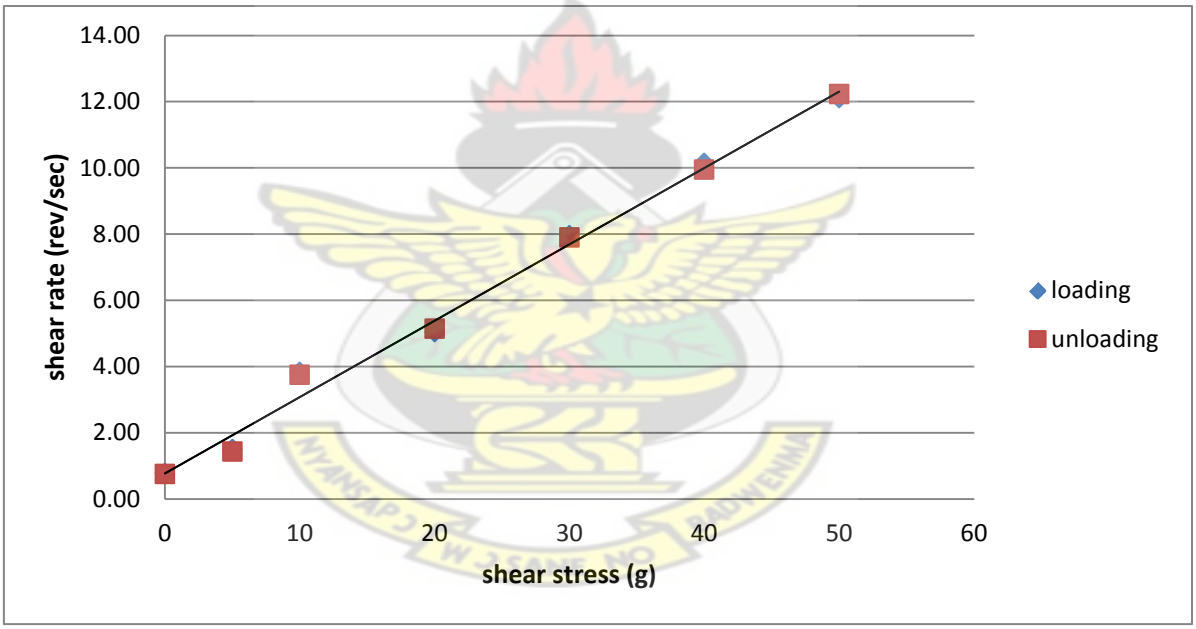

Figure 4-9 Rheogram for 2.0 %w/v cashew gum mucilage

Table 4-10 Rheogram for 5%w/v cashew gum mucilage

LOADING			UNLOADING		
weight /g	time /sec	revs /sec	weight /g	time /sec	revs /sec
0	41.15	2.43	50	8.61	11.62
5	20.49	4.88	40	9.55	10.47
10	17.09	5.85	30	10.99	9.10
20	13.18	7.59	20	13.18	7.59
30	10.96	9.12	10	17.18	5.82
40	9.60	10.42	5	20.20	4.95
50	8.61	11.61	0	41.67	2.40

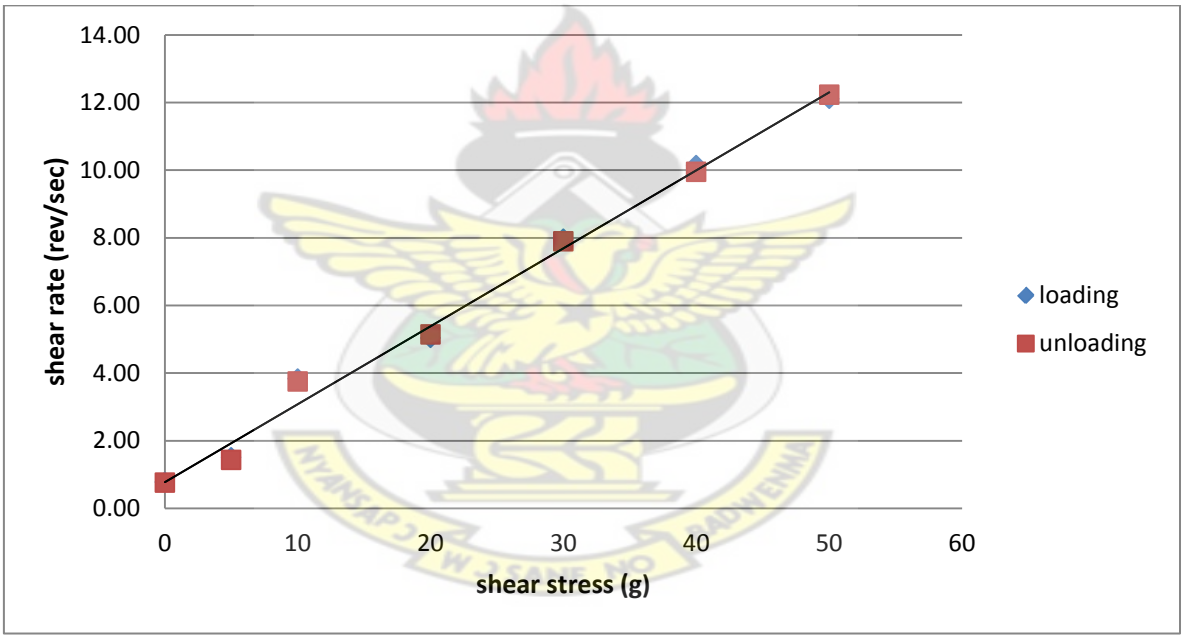

Figure 4-10 Rheogram for 5.0 %w/v cashew gum mucilage

Table 4-11 Rheogram for 10 %w/v cashew gum mucilage

LOADING			UNLOADING		
weight /g	time /sec	revs /sec	weight /g	time /sec	revs /sec
0	128.21	0.78	50	8.18	12.23
5	66.23	1.51	40	10.05	9.95
10	26.04	3.84	30	12.66	7.90
20	19.84	5.04	20	19.46	5.14
30	12.55	7.97	10	26.67	3.75
40	9.85	10.15	5	69.93	1.43
50	8.26	12.11	0	131.58	0.76

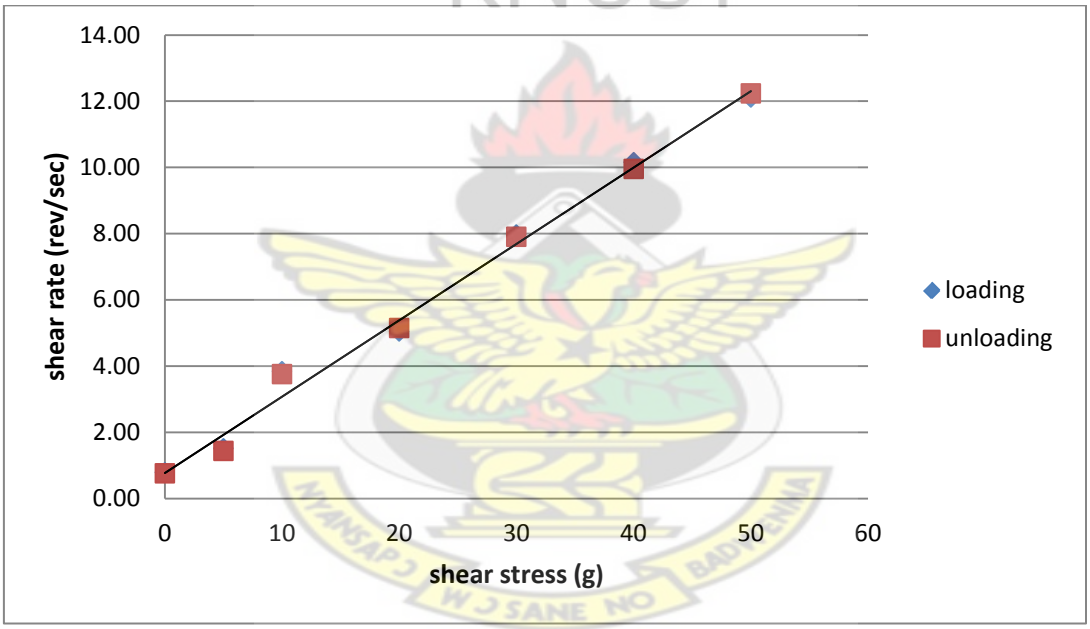

Figure 4-11 Rheogram for 10 %w/v cashew gum mucilage

4.4 SWELLING CAPACITY OF XANTHAN GUM

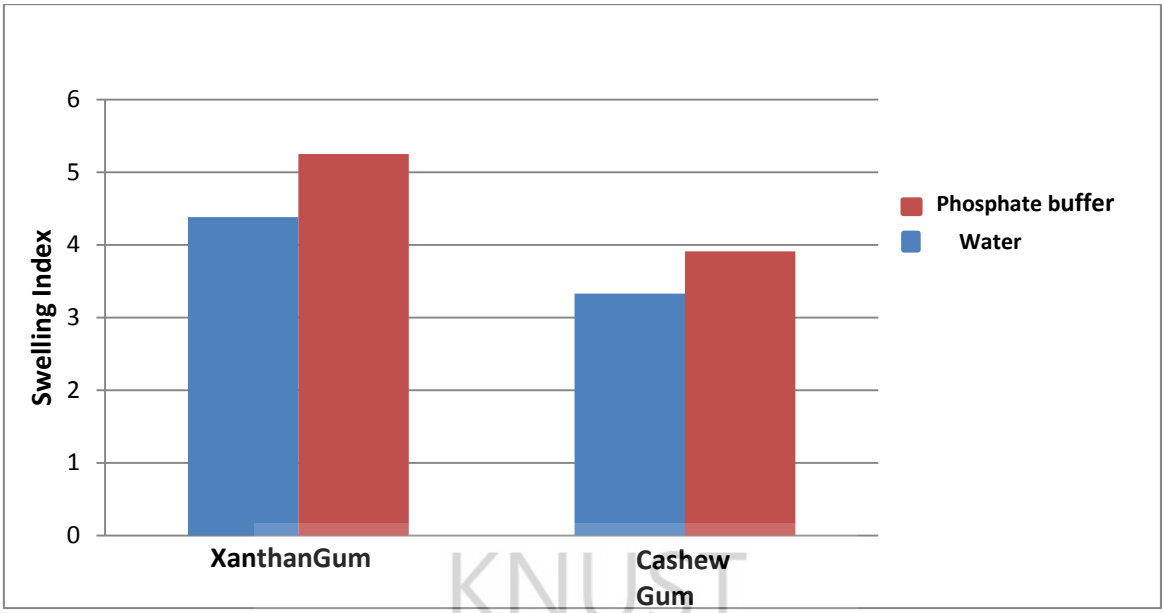

Figure 4-12 Swelling indices of xanthan and cashew gums in distilled water and phosphate buffer

4.6 FLOW PROPERTIES OF THE GUMS

Weight of gum used = 10 g

Number of tapping = 100 times

Table 4-12 Bulk density measurements of xanthan and cashew gums

Sample	Initial vol(ml)	Tapped vol(ml)	Bulk density(Do)	Tapped density (Df)	Hausner's ratio	Carr's index (%)	Angle of repose(°)
xanthan gum	20	18	0.50	0.56	1.12	10.71	14.58
cashew gum	17	16	0.59	0.63	1.07	6.35	24.67

4.7 PARTICLE SIZE ANALYSIS

4.7.1 Particle size distribution of xanthan gum

Weight of xanthan gum powder used = 120 g

Table 4-13 Particle size distribution of xanthan gum

sieve number	aperture size(µm)	range(µm)	weight retained(g)	% weight retained
60	250	250 – 425	1.98	1.65
80	180	180 – 250	4.45	3.71
200	75	75 – 180	95.12	79.27
Pan		< 75	18.45	15.38

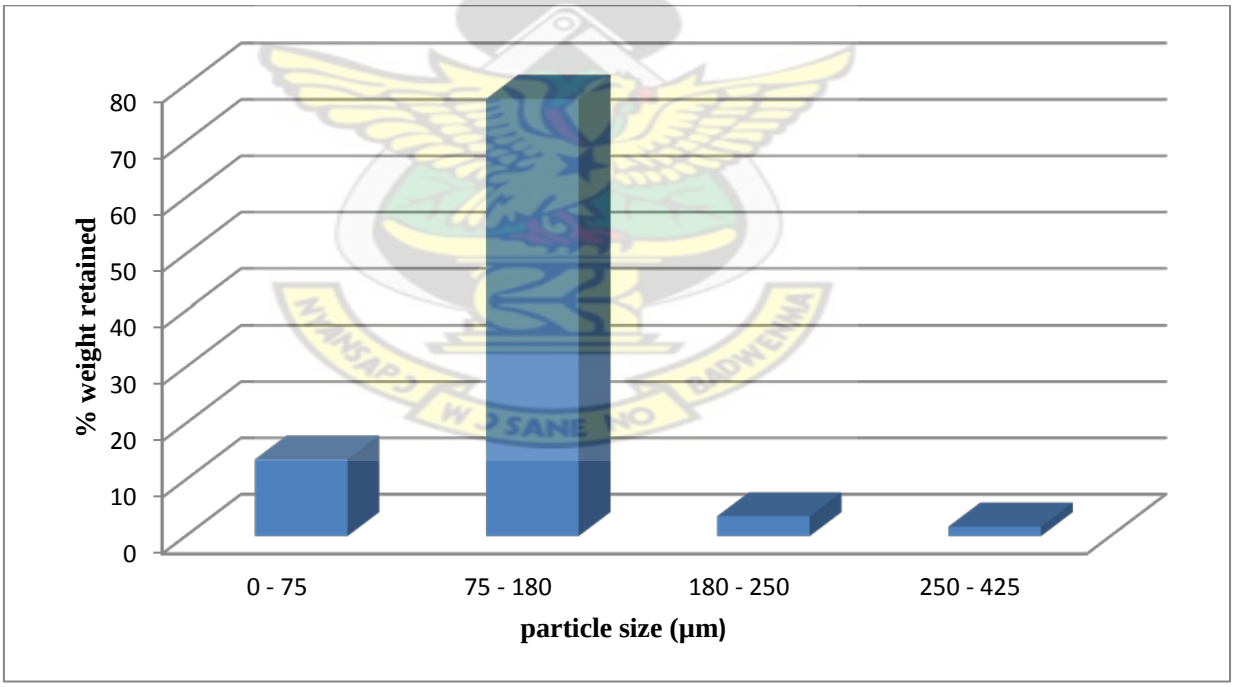

Figure 4-13 Particle size distribution of xanthan gum

4.7.2 Particle size distribution of cashew gum

Weight of cashew gum powder used = 120 g

Table 4-14 Particle size distribution of cashew gum

sieve number	aperture size(µm)	range(µm)	weight retained(g)	% weight retained
40	425	425 – 850	9.19	7.66
60	250	250 – 425	75.58	62.15
80	180	180 – 250	32.34	26.95
200	75	75 – 180	2.86	2.38
Pan		< 75	1.03	0.86

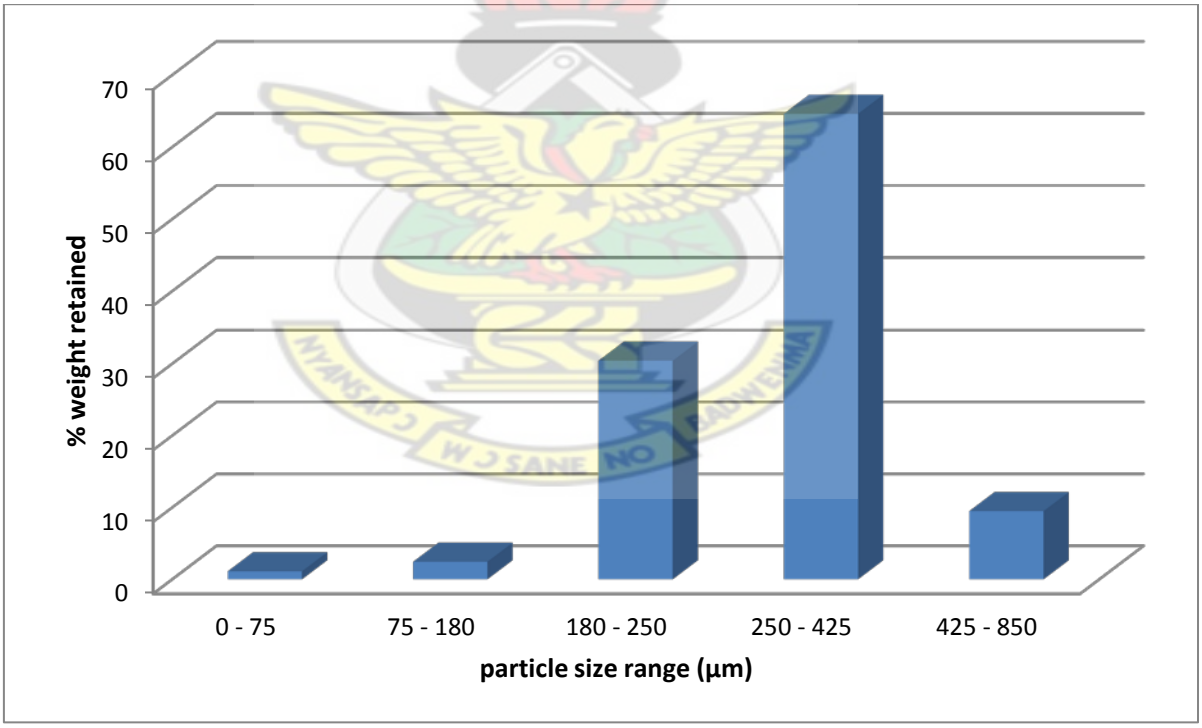

Figure 4-14 Particle size distribution of cashew gum

4.8 FLOW PROPERTIES OF DICLOFENAC SODIUM GRANULES

Table 4-15 Bulk density measurements of diclofenac sodium granules prepared

Batch No	Loose bulk density g/mL	Tapped bulk density g/mL	Hausner's Ratio	Compressibility Index (%)	Angle of repose (º)
1	0.56	0.59	1.05	5.1	30.80 ± 0.006
2	0.45	0.48	1.07	6.3	32.41 ± 0.012
3	0.45	0.5	1.11	10.0	28.55 ± 0.026
4	0.50	0.53	1.06	5.7	31.50 ± 0.076
5	0.50	0.56	1.12	10.7	27.11 ± 0.113
6	0.48	0.5	1.04	4.0	35.30 ± 0.006
7	0.45	0.5	1.11	10.0	26.41 ± 0.017
8	0.50	0.56	1.12	10.7	29.60 ± 0.115
9	0.48	0.53	1.10	10.4	31.74 ± 0.092
10	0.53	0.59	1.11	10.2	30.20 ± 0.010
11	0.48	0.53	1.10	9.4	34.86 ± 0.029
12	0.53	0.59	1.11	10.2	25.90 ± 0.012
13	0.53	0.56	1.06	5.3	33.42 ± 0.006
14	0.45	0.5	1.11	10.0	30.65 ± 0.010
15	0.53	0.56	1.06	5.3	32.15 ± 0.026

4.9 COMPRESSION OF DICLOFENAC SODIUM MATRIX TABLETS

Tablet weight = 420 mg

Number of Tablets = 80 tablets per batch (15 batches in all)

Practical yield = 958 tablets

4.10 QUALITY CONTROL TESTS CARRIED OUT ON TABLETS

4.10.1 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 tablets, B = Average weight of 20 tablets

Table 4-16 Uniformity of weight of the batches of diclofenac sodium matrix tablets

Batch No.	Total tablet weight (g)	Average weight (g) ± SD	Max % deviation	Inference
1	8.814	0.441 ± 0.012	4.833	passed
2	8.666	0.433 ± 0.007	2.977	passed
3	8.337	0.417 ± 0.011	4.893	passed
4	8.557	0.428 ± 0.009	4.021	passed
5	8.564	0.428 ± 0.011	4.52	passed
6	8.507	0.425 ± 0.011	4.372	passed
7	8.388	0.419 ± 0.012	3.672	passed
8	8.487	0.424 ± 0.011	4.689	passed
9	8.553	0.428 ± 0.012	4.139	passed
10	8.342	0.417 ± 0.010	4.363	passed
11	8.317	0.416 ± 0.012	3.175	passed
12	8.350	0.418 ± 0.009	4.335	passed
13	8.625	0.431 ± 0.010	3.617	passed
14	8.159	0.408 ± 0.009	3.137	passed
15	8.345	0.417 ± 0.011	3.209	passed

4.11 CRUSHING STRENGTH (HARDNESS)

Table 4-17 Crushing strength of the diclofenac sodium matrix tablets

Batch Number	Mean force applied (Kg)
1	4.4 ± 1.11
2	6.8 ± 1.60
3	3.8 ± 0.75
4	4.0 ± 0.81
5	4.0 ± 0.77
6	4.1 ± 1.22
7	4.1 ± 0.65
8	4.3 ± 0.64
9	5.2 ± 1.18
10	4.1 ± 0.83
11	5.3 ± 1.91
12	4.0 ± 0.63
13	4.1 ± 0.70
14	6.6 ± 1.85
15	5.7 ± 1.72

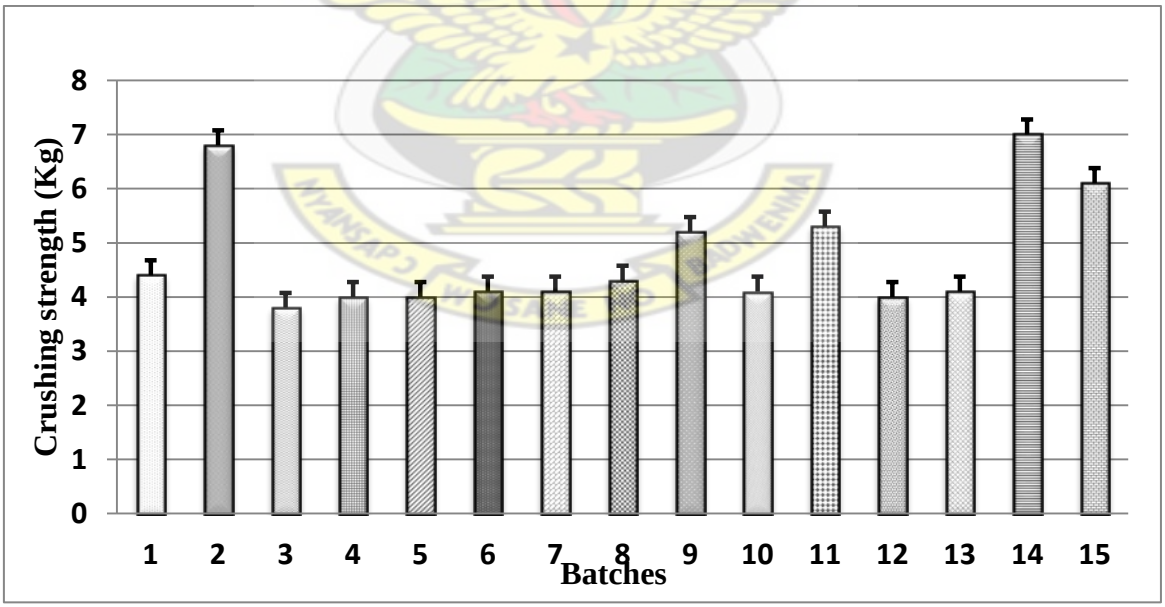

Figure 4-15 Crushing strength of the diclofenac sodium matrix tablets

4.12 FRIABILITY

Table 4-18 Friability of the diclofenac sodium matrix tablets

Batch	Initial weight (Wi)	Final weight (Wf)	Weight loss	% loss
1	6.01	5.95	0.06	1.00
2	6.28	6.27	0.01	0.16
3	6.28	6.24	0.04	0.64
4	6.36	6.29	0.07	1.10
5	6.35	6.30	0.05	0.79
6	6.36	6.33	0.03	0.47
7	6.31	6.30	0.01	0.16
8	6.29	6.24	0.05	0.80
9	6.36	6.32	0.04	0.63
10	6.19	6.11	0.08	1.30
11	6.19	6.14	0.05	0.81
12	6.2	6.19	0.01	0.16
13	6.1	6.09	0.01	0.16
14	6.12	6.08	0.04	0.65
15	6.05	6.01	0.04	0.66

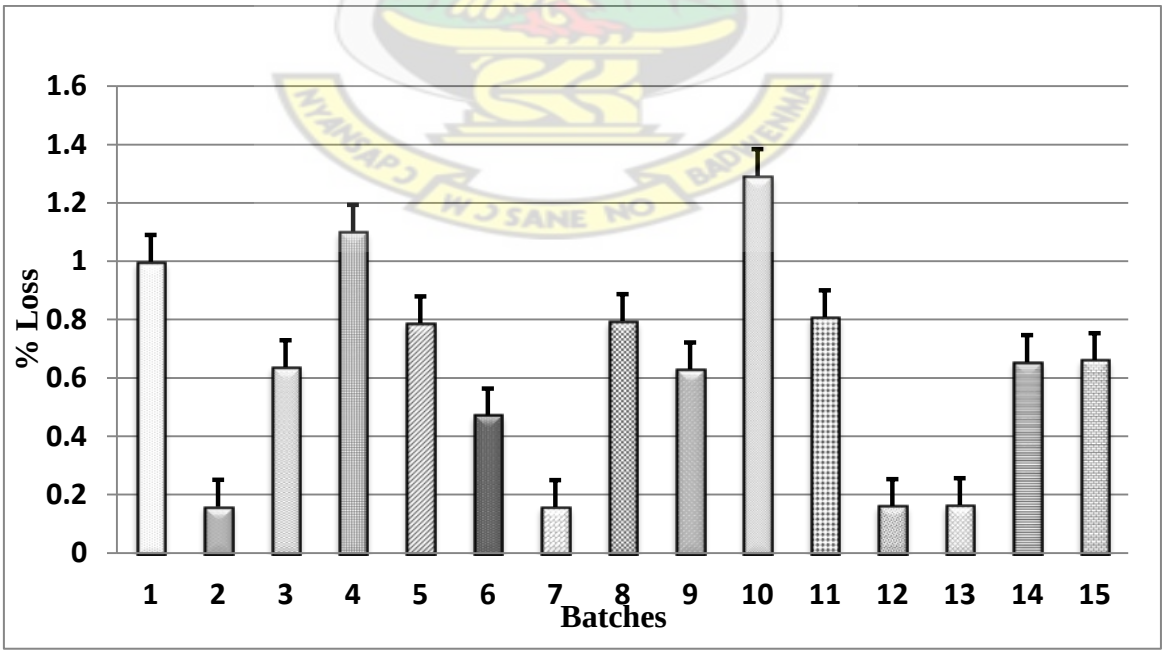

Figure 4-16 Friability of the diclofenac sodium matrix tablets

4.13 CRUSHING STRENGTH FRIABILITY RATIO (CSFR)

Crushing Strength – CS

Friability – F

$$CSFR = \frac{CS}{F}$$

Table 4-19 Crushing strength friability ratio of the diclofenac sodium matrix tablets

Batch	Crushing Strength	Friability	CSFR
1	4.4 ± 1.11	1.00	4.4
2	6.8 ± 1.60	0.16	42.8
3	3.8 ± 0.75	0.64	6.0
4	4.0 ± 0.81	1.10	3.6
5	4.0 ± 0.77	0.79	5.1
6	4.1 ± 1.22	0.47	8.7
7	4.1 ± 0.65	0.16	25.9
8	4.3 ± 0.64	0.80	5.4
9	5.2 ± 1.18	0.63	8.3
10	4.1 ± 0.83	1.29	3.2
11	5.3 ± 1.91	0.81	6.6
12	4.0 ± 0.63	0.16	24.8
13	4.1 ± 0.70	0.16	25.0
14	6.6 ± 1.85	0.65	10.1
15	5.7 ± 1.72	0.66	8.6

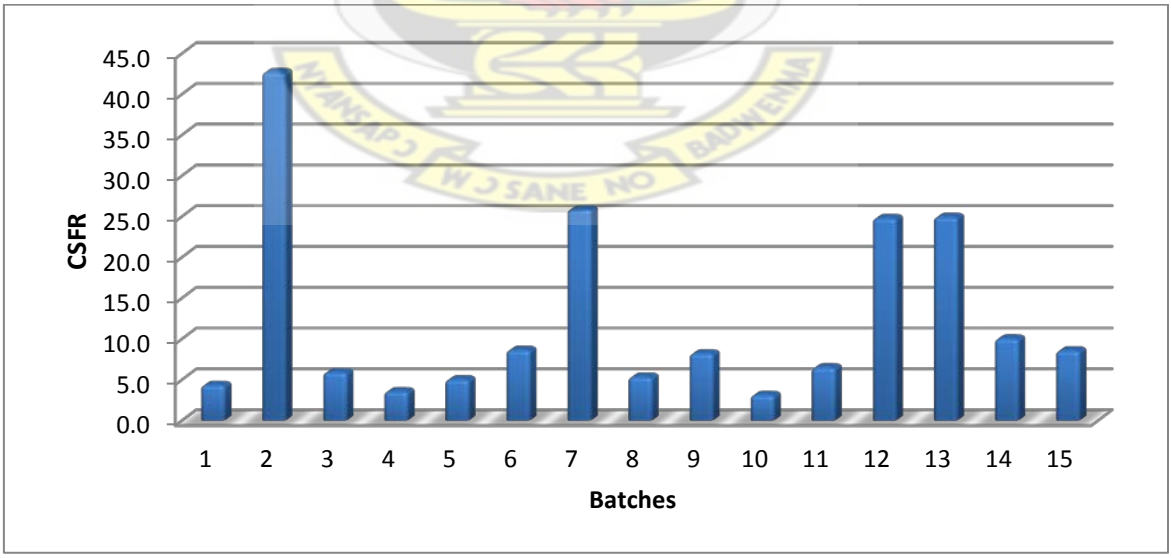

Figure 4-17 Crushing Strength Friability Ratio (CSFR) of the different batches of diclofenac sodium matrix tablets

4.14 TABLET THICKNESS

Table 4-20 Thickness of the diclofenac sodium matrix tablets

BATCH	TABLET THICKNESS(mm)
1	5.70 ± 0.400
2	5.75 ± 0.403
3	6.50 ± 0.387
4	6.30 ± 0.510
5	6.30 ± 0.400
6	6.75 ± 0.403
7	6.85 ± 0.391
8	7.10 ± 0.374
9	6.95 ± 0.415
10	6.90 ± 0.436
11	6.20 ± 0.400
12	6.55 ± 0.415
13	5.85 ± 0.391
14	6.15 ± 0.450
15	6.30 ± 0.458

4.15 SWELLING INDEX OF DICLOFENAC SODIUM MATRIX TABLETS

Table 4-21 Swelling index of the diclofenac sodium matrix tablets

	% WATER ABSORBED														
Time (hr)	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9	Batch 10	Batch 11	Batch 12	Batch 13	Batch 14	Batch 15
0.08	4.7	28.6	7.1	11.9	11.4	6.8	21.4	22.5	16.7	25.0	41.9	25.0	25.6	19.0	34.9
0.25	11.6	54.8	7.1	11.9	6.8	11.4	38.1	32.5	23.8	61.4	67.4	47.7	46.5	28.6	60.5
0.50	4.7	85.7	0.0	0.0	0.0	11.4	57.1	57.5	26.2	79.5	144.2	81.8	74.4	50.0	104.7
1.00	0.0	92.9	0.0	0.0	0.0	2.3	66.7	60.0	19.0	93.2	167.4	97.7	79.1	66.7	123.3
2.00	0.0	116.7	0.0	0.0	0.0	0.0	90.5	67.5	9.5	118.2	195.3	106.8	81.4	59.5	151.2
4.00	0.0	150.0	0.0	0.0	0.0	0.0	111.9	77.5	0.0	152.3	200.0	90.9	69.8	40.5	139.5
6.00	0.0	190.5	0.0	0.0	0.0	0.0	140.5	62.5	0.0	184.1	218.6	81.8	62.8	28.6	114.0
8.00	0.0	242.9	0.0	0.0	0.0	0.0	159.5	55.0	0.0	197.7	218.6	52.3	27.9	16.7	72.1
10.00	0.0	269.0	0.0	0.0	0.0	0.0	178.6	35.0	0.0	211.4	216.3	18.2	0.0	0.0	65.1
12.00	0.0	285.7	0.0	0.0	0.0	0.0	223.8	0.0	0.0	236.4	214.0	0.0	0.0	0.0	18.6
15.00	0.0	288.1	0.0	0.0	0.0	0.0	231.0	0.0	0.0	250.0	220.9	0.0	0.0	0.0	0.0
18.00	0.0	285.7	0.0	0.0	0.0	0.0	235.7	0.0	0.0	250.0	218.6	0.0	0.0	0.0	0.0

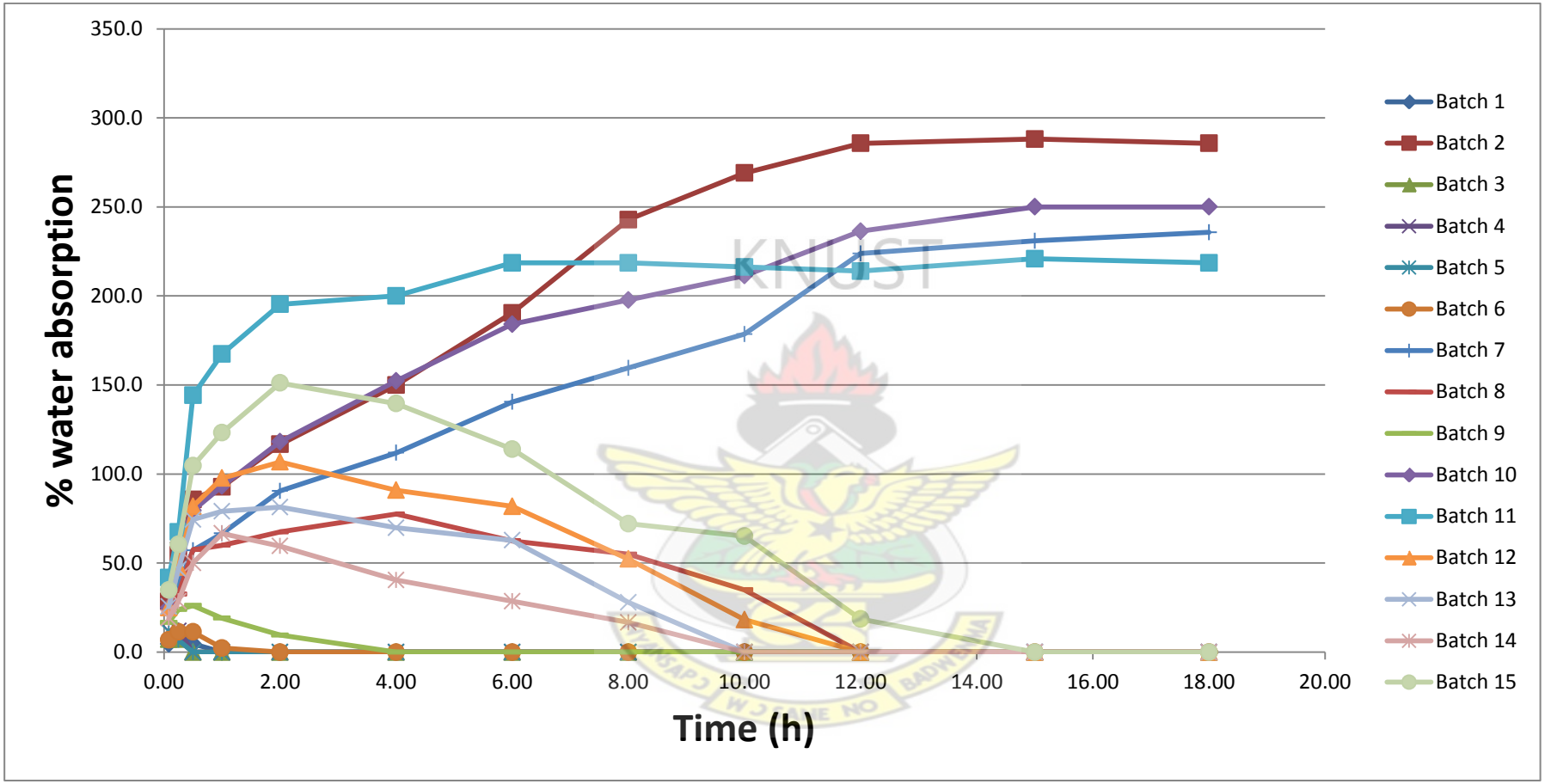

Figure 4-18 Swelling index of the batches of tablets compressed

4.16 ASSAY OF DICLOFENAC SODIUM MATRIX TABLETS

4.16.1 Calibration curve for diclofenac sodium in 0.1M NaOH at a wavelength of 276 nm

Blank used: 0.1M NaOH

Table 4-22 Absorbance of pure Diclofenac Sodium in 0.1M NaOH

Concentration (%w/v)	Absorbances
0.00250	0.762
0.00150	0.441
0.00125	0.356
0.00100	0.276
0.00075	0.162

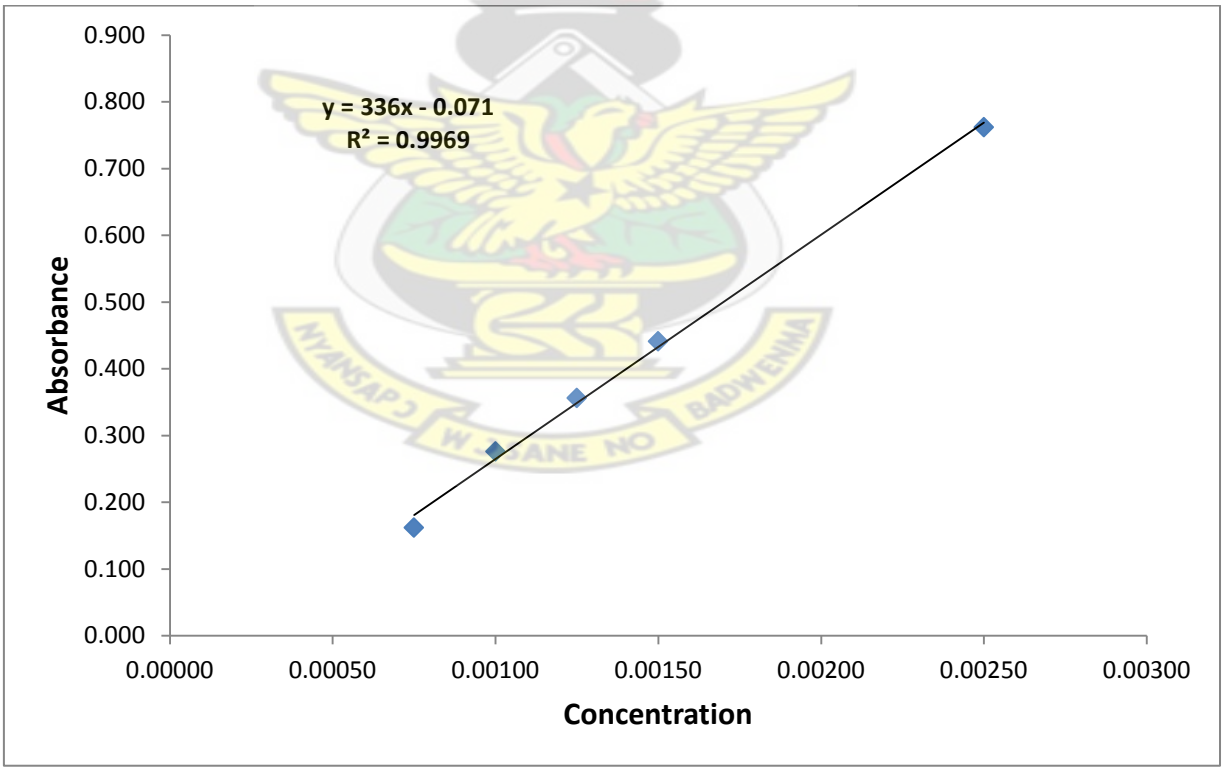

Figure 4-19 Calibration curve for diclofenac sodium in 0.1M NaOH

4.17 ASSAY OF DICLOFENAC SODIUM MATRIX TABLETS

Table 4-23 Assay of diclofenac sodium matrix tablets compressed

Batch No	Expected weight(g)	Actual weight (g)	Conc (%w/v)	Average Abs	A (1% 1cm)	Assay (%)
1	0.4407	0.4410	0.002001	0.660	329.776	101.5 ± 0.408
2	0.4332	0.4332	0.002000	0.641	320.500	98.7 ± 0.510
3	0.4168	0.4164	0.001998	0.645	322.810	99.4 ± 0.205
4	0.4278	0.4275	0.001999	0.647	323.727	99.7 ± 0.510
5	0.4282	0.4279	0.001999	0.646	323.226	99.5 ± 0.249
6	0.4254	0.4256	0.002001	0.654	326.846	100.6 ± 0.566
7	0.4194	0.4193	0.002000	0.649	324.577	99.9 ± 0.216
8	0.4244	0.4242	0.001999	0.645	322.652	99.3 ± 0.170
9	0.4276	0.4275	0.002000	0.642	321.075	98.9 ± 0.249
10	0.4171	0.4173	0.002001	0.647	323.345	99.5 ± 0.170
11	0.4158	0.4160	0.002001	0.646	322.845	99.4 ± 0.170
12	0.4175	0.4173	0.001999	0.644	322.154	99.2 ± 0.249
13	0.4313	0.4314	0.002000	0.648	323.925	99.7 ± 0.497
14	0.4080	0.4080	0.002000	0.646	323.000	99.4 ± 0.125
15	0.4173	0.4172	0.002000	0.653	326.578	100.5 ± 0.478
Pure sample	**0.1000**	**0.1002**	**0.002004**	**0.651**	**324.850**	

4.18 DISSOLUTION PROFILE OF DICLOFENAC SODIUM TABLETS FORMULATED WITH DIFFERENT GUM RATIOS

4.18.1 Calibration curve for diclofenac sodium in phosphate buffer pH 7.5 at a wavelength of 276 nm

Blank used: Phosphate buffer, pH 7.5

Table 4-24 Absorbance of pure Diclofenac Sodium in Phosphate buffer pH 7.5

Concentration (%w/v)	Absorbance
0.00250	0.760
0.00150	0.438
0.00125	0.356
0.00100	0.274
0.00075	0.165

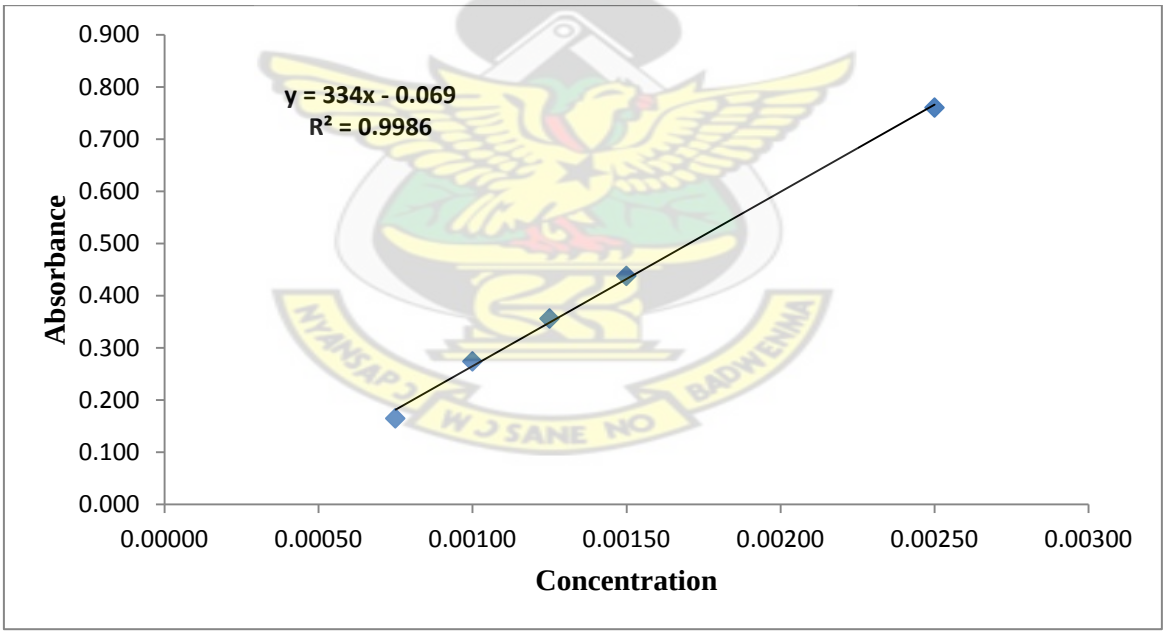

Figure 4-20 Calibration curve for diclofenac sodium in phosphate buffer pH 7.5

Calculation of percentage release

Dose of diclofenac sodium = 100 mg

Volume of dissolution medium = 900 ml

Concentration of solution if all 100 mg of drug dissolves =

4.19 DRUG RELEASE PROFILES

Table 4-25 Drug release profile of tablets in Batch 1

Time/hr.	Mean Absorbance	Concentration (%w/v)	Percentage Release
0.083	0.172	0.00649	6.49 ± 0.055
0.25	0.121	0.00512	5.19 ± 0.005
0.5	0.187	0.00703	7.03 ± 0.003
1	0.209	0.00770	7.70 ± 0.010
2	0.392	0.01269	12.69 ± 0.003
4	0.651	0.01983	19.83 ± 0.007
6	0.861	0.02574	25.74 ± 0.035
8	1.109	0.03266	32.66 ± 0.056
10	1.274	0.03745	37.45 ± 0.062
12	1.372	0.04051	40.51 ± 0.034
15	1.358	0.04061	40.61 ± 0.030
18	1.368	0.04124	41.24 ± 0.034
21	1.350	0.04122	41.22 ± 0.027
24	1.322	0.40890	40.89 ± 0.030

Table 4-26 Drug release profile of tablets in Batch 2

Time/hr	Mean Absorbance	Concentration (%w/v)	Percentage Release
0.083	0.008	0.00207	2.07 ± 0.003
0.25	0.000	0.00188	1.88 ± 0.000
0.5	0.134	0.00551	5.50 ± 0.028
1	0.041	0.00307	3.06 ± 0.004
2	0.122	0.00529	5.29 ± 0.005
4	0.274	0.00943	9.43 ± 0.019
6	0.378	0.01230	12.30 ± 0.012
8	0.510	0.01603	16.03 ± 0.011
10	0.612	0.01900	19.00 ± 0.012
12	0.771	0.02331	23.31 ± 0.051
15	1.003	0.02986	29.86 ± 0.012
18	1.140	0.03398	33.98 ± 0.019
21	1.204	0.03604	36.04 ± 0.009
24	1.328	0.03976	39.76 ± 0.009

Table 4-27 Drug release profile of tablets in Batch 3

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.199	0.00722	7.22 ± 0.004
0.25	0.423	0.01338	13.38 ± 0.051
0.5	0.542	0.01673	16.73 ± 0.098
1	0.716	0.02156	21.56 ± 0.084
2	0.962	0.02843	28.43 ± 0.045
4	1.456	0.04209	42.09 ± 0.054
6	1.545	0.04492	44.92 ± 0.003
8	2.019	0.0582	58.20 ± 0.365
10	1.555	0.04633	46.33 ± 0.020
12	1.538	0.04631	46.31 ± 0.014
15	1.574	0.04776	47.76 ± 0.023
18	1.480	0.04573	45.73 ± 0.002
21	1.528	0.04745	47.45 ± 0.026
24	1.621	0.05043	50.43 ± 0.055

Table 4-28 Drug release profile of tablets in Batch 4

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.122	0.00515	5.15 ± 0.008
0.25	0.198	0.00726	7.26 ± 0.055
0.5	0.266	0.00917	9.17 ± 0.014
1	0.554	0.01704	17.04 ± 0.023
2	0.882	0.02602	26.02 ± 0.051
4	1.373	0.03957	39.57 ± 0.029
6	1.645	0.04734	47.34 ± 0.028
8	1.675	0.04863	48.63 ± 0.032
10	1.641	0.04828	48.28 ± 0.038
12	1.672	0.04959	49.59 ± 0.017
15	1.684	0.05041	50.41 ± 0.051
18	1.631	0.04953	49.53 ± 0.007
21	1.615	0.04964	49.64 ± 0.025
24	1.684	0.05195	51.95 ± 0.052

Table 4-29 Drug release profile of tablets in Batch 5

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.234	0.00816	8.16 ± 0.049
0.25	0.238	0.00836	8.36 ± 0.019
0.5	0.295	0.00998	9.98 ± 0.011
1	0.465	0.01469	14.69 ± 0.035
2	0.716	0.02165	21.65 ± 0.032
4	1.132	0.03309	33.09 ± 0.041
6	1.492	0.04315	43.15 ± 0.032
8	1.471	0.04302	43.02 ± 0.032
10	1.513	0.04458	44.58 ± 0.005
12	1.524	0.04535	45.35 ± 0.014
15	1.517	0.04562	45.62 ± 0.012
18	1.508	0.04590	45.90 ± 0.015
21	1.501	0.04617	46.17 ± 0.013
24	1.487	0.04624	46.24 ± 0.012

Table 4-30 Drug release profile of tablets in Batch 6

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.301	0.00997	9.97 ± 0.028
0.25	0.278	0.00946	9.46 ± 0.062
0.5	0.447	0.01411	14.11 ± 0.065
1	0.544	0.01687	16.87 ± 0.028
2	1.038	0.03035	30.35 ± 0.059
4	1.530	0.04398	43.98 ± 0.031
6	1.620	0.04686	46.86 ± 0.010
8	1.607	0.04707	47.07 ± 0.022
10	1.628	0.04807	48.07 ± 0.025
12	1.589	0.04758	47.58 ± 0.020
15	1.616	0.04878	48.78 ± 0.016
18	1.567	0.04798	47.98 ± 0.016
21	1.592	0.04917	49.17 ± 0.018
24	1.599	0.04977	49.77 ± 0.028

Table 4-31 Drug release profile of tablets in Batch 7

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.189	0.00695	6.95 ± 0.016
0.25	0.199	0.00728	7.28 ± 0.005
0.5	0.335	0.01106	11.06 ± 0.017
1	0.568	0.01748	17.48 ± 0.144
2	0.892	0.02637	26.37 ± 0.072
4	1.507	0.04326	43.26 ± 0.175
6	1.638	0.04723	47.23 ± 0.171
8	2.214	0.06324	63.24 ± 0.165
10	2.253	0.06502	65.02 ± 0.119
12	2.541	0.07342	73.42 ± 0.067
15	2.555	0.07460	74.60 ± 0.056
18	2.435	0.07219	72.19 ± 0.027
21	2.422	0.07254	72.54 ± 0.017
24	2.463	0.07439	74.39 ± 0.014

Table 4-32 Drug release profile of tablets in Batch 8

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.225	0.00792	7.92 ± 0.023
0.25	0.203	0.00742	7.42 ± 0.014
0.5	0.227	0.00815	8.15 ± 0.015
1	0.326	0.01086	10.86 ± 0.019
2	0.599	0.01838	18.38 ± 0.039
4	1.225	0.03548	35.48 ± 0.033
6	1.743	0.04977	49.77 ± 0.038
8	1.891	0.05527	55.27 ± 0.034
10	2.353	0.06836	68.36 ± 0.039
12	2.581	0.07519	75.19 ± 0.030
15	2.598	0.07648	76.48 ± 0.026
18	2.625	0.07798	77.98 ± 0.050
21	2.610	0.07818	78.18 ± 0.052
24	2.643	0.07998	79.98 ± 0.039

Table 4-33 Drug release profile of tablets in Batch 9

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.254	0.00870	8.70 ± 0.045
0.25	0.285	0.00960	9.60 ± 0.004
0.5	0.402	0.01290	12.90 ± 0.037
1	0.659	0.01994	19.94 ± 0.012
2	1.056	0.03086	30.86 ± 0.034
4	1.842	0.05240	52.40 ± 0.027
6	2.003	0.05727	57.27 ± 0.010
8	2.664	0.07569	75.69 ± 0.011
10	2.734	0.07841	78.41 ± 0.017
12	2.743	0.07955	79.55 ± 0.012
15	2.689	0.07889	78.89 ± 0.033
18	2.638	0.07832	78.32 ± 0.031
21	2.623	0.07873	78.73 ± 0.014
24	2.572	0.07824	78.24 ± 0.014

Table 4-34 Drug release profile of tablets in Batch 10

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.186	0.00687	6.87 ± 0.011
0.25	0.219	0.00784	7.84 ± 0.008
0.5	0.422	0.01336	13.36 ± 0.011
1	0.657	0.01991	19.91 ± 0.014
2	0.804	0.02403	24.03 ± 0.014
4	1.098	0.03219	32.19 ± 0.006
6	1.505	0.04354	43.54 ± 0.016
8	1.929	0.05561	55.61 ± 0.022
10	2.233	0.06431	64.31 ± 0.036
12	2.317	0.06720	67.20 ± 0.051
15	2.525	0.07351	73.51 ± 0.049
18	2.629	0.07729	77.29 ± 0.047
21	2.646	0.07840	78.40 ± 0.011
24	2.675	0.07991	79.91 ± 0.043

Table 4-35 Drug release profile of tablets in Batch 11

Time/hr.	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.293	0.00975	9.75 ± 0.036
0.25	0.694	0.02067	20.67 ± 0.007
0.5	0.995	0.02904	29.04 ± 0.009
1	1.250	0.03616	36.16 ± 0.006
2	1.382	0.04005	40.05 ± 0.003
4	1.694	0.04898	48.98 ± 0.001
6	1.893	0.05491	54.91 ± 0.002
8	1.995	0.05820	58.20 ± 0.001
10	2.229	0.06512	65.12 ± 0.006
12	2.239	0.06591	65.91 ± 0.006
15	2.425	0.07180	71.80 ± 0.005
18	2.442	0.07305	73.05 ± 0.007
21	2.481	0.07480	74.80 ± 0.018
24	2.505	0.07630	76.30 ± 0.010

Table 4-36 Drug release profile of tablets in Batch 12

Time/hr.	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.279	0.00930	9.30 ± 0.002
0.25	0.420	0.01310	13.10 ± 0.009
0.5	0.771	0.02284	22.84 ± 0.010
1	1.381	0.03959	39.59 ± 0.024
2	1.590	0.04562	45.62 ± 0.051
4	1.621	0.04692	46.92 ± 0.045
6	1.650	0.04823	48.23 ± 0.020
8	1.797	0.05274	52.74 ± 0.019
10	2.112	0.06180	61.80 ± 0.001
12	2.456	0.07165	71.65 ± 0.010
15	2.653	0.07771	77.71 ± 0.018
18	2.657	0.07872	78.72 ± 0.012
21	2.682	0.08014	80.14 ± 0.012
24	2.694	0.08136	81.36 ± 0.019

Table 4-37 Drug release profile of tablets in Batch 13

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.189	0.00695	6.95 ± 0.004
0.25	0.274	0.00928	9.28 ± 0.007
0.5	0.454	0.01428	14.28 ± 0.001
1	0.773	0.02304	23.04 ± 0.039
2	1.359	0.03909	39.09 ± 0.008
4	1.632	0.04682	46.82 ± 0.011
6	1.668	0.04831	48.31 ± 0.017
8	2.189	0.06283	62.83 ± 0.096
10	2.336	0.06751	67.51 ± 0.040
12	2.553	0.07413	74.13 ± 0.026
15	2.632	0.07702	77.02 ± 0.039
18	2.634	0.07783	77.83 ± 0.016
21	2.755	0.08184	81.84 ± 0.015
24	2.696	0.08118	81.18 ± 0.020

Table 4-38 Drug release profile of tablets in Batch 14

Time/hr.	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.158	0.00229	2.29 ± 0.009
0.25	0.268	0.00911	9.11 ± 0.012
0.5	0.381	0.01223	12.23 ± 0.005
1	0.708	0.02126	21.26 ± 0.029
2	0.892	0.02649	26.49 ± 0.028
4	1.195	0.03494	34.94 ± 0.032
6	1.225	0.03615	36.15 ± 0.061
8	1.346	0.03974	39.74 ± 0.012
10	1.851	0.05376	53.76 ± 0.066
12	1.982	0.05793	57.93 ± 0.031
15	2.154	0.06314	63.14 ± 0.032
18	2.371	0.06961	69.61 ± 0.028
21	2.463	0.07284	72.84 ± 0.033
24	2.482	0.07410	74.10 ± 0.002

Table 4-39 Drug release profile of tablets in Batch 15

Time/hr.	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.206	0.07400	7.40 ± 0.007
0.25	0.406	0.01290	12.90 ± 0.011
0.5	0.742	0.02212	22.12 ± 0.002
1	1.114	0.03236	32.36 ± 0.004
2	1.456	0.04191	41.91 ± 0.015
4	1.648	0.04757	47.57 ± 0.033
6	1.861	0.05378	53.78 ± 0.037
8	2.099	0.06076	60.76 ± 0.053
10	2.413	0.07291	72.91 ± 0.020
12	2.632	0.07659	76.59 ± 0.026
15	2.639	0.07760	77.60 ± 0.029
18	2.644	0.07841	78.41 ± 0.041
21	2.681	0.08022	80.22 ± 0.021
24	2.677	0.08104	81.04 ± 0.033

Table 4-40 Drug release profile of reference standard (Voltaren Retard tablets)

Time/hr.	Mean absorbance	Concentration (%w/v)	Percentage release
0.083	0.259	0.00882	8.82 ± 0.055
0.25	0.326	0.01070	10.70 ± 0.051
0.5	0.632	0.01912	19.12 ± 0.019
1	0.818	0.02433	24.33 ± 0.007
2	1.052	0.03090	30.90 ± 0.010
4	1.376	0.03994	39.94 ± 0.011
6	1.622	0.04706	47.06 ± 0.005
8	1.978	0.05717	57.17 ± 0.013
10	2.141	0.06218	62.18 ± 0.004
12	2.314	0.06744	67.44 ± 0.004
15	2.663	0.07755	77.55 ± 0.006
18	2.673	0.07867	78.67 ± 0.006
21	2.776	0.08229	82.29 ± 0.010
24	2.764	0.08274	82.74 ± 0.003

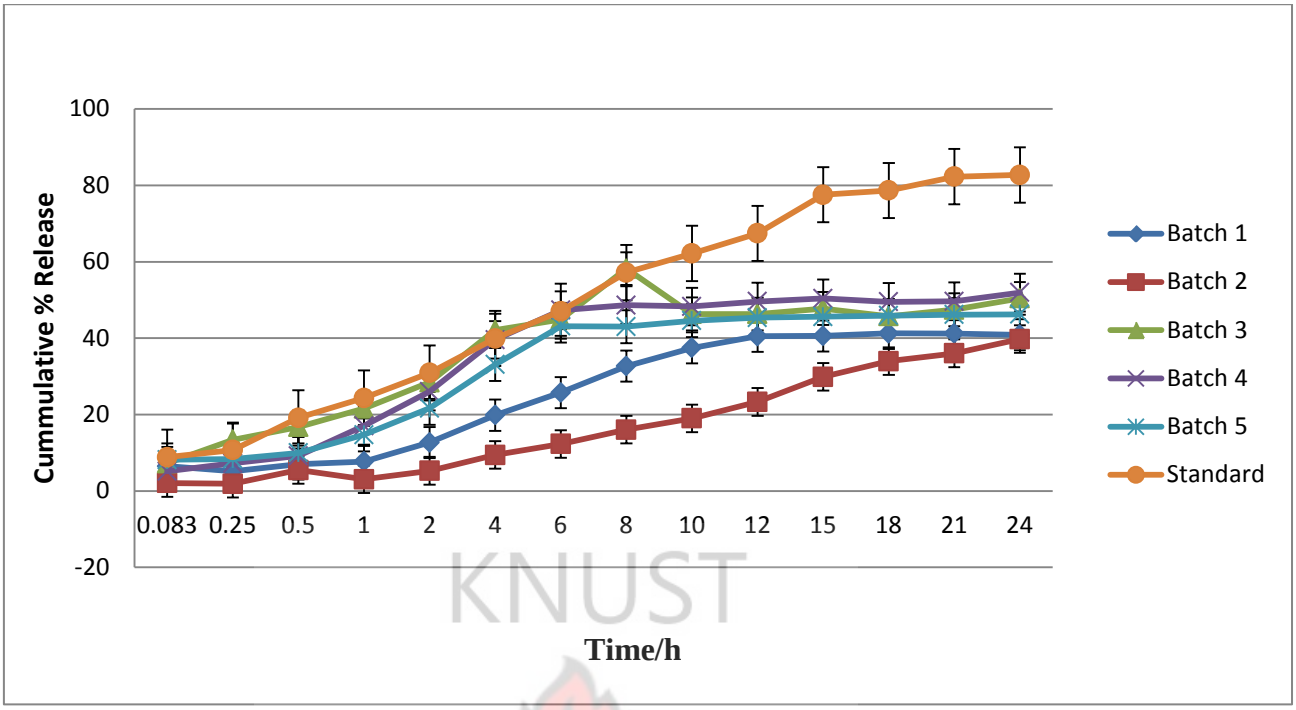

Figure 4-21 Dissolution profiles of tablets in batches 1 to 5

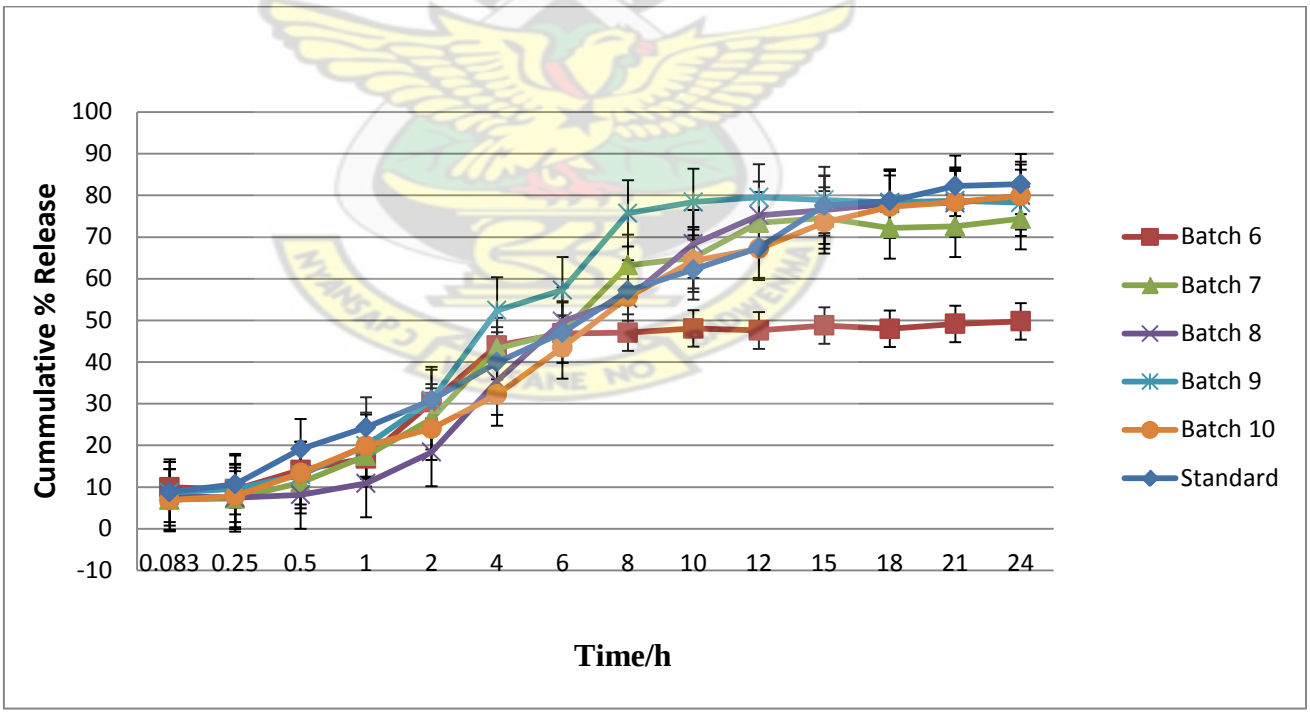

Figure 4-22 Dissolution profiles of tablets in batches 6 to10

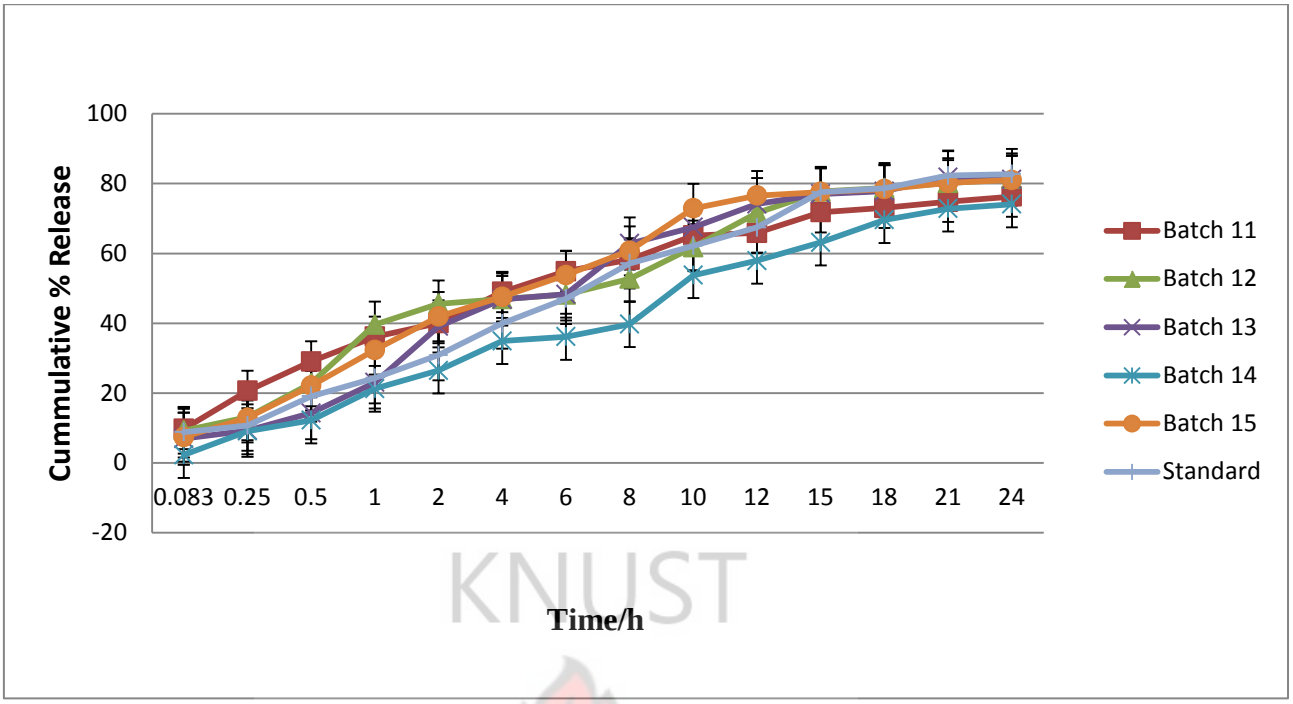

Figure 4-23 Dissolution profiles of tablets in batches 11 to15

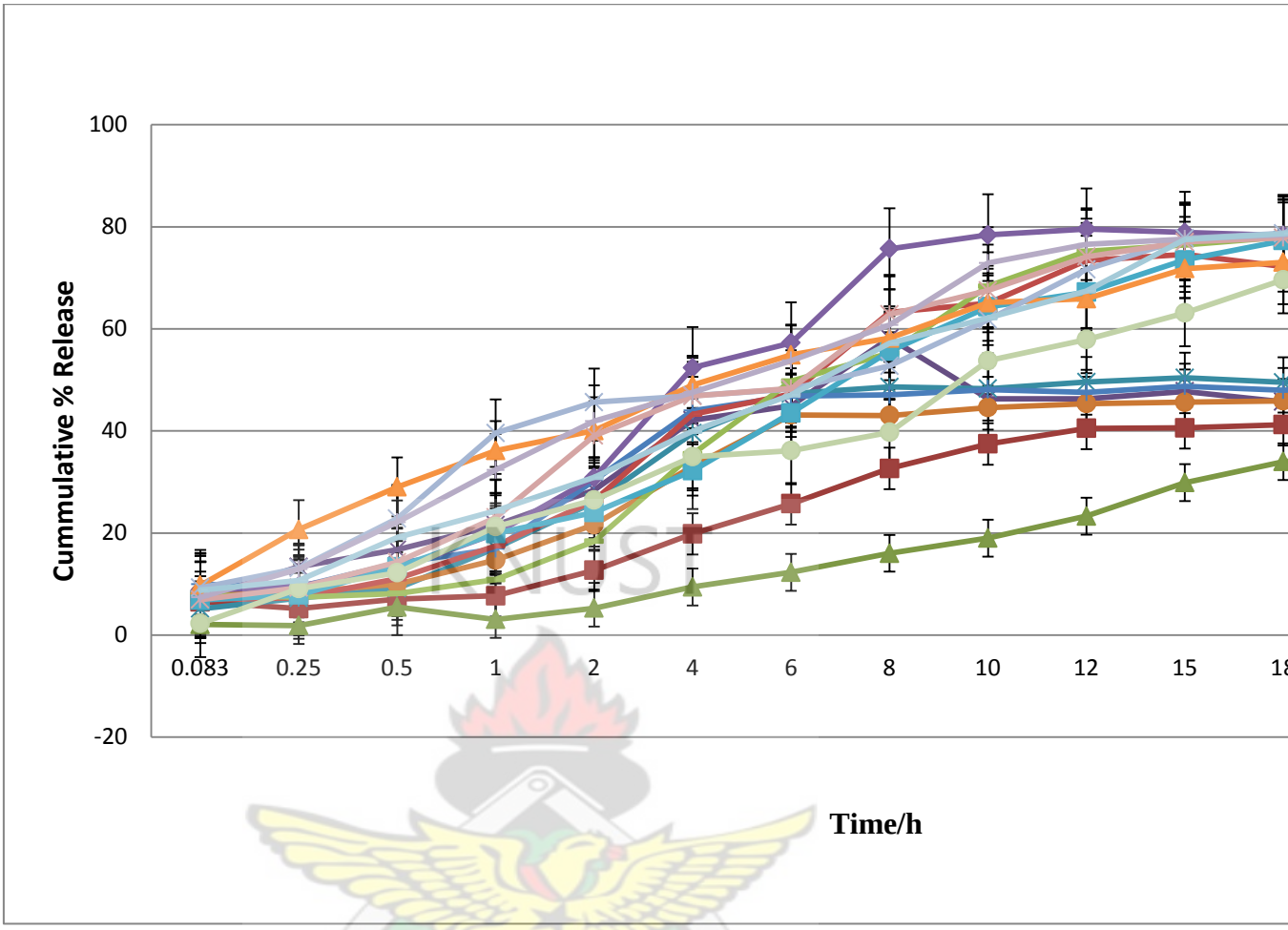

Figure 4-24 Dissolution profiles of all batches of tablets compressed

4.20 DIFFERENCE AND SIMILARITY FACTORS OF THE DICLOFENAC SODIUM MATRIX TABLETS

$f_1 = \{[\Sigma\, t_{=1}^{n} |Rt-Tt|] / [\Sigma\, _{t=1}^{n} Rt]\} \times 100$……*eqn* 21

$f_2 = 50 + \log \{[1+ (1/n) \sum_{t=1} * n (R_t-T_t)^2]^{-0.5} * 100\}$……..*eqn* 22

The cumulative percent release of the diclofenac sodium matrix tablets and the reference drug (Voltaren Retard) were fitted into the equations above to calculate the difference and similarity factors respectively.

4.20.1 Difference factor

Table 4-41 Difference factors of the diclofenac sodium matrix tablets

BATCH	DIFFERENCE FACTOR(f_1)
1	48
2	66
3	27
4	28
5	34
6	27
7	10
8	11
9	13
10	7
11	13
12	8
13	7
14	17
15	10

4.20.2 Similarity factor

Table 4-42 Similarity factors of the diclofenac sodium matrix tablets

BATCH	SIMILARITY FACTOR (f_2)
1	29
2	23
3	36
4	38
5	34
6	37
7	62
8	59
9	52
10	69
11	57
12	60
13	68
14	52
15	60

4.21 MECHANISM AND RELEASE KINETICS OF THE DICLOFENAC SODIUM MATRIX TABLETS

Table 4-43 Mechanism and release kinetics of the diclofenac sodium matrix tablets produced

	Zero Order		First Order		Higuchi		Hixson-Crowell	
Batch No	**K_o**	**R^2**	**K_1**	**R^2**	**K_H**	**R^2**	**K_{HC}**	**R^2**
1	0.0278	0.8107	0.0006	0.7088	1.2050	0.9325	0.0012	0.748
2	0.0273	0.9880	0.0009	0.8257	1.0842	0.9563	0.0015	0.909
3	0.0237	0.5265	0.0004	0.4700	1.1279	0.7310	0.0009	0.498
4	0.0298	0.6313	0.0005	0.5209	1.3794	0.8308	0.0011	0.562
5	0.0268	0.6664	0.0005	0.5854	1.2228	0.8542	0.0010	0.615
6	0.0257	0.5913	0.0004	0.5221	1.2023	0.7952	0.0009	0.547
7	0.0493	0.7735	0.0006	0.6305	2.1720	0.9231	0.0015	0.687
8	0.0568	0.8392	0.0007	0.7080	2.4360	0.9493	0.0017	0.757
9	0.0507	0.6997	0.0006	0.5969	2.2861	0.8753	0.0015	0.637
10	0.0535	0.8816	0.0006	0.7068	2.2722	0.9750	0.0016	0.779
11	0.0391	0.7951	0.0004	0.5752	1.7170	0.9404	0.0010	0.659
12	0.0465	0.8247	0.0005	0.5978	1.9622	0.9373	0.0012	0.682
13	0.0513	0.8119	0.0006	0.6147	2.2378	0.9497	0.0015	0.689
14	0.0479	0.9147	0.0007	0.5975	2.0062	0.9873	0.0015	0.741
15	0.0475	0.7863	0.0005	0.5748	2.0901	0.9363	0.0013	0.657

Chapter 5

DISCUSSION

5.1 YIELD FROM THE EXTRACTION PROCESS

The percentage yield obtained from the extraction process and subsequent purification of cashew gum was 72.26 %. From the results, it can be said that the method of extraction and subsequent purification of the cashew gum was a very viable process because a lot of the crude cashew gum was recovered after purification. Also the purification process can be said to have been successful. Crude gums are generally known to contain among other things pigments, dirt and debris, scraps of bark e.t.c. These constituents were removed during purification thus the gum can be used industrially

5.2 MACROSCOPIC PROPERTIES OF CASHEW GUM

Table 4.1 shows the macroscopic properties of cashew gum. The colour of the cashew gum ranged from glassy white to golden yellow. The colour of the gum is normally dependent on how long it has remained on the bark of the tree. Gums stuck to tree barks for long have a lot of tannins which tend to influence their colour (Smith and Montogomery, 1959). The odour of the gum was somewhat characteristic but not that strong, but its use in formulation did not affect the odour of the formulation. The taste of the gum is bland or tasteless and makes it suitable for pharmaceutical use.

5.3 MOISTURE CONTENT AND INSOLUBLE MATTER OF CASHEW GUM

Table 4.2 showed that the amount of moisture found in the purified and crude gum was 11.14 % and 13.84 % respectively. The difference between the moisture content of the purified and crude gums can be attributed to the purification and drying process of the crude gum. The moisture content calculated, complied with the required standard set in the British Pharmacopoeia (2009) as 15 % w/w. The moisture content affects the storage conditions, microbiological stability, viscosity and the flow properties of powders (Ejikeme, 2008).

Fig 4.2 shows that the purified form of the gum had a relatively low insoluble matter compared to the crude form. The purification process and the method employed certainly

removed most of the impurities in the crude gum. The gum was dissolved, filtered and re-precipitated so the purified gum will have less impurity as compared to the crude gum. Crude cashew gum had 0.45 %w/w of insoluble matter present. Though this value falls within the British Pharmacopoeia limit (0.5 % w/w) and United States Pharmacopoeia limit (0.5 % w/w), comparing it to that of the purified gum which was 0.26 % w/w, the percentage of insoluble matter in the crude was high. This implies that, improving upon the process of harvesting and cleaning of the gums would result in decreased levels of impurity and contamination.

5.4 RHEOLOGY OF XANTHAN AND CASHEW GUM MUCILAGES

From the results shown in Tables 4.3 and 4.4 and Figures 4.3 and 4.4, the viscosities of gum mucilage changed with concentration. At all concentrations used, the viscosity of xanthan gum was higher than that of cashew gum. It also showed that as the concentration of the gums increased, the viscosity also increased steadily. This was consistent with the observations made by (Mothé and Correia, 2003). The viscosity of gums is also affected by the nature and treatment of the gum such as purification and age at which the gum was picked (Smith and Montogomery, 1959).

Figures 4.5 to 4.11 show the flow curves of the xanthan and cashew gum mucilages. Both gums showed a pseudoplastic flow (Shalviri et al., 2010). This indicates a shear thinning property where viscosity decreases as the rate of flow increases. This was similar to what was stated by Merrill (1956).

5.5 SWELLING CAPACITIES OF GUMS IN DIFFERENT MEDIA

The swelling capacities of the gums are shown in Figure 4.12 and it shows a higher swelling index for xanthan gum than cashew gum in both distilled water and phosphate buffer pH 7.5. Also, it was observed that for both gums, the swelling index recorded for phosphate buffer pH 7.5 was higher than in distilled water. It can be said that the presence of ions in a medium can cause the swelling of xanthan gum (Andreopoulos and Tarantili, 2001). Therefore it can be expected that xanthan gum will show good swelling properties when a phosphate buffer pH 7.5 is used as a dissolution medium for the release of the drug.

5.6 FLOW PROPERTIES OF THE GUMS

Table 4.12 shows the results of bulk density measurements determined on the xanthan and cashew gums. It can be observed that the gums showed good flow properties characterized by the values obtained for angle of repose, Carr's index and Hausner's ratio. Hausner's ratio of 1.12 and 1.07 were obtained for xanthan and cashew gums respectively. Carr's index of 10.71% and 6.35% were also obtained for xanthan and cashew gums respectively. These values represented good flow properties for the gums (Talukdar et al., 1996). An angle of repose of 14.58 º obtained for xanthan gum and 24.67 º for cashew gum indicates good flowability (Talukdar et al, 1996). The good flow properties achieved may be due to the low moisture content of the gums. Also the shape of the particles may have played a role. Thus, most of the gum patrticles might be spherical in shape so were able to go through the sieves used for the determination of paticle size.

5.7 PARTICLE SIZE ANALYSIS OF THE GUMS

From Tables 4.13 and 4.14 and Figures 4.13 and 4.14, it was realized that most of the particles of xanthan gum fell in the range of 75 – 180 µm (77.52 %) and that of cashew gum fall in the range of 250 – 425 µm (64.62 %). This showed that the xanthan and cashew gums used for the experiment were very fine powder. The particle size range obtained for the xanthan gum conformed to official values (Vanzan, 2010). Also the particle size range of the cashew gum conformed to literature values (Da Silveira Nogueira Lima et al., 2002; McGovern, 2001)

5.8 FLOW PROPERTIES OF THE GRANULES PREPARED

The Hausner's ratio and the Carr's index or percent compressibility, which are measures of interparticle friction and the potential powder arch or bridge strength and stability, respectively, have been widely used to estimate the flow properties of powders and extrapolated to that of granules. According to Aulton (2002), a Hausner's ratio value of less than 1.25 is indicative of good flowability of the material, whereas a value of 1.25 or higher suggests a poor flow display by the material. According to Carr (1965), a Carr's index between 5 and 15, 12 and 16, 18 and 21, and 23 and 28 indicates excellent, good, fair, and poor flow properties of the material, respectively.

Table 4.15 shows the results of the bulk density measurements of the different batches of granules prepared for compression. From the results, the value for Hausner's ratio ranged from 1.05 to 1.12 indicative of a good flow of the granules. The Carr's index obtained ranged from 5.1% to 10.7% which indicates an excellent flow of the granules. The angles of repose obtained also ranged between 25.9 º and 34.86 º. This shows that the granules had a good flow because it falls within the range, 20 – 35 stated in Aulton (2002). Magnesium stearate and talc were added to the granules to serve as glidant and lubricant respectively.

5.9 QUALITY CONTROL TESTS ON DICLOFENAC SODIUM MATRIX TABLETS COMPRESSED

The uniformity of weight test carried out on tablets prepared with different concentrations of the gums showed that all the formulated tablets had uniform weight. This is indicative of the good flow properties of the granules. The uniformity of weight test gives an indication of how the weights of the individual tablets are scattered about the average weight. By British Pharmacopoeia standards for uncoated tablets, the permitted percentage deviation for a tablet of weight greater than 250 mg is 5 % and not more than two of the individual tablets should deviate from the average weight by more than the permitted percentage deviation and none should deviate by twice the permitted deviation. From Table 4.16, none of the batches of tables failed the uniformity of weight test. The average weight of the tablet produced ranged from 0.408 g ± 0.009 to 0.441 g ± 0.012. The tablets produced had an average thickness ranging from 5.70 mm ± 0.400 to 7.10 mm ± 0.374 as shown in Table 4.20. The results could be due to the good flow properties exhibited by the granules prepared and the uniform compression force used in tablet compression.

All the batches of tablets compressed passed the crushing strength test, with the exception of those in batch 3 which contained only HPMC. From Table 4.17 and Figure 4.15, the force required to crush the tablets ranged from 3.8 kg ± 0.75 to 6.8 kg ± 1.6. The United States Pharmacopoiea stipulates that at least 4 kg of force is required to crush a tablet. The tablets in batch 3 contained only hydroxypropyl methylcellulose (HPMC) as drug release modifier. Under normal circumstances, pressure variation on the tableting machine leads to difference in hardness, but in this case, all parameters were set equally on the compression

machine due to the comparative nature of this study, so it can be inferred that the nature and concentration of the gum used in tablet preparation affected the hardness of the tablets.

Table 4.18 and Figure 4.16 showed the friability of the different batches of tablets. The maximum permitted loss in weight of a batch of tablets subjected to friability testing is 1 % (British Pharmacopoeia, 2009). This parameter assesses the ability of the tablet to withstand stress and abrasion associated with handling, packaging and transportation and chipping. This property of the tablet is affected by the nature and amount of binder used. Binders impart the cohesive nature to the particles in the tablets.

From the results obtained, all the batches of tablets passed the friability test except those in batch 4 and batch 10 which had percentage friability of 1.101 % and 1.292 % respectively. Tablets in batch 7 were the least friable compared to the other batches. The tablets in batch 4 contained HPMC and cashew gum in a ratio of 80:20 and those in batch 10 contained xanthan and cashew gums in the ratio 80:20. The least friable tablets contained xanthan gum and HPMC in the ratio 80:20. A specific trend was not observed to relate the concentration of gum to the friability of the tablets so the failure of the tablets to pass the test may be due to the force of compression.

The crushing strength and friability ratio was used as an assessment of the mechanical strength of the tablets. While crushing strength indicates the strength of the tablet, friability values provide a measure of tablet weakness. The crushing strength-friability ratio (CSFR) also provides a parameter for measuring tablet strength (Odeku and Itiola, 2003). Generally, the higher the CSFR value the stronger the tablet (Itiola et al., 2006). Table 4.19 and Figure 4.17 show the results of CSFR which ranged from 3.2 to 42.8. The highest CSFR value was achieved with batch 2 which contained only xanthan gum as binder. It can therefore be said that higher concentration of the gums, especially xanthan gum can yield very strong tablets.

In the assay of the batches of diclofenac sodium matrix tablets compressed, uv-spectroscopy was used. The United States Pharmacopoeia (2002), states that diclofenac sodium delayed-release tablets should contain not less than 90.0 percent and not more than 110.0 percent of the labelled amount of diclofenac sodium. Table 4.22 showed that the content of diclofenac in the batches fell in the range of 98.7 ± 0.510 to 101.5 ± 0.408

meaning they all fell in the normal range. This shows that all the batches of diclofenac tablets produced contained the required amount of active ingredient needed to ellicit the needed therapeutic effect.

5.10 SWELLING INDEX OF THE TABLETS

The release of drugs from matrix formulations has been linked to the nature of matrix material, as well as complex processes such as swelling, diffusion and erosion (Oyi et al., 2010). Table 4.21 shows the percentage of water absorbed by the matrix tablets produced. It was observed from Figure 4.18 that most of the tablets swelled within the first two hours and erosion began to take place. However, batches 2,7,10 and 11 showed good swelling behaviour even up to 18h with batch 2 showing the greatest water absorption. Other batches also achieved very good swelling indices, e.g. batches 8, 12, 13 and 15. It was observed that most of the batches that had very good water absorption contained a high concentration of xanthan gum. This also proved the assertion that xanthan gum achieves good swelling in phosphate buffer pH 7.5 due to the ions present (Andreopoulos and Tarantili, 2001). It can also be said that the mechanism of release may be due to swelling and subsequent erosion of the matrix to release the active drug.

5.11 DISSOLUTION PROFILE OF THE DICLOFENAC TABLETS

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. The basic step in drug dissolution is the reaction of the solid drug with the fluid and/or the components of the dissolution medium. This reaction takes place at the solid – liquid interface and therefore dissolution kinetics are dependent on three factors, namely the flow rate of the dissolution medium toward the solid – liquid interface, the reaction rate at the interface, and the molecular diffusion of the dissolved drug molecules from the interface toward the bulk solution (Singhvi and Singh, 2011).

From the calibration curve, Figure 4.19, it was observed that the R^2 value was 0.9986 which was indicative of good linearity of the calibration curve and made the subsequent determinations from the calibration curve valid.

According to the US Food and Drugs Administration (Guidance for Industry SUPAC-MR: Modified – Release Solid Oral Dosage Forms Scale-Up and Post Approval Changes: Chemistry, 1997), at least there should be 80 % dissolution within the test period. It also states that there should be about 20 – 30 % release within the first two hours and about 50% release after eight hours. After twenty-four hours about 80 % of the drug should be released. Tables 4.24 – 4.38 and Figures 4.21 – 4.24 show the results of the dissolution test conducted. From the parameters used in the assessment, tablets from batches 1 to 6 were not able to cause sustained release of the drug and thus failed the dissolution test. Tablets in batches 7 to 15 showed good sustained release activity and thus passed the test for dissolution.

The failure of batches 1 to 6 may be due to the very high concentration of the polymers which may have restricted the release of the diclofenac sodium. But as the concentrations were reduced a good and desirable sustained effect was achieved. These batches of tablets that passed the dissolution test achieved a release similar to that shown by the reference drug, Voltaren Retard, whose results have been shown in Table 4.39. The tablets were compressed from granules that had good flow property and also contained an optimum amount of the gum combination thus made the tablets pass the dissolution test. This demonstrates that combination of xanthan and cashew gums may show synergism in controlling diclofenac sodium release. Combination of xanthan and cashew gums with HPMC led to even greater sustained release action of the drug.

5.12 DIFFERENCE AND SIMILARITY FACTORS

The difference factor (f_1) is proportional to the average difference between two dissolution profiles, whereas similarity factor (f_2) is inversely proportional to the average squared difference between two profiles, with emphasis on the larger difference among all the time-points. The similarity factor (f_2) measures the closeness between the two profiles. The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves. This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available (Suvakanta et al., 2010). Conventionally, a test batch is considered similar to that of a reference batch if the f_2 value

of the two profiles is between 50 and 100. Also, a difference factor between 0 and 15 ensures minor difference between two products (Mukesh et al., 2005).

The results obtained for difference and similarity factors are shown in Table 4.40 and Table 4.41. Batches 7 to 15 fell within the specified range for similarity (52 – 68) while batches 1 to 6 fell out of the required range (23 – 38). For the diference factor, batches 7 to 13 and 15 fell within the acceptable range (7 – 13) and thus show minor difference in terms of release of active ingredient with the reference drug. The difference factors for batches 1 to 6 and 14 however fell out of the required range and thus the release profiles are different from that of the reference drug. The dissolution of the test and the reference samples were subjected to the same conditions hence adequate comparison can be made. The lower acceptable f_2 value obtained in a test (f_2 = 50) corresponds to 10% average absolute difference between a reference product and a test product at each time point (Mukesh et al., 2005).

From the f_1 and f_2 studies conducted, batches 7 - 15 tablets produced had acceptable similarity and minor with Voltaren Retard and could possibly be used interchangeably.

5.13 DRUG RELEASE KINETICS AND MECHANISM OF RELEASE

Ideal delivery of drugs would follow "zero-order kinetics", wherein blood levels of drugs would remain constant throughout the delivery period. This ideal delivery is particularly important in certain classes of medicines intended, for example, for antibiotic delivery, heart and blood pressure maintenance, pain control and antidepressants. Consequently, there has been substantial activity by scientists searching for improved methods of achieving both controlled and sustained delivery of drugs (Landgraf et al., 2003). The use of mathematical modeling turns out to be very useful as this approach enables, in the best case, the prediction of release kinetics before the release systems are realized. More often, it allows the measurement of some important physical parameters, such as the drug diffusion coefficient and resorting to model fitting on experimental release data (Suvakanta et al., 2010).

The kinetic models used in the assessment of the dissolution data in this study were the Zero order, First order, Higuchi and Hixson-Crowell models while Korsmeyer-Peppas model was used to determine the mechanism of drug release. The results of these

determinations are summarized in Table 4.42. The dissolution data of the various batches of tablets were fitted into the various kinetic models and their regression values used to assess the best fit. The higher the R^2 value (i.e. the more linear the graph), the better the fit of the dissolution profile to that kinetic model. From the results obtained from the study, higher R^2 values were obtained for the Higuchi model than the other kinetic models. This happened especially in the batches that passed the dissolution test (i.e. batches 7 to 15). Higuchi describes drug release as a diffusion process based on the Fick's law, square root time dependent (Kalam et al., 2007). This model can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs (Suvakanta et al., 2010).

The dissolution data was fitted into the Korsmeyer-Peppas model to determine the exact mechanism of drug release. This model is generally used to analyze the release of polymeric dosage form, where the release mechanism is not well known or when more than one type of release phenomenon could be involved (Kalam et al., 2007).

The graphs of log cumulative percent release against log time was plotted and the release rate constant, k, and the release exponent, n, determined. The results showed that most of the 'n' values fell between 0.45 and 0.89. From literature, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport (Suvakanta et al., 2010). Therefore it can be inferred that the drug may have followed anomalous or non-Fickian diffusion. This means drug release is a complex mechanism involving swelling of the matrix tablets and subsequent erosion. Hydrophilic matrix tablets swell upon ingestion, and a gel layer forms on the tablet surface. This gel layer retards further ingress of fluid and subsequent drug release. It has been shown that in the case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug-release rate (Gohel et al., 2000).

Chapter 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

- Cashew gum can be purified to achieve a good yield
- Both cashew and xanthan gums showed pseudoplastic flow
- All the batches of tablets passed the uniformity of weight test and drug content test
- All the batches of tablets but batch 3 passed the crushing strength test
- All the batches of tablets but batches 4 and 10 passed the friability test.
- Tablets containing only xanthan gum as release modifier achieved the highest crushing strength friability ratio (CSFR) with those in batch 10 having the lowest.
- Tablets in batch 2 had the highest swelling index and those in batch 3 had the lowest swelling index.
- The study has shown that cashew and xanthan gums used alone cannot efficiently control drug release.
- Batches 7 and 8 containing xanthan gum and HPMC was able to cause sustained drug release comparable to Voltaren Retard
- The formulation containing xanthan and cashew gums in batches 10, 11, 12 showed good sustained release properties similar to the reference sample.
- Batches 13 and 15 which contained all three combinations were also able to provide sustained drug release similar to Voltaren Retard
- The release profile fit the Higuchi equation better than the rest thus drug may have been released through the Higuchi model of drug kinetics
- The release exponent 'n' determined was between 0.45 and 0.89 thus the drug is release through anomalous or non – Fickian diffusion.

6.2 RECOMMENDATIONS

- Fourier Transform–Infra Red (FT-IR) spectroscopy can be employed to evaluate the compatibility of the drug and the polymers used.
- In – vivo studies should be performed to ascertain the effectiveness of the formulations

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APPENDIX

PREPARATION OF TEST SOLUTIONS

1. 0.1M HCl solution - 0.89 ml of Conc. HCl (36% purity, 1.18 g/ml) was measured into a 100 ml volumetric already containing some amount of distilled water, the measuring cylinder was rinsed qualitatively and quantitatively into the volumetric flask. The solution was made up to volume to produce 100 ml**.** (Higher volumes were prepared using the same ratios)

2. 0.1M NaOH: 4.01 g of sodium hydroxide pellets were weighed into a beaker which already contained an amount of water to dissolve the pellets. The solution obtained was tansferred into a 1000 ml volumetric flask and water used to make up to volume. (Higher volumes were prepared using the same ratios)

3. Preparation of Xanthan gum 0.5 %w/v mucilage – 0.5 g of xanthan gum was weighed into a clean mortar. About 100 ml of distilled water was measured and added to the gum gradually, whilst triturating, until the whole quantity of water was added and a uniform mucilage was formed.

   This method was used in the preparation of the xanthan and cashew gum mucilages for the rheological assessment and the preparation of the diclofenac sodium tablets.

4. Phosphate buffer (pH 7.4): 2.3156 g of sodium dihydrogen phosphate and 4.3582 g of disodium hydrogen phosphate were weighed into a beaker containing about 800 ml of distilled water. Distilled water was then added to make the volume up to 1000 ml. The pH of the buffer was adjusted using phosphoric acid and 0.1M NaOH solution. (Higher volumes were prepared using the same ratios)