DEVELOPMENT OF ACACIA GUM (*ACACIA SEYAL)* CROSSLINKS AS MATRIX IN SUSTAINED-RELEASE SALBUTAMOL SULPHATE TABLETFORMULATIONS

BY

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A DISSERTATION SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES, AHMADU BELLO UNIVERSITY, ZARIA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF SCIENCE IN PHARMACEUTICS

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DECLARATION

I declare that the work in this dissertation entitled "Development of Acacia Gum (*Acacia seyal*) Crosslinks as Matrix in Sustained-Release Salbutamol Sulphate Tablet Formulations"has been carried out by me in the Department of Pharmaceutics and Pharmaceutical Microbiology under the supervision of Prof. A.B. Isah and Dr. A.K. Olowosulu. The information derived from the literature has been duly acknowledged in the text and list of references provided. No part of this dissertation was previously presented for another degree or diploma at this or any other institution.

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CERTIFICATION

This dissertation entitled DEVELOPMENT OF ACACIA GUM (*ACACIA SEYAL*) CROSSLINKS AS MATRIX IN SUSTAINED-RELEASE SALBUTAMOL SULPHATE TABLET FORMULATIONSby Akila BwalaJAMES meets the regulations governing the award of the degree of M.Sc. Pharmaceutics of the Ahmadu Bello University, and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

This work is dedicated to the Glory of the Almighty God.

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ABSTRACT

This study evaluated the potential of cross-linked *Acacia seyal* gumas matrix in sustained-release salbutamol sulphate tablet formulations prepared by direct compression method.Cross-linking which involves re-enforcing bonds with chemical bridges between molecules or polymer chains is expected to reduce the solubility of hydrophilic polymers, making them more reliable as sustained release matrix formers. The crude *Acacia seyal* gum was purified and labeled as "EG", thencross-linked with freshly prepared 1.0 M calcium chloridesolution to obtain "CG".The cross-linking was confirmed by the percentage yield, differential scanning calorimetry (DSC) and Fourier transform infra-red (FT-IR) spectrophotometry. The colour, texture, taste and odour were used to describe the organoleptic characters of the polymers, while determination of the moisture loss on drying, solubility, viscosity, swelling ratio, swelling rate, hydration capacity, pH,moisture sorption profile, particle size distribution, bulk density, tapped density, true density, flow rate, angle of repose, compressibility index and Hausner's ratiowere used to characterize the physicochemical and flow properties of the polymers.Directly compressed tablets were formulated, with a constant quantity of salbutamol sulphate (8 mg), while the matrix material varied between 30, 40 and 50 percent (%), resulting in formulations T1, T2 and T3 containing EG; T4, T5 and T6 containingCGand; T7, T8 and T9containinghydroxypropyl methylcellulose (HPMC) respectively. The tablets were then evaluated for various tableting properties, which include weight, diameter, thickness, friability, crushing strength, tensile strength, disintegration time,drug content and dissolution.

The results showed DSC thermogramand FT-IR spectrum of CG with theappearance of new peak and new bands respectively. CG was light brown, gritty, bland and odourless. CG with low moisture content,reduced solubility in water,lower viscosity, higher swelling ratio and rate, low

hydration capacity and higher pHwas able to sorp water and swell. The lower coarse particles,bulk density, tapped density, true density,flow rate, and angle of repose,compressibility indexand Hausner's ratio demonstratedgood flowability of CG. The formulated tabletshad weight, diameter, thickness, friability, crushing strength, tensile strength, disintegration time anddrug content within acceptable B.P. standards forsustained-release dosageform tablets with weight between 131 – 325 mg. Drug releasewas studied in a solution of 0.1N HCl, pH 1.0, for 2 hthen the medium changed to a buffer solution, pH 6.8, for 6 h. Cumulative percent drug releaseshowed that T_{50} waslonger for the CG matrices compared with the EG and HPMC matrices. Formulation T4 (30 % CG proportion) showedT_{50}value of 2.44 h and release of 78.78 % at the 8^{th} h, the closest release to the expected theoretical release of 66.66 %. Based on these and the statistical analysis, T4 that sustained the release of salbutamol sulphate for about 12 h was selected as the optimum formulation in this study.It is thus safe to conclude that cross-linking*Acacia seyal* gum with calcium chloride imparted sustained release properties to salbutamol sulphate tablets produced by direct compression method.

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ACRONYMS AND ABBREVIATIONS

B.P:	British Pharmacopoeia
CG:	Cross-linked *Acaciaseyal* gum
EG:	Extracted *Acaciaseyal* gum
F:	Force
Fig:	Figure
g:	Gram
h/hr:	Hour
HCl:	Hydrochloric acid
Kg:	Kilogram
Km:	Kilometer
L:	Liter
M:	Molar
ml:	Milliliter
mg:	Milligram
min:	Minutes
mm:	Millimeter
N:	Newtons
s:	Seconds
SD:	Standard Deviation
SEM:	Standard error of the mean
Sq:	Square
U.S.P:	United States Pharmacopoeia

Vol.:	Volume
%:	Percent/Percentage
^{0}:	degrees
C:	Celsius
<:	less than
>:	greater than
±:	plus or minus

CHAPTER ONE

1.0 GENERAL INTRODUCTION

1.1 Preamble

Over the years, man has always relied on drugs and medicines to treat, ameliorate, diagnose or prevent diseases and to maintain a good health. Tablets are the unit solid dosage forms meant for oral use and are manufactured by using tablet compression machines, by compressing the active pharmaceutical ingredient with other excipients (could be inert or not but majorly to help in giving the formulation some desired characteristics that enables its handling or renders some kind of function)(Nagashree, 2015). An excipient is a natural or synthetic substance formulated alongside the active ingredient of a medication, included for the purpose of bulking-up formulations that contain potent active ingredients (thus often referred to as “bulking agents”, “fillers” or “diluents”) or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption or solubility (Narang *et al*., 2017).

Research and development laboratories are presently finding it difficult to come forth with new drug molecules and even some of the ones existing already are having difficulties in achieving their full profile. There is therefore a need for change in operation to a more optimized way of making drugs more effective by slight modification in their delivery process and one of the ways by which this can be achieved is to sustain the release of the drug. Excipient research and development is an area in pharmaceutics that has gained popularity, especially with the renewed desire to shift from the conventional dosage forms to the modified release dosage forms, which impart some characteristics to the release profile of the active drug. Drug modification involves

altering the release profile, site of absorption or the rate of absorption of the drug in plasma in order to either reduce the frequency of drug administration, improve patient compliance and/or to reduce the side effects of the drug. Modified release dosage forms are dosage forms having drug release features based on time, course and/or location designed to achieve therapeutic objectives not offered by the conventional or immediate release dosage forms(Hong, 2016).

1.2 Excipients inTablet Formulation

Excipients are of various origins: animal (example, lactose, gelatin, and stearic acid), plant (example, starches, gums, sugars, cellulose, and alginates), mineral (example, calcium phosphate, silica) and synthetic (example, polyethylene glycols (PEG), polysorbates, povidone). Their origin and use do not often guarantee the quality required by the pharmaceutical industry, which must therefore submit them to more thorough-going analytical controls. In order to carry out the numerous functions required, new classes of excipients have now become available, derived from old and new materials, alone or in combination, adapted to the manufacture of high-performance pharmaceutical dosage forms. It is also to be borne in mind that the ratio of their weight to that of the active principles is usually very high in a formulation, and such as to cause possible action due to their mass (Shalini, 2012). Natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable and widely available (Goswami and Naik, 2014). They can also be modified in different ways to obtain tailor-made materials for drug delivery systems.

1.2.1 Diluents

Diluents are fillers used to increase the bulk volume of a tablet or capsule. By combining a diluent with the active pharmaceutical ingredients, the final product is given adequate weight and size to assist in production and handling.

To provide satisfactory performance in a tablet dosage form, a diluent should be:

i. Inert so as not to cause pharmacological activity of its own.
ii. Compatible with the drug substance and other excipients used in the formulation.
iii. Non-hygroscopic so the formulation does not absorb significant amounts of moisture from its surroundings.
iv. Compactable and of similar particle size to the active ingredient.

Diluents may serve multiple functions in addition to being filler. Multifunctional starch excipients, such as Starch Rx1500® partially pregelatinized maize starch and StarCap 1500® co-processed starch excipient can serve as binders, disintegrants, flow aids, lubricants and/or taste masking(Cunningham, 2018).

1.2.2 Binders

Binders are used in the formulation of solid oral dosage forms to hold the active pharmaceutical ingredient and inactive ingredients together in a cohesive mix. Binders hold the ingredients in a tablet together and ensure that tablets and granules can be formed with required mechanical strength and gives volume to low active dose tablets (Shalini, 2012).

Some binders include;

1. Saccharides and derivatives; Example, sucrose, lactose, starches, cellulose or modified cellulose such as microcrystalline cellulose, cellulose ether like hydroxypropyl cellulose (HPC), xylitol, sorbitol and manitol.
2. Proteins: example, gelatin.
3. Synthetic polymers: example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG).

Binders are classified according to their application;

a. Solution binders; they are dissolved in a solvent (example, water or alcohol) and can be used in wet granulation processes. Examples are gelatin, cellulose, cellulose derivatives, PVP, starch, sucrose and PEG.
b. Dry binders; they are added to the powder blend either after a wet granulation or as part of a direct powder compression (DC) formula. Examples are cellulose, methylcellulose, PVP and PEG.

1.2.3 Disintegrants

The efficacy of a drug mixture can be dependent on the rate at which the tablet or capsule disintegrates in the patient's gastrointestinal tract. For all solid oral dosages, disintegrants may be added to a drug formulation as functional fillers. Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption. Types of disintegrants include:

1. Water uptake facilitators
2. Tablet rupture promoters

The mechanism of disintegration of tablets show that disintegrants are very hydrophilic and on contact with water or other liquids, these spherical particles which are evenly distributed in the tablet swell, allowing a significant increase in volume, causing the tablet to disintegrate into smaller fragments which have greater surface area thereby, increasing the dissolution of the drug (Desai *et al*., 2016).

Examples of disintegrants include:

1. Cross-linked polymers: cross-linked polyvinylpyrrolidone (crospovidone), cross-linked sodium carboxymethyl cellulose (croscarmellose sodium).
2. The modified starch, sodium starch glycolate.
3. Conventional disintegrants such as starch

1.2.4 Lubricants

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule-filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Common minerals like talc or silica, and fats, example vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules. Lubricants are added in small quantities to tablet and capsule formulations to improve certain processing characteristics(Varma, 2016).

1.2.5 Coating agents

Tablet coatings protect tablet ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow. For most coated tablets, a cellulose ether, hydroxypropyl methylcellulose (HPMC) film coating is used which is free of sugar and potential allergens. Occasionally, other coating materials are used, for

example synthetic polymers, shellac, corn protein zein or other polysaccharides(Alamgir, 2018). Film coatings offer many advantages for all phases of pharmaceutical and nutritional solid oral dose development as well as benefits for the consumer. Some of these benefits include reducing operation costs, drug protection, modifying drug release, creating a strong recognizable brand, and ensuring product safety and effectiveness.

1.2.6 Glidants

Glidants are used to promote powder flow by reducinginterparticle friction and cohesion. They are used in combination with lubricants, as they have no ability to reduce die wall friction (Kanher *et al*., 2017). Examples include fumed silica, talc, and magnesium carbonate.

1.2.7 Antiadherents

They reduce the adhesion between the powder (granules) and the punch faces and thus prevents sticking to tablet punches by offering a non-stick surface (Kanher *et al*., 2017). Example is magnesium stearate.

1.2.8 Flavours

Flavours can be used to mask unpleasant tasting active ingredients and improve the likelihood that the patient will complete a course of medication. Flavourants may be natural (example, fruit extract) or artificial.

For example, to improve:

- a bitter product - mint, cherry or anise may be used
- a salty product - peach, apricot or liquorice may be used
- a sour product - raspberry or liquorice may be used
- an excessively sweet product - vanilla may be used (Alamgir, 2018)

1.2.9 Colours

Colours are added to improve the appearance of a formulation. Colour consistency is important as it allows easy identification of a medication. Example is titanium oxide.

1.2.10 Preservatives

A preservative is a substance that is added to products such as foods, pharmaceuticals, paints, biological samples, wood, etc., to prevent decomposition by microbial growth or by undesirable chemical changes. Some typical preservatives used in pharmaceutical formulations are

a. Antioxidants like vitamin A, vitamin E, vitamin C, retinyl palmitate.
b. The amino acids cysteine and methionine
c. Citric acid and sodium citrate
d. Synthetic preservatives like the parabens: methyl paraben and propyl paraben.

1.3 Modified Release Delivery Systems

Modified release delivery systems are defined by the USP as those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms(Hong, 2016). They may be classified into five categories:

1. Delayed Release: Here, the drug release is delayed after administration for some period of time to evade deleterious environmental conditions such as gastrointestinal pH.

2. Repeat action: This contains two or more doses of the drug, one for immediate release and subsequent doses for delayed release.

3. Receptor targeting: These systems of delivery refers to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue.

4. Site specific targeting: These systems refer to targeting of a drug directly to a certain biological location, the target being adjacent to or in the diseased organ or tissue.

5. Sustained release: Here, the system provides an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release of drug over an extended period of time. It can also provide some control of drug release in the body, whether this be of a temporal or spatial nature, or both. Or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

i) Controlled Release Systems**:** These systems include any drug delivery system that release drug at a constant rate and provide plasma concentrations that remain invariant with time.

ii) Extended Release Systems:These are pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate, and necessarily reduce the dosage frequency by two folds.

Interestingly, the USP considers that the terms controlled release, prolonged release and sustained release are interchangeable with extended release but from a biopharmaceutical point of view, this is not strictly a concern (Alderborn, 2007).

To achieve sustained release of drugs, two design systems; reservoir system and monolithic (matrix) systems can be utilized. In the reservoir system, the drug first partitions into the membrane from the reservoir and then diffuses to the other side of the membrane, where it is taken up by the receiving medium. As the reservoir becomes

saturated, a constant concentration gradient of the drug is sustained in the membrane, the rate of drug flux is constant, and zero order release is attained. Finally, the drug concentration in the reservoir drops below saturation, and the gradient across the membrane and release rate both deteriorate. Here, the purpose of the membrane is to mediate diffusion of the drug. Because of their simplicity of mechanism and their ability to produce zero order release, reservoir systems would appear to be greatly advantageous. However, reservoir systems can be challenging to fabricate reliably as minor defects and cracks in the membrane can lead to dose dumping. These problems however are avoided in matrix systems in which the drug is loaded directly into a polymer, which now acts as both a storage medium and a mediator of diffusion. The drug is typically loaded homogenously into the matrix device, and the drug release is controlled by its diffusion through the matrix material or through aqueous pores. Matrix devices typically exhibit an initial burst release from the surface but, as time passes, the release rate decreases because the drug that is deeper inside the matrix must first diffuse to the surface, and since it has to travel farther, the quadratic relation between distance and time becomes important. This effect which occurs in planar monoliths becomes even more prominent with cylinders or spheres, as the amount of drug available decreases with distance from the surface (Siegel and Rathbone, 2012).

1.4 Polymers Used as Matrix Formers in Sustained Release Delivery Studies

Hydrophilic and/or hydrophobic polymers have been used over the years to modify the release of drugs. Hydrophobic polymers such as ethylcellulose, polyethylene and polypropylene are insoluble matrices in which the drug becomes available as a solvent enters the matrix system and dissolves the drug particles. Penetration of fluid into the

hydrophobic matrix device must precede drug release from such a matrix, which is then followed by dissolution of the drug particles and diffusion through fluid-filled pores. Hydrophobic matrices have been found to release the drug by Higuchi model, which involves diffusion. This type of matrix system is however not suitable for insoluble or low aqueous solubility compounds. On the other hand, hydrophilic polymers such as methylcellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), amongst others are soluble, with the drug becoming available as the matrix dissolves or swells and dissolves. Drugs dispersed in this type of matrix rely on a slow dissolution of the matrix to provide sustained release. When a matrix of this sort is presented with a conventional tablet geometry, then on contact with dissolution media the surface area of the matrix decreases with time, with a concomitant decrease of drug release (Alderborn, 2013). Hydrophilic matrices have been shown to release the drug by case II transport or by a combination of case II transport and Fickian diffusion (Singhvi and Singh, 2011).

The above mentioned polymers which are mostly synthetic or semisynthetic are not the only polymers than can be used as matrix formers. Hydrophilic natural polymers which are obtained from plants abound in the natural habitat and have also been shown to be effective as release modifying matrices. Guar gum, acacia gum, locust bean gum, cashew gum, amongst others have been used both in their natural and derivatized forms to have excellent potentials as carrier materials in matrix type controlled release dosage forms (Krishnaiah *et al.,* 2002; Beneke *et al.*, 2009; Abdulsamad *et al.,* 2015). A combination of natural and semisynthetic polymers; *Khaya senegalensis* gum and sodium carboxymethylcellulose (SCMC) have also been used as release modifiers, which release

the drug via fickian diffusion and case II transport (Mahmud *et al.,* 2016). Ogaji *et al.* (2012) studied a combination of two natural gums (locust bean gum and chitosan) and concluded that this combination can be used to modify the release of mesalazine.

1.4.1 Acacia gum

Acacia gum also known as Arabic gum are dried exudates acquired from the stems and branches of natural species of *Acaciasenegal* (L) Willdenow or other closely related species of *Acaciaseyal*or *A. sieberiana* (Family *Leguminosae*), with over 300 species in this family (Al-Assaf *et al.,* 2007). In Hausa, *Acacia senegal*is called Ɗákwàráá or Dííshèè (Kano), while *Acacia seyal* is called Dúmshèè (Sokoto/Katsina), Dúmshìshèè (Daura), Dúndúshèè (Katsina), Gishishiya (Zamfara), Irahi (Sokoto/Zaria) (Blench and Dendo, 2007). In Gombe, the locals call Acacia 'kwaro', differentiating the species by their grade. In kanuri, *Acacia senegal* is called Kolkol while *Acacia seyal* is called Karamga(Gary and Ryan, 2002). In Yoruba, *Acacianilotica* is called Baani/Booni(Kadiri *et al.*, 2008; Jorjette, 2016). The plant matures and ready for tapping 4 years after planting. The gummy exudate emanates from the stems and branches usually under stress conditions such as drought, poor soil fertility, and injury and appears in form of dry, hard nodules about 10 – 50 mm in diameter, and ranging from almost colourless to brown (Mariana *et al.*, 2012).

Nigerian gum Arabic is sorted into three grades:

- Grade 1 (The top grade) is gum produced from *A. senegal*. Grade 1 Arabic gum is often light warm coloured, from clear to orange to amber, with no dark pieces.

- Grade 2 is gum produced from other species of *Acacia* (such as *A. seyal*and *A. sieberiana*). Grade 2 is sometimes much darker, or has a red or brown tint to it (Gary and Ryan, 2002).
- Grade 3 gum is much darker and very mixed in quality; it mayconsist of gum from species other than *Acacia* (such as *Combretum* and *Albizia*) (Coppen, 1995).

Sudan has traditionally been the main acacia gum producer (mainly *Acaciasenegal*) while Chad and Nigeria produce mainly *Acaciaseyal*(Mario, 2018). Although they are from the same family, they have very different characteristics. The two species prefer different climates and soil types, so they usually do not grow together (Rabah *et al.*, 2016). In Nigeria and Sudan variety *senegal* is relatively abundant, whereas in Kenya and Senegal, the variety *karensis* exists, in South Africa and Zimbabwe, variety *rostrata* is found, while the fourth variety, *leirhochis* is found in most other African countries (Aghughu *et al.*, 1997). Gum arabic has huge foreign exchange potentials. For example, in the year 2017, Nigeria's minister of agriculture and rural development stated in a briefing with state house correspondents after a Federal Executive Council meeting that Nigeria exported gum arabic estimated at US$43 million in the year 2016 and stated the government's resolve to increase funding of the production and export of the commodity (Punch Newspaper, 2017). The gum can be obtained either by organized and controlled (tapping), natural cracks/stem burst or injury resulting from either pruning of the lateral branches or cutting of the branches as livestock fodder. Nigeria is a major gum arabic producer in the world. Her production has declined in recent times from second world producer to third position due to neglect of agriculture by successive governments at all levels (Chidume, 2009).

In Nigeria, production of gum arabic covers about 250,000 sq km in the entire sahelian region spreading across twelve states namely Bauchi, Borno, Gombe, Jigawa, Kano, Katsina, Kebbi, Sokoto, Yobe, Adamawa, Zamfara and Taraba. Nigeria along with Chad has a comparative advantage over Sudan in the production of *Acaciaseyal*and both countries have a very vast area of untapped *Acacia seyal*that produces grade II gum (Aghughu and Mokwunye, 2010). In 1998, *Acacia seyal*was certified by the Codex Alimentarious Commissionof Food and AgricultureOrganization (FAO), to have the same status with*Acacia senegal*in food and pharmaceuticalapplications. The upgrading of*Acacia seyal*to have equal status with *Acacia senegal*hasthreatened Sudan's leadership of the world market forgum Arabic. While Chad has given this a serious exploitation status, Nigeria however has only paid little attention to this, even though there is the claim by Indian buyers thatthe colour of Nigerian *Acacia seyal*is superior to thecolors of *Acacia seyal*produced from any other countryand are willing to pay up to 10 % premium forNigerian *Acacia seyal*over the price paid for *Acacia seyal*produced in any other country (Aghughu and Mokwunye, 2010).

Both gums are used in confectionery products as emulsifier and to fix flavour, in pharmaceuticals, brewery, cosmetics, textile, paints, and lithographic industries. Acacia gum as a pharmaceutical excipient is used in pharmaceutical preparations and as a carrier of drugs since it is considered a physiologically harmless substance. Natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable and widely available (Mariana *et al.,* 2012). They can also be modified in different ways to obtain tailor-made materials for drug delivery systems (Dhiren*et al.*, 2009).

1.5 Suitability of Drug for Formulation as Sustained-Release Dosage Form

Suitability of the drug has to be considered before development of sustained-release dosage form. According to Ratnaparkhi and Gupta (2013), the following characteristics must be taken into consideration;

1. **Solubility of the drug in aqueous media and the intestinal permeability of the drug:** drugs with high solubility and permeability are most suited for extended-release delivery as drug release from the dosage forms can be the rate-limiting step in the process (low solubility; <1 mg/ml). Drugs with low permeability ($<0.5x10^{-6}$ mms^{-1}) are unlikely to be suited for extended-release as they are already rate-limited in their absorption.

2. **Elimination from blood stream:** the most suitable drugs may have relatively short half-lives of 4 – 6 h.

3. **Dose:** to limit the size of the dosage form, the potency of the drug in the modified-release form can be critical. Up to 1000 mg potency tablets are available but this is only achieved by using very large tablets, which may not always be acceptable for some patient populations.

1.5.1 Salbutamol

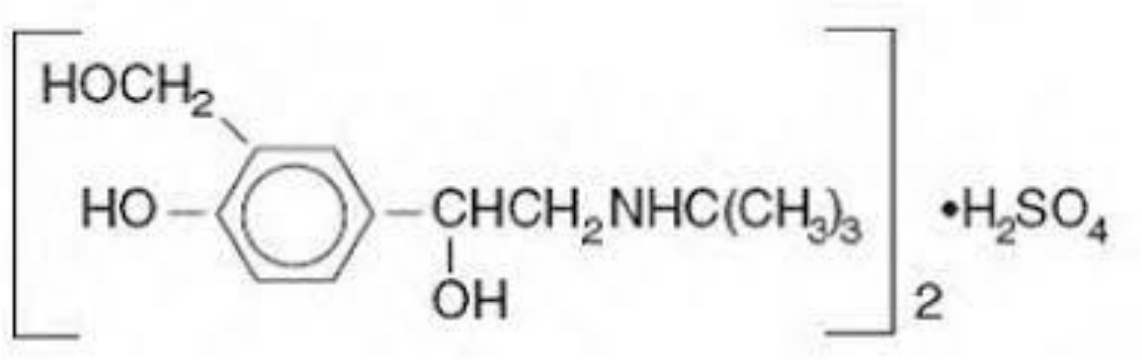


Figure 1.1: Chemical structure of salbutamol sulphate

Salbutamol sulphate is a white or almost white odourless powder. It is soluble in four parts of water and chemically described as 1-(4-hydroxy-3-hydoxymethylphenyl)-2-(tert-buty amino) ethanol sulphate. As a β-$_2$ adrenergic bronchodilator, it is useful in the treatment of asthma and chronic obstructive pulmonary disease (COPD) at a therapeutic dose of 2 – 4 mg, up to a maximum daily dose of 16 mg. Salbutamol sulphate must be dosed three to four times daily to maintain its bronchodilatation effect, due to its short half-life of 2.7 - 5 h. Therefore, to reduce the frequency of administration and to improve patient compliance, a once or twice daily sustained release formulation of salbutamol sulphate is desirable. As a result of its free solubility in water, a judicious selection of release retarding excipients is necessary to achieve a constant *in-vivo* input rate of the drug (Purushothaman *et al.,* 2012; Gowthami *et al.,* 2012).

1.6 Statement of the Research Problem

Research and development of tablet have shifted to the more systematic modified-release systems, thus the need to find ways of improving the delivery of drugs. This has been made possible by the greater opportunities presented by research into gums and other polysaccharide excipients and their derivatives used in tablet formulations.

Though pharmaceutical excipients are mostly obtained from natural sources, the importation of drugs and excipients have been the main stay of the pharmaceutical industry in the developing nations, leading to huge loss of foreign exchange revenue. However, most of these active agents and excipients needed for the production of such medicines can be found relatively available in such nations and where they are absent, suitable substitutes are present.

Acaciaseyal is a natural plant which produces a polysaccharide gummy exudate and has been a commodity of international and local trade in many developing countries, including Nigeria. *Acaciaseyal* gum in its natural for can form matrices but they are required in high quantities to attain sustained release thus, the need to find ways of improving the release profile.

Asthmatic and chronic obstructive pulmonary disease (COPD) patients require continuous drug therapy for a longer period. Salbutamol as a very important drug used in treatment of these diseases however has a high pill burden which can be overcomed by the use of sustained release formulations to reduce the pill burden.

1.7 Justification

The developing nations rely mostly on the import of pharmaceutical excipients and drugs to meet the ever increasing need for healthcare at affordable rates. It has become appropriate that the developing nations like Nigeria look within its shores and source for alternative means of meeting the increasing demand for drugs/drug products and excipients. Local sourcing of Pharmaceutical ingredients can boost our source of foreign earnings and ultimately reduce the overall cost of healthcare delivery.

Acacia tree grows well in the sahelian zone of Nigeria including Borno, Yobe, Gombe, Bauchi, Adamawa, Jigawa, Kano, Katsina, Sokoto, Kebbi, Taraba, Nasarawa, Niger and Plateau. These states being hit with high level of poverty can improve the standard of living of their common people if acaciaplantations can be established due to its beneficial economic influences on the common man and the nation in general.

The ability of acacia gum to form matrices in its natural and derivatized form, its abundance especially in the sahel region of Nigeria and the significance of the sustained-

release dosage forms in medicine attracts full investigation into its application as hydrophilic matrix in the preparation of sustained-release formulations. Sustained-release dosage forms are important in the treatment of diseases because of reduced pill burden and improved compliance.

Cross-linking of *Acacia seyal* gum, which involves re-enforcing bonds with chemical bridges is expected to reduce its solubility, increase its ability to hold water and decrease the rate at which the drug contained in the matix becomes available for release thus, extending the release of the drug and this can be achieved with a lower quantity of the gum.

This study is concerned with the development of *Acacia seyal* cross-links, application of the cross-links so prepared in the formulation of sustained-release salbutamol sulphate matrix tablets by direct compression and evaluation of the tablets for suitability in the reduction of incidences of nocturnal and early morning asthmatic attacks, better patient convenience and a pharmacoeconomic drug delivery system, for effective treatment of chronic obstructive pulmonary disease (COPD).

1.8 Aim

The aim of this study is to evaluate the potential of cross-linked *Acaciaseyal* gum as a matrix former in sustained-release salbutamol sulphate tablet formulations prepared by direct compression method.

1.9 Specific Objectives

The specific objectives include:

a. *Acaciaseyal* gum powder production and evaluation of properties.

b. To crosslink and evaluate properties of the crosslinked polymer.

c. To produce sustained-release salbutamol sulphate tablet formulations using the gum powders prepared and hydroxypropyl methylcellulose (standard) as matrix former, by direct compression method.

d. To evaluate some tableting properties and study the drug release profile of the tablet formulations.

1.10 Hypothesis

Null hypothesis: Cross-linking *Acacia seyal* gum with calcium chloride will not impart sustained-release properties to salbutamol sulphate tablets prepared by direct compression method.

Alternate hypothesis: Cross-linking *Acacia seyal* gum with calcium chloride will impart sustained-release properties to salbutamol sulphate tablets prepared by direct compression method.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Cross-Linking

Natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable and widely available. They can also be modified in different ways to obtain tailor-made materials for drug delivery systems (Shalini, 2012). Cross-linking involves re-enforcing bonds with chemical bridges between the molecules or polymer chains. A cross-link is a bond that links one polymer chain to another and they can be covalent bonds or ionic bonds. Cross-linking of polymers is done to influence the molecular structure, which affects their physical characteristics such as particle properties, hydration and water sorption capacities. As a result, the cross-linked gum may become more resistant to solvent effect, high temperature, and high shear and may have improved textural properties than the natural gum (Mbah *et al.,* 2012). In the ionic gelation technique, the cross-linking agent induces an interaction between the ionic or functional moiety and the polymer chain leading to formation of a more strongly bonded molecular chain network (Patil *et al.,* 2010). Interactions between the positively charged groups of the cross-linking agent and the negatively charged groups of the gum mainly contribute towards ionic interactions inside the network. Apart from the negatively charged groups of the gum (example; $–COO^-$, $–CH_2COO^-$, etc.), other groups within the chain of the gum derivatized such as hydroxyl groups can also react with ionic cross-linkers and additional interactions such as hydrophobic interactions or inter chain hydrogen bonds due to reduced electrostatic repulsion after neutralisation of gum derivatives by the cross-linker can also occur inside the network (Rana *et al.,* 2011).

Basically, two methods of crosslinking are available;

a. Physical method—a molecular interaction between polymers can be achieved by exposure to dry heat, saturated steam, microwave technology, UV, and gamma radiation.
b. Chemical method—polymers are treated with chemicals like aldehydes, epichlorhydrin, borax, calcium chloride or glutaraldehyde.

Temperature is one of the most favourable methods of cross-linking because it avoids both the application of harsh chemical materials for large-scale production and the diversity of equipment and methods used in their application (Dhiren *et al.,* 2009).

2.2 Significance of Cross-Linking Excipients

In recent years there have been important developments in different dosage forms for existing and newly designed drugs. Natural products and semi-synthetic as well as synthetic excipients often need to be used for a variety of purposes. These natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable and widely available (Shalini, 2012). They can also be modified in different ways to obtain tailor-made materials for drug delivery systems. Cross-linking of polymers is done to influence the molecular structure, which affects its physical characteristics such as particle properties, hydration and water sorption capacities, to mention a few (Mbah *et al.*, 2012).

2.2.1 Gums and Mucilages

The term ‘gum’ as applied to water-soluble substances refers to natural non-starch polysaccharides and their structurally modified derivatives. ‘Mucilages’ is a term that was used to describe the slimy aqueous dispersions produced by plants, animals and microbes, which consist basically of water-soluble polysaccharides including starches and modified starches (BeMiller, 2008).

Gums are usually pathological products, produced when the plant is growing under unfavorable conditions or when injured. These hydrophilic polymers are useful as tablet binders, disintegrants, emulsifiers, suspending agents, gelling agents, stabilizing agents, thickening agents, film forming agents in transdermal and periodontal films buccal tablets as well as sustaining agents in matrix tablets and coating agents in microcapsules including those used for protein delivery (Dhiren *et al.,* 2009). Various gums with their common names, biological sources, family and applications are listed in Tables 2.1 – 2.3.

Table 2.1: Pharmaceutical applications of natural gums

Common name	**Botanical name**	**Family**	**Pharmaceutical Applications**
Cashew gum	*Anacardium occidentale*	Anacardiaceae	Suspending agent
Guar gum	*Cyamompsis tetraganolobus*	Leguminoseae	Binder, disintegrant, thickening agent, emulsifier
Gum acacia	*Acacia Arabica*	Leguminoseae	Suspending agent, emulsifying agent, binder in tablets
Karaya gum	*Sterculia urens*	Sterculiaceae	Suspending agent, emulsifying agent, dental adhesive, sustaining agent in tablets, bulk laxative

(Adapted from Dhiren *et al.,* 2009)

Table 2.2: Applications of Natural Gums in Novel Drug Delivery System (NDDS).

Common name	Botanical name	Family	Pharmaceutical Applications
Guar gum	*Cyamompsis tetraganolobus*	Leguminoseae	Colon targeted drug delivery, cross-linked microspheres
Gum acacia	*Acacia Senegal*	Leguminoseae	Osmotic drug delivery
Karaya gum	*Sterculia urens*	Sterculiaceae	Mucoadhesive and buccoadhesive
Xanthan gum	*Xanthomonas campestris*	—	Pellets, controlled drug delivery system

(Adapted from Dhiren *et al.,* 2009)

Table 2.3: Examples of modified gums with their applications.

Gums	Modification technique	Application
Acacia gum	Chemical modification of acacia gum using epichlorhydrine.	Disintegrating agent
Cross-linked cellulose	Chemical modification of cellulose by epichlorhydrine.	Disintegrating and binding agent
Guar gum	Chemical modification of guar gum	Disintegrating agent
Guar gum	Chemical modification of guar gum with glutaraldehyde for colonic delivery, chemical modification using isopropanol as a film-coating material	Colonic delivery, film coating, hydrogel
Tragacanth	Chemical modification of tragacanth using epichlorhydrine.	Disintegrating agent

(Adapted from Dhiren *et al.*, 2009)

2.2.1.1 Guar gum

Guar gum (GG) is also called guaran, cluster bean, calcutta, lucern, gum cyamopsis, cyamopsis gum, guarina, glucotard and guyarem (Gamal-Eldeen *et al.*, 2006). GG is a galactomannan, which occurs as a storage polysaccharide in the seed endosperm of the plant *Cyamopsis tetraganolobus* in the Fabaceae family. GG has recently been highlighted as an inexpensive and flexible carrier for oral extended release drug delivery (Varshosaz *et al.*, 2006).

Glutaraldehyde has been used extensively for cross-linking polymers containing hydroxyl groups. It was observed that with an increase in the concentration of glutaraldehyde there was an increase in the cross-link density and as a result there was a decrease in buffer uptake (Kabir, 1998). Drying of the hydrogel to form discs introduced irreversible changes in the hydrogel thus, it was observed that when discs were formed by physical entanglements in the polymer network, it resulted in a change in the degree of swelling. However, it was observed that high amounts of glutaraldehyde were required for the cross-linking reaction suggesting that the cross-linking efficiency was low. This could be attributed to:

(a) low reactivity of guar gum hydroxyl groups as a result of limited water solubility,

(b) glutaraldehyde polymerisation during the cross-linking process and

(c) possible masking effect of the hexose units of the branched polymer.

However, the cross-linked products retained the ability of guar gum to be degraded *in vitro* by a mixture of galactomannase and galactosidase (Kabir, 1998).

In another investigation carried out by Soppirnath, (2000), interpenetrating network microspheres of polyvinyl alcohol and guar gum were prepared. These microspheres

were cross-linked with glutaraldehyde. The aldehyde groups of glutaraldehyde reacted with the hydroxyl groups of the polymers to form acetal cross-links. The IR spectra exhibited a corresponding peak at 1251cm^{-1}. Similarly, DSC studies showed an increase in ΔH value. This increase in the ΔH value may be attributed to the high amount of energy required to break the highly cross-linked polymeric network structure. This also suggested the formation of a highly crystalline polymeric matrix due to increase in cross-linking agent density. The crystalline nature of the polymeric matrix dictates its water uptake. An increase in cross-linking leads to formation of a dense macromolecular network. Therefore, a decrease in molecular transport of liquid within such polymeric matrices was observed, resulting in reduced swelling. The *in vitro* release of nifedipine from these microspheres was observed to depend on the extent of cross-linking. This was due to the fact that the solvent uptake by the microspheres decreased with increased cross-linking. Thus, the drug release continued for several hours. The release of the drug from these microspheres increased initially due to the polymer relaxation process as water penetrated and converted the glassy polymer into a rubbery one. However, the latter part of the release profile from the fully swollen polymer was due to a diffusion process.

Das, (2006) prepared glutaraldehyde cross-linked guar gum hydrogel discs and showed that cross-linking resulted in significant reduction in the swelling of the guar gum. Studies also showed that percentage drug release increased with increasing glutaraldehyde concentration.

2.2.1.2 Acacia gum

Plant exudate is produced by plant cells as a response to wound at the site of an injury, which gives out a sticky viscous fluid secreted to cover or seal the opening and eventually becoming a glossy, translucent hard mass as seen with acacia plants (Gashua *et al.*, 2013). Acacia gum also known as Arabic gum is a dried exudate acquired from the stems and branches of natural species of *Acacia senegal* (L) Willdenow or other closely related species of *Acacia seyal* or *A. sieberana* (Family *Leguminosae*). Structurally, gum arabic is a branched molecule with the main chain consisting of 1,3-linked β-D-galactopyranosyl units with other carbohydrates such as arabinose, glucuronic acid and rhamnose also present (Al-Assaf *et al.,* 2007).

The exudate emanates from the stems and branches usually under stress conditions such as drought, poor soil fertility, and injury and appears in form of dry, hard nodules about 10-50 mm in diameter, and ranging from almost colourless to brown (Mariana *et al.*, 2012).

Acacia gum as a pharmaceutical excipient is used in pharmaceutical preparations and as a carrier of drugs since it is considered a physiologically harmless substance. Gum Arabic was successfully used as a matrix-microencapsulating agent for the enzyme, endoglucanase, which proved to give slow release of the encapsulated enzyme and in addition increased its stability (Ramakrishnan *et al.,* 2007). Gum Arabic was used as an osmotic suspending and expanding agent to prepare a monolithic osmotic tablet system. The optimum system delivered the water-insoluble drug, naproxen, at a rate of approximately zero order for up to 12 h at a pH of 6.8 (Lu *et al.,* 2003).

Reis, (2006) prepared pH-responsive hydrogel from Arabic gum (AG) chemically modified with glycidyl methacrylate (GMA). Water uptake tests of Arabic gum–glycidyl methacrylate (AG–MA) hydrogels showed significant pH dependence, which affected the water absorption transport mechanism. In the studied pH range, it was found that the transport of water in AG–MA hydrogel was controlled by Fickian diffusion and polymer relaxation (anomalous transport). At high pH values, the water transport profile became more dependent on polymer relaxation. This effect was attributed to the increase in the ionized groups of glucuronic acid segments, which contributed to electrostatic repulsion among the groups and resulted in expansion of the gel polymer network. AG–MA hydrogels exhibited pH-responsive behaviour, demonstrating them to be appropriate materials for delivering drugs to specific regions in the gut.

Mbah *et al.* (2012) cross-linked *Acacia senegal* using calcium chloride as the cross-linking agent and evaluated some of the physicochemical properties of the cross-links obtained. The cross-linking was done by ionic gelation with calcium chloride in distilled water and some physicochemical properties of both the natural and cross-linked gum were determined. The pH, flowability and moisture sorption of the cross-linked gum were significantly ($P<0.005$) increased over those of the natural gum. It was suggested that the cross-linked gum may be more suitable for solid dosage formulations of moisture stable drugs and may be used for coating and as matrices for embedding medicinally active substances or drugs for the purposes of controlled drug delivery.

2.2.1.3 Cashew gum

Cashew gum (CG) is one of the versatile naturally occurring biopolymer that is finding increasing applications in the pharmaceutical and biotechnology industry. The cashew

(Anacardium occidentale L.), is a multipurpose tree with great economic importance, that is well adapted to seasonally wet/dry tropical climates (Abdulsamad *et al*., 2012). CG have been used in the food and beverage industry as a thickening agent, a gelling agent and for many other purposes but recently, the role of these gums in enveloping controlled drug delivery systems has increased significantly and CG is gaining lot of attraction towards this application (Moin *et al*., 2014).

Cross-linking of gums requires availability of active functional groups in their basic structure hence, cashew gum among other gums that possess free alcoholic and/or carboxylic units seems to be a good choice for modification by cross-linking. However, it is essential to investigate the vulnerability of the cross-linking to different pH in order to use the modified molecule for site-specific delivery.

Abdulsamad *et al.* (2014) extracted and purified cashew gum (CG) using acetone then cross-linked it using epichlorohydrin (EPC) in a 2-step heating process. The gum, 5M NaOH, deionized water (DI) and EPC were homogenized and heated at 40 ^{o} C for 24 h followed by a second heating time of 15 h at 70 ° C. The resulting polymer (CG:EPC) was used as drug release enhancing agent at 3 $\%^{w}/_{w}$ concentration to formulate venlafaxine HCl (ven.HCl) tablets using hydroxypropyl methylcellulose (HPMC ER) as binder at 7.5% w/w. Granules formed were evaluated and the tablets assessed. Results showed the formation of a polymeric material capable of swelling when in contact with water. Tablets formed passed all the stipulated tests and demonstrated ability to enhance ven.HCl release from the tablets. Drug release by CG:EPC however, did not surpass that by the known superdisintegrants - croscamellose and crospovidone.

2.2.1.4 Psyllium

Psyllium mucilage is obtained from the seed coat of *Plantago ovata* by milling the outer layer of the seeds. It has been evaluated for its tablet binding properties (Kulkarni *et al.*, 2002) and also its ability to form hydrogels through radiation-induced cross-linking for controlled release of 5-fluorouracil as model drug (Singh *et al.*, 2008).

Psyllium and methacrylamide based hydrogels were prepared by using N, N-methylene-bis-acrylamide as cross-linker, which were then loaded with insulin. These cross-linked hydrogels showed controlled release of the active ingredient by means of non-Fickian diffusion of the drug through polymer chain relaxation during swelling (Singh and Chauhan, 2009).

2.2.1.5 Pectin

Pectin is a family of complex polysaccharides present in the walls that surround growing and dividing plant cells. It is also present in the junctional zone between cells within secondary cell walls including xylem and fiber cells in woody tissue (Ridley *et al.*, 2001). Pectin is an essential component in the initial growth and ripening process of fruit and is often a waste material from the food and fruit processing industry with a consequent high availability (Bhatia *et al.*, 2008). The composition of pectin can vary based on the botanical source, for example pectin from citrus contains less neutral sugars and has a smaller molecular size compared to pectin obtained from apples (Fry, 2004).

Pectin has been investigated as an excipient in many different types of dosage forms such as film coating of colon-specific drug delivery systems when mixed with ethyl cellulose, micro-particulate delivery systems for ophthalmic preparations and matrix type transdermal patches. It has high potential as a hydrophilic polymeric material for

controlled release matrix drug delivery systems, but its aqueous solubility contributes to premature and fast release of the drug from these matrices (Shirwaikar *et al.,* 2008).

Cross-linking of pectin with calcium ions inhibits the release of the incorporated drug from pectin tablets by suppressing both the dissolution and swelling of these systems (Sinha and Kumria, 2001; Chourasia and Jain, 2004; Bhatia *et al.*, 2008).

2.2.1.6 Alginates

Alginates or alginic acids are linear, unbranched polysaccharides found in brown seaweed and marine algae such as *Laminaria hyperborea, Ascophyllum nodosum* and *Macrocystis pyrifera.* These polymers consist of two different monomers in varying proportions, namely β-D-mannuronic acid and α-L-guluronic acid linked in α- or β-1,4 glycosidic bonds as blocks of only β-D-mannuronic acid or α-L-guluronic acid in homopolymers or alternating the two in heteropolymeric blocks. Alginates have high molecular weights of 20 to 600 kDa (Liew *et al.,* 2006).

The gelling properties of alginate's guluronic residues with polyvalent ions such as calcium or aluminium allow cross-linking with subsequent formation of gels that can be employed to prepare matrices, films, beads, pellets, microparticles and nanoparticle (Sarmento *et al.,* 2007; Ching *et al.,* 2008). Dual drug-loaded alginate beads containing drug in inner and outer layers were prepared by dropping single-layered alginate beads into a $CaCl_2$ solution and their drug release characteristics were investigated in simulated gastric fluid followed by intestinal fluid. The beads protected the drug in the gastric fluid with no release of the drug, while a biphasic release (i.e. a linear release for the first four hours and another linear phase thereafter) was obtained when the dissolution medium was changed to intestinal fluid (Lee *et al.*, 1998).

2.2.1.7 Carrageenans

Carrageenans is the generic name for a family of high molecular weight sulphated polysaccharides obtained from certain species of red seaweeds belonging to the class *Rhodophyceae,* especially *Chondruscrispus, Euchema spp, Gigartina stellata* and *Iridaea spp* (Coviello *et al.*, 2007; Nerurkar *et al.,* 2005). Carrageenan extracted from seaweed is not assimilated by the human body and provides only bulk but no nutrition.

Hydrogel beads were prepared from a mixture of cross-linked κ-carrageenan with potassium and cross-linked alginate with calcium and they exhibited a smoother surface morphology than that of the one-polysaccharide network beads. The carrageenan parts of the hydrogel pronouncedly enhanced the thermostability of the polymeric network. These beads were introduced as novel carriers for controlled drug delivery systems (Mohamadnia *et al.*, 2008).

2.2.1.8 Tamarind seed polysaccharide (TSP)

TSP is a galactoxyloglucan isolated from seed kernel of *Tamarindusindica*. Xyloglucan is a major structural polysaccharide in the primary cell wall of higher plants. It possesses properties like high viscosity, broad pH tolerance and adhesively. This has led to its application as stabilizer, thickener, gelling agent and binder in food and pharmaceutical industries. In addition to these, other important properties of TSP have been identified recently. They include non-carcinogenicity, mucoadhesivity, biocompatibility, high drug holding capacity and high thermal stability. This led to its application as excipient in hydrophilic drug delivery system (Rashmi *et al.*, 2014; Kharkwal *et al*., 2014).

Tamarind seed polysaccharide (TSP) has been cross-linked with epichlorohydrin and the cross-linking confirmed by FTIR. The cross-linked TSP exhibits superior wicking and

swelling action and hence can be used as a super-functional disintegrant. Cross-linked TSP was found to be more effective in retarding the drug release compared to TSP without cross-linking (Sumathi and Ray, 2002).

2.2.1.9 Gelatin

Gelatin (from Latin: *gelatus* meaning "stiff", "frozen") is a translucent, colourless, brittle (when dry), flavourless solid substance, obtained by partial hydrolysis of collagen derived from skin, white connective tissue and bones of various animals such as domesticated cattle, chicken, pigs, and fish. Photographic and pharmaceutical grades of gelatin are generally made from beef bones (Kharkwal *et al*., 2014). It is used in preparation of suppositories, pastes, pastilles, coating of tablets and formation of hard and soft capsule shells. It is also used for microencapsulation of drugs. Gelatin typically constitutes the shells of pharmaceutical capsules in order to make them easier to swallow. Gelatin beads as sustained release drug delivery system were prepared by Pathan *et al.* (2014) using emulsion cross-linking method. In this method, drug was dissolved in aqueous gelatin solution, which was previously heated for 1 hr at 40 ° C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 ° C, resulting in w/o emulsion. Further stirring was done for 10 min at 15 ° C. The produced beads were washed three times with acetone and isopropyl alcohol, respectively, air- dried and dispersed in 5 mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 h for cross-linking. Afterward, beads were treated with 100 ml of 10 mm glycine solution containing 0.1% $^{w}/_{v}$ of tween 80 at 37 ° C for 10 min to block un-reacted glutaraldehyde.The study result showed that the formulation i.e. gelatin beads so prepared could sustain the release of Propranolol HCl for

significance of combination of different types of gelatins for sustained release of the drug.

2.2.2 Cellulose

Cellulose is an essential structural component of cell walls in higher plants and is the most abundant organic polymer on earth. This linear, unbranched polysaccharide consists of β-1,4-linked D-glucose units and many parallel cellulose molecules form crystalline microfibrils that are mechanically strong and highly resistant to enzymatic attack. These long crystalline ribbons are aligned with each other to provide structure to the cell wall. Cellulose is insoluble in water and indigestible by the human body (Aquilera and Stanley, 1999; Cosgrove, 2005)

Powdered cellulose is mechanically disintegrated cellulose obtained as a pulp from fibrous materials such as wood or cotton and although it was used in pharmaceutical applications such as filler in tablets, it is microcrystalline cellulose that represents a novel and more useful cellulose powder. Microcrystalline cellulose is partially depolymerized cellulose prepared by treating high quality cellulose with hydrochloric acid to produce free flowing non-fibrous particles. Microcrystalline cellulose is mainly used in the pharmaceutical industry as a diluent/binder in tablets for both the granulation and direct compression processes (Kibbe, 2000). The hydroxyl moieties on the D-glucopyranose units of the cellulose polymer offer a variety of possibilities for the formation of derivatives. Cellulose derivatives can be made by means of etherification (example hydroxypropyl methylcellulose, carboxymethylcellulose), esterification (cellulose nitrate, cellulose acetate, and cellulose acetate phthalate), cross-linking or graft copolymerization (Hon, 1996). Cross-linked cellulose (CLC) and cross-linked cellulose derivatives such as

cross-linked sodium carboxymethylcellulose (NaCMC) can be used as excellent binders in pharmaceuticals (Chebli and Cartilier, 1998).

In recent years, the classic disintegrants have been gradually replaced with the newer ones called super-disintegrants. Super-disintegrants can act in lower concentrations than starch and have no detrimental effect on compressibility and flowability of formulations. Three main groups of these excipients are: modified starches like sodium starch glycolate (Primogel®, Explotab®) with 4-6% effective concentration, cross-linked polyvinyl pyrrolidones like crospovidone (Polyplasdone XL®, Kollidon CL®) with 2 – 4 % effective concentration and modified cellulose like cross-linked sodium carboxymethyl cellulose or croscarmellose (Ac-Di-Sol™ and Nymcel) with 2 – 4 % effective concentration in wet granulation process. Modified cellulose compounds are very efficient disintegrants and additionally, can accelerate the dissolution rate of drugs in aqueous environment (Chebli and Cartilier, 1998).

2.2.3 Hemicellulose

Hemicellulose consists of a group of complex polysaccharides that are bound to the surface of cellulose microfibrils but their structure prevents them from forming microfibrils by themselves. Hemicellulose polysaccharides consist of xyloglucans, xylans and mannans that can be extracted from the plant cell wall with a strong alkali. They have backbones made up of β-1,4-linked D-glycans. Xyloglucan has a similar backbone as cellulose, but contains xylose branches on 3 out of every 4 glucose monomers. The β-1,4-linked D-xylan backbone of arabinoxylan contains arabinose branches (Aquilera and Stanley, 1999; Cosgrove, 2005; Lerouxel *et al.*, 2006; Chaa *et al.*, 2008).

Glucomannan is a hydrocolloidal polysaccharide of the mannan family consisting of β-1, 4 linked D-mannose and D-glucose monomers (with acetyl side branches on some of the backbone units), but the mannose:glucose ratio may differ depending on the source. The acetyl groups contribute to its solubility and swelling capacity and assist in making it a soluble natural polysaccharide with the highest viscosity and water-holding capacity. It is very abundant in nature and this polysaccharide is specifically derived from softwoods, roots, tubers and plant bulbs. The most commonly used type of glucomannan is referred to as konjacglucomannan, which is extracted from the tubers of *Amorphophallus konjac K*., Koch and is a very promising polysaccharide for incorporation into drug delivery systems. Since konjacglucomannan by itself forms very weak gels, it has been investigated as an effective excipient in controlled release drug delivery devices in combination with other polymers or by modifying its chemical structure (Liu *et al*., 2007; Alvarez-Manceñido *et al.*, 2008). Konjacglucomannan cross-linked with trisodium trimetaphosphate formed hydrogel systems that could sustain hydrocortisone release depending on cross-linking density and enzymatic degradation (Beneke *et al.*, 2009).

2.2.4 Chitosan

Chitosan comes from the deacetylation of chitin, a natural biopolymer originating from crustacean shells. Chitosan is a biocompatible, biodegradable, and nontoxic natural polymer with excellent film-forming ability. Being of cationic character, chitosan is able to react with polyanions giving rise to polyelectrolyte complexes hence, chitosan has become a promising natural polymer for the preparation of microspheres/nanospheres and microcapsules (Kharkwal *et al*.,2014). The techniques employed to microencapsulate with chitosan include ionotropic gelation, spray drying, emulsion phase separation,

simple and complex coacervation. The development of procedures to cross-link cationic polysaccharides has increased their applications. Polymer hydrogels with adequate mechanical properties and high drug loading capability show a big potential as the basis of controlled drug delivery systems (Peppas *et al.*, 2000). In the case of chitosan, the amino groups of the polymer may allow the establishment of different types of interactions with both non-ionic and ionic drugs (Kumbar *et al.*, 2002) and also provide pH-sensitive systems, which swell in gastric conditions allowing a site-specific release (Hejazi and Amiji, 2003). Several cross-linking reagents have been used for cross-linking of chitosan such as glutaraldehyde, genipin, ethylene glycol, diglycidyl ether and diisocyanate.

Gupta and Jabrail (2007) prepared cross-linked chitosan microspheres by dropping a polysaccharide solution into a methanolic solution of NaOH and then adding a solution of glutaraldehyde for cross-linking. They demonstrated that the obtained microspheres were non-toxic and biodegradable, and hence may be considered as suitable candidate for oral drug delivery.

The formation of hydrogels from polymers using non-covalent cross-linking is a useful method to prepare hydrogels for drug delivery. These gels are likely to be biocompatible as gel formation does not require the use of organic solvents or chemical reactions, which may be potentially deleterious to the drug load. Such physically cross-linked chitosan based gels are formed by exploiting either hydrogen bonding or hydrophobic attractions (Giovanna and Laurienzo, 2008).

The use of tripolyphosphate (TPP) in ionic gelation as a polyanion to cross-link with the cationic chitosan through electrostatic interaction could avoid possible toxicity of

reagents used in chemical cross-linking (example glutaraldehyde). TPP cross-linked chitosan beads can be prepared simply by dropping chitosan droplets into TPP solution and this procedure was found to be useful in the pharmaceutical industry (Shu and Zhu, 2000).

2.2.5 Starch

Starch is one of the most important but flexible food ingredients possessing value added attributes for innumerable industrial applications. The most common sources of food starch are corn, potato, wheat, cassava/tapioca and rice. Practically every industry in existence uses starch or its derivatives in one form or another. In foods and pharmaceuticals, starch is used to influence or control such characteristics as texture, moisture, consistency and shelf stability. It can be used to bind or to disintegrate; to expand or to densify; to clarify or to opacify; to attract moisture or to inhibit moisture; to produce smooth texture or pulpy texture, soft coatings or crisp coatings. It can be used to stabilize emulsions or to form oil resistant films (Akpa, 2012).Starch is comprised of two polymers namely amylose (a non-branching helical polymer consisting of α-1, 4 linked D-glucose monomers) and amylopectin (a highly branched polymer consisting of both α-1, 4 and α-1,6 linked D-glucose monomers). Most common cereal starches contain 15 – 30 % amylose, but discovery of a recessive gene responsible for production of starch enriched with amylose led to the use of a genetically modified crop for the production of different starches for specific purposes. This has led to the creation of corn producing high amylose starch with a content of 50 %, 70 % and even up to 90 % amylose. Distinct X-ray diffraction patterns are obtained from the crystalline form of starch in granules to distinguish between different types. Type A crystalline structure is characteristic of

cereals such as rice wheat and maize, which is favoured by amylopectin with short lateral chains and branching points close to each other. Type B is typical of starch from potato and banana and is favoured by long side chains as well as distant branching points. Type C is found in legumes and is a mixture of the A- and B-type crystalline structures. Starch can also adopt a V-type crystalline structure (derived from the German word 'Verkleisterung' meaning 'gelatinised starch'), which is common for modified starch but is also observed in the endosperm of some native starch granules (Cummings and Stephen, 2007; Thérien-Aubin and Zhu, 2009).Pregelatinised starch is modified starch by chemical and/or mechanical means to rupture its granules, which results in starch with enhanced flow properties that are directly compressible. Partially pregelatinised grades are commercially available where pregelatinised starch is mixed with free amylase, free amylopectin and unmodified starch in specified ratios. Pharmaceutical grade pregelatinised starch does not contain chemical additives (example salts or bases as gelatinistion aids) and is produced by heating and subsequent drying (Kibbe, 2000). Starch retrogradation refers to aggregation and crystallisation of starch chains (or precipitation) in gels to form a rigid tri-dimensional network with increased stiffness of the sample (Thérien-Aubin and Zhu, 2009).Native starch may not be suitable in controlled release drug delivery systems due to substantial swelling and rapid enzymatic degradation resulting in too fast release of many drugs. This has led to the use of derivatives of starch that are more resistant to enzymatic degradation as well as cross-linking and formation of co-polymers. Starch acetate prepared by acetyl esterification has shown retarded enzymatic degradation with the potential to be used as a colon-targeted drug delivery carrier (Chen *et al.*, 2007). Cross-linked high amylose starches have been

developed as suitable excipients for controlled release solid oral dosage forms with high loading capacities of active ingredient and with the capability of achieving quasi-zero order release for most drugs. Other advantages include absence of erosion, limited swelling and the ability to control the rate of drug release by changing the degree of cross-linking (Lenaerts *et al*., 1998).

Cross-linked high amylose starch (corn starch) biodegradable implants for sustained delivery of ciprofloxacin hydrochloride was studied by Pawar *et al.* (2013). The high amylose starch has reactive hydroxyl groups that can be modified chemically for various biomedical and pharmaceutical applications. Cross-linking was done with epichlorohydrin, which interacts with the carboxyl groups present in the strach. Different formulations were developed by varying drug to polymer ratio. Preparation of cross-linked high amylose starch based implants was carried out by direct compression technique.

Results from the study showed that the cross-linked starch implants were characterized by minimal swelling, erosion and water uptake. The release from all developed formulations was based on water uptake i.e. the formulations having more water uptake shows higher cumulative % release and the formulations having low water uptake shows lesser cumulative % release. The optimized CS3 implant formulation showed a slow zero order kinetics of drug release. The prolonged drug release was observed with higher drug loading. The study by Pawar *et al.* (2013) proved that, the cross-linked starch implant had potential to retard the drug release for more than five weeks in the treatment of osteomyelitis and bone infections.

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Materials

Excipients:

Acacia seyal gum; grade 2 acacia gum obtained from Dadin kowa, Gombe, Nigeria, hydroxypropyl methylcellulose (JRS PHARMA, HPMC grade E15, Zacapu, Mexico), lactose anhydrous (BDH, England), magnesium stearate (BDH, England), talc (BDH, England).

Chemicals:

Calcium chloride (Kermel, China), acetone (BDH, England), distilled water, deionized water, salbutamol sulphate (Avrishtava PVT, India), potassium dihydrogen phosphate (Kermel, China), sodium hydroxide pellets (Yueqiao, China). All reagents used were of analytical grade.

Equipment*:*

Mechanical flask shaker (Gallenkamp, England), Centrifuge (Beckman, Germany), Desiccator (Top instrument, China), pH meter (Hanna Instruments, pH 213, Romania), Thermostated water bath (Julabo SW 121, China), Monsato hardness tester (Vinsyst, India), Ultraviolent – Visible spectrophotometer (Shimadzu corporation model China), USP type I dissolution apparatus (Tian Jin Optical Instruments Factory; RC-6 Dissolution, China), Disintegration tester (Coupley DTG 4000, UK), Laboratory blender (Thomas Scientific, USA), Sieve shaker (Endecotts, UK), Eccentric tablet press (Erweka EK 400, Germany).

Glasswares/Others:

Cornical flasks, beakers, measuring cylinders, density bottle, funnel, petri dish, aluminium foil, muslin cloth, screw-capped containers.

3.2 Methods

3.2.1 Sample Collection and Identification

The crude acacia gum exudates (grade 2) was collected from Gombe State, Nigeria and taken to the Herbarium section of the Department of Biological Sciences, Ahmadu Bello University, Zaria for identification and then identified and given a voucher number.

3.2.2 Extraction and Purification

The method used by Abdulsamad *et al.*(2012) was adopted. Five hundred grams (500 g) of the *Acacia seyal* gum exudates was weighed and dissolved by stirring in 1.5 L of distilled water contained in a 3 L beaker. The mucilage formed was then filtered using suction through a fine muslin cloth to remove any extraneous matter. One (1) liter of acetone was gradually added into the beaker containing the mucilage while stirring and as the gum started precipitating, further additions of the acetone led to the gum becoming more solid. The mixture was decanted and 500 ml acetone was added gradually onto the slimy gum while squeezing out the remaining water entrapped using hands protected with hand gloves until the gum started to crumble and eventually got finely dispersed in the acetone, signifying the near exhaustive separation of the gum from the water. The gum was then separated from the acetone by filtration, spread on non-stick baking trays and dried in an oven (Galenkamp, Germany) at 40 ° C for 5 h. The gum was then removed from the oven and dried at room temperature overnight. This was then blended in a laboratory blender for 30 s and weighed. The powder so obtained was then transferred to a screw-capped glass container, labelled as 'EG' and stored for future use.

The extraction yield (%) was calculated using the relationship:

$$\%\, Yield = \left(\frac{W2}{W1}\right) \times 100 \qquad \text{.....(1)}$$

Where W_1 is the weight of the *Acacia seyal* gum exudates used for the purification, W_2 is the weight of the dried *Acacia seyal* gum purified.

3.2.3 Cross-linking of the Purified *Acacia seyal* gum (EG) Using Calcium Chloride

The ionic gelation method used to cross-link *Acacia senegal* by Mbah *et al.*(2012) was adapted for this process. One hundred grams (100 g) of the purified *Acacia seyal* gum (EG) powder was dispersed properly in two (2) liters of distilled water in a beaker. This was then divided equally into four separate 500 ml conical flasks and shaken for 24 h using a mechanical flask shaker (Gallenkamp, England). After shaking, the contents of the four flasks were then transferred into a plastic container and one (1) liter of freshly prepared 1M calcium chloride solution was added gently with intermittent stirring. This solution was divided into six different 500 ml conical flasks and then shaken for 6 h then transferred into a clean plastic container and allowed to stand for another 6 h. The hydrated gum particles were precipitated by washing serially with cold acetone to remove any residual water and filtered using a clean muslin cloth. The harvested gum was dried on a non-stick tray in an oven at 40 ° C for 5 h and then air dried at room temperature overnight. This was then blended in a laboratory blender for 30 s and weighed. The powder was then transferred into a screw-capped container, labelled as 'CG' and stored for future use.

The cross-linked gum yield with reference to the initial starting material was calculated using equation (2) below and recorded accordingly.

$$\%\, Yield = \left(\frac{W2}{W1}\right) \times 100 \qquad \text{.....(2)}$$

Where W_1 is the weight of the crude*Acacia seyal* gum used for the purification process (500 g) and W_2 is the weight of the cross-linked *Acacia seyal* gum powder (CG) obtained.

3.2.4 Differential Scanning Calorimetry (DSC)

Heat flux differential scanning calorimeter (NETZSCH-Geratebau, Germany) was used to obtain valuable information on the cross-link formation between the gum and the calcium chloride. Samples (10 mg) of the purified *Acacia seyal* gum (EG) and the cross-linked *Acacia seyal* gum (CG) were respectively encapsulated in aluminium disposable pans. DSC scans were ran to measure the energy changes associated with heating the samples upto 300° C at a scan rate of 10° C/min for a total of 25 min, using nitrogen as purge gas. Differences in the thermograms of the two polymers was then noted. Appearance or disappearance of peak(s) suggests the formation of new bonds/structures (Saunders, 2008).

3.2.5 Fourier Transform Infra Red (FT-IR) studies

FT-IR spectra of purified *Acacia seyal* gum powder (EG) and cross-linked *Acacia seyal* gum powder (CG) were obtained using JASCO IR spectrophotometer (model 4200, Jasco Inc. Japan). The powdered samples were mixed with potassium bromide (KBr), compressed into pellets and analysed between 400 and 4000 cm^{-1}. The spectra of EG and that of CG were then compared to reveal the presence or absence of IR absorption bands representative of the respective functional groups of interest. Appearance, disappearance or broadening of absorption band(s) on the spectra of CG in comparison with that of EG was used to assess the crosslinking of the purified *Acacia seyal* gum powder (EG) (Hsu, 1997; Coates, 2000).

3.2.6 Organoleptic Characterization

The polymers (EG and CG) were observed for their colour, texture, taste and odour using the sense organs.

3.2.7 Physicochemical Characterization

3.2.7.1 Moisture Loss on Drying (MLD)

The method described by Abdulsamad *et al.* (2012) was adopted. Two (2) g of the polymer was weighed (W_1) and dispersed into three tarred and conditioned evaporating dishes. The dishes were conditioned by heating at 105° C for 30 min followed by cooling in a desiccator for 30 min. The samples were heated at 105° C for 2 h, cooled in a desiccator for 30 min and weighed. The samples were heated again for another 2 h and cooled for 30 min in a desiccator then weighed (W_2). The MLD was determined using the following relationship:

$$\% MLD = \frac{(W_1 - W_2)100}{W_1} \quad \text{.....(3)}$$

Where W_1 and W_2 are weights of the samples before and after drying, respectively.

3.2.7.2 Determination of Solubility of the Polymers

The qualitative method of evaluating solubility as reported by Abdulsamad *et al*. (2014) was adapted. Two hundred (200) mg each of EG and CG were weighed and respectively dispersed in 10 ml each of some solvents contained in test tubes. Non-polar solvents (diethyl ether and toluene), polar aprotic solvents (ethyl acetate and dimethylsulfoxide (DMSO) and polar protic solvents (isopropanol and water) were used as solvents. At ambient temperature, the tubes were shaken using flask shaker for 10 min, allowed to stand for 10 min and visually observed for the ability of the polymers to go into solution.

The aqueous solubility of EG and CG was determined quantitatively in distilled water (30° C). A 1 g quantity of the gum was added to 10 ml of distilled water and left overnight. The clear supernatants (5 ml) were taken and placed in small pre-weighed evaporating dishes and heated to dryness over a digital thermostatic water bath. The weights of the dried residue with reference to the volume of the solutions were determined and recorded (Kipo *et al.*, 2014).

3.2.7.3 Viscosity Determination

The viscosity of a 2 %aqueous dispersion of the polymer was determined using an Ostwald viscometer, clamped vertically in a beaker of water at room temperature and allowed to equilibrate. The time taken for the solution to flow through the marked points of the Ostwald viscometer was then recorded. The average time in seconds (s) was determined. The test was first conducted using water as the fluid and the time of flow determined. Using the equation below, the kinematic viscosity of the polymer solution was then calculated.

$$\eta_g = \eta_w \left(\frac{t_g}{t_w}\right) \quad \text{..... (4)}$$

where η_g = dynamic viscosity of the gum; η_w = dynamic viscosity of water at 30 ° C = 798 m^{-2}; t_g = time (s) for the gum dispersion to flow through the Ostwald viscometer; t_w = time (s) for water to flow through the Ostwald viscometer.

3.2.7.4 Swelling Ratio/ Rate Determination

A 1 g sample of the polymer was weighed and transferred into a clean 10 ml measuring cylinder. The volume occupied by the polymer was then recorded. Distilled water was added up to the 10 ml mark and the cylinder allowed to stand for 24 h and the new volume occupied by the swollen polymer recorded. The swelling property of the polymer observed within 24 h was expressed both as the swelling ratio and swelling rate. The swelling ratio (Q_d) for the polymer was calculated from the equation below (Siriporn *et al.*, 2007).

$$Q_d = \frac{V_s - V_d}{V_d} \quad \text{.....(5)}$$

Where V_d and V_s represents the volume of the initial dried polymer and the final volume of swollen polymer, respectively. The swelling rate was calculated as the volume increase: V_d - V_s per h.

3.2.7.5 Hydration Capacity (HC)

The method used by Olorunsola *et al.*(2016) was modified and used for the determination of the hydration capacity. The samples EG and CG (1 g each) were dispersed seperately in 10 ml distilled water in a preweighed centrifuge tube. This was then mixed by stirring for 2 min, stoppered and centrifuged for 5 min. The supernatant was decanted, leaving the sediments. The tubes were then placed in a forced-draft air oven (Galenkamp, Germany) at an angle of 15 – 20 º, allowed to dry at 50° C for 25 min, cooled in a desiccator for 25 min and then weighed to obtain the weight of the sediment, W_2 (Abdulsamad *et al*., 2014).

The hydration capacity (H.C) was calculated using the equation:

$$HC = \frac{W_2}{W_1} \qquad \text{.....(6)}$$

Where W_1 = initial weight of dry polymer and; W_2= weight of the sediment.

3.2.7.6 pH Determination

Dispersions (1 % $^{w}/_{v}$) of the samples were prepared and their pH measured using a microprocessor pH meter (Hanna Instruments, pH 213, Romania) after standardization with standard buffer solutions (pH 4.0, 7.0 and 9.2 respectively). The procedure was performed three times per sample and the mean calculated (Mbah *et al.*, 2012).

3.2.7.7 Moisture Sorption Profile

The sample (1 g) was spread evenly over the surface of a 0.70 mm tarred aluminium dish. The sample were then placed in a large desiccator containing deionised water in its reservoir to mimic a relative humidity of 100 %, at room temperature. Over a period of 5 days, at regular intervals of 24 h, the weight gained by the exposed sample was recorded and the amount of moisture absorbed was calculated from the weight difference. The percentage moisture sorption was calculated using equation 7(Mbah *et al.*, 2012).

$$Moisture\ Uptake = \frac{M_e}{M_d} \times 100\ \% \quad \text{.....(7)}$$

Where M_e= amount of moisture absorbed and;

M_d= weight of the dry powder

3.2.7.8 Particle Size Distribution

Sieves of different sizes were washed, allowed to dry and arranged such that 500 µm was on top, followed by 250 µm, 150 µm, 90 µm, 75 µm and finally 45 µm. The powder sample (50 g) was then weighed and placed on the uppermost sieve (500 µm) and the cover placed over it. The stack of sieves were then placed on the laboratory sieve shaker (EndecottsLimited, London, UK) and set into vibration for 10 min. The sieves were separated, the powder particles retained on each sieve collected separately and then weighed.

3.2.7.9 Bulk density

The sample (50 g) was weighed and transferred into a 100ml plastic measuring cylinder. The volume occupied was recorded and the bulk density calculated from the expression below:

$$Bulk\ density\ (g/cm^3) = \frac{Weight}{Volume} \quad \text{.....(8)}$$

The procedure was carried out three times and the mean bulk density calculated.

3.2.7.10 Tapped Density

The sample (50 g) was weighed and transferred into a 100ml plastic measuring cylinder using a glass funnel. The cylinder was then dropped continuosly from a 2 cm height onto the work bench until constant volume was attained (200 taps). The volume attained was noted and the tapped density calculated from the expression:

$$Tapped\ density\ (g/cm^3) = \frac{Weight}{final\ \ volume} \quad \text{.....(9)}$$

The procedure was carried out three times and the mean calculated.

3.2.7.11 True Density (D_t)

The fluid displacement method was used for determination of the true density of the samples according to Mbah *et al*. (2012). A density bottle was washed, dried thoroughly in an oven and weighed. The density bottle was filled with xylene as the displacement fluid and weighed. A 1 g quantity of the sample was weighed and transfered into the xylene-containing bottle and then weighed. The true density, D_t was calculated from the relationship:

$$D_t = \frac{W}{[(a+W)-b]} \times SG \quad \text{.....(10)}$$

Where W = weight of the sample

a = weight of density bottle + xylene;

b = weight of density bottle + xylene + sample

SG = specific gravity of the displacement fluid, xylene = 0.863

3.2.7.12 Particle Flow Properties

The static angle of repose was measured according to the fixed funnel and free standing cone method (Etubi *et al*., 2011).

A 50 g quantity of sample was carefully poured into a stoppered glass funnel, clamped 10 cm above a flat surface using a retort stand. The stopper was then removed and the time taken for the powdered sample to flow through, forming a cone, was recorded. The mean diameter and the height of the powder cone formed were measured. The internal angle of repose was calculated using equation 11, while the flow rate was calculated as grams per second. This was repeated thrice and the mean calculated.

$$Angle\ of\ repose = \tan A = \frac{2h}{D} \quad \text{.....(11)}$$

Where *h* = height of the powder cone; *D* = diameter of base of the powder cone.

The compressibility indices and Hausner's ratios of samples EG and CG were determined with the data obtained from the bulk and tapped densities, using equations 12 and 13 below.

$$Compressibility\ (\%) = \frac{Tapped\ \ density - Bulk\ \ density}{Tapped\ \ density} \times 100 \quad \text{.....(12)}$$

$$Hausner's\ Ratio = \frac{Tapped\ \ density}{Bulk\ \ density} \text{.....(13)}$$

3.2.8 Preparation of Salbutamol Sulphate Sustained-Release Tablet Formulations by Direct Compression Method

The formula for preparation of sustained release tablets of salbutamol sulphate, using varying concentrations (30 %, 40 % and 50 %) of the different polymers as matrix former is as shown in Table 3.1. A total of 70 tablets per batch was made. The concentration of salbutamol sulphate was kept constant for all batches and the target weight of each tablet was 200 mg. Salbutamol sulphate and all excipients except talc and magnesium sterate were weighed accurately, after which they were blended in a mortar with the help of a pestle for 5 – 10 min. After mixing, the required amount of talc and magnesium stearate were added and further mixing was done for 4 – 5 min. The powder blends as demonstrated in Table 3.1 were compressed using Erweka EK AR 400 Eccentric Tablet Press (Germany) with the diameter of the punch and die as 8 mm and a compression pressure of 7 KgN. The compressed tablets were of convex round shape.

Table 3.1: Formula for the Formulation of Sustained-Release Salbutamol Sulphate Tablets

INGREDIENTS		BATCH (mg)								
	T (%) $^{w}/_{w}$	T1	T2	T3	T4	T5	T6	T7	T8	T9
Salbutamol sulphate	4	8	8	8	8	8	8	8	8	8
Matrix former	30, 40, 50									
EG		60	80	100	-	-	-	-	-	-
CG		-	-	-	60	80	100	-	-	-
HPMC		-	-	-	-	-	-	60	80	100
Lactose	Qs	126	106	86	126	106	86	126	106	86
Magnesium stearate	1	2	2	2	2	2	2	2	2	2
Talc	2	4	4	4	4	4	4	4	4	4
Target weight	**100**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Key: Extracted acacia gum = EG

Cross-linked acacia gum = CG

Hydroxylpropylmethyl cellulose = HPMC

3.3 Evaluation of the Tablets

All batches of the prepared tablets were evaluated for various tableting parameters as follows:

3.3.1 Weight Variation

For uniformity of weight, twenty tablets from each batch of formulation were selected at random and their individual weights determined by using an electronic balance. The average weight and standard deviation of the tablets were then calculated.

3.3.2 Diameter

Ten tablets from each batch of the formulations were selected randomly and their diameters measured using a digital caliper. The average value of diameter wasthen calculated for each batch.

3.3.3 Thickness

Ten tablets from each batch of the formulations were selected randomly and their thickness measured using a digital caliper. The average value of thickness was calculated for each batch.

3.3.4 Friability

Friability test is performed to evaluate the ability of the tablet to withstand wear and tear during packaging, handling and transportion. Friability test was done using Roche Friabilator. Five (5) tablets were weighed (W_o) and subjected to combined effect of attrition and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inch with each revolution, operated for 100 revolutions. The

tablets where then dusted, reweighed (W) and the percentage friability calculated using equation 14.

$$\%Friability = \frac{W_0 - W}{W_0} \times 100 \quad \text{.....(14)}$$

3.3.5 Crushing Strength

Tablet crushing strength indicates the pressure which is needed to break the tablet. The crushing strength (KgF) of the prepared tablets were determined by using a Monsanto hardness tester. The crushing strength tests was performed for each batch of prepared tablets in triplicate. The average crushing strength and standard deviation were then determined. Crushing strength of 4 kg is considered to be minimum for a satisfactory tablet.

3.3.6 Tensile strength

The equation below adopted from Mahmud *et al.* (2016) was used to calculate the tablet tensile strength for the tablets prepared.

$$T = \frac{2F}{\pi dt} \qquad \text{……..…….…(15)}$$

where T = Tensile strength; F = Crushing strength; d = diameter; t = thickness

3.3.7 Disintegration Test

This test was carried out using the disintegration tester (Coupley DTG 4000, UK). Three tablets selected at random per batch were placed in the cylindrical tubes and set into up and down motion, mimicking the GI movement, using deionized water as the disintegration fluid. The disintegration time was recorded as the time taken for the last palpable fragment of the tablet to leave the mesh in the cylinder (Alderborn, 2013).

3.3.8 Uniformity of Drug Content

Assay of the sustained release tablets of salbutamol sulphate was carried out to find out the amount of drug present in one tablet. Five tablets selected at random wereweighed individually and the mean weight determined. The tablets were then powdered in a porcelain mortar, and 200 mg equivalent of the tablet triturate was taken in a 100 ml volumetric flask. The volume was made up to mark with simulated gastric fluid (0.1N HCl) to give stock solution I. Stock solution I (10 ml) was transferred to a precalibrated 100 ml volumetric flask and diluted up to the 100 ml mark with 0.1N HCl (Stock solution II). The solution was filtered through a filter paper and its absorbance was measured spectrophotometrically (model UVPC 1601, Shimadzu, Kyoto, Japan), with 0.1N HCl as blank, at 277 nm (Afrasim *et al.*, 2012).

3.3.9 *In-vitro* Drug Release Studies

In-vitro release of salbutamol sulphate from sustained release tablets was determined using USP type II dissolution apparatus in 900 ml of 0.1N HCl for two (2) h and phosphate buffer (pH 6.8) for six (6) h at constant temperature of 37±0.5 ° C and 100 rpm. Aliquots (5 ml) of the solutions were withdrawn from the dissolution apparatus at different time intervals and replaced with fresh dissolution medium to maintain the sink condition. These aliquots were then filtered and the absorbance measured using a double beam ultra-violet spectrophotometer (model UVPC 1601, Shimadzu, Kyoto, Japan) at 277 nm against fresh 0.1N HCl (pH 1.0) and phosphate buffer (pH 6.8) solutions as blanks, based on the dissolution media used for a particular sample. The percent drug release and cummulative percent drug released were then calculated using the data obtained from the calibration plot of salbutamol sulphate.

3.3.10 Release Kinetics

Data obtained from *in-vitro* release studies were fitted into various kinetic equations to find out the mechanism of drug release from the polymers. The following kinetic models were used:

$Q_t = Q_0 + K_0 t$ (zero-order equation) .....(16)

$\log C = \log C_0 - \frac{Kt}{2.303}$ (first-order equation) .....(17)

$f_t = Q = K_H \times t^{1/2}$ (Higuchi equation based on Fickian diffusion) ....(18)

$W_0^{1/3} - W_t^{1/3} = Kt$ (Hixon-Crowell) .....(19)

$M_t / M_\infty = Kt^n$ [Korsenmeyer-Peppas equation (power law)] .....(20)

Determining the correlation coefficient helped assess fitness of the data into various kinetic models. The rate constants for the respective models were obtained from the slopes of the graphs plotted.

3.3.11 Statistical Analysis

The results obtained from the tests that required analysis were analysed as mean ± standard deviation (±SD), using Microsoft Excel (Office 2013 version) and the release profiles were analysed using Univariate analysis of variance (IBM SPSS Statistics v20)at significance level of $p \leq 0.05$.

CHAPTER FOUR

4.0 RESULTS

4.1 Sample Collection and Identification

The crude *Acacia seyal* gum exudates was collected from Gombe State, Nigeria. It was identified as *Acacia seyal*, Family *Leguminosae* and given the voucher number 900248 at the Department of Biological Sciences, Ahmadu Bello University Zaria, Nigeria. The picture of the crude acacia exudates is shown in Plate I.

4.2 Extraction and Purification Yield

A 500 g sample of crude *Acacia seyal* gum was used and the yield obtained after purification was 298 g. The percentage extraction yield of the purified *Acacia seyal* gum (EG) was calculated to be 60 %. The picture of the extracted and purified acacia gum flakes is shown in Plate II.



Plate I: Crude *Acacia seyal* gum exudates before purification



Plate II: Purified *Acacia seyal* gum flakes before size reduction

4.3 Cross-link Yield

A 100 g quantity of the purified *Acacia seyal* gum was used for the cross-linking. The quantity of cross-linked gum (CG) recovered was 81 g.

The percentage yield of the cross-linked *Acacia seyal* gum with reference to the crude gum was therefore calculated as 48 %.

4.4 Thermal Analysis Using Differential Scanning Calorimetry (DSC)

The DSC thermograms for the purified *Acacia seyal* gum (EG) and the cross-linked *Acacia seyal* gum (CG) are shown in Figures 4.1 and 4.2 respectively. The test was carried out under a temperature range that span from 50° C to 300 ° C over a period of 25 min.The extrapolated peak of EG was obtained as 49.96° C, while that of CG was 118.10° C. The minimum heat flow of EG is – 6.12 mW at 88.13° C, while the maximum was 18.65 mWat 300.41° C. CG on the other hand had a minimum heat flow of – 3.48 mW at 197.67° C and a maximum of 10.09 mW at 300.59° C. The two samples showed similarities in degradation temperature with EG having 300.41 ° C, while CG had 300.59 ° C. The appearance of a new peak at about 240 – 250 ° C on the thermogram of CG, which was not present on EG is an important event to note.

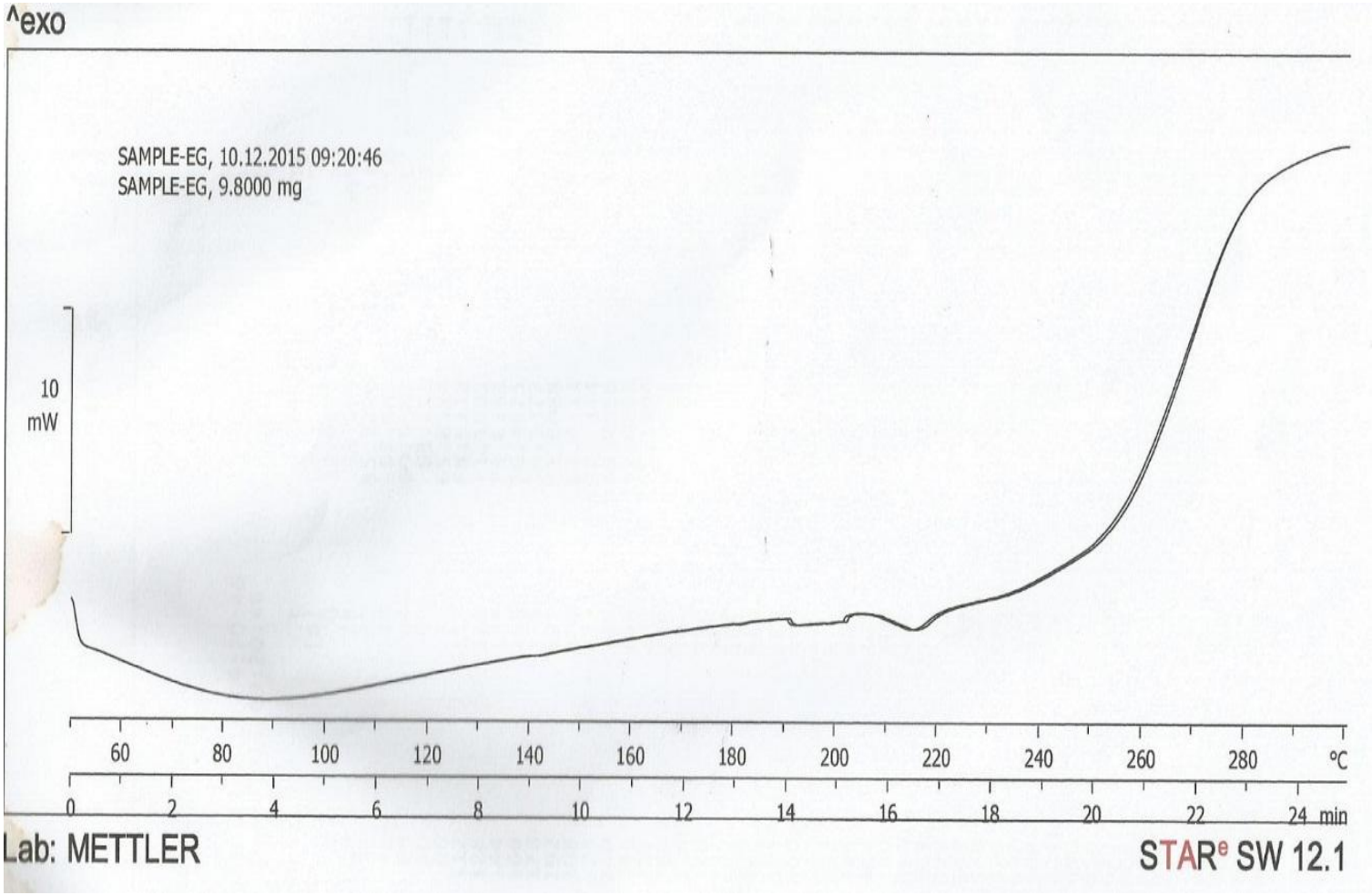


Figure 4.1: DSC thermogram of the purified*Acacia seyal*gum (EG)

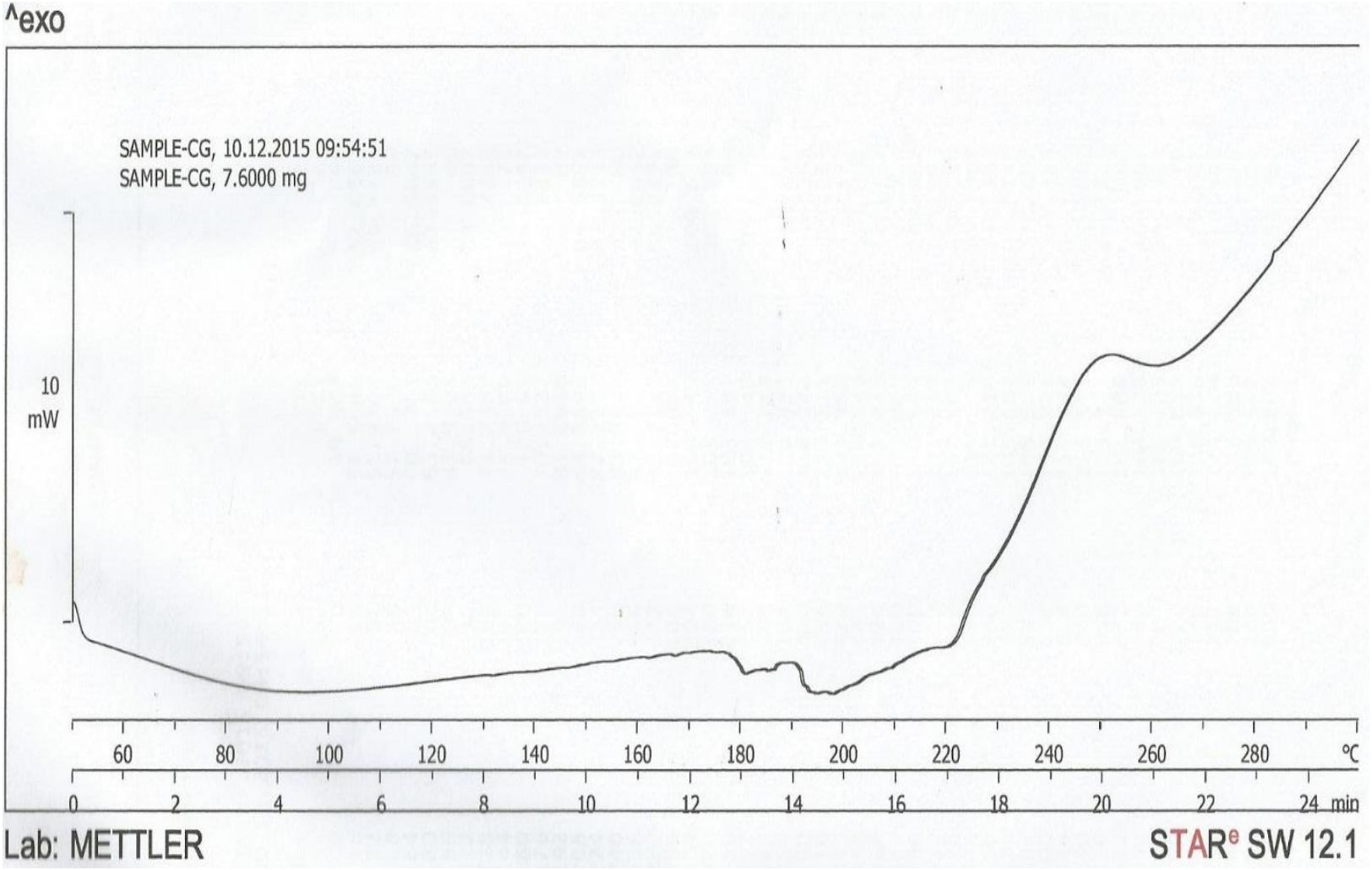


Figure 4.2: DSC thermogram of the cross-linked *Acacia seyal* gum (CG)

4.5 Fourier Transform Infra-Red (FT-IR) Studies

The FT-IR spectrum for EG is depicted in Figure 4.3, while Figure 4.4 depicts that of CG. The FT-IR spectrum of EG shows characteristic bands, which are associated with the simple sugars of carbohydrates. The H bonded O-H group stretching and the C-H methylene stretching which are characteristic of carboxylic acid at positions 3421.04 and 2928.30 respectively of EG were retained in the cross-linked polymer (CG) at positions 3412.75 and 2929.66 respectively. On the spectra of CG, the appearance of bands at positions 1845, 1793 and 878 are worthy of note. The polymer backbones of EG were however mostly retained in CG. On the spectra of EG, absorption bands appeared at positions 599.58 and 544.99 but on the spectra of CG, a band at position 668.53 replaced the 599.58 absorption band.

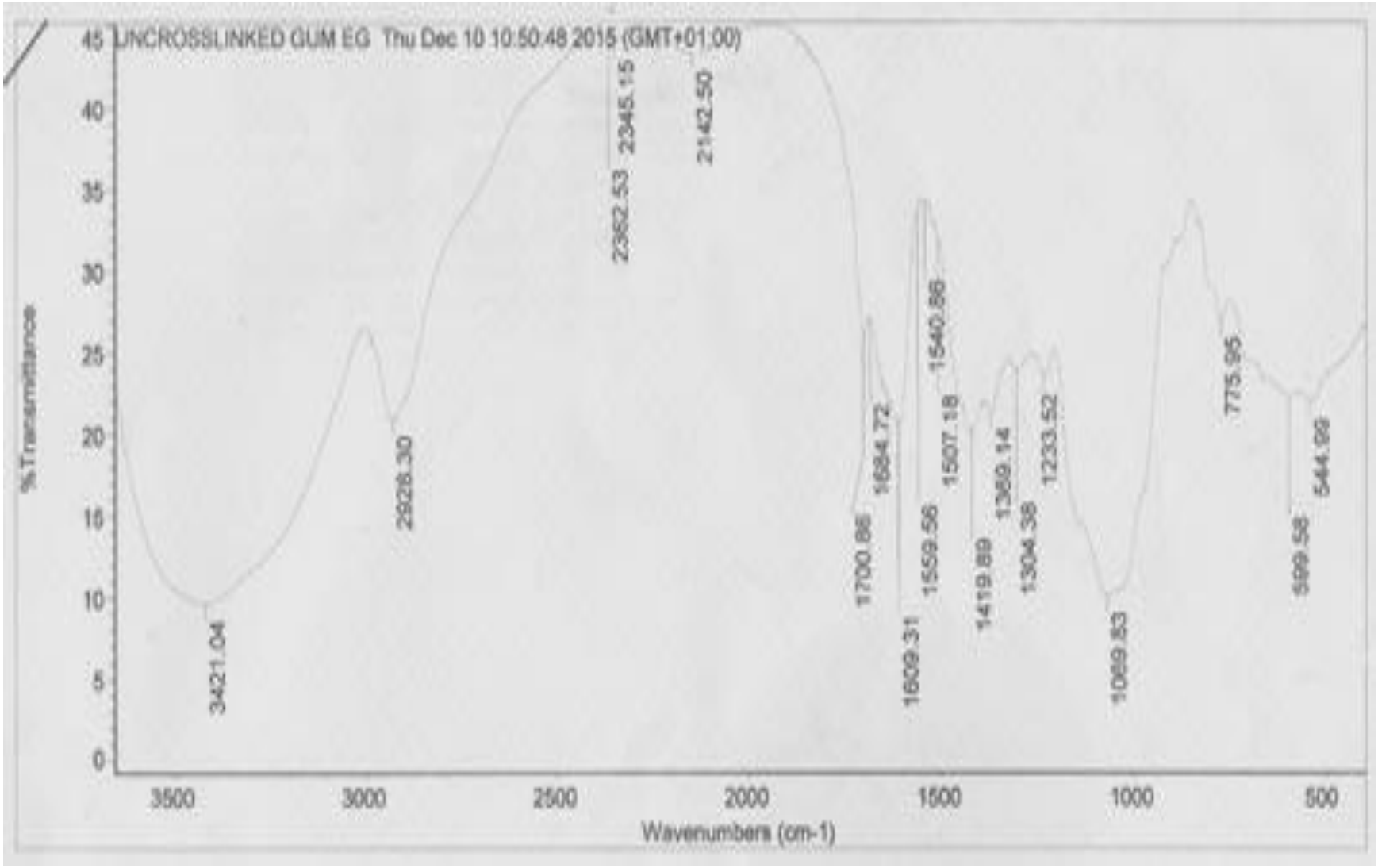


Figure 4.3: FT-IR spectra of the purified *Acacia seyal* gum (EG)

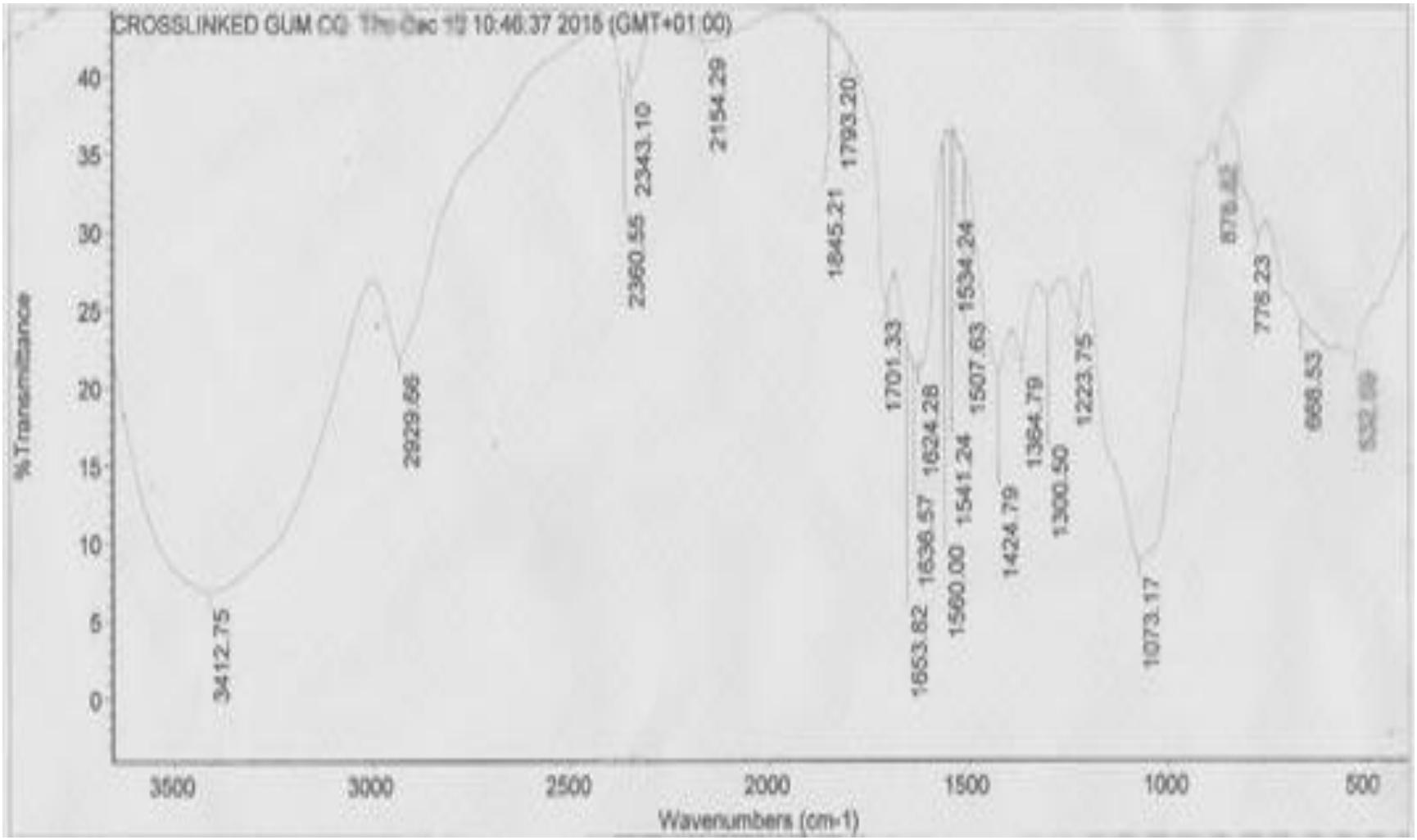


Figure 4.4: FT-IR spectra of the cross-linked *Acacia seyal* gum (CG)

4.6 Organoleptic and Some Physicochemical Characteristics

The results of organoleptic and physicochemical properties of EG and CG is shown in Table 4.1. EG showed an off-white colour, which was slightly glossy in appearance while the colour of CG was light brown. EG and CG were both gritty and had a slightly acidic tastethough, CG presented with a slight astringent feel on the tongue. They were both odourless.The moisture loss on drying (%) carried out showed EG had a higher percentage moisture than CG, with values of 12.00 ±1.00 % and 7.00 ±0.5 % respectively. The ability of EG and CG to go into solution in various solvents (selected based on polarity) was demonstrated. EG was soluble (0.1056 g/ml) in water at 30 ° C, while CG was sparingly soluble (0.0736 g/ml). In the other solvents however, both EG and CG were insoluble. The kinematic viscosity of EG was 2,397 mPas, while that of CG was lower, having a value of 1,569 mPas. The swelling ratio of EG was found to be 0.37±0.04, with a swelling rate of 0.015±0.001 ml/h while that of CG was 0.63±0.25, with a swelling rate of 0.03±0.01 ml/h. This shows that CG has a better capacity to swell and at a faster rate too.The hydration capacity of EG was higher than that of CG with values of 2.31±0.035 and 1.62±0.090 respectively.The pH of EG at 25 ° C was found to be 5.52 ± 0.08 (slightly acidic). The crosslinking seems to have reduced the acidity by increasing the pH towards neutrality thus, CG at 25 ° C was found to have a pH of 6.25 ± 0.11.

Table 4.1: Organoleptic and Some Physicochemical Characteristics of the Powdered Polymers

PROPERTY	**EG**	**CG**
Colour	Off-white colour	Light brown colour
Texture	Gritty	Gritty
Taste	Slightly acidic	Slightly acidic
Odour	Odourless	Odourless
Moisture Loss on Drying (%)	12.00±1.00	7.00±0.50
Aqueous Solubility (g/ml)	Soluble	Sparingly soluble
	0.1056	0.0736
Viscosity (mPa.s)	2,397	1,569
Swelling Ratio	0.37±0.04	0.63±0.25
Swelling Rate (ml/h)	0.015±0.001	0.03±0.01
Hydration Capacity	2.31±0.035	1.62±0.090
pH (25 ° C)	5.52±0.08	6.25±0.11

Key: ± Standard deviation

4.7 Moisture Sorption Profile

A graphical representation of the moisture sorption profiles of EG and CGis presented in Figure 4.5. It can be seen that CG possess a higher moisture sorption ability compared to EG as was observed over a period of 5 days. There was more moisture sorption on the first day for both polymers but on the subsequent days, moisture sorption was not so pronounced.

4.8 Particle Size Distribution

The comparative particle size distribution of EG and CG is presented as histogram in Figure 4.6, with both powders having particles distributed majorly between 75 µm and 250 µm. EG is shown to have more particle proportions that skewed towards the larger sizes, with a mean particle diameter of 149.45µm,while CG has more particle proportions that skewed towards the smaller sizes, with a mean particle diameter of 139.08µm.

4.9 Flow Properties

The flow properties of the powdered polymers (EG and CG) are presented in Table 4.2. The bulk, tapped and true densities of EG were found to be higher than those of CG. The higher densities of EG as against CG resulted to its higher Carr's compressibility index, Hausner's ratio and flow rate as observed. EG was also found to possess a higher angle of repose compared to CG but both were however above 30°.

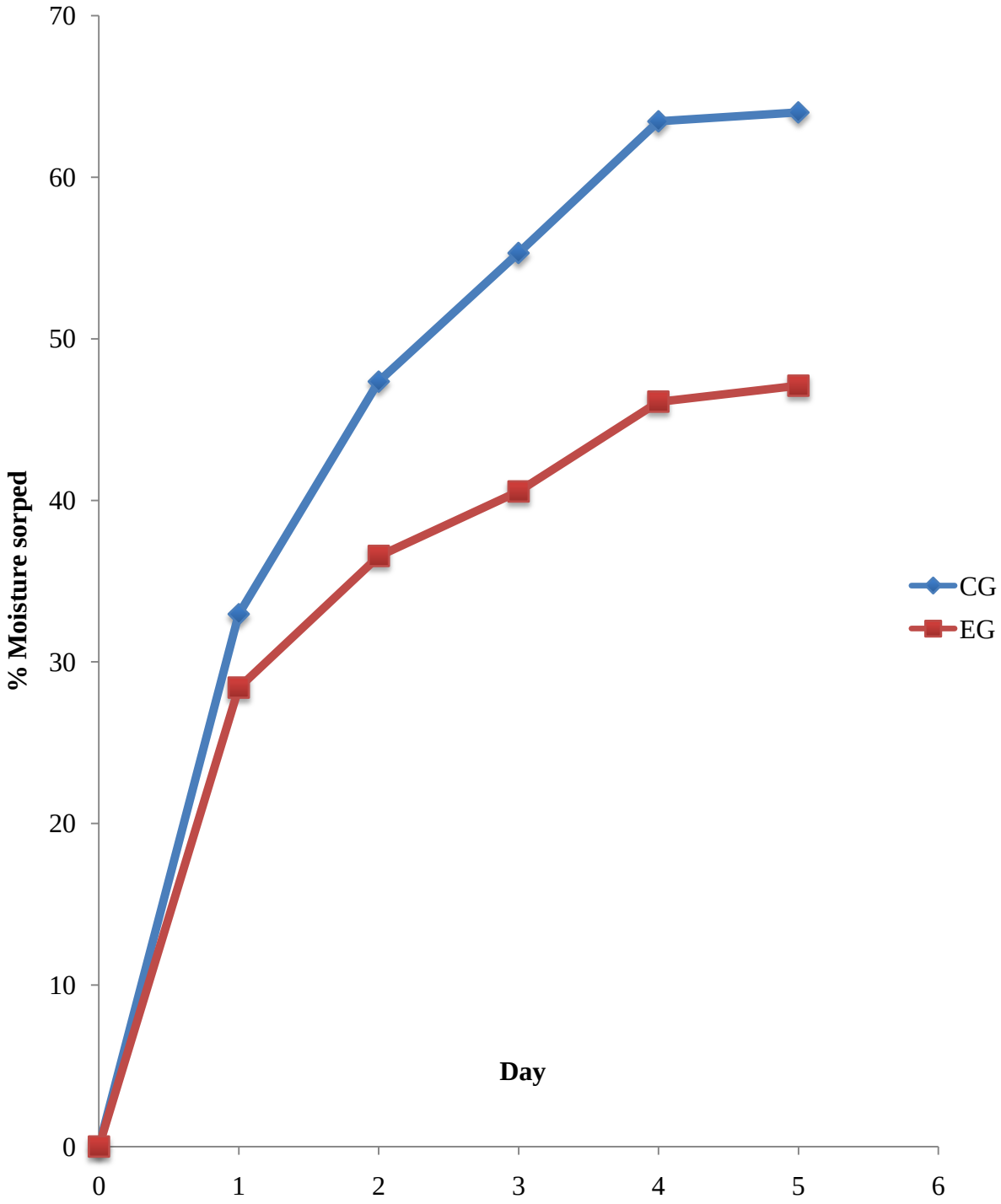


Figure 4.5: Moisture sorption profiles of EG and CG

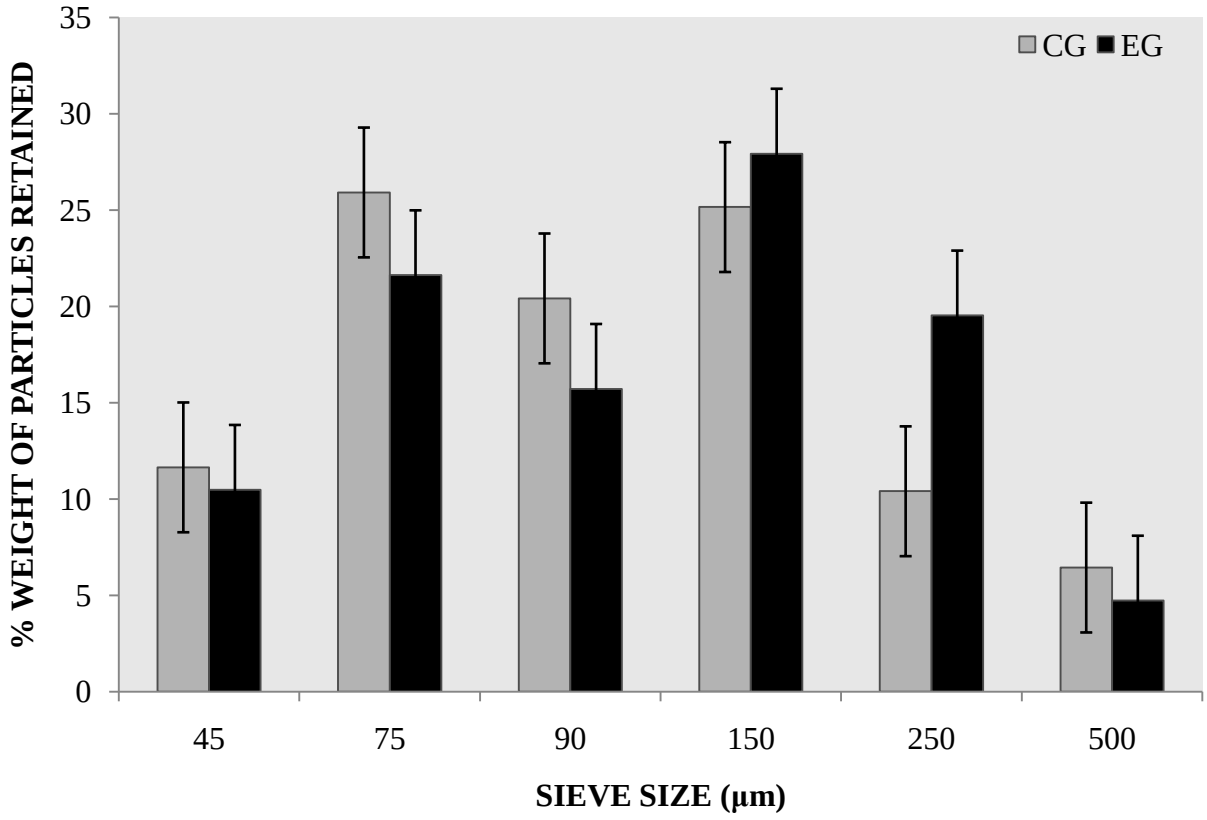


Figure 4.6: Histogram showing percent frequency of particles retained on each sieve

Key: EG = Extracted gum; CG = Cross-linked gum

Table 4.2: Flow Properties of the Powdered Polymers

S/No.	PARAMETER	EG	CG
1	Bulk density (g/cm^3)	0.72±0.01	0.63±0.01
2	Tapped density $_{(200\ taps)}$ (g/cm^3)	0.92±0.01	0.74±0.01
3	True density (g/cm^3)	1.438 ±0.00	1.199±0.00
4	Flow rate (g/s)	4.73±0.26	3.39±0.14
5	Angle of repose (^{o})	35.04±1.68	33.29±1.00
6	Compressibility index (%)	21.77±0.35	15.81±0.58
7	Hausner's ratio	1.28±0.01	1.19±0.01

Key: ± Standard deviation

4.10 Tablet Formulation Properties

The properties of salbutamol sustained-release tablets compressed using varying concentrations of the three (3) polymers as matrix formers are as shown in Table 4.3. Compression pressure was kept at 7KgF on an Erweka rotary press, using a punch size of 8 mm.

The tablets formulated showed some uniformity in weight and diameter across batches and this is evident in the low standard deviations observed. The thickness however varied between batches with T5 having the lowest mean thickness, while T9 had the highest mean thickness. The thickness of T1, T2 and T3 (EG as matrix) were fairly uniform, between 3.44 – 3.48 mm, while thickness of T4, T5 and T6 (CG as matrix) ranged between 3.43 – 3.45 mm. T7, T8 and T9 (HPMC as matrix) had higher thickness, ranging between 3.55 – 3.85 mm.

The friability varied between batches but was generally below 1%. Batches with CG as matrix (T4, T5 and T6) showed the lowest friability, while batches of EG as matrix (T1, T2 and T3) and HPMC as matrix (T7, T8 and T9) had higher degree of friability. The crushing strengths varied between batches, with T8 having the lowest as against T4 that had the highest crushing strength. This same pattern was reflected on the tensile strengths of the various batches.

The tablets formed in all batches did not breakup during the disintegration test but rather eroded gently. Within the EG matrix batches (T1, T2 and T3), T2 had the lowest disintegration time, while T3 had the highest. Within the CG matrix batches (T4, T5 and T6), T5 had the lowest disintegration time, while T6 had the highest. Within the HPMC matrix batches (T7, T8 and T9), T7 had the lowest disintegration time, while T9 had the highest. Comparing between batches of the three (3) different polymers based on the concentration of the polymer used as matrix former (30 $\%^{w}/_{w}$, 40 $\%\ ^{w}/_{w}$ and 50 $\%\ ^{w}/_{w}$), at 30 $\%\ ^{w}/_{w}$ matrix concentration, (T1, T4 and T7), T7 had the lowest disintegration time (131.00±6.12 min) while T4 had the highest disintegration time

(283.33±63.25 min). At 40 % $^{w}/_{w}$ matrix concentration (T2, T5 and T8), T2 had the lowest disintegration time, while T5 had the highest time (237.33±53.15 min). At 50 % $^{w}/_{w}$ matrix concentration (T3, T6 and T9), T3 had the lowest disintegration time (292.33±48.53 min), while T6 had the highest disintegration time (382.00±56.04 min).On a general note, batch T7 had the lowest disintegration time of 131.00±6.12 min, while T6 had the highest disintegration time of 382.00±56.04 min.

The drug content uniformity test result shows T5 having the highest drug content of 108.8 % while T6 had the lowest drug content of 90.2 %. However, all were within the approved U.S.P. range of 90 – 110 % for oral tablet formulations.

Table 4.3: Properties of Formulated Sustained-Release Salbutamol Sulphate Tablets

Batch	Weight variation (g±SD)	Diameter (mm±SD)	Thickness (mm±SD)	Friability (%)	Crushing strength (KgF±SD)	Tensile strength (Nm^{-2})	Disintegration time (min)	% Drug content
T1	0.204±0.004	8.01±0.009	3.48±0.026	0.48	10.2±0.327	2.33	246.07±42.080	95.592
T2	0.201±0.004	8.02±0.004	3.44±0.032	0.50	9.0±0.655	2.08	198.00±76.440	103.009
T3	0.202±0.003	8.02±0.006	3.44±0.017	0.50	8.7±0.356	2.01	292.33±48.530	96.829
T4	0.202±0.003	8.02±0.005	3.45±0.025	0.49	11.4±0.665	2.62	283.33±63.250	97.241
T5	0.201±0.004	8.02±0.007	3.43±0.031	0.49	10.3±0.294	2.38	237.33±53.150	108.778
T6	0.201±0.004	8.01±0.005	3.45±0.023	0.48	10.0±0.602	2.30	382.00±56.040	90.236
T7	0.203±0.004	8.02±0.005	3.55±0.035	0.50	8.7±0.340	1.94	131.00±6.120	99.301
T8	0.202±0.004	8.02±0.004	3.76±0.038	0.50	8.5±0.411	1.79	211.00±4.140	92.708
T9	0.203±0.003	8.01±0.008	3.85±0.048	0.48	9.9±0.294	2.04	313.33±9.050	93.120

Key: ± Standard deviation

T1 = 30 % EG as matrix T4 = 30 % CG as matrix T7 = 30 % HPMC as matrix

T2 = 40 % EG as matrix T5 = 40 % CG as matrix T8 = 40 % HPMC as matrix

T3 = 50 % EG as matrix T6 = 50 % CG as matrix T9 = 50 % HPMC as matrix

*EG = Extracted acacia gum

*CG = Crosslinked acacia gum

*HPMC = Hydroxylpropylmethyl cellulose.

4.11 Dissolution Studies

Comparing the cumulative percent released over a period of 8 h, based on different percent proportion of the same polymer used as matrix former, it can be seen from Figure 4.7 that when EG was used as the matrix former at varying proportions, T1 (30% $^{w}/_{w}$) showed an intermediate cumulative percent release, while T2 (40% $^{w}/_{w}$) showed the lowest cumulative percent release (85.7 %). T3 (50% $^{w}/_{w}$) with the highest proportion of matrix former however showed the highest cumulative percent release, with about 97.3% of the salbutamol sulphate being released at about 4 h into the dissolution and then dropping continuously over the remaining 4 h of the dissolution period. T4 showed the lowest cumulative percent released over time, attaining a maximum of 78.8 % at 8 h, while T6 attained a cumulative percent release of 80.4 % at 8 h. Finally, T5 attained a cumulative percent release of 82.5 % at 8 h. From Figure 4.7, it can be seen that at about 3 h into the dissolution process, T7 had a percent cumulative release of 128.4 %, while T8 has a percent cumulative release of 124.1 % and T9 has a percent cumulative release of 117.7 %. For all batches (T7, T8 and T9), there was a decrease in the percent cumulative release at the 4th h of dissolution.

Comparing the cumulative percent released based on the percent proportion of the polymer used in the formulation, T1, T4 and T7 (30% $^{w}/_{w}$ polymer proportion), T1 showed an intermediate cumulative percent release, while T4 showed a lower cumulative percent release and finally T7 showed the highest cumulative percent release over the entire 8 h dissolution period. For T2, T5 and T8 (40 % $^{w}/_{w}$ polymer proportion), T2 showed an intermediate cumulative percent release, T5 showed a lower cumulative percent release, while T8 showed the highest cumulative percent release over the 8 h dissolution period. Finally, at 50 % $^{w}/_{w}$ polymer proportion, it can be seen that T3 had an intermediate cumulative percent release, while T6 has the lowest and T9 has the

highest cumulative percent release. Comparing between polymers used to make the matrix, T1, T2 and T3 (EG matrices) showed an intermediate cumulative percent release; T4, T5 and T6 (CG matrices) showed a lower cumulative percent release; and finally, T7, T8 and T9 (HPMC matrices), which served as the control for this study showed a higher cumulative percent release over the entire 8 h period of the dissolution test.Overall, T4 showed the lowest cumulative percent release, while T7 showed the highest cumulative percent release over time.

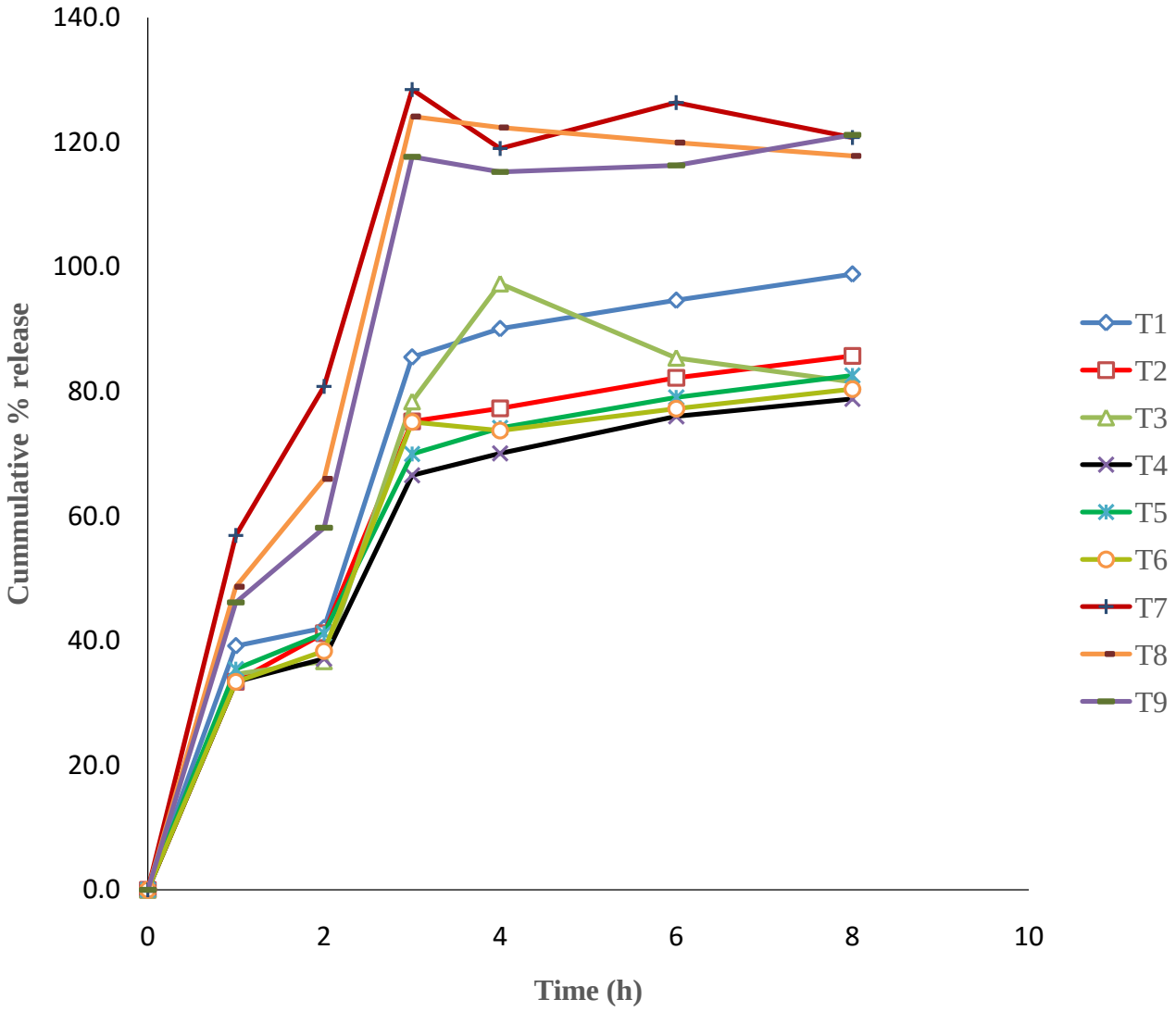


Figure 4.7: *In vitro* release profile of salbutamol sulphate from all batches (T1 – T9) of the matrix tablets carried out in pH 1.0 (for 2 hours) and then changed topH 6.8 (for 6 hours), to mimic stomach and intestinal pH respectively.

Key:

T1 = 30 % $^{w}/_{w}$EG T4 = 30 % $^{w}/_{w}$CG T7 = 30 % $^{w}/_{w}$HPMC

T2 = 40 % $^{w}/_{w}$ EG T5 = 40 % $^{w}/_{w}$ CG T8 = 40 % $^{w}/_{w}$HPMC

T3 = 50 % $^{w}/_{w}$ EG T6 = 50 % $^{w}/_{w}$CG T9 = 50 % $^{w}/_{w}$ HPMC

*EG = Extracted acacia gum *CG = Crosslinked acacia gum

*HPMC = Hydroxylpropylmethyl cellulose.

4.12 Mathematical Models of Formulated Matrix Tablets

A multi model release kinetic was observed in this study for the various formulations based on the dissolution data fitted into the different release models. The mathematical models were used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data was selected based on the correlation coefficient (R^2) value in various models. The model that gave higher "$R^{2"}$ value is considered as the best fit of the release data. It was observed that for the first order kineticsas shown in Table 4.4, all the *k*-values were negative.It can also be seen from the R^2 values that Higuchi release kinetics was the most predominant release pattern for all the formulations except T1, which showed a predominantly first order kinetic release pattern.

The *n*-values showed batch T7 having the lowest value of 0.3838, while batch T1 has the highest value of 0.5116. However, except for batch T7, all batches had*n*-values ≥ 0.45 but < 0.89.

Table 4.4: Release kinetics and mechanism of salbutamol sulphate transport from the sustained-release tablets formulated

BATCHES	RELEASE MODELS					
	ZERO ORDER	FIRST ORDER	HIGUCHI	HIXSON CROWELL	KORSMEYER PEPPAS	
	R^2	R^2	R^2	R^2	R^2	*n*-Value
T1	0.76	0.9666	0.9100	0.6807	0.8224	0.5116
T2	0.7565	0.877	0.9206	0.6899	0.8624	0.4974
T3	0.628	0.3552	0.8039	0.5095	0.7124	0.5103
T4	0.7704	0.8799	0.9327	0.7251	0.8627	0.4675
T5	0.7619	0.8881	0.9347	0.7263	0.8777	0.4513
T6	0.7177	0.7953	0.8931	0.6382	0.8117	0.4723
T7	0.6119	0.6907	0.8472	0.5148	0.7714	0.3838
T8	0.6292	0.683	0.8346	0.515	0.7611	0.4662
T9	0.6952	0.6778	0.8702	0.5956	0.7996	0.5082

Key:

Zero order if $R^2 \geq 0.975$, near Zero order if $R^2 \geq 0.950 < R^2 < 0.975$

No Zero order if $R^2 \leq 0.950$.

Fickian diffusion: $n \leq 0.45$;

Anomalous diffusion or Non-Fickian diffusion (refers to combination of both diffusion and erosion controlled rate release): $0.45 < n < 0.89$

Case II relaxation or super case transport II (refers to erosion of the polymeric chain):

n = 0.89 and above. (Mahmud *et al*., 2016; Nep *et al.*, 2016)

4.13 Statistical Analysis

Statistical analysis of the formulated matrix tablets (T1 – T9), made with varying proportions (30, 40 and 50 % $^{w}/_{w}$) of the matrix materials (EG, CG and HPMC), as performed using Univariate Analysis of Variance was to examine the difference in the average drug release profileat$p \leq 0.05$. The descriptive statistics observed that T4 has the minimum mean release of salbutamol, while T9 has the maximum mean release of salbutamol.The tests of between-subjects effects showed a statistically significant difference ($p = 0.000$) in the release profile of the three (3) different polymers used as matrix former.The effect of the proportion of use of the various polymer materials used as matrix formers in the release of salbutamol sulphate from the tablet formulations gave a*p-value* of 0.534. Turkey's test comparing EG with CG gave a mean difference of 6.86279 and a significance of 0.26. Turkey's test comparing HPMC with EG gave mean difference of 11.49004 and a significance of 0.000, while comparing HPMC and CG gave a mean difference of 18.35283 and a significance of 0.000.

CHAPTER FIVE

5.0 DISCUSSION

Natural biopolymers from plant sources contain many impurities (e.g., fat, protein, fiber, natural pigment and endogenous enzymes), therefore, an efficient purification process is recommended to minimize these impurities and consequently improve the functional properties of the biopolymer (Amid and Mirhosseini, 2012). The extraction yield of 60 % obtained on purification of the crude *Acacia seyal* gum can be justified as the presence of impurities in the crude exudates could add to the weight of the sample. The extraction and purification process is expected to have lowered or removed these impurities considerably so that the weight of the gum recovered was reduced. A yield of 48 % with reference to the crude exudates, obtained after cross-linking EG with calcium chloride is most likely associated with the quality of the extraction process. There is however possibility that both yields could have been affected by loss of materials due to the difficulty in totally recovering the gum from the sieve cloth and/or due to spillage but, these were considerably taken care of by adhering to precautions. The purification yield value was higher than the purification yield reported for fenugreek gum (22 %) (Brummer *et al*., 2003), locust bean gum (26.66 % to 33.16 %) (Bouzouita *et al*., 2007) and within the range reported for guar gum (22 % to 78 %) (Cunha *et al*.,2007) and for durian seed gum (30.9 % to 72.4 %) depending on the purification method (Amid and Mirhosseini, 2012). The crosslink yield (48 %), was lower than the value reported for crosskinked high amylose starch (95 %) (Pawar *et al*., 2013). Generally, the more processing procedures or steps, the more the chances that the yield is expected to reduce. The quality of the acetone used as precipitating agent, the time of exposure to the

precipitating agent and the method used may also have affected the yields obtained (Cunha *et al*., 2007;Amid and Mirhosseini, 2012; Abdulsamad *et al.,* 2012).

The result from DSC studies, Figures 4.1 and 4.2, revealed that the cross-linked gum (CG) had a higher extrapolated peak of 118.10° C, while the extrapolated peak of EG was 49.96 ° C. The events shown between 24 to 100 ° C may be attributed to evaporation of solvent (Silva, 2006). The minimum heat flow of EG is – 6.12 mW at 88.13 ° C, while the maximum had 18.65 mW at 300.41 ° C. CG on the other hand had a higher minimum heat flow of – 3.48 mW at 197.67 ° C and a maximum of 10.09 mW at 300.59 ° C. The two samples showed similarities in degradation temperature because of their insignificant difference, 300.41 ° C and 300.59 ° C for EG and CG respectively, that fall within the maximum degradation temperature range of 270 – 320 ° C determined for polysaccharides by Silva (2006). This shows that, and as the name connotes, cross-linking did not tamper with the structural framework of the CG but simply linked strands of the polymer. The appearance of a new peak at about 240 – 250 ° C at about 20 min into the scanning process on the thermogram of CG, which was initially absent on the thermogram of EG is an important event to note as the appearance or disappearance of peak(s) suggests the formation of new bonds or structures (Saunders, 2008).The modification of the gum may have led to these changes in the heat thermogram of CG, suggesting that it may be as a result of a stronger bond between molecules of the polymer chain. Abdulsamad *et al.* (2014) observed that cross-linking of cashew gum with epichlorohydrin led to the slight increase in the degradation temperature and opined that this may be as a result of the presence of "impurities" which are most likely the cross-linking agent. The appearance and disappearance of a peak may also be used to denote

modification in structure of compounds, as a result of addition or removal of some groups. This also goes to show that CG has a higher degree of stability in the presence of heat than EG.

A Fourier transform infra-red (FT-IR) spectrum involves an observation of the vibrational patterns of molecules as this is considered to be a unique physical property and is characteristic of the molecule (Coates, 2000). Generally as shown in Figures 4.2 and 4.3, there was retention of some bands in the polymer backbone as shown by hydrogen bonding, which has a significant influence on the peak shape and intensity, causing the broadening of the peak as it ranges between 3500 - 2400 cm^{-1} (Hsu, 1997). There was retention of the bands at positions 2928.30, which indicates C–H (Methylene) stretching and at position 1609.30, which indicates –C=C – stretch. On the spectra of CG, the appearance of bands at positions 1845 and 1793 cm^{-1}which are within the group frequency suggestive of carbonyl compounds and 878 cm^{-1}, which is within the group frequency assigned for C=O stretch for oxy compounds may be indicative of a change caused by the cross-linking process. Finally, the 668.53 cm^{-1} band of CG replaced the 599.58 cm^{-1}absorption band of EG. This may be an indication of a replacement reaction due to the crosslinking agent as generally, peak values < 667 cm^{-1}indicate the presence of iodide or bromide ions, while values between 800 – 600 $cm^{-1}$are indicative of chloride ions (Coates, 2000). These may serve as a pointer that the cross-linking has taken place as appearance, disappearance or broadening of absorption band(s) on the spectra of CG in comparison with that of EG was used to assess the crosslinking of the purified gum.

From the results shown in Table 4.1, sample EG had an off-white colouration but on cross-linking, CG showed a darker colouration which was brownish although, both were

gritty in texture. This change in colour intensity is most likely as a result of the addition of new substances introduced by the cross-linking process or as a result of the drying process, which may have denatured some of the surface polymers. The slightly acidic taste of EG and CG implies that the polymers may be used in tableting without the need for sweetening agent. Both gums being odourless implies that there is no need to add flavourants to the tablet formulation and this justify their use in tableting, as patients prefer medicines that are either odourless or of a nice fruity aroma.

The moisture loss on drying (%) gives a quantitative view of the amount of volatile matter of any kind that is driven off under any specified condition (Abdulsamad *et al.*,2015). From Table 4.1, the moisture loss on drying was found to be 12.00±1 % and 7.00±0.5 % for EG and CG respectively. This shows that EG has a fairly higher moisture content than CG and this result is similar to the report by Mbah *et al.* (2012), who reported a moisture content of 14.00±1.32 % for the natural acacia (*Acaciasenegal*) polymer and 5.00±0.90 % for its cross-linked derivative. In an evaluation of cashew gum cross-linked with citric acid by Abdulsamad *et al.* (2015), a loss on drying (%) of 8.47 for the crude gum and 7.21 for the cross-linked gum was reported. The result reported in this study therefore showed a similar pattern of moisture loss on drying (MLD %), with the cross-linked gum having a lower moisture content compared to the purified gum. According to Kibbe (2000), official recommendations specify that MLD of acacia should be $\leq$ 15 % and the values obtained in this study falls within this recommended limit. As such, CG might be less prone to microbial contaminations because of its lower moisture content. The ability of the two polymers to go into solution in various solvents selected based on polarity showed that they were both insoluble in all other solvents (diethyl

ether, DMF sulfoxide, toluene, ethyl acetate, isopropanol and ethanol) except in water (30 ° C) as shown in Table 4.1, which was able to dissolve EG and form a soluble solution (0.1056 g/ml) while CG formed a very cloudy dispersion described as sparingly soluble (0.0736 g/ml). This agreed with results obtained based on visual observation by Abdulsamad *et al*. (2014), when cashew gum was cross-linked with epichlorohydrin. The reduced solubility of CG in water when compared to EG could be as a result of the presence of certain ions such as calcium, which when present in large amount causes aqueous insolubilities of gums (Oppong and Kipo, 2012). It can thus be said that cross-linking reduces solubility or even renders a soluble material insoluble (Peppas *et al.*, 2000). This also buttresses the fact that the polymers are hydrophilic in nature, though the cross-linking process reduced the degree of hydrophilicity.

The kinematic viscosity shown in Table 4.1, as obtained using an Ostwald viscometer showed that CG has lower viscosity (1,569 m.Pas) compared to EG (2,397 m.Pas). It can be said that because of the insolubility of CG, it did not have the capacity to form a smooth gel and as such this may have led to the lower viscosity observed when compared to EG which was able to fully go into solution, forming a gel that is able to cause the increase in the bulk viscosity. According to Alderborn (2007), bulk viscosity is not a good test for the functionality of true gels as a type of hydrophilic matrix system and does not generally correlate well with diffusion thus, justifying the application of CG in sustained release tableting.

Swelling, described as the increase in weight, volume or length has an important place in defining the performance of a polymeric material with regards to solute diffusion in drug delivery. Hydrophilic cross-linked polymers owing to their swelling capacity have found

use as swellable matrices, superdisintegrants and swelling devices in drug delivery (Abdulsamad *et al.,* 2014). The purified gum even though it absorbed some amount of water as shown by the moisture sorption profile in Figure 4.5 and the hydration capacity as shown in Table 4.1, did not swell as much as the cross-linked gum, but rather most of it went into solution because of its high solubility, and this result is similar to the report by Abdulsamad *et al*. (2012). Cross-linking EG caused the material to take up more liquid without going into solution, as the structural integrity of the gum was retained, thus imparting a notable swelling property on the polymer (CG). This may be because the macroporous structures of the cross-linked polymer make transfer of water molecules easier between the polymer matrix and the external aqueous phase (Abdulsamad *et al.*, 2015). CG can thus be employed as a disintegrant in tablet formulation studies.

Hydration capacity indicates the degree to which a material is capable of absorbing its own equivalent weight of water or how the gum retains water or how rapid water penetrates the gum (Ohwoavworhua, *et al*., 2004; Kipo *et al.,* 2014). The hydration capacity of EG, being higher than that of CG as shown in Table 4.1, goes to show that CG may have become more hydrophobic due to less inter-particulate spaces arising from the bridging of the ionic moiety and the polymer chain, resulting to its insolubility and thus its inability to absorb large quantity of water. A similar pattern was reported by Moin *et al.* (2014), who investigated the potential of cashew gum and its cross-linked derivative in formulating sustained release delivery system using theophylline as a model drug. They reported a strong degree of water uptake (hydration) by the cashew gum formulations (184.6 %), while in contrast; the cross-linked cashew gum formulations displayed a much-lowered increase (66.5 %). Determination of the water holding

capacity of a hydrogel made from carbohydrate polymers for use in foods and pharmaceuticals is required to provide information on the storage and handling precautions to be adopted to avoid spoilage of the product (Abdulsamad *et al.,* 2015).

The moisture sorption profile of a material tells of its sensitivity to moisture and its stability under humid conditions. In both polymers, the moisture sorption as shown in Figure 4.5, rose sharply on the first day but reduced as the days went by, indicating the beginning of saturation. As such, CG is expected to have the capacity to do better in humid conditions as its matrix will be retained while EG when used as a matrix may deteriorate at a faster rate and to a greater extent too. This may result in EG being affected more by microbial contaminants compared to CG and as such; CG can be applied comfortably in tableting to minimize the storage challenge that may arise in relatively humid environments.

As shown in Table 4.1, the pH of EG (5.52±0.08) was found to be lower than that of CG (6.25±0.11), implying that the cross-linking process has reduced the acidity of EG, taking it closer towards neutrality. Generally, acacia gum is known to be naturally neutral to slightly acidic (British Pharmacopoeia, 2004). The result obtained is similar to that reported by Mbah *et al*. (2012), who showed a pH of 4.730±0.78 and 7.730±0.50 for natural and cross-linked acacia respectively, stating that the increase in pH may be attributed to replacement of hydrogen ion-containing moiety in the polymer chain network and this may reduce the adhesive property. This neutralization of the gum by the cross-linker may also lead to the formation of a stronger ionic bond due to better inter chain hydrogen bond that reduces the electrostatic repulsion within the gum network (Rana *et al.,* 2011).

From Table 4.2, the bulk, tapped and true densities of EG being higher than those of CG imply that EG is denser than CG. The lower densities of CG may have resulted in its improved compressibility index and Hausner's ratio. The compressibility index and Hausner's ratio of a powder are pointers to the powder's ability to diminish in volume and its degree of inter-particulate friction respectively (Alderborn, 2007). It is reported that compressibility index below 16 % is indicative of good powder flowability and values above 35 % are indicative of cohesiveness while Hausner's ratio greater than 1.25 is indicative of poor flow. For pharmaceutical powders, an angle of repose ranging between 25 ° – 45 ° is said to be satisfactory and signifies a good flow. These three parameters are considered as an indirect measurement of powder flowability. In this study, the particle size distribution, Figure 4.6, showed EG to have more coarse particles than CG, with mean particle diameters of 149.45 µm and 139.08 µm respectively. The angle of repose (33.29±1.00 °), compressibility index (15.81±0.58 %) and Hausner's ratio (1.19±0.01) all suggest that CG has fairly better flowability than EG and his result followed a similar pattern as reported by Mbah *et al.* (2012). The relatively smaller angle of repose of CG compared to EG may be attributed to the fairly better particle size distribution of CG. CG however was found to interestingly have a lower flow rate than EG even though it had better compressibility index, Hausner's ratio and angle of repose. This however may be attributed to the presence of less coarse particles in CG compared to EG which had more coarse particles, as the smaller particles have larger surface area which may inhibit flow due to surface friction. On a general note however, both powders showed properties that were within both B.P and U.S.P recommendation of good flowability.

The ease, simplicity and requirement for absence of moisture due to the formulation components informed the choice of direct compression method for this research. Although the choice of manufacturing processes such as direct blending or granulation typically does not affect product performance significantly, however exceptions do exist (Siegel and Rathbone, 2012).

Weight variation is mainly due to poor flow of material into the die, which leads to improper filling of the die. Weight variation observed for all batches, as depicted in Table 4.3, ranged between 0.201±0.004 g to 0.204±0.004 g and this is within the USP and BP recommendations, which allows a 7.5 % variation (±15 mg in this case), for tablets with weight between 131 mg – 325 mg.

Tablet thickness, diameter and crushing strength are widely used by tablet manufacturers to check the quality of a batch and are important quality control tests for tablet packaging. The thickness of the tablet can affect the therapeutic effectiveness of tablets and very thick tablets affect packaging either in blister or plastic container. Tablet thickness is usually controlled to minimize appearance problems to assure that the tablet fit into the container and gives assurance that they can be accurately counted by the filling equipment as some filling equipment depend on the uniform thickness of the tablets as a counting mechanism. B.P and U.S.P standards suggest that all of the percentage average deviation value must not exceed ±5 % for tablets with diameter less than 12.5 mm.

Tablets must have a certain degree of strength to be able to withstand and overcome the rigors of mechanical shock so that they do not break easily. They should be able to also withstand reasonable abrasion and friction. Adequate tablet hardness and resistance to

powdering and friability are necessary requisites for consumer acceptance. It also may influence disintegration and affect the dissolution rate. It may be especially important to carefully monitor crushing strength for drug products that possess real or potential bioavailability problems or are sensitive to altered dissolution-release profiles as a function of the compressive force employed. The friabilities of all the batches, as shown in Table 4.3, were within the recommended limit of < 1 %, as they ranged between 0.48 to 0.50 %. However, this may have been caused by the relatively high concentration of the binders used as matrix former. Oral tablets normally have a crushing strength of 4 – 8 KgF. However, hypodermic and chewable tablets are much softer (3 KgF) and some sustained release tablets are much harder (10 – 20 KgF). The higher crushing strength values obtained with batches containing CG and EG as matrix formers, as shown in Table 4.3, compared to those formulated with HPMC might be due to the fact that CG and EG are less dense than HPMC, thereby allowing effective pressure transmission during compression which resulted in to well knitted particles observed with CG (Mahmud *et al*., 2016).

Disintegration is considered to be that state in which any residue, except fragments of insoluble coating remaining on the screen is a soft mass having palpable firm core (B.P., 2004). The disintegration time observed in Table 4.3, had a range between 131.00±6.12 min to 382.00±56.04 min. Disintegration test is however not really applicable to sustained release systems as they are made to either swell or erode gently to release the active agent. The prolonged disintegration (in this case erosion) time observed can be a pointer to the fact that the tablets formulated are not immediate release tablets but modified for a longer delivery of the active ingredient (salbutamol sulphate). Generally,

the higher the concentration of the matrix material, the longer it takes for the tablet to get eroded. A disintegration time of 15 to 30 min is allowed for uncoated tablets but for delayed-release and coated tablets that are formulated for timed release of their active ingredients, disintegration time can last for over 1 h (World Health Organization, 2011).

The uniformity of drug content is an important quality evaluation test for tablets with potent drug contents, which are administered in low doses, the excipients forming the greater part of the tablet weight (Alderborn, 2007). A range of 90 – 110 % of drug content for oral tablet formulations is acceptable and from the results obtained in this study, as shown in Table 4.3, it can be seen that all the batches fell within the required standard (U.S.P, 2017).

The results from the dissolution studies, Figure 4.7, generally reveal that the release in pH 1.0 was higher than the release in pH 6.8. This was thought to be as a result of dissolution of the drug from the surface and near the surface of the matrix, which occurred while the polymer was undergoing hydration to form the gel layer. This result is in line with reports by Nep *et al.* (2016) who studied the release of theophylline from sesamum gum and by Langer and Peppas (1987), who suggested that the drug diffusion front movement was the main parameter affecting drug release rate. Also worthy of note from the dissolution studies is the fact that formulations made with CG as polymer matrix exhibited better salbutamol-sustaining ability when compared with the other polymers (EG and HPMC). This goes to mean that the cross-linking procedure may have conferred on the gum some properties that made it a better polymer in sustaining the release of the salbutamol from its matrix. Some of the abilities that may have been conferred on the gum on crosslinking are reduced solubility and higher molecular

weight. From the physicochemical characterizations done, it was shown that CG was only sparingly soluble in water, has a better hydration capacity, swelling ratio and swelling rate as compared to EG. Once the tablets were in contact with the dissolution medium, the penetrating water causes CG to swell rapidly. The thickness and decreased porosity of the diffusion layer thus formed inhibits the passage of the drug molecules and this may have been the reason for the better drug release retarding property of CG, as water could not penetrate easily to dissolve the salbutamol in the formulation (Siripon *et al*., 2007). Drug release from sustained release formulations is influenced by polymer molecular weight probably because at higher molecular weights, the polymer was entangled and the effective molecular diffusion area reduced (Balaji and Wu, 2000). It has been reported that there is a linear correlation between the proportion of polymer in the tablets and the extension of drug retardation. This is because the concentration of the polymer affects the gel strength, resulting in stronger diffusional layer that is resistant to diffusion or erosion, ultimately slowing down drug release. On one hand, lactose (used as diluent/filler/bulking agent) dissolves quickly, leaving fluid filled pores and channels that allow quicker medium penetration and drug release; on the other hand, the polymer swells and the resultant gel blocks the pathway of the medium and the drug, thus slows down medium penetration and drug release (Gao *et al*., 1996; Siripon *et al*., 2007; Balaji and Wu, 2000). However, in this study, this relationship was not fully obeyed as it can be seen that some of the lower polymer proportions exhibited better sustaining capacity as observed with T4 (30 % CG proportion), which sustained drug release better than T5 (40 % CG proportion) and T6 (50 % CG proportion); T2 (40 % EG proportion), which sustained better than T1 (30 % EG proportion) and T3 (50 % EG proportion). The

HPMC matrices were however different as they obeyed this relationship fully, with T9 (50 % HPMC proportion) sustaining better than T8 (40 % HPMC proportion) and T7 (30 % HPMC proportion). Results from the work of Kuldeep *et al*. (2013) suggests similar pattern with the result reported in this study but they failed to report any reason for this anomaly. A possible reason for this anomaly may be the high crushing and tensile strengths of some of the tablet formulations. T4 from this study showed an exceptional crushing strength of 11.4 KgF and a tensile strength of 2.62 Nm^{-2}. Nep *et al*. (2016) reported that harder compacts result from highly compactible polymers and this leads to higher crushing strength, probably due to increased number of inter-particulate hydrogen bonds during compaction. The cross-linking step may have conferred this highly compactible property to CG as formulations using this polymer showed higher crushing strength values compared to EG and HPMC.

The time for 50 % drug release (T_{50}) was longer for CG matrices compared to those of EG and HPMC matrices. T_{50} values for formulations T1, T4 and T7 were found to be 2.18 h, 2.44 h and 0.88 h respectively. This is to say that formulation T4 took a longer time to release the salbutamol sulphate from its matrix, followed by T1 and finally T7, which released 50 % of its content in less than an hour. This is also a pointer that formulation T4 has a better drug release sustaining ability. The definition of sustained release dosage forms by Alderborn (2007) as a system that provides an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release of drug over an extended period of time is justified by the actual quantity of drug released at the first 2 h of the dissolution. About 2.97 mg of salbutamol sulphate was released by formulation T4 after 2 h. This is considered to be sufficient enough to

provide a therapeutic dose that will elicit a pharmacological effect as the therapeutic dose of salbutamol is 2 – 4 mg.

The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in a predetermined manner (Purushothman *et al.*, 2012). It is expected that the developed formulations should have a theoretical drug release profile of about 67 % at the 8^{th} h when using a target time of 12 h. From the result of this study, T4 is shown to have a cumulative percent release of about 79 % at the 8^{th} h, and this is the closest any of the formulations got to the theoretical release. It can thus be concluded that T4 sustained the release of salbutamol more than any of the other formulations made, so that the release is for a longer period of time and is thus more bioavailable. For these reasons, T4 was considered the optimum formulation of this study.

Based on the R^2 values from the release kinetic studies, Table 4.4, the release of salbutamol from the matrices followed predominantly Higuchi model. This describes drug release that is largely governed by diffusion through water-filled pores in the matrices. Only T1 followed a predominantly first order release model, which can be used to describe the drug dissolved in pharmaceutical dosage forms like those containing water-soluble drugs in porous material (Shalkh *et al*., 2015). The *n*-values, Table 4.4, when the dissolution data were fitted into Korsmeyer-Peppas model, except for T7 which showed Fickian diffusion, all showed values that suggest an anomalous or non-Fickian diffusion. This is expected since the drug release involved a combination of both diffusion and erosion controlled rate release (Korsmeyer *et al.*, 1983; Nep *et al*., 2016; Mahmud *et al*., 2016).

A univariate analysis of variance was carried out and the effect of the polymers (materials) and their proportion of use, in the release of salbutamol from the matrix tablets formulated were examined. The descriptive statistics observed that T4 has the minimum mean release of salbutamol, while T9 has the maximum mean release of salbutamol. With this, T4 can thus be selected as the better formulation to sustain the release of salbutamol sulphate from the matrix tablets formulated. The tests of between-subjects effects showed a statistically significant difference (p = 0.000) in the release profile of the three (3) different polymers used as matrix former at 0.05 level of significance. This implies that there is enough evidence to reject the null hypothesis which states that cross-linking *Acacia seyal* gum with calcium chloride will not impart sustained-release properties to salbutamol sulphate tablets prepared by direct compression method. We therefore concluded that cross-linking *Acacia seyal* gum with calcium chloride would impart sustained-release properties to salbutamol sulphate tablets prepared by direct compression method. We can conclude that there is difference in the mean release of salbutamol sulphate amongst the different polymers used as matrix formers in this study. The effect of the proportion of use of the various polymer materials used as matrix formers in the release of salbutamol sulphate from the tablet formulations was also examined and at 0.05 level of significance, the p-value of 0.534 obtained shows there is no statistically significant difference in their mean. This implies that there is no enough evidence to say that the proportion of use of the polymer material used as matrix former affects the release of the salbutamol sulphate from the tablets formulated.

Since there was mean difference in the release profile amongst the polymers used as matrix former, there was thus need to compare these materials using the post hoc test. The Turkey's test was used to compare EG (material 1), CG (material 2) and HPMC (material 3). By comparing EG with CG at 0.05 level of significance, a mean difference of 6.863 and a significance of 0.26 was observed. It can thus be said that EG has higher mean release of salbutamol sulphate than CG. Comparing HPMC with EG at 0.05 level of significance, the mean difference of 11.490 and a significance of 0.000 was observed. It can thus be said that HPMC has higher mean release of salbutamol sulphate than EG. Comparing HPMC and CG at a significance level of 0.05, a mean difference of 18.353 and a significance of 0.000 were observed and this implies that HPMC has higher mean release of salbutamol sulphate than CG. On a general note, CG has the better drug release sustaining property as seen from its lower mean difference compared to EG and HPMC, but the proportion of use does not show statistical significance in this study.

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APPENDICES

Appendix I: Solubility of EG and CG in Different Solvents Based on Polarity.

SOLVENT	CG	EG
Water	Sparingly soluble	Soluble
Isopropanol	Insoluble	Insoluble
Ethanol	Insoluble	Insoluble
Diethyl ether	Insoluble	Insoluble
Toluene	Insoluble	Insoluble
DMF Sulfoxide	Insoluble	Insoluble
Ethyl acetate	Insoluble	Insoluble

Aqueous Solubility (30°C)

	CG	EG
Weight of empty crucible	35.313 g	36.513 g
Weight of crucible after drying	35.681 g	37.041 g
Weight of gum recovered	0.368 g	0.528 g
Conc. (g/ml)	**0.0736 g/ml**	**0.1056 g/ml**

EG: If 0.528 g is recovered in 5 ml

X is contained in 1 ml

X = 0.528/5 = 0.1056 g/ml

Appendix II: Moisture Sorption Profile

DAY	% Moisture sorption	% Moisture sorption
	CG	EG
0	0.00	0.00
1	32.95	28.40
2	47.35	36.55
3	55.30	40.55
4	63.45	46.10
5	64.00	47.10

Appendix III: Sieve analysis

Sieve Size (µm)	Particles retained (g)		% Frequency of particles retained (g)		% Cumulative frequency (Oversized) of particles retained		$\frac{mesh\ size\ x\ \%\ retained}{100}$	
	CG	EG	CG	EG	CG	EG	CG	EG
500	3.22	2.35	6.45	4.73	6.45	4.73	32.25	23.65
250	5.2	9.71	10.41	19.53	16.85	24.25	26.03	48.83
150	12.57	13.89	25.16	27.93	42.01	52.18	37.74	41.90
90	10.2	7.82	20.42	15.72	62.43	67.91	18.38	14.15
75	12.95	10.75	25.92	21.62	88.35	89.52	19.44	16.22
45	5.82	5.21	11.65	10.48	100.00	100.00	5.24	4.72
TOTAL	**49.96**	**49.73**	**100.00**	**100.00**				
Mean Diameter(µm)							**139.08**	**149.45**

Mean particle diameter was calculated using the formula:

$$Mean\ particle\ diameter = \sum \frac{Mesh\ size\ X\ \%\ Retained}{100}$$

Appendix IV: Crushing strength

TABLET	BATCH/ CRUSHING STRENGTH (KgF)								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
1	10.6	9.8	9.0	11.8	10.7	10.3	8.8	8.6	9.5
2	10.2	8.9	8.2	10.5	10.0	9.2	9.0	9.0	10.0
3	9.8	8.2	8.9	12.0	10.2	10.6	8.2	8.0	10.2
MEAN	**10.2**	**9.0**	**8.7**	**11.4**	**10.3**	**10.0**	**8.7**	**8.5**	**9.9**
SD	0.327	0.655	0.356	0.665	0.294	0.602	0.340	0.411	0.294

SD = Standard deviation

Appendix V: Tablet Thickness

TABLET	BATCH/THICKNESS (mm)								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
1	3.48	3.42	3.43	3.5	3.43	3.42	3.54	3.76	3.81
2	3.45	3.42	3.4	3.47	3.46	3.43	3.54	3.76	3.91
3	3.43	3.42	3.45	3.48	3.36	3.42	3.51	3.8	3.85
4	3.46	3.38	3.44	3.42	3.42	3.48	3.61	3.81	3.8
5	3.51	3.48	3.45	3.43	3.48	3.47	3.52	3.7	3.8
6	3.52	3.43	3.44	3.44	3.42	3.46	3.53	3.77	3.9
7	3.49	3.48	3.45	3.43	3.44	3.44	3.53	3.8	3.92
8	3.47	3.46	3.46	3.44	3.45	3.48	3.52	3.75	3.88
9	3.47	3.48	3.44	3.48	3.45	3.47	3.61	3.71	3.86
10	3.5	3.46	3.42	3.45	3.42	3.44	3.58	3.71	3.78
MEAN	**3.48**	**3.44**	**3.44**	**3.45**	**3.43**	**3.45**	**3.55**	**3.76**	**3.85**
SD	0.026	0.032	0.017	0.025	0.031	0.023	0.035	0.038	0.048

Appendix VI: Tablet Diameter

TABLET	BATCH/DIAMETER (mm)								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
1	8.01	8.02	8.02	8.01	8.00	8.00	8.01	8.02	8.00
2	8.02	8.02	8.02	8.01	8.02	8.00	8.02	8.02	8.00
3	8.01	8.02	8.01	8.02	8.01	8.01	8.01	8.01	8.02
4	8.01	8.02	8.01	8.01	8.02	8.01	8.02	8.02	8.01
5	8.01	8.01	8.02	8.01	8.01	8.00	8.02	8.02	8.01
6	8.02	8.02	8.02	8.02	8.02	8.00	8.02	8.02	8.01
7	8.02	8.02	8.02	8.02	8.02	8.00	8.01	8.01	8.02
8	8.02	8.02	8.01	8.01	8.01	8.01	8.02	8.02	8.01
9	8.01	8.01	8.03	8.02	8.02	8.01	8.01	8.02	8.02
10	8.00	8.02	8.02	8.02	8.02	8.01	8.02	8.02	8.00
MEAN	**8.01**	**8.02**	**8.02**	**8.02**	**8.02**	**8.01**	**8.02**	**8.02**	**8.01**
SD	0.006	0.004	0.006	0.005	0.007	0.005	0.005	0.004	0.008

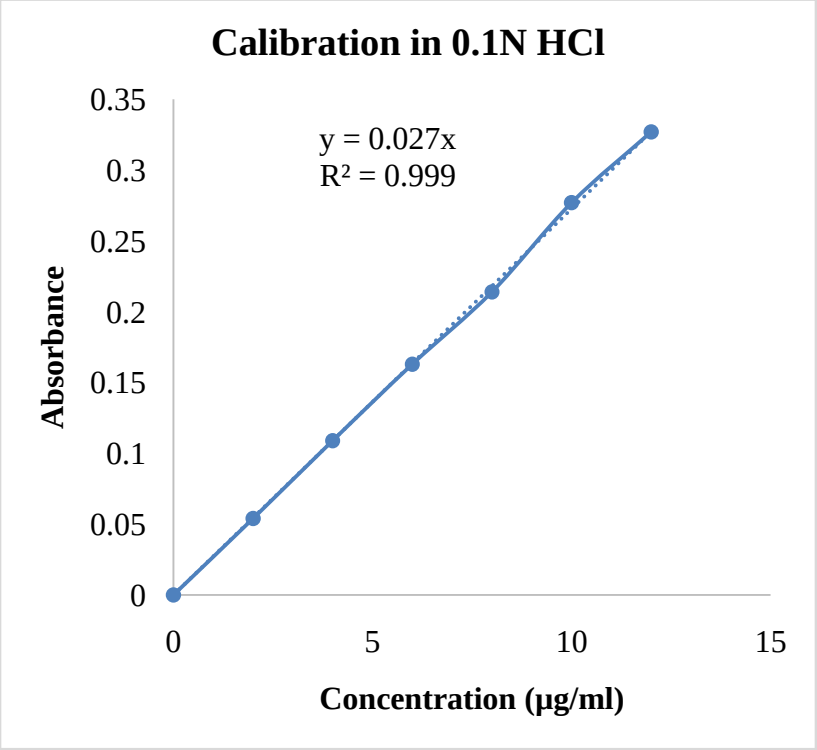
Appendix VII: Weight variation

TABLET	BATCH /WEIGHT(g)								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
1	0.203	0.202	0.201	0.207	0.205	0.204	0.207	0.208	0.203
2	0.207	0.211	0.201	0.203	0.200	0.200	0.203	0.202	0.206
3	0.206	0.204	0.204	0.201	0.206	0.198	0.195	0.197	0.200
4	0.207	0.203	0.199	0.200	0.198	0.198	0.207	0.199	0.198
5	0.207	0.196	0.203	0.206	0.198	0.199	0.206	0.195	0.202
6	0.198	0.200	0.201	0.203	0.199	0.206	0.204	0.206	0.202
7	0.206	0.206	0.200	0.200	0.206	0.197	0.202	0.204	0.205
8	0.203	0.194	0.205	0.202	0.197	0.206	0.200	0.205	0.205
9	0.209	0.208	0.203	0.203	0.202	0.197	0.209	0.199	0.202
10	0.201	0.201	0.200	0.204	0.204	0.202	0.200	0.205	0.205
11	0.204	0.202	0.202	0.206	0.195	0.199	0.204	0.206	0.203
12	0.208	0.198	0.199	0.203	0.204	0.204	0.201	0.195	0.207
13	0.205	0.199	0.208	0.205	0.199	0.199	0.193	0.197	0.198
14	0.208	0.197	0.204	0.206	0.200	0.202	0.203	0.209	0.206
15	0.195	0.200	0.202	0.200	0.195	0.195	0.198	0.202	0.200
16	0.203	0.198	0.202	0.200	0.206	0.206	0.201	0.205	0.203
17	0.204	0.204	0.201	0.205	0.204	0.204	0.205	0.206	0.207
18	0.201	0.205	0.198	0.196	0.208	0.208	0.208	0.197	0.207
19	0.201	0.201	0.201	0.199	0.201	0.201	0.202	0.202	0.205
20	0.200	0.200	0.207	0.200	0.201	0.201	0.202	0.201	0.201
MEAN	**0.204**	**0.201**	**0.202**	**0.202**	**0.201**	**0.201**	**0.203**	**0.202**	**0.203**
SD	0.004	0.004	0.003	0.003	0.004	0.004	0.004	0.004	0.003

Appendix VIII: Salbutamol Calibration Plot

Calibration in 0.1N HCl, pH 1.0

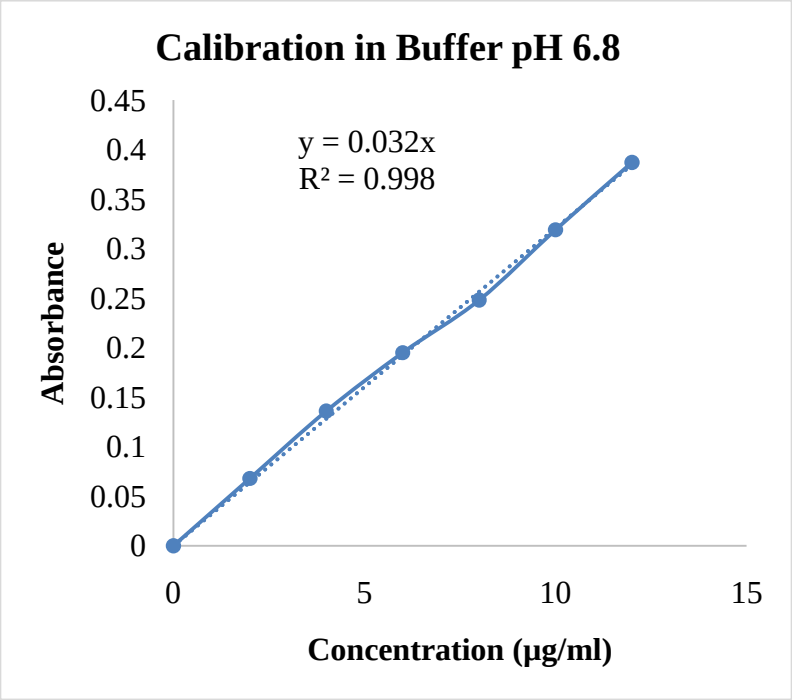
Stock solution of Salbutamol was prepared by dissolving 100 mg in 100 ml of acid buffer (pH 1.0) to obtain a 1000 µg/ml concentration. From this stock solution prepared, sample solutions were made by taking known aliquots of the stock solution and diluting serially with the acid buffer to obtain the different concentrations. The absorbance of each solution was then read at 277 nm in a UV-Visible spectrophotometer against a blank solution of the acid buffer (pH 1.0). A Plot of absorbance VS concentration (µg/ml) was done as the standard calibration curve, and the equation for the plot was obtained.



Conc(µg/ml)	Absorbance
0	0
2	0.054
4	0.109
6	0.163
8	0.214
10	0.277
12	0.327

Calibration in Phosphate buffer, pH 6.8

Stock solution of Salbutamol was prepared by dissolving 100 mg in 100 ml of phosphate buffer (pH 6.8) to obtain a 1000 µg/ml concentration. From this stock solution prepared, sample solutions were made by taking known aliquots of the stock solution and diluting serially with the buffer to obtain the different concentrations. The absorbance of each solution was then read at 277 nm in a UV-Visible spectrophotometer against a blank solution of the buffer (pH 6.8). A Plot of absorbance VS concentration (µg/ml) was done as the standard calibration curve, and the equation for the plot was obtained.



Conc(µg/ml)	Absorbance
0	0
2	0.068
4	0.136
6	0.195
8	0.248
10	0.319
12	0.387

Appendix IX: Drug Content Uniformity

Batch	Absorbance	Conc (µg/ml)	% Drug content
T1	0.232	8.498	95.603
T2	0.250	9.158	103.021
T3	0.235	8.608	96.839
T4	0.236	8.645	97.252
T5	0.264	9.670	108.790
T6	0.219	8.022	90.246
T7	0.241	8.828	99.312
T8	0.225	8.242	92.719
T9	0.226	8.278	93.131

The concentration was calculated from the equation of the calibration curve of salbutamol in 0.1 N HCl, which has a pH of 1.0.

The percentage drug content was obtained using the formula;

$$\%\ Drug\ content = \frac{Concentration\ obtained}{Expected\ concentration}\ x\ 100$$

Where the expected concentration was obtained as 8.889 µg/ml, based on the dilutions done during the drug content uniformity test.

Appendix X: Dissolution Absorbance Data

TIME (h)	ABSORBANCE								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	0.095	0.081	0.084	0.081	0.086	0.081	0.138	0.118	0.112
2	0.102	0.100	0.089	0.090	0.100	0.093	0.196	0.160	0.141
3	0.124	0.097	0.119	0.084	0.082	0.105	0.136	0.166	0.170
4	0.137	0.103	0.173	0.094	0.094	0.101	0.109	0.161	0.163
6	0.150	0.117	0.139	0.111	0.108	0.111	0.130	0.154	0.166
8	0.162	0.127	0.128	0.119	0.118	0.120	0.114	0.148	0.180

Appendix XI: Concentration of drug released

Concentration of drug released at specific times during dissolution was calculated using the equations obtained from the calibration curves above. The equation from pH 1.0 calibration plot was used to calculate the concentrations at times 0 hr, 1 hr and 2 hr while, the equation from pH 6.8 calibration plot was used to calculate the concentrations at times 3 hr, 4 hr, 6 hr and 8 hr.

Time (h)	Concentration (µg/ml)								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	3.48	2.97	3.08	2.97	3.15	2.97	5.05	4.32	4.10
2	3.74	3.66	3.26	3.30	3.66	3.41	7.18	5.86	5.16
3	3.86	3.02	3.71	2.62	2.55	3.27	4.24	5.17	5.30
4	4.27	3.21	5.39	2.93	2.93	3.15	3.40	5.02	5.08
6	4.67	3.64	4.33	3.46	3.36	3.46	4.05	4.80	5.17
8	5.05	3.96	3.99	3.71	3.68	3.74	3.55	4.61	5.61

Appendix XII: Percent drug released

This was calculated using the equation;

$$\%\ Drug\ Released = \frac{Concentration\ at\ time, t}{Expected\ concentration}\ x\ 100$$

Where the expected concentration is the maximum concentration of the drug that can be obtained when the tablet is completely dissolved in the 900 ml dissolution media. This was calculated as 8.889 µg/ml.

Time (h)	% Drug Released								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	39.143	33.375	34.611	33.375	35.435	33.375	56.861	48.620	46.148
2	42.028	41.204	36.671	37.083	41.204	38.319	80.759	65.926	58.097
3	43.453	33.991	41.700	29.436	28.735	36.794	47.658	58.170	59.572
4	48.008	36.094	60.623	32.940	32.940	35.393	38.196	56.418	57.119
6	52.564	41.000	48.709	38.897	37.846	38.897	45.555	53.965	58.170
8	56.769	44.504	44.854	41.700	41.350	42.051	39.948	51.863	63.076

Appendix XIII: Cumulative percent drug released

Since the dissolution media was changed from 0.1 N HCl to buffer of pH 6.8 after the first 2 hours of dissolution, it becomes necessary that the cumulative percent drug release be calculated for the remaining part of the dissolution period. This was done by adding the percent drug released at 2 hours to that released at 3 hr, 4 hr, 6 hr and 8 hr to obtain the cumulative percent drug released at these times.

Time (Hour)	Cumulative % Released								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	39.143	33.375	34.611	33.375	35.435	33.375	56.861	48.620	46.148
2	42.028	41.204	36.671	37.083	41.204	38.319	80.759	65.926	58.097
3	85.480	75.195	78.372	66.519	69.938	75.114	128.417	124.096	117.669
4	90.036	77.297	97.295	70.023	74.143	73.712	118.955	122.344	115.216
6	94.591	82.203	85.380	75.980	79.049	77.216	126.314	119.891	116.267
8	98.796	85.707	81.525	78.784	82.554	80.370	120.707	117.789	121.173

T_{50} interpolation for T1, T4 and T7

Batch	T_{50} (h)
T1	2.18
T4	2.44
T7	0.88

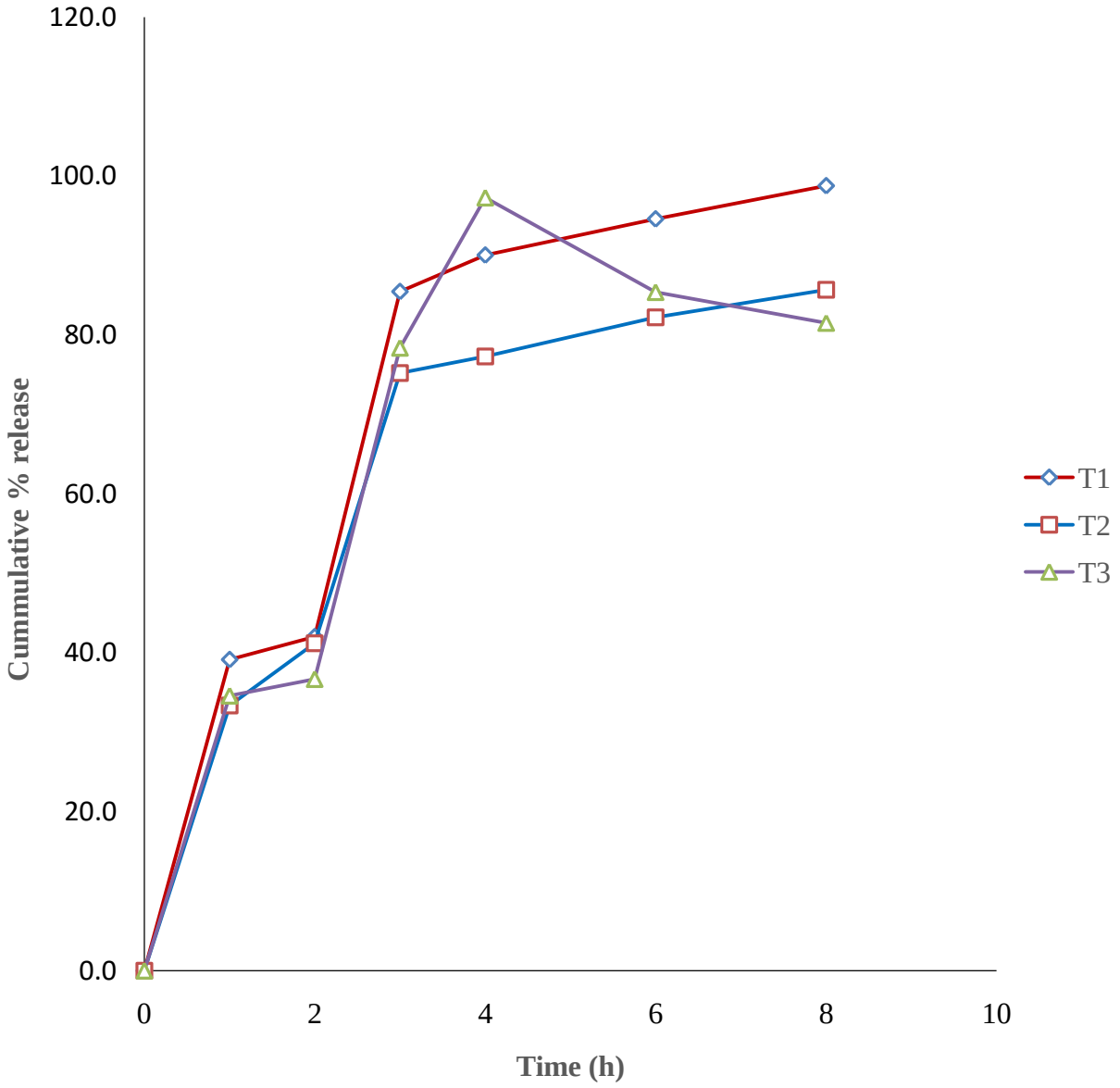
This was calculated using the interpolation formula;

$Y = y_1 + (X - x_1)\frac{y_2 - y_1}{x_2 - x_1}$; Where Y=50 %, X= unknown time; y_1, y_2, x_1 and x_2 are known points on the y and x-axis respectively, that the point to be determined falls in between.

Actual quantity of salbutamol sulphate released at specific times of dissolution

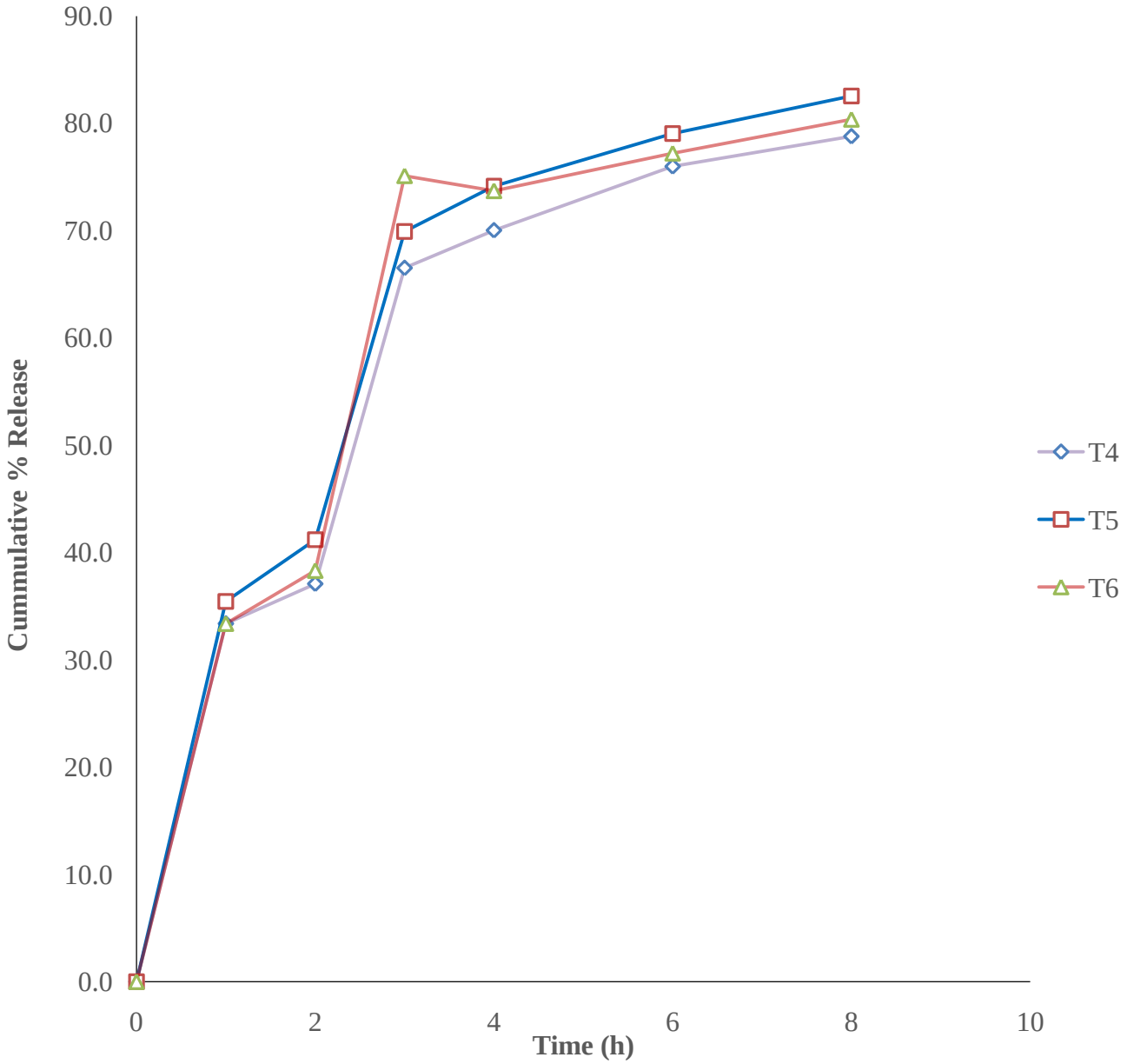
Time (h)	Quantity of drug released at specific times of dissolution (mg)								
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	3.13	2.67	2.77	2.67	2.83	2.67	4.55	3.89	3.69
2	3.36	3.30	2.93	2.97	3.30	3.07	6.46	5.27	4.65
3	6.84	6.02	6.27	5.32	5.60	6.01	10.27	9.93	9.41
4	7.20	6.18	7.78	5.60	5.93	5.90	9.52	9.79	9.22
6	7.57	6.58	6.83	6.08	6.32	6.18	10.11	9.59	9.30
8	7.90	6.86	6.52	6.30	6.60	6.43	9.66	9.42	9.69

$$Quantity\ of\ drug\ released\ at\ time\ t = \frac{\%\ Cummulative\ released}{100}\ X\ 8\ mg$$



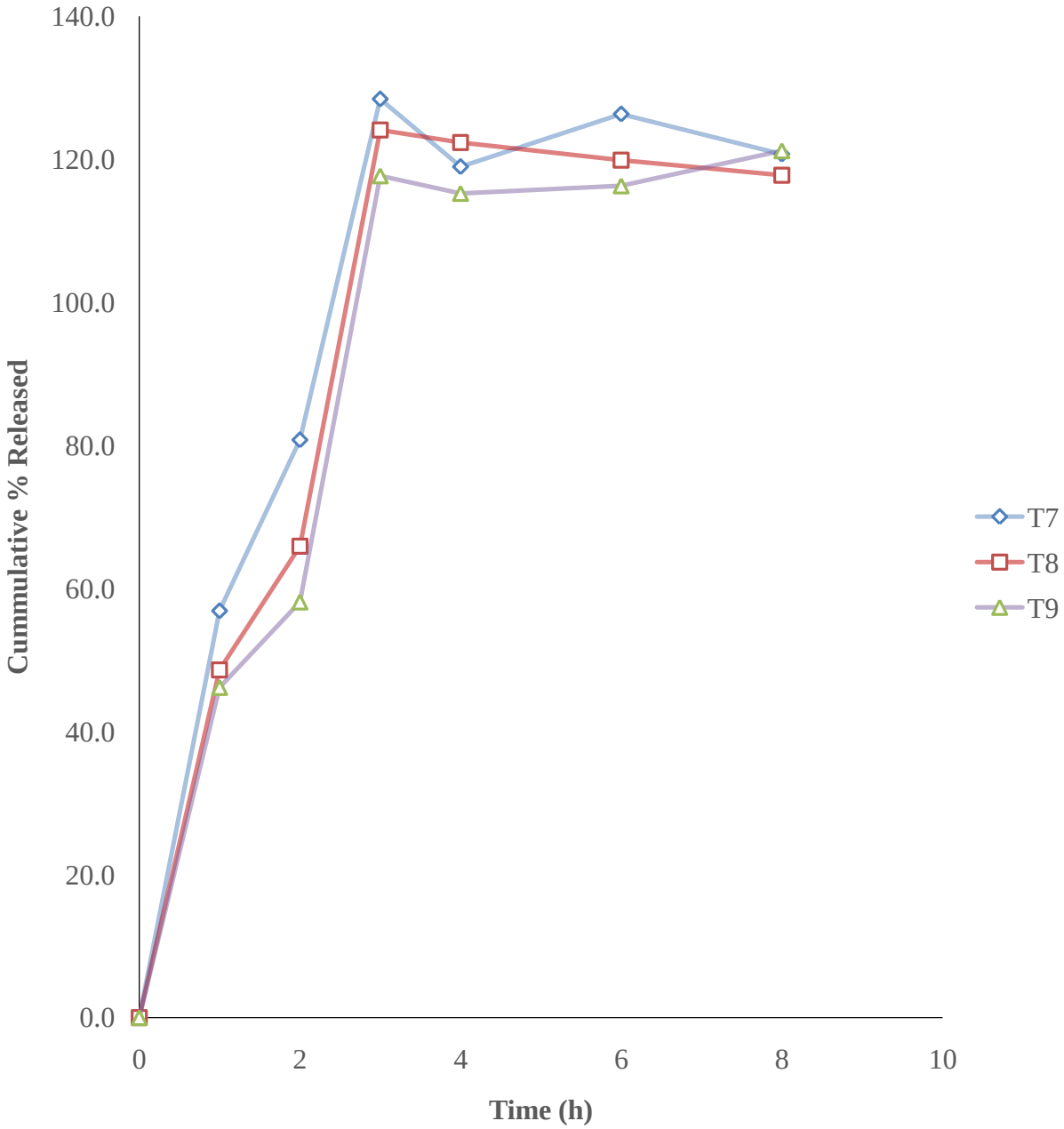
In vitro release profile of salbutamol sulphate from T1, T2 and T3 matrix tablets in pH 1.0 (for 2 hours) and pH 6.8 (for 6 hours).

Key: T1 = 30 % $^{w}/_{w}$EG concentration; T2 = 40 % $^{w}/_{w}$EG concentration; T3 = 50 % $^{w}/_{w}$EG concentration



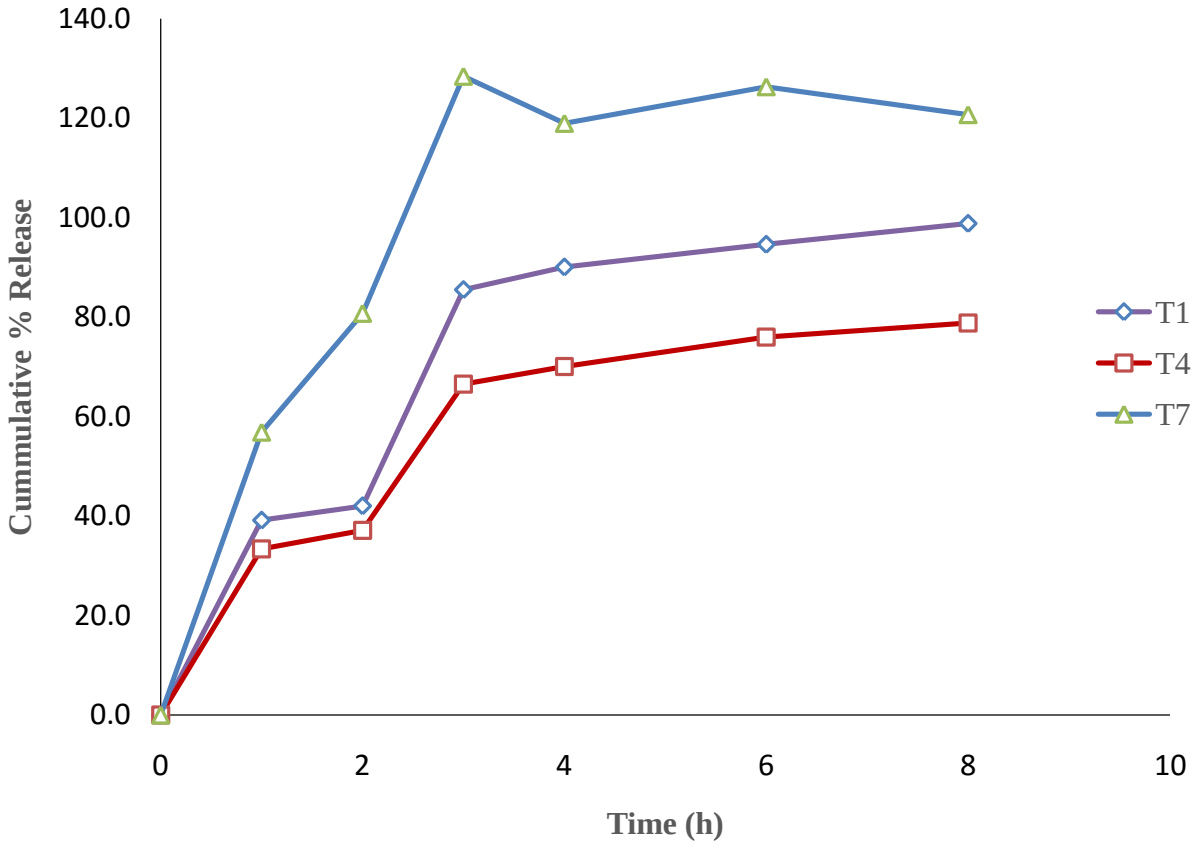
In vitro release profile of salbutamol sulphate from T4, T5 and T6 matrix tablets in pH 1.0 (for 2 hours) and pH6.8 (for 6 hours).

Key: T4 = 30 % $^{w}/_{w}$ CG concentration; T5 = 40 % $^{w}/_{w}$ CG concentration; T6 = 50 % $^{w}/_{w}$ CG concentration



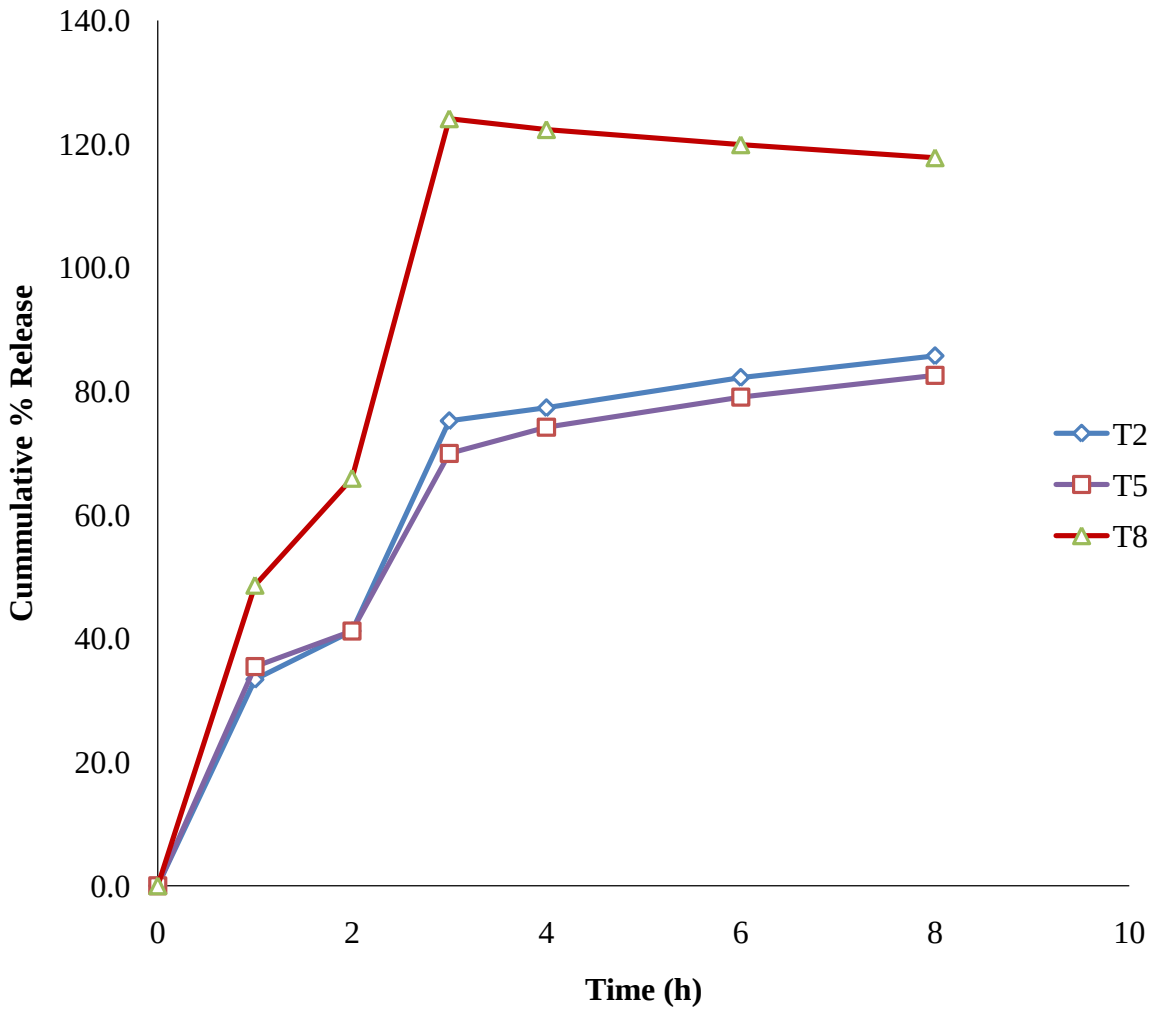
In vitro release profile of salbutamol sulphate from T7, T8 and T9 matrix tablets in pH 1.0 (for 2 hours) and pH 6.8 (for 6 hours).

Key: T7 = 30 % $^{w}/_{w}$ HPMC concentration; T8 = 40 % $^{w}/_{w}$ HPMC concentration; T9 = 50 % $^{w}/_{w}$ HPMC concentration



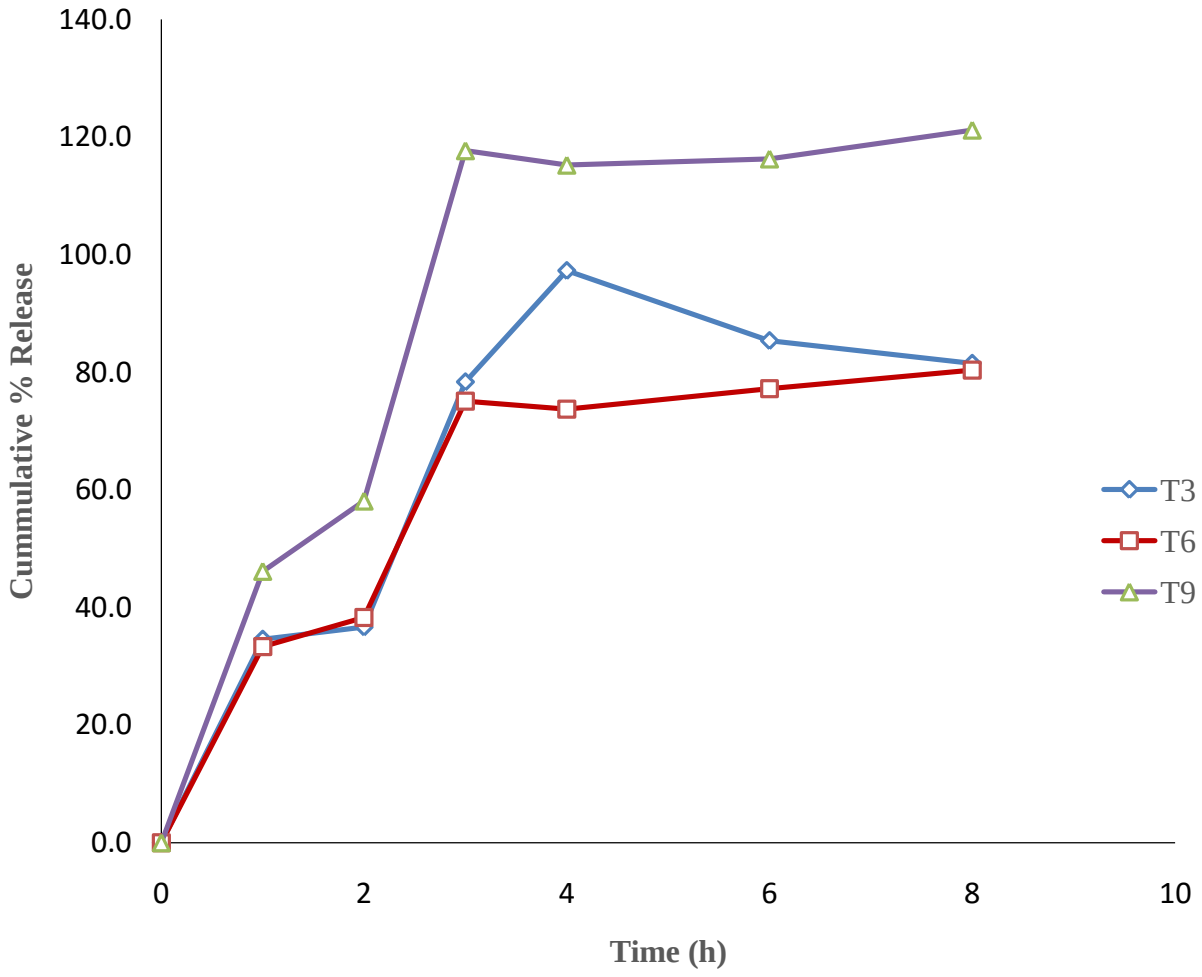
In vitro release profile of salbutamol sulphate from T1, T4 and T7 matrix tablets in pH 1.0 (for 2 hours) and pH 6.8 (for 6 hours).

Key: T1 = 30 % $^{w}/_{w}$ EG concentration; T4 = 30 % $^{w}/_{w}$ CG concentration; T7 = 30 % $^{w}/_{w}$ HPMC concentration



In vitro release profile of salbutamol sulphate from T2, T5 and T8 matrix tablets in pH 1.0 (for 2 hours) and pH 6.8 (for 6 hours).

Key: T2 = 40 % $^{w}/_{w}$ EG concentration; T5 = 40 %$^{w}/_{w}$ CG concentration; T8 = 40 % $^{w}/_{w}$ HPMC concentration



In vitro release profile of salbutamol sulphate from T3, T6 and T9 matrix tablets in pH 1.0 (for 2 hours) and pH 6.8 (for 6 hours).

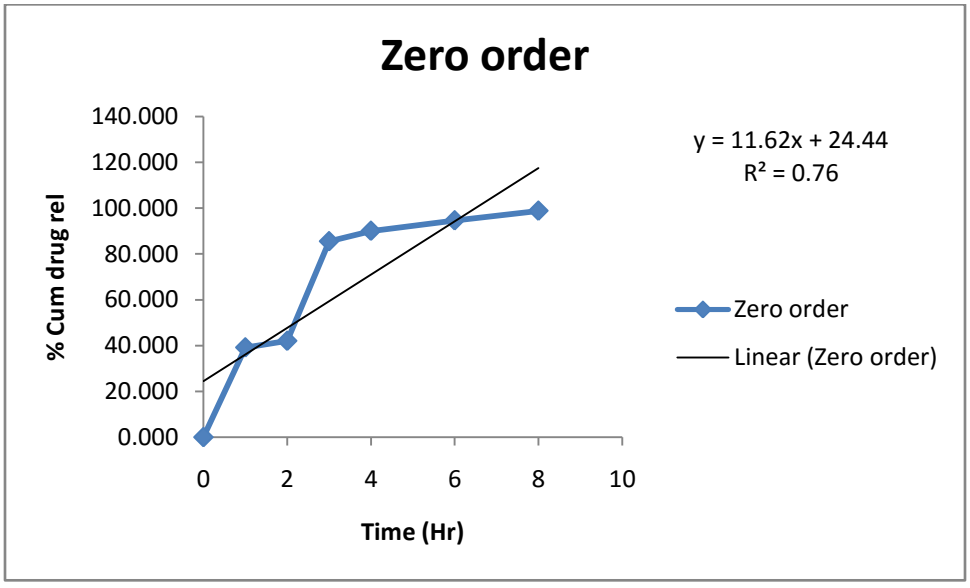
Key: T3 = 50 % $^{w}/_{w}$ EG concentration; T6 = 50 % $^{w}/_{w}$ CG concentration; T9 = 50 %

Time (h)	% Drug released	% Cumulative drug	% Cumulative drug	Log % Cumulative drug	Log % Cumulative drug	Square Root Time	LOG Time	Cube-Root % cumulative

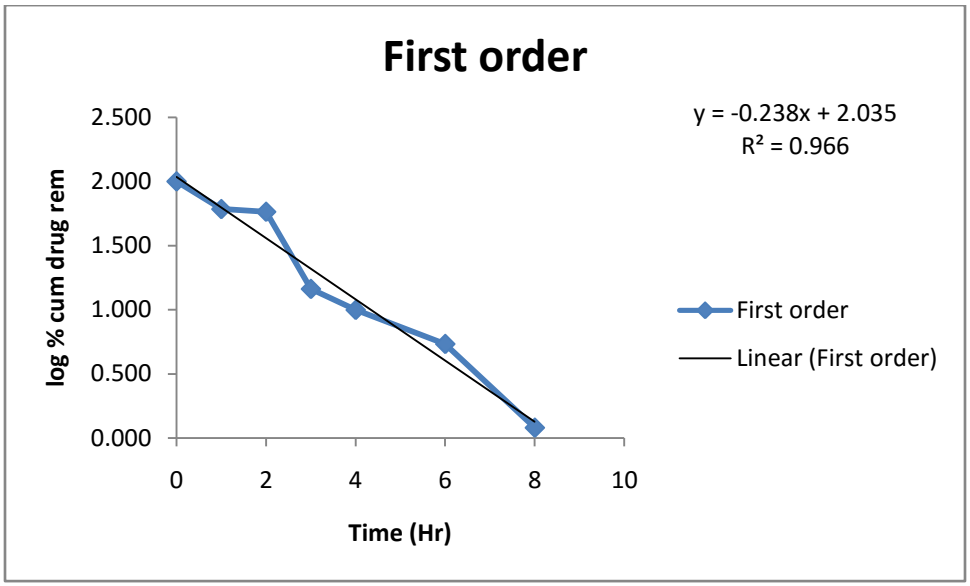
$^{w}/_{w}$HPMC concentration

		released	remaining	released	remaining			drug released
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000
1	39.143	39.143	60.857	1.593	1.784	1.000	0.000	3.395
2	42.028	42.028	57.972	1.624	1.763	1.414	0.301	3.477
3	43.453	85.480	14.520	1.932	1.162	1.732	0.477	4.405
4	48.008	90.036	9.964	1.954	0.998	2.000	0.602	4.482
6	52.564	94.591	5.409	1.976	0.733	2.449	0.778	4.556
8	56.769	98.796	1.204	1.995	0.081	2.828	0.903	4.623

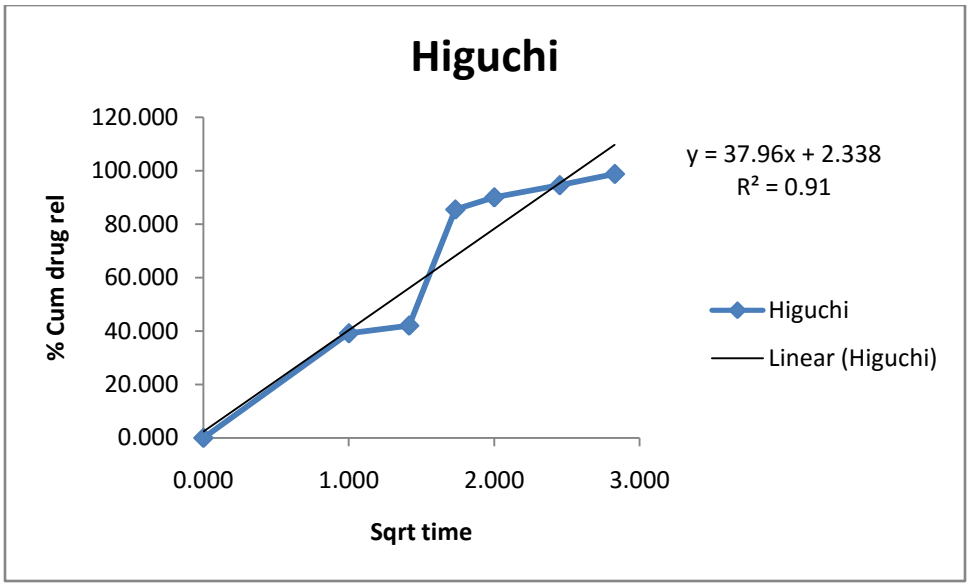
Appendix XIV: Kinetics of drug release for T1



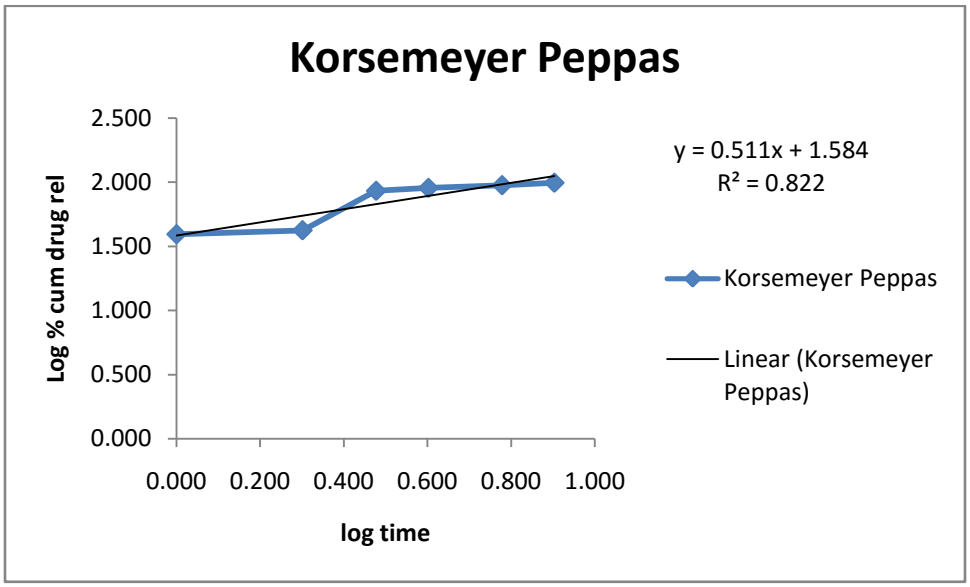
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



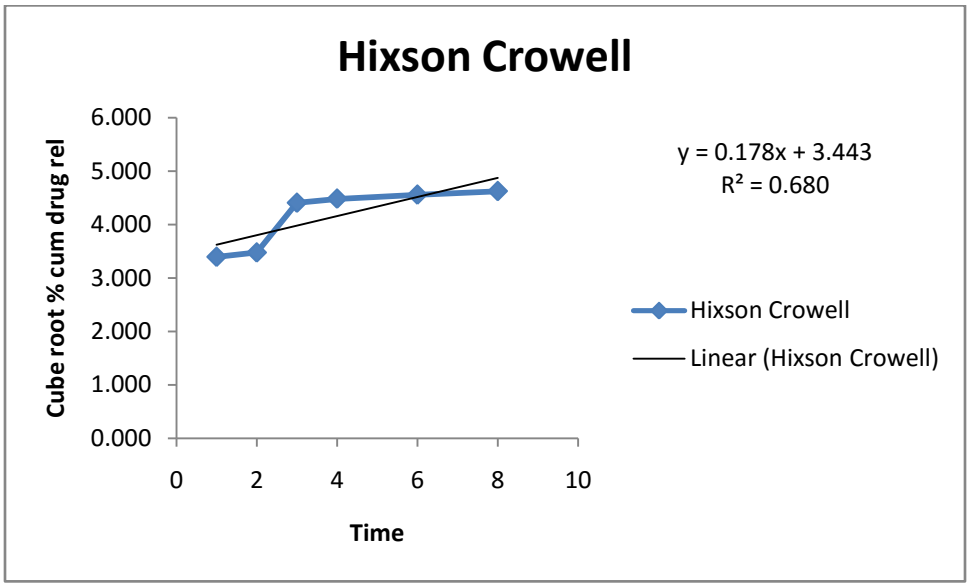
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

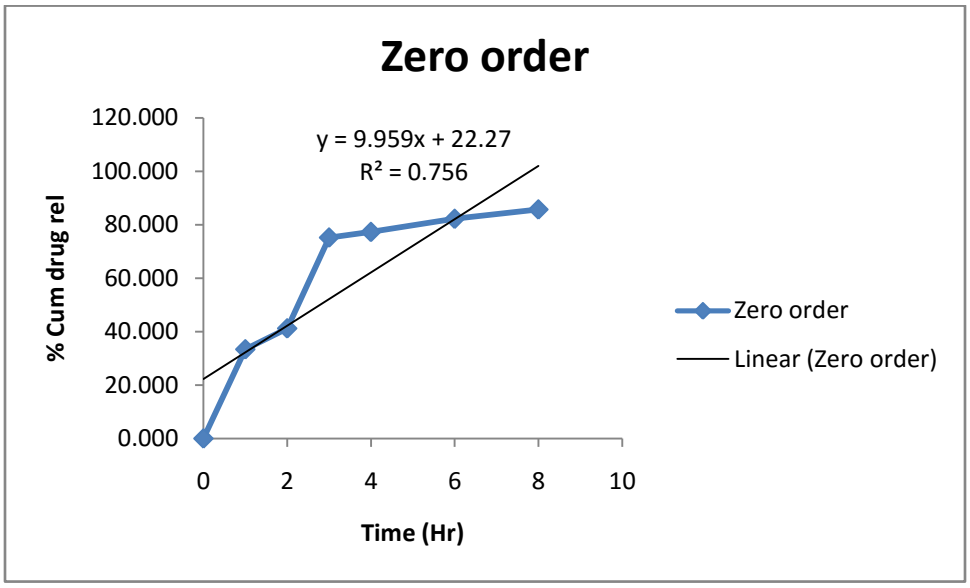


HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time

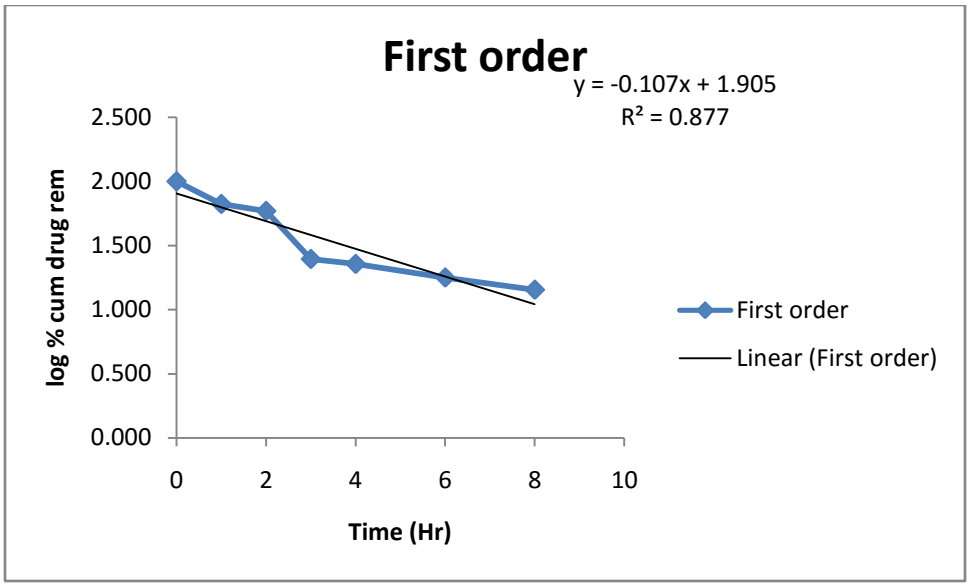
Appendix XV: Kinetics of drug release for T2

Time (h)	% Drug released	% Cumulative drug released	% Cumulative drug remaining	Log % Cumulative drug released	Log % Cumulative drug remaining	Square Root Time	LOG Time	Cube-Root % cumulative drug released

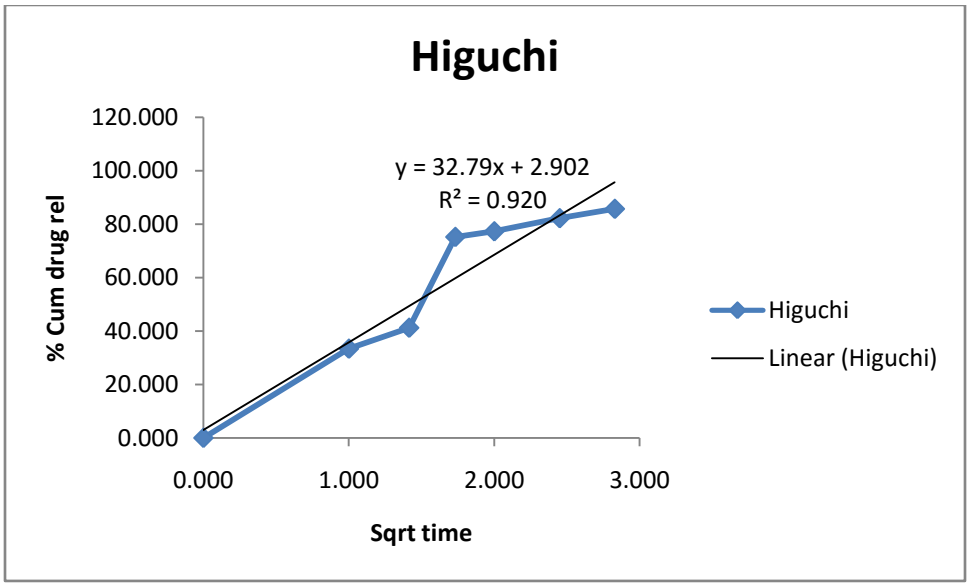
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000
1	33.375	33.375	66.625	1.523	1.824	1.000	0.000	3.220
2	41.204	41.204	58.796	1.615	1.769	1.414	0.301	3.454
3	33.991	75.195	24.805	1.876	1.395	1.732	0.477	4.221
4	36.094	77.297	22.703	1.888	1.356	2.000	0.602	4.260
6	41.000	82.203	17.797	1.915	1.250	2.449	0.778	4.348
8	44.504	85.707	14.293	1.933	1.155	2.828	0.903	4.409



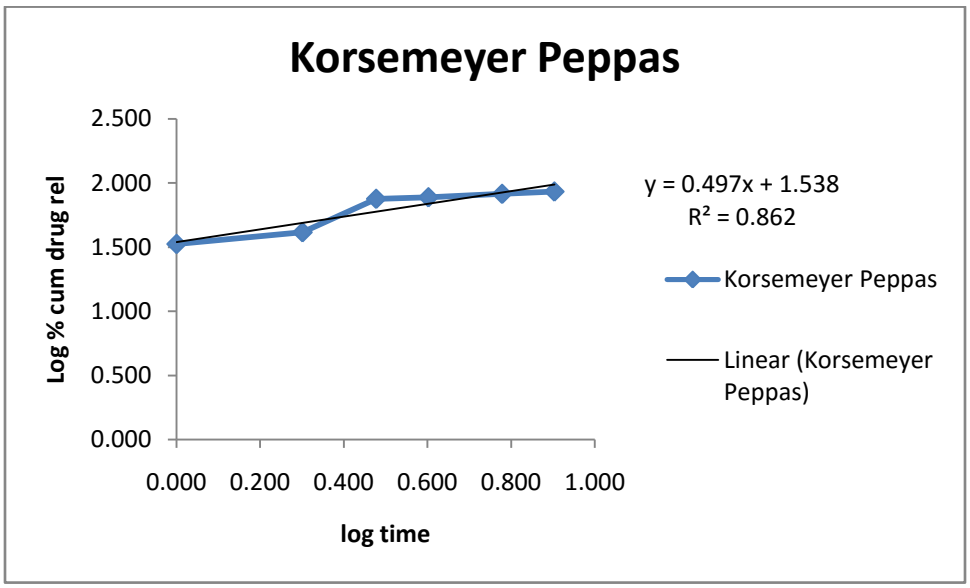
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



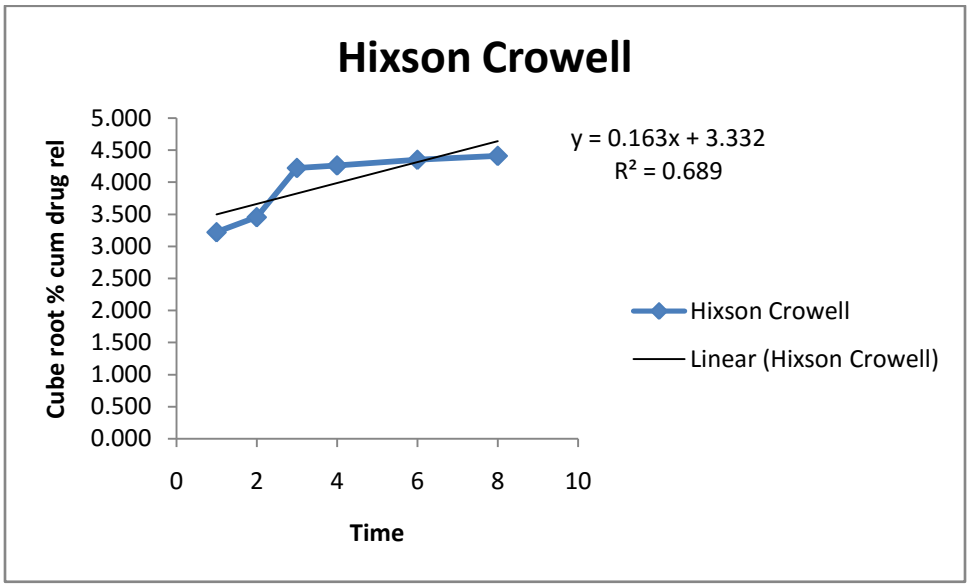
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

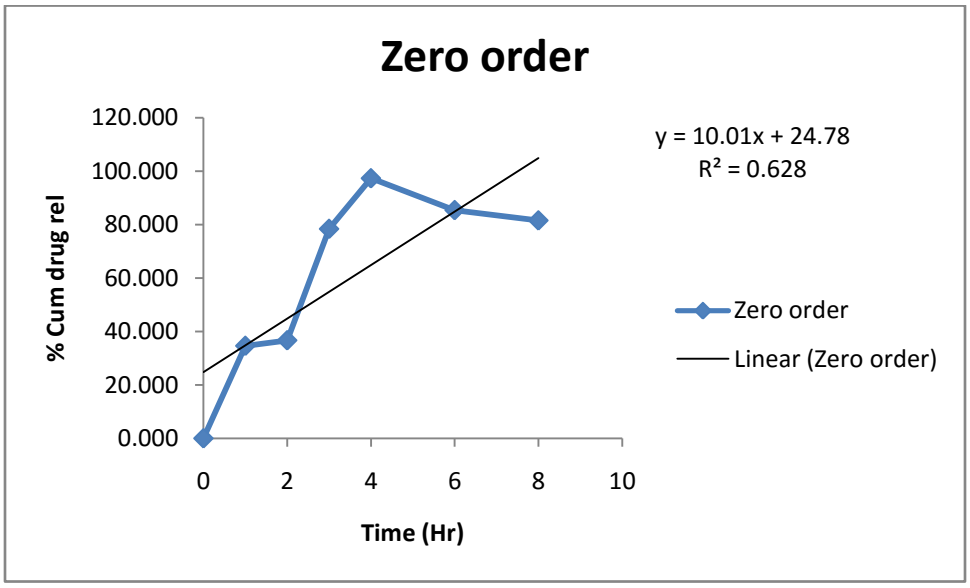


HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time

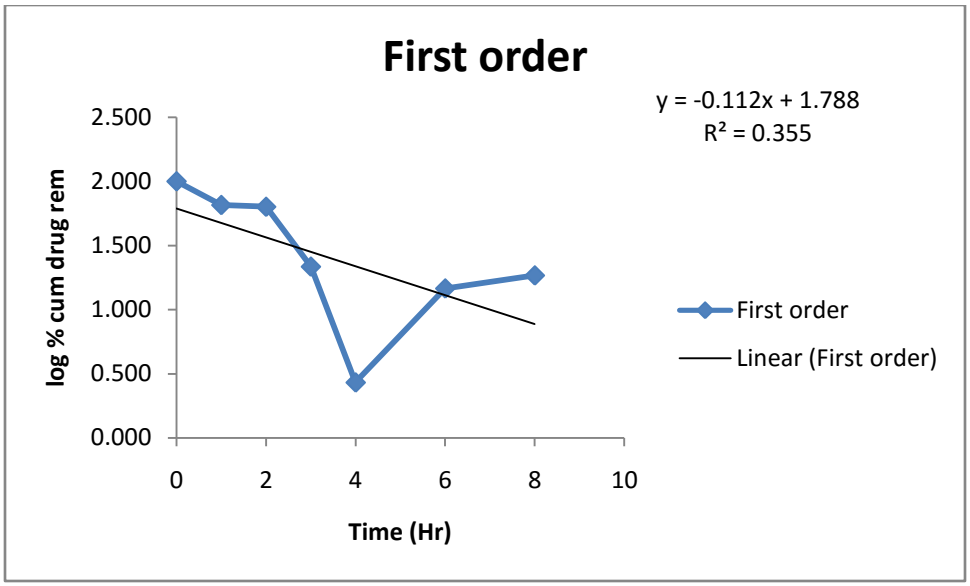
Appendix XVI: Kinetics of drug release for T3

Time (h)	% Drug released	% Cumulative drug released	% Cumulative drug remaining	Log % Cumulative drug released	Log % Cumulative drug remaining	Square Root Time	LOG Time	Cube-Root % cumulative drug released
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000
1	34.611	34.611	65.389	1.539	1.816	1.000	0.000	3.259

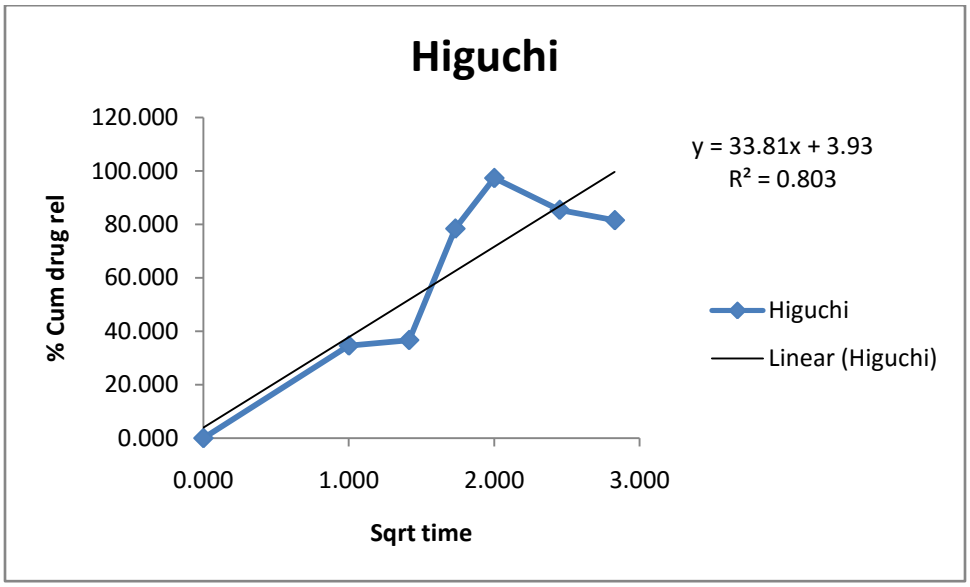
2	36.671	36.671	63.329	1.564	1.802	1.414	0.301	3.322
3	41.700	78.372	21.628	1.894	1.335	1.732	0.477	4.279
4	60.623	97.295	2.705	1.988	0.432	2.000	0.602	4.599
6	48.709	85.380	14.620	1.931	1.165	2.449	0.778	4.403
8	44.854	81.525	18.475	1.911	1.267	2.828	0.903	4.336



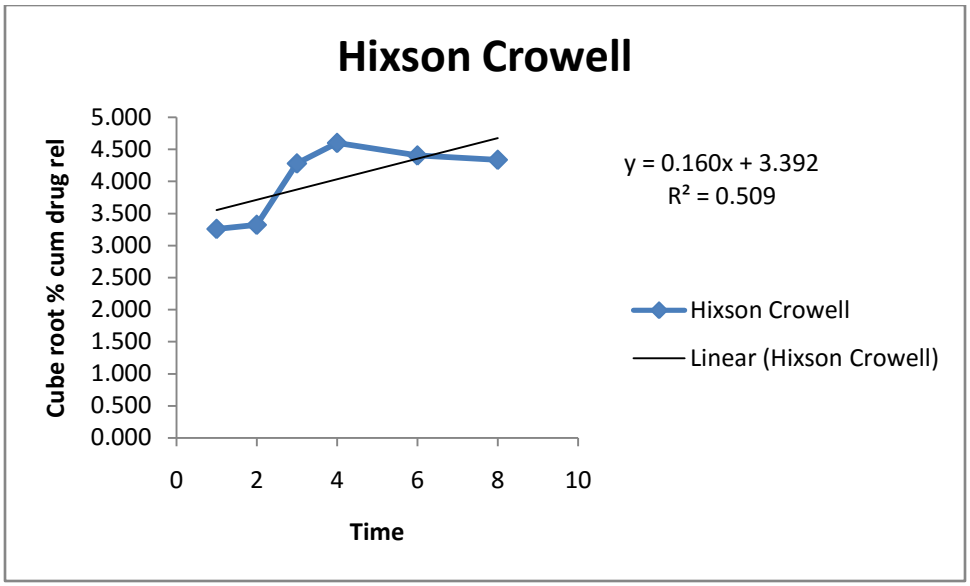
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



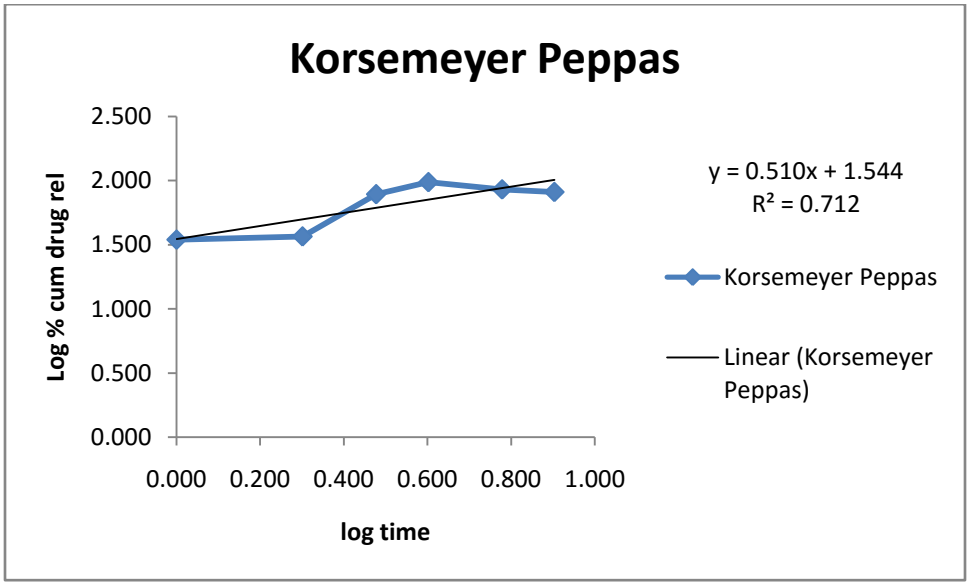
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time

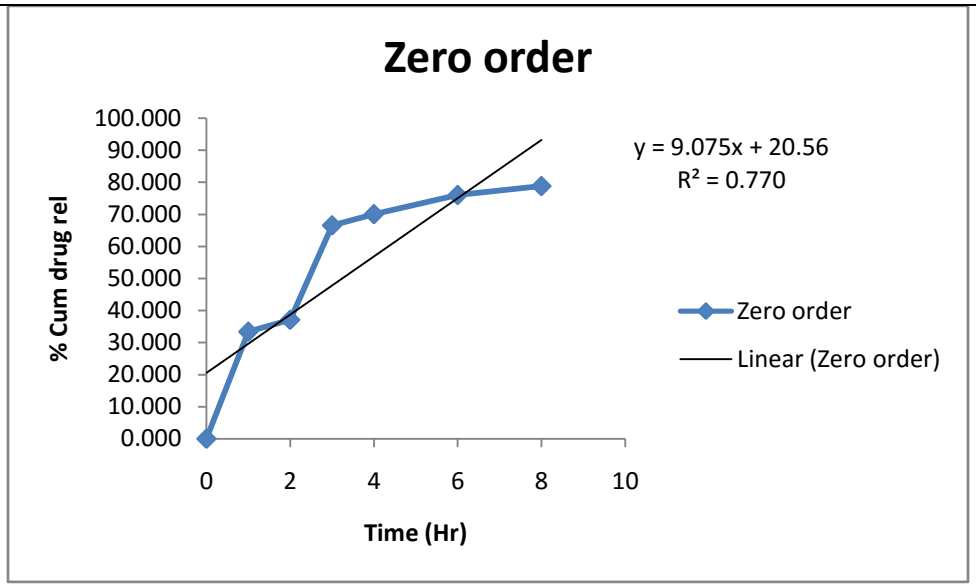


KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

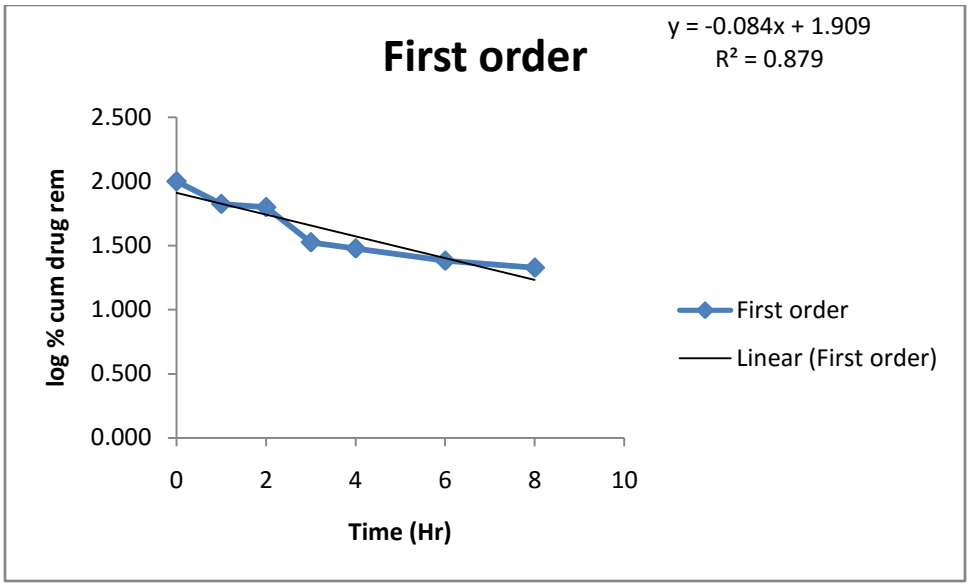
Appendix XVII: Kinetics of drug release for T4

Time (h)	% Drug released	% Cumulative drug released	% Cumulative drug remaining	Log % Cumulative drug released	Log % Cumulative drug remaining	Square Root Time	LOG Time	Cube-Root % cumulative drug released
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000

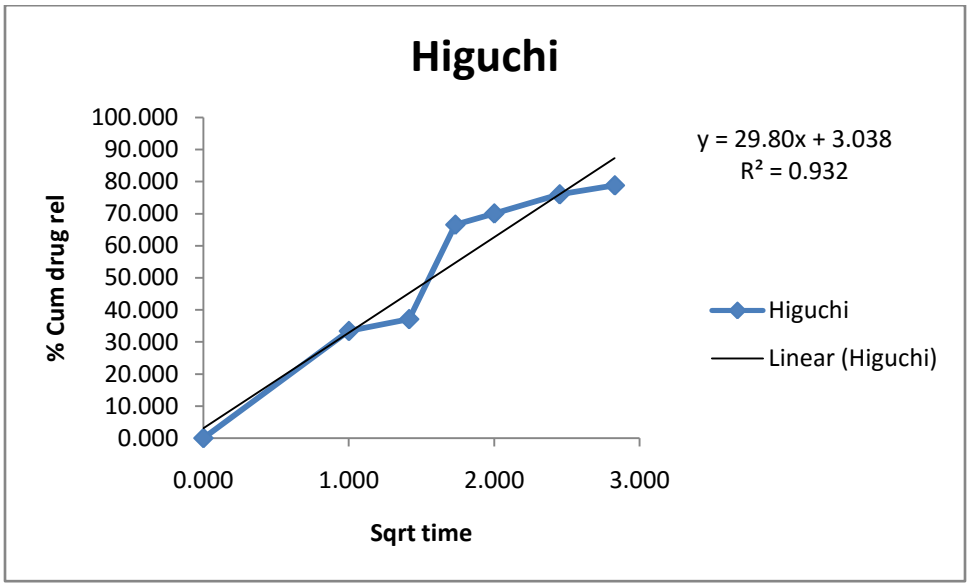
1	33.375	33.375	66.625	1.523	1.824	1.000	0.000	3.220
2	37.083	37.083	62.917	1.569	1.799	1.414	0.301	3.335
3	29.436	66.519	33.481	1.823	1.525	1.732	0.477	4.052
4	32.940	70.023	29.977	1.845	1.477	2.000	0.602	4.122
6	38.897	75.980	24.020	1.881	1.381	2.449	0.778	4.235
8	41.700	78.784	21.216	1.896	1.327	2.828	0.903	4.287



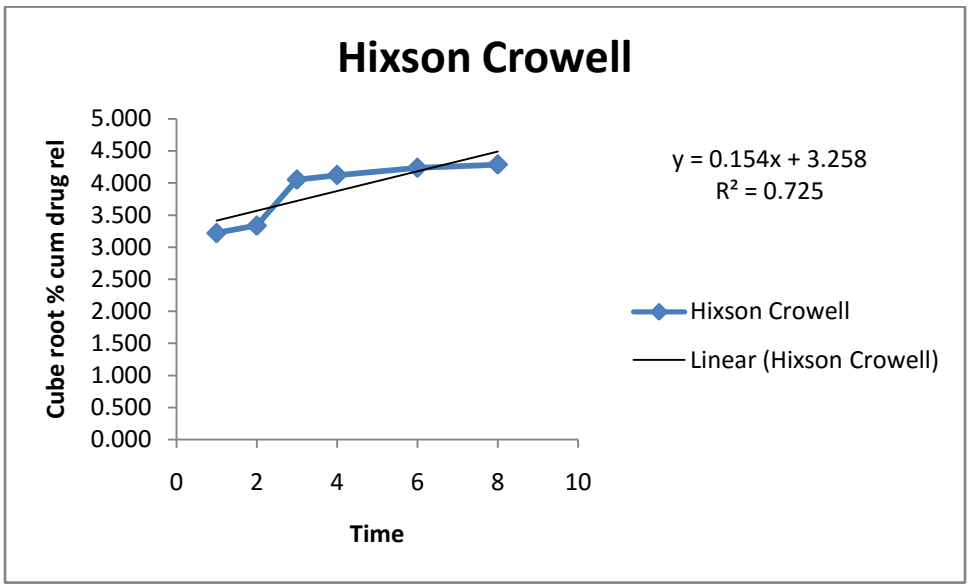
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



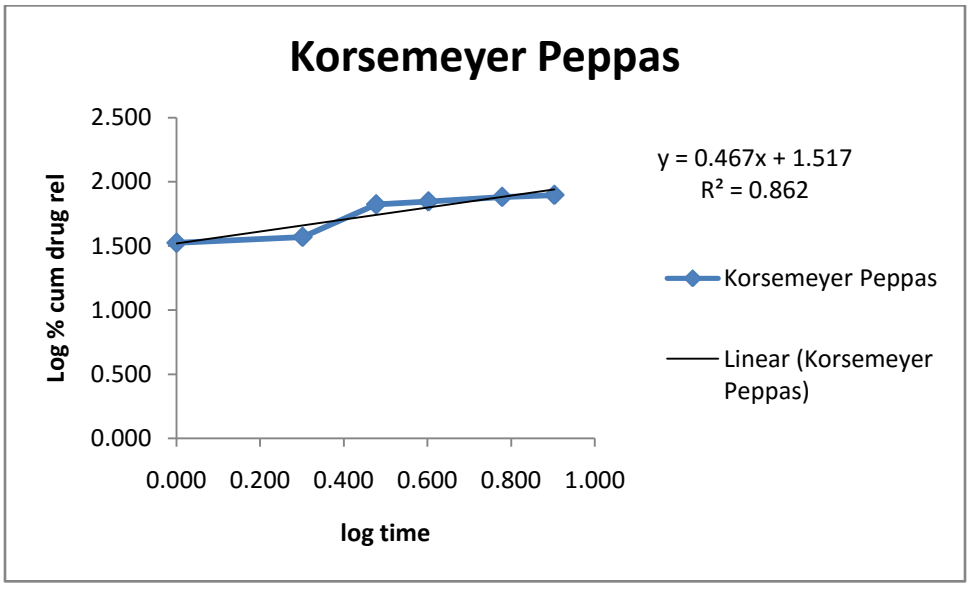
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



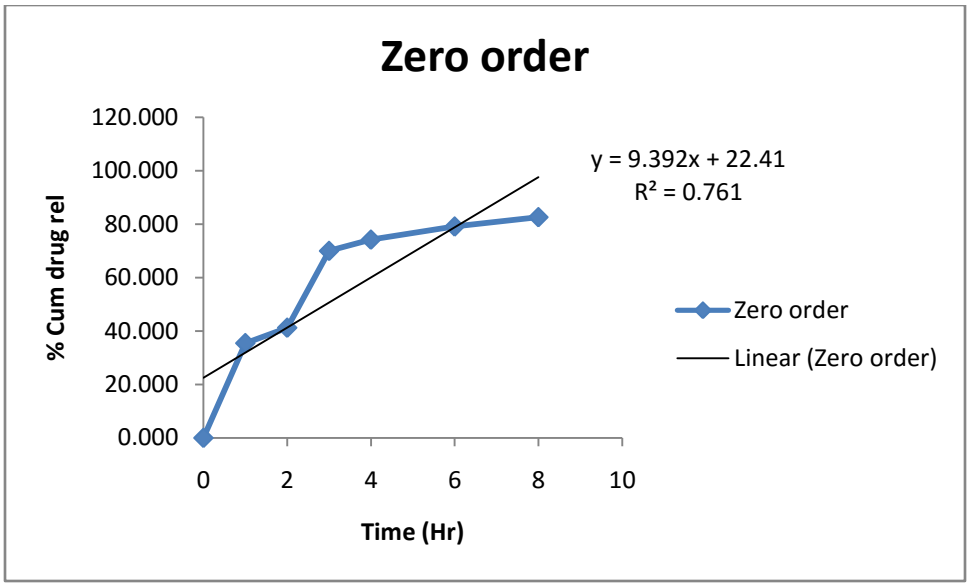
HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time



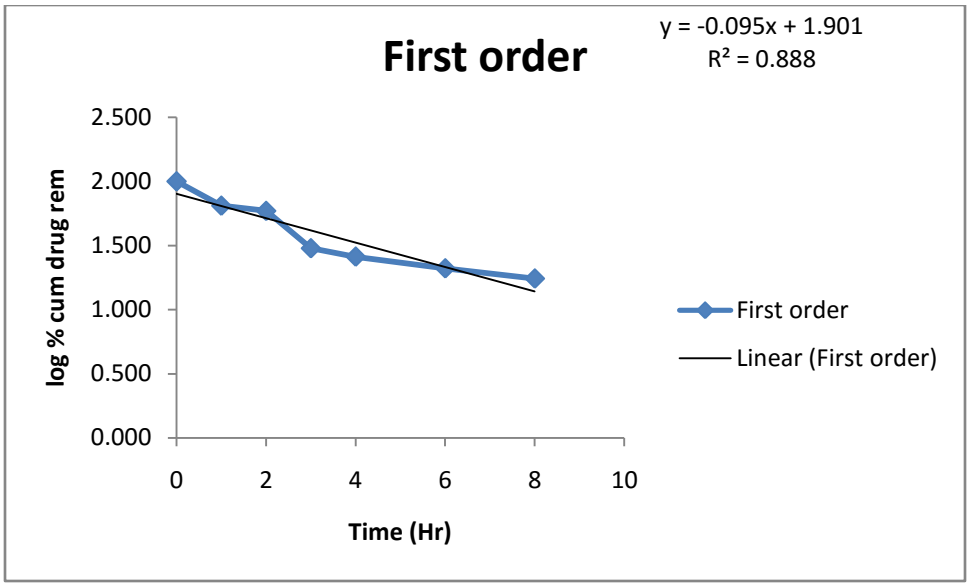
KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

Appendix XVIII: Kinetics of drug release for T5

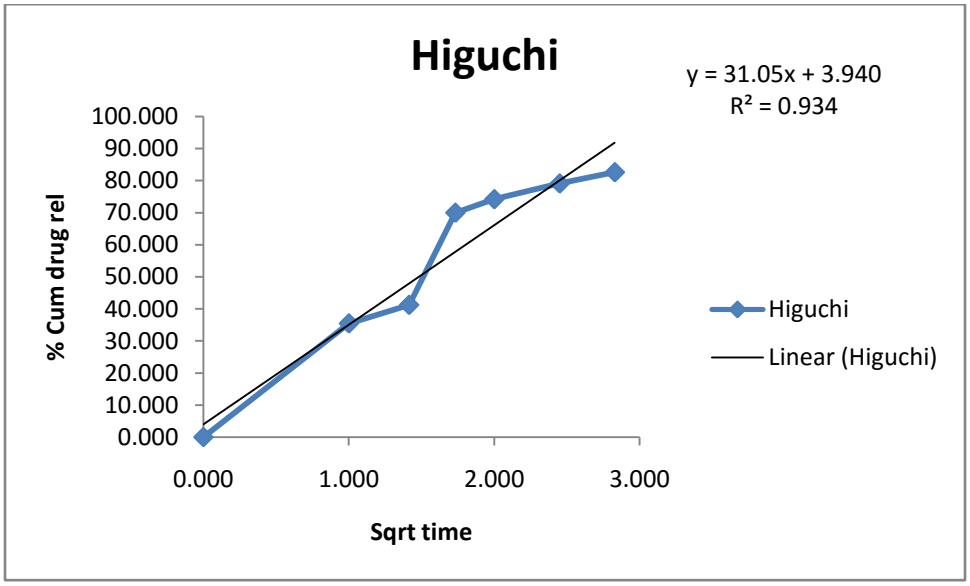
Time (h)	% Drug released	% Cumulative drug released	% Cumulative drug remaining	Log % Cumulative drug released	Log % Cumulative drug remaining	Square Root Time	LOG Time	Cube-Root % cumulative drug released
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000
1	35.435	35.435	64.565	1.549	1.810	1.000	0.000	3.285
2	41.204	41.204	58.796	1.615	1.769	1.414	0.301	3.454
3	28.735	69.938	30.062	1.845	1.478	1.732	0.477	4.120
4	32.940	74.143	25.857	1.870	1.413	2.000	0.602	4.201
6	37.846	79.049	20.951	1.898	1.321	2.449	0.778	4.292
8	41.350	82.554	17.446	1.917	1.242	2.828	0.903	4.354



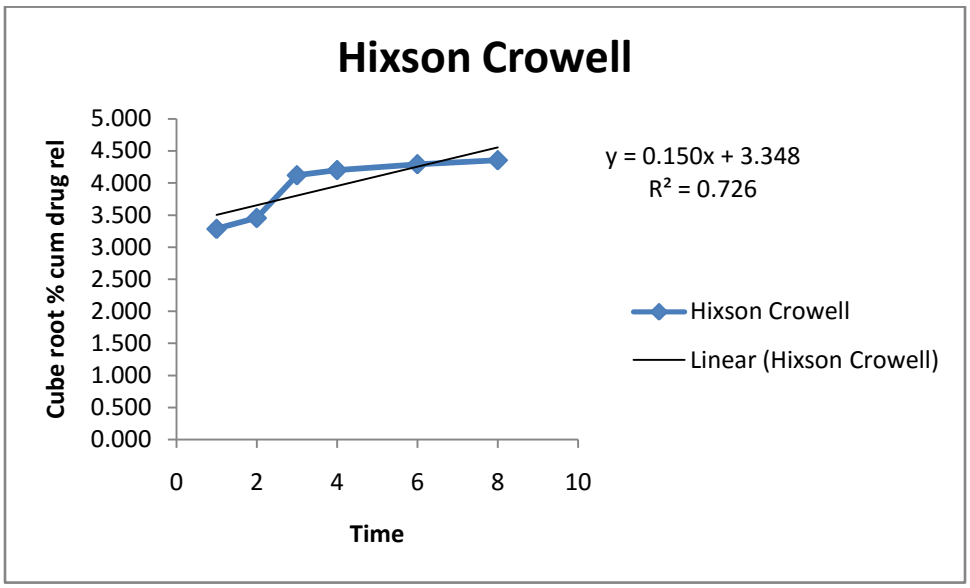
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



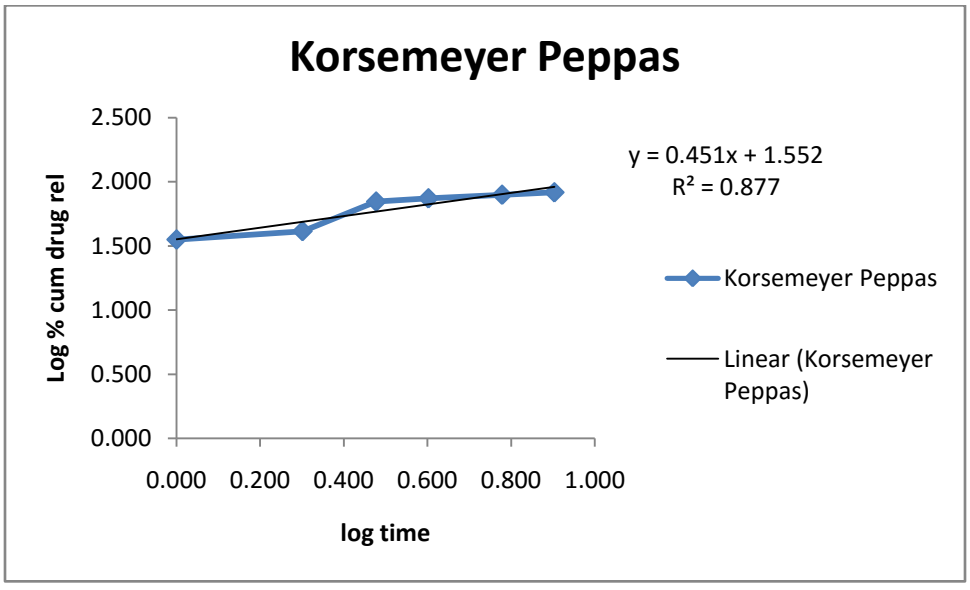
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time

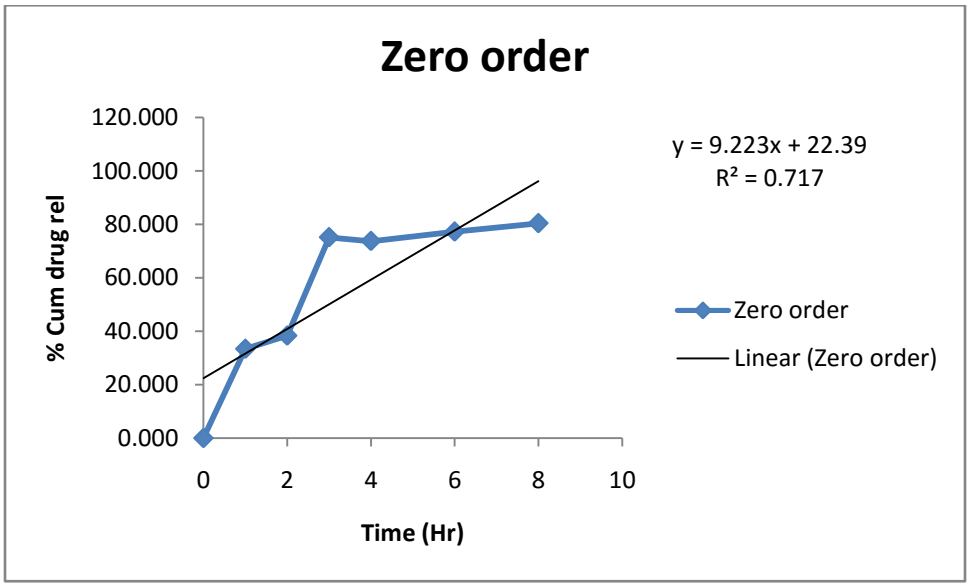


KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

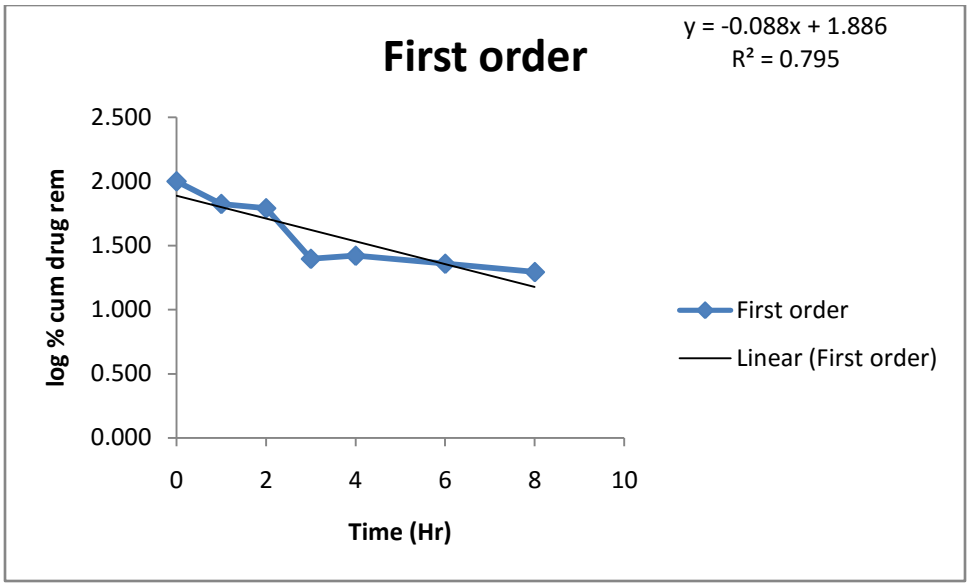
Appendix XIX: Kinetics of drug release for T6

Time (h)	% Drug released	% Cumulative drug released	% Cumulative drug remaining	Log % Cumulative drug released	Log % Cumulative drug remaining	Square Root Time	LOG Time	Cube-Root % cumulative drug released
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000
1	33.375	33.375	66.625	1.523	1.824	1.000	0.000	3.220
2	38.319	38.319	61.681	1.583	1.790	1.414	0.301	3.371

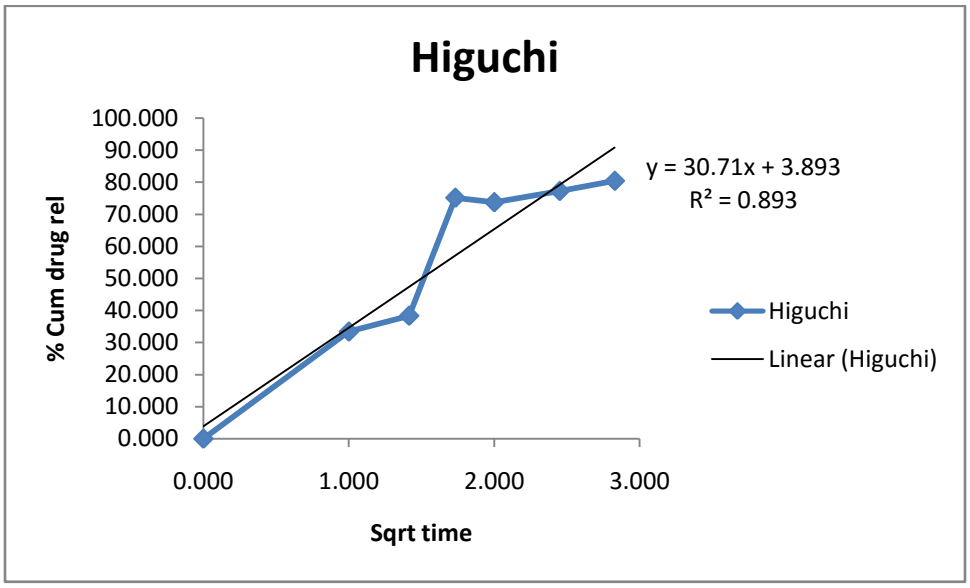
3	36.794	75.114	24.886	1.876	1.396	1.732	0.477	4.219
4	35.393	73.712	26.288	1.868	1.420	2.000	0.602	4.193
6	38.897	77.216	22.784	1.888	1.358	2.449	0.778	4.258
8	42.051	80.370	19.630	1.905	1.293	2.828	0.903	4.316



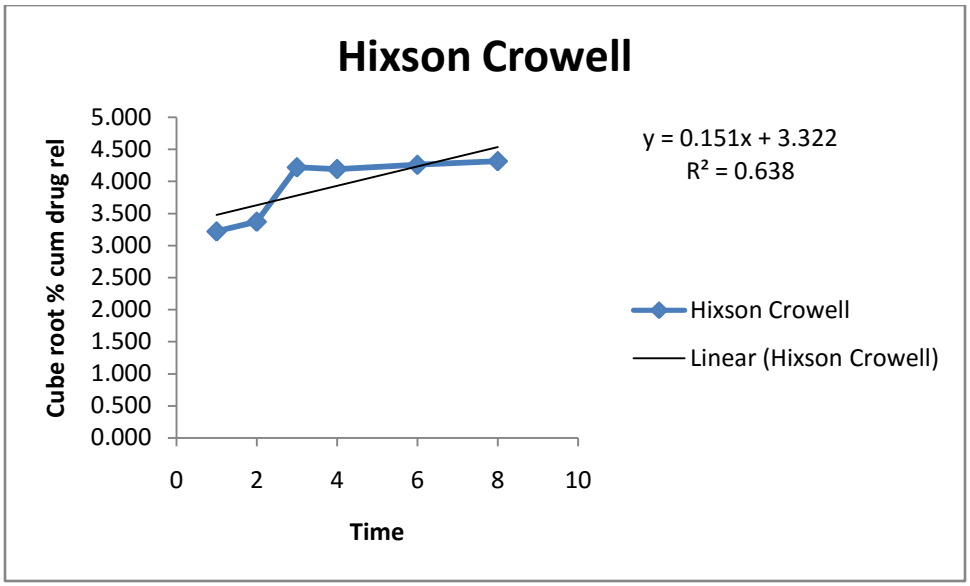
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



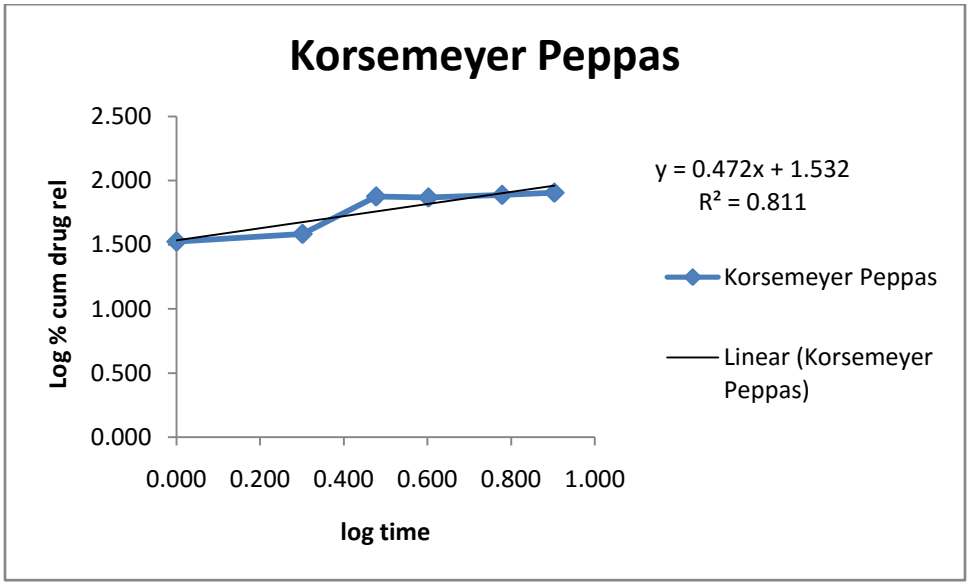
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time

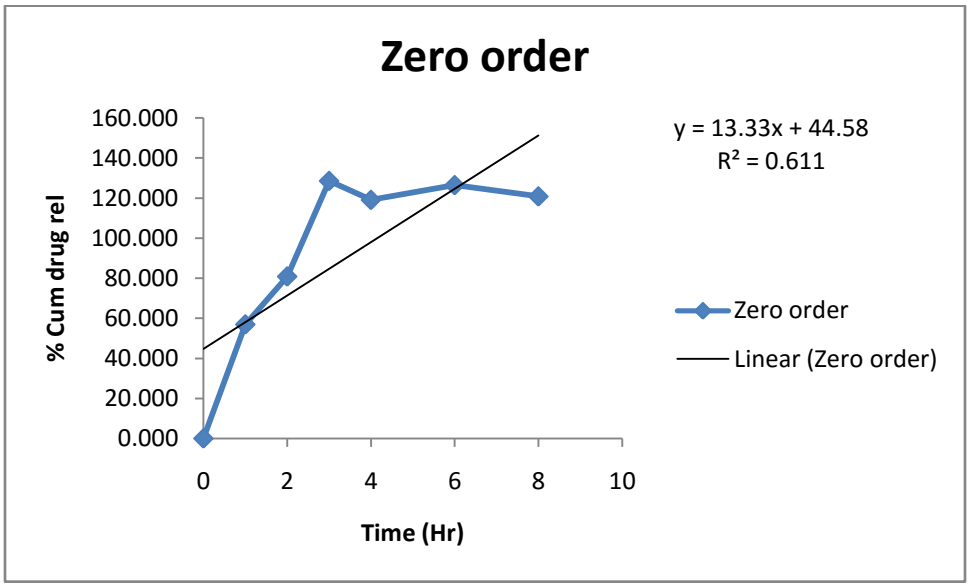


KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

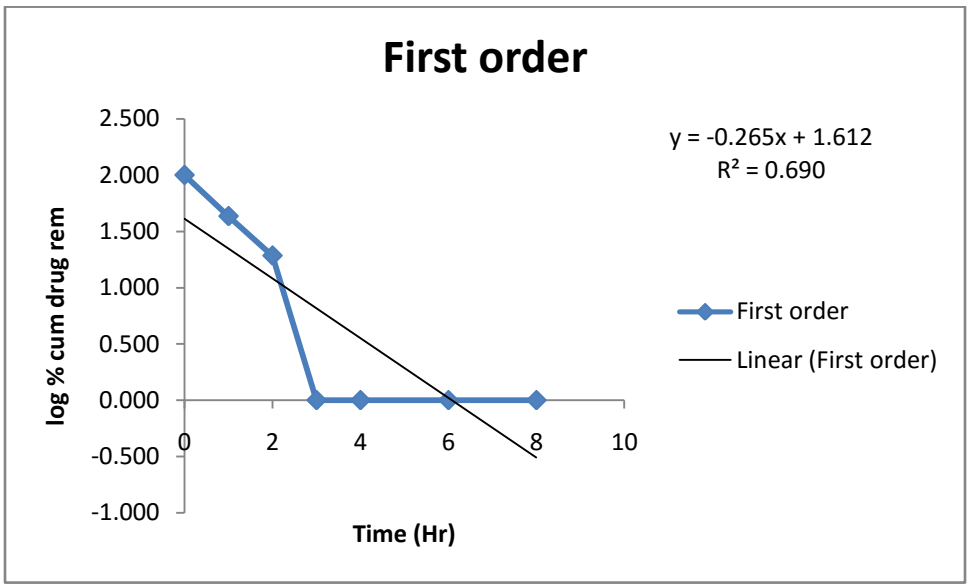
Appendix XX: Kinetics of drug release for T7

Time (h)	% Drug released	% Cumulative drug released	% Cumulative drug remaining	Log % Cumulative drug released	Log % Cumulative drug remaining	Square Root Time	LOG Time	Cube-Root % cumulative drug released
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000
1	56.861	56.861	43.139	1.755	1.635	1.000	0.000	3.845
2	80.759	80.759	19.241	1.907	1.284	1.414	0.301	4.322

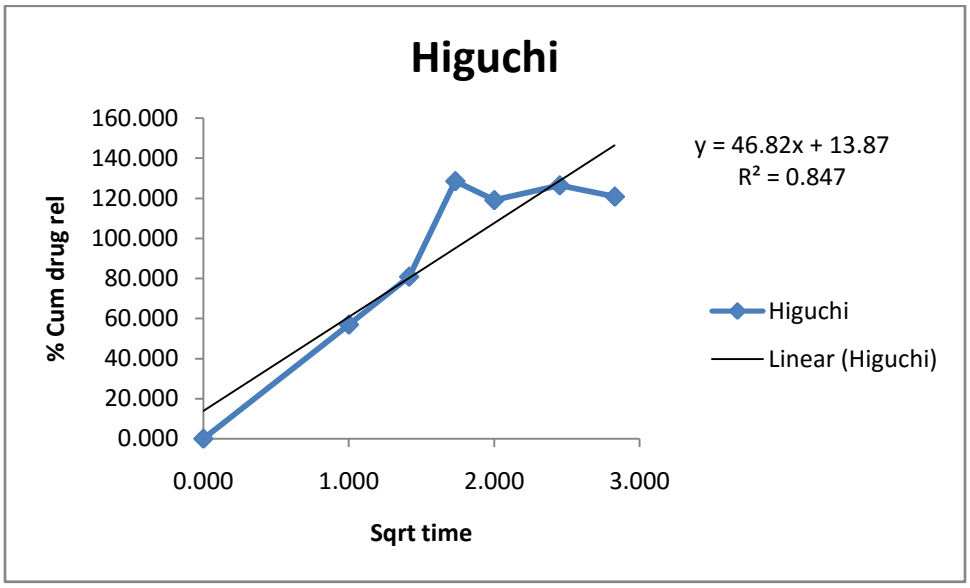
3	47.658	128.417	-28.417	2.109	1.732	0.477	5.045
4	38.196	118.955	-18.955	2.075	2.000	0.602	4.918
6	45.555	126.314	-26.314	2.101	2.449	0.778	5.017
8	39.948	120.707	-20.707	2.082	2.828	0.903	4.942



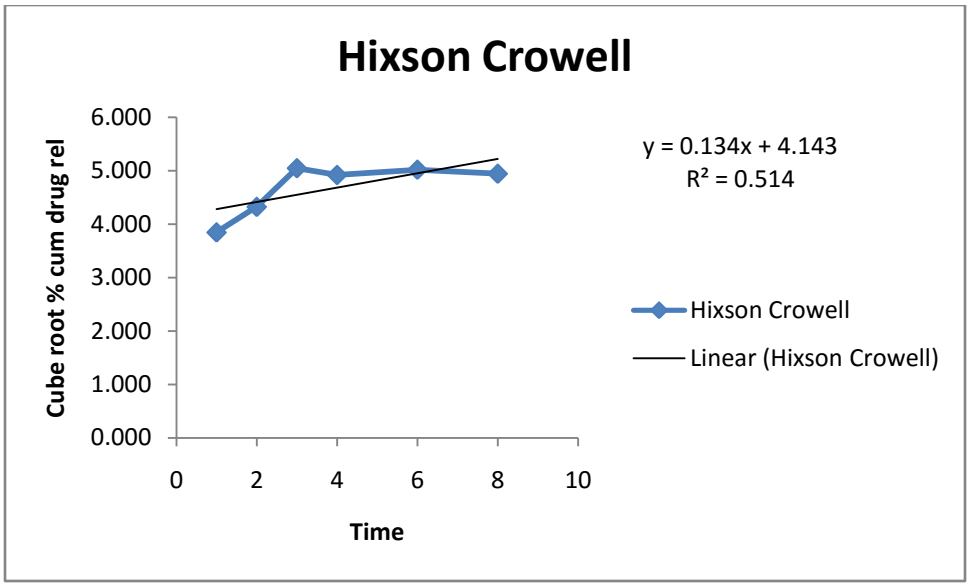
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



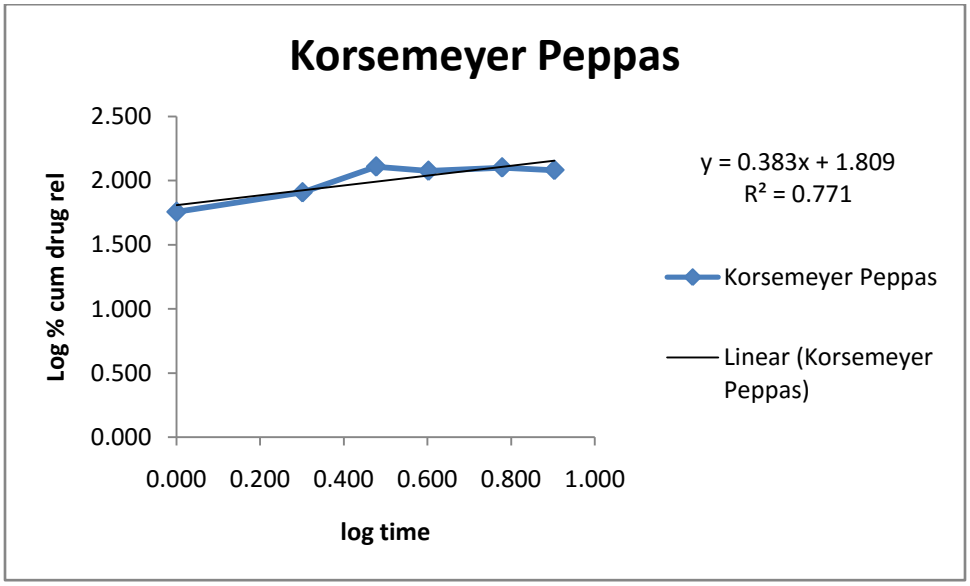
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time

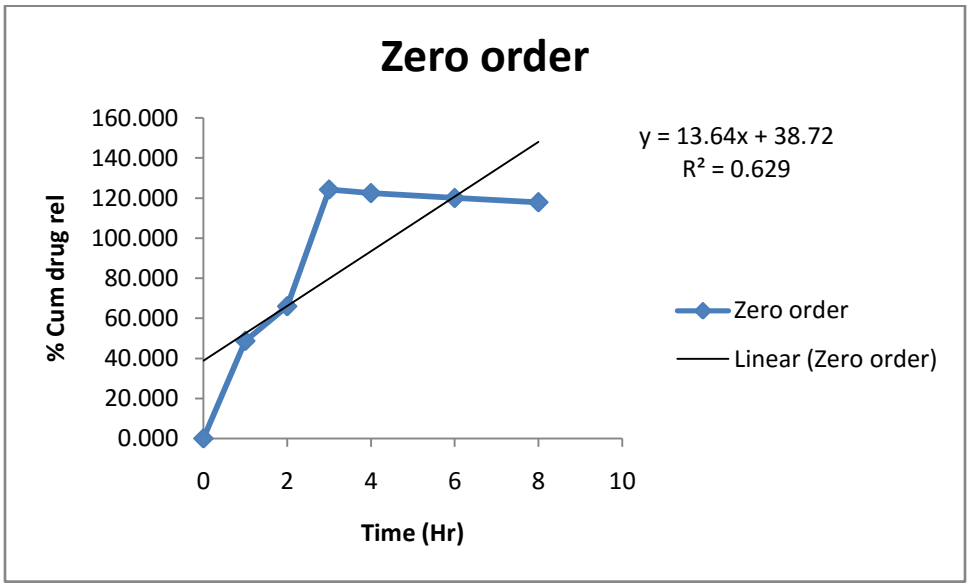


KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

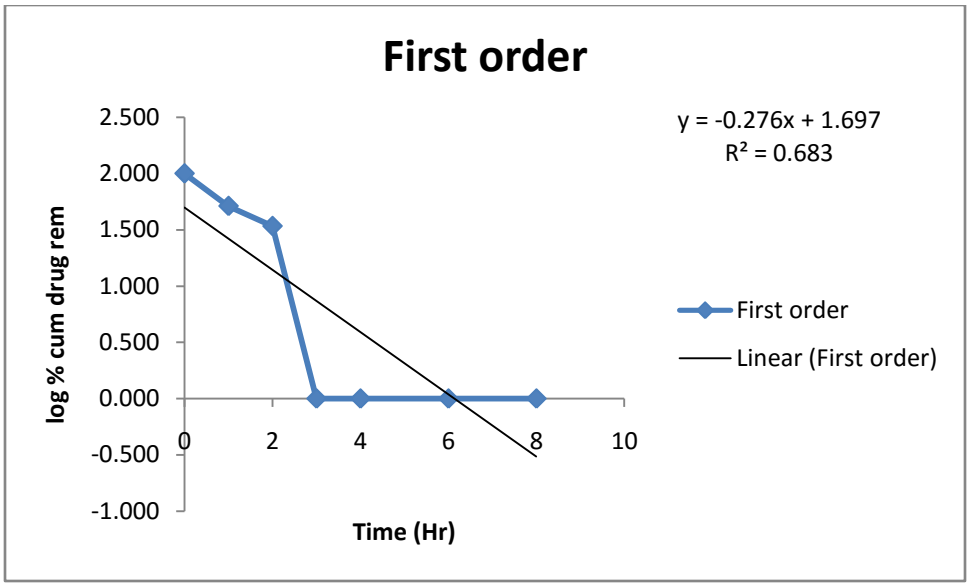
Appendix XXI: Kinetics of drug release for T8

Time (h)	% Drug released	% Cumulative drug released	% Cumulative drug remaining	Log % Cumulative drug released	Log % Cumulative drug remaining	Square Root Time	LOG Time	Cube-Root % cumulative drug released
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000
1	48.620	48.620	51.380	1.687	1.711	1.000	0.000	3.650
2	65.926	65.926	34.074	1.819	1.532	1.414	0.301	4.040

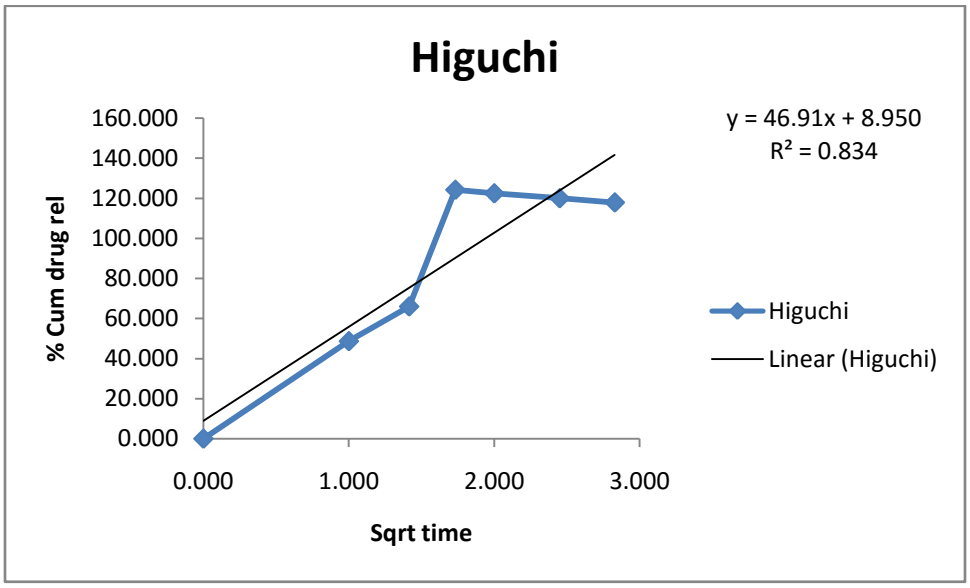
3	58.170	124.096	-24.096	2.094	1.732	0.477	4.988
4	56.418	122.344	-22.344	2.088	2.000	0.602	4.964
6	53.965	119.891	-19.891	2.079	2.449	0.778	4.931
8	51.863	117.789	-17.789	2.071	2.828	0.903	4.902



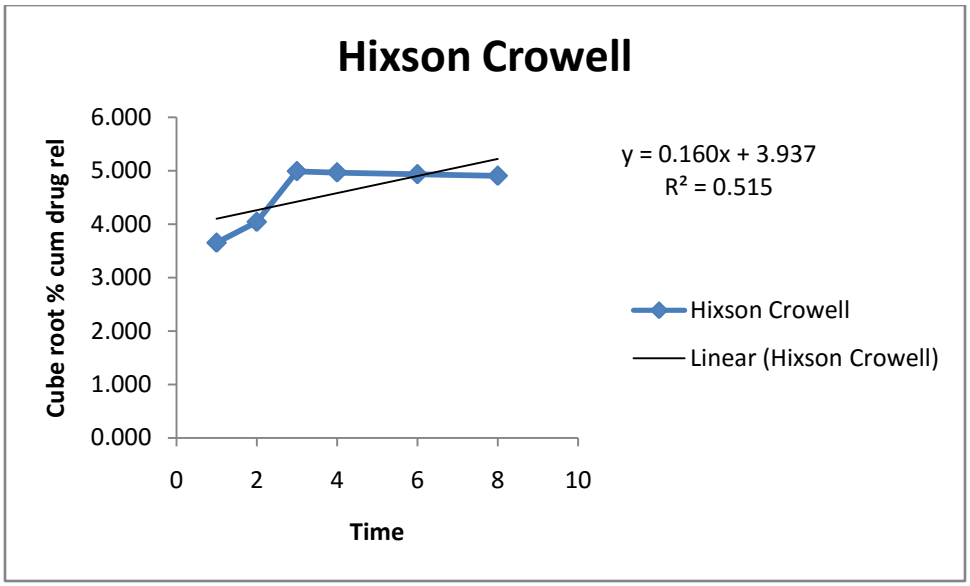
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



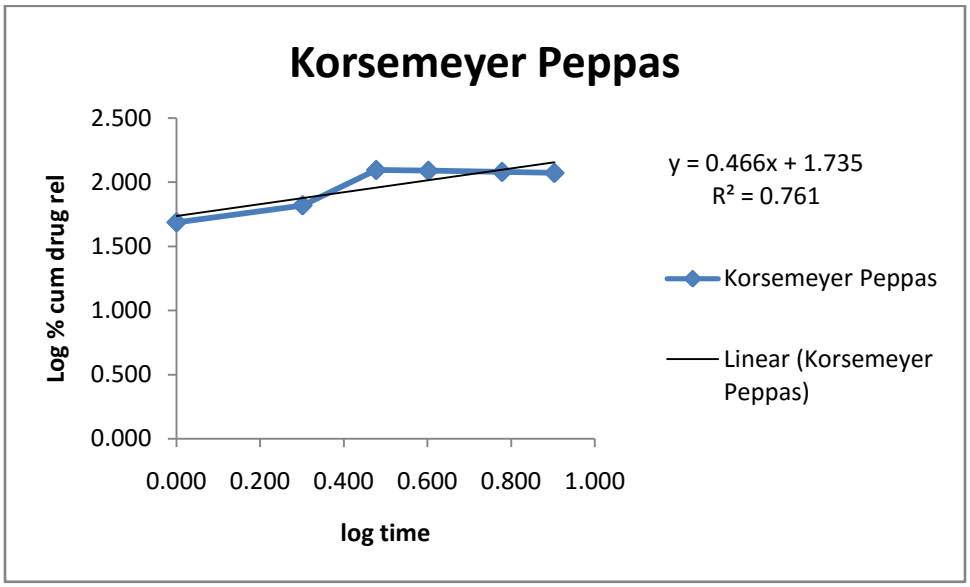
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time

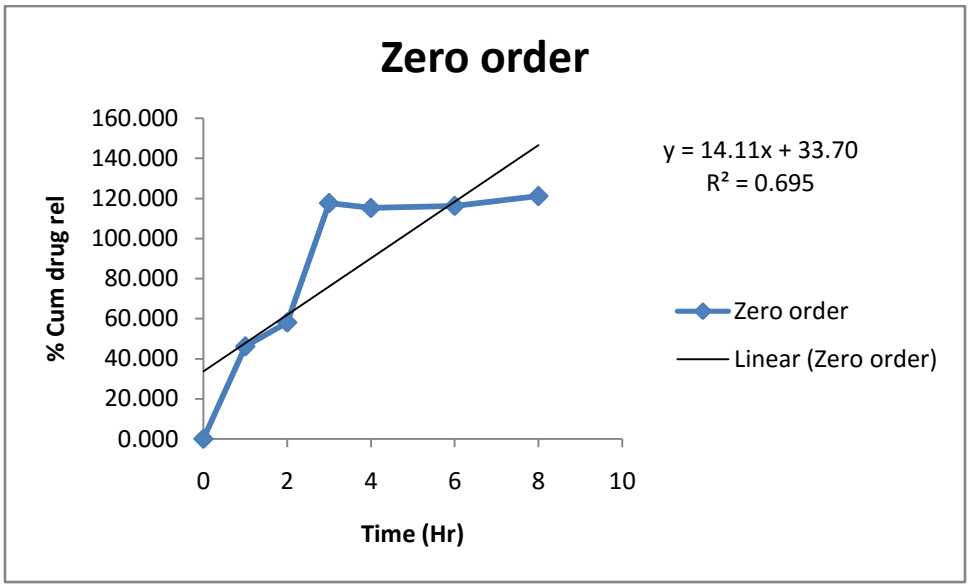


KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

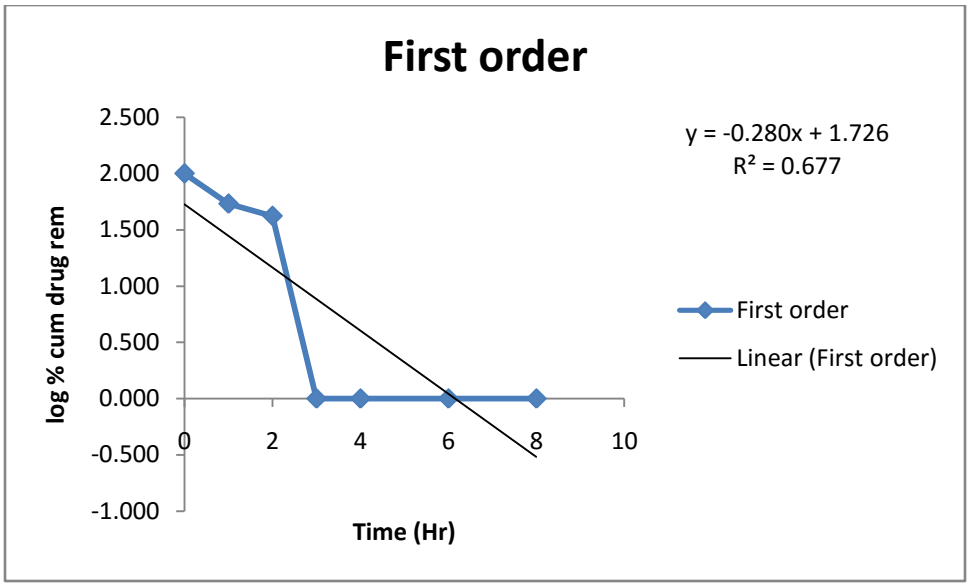
Appendix XXII: Kinetics of drug release for T9

Time (h)	% Drug released	% Cumulative drug released	% Cumulative drug remaining	Log % CumulativeDrug Released	Log % CumulativeDrug Remaining	Square Root Time	LOG Time	Cube-Root % Cumulative Drug Released
0	0.000	0.000	100.000	0.000	2.000	0.000	0.000	0.000
1	46.148	46.148	53.852	1.664	1.731	1.000	0.000	3.587
2	58.097	58.097	41.903	1.764	1.622	1.414	0.301	3.873
3	59.572	117.669	-17.669	2.071		1.732	0.477	4.900

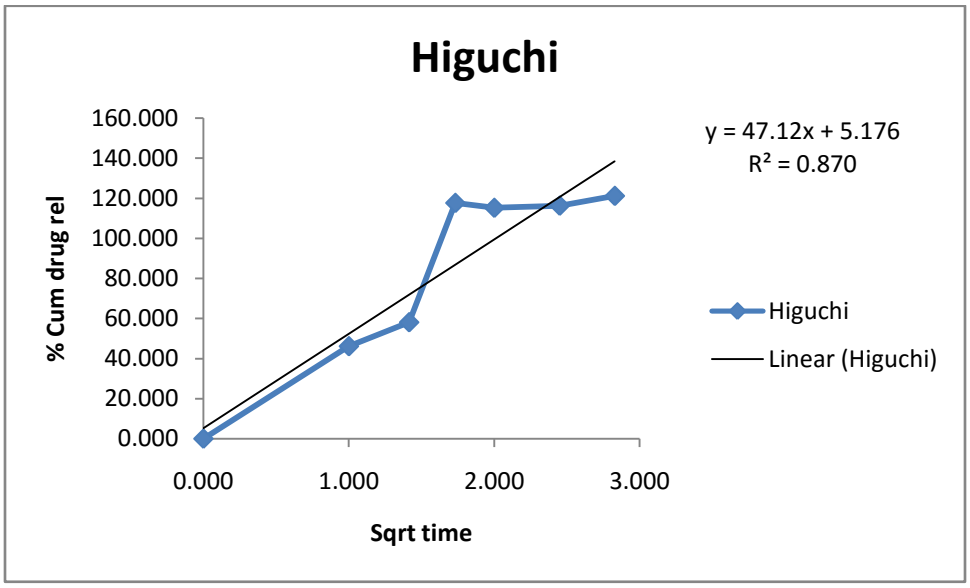
4	57.119	115.216	-15.216	2.062		2.000	0.602	4.866
6	58.170	116.267	-16.267	2.065		2.449	0.778	4.881
8	63.076	121.173	-21.173	2.083		2.828	0.903	4.948



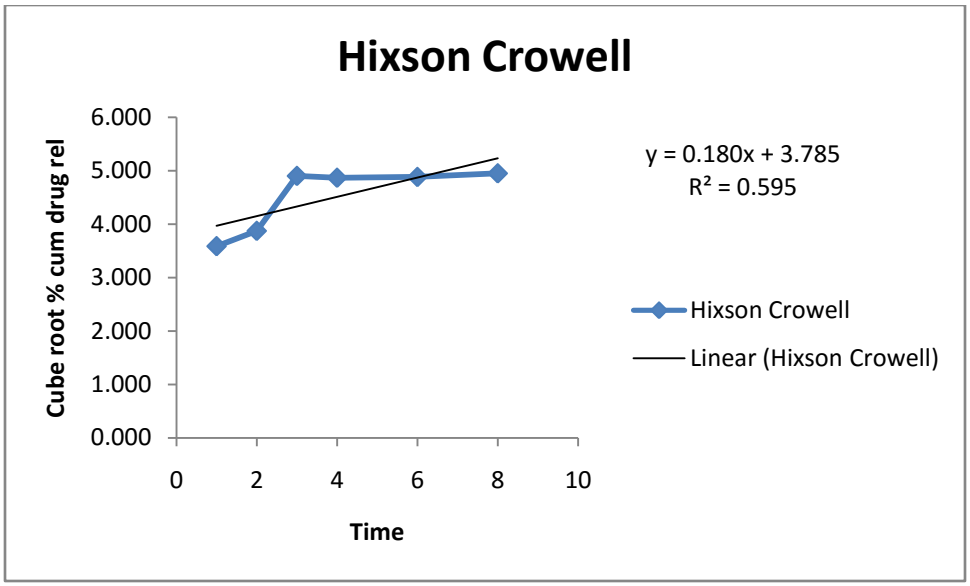
ZERO ORDER KINETICS = Plot of % Cum Drug Rel vs Time



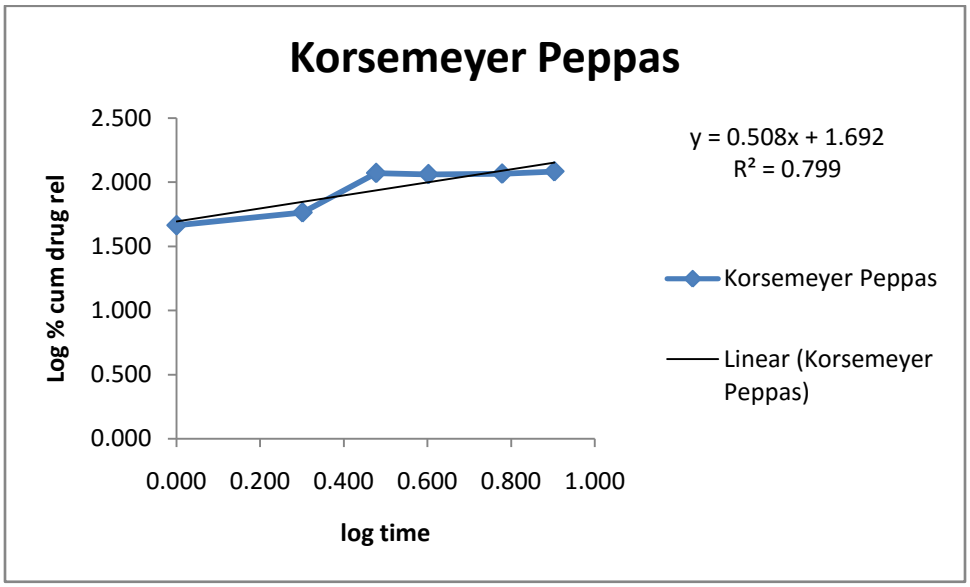
FIRST ORDER KINETICS= Plot of log % cum drug Rem vs Time



HIGUCHI MODEL = Plot of % Cum Drug Rel vs Squar Root Time



HIXSON CROWELL = Plot of Cube Root % Cum Drug Rel vs Time



KORSMEYER PEPPAS = Plot of Log % Cum Drug Rel vs Log Time

Appendix XXIII: DESCRIPTIVE STATISTICS

DEPENDENT VARIABLE: MEASUREMENT

MATERIAL	PROPORTION	BATCH	Mean	Std. Deviation	N
1(EG)	1 (30 %)	**T1**	46.99405	6.729534	6
	2 (40 %)	**T2**	38.36133	4.513974	6
	3 (50 %)	**T3**	44.52800	9.430938	6
	Total		43.29446	7.709017	18
2(CG)	1 (30 %)	**T4**	35.57183	4.478747	6
	2 (40 %)	**T5**	36.25167	4.923309	6
	3 (50 %)	**T6**	37.47150	3.009406	6
	Total		36.43167	4.043085	18
3(HPMC)	1 (30 %)	**T7**	51.49617	15.782132	6
	2 (40 %)	**T8**	55.82700	5.982473	6
	3 (50 %)	**T9**	57.03033	5.725029	6
	Total		54.78450	9.970163	18
Total	1		44.68735	11.834020	18
	2		43.48000	10.253873	18
	3		46.34328	10.378644	18
	Total		44.83688	10.705074	54

Key: *EG = Extracted acacia gum *CG = Crosslinked acacia gum

*HPMC = Hydroxylpropylmethyl cellulose.

Appendix XXIV: Tests of Between-Subjects Effects

Dependent Variable: MEASUREMENT

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	3445.719[a]	8	430.715	7.375	.000
Intercept	108558.655	1	108558.655	1858.876	.000
MATERIAL	3095.673	2	1547.836	26.504	.000
PROPORTION	74.389	2	37.194	.637	.534
MATERIAL * PROPORTION	275.657	4	68.914	1.180	.332
Error	2628.007	45	58.400		
Total	114632.381	54			
Corrected Total	6073.726	53			

a. R Squared = .567 (Adjusted R Squared = .490)

Appendix XXV: ESTIMATED MARGINAL MEANS (PROPORTION)

Dependent Variable: MEASUREMENT

PROPORTION	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
1(30 %)	44.687	1.801	41.059	48.315
2(40 %)	43.480	1.801	39.852	47.108
3(50 %)	46.343	1.801	42.715	49.971

Appendix XXVI: ESTIMATED MARGINAL MEANS (MATERIAL * PROPORTION)

Dependent Variable: MEASUREMENT

MATERIAL	PROPORTION	Mean	Std. Error	95% Confidence Interval		BATCH
				Lower Bound	Upper Bound	
	1(30 %)	46.994	3.120	40.710	53.278	T1
1(EG)	2(40 %)	38.361	3.120	32.078	44.645	T2
	3(50 %)	44.528	3.120	38.244	50.812	T3
	1(30 %)	35.572	3.120	29.288	41.856	T4
2(CG)	2(40 %)	36.252	3.120	29.968	42.535	T5
	3(50 %)	37.472	3.120	31.188	43.755	T6
	1(30 %)	51.496	3.120	45.212	57.780	T7
3(HPMC)	2(40 %)	55.827	3.120	49.543	62.111	T8
	3(50 %)	57.030	3.120	50.747	63.314	T9

Key: *EG = Extracted acacia gum

*CG = Crosslinked acacia gum

*HPMC = Hydroxylpropylmethyl cellulose.

Appendix XXVII: ESTIMATED MARGINAL MEANS (MATERIAL)

Dependent Variable: MEASUREMENT

MATERIAL	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
1(EG)	43.294	1.801	39.667	46.922
2(CG)	36.432	1.801	32.804	40.060
3(HPMC)	54.785	1.801	51.157	58.412

Key: *EG = Extracted acacia gum

*CG = Crosslinked acacia gum

*HPMC = Hydroxylpropylmethyl cellulose.

Appendix XXVIII: POST HOC TESTS (Multiple Comparisons)

Dependent Variable: MEASUREMENT

Tukey HSD

(I) MATERIAL	(J) MATERIAL	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	6.86279*	2.547333	.026	.68904	13.03655
	3	-11.49004*	2.547333	.000	-17.66379	-5.31629
2	1	-6.86279*	2.547333	.026	-13.03655	-.68904
	3	-18.35283*	2.547333	.000	-24.52659	-12.17908
3	1	11.49004*	2.547333	.000	5.31629	17.66379
	2	18.35283*	2.547333	.000	12.17908	24.52659

Based on observed means.

The error term is Mean Square (Error) = 58.400.

*. The mean difference is significant at the 0.05 level.

Key: Material 1 = EG

Material 2 = CG

Material 3 = HPMC